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EDITORIAL COMMENT
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Individualized Repetitive Transcranial Magnetic Stimulation for Depression Based on Magnetic Resonance Imaging

Major depressive disorder (MDD) is a common mental disorder with the characteristics of high suicide rate, high self-harm rate, and high recurrence rate, and is the leading cause of disability worldwide.[1,2] About 30%-50% of MDD patients suffer from treatment-resistant depression.[3] Repetitive transcranial magnetic stimulation (rTMS) is a neuromodulation therapy for depressive symptom improvement approved by the US Food and Drug Administration.[4] However, a meta-analysis indicated that the average response rate of MDD patients was only 29.3% after receiving the high frequency rTMS treatment to the left dorsolateral prefrontal cortex (DLPFC),[5] which may be one of the important reasons related to the inaccurate location of the stimulation target.

The scalp-based measurement and neuroimaging-based targeting are the 2 types of localization methods for rTMS treatment. The "5 cm method" and the "Beam F3 method" are the commonly used localization methods based on scalp-based measurement, while the neuroimaging-based targeting methods locate the target based on the patient's individual structural, resting-state, or task-related functional magnetic resonance imaging (MRI). The neuroimaging-based targeting methods based on the patient's individual neuroimaging fully consider the individual differences in brain structure or function, which can significantly improve the antidepressant efficacy of rTMS.[6] In the current editorial, we summarize the different localization methods of rTMS and compare their relative strengths and weaknesses, pointing out the existing problems in the current rTMS research and looking forward to the future development direction.

Repetitive Transcranial Magnetic Stimulation Treatment Based on Scalp-Based Measurement

The left DLPFC is the most commonly used target for rTMS treatment of depression. The "5 cm method" and "Beam F3 method" are the commonly used scalp-based measurement localization methods for the localization of DLPFC in clinical rTMS treatment. The "5 cm method" is defined as 5 cm in front of the area where the stimulus could best elicit the motor response of the contralateral abductor pollicis brevis muscle. And the "Beam F3 method" refers to the DLPFC localization by combining the international 10-20 system with the F3 position of electroencephalogram electrode. However, although simple to operate, these localization methods ignore the individual differences in anatomical structure and brain size, which may result in localization errors between the actual stimulus region and the target DLPFC region. And the localization errors may not only lead to unsatisfactory antidepressant efficacy of rTMS treatment, but also cause physical discomfort due to the stimulation of other brain regions.

Individualized Repetitive Transcranial Magnetic Stimulation Treatment Based on Structural Magnetic Resonance Imaging

The combination of individual structural MRI and neuronavigation technology can localize the target more accurately and avoid the localization error caused by the scalp-based measurement. The localization method based on individual structural MRI refers to reconstructing the patient's head model based on the structural MRI data, and then using the neuronavigation technology to accurately navigate to the target area. In the study by Fitzgerald et al,[7] the rTMS treatment with target localization based on individual structural MRI showed better efficacy compared to the "5 cm method." Nevertheless, although the target localization

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method based on individual structure MRI can identify the target more accurately than the scalp-based measurement, it requires the patient to undergo a structural MRI scan in advance, which is inconvenient for those patients with contraindications to MRI scans.

Individualized Repetitive Transcranial Magnetic Stimulation Treatment Based on Resting-State Functional Magnetic Resonance Imaging

The localization method based on individual structural MRI is limited to more accurate identification of the target anatomical structure, but lacks consideration of brain functional heterogeneity. However, baseline aberrant functional connectivity (FC) was found to correlate with symptom improvement after rTMS treatment in depressed patients. Cole et al[8] reported a significant improvement in depressive symptoms when rTMS was used to stimulate the brain region of the DLPFC with the strongest negative FC to the subgenual anterior cingulate cortex. And, Singh et al[9] found a significant decrease in negative emotions among healthy subjects after individualized rTMS treatment with the stimulation targets of the left DLPFC negatively related to subgenual anterior cingulate cortex. In addition, Iwabuchi et al[10] calculated the coordinates that had the strongest negative effect with the right anterior insula in the left DLPFC as the target for rTMS stimulation. After the 1-month rTMS treatment, 63.64% of the patients had Hamilton Depression Rating Scale score reductions greater than 50%. However, the reproducibility of current resting-state functional MRI results is relatively poor, and it needs to be further verified by large-sample clinical trials in the future.

Individualized Repetitive Transcranial Magnetic Stimulation Treatment Based on Task-Related Functional Magnetic Resonance Imaging

At present, besides the stimulation target based on resting-state functional MRI being used for individualized localization, the stimulation target based on task-state functional MRI is also considered to be an alternative localization method that can improve the antidepressant efficacy of rTMS. Neacsiu et al[11] utilized the goal priming task to identify the regions of peak activation as the stimulation target for rTMS intervention, and the patients' depressive symptoms tended to decrease with the individualized rTMS treatment. In a study by Zhang et al,[12] the visual task-related peak voxel of visual cortex (VC) was targeted for individualized rTMS treatment. Compared to either the standard or sham VC rTMS treatment group, the individualized group had a higher number of responders, and changes in VC task-related functional MRI in the individualized group were found to be associated with symptom reduction. Similarly, rTMS treatments with the stimulation targets of the peak areas of the left DLPFC obtained from arterial spin labeling images of the 2-back minus 1-back task can significantly improve depressive symptoms.[13] Fan et al[14] employed the n-back task (2-back - 0-back) to identify the strongest activation of left DLPFC as the stimulation targets for rTMS treatment, and a treatment response rate of 44% were found in depresssed patients. However, task-state functional MRI scan requires the patients to remain still in a narrow space and complete the task within a limited time, which is difficult to perform and requires high cooperation from the patients.

Different localization methods have their own relative strengths and weaknesses. The localization method based on scalp-based measurement takes less time and money and is easy to operate, but its localization is inaccurate. Individual MRI-based targeting takes into account the individual variations in brain anatomy and function and allows for targeted stimulation of specific brain regions implicated in depression, having the potential to enhance the antidepressant efficacy of rTMS treatment. However, it requires the patient to undergo an MRI scan in advance and even to complete corresponding tasks, which requires a lot of time and effort.

The calculation of individualized targets based on resting-state and task-state functional MRI should be the focus of future research. Yet, although many studies have used functional MRI to identify the targets for individualized rTMS treatment, the sample size is relatively small. And most studies only compare the individualized rTMS treatment with sham stimulation, but there is no direct comparison of the superiority between the different localization methods. In the future, randomized clinical trials should further expand the sample size and compare the antidepressant efficacy of different localization methods. The individualized rTMS stimulation target should be further identified according to the depression subtypes and accompanying symptoms, and the effectiveness of individualized rTMS stimulation targets should be verified by repeated studies.

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