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One hertz versus ten hertz repetitive TMS treatment of PTSD: A randomized clinical trial

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ABSTRACT

The purpose of this trial was to test whether right prefrontal cortex 1 Hz versus 10 Hz rTMS provides a significantly greater improvement in PTSD symptoms and/or function. Veterans 18 to 50 years of age suffering from PTSD were randomized to right prefrontal 1 Hz rTMS [2400 pulses/session] versus right prefrontal 10 Hz rTMS [2400 pulses/session]. The treatments were performed 5 days a week for 6 weeks with a 3-week taper using the NeuroStar system. There were one month and three months post treatment follow-up evaluations. Forty-four participants were enrolled with 17 being randomized to 1 Hz rTMS and 18 to 10 Hz rTMS. Both groups had significant improvement in PTSD and depression scores from baseline to the end of acute treatment. The 10 Hz group but not the 1 Hz group demonstrated significant improvement in function. Although both groups demonstrated significant improvement in PTSD and depression symptoms, a significant advantage for either the 1 Hz or 10 Hz frequency group on any of the scales acquired was not demonstrated. Further work is required with larger samples sizes to test whether low or high frequency is superior or if individual differences would indicate the more effective frequency.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a severe brain disorder that is a significant public health problem. National lifetime prevalence rates of PTSD in the community have ranged from 7.8% (Kessler et al., 1995, 2005) to 6.4% (Pietrzak et al., 2011). In military samples, the chronicity of the disorder has been demonstrated by the National Vietnam Veterans Longitudinal Study which reported that between 4.5–11.2% of males and 6.1–8.7% of females still suffer from current war-zone PTSD (Marmar et al., 2015). More recent conflicts likewise demonstrate a very high prevalence rate. A meta-analysis has estimated prevalence of PTSD from deployments to Iraq and Afghanistan to be 23% (Fulton et al., 2015). In addition to its high prevalence rate, PTSD results in significant functional impairment (Kozel et al., 2016; Rodriguez et al., 2012; Shea et al., 2010).

There are several treatment approaches including psychotherapy (Foa et al., 1999; Rauch et al., 2009; Resick et al., 2002, 2017; Schnurr et al., 2007) and medication (Shiner et al., 2018) that have demonstrated benefit in treating PTSD, but a significant portion of patients continue to suffer disabling symptoms (Steenkamp et al., 2015). Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe and non-invasive technique that has demonstrated promise and effectiveness in treating a number of neuropsychiatric conditions - especially Major Depressive Disorder (MDD) (Gaynes et al., 2014; George et al., 2010;

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Kozel and George, 2002; O'Reardon et al., 2007). There have been a number of small studies using multiple treatment parameters that have demonstrated the effectiveness of rTMS for PTSD to varying degrees (Clark et al., 2015; Karsen et al., 2014; Kozel, 2018) with some of the strongest support involving the combination of rTMS with Cognitive Processing Therapy for PTSD (Kozel et al., 2018). The majority of studies of rTMS for PTSD have stimulated over the right prefrontal cortex versus the left prefrontal cortex that is more commonly targeted in depression (Kozel, 2018). A critical question is whether low or high frequency rTMS will result in better outcomes in the treatment of PTSD. Stimulation applied at 1 Hz over the prefrontal cortex produces an inhibitory effect on the subjacent brain structures (Kozel et al., 2009), while higher frequencies produce an excitatory brain effect (Speer et al., 2000). One study by Cohen et al. directly compared 1 Hz versus 10 Hz to the right dorsolateral prefrontal cortex (rDLPFC) in PTSD. Due to the difference in number of pulses used for 1 Hz (100 pulses/day for 10 days) and 10 Hz (200 pulses/day for 10 days) rTMS, the 10 Hz group improvement over the 1 Hz group may have been due to differences in pulse number versus frequency (Cohen et al., 2004). Yan et al. performed a review and meta-analysis of different frequencies of rTMS for PTSD to assess which were more effective. They found that the different frequencies used were safe and likely effective but identified the need for additional study (Yan et al., 2017). Thus, for this study, 1 Hz rDLPFC was compared to 10 Hz rDLPFC rTMS in participants with PTSD using the same number of pulses, time for treatment, dose, and treatment location for both groups. The primary outcomes were change in PTSD symptoms as assessed by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2013) and the functional status of veterans as measured using the Inventory of Psychosocial Functioning (IPF) (Rodriguez et al., 2012).

2. Methods

2.1. Participants

Veteran outpatients 18 to 50 years of age suffering from PTSD with and without depressive symptoms were recruited from the James A. Haley Veterans' Administration Hospital outpatient clinics and surrounding community. Participants were phone screened for safety and appropriateness of trial. In addition, the clinical information in the Veterans' Administration electronic medical records was reviewed. Veterans eligible to enroll and interested in participating in the study were scheduled for the initial screening/baseline visit and sent a copy of the informed consent. Those found to not be eligible or not interested in the study were referred to their primary mental health clinician or offered contact information for clinical care, if not already established with a provider.

Participants were required to meet all of the inclusion criteria in order to participate in this study, which included being male or female between the ages of 18–50 years. They had to meet DSM-5 criteria for PTSD as determined by clinical interview using CAPS for DSM-5 and have a PTSD checklist for DSM-5 (PCL-5) score greater than or equal to 45. Participants were also required to be on a stable medication regimen and psychotherapy for at least one month as well as be able to maintain this regimen for the duration of the treatment portion of the trial. The stability of the treatment regimen was assessed as part of the baseline history by an experienced psychiatrist. All participants had capacity to provide written informed consent. Candidates meeting any of the exclusion criteria at baseline were excluded from study participation. During the study, veterans could not be enrolled in an acute treatment of PTSD using evidence-based psychotherapy including Prolonged Exposure Therapy (PE), Cognitive Processing Therapy (CPT), or Eye Movement Desensitization and Reprocessing (EMDR). For safety reasons, the standard exclusions for rTMS studies were applied and included: any metal or device implants that would increase risk of rTMS; history of epilepsy or seizure disorder, mass brain lesions, cerebrovascular accident, metal in the skull, a history of major head trauma defined as greater than mild TBI; any neurologic or medical condition likely to increase risk of rTMS; taking any medication that significantly lowered the seizure threshold (e.g., stimulants, tricyclic antidepressants (TCA), theophylline, first generation antipsychotics, etc.); or inability to determine the motor threshold in the subject. Many psychiatric comorbidities were allowed with the exceptions of: suicidal risk that precludes safe participation defined as clinical impression that the subject is at significant risk for suicide; lifetime history of schizophrenia, schizoaffective, other psychotic disorder, bipolar disorder type I or II, dementia, or dissociative disorders; personality disorder so severe that participant would be unlikely to be able to complete study protocol requirements; and history of problematic Substance Use Disorder in the last 3 months except for nicotine and caffeine. Female participants could not be pregnant, breast feeding, or not using medically accepted form of contraception when engaged in sexual intercourse. Finally, veterans could not have received prior Vagus Nerve Stimulation, Electroconvulsive Therapy, or be enrolled in another PTSD treatment study.

2.2. Procedures

2.2.1. Overview

The screening/baseline visit began by acquiring written informed consent. Subsequently, evaluations to determine safety and appropriateness, as well as clinical ratings and laboratory testing (Urine Drug Screen (UDS) and urine pregnancy testing) were performed. Those meeting eligibility criteria, including ability to obtain motor threshold, were randomized to 1 Hz versus 10 Hz stratified by significant depression (Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) > 19). Participants were treated for 5 days a week for 6 weeks with a 3-week taper (3 treatments per week for 1 week, 2 treatments per week for 1 week, and then 1 treatment per week for 1 week). Participants underwent clinical evaluation weekly for clinical effect during the treatment, at the end of the taper and at 1- and 3-months post treatment. In addition, safety was assessed prior to each treatment and/or evaluation.

2.2.2. Screening/Baseline visit

Participants first were informed about the study and given an opportunity to have all questions answered. When the veteran understood the protocol and was comfortable with participating, written consent was obtained. After consent, the Veteran underwent the following evaluations for safety and to confirm the appropriateness of entry into the trial: basic demographics; Transcranial Magnetic Stimulation and Safety Screen (TASS) (Keel et al., 2001); a history and physical by a TMS credentialed physician; and a UDS for all participants and a urine pregnancy test for all women of child-bearing potential. Clinical evaluations consisted of measures of PTSD, function, depression, traumatic brain injury (TBI), pain, and handedness with the Annette Handedness Scale (Annett, 1970). Clinician Administered PTSD Scale (CAPS-5) (Blake et al., 1995; Weathers et al., 2013) was used for baseline/screening as well as for post treatment evaluation. The CAPS-5 was developed by the National Center for PTSD and has become the "gold standard" for assessing PTSD in individuals over age 15. The evaluation provided a measure of symptom severity and sufficient criteria to determine whether a current diagnosis of PTSD was valid. The PCL-5 was used at the Screening/Baseline visit and during each Clinical Evaluation to assess PTSD symptoms (Blevins et al., 2015; Wortmann et al., 2016). This measure provided a minimum score for PTSD symptom severity as well as a secondary measure of PTSD symptoms. The functional status of veterans was measured using the Inventory of Psychosocial Functioning (IPF) (Rodriguez et al., 2012). The IPF is an 80 question self-report scale that assessed function in the areas of family, work, friendships and socializing, parenting, education, self-care, and romantic relationships with spouse or partner.

The Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and Quick Inventory of Depressive Symptomatology-Self Report version (QIDS-SR) (Rush et al., 2003, 2005) assessed the severity of depressive symptoms. The MADRS score was also used to stratify the randomization (MADRS > 19 for depressed group) as well as a secondary measure of depressive symptoms. The QIDS-SR assessed change in depressive symptoms during the trial. The QIDS-SR was administered during initial screening and during the Clinical Evaluation visits to track any change in depressive symptomatology. In addition, a physical pain score was obtained at baseline/screening and at every Clinical Evaluation. The participant was asked to rate overall physical pain in the last 7 days on a scale of 0 to 10, with 0 corresponding to no pain and 10 corresponding to the most severe pain ever experienced. The Neurobehavioral Symptom Inventory (NSI) (King et al., 2012) assessed possible post-concussive symptoms associated with mild TBI. The scale is a 22 item self-report measure.

2.2.3. Evaluations

A safety assessment was performed prior to each treatment or at any time clinically indicated (e.g., significant side effect during or between treatments) consisting of asking about: 1) side effects, 2) changes in medication, 3) changes in medical conditions, and 4) changes in psychiatric symptoms (e.g., suicidality, plans to harm others). The Clinical Evaluations were performed after every 5 treatments for first 30 treatments, at the end of treatment taper, and at 1- and 3-month post-treatment follow-ups. The Clinical Evaluations consisted of PCL, QIDS-SR, and pain score on every evaluation visit. The IPF was obtained at baseline, after 15 treatments, after 30 treatments, at the end of treatment, and at the post treatment 1- and 3- month follow-ups. CAPS, MADRS, and NSI were obtained at baseline/screening and after the 30th treatment.

2.2.4. Repetitive Transcranial Magnetic Stimulation

The veterans were placed in the NeuroStar chair (Neuronetics, Malvern, PA) with hearing protection in place, and the motor threshold (MT) was determined. The MT was defined as the stimulus intensity of stimulation that induces visually perceptible movement of the contralateral (in this case, the left) abductor pollicus brevis (APB) 50% of the time (Pridmore et al., 1998). Once the spot of maximal contraction was determined, a PEST algorithm (Mishory et al., 2004) was used to determine the MT four times. The mean of these four MT's served as the MT used in the study. After motor threshold determination, a stratified randomization was performed based on significant depressive symptoms, which were defined as a MADRS score > 19. Using a computer randomization schedule, an investigator who was independent of any treatments generated two random lists of active and sham index cards (i.e., with and without significant depression) that were placed in envelopes prior to the trial beginning. When the participant was ready to begin the first treatment, the treater opened the next envelope in line for the appropriate group to determine the randomization assignment. The participant knew the assignment as well as the treater, but the investigators assessing all the clinician rating scales were masked to assignment.

After the randomization, the stimulator coil was positioned over the dorsolateral prefrontal cortex - DLPFC (Brodmann Area 9/46). The right dorsolateral prefrontal cortex was targeted using head measurements and a computerized program that provides coordinates for the approximate F4 electrode site under the 10/20 electrode convention (Beam et al., 2009). The dose of rTMS over the DLPFC was 110% of MT. The intensity of 110% MT was chosen as our sample was limited to 18–50 years of age. The 110% MT was thought to be a reasonable option to balance adequate dose to overcome distance from coil to cortex (Kozel et al., 2000; Nahas et al., 2004) and tolerability. For those randomized to 1 Hz frequency, the 1 Hz rTMS was continuous for 40 min for a total of 2400 pulses/session. For those randomized to 10 Hz, rTMS was 4 s on and 36 s off for 40 min for a total of 2400 pulses/session. For both groups, the total number of treatments per participant was 36, and the total number of pulses per participant was 86,400. The interstimulus interval of the 10 Hz group was extended past the standard 26 s to 36 s in order that the time of treatments was equal for both groups. Both pulse parameters were within the safety profile of rTMS (Rossi et al., 2009; Wassermann, 1998). If subjects were initially intolerant of 110% MT, then the coil could be rotated to find a more tolerable position. If that did not make the rTMS tolerable, then the rTMS output was reduced to 100% of MT to enable the veteran to become used to the stimulation. All participants were quickly raised to 110% MT.

For return TMS visits, participants were interviewed for side effects, medication changes, medical and psychiatric changes. A TMS credentialed physician reviewed any changes prior to treatment. After hearing protection was in place, the TMS coil was positioned based on previous measurement and the patient underwent treatment. Participants were allowed to continue current medications as long as they did not increase the risk of rTMS and were held constant during the six weeks of the trial. Participants were compensated for their time in a prorated manner up to $350 if all visits were completed.

2.3. Data analysis

Data were double entered into an Access database and cross-checked for discrepancies prior to analysis. Discrepancies were resolved by returning to primary sources. Descriptive statistics were reported for the demographic and clinical characteristics of the obtained sample, including age, sex, education, employment, baseline function (IPF), baseline severity of PTSD (CAPS and PCL-5), baseline depression (QIDS-SR, MADRS), baseline pain (Pain Score), and baseline post-concussive symptoms (NSI). Categorical variables were expressed as frequencies with percentages, and continuous variables as means with standard deviations. To assess how well the samples were randomized, the two active treatment groups were compared on baseline variables including demographics and the outcomes. No missing data imputation was performed. Chi-square tests and Fisher's Exact Test (whenever cell count is less than 5) were used to compare categorical variables*; t-tests were* used to compare continuous variables within and between groups.

For the primary hypothesis, a Welch two-sample *t*-test that assumes unequal variances was used to investigate whether 1 Hz rTMS versus 10 Hz rTMS provides a significantly greater improvement in PTSD symptoms (CAPS score) and/or function (IPF score) by 30th treatment. Improvement in an outcome was primarily defined as change in scores from pre-treatment baseline to post 30 treatments. The presence of a significant improvement from baseline to post 30 within each treatment group was also tested by performing a paired *t*-test.

Secondarily, improvement was also evaluated as the proportion of responders and remitters by post 30 treatments. Response was defined as score reduction of 50% (QIDS-SR and MADRS) or 30% (PCL-5 and CAPS-5). Remission was defined using the following score thresholds: 5 or less for QIDS-SR; 10 or less for MADRS; 33 or less for PCL-5; and no longer meeting criteria of PTSD on the CAPS-5. Other secondary analyses were similarly performed on QIDS-SR, pain, NSI, MADRS and PCL-5 scores.

Additionally, sustainability of these treatment effects was investigated using loess (local least square regression), a non-parametric approach suitable for smoothing our numerical vector, of repeated observations. Loess fits least squares regressions to localized subsets of outcome data to produce graphical description of nonlinear empirical relationships (Jacoby, 2000). The graphical displays included smooth curves plus 95% confidence bounds which allowed us to evaluate a statistically significant difference between the mean trajectory over time versus its starting baseline score. We preferred the loess method to the simple pointwise plot of estimates of the mean for two reasons: addition of pointwise 95% confidence intervals will result in less efficient use of data compared to the loess estimates that are based on

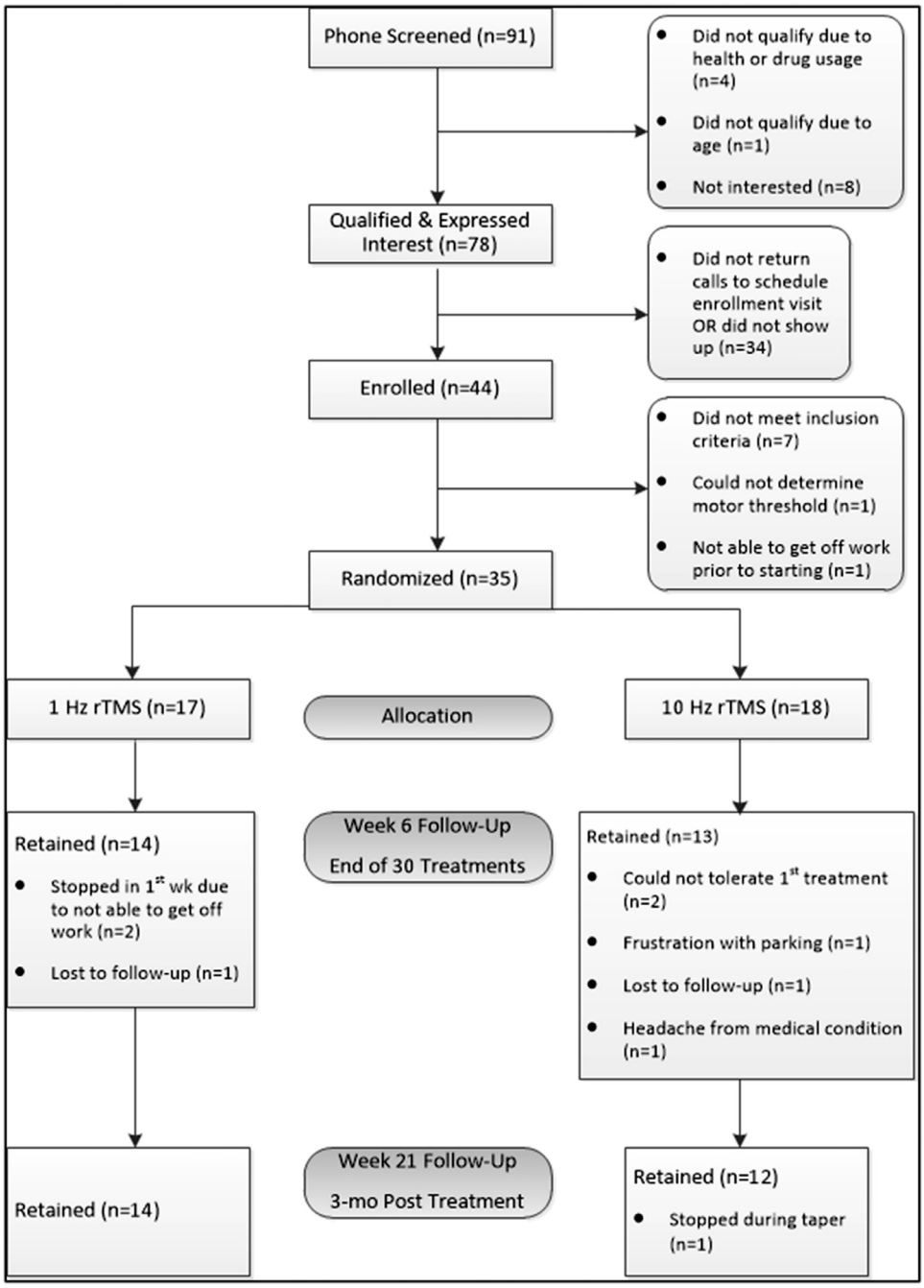

Fig. 1. rTMS Trial CONSORT Diagram.

regressions in local neighborhood of each time point; and an alternative use of standard error of the mean around each estimate is not appropriate for inference as it underestimates the variability between individuals within the study sample (Diong et al., 2018; Nagele, 2003).

The proportions of side effects and dropouts per group were captured. Given the low proportions, a nonparametric binomial test was used to test for significant group difference in their proportions. Two-sided p-values were calculated and used to assess statistical significance defined as $p < 0.05$. All statistical analysis was carried out using the R statistical application.

3. Results

3.1. Patient population

Participant recruitment, enrollment, assignment to study conditions, and study retention are presented as a Consort diagram in Fig. 1. Forty-four participants were enrolled with data being acquired from September 2014 until February 2018. Nine veterans were not randomized with six failing to meet diagnostic criteria by CAPS-5, one was determined to have a history of seizures, one was unable to get off work, and one was unable to have motor threshold determined. Of the 35 randomized, 17 were allocated to the 1 Hz group and 18 to the 10 Hz group. Of the 17 veterans in the 1 Hz group, 14 completed the primary endpoint and all subsequent visits. The three participants who did not reach the primary endpoint included two that stopped due to work

Table 1
Veterans' characteristics and baseline rating scales by treatment groups.

	Mean (SD) or Count (%) 1 Hz rTMS (n = 17)	10 Hz rTMS (n = 18)	Group difference test
Age	38.0 (6.7)	39.0 (6.0)	*t (32) = −0.65, p = 0.52*
Gender			*OR = 0.62, p = 0.71*[*]
Female	4 (23.5)	6 (33.3)	
Male	13 (76.5)	12 (66.7)	
Race			*χ^2 (1) = 0.77, p = 0.38*
White	11 (64.7)	9 (50)	
Non-white	6 (35.3)	9 (50)	
Ethnicity			*OR = 1.6, p = 0.71*[*]
Non-Hispanic	13 (76.5)	12 (66.7)	
Hispanic	4 (23.5)	6 (33.3)	
Education			*χ^2(4) = 1.9, p = 0.81*[*]
Less than high school	0 (0)	0 (0)	
High school graduate/GED	2 (13)	2 (12)	
Some college but no degree	3 (20)	7 (41)	
Bachelor's degree	6 (40)	4 (23)	
Master's degree	2 (13)	2 (12)	
Ph.D. or other professional degree	0 (0)	0 (0)	
Employment			*χ^2(1) = 1.4, p = 0.24*
Not working	9 (52.9)	13 (72.2)	
Working (part- or full-time)	8 (47.1)	5 (27.8)	
Service years	7.4 (5.6)	11.2 (6.6)	*t(31) = −1.8, p = 0.08*
Baseline rating scales			
CAPS-5	47.8 (10.9)	47.6 (13.3)	*t(32.3) = 0.07, p = 0.95*
IPF	3.7 (0.7)	4.1 (1.3)	*t(25.5) = −1.21, p = 0.24*
MADRS	32.9 (8.0)	31.1 (9.0)	*t(32.9) = 0.66, p = 0.52*
NSI	39.7 (12.6)	41.4 (15.9)	*t(32.0) = −0.36, p = 0.72*
PCL-5	59.2 (8.3)	59.9 (8.9)	*t(33.0) = −0.24, p = 0.81*
QIDS-SR	15.2 (4.5)	16.9 (3.7)	*t(31.2) = −1.18, p = 0.25*

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; IPF: Inventory of Psychosocial Functioning; MADRS: Montgomery-Asberg Depression Rating Scale; NSI: Neurobehavioral Symptom Inventory; PCL-5: PTSD checklist for DSM-5; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self Report

[*] Fisher's Exact Test: Alternative hypothesis: true odds ratio is not equal to 1.

Table 2
Within-group comparison of outcomes (baseline vs. post-30 treatment) [#] and between-group comparison of their change scores (1 Hz vs. 10 Hz)[*].

Variable 1 Hz vs. 10 Hz:	Mean (SD) 1 Hz	10 Hz	Mean difference (95% CI)	t-statistic (df)	P-value
CAPS-5 Change-score	−9.4 (14.5)	−10.9 (11.7)	1.5 (−8.9, 11.9)	0.3 (24.5)	0.77
IPF Change-score	−0.40 (0.77)	−0.50 (0.58)	0.10 (−0.43, 0.64)	0.4 (23.9)	0.69
	Baseline	Post 30			
1 Hz rTMS (n = 17)					
CAPS-5	48 (11)	39 (18)	−9.4 (−18, −1.1)	−2.4 (13)	0.03
IPF	3.7 (0.73)	3.3 (0.98)	−0.4 (−0.84, 0.046	−1.9 (13)	0.075
MADRS	33 (8)	22 (12)	−11 (−17, −5.7)	−4.3 (13)	< 0.001
NSI	40 (13)	35 (15)	−6.6 (−14, 0.98)	−1.9 (13)	0.082
PCL-5	59 (8.3)	42 (19)	−18 (−27, −9.5)	−4.4 (13)	< 0.001
QIDS-SR	15 (4.5)	11 (5.3)	−4.7 (−7.1, −2.3)	−4.2 (13	0.001
Pain score	5.7 (2.5)	6 (2.3)	−0.5 (−1.3, 0.28)	−1.4 (13)	0.19
10 Hz rTMS (n = 18)					
CAPS-5	48 (13)	40 (21)	−11 (−18, −3.9)	−3.4 (12)	0.006
IPF	4.1 (1.3)	3.6 (1.1)	−0.5 (−0.85, −0.16)	−3.2 (12)	0.008
MADRS	31 (9)	24 (14)	−8.6 (−15, −2.5)	−3.1 (12)	0.01
NSI	41 (16)	30 (17)	−11 (−18, −4.4)	−3.6 (12)	0.004
PCL-5	60 (8.9)	38 (21)	−22 (−33, −10)	−4.1 (12)	0.001
QIDS-SR	17 (3.7)	10 (6)	−6.8 (−9.6, −4.1)	−5.4 (12)	< 0.001
Pain score	5.3 (2.5)	4.8 (2.6)	−0.23 (−0.84, 0.38)	−0.82 (12)	0.43

Value entries contain rounding errors

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; IPF: Inventory of Psychosocial Functioning; MADRS: Montgomery-Asberg Depression Rating Scale; NSI: Neurobehavioral Symptom Inventory; PCL-5: PTSD checklist for DSM-5; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self Report

Keys:

[#] two-sided paired *t*-test used

[*] two-sided 2-sample *t*-test used

Table 3
Comparison of veterans' response and remission rates by 30th treatment using Fisher's Exact Test*.

	Count(percent)		Group difference test
	1 Hz rTMS (n = 17)	10 Hz rTMS (n = 18)	
Response by 30th treatment			
CAPS-5			*OR = 1.11, p = 1.0*
Response	4 (29)	4 (31)	
No response	10 (71)	9 (69)	
MADRS			*OR = 0.81, p = 1.0*
Response	5 (36)	3 (25)	
No response	9 (64)	9 (75)	
PCL-5			*OR = 0 0.60, p = 0.70*
Response	6 (43)	4 (31)	
No response	8 (57)	9 (69)	
QIDS-SR			*OR = 2.08, p = 0.44*
Response	4 (29)	6 (46)	
No response	10 (71)	7 (54)	
Remission by 30th treatment			
CAPS-5			*OR = 1.79, p = 0.67*
Remission	3 (21)	4 (33)	
No remission	11 (79)	8 (67)	
MADRS			*OR = 0.76, p = 1.0*
Remission	4 (29)	3 (23)	
No remission	10 (71)	10 (77)	
PCL-5			*OR = 1.11, p = 1.0*
Remission	4 (29)	4 (31)	
No remission	10 (71)	9 (69)	
QIDS-SR			*OR = 1.60, p = 0.68*
Remission	3 (21)	4 (31)	
No remission	11 (79)	9 (69)	

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; MADRS: Montgomery-Asberg Depression Rating Scale; PCL-5: PTSD checklist for DSM-5; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self Report

* Fisher's Exact Test: Alternative hypothesis: true odds ratio is not equal to 1.

concerns and one who was lost to follow-up. Of the 18 veterans in the 10 Hz group, 13 completed the primary endpoints with one of those not completing the taper or follow-up visits. The five who did not reach the primary endpoint included two that could not tolerate the first treatment, one stopped due to headaches from another medical condition, one was too frustrated by parking, and one was lost to follow-up. A total of 27 who completed the primary end points constituted the final sample for testing the primary hypothesis, and they had no missing data on the tested outcomes.

There were no significant differences between treatment groups on their baseline assessment scores, including demographic and baseline rating scales (Table 1).

3.2. Effects at the end of 30 treatments

The results of the two-sample t-tests failed to reject the null hypothesis of no significant difference between the two treatment groups (Table 2) in improvement on the CAPS (p = 0.77) and IPF (p = 0.69) scores from baseline to post-30.

The secondary analyses, however, yielded some significant findings with respect to the primary outcomes (Table 2). For the 1 Hz group, a paired t-test indicated that PTSD symptoms as measured by CAPS scores were significantly lower by the 30th treatment (improved, p = 0.03). The scores on MADRS, PCL-5, and QIDS-SR also significantly improved. The change in function as measured by the IPF, however, did not quite reach significance (p = 0.075) in the 1 Hz group. In contrast, the 10 Hz group demonstrated significant improvement from baseline to the 30th treatment on all outcomes listed except pain score. (Table 2) Similarly, there was failure to reject the null hypothesis of no relationship between the groups on either response or remission rate by 30th treatment (Table 3).

3.3. Effects at 3 months post treatment

Figs. 2 and 3 present trajectories of study outcomes using loess smooth curves (with 95% confidence bounds), which track changes in repeated assessment scores from baseline to 3 months post treatment. The top graph of Fig. 2 fitted one trajectory to the whole sample (combined groups). It demonstrated that the average PCL-5 score declined below the lower 95% confidence limit of the baseline estimate (lower score is better) and stayed below this limit for up to 3 months post treatment.

The bottom graph (Fig. 2) displays the loess curve split by group to investigate group difference in the trends. By showing overlap of their 95% confidence bounds everywhere the curves failed to reject the null hypothesis of no difference in the effects of 1 Hz versus 10 Hz rTMS treatments on PCL-5 over time. Similar patterns with equivalent interpretations for depression symptoms (QIDS-SR) are shown in Fig. 3. The loess curves for IPF and Pain score (not shown) also did not reveal a significant change in trend or treatment group difference.

3.4. Tolerability of treatment

With respect to patient safety, there were no significant events related to the treatment in this trial. There were two Serious Adverse Events (SAE) that were unrelated to the study interventions. There were no seizures and no continuing complications. The 10 Hz group had two participants (2/18 or 11%) that could not tolerate the treatment at the first visit but no such report from the 1 Hz participants (see Fig. 1). Exact binomial tests (2-sided) failed to show significant differences between the two randomized groups on the proportions of Veterans who reported headache, site pain during treatment, or stopped treatment due to side effects (Table 4).

3.5. Post-hoc power calculations

Given that the final group sample sizes of 14 and 13 (see Fig. 1) used to test our primary hypothesis fell short of our anticipated evaluable sample of 40, inadequate statistical power was suspected. Therefore, post-hoc power calculations were performed based on the statistics obtained from the results of t-tests for CAPS-5 (Table 2). Using a paired samples t-test with alpha of 0.05, there were 98% and 76% power (for 10 Hz and 1 Hz groups respectively) to reject the null hypothesis of no difference between the baseline and post-30 scores (that the mean of the paired differences is zero); which support the conclusions reached from our significant results. For the nonsignificant results of 1 Hz versus 10 Hz, however, there was low power to reject the null hypothesis of no difference in group means using a two-sided two-sample unequal-variance t-test with alpha of 0.05. Therefore, no definitive conclusion can be derived from any failure to reject the null (i.e., non-significant findings) in this study. Although we did not find a definitive conclusion with our study, the preliminary results are that if a difference exists at the group level, it is not likely a large clinical difference.

4. Discussion

Posttraumatic stress disorder is a severe brain disorder that causes considerable suffering for both civilians and military personnel. There are evidence-based treatments available, but additional treatment options are critically needed to address this public health issue. The focus of this study was to determine if one treatment parameter, frequency of stimulation (1 Hz versus 10 Hz), provided a substantial relative benefit

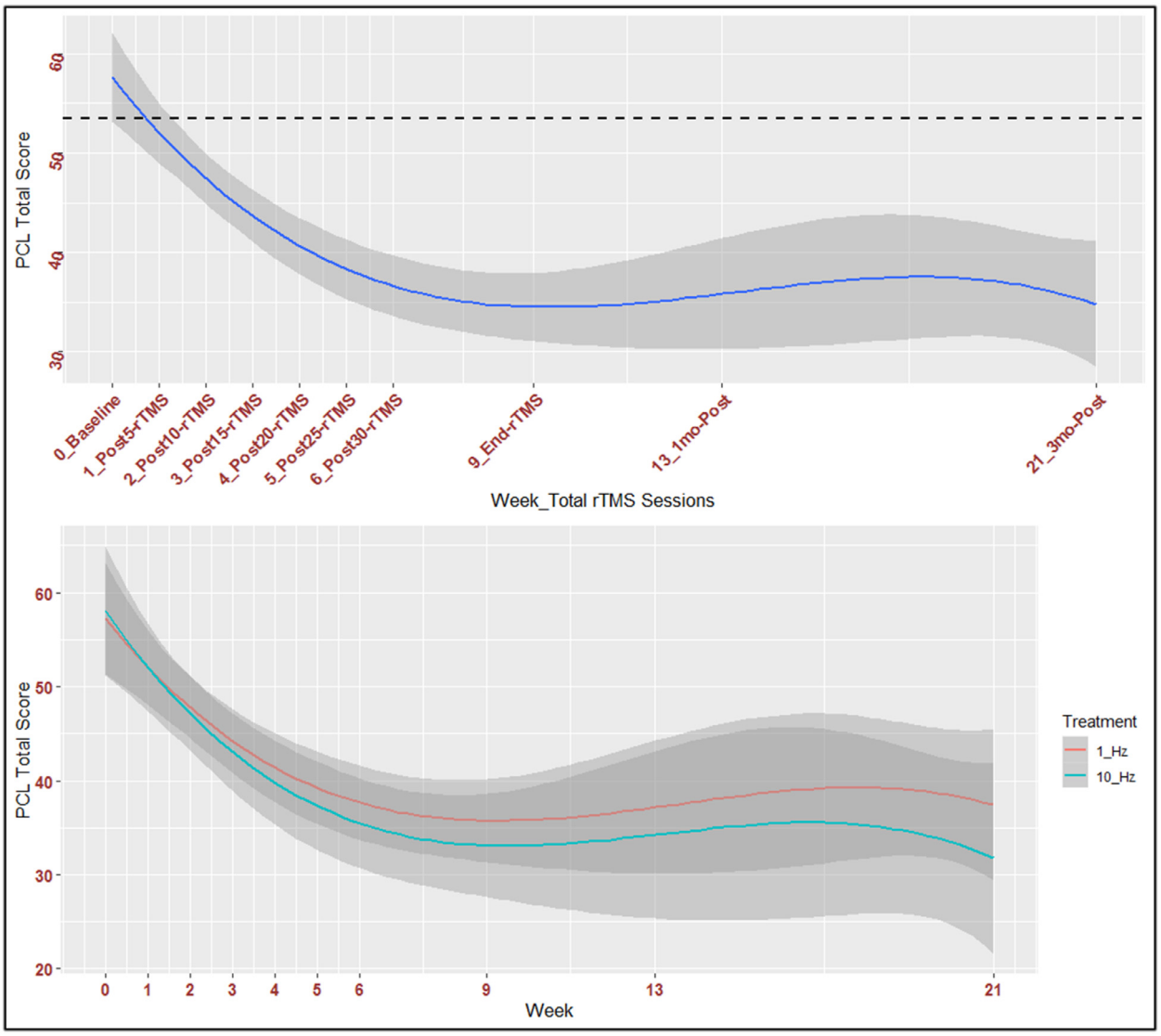

Fig. 2. Loess smooth curves of PCL-5 scores over time plus 95% confidence bounds: for the whole sample and by treatment group.
Key:
PCL: PTSD checklist for DSM-5
The *x*-axis ticks and labels depict the specific time points (weeks) of data collection which the loess curves smoothed over. The labels also include information on the total number of rTMS treatment sessions received by that time point (e.g., 6_Post30-rTMS = 6th week of study, after 30 sessions; 21_3mo-Post = 21st week of study, 3 months after end of treatment sessions).
The horizontal dashed line marks the lower limit of the 95% confidence interval (CI) of the baseline sample mean as estimated by loess (local least square regression). An estimated mean (plus 95% CI) corresponding to a specific time point is significantly lower than the value at baseline if that mean falls below the dashed line.

for treating PTSD. Although both groups significantly improved in self-rated (PCL-5) and clinician rated (CAPS-5) PTSD scales, this study was unable to demonstrate a meaningful difference between them. For measures of function (IPF), the 1 Hz group did not reach significance ($p = 0.075$) while the 10 Hz group did significantly improve ($p = 0.008$). However, the two groups did not demonstrate significant difference in self-reported measures of impairment in function. Like the PTSD scales, both depression (QIDS-SR, MADRS) and post-concussive symptoms associated with mild TBI (NSI) demonstrated significant improvement for both groups with no significant demonstrated difference between groups. Conversely, the self-rated general pain scores showed no significant improvement for either group. Given the statistical power for the tests carried out in this study, however, no definitive statistical conclusion can be derived from the failure to demonstrate a significant difference between the two treatment groups on both the primary and secondary outcomes.

In addition to the acute improvement in trauma and depression rating scales, the self-rated scales for trauma and depression demonstrated sustained improvement up to 3 months. This is a critical indicator of a treatment outcome that is required to provide meaningful improvement in patients' lives. Other studies have demonstrated the sustainability of treatment effect of rTMS in depression (Dunner et al., 2014) and PTSD (Kozel et al., 2018) which may be a unique advantage of rTMS. The treatments were very well tolerated for both groups with no serious adverse events including no seizures. There was no significant group difference in reports of treatment related headaches, site pains or drop outs.

Although there is a growing body of evidence that TMS may be an effective treatment for PTSD, future studies are critically needed to establish it as an evidenced based treatment (Kozel, 2018). One crucial question is whether the choice of frequency has a significant impact on the effectiveness of the treatment. Given that many studies have

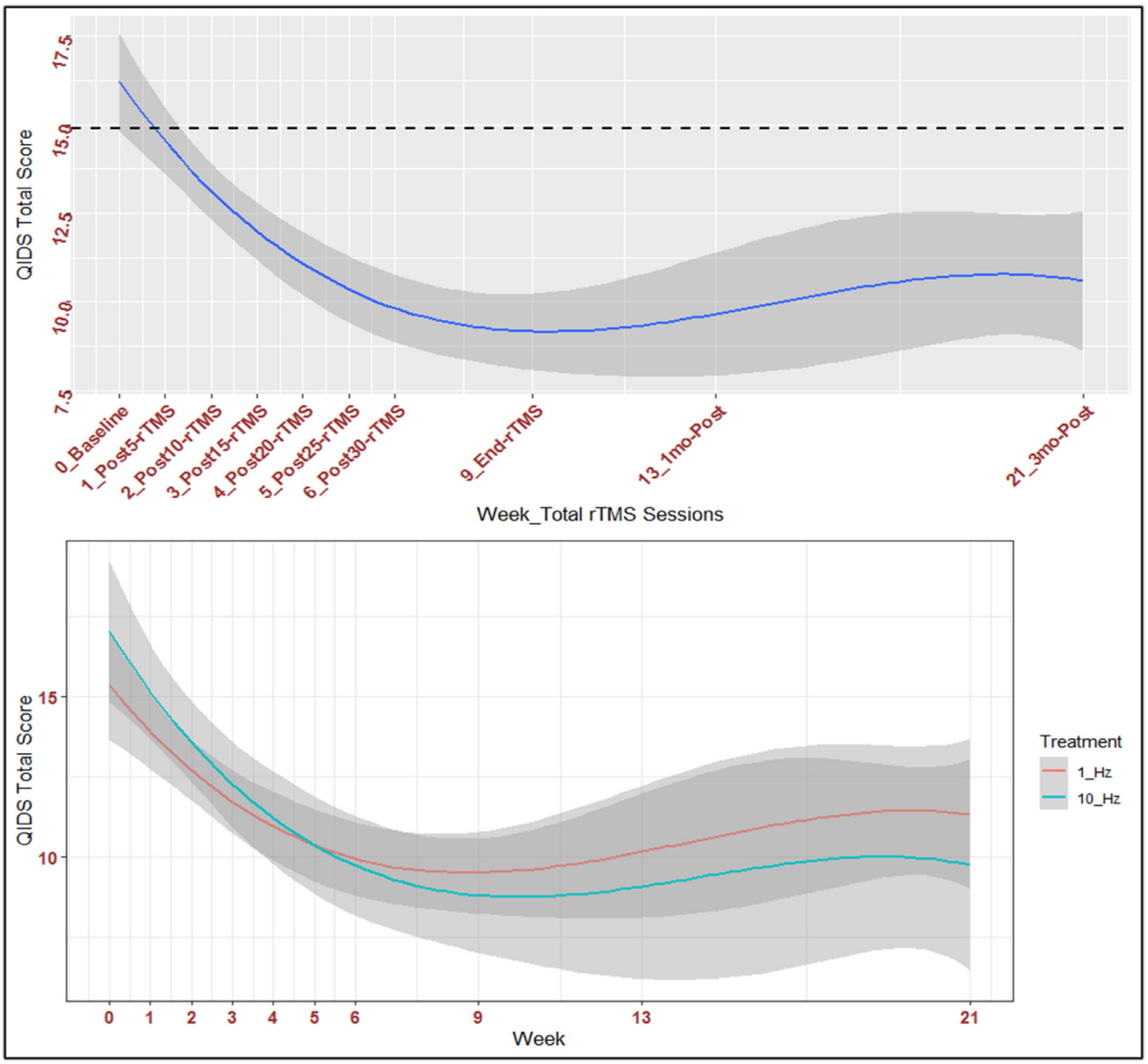

Fig. 3. Loess smooth curves of QIDS-SR scores over time plus 95% confidence bounds: for the whole sample and by treatment group.
Key:
QIDS: Quick Inventory of Depressive Symptomatology-Self Report
The *x*-axis ticks and labels depict the specific time points (weeks) of data collection which the loess curves smoothed over. The labels also include information on the total number of rTMS treatment sessions received by that time point (e.g., 6_Post30-rTMS = 6th week of study, after 30 sessions; 21_3mo-Post = 21st week of study, 3 months after end of treatment sessions).
The horizontal dashed line marks the lower limit of the 95% confidence interval (CI) of the baseline sample mean as estimated by loess (local least square regression). An estimated mean (plus 95% CI) corresponding to a specific time point is significantly lower than the value at baseline if that mean falls below the dashed line.

Table 4
Comparison of Counts (proportions) of side effects by treatment group.

	1 Hz rTMS (n = 17)	10 Hz rTMS (n = 18)	Total (N = 35)	2-sided exact binomial test of group difference
Headache	8 (0.47)	7 (0.39)	15 (0.43)	$p = 0.6$
Site pain during treatment	1 (0.06)	2 (0.11)	3 (0.09)	$p = 1.0$
Stopped treatment due to side effects	0 (0.00)	2 (0.11)	2 (0.06)	$p = 0.2$

Values in the parentheses represent proportions of the group

demonstrated differences in brain response for the 1 Hz (typically inhibitory brain effect) versus 10 Hz (typically excitatory brain effect) stimulation, there are a number of possible explanations - in addition to lack of statistical power due to small sample sizes with minimal differences in outcomes - for our finding of no difference in clinical response between treatment frequencies. One possibility is that although at the group level there was no difference, at the individual level, there may have been variation in treatment impact along baseline risk profiles, and/or post-baseline individual-level subgroups defined after the random assignment to treatment (Schochet et al., 2014). Thus, in each group, there were those participants who were responsive to the assigned frequency and those who were not going to respond. Future

work is needed to assess if switching to another frequency results in significant improvement, controlled for effect of time and extra treatments, and evaluating treatment-baseline interactions would provide greater insight into the response of rTMS for PTSD. Interestingly, this has been partially done in the treatment of depression with rTMS and did not show a benefit with switching from right 1 Hz or sequential bilateral (right 1 Hz followed by left 10 Hz) compared to continuing left 10 Hz (Fitzgerald et al., 2018). If there is a difference in response based on frequency, the ideal would be to have a biological or clinical marker that would help clinicians choose their parameters. Unfortunately, such a marker does not currently exist, although work is ongoing to discover such a determinant. Another possibility for lack of difference between the two frequencies not having an impact on clinical outcome is that the differences in brain changes measured for the two frequencies are not the "active ingredient" in determining the mechanism of action. As a hypothetical example, the degree of "activation" or "deactivation" of the brain (Speer et al., 1999) does not determine if the patient will respond, while the degree of increase in white matter integrity may be the critical factor (Kozel et al., 2011). A third possibility, given that we did not have a sham arm, is that the positive changes were largely due to non-rTMS aspects of the study, and thus would not be dependent on treatment frequency. There was no sham arm in this study as the primary question was not testing efficacy of rTMS for PTSD, but whether one frequency provided a significant advantage over the other. Future studies with a sham arm would help determine degree of change related to rTMS versus non-rTMS factors.

There were several additional limitations that need to be addressed. The treater and patients were not masked to treatment allocation. Although the raters were kept masked and separated from the treatments and there were no clear expectations of outcome that would occur in an active versus sham design, future studies should consider methods to conceal the parameters used to avoid any chance of bias. Also, no biomarkers were obtained as part of this trial. Future studies should acquire brain-based measures to better investigate any differences observed. Finally, there were no significant changes in pain scores for either group. This is somewhat surprising given the support in the literature of rTMS for pain (Lefaucheur et al., 2014). This study, however, did not select participants based on pain scores and the assessments were simple self-rated Likert scales of pain over the last week. More specific causes of pain, different brain targets, or superior pain assessment tools may demonstrate different results.

Although both the 10 Hz and 1 Hz right prefrontal rTMS resulted in significant improvement in PTSD and depressive symptoms, our findings failed to show an advantage in using either stimulation frequency for any measure. Future work is required to determine if larger sample sizes or individual differences can be used to determine optimal treatment frequency for a particular patient. This work is critically important in the development of novel treatment strategies and furthering our understanding of the complexities of military-related PTSD.

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Previous Presentation:

Kozel FA, Van Trees KA, Larson V, Phillips S, Hashimie J, Gadbois B, Johnson S, Gallinati J, Dreschnack D, Barrett B, Toyinbo P, Weisman M, Centorino M, Gibson CA, Glenn Catalano. Targeting Disability from PTSD with Transcranial Magnetic Stimulation. Society of Biological Psychiatry's 72nd Annual Scientific Convention and Program. San Diego, CA. 20 May 2017 (poster).

Kozel FA, Van Trees KA, Larson V, Phillips S, Hashimie J, Gadbois B, Johnson S, Gallinati J, Dreschnack D, Barrett B, Toyinbo P, Weisman M, Centorino M, Gibson CA, Glenn Catalano. Targeting Disability from PTSD with Transcranial Magnetic Stimulation. 2017 Military Health System Research Symposium (MHSRS). Kissimmee, FL. Aug 2017 (poster).

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