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Research report

Opposite effects of high and low frequency rTMS on mood in depressed patients: Relationship to baseline cerebral activity on PET

A.M. Speer [a], B.E. Benson [a], T.K. Kimbrell [b], E.M. Wassermann [c], M.W. Willis [d], P. Herscovitch [e], R.M. Post [a,*]

[a] *Biological Psychiatry Branch, NIMH, NIH, Bethesda, Maryland, United States*
[b] *VA Medical Center, North Little Rock, Arkansas, United States*
[c] *NINDS, NIH, Bethesda, Maryland, United States*
[d] *Dept of Psychiatry, USUHS, Bethesda, Maryland, United States*
[e] *PET Department, NIH Clinical Center, Bethesda, Maryland, United States*

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Abstract

Background: Optimal parameters of rTMS for antidepressant efficacy in general, or within patients, have not been adequately delineated.
Methods: Using a double-blind, sham-controlled, cross-over design, 22 adult patients with treatment refractory major depression ($n=9$; bipolar disorder, depressed phase) were randomized to active rTMS (20-Hz or 1-Hz) or sham rTMS conditions and given 5 rTMS treatments per week for two weeks. Repetitive TMS was administered at 100% of motor threshold for 1600 pulses over the left prefrontal cortex using a figure-eight coil. Patients initially randomized to sham rTMS were then exposed to two weeks of active rTMS with each frequency under blinded conditions. Those who received active 20-Hz and 1-Hz rTMS were crossed over to the opposite frequency for two weeks. Improvement in Hamilton Depression ratings were assessed after each two-week treatment phase. PET imaging was used to evaluate the patient's baseline absolute regional cerebral activity (blood flow and metabolism) as potential predictor of clinical response.
Results: Changes in depression severity on 1-Hz and 20-Hz rTMS were inversely correlated. PET scans with baseline hypoperfusion (but not hypometabolism) were associated with better improvement on 20-Hz rTMS as predicted.
Limitations: The magnitude of the clinical change with either frequency at 100% motor threshold was not robust, and larger studies with higher intensities of rTMS for longer durations of time should be explored.
Conclusions: High and low frequency rTMS exerts differential effects on depressed mood within individual subjects. The brain activity predictors and correlates of an optimal antidepressant response to rTMS remain to be better defined.

Keywords: Repetitive transcranial magnetic stimulation; Depression; Positron emission tomography; Regional cerebral blood flow; Hypoperfusion; Hyperperfusion

* Corresponding author. Psychiatry, George Washington and Penn State Schools of Medicine and Bipolar Collaborative Network, 5415 W. Cedar Lane, Suite 201B Bethesda, MD 20814, United States. Tel.: +1 301 530 8245; fax: +1 301 530 8247.
E-mail address: robert.post@speakeasy.net (R.M. Post).

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1. Introduction

Several recent meta-analyses have suggested the efficacy of active repetitive transcranial magnetic stimulation (rTMS) over the left prefrontal cortex compared with sham control procedures in the treatment of acute depression (Burt et al., 2002; Kozel and George, 2002; Martin et al., 2003). However, some recent controlled studies have failed to observe differences from controls (Nahas et al., 2003; Hoppner et al., 2003; Loo et al., 2003a; Mosimann et al., 2003; Hausmann et al., 2004; Poulet et al., 2004).

There is suggestive evidence that treatment involving more robust rTMS parameters (such as higher intensities of stimulation for longer periods of time) are more likely to yield positive effects compared with studies with less robust procedures (George et al., 2000; Padberg et al., 2002; Rossini et al., 2005; O'Reardon et al., 2007).

The optimal frequency and location of rTMS remain largely unresolved factors in general, as do the optimal parameters for a given patient in particular (George et al., 2000). The studies that combined high frequency rTMS over the left prefrontal cortex, with low frequency rTMS over the right prefrontal cortex show significantly greater effects than sham in two studies (Garcia-Toro et al., 2006; Fitzgerald et al., 2006); but not another (Conca et al., 2002).

In the study of Kimbrell et al. (1999) in patients with major depression, opposite effects of 1- and 20-Hz stimulation (at 80% of motor threshold; MT) were observed in individual patients, i.e., patients who improved on one frequency tended to worsen on the other frequency ($r=-0.797$; $p<0.0004$). We also found that 1- and 20-Hz rTMS exert opposite effects on regional brain activity lasting 48 h after ten treatments (Speer et al., 2000); blood flow increased in a widespread fashion with 20 Hz and decreased to a lesser extent with 1-Hz rTMS. As predicted, those with lower levels of baseline metabolism on positron emission tomography (PET) tended to show better response to 20-Hz rTMS, whereas those with higher levels showed better response to 1 Hz (Kimbrell et al., 1999).

Given the data showing that high frequency rTMS increases regional cerebral blood flow (rCBF) and low frequency rTMS decreases it (Speer et al., 2000; Loo et al., 2003b), and that patients show differential frequency-dependent antidepressant responsiveness (Kimbrell et al., 1999), we sought to further examine possible regional cerebral predictors of improvement in depressed mood in response to higher intensity rTMS, i.e., 100% of MT. We predicted that depressed patients with low baseline regional cerebral activity measured by PET would experience better antidepressant response to high frequency (20-Hz) rTMS, while those with high baseline activity would respond better to low frequency (1-Hz) rTMS.

2. Methods

2.1. Subjects

Twenty-two highly treatment-resistant depressed patients meeting DSM-IV criteria for either bipolar illness ($n=9$) or unipolar major depression ($n=13$) were included. Patients gave oral and written informed consent for the rTMS and associated brain imaging studies, and other procedures involved. The study was approved by both the Radiation Safety Committee of the National Institutes of Health and the Institutional Review Board of the NIMH. Two patients dropped out of the study prior to rTMS randomization.

Patients were randomized to receive 10 daily sessions of rTMS (5/week) over the left prefrontal cortex with either active (1-Hz or 20-Hz) or sham rTMS. Those receiving active rTMS were crossed over to the opposite frequency in the second two weeks to evaluate response within individuals. Those receiving sham rTMS first were then exposed to both of the other rTMS frequencies for two weeks (20-Hz rTMS; 1-Hz). After patients were exposed to both active frequencies, they were allowed to enter a continuation phase (at the rTMS frequency to which they had responded the best) for treatment confirmation and optimization. The rTMS was then tapered and pharmacological treatment begun prior to discharge. Two patients received only one frequency rTMS and declined further rTMS phases. Patients remained off of all psychotropic medication throughout the rTMS study except for three of the bipolar patients who were maintained on their prophylactic medication (one patient on valproate, one on carbamazepine, and one on T4 replacement).

2.2. Ratings

The Hamilton Rating Scale for Depression (HAM-D, 28-item expanded version) (Hamilton, 1960) was administered by highly-trained research assistants at: (1) baseline; (2) the end of weeks 1 and 2 of each rTMS treatment phase; and (3) on the day of the PET procedure. The raters and all other ward staff were blind to treatment assignment. The change from baseline until after two weeks of each phase was evaluated by paired t and response to high and low frequency rTMS using Pearson's correlation coefficient (r).