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The Effect of Daily Prefrontal Repetitive Transcranial Magnetic Stimulation Over Several Weeks on Resting Motor Threshold

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Abstract

Background: The resting motor threshold (rMT) is an important factor in the selection of treatment intensity for patients receiving repetitive transcranial magnetic stimulation (rTMS). In many clinical studies to date, due to concerns about potential drift, the rMT has been routinely re-measured weekly or every fifth session.

Objective: Our aim is to investigate whether ongoing treatment with rTMS affects the rMT, the degree of change, and whether frequent remeasurement is needed.

Methods: Clinical data were drawn from 50 medication free patients receiving treatment for major depression with rTMS in a large U.S. NIH-sponsored multisite study. Four measurements of rMT were obtained including before and after the double blind phase, followed by weekly measurements during the open phase. Active treatment consisted of 75 four second trains of 10Hz stimulation applied over 37.5 minutes with the coil over the left DLPFC at 120% rMT.

Results: For the group as a whole, there was no significant change in the rMT during a minimum of 2 weeks of treatment with prefrontal rTMS ($p=0.911$, one way ANOVA). The average within-subject coefficient of variation was 6.58%. On average the last rMT was 2.45% less than the baseline rMT (range 32.3% increase, 40.6% decrease).

Conclusion: Daily left prefrontal rTMS over several weeks as delivered in this trial does not cause systematic changes in rMT. While most subjects had <10% variance in rMT over time, 5 subjects had changes of ~20% from baseline, raising dosing and safety issues if undetected. We recommend that clinical trials of rTMS have periodic retesting of rMT, especially if the dose is at or near the edge of the TMS safety tables.

Keywords

rTMS; rMT; Major Depression; Safety

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Introduction

Most current clinical studies investigating daily repetitive transcranial magnetic stimulation (rTMS) as a potential treatment follow the convention of periodically remeasuring the resting motor threshold (rMT) over the treatment course. Many recent large studies re-measure the rMT every fifth session, effectively each week (1-3). Measurements of rMT may be time consuming for patient and provider. The rMT is a critical factor for the selection of treatment intensity and the prevention of seizures (4). Before large treatment studies of rTMS were conducted, it was hypothesized that ongoing rTMS might change the rMT, or that the background rMT would change drastically in given individuals, rendering an initially 'safe' dose for the patient potentially unsafe, if the rMT had decreased. Alternatively, if the rMT were to increase with no change in the actual dose delivered from study entry, then patients might be underdosed. Thus for both safety and dosing reasons, scientists have routinely remeasured the rMT in TMS treatment studies. Additional supporting evidence was extrapolated from the observation that the seizure threshold increases over a course of ECT (5,6). Animal studies showed rTMS to increase the seizure threshold (7-9). Furthermore, Triggs reported that left prefrontal rTMS administered at 20 Hz and 80% rMT was associated with a decrease in the rMT in 9 out of 10 patients undergoing 10 sessions of treatment for major depression (10). The field thus adopted a cautious approach involving frequent measurements of rMT.

However, the published literature supporting a change in rMT over a treatment course of rTMS is mixed. Bajbouj found no significant change in rMT after 10 sessions of 20 Hz stimulation at 100% rMT applied to the left prefrontal cortex in 30 depressed patients (11). Similarly, Dolberg found no significant change in rMT after 20 sessions of 10 Hz stimulation at 90% rMT applied to the left prefrontal cortex in 46 depressed patients (12). Although our primary interest involves high frequency stimulation of the left prefrontal cortex, other studies have investigated stimulation of the motor cortex with lower frequencies. Cantello did not find any significant difference in the rMT between active (0.3 Hz) and sham stimulation of the vertex over five sessions in 43 patients with treatment resistant epilepsy (13). Although the available studies suggest that rTMS may not have a significant effect on the rMT, no clear pattern emerges.

Other factors besides rTMS have been investigated for their effect on the rMT. Chronic use of benzodiazepines increases the rMT (14) but acute use has not been shown to have an effect (15,16). Numerous other medications can affect the rMT (for review see Paulus et al, (17)). No change in rMT has been found for healthy controls with sleep deprivation (18), alcohol intoxication(19) or over anovulatory or ovulatory cycles in healthy women (20). Other unidentified factors may affect the rMT, but have not been investigated and reported to date.

Our aim is to investigate whether rTMS at the increased intensities used in current treatment studies alters the rMT in a large sample of patients with major depression. We hypothesized that, for the group, there would be no significant change in rMT over the course of rTMS. We were also interested in the variance or spread of changes in rMT examined at the individual level, in order to determine the likelihood of over or under-stimulating any specific patient with changes in their rMT.

Methods

Patients

Our sample included 50 patients participating in an ongoing NIH-sponsored multisite clinical trial of rTMS, referred to as the Optimization of TMS for the Treatment of Depression Trial, or OPT-TMS. Data were collected at 4 sites in the United States (Seattle, WA; Atlanta, GA; Charleston, SC; and New York, NY). The design involves an initial sham controlled phase

lasting for at least 3 weeks. Clinical non-responders are then offered entry into a compassionate open phase, lasting up to 6 weeks if there is clinical response. This is a dynamically adaptive design. The diagnosis of major depression (MDD) was made using the Structured Clinical Interview for Diagnosis for DSM-IV (SCID-P). All patients scored greater than 20 on the Hamilton Rating Scale for Depression (24 item) and all had treatment resistance defined as the failure to respond to at least one, but no more than four, adequate trials of medication in the current episode of depression (ATHF - Sackeim 2001) or they must have been intolerant to at least 3 antidepressant medications during their lifetime. Patients underwent antidepressant medication washout before entering the study. They were allowed a dose of up to 3mg/day of lorazepam or equivalent. Exclusion criteria included: a history of psychosis, bipolar disorder, a prior trial of rTMS or vagus nerve stimulation, lack of response to an adequate trial of ECT, ECT within the past 3 months, unstable medical conditions, or a history of neurological disorder or seizure. All patients provided written informed consent. This study was approved by the Human Subjects Review Board of the University of Washington as well as IRBs at each of the involved sites (Emory University, Medical University of South Carolina, New York State Psychiatric Institute).

TMS procedure

TMS was performed with a Model 2100 magnetic stimulator (Neuronetics Inc., Malvern, Pennsylvania), consisting of a controller/power supply and a head coil suspended on a support arm with six degrees of freedom. Four dimensions are calibrated and recorded for consistent coil position. Subjects were seated in a reclining chair with the whole body at rest and the head supported by a foam headset for stabilization and to facilitate repositioning during subsequent sessions. The site of stimulation was defined as the scalp position at which TMS induced motor-evoked potentials (MEPs) of maximal peak-to-peak amplitude in the *abductor pollicis brevis* (APB). The site of stimulation was determined in a iterative process with the coil initially positioned over an imaginary line between the vertex of the head and the top of the of the subject's left ear, 30 degrees from the patient's vertical axis, also known as the left superior oblique angle (LSOA). Next coil position is varied in a grid like fashion over the anterior/posterior and LSOA dimensions. Magnetic power is gradually increased during the site determination find the smallest power level to evoke a twitch in the APB. Surface electromyography (EMG) was recorded from the APB bilaterally using 9-mm Ag-AgCl electrodes in a belly-tendon montage. The raw EMG signal was amplified by a gain of 50 and band-pass filtered, with a High Performance Band pass Filter Model V-75-48 (Coulbourn Instr, Whitehall, PA) or the equivalent in different labs. One circular ground electrode was placed on the forearm bilaterally and linked to a common ground. Muscle relaxation was verified by EMG. RMT was defined as the lowest intensity that produced a MEP of greater than 50 μ V in 5 out of 10 trials in the resting APB. MT Assist software (Neuronetics Inc.) was used in our study. This software uses an iterative method to arrive at the rMT by adjusting the power level based on the presence of a response in preceding trials. Usually 6 to 8 trials are required for each block or rMT measurement. Two blocks approach the true rMT from the subthreshold direction and two from the suprathreshold direction. A mean rMT was calculated by averaging the values obtained in four blocks. RMT determination took place at baseline before the blind phase and then once every week in the open phase, for a total of 4 measurements. Approximately half of the subjects received 15 sessions of rTMS between the baseline rMT and the first open phase rMT. The other half received 15 sessions of active sham TMS treatment. (See Figure 1). As the study is still ongoing we cannot at this point determine who received which form in the initial 3 weeks. In this dataset all subjects then received 5 sessions of rTMS between each rMT determination in the later open phase. Repetitive TMS was delivered to the left DLPFC at a frequency of 10 Hz at 120% rMT. Each session consisted of seventy-five 4 second trains (3000 pulses per session) with a 26 second inter-train interval.

Data analysis

A one-way ANOVA was employed to assess for a difference in the mean rMT between visits, from visit 1 to 4. The left rMT was used as the dependent variable in our analysis. Age (divided in 3 equal groups), gender and benzodiazepine use were subsequently controlled for with a four-way ANOVA. A *p* value of less than 0.05 was set to define the level of significance in all cases. SPSS 13.0 was used for all of the statistical procedures.

Results

Demographic and clinical characteristics are shown in Table 1

Table 2 summarizes the mean rMT for each visit as a group. No significant difference was found in the rMT between visits ($p=0.911$, one way ANOVA).

As shown in table 3, when accounting for cofactors such as gender, age and benzodiazepine use, there was no evidence of any significant interaction between visit number and rMT ($p>0.05$).

On average, the within subject change from visit 1 to visit 4 was -1.39 units MT (decrease by 2.45% from visit 1). The largest decrease was 26 units MT (decrease by 40.6% from visit 1) and the largest increase was 10 units of MT (increase by 32.3% with respect to visit 1). A scatter plot of all subjects is shown in Figure 2. The average subject change -1.39 (SD 7.23) was not significantly different from zero change with *p*-value of 0.172. Over all four measurements of rMT, the average within subject standard deviation is 4.44 units MT. Average within subject coefficient of variation (CV) is 6.58%. The smallest CV observed was 0.00% and the largest CV observed was 31.4%.

Discussion

In support of our hypothesis, we did not find a significant effect of treatment with rTMS on the rMT. Our sample size of 50 depressed patients is the largest sample in the TMS treatment literature where rMT has been reported. We also used the most intense stimulation at 120% rMT and 3000 stimuli per day. In spite of the larger sample size and increased intensity we were still unable to find a significant change in the rMT measured at a group level. Furthermore, no effect of rTMS on rMT was found after controlling for age, gender and benzodiazepine use.

Examining the data with respect to individual changes over time, we found that the greatest change from study baseline was of magnitude 26 units MT (a decrease of 40.6%). Two other measurements from this subject during the open phase were more closely clustered with the final measurement and were within 6 units MT (15.6%). Possible explanations of the large change after the first measurement include changes in benzodiazepine use. Chronic (14), but not acute use of benzodiazepines (15,16) has been shown to raise the rMT. Although there are no recorded changes in this patient's prescription of clonazepam and zolpidem, it is possible that this patient became non-compliant shortly after their first RMT and abstained from benzodiazepines through the subsequent measurements three weeks later. Antidepressants and other psychotropic medications were not allowed in these phases of the study. Sleep deprivation (18), alcohol intoxication (19) treatment response (11) and menstrual cycle (20) have all been found to have no systematic effect on the rMT. We can not rule out the possibility of variability in rMT arising as a result in variation in coil placement and other technical differences during rMT measurement.

Our study focused on changes in the rMT because of its practical application in the treatment of major depression with rTMS. Other measures of cortical excitability have been investigated

and examined for changes with repeated daily rTMS. Bajbouj reported that treatment responders had a significant increase in cortical silent period and intracortical inhibition over ten sessions of 20 Hz rTMS applied to the left prefrontal cortex, suggesting a decrease in cortical excitability (11). The increased seizure threshold with rTMS seen in animal studies (7-9) could reflect changes in the same cortical mechanisms. It appears that the mechanisms underlying cortical silent period, intracortical inhibition, and seizure threshold may be different than the mechanisms underlying the rMT.

We failed to find an overall effect of daily rTMS on measured rMT, thus suggesting that repeated weekly measurements are not needed. However, our discovery of an individual with a change of 40% from baseline and 5 subjects with changes greater than 20%, even with well-trained technicians and a standardized method of rMT assessment, highlights the need for continued periodic retesting, especially if the dose is at or near the edge of the TMS safety tables. Retesting is indicated after changes in the subjects' sleep patterns or medications. We recommend continued emphasis on investigator training and attention to technique and possible subject factors (medications, stimulants, etc.) that might alter the rMT.

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Dr. George currently receives funding from 5 R01 MH069887-04, 5 P20 DA022658-02, 1 R21 MH078046-01. Dr. George owns no stock or equity in any device or pharmaceutical company. He is a paid consultant to several device manufacturers, including Neupace (DBS) and Cyberonics (VNS). He is an unpaid consultant to several TMS manufacturers (Neuronetics, Brainsway), and served as head of the DSMB for Aspect Medical. For the past decade, his entire yearly compensation from all manufacturers and speaking engagements is less than 20% of his university salary. He is the editor-in-chief of a new journal published by Elsevier, entitled *Brain Stimulation* and has written several books in this area. MUSC holds several patents in his name involving brain stimulation and imaging, one using fMRI (not EEG) to determine the best dose of VNS for a patient.

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Figure 1.

The timing of rMT measurements relative to rTMS treatment. RMT was measured once during initial screening and once a week during the blind phase but is not shown above for clarity. . Approximately half of subjects in blind rTMS phase received active rTMS, with the others receiving active sham.

Figure 2.

A scatterplot of all subjects. Baseline rMT is on X Axis. Final rMT is on Y Axis. Solid line indicates no change between baseline and final measurement. Dashed lines indicate positive or negative variation of 10 percent.

Table 1

Demographic and Clinical Characteristics of the Patients Enrolled in the Study

	Mean (SD)
Age	46.9 (10.7)
HRSD	26.1 (4.81)
	% (N)
Gender (% female)	52.0% (26)
Benzodiazepine use (Yes)	48.0% (24)

Table 2

RMT mean by visit number

Visit Number	RMT mean (SD)
1	56.72 (12.1)
2	55.24 (10.8)
3	55.90 (10.9)
4	55.33 (11.7)

Table 3

Tests of Between Subjects Effects (Dependant Variable: RMT). For purposes of ANOVA, subjects were divided into 3 equal age groups, 24-42 yo, 43-51 yo, 52-69 yo.

	<i>P value</i>
Visit Number	0.820
Gender	0.629
Age Group	0.247
Benzodiazepine Use	0.951
Visit Number*Gender	0.616
Visit Number*Benzodiazepine Use	0.767
Visit Number*Age Group	0.913
Benzodiazepine Use*Age Group	0.301
Benzodiazepine Use*Gender	0.117
Age Group*Gender	0.046
Visit Number*Gender*Benzodiazepine Use	0.960
Visit Number*Gender*Age Group	0.911
Visit Number*Benzodiazepine Use*Age Group	0.884
Benzodiazepine Use*Age Group*Gender	0.253
Visit Number*Gender*Benzodiazepine Use*Age Group	0.863