Background and Purpose—A recent report has demonstrated that the contralesional primary motor cortex (M1) inhibited the ipsilesional M1 via an abnormal transcallosal inhibition (TCI) in stroke patients. We studied whether a decreased excitability of the contralesional M1 induced by 1 Hz repetitive transcranial magnetic stimulation (rTMS) caused an improved motor performance of the affected hand in stroke patients by releasing the TCI.

Methods—We conducted a double-blind study of real versus sham rTMS in stroke patients. After patients had well-performed motor training to minimize the possibility of motor training during the motor measurement, they were randomly assigned to receive a subthreshold rTMS at the contralesional M1 (1 Hz, 25 minutes) or sham stimulation.

Results—When compared with sham stimulation, rTMS reduced the amplitude of motor-evoked potentials in contralesional M1 and the TCI duration, and rTMS immediately induced an improvement in pinch acceleration of the affected hand, although a plateau in motor performance had been reached by the previous motor training. This improvement in motor function after rTMS was significantly correlated with a reduced TCI duration.

Conclusions—We have demonstrated that a disruption of the TCI by the contralesional M1 virtual lesion caused a paradoxical functional facilitation of the affected hand in stroke patients; this suggests a new neurorehabilitative strategy for stroke patients. ([Stroke. 2005;36:2681-2686.])

Key Words: stroke ■ repetitive transcranial magnetic stimulation ■ corpus callosum ■ rehabilitation

It has been considered that if the brain was damaged by a stroke, the surviving structures and networks would compensate for the dysfunction.1 Various motor-related regions have been reported to contribute to motor recovery after a stroke.1–3 Of these motor-related regions, it seems clear that the ipsilesional primary motor cortex (M1) contributes to the motor recovery after a stroke,4 but the role of the contralesional M1 is still uncertain.1 A reaction time study using transcranial magnetic stimulation (TMS) has reported that the contralesional M1 did not contribute to motor recovery after a stroke.4 In addition, a recent study by Murase et al5 has investigated chronic stroke patients and demonstrated that the contralesional M1 inhibited the ipsilesional M1 via an abnormal transcallosal inhibition (TCI). Thus, it is possible that the contralesional M1 impairs, rather than facilitates, motor performance in some stroke patients. It has, therefore, been proposed by Ward and Cohen1 that a downregulation of the contralesional M1 might be effective for the facilitation of motor recovery after a stroke.

Repetitive TMS (rTMS) is a noninvasive method that can change the excitability of the human cortex for at least several minutes.6 In particular, a 1-Hz, low-frequency, rTMS applied to the M1 can induce a downregulation of M1 under stimulation.7 In the present study, we hypothesized that reducing the cortical excitability of the contralesional M1 by using 1-Hz rTMS may improve a motor performance of the affected hand in a stroke patient by releasing TCI from the contralesional M1. This hypothesis is consistent with a previous report that a dysfunctional unilateral hemisphere can modulate activity in the contralateral hemisphere, which can then result in a paradoxical functional facilitation.8 Moreover, a recent study of normal controls that demonstrated a facilitation in the opposite M1 and improvement of motor function of the ipsilateral hand after a unilateral M1 virtual lesion produced by 1-Hz rTMS9 appears to support our hypothesis.

Methods

The study group consisted of 20 patients with a first-time cerebral infarct (Table; mean age, 59.0 ±9.6 years). They were tested 6 months after a stroke. The patients had a subcortical infarction that was confirmed by MRI. All of the patients had a normal Mini-Mental State Examination score. Subjects were randomly divided into 2 groups; one group (10 patients) received real rTMS and the other group (10 patients) received sham stimulation. All of the subjects gave their written informed consent, and the protocol was approved.
Various measurements of the motor task (pinch force and acceleration) were obtained from the affected hand at pretraining (Baseline), post-training (Post-T), pre-rTMS, and post-rTMS (Post 1, immediately after rTMS; Post 2, 30 minutes after rTMS). Measures of TMS data [rest motor threshold (rMT), amplitude of the motor-evoked potentials (MEPs), and TCI duration] were evaluated at pre-rTMS and post-rTMS (Post 1 and Post 2). Figure 1 shows the time course of our experiment. TMS was performed with a 70-mm figure-8 coil and a Magstim 200 for single TMS and a Magstim Rapid stimulator (Magstim Company) for rTMS. The coil was placed tangentially over the contralesional M1 at the optimal site for the first dorsal interosseous (FDI) muscle. The optimal site was defined as the location where stimulation of a slightly suprathreshold intensity elicited the largest MEPs in the FDI. Electromyographic (EMG) activity was recorded from silver-silver-chloride electrodes positioned in a belly-tendon montage on the skin overlying the FDI, and the signal was amplified, filtered (50 to 2000 Hz) and digitized at a sampling rate of 5000 Hz for off-line analysis (Neuropack; Nihon Koden). The rMT was determined separately for each stimulator and defined as the lowest stimulator output that could activate MEPs with a peak-to-peak amplitude \( \geq 50 \) microvolts in at least half of the 10 trials. The peak-to-peak amplitude of 10 averaged re-

**Clinical Characteristics of Stroke Patients**

<table>
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<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Duration after Stroke, m</th>
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<th>FMS Upper Limb, %</th>
<th>Hand, %</th>
<th>Lesion Site</th>
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<td>58</td>
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<td>lt</td>
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<td>M</td>
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<td>58</td>
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<td>27</td>
<td>lt</td>
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FMS indicites Fugle-Meyer scale\(^{12}\) (percentages of maximum points in the upper limb \(66\) points and in hand \(24\) points); F, female; M, male; lt, left; rt, right.

by the local ethical committee of the Hokkaido University Graduate School of Medicine.

Various measurements of the motor task (pinch force and acceleration) were obtained from the affected hand at pretraining (Baseline), post-training (Post-T), pre-rTMS, and post-rTMS (Post 1, immediately after rTMS; Post 2, 30 minutes after rTMS). Measures of TMS data [rest motor threshold (rMT), amplitude of the motor-evoked potentials (MEPs), and TCI duration] were evaluated at pre-rTMS and post-rTMS (Post 1 and Post 2). Figure 1 shows the time course of our experiment. TMS was performed with a 70-mm figure-8 coil and a Magstim 200 for single TMS and a Magstim Rapid stimulator (Magstim Company) for rTMS. The coil was placed tangentially over the contralesional M1 at the optimal site for the first dorsal interosseous (FDI) muscle. The optimal site was defined as the location where stimulation of a slightly suprathreshold intensity elicited the largest MEPs in the FDI. Electromyographic (EMG) activity was recorded from silver-silver-chloride electrodes positioned in a belly-tendon montage on the skin overlying the FDI, and the signal was amplified, filtered (50 to 2000 Hz) and digitized at a sampling rate of 5000 Hz for off-line analysis (Neuropack; Nihon Koden). The rMT was determined separately for each stimulator and defined as the lowest stimulator output that could activate MEPs with a peak-to-peak amplitude $\geq 50$ microvolts in at least half of the 10 trials. The peak-to-peak amplitude of 10 averaged re-

**Figure 1.** Time course of the experiment. (a) measurement of the motor task performance (pinch force, acceleration); (b) measurement of the the TMS parameters (rMT, amplitude of the MEPs, TCI duration).

rTMS over the contralesional M1 (1Hz, 90% rMT, 25 min) or sham
sponses of the unimpaired FDI obtained with an intensity of 120% rMT was also determined.

In the TCI procedure, the contralesional M1 was stimulated 20 times with an intensity of 150% rMT during a unilateral maximal tonic contraction of the affected FDI. During each stimulation, the subjects maintained a sustained maximal tonic contraction of the FDI muscle for ≈2 seconds with visual and auditory feedback of the muscle activity. To avoid central or peripheral fatigue, a subject paused for 3 minutes after 10 stimuli. The stimuli were applied with a frequency of 0.1 Hz. Twenty EMG signals of the affected FDI were rectified and averaged in order to evaluate the TCI. The TCI was quantified by the period of relative EMG suppression after the stimulus, that is, when the EMG activity dropped below the background activity. The mean amplitude of the rectified and averaged EMG before the stimulus for 100 ms was defined as the background activity. The TCI duration was measured from where the EMG activity clearly fell below the background activity to where the EMG activity again reached the background activity.10

rTMS over contralesional M1 (1 Hz, 90% rMT, 25 minutes) was applied with a figure-8 coil connected to a Magstim Rapid stimulator. Sham stimulation was given positioning the coil perpendicularly to the scalp of the contralesional M1 at the same frequency and intensity as real rTMS.

Before the rTMS study, each patient performed the motor training protocol and “pinching” task described in a previous report11 to minimize the possibility that motor measurement of the rTMS session itself will become motor training. The pinching task using the index finger and the thumb of the affected hand was metronome paced and performed as quickly as possible (frequency individualized between 0.3 and 0.5 Hz). Practice 1 involved performance of this pinching task for 60 minutes interrupted by a 15-minute break to rest after 30 minutes. In practice 2, the patients performed the same pinching task for 15 minutes per day for 7 days from the day after the end of practice 1 until the day before the rTMS procedure.

The maximum pinch force of the affected hand was determined using a pinch gauge (Pinch Meter SPR-641; Sakai Medical). The subjects were instructed to use only their thumb and index finger for this pinching task for 15 minutes per day for 7 days from the day after stroke, or the Fugl-Meyer scale (Table).

Data analysis was performed by an investigator blind to the stimulation type. The data (rMT, age, Fugl-Meyer scale,12 and duration after stroke) from the group of rTMS and the group of sham were compared by using a Student t test. The effect of motor training or rTMS was evaluated with an ANOVA for repeated measures with “time” as a within-subjects factor and “condition” (rTMS and sham) as a between-subjects factor. A post-hoc analysis was performed with a Scheffe F test. Any possible correlation between changes of the various parameters was determined by using a Pearson correlation coefficient test. All of the data were normalized by conversion to a percentage change from baseline or pre-rTMS.

Results

Subjects did not report any adverse side effects during the course of the study. No difference has been observed between the rTMS group and the sham group in rMT of contralesional M1 (mean 48.2±5.7% versus 45.4±7.7%), age, the duration after stroke, or the Fugl-Meyer scale (Table).

Figure 2a and 2b show the effect of motor training. A repeated-measure ANOVA for motor function showed no significant interaction between time and condition (pinch: F[2, 36]=0.50; P=0.61; acceleration: F[2, 36]=0.13; P=0.88) or condition (pinch: F[1, 18]=1.09; P=0.31; acceleration: F[1, 18]=0.03; P=0.86) but significant effect of time (pinch: F[2, 36]=17.9; P<0.01; acceleration: F[2, 36]=13.6; P<0.01), reflecting that there was no difference between the rTMS group and sham group in motor training. Post-hoc testing revealed that the patients of both groups rapidly improved, and the pinch force and acceleration increased after first training (rTMS group: pinch force, P<0.05; acceleration, P<0.01; sham group: pinch force, P<0.01; acceleration, P<0.05). Additional practice did not lead to an additional improvement in both groups. This result is in agreement with a previous report of the effects of motor training of stroke patients.11

Figure 3a and 3b show the motor function after rTMS. A repeated-measure ANOVA showed a significant interaction between time and condition in acceleration (F[2, 36]=5.98; P<0.01) but not pinch force (F[2, 36]=0.76; P=0.47). And the repeated-measure ANOVA for acceleration showed a significant effect of time (F[2, 36]=7.88; P<0.01). Post-hoc testing showed that an additional improvement on acceleration was immediately produced by rTMS (P<0.05) but not by sham. However, this effect did not last for 30 minutes after the rTMS.

A repeated-measure ANOVA for rTMS (rTMS group: 101.4±3.7% at Post 1 [% of pre-rTMS] and 99.4±4.7% at Post 2; sham: 101.2±6.4% at Post 1 and 101.4±4.6% at Post 2) did not show a significant interaction between time and condition.

Figure 2. The effects of motor training. (a) pinch force; (b) acceleration. *P<0.05; **P<0.01; error bar, SD; ■, rTMS group; ▲, sham group.
(F[2, 36]=0.68; P=0.51), condition (F[1, 18]=0.22; P=0.65), or time (F[2, 36]=0.78; P=0.47). Figure 3c and 3d shows TMS parameters after rTMS. A repeated-measure ANOVA for the amplitude and TCI showed significant interaction time and condition (amplitude: F[2, 36]=8.12; P<0.01; TCI duration: F[2, 36]=5.65; P<0.01) and time (amplitude: F[2, 36]=4.61; P<0.05; TCI duration: F[2, 36]=9.39; P<0.01). Post-hoc tests revealed that immediately after rTMS the amplitude and TCI duration were significantly decreased from the values of pre-rTMS (amplitude, P<0.01; TCI duration, P<0.01). Figure 4 shows the raw TCI data of the pre-rTMS and after rTMS. However, these changes did not last for 30 minutes after rTMS. A reduction in TCI duration was significantly associated with a reduction in amplitude of the MEPs in rTMS group (Figure 5a; r=0.89, P<0.01).

The improvement of motor function after rTMS (Post 1) was significantly associated with the reduction of TCI duration in rTMS group (Figure 5b; r=0.73, P<0.05). This improvement of motor function had no significant correlation with a patient’s age (r=0.39, P=0.26), Fugl-Meyer scale (upper limb: r=0.31, P=0.38; hand: r=0.21, P=0.56), or duration after stroke (r=0.50, P=0.14). There was no correlation between the change in the TCI and motor function after sham stimulation (r=0.23, P=0.53).

Discussion

This study reports for the first time that a noninvasive cortical stimulation using rTMS over contralesional M1 can reduce the TCI and improve the motor function of the affected hand of stroke patients. These results demonstrate that the TCI from contralesional M1 to ipsilesional M1 suppressed the affected hand function of stroke patients.

We found that 1-Hz rTMS reduced the excitability of M1; this result is in agreement with previous reports.7 rTMS over
contralesional M1 reduced the TCI from contralesional to ipsilesional M1. This result is also consistent with a recent study, which reported that 1-Hz rTMS could reduce the TCI. Moreover, the decreased TCI after rTMS correlated with the improvement in the motor function of the affected hand. Murase et al have demonstrated that when stroke patients move their affected hand, there is an abnormally high TCI from contralesional to ipsilesional M1. Taking these findings into consideration, 1-Hz rTMS can lead to an improvement in the motor function of the affected hand by reducing the TCI from contralesional M1 to ipsilesional M1. A previous study has reported that reduced intracortical inhibition was accompanied by a disruption of TCI after a stroke. Moreover, Kobayashi et al have reported that rTMS over the M1 induced disinhibition in the contralateral M1. A decrease of inhibition rapidly acts to unmask preexisting, functionally latent neural networks around the lesion contributing to cortical reorganization. We found improvement of the affected hand immediately after rTMS. It is possible that the disinhibition of the affected M1, induced by disruption of the TCI, partly contributed to the improvement of the affected hand by the unmasking of latent networks. By another mechanism, rTMS over M1 might induce a facilitation of the activity in dorsal premotor cortex (PMd) in the contralateral hemisphere. Several reports have suggested that the PMd in the ipsilesional hemisphere contributed to the recovery of motor function after stroke. Therefore, it is a possibility that the activity of ipsilesional PMd because of rTMS over the contralesional M1 induced an improvement of the affected function. This hypothesis needs more research with brain function imaging.

A reaction-time study noted that the contralesional M1 did not contribute to motor recovery after a stroke. Furthermore, Murase et al reported that contralesional M1 inhibited ipsilesional M1 via the TCI in stroke patients. Therefore, it is possible that the reduced excitability of contralesional M1 produced by rTMS can improve the motor function of the affected hand without deteriorating the affected hand. This result suggests that contralesional M1 might not compensate for the damage to the corticospinal projection in stroke patients but impair the affected hand via the TCI. However, Ward et al have reported a negative correlation between the outcome of the motor function in patients with stroke and the size of activation in contralesional posterior M1 but not anterior M1. TMS is less likely to disrupt the posterior M1 region because this area is situated deep in the central sulcus and the depth of the electrical field induced by TMS is limited. Considering the limitation of TMS for the posterior M1, we could not confirm the role of entire contralesional M1 for the affected hand.

Although 1-Hz rTMS over M1 modulated the excitability of the stimulated M1, it could not convincingly change the manual motor function controlled by this stimulation site in healthy subjects. It has also been reported that 1-Hz rTMS over M1 could not change simple motor performance with the ipsilateral hand in healthy subjects and in stroke patients. However, Kobayashi et al have reported that 1-Hz rTMS over the unilateral M1 could improve the motor function of the ipsilateral hand of healthy subjects. Of course, there were several methodological differences noticeable in previous reports. We considered that the intensity of the stimulation might play a highly critical role in several of the methodologies. The intensity of our stimulus, and the stimulus used in Kobayashi’s study (90% rMT), is less than the intensity (115% rMT and 150% rMT) that did not have any effect on motor performance ipsilateral to the stimulated hemisphere. A stimulation that is subthreshold to the rMT may act by local inhibition of the stimulation site, but a suprathreshold stimulation may inhibit not only the stimulation site but also the opposite homogenous motor cortex via TCI. An activation of TCI by suprathreshold stimulation might cancel out the effect of relative facilitation of the contralateral M1 by a reduced excitability of the stimulated M1, with the result that the motor function would not change.
Although hand function had reached a plateau with the previous motor training, rTMS to the contralesional M1 immediately produced an additional improvement. However, the improvement in acceleration was not observed to continue for 30 minutes. A change in the pinch force was also not observed after rTMS. Sohn et al.\textsuperscript{20} reported that changing the pinch force was more difficult than changing the acceleration. For rehabilitating stroke patients, it may be important to impart additional motor training, whereas the change is generated by a decreased TCI; this would sustain the effect of rTMS and improve the pinch force.

In conclusion, our results have demonstrated that rTMS over the contralesional M1 could lead to an improvement of motor function in the affected hand of patients with chronic stroke. This improvement of the affected hand correlated with decreased TCI from the contralesional M1. These findings will possibly be relevant for the design and optimization of neurorehabilitative strategies for stroke.

Acknowledgments

This work was supported by research project grant-in-aid for scientific research number 17300179 from the Japan Society for the Promotion of Science. We thank Prof. Yukio Mano at the Department of Rehabilitation Medicine, Hokkaido University Graduate School of Medicine, for supervision and expertise. We also thank Mami Onodera for technical support.

References


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Repetitive Transcranial Magnetic Stimulation of Contralesional Primary Motor Cortex Improves Hand Function After Stroke
Naoyuki Takeuchi, Takayo Chuma, Yuichiro Matsuo, Ichiro Watanabe and Katsunori Ikoma

Stroke. 2005;36:2681-2686; originally published online October 27, 2005;
doi: 10.1161/01.STR.0000189658.51972.34
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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