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EDITORIAL

Connectome-guided transcranial magnetic stimulation treatment in depression

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Major depressive disorder (MDD) is characterized by continuous mood disturbances, loss of interest in activities, and deficits in cognitive functions. It is estimated that over 322 million people around the world live with MDD, and and the lifetime and 12-month prevalence of MDD were 11.0% and 7.5%, respectively, among adolescents aged 13- to 18-year-olds in the United States [1], contributing to the most years-of-life lived with disability globally [2]. Psychotherapy and pharmacotherapy are currently the most widely used treatments in clinical applications for depression [3]. However, as few as 30% of depressed patients achieve remission after first-line therapies, and about one-third of individuals are categorized as having treatment-resistant depression, who fail to respond to multiple treatments [4]. There is an urgent need for new therapeutic approaches to improve the efficacy of treatment for patients with depression.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique, using powerful, focused, and pulsed magnetic fields to induce durable changes in brain activity and further mediate brain functions through networks. TMS is approved by the US Food and Drug Administration as a practical treatment option for patients with treatment-resistant depression. In this issue, Sigrist et al. [5] conducted a systematic review and meta-analysis of 10 studies, aiming to summarize the currently existing data on the efficacy of TMS treatment in adolescent MDD and examine the potential patient- and treatment-related factors. They showed a significant reduction in symptoms and a mean response rate of 41.3% in post-treatment depressed adolescents, which is comparable to previous reports in adult patients [6]. Exploratory individual patient data analysis revealed that TMS might be more effective in younger individuals and individuals with more severe depression, as well as in certain treatment modality settings. This work provides an important quantitative synthesis for the use of TMS in adolescents with MDD, informing clinically meaningful efficacy of the TMS practice. Notably, TMS treatment is not effective for all individuals, with the response and remission rates being approximately 29–46% and 18–31%, respectively [7]. While optimal stimulation parameters and treatment duration are important, searching for and optimizing stimulation targets is one of the major concerns for improving treatment outcomes.

Depression has been conceptualized as a brain dysconnectivity disorder [8]. Recent advances in combining multimodal neuroimaging big data and the connectomics framework provide an unprecedented opportunity for the noninvasive exploration of brain network dysfunction in this disorder [8]. Reproducible depression-related alterations in either structural or functional brain networks have been well documented, involving multiple core network nodes and connections located in both primary and high-order systems (e.g., the visual and sensorimotor regions, dorsolateral prefrontal cortex, and medial and parietal cortex regions) [9–12]. These network abnormalities could be normalized after antidepressant treatment and are capable of predicting individual treatment outcomes [10, 13, 14]. Currently, the left dorsolateral prefrontal cortex (DLPFC) is typically targeted during TMS treatment. However, exploring optimized cortical TMS targets that can mediate specific network abnormalities is likely to offer better treatment outcomes for MDD.

Brain network nodes have highly heterogeneous connectivity profiles across individuals. This nature could lead to a great variation across individuals, even in the

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same stimulation region such as DLPFC. Great efforts have been made to develop individualized optimal stimulation targets via identifying individual-specific connections in brain networks. For example, Fox et al. [15] proposed that the foci in the left DLPFC showing the most negative functional connectivity with the subgenual anterior cingulate cortex (sgACC) could be used as an individualized stimulation target. Using this localization method, the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol achieved a remission rate of 90.5% (19 of 21) in patients with treatment-resistant depression [16]. In another small-sample double-blind randomized controlled trial study, the Montgomery Depression Scale (MADRS) scores of the patients who received SAINT (n = 14) were reduced by a mean of 52.5% compared to baseline, which was significantly higher than the 11.1% in the sham stimulation group (n = 15) [17]. Besides the DLPFC-sgACC connectivity, several other network connections were also considered for optimizing stimulation targets, such as the connectivity between the left DLPFC and the right anterior insula [18], and connections between the DLPFC and the frontoparietal network [19]. Although further validations are required on large-scale double-blind randomized sham-controlled trial studies, these findings suggest the potential of individual connectome-guided TMS therapy in increasing the clinical outcomes of depression treatment.

Several future directions are worth exploring. First, the collection of multimodal neuroimaging connectome big data from several recently initiated projects in psychiatry [9–11] offers valuable resources to identify and validate reproducible brain alterations in MDD. These findings could potentially provide additional stimulation targets for TMS treatment. Second, depression is a highly heterogeneous clinical syndrome. Subtyping patients on a neurobiological basis may increase the sensitivity and specificity of treatment selection and prediction for bio-subtypes. Third, the development of brain networks during adolescence is of importance in supporting normal cognitive functions and behaviors. Future studies should pay closer attention to the complex interaction between development and depression, and establish reliable identification and prevention methods for adolescent depression. Finally, large-scale double-blind randomized sham-controlled trial studies are required to evaluate connectome-guided TMS strategies, as well as to test the optimal parameter settings in TMS treatment. Collectively, leveraging the power of imaging connectome big data, we hope that connectome-guided individual TMS treatment can yield precision therapeutic plans to ultimately improve treatment outcomes for depressed patients.

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