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Advances in functional MRI research in bipolar disorder: from the perspective of mood states

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ABSTRACT

Bipolar disorder is characterised by recurrent and alternating episodes of mania/hypomania and depression. Current breakthroughs in functional MRI techniques have uncovered the functional neuroanatomy of bipolar disorder. However, the pathophysiology underlying mood instability, mood switching and the development of extreme mood states is less well understood. This review presents a comprehensive overview of current evidence from functional MRI studies from the perspective of mood states. We first summarise the disrupted brain activation patterns and functional connectivity that have been reported in bipolar disorder, irrespective of the mood state. We next focus on research that solely included patients in a single mood state for a better understanding of the pathophysiology of bipolar disorder and research comparing patients with different mood states to dissect mood state-related effects. Finally, we briefly summarise current theoretical models and conclude this review by proposing potential avenues for future research. A comprehensive understanding of the pathophysiology with consideration of mood states could not only deepen our understanding of how acute mood episodes develop at a neurophysiological level but could also facilitate the identification of biological targets for personalised treatment and the development of new interventions for bipolar disorder.

INTRODUCTION

Bipolar disorder is a chronic and debilitating mental disorder characterised by recurring episodes of depression and mania/hypomania. Typically, bipolar depression manifests low mood, loss of interest and energy and psychomotor retardation, whereas bipolar mania/hypomania presents extreme happiness, irritability, increased activity and energy and distractibility. Even in euthymic states, patients with bipolar disorder show subthreshold mood symptoms and mild cognitive deficits. The illness is associated with lifelong conditions, a high risk of recurrence and high rates of coexisting psychiatric conditions.[1] However, partially due to the poor understanding of the pathophysiological mechanisms of bipolar disorder, the diagnosis of the illness is often delayed and its management is unsatisfactory, leading to a poor prognosis and increased mortality. The identification of objective diagnostic biomarkers will not only aid in our understanding of the pathophysiological mechanisms underlying bipolar disorder but will also facilitate biological targets for personalised treatment and the development of new interventions for bipolar disorder.[2]

Recent advances in functional MRI (fMRI) technologies have led to accumulating evidence of brain functional alterations in bipolar disorder.[3] Despite this advance, conflicting results are common in neuroimaging studies of bipolar disorder due to various factors, such as methodological approaches and patient heterogeneity. Some studies have proposed that functional alterations are highly sensitive to current mood states in bipolar disorder.[2 4] Studies examining at least both acute mania and depression have reported that brain activation alterations in the limbic–striatal circuit,[5 6] the medial prefrontal cortex (mPFC)[7] and the dorsolateral prefrontal cortex (dlPFC)[8] may manifest as trait markers of bipolar disorder-related dysfunction. In contrast, others have noted state-dependent effects regarding emotional valence.[9 10] Such diverse findings emphasise the need for a better understanding of the pathophysiology underlying differences in mood states, for this could lead to improved prediction of mood state shifts and the identification of more precise potential therapeutic targets regarding specific mood states. Thus, the aim of this review is to scrutinise previous fMRI studies on bipolar disorder from the perspective of mood states. Specifically, the focus will be both on studies conducted in patients with specific mood states and on studies comparing patients between mood states.

OVERVIEW OF FUNCTIONAL NEUROIMAGING STUDIES IN BIPOLAR DISORDER

Earlier task-related fMRI studies mainly focused on assessing abnormal neural circuits involved in emotion processing and regulation. These investigations suggest that the frontal-limbic circuit plays a key role, including the ventromedial prefrontal cortex (vmPFC), ventrolateral prefrontal cortex (vlPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and amygdala, and contributes to mood instability in bipolar disorder.[11 12] In recent decades, some brain activation research on bipolar disorder has focused on reward circuits, suggesting that an overactive left-lateralised ventral striatum (VS)–vlPFC reward processing circuitry may be associated with bipolar disorder.[2] Although less attention has been paid to substrates of the functional neuroanatomy underlying cognitive deficits, existing evidence suggests patients with bipolar disorder show decreased activation in the ACC and prefrontal cortex (PFC) during cognitive control paradigms.[11]

Resting-state fMRI studies have built upon traditional task-related findings, mainly by examining regional homogeneity (ReHo) and intrinsic fluctuation of brain regions showing abnormal activation and connectivity disturbances between these regions. Prominent among these are reports of ReHo changes in the middle frontal gyrus (MFG), the hippocampus/parahippocampus, the motor cortex, the precuneus and the insula and altered amplitude of low-frequency fluctuations in the caudate and putamen. Weaker functional connectivity among the frontal-limbic system has also been reported in the resting state,[13 14] including the amygdala, vlPFC, dlPFC, mPFC and OFC. In the last decade, a substantial body of contemporary connectomic studies has identified abnormal connections within and among the default mode network (DMN),[15] frontoparietal network (FPN) and salience network.[16]

FUNCTIONAL NEUROIMAGING STUDIES IN INDIVIDUALS WITH BIPOLAR DISORDER DURING A SINGLE MOOD STATE

Most previous fMRI studies in bipolar disorder have been conducted only in euthymic patients with bipolar disorder. However, some studies have suggested that these patients exhibit altered functional activity compared with patients in a depressive or (hypo)manic episode.[17 18] In addition, other studies have uncovered specific functional network abnormalities associated with manic symptoms.[19] It seems that functional abnormalities are highly sensitive to current mood states in bipolar disorder.[4] Thus, considering the potential confounds of mood states, Strakowski *et al* have proposed that symptomatically homogeneous patients with bipolar disorder should be recruited to give insight into the pathophysiology of bipolar disorder.[4] Regarding this consideration, many fMRI studies have solely investigated a specific mood state. In the following section, we will describe advances in fMRI studies that included patients with bipolar disorder in a single mood state.

Functional neuroimaging studies of bipolar depression

Brain functional alteration during emotional tasks

Research on bipolar depression has been investigating the neural substrates underlying the psychopathological symptoms of the illness. Brain circuits involving emotional processing have been the research hot spot for years.

Numerous studies have investigated the amygdala response to emotional stimuli in bipolar depression.[12] During the reception of emotional stimuli, including emotional faces, voices and scenes, patients with bipolar depression have shown reduced activation in the bilateral OFC but comparable activation in the amygdala compared with healthy controls.[20] Another study estimated brain activation while matching negative facial expressions (eg, panic and fear) in unmedicated patients with bipolar depression and found decreased activation in the right amygdala.[21] Given the inconsistencies, investigators began investigating the underlying mechanisms of abnormal emotional processing by applying finer emotional paradigms. One study observed increased amygdala responses to mild expressions of happiness but decreased amygdala responses to intense expressions of happiness.[22] However, increased amygdala responses to intense expressions of fear were also observed. Almeida *et al*[23] included patients with bipolar depression, bipolar euthymia, unipolar depression and healthy controls. They found that amygdala hyperactivation was specifically present in patients with bipolar depression and was specifically associated with mildly negative facial expressions. These findings suggest that abnormal amygdala activation in bipolar depression may be associated with the emotional intensity and valence (positive or negative) of emotional stimuli.[12 23]

Patients with bipolar depression also exhibit abnormal amygdala–PFC functional connectivity during the processing of emotional information. For example, decreased negative functional connectivity between the right vlPFC and right amygdala was found in unmedicated patients[21]; reduced functional connectivity in both the top-to-bottom connection (medial OFC-amygdala) and the bottom-to-top connection (amygdala-medial OFC) was found during the recognition of happy faces.[24] However, patients with bipolar depression showed enhanced resting-state functional connectivity within the FPN, including the brain regions closely associated with emotional processing, such as the vlPFC and dlPFC.[25] These studies suggest that prefrontal dysfunction and dysfunctional amygdala–prefrontal connectivity are not only present during emotional processing but are also functional features of the underlying brain activity in patients with bipolar depression.

Brain functional alterations during cognitive tasks

While abnormal activation associated with deficits in response inhibition has garnered increased attention in

patients with (hypo)mania, task-fMRI studies in bipolar depression have primarily focused on the neural substrates of impaired working memory. Notably, while performing the n-back working memory task, patients with bipolar depression exhibited a significant reduction in activation within the dlPFC,[26] including the MFG and superior frontal gyrus (SFG),[27] which was associated with the severity of depression.[26] Intriguingly, when subjected to sadness induction, patients with bipolar depression exhibited a sadness-specific hyperactivation in the dlPFC.[28] Besides, failure of deactivation in the mPFC was observed in both bipolar depression and unipolar depression,[26 29] with a more pronounced extent evident in bipolar depression compared with its unipolar counterpart.[29]

Aberrant activation in the posterior cingulate cortex,[30] inferior frontal gyrus (IFG) and MFG[31] was observed during tasks that require response inhibition, such as the Stroop task and the Go/No Go task. However, the existing findings are divergent. An underexplored region, the parietal cortex, was reported to be overactivated during the performance of visuospatial planning, a task requiring executive function.[32]

Altered resting-state functional connectivity and spontaneous brain activity

Resting-state neuroimaging research on bipolar depression particularly focuses on the discrimination between bipolar depression and unipolar depression (ie, major depressive disorder) because of the similar clinical profiles of the two diseases that often lead to misdiagnosis. The misdiagnosis may result in inappropriate treatment, a poor prognosis and functional outcome, and medical burden. Thus, increasing investigations are emerging to identify neural markers in neuroimaging measures for distinguishing bipolar depression from unipolar depression. At the brain network level, patients with bipolar depression present enhanced functional connectivity in functional brain networks,[33] such as the within-FPN functional connectivity[25] and the FPN-salience network functional connectivity.[34] Evidence of the functioning of the DMN is mixed.[15] At the region level, several pieces of evidence from Wang *et al* indicate that the insula and cerebellum may be key regions underexplored.[35] A most recent meta-analysis revealed significant convergence in the right ventral posterior cingulate cortex when evaluating the effect of a depressive state on resting-state differences.[36] Interestingly, no significant results were found in bipolar (hypo)mania or bipolar euthymia.[36] Despite this progress, we should notice the diversity of neuroimaging measures and the heterogeneity of study samples, which makes interpreting these findings more challenging.

Functional neuroimaging studies in bipolar mania/hypomania

Brain functional alterations during emotional tasks

During processing emotional faces, normal individuals present a negative functional connectivity between the amygdala and vlPFC, suggesting that the vlPFC may exert an inhibitory effect on the amygdala in the cognitive assessment of emotions.[37] Interestingly, this functional connectivity is blunted in patients with (hypo)mania and is associated with reduced mood control. Mounting evidence has found that compared with healthy controls, patients with (hypo)mania exhibit amygdala hyperactivation[38] and hypoactivation in the vlPFC and lateral OFC[39] when processing external emotion-related information. Foland *et al* found decreased negative functional connectivity between the amygdala and vlPFC, suggesting a reduced regulation of the vlPFC on the amygdala, leading to hyperactivation of the amygdala, as evidenced by an abnormal perception of emotional states.[38]

However, other studies did not observe amygdala hyperactivation in emotional tasks. Strakowski *et al* observed hypoactivation instead of hyperactivation of the amygdala in patients with (hypo)mania while performing a continuous performance task with emotional and neutral distracters.[39] The authors suspected that discrepant findings among studies most likely reflect differences among tasks. A meta-analysis, including eight task-based MRI studies of bipolar (hypo)mania (both emotional processing and cognitive functional tasks), did not observe increased amygdala activation, further suggesting that the effects of varying paradigms on amygdala activation are clearly warranted.[20] However, only a small number of studies on bipolar disorder were included in this meta-analysis; thus, the low statistical validity may account for the non-significant finding.[20]

Brain functional alterations during cognitive tasks

Blunted activation in the vlPFC and lateral OFC is seen not only during emotional processing but also during cognitive processing. Earlier studies and recent meta-analyses have shown blunted activation in the vlPFC[40] and the lateral OFC[41] during tasks that require response inhibition, specifically involving the right IFG and left MFG, etc.[42] A previous study compared the brain activation differences between patients with (hypo)mania and normal controls during the performance of an emotional Go/No Go task. Compared with orthographic targets, controls showed a greater vlPFC response to semantic targets, suggesting they were working harder to inhibit irrelevant information under the semantic condition. In contrast, patients with (hypo)mania exhibited a comparable vlPFC response to the semantic condition compared with the easier orthographic condition. This finding suggests that patients with (hypo)mania fail to activate the vlPFC under a higher-level response inhibition condition.[43]

Goikolea *et al*[44] examined the functional changes during a working memory task in patients with first-episode mania for the first time. During the two-back task, controls exhibited attenuated DMN activation, while patients with (hypo)mania showed less deactivation in the anterior part of the DMN, which parallels findings from a recent meta-analysis.[45] Moreover, patients with (hypo)mania showed increased functional connectivity between the vmPFC and SFG, indicating a failure to shift

from their mental activity to ongoing cognitive tasks. The increased functional connectivity between the vmPFC and SFG may serve as a compensatory mechanism for completing working memory tasks.

Altered resting-state functional connectivity and spontaneous brain activity

Functional connectivity between the cortex and subcortical nuclei, such as the amygdala[46 47] and the striatum,[48] was found to be aberrant in patients with (hypo)mania. Subcortical functional connectivity, such as functional connectivity between the serotonin (5HT)-related raphe nuclei and the basal ganglia/thalamus, was found to be reduced,[49] suggesting a potential link between disconnection of neurotransmitter areas and the pathophysiology of bipolar disorder. At a brain network level, patients with (hypo)mania show reduced functional connectivity within the DMN[50 51] and elevated functional connectivity within the dorsal attention network.[52] Altered intrinsic brain activity in the sensorimotor network (SMN) is found to be associated with the severity of manic symptoms.[53] Lee *et al*[19] employed a novel imaging analysis method, lesion network mapping, to investigate the shared network disruptions of people with manic symptoms with diverse pathophysiological processes and replicated the findings in patients with (hypo)mania. The authors revealed that the key regions of the brain network disruptions causing manic symptoms are the dorsolateral prefrontal, temporal and orbitofrontal cortices. These disruptions suggest shared circuit dysfunction associated with manic symptoms irrespective of diverse pathogenesis. Findings from another excellent work using the lesion network mapping method with a larger sample size also support that of Lee *et al*, where mania-causing lesions showed a unique pattern of functional connectivity to the OFC, inferior temporal gyrus and frontal pole.[54]

Functional neuroimaging studies in bipolar euthymia

Brain functional alterations during emotional tasks

There are discrepancies in the amygdala responses to emotional stimuli in bipolar euthymia. Most studies found no significant differences in amygdala activation between euthymic patients with bipolar disorder and healthy controls.[12 55 56] However, a meta-analysis revealed amygdala overactivation in euthymic patients in emotional tasks,[20] such as the facial expression recognition task. Euthymic patients also show activation differences in other regions in the limbic circuit involved in emotional processing, such as the hippocampus[57] and the striatum.[55] Malhi *et al* found an abnormal response to the face of fear in the hippocampus rather than the amygdala in euthymic patients. Malhi *et al*[57] proposed that the amygdala activates the fusiform gyrus and occipital lobe during the emotional processing of fear. However, the activation of the latter regions was intact in this study; therefore, amygdala hyperactivation was not observed. Interestingly, the authors proposed that hippocampal hyperactivation of the fear memory may reflect negative memories of previous episodes or past stressful events.[57] Furthermore, Hassel *et al*[55] observed hyperactivation of the left putamen and caudate nucleus when facing happy faces. Considering that the striatum is involved in the processing of joyful emotions, the hyperactivation of these regions may be associated with reward sensitivity in patients with bipolar disorder.

Despite the absence of acute episodes, euthymic patients show blunted frontal activity in emotion processing. The dlPFC activation is reduced during both automatic emotion processing and voluntary emotion regulation.[55 58] Moreover, euthymic patients consistently exhibit reduced vlPFC activation when passively gazing at emotional faces[58] or matching and labelling emotional faces.[56] Studies also reported decreased negative functional connectivity between the vlPFC and amygdala during downregulating emotional responses,[58] which is associated with the patient's emotions and external emotional stimuli.[59]

Brain functional alterations during cognitive tasks

Abnormal activation in the frontal lobe and insula is commonly implicated in bipolar euthymia during cognitive processing. BA47, the orbital part of the IFG, is a key part of the vlPFC. Several studies have found that BA47 is associated with the response inhibition capacity, with euthymic patients showing lower BA47 activation in response inhibition[42] and a negative correlation between its activation and the number of previous manic episodes in patients.[60] Insular hyperactivation has also been frequently reported in euthymic patients during a sustained attention task.[61 62] For example, Sepede G *et al*[62] found that patients and first-degree relatives showed a larger activation in the bilateral insula and posterior middle cingulate gyrus during error in target recognition, while the patients failed to activate the insular during correct target response. The insula is typically involved in emotion activation and monitoring, and its enhanced activation in non-emotional tasks suggests that patients may inappropriately allocate emotional resources during a non-emotional task.[61]

The PFC is considered a key brain region for working memory. Euthymic patients show reduced activation in the vlPFC and vmPFC in the working memory task paradigm.[63] Two studies[64] evaluated the working memory capacity of euthymic patients; the results suggested that the activation level of the PFC may be an underlying compensatory mechanism when completing cognitive tasks. That is, at a lower level of task difficulty, the PFC was found to be overactivated. By contrast, when the task difficulty increased, the PFC failed to compensate and showed decreased activation.

Altered resting-state functional connectivity and spontaneous brain activity

Convergent evidence based on independent component analysis has shown no significant differences in the functional connectivity within the DMN,[65 66] FPN[65]

and salience network[66 67] between euthymic patients and healthy controls, suggesting that the stability of resting-state functional connectivity in these brain networks may reflect a relatively stable emotional state during the euthymic state. However, abnormalities in the between-network functional connectivity have been found, such as between the FPN and the limbic networks[67] and between the cingulo-opercular and the cerebellar–midbrain networks.[66] Other studies have investigated seed-based functional connectivity alterations. Building on previous evidence related to emotional and cognitive tasks, the regions of interest that have been frequently investigated include the amygdala, mPFC, dlPFC, vlPFC, ACC and OFC.[68] Related findings indicate that localised functional connectivity alterations may be related to the persistency of subthreshold emotional symptoms[68] and mild cognitive impairment[69] in euthymic patients with bipolar disorder.

FUNCTIONAL NEUROIMAGING STUDIES COMPARING INDIVIDUALS WITH BIPOLAR DISORDER ACROSS DIFFERENT MOOD STATES

While including mood state-narrowly defined patients with bipolar disorder may help control for the potential confounds of symptomatic epiphenomena, including patients in different mood states simultaneously within a single sample may provide novel insight into the mechanisms underlying episodic symptomatology. What remain less clear are the differences between mood states and the extent to which mood states may share abnormalities. In other words, it is unclear which deficits are state specific and which are trait markers of bipolar disorder. Therefore, to better explore trait fMRI markers and state-dependent impairments, increasing numbers of studies have included patients with bipolar disorder in different mood states simultaneously, allowing for better homogeneity and more reliable conclusions (figure 1).

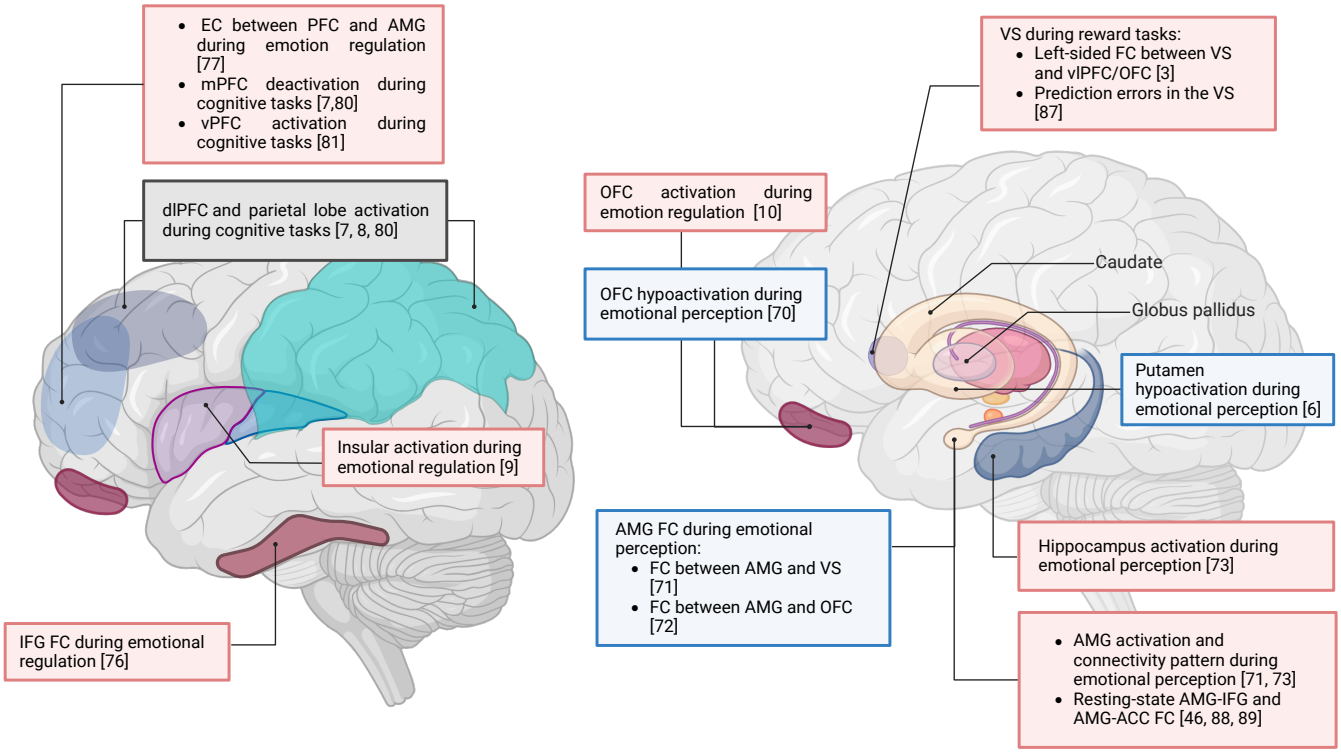

Figure 1 Schematic summary of trait and state-related functional neuroimaging measures in bipolar disorder. The blue boxes indicate trait-related measures. The red boxes indicate state-related measures. The grey box indicates measures reported to be both trait and state related. ACC, anterior cingulate cortex; AMG, amygdala; dlPFC, dorsolateral prefrontal cortex; EC, effective connectivity; FC, functional connectivity; IFG, inferior frontal gyrus; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; vPFC, ventral prefrontal cortex; VS, ventral striatum. This figure is made with https://www.biorender.com/.

Brain functional alterations during emotional tasks

Emotional paradigmsmi include emotion perception and emotion regulation. Investigators have explored the role of the prefrontal–limbic loop circuit in the transitions between mood states in terms of both processes.[12]

The perception of emotional information can be decomposed into two consecutive processes: the initial examination of the received emotional information and the subsequent understanding of the content of the information. The perception of emotional information is usually assessed using the following emotional tasks: passively viewing expressions, face affect matching, emotional face recognition/labelling and intensity of emotional face evaluation. These studies have demonstrated that patients with bipolar disorder show trait brain functional activations in the limbic system (eg, amygdala and striatum) and the PFC (eg, orbitofrontal, medial and lateral prefrontal cortex) in the perception of emotional information. These functional alterations seem to be independent of the mood states of bipolar disorder, which may shed light on the neural substrates of bipolar disorder. For example, patients with bipolar disorder showed hyperactivation in the putamen,[6] hyporesponsiveness to emotional stimuli in the OFC,[70] increased amygdala–VS functional connectivity to positive faces[71] and increased amygdala–OFC functional connectivity to sad faces.[72] However, findings of state-dependent impairments show low consistency, which may be due to the small number of studies and the difference in the mood states included in these studies. Man *et al* found that patients in a manic state showed a specific pattern of amygdala connectivity that is correlated with manic symptoms, which can be distinguished from patients in a depressive state.[71] A longitudinal follow-up study showed that, compared with the euthymic state, patients in a manic state showed enhanced responses in the hippocampus and amygdala during emotion perception.[73] Hence, the reduced activation of the hippocampus and amygdala during mania may underlie the emotion-processing deficits during mania, leading to clinical manifestations of elevated mood, emotional instability and behavioural disinhibition.

The underlying mechanism of emotional instability in bipolar disorder may be impaired emotion regulation. Therefore, several studies have explored changes in brain function in patients during emotional regulation and revealed several state-dependent changes underlying the switching of mood states in bipolar disorder.[74] Phillips *et al* refined emotional regulation into two processes: voluntary mood regulation, which is associated with the dorsal brain regions (eg, hippocampus, dorsal ACC and dorsal PFC), and automatic emotion regulation, which is associated with the ventral brain regions (eg, amygdala, insula, VS, ventral ACC and ventral PFC).[75] One can employ several strategies during emotional regulation: behavioural control, attentional control and cognitive change.[75] During voluntary emotional suppression, the insula and IFG show mood state-dependent activation changes, regardless of attentional control or cognitive change strategies.[9 76] During automatic emotion regulation, by requiring the patients to shift their attention from the emotional information of faces to non-emotional information, such as colour and sex, Perlman *et al*[77] found that the effective functional connectivity between the amygdala and PFC is a characteristic difference between patients in a depressive state and patients in a euthymic state. Liu *et al*[10] observed that the response to negative emotions in the OFC could distinguish between depressive and manic states. Specifically, patients in a (hypo) manic state showed hyperactivation of the cingulate gyrus and SFG, but patients in a depressive state did not, which could be explained by the contradiction between the individual's current mood state and external emotional stimuli.[5]

Brain functional alterations during cognitive tasks

Deficits of executive function in patients with bipolar disorder have also been extensively studied. The normal function of working memory requires dlPFC, IFG and parietal lobes of the FPN in normal individuals.[78] However, abnormalities in these brain regions may lead to working memory deficits in patients with bipolar disorder.[79] Both cross-sectional[7] and longitudinal studies[80] showed that patients in acute mood states exhibited reduced activation in the dlPFC and parietal lobe and failed deactivation in the mPFC, while patients in euthymic states exhibited normalisation of the dlPFC and parietal lobe and failed normalisation of mPFC.[80] This evidence indicates that reduced dlPFC and parietal lobe activation may serve as a state characteristic and failure of mPFC deactivation as a trait marker of bipolar disorder. However, conflicting evidence reports that aberrant dlPFC and parietal lobe activation seem to be trait markers.[8] The Stroop task is also commonly used to measure the patient's executive function. It requires attention and response inhibition. Using this task, Blumberg *et al*[81] found that activation changes in the rostral region of the ventral PFC could distinguish between depressive and manic states.

Brain functional alterations during reward tasks

Dopaminergic projections from the ventral tegmental area to the VS and PFC play an important role in reward processing. During reward anticipation, enhanced activation was evidenced in the vlPFC and OFC in patients in a (hypo)manic state,[82 83] suggesting an increased reward sensitivity during the manic state. Behavioural activation system theory proposes that this reward hypersensitivity represents a characteristic of bipolar disorder.[84] However, the abnormalities in reward-related activity during depressive and euthymic states remain unknown. The direction of striatal activation changes during reward anticipation and reward feedback varies considerably across studies.[85] To conclude, Phillips and Swartz proposed a left-lateralised nature of the reward circuitry. That is, abnormally elevated left-sided VS–vlPFC/OFC circuitry during reward anticipation and processing in adults with bipolar disorder may represent a neural

mechanism for heightened reward sensitivity.[2] Mason *et al*[86] proposed a plausible neurobiological mechanism for mood fluctuations, which claimed that mood state changes are driven by mood-biased reward prediction errors in the VS. For those with bipolar disorder, when in a high mood, the perceived reward value is better than the actual rewards, and vice versa. The tipping point is when the overhigh/overlow expectations result in a negative/positive surprise, triggering a depressive/manic cycle.[87]

Altered resting-state functional connectivity and spontaneous brain activity

In the resting state, patients with bipolar disorder also have abnormal functional brain connectivity patterns. Previous resting-state imaging studies have built on the findings of task studies and explored the functional connectivity abnormalities of these target brain regions, such as the amygdala and striatum. These studies reported impaired functional connectivity in the corticolimbic system during resting state. For example, reduced functional connectivity between the amygdala and IFG[88] and the amygdala and ACC[46 89] was reported in patients in a manic state compared with patients in other mood states. Furthermore, both patients with depression and those with (hypo)mania exhibit extensive functional connectivity abnormalities between the subregions of the striatum and frontal cortex, limbic system and midbrain structures.[48]

Martino *et al* conducted several studies on patients with bipolar disorder in all three mood states.[90–92] They found that patients in a manic state showed reduced functional connectivity within the DMN and increased functional connectivity within the SMN, with a positive correlation with the severity of manic symptoms. In contrast, patients in a depressive state showed increased functional connectivity within the DMN and reduced functional connectivity within the SMN, also with a positive correlation with the severity of depressive symptoms. Thus, the functional connectivity of the DMN and SMN appears to be a possible neural substrate of manic and depressive states. During the manic state, the diminished functional connectivity of the DMN is associated with racing thoughts and distraction, and the enhanced functional connectivity of the SMN is associated with high energy, increased speech rate and activity. During the depressive state, enhanced functional connectivity of the DMN is associated with rumination thinking and a focus on internal contents, and diminished functional connectivity of the SMN is associated with psychomotor inhibition.

FUNCTIONAL NEUROIMAGING STUDIES IN INDIVIDUALS WITH BIPOLAR DISORDER DURING A MIXED STATE

Functional neuroimaging investigations that specifically concentrate on mixed states in bipolar disorder are notably scarce. Several studies face limitations, such as very small sample sizes (≤5) for patients in mixed states.[93 94] Additionally, certain studies merged patients in a hypo/manic state and those in a mixed state into one group.[39 44 74 95 96] Notably, only one study, characterised by a somewhat larger sample size (n=8 for patients during a mixed state and n=10 for patients during a depressive state), examined functional brain alterations specifically in patients during a mixed state.[97] Preliminary evidence from this study showed that compared with patients in a depressive state, patients in a mixed state exhibited a distinct pattern of increased brain activation in the thalamus, cerebellum and IFG while performing a Go/No Go task.[97]

CURRENT THEORETICAL MODELS AND FUTURE DIRECTIONS

Early fMRI studies of bipolar disorder supported the role of corticolimbic circuit in bipolar disorder, which suggests that the aberrant prefrontal–striatal–pallidum–thalamic–limbic circuit may be the underlying pathophysiological mechanisms of mood switching in bipolar disorder. However, most of these studies are only preliminary investigations, with conflicting results that do not completely explain the mood fluctuations in bipolar disorder. This does not necessarily mean that the hypothesis related to the corticolimbic circuit is not applicable but rather suggests that emotional regulation circuits are complex and interactive and not explained by single or specific functional connectivity.[58]

As the classic hypotheses centred on the corticolimbic circuit are yet insufficient to explain the pathogenesis of bipolar disorder, several investigators have proposed new plausible neurobiological mechanisms in recent years. For example, Mason *et al*[86] proposed a neurocomputational model linking mood instability and reward dysregulation. Perry *et al*[14] described the phenotype of bipolar disorder as a 'psychosis of interoception'. Martino and Magioncalda [53] proposed a three-dimensional model of the relationship among psychomotricity, affectivity and thought. Northoff *et al*[98] have demonstrated that bipolar disorder can be traced to desynchronisation or dissociation between inner and outer time, which can be explained by opposite neuronal variability patterns in somatomotor and sensory networks. These frameworks emphasise the possible mechanism of mood switching/fluctuations and provide a new perspective of the pathological mechanisms of the disorder. The current theories of bipolar disorder tend to focus on the integrative role of large-scale brain networks rather than focusing solely on cognitive and emotional function in segregated, functionally specialised regions.[18] The DMN, FPN, SMN and salience networks are the most frequently reported brain networks in fMRI studies of bipolar disorder. The imbalance of the network connections may underlie the pathophysiology of bipolar disorder and contribute to the transition of mood states.

Table 1 Future neuroimaging research in bipolar disorder

Future directions	Study design	Methodological approaches or neuroimaging techniques
► Different subtypes of the disease	► Clarifying the definition of the subgroup population of patients with bipolar disorder and collecting homogeneous clinical samples	► Task activation, localised functional measures and seed-based functional connectivity are particularly useful when directly testing specific theoretical hypotheses.
► Different mood states of the disease	► Recruiting patients with first-episode mania or hypomania	► Data-driven voxel-based and connectome approaches could provide a more comprehensive view.
► The identification and mechanism of mixed features in bipolar disorder	► Recruiting unmedicated patients with bipolar disorder	► The use of multimodal imaging tools should be encouraged.
► Brain circuits underlying cognitive deficits	► Conducting studies of unaffected first-degree relatives of patients with bipolar disorder or their monozygotic twins	► The use of machine learning methods for imaging data analysis is recommended.
► Brain circuits related to reward dysfunction	► Conducting large, multicentre studies with larger sample size	
► Early identification, progression and vulnerability of the disease	► Conducting longitudinal studies across different stages of the disease	
► Neural markers in neuroimaging measures for discriminating between bipolar disorder and other diseases		

The heterogeneity of clinical samples between studies and the diversity of technical issues related to measuring brain function limit the interpretation of current imaging findings.[18] The inconsistency may arise from the differences in phenotype, mood states, comorbidity and disease course. With these considerations in mind (table 1), future research may benefit from studying the following: (1) different subtypes of the disease; (2) different mood states of the disease; (3) the identification and mechanism of mixed features in bipolar disorder; (4) brain circuits underlying cognitive deficits; (5) brain circuits related to reward dysfunction; (6) early identification, progression and vulnerability of the disease; (7) neural markers in neuroimaging measures for discriminating between bipolar disorder and other diseases; and (8) neural markers predicting treatment response in bipolar disorder.

Research design and neuroimaging techniques should be carefully considered based on the aim of the study. The following issues could be considered for future neuroimaging studies of bipolar disorder when designing a study: (1) clarifying the definition of the subgroup population of patients with bipolar disorder and collecting homogeneous clinical samples; (2) recruiting patients with first-episode mania or hypomania; (3) recruiting unmedicated patients with bipolar disorder; (4) conducting studies of unaffected first-degree relatives of patients with bipolar disorder or their monozygotic twins; (5) conducting large, multicentre studies with a larger sample size; (6) conducting longitudinal studies across different stages of the disease; and (7) conducting longitudinal studies across different mood states. When using a cross-sectional design, potential confounding factors, such as the subtype of the disease, mood state, psychotropic medication use, duration of illness and comorbidities, may impact the neuroimaging measures. Thus, the study should be designed to control for these potential confounding effects whenever possible. Despite the challenges in implementing a longitudinal study, longitudinal designs have relatively higher statistical power. Thus, longitudinal studies are essential for bipolar disorder research. In terms of the methodological approaches or neuroimaging techniques, the following strategies could be considered: (1) task activation, localised functional measures and seed-based functional connectivity are particularly useful when directly testing specific theoretical hypotheses and when validating findings at other research levels (eg, molecular and cellular levels), such as the neuroanatomy basis of a specific molecular pathway; (2) data-driven voxel-based approaches and connectome approaches could provide a more comprehensive view and prevent limited inferences about the potential roles of neural circuitry that are not a priori interest; (3) the use of multimodal imaging tools; and (4) the use of machine learning methods for imaging data analysis.

CONCLUSION

In conclusion, with its in vivo and non-invasive advantages, fMRI technology has become an important technique for studying the pathophysiological mechanisms of bipolar disorder. Recent fMRI studies in bipolar disorder

have provided preliminary neurobiological evidence for the pathogenesis of the disease. However, given the complexity of the disease, the heterogeneity of study samples and the various methodological approaches, current findings remain inconsistent. Studies dedicated to searching for objective markers for disease diagnosis still have a long way to go. Translational studies seeking to identify targets for therapeutic interventions will undoubtedly have further important implications for clinical investigations.

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