Biological Psychiatry

Early Career Investigator Commentary

Structural Brain Networks Shape Cortical Atrophy in Depression: Implications and Future Directions

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White matter (WM) structural networks serve as a fundamental anatomical scaffold of the human brain, supporting interregional signaling of neural activity as well as the transport of molecules. The architecture of structural networks not only plays a foundational role in normal brain development and functional organization (1,2) but also is widely regarded as a key substrate mediating the spread of pathological agents within the brain (2). In the current issue of *Biological Psychiatry*, Shen *et al.* (3) leveraged connectome-based constraint models to elucidate how the WM network architecture shaped the cortical morphological abnormalities in major depressive disorder (MDD). Using large-scale multisite structural magnetic resonance imaging (MRI) data from a homogeneous Chinese cohort comprising 1442 patients with MDD and 1277 healthy control individuals, this study (3) showed that regional morphological alterations in MDD were highly correlated with alterations in their structurally connected neighbors, providing a reliable characterization of network-level alterations in depression. Network diffusion analyses further pointed to the lateral prefrontal cortex as a potential epicenter of pathological propagation. Moreover, the strength of this constraint varied across illness stages, exhibiting a gradual reduction with increasing illness duration. These findings advance our understanding of the network-level mechanisms of cortical atrophy in this disorder and underscore the importance of lateral prefrontal regions for neuromodulatory targets.

Connectome-based constraint models are grounded in evidence from neurological disorders, where disease progression is thought to involve the transregional spread of pathogenic agents (such as misfolded proteins) along synaptic connections (2). Numerous previous studies have used this framework to capture the spatial distribution of cortical atrophy in dementia (4) and Parkinson's disease (5). More recently, converging evidence has also emerged from studies of schizophrenia (6), suggesting a critical role of structural network architecture in shaping cortical abnormalities in psychiatric disorders. In this context, the work by Shen *et al.* (3) represents an important extension of prior research by systematically applying network-based constraint modeling to MDD. Their findings were robust across 5 different network resolutions, 2 different cortical parcellation schemes, and both single-ethnicity and cross-ethnicity datasets (3).

Identifying disease epicenters—defined as regions that serve as potential sources or organizational hubs of pathological spread—is an important application of connectome-based constraint models. In this study, Shen *et al.* (3) used two complementary strategies to localize candidate epicenters: a diffusion-based approach and a rank-based approach (3). The convergence of these results supports the stability of the identified lateral prefrontal epicenters. Notably, as approaches for epicenter identification continue to expand (1,6–8), future studies should systematically compare alternative strategies and integrate longitudinal data to evaluate their physiological relevance, thereby providing clearer guidance for subsequent mechanistic and translational research.

Another interesting finding from this study (3) is that the strength of structural network constraint on cortical atrophy is dependent on illness duration, with a progressive attenuation observed from first-episode to early-stage and chronic MDD subgroups. Although this finding still needs further validation in independent datasets, it introduces the possibility of viewing connectome constraint not as a static property but instead as a feature that may change dynamically over the course of illness. This perspective provides an interesting direction for future research to systematically examine the role of structural network constraints from a temporal dimension. In particular, stages that show stronger constraint effects may represent a potential optimal window for neuromodulation, during which WM pathways still retain a substantial capacity to limit pathological spreading. Shen *et al.* (3) speculated that progressive disruption of WM fiber integrity over the course of illness may gradually reduce the capacity of WM pathways to constrain the spatial pattern of cortical atrophy. This interpretation points to a methodological limitation in this study: connectome-based constraint models rely on reference structural networks derived from healthy cohorts, which may overlook alterations in WM pathways that occur with disease progression. Future studies incorporating longitudinal multimodal diffusion and structural MRI data with multiple, densely sampled time points would provide valuable insights into how disruptions in WM integrity influence connectome-based constraints on cortical abnormalities, as well as the trajectory of constraint strength across the course of illness.

In this study, Shen *et al.* (3) identified disease-related cortical morphological abnormalities using a case-control analytical framework that implicitly assumes relative homogeneity of changes across patients. However, MDD exhibits pronounced clinical heterogeneity, with hundreds of symptom combinations satisfying diagnostic criteria, and accumulating evidence indicates that depression can be categorized into distinct subtypes (9). If different depression subtypes exhibit distinct patterns of cortical morphological abnormalities, there

SEE CORRESPONDING ARTICLE ON PAGE 682

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could exist subtype-specific network constraints. Such specificity may arise at two complementary levels: subtype-dependent differences in constraint patterns within the same network architecture, or the involvement of distinct modes of network propagation within a given subtype. An avenue of extension for this work would be to integrate multiple network communication models (2) to investigate subtype-specific network constraint mechanisms, corresponding epicenters, and key pathways of pathological propagation. Going a step further, future studies could incorporate brain charts to characterize individual deviations from normative reference trajectories (10), enabling the investigation of connectome constraints on cortical abnormalities at the individual level and the identification of potential target regions. Such an approach would provide an important methodological and theoretical foundation for personalized neuromodulatory strategies.

Overall, Shen *et al.* (3) provide compelling evidence that the spatial pattern of cortical atrophy in MDD is shaped by underlying structural network architecture. By further suggesting that the strength of this network constraint varies across illness stages, the work moves beyond a static view of connectome influence and opens new avenues for understanding how structural brain networks shape cortical atrophy across the course of depression. To strengthen the translational applicability of this framework, future studies should account for patient heterogeneity, incorporate longitudinal data, and explicitly characterize individual-level normative network constraint patterns across cortical development. These efforts would deepen mechanistic insight into the neural basis of clinical heterogeneity in depression and help establish a methodological and theoretical foundation for the development of precision neuromodulation.

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Article Information

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