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Review Article

Emotion processing and regulation in bipolar disorder: a review

Townsend J, Altshuler LL. Emotion processing and regulation in bipolar disorder: a review.
Bipolar Disord 2012: 00: 000–000. © 2012 The Authors.
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Objectives: Bipolar disorder (BP) is characterized by a dysfunction of mood, alternating between states of mania/hypomania and depression. Thus, the primary abnormality appears to be an inability to regulate emotion, the result of which is emotional extremes. The purpose of this paper is to review the current functional magnetic resonance imaging (fMRI) literature on adult patients with BP using emotion processing or regulation paradigms.

Methods: A search was conducted on PubMed using the keywords: *bipolar disorder, fMRI, mania, bipolar depression, bipolar euthymia, emotion, and amygdala*. Only those studies that were conducted in adult patients using an emotion activation task were included in the final review.

Results: Using tasks that assess neural functioning during emotion processing and emotion regulation, many fMRI studies have examined BP subjects during mania and euthymia. Fewer fMRI studies have been conducted during depression, and fewer still have included the same subjects in multiple mood states. Despite these limitations, these studies have demonstrated specific abnormalities in frontal–limbic regions. Using a variety of paradigms, investigators have specifically evaluated the amygdala (a structure within the limbic system known to be critical for emotion) and the prefrontal cortex (PFC) (a region known to have a regulatory function over the limbic system).

Conclusions: These investigations reveal that amygdala activation varies as a function of mood state, while the PFC remains persistently hypoactivated across mood states. Emotional dysregulation and lability in mania and depression may reflect disruption of a frontal–limbic functional neuroanatomical network.

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doi: 10.1111/j.1399-5618.2012.01021.x

Key words: amygdala – bipolar disorder – emotion processing – emotion regulation – functional neuroimaging – vlPFC

Received 27 September 2011, revised and accepted for publication 22 March 2012

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BDI Journal Name 1021 Manuscript No. B
Dispatch: 26.4.12 Journal: BDI CE: Kannan
Author Received: No. of pages: 14 PE: Gomathi V

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Emotion processing involves the detection and evaluation of salient stimuli as well as the regulation of one's emotional (affective) response to these stimuli (1). Models of emotional processes include a number of components, such as: (i) attention to and perception of information that could potentially elicit emotional responses, (ii) subsequent emotional arousal to such stimuli, and (iii) the regulation of that arousal via several potential mechanisms (i.e., altering attention or perception of stimuli and arousal responses and/or using cognitive reappraisal or other cognitive or behavioral strategies to modulate arousal level). Dysregulated emotional responses can lead to pathological mood states, including those seen in bipolar disorder (BP) (2, 3). BP is distinguished primarily by acute dysfunctional mood states, alternating between mania [BP type I (BP-I)] or hypomania [BP type II (BP-II)], and depression. This characteristic mood lability suggests a possible dysfunction in neural networks involved in emotion processing and regulation. BP exacts a tremendous cost not only to the patient, family, and friends, but also to society. The World Health

Organization regards BP as one of the leading causes of disability throughout the world (4). With the high direct and indirect financial (5) and emotional costs of BP, it is imperative to better understand and delineate its underlying causes for the ultimate purpose of improved diagnosis and treatment.

As BP is primarily a disorder of mood, many BP functional magnetic resonance imaging (fMRI) studies utilize tasks involving emotion processing and regulation. The inability to regulate emotion is the primary abnormality of BP, the result of which is the characteristic acute mood states of the disorder. Using a variety of paradigms, many neuroimaging studies specifically investigated the amygdala, a structure within the limbic system known to be critical for emotion, and the prefrontal cortex (PFC), a region known to have a regulatory function over the limbic system. Most fMRI studies examine BP subjects while euthymic, while fewer fMRI studies have been conducted on subjects during mania and depression, and fewer still include the same subjects in multiple mood states. Despite these limitations, structural and functional imaging studies have demonstrated specific abnormalities in frontal–limbic regions and suggest that abnormalities in these circuits may result in the emergence of the manic and depressive symptoms seen in BP (6, 7). This review will focus only on the fMRI literature on emotion and emotion regulation in adults with BP. There exists considerable controversy on the childhood and adolescent diagnosis of BP, and such discussion is beyond the scope of this review. Emotional dysregulation in mania and depression may reflect disruption of a functional neuroanatomical network with potential structural correlates, and this network will be the main focus of this review.

Healthy functioning

The amygdala, insula, anterior cingulate cortex (ACC), medial PFC (mPFC), and ventral lateral PFC (vlPFC) are considered key neural substrates of an emotion processing and regulation circuit (1). Neuroimaging studies have demonstrated a role for the amygdala and insula in normal emotion processing, and for the medial and lateral regions of the vlPFC in mood regulation (8, 9) and associative emotional memory functions (10, 11).

The amygdala plays a key role in signaling danger and, more generally, signaling the emotional salience of sensory information to the rest of the brain in preparation for an appropriate response (12). Functional neuroimaging studies in healthy subjects, using neuropsychological paradigms that involve simple viewing of emotion stimuli, reliably activate the amygdala (13–15). Most emotion studies of healthy subjects use emotional faces as stimuli and demonstrate robust bilateral amygdala activation in response to faces with both positive and negative valence (for a review, see 16), with the strongest amygdala activation occurring during the viewing of fearful faces. The amygdala is activated by valenced stimuli and may serve to strengthen the portrayal of emotional stimuli in sensory representation areas of the occipital and temporal cortex (17, 18). Through neuronal projections to the brainstem and hypothalamus, amygdala activation stimulates the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis. This neural activity promotes physical and behavioral responses to the stimuli. The actions of the fast-acting ANS and slower-acting HPA system enable an adaptive modulation of the stress response (19). Thus, the amygdala plays an essential role in both the perception of emotional stimuli and the subsequent arousal reactions to such incoming information. As such, it has been studied extensively in healthy populations and in patients with mood disorders.

Emotion regulation involves the initial steps of emotion processing (i.e., attention and perception of information eliciting emotional arousal) and the subsequent mechanisms of modulating emotional arousal. fMRI studies that involve modifying emotional arousal, regardless of the mechanism employed, typically reduced amygdala activation and activated the vlPFC and other frontal regions (13–15, 20). The vlPFC has been implicated in processing emotional salience (21) and motivation (22), and plays a role in integrating emotional information and regulating the intensity of emotional responses (21, 23). Emotion regulation may occur via pathways between the vlPFC and autonomic systems that govern visceral responses associated with affective stimuli (24). The vlPFC has been implicated in other behavioral (response) inhibition studies and may serve a broader role in inhibiting undesirable or inappropriate states or actions (25). Dysfunction in this region may provide a mechanism for understanding the failure to modulate a region's underlying affect, such as the amygdala.

Tasks that require simple emotion processing (as in the case of passive viewing) show greater amygdala activation than tasks that require emotion regulation (15, 26, 27). Emotion regulation can generally be seen as the alteration of ongoing emotional responses through processes like altered attention via the ACC or through implicit or

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explicit emotion regulation via frontal lobe activation (28, 29). The frontal lobe connections to amygdala and other limbic structures may be inhibitory in nature, allowing for a dampening or reduction of amygdala activation and, in turn, perhaps a dampening of emotional arousal. fMRI studies of emotion regulation in healthy subjects demonstrate engagement of frontal regions, including the vlPFC and ACC (27, 29, 30), and downregulation of limbic regions by way of vlPFC activation (15, 28).

One commonly used technique to regulate emotion is cognitive reappraisal, wherein subjects recruit cognitive resources to consciously reframe the context of salient emotional stimuli to modulate their emotional response. In behavioral studies, downregulation of emotion via cognitive reappraisal has been shown to decrease physiological arousal (31–33) and subjective reports of distress (34). Emotion regulation studies using cognitive reappraisal in healthy subjects demonstrate reliable activation in the vlPFC, pre-supplementary motor area (pre-SMA), and less frequently in the ACC (34–39). Specifically, during emotion downregulation using cognitive reappraisal, healthy subjects show increased activation in the vlPFC, mPFC, and ACC (34, 40). These regulation studies also demonstrate reduced activity in the amygdala during cognitive reappraisal, consistent with the vlPFC's putative role in inhibiting limbic activity.

The regions implicated in emotion regulation studies have extensive anatomical connections with the amygdala (23, 24, 41). The amygdala has extensive reciprocal connections with the frontal lobe, with direct connections to the mPFC and vlPFC (42). Modulatory input from cortical brain regions, including the mPFC and vlPFC, dampen amygdala activation in the wake of emotionally arousing events (12). Human (43) and non-human primate (44) anatomical studies show extensive reciprocal connections between the amygdala and PFC. Neurochemical studies in animals suggest that this inhibitory connection between the amygdala and PFC is modulated via GABAergic interneurons (45, 46). Prior studies of non-human primates have demonstrated a range of cortical regions, including the vlPFC, mPFC, insula, and temporal lobe, with reciprocal connections to the amygdala (47, 48). The mPFC, with dense reciprocal connections to the amygdala (49), may serve to modulate amygdala activity or, more specifically, to regulate emotional response to salient stimuli. The insula is another region commonly implicated in emotion processing and also has extensive anatomical connections and shows significant effective connectivity with the amygdala, ACC, and vlPFC (50–52). Sad and disgusted faces are known to preferentially activate the insula in healthy subjects (16), and this region may be recruited during the emotional response to potentially distressing interoceptive stimuli (53).

In addition to studies investigating anatomical connections between the amygdala and frontal regions, functional and effective connectivity studies have demonstrated specific changes in connectivity as a response to emotional stimuli. Studies of healthy subjects report significant effective connectivity between the amygdala, vlPFC, insula, and ACC (52), and significant negative functional connectivity between the amygdala and frontal regions (15, 27). Researchers have found increased functional connectivity between the amygdala and regions mediating autonomic activity, such as the ACC and brainstem, during stress induction (54). These studies suggest an antagonistic relationship (i.e., negative connectivity) between the amygdala – which attributes emotion salience to stimuli – and regions of the PFC and ACC, which are involved in attention and cognition regulation. Thus, the amygdala can be seen as part of an adaptive system that increases the salience of emotional information (12). A counteractive system involving the PFC may regulate the impact of emotional stimuli, especially when such limbic activity interferes with current task demands (18). As such, the effects of a stressor may relate to activation of the autonomic stress response by the amygdala (54). Prolonged amygdala activation (or diminished frontal modulation) during the recovery period following exposure to emotion stimuli may relate to the development of psychopathology. An overload in stress may impact the feedback circuit between the amygdala and vlPFC and mPFC, and contribute to the pathogenesis of mood and anxiety disorders. This amygdala–ACC–mPFC and amygdala–vlPFC connectivity in healthy subjects is balanced to reflect emotion regulation through cognitive control, and such a balance may be disrupted in psychiatric populations (55). The decoupling of these regions has been demonstrated in relation to emotion dysregulation (2) and remains to be fully explored, specifically in BP.

Mania

Functional imaging studies during mania have been limited, no doubt because of difficulties in having manic patients remain still during scanning. Activation studies published to date have primarily assessed frontal–amygdala activity using paradigms known to activate the amygdala in healthy

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subjects (15, 56–58). As an enlarged amygdala (59–61) and heightened activation (62) have been reported in some subjects with BP, many fMRI studies utilized emotion paradigms, such as those involving emotional faces or scenes known to activate the amygdala (15), in order to assess emotion reactivity and frontal–amygdala circuitry during mania. Table 1 reviews the current fMRI literature on adult subjects with BP while performing a variety of task involving emotion.

One of the most consistent findings in mania is heightened limbic activation in response to emotional stimuli, primarily emotional faces. A number of studies specifically found increased left amygdala activation compared to healthy subjects during simple emotion processing (i.e., viewing) of emotional faces (63), emotional scenes (64), positive pictures (65), and during implicit, but not explicit, emotion processing (66). Another study, using patients in a variety of mood states, also found increased left amygdala activation in response to fearful faces (62), stimuli known to activate the amygdala most reliably (16). This increased left amygdala response during mania correlated positively with Young Mania Rating Scale (YMRS) scores (65). These studies are interesting in light of several structural MRI studies that reported an enlarged amygdala in subjects with BP (59, 60), although not all structural studies in BP have found amygdala enlargement (67). Although there is considerable convergence in amygdala findings, particularly in the left amygdala, at least one study found no significant differences in overall amygdala activation between manic and healthy subjects (68). This may have been due to the relatively small sample size (n = 10) or the use of sad faces only in this study. However, manic subjects did exhibit a decreased load response in the bilateral amygdala when examining sad faces of increasing intensity (68), suggesting that the intensity of the emotional stimuli may contribute to why not all studies in mania found amygdala hyperactivation. Another study found hyperactivation of the left amygdala in manic subjects irrespective of the valence of the stimuli, but found hypoactivation of the right amygdala only during negative emotion scenes (but not other stimuli) (64). Of the ten emotion studies

Table 1. Amygdala and prefrontal cortex results of functional magnetic resonance imaging emotion studies in mania

Study	N	Paradigm	Method	Amygdala	vlPFC
Elliot et al. 2004 (71)	M = 8 HS = 11	Emotional Go/NoGo (happy and sad words)	3T Whole-brain	NS	↓ L/R
Lennox et al. 2004 (68)	M = 10 HS = 12	Faces (happy, sad)	3T Whole-brain	NS[a]	NS
Altshuler et al. 2005 (63)	M = 9 HS = 9	Faces (negative): match	3T ROI: amygdala	↑ L	↓ L/R
Chen et al. 2006 (66)	M = 8 D = 8 HS = 8	Faces (fear, sad, happy): implicit and explicit processing	3T Whole-brain	↑ Implicit ↓ Explicit	NS
Foland et al. 2008 (27)	M = 9 HS = 9	Faces (negative): match and label	3T Whole-brain PPI	↑ L	↓ L/R
Killgore et al. 2008 (72)	M = 13 HS = 13	Faces (fear): passive view	1.5T Whole-brain ROI: amygdala	NS	↓ R
Bermpohl et al. 2009 (65)	M = 10 HS = 10	IAPS	1.5T Whole-brain	↑ L	NS
Chen et al. 2010 (74)	M = 12 E = 9 HS = 12	Faces (happy, sad, disgust, fear, surprise, anger): rate intensity	1.5T ROI: amygdala, OFC	—	↑ R
Van der Schot et al. 2010 (69)	M = 12 E = 18 D = 12 HS = 18	Faces (neutral, happy, fearful): masked and unmasked	1.5T ROI: amygdala, OFC	↓ L/R	↓ L/R
Strakowski et al. 2011 (64)	M = 40 HS = 36	CPT-END: IAPS	4T ROI: amygdala, vlPFC	↑ L ↓ R[b]	↓ L/R

vlPFC = ventral lateral prefrontal cortex; M = manic subjects; HS = healthy subjects; D = depressed subjects; E = euthymic subjects; IAPS = International Affective Picture Set; CPT-END = Continuous Performance Task with Emotional and Neutral Distracters; ROI = region of interest; PPI = prepulse inhibition; OFC = orbitofrontal cortex; NS = not significant; L = left; R = right.

[a]Amygdala increases as load increase in healthy subjects, but not in manic subjects.

[b]No main group effect. Interaction effects with healthy subjects emotion cues > manic emotional cues.

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in mania, only two (66, 69) found decreased amygdala activation in manic subjects compared to healthy subjects. In one of these studies, Chen et al. (66) did report increased amygdala activation in manic compared to euthymic BP subjects. Both of these studies had relatively modest sample sizes ($n = 8$ and $n = 12$, respectively) and utilized both positive and negative valenced faces. These varied results suggest that the nature of amygdala abnormalities observed during mania may depend, in part, on the valence and salience of the stimuli used. Future studies that utilize more standardized paradigms may help to alleviate some of the ambiguity in the literature.

Several neuroimaging studies demonstrated attenuated vlPFC function and/or heightened amygdala activation in manic compared to healthy subjects (58, 63, 66, 70, 71). fMRI studies of mania specifically probing emotion processing demonstrate hypoactivation of the vlPFC during the processing of negative faces (63), fear perception (72), masked positive and negative faces (69), emotional and neutral cues (64), and negatively captioned pictures (73). In fact, of the ten studies of emotion in mania, six found evidence of hypoactivation of the vlPFC (27, 63, 64, 69, 71, 72), three found no group differences (65, 66, 68), and only one found increased vlPFC activation in manic subjects (74). While the previous studies utilized negative emotional stimuli, it is important to note that the one study of mania that found increased vlPFC activation used both positive and negative emotional faces (74). This result is of interest because studies of healthy comparison subjects found engagement of the vlPFC during the processing of negative (i.e., fearful and angry) but not positive (happy) faces (16). As for the three studies that failed to report any group differences in the vlPFC, it is difficult to draw any specific conclusions since all three studies had relatively modest sample sizes ($n \leq 10$) and may have been underpowered to detect such differences.

Increased amygdala activation and decreased negative connectivity between the vlPFC and amygdala (27, 75) and between the amygdala and ACC (76) have also been reported during mania. The amygdala has extensive reciprocal connections to the frontal lobe, including direct connections to the mPFC, including the ACC and the orbitofrontal cortex (OFC) (42). There is a striking convergence of studies using not only emotion paradigms, but also response inhibition paradigms, which suggests an attenuation of vlPFC function during mania (58, 71). Furthermore, hypoactivation of other frontal regions, including the dorsolateral PFC (dlPFC) and mPFC, have also been reported during mania (62, 72). Extensive anatomical connectivity exists between the vlPFC, amygdala, cingulate, and other frontal regions (23, 24, 41). Ventral prefrontal areas are also connected with the temporal polar and entorhinal temporal cortex and so have connections to the limbic cortex (42, 77). Thus, it is not surprising to see abnormalities in these same regions during mania.

Finally, one study of manic patients found increased left insular activation in response to sad faces (68). The presence of an attenuated vlPFC response and a heightened amygdala and insula response suggests another aspect to the alterations in prefrontal–limbic circuits seen in mania. Studies of healthy subjects reported significant effective connectivity between the amygdala, insula, ACC, and vlPFC (52). Dysfunction in the vlPFC could help to explain a failure to appropriately modulate other limbic brain regions and perhaps result in a range of intensity of mood shifts to hypomania and mania in patients with BP.

Depression

Patients with BP spend the majority of their time in episodes of depression, not mania (78–80). As bipolar depression is associated with high levels of morbidity and mortality across the life span, efforts aimed at identifying biological mechanisms that contribute to this phase of the illness are imperative. Functional neuroimaging studies of patients with unipolar depressive disorder have begun to reveal dysregulated neuroanatomical circuits associated with this syndrome (2, 81). Similar studies in patients with bipolar depression are more limited.

Relatively few fMRI studies have been performed in patients with BP during the depressed phase using emotion processing paradigms known to activate limbic structures (66, 70, 73, 76, 82–84), with the latter two studies using subjects in different mood states (see Table 2 for a summary of the amygdala and vlPFC fMRI findings in patients with BP while depressed). Unlike studies in mania, there was greater variability in the activation patterns reported in bipolar depressed versus healthy comparison samples. In a study involving positive- versus neutral-captioned pictures, distinct patterns of regional activation were found with bipolar depressed patients, showing increased right-sided subcortical activation (basal ganglia, thalamus, hypothalamus, and left amygdala) compared to healthy subjects (73). A trend of left amygdala hyperactivation was observed in another study using sad faces as stimuli, but this amygdala hyperactivation was not statistically significant or was not seen for other emotion

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Table 2. Amygdala and prefrontal cortex results of functional magnetic resonance imaging emotion studies in bipolar depression

Study (depressed)	N	Paradigm	Method	Amygdala	vlPFC
Malhi et al. 2004 (73)	D = 11 HS = 10	Captioned pictures (negative, neutral, positive): passive view	1.5T Whole-brain	↑ L	↓[a]
Chen et al. 2006 (66)	M = 8 D = 8 HS = 8	Faces (fear, sad, happy): implicit and explicit processing	3T Whole-brain	NS	NS
Altshuler et al. 2008 (82)	D = 11 HS = 17	Faces (negative): match	3T Whole-brain	NS	↓ L/R
Almeida et al. 2010 (84)	D = 15 E = 15 HS = 15	Faces (fear, happy, sad): label	3T ROI: amygdala	NS[b]	N/A
Van der Schot et al. 2010 (69)	M = 12 E = 18 D = 12 HS = 18	Faces (neutral, happy, fearful): masked and unmasked	1.5T ROI: amygdala, OFC	NS	↓ L/R

vlPFC = ventral lateral prefrontal cortex; D = depressed subjects; HS = healthy subjects; M = manic subjects; E = euthymic subjects; ROI = region of interest; OFC = orbitofrontal cortex; L = left; R = right; NS = not significant; N/A = not applicable.
[a] Decrease observed in another region of the inferior frontal gyrus (Brodmann's area 9) in the negatively valenced condition.
[b]Trend level increased amygdala in bipolar depressed group.

stimuli (84). The remaining studies of emotion processing in bipolar depression did not consistently find limbic hyperactivation. Using a paradigm to assess implicit versus explicit facial emotion recognition, one study found that bipolar depressed subjects tended to overactivate fronto–striato–thalamic regions, but not the amygdala, in response to fearful faces (66). A more recent study using masked fearful and happy faces found no significant differences between bipolar depressed and healthy subjects in the amygdala, but did find frontal hypoactivation, including of the vlPFC, in bipolar depressed subjects (69). This decreased frontal lobe activation in bipolar depressed subjects was found in other studies using a variety of emotion paradigms (69, 73, 82) and represents a more consistent finding in bipolar depression.

A few studies suggest reduced limbic activation in bipolar depression. Unlike the previous studies, hyperactivation of amygdala was not seen in bipolar depressed subjects while performing a face-matching task. In fact, there was no significant amygdala activation seen in bipolar depressed subjects (82), while reduced activations were seen in bilateral vlPFC [Brodmann's area (BA) 47] and right dlPFC, and increased activation was reported in mPFC (BA10) (82) in response to faces with negative emotions. Using functional connectivity techniques, Versace et al. (83) found increased right and left amygdala–vlPFC connectivity in bipolar depressed subjects compared to healthy subjects while viewing sad faces, but decreased amygdala–OFC connectivity in response to happy faces. These results are consistent with findings in mania that also show reduced amygdala–vlPFC connectivity (27, 75) and suggest alterations in healthy functional connectivity in both mania and depression. The latter study (75) followed BP subjects from initial manic mood state to the presentation of a depressed mood and found that functional connectivity between the amygdala and frontal region changed as subjects changed mood states. Another study, examining subjects in all three mood states, also found decreased frontal–limbic connectivity while viewing fearful and happy faces (76).

These studies suggest hypoactivation of the frontal lobe, especially the vlPFC, and abnormal connectivity between frontal and limbic structures that may vary as a function of mood state and of the specific emotion stimuli used. Abnormal amygdala activation is reported across many of the studies, but the direction of the finding may be dependent on the specific stimuli used. Significant increased amygdala activation was reported in only one study that utilized negative-captioned pictures (with the pictures themselves designed to evoke no emotional response) (73). Studies using negative emotional faces as stimuli found no significant amygdala differences (66, 69), with one finding a trend level of decreased amygdala activation (82) between bipolar depressed and healthy groups. Given the multiplicity of paradigms used, the small sample sizes used (all studies had $n \leq 15$), and the heterogeneity of results, it is difficult at this time to discern a clear functional neuroanatomical circuit abnormality consistently demonstrated during bipolar depression, apart from frontal hypoactivation and decreased frontal–limbic connectivity. Clearly, more studies are needed, with larger sample sizes.

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Euthymia

The enduring impairments in euthymic patients provide clues to the brain regions involved in the primary pathology of BP or that are impacted by the presence of the disorder. Studies suggest that patients with BP continue to display mood instability or increased mood reactivity even in the absence of an acute episode (78, 79). An enduring brain region abnormality in euthymia may affect the neural circuit involved in homeostatic mood regulation. This abnormality, in turn, may predispose BP patients to relapse into acute mood states.

Of the 14 studies examining emotion processing in euthymic BP subjects, the majority – nine studies – found no significant differences between euthymic BP subjects and healthy subjects in amygdala activation (85–90). Table 3 provides a summary of the current fMRI literature of emotion processing and regulation in bipolar euthymia. It is interesting to note that all of the studies that found no significant amygdala differences between euthymic BP and healthy groups employed negative emotional faces as stimuli. Two of these studies examined medication effects and neither found significant effects of medication on amygdala activation in bipolar euthymia (88, 90). By contrast, three studies found increased amygdala activation in the right hemisphere using an emotional Stroop task (91) and an emotional face task (74), and in the left hemisphere using happy faces (92). Finally, two studies found decreased amygdala activation in euthymic BP subjects compared to healthy comparison subjects. One study, using the emotional Stroop task, found decreased left

Table 3. Amygdala and prefrontal cortex (PFC) results of functional magnetic resonance imaging (fMRI) emotion studies in bipolar euthymia

Study (Euthymic)	N	Paradigm	Method	Amygdala	vlPFC
Malhi et al. 2005 (93)	E = 12 HS = 12	Emotional Stroop: (affective versus neutral)	3T Whole-brain, GSR	↓ L	↓ L
Lagopoulos and Malhi 2007 (91)	E = 10 HS = 10	Emotional Stroop: (negative versus neutral)	3T Whole-brain, GSR	↑ R	↓ L/R (PFC)
Malhi et al. 2007 (89)	E = 10 HS = 10	Faces (fear, disgust, neutral): label	3T Whole-brain	NS	↓ L
Wessa et al. 2007 (101)	E = 17 HS = 17	Emotional Go/NoGo: (fear, happy, and neutral faces)	1.5T Whole-brain	NS	NS
Hassel et al. 2008 (88)	E = 19 HS = 24	Faces (happy, fear, neutral): label	3T Whole-brain ROI: amygdala	NS	↓ L/R (PFC)
Robinson et al. 2008 (90)	E = 15 HS = 16	Faces (negative): match and label	3T Whole-brain ROI: amygdala, vlPFC	NS	↑ R
Almeida et al. 2009 (85)	E = 21 HS = 25	Faces (happy, neutral): label	3T Whole-brain DCM: parahippocampus, vmPFC, dlPFC	NS	NS
Hassel et al. 2009 (87)	E = 14 HS = 16	Faces (happy, fear): label	3T ROI: amygdala, dPFC	NS	↓ R
Almeida et al. 2010 (84)	D = 15 E = 15 HS = 15	Faces (fear, happy, sad): label	3T ROI: amygdala	NS	N/A
Chen et al. 2010 (74)	M = 12 E = 9 HS = 12	Faces (happy, sad, disgust, fear, surprise, anger): rate intensity	1.5T ROI: amygdala, OFC	↑ R	↑ R
Surguladze et al. 2010 (92)	E = 20 HS = 20	Faces (happy, fear): label	Whole-brain ROI: amygdala	↑ L[a]	NS
Van der Schot et al. 2010 (69)	M = 12 E = 18 D = 12 HS = 18	Faces (neutral, happy, fearful): masked and unmasked	1.5T ROI: amygdala, OFC	↓ L/R	↓ L/R
Lagopoulos and Malhi 2011 (99)	E = 11 HS = 11	Faces (neutral or disgust): label	3T fMRI, GSR	NS	NS

vlPFC = ventral lateral prefrontal cortex; E = euthymic subjects; HS = healthy subjects; D = depressed subjects; M = manic subjects; GSR = galvanic skin response; ROI = region of interest; DCM = dynamic causal modeling; vmPFC = ventromedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; dPFC = dorsal prefrontal cortex; OFC = orbitofrontal cortex; L = left; R = right; NS = not significant; N/A = not applicable.

[a]For intense happy faces only.

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amygdala activation in a small sample (n = 12) of euthymic BP women (93); and another study, using masked emotional faces, found bilateral amygdala hypoactivation (69). From the literature, it appears that abnormalities of amygdala activation are more consistently found during acute mood states than during euthymia.

Similar to these fMRI studies, positron emission tomography (PET) studies also suggest frontal–limbic circuit abnormalities in euthymic BP patients. One PET study measured regional blood flow while euthymic subjects completed a novel motor sequence task (94). Patients displayed a unique pattern of widespread limbic network activity in response to the new sequence, whereas healthy subjects activated a spatial attention circuit. Patients failed to allocate attentional resources and instead utilized limbic circuitry (i.e., suggesting arousal rather than attention) to alter their performance on a non-emotional task. This pattern of BP subjects showing significantly greater engagement of limbic regions in response to non-emotional tasks was seen in a number of fMRI studies (95–97). This finding was also replicated in an fMRI study using medication-free euthymic patients (98). These common abnormalities during euthymia – of increased limbic activation during non-emotional tasks and decreased vlPFC activation during emotion processing – suggest enduring trait deficits of BP. Thus, euthymic BP subjects appear to engage limbic structures similarly during emotional tasks, but differ from control subjects by activating these same regions even in the absence of emotional stimuli.

While amygdala function appears normalized during emotion tasks, many of the previous studies reported abnormalities in frontal functioning during emotion processing in euthymia. Many studies, using a variety of emotional stimuli, found decreased frontal activation in bipolar euthymia (69, 88, 91, 93, 99), most frequently in the vlPFC. Decreased activation in the vlPFC during emotion processing was also observed in two studies of BP subjects in euthymic or depressed mood states (100). However, not all studies have reported this frontal hypoactivation. Two studies found increased activation in the right vlPFC (74, 90) in euthymic compared to healthy subjects while viewing emotional faces. It is less clear why these two studies found frontal abnormalities in the opposite direction from those in the majority of studies; differences in task design [region of interest (ROI) in one versus whole-brain analysis] and subjects (small sample size of n = 9 in the other) likely contributed to the vlPFC differences between these two studies and the other 12.

Decreases in dlPFC activation were also reported in a number of these studies (88, 91), perhaps suggesting impairment in frontal regions beyond those predictably activated in studies of emotion in healthy subjects. Furthermore, five studies of emotion in bipolar euthymia found hyperactivation of striatal regions, including the bilateral caudate (99, 101), left (92) and right (87) putamen, and left caudate/putamen (88). Imaging studies using affective induction and emotion regulation paradigms that are designed to identify regions most sensitive to provocation by external stressors may help to elucidate the mechanisms mediating clinical relapse into mania or depression. Neural correlates of these clinical trait or disease diathesis markers are just beginning to be characterized.

Comparison of mood states

Very few neuroimaging studies have directly compared BP groups in different mood states using the same scanning protocol and fewer still have compared the same subjects while in different mood states. To date, only five studies have directly compared BP groups using the same emotional paradigm (66, 69, 74, 83, 85) and only one used the same subject in two mood states (74). Manic subjects, when compared directly to bipolar depressed subjects, show hyperactivation of the amygdala and left fusiform gyrus, a region important in the processing of emotional faces, during an implicit emotion processing task (66). Other studies, however, found less amygdala activation in manic compared to euthymic subjects (74) and between manic and depressed subjects (69). Both of these studies included both positive and negative emotional faces. Chen et al. (74), as the only study that compared the same subjects during mania and euthymia, found a significant effect of time × group only in the left amygdala/hippocampus. From studies of healthy subjects, amygdala activation is most robust during the viewing of fearful and then sad faces (16). As such, the direction of amygdala abnormalities seen in mania may depend on the specific valence of the stimuli used. Future studies that specifically explore these issues are needed, especially using larger sample sizes of subjects in multiple mood states.

Manic subjects, compared to depressed subjects, show hypoactivation in frontal lobe regions, including the vlPFC (66, 69) and dlPFC (69). These same abnormalities are found in BP subjects across mood states, but these studies provide evidence that the most profound hypoactivation is seen during mania and that although frontal lobe

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activation normalizes during euthymia, it remains hypoactive compared to healthy comparison subjects. This similar pattern of more pronounced abnormalities emerging during the acute mood states is seen in bipolar depression. Bipolar depressed subjects compared to bipolar euthymic subjects showed hyperactivation of the left amygdala to sad faces (85) and of the right amygdala to masked emotional faces (69). Bipolar depressed subjects, but not bipolar euthymic subjects, also showed decreased amygdala–vlPFC functional connectivity compared to healthy subjects while viewing happy faces (83).

Our group, using a well-validated emotional faces paradigm in previously published groups of manic (63) and depressed (82) BP subjects, performed direct comparisons of these manic and depressed groups, as well as a direct comparison to bipolar euthymic subjects. Prior published work showed significant amygdala hyperactivation in manic compared to healthy subjects. Manic subjects (n = 9) also showed significant amygdala hyperactivation compared to both bipolar depressed (n = 11) and bipolar euthymic (n = 9) subjects (Fig. 1). Unfortunately, there were too few subjects in the same mood state to provide any meaningful analysis, but, clearly, future longitudinal studies will provide valuable information in the state versus trait issues that are raised in BP neuroimaging studies.

Limitations

Some of the limitations of the bipolar neuroimaging literature are general to neuroimaging, while others are specific to this patient population. Problems with neuroimaging studies, particularly with psychiatric populations, include the use of relatively small sample sizes that may have underpowered the studies. Also, neuroimaging is a relatively new science and uses techniques not yet perfected, leading to interpretations of data that are not yet fully understood (102). As such, careful attention to the design of studies, with the limitation of each specific neuroimaging method in mind (i.e., PET studies have poor spatial resolution, while fMRI studies have poor temporal resolution) is required. For example, the use of global signal scaling in many studies has been called into question, since use of such a statistical method may greatly distort findings in structures related to emotional processing. This distortion may contribute to conflicting findings (103). In addition, the amygdala and vlPFC are regions sensitive to signal loss and image distortions from susceptibility near the air/tissue borders (104). As such, it is important to recognize that the regions most implicated in BP are also the same regions most challenging to image using fMRI. The use of sequences optimized to minimize such artifacts, such as using a short echo time, are essential in emotion studies.

LOW RESOLUTION COLOR FIG

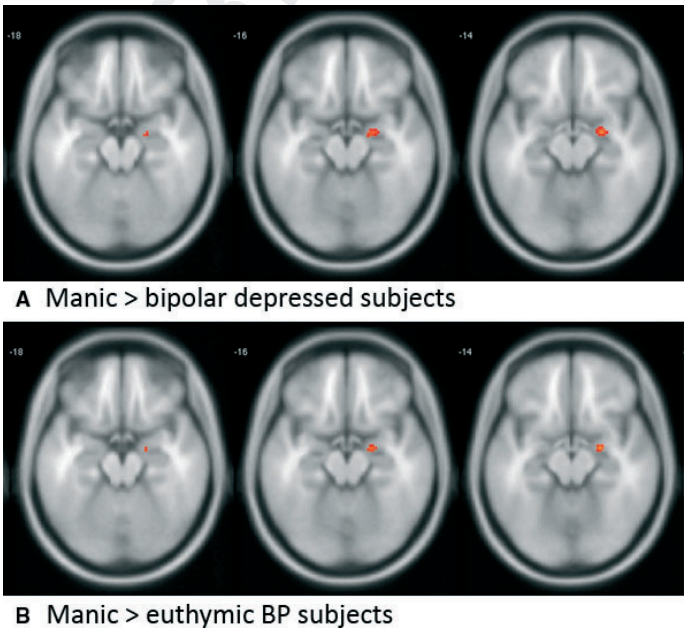

Fig. 1. Manic bipolar disorder (BP) subjects (n = 9) show significant amygdala hyperactivation compared to (A) bipolar depressed subjects (n = 11) (x = –24, y = –8, z = –14) and (B) euthymic BP subjects (n = 9) (x = –18, y = –6, z = –16) during an emotional face matching task.

Other limitations are present that are inherent in working with this population. The first and perhaps most pertinent is the effect of medication on both the neuroimaging data and the interpretation of findings. Virtually all studies using BP populations include patients on a variety of psychotropic medications, which limits the ability to compare across groups. Studies that try to avoid this complication by using unmedicated populations (98) also limit the ability to generalize their findings, since these unmedicated patients may be an unrepresentative subset of BP patients. The ethics of stopping or delaying medication for research make it difficult to design a controlled, double-blind study that could provide more definitive results. Also, certain medications may affect blood flow, which is indirectly measured in fMRI studies (105), may affect activation in select regions (7), and can change gray matter volume in BP patients (106). Thus, medication issues must be considered when reviewing, interpreting, and generalizing findings from studies. However, it is possible that future studies could recruit patients as soon as they present with acute mood systems and carefully monitor the effects of medication on both mood state and neural functioning.

The emotion dysregulation seen in both depression and mania suggests possible dysfunction of neural networks involved in emotion regulation and network interconnectivity. Connectivity among neural networks involved in emotion regulation remains understudied in BP, despite the fact that emotion dysregulation is a defining criterion for the disorder. Future studies that incorporate functional and structural connectivity will help to deepen our understanding of the underlying pathophysiology in BP.

Another problem, not specific to neuroimaging, is the use of heterogeneous populations by including multiple mood states in a single study without accounting for state differences (70, 107–109) or failing to report the mood state (96). A similar confound arises from combining BP-I/BP-II patients (110). In addition, many studies either fail to report the presence/absence of other psychiatric comorbidities, including substance abuse and attention-deficit hyperactivity disorder (ADHD), or fail to take these comorbidities into account in the analysis. BP subjects may also be heterogeneous with regard to illness duration, number of prior acute mood episodes, and past history of psychosis. These potential confounds make it difficult to differentiate trait differences from medication and illness effects on fMRI activation patterns. Nevertheless, neuroimaging provides a useful and powerful tool to extend the existing psychological literature and is essential for linking underlying anatomical and functional changes to those seen behaviorally.

Conclusions

Despite the heterogeneity of findings, most studies converge with regard to the amygdala and vlPFC. In subjects with BP, the amygdala shows *hyperactivation* in mania, *variable activation* during depression, and *normal activation* during euthymia when compared to healthy subjects. The other regions that show state-dependent findings include the ACC, which shows reduced activation during mania (64, 68, 72), and the striatum, which shows increased activation during euthymia (87, 88, 92, 99, 101). These regions are involved in the emotion salience network and the response inhibition network, respectively, and have been implicated in BP.

The trait-related characteristic seen that endures across mood states is hypoactivation of the ventral PFC. Reduced vlPFC activation has been reported in the literature in manic, depressive, and euthymic mood states (111–113). The vlPFC may therefore participate in aspects of emotional processing and expression that are not exclusively related to a specific valence of emotion. Lack of normal functioning in this region might result in dysregulation of mood to either pole, and dysfunction of the vlPFC–amygdala circuit may represent a trait-dependent phenomenon of BP. Lesion studies support the role of the vlPFC in emotion regulation, as impairment is associated with manic and depressive symptoms (111, 112). Decreased vlPFC thus may be a trait-related characteristic that endures across mood states in BP (114) and may participate in the modulation of emotion not exclusively related to a specific valence of emotion. Both structural and functional neuroimaging studies demonstrate abnormalities in frontolimbic circuits in both the manic and depressive symptoms seen in BP (6, 7).

The vlPFC hypoactivation in subjects with BP has been reported not only in emotion regulation tasks, but also in other tasks requiring cognitive control, including response inhibition studies in mania during both emotion (71) and neutral contexts (115). Similar hypoactivation of the vlPFC is seen during bipolar depression (57) and euthymia (57, 91, 116, 117). Chronic vlPFC hypoactivation and abnormal modulatory control of limbic structures may help to explain the continued mood instability and reactivity that BP patients exhibit even in the absence of an acute episode (78, 79). It is possible that dysfunction of the frontal–limbic circuit increases the vulnerability of BP subjects to lapse into mood episodes, as numerous

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studies have shown stressful life events predict relapse into acute mood states in BP (see 117 for a review). This vlPFC hypoactivation may represent a state-independent neural marker of BP, responsible for a range of cognitive and emotional differences in BP subjects compared to their healthy counterparts. The vlPFC may act as a brake on the experience of extreme emotion in mania and as an accelerator in depression. Hypoactivation of this region in BP may leave this region unable to regulate limbic structures when it is needed. vlPFC dysfunction may result in a dysregulation of emotional reactions and the susceptibility of BP subjects to lapse into mania or depression.

Future aims

As previously noted, few existing studies involve medication-free subjects. Thus, the issue of medication is a confound in almost all of the existing literature, and future studies are needed to clarify specifically the effects of medication on the various neurocognitive domains measured. Questions also remain as to what extent cognitive dysfunctions are present before illness onset. Longitudinal studies following at-risk subjects might not only help to answer these questions, but also address whether cognitive impairments are stable or progressive, and help us to develop insight into the process underlying the mechanism for switches into acute mood states. Traditional fMRI methods combined with more nascent technologies, such as resting-state neuroimaging, will continue to shed light on trait deficits in BP and help us to define the functional neuroanatomical underpinnings of this complex condition.

Disclosures

LLA has received past funding from Forest Laboratories (advisory board honoraria, March 2008), Sepracor (advisory board honoraria, January 2010), and Eli Lilly & Co. (consultant, September 2010). JT does not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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