Neurorehabilitation potential of repetitive transcranial magnetic stimulation in post-stroke motor and speech recovery

Henry Liu

ABSTRACT

Ischemic stroke is a consequence of diminished cerebral blood flow to cortical regions, resulting in subsequent reductions in excitability. The brain undergoes immense cortical remapping following a stroke, which can be facilitated by neuronal excitability. However, analyses of electrophysiologic recordings, cortical stimulation, and fMRI reveal a decline in the excitability of the ipsilesional hemisphere following an ischemic stroke and an increase in interhemispheric inhibition by the contralesional hemisphere. Recent findings have implicated non-invasive stimulation with post-stroke recovery through the induction of synaptic plasticity and recruitment of neurotrophic factors to the peri-infarct region. The aim of this paper is to review recent research that has been devoted to repetitive transcranial magnetic stimulation (rTMS) and its use as a therapeutic tool in motor and speech rehabilitation via the alteration of excitability in the brain post-ischemic stroke.

INTRODUCTION

Each year approximately 15 million people suffer from stroke, constituting the third leading cause of mortality in Canada as well as a major cause of prolonged neurological disabilities.^{1,2} In spite of improvement in treatment strategies during the therapeutic window, including reperfusion therapies and thrombectomy,³ recovery following stroke has not changed much the past decade.⁴ Of those who undergo this debilitating experience, two-thirds require intensive rehabilitation designed to assist survivors relearn lost motor function.⁵ Impairments can include movement paralysis, sensory disruptions, and cognitive deficits ranging from memory and speech impairments to significant emotional disturbances.⁵ Despite some patients reporting spontaneous recovery within the first 3 months following intensive rehabilitation, less than 40% of patients are able to fully recover.⁶

NEUROPLASTICITY POST-STROKE AND REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS)

Immediately post-stroke, a loss of physiological brain function occurs around the peri-infarct cortex. Remapping of functions within the peri-infarct regions promotes recovery of these neurons situated in the lesional and peri-infarct region of the affected hemisphere (AH).⁶ Analysis of electrophysiologic recordings, cortical stimulation, and fMRI reveal a decline in the excitability of the AH following an ischemic stroke.⁷ Such phenomenon is attributed to the damage of the excitatory glutamate receptor expression from neurons in the lesional cortex.⁵

Another factor hindering recovery is increased interhemispheric inhibition.⁸ In a normal brain, there is constant inhibition mediated

by the inhibitory neurotransmitter GABA.⁹ An equilibrium is achieved between both hemispheres because they each inhibit the excitation of the other to maximize cortical output.⁹ During a stroke, however, the lesional side can no longer exert the same inhibitory signals.¹⁰ Thus, transcallosal or interhemispheric inhibition from the AH to the unaffected hemisphere (UH) is reduced, rendering the UH disinhibited. The UH in turn creates additional inhibition over the affected hemisphere, significantly disrupting the equilibrium of interhemispheric inhibition.¹⁰ The interhemispheric competition hypothesis suggests that a balance in excitability directly correlates to the overall functioning of the respective primary motor cortex (M1).⁵

rTMS offers a revolutionary approach to stroke recovery through direct non-invasive stimulation of the cortex.¹¹ Presently, it involves administering frequency- and intensity-controlled magnetic pulses of changing electric current over the scalp of conscious human subjects to alter the neurochemistry of the brain and affect the neuronal firing patterns. It has been utilized for treatment of several neuropsychiatric disorders, including depression, bipolar disorder, obsessive compulsive disorders, and schizophrenia.¹² In the mid-1990s, technological advances allowed the delivery of rhythmic trains of magnetic pulses in a rapid sequence up to a 100 Hz repetition rate, which is referred to as rTMS.¹¹ In animal models, rTMS has been shown to increase the expressions of brain-derived neurotrophic factors as well as pre- and post-synaptic proteins (including NR2B and SYP), thereby enhancing synaptic plasticity.¹³

RTMS IN MOTOR REHABILITATION

Experimental consensus indicates that the application of high frequency rTMS, that is 5 Hz or greater, induces increased excitability by inducing brain-derived neurotrophic factors, which are involved in neuronal survival and synaptic plasticity.¹⁴ In an early study of 15 patients with chronic hemiparetic stroke, high frequency 10 Hz rTMS stimulation of the M1 of the AH was found to increase the motor-evoked potential amplitude in the treatment group and also cause an associated improvement in post-treatment hand movement accuracy.¹⁵

Low frequency rTMS of 1 Hz or less decreases cortical excitability.¹⁶ The decreased excitability in the UH will in turn reduce interhemispheric inhibition on the lesional side. The application of low frequency rTMS on the UH was first employed in a study by Takeuchi et al.¹⁰ Twenty patients with subcortical infarctions were recruited and were administered rTMS treatment or sham rTMS. The study confirmed that 1 Hz stimulation reduced the excitability of M1. Moreover, rTMS over the UH M1 reduced

the amount of interhemispheric inhibition exerted onto the AH by the UH and was associated with the improvement of movement in the affected hand.

Combination therapy has also been documented by Emara et al who directly compared the effect of high frequency stimulation on the AH and low frequency stimulation over the UH in 60 patients recruited with ischaemic stroke with hemiparesis.¹⁷ Results from finger tapping test and activity index scores showed a significant improvement from both treatment groups (5 Hz ipsi-lesional rTMS group and 1 Hz contra-lesional rTMS group) after 2 weeks and sustained recovery over the 12-week period compared to the control.

Despite encouraging results from preliminary studies, there is conflicting evidence for the benefits of rTMS therapy in post-stroke recovery in subsequent heterogenous meta-analyses compared to the individual trials. A review of 19 randomized controlled trials of post-stroke rTMS, excluding studies that only involved electrophysiological parameters, did not reveal any improvement in motor function.¹⁸ In contrast, a meta-analysis by Hsu et al of 18 studies demonstrated an improvement in motor function for patients with subcortical infarcts using low frequency stimulation over the UH.¹⁹

RTMS IN APHASIA

Apart from recovery in limb function, prior literature suggests that rTMS may also be effective in patients with predominantly motor aphasia.²⁰ Recovery of language post-stroke is dictated by 1) the recruitment of the lesional and perilesional left hemisphere responsible for language, 2) ability to acquire language skills by the right hemisphere, and 3) interhemispheric inhibition from the non-dominant hemisphere that may interfere with language recovery.²⁰ One study applied excitatory rTMS to the left peri-stroke areas of the participants and demonstrated significant improvement in semantic fluency.²¹ This study further corroborates the involvement of the ipsilateral perilesional area and the modulatory effect of excitatory rTMS in facilitating short and long-term cortical excitability in aphasia recovery.

Indeed, patients with motor aphasia also exhibit hyperexcitability in the Broca homologue area in the right hemisphere. One study examined the use of rTMS in the right anterior Broca area (pars triangularis) for 10 minutes at an inhibitory frequency of 1 Hz and observed a transient enhancement in naming ability and reaction time in a picture naming task.²² In a larger study which involved 20 minute sessions of 1 Hz pulses delivered over the homologous language sites for 10 days, the improvement in naming performance and other aspects of expressive language and auditory comprehension was sustained longitudinally at 2 months post-stimulation. These studies further supported the theory of rTMS modulating transcallosal disinhibition and reintegration of the left hemisphere in post-stroke aphasia.²³

AVENUES FOR FUTURE RESEARCH

Given the effectiveness of rTMS in downregulating the excitability of the UH in driving cortical changes, potential studies

can explore more potent stimulation protocols. For instance, it may be more effective to prime the brain, a process that serves to enhance the physiological effects of low-frequency stimulation, before actual application of inhibitory stimulation. A pilot study by Kakuda et al employed a priming phase with a 6 Hz intermittent rTMS in 5-second trains on patients with post-stroke non-fluent aphasia.²⁴ This first phase was ensued by the regular 1 Hz continuous inhibitory rTMS to the most active regions on MRI scans. The authors noted that this added priming protocol resulted in an overall improvement in language function and is a safe and feasible method with immense neurorehabilitative value.

Future research may also employ structural and functional neuroimaging in order to better elucidate the mechanism of recovery following rTMS. It would be important to evaluate the degree and location of cerebral plasticity that occurs post-intervention. Lastly, pharmacological agents such as levodopa, fluvoxamine and amantadine also function in improving the plasticity of cortical neurons via their interactions with the dopaminergic pathway.^{25,26} As such, it is possible to administer these drugs alongside rTMS treatments to examine whether additive or multiplicative improvements in recovery may be observed. Ultimately, the most effective and appropriate combinational strategy remains to be explored in order to maximize the gains of the recovery process of patients afflicted with post-stroke deficits.

CONCLUSION

Although the application of rTMS in post-stroke rehabilitation is still in its preliminary stage, it remains a potentially valuable tool in modulating neuroplasticity. Particularly, high frequency stimulation has been shown to increase excitability of the lesioned cortex and low frequency stimulation over the UH have been shown to decrease cortical excitability and dampen the effect of interhemispheric inhibition of UH. Further multi-centered trials are still required before the application of rTMS in a broader clinical context.

REFERENCES

1. Kuklina EV, Tong X, George MG, et al. Epidemiology and prevention of stroke: a worldwide perspective. Expert review of neurotherapeutics. 2012 Feb;12(2):199-208. <https://doi.org/10.1586/ern.11.99>
2. Krueger H, Koot J, Hall RE, et al. Prevalence of individuals experiencing the effects of stroke in Canada: trends and projections. Stroke. 2015 Aug;46(8):2226-31. <https://doi.org/10.1161/STROKEAHA.115.009616>
3. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359(13):1317-29. <https://doi.org/10.1056/NEJMoa0804656>
4. Stineman MG, Maislin G, Fiedler RC. A prediction model for functional recovery in stroke. Stroke. 1997 Mar;28(3):550-6.
5. Carmichael ST. Brain excitability in stroke: the yin and yang of stroke progression. Arch Neurol. 2012 Feb;69(2):161-7. <https://doi.org/10.1001/archneurol.2011.1175>

6. Dimyan MA, Cohen LG. Neuroplasticity in the context of motor rehabilitation after stroke. *Nat Rev Neurol*. 2011 Feb;7(2):76. <https://doi.org/10.1038/nrneurol.2010.200>
7. Mäkelä JP, Lioumis P, Laaksonen K, et al. Cortical excitability measured with nTMS and MEG during stroke recovery. *Neural Plast*. 2015 Sep;2015. <https://doi.org/10.1155/2015/309546>
8. Murase N, Duque J, Mazzocchio R, et al. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*. 2004 Mar;55(3):400-9. <https://doi.org/10.1002/ana.10848>
9. Nair DG, Hutchinson S, Fregni F, et al. Imaging correlates of motor recovery from cerebral infarction and their physiological significance in well recovered patients. *Neuroimage*. 2007 Jan;34(1):253–63. <https://doi.org/10.1016/j.neuroimage.2006.09.010>
10. Takeuchi N, Chuma T, Matsuo Y et al. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke*. 2005 Dec;36(12):2681-6. <https://doi.org/10.1161/01.STR.0000189658.51972.34>
11. Lefaucheur JP, André-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014 Nov;125(11):2150-206. <https://doi.org/10.1016/j.clinph.2014.05.021>
12. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*. 2002 Mar;5(1):73-103. <https://doi.org/10.1017/S1461145702002791>
13. Shang Y, Wang X, Shang X, et al. Repetitive transcranial magnetic stimulation effectively facilitates spatial cognition and synaptic plasticity associated with increasing the levels of BDNF and synaptic proteins in Wistar rats. *Neurobiol of Learn Mem*. 2016;134:369-78. <https://doi.org/10.1016/j.nlm.2016.08.016>
14. Maeda F, Pascual-Leone, A. Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders. *Psychopharmacology*. 2003 Aug;168(4):359-76. <https://doi.org/10.1007/s00213-002-1216-x>
15. Kim YH, You SH, Ko MH, et al. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke*. 2006 Jun;37(6):1471-6. <https://doi.org/10.1161/01.STR.0000221233.55497.51>
16. Nakayama H, Jorgensen H, Raaschou H, et al. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil*. 1994 Apr;75(4):394-8.
17. Emara TH, Moustafa RR, Elnahas NM, et al. Repetitive transcranial magnetic stimulation at 1Hz and 5Hz produces sustained improvement in motor function and disability after ischaemic stroke. *Eur J Neurol*. 2010 Sep;17(9):1203-9. <https://doi.org/10.1111/j.1468-1331.2010.03000.x>
18. Hao Z, Wang D, Zeng Y, et al. Repetitive transcranial magnetic stimulation for improving function after stroke. *Sao Paulo Med J*. 2013 May;131(6):440-440. <https://doi.org/10.1002/14651858.CD008862.pub2>
19. Hsu WY, Cheng CH, Liao KK, et al. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. *Stroke*. 2012 Jul;43(7):1849-57. <https://doi.org/10.1161/STROKEAHA.111.649756>
20. Kubis N. Non-invasive brain stimulation to enhance post-stroke recovery. *Front Neural Circuits*. 2016 Jul;10:56. <https://doi.org/10.3389/fncir.2016.00056>
21. Szaflarski JP, Vannest J, Wu SW, et al. Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. *Med Sci Monit*. 2011 Feb;17(3):CR132-9. <https://doi.org/10.12659/MSM.881446>
22. Naeser MA, Martin PI, Theoret H, et al. TMS suppression of right pars triangularis, but not pars opercularis, improves naming in aphasia. *Brain Lang*. 2011 Dec;119(3):206-13. <https://doi.org/10.1016/j.bandl.2011.07.005>
23. Barwood CH, Murdoch BE, Whelan BM, et al. Improved language performance subsequent to low frequency rTMS in patients with chronic non fluent aphasia post stroke. *Eur J Neurol*. 2011 Jul;18(7):935-43. <https://doi.org/10.1111/j.1468-1331.2010.03284.x>
24. Kakuda W, Abo M, Momosaki R, et al. Therapeutic application of 6-Hz-primed low-frequency rTMS combined with intensive speech therapy for post-stroke aphasia. *Brain Inj*. 2011 Sep;25(12):1242-8. <https://doi.org/10.3109/02699052.2011.608212>
25. Bakheit AM. Drug treatment of poststroke aphasia. *Expert Rev Neurother*. 2004 Mar;4(2):211-7. <https://doi.org/10.1586/147371754.2.211>
26. de Boissezon X, Peran P, de Boysson C, et al. Pharmacotherapy of aphasia: myth or reality?. *Brain Lang*. 2007 Jul;102(1):114-25. <https://doi.org/10.1016/j.bandl.2006.07.004>