What Is Bipolar Disorder?

It is easy to forget that bipolar disorder, as we now know it, is a recent construct. About 100 years ago, Kraepelin described a recurrent affective disorder (1), but bipolar disorder was not differentiated from major depressive illness until the work of Leonhardt 50 years later (2). Bipolar disorder is now recognized as a potentially treatable psychiatric illness that has substantial mortality and high social and economic impact. Every aspect of its definition, boundaries, mechanisms, and treatment, however, is subject to debate. In fact, there is no objective measure that can determine that one has bipolar disorder or does not have it.

Given these problems, we are far from a rigorous definition of bipolar disorder. Our current definition is syndromal and based on affective symptoms (DSM-IV). It is highly reliable, but the requirement of mania-like states is clearly a problem because, for most patients, the illness appears to start with depressive episodes, and a depressive first episode predicts a more severe course of illness (3). We need to understand bipolar illness well enough that we will no longer have to wait for a manic episode before we can make the diagnosis. We also must understand the illness well enough to avoid the corresponding problem of overdiagnosis. Neither underdiagnosis nor overdiagnosis provides a service to patients with this illness.

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Most of our current understanding of bipolar disorder is based on properties of patients experiencing depressive or manic syndromes; too little information is available on what predisposes people to these episodes and on the factors that determine the course of illness. The development of functional brain imaging techniques has the potential to identify neural processes that underlie bipolar disorder. If this promise is to be realized, however, we need a framework that can integrate brain imaging with basic, clinically observable processes of bipolar disorder. In developing this framework, we must question our assumptions about bipolar disorder. Is affective disturbance basic to bipolar disorder, or is affect an epiphenomenon of a more fundamental disturbance in regulating something like motivation, arousal, or reinforcement? How independent are the inherited mechanisms that underlie the symptomatic syndromes and course of bipolar disorder? Are there potential physiological or behavioral markers that can be used clinically to identify bipolar disorder before an individual is manic?

The report by Krüger et al. in this issue of the *Journal* touches on three potentially fundamental—and poorly understood—areas of bipolar disorder. The first is the presence of specific mechanisms leading to susceptibility to affective symptoms and, presumably, to episodes of illness. In this study, the focus is on regulation of responses to emotional stimuli. More important than the specific mechanism, however, is the development of a testable model based on specific mechanisms of susceptibility. It is not appreciated enough that the basis of bipolar disorder is not depression or mania; rather, bipolar disorder is an illness that confers abnormal susceptibility to these states.

A second area is that of resilience. Protective mechanisms may prevent the occurrence of symptomatic illness in susceptible individuals. In this regard, it is tantalizing that first-degree relatives of individuals with bipolar disorder have been reported to function better in many spheres than comparison subjects (4). Krüger et al. demonstrated that subjects with bipolar disorder differed from siblings of lithium-responsive subjects in medial frontal cortical responses to an experimental affective stimulus. The enhanced medial frontal cortex response was not found in an earlier study of healthy subjects carried out by the same investigators using the same instrument. One model of

susceptibility to bipolar disorder, based on these findings, is that genetic susceptibility to bipolar disorder is related to the set of responses that was common to the three subject groups in the study by Krüger et al. and that the ability to raise, rather than lower, regional cerebral blood flow (rCBF) in the medial frontal cortex is protective. Is this characteristic an additional property of some individuals who are otherwise susceptible to bipolar disorder (making the model somewhat more complex) or did the affective stimulus in healthy subjects lack the salience to activate this putative protective system? Finally, the observation that medial frontal cortical activity was increased in siblings and reduced in patients raises the possibility that this differential change is secondary to a response that occurs (or does not) elsewhere.

Third, and perhaps most important, is the question of course of illness. Kraepelin (1) was the first of many to observe that impairment associated with recurrent affective disorders was related more to the degree of recurrence than to the severity of a given episode. Others have reported that course of illness is heterogeneous—some patients experience an episodic-stable course, and others have more mood instability with more frequent episodes, mixed states, and susceptibility to problems like substance abuse (5). Robust response to lithium appears to be familial (6) and to be related to the more episodic-stable course of illness (7). Therefore, there may be specific mechanisms that confer an unstable course or protect against it. This vital area is the focus of an almost secondary aspect of the study by Krüger et al., the group of valproate responders.

The lithium- and valproate-responsive subjects shared certain responses to the affective stimulus, including the reduction in medial frontal cortex rCBF that differentiated lithium-responsive subjects from their siblings. They differed in rCBF responses in the anterior cingulate cortex (increased in lithium responders and decreased in valproate responders) and in the dorsolateral prefrontal cortex (decreased in valproate responders). Course of illness was quite different in these groups: lithium-responsive subjects did not have histories of substance use disorders and had been episode-free for at least 3 years, but valproate-responsive subjects had more complicated histories and had been relatively stable for only 6 months. The differences between the subject groups in rCBF responses to the emotional stimulus could be consequences of the differences in course of illness, could be mechanisms underlying it, or could result from complications of bipolar disorder such as substance abuse or trauma. These possibilities can generate testable hypotheses that will require genetic and physiological studies in addition to brain imaging.

As powerful as functional brain imaging may be, it raises important questions that underscore the necessity of complementary, convergent experimental approaches. In general terms, these include the validity of voluntary mood-induction methods as a measure of susceptibility to affective episodes and the validity of the detailed inferred interpretations of presumed roles of specific brain areas. In terms of the specific design, a major strength of the study by Krüger et al. was the use of groups with contrasting courses of illness and comparison of genetically similar patients and nonpatients. Aspects that raise questions are the lack of concurrent controls (comparison subjects were studied a year earlier using the same techniques and PET instrument), the small number of subjects, questions of whether either group of subjects is representative, the validity of voluntary mood-induction methods, and specific technical questions about the interpretations of the imaging techniques. Any of these matters could be discussed at length, but they are less important than the implications of the study's findings.

If we are ever going to understand bipolar disorder in a useful manner, we will need to deconstruct the susceptibility, protective, and illness-course mechanisms that underlie the illness. Studies like the one by Krüger and associates are important steps in this direction.

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