Excitability out of balance

Treating hemineglect with transcranial magnetic brain stimulation

Heidi M. Schambra, MD
Randolph S. Marshall, MD, MS

Correspondence & reprint requests to Dr. Marshall: rsm2@columbia.edu

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Rehabilitation of hemineglect is vexingly inadequate. Beyond its direct detrimental effect on visual-spatial function, hemineglect interferes with rehabilitation of cognitive and motor function.[1] Interventions targeting this condition include relearning appropriate visuospatial scanning behaviors through practice and cuing, engaging the attentional system with exogenous sensory stimulation, and changing excitability at the level of the brain.[2] This last approach is based on Kinsbourne's[3] theory of hemispheric rivalry, which posits that contralateral attention is subserved by each hemisphere, and mutual transcallosal inhibition checks overactivity in the opposite hemisphere to keep attention evenly distributed. Unilateral stroke is thought to disrupt this balance by reducing inhibition from the lesioned hemisphere to the contralesional hemisphere, resulting in greater overactivity in the contralesional hemisphere which in turn increases inhibition to the lesioned hemisphere; the end result is an asymmetric attentional field manifested as hemineglect. Changing cortical excitability by noninvasive brain stimulation is an emerging approach that aims to restore the functional balance, by either increasing activity in the lesioned hemisphere or suppressing overactivity in the contralesional hemisphere. Repetitive transcranial magnetic stimulation (rTMS) has been recognized as a safe, effective means of transiently altering brain excitability and changing behavior after stroke.[4] Continuous theta-burst stimulation (cTBS) is a type of rTMS that efficiently decreases excitability in the stimulated cortex for up to an hour.[5]

In this issue of *Neurology*®, Koch et al.[6] use this method for rehabilitation of hemispatial neglect. The study builds on their prior work probing the physiologic circuit of the left posterior parietal cortex (PPC) acting on the ipsilateral primary motor cortex (M1).[7] In right hemisphere stroke, the left PPC-M1 circuit is pathologically overexcited in patients with neglect compared to those without, and the magnitude of overexcitability correlates with neglect severity.[8] Others found that a single session of cTBS given to the left PPC reduces parieto-frontal excitability and improves right-sided neglect for up to 32 hours.[9] Here, Koch et al. employ a similar strategy in subacute stroke patients with right hemisphere damage and neglect, but expand the intervention to daily sessions over 2 weeks. The authors evaluated the behavioral and physiologic effects of real vs sham cTBS paired with conventional neglect rehabilitation. Relative to controls, stimulated patients showed improvements in overall Behavioral Inattention Test scores at the end of the intervention, which were sustained 2 weeks later at retest. Single-pulse TMS probes also demonstrated that abnormal overexcitability in the left PPC-M1 circuit had normalized in the cTBS group after treatment. These changes persisted out to 2 weeks after the completion of treatment, suggesting that neuroplasticity may have taken place at the cellular level.

Limitations of the current investigation are reflected by its status as a Class III study. The sample size was small, interventions were initiated at different time points after stroke, there were inconsistent effects across individual behavioral subtests, and there was a modest overall effect size that may not be clinically meaningful at the level of disability. It is also is unclear to what degree these behavioral and neurophysiologic effects are attributable to cTBS alone vs the combined effects of stimulation and rehabilitation therapy. In neuromodulation research, it is generally believed that noninvasive brain stimulation alone is insufficient to induce behaviorally meaningful neuroplasticity, but rather that it primes a system to better engage adjunctive therapies. The authors do not report how much time elapsed between brain stimulation and conventional neglect therapy for each patient. Furthermore, only the duration of conventional therapy was reported; it unclear how it varied qualitatively or quantitatively between groups, and whether there were group differences between when therapy was given in the afternoon.

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From the Burke Rehabilitation Hospital (H.M.S.), White Plains; Weill Cornell Medical College (H.M.S.), New York; and Columbia University Medical Center (R.S.M.), New York, NY.

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Nonetheless, this study represents an important step forward in the effort to rehabilitate neglect, and presents us with some general principles that help to advance an emerging approach in neurorehabilitation. Critical to the success of neurorehabilitation will be studies, such as this one, that systematically pursue the parameters that maximize an intervention's efficacy. Here the investigators successfully expanded a single-session approach to 2 weeks. It remains to be determined whether efficacy can be further enhanced by pushing the stimulation dose higher (e.g., adding more days, more sessions per day, or more stimuli per session) or by shortening the interval between stimulation and behavioral intervention. There is emerging evidence that intervention beginning in the first week after stroke may improve therapeutic efficacy by taking advantage of an enhanced window of plasticity.[10] Prior to the adoption of neuromodulation into standard clinical practice, larger studies are needed that standardize the timing post stroke, evaluate the optimal parameters for stimulation, and control for the timing and amount of conventional rehabilitation given with cTBS. In addition, outcome measures of disability and quality of life are needed to establish clinical importance. The authors are to be commended for executing a double-blind, randomized, placebo-controlled study in subacute stroke patients, while providing TMS evidence to suggest a physiologic mechanism for behavioral effects. Though difficult, such studies are imperative for advancing the field of neurorehabilitation and for translating neuromodulation to clinical practice.

AUTHOR CONTRIBUTIONS

Dr. Schambra: drafting/revising the manuscript, analysis or interpretation of data. Dr. Marshall: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

DISCLOSURE

Dr. Schambra received a NINDS Intramural Competitive Postdoctoral Research Fellowship. Dr. Marshall has a patent pending re: Novel use of a drug for post-stroke dystonia; receives publishing royalties for *OnCall Neurology* (Elsevier, 2003–present); has received speaker honoraria from Ferrer International; and receives research support from the NIH/NINDS.

REFERENCES

1. Cherney LR, Halper AS, Kwasnica CM, Harvey RL, Zhang M. Recovery of functional status after right hemisphere stroke: relationship with unilateral neglect. Arch Phys Med Rehabil 2001;82:322–328.
2. Marshall RS. Rehabilitation approaches to hemineglect. Neurologist 2009;15:185–192.
3. Kinsbourne M. Hemi-neglect and hemisphere rivalry. Adv Neurol 1977;18:41–49.
4. Khedr EM, Abdel-Fadeil MR, Farghali A, Qaid M. Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol 2009;16:1323–1330.
5. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–206.
6. Koch G, Bonnì S, Giacobbe V, et al. Theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. Neurology 2012;78:24–30.
7. Koch G, Fernandez Del Olmo M, Cheeran B, et al. Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 2007;27:6815–6822.
8. Koch G, Oliveri M, Cheeran B, et al. Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain 2008;131:3147–3155.
9. Nyffeler T, Cazzoli D, Hess CW, Muri RM. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 2009;40:2791–2796.
10. Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature 2010;468:305–309.

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