A Critical Appraisal of Neuroimaging Studies of Bipolar Disorder: Toward a New Conceptualization of Underlying Neural Circuitry and a Road Map for Future Research

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Objective: In this critical review, the authors appraise neuroimaging findings in bipolar disorder in emotion-processing, emotion-regulation, and reward-processing neural circuitry in order to synthesize the current knowledge of the neural underpinnings of bipolar disorder and provide a neuroimaging research road map for future studies.

Method: The authors examined findings from all major studies in bipolar disorder that used functional MRI, volumetric analysis, diffusion imaging, and resting-state techniques, integrating findings to provide a better understanding of larger-scale neural circuitry abnormalities in bipolar disorder.

Results: Bipolar disorder can be conceptualized, in neural circuitry terms, as parallel dysfunction in prefrontal cortical (especially ventrolateral prefrontal cortical)-hippocampal-amygdala emotion-processing and emotion-regulation circuits bilaterally, together with an "overactive" left-sided ventral striatal-ventrolateral and orbitofrontal cortical reward-processing circuitry, resulting in characteristic behavioral abnormalities associated with bipolar disorder: emotional lability, emotional dysregulation, and heightened reward sensitivity. A potential structural basis for these functional abnormalities is gray matter volume decreases in the prefrontal and temporal cortices, the amygdala, and the hippocampus and fractional anisotropy decreases in white matter tracts connecting prefrontal and subcortical regions.

Conclusions: Neuroimaging studies of bipolar disorder clearly demonstrate abnormalities in neural circuits supporting emotion processing, emotion regulation, and reward processing, although there are several limitations to these studies. Future neuroimaging research in bipolar disorder should include studies adopting dimensional approaches; larger studies examining neurodevelopmental trajectories in youths with bipolar disorder or at risk for bipolar disorder; multimodal neuroimaging studies using integrated systems approaches; and studies using pattern recognition approaches to provide clinically useful individual-level data. Such studies will help identify clinically relevant biomarkers to guide diagnosis and treatment decision making for individuals with bipolar disorder.

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Identifying biomarkers is a key goal of neuroimaging research in bipolar disorder, to provide objective neurobiological markers to increase diagnostic precision, identify markers of risk for future bipolar disorder, and pave the way for personalized treatments based on an enhanced understanding of underlying neuropathophysiological processes. Our purpose in this critical review is fourfold. We first provide a new conceptualization of neural circuitry abnormalities in bipolar disorder based on the most consistent themes emerging from neuroimaging research. We then identify areas of neuroimaging research that are needed to confirm this model of neural circuitry in bipolar disorder and elucidate as yet unknown neuropathophysiological processes in the disorder. Next, we describe other areas of bipolar disorder neuroimaging research that are currently understudied but will be critical in fully informing our understanding of the neuropathophysiology of bipolar disorder. We end the review with a suggested road map for future neuroimaging studies of bipolar disorder to provide a research framework that will permit elucidation of the neuropathophysiology of bipolar disorder and eventually identify biomarkers for diagnosis, risk identification, and targets to guide personalized treatment.

The Scope of Neuroimaging Studies in the Review

We integrate findings from all major studies of bipolar disorder that have used neuroimaging modalities, to provide a better understanding of larger-scale neural circuitry abnormalities in bipolar disorder. We first review functional

TABLE 1. Main Themes From Functional Neuroimaging Studies in Bipolar Disorder[a]

Theme 1	Abnormally decreased ventrolateral prefrontal cortex activity during emotion processing, emotion regulation, and response inhibition (9–19)
Theme 2	Abnormally increased amygdala, striatal, and medial prefrontal cortical activity and decreased functional connectivity between amygdala and prefrontal cortex, to positive emotional stimuli (9, 10, 20–22)
Theme 3	Abnormally increased amygdala, orbitofrontal cortex, and temporal cortical activity during nonemotional, cognitive task performance (23–28)
Theme 4	Abnormally increased left ventrolateral prefrontal cortex and orbitofrontal cortex, and ventral striatum activity during reward processing (40–45)

[a] See Table S1 in the online data supplement for more detailed information regarding the design and findings of the studies associated with each of these themes.

neuroimaging studies examining the functional integrity of neural circuits relevant to neuropathophysiological processes in bipolar disorder by measuring regional activity (using blood-oxygen-level-dependent signal change) and functional connectivity, using techniques that examine the extent of coupling of time series of activity between neural regions of interest. We also review studies examining gray matter regional volumes and diffusion imaging studies examining the structure of white matter in key tracts in these circuits, to help inform interpretation of functional abnormalities in these circuits in bipolar disorder. We include findings from studies examining intrinsic (resting state) connectivity in neural circuits of relevance to bipolar disorder. We have not included findings from studies using other methods (e.g., magnetic resonance spectroscopy or positron emission tomography) that examine regional neurotransmitter concentration and neuroreceptor density, given our focus here on larger-scale circuits relevant to bipolar disorder.

Major Themes That Emerge From Neuroimaging Studies

Theme 1: Abnormalities in Emotion-Processing and Emotion-Regulation Neural Circuitry

Emotional overreactivity and emotion dysregulation are characteristic symptoms of bipolar disorder (1). A large number of functional neuroimaging studies have thus examined emotion-processing and emotion-regulation neural circuitry function in individuals with bipolar disorder during performance of emotion-processing and emotion-regulation tasks (Table 1; see also Table S1 in the data supplement that accompanies the online edition of this article). This circuitry includes the amygdala, a region with a key role in emotion processing (2), threat, and salience perception (3), and prefrontal cortical regions implicated in emotion regulation. Emotion regulation has been categorized into voluntary and automatic (implicit) subprocesses, each implicating different prefrontal cortical regions, including the orbitofrontal cortex, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, and medial prefrontal cortex (encompassing the anterior cingulate cortex and mediodorsal prefrontal cortex) (4). Here, a predominantly lateral prefrontal cortical system (centered on the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex) mediates voluntary emotion-regulation subprocesses, while a medial prefrontal cortical system (including the orbitofrontal cortex, anterior cingulate cortex, mediodorsal prefrontal cortex, and hippocampus) mediates automatic emotion-regulation subprocesses. The dense connections between temporal limbic regions and the ventrolateral prefrontal cortex (5) and the role of this region in set shifting and reversal learning (6, 7) (inhibitory control processes common to voluntary emotion-regulation subprocesses) have motivated a focus on the ventrolateral prefrontal cortex in particular in research on voluntary emotion-regulation circuitry (for example, see reference 8).

Early neuroimaging studies of individuals with bipolar disorder indicated predominant patterns of abnormally elevated amygdala activity in response to emotional stimuli (9, 10) and abnormally reduced activity in lateral and medial prefrontal cortical regions supporting emotion regulation (4, 11). More recent studies have used more sophisticated functional connectivity techniques and identified fronto-subcortical functional abnormalities in adults with bipolar disorder during emotion regulation and inhibitory control during different mood states (12). Specifically, these studies report abnormally decreased inferior frontal cortical activity, especially in the ventrolateral prefrontal cortex, and abnormally decreased ventrolateral prefrontal cortex-amygdala functional connectivity during different positive and negative emotion-processing and emotion-regulation tasks in adults with bipolar disorder across different mood states (13–18). These findings parallel earlier findings of abnormally decreased ventrolateral prefrontal cortex activity and ventrolateral prefrontal cortex-amygdala functional connectivity during emotion processing in manic adults with bipolar disorder (19).

Theme 2: Abnormal Activity in Emotion-Processing Circuitry to Positive Emotional Stimuli

A second theme, building on the first, is a pattern of abnormally elevated amygdala and striatal and medial prefrontal cortical activity in response to positive emotional stimuli in individuals with bipolar disorder (9, 10) (Table 1; see also Table S1 in the online data supplement). More recent studies in adults with bipolar disorder have demonstrated abnormally increased amygdala and medial prefrontal cortex activity (20, 21) and abnormally decreased positive orbitofrontal cortex-amygdala effective connectivity bilaterally (22) in response to emotional—especially happy—faces, suggesting a dysregulated amygdala response to these stimuli. These findings may reflect an underlying attentional bias to positive emotional stimuli in bipolar disorder, predisposing to mania.

Theme 3: Abnormal Activity in Emotion-Processing Neural Circuitry During Performance of Nonemotional Tasks

A third theme is abnormal activity in emotion processing circuitry including the amygdala, orbitofrontal cortex, and temporal cortex during nonemotional cognitive task performance in bipolar disorder (23, 24) (Table 1; see also Table S1 in the online data supplement). For example, studies have reported abnormally elevated amygdala activity in adults with bipolar disorder across different mood states during performance of a variety of cognitive tasks (25–27) and increased amygdala activity during motor response inhibition in manic compared with remitted adults with bipolar disorder (28). These findings suggest a heightened perception of emotional salience in nonemotional contexts in bipolar disorder.

Theme 4: Abnormalities in Reward-Processing Neural Circuitry

In addition to emotional overreactivity and emotion dysregulation, another feature of bipolar disorder is heightened reward sensitivity, indicated by behavioral and event-related-potential studies (29–31). The key role of the ventral striatum (nucleus accumbens) in response to reward cues and reward receipt is well established (32, 33), although specific prefrontal cortical regions also have roles. The ventrolateral prefrontal cortex, in addition to its role in emotion regulation described above, is activated during arousal in the context of emotional stimuli (34, 35), while the orbitofrontal cortex plays a role in encoding reward value (36). In humans, both of these regions may have excitatory afferent connections with the ventral striatum, as suggested by studies reporting excitatory afferent connections between the homologues of these prefrontal cortical regions and the ventral striatum in rodents (37). The medial prefrontal cortex regulates the ventral striatum and appetitive behaviors in potentially rewarding contexts (38, 39).

Functional neuroimaging studies of reward-processing neural circuitry in individuals with bipolar disorder indicate abnormally elevated activity in the ventral striatum and left prefrontal cortex, in particular the left orbitofrontal cortex and left ventrolateral prefrontal cortex, during reward processing. Studies have reported abnormally increased left ventrolateral prefrontal cortex and ventral striatal activity in response to reward anticipation in adults with bipolar disorder in different mood states (40–42); abnormally elevated left orbitofrontal cortex and amygdala activity in response to reward reversal and elevated left orbitofrontal cortex activity in response to reward in euthymic adults with bipolar disorder (43); and elevated ventral striatal activity in response to reward cues and outcomes in individuals with subthreshold hypomania (44). One study, however, reported no differential activity in the ventral striatum in response to reward receipt versus omission in manic adults with bipolar disorder (45) (Table 1; see also Table S1 in the online data supplement).

TABLE 2. Structural Neuroimaging and Diffusion Imaging Studies in Bipolar Disorder[a]

Main findings from structural neuroimaging studies supporting the main themes from functional neuroimaging studies
Cortical findings
Decreased gray matter volume, decreased white matter volume, and decreased cortical thickness in prefrontal, anterior temporal and insula cortices. Decreased gray matter volume in particular in right ventrolateral prefrontal cortex and orbitofrontal cortex (49–65)
Subcortical findings
Decreased volume of amygdala and hippocampus. Altered striatal volumes (55, 56, 60, 63, 65–74)
Main findings from diffusion imaging studies supporting the main themes from functional neuroimaging studies
White matter tract findings
Altered fractional anisotropy, and increased radial diffusivity, in frontally situated white matter (51, 56, 75–103)

[a] See Tables S2 and S3 in the online data supplement for more details regarding the design and specific findings of these studies.

Structural Neuroimaging Studies Providing Support for the Main Themes

Early studies focused on structural neuroanatomical changes in bipolar disorder. Key findings were an increased number of white matter hyperintensities (46), as well as enlarged amygdala gray matter volumes (47, 48), highlighting the potential role of abnormalities in emotion processing neural circuitry in the disorder. More recent studies have examined regional gray matter volumes in cortical and subcortical regions in adults with bipolar disorder, and emerging findings coalesce into two main themes largely relating to emotion-processing and emotion-regulation neural circuits (Table 2; see also Table S2 in the online data supplement). First, many studies have examined cortical regions implicated in emotion processing and cognitive processes that are important for emotion regulation—the prefrontal and anterior temporal cortices—and cortical regions that underlie salience perception—the insula and the dorsal anterior cingulate cortex (4, 12). Findings indicate a predominant pattern of abnormally decreased gray matter volume, decreased white matter volume, and decreased cortical thickness in these regions in individuals with bipolar disorder or at risk for bipolar disorder (49–57, although see also references 58, 59). Another study reported a negative association between right ventrolateral prefrontal cortex gray matter volume and illness duration and smaller right ventrolateral prefrontal cortex gray matter volume in adults with bipolar disorder with long-term illness and minimal lifetime exposure to lithium compared with healthy adults, but abnormally increased right ventrolateral prefrontal cortex gray matter volume in relatives of individuals with bipolar disorder and in younger adults in early stages of bipolar disorder (60). Orbitofrontal cortical volume reductions in adults with bipolar disorder may be

more evident during depressive episodes (61). Prefrontal cortical gray matter volumes in general may decrease with illness progression (62) but normalize (or even increase) with lithium treatment (60, 63). Studies have also reported widespread decreases in frontal cortical thickness bilaterally, especially in the right hemisphere, and abnormally decreased temporal and parietal cortical thickness bilaterally in adults with bipolar disorder (64, 65).

A second key finding relating to emotion processing and regulation neural circuits is decreased subcortical regional volumes, especially in the amygdala and hippocampus. Studies have reported decreased amygdala volume in adults with bipolar disorder (66), particularly during depressive episodes (67), that may normalize with lithium treatment (68). One meta-analysis reported amygdala volume decreases in youths but not adults with bipolar disorder (69), suggesting a normalization of this structure over the course of development in bipolar disorder, potentially due to medication (60, 63). Abnormally decreased hippocampal and parahippocampal volumes have also been reported in adults with bipolar disorder (55, 65, 66), although such abnormalities may be masked by lithium treatment (68, 70, 71). Furthermore, one study demonstrated that larger hippocampal volumes in adult bipolar disorder may decrease with illness duration and number of illness episodes (72).

In addition, a small number of studies have reported altered volumes of striatal nuclei in adults with bipolar disorder compared with healthy adults, paralleling functional neuroimaging findings of altered functioning in these regions, especially during reward processing. These findings include decreased volume and resulting change in shape of the ventromedial surface of the caudate nucleus (73); decreased left putamen volume (55); decreased right caudate, putamen, and ventral striatum volumes (56); and increased right putamen volume (71).

Overall, the predominant pattern of reduced gray matter in the ventral prefrontal cortex in adults with bipolar disorder, especially in the right ventrolateral prefrontal cortex, suggests a structural basis for functional MRI (fMRI) findings of decreased activity in this region during emotion processing and emotion regulation tasks. The predominant pattern of reduced subcortical gray matter volumes in adults with bipolar disorder may result from a neurotoxic effect of elevated activity in these structures, indicated by fMRI studies, and may become more apparent with increasing illness duration but may be normalized, or increased, by lithium (74).

Diffusion Imaging Studies Providing Support for the Main Themes

Diffusion imaging techniques identify changes in white matter by measuring the extent of diffusion of water molecules along longitudinal and perpendicular axes of white matter tracts. Owing to the hydrophobic nature of axonal membranes and myelin sheaths, in white matter tracts that have densely packed, collinear axons, water molecules will diffuse predominantly along the longitudinal direction. In white matter containing noncollinear axons (e.g., in white matter containing crossing tracts), however, water molecules will diffuse in two or more directions. Diffusion imaging measures include longitudinal/axial diffusivity—the diffusivity along the principal axis; radial diffusivity—the diffusivity along transverse directions perpendicular to the longitudinal axis; and fractional anisotropy—the ratio of longitudinal to transverse diffusivity in white matter tracts. Fractional anisotropy will thus be high in white matter tracts with densely packed collinear axons, but low in white matter with noncollinear axons. Radial diffusivity will be high in white matter with noncollinear axons, but also high in white matter with damaged axonal membranes and/or myelin sheaths. The combination of fractional anisotropy and radial diffusivity measures in between-group studies can thus help determine group differences in the collinearity of axons in specific white matter regions; it can also help identify specific white matter tracts that may show pathological changes in the non-control group (e.g., individuals with bipolar disorder). These studies can thus provide important information about the structure of key white matter tracts in neural circuits showing functional and gray matter abnormalities in individuals with bipolar disorder.

Initial diffusion imaging studies reported white matter abnormalities in frontally situated tracts in adults with bipolar disorder (75–79). The more specific finding from recent diffusion imaging studies of adults with bipolar disorder is abnormally reduced fractional anisotropy, paralleled in many cases by abnormally increased radial diffusivity, in frontally situated white matter (80–85), including white matter tracts connecting prefrontal cortical and anterior limbic structures (86, 87) supporting emotion regulation, and in temporal white matter (88, 89) (Table 2; see also Table S3 in the online data supplement). White matter tracts that most consistently show these abnormalities are the anterior regions of the corpus callosum (56, 82, 85, 87, 90), the anterior cingulum (82, 84, 87), the uncinate fasciculus (81, 82, 86, 91), and the superior longitudinal fasciculus (51, 81, 87, 90, 92). These abnormalities may be more apparent in depressive episodes than in remission (93). Studies have also reported decreased fronto-temporal white matter fractional anisotropy in at-risk relatives of individuals with bipolar disorder (51, 88, 90, 94). A recent diffusion imaging study reported abnormal nodal networks in the left ventrolateral prefrontal cortex, the left hippocampus, and the left and right mid-anterior cingulate cortex in adults with bipolar disorder compared with healthy adults (95), which may suggest a specific white matter structural basis for the observed pattern of abnormal activity in the left ventrolateral prefrontal cortex and orbitofrontal cortex during reward processing in bipolar disorder. There are some

discrepant findings of abnormally increased fractional anisotropy in frontal white matter in adults with bipolar disorder (81, 96, 97), while other studies have reported more widespread reductions in fractional anisotropy and increases in radial diffusivity (98–101).

Findings from diffusion imaging studies in adults with bipolar disorder thus suggest either abnormal myelination or abnormal orientation of axons in predominantly frontal and temporal white matter regions that include tracts connecting prefrontal cortical and subcortical regions in neural circuits important for emotion regulation and reward processing. While abnormal white matter in these tracts may be associated with the functional and gray matter abnormalities in emotion-processing, emotion-regulation, and reward-processing neural circuitry (102, 103), the causal nature of these structure-function relationships remains to be clarified.

Conceptualizing Bipolar Disorder in Terms of Abnormalities in Large-Scale Neural Circuits

Findings from functional neuroimaging studies indicate abnormalities in adults with bipolar disorder in prefrontal cortical-amygdala-centered emotion-regulation circuitry and prefrontal cortical-striatal reward circuitry. Altered functioning within, and functional coupling between, the ventrolateral prefrontal cortex and the amygdala may represent a neural mechanism for the emotion dysregulation that characterizes bipolar disorder, given the key roles of these regions in emotion regulation (2–4, 6, 8). Abnormally elevated activity in the left ventrolateral prefrontal cortex and orbitofrontal cortex during reward anticipation and processing in adults with bipolar disorder may represent a neural mechanism for heightened reward sensitivity, given the association of these regions with arousal in potentially rewarding contexts and reward value encoding (32, 35–37). These findings also suggest a left hemisphere focus for abnormally increased activity in reward-processing neural circuitry in bipolar disorder, consistent with EEG studies showing increased left frontal activity in response to challenging and potentially rewarding events (104) and an association between increased left frontal activity and conversion to bipolar I disorder in individuals with cyclothymia or bipolar II disorder (105). Given the hypothesized role of the left hemisphere in approach-related emotions (106), the left-lateralized nature of reward-circuitry findings in bipolar disorder provides further support for heightened processing of reward- and approach-related stimuli, which may predispose to mania or hypomania. Parallel gray matter decreases in the prefrontal and temporal cortices, the amygdala, and the hippocampus and fractional anisotropy decreases in white matter tracts connecting prefrontal and subcortical regions suggest a structural basis for the functional abnormalities in emotion-processing, emotion-regulation, and reward-processing circuitry in bipolar disorder.

Bipolar disorder can thus be conceptualized, in neural circuitry terms, as parallel dysfunction in prefrontal cortical (especially ventrolateral prefrontal cortex and orbitofrontal cortex)-hippocampal-amygdala emotion processing and emotion regulation circuits bilaterally, together with an "overactive" left-sided ventral striatal-ventrolateral prefrontal cortex reward-processing circuitry, that may, together, result in the characteristic behavioral abnormalities associated with the disorder—emotional lability, emotional dysregulation, and reward sensitivity (Figures 1 and 2).

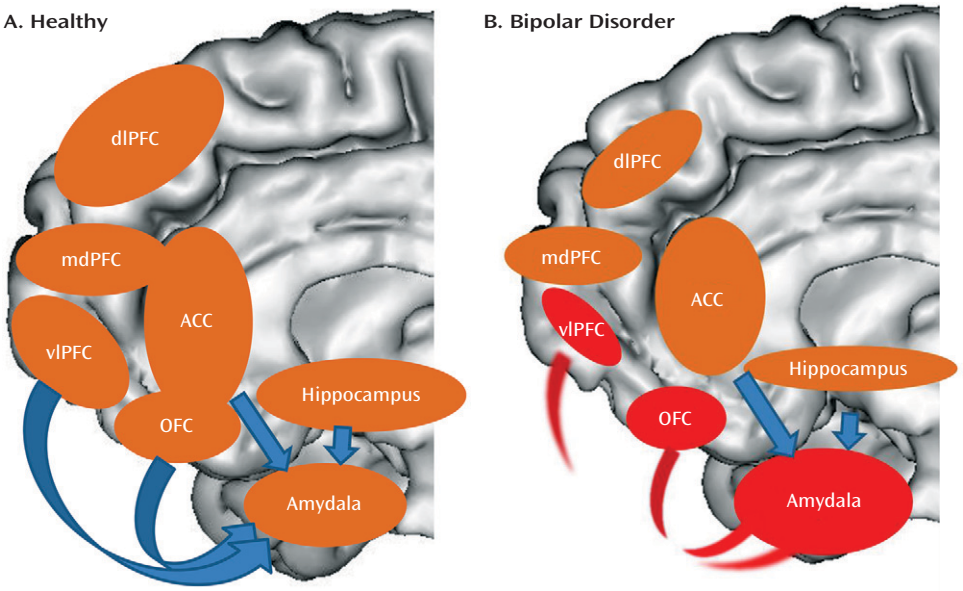
What remains to be determined is the extent to which dysfunction in these circuits produces switching between mood states and the extent to which intrinsic functional abnormalities in these circuits play a role in the neuropathophysiology of bipolar disorder. We next examine findings from the small number of studies comparing neural circuitry in individuals with bipolar disorder in different mood states and findings from resting-state studies in bipolar disorder as areas of research that need further study before our conceptualization of bipolar disorder can be confirmed.

Neuroimaging Research Needed to Support This Conceptualization of Bipolar Disorder Neural Circuitry

Mood State-Specific Functional Abnormalities in Circuits Supporting Emotion Processing, Emotion Regulation, and Reward Processing

A small number of cross-sectional studies have examined individuals with bipolar disorder in different mood states during emotion processing and emotion regulation. One finding is abnormally decreased orbitofrontal cortex activity during emotion processing across different mood states (107, 108). Mood state-specific patterns of decreased right orbitofrontal cortex activity in response to fearful and neutral faces in adults with bipolar disorder in hypomanic, manic, or mixed mood states compared with healthy adults were also reported (107). Other findings indicate differing roles of the insula and the ventrolateral prefrontal cortex in adults with bipolar disorder across different mood states during emotion regulation (109); different mood state-specific increases in amygdala activity in response to negative emotional faces (110); abnormally decreased right dorsolateral prefrontal cortex activity during nonemotional working memory across different mood states (111); and increased ventrolateral prefrontal cortical-thalamic activity during response inhibition in adults with bipolar disorder in mixed mood episodes compared with depressive episodes (27). Longitudinal studies have reported differential patterns of amygdala functional connectivity in the same individuals with bipolar disorder during mania and depression (112) and normalized activity in the

FIGURE 1. Emotion-Processing and Emotion-Regulation Circuitry[a]



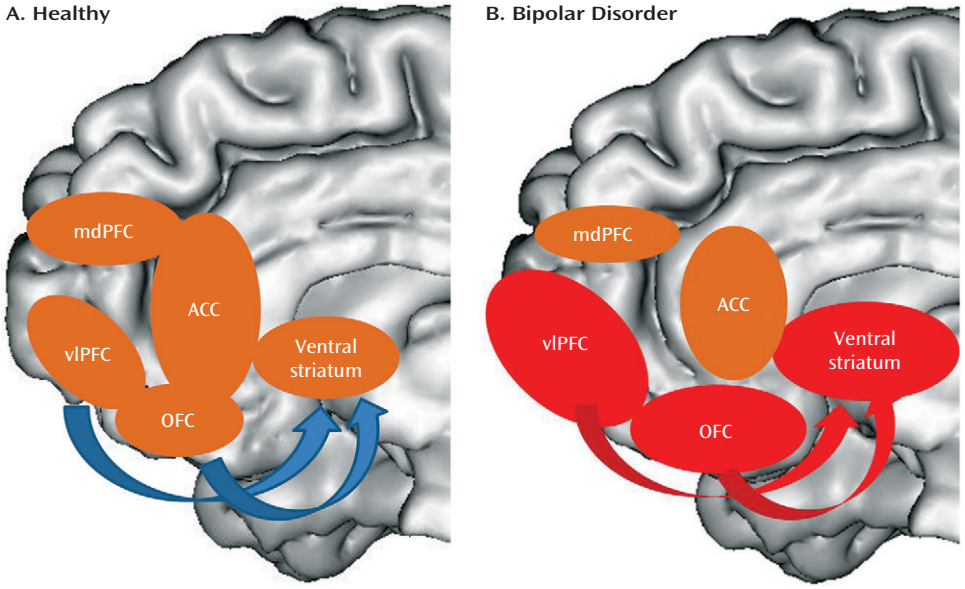
[a] Panel A is a schematic diagram highlighting key nodes in emotion-processing and emotion-regulation neural circuitry in healthy individuals; arrows represent key regulatory connections between prefrontal cortical regions and the amygdala. In panel B, key functional abnormalities in individuals with bipolar disorder are highlighted in red (in regions and connections between regions); these include abnormally increased amygdala activity during emotion processing, emotion regulation, and performance of nonemotional tasks; abnormally decreased activity in the ventrolateral prefrontal cortex and orbitofrontal cortex during emotion regulation; and decreased functional connectivity between these prefrontal cortical regions and the amygdala during emotion regulation. In parallel, there are widespread abnormal decreases in gray matter volume and cortical thickness in prefrontal cortical regions, decreased gray matter volume in the amygdala and hippocampus, and abnormally decreased fractional anisotropy in white matter tracts connecting the ventral prefrontal cortex and anterior temporal regions. These changes are indicated by smaller sizes of ovals representing these regions. ACC=anterior cingulate cortex; dlPFC=dorsolateral prefrontal cortex; mdPFC=mediodorsal prefrontal cortex; OFC=orbitofrontal cortex; vlPFC=ventrolateral prefrontal cortex.

amygdala and prefrontal cortical regions in remitted compared with manic adults with bipolar disorder during reward and cognitive tasks (28, 42). While there are no clear patterns of mood state-specific functional neural abnormalities in bipolar disorder, findings suggest amygdala-prefrontal cortical functional abnormalities across different mood states and normalization with remission, which supports our conceptualization of bipolar disorder neural circuitry. No studies have yet examined mood state differences in reward-processing circuitry in bipolar disorder, however. Clearly, more longitudinal within-subject studies are required to identify functional abnormalities in neural circuits that predispose to switches between different mood states in bipolar disorder.

Intrinsic (Resting-State) Connectivity Studies

These studies provide measures of tonic functional connectivity, rather than of stimulus-related, phasic functional connectivity, in neural circuits of interest and can thereby identify context-independent functional abnormalities, which potentially represent core functional abnormalities in such circuits in a given disorder. The majority of these studies in bipolar disorder have employed a region-of-interest approach to examine functional connectivity among a priori regions of interest at rest, measuring, for example, correlations between time series of low-frequency fluctuations in activity among these regions. The main finding is abnormally decreased positive or negative (inverse) resting connectivity among frontal, temporal, and subcortical regions in adults with bipolar disorder (113–115), which suggests a decoupling of resting connectivity among these regions, although one study reported abnormally increased resting connectivity between the right amygdala and the right ventrolateral prefrontal cortex (116). Studies focusing on larger-scale networks have reported, in adults with bipolar disorder in different mood states, diverse patterns of abnormally increased resting connectivity in paralimbic and fronto-temporal/paralimbic networks (117), abnormally decreased connectivity in the medial prefrontal cortex (118), and abnormal positive resting connectivity between the medial prefrontal cortex and the ventrolateral prefrontal cortex and between the medial prefrontal cortex and the insula, together with abnormal decoupling between the mediodorsal prefrontal cortex and the dorsolateral prefrontal cortex (119). Other studies have reported reduced global connectivity with the mediodorsal prefrontal cortex and thalamo-cortical disconnectivity in euthymic adults with bipolar disorder with a history of psychosis compared with healthy adults (115, 120). Recent studies have employed different techniques to examine the amplitude of low-frequency fluctuations and the homogeneity of time series within specific neural regions and have reported

FIGURE 2. Reward-Processing Neural Circuitry[a]



[a] Panel A is a schematic diagram highlighting key nodes in reward-processing circuitry in healthy individuals. In panel B, key functional abnormalities in individuals with bipolar disorder are highlighted in red; these include abnormally increased activity in the ventral striatum, ventrolateral prefrontal cortex, and orbitofrontal cortex during reward processing, especially during reward anticipation. While not yet reported in the literature, it is likely that patterns of aberrant functional connectivity among these regions are exhibited by individuals with bipolar disorder during reward processing. In parallel, there are widespread decreases in gray matter volume and cortical thickness in prefrontal cortical regions and striatal regions in individuals with bipolar disorder. ACC=anterior cingulate cortex; mdPFC=mediodorsal prefrontal cortex; OFC=orbitofrontal cortex; vlPFC=ventrolateral prefrontal cortex.

increased amplitude of low-frequency fluctuations in fronto-temporal-striatal regions, decreased amplitude of low-frequency fluctuations in left postcentral-parahippocampal regions (121), and greater regional homogeneity in left fronto-parietal cortices (122) in depressed adults with bipolar disorder (subtype unspecified) compared with healthy adults.

These studies indicate intrinsic, context-independent abnormalities in adults with bipolar disorder, both in functional connectivity between regions and in the amplitude and homogeneity of low-frequency fluctuations within neural regions, predominantly within fronto-temporal-striatal circuitry. The findings thereby provide some support for our conceptualization of bipolar disorder neural circuitry, but they are highly variable across studies. Furthermore, given the paucity of studies combining resting state with other neuroimaging modalities, it is difficult to determine how these findings relate to the functional and structural abnormalities in neural circuits relevant to bipolar disorder.

Future Neuroimaging Research in Bipolar Disorder

Limitations of Extant Studies

The above inferences aside, there are many limitations of existing neuroimaging studies in bipolar disorder. First, the majority of studies, especially those employing fMRI or resting state, recruited relatively modest numbers of participants per group (e.g., <30), thereby allowing only limited conclusions to be drawn about the generalizability of the findings to the wider population of individuals with bipolar disorder. Similarly, few studies have compared individuals with bipolar disorder across different mood states, and there have been few replication findings, especially for fMRI and resting-state studies. For resting-state studies, this is likely due to the different resting-state methodologies used, in addition to modest sample sizes. Clearly, there is a need in bipolar disorder research for more neuroimaging studies with larger samples and for more resting-state studies using similar techniques. Many studies have focused solely on a priori prefrontal cortical-subcortical regions of interest, with little reporting of findings in other regions, thereby limiting inferences about the potential roles of other neural circuits in bipolar disorder. Furthermore, there is a dearth of neuroimaging studies directly comparing different bipolar disorder subtypes (e.g., bipolar I and II disorders) or bipolar disorder and other major psychiatric disorders (e.g., schizophrenia). It is therefore difficult to determine the extent to which bipolar disorder subtypes, or different psychiatric disorders, share, or are distinguished by, underlying neural mechanisms. Such studies have the potential to identify neural biomarkers reflecting these neural mechanisms and thus aid diagnosis and treatment choice, particularly for disorders that are often difficult to distinguish on the basis of clinical assessment alone—for example, bipolar I disorder versus bipolar II disorder, bipolar I and II disorders versus major

depressive disorder, and bipolar disorder versus schizophrenia. There have also been few multimodal neuroimaging studies examining relationships between structure and function in neural circuits of interest in bipolar disorder or between resting and task-related functional connectivity in these circuits in bipolar disorder. Such studies will facilitate a more in-depth understanding of neural mechanisms underlying bipolar disorder.

Another major criticism of neuroimaging studies in bipolar disorder is the potentially confounding effects of psychotropic medication on neuroimaging measures. An increasing number of studies in bipolar disorder suggest that psychotropic medications either have normalizing effects on neuroimaging measures or do not have a significant impact on these measures (123), although, as is apparent from the description of studies above, lithium in particular may have neurotrophic effects in some neural regions in bipolar disorder, while antipsychotic medications are associated with gray matter decreases (124). Further studies are thus needed to determine the nature of effects specific medications have on the neural circuits of interest in bipolar disorder. Longitudinal neuroimaging studies examining individuals before and after medication can address this important point, as can large cross-sectional studies comparing medication-free individuals with those taking different medication types.

Newer Research Areas

Neuroimaging studies of different bipolar disorder subtypes. Few MRI studies have focused on adults with bipolar II disorder. One fMRI study that focused exclusively on bipolar II disorder reported decreased activity in the right amygdala and the left and right ventrolateral prefrontal cortex and reduced functional connectivity between the amygdala and both the orbitofrontal cortex and the dorsolateral prefrontal cortex during emotional face processing in depressed adults with bipolar II disorder compared with healthy adults (125). The finding of decreased ventrolateral prefrontal cortex activity parallels that reported for similar tasks in euthymic and depressed adults with bipolar I disorder (13–16, 19) and suggests that reduced ventrolateral prefrontal cortex activity during emotion processing and emotion regulation may be a trait marker of bipolar I and II disorders. An fMRI study that directly compared euthymic adults with bipolar I and II disorders and healthy adults reported significantly increased activity in the ventral striatum and the left ventrolateral prefrontal cortex in adults with bipolar II disorder compared to those with bipolar I disorder and healthy adults during reward anticipation (126), again paralleling previous studies that highlighted abnormally increased activity in the left ventrolateral prefrontal cortex and ventral striatum during reward anticipation in euthymic and depressed adults with bipolar I disorder (40, 41). Interestingly, findings from that study are the first to suggest that bipolar II disorder may be characterized by a greater magnitude of functional abnormalities in reward neural circuitry than bipolar I disorder, supporting findings associating bipolar II disorder with more disabling functional impairments in daily living than bipolar I disorder (127, 128). One structural study reported more widespread gray matter reduction in prefrontal, temporal, and parietal cortices in euthymic or moderately depressed adults with bipolar I disorder compared with depressed adults with bipolar II disorder (129). The two diffusion imaging studies that compared individuals with bipolar I and II disorders reported abnormalities in fronto-thalamic-temporal white matter in both disorders, although findings across the two studies were inconsistent (130, 131). There is clearly a need for more neuroimaging studies comparing individuals with bipolar I disorder with those with bipolar II disorder and those with other bipolar disorder subtypes.

Neuroimaging studies comparing bipolar disorder with other major psychiatric disorders. An increasing number of studies have focused on identifying measures of neural circuitry structure and function that distinguish bipolar disorder from other disorders. Studies have compared depressed adults with bipolar disorder and those with major depressive disorder (132) and adults with bipolar disorder and those with schizophrenia (117, 133). These studies suggest that functional abnormalities in prefrontal cortical-subcortical circuitry may distinguish different disorders; they are paving the way to identification of clinically useful biomarkers guiding diagnosis and treatment choices.

Multimodal neuroimaging studies. Another area for future neuroimaging research in bipolar disorder is the use of multimodal techniques to identify structure-function relationships in neural circuitry. A small number of studies have examined structure-function relationships in prefrontal cortical-amygdala circuitry in adults with bipolar I and II disorders (102, 103, 126), but there is a need for more such studies in individuals across the mood disorders spectrum. In parallel, studies are beginning to identify relationships between genetic variants and functioning within neural circuitry in adults and youths with bipolar disorder (134). Ultimately, an integrated systems approach will help identify biomarkers that reflect neuropathophysiological processes in individuals with mood, psychotic, and other psychiatric disorders that span genetic, molecular, neural circuitry, and behavioral levels of investigation (135–137).

In addition, neuroimaging studies in more novel areas of bipolar disorder research can further elucidate neural mechanisms of the disorder and provide clinically useful biomarkers. These include 1) studies in youths with bipolar disorder and those at risk for bipolar disorder to help identify biomarkers conferring risk for future development of the disorder without confounding by potential scarring effects due to present illness and illness history; 2) studies identifying dimensions of pathology that may cut across conventionally defined diagnostic categories; and 3) studies

using pattern recognition approaches to help provide clinically useful individual-level neuroimaging biomarkers.

Neuroimaging studies in youths with bipolar disorder and those at risk for bipolar disorder. These studies have examined youths with bipolar disorder and those at risk for bipolar disorder to determine the extent to which abnormalities in neural circuitry identified in adult bipolar disorder originated in youth. Studies have reported patterns in youths with bipolar disorder similar to those in adult bipolar disorder, with abnormally increased amygdala activity and decreased prefrontal cortical-amygdala functional connectivity during emotion-processing and emotion-regulation paradigms (138–142). Abnormally increased amygdala activity may be more evident in youths than in adults with bipolar disorder (139). Studies in youths with bipolar disorder have also demonstrated abnormally decreased amygdala volumes (69, 142, 143); decreased orbitofrontal cortex and anterior cingulate cortex gray matter volumes (142); abnormally reduced fractional anisotropy in white matter tracts connecting prefrontal and subcortical regions (144–147) (and similar findings in at-risk youths [148]); and altered resting state in prefrontal cortical circuitry (149) and large-scale networks (150). Longitudinal studies are clearly needed to examine developmental trajectories of structural and functional changes in prefrontal cortical-subcortical circuitry in individuals with bipolar disorder and in youths at risk for future mood and psychotic disorders. Such studies will help identify abnormal developmental trajectories in this circuitry that are associated with bipolar disorder or other mood disorders in youth and biomarkers that can help identify which at-risk youths are most likely to develop these disorders.

Neuroimaging studies adopting dimensional approaches. Guided by the National Institute of Mental Health's Research Domain Criteria initiative, neuroimaging studies are beginning to adopt a dimensional approach to bipolar disorder. One recent study reported a positive correlation between reward sensitivity (fun-seeking) and ventral striatal activity across adults with bipolar I disorder, adults with bipolar II disorder, and healthy adults (126). The study thus associated patterns of function in reward circuitry with information-processing domains that cut across diagnostic boundaries. Conceptualizing bipolar I disorder, bipolar II disorder, other bipolar disorder subtypes, and even major depressive disorder in terms of a mood disorders spectrum may lead to a better understanding of neuropathophysiological processes in these illnesses (136).

Neuroimaging studies using pattern recognition approaches. A key criticism of neuroimaging studies is their reliance on group-level statistics, rather than providing data that are useful at the individual level. If neuroimaging techniques are to provide clinically relevant information, then useful individual-level measures of brain structure and function must be obtained from these techniques. One recent advance has been to combine neuroimaging with pattern recognition approaches that develop algorithms to automatically learn and recognize complex patterns to inform decision making based on large data sets. Studies combining these approaches have been able to help classify individuals, case by case, into different diagnostic categories, including bipolar disorder versus major depression, based on their patterns of neural function (151, 152). They have also accurately discriminated between individual healthy youths at high genetic risk for bipolar disorder and those at low risk (153). Combining neuroimaging with pattern recognition

TABLE 3. A Road Map for Future Neuroimaging Research in Bipolar Disorder

Strategy 1: Dimensional approaches	Dimensional approaches to identify emotion-processing, emotion-regulation, and reward-processing neural circuitry abnormalities associated with dimensions of pathological behaviors that cut across conventionally defined bipolar disorder and other mood disorder diagnostic categories. The inclusion of longitudinal designs will help identify the extent to which alterations in these circuitry abnormalities are associated with changes in affective state.
Strategy 2: Developmental studies	Longitudinal follow-up studies examining developmental trajectories of these neural circuits in individuals with bipolar disorder across the lifespan and in youths at risk for mood disorders
Strategy 3: Multimodal neuroimaging and systems-level approaches	Multimodal neuroimaging studies and studies adopting biological system-level approaches to examine the impact of genetic variation and molecular-level processes on neural circuitry development in at-risk individuals and individuals with bipolar disorder and other mood disorders
Strategy 4: Techniques to identify individualized patterns of neuroimaging measures	Studies using neuroimaging in combination with pattern recognition techniques to identify individual-level neural circuitry markers that help classify individuals into diagnostic groups and help predict individual-level future clinical course
Strategy 5: Combinations of the above strategies	These studies will a) help elucidate more complex neuropathophysiological processes underlying dimensions of abnormal behaviors associated with affective pathology across different diagnostic categories; and b) yield individual-level biological markers reflecting these processes with clinical utility for diagnosis, predicting future illness development, and guiding personalized treatment choice.

techniques thus holds much promise for the elucidation of clinically useful individual-level biomarkers to inform diagnosis, risk identification, and personalized treatment choice.

A Neuroimaging Research Road Map For Bipolar Disorder

The field of neuroimaging in bipolar disorder is progressing considerably, with research findings making significant contributions to our understanding of the neuropathophysiology of bipolar disorder. In order to move the field forward, the next wave of bipolar disorder neuroimaging studies should aim to adopt the following strategies.

1. Studies should examine functional, structural, white matter, and intrinsic connectivity abnormalities in emotion-processing, emotion-regulation, and reward-processing neural circuitry associated with dimensions of pathological behaviors that cut across conventionally defined bipolar disorder and other mood disorder diagnostic categories. These studies should also include longitudinal designs to identify the extent to which alterations in these neural circuitry abnormalities are associated with changes in affective state. This approach has the potential to identify neural circuitry markers that better reflect neuropathophysiological processes in bipolar disorder and other mood disorders and the nature of neural mechanisms underlying abnormal mood switches.

2. Studies should use longitudinal follow-up designs to examine the developmental trajectories of these neural circuits in individuals with bipolar disorder across the lifespan and in at-risk youths. This approach will identify neural circuitry markers that can help identify those individuals at highest risk of developing affective pathology, and thereby pave the way for studies that utilize these markers to guide early intervention and prevention strategies.

3. Studies should incorporate multimodal neuroimaging techniques and biological system-level approaches to examine the impact of genetic variation and molecular-level processes on neural circuitry development in at-risk individuals and individuals with bipolar disorder and other mood disorders.

4. Studies should take advantage of advances in the application of pattern recognition techniques to neuroimaging to identify individual-level neural circuitry markers that help classify individuals into diagnostic groups and also help predict clinical course at the individual level.

Collectively, these four approaches will help elucidate more complex neuropathophysiological processes underlying dimensions of abnormal behaviors associated with affective pathology and yield individual-level biological markers reflecting these processes. Such markers will have clinical utility for diagnosis, prediction of future illness development, and the guiding of personalized treatment choice in individuals with mood disorders or those at risk of developing mood disorders (Table 3).

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