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rTMS with Motor Training Modulates Cortico-Basal Ganglia-Thalamocortical Circuits in Stroke Patients

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Abstract

Background and Purpose—Repetitive transcranial magnetic stimulation (rTMS) may enhance plastic changes in the human cortex and modulation of behavior. However, the underlying neural mechanisms have not been sufficiently investigated. We examined the clinical effects and neural correlates of high-frequency rTMS coupled with motor training in patients with hemiparesis after stroke.

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Methods—Twenty-one patients were randomly divided into two groups, and received either real or sham rTMS. Ten daily sessions of 1,000 pulses of real or sham rTMS were applied at 10 Hz over the primary motor cortex of the affected hemisphere, coupled with sequential finger motor training of the paretic hand. Functional MRIs were obtained before and after training using sequential finger motor tasks, and performances were assessed.

Results—Following rTMS intervention, movement accuracy of sequential finger motor tasks showed significantly greater improvement in the real group than in the sham group ($p<0.05$). Real rTMS modulated areas of brain activation during performance of motor tasks with a significant interaction effect in the sensorimotor cortex, thalamus, and caudate nucleus. Patients in the real rTMS group also showed significantly enhanced activation in the affected hemisphere compared to the sham rTMS group.

Conclusion—According to these results, a 10 day course of high-frequency rTMS coupled with motor training improved motor performance through modulation of activities in the cortico-basal ganglia-thalamocortical circuits.

Keywords

Stroke; Repetitive transcranial magnetic stimulation; Functional MRI; Motor function; Cortico-basal ganglia-thalamocortical circuits

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) can promote recovery of motor function after stroke; however, an optimal strategy and mechanisms of action remain unclear. Two strategies have been used for enhancement of motor function after stroke; application of high-frequency rTMS to the affected hemisphere and low-frequency stimulation of the unaffected hemisphere (Takeuchi et al., 2005; Fitzgerald et al., 2006; Kim et al., 2006). Meanwhile, Takeuchi et al (Takeuchi et al., 2005; Takeuchi et al., 2009) have reported that low-frequency rTMS to the contralesional M1 coupled with motor training leads to increased pinch force in the affected hand of stroke patients, whereas no improvement was observed with rTMS alone. Recently, theta burst stimulation and standardised motor training on upper-limb function led to task-specific improvements in patients with chronic stroke (Ackerley et al., 2010). Therefore, it appears that the effects of rTMS may be modulated by concomitant motor training.

With regard to the mechanisms of action of rTMS, functional neuroimaging studies have revealed the effects of high-frequency rTMS on cortical activity (Bestmann et al., 2004, 2005; Yoo et al., 2008). Findings from recent fMRI studies of healthy subjects have demonstrated the short-term modulatory effect of high-frequency rTMS on the cortical and subcortical sensorimotor network associated with motor performance and motor learning (Yoo et al., 2008). We hypothesised that high-frequency rTMS applied over the M1 coupled with concomitant motor training might result in enhanced motor performance in stroke patients through modulation of brain activity along a cortico-subcortical motor learning network. We also hypothesised that high-frequency rTMS with motor training could be transferred to subsequent recovery of functional hand movement. To test our hypothesis, we used functional MRI and motor function assessments, and investigated changes in motor network activity in order to delineate the underlying mechanisms of repeated sessions of high-frequency rTMS coupled with motor training.

2. Materials and Methods

2.1. Subjects

Hemiparetic stroke patients were recruited for this study according to the following inclusion criteria: (1) first-ever stroke; (2) post-onset duration of over 3 months; (3) existence of individual finger motion with coordination deficit in the affected hand. Exclusion criteria included the following: (1) post-stroke seizure disorder; (2) evidence of epileptic spikes on EEG; (3) direct injury to the primary motor cortex; and (4) internal carotid artery occlusion on the lesion side.

Fifty-five first-ever stroke patients underwent assessment for participation in the study. Among them, twenty-one stroke patients were recruited according to the above inclusion criteria. Patients were randomly divided into two experimental groups: a real rTMS group or a sham group. Four patients dropped out during the experimental procedure due to various personal reasons. Therefore, seventeen patients were finally included in behavioral and fMRI analysis (Fig. 1). The local ethics committee approved all experimental procedures, and all participants provided written informed consent.

2.2. Experimental Design

The present study was designed as a single-blind, sham-controlled, parallel group trial. As outlined in Fig. 2A, all patients underwent the following: (1) familiarization with experimental procedures, including imaging and motor tasks; (2) pre-rTMS hand function test and fMRI using the sequential finger motor task; (3) motor cortex mapping of the hot spot of M1 representation corresponding to the affected hand, and determination of resting motor threshold; (4) ten daily sessions of finger motor training preceded by real or sham rTMS; (5) post-rTMS hand function test and fMRI using different sequential finger motor tasks; and (6) follow up hand function test one month after the experiment.

2.3. Determination of the Motor Cortex and Motor Threshold

For mapping of the motor cortex, each patient was instructed to sit in an armchair, in a relaxed and comfortable position. A Synergy electromyography (EMG)/evoked potentials (EP) system (Medelec Co. Ltd, Kingswood, Bristol, UK) was used for recording and monitoring of the activity of the contralateral first dorsal interosseus (FDI) muscle. TMS was applied with a Magstim Rapid2® stimulator (Magstim Co. Ltd, Spring Gardens, Whitland, Carmarthenshire, Wales, UK) equipped with a 70-mm figure-of-eight coil. Using TMS, the optimal scalp location ("the hot spot") for activation of the contralateral FDI muscle was determined as the scalp location from which TMS induced motor evoked potentials (MEPs) of maximum peak-to-peak amplitude in the contralateral FDI muscle. Specifically, the figure-of-eight coil was positioned tangentially to the scalp at an angle of 45° from the mid-sagittal line (Brasil-Neto et al., 1992). Resting motor threshold (RMT) was defined as the lowest stimulus intensity needed for induction of MEPs of ≥50 μV peak-to-peak amplitude in 5 of 10 consecutive trials (Rossini et al., 1994).

2.4. rTMS Intervention

According to safety recommendations (Wassermann et al., 1996), a figure-of-eight shaped coil connected to a Magstim Rapid® stimulator with two Booster Modules (Magstim Co Ltd., Spring Gardens, Whitland, Carmarthenshire, Wales, UK) was used. Fifty pulses of 10 Hz rTMS were applied with an intensity of 80% RMT over a period of 5 seconds. Twenty trains of rTMS were applied at 55 second intertrain intervals; therefore, a total of 1,000 stimuli were applied during 20 minutes of training session. A fifty second period of sequential finger motor learning tasks was undertaken immediately following cessation of each rTMS train (Fig. 2A). Using the one-wing sham method (Kim et al., 2006), sham

stimulation was performed at the same site, and at the same frequency and intensity as that of real rTMS. Each experiment included 10 daily training sessions, 5 days per week over a period of two consecutive weeks.

2.5. Sequential Motor Learning Task

The sequential motor learning task was programmed using SuperLabPro 2.0 software (Cedrus Co., Phoenix, AZ). A 7-digit sequence of numbers was presented at the center of the monitor. Patients were instructed to repeatedly push the five numbered response buttons as accurately and quickly as possible using their paretic hand (Fig. 2B) (Kim et al., 2004; Kim et al., 2006; Yoo et al., 2008). The motor test involved repeating the 50-second task blocks ten times, with a pause of 5 seconds after each task. In order to familiarize themselves with the experimental procedure, patients were allowed to perform two blocks of practice prior to starting a test block. For each experiment, motor performance was assessed by recording the movement accuracy (MA) and time (MT) during fMRI scanning before and after rTMS intervention. MA was defined as the total number of correct pushbutton responses. MT represented the time required to complete a subsequent sequential finger movement.

2.6. Motor Performance Measurement

For assessment of motor performance of the affected hand, MA and MT were recorded during fMRI scanning before and after rTMS intervention. Also, to evaluate the transfer of the sequential motor training effect to the functional hand movement, the Jebsen hand function test (JHFT) (Jebsen et al., 1969), was applied before, immediately after, and one month after the treatment period.

2.7. fMRI Data Acquisition

Using a 3T Philips Achieva® scanner (Philips, Netherland), fMRI was performed before and after rTMS intervention. The block designed sequential finger motor task was used as an fMRI activation paradigm. The second set of fMRI scans were conducted within a week after completion of the experimental period. To prevent possible head-movement artifacts, the subject's head was firmly fixed during scanning using a strap on the subject's forehead and further secured by calipers built into the head coil. An MRI-compatible (non-magnetic) button box was provided to allow the subject to respond to the stimuli. Stimuli were presented on a screen and the subject's responses were recorded using SuperlabPro 2.0 software (Cedrus Co., Phoenix, AZ). Twenty-eight slices were acquired using a single-shot echo-planar imaging (EPI) sequence (TR/TE = 3000/30 ms, flip angle 70°, matrix = 64 × 64, slice thickness 5 mm). In all functional runs, the MR signal was allowed to achieve equilibrium over five scans that were excluded from the analysis. Each EPI run included four alternating rest and task blocks and five dummy scans. Anatomic images were acquired using a 3D MPGR sequence with the following imaging parameters: TR/TE = 11/5.7 ms, flip angle = 10° FOV = 220, matrix = 224 × 256, slice thickness 1 mm. All anatomic and functional slices were obtained in transaxial planes parallel to the AC–PC line.

2.8. Data Analysis

Behavioral data analysis—To analyze the behavioral data from the sequential motor learning task and JHFT, we used an independent *t*-test and repeated measure ANOVA with time as the within-patient factor. Group (real rTMS versus sham) was designated as the between-patient factor for the parametric data with normal distribution to evaluate the effects of rTMS across all time points (pre-rTMS, post-rTMS, and 1 month later). We used Bonferroni's correction to address the problem of multiple comparisons (Bland, 2000). The corrected p-values less than 0.05 were considered to be statistically significant.

fMRI data analysis—The SPM5 software package (Wellcome Department of Imaging Neuroscience, University College London, London, U.K.) was used for analysis of fMRI data. In case patients had right brain lesions, the lesion side for all patients was set to the left side of the functional image by left-right flipping of the functional image prior to processing of functional images. All functional images were realigned to the first image, co-registered with the T1-weighted structural image, spatially normalised to the Montreal Neurological Institute (MNI) space, and spatially smoothed using an 8-mm Gaussian kernel.

Based on a general linear model in SPM5, a multisubject fixed effects model utilized contrast images from individual-level analysis (Friston et al., 1995; Ward et al., 2007). Contrast images of each subject were grouped for each intervention (real vs. sham) as a difference between two time points (post-rTMS – pre-rTMS). *t*-maps that resulted from these tests were given a threshold of $P < .001$ (uncorrected), and clusters comprising 5 or more simultaneously activated voxels were selected. In addition, we tested the contrast [$(\text{post} - \text{pre-rTMS})_{\text{real}} - (\text{post} - \text{pre-rTMS})_{\text{sham}}$] and [$(\text{post} - \text{pre-rTMS})_{\text{sham}} - (\text{post} - \text{prerTMS})_{\text{real}}$] to illustrate interaction effects between intervention and time. Interaction contrasts were inclusively masked with the contrast maps obtained for positive effects $(\text{post} - \text{pre-rTMS})_{\text{real}}$ and $(\text{post} - \text{pre-rTMS})_{\text{sham}}$, respectively, with a threshold of $P < .05$ (uncorrected). For the interaction effects, all clusters with more than 5 contiguous voxels were reported at an individual voxel height threshold of $P < .001$ (uncorrected). MRIcro software (MRIcro software, www.mricro.com) was used for matching of a Brodmann map to the MNI/ICBM single-subject MRI template.

3. Results

All patients successfully completed the experimental procedures for rTMS and motor training with no side effects. No difference in age, sex, handedness, type of stroke, time since stroke or RMT was observed between the groups (Table 1).

3.1. Behavioral Results

No differences in either MT or MA score were observed between the groups during baseline fMRI. The real rTMS group showed significant improvement in MA after completion of rTMS and motor training ($P < .05$, Fig. 3); however, the sham group did not. A significant interaction was observed between the type of intervention (real vs. sham) and time (pre-rTMS vs. post-rTMS) for MA [$F(1,28) = 4.62$, $P = .04$]. These findings suggest that real rTMS treatment resulted in improved MA compared to the sham group. No significant change in MT was observed in either group.

No differences in any of the subtasks in the JHFT were observed between the groups at baseline. Results from the JHFT revealed improved performance time for the simulated feeding subtask in the real rTMS group after training ($P < .05$, Fig. 3), but not in the sham group. This improvement lasted for 1 month following cessation of training. A significant interaction was found between type of intervention (real vs. sham) and time (pre-rTMS vs. post-rTMS vs. 1 month later) for performance of the simulated feeding task [$F(2,14) = 2.136$, $P = .044$]. These findings suggest that compared to the sham group, real rTMS treatment improved performance in the simulated feeding task lasting 1 month after treatment. However, other subtasks and total JHFT scores failed to show significant changes in either of the groups.

3.2. Functional Imaging Results

When compared to their pre-rTMS fMRI, the sham group showed significantly increased activation in the supplementary motor area (SMA) of the affected hemisphere, sensorimotor

cortex, and bilateral cerebellar hemisphere, supramaginal gyrus, putamen, and insula of the unaffected hemisphere (uncorrected $P < .001$) (Table 2) (Fig. 4A).

By contrast, following rTMS intervention, patients in the real rTMS group showed significantly enhanced activation in the SMA, superior parietal lobe of the affected hemisphere, caudate nucleus and thalamus of the bilateral hemisphere, and insular cortex of the unaffected hemisphere, when compared to their pre-rTMS fMRI (uncorrected $P < .001$) (Table 2) (Fig. 4B).

As highlighted in Table 2 and Fig. 4C, brain areas that are associated with a significant interaction between intervention (real > sham) and time (post-rTMS > pre-rTMS) were observed in the sensorimotor cortex of the affected hemisphere (coordinates; x = -34, y = -36, z = 60, Z score = 4.47, cluster = 98), thalamus of the affected hemisphere (coordinates; x = -18, y = -16, z = 18, Z score = 5.47, cluster = 61), and caudate nucleus of the unaffected hemisphere (coordinates; x = 8, y = 6, z = 12, Z score = 4.21, cluster = 37) (uncorrected $P < .001$). Compared to pre-rTMS fMRI, no significant decreases in activation were observed after rTMS in either the real or sham group (uncorrected $P < 0.001$).

4. Discussion

To the best of our knowledge, this is the first neuroimaging study to provide evidence of modulation of the brain motor network associated with repeated sessions of high-frequency rTMS coupled with motor training. Unveiling of the mechanisms of rTMS-induced modulation in motor function and motor network reorganization has theoretical and clinical implications. As predicted by our hypothesis, repeated sessions of high-frequency rTMS over the M1 coupled with motor training induced modulatory effects in the motor networks that were demonstrable by fMRI and accompanied by enhancement of motor performance. On the other hand, evidence of the transfer of the rTMS effect to long-term functional recovery of the hand was insufficient and only partially established.

Significant clinical effects have been achieved with high-frequency rTMS in individuals with motor impairment (Pascual-Leone et al., 1994; Siebner et al., 2000; Kim et al., 2006). Demonstration of longer lasting effects after stimulation is important for promotion of therapeutic use of high-frequency rTMS. Some attempts have been made to obtain a greater and longer lasting benefit of rTMS by repeated sessions of stimulation for several days (Khedr et al., 2005), or by a different stimulation paradigm, such as theta burst stimulation (Talelli et al., 2007) or dual paradigm (Uy et al., 2002). In this study, we coupled rTMS with motor training. Even though the behavioral data comparing the post-rTMS performance between the real and sham groups showed a limited result, our results demonstrated that combining rTMS with motor training might enhance the effects of motor training alone (preceded by sham rTMS) on hand function. In our study, one task (simulated feeding) in the JHFT showed a significant lasting effect, while the other tasks in JHFT or total score showed no significant difference. It is well known that the JHFT has a capacity for detection of performance changes in tasks that resemble ADLs (Jebsen et al., 1969; Hackel et al., 1992), this result might represent a relatively low inter-task transfer to the motor system. However, it does not necessarily mean a low efficacy of rTMS to improve functions itself. A small number of participants might be also one of the reasons for our insignificant results. Therefore, this study alone could not demonstrate the beneficial effects of rTMS and motor training on improvement of hand function that last for a month following cessation of stimulation, and this topic should be further investigated.

After training, both groups showed increased activation of distinct areas of the brain that are associated with sensorimotor processing and learning. However, the activation pattern

between the two groups was different. The sham group showed significant activation in the sensorimotor cortex, SMA, cerebellar hemisphere of the ipsilesional brain and sensorimotor cortex, supramaginal gyrus, putamen, insula, and cerebellar hemisphere of the contralesional brain. These results appeared to reflect the effects of complex finger motor training in unilateral stroke patients, which showed increased activation in the widespread contralesional hemisphere. On the other hand, the real rTMS group showed a distinct pattern of activation changes, with significantly enhanced activation in the affected SMA, superior parietal lobe, caudate nucleus, thalamus of the ipsilesional brain and unaffected insular cortex, caudate nucleus, and thalamus of the contralesional brain. Thus, the real group showed more ipsilesional activations than the sham rTMS group. Previous studies have addressed changes in brain activity associated with motor improvement after stroke (Strafella et al., 2001; Holler et al., 2006). Johansen-Berg et al (Johansen-Berg et al., 2002) reported on the association of motor improvement after stroke with increased activity in ipsilesional areas of the brain and decreased activity in contralesional areas that are associated with sensorimotor processing. Ward et al. (Ward et al., 2003) reported that recovery of motor function after stroke was correlated with focusing of activation and that initial widespread activation of areas of the brain that are associated with sensorimotor processing became less prominent. Our results demonstrate that improvements in motor function induced by rTMS with motor training appear to have an association with a shift in laterality and focusing of activation. However, it could not be clearly stated that the fMRI results were causally related to the respective performance improvement, since no correlation analysis was performed between fMRI and behavioral data.

Both motor training and rTMS could result in increased activation of distinct brain areas that are associated with sensorimotor processing and learning. Previous studies have shown that subthreshold stimulation with high-frequency rTMS over the motor cortex induced activation in distant areas of the cortico-subcortical network, thalamus, and cerebellum, with no activation of the site of direct stimulation (Bestmann et al., 2004, 2005; Yoo et al., 2008). Results from our recent neuroimaging study also demonstrated a short-term modulatory effect by rTMS on the sensorimotor network in the basal ganglia, thalamus, cerebellum, and several cortical areas (Yoo et al., 2008). Compared to results from our previous study of the short-term effect of rTMS (Yoo et al., 2008), the present findings certainly showed more distinguishable activation of cortico-basal ganglia-thalamocortical circuits, including the caudate nucleus and ventrolateral thalamus. Activation of the caudate nucleus and thalamus was distinct in the real rTMS group, and a significant interaction effect was demonstrated after multiple comparisons. These changes in brain activity reflect rTMS modulation of subcortical motor circuitry activity and might contribute to the long-lasting effect of motor performance in the real rTMS group. The mechanisms though which modulation of distinct neural networks leading to behavioral and motor differences between the real and sham rTMS groups are unclear. Further study will be needed to elucidate these processes.

Despite some limitations previously mentioned, results from this study provide novel insights into mechanisms of action of rTMS-primed motor training for patients with motor disorder after stroke. Repeated rTMS over the M1 coupled with motor training resulted in better enhancement of motor performance compared to motor training with sham stimulation, but with a limited transfer effect to functional hand movement. As revealed by fMRI, the effects of real rTMS appear to have an association with modulation of activity along sensorimotor cortico-basal ganglia-thalamocortical circuits.

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References

Ackerley SJ, Stinear CM, Barber PA, Byblow WD. Combining theta burst stimulation with training after subcortical stroke. Stroke. 2010; 41(7):1568–1572. [PubMed: 20489170]

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci. 2004; 19(7):1950–1962. [PubMed: 15078569]

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. Neuroimage. 2005; 28(1):22–29. [PubMed: 16002305]

Bland, M. An introduction to medical statistics. 3rd ed.. Oxford University Press; Oxford: 2000.

Brasil-Neto JP, Cohen LG, Panizza M, Nilsson J, Roth BJ, Hallett M. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J Clin Neurophysiol. 1992; 9(1):132–136. [PubMed: 1552001]

Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol. 2006; 117(12):2584–2596. [PubMed: 16890483]

Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R. Analysis of fMRI time-series revisited. Neuroimage. 1995; 2(1):45–53. [PubMed: 9343589]

Hackel ME, Wolfe GA, Bang SM, Canfield JS. Changes in hand function in the aging adult as determined by the Jebsen Test of Hand Function. Phys Ther. 1992; 72(5):373–377. [PubMed: 1631206]

Holler I, Siebner HR, Cunnington R, Gerschlager W. 5 Hz repetitive TMS increases anticipatory motor activity in the human cortex. Neurosci Lett. 2006; 392(3):221–225. [PubMed: 16203086]

Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. Arch Phys Med Rehabil. 1969; 50(6):311–319. [PubMed: 5788487]

Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain. 2002; 125(Pt 12): 2731–2742. [PubMed: 12429600]

Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry. 2005; 76(6):833–838. [PubMed: 15897507]

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(2):181–185. [PubMed: 15331148]

Kim YH, You SH, Ko MH, Park JW, Lee KH, Jang SH, Yoo WK, Hallett M. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. Stroke. 2006; 37(6):1471–1476. [PubMed: 16675743]

Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cohen LG, Hallett M. Akinesia in Parkinson's disease. I. Shortening of simple reaction time with focal, single-pulse transcranial magnetic stimulation. Neurology. 1994; 44(5):884–891. [PubMed: 8190292]

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 1994; 91(2):79–92. [PubMed: 7519144]

Siebner HR, Mentschel C, Auer C, Conrad B. Repetitive transcranial magnetic stimulation has a beneficial effect on bradykinesia in Parkinson's disease. Neuroreport. 1999; 10(3):589–594. [PubMed: 10208595]

Siebner HR, Peller M, Willoch F, Minoshima S, Boecker H, Auer C, Drzezga A, Conrad B, Bartenstein P. Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. Neurology. 2000; 54(4):956–963. [PubMed: 10690992]

Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci. 2001; 21(15):RC157. [PubMed: 11459878]

Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain. 2003; 126(Pt 12):2609–2615. [PubMed: 12937078]

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(12): 2681–2686. [PubMed: 16254224]

Takeuchi N, Tada T, Toshima M, Matsuo Y, Ikoma K. 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. [PubMed: 19894000]

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. [PubMed: 17166765]

Uy J, Ridding MC, Miles TS. Stability of maps of human motor cortex made with transcranial magnetic stimulation. Brain Topogr. 2002; 14(4):293–297. [PubMed: 12137362]

Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain. 2003; 126(Pt 11):2476–2496. [PubMed: 12937084]

Ward NS, Newton JM, Swayne OB, Lee L, Frackowiak RS, Thompson AJ, Greenwood RJ, Rothwell JC. The relationship between brain activity and peak grip force is modulated by corticospinal system integrity after subcortical stroke. Eur J Neurosci. 2007; 25(6):1865–1873. [PubMed: 17432972]

Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, Hallett M. Use and safety of a new repetitive transcranial magnetic stimulator. Electroencephalogr Clin Neurophysiol. 1996; 101(5):412–417. [PubMed: 8913194]

Wickens JR, Reynolds JN, Hyland BI. Neural mechanisms of reward-related motor learning. Curr Opin Neurobiol. 2003; 13(6):685–690. [PubMed: 14662369]

Yoo WK, You SH, Ko MH, Tae Kim S, Park CH, Park JW, Hoon Ohn S, Hallett M, Kim YH. High frequency rTMS modulation of the sensorimotor networks: behavioral changes and fMRI correlates. Neuroimage. 2008; 39(4):1886–1895. [PubMed: 18086536]

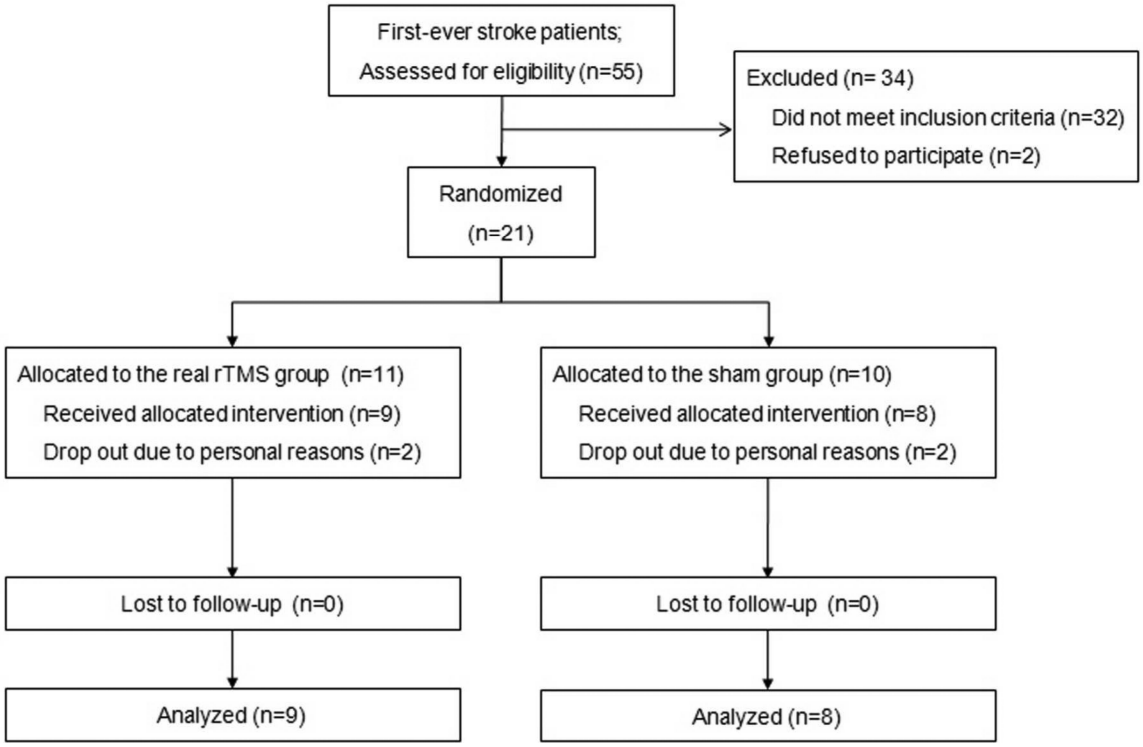

Fig. 1.
Randomization Process of Subjects by CONSORT diagram

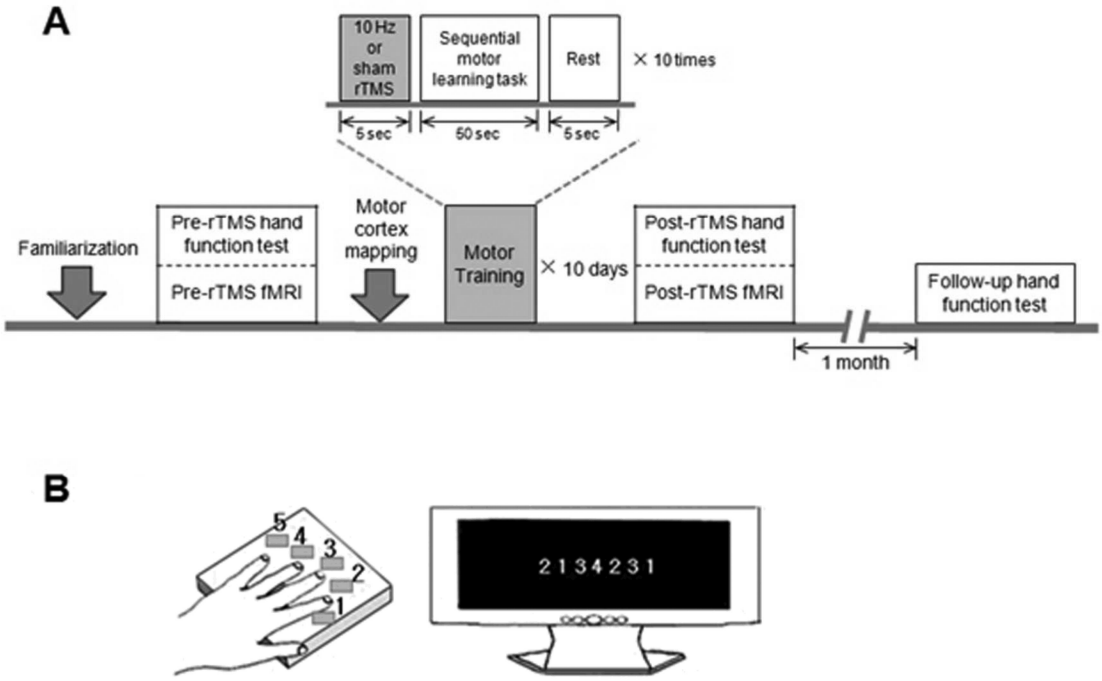

Fig. 2.

Experimental design. **A.** rTMS and motor training. **B.** Sequential finger training task.

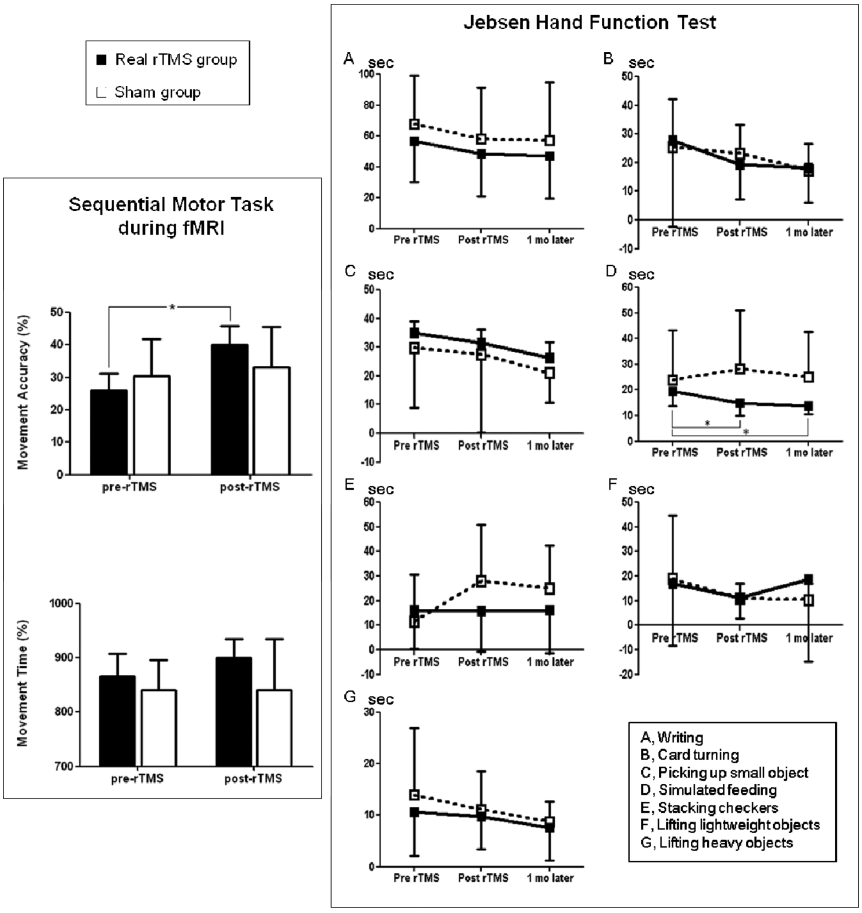

Fig. 3.

Behavioral results. **Left**: Changes in Motor Performance during fMRI before and after rTMS. Upper: The real rTMS group showed significant improvement in movement accuracy with interaction effect between time and intervention. Lower: No significant changes in movement time were observed in either group. **Right**: Results of the Jebsen hand function test before, after, and 1 month after rTMS. The real rTMS group showed significant improvement in performance time for the simulated feeding task (D) with a significant interaction effect between time (pre-rTMS vs. post-rTMS vs. I month later) and type of intervention (real vs. sham stimulation). * $p < 0.05$; comparison with before rTMS sessions. Error bars indicate the standard deviation.

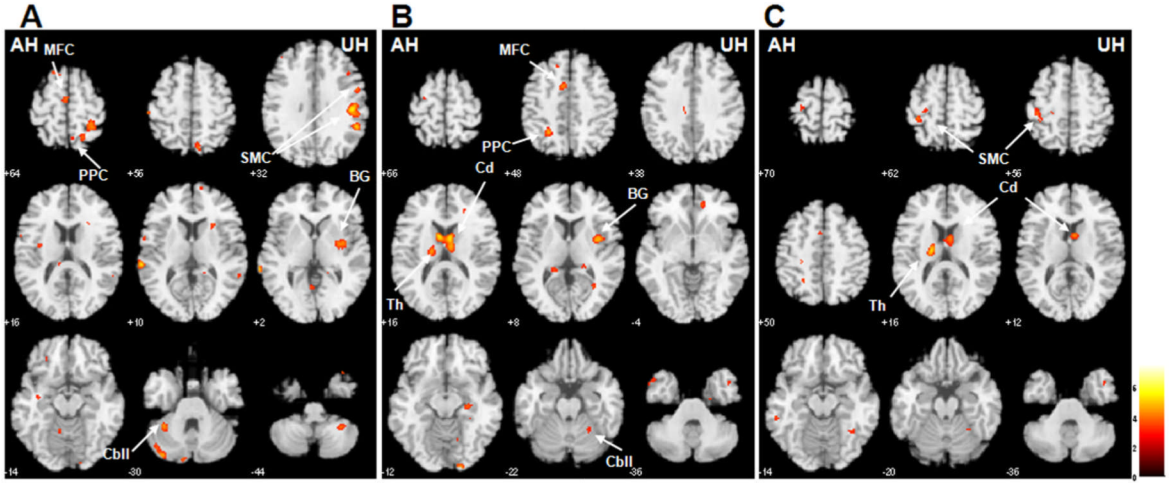

Fig. 4.

A-B. fMRI results for performance of the sequential finger motor task in the sham (A) and rTMS (B) groups. **C.** The ipsilesional sensorimotor cortex, ipsilesional thalamus, and contralesional caudate nucleus were defined as areas of significant interaction between the real and sham groups after rTMS intervention. AH, Affected hemisphere; UH, Unaffected hemisphere; SMC, Sensorimotor cortex; MFC, Medial frontal cortex; PPC, Posterior parietal cortex; Cbll, Cerebellum; BG, Basal ganglia; Cd, Caudate nucleus; Th, Thalamus

Table 1

Demographic and Clinical Characteristics of the Patients

No.	Sex	Age (yrs)	Handedness	Brain Lesion	Type of Stroke	Risk Factors	TSS (mo)	RMT (%)
Real								
1	M	59	Rt	Lt. Pons	I	DM, Dyslipid	9	55
2	M	53	Rt	Lt. CR	I	HTN, Alc, Sm	5	50
3	M	46	Rt	Lt. F-P	I	A-fib, Sm	5	68
4	F	59	Rt	Lt. Pons	I	DM, HTN	17	90
5	M	70	Rt	Lt. CR	I	HTN	6	50
6	F	55	Rt	Rt. BG, CR	H	HTN	43	50
7	M	60	Rt	Lt. BG	H	None	8	54
8	M	75	Rt	Rt. CR	I	HTN, Alc, Sm	7	40
9	F	46	Rt	Rt. CR	I	HTN	6	60
Mean	M=6 ; F=3	58.1			I=7 H=2		11.8	57.4
Sham								
1	F	60	Rt	Lt. Pons	I	DM	6	54
2	F	52	Rt	Lt. CR	I	HTN	9	43
3	F	76	Rt	Rt. Frontal	I	HTN	6	65
4	F	65	Rt	Rt. Th, IC	H	None	12	68
5	M	58	Rt	Lt. Pons	I	HTN, Dyslipid, Sm	9	86
6	M	47	Rt	Lt. Pons	I	DM, Smoking	7	78
7	M	73	Rt	Rt. BG, CR	I	HTN, Dyslipid, Alc	10	48
8	M	45	Rt	Lt. BG, CR	I	DM, HTN	6	44
Mean	M=4 ; F=4	59.5			I=7 H=1		8.1	60.8

TSS, time since stroke; RMT, resting motor threshold; M, male; F, female: Rt, right; Lt, left; CR, coronaradiata; F-P, frontoparietal; BG, basal ganglia; Th, thalamus; I, infarction; H, hemorrhage; DM, diabetes mellitus; Dyslipid, dyslipidemia; HTN, hypertension; Alc, alcohol; Sm, smoking

Table 2

rTMS-induced Motor Network Activation

Brain region	Laterality	Brodmann area	Coordinates			Voxel count	*Z*-score	*P*-value
			x	y	z			
rTMS group								
Superior parietal gyrus	AH	7	-24	-50	50	55	4.57	<0.001
SMA	AH	6, 24, 32	-4	8	50	75	4.37	<0.001
Caudate nucleus	AH		-8	4	14	25	5.17	<0.001
	UH		8	2	16	51	5.09	<0.001
Thalamus	UH		8	-10	18	86	4.90	<0.001
	AH		-16	-16	18	73	4.79	<0.001
Insula	UH	48	36	0	10	78	4.96	<0.001
Sham group								
SMA	AH	6	-2	-10	66	27	4.31	<0.001
Sensorimotor cortex	UH	2, 3	48	-24	34	68	5.29	<0.001
	UH	2, 3, 7	30	-44	64	66	4.19	<0.001
	UH	5, 7	58	0	28	92	4.65	<0.001
	AH	1, 3	-52	-28	58	14	4.79	<0.001
Supramarginal gyrus	UH	48	50	-22	32	316	5.42	<0.001
Putamen	UH	48	34	-6	2	49	4.33	<0.001
Insula	UH	48	38	-6	0	56	4.25	<0.001
Cerebellar hemisphere	AH	19	-36	-82	-28	122	4.65	<0.001
	AH	37	-34	-46	-32	105	4.50	<0.001
	AH	18, 19	-10	-52	-20	88	4.25	<0.001
	UH		34	-46	-42	59	4.12	<0.001
rTMS group > Sham group								
Sensorimotor cortex	AH	2, 3, 4	-34	-36	60	98	4.47	<0.001
Thalamus	AH		-18	-16	18	61	5.47	<0.001
Caudate nucleus	UH		8	6	12	37	4.21	<0.001

AH, affected hemisphere; UH, unaffected hemisphere; SMA, supplementary motor area