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No Change in Neuropsychological Functioning After Receiving Repetitive Transcranial Magnetic Stimulation (TMS) Treatment for Major Depression

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Abstract

Early studies of transcranial magnetic stimulation (TMS) have shown no adverse effects on neuropsychological function. However, further research is needed using higher TMS intensities, a greater number of TMS pulses, and larger sample sizes. We studied 68 patients with Major Depressive Disorder who were randomized to receive either 15 sessions of sham or real TMS at 110% of the estimated prefrontal cortex threshold to the left dorsolateral prefrontal cortex. Each session consisted of 32 5-second trains of 10 Hz repetitive TMS at 110% adjusted motor threshold. A total of 24,000 pulses were given. Neuropsychological function was assessed before and immediately after TMS treatment with a battery of 8 tests. Using a higher TMS intensity, a greater number of pulses and a larger sample size compared to most previous studies, this study found no negative neuropsychological effects of TMS. Changes in neuropsychological function were unrelated to changes in depression.

Keywords

Transcranial magnetic stimulation; major depression; neuropsychological function

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Introduction

Repetitive transcranial magnetic stimulation (TMS) is a non-invasive form of brain cortical stimulation that has shown to be effective in decreasing depressive symptoms in individuals with Major Depressive Disorder¹⁻⁵. As a possible alternative treatment to electroconvulsive therapy (ECT) among treatment-resistant depressed individuals, TMS has been shown to have a better safety profile, particularly with respect to the neuropsychological effects of the treatment⁶⁻⁹. In contrast to the negative cognitive effects of ECT,¹⁰⁻¹² TMS has shown no negative effects on neuropsychological function in almost all randomized, sham-controlled trials^{4,13-20}. One exception was a study done by Loo and colleagues in 2007 where the researchers administered TMS twice-daily for the first two weeks of treatment and found a decrement in psychomotor speed at the end of week two that resolved by weeks three and four of treatment. There is strong evidence that TMS does not negatively affect neuropsychological functioning within the treatment parameters used to date.

Further, in some studies, TMS, compared to sham stimulation, improves verbal memory^{21,22}, cognitive flexibility and conceptual tracking²³, and motor retardation²⁴. Similar to the results of sham-controlled studies, some open studies have also found TMS treatment to be associated with either no change in neuropsychological test scores²⁵⁻²⁸ or improvements in verbal memory²⁹⁻³¹, reaction time³², concept-shifting³¹ and attention^{33,34}. Improvements may even be enduring, as Triggs and associates showed by demonstrating increases from baseline in a test associated with dorsolateral frontal functioning to last for 3 months post treatment in an open-label study of 20 Hz TMS³⁵. More research is needed to determine if TMS improves neuropsychological functioning and what aspects of functioning may improve, and how improvements depend on TMS treatment parameters.

It is unknown whether the possible neuropsychological improvements are associated with relief in depressive symptomatology or whether they are independent effects of TMS. Interestingly, one session of 10 Hz TMS to the left dorsolateral prefrontal cortex (LDLPFC) improved selective attention in non-depressed individuals without inducing a change in mood³⁶. In a clinical trial, Pallanti and colleagues found that improvements in depression were independent of improvements in the Corsi Block Tapping test and verbal fluency³⁷. Similarly, Kedzior and colleagues found that neuropsychological variables did not correlate with depression scores after 20 sessions of TMS³¹. However, two open studies of TMS, one in vascular depression³⁸ and one in Major Depressive Disorder {O'Connor, 2005 #17} showed that improvements in neuropsychological variables were associated with improvements in depressive symptoms. It is important to note that each of these studies used different neuropsychological test batteries and TMS treatment parameters, factors that may account for the seemingly conflicting results. It is unknown whether changes in depressive symptoms are related to changes in neuropsychological functioning.

We explored data from our clinical trial³⁹ to address the effect of TMS treatment on neuropsychological functioning. We hypothesized that TMS would have no negative effect on neuropsychological functioning. We also explored post-hoc whether changes in neuropsychological functioning were independent of changes in depressive symptoms.

Materials and Methods

For a complete description of study procedures, see the related efficacy paper in which we found significant antidepressant effects of the TMS treatment above that of sham treatment³⁹.

Participants

Sixty-eight participants were randomized to receive TMS treatment. Thirty-five participants received TMS and 33 participants received sham TMS, with 63 participants completing the protocol with complete data (32 TMS, 31 sham). The University of Washington Human Subjects Committee approved the study and participants signed written informed consent before initiating study procedures. All participants met criteria for Major Depressive Disorder according to the Structured Clinical Interview for DSM-IV⁴⁰ and were between the ages of 21 and 65. Participants had to have failed to respond to or have been unable to tolerate at least two adequate trials of antidepressant medications according to the Antidepressant Treatment History Form⁴¹. Exclusion criteria were active suicidal ideation or recent suicide attempt, Hamilton Depression Rating Scale (HDRS) 17-item score of less than 18, previous TMS exposure, Bipolar Disorder, history of non-response to ECT, current major depressive episode longer than five years, substance abuse or dependence in the past two years, Antisocial or Borderline Personality Disorder, psychosis, history of seizure or head injury with loss of consciousness for more than 15 minutes, or brain surgery. Twenty participants (11 TMS/ 9 sham) were on antidepressant medications during TMS at stable doses for at least four weeks prior to, during, and two weeks after TMS treatment.

TMS Treatment

An Investigational Device Exemption was received from the U.S. Food and Drug Administration. Participants were treated with the Dantec MagPro Magnetic Stimulator (Medtronic, Inc., Minneapolis, Minnesota) with a 70-mm figure-eight coil at Harborview Medical Center in Seattle, Washington. They were given 15 treatment sessions over a three to four week period. Stimulation location was defined as the point 5 cm anterior to the site in the motor cortex that maximally stimulated the right first dorsal interosseous muscle. The estimated prefrontal threshold was estimated based on the motor threshold and the differences in scalp cortical distances in the motor cortex and the prefrontal cortex³⁹. TMS treatment was delivered at 110% of the estimated prefrontal threshold at 10 Hz in five second trains with a 25-30 second inter-train interval (1,600 pulses per session; 24,000 total pulses). Sham treatment was delivered in the same manner as real TMS, but with the coil angled at 90° away from the surface of the scalp. Participants were randomized to treatment allocation during screening and blinded to group status. Participants were assessed with the HDRS at screening, baseline, and TMS treatments 5, 10, 15, visit 16 (one week post TMS), and visit 17 (two weeks post TMS) by a blinded clinical rater. Response criteria was defined as a decrease of 50% in the HDRS score at visit 16 that persisted until visit 17. Non-responders to sham were crossed over to receive 15 open TMS treatments.

Neuropsychological Testing

Tests administered included the Rey Auditory Verbal Learning Test [RAVLT, testing initial learning, short term and long term verbal memory, and word recognition ⁴²]; Digit Symbol [processing speed, from the Wechsler Adult Intelligence Scale-Revised ⁴³]; Digit Span forwards and backwards [auditory attention span; from the Wechsler Memory Scale-Revised ⁴⁴]; Trail Making Test Parts A and B [psychomotor speed, scanning and visuomotor tracking, divided attention, and cognitive flexibility ⁴⁵⁻⁴⁷]; Mini-Mental Status Examination [MMSE; orientation and general mental status ⁴⁸]; Controlled Oral Word Association Test [COWAT; verbal fluency, which is associated with dorsolateral frontal functioning of the language dominant hemisphere ^{47,49}]; Logical Memory [verbal anterograde memory, from the Wechsler Memory Scale-Revised ⁴⁴]; and the color card Stroop Test [selective attention, set shifting, and response inhibition ^{50,51}].

Alternate equivalent test forms were used for the RAVLT, Logical Memory, Trails, and COWAT. The neuropsychological battery was given at screening, baseline and approximately one hour after the 15th TMS treatment. The Galveston Orientation and Amnesia Test [GOAT ⁵²] is a 0-100 scale of general orientation, consciousness and amnesia and was administered immediately following each of the 15 TMS treatments. For the randomized trial, baseline scores were compared to post-treatment scores. For the open trial, post-treatment scores from the randomized trial were compared to post-treatment scores for the open trial. Two sets of neuropsychological tests were given before TMS (at screening and baseline) to minimize practice effects between the pre and post randomized TMS comparisons.

Statistics

Randomized data were analyzed with 2 X 2 Mixed ANOVAs with one within subjects factor (time: pre, post) and one between subjects factor (treatment condition: sham, TMS). Bonferroni corrections were applied to account for the 16 variables tested. Open data were analyzed with dependent groups t-tests with Bonferroni corrections from pre treatment (visit 15 in the randomized study) to post treatment (visit 15 in the open study). GOAT scores were analyzed with a 15 X 2 Mixed ANOVA with time as the within subjects factor (TMS treatment 1, 2, 3, etc.) and treatment condition as the between subjects factor (TMS, sham). Correlations between changes in HDRS scores and changes neuropsychological variables from pre (baseline) to post treatment (visit 15) were analyzed with the Pearson *r* values separately for the TMS and sham groups, and combined for TMS and crossover TMS. We set the alpha level = .05, two-tailed.

Results

The TMS treatment was more effective than the sham treatment in decreasing depressive symptomatology according to HDRS scores. Response rates for the TMS and sham groups were 30.6% and 6.1%, respectively, Fisher's *p* = .008. Remission rates for the TMS and sham groups were 20% and 3%, Fisher's *p* = .033.

GOAT scores were analyzed with a 15 (time: treatments 1-15) $\times$ 2 (group: TMS, sham) mixed ANOVA. There were no significant main effects of time or group and no interactions. Means were consistent and high with the overall $M = 99.98$, $SD = .07$, $n = 44$.

We analyzed neuropsychological test data from the randomized and open portions of the study separately. For the randomized trial data, there were no significant time by treatment interactions in any of the 16 variables tested (see Table 1 for a summary of statistics for the randomized neuropsychological testing data).

Data from the open study revealed improvements in verbal memory, and no deterioration for the remaining tests. Dependent groups t-tests with Bonferroni corrections were used to analyze differences from pre- to post-treatment. Participants improved on both domains (immediate and delayed recall) of the Logical Memory test. More words from the stories were remembered post TMS treatment (immediate $M = 17.73$, $SD = 2.86$, delay $M = 16.94$, $SD = 3.58$) than pre-treatment (immediate $M = 15.62$, $SD = 2.82$, delay $M = 14.65$, $SD = 3.20$), immediate $t(25) = 5.60$, $p_{\text{Bonferroni}} = .0003$, delay $t(25) = 4.03$, $p_{\text{Bonferroni}} = .02$.

We calculated Pearson correlations (r) between the change in HDRS and the change in each of the 16 neuropsychological variables separately for sham and TMS groups in the randomized portion, and separately with the open-label data to test the hypothesis that change in depressive symptoms is related to change in neuropsychological performance. None of the correlations in the TMS or sham group, or in the open-label data, were significant. In order to increase power, we also combined all subjects, looking at scores when participants received either randomized TMS or open label TMS ($n = 58$). Again, no correlations were significant.

Discussion

Data from the present study are consistent with previous studies on neuropsychological functioning and TMS in depression, showing no evidence of negative neuropsychological effects of the treatment. This is in contrast to the negative cognitive effects associated with ECT^{7,9-11}. This contributes to the safety literature of TMS as we used more total TMS pulses and higher TMS intensity and frequency than all previous sham-controlled studies except four^{4,15,17,53}. We also had a larger sample size than all previously published studies in treatment-resistant depression except one⁴, and hence, more power to detect negative effects if present.

We found little evidence to suggest the treatment improved neuropsychological function. While we did note two out of 16 improvements in the open phase, we cannot rule out placebo or test-retest effects. In fact, this pattern of results is consistent with data from the randomized study, which showed some significant effects of time, where both the sham and TMS groups improved in their scores from pre- to post-treatment. However, it is interesting that the improvement noted in the open phase was in verbal memory; the same area of neuropsychological function that has shown improvements in three previous studies^{21,22,29}. Differences in stimulation parameters may account for why not all studies find improvements, as two of the studies that found neuropsychological improvements used 20

Hz stimulation^{23,24}, whereas most studies that failed to find the key time by treatment interaction used 10 Hz TMS, as we did^{13,15-17,22}. More randomized controlled studies with larger sample sizes are needed to clarify whether TMS has positive effects on verbal memory or other domains of neuropsychological functioning, and whether this is dependent upon TMS stimulation parameters.

We found no evidence that changes in depressive symptoms associated with TMS treatment are related to changes in neuropsychological functioning. Therefore, it is unlikely that alleviation of depressive symptomatology alone can explain possible improvements in neuropsychological test performance following treatment with TMS, and leaves open the possibility that the TMS treatment may be independently responsible for these effects.

One limitation of this study was a lack of a follow-up period for neuropsychological assessments. Since TMS may have antidepressant effects that endure past the time of immediate treatment administration, it is feasible that possible neuropsychological effects could be enduring as well, as Triggs and associates found in their 3-month follow-up³⁵.

Data from the present study are consistent with the existing literature that indicates that TMS is a safe procedure with no negative neuropsychological effects, even when a greater total number of TMS pulses, higher frequencies and intensities are utilized. More studies are needed to determine if TMS has positive effects on neuropsychological performance, and if possible improvements in cognitive functioning are independent effects of TMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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