
A Randomized Clinical Trial of Repetitive Transcranial Magnetic Stimulation in the Treatment of Major Depression

Robert M. Berman, Meera Narasimhan, Gerard Sanacora, Alexander P. Miano, Ralph E. Hoffman, X. Sylvia Hu, Dennis S. Charney, and Nashaat N. Boutros

Background: Multiple groups have reported on the use of repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant major depression. The purpose of this study is to assess the efficacy of rTMS in unmedicated, treatment-resistant patients who meet criteria for major depression.

Methods: Depressed subjects, who had failed to respond to a median of four treatment trials, were assigned in a randomized double-blind manner to receive either active ($n = 10$; 20 2-sec trains of 20 Hz stimulation with 58-sec intervals; delivered at 80% motor threshold with the figure-of-eight coil positioned over the left dorsolateral prefrontal cortex) or sham ($n = 10$; similar conditions with the coil elevated and angled 45 degrees tangentially to the scalp) rTMS. These sequences were applied during 10 consecutive weekdays. Continuous electroencephalogram sampling and daily motor threshold determinations were also obtained.

Results: The group mean 25-item Hamilton Depression Rating Scale (HDRS) score was 37.2 (± 2.0 SEM) points. Adjusted mean decreases in HDRS scores were 14.0 (± 3.7) and 0.2 (± 4.1) points for the active and control groups, respectively ($p < .05$). One of 10 subjects receiving active treatment demonstrated a robust response (i.e., HDRS decreased from 47 to 7 points); three other patients demonstrated 40–45% decreases in HDRS scores. No patients receiving sham treatment demonstrated partial or full responses.

Conclusions: A 2-week course of active rTMS resulted in statistically significant but clinically modest reductions of depressive symptoms, as compared to sham rTMS in a population characterized by treatment resistance. *Biol Psychiatry* 2000; 47:332–337 © 2000 Society of Biological Psychiatry

Key Words: Major depression, transcranial magnetic stimulation, randomized clinical trial, medication resistance, neuroanatomy, dorsolateral prefrontal cortex

Introduction

Prevailing hypotheses on the pathophysiology of psychiatric illnesses such as major depressive disorder have been founded predominantly on receptor-based models. With advances in functional neuroimaging, hypotheses on the neurocircuitry of depression have been offered (Drevets 1998; Mayberg 1997). Until the development of transcranial magnetic stimulation (TMS), no practical tools have been available to directly exploit this understanding in the treatment of major depression. Multiple groups have reported that repetitive transcranial magnetic stimulation (rTMS) may be efficacious in treatment-refractory major depression. To date, most of these published studies are limited by either open-label design or inclusion of medicated depressed subjects. In one report (George et al 1997), active rTMS treatment (80% motor threshold [MT]; 20 Hz; 20 2-sec trains; 58-sec off-intervals; 5 cm anterior to the point yielding maximal stimulation of the right abductor pollicis brevis muscle) resulted in greater decline on the Hamilton Depression Rating Scale (HDRS) than sham rTMS. In another report (Pascual-Leone et al 1996), rTMS applied over a similarly defined area resulted in clinically and statistically superior improvement in depressive symptoms when compared to four other locations. More recent blinded (Klein et al 1999) and open-label reports have also lent compelling support to the efficacy of TMS in the treatment of major depressive disorder (Epstein et al 1998); however, discordant findings have also been reported (Loo et al 1999).

The purpose of the present study was to assess the efficacy of rTMS under controlled conditions in unmedicated, treatment-refractory patients who met criteria for major depressive disorder, employing parameters that were previously reported to be successful.

From the Yale University School of Medicine, Department of Psychiatry (RMB, MN, GS, APM, REH, XSH, DSC, NNB) and School of Epidemiology and Public Health (XSH), New Haven; Clinical Neuroscience Research Unit, Connecticut Mental Health Center, New Haven (RMB, APM, DSC); Affective Disorders Program, VA Connecticut Healthcare System, West Haven Campus, West Haven (MN, GS, DSC, NNB); and Yale Psychiatric Institute, New Haven (REH), Connecticut.

Address reprint requests to Robert M. Berman, M.D., Clinical Neuroscience Unit (Rm. 360), Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519.

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Methods and Materials

Twenty patients between the ages of 18 and 70 years who met DSM-IV criteria for major depressive episode on initial phone interview were screened via a modified 25-item HDRS (Berman et al 1999; Mazure et al 1986), a structured clinical interview for DSM-IV (SCID; Spitzer et al 1999), a physical examination, medical as well as psychiatric histories, routine blood as well as urine laboratory analyses, an electrocardiogram, and an electroencephalogram (EEG). Eligible patients met DSM-IV criteria for a major depressive episode; were deemed treatment-resistant (i.e., failed at least one adequate pharmacologic trial during the current episode or previous episodes); did not meet criteria for a substance or alcohol abuse diagnosis; if female, had negative serum β -human chorionic gonadotropin tests and were adhering to adequate methods of birth control; did not have a history of significant neurologic illnesses, such as seizures or head trauma; did not have EEG abnormalities suggestive of an epileptic predisposition; and did not have significant, unstable medical illnesses. (Only two patients, both from the sham group, were on medications. One patient took amlodipine and lisinopril for hypertension. Another patient took glyburide, digoxin, and warfarin sodium for non-insulin-dependent diabetes mellitus, chronic atrial fibrillation, and hypertension. Medical evaluation for both of these patients included consultation with their internists.) Patients with comorbid psychiatric diagnoses were included, provided that the onset occurred after the development of major depression (for axis I diagnoses) and that the symptoms of major depression were more prominent (for axis I and II diagnoses), as determined by consensus of two research psychiatrists. Qualifying patients were enrolled after complete discussion of the study and their written consent was obtained. Treatment histories were typically obtained via clinical interviews and contact with the most recent prescribing physician. Trials counted in the demographics table consisted of a minimal 4 weeks of treatment with at least 200 mg/d of imipramine, 20 mg/d fluoxetine, 60 mg/d phenelzine, 225 mg/d venlafaxine, and 30 mg/d mirtazapine (Prudic et al 1996); augmentation agents included lithium, stimulants, buspirone, and thyroid hormone. The review board of the human investigations committee and the U.S. Food and Drug Administration approved the protocol and consent forms.

All subjects were free of antidepressants, neuroleptics, and benzodiazepines for the week prior to initiating TMS treatment, tapers beginning earlier as necessary. Patients met with clinicians at least weekly during the pretreatment period and all were offered an inpatient admission to the Clinical Neuroscience Research Unit (Connecticut Mental Health Center, New Haven, CT). Inpatients were allowed chloral hydrate (500 mg qHS p.r.n.) for severe insomnia. Patients were randomly assigned to receive a course of active or sham TMS via a high-speed magnetic stimulator (Cadwell Inc., Kennewick, WA) with a figure-of-eight, water-cooled coil. Motor threshold (MT) was determined daily (Pridmore et al 1998) and was defined at the point of maximal stimulation for the right abductor pollicis brevis or other hand muscles, as

visually detected, with the paddle axis oriented laterally. The treatment site, designated left dorsolateral prefrontal cortex (LDLPFC), was defined as 5 cm anterior to this point. Over 10 consecutive weekdays (starting on Mondays), patients received 20 2-sec, 20 Hz trains delivered at 80% MT with 58-sec inter-train intervals. For active treatment, the coil was placed tangentially on the scalp with the paddle axis oriented toward the bridge of the nose. For sham treatment, the paddle was angled approximately 30–45 degrees off of the scalp with the bottom coil margin elevated approximately one-half cm from the scalp and the lucite paddle casing firmly applied against the scalp. Physicians administering the treatment had minimal clinical contact with the patient and blinded raters.

Patients were assessed daily by a blinded research assistant with the following: a modified 25-item HDRS (Mazure et al 1986); side effect checklist (SECL; Woods et al 1988); Beck Depression Inventory (BDI; Beck et al 1961); and, Hamilton Anxiety Scale (HAS; Hamilton 1959). The SECL is a questionnaire that assesses 23 potential side effects and their severity over the previous week, with ordinal scores from 0 (“none at all”) to 3 (“severe”). Assessed items included poor memory, nausea or vomiting, headache, constipation, drowsiness, blurred visions, increased appetite, dry mouth, decreased appetite, tremors or shakiness, nightmares, difficulty sitting still, difficulty starting urination, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor coordination, and muscle stiffness. For the last 15 subjects, patients and raters were administered an assessment of blinding, in which they were asked to guess the blind (active vs. sham) and give the certainty of the guess on an ordinal scale (i.e., 1, “not at all”; 4, “somewhat”; and, 8, “absolutely”).

All patients had one baseline EEG. Baseline EEGs were 30–40 min of recording using the 10/20 international electrode placement system. Both bipolar and referential montages were used. The majority of the records contained at least a brief period of sleep. Recordings were not repeated if sleep was not obtained and the awake record was normal. Hyperventilation was performed for 3 minutes. Additional prestimulation EEG was obtained for 2–3 min prior to each rTMS session. The EEG was then monitored for 30–40 sec starting approximately 3 sec after the termination of each train (40 stimuli). At the end of the each session 2–3 additional minutes of EEG were obtained. A 16-channel Grass Model 8 (Astro-Med, Braintree, MA) was used for all EEG recordings.

The different linear trends of primary (HDRS) and secondary (BDI, HAS) efficacy variables across time between the two treatment groups were evaluated via use of a random effects model using SAS PROC MIXED (SAS Institute, Cary, NC). Considering time as a continuous variable and treatment group as a class variable, the fixed effects in the random effects model were time and time \times treatment interactions. The treatment effect was evaluated by testing the time \times treatment interactions using the Wald test. The adjusted mean decreases in outcome variables over the course of the trial

Table 1. Demographics

Identification number/ age-race-gender ^a	Randomization (active, sham)	Diagnosis ^b	Current episode duration (yrs)	Age of first depression (yrs)	Medication trials for current episode ^c	Augmentation trials for current episode	ECT for current episode ^d	Baseline Hamilton Depression score	Terminal Hamilton Depression score
1/37WM	Active	UD, m	5	32	10	3	-	36	32
2/51WF	Active	UD	8	<12	5	1	+	48	7
3/45WM	Active	UD, m	5	19	5	0	...	48	27
4/47WM	Active	UD, m & p	1	24	3	1	...	52	31
5/28WF	Active	UD	4	<12	7	2	...	39	35
6/47WM	Active	UD	10	22	5	1	...	31	26
7/44HM	Active	UD	4	18	1	0	...	25	16
8/63WM	Active	UD	6	25	3	1	...	24	14
9/52WM	Active	UD	10	19	3	1	...	32	26
10/38WM	Active	UD	26	<12	6	2	+	36	32
11/50WM	Sham	UD	3	45	5	0	...	26	48
12/45WM	Sham	BP2	13	33	4	1	...	49	40
13/32HM	Sham	UD	0.8	13	4	1	...	50	47
14/62WM	Sham	UD, m	3	42	5	2	-	43	45
15/34WF	Sham	UD	0.8	18	1	0	...	29	20
16/29WF	Sham	UD	1.5	19	3	2	...	31	33
17/29WF	Sham	UD, a	1.5	<12	2	1	...	41	34
18/30WM	Sham	UD	8	12	1	0	...	31	29
19/41WM	Sham	UD	0.25	28	0	0	...	33	29
20/42WF	Sham	UD, a	6	20	9	3	...	40	39

^aSubjects included inpatients (4, 5, 7, 10, 13, 14, 19, 20) and outpatients patients; patients with (4, 14, 15, 7, 8) and without a remote history of a suicide attempt; and patients with (2, 13, 4, 15, 20) and without a reported history of childhood trauma.

^bAll patients carried diagnosis of Major Depressive Disorder, unipolar type (UD) or Bipolar II, depressed (BP2). Some patients also demonstrated melancholic (m), psychotic (p), or atypical (a) features. Patients 2, 11, 13, 5, 8 carried diagnoses of substance abuse in remission (range 4-29 years); other comorbid diagnosis included obsessive-compulsive disorder (3); panic disorder (2, 17); social phobia (7, 10); and trichotilomania (20)

^cSee text for definition of trials. Patient 4 additionally received trials of perphenazine and risperidone. Patient 19 had a history of ECT response during four previous depressive episodes, during which he demonstrated medication resistance.

^dOf the four patients with a trial of electroconvulsive therapy (ECT) during the present episode, each patient demonstrated a transient full (2) and partial (10) response to bilateral ECT; however, debilitating post-ECT cognitive side effects prevented continuing with ECT. Two other subjects demonstrated minimal benefits (signified as "-") at least six sessions of bilateral ECT.

Race: W, white; H, Hispanic. Gender: M, male; F, female.

were estimated by multiplying the estimated slope of change and time duration (10 days). Various within-patient covariance structures were compared by log likelihood ratio tests. The first-order autoregression structure was selected. Categorical "response" criteria (i.e., 50% decrease from baseline HDRS and maximum absolute score of 15 points) were assessed via two-tailed Fisher Exact tests.

Results

Patient Attributes and Disposition

Baseline characteristics of study subjects are shown in Table 1. Overall, this sample represented a treatment-resistant population of depressed patients with 4.5 median medication trials (5 for the active group; 3.5 for the sham group) with a median 1 augmentation agent (both groups) for the current episode. The mean duration of episode for the active (7.9 years \pm 2.2 SEM) and sham (3.8 \pm 1.3) groups did not significantly differ ($p = .12$). Three of 10 subjects receiving sham treatment discontinued early because of lack of response (i.e., after 3, 4, and 6 sham treatments); whereas, none in the active group terminated

early (Fisher Exact, $p = .21$). All decisions to discontinue were based on severity of depressive symptoms and made in consultation with the research psychiatrist blind to treatment assignment.

Efficacy

Figure 1 depicts mean HDRS scores, last observation carried forward. In the active TMS group, HDRS decreases averaged 14.0 (\pm 3.7 SEM) points over the course of the trial (df = 141; $t = 3.75$; $p < 0.001$); whereas, decreases in the sham TMS averaged 0.2 (\pm 4.1 SEM) over the same period (df = 141; $t = 0.05$; $p = .96$), a statistically significant difference between the two groups (df = 141; $t = 2.97$; $p < .01$). Note that these adjusted mean HDRS decreases are based on the best fit slopes of all data points throughout the study and hence differ slightly from the mean baseline minus termination HDRS scores. Subanalysis of the HDRS mood item revealed mean changes of 1.4 (\pm 0.3) point decrease (df 139; $t = -3.73$; $p < .001$) versus a 0.1 (\pm 0.4) point increase (df 139; $t = 0.37$; $p = .71$),

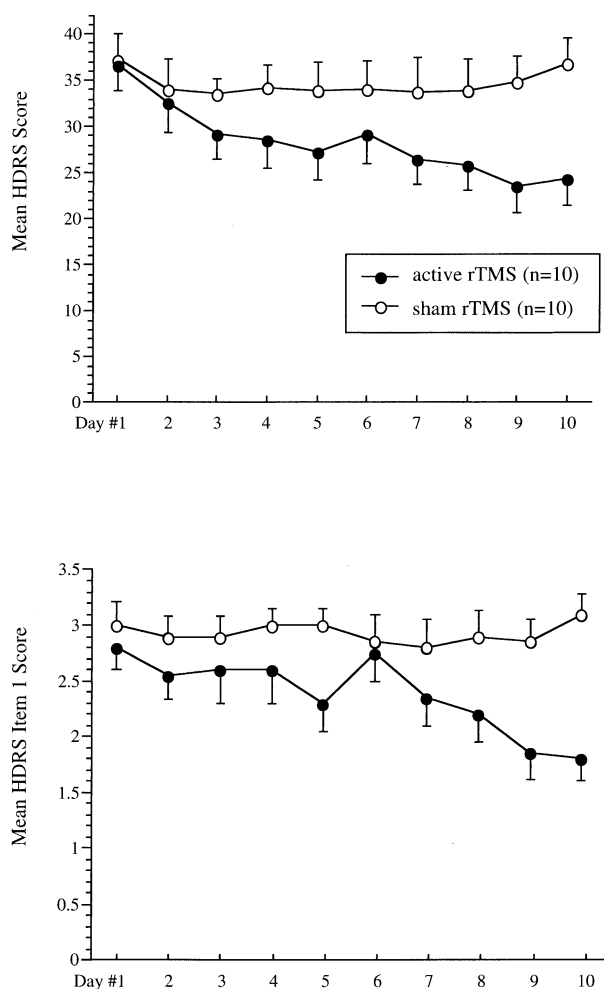


Figure 1. Effects of active and sham rTMS on Hamilton Depression Rating Scale (HDRS) scores. Repetitive transcranial magnetic stimulation (rTMS) resulted in statistically significant reductions in total HDRS scores (top panel) and in the core mood subitem (bottom panel), as compared to sham rTMS. Data represents group means \pm SEM.

respectively, for the active and sham TMS groups, again a statistically significant intergroup difference ($df = 139$; $t = -3.48$; $p = .001$).

Changes in HAS revealed mean decreases of $8.7 (\pm 0.3)$ and $9.1 (\pm 0.3)$ points over the course of the study for active and sham groups, respectively; intergroup differences were not statistically significant ($df = 168$; $t = 0.12$; $p = .91$). Mean BDI scores decreased a significant $11.4 (\pm 5)$ over the course of treatment for the active group ($df = 130$; $t = -2.24$; $p = .03$), and mean decreases of $4.7 (\pm 6)$ points were not significant for the sham TMS group ($df = 130$; $t = -0.80$; $p = .42$). Intergroup differences were not significant ($df = 130$; $t = -1.11$; $p = .27$).

Categorical Analysis of the Data

One of 10 subjects receiving active treatment demonstrated a full response (i.e., HDRS decreased from 47 to 7 points); three other patients demonstrated 40–45% decreases in HDRS scores. No patients receiving sham treatment demonstrated partial or full responses (Fisher Exact, $p = .09$). The full responder remained a responder as of 2 months follow-up. For the three partial responders, symptom severity returned to baseline within 1 week ($n = 1$; as determined by HDRS scores) or 2 weeks ($n = 2$; as determined by HDRS scores in one patient and retrospective assessment for the other patient in the third week after study completion) after study completion. The patient who demonstrated an enduring response period did not prominently differ from other subjects with regard to baseline symptom characteristics, serial EEG results, or motor threshold observations (i.e., between 70% and 80% MT throughout the study).

Side Effects, EEG, and Motor Threshold

As partially reported previously (Boutros et al, in press), among the 10 patients who received sham rTMS, nine had normal baseline EEG. The tenth subject demonstrated minimal slowing on the left temporal region. None of the patients demonstrated any EEG changes during the 10 days of stimulation. Among the 10 patients who received active rTMS, nine had completely normal baseline EEGs. The one patient who had demonstrated a diffusely slow EEG background (7.5 Hz) at baseline without any clinical correlates of organic cerebral disorder, had no EEG changes during rTMS. Another patient exhibited rare slow wave transients (theta activity) on the left temporal lobe region, a phenomenon that was observed only on the fourth stimulation day without attendant clinical complaints. An additional patient, a chronic migraneur, complained of a severe migraine headache on the morning of the third session that was typical of his usual episodes and associated with minimal slowing (theta activity) in the occipital regions, a finding that normalized by the next day.

Baseline motor threshold levels (expressed as percent maximal output from the Cadwell stimulator) were modestly higher for the sham (81 ± 7.7 SD) than the active (72 ± 13) groups ($p = .06$). Both the active and sham groups demonstrated similar mean decreases (3 ± 9.5 and 5 ± 11 , respectively; paired t tests, $ps > .25$). Among completers, standard deviations of MT over 10 days did not differ between the active (4.6 ± 2.0 SD) and sham (5.6 ± 1.9 SD) groups ($p = .36$). Intergroup differences of the maximal score from each SECL item during the study course was compared. No significant differences were

achieved after correction for multiple comparisons. Without such correction, "difficulty starting urination" was greater in the active (2.0 ± 1.1) than sham (1.1 ± 0.3) group ($p = .03$). A common complaint, 11 subjects reported at least one moderate or severe headache during the study course (6, active; 5, sham). No subjects withdrew because of side effects.

Adequacy of Blind

Patients guessed their blind accurately in 10 out of 15 (67%) assessed cases ($p = .56$); whereas raters guessed blind correctly in 12 out of 15 (80%) cases ($p = .04$). Certainty score of correctly versus incorrectly guessing patients ($5.6 \pm .3$ SEM vs. 5.8 ± 0.5 , respectively; $p = .79$) and raters (4.0 ± 0.6 vs. 4.7 ± 0.2 ; $p = .19$) were not significantly different. Excluding patients whose HDRS score changed by a minimal 10 points and noncompleters, rater accuracy diminished to 8 out of 11 (73%) (Fisher Exact, $p = .24$). For both patients and raters, clinical response was identified as the prime reason for guess.

Discussion

A 2-week course of active rTMS reduced depressive symptoms greater than sham rTMS, in a population characterized by treatment-resistant depression. In those subjects who modestly responded to active treatment, clinical benefits were generally short lived (i.e., no longer evident 2 weeks after the treatment ended). One notable exception is a patient who experienced a rapid, enduring, and robust response. EEG monitoring and side-effects data suggest that rTMS given with the parameters used in this study is safe, as there were no persistent effects on the EEGs of our patients nor significant differences in side effects between groups. Overall, our findings are consistent with a previous randomized clinical trial performed under similar conditions (George et al 1997) in demonstrating modest, yet statistically significant, improvement in depressive symptoms induced by active rTMS. Given the high level of refractoriness in this patient population, these results lend further credibility to the development of TMS as a potential treatment for depression.

Consideration to several methodologic limitations merits attention. Inadequacy of blind preservation may have biased in favor of a finding; however, when questioned about which treatment condition patients may have received, patients and raters did not have strong beliefs regarding treatment assignment, and no patients identified personnel's behaviors as suggestive of assignment. Accurate guessing of blind by raters may be attributed, at least in part, to the patients' clinical response. Another potential bias, small sample size, may have led to uneven patient

assignment; however, confounding factors were not conspicuous by inspection of the patient demographics. Although the very weak placebo response in the sham group was unanticipated, it is consistent with the high level of treatment refractoriness in this study cohort.

Assessing the role of rTMS in the therapeutic armamentarium for major depression requires further work on the determination of optimal treatment parameters that may lead to a more complete and enduring response. Although preliminary trends are emerging to suggest that efficacy may be related to stimulus frequency and intensity (George et al 1999), important treatment variables potentially include cognitive/affective state during stimulation (Post et al 1997), stimulus localization, coil shape, capacitor discharge characteristics, number of stimulations, and duration of treatment.

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