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# A Review of Transcranial Magnetic Stimulation as a Treatment for Post-Traumatic Stress Disorder

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**Abstract** Patients with post-traumatic stress disorder (PTSD) may fail to achieve adequate relief despite treatment with psychotherapy, pharmacotherapy, or complementary medicine treatments. Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation procedure that can alter neuronal activity through administration of various pulse sequences and frequencies. TMS may theoretically have promise in correcting alterations observed in patients with PTSD. While the precise treatment location and pulse sequences remain undefined, current evidence suggests two promising targets, the right dorsolateral prefrontal cortex and the medial prefrontal cortex. The beneficial effects may be due to the secondary or indirect regulation of other brain structures that may be involved in the mood regulatory network. TMS may be an effective part of a comprehensive treatment program for PTSD, although significant work remains to define optimal treatment parameters and clarify how it fits within a broader traditional treatment program.

**Keywords** Post-traumatic stress disorder (PTSD) · Transcranial magnetic stimulation (TMS) · Military · Combat

This article is part of the Topical Collection on *Military Mental Health*

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## Introduction

From 2001 to 2014, over 2.5 million U.S. Service Members (SMs) were deployed in combat operations. The risk of post-traumatic stress disorder (PTSD) is increased in combat veterans due to exposure to traumatic events, combat-related injury, and traumatic brain injury (TBI). Diagnosis of PTSD requires an individual to meet *Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition* (DSM-V) criteria for intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. After deployment, the prevalence of PTSD is 12–20 and 6–12 %, after returning from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), respectively [1].

PTSD rarely occurs in isolation from other psychiatric morbidities, and many patients do not adequately respond to traditional therapies. Standard treatment options include psychotherapy and pharmacology. Much psychotherapy work has focused on exposure therapy, where patients recall traumatic events with the goal of inducing extinction of the resulting negative symptoms. Unfortunately, intense emotions triggered by this therapy can be intolerable and may lead some patients to discontinue treatment [2]. The selective serotonin reuptake inhibitors (SSRI) paroxetine and sertraline are Food and Drug Administration (FDA)-approved for the treatment of PTSD, but their limited efficacy and poor compliance due to side effects limits some of their utility [3••]. While not FDA-approved, prazosin has been used for sleep disturbance and nightmares associated with PTSD, but compliance and intolerance can also be problematic [4].

Given the limits of traditional therapies for PTSD, other modalities should be examined for potential benefit. Transcranial magnetic stimulation (TMS) is a procedure that alters neuronal activity and is currently cleared by the FDA for the treatment of depression that has failed to respond to prior

antidepressant medication administration. This paper will review the use of TMS in patients with PTSD.

## Mechanics of Transcranial Magnetic Stimulation Delivery

TMS uses a pulsed magnetic field to non-invasively modulate neuronal activity. This is accomplished by the TMS device sending a variable electrical current through a coil placed close to or in contact with the scalp, which creates regional lines of magnetic flux that transmit through the skull and create an electric field within a targeted neuronal area [5, 6]. While a focal area is directly stimulated by TMS, neural network connectivity leads to downstream effects that can alter neuronal function in areas distant from the stimulation site. Multiple variables modulate the interaction of the device with the natural electrical conductivity of the brain, including the type of coil utilized, the frequency of stimulus delivery, the duration of pulse sequence, inter-stimulation rest periods, the strength of the magnetic field, the total number of pulses in each session, and the regularity of administered treatments during a week [7]. When TMS is delivered repetitively, it may be referred to as rTMS.

There are multiple coil designs which produce different magnetic fields influencing field depth, spatial resolution, and field strength. These impact the characteristics of stimuli delivery to the region of interest and can be supplemented by variables controlled by the clinician, such as pulse frequency, train length, or number of pulses per session [8]. For an excellent review of coil design and the resulting magnetic field stimulation patterns, please see Deng et al. [9•].

The frequency of stimuli delivery refers to the number of pulses delivered over time. Pulses delivered at greater than 5 Hz are considered to have long-term potentiating effects, and those delivered at, or less than, 1 Hz are considered to promote long-term inhibition [10]. Local stimulation can have wide reaching implications throughout the central nervous system as transmission through neural networks can have variable impact on downstream regions.

Pulses are typically delivered in groupings referred to as trains. For example, a 10-Hz frequency would be administered over 4 s which would total 40 pulses in that train. A resting interval, a period in which no stimuli is delivered, occurs between trains. The combination of the total pulse trains and rest intervals determine the treatment duration, usually lasting approximately 20 to 40 min per session. Higher stimulation frequency, longer train sequences, or shorter recovery interval increase the risk of secondary generalization of the stimulation, which could result in a subsequent induction of seizure activity. International guidelines exist for these parameters to ensure safe delivery of TMS [11].

The frequency, length of the pulse train, and the number of trains delivered determine the total number of pulses per session. For depression, usually either 1980 or 3000 pulses are delivered per session, depending on the particular device being used. The optimal number of pulses per session remains undefined and likely is condition, treatment site, and device dependent. Up to 18,000 pulses per day have been administered and found to be safe and well tolerated [12]. For depression, TMS is usually delivered five times per week. Given the average length of each session and the frequency of treatment delivery, TMS requires a significant time investment from both the patient and providers.

The strength of the magnetic field delivery is reported as a percentage of the motor threshold, which is the amount of magnetic field needed to depolarize cortical neurons in the primary motor cortex which results in a subsequent muscle contraction. This is usually determined at the area corresponding to the abductor pollicis brevis. Motor threshold varies by an individual's neuronal physiology and can be affected by medications that alter neuronal excitability [8]. The long-term potentiation or inhibition of rTMS when considering the combination of field strength and pulse frequency remains uncertain.

## Mechanisms of Transcranial Magnetic Stimulation as a Treatment for PTSD

A range of potential mechanisms for the development of PTSD have been proposed. Functional imaging studies have provided insight about the neuropathological structural and functional changes in PTSD [13, 14]. One anatomical region of interest is the dorsolateral prefrontal cortex (DLPFC), which is involved in several complex cognitive and behavioral functions, including working memory, supervisory attentional control, decision-making, temporal organization of behavior, and cognition. Additionally, the DLPFC can indirectly regulate the mood regulatory network, which includes the amygdala and hippocampus, and these brain regions have been implicated in the pathophysiology of PTSD [14, 15]. In addition to imaging studies, neuropsychological testing has also suggested the involvement of paralimbic and right limbic structures in PTSD [15, 16]. Other functional imaging has identified hypo-activation of the prefrontal cortex [medial (mPFC) and DLPFC] and hyper-responsivity of the amygdala in individuals diagnosed with PTSD [17, 18].

TMS can be used for assessment of central nervous system function. GABAergic and glutamatergic tone can be assessed using TMS-paired pulse sequences, where a conditioning pulse is followed rapidly by a stimulating pulse. The interval between the two pulses will result in a motor threshold stimulation that is dependent on GABA and glutamate tone reflected in short-latency intracortical inhibition and long-latency intracortical inhibition respectively. Using this technique, PTSD may be associated with bilateral hemispheric decreases in GABAergic tone and an increase in right hemispheric glutamatergic tone, which might be amenable to TMS therapy. [19, 20].

Positron emission tomography (PET) analysis confirmed a right-sided lateralization in individuals with PTSD by demonstrating increased blood flow in right-sided limbic and paralimbic regions when study participants were presented with traumatic scripts compared to neutral scripts [14].

In addition to preliminary data suggesting a significant role for the DLPFC in the response of individuals with PTSD to TMS, the mPFC may also be a viable target. Francati et al. reported a reduced activation of the mPFC in individuals with PTSD [21]. Furthermore, treatments associated with activation of the mPFC may reduce PTSD symptom severity [22]. A combination of high-frequency TMS stimulation targeting the mPFC and brief exposure therapy significantly improved symptoms of PTSD [23••]. More specifically, it limited the intrusive component of the Clinician-Administered PTSD Scale (CAPS), which may be indicative of mPFC facilitated extinction of fear responses during traumatic memories. This outcome may be attributable to the regulatory control exerted over the amygdala by the mPFC, which has previously been demonstrated to achieve and preserve extinction of acquired fear responses [22].

## Recent Research Findings

Between 1998 and 2015, a number of open trial, crossover, retrospective, and randomized-controlled studies have been published on the use of TMS for the treatment of PTSD with various parameters of administration and patient populations. Here, we have reviewed ten primary studies, one systemic review, and two meta-analyses of the use of TMS as a treatment for PTSD and which used various instruments to provide outcome measures.

In 1998, two research groups reported the initial uses of rTMS in human subjects for possible treatment of PTSD symptoms. Grisaru et al. investigated using rTMS for PTSD symptoms in an open-label trial using low-frequency bilateral stimulation of the motor cortex [24]. Ten subjects with PTSD (including combat-related and assault) were included in the trial. The rTMS protocol used was described in Table 1. The outcome measures were Clinical Global Impression (CGI), Impact of Events Scale (IES), and the Symptom Checklist-90 (SCL-90). Each assessment was performed at four time points (2 h before TMS, 24 h following TMS, and 1 week and 28 days after the single session). Within 24 h of treatment, a significant improvement in the avoidance subscale of the IES ($p=0.033$) and the CGI ($p<0.001$) was reported. The anxiety portion of the SCL-90 also demonstrated improvement ($p=0.009$). It should be noted, however, that despite the persistence of the improvements to 28 days, there was a trend toward baseline.

In a two-subject case study, McCann et al. examined rTMS in the treatment of PTSD [7]. Both subjects had PTSD and one subject also experienced comorbid refractory depression. The rTMS protocol used was described in Table 1. Outcome measures included Modified PTSD Symptom Scale (MPSS) and PET. Prior to rTMS and again within 24 h of each subject's last treatment, both subjects underwent PET to obtain regional cerebral glucose metabolic rates. In both participants, the PTSD checklist (PCL) significantly improved at times during treatment but returned to baseline scores 1 month after discontinuation. The baseline, pretreatment medication-free PET in both patients demonstrated marked hyperactivity. The PET, after the final treatment in both cases, revealed global reduction of cerebral metabolism toward the age- and sex-adjusted norms with more prominent decrease over the right hemisphere.

Although limited in scope, these initial two reports did suggest that rTMS could be successfully employed as part of a treatment program for PTSD. Following the publications of these studies, other researchers began publishing additional open-label trials or larger-scale controlled trials. The first two of these follow-up studies investigated the relative efficacy of high-frequency stimulation compared to low-frequency stimulation. In an open-label trial, Rosenberg et al. examined rTMS as an adjunct to antidepressant medications for patients with PTSD and comorbid major depression [25]. Twelve participants were randomly assigned to either 5 or 1 Hz rTMS over the left DLPFC. The rTMS protocol used was described in Table 1. The outcome measures included Hamilton Depression Rating Scale (HAM-D), Profile of Mood States (POMS), University of Southern California Repeatable Episodic Memory Test (USC-REMT), and Mississippi Scale of Combat Severity (MISS). There was no significant difference in outcomes between the low-frequency and high-frequency groups. Depressive symptoms were improved after rTMS treatment and at 2-month follow-up ($p<0.05$). PTSD symptoms were only improved at 2-month follow-up ($p<0.05$). Subscales suggest that improvements in PTSD were affective-related and not with core symptoms of intrusion, hypervigilance, and avoidance. The USC-REMT resulted in no significant change from baseline or between treatment arms.

In a sham double-blinded placebo-controlled trial, Cohen et al. examined the efficacy of high-frequency rTMS compared to low-frequency rTMS or sham treatment using a 9-cm circular coil [26]. Twenty-nine subjects with PTSD (4 combat-related) were randomly assigned to one of the three groups. The rTMS protocol used was described in Table 1. The outcome measures were PCL, Treatment Outcome PTSD Scale (TOP-8), Hamilton Anxiety Rating Scale (HAM-A), HAM-D, and CAPS. High-frequency stimulation significantly improved anxiety and PTSD core symptoms (avoidance and re-experiencing) in comparison to low-frequency and sham groups ($p<0.05$)

Differences in these two reports could be attributable to different treatment locations, pulse sequences, treatment

**Table 1** Parameters and outcomes from studies utilizing TMs as a treatment for PTSD

| Study (type) | Placement | Motor threshold | Course | Treatment parameters | Pulses | Primary outcomes |
|---|---|---|---|---|---|---|
| Figure 8 Coil | | | | | | |
| Oznur et al. 2014 Retrospective | Right DLPFC | 80 % | 4 weeks/5 days a week | 40 stimulations at 1 Hz, followed by 20 s rest per min. 15 min duration. | 600 pulses/day; 12,000 pulses total | Only decrease in IES hyperarousal score was significant ($p$=0.02) |
| Nam et al. 2013 Randomized clinical trial | Right PFC | 100 % | 3 weeks/5 days a week | Group 1: continuous 1 Hz for 20 min<br>Group 2: sham | 1,200/day 18,000 pulses total | Active rTMS showed significant time by treatment group effect improvement in totals CAPS score ($p$=0.008) and in the CAPS re-experiencing subtest ($p$=0.004) compared to sham. |
| Watts et al. 2012 Randomized clinical trial | Right DLPFC | 90 % | 2 weeks/5 days a week | Group 1: 20 stimulations at 1 Hz for 20 s followed by 40 s rest per min. 20 min duration<br>Group 2: sham | 400/day 4000/total | TMS group significantly improved symptoms of PTSD and depression compared to sham, as defined by CAPS ($p$=0.009), PCL ($p$=0.0002), and BDI ($p$<.05). |
| Boggio et al. 2010 Randomized clinical trial | Group 1: Right DLPF<br>Group 2: left DLPFC<br>Group 3: sham | 80 % | 2 weeks/5 days a week | Group 1: right DLPFC –2 s of 20 Hz stimulation followed by 28 s of rest. 20 min duration<br>Group 2: left DLPFC –2 s of 20 Hz stimulation followed by 28 s of rest. 20 min duration<br>Group 3: sham | 1,600/day 16000/total | Both active rTMS conditions significantly decreased PTSD symptoms, but right-sided rTMS had a greater improvement compared to left<br>Mood scores improved for only the left-sided treatment ($p$<0.001). Anxiety scores improved only with right-sided treatment ($p$<.01). |
| Osuch et al. 2009 Crossover design clinical trial | Right DLPFC | 100 % | 3-5/week; 2 week washout period prior to crossover | Group 1: 1 Hz continuous stimulation for 30 min with exposure<br>Group 2: sham with exposure | 1800/day up to 36,000/total | No differences were observed between TMS or sham treatments ($p$>0.05). |
| Rosenberg et al. 2002 Open label | Left DLPFC | 90 % | 2 weeks/5 days a week | Group 1: 40 s stimulation at 1 Hz followed by 20 s rest. Duration 15 min<br>Group 2: 8 s stimulation at 5 Hz followed by 52 s rest. Duration 15 min | 600/day 6000/total | Both groups had improvements in depressive symptoms. Both groups had a modest improvement in PTSD symptoms at two months post rTMS. |
| McCann et al. 1998 Case study | Right frontal region (exact region unreported) | 80 % | 3–5/week; Patient 1: 17 sessions over 4 weeks Patient 2: 30 sessions over 6 weeks. | 1 Hz for 20 min | 1200/day P1: 20,400 total P2: 36.000 | Patient 1: PTSD significantly decreased only during week 4 ($p$=0.05). Patient 2: PTSD significantly decreased during weeks 2, 3, and 5 ($p$<0.01). Both patient's symptoms returned to baseline one month after treatment discontinuation. |
| H-Coil | | | | | | |
| Isserles et al. 2013 Randomized clinical trial; crossover design | Bilateral medial prefrontal cortex | 120 % | 4 weeks/ 3 days a week | Group 1: 2 s stimulation at 20 Hz followed by 20 s interval for 42 total trains with traumatic script pairing<br>Group 2: same treatment with exposure therapy with non-traumatic script pairing<br>Group 3: sham with traumatic script pairing | 1680/day 20,160 total | Group 1 significantly improved intrusion component of CAPS ($p$<0.05). |

**Table 1** (continued)

| Study (type) | Placement | Motor threshold | Course | Treatment parameters | Pulses | Primary outcomes |
|---|---|---|---|---|---|---|
| 9-cm Circular | | | | | | |
| Cohen et al., 2004 Randomized Clinical Trial | Right DLPFC | 80 % | 2 weeks, 5 days a week | Group 1: sham<br>Group 2: 5 s stimulation at 1 Hz followed by 55 s rest. 20 min duration.<br>Group 3: 2 s stimulation at 10 Hz followed by 58 s rest. 20 min duration. | Group 2: 100/day<br>Group 3: 400/day | High-frequency stimulation significantly improved anxiety and PTSD core symptoms (avoidance and re-experiencing) in comparison to low-frequency and sham groups ($p<0.05$) |
| Angular shape, 14-in diameter | | | | | | |
| Grisaru et al., 1998 Open label | C3/C4 motor cortex, bilateral | 100 % of machine capacity, field strength of 2.5 T | 1 session | 15 stimulations with 1 min intervals between them. Performed first on right, then repeated on left. | 30 total | Significantly lowered symptoms of anxiety, somatization, and avoidance ($p<0.05$). |

intensities, and total number of pulses delivered. With no conclusive results, future studies continued to use different stimulation frequencies (i.e., low or high) applied to different regions of the brain to better characterize the effects of rTMS as a potential treatment for PTSD. In a stratified randomization of a double-blinded placebo-controlled study, Boggio et al. examined the efficacy of high-frequency rTMS of right or left DLPFC compared with sham in the treatment of PTSD [3••]. Thirty subjects with PTSD, none related to military combat, were randomly assigned to 1 of 3 treatment groups: rTMS targeting the right DLPFC, rTMS targeting the left DLPFC, or sham rTMS treatment. The rTMS protocol used was described in Table 1. Outcome measures included the PTSD checklist (PCL), TOP-8, HAM-A, and HAM-D. Right- or left-sided DLPFC stimulation significantly improved core PTSD symptoms based on the PCL at day 5 ($p=0.018$, right-sided; $p=0.012$, left-sided) and day 10 ($p=0.0042$, right-sided; $p=0.012$, left-sided). A similar improvement also observed the TOP-8 at day 5 ($p=0.02$, right-sided; $p=0.0042$, left-sided) and day 10 ($p=0.008$, right-sided; $p=0.0039$, left-sided). No effects ($p>0.05$) were observed in the sham treatment group. Improvement in core PTSD symptoms was greater with right-sided stimulation compared to left based on PCL ($p=0.03$) and the TOP-8 ($p=0.051$). Only left-sided rTMS significantly improved scores on the HAM-D at day 5 ($p=0.0001$) and day 10 ($p=0.0006$). In contrast, only right-sided rTMS significantly improved scores on the HAM-A at day 5 ($p=0.0066$) and day 10 ($p=0.0096$). In summary, administration of rTMS improved measures of PTSD with right-sided treatment favored over left for core symptoms. Anxiolytic effects were favored in right-sided treatment, and antidepressant effects were favored in left-sided treatment.

Since the results published by Boggio et al. , several trials have focused on low-frequency stimulation of the right DLPFC. In a double-blinded sham-controlled study, Watts et al. examined the efficacy of low-frequency rTMS over the right DLPFC in 20 participants, 18 male and 2 female, with PTSD resulting from various traumas. Inclusion required a primary diagnosis of PTSD, as assessed by the Structured Clinical Interview for Diagnosis (SCID) and a CAPS score greater than 50. The rTMS protocol used was described in Table 1. Outcome measures included the CAPS, PCL, Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), and Brief Neuropsychological Cognitive Examination (BNCE). The active treatment arm significantly improved compared to baseline on both CAPS and PCL with a 27.7 point reduction ($p<0.0001$) and a 16.2 point reduction ($p<0.0001$), respectively. The CAPS and PCL also improved significantly when compared with sham ($p=0.009$ and $p=0.0002$, respectively). Duration of effect showed that mean CAPS at 1- and 2-month post-treatment remained improved, although there was a worsening trend in symptoms suggesting loss of durability. The BDI was also significantly improved

post treatment in the active treatment group compared to sham ($p$=0.03). Anxiety symptoms improved within the active arm compared to baseline; however, when compared with sham, the improvement was not statistically significant ($p$=0.06). BNCE demonstrated no change in cognitive function in either the active or sham arm. In summary, low-frequency rTMS delivered to the right DLPFC demonstrated significant therapeutic effects on PTSD and depressive symptoms compared to sham treatments.

In a randomized-controlled double-blinded study, Nam et al. examined the therapeutic effects of low-frequency right DLPFC rTMS compared to sham treatment [27]. Eighteen subjects with non-military-related PTSD were enrolled, and 16 subjects completed the study. The two participants that did not complete the study were unrelated to side effects. All participants continued to receive medications and supportive psychotherapy. The rTMS protocol used was described in Table 1. The primary outcome measures were CAPS and its subscales at baseline and weeks 2, 4, and 8. The time by treatment group effect demonstrated significant improvement on the CAPS re-experiencing score ($p$=0.004) and total CAPS score ($p$<0.008). Furthermore, there was a trend toward a significant response in CAPS avoidance ($p$=.0055). Hyperarousal was not affected by treatment. Based on these results, the authors suggested that individuals with PTSD may benefit from low-frequency rTMS over the right DLPFC, with symptom cluster specific responses.

In a retrospective review, Oznur et al. examined the effects of a low-frequency right DLPFC rTMS, in combination with standard medication therapies, on 20 male subjects, with combat-related treatment-resistant PTSD and comorbid major depression [28]. The rTMS protocol used was described in Table 1. The BDI, Beck Anxiety Inventory (BAI), and Impact of Event Scale–Revised (IES-R) were administered to patients before and after their rTMS treatment course. rTMS treatment significantly decreased the IES-R hyperarousal score (pre-treatment 21.4±4.7, post-treatment 19.0±4.2; $p$=0.02). Total IES-R score, IES-R intrusion and avoidance scores, BDI, or BAI were not affected by treatment. These results would appear to suggest that low-frequency right DLPFC rTMS may be effective for hyperarousal symptoms in patients with treatment-resistant PTSD.

Some investigators have coupled exposure-based therapies with rTMS in hopes of facilitating the fear extinction response sought with this modality. In a double-blind sham-controlled crossover study, Osuch et al. examined the effects of low-frequency right DLPFC rTMS with exposure therapy in PTSD subjects [29]. Nine subjects (eight female), with treatment-refractory chronic PTSD and comorbid major depression, all of whom had distressing flashbacks, were consecutively assigned to either the active rTMS treatment or sham. The rTMS protocol used was described in Table 1. After the conclusion of the first phase of 20 sessions, there was a minimum 2 week washout period prior to crossover to the alternative study arm. Outcome measures included CAPS, HAM-D, IES, along with biologic measures such as 24-h urine cortisol, dopamine, epinephrine, norepinephrine, serum cortisol, thyroid hormone, and prolactin. The rTMS treatment moderately improved the hyperarousal measure on the CAPS score in comparison to the sham treatment, but this did not reach statistical significance. No significant changes were reported in avoidance or intrusion symptoms on CAPS or IES, or any other behavioral or biological outcome measures.

Isserles et al. combined rTMS stimulation of the medial prefrontal cortex with script-driven exposure therapy in an effort to facilitate extinction of the fear response [23••]. This was completed in a randomized, double-blinded, placebo-controlled study, with a crossover phase. Thirty subjects with PTSD, who did not respond to earlier treatments, were enrolled and randomly assigned to 1 of 3 treatment groups. Participants were excluded for other DSM diagnoses, with the exception of depression. There were three study groups: group 1 received deep TMS (dTMS) after exposure to script-driven traumatic-event imagery, group 2 received dTMS after exposure to script-driven positive-event imagery, and group 3 received sham treatment after exposure to script-driven traumatic-event imagery. The rTMS protocol used was described in Table 1. Outcome measures were CAPS, Post-Traumatic Symptom Scale-Self-Report (PSS-SR), HDRS-24, and BDI-II. Total CAPS score, intrusion sub-scores, avoidance/numbness sub-scores, arousal sub-scores, and the other measures of PSS-SR, HDRS-24, and BDI-II were all significantly improved in group 1 (dTMS with exposure) with no significant changes noted on any of the assessments in the other groups. After the first phase of the study was concluded, ten subjects (four from group 2 and six from group 3) were crossed over to receive the same treatment administered to group 1. A CAPS assessment was performed on this crossover group. As with the initial group 1, the individuals in the crossover group significantly improved on the CAPS total score from baseline to end of the crossover phase assessment ($p$=0.037). The duration of therapeutic benefits were evaluated in group 1 and in the crossover group was well-preserved at 2 weeks and 2 months after treatment.

## Systemic Reviews

Wahbeh et al. conducted a systemic review on the treatment of PTSD using complementary and alternative medicine [30]. For the purposes of their review, rTMS was considered an alternative medicine. In this study, four TMS trials were included [3••, 24, 26, 31]. Quality assessment methodology was applied based on the Cochrane Risk of Bias Tool and the Quality Assessment Tool. Each study was interpreted as either positive, mixed, negative, or neutral based on the PTSD treatment outcomes. For the entire modality of TMS, the evidence

of grading was based on the natural standard evidence-based grading rationale. rTMS received a grade A, suggesting strong scientific evidence for this treatment modality for PTSD.

### Meta-analyses

Berlim et al. conducted a meta-analysis of published randomized double-blind and sham-controlled studies that used rTMS over the DLPFC for treatment of PTSD [32]. Based on study selection criteria, three studies were included in this meta-analysis [3••, 26, 31]. A pooled Hedges *g* effect size analysis was completed that demonstrated outcome favoring right DLPFC rTMS based on changes from baseline clinician-reported PTSD symptoms ($p<0.001$) and from baseline self-reported PTSD symptoms ($p<0.001$). Improvement in anxiety and depressive symptoms from baseline was also demonstrated via pooled Hedges *g* effect size 1.24 ($p=0.02$) and 0.85 ($p=0.001$) respectively. Only the subgroup from Boggio et al. was available for left DLPFC analysis, which was superior compared to sham.

In a combined meta-analysis and systemic review, Karsen et al. reviewed the effectiveness of TMS for the treatment of PTSD [33]. In the systemic review section, eight studies were discussed, while for the meta-analysis section, only three studies were included [3••, 26, 31]. The three studies provided five treatment arms to be analyzed. It was determined that four of the five treatment arms using active rTMS for PTSD were statistically significant; overall, for the five treatment arms, the Hedges *g* effect sizes ranged from 0.73 to 3.78. Depressive symptoms were also evaluated based on those five treatment arms with the same four of five displaying improvement in symptoms; the Hedges *g* effect sizes ranged from 0.83 to 3.6. A trend was noted for correlation between effect size and total number of pulses; however, statistical significance was not reached ($r=0.798$, $p=0.061$). The authors suggest that right-sided treatment may be more efficacious for the treatment of PTSD than left-sided treatment. Additionally, no differences were noted between high- and low-frequency stimulation.

## Discussion

Pharmacotherapy is one option for treating PTSD, but carries with it risks of intolerance, side effects, non-compliance, and contribution to polypharmacy. Psychotherapy is another commonly recommended treatment, but can be labor intensive and requires training in specific evidence-based techniques. TMS may offer a non-pharmacologic method of symptom relief, and there are neurophysiologic constructs that theoretically suggest mechanisms of action. While early data on the role of TMS for PTSD seems promising, there are many questions that remain regarding its use.

### Treatment Delivery

There remains significant variability in the treatment delivery of rTMS. There is a lack of consensus on the optimal pulse sequences, with continued inconsistency in pulse trains, frequency, rest intervals, total number of pulses per session, intensity of magnetic field delivery as percent of the motor threshold, frequency of treatment per week, and total number of treatments session. These variables may be interrelated and changes in any one parameter may influence the impact of the remaining treatment variables. Rather than a specific parameter being optimal in all treatment sequences, defining a unique constellation of parameters may be more effective.

Data from the studies reviewed failed to clarify whether low- or high-frequency stimulation is preferred. Further clouding the high- or low-frequency consideration is the varying levels of stimulation used in each of the trials. It is unclear if stimulation applied below the motor threshold has the same effect as that applied at or above the motor threshold, thus frequency alone may not predict focal neuromodulation effects. Without consensus as to the neuropathophysiology and the effects of varying rTMS stimulation patterns, optimal TMS pulse sequences will be elusive.

### Treatment Location

Three neurobiologic theories have helped shape rTMS techniques for PTSD which helped inform coil design choices involved in the above studies, each with unique stimulation focality and depth. The first is based on the theory of hyperactivity of the right hemisphere, prompting the low-frequency inhibitory stimulation of the right DLPFC. The mPFC is an appealing target given its modulatory effects on the amygdala and its role in the fear response, though this location requires a coil with a reasonable magnetic field depth of penetration. Finally, the left DLPFC has network connectivity to limbic structures and is already a target for treating depressive symptoms. Given the affective comorbidities in PTSD, it too is a potential viable target. Until there are standardized methods of characterizing neurologic functional activity and aberrations present in PTSD, variance of results for each of these targets is likely to continue.

### rTMS with Exposure Therapy

Osuch et al. and Isserles et al. utilized a combination of exposure-based therapies with rTMS in an effort to facilitate the fear extinction sought with this psychotherapeutic modality. Osuch et al. chose to stimulate the right DLPFC but no benefit was shown in active or sham treatment groups. It should be noted that this was a limited scale trial. Isserles et al. demonstrated the benefit in the active treatment group which received mPFC stimulation. Given the strong

connection between the amygdala and mPFC, targeting this area may have greater utility in future trials.

### TMS Effect on Symptom Clusters

Despite general improvements in PTSD, the effect of TMS on specific PTSD clusters is unclear. The CAPS score identifies three symptom clusters (intrusion, avoidance, and hyperarousal). Osuch et al. specifically investigated the use of rTMS on the three clusters and found that rTMS marginally improved the hyperarousal cluster in comparison to sham treatments ($p<0.08$), but did not affect either intrusion or avoidance. Oznur et al., who also performed low-frequency stimulation of the right DLPFC, found similar results in their study. These results suggest that it may be possible to target specific symptom clusters depending on the constellation of stimulation parameters and brain regions being targeted.

### Duration of Symptom Benefit

The duration of TMS-mediated improvement in PTSD has not been well-characterized. To date, most studies have only short-term follow-up assessments that are typically performed. At this point, it is unclear if sustained durability of symptom relief is possible with a single course of rTMS or if ongoing maintenance treatments at less frequent intervals would be needed. The data thus far on the relative permanence of TMS responses in the brain has been contradictory. Rosenberg et al. demonstrated a 6 % reduction in PTSD symptoms that persisted 2 months after the treatment ended. In contrast, in separate reports, Gisaru and McCann demonstrated returns to baseline symptoms within 4 weeks of treatment cessation [7, 24]. It is possible that a longer treatment course or greater number of pulses delivered may effect durability of treatment response. In some patients, maintenance sessions may be required, although there is currently no data to guide the development of treatment plans.

### Limitations

Perhaps the most serious limitations have been the limited sample size in the clinical trials performed thus far. The studies discussed here all had relatively small samples sizes, with the largest treatment group consisting of 20 participants, and most other studies including far fewer. An additional challenge is the varied applications of treatments across trials. With a nearly endless number of combinations of stimulation parameters that can be applied to a further combination of brain regions, determining the most effective treatment program from a relatively small number of trials is challenging. Localization of treatment delivery commonly involves distance measures over the scalp from the motor threshold relevant to the abductor pollicis brevis. Neuronavigation allows for more accurate targeting of cortical structures but is mostly unavailable in a clinical setting. Even with consistent measures used in treatment delivery, it is likely that there is high variance in cortical target affected by magnetic field stimulation.

### Future

A significant amount of work remains before rTMS for PTSD can be brought to the routine clinical setting. Even if offered to patients in an off-label status, a lack of consensus for treatment delivery adds uncertainty for the provider's potential treatment plan. To further expand knowledge of treatment for PTSD by rTMS, more simulation parameters need to be observed and explored on a large number of diverse patients and their long-term therapeutic effects documented with controlled scales [6]. While more parameters are studied, further engineering on coil design and coil arrangements would open more targeting options.

## Conclusion

rTMS is a potentially attractive option for the treatment of PTSD, particularly for those individuals that fail to respond to conventional therapies. Research to date has a high level of variability, but the right DLPFC and mPFC are promising targets for stimulation. Further research defining treatment delivery and pulse sequences should bring this treatment modality closer to routine clinical application.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Caroline Clark, Jeffrey Cole, Christine Winter, Kathy Williams, and Geoffrey Grammer declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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