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EDITORIAL

Towards dysfunctional connectome development in depressed adolescents

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Major depressive disorder (MDD) is a highly prevalent and debilitating psychiatric disorder that commonly emerges during adolescence and can persist into adulthood. The rising incidence of MDD in adolescents over the past decade presents a significant public health challenge [1]. Adolescence is a critical period for the maturation of brain structure and function, as well as cognitive and social–emotional abilities. Episodes of MDD during this period can result in long-term and wide-ranging impairments for future lives. Compared to adult MDD patients, adolescents with MDD face a high risk of recurrence, more severe symptoms, and a poorer prognosis. Currently, the neurophysiological mechanisms that underlie MDD in adolescence remain largely unknown. Elucidating the neurobiological substrates of adolescent MDD and identifying potential imaging biomarkers are critical for improving disease prevention, diagnosis, and treatment strategies.

Recent advances in functional brain connectomes, through the combination of resting-state functional magnetic resonance imaging (R-fMRI) and graph theory, have been widely used to investigate network dysfunctional mechanisms in MDD. In the current issue, Zheng et al. [2] furthered this work by highlighting large-scale connectome dysfunctions in adolescents with MDD. Specifically, they collected unique R-fMRI data from a cohort of first-episode drug-naïve adolescents with MDD and typically developing controls. Whole-brain functional connectome was first reconstructed for each individual by computing temporal correlations among brain voxels. Then, voxel-wise network degree centrality (NDC) maps were generated to quantify the connectivity density of network nodes. Compared with controls, adolescents with MDD showed lower NDC values in several brain nodes involving the bilateral hippocampus, left amygdala, and right insula. Seed-based connectivity analyses further revealed a hypoconnectivity between the hippocampus and the anterior nodes of the default-mode network (e.g., medial prefrontal regions and pregenual anterior cingulate) in patients. Furthermore, the altered NDC values in the hippocampus correlated with the Hamilton Depression Rating Scale scores and duration of the illness in patients. These results align with previous R-fMRI studies showing decreased functional connectivity in the hippo-orbitofrontal–insular circuit in first-episode drug-naïve adolescents with MDD [3]. Importantly, Zheng et al.'s work [2] expands our understanding of the network-level dysfunctional mechanisms of this disorder from a connectomics perspective and indicates the relationship between the circuit abnormalities and the clinical manifestations of adolescents with MDD.

Adolescence is a critical period of brain development, characterized by heterogeneous trajectories of brain maturation across different regions. Disruptions in the developed brain networks, such as the limbic/paralimbic and prefrontal related connections, may lead to vulnerabilities in emotional and cognitive processing for adolescents. Notably, neuroimaging findings from adolescent MDD do not always coincide with those of adult MDD, indicating the neurobiological differences between adolescent and adult patients. For example, the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium utilized a large sample structural MRI dataset from 20 sites and reported lower surface area in the frontal regions and smaller hippocampus volumes in adolescents with MDD, while cortical thickness reductions were observed in adults with MDD

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[4, 5]. In terms of functional connectomes, a recent study using multicenter large R-fMRI datasets showed more severe connectome gradient disruptions in MDD patients with an onset in adolescence as compared to those with an onset in adulthood [6]. Besides, only few studies based on small samples explored the different dysconnectivity patterns between adolescent and adult MDD patients. Moreover, the majority of the current MDD connectome studies including Zheng et al. [2] only considered age effects as a covariate using conventional statistical methods. The complex age-disorder interactions are largely understudied. More connectomics studies involving large samples of adolescents and adults are vital to unveil the network-level mechanisms of MDD across different age stages.

An important challenge in imaging connectomics studies of adolescents with MDD is the heterogeneity of the results. For example, several studies have reported higher NDC values in the hippocampus, amygdala, and insula in first-episode drug-naïve adolescents with MDD [7], which is in contrast to Zheng et al.'s findings showing lower NDC values in adolescent MDD [2]. These results suggest heterogeneity of functional connectome findings in adolescent MDD studies. One possibility is that these seemingly inconsistent findings across studies could be due to the involvement of distributed brain networks that are related to emotional and cognitive processing [8]. Another possibility is that there exist neurophysiological subtypes in MDD that have potential clinical value. Future research aimed at identifying and parsing neurophysiological heterogeneity and subtypes in adolescents with MDD will be essential to better link the complex biological substrates with the varied clinical manifestations, thus facilitating more precise prevention and treatment allocation for patients.

Several important issues are worth further addressing. First, several brain nodes (e.g., amygdala, hippocampus, medial prefrontal cortex, and anterior cingulate cortex) that were identified in Zheng et al.'s study [2] have been shown to be related to the treatment response of adolescents with MDD. While several longitudinal studies have reported altered NDC values in the hippocampus and altered amygdala-related functional connectivity in adolescent MDD patients before and after receiving electroconvulsive therapy [9] or antidepressant treatment with a selective serotonin reuptake inhibitor [10], further longitudinal clinical assessments are needed to validate the effects of these treatment approaches on large-scale brain networks in adolescents with MDD. Second, multimodal imaging techniques, such as structural MRI and diffusion MRI, have demonstrated alterations of anatomical structures and white matter connectivity in adolescents with MDD. However, further analysis is required to determine how to best integrate these different measures of multimodal features to identify valuable disease biomarkers. Finally, MDD in adolescents may arise from various factors, including genetic liability, multiple psychosocial stressors, and chronic social adversity. Therefore, further studies that incorporate genetic and environmental data could shed light on the underlying causes of neurobiological alterations in this population, thereby facilitating early intervention and treatment for adolescents with MDD.

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