



Synchronized transcranial magnetic stimulation for posttraumatic stress disorder and comorbid major depression

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Introduction

Posttraumatic stress disorder (PTSD) is a highly prevalent psychiatric disorder associated with high degrees of comorbidity (e.g., major depressive disorder; MDD), poor quality of life, and significant social and occupational dysfunction [1]. Currently available evidence-based pharmacological and psychological treatments for PTSD have only modest efficacy [2], and thus further research is necessary to develop novel approaches that can reduce symptoms in patients with this real-world comorbidity.

The use of non-invasive neuromodulation techniques is rapidly growing across psychiatric disorders; for example, repetitive transcranial magnetic stimulation (rTMS; hereafter simply TMS) is effective in reducing symptoms of MDD [3,4], with emerging evidence for efficacy in PTSD (e.g., Refs. [5–8], reviewed in Ref. [9]). However, currently available TMS treatments require that a patient travel to an outpatient facility daily, for 6–8 weeks, often for at least 30 minutes each day. This can be an inconvenience and poses an additional burden for individuals that already struggle with societal integration and social/occupational dysfunction. Thus, further exploration and development of non-invasive brain stimulatory devices with the same (or better) effectiveness as rTMS, that can be adapted to be utilized in an at home setting, would revolutionize the treatment of PTSD.

Synchronized transcranial magnetic stimulation (sTMS, NeoSync Inc.) represents a novel approach to non-invasive brain stimulation. Using three rotating neodymium magnets, sTMS can deliver very low energy, sinusoidal magnetic fields synchronized to an individual's intrinsic alpha frequency (IAF), providing a potential future at-home brain stimulation system. Prior research demonstrated that sTMS might reduce depressive symptoms in MDD [10]. Furthermore, recent work indicates that patients with higher burden of depressive and comorbid anxiety symptoms may respond better to active stimulation compared to sham [11].

We conducted a prospective, sham-controlled, multisite pilot study of sTMS delivered to patients who were symptomatic despite ongoing pharmacotherapy for PTSD and MDD, hypothesizing sTMS would be feasible, safe and effective at reducing these symptoms.

Methods

Thirty-two participants were screened, and twenty-three were randomized; one was excluded because baseline IAF could not be determined; thus 22 veterans with comorbid PTSD and MDD (ages 54.2 years, SD 12.0, range 28–70; 22% female; no significant group differences on any demographic variables) were included in the study. The principle inclusion criteria were comorbid PTSD and MDD, defined as score of >33 on the PTSD Checklist for DSM-5 (PCL) [12] and score of >10 on the Quick Inventory of Depressive Symptoms, Self-Report (QIDS) [13], between the ages of 18–70, and if applicable, symptomatic despite stable treatment (medications and/or psychotherapy) for at least 6 weeks prior to study procedures. Ongoing treatment was allowed to continue unchanged during the entirety of participation. Exclusion criteria followed standard safety criteria used in recent neuromodulation studies in MDD and PTSD (e.g., Refs. [7,10]). The Institutional Review Boards at the Providence and White River Junction VA approved all procedures. The study was registered at clinicaltrials.gov (NCT02981381).

After signing informed consent, participants were randomized (in blocks of four, balanced across both sides), and then their IAF was measured using a two-electrode system (FPz and Oz, using the international 10–20 EEG nomenclature; mean $IAF \pm SD = 10.0 \pm 1.1$; no group differences). Participants then received four weeks (i.e., 5 treatment sessions per week) of active or sham sTMS, followed by four weeks of optional unblinded sTMS. Sham stimulation was identical except that it did not use rotating magnets; the system delivering unblinded stimulation was a separate device from those used in blinded stimulation. Clinical assessments included the PCL to evaluate total symptom score and count of items rated moderate or higher (i.e., threshold). Self-reported MDD symptom severity was measured using the QIDS. Clinical rating scales were measured at pretreatment baseline, then assessed at the end of every five treatment sessions throughout participation. We used a growth curve mixed model to test the linear change in symptoms over time, both within and across treatment groups (active vs. sham). The targeted hypothesis tests presented were for change in symptoms at 8 weeks, as estimated by the model. Side effects were assessed by participant self-report at each treatment session.

Table 1

Mixed model (linear growth curves) outcomes comparing active and sham sTMS up to eight weeks of treatment.

Measure	Active sTMS (pre/post)(n = 10)				Sham sTMS (pre/post)(n = 13)				Active vs. Sham			
	B	SE	t	p	B	SE	t	p	B	SE	t	p
PCL-5 total score	−17.22	3.30	−5.22	<0.001	−10.10	2.41	−4.20	<0.001	−7.11	4.08	−1.74	0.083
PTSD threshold symptoms	−7.27	1.39	−5.21	<0.001	−2.81	1.02	−2.76	0.007	−4.44	1.73	−2.57	0.011
QIDS-SR total score	−6.86	1.16	−5.91	<0.001	−4.41	0.851	−5.19	<0.001	−2.45	1.44	−1.70	0.091

Key: sTMS, synchronized transcranial magnetic stimulation; B, estimate of difference (pre-post for within group, between groups for active vs. sham); PCL-5, PTSD checklist for DSM-5; PTSD threshold symptoms, frequency (count) of PCL-5 items with a rating of $\geq$ moderate severity; QIDS-SR, Quick Inventory of Depressive Symptoms – Self-Report.

Results

Ten participants were randomized to active, and thirteen to sham sTMS. Participants were not able to accurately guess their group assignment (Fischer's exact test $p = .3$). Treatment was well tolerated. There were no statistically significant differences in adverse event reporting across groups. Of note, $n = 2$ participants in the active group (vs. zero in the sham group) reported headaches, and $n = 1$ participant reported nausea with active sTMS. There were no seizures. All participants demonstrated significant reductions in PTSD and MDD symptoms (all $p < .001$). As expected, there were significant reductions in symptoms in both treatment groups, but active stimulation did provide greater reductions in count of PTSD moderate-to-severe symptoms ("threshold PTSD" symptom count as measured on the PCL; difference of -4.44), PTSD symptom severity (PCL score difference of -7.11 points) and depression severity (QIDS score difference of -2.45 points)(Table 1).

Discussion

These results support the feasibility, tolerability and potential efficacy of sTMS for comorbid PTSD and MDD. Although results from a relatively small pilot study should be interpreted cautiously [14], the direction of effects on all measured variables was in the hypothesized direction favoring active stimulation. The greater separation between groups with more TMS treatment sessions is consistent with other studies of brain stimulation in PTSD, where greater exposure over time to active stimulation appears to be associated with superior outcomes [15,16]. Future work in larger samples will require attention to whether biological metrics, such as baseline IAF, can be used to predict clinical outcomes [11]. Limitations of this study include those inherent to small, pilot feasibility studies. Additionally, this study did not include an active stimulation group not using IAF to guide treatment. However, this study represents the first use of sTMS in this patient population with promising results; if replicated with a larger sample size, this represents an important step forward for novel treatment development that could be potentially used outside of the clinic setting, including home use.

Conflicts of interest

The authors report no biomedical conflicts of interest related to this work. Neosync Inc. provided equipment and training for this study. Dr. Holtzheimer receives royalties from Oxford University Press and UpToDate.

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