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A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and roadmap for future research

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Abstract

Objective—This critical review appraises neuroimaging findings in bipolar disorder in emotion processing, emotion regulation, and reward processing neural circuitry, to synthesize current knowledge of the neural underpinnings of bipolar disorder, and provide a neuroimaging research "roadmap" for future studies.

Method—We examined findings from all major studies in bipolar disorder that used fMRI, volumetric analyses, diffusion imaging, and resting state techniques, to inform current conceptual models of larger-scale neural circuitry abnormalities in bipolar disorder

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

Conclusion—Neuroimaging studies of bipolar disorder clearly demonstrate abnormalities in neural circuitries 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 bipolar disorder and at-risk youth; 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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Introduction

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 enhanced understanding of underlying neuropathophysiological processes. The purpose of this critical review is fourfold. We first provide a new conceptualization of bipolar disorder neural circuitry abnormalities based on the most consistent themes emerging from extant neuroimaging studies. We then identify areas of neuroimaging research that are needed to confirm this model of bipolar disorder neural circuitry and elucidate as yet unknown neuropathophysiological processes in bipolar disorder. We next describe other areas of bipolar disorder neuroimaging research that are currently under-studied, and yet will be critical to fully inform our understanding of bipolar disorder neuropathophysiology. We end the review with a suggested “roadmap” for future neuroimaging studies of bipolar disorder to provide a research framework that will permit elucidation of the neuropathophysiology of bipolar disorder, and provide biomarkers for diagnosis, risk identification, and targets to guide personalized treatment for individuals with bipolar disorder.

The scope of neuroimaging studies in the review

We integrate findings from all major studies of bipolar disorder that used neuroimaging modalities to provide a better understanding of larger-scale neural circuitry abnormalities in bipolar disorder. We first review functional neuroimaging studies examining the functional integrity of neural circuitries relevant to neuropathophysiological processes in bipolar disorder, by measuring regional activity, using blood–oxygen level dependent (BOLD) signal change, and functional connectivity, using techniques examining 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 neural circuitries, to help inform interpretation of functional abnormalities in these circuitries in individuals with bipolar disorder. We include findings from studies examining intrinsic (resting state) connectivity in neural circuitries 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 examined regional neurotransmitter concentration and neuroreceptor density, given our focus in this review on larger-scale neural circuitries relevant to bipolar disorder.

Major themes that emerge from neuroimaging studies of bipolar disorder

Theme 1: Abnormalities in emotion processing and emotion regulation neural circuitry—Emotional over-reactivity and emotion dysregulation are characteristic symptoms of bipolar disorder(1). A large number of functional neuroimaging studies of bipolar disorder thus examined emotion processing and emotional regulation neural circuitry function in individuals with bipolar disorder during performance of emotion processing and emotional regulation tasks(Table 1;ST1). This neural circuitry includes the amygdala, a region with a key role in emotion processing(2), threat and salience perception(3), in addition to prefrontal cortical regions implicated in emotion regulation. Emotion regulation

has been categorized into voluntary and automatic (implicit) subprocesses, with different prefrontal cortical regions, including orbitofrontal cortex, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex , and medial prefrontal cortex (encompassing the anterior cingulate cortex and mediodorsal prefrontal cortex), implicated in these different subprocesses(4). Here, a predominantly lateral prefrontal cortical system (centered on dorsolateral prefrontal cortex and ventrolateral prefrontal cortex) mediates voluntary emotion regulation subprocesses, while a medial prefrontal cortical system (including orbitofrontal cortex, anterior cingulate cortex, mediodorsal prefrontal cortex, and also hippocampus) mediates automatic emotion regulation sub-processes. The dense connections between temporal limbic regions and 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 in voluntary emotion regulation neural circuitry, e.g.,(8).

Early neuroimaging studies of individuals with bipolar disorder indicated predominant patterns of abnormally elevated amygdala activity to emotional stimuli (9,10), and abnormally reduced activity in lateral and medial prefrontal cortical regions supporting emotion regulation(4,11). More recent studies utilized more sophisticated functional connectivity techniques and identified fronto-subcortical functional abnormalities in adults with bipolar disorder during emotion emotional regulation and inhibitory control during different mood states(12). Specifically, these studies report abnormally decreased inferior frontal cortical activity, especially in 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 theme, is a pattern of abnormally elevated amygdala and striatal and medial prefrontal cortical activity to positive emotional stimuli in individuals with bipolar disorder(9,10)(Table 1;ST1). More recent studies demonstrated in adults with bipolar disorder abnormally increased amygdala and medial prefrontal cortex activity(20,21) and abnormally decreased positive bilateral orbitofrontal cortex-amygdala effective connectivity(22) 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 non-emotional tasks—A third theme is abnormal activity in emotion processing circuitry, including amygdala, orbitofrontal cortex and temporal cortex, during non-emotional, cognitive task performance in bipolar disorder(23,24)(Table 1;ST1). For

example, studies 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 versus remitted adults with bipolar disorder(28).These findings suggest a heightened perception of emotional salience in non-emotional contexts in bipolar disorder.

Theme 4: Abnormalities in reward processing neural circuitry—In addition to emotional over-reactivity, 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, given studies reporting excitatory afferent connections between the homologs 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 ventral striatum and left prefrontal cortex, in particular, left orbitofrontal cortex and left ventrolateral prefrontal cortex, during reward processing .Here, studies reported abnormally increased left ventrolateral prefrontal cortex and ventral striatal activity to reward anticipation in adults with bipolar disorder in different mood states(40-42); abnormally elevated left orbitofrontal cortex and amygdala activity to reward reversal and elevated left orbitofrontal cortex activity to reward in euthymic adults with bipolar disorder(43); and elevated ventral striatal activity to reward cues and outcomes in individuals with subthreshold hypomania(44). One study, however, reported no differential activity in ventral striatum to reward receipt versus omission in manic adults with bipolar disorder(45)(Table 1; ST1).

Structural neuroimaging studies providing support for the main themes—Early studies focused upon structural neuroanatomical changes in bipolar disorder. Key findings were increased number of white matter hyperintensities(46), but also enlarged amygdala gray matter volumes(47,48), highlighting the potential role of abnormalities in emotion processing neural circuitry in bipolar disorder. More recent studies 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 regulation neural circuitries(Table 2;ST2). First, many studies examined cortical regions implicated in emotion processing and cognitive processes important for emotion regulation: prefrontal and anterior temporal cortices, and cortical regions underlying salience perception: insula, 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 and

individuals at risk for bipolar disorder(49-57), although see(58,59). Another study reported a negative association between right ventrolateral prefrontal cortex gray matter volume and illness duration, smaller right ventrolateral prefrontal cortex gray matter volume in adults with bipolar disorder with long-term illness and minimal lifetime exposure to lithium versus healthy adults, although 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 also reported widespread decreases in bilateral frontal cortical thickness, especially in the right hemisphere, and abnormally decreased bilateral temporal and parietal cortical thickness in adults with bipolar disorder(64,65).

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

In addition, a small number of studies reported altered volumes of striatal nuclei in adults with bipolar disorder versus 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 VS volumes(56), although increased right putamen volume(71).

Overall, the predominant pattern of reduced gray matter in ventral prefrontal cortex in adults with bipolar disorder, especially in right ventrolateral prefrontal cortex, suggests a structural basis for findings from fMRI studies 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, that 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 those white matter tracts

with densely-packed, collinear axons, water molecules will diffuse predominantly along the longitudinal direction. In white matter containing non-collinear 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 versus 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 non-collinear axons. Radial diffusivity will be high in white matter with non-collinear 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, and 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 thereby provide important information about the structure of key white matter tracts in neural circuitries 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 temporal white matter(88,89) (Table 2;ST3). 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 episode than in remission(93). Studies 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 left ventrolateral prefrontal cortex, left hippocampus and bilateral mid anterior cingulate cortex in adults with bipolar disorder versus healthy adults(95), that may suggest a specific white matter structural basis for the observed pattern of abnormal left ventrolateral prefrontal cortex and orbitofrontal cortex activity 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 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 circuitries 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 circuitries(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 circuitries supporting emotion processing, emotion regulation and reward processing

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 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 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 to challenging and potentially rewarding events(104), and an association between increased left frontal activity and conversion to bipolar disorder type I in individuals with cyclothymia or bipolar disorder type II(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 in individuals with the illness, that may predispose to hypo/mania. Parallel gray matter decreases in prefrontal and temporal cortices, amygdala and hippocampus, and fractional anisotrophy 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 circuitries in bipolar disorder.

Bipolar disorder can thus be conceptualized in neural circuitry terms as parallel dysfunction in bilateral prefrontal cortical (especially ventrolateral prefrontal cortex and orbitofrontal cortex)– hippocampal-amygdala emotion processing and emotion regulation neural circuitries, 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 bipolar disorder: emotional lability, emotional dysregulation and reward sensitivity(Figures 1 and 2).

What remains to be determined is the extent to which dysfunction in the above neural circuitries produces switching between mood states, and the extent to which intrinsic functional abnormalities in these circuitries 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 in order to confirm our conceptualization of bipolar disorder.

Neuroimaging research needed to support this conceptualization of bipolar disorder neural circuitry

Studies examining mood state-specific functional abnormalities in neural circuitries supporting emotion processing, emotion regulation and reward processing in bipolar disorder—A small number of cross-sectional studies 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 to fearful and neutral faces in adults with bipolar disorder in hypo/manic/mixed mood versus healthy adults were also reported(107). Other findings indicate differing roles of insula and ventrolateral prefrontal cortex in adults with bipolar disorder across different mood states during emotion regulation(109); different mood state-specific increases in amygdala activity to negative emotional faces (110); abnormally decreased right dorsolateral prefrontal cortex activity during non-emotional working memory across different mood states(111); and increased ventrolateral prefrontal cortex-thalamic activity in adults with bipolar disorder in mixed mood episode versus depression during response inhibition(27). Longitudinal studies reported differential patterns of amygdala functional connectivity in the same individuals with bipolar disorder during mania versus depression(112), and normalized activity in amygdala and prefrontal cortical regions in remitted versus 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, that normalize with remission, in support of our conceptualization of bipolar disorder neural circuitry. No studies have 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 circuitries that predispose to switches between different mood states in bipolar disorder.

Intrinsic (resting state) connectivity studies—These studies provide measures of tonic functional connectivity in neural circuitries of interest, rather than stimulus-related, phasic functional connectivity in these circuitries, and can thereby identify context-independent functional abnormalities, that potentially represent core functional abnormalities in such circuitries, in a given disorder. The majority of these studies in bipolar disorder 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), suggesting a decoupling of resting connectivity among these regions, although one study reported abnormally increased resting connectivity between right amygdala and right ventrolateral prefrontal cortex in adults with bipolar disorder(116). Studies focusing on larger-scale networks 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 medial prefrontal cortex(118), and abnormal positive

resting connectivity between medial prefrontal cortex and ventrolateral prefrontal cortex, and between medial prefrontal cortex and insula, together with abnormal decoupling between mediodorsal prefrontal cortex and dorsolateral prefrontal cortex(119). Other studies reported reduced global connectivity with mediodorsal prefrontal cortex, and thalamo-cortical disconnectivity, in euthymic adults with bipolar disorder with a history of psychosis versus healthy adults(115,120). Recent studies employed different techniques to examine the amplitude of low frequency fluctuations, and the homogeneity of time series, within specific neural regions, and reported 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 bipolar disorder (subtype unspecified) versus healthy adults.

These studies indicate intrinsic, context-independent abnormalities, 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 in adults with bipolar disorder. Findings thereby provide some support for our conceptualization of bipolar disorder neural circuitry, but are very variable across different 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 circuitries of relevance 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 studies employing fMRI or resting state, recruited relatively modest (e.g.,<30) numbers of participants per group, thereby allowing only limited conclusions about the generalizability of the findings to the wider population of individuals with bipolar disorder. Similarly, there are few studies comparing individuals with bipolar disorder across different mood states, and 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 participant samples, and for more resting state studies using similar techniques. Many studies focused solely on a priori prefrontal cortical-subcortical regions of interest, with little reporting of findings in other regions, thereby limiting inferences about potential roles of other neural circuitries in bipolar disorder. Furthermore, there is a dearth of neuroimaging studies directly comparing different bipolar disorder subtypes (e.g, bipolar disorder type I versus bipolar disorder type II), or bipolar disorder versus 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 potential to identify neural biomarkers reflecting these neural mechanisms that can aid diagnosis and treatment choice, particularly for those disorders that are often difficult to distinguish based on clinical assessment alone, e.g., bipolar disorder type I versus bipolar disorder type II, bipolar disorder types I and II versus major depressive disorder, and bipolar

disorder versus schizophrenia. There are also few multimodal neuroimaging studies examining relationships between structure and function in neural circuitries of interest in bipolar disorder, or between resting and task-related functional connectivity in these neural circuitries in bipolar disorder. These studies will facilitate 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 upon neuroimaging measures. An increasing number of studies in bipolar disorder suggest that psychotropic medications have either normalizing effects on neuroimaging measures, or do not significantly impact 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 of specific medications on neural circuitries of interest in bipolar disorder. Longitudinal neuroimaging studies examining individuals pre and post 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 focused on adults with bipolar disorder type II. One fMRI study focused exclusively on bipolar disorder type II, and reported decreased amygdala and bilateral ventrolateral prefrontal cortex activity, and reduced amygdala-orbitofrontal cortex and amygdala-dorsolateral prefrontal cortex functional connectivity, during emotional face processing in depressed adults with bipolar disorder type II versus healthy adults(125). The finding of decreased ventrolateral prefrontal cortex activity parallels that shown during similar tasks by euthymic and depressed adults with bipolar disorder type I(13-16,19), and suggests that reduced ventrolateral prefrontal cortex activity during emotion processing and emotion regulation may be a trait marker of bipolar disorder type I and bipolar disorder type II. A second fMRI study directly compared euthymic adults with bipolar disorder type I and bipolar disorder type II and healthy adults, and reported significantly increased VS and left ventrolateral prefrontal cortex activity in adults with bipolar disorder type II versus adults with bipolar disorder type I and healthy adults during reward anticipation(126), again paralleling previous studies that highlighted abnormally increased left ventrolateral prefrontal cortex and ventral striatal activity during reward anticipation in euthymic and depressed adults with bipolar disorder type I(40,41). Interestingly, findings from this study are the first to suggest that bipolar disorder type II may be characterized by greater magnitude of functional abnormalities in reward neural circuitry than bipolar disorder type I, supporting findings associating bipolar disorder type II with more disabling functional impairments in daily living than bipolar disorder type I(127,128). One structural study reported more widespread gray matter reduction in prefrontal, temporal, parietal cortices in euthymic/moderately depressed adults with bipolar disorder type I versus depressed adults with bipolar disorder type II(129). The two diffusion imaging studies that compared individuals with bipolar disorder type II and bipolar disorder type I reported abnormalities in fronto-thalamic-

temporal white matter in both disorders, although findings across these two studies were inconsistent(130,131). There is clearly a need for more neuroimaging studies comparing individuals with bipolar disorder type I with those with bipolar disorder type II and those with other bipolar disorder subtypes.

Neuroimaging studies comparing bipolar disorder with other major psychiatric disorders: An increasing number of studies focused on identifying measures of neural circuitry structure and function that distinguish bipolar disorder from other disorders. Here, studies compared depressed adults with bipolar disorder versus those with MDD(132), and adults with bipolar disorder versus those with schizophrenia(117,133).These studies suggests functional abnormalities in prefrontal cortical-subcortical circuitry may distinguish different disorders, and are paving the way forward for identifying clinically-useful biomarkers guiding diagnosis and treatment choices.

Multimodal neuroimaging studies: Another future area for neuroimaging research in bipolar disorder is the use of multimodal techniques to identify structure-function relationships in neural circuitry. A very small number of studies examined structure-function relationships in prefrontal cortical-amygdala circuitry in adults with bipolar disorder type I and bipolar disorder type II(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 youth 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 bipolar disorder, and provide clinically-useful biomarkers. These include: 1. neuroimaging studies in youth with bipolar disorder, and those at risk for bipolar disorder, to help identify biomarkers conferring risk for future development of bipolar disorder, that are not confounded by potential scarring effects due to present illness and illness history; 2. neuroimaging studies identifying dimensions of pathology that may cut across conventionally-defined diagnostic categories; and 3. neuroimaging studies using pattern recognition approaches to help provide clinically useful, individual-level neuroimaging biomarkers.

Neuroimaging studies in youth with bipolar disorder and youth at risk for bipolar disorder: These studies examined youth with bipolar disorder, and youth at future risk for bipolar disorder, to determine the extent to which neural circuitry abnormalities identified in adult bipolar disorder originated in youth. While beyond the scope of this review to describe these studies in detail, key findings are summarized here. Studies reported in youth with bipolar disorder similar patterns to those in adult bipolar disorder of 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 youth than in adults with bipolar disorder(139). Studies in bipolar disorder youth also demonstrated abnormally decreased amygdala

volumes(69,142,143); decreased orbitofrontal cortex and anterior cingulate cortex gray matter(142); abnormally reduced fractional anisotropy in white matter tracts connecting prefrontal and subcortical regions(144-147); and also in at-risk youth(148); and altered resting state in prefrontal cortical circuitry(149), and largescale 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 those youth at risk of future mood and psychotic disorders. Such studies will help identify abnormal developmental trajectories in this circuitry that are associated with having bipolar disorder or other mood disorders in youth, and biomarkers that can help identify which at-risk youth are most likely to develop these disorders in the future.

Neuroimaging studies adopting dimensional approaches: Guided by the NIMH 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 disorder type I, adults with bipolar disorder type II and healthy adults(126). This study thus associated patterns of function in reward circuitry with information processing domains that cut across diagnostic boundaries. Conceptualizing bipolar disorder type I, bipolar disorder type II, 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 upon group-level statistics, rather than providing data that is useful at the individual level. If neuroimaging techniques are to provide clinically-relevant information, then useful individual-level measures of brain structure and function need to 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 datasets. 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), and also accurately discriminated between individual healthy youth at high genetic risk, versus those at low risk, for future bipolar disorder(153). Combining neuroimaging with pattern recognition techniques thus holds much promise for future elucidation of clinically-useful, individual-level biomarkers to inform diagnosis, risk identification, and personalized treatment choice.

Summary: A neuroimaging research roadmap for bipolar disorder

The field of neuroimaging in bipolar disorder is progressing considerably, with findings from these studies making significant contributions to 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 emotion processing, emotion regulation and reward neural circuitry functional, structural, white matter and intrinsic connectivity abnormalities 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 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 examine developmental trajectories of these neural circuitries in individuals with bipolar disorder across the lifespan and at-risk youth, with longitudinal follow-up designs. This approach will identify neural circuitry markers that can help identify those individuals at highest risk of developing future affective pathology, and thereby pave the way forward 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 upon 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 not only help classify individuals into present diagnostic groups but also help predict individual-level future clinical course. 5. 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 that have clinical utility for diagnosis, future illness development prediction, and guiding personalized treatment choice in at-risk and mood-disordered individuals(Table 3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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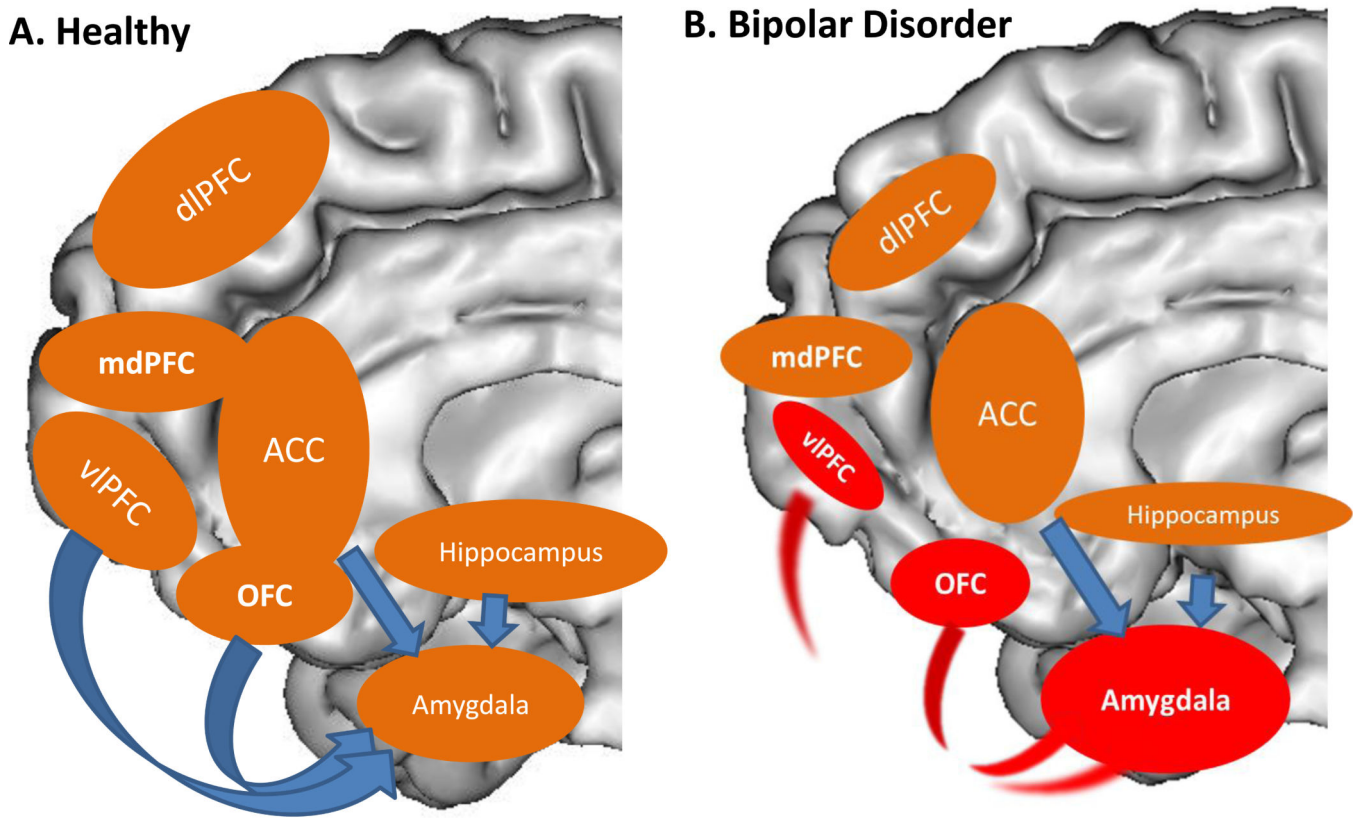

Figure 1.

A. A schematic diagram highlighting key nodes in emotion processing and emotion regulation and neural circuitries in healthy individuals. dlPFC: dorsloateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; mdPFC: mediodorsal prefrontal cortex; ACC: anterior cingulate cortex. Arrows represent key regulatory connections between prefrontal cortical regions and amygdala.

B. A schematic diagram highlighting key functional abnormalities in red in regions and connections between regions in individuals with bipolar disorder. These include abnormally increased amygdala activity during emotion processing, emotion regulation and during performance of non-emotional tasks; abnormally decreased activity in vlPFC and OFC during emotion regulation; and decreased functional connectivity between these prefrontal cortical regions and 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 amygdala and hippocampus, and abnormally decreased fractional anisotropy in white matter tracts connecting ventral prefrontal cortex and anterior temporal regions. These changes are indicated by decreased sizes of ovals representing these regions.

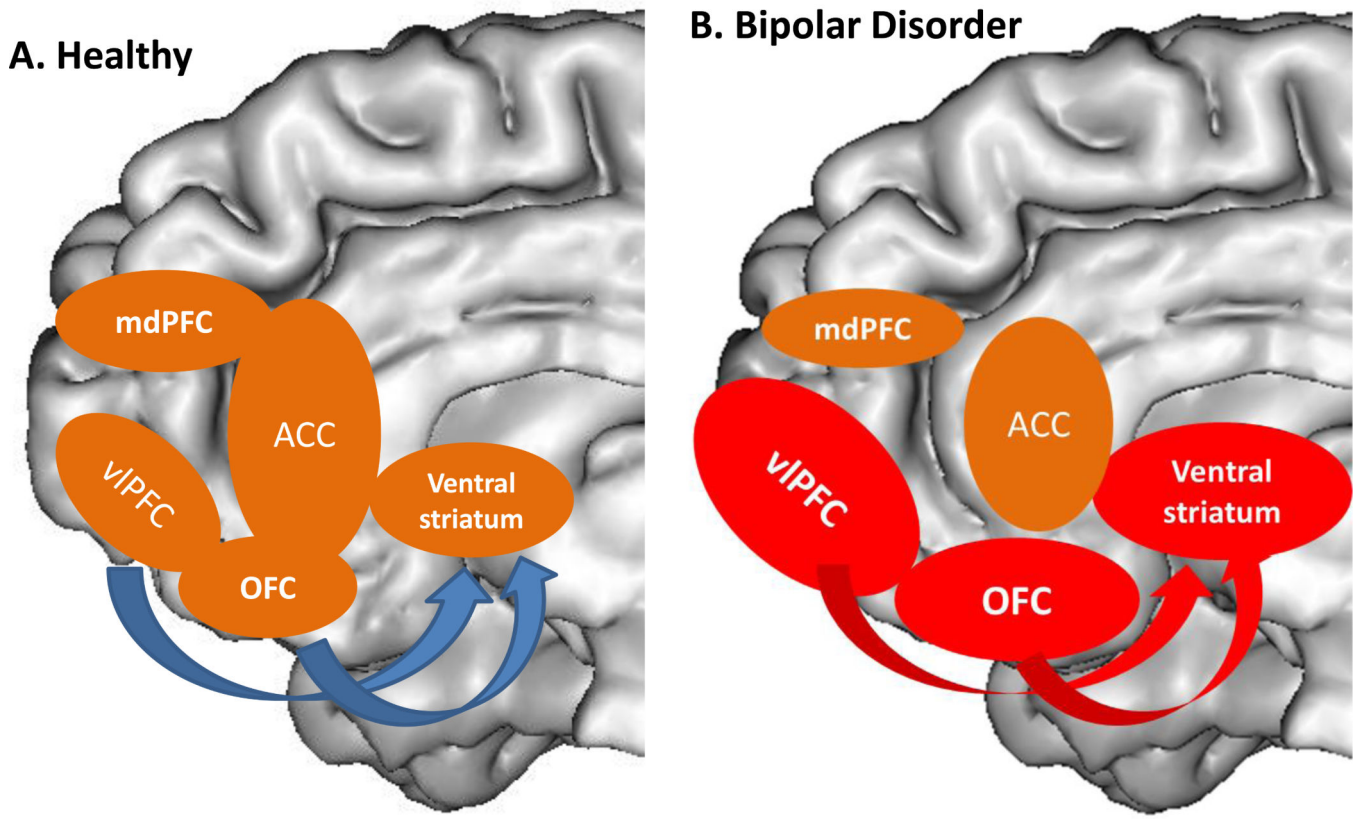

Figure 2.

A. A schematic diagram highlighting key nodes in reward processing neural circuitry in healthy individuals. Abbreviations are as for Figure 1.

B. A schematic diagram highlighting key functional abnormalities in red in regions in individuals with bipolar disorder. These include abnormally increased VS, vlPFC and OFC activity 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 shown 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.

Table 1

Main themes from functional neuroimaging studies in BD

Theme 1	Abnormally decreased vlPFC activity during emotion processing, emotion regulation, and response inhibition (see 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 (see 9, 10, 20-22)
Theme 3	Abnormally increased amygdala, OFC and temporal cortical activity during non-emotional, cognitive task performance (see 23-28)
Theme 4	Abnormally increased left vlPFC and OFC, and VS activity during reward processing (see 40-45)

Please see ST1 in supplemental materials for more detailed information regarding the design and findings of the studies associated with each of these main themes.

Table 2

Structural neuroimaging and diffusion imaging studies

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 vlPFC and OFC (see 49-65)
Subcortical findings	Decreased volume of amygdala and hippocampus. Altered striatal volumes (see 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 (FA), and increased radial diffusivity (RD), in frontally-situated white matter (see 51, 56, 75-103)

Please see ST2 and ST3 in supplemental materials for more details regarding the design and specific findings of these studies

Table 3

A roadmap for future neuroimaging research in BD

Strategy 1: Dimensional approaches	Dimensional approaches to identify emotion processing, emotion regulation and reward neural circuitry abnormalities associated with dimensions of pathological behaviors that cut across conventionally-defined BD and other mood disorder diagnostic categories. The inclusion of longitudinal designs will help identify the extent to which alterations in these neural circuitry abnormalities are associated with changes in affective state
Strategy 2: Developmental studies	Longitudinal follow-up studies examining developmental trajectories of these neural circuitries in individuals with BD across the lifespan and mood disorders at-risk youth
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 upon neural circuitry development in at-risk individuals and individuals with BD 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 present 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 b)Yield individual-level biological markers reflecting these processes with clinical utility for diagnosis, predicting future illness development, and guiding personalized treatment choice