Research paper

Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: A randomized clinical trial

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ABSTRACT

Background: The objective was to test whether repetitive Transcranial Magnetic Stimulation (rTMS) just prior to Cognitive Processing Therapy (CPT) would significantly improve the clinical outcome compared to sham rTMS prior to CPT in veterans with PTSD.

Methods: Veterans 18–60 years of age with current combat-related PTSD symptoms were randomized, using a 1:1 ratio in a parallel design, to active (rTMS + CPT) versus sham (sham + CPT) rTMS just prior to weekly CPT for 12–15 sessions. Blinded raters evaluated veterans at baseline, after the 5th and 9th treatments, and at 1, 3, and 6 months post-treatment. Clinician Administered PTSD Scale (CAPS) was the primary outcome measure with the PTSD Checklist (PCL) as a secondary outcome measure. The TMS coil (active or sham) was positioned over the right dorsolateral prefrontal cortex (110% MT, 1 Hz continuously for 30 min, 1800 pulses/treatment).

Results: Of the 515 individuals screened for the study, 103 participants were randomized to either active (n = 54) or sham rTMS (n = 49). Sixty-two participants (60%) completed treatment and 59 (57%) completed the 6-month assessment. The rTMS + CPT group showed greater symptom reductions from baseline on both CAPS and PCL across CPT sessions and follow-up assessments, $t(df \geq 325) \leq -2.01$, $p \leq 0.023$, one-tailed and $t(df \geq 303) \leq -2.14$, $p \leq 0.017$, respectively.

Limitations: Participants were predominantly male and limited to one era of conflicts as well as those who could safely undergo rTMS.

Conclusions: The addition of rTMS to CPT compared to sham with CPT produced significantly greater PTSD symptom reduction early in treatment and was sustained up to six months post-treatment.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a major military and civilian public health problem. The National Co-morbidity Survey (NCS) reported a lifetime prevalence rate of 7.8% for PTSD in a national sample (Kessler et al., 2005, 1995), while the data from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions found the lifetime prevalence of PTSD to be 6.4% (Pietrzak et al., 2011). The National Vietnam Veterans Readjustment study reported that 31% of males and 27% of females met full criteria for PTSD using DSM-IV-TR criteria over their lifetime (n = 3016) and that 15% of males and 9% of females met full criteria for PTSD at the time of the study (Kulka et al., 1990). The more recent National Vietnam Veterans Longitudinal Study demonstrated that between 4.5–11.2% of males and 6.1–8.7% of females suffer from current war-zone PTSD depending on the assessment method utilized (Marmar et al., 2015). With respect to veteran deployments, 15.6–17.1% of those deployed to Iraq and 11.2% of those deployed to Afghanistan met screening criteria for PTSD, major depression, or general anxiety disorder upon return (Hoge et al., 2004). Another study found estimated prevalence rates of PTSD based on DSM-

IV symptoms were from 20.7% to 30.5% at 3 and 12 months post deployment (Thomas et al., 2010). More recently, a meta-analysis estimated prevalence of PTSD from deployments to Iraq and Afghanistan to be 23% (Fulton et al., 2015). In addition to being a common sequela of deployment to combat regions, PTSD results in significant functional impairment (Rodriguez et al., 2012; Shea et al., 2010).

Evidence based psychotherapies such as prolonged exposure (PE) and cognitive processing therapy (CPT) are supported by clinical research with veteran, active duty military personnel, and civilian samples (Foa et al., 1999; Rauch et al., 2009; Resick et al., 2002, 2017; Schnurr et al., 2007). These treatments are also recommended in the VA/DOD Clinical Practice Guidelines for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder 2017 and by the Institute of Medicine (IOM Institute of Medicine, 2014). However, many individuals have difficulty completing these therapies (Miles and Thompson, 2016; Najavits, 2015; Niles et al., 2017; Steenkamp et al., 2015). Furthermore, a recent review of randomized clinical trials for military-related PTSD demonstrated that although these therapies do result in meaningful improvement in patients with PTSD, approximately two-thirds of patients continued to meet full criteria for PTSD (Steenkamp et al., 2015). Thus, new treatment approaches or approaches that augment the benefits of PE and CPT are critically needed to improve treatment outcomes.

Cognitive Processing Therapy (CPT) was originally developed to treat victims of sexual assault (Resick and Schnicke, 1992) and has been revised specifically for combat veterans with PTSD within the VA Healthcare system. The Cognitive Processing Therapy Veteran Military Version manual (2007) was utilized for this study (Monson et al., 2006). CPT is a trauma-focused therapy that combines elements of exposure and cognitive therapy to reduce PTSD symptoms and associated symptoms such as depression, anxiety, guilt, and shame. CPT involves eliciting memories of traumatic events and directly confronting conflicts and maladaptive beliefs associated with those memories (Resick and Schnicke, 1992). The therapy also seeks to facilitate the expression of the appropriate affect associated with the trauma while assisting the patient with the development of an alternative view of the trauma that is balanced and realistic as well as the modification of extreme beliefs or cognitions that prevent the individual from having disconfirming experiences.

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 including Major Depressive Disorder (Gaynes et al., 2014; George et al., 2010; Kozel and George, 2002; O'Reardon et al., 2007). Although not definitive, there is growing evidence that the symptoms of PTSD can be ameliorated by rTMS (Berlim and Van Den Eynde, 2014; Boggio et al., 2010; Clark et al., 2015; Cohen et al., 2004; Grisaru et al., 1998; Karsen et al., 2014; McCann et al., 1998; Nam et al., 2013; Oznur et al., 2014; Philip et al., 2016; Rosenberg et al., 2002; Watts et al., 2012). Relevant to the current study, 1 Hz stimulation applied over the prefrontal cortex produced an inhibitory effect on the subjacent brain structures (Kozel et al., 2009; Speer et al., 2000), including reduction of the event-related potential (ERP) P3a hyperarousal response to combat-relevant threatening stimuli in PTSD (Tillman et al., 2011). PTSD patients also have shown increased amygdala response when engaged in PTSD-related script-driven imagery (Rauch et al., 1996; Shin et al., 1997) and when shown fearful stimuli (Rauch et al., 2000), suggesting dysfunctional amygdala hyperactivation. Importantly, rTMS administered to right dorsolateral prefrontal cortex (rDLPFC) has been shown to decrease amygdala activation to threatening stimuli (Baeken et al., 2010).

There also have been studies that have combined rTMS with exposure psychotherapy as well as script driven imagery. Osuch et al. 2009 (n = 9) combined exposure therapy with either 1 Hz or sham rTMS and found moderate improvement in hyperarousal symptoms on the clinician-administered PTSD scale (CAPS) with exposure plus active rTMS; however, the difference between active and sham was not significant (Osuch et al., 2009). Isserles et al. tested (n = 30) an H-coil also called Deep TMS (DTMS) with script driven imagery from a traumatic event to relieve the symptoms of PTSD. DTMS after imagery of traumatic experience demonstrated a significant improvement in the intrusive component of the CAPS score and a trend for improvement in the total CAPS score. Conversely, the DTMS after imagery of positive experience group and the sham DTMS after imagery of traumatic experience group demonstrated no significant improvement (Isserles et al., 2013). (See Supplementary information for rTMS studies in PTSD and rational for rTMS parameters.)

Overall, the studies combining rTMS with re-exposure or script-driven imagery showed improved symptom reduction with the addition of rTMS or resulted in no "significant" change in symptoms. There are no studies demonstrating worsening of symptoms. Also, several meta-analyses have shown rTMS alone to lead to symptom reduction in PTSD (Berlim and Van Den Eynde, 2014; Karsen et al., 2014; Trevizol et al., 2016). With these studies and our finding that 1 Hz right DLPFC rTMS resulted in significant reduction in ERP P3 hyperarousal response to combat threatening stimuli in PTSD, we hypothesized that right prefrontal 1 Hz rTMS would work synergistically with CPT to reduce PTSD symptoms in combat veterans. To test our hypothesis, we used a parallel design in which we randomized veterans with combat related PTSD to active versus sham [1:1 ratio] 1 Hz rTMS to right prefrontal cortex just prior to CPT. The Clinician Administered PTSD Scale (CAPS) served as the primary outcome measure of PTSD symptom severity. The PTSD Checklist (PCL), the Mississippi Scale for Combat Related PTSD (M-PTSD), the Quick Inventory of Depressive Symptomatology (QIDS), and the Inventory of Psychosocial Functioning (IPF) served as additional measures. The treatment schedule of rTMS was determined by the standard treatment schedule of CPT, as rTMS was delivered just prior to each CPT session.

2. Methods

2.1. Participants

Veterans previously deployed to combat regions from 2001 to present (e.g., Operation Enduring Freedom (OEF), Operation Iraq Freedom (OIF), and Operation New Dawn (OND)) with current combat-related PTSD symptoms were recruited from the community (ClinicalTrials.gov NCT01391832). Recruitment focused on military installations, Veteran Affairs Hospitals, Veteran Centers, local universities and colleges with veteran enrollment, and various non-profit veteran associated service organizations. Potential participants initially underwent a phone screening during which participants were provided a general overview of the study (e.g., expected time commitments, brief descriptions of the therapies, etc.) and were asked about potential contra-indicators for rTMS and fMRI. Additionally, potential participants were asked to confirm their involvement in deployments for combat operations in OIF, OEF, or OND. Potential participants were then scheduled to come in for a complete study overview session. During the overview session, a therapist informally assessed for possible symptoms of PTSD as well as provided more detailed descriptions of the therapies and expectations while fully informing the potential participant of the risks, benefits, and procedures described in the written consent form. Interested potential participants were then scheduled for a baseline evaluation, which included a formal assessment of PTSD based on CAPS using the F1/I2 scoring rule (Weathers et al., 1999). The study acquired data from July 2011 to January 2016. Participants were aware that information acquired in this study was protected by a Certificate of Confidentiality and independent of any disability determination.

Prior to any procedures or evaluation at the baseline visit, the study was reviewed with the participants in detail and all questions were answered at the study overview. For those still interested in participating, written informed consent was obtained using procedures that were approved by the Investigation Review Boards (IRB) at the

University of Texas Southwestern Medical Center (IRB of record), the University of Texas at Dallas (UTD) IRB, as well as the Army Human Research Protection Office. After written informed consent was obtained, self-rated and clinician administered scales were administered to evaluate whether the participant met screening criteria, to provide background information on the sample being studied, and to assess the severity of PTSD, depression, and function.

Participants included male and female veterans between the ages of 18 and 60 years who had a current diagnosis of combat-related PTSD. Participants were recruited, screened, and included in the study in an unbiased fashion with regards to race, ethnicity, or gender. Participants were allowed to continue their medications, including psychiatric medications, but were encouraged to keep their medication regimen as stable as possible. Veterans were excluded from the study if taking a medication contraindicated for safety reasons (e.g., stimulants). Veterans were excluded for primarily safety reasons, including a history of a significant neurological or medical disorder, and for a history of psychiatric comorbidities including eating disorders, psychotic symptoms, and current (less than 3 months) substance dependence or abuse. Exclusionary criteria also included a history of a significant neurological/medical disorder such as seizure, traumatic brain injury (moderate or severe TBI), brain tumors, stroke, blood vessel abnormalities in the brain, dementia, Parkinson's disease, Huntington's chorea, multiple sclerosis, cardiac pacemaker, implanted medication pumps of any sort that would increase the risk of rTMS, history of significant heart disease (e.g., history of myocardial infarction, tachyarrhythmia, congestive heart failure, valvular disease), or any metal objects in or near the head (most dental work was allowed) which could not be safely removed for TMS treatments. Traumatic brain injury was screened by both history and structural MRI scans that were reviewed for significant lesions indicative of TBI. Veterans with greater than mild TBI (i.e., loss of consciousness greater than 30 min, post traumatic amnesia greater than 1 day, penetrating trauma, or evidence of structural injury on MRI) were excluded. Veterans were also excluded if unable or unwilling to stop taking a prescription medication (e.g., stimulants) or illegal substances (e.g., cocaine) that significantly lower the seizure threshold. Women who were pregnant or breastfeeding were also excluded for safety reasons as there is very little information regarding rTMS and pregnancy or breastfeeding. Non-English speakers were also excluded because some of the screening forms, questionnaires, and tests were only available in English. Participants could not start any new psychological treatment for PTSD while being in the study; however, prior psychotherapy, including previous CPT, was allowed. See Supplemental information on Prior CPT.

2.2. Procedures

The clinical data obtained included the CAPS based on the DSM-IV criteria, the Structured Clinical Interview for DSM-IV (SCID), the Self-Administered Comorbidity Questionnaire (SC-Q), the Adverse Childhood Experiences scale (ACE), the Mini Mental State Exam (MMSE), the Wechsler Abbreviated Scale of Intelligence (WASI), the Deployment Risk and Resiliency Inventory (DRRI), the Full Combat Exposure Scale (FCES), a medication log, the Transcranial Magnetic Stimulation Safety Screen (TASS), M-PTSD, the Posttraumatic Stress Disorder Checklist for any specific traumatic event (PCL) based on the DSM-IV criteria, the QIDS – 16 Item Self Report, and IPF. (See Supplementary information for information on scales and brain measures.) In addition, demographic information was acquired by self-report and a urine sample was obtained to test for drugs of abuse and for pregnancy in women of childbearing potential.

Participants that met full criteria for entry were scheduled for a subsequent visit to undergo active or sham rTMS with CPT (rTMS + CPT and sham + CPT). Once the safety of the subject to participate was reviewed, the participant underwent determination of motor threshold (MT). The intensity of the pulses delivered by the rTMS device

(Magstim Rapid[2] Stimulator using a Double 70 mm Air Cooled Coil, Magstim, Whitland, Wales) was calibrated for each individual in the following manner. The MT was defined as the stimulus intensity that induced visually perceptible movement of the contralateral (i.e., left) abductor pollicus brevis (APB) 50% of the time. The TMS coil was moved to the spot on the scalp that gave the maximal contraction of the left thumb. After the location on the scalp at which stimulation elicited maximal contraction was determined, a parameter estimation (PEST) algorithm was used to determine the MT two times (Mishory et al., 2004) and the mean served as the MT for the study.

After the MT was determined, participants were asked to leave the TMS room. The participant was then randomized to receive either sham rTMS or active rTMS [1:1 ratio] treatment prior to CPT. The randomization was previously generated using a computer randomization function. The assignments were recorded on cards and placed in sealed envelopes that were sequentially numbered by an investigator not involved with the participants. Randomization assignment was performed by pulling the card out of the subsequently numbered envelope. The patients, CPT therapists, CPT supervisor, fidelity monitor (CPT expert), and raters were masked to the patients' treatment conditions throughout the study. Participants were never informed of which treatment they were assigned. The only difference between the treatment for active and sham group for receiving rTMS was that one utilized an active coil and the other group used a sham coil. The TMS treater used the coil determined by randomization and was not blinded to treatment group. Throughout the study, the treaters were isolated from other study staff members and only had minimal interaction with participants during TMS treatment. The two coils looked and sounded very similar but the sham coil did not produce any significant magnetic fields. While the active coil could produce stimulation of underlying facial muscles, the sham coil did not induce a similar stimulation. Once the respective coil (active or sham) was in place, the participant returned to the TMS room to receive treatment. After the first 15 randomized participants, however, investigators became concerned that having the active or sham TMS immediately after the MT determination would bias the results. Therefore, the MT appointment was built into a second baseline appointment, which also included an introduction to CPT. This allowed for a week between exposure to active TMS for MT and the first TMS session (see Supplementary information for MT same Day as First Treatment).

For both active and sham rTMS treatment, the stimulator coil was positioned over the right dorsolateral prefrontal cortex - DLPFC (Brodmann Area 9/46). The right DLPFC was targeted using head measurements and a computerized program that locates the F4 electrode site under 10/20 electrode convention (Beam et al., 2009). The rTMS over the DLPFC was at 110% of motor threshold at 1 Hz rTMS continuously for 30 min for a total of 1800 pulses. Treatment at 110% motor threshold and 1800 pulses per day were chosen based on the literature available at the time of starting the study in 2011. The percent motor threshold was higher than reported treatment parameters at that time for PTSD and took into account the fact that the group being studies was limited to 18–60 years (i.e., younger and not needing to overcome greater coil to cortex distances over prefrontal cortex than motor cortex (Kozel et al., 2000; Nahas et al., 2001)) as well as maximizing tolerability. The number of pulses per day were chosen based on the Osuch et al. (2009) study (See Supplementary information for more information on Safety Monitoring of TMS).

Immediately following the rTMS treatment, CPT sessions were administered that lasted approximately 60 min per session. For both of the treatment groups, the participants received rTMS or sham rTMS immediately followed by CPT treatments typically one day per week for 12 sessions. Participants who did not complete all 12 sessions were considered to have withdrawn from the program, and none of these participants completed post-intervention assessments. Up to three additional sessions beyond the prescribed 12 were allowed if the therapist and participant agreed that the review of a particular aspect of CPT was
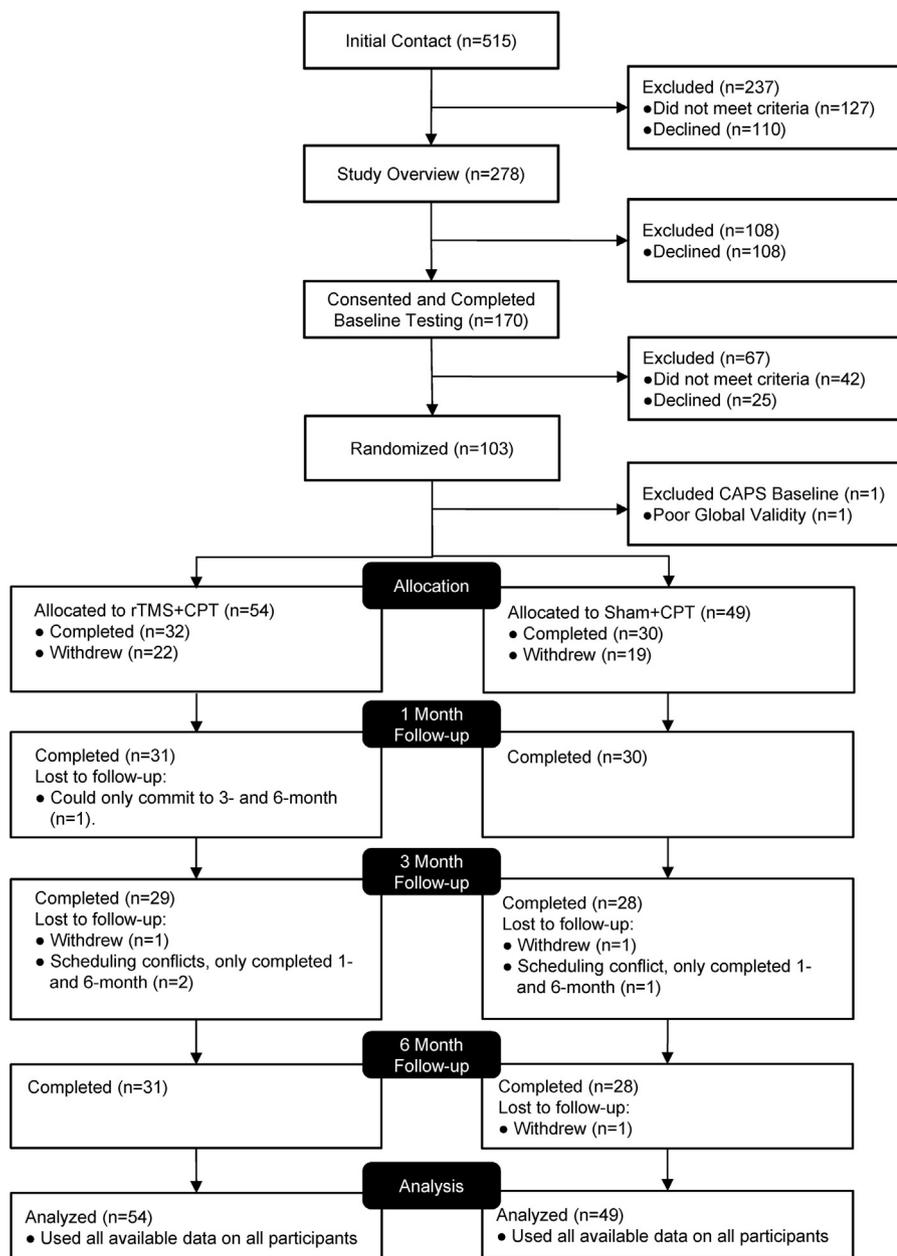
Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram illustrating flow of participants through the trial.

necessary to proceed or when the protocol was briefly suspended to include a crisis management session that was deemed therapeutically necessary. Patients were assigned to one of two CPT trained therapists, and the assigned therapist provided all 12 CPT treatments to the patient. Both CPT therapists were determined adequately proficient in the therapy technique by a CPT supervisor before starting any treatment in the study. Therapists' adherence to the protocol and therapists' competency were monitored throughout the trial. To ensure that evidenced based CPT was performed, each session was videotaped. The fidelity supervisor reviewed 9% (80/885) of all CPT sessions. When necessary, the fidelity supervisor would contact the CPT therapist and advise on corrections on administration to ensure consistency. The fidelity monitoring ratings for both Unique and Essential Elements (UEE) and Essential but not Unique Elements (EbnUE) for the two therapists averaged between *Very Good* and *Excellent* on a seven-point scale ranging from *Poor* to *Excellent* (Therapist 1: 55 sessions, UEE $M = 6.86$, EbnUE $M = 6.88$; Therapist 2: 25 sessions; UEE $M = 6.65$, EbnUE $M = 6.85$).

The CAPS, PCL, M-PTSD, and QIDS were performed at baseline, and

repeated after the 5th treatment session (session-5), 9th treatment session (session-9), 1 month post-treatment (1-month), 3 months post-treatment (3-month), and 6 months post-treatment (6-month). The IPF was acquired at baseline, 1 month post-treatment (1-month), 3 months post-treatment (3-month), and 6 months post-treatment (6-month).

2.3. Data analysis

Baseline characteristics for the group that completed therapy versus the group that withdrew were evaluated using ANOVA for continuous outcome and demographic data and logistic regression for non-continuous data. To test our hypotheses of rTMS further enhancing CPT's treatment-related symptom reduction in CAPS Total and PCL Total, an intent-to-treat analysis was carried out using a mixed linear model with treatment (rTMS + CPT vs. sham + CPT) as the between groups factor, time (baseline, session-5, session-9, 1-month, 3-month, and 6-month) as the within-subjects factor, and subjects as random effects (with a compound symmetry covariance structure specified). The model also included a factor coding for therapist in the event that our primary

hypotheses depended on the efficacy of the therapist administering CPT. Restricted maximum likelihood estimators (ReML) of the variance components were used to compute the maximum likelihood estimators of the fixed effects parameters (i.e., group, time, therapist, all two-way interaction terms, and the three-way interaction term). Thus, we did not exclude participants with missing time points. All available data on all participants who 1) met inclusion/exclusion criteria, 2) had been randomly assigned to groups, and 3) provided baseline data were used regardless of whether they completed the trial. Based on prior research showing PTSD symptom reduction when rTMS was paired with exposure-based psychotherapies (Isserles et al., 2013; Osuch et al., 2009) and prior research showing that rTMS alone led to PTSD symptom reduction (Berlim and Van Den Eynde, 2014; Karsen et al., 2014; Trevizol et al., 2016), the primary research hypothesis, that rTMS + CPT would lead to greater symptom reduction than sham + CPT (i.e., Group × Time interaction effects), was evaluated with interaction contrasts (i.e., t-contrasts using ReML variance estimates with Satterthwaite estimates of the effective degrees of freedom) and predicted effects on symptom reduction were evaluated with α = 0.05 for *one-tailed* t-distributions, recommended for designs examining efficacy of therapeutic interventions (Overall, 1991). Cohen's *d* effect-size estimates were calculated using the ReML variance estimates with a negative Cohen's *d* indicating improvement of rTMS + CPT versus sham + CPT (See Supplemental for more information on Data Analysis Methods).

3. Results

Five hundred fifteen individuals were contacted or inquired about participating in the study; of whom 103 participants were randomized to either the active or sham rTMS (rTMS + CPT n = 54, sham + CPT n = 49) (see Fig. 1). One participant in the rTMS + CPT group was considered by the assessors to have given responses with substantially reduced validity on CAPS at baseline (i.e., Global Validity = 3), although acceptably valid responses were given at all other assessment sessions. Thus, this participant's CAPS baseline data were excluded from the analyses. Two-way ANOVA and logistic regression on the demographic and outcome measures at baseline revealed completion effects but no Completion × Group interaction effects (see Table 1). Compared to those who completed the study, subjects who withdrew had significantly higher PCL total scores, less formal education, lower WASI scores, and were more likely to be current college students (all p < 0.05; see Supplementary information for additional details regarding baseline data of completion, group, and interaction effects). Seventy (68%) participants completed the session-5 assessments (rTMS

+ CPT n = 35, sham + CPT n = 35), and 61 (59%) completed the session-9 assessments (rTMS + CPT n = 31, sham + CPT n = 30). The majority of participants who were randomized and then subsequently withdrew did so before session-5 (rTMS + CPT n = 19, sham + CPT n = 14), although the proportion of dropouts prior to versus after session-5 did not significantly differ between groups, $\chi^2(1, n = 103) = 1.40, p = 0.24$. Session-4 and -5 involved the trauma account with the practice assignment of writing the account being given in session-3. Sixty-two participants (60%) completed the 12 prescribed CPT sessions (rTMS + CPT n = 32, sham + CPT n = 30), 61 (59%) participants completed the 1-month post-treatment evaluation (rTMS + CPT n = 31, sham + CPT n = 30), 57 (55%) participants completed the 3-month post-treatment evaluation (rTMS + CPT n = 29, sham + CPT n = 28), and 59 (57%) participants completed the 6-month post-treatment evaluation (rTMS + CPT n = 31, sham + CPT n = 28).

Both groups showed significant symptom reduction on CAPS from baseline at session-5, session-9, 1-month, 3-months, and 6-months post treatment assessments (*rTMS + CPT* all *ts*[df ≥ 325] ≤ −5.35, *ps* < 0.001, one-tailed, 1.36 ≤ *d* ≤ 3.42, and *sham + CPT* all *ts*[df ≥ 324] ≤ −2.09, *ps* ≤ 0.019, one-tailed, 0.57 ≤ *d* ≤ 2.60). Importantly, the rTMS + CPT group showed greater symptom reduction from baseline over the sham + CPT group during CPT across sessions and at the follow-up assessments, with significant differences at the session-5, 3-month, and 6-month assessments, t(df ≥ 325) ≤ −2.01, p ≤ 0.023, one-tailed, *d* ≥ 0.79 (see Fig. 2 – CAPS Total Score). Similarly for PCL score, both groups showed significant symptom reduction from baseline to treatment at session-5, session-9, 1-month, 3-months, and 6-months post treatment assessments (*rTMS + CPT* - PCL all *ts*[df ≥ 304] ≤ −7.02, *ps* < 0.001, one-tailed, 1.81 ≤ *d* ≤ 3.64, and *sham + CPT* - PCL all *ts*[df ≥ 301] ≤ −3.29, *ps* ≤ 0.006, one-tailed, 0.92 ≤ *d* ≤ 2.29). For PCL, the rTMS + CPT group showed significantly greater symptom reduction from baseline over the sham + CPT group at both session and all follow-up assessments, all *ts*(df ≥ 303) ≤ −2.14, *ps* ≤ 0.017, one-tailed, *ds* ≥ 0.89 (see Fig. 3 – PCL Score) (See Table 2).

Additionally, for M-PTSD total scores, both groups demonstrated significant improvement from baseline to treatment at session-5, session-9, 1-month, 3-months, and 6-months post treatment assessments (rTMS + CPT - M-PTSD all *ts*[df ≥ 301] ≤ −3.80, *ps* < 0.001, one-tailed, 0.98 ≤ *d* ≤ 3.02, and sham + CPT – M-PTSD all *ts*[df ≥ 301] ≤ −3.08, *ps* ≤ 0.001, one-tailed, 0.86 ≤ *d* ≤ 2.07). rTMS + CPT also led to significantly greater symptom reduction from baseline over sham + CPT at the 6-month post treatment assessment (rTMS + CPT *M* = −28.04, SE = 2.57, sham + CPT *M* = 17.67, SE = 2.86), t(303) = −2.70, *p* = 0.004, one-tailed, *d* = 1.12.

Table 1
Mean outcome measures at baseline as functions of treatment group and study completion.

	Withdrew from treatment				Completed treatment			
	rTMS + CPT		sham + CPT		rTMS + CPT		sham + CPT	
CAPS Total	75.96	(4.45)	78.05	(4.25)	73.87	(3.98)	69.90	(3.72)
PCL Total[a]	58.18	(2.48)	56.78	(2.30)	54.94	(2.19)	50.43	(1.90)
M-PTSD Total	108.05	(3.29)	111.58	(3.91)	106.78	(2.92)	103.80	(3.40)
QIDS Total	9.86	(0.91)	12.53	(0.95)	10.91	(0.79)	11.43	(0.97)
IPF Total	3.14	(0.19)	3.62	(0.24)	3.30	(0.19)	3.40	(0.17)
IPF Family	4.01	(0.30)	4.50	(0.26)	3.70	(0.25)	4.08	(0.26)
IPF Work	2.31	(0.22)	2.17	(0.20)	2.56	(0.20)	2.45	(0.17)
IPF Friendship	3.56	(0.34)	3.81	(0.28)	3.55	(0.24)	3.64	(0.21)
IPF Parenting	1.82	(0.23)	2.65	(0.19)	2.39	(0.24)	2.52	(0.31)
IPF Education	2.71	(0.25)	2.96	(0.30)	2.87	(0.39)	2.80	(0.28)
IPF Self Care	3.44	(0.26)	3.88	(0.23)	3.52	(0.22)	3.42	(0.20)
IPF Romance	3.62	(0.28)	3.56	(0.30)	3.27	(0.19)	3.10	(0.22)

All *ns* = 103, except CAPS (n = 102) IPF Total (n = 75).
SEM shown in parentheses.
CAPS = Clinician Administered PTSD Scale; PCL = PTSD Checklist for any specific trauma event; M-PTSD = Mississippi Scale for Combat Related PTSD; QIDS = Quick Inventory of Depressive Symptomatology-Self Report version; IPF = Inventory of Psychosocial Functioning
[a] Mean PCL Total scores was higher for the group who withdrew from the study compared to the group who completed the study, F(1,78) = 5.93, p < 0.05.
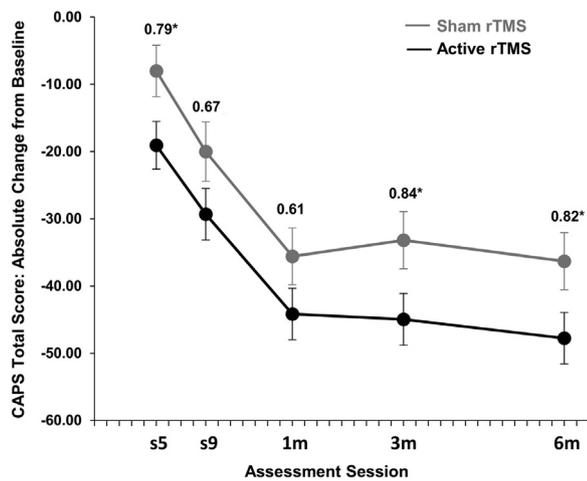
Fig. 2. Clinician Administered PTSD Scale (CAPS) Score absolute change from baseline as a function of group and assessment session. Sham + CPT shown in gray, and rTMS + CPT shown in black. Assessment sessions indicated are session-5 (s5) and session-9 (s9) of the Cognitive Processing Therapy sessions and 1-, 3-, and 6-Month (1 m, 3 m, and 6 m, respectively) post treatment assessment sessions. Bars represent SEM of the difference from baseline, with *p < 0.05, and Cohen's *d* effect-size estimates of rTMS + CPT improvement greater than sham + rTMS shown for each assessment session. Note: Baseline sham + CPT (*n* = 49) *M* = 73.88, *SE* = 3.51; rTMS + CPT (*n* = 53) *M* = 75.28, SE = 3.24; s5 (sham + CPT *n* = 35; rTMS + CPT *n* = 35) *t*(325) = −2.11; s9 (sham + CPT *n* = 30; rTMS + CPT *n* = 31) *t*(326) = −1.59; 1 m (sham + CPT *n* = 30; rTMS + CPT *n* = 31) *t*(327) = −1.51; 3 m (sham + CPT *n* = 28; rTMS + CPT *n* = 29) *t*(327) = −2.05; 6 m (sham + CPT *n* = 28; rTMS + CPT *n* = 31) *t*(327) = −2.01.
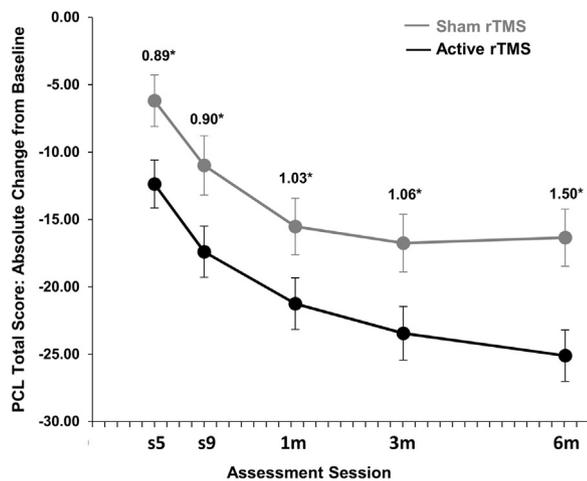
Fig. 3. PTSD Checklist (PCL) Score absolute change from baseline as a function of group and assessment session. Sham + CPT shown in gray, and rTMS + CPT shown in black. Assessment sessions indicated are session-5 (s5) and session-9 (s9) of the Cognitive Processing Therapy sessions and 1-, 3-, and 6-Month (1 m, 3 m, and 6 m, respectively) post treatment assessment sessions. Bars represent SEM of the difference from baseline, with *p < 0.05, and Cohen's *d* effect-size estimates of rTMS + CPT improvement greater than sham + rTMS shown for each assessment session. Note: Baseline sham + CPT (*n* = 48) *M* = 52.82, *SE* = 2.05; rTMS + CPT (*n* = 54) *M* = 55.93, *SE* = 1.83; s5 (sham + CPT *n* = 34; rTMS + CPT *n* = 34) *t*(303) = −2.36; s9 (sham + CPT *n* = 30; rTMS + CPT *n* = 31) *t*(303) = −2.14; 1 m (sham + CPT *n* = 30; rTMS + CPT *n* = 29) *t*(304) = −2.50; 3 m (sham + CPT *n* = 25; rTMS + CPT *n* = 26) *t*(303) = −2.49; 6 m (sham + CPT *n* = 27; rTMS + CPT *n* = 29) *t*(304) = −3.61.

Both groups exhibited significant symptom reduction from baseline on QIDS at session-5, session-9, 1-month, 3-month, and 6-month assessments (rTMS + CPT all *ps* ≤ 0.011, one-tailed, and sham + CPT all *ps* ≤ 0.001, one-tailed), but rTMS + CPT was not superior to sham + CPT, (all *ps* ≥ 0.18, one-tailed, −0.29 ≤ *d* ≤ 0.37). Similarly, both groups exhibited significant reductions from baseline on IPF at 1-month, 3-month, and 6-month assessments (rTMS + CPT all *ps* ≤ 0.002, one-tailed, and sham + CPT all *ps* ≤ 0.005, one-tailed), but rTMS + CPT was

not superior to sham + CPT (all *ps* ≥ 0.49, one-tailed, −0.34 ≤ *d* ≤ 0.01).

The rTMS treatments were very well tolerated without any serious adverse events related to the study. There were no seizures during this trial. Two participants assigned to receive rTMS and one participant assigned to receive sham rTMS reported headaches and requested termination of the rTMS portion of the therapy. Another participant assigned to receive sham was withdrawn due to the participant being diagnosed with alcohol dependence (See Supplemental information for details of individual participants and method of handling for analysis).

Of the 103 participants randomly assigned to treatment groups, 55 (rTMS + CPT N = 25; sham + CPT N = 30) were taking PTSD-, depression-, or pain-related medications during the study. All participants were on stable treatment for at least one month prior to beginning treatment except for 1 participant who added a psychiatric medication from initial screening to baseline. This participant was randomized to the rTMS + CPT condition and dropped out after the 3rd CPT treatment so only contributed baseline data. Medication changes during the study were made for 26% (N = 14) of the rTMS + CPT and 24% (N = 12) of the sham + CPT group, including adding, discontinuing, and switching medications, with N = 11 and N = 10, in the rTMS + CPT and sham + CPT groups respectively, of those making medication changes completing the 6-month evaluation. The association between group and medication change was not significant for the total sample or those who completed the trial. Some participants completely ceased taking medications for certain symptoms, including opioids (rTMS + CPT N = 1; sham + CPT N = 2), anti-depressants (rTMS + CPT N = 6; sham + CPT N = 1), benzodiazepine (rTMS + CPT N = 2), atypical neuroleptic (rTMS + CPT N = 1), α1-blocker (rTMS + CPT N = 1; sham + CPT N = 1) and zolpidem (rTMS + CPT N = 1; sham + CPT N = 2), but most remained on medications for specific symptoms throughout the study.

The motor threshold was successfully determined for all participants. For five of the participants (four rTMS + CPT), the motor threshold was too high to enable an increase to 110%. For these participants, the stimulation was set as high as possible resulting in stimulation between 100% MT to slightly less than 110% MT. No participant required adjustment of dose for tolerability.

4. Discussion

The addition of rTMS to CPT produced greater PTSD symptom reduction compared to sham + CPT. The strength of the effect, however, did differ across PTSD measures. Both the rTMS + CPT and sham + CPT groups showed statistically significant improvements in clinician (i.e., CAPS) and patient (i.e., PCL) rated symptom severity. However, although patient-rated symptom severity for the rTMS + CPT was statistically significantly lower at all assessment periods compared to the sham + CPT group, clinician rated symptom severity was statistically significantly lower for the active rTMS group at session 5, 3-months, and 6-months but not session 9 and 1-month. Based on estimates of minimally clinically important differences of 7.9 for PCL and 10.4 for CAPS (Stefanovics et al., 2017), difference between the rTMS + CPT and sham + CPT groups on PCL exceeded the minimally clinically important difference criterion at all assessment sessions but on CAPS only exceed the criterion at the Session 5, 3-month, and 6-month sessions. Thus, the effect of rTMS was weaker based on clinician versus patient rated symptom severity.

Previous research has shown both convergent and discriminant patterns of change following psychotherapy in clinician versus patient rated symptom severity in PTSD (Monson et al., 2008), that is, change on CAPS and PCL. In Monson et al. (2008), change was found to be correlated, both on total and symptom cluster scores, but the degree of change in clinician rated symptoms (i.e., CAPS) was found to be reduced compared to patient rated symptoms (i.e., PCL) (i.e., with change in CAPS at 0.75–0.82 standard deviation for every standard deviation change in PCL). Contextual factors (e.g., participation in novel

Table 2
Mean score of scales by group for each assessment session.

Group	Session	CAPS Total	PCL Total	M-PTSD	QIDS	IPF
Sham + CPT	Baseline (n = 49/48/49/49/48)	73.88(3.51)	52.82(2.05)	108.25(2.90)	12.10(0.73)	3.61(0.14)
	s5 (n = 35/34/35/35)	65.86(4.10)	46.51(2.29)	100.30(3.25)	9.56(0.85)	
	s9 (n = 30/30/29/30)	53.86(4.66)	42.35(2.53)	97.28(3.58)	9.18(0.97)	
	1 m (n = 30/30/30/29/30)	38.29(4.46)	38.78(2.45)	91.71(3.46)	7.39(0.93)	3.18(0.18)
	3 m (n = 28/25/26/26/26)	40.68(4.49)	37.04(2.48)	88.98(3.49)	7.39(0.94)	2.97(0.18)
	6 m (n = 28/27/28/28/28)	37.57(4.49)	38.08(2.46)	90.58(3.47)	8.12(0.93)	3.09(0.18)
rTMS + CPT	Baseline (n = 53/54/54/54/49)	75.28(3.24)	55.93(1.83)	107.01(2.67)	10.05(0.67)	3.23(0.13)
	s5 (n = 35/34/34/35)	56.21(3.80)	43.47(2.10)	97.88(3.01)	8.35(0.79)	
	s9 (n = 31/31/29/31)	45.95(4.04)	39.25(2.20)	93.10(3.17)	7.59(0.84)	
	1 m (n = 31/29/28/30/28)	31.11(4.04)	34.80(2.21)	85.58(3.17)	5.44(0.84)	2.80(0.16)
	3 m (n = 29/26/25/26/26)	30.32(4.07)	32.86(2.29)	83.46(3.27)	5.55(0.88)	2.77(0.17)
	6 m (n = 31/29/31/30/31)	27.51(4.04)	30.87(2.15)	78.97(3.15)	4.98(0.84)	2.72(0.16)

Mean value of scale for time point; SEM within parentheses adjacent to mean; Number of participants (n) per scale per time point shown in parentheses under Session; CAPS = Clinician Administered PTSD Scale; PCL = PTSD Checklist; M-PTSD = Mississippi PTSD Scale; QIDS = Quick Inventory of Depressive Symptoms; IPF = Inventory of Personal Functioning; s5 = fifth CPT session; s9 = ninth CPT session; 1 m = one month post-treatment; 3 m = three months post-treatment; 6 m = six months post-treatment.

therapeutic research, effective informed content conveying protection of data, etc.) were thought to explain the finding of greater change in subjective ratings compared to clinician-based ratings. However, the observed differences in the strength of the effects on PCL versus CAPS in the present study were in the differences between the rTMS + CPT and sham + CPT groups. Thus, previously suggested contextual factors seem less likely to have been important contributors to the differences we found. The differences in the longitudinal patterns of effects of rTMS + CPT compared to sham + CPT across clinician and participant rated symptom reductions instead might reflect partially unique aspects of the measures being affected by rTMS. With CAPS, clinicians assess frequency and intensity of symptoms experienced, but with PCL, the patient assesses personal distress due to symptoms experienced (i.e., rating the degree to which they are bothered by symptoms). Thus, the stronger and more consistent longitudinal effects on PCL might reflect the added influences of rTMS on brain circuits mediating the experience of personal distress experienced by the PTSD patient. However, correspondence between clinician and patient PTSD symptom severity evaluations and changes in symptom severity with treatment has yet to be clarified.

Although depression and overall function improved for both groups, there was no benefit for the rTMS + CPT group over the sham + CPT group on QIDS and IPF. Thus, the improvement in PTSD symptoms were not likely to be simply from rTMS treating the depressive symptoms or some general overall improvement in well-being. The lack of significant difference in depressive symptoms is not surprising given that rTMS once a week for 12 sessions is underpowered from the standpoint of a typical antidepressant treatment. Also, we previously demonstrated in this cohort that depression is the dominant factor in determining functional level in patients with PTSD (Kozel et al., 2016). Given that there was no difference in depression ratings (QIDS), it is also not surprising that there would be no difference in functional status (IPF) between the rTMS + CPT and sham + CPT groups.

One potential explanation, although speculative, for the sustained improvement of the rTMS + CPT versus the sham + CPT is that rTMS induced circuit level metaplastic changes in the brain. Metaplasticity is a term first coined by Abraham and Bear (1996) to describe the phenomenon of prior activity at the synapse or cell leading to a persistent change in synaptic plasticity (Abraham and Bear, 1996). Schmidt et al. expanded the concept from synaptic level to alterations in learning and memory and referred to it as "behavioral metaplasticity"(Schmidt et al., 2013). Metaplasticity has been demonstrated in the human cortex using rTMS and other forms of brain stimulation but primarily in the motor circuit (Muller-Dahlhaus and Ziemann, 2015; Weise et al., 2016). We posit that rTMS administered prior to CPT induced a behavioral metaplasticity (and presumably underlying neural metaplasticity) that produced a greater reduction in symptoms of PTSD that were sustained

for at least up to 6 months after treatment completion. The metaplasticity could result in greater prefrontal cortex functionality and/or connectivity with deeper limbic structures. Future work will be required to better understand the mechanisms and replicate these results. In addition, testing whether rTMS added to other forms of psychotherapy for trauma would be important to determine if rTMS's effect is restricted to CPT or more generalized to other forms of therapy.

The study has several limitations. Participants were predominantly male, from one particular era of combat, and with PTSD primarily from combat experiences. Also, due to safety concerns, the sample was limited to participants who could be safely enrolled in the study, which eliminated subjects with conditions such as moderate to severe TBI. Additionally, while participants were strongly encouraged to keep medications stable during the study, they were allowed to make clinically indicated changes authorized by their primary mental health provider. There were, however, no differences between groups in medication use or changes during the study. Although keeping medications completely stable prior to starting and during the trial is an important consideration, it must be balanced with flexibility in order to increase the generalization of the results to typical patients receiving treatment for combat-related PTSD. Also, our study did not incorporate an "active" sham that produced similar scalp sensations as the active coil. In addition, the treater was not blind to which treatment the participant received. Future studies should attempt to better match the active and sham treatments as well as have the treater blind to the group assignment. Finally, the study was started when the standard in psychiatry for diagnosis and measurement were based on DSM-IV criteria. With the adoption of DSM-5, and resulting changes in criteria for PTSD, these results should be replicated using the new standards.

As this was an initial study investigating whether rTMS added to CPT could improve participants symptoms, there were only a small number of treatment parameters investigated. There is a growing body of information in rTMS indicating that factors such as increasing number of sessions, location of stimulation, adequacy of target engagement, and personalizing treatment may improve treatment outcomes. Due to the timing of the rTMS with respect to the CPT being fixed in our study (i.e., rTMS immediately prior to CPT), the question of whether there is an optimal timing of rTMS to the CPT and whether the benefits are limited to CPT versus other psychotherapies that have been shown to reduce PTSD symptoms will also need to be addressed in future studies. A final consideration is that although data from every visit was included in the analysis, once a participant opted to end treatment, we did not acquire any subsequent data on that participant for the remaining assessment sessions. One option for the future is to allow participants to continue providing clinical ratings even if they decide to end treatment.

5. Conclusions

Combining CPT with rTMS led to improved symptom reduction in combat veterans with PTSD. Thus, the results show that rTMS combined with psychotherapy can augment the benefits of psychotherapy alone and improve treatment outcomes. Further work, however, is required before this treatment approach can be considered as standard clinical care.

Disclaimer statement

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of Defense, the Department of Veteran Affairs, or the U.S. Government. Neither the James A. Haley VAH nor VA health care providers were involved with this study during VA duty time.

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Greater than 3 years ago: The National Institute of Mental Health K23 NIMH 5 K23 MH070897-02, Role: PI 2005–2009; NIH/NCRR 5 UL1 RR024982-02 Packer (PI) Role: Pilot Study PI; Neuronetics Grant-in-kind support for supplies and use of equipment; the Defense Academy for Credibility Assessment, W74V8H-04-1-0010 (PI - Kozel)

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None.Speaking

None.Equity holdings (exclude mutual funds)

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Patents as an inventor through the Medical University of South Carolina on fMRI Detection of Deception, patents pending for Guided rTMS Inhibition of Deception, Optimizing VNS dose with rTMS.

Trial registration

clinicaltrials.gov; NCT01391832; Novel Treatment of Emotional Dysfunction in Post Traumatic Stress Disorder (PTSD); https://clinicaltrials.gov/ct2/show/NCT01391832.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2017.12.046.

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