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Review Article

A quantitative meta-analysis of fMRI studies in bipolar disorder

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Objectives: Functional magnetic resonance imaging (fMRI) has been widely used to identify state and trait markers of brain abnormalities associated with bipolar disorder (BD). However, the primary literature is composed of small-to-medium-sized studies, using diverse activation paradigms on variously characterized patient groups, which can be difficult to synthesize into a coherent account. This review aimed to synthesize current evidence from fMRI studies in midlife adults with BD and to investigate whether there is support for the theoretical models of the disorder.

Methods: We used voxel-based quantitative meta-analytic methods to combine primary data on anatomical coordinates of activation from 65 fMRI studies comparing normal volunteers (n = 1,074) and patients with BD (n = 1,040).

Results: Compared to normal volunteers, patients with BD underactivated the inferior frontal cortex (IFG) and putamen and overactivated limbic areas, including medial temporal structures (parahippocampal gyrus, hippocampus, and amygdala) and basal ganglia. Dividing studies into those using emotional and cognitive paradigms demonstrated that the IFG abnormalities were manifest during both cognitive and emotional processing, while increased limbic activation was mainly related to emotional processing. In further separate comparisons between healthy volunteers and patient subgroups in each clinical state, the IFG was underactive in manic but not in euthymic and depressed states. Limbic structures were not overactive in association with mood states, with the exception of increased amygdala activation in euthymic states when including region-of-interest studies.

Conclusions: In summary, our results showed abnormal frontal-limbic activation in BD. There was attenuated activation of the IFG or ventrolateral prefrontal cortex, which was consistent across emotional and cognitive tasks and particularly related to the state of mania, and enhanced limbic activation, which was elicited by emotional and not cognitive tasks, and not clearly related to mood states.

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Bipolar disorder (BD) is characterized by episodes of mania and depression separated by periods of remission, with a lifetime prevalence of 1.5–3% (1–3). Theoretical models suggest that BD is underpinned by functional and structural abnormalities in the fronto-limbic circuits. Strakowski et al. (4–6) propose a model of BD that involves dysfunction within the anterior limbic system including subcortical (striatal-thalamic) prefrontal networks and the limbic structures. The authors suggest that there may be diminished prefrontal modulation of subcortical and medial temporal

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structures that results in dysregulation of mood (6). Phillips et al. (7) describe a neural model of emotional circuitry comprising a ventral system including the amygdala, insula, ventral striatum, and ventral anterior cingulate cortex (ACC) and prefrontal cortex (PFC), and a dorsal system including the hippocampus, dorsal ACC, and PFC. These ventral and dorsal systems are responsible for emotion perception and regulation, respectively. Overactivation in the ventral system and underactivation in the dorsal system may underlie the neurobiology of BD (8). Based on this model, Phillips et al. (9) examined the existing literature and found that the most consistent findings derived from paradigms engaging automatic regulatory processes such as Stroop tasks, which showed reduced activity in the inferior frontal cortex (IFC), orbitofrontal cortex (OFC), and dorsomedial PFC (10, 11). Other authors also suggest dysfunctional emotion regulation in BD (12–14) and propose the ventral PFC as a key region implicated in the pathophysiology of BD (15).

Although neuroimaging studies have accumulated evidence to substantially enhance our understanding of the neurobiology of BD, findings from these studies have not been entirely consistent with each other. Previous reviews have detailed such studies comprehensively in a narrative way (6, 8, 9, 12, 15–25). However, it is difficult to achieve an integrated insight into the functional neuroanatomy of BD and related clinical mood states (mania and depression) from the large body of primary literature.

This review aimed to synthesize current evidence from fMRI studies in midlife adults with BD and to investigate whether there is support for the theoretical models of the disorder. We used voxel-based quantitative meta-analysis (26) as a tool to formally synthesize the results of fMRI studies in the primary literature that had compared task-related brain functional activation in patients with BD and normal volunteers (see Table 1). Patients were subgrouped according to their current clinical mood state (manic, depressed, or euthymic). We used meta-analysis to define brain functional abnormalities in all patients compared to normal volunteers and to define brain functional abnormalities in specific clinical states. A variety of activation paradigms were used experimentally, which we aggregated into two broad classes: *cognitive* or *emotional* (see Table 1). We repeated the meta-analysis of each clinical group on both cognitive and emotional tasks separately. We hypothetically predicted that BD would be associated with hypofrontal and hyperlimbic activation by emotional tasks and hypofrontal activation by cognitive tasks. We also predicted that there would be evidence for persistent functional abnormalities in euthymic patients, consistent with trait-like aspects of the disorder, and evidence for exacerbated abnormalities specifically in manic and depressed patients, reflecting state-related aspects of the disorder.

Methods

Primary literature search and selection

We identified primary studies by a search of the MEDLINE (using both free-text and MeSH search) and ISI Web of Science databases using the following keywords: *bipolar disorder*, *manic-depressive*, *mania*, *mood disorder*, *fMRI*, and *brain imaging*. We also searched the reference lists of review articles on BD and the studies identified for inclusion to check any additional studies not identified by computerized literature search. We only included fMRI, not other imaging modalities. An initial list of studies was produced that included any report of fMRI studies of BD published in print or online before June 2010. The inclusion criteria below were then applied to create a definitive list of primary studies for the planned meta-analyses in this study.

All reports included in the meta-analysis satisfied the following criteria:

- They statistically compared a group of patients with BD to a group of healthy volunteers.
- They conducted a whole-brain analysis as opposed to adopting a region-of-interest (ROI) approach; however, studies that conducted an initial within-group, whole-brain analysis and then used the resulting maps of significant task-related activation to constrain the subsequent between-group comparison were also included (ROI studies were included in a separate set of meta-analyses; see below).
- They provided standard Talairach or Montreal Neurological Institute (MNI) spatial coordinates for key results.
- Patients with bipolar and unipolar disorders were not classified as a single patient group of affective disorders.
- For the analysis of state characteristics, only studies reporting the states of the patients were included.
- There were at least five subjects in each of the patient and healthy comparison groups.

We conducted a meta-analysis where there were at least three studies meeting these criteria. Studies that found no significant results were also included.

Table 1. Primary fMRI studies of bipolar disorder (BD) included in the meta-analysis using a whole-brain approach

Primary study	Sample size	Bipolar mood states	Task
Curtis et al. 2001 (53)	5 BD, 5 CON, 5 SZ	Euthymic (n = 5)	Verbal fluency task (C) Semantic decision making task (C)
Blumberg et al. 2003 (10)	36 BD, 20 CON	Manic (n = 11) Depressed (n = 10) Euthymic (n = 15)	Color–word Stroop task (C)
Adler et al. 2004 (51)	15 BD, 15 CON	Euthymic (n = 15)	N-back task (C)
Elliott et al. 2004 (33)	8 BD, 11 CON	Manic (n = 7) Hypomanic (n = 1)	Affective go/no-go task (E)
Lawrence et al. 2004 (39)	12 BD, 11 CON, 9 MDD	Depressed (n = 11) Euthymic (n = 3)	Implicit facial affect task (E)
Lennox et al. 2004 (40)	10 BD, 12 CON	Manic (n = 10)	Explicit facial affect recognition task (E)
Mitchell et al. 2004 (44)	11 BD, 13 CON, 12 SZ	Not specified	Emotional prosody task (E)
Monks et al. 2004 (65)	12 BD, 12 CON	Euthymic (n = 12)	Two-back task (C)
Strakowski et al. 2004 (4)	10 BD, 10 CON	Euthymic (n = 10)	Continuous performance task (C)
Altshuler et al. 2005 (52)	11 BD, 13 CON	Manic/hypomanic (n = 11)	Go/no-go task (C)
Blumberg et al. 2005 (30)	17 BD, 17 CON	Mixed (n = 2) Euthymic (n = 9) Depressed (n = 3) Manic (n = 2) Hypomanic (n = 1)	Facial affect perception task (E)
Malhi et al. 2005 (41)	12 BD, 12 CON	Euthymic (n = 12)	Emotional Stroop task (E)
Strakowski et al. 2005 (5)	16 BD, 16 CON	Euthymic (n = 16)	Counting Stroop task (C)
Chen et al. 2006 (31)	16 BD, 8 CON	Manic (n = 8) Depressed (n = 8)	Explicit and implicit face recognition task (E)
Kronhaus et al. 2006 (11)	10 BD, 11 CON	Euthymic (n = 10)	Color-word Stroop task (C)
Roth et al. 2006 (67)	11 BD, 11 CON	Mixed (n = 4) Manic (n = 1) Depressed (n = 1) Euthymic (n = 5)	Counting Stroop task (C)
Curtis et al. 2007 (54)	12 BD, 12 CON	Euthymic (n = 12)	Language tasks (C)
Frangou et al. 2007 (70)	7 BD, 7 CON	Euthymic (n = 7)	N-back task (C)
Lagopoulos et al. 2007 (60)	10 BD, 10 CON	Euthymic (n = 10)	Sternberg task (C)
Lagopoulos and Malhi 2007 (38)	10 BD, 10 CON	Euthymic (n = 10)	Emotional Stroop task (E)
Malhi et al. 2007 (42)	10 BD, 10 CON	Euthymic (n = 10)	Explicit facial emotion recognition task (E)
Malhi et al. 2007 (43)	10 BD, 10 CON	Euthymic (n = 10)	Implicit affect induction task (E)
Marchand et al. 2007 (61)	14 BD, 15 CON	Depressed (n = 14)	Paced motor activation task (C)
Wessa et al. 2007 (46)	17 BD, 17 CON	Euthymic (n = 17)	Emotional go/no-go task (E)
Altshuler et al. 2008 (29)	11 BD, 17 CON	Depressed (n = 11)	Face-matching task (E)
Deckersbach et al. 2008 (32)	9 BD, 17 CON	Depressed (n = 9)	N-back mood induction task (E)
Foland et al. 2008 (34)	9 BD, 9 CON	Manic/hypomanic (n = 9)	Face-matching task (E)
Hassel et al. 2008 (48)	19 BD, 24 CON	Euthymic (n = 19)	Facial expression task (E)
Jogia et al. 2008 (35)	12 BD, 12 CON	Not specified	Sad affect face recognition task (E)
Drapier et al. 2008 (55)	20 BD, 20 relatives; 20 CON	Euthymic (n = 20)	N-back task (C)
Killgore et al. 2008 (36)	14 BD, 13 CON	Not specified	Fearful face perception task (E)
Malhi et al. 2008 (47)	20 BD, 20 CON	Euthymic (n = 20)	Theory of mind task (E)
McIntosh et al. 2008 (63)	42 BD, 37 CON, 27 SZ	Not specified	Hayling Sentence Completion task (C)
Mechelli et al. 2008 (64)	29 BD, 45 CON, 41 SZ	Not specified	Verbal fluency task (C)
Strakowski et al. 2008 (68)	16 BD, 16 CON	Manic (n = 16)	Response inhibition task (C)
Taylor Tavares et al. 2008 (45)	12 BD, 13 MDD, 15 CON	Depressed (n = 12)	Probabilistic reversal learning task (E)
Hall et al. 2009 (57)	14 BD, 15 SZ, 14 CON	Stable (n = 14)	Face-name pair memory task (C)
Hamilton et al. 2009 (73)	21 BD, 20 SZ, 38 CON	Euthymic (n = 21)	Working memory task (C)
Kaladjian et al. 2009 (59)	20 BD, 20 CON	Euthymic (n = 20)	Go/no-go task (C)
Kaladjian et al. 2009 (58)	10 BD, 10 CON	Manic → euthymic (n = 10)	Go/no-go task (C)
Kim et al. 2009 (37)	14 BD, 14 CON	Euthymic (n = 14)	Virtual social cognition task (E)
Mazzola-Pomietto et al. 2009 (62)	16 BD, 16 CON	Manic (n = 16)	Go/no-go task (C)
Robinson et al. 2009 (66)	15 BD, 15 CON	Euthymic (n = 15)	Delayed-non-match-to-sample task (C)
Welander-Vatn et al. 2009 (69)	27 BD, 28 CON	Euthymic (n = 15) Depressed (n = 12)	Go/no-go task (C)

Table 1. (*Continued*)

Primary study	Sample size	Bipolar mood states	Task
Whalley et al. 2009 (50)	14 BD, 15 SZ, 14 CON	Not specified	Emotional memory task (E)
Allin et al. 2010 (71)	18 BD, 19 relatives; 19 CON	Euthymic (n = 18)	Verbal fluency task (C)
Bermpohl et al. 2010 (88)	15 BD, 26 CON	Manic (n = 15)	Monetary incentive delay task (E)
Glahn et al. 2010 (72)	15 BD, 24 CON	Euthymic (n = 15)	Face-name association task (C)
Gruber et al. 2010 (56)	18 BD, 18 CON	Euthymic (n = 18)	Delayed matching to sample task (C)
Surguladze et al. 2010 (49)	20 BD, 20 relatives; 20 CON	Euthymic (n = 18)	Facial emotion task (E)
Townsend et al. 2010 (74)	42 BD, 14 CON	Manic (n = 13) Depressed (n = 14) Euthymic (n = 15)	N-back task (C)

CON = control; SZ = schizophrenia; MDD = major depressive disorder; C = cognitive task; E = emotional task.

We did not include studies specifically investigating pediatric or geriatric populations in BD, which involve topics concerning neurodevelopment and neurodegeneration that are beyond the scope of this review.

After conducting a meta-analysis of all studies comparing patients with BD, regardless of mood state, with healthy controls, we further divided the tasks into two categories: *cognitive* and *emotional*. The cognitive tasks were designed to examine a range of effortful, attention-demanding, higher-order executive or symbolic functions such as motor response, attention, working memory, and language. They were typically associated with activation in a distributed cortical network. The emotional tasks encompassed a variety of activation paradigms; however, the commonality across them was that emotionally salient stimuli were used. They included emotional perception of facial emotions or prosody, affect induction, or interference tasks such as affective go/no-go and Stroop tasks. These tasks recruit regions particularly implicated in processing emotional information, including the amygdala, basal ganglia, thalamus, insula, hippocampus, and the ACC, IFG, and OFC. The criterion used to define a task as cognitive or emotional in this review was whether the paradigm or the contrast in the experiment utilized emotionally valenced or salient stimuli (see Table 1).

Subsequently, we performed a series of meta-analyses of each clinical group on both cognitive and emotional tasks together and also separately as described above for the analysis of the patient group regardless of mood state. Finally, we repeated the same meta-analytic procedure but included studies using ROI methodology (see Table 2). This comprehensive meta-analytical approach, which analyzes ROI studies both separately and together with whole-brain studies, is recommended (http://www.brainmap.org/ale/) to ensure that the results derived from studies with strong *a priori* regional hypotheses are also taken into account.

Meta-analysis methods

Meta-analyses were performed using the revised activation likelihood estimation (ALE) software implemented in GingerALE 2.0 (http://www.brainmap.org/ale/) (26–28). The key modifications in the revised ALE software include the change from fixed-effects (convergence between foci) to random-effects (convergence between studies but not individual foci reported for the same study) inference, as well as greater meta-analytic weighting for primary studies that included more subjects (28). Like the classic ALE analysis, a set of spatial coordinates derived from included studies was tested to search for anatomical concordance among studies. The input coordinates were weighted to form estimates of activation likelihood for each intracerebral voxel. The activation likelihood of each voxel in standard space was then combined to form a statistic map of the ALE score at each voxel. Statistical significance of the ALE scores was determined by a permutation test controlling the false discovery rate (FDR) at $p < 0.05$. The statistic maps were thresholded by default at this critical value, and a minimum cluster size of suprathreshold voxels exceeding 100 mm^3 was imposed.

Activation coordinates reported in the MNI space were converted to Talairach coordinates using the Lancaster transform (icbm2tal) in GingerALE. Talairach coordinates which had been generated by the Brett transform were converted back to MNI coordinates and then to Talairach coordinates with the Lancaster transform in GingerALE as recommended (26).

We focused on the results showing a convergence of reported activation based on at least three

Table 2. Primary fMRI studies of bipolar disorder (BD) included in the meta-analysis using a region-of-interest (ROI) approach

Primary study	Sample size	Bipolar mood states	Task	ROI	Results
Yurgelun-Todd et al. 2000 (86)	14 BD, 10 CON	Stable (n = 14)	Facial expression task (E)	Amygdala	↑
				DLPFC	↓
Caligiuri et al. 2003 (78)	24 BD, 13 CON	Manic or mixed (n = 9)	Reaction time task (C)	M1	↑
				SMA	↑
				Caudate	–
				Putamen	–
				Pallidum	↑
				Thalamus	–
		Depressed (n = 15)		M1	↑
				SMA	–
				Caudate	–
				Putamen	–
				Pallidum	–
				Thalamus	–
Caligiuri et al. 2004 (79)	18 BD, 13 CON	Manic (n = 12) Depressed (n = 6)	Reaction time task (C)	M1	↑
Gruder et al. 2004 (81)	11 BD, 10 CON	Stable (n = 11)	Stroop task (C)	ACC	↓
				DLPFC	↑
Lennox et al. 2004 (40)[a]	10 BD, 12 CON	Manic (n = 10)	Explicit facial affect recognition task (E)	Amygdala	↓
Altshuler et al. 2005 (76)	9 BD, 9 CON	Manic (n = 9)	Matching facial expression paradigm (E)	Amygdala	↑
Blumberg et al. 2005 (30)[a,b]	17 BD, 17 CON	Unmedicated (n = 5)	Facial affect perception task (E)	Amygdala	↑
		Medicated (n = 12)		Amygdala	↓
Abler et al. 2007 (75)[b]	12 BD, 12 SZ, 12 CON	Manic (n = 8) Mixed (n = 3) Hypomanic (n = 1)	Monetary reward task (E)	vStriatum	↓
				Brainstem	–
				VTA	–
Deckersbach et al. 2008 (32)[a,b]	9 BD, 17 CON	Depressed (n = 9)	N-back mood induction task (E)	ACC	↑
				PFC	↑
Hassel et al. 2008 (48)[a]	19 BD, 24 CON	Euthymic (n = 19)	Facial expression task (E)	Amygdala	–
Robinson et al. 2008 (83)[b]	15 BD, 16 CON	Euthymic (n = 15)	Affective face matching task (E)	Amygdala	–
				IFG	↑
Taylor Tavares et al. 2008 (45)[a,b]	12 BD, 13 MDD, 15 CON	Depressed (n = 16)	Probabilistic reversal learning task (E)	dmPFC	↑
				vlPFC	–
				Amygdala	–
Bermpohl et al. 2009 (77)[b]	10 BD, 10 CON	Manic (n = 10)	Emotional picture viewing task (E)	Amygdala	↑
Costafreda et al. 2009 (80)	28 BD, 7 cotwins; 39 SZ, 10 cotwins; 48 CON	Stable (n = 28)	Verbal fluency task (C)	BA 44/45	–
Hassel et al. 2009 (82)	14 BD, 16 CON	Euthymic (n = 14)	Facial expression task (E)	dPFC	↓
				Putamen	↑
				Caudate	–
				Amygdala	–
Hall et al. 2009 (57)[a]	14 BD, 15 SZ, 14 CON	Stable (n = 14)	Face-name pair memory task (C)	Hippocampus	–
Hamilton et al. 2009 (73)[a]	21 BD, 20 SZ, 38 CON	Euthymic (n = 21)	Working memory task (C)	DLPFC	–

Table 2. (*Continued*)

Primary study	Sample size	Bipolar mood states	Task	ROI	Results
Shah et al. 2009 (84)[b]	30 BD, 48 CON	Euthymic (n = 30)	Facial expression task (E)	vACC	↓
				Amygdala	–
Welander-Vatn et al. 2009 (69)[a]	27 BD, 28 CON	Euthymic (n = 15) Depressed (n = 12)	Go/no-go task (C)	dACC/pre-SMA	–
Whalley et al. 2009 (50)[a,b]	14 BD, 15 SZ, 14 CON	Not specified	Emotional memory task (E)	Hippocampus	↑
Almeida et al. 2010 (87)[b]	30 BD, 15 MDD, 15 CON	BD depressed (n = 15) BD euthymic (n = 15) MDD depressed (n = 15)	Facial expression task (E)	Amygdala	↑
Bermpohl et al. 2010 (88)[a,b]	15 BD, 26 CON	Manic (n = 15)	Monetary incentive delay task–expectation of gain (E)	OFC	↑
			Monetary incentive delay task–expectation of loss (E)	OFC	↓
Chen et al. 2010 (89)[b]	12 BD, 12 CON	Manic (n = 12) → euthymic (n = 9)	Facial expression task (E)	OFC	↑
				PCC	↓
Glahn et al. 2010 (72)[a]	15 BD, 24 CON	Euthymic (n = 15)	Face-name association task–encoding (C)	Hippocampus	–
				DLPFC	↑
			Face-name association task–recognition (C)	Hippocampus	↓
				DLPFC	↓
Surguladze et al. 2010 (49)[a,b]	20 BD, 20 relatives; 20 CON	Euthymic (n = 18)	Facial emotion task (E)	Amygdala	↑
Thermenos et al. 2010 (85)[b]	19 BD, 18 relatives; 19 CON	Stable (n = 19)	N-back task (C)	Front. cortex	↓
				IFG	–
				OFC	–
				ACC	–
				Insula	↑
				Amygdala	–
				SPC	–

CON = control; MDD = major depressive disorder; SZ = schizophrenia; C = cognitive task; E = emotional task; DLPFC = dorsolateral prefrontal cortex; M1 = primary motor cortex; SMA = supplementary motor area; ACC = anterior cingulate cortex; vStriatum = ventral striatum; IFG = inferior frontal cotex; VTA = ventral tegmental area; dmPFC = dorsomedial prefrontal cortex; vlPFC = ventrolateral prefrontal cortex; dPFC = dorsal prefrontal cortex; vACC = ventral anterior cingulate cortex; OFC = orbitofrontal cotex; PCC = posterior cingulate cortex; Front. cortex = frontopolar cortex; SPC = superior parietal cortex; dACC = dorsal anterior cingulate cortex; ↑ = increased activation (BD patients); ↓ = decreased activation (BD patients); – = no difference between BD patients and healthy controls.

[a]Studies using a whole-brain analysis.

[b]These ROI studies showed significantly different activation in case-control comparison and provided coordinates in standard space for results.

primary studies. The convergent regions supported by only two studies were regarded as suggestive results.

Results

Primary literature

The meta-analysis of all fMRI studies in BD included 50 whole-brain-based studies on 779 patients and 797 healthy controls. The average sample size per study was 15.6 ± 7.84 patients and 15.9 ± 7.68 controls. The gender ratio of patient samples was approximately even (49.55% females). From those studies in which the clinical states of patients were specified, 371 euthymic, 91 manic, and 80 depressed patients were included in the planned meta-analyses. The average sample size per study was 14.3 ± 4.49 euthymic, 11.4 ± 3.29 manic, and 11.4 ± 2.30 depressed patients. There were 22 studies using emotional paradigms (29–50) and 28 studies using cognitive paradigms (4, 5, 10, 11, 51–74). In addition, we also included 26 studies using an ROI analysis in a separate set of meta-analyses. Eleven of these 26 studies also used a whole-brain analysis approach; thus, there were 15 additional primary studies included (75–89), resulting in 65 primary studies overall.

Some studies were included in more than one meta-analysis since they implemented more than one kind of task or included more than one type of patient population. The numbers of primary studies included in each meta-analysis are listed in Table 3 for whole brain-based studies only and in *Supplemental Table 1* for meta-analyses combining whole-brain and ROI-based studies.

BD versus healthy controls

The meta-analysis of case-control studies comparing patients with BD regardless of mood state with healthy controls consisted of 50 primary studies. The results showed significantly increased activation in BD patients relative to healthy controls in medial temporal lobe structures (extending from parahippocampal gyrus and amygdala to hippocampus) and putamen and pallidum [reported by six primary studies (34, 35, 38, 39, 42, 49)] and caudate [reported by three studies (31, 40, 51)]. Decreased activation in BD patients was shown in the IFG [reported by six studies (29, 34, 52, 60, 62, 67)], lingual gyrus [reported by six studies (33, 43, 50, 53, 66, 73], and putamen [reported by five studies (5, 36, 41, 58, 72)] (Table 3).

Subsidiary meta-analyses based on appropriate subsets of the primary data consisted of 22 studies using emotional tasks and 29 studies using cognitive tasks [one study implemented both emotional and cognitive contrasts in its analysis (33)]. On emotional tasks, patients with BD demonstrated abnormally increased activation in the medial temporal lobe, putamen, and pallidum, as well as abnormally decreased activation in the IFG (*Supplemental Table 2*). On cognitive tasks, patients with BD demonstrated abnormally decreased activation in the IFG, lingual gyrus, and putamen; there was much less evidence for abnormal subcortical or limbic activation by cognitive tasks than for emotional tasks.

Euthymic states versus healthy controls

The meta-analysis of the studies comparing euthymic BD patients with healthy controls consisted of 26 primary studies. Decreased activation in euthymic patients was shown in the lingual gyrus [reported by four studies (43, 53, 66, 73)] (see Table 3). Subsidiary meta-analyses showed decreased lingual activation on cognitive tasks.

Manic states versus healthy controls

The meta-analysis of the comparison between manic patients and healthy controls consisted of eight primary studies. The results showed significantly decreased activation in BD patients relative to healthy controls in the IFG [reported by three studies (34, 52, 62)] (Table 3). Subsidiary meta-analyses showed no evidence of replicable abnormalities of brain activation in manic patients on either emotional or cognitive tasks, probably reflecting the much smaller number of primary studies (*Supplemental Table 2*).

Depressed states versus healthy controls

The meta-analysis on the comparison between depressed patients and healthy controls consisted of seven primary studies. No single region was convergently activated by more than two primary studies in the meta-analyses of depressed states (Table 3, *Supplemental Table 2*).

Meta-analysis including ROI primary studies

We also conducted a separate set of meta-analyses of all the primary data, including both whole-brain and ROI-based studies. The resulting pattern was very similar to that obtained from the previous analyses, in which only the whole-brain-based studies were included, apart from increased

Table 3. Activation likelihood estimation meta-analytical results (including whole brain-based studies only)

Regions	Peak coordinates			BA	Cluster size (mm^3)	Contributing study reference numbers
	x	y	z			
Bipolar versus control[a]						
↑ **Bipolar**						
Parahippocampal gyrus	−24	−20	−10	28	1432	(34, 35, 38, 39, 42, 49)
Hippocampus						
Amygdala						
Putamen	−26	−4	4			
Pallidum	−20	−8	−6			
Precentral gyrus	54	4	36	6	960	(33, 66)
Caudate	−14	14	18		488	(31, 40, 51)
Cerebellum	14	−68	−10		328	(31, 53)
Caudate	−20	26	0		288	(31, 39)
Superior frontal gyrus	−18	56	8	10	248	(37, 46)
Superior temporal gyrus	−46	−50	6	39	232	(37, 63)
Thalamus	−8	−26	6		208	(31, 34)
Medial frontal gyrus	−2	46	18	9	208	(49, 66)
Middle occipital gyrus	−28	−82	16	19	152	(4, 42)
Middle frontal gyrus	−38	38	−2	47	136	(4, 33)
↓ **Bipolar**						
Lingual gyrus	18	−84	−4	18	3112	(33, 43, 50, 53, 66, 73)
Inferior frontal gyrus	40	24	2	47	2520	(29, 34, 52, 60, 62, 67)
Putamen	−22	2	2		720	(5, 36, 41, 58, 72)
Inferior frontal gyrus	−36	22	−2	47	640	(34, 62, 65)
Putamen	24	4	2		448	(58, 72)
Anterior cingulate cortex	−18	40	−6	32	272	(10, 11)
Cerebellum	12	−32	−12		240	(43, 60)
Amygdala	22	−4	−10		192	(39, 59)
Euthymia versus control[b]						
↑ **Bipolar**						
Medial frontal gyrus	−2	46	18	9	456	(49, 66)
Superior frontal gyrus	−18	56	8	10	448	(37, 46)
Middle occipital gyrus	−28	−82	16	19	304	(4, 42)
Superior frontal gyrus	30	54	12	10	288	(46, 51)
Superior temporal gyrus	46	−36	6	22	272	(46, 51)
Parahippocampal gyrus	−24	−20	−10	28	232	(38, 42)
Cingulate cortex	−12	8	26	24	200	(46, 51)
Caudate	−14	12	22			
Putamen	−26	−4	4		184	(42, 49)
↓ **Bipolar**						
Lingual gyrus	20	−84	−2	17	2608	(43, 53, 66, 73)
Mania versus control[c]						
↑ **Bipolar**						
Thalamus	−4	−34	10		360	(34, 40)
↓ **Bipolar**						
Inferior frontal gyrus	34	24	2	47	2144	(34, 52, 62)
Inferior frontal gyrus	−34	24	−2	47	808	(34, 62)
Depression versus control[d]						
↑ **Bipolar**						
Caudate	−20	26	0		528	(31, 39)
Precentral gyrus	−52	−14	34	4	336	(31, 32)
Caudate	−10	10	4		200	(31, 61)
↓ **Bipolar**						
Inferior frontal gyrus	48	12	28	9	656	(29, 39)

Talairach coordinates are reported. BA = Brodmann area.
[a]Based on 50 studies.
[b]Based on 26 studies.
[c]Based on 8 studies.
[d]Based on 7 studies.

amygdala activation in euthymic states and decreased cingulate activation in BD patients (*Supplemental Tables 1 and 3*).

Discussion

This meta-analysis was undertaken to test current theoretical models of BD that propose abnormal ventral frontal and limbic activity. Our main results are that patients with BD regardless of current mood state exhibit underactivation in the IFG during both emotional and cognitive processing and overactivation in the medial temporal lobe and basal ganglia during emotional processing. In the meta-analyses for each mood state, IFG underactivation was seen in state of mania, and when ROI studies were included in the meta-analysis, amygdala overactivation was found in euthymia (see Fig. 1).

Decreased inferior frontal activity

The meta-analytic results demonstrated that BD patients exhibit decreased IFG activation on both emotional and cognitive tasks, particularly in the state of mania. The IFG is thought to be central to the inhibition of a prepotent response, and several of the primary studies demonstrating abnormal IFG activation utilized paradigms engaging regulatory processes such as Stroop tasks and go/no-go tasks (52, 62). However, a decrease in IFG activation was not solely related to impaired response

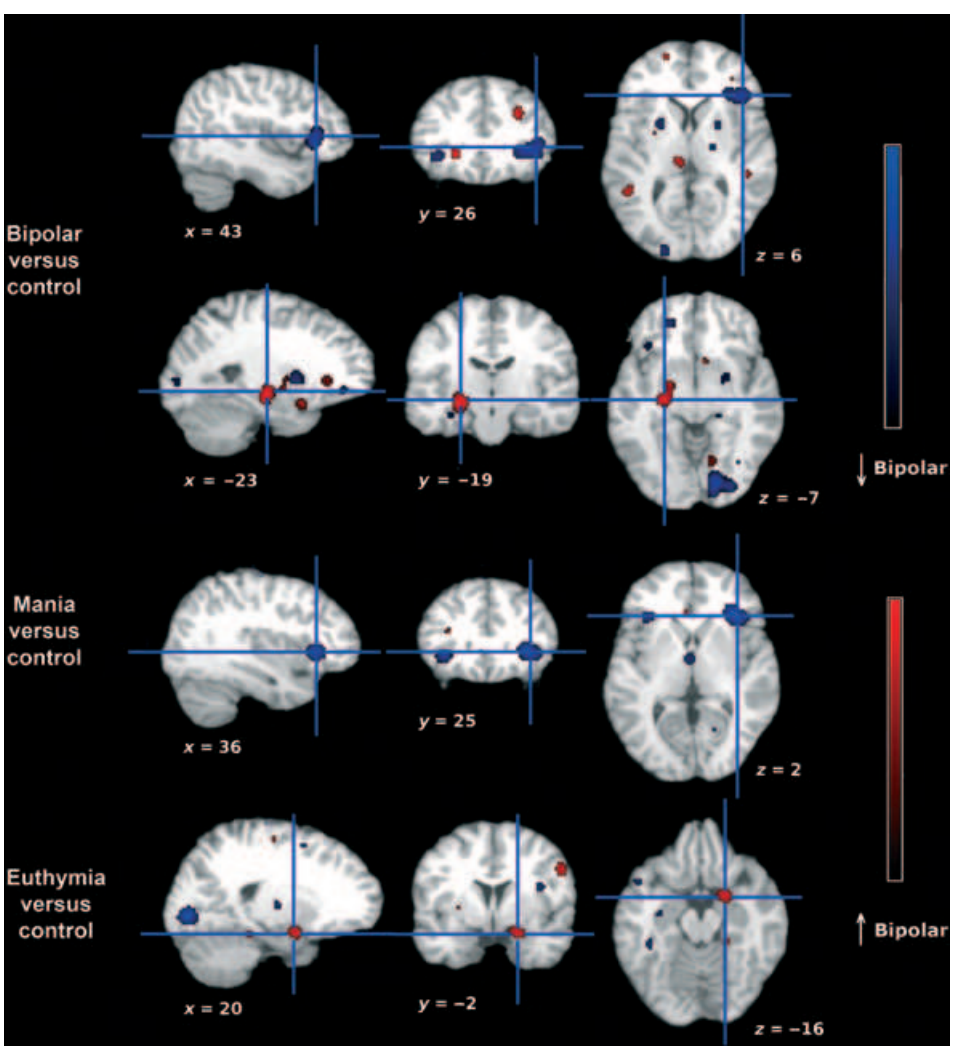

Fig. 1. Meta-analytic maps of brain functional changes in patients with bipolar disorder compared to healthy controls. The first two rows show abnormal brain activation in bipolar disorder patients regardless of current mood states compared to healthy controls. The third and fourth rows show abnormal brain activation in manic and euthymic patients compared to healthy controls, respectively. Relative under-activation in bipolar disorder is indicated by blue voxels and relative over-activation by red voxels. R and L markers denote the side of the brain. Numbers denote x, y, and z coordinates of each slice in Talairach space.

inhibition, because other studies using working memory (60) and facial affect matching tasks (29, 34) also provided evidence for abnormal activation in this region. Decreased IFG activation may also relate to aspects of the abnormal mental state in BD such as impulsivity, distractibility, and emotion regulation. This result is in agreement with current neurobiological models, which suggest emotion dysregulation in BD (6, 8, 9, 12). It is worth noting that our results did not show distributed frontal abnormalities; instead, these were localized primarily in the ventrolateral PFC, including the IFG and the superior part of the OFC, but not in the dorsal PFC. Although we found robustly decreased IFG activation, several studies using emotional tasks reported elevated ventral PFC activation especially in the OFC (39, 89), implying some paradigm-specific or mood-state-related variation, which is not shown in our meta-analysis.

Abnormal limbic activity

The meta-analysis revealed a convergence of increased activation in the left medial temporal structures, extending from parahippocampal gyrus and hippocampus to amygdala, in BD based on six studies. However, decreased activation was also reported in similar regions, but in the right hemisphere, by two studies (Table 3). There are different possible interpretations of this result. The amygdala is a region that has been consistently identified as playing a crucial role in emotional perception and arousal (90, 91), whereas the hippocampus and parahippocampal gyrus are associated with regulatory function during emotional processing (9, 13, 92) and have been implicated in BD (93). These regions are reciprocally and intensively interconnected functionally and anatomically. They frequently coactivate during performance of emotional tasks in fMRI studies on normal emotional processing, presumably due to interplay between production and regulation of emotion (7, 94). It is therefore difficult to differentiate whether activation in this region represents increased emotional arousal or regulation, either of which may be abnormal in patients with BD. Furthermore, although amygdala reactivity corresponds to perceiving both negative and positive stimuli, it largely reacts to stimuli that signal danger, uncertainty and novelty. In this capacity it is generally thought to act as a vigilance center, and increased amygdala activation may be associated with increased sensitivity to either positively or negatively valenced stimuli. Thus, definitive conclusions on the role of the amygdala in mood-congruent or -incongruent processing in BD remain lacking. Apart from the difficulty in interpreting results, the results on these regions are also conflicting in the literature. Several ROI studies specifically testing the difference in amygdala activation between BD patients and healthy controls either failed to find significant results (45, 82–85) or found both increased (76, 77, 86) and decreased amygdala activation (40). This question can be investigated further following the publication of sufficient studies that stratify patients by mood state and use stimuli with both positive and negative affective valence. Our findings also showed increased basal ganglia activation in BD, although we also found decreased putamen activation. Future work is similarly needed to clarify this inconsistency.

Euthymic, manic, and depressed states

The meta-analytical results of each specific state are regarded as preliminary because most of them were derived from only two studies (apart from the results from manic states showing decreased IFG activity). These results demonstrate decreased activity in the IFG in the state of mania, but not in euthymia, suggesting that frontal abnormalities might be ameliorated during remission. The subsidiary analysis including ROI studies showed increased amygdala activation in euthymic states. Our previous longitudinal study showed elevated amygdala activation in euthymic patients compared to healthy controls and compared to the patients' previous manic episodes, but amygdala activation was not increased relative to healthy controls when patients were manic (89). This implies state-related activation changes in the limbic areas, but our meta-analysis did not demonstrate this variation. Absence of limbic abnormalities in mania and depression is surprising. There is the possibility that pathological processes in these regions are present, but the low statistical power available obscures their detection. It is also likely that limbic abnormalities in mania and depression may be more apparent by examining their structural and functional connectivity to the frontal cortex (95, 96).

Distinct and overlapping activation with emotional and cognitive tasks

The IFG showed abnormal activation on both emotional and cognitive tasks. However, in contrast to the involvement of the fronto-limbic system on emotional tasks, abnormal brain activation was constrained to neocortical areas, par-

ticularly frontal regions, during performance of cognitive tasks in BD. The direction of these abnormalities was also different between emotional and cognitive tasks. For emotional tasks, BD patients exhibited both abnormally increased and decreased activation, while for cognitive tasks there was only decreased activation. Both increased and decreased activation in response to emotional stimuli in BD could reflect the interaction between mood states and valence of experimental stimuli as discussed above. Decreased activation during cognitive tasks is consistent with neuropsychological studies that show deficits of attention, memory, and executive functions in BD (97–102). As shown in our results, there is relatively normal activation during cognitive tasks in euthymia (*Supplemental Table 2*), suggesting that cognitive deficits are improved during remission. This result is supported by a recent study demonstrating enhanced PFC activity in stable BD patients after six weeks of lamotrigine treatment (103).

Comments on the primary literature regarding patient population

The primary studies included in our meta-analysis encompass heterogeneous demographic features of the BD population. A majority of the studies had a patient cohort of BD type I, with a couple of studies also including BD type II patients (46, 69). Although recruitment was sometimes exclusively of female or male patients, the gender ratio averaged across primary studies was approximately even. Thus, our results captured the neurobiological characteristics of BD patients from both genders.

In 52% of primary studies a minority of patients were medication free. The great majority of patients were taking a range of medications, including mood-stabilizer monotherapy, either alone or with other psychotropic medications (e.g., antipsychotics, antidepressants, and anxiolytics). The heterogeneity of regimens across primary studies limits the possibilities for a straightforward subsidiary analysis of medication effects in our quantitative meta-analysis. Nevertheless, by reviewing the primary studies, we found no bias toward any particular type of medication, and thus our results were not confounded by medication type. There was also no bias toward any subclinical group; that is, none of the mood-state analyses was differentially confounded by medication. However, our results could be confounded by overall medication effects inherent in the primary studies. A recent review on medication effects in neuroimaging studies of BD concluded either no significant effect or ameliorative effects of medication, which may normalize hypofrontal and hyperlimbic abnormalities (104). For example, greater ACC and dorsolateral PFC activation was reported in patients receiving medication than in unmedicated patients during selective attention (5). Elevated amygdala response was observed in unmedicated BD patients, while decreased activation was seen in medicated patients (30); however, another study showed the opposite pattern in euthymic patients (87). Some other studies found no significant association between medication and brain activity (11, 48–50, 72, 88). Due to a lack of consistent and obvious medication effects in the primary studies as well as a mixture of medication statuses across studies, we did not model medication effects in our meta-analysis; we acknowledge this as a limitation. It is possible that medication may be masking fronto-limbic abnormalities in patients with BD. A diagnosis of comorbid disorders is another source of heterogeneity in the patient sample. Some studies excluded patients with a diagnosis of current comorbid disorders (29, 32), while others excluded patients with both a current and past history of comorbidity (38, 41). We included all these studies, covering a wide range of patient characteristics without further categorizing them into subgroups due to an insufficient number of studies. This is a limitation of this study, given that the contributions of medication and comorbid disorders to brain activity in BD have been documented (30, 82). However, at the same time, heterogeneous samples also increase the representativeness of this meta-analysis of BD, generalizing the results to larger patient populations.

Methodological limitations

Several factors need to be considered when interpreting these meta-analytic results. Comparison of imaging studies of BD is complicated by the various activation paradigms employed and the different demographic features of patients enrolled in the studies. Thus, although meta-analytical results across studies help us to identify any consistency in the literature, they may also lack specificity as to the nature of any abnormality. Also, there are different criteria between studies regarding how patient mood state is measured and defined. In particular, patients reported as being euthymic may have subclinical manic or depressive symptoms. A further limitation is the small sample size per study, limiting statistical power and leading to a risk of type II error in the meta-analysis. Thus, the regions identified likely represent only the most robust findings in the literature.

Conclusion

It is encouraging to see that there are some important consistencies across the primary functional neuroimaging literature on BD. Patients with BD demonstrated abnormal activation in fronto-limbic systems, namely the IFG, medial temporal structures, and basal ganglia as anticipated by current neurobiological models. Patients with BD exhibited different functional abnormalities on emotional and cognitive tasks, with increased limbic activity in BD in response to emotional tasks and underactivation of the IFG in both cognitive and emotional tasks. The observation of IFG abnormality is robust in this meta-analysis and it is particularly associated with manic states. No limbic abnormalities in manic and depressed states specifically were identified in the meta-analysis, potentially due to low statistical power, which also emphasizes the need for future work in this research area.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1. Activation likelihood estimation meta-analytical results [including both whole-brain and region of interest (ROI)-based studies].

Table S2. Activation likelihood estimation meta-analytical results of emotional or cognitive studies (including whole-brain-based studies only).

Table S3. Activation likelihood estimation meta-analytical results of emotional or cognitive studies [including both whole-brain and region of interest (ROI)-based studies].

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