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REPETITIVE TMS COMBINED WITH EXPOSURE THERAPY FOR PTSD: A PRELIMINARY STUDY

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Abstract

Treatment for anxiety and posttraumatic stress disorder (PTSD) includes exposure therapy and medications, but some patients are refractory. Few studies of repetitive transcranial magnetic stimulation (rTMS) for anxiety or PTSD exist. In this preliminary report, rTMS was combined with exposure therapy for PTSD. Nine subjects with chronic, treatment-refractory PTSD were studied in a placebo controlled, cross-over design of imaginal exposure therapy with rTMS (1Hz) versus sham. PTSD symptoms, serum and twenty-four hour urine were obtained and analyzed. Effect sizes for PTSD symptoms were determined using Cohen's d. Active rTMS showed a larger effect size of improvement for hyperarousal symptoms compared to sham; 24-hour urinary norepinephrine and serum T4 increased; serum prolactin decreased. Active rTMS with exposure may have symptomatic and physiological effects. Larger studies are needed to confirm these preliminary findings and verify whether rTMS plus exposure therapy has a role in the treatment of PTSD.

Keywords

post-traumatic stress disorder (PTSD); transcranial magnetic stimulation (TMS); psychological desensitization; psychological therapies; extinction

Introduction

Transcranial magnetic stimulation (TMS) is a method of inducing firing of cortical neurons. Studies examining prefrontal repetitive TMS (rTMS) show effects on cerebral oxygen perfusion in both local and distant brain regions (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2005; Chouinard, Van Der Werf, Leonard, & Paus, 2003; Ohnishi et al., 2004; Paus, Castro-Alamancos, & Petrides, 2001). Speer et al. (2000) have suggested that low- and high-frequency rTMS have opposite effects on cerebral perfusion. Specifically, high-frequency (20 Hz) rTMS increases cerebral perfusion, and low-frequency (1Hz) rTMS decreases it. Other studies have verified that low-frequency rTMS reduces cortical excitability (Hoffman & Cavus,

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2002; Huang, Edwards, Bhatia, & Rothwell, 2004). In addition, one study in mice demonstrated that rTMS normalized the hypothalamic-pituitary-adrenal (HPA) axis following stress (Czeh et al., 2002).

Repetitive TMS is emerging as a potentially effective treatment for mood symptoms including depression (Berman et al., 2000; George et al., 2000; Klein et al., 1999). One research group has conducted a placebo controlled trial of high-frequency (10 Hz) rTMS in humans for posttraumatic stress disorder (PTSD) with some success (Cohen et al., 2004; Grisaru, Amir, Cohen, & Kaplan, 1998), but this has yet to be replicated by other investigators. Open case series of TMS in PTSD have also been encouraging (McCann et al., 1998; Rosenberg et al., 2002).

Early functional neuroimaging research on PTSD reported increased oxygen perfusion in the right prefrontal cortex as subjects were reminded of their traumatic experiences (Rauch et al., 1996). This was replicated in some but not all subsequent studies, and led to the general interpretation that right-sided activity in PTSD was related to the role of the right hemisphere in anxiety and other adverse emotional experiences (Rauch et al., 1996; Simmons, Matthews, Stein, & Paulus, 2004). If low-frequency rTMS could decrease activity in right hemispheric cortical areas, it might prove to be helpful for improving functional brain abnormalities associated with PTSD.

Anxiety disorders can be treated by systematically exposing patients to the objects and events that induce anxiety or distress, or to reminders of them (Echeburua, de Corral, Zubizarreta, & Sarasua, 1997; Pitman et al., 1996). Imaginal exposure is used to treat PTSD by exposing patients to memories of the traumatic event(s) in a controlled setting, thereby desensitizing them to the event(s) and teaching them that they are no longer in danger (Cahil & Foa, 2005). Evidence from animal research suggests that paradoxically, rather than relaxation and autonomic deactivation, autonomic excitation improves the results of extinction training (Cain, Blouin, & Barad, 2004), the theoretical basis of exposure therapy. The same has been found for human anxiety disorder treatment, as well summarized by Craske and Mystkowski (Craske & Mystkowski, 2006). Because of emerging model of PTSD as a failure of fear extinction it is likely to be especially important to bring the neural circuits and the autonomic arousal involved in the conditioned fear “on line” when attempting to extinguish the fear response.

Because of this previous research on fear extinction, application of rTMS to actively engaged, rather than passive, brain circuits may be a more effective method of modifying brain circuits. The use of rTMS as an enhancement to fear extinction in PTSD has been suggested by Milad et al.(Milad, Rauch, Pitman, & Quirk, 2006). To date, there have been no studies investigating the effects of low frequency rTMS for decreasing cortical excitability during recollection of unpleasant traumatic memories. In this study we combined low frequency rTMS and exposure for the treatment of long-standing, treatment-refractory PTSD.

Materials and Methods

Subjects

Eight women and 1 man with chronic, long-standing PTSD were recruited into the study because they had treatment-refractory PTSD. Specifically, previous treatments lasted over two years in duration and had included psychopharmacology and psychotherapy (except eye movement desensitization and reprocessing—EMDR) yet all patients continued to meet criteria for PTSD and have distressing intrusion symptoms including flashbacks. Mean age was 41.4 years (SD=12.3, range 24–56) and mean time since index traumatic event was 22.3 years (SD=13.0, range 2–37). All but one subject was right-handed. The project was approved

by the Institutional Review Board at the NIMH Intramural Research Program. The study was described to the subjects and written informed consent was obtained.

Subjects underwent PET scans before rTMS and demonstrated positive blood flow correlated with flashback intensity in brainstem, lingual, bilateral insula, right putamen, left hippocampal and perihippocampal regions, left somatosensory cortex, and cerebellum. They showed inverse correlations between blood flow and degree of disturbance with flashback in the bilateral dorsolateral prefrontal and right fusiform and medial temporal cortices, as previously described (Osuch et al., 2001). All subjects met criteria for current major depression and comorbid anxiety diagnoses were common. All had a history of prior substance abuse, but 8 out of 9 had not been using drugs or alcohol for at least 3 months prior to study. Patients were tapered off antipsychotics and/or mood stabilizers prior to study, but the co-administration of antidepressants and benzodiazepines was permitted due to the ongoing severity of symptoms. Doses of these medications were maintained constant for at least 3 weeks before imaging or the onset of rTMS treatment. As mentioned, upon study entry all subjects endorsed the presence of intermittent, disturbing flashbacks.

Subjects were evaluated at the start of the study with the following measures. The Schedule for Affective Disorders and Schizophrenia (SADS), Lifetime Version, Modified to Anxiety Disorders, a structure interview used to detect diagnosable Axis I anxiety and mood disorders. The Clinician Administered PTSD Scale (CAPS) was used to verify the diagnosis of PTSD and to detect the presence or absence of PTSD symptoms in the three different symptom clusters of PTSD (intrusion, avoidance, hyperarousal). The Hamilton Depression Rating Scale (HDRS), a clinician-rated measure of depressed mood; and the Impact of Events Scale (IES), a self-report measure of severity of avoidance and intrusion symptoms of PTSD, were also administered.

Procedure

The protocol involved a double-blind, sham-controlled cross-over design, with consecutive subjects alternately receiving 20 sham or active rTMS sessions as the initial experimental condition. Neither the patient nor the researcher assessing symptoms knew which phase was active. The individual administering the rTMS was not blind to phase. Active or sham rTMS was given at least 3 sessions per week and no more than 5 per week. Each session lasted 30 minutes. There was a minimum two-week washout period between the first and second conditions. The crossover design was chosen as the most likely way of showing within-subject differences in a population heterogeneous for type of traumatic exposure and duration and severity of symptoms.

Patients were asked to complete a list of 10 events or cues to be used during sessions of systematic exposure during active and sham rTMS. These lists began with an item #0, chosen by the subjects as a calming or soothing experience. The next item (#1) was a neutral experience. From #2 to #9 the subjects listed aspects of an event related to their traumatic experience(s) that they felt would elicit successively increasing levels of distress. These personalized lists were then used during the exposure sessions as a means of activating brain circuitry involved in the patients' intrusive flashback symptoms.

Sessions began with five minutes of rTMS with the patient sitting quietly at rest. During the first and second sessions in each condition, subjects were then instructed to talk about item #0 and item #1, respectively, for 5 minutes in order to become acclimated to the experimental situation. In subsequent sessions subjects could speak for 5 minutes about any of the 10 items on their list of their choosing, or remain silent. The aim was for subjects to have complete control over the degree of traumatic exposure they experienced during each session. They where informed when the five minutes of designated speaking time was over, but were allowed

to talk for longer if they desired. Except rarely, subjects spoke for the remainder of the 30 minutes. Subjects reached similar levels of traumatic recall during the two experimental conditions.

Magnetic Stimulation

Magnetic stimulation was performed using a Cadwell High Speed Magnetic Stimulator and a figure-eight-shaped, water-cooled coil (Cadwell, Inc, Kennewick, WA) mounted on a swivel arm to minimize magnet movement.

Immediately prior to beginning experimental treatment, subjects underwent motor threshold determination. This was ascertained by activation of the abductor pollicis brevis (APB) muscle with a single stimulus delivered to the right M1 area of primary motor cortex using surface electromyography. Threshold was defined as the intensity required to produce motor evoked potentials (MEPs) of ≥50μV in the APB with five of ten consecutive stimuli when the coil was placed over the optimal position for APB activation, and100% motor threshold was then used for all active and sham rTMS sessions.

The stimulation site was defined as the region 5 cm rostral in the same sagittal plane as the optimal site for MEP production in the left ABP muscle. This means of locating the dorsolateral prefrontal cortex has been used in rTMS studies of depression (Kimbrell et al., 1999), obsessive compulsive disorder (Greenberg et al., 1997) and motor learning (Pascual-Leone, Wassermann, Grafman, & Hallett, 1996). Treatment involved 30 minutes of continuous 1 Hz right frontal active or sham stimulation (1800 stimulations per session; for a total of 36,000 stimuli in each condition), during which time patients spoke about events as described above.

In the sham condition the rTMS coil was placed at a 45 degree angle to the head. The plastic shell of the magnet remained in contact with the head, but the point of maximal activation was superficial compared with active stimulation. This produced nerve and muscle stimulation on the face and scalp, and has been used as a sham in previous studies (George et al., 1997; Kimbrell et al., 1999; Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998) although some have suggested it has a significant active component (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001; Loo et al., 2000).

Outcome Measures

Assessments occurred at baseline (within three days before the first condition); on the final day of the first condition; on the day before the onset of the second condition; and on the last day of the second condition. Subjects were evaluated using the CAPS, IES and the HDRS at these time points. Concurrent biological measures included 24-hour urine collection for cortisol, dopamine, epinephrine, norepinephrine, as well as serum analyses of cortisol, thyroid hormones and prolactin. Not all data were available on all subjects in each session because one subjects ended the study during the sham treatment due to symptom severity. An additional subject did not complete all urine and serum sampling.

Data Analysis

Linear mixed models were used to examine the difference between the active and sham conditions of treatment over time for behavioral measures, where a compound symmetry variance-covariance structure was the best fitting matrix. Planned least-significant-difference comparisons were used to examine the pre-post differences in each condition. Paired t-tests were used to compare biological variables in active and sham conditions for each individual. Cohen's d is reported for the difference between those conditions, where negative values indicate lower scores at the end of the condition from baseline, and positive scores reflect increased scores at the end of the experimental condition. For behavioral measures, the effect-

size for pre-post differences within conditions is also provided. Cohen's d is generally interpreted as follows: ≥1.0 very large; ≥0.8 large; ≥0.5 moderate; 0.2–0.4 small. Given the small sample size of this preliminary study, other statistics were not performed.

Results

Behavioral results are presented in Table 1, showing the effects of active and sham rTMS on PTSD symptom clusters and depressive symptoms.

Linear mixed models showed no statistically significant differences on any behavioral measure. However, planned comparisons showed that hyperarousal symptoms on the CAPS showed moderate improvement and effect size with exposure plus active rTMS but no effect with exposure plus sham rTMS. Hyperarousal symptoms on active treatment were lower at endpoint relative to sham. The CAPS and IES scores of avoidance and intrusion symptoms were not changed with active rTMS.

Table 2 shows the effects of the active and sham rTMS plus exposure therapy on 24-hour urine and serum catecholamine and hormone levels. While no differences were statistically significant, biological variables that demonstrated the greatest effect sizes were urinary norepinephrine and serum T4, both of which were higher with active compared with sham rTMS; and serum prolactin, which was lower with active rTMS compared to sham. The effect size of T4 was very large, that of norepinephrine was large and that of prolactin was moderate.

Discussion

Exposure therapy for PTSD is considered an effective treatment because it reduces the exaggerated reactions individuals have in response to reminders of the traumatic event or other stimuli (Cahil & Foa, 2005) through fear extinction (McNally, 2007). Exposure alone results in desensitization to arousing stimuli and higher tolerance for intrusive traumatic reminders, which is usually associated with less avoidance. Not all patients respond to exposure therapy. This preliminary study of active rTMS plus exposure with a chronic, treatment-refractory population was largely negative, though greater reduction in hyperarousal scores on CAPS were observed. The procedure was well-tolerated by this subject population, in spite of their being on reduced medication regimens.

PTSD has been associated with low plasma cortisol, TSH and prolactin (Olff, Guzelcan, de Vries, Assies, & Gersons, 2006) and elevated T3 and other thyroid hormones (Friedman, Wang, Jalowiec, McHugo, & McDonagh-Coyle, 2005; Karlovic, Marusic, & Martinac, 2004). Acute TMS has been shown to activate the hypothalamic pituitary adrenal and hypothalamic pituitary thyroid axes, but to have no effect on prolactin (Szuba, O'Reardon, & Evans, 2000). Our results show relatively greater T4 following the 20 sessions of active rTMS and relatively lower prolactin with active rTMS. While seizures and electroconvulsive therapy increase prolactin and TMS is reported to have no effect on it (Szuba, O'Reardon, & Evans, 2000), this study suggested lower prolactin in the active versus sham rTMS group.

One potential confound is a possible treatment order effect. Active rTMS applied during the first phase of the study showed more improvement than during the second. When the first phase was examined independently, active rTMS produced changes in psychometric scores in the direction of improvement in 3 of the 6 measures (CAPS Intrusion, CAPS Hyperarousal, and IES Avoidance). This was not true during the second arm of treatment. This suggests that a parallel study of active versus sham rTMS with exposure may have shown a stronger affect of rTMS.

A major limitation of this study is the small number of subjects who participated. In addition, subjects were complicated with comorbid depression, anxiety and histories of substance abuse. They were on constant levels of antidepressant and/or benzodiazepine medications. A medication-free condition was avoided to reduce the risk of a confounding period of potential symptom exacerbation, with clinical deterioration that could have prohibited study participation. Subjects were a distinctly treatment-refractory group who, on average, had not responded to many years of psychopharmacology or various psychotherapies as provided in the community and in psychiatric hospitals.

The particular sham technique in this study has been shown to have some active effects (Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001). This may have resulted in a failure to find significant differences between the active and sham groups. Repeat of this procedure with a less active sham may have led to more promising results.

The parameters used during the rTMS treatment were selected with the hopes of diminishing hyperactivity in the right frontal cortex reported in individuals with PTSD. One Hz was chosen as likely to dampen hyperexcitability associated with trauma re-experiencing similar to that seen in 1Hz stimulation of temporal-parietal cortex for suppression of refractory auditory hallucinations in schizophrenia (Aleman, Sommer, & Kahn, 2007; Hoffman et al., 1999; Hoffman & Cavus, 2002). But the consistency and specificity of right frontal hyperactivity in PTSD remains to be further clarified. In fact, the group studied here did not demonstrate right prefrontal hyperactivity (Osuch et al., 2001). Furthermore, to the extent that desensitization involves new learning requiring activation of glutamatergic NMDA receptors, as revealed by the findings that cycloserine facilitated extinction of phobic anxiety by Davis et al., (Davis, Ressler, Rothbaum, & Richardson, 2006), it is possible that higher frequencies of rTMS (10–20 Hz), which tend to be associated with LTP and brain activation (Post et al., 1999; Post, Speer, Weiss, & Li, 2000) might be preferable to the 1 Hz chosen here to dampen postulated hyperexcitability. Further exploration of the optimal rTMS parameters to facilitate exposure therapy for chronic, refractory PTSD appears warranted. The process of parameter optimization might also be enhanced by attempts to more systematically match rTMS parameters to an individual's brain networks of maximal abnormality as revealed on functional brain imaging. The intercleaved online approach of George and Bohning et al., with active rTMS in between fMRI scans (Bohning et al., 1999) would appear to have considerable merit for this individualized type of exploration.

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Table 1

Treatment Versus Baseline

	Active				Sham				Difference
	n	Mean Difference* (SE)	p	d**	n	Mean Difference* (SE)	p	d**	d***
CAPS B (Intrusion)	9	−0.22 (0.31)	.48	− 0.30	8	−0.19 (0.32)	.56	− 0.25	0.45
CAPS C (Avoidance)	9	−0.33 (0.62)	.60	− 0.23	8	−0.72 (0.65)	.28	− 0.47	0.00
CAPS D (Hyperarousal)	9	−1.00 (0.55)	.08	− 0.76	8	−0.09 (0.57)	.87	− 0.07	− 0.42
Hamilton (HDRS)	9	2.67 (2.11)	.22	0.52	9	−0.22 (2.11)	.92	− 0.04	− 0.34
Impact of Events: Avoidance	9	0.44 (1.37)	.75	0.13	9	0.00 (1.37)	1.00	0.00	0.30
Impact of Events: Intrusion	9	1.44 (1.50)	.35	0.39	9	−0.78 (1.50)	.61	− 0.21	0.09

* Note: 80 Mean = Treatment – Baseline.

** Negative values for the effect size indicate decreased values relative to baseline (improvement); positive effect size indicates increased values relative to baseline (worsening).

*** Cohen's d is positive if active is greater, negative if sham is greater.

Table 2

Active Versus Sham

	n	Active Mean (SD)	Sham Mean (SD)	p	d*
Urine (mcg/24°)					
Cortisol	9	43.2 (32.1)	40.3 (21.1)	.82	0.16
Dopamine	7	207.3 (36.2)	218.7 (54.5)	.55	− 0.52
Epinephrine	7	4.14 (1.63)	3.69 (1.90)	.58	0.48
Norepinephrine	7	48.1 (28.4)	43.7 (33.2)	.32	0.88
Serum					
Cortisol (mcg/dL)	8	8.26 (3.38)	8.46 (3.81)	.93	− 0.07
Free T4 (mcg/dL)	8	1.08 (0.16)	1.04 (0.22)	.40	0.68
T4 (nmol/L)	7	7.84 (1.25)	7.01 (1.39)	.13	1.43
T3 (ng/dL)	7	124.4 (10.0)	130.1 (23.3)	.48	− 0.62
TSH (micro IU/mL)	8	0.84 (0.29)	0.76 (0.47)	.63	0.39
Prolactin (mcg/L)	8	7.25 (1.98)	8.50 (3.12)	.33	− 0.79

*Cohen’s d is positive if active is greater, negative if sham is greater.