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ORIGINAL REPORT

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OVER BILATERAL HEMISPHERES ENHANCES MOTOR FUNCTION AND TRAINING EFFECT OF PARETIC HAND IN PATIENTS AFTER STROKE

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Objective: **The interhemispheric competition model proposes that the functional recovery of motor deficits in patients after stroke can be achieved by increasing the excitability of the affected hemisphere or decreasing the excitability of the unaffected hemisphere. We investigated whether bilateral repetitive transcranial magnetic stimulation might improve the paretic hand in patients after stroke.**
Design: **A double-blind study.**
Patients: **Thirty patients with chronic subcortical stroke.**
Methods: **The patients were randomly assigned to receive 1 Hz repetitive transcranial magnetic stimulation over the unaffected hemisphere, 10 Hz repetitive transcranial magnetic stimulation over the affected hemisphere, or bilateral repetitive transcranial magnetic stimulation comprising both the 1 Hz and 10 Hz repetitive transcranial magnetic stimulation. All patients underwent motor training following repetitive transcranial magnetic stimulation.**
Results: **Bilateral repetitive transcranial magnetic stimulation and 1 Hz repetitive transcranial magnetic stimulation immediately improved acceleration in the paretic hand. Compared with 1 Hz repetitive transcranial magnetic stimulation, bilateral repetitive transcranial magnetic stimulation decreased the inhibitory function of the affected motor cortex and enhanced the effect of motor training on pinch force. Moreover, this effect of motor training lasted for one week. On the other hand, 10 Hz repetitive transcranial magnetic stimulation had no effect on the motor function.**
Conclusion: **Bilateral repetitive transcranial magnetic stimulation improved the motor training effect on the paretic hand of patients after stroke more than unilateral stimulation in pinch force; this might indicate a new neurorehabilitative strategy for stroke.**

Key words: repetitive transcranial magnetic stimulation, motor training, stroke, neuronal plasticity, rehabilitation.

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method that can change the excitability of the human cortex for at least several minutes. The nature of the after-effect depends on the frequency, intensity, and pattern of stimulation. High-frequency rTMS (more than 5 Hz) increases cortical excitability, whereas low-frequency rTMS (1 Hz or less) leads to suppression of cortical excitability (1).

The interhemispheric competition model proposes that motor deficits in patients after stroke are due to a reduced output from the affected hemisphere and excess transcallosal inhibition of the affected hemisphere from the unaffected hemisphere (2, 3). Therefore, improvement of motor deficit could be achieved by increasing the excitability of the affected hemisphere or decreasing the excitability of the unaffected hemisphere by using rTMS. Research has demonstrated that low-frequency rTMS over the unaffected hemisphere decreased the excitability of the unaffected hemisphere and improved the motor function of the paretic hand in patients after stroke (4, 5). High-frequency rTMS over the affected hemisphere also improved the motor function of the paretic hand by increasing the excitability of the affected motor cortex (6). Moreover, low-frequency rTMS over the unaffected hemisphere improved the motor training effect (7). Therefore, the application of rTMS has been proposed to promote functional recovery of the paretic hand in stroke patients owing to the induced neuroplasticity.

Considering the interhemispheric competition model of patients after stroke, adding high-frequency rTMS over the affected hemisphere along with low-frequency rTMS over the unaffected hemisphere might improve the motor function of the paretic side in the patients after stroke by a greater degree than would unilateral rTMS alone. To our knowledge, there is no report that has combined both high-frequency and low-frequency rTMS in patients after stroke. In the present study, we hypothesized that bilateral rTMS might improve the motor training effect on the paretic hand in patients after stroke.

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METHODS

The study population comprised 30 patients after stroke. The inclusion criteria were as follows: (*i*) first-time stroke of more than 6 months duration; (*ii*) only subcortical lesion confirmed by magnetic resonance imaging (MRI); (*iii*) motor deficits of the unilateral upper limb that had improved to the extent that patients could perform pinching tasks; and (*iv*) normal Mini-Mental State Examination score. The exclusion criteria included the following: (*i*) severe internal carotid artery stenosis; (*ii*) seizure; and (*iii*) an intracranial metallic implant. Participants were randomly divided into 3 groups (Table I). The unaffected rTMS group received rTMS over the unaffected hemisphere, the affected rTMS group received rTMS over the affected hemisphere, and the bilateral rTMS group received rTMS over both the unaffected and affected hemispheres. All the subjects gave their written informed consent, and the protocol was approved by the local ethics committee of the Hokkaido University Graduate School of Medicine.

The measurements for assessing the motor function (acceleration and pinch force) were performed at pre-rTMS and post-rTMS (Post 1: immediately after the rTMS; Post 2: after motor training; and Post 3: 7 days after rTMS). The parameters of TMS (i.e. resting motor threshold (rMT), amplitude of motor evoked potentials (MEPs), and intracortical inhibition (ICI)) were evaluated at pre-rTMS, Post 1, and Post 3. We did not evaluate the rMT, MEPs, and ICI immediately after motor training (Post 2) because the motor performance modulates the excitability of the motor cortex and ICI (9). Patients and the experimenter performing the evaluations were blinded to the type of stimulation.

Single-pulse TMS was performed using a 70-mm figure-of-8 coil and Magstim 200 (Magstim Co., Dyfed, UK), and rTMS was applied using the same coil and a Magstim Rapid stimulator (Magstim Co.). The coil was placed tangentially over the motor cortex at an optimal site for the first dorsal (FDI) muscle. The optimal site was defined as the location where stimulation at a slightly suprathreshold intensity elicited the largest MEPs in the FDI. This position was marked on the scalp and used throughout the experiment. The rMT was determined separately for each stimulator and defined as the lowest stimulator output that could produce MEPs with a peak-to-peak amplitude greater than 50 microvolts in at least half of the 10 trials. The peak-to-peak amplitude of 10 averaged FDI responses obtained at 120% rMT was also determined by using the Magstim 200 (Magstim Co.).

Paired-pulse stimulation was performed to investigate ICI in the affected motor cortex. To apply paired pulses, a figure-of-8 coil was connected to a Bistim device (Magstim Co.) that triggered 2 magnetic stimulators. The stimulus intensity of the first conditioning shock was 80% rMT and that of the second pulse was 120% rMT. We performed the tests at interstimulus intervals (ISI) of 2 and 3 msec. Ten trials were recorded for each ISI, and unconditioned trials (controls) were recorded during complete relaxation. The paired stimulation with each ISI was randomly mixed with the control stimulation. The MEPs amplitudes obtained by paired-pulse stimulation were expressed as a percentage of the mean control MEPs amplitude, and the ICI was then calculated by averaging these values. We obtained ipsilesional TMS data from 19 patients. The exclusion of patients with no ipsilesional TMS data might have weakened the power of the ipsilesional TMS parameter analysis. However, we excluded patients who did not display MEPs in the affected hemisphere from the ipsilesional TMS study section, i.e. patients in whom MEPs were not induced even at 100% stimulator output (4 patients in bilateral rTMS group, 3 patients in unaffected rTMS group, and 4 patients, affected rTMS group).

We alternatively applied the 1 Hz rTMS over the unaffected hemisphere and 10 Hz rTMS over the affected hemisphere by using 2 Magstim Rapid stimulators (Magstim Co.). This was because it was difficult to apply rTMS over the affected and unaffected hemispheres simultaneously due to the mechanical limitation of the overlap of the 2 figure-of-8 coils in the patient's head. Fig. 1 shows the rTMS protocols. In the bilateral rTMS group, the patients were stimulated at 90% rMT, 1 Hz, and 50 sec train duration over the unaffected hemisphere (50 stimuli) alternating with 90% rMT, 10 Hz, and 5 sec train duration over the affected hemisphere (50 stimuli), with an interval of 5 sec for 20 times, resulting in 1000 stimuli for each hemisphere. High-frequency rTMS protocols with a lower stimulator intensity are desirable for preventing seizures in patients after stroke (10). The rMT of the affected hemisphere is often higher than that of the unaffected hemisphere in patients after stroke. Therefore, we used the stimulation power according to the rMT of the unaffected hemisphere at both the 1 Hz and 10 Hz rTMS in order to avoid a risk of seizure. In the event that MEPs of the affected hemisphere could not be elicited at the maximal stimulator output, the coil was fixed at a location over the affected hemisphere that was homologous to the optimal site of the unaffected hemisphere. In the unaffected rTMS group, active rTMS was applied over the unaffected hemisphere and sham stimulation was applied over the affected hemisphere at the same frequency and intensity used for bilateral rTMS. Sham stimulation was applied over the optimal site by positioning the coil perpendicular to the scalp (11). Similarly, in the affected rTMS group, active rTMS was applied over the affected hemisphere and sham stimulation was applied over the unaffected hemisphere. After rTMS, the patients performed a pinching task for 15 min as motor training, as described in a previous report (12). During the pinching task, the patients were asked to perform a metronome-paced pinch of their index finger and thumb of the affected hand as fast as possible (frequency individualized between 0.3 and 0.5 Hz). For assessing the motor function, we checked the pinch force and acceleration as described previously (5). In each session, 10 pinch force values and 15 acceleration values were averaged. The patients were allowed to familiarize themselves with this motor evaluation on the previous day of the rTMS experiment.

The clinical characteristics data (Table I) were compared between the bilateral rTMS, unaffected rTMS, and affected rTMS groups by analysis of variance (ANOVA) or the χ^2 test, depending on the variable type. The effects of rTMS and motor training were evaluated using an ANOVA for repeated measures with TIME as a within-subjects factor and CONDITION (bilateral rTMS, unaffected rTMS, and affected rTMS) as a between-subjects factor. A *post-hoc* analysis was performed with Bonferroni's correction. Any possible correlation between the changes in the various parameters was determined by Pearson's correlation coefficient test as an exploratory analysis. All data were normalized by conversion to percentage change from the mean values of pre-rTMS.

Table I. *Clinical characteristics of patients after stroke*

	Bilateral rTMS group $n=10$	Unaffected rTMS group $n=10$	Affected rTMS group $n=10$
Age, years, mean (SD)	60.9 (12.4)	58.1 (12.3)	59.0 (12.7)
Gender, *n*			
Male	8	7	7
Female	2	3	3
Paretic side, *n*			
Right	6	7	5
Left	4	3	5
Duration after stroke, months, mean (SD)	26.1 (28.0)	24.7 (28.9)	35.6 (38.7)
Fugl-Meyer scale, mean (SD)			
Total, %	66.4 (17.5)	71.8 (17.3)	66.2 (21.5)
Hand, %	67.1 (26.2)	71.7 (23.9)	64.4 (24.2)

Fugl-Meyer scale (8) (percentages of maximum points in the upper limb (66 points) and in hand (24 points)).

rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation.

RESULTS

The subjects did not report any adverse side-effects during the course of the study. No difference was observed between the bilateral, affected, and unaffected rTMS groups with regard

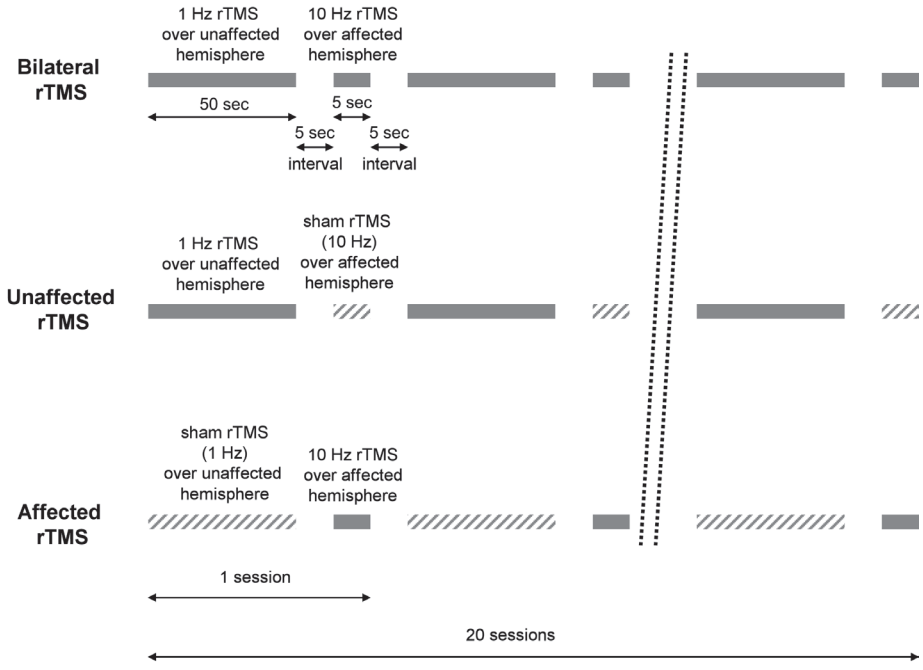

Fig. 1. The protocol of repetitive transcranial magnetic stimulation (rTMS). In the bilateral rTMS group, the patients were stimulated at 1 Hz and 50 sec train duration over the unaffected hemisphere, alternating with 10 Hz and 5 sec train duration over the affected hemisphere, with an interval of 5 sec for 20 times. In the unaffected rTMS group, active rTMS (*solid grey bar*) was applied over the unaffected hemisphere and sham stimulation (*hashed grey bar*) was applied over the affected hemisphere at the same frequency and intensity used for bilateral rTMS. Similarly, in the affected rTMS group, active rTMS was applied over the affected hemisphere and sham stimulation was applied over the unaffected hemisphere.

to age, gender, paretic side, the duration after stroke, or the Fugl-Meyer scale (Table I). There was no difference between the bilateral, affected, and unaffected rTMS groups with regard to acceleration, pinch force, amplitude of the contralesional MEPs, amplitude of the ipsilesional MEPs, ICI of the affected hemisphere, rMT of unaffected hemisphere, or rMT of affected hemisphere in pre-rTMS (Table II).

Fig. 2 shows the change in motor function after rTMS and motor training. A repeated-measures ANOVA showed a significant interaction between TIME and CONDITION with respect to acceleration ($F6,81 = 2.743$, $p = 0.018$) and pinch force ($F6,81 = 5.539$, $p < 0.001$). It also showed a significant effect of TIME on both acceleration ($F6,81 = 21.014$, $p < 0.001$) and pinch force ($F6,81 = 31.191$, $p < 0.001$). The *post-hoc* test revealed an improvement in acceleration immediately after bilateral rTMS (pre-rTMS vs Post 1: $p = 0.002$) and unaffected rTMS (pre-rTMS vs Post 1: $p = 0.008$). The motor training did not induce an additional improvement in acceleration after bilateral rTMS or unaffected rTMS. These improvements in acceleration lasted for one week after bilateral rTMS (pre-rTMS vs Post 3: $p < 0.001$) and unaffected rTMS (pre-rTMS vs Post 3: $p < 0.001$). Compared with unaffected rTMS, bilateral rTMS increased the acceleration during all the sessions, albeit not significantly. In the affected rTMS group, the *post-hoc* test did not show a significant improvement in acceleration after rTMS or motor training. Bilateral rTMS (Post 1: $p = 0.034$; Post 2: $p < 0.001$; Post 3: $p = 0.001$) and unaffected rTMS (Post 2: $p < 0.001$; Post 3: $p = 0.022$) resulted in a greater increase in acceleration than affected rTMS.

The *post-hoc* test did not show a significant improvement in pinch force immediately after bilateral rTMS or unaffected rTMS. However, the motor training induced an improvement in pinch force after bilateral rTMS (pre-rTMS vs Post 2: $p < 0.001$; Post 1 vs Post 2: $p < 0.001$) and unaffected rTMS (pre-rTMS vs Post 2: $p = 0.008$). These improvements in pinch force also lasted for one week after bilateral rTMS (pre-rTMS vs Post 3: $p < 0.001$) and unaffected rTMS (pre-rTMS vs Post 3: $p = 0.009$). The effect of motor training after rTMS on pinch force was more enhanced by bilateral rTMS than by unaffected rTMS (Post 2: $p = 0.004$; Post 3: $p = 0.010$). In the affected rTMS group, the *post-hoc* test did not show a significant improvement in pinch force after rTMS or motor training. Bilateral rTMS increased the pinch force compared with affected rTMS (Post 2: $p < 0.001$; Post 3: $p < 0.001$).

Table II. *Physiological parameters of pre-repetitive transcranial magnetic stimulation (rTMS)*

	Bilateral rTMS group	Unaffected rTMS group	Affected rTMS group
Acceleration, m/sec^2, mean (SD)	1.9 (1.7)	1.9 (1.2)	2.2 (1.4)
Pinch force, N, mean (SD)	25.7 (10.3)	27.7 (10.2)	30.1 (14.2)
Amplitude of contralesional MEPs, μV, mean (SD)	696.3 (619.7)	797.4 (828.8)	664.6 (585.5)
Amplitude of ipsilesional MEPs, μV, mean (SD)	337.0 (293.2)	401.3 (320.7)	432.0 (307.3)
ICI of affected hemisphere, %, mean (SD)	59.2 (16.6)	63.4 (24.7)	70.7 (28.3)
rMT of unaffected hemisphere, %, mean (SD)	48.1 (7.4)	48.3 (14.5)	50.5 (8.3)
rMT of affected hemisphere, %, mean (SD)	62.0 (12.5)	55.3 (14.4)	56.0 (16.1)

ICI: intracortical inhibition; MEPs: motor evoked potentials; rMT: resting motor threshold: SD: standard deviation.

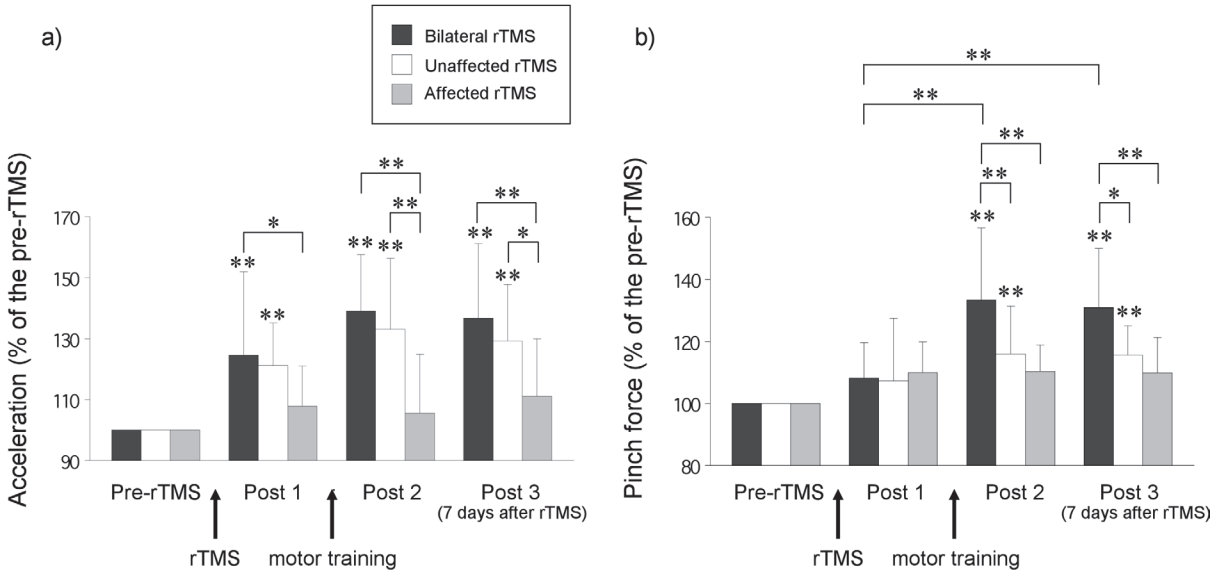

Fig. 2. The effects of repetitive transcranial magnetic stimulation (rTMS) and motor training; (a) acceleration; (b) pinch force. Bilateral and unaffected rTMS improved the acceleration of the paretic hand (pre-TMS vs Post 1: bilateral, $p=0.002$; unaffected, $p=0.008$) and this improvement in acceleration lasted for one week after rTMS and motor training (pre-TMS vs Post 3: bilateral, $p<0.001$; unaffected, $p<0.001$). The motor training improved the pinch force of the paretic hand after bilateral rTMS (pre-rTMS vs Post 2: $p<0.001$; Post 1 vs Post 2: $p<0.001$) and unaffected rTMS (pre-rTMS vs Post 2: $p=0.008$). This improvement in pinch force also lasted for one week after rTMS and motor training (pre-rTMS vs Post 3: bilateral, $p<0.001$; unaffected, $p=0.009$). The effect of motor training on pinch force was more enhanced by bilateral rTMS than by unaffected rTMS (Post 2: $p=0.004$; Post 3: $p=0.010$). *$p<0.05$; **$p<0.01$ (asterisk without a line indicates a p-value comparison with pre-rTMS); error bar, standard deviation.

Fig. 3 shows the change in the corticospinal excitability after rTMS. A repeated measures ANOVA for MEPs showed a significant interaction between TIME and CONDITION (contralesional MEPs: $F4,54=3.277$, $p=0.018$; ipsilesional MEPs: $F4,32=3.654$, $p=0.015$) and a significant effect of TIME on MEPs (contralesional MEPs: $F4,54=4.188$, $p=0.020$; ipsilesional MEPs: $F4,32=9.012$, $p<0.001$). The *post-hoc* test revealed that a decreased amplitude of contralesional MEPs was produced immediately by unaffected rTMS ($p=0.001$) but not by bilateral rTMS or affected rTMS. The *post-hoc* test revealed that an increased amplitude of ipsilesional MEPs was produced immediately by unaffected rTMS ($p<0.001$)

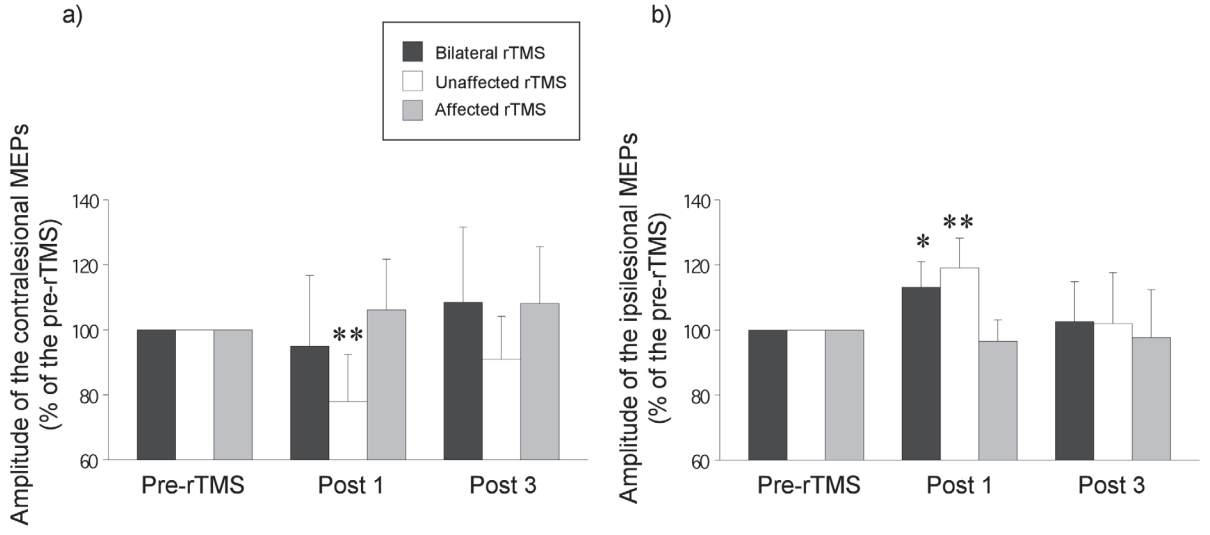

Fig. 3. The change in the corticospinal excitability after repetitive transcranial magnetic stimulation (rTMS). (a) Amplitude of the contralesional MEPs. (b) Amplitude of the ipsilesional motor evoked potentials (MEPs). Unaffected rTMS decreased the amplitude of contralesional MEPs (pre-rTMS vs Post 1: $p=0.001$) and increased the amplitude of ipsilesional MEPs (pre-rTMS vs Post 1: $p<0.001$). Bilateral rTMS increased the amplitude of ipsilesional MEPs (pre-rTMS vs Post 1: $p=0.021$). However, the changes induced by rTMS were observed to be diminished at 7 days after rTMS. *$p<0.05$; ** $p<0.01$; error bar, standard deviation.

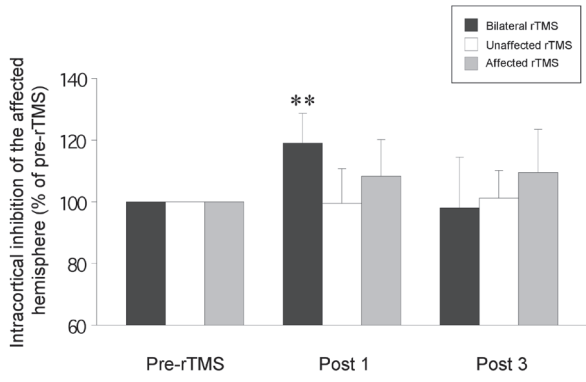

Fig. 4. The change in the intracortical inhibition after repetitive transcranial magnetic stimulation (rTMS). A decreased intracortical inhibition of the affected hemisphere was produced by bilateral rTMS (pre-rTMS vs Post 1: $p=0.002$). However, the change induced by rTMS was observed to be diminished at 7 days after rTMS. $^{**}p<0.01$; error bar, standard deviation.

and bilateral rTMS ($p=0.021$), but not by affected rTMS. There was no significant difference in the ipsilesional MEPs changes between bilateral rTMS and unaffected rTMS. The MEPs changes diminished at 7 days after bilateral rTMS and unaffected rTMS.

Fig. 4 shows the change in the inhibitory function of affected hemisphere after rTMS. A repeated measures ANOVA for ipsilesional ICI showed a significant interaction between TIME and CONDITION ($F4,32=3.021$, $p=0.032$) and a significant effect of TIME on ipsilesional ICI ($F4,32=3.398$, $p=0.046$). The *post-hoc* test revealed that a decreased ipsilesional ICI was produced immediately by bilateral rTMS (pre-rTMS vs Post 1: $p=0.002$) but not by unaffected rTMS or affected rTMS. However, the ICI change diminished at 7 days after bilateral rTMS.

A repeated-measures ANOVA for contralesional and ipsilesional rMT did not show a significant interaction between TIME and CONDITION; furthermore, no significant effect of CONDITION or TIME was observed. In both the bilateral and unaffected rTMS groups, the improvement in the motor function after rTMS (Post 1) or motor training (Post 2) showed no significant correlation with the age, duration after stroke, the Fugl-Meyer scale, and the changes in ipsilesional MEPs and ICI.

DISCUSSION

This study reports that bilateral rTMS and unaffected rTMS therapy can improve the motor training effect in the paretic hand of patients after stroke. Moreover, bilateral rTMS could improve the motor function more than unaffected rTMS. Our study results suggest that stimulating the affected hemisphere along with inhibition of the unaffected hemisphere by bilateral rTMS appears to improve the motor function of the paretic side in patients after stroke, while the procedure remains safe and well tolerated.

We found that 1 Hz rTMS over the unaffected hemisphere increased the corticospinal excitability of the affected hemisphere; this result is in agreement with previous reports (7). The inhibition of the excitability of the unaffected hemisphere by 1 Hz rTMS would result in a decrease in the transcallosal inhibition from the unaffected to the affected hemisphere and an increase in the excitability of the affected hemisphere (5, 7). The enhancement of motor cortex excitability appeared to be a necessity for motor learning (13). Therefore, artificially increasing cortical excitability with rTMS could facilitate motor learning and recovery after stroke (6, 7). However, bilateral rTMS could increase the corticospinal excitability of the affected hemisphere as well as could unaffected rTMS, despite the fact that bilateral rTMS could improve the motor training effect in the paretic hand more than unaffected rTMS. Therefore, in addition to increasing the cortical excitability of the affected hemisphere, bilateral rTMS might have another mechanism that could improve the motor function. By this other mechanism, the disinhibition induced by bilateral rTMS might contribute to the functional improvement of the paretic hand. Kobayashi et al. (14) have reported that 1 Hz rTMS over the motor cortex induced the disinhibition of the contralateral motor cortex, which might be induced by the disruption of transcallosal inhibition (14). High-frequency rTMS could also induce the disinhibition of the stimulated motor cortex (15). In this study, only affected rTMS or unaffected rTMS caused no change in the inhibitory function of the affected hemisphere, but bilateral rTMS could decrease the inhibitory function of the affected hemisphere by using 2 rTMS protocols that had the ability to induce disinhibition. A decrease in the inhibition unmasks the pre-existing, functionally latent neural networks around the lesion, thereby contributing to cortical reorganization (16). Based on these findings, the increased excitability and decreased inhibitory function of the affected motor cortex after bilateral rTMS might contribute to a more suitable environment for reorganization of the affected motor cortex by motor training.

A previous study (6) reported that high-frequency rTMS over the affected hemisphere improved the motor function of a paretic hand. However, in the present study, 10 Hz rTMS over the affected hemisphere had no effect on motor function. There are several possible reasons for this, as follows. First, we did not use a stereotactic system with integrated MRI data to stimulate the affected motor cortex; this might have resulted in inadequate stimulation because of the anatomical changes that occur after stroke. Secondly, we conducted a sham stimulation to ensure that the conditions between affected rTMS and bilateral rTMS were as similar as possible. However, it is possible that the patients could differentiate between the active and sham stimulations based on the physical scalp sensations; this might influence the results of affected rTMS. Thirdly, the stimulation power according to the rMT of the unaffected hemisphere might be too weak to increase the cortical excitability by only affected rTMS. This is because the rMT of the unaffected hemisphere is often lower than that of the affected hemisphere in stroke patients. Thus, the fact that affected rTMS had no effect on the motor function might also be because of the insufficient stimulation power.

Nevertheless, the method used in our study has some advantages. First, the use of a low-power stimulation for the affected hemisphere increased the safety of bilateral rTMS. Theoretically, compared with unaffected rTMS, bilateral rTMS involving direct high-frequency stimulation of the affected hemisphere can increase the excitability of the affected hemisphere to a greater extent; this is because high-frequency rTMS is known to increase the cortical excitability (1). However, there was no significant difference in the excitability of the affected hemisphere between bilateral rTMS and unaffected rTMS. Thus, bilateral rTMS may be a safe and well-tolerated procedure because it does not cause excessive excitability of the affected hemisphere. The fact that we did not perform affected rTMS and unaffected rTMS simultaneously is another advantage of our study. Nitsche et al. (17) had demonstrated that homeostatic plasticity acted when both excitability-changing protocols were applied simultaneously. If affected rTMS and unaffected rTMS are applied simultaneously, homeostatic plasticity might work to maintain the global network function within the normal physiological range, thereby nullifying the effects of both affected rTMS and unaffected rTMS. Future studies should therefore aim to clarify whether homeostatic plasticity can develop with simultaneous application of rTMS and transcranial direct current stimulations, which can stimulate small areas and can alter the cortical excitability as efficiently as rTMS.

In conclusion, our results have demonstrated that the combination of 1 Hz rTMS over the unaffected hemisphere and 10 Hz rTMS over the affected hemisphere could lead to an improvement in the motor function of the paretic hand of patients with chronic stroke. These findings will probably be pertinent to the design and optimization of neurorehabilitative strategies for stroke.

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