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Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression

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CONVERGING evidence points to hypofunction of the left prefrontal cortex in depression. Repetitive transcranial magnetic stimulation (rTMS) activates neurons near the surface of the brain. We questioned whether daily left prefrontal rTMS might improve mood in depressed subjects and report a pilot study of such treatment in six highly medication-resistant depressed inpatients. Depression scores significantly improved for the group as a whole (Hamilton Depression Scores decreased from 23.8 ± 4.2 (s.d.) at baseline to 17.5 ± 8.4 after treatment; t = 3.03, 5DF, p = 0.02, two-tailed paired t-test). Two subjects showed robust mood improvement which occurred progressively over the course of several weeks. In one subject, depression symptoms completely remitted for the first time in 3 years. Daily left prefrontal rTMS appears to be safe, well tolerated and may alleviate depression.

Key words: Depression; transcranial magnetic stimulation; Prefrontal cortex; Treatments; Affective disorders

Introduction

Several lines of evidence indicate that the left prefrontal cortex is dysfunctional in depression.[1] Most functional neuroimaging studies of depressed subjects have found decreased left prefrontal activity, often in proportion to the rated severity of depression. Additionally, some studies have found that patients with left prefrontal strokes have an increased risk of developing depression. Finally, left unilateral electroconvulsive therapy (ECT) is more effective than right. Recently the technology of transcranial magnetic stimulation (TMS) has been developed and refined, providing the ability to stimulate superficial neurons of the cerebral cortex safely and subconvulsively. The ability to repeat quickly the magnetic stimulus (repetitive TMS; rTMS), has opened up yet another dimension of cortical activation and inhibition. In motor cortex, rTMS has different properties and neurobiological effects to those of single pulse TMS, perhaps because of the ability to stimulate during a neuron's refractory period.[2] Initially used to study motor function, rTMS has now been used to explore other brain functions[3] as well as to improve the slowed movement of Parkinson's disease temporarily when applied over the motor cortex.[4]

There has been recent interest in whether rTMS might have antidepressant actions if applied to the proper regions and with the appropriate dosing and frequency parameters.[5] Work in animal models of depression has demonstrated that TMS applied to the whole cortex has an antidepressant effect.[6] In humans, there have been two case reports of single pulse TMS (not repetitive) applied through circular coils centered over the vertex, with possible antidepressant action.[7,8] We hypothesized that the most effective antidepressant action of magnetic stimulation might be obtained by applying it frequently and repetitively (rTMS) to the left prefrontal cortex.

Subjects and Methods

We administered rTMS each morning for at least one week (5 days) to the left prefrontal cortex of six medication-resistant subjects, (mean age 46.5 years)

with primary mood disorders (one unipolar, five bipolar disorder type II) who were actively depressed (mean entry Hamilton Depression Rating score 23.8 ± 4.2 (s.d.) on the 17-item scale). Each morning subjects received 20 2-s trains of rTMS at 20 Hz, at 80% of motor evoked potential threshold in the abductor pollicis brevis (APB), over 20 min. rTMS was applied to the left prefrontal region using a hand-held figure-of-eight shaped coil (~5 cm anterior to the optimal surface site for activation of the contralateral APB). This position as measured from the presumed site of the central sulcus was chosen after consulting the Talairach brain atlas, and was designed to maximally stimulate the left dorsolateral prefrontal cortex. rTMS was continued if a clinical response was noted after the first 5 days. Four patients were on blinded placebo compounds, while two (one responder) were on a blinded mood stabilizing compound (carbamazepine) that was held constant.

Results

Daily left prefrontal rTMS at these settings was safe and well-tolerated, the main side-effect being development of mild headaches that responded to aspirin or acetaminophen in two subjects. For the group as a whole, there was a significant improvement in mood (Hamilton decreased from 23.8 ± 4.2 at baseline to 17.5 ± 8.4 after treatment; t = 3.03, 5DF, $p = 0.02$, two-tailed paired *t*-test). Two subjects had no clinically apparent change in mood with daily rTMS. Both were also ECT non-responders. Two subjects showed a slight clinical antidepressant response, while two medication-refractory patients had a robust clinical antidepressant response, as described below.

Case 1 was a 47-year-old woman with recurrent unipolar depression beginning at age 40. Prior to admission to the NIMH she had undergone five hospitalizations, one suidide attempt, and had failed to respond to more than 10 different antidepressant medications and mood stabilizers either alone or in combination. She had previously responded to ECT. During her NIMH stay she partially but inadequately responded to a double-blind trial of the dihydropyridine, L-type calcium channel blocker nimodipine. While on blinded placebo compounds, she was given rTMS daily over the left prefrontal cortex in three separate blocks in an on-off-on-off-on design to establish the antidepressant effect of rTMS. During the first 10 days her mood improved (Figure 1). rTMS was stopped, and her mood relapsed over the next few days of placebo treatment. rTMS was then restarted, with a corresponding mood improvement. The patient then developed a medical illness unrelated to rTMS (diverticulitis). Upon recovery from surgery her mood again declined, and daily rTMS was restarted (day 59). Her mood gradually improved and she became mildly hypomanic after nine treatments over 10 days (day 69), manifested by speeded thoughts, inner restlessness, and decreased need for sleep. rTMS was therefore decreased to every other day, the hypomania resolved, and rTMS was gradually tapered. She reported that she felt completely well for the first time in 3 years and was no longer anhedonic. Prior to discharge she was started on prophylactic treatment with another dihydropyrine L-type calcium channel blocker, isradipine, which we have observed is also an effective mood stabilizer in patients responding to nimodipine. After discharge she remained euthymic for 10 weeks and then relapsed. She was readmitted and was initially treated with 2 weeks of daily left prefrontal rTMS at low frequency to explore the importance of the frequency of stimulation (80% MT, 1 Hz, continuously over 10 min). Her depression worsened over these 2 weeks. She was then treated with daily left prefrontal rTMS as above (80% MT, 20 Hz, 2 s, 20 times over 20 min), responded over 2 weeks and was discharged on isradipine and venlafaxine (started at discharge).

Serial FDG PET scans were performed with arterial sampling to yield absolute cerebral glucose metabolism, while the patient performed an auditory continuous performance task (CPT) with eyes patched. These revealed global hypometabolism while depressed and on placebo compounds prior to starting rTMS treatment (Fig. 1, upper left). She also underwent a split dose FDG study when recovered (day 87). This consisted of a regular study showing normal metabolism (Fig. 1, upper right), followed later in the day by an FDG study with the FDG uptake during an actual rTMS session, with eyes patched and performing the CPT. This image (Fig. 1, lower right) revealed changes in brain metabolism, particularly in areas remote from the stimulation site.

The second rTMS responder was a 50-year-old bipolar type II woman who had suffered from recurrent mild depression beginning at age 17 and severe depression beginning at 42. She had more than 10 hospitalizations, one suicide attempt, and had failed to respond to 14 medication trials before and during her admission to the NIMH, when she also failed to respond to double-blind nimodipine, carbamazepine, valproic acid and buproprion, either alone or in combination. Following daily left prefontal rTMS, her Hamilton depression scores gradually improved from 20 to 12, in a partially dose-dependent manner. That is, each treatment was associated with some improvement but she tended to relapse in the afternoon; this improved with added afternoon sessions. She also relapsed over weekends with no rTMS and maintained improvement with daily treatments. At the beginning of rTMS treatment, she suffered from psychomotor retardation, impaired cognition, flat or tearful affect, and diffuse neck and

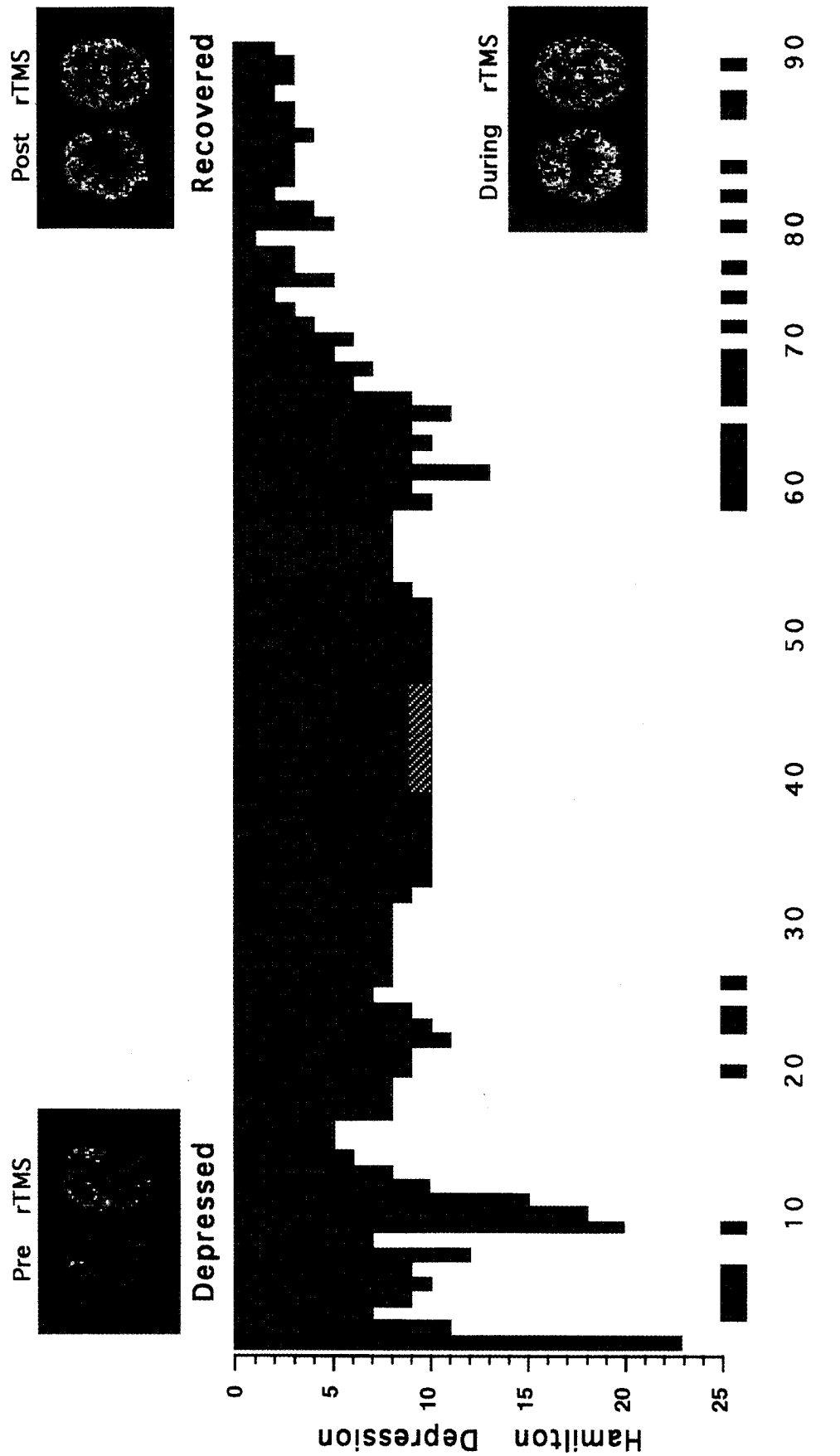

FIG. 1. Clinical antidepressant response to daily rTMS in Case 1. Daily 17-item Hamilton depression scores are graphed in an inverted fashion in blue. Red blocks (bottom) show rTMS treatments. Inserts show serial axial FDG PET scans of absolute data (therefore calibrated across scans) at two different levels with diffuse hypometabolism on placebo before beginning treatment (upper left), which later normalized when her depression resolved (upper right). Another scan was obtained later on the same day, during an actual rTMS session (lower right), demonstrating probable increased brain metabolism, even in regions remote from the stimulation. The hatched area around day 40 represents missing and interpolated data around diverticulitis. This patient's depression responded on three separate occasions to daily rTMS, with the last session resulting in euthymia for the first time in 3 years.

back pains. During each rTMS session these symptoms cleared across the 20 min, commonly after the first 10 min.

Discussion

These two clinical improvements (one complete remission, the other significant improvement with some residual symptoms) in patients who were refractory to most antidepressant medications support the notion that left prefrontal rTMS may have antidepressant properties. rTMS was applied in an open fashion in these individuals due to the lack of previous studies suggesting antidepressant efficacy with these stimulation characteristics. In our treatment refractory patients, placebo responses are uncommon and would not have been expected given multiple psychopharmacological and other relatively novel and invasive interventions such as i.v. injections with procaine, sleep deprivation, and intrathecal injection of TRH.[9]

The development and refinement of ECT has been one of the major advances in psychiatry in this century. However, despite its demonstrated effectiveness in treating clinical depression, its mechanisms of action remain unspecified. Further, ECT entails the risks, costs and stigma of an induced seizure and general anesthesia, and in some instances side effects such as memory loss. If the current preliminary rTMS results are confirmed, they may help clarify the mode of action of the antidepressant effects of ECT,[5] and suggest for the first time that substantial therapeutic benefit could result from use of non-convulsive brain stimulation.

The putative antidepressant mechanisms of rTMS are unknown, although the FDG PET images demonstrate that focal rTMS over the left prefrontal cortex probably has actions at many brain regions, including those far from the original site. In healthy controls, prefrontal but not occipital or cerebellar rTMS raises serum TSH, hinting at a possible effect on TRH.[10]

Clearly much future work is necessary in refining the stimulation parameters (intensity, frequency, pattern and duration), neuroanatomical location, coil design and different schedules for administering rTMS in treating depression. These pilot results demonstrate that daily left prefontal rTMS is safe, generally well tolerated, and could have antidepressant properties in severely depressed subjects who had previously failed to respond to multiple open and blind trials with traditional and investigative pharmacological antidepressants. Double-blind cross-over studies in both severe and mild depression are now underway, with encouraging results in the five subjects studied so far. These additional studies will expand on these preliminary findings and their potential implications for a novel mode of therapeutic intervention in neuropsychiatric disorders.

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General Summary
Electroconvulsive therapy (ECT) is an effective treatment for clinical depression. Unfortunately, ECT requires general anesthesia and has side-effects in some individuals such as severe memory disturbance. Further, it has long been thought, but not entirely proven, that ECT works by inducing a seizure, and that a seizure is therefore necessary to treat depression with direct brain stimulation. Recently, a new technology has been developed where one can place a small but powerful electromagnet on the scalp, and, by turning it on and off, stimulate nerve cells directly below the skull. We wondered whether chronic daily stimulation with this device (known as repetitive transcranial magnetic stimulation (rTMS)), might improve depression without causing a seizure. In 6 patients who had failed multiple previous medications we found a significant improvement for the group as a whole, and two individuals had marked individual responses. Chronic daily rTMS is safe and might be another treatment for depression.