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Toward Understanding the Functional Relevance of White Matter Deficits in Bipolar Disorder

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Neurobiological research in psychiatry has increasingly placed emphasis on understanding how neural systems go awry in psychiatric disorders. Toward this end, advanced imaging methods go beyond the study of isolated brain areas, probing the connections within neural networks. Diffusion imaging (DI) assesses white matter (WM) microstructure, informing us about the physical state of these connections (the wiring within a system). More than 50 DI studies have been published in bipolar disorder (BD) in the past decade, most commonly reporting lower fractional anisotropy (FA) in a range of different brain areas. This issue of *JAMA Psychiatry* contains an important contribution to the DI literature in a study with a large enough sample to address 2 important questions in DI BD research: where WM deficits are most consistent and how abnormalities vary across subtypes of BD.

In this issue, Sarrazin and colleagues¹ report findings from the largest sample to date using advanced methods to examine WM integrity in an international sample of 118 patients with BD and 86 healthy control individuals across 3 countries. This study used a standard DI acquisition on identical 3-T platforms, with application of a q-ball model for analysis followed by tractography to delineate 22 WM tracts. The authors examined generalized FA (GFA; similar to diffusion tensor imaging's FA) within these tracts between patients with BD and healthy control individuals. Replicating and extending previous smaller studies, they confirmed lower GFA in the corpus callosum, cingulum, and arcuate fasciculus in patients with BD. Furthermore, they compared how GFA differed in subgroups of patients with BD with vs without psychosis, finding lower GFA in the body of the corpus callosum in the patients with psychosis. This finding makes intuitive sense: the patient group with more severe psychopathology showed a more severe biological abnormality.

An emerging body of research has begun to examine the question of when in the course of development, risk, and illness WM deficits emerge in BD. Family risk studies have found attenuated WM deficits in unaffected relatives of patients with BD,² suggesting that these biological abnormalities are associated with risk for illness and are present before illness onset. A multiple-hit principle more general to psychopathology may apply, in which when less extensive deficits occur, they represent vulnerabilities that can be overcome by using other strengths in the system, but that when more extensive aberrations occur, they impact network dynamics sufficiently to impair function.

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Although BD DI studies have suggested that WM impairments can occur throughout the brain, this larger study confirms previous work highlighting deficits in the corpus callosum. These findings support a theory that patients with BD have reduced interhemispheric connectivity. Pettigrew and Miller³ first articulated the interhemispheric connectivity hypothesis, documenting that patients with BD had a slower rate of perceptual alternation in binocular rivalry. Pettigrew and Miller argued that “the clinical manifestations of BD may be explained by hemispheric activation being ‘stuck’ on the left (mania) or on the right (depression).”³ Although clearly bipolar pathophysiology is more complex than simply getting “stuck” in a happy or sad mood, the consistency of findings over the years adds weight to these early ideas and may provide important clues for new research investigating how corpus callosum abnormalities contribute to altered brain functioning relevant to BD using more advanced technologies.

Results from the article in this issue and other DI studies provide further evidence that patients with BD have WM deficits, expanding our knowledge about when and where in the brain these abnormalities most frequently occur. Moving forward, the next stage of investigation will need to ask questions about the why and how; in other words, we need to understand the functional relevance of these findings. To clarify the role of faulty wiring in the overall pathophysiology, new research will benefit from multimodal approaches. For example, a recent study of patients with BD and their unaffected relatives using both DI and cognitive assessment found network-specific links between WM impairments and neuro-cognitive performance.⁴ Another recent example of integrative work reported that FA was inversely linked with serum lipid hydroperoxide, a marker of oxidative stress, in patients with BD, suggesting a possible mechanism for damage to WM in these patients.⁵ Prior research has implicated genes encoding oligodendrocyte and myelin development-related proteins in BD, and recent genetic work in combination with DI has identified links between these genes and WM integrity in healthy young adults.⁶ Very little work has been done using multimodal magnetic resonance imaging techniques in BD, but well-designed research probing specific circuits with both DI and functional magnetic resonance imaging hold promise to advance our understanding of these systems. Neuromodulation techniques provide another promising approach for probing neural circuitry that could be combined with DI to assess how structural connectivity leads to altered neural transmission in vivo.

When considering the next steps of DI research, it is important to acknowledge that microstructural WM deficits are not specific to BD; rather, this pattern has been reported across psychiatric disorders. Disease-specific patterns have not emerged; so far, we do not have clear evidence that certain disorders involve WM impairments in a specific set of tracts. In keeping with the National Institute of Mental Health Research Domain Criteria initiative, how WM deficits are related to fundamental dimensions that cut across traditional disorder categories needs to be examined. Ideally, new Research Domain Criteria research would recruit patients to clinical studies based on these fundamental dimensions rather than psychiatric disorders and then use multimodal neuroscience approaches to shed light on the whole picture of these systems.

Finally, as the functional meaning of WM abnormalities becomes clearer, the next advance is to investigate how to use WM microstructure information to plan and monitor the

treatment of BD. Identifying the regions that have altered connectivity may provide us with new strategies to enhance, restore, and/or compensate to improve function. For example, recent work in other psychiatric/neurological illnesses has used DI techniques to optimize planning for deep brain stimulation.⁷ Novel neuromodulation strategies that are emerging, such as transcranial direct current or magnetic stimulation, will benefit tremendously from individual information about circuitry disruption. Furthermore, it is currently unclear whether and how WM microstructure deficits may be mitigated by treatment. There may be interventions that could specifically target WM abnormalities such as those addressing oxidative stress.

In conclusion, Sarrazin and colleagues¹ conclusively affirm prior reports suggesting impaired FA in WM tracts, including the corpus callosum, in a large study using state-of-the-art methods. Exciting contributions are the documentation of a more severe biological abnormality in the subgroup of patients with psychosis and additional evidence supporting an interhemispheric dysconnectivity theory in BD. Growing evidence shows that WM deficits occur across psychiatric disorders and are present in unaffected relatives, suggesting that these abnormalities lead to psychopathology in a pattern where greater extent of the deficit leads to greater functional impairment. The next step in the field is to further understand the functional relevance of these findings—how they fit in with the overall pathophysiology of BD and other conditions, and whether in light of an individual's specific deficits, interventions could be tailored to enhance the capacity of neural systems to best compensate for these abnormalities.

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