COMMENTARY

Brain Structural Response in Individuals at Familial Risk for Bipolar Disorder: A Tale of Two Outcomes

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Bipolar disorder (BD) is a chronic psychiatric disorder with high morbidity and mortality, deserving of efforts to understand who are at highest risk for developing this disorder. So far, the most reliable risk factor is a family history of BD. Twin and family studies have reported a 59–87% heritability of BD suggesting that first-degree relatives of probands with BD are at particularly high risk for developing BD themselves (1). Indeed, family members of BD probands also have high rates of mood and other psychiatric disorders. However, longitudinal follow-up of offspring of parents with BD, for example, show variable rates of conversion to full mood syndromes influenced by a variety of factors that have modest predictive power. Researchers are turning to neuroimaging to identify biologic targets such as aberrant brain structures in individuals who have a familial risk for developing BD to bridge a clinical assessment of emotion dysregulation with biologically mediated brain abnormalities to advance our understanding of the pathophysiology of BD development. In this issue of *Biological Psychiatry,* Hajek *et al.* (2) and Mahon *et al.* (3) present the findings of two studies aimed at addressing this important area.

Using structural brain magnetic resonance imaging, Hajek *et al.* (2) found that individuals with BD as well as their affected and unaffected relatives had a significantly larger right inferior frontal gyrus (IFG) than did healthy control subjects. Although others have found an enlarged IFG in BD subjects in early stages of the illness (4), this appears to be the first time that enlargement in this region has also been found in family members of individuals with BD with or without the illness. The authors suggest that this finding might be a biomarker for the development of BD, an assertion that makes sense, given what is known about the integral function of the IFG, specifically Brodmann area 47, in emotional regulation and socioemotional learning.

The IFG has been implicated in the pathophysiology of affective disorders. Increased activation in the IFG has been found in youth with BD in response to emotional tasks (5), and abnormal functional connectivity of this region with the amygdala was recently reported in adults with BD (6). However, this region has also been implicated in risk for developing other mental disorders such as schizophrenia (7), reducing the potential specificity of this finding. Moreover, the IFG is highly lateralized in function such that the right side mediates processing of nonverbal material, whereas the left side mainly governs language-related function. It is not known which among these functions of the IFG are most relevant to emotional processing in BD. Moreover, it is also unknown whether the structural changes in this region are caused by abnormal functional demands or by impaired white matter connections. Additional study of this region in the context of bipolar illness development could clarify these issues.

Using a similar high-risk design, Mahon *et al.* (3) examined white matter integrity (assessed via fractional anisotropy [FA]) using diffusion tensor imaging in patients with BD, unaffected siblings of patients with BD, and healthy volunteers to identify biomarkers of genetic risk in cortical white matter. They found that FA differed significantly ($p < .05$; corrected) among the three groups within the right temporal white matter. Specifically, unaffected siblings had FA values that were intermediate to and significantly different from those of healthy volunteers and patients with BD (healthy controls greater than unaffected siblings greater than bipolar disorder). Moreover, FA values in this region were negatively correlated with trait impulsivity in unaffected siblings. Probabilistic tractography also indicated that the regional abnormality lies along the inferior frontal occipital fasciculus, a large intrahemispheric association pathway. These results suggest that lower white matter integrity in the right temporal lobe may be a biomarker for genetic risk of BD. The attenuated nature of these white matter abnormalities present in unaffected siblings may allow for some preservation of adaptive emotional regulation, whereas more pronounced alterations observed in affected patients may be related to the marked emotional dysregulation characteristic of BD.

Volumetric reductions have been commonly described in individuals with BD possibly because of neurobiologic consequences of illness burden (8), whereas increased volumes have been described in unaffected offspring of individuals with BD (9,10) as a putative indicator of resilience. Risk and resilience represent two contrasting outcomes in individuals with a familial risk for BD. Whereas a family history of BD, maladaptive behavior, or social disadvantage in certain individuals confer risk, others find positive adaptations that lead to more resilient outcomes. Hajek *et al.* (2) explained that in their study, increased IFG volumes may be present early in the course of illness as a compensatory mechanism that, with time and illness burden, is reversed by the neurotoxic effects of the illness causing decreases in gray matter volume in this region. The overall size of the inferior frontal gyrus may depend on the sum of these two opposing processes such that early in the course of illness, neural mechanisms overcompensate for the potential toxic effects of illness onset, resulting in increased volume in inferior frontal gyrus. With illness progression, toxic effects of the disorder accumulate and the compensatory mechanisms become insufficient, resulting in reduced volume in this region. This may be an example of structural plasticity of the brain in individuals at risk for BD that may be involved in both risk and resilience. Mahon *et al.* (3) found that unaffected siblings show an intermediate structural phenotype in white matter, suggesting a dose-related effect in the evolution of structural abnormalities and BD illness. Both studies compared cohorts at different stages on the illness continuum, but the analyses were cross-sectional. To confirm that gray and white matter abnormalities among at-risk and fully syndromal individuals with BD represent endophenotypes of illness, individuals at risk for BD need to be prospectively followed up from health to illness development.

In combination, these two studies point to gray and white matter structural abnormalities that may be associated with bipolar illness development in individuals with a familial risk for BD. However, what remains unexplained is whether these structural differences represent early risk markers or compensatory mechanisms

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that may help prevent the onset of BD in familially at-risk individuals. Although neural circuit abnormalities in BD have been well described, we have not been able to distinguish this disorder neurally from other disorders. In addition, we lack a biologic perspective on the mechanisms that confer a risk for or resilience from BD, and we have no reliable prognostic markers for which individuals will go on to develop lifelong illness and which will not. The potential impact of determining the relations of these structural abnormalities to the onset and course of BD is high because it can elucidate ideal times for intervention to preempt onset and prevent neuroanatomical consequences of recurrent illness.

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