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Identifying Functional Neuroimaging Biomarkers of Bipolar Disorder: Toward *DSM-V*

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Bipolar disorder is one of the most debilitating and common illnesses worldwide. Individuals with bipolar disorder frequently present to clinical services when depressed but are often misdiagnosed with unipolar depression, leading to inadequate treatment and poor outcome. Increased accuracy in diagnosing bipolar disorder, especially during depression, is therefore a key long-term goal to improve the mental health of individuals with the disorder. The attainment of this goal can be facilitated by identifying biomarkers reflecting pathophysiologic processes in bipolar disorder, namely impaired emotion regulation, impaired attention, and distractibility, which persist during depression and remission and are not common to unipolar depression. In this critical review, we examine the feasibility of identifying biomarker of bipolar disorder by discussing existing findings regarding functional abnormalities in neural systems underlying emotion processing (amygdala centered), working memory, and attention (dorsolateral prefrontal cortex centered) that persist through bipolar depression and remission and are bipolar specific rather than common to unipolar depression. We then focus on future research goals relating to major clinical problems in bipolar disorder, including, the identification of biomarkers allowing detection of individuals at risk of subsequent development of the disorder. Bipolar disorder is a common, debilitating, and potentially fatal disorder. Current and future research in bipolar disorder should focus on identification of disorder biomarkers to improve diagnostic accuracy and the mental heath of those with the disorder.

Key words: pathophysiology/mood disorder/amygdala/prefrontal cortex/neuroimaging

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Introduction

Bipolar disorder remains one of the 10 most debilitating illnesses worldwide,[1] with a prevalence of at least 1%. Bipolar disorder type I (BPI), characterized by the presence of episodes of mania and depression, in particular is associated with a poor clinical and functional outcome, a high suicide rate,[2] and a huge societal cost.[3] One reason for the poor prognosis is the frequent misdiagnosis or late diagnosis of the disorder,[4,5] leading to delays in the initiation of appropriate treatment. Indeed, while depression is a more common presentation and a cause of greater disruption of occupational, family, and social functioning than mania in individuals with bipolar disorder,[6] bipolar depression continues to be frequently misdiagnosed and inappropriately treated as unipolar depression in individuals without a clear previous history of manic episodes.[7–10] Increased accuracy in diagnosing bipolar disorder in individuals when they present during depression therefore remains a key goal to help improve the mental health, treatment, and clinical and functional outcomes of individuals with all subtypes of the disorder.

The recent research agenda for *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-V*), has emphasized a need to translate basic and clinical neuroscience research findings into a new classification system for all psychiatric disorders based upon pathophysiologic and etiological processes.[11–14] These pathophysiologic processes involve complex relationships between genetic variables, abnormalities in brain systems, and related neuropsychological function and behavior and may be represented as biomarkers of a disorder.[15] Abnormalities that are persistent rather than episodic or state features of a disorder can be more readily used to identify those individuals with the disorder.[16] Measurement in individuals with bipolar disorder of brain system abnormalities underlying characteristic behavioral impairments that are "common to remission and depression" may therefore help to identify future biomarkers of the disorder,[17,18] as will examination of brain system abnormalities that are "specific to bipolar disorder" and not common to unipolar depression. These studies will facilitate future increases in accuracy of diagnosis of bipolar disorder and subsequent treatment improvements in depressed individuals presenting without a clear history of mania.

There may be several different symptom domains in the traditional BPI.[14] One important symptom domain is mood instability leading to variability in depression and/or hypomanic/manic states as well as other aspects of mood variability which might be expressed as irritability or sadness. This may be related to impaired processing of emotionally salient information in the environment. A second major symptom domain is impaired cognitive control and executive dysfunction, which includes symptoms such as the inability to concentrate, difficulty in decision making, and memory difficulties. Together, these 2 symptom domains may confer an inability to regulate emotional states in any given context, as individuals are unable to employ appropriate cognitive control processes, including reappraisal, suppression, or inhibitory processes,[19] either with or without overt awareness, to regulate and inhibit the generation of inappropriate emotional states. Subsyndromal levels of these symptom domains persist during remission in individuals with the disorder[20] and may underlie the vulnerability to subsequent severe mood episodes.[21] Thus, examination of activity in neural systems associated with (1) initial identification and generation of emotional states in response to emotionally salient material and (2) covert and overt cognitive control processes that may be linked with the ability to regulate emotional states[22] is a first stage toward the longer term goal of identifying biomarkers of bipolar disorder.

We therefore next describe experimental paradigms which can be employed in neuroimaging studies to measure activity in neural systems that are associated with these 2 major symptom domains in bipolar disorder. These include neural systems underlying (1) emotion processing, specifically, neural systems implicated in the initial identification and generation of emotional states in response to emotionally salient material and (2) cognitive control processes, including attention, working memory, inhibitory control, strategy development, and cognitive flexibility.[23] Abnormal function in these 2 neural systems may be linked, respectively, with the mood instability and impaired cognitive control processes that are commonly observed in bipolar disorder. We therefore subsequently describe the functional abnormalities in these neural systems that have been reported in bipolar disorder using paradigms designed specifically to examine activity in these neural systems and the extent to which these abnormalities may be specific to bipolar disorder rather than being common to unipolar depression.

Paradigms Measuring Neural Responses During Emotion Processing, Working Memory, Attention, and Emotion Regulation

Paradigms to examine activity associated with the first symptom domain, mood instability, that may be associated with impaired processing of emotionally salient information have included displays of facial expressions. These stimuli are highly salient social signals of emotional states, the correct recognition of which is crucial for social interaction. Facial expression identification tasks have therefore been widely used in the examination of emotion-processing abilities in healthy and psychiatric populations.[21,24] In healthy individuals, findings from neuroimaging studies have implicated a network of subcortical, predominantly anterior limbic regions. In response to presentations of different facial expressions, including ventral striatum, amygdala, anterior hippocampus, and anterior insula,[24–28] numerous other types of emotional stimuli have been employed in the examination of neural systems implicated in emotion processing. These include emotional scenes, emotional words, and emotional material presented in different sensory modalities.[21]

The second symptom domain, impaired cognitive control and executive dysfunction, maps to dysfunction in a lateral prefrontal cortical system, comprising dorsolateral and ventrolateral prefrontal cortex (DLPFC and VLPFC), which is important for cognitive and executive function (eg, Monchi et al[29]), and the hippocampus, important for memory. One commonly employed task of working memory and attention is the digit-sorting task. This task requires the sorting of digits into numerical order and memorization of the digit with the middle value. The performance of this task has been reliably associated with DLPFC activity in healthy individuals.[30] Numerous studies employing attentional tasks, including the Stroop interference task, in which individuals selectively attend to the color ink in which a color word is written rather than the color word per se, have further implicated the DLPFC,[31] dorsal regions of the anterior cingulate gyrus,[32–35] and ventral prefrontal cortex (VPFC)[36] during performance of these tasks in healthy individuals.

Fewer studies have specifically focused on examination of neural systems underlying regulation of emotion. Recent studies have implicated dorsal prefrontal cortical regions both in the suppression of arousal to emotive stimuli[37] and reappraisal of emotive scenes[38,39] during attempts to reduce emotional experience. Another method of examining emotion regulatory processes less confounded by interindividual differences in emotion regulatory strategies is to employ paradigms measuring the impact of emotional contexts upon subsequent performance of executive control or attentional tasks. This method has previously been employed in healthy individuals and those with unipolar depression,[30] with findings indicating reciprocal relationships between amygdala and dorsolateral prefrontal cortical responses during the attentional component of such tasks. Clearly, further study is required in healthy individuals of the nature of neural systems that are specifically implicated in the different cognitive control processes implicated in emotional state regulation.

In the following sections, evidence is presented for abnormalities in neural response during performance of these tasks in remitted individuals with bipolar disorder compared with healthy individuals. Findings are then described from studies examining neural responses during these tasks in depressed individuals with bipolar disorder compared with healthy individuals, and in depressed individuals compared with remitted individuals with bipolar disorder, to examine the extent to which such abnormalities are common in remission and depression.

Functional Abnormalities in Neural Systems Underlying Emotion Processing and Cognitive Control Processes in Bipolar Remission

The few existing studies examining neural responses to emotional stimuli have indicated increased amygdala and ventral striatal activity to mild happy[40] and intense fearful expressions[40,41] in remitted, and increased amygdala activity to happy expressions in a mixed group of remitted and unwell,[42] individuals with bipolar disorder. Findings also show decreased DLPFC activity to fearful expressions[39] in remitted individuals with bipolar disorder (predominantly the bipolar I subtype) compared with healthy individuals. No significant relationship between subsyndromal depression severity and amygdala responses to happy and fearful facial expressions has been observed in remitted individuals with bipolar disorder.[40] Interestingly, other studies have demonstrated widespread decreases in prefrontal cortical and subcortical neural activity to emotional words in remitted individuals with BPI.[43,44] It is therefore possible that emotional facial expressions are processed as particularly significant in individuals with bipolar disorders during remission.

During performance of attentional tasks, findings in remitted, euthymic individuals with bipolar disorder compared with healthy individuals have indicated reduced activity in dorsal and ventral prefrontal cortical regions[36] and reduced activity within dorsal regions of the anterior cingulate gyrus, although increased DLPFC activity,[45] during a Stroop interference task. Other studies have demonstrated reduced DLPFC activity in euthymic individuals with bipolar disorder during working memory and verbal encoding tasks.[46,47] Increases in activity within subcortical regions associated with emotion processing rather than working memory or attention have also been demonstrated in remitted, euthymic individuals with bipolar disorder during performance of a continuous performance task[48] and a working memory task[49] and in adolescents with bipolar disorder during performance of a Stroop attentional task.[50]

These findings suggest "increased amygdala and subcortical" activity but predominantly "decreased DLPFC" activity during emotion-processing and cognitive control tasks in bipolar remission. There are some inconsistencies that may relate to the nature of the emotional stimuli employed in these tasks. Findings indicate that facial expressions may be processed as particularly salient stimuli in remitted individuals with bipolar disorder. We next describe findings from studies examining neural responses during these tasks in bipolar depression.

Are There Functional Abnormalities in Neural Systems Common to Bipolar Remission and Depression?

Findings indicate increased subcortical activity to negative scenes during the generation of emotional states in bipolar depressed individuals (including rapid cycling) compared with healthy individuals,[51] and decreased activity in medial prefrontal cortex during sad mood induction in remitted[52] more than depressed bipolar individuals.[53] One study has reported relative increases in activity in a number of subcortical regions to happy facial expressions in bipolar depressed compared with manic individuals and healthy individuals,[54] but further study focused upon amygdala and prefrontal cortical responses is required in larger numbers of bipolar depressed and remitted individuals. Increased amygdala activity has been demonstrated in both bipolar depressed and remitted individuals (approximately 50% type I) compared with healthy individuals at rest.[55] During a sustained attention task, findings have indicated decreased absolute prefrontal cortical and increased subcortical metabolism, with negative and positive correlations between metabolism in these prefrontal cortical and subcortical regions, respectively, and depression severity in bipolar depressed (predominantly rapid cycling) compared with healthy individuals.[56]

Of the few studies directly comparing neural activity during performance of attentional tasks in remitted or euthymic vs depressed individuals with bipolar disorder, relative *increases* in ventrolateral prefrontal cortical activity have been reported in bipolar depressed compared with euthymic individuals during performance of a Stroop task.[36] Similarly, during performance of a Stroop attentional task, depression severity correlated negatively with the magnitude of the ventral prefrontal cortical *decreases* in individuals with bipolar disorder.[57] These findings suggest common functional abnormalities in subcortical and prefrontal cortical regions during bipolar depression and remission compared with healthy individuals. They also indicate further depression-related abnormalities, in particular, relative increases in prefrontal cortical activity during attentional tasks in bipolar depressed compared with remitted individuals. Further study is required to identify abnormal neural responses during emotion-processing, attentional, and working memory tasks and tasks involving emotion regulatory processes, which persist and are therefore common to remission and depression in bipolar disorder. Current data comparing bipolar depressed and remitted individuals suggest a positive association between increased prefrontal

cortical activity and increased depression severity during attentional tasks.

There is a lack of studies specifically examining the relationship between change in depression severity over time in individuals with bipolar disorder and change in the nature and magnitude of abnormal neural activity during emotion and cognitive challenge tasks. This seriously limits current understanding of the neural mechanisms associated with change in depression severity over time in bipolar depression. Longitudinal examination of the relationship between depression severity and abnormal neural activity is therefore required to better understand these neural mechanisms. Another problem is the paucity of studies comparing neural activity during emotion and cognitive challenge tasks in bipolar and unipolar depressed populations. This limits understanding of the extent to which abnormalities observed in bipolar depression are bipolar specific or depression related and therefore common to both bipolar and unipolar populations. We next describe findings from studies which have employed these tasks in unipolar depressed compared with healthy individuals and the few findings from studies that have directly compared neural activity in bipolar and unipolar populations.

The link With Mania: Are There Similar Functional Neural Abnormalities Evident in Mania, Depression, and Remission in Bipolar Disorder?

A clear history of mania indicates a diagnosis of bipolar disorder rather than unipolar depression. To fully understand the pathophysiologic mechanisms underlying bipolar disorder, it is important to consider the nature of functional abnormalities in neural systems that may persist across mania, depression, and remission. Few studies have examined activity in neural systems associated with the 2 symptom domains in individuals during mania. To date, studies have reported in manic individuals relative to healthy individuals increased amygdala,[58] insula,[59] and subcortical activity per se[54] to negative emotional facial expressions and to negative scenes,[60] increased ventral striatal activity at rest[61] and during motor tasks,[62] and decreased ventral prefrontal cortical activity during performance of a variety of different cognitive control tasks.[63–66]Together with findings from functional neuroimaging studies of depressed and remitted individuals with bipolar disorder, these data suggest patterns of increased amygdala and subcortical activity to emotional—at least negative emotional—stimuli and decreases in activity in prefrontal cortical regions implicated in cognitive control processes that may be common to all 3 phases of bipolar illness. More study is required, however, examining the nature of functional abnormalities in emotion-processing neural systems to different categories of emotional stimuli (eg, positive vs negative emotional stimuli) and during different cognitive control tasks in individuals during mania.

Abnormal Neural Responses in Unipolar Depressed Individuals

The majority of functional neuroimaging studies of unipolar depressed individuals pre- and postremission after treatment with pharmacological and psychological interventions have been performed during resting state and not during performance of specific emotion-processing or attentional tasks.[67–76] There are discrepant findings from these studies. Some studies report increases in dorsal and ventral prefrontal cortical activity[67,68,72,76,77] or decreases in subcortical and ventral prefrontal cortical responses[74] in unipolar depressed individuals and in mixed groups of individuals with unipolar and bipolar depression after depression improvement with pharmacological intervention. Other studies suggest decreases in dorsolateral and ventrolateral prefrontal cortical activity after successful psychological and pharmacological interventions[69,71,75,78] or relative increases only in subcortical, limbic regions after both types of intervention in unipolar depressed individuals.[74] Studies have also reported an inverse relationship between depression severity and dorsal prefrontal cortical and anterior cingulate gyral activity in unipolar depressed individuals at rest.[67,79] Regarding neural responses during performance of emotion-processing tasks, abnormal increases in amygdala or ventral striatal activity have been demonstrated by unipolar depressed individuals to negative emotional expressions,[80–82] and similar patterns of decreased ventromedial prefrontal activity during sad mood induction compared with healthy individuals have been reported in unipolar remitted and depressed individuals.[83] Decreased activity in left DLPFC relative to healthy individuals has been reported in unipolar depressed individuals during working memory trials following negative stimuli[30] and during working memory and attention.[84–86] In the majority of studies, an amelioration of the abnormal pattern of neural response during depression has been demonstrated in unipolar depressed individuals after remission. For example, abnormal increases in amygdala or ventral striatal activity to negative emotional expressions in unipolar depressed individuals[80–82] significantly reduce in remission after treatment with antidepressant medication.[80,81] Increases after remission in insular and anterior cingulate gyral activity to negative vs neutral scenes have also been reported.[87]

In summary, while findings regarding neural responses during at rest studies are somewhat discrepant in unipolar depressed individuals, findings from studies employing emotional challenge paradigms suggest that, similar to individuals with bipolar disorder, unipolar depressed individuals show increased amygdala and subcortical activity to emotional stimuli relative to healthy individuals. Unlike individuals with bipolar disorder, however, in unipolar depressed individuals this abnormal pattern of neural activity is predominantly negative rather than

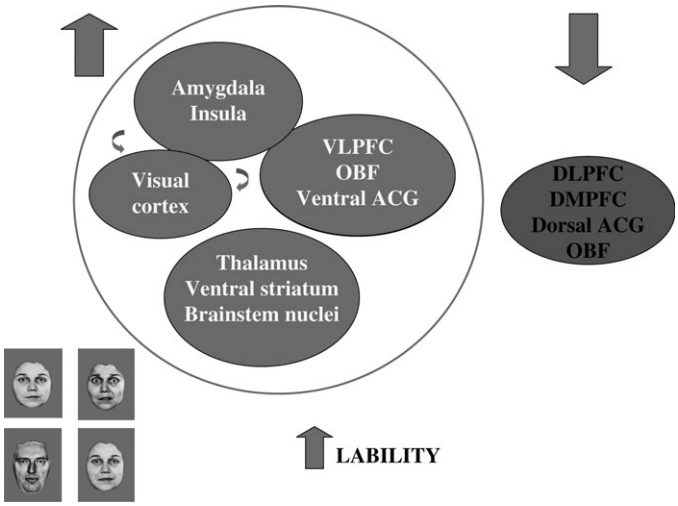

Fig. 1. This Depicts a Schematic Model for the Neural Basis of the Affective Instability in Individuals with Bipolar Disorder. In bipolar disorder, it is postulated that to many emotional stimuli, including the different categories of facial expression depicted here, although not consistently to emotional words, a pattern of increased activity occurs in an amygdala- and subcortical-centered neural system important for the identification of emotional information and the generation of emotional states (depicted in dark gray). This, together with reduced activity in a DLPFC- and VLPFC-centered system important for cognitive control processes involved in the regulation of behavioral responses to emotional stimuli (depicted in light gray), may lead to impaired emotion regulation and increased lability of mood frequently observed in individuals with bipolar disorder. VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ACG, anterior cingulate gyrus; OBF, orbitofrontal cortex.

positive emotional stimuli. Furthermore, these abnormalities appear to be *depression dependent* in unipolar depressed individuals rather than abnormalities common throughout depression and remission. Only 1 study to date has directly compared neural activity in bipolar and unipolar individuals. Here, we showed increases in amygdala and subcortical activity predominantly not only to mild happy expressions but also to fearful facial expressions, vs neutral expressions in remitted bipolar relative to unipolar depressed individuals.[40] There is thus clearly a need for studies comparing neural activity in bipolar and unipolar populations during emotional and cognitive challenge paradigms, but data to date suggest that examination of patterns of subcortical neural activity to negative and positive stimuli may help distinguish individuals with bipolar disorder from those with unipolar depression. Furthermore, there is a need to examine the extent to which relationships between changes in depression severity over time and changes in neural activity differentiate bipolar and unipolar populations.

A Neural Model of Bipolar Disorder

Current findings require replication in larger numbers of participants but suggest that bipolar disorder can be modeled as dysfunction in 2 neural systems that are implicated in 2 major symptom domains in bipolar disorder: (1) abnormally increased activity in an amygdala- and subcortical-centered system underlying emotion processing that may be linked with the mood instability commonly observed in individuals with bipolar disorder and (2) abnormally decreased activity in a prefrontal cortical neural system comprising predominantly DLPFC and VPFC underlying cognitive control processes, including attention, working memory, inhibitory control, strategy development, and cognitive flexibility,[21,23,29] that may be linked with impaired cognitive control and executive dysfunction observed in bipolar disorder (figure 1). The former (1) may underlie the emotional lability, the latter (2) the impaired attention and distractibility, and the combination of both abnormalities, the inability to employ cognitive control strategies, either with covert or overt awareness, to successfully regulate emotional states that are common clinical features of bipolar disorder. While functional regulation of the amygdala may be directly mediated by ventromedial prefrontal cortex,[88] functional abnormalities in these 2 neural systems are suggested by the few functional neuroimaging studies to date in bipolar disorder. Findings suggest that abnormalities described in (1) to emotional stimuli may occur both in remitted[40] and depressed[54] bipolar individuals, but no studies have directly compared neural activity during emotion-processing paradigms in these 2 populations. Findings further suggest relative increases in activity in the prefrontal cortical-centered system in bipolar depression compared with bipolar remission during attention tasks.[36,55] In unipolar depression, unlike bipolar disorder, findings suggest that abnormalities described in (1) above may occur to some negative, but not positive, emotional stimuli and may thus distinguish bipolar from unipolar populations[40,70] (table 1). To date, only 1 study has directly compared bipolar and unipolar individuals[40] and provides some support for this potential distinction between bipolar remitted and unipolar depressed individuals. Clearly, there is a need for far more research in this burgeoning area of clinical neuroscience. Specifically, future studies should focus on the employment of experimental paradigms to examine the nature of functional abnormalities in the 2 neural systems described above that map closely to common symptom domains in bipolar disorder and the extent to which these abnormalities may help distinguish individuals with bipolar disorder, especially when presenting during depressed episode, from individuals with unipolar depression.

The Effect of Structural Volume Abnormalities, Medication, and Other Clinical Variables Upon Functional Neural Abnormalities

Here, we describe other factors which may impact upon measurements of functional neural response during task

Table 1. Neural Activity During Emotion and Cognitive Challenge Tasks in Bipolar Disorder and Unipolar Depression

	Bipolar Remitted	Bipolar Depressed	Bipolar Mania	Unipolar Depressed
Emotion processing	Increased amygdala and ventral striatal activity to positive and negative stimuli Decreased subcortical activity to emotional words	Increased amygdala and ventral striatal activity to positive and negative stimuli	Increased amygdala activity and ventral striatal to negative emotional stimuli	Increased amygdala activity to negative, but not positive, stimuli
Cognitive control tasks	Decreased DLPFC and VPFC activity	Increased DLPFC and VPFC activity relative to bipolar remitted	Decreased VPFC activity	Decreased DLPFC and VPFC activity

Note: DLPFC, dorsolateral prefrontal cortex; VPFC, ventral prefrontal cortex.

performance in individuals with bipolar disorder (some findings including other bipolar subtypes), but which remain relatively unexamined. These include effects of regional structural neural volume abnormalities, psychotropic medication, and other clinical variables, including illness duration, subsyndromal symptoms of depression and mania in remitted individuals with bipolar disorder comorbid anxiety, history of psychotic symptoms, and history of alcohol and illicit substance abuse. Regarding regional structural volume abnormalities, findings have indicated amygdala volume increases in adult individuals with bipolar disorder,[89–94] although decreases in adolescent individuals with BPI.[95–101] Other studies have reported increased ventral striatal (caudate nucleus and putamen) volumes[93,99,101] and decreased anterior thalamic volumes.[102] In contrast, smaller amygdala (and hippocampal) volumes have been more consistently reported in unipolar depressed individuals.[103–105] Findings regarding prefrontal cortical volumes have indicated decreased volume and gray matter density in anterior cingulate and subgenual cingulate gyri[106–109] and dorsal prefrontal cortex and VPFC [92,108,110–112] and reduced density in the right subgenual anterior cingulate and adjacent white matter in individuals with bipolar disorder compared with healthy individuals.[113] Recent findings further indicate gray matter volume reductions in the lateral orbitofrontal cortex of medicated individuals with bipolar subtypes I and II compared with healthy individuals.[114] There have also been reports of no significant differences in prefrontal cortical volumes between individuals with bipolar disorder and healthy individuals, however.[115,116] Similar patterns of reduced prefrontal cortical volume have been shown in unipolar depressed individuals,[103,117–119] particularly elderly unipolar depressed individuals.[120] Overall, while findings indicate structural volume abnormalities in amygdala and prefrontal cortical volumes,[121] a recent meta-analysis has indicated that the most consistent structural abnormality is an increase in right ventricular volume in individuals with bipolar disorder.[122]

Mood-stabilizing medications, including divalproex sodium and lithium, have been reported as either decreasing prefrontal cortical blood flow or having no effect. In healthy individuals, benzodiazepine dose inversely correlates with amygdala response to facial expressions,[123] while acute administration of selective serotonin reuptake inhibitor antidepressant medication has been associated with decreased amygdalar response to fearful facial expressions and aversive scenes[124–126] and a suppressed electrophysiological response in frontal and occipital cortices to unpleasant scenes.[127] Administration of the atypical neuroleptic sultopride has been associated with decreased amygdalar response to aversive compared with neutral scenes in healthy individuals.[125] In bipolar depressed individuals, antidepressant medication has been associated with relative increases in prefrontal cortical metabolism at rest.[67] Mood stabilizer medication has been associated with relative decreases in amygdala activity in remitted individuals with bipolar disorder (50% type I) at rest[55] and decreases in amygdala activity in a mixed group of remitted and unwell individuals with bipolar disorder to emotional facial expressions.[42] Other studies have shown a significant positive correlation between neuroleptic medication dose (in chlorpromazine equivalents) and activity in rostral anterior cingulate gyrus and DLPFC in remitted, euthymic individuals with BPI[45] and increased DLPFC activity in medicated compared with unmedicated euthymic individuals with bipolar disorder[128] during Stroop task performance, although no significant effect of any psychotropic medication was reported in individuals with bipolar disorder during a working memory task.[49] Long-term psychotropic medication use[114] and antidepressant exposure[110] have been associated with relative decreases in ventral prefrontal cortical gray matter volume in individuals with bipolar disorder, but long-term effects of psychotropic medication

upon regional structural volumes remain unclear.[128,129] The effect of medication upon neural responses during task performance in bipolar populations therefore requires further study.

Together, these findings indicate structural abnormalities in prefrontal cortical and subcortical regions that are components of neural systems implicated in 2 symptom domains of bipolar disorder. Furthermore, psychotropic medications that are commonly taken by individuals with bipolar disorder may impact activity, at least in part, in these neural regions of interest in individuals with bipolar disorder. As there is so little study of the nature of structural-functional relationships in these neural regions or the effect of psychotropic medication upon activity in these regions in bipolar study, these remain important areas for future research.

Future Research: Can We Identify Biomarkers of Risk for Bipolar Disorder?

Elucidation of neural system abnormalities that are persistent and bipolar disorder specific remains a main focus of research aiming to identify biomarkers of bipolar disorder. A subsequent stage will be the examination of the extent to which these abnormalities are shared with bipolar subtypes other than the traditional bipolar I subtype.[130,131] Another goal for longer term, future research in bipolar disorder that reflects major clinical problems associated with the disorder is the identification of biomarkers that allow us to predict the *degree* of risk of subsequent development of bipolar disorder in individuals who are at risk for, but as yet undiagnosed with, the disorder.

Findings from studies examining neural system abnormalities in bipolar disorder will ultimately lead to future studies examining the extent to which such neural system abnormalities exist as potential biomarkers of risk for bipolar disorder. Thus, future research should focus on examination of neural system abnormalities that are common to individuals with bipolar disorder and those as yet undiagnosed with the disorder, for example, individuals presenting with depression but yet to develop a manic or hypomanic episode, and individuals at high genetic risk for the disorder, for example offspring and as yet unaffected siblings of individuals with bipolar disorder. Only one study to date has examined functional neural abnormalities in individuals with bipolar disorder and their healthy siblings.[52] In this study, the authors measured regional cerebral blood flow (rCBF) with [^{15}O] water positron emission tomography after induction of transient sadness in 9 euthymic individuals with bipolar disorder who had responded to lithium and 9 healthy siblings. Common to both groups and a group of individuals with bipolar disorder who had responded to sodium valproate were rCBF increases in the dorsal/rostral anterior cingulate and anterior insula and decreases in the orbitofrontal and inferior temporal cortices. The authors noted that changes in rCBF during sadness induction were not seen previously in healthy subjects without a family history of mood disorder. The study's findings are therefore a first stage toward the identification of biomarkers of risk for bipolar disorder. Another study has demonstrated an association between genetic risk for bipolar disorder (in healthy siblings of adults with bipolar disorder) with gray matter volume deficits specifically within the right anterior cingulate gyrus and ventral striatum.[132]

To date, there have been no studies examining neural system abnormalities in healthy offspring of individuals with bipolar disorder. One study has, however, examined neurochemical abnormalities in offspring diagnosed with mood disorders (but not bipolar disorder) of adults with bipolar disorder using proton magnetic resonance spectroscopy.[133] Similar to findings in adults with bipolar disorders, neurochemical abnormalities were demonstrated within frontal cortex and cerebellar vermis in these offspring. There is clearly much scope for future research to employ different functional neuroimaging techniques to examine potential biomarkers of risk for bipolar disorder.

Conclusion

The recent research agenda for *DSM-V* highlights a need to translate basic and clinical neuroscience research findings into a new classification system for all psychiatric disorders based upon pathophysiologic and etiological processes. Furthermore, identification of neural system abnormalities in individuals with bipolar disorder is of critical importance for the advance in diagnosis and subsequent treatment of this frequently misdiagnosed disorder, particularly in individuals presenting with depression without a clear history of mania. A first stage toward the identification of biomarkers of bipolar disorder is the examination of functional abnormalities in neural systems directly related to common symptom domains of bipolar disorder that are common to depression and remission, rather than remission- or depression specific, and those abnormalities that are specific to bipolar disorder rather than common to unipolar depression. Such common symptom domains include mood instability, linked with impaired emotion processing, and impaired cognitive control processes, linked with cognitive dysfunction, that together may underlie the inability to regulate emotional states in individuals with bipolar disorder. Findings from a small number of studies indicate increased amygdala activity to mild happy and fearful facial expressions and decreased DLPFC activity to fearful expressions, although no consistent pattern of emotion identification deficits, in remitted individuals with bipolar disorder. There are more consistent findings indicating impaired performance on working memory and

attentional tasks in remitted individuals with bipolar disorder. Findings also indicate decreased prefrontal cortical, in particular ventrolateral and dorsal anterior cingulate gyral, activity, but also increased subcortical activity, during attentional task performance in these individuals. Data suggest relative increases in prefrontal cortical activity during attentional task performance in depressed compared with remitted individuals with bipolar disorder. There are limited data examining abnormalities that are common to remitted and depressed individuals with bipolar disorder—or even examining abnormalities that may persist throughout mania—in addition to depression and remission. Very few neuroimaging studies have directly compared bipolar and unipolar populations. Similarly, the relationship between structural and functional neural abnormalities and effects of psychotropic medication upon patterns of abnormal neural responses also remain unclarified in bipolar disorder. Current research should focus upon elucidation of neural system abnormalities that can be identified as biomarkers of bipolar disorder to help improve diagnostic accuracy in individuals in earlier stages of illness using paradigms. Major future goals are then to identify biomarkers that reflect risk for subsequent development of bipolar disorder and biomarkers that enable us to predict treatment response in individuals with the disorder.

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