Exposure Therapy and Simultaneous Repetitive Transcranial Magnetic Stimulation

A Controlled Pilot Trial for the Treatment of Posttraumatic Stress Disorder

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Objectives: This is a small preliminary but novel study assessing the feasibility of repetitive transcranial magnetic stimulation (rTMS) delivery to veterans with posttraumatic stress disorder (PTSD) while they simultaneously receive prolonged exposure (PE) therapy.

Methods: A prospective, randomized, double-blinded, active sham-controlled design combined weekly sessions of rTMS and standard PE at the Veterans Administration Hospital. Eight adult patients received a full course of protocol-driven PE therapy and were randomly assigned to receive either rTMS or sham rTMS. Repetitive transcranial magnetic stimulation was delivered to the right or left prefrontal cortex with a figure-eight solid core coil at 120% motor threshold, 10 Hz, 5-second train duration, and 10-second intertrain interval for 30 minutes (6000 pulses) weekly for 5 weeks (30,000 stimuli).

Results: Of the 12 veterans consented, 8 completed the study treatment protocol. The dropout rate was 34%, roughly equivalent to the pooled average dropout rates observed in traditional PE therapy with Operation Enduring Freedom/Operation Iraqi Freedom veterans with PTSD, suggesting that veterans had no difficulty tolerating the addition of rTMS to PE therapy and that this is a feasible study design for larger trials in the future. Clinician-Administered PTSD Symptom scores reflected a general nonsignificant trend toward improvement, and subjects with comorbid major depression appeared to experience significant antidepressant benefit with treatment despite the fact that the doses used in this protocol were much smaller than those used to treat patients with major depressive disorder.

Conclusions: This pilot study demonstrates the safety and feasibility of rTMS delivery to PTSD patients while they simultaneously receive PE. This unique approach to the treatment of PTSD highlights the need for further studies with larger sample sizes to assess treatment outcomes.

Key Words: posttraumatic stress, exposure therapy, rTMS, transcranial magnetic stimulation, PTSD

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Posttraumatic stress disorder (PTSD) is a severe psychiatric illness characterized by core symptoms including hyperarousal, negative cognition and mood, avoidance, and reexperiencing.[1] Commonly associated with medical comorbidities, disability, and unemployment, PTSD results not only in a great deal of personal suffering but also in escalating social and economic costs, in both the private and military sectors.[2] Lifetime prevalence reaches 8% in community samples,[3] and 3 separate large-scale studies of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) military personnel estimate a postdeployment PTSD rate of 10% to 20%.[4–7] Exposure therapies (cognitive processing therapy and prolonged exposure [PE] therapy), accompanied by a limited array of pharmacotherapies (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, Prazosin),[8] are considered the criterion standard treatment option for PTSD.[9–11] Unfortunately, cognitive processing therapy and PE also share an elevated attrition rate,[12,13] which remains a significant barrier to treatment efficacy and highlight the need for novel treatments.

The growing acceptance and availability of repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder (MDD)[14] has evoked the question of its potential efficacy for PTSD. A search of PubMed, Ovid/Medline, PsycInfo, and CINAHL databases for published studies regarding the potential efficacy of rTMS for PTSD produced 4 randomized sham-controlled trials (RCTs),[1,15–17] 1 randomized crossover study,[18] 3 case studies,[19–21] and 5 open-label trials[22–26] (Table 1). A pooled analysis[27] of data from 3[1,15,16] of the aforementioned 4 sham-controlled trials has suggested that patients who received rTMS, applied to the left or right dorsolateral prefrontal cortex (DLPFC), achieved clinically significant reduction of PTSD core symptoms independent of depressive symptoms. However, across studies, results were achieved within a wide range of treatment parameters, limiting conclusions regarding outcomes or optimal treatment parameters for future studies. In general, little is known about treatment paradigms that combine talk therapies with rTMS treatment. One large naturalistic study found that a combination treatment of rTMS and cognitive behavioral therapy for MDD was feasible and appeared to positively influence outcomes.[28] To our knowledge, there is but a single case report[18] describing a combined psychotherapy and rTMS treatment approach to PTSD.

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Relationship with the vendor: Although the equipment was loaned for this trial from one vendor (Neuronetics), significant firewalls existed between the vendor and the trial, similar to the National Institutes of Health OPTTMS trial. None of the investigators has any financial conflict of interest with the vendor, other than other transcranial magnetic stimulation research studies, nor have they for the past 5 years. Second, the equipment was loaned for the trial but the study design, conduct, data, data analysis, and articles to emerge are independent of the vendor and did not involve the vendor. The vendor was notified of safety issues and device malfunctions as they must notify the Food and Drug Administration about this regarding their device.

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TABLE 1. Summary of TMS PTSD Studies

Article	Study Type	N	Inclusion	Years Since Trauma	Trauma Type	Coil
Rosenberg et al (2002)[25]	Open-label trial	12 (All male)	PTSD/MDD; HAM-D >17	22.3	n/a	Figure 8 coil
Cohen et al (2004)[15]	RCT (double-blind, placebo controlled)	24 (17 Male)	PTSD/MDD	5.4	Combat (4), MVC (11), sexual abuse (2)	9 cm circular coil
McCann et al (1998)[21]	Case study	2 (Both females)	PTSD/MDD	18	Shooting	Figure 8 coil
Grisaru et al (1998)[24]	Open label	10 (7 Males)	PTSD/MDD	5.5 (Avg)	Accident (7), combat (2), assault (1)	Angular-shaped coil 14 cm diameter
Osuch et al (2009)[26]	Double-blind placebo-controlled cross-over (alternate assignment to consecutive patients)	9 (8 Females)	PTSD/MDD	5.4	n/a	Figure 8 coil
Boggio et al (2010)[16]	Double-blind placebo controlled (stratified randomization by medication type)	30 (21 Females)	PTSD	3.9	Assault (6), sexual abuse (5), death of relative (15), perceived threat of harm (4)	Figure 8 coil
Nam et al (2013)[17]	RCT (double-blind, placebo-controlled)	16 (7 Active; 9 sham; 10 females)	PTSD, continued meds and supportive psychotherapy	n/a	Nonmilitary trauma	Figure 8 coil
Oznur et al (2014)[22]	Open, retrospective	20 (All males)	PTSD and MDD	n/a	Combat-related	Figure 8
Watts et al (2012)[1]	RCT (double-blind, placebo-controlled)	20 (18 Males)	PTSD, CAPS >50	39.8	Combat (8), sexual abuse (1), assault (1), multiple (10)	Figure 8 coil

Placement (Active)	Motor Threshold	Course	Treatment Parameters	Pulses	Primary Outcomes
L DLPFC	90%	10 Consecutive weekdays	Group 1 (1 Hz, 40 s stim, 20 s int, 15 min); group 2 (5 Hz, 8 s stim, 52 s int, 15 min)	600/d, 6000/total	75% had antidepressant response after rTMS to L DLPFC; minimal improvement in core PTSD symptoms
R DLPFC	80%	10 Working days	Group 1 (1 Hz 5 s stim, 55 s int, 20 min); group 2 (10 Hz, 2 s stim, 58 s int, 20 min); group 3 (sham)	Group 1 (100/d, 1000/total); group 2 (400/d, 4000/total)	PTSD core symptoms of reexperiencing, avoidance, as well as depressive symptoms and anxiety symptoms improved with HF-rTMS over R DLPFC. Measures: Treatment Outcome PTSD Scale ($P < 0.006$); PTSD Checklist ($P < 0.00009$) HAM-D ($P < 0.07$); HAM-A ($P < 0.001$)
R frontal (unreported region)	80%	3–5/wk, 17 sessions and 30 sessions	1 Hz, unreported interval	1200/d, 20,400 total; 1200/d, 36,000 total	Measures: Decrease in modified PTSD symptom scale scores ($P = 0.004$). Posttreatment PET scans showed global decreases in regional cerebral metabolism toward the age- and sex-adjusted norm, with more prominent decreases over the right hemisphere.
C3/C4 L and R hemispheres	100%	1 Session	0.3 Hz, 15 stimulations, 1 min rest interval, 15 stimulations	30 Total	Transient improvement in IES avoidance subscale ($P = 0.033$), anxiety ($P = 0.009$), and somatization ($P = 0.038$) on SC-90;
R DLPFC	100%	3–5/wk, two 20-session treatments, 2-wk washout period prior to cross-over	Each group received option of systematic exposure; group 1 (1 Hz, continuous stimulation); group 2 (sham)	1800/d, 36,000/total	Active rTMS showed a larger effect size of improvement for hyperarousal symptoms compared with sham; 24-h urinary norepinephrine and serum T4 increased;serum prolactin decreased
R or L DLPFC	80%	10 Consecutive working days	Group 1 (L, 20 Hz, 2 s stim, 28 s int, 20 min); group 2 (R, 20 Hz, 2 s stim, 28 s int, 20 min); group 3 (sham)	1600/d, 16,000/total	Both active rTMS conditions significantly decreased PTSD symptoms, but right-sided rTMS had a greater improvement compared to left-sided; mood scores improved only for L-sided treatment ($P < 0.001$). Anxiety scores improved only with R-sided treatment ($P < 0.01$)
R DLPFC	100%	5/wk × 3 wk	Group 1 (1 Hz cont, 20 min); group 2 (sham)	1200/d, 18,000/total	Active rTMS showed significant improvement in total CAPS score ($P = 0.008$) and reexperiencing subtest ($P = 0.004$) when c/t sham. Results comparing pretreatment and 5 wk after completion of the 3-wk treatment course).
R DLPFC	80%	5/wk × 4 wk	40 Stimulations at 1 Hz, 20 s int, 15 min	600/d, 12,000/total	BDI and BAI scores were not affected; only decrease in IES hyperarousal score was significant ($P = 0.02$)
R DLPFC	90%	10 Consecutive working days	Group 1 (1 Hz, 20 s stim, 40 s int, 20 min); group 2 (sham)	400/d, 4000/total	TMS group significantly improved sxs of PTSD and depression c/t sham, as defined by CAPS ($P = 0.009$), PCL ($P = 0.0002$), and BDI ($P < 0.05$).

Continued next page

TABLE 1. *(Continued)*

Article	Study Type	N	Inclusion	Years Since Trauma	Trauma Type	Coil
Isserles et al (2013)[18]	RCT, crossover	26 (20 Males)	PTSD treatment failure with antidepressant or trauma-focused therapy	15.8	Military (15), other (11)	H-coil
Tillman et al (2011)[19]	Case study	1 (Male)	PTSD and MDD	n/a	Combat trauma	Coil not specified
Nakama et al (2013)[20]	Case study	1 (Male)	PTSD and MDD	n/a	Combat trauma	Figure 8 coil
Philip et al (2016)[23]	Open label, retrospective	10 (8 Males)	PTSD and MDD	n/a	Combat (6), MST (2), other (2)	Figure 8 coil

RCT indicates randomized controlled trial; MVC, motor vehicle collision; stim, stimulation; s, second; int, interval; Hz, hertz; L, left; R, right; cont, continuous; c/t, compared to; DLPFC, dorsolateral prefrontal cortex; n/a, not available; hf-rTMS, high frequency rTMS; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; CAPS, Clinician Administered PTSD Scale; HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; PCL-M, PTSD Checklist (military); SC-90, Symptom Checklist 90; IES, impact of events scale; MST, military sexual trauma; MPFC, medial prefrontal cortex; EEG, electroencephalogram; QIDS, quick inventory of depression symptomatology; incr, increased.

This study's objective was to pilot, test, and develop the technique of using standard left or right prefrontal rTMS during PE to potentially acutely treat PTSD symptoms. The intervention would be considered feasible if at least 64% of consented participants completed all required sessions, equaling the national pooled average of adherence to traditional PE therapy in OEF/OIF veterans with PTSD.[12]

MATERIALS AND METHODS

The study was conducted at the Ralph H. Johnson Veterans Administration (VA) Medical Center, associated with the Medical University of South Carolina in Charleston, South Carolina. Active enrollment extended from July 2011 to March 2013. This study was funded by the United States Department of Defense through Telemedicine and Advanced Technology Research. The local VA Institutional Review Board and the United States Army Medical Research Acquisition and Activity Institutional Review Board approved the protocol, and all subjects provided written informed consent.

Participants

Inclusion criterion was as follows: VA patients aged 21 to 50 years with PTSD, who met the Clinician-Administered PTSD Symptom (CAPS)[29] and Structured Clinical Interview for DSM-IV[30] to ensure that they met diagnostic criteria for a positive diagnosis of PTSD. In addition, subjects must have served in OIF or OEF, and their index trauma must have been war-related, regardless of childhood trauma. Exclusion criteria included prior or current psychosis, substantial substance abuse, prior head trauma, seizures, metal in or near their head, unstable medical comorbidities, or currently taking medications known to lower seizure threshold (eg, methylphenidate, bupropion) or benzodiazepines (may block activation of the anxiety circuit during exposure therapy). Patients enrolled as subjects in the trial were allowed to remain on their current medications but were required to be fixed and stable for the 2-month trial.

Randomization

All subjects received standard clinical PE therapy. Study subjects were randomized into 1 of 4 rTMS cells (left prefrontal cortex active or sham; right prefrontal cortex active or sham).

rTMS Treatment Sessions

A Neuronetics (Neuronetics Inc, Malvern, Pa) Model 2100 magnetic stimulator (NS 0226 A 15VAC-C) was used for all rTMS sessions. The device was the same TMS system used in the optimizing TMS for depression trial,[14] but used a *smart card* system (preprogrammed credit card–sized plastic card imbedded with a flash memory chip) to control active versus sham stimulation delivery. After randomization (simple randomization method), each subject was assigned an initial smart card (active or sham). An open-label coil was used for all subjects to determine the

Placement (Active)	Motor Threshold	Course	Treatment Parameters	Pulses	Primary Outcomes
Bilateral MPFC	120%	3/wk × 4 wk	Group 1 (traumatic then neutral script, 20 Hz, 2 s stim, 20 s int); group 2 (positive then neutral script, 20 Hz, 2 s stim, 20 s int); group 3 (traumatic then neutral script, sham stim)	1680/d, 20,160/total	Significant improvement over control groups ($P = 0.02$) in CAPS-intrusive subscale in patients that received active DTMS after exposure to the traumatic event script
R DLPFC and then L DLPFC	100%	5/wk × 3 wk	1 Hz, unreported interval	Not reported	Initial treatment (R DLPFC) reduced hyperarousal symptoms during treatment course; a second course of TMS targeting L DLPFC failed to produce this effect.
—	120%	5/wk × 3 wk	10 Hz, 4-s stim, 26-s int	3000/total	Improvement in both PTSD and MDD symptoms (PCL-M and BDI scores on week 1 of treatment and 3 wk posttreatment decreased from 54 to 20 and 20 to 7, respectively.
L DLPFC (coil over F3 using EEG coord)	120%	5/wk × 6 wk (plus or minus a 6-treatment taper) for total of 30–36 treatments	5 Hz, 4-s train, 12-s int	3000/session, incr to 4000/session if no improvement by 15th session; total of 30 sessions	Depression symptoms: 50% achieved response based on QIDS scores pretreatment and posttreatment ($P = 0.003$). PTSD symptoms: 80% experienced decrease in PCL-M scores, 40% achieved response ($P = 0.005$)

individual's motor threshold using the parameter estimation with sequential testing algorithm and visible movement in the right hand.

rTMS Treatment Parameters

Transcranial magnetic stimulation was delivered to either the left or right DLPFC (depending on randomization), a location defined as 6 cm anterior to the right hand motor thumb area. Trained treaters, who were not raters, delivered the treatment. Repetitive transcranial magnetic stimulation was delivered with a figure-eight solid core coil at 120% motor threshold, 10 Hz, 5-second train duration, and 10-second intertrain interval for 30 minutes (6000 pulses) once a week for 8 weeks (total 48,000 pulses). These parameters did slightly exceed rTMS safety guidelines[31] but allowed 6000 pulses to be delivered within a single weekly 30-minute PE session.

PE Therapy

For this study, PE sessions were conducted per the normal PE protocol. No modification of the in-session imaginal exposure protocol was needed except the requirement that all imaginal exposures last for at least 40 minutes. Subjects listened to the audio recording of their PE session done with and without rTMS one time during the week between regular PE sessions. Before the start of rTMS, 5 minutes of imaginal exposure were heard before turning on the rTMS. The treatment lasted 30 minutes, leaving at least 5 minutes of imaginal exposure to be listened to after the rTMS stopped.

Outcome Measures

Treatment dropout was defined as any subject who does not complete the entire active treatment program. Subjects who occasionally missed a session or failed to complete their homework assignments were not considered dropouts, as they were allowed to have make-up sessions as necessary. Several secondary measures were administered weekly, to monitor mood and PTSD symptoms throughout treatment. These included the CAPS, Hamilton Rating Scale for Depression[32] and Anxiety,[33] and the PTSD Checklist.[34]

RESULTS

Subjects

Fourteen VA patients were screened, and 12 were consented. Of these, 4 subjects left the study after completing baseline measures, and 8 were ultimately randomized (3 sham, 5 active) (see Table 2 for demographics and Figure 1 for Consolidated Standards of Reporting Trials diagram).

Safety

No adverse events or serious adverse events occurred during the study.

TABLE 2. Demographic

	Control (n = 3)	Experimental (n = 5)
Age	30 ± 2.6	27 ± 2.1
Baseline CAPS	73 ± 28.9	84 ± 25.7
Baseline HRSD24	38 ± 11.5	15 ± 8.6
Sex, M/F	2/1	5/0
SSRI (Y/N)	2/1	2/3
AP (Y/N)	2/1	0/5
BZ (Y/N)	0/3	0/5
AH (Y/N)	2/1	0/5
Alcohol use (Y/N)	2/1	3/2
Cannabis use (Y/N)	1/2	1/4
Opiate use (Y/N)	0/3	1/4
Tobacco use (Y/N)	2/1	0/5

HRSD24 indicates Hamilton Rating Scale for Depression; SSRI, selective serotonin reuptake inhibitor; AP, antipsychotic; BZ, benzodiazepine; AH, auditory hallucinations.

Data

A 55% reduction in CAPS scores (90% confidence interval, 18.5–53.5) was observed at session 5 in the active rTMS group, compared with a reduction of 40% (90% confidence interval, 13.6–73.0) in the sham group. In addition, there was a significant time by treatment interaction found on the Hamilton Rating Scale for Depression (HRSD24) ($F_{5,21.1} = 2.96$, $P = 0.035$), suggesting that those receiving active rTMS along with PE had significantly lower depression scores at the fourth ($P = 0.013$) and fifth ($P = 0.002$) sessions relative to baseline and compared with those receiving sham. Data sets for the other secondary outcome measures were incomplete and, thus, not included here in results.

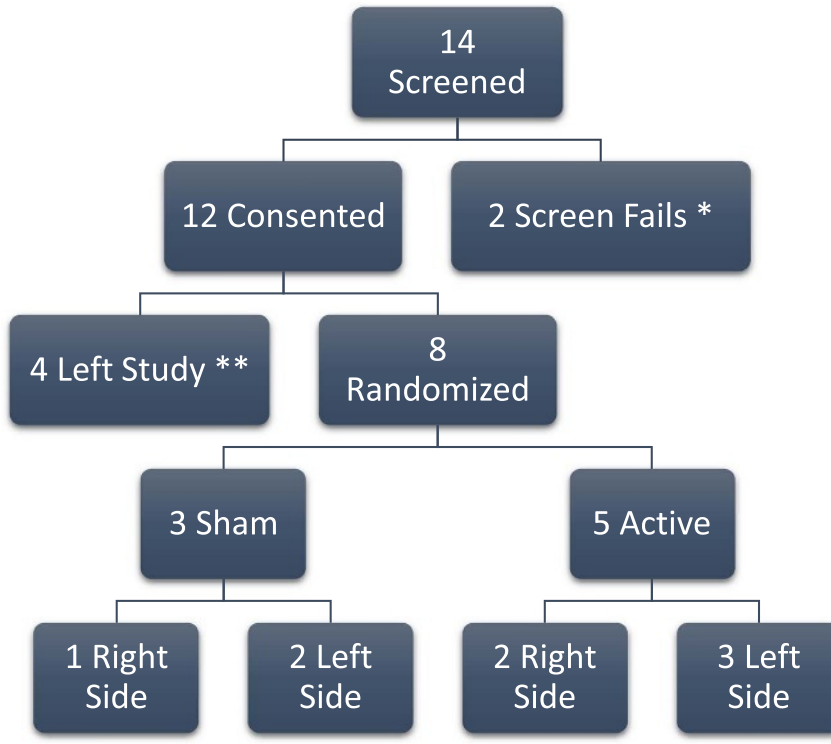
DISCUSSION

This is a small preliminary but novel study that demonstrates the safety and feasibility of rTMS delivery to PTSD patients while they simultaneously receive PE. Eight of the 12 consented individuals completed the treatment. Translating to 67%, this pilot's adherence rate approximated the national average (64%) for OEF/OIF veterans who enroll in traditional clinical treatment for PTSD. It is worth noting that all 4 of this study's drop-outs left the study immediately after baseline assessment (before receiving any rTMS or PE therapy), suggesting that the addition of rTMS did not impair the participant's ability or willingness to complete the course of PE therapy.

This study is not powered to investigate treatment outcomes in terms of efficacy of combined rTMS and PE therapy. However, a few clinical observations can be made about the treatment courses of study subjects. The CAPS scores reflected a general nonsignificant trend toward improvement. Consistent with previous studies, subjects with comorbid major depression appeared to experience significant antidepressant benefit with treatment despite the fact that the doses used in this protocol were much smaller than those used to treat patients with MDD (daily for 4–6 weeks).

Limitations

The main limitation of this study is its small sample size. In this case, the use of a blinded study design with 4 treatment



* Screen fails due to (1) viral infection and (2) not meeting PTSD criteria
** Four Subjects left after completing baseline rating scales

FIGURE 1. Consolidated Standards of Reporting Trials diagram.

cells for this small of a pilot, although helpful in terms of piloting a study design for future larger studies, did limit our ability to glean meaningful initial observations on the protocol's clinical effectiveness. An open-label study design may have been more conducive to the testing of our primary hypothesis (feasibility). Incomplete data collection for secondary outcome measures contributed an addition limitation. Larger studies are needed to make direct comparisons between low- and high-frequency rTMS, short- and long-term treatment periods, target site, and laterality. In addition, larger sample sizes will allow for exploration of differential efficacy for various subtypes of PTSD and/or PTSD with comorbid depression, as well as treatment paradigms that combine talk therapy with neuromodulation.

SUMMARY

Results from this study suggest that delivering rTMS to PTSD patients while they simultaneously receive PE is feasible. Although results indicate significant and nonsignificant trends favoring combination treatment for PTSD and comorbid depressive symptoms, any conclusions regarding the therapeutic outcomes of PE therapy plus rTMS are limited by small sample size.

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