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Improved executive functioning following repetitive transcranial magnetic stimulation

[Brief Communications]

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Abstract

The cognitive effects of active and sham repetitive transcranial magnetic stimulation (rTMS) were examined in 19 middle-aged and elderly patients with refractory depression. Patients received either active (n = 9) or sham (n = 10) rTMS targeted at the anterior portion of the left middle frontal gyrus. Patients in the active rTMS group improved significantly on a test of cognitive flexibility and conceptual tracking (Trail Making Test–B).

Repetitive transcranial magnetic stimulation (rTMS) can induce alterations of neuronal activity that may affect mood and cognition. Much of the research in this area has focused on the antidepressant effects of rTMS, with some studies yielding positive findings [1,2] and other studies finding no difference between active and sham rTMS treatment. [3,4] Regarding cognition, it has been demonstrated that rTMS of the left dorsolateral prefrontal cortex can temporarily impair performance on certain neuropsychological tasks. [5] Other rTMS/neuropsychological studies have indicated that rTMS does not have persisting negative effects on performance, and some have revealed poststimulation *improvement* in a range of neuropsychological domains including executive functioning, memory, and language. [6,7]

We conducted a randomized study of active vs sham rTMS in a group of 19 middle-aged and elderly individuals with refractory depression. Based on previous studies and on the literature concerning cognitive changes in the treatment of depression, we hypothesized that the active rTMS group would show significantly greater changes in executive function than the sham rTMS group, and that performance in other neuropsychological domains would be unchanged.

Methods

This study was approved by the University of Iowa Institutional Review Board.

Subjects.

Subjects were 19 men and women (age range: 48–78 years) who had refractory depression and had been unresponsive to an average of 4 prior medications. Subjects provided informed consent, were tapered from medications, and were randomly assigned to receive either sham or active rTMS of the anterior portion of the left middle frontal gyrus.

Protocol.

Stimulation was performed using a Super Rapid 1- to 50-Hz magnetic stimulator (The Magstim Company Limited, Whitland, South West Wales, UK). The motor threshold of the right abductor pollicis brevis muscle was determined for each subject, using the method of limits. [8] We then stimulated at 80% of this intensity for the rest of the study. Subjects received either 5 sessions of active stimulation (20 Hz at 80% motor threshold for 2 seconds, with 20 trains separated by 1-minute pauses) or 5 sessions of sham stimulation (same parameters but with the figure eight coil above the top of the skull with the handle placed against the head). After participation, subjects were unaware whether they had received active or sham stimulation.

All subjects underwent neurologic examination and structural three-dimensional brain MRI. We identified a consistent anatomic site for stimulation in the anterior portion of the middle frontal gyrus using fiducial markers on a skullcap overlaid on the three-dimensional MRI reconstruction of the brain. The target site was located an average of 5.3 cm anterior and in a parasagittal plane from the point of maximum stimulation of the right abductor pollicis brevis muscle. MRI scans also were used to obtain quantitative measures of total brain volume, volumes of the frontal, temporal and parietal lobes, ventricles, and subarachnoid CSF, and to determine the size and location of white matter hyperintensities, using methods described elsewhere. [9]

Psychiatric and neuropsychological assessments were conducted at baseline and after stimulation. Because of circumstances unrelated to neuropsychological function, one subject in the sham group was not administered the Trail Making Test–B. The interval between final stimulation and follow-up testing was not significantly different between the two groups (mean = 3 days for each group),

and no medications were resumed before follow-up testing. Testing was conducted by an examiner blinded to subject group.

Depression was measured using the Hamilton Depression Scale. The neuropsychological battery included the following: a) *Executive*: Trail Making Test–A and –B, The Stroop Test, WAIS-R Digit Symbol; Controlled Oral Word Association; b) *Language*: Boston Naming Test (30-item form), Sentence Repetition; c) *Memory*: Rey Auditory Verbal Learning Test—% of learned words recalled after delay; d) *Visuospatial*: Judgment of Line Orientation.

Statistical analyses.

Baseline sham vs active rTMS group demographics and neuropsychological scores were compared using two-tailed Mann–Whitney *U* tests. Baseline and follow-up neuropsychological test scores were compared using two-tailed Wilcoxon Signed-Rank Tests. These nonparametric tests were used to be as conservative as possible within the context of our small group sizes. When it was determined that Trail Making Test–B scores were significantly improved in the active rTMS group, simple correlations were conducted between Trail Making Test–B scores (baseline and follow-up), education, and baseline-to-follow-up change in Hamilton Depression Scale scores.

Results.

Demographics and baseline neuropsychological and MRI data

The active and sham rTMS groups did not differ significantly in age or years of education (active group: mean age = 61.22, SD = 10.30; mean education = 15.22, SD = 2.22; sham group: mean age = 60.90, SD = 10.20, mean education = 13.30, SD = 1.83). Regarding baseline neuropsychological test performance, the active group had higher Digit Symbol scores than the sham group ($U = 18.5$, $p < 0.05$), but there were no other significant differences in baseline test scores. The two groups did not differ significantly on any of the MRI-based anatomic volumes and there was no significant difference between the groups in the size or location of white matter hyperintensities.

Depression scores.

As recently reported, [4] follow-up Hamilton Depression Scale scores were less than baseline scores across both groups [$z = -0.351$, $p < 0.001$], but active and sham group mean scores were nearly identical to each other at both time points. The active group began the study with a mean Ham-D score of 22.33 (SD = 5.34), which decreased to a mean of 15.11 (SD = 6.37), whereas the mean Ham-D score decreased from 22.70 (SD = 7.07) to 15.50 (SD = 9.09) in the sham group.

Change in neuropsychological performance.

The active rTMS group showed an improvement across the course of the study on Trail Making Test–B ($z = 2.134$, $p < 0.05$; effect size: Cohen $d = 0.793$). Other neuropsychological tests did not show significant pre- to post-study

changes for either group (see the table). Neither education nor Hamilton Depression Scale scores were significantly correlated with baseline or follow-up Trail Making Test–B scores.

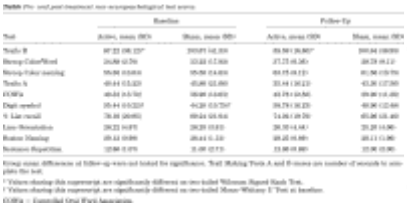

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Table. Pre- and post-treatment raw neuropsychological test scoresGroup mean differences at follow-up were not tested for significance. Trail Making Tests A and B scores are number of seconds to complete the test.* Values sharing this superscript are significantly different on two-tailed Wilcoxon Signed Rank Test.† Values sharing this superscript are significantly different on two-tailed Mann–Whitney *U* Test at baseline.COWA = Controlled Oral Word Association.

Discussion.

The significant improvement in Trail Making Test–B performance shown by the active rTMS group suggests the intriguing possibility that rTMS may improve specific aspects of executive functioning independent of changes in depression and overall cognitive functioning. The amount of improvement shown was significant, raising the active group's mean score from just slightly less than the normative mean to the cusp of the average and high average ranges. Although the precise mechanism of change is unclear, it is noteworthy that dorsolateral prefrontal cortex, the target of stimulation in this study, is integrally involved in the types of cognitive processes required by Trail Making Test–B, whereas other cognitive skills (e.g., memory, language, visuospatial skills) mediated primarily by other, nontargeted brain regions were relatively unaffected. Notably, the effect remained with the use of a conservative nonparametric statistical approach, and improvement was not associated with factors such as level of education or pre- to post-study changes in depression. The failure of active and sham rTMS to show differential effects on depression in this study is discussed elsewhere. 4

One limitation of this study is the interval between stimulation and follow-up testing, but it is noteworthy that the groups did not differ significantly in the timing of follow-up testing, and that it has been shown that rTMS can produce changes in regional cerebral blood flow that persist for at least 3 days. 10 We are attempting to replicate these preliminary findings in a larger sample, using a more detailed assessment of executive functioning.

Acknowledgment

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