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Common and distinct neural correlates of emotional processing in Bipolar Disorder and Major Depressive Disorder: A voxel-based meta-analysis of functional magnetic resonance imaging studies

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Abstract

Neuroimaging studies have consistently shown functional brain abnormalities in patients with Bipolar Disorder (BD) and Major Depressive Disorder (MDD). However, the extent to which these two disorders are associated with similar or distinct neural changes remains unclear. We conducted a systematic review of functional magnetic resonance imaging studies comparing BD and MDD patients to healthy participants using facial affect processing paradigms. Relevant spatial coordinates from twenty original studies were subjected to quantitative Activation Likelihood Estimation meta-analyses based on 168 BD and 189 MDD patients and 344 healthy

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controls. We identified common and distinct patterns of neural engagement for BD and MDD within the facial affect processing network. Both disorders were associated with increased engagement of limbic regions. Diagnosis-specific differences were observed in cortical, thalamic and striatal regions. Decreased ventrolateral prefrontal cortical engagement was associated with BD while relative hypoactivation of the sensorimotor cortices was seen in MDD. Increased responsiveness in the thalamus and basal ganglia were associated with BD. These findings were modulated by stimulus valence. These data suggest that whereas limbic overactivation is reported consistently in patients with mood disorders, future research should consider the relevance of a wider network of regions in formulating conceptual models of BD and MDD.

1. Introduction

Bipolar Disorder (BD) and Major Depressive Disorder (MDD) are amongst the leading causes of disability worldwide (Murray and Lopez, 1997). Although syndromal mania is unique to BD, both disorders present with recurrent depressive episodes as well as similar subsyndromal affective symptoms (Judd et al., 2002, 2003; Angst et al., 2010). Evidence from genetic studies also suggests both distinct and common contributions to their aetiology (McGuffin et al., 2003).

Current neurobiological models propose that mood disorders arise from disruption in prefrontal, limbic and subcortical regions (particularly the amygdala/hippocampus, and striatum) that support the adaptive regulation of affect (Savitz and Drevets, 2009). Within this general framework, much research effort in neuroimaging is directed towards identifying overlapping and diagnosis-specific brain abnormalities for BD and MDD. Several reviews and meta-analysis have attempted to summarise and synthesise the available evidence (Savitz and Drevets, 2009; Konarski et al., 2008). In the most recent quantitative meta-analysis (Kempton et al., 2011), we showed that volume reductions in the basal ganglia and hippocampus appear specific to MDD patients and differentiated MDD from BD. We now focus on the neural correlates of emotional processing in BD and MDD, which may relate more directly to the core abnormalities underpinning mood disorders. Our understanding of the neural circuitry involved in emotional processing in healthy individuals is mostly based on studies using facial affect as a probe (Phan et al., 2002; Murphy et al., 2003; Fusar-Poli et al., 2009; Vytal and Hamann, 2010). Facial affect processing is mediated by a distributed neural network that encompasses visual, limbic, and prefrontal regions (Phan et al., 2002; Murphy et al., 2003; Fusar-Poli et al., 2009; Vytal and Hamann, 2010). This network shows significant overlap with that implicated in mood disorders (Savitz and Drevets, 2009). We used Activation Likelihood Estimation (ALE) (Turkeltaub et al., 2002; Laird et al., 2005; Eickhoff et al., 2009), a quantitative meta-analytic approach which allows integration of neuroimaging results across studies, to investigate the neural correlates of facial affect processing in BD and MDD.

The main goals are threefold. First, to consolidate neuroimaging findings associated with emotional processing in patients with BD or MDD and to examine whether meta-analytic synthesis of this empirical evidence aligns with current theoretical models of mood disorders (Cerullo et al., 2009; Savitz and Drevets, 2009). Second, to determine whether stimulus valence modulates disease-related activity within the face processing network based on findings that neural activity and connectivity may differ between BD and MDD in response to positive and negative stimuli (Almeida et al., 2009; Almeida et al., 2010). Third, to identify common and distinct brain functional changes in BD and MDD.

2. Method

2.1. Data sources and inclusion criteria

Studies investigating facial affect processing in either BD or MDD patients were identified through a comprehensive MEDLINE, EMBASE and PsycINFO search of the English-language literature covering publications between January 2000 and December 2010. The search keywords were "mania", "depression", "bipolar disorder", "major depressive disorder" and "facial affect", "emotional processing", "fMRI" and their combinations as well as terms specifying individual facial affect (fear, happiness, sadness, anger and disgust). Additional articles were identified through the reference lists of these papers.

Studies were included if they (a) reported comparisons between patients with BD or MDD with healthy controls (b) employed functional magnetic resonance imaging (fMRI) (c) assessed brain activation by using human facial identities (d) used image subtraction methodology to identify foci of task-related neural changes contrasting an active (emotional faces) and control (neutral faces or shapes) condition, and (e) reported their results in standard stereotactic coordinates (either Talairach or Montreal Neurological Institute [MNI] space).

We excluded studies that (a) used facial affect stimuli to investigate processes not directly involved in emotional processing (e.g. memory, attention), (b) involved non-facial identities such as emotional pictures, (c) grouped together stimuli displaying positive and negative facial affect, and (d) used the same patient sample. The threshold of statistical inference varied but we accepted the results reported as significant based on the criteria of the primary studies.

2.2. Quantitative meta-analytical voxel-based procedure

We investigated facial affect processing in BD and MDD by focusing on the contrast between facial affect and control conditions using Activation Likelihood Estimation (ALE) implemented in GingerALE 2.0.4 (http://brainmap.org/Ale). This ALE version uses a random effect model and weighting for sample size of the original studies (Eickhoff et al., 2009). Coordinates of the foci of activation reported in the primary literature were transformed into Talairach space using the Lancaster transform (icbm2tal tool) in GingerALE. For each study, peaks were modelled as the centre of a 3D Gaussian distribution and a modelled activation (MA) map was then

Table 1 Studies included in the meta-analyses (alphabetical order).

Study	Participants (Male/female)	Age Mean, years (standard deviation)	Design	Contrast used in meta-analysis
Almeida et al. (2010)	BD (remitted) 15 (5/10) BD (depressed) 15 (1/14) 15 MDD (2/13) 15 HC (3/12)	BD (remitted): 33.2 (7.8) BD (depressed): 36.5 (11.8) MDD: 32.7 (9.8) HC: 32.6 (8)	Explicit facial affect labelling Event related	Sad>neutral
Altshuler et al. (2008)	11 BD(5/6) 17 HC (9/8)	BD: 32 (7.3) HC: 29.5 (6.6)	Explicit facial affect matching Block	Fear and angry> shapes
Blumberg et al. (2005)	17 BD (10/7) 17HC (7/10)	BD: 40 (12.3) HC: 33.2 (10.8)	Implicit facial affect processing Block	Happy>fixation cross
Chen et al. (2006)	8 BD (depressed) (5/3) 8 BD (manic) (8/0) 8 HC (2/6)	BD (depressed): 41.8 (12) BD (manic): 39 (13.4) HC: 38.7 (12.5)	Explicit and implicit facial affect recognition Event related	Fear>neutral (explicit) Happy>neutral (explicit)
Foland et al. (2008)	9 BD (3/6) 9 HC (3/6)	BD: 34.6 (8.0) HC: 30.4 (7.6)	Explicit facial affect matching Block	Fear and anger> shapes
Fu et al. (2007)[1]	19 MDD (6/13) 19 HC (8/11)	MDD:43.2 HC:42.8	Implicit Facial Affect Processing Event-Related	Happy>fixation
Gotlib et al. (2005)	18 MDD (5/13) 18 HC (5/13)	MDD: 35.2 HC:30.8	Implicit facial affect processing Block	Happy>neutral Sad>neutral
Hassel et al. (2008)	19 BD (10/9) 24 HC (11/13)	BD: 32.47 HC: 27.78	Implicit facial affect processing Event-related	Happy>neutral
Jogia et al. (2008)[1]	12 BD (5/7) 12 HC (5/7)	BD: 42.1 (11.8) HC: 41.8 (10.9)	Explicit facial affect recognition Event-related	Sad>neutral
Killgore et al.(2008)	14 BD (11/3) 13 HC (12/1)	BD: 28.1 (11.2) HC: 25.5 (4.7)	Implicit facial affect processing Block	Fear>fixation

Lawrence et al. (2004)	20 BD 9 MDD 11 HC 60% male	Overall mean 41 (11)	Implicit facial affect processing Event-related	Fear>neutral Happy>neutral Sad>neutral
Lee et al. (2008)	21 MDD (3/18) 15 HC (2/13)	MDD: 46.8 (9.1) HC: 48.7 (3.5)	Explicit facial affect rating block	Sad>fixation
Lennox et al. (2004)	10 BD (8/2) 12 HC (6/6)	BD: 37.3 (12.8) HC: 32.6 (10.7)	Explicit facial affect rating Event-related	Sad>neutral
Malhi et al. (2007)	10 BD (0/10) 10 HC (0/10)	BD: 33.5 (8.7) HC: 32.4 (6.4)	Explicit facial affect recognition Event-related	Fear>neutral
Norbury et al. (2010)	16 MDD (7/9) 21 HC (11/10)	MDD: 36.2 HC: 32.3	Explicit facial affect matching Block	Fear>Shapes
Suslow et al. (2010)	30 MDD (17/13) 26 HC (12/14)	MDD: 38.8 (11.4) HC: 36.2 (13.4)	Implicit facial affect processing Event-related	Sad>neutral
Scheuerecker et al. (2010)	13 MDD (10/3) 15 HC (10/5)	MDD: 37.9 (10.1) HC: 35.5 (10.9)	Implicit and explicit facial affect matching Block	Sad and angry> shapes (implicit)
Thomas et al. (2010)	30 (remitted) MDD (9/21) 35 HC (12/23)	MDD: 32.8 (10.4) HC: 31.7 (9.8)	Implicit facial affect processing Block	Sad>neutral Fear>neutral
Townsend et al. (2010)	15 MDD (9/6) 15 HC (9/6)	MDD: 45.6 (11.2) HC: 44.8 (11.7)	Explicit facial affect matching Block	Sad and angry> shapes
Van Wingen et al. (2010)	18 MDD (first episode) (7/11) 21 (remitted) MDD (4/17) 30 HC (13/17)	MDD (first episode): 33.3 (11.7) MDD (recovered): 34.5 (11.4) HC: 35 (12)	Explicit facial affect matching Block	Fear and angry> shapes

BD = Bipolar Disorder; MDD = Major Depressive Disorder; HC = Healthy Controls; 1 = only baseline data used; 2 = study also included 20 first degree relatives.

Table 2 Clinical description of MDD and BD patients includes in the meta-analyses.

Study	Psychopathology measures Mean, total score (standard deviation)	Duration of illness Mean, years (standard deviation)	Psychotropic medication (number of patients)	Diagnostic instrument	Comorbidity (number of patients with comorbidity/ total sample)	First or multiple episodes
Almeida et al. (2010)	YMRS score BD (depressed): 21.5 (6.4) BD (remitted): 1.4 (1.1) MDD: 24.4 (6.1)	BD (depressed): 14.2 (9.8) BD (remitted): 14.6 (5.4) MDD: 13.6 (9.8)	Unspecified	SCID	9/30 BD substance abuse 3/15 MDD substance abuse	All patients had experienced at least two episodes of illness in the last 4 years
Altshuler et al. (2008)	YMRS score BD:2.9 (1.9) HDRS score BD: 20.8 (3.3)	Unspecified	Medication free (2), Li (1), anticonvulsants (7), atypical antipsychotics (2), antidepressants (3)	SCID	No comorbid axis I and II disorders	Unspecified
Blumberg et al. (2005)	HDRS ARSM Unspecified scores	Unspecified	Medication free (5), Li (4), anticonvulsants (8), atypical antipsychotics (1), antidepressants (3)	Unspecified	9/12 lifetime history of alcohol dependence; >1.5 years in remission	Unspecified
Chen et al. (2006)	YMRS score BD(manic): 24.1 (8.2) BD(depressed): 0.4 (0.5) HDRS score BD (manic): 2 (2.9) BD (depressed): 18.3(6.4)	Unspecified	Li (11), anticonvulsants (9), typical (2) and atypical antipsychotics (3), antidepressants (2)	Unspecified	No comorbid axis I and II disorders	All patients had at least 2 previous episodes of mania and depression
Foland et al. (2008)	YMRS score BD: 15.1 (3.7) HDRS scores BD: 9.1 (5.3)	14.8 (5.1)	Li (20), anticonvulsants (6), atypical antipsychotics (1)	SCID	No comorbid axis I disorders	Mean manic episodes 4.2 (2)
Fu et al. (2007)	HDRS score MDD: 21.1 (2.3)	Unspecified	Medication free at baseline	SCID	No comorbid axis I and II disorders	Multi-episode unspecified

Gotlib et al. (2005)	BDI score MDD: 24.6 (8.3)	Unspecified	Antidepressants (8)	SCID	No comorbid axis I and II disorders	Multi-episode unspecified
Hassel et al. (2008)	YMRS score BD:<10 HDRS scores BD: <7	BD: 10.6 (6.61)	Li (6), anticonvulsants (7), typical (2) and atypical (12) antipsychotics, antidepressants (9), benzodiazepines (4)	SCID	3/19 eating disorders 5/19 substance abuse 11/19 anxiety disorders	Multi-episode unspecified
Jogia et al. (2008)	YMRS score BD:<7 HDRS score BD:<14	Unspecified	anticonvulsants (12)	SCID	No comorbid axis I and II disorders	Mean total episodes 10.1 (6.5)
Killgore et al.(2008)	YMRS score BD: 14.3 (8.9) HDRS score BD: 15.6 (9.9)	<1 year	Li or anticonvulsants (5), atypical antipsychotics (12), antidepressants (1), benzodiazepines (4)	SCID	Unspecified	First hospitalisation
Lawrence et al. (2004)	BDI score BD: 15.3 (9.2) MDD: 31.8 (11.8)	BD: 15.4 (13.4) MDD: 8 (5)	Li (3), antiepileptics (7), atypical antipsychotics (5), antidepressants (5)	Unspecified	No comorbid axis I and II disorders	Multi-episode unspecified
Lee et al. (2008)	HDRS score MDD: 22.2 (4)	MDD: 14.9 (8.8)	Antidepressants (10)	SCID	No comorbid axis I and II disorders	Mean depressive episodes 1.9 (0.8)
Lennox et al. (2004)	YMRS score BD: 27.7 (7.9) HDRS score BD: 0 (0)	Unspecified	Li (8), antiepileptics (7), typical antipsychotics (4), atypical antipsychotics (3)	Unspecified	Unspecified	Unspecified
Malhi et al. (2007)	YMRS score BD: <6 HDRS score BD:<6	BD: 12 (7.7)	Li (3), anticonvulsants (5)	SCID	No comorbid axis I and II disorders	Mean depressive episodes 10.4 (8.7) Mean manic episodes 4.7 (3.4)
Norbury et al. (2010)	BDI score MDD: 3.5 (3.7)	Unspecified	medication free	Unspecified	1/16 anxiety disorders 2/16 alcohol misuse	Patients with at least 2 previous episode of depression

(continued on next page)

Table 2 (*continued*)

Study	Psychopathology measures Mean, total score (standard deviation)	Duration of illness Mean, years (standard deviation)	Psychotropic medication (number of patients)	Diagnostic instrument	Comorbidity (number of patients with comorbidity/ total sample)	First or multiple episodes
Scheuerecker et al. (2010)	HDRS score MDD: 20.5 (4.7)	MDD: 52.3 (71.5)	Medication free	SCID	No comorbid axis I and II disorders	8 patients with first episodes and 5 with recurrent episodes Mean depressive episodes 1.4 (0.6)
Suslow et al. (2010)	HDRS score MDD: 24.8 ± 4.9	MDD: 6 (6.2)	Antidepressants (30)	SCID	13/30 anxiety disorders 3/30 dysthymia 1/30 pain disorder	Mean depressive episodes 2.7 (2)
Thomas et al.(2010)	MADRS score MDD: 2.3 (3.2)	Unspecified	Antidepressants (3)	SCID	No comorbid axis I and II disorders	Unspecified
Townsend et al. (2010)	HDRS score MDD: 20.1 (4.9)	MDD: 14.7 (13.3)	Medication free	SCID	No comorbid axis I and II disorders	Median depressive episodes 3
Van Wingen et al. (2010)	HDRS score MDD (depressed): 21.8 (4.2) MDD (recovered): 3.3 (2)	Unspecified	Medication free	SCID	No comorbid axis I and II disorders	18 with first MDE and 18 recovered from a first MDE

ASRM = Altman Self-Rating Mania Scale; BD = Bipolar Disorder; BDI = Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; MDD = Major Depressive Disorder; SCID = Structured Clinical Interview for DSM-IV; YMRS = Young Mania Rating Scale.

Table 3 Results from the global Activation Likelihood Estimation (ALE) analyses of facial affect processing in Bipolar Disorder and Major Depressive Disorder ($p<0.05$ False Discovery Rate corrected).

Brain region	Side	Centre of maximum ALE			Volume, mm^3	Maximum ALE value
		X	Y	Z		
Bipolar Disorder>healthy controls						
Parahippocampal gyrus	L	−18	−4	−16	1048	0.01
Parahippocampal gyrus		−18	−18	−8		
Putamen		−26	−6	−8		
Parahippocampal gyrus	R	24	−4	−14	392	0.01
Thalamus (Pulvinar)	L	−6	−26	4	368	0.01
Healthy controls>Bipolar Disorder						
Inferior frontal gyrus	L	−34	26	−8	480	0.01
	R	36	30	−8	872	0.01
Major Depressive Disorder>healthy controls						
Parahippocampal gyrus (amygdala)	R	28	0	−16	232	0.01
		30	−4	−20		
Healthy controls>Major Depressive Disorder						
Putamen	R	28	−1	0	400	0.01
Caudate	L	−36	−14	−10	256	0.01
Bipolar Disorder>Major Depressive Disorder						
Parahippocampal gyrus (amygdala)	L	−18	−4	−14	2984	0.01
		−18	−30	−8		0.008
		−24	6	−16		0.006
	R	22	−6	−12	376	0.008
Thalamus (Pulvinar)	L	−6	−26	6	584	0.01
Anterior cingulate gyrus (ventral)	R	8	24	24	376	0.007
	R	6	30	28		
Major Depressive Disorder>Bipolar Disorder						
Anterior cingulate gyrus (dorsal)	L	−20	−18	46	416	0.007

L=left; R=right; x=sagittal, y=coronal, z=axial coordinates according to Talairach and Tournoux.

computed. ALE scores from the convergent MA maps were then calculated on a voxel-by-voxel basis to test for convergent (random-effects) rather than study specific foci (fixed-effects). All ALE data processing was performed using the BrainMap Search and View software (http://brainmap.org).

First we performed two separate global meta-analyses (a) all studies comparing BD patients to controls, and (b) all studies comparing MDD patients to controls. Differences between diagnostic groups were tested by computing the voxel-wise difference between the ensuing ALE maps. Statistical inference was based on a threshold of $p<0.05$ with False Discovery Rate (FDR) correction and a minimum cluster size of 200 mm^3. At a second stage, we conducted a series of subsidiary meta-analyses within each diagnostic group depending on stimulus valence. Based on data availability, we focused on fearful and happy facial expressions as exemplars of negative and positive valence. For all analyses, all ALE maps were imported into Mango and overlaid on an anatomical template (http://ric.uthscsa.edu/mango/) for representation purposes. Coordinates of the maximum ALE and corresponding Brodmann areas are reported.

3. Results

We identified 37 studies that used facial affect paradigms in patients with BD or MDD of which twenty fulfilled all inclusion criteria, giving a total sample of 168 BD and 189 MDD patients and 344 healthy controls (HC) (Table 1). Excluded studies (a) grouped mood disorder patients together with other diagnostic groups (Lau et al., 2009), (b) grouped positive and negative facial stimuli together (Matthews et al., 2008; Yang et al., 2010; Anderson et al., 2011), (c) did not provide coordinates of the case–control comparison (Yurgelun-Todd et al., 2000; Gaffrey et al., 2010; Liu et al., 2010; Versace et al., 2010) or of the emotional versus neutral facial expressions contrast (Victor et al., 2010; Frodl et al., 2010), (d) did not include a control group (Keedwell et al., 2009), (e) implemented functional connectivity (Almeida et al., 2009) or pattern classification analyses (Fu et al., 2008), (f) used facial affect stimuli to examine other processes (e.g. interference) (Keedwell et al., 2005; Fales et al., 2008), and (g) examined the same patient group as other included studies (Haldane et al., 2008; Fu et al., 2004).

Demographic details for all participants and clinical information about BD and MDD patients in the studies included are shown in Table 2. As the definitions of participants' mental state differed in the primary studies we provided the mean psychopathology rating scales' scores (Table 2). With the exception of 5 studies which included medication free patients, patients received combinations of different psychotropics.

3.1. Global meta-analyses

3.1.1. Bipolar Disorder vs. controls

BD patients compared to controls showed (a) increased activation in the parahippocampal gyrus (extending to the amygdala) bilaterally, in the left putamen and left pulvinar (14 studies; 50 foci; 379 subjects) (Table 3), and (b) decreased activation bilaterally in the ventrolateral prefrontal cortex, within the inferior frontal gyrus (BA47) (Table 3) (Fig. 1).

3.1.2. Major Depressive Disorder vs. controls

MDD patients compared to controls showed (a) increased activation in the right parahippocampal gyrus (extending to the amygdala) (7 studies; 24 foci; 280 subjects) (Table 3), and (b) decreased activation in the right putamen, and left caudate (10 studies; 44 foci; 423 subjects) (Table 3) (Fig. 1).

3.1.3. Bipolar Disorder vs. Major Depressive Disorder

BD patients showed greater likelihood of activation than MDD patients in the parahippocampal gyrus (cluster included the amygdala), in the ventral anterior cingulate gyrus bilaterally and in the left pulvinar. Conversely, MDD patients had increased likelihood of activation than BD patients in dorsal anterior cingulate gyrus (Table 3).

3.2. Stimulus valence sub-analyses

3.2.1. Fear faces

3.2.1.1. Bipolar Disorder. In the fearful>non emotional stimuli contrast BD patients, compared to controls, showed (a) increased activation in the left parahippocampal gyrus (BA 28 and 35), left putamen and left pulvinar thalamus (7 studies; 30 foci; 166 subjects), and (b) decreased activation in the inferior frontal gyrus (BA47/45) bilaterally and in the left anterior cingulate gyrus (BA32) (7 studies; 23 foci; 170 subjects) (Table 4).

3.2.1.2. Major Depressive Disorder. In the same contrast (fearful>non emotional stimuli) (4 studies; 14 foci; 97 subjects) MDD patients showed decreased activation in sensorimotor cortices within the left precentral gyrus (BA6) (Table 4).

3.2.2. Happy faces

3.2.2.1. Bipolar Disorder. Compared to controls, in the happy>non emotional stimuli BD patients showed (a) increased activation in the caudate bilaterally and left parahippocampal gyrus (BA34) (4 studies; 16 foci; 132 subjects) and (b) decreased activation in the right anterior cingulate gyrus (BA32) (3 studies; 23 foci; 95 subjects) (Table 4).

3.2.2.2. Major Depressive Disorder. In the same contrast (happy>non emotional stimuli) (3 studies; 14 foci; 130 subjects) activation was decreased in the right pulvinar thalamus in MDD patients compared to controls (Table 4).

4. Discussion

The results of this meta-analysis provide evidence for common and distinct patterns of neural engagement in BD and MDD during facial affect processing. There are four key findings. First, both BD and MDD patients showed increased activation, relative to controls, in limbic regions, irrespective of stimulus valence. Second, BD was associated with reduced ventrolateral prefrontal cortical activation while MDD with decreased engagement of somatosensory cortices. Third, activation in the pulvinar thalamus and basal ganglia was increased in BD compared to controls and MDD patients. Fourth, these findings showed evidence of modulation by stimulus valence.

4.1. Increased limbic engagement: a common feature of BD and MDD

Our findings broadly confirm the prevailing view that mood disorders are associated with increased limbic activation during emotional processing (Savitz and Drevets, 2009). Our data question however the current "amygdalocentric" models for mood disorders. Clusters of abnormal medial temporal activation in both BD and MDD centred on the parahippocampal gyrus although they extended to include the amygdala. Chen et al. (2011) reported a similar pattern in a previous meta-analysis of fMRI studies in BD (Chen et al., 2011) and we now extend these observations to MDD. The parahippocampal gyrus and amygdala lie very close to each other and frequently co-activate during emotional processing (Fusar-Poli et al., 2009; Vytal and Hamann, 2010). Therefore the accuracy in locating the peak of activation within medial lobe structures could be influenced by smoothing and transforming data from individual subjects into a common stereotactic space. Other methodological considerations may relate to the type of paradigm or mood state. For example the amygdala become more engaged when facial expressions are processed outside the focus of attention (Hariri et al., 2003) and their activation may "normalise" with symptomatic remission, especially in MDD (Delaveau et al., 2011). Alternatively, it is possible that our results genuinely reflect greater parahippocampal involvement, relative to the amygdala, in mood disorders. The parahippocampal gyrus and the amygdala are thought to subserve partially segregated dimensions of emotional processing; amygdala engagement may signal salience or ambiguity (Gerber et al., 2008; Santos et al., 2011) while parahippocampal activation may reflect context appraisal (Gerdes et al., 2010). Whether these processes are differentially affected in mood disorders requires further investigation. In any case our results add to the emerging consensus that a more detailed evaluation of the role of limbic structures in mood disorders is warranted and this should crucially involve a revaluation of the central role currently ascribed to the amygdala. This is timely as within the field of affective neuroscience the role of the amygdala is undergoing major reappraisal with greater emphasis being placed on the contribution of other cortical and subcortical structures (Pessoa and Adolphs, 2010).

4.2. Distinct cortical involvement in BD and MDD

BD, but not MDD, was associated with reduced engagement in ventrolateral prefrontal regions within the inferior frontal gyrus. The ventrolateral prefrontal cortex is involved in inhibitory control across a number of paradigms including

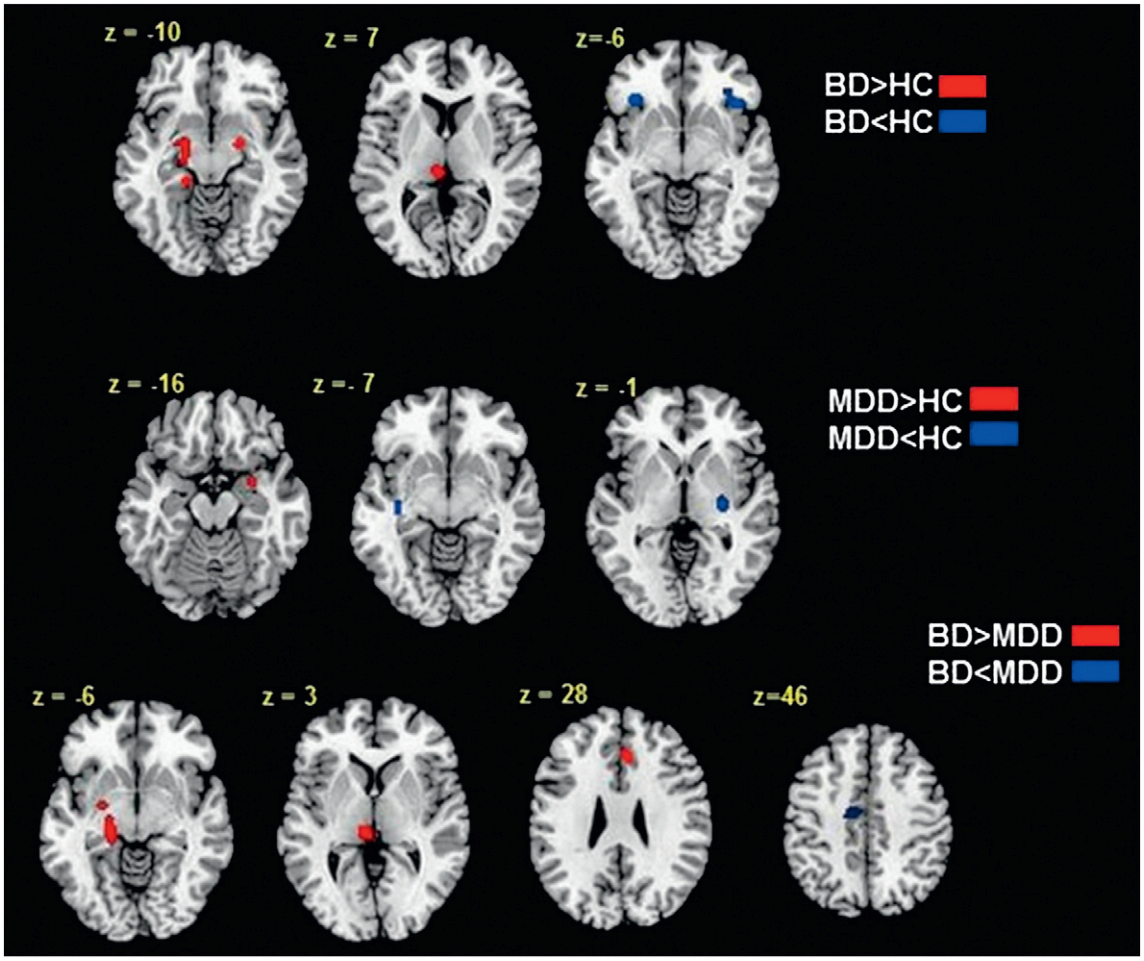

Figure 1 Activation Likelihood Estimation (ALE) maps representing regional activity consistently associated with Bipolar Disorder (BD) or Major Depressive Disorder (MDD). Clusters of relative overactivation or underactivation are shown in red and blue respectively; numbers represent axial (z) coordinates of each slice in Talairach space; $p<0.05$ False Discovery Rate corrected for multiple comparisons. Top row: statistical map of significant ALE clusters for the comparison of BD patients to healthy controls (HC). Middle row: statistical map of significant ALE clusters for the comparison of MDD patients to healthy controls (HC). Bottom row: statistical maps of significant ALE clusters associated with the contrast of BD and MDD.

emotional processing (Quirk and Beer, 2006). Dysfunction within this region is therefore thought to reflect reduced inhibitory capacity in BD (Cerullo et al., 2009; Chen et al., 2011). The degree of dysfunction in this region may be modulated by valence as it was most consistently observed when BD patients processed negative facial expressions. Ventrolateral PFC engagement regulates stimulus-driven action by modulating the influence of emotional stimuli on cognition with respect to contextually (or socially) appropriate behaviour (Quirk and Beer, 2006). In this respect ventrolateral PFC dysfunction may be relevant to stimulus-driven, socially inappropriate behaviour observed during mania.

Further diagnosis-related differences were observed in somatosensory regions where MDD patients showed decreased responsiveness compared to healthy individuals, particularly when viewing negative facial expressions. Somatosensory cortices contribute to the recognition of facial emotions (Adolphs, 2002) possibly through a process of invoking or "mirroring" internal representations of the pertinent emotional experience (Adolphs et al., 2000). Since MDD patients experience negative emotions frequently as part of the clinical syndrome of depression this finding could be suggestive of adaptive down-regulation of processing of negative stimuli. Similar observations of reduced emotional reactivity in MDD have been made previously in a variety of experimental settings and are thought to reflect emotion-context insensitivity (Rottenberg et al., 2005).

4.3. Common and distinct thalamic engagement in BD and MDD

Our results suggest that thalamic involvement in mood disorders is complex. Increased thalamic engagement was uniquely associated with BD. However, thalamic activation may be influenced by stimulus valence. Increased pulvinar activation was observed in BD during the processing of negative facial expressions while decreased activation in the same nucleus was noted in MDD during the processing of happy faces. The pulvinar is considered a "higher order"

Table 4 Results from the valence Activation Likelihood Estimation (ALE) sub-analyses of facial affect processing in Bipolar Disorder and Major Depressive Disorder ($p<0.05$ False Discovery Rate corrected).

Brain region	Side	Centre of maximum ALE			Volume, mm^3	Maximum ALE value
		X	Y	Z		
Fear						
Bipolar Disorder>healthy controls						
Parahippocampal Gyrus	L	−18	−12	−12	584	0.01
Putamen	L	−26	−6	−8		0.008
Thalamus (Pulvinar)	L	−6	−26	4	376	0.01
Healthy controls>bipolar disorder						
Inferior frontal Gyrus (BA47)	L	−34	24	−8	480	0.01
	R	44	22	−2	1080	0.01
Inferior frontal gyrus (BA45)	R	52	12	28	408	0.01
Anterior cingulate (BA32)	L	−8	34	12	424	0.01
Major Depressive Disorder>healthy controls						
No suprathreshold clusters						
Healthy controls>Major Depressive Disorder						
Precentral gyrus	L	−58	0	12	96	0.009
Happy						
Bipolar Disorder>healthy controls						
Caudate	L	−18	20	14	80	0.009
	R	14	10	16	96	0.009
		18	24	−6	80	0.009
Parahippocampal gyrus	L	−26	6	−16	80	0.008
Healthy controls>Bipolar Disorder						
Anterior cingulate gyrus	R	20	14	34	80	0.009
Major Depressive Disorder>healthy controls						
No supratheshold clusters						
Healthy controls>Major Depressive Disorder						
Thalamus	R	6	−28	4	368	0.01

L=left; R=right; x=sagittal, y=coronal, z=axial coordinates according to Talairach and Tournoux.

nucleus because of its widespread bidirectional cortical connections (Pessoa and Adolphs, 2010). The pulvinar is directly involved in visual perception (Pessoa and Adolphs, 2010), particularly in directing and maintaining attention towards salient stimuli (Desimone et al., 1990). Our results suggest that in BD the pulvinar overactivation may act to amplify neural engagement for emotionally salient, particularly negative stimuli. The reverse appears to be the case in MDD when processing happy faces; this is in line with current views that MDD may be characterised by reduced reactivity to positive stimuli (Rottenberg et al., 2005).

4.4. Distinct basal ganglia involvement in BD and MDD

Diagnosis related changes were also noted in the basal ganglia where increased engagement was observed in BD compared to controls while the reverse was the case for MDD. Specifically, BD patients expressed increased activation in the putamen and in the caudate in response to negative and positive facial expressions respectively. The putamen is mainly involved in sensorimotor processing and is thought to contribute to the motor production of facial expressions during negative affect recognition (Adolphs, 2002). Increased putamen activation in BD patients may reflect either greater facial mimicry or greater amplification of sensorimotor processing of negative facial affect. The latter interpretation is supported by the increased engagement of the pulvinar.

During happy facial affect processing BD patients, compared to controls, expressed increased activation in the caudate nucleus. This is in line with findings implicating the caudate in processing rewarding stimuli (Schultz et al., 1997; O'Doherty et al., 2003) including happy facial expressions (Phan et al., 2002). As activation in reward-circuitry structures correlates positively with valence (Gerdes et al., 2010) our results indicate that happy facial stimuli may have greater reward value for BD patients. This observation may relate to the inappropriate and generalised activation of reward-related structures in mania (Abler et al., 2008).

5. Methodological considerations

Activation Likelihood Estimation represents a powerful approach for the meta-analytic treatment of neuroimaging data. Still, a number of factors should be considered in the interpretation of the current set of findings. First, our initial review revealed great variability in the emotional processing paradigms used which coupled with small sample sizes impacts on the ability to draw statistically robust conclusions

from this literature. To minimise variability due to study design we focused exclusively on studies using comparable versions of facial affect processing tasks. Second, we included results reported as significant in the original studies since ALE analyses do not allow weighting based on the threshold of significance employed in each individual study. Third, there was significant variability in the level of patients' symptomatology at the time of testing and in the definition of "remitted" or "euthymic" states (Table 2). Separate analyses of the available studies according to mood states would not have been statistically feasible. Therefore, the changes in regional brain activity identified here cannot be clearly categorised as trait or state. Fourth, as shown in Table 2, with the exception of 5 studies, patients were medicated and were prescribed combinations of psychotropics. Given the inter-study variability in medication regimes a systematic bias influencing our results is improbable. Additionally psychotropic medication predominantly acts to reduce case–control differences in neural activity in mood disorders (Phillips et al., 2008; Delaveau et al., 2011). Fifth, sex differences have been found during facial affect processing (Fusar-Poli et al., 2009). Although it was not possible to examine this directly, the original studies included samples that were generally balanced and matched for sex (Table 1), thus minimising the likelihood of a systematic sex-related bias confounding the effect of diagnosis. Sixth, since most original studies examined multi-episode BD or MDD patients (Table 2), further investigation is required to clarify the relevance of our results to the initial stages of mood disorders. Seven, current meta-analytic algorithms cannot adequately address the effect of demographic, behavioural or clinical variables on the distribution of the reported brain activation patterns. Such questions would be ideally investigated in large neuroimaging data sets where the quantitative impact of these variables could be directly assessed. Finally, this meta-analysis provides an estimate of the probability that activity in particular brain regions may differ between groups (e.g. BD vs. controls). It is not an estimate of the mean difference in regional signal change and therefore traditional measures of heterogeneity and publication bias that are based on effect size are not applicable. Although we cannot exclude a publication bias against negative studies, this would have had no effect on the current results.

6. Conclusion and future directions

In conclusion, we provided evidence for common and distinct neural correlates in BD and MDD in response to emotional faces. Our results point to three new avenues of enquiry in mood disorders. Firstly, they suggest the need for more detailed examination of the relative contribution of medial temporal regions and particularly the interaction between amygdala and parahippocampus. Second, they underscore the contribution of cortical, thalamic and basal ganglia regions to the pathophysiology of mood disorders and suggest that examination of these cortico-thalamic-basal ganglia circuits may shed light to mechanisms differentiating BD from MDD. Third, they point to stimulus valence as an important modulator of activity within the neural networks underlying emotional processing in mood disorders.

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Contributors

All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare no conflict of interest.

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