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A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder

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Background
Posttraumatic stress disorder (PTSD) is a commonly occurring and often debilitating psychiatric condition. There currently is not definitive information regarding the efficacy of repetitive transcranial magnetic stimulation (rTMS) for PTSD.

Objective
This study seeks to examine the efficacy of rTMS for PTSD.

Methods
Twenty subjects with PTSD were randomly assigned to receive either 10 rTMS sessions delivered at 1 Hz to the right dorsolateral prefrontal cortex (DLPRC) or 10 sham rTMS sessions to the same area. A blinded rater assessed PTSD, depressive, anxiety, and neurocognitive symptoms before treatment, after the treatment series, and during a 2-month follow-up period.

Results
Trancranial magnetic stimulation delivered at 1 Hz to the right DLPRC resulted in statistically and clinically significant improvements in core PTSD symptoms and depressive symptoms compared with sham treatments. The effectiveness showed some degradation during the 2 months after treatments were stopped.

Conclusions
This blinded sham controlled trial supports the efficacy of 10 sessions of right DLPRC rTMS delivered at 1 Hz for the treatment of PTSD symptoms.
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Keywords posttraumatic stress disorder; transcranial magnetic stimulation; clinical trial

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Posttraumatic stress disorder (PTSD) is a common psychiatric condition resulting in significant symptoms and psychosocial dysfunction. PTSD occurs in individuals who have sustained or witnessed a trauma, as defined by the Diagnostic and Statistical Manual of Mental Disorders Version IV as "an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of self or others."[1] PTSD manifests through three separate symptom clusters: the reexperiencing symptoms cluster, the avoidant symptoms cluster, and the hypervigilance cluster. Symptoms must be consistently present for 1 month, but are often present for many decades.

It is estimated that more than 7% of the United States population experiences PTSD during their lifetime.[2] Epidemiologic studies reveal that between 48% and 71% of veterans are exposed to one or more traumatic events during their military service.[3] Large studies indicate that approximately 15% of veterans (over a half million veterans) are currently diagnosed with PTSD.[4] PTSD is associated with a range of comorbid conditions (eg, depression, substance abuse, physical health problems) and functional difficulties (eg, unemployment, legal problems).[3] A recent study estimated that PTSD-related work impairments were estimated to cost in excess of $3 billion in annual productivity loss in the United States.[5] Currently, treatment of PTSD is largely psychotherapy and antidepressant medications.[6] Although effective for some, as many as 50% of patients in clinical trials continue to experience significant symptoms of PTSD despite undergoing available treatments.[7]

Repetitive transcranial magnetic stimulation (rTMS) is a technique that uses an electromagnetic field to noninvasively stimulate cortical neurons. Electromagnetic energy passes through the scalp and skull, without causing pain or injury, and results in depolarization of neurons. This stimulation can lead to an increase or decrease in brain activity in specific regions and can cause changes in brain monoamines.[8-10] rTMS has been shown to be effective in treating major depressive disorder (MDD).[11] There is preliminary evidence that it may be effective in other psychiatric conditions, including anxiety disorders.[12]

There has been preliminary research to examine the efficacy of rTMS for PTSD. Two uncontrolled case series of rTMS for PTSD suggested that rTMS may be effective for PTSD.[13,14] Grisaru et al.[14] treated 10 patients bilaterally using 0.3 Hz for 30 stimuli in a single session. McCann and colleagues[13] treated two patients with 10 treatments of left frontal at 20 Hz. An uncontrolled clinical trial of rTMS for veterans with PTSD and MDD found left dorsolateral prefrontal cortex (DLPFC) stimulation at either 1 Hz or 5 Hz has robust effects on depressive symptoms and smaller, but statistically significant, effects on PTSD symptoms.[15] A blinded sham controlled trial examined the effect of right DLPRC stimulation at either 1 Hz or 10 Hz for patients with PTSD. That trial found that rTMS at 10 Hz was effective for the treatment of PTSD (as well as depressive symptoms associated with PTSD), whereas 1 Hz was not effective for PTSD (or the associated depressive symptoms).[16] A sham controlled trial of rTMS delivered at 20 Hz demonstrated efficacy for the treatment of PTSD.[17] That trial demonstrated that right side rTMS was more effective than left side rTMS. Finally, Osuch et al.[18] found no effect for right frontal rTMS at 1Hz combined with prolonged exposure psychotherapy in nine highly treatment refractory patients with PTSD. These studies suggest that right side rTMS particularly at higher frequencies (10 Hz and greater) are effective for the treatment of PTSD. The effectiveness of rTMS at lower frequencies remains unclear.

Our study attempted to resolve these somewhat divergent results. Specifically, we aimed to compare right DLPFC rTMS at 1 Hz with sham treatment. We also sought to obtain pilot data regarding longer-term maintenance of any clinical effect, as currently incomplete information is available regarding longer-term effects of rTMS for PTSD.

Materials and methods

Subjects

Twenty subjects were recruited from the Behavioral Sciences Service Line at the White River Junction Veterans Affairs Medical Center in White River Junction, VT. Subjects were eligible for inclusion if they meet the following criterion: (1) primary diagnosis of Posttraumatic Stress Disorder on Structured Clinical Interview for Diagnosis (SCID); (2) Clinician Administered PTSD Scale (CAPS) score greater than 50; (3) no change in psychotropic medication, either dose or agent, for 2 months before rTMS; (4) no change in psychosocial treatments (eg, individual or group therapy) for the 2 months before rTMS; (5) age greater than 20 years and less than 70 years; and (6) competent to sign informed consent. Subjects were excluded from the trial if they met any of the following criteria: (1) any metal object or implant in brain, skull, scalp, or neck; (2) implantable devices, including cardiac pacemakers and defibrillators; (3) seizure within the last year; (4) substance abuse within the past 3 months; (5) acute medical illness; (6) any significant central nervous system disorders such as brain mass, stroke, or epilepsy; and (7) treatment with a medication known to decrease the seizure threshold. During the period of assessment (entry, treatment, and follow-up) patients could have no change in psychotropic medications or psychosocial treatments for PTSD.

After receiving a full explanation of the potential risks and benefits of study participation subjects signed a written informed consent document that was approved by the Dartmouth Committee for Protection of Human Subjects (CPHS ID16744). Subjects were then randomly assigned to either active rTMS treatment or sham rTMS.

Table 1 Baseline and post treatment comparisons of mental health outcomes for rTMS and control groups

	Baseline		Posttreatment		
	Sham	rTMS	Sham	rTMS	*P* value[a]
CAPS	72.3 (12.2)	81.6 (9.5)	61.7 (11.1)	53.9 (15.3)	.009
PCL	57.3 (3.7)	64.9 (6.5)	54.8 (5.0)	48.7 (9.9)	.0002
BDI	22.7 (10.3)	25.5 (8.6)	21.4 (8.5)	17.7 (6.3)	.02
STAI	54.5 (6.1)	57.3 (10.9)	52.2 (5.6)	47.4 (13.4)	.06
BNCE	27.3 (4.1)	28.5 (1.6)	27.9 (2.4)	28.9 (1.5)	.55

rTMS = Repetitive transcranial magnetic stimulation; CAPS = Clinician Administered PTSD Scale; PCL = PTSD Checklist; BDI = Beck Depression Inventory; STAI = State Trait Anxiety Inventory; BNCE = Brief Neurobehavioral Cognitive Examination.

[a] There were no statistically significant differences between groups.

Study protocol

The magnetic stimulation was done using the Neuronetic 2100 (Neuronetics, LLC, Marietta, GA). The stimulator used a figure-eight coil (MCB70 coil, inner radius = 10 mm, outer radius = 50 mm, 2 × 10 windings, winding height 6 mm). Ten rTMS treatments were delivered on 10 consecutive weekdays. Before the first session, the right motor threshold was determined by increasing the intensity of stimulation by 2.5% increments over the right motor cortex until there is any movement of the digits of the left hand. For subsequent treatments the coil was placed 4 cm anterior parasagittally and 2 cm laterally of the motor strip location that caused hand movement.[19] This placement approximated the location of the right DLPFC. Active rTMS was delivered to the right DLPFC at 90% of motor threshold in cycles of 1 Hz for a total of 20 minutes per day. Each 1 minute cycle consisted of a 20-second stimulation train with a 40-second intertrain interval. Patients randomly assigned to receive sham treatments had their motor threshold elicited as above, but all subsequent treatments were given using a sham magnetic coil that looks and sounds identical to the active coil, but prevents magnetic energy from leaving the device. If the subjects' motor threshold could not be accurately determined, they were excluded from the study.

Assessments

All assessments were completed by research psychologist (B.L.) blinded to whether the patients were receiving active or sham treatments. Subjects were assessed at baseline, after 10 rTMS sessions, 1 month after the last session, and 2 months after the last session. The following instruments were used.

The Structure Clinical Interview for DSM Disorders Part 1 and Part 2 (SCID I and SCID II) are semistructured clinician administered diagnostic interviews designed to make a DSM IV diagnosis.[20-22] The SCID I and SCID II were performed only once before starting treatments.

The CAPS is a structured interview for assessing PTSD symptoms according to the DSM IV criterion. The CAPS assesses the frequency and severity of each of the core symptoms of PTSD.[23]

The PTSD Checklist (PCL) is a self-report scale that measures the 17 core symptoms of PTSD. Each symptom is rated by the subject from "not at all" to "extremely."[24] The Beck Depression Inventory (BDI) is 23-item self-report scale of depressive symptoms. The State Trait Anxiety Inventory (STAI) is a 20-item self-report scale of anxiety symptoms.[25] The Brief Neurobehavioral Cognitive Examination (BNCE) is a short screening instrument designed to detect cognitive impairment.[26] Each assessment, except the SCID I and II, were performed at baseline, after the last treatment, 1 month after the last treatment, and 2 months after the last treatment.

Statistical analysis

This study was designed to demonstrate changes in symptom measures. Continuous variables are reported as means with the associated standard deviations (SD); categorical variables are presented as counts and percentages. Because of the small sample size, continuous variables before and after treatment were compared using the Mann-Whitney test (Table 1). Fisher exact tests were used to compare proportions (Table 2). A two-sided *P*-value of less than .05 was considered statistically significant. All statistical analyses were performed with STATA software version 10.0 (College Station, TX).

Results

Characteristics of the study population including age, gender, and index trauma leading to PTSD are summarized in Table 2. This was largely a sample of white men in their early 50s. Typically they had experienced combat trauma several decades earlier.

Baseline and posttreatment scores on the standardized psychiatric scales (including CAPS, PCL, BDI, STAI, BNCE) are summarized in Table 1. Overall, there was a clinically and statistically significant reduction in PTSD symptoms measured by both the CAPS and PCL. The

Table 2 Baseline characteristics of rTMS and control patients

	Controls	rTMS
Age	57.8 (SD 11.8)	54.0 (SD 12.3)
Gender (% female)	10% (n = 1)	10% (n = 1)
Race (% white)	100% (n = 10)	100% (n = 10)
Trauma type		
Combat	40% (n = 4)	40% (n = 4)
Sexual trauma	—	10% (n = 1)
Assault	10% (n = 1)	—
Accident	—	—
Multiple	50% (n = 5)	50% (n = 5)
Time elapse since trauma (y)	41.3 (SD 13.8)	38.2 (SD 14.1)
Time in PTSD treatment (y)	30.3 (SD 10.2)	29.6 (SD 11.4)
Diagnosis		
PTSD	100% (n = 10)	100% (n = 10)
Major depression	70% (n = 7)	90% (n = 9)
Panic disorder	40% (n = 4)	30% (n = 3)
Obsessive compulsive disorder	10% (n = 1)	30% (n = 3)
Substance use disorder	0% (n = 0)	30% (n = 3)

rTMS = Repetitive transcranial magnetic stimulation; SD = standard deviation; PTSD = posttraumatic stress disorder.

group receiving rTMS showed a nearly 30 point reduction in CAPS score (81.6-53.9, $P < .0001$) and greater that 15 point reduction in PCL scores (64.8-48.7, $P < .0001$). The sham rTMS showed a nonsignificant reduction on the CAPS (72.3-61.7, $P = .09$) and the PCL (57.3-54.8, $P = .45$). The active rTMS showed a statistically significant reduction compared with sham rTMS on both the CAPS ($P = .009$) and the PCL ($P = .0002$). There were no differences in the effectiveness of rTMS across the three clusters of PTSD symptoms.

We also evaluated the effect of rTMS on the symptoms of depression and anxiety. Treatment with rTMS was associated with a reduction in depressive symptoms as measured by the BDI (25.5-17.7, $P < .05$), whereas the sham group showed little change (22.7-21.4, $P = .42$). The difference is a statistically significant improvement in depressive symptoms ($P = .03$) with active rTMS compared with sham rTMS.

Similarly, anxiety symptoms as measured by the STAI were improved with rTMS (57.3-47.4, $P < .05$) but not sham (54.5-52.2, $P = .38$). In this case, the improvement seen with rTMS was not statistically superior to sham ($P = .06$).

There was no change in cognitive function as measured by the BNCE with either active treatment or sham. Importantly, there was no worsening of cognition associated with rTMS.

We were interested in examining the maintenance of the clinical effect after rTMS was completed. The mean CAPS scores at both 1 month and 2 month posttreatment remained significantly improved from baseline in the group of subjects receiving rTMS (81.6 at baseline, 63.9 at 1 month, and 64.2 at 2 months, $P = .001$). However, closer examination of the data suggests some erosion of clinical effect. Of the 10 subjects who received rTMS, six showed a 10 point or greater worsening in PTSD symptoms between the immediate posttreatment assessment and the 2 month posttreatment assessment.

Conclusions

In this study, 20 patients with PTSD were randomly assigned to receive either 1 Hz rTMS to the right DLPFC or sham rTMS to the right DLPFC. The results suggest that rTMS treatment is associated with improvements in PTSD symptoms when compared with sham-treated subjects. These effects were seen in both the CAPS and PCL. A similar pattern of improvement was seen in depressive symptoms as measured by the BDI. Although these results remained present 2 months after the final rTMS treatment, there were subtle signs that the effect of rTMS was beginning to wane. Anxiety symptoms showed improvement with rTMS, but those improvements were not statistically significant compared with sham. Little change in cognition was seen with rTMS.

Our findings support the findings of Cohen et al.[16] and Boogio et al.[17] that right sided rTMS treatments appear to be effective for PTSD, and diverged from Cohen et al.[16] regarding the efficacy of low-frequency rTMS, as that study found only higher-frequency rTMS was effective for PTSD. Cohen et al.[16] found that rTMS at 1 Hz was not effective for PTSD, whereas we found effects with this treatment parameter. There are a number of possibilities which may explain this discordant finding. Our study of rTMS at 1 Hz showed a 25% improvement in PCL scores; Cohen et al.[16] found a 31% improvement with 10 Hz; Boggio et al.[17] found a 37% improvement with 20 Hz. Thus, it is possible that 1 Hz rTMS may be both effective for PTSD symptoms, and yet still inferior to higher frequency stimulations.

The total number of stimulations may be an important factor to consider. In the Cohen et al.[16] study patients who

were randomly assigned to 1 Hz received a total of 1000 stimulations, during the 2 weeks of treatments, whereas those receiving 10 Hz received a total of 4000 stimulations. Patients in this study also received 4000 stimulations. Thus, it is possible that the total number of stimulations rather than the frequency of delivery may be responsible for the clinical efficacy.

Considerable caution is urged when using evidence from clinical trials to attempt to explain the underlying neurobiology of mental disorders or even the mechanism by which the treatments work. With this important caution, we believe this trial may contribute to understanding of potential mechanisms. This trial supports the idea of right side laterality in PTSD, or at least treatment of PTSD with rTMS.[17,27] However, this evidence may not support the conventional model of the neurocircuitry PTSD and its treatment with rTMS. That model holds that PTSD is a condition of relative hypoactivity of frontal regions and hyperactivity of deeper regions such as the amygdala.[28] Conventional thought is that high-frequency rTMS activates brain regions, whereas low-frequency rTMS is inhibitory to underlying brain tissue.[29,30] Thus, the conventional model would predict that high-frequency rTMS to the right DLPFC would be effective for treatment of PTSD, whereas low-frequency stimulation of the same area would not be effective. Importantly, that is not what we found. In this study, low-frequency rTMS to the right DLPFC was effective in reduction of symptoms of PTSD. Our results are, however, consistent with the neuroimaging model put forth by McCann et al.,[13] which demonstrated right frontal hyperactivity in patients with PTSD.

Our study raises the possibility that right rTMS may have a conventional dose response relationship, independent of frequency, in the treatment of PTSD.[31,32] This dose response relationship could plausibly explain the results found by that Cohen et al.[31] that treatments at 1 Hz, with a total of 1000 total stimulations, had little effect, whereas treatments at 10 Hz with a total of 4000 total stimulations, was effective. This study also had a total of 4000 total stimulations and the results were similarly effective for PTSD. It would also explain why Boggio et al.[17] with treatments at 20 Hz, with a total of 16,000 stimulations appears to be the most effective protocol. It is important to remember that only 18 patients were treated with low-frequency (1 Hz) rTMS in the two combined studies. Firm conclusions are not possible with such a limited sample size.

There are a number of important limitations to our study. Although we did use a sham device and every effort was made to blind subjects to treatment assignment, it is possible that our blinding was not effective. Secondly, pilot studies such as this study, with limited sample size, are prone to bias from any number of random events. Lastly, we make no claim about the ability to generalize of these findings because of a relatively homogenous patient population and a group of patients who showed significantly chronic symptoms. It is possible our findings would not extend to different racial groups, noncombat veterans, or patients with less chronic PTSD.

In summary, this blinded sham controlled trial of 10 sessions of 1 Hz rTMS delivered to the right DLPRC showed that patients with PTSD demonstrate therapeutic effects for PTSD greater than sham rTMS to the same region. This was a small pilot study that supports the growing evidence for the effectiveness of rTMS for the treatment of PTSD.

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