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Commentary

Neural Markers That Distinguish Bipolar Disorder From Major Depressive Disorder: Moving Closer to a Reality

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Bipolar disorder is the fourth leading cause of disability in the world (1) and is associated with 180 million lost workdays per year, $25.9 billion in salary-equivalent lost productivity per year (2), a 9.2-year reduction in expected life span, and a 20 to 30 times greater suicide risk than in the general population (3). Yet because many individuals with bipolar disorder present to clinicians during a depressive episode without reporting a clear history of hypomanic or manic episodes, bipolar disorder is frequently misdiagnosed as major depressive disorder; this is one of the reasons why more than one third of individuals with bipolar disorder have to wait 10 years to receive the correct diagnosis (4). Identifying objective markers reflecting underlying pathophysiological processes of bipolar disorder is thus a critical goal to facilitate earlier and more accurate diagnosis. In the last 10 years, several studies have used neuroimaging techniques to identify neural markers that differentiate individuals with bipolar disorder from those with major depressive disorder (5). The majority of these studies focused on emotional regulation circuitry (centered on the amygdala, striatum, hippocampus, insula, and prefrontal cortical regions), given that emotional dysregulation is a characteristic feature of the disorder. Findings from these studies indicate differential patterns of abnormal activity and functional connectivity among these regions in the two disorders (6).

A major limitation of these previous studies, however, is the focus predominantly on individuals during the depressive phase of illness. While such a focus is necessarily important, given that it is during this phase of illness that most individuals present for treatment, this precludes identification of mood state–independent (i.e., trait-like) neural markers that can be used to identify bipolar disorder in individuals regardless of phase of illness. In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Korgaonkar *et al.* (7) make a significant contribution to the published literature by examining individuals with bipolar disorder and major depressive disorder during remission. Using an established face emotion paradigm including both supraliminal and subliminal presentations of happy, angry, disgusted, fearful, sad, and neutral facial expressions, Korgaonkar *et al.* (7) report significantly lower amygdala activation to supraliminal presentations of disgust, fear, sadness, and neutral expressions, and to subliminal presentations of all emotions, in individuals with bipolar disorder relative to those with major depressive disorder—and significantly lower activation in this region to all subliminal presentations relative to healthy individuals. Furthermore, individuals with bipolar disorder showed distinct patterns of amygdala functional connectivity to supraliminal and subliminal presentation of these facial expressions that distinguished them from individuals with major depressive disorder and healthy individuals. Here, the most striking pattern of bipolar disorder–specific functional connectivity abnormalities was a combination of 1) abnormal reductions in amygdala-hippocampus functional connectivity to supraliminal presentations of sad and neutral faces and in amygdala-putamen functional connectivity to supraliminal presentations of happy faces, and 2) abnormal reductions in amygdala-hippocampus and amygdala-insula functional connectivity to subliminal presentations of anger and disgust (Table 1). Using logistic regression analyses including those activation and functional connectivity measures that showed significant between-group differences, Korgaonkar *et al.* (7) also demonstrated a diagnostic classification accuracy for bipolar disorder versus major depressive disorder of 88.6% in the patient groups. Korgaonkar *et al.* (7) indicate that these neural measures thus have the potential to aid in the early diagnosis of bipolar disorder.

The consistent finding in individuals with bipolar disorder of abnormal amygdala hypoactivation and abnormally reduced functional connectivity with the hippocampus across different emotions to both supraliminal and subliminal presentations deserves further comment. The functional coupling between the amygdala and hippocampus is critical for the appraisal and contextual processing of facial emotion, given the pivotal role of the hippocampus in automatic, i.e., covert, reappraisal during emotional regulation (8). That amygdala activation and functional connectivity between the amygdala and hippocampus were significantly lower to negative emotional facial expressions in individuals with bipolar disorder relative to both healthy individuals and individuals with major depressive disorder suggests that these appraisal process abnormalities during negative facial emotion processing are specific to bipolar disorder and are not common to both mood disorders. Indeed, Korgaonkar *et al.* (7) report that individuals with major depressive disorder showed significantly greater amygdala-hippocampus functional connectivity than healthy individuals to supraliminal presentations of sad facial expressions. This pattern of abnormally lowered amygdala-hippocampus connectivity across different negative facial expressions may thus underlie the difficulty in facial expression discrimination and associated social processing difficulties experienced by many individuals with bipolar disorder (5,8). Given the role of the anterior insula in

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Table 1. Main Patterns of Significantly Reduced Activation and Functional Connectivity to Supraliminal and Subliminal Presentations of Emotional Facial Expressions That Distinguished Individuals With Bipolar Disorder From Individuals With Major Depressive Disorder and Healthy Individuals

Emotion	Lower Activation	Lower Functional Connectivity
Supraliminal		
Happy		Amygdala-putamen
Angry		
Disgust	Amygdala (vs. MDD only)	
Fear	Amygdala (vs. MDD only)	
Sad	Amygdala (vs. MDD only)	Amygdala-hippocampus
Neutral	Amygdala (vs. MDD only)	Amygdala-hippocampus
Subliminal		
Happy	Amygdala	
Angry	Amygdala	Amygdala-hippocampus and amygdala-insula
Disgust	Amygdala	Amygdala-hippocampus and amygdala-insula
Fear	Amygdala	
Sad	Amygdala	
Neutral	Amygdala	

MDD, major depressive disorder.

interoceptive processing (9), as Korgaonkar *et al.* (7) note in the discussion section of their article, the pattern of abnormally reduced amygdala-insula functional connectivity observed in individuals with bipolar disorder to anger and disgust may reflect aberrant interoceptive processing during appraisal of these threat-related facial emotions. This may in turn be associated with the difficulty in regulating responses to threatening cues, and in emotional regulation in general, in individuals with bipolar disorder.

Another interesting feature of the study was the inclusion of both supraliminal and subliminal presentations of facial emotion in the neuroimaging task, with findings indicating differential patterns of reduced amygdala-hippocampus (and amygdala-insula) functional connectivity in bipolar disorder to different types of negative facial emotion during supraliminal and subliminal presentations. Specifically, the findings indicate that aberrant functional connectivity was evident to distress-related negative emotions, i.e., sad faces, as well as to neutral faces presented supraliminally, but to threat-related negative emotions (anger and disgust) presented subliminally. These findings point to specific appraisal deficits of covert threat and overt sadness in bipolar disorder and may reflect the fact that in the general population, sad, angry, and disgusted facial expressions are often more difficult to recognize than happy facial expressions, while fearful facial expressions are among the least well identified of facial expressions (10). Thus, any deficit in appraising and recognizing facial expressions in individuals with bipolar disorder relative to healthy individuals might become particularly apparent for those specific facial expressions for which there are neither ceiling effects in recognition accuracy, unlike happy faces, nor floor effects in recognition accuracy, unlike fearful faces. It is unclear why the between-group differences in functional connectivity for anger and disgust versus sad expressions were evident in different contexts, however, and this should be the focus of future studies.

Clearly, these are important findings and extend the extant literature by identifying for the first time mood state–independent patterns of abnormal activity and functional connectivity in emotional regulation neural circuitry that distinguish individuals with bipolar disorder from those with major depressive disorder. As Korgaonkar *et al.* (7) note, however, there were several limitations to the study, including the focus only on remitted individuals. Longitudinal studies, ideally examining individuals as they develop different mood states, are needed to determine the extent to which there are persistent abnormalities in neural measures that in turn can distinguish individuals with bipolar disorder from those with major depressive disorder. Replication in larger, independent samples is another next step. The diagnostic classification analysis, while an innovative step to demonstrate how neuroimaging findings might be used to aid diagnosis, is similarly limited by the absence of an independent test sample. The latter will be critical to test the extent to which the between-group findings reported by Korgaonkar *et al.* (7) indeed represent useful neural markers to guide the diagnosis of bipolar disorder.

There is an increasing research focus on demonstrating how advances in neuroimaging can be harnessed to increase understanding the neurobiology of psychiatric disorders to aid diagnosis, risk identification, and novel treatment developments. Korgaonkar *et al.* (7) provide an important example of how neuroimaging methodologies can be used to obtain clinically useful disease markers, and thereby provide further evidence of how such methodologies can aid the translation of research findings into clinically relevant information.

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