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A Controlled Study of Repetitive Transcranial Magnetic Stimulation as a Treatment of Depression in the Elderly

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ABSTRACT. Rapid transcranial magnetic stimulation (rTMS) applied to the left dorsal lateral frontal cortex has been shown to produce antidepressant effects. Older depressed patients, however, in one study showed a lower response rate than younger patients. The current study examined treatment response in 20 depressed, treatment-refractory patients (mean age 60.7 ± 9.8 years) given five sessions of rTMS at 20 Hz for 2 seconds over 20 trains at 80% of motor threshold or identical placebo stimulation, after patients had been withdrawn from their antidepressants. There were no significant differences in Hamilton Depression Scale scores either before or after treatment at 7 days' follow-up. There were three responders to active treatment and three to sham treatment and responders had significantly greater frontal lobe volume than nonresponders ($p = .03$). These findings suggest that the stimulation parameters used in this study were probably insufficient to produce treatment response and that frontal atrophy may interfere with the effectiveness of rTMS.

Transcranial magnetic stimulators capable of discharging repetitively in trains have provided a technology that allows modulating human cortical excitability noninvasively, safely, and practically painlessly (Pascual-Leone et al., 1996). Earlier reports (George et al., 1995; Pascual-Leone et al., 1996) have suggested that repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex may have an antidepressant effect. In a double-blind, placebo-controlled study, Pascual-Leone and colleagues (1996) showed that left prefrontal rTMS for 5 days significantly improved mood in 17 psychotically depressed subjects who were 38 to 59 years old. George and coworkers (1995) employed an open rTMS trial in six treatment-refractory unipolar or bipolar depressed patients, with improvements in two patients aged 47 and 50 years. In a later placebo-controlled crossover trial, George and colleagues (1997) using left

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prefrontal rTMS for 10 days showed a significant improvement in mood as a function of rTMS treatment in a group of mainly unipolar depressed outpatients aged 20 to 64 years. In another recent study, Figiel and colleagues (1998) reported the efficacy of rTMS in treating a larger sample of patients with refractory depression. The patients ranged in age from 22 to 89 years. Interestingly, 56% of the young patients responded, but only 23% of the elderly patients responded to rTMS.

Depression is one of the most common mental health problems of the elderly (Baldwin & Simpson, 1997). Depression in the elderly may be difficult to treat because of associated medical conditions and greater vulnerability of elderly subjects to the side effects of electroconvulsive therapy and medication. Predictors of recovery from depression in late life include neurobiological factors such as the nature and severity of cognitive impairment, neuroendocrine abnormalities, and the occurrence of sleep disturbance (Dew et al., 1997). In addition, brain morphometric measures may reflect neurological differences that may be related to a more protracted and refractory course. For instance, Young and colleagues (1999) reported that the ventricular brain ratio in geriatric patients with major depression was negatively associated with outcome after 6 weeks of nortriptyline treatment.

Alternative treatment modalities are needed for depressed elderly. An important issue that has not been fully investigated is whether rTMS might be an effective treatment for resistant depression in the elderly. In the present study, using a randomized, double-blind, parallel-group design, we examined the usefulness of rTMS in a group of elderly patients with refractory depression.

METHODS

We recruited 20 depressed outpatients from the Iowa City area (10 men, 10 women) who met diagnostic criteria for major or minor depression outlined in the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV; American Psychiatric Association, 1994). Patients were enrolled through local advertisements but were not paid. All patients were White and 50 years or older (mean age = 60.7±9.8 years). All subjects had failed one or more 4-week trial(s) with adequate pharmacological treatment. This was defined as failure to respond to the highest tolerated dose of an antidepressant drug. Before patients were entered into the study, they were withdrawn over 5 days from all antidepressant medications so they were drug-free for 4 days before treatment (no fluoxetine withdrawals were needed). This allowed evaluation of rTMS without pharmacological interference. Withdrawal of medication was well tolerated by all patients with only mild worsening of depression and no suicidal thoughts. Total experiment study took 3 weeks—1 to enroll and taper patients' medications, 1 for the stimulation phase (a total of five stimulation sessions), and 1 for follow-up of mood after the treatment.

Subjects were screened with a neurological examination and a magnetic resonance imaging (MRI) scan of the head. A locally developed software package, BRAINS, was employed to generate volumetric data (e.g., total brain volume, gray-matter volume, ventricular volume, frontal lobe volume, etc.) from MRI image sets. This software permits cross-modality image registration, tissue classification, volume and surface measurement, and three-dimensional (3-D) visualization of brain surfaces. The validity and reproduc-

ibility of morphometric analysis using the aforementioned software have been reported in previous studies (Andreasen et al., 1993, 1996; Magnotta et al., 1999). Structural 3-D MRI was also used to assess hyperintense MRI lesions, which have been associated with depressive symptoms in the elderly, and to identify the site of stimulation (left dorsolateral prefrontal cortex or area 46). Using an anatomical method developed in our laboratory (Manes et al., 1999), we identified a consistent anatomical site for stimulation in the posterior portion of the middle frontal gyrus using fiducial markers on a skull cap overload on the 3-D MRI reconstruction of the brain. The area 46 point was located on average 5.3 cm anterior and in a parasagittal plane from the point of maximum stimulation of the right first dorsal interosseus muscle.

Patients also received an electroencephalogram (EEG) recorded for 20 minutes using a standard 10-20 international electrode placement before the first stimulation and after the five sessions. Magnetic stimulation was performed using a Super Rapid 1-50 Hz magnetic stimulator (The Magstim Company Limited, Whitland, UK). Subjects were randomized into two groups: one group (10 patients) received 20 Hz, 80% motor threshold, 2 seconds, x 20 trains separated by 1-minute pauses (treatment group), and the second group (10 patients) received the same frequency of stimulation but the figure-eight coil was above the top of the skull and the handle was placed against the head (placebo group). Because patients felt the stimulation against their skull and all the rTMS noises and vibrations, they were unable to distinguish active from placebo treatment. The choice of these stimulation variables was based on a previous double-blind, placebo-controlled crossover study that showed mood improvement in depressed outpatients (George et al., 1997). At entry, the motor threshold of the right abductor pollicis brevis muscle (the thumb) for the subjects was determined by using the method of limits as previously described (Pascual-Leone et al., 1992). We then stimulated at 80% of this intensity for the rest of the study.

The psychiatric diagnosis was made using symptoms elicited by a semistructured interview (Present State Examination) and DSM-IV diagnostic criteria (Epstein et al., 1998). Severity ratings of depressive symptoms were scored using the Hamilton Depression Rating Scale (HDRS; Katona et al., 1997). Patients were also administered the Mini-Mental State Examination (MMSE; Baldwin & Simpson, 1997). Patients had a baseline and five daily ratings of depressive symptoms and MMSE after each day's treatment performed by a psychiatrist who was blind to their treatment status. Follow-up ratings were performed 1 week after the end of the last treatment. This study was approved by the Institutional Review Board of the University of Iowa, and the Food and Drug Administration, and all patients provided informed consent.

RESULTS

All patients had normal results of neurological examinations. There were four patients in the active rTMS group and four patients in the sham stimulation group who had diffuse and symmetric white-matter hyperintensities. White-matter hyperintensities were defined as signal hyperintensities at the level of the frontal, temporal dorsal, parietal, occipital dorsal, and temporo-occipital regions, and all were less than 3 mm. There were two patients in

the active group and two patients in the placebo group who had moderate cortical atrophy. Pre-and post-rTMS EEGs were visually assessed using a semiquantitative rating scale by a neurologist who is expert in electroencephalography (T. Y.), and there were no changes in the overall pattern of the EEGs between pre- and post-rTMS.

There were no significant between-group differences on HDRS scores ($F = 0.19$, $df = 1, 18$, $p > .66$) (Table 1) and MMSE scores ($F = 0.68$, $df = 1, 18$, $p > .41$) (Table 2). When we restricted the analyses to patients with major depression only, we continued to find no significant group-by-treatment interaction ($F = 0.7742$, $df = 1, 16$, $p = .3919$).

The longitudinal evolution of HDRS and MMSE scores was analyzed using a repeated-measure analysis of variance. There were no statistically significant treatment-by-time interactions for either the HDRS or MMSE scores. Comparison between active and sham stimulation groups was also made based on the frequency of responders and nonresponders. Subjects were considered full responders if there was a 50% or greater reduction in the HDRS score and they no longer met criteria for major or minor depression. There were three full responders (30%) in the active stimulation group and three responders (30%) in the sham stimulation group. When recovered patients, defined as final HDRS scores of less than 8, were compared, there were two in the active stimulation and two in the sham stimulation group.

We have compared the clinical correlates of responders and nonresponders to active left prefrontal rTMS. There were no significant differences between responders and nonresponders in age, sex, education, or degree of cognitive impairment as measured by initial MMSE scores. In addition, responders and nonresponders did not differ in the frequency of major or minor depression, severity of depression as measured by initial HDRS scores, number of previous antidepressant treatments, or the frequency of a family history of mood disorder.

TABLE 1. Background Characteristics

	Active ($n = 10$)	Placebo ($n = 10$)
Age, years ± *SD*	60.5 ± 3.4	60.9 ± 2
Sex, % females	50	50
Race, % White	100	100
Education, years, mean ± *SD*	15.2 ± 2.2	13.3 ± 1.8
Marital status		
% divorced	20	10
% married	70	40
% single/widowed	10	50
Prior treatment trials, mean ± *SD*	4 ± 2.3	4 ± 1.2
Age at onset of depression, years	33 ± 4.5	30 ± 3.4
Family history of psychiatric disorders	40%	30%
Depression diagnosis		
% major depression	80	100
% dysthymic disorders	20	0

TABLE 2. Hamilton Depression and MMSE Scores

	Active	Placebo
Depression severity		
Ham-D baseline, mean ± *SD*	22.7 ± 5.2	22.7 ± 7.1
Ham-D Day 5	13.7 ± 5.4	16.2 ± 8.5
Ham-D 7-day follow-up	14.4 ± 6.4	15.5 ± 9.1
Cognitive function		
MMSE baseline	28.7 ± 1.4	28.6 ± 1.3
MMSE Day 5	29.6 ± 0.7	29.3 ± 0.7
MMSE 7-day follow-up	29.6 ± 0.8	29.2 ± 0.8

Note. Ham-D = Hamilton Depression Scale; MMSE = Mini-Mental State Examination.

There were no significant differences in total brain volume or total ventricular volume between patients that responded to rTMS and patients who did not respond. However, after controlling for total brain volume, responders showed significantly greater frontal lobe volume than patients who did not respond ($F = 7.4$, $p = .03$).

Patients receiving active stimulation experienced more side effects than patients receiving sham stimulation. In the active treatment group, one patient had local pain, four had mild headaches, and four had local discomfort. In the sham stimulation group, four patients had local discomfort and one experienced anxiety. These side effects subsided in all patients without medications within 2 hours after the treatment.

DISCUSSION

To our knowledge, this is the first randomized, double-blind, parallel-group study of rTMS for the treatment of refractory depression in the elderly. Although the active treatment group had lower mean HDRS scores throughout the study, this difference was not statistically significant.

Compared with prior rTMS studies, two important differences of this study should be noted. First, in order to control for differences in brain morphology, the site of stimulation was anatomically defined using an MRI-guided method and this site generally coincided with stimulation sites used in prior reports where rTMS improved mood in depressed patients (Manes et al., 1999). Second, our patients tolerated the withdrawal of medication well; therefore, we evaluated the rTMS effects without pharmacological interference.

Before discussing these findings, some limitations of this study should be acknowledged. Many current studies of rTMS in depression are being done using higher stimulation intensities (i.e., 110% of motor threshold) and 10 sessions, rather than the 5 sessions used in this study. We chose 5 sessions and 80% of motor threshold intensity based on prior reports (George et al., 1995; Pascual-Leone et al., 1996) that showed mood improvement with these parameters. Although the reason for our failure to demonstrate a significant antidepressant effect of rTMS may have been due to these "subthreshold" stimulation parameters, it is important that controlled

treatment trials established the lower, as well as upper, end of the stimulation parameters in the elderly.

Apart from the possibly low stimulation parameters, the most obvious question is whether there are other reasons elderly depressed patients did not respond to rTMS. Several authors (Epstein et al., 1998; George et al., 1995, 1997; Pascual-Leone et al., 1996) reported mood improvement in young and middle-aged refractory depressed patients while receiving active rTMS. However, these studies did not use elderly treatment-resistant patients, and some of them allowed concurrent medication (Pascual-Leone et al., 1996).

There have been relatively few studies that have examined the effectiveness of rTMS among resistant patients, and to our knowledge the effectiveness of rTMS in the elderly has not been studied. Also using a double-blind, controlled study, Loo and colleagues (1999) tested the efficacy of 2 weeks of left prefrontal rTMS in patients with resistant major depression (aged 47.5 years old in the real treatment group and 50.9 years old in the sham group). They found no significant difference between groups. In another study, Padberg and colleagues (1999) compared the action of fast (10 Hz), slow (0.3 Hz), and sham rTMS in 18 patients with pharmacotherapy-resistant major depression for 5 successive days. In this study, rTMS did not show any clinically meaningful antidepressant efficacy. More recently, Berman and colleagues (2000) assessed the efficacy of rTMS in unmedicated, treatment-resistant patients with major depression in a population characterized by treatment resistance. A 2-week course of active rTMS resulted in statistically significant but clinically modest reductions of depressive symptoms, as compared to sham rTMS.

In an open, prospective trial that examined the use of left prefrontal rTMS in the treatment of patients with depression, Figiel and colleagues (1998) found that 56% of the young patients responded, but only 23% of the elderly patients responded to rTMS. They suggested that the high incidence of structural brain changes in elderly depressed patients may explain the poor response from rTMS found in their elderly depressed patients. This is consistent with our finding of reduced frontal lobe volume in patients who did not respond to rTMS. Because intensity of stimulation decreases inversely with distance of the stimulation site from the coils, we probably needed to increase stimulation intensity in patients with frontal lobe atrophy. In addition, several authors (Baldwin & Simpson, 1997; Katona et al., 1997) have suggested that older people have a different pattern of depressive symptoms than their younger counterparts and chronicity of symptoms is a potent predictor of poor outcome. Such characteristics of elderly depressed patients may also contribute to the poor response of our patients to rTMS.

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