



Letter to the Editor

Antidepressant Effect of Low-Frequency Right-Sided rTMS in Two Patients with Left Frontal Stroke



Dear Editor:

Repetitive transcranial magnetic stimulation (rTMS) administered at high frequency over left frontal cortex or low frequency over right frontal cortex [1], has been found effective for treating medication-resistant depression. High frequency left frontal rTMS has also been found effective for treating clinically-defined vascular depression [2] and depression following subcortical or right hemispheric stroke [2,3]. However, when the stroke involves left frontal cortex, the standard rTMS target and therapeutic mechanism may be compromised, with little data upon which to guide treatment or prognosis. We describe two patients with left frontal stroke who benefitted from low frequency rTMS over right frontal cortex.

“Mr. A” was an 84-year-old, right-handed man with a history of anxiety, left frontal stroke, and depression for the past six years refractory to fluoxetine, citalopram, escitalopram, venlafaxine, mirtazapine, and bupropion. His stroke occurred thirty-two years prior when he awoke with temporary speech problems. He reported full neurological recovery with no onset of depressive symptoms until 26 years post-stroke. Pre-TMS neurological exam showed a slight decrease in right arm swing but no speech or language deficits with intact strength and symmetric reflexes. A head CT obtained just prior to his TMS evaluation showed sequelae of a chronic left frontal stroke (Fig. 1A).

“Ms. B” was a 72-year old left-handed woman with a history of anorexia nervosa, left frontal stroke, breast cancer, and episodic depression since her late 30s. Her stroke occurred 8 months prior to presentation with acute onset of transient speech arrest and subsequent worsening of her long-standing depression. Brain MRI obtained one week after symptom onset showed subacute stroke of the left frontal cortex, with a smaller focus in right frontal cortex (Fig. 1B). Since this stroke she reported full neurological recovery, but worsening of her depression which was refractory to fluoxetine, citalopram, venlafaxine, duloxetine, mirtazapine, and nortriptyline. Pre-TMS neurological exam showed subtle weakness of her right face and arm, but normal speech, language, and reflexes.

In both patients, rTMS was administered using a MagStim Rapid2 Device (1600 pulses at 1 Hz, one session per day, five days a week, 30 sessions total) to the right frontal cortex (5.5 cm anterior to the motor hotspot for the first dorsal interosseous muscle of the left hand). This protocol was chosen for several reasons. First, high-frequency rTMS administered in close proximity to a prior stroke could increase the risk of induced seizure [4]. Second, stroke can

alter the current induced by rTMS [5] making safety and stimulation effects hard to predict. Finally, stroke near the stimulation site could undermine therapeutic efficacy by altering the local or remote network effects of rTMS [6,7].

Treatment response was measured using the 24-item Hamilton Psychiatric Rating Scale for Depression (HamD) and The Beck Depression Inventory-II (BDI). Standardized cut-offs for response (a 50% reduction in score on the BDI or Ham-D) and remission (a score ≤ 12 on the BDI or ≤ 11 on a 24-item HamD) were used [8].

Both patients met criteria for response and remission after 30 sessions of rTMS. In Mr. A, BDI improved from 19 to 8 and HAMD improved from 18 to 10. In Ms. B, BDI score improved from 31 to 1 and HamD improved from 23 to 6. In both patients rTMS was safe, well tolerated, with no complications or adverse side effects.

Although limited to two case reports, these data suggest that low-frequency rTMS over right frontal cortex may be effective in patients with medication-refractory depression and left frontal stroke. Whether the left frontal stroke contributed to depression in these cases is unknown. Our positive clinical results are consistent with data suggesting that low-frequency rTMS to right frontal cortex is effective in primary depression [1,2] and data suggesting that low frequency stimulation contralateral to the lesion can improve stroke symptoms such as hemiparesis [9], visual impairments [10], and neglect [11]. Low frequency stimulation has the added benefit of reducing seizure risk in a patient population at increased risk [5].

Acknowledgments

We would like to thank the TMS technicians at the Berenson-Allen Center for Noninvasive Brain Stimulation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Kevin A. Caulfield¹

Brain Stimulation Laboratory, Medical University of South Carolina, Charleston, SC, USA

Berenson-Allen Center for Non-Invasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Margo H. Bernstein¹

Berenson-Allen Center for Non-Invasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

¹ Denotes equivalent contributions.

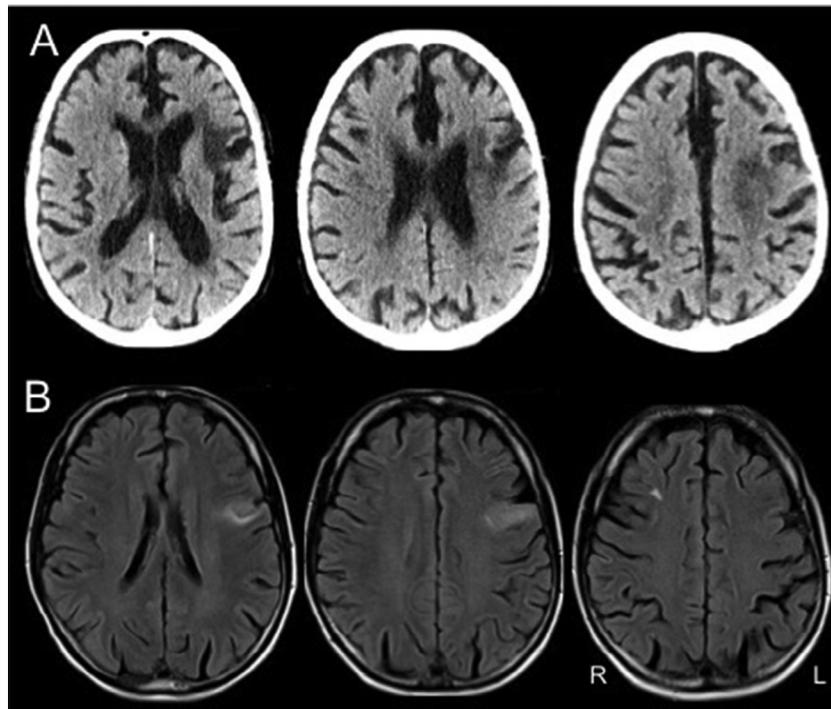


Figure 1. Brain imaging showing stroke locations. A) Head CT obtained 32 years post stroke in Mr. A shows hypodensity in the left frontal cortex consistent with chronic infarct. B) Brain MRI obtained 1-week post stroke in Ms. B shows FLAIR hyperintensity in the left frontal cortex (with a smaller secondary focus in right frontal cortex) consistent with subacute infarct. Images are radiographic with left (L) and right (R) sides as indicated.

Adam P. Stern, Alvaro Pascual-Leone, Daniel Z. Press
 Berenson-Allen Center for Non-Invasive Brain Stimulation,
 Department of Neurology, Beth Israel Deaconess Medical Center,
 Harvard Medical School, Boston, MA, USA

Division of Cognitive Neurology, Department of Neurology,
 Beth Israel Deaconess Medical Center, Harvard Medical School,
 Boston, MA, USA

Michael D. Fox*

Berenson-Allen Center for Non-Invasive Brain Stimulation,
 Department of Neurology, Beth Israel Deaconess Medical Center,
 Harvard Medical School, Boston, MA, USA

Division of Cognitive Neurology, Department of Neurology,
 Beth Israel Deaconess Medical Center, Harvard Medical School,
 Boston, MA, USA

Department of Neurology, Massachusetts General Hospital, Harvard
 Medical School, Boston, MA, USA

Athinoula A. Martinos Centre for Biomedical Imaging,
 Charlestown, MA, USA

* Corresponding author. Beth Israel Deaconess Medical Center,
 330 Brookline Ave, KS-158, Boston, MA 02215, USA
 E-mail address: foxmdphd@gmail.com (M.D. Fox)

Received 13 September 2016
 Available online 6 October 2016

<http://dx.doi.org/10.1016/j.brs.2016.10.002>

References

- [1] Chen J, Zhou C, Wu B, Wang Y, Li Q, Wei Y, et al. Left versus right repetitive transcranial magnetic stimulation in treating major depression: a meta-analysis of randomised controlled trials. *Psychiatry Res* 2013;210:1260–4. doi:10.1016/j.psychres.2013.09.007.
- [2] Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry* 2008;65:268–76. doi:10.1001/archgenpsychiatry.2007.45.
- [3] Jorge RE, Robinson RG, Tateno A, Narushima K, Acion L, Moser D, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biol Psychiatry* 2004;55:398–405. doi:10.1016/j.biopsych.2003.08.017.
- [4] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, The Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39. doi:10.1016/j.clinph.2009.08.016.
- [5] Wagner T, Fregni F, Eden U, Ramos-Estebanez C, Grodzinsky A, Zahn M, et al. Transcranial magnetic stimulation and stroke: a computer-based human model study. *Neuroimage* 2006;30:857–70. doi:10.1016/j.neuroimage.2005.04.046.
- [6] Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry* 2012;72:595–603. doi:10.1016/j.biopsych.2012.04.028.
- [7] Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry* 2014;76:517–26. doi:10.1016/j.biopsych.2014.01.023.
- [8] Riedel M, Moller HJ, Obermeier M, Schennach-Wolff R, Bauer M, Adli M, et al. Response and remission criteria in major depression – a validation of current practice. *J Psychiatr Res* 2010;55:1063–8. doi:10.1016/j.jpsychires.2010.03.006.
- [9] Tretriluxana J, Kantak S, Tretriluxana S, Wu AD, Fisher BE. Low frequency repetitive transcranial magnetic stimulation to the non-lesioned hemisphere improves paretic arm reach-to-grasp performance after chronic stroke. *Disabil Rehabil Assist Technol* 2012;8:121–4. doi:10.3109/17483107.2012.737136.
- [10] Agosta S, Herpich F, Miceli G, Ferraro F, Battelli L. Contralesional rTMS relieves visual extinction in chronic stroke. *Neuropsychologia* 2014;62:269–76. doi:10.1016/j.neuropsychologia.2014.07.026.
- [11] Jacquin-Courtois S. Hemispatial neglect rehabilitation using non-invasive brain stimulation: or how to modulate the disconnection syndrome? *Ann Phys Rehabil Med* 2015;58:251–8. doi:10.1016/j.rehab.2015.07.388.