

Bipolaroids: functional imaging in bipolar disorder

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Objective: To evaluate the literature pertaining to the use of functional magnetic resonance imaging (fMRI) in bipolar disorder research.

Method: A search for papers published in English in journals from 1984 onwards was conducted using MedLine and EMBASE with the following terms: functional neuroimaging or fMRI and depression or bipolar disorder. In addition, retrieved papers and literature known to the authors was also scrutinized for further relevant reports.

Results: The research findings from 26 articles are tabulated and the results from 10 articles dealing specifically with bipolar disorder are discussed in detail.

Conclusion: fMRI is a useful tool for investigating bipolar disorder. Preliminary studies point to trait and state abnormalities involving structures known to be associated with the generation and modulation of emotion. The patterns of fMRI activation are different to those found in healthy subjects and patients with major depression. FMRI studies are likely to provide valuable insights into the pathophysiology of bipolar disorder.

**G. S. Malhi,^{1,2,3} J. Lagopoulos,^{1,2,3}
A. M. Owen,⁴ L. N. Yatham⁵**

¹School of Psychiatry, The University of New South Wales; ²The Mood Disorders Unit, Black Dog Institute, Prince of Wales Hospital; ³Mayne Clinical Research Imaging Centre, Prince of Wales Medical Research Institute, Sydney, Australia; ⁴MRC Cognition and Brain Sciences Unit, Cambridge, UK; ⁵University of British Columbia, Department of Psychiatry, UBC Hospital, Vancouver, British Columbia, Canada

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Dr Gin S. Malhi, Mayne Clinical Research Imaging Centre, Prince of Wales Medical Research Institute, Barker Street, Randwick, NSW 2031, Sydney, Australia
E-mail: g.malhi@unsw.edu.au

Introduction

For more than a century scientists around the world have made a concerted effort to localize brain function using all manner of research tools. This quest to unravel the mind has been boosted by the rapid development of neuroimaging technology and its widespread availability and application in both research and clinical settings. In psychiatry, schizophrenia and dementia have probably received the most attention thus far, with research in major depression now also gaining momentum. In contrast, bipolar disorder has been largely overlooked with few neuroimaging studies focusing specifically on mania or bipolar depression. One of the reasons for this is that clinically it is difficult to disentangle bipolar disorder from major depression and schizophrenia because of overlapping phenomenology. For instance, patients presenting for the first time with acute mania can sometimes be difficult to differentiate from drug-induced or schizophrenia-related psychoses and are often loosely categorized as having 'first-episode

psychosis'. Similarly, patients that present initially with bipolar depression are regarded and managed as having major depression until they manifest clear-cut symptoms of mania or hypomania. As a consequence, definitive diagnosis is often delayed, in some cases by up to a decade. Hence in most early studies patients with bipolar disorder were included largely for comparison. The majority of such studies used positron emission tomography (PET) and single photon emission computed tomography (SPECT) to examine cerebral blood flow. Collectively, they identified decreased anterior paralimbic and cortical activity signalling a prefrontal cortical deficit in depressed patients that attenuates with successful treatment of the illness. Additionally, in depressed bipolar patients there is increased metabolism in subcortical paralimbic structures (1), a finding that supports the limbic-cortical dysregulation model of depression (2, 3), in which dorsal neocortical hypofunction can produce ventral paralimbic overactivity (4). Clearly interpretation of these findings in patient populations is difficult and necessitates an understanding

of the normal functional anatomy of emotion in health. However, a detailed discussion of this is beyond the scope of this article, which focuses on functional neuroimaging; a broad term that incorporates a number of technologies such as positron emission tomography (PET), single photon emission computed tomography (SPECT), spectroscopy and functional magnetic resonance imaging (fMRI).

Aim of the study

fMRI is underutilized in bipolar disorder research and therefore the aim of this review is to summarize the data from studies that have been conducted using fMRI and provide some directions for future research.

Material and methods

A search for papers published in English in journals from 1984 onwards was conducted using MedLine and EMBASE with the following terms; functional neuroimaging or fMRI and depression or bipolar disorder. A total of 109 articles were identified. Reviews of the literature and articles that did not focus specifically on dissecting emotion as relevant to depression/bipolar disorder were excluded. Additional searches of the literature known to the authors furthered the number of articles available and a total number of 58 papers were eventually identified. Of these only 26 studies using fMRI were examined in greater detail. Papers using other technologies or examining non-clinical aspects of emotion were excluded. However, because of diversity within this field of research and the variable use of keywords it is possible that some relevant articles may have been overlooked.

Results

Functional Magnetic Resonance Imaging (fMRI)

Functional information using MRI can be acquired in a number of ways (Table 1). The most commonly used fMRI technique is that of BOLD-fMRI, which exploits the paramagnetic properties of oxyhaemoglobin and de-oxyhaemoglobin, effectively using the latter as a contrast agent. Brain activity results in oxygen uptake and increases blood flow. This alters the MRI signal, allowing the regions in which such change occurs to be identified using BOLD-fMRI. In this manner brain activity can be investigated by presenting stimuli to subjects whilst in the scanner. This advance in technology, just over a decade ago, has

allowed unprecedented access to the working brain. The absence of radiation makes it extremely safe and has the added advantage of permitting repeat scans within subjects, a desirable attribute in clinical studies. Functional MRI also provides excellent spatial and temporal resolution — imaging the brain every few seconds, however, by virtue of this it is exquisitely sensitive to movement and this limits its use in certain patient populations. It is also important to note that fMRI measures relative changes in blood flow and that as a consequence stimuli used in experiments must vary so as to generate detectable change.

In recent years the use of fMRI to investigate clinical populations has increased and many studies have successfully examined the neuronal mechanisms that subservise emotion in healthy subjects and patients with major depression and bipolar disorder (Table 2).

fMRI studies in major depression

The majority of functional imaging studies in mood disorders have examined major depressive disorder, and this body of research that includes many PET studies has repeatedly implicated several key brain regions in the generation and modulation of emotion, both in health and disease. On the basis of such studies investigators have developed useful functional models of major depression (3,5), which in turn have themselves been tested using fMRI. Prominent amongst these brain regions are the medial prefrontal cortex, anterior cingulate and amygdala, however, it is the connectivity of these regions and their ‘functionality’ that is perhaps of greater interest.

fMRI studies in bipolar disorder

In comparison to major depression, neuroimaging research in bipolar disorder is still in its infancy and is limited by the lack of a theoretical/functional model that has both research validity and clinical salience. However, several research groups have made a promising start and bipolar fMRI research is slowly gathering pace.

Table 1. Functional information from the different types of fMRI

Functional MRI	Parameter measured
Blood-oxygenation level-dependent (BOLD)	Regional differences in oxygenated blood
Perfusion	Regional cerebral blood flow
Spectroscopy	Cerebral metabolites
Diffusion-weighted	Movement of water molecules

Table 2. Mood disorder-related fMRI studies

Study	Subjects	fMRI Stimuli	Principal Findings	Interpretation
Schneider <i>et al.</i> 1997 (38)	12 healthy volunteers (7 male). (Mean age: 29.7)	Sad and happy facial expressions	Activation during mood induction in L amygdala and cingulum	Implicated amygdala and cingulum in emotion and recognition of facial expressions
Beauregard <i>et al.</i> 1998 (39)	7 patients with major depression (3 male) (Mean age: 42) & 7 controls (3 male). (Mean age: 45)	Passive viewing of emotional (sad) and neutral film clips	Widespread activations in both patients and controls	Implicated R cingulate gyrus and L medial prefrontal cortices in major depression
Baird <i>et al.</i> 1999 (40)	12 healthy adolescents (5 male). (Mean age: 13.9)	Ekman & Friesen fearful faces	Amygdala activation in response to fearful faces	Demonstrated the role of the limbic system in affect recognition in particular the role of the amygdala in adolescents
Loeber <i>et al.</i> 1999 (6)	10 patients with bipolar disorder (8 male) (Mean age: 28), 10 patients with schizophrenia (8 male) (Mean age: 30), 10 healthy volunteers (8 male) (Mean age: 30)	Nil	Significant differences in mean cerebellar blood volume. Schizophrenia patients > Controls > Bipolar patients	Implicated cerebellum in affect modulation on the basis of connections between cerebellum and limbic and paralimbic regions and hypothalamus
Teasdale <i>et al.</i> 1999 (14)	6 healthy volunteers (3 male) (Mean age: 29.8)	Passive viewing of Picture-pairs. Positive, negative and captioned neutral affect	Significant affect-related activations in medial prefrontal cortex, anterior cingulate, thalamus and insula	Implicated medial prefrontal cortex in cognitive processing of affective meaning
Elliott <i>et al.</i> 2000 (41)	12 healthy volunteers (4 male). Age range: 24–59	Variants of go/no-go task incorporating happy and sad distracters	Inferior frontal gyrus and dorsal anterior cingulate (AC) activation was associated with meaning of words. Happy targets activated ventral AC and happy and sad targets activated subgenual cingulate	Medial prefrontal regions important in healthy emotional processing
Yurgelun-Todd <i>et al.</i> 2000 (8)	14 patients with bipolar disorder (7 male) (Mean Age: 31.6), and 10 healthy volunteers (5 male) Mean age: not available	Recognition of happy and fearful affect	Diminished activation in R prefrontal region and increased activation in L amygdala in bipolar patients	Reduction of frontal cortical function in patients with bipolar disorder is associated with affective and attentional processing deficits
Sheline <i>et al.</i> 2001 (42)	11 patients with major depression (5 male) Mean age: 40.3) and 11 healthy volunteers (5 male) (Mean age: 39.8)	Masked faces paradigm-happy, fearful and neutral stimuli	Depressed patients had exaggerated activation to all stimuli, greater for fearful faces only in L amygdala. This diminished with successful treatment	Depressed patients have L amygdala hyperarousal, which normalises with antidepressant treatment
Berthoz <i>et al.</i> 2002 (43)	16 healthy volunteers (all male). Eight with alexithymia and 8 without. (Mean age: 21.5)	Positive, negative and neutral pictures from the IAPS	Alexithymic subjects had less left medio-frontal-paracingulate cortex activation in response to negative stimuli and more anterior cingulate, mediofrontal cortex and middle frontal gyrus activation in response to positive stimuli	Alexithymia, a personality trait that contributes to affect regulation, is associated with valence-dependent differences in the anterior cingulate and mediofrontal cortices during emotional stimuli processing
Smith <i>et al.</i> 2002 (44)	10 patients with major depression in remission (all female) (Mean age: 38.5) and 8 healthy volunteers (all female) (Mean age: 31.9)	Noxious & non-noxious thermal stimuli associated with differential colour display	Relative to controls, patients recovered from depression had reduced cerebellar response during anticipation of noxious as compared with non-noxious stimuli	Abnormal cerebellar function could be a marker of vulnerability to recurrent depression
Siegle <i>et al.</i> 2002 (45)	7 patients with major depression (4 male) (Mean age: 34.3) and 10 healthy volunteers (4 male) (Mean age: 36.1)	Valence identification task: positive, negative and neutral words (from ANEW) and Sternberg memory task	Depressed patients had sustained amygdala responses to negative words whereas controls responded to all stimuli but the responses were not sustained	Depression is associated with sustained activity in brain regions associated with emotional processing
Kumari <i>et al.</i> 2003 (15)	6 patients with treatment-resistant major depression (all female) (Mean age: 47); and six healthy volunteers (all female) (Mean age: 44)	Passive viewing of Picture-captioned pairs. Positive, negative and neutral affect	Patients had altered responses in anterior and subgenual cingulate, medial frontal, middle temporal, hippocampal, and parahippocampal gyri and some subcortical nuclei	Reduced medial/middle prefrontal and hippocampal activity may account for positive affect disturbances and temporal lobe hyperactivity for negative affect disturbances in treatment resistant depression

Table 2. Continued

Study	Subjects	fMRI Stimuli	Principal Findings	Interpretation
Davidson <i>et al.</i> 2003 (46)	12 depressed patients (4 male) (mean age: 38.2) and 5 healthy volunteers (4 male) (mean age: 27.8)	Negative, positive and neutral stimuli from IAPS-presented before, during and after response to an antidepressant	Group by time interactions were found in response to negative vs. neutral stimuli in L insular cortex and L anterior cingulate	Functional changes in the neural circuitry that subserves negative affect in depression can be altered in two weeks of treatment
Posse <i>et al.</i> 2003 (47)	6 healthy volunteers (2 male) (Mean age: 27.8)	Visual presentation of sad and neutral faces coupled with instructions for self-induced sadness	Real-time fMRI with feedback of activation to subjects resulted in L amygdala activation that correlated with self-rating	Amygdala activation may be closely associated with self-induced sadness
Keightley <i>et al.</i> 2003 (48)	6 healthy volunteers (five male) (Mean age: 23)	Passive viewing of positive and negative emotional faces and pictures	Indirect and direct processing ere represented by more dorsal prefrontal and parietal activity, respectively	Brain activity during processing of emotional content is critically task and stimulus dependent. The pattern of activity in the emotional network can be influenced by cognitive factors
Caligiuri <i>et al.</i> 2003 (9)	24 patients with bipolar disorder –15 depressed and 9 manic(12 male) (Mean age: 45.7; 13 healthy volunteers (7 male) (Mean Age 35.6)	Visual cue ('Go') prompted thumb flexion and reaction time was measured	Both manic and depressed patients had elevated responses in cortical and subcortical regions. In comparison to depressed bipolar subjects manic patients showed increased L globus pallidus but decreased R globus pallidus activity	Affective state in bipolar disorder is related to dysfunction of inhibitory regulation within the basal ganglia
Mitterschiffthaler <i>et al.</i> 2003 (49)	7 depressed patients with anhedonia (all female) (mean age: 46.3) and 7 healthy controls (all female) (Mean age: 48.3)	Positive and neutral pictures selected from the IAPS	Differential activation in the frontal, lobe thalamus, basal ganglia and insula	Implicated these structures in the pathophysiology of anhedonia and depression
Blumberg <i>et al.</i> 2003 (10)	36 patients with bipolar disorder (18 male): 11 manic /hypomanic /mixed, 10 depressed and 15 euthymic (Mean age: 39.1). 20 healthy volunteers (10 male) (Mean age 31.7)	Colour-naming Stroop task	Ventral prefrontal cortex (VPC) increase in signal blunted on R-side in patients with elevated mood but exaggerated on L-side in depressed patients in comparison to euthymic patients. Patients vs. controls: mood state independent blunted activation in rostral region of L-VPC	Posited that bipolar disorder is associated with a trait abnormality in L-VPC and that additional VPC abnormalities may be state dependent
Blumberg <i>et al.</i> 2003 (11)	10 adolescents with bipolar disorder(4 male) (Mean age: 13.6), and 10 healthy adolescents for comparison (4 male) (Mean age: 14.6)	Colour-naming Stroop task	Significantly increased L putamen and thalamus activation in patients. Ventral striatum activation correlated positively with depressive symptoms	Suggestive of subcortical frontalstriatal circuit dysfunction in adolescents with bipolar disorder. Contrast with adult pattern of activations suggests developmental pathophysiology
Hugdahl <i>et al.</i> 2004 (50)	12 patients with major depression (5 male) (Mean age: 32.8), 12 patients with schizophrenia (6 male) (Mean age: 32.4) and 12 healthy volunteers (5 male) (Mean age: 31.0)	Number-based vigilance task and a simple arithmetic task	Both patient groups had equal performance impairment. The patients with schizophrenia but not those with depression had less prefrontal brain region activation. Schizophrenia patients had greater parietal activation	Schizophrenia patients failed to recruit frontal lobe cognitive processes (unlike depressed patients) and compensated by use of the parietal lobe
Michael <i>et al.</i> 2004 (19)	5 patients with major depression and 6 patients with bipolar depression (mean age: 50.6) and 11 healthy gender-matched volunteers (Mean age: 34.8)	Binaural auditory stimulation consisting of digitally generated pulsed sine tones	6 patients had habituation in the auditory cortex and 5 had an abnormal habituation pattern	Abnormal pattern of habituation in subgroup of depressed patients may indicate a functional deficit in auditory processing-occurring in depression
Lawrence <i>et al.</i> 2004 (16)	12 patients (euthymic and depressed) with bipolar disorder; 9 patients with major depression (MDD) and 11 healthy volunteers (19 male and 13 female) (age-matched; overall-mean age: 41)	Faces with varying intensity of one emotion (sadness, happiness or fear) vs. neutral expressions	Patients with bipolar disorder had increased subcortical and VPC responses to all 3 emotions whereas patients with MDD had diminished responses to fear and happiness. Depression severity correlated with hippocampal responses in both patient groups	Bipolar patients demonstrated increased subcortical and ventral prefrontal cortical responses to both positive and negative emotional experiences in comparison to patients with major depression and healthy controls

Table 2. Continued

Study	Subjects	fMRI Stimuli	Principal Findings	Interpretation
Malhi <i>et al.</i> 2004 (12)	10 bipolar depressed patients (all female) (Mean age: 34.3) and 10 age and gender matched healthy volunteers (Mean age: 34.0)	Passive viewing of Picture-captioned pairs. Positive, negative and neutral affect	Activation in bipolar depressed patients included additional subcortical regions-amygdala, thalamus, hypothalamus and medial globus pallidus	Depressed bipolar patients recruit additional subcortical limbic systems for emotional evaluation
Mitchell <i>et al.</i> 2004 (18)	11 patients with bipolar disorder (mean age: 42.8), 12 patients with schizophrenia (Mean age: 45.7) and 13 healthy volunteers (Mean age 32.2)	Pure prosodic stimuli comprising happy, sad and neutral sentences	Patients with bipolar disorder had less bilateral superior temporal gyri activation in response to pure emotional prosody and greater activation of the L superior temporal gyrus in response to unfiltered emotional prosody	Patients with bipolar disorder and schizophrenia may display some L-lateralization of the normal R-lateralized temporal lobe response to emotional prosody
Irwin <i>et al.</i> 2004 (51)	12 depressed patients (4 male) (Mean age: 38); 14 healthy volunteers (7 male) (Mean age 28)	Passive viewing of neutral and negatively valenced visual stimuli from IAPS	Bilateral dorsal amygdala region activation in both patients and healthy controls	Along with PET data suggested that depressed patients have greater amygdala interhemispheric connectivity
Malhi <i>et al.</i> 2004 (13)	10 bipolar hypomanic patients (all female) (Mean age: 37.1) and 10 age and gender matched healthy volunteers (Mean age: 35.8)	Passive viewing of Picture-captioned pairs. Positive, negative and neutral affect	Activation in hypomanic patients included additional subcortical regions-caudate and thalamus	Hypomanic patients recruit additional subcortical limbic systems for emotional evaluation

IAPS: International Affective Picture System

One of the first studies to examine bipolar disorder patients using fMRI (6) actually used a dynamic susceptibility contrast agent coupled with MRI so as to gain greater accuracy when determining regional blood volume. This study compared bipolar, and schizophrenic patients and healthy volunteers. The mean cerebellar blood volume in bipolar patients was found to be less, and in schizophrenic patients more, than that in controls, especially in the tonsillar region. This perhaps reflects connectivity between the cerebellum and the hypothalamus and the paralimbic and limbic regions via which the cerebellum may be able to modulate affect. Indeed other studies have implicated the cerebellum in the processing of emotion (7).

Yurgelun-Todd *et al.* (8) were possibly the first group to specifically examine affect modulation in bipolar disorder using fMRI. Their paradigm involved a happy and fearful facial affect recognition task. Bipolar patients had reduced right prefrontal area activation and increased left amygdala activation in response to fearful stimuli suggesting the disruption of frontal networks in bipolar disorder. More specifically, the study implicated the dorsolateral prefrontal cortex in affective processing in bipolar disorder and found that female patients in particular showed a differential pattern of activation when having to discriminate facial affect.

Examining primarily the role of the motor cortices, basal ganglia and thalamus in bipolar

disorder, Caligiuri *et al.* (9) used a manual reaction time task to identify cortical and subcortical activity in bipolar patients in different phases of the illness. Both manic and depressed patients had elevated cortical and subcortical responses. However, the latter is of particular interest as it supports the hypothesis of a subcortical mechanism in bipolar disorder in which there is a dysfunction of inhibitory regulation within the basal ganglia. Importantly this study also highlighted the fact that medication can alter fMRI responses, suggesting that antipsychotics and mood stabilizers may normalize cortical and subcortical hyperactivity, and that therefore these are important confounds to consider.

A robust pair of studies by Blumberg *et al.* (10,11) also identified subcortical activation in bipolar patients but perhaps more significantly successfully partitioned trait and state effects. The first study (10) involved adults in all three phases of bipolar disorder and used the colour-naming Stroop task to predictably activate prefrontal and dorsal anterior cingulate cortices across all groups. However, in comparison to euthymic patients, the ventral prefrontal cortex increase in signal was blunted on the right side in patients with elevated mood but exaggerated on the left side in depressed patients. Furthermore in comparison to healthy controls, patients had blunted activation in a rostral region of the left ventral prefrontal cortex that was independent of mood state and spatially distinct. The authors thus suggested that bipolar

disorder is associated with trait abnormality in the left ventral prefrontal cortex and that additional lateralized abnormalities may relate to the valence of the mood episode. Using the same fMRI task this group also examined adolescents with bipolar disorder. This unique study (11) identified increased activation in the left thalamus and putamen in bipolar adolescents in comparison to healthy controls supporting the hypothesis of subcortical dysfunction in bipolar disorder. A correlation between signal increases in the ventral striatum and depressive symptoms was also reported; however, the abnormalities found in adults were absent. This suggests that prefrontal dysfunction maybe developmental and that it emerges during adolescence. Using consistent stimuli across experiments in this manner is clearly helpful as it allows better comparison be it across ages, gender, phenotypes or phases.

Malhi *et al.* (12,13) did the same and adopted a picture-caption cognition-based mood induction paradigm that had been successfully used in fMRI experiments in healthy subjects (14) and patients with major depression (15), to investigate the patterns of activation in bipolar patients when depressed (12), and hypomanic (13). These studies found that the fMRI patterns of activation in bipolar patients differed from healthy subjects and patients with major depression, and that bipolar patients additionally recruited subcortical brain regions for the process of emotional evaluation. Specifically, hypomanic patients activated the caudate and thalamus and bipolar depressed patients activated the thalamus, amygdala, hypothalamus and medial globus pallidus. Thus bipolar patients may have state or trait-related prefrontal cortical dysfunction and subcortical activation may be an attempt to compensate when advanced prefrontal cognitive processing is no longer sufficient.

Another study that corroborates this pattern of fMRI responses used faces with varying intensity of fearful, happy or sad emotion to contrast the patterns of activation across depressive phenotypes. Lawrence *et al.* (16) found that, in comparison to patients with major depression and healthy controls, patients with bipolar disorder had increased subcortical and ventral prefrontal cortex responses to both positive and negative emotional experiences. Furthermore, depression severity in both patient groups correlated with hippocampal responses. This is particularly interesting because the hippocampus plays a pivotal role in the cognitions of depression and is susceptible to stress (17). Clearly there are commonalities across phenotypes and this is not particularly

surprising given the phenomenological overlap between bipolar disorder and major depression and between bipolar disorder and schizophrenia.

A recent study (18) that compared patients with bipolar disorder, patients with schizophrenia and healthy volunteers using emotional prosody found that patients with bipolar disorder had less bilateral superior temporal gyri activation in response to pure emotional prosody and greater left superior temporal gyrus activation in response to unfiltered emotional prosody. Like patients with schizophrenia bipolar patients may therefore have left lateralization of normally right lateralized temporal lobe responses to emotional prosody. Another study that also points to some auditory dysfunction in bipolar patients used aural stimuli (19) to examine healthy volunteers and depressed patients with both bipolar and major depression. However, because patient groups were not separated it is unclear to what extent, if any, the abnormal habituation pattern found in the depressed group indicates a functional deficit in auditory processing in bipolar disorder.

A useful working model for bipolar disorder similar to the functional models for major depression is yet to be formulated however, studies that have examined patients with bipolar disorder thus far do seem to suggest a pattern (20,21) of abnormal affective responsiveness in particular, a difficulty with emotional discrimination (8). This is interesting and highlights the importance of functional imaging investigations examining bipolar disorder emotional processing in the context of their interplay with cognitive and executive functions.

As reviewed above, functional neuroimaging studies utilizing a wide variety of affective stimuli have begun to identify the brain regions that are key to the emotional experiences of bipolar disorder. However, many of these findings are as yet unreplicated as successive experiments have used different stimuli and stimuli presentation paradigms, across a number of demographic and clinical variables.

Discussion

With respect to unipolar major depression, a relatively consistent finding across functional neuroimaging studies is that of diminished blood flow to the dorsal prefrontal cortex (BA9), which improves with effective treatment (4,7). Responses in this region have also been reported in healthy subjects during memory-driven sadness and happiness (22) suggesting that the right prefrontal cortex (BA9) is an important destination for limbic

projections and that it perhaps plays a role in modulating attention in affective states. Specifically, BA9 activations may indicate emotional awareness that entails attention to internal emotional state (23) and involves greater cognitive emotional processing. The medial prefrontal cortex may therefore have a general role in emotional processing that involves the modulation and evaluation of emotion and emotion-dependent decision-making (24,25).

Another region that is integral to emotional decisions and is functionally pivotal to the experience of emotion by virtue of its reciprocal connections to the orbitofrontal cortex, amygdala, insula, septal nuclei and hypothalamus is the anterior cingulate (26). Functional activation and resting-state treatment studies (7,22,27), like neuropsychological and lesion studies (28,29) strongly implicate the subgenual cingulate (BA25) in the pathogenesis of clinical depression, a region that is involved in autobiographical script-induced sadness (7,22,30). However, the latter is not definitive as, opposed to sadness, it may simply process the cognitive aspects of internally generated emotion.

The amygdala, a region of great interest, is activated across a wide range of functional imaging studies but especially those that impinge upon the detection of environmental threat and the experience of fear (31). It is possible however, that its function is more general, determining for instance the 'dangerousness' of affective stimuli or indeed their salience irrespective of valence. Hence in addition to fearful and aversive stimuli (32,33), sad and happy affect (34) can also produce amygdala activation in functional imaging experiments in healthy volunteers and patients with major depression and bipolar disorder.

As regards fMRI research in bipolar disorder there are several unique aspects of the illness worth noting. By its very nature bipolar disorder is a phasic illness and hence capturing patients in comparable and reproducible states is all the more difficult. This also means that trait and state abnormalities can be easily confused especially because the phases themselves are not always pristine. Indeed it has been suggested that mixed affective states are much more common than originally anticipated and may even be the norm (35). Consequently, for many patients euthymia is very difficult to define and for some there is no true baseline that they can confidently gauge. This is critical in longitudinal neuroimaging studies of bipolar disorder, which are needed to further dissect state and trait markers. However, even well defined euthymic patients are not ideal because most are maintained on long-term

prophylactic medication. Withdrawal of medication such as mood-stabilizers for the purposes of research can precipitate an episode of depression or mania and this is hard to justify given that illness incurs a significant risk of suicide and regaining stability is not guaranteed (36,37). However, many research groups have managed to successfully overcome some of these obstacles and there is now a growing interest in functional neuroimaging research in bipolar disorder. From the studies conducted to date, the majority of findings are at best speculative as they incorporate the confounding effects of long-term medication and past substance misuse. All that can be said somewhat tentatively, is that in comparison to healthy individuals, adults with bipolar disorder appear to have a ventral prefrontal cortex dysfunction and that during emotional processing they are more likely to engage subcortical networks. Furthermore, some of these 'functional deficits' may well be developmental.

Conclusion

Functional neuroimaging and in particular fMRI has provided researchers with truly exciting possibilities. With a genuine confluence of technology and cognitive neuroscience, sophisticated neuropsychological stimuli can now be presented within the scanner environment to generate specific emotions. This has allowed investigators to 'visualize' the brain regions involved in emotional appreciation. The anterior cingulate is strongly implicated — perhaps as a decision-making modulator impinging upon brain regions that generate emotions cognitively, such as the orbitofrontal and medial prefrontal cortices. These brain regions via iterative connections with limbic and subcortical centres, such as the thalamus, regulate emotional processing while at the same time accommodating contextual and environmental information. Dysfunction in any of these brain regions, or indeed their connections, could manifest in the many subtypes of affective disorders and perhaps explain how patients with bipolar disorder not only swing from one extreme to the other but also have mixed states in which they experience composites of emotions. The differential patterns of activation that are emerging from fMRI studies of bipolar disorder may eventually prompt revision of our typology of mood disorders. More significant, however, is the fact that functional imaging is likely to provide valuable insight into the pathophysiology of bipolar disorder and enable not only better diagnosis but also the development of better management strategies. In order to achieve this

more homogenous populations need to be examined and longitudinal fMRI studies are necessary.

Declaration of interest

One or more authors have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest: Grant/Research Support: Eli Lilly & Company. Consultant: AstraZeneca, Eli Lilly & Company, GlaxoSmithKline, Wyeth. Lecture Honoraria: AstraZeneca, Eli Lilly & Company, Pfizer, GlaxoSmithKline, Wyeth, Organon.

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