

# World Journal of *Clinical Cases*

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## Repetitive transcranial magnetic stimulation for post-traumatic stress disorder: Lights and shadows

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### Abstract

We have read with interest the publication that describes the available data related to the use of neuromodulation strategies for the treatment of post-traumatic stress disorder (PTSD). Despite treatment advances, however, a substantial proportion of PTSD patients receiving psychological and/or pharmacological treatment do not reach an adequate clinical response. In their paper, the authors draw attention to the current understanding of the use of repetitive transcranial magnetic stimulation (rTMS) as a potential treatment for PTSD. Most of the previous studies indeed applied both inhibitory (1 Hz) and excitatory (> 1 Hz, up to 20 Hz) rTMS to the right and/or left dorsolateral prefrontal cortex. Despite larger therapeutic effects observed when high-frequency stimulation was applied, the question of which side and frequency of stimulation is the most successful is still debated. The authors also reported on the after-effect of rTMS related to neuroplasticity and identified the intermittent theta burst stimulation as a technique of particular interest because of it showed the most effective improvement on PTSD symptoms. However, although numerous studies have highlighted the possible beneficial use of rTMS protocols for PTSD, the exact mechanism of action remains unclear. In their conclusions, the authors stated that rTMS has been demonstrated to be effective for the treatment of PTSD symptoms.



Nevertheless, we believe that further research with homogeneous samples, standardized protocols, and objective outcome measures is needed to identify specific therapeutic targets and to better define significant changes when active and sham stimulation procedures are compared.

**Key Words:** Post-traumatic stress disorder; Neuromodulation; Repetitive transcranial magnetic stimulation; Translational neuroscience; Neuroplasticity; Metaplasticity

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**Core Tip:** The interesting publication of the basic principle, current applications, and future directions of repetitive transcranial magnetic stimulation for the non-pharmacological treatment of post-traumatic stress disorder (PTSD) have been summarized. Therapeutic effects on core PTSD symptoms, such as avoidance, hyperarousal, and intrusions, appear to be larger when high-frequency stimulation over the right dorsolateral prefrontal cortex was used. However, although the technique has demonstrated safety and efficacy, several concerns remain related to the mechanisms of action and protocols to be adopted, including the heterogeneity in the sample selection, stimulation procedures, and outcome measures.

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## TO THE EDITOR

We have read with interest the recent publication by Cheng *et al*[1] summarizing the current understanding on the use of transcranial magnetic stimulation (TMS) as a potential treatment for post-traumatic stress disorder (PTSD). As known, PTSD is a mental health disorder that may occur after experiencing or witnessing a significantly traumatic event. Symptoms include flashbacks, nightmares, and severe anxiety, as well as uncontrollable thoughts about the event, affective symptoms, and negative cognition[2]. These symptoms can significantly impact personal relationships and social and work activities, thus impairing functional independence and quality of life[3,4].

Neuromodulation strategies based on non-invasive brain stimulation techniques, such as repetitive TMS (rTMS) and transcranial direct current stimulation, have been recently investigated and applied in PTSD patients who did not reach an adequate clinical response with conventional therapy[5,6]. TMS has been widely used for the treatment of other psychiatric disorders, in particular it has shown to be highly effective in adults with drug-resistant major depressive disorder[7], including long-lasting effects on depressive-associated cognitive dysfunction[8]. Regarding PTSD, the latest evidence-based guidelines on the therapeutic use of rTMS concluded that level B evidence (probable efficacy) was reached for high-frequency (excitatory) rTMS over the right dorsolateral prefrontal cortex (DLPFC)[9]. However, these recommendations are based on the differences reached in therapeutic efficacy of real *vs* sham (fictitious) stimulation replicated in a sufficient number of independent studies, but this does not mean that the benefit produced by rTMS inevitably reaches a clinical relevance[9].

In their paper, Cheng *et al*[1] suggested the role of rTMS as an effective and promising treatment for PTSD. However, the previous literature they reviewed mainly shows considerable variation regarding stimulation parameters, type of traumatic events, and sample characteristics. Regarding the stimulation area, most of the previous studies identified the DLPFC as the preferential stimulation target, although differences were observed between either the frequency or the side of stimulation. The interest in targeting the right DLPFC comes from previous evidence showing that high-frequency rTMS was able to increase neural activity and blood flow in the right hemisphere, thus improving some of the core PTSD symptoms, such as avoidance, hyperarousal, and intrusions[10]. Conversely, high-frequency rTMS over the left DLPFC has been mainly used as a neuromodulatory protocol for mood disorders[7], suggesting its application for the PTSD-related affective symptoms.

Regarding the rTMS protocols, most studies applied a stimulation intensity of 120% of the individual's resting motor threshold. Subjects who underwent 1-Hz (inhibitory) stimulation usually received 2250 pulses over 37.5 min, whereas those stimulated at 10-Hz (excitatory) received 3000 pulses over the same time period (4-s stimulation train, with 26-s intertrain interval), for 2 wk of daily treatments[11-14], although some more recent rTMS trial designs in PTSD have delivered more treatments[15-17]. However, the question of which side and frequency of stimulation is the most successful in terms of remission or response from PTSD symptoms is still debated.



Regarding the side of stimulation, it seems that rTMS could be effective over both the left and right DLPFC, as suggested by the authors themselves[1]. Of clinical relevance is also the finding of a better treatment outcome for the high-frequency rTMS applied over the right than the left DLPFC. This is in line with a recent meta-analysis by Harris and Reece[10], who discussed the effects of rTMS on episodic memory retrieval and reiteration of the traumatic event, which is responsible for the flashback symptoms. They suggested that the DLPFC might be involved in the recurrence of trauma reminiscence and, therefore, may participate in the inhibition of the trauma memory. Likewise, Cheng *et al*[1] reported of a previous work by Parson and Ressler[18] on the correlation between dysregulated response to fear and PTSD symptoms. Overall, it appears that DLPFC is involved in emotional regulation, being also thought to influence the activity between the ventral medial prefrontal cortex (vmPFC) and the amygdala[19]. Accordingly, other studies highlighted the role of the vmPFC in modulating fear responsivity[20], as well other cerebral areas, such as the temporal-insular cortex[21].

It should be also considered that an earlier study suggested that the effectiveness of rTMS might depend not only on PTSD symptoms only, but also on the patient's personality traits, such as impulsivity, risk proneness, and sensation seeking[22]. DLPFC plays indeed a key role in mood-affect and impulsivity regulation and a hyperactivity of the limbic structures has been related to behavioral instability[23]. Emotional dysregulation and disturbed impulse control are also common borderline personality traits. In this context, a previous TMS report explored the influence of comorbid borderline personality traits on treatment response to TMS in major depressed patients[24], whereas a recent study by Ward *et al*[25] reported that borderline personality traits did not affect treatment response to DLPFC-TMS in a large naturalistic dataset of patients receiving conventional clinical treatment for depression. In their conclusion, the authors stated that the antidepressant efficacy of rTMS was independent from comorbid borderline personality disorder.

Interestingly, Cheng *et al*[1] also reported on the after-effect of rTMS on neuroplasticity, and in particular on long-term potentiation and long-term depression, phenomena likely related to glutamatergic (especially to AMPA and NMDA receptor) and GABAergic activity, respectively. They further identified the intermittent theta burst stimulation (iTBS) as a technique of particular interest, because of its most effective improvement on PTSD symptoms. The authors also reported on a sham-controlled study by Philip *et al*[26], who indicated which PTSD symptoms, including depression, improved the most after iTBS treatment and hypothesized the effects on hippocampal synaptic activity and connections.

Among the cellular and molecular mechanisms underlying distinct forms of synaptic plasticity, however, we believe that more attention should be paid to metaplasticity, which refers to the activity-dependent modulation of synaptic plasticity. This pivotal determinant of learning, memory, and other functions represents a higher order of synaptic plasticity that acts on the threshold for modifying synaptic strength[27]. Moreover, impaired synaptic plasticity, the so-called "maladaptive plasticity", has been associated with the pathogenesis and trajectory of several brain diseases, including contributions to the dysfunctional remodeling of underlying neural networks[28]. Given its role in regulating synaptic plasticity, alterations to metaplastic mechanisms are likely to represent an important element of many neurological and psychiatric disorders, including PTSD. The development of non-invasive brain stimulation techniques has allowed to induce and modulate metaplasticity in human subjects, both in normal and pathological conditions. In support of this, Thomson and Sack[29] focused on the use of iTBS to develop metaplasticity-based treatments to induce or restore the desired level of plasticity. They further identified accelerated iTBS at longer intervals (60 min) as being of particular interest, as it seems to maximize metaplasticity effects and clinical outcomes[29].

In their conclusions, the authors stated that rTMS demonstrated to be a safe and effective neurostimulation treatment for PTSD[1]. However, although several studies highlighted the beneficial use of TMS protocols for PTSD, the exact mechanism of action remains unclear. Therefore, we believe that further research with homogeneous samples, standardized protocols, and objective outcome measures is needed to better define the optimal stimulation settings (including the active and sham stimulation comparison) and to clarify whether these interventions may be applied not only to the core symptoms of PTSD but also on its cognitive and mood-affect manifestations.

## FOOTNOTES

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