REVIEW
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Advances in Repetitive Transcranial Magnetic Stimulation for the Treatment of Post-traumatic Stress Disorder

ABSTRACT

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that develops and persists after an individual experiences a major traumatic or life-threatening event. While pharmacological treatment and psychological interventions can alleviate some symptoms, pharmacotherapy is time-consuming with low patient compliance, and psychological interventions are costly. Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe and effective technique for treating PTSD, with advantages such as high compliance, low cost, and simplicity of implementation. It can even simultaneously improve depressive symptoms in some patients. Current research indicates that high-frequency rTMS shows better therapeutic effects compared to low-frequency rTMS, with no significant difference in the likelihood of adverse reactions between the two. Theta Burst Stimulation (TBS) exhibits similar efficacy to high-frequency rTMS, with shorter duration and significant improvement in depressive symptoms. However, it carries a slightly higher risk of adverse reactions compared to traditional high-frequency rTMS. Combining rTMS with psychological therapy appears to be more effective in improving PTSD symptoms, with early onset of effects and longer duration, albeit at higher cost and requiring individualized patient control. The most common adverse effect of treatment is headache, which can be improved by stopping treatment or using analgesics. Despite these encouraging data, several aspects remain unknown. Given the highly heterogeneous nature of PTSD, defining unique treatment methods for this patient population is quite challenging. There are also considerable differences between trials regarding stimulation parameters, therapeutic effects, and the role of combined psychological therapy, which future research needs to address.

Keywords: Post-traumatic stress disorder, repetitive transcranial magnetic stimulation, noninvasive brain stimulation

Background

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that develops and persists after an individual experiences a major traumatic or life-threatening event. Based on data from the World Mental Health Survey, the lifetime prevalence of PTSD is approximately 3.9% globally, and 5.6% among individuals who have experienced trauma exposure.[1] The disorder has a long course, poor prognosis, and about 75% of patients have co-morbidities with other psychiatric disorders.[2] It imposes a heavy burden on countries, especially low- and middle-income countries.[3]

According to the Veterans Affairs/Department of Defense, the American Psychiatric Association, and the International Society for the Study of Traumatic Stress, the guidelines include medication and psychotherapy as equivalent first-line treatment options for PTSD.[4] Selective serotonin reuptake inhibitors and tricyclic antidepressants such as amitriptyline can improve PTSD symptoms, but have disadvantages such as long treatment duration and low compliance.[5,6] Trauma-focused cognitive-behavioral therapy, eye movement desensitization and reprocessing therapy can likewise improve PTSD symptoms with good patient compliance. However, psychotherapy still has some limitations, such as resource constraints

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of professional counselors and high economic costs.[7-10] Transcranial magnetic stimulation is used as an advanced neuromodulation technique in a variety of diseases, based on the principle of generating a magnetic field by placing a coil in the brain area of interest, which induces the generation of electrical currents to alter the excitability of neurons, resulting in a series of physiological and biochemical responses.[11-14] The most commonly used mode of repetitive Transcranial magnetic stimulation (rTMS) is non-invasive, highly compliant, and cost-effective, with the ability to improve PTSD symptoms in a short period. The United States Food and Drug Administration has approved rTMS for the treatment of severe depression and obsessive-compulsive disorder.[15] Numerous studies have shown that rTMS can improve symptoms in PTSD patients,[16,17] but the mechanism of action, targets, treatment parameters, and the need to combine with other therapies are still variables that need to be discussed. This study primarily conducted Mesh term searches using "Transcranial Magnetic Stimulation" and "Stress Disorders, Post-Traumatic." Additionally, we conducted keyword searches using "Repetitive transcranial magnetic stimulation," "Transcranial Magnetic Stimulation," "Post-traumatic Stress Disorder," and "PTSD," focusing on literature from the past 20 years. We also reviewed the possible pathological mechanisms of PTSD and research on the improvement of PTSD symptoms by rTMS, discussing the mechanisms of action and intervention effects of rTMS, providing certain reference for the related research and clinical application of rTMS in PTSD.

Pathological Mechanisms of Post-traumatic Stress Disorder

Mechanisms of Abnormal Changes in Brain Regions

The current understanding of the pathogenesis of PTSD is characterized by hypofunction of the prefrontal cortex and functional overactivation of other structures. Neuroimaging studies have shown that patients with PTSD primarily experience abnormal functional and structural changes in the amygdala, prefrontal cortex, and the hippocampus.[18]

The amygdala is the brain tissue that produces, recognizes, and regulates emotions and is associated with fear extinction.[19] Studies have shown that the left amygdala is significantly reduced in patients with PTSD.[20] Additionally, studies have found that PTSD female patients who experienced childhood trauma have a reduced volume in the right amygdala.[21] In studies of veterans, it has been found that patients with PTSD exhibit a smaller size of the lateral nucleus and larger volumes of the central and medial nuclei.[22] These studies all suggest that PTSD symptoms may be related to changes in the size and shape of the amygdala.

MAIN POINTS

- *Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive physical therapy method.*
- *Repetitive transcranial magnetic stimulation demonstrates significant efficacy and safety in treating post-traumatic stress disorder (PTSD).*
- *In the treatment of PTSD, high-frequency rTMS and theta burst stimulation demonstrates superior efficacy.*
- *In the treatment of PTSD, the most common adverse reaction is a headache.*

The prefrontal cortex is the anatomical basis for the generation of complex mental activities in humans and plays an important role in various mental activities. The prefrontal cortex regulates the process of fear memory extinction by modulating the amygdala.[23] Mehta et al. found that the regulation of the amygdala by the prefrontal cortex is diminished in PTSD patients, which may be related to the severity of PTSD symptoms.[24] Yang et al[25] found that PTSD patients were associated with a thinner prefrontal cortex. This represents that the prefrontal cortex may be an important target for the treatment of PTSD patients.

The hippocampus is mainly responsible for functions such as storage conversion and orientation of short-term memory, and it is coactivated with the amygdala when subjected to negative stimuli.[22] The hippocampus has an important role in the modulation of fear memories in patients with PTSD.[26] Larger right hippocampal volume has a protective effect against PTSD, whereas the left hippocampal volume is positively correlated with the symptoms of PTSD.[27,28] The hippocampus can be divided into subregions such as CA1, CA2, CA3, and the dentate gyrus, in which alterations in the CA2-3/dentate gyrus subregion may be related to the formation of intrusive traumatic memories in PTSD.[29] A research indicates that individuals with PTSD exhibit changes in the volume of the CA1 and CA2-3/dentate gyrus regions of the hippocampus. Specifically, alterations in the CA1 region are associated with uncontrollable re-experiencing of intrusive memories, while changes in the CA2-3/dentate gyrus region may be related to excessive generalization of fear.[30] This suggests that inhibition of the corresponding hippocampal region may improve clinical symptoms in patients with PTSD.

The abnormal functionality and morphology of various brain regions may be important factors contributing to PTSD, which provides us with some reference value when studying its treatment mechanism.

Neural Network Mechanisms

Post-traumatic stress disorder is a state of post-traumatic psychological imbalance that affects 3 main cortical networks: the default network, the central executive network, and the salience network. Each network includes different brain structures that are either functionally inhibited or hyperactivated in patients with PTSD.[31] The default mode network includes posterior cingulate cortex, precuneus, medial prefrontal cortex, inferior parietal lobule, and bilateral temporal cortex. The network consists of brain regions that continue to engage in certain functional activities during rest, and it is associated with emotion processing, memory retrieval, and related functions. A substantial body of research has found decreased connectivity strength within this network in individuals with PTSD.[32] The central executive network includes several medial prefrontal cortex and inferior frontal, inferior parietal regions, with a core area in the dorsolateral prefrontal cortex (DLPFC), and these brain regions are mostly associated with activity inhibition, emotions, etc., and show abnormal activity in patients with PTSD.[33] The salience network primarily involves the dorsal anterior cingulate cortex, anterior insula, and amygdala, responsible for categorizing external stimuli and internal events, and switching to relevant processing systems. Enhanced connectivity within this network has been observed in PTSD patients, which can strengthen further with increased stimulation.[33,34] The current findings suggest that these changing networks may serve as clinical measures for assessing PTSD symptom severity and contribute to our understanding of the neural mechanisms of PTSD.[31,35]

The aberrant neurobiological mechanisms in PTSD patients often involve multiple brain regions and are intricately complex. Reduced regulation of the amygdala by the prefrontal cortex leads to heightened reactivity of the amygdala. Given the indirect connection between the amygdala and the hippocampus, we can potentially normalize the corresponding neurobiological mechanisms by modulating aberrant activity in the prefrontal cortex using rTMS. This approach aims to ameliorate PTSD symptoms.

Genetic Mechanisms

Behavioral genetics approaches are important tools for understanding the etiology of PTSD. Existing behavioral genetics research suggests that PTSD symptoms have a moderate genetic component, with heritability estimated at approximately 49%.[36-38] Candidate gene studies have mainly focused on gene sets related to serotonin, dopamine, and neuroendocrine function, but results have been inconsistent.[39] Genetic research on PTSD has entered the era of genome-wide association studies, which have identified some previously undiscovered variants and new loci.[40-42] Epigenetics has also gradually been applied to PTSD research, focusing primarily on mechanisms such as histone modification, DNA methylation, and non-coding RNA. Many relevant genes have been identified, offering significant promise for identifying genetic factors related to PTSD.[43,44]

The development of genetics fundamentally lays a solid foundation for exploring the genetic and pathological mechanisms of PTSD, offering hope for future regulation of PTSD at the genetic level.

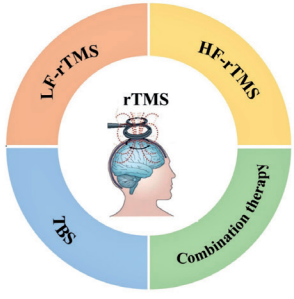
Clinical Application of Repetitive Magnetic Transcranial Stimulation in Post-traumatic Stress Disorder

Mechanism of Repetitive Magnetic Transcranial Stimulation

Generally, rTMS is categorized into 2 modes, low-frequency rTMS and high-frequency rTMS. Low-frequency rTMS reduces cortical excitability, whereas high-frequency rTMS increases cortical excitability,[45] Theta-Burst Stimulation (TBS) can be considered as a mode of high-frequency rTMS. The main mechanisms of action of rTMS are currently thought to include the following: (1) rTMS acts on the motor cortex of the human brain by inducing a mechanism similar to synaptic plasticity.[46] Long-term potentiation (LTP) and long-term depression (LTD) are considered essential elements of synaptic plasticity, and both are induced by changes in postsynaptic Ca^{2+} concentration.[47] Repetitive magnetic transcranial stimulation can vary the stimulation parameters to induce changes in Ca^{2+} concentration, prolonged low-frequency rTMS can induce LTD, whereas short-duration high-frequency rTMS can induce LTP.[48,49] Synaptic plasticity can improve PTSD symptoms by improving abnormal brain regions and promoting their return to normal morphology. (2) Repetitive magnetic transcranial stimulation produces therapeutic effects by modulating cortical excitability. Cortical excitability is observed primarily as amplitude in motor evoked potentials.[50] It is generally accepted that high-frequency rTMS increases motor cortical excitability for a period of time after stimulation, which is similar to LTP, and that low-frequency rTMS decreases cortical motor excitability by decreasing the amplitude of motor evoked potentials, which corresponds to LTD.[51,52] Enhancing or attenuating the connectivity of brain network mechanisms by modulating cortical excitability may be the main reason why rTMS improves PTSD symptoms. (3) Repetitive magnetic transcranial stimulation exerts therapeutic effects by regulating certain gene expression and protein synthesis (Figure 1). Some studies have shown that rTMS can regulate cortical network activities by modulating gene expression of c-Fos, GABAergic and glutamatergic and inhibiting calcium-binding proteins, CKD-95, etc.[53-56] These genes and proteins are closely related to recovery after brain injury, can improve the brain regions damaged by PTSD and promote their functional recovery, and can also help us determine the effectiveness of PTSD treatment.

Stimulation Targets of Repetitive Magnetic Transcranial Stimulation for Post-traumatic Stress Disorder

Repetitive magnetic transcranial stimulation produces different therapeutic effects by individualizing treatment parameters.[57] Numerous studies have shown that patients with PTSD have functional abnormalities and connectivity disturbances in various brain



Mechanism

Induce a mechanism similar to synaptic plasticity	Modulate cortical excitability	Regulate certain gene expression and protein synthesis

KEY FINDINGS

- rTMS is a non-invasive physical therapy method with few adverse reactions.
- rTMS demonstrates significant efficacy and safety in treating PTSD.
- The low-frequency rTMS appears to have no effect in treatment.
- The efficacy of high-frequency rTMS and TBS is more pronounced.
- The main adverse reaction of rTMS is headache.

Figure 1. Research findings and mechanism. PTSD, Post-traumatic stress disorder; rTMS, repetitive –magnetic transcranial stimulation; HF-rTMS, high-frequency rTMS; LF-rTMS, low-frequency rTMS; TBS, theta burst stimulation.

regions, mainly in the right hemisphere, which is in charge of avoidance-related emotions, and therefore the right side is often chosen as a therapeutic target for rTMS.[21,58] The DLPFC, which plays a central role in emotion regulation, is the main target of action. A phase II, double-blind, placebo-controlled trial of 20-Hz stimulation of the DLPFC on the left and right sides of patients with PTSD showed that PTSD symptoms improved in both groups, but the improvement was better in the right rTMS group.[59] Stimulation of both the left and right DLPFC in patients with PTSD seems to improve symptoms, but fewer studies have stimulated the left DLPFC, and there have been studies comparing the efficacy of stimulation of the right DLPFC alone with the stimulation of both DLPFC and did not find a significant difference in efficacy, which means that we cannot rule out a therapeutic modality of treatment using bilateral rTMS.[60-62] The right DLPFC is the most commonly used stimulation target for rTMS and has significant efficacy in improving PTSD symptoms. Stimulation of the left DLPFC seems to improve PTSD symptoms, but the improvement of depression is more prominent. Although the way to stimulate bilateral DLPFC cannot be ruled out, it can be determined that DLPFC as a stimulation target is indeed effective in improving PTSD symptoms.

Low-Frequency Repetitive Magnetic Transcranial Stimulation for Post-traumatic Stress Disorder

The optimal rTMS frequency for treating patients with PTSD is a hot topic of clinical exploration. Grisaru et al[63] set a precedent for the use of low-frequency rTMS for the treatment of PTSD by using 0.3 Hz low-frequency rTMS to stimulate 10 patients with PTSD and found that the subjects' PTSD symptoms had improved at the end of the stimulation. Thereafter, Nam et al[64] included 18 subjects with PTSD who were randomly assigned to the 1 Hz low-frequency rTMS group and the sham-operated group, and after 3 weeks of stimulation, they found that patients in the low-frequency rTMS group showed a significant improvement in PTSD symptoms compared with the sham-operated group. However, Osuch et al[65] randomized patients with PTSD into a 1 Hz rTMS group and a sham treatment group, and did not find that the low-frequency rTMS group had improved symptoms compared to the sham treatment group.[65]

The efficacy of low-frequency rTMS appears to be useful, but the number of available studies is small, the quality of the evidence is low, and more research is needed to demonstrate the efficacy of low-frequency rTMS in reducing PTSD symptoms (Table 1).

High-Frequency Repetitive Magnetic Transcranial Stimulation for Post-traumatic Stress Disorder

Studies of high-frequency rTMS have focused on 5 Hz, 10 Hz, and 20 Hz. Morris et al[66] found an improvement in both PTSD and depressive symptoms in patients with PTSD comorbid with major depressive disorder after rTMS treatment at 5 Hz. This is consistent with the findings of Philip's study.[67] Leong et al[68] recruited 31 civilian patients with PTSD and randomized them to 1 Hz rTMS stimulation and 10 Hz rTMS stimulation. After 2 weeks of continuous treatment, the low-frequency stimulation group significantly improved PTSD symptoms, and the high-frequency stimulation group showed an improvement in depressive symptoms, but the improvement in PTSD symptoms was unclear. In a randomized controlled trial by Kozel et al,[69] veterans with PTSD were randomly assigned to a 1 Hz rTMS group versus a 10 Hz rTMS group. At the end of the treatment, PTSD and depression scores improved in both groups, but efficacy did not show a significant difference between the 2 groups. In a double-blind, placebo-controlled phase II trial, 30 patients with PTSD were randomly assigned to receive either active 20-Hz rTMS of the right DLPFC, active 20-Hz rTMS of the left DLPFC, or sham rTMS. The treatment results showed that 20-Hz rTMS of both the right and left DLPFC significantly reduced PTSD symptoms, but the effect of right rTMS was greater than left rTMS[59] (Table 2). Both meta-analyses showed that both high-frequency and low-frequency rTMS improved PTSD symptoms, and the improvement was more pronounced with high-frequency rTMS.[62,70]

High-frequency rTMS demonstrates better therapeutic effects compared to low-frequency rTMS, with no significant difference in the likelihood of adverse reactions between the 2. However, the outcomes of PTSD symptom improvement are inconsistent, and stimulation frequency remains a variable that needs to be discussed.

Theta Burst Stimulation for Post-traumatic Stress Disorder

Theta burst stimulation is often considered a mode of rTMS that delivers very high-frequency stimulation over a short period of time and is generally categorized as intermittent TBS (iTBS) and continuous TBS (cTBS). Philip et al[71] included 50 veterans with PTSD and randomly assigned them to the sham stimulation group and the

Table 1. Low-Frequency Repetitive Magnetic Transcranial Stimulation for Post-traumatic Stress Disorder

Study	Sample Size	Brain Target	Stimulation Frequency	Stimulation Time	Outcome Measure	Adverse Events
Grisaru et al (1988)[63]	10	Bilateral motor	0.3 Hz	One session of slow TMS with 30 pulses of 1 m/s each, 15 to each side of the motor cortex.	IES: Pre 2.77 (1.25); Post 2.21 (1.18) (Improvement 20.2%) SCL-90: Pre 2.1 (0.94); Post 1.85 (0.68) (Improvement 11.9%)	1. Headache: n = 1 (10%) 2. Increase in intrusive thoughts: n = 1 (10%)
Nam et al (2013)[64]	16	Right DLPFC	1 Hz	1200 pulses/session, 5 sessions/week, 15 sessions in total	All CAPS scores increased significantly	1. Headache: n = 3 (42.9%) 2. Dizzy: n = 1 (14.3%)
Osuch et al (2009)[65]	9	Right DLPFC	1 Hz	1800 pulses/session, 3-5 sessions/week, 20 sessions in total	CAPS: CAPS (intrusion) - 0.22 (Improvement 31%) CAPS (avoidance) - 0.33 (Improvement 62%) CAPS (hyperarousal) - 1.00 (Improvement 55%)	No adverse events or serious adverse events

CAPS, The Clinician Administered PTSD Scale; DLPFC, dorsolateral prefrontal cortex; IES, Impact of Event Scale; PTSD, post-traumatic stress disorder; rTMS, repetitive Magnetic Transcranial Stimulation; SCL-90, symptom checklist 90.

Table 2. High-Frequency Repetitive Magnetic Transcranial Stimulation for Post-traumatic Stress Disorder

Study	Sample Size	Brain Target	Stimulation Frequency	Stimulation Time	Outcome Measure	Adverse Events
Morris et al (2013)[66]	23	Right DLPFC	5 Hz	3000-4000 pulses/ session, 1 session/day, no more than 40 sessions	Mean decrease in PCL-5 score of 39.0 %	Not mentioned
Philip et al (2017)[67]	40	Left DLPFC	5 Hz	40 daily sessions followed by a 5-session taper	PCL-5: Pre 52.2 (13.1); Post 34.0 (21.6) (Improvement 34.6%)	Not mentioned
Leong et al (2020)[68]	31	Right DLPFC	1 Hz (n = 11) 10 Hz (n = 10) Sham (n = 10)	1 Hz group: 2250 pulses/ session, 5 sessions/week, 10 sessions in total; 10 Hz group: 3000 pulses/session, 5 sessions/week, 10 sessions in total	CAPS-5: Pre 1 Hz 72.27 (25.34); 10Hz 69.44 (18.29); Post 1 Hz 59.80 (35.83); 10 Hz 74.00 (30.97) (1 Hz Improvement 17.3%； 10 Hz Reduction of 6.6%) PCL-C: Pre 1 Hz 59.40 (16.44); 10 Hz 65.33 (11.40); Post 1 Hz 48.10 (23.54); 10Hz 53.44 (22.80) (1 Hz Improvement 19.0%; 10 Hz Improvement 18.2%)	1.Suicidal ideation: 1 Hz group n = 1 (9%)
Kozel et al (2019)[69]	35	Right DLPFC	1 Hz (n = 17) 10 Hz (n = 18)	1 Hz group: 2400 pulses/ session, 5 sessions/week, 36 sessions in total; 10 Hz group: 3000 pulses/session, 5 sessions/week, 10 sessions in total	CAPS-5: Pre 1 Hz 48 (11); 10 Hz 48 (13); Post 1 Hz 39 (18); 10 Hz 40 (21) (1 Hz Improvement 18.8%; 10 Hz Improvement 16.7%) PCL-5: Pre 1 Hz 59 (8.3); 10 Hz 60 (8.9); Post 1 Hz 42 (19); 10 Hz 38 (21) (1 Hz Improvement 28.8%; 10 Hz Improvement 36.7%);	• 1.Headache:1 Hz group n = 8* (47%); 10 Hz group n = 7 (39%) 2.Localized pain during treatment: 1 Hz group n = 1 (6%);10 Hz group n = 2 (11%) 3. Discontinuation of treatment due to side effects: 1 Hz group n = (0%); 10 Hz group n = 2 (11%)
Boggio et al (2010)	30	Left DLPFC or Right DLPFC	20 Hz	1800 pulses/session, 5 sessions/week, 10 session in total	Induced a significant decrease in PTSD symptoms as indexed by the PTSD Checklist and Treatment Outcome PTSD Scale	Not mentioned

CAPS-5, The Clinician Administered PTSD Scale-5; DLPFC, dorsolateral prefrontal cortex; PCL-5, PCL-C, PTSD checklist-C; PTSD checklist-5; PTSD, post-traumatic stress disorder; rTMS, repetitive Magnetic Transcranial Stimulation.

iTBS group, with 9.6 minutes of treatment per day for 10 working days before all participants received an additional 10 non-blinded sessions of iTBS, which resulted in a 19.4% improvement in CAPS scores and a 28.1% improvement in PCL scores after 2 weeks of treatment. Nursey et al[72] administered bilateral DLPFC iTBS to 8 subjects, treating them 5 times per week for 4 weeks, and all subjects showed improvement in PTSD symptoms and a 21.9% improvement in CAPS-5 scores. A retrospective study demonstrated that bilateral TBS administered to patients with PTSD comorbid with refractory depression significantly improved the patients' PTSD symptoms.[73] Chang et al[74] reported a case of bilateral TBS in which they administered both right cTBS and left iTBS to a 25-year-old female patient with PTSD co-morbid refractory depression, and at the end of the stimulation, left iTBS was administered again at 20-minute intervals, and after 10 days of treatment, they found that the symptoms of PTSD had improved significantly, with a 32.3% improvement in DTS scores[74] (Table 3).

Theta burst stimulation may represent a novel form of rTMS for treating PTSD, achieving similar therapeutic effects to high-frequency rTMS in a short period. Additionally, it can significantly improve depressive symptoms in patients. However, due to the high frequency of stimulation in TBS, there may be a slightly higher probability of adverse reactions compared to traditional high-frequency rTMS. In the future, larger sample sizes, randomized, double-blind, and placebo-controlled trials are necessary to validate our research findings.

Combination Therapy for Post-traumatic Stress Disorder

Several studies have used rTMS in combination with other therapies for patients with PTSD in an attempt to discover if there is better efficacy. Kozel et al[75] randomly assigned 103 subjects with PTSD to the cognitive processing therapy + rTMS group and the cognitive processing therapy + sham stimulation group, and at the end of the treatment, they found that the combination of cognitive processing therapy and rTMS significantly improved PTSD symptoms early on in the treatment and persisted until 6 months after the end of treatment. Both Osuch's crossover-controlled trial and Fryml's randomized double-blind controlled trial demonstrated that rTMS combined with exposure therapy is feasible and effective in treating patients with PTSD, but because of the small sample sizes, both studies indicated that larger samples were needed for validation (Table 4).[65,76]

Combining psychotherapy appears to be safe and feasible and may even be more effective than using rTMS alone. However, psychotherapy also requires individualized planning, posing significant challenges for researchers. Moreover, overstimulation may lead to

Table 3. Theta Burst Stimulation for Post-traumatic Stress Disorder

Study	Sample Size	Brain Target	Stimulation Frequency	Stimulation Time	Outcome Measure	Adverse Events
Philip et al (2019)[71]	25	Right DLPFC	iTBs	1800 pulses/session, 5 sessions/week, 10 sessions in total	CAPS-5: Active 47.9-38.6 (Improvement 19.4%); Sham 47.4-39.4 PCL-5: Active 49.4-35.5 (Improvement 28.1%); Sham 50.0-39.4	1.Headache: n = 6 (24%)
Nursey et al (2020)[72]	8	Bilateral DLPFC	iTBS	600 pulses/session, 5 sessions/week, 20 sessions in total	CAPS-5: Pre 47.38 (6.16); Post 37 (9.04) (Improvement 21.9%)	1.Mild-to-moderate site-specific cranial pain: n = 2 (25%) 2.Headaches during stimulation: n = 3 (37.5%)
Vaithian et al (2022)[73]	8	Bilateral DLPFC	Right cTBS Left iTBS	Right cTBS 603 pulses/session while left iTBS 600 pulses/session for a total of 19-30 sessions over 4-6 weeks	PCL-5: Pre 43.5 (18.57); Post 29.8 (18.3) (Improvement 31.5%)	Muscle contractions, pain/discomfort, scalp irritation, and systolic blood pressure changes
Chang et al (2023)[74]	1	Bilateral DLPFC	Right cTBS Left iTBS	600 pulses of right cTBS followed by 600 pulses of left iTBS, with a 20-minute rest, followed by 600 pulses of left iTBS again,30 sessions in total in 4 weeks.	DTS: 62-42 (Improvement 32.3%)	Dizziness or headaches

cTBS, continuous TBS; DLPFC, dorsolateral prefrontal cortex; iTBS, intermittent TBS; PTSD, post-traumatic stress disorder; TBS, theta burst stimulation.

retraumatization. Whether to combine psychotherapy and the specific approach to combined psychotherapy remains a variable worth exploring.

Safety and Adverse Reactions

Most studies have demonstrated positive effects of rTMS in the treatment of patients with PTSD, but its safety remains a concern. Wasserman[77] recommended a guideline based on the side effects associated with rTMS, including seizures, headaches, scalp pain, effects on hearing, and effects on mood. This guideline addresses ethical and legal considerations, selection of safe and appropriate stimulation parameters, physiologic monitoring of data, and contraindications to rTMS, following specific criteria for frequency, intensity, duration, and repetitive pulse parameters based on motor-evoked potentials to maintain safety and efficacy, and is the most widely used guideline available.

Table 4. Combination Therapy for Post-Traumatic Stress Disorder

Study	Sample Size	Brain Target	Stimulation Frequency	Stimulation Time	Outcome Measure	Adverse Events
Osuch et al (2009)[65]	9	Right DLPFC	1 Hz rTMS combined with exposure therapy	1800 pulses/session, 3-5 sessions/week, 20 sessions in total	Treatment post-baseline score for each condition (improvement rate): Active: CAPS (intrusion) - 0.22 (Improvement 31%); CAPS (avoidance) - 0.33 (Improvement 62%); CAPS (hyperarousal) - 1.00 (Improvement 55%); IES (Avoidance) 0.44 (Improvement 137%); IES (Intrusion) 1.44 (Improvement 150%) Sham: CAPS (intrusion)—0.19 CAPS (avoidance)—0.72 CAPS (hyperarousal)—0.09 IES (Avoidance)—0.00 IES (Intrusion)—0.78	No adverse events or serious adverse events
Kozel et al (2022)[75]	103	Right DLPFC	1 Hz rTMS combined with cognitive processing therapy	1800 pulses/session, 12-15 sessions in total	CAPS: pre-active 75.02 (2.05), sham 73.06 (3.08); post-active 32.91 (3.55) (improvement 56.1%), sham 37.57 (3.64) PCL-5: Pre-active 56.26 (1.65), sham 52.81 (1.75); Post-active 35.02 (1.97) (improvement 37.8%), sham 37.29 (2.00)	No adverse events or serious adverse events
Fryml et al (2019)[76]	8	Left or right DLPFC	10 Hz rTMS combined with exposure therapy	6000 pulses/session, 1 session/week, 5 sessions in total	CAPS (improvement rate): Active (improvement 55%); sham (improvement 40%)	No adverse events or serious adverse events

DLPFC, dorsolateral prefrontal cortex; PTSD, post-traumatic stress disorder; rTMS, repetitive magnetic transcranial stimulation.

The 3 main adverse effects when treating patients with PTSD are headache, malaise, and somatic symptoms such as neck pain, dizziness, and to a lesser extent also scalp pain, hearing impairment, and mood effects, but all are mild and transient.[62,78,79] A very small number of patients may also be suicidal, but their flu-like symptoms prior to treatment may not be related to rTMS.[68] There have also been studies reporting that rTMS induces epilepsy, but the number is extremely small.[17,45] The probability of adverse effects in low-frequency rTMS studies is generally less than that of high-frequency rTMS, but the exact mechanism is unclear and may be related to the stimulation parameters of rTMS. TBS exhibits efficacy similar to high-frequency rTMS, with a shorter duration and significant improvement in depressive symptoms. However, it carries a slightly higher risk of adverse reactions than traditional high-frequency rTMS. There have been no reports of severe adverse events associated with existing combined treatment regimens. In summary, rTMS is a safe, non-invasive stimulation method that shows promising efficacy in improving core symptoms of PTSD, and holds great potential to become a formal treatment modality for PTSD.

Conclusion

Currently, rTMS has been demonstrated by multiple studies to improve PTSD symptoms.[62,80] This review updates the latest evidence based on existing research and adds content on bilateral sequential TBS and combined therapy for PTSD. Compared to conventional medication and psychological intervention therapies, the advantages of using rTMS lie in its high compliance and low cost, allowing for symptom improvement within a relatively short period. The disadvantages include the potential risk of inducing seizures, although this is an extremely rare occurrence. Additionally, there is a significant challenge for researchers in adjusting personalized stimulation parameters for patients. High-frequency rTMS demonstrates better therapeutic effects compared to low-frequency rTMS, with no significant difference in the likelihood of adverse reactions between the 2. Theta burst stimulation exhibits efficacy similar to high-frequency rTMS, with a shorter duration and significant improvement in depressive symptoms. However, it carries a slightly higher risk of adverse reactions than traditional high-frequency rTMS. Combining rTMS with psychological therapy seems to more effectively improve PTSD symptoms, with early onset of effects and longer duration. However, this approach is associated with higher costs and requires individualized patient control.

Despite these promising findings, the pathophysiology of PTSD and the mechanisms underlying the improvement of PTSD symptoms by rTMS remain subjects of discussion. Existing studies suffer from small sample sizes and variations in outcome measures assessing treatment efficacy. Further research is warranted to bolster our assertions.

Availability of Data and Materials: *Data generated and/or analyzed in the research report can be requested from the corresponding authors.*

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