

Optimization Strategies of Transcranial Magnetic Stimulation in Major Depressive Disorder

Major depressive disorder (MDD), a widely prevalent and incapacitating illness, imposes a significant burden on individuals and society.¹⁻³ Alongside pharmacological and psychological interventions, nonsurgical brain stimulation techniques, such as transcranial magnetic stimulation (TMS), are frequently employed to treat MDD.⁴ Conventional repetitive TMS (rTMS) includes low-frequency (LF) and high-frequency (HF) magnetic stimulation to the right and left dorsolateral prefrontal cortex, respectively. However, standard rTMS protocols may not be effective for all patients with MDD. Hence, optimization strategies of conventional rTMS, such as deep, priming, accelerated, or synchronized TMS or theta burst stimulation (TBS), including intermittent, continuation, and bilateral TBS, have been developed to enhance the treatment outcomes.⁴

Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation

In rTMS, HF-rTMS is an U.S. Food and Drug Administration (FDA)-approved technique for the treatment of treatment-resistant depression (TRD).⁵ Bilateral rTMS⁶ and accelerated rTMS⁷ are promising techniques for treating MDD. A meta-analysis reported that bilateral rTMS is a potentially effective treatment for MDD, offering clinically significant benefits over standard antidepressant medications and unilateral rTMS.⁶ Furthermore, daily multiple treatment sessions of accelerated rTMS can reduce the overall treatment duration, enhance clinical efficiency, and expedite the onset of antidepressant effects.⁷ Notably, 4 sessions per day of accelerated rTMS were found to be more effective than intranasal esketamine.⁸

Deep Transcranial Magnetic Stimulation

Deep TMS is an FDA approved technique for treating TRD.⁹ Using a specific coil configuration (helmet-like H-coil), wider cortical penetration and deeper brain region stimulation can be achieved by deep TMS, thereby augmenting its therapeutic effectiveness.¹⁰ A multicenter study reported that deep TMS is a promising intervention for MDD and its therapeutic effects last for at least 3 months during the maintenance phase of the treatment.¹¹ Furthermore, accelerated deep TMS protocols involving multiple sessions per day (2, 3, 5, or 10 times per day), are safe and effective therapeutic options for MDD.¹² These protocols offer a treatment alternative with a rapid onset of action and prolonged durability.¹²

Priming Transcranial Magnetic Stimulation

Priming TMS is a variant of LF-rTMS with a specific protocol that involves a brief administration of low-intensity HF-rTMS or "priming stimulation," followed by the main treatment of LF-rTMS targeted to the right dorsolateral prefrontal cortex (DLPFC).⁴ Iyer et al¹³ discovered that a more pronounced depression of motor cortex excitability through 1 Hz treatment can be achieved when it is preceded by a priming rTMS at 6 Hz.¹³ Research indicates that the utilization of low-intensity, HF priming stimulation may enhance the efficacy of LF-rTMS stimulation.^{4,14} Additionally, a network meta-analysis revealed that priming TMS exhibits a greater response compared to continuous TBS.⁴ Notably, compared to sham stimulation, priming TMS also exhibited lower rates of participant attrition.⁴

Synchronised Transcranial Magnetic Stimulation

Synchronized TMS is a therapeutic technique that is synchronized with the alpha frequency of an individual's electroencephalogram.¹⁵ This technique has been reported to offer greater advantages for patients with more pronounced depression severity and heightened anxiety levels at baseline compared to sham synchronized TMS.¹⁵ Conversely, a network meta-analysis



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has also reported that synchronized TMS does not exhibit superior antidepressant efficacy compared to sham for treating MDD.⁴

Theta Burst Stimulation

Intermittent Theta Burst Stimulation

Intermittent TBS is a recently developed TMS technique (3 minutes and 9 seconds) that has demonstrated comparable effectiveness to HF-rTMS (37.5 minutes) in treating MDD¹⁶ and has been approved by the FDA for treating TRD.¹⁷ A study reported that Stanford neuromodulation therapy (SNT) through resting-state functional connectivity magnetic resonance imaging to specifically target high-dose intermittent TBS comprising 10 daily sessions of 18 000 pulses per day for 5 consecutive days, totaling 90 000 pulses, demonstrated superior effectiveness compared to sham stimulation for TRD.¹⁸ A recent systematic review found that SNT is effective in the treatment of TRD.¹⁹ Similarly, a recent meta-analysis revealed that active accelerated intermittent TBS protocols of ≥ 2 sessions per day exhibited a greater study-defined response compared to sham stimulation,²⁰ indicating that faster treatment protocols can reduce treatment duration while maintaining comparable efficacy.

Continuation Theta Burst Stimulation

In contrast to LF-rTMS (e.g., 1 Hz), which requires >20 minutes of continuous stimulation, continuous TBS produces 20 minutes of suppression with 20-second stimulation.²¹ A single-arm prospective study determined that continuous TBS is a safe, well-tolerated, and effective treatment for patients with depression.²² However, 3 randomized controlled trials (RCTs) investigating the efficacy and safety of active continuation TBS compared to sham stimulation in individuals with depression did not reveal any significant advantage in improving depressive symptoms.²³⁻²⁵ A recent meta-analysis found that cTBS is not effective for treating major depressive episodes.²⁶

Bilateral Theta Burst Stimulation

In addition to unilateral TBS, the application of left facilitatory and right inhibitory stimulation from bilateral TBS seems to be equally effective in the treatment of MDD.^{24,27} A recent meta-analysis of RCTs ($n = 285$) revealed that bilateral TBS, specifically intermittent TBS over the left DLPFC and continuous TBS over the right DLPFC, is a well-tolerated form of rTMS that exhibits significant antidepressant effects, particularly in individuals with MDD.²⁸ Notably, bilateral TBS showed similar improvement in depressive symptoms when compared to standard bilateral rTMS in older adults.²⁹ Presently, no head-to-head studies have been published comparing bilateral TBS with bilateral rTMS for the treatment of depression in adults or adolescents.

Beyond pharmacological and psychological interventions, non-surgical brain stimulation techniques, including rTMS, represent a tertiary approach to managing MDD. The latest Canadian Network for Mood and Anxiety Treatments guidelines regard rTMS as the primary recommendation for individuals with MDD who exhibited an insufficient response to at least 1 trial of antidepressant medication.³⁰ The generalizability and treatment capacity of standard rTMS protocols have been limited by their long treatment sessions (37.5 minutes). To address this limitation, optimization strategies, such as the use of intermittent TBS with shorter sessions (3 minutes and 9 seconds), have been implemented clinically. Further research is warranted to explore the most effective dosing regimen for each optimization strategy of standard rTMS, including the determination

of the optimal frequency of daily sessions, total sessions, and temporal distribution of treatment days.

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