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Toward the identification of biomarkers in bipolar disorder: lessons from functional neuroimaging studies

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Bipolar disorder (BP) is among the ten most debilitating illnesses worldwide[1]. BP depression continues to be frequently misdiagnosed and inappropriately treated as the depression associated with major depressive disorder (MDD) in depressed individuals who do not have a clear previous history of mania[2]. A major challenge for improving the mental health of depressed individuals is therefore improving the ability to accurately distinguish BP depression from the depression of MDD. Neurocognitive and neuroimaging variables are indirect and direct measures, respectively, of abnormal activity in brain systems that may be related to underlying pathophysiological processes of MDD and BP depression. Such measures may therefore facilitate the identification of diagnostically-relevant biomarkers of each disorder to meet this major clinical challenge.

CAN STUDIES EMPLOYING NEUROCOGNITIVE PARADIGAMS AND NEUROIMAGING TECHNIQUES HELP IMPROVE DIAGNOSTIC ACCURACY OF BP DEPRESSION?

The recent research agenda for 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[3-5]. 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[6]. Measurement of neurocognitive and neuroimaging variables that represent, respectively, indirect and direct measures of abnormal activity in brain systems related to pathophysiological processes associated with depression in BP, can be employed as a first stage toward identifying these biomarkers of BP depression to achieve the longer-term goal of improving diagnostic accuracy of these disorders.

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CORE DOMAINS OF PATHOLOGY IN BPI DEPRESSION

BP is becoming increasingly recognized as a multisystem disorder involving disturbance in different symptom domains[5]. Mood instability is a core domain of pathology in MDD and BP depression, and leads to variability in depression and to other aspects of mood variability, including irritability or anxiety, in both disorders, in addition to hypomanic/manic states in BP. Another domain of pathology common to the depression of both disorders is impaired cognitive and executive control, which includes such symptoms as the inability to concentrate, difficulty in decision making, and memory difficulties, and may result in impaired ability to control or regulate mood[7].

NEURAL SYSTEMS ASSOCIATED WITH EMOTION PROCESSING AND COGNITIVE AND EXECUTIVE CONTROL

Existing data from functional neuroimaging studies in healthy individuals point toward distinguishable neural systems for mood stability/normal emotion processing and cognitive and executive control. Normal emotion processing has been mapped to a neural system centered on subcortical limbic neural regions, including the amygdala and the ventral striatum, and ventromedial prefrontal cortex[8]. Cognitive and executive control (referring to a combination of planning, working memory, inhibitory control, strategy development, and cognitive flexibility) has been mapped to a lateral prefrontal cortical system, comprising dorsolateral and ventrolateral prefrontal cortices (DLPFC and VLPFC), important for cognitive and executive function[9], and the hippocampus, important for memory[10]. We next examine the extent to which existing studies using functional neuroimaging measures have provided evidence for functional abnormalities in these two neural systems in BP depression, and then go on to examine the extent to which functional

abnormalities in these neural systems may distinguish BP depression from MDD.

FUNCTIONAL NEUROIMAGING STUDIES IN BP DEPRESSION

Findings from functional neuroimaging studies comparing patients with BP and healthy individuals indicate abnormally increased subcortical limbic activity to emotional stimuli in remitted and subsyndromally depressed patients with BP (type 1[11-13]), and to negative scenes in depressed patients with BP (including rapid cycling[14]). Decreased blood flow has been reported in medial prefrontal cortex during sad mood induction relative to baseline in remitted and depressed patients with BP (type 1[15]), but this study did not include a group of comparison healthy individuals. One study reported relative increases in subcortical limbic activity to happy faces in depressed compared with manic patients with BP (type 1) and healthy individuals[16]. Findings have also indicated decreased DLPFC/VLPFC activity during attention task performance in depressed and remitted patients with BP (type 1) compared with healthy individuals[17,18]. Increased subcortical limbic activity (predominantly in the amygdala) has been demonstrated in depressed and remitted BP patients (approximately 50 % type 1) relative to healthy individuals, but at rest rather than during emotion challenge[19]. In BP depression, findings from these indirect and direct measures of activity in neural systems underlying mood stability and cognitive control/executive control therefore suggest increased activity in subcortical limbic neural regions associated with mood stability, and decreased activity in DLPFC/VLPFC and hippocampus, associated with cognitive and executive control and memory.

A COMPARISON OF FUNCTIONAL NEUROIMAGING STUDIES IN MDD VERSUS BP DEPRESSION: TOWARD DIAGNOSTIC BIOMARKERS OF BP?

While findings regarding neural activity during at rest studies are somewhat discrepant in depressed patients with MDD, findings from studies employing emotional challenge paradigms suggest that these patients show increased amygdala and subcortical limbic activity to emotional stimuli relative to healthy individuals. Unlike remitted and depressed patients with BP, however, in depressed MDD patients this abnormal pattern of neural activity is predominantly to negative rather than positive emotional stimuli[20,21] (table 1). Furthermore, these abnormalities appear to be depression-dependent in MDD rather than abnormalities common throughout depression and remission[22]. Only one study to date has directly compared neural activity in BP patients and depressed MDD patients. Here, increases in amygdala and subcortical limbic activity were shown predominantly to mild happy, but also to fearful, facial expressions versus neutral facial expressions in remitted, but subsyndromally depressed, BP (type 1) patients relative to depressed MDD patients[12].

Table 1 Neural activity during emotion and cognitive challenge tasks in bipolar depression and MDD

	Bipolar remitted	Bipolar depressed	MDD
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 to negative, but not positive, stimuli
Cognitive control task	Decreased DLPFC and VPFC VPFC activity	Increased DLPFC and VPFC activity relative to bipolar remitted	Decreased DLPFC and VPFC activity

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

There is clearly a need for studies that focus on comparing neural activity in depressed MDD and depressed BP patients during emotional and cognitive challenge paradigms.

SUMMARY

Together, findings from neurocognitive and neuroimaging studies indicate that MDD and BP depression can be distinguished, at least in part, by indirect and direct measures of abnormal activity in neural systems underlying emotion processing and cognitive and executive control. These abnormalities may underlie, respectively, the mood instability and impaired cognitive control of emotion that are observed clinically in both disorders. Increased subcortical limbic activity to happy stimuli may, in particular, be an important pathophysiologic process distinguishing the depression associated with BP from that associated with MDD.

It is clear that in the future, studies employing new neurocognitive paradigms and those embracing the new developments in functional neuroimaging may be able to draw us closer to meeting the critical challenges of early and accurate diagnosis that lead to early optimization of treatment of both MDD and BP depression.

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