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Euthymia, Depression, and Mania: What Do We Know About the Switch?

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The holy grail for research in bipolar disorder (BD) is the mechanism that underlies the switch to acute manic and depressive episodes. Armed with knowledge of the switch, researchers could more effectively prevent and treat episodes of this disorder. However, the switch mechanism has been elusive and the quest continues.

The Hulvershorn et al. study in this issue (1), provides an important step forward. It is one of the few published functional neuroimaging investigations of individuals with BD experiencing elevated, depressed and euthymic mood states, who are also medication-free. The study demonstrates abnormalities in brain responses to negative emotional stimuli during euthymia in the BD group that may be trait features of BD and perhaps biomarkers of the vulnerability to mood cycling. Differing regional patterns of dysfunction were also observed in mania/hypomania or depression that may reflect neural mechanisms underlying these mood states.

Phenotypic Clues

In the 1970's, data emerged from careful, systematic, longitudinal observation of unmedicated individuals with BD, providing what remain some of the most important leads for researching the mechanisms underlying the switch. Sleep changes, including decreases overall and in rapid eye movement sleep, often occurred at the time of the switch to mania, observed prior to the emergence of full manic symptoms. Disturbed sleep patterns were also associated with circadian fluctuations in body temperature, hormone secretion as well as catecholamine increases (2). These findings implicated the neurobiology underlying sleep and other circadian disturbances in the switch process. Direct study of brain structures controlling circadian rhythms, such as the hypothalamus, are difficult to accomplish with current functional magnetic resonance imaging (fMRI) methods, which may limit the utility of current fMRI approaches for studying switch mechanisms. However, findings by Hulvershorn et al. (1) in amygdala and orbitofrontal cortex (OFC), important nodes in hypothalamic neural systems, are consistent with a notable convergence of findings in the amygdala and OFC amongst neuroimaging studies of BD (3). New research strategies are needed for simultaneous study of the hypothalamus and other components of this neural system.

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Changes in social cognition may accompany increases in motor activity and spontaneous speech that also mark the transition to mania. For example, when switching from euthymia to mania, individuals with BD show increased awareness of the environment and perceptiveness about the feelings of others that may intensify during mania (2). Abnormalities in the neural processing of facial emotions have been reported in BD, particularly involving the amygdala (3). Although shown in depression and euthymia, amygdala findings were not detected in mania in the Hulvershorn et al. study (1); however, face processing also occurs in the OFC, which did show reduced activation during mania/hypomania.

The Hulvershorn et al. study (1) reported increased activation in the insula during euthymia and mania/hypomania, highlighting the potential role of this understudied region in BD. The insula is implicated in monitoring of internal affective states, the processing of social cues, and empathy. Differences in insula activation in BD have been shown previously in neuroimaging studies performed during emotion processing and social cognition tasks (4). A recent study noted volume decreases in the insula in adolescents with BD, suggesting that insula differences may be early features that are involved in vulnerability to developing the disorder (5). Perhaps insula changes, such as observed in Hulvershorn et al. (1), contribute to the differences in interpersonal awareness observed at the times of the switch.

Building on Early Biological Models

The early longitudinal studies of the 1970's included the collection of valuable biological data at the time of the switch. Investigations documented increases in catecholamines and their metabolites just prior to the switch, and during, mania (2). In one model, as mania tends to follow depression, low catecholamine levels in depression were theorized to lead to postsynaptic receptor supersensitivity that might interact with the elevated catecholamine levels precipitating manic states. Later support for this model was suggested by a study in which hypomanic symptoms emerged in remitted individuals with BD taking lithium in the days following catecholamine depletion with alpha-methylparatyrosine (6). This is one of many possible mechanisms that could contribute to cortical activity increases in mania, relative to depression, as observed in Hulvershorn et al. (1).

Monoaminergic transmission continues to be implicated in the switch. Effects of related genetic variations have been a focus of more recent studies. Variations in genes that can influence monoaminergic function have been associated with differing cycling rates, such as seen in association with the catechol-O-methyl transferase gene. Early observations of switches after initiation of antidepressant treatments that alter monoaminergic function, noted in subsets of patients with BD, have been observed more recently, although findings have conflicted. In one study, variation in the serotonin transporter promoter polymorphism (5-HTTLPR) was associated with switching with antidepressants, although this finding has not been replicated (7). Together with fMRI data that 5-HTTLPR variation influences corticolimbic responses to emotional stimuli in BD (8), overall findings suggest that there may be subsets of individuals with BD, with differing genetic backgrounds related to monoaminergic transmission, who may have different neural system patterns and vulnerabilities to the switch. Glutamatergic mechanisms are also increasingly being investigated in BD and its treatment, although medications such as lamotrigine, and more recently riluzole, which inhibit glutamate release have shown effectiveness in treating depression in BD but have not been shown to induce a switch (7).

More recent candidate mechanisms for the switch have included mechanisms within monoaminergic signaling pathways. For example, preclinical research implicates protein kinase C, as well as glycogen synthase kinase 3, which also has a role in circadian rhythms.

Cyclic adenosine monophosphate response element binding protein and brain derived neurotrophic growth factor (BDNF) have also been implicated. There is some further support in clinical studies, as the BDNF *Val66* allele may be associated with cycling and is preferentially transmitted in adults and youths with BD (7). New candidates, identified in genome-wide association studies, such as *CACNA1C* have received little study with respect to the switch; however, recent findings (9) that *CACNA1C* influences the functioning of the Hulvershorn et al. (1) regions suggest that further study may hold promise.

Given the circadian patterns in the disorder, an interesting line of research is in genes associated with circadian rhythms such as the *CLOCK* gene. *CLOCK* mutant mice have features of BD including both sleep changes and hyperactivity, and *CLOCK* variation in humans may influence illness recurrence. Studies are now beginning to emerge that integrate investigation of circadian genes with fMRI assessments of subjects with mood disorders (9).

The triggering of mood switching by stress implicates the hypothalamic pituitary adrenal (HPA) axis in the switch. Administration of glucocorticoids has long been associated with the switch to manic states, and their withdrawal with the emergence of depression. Stress has been shown to have effects on the circuitry studied in Hulvershorn et al. (1), including on dendritic remodeling, gray matter decreases and dysfunction in prefrontal cortex and limbic structures (11). Glucocorticoid treatment for multiple sclerosis has been associated with mood symptoms, however, the disorder itself has long been suggested as a potential model for the switch. There is a resurgence of interest in this model as immune factors are increasingly implicated in mood disorders. Moreover, abnormalities in the structural integrity of white matter, associated with functional connectivity abnormalities, have been reported in BD (2). Connectivity abnormalities could contribute to regional findings such as those in Hulvershorn et al. (1) and are additional mechanisms that could underlie vulnerability to the switch.

In the Road Ahead

Of the many candidate molecular mechanisms, it is not known which generate the switch, and which are downstream neural and behavioral consequences of the switch. Functional neuroimaging findings from studies performed during full-blown episodes may reflect the latter. Some of the early investigations of the switch were so fruitful, as research participants could be observed longitudinally, while unmedicated, in inpatient settings, with data collected before and at the early stages of the switch. This is far more difficult to accomplish today and new strategies are needed. A substantial challenge for the field has been the limited number of animal models for BD. Although there has been considerable progress in research in animal models of mood disorders, the ability of these models to provide mechanistic insights into mood cycling is still limited. Integrated switch models are needed that investigate molecular mechanisms, their influences on brain circuitry, and that capture, in addition to emotion-related changes, other key aspects of the disorder including cycling, circadian rhythm and activity changes. In humans, studies that integrate methods such as those of Hulvershorn et al. (1) with imaging or non-imaging molecular as well as behavioral approaches, and assessment at time of the switch, are needed in the next steps forward on the complex journey ahead towards the grail.

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