
A5 Aging and Dementia: Therapeutics

Functional Imaging and Neurocognitive Correlates of Targeted High Frequency Repetitive Transcranial Magnetic Stimulation in Patients with Alzheimer's Disease (P04.190)

Gayatri Devi¹, Dani Levine², Henning Voss³, Michael de Boisblanc⁴, Linda Heier⁵ and James Halper⁶

¹ Neurology, New York University School of Medicine New York Memory Services New York NY

² New York Memory Services New York NY

³ Radiology Weill Cornell Medical College New York NY

⁴ New York Memory Services New York NY

⁵ Radiology Weill Cornell College of Medicine New York NY

⁶ Psychiatry New York University School of Medicine New York NY

Objective: To assess whether 1) repetitive transcranial magnetic stimulation (rTMS) can ameliorate aphasia in Alzheimer's disease (AD) patients and 2) whether there are changes in activation patterns in relevant cortical areas using functional brain imaging subsequent to rTMS.

Background Among the earliest manifestations of AD are deficits in language that significantly impair patients' quality of life. Currently approved agents for slowing progression of AD do not target aphasia. Studies have demonstrated beneficial effects of rTMS in improving cognition and language deficits in patients with neurological disorders. rTMS may be a potential therapeutic tool to help improve aphasia in AD patients.

Design/Methods: Eleven AD patients with aphasia underwent 4 sessions of rTMS applied to the dorsolateral prefrontal cortex at a frequency of 10-15 Hz over two weeks. They underwent standardized cognitive tests at baseline, immediately after completing the course of rTMS, and 4-weeks after the last rTMS treatment. All patients underwent concomitant functional MRI (fMRI) scans at the time of the tests while performing cognitive paradigms in the scanner.

Results: All patients completed the cognitive portions of the study. Three patients could not tolerate imaging and therefore did not complete the imaging portion of the study. There was improvement in verbal and non-verbal agility on testing that was seen 4-weeks post-treatment relative to baseline ($p < 0.05$). In two of the three patients where the TMS coil placement was guided by structural MRI in addition to localization relative to motor cortex, the word generation paradigm on the fMRI revealed increased activation of Broca's area.

Conclusions: These preliminary results suggest that rTMS may serve as an effective adjunctive treatment for aphasia found in AD patients. Further research using control stimulation is needed.

Disclosure: Dr. Devi has nothing to disclose. Dr. Levine has nothing to disclose. Dr. Voss has nothing to disclose. Dr. de Boisblanc has nothing to disclose. Dr. Heier has nothing to disclose. Dr. Halper has nothing to disclose.

Functional Imaging and neurocognitive correlates of targeted high frequency repetitive Transcranial Magnetic Stimulation in Patients with Alzheimer's disease

Gayatri Devi, M.D.^{1,2,3}, Henning Voss, Ph.D.^{4,5}, Linda Heier M.D.⁴, Sandy Lowe, M.D.^{1,3}, James Halper, M.D.^{1,3}, Dani Levine¹, Mike de Boisblanc¹
 New York Memory and Healthy Aging Services¹, New York University School of Medicine Department of Neurology² and Psychiatry³, Weill-Cornell Medical College Department of Radiology⁴ and Citigroup Biomedical Imaging Center⁵

Background

Repetitive transcranial magnetic stimulation (rTMS) is non-invasive technology used to stimulate or inhibit specific cortical areas. Recently, high frequency stimulation over the dorsolateral prefrontal cortex (DLPFC) in Alzheimer's Disease (AD) patients was found to improve language and cognitive paradigms for up to 8 weeks after cessation of treatment. [1-5].

Objectives

We wished to assess whether 1) bilateral rTMS over the DLPFC can ameliorate aphasia in AD patients; 2) increasing levels of stimulation was associated with greater efficacy of treatment and 3) whether changes in activation patterns in relevant cortical areas were observed using functional magnetic resonance imaging (fMRI) after stimulation.

Methods

All subjects were recruited from the New York Memory and Healthy Aging Services. Eligible subjects had a diagnosis of probable or possible Alzheimer's disease using criteria established by the National Institute of Neurological and Communicative Disorders and Stroke as well as the Alzheimer's Disease and Related Disorders Association.

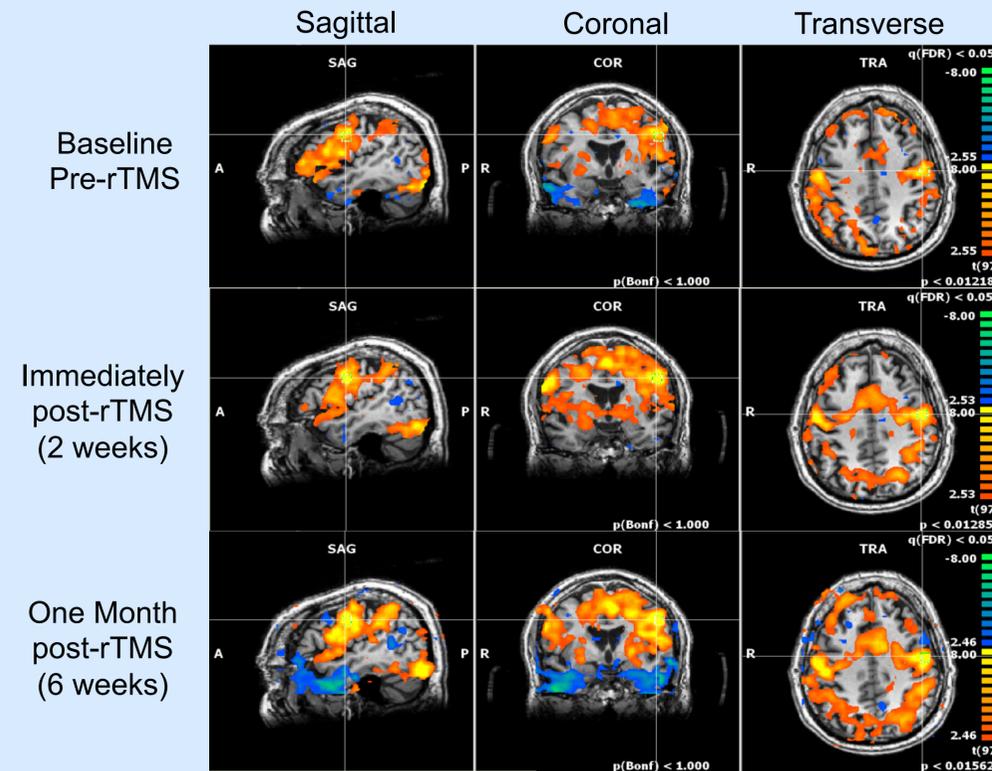
In addition, eligible patients had to have evidence of aphasia based on scores on the Boston Diagnostic Aphasia Examination (BDAE).

The stimulation site was localized using the 10-20 electroencephalography system, as halfway between areas F3 and F5 (on the left) and F4 and F6 (on the right) as corresponding to the DLPFC on either side. This was further verified as 6 cm anterior and 1 cm ventral to the point of motor stimulation of the first dorsal interosseous muscle.

The stimulation intensity was at 90% of the motor threshold. The Magstim Rapid-2 stimulator with a peak magnetic field of 0.5-3.5 Tesla at 100% output was used. Half of enrolled patients were to be stimulated at 10 Hz frequency for a total of 2000 pulses per session for 4 sessions over 2 weeks. The other half would be stimulated at 15 Hz for a total of 3000 pulses per session for 4 sessions over 2 weeks.

Subjects underwent standardized cognitive assessments at baseline, immediately post rTMS (end of week 2) and 4 weeks post rTMS cessation. These were the mini-mental state examination (MMSE), the Controlled Oral Word Association Test (COWAT) using C,F,L and selected sub-tests of the BDAE.

fMRI scans of Study Patient #10 during Word Generation Task



Results

14 patients consented and were enrolled. Two patients dropped out before their baseline visits. Of the remainder, all 12 completed and tolerated their rTMS stimulations and their cognitive assessments. 9 patients completed the fMRI portion of the study.

Cognitive assessment scores were evaluated using Student Paired t-tests in the SPSS statistical package comparing values at pre-rTMS, immediately post-rTMS, and 4 weeks after final stimulation.

There was improvement in verbal and non verbal agility that persisted for one month after stimulation. fMRI analysis indicated increased activation of DLPFC in some patients post rTMS, but no statistically significant change was observed overall. Additionally, stratifying by intensity of stimulation failed to yield observable differences, confounded by the low numbers in each group.

Conclusion

Limited (four sessions) bilateral rTMS stimulations over DLPFC resulted in sustained improvement in oral expression (verbal and non-verbal agility) in AD patients. The effect was observed immediately after cessation of stimulation as well as 4 weeks post treatment relative to baseline. Further research using a control, sham stimulation group would be helpful.

Cognitive Examination Scores (N=12)

Test	Baseline (pre-rTMS)	Immediately post-rTMS	4 weeks post-rTMS	P Value
MMSE	25.08	25.25	24.58	NS
COWAT(C,F,L)	53.42	56.58	57.17	NS
BDAE Naming	12.75	13.08	12.42	NS
BDAE Commands	14.25	14.00	14.00	NS
BDAE Complex Ideational	6.42	7.00	6.42	NS
BDAE Nonverbal Agility	8.33	9.50	10.17	P < 0.03
BDAE Verbal Agility	11.58	12.42	12.58	P < 0.02

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Contact Information

Gayatri Devi, MD

65 East 76th Street, New York, NY 10021

gd@nymemory.org

212-517-6881