



Repetitive TMS combined with exposure therapy for PTSD: A preliminary study[☆]

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ABSTRACT

Treatment for anxiety and post-traumatic 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, crossover design of imaginal exposure therapy with rTMS (1 Hz) versus sham. PTSD symptoms, serum and 24 h 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-h 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.

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1. 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 perfu-

sion. Specifically, high-frequency (20 Hz) rTMS increases cerebral perfusion, and low-frequency (1 Hz) rTMS decreases it (Speer et al., 2000). Other studies have verified that low-frequency rTMS reduces cortical excitability (Hoffman & Cavus, 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 post-traumatic 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).

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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 (2006). Because of emerging models 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, Rauch, Pitman, and 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.

2. Materials and methods

2.1. Subjects

Eight women and one man with chronic, long-standing PTSD were recruited into the study because they had treatment-refractory symptoms. Specifically, previous treatments lasted over 2 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 (S.D. = 12.3, range 24–56) and mean time since index traumatic event was 22.3 years (S.D. = 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.

2.2. Procedure

The protocol involved a double-blind, sham-controlled crossover 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 min. There was a minimum 2-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

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