NEURAL REGENERATION RESEARCH
Volume 7, Issue 8, March 2012
www.nrronline.org

Cite this article as: Neural Regen Res. 2012;7(8):627-634.

Clinical application of repetitive transcranial magnetic stimulation in stroke rehabilitation☆

Joonho Shin, EunJoo Yang, KyeHee Cho, Carmelo L Barcenas, Woo Jin Kim, Yusun Min, Nam-Jong Paik

Department of Rehabilitation Medicine, Bundang Hospital, College of Medicine, Seoul National University, Seongnam 463-707, Republic of Korea

Abstract
Proper stimulation to affected cerebral hemisphere would promote the functional recovery of patients with stroke. Effects of repetitive transcranial magnetic stimulation on cortical excitability can be can be altered by the stimulation frequency, intensity and duration. There has been no consistent recognition regarding the best stimulation frequency and intensity. This study reviews the intervention effects of repetitive transcranial stimulation on motor impairment, dysphagia, visuospatial neglect and aphasia, and summarizes the stimulation frequency, intensity and area for repetitive transcranial magnetic stimulation to yield the best therapeutic effects.
Key Words: stroke; repetitive transcranial magnetic stimulation; rehabilitation; review
Abbreviations: rTMS, repetitive transcranial magnetic stimulation; TBS, theta burst stimulation; fMRI, functional magnetic resonance imaging

Joonho Shin☆, M.D., Department of Rehabilitation Medicine, Bundang Hospital, College of Medicine, Seoul National University, Seongnam 463-707, Republic of Korea

Corresponding author: Nam-Jong Paik, M.D., Ph.D., Department of Rehabilitation Medicine, Bundang Hospital, College of Medicine, Seoul National University, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do, 463-707, Republic of Korea
njpaik@snu.ac.kr

Received: 2011-11-05
Accepted: 2012-02-03
(NY20111011004/H)

Shin J, Yang EJ, Cho KH, Barcenas CL, Kim WJ, Min Y, Paik NJ. Clinical application of repetitive transcranial magnetic stimulation in stroke rehabilitation. Neural Regen Res. 2012;7(8):627-634.

www.crter.cn
www.nrronline.org

doi:10.3969/j.issn.1673-5374.2012.08.011

INTRODUCTION

Many interventions, such as pharmacological treatments, physical and behavioral therapies have been largely applied to improve diverse post-stroke neurologic deficits, including visuospatial neglect, aphasia, dysphagia and motor impairment, using brain plasticity[1]. Occurrence of cortical reorganization after stroke[2] has been reported in previous studies and suggested that increased cortical activity in the affected cerebral hemispheres would promote recovery from stroke[3].

Repetitive transcranial magnetic stimulation (rTMS) has gained growing importance in the field of stroke rehabilitation. Based on the ability to modulate excitability, the useful therapeutic effect of TMS has been proposed by many studies as a potential treatment for various disorders of stroke[4], such as motor performance[5-8], dysphagia[9] and neglect[10]. Although the concepts of interhemispheric inhibition and change in synaptic plasticity are considered possible mechanisms, no complete interpretation of rTMS has been formulated[11-12].

Effects of rTMS on cortical excitability can be altered by the stimulation frequency, intensity and duration[13]. However, a recent review concluded that the evidence remains insufficient regarding the optimum frequency or 'dose' of rTMS[14]. In this article, the effects of rTMS on various dysfunctions post-stroke in adult patients are reviewed.

EFFECTS OF RTMS ON MOTOR IMPAIRMENT POST-STROKE

(Table 1)

Natural recovery is no longer expected in many chronic stroke patients. Sustained improvement for up to 3 months was observed in one study[15]. rTMS exhibits much stronger and longer lasting effects in patients with acute stroke. Khedr *et al* [16] demonstrated that the yield of 1 Hz rTMS was 48.3% larger than sham stimulation, in terms of Barthel index in acute stroke, and the sustained effects lasted for over 1 year beyond the stimulation[6].

The results were consistent regardless of injury site, showing improvement in not only cortical, but subcortical stroke and pontine hemorrhagic patients, due to the control of corticospinal excitability, although no direct stimulation to deep structure prevailed[7, 17]. However, some studies showed a gap between the functional results and corticospinal excitability[5, 18], and the results of rTMS in stroke patients did not seem to be related to the regional blood flow.

The mechanism underlying the motor recovery after rTMS application needs further investigation. Various frequencies between 1 to 20 Hz had been tried. Typically, low-frequency rTMS reduces excitability while high-frequency rTMS exerts facilitatory effects.

Table 1 rTMS on motor impairment

Source	Design	Size	Lesion site	Time after stroke	Frequency, intensity, pulse number and duration	Stimulated area	Outcome measures	Results
Khedr *et al*, 2005[5]	RCT	26 real, 26 sham*	MCA territory (24 RH, 28 LH)	Real: 7.1±1.4 days, sham: 7.3±1.5 days	3 Hz, 120% RMT, 3 000 pulses, 10 sessions	AH	Scandinavian stroke scale, NIHSS, Barthel index	Improvement of motor function
Khedr *et al*, 2010[6]	RCT	16 real 3 Hz, 16 real 10Hz, 16 sham	MCA (21 RH, 27 LH)	3 Hz: 8.0±5.1 days 10 Hz: 6.0±2.8 days sham: 6.2±1.5 days	3 Hz, 130% RMT, 750 pulses, 5 sessions 10 Hz, 100% RMT, 750 pulses, 5 sessions	AH	Muscle strength, NIHSS, mRS	Improvement of motor function over 1 year
Fregni *et al*, 2006[7]	RCT	10 real, 5 sham	Various lesions (3 RH, 12 LH)	Real: 3.5±2.9 years, sham: 4.0±2.6 years	1 Hz, 100% MT, 1 200 pulses, 5 sessions	UH	Jebsen-taylor hand function test, simple reaction time, choice reaction time, Purdue pegboard, MMSE, digit span, Stroop test	Improvement of motor function only in the affected hand over 2 weeks
Takeuchi *et al*, 2005[8]	RCT	10 real, 10 sham	Subcortex (12 RH, 8 LH)	28.7±16.7 months	1 Hz, 90% RMT, 1 500 pulses, 1 session	UH	Pinch force, acceleration	Improvement of motor function
Emara *et al*, 2010[15]	RCT	20 real 1 Hz, 20 real 5 Hz 20 sham	29 RH, 31 LH	1 Hz: 6.5 months, 5 Hz: 2.5 months, sham: 3.5 months	1 Hz, 110–120% MT, 1 500 pulses, 10 sessions, 5 Hz, 80–90% MT, 7 500 pulses, 10 sessions	1 Hz: UH, 5 Hz : AH	Thumb-index finger tapping test, activity index, mRS	Improvement of motor function over 12 weeks in 1 Hz and 5 Hz rTMS
Khedr *et al*, 2009[16]	RCT	12 real 1 Hz 12 real 3 Hz 12 sham	MCA (23 RH, 13 LH)	1 Hz: 16.3±3.6 days 3 Hz: 17.2±3.6 days sham: 17.7±3.8 days	1 Hz, 130% RMT, 900 pulses, 5 sessions, 3 Hz, 130% RMT, 900 pulses, 5 sessions	1 Hz: UH 3 Hz: AH	Grip strength, keyboard tapping, pegboard task, NIHSS, Barthel index	Improvement of motor function over 3 months (1 Hz rTMS was better than 3 Hz rTMS)
Liepert *et al*, 2007[17]	RCT	12	10 subcortex, 2 pons	7.3±4.5 days	1 Hz, 90% RMT, 1 200 pulses, 2 sessions (crossover: real and sham)	UH	Grip strength, nine hole peg test	Improvement of dexterity of only affected hand
Pomeroy *et al*, 2007[18]	RCT	6 real with VMC, 5 real without VMC, 9 sham with VMC, 7 sham without VMC	MCA (13 RH, 14 LH)	Real with VMC: 25.2 ± 9.3 days, real without VMC: 32.4±29.8 days; sham with VMC: 24.1±15.0 days, sham without VMC: 26.9±13.6 days	1 Hz, 120% MT, 200 pulses, 8 sessions	AH	Peak torque of the elbow joint, action research arm test	No difference between each group
Takeuchi *et al*, 2009[19]	RCT	10 AH, 10 UH, 10 bilateral	Subcortex (12 RH, 18 LH)	AH: 35.6±38.7 months, UH: 24.7±28.9 months, bilateral: 26.1±28.0 months	AH: 10 Hz, 90% RMT, 1 000 pulses, 1 session; UH: 1 Hz, 90% RMT, 1 000 pulses, 1 session; bilateral: alternating	AH, UH, Bilateral	Pinch force, acceleration	AH: no effect, UH, bilateral: improvement of acceleration, bilateral > UH
Malcolm *et al*, 2007[20]	RCT	9 real, 10 sham	10 RH, 10 LH	Real: 3.9±3.1 years, sham: 3.8±3.7 years	20 Hz, 90% MT, 2 000 pulses, 10 sessions	AH (homologue to the hand area of the UH)	Wolf motor function test, motor activity log, box and block test	No improvement of motor function
Ackerley *et al*, 2010[21]	RCT	10 patients	Subcortex (4 RH, 6 LH)	28.0±25.0 months	Continuous TBS: 90% AMT, 600 pulses, 1 session; intermittent TBS: 90% AMT, 600 pulses, 1 session; sham TBS (crossover)	Continuous TBS: UH, intermittent TBS: AH	Grip-lift kinetics, action research arm test	Improvement of grip-lift kinetics with real TBS, decrement of action research arm test with continuous TBS
Talelli *et al*, 2007[23]	RCT	6 patients	MCA (1 RH, 5 LH)	31.0±37.9 months	Continuous TBS: 5 Hz, burst of 3 pulses at 50 Hz, 80% AMT, 300 pulses, 1 session; intermittent TBS: 5 Hz, 20 bursts of 10 pulses at 50 Hz, every 8 seconds, 80% AMT, 600 pulses, 1 session; sham TBS	Continuous TBS:UH, intermittent TBS: AH	Simple reaction time and grip strength, choice reaction time, fatigue, attention	Improvement of simple reaction time only by intermittent TBS over 20 minutes

rTMS: Repetitive transcranial magnetic stimulation; RCT: randomized controlled trial; AH: affected hemisphere; UH: unaffected hemisphere; RH: right hemisphere; LH: left hemisphere; MCA: middle cerebral artery; TBS: theta burst stimulation; MT: motor threshold; RMT: resting motor threshold; AMT: active motor threshold; MMSE: Mini-Mental State Examination; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; VMC: voluntary muscle contraction.

*'Real' group received real rTMS while 'sham' group received rTMS applied with coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation.

The use of 1 Hz rTMS has been proven to be effective, although there is some discrepancy among measurement tools[7-8, 15-17]. Low-frequency rTMS on unaffected hemisphere produces better effects than high-frequency rTMS on affected hemisphere[15-16]. Khedr *et al* [16] reported that 1 Hz stimulation on unaffected hemisphere exhibited greater motor function improvement than 3 Hz stimulation. This occurs because 3 Hz stimulation over the affected hemisphere only increased the cortical excitability of affected hemisphere without changes of unaffected hemisphere. Evidence exists that low-frequency rTMS changed cortical excitability in bilateral hemispheres at the same time, whereas high-frequency rTMS is successful only on the affected hemisphere[7]. Application of high-frequency rTMS alone on the affected hemisphere would not produce consistent results[19-20]. Recently, high-frequency combined with low-frequency rTMS is better than low-frequency rTMS alone in recovery of motor function[19]. Theta burst stimulation (TBS) is a pattern of rTMS that can facilitate M1 excitability when delivered intermittently or suppress M1 excitability when delivered continuously. Although interhemispheric inhibition is considered as one of the mechanisms of rTMS, continuous TBS (cTBS) shows no relationship between motor function improvement and interhemispheric inhibition[2], and even causes deteriorated motor activity[1, 21]. Therefore, TBS is considered against the simple application of the concept of interhemispheric inhibition.

Nonetheless, TBS has an advantage in safety, because it employs lower intensity compared to the usual rTMS, allowing it to be safer and more effective after securing the underlying mechanism and the precise usage[22]. Therefore, further research is needed to find out the optimal TBS protocols to induce better motor recovery. The intensity of the stimulation might play a highly critical role. Subthreshold stimulation may act by local effect of the stimulation area, but a suprathreshold stimulation may change not only the stimulation area but also the opposite homogenous motor cortex[5-8]. Pomeroy *et al* [18] found that motor function did not change after suprathreshold (120%) stimulation. Effects of rTMS using different measurement tools were various, as shown in one study where outcomes of dexterity and grip strength were different[17].

Choice reaction time, grip strength and cognitive performance[7, 23] are seldomly improved, which can be explained by activation of more distributed cortical areas for such parameters.

rTMS has been shown to be effective for spasticity, hyperkinetic disorder and simple motor function[22, 24]. rTMS has proved its effectiveness while conventional rehabilitation results in unsatisfactory outcomes, so rTMS is speculated to be a superb[25]. Task-specific rehabilitation combined with rTMS can improve motor function[23-24]. The capability of rTMS to facilitate motor learning through motor cortex excitability[26] is one of the important elements of rehabilitation, and therefore can be applied as an adjuvant therapy for the treatment of motor impairment.

A limitation of the review is the relatively small sample size. The outcomes are collected and analyzed within a short period of time. In addition, the protocols in each study[5-8, 15-22] are not standardized. For this reason, the rTMS effects would not be better demonstrated. Further studies involving larger number of patients and using standard assessment of functional outcomes are needed.

EFFECTS OF RTMS ON DYSPHAGIA

(Table 2)

Dysphagia can be managed by modified diet, compensatory swallowing technique and training[9]. rTMS has been tried to treat dysphagia, since it can stimulate the cortical input to the swallowing center[9]. Khedr *et al* [9] reported that post-stoke dysphagia improved after daily treatment sessions using rTMS, with an excitatory frequency of 3 Hz on the esophageal motor area of affected hemisphere.

Table 2 rTMS on dysphagia

Source	Design	Size	Lesion site	Time after stroke	Frequency, intensity, pulse number and duration	Stimulated area	Outcome measures	Results
Khedr *et al*, 2009[9]	RCT	12 real, 14 sham*	12 RH, 14 LH	5–10 days	3 Hz, 120% RMT, 300 pulses, 5 sessions	Esophageal motor cortex of AH	Dysphagia outcome and severity scale, Barthel index, grip strength	Improvement of dysphagia and motor disability over 2 months
Khedr & Abo-Elfetoh, 2010[27]	RCT	11 real, 11 sham	11 lateral medulla, 11 brainstem	1–3 months	3 Hz, 130% RMT, 300 pulses, 5 sessions	Esophageal motor cortex of bilateral hemispheres	Dysphagia outcome and severity scale, Barthel index, NIHSS, grip strength	Improvement of dysphagia over 2 months
Verin *et al*, 2009[28]	Case study	7 patients	4 RH, 3 LH	56 ± 50 months	1 Hz, 20% above mylohyoid MT, 1 200 pulses, 5 sessions	UH	Deglutition handicap index, videofluoroscopic study	Improvement of swallowing coordination and aspiration

rTMS: Repetitive transcranial magnetic stimulation; RCT: randomized controlled trial; AH: affected hemisphere; UH: unaffected hemisphere; RH: right hemisphere; LH: left hemisphere; RMT: resting motor threshold; MT: motor threshold; NIHSS: National Institute of Health Stroke Scale.
*'Real' group received real rTMS while 'sham' group received rTMS applied with coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation.

Based on this research, Khedr *et al* [27] tested the effects of 3 Hz rTMS on the esophageal motor cortex of bilateral hemispheres in patients with vertebrobasilar stroke, which induces severe dysphagia symptoms. All patients recovered swallowing function immediately after five sessions of rTMS applied on bilateral hemispheres with the same frequency. Although swallowing is controlled by bilateral hemispheres, interhemispheric asymmetry exists[29-30], allowing swallowing function to be controlled by either direct inhibition of unaffected hemisphere or facilitation of affected hemisphere. Based on the interhemipheric rivalry concept, the unaffected hemisphere was stimulated with a frequency of 1 Hz[28], whereas the esophageal motor cortex of affected hemisphere was stimulated with a frequency of 3 Hz[9]. According to the studies, various recovery mechanisms have been suggested, including increased excitability of the corticobulbar projections from bilateral hemispheres[9] or activation of remaining unaffected premotor cortex and contralateral medulla[27]. While motor area of cerebral cortex controls swallowing initiation, brainstem has a role in the swallowing reflex. Since rTMS exerts corticobulbar tract through the cerebral cortex, it activates both oral and pharyngeal stages of the coordinated swallowing process at the same time[28]. Thus, rTMS might be a better adjuvant therapy, compared to the swallowing functional electrical stimulation.

EFFECTS OF RTMS ON VISUOSPATIAL NEGLECT

(Table 3)

Visuospatial neglect is a common, yet frequently overlooked, neurological disorder following stroke characterized by a deficit in attention and appreciation of stimuli on the contralesional side of the body[31]. It is common, with an incidence of 24.7% in acute stroke patients[32]. In addition to a number of treatments attempted over the last few years, including scanning, limb activation, eye patching, neck vibration and prism[33], rTMS also has been used as an adjuvant therapy for neglect.

Initial studies demonstrated that rTMS of the unaffected hemisphere during the execution of a line bisection task transiently decreased the magnitude of neglect, followed by sustained effects after stimulation[34-40]. 25 Hz rTMS on unaffected parietal cortex was performed by means of an online approach by Oliveri *et al* [34]. Low-frequency rTMS on the unaffected hemisphere was used in five[35-39] out of seven[36-41] studies, and the effect was explained by the control of interhemispheric rivalry. Koch *et al* [35] applied 1 Hz rTMS (600 pulses, 90% resting motor threshold) over the unaffected posterior parietal cortex, to evaluate the sustained effect after the stimulation period, and showed reduction of the pathological hyperactivity of the intact hemisphere and improved performance immediately after rTMS.

Table 3 rTMS on visuospatial neglect

Source	Design	Size	Lesion site	Time after stroke	Frequency, intensity, pulse number and duration	Stimulated area	Outcome measures	Results
Oliveri *et al*, 2001[34]	Case study	7 patients	5 RH, 2LH	15.1±19.1 weeks	25 Hz, 115% MT, 10 pulses, 1 session	UH (P5 or P6)	Length judgment of bisected line	Improvement of visuospatial neglect
Koch *et al*, 2008[35]	Case study	10 patients, 5 neglect (−) patients	RH	Patients: 32−172 days, neglect (−) patients: 31−158 days	1 Hz, 90% RMT, 600 pulses, 1 session	UH	Naming visual chimeric objects	Improvement of visuospatial neglect
Song *et al*, 2009[36]	RCT	7 rTMS, 7 rTMS (−)	RH	rTMS: 38.4 ± 15.2 days, rTMS (−): 31.6±11.5 days	0.5 Hz, 90% MT, 450 pulses, 20 sessions	UH (P3)	Line cancellation, line bisection	Improvement of visuospatial neglect
Lim *et al*, 2010[37]	Case study	7 rTMS, 7 rTMS (−)	RH	rTMS: 61.9 ± 111.1 days, rTMS (−): 139.0±194.8 days	1 Hz, 90% MT, 900 pulses, 10 sessions	UH	Line bisection, Albert test	Improvement of line bisection test, but not of Albert test
Shindo *et al*, 2006[38]	Case study	2 patients	RH	180.5±7.8 days	0.9 Hz, 95% MT, 900 pulses, 6 sessions	UH (P5)	Behavioral inattention test, MMSE or Revised Hasegawa dementia scale, Brunnstrom recovery stage, Barthel index	Improvement of visuospatial neglect until 6 weeks after rTMS
Brighina *et al*, 2003[39]	Case study	3 patients, 5 rTMS (−) healthy control	RH	3−5 months	1 Hz, 90% MT, 900 pulses, 7 sessions	UH (P5)	Line bisection test, clock drawing	Improvement of visuospatial neglect until 15 days after rTMS
Nyffeler *et al*, 2009[40]	Case study	11 patients 5 2 trains TBS, 5 4 trains TBS, 5 sham, 5 control*	RH	7.1±13.0 months	Continuous TBS: 30Hz, burst of 3 pulses, every 100 msec, 100% RMT, 801 pulses, 2 or 4 trains	UH (P3)	Subtask of Vienna test system	Improvement of visuospatial neglect, lasting effect of neglect: 4 TBS trains was longer than 2 TBS trains

rTMS: Repetitive transcranial magnetic stimulation; RCT: randomized controlled trial; TBS: theta burst stimulation; MT: motor threshold; RMT: resting motor threshold; P3/P5: left parietal cortex according to the International 10-20 EEG coordinate system; P6: right parietal cortex according to the International 10-20 EEG coordinate system; MMSE: Mini-Mental State Examination. Four experiments were performed, and each experiment included five patients. Therefore, three patients participated in two experiments and three patients in three experiments.

Song *et al* [36] applied low-frequency rTMS on unaffected posterior parietal cortex twice a day for 2 weeks, (0.5 Hz, 90% motor threshold) and reported significant improvement for 2 weeks. In contrast, Oliveri *et al* [34] revealed the beneficial effects of high-frequency rTMS on unaffected hemisphere, contradicting the findings from other studies. The same parameters should be applied with caution, since it was the only study to use high-frequency rTMS for neglect. Nyffeler *et al* [40] applied cTBS over unaffected hemisphere with different numbers of trains and reported that repeated applications of TBS over the contralesional posterior parietal cortex on the same day specifically and significantly improved the perception of visual targets presented on the left side up to 32 hours. Most of the studies demonstrated positive results for visuospatial neglect[33-36, 38-40]. Song *et al* [36] demonstrated that 20 sessions of low-frequency rTMS over the unaffected hemisphere improved line cancellation and bisection. However, dissociations were found among different types of measurement tools, because of varying sensitivities for the diagnosis of neglect[41]. It was well known that there were dissociations between two cardinal diagnostic tests, *i.e*. cancellation and line bisection[42]. Furthermore, the heterogeneous mechanisms of visuospatial neglect are thought to be another cause for such differences in results. Attention was one of the mechanisms that build up neglect, and rTMS improved attention to greater extent than visuospatial function[37-38]. Long-term effect after rTMS stimulation was investigated[36-37, 39]. Peak behavioral inattention test score of the patients at 6 weeks after rTMS stimulation remained better than that of pre-rTMS stimulation[36]. rTMS exhibits longer after-effect on visuospatial neglect than other treatment modalities. A direct comparison would be necessary, since no such comparison has been attempted. Koch *et al* [35] found that 1 Hz rTMS over left primary parietal cortex inhibited the over-excitability of left posterior parietal cortex-primary motor cortex circuits and also impacted visual neglect. However, the improvement did not correlate with the size of the normalization of the over-excitability. Further studies are necessary to elucidate the effects and mechanisms, and to establish the optimal protocols of rTMS for visuospatial neglect improvement. The effects of affected hemisphere stimulation should be identified, and it is preferable to compare the effects of rTBS with other types of TMS.

EFFECTS OF RTMS ON APHASIA

(Table 4)

Table 4 rTMS on aphasia

Source	Design	Size	Type of aphasia	Time after stroke	Frequency, intensity, pulse number and duration	Stimulated area	Neuro-navigation	Outcome measures	Results
Naeser *et al*, 2005[43]	Case study	4	Global, motor, conduction aphasia	5–11 years	1 Hz, 90% MT, 1 200 pulses, 10 sessions	Right Broca's homologue[51]	Yes	Snodgrass and Vanderwart picture naming, BNT, Boston diagnostic aphasia exam	Improvement of picture naming over 8 months in 3/4 patients
Martin *et al*, 2009[44]	Case study	2	Motor aphasia	10, 2 years	1 Hz, 90% MT, 600 pulses, 10 sessions	Right pars triangularis	Yes	BNT	Improvement of naming in 1/2 patients
Martin *et al*, 2004[45]	Case study	4	Motor aphasia	5–11 years	1 Hz, 90% MT, 1 200 pulses, 10 sessions	Right Brodmann area 45	Yes	BNT, Boston diagnostic aphasia exam	Improvement of picture naming over 2 months
Hamilton *et al*, 2010[46]	Case study	1	Motor aphasia	5 years	1 Hz, 90% MT, 1 200 pulses, 10 sessions	Right pars triangularis	Yes	WAB, Cooke theft picture description, naming	Improvement of naming, picture description,spontaneous speech
Kakuda *et al*, 2010[47]	Case study	2	Sensory aphasia	7, 8 months	1 Hz, 90% MT, 1 200 pulses, 10 sessions for a week and weekly for 3 months	Wernicke's area	No	Token test, auditory comprehension of standard language test of aphasia	Improvement of auditory and visual comprehension, spontaneous speech, writing, repetition and naming
Winhuisen *et al*, 2005[48]	Case study	11	Global, motor, sensory aphasia	2 weeks	4 Hz, 20% max output (2.1 T), 40 pulses	Right or left IFG (activated region in PET)	No	Aachen aphasia test battery	Improvement of verb generation (left IFG > right IFG)
Kakuda *et al*, 2010[49]	Case study	4	Motor aphasia	13.8 ± 10.7 months	1 Hz, 90% MT, 1 200 pulses, 10 sessions	Homologous to activated region in fMRI during word repetition task	Yes	WAB, Standard language test of aphasia	Improvement of naming, spontaneous speech, writing and repetition

rTMS: Repetitive transcranial magnetic stimulation; MT: motor threshold; BNT: Boston Naming Test; WAB: Western Aphasia Battery; IFG: inferior frontal gyrus; PET: positron emission tomography; fMRI: functional magnetic resonance imaging.

The effectiveness of widely used speech-language therapy is generally known to diminish, as gradually moving on from acute to chronic stage in stroke patients[50]. Studies showed that recovery could take place for extended period of time after stroke in patients who received conventional aphasia rehabilitation[51-53]. rTMS can be considered a novel therapy for aphasia because it can promote recovery of chronic aphasia. rTMS used for up to 11 years showed effects in chronic aphasic patients[43-45], even in those who showed stable deficits of elicited propositional speech[46]. rTMS has effects on a variety of language problems, ranging from naming difficulty to speech arrest, depending on the stimulation parameter and area of rTMS.

rTMS applied to an anterior portion of right Broca's homologue has shown to affect language behaviors, including naming, in stroke patients with chronic, nonfluent aphasia[43-45], with a frequency of 1 Hz. The mechanism of this protocol is to reduce interhemispheric inhibition towards the left hemisphere, which contains the main language area. On the contrary, Kakuda *et al* [47] applied low-frequency rTMS at Wernicke's area for sensory aphasia patients. Winhuisen *et al* [48] applied 4 Hz rTMS over activated region on positron emission tomography during semantic matching task and showed improvement of verb generation. Bilateral hemispheres were thought to have roles in supporting language recovery as proved by functional magnetic resonance imaging (fMRI) study[49]. Therefore, rTMS using the simple concept of interhemispheric inhibition might deteriorate recovery of aphasia. Kakuda *et al* [47] revealed that 1 Hz rTMS applied to the area homologous to the most activated site on fMRI seemed to be a feasible approach for post-stroke aphasic patients. The frameless stereotaxic system was used to guide the specific area on the scalp during rTMS application for aphasia. Bashir *et al* [54] proved the superiority of navigated rTMS in terms of both physiologic and behavioral effects[54] by maximizing accurate and consistent targeting. Therapeutic applications of rTMS are expected to benefit greatly with navigating electric field. As the recovery of language function was mediated by different parts of brain at different stages in terms of time[55], new therapeutic strategies, combining with fMRI or neuronavigation system, should be established for enhanced aphasia treatment in the future.

CONCLUSION

Reviewing the studies on effects of rTMS in post-stroke patients, the role of rTMS as an adjuvant therapy can be reaffirmed despite some conflicting outcomes. Nonetheless, it is imperative to further establish rTMS protocols including frequency, intensity and location to maximize the benefits of rTMS.

All the studies with the use of 1 Hz rTMS were proven to be effective and low-frequency rTMS on unaffected hemisphere was better than high-frequency rTMS on affected hemisphere[15-16]. In addition, high-frequency combined with low-frequency rTMS was better than low-frequency rTMS alone, in terms of motor training[19]. Suprathreshold stimulation may change not only the stimulation site but also the opposite homogenous motor cortex[5-8, 18] and showed less effectiveness compared with the subthreshold stimulation.

Swallowing function can be controlled by either direct inhibition of unaffected hemisphere or facilitation of affected hemisphere[28-29]. A previous study using TMS demonstrated that post-stroke dysphagia recovery was asymmetric between two hemispheres and was accompanied with activation of the unaffected hemisphere[56]. Application of 5 Hz rTMS to the unaffected pharyngeal motor cortex increased pharyngeal cortical excitability and improved swallowing behavior[57]. Similar findings have been identified by other studies using brain imaging techniques[58-59]. Such asymmetries have been explained by a lack of transcallosal inhibition between hemispheres in swallowing function[60-61]. Based on the interhemipheric rivalry concept, the unaffected hemisphere was stimulated with low-frequency rTMS[30], whereas the affected hemisphere was stimulated with high-frequency rTMS[9]. Both hemispheres have roles and recently rTMS is applied over the most activated sites on functional image during task[52]. In the future, optimal stimulation of rTMS using fMRI or neuronavigation system should be established for clinical application for the stroke patients.

Funding: This study was supported by grant of the Korea Healthcare technology R&D Project, Ministry of Health & Welfare, Republic of Korea, No. A101901.

Author contributions: Joonho Shin and KyeHee Cho were responsible for data acquisition. Joonho Shin, EunJoo Yang and Nam-Jong Paik were in charge of study concept and design. All authors participated in manuscript development, oversight and instruction.

Conflicts of interest: None declared.

REFERENCES

[1] Johansson BB. Brain plasticity and stroke rehabilitation. The willis lecture. Stroke. 2000;31(1):223-230.

[2] Ward NS, Cohen LG. Mechanisms underlying recovery of motor function after stroke. Arch Neurol. 2004;61(12):1844-1848.

[3] Williams JA, Imamura M, Fregni F. Updates on the use of non-invasive brain stimulation in physical and rehabilitation medicine. J Rehabil Med. 2009;41(5):305-311.

[4] Khedr EM, Rothwell JC, Ahmed MA, et al. Modulation of motor cortical excitability following rapid-rate transcranial magnetic stimulation. Clin Neurophysiol. 2007;118(1):140-145.

[5] Khedr EM, Ahmed MA, Fathy N, et al. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology. 2005;65(3):466-468.

[6] Khedr EM, Etraby AE, Hemeda M, et al. Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. Acta Neurol Scand. 2010;121(1):30-37.

[7] Fregni F, Boggio PS, Valle AC, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke. 2006;37(8): 2115-2122.

[8] Takeuchi N, Chuma T, Matsuo Y, et al. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke. 2005;36(12): 2681-2686.

[9] Khedr EM, Abo-Elfetoh N, Rothwell JC. Treatment of post-stroke dysphagia with repetitive transcranial magnetic stimulation. Acta Neurol Scand. 2009;119(3):155-161.

[10] Cazzoli D, Muri RM, Hess CW, et al. Treatment of hemispatial neglect by means of rTMS--a review. Restor Neurol Neurosci. 2010;28(4):499-510.

[11] Johansson BB. Current trends in stroke rehabilitation. A review with focus on brain plasticity. Acta Neurol Scand. 2011;123(3): 147-159.

[12] Hoogendam JM, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimul. 2010;3(2):95-118.

[13] Pape TL, Rosenow J, Lewis G. Transcranial magnetic stimulation: A possible treatment for TBI. Head Trauma Rehabil. 2006;21(5): 437-451.

[14] Hiscock A, Miller S, Rothwell J, et al. Informing dose-finding studies of repetitive transcranial magnetic stimulation to enhance motor function: A qualitative systematic review. Neurorehabil Neural Repair. 2008;22(3):228-249.

[15] 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;17(9):1203-1209.

[16] Khedr EM, Abdel-Fadeil MR, Farghali A, et al. Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol. 2009;16(12): 1323-1330.

[17] Liepert J, Zittel S, Weiller C. Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in acute stroke: A double-blind placebo-controlled crossover trial. Restor Neurol Neurosci. 2007;25(5-6):461-465.

[18] Pomeroy VM, Cloud G, Tallis RC, et al. Transcranial magnetic stimulation and muscle contraction to enhance stroke recovery: A randomized proof-of-principle and feasibility investigation. Neurorehabil Neural Repair. 2007;21(6):509-517.

[19] Takeuchi N, Tada T, Toshima M, et al. Repetitive transcranial magnetic stimulation over bilateral hemispheres enhances motor function and training effect of paretic hand in patients after stroke. J Rehabil Med. 2009;41(13):1049-1054.

[20] Malcolm MP, Triggs WJ, Light KE, et al. Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: An exploratory randomized controlled trial. Am J Phys Med Rehabil. 2007;86(9):707-715.

[21] Ackerley SJ, Stinear CM, Barber PA, et al. Combining theta burst stimulation with training after subcortical stroke. Stroke. 2010; 41(7):1568-1572.

[22] Di Lazzaro V, Dileone M, Pilato F, et al. Repetitive transcranial magnetic stimulation of the motor cortex for hemichorea. J Neurol Neurosurg Psychiatry. 2006;77(9):1095-1097.

[23] Talelli P, Greenwood RJ, Rothwell JC. Exploring theta burst stimulation as an intervention to improve motor recovery in chronic stroke. Clin Neurophysiol. 2007;118(2):333-342.

[24] Izumi S, Kondo T, Shindo K. Transcranial magnetic stimulation synchronized with maximal movement effort of the hemiplegic hand after stroke: A double-blinded controlled pilot study. J Rehabil Med. 2008;40(1):49-54.

[25] Mally J, Dinya E. Recovery of motor disability and spasticity in post-stroke after repetitive transcranial magnetic stimulation (rTMS). Brain Res Bull. 2008;76(4):388-395.

[26] Pascual-Leone A, Tarazona F, Keenan J, et al. Transcranial magnetic stimulation and neuroplasticity. Neuropsychologia. 1999;37(2):207-217.

[27] Khedr EM, Abo-Elfetoh N. Therapeutic role of rtms on recovery of dysphagia in patients with lateral medullary syndrome and brainstem infarction. J Neurol Neurosurg Psychiatry. 2010;81(5): 495-499.

[28] Verin E, Leroi AM. Poststroke dysphagia rehabilitation by repetitive transcranial magnetic stimulation: A noncontrolled pilot study. Dysphagia. 2009;24(2):204-210.

[29] Khedr EM, Abo-Elfetoh N, Ahmed MA, et al. Dysphagia and hemispheric stroke: A transcranial magnetic study. Neurophysiol Clin. 2008;38(4):235-242.

[30] Hamdy S, Aziz Q, Thompson DG, et al. Physiology and pathophysiology of the swallowing area of human motor cortex. Neural Plast. 2001;8(1-2):91-97.

[31] Heilman KM, Valenstein E. Mechanisms underlying hemispatial neglect. Ann Neurol. 1979;5(2):166-170.

[32] Ringman JM, Saver JL, Woolson RF, et al. Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. Neurology. 2004;63(3):468-474.

[33] Pierce SR, Buxbaum LJ. Treatments of unilateral neglect: A review. Arch Phys Med Rehabil. 2002;83(2):256-268.

[34] Oliveri M, Bisiach E, Brighina F, et al. Rtms of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. Neurology. 2001;57(7):1338-1340.

[35] 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(Pt 12):3147-3155.

[36] Song W, Du B, Xu Q, et al. Low-frequency transcranial magnetic stimulation for visual spatial neglect: A pilot study. J Rehabil Med. 2009;41(3):162-165.

[37] Lim JY, Kang EK, Paik NJ. Repetitive transcranial magnetic stimulation to hemispatial neglect in patients after stroke: An open-label pilot study. J Rehabil Med. 2010;42(5):447-452.

[38] Shindo K, Sugiyama K, Huabao L, et al. Long-term effect of low-frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. J Rehabil Med. 2006;38(1):65-67.

[39] Brighina F, Bisiach E, Oliveri M, et al. 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. Neurosci Lett. 2003;336(2):131-133.

[40] Nyffeler T, Cazzoli D, Hess CW, et al. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke. 2009;40(8):2791-2796.

[41] Milner AD, McIntosh RD. The neurological basis of visual neglect. Curr Opin Neurol. 2005;18(6):748-753.

[42] Adair JC, Barrett AM. Spatial neglect: Clinical and neuroscience review: A wealth of information on the poverty of spatial attention. Ann N Y Acad Sci. 2008;1142:21-43.

[43] Naeser MA, Martin PI, Nicholas M, et al. Improved picture naming in chronic aphasia after tms to part of right broca's area: An open-protocol study. Brain Lang. 2005;93(1):95-105.

[44] Martin PI, Naeser MA, Ho M, et al. Research with transcranial magnetic stimulation in the treatment of aphasia. Curr Neurol Neurosci Rep. 2009;9(6):451-458.

[45] Martin PI, Naeser MA, Theoret H, et al. Transcranial magnetic stimulation as a complementary treatment for aphasia. Semin Speech Lang. 2004;25(2):181-191.

[46] Hamilton RH, Sanders L, Benson J, et al. Stimulating conversation: Enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. Brain Lang. 2010;113(1):45-50.

[47] Kakuda W, Abo M, Uruma G, et al. Low-frequency rtms with language therapy over a 3-month period for sensory-dominant aphasia: case series of two post-stroke Japanese patients. Brain Inj. 2010;24(9):1113-1117.

[48] Winhuisen L, Thiel A, Schumacher B, et al. Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: A combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke. 2005;36(8):1759-1763.

[49] Kakuda W, Abo M, Kaito N, et al. Functional mri-based therapeutic rtms strategy for aphasic stroke patients: A case series pilot study. Int J Neurosci. 2010;120(1):60-66.

[50] Robey RR. The efficacy of treatment for aphasic persons: A meta-analysis. Brain Lang. 1994;47(4):582-608.
[51] Vitali P, Abutalebi J, Tettamanti M, et al. Training-induced brain remapping in chronic aphasia: A pilot study. Neurorehabil Neural Repair. 2007;21(2):152-160.
[52] Lazar RM, Antoniello D. Variability in recovery from aphasia. Curr Neurol Neurosci Rep. 2008;8(6):497-502.
[53] Smania N, Gandolfi M, Aglioti SM, et al. How long is the recovery of global aphasia? Twenty-five years of follow-up in a patient with left hemisphere stroke. Neurorehabil Neural Repair. 2010;24(9): 871-875.
[54] Bashir S, Edwards D, Pascual-Leone A. Neuronavigation increases the physiologic and behavioral effects of low-frequency rtms of primary motor cortex in healthy subjects. Brain Topogr. 2010.
[55] Menke R, Meinzer M, Kugel H, et al. Imaging short- and long-term training success in chronic aphasia. BMC Neurosci. 2009;10:118.
[56] Hamdy S, Aziz Q, Rothwell JC, et al. The cortical topography of human swallowing musculature in health and disease. Nat Med. 1996;2(11):1217-1224.
[57] Jefferson S, Mistry S, Michou E, et al. Reversal of a virtual lesion in human pharyngeal motor cortex by high frequency contralesional brain stimulation. Gastroenterology. 2009;137(3): 841-849, 849. e1.
[58] Hamdy S, Mikulis DJ, Crawley A, et al. Cortical activation during human volitional swallowing: An event-related fmri study. Am J Physiol. 1999;277(1 Pt 1):G219-225.
[59] Hamdy S, Rothwell JC, Brooks DJ, et al. Identification of the cerebral loci processing human swallowing with H2(15)O PET activation. J Neurophysiol. 1999;81(4):1917-1926.
[60] Mistry S, Verin E, Singh S, et al. Unilateral suppression of pharyngeal motor cortex to repetitive transcranial magnetic stimulation reveals functional asymmetry in the hemispheric projections to human swallowing. J Physiol. 2007;585(Pt 2): 525-538.
[61] Hamdy S, Aziz Q, Rothwell JC, et al. Sensorimotor modulation of human cortical swallowing pathways. J Physiol. 1998;506 (Pt 3):857-866.

(Edited by Du YL, Zhan SQ/Song LP)