# Repetitive Transcranial Magnetic Stimulation–Induced Corticomotor Excitability and Associated Motor Skill Acquisition in Chronic Stroke

Yun-Hee Kim, MD, PhD; Sung H. You, PT, PhD; Myoung-Hwan Ko, MD, PhD; Ji-Won Park, PhD; Kwang Ho Lee, MD, PhD; Sung Ho Jang, MD; Woo-Kyoung Yoo, MD; Mark Hallett, MD

***Background and Purpose***—Although there is some early evidence showing the value of repetitive transcranial magnetic stimulation (rTMS) in stroke rehabilitation, the therapeutic effect of high-frequency rTMS, along with the physiology of rTMS-induced corticomotor excitability supporting motor learning in stroke, has not been established. This study investigated high-frequency rTMS-induced cortical excitability and the associated motor skill acquisition in chronic stroke patients.

***Methods***—Fifteen patients with chronic hemiparetic stroke (13 men; mean age 53.5 years) practiced a complex, sequential finger motor task using their paretic fingers either after 10 Hz or sham rTMS over the contralateral primary motor cortex (M1). Both the changes in the behavior and corticomotor excitability before and after the intervention were examined by measuring the movement accuracy, the movement time, and the motor-evoked potential (MEP) amplitude. A separate repeated-measures ANOVA and correlation statistics were used to determine the main and interaction effects as well as relationship between the changes in the behavioral and corticomotor excitability.

***Results***—High-frequency rTMS resulted in a significantly larger increase in the MEP amplitude than the sham rTMS ($P<0.01$), and the plastic change was positively associated with an enhanced motor performance accuracy ($P<0.05$).

***Conclusions***—High-frequency rTMS of the affected motor cortex can facilitate practice-dependent plasticity and improve the motor learning performance in chronic stroke victims. **(*Stroke*. 2006;37:1471-1476.)**

**Key Words:** motor activity ■ stroke ■ transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS), unlike invasive cortical stimulation, is a noninvasive, effective therapeutic stimulation that modulates the cortical excitation in individuals with stroke.[1,2] The affected motor cortex of the stroke patients shows a reduced cortical excitability[3,4] and a suppression of the topographical representation of the affected muscles, whereas the unaffected motor cortex shows increased excitability and an enlarged cortical motor output.[5–7]

Depending on the frequency range, inhibitory and facilitatory modulation effects have been suggested to occur when rTMS is applied to the hand motor cortex. In particular, low-frequency (<1 Hz) rTMS can inhibit the cortical excitability,[2,8–11] whereas high-frequency (5 to 20 Hz) rTMS can facilitate the corticomotor excitability.[12,13] Clinical trials using low-frequency rTMS applied to the unaffected hemisphere demonstrated decreased interhemispheric inhibition of the affected hemisphere with the associated behavioral changes in stroke patients.[2,14] On the other hand, high-frequency rTMS directly applied to the motor cortex was reported to have a facilitative effect, which increases the corticomotor excitability in the stimulated hemisphere and to enhance the short-term motor function in healthy individuals and patients with Parkinson disease.[12,15,16]

Despite there being clinical evidence suggesting that electrical cortical DC stimulation to the affected hemisphere[1] and low-frequency rTMS to the unaffected hemisphere[2] can modulate the cortical excitability and produce measurable hand motor improvement in stroke patients, the efficacy of high-frequency rTMS on the corticomotor excitability and the acquisition of motor skills in chronic stroke patients have not been explored. Therefore, we implemented a crossover, sham-controlled, single-blind study to investigate the effects of 10 Hz rTMS

Received December 25, 2005; final revision received February 10, 2006; accepted March 21, 2006.

From the Department of Physical Medicine and Rehabilitation, Stroke and Cerebrovascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (Y.H.K.); Hampton University, Doctor of Physical Therapy Program, Hampton, Va (S.H.Y.); Department of Physical Medicine and Rehabilitation, Research Institute of Clinical Medicine, Chonbuk National University Medical School, Jeonju, Republic of Korea (M.H.K.); Department of Physical Therapy, College of Health Science, Catholic University of Daegu, Daegu, Republic of Korea (J.W.P.); Department of Neurology, Stroke and Cerebrovascular Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (K.H.L.); Department of Physical Medicine and Rehabilitation, School of Medicine, Yeungnam University, Daegu, Republic of Korea (S.H.J.); Department of Physical Medicine and Rehabilitation, Hallym University Sacred Heart Hospital, Dongan-ku, Anyang, Republic of Korea (W.K.Y.); and National Institute of Neurological Disorders and Stroke, Human Motor Control Section, National Institutes of Health, Medical Neurology Branch, Bethesda, Md (M.H.).

Reprint requests to Yun-Hee Kim, Department of Physical Medicine and Rehabilitation, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Kangnam-ku, Seoul, 135-710, Republic of Korea. E-mail: yunkim@smc.samsung.co.kr



*Stroke* **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000221233.55497.51**

applied to the affected motor cortex in chronic stroke on the behavioral changes of the paretic hand movement.

## Materials and Methods

### Patients

Fifteen stroke patients with hemiparesis (13 men; mean age 53.5±4.5 years) were enrolled in this study. The inclusion criteria were: (1) >3 months after the onset of the first-ever stroke, and (2) motor deficits of the unilateral upper limb that had improved to the extent of being able to move fingers individually. The exclusion criteria included: (1) severe internal carotid artery stenosis, (2) direct damage to the primary motor cortex, (3) seizure, and (4) an intracranial metallic implant. The local ethics committee approved the study protocol, and informed consent was obtained from all subjects before the study.

### Clinical Examination

Routine clinical examinations were performed to determine the presence of a motor dysfunction and the risk factors associated with stroke (Table). Patients' medications remained unchanged during this experiment.

### Motor Cortex Mapping

Patients were comfortably seated in a reclining armchair with both hands pronated on a pillow. The electromyography (EMG) data were collected from the contralateral first dorsal interosseus muscle via surface electrodes that had been placed over these muscles in a belly-tendon montage. The EMG activity was amplified using a conventional EMG machine (Synergy EMG/EP system), and the data were band-pass filtered at 10 to 2000 kHz. The optimal scalp location ("hot spot") was determined using a Magstim Rapid stimulator (Magstim Ltd) and the 70-mm figure-of-eight coil. The handle of the coil was oriented to a direction posterior to the midline at a 45° angle in order for the electromagnetic currents to flow perpendicular to the central sulcus,[17] and the stimulator was moved over the scalp in 1-cm steps. Once a hot spot was identified, single-pulse TMS was delivered to the location to determine the resting motor threshold (RMT) that had been defined as the lowest stimulus intensity necessary to produce a motor-evoked potentials (MEPs) of a ≥50 $\mu$V peak-to-peak amplitude in 5 of 10 subsequent trials. The muscle activity was carefully monitored by real-time EMG to confirm the relaxed status before the stimulation.

### rTMS Intervention

The rTMS was delivered to the scalp over the motor cortex of the affected hemisphere using a Magstim Rapid stimulator with 2 booster modules (Magstim Co, Ltd). Real rTMS involved a train of 20 pulses at 10 Hz and 80% RMT (total duration of 2 seconds) applied through the coil over the target motor cortex area corresponding to the paretic hand. This train was repeated 8 times, and a total of 160 pulses were delivered over an 8-minute session with a 58-second intertrain interval. The motor cortex was stimulated by holding the figure-of-eight coil tangentially to the skull. Sham rTMS was performed with the coil held at an angle of 90° to the scalp using the same stimulation parameters (noise, time, frequency) as with real rTMS. All the patients participated in the experimental session twice at a 1-week interval, and they were administered either the real or sham stimulations in a pseudorandomized order. Eight patients received real rTMS in the first session (real-first group), whereas the remainder received sham rTMS in the first session (sham-first group).

### Motor Practice

Immediately after each rTMS train, the patients were instructed to practice a block of sequential finger motor tasks for 40 seconds during the intertrain intervals (Figure 1A). The sequential motor learning paradigm involved the patient's repetitive push-button task in response to a 7-digit number stimulus presented on a computer. The patients were seated 50 cm away from the front of a 15-inch monitor. A 7-digit sequence of numbers, which was a combination of 1, 2, 3, or 4 in a random order, was presented at the center of the monitor for 3 seconds. The patients were instructed to repeatedly push

**Patient Demographic and Clinical Characteristics**

| | | | | | | Grip Power, kg | | Purdue Pegboard Test | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Patients | Gender | Age, y | Lesion | Risk Factors | POD, mo | A | U | A | U | mRS |
| 1 | M | 45 | Rt thalamus hemorrhage | HTN | 10.5 | 16 | 39 | 3 | 14 | 2 |
| 2 | M | 53 | Lt. temporal lobe infarction | None | 30.5 | 25 | 35 | 8 | 15 | 2 |
| 3 | M | 52 | Lt temporal lobe hemorrhage | cig | 14 | 14 | 40 | 4 | 14 | 3 |
| 4 | M | 56 | Lt ACA infarction | Hchol | 28 | 23 | 27 | 12 | 14 | 2 |
| 5 | M | 43 | Rt BG hemorrhage | Hchol | 6 | 15 | 32 | 6 | 16 | 2 |
| 6 | M | 48 | Rt SC infarction | HTN, NIDDM | 33 | 16 | 34 | 2 | 10 | 2 |
| 7 | M | 65 | Lt SC infarction | HTN, cig, Hchol | 8 | 30 | 35 | 11 | 13 | 2 |
| 8 | M | 50 | Lt SC infarction | cig | 11.5 | 14 | 40 | 5 | 15 | 2 |
| 9 | F | 58 | Lt SC infarction | HTN | 9 | 12 | 23 | 8 | 13 | 2 |
| 10 | M | 57 | Lt CR infarction | HTN, cig, Hchol | 11 | 15 | 28 | 8 | 15 | 2 |
| 11 | M | 58 | Lt CR infarction | HTN, cig, Hchol | 13 | 25 | 44 | 6 | 10 | 1 |
| 12 | M | 60 | Rt. thalamus infarction | cig | 3.5 | 10 | 36 | 10 | 13 | 3 |
| 13 | M | 49 | Lt ACA infarction | Hchol | 17 | 33 | 36 | 12 | 13 | 3 |
| 14 | F | 57 | Lt ACA infarction | HTN | 41 | 17 | 23 | 11 | 13 | 3 |
| 15 | M | 51 | Lt CR infarction | NIDDM, cig | 14 | 13 | 35 | 3 | 16 | 2 |
| Mean | M=13; F=2 | 53.5 | Infarction=12<br>hemorrhage=3 | | 16.7 | 18.5 | 33.8 | 7.3 | 13.6 | |

POD indicates postonset duration; A, affected side; U, unaffected side; mRS; modified Rankin Scale; M, male; F, female; Rt, right; Lt, left; ACA, anterior cerebral artery; BG, basal ganglia; SC, striatocapsular; CR, Corona radiate; HTN, hypertension; cig, cigarette smoking; Hchol, hypercholesterolemia; NIDDM, noninsulin-dependent diabetes mellitus.

The Purdue pegboard score refers to the total No. of pegs to be completely assembled in the board within 30 seconds.

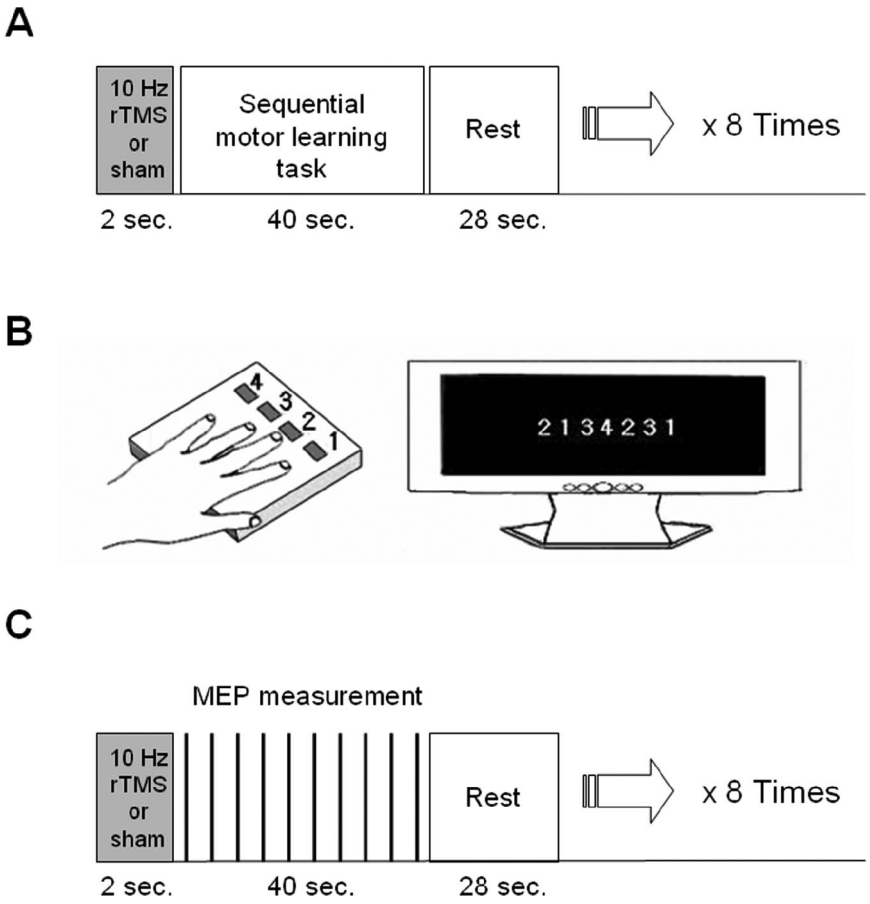


**Figure 1.** Experimental setup. A, Intervention. Twenty pulses of 10 Hz (or sham) rTMS were applied to the subject immediately before the motor task block (repeated 8 times). B, Motor practice. Patients were instructed to push the corresponding buttons of a 7-digit sequence using their paretic fingers. C, MEP measurement. Ten MEPs were measured before (baseline) and immediately after each train of real or sham rTMS.

the 4 numbered response buttons as accurately and quickly as possible using the paretic fingers during the following 40 seconds. Each button was labeled with a number representing the finger to be used; 1, 2, 3, and 4 represented the index, the middle, the ring, and the little fingers, respectively (Figure 1B). The motor practice task block was repeated 8 times.

### Behavioral Measure: Motor Skill Acquisition

The motor performance was determined by assessing the movement accuracy (MA) and movement time (MT) using SuperLabPro 2.0 software. The MA is a unitless scale that represents a total number of correct buttons presses of the maximal potential score (in normal adults, maximal MA=≈90).[16] The MT represents the time required to complete the motor task and is expressed in milliseconds. Different 7-digit sequences were given in each experimental session.

### Corticospinal Excitability Measurement

The changes in the corticospinal excitability after applying real or sham rTMS were measured during separate sessions. Single magnetic stimulations at 120% of the RMT were administered over the motor hot spot of the affected hemisphere using a 70-mm figure-of-eight coil. The MEPs were recorded on the contralateral first dorsal interosseus muscle. The stimuli were delivered with ≥5-second intervals. Ten sweeps of the data were collected, and the mean peak-to-peak amplitude of the MEPs was calculated as the baseline MEP magnitude. A train of 20 rTMS or sham stimulation was applied at 10 Hz over a period of 2 seconds with an RMT of 80%. The rTMS train or sham stimulation was repeated 8 times with an intertrain interval of 68 seconds in the same manner described above. During each intertrain interval, 10 sweeps of the MEPs were collected as mentioned above. Thereafter, the amplitudes of the responses were converted to a percentage of a single stimulation response. The mean amplitude of the MEPs at each rTMS intertrain interval was taken as a measure of the corticospinal excitability (Figure 1C). Eight of 15 patients completed this experiment twice, at a 1-week interval, for the real or sham stimulations applied in a pseudorandomized order.

### Data Analysis

A separate repeated-measures ANOVA with intervention considered a within-subject factor was performed to evaluate the influence of rTMS on the motor performance scores and on the changes in the corticomotor excitability recorded with MEPs. Additional *t* test and post hoc analyses using Tukey Honestly Significantly Different were performed to interpret the significant effects. Mixed analyses were performed to determine the relationship between the changes in the corticomotor excitability and the motor performance measures: MA and MT, respectively. Homogeneity of variance assumption was evaluated with Box M test, and uncorrelation was evaluated with the Mauchly sphericity test. If this assumption was not satisfied, Greenhouse–Geisser correction was used at significance level of $P<0.05$. The carryover effect was determined by using paired *t* test.

## Results

### Behavioral Data: Motor Skill Acquisition

Figure 2A and 2B show that there were significant group×time factor interaction effects for both MA ($F_{(7,196)}=6.92$; $P<0.01$) and MT ($F_{(7,196)}=3.51$; $P<0.01$). Post hoc analysis revealed that the real rTMS plus motor practice resulted in a significantly larger increase in both MA and MT scores than the sham rTMS with motor practice ($P<0.05$). Hence, this finding suggests that the subjects who received the real rTMS showed an enhancement in the MA and movement speed.

Taking the respective block 1 MA and MT data of the first and the second session of the crossover design in the real-first

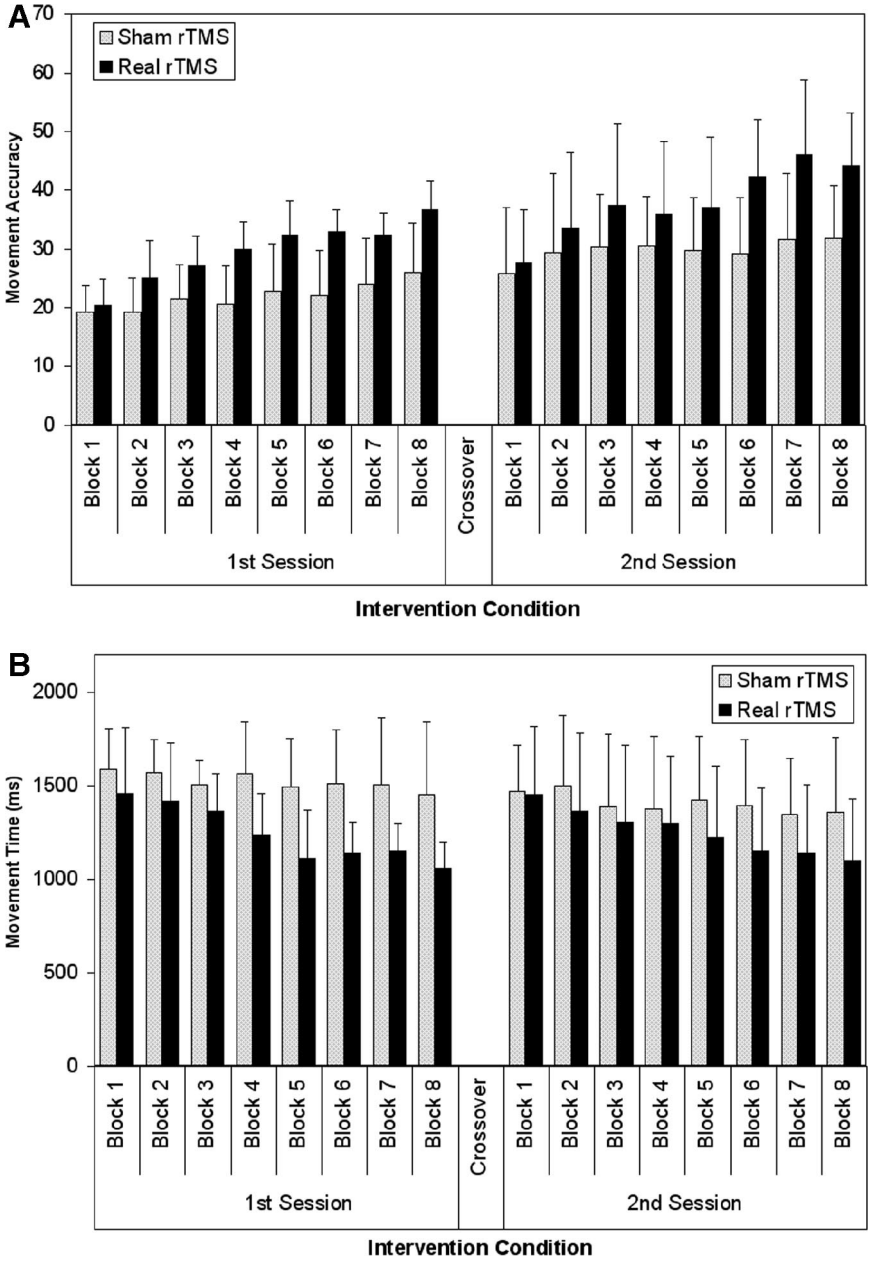


**Figure 2.** A, The mean MA of the real and sham rTMS group at the first and second experimental session (n=15). When the data from 2 sessions were compared, repeated-measures ANOVA showed a significant interaction between group×time factor ($P<0.01$). Values are mean±SD. B, Mean MT of the real and sham rTMS group at the first and second experimental sessions (n=15). Repeated-measures ANOVA showed a significant interaction between group×time factor ($P<0.01$). Values are mean±SD.

group, paired *t* test revealed no significant carryover effect ($P=0.17$ for MA and $P=0.86$ for MT, respectively). In addition, independent-samples *t* test revealed no significant difference between the block 1 MA and MT of the first session in the sham-first group and those of the second session in the real-first group ($P=0.15$ for MA and $P=0.33$ for MT, respectively). All the participants successfully completed the experimental procedure. No subjects reported any side effects after the intervention.

## Corticomotor Excitability: MEP Amplitude

The mean amplitude of the MEP at the baseline was 3.93±2.28 mV in the unaffected hemisphere and 2.05±1.93 mV in the affected hemisphere. The RMT was 59.75±5.42% and 71.5±8.98%, respectively. Figure 3 shows the results of repeated-measures ANOVA highlighting the main effect in each group ($F_{(1,14)}=28.92$; $P<0.01$) and a main effect in time factor after rTMS ($F_{(8,112)}=20.54$; $P<0.01$). There was a significant interaction between group and time factor ($F_{(8,112)}=17.01$; $P<0.01$). Post hoc analysis confirmed that the real rTMS resulted in a significantly larger increase in the mean peak amplitude of MEP over time compared with the sham rTMS ($P<0.01$). This suggests that focal rTMS modulation to the affected motor cortex can enhance the corticomotor excitability.

## Relationship Between Motor Performance and Corticomotor Excitability

Mixed analysis revealed a significant correlation between the changes in the MEP amplitudes and the MA in the real rTMS session ($F_{(1,47)}=4.33$; $P=0.04$). The regression plot in Figure 4 highlights significant correlation between the MEP amplitude and MA variables ($y=0.075\times+17.08$). The changes in

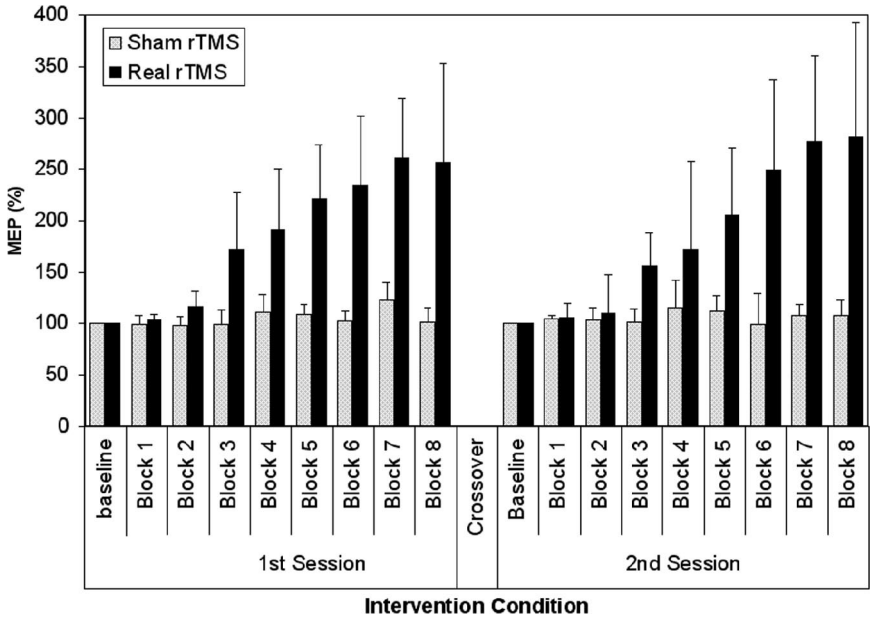


**Figure 3.** The mean MEP amplitude of the real and sham rTMS group at the first and second experimental session (subset n=8). Repeated-measures ANOVA showed a significant interaction between group×time factor ($P<0.01$). Values are mean±SD.

the MT did not show significant correlation with the MEP amplitude ($F_{(1,47)}=2.89$; $P=0.09$).

## Discussion

The basic hypothesis of this study was that focal 10-Hz rTMS to the motor cortex of the affected hemisphere in conjunction with motor practice intervention paradigm would enhance the corticomotor excitability, which would improve the motor performance in chronic stroke patients. As anticipated, high-frequency rTMS produced a larger increase in corticospinal excitability than the sham stimulation. Moreover, this corticomotor excitability change was associated with enhanced motor skill acquisition. These findings are consistent with previous studies, which reported an enhancement in motor performance by magnetic or electrical cortical stimulation in healthy adults[12,16,18] and stroke patients.[1,19]

Although the neural control mechanisms associated with practice-dependent neuroplasticity in the presence of TMS are not clearly understood, it has been suggested that the enhanced cortical excitability and effective synaptic transmission by long-term potentiation[20] can account for the neuroplasticity. Certainly, our TMS findings suggest that high-frequency rTMS is safe and effective enough in increasing the cortical excitability in the selected patients and thus enhanced the motor performance accuracy and time during a complex finger movement. Most important, this plastic change in the motor cortex of chronic stroke patients occurs even after their maximal potential motor recovery. Indeed, the focal high-frequency rTMS-induced corticomotor excitability was correlated with a notable functional gain in the finger MA, whereas the motor performance and cortical excitability was unaffected by the sham TMS.

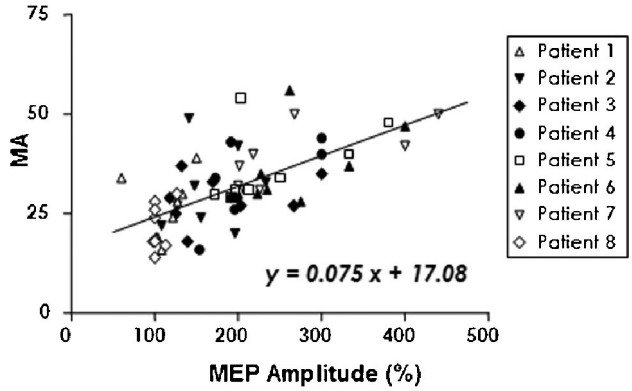


**Figure 4.** The regression plot showed a significant correlation between the MEP amplitude and MA variables (y=0.075× +17.08).

One plausible mechanism is that after stroke, the unaffected motor cortex might be disinhibited by the reduction in the transcallosal inhibition from the affected motor cortex.[21,22] Subsequently, this phenomenon leads to an increased interhemispheric inhibition of the affected motor cortex by the disinhibited, unaffected motor cortex, which would impede the functional motor recovery. A previous low-frequency rTMS applied to the unaffected hemisphere in stroke patients was reported to effectively suppress the interhemispheric inhibition of the affected hemisphere and produce an improvement in motor performance.[2,14] The effects of modulation of the affected motor cortex by high-frequency rTMS observed in this study may directly affect the corticospinal excitability and also indirectly via an interhemispheric reciprocal mechanism in part (ie, the increased excitability of the affected hemisphere may influence the disinhibited hemisphere via the transcallosal pathway).

The dynamic neural motor substrates, which are composed of extensive, hard-wired, and overlapping motor networks, may have rapidly been remodeled or unmasked by motor practice.[23–25] According to our results, this motor learning effect was dramatically amplified after high-frequency rTMS in the affected hemisphere. Empirical evidence has suggested that high-frequency rTMS over the motor cortex can facilitate the sequential motor learning of the contralateral hand in healthy volunteers.[16] However, the therapeutic effect of these

techniques in stroke patients has not been established. Recent reports on the improvement of the hand motor function with the use of DC stimulation in patients with stroke further supports a benefit from our approach.[1] Because there is a possibility of adverse effects from rTMS depending on the frequency and intensity of the stimulus, particularly in a diseased brain, the safety guidelines should be strictly followed and the exclusion of seizure-prone patients is most important in a clinical setting.[26] Therefore, this study was designed to deliver short rTMS trains with adequate intertrain intervals. This brief subthreshold stimulation was well tolerated by the subjects, and no participant reported any adverse effect or seizures. In particular, the behavioral improvement was associated with increased MEP amplitude in the contralateral motor cortex. The effects of rTMS seemed to be significantly augmented when it was used in conjunction with a motor practice paradigm. High-frequency rTMS provides a fast, effective, painless, noninvasive treatment for motor disorders during the rehabilitation of chronic stroke patients with whom there are currently few therapeutic options available. Further studies will be needed to assess the clinical generalization of this intervention technique for stroke and other similar neurological patients with functional motor impairments in their daily activities.

## Summary

The results of this study are expected to improve the understanding of rTMS-modulated enhancement in motor learning and contribute to the development of effective neurorehabilitation strategies. Further studies need to be performed to determine the potential long-term effects of rTMS on the motor performance with a larger sample size.

## Acknowledgments

This research was supported by the Brain Research Center of the 21st Century Frontier Research Program funded by the Ministry of Science and Technology of Republic of Korea (grant M103-KV010014 03-K2201 01430).

## References

1. Hummel F, Cohen LG. Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. *Neurorehabil Neural Repair*. 2005;19:14–19.
2. Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, Wagner T, Rigonatti SP, Marcolin MA, Pascual-Leone A. A sham stimulation-controlled trial of rtms of the unaffected hemisphere in stroke patients. *Neurology*. 2005;64:1802–1804.
3. Manganotti P, Patuzzo S, Cortese F, Palermo A, Smania N, Fiaschi A. Motor disinhibition in affected and unaffected hemisphere in the early period of recovery after stroke. *Clin Neurophysiol*. 2002;113:936–943.
4. Liepert J, Restemeyer C, Kucinski T, Zittel S, Weiller C. Motor strokes: the lesion location determines motor excitability changes. *Stroke*. 2005; 36:2648–2653.
5. Cicinelli P, Traversa R, Rossini PM. Post-stroke reorganization of brain motor output to the hand: a 2–4 month follow-up with focal magnetic transcranial stimulation. *Electroencephalogr Clin Neurophysiol*. 1997; 105:438–450.
6. Traversa R, Cicinelli P, Bassi A, Rossini PM, Bernardi G. Mapping of motor cortical reorganization after stroke. A brain stimulation study with focal magnetic pulses. *Stroke*. 1997;28:110–117.
7. Liepert J, Graef S, Uhde I, Leidner O, Weiller C. Training-induced changes of motor cortex representations in stroke patients. *Acta Neurol Scand*. 2000;101:321–326.
8. Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clin Neurophysiol*. 2000;111:800–805.
9. Theoret H, Halligan E, Kobayashi M, Merabet L, Pascual-Leone A. Unconscious modulation of motor cortex excitability revealed with transcranial magnetic stimulation. *Exp Brain Res*. 2004;155:261–264.
10. Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, Boroojerdi B, Poewe W, Hallett M. Early consolidation in human primary motor cortex. *Nature*. 2002;415:640–644.
11. Kobayashi M, Hutchinson S, Theoret H, Schlaug G, Pascual-Leone A. Repetitive tms of the motor cortex improves ipsilateral sequential simple finger movements. *Neurology*. 2004;62:91–98.
12. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol*. 1998;15:333–343.
13. Peinemann A, Reimer B, Loer C, Quartarone A, Munchau A, Conrad B, Siebner HR. Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive tms to the primary motor cortex. *Clin Neurophysiol*. 2004;115:1519–1526.
14. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke*. 2005;36:2681–2686.
15. Siebner HR, Rossmeier C, Mentschel C, Peinemann A, Conrad B. Short-term motor improvement after sub-threshold 5-hz repetitive transcranial magnetic stimulation of the primary motor hand area in parkinson's disease. *J Neurol Sci*. 2000;178:91–94.
16. Kim YH, Park JW, Ko MH, Jang SH, Lee PK. Facilitative effect of high frequency subthreshold repetitive transcranial magnetic stimulation on complex sequential motor learning in humans. *Neurosci Lett*. 2004;367: 181–185.
17. Brasil-Neto JP, Cohen LG, Pascual-Leone A, Jabir FK, Wall RT, Hallett M. Rapid reversible modulation of human motor outputs after transient deafferentation of the forearm: a study with transcranial magnetic stimulation. *Neurology*. 1992;42:1302–1306.
18. Butefisch CM, Khurana V, Kopylev L, Cohen LG. Enhancing encoding of a motor memory in the primary motor cortex by cortical stimulation. *J Neurophysiol*. 2004;91:2110–2116.
19. Uy J, Ridding MC, Hillier S, Thompson PD, Miles TS. Does induction of plastic change in motor cortex improve leg function after stroke? *Neurology*. 2003;61:982–984.
20. Siebner HR, Rothwell J. Transcranial magnetic stimulation: New insights into representational cortical plasticity. *Exp Brain Res*. 2003;148:1–16.
21. Cicinelli P, Pasqualetti P, Zaccagnini M, Traversa R, Oliveri M, Rossini PM. Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: A paired-pulse transcranial magnetic stimulation study. *Stroke*. 2003;34:2653–2658.
22. Liepert J, Uhde I, Graf S, Leidner O, Weiller C. Motor cortex plasticity during forced-use therapy in stroke patients: a preliminary study. *J Neurol*. 2001;248:315–321.
23. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci*. 1996;16:785–807.
24. Toni I, Krams M, Turner R, Passingham RE. The time course of changes during motor sequence learning: a whole-brain fMRI study. *NeuroImage*. 1998;8:50–61.
25. Ziemann U, Muellbacher W, Hallett M, Cohen LG. Modulation of practice-dependent plasticity in human motor cortex. *Brain*. 2001;124: 1171–1181.
26. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the international workshop on the safety of repetitive transcranial magnetic stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108:1–16.