

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.

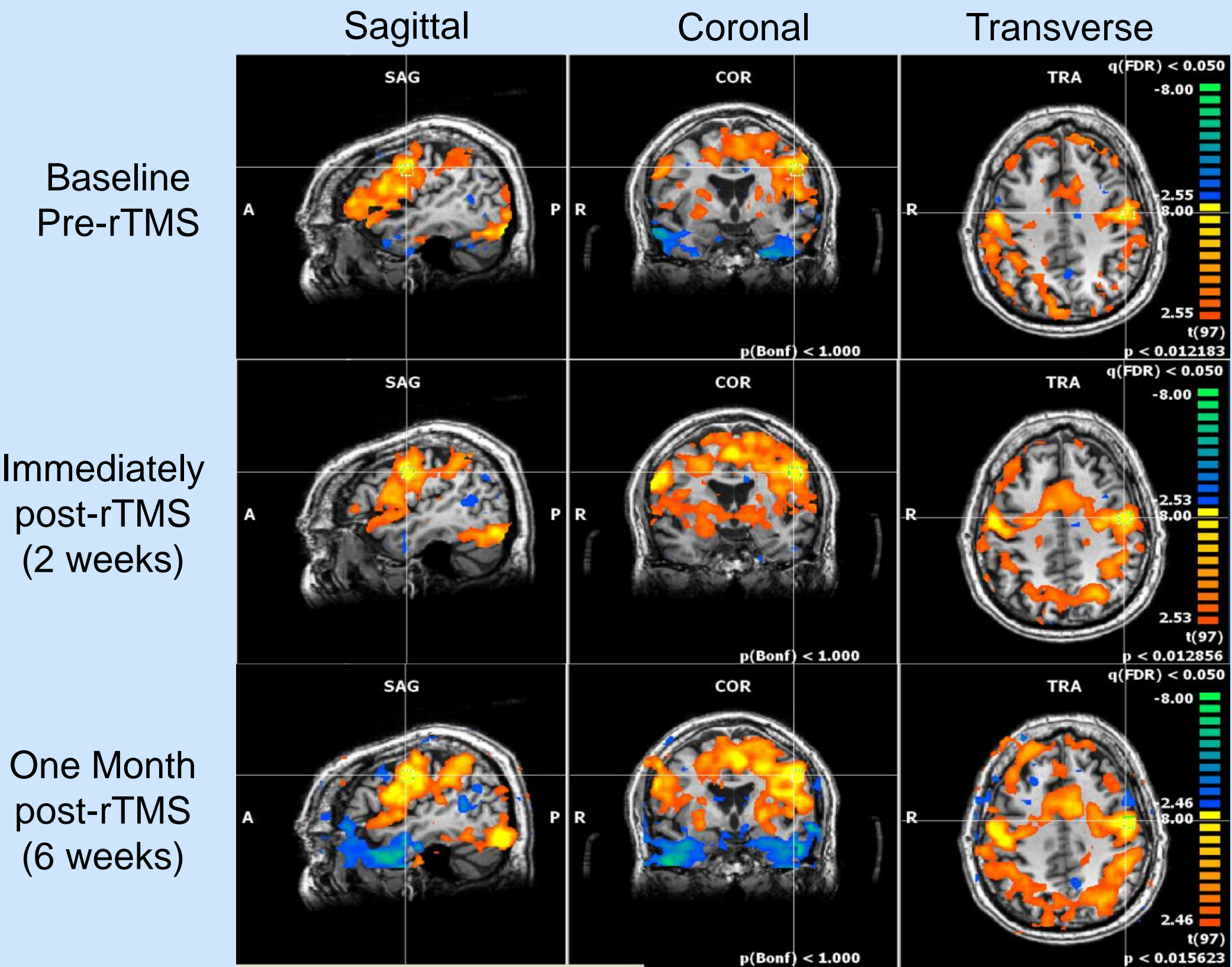
In addition, eligible patients had to have evidence of aphasia based on scores on the Boston Diagnostic Aphasia Examination (BDAE).

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.

References

1. Cotelli et al. Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease. Arch Neurol 2006; 63(11): 1602-4
2. Cotelli et al. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. Eur J Neurol 2008; 15(12): 1286-92
3. Bentwich et al. Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study. J Neural Transm 2011; 118(3): 463-71
4. Cotelli et al. Improved language performance in Alzheimer disease following brain stimulation. J Neurol Neurosurg Psychiatry 2011; 82(7): 794-7
5. Ahmed MA et al. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. J Neurol 2012; 259(1): 83-92

Contact Information

Gayatri Devi, MD
65 East 76th Street, New York, NY 10021
gd@nymemory.org
212-517-6881

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