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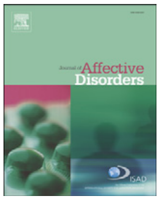

Research report

Neuroimaging-based markers of bipolar disorder: Evidence from two meta-analyses

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ABSTRACT

Background: Bipolar disorder (BD) is often misdiagnosed or tardily detected, leading to inadequate treatment and devastating consequences. The identification of objective biomarkers, such as functional and structural brain abnormalities of BD might improve diagnosis and help elucidate its pathophysiology.

Methods: To identify neurobiological markers of BD, two meta-analyses, one of functional neuroimaging studies related to emotional processing and a second of structural whole-brain neuroimaging studies in BD were conducted in the present study. Conducting a literature search on studies published up to September 2009 we identified 28 studies that were eligible for the meta-analyses: 13 functional magnetic resonance imaging studies, related to emotional processing and 15 structural imaging studies using whole-brain voxel-based morphometry. Only studies comparing patients with bipolar disorder to healthy controls were considered. Data were extracted or converted to a single anatomical reference (Talairach space). The activation likelihood estimation technique was used to assess the voxel-wise correspondence of results between studies.

Results: In patients with BD, decreased activation and diminution of gray matter were identified in a cortical-cognitive brain network that has been associated with the regulation of emotions. By contrast, patients with BD exhibited increased activation in ventral limbic brain regions that mediate the experience of emotions and generation of emotional responses. The present study provides evidence for functional and anatomical alterations in BD in brain networks associated with the experience and regulation of emotions.

Conclusions: These alterations support previously proposed neurobiological models of BD and might represent valid neurobiological markers of the disorder. The specificity of these results to unipolar depression remains to be explored.

1. Introduction

Bipolar disorder (BD) is the sixth largest cause of disability-adjusted life years (Murray and Lopez, 1996) and its prevalence worldwide is at least 1% (Merikangas et al., 2007). This high prevalence is associated with under-recognition (Hirschfeld et al., 2003) and delayed diagnosis leading to inadequate treatment, huge medical costs and high rates of comorbidity (Keck et al., 2008). As a consequence, there is a clear need to improve diagnostic tools and to identify objective biomarkers. Specific functional and structural brain abnormalities underlying cognitive and emotional trait impairments that are present during both acute episodes

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and remission have been proposed as promising candidates for biomarkers of bipolar disorders (Phillips and Vieta, 2007; Singh and Rose, 2009).

One of the characteristic impairments of BD is abnormal emotional liability reflected by extreme fluctuations in mood and emotions, and heightened emotional reactivity during all phases of the illness (Henry et al., 2003; Henry et al., 2008). The diagnostic criteria for BD, including euphoria, irritability and depression, suggest that not only is emotional reactivity increased but also that the capacity to regulate emotional states is impaired in these patients. On a neurobiological level, excessive emotional reactivity and difficulties in regulating emotions in patients with BD has been proposed by some investigators to result from an imbalance between a functionally hyperactive ventral-limbic pathway and a functionally hypoactive cortical-cognitive pathway (Blumberg et al., 2002; Phillips et al., 2003; Phillips et al., 2008). The ventral-limbic pathway involves the orbitofrontal cortex (OFC), the subgenual cingulate cortex (SGC), the amygdala and the hippocampus. By contrast, deficient emotion regulation is thought to be mediated by a network of brain regions including the dorsolateral prefrontal cortex (dlPFC), the dorsal ACC (dACC), the posterior cingulate cortex (PCC) and the precuneus. Consequently prefrontal and cingulate systems may exert weaker than normal inhibitory control of subcortical structures (Ochsner and Gross, 2005; Strakowski et al., 2005) resulting in impaired emotion regulation. As the ventrolateral prefrontal cortex (vlPFC; Brodmann Area (BA) 45/47) plays an important role in the regulation of emotional states (Kalisch, 2009; Kanske et al., 2010) it has been included in the cortical-cognitive rather than the ventral-limbic path in more recent models of BD (Phillips et al., 2008). These neurobiological models of BD overlap with models for major depression (MD) as introduced by Mayberg (1997; 2003). The models differ, however, in the assumption that the suggested neurobiological alterations mediate a general emotional hyperactivity, i.e. to positive and negative stimuli, whereas for MD this is only expected for negative stimuli. Yet, the specificity of neurobiological alterations has still to be investigated and unfortunately most studies did not use or analyze positive and negative stimuli separately.

In line with the above described neurobiological models of BD, greater than normal activation in ventral-limbic brain structures has indeed been demonstrated in symptomatic and remitted patients with BD, particularly in response to emotional stimuli (Strakowski et al., 2005; Wessa and Linke, 2009). There is also empirical evidence of hypoactivation of cortical-cognitive prefrontal and parietal regions in these patients (Wessa and Linke, 2009), although the relevant findings are inconsistent.

Interestingly, structural neural abnormalities corresponding to these observed functional neural alterations have been described. A recent review (Savitz and Drevets, 2009) and meta-analysis (Arnone et al., 2009) suggest that the prefrontal lobe in general and cortical-cognitive network components such as the dlPFC, in particular, are smaller in BD patients. Diverse findings have been reported for ventral-limbic structures with increased amygdala volume, normal size of the hippocampus and smaller than normal gray matter content in the orbitofrontal cortex, the SGC and the rostral ACC (Hajek et al., 2009; Savitz et al., 2009).

Overall, findings from functional and structural neuroimaging studies of BD seem to support the neurobiological model and the pattern of abnormalities described may thus be a core feature, or biomarker, of bipolar disorder. However, this conclusion is weakened by the inconsistency of empirical findings that may be linked to heterogeneity across studies. Furthermore, most neuroimaging studies of BD are underpowered, with a high risk of type II error (Kempton et al., 2008), leading to false negative findings. On the other hand, false positives may occur from studies undertaking too many statistical comparisons. One methodological approach to at least partly overcome these problems is to use meta-analysis, a method searching for communalities across different studies investigating patients with diverse clinical features (e.g., mood state) and using disparate methodologies. For the purpose of neuroimaging studies in BD this means to search for neurobiological abnormalities common to different samples of patients and using different methodologies.

Meta-analytic tools are now available for functional and structural neuroimaging studies (e.g., Anatomical Likelihood Estimation (ALE)) (Turkeltaub et al., 2002; Laird et al., 2005a; Laird et al., 2005b; Eickhoff et al., 2009) and as the meta-analytic approach explores the generalizability of findings (Rosenthal and DiMatteo, 2001), meta-analyses of neuroimaging data now allow the identification of findings common to several MRI studies without subjective bias. Additionally, meta-analytic tools for neuroimaging data make brain localizations in different studies comparable by transforming them into a single common stereotactic space (Talairach) and using a single terminology. In the last few years, several studies have used the ALE approach to identify functional brain networks underlying diverse executive functions (Minzenberg et al., 2009) and diverse emotional tasks (Fusar-Poli et al., 2009) as well as aberrant neural networks in different mental disorders (obsessive compulsive disorder: Rotge et al., 2010; schizophrenia: Li et al., 2009). No meta-analysis of functional alterations associated with emotional processing has been conducted in bipolar disorder, despite abnormal emotional reactivity appearing to be a core feature of the disease.

Most meta-analyses addressing structural changes have focused on particular regions of interest (ROI) (McDonald et al., 2004; Kempton et al., 2008; Arnone et al., 2009), such as the amygdala; the ALE approach has recently been used to analyze whole-brain voxel-wise differences in gray matter volume (voxel-based morphometry (VBM)) in adult and pediatric bipolar disorder (Ellison-Wright and Bullmore, 2010).

We describe here a meta-analytic approach to looking for functional and structural cerebral biomarkers of bipolar disorder by combining results from functional magnetic resonance imaging (fMRI) studies related to emotional processing and whole-brain VBM studies of gray matter. We used the same ALE strategy for two parallel meta-analyses in adult patients with BD, one addressing functional, the other structural gray matter changes in order to ease comparison of results from both meta-analyses. For the same reason, we restricted the structural meta-analysis to the gray matter. We only included studies of adult patients as neurodevelopment during the adolescence influences the neural modifications in bipolar disorder (Blumberg et al., 2004). We hypothesized that activity in ventral-limbic brain regions implicated in increased emotional reactivity would be higher in patients with BD than controls, whereas the activity in the cortical-cognitive network, implicated in the regulation of emotional states, would be lower. We also expected that BD patients would have more than normal gray matter in these limbic-ventral regions (parahippocampal, amygdala, SGC) and less than normal gray matter in the cortical-cognitive network (DLPFC, dACC, PCC, precuneus).

2. Methods and materials

2.1. Study selection

For both meta-analyses we conducted PubMed literature searches of English-language, peer-reviewed studies, published before September 2009 that investigated either the neural correlates of emotional processing by functional magnetic resonance imaging (fMRI) or whole-brain gray matter abnormalities by MRI in adult patients with BD (Type I and II) and matched healthy controls. We also checked reference lists of the studies identified and relevant scholarly reviews.

For both meta-analyses, studies were excluded if (1) study participants were children or adolescents with BD (Chang et al., 2004; Wilke et al., 2004; Dickstein et al., 2005; Farrow et al., 2005; Dickstein et al., 2007; Pavuluri et al., 2007; Pavuluri et al., 2008), (2) insufficient data were reported to extract the number of participants in each group, (3) no between-group comparisons were computed between patients with BD and healthy controls (Malhi et al., 2004a; Malhi et al., 2004b; Kempton et al., 2009; Matsuo et al., 2009; Matsuo et al., 2010; Sarnicola et al., 2009; Walterfang et al., 2009), (4) the data contributed to another publication that was already included in the meta-analysis, (5) results were not reported as 3-dimensional coordinates in standard stereotactic space or (6) if only results from single regions of interests (ROI) were reported, i.e. for both fMRI and VBM meta-analyses only studies conducting whole-brain analyses were included. Table 1 gives an overview of the studies included with details of demographic and clinical characteristics of the respective studies and Table 2 provides information on the experimental and methodological details of the included studies. For studies comparing different patient groups with each other (Lawrence et al., 2004; McIntosh et al., 2004; Chen et al., 2006; Ha et al., 2009), only comparisons between patients with BD and healthy controls were included in the analyses. Contrasts comparing different groups of patients, e.g. manic and depressive bipolar patients, were not included in the analyses. For one VBM study (Ha et al., 2009), two groups of patients with BD (BDI and BDII) were compared to the same control group; only comparison between BD I patients and controls was considered so as not to increase artificially the statistical impact of the healthy controls.

The details of the literature search are described separately below for each meta-analysis.

2.1.1. fMRI meta-analysis

For the PubMed literature search we used a combination of the following keywords “BD”, “patients with BD”, “mania”, “bipolar depression”, “euthymia”, “euthymic”, “fMRI”, “functional magnetic resonance imaging”, “emotion”, “emotional”, “emotional processing”, “affective” and “affect”. We searched for studies that used task paradigms visually presenting emotional stimuli (e.g., emotional words, pictures or faces). Thirteen studies published prior to September 2009 met these criteria and those described above. The paradigms used in the studies included explicit and implicit affect recognition tasks (Lennox et al., 2004; Chen et al., 2006; Malhi et al., 2007b; Hassel et al., 2008; Jogia et al., 2008), emotional go/nogo tasks (Elliott et al., 2004; Wessa et al., 2007), the emotional Stroop task (Malhi et al., 2005; Lagopoulos et al., 2007), an emotional Sternberg memory task (Malhi et al., 2007a) and an emotional face-matching paradigm (Altshuler et al., 2008; Foland et al., 2008).

2.1.2. VBM meta-analysis

The PubMed literature search was performed using “bipolar disorder” and one of the following terms as key words: “MRI”, “VBM”, “Voxel-Based Morphometry” or “Voxel-Based”. We only included studies that conducted whole brain VBM analyses of gray matter (Ashburner and Friston, 2000; Good et al., 2001). Results obtained through small volume corrections were not included. Three studies found no significant group differences but were nevertheless included in the analysis (Bruno et al., 2004; McDonald et al., 2005; Scherk et al., 2008). We conducted meta-analyses independently for increases and decreases in gray matter.

2.2. Data extraction and statistical analysis

The analyses were conducted in the Talairach space, using the activation likelihood estimation technique (ALE) implemented in GingerALE 2.0.4 software (Eickhoff et al., 2009). This technique assesses the voxel-wise correspondence of neuroimaging results between studies. Nine of thirteen studies included in our fMRI meta-analysis were entered into the database by the authors themselves (CD/JF/MW) using Scribe 1.1 (Laird et al., 2005b). The studies by Lagopoulos et al. (2007), Lawrence et al. (2004), Lennox et al. (2004) and Wessa et al. (2007) had already been entered by research assistants from the University of Texas (Health Science Center, San Antonio Research Imaging Center) and the Texas Lutheran University before we started our project. On entry, the spatial normalization template used by each study was noted and automatically converted into the Talairach coordinate system using the Lancaster transformation (icbm2tal) implemented in GingerALE 2.0 (http://brainmap.org/gingerale); this algorithm has been shown to provide a better fit than the mni2tal transformation (Lancaster et al., 2007). Talairach coordinates from studies that used the Brett transform were transformed back into MNI space and then into Talairach by the Lancaster algorithm.

Using GingerALE 2.0.4, ALE values were calculated for each voxel in the brain using the mask provided by the software. This ALE score represents the probability that at least any focus lies within a given voxel (Turkeltaub et al., 2002; Laird et al., 2005a, Eickhoff et al., 2009). It represents the convergence of foci at that position with higher scores indicating higher convergence. A test to determine the null distribution of the ALE statistic was performed at each voxel.

Table 1
Demographic and clinical data of samples included in the studies underlying the meta-analyses.

Nr.	First author (year)	N patients with bipolar disorder (male) [a]	Symptom ratings (HDRS/YMRS)	Mean age	Age of onset/mean illness duration	Current treatment [b]	N healthy controls (male)
fMRI meta-analysis							
1	Malhi et al. (2005)	12 E (0)	4.3 ± 1.1/0.9 ± 0.5	34.9 ± 9.1	NA/11.9 ± 7.1	8 MS, 4 N	12 (0)
2	Lagopoulos et al. (2007)	10 E (0)	4.1 ± 1.6/0.9 ± 0.7	31.3 ± 8.1	NA/10.1 ± 9.1	7 MS, 3 N	10 (0)
3	Wessa et al. (2007)	17 E (10)	1.4 ± 1.4/0.7 ± 2.0	44.9 ± 12.7	22.6 ± 10.5/21.9/12.7	2 N	17 (11)
4	Elliott et al. (2004)	8 M (4)	NA/28.1 (NA)	33.5 ± NA [c]	NA/NA	7 MS, 7 O, 1 N	11 (3)
5	Malhi et al. (2007a)	10 E (0)	4.2 (1.0)/0.9 (0.8)	32.4 ± 10.8	NA/8.8 ± 5.8	7 MS, 3 N	10 (0)
6	Chen et al. (2006)	8 M (5)	0.4 ± 0.5/24.1 ± 8.2	39.0 ± 13.4	NA/NA	8 MS, 2 O	8 (2)
		8 D (8)	18.4 ± 6.4/2.0 ± 3.0	41.9 ± 12.1			
7	Lennox et al. (2004)	10 M (8)	0.0 ± 0.0/27.7 ± 7.9	37.3 ± 12.8	NA/NA	8 L, 7 MS, 7 O	12 (6)
8	Malhi et al. (2007b)	10 E (0)	4.4 ± 1.1/0.9 ± 0.5	33.5 ± 8.7	NA/12.0 ± 7.7	3 L, 4 O, 3 N	10 (0)
9	Jogia et al. (2008)	12 (3)	13.8 ± 2.4/1.0 ± 1.3	42.1 ± 11.8	23.1 ± 5.6/NA	12 MS	12 (3)
10	Hassel et al. (2008)	19 E (10)	1.9 ± 2.6/1.4 ± 2.7	32.5 ± 8.8	22.5 ± 8.0/10.7 ± 6.6	13 MS, 27 O	24 (11)
11	Lawrence et al. (2004)	12 E (8)	BDI: 15.3 ± 9.2	41 ± 11	NA/15.4 ± 13.4	9 MS, 10 O	12 (7)
12	Altshuler et al. (2008)	11 D (5)	20.8 ± 3.3/2.9 ± 1.9	32.0 ± 7.3	NA/NA	8 MS, 5 O, 2 N	17 (9)
13	Foland et al. (2008)	9 M (3)	9.1 ± 5.3/15.1 ± 3.7	34.6 ± 8.0	NA/14.8 ± 5.1	2 L, 6 MS, 2 O, 2 N	9 (3)
VBM meta-anaylsis							
1	Lyoo et al. (2004)	22 D	17.4 ± 6.7/NA	38.3 ± 11.6	18.6 ± 7.0/NA	10 L, 7 MS, 7 O, 15 N	43 (19)
		17 M (16 male for total sample)	NA/14.2 ± 6.7				
2 [d]	Lochhead et al. (2004)	11 (6)	18 ± 40.2/NA	38.2 ± 10.8	24.3 ± 9.2/NA	1MS, 10 N (for 14 days minimum)	31 (16)
3 [d]	Bruno et al. (2004)	39 (13)	NA	38.8 (21–63)	NA/13.2 (1–32)	23 L, 10 MS, 3 N,	35 (10)
4	McIntosh et al. (2004)	19 (7)	NA	39.74 ± 9.2	NA/NA	NA	49 (23)
5	Doris et al. (2004)	11(6)	8.3 ± 3.1/NA	40.5 ± 11.6	24.3 ± 5.1/16.2 ± 11.1	7 MS, 5 O	16 (7)
6 [d]	Adler et al. (2005)	5 M, 2D, 25 E (19 male for total sample)	NA	31.2 ± 9.4	22.5 ± 7.7/8.7 ± 9.2	9 N	27 (12)
7	McDonald et al. (2005)	37 (15)	NA	39.3 ± 14.8	NA/NA	31 MS	52
8	Nugent et al. (2006)	20 D (5)	NA	41 ± 8.3	18 ± 8.8/23 ± 9.0	12 L, 6 MS, 2 O, 0 N	65 (19)
9 [d]	Chen et al. (2007)	24 (6)	NA	38.2 (19–59)	NA/14.2 ± 10.2	12 MS, 12 L, 4 N	25 (7)
10	Yatham et al. (2007)	15 M (6)	NA/27 ± 5.9	36 ± 13	NA/3.9 ± 8.1	NA	15 (6)
11 [d]	Scherk et al. (2008)	35 E (18)	NA/2.54 ± 2.79	43.3 ± 12.5	28.4 ± 8.9/14.4 ± 10.9	12 L, 27 MS, 18 O	32 (12)
12	Haldane et al. (2008)	44 (20)	5 ± −13/1.2	42.7 ± 11	25.6 ± 9.1	31 MS, 22 O	44 (20)
13	Almeida et al. (2009)	10 D, 17 E (10 male total)	NA	31.9 ± 7.3	20.3 ± 6.1/11.1 ± 7.0	12 L, 2 MS, 26 O, 3 N	28 (13)
14	Stanfield et al. (2009)	66 (30)	1 ± 1.44/3 ± 7.4	36.4 ± 11.1	NA/15.4 ± 10.0	28 MS	66 (31)
15	Ha et al. (2009)	23 (8)	8.8 ± 6.81/NA	35.6 ± 11.1	25.2 ± 10.2/10.4 ± 8.8	8 L, 7 MS, 10 O, 6 N	23 (8)

[a] E = euthymic, M = manic/hypomanic/mixed, D = depressed.
[b] L = Lithium, MS = Other Mood Stabilizers (Anticonvulsivants), O = Other, N = None.
[c] No variability index (standard deviation, variance) available; NA = Information Not Available.
[d] Included in both decreased and increased gray matter meta analysis.

By contrast to previous GingerALE versions, the version used determined full-width at half maximum (FWHM) smoothing values from the number of subjects included in each study (see Eickhoff et al. for details (Eickhoff et al., 2009)). The resulting *P* values were used for the calculation of the final ALE maps. GingerALE 2.0.4 now uses a random-effects model, and not a fixed-effects model, to test for statistical significance and thus allows a between study correspondence. Final ALE maps for our meta-analyses were thresholded at $P<0.05$ (FDR corrected) with an extent threshold as recommended by GingerALE 2.0. Following a recommendation by the software's authors, we excluded clusters resulting from a single study. The resulting map was overlaid onto a template in Talairach space and anatomical labels of the significant clusters were determined by the Talairach Daemon (http://ric.uthscsa.edu/TDInfo).

For *fMRI* studies, separate ALE maps were computed for the following six statistical comparisons: (1a) greater neural activation in all patients with BD (manic, depressive, euthymic) than in healthy individuals, (1b) greater neural activation in euthymic patients with BD than in healthy individuals, (1c) greater neural activation in manic patients with BD than in healthy individuals, (2a) greater neural activation in healthy individuals than in all patients with BD (manic, depressive, euthymic), (2b) greater neural activation in healthy individuals than in euthymic patients with BD and (2c) greater neural activation in healthy individuals than in manic patients with BD. We did not perform meta-analyses on studies investigating depressive bipolar patients, as for this type of analyses not enough studies ($N=2$) and not enough foci were available ($N<20$).

For the calculation of ALE maps we included all within-group contrasts (called “experiment” in BrainMap terminology) of one study unless redundant information (e.g., the stimuli) was used. With respect to between-group contrasts, we did not include contrasts that compared different patient groups (e.g., manic and depressed patients) but only those contrasts, comparing one or all BD groups to healthy controls. Table 2 provides information about the included within- and between-group contrasts.

Table 2
Details on acquisition of data, experimental designs and statistical contrasts included in the fMRI meta-analyses.

Nr.	First author (year)	FS	FWHM	Experimental task	Types of stimuli	Emotional quality of stimuli	Statistical comparison included in the meta-analyses	
							Within-group	Between-group
1	Malhi et al. (2005)	3.0	4×4×5	Emotional Stroop task	Words			
2	Lagopoulos et al. (2007)	3.0	4×4×8	Emotional Stroop task	Words	Negative	Negative words (implicit BL)	BD>HC BD<HC
3	Wessa et al. (2007)	1.5	8×8×8	Emotional go/nogo task	Faces	Negative, positive	(1) Emotional targets vs. control targets	
							(2) Emotional vs. neutral Distractors	BD>HC
4	Elliott et al. (2004)	2.0	10×10×10	Emotional go/nogo task	Words	Negative, positive	(1) Semantic vs. orthographic targets	BD (manic)>HC
							(2) Emotional vs. neutral targets	
							(3) Happy vs. neutral distractors	
							(4) Sad vs. neutral distractors	
5	Malhi et al. (2007a)	1.5	12×12×12	Emotional sternberg task	Words	Negative, positive	(1) Negative words (implicit BL)	BD<HC
							(2) Positive words (implicit BL)	
6	Chen et al. (2006)	3.0	12×12×12	Explicit and Implicit Facial recognition task	Faces	Negative	Fearful faces (implicit BL)	BD-M + BD-D>HC
7	Lennox et al. (2004)	3.0	12×12×12	Explicit facial Recognition task	Faces	Negative, positive	Sad vs. neutral faces	BD>HC BD<HC
8	Malhi et al. (2007b)	3.0	4×4×5	Explicit facial recognition task	Faces	Negative	Disgust faces (implicit BL)	BD>HC
							Fearful faces (implicit BL)	BD<HC
9	Jogia et al. (2008)	1.5	8×8×8	Explicit recognition task	Faces	Negative	Sad vs. neutral faces	BD (BL)>HC BD (BL)<HC
10	Hassel et al. (2008)	3.0	6×6×6	Implicit facial recognition task	Faces	Negative, positive	(1) Happy faces (implicit BL)	BD>HC
							(2) Fearful faces (implicit BL)	BD<HC
11	Lawrence et al. (2004)	1.5	7.2×7.2×7.2	Implicit facial recognition task	Faces	Negative, positive	(1) 50% fear vs. neutral	BD>HC
							(2) 100% fear vs. neutral	BD<HC
							(3) 50% happy vs. neutral	
							(4) 100% happy vs. neutral	
							(5) 50% sad vs. neutral	
							(6) 100% sad vs. neutral	
12	Altshuler et al. (2008)	3.0	6×6×6	Face matching paradigm	Faces	Negative	Match faces vs. match forms	BD>HC BD<HC
13	Foland et al. (2008)	3.0	6×6×6	Face matching paradigm	Faces	Negative	(1) Emotion vs. shape Perception	BD>HC BD<HC
							(2) Emotion vs. shape Labeling	

Abbreviations: BD = Patients with Bipolar Disorder; HC = Healthy Controls; BD-M = manic patients with bipolar disorder; BD-D = depressed patients with bipolar disorder; BL = Baseline; FS = Field Strength; FWHM = Full-Width at Half Maximum.

For *VBM* studies, separate ALE maps were computed for those identifying increases and decreases in gray matter.

3. Results

3.1. fMRI meta-analysis

3.1.1. Studies included

A total of 13 studies identified by the literature search were judged to be eligible for inclusion according to the criteria outlined above. ALE maps for greater activation in patients with bipolar disorder as compared to healthy comparison subjects were calculated from (1) 130 patients and 141 healthy controls and 75 foci for the comparison between all patients and healthy controls, (2) 68 patients and 73 controls and 40 foci for the comparison between euthymic patients with BD and healthy controls and (3) 35 patients and 40 controls and 21 foci for manic patients with BD and healthy controls.

For the reverse comparisons (increase in controls relative to patients) ALE maps were calculated from (1) 139 patients and 142 healthy controls and 155 foci for the comparison with all patients with BD, (2) 63 euthymic patients and 68 healthy controls and 87 foci for the comparison with euthymic patients with BD and (3) 27 manic patients and 32 healthy controls and 22 foci for the comparison with manic patients with BD.

The respective ALE maps for increased and decreased activation (BD>HC and HC>BD, respectively) do not have the same database, i.e. number of patients, number of controls and number of foci as some studies found only increased or only decreased activation in patients with BD.

3.1.2. All patients with BD > healthy comparison subjects

The ALE map for the areas more activated in all patients (euthymic, manic, and depressive) than in controls revealed significant clusters in left-sided subcortical structures (see Fig. 1 and Table 2 for details on localization, size and statistical indices for significant clusters): the parahippocampal gyrus extending to the amygdala, the caudate nucleus and the

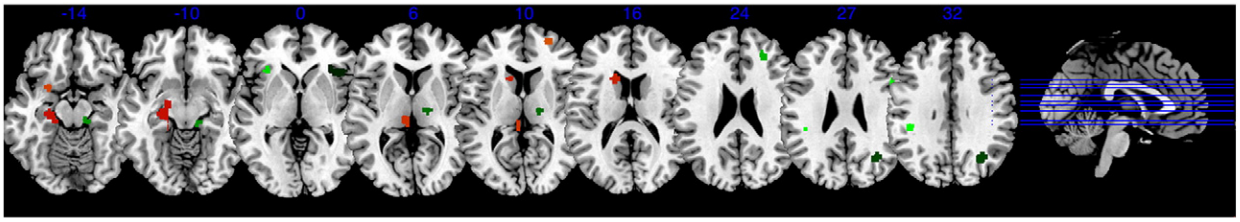

Fig. 1. Increased (red/orange) and decreased (green) brain activation in patients with bipolar disorder relative to controls. Legend: Transverse sections at Talairach space level z = -14, -10, 0, 6, 10, 16, 24, 27, 32. Right: corresponding slices on parasagittal view.

thalamus. A cluster of increased activation was also observed in the right middle frontal gyrus (BA 10).

3.1.3. Euthymic patients with BD > healthy comparison subjects

Calculating an ALE map for studies only investigating euthymic patients with BD, one significant cluster signifying increased activation in patients as compared to healthy controls was found comprising the left parahippocampal gyrus and amygdala (peak voxel: x = −24, y = 20, z = −8; cluster size: 1072).

3.1.4. Manic patients with BD > healthy comparison subjects

The ALE map calculated from studies investigation only manic patients with BD revealed clusters of increased activation in patients as compared to controls in the amygdala and parahippocampal gyrus (peak voxel: x = −18, y = −8, z = −8; cluster size: 640), the left thalamus (peak voxel: x = −4, y = −34, z = 10; cluster size: 344) and the right middle frontal gyrus (BA 9/10; peak voxel: x = 28, y = 32, z = 38; cluster size: 224).

3.1.5. Healthy comparison subjects > all patients with BD

The reverse ALE map (activation higher in controls than all patients with BD) revealed five significant clusters, all in the right hemisphere of the brain: the right inferior frontal gyrus (BA 47), the right precuneus (BA 7/39), the right middle frontal gyrus (BA 9), the right thalamus and the right cerebellum (see Fig. 1 and Table 3 for details on localization, size and statistical indices for significant clusters).

3.1.6. Healthy comparison subjects > euthymic patients with BD

Comparing healthy comparison subjects to euthymic patients with BD revealed significant clusters in the right precuneus (BA 39; peak voxel: x = 32, y = −64, z = 32; cluster size: 968), the right thalamus (peak voxel: x = 16, y = −16, z = 8; cluster size: 528) and the right cerebellum (peak voxel: x = 14, y = −28, z = −12; cluster size: 352).

3.1.7. Healthy comparison subjects > manic patients with BD

Calculating the ALE map for increased activation in healthy comparison subjects as compared to manic patients with BD revealed one significant cluster in the right inferior frontal gyrus (BA 47; x = 32, y = 26, z = 0).

3.2. VBM meta-analysis

3.2.1. Studies included

Fifteen studies identified by the literature search were judged to fulfill the inclusion criteria. All the studies were included in the analysis of gray matter decreases in patients with BD, and consequently, 442 patients and 551 healthy controls and 57 foci were analyzed. For the reverse analysis (less gray matter in controls than patients), a total of 222 patients and 246 healthy controls, and 11 foci were included in the meta-analysis.

3.2.2. Patients with BD > healthy comparison subjects

We identified no significant cluster of sites with more gray matter in patients with BD than in healthy controls.

3.2.3. Healthy comparison subjects > patients with BD

Meta-analysis identified three significant clusters of gray matter reduction in patients with BD relative to controls: right precentral gyrus (BA 44), right anterior cingulate (BA 32), left inferior frontal gyrus (BA 47) (see Fig. 2). Their exact localization and size as well as studies contributing to these clusters are summarized in Table 3.

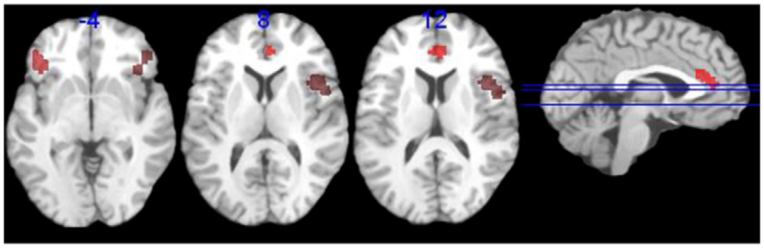

Fig. 2. Gray matter decreases in bipolar disorder. Legend: Transverse sections at Talairach space level z = −4, 8 and 12. Red represents areas of gray matter decreases in patients with bipolar disorder. Right: corresponding slices on a parasagittal view.

Table 3
Significant clusters revealed by the fMRI and VBM meta-analyses.

Brain region	Volume, mm^3	ALE value	Brodmann area	Talairach coordinates, x, y, z	Studies contributing to the cluster
fMRI meta-analysis					
Patients with bipolar disorder > Healthy controls					
Left parahippocampal gyrus (extending to amygdala)	2264	0.0020	28/35	−24, −20, −10	2, 8 (2 foci), 9, 11, 13 (4 foci)
Left caudate nucleus (body)	736	0.0021	–	−16, 16, 16	6, 10, 7
Left thalamus (pulvinar)	512	0.0016	–	−6, −26, 6	6, 13, 7
Right middle frontal gyrus (anterior PFC)	264	0.0014	10	28, 54, 10	3, 4
Healthy controls > patients with bipolar disorder					
Right superior frontal gyrus (dlPFC)	328	0.0016	9	26, 38, 24	4, 5
Right inferior frontal gyrus (dlPFC)	264	0.0018	9	48, 12, 28	11, 12
Right inferior frontal gyrus (vlPFC)	1136	0.0021	47	42, 22, 0	4, 12, 13 (4 foci)
Right precuneus	960	0.0029	7/39	32, −64, 32	8 (3 foci), 10
Right thalamus (ventral posterior lateral nucleus)	512	0.0019	–	16, −16, 8	1, 5 (2 foci)
Right cerebellum (culmen)	328	0.0016	–	14, −28, −12	5 (2 foci), 11
VBM meta-analysis					
Healthy controls > patients with bipolar disorder					
Right precentral gyrus/inferior frontal gyrus (dlPFC + vlPFC)	3672	0.0151	44/47	42, 12, 8	1 (2 foci), 4 , 12, 14, 15
Left inferior frontal gyrus (vlPFC)	1864	0.0155	47	−40, 26, −4	8, 14, 15
Right anterior cingulate (dACC)	1608	0.008	32	4, 36, 12	2, 10, 15
Patients with bipolar disorder > healthy controls					
No significant clusters found					

4. Discussion

We report the first systematic meta-analyses of functional neuroimaging studies related to emotional processing and of structural voxel-based MRI studies in adult BD. Our aim was to contribute to the identification of potential biomarkers of the disorder for diagnosis and to guide future research.

The strength of meta-analysis of neuroimaging data lies in the objectivity and clarity of its results, based both on a standardized procedure without subjective bias and on a single terminology. One strong point of our analyses is that only whole-brain studies were included. This results in conservative testing of neurobiological models of BD and allows the models to be refined. Interestingly, the two meta-analyses gave convergent results, identifying brain regions mostly of the cortical-cognitive pathway (vlPFC, dlPFC, ACC, precuneus), showing either lower neural activation or less than normal gray matter or both in BD patients. The fMRI meta-analysis further indicated that patients with BD showed increased activation in ventral-limbic brain structures (parahippocampal gyrus and amygdala). One region of the fMRI meta-analysis overlap with the structural meta-analysis: the cluster found in the right vlPFC in the fMRI meta-analysis (decreased activation) overlaps with the cluster identified in the right dlPFC + vlPFC in the VBM meta-analysis (decreased gray matter). It is notable that these converging results that were consistent with what has been expected, emerged despite the heterogeneity of both the samples investigated in the studies (e.g., with respect to mood states) and the methods used (e.g., different experimental tasks). The ventral-limbic overactivation was even found in two separate meta-analyses performed on a sample of euthymic and manic patients with BD, respectively.

We found that diminished activation and gray matter decreases in adult patients with BD were predominantly located in the cortical-cognitive network described in neurobiological models of BD (Blumberg et al., 2002; Phillips et al., 2003; Phillips et al., 2008) and affective disorders in general (Mayberg, 1997; Mayberg, 2003). Functional and structural deficits were found in the vlPFC (inferior frontal gyrus; BA 47) and dlPFC (superior/middle frontal gyrus; BA 9; precentral gyrus, BA 44). In addition, activation was weaker in the precuneus and gray matter in the dorsal ACC (BA 32) was less abundant in BD patients than healthy controls. This cognitive-cortical neural network has been associated with the voluntary (Phillips et al., 2008; Kalisch, 2009) and cognitive top-down regulation of emotions (Ochsner and Gross, 2005). The involvement of the vlPFC (BA 47) in neurobiological models of BD is a subject of debate, some authors including it in the cortical-cognitive pathway (Phillips et al., 2008) while earlier findings placed it in the ventral pathway (Phillips et al., 2003). Our findings are in favor of it being part of the cortical-cognitive pathway, and this view is strengthened by a recent meta-analysis (Kalisch, 2009) highlighting the role of the vlPFC in the regulation of emotion, a process believed to be impaired in patients with BD.

In addition to the finding of hypoactivation and gray matter reductions in cortical-cognitive brain structures in patients with BD, the fMRI meta-analysis revealed increased brain activity predominantly in left ventral-limbic brain structures, namely the parahippocampal gyrus extending to the amygdala, the thalamus and the caudate nucleus. Again, this is consistent with the neurobiological models of BD and with results of studies reporting increased amygdala activity in patients with BD (Altshuler et al., 2005; Bermpohl et al., 2009).

The strength and significance of the parahippocampal hyperactivation is further supported by the fact that the five studies contributing to the corresponding cluster identified by the fMRI meta-analysis comprised euthymic, manic and depressed patients with BD, and used different experimental tasks. This strongly suggests that this limbic hyperactivation is a valid neurobiological marker of BD. Indeed, all clusters identified by our fMRI meta-analysis point to a hyperactive subcortical network and a hypoactive cortical-cognitive network, thus supporting the neurobiological models of BD and suggesting that an imbalance between ventral-limbic and cortical-cognitive brain regions is a major marker of the disorder.

Conflicting with our expectations, we did not detect either increased activation or structural abnormalities in the subgenual cingulate cortex. This finding is in contrast to a very recent meta-analysis of VBM studies in BD that was published during the preparation of this manuscript (Ellison-Wright and Bullmore, 2010) and that reported less gray matter in right insula, close to our precentral/inferior frontal cluster, as well as in perigenual anterior cingulate, not far from our right anterior cingulate. This study also found deficits in subgenual anterior cingulate (BA 25) that we did not identified. There are several possible explanations for this discrepancy. Ellison-Wright included pediatric and adult patients with BD, whereas we included only adult patients because functional and particularly structural modifications might be substantially influenced by developmental processes. Therefore results from both pediatric/adolescent and adult patient samples can be very heterogeneous. For example, a recent meta-analysis has shown that amygdala volume is positively correlated with age in BD patients suggesting that it is reduced at illness onset (often in youth) and increases with age (Usher et al., 2010). In addition, methodological differences might explain discrepancies between our results and those of Ellison-Wright and Bullmore (2010), who used a rank-based modification of ALE. Another very-recent meta-analysis of structural studies (Bora et al., 2010), including adult and children patients with another technique (signed differential mapping) did not find any difference in BA25. This study identified similar clusters of gray matter deficits to ours in right and left inferior frontal gyri. They also found decreased gray matter in left anterior cingulate/medial frontal cortex that we did not identified in our study. We additionally identified gray matter deficits in the right dorsal anterior cingulate that they have not found.

In contrast to our hypotheses, the present fMRI meta-analysis revealed hyperactivation in the anterior prefrontal cortex (aPFC; BA 10) in patients with BD relative to controls. This region has been associated with executive functioning (Koechlin et al., 2003) and the maintenance of attention and response consistency (Burgess et al., 2007). Interestingly, both studies contributing to this cluster used an emotional go/nogo task and did not reveal any behavioural task deficits in patients with BD. Thus, the hyperactivation of the aPFC observed in these studies might relate to greater attentional effort by patients than controls. However, due to the small number of contributing studies, this hyperactivation should not be considered to be a valid neurobiological marker of BD until these findings are replicated in studies using other experimental tasks.

The current fMRI meta-analysis revealed clear lateralization of functional brain abnormalities in patients with BD, with increased ventral-limbic activation in the left hemisphere and decreased cortical-cognitive brain activation in the right hemisphere. Such lateralization effects were not found by the VBM meta-analysis. Previous studies have reported brain abnormalities in patients with BD that were restricted to the left hemisphere (Fountoulakis et al., 2008). However, the pathophysiological mechanisms and the functional relevance of this lateralization effect are unclear and should be investigated further.

Whereas this is the first report of a meta-analysis of functional neuroimaging studies in patients with BD, our structural analyses should be viewed in light of recent meta-analyses on structural neuroimaging studies in BD. These analyses include studies involving volumetric measurements of specific ROIs, the ventricles and white matter hyperintensities. Their most consistent finding is lateral ventricle enlargement (McDonald et al., 2004; Arnone et al., 2009; Kempton et al., 2009). In addition, BD has been associated with a decreased area of the corpus callosum, increased rates of deep white matter hyperintensities (Kempton et al., 2008) and significant whole brain and prefrontal lobe volume reductions and increased globus pallidus volume (Arnone et al., 2009). Another recent meta-analysis (Vita et al., 2009) reports reductions for white matter and total intracranial volumes, but not for gray matter and whole brain volumes in patients with first-episode BD. Finally, Hajek (Hajek et al., 2009) and colleagues focused on amygdala volume and did not find significant differences between patients with BD and healthy controls, whereas Usher found age-specific changes in amygdala volume (Usher et al., 2010). In summary, these previous meta-analyses found generally non-specific differences between patients with BD and controls which may be attributed to methodological issues as the ROIs assessed in these studies were usually large or restricted to easily delineable, mostly subcortical areas. Nevertheless, neurobiological models of BD implicate gray matter regions that are not easy to delineate, including the OFC and dlPFC. Our approach, using only studies with whole-brain analyses avoided this problematic issue and, as a result, this allowed us to identify cortical and subcortical abnormalities associated with BD.

To be a useful additional diagnostic marker, any biomarker of mental disorder has to be specific. A comparison of the present findings in bipolar disorder with results from meta-analyses in related diseases, such as unipolar depression and schizophrenia, is therefore indispensable. Various meta-analyses of structural abnormalities in schizophrenic patients point to a more widespread reduction in gray matter in frontal, temporal, thalamic, striatal, insular and cingulate regions (Glahn et al., 2008; Fornito et al., 2009; Ellison-Wright and Bullmore, 2010). All these studies found a cluster of reduced gray matter in the right insula, next to, but a little below, our larger cluster of gray matter decrease in BD (in the right inferior frontal gyrus). Meta-analyses of gray matter decreases in unipolar depression identified a widespread reduction in gray matter in frontal regions, including the right anterior cingulate as in our study (Koolschijn et al., 2009). Nevertheless, recent reviews of structural studies in depression have associated this reduction in frontal gray matter with orbitofrontal cortex and subgenual prefrontal cortex gray matter decrease (Lorenzetti et al., 2009). In patients with schizophrenia, increased gray matter in striatal regions has been reported and linked to use of antipsychotics (Ellison-Wright et al., 2008; Glahn et al., 2008; Ellison-Wright and Bullmore, 2010); no increases in gray matter volumes were identified in our meta-analysis.

Finally, with respect to functional cerebral markers of BD, the subcortical hyperactivation we report in patients with BD appears to be specific for mood disorders, as a recent meta-analysis (Li et al., 2009) of neural correlates of emotion processing in schizophrenia yielded an opposite finding, i.e. reduced subcortical activation in patients with schizophrenia. In unipolar depression, an overactivation of limbic brain structures, such as the amygdala and subgenual cingulate cortex, has – equally to bipolar disorder – been proposed as central pathophysiological mechanism of the disorder (Ressler and Mayberg, 2007). Indeed, increased activation of the amygdala/hippocampus and thalamus during rest has been observed in a meta-analysis. In addition, increased activity of the subgenual cingulate to positive and increased amygdala activity to negative stimuli was present in patients with unipolar depression as compared to healthy controls (Fitzgerald et al., 2008). In line with these results, a more recent, not yet published meta-analysis including a larger database observed increased amygdala activation to negative but not to positive stimuli in patients with unipolar depression as compared to healthy controls (Carsten Diener, personal communication). It has therefore been suggested that the patterns of increased subcortical limbic activity to positive emotional stimuli may distinguish BD from major depressive disorder (Pan et al., 2009). Unfortunately, in the present study, we are not able to perform separate meta-analyses for positive and negative emotional stimuli, as for these sub-analyses not enough studies ($N=3$) and thus foci were available ($N<20$) and results yielded from meta-analyses with less than 3 studies or less than 20 foci are not supposed to be reliable and valid. Many studies either investigated negative stimuli only or collapsed the results of positive and negative emotional stimuli (e.g. Elliott et al., 2004; Wessa et al., 2007). Concomitant to the limbic hyperactivation, lower activation of the previously described cortical-cognitive pathway has been proposed to underlie cognitive deficits and impairments in emotion regulation in bipolar disorder but also in unipolar depression. Our results suggest deactivation of ventrolateral prefrontal areas in bipolar disorder, whereas in the already mentioned meta-analysis in patients with unipolar depression this region appeared to be hyperactivated to positive and negative stimuli in patients relative to controls (Fitzgerald et al., 2008). Similarly, in line with the proposed models of bipolar disorder, bipolar patients showed deactivations of the parietal cortex whereas in patients with unipolar depression increased activation of these brain regions was observed (Fitzgerald et al., 2008). Although this comparison partly suggests that our findings are specific to bipolar disorder, it has to be interpreted with caution, because some of the patients included in our meta-analysis also suffer from (bipolar) depression. We therefore realized a sub-analysis of the fMRI studies including only euthymic patients: in line with the complete sample of bipolar patients, we could observe increased activation in the left parahippocampal gyrus/amygdala in euthymic (and also manic) patients as compared to controls. A separate meta-analysis in depressive samples only was not possible due to an insufficient database (2 studies; $N<20$ foci).

Some limitations of the here presented meta-analyses hamper interpretation of the results. First, the version of the ALE algorithm implemented in GingerALE 2.0.4 with respect to image smoothing was designed for functional neuroimaging studies (Eickhoff et al., 2009) and is not necessarily appropriate for structural meta-analysis. Nevertheless, ALE-based meta-analyses have been successfully conducted with structural VBM data (Ellison-Wright et al., 2008; Rotge et al., 2010) and the GingerALE manual explicitly proposes the possibility of using this algorithm for pooling anatomical data, e.g. from VBM or diffusion tensor imaging studies. The current version of the algorithm has the advantage of introducing a FWHM smoothing kernel that depends on the number of subjects in the study. This FWHM is calculated from an estimation of between-subject and between-template variance for fMRI studies only. Nevertheless, the range of FWHM values is only from 8.4 mm (for a study including an infinite number of subjects) to 11.36 mm (for a study including five subjects). All the FWHM of the voxel-based structural studies included here were between 4 and 12 mm, so a significant bias associated with the evaluation of FWHM can be excluded.

Second, the studies included differed with respect to a number of clinical variables (e.g., mood state, BD I and II, age of illness onset, illness duration, history of substance abuse, axis I comorbidity and medication), methodological parameters (e.g., field strength of the scanner, voxel size, smoothing kernel and software) and experimental tasks (for fMRI studies). Although this may be viewed as limitation, we believe that the heterogeneity of studies with respect to these variables also represents a strength as it allows the identification of neural networks underlying emotional processing associated with bipolar disorder across patients with different clinical expressions and across different experimental tasks. Unfortunately, due to the relatively small number of studies available we were not able to calculate separate meta-analyses for all mood-states of patients of type of emotional stimuli although this would have been important to answer questions of mood state dependency and diagnostic specificity of results. Whereas enough foci were available to perform analyses on euthymic and manic patients only, this was not the case for depressive patients with BD. Furthermore only few studies investigating both positive and negative stimuli and analyzing them separately were available. In addition, the ALE technique as such did not allow us to calculate heterogeneity biases (for example with respect to mood states), as is usual in meta-analyses (Hajek et al., 2008; Hajek et al., 2009) and we could not perform meta-regression type analysis, e.g. for lithium effect. However, the ALE technique has previously allowed the successful investigation of common networks involved in various emotional (Fusar-Poli et al., 2009) or executive tasks (Minzenberg et al., 2009).

Third, the fMRI and VBM meta-analyses only yielded partly similar results. The relationship between functional and structural gray matter abnormalities has not been fully determined. Decreased cerebral blood flow in one region was reported to be accompanied by a gray matter decrease in the same region in mood disorders (Drevets et al., 1997). However, this clear connection has not been found consistently and functional abnormalities may also be observed without any associated macroscopic modifications (Hajek et al., 2008). We found some regions (vlPFC, dlPFC) to be both under activated and volumetrically diminished, whereas other brain regions were either functionally or structurally altered, but not both. Most remarkably, the VBM meta-analysis identified no gray matter changes in subcortical regions in patients with BD despite marked hyperactivation.

5. Conclusion

In conclusion, our meta-analyses of structural and functional neuroimaging studies in BD identified decreased activation and gray matter content in cortical-cognitive brain networks implicated in both voluntary regulation and cognitive control of emotion. Further, marked hyperactivity of subcortical, limbic brain regions, responsible for automatic emotion processing, was observed. These results support and refine previously proposed neurobiological models of the disorder and suggest that an imbalance between cortical-cognitive and limbic brain networks may serve as a neurobiological marker of BD. The significance of the potential biomarkers identified by the present meta-analyses and their specificity particularly relative to unipolar depression as well as their predictive value for the diagnosis of BD need to be evaluated and confirmed by further studies.

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Conflict of interest

None.

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