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Brief report

Repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of Panic Disorder (PD) with comorbid major depression

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Abstract

Background: Studies suggest that the dorsolateral prefrontal cortex (DLPFC) participates in neural circuitry that is dysregulated in Panic Disorder (PD) and Major Depressive Disorder (MDD). We tested whether low-frequency repetitive Transcranial Magnetic Stimulation (rTMS) could normalize the overactivity of right frontal regions and thereby improve symptoms.
Methods: Six patients with PD and comorbid MDD were treated with daily active 1-Hz rTMS to the right DLPFC for 2 weeks in this open-label trial.
Results: Clinical improvements were apparent as early as the first week of treatment. After the second week, 5/6 of patients showed improvements in panic and anxiety, and 4/6 showed a decrease in depression, with sustained improvement at 6 months of follow-up. Right hemisphere resting motor threshold increased significantly after rTMS.
Limitations: Limitations of this study are the open design and the small sample size.
Conclusions: Slow rTMS to the right DLPFC resulted in significant clinical improvement and reduction of ipsilateral motor cortex excitability. Replications in larger sample will help to clarify the relevance of this preliminary data and to define the potential role of right DLPFC rTMS in panic with major depression.

Keywords: Repetitive Transcranial Magnetic Stimulation (rTMS); Resting Motor Threshold; Panic Disorder (PD); Major Depressive Disorder (MDD)

1. Introduction

The dorsolateral prefrontal cortex (DLPFC) is one among several brain regions implicated in Panic Disorder (PD), and functional abnormalities in DLPFC

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have also been consistently replicated in Major Depressive Disorder (MDD). Lateral asymmetries in DLPFC activity have been reported in both PD and MDD (van den Heuvel et al., 2005; Mayberg et al., 1999). For example, unmedicated panic patients showed more asymmetry of activation (right>left) in DLPFC and, when treated with Cognitive Behavioral Therapy or antidepressants, showed decreases in prefrontal metabolism with a prominent right>left difference (Nordahl et al., 1998; Prasko et al., 2004). Moreover, anxiety-depression comorbidity has been characterized by more right than left frontal activity in MDD subjects, consistent with a key role of right PFC in anxiety disorders (Pizzagalli et al., 2002).

A few groups have examined whether PD could be treated by targeting right DLPFC overactivity with low-frequency repetitive Transcranial Magnetic Stimulation (rTMS), reported to have inhibitory action on cortical excitability (Chen et al., 1997). To date, only 4 PD patients have been treated with right DLPFC 1-Hz rTMS. Zwanzger et al. (2002) found reduced panic symptoms with marked improvement in anxiety lasting 1 month in 1 patient. Three patients in an open case series experienced modest symptom improvements. Alternating 1-Hz with 20-Hz rTMS on left DLPFC added no benefit (Garcia-Toro et al., 2002). While most of the work with rTMS in depression has focused on the left DLPFC (Lisanby et al., 2002), two studies suggest that right DLPFC 1-Hz rTMS has antidepressant activity (Klein et al., 1999; Fitzgerald et al., 2003). The use of 1-Hz rTMS in patients with comorbid panic and depression has not previously been reported.

We present an open trial of rTMS in PD and comorbid depression, and the first data on its effect on motor cortex excitability.

2. Methods

This was a pilot study of rTMS in adults resistant to at least 1 medication taken at recommended dosage for at least 12 weeks or intolerant to medications when side effects prevented them from being able to take the recommended dosage for at least 12 weeks. Six right-handed outpatients (3 male; mean age=50 years, SD=18.46) who met DSM-IV-TR criteria for PD and unipolar depression in a current major depressive episode were recruited from the psychiatric clinic at Siena University Polyclinic "Le Scotte." Patients had a number of previous major depressive episodes equal to 6.5±5.2. Patients meeting criteria for other axis I and/or II disorders (Structured Clinical Interview-I and -II) and those with a history of seizure or head trauma were excluded. All patients gave written informed consent, and the protocol was approved by the Local Ethics Committee.

Three patients were taking psychotropic medications (paroxetine, mirtazapine, alprazolam, lorazepam, gabapentin), held constant for 12 weeks before and during rTMS. The other three had a history of drug-intolerance and were off medications. We used a 70-mm figure-eight shaped coil and the MAGSTIM super-rapid stimulator (Magstim Company, Ltd., Whitland, U.K.). Resting Motor Threshold (RMT) was recorded daily, and defined as the intensity required to elicit at least 5 MEPs of 50 μV in peak-to-peak amplitude in 10 consecutive stimulations when the coil is placed over the optimal position to activate the left abductor pollicis brevis. The right DLPFC was localized 5 cm anterior to the optimal site. rTMS was delivered in 4 daily trains at 100% of RMT, 1 Hz, for 5 min, and with 2-minute inter-train interval (1200 stimuli/day), for a total of 10 days.

Observer- and self-reported scales were administered at baseline and after 1 and 2 weeks of stimulation: Sheehan Clinician Rated Anxiety Scale (SCRAS), Hamilton Anxiety Rating Scale (HARS), Hamilton Depression Rating Scale (HDRS), Clinical Global Impression (CGI), Panic Disorder Severity Scale-Self Reported (PDSS), Beck Depression Inventory (BDI), Symptoms Check-List (SCL-90), Social-Adaptation Self-evaluation Scale (SASS). CGI was repeated 1, 3, and 6 months after completion of treatment to evaluate the long-term clinical stability.

Statistical analyses were performed using SPSS library, 11.0 version. Repeated-measures analysis of variance (ANOVA), with adjustments for non-sphericity, was applied to evaluate time-dependent effects of rTMS on PD and anxiety (SCRAS, PDSS, HARS), depression (HDRS, BDI), general psychopathology (SCL-90) and social adjustment (SASS), followed by LSD post-hoc tests. We used the same approach to test whether rTMS affected RMT. A between-subjects analysis was performed to test whether patients on medications had a different response to rTMS when compared with those without meds. Pearson correlations were used to examine whether changes in panic and depression correlate. Baseline HDRS score was used as covariate in the ANOVA to examine the effect of depression on panic symptoms changes. Student *t*-test was used to compare to baseline CGI scores obtained at 1, 3, and 6 months.