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5-Hz Transcranial Magnetic Stimulation for Comorbid Posttraumatic Stress Disorder and Major Depression

Noah S. Philip¹, Samuel J. Ridout², Sarah E. Albright¹, George Sanchez¹, and Linda L. Carpenter²

¹Center for Neurorestoration and Neurotechnology, Providence VA Medical Center, Providence, Rhode Island, USA

²Laboratory for Clinical and Translational Neuroscience, Butler Hospital, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, Rhode Island, USA

Abstract

Current treatment options for posttraumatic stress disorder (PTSD) offer modest benefits, underscoring the need for new treatments. Repetitive transcranial magnetic stimulation (rTMS) depolarizes neurons in a targeted brain region with magnetic fields typically pulsed at low (1 Hz) or high (10 Hz) frequency to relieve major depressive disorder (MDD). Prior work suggests an intermediate pulse frequency, 5 Hz, is also efficacious for treating comorbid depressive and anxiety symptoms. In this chart review study, we systematically examined the clinical and safety outcomes in 10 patients with comorbid MDD and PTSD syndromes who received 5-Hz rTMS therapy at the Providence VA Medical Center Neuromodulation Clinic. Self-report scales measured illness severity prior to treatment, after every 5 treatments, and upon completion of treatment. Results showed significant reduction in symptoms of PTSD ($p = .003$, effect size = 1.12, 8/10 with reliable change) and MDD ($p = .005$, effect size = 1.09, 6/10 with reliable change). Stimulation was well tolerated and there were no serious adverse events. These data indicate 5-Hz rTMS may be a useful option to treat these comorbid disorders. Larger, controlled trials are needed to confirm the benefits of 5-Hz protocols observed in this pilot study.

The impact of posttraumatic stress disorder (PTSD) cannot be overstated. PTSD is highly prevalent in U.S. military veterans (Hoge et al., 2008; Magruder et al., 2005), and is commonly associated with major depressive disorder (MDD), physical health problems, and unemployment. Evidence-based pharmacotherapy and psychotherapy approaches have had fair, albeit modest success in improving symptoms and function in veterans with PTSD (Watts et al., 2013). Therefore, there is a pressing need to identify novel, effective treatments for PTSD.

Repetitive transcranial magnetic stimulation (rTMS) was approved in 2008 by the U.S. Food and Drug Administration (FDA) for MDD that does not remit with pharmacotherapy. This noninvasive technique uses a pulsed magnetic field to induce neuronal depolarization in a

targeted brain region, typically the left dorsolateral prefrontal cortex (DLPFC) for MDD. Several different FDA-cleared devices are available that use a variety of different coils and treatment approaches. It is an outpatient procedure and does not require anesthesia. A typical treatment includes initial determination of an individual motor threshold—an index of cortical excitability to which the treatment intensity is calibrated. The coil is then placed over the left DLPFC and 3,000 pulses are delivered at 10 Hz over 45 min. An acute course of rTMS is comprised of up to 30 daily treatments over 6 weeks, followed by several weeks of tapering treatment session frequency. The side effect profile is generally benign, and includes scalp discomfort, twitching, and rarely, seizure (Rossi et al., 2009).

Although rTMS has been developed as an effective treatment for MDD (Berlim, van den Eynde, Tovar-Perdomo, & Daskalakis, 2014) over the last decade, there has been less attention to determining optimal stimulation parameters for PTSD. Early reports (Cohen et al., 2004; Grisaru et al., 1998; McCann et al., 1998; Rosenberg et al., 2002) suggested that rTMS could reduce symptoms of PTSD. Recently, several sham-controlled studies demonstrated rTMS efficacy for PTSD, producing mixed results regarding superiority of specific parameters such as which side of the head should be treated (laterality) and which pulsing frequency (Hz) works best. One study ($n = 30$; Boggio et al., 2010) found that 10 rTMS sessions delivered at a high frequency (20 Hz) on either the left or right side was associated with clinical improvement compared to sham treatments. Interestingly, left-sided 20 Hz rTMS appeared to benefit mood symptoms, Hedges $g = 3.78$, 95% confidence interval (CI) [2.32, 5.25], whereas right-sided treatment improved anxiety, $g = 2.68$, 95% CI [1.47, 3.88]. Another study ($n = 20$; Watts, Landon, Groft, & Young-Xu, 2012) found significant and persistent improvement in PTSD alongside mood benefits following 10 sessions delivered at a low (1 Hz) frequency to right DLPFC, $g = 1.99$, 95% CI [0.92, 3.06].

Owing to the number of parameters that contribute to the overall dose of rTMS and the need to manipulate one parameter in each study, little work has explored the efficacy of pulse frequencies other than 1, 10, and 20 Hz. Older studies examined 5 Hz to the left DLPFC and generated data that suggested equivalent efficacy in symptom reduction with 10 Hz for MDD or bipolar depression (George et al., 2000; Li, Nahas, Anderson, Kozel, & George, 2004; Rumi et al., 2005; Su et al., 2005). One open-label study demonstrated 2-month improvements in MDD and PTSD using 1 Hz or 5 Hz to the left DLPFC (Rosenberg et al., 2002), but that protocol included only 600 pulses per day and 10 treatments, which is an inadequate dose by current standards.

We recently described our clinical experience with left-sided 5 Hz for the treatment of MDD, and confirmed efficacy of 5 Hz versus standard 10 Hz in severely depressed patients ($g = 1.95$; Philip et al., 2015). This pulse frequency was chosen based on the literature above, to incorporate potential benefits of improved tolerability and reduced seizure risk compared to higher frequency stimulation. The 5-Hz treatment was used to address high levels of comorbid anxiety or activation that emerged during 10-Hz treatment, informed by the literature showing lower frequencies might be more anxiolytic (e.g., Boggio et al., 2010).

Building on our prior work, we investigated 5-Hz rTMS to the left DLPFC as a treatment for 10 veterans with comorbid PTSD and MDD to describe clinical outcomes and safety features.

Method

Participants

We reviewed charts of the first 10 patients (age $M = 58.1$ $SD = 13.9$ years) with comorbid PTSD and MDD who had received 5-Hz rTMS as part of their clinical care at the Providence VA Psychiatric Neuromodulation Clinic (Providence, RI) from September 2012 through October 2014. Patients treated were 80% male, 90% Caucasian, and had a variety of overlapping trauma exposures consistent with VA populations (Table 1). Prior to rTMS, all patients met current criteria for PTSD, were in treatment at the Providence VA PTSD clinic, inclusive of medications and psychotherapy. Clinical diagnoses were confirmed through clinical interview by a psychiatrist (N.S.P.) with experience treating MDD and PTSD corroborated with clinical rating scales (below). Written consent for the clinical procedure was obtained prior to rTMS initiation. The Providence VA Institutional Review Board approved this chart review.

Procedures

Clinical patients were referred to the neuromodulation service if they demonstrated MDD symptoms despite adequate pharmacology (defined as > 6 weeks of an adequate dose of an antidepressant), if they were considering electroconvulsive therapy, or if they were unable to tolerate pharmacotherapy. Following clinic policy, patients had no contraindications to rTMS. Individual motor threshold (MT) was established at the first session, and treatments were delivered at 120% MT to the left DLPFC, with approximate coil position over F3 using standard 10/20 electroencephalogram (EEG) coordinates. Stimulation was delivered in 4-s trains, with a 12-s intertrain interval for 3,000 pulses per session. If significant improvement was not observed by the 15th session, pulses per session were increased to 4,000, and the intertrain interval reduced to 11 s to complete each session within 1 hr. All patients were offered up to 36 rTMS treatments (i.e., 30 plus 6 taper treatments over 3 weeks).

Measures

Symptom severity was assessed following standard clinic procedures, which included patient-rated symptom scales at baseline (i.e., at time of consultation or, if there was > 1 month between consultation and rTMS, scales were obtained prior to the first session), following every five treatments, and at the end of the treatment series. PTSD symptoms were rated using the PTSD Checklist (PCL, Cronbach's $\alpha = .94$; Weathers et al., 2013), and depression symptoms were measured using the Quick Inventory of Depressive Symptomatology (QIDS; Cronbach's $\alpha = .86$; Rush et al., 2003). For these measures, we used a reliable change defined as symptom score change of 10 for the PCL (Weathers et al., 2013) and > 5 for the QIDS.

Data Analysis

A paired t test was used to evaluate change in symptom scores comparing baseline to endpoint. The Reliable Change Index (RCI; Jacobson & Truax, 1991) was used to evaluate effect size of treatment effects given the small sample size of the study, where RCI values > 1.96 represented significant results. Patients could elect to stop treatment prior to completion of the full 36-treatment course as with any clinical procedure elected voluntarily. Therefore, study data were censored at the point of last treatment, and these censored values were used to compare baseline to endpoint response in the sample. There were no missing data. We also calculated the percentage of patients with at least 50% improvement in PTSD symptoms compared to baseline, comparable to operational definitions of clinical response in the MDD literature (Rush et al., 2003).

Results

Patients exhibited moderate to severe symptoms at baseline, with a mean PCL score of 57.70, $SD = 12.11$, and a mean QIDS score of 21.5, $SD = 5.54$ (Table 2). The mean number of rTMS treatments was 30.80 ($SD = 7.11$, range = 18 to 36), and six (60.0%) patients completed the full course of 36 sessions (Table 2). We observed a significant baseline-to-endpoint improvement in PTSD and MDD (PCL = 8/10 participants with reliable reductions in symptoms, $p = .003$, and QIDS = 6/10 patients with reliable reductions, $p = .005$), and reductions in scores to $M = 38.60$, $SD = 18.14$ (PCL), and $M = 13.40$, $SD = 8.21$ (QIDS), consistent with mild symptoms. Five patients (50%) demonstrated at least 50% improvement in depressive symptoms, and 4 (40%) demonstrated at least 50% improvement in PTSD symptoms. One patient demonstrated worsening in depressive symptoms, with QIDS increased from 25 (baseline) to 30 (endpoint), and essentially no change in PCL of 74 at baseline to 75 at endpoint. No patients stopped treatment due to intolerable side effects; there were no seizures observed; and no patients stopped early due to lack of efficacy. Medication changes during rTMS were minor; in three patients bupropion dose was reduced after emergence of insomnia or anxiety.

Discussion

These open-label case series data showed preliminary efficacy and tolerability of 5-Hz rTMS therapy in a group of 10 patients with comorbid PTSD and MDD. Although we recognize that outcomes in an open-label case series should be interpreted with caution, these data suggested that 5-Hz rTMS appeared to reduce symptoms of MDD and PTSD, and suggested 5 Hz may be well suited for this comorbidity. The outcomes reported here were consistent with our prior experience with 5 Hz in patients with MDD with comorbid anxiety (Philip et al., 2015), which found this parameter was efficacious in reducing symptoms in a patient population with an otherwise poor prognosis for clinical response.

The potential impact of the 5Hz parameter merits discussion. This frequency approximates θ band (4–7 Hz) signals on EEG; several lines of investigation suggest that negative emotion is associated with abnormal θ activity, including excess frontal θ and inadequate θ modulation of β signals in PTSD (Cohen et al., 2013). Entrainment of endogenous oscillatory rhythms has been proposed as a mechanism of action of rTMS (Leucter, Cook, Jin, & Phillips, 2013).

The 10-Hz stimulations entrain α rhythms (8–12 Hz; Thut et al., 2011); therefore, 10 Hz may not be appropriate for modulating θ activity. Hence, 5-Hz rTMS, in theory, has more potential to modulate oscillatory activity in individuals with PTSD than 10 Hz.

The limitations to this study were those inherent in a case series: Treatments were open-label and some component of the response was likely due to placebo. Most patients, however, had severe MDD and PTSD, and patients with more severe illness may have reduced placebo response (Brunoni, Lopes, Kaptchuk, & Fregni, 2009). Because all patients were on medications, rTMS may have improved the efficacy of concurrent psychopharmacology rather than being the active ingredient in change. Unfortunately, we also did not collect data on ongoing therapy, but an additional possibility is that rTMS facilitated beneficial participation in psychotherapy if that occurred. Based on the small sample size we were unable to evaluate differential patterns of response based on trauma type (e.g., combat PTSD vs. military sexual trauma). Nevertheless, this is an important area for future research.

Taken together, these chart review data supported the use of 5-Hz rTMS in veterans with MDD and PTSD. Controlled studies are needed to confirm efficacy in larger and more diverse samples to examine the presence and durability of symptomatic improvement, effects of laterality, and the relationship between frequency of sessions and treatment outcomes.

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References

- Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychological Medicine*. 2014; 44:225–239. [PubMed: 23507264]
- Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanhã C, Fregni F. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *Journal of Clinical Psychiatry*. 2010; 71:992–999. [PubMed: 20051219]
- Brunoni AR, Lopes M, Kaptchuk TJ, Fregni F. Placebo response of non-pharmacological and pharmacological trials in major depression: A systematic review and meta-analysis. *The Public Library of Science One*. 2009; 4:e4824. [PubMed: 19293925]
- Cohen H, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: A double-blind, placebo-controlled study. *American Journal of Psychiatry*. 2004; 161:515–524. [PubMed: 14992978]
- Cohen JE, Shalev H, Admon R, Hefetz S, Gasho CJ, Shachar LJ, Friedman A. Emotional brain rhythms and their impairment in post-traumatic patients. *Human Brain Mapping*. 2013; 34:1344–1356. [PubMed: 22331598]
- Grisaru N, Amir M, Cohen H, Kaplan Z. Effect of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. *Biological Psychiatry*. 1998; 44(1):52–55. [PubMed: 9646883]

- George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li XB, Arana GW, Risch SC, Ballenger JC. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry*. 2000; 48(10):962–970. 10.1016/S0006-3223(00)01048-9. [PubMed: 11082469]
- Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems and barriers to care. *US Army Medical Department Journal*. 2008;7–17. [PubMed: 20088060]
- Jacobson NS, Truax P. Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*. 1991; 59:12–19. [PubMed: 2002127]
- Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. *Frontiers in Human Neuroscience*. 2013; 26:37. [PubMed: 23550274]
- Li X, Nahas Z, Anderson B, Kozel FA, George MS. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depression and Anxiety*. 2004; 20:98–100. [PubMed: 15390210]
- Magruder KM, Frueh BC, Knapp RG, Davis L, Hamner MB, Martin RH, Arana GW. Prevalence of posttraumatic stress disorder in Veterans Affairs primary care clinics. *General Hospital Psychiatry*. 2005; 27:169–179. [PubMed: 15882763]
- McCann UD, Kimbrell TA, Morgan CM, Anderson T, Geraci M, Benson BE, Post RM. Repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Archives of General Psychiatry*. 1998; 55:276–279. [PubMed: 9510224]
- Philip NS, Carpenter SL, Tyrka AR, Sanchez G, Price LH, Carpenter LL. 5 Hz repetitive transcranial magnetic stimulation to left prefrontal cortex for major depression. *Journal of Affective Disorders*. 2015; 186:13–17. [PubMed: 26210705]
- Rosenberg PB, Mehndiratta RB, Mehndiratta YP, Wamer A, Rosse RB, Balish M. Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2002; 14:270–276. [PubMed: 12154150]
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*. 2009; 120:2008–2039. [PubMed: 19833552]
- Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, Marcolin MA. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: A double-blind placebo-controlled study. *Biological Psychiatry*. 2005; 57:162–166. [PubMed: 15652875]
- Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*. 2003; 54:573–583. [PubMed: 12946886]
- Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: A randomized, double-blind, sham-controlled trial in Chinese patients. *Journal of Clinical Psychiatry*. 2005; 66:930–937. [PubMed: 16013911]
- Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. *Archives of General Psychiatry*. 2010; 67:614–623. [PubMed: 20530011]
- Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J. Rhythmic TMS causes local entrainment of natural oscillatory signatures. *Current Biology*. 2011; 21:1176–1185. [PubMed: 21723129]
- Watts BV, Landon B, Groft A, Young-Xu Y. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Brain Stimulation*. 2012; 5:38–43. [PubMed: 22264669]

- Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. *Journal of Clinical Psychiatry*. 2013; 74:e541–e550. [PubMed: 23842024]
- Weathers, FW.; Litz, BT.; Keane, TM.; Palmieri, PA.; Marx, BP.; Schnurr, PP. The PTSD Checklist for DSM-5 (PCL-5). Washington, DC: U.S. Department of Veterans Affairs, the National Center for PTSD; 2013.

Table 1

Demographic Characteristics of 10 Veterans Who Received rTMS

Variable	<i>n</i>
Gender (male)	8
Race (Caucasian)	9
Combat-related PTSD	6
Noncombat-related PTSD	3
PTSD from military sexual trauma	2

Note. rTMS = repetitive transcranial magnetic stimulation; PTSD = posttraumatic stress disorder.

Table 2

Baseline, Endpoint, Reliable Change Symptom Scores, and Number of rTMS Treatments for 10 Subjects

S	QIDS			PCL			n rTMS
	Baseline	Endpoint	Rel. change	Baseline	Endpoint	Rel. change	
1	15	12	–	53	42	+	36
2	15	7	+	41	27	+	28
3	12	5	+	45	38	–	36
4	25	20	–	74	64	+	36
5	25	4	+	75	37	+	18
6	29		–	56	45	+	23
7	23	10	+	51	22	+	36
8	25	30	–	74	75	–	36
9	19	8	+	47	20	+	36
10	27	14	+	61	16	+	23

Note. QIDS = Quick Inventory of Depressive Symptoms, Self-Report; PCL = PTSD Checklist; Rel = reliable.