

Treatment of Vascular Depression Using Repetitive Transcranial Magnetic Stimulation

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Context: The term *vascular depression* (VD) has been used to describe late-life depressive disorders in patients with clinical evidence of cerebrovascular disease. Preliminary data on poststroke depression suggest that repetitive transcranial magnetic stimulation (rTMS) might also be effective among patients with VD.

Objective: To examine the efficacy and safety of rTMS to treat VD.

Design: Prospective, randomized, sham-controlled study.

Setting: University hospital.

Methods: After discontinuation of antidepressant therapy, 92 patients with clinically defined VD were randomly assigned to receive active or sham rTMS of the left dorsolateral prefrontal cortex. Approximately half of the patients met criteria for magnetic resonance imaging-defined VD. In experiment 1, we administered a total cumulative dose (TCD) of 12 000 pulses (TCD-12K); in experiment 2, 18 000 pulses (TCD-18K). Sham stimulation was performed using a sham coil.

Results: In experiment 1, the sham group showed a 13.6% decrease in the 17-item Hamilton Depression Rating Scale (HAM-D-17) scores compared with a 33.1% decrease in the TCD-12K group ($P=.04$). Response rates were 6.7% in the sham group and 33.3% in the active-stimulation group ($P=.08$); remission rates were 6.7% and 13.3%, respectively ($P=.50$). In experiment 2, the sham group showed a 17.5% decrease in the 17-item Hamilton Depression Rating Scale scores compared with a 42.4% decrease observed in the TCD-18K group ($P<.001$). Response rates were 6.9% in the sham group and 39.4% in the active-stimulation group ($P=.003$); remission rates were 3.5% and 27.3%, respectively ($P=.01$). Response rates to rTMS were negatively correlated with age and positively correlated with higher frontal gray matter volumes.

Conclusions: To our knowledge, this is the first controlled trial that demonstrates the efficacy of rTMS among geriatric patients with VD. Older age and smaller frontal gray matter volumes were associated with a poorer response to rTMS.

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THE TERM *VASCULAR DEPRESSION* (VD) has been used to describe late-life depressive disorders in patients with clinical and/or neuroimaging evidence of cerebrovascular disease. Subcortical hyperintensities found in late-life depressive disorders correlate with psychomotor slowing,¹⁻³ a negative family history of depression,¹ functional impairment,⁴ executive dysfunction,^{2,5,6} and other types of cognitive impairment.^{2,5,6} It has been estimated that approximately 54% of patients with late-life depressive disorders meet criteria for VD.⁷ In addition, patients with subcortical ischemic lesions and depression are older, have lower frequency of a family history of mental illness, and are less likely to have loss of libido compared with elderly depressed patients without subcortical ischemic lesions.⁷ Some studies have suggested that VD is more chronic and more treatment

resistant than early-onset depression.¹⁻³ Investigators at Duke University⁸ have reported that persistent depressive symptoms are associated with small basal ganglia lesions and large cortical white matter lesions, and that deep white matter hyperintensities (WMHs), but not periventricular WMHs or subcortical gray matter hyperintensities (SGMHs), are significantly associated with increased mortality in depressed patients. Other recent studies, however, have found that the existence of subcortical hyperintensities do not predict response of depression to treatment.⁹

During the past few years, international literature on the antidepressant efficacy of repetitive transcranial magnetic stimulation (rTMS) has continued to grow. However, there continues to be a remarkable paucity of studies conducted among elderly patients, and almost none have focused on patients with coexistent cere-

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brovascular disease. However, we previously reported a small randomized, parallel, double-blind study of patients with refractory poststroke depression undergoing active vs sham left prefrontal rTMS. When compared with sham stimulation, the use of 10 sessions of active rTMS of the left dorsolateral prefrontal cortex (DLPC) (10 Hz, 110% of the motor threshold) was associated with a significant reduction of depressive symptoms.¹⁰ In addition, there is only 1 study, to our knowledge, that has examined response to rTMS in VD.¹¹ That open study of 11 patients with late-onset treatment-resistant VD used rTMS of the left DLPC (10 Hz, 100% of the motor threshold, 10 sessions). The results demonstrated that 5 of 11 patients were treatment responders, with a drop in Hamilton Depression Rating Scale (HAMD) scores of 10 to 14 points.

In the present study, we examined the following hypothesis: using a similar stimulation protocol to the one that was implemented among patients with poststroke depression, active left prefrontal rTMS will be associated with a significantly greater reduction of depressive symptoms and increased response and remission rates among patients with clinically defined VD, compared with sham stimulation.

METHODS

OVERVIEW

We conducted 2 sequential randomized controlled trials of the efficacy of active vs sham rTMS for the treatment of VD. In experiment 1, we administered a total cumulative dose (TCD) of 12 000 magnetic pulses (10 sessions of approximately 30 minutes duration each) (TCD-12K group) for 15 patients and sham stimulation in 15 patients. The findings from 10 of these patients were included in a pilot study.¹⁰ In experiment 2, we administered a TCD of 18 000 magnetic pulses (15 sessions) (TCD-18K group) for 33 patients and sham stimulation in 29. To maintain the blind for raters and patients (ie, the raters and the patients were not told that the TCD was being increased compared with experiment 1), all patients were treated during a 10-day period (ie, the TCD-18K group had 2 sessions/d for 5 of their stimulation days).

SUBJECTS

We enrolled 92 patients with onset of major depressive disorder (as diagnosed by *DSM-IV* criteria) at age 50 years or older, a history of subcortical stroke, and/or at least 3 of the following cardiovascular risk factors: arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, and smoking. Patients were recruited from the outpatient and inpatient units of the Department of Psychiatry at The University of Iowa Hospitals and Clinics and the Department of Psychiatry at the Iowa City Veterans Affairs Medical Center, as well as advertisements in Des Moines and other metropolitan areas of the state.

All patients were required to have had major depression during the current depressive episode, but some were partially treated and met only *DSM-IV-TR* minor depression criteria at the time of enrollment in the study. In addition, we required evidence that the depression was unresponsive to at least 1 course of treatment with antidepressants given in adequate doses. Adequate antidepressant treatment was defined as a score of 3 or greater on the Antidepressant Treatment History Form.¹² If the

patient was taking antidepressants when enrolled in the study, the therapy was tapered and discontinued for at least 4 days (except for fluoxetine hydrochloride, for which a period of 3 weeks was necessary) before initiation of rTMS.

General exclusionary criteria included the presence of severe heart or respiratory failure, the presence of renal or hepatic failure, or the occurrence of an ongoing neoplastic process. We also excluded patients with neurodegenerative disorders such as idiopathic Parkinson disease or probable Alzheimer disease and patients with clinical evidence of dementia (Clinical Dementia Rating Scale score >0.5). Depressed patients who were actively suicidal, who presented with prominent psychotic features, or with comorbid alcohol or other drug abuse that was active within the 2 years before the study were also excluded.

Exclusionary criteria related to rTMS treatment were prior occurrence of induced seizures, major head trauma, and a history of epilepsy. In addition, we excluded patients with metal in the skull, cranial cavity, or brain parenchyma, as well as patients with a cardiac pacemaker, an implanted defibrillator, or a medication pump.

This study was approved by The University of Iowa institutional review board. Written informed consent was obtained from all subjects after presentation of consent form materials and a thorough discussion of the study's procedures, risks, and benefits.

PSYCHIATRIC AND COMORBID MEDICAL CONDITIONS ASSESSMENTS

Diagnoses of depression due to cerebral vascular disease with a major depressivelike episode or minor depression (research criteria) were made using the Structured Clinical Interview for *DSM-IV* and *DSM-IV* diagnostic criteria. The diagnosis was made by a psychiatrist who was blind to the patient treatment status.

The Cumulative Illness Rating Scale¹³ was used to assess the presence and severity of comorbid medical conditions in each organ system. Participants also underwent evaluation for the presence of vascular risk factors that were ascertained by means of the medical history and results of the physical examination and laboratory tests. Hypertension was defined by a systolic blood pressure of more than 140 mm Hg, by a diastolic blood pressure of more than 90 mm Hg, or by self-reported hypertension diagnosis and use of antihypertensives. Diabetes mellitus was defined as a fasting blood glucose level of more than 126 mg/dL (to convert glucose to millimoles per liter, multiply by 0.0555) or treatment with hypoglycemic agents and/or insulin in the year before enrollment. Obesity was diagnosed as a body mass index (calculated as weight in kilograms divided by height in meters squared) of at least 30. Cigarette smoking and alcohol consumption were assessed by questionnaires.

OUTCOME PARAMETERS

The primary outcome parameter, the 17-item HAMD (HAMD-17) score,¹⁴ constitutes a valid and reliable measure of the severity of depressive symptoms among patients with cerebrovascular disease.¹⁵ The HAMD-17 scores were obtained at baseline and after completing the course of rTMS.

Secondary outcome parameters included response, remission, and relapse rates. Response was defined as a decrease in the HAMD-17 total score of at least 50%. Patients with HAMD-17 scores of less than 8 and who did not meet criteria for major or minor depression were considered to be in remission. Efficacy parameters were assessed by an independent rater who was blind to the patient treatment status.

COGNITIVE FUNCTIONING

A neuropsychological battery was used to monitor the safety of participants in a quantitative, standardized manner. The battery focused on memory and executive functions. Verbal memory was assessed using the Rey Auditory Verbal Learning Test.¹⁶ Executive functions were assessed using the Stroop Color and Word Test,¹⁷ Trail Making Tests A and B,¹⁸ and the Controlled Oral Word Association Test.¹⁹ Most of these tests have alternate forms that were used at baseline and follow-up. We therefore assume that practice effects were minimal.

ACTIVITIES OF DAILY LIVING

Activities of daily living (ADLs) were assessed using the Functional Independence Measure.²⁰ The Functional Independence Measure is an 18-item, 7-level, ADL scale that has been shown to be valid and reliable among patients with cerebrovascular disorders. Higher scores indicate less impairment.

NEUROIMAGING

Magnetic resonance imaging (MRI) was performed in every patient at the time of enrollment in the study. The MRIs were obtained using a 1.5-T scanner (Siemens Avanto; Siemens, New York, New York) from the MRI facility of The University of Iowa Hospitals and Clinics. Four different image sets were acquired for the MRI standard workup: (1) a 3-dimensional, T1-weighted magnetization-prepared rapid gradient echo sequence in the coronal plane; (2) a 2-dimensional, proton density-weighted turbo spin-echo sequence in the coronal plane; (3) a 2-dimensional, T2-weighted turbo spin-echo sequence in the coronal plane; and (4) a 2-dimensional fluid-attenuated inversion recovery sequence in the axial plane.

We used the tools of a locally developed software package (BRAINS-2; The University of Iowa) to generate data from the 4 image sets.²¹⁻²⁴ White and gray matter hyperintensities, which appear as hyperintense signals on proton density- and T2-weighted images, were manually traced. Interrater reliability of deep WMH and SGMH tracing was assessed between 2 trained operators (including L.A.) for 10 MRIs showing these subcortical changes (intraclass correlation > 0.94). In addition, deep WMH and SGMH were assessed using a semiquantitative scale.²⁵

The distance from the stimulation site to the cerebral cortex was measured in millimeters with the BRAINS-2 software tools on the coronal plane of the T1-weighted image. Interrater reliability for distance determination was calculated between 2 trained operators (including L.A.) for 10 patients (intraclass correlation, > 0.97).

rTMS PROTOCOL

We obtained the appropriate investigational device exemption from the US Food and Drug Administration (investigational device exemption No. G980216). Repetitive TMS was performed using a commercially available stimulator (Magstim Super Rapid Stimulator; Jali Medical, Inc, Wellesley Hills, Massachusetts) and 70-mm, figure 8-shaped butterfly coils.

Tapering of antidepressant therapy occurred during a 2-week period before the stimulation phase (at least 3 weeks in the case of fluoxetine therapy). Patients were contacted on a daily basis during the therapy taper period to ensure that psychotic symptoms or suicidal ideation did not emerge. All baseline testing was performed when patients were not receiving antidepressants.

Localization of the stimulation site in the prefrontal cortex was performed using image normalization to the Talairach coordi-

nate system. A landmark is picked up on the cortex corresponding to the midpoint of the middle frontal gyrus, and its position is checked on the 3 image planes and on the surface reconstruction to confirm that it falls on the middle frontal gyrus. This landmark, and thus the stimulation site, should lie within the conservative range of Talairach coordinates for Brodmann area 46, as proposed by Rajkowska and Goldman-Rakic.²⁶

Experiment 1

Subjects were randomized into 2 groups for active or sham stimulation, receiving 10 rTMS sessions in the left DLPC at a frequency of 10 Hz and an intensity of 110% of the motor threshold during a 6-second period, with a total of 20 trains separated by 1-minute pauses. Treatment was administered during a 10-day period for a TCD of 12 000 pulses (ie, TCD-12K group).

Experiment 2

Subjects were randomized into 2 groups for active or sham treatment, receiving 15 rTMS sessions in the left prefrontal cortex at a frequency of 10 Hz and an intensity of 110% of the motor threshold during a 6-second period, with a total of 20 trains separated by 1-minute pauses. Treatment was administered during a 10-day period with 2 sessions per day for 5 days to achieve a TCD of 18 000 pulses (ie, TCD-18K group).

In both experiments, sham stimulation was performed using a specially designed coil that looks exactly like the standard stimulating coil but generates a small localized field that drops off very fast, producing a scalp sensation without actual cortical stimulation.

rTMS Dosing

At entry, we determined each subject's resting motor threshold, and all rTMS doses were given relative to this value. Resting motor threshold was determined as follows: (1) using "threshold hunting" software (MLS-PEST²⁷), a target intensity was determined in the resting first dorsal interosseous muscle²⁷; and (2) starting with a stimulus intensity 2% greater than this target intensity, the stimulator output was reduced by 1% decrements until the lowest stimulator intensity that induced a motor evoked potential of at least 50 μ V (peak-to-peak amplitude) in at least 5 of 10 trials was reached.²⁷ Adverse effects (eg, local discomfort at the stimulation site or tension headaches) were recorded for all patients.

STATISTICAL ANALYSIS

Comparison of the groups used simple χ^2 analyses or Fisher exact test as appropriate. Because some of our continuous measures were not normally distributed, we chose Kruskal-Wallis tests for comparing the groups. To remain consistent, we used the Kruskal-Wallis test for all such comparisons. We used logistic regression to examine MRI predictors of antidepressant response and a backward-stepwise procedure to define the final multivariate model. We examined neuropsychological and MRI volumetric variables using a version of multivariate analysis of variance based on ranks.

RESULTS

SUBJECTS

The flowchart of the trial appears in **Figure 1**. A total of 502 depressed patients underwent screening during a 4-year

period. Of these 502 patients, 97 met our inclusion criteria and signed an informed consent to be enrolled in the study. Of these 97 patients, 5 withdrew from the study before tapering their antidepressant therapy and receiving the first rTMS session. Reasons for withdrawal were reconsideration of the risks and benefits of the study and/or unwillingness to come to the hospital for more than 2 weeks on a daily basis. Thus, 92 patients had the first rTMS session, constituting the intention-to-treat population. Fortunately, all of these patients completed the rTMS protocol without significant complications.

We decided to use clinically defined VD as our inclusion diagnosis to mimic the conditions that would be encountered in clinical practice. However, we have also examined the subgroup of patients who met the stricter criteria for MRI-defined VD (ie, score of ≥ 2 on the deep WMH or SGMH of the Coffey-modified Fazekas rating scale).^{25,28} Of the 92 patients who completed the protocol, 51 (55%) met MRI criteria for VD. When compared with patients with less extensive subcortical lesions, patients with MRI-defined VD were significantly older (Kruskal-Wallis $\chi^2=13.7$; $P<.001$) and had significantly fewer years of education (Kruskal-Wallis $\chi^2=9.0$; $P=.003$). There were no other significant differences in demographic variables. In addition, there were no significant differences between the clinically and MRI-defined VD groups in baseline psychiatric variables, medical burden measured by the Cumulative Illness Rating Scale scores, number of vascular risk factors, or ADL impairment as measured by the Functional Independence Measure scores. After controlling for age and education, the MRI-defined VD group was not significantly more impaired than the clinically defined group in cognitive functioning as measured by neuropsychological test scores.

BACKGROUND CHARACTERISTICS

The demographic features, medical comorbidity, and functional independence of the patients enrolled in experiments 1 and 2 are summarized in **Table 1**. There were no significant differences between the active and sham stimulation groups in background characteristics.

BASELINE PSYCHIATRIC AND NEUROPSYCHOLOGICAL VARIABLES

The type, severity, and clinical course of depressive disorders and the baseline neuropsychological variables of the patients in each of the experiments are summarized in **Table 2** and **Table 3**, respectively. There were no significant differences between patients receiving active rTMS or sham stimulation in their baseline psychiatric status. In addition, there were no significant differences in neuropsychological variables (multivariate analysis of variance, Wilks $\Lambda=1.11$; $P=.35$).

EFFICACY OF rTMS AS TREATMENT FOR VD

Experiment 1

After completion of the rTMS phase of the protocol (3 weeks), the group of patients who received sham stimu-

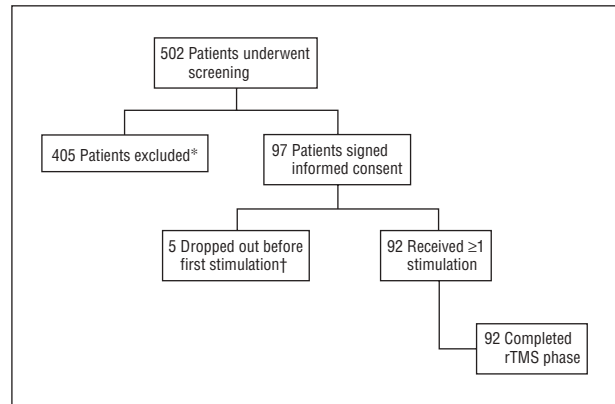


Figure 1. Enrollment of patients in the prospective, randomized, sham-controlled study of repetitive transcranial magnetic stimulation (rTMS). *Patients met exclusionary criteria, were unable to come for daily rTMS, or were reluctant to taper and discontinue antidepressant therapy. †Four patients withdrew voluntarily and 1 was excluded for drug abuse.

lation of the left DLPC showed a 13.6% decrease in HAMD-17 scores compared with a 33.1% decrease in the TCD-12K group (Kruskal-Wallis $\chi^2=4.1$; $P=.04$) (**Figure 2**). Response rates were 6.7% in the sham-stimulation group and 33.3% in the TCD-12K group (Fisher exact test, $P=.08$); remission rates, 6.7% in the sham-stimulation group and 13.3% in the TCD-12K group (Fisher exact test, $P=.50$) (**Figure 3**).

Patients with MRI-defined VD were not significantly different from patients with clinically defined VD in the reduction of HAMD-17 scores (MRI defined, 23.3%; clinically defined, 44.3%; Kruskal-Wallis $\chi^2=2.3$; $P=.13$) or in the response and remission rates observed after active rTMS.

Experiment 2

In experiment 2, the sham stimulation group showed a 17.5% decrease in HAMD-17 scores compared with a 42.4% decrease observed in the TCD-18K group (Kruskal-Wallis $\chi^2=15.1$; $P<.001$) (Figure 2). Response rates were 6.9% in the sham-stimulation group and 39.4% in the TCD-18K group (Fisher exact test, $P=.003$); remission rates, 3.5% in the sham group and 27.3% in the TCD-18K group (Fisher exact test, $P=.01$) (Figure 3).

Patients with MRI-defined VD were not significantly different from patients with clinically defined VD in the reduction of HAMD-17 scores (MRI defined, 41.8%; clinically defined, 43.4%; Kruskal-Wallis $\chi^2=0.04$; $P=.84$) or in the response and remission rates observed after active rTMS.

NEUROPSYCHOLOGICAL AND ADL ASSESSMENT

When compared with sham stimulation, active rTMS at TCD-12K and TCD-18K was not associated with significant changes in ADLs as measured by the Functional Independence Measure or in most neuropsychological tests assessing memory and executive functions. However, after controlling for baseline Trail Making Test B time, patients receiving active rTMS had significantly decreased (ie, improved) Trail Making Test B times compared with

Table 1. Demographic Characteristics and Medical Comorbidity^a

Characteristic	Stimulation Group				P Value
	Experiment 1		Experiment 2		
	TCD-12K (n=15)	Sham (n=15)	TCD-18K (n=33)	Sham (n=29)	
Age, y	62.9 (7.2)	66.1 (11.0)	64.3 (9.4)	62.1 (8.5)	.97
Female, No. (%)	6 (40)	8 (53)	20 (61)	17 (59)	.54
Married, No. (%)	11 (73)	11 (73)	25 (76)	20 (69)	.31
Education, y	13.6 (2.3)	12.9 (1.8)	14.3 (2.3)	14.1 (2.1)	.26
SES classes IV and V, No. (%) ^b	6 (40)	5 (33)	9 (27)	6 (21)	.08
Cumulative Illness Rating Scale score	1.70 (0.3)	1.76 (0.4)	1.66 (0.5)	1.73 (0.3)	.76
No. of cardiovascular risk factors	2.6 (0.9)	2.7 (0.3)	2.6 (0.9)	2.6 (0.8)	.88
Functional Independence Measure score	68.0 (1.2)	67.6 (4.8)	66.8 (5.5)	66.5 (4.9)	.91

Abbreviations: 18K, 18 000 magnetic pulses; SES, socioeconomic status; TCD, total cumulative dose; 12K, 12 000 magnetic pulses.

^aGroups are described in the "Overview" subsection of the "Methods" section. Unless otherwise indicated, data are expressed as mean (SD).

^bDetermined according to the Hollingshead scale.²⁹

Table 2. Baseline Psychiatric Variables

Variable	Stimulation Group ^a				P Value
	Experiment 1		Experiment 2		
	TCD-12K (n=15)	Sham (n=15)	TCD-18K (n=33)	Sham (n=29)	
Major depression, No. (%) of patients	12 (80)	12 (80)	28 (85)	22 (76)	.82
Mean (SD) HAMD-17 score					
Screening	17.4 (4.6)	20.1 (7.1)	17.5 (4.6)	17.2 (6.0)	.89
Baseline	19.5 (5.8)	19.9 (5.4)	18.4 (3.4)	17.6 (5.6)	.90
Recurrence, No. (%) of patients with ≥ 3 episodes	6 (40)	5 (33)	12 (36)	13 (45)	.87
Family history of mood disorders, No. (%) of patients	7 (48)	5 (33)	16 (48)	15 (52)	.59
Antidepressant treatment intensity ¹²	3.9 (0.9)	3.3 (0.7)	3.4 (0.6)	3.5 (0.7)	.88

Abbreviations: 18K, 18 000 magnetic pulses; HAMD-17, 17-item Hamilton Depression Rating Scale; TCD, total cumulative dose; 12K, 12 000 magnetic pulses.

^aGroups are described in the "Overview" subsection of the "Methods" section.

Table 3. Baseline Neuropsychological Variables

Variable	Stimulation Group, Mean (SD) Scores ^a				P Value
	Experiment 1		Experiment 2		
	TCD-12K (n=15)	Sham (n=15)	TCD-18K (n=33)	Sham (n=29)	
MMSE score	28.1 (1.6)	26.9 (2.8)	28.2 (1.4)	28.6 (1.7)	.61
RAVLT trials 1-5, score	42.1 (11.3)	36.2 (12.4)	41.7 (10.1)	44.2 (9.6)	.34
RAVLT delayed recall, score	7.6 (4.1)	5.4 (2.4)	7.5 (3.8)	8.2 (3.3)	.16
Trail Making Test B, s	124.8 (67.6)	117.0 (58.7)	99.5 (59.4)	106.8 (63.0)	.24
Stroop Color and Word Test, interference	29.7 (8.3)	29.4 (11.7)	33.5 (9.2)	30.3 (10.0)	.46
COWAT score	38.5 (14.0)	27.7 (9.9)	35.3 (11.4)	39.6 (12.9)	.08

Abbreviations: COWAT, Controlled Oral Word Association Test; 18K, 18 000 magnetic pulses; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; TCD, total cumulative dose; 12K, 12 000 magnetic pulses.

^aGroups are described in the "Overview" subsection of the "Methods" section.

patients receiving sham stimulation, for the TCD-12K group ($F_1=7.7$; $P=.01$) and TCD-18K group ($F_1=4.9$; $P=.03$). There were no significant differences in Trail Making Test B times between responders and nonresponders, suggesting that this effect was, in fact, independent of mood.

FACTORS MODIFYING ANTIDEPRESSANT RESPONSE TO rTMS

We have examined the factors that might modify the patients' response to active rTMS. We compared patients who responded to active rTMS of the left DLPC

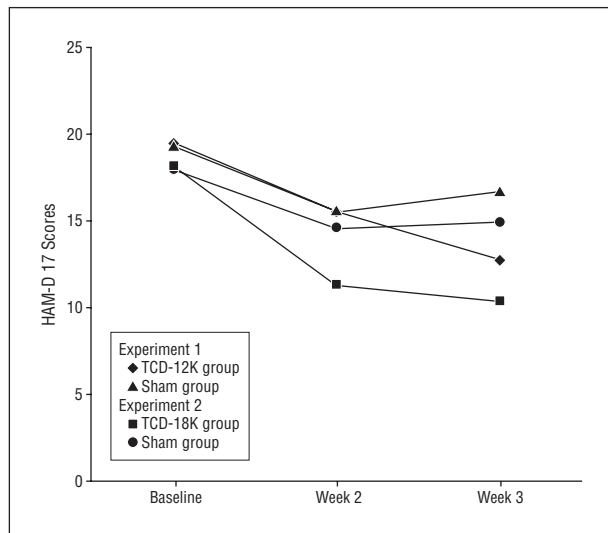


Figure 2. Efficacy of left prefrontal repetitive transcranial magnetic stimulation by changes in the 17-item Hamilton Depression Rating Scale (HAMD-17) scores. Patients were randomized to active or sham stimulation. Total cumulative doses (TCDs) were 12 000 (TCD-12K) and 18 000 (TCD-18K) magnetic pulses in experiments 1 and 2, respectively.

with patients who did not respond to active stimulation. With regard to demographic variables, there were no differences between the responder and nonresponder groups in sex, race, marital or socioeconomic status, or years of education. With regard to psychiatric variables, there were no significant differences between responders and nonresponders in the severity of depression, duration of the current depressive episode, number of previous depressive episodes, or intensity of previous antidepressant treatment. In addition, there were no significant differences between responders and nonresponders in neuropsychological performance in executive function tests.

Consistent with previous studies,³⁰⁻³² we observed a significant effect of age. We used 2-way analysis of variance to examine the percentage of decrease of HAMD-17 scores among patients who received active rTMS and who were categorized along the following 2 grouping variables: first, the experimental group (ie, TCD-12K vs TCD-18K) and, second, age (ie, ≥ 65 years or < 65 years). Analysis of the individual variables showed statistically significant effects for age ($F_1=7.3$; $P=.01$) and for the interaction of age \times TCD ($F_1=6.8$; $P=.01$). Further analysis of the latter significant interaction showed that it was owing to the fact that older patients showed a significantly greater decrease of HAMD-17 scores to TCD-18K than to TCD-12K magnetic pulses (42.1% vs 16%; $F_{1,44}=7.33$; $P=.01$). These findings suggest that increasing rTMS dose had a significantly greater impact on the antidepressant response of patients 65 years or older compared with those younger than 65 years. For active rTMS in the TCD-18K group, the response and remission rates for patients 65 years or older were 40% and 20%, respectively, compared with those observed for patients younger than 65 years, which were 38.9% and 33.3%, respectively.

The intensity of the magnetic field delivered by a stimulating coil will exponentially decrease as a function of dis-

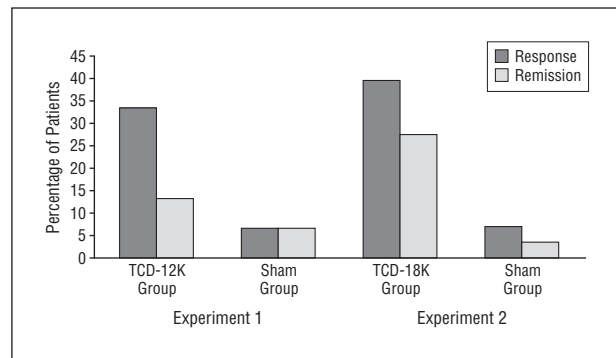


Figure 3. Week 3 response and remission rates obtained after double-blind active vs sham repetitive transcranial magnetic stimulation consisting of a total cumulative dose (TCD) of 12 000 (TCD-12K) and 18 000 (TCD-18K) magnetic pulses to the left dorsolateral prefrontal cortex in experiments 1 and 2, respectively. Although the doses were examined sequentially with different exposure times to the operator, the response rate in the sham group in experiment 1 was 6.7%, and in the sham group in experiment 2 was 6.9%.

tance. Thus, it is reasonable to predict that antidepressant response will be determined (at least in part) by this factor.³² We did not observe a significant correlation between distance from the stimulation site and the percentage of change in HAMD-17 scores in experiment 1 (Spearman $\rho=0.09$) or in experiment 2 (Spearman $\rho=0.18$). However, after including left and right frontal gray matter volumes, left and right frontal white matter volumes, volume of frontal deep WMH and SGMH, total intracranial volume, and experimental group (ie, TCD-12K vs TCD-18K) as predictors of response to active rTMS, a stepwise logistic regression model showed that greater left frontal gray matter volume (Wald $\chi^2=6.2$; $P=.01$) and right frontal gray matter volume (Wald $\chi^2=7.2$; $P=.007$) were the only variables associated with response to rTMS.

SUCCESS OF BLINDING PROCEDURE

During our present study, we asked the patient and the rater to guess whether the patient had received active or sham stimulation during their course of therapy. The accuracy among patients was 62% ($n=62$) ($P=.18$) (48% for sham and 70% for active stimulation), and the accuracy among raters was 50% ($n=62$) ($P=.94$) (48% for sham and 51% for active stimulation). The overall κ value was 0.18 ($P=.75$). Thus, 22 of the 44 sham-treated patients (50%) thought they were receiving active treatment and 14 of the 48 active-treated patients (29%) thought they were receiving sham stimulation.

ADVERSE EVENTS

Table 4 shows adverse events for the 92 study completers. There were no significant differences between the active and sham stimulation groups in the frequency of headaches or local discomfort. As expected, none of the patients experienced a seizure. In addition, headaches were mild and responded in all cases to low doses of common analgesics.

Table 4. Adverse Events

Event	Stimulation Group, No. (%) of Patients ^a			
	Experiment 1		Experiment 2	
	TCD-12K (n=15)	Sham (n=15)	TCD-18K (n=33)	Sham (n=29)
Local pain	1 (7)	1 (7)	1 (3)	0
Headaches	5 (33)	4 (27)	7 (21)	3 (10)
Local discomfort	4 (27)	5 (33)	3 (9)	1 (3)
Anxiety	2 (13)	0	0	0

Abbreviations: 18K, 18 000 magnetic pulses; TCD, total cumulative dose; 12K, 12 000 magnetic pulses.

^aGroups are described in the "Overview" subsection of the "Methods" section.

COMMENT

To our knowledge, these are the first randomized controlled trials of the efficacy of rTMS to treat VD and the largest controlled trial in late-life depressive disorders. In experiments 1 and 2, we showed significantly greater reductions of HAMD-17 scores among patients receiving active compared with sham treatment. In experiment 2, we showed significantly greater response and remission rates among those receiving active compared with sham treatment.

We should acknowledge some methodological limitations of this study. First, although we performed MRI in each patient, we decided to use clinically defined VD as our inclusion diagnosis to mimic the conditions that would be encountered in clinical practice. In fact, when comparing patients with MRI-defined VD²⁸ with the group of patients who had less severe white matter disease and did not meet the latter criteria, we did not find significant differences in antidepressant response as measured by change in HAMD-17 scores or response or remission rates. Second, although the sham coil used in our studies was designed to provide sensory stimulation identical to that of the active coil, we acknowledge that a patient might have been aware of subtle differences in, for instance, scalp sensation. However, we showed that neither patients nor raters were able to accurately guess their assignment to active or sham treatment. Finally, the rTMS operator was not blinded to the type of stimulation being delivered. The raters of primary and secondary outcomes, however, were shown to be blind to treatment status and had no contact with the operator.

Given these limitations, what are the implications of this study? Although there is still controversy, rTMS has been shown to be a safe and effective antidepressant treatment among younger depressed patients. Loo and Mitchell³³ recently reviewed 7 meta-analyses of sham-controlled studies of rTMS for major depression. Varying inclusion criteria produced a range in the number of studies reviewed of 5 to 16. Only 1 meta-analysis concluded that significant evidence of the efficacy of rTMS was lacking,³⁴ whereas 5 found clear evidence of efficacy.

However, is rTMS an effective antidepressant treatment among elderly patients with chronic depressive dis-

orders? Two previous small controlled studies failed to show a significant effect of active rTMS.^{35,36} The first of them was conducted by our group³⁵ using suboptimal stimulation parameters and inadequate trial length (5 days). In the second study, Mosimann et al³⁶ gave high-frequency left prefrontal rTMS (20 Hz; 100% of the motor threshold; 10 sessions; TCD of 16 000 pulses) with no specific effect on depression. In addition to the small sample size, this study had several methodological limitations, such as the inclusion of several patients with bipolar disorder or early-onset recurrent depressive disorder in the active but not the sham treatment group, an inadequate sham procedure, and a relatively low stimulation intensity (100% of the motor threshold) for this age group. Furthermore, they used an empirical algorithm to localize the stimulation site that does not guarantee that they were actually stimulating the DLPC.³⁶ Thus, our findings constitute the best available evidence so far of the antidepressant efficacy of rTMS among a geriatric population.

If rTMS is effective, how does it compare with other treatments of late-life depressive disorders and VD? Antidepressants have been shown to be more efficacious than placebo in previous well-controlled trials conducted among patients with late-life depression. Response rates have varied from 35% to 72%, whereas remission rates have varied from 28% to 44%.³⁷ According to recent studies, approximately half of the patients with late-life depressive disorders would meet criteria for VD. In addition, a significant number of subjects enrolled in previous trials to treat late-life depressive disorders were not treatment resistant. We found similar response and remission rates following rTMS in a group of treatment-resistant patients with VD. The low response and remission rates observed following sham stimulation are consistent with treatment resistance observed among patients with chronic depression and cerebrovascular disease. With regard to treatment trials restricted to patients with VD, Taragano et al³⁸ found that 21 of 84 patients (25%) had HAMD scores of less than 11 following standard antidepressant therapy. After augmentation therapy with nimodipine, 45 (54%) met this criteria following 60 days of treatment. Using similar criteria, our remission rates were better than remission rates following standard medication and comparable to the augmented medication response.

A higher dose of rTMS of the left DLPC might be associated with greater antidepressant efficacy. It is probable that we have not yet found an optimal TCD of rTMS to achieve maximal response and remission rates. Overall, rTMS trials have moved in the direction of administering longer-duration protocols with higher intensities and greater TCDs of magnetic pulses.³⁹⁻⁴¹ The largest and most recent randomized trial administered 5 sessions per week for a maximum of 6 weeks, and differences in depression scores between the rTMS and sham treatment groups grew substantially from weeks 2 to 4.⁴²

These clinical studies suggest that treating depressed patients with higher doses improves response and remission rates with rTMS. In support of this suggestion, Anderson et al⁴³ demonstrated that daily doses of up to 12 000 magnetic pulses could be safely administered to healthy vol-

unteers, suggesting that rTMS doses can probably be substantially but safely increased in clinical populations.

Consistent with previous studies,³⁰⁻³² we found that age was a significant predictor of the antidepressant response to rTMS, probably related to the presence of brain atrophy. However, we did not find an association between response to rTMS and the distance between the scalp stimulation site and the DLPC. Factors other than the decrease of the intensity of the magnetic field associated with the progressive increase in the distance from the scalp to the cerebral cortex may have been responsible for the reduced antidepressant effect. For instance, lower frontal gray matter volumes were associated with a poorer response to rTMS, suggesting that structural changes in prefrontal circuits may have a significant influence on rTMS effects.

The volume of the WMH, however, was not associated with the antidepressant response to rTMS. This phenomenon has been observed in other treatment studies as well.^{9,44} For instance, there was no significant correlation between quantitative measures of white matter lesions and response to antidepressant treatment with citalopram hydrobromide among very old depressed patients.⁴⁴ We can hypothesize that, rather than the total burden of lesions, the location of ischemic damage plays a significant role in the clinical response to different antidepressants. For instance, lesions of the white matter pathways connecting the left DLPC and the left anterior cingulate cortex might be selectively associated with a poor response to rTMS.⁴⁵

In summary, this is, to our knowledge, the first study to demonstrate that active rTMS is superior to sham stimulation in the treatment of VD. Repetitive TMS was safe and did not produce cognitive deficits among this highly vulnerable group. In addition, higher doses of rTMS improved response and remission rates. A new generation of rTMS studies will be able to determine the optimal stimulation parameters and administration protocol. These studies should be carefully designed and incorporate new developments in sham techniques. It is now crucial for controlled treatment trials to determine the maximum response and remission rates that can be obtained at higher doses of rTMS.

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