Received: October 13, 2022 Revised: February 7, 2023 Accepted: February 27, 2023

https://doi.org/10.1016/j.neurom.2023.02.082

Theta Burst Stimulation Is Not Inferior to High-Frequency Repetitive Transcranial Magnetic Stimulation in Reducing Symptoms of Posttraumatic Stress Disorder in Veterans With Depression: A Retrospective Case Series

Mohammad Ali Shenasa, BS, MS[1,3]; Em Ellerman-Tayag, BSN RN[1]; Philippe Canet, BSN RN[1]; Brian Martis, MD[1,3]; Jyoti Mishra, PhD[3]; Dhakshin S. Ramanathan, MD, PhD[1,2,3]

ABSTRACT

Objectives: Two commonly used forms of repetitive transcranial magnetic stimulation (rTMS) were recently shown to be equivalent for the treatment of depression: high-frequency stimulation (10 Hz), a protocol that lasts between 19 and 38 minutes, and intermittent theta burst stimulation (iTBS), a protocol that can be delivered in just three minutes. However, it is unclear whether iTBS treatment offers the same benefits as those of standard 10-Hz rTMS for comorbid symptoms such as those seen in posttraumatic stress disorder (PTSD).

Materials and Methods: In this retrospective case series, we analyzed treatment outcomes in veterans from the Veterans Affairs San Diego Healthcare System who received 10-Hz ($n = 47$) or iTBS ($n = 51$)-rTMS treatments for treatment-resistant depression between February 2018 and June 2022. We compared outcomes between these two stimulation protocols in symptoms of depression (using changes in the Patient Health Questionnaire-9 [PHQ-9]) and PTSD (using changes in the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, or Patient Checklist [PCL]-5).

Results: There was an imbalance of sex between groups ($p < 0.05$). After controlling for sex, we found no significant difference by stimulation protocol for depression (PHQ-9, F [1,94] = 0.16, $p = 0.69$, eta-squared = 0.002), confirming the original study previously noted. We also showed no difference by stimulation protocol of changes in PTSD symptoms (PCL-5, F [1,94] = 3.46, $p = 0.067$, eta-squared = 0.036). The iTBS group showed a decrease from 41.9 ± 4.4 to 25.1 ± 4.9 (a difference of 16.8 points) on the PCL-5 scale whereas the 10-Hz group showed a decrease from 43.6 ± 2.9 to 35.2 ± 3.2 on this scale (a difference of 8.4 points). Follow-up analyses restricting the sample in various ways did not meaningfully change these results (no follow-up analyses showed that there was a significant difference between stimulation protocols).

Conclusions: Although limited by small sample size, nonblind, and pseudorandomized assignment, our data suggest that iTBS is similar to 10-Hz stimulation in inducing reductions in PTSD symptoms and depression in military veterans.

Keywords: Neuromodulation for PTSD, rTMS in veterans, theta burst rTMS, theta burst vs 10-Hz rTMS

Conflict of Interest: The authors reported no conflict of interest.

Address correspondence to: Dhakshin S. Ramanathan, MD, PhD, Department of Psychiatry, University of California San Diego, La Jolla, CA 92093, USA. Email: dramanathan@health.ucsd.edu

[1] Mental Health Care Line, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA;
[2] Center of Excellence for Stress and Mental Health, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA; and
[3] Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please see the journal's Guide for Authors.

Source(s) of financial support: The authors reported funding from the Veterans Affairs Center of Excellence in Stress and Mental Health and the Burroughs–Wellcome Fund Award (Dhakshin S. Ramanathan).

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) has been cleared by the US Food and Drug Administration (FDA) for treatment-resistant depression (TRD) since 2006.[1,2] In clinical rTMS treatment protocols for depression, a magnetic coil is placed against the scalp to deliver electromagnetic pulses to the dorsolateral prefrontal cortex (DLPFC), a target thought to improve affective regulation and functional connectivity with core nodes of the depression network.[3] The initial FDA-cleared clinical protocol used a 4-second train of pulses, delivered at a frequency of 10 Hz (ie, 40 total pulses), followed by an intertrain "rest" period ranging from 12 to 26 seconds, for a total of 3000 pulses. These sessions are typically offered five days a week for four to six weeks and for a total of 20 to 30 treatments.[4–6] Recently, intermittent theta burst stimulation (iTBS) has emerged as an FDA-cleared alternative rTMS protocol for depression. iTBS entails delivery of three short pulses (a triplet burst delivered at 50 Hz) repeated every 200 milliseconds (5 Hz, the classical theta rhythm).[7,8] In a large multicenter trial, iTBS was noninferior to the standard 10-Hz rTMS treatment in patients with TRD.[9] iTBS offers benefits primarily due to its shorter treatment duration (3 vs 37.5 minutes),[9] easing patient burden and improving efficiency and access to this expensive treatment. Furthermore, iTBS allows accelerated protocols in which multiple treatments can be delivered daily, allowing more rapid treatment effects.[10]

Repetitive transmagnetic stimulation (TMS) has also been applied to reduce symptoms of posttraumatic stress disorder (PTSD), a distressful and potentially disabling condition (a comprehensive review is provided by Petrosino et al[11]). PTSD is marked by intrusive memories, avoidance of stimuli, negative changes in mood, cognition, and arousal, and hyperreactivity.[12] Importantly, most patients with PTSD also have comorbid depression,[13] and the interaction between comorbid depression and PTSD has been reported to worsen both conditions.[14] There has been conflicting evidence regarding whether comorbid PTSD symptoms/diagnoses affect the response to rTMS in the treatment of depression. For example, in one study of patients with depression, response and remission rates after rTMS were similar between those with and without PTSD,[15] whereas a randomized controlled trial (RCT) reported that remission rates were lower in patients with comorbid PTSD.[16] Despite this conflicting evidence (and a lack of FDA clearance for the treatment of PTSD), rTMS has been shown in smaller research studies to improve PTSD symptoms, with and without comorbid depression, using high and low frequencies applied to left, right, or bilateral sites.[11,17–21] The most recent meta-analysis of rTMS in patients with PTSD indicated great improvements in PTSD symptoms (19 studies, 376 subjects, d = 1.17, 95% CI 0.89–1.45, $p < 0.001$).[18] A recent retrospective analysis of treatment outcomes in veterans treated at multiple Veterans Affairs (VA) facilities across the country revealed that 70% of the veterans in this analysis had comorbid PTSD, with most being treated with 10-Hz rTMS applied to the left DLPFC.[22] The authors found significant improvement in depression and PTSD symptoms measured by the Patient Health Questionnaire-9 (PHQ-9) and Patient Check List (PCL)-5, respectively. Strikingly, among veterans with comorbid PTSD, 65.3% experienced clinically meaningful reduction, and 46.1% no longer met the PTSD criteria.[22] This cohort study serves as proof of concept for the efficacy of left DLPFC-targeted rTMS in veterans with depression and PTSD.

In trials aiming to alleviate PTSD symptoms, the use of right-sided iTBS has shown promise.[23] Specifically, iTBS applied to the right DLPFC was shown to be significantly superior to sham stimulation.[23] This superiority was indicated through improved PTSD symptoms as measured by PCL and Clinician-Administered PTSD Scale and depression as measured by the Inventory of Depressive Symptomatology-Self-Report (IDS-SR), in addition to social and occupational function. Another study compared the efficacy of iTBS with that of 5-Hz rTMS, both targeting the left DLPFC, in a small retrospective analysis ($n = 20$) of veterans receiving care at the Providence VA Healthcare System.[24] Surprisingly, the authors found that although both protocols were well tolerated and significantly effective in symptom reduction, iTBS produced inferior outcomes for PTSD (treatment protocol x time $p = 0.011$). iTBS also provided smaller effect sizes than those of 5-Hz rTMS for both PTSD and depression as measured through the PCL-5 and IDS-SR, respectively. Although this study had an overall small sample size of a unique patient population and was neither randomized nor blind, it raises concern for whether an iTBS protocol targeted at left DLPFC is suboptimal for patients with depression and concurrent PTSD more generally and reiterates the importance of determining optimized treatment options for patients with comorbid PTSD and depression.

The VA San Diego Healthcare System has been providing rTMS to eligible patients with TRD since early 2018. The program primarily used 10-Hz rTMS, targeted to the left DLPFC. After the FDA cleared iTBS to be used for TRD, the program switched to primarily offering iTBS targeting the left DLPFC, starting in October 2019. Given the well-documented efficacy of rTMS for PTSD and the high prevalence of comorbid PTSD and depression in our patient sample, we consistently measured symptoms of both depression and PTSD in our clinic using established self-report questionnaires. In this retrospective case series, we investigated whether there was any difference in efficacy between iTBS and 10-Hz rTMS for treatment of both depression and comorbid PTSD in veterans. We hypothesized that there would be no difference between stimulation protocols on changes in depression symptoms, thus replicating the initial THREE-D trial,[9] and further hypothesized that there would be no significant difference in alleviating PTSD symptoms.

MATERIALS AND METHODS

Data are reported following STrengthening the Reporting of OBservational studies in Epidemiology guidelines.

Veterans Included in Analysis

This study was approved as an institutional review board (IRB) exemption by the VA San Diego Medical Center IRB committee. We conducted a chart review of patients referred to the VA San Diego neuromodulation program who, after consultation, were deemed appropriate for a trial of rTMS (from February 2018 to May 2022). Veterans were included for analysis if they received at least two weeks of treatment and for whom we had at least two measures of their PHQ-9/PCL-5 (with the first acquired within the first week of treatment). Data from 98 veterans were included in this analysis (Table 1 provides more details).

All veterans were initially referred to the VA San Diego neuromodulation program by their primary psychiatrists for an evaluation and potential treatment with either rTMS, electroconvulsive

Table 1. Differences Between Patients Receiving Either Stimulation Protocol.*

Pretreatment characteristics	iTBS	10 Hz	Significance
Age	49.4 ± 15.7	49.3 ± 12.8	$p = 0.9$
Sex	5 F, 46 M	16 F, 31 M	$p = 0.003$
Pretreatment PHQ-9	18.4 ± 5.4	18.1 ± 5.87	$p = 0.8$
Pretreatment PCL-5	43.76 ± 19.3	44.6 ± 18.2	$p = 0.8$

F, female; M, male.
*We collected information related to age, gender, pretreatment PHQ-9 and PCL-5. We only found a significant difference by gender (two-sided chi-squared test).

therapy, or ketamine. Veterans included in this retrospective analysis may thus have been started on rTMS upon initial referral to this program or could have been switched to rTMS after not adequately responding to some other treatment. The eligibility criterion for referral was generally a failure of at least one antidepressant. The exclusion criteria for rTMS followed standard guidelines for rTMS: no history of seizures/seizure disorder; no metallic/electrical objects implanted above the head/neck; lack of imminent suicidality; and lack of recent substance dependence/misuse (within the last two months). Repetitive TMS in our clinic during this period was generally performed five days per week, with an initial treatment course defined as 30 treatments. Veterans were administered rTMS alongside treatment as usual and were encouraged/asked not to change medications during treatment, although we did not stop treatment if veterans did change medications.

Assessments

All data analyzed in this manuscript were gathered as part of clinical care consistent with the clinical program protocol. Veterans were administered a PHQ-9 to monitor symptoms of depression and a PCL-5 to monitor PTSD symptoms before the start of rTMS treatment. Scales were then collected weekly after the start of treatment. The PHQ-9 was first developed and validated as a tool for screening for depression in primary care settings but has been tested and validated in psychiatric populations more generally,[25] and as a tool to measure depression-related symptoms at the VA.[26] The PCL-5, a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition updated version of the PCL, is one of the most widely used self-reported measures of PTSD. It has been validated for use in veterans[27] and is often deployed clinically within the VA system as an easy measure of PTSD severity. We performed a chart review to gather auxiliary data that included age, sex, and formal PTSD diagnosis.

Stimulation Protocols

Both 10-Hz rTMS and iTBS entailed five days per week of treatment for 30 days of treatment during the initial course. Both protocols also entailed stimulation delivered to the left DLPFC, typically at 120% of the motor threshold. The 10-Hz protocol used in the clinic was specified as ten pulses per second for 4 seconds (40 total pulses/train), followed by a 12-to-26–second intertrain interval. We delivered 75 trains, lasting from between 19 and 37.5 minutes per day of stimulation, for a total of 3000 pulses per session.[4] The iTBS protocol used in the clinic was specified as a 50-Hz burst of three pulses, with bursts timed to occur every 200 milliseconds for 2 seconds (40 pulses/train), followed by an 8-second intertrain interval. Twenty such trains were delivered for a total of 600 pulses,[8] and this stimulation protocol lasted approximately 3 minutes. We included four individuals in the iTBS group who received bilateral treatments (two with continuous Theta Burst Stimulation on the right, and two with 1 Hz treatment on the right). Individuals who were receiving other stimulation protocols (exclusively right-sided treatment or 1-Hz treatment, for example) were excluded from further analysis.

Statistical Analyses

We focused on three primary questions in this paper:

1) Were there statistically significant and clinically meaningful differences in reductions of either PHQ-9 or the PCL-5 summary score by stimulation type? To analyze this, we implemented a mixed-effects 2 × 2 analysis of variance (ANOVA) model, with time as a within-group repeated measure (prestimulation as T1 and final treatment as T2) and stimulation type as a between-group factor, for both the PHQ-9 and the PCL-5 symptom scales. For T2, we used the symptom score at treatment 30, or the patient's last reported score if they stopped treatment early. A total of 98 veterans were included in this analysis.
2) Would our results vary if restricted to veterans with clinically verified and active PTSD? We repeated analyses in veterans with both clinically verified PTSD diagnoses (ie, a listed diagnosis of PTSD in the medical record) and with clinically significant PTSD symptoms (PCL-5 score > 33, before starting rTMS treatment, $n = 56$).
3) Were baseline PTSD symptom scores a predictor (positive or negative) for antidepressant response? We measured this using an ANOVA model with change in PHQ-9 as the outcome and PTSD as a fixed factor, and a Pearson regression between PCL-5 pretreatment values and change in PHQ-9 values. We also included stimulation type as a factor in this analysis.

We also looked at differences in the veterans between groups on age, baseline PHQ-9 and PCL-5 scores (using *t*-tests), and sex (using the chi-squared test). Lastly, to evaluate whether there was a difference in early termination between the two groups, we performed a chi-squared test.

Statistical Analyses and Reporting

For all ANOVA analyses reported here, we followed three steps: 1) normality of score distributions was tested before performing further statistical testing using the Shapiro-Wilk test ($p > 0.05$ suggestive of normal distribution); 2) all models were interpreted using a significance level (alpha) of 0.05; and 3) for ANOVA models, we reported the F statistic (F). Repeated-measures ANOVA used Greenhouse-Geisser correction. For all tests (*t*-test, regression, chi-squared test), we report two-sided *p* values.

RESULTS

Pretreatment information that was collected for this manuscript is included in Table 1. We first examined whether there was a difference in baseline PHQ-9 or PCL-5 scores between stimulation types. Scores of 5, 10, 15, and 20 on the PHQ-9 have been validated to correspond with mild, moderate, moderately severe, and severe depression, respectively.[28] We included in our analysis only patients who reported clinically meaningful depression scores (≥ 5)

during treatment. We observed no significant differences in either baseline PHQ-9 scores (t [96] = 0.25, $p = 0.8$) or in the PCL-5 scores (t [96] = 0.2, $p = 0.8$) between the 10-Hz and iTBS groups. There were also no significant differences in age between groups. There was a significant difference in sex distribution, with five women (46 men) in the 10-Hz group and 16 women (31 men) in the iTBS group ($p = 0.003$, chi-squared test). The average stimulation intensity calculated as 120% of the motor threshold was 75.5 ± 15 (mean ± SD) in the 10-Hz group and 54.7 ± 12 in the iTBS group, likely reflecting different magnet manufacturers (Magstim for the 10-Hz group and MagVenture for the iTBS group). We also examined substance use. The 10-Hz stimulation group included two patients with current tobacco use, 12 with current cannabis use, and six with a chart-reported history of alcohol use disorder, whereas the iTBS group reported eight, eight, and nine patients with such characteristics, respectively. We found no significant difference between the two groups for any substance use characteristics (two-sided Wald tests $p > 0.05$).

Our initial analysis of changes in PHQ-9 scores with treatment showed that both iTBS and 10 Hz resulted in significant and clinically meaningful reductions in depression (Fig. 1a**)**. A mixed-effects ANOVA was performed to measure whether the change in PHQ-9 scores differed by stimulation type. The model specification included between-group factors of stimulation type (10 Hz vs iTBS) and sex (male vs female) and a repeated-measures factor of time (pre- vs posttreatment PHQ-9 score). There was an overall effect of time (F [1,94] = 82.5, $p < 0.001$, $h_p^2 = 0.47$) and a significant effect by sex (F [1,94] = 4.5, $p < 0.05$, $h_p^2 = 0.046$). A post hoc analysis of the sex × time effect revealed that women ($n = 21$) showed a change in PHQ-9 symptoms from 17.1 ± 1.4 to 8.4 ± 1.6, whereas men showed a change from 18.1 ± 0.65 to 12.7 ± 0.76. Thus, women in our analysis showed a larger overall decrease in depression symptoms because of rTMS. There was no time × stimulation type effect (F [1,94] = 0.16, $p = 0.69$) or time × sex × stimulation type effect (F [1,94] = 1, $p = 0.32$), suggesting that stimulation type did not affect treatment outcome. Post hoc analyses in this model showed that after accounting for sex differences, the group receiving iTBS showed a decrease in PHQ-9 scores of 16.7 ± 1.31 to 9.4 ± 1.38 (a 7.3 point reduction), whereas the group receiving 10 Hz treatment showed a decrease in the PHQ-9 of 18.5 ± 0.86 to 11.78 ± 1 (a 6.7 point reduction).

We next analyzed changes in PCL-5 scores. We found that both iTBS and 10-Hz stimulation resulted in significant and clinically meaningful reductions in PTSD symptoms as measured using the PCL-5 (Fig. 1b**)**. A mixed-effects model was specified as previously mentioned with between-group factors of stimulation type and sex and a repeated-measures factor of time. This model showed that for PTSD symptoms, the two types of treatments were similar. There was an overall effect of treatment (F [1,94] = 31.8, $p < 0.001$, $h_p^2 = 0.25$). There was not a significant sex × time effect (F [1,94] = 1.5, $p = 0.2$), stimulation type × time effect (F [1,94] = 3.46, $p = 0.07$, $h_p^2 = 0.036$), or sex × time × stimulation type effect (F [1,94] = 0.55, $p = 0.46$). Follow-up post hoc analyses showed that the iTBS group showed a decrease from 41.9 ± 4.4 to 25.1 ± 4.9 (a difference of 16.8 points) whereas the 10-Hz group showed a decrease from 43.6 ± 2.9 to 35.2 ± 3.2 (a difference of 8.4 points). Thus, we found no evidence that iTBS was inferior to 10-Hz treatment in the reduction of PTSD symptoms.

We followed this up by analyzing changes in the PCL-5 with treatment only in veterans with documented, clinically active PTSD (ie, diagnosis of PTSD in the chart and a pretreatment PCL-5 score > 33). In this smaller sample ($n = 56$ total, 31 with iTBS and 25 with 10-Hz treatment, with 12 women and 44 men), we found generally similar effects as previously reported. There was a similar overall effect of treatment (F [1,52] = 36.5, $p < 0.001$) but no difference by stimulation type (F [1,54] = 2.4, $p = 0.13$) for the change in PCL-5 symptoms. Again, as previously noted, post hoc analysis indicated a 20.7 ± 4.5-point reduction in the iTBS group compared with a 12.3 ± 3.1-point reduction in the 10-Hz group. Thus, we observed no differences between iTBS and standard 10-Hz treatment in the reduction of PTSD symptoms in veterans, using either the full cohort of veterans or only those with documented clinically active symptoms of PTSD.

There was a difference in the number of early dropouts between the 10-Hz and iTBS groups. In our sample, 12 veterans dropped out of treatment before 4 weeks in the 10-Hz group, whereas none dropped out of treatment early in the iTBS group. It is possible that these differences in dropout might have affected the analysis. Although our initial analysis followed an intent-to-treat type of analysis, we performed a follow-up analysis in which we excluded dropouts and reanalyzed the data (following a "per-protocol" type of analysis). In this analysis ($n = 51$ iTBS group and $n = 35$ 10-Hz group, using a mixed-effects model as previously noted, specifying between-group factors of sex and stimulation type and repeated-measures factors of pre- vs posttreatment), we again found no difference for either change in PHQ-9 or PCL-5 between the two stimulation protocols. For the PHQ-9, we found an overall effect of time (F [1,82] = 77.7, $p < 0.001$). The effect of time × stimulation type was not significant (F [1,82] = 0.03, $p = 0.96$). The change in the iTBS group was 16.7 to 9.4, a difference of 6.6 ± 0.8 (SEM), and the change in the 10 Hz group was 17 to 9.6, a within-group difference of 6.6 ± 0.7 (SEM). For the PCL-5 reanalysis, we found an overall significant effect of time (F [1,82] = 37.1, $p < 0.001$) and a nonsignificant effect of stimulation type × time

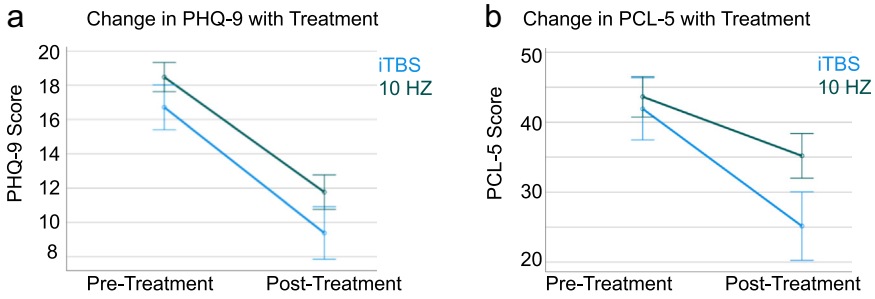

Figure 1. Differences between stimulation protocols in treatment outcomes. [Color figure can be viewed at www.neuromodulationjournal.org]

(F [1,82] = 0.85, $p = 0.36$). The change in PCL-5 in the iTBS group was 41.9 to 25.1, a difference of 13.2 ± 2.3 (SEM), and the change in the 10-Hz group was 41.7 to 29.4, a difference of 11.4 ± 2.7 (SEM). Thus, the per-protocol analysis further validates that the two stimulation protocols are overall similar in their effects on PTSD-like symptoms.

In our final analysis, we measured whether there was an overall relationship between pretreatment PTSD and antidepressant outcomes because an earlier study suggested this.[16] We performed several analyses to measure this. First, using our designation of "clinically active PTSD" noted above, we performed an ANOVA model using change in PHQ-9 as our outcome measure and the presence of clinically active PTSD as a fixed factor (56 veterans with clinically active PTSD, 42 veterans without). This model did not show a significant effect of PTSD on the change in PHQ-9 scores with treatment (F [1,95] = 0.85, $p = 0.4$). We performed a follow-up analysis in which we conducted a Pearson regression between PCL-5 pretreatment scores and change in PHQ-9 scores. This model was likewise not significant ($r = 0.02$, $p = 0.9$). Thus, there is no evidence in our data that PTSD symptoms, either as a binary (absence or presence) or as a function of symptom severity (correlation analysis), were related to change in depression symptoms.

DISCUSSION

In this study, we investigated whether there were any differences between iTBS and 10-Hz rTMS treatment in overall reduction of depression and PTSD symptoms among veterans. We found no clinically meaningful differences in the reduction of either depression or PTSD symptoms based on the type of stimulation. Although the reduction of PCL-5 scores between patients receiving iTBS and 10 Hz approached but did not reach statistical significance as defined by a $p < 0.05$, PCL-5 scores were reduced by a greater magnitude and decreased to a mean value (25.1 ± 4.9), a level that is, on average, below the cutoff of clinical significance (33). Although this difference decreased when accounting for differences in treatment dropout, it is possible that in a larger, controlled, and well-powered study, iTBS may in fact be more effective than 10-Hz rTMS in treatment of PTSD. Furthermore, there are notable differences between the THREE-D trial and individuals reported in this study. This includes our different patient population (veterans vs civilians), less stringent inclusion criteria (in terms of treatment resistance), and possible demographic differences related to age/sex and geographic location. Veterans are known to have elevated rates of PTSD compared with civilians[29] and may have disproportionate elevation of several other critical psychosocial variances compared with civilians, including differences in racial/ethnic/socioeconomic characteristics, adverse childhood experiences,[30] substance-use disorders,[31] chronic pain,[32] and traumatic brain injuries.[33,34] It is thus reassuring that despite the numerous differences between our analysis and the THREE-D trial of Blumberger et al,[9] our findings are consistent with the premise established by their study because we found iTBS is similar in efficacy to 10-Hz rTMS for depression. In turn, both iTBS and 10-Hz protocols have established efficacy in veterans and civilians. However, it is difficult to assess ways these factors may affect the external validity and generalizability of our findings in civilians with comorbid depression and PTSD. Our findings are also generally consistent with other recent studies from the VA showing that rTMS can improve symptoms of PTSD, although previous reports focused mostly on standard 10-Hz stimulation protocols.[22,35] Our findings, that rTMS can relieve PTSD symptoms in veterans, are also consistent with those from an RCT determining the efficacy of active iTBS targeted to right DLPFC on PTSD symptoms because the authors found significant improvement in both PTSD and depression from the active arm of the trial at one-month follow-up.[23] The patient population in that trial mirrored ours because it included veterans with PTSD, most of whom (90%) also had comorbid depression.

Our outcomes differ from those observed by Philip et al,[24] who found that iTBS targeted to the left DLPFC was less effective than 5-Hz stimulation in reducing PTSD symptoms. Their study was, however, notably distinct from ours. Firstly and most importantly, their study compared a 5-Hz stimulation protocol vs iTBS targeted to the left hemisphere, whereas we were comparing the more standard 10-Hz treatment with iTBS targeted to the left hemisphere. Although there is no clearly identified optimal treatment or stimulation frequency for PTSD (as reviewed thoroughly by Petrosino et al[11]), the different frequencies each study used to compare with iTBS may explain the diverging results, with 5 Hz being possibly superior to standard (10 Hz/iTBS) for treatment of PTSD.[24] The dissimilar outcomes may also be due to other characteristics. Both studies had small samples (the study by Philip et al had 20 subjects, and even our study only had 56 veterans with clinically verifiable PTSD symptoms), and both rely on nonrandomization and nonblind protocols. Thus, further research using appropriate controls/blinding and randomization is needed.

Contrary to the findings of Yesavage et al,[16] we did not find that PTSD symptoms (as defined by both formally diagnosed and pretreatment PCL-5 values > 33) were associated with less improvement in depression scores either categorically (as defined by both formally diagnosed and pretreatment PCL-5 values > 33) or as a function of symptom scores. Rather, our study participants and results are consistent with those from Hernandez et al[15] and Wilkes et al.[35] In both studies, veterans with depression and comorbid PTSD treated with rTMS experienced significant improvements in both disorders, with similar improvements in their depression symptoms to those of veterans without PTSD.

In general, iTBS shows several clear advantages over 10-Hz treatments. First, accelerated rTMS protocols (in which multiple treatments are delivered on the same day) were recently FDA-cleared for the treatment of depression.[10] Accelerated protocols rely on short iTBS treatments to adequately space out repeated treatments. Our results support the idea that accelerated protocols may also be useful in PTSD and warrant further research in this area. In addition, psychotherapy is fundamental to the treatment of PTSD, and recently, various trials have been published combining rTMS with various forms of psychotherapy. For instance, an RCT has shown that 10-Hz rTMS in conjunction with cognitive processing therapy (CPT) yields a significantly greater improvement than do sham stimulation and CPT.[36] It is possible that iTBS, owing to shorter stimulation periods, will allow improved or novel treatment paradigms in which rTMS can be combined with various forms of psychotherapy.

There are limitations to our study that need to be factored into the interpretation of the findings. First, this is a retrospective and nonrandomized design and is associated with the usual challenges of interpreting such data. Owing to the nonrandom allocation, the

two groups of subjects may possess different qualities or attributes. Among these differences, patient sex warrants further discussion. An analysis of > 5000 patients treated with rTMS for depression found female participants more likely to respond to treatment and enter remission.[37] Several possible biological explanations stemming from differences in patient sex have since been described.[38] We reported unbalanced sex distribution among the two groups, with the 10-Hz group having more women overall and as a higher proportion of participants. We did indeed show an effect of sex and included this as a factor in our models, but these differences would be better accounted for by proper randomization. The groups for the most part underwent treatment across nonoverlapping periods, and importantly, the COVID-19 pandemic overlapped with the treatment delivered during the iTBS period. The psychiatric burden of the pandemic could have confounded the baseline of the group receiving iTBS. The treatments also used different devices: 10-Hz treatments were delivered using a MagStim device, whereas iTBS treatments were delivered using a MagVenture device, a discrepancy which is reflected in each group's average stimulation intensity. Other limitations include a medium sample size and thus a limitation in the effect size difference we were powered to observe. Finally, in this study, we were not specifically treating veterans with PTSD, rather veterans who initially presented for treatment of depression, and effects may differ in veterans who are primarily presenting for treatment of PTSD. However, studies show that most veterans with resistant depression have comorbid PTSD, and thus, our results are likely relevant to many veterans receiving treatment.

Considering these limitations, there are several positive aspects to our study. First, despite all these complexities, it is important to note that we did replicate the overall effects observed previously in the large, randomized/blind THREE-D trial.[9] This allows us to have greater confidence that despite nonrandomization, there were not fundamental differences in the level of treatment resistance or response between the two groups. Second, although we did not randomize veterans to the two treatments, there was a "pseudo-randomization" built in to how the treatments were offered (for two years, only 10-Hz treatments were offered, and after we switched to iTBS, iTBS became the default treatment of choice in our clinic). This somewhat mitigates the lack of randomization, in that it was less likely that veteran characteristics or some other aspect related to depression severity itself influenced which treatment was offered. Finally, there is no evidence to date that outcomes differ on the basis of device manufacturer, given similar magnet geometries (ie, both groups used a figure-of-eight treatment coil). Indeed, FDA clearance for these different devices is predicated on them being overall similar in their ability to provide brain stimulation.

Authorship Statements

Mohammad Ali Shenasa and Dhakshin S. Ramanathan jointly developed the idea for the analysis. Dhakshin S. Ramanathan, Em Ellerman-Tayag, and Philippe Canet were involved in data collection, acquisition, and analysis. Mohammad Ali Shenasa and Dhakshin S. Ramanathan analyzed data. Mohammad Ali Shenasa prepared the manuscript draft with important intellectual input from all coauthors. All authors approved the final manuscript. This work represents the viewpoint of the authors and does not represent the viewpoint of the employer (Veterans Affairs San Diego Healthcare System).

How to Cite This Article

Shenasa M.A., Ellerman-Tayag E., Canet P., Martis B., Mishra J., Ramanathan D.S. 2023. Theta Burst Stimulation Is Not Inferior to High-Frequency Repetitive Transcranial Magnetic Stimulation in Reducing Symptoms of Post-traumatic Stress Disorder in Veterans With Depression: A Retrospective Case Series.
Neuromodulation 2023; 26: 885–891.

REFERENCES

1. Gaynes BN, Lloyd SW, Lux L, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014;75:477–489 [quiz: 489]. https://doi.org/10.4088/JCP.13r08815.
2. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry*. 2012;72:595–603. https://doi.org/10.1016/j.biopsych.2012.04.028.
3. Sehatzadeh S, Daskalakis ZJ, Yap B, et al. Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a meta-analysis of randomized controlled trials over 2 decades. *J Psychiatry Neurosci*. 2019;44:151–163. https://doi.org/10.1503/jpn.180056.
4. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. 2010;67:507–516.
5. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009;34:522–534.
6. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007;62:1208–1216. https://doi.org/10.1016/j.biopsych.2007.01.018.
7. Chistyakov AV, Rubicsek O, Kaplan B, Zaaroor M, Klein E. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. *Int J Neuropsychopharmacol*. 2010;13:387–393. https://doi.org/10.1017/S1461145710000027.
8. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45:201–206. https://doi.org/10.1016/j.neuron.2004.12.033.
9. Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *Lancet*. 2018;391:1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2.
10. Cole EJ, Stimpson KH, Bentzley BS, et al. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. *Am J Psychiatry*. 2020;177:716–726. https://doi.org/10.1176/appi.ajp.2019.19070720.
11. Petrosino NJ, Cosmo C, Berlow YA, Zandvakili A, van 't Wout-Frank M, Philip NS. Transcranial magnetic stimulation for post-traumatic stress disorder. *Ther Adv Psychopharmacol*. 2021;11:20451253211049921. https://doi.org/10.1177/20451253211049921.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596.
13. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues Clin Neurosci*. 2015;17:141–150.
14. Shalev AY, Freedman S, Peri T, et al. Prospective study of posttraumatic stress disorder and depression following trauma. *Am J Psychiatry*. 1998;155:630–637. https://doi.org/10.1176/ajp.155.5.630.
15. Hernandez MJ, Reljic T, Van Trees KV, et al. Impact of comorbid PTSD on outcome of repetitive transcranial magnetic stimulation (TMS) for veterans with depression. *J Clin Psychiatry*. 2020;81:8636. https://doi.org/10.4088/JCP.19m13152.
16. Yesavage JA, Fairchild JK, Mi Z, et al. Effect of repetitive transcranial magnetic stimulation on treatment-resistant major depression in US veterans: a randomized clinical trial. *JAMA Psychiatry*. 2018;75:884–893. https://doi.org/10.1001/jamapsychiatry.2018.1483.
17. Berlim MT, Van Den Eynde F. Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: an exploratory meta-analysis of randomized, double-blind and sham-controlled trials. *Can J Psychiatry*. 2014;59:487–496. https://doi.org/10.1177/070674371405900905.
18. Harris A, Reece J. Transcranial magnetic stimulation as a treatment for post-traumatic stress disorder: a meta-analysis. *J Affect Disord*. 2021;289:55–65. https://doi.org/10.1016/j.jad.2021.04.003.

19. Kan RLD, Zhang BBB, Zhang JJQ, Kranz GS. Non-invasive brain stimulation for posttraumatic stress disorder: a systematic review and meta-analysis. *Transl Psychiatry*. 2020;10:168. https://doi.org/10.1038/s41398-020-0851-5.
20. Karsen EF, Watts BV, Holtzheimer PE. Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. *Brain Stimul*. 2014;7:151–157. https://doi.org/10.1016/j.brs.2013.10.006.
21. Yan T, Xie Q, Zheng Z, Zou K, Wang L. Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): a systematic review and meta-analysis. *J Psychiatr Res*. 2017;89:125–135. https://doi.org/10.1016/j.jpsychires.2017.02.021.
22. Madore MR, Kozel FA, Williams LM, et al. Prefrontal transcranial magnetic stimulation for depression in US military veterans – a naturalistic cohort study in the veterans health administration. *J Affect Disord*. 2022;297:671–678. https://doi.org/10.1016/j.jad.2021.10.025.
23. Philip NS, Barredo J, Aiken E, et al. Theta-burst transcranial magnetic stimulation for posttraumatic stress disorder. *Am J Psychiatry*. 2019;176:939–948. https://doi.org/10.1176/appi.ajp.2019.18101160.
24. Philip NS, Doherty RA, Faucher C, Aiken E, van 't Wout-Frank M. Transcranial magnetic stimulation for posttraumatic stress disorder and major depression: comparing commonly used clinical protocols. *J Trauma Stress*. 2022;35:101–108. https://doi.org/10.1002/jts.22686.
25. Beard C, Hsu KJ, Rifkin LS, Busch AB, Björgvinsson T. Validation of the PHQ-9 in a psychiatric sample. *J Affect Disord*. 2016;193:267–273. https://doi.org/10.1016/j.jad.2015.12.075.
26. Katz IR, Liebmann EP, Resnick SG, Hoff RA. Performance of the PHQ-9 across conditions and comorbidities: findings from the Veterans Outcome Assessment survey. *J Affect Disord*. 2021;294:864–867. https://doi.org/10.1016/j.jad.2021.07.108.
27. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. *J Trauma Stress*. 2015;28:489–498. https://doi.org/10.1002/jts.22059.
28. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
29. Lehavot K, Katon JG, Chen JA, Fortney JC, Simpson TL. Post-traumatic stress disorder by gender and veteran status. *Am J Prev Med*. 2018;54:e1–e9. https://doi.org/10.1016/j.amepre.2017.09.008.
30. Katon JG, Lehavot K, Simpson TL, et al. Adverse childhood experiences, military service, and adult health. *Am J Prev Med*. 2015;49:573–582. https://doi.org/10.1016/j.amepre.2015.03.020.
31. Teeters JB, Lancaster CL, Brown DG, Back SE. Substance use disorders in military veterans: prevalence and treatment challenges. *Subst Abuse Rehabil*. 2017;8:69–77. https://doi.org/10.2147/SAR.S116720.
32. Nahin RL. Severe pain in veterans: the effect of age and sex, and comparisons with the general population. *J Pain*. 2017;18:247–254. https://doi.org/10.1016/j.jpain.2016.10.021.
33. Loignon A, Ouellet MC, Belleville G. A systematic review and meta-analysis on PTSD following TBI among military/veteran and civilian populations. *J Head Trauma Rehabil*. 2020;35:E21–E35. https://doi.org/10.1097/HTR.0000000000000514.
34. Reid MW, Velez CS. Discriminating military and civilian traumatic brain injuries. *Mol Cell Neurosci*. 2015;66:123–128. https://doi.org/10.1016/j.mcn.2015.03.014.
35. Wilkes S, Ona C, Yang M, et al. Impacts of rTMS on refractory depression and comorbid PTSD symptoms at a military treatment facility. *Mil Med*. 2020;185:e1420–e1427. https://doi.org/10.1093/milmed/usaa148.
36. Kozel FA, Motes MA, Didehbani N, et al. Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: a randomized clinical trial. *J Affect Disord*. 2018;229:506–514. https://doi.org/10.1016/j.jad.2017.12.046.
37. Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with transcranial magnetic stimulation. *J Affect Disord*. 2020;277:65–74. https://doi.org/10.1016/j.jad.2020.08.005.
38. Hanlon CA, McCalley DM. Sex/gender as a factor that influences transcranial magnetic stimulation treatment outcome: three potential biological explanations. *Front Psychiatry*. 2022;13:869070. https://doi.org/10.3389/fpsyt.2022.869070.

COMMENT

The presented data suggest that 10-Hz TMS and intermittent theta burst stimulation, both targeting the left dorsolateral prefrontal cortex, are clinically comparable for treatment-resistant depression and comorbid posttraumatic stress disorder. These results fit with other more recent data, which is relevant because knowing whether a particular TMS protocol is clinically more effective should guide treatment implementation. In addition, there is a strong push in the field to accelerate TMS protocols, to which some protocols might better lend themselves than others.

Mascha Van't Wout, PhD
Providence, RI, USA