Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements

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Abstract—Background: Disruption of cortical function can improve behavior. Motor cortex (M1) transcallosal interactions are mainly inhibitory; after unilateral damage to M1, there is increased excitability of the unaffected M1. Repetitive transcranial magnetic stimulation (rTMS) of M1 produces a temporary reduction in cortical excitability in the same M1 that outlasts the duration of the rTMS train. The authors hypothesize that reducing cortical excitability of M1 by rTMS may improve motor performance in the ipsilateral hand by releasing the contralateral M1 from transcallosal inhibition. Methods: Sixteen healthy volunteers participated. Using a sequential key-pressing task with the index finger, motor performance was monitored before and after rTMS (1 Hz for 10 minutes with the intensity below motor threshold) applied to the ipsilateral M1, contralateral M1, ipsilateral premotor area, or vertex (Cz). Results: rTMS of M1 shortened execution time of the motor task with the ipsilateral hand without affecting performance with the contralateral hand. This effect outlasted rTMS by at least 10 minutes, was specific for M1 stimulation, and was associated with increased intracortical excitability in the unstimulated M1. Conclusions: The authors' results support the concept of an interhemispheric "rivalry." They demonstrate the utility of repetitive transcranial magnetic stimulation to explore the functional facilitation of the unstimulated counterpart motor cortex, presumably via suppression of activity in the stimulated motor cortex and transcallosal inhibition.

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The two cerebral hemispheres are functionally coupled and balanced.[1-3] Unilateral dysfunction disrupts this balance and leads to the release of the unaffected hemisphere, which can result in a paradoxical functional improvement.[4,5] This phenomenon has been documented in the setting of hemispatial attention. For example, in normal subjects, suppression of one parietal cortex by repetitive transcranial magnetic stimulation (rTMS) improves attention to targets in the ipsilateral visual field.[3] In patients who have had a stroke, a subsequent disruption of the healthy hemisphere by another stroke[6] or rTMS[7] may lead to an improvement of attention.

Studies on stroke patients have also suggested the presence of such interhemispheric "rivalry" between bihemispheric motor areas. Patients who have had strokes involving the motor cortex have increased cortical excitability and enlarged cortical motor output maps in the unaffected motor cortex.[8-11] Intracortical inhibition is suppressed in the unaffected motor cortex of patients who have had a cortical stroke, and such suppression is associated with, and presumably the result of, disrupted transcallosal inhibition.[11] The interhemispheric interaction between primary motor areas (M1) is strong and effective,[12] although commissural fibers are relatively sparse.[13] Inhibitory and facilitatory interactions are postulated, but when TMS is applied to the hand motor area, the interaction appears to be mostly inhibitory in humans.[14-16]

Low-frequency (1 Hz) rTMS of the motor cortex can suppress cortical excitability for seconds to minutes (depending on the duration of the stimulation) and produce a transient virtual lesion in the targeted cortical region, leading to measurable physiologic and behavioral effects.[17-22] rTMS of motor cortex can also change the metabolic rate in the contralateral motor area and therefore may lead to behavioral or functional effects ipsilateral to the side of stimulation.[23-25] In the present study, we hypothesized that suppression of the hand representation in one M1 by low-frequency rTMS would lead to a tran-

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scallosal disinhibition of the unstimulated motor cortex and so to a facilitation of movements with the ipsilateral hand. A recent study in adult rats that demonstrated facilitation in motor skill learning with the ipsilateral, unaffected forelimb after unilateral sensorimotor cortex lesions appears to support this hypothesis.[26]

Subjects and methods. *Subjects.* Sixteen healthy volunteers (12 men and 4 women; aged 25 to 35 years; mean age, 29.6 ± 3.6 years) were recruited. No subject had any psychiatric or major medical history or any contraindications to TMS.[27] All subjects were strongly right-handed according to the 12-item Annett questionnaire.[28] The study was approved by the local Institutional Review Board, and all participants gave their written informed consent.

Motor task and behavioral measure. The motor task consisted of the serial rapid pressing of four horizontally arranged keys in a given order sequence (figure 1A). The subjects were instructed to repeat the sequence 12 times as quickly and precisely as possible using their right or left index finger while accuracy and execution times were measured. The motor task was repeated five times with a short pause of 30 seconds between the tasks to minimize subjects' fatigue (240 pressings in one block). Each block of the motor task took approximately 5 minutes to complete. The thumb and ring finger of the same hand were placed and fixed beside the number pad to prompt subjects to use only hand muscles, minimizing movements of the forearm and proximal arm. The height of the chair and keyboard were adjusted for subject comfort and kept constant during all experiments. In each experiment, the subject's motor performance was recorded with a personal computer using SuperLab software (Cedrus Corp., Phoenix, AZ). The mean execution time, the interval between every two sequential key presses, and error rate (pressing an incorrect key) were calculated for each block.

The subjects practiced the motor task for more than 30 minutes on the day before each experiment so that all of them could perform the task fluently with few mistakes. Their performance reached plateau after approximately 20 minutes (figure 1C). In addition, before each experiment, the subjects performed 3 warm-up blocks, 720 key presses, with 3-minute rests between blocks to minimize the effect of learning and initial practice in the experiment.

Transcranial magnetic stimulation and recording technique. The subjects were seated in a reclining chair that allowed them to keep their arms and hands relaxed during TMS and recording of motor evoked potentials (MEPs). A tight-fitting white Lycra (Invista, Inc., Wilmington, DE) swimming cap was placed on their head to mark the optimal scalp position for TMS. TMS was performed with a 70-mm figure-eight coil and a Magstim Rapid stimulator (Magstim, Dyfed, UK) for rTMS and a Magstim 200 and Bistim module (Magstim) for single- and paired-pulse TMS. MEPs were recorded from the first dorsal interosseous (FDI) using surface electrodes and a Dantec Counterpoint EMG (Dantec, Skovlunde, Denmark) with a band pass of 20 to 2,000 Hz. Motor threshold (MT) was defined as the minimum TMS intensity required to induce MEPs of >50 μV peak-to-peak amplitude in at least 5 of 10 trials in the contralateral target muscle, determined with TMS delivered to the optimal scalp site for induction of MEPs from the contralateral FDI. The coil was placed tangentially to the scalp, with the handle pointing 45° posterolaterally.

Low-frequency rTMS. Focal 1-Hz rTMS was performed according to current safety recommendations.[27] The intensity of rTMS was set at 90% of the MT for the targeted hemisphere. For rTMS of the control position vertex (Cz; as defined by the 10–20 International System for EEG electrodes), we used 90% of the highest MT between the two hemispheres. Each rTMS train consisted of 600 pulses. Repetitive TMS was delivered to the contralateral M1 (the optimal position for the FDI of the tested hand), ipsilateral M1 (the optimal position for the FDI of the untested hand), ipsilateral dorsolateral premotor area, or Cz (see figure 1A). The optimal scalp position defined by TMS has been shown to correspond closely to the locus of cortical activation in the anterior bank of the central sulcus during volitional hand movements as identified by fMRI or PET.[29,30] The dorsolateral premotor cortex was defined as being 2.5 cm anterior to the optimal position for FDI according to recent functional imaging studies.[31] These positions were confirmed in four subjects by an image-guided frameless stereotaxy system (Brainsight, Rogue Research, Montreal, Canada) to localize the sites of TMS of the hand motor area and the dorsolateral premotor cortex. The coil was held tangentially to the skull with the handle pointing 45° posterolaterally for stimulation of the M1 and premotor cortex or pointing posteriorly for Cz.

Paired-pulse TMS. Paired-pulse TMS consisted of a conditioning stimulus with an intensity of 80% MT and a test stimulus with approximately 120% MT that was adjusted to reproducibly evoke MEPs of peak-to-peak amplitude of approximately 0.5 mV. The short (1, 2, and 3 ms) and long (9, 12, and 15 ms) interstimulus intervals (ISIs) between conditioning and test stimulus were used to assess intracortical inhibition and facilitation.[32] Ten MEPs were recorded at each ISI and at conditioning and test stimulus alone. The order of the trials was pseudorandomly varied using the CED PC interface (Cambridge Electronic Device, Cambridge, UK).

Experiment 1. The rTMS effects of ipsilateral and contralateral M1 on hand motor performance were tested in 12 subjects. rTMS was applied over one of three different scalp locations: ipsilateral M1, contralateral M1, and Cz as a control site (see figure 1A). On the first day of the experiment, subjects practiced extensively with the right or left hand until their motor performance reached a plateau. On the following 3 days, each subject received a single, continuous train of 600 pulses of 1-Hz rTMS, and their motor performance was monitored before, immediately, and 10 minutes after rTMS (figure 1B). The three rTMS sites were tested on three separate days to avoid a carry-over effect of the preceding rTMS. The order of the targeted sites of rTMS application was counterbalanced across subjects. After all three rTMS sessions for one hand were completed, the experiments for the other hand were performed. Subjects learned the motor task with the other hand on the first day, and the rTMS sessions of the three sites were conducted on the subsequent 3 days. Half of 12 subjects underwent the studies first for their right hand; the other 6 were studied first with the left hand.

Experiment 2. In the second experiment, we examined the duration of the effect of rTMS over the ipsilateral M1 on hand motor behavior in seven subjects, including six subjects from Experiment 1. This experiment was performed using their left hands because the effects of rTMS were greater for the left hand than for the right in Experiment 1. On the day before this experiment, all subjects practiced the motor task with their left hand, and on the following day, they received 600 pulses of 1-Hz rTMS over the left M1, and their motor behavior was monitored before and immediately after rTMS and 10, 20, 40, and 60 minutes later (see figure 1B).

Experiment 3. There is a tight coupling of premotor and motor cortex,[33,34] and the commissural fibers between both premotor cortices occupy a large part of the corpus callosum.[35] Therefore, it was important to assess whether the behavioral effects observed in Experiments 1 and 2 were secondary to a nonspecific spread of rTMS to the premotor cortex from the targeted M1. In this experiment, we examined the effect of rTMS over the ipsilateral premotor area in six subjects, including four subjects from Experiment 1. Subjects practiced the task with their left hands the day before the experiment. On the subsequent 3 days, each subject received 600 pulses of 1-Hz rTMS over one of three different scalp locations: left M1, left dorsolateral premotor cortex, and Cz. Therefore, this experiment tested the reliability of the results of Experiment 1 and expanded them to include the premotor area. The hand motor performance was assessed before, immediately after, and 10 and 20 minutes after rTMS (see figure 1, A and B). The order of the targeted brain areas was counterbalanced across subjects.

Experiment 4. To investigate the mechanisms underlying behavioral changes, we assessed the effects of rTMS on the corticospinal and intracortical excitability of the unstimulated, contralateral M1. The right M1 was stimulated to induce MEPs of the left FDI with single- and paired-pulse TMS before and immediately after 1-Hz rTMS of the left M1. The MT, the size of MEPs, and the results of intracortical inhibition and facilitation as elicited by paired-pulse TMS in the right M1 were compared before and after rTMS of the left M1. To compare the size of MEPs before and after rTMS, 10 MEPs were recorded with single-pulse TMS of

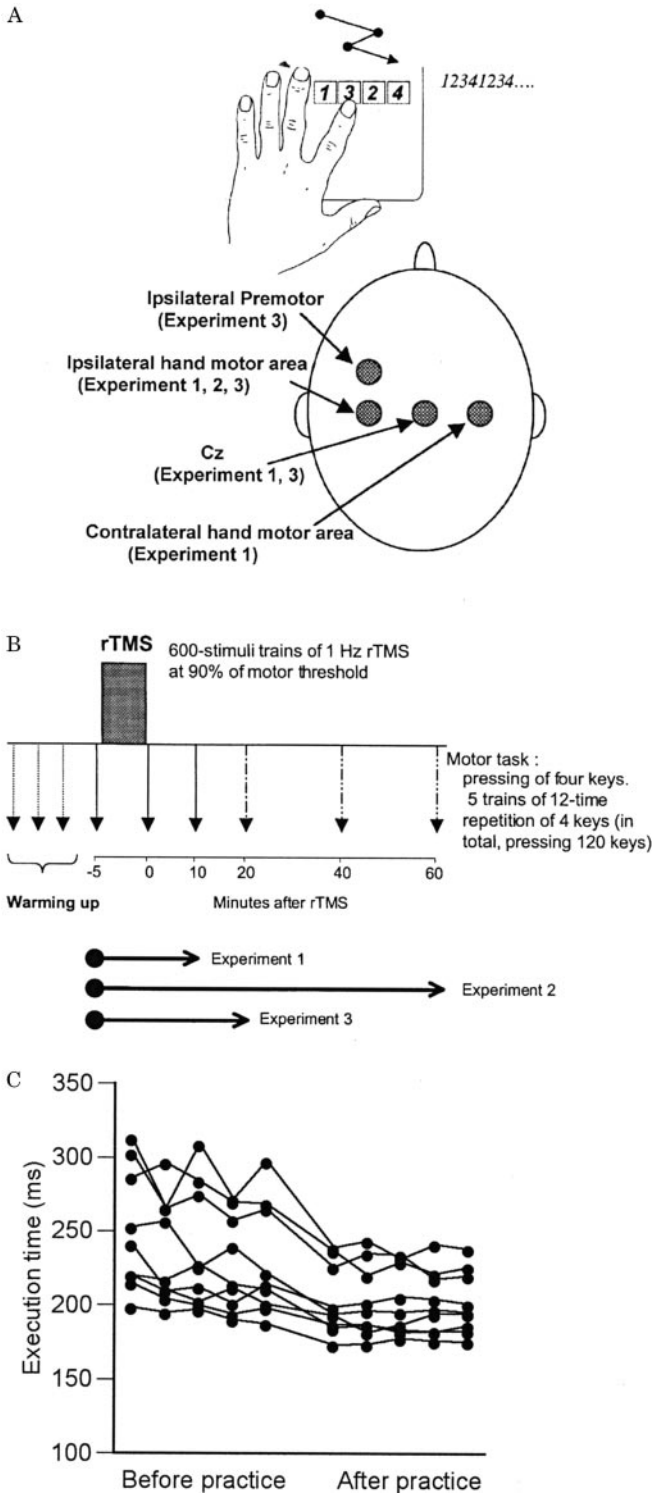

Figure 1. (A) The sequence of index finger movement and site of repetitive transcranial magnetic stimulation (rTMS). Subjects were instructed to press the keys in the numbered order in the right or left index finger. During each rTMS session, 1-Hz rTMS with 90% MT was applied either over the ipsilateral or contralateral hand motor area (M1), ipsilateral premotor area (2.5 cm anterior to M1), or vertex. (B) Time course of rTMS and motor tasks. Three warming-up blocks were performed before each experiment. Motor performance of key pressing was monitored immediately and 10 minutes after rTMS for Experiment 1 and also 20 minutes after rTMS for Experiment 3. In Experiment 2, motor performance was monitored until 60 minutes after rTMS to examine the duration of the effect of the rTMS. (C) Execution time in nine subjects before practice and after 20 minutes of practice. The motor task was performed with the left hand. After 20 minutes of practice, most subjects' motor performance improved and reached plateau. Each dot indicates the averaged execution time in one run of the motor task of each subject.

a constant intensity of approximately 120% MT (an intensity that could evoke MEPs of peak-to-peak amplitude of approximately 0.5 mV before rTMS). For paired-pulse TMS studies, the MEP sizes evoked by test TMS alone were matched before and after rTMS, adjusting the intensity of test TMS if necessary. This experiment was performed in eight subjects, including five subjects from Experiment 1.

Data analysis. Mean execution time and error rate were calculated from the 240 key presses in each block. To examine the variance of the mean execution time, SD in each block was also calculated. The baseline of each parameter was the mean before rTMS. The results are reported as mean ± SEM. The changes in execution time, error rate, and SD after rTMS of each site were subjected to analysis of variance (ANOVA) with repeated measures. Paired t-tests with Bonferroni correction or Scheffe F-test were used for post hoc analysis.

For the analysis of the results in Experiment 4, mean MEP area-under-the-curve was calculated for each condition. The change of the MEP size induced by single-pulse TMS before and after rTMS was examined by a paired t-test comparison. For the paired-pulse studies, the baseline was the mean MEP area calculated from trials with test TMS alone, and all values for the different ISIs were expressed as a percentage of the baseline responses. Thereafter, data with different ISIs were divided into two groups: ISI of 1 to 3 ms (intracortical inhibition) and ISI of 9 to 15 ms (intracortical facilitation). The effect of the rTMS on intracortical inhibition and facilitation was analyzed using ANOVA with repeated measures, followed by post hoc paired t-tests with Bonferroni correction. The results are reported as mean ± SEM. For all analyses, the level of significance was set at $p < 0.05$.

Results. No subject experienced any adverse effects during or after the rTMS procedure. There was no significant change of MT in any of the subjects during the experiments. The mean execution time of the right finger was much shorter than that of the left finger in all subjects, as might be expected given their right-handedness (the mean baseline execution time for 3 days in Experiment 1: 208.2 ± 19.8 and 184.6 ± 18.3 ms for left and right hand; $p < 0.0001$, paired t-test).

Effect of rTMS of ipsilateral and contralateral hand motor area (Experiment 1). The left column of figure 2 shows the main result of our study. For both hands, repeated-measures ANOVA revealed an effect of "time course" on execution time ($F(2,66) = 9.449$, $p < 0.0005$; $F(2,66) = 20.246$, $p < 0.00001$ for right and left hand) and an interaction between "time course" and "site of rTMS" ($F(4,66) = 2.59$, $p < 0.05$; $F(4,66) = 6.430$, $p < 0.0005$ for right and left hand). Post hoc tests demonstrated that the interaction was the result of the significant decrease of execution times when rTMS was applied over the ipsilateral M1. The shortening of execution time was significant 10 minutes after rTMS for the right hand and immediately after and 10 minutes after rTMS for the left hand. After rTMS to the ipsilateral, left M1, 5 of 12 participants reported spontaneously that they could perform the task with their left fingers "faster" and "more easily." There was no significant difference in error rates according to

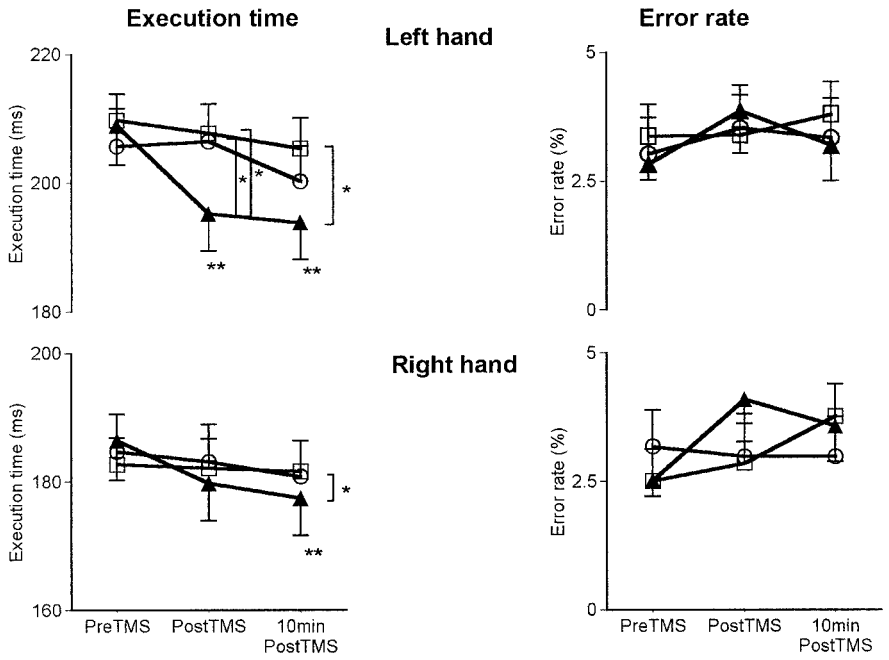

Figure 2. Change in execution time and error rate of each hand after repetitive transcranial magnetic stimulation (rTMS) to each site. Different symbols indicate the different sites of rTMS: Cz = open squares; contralateral M1 = open circles; and ipsilateral M1 = filled triangles. (Left) Execution time of each hand before and after rTMS. After rTMS on the ipsilateral M1, the execution times decreased in both hands, especially in the left, compared with those after rTMS of other sites ($p < 0.05$). Decrease from the baseline (preTMS) was detected only after rTMS of ipsilateral M1 (**$p < 0.05$). (Right) Error rate remained constant across all sessions of experiment. Error bar indicates standard errors.*

protocol or time course, indicating no effect on the accuracy and ruling out a speed–accuracy trade-off that might have accounted for the rTMS effects on execution time (see figure 2, right columns). There was no significant change in the SD of the execution times according to the TMS protocol or time courses.

Daily changes of the execution time before rTMS were also analyzed. The execution time before rTMS was shorter on day 3 than on day 1 ($p < 0.05$, left hand: 209.9 ± 5.6 and 204.7 ± 5.6 for days 1 and 3; right hand: 190.0 ± 5.6 and 181.0 ± 6.1 for days 1 and 3). However, there was no difference of the baseline execution time according to the sites of rTMS (ANOVA, $p = 0.581$). These results indicate that the motor performance of the subjects improved daily during experiments, which was, nevertheless, successfully controlled for by varying the order of stimulating sites across subjects.

Duration of the effect of rTMS (Experiment 2). The time course of the changes in execution time of the left hand after rTMS of the ipsilateral, left M1 in each subject. Repeated-measures ANOVA showed an effect of time course after rTMS ($F(5,30) = 3.01$; $p < 0.05$), and post hoc tests revealed that the execution time was significantly shorter immediately after and 10 minutes after rTMS than before rTMS, indicating that the effect of a 10-minute rTMS train on the motor behavior of the ipsilateral hand may last up to 10 minutes but less than 20 minutes. One of the subjects showed a shorter execution time than the others, but his performance was within 2 SD from the mean execution time of all subjects. The exclusion of this subject's data did not change the results of the statistical analysis, ruling out that an outlier may account for our findings. The figure displaying these data is available on the Neurology Web site (see figure E-1 on the Neurology Web site).

Effect of rTMS of the ipsilateral premotor cortex (Experiment 3). Figure 3A shows the changes in execution times after rTMS of the ipsilateral premotor cortex, ipsilateral M1, or Cz. Repeated-measures ANOVA revealed an effect of time course after rTMS ($F(3,45) = 3.948$; $p < 0.05$) with an interaction between time course and sites of rTMS ($F(5,66) = 2.47$; $p < 0.05$). Post hoc analysis revealed that the execution times were shorter immediately after and 10 minutes after rTMS of the ipsilateral M1 than after that of Cz (Scheffe test, $p < 0.05$). Figure 3B shows the ratio of execution times after rTMS of these three sites. An ANOVA with repeated measures revealed an effect of the sites of rTMS ($F(2,15) = 6.64$; $p < 0.01$) but without an effect of time course ($F(2,30) = 1.26$; $p = 0.299$) or interaction between them ($F(4,30) = 0.75$; $p = 0.572$). Post hoc analysis detected that the execution times were shorter after rTMS of the ipsilateral M1 than after rTMS of Cz (Scheffe test, $p < 0.01$) but not after rTMS of the ipsilateral premotor area. Therefore, rTMS of the premotor cortex exerted similar, although less robust, effects on ipsilateral motor performance than rTMS of M1.

Modulation of cortical excitability after rTMS of the primary motor area of the other hemisphere (Experiment 4). The MT of the right M1 and the size of the MEPs evoked in the left FDI by single-pulse TMS did not change after rTMS of the left M1 (paired t-test, $p = 0.51$ and $p = 0.64$). However, figure 4A shows the changes in size of the MEPs evoked in the left FDI by paired-pulse TMS with various ISIs before and after rTMS of the left M1. The changes in MEP length at short (1 to 3 ms) and long (9 to 15 ms) paired-pulse TMS intervals were averaged (figure 4B) to generate measures of intracortical inhibition and facilitation, respectively.[32,36] A two-way ANOVA with repeated measures showed effects of rTMS ($F(1,14) = 5.72$; $p < 0.05$) and ISIs (long vs short, $F(1,14) = 10.313$; $p < 0.01$) without an interaction ($F(1,12) = 1.09$; $p = 0.31$). Post hoc tests revealed that the changes were larger with long ISIs than with short ones (Scheffe test, $p < 0.01$), reflecting intracortical facilitation and inhibition, and that they were also larger after rTMS than before ($p < 0.05$). These results indicate that rTMS of M1 suppressed intracortical inhibition and enhanced intracortical facilitation in the

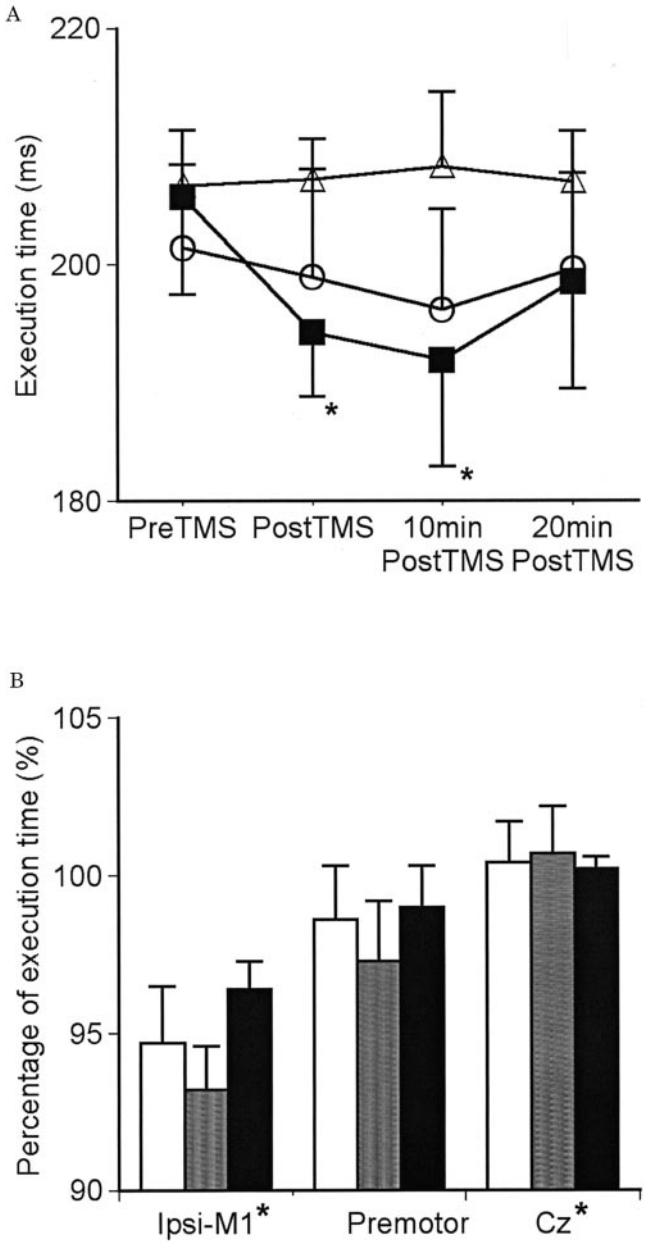

Figure 3. (A) Execution time after repetitive transcranial magnetic stimulation (rTMS). Change in execution time after the rTMS on the ipsilateral premotor (open circles), primary motor cortex (filled squares), or vertex (Cz; open triangles). The execution times were shorter immediately and 10 minutes after rTMS of the ipsilateral primary motor area than after that of Cz ($p < 0.05$). However, there was no difference between execution times after rTMS of premotor area and other sites. (B) Ratio of execution times after rTMS of these three sites. Empty, gray, and filled columns show the ratio of execution times immediately, 10, and 20 minutes after rTMS. The execution times were significantly shorter after rTMS of the ipsilateral primary motor area than after that of Cz (*), but there was no significant difference between those after rTMS of the ipsilateral premotor area and others. Error bar indicates standard errors.*

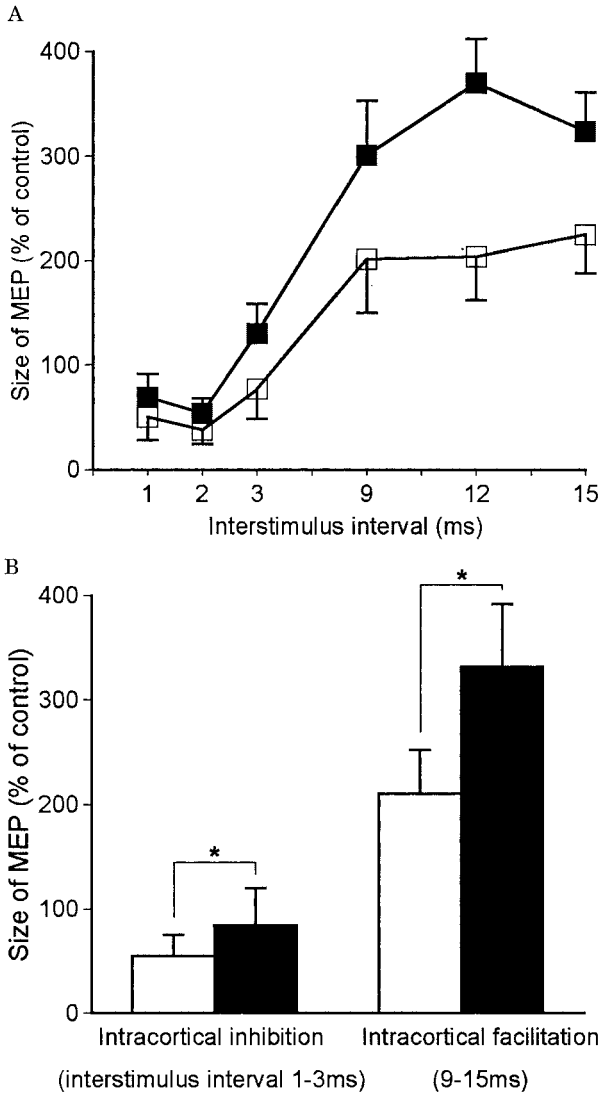

Figure 4. (A) The changes in motor evoked potential (MEP) sizes of the left first dorsal interosseous (FDI) evoked by paired-pulse transcranial magnetic stimulation (TMS) with various interstimulus intervals (ISIs). Empty and filled squares show the curves before and after repetitive TMS (rTMS) of the left hand motor area. (B) Averaged change of MEPs by paired-pulse TMS with short (1 to 3 ms) and long (9 to 15 ms) intervals before and after rTMS of ipsilateral, left motor area. MEP sizes were larger with long ISIs than with short ones, reflecting intracortical facilitation and inhibition. In both conditions, percentage of MEP size was larger after rTMS than before ($p < 0.05$). These results indicate that rTMS of the one primary motor area suppressed intracortical inhibition and enhanced intracortical facilitation. Empty and filled columns show the percentages of MEP sizes before and after rTMS. Error bar indicates standard errors.*

contralateral M1, whereas corticospinal excitability remained unchanged.

Discussion. Using rTMS, we demonstrate that suppression of excitability of one motor cortex can enhance motor performance with the ipsilateral

hand in humans, presumably through suppression of transcallosal inhibition and hence release of excitability of the unstimulated, contralateral motor cortex. Participants did not show changes in their error rates, indicating that their performance improvement was not caused by speed–accuracy trade-off.[37,38] These findings support the fundamental notion of a balance of rivalry controlling interhemispheric interactions critical to behavior. In addition, our results have possible implications for patients with motor deficits resulting from brain damage because they suggest that suppression of activity in the undamaged motor cortex may contribute to functional recovery.

Constraint-induced therapy, the forced use of the affected limb by immobilization of the healthy arm, can enhance functional recovery in patients with motor deficits after a stroke.[39] These beneficial effects are associated with the decrease of excitability of the healthy motor cortex and an increase in excitability of the affected motor cortex.[9] Reduction of excitability in the healthy motor cortex is the consequence of the immobilization and may lead to decreased transcallosal inhibition and the subsequent increase of the cortical excitability in the affected motor area.[40] In this sense, direct suppression of motor cortical excitability by rTMS may represent a kind of "central constraint-induced therapy," although the behavioral effects of rTMS are short lived (as shown in Experiment 2), and a different strategy, possibly through more continuous cortical stimulation, may be necessary to make these effects more sustainable.

There are facilitatory and inhibitory interactions between M1s.[12,41] However, facilitation has not always been observed between M1 hand representations in animal or human studies,[12,14-16,41] and the inhibitory interaction seems more prominent especially when TMS is applied to one M1.[14] One possible mechanism to explain our results would be that rTMS suppressed the interhemispheric inhibitory interactions, resulting in a disinhibition of the contralateral, unstimulated motor cortex (see figure 4) and improved motor performance with the ipsilateral hand. This observation is in keeping with previous reports showing that reduced intracortical inhibition is accompanied by disrupted transcallosal inhibition after a stroke involving the motor cortex[11] or after ischemic nerve block of one hand.[42]

Another possible mechanism to account for our results may be that a decrease in M1 cortical excitability after rTMS allows its contralateral homolog to perform without the need to suppress mirror movements and hence results in more efficient motor control. Even simple unimanual movements can evoke the activation of both sensorimotor areas and may evoke activities of ipsilateral homologous muscles, i.e., mirror movements.[43] Transcallosal inhibitory control is essential to prevent undesirable mirror movements and interference from the opposite hemisphere.[43-46] Such inhibitory control would be less necessary after suppression of cortical excitability of one motor cortex, and its reduction might result in enhanced corticospinal control.

Based on interhemispheric inhibition, both aforementioned hypotheses would be consistent with our observation that the effect of rTMS over the ipsilateral M1 is greater for the left than for the right hand because interhemispheric interactions from the dominant to the nondominant side are stronger than those in the opposite direction.[47-49] We show that focal rTMS to one motor cortex changed the intracortical excitability in the unstimulated motor cortex as measured by paired-pulse TMS. This appears to suggest that the effect of rTMS may be mediated via transcallosal fibers between the two M1s. However, anatomic studies in primates have shown that transcallosal fibers between M1s are sparse. One possibility would be that rTMS of M1 might have spread to affect the premotor cortex. Interhemispheric transcallosal connections between the two premotor cortices are greater than between M1s in primates.[13] However, we failed to find an effect of rTMS of the premotor cortex on motor performance in our study. Further studies are required to clarify the neurophysiology of our findings, but interhemispheric interactions between M1s seem most likely.

There are several previous human and animal studies that have shown paradoxically increased excitability of the unaffected motor cortex and behavioral facilitation of the unaffected limb after lesion or transient suppression of unilateral motor cortex. These authors propose that changes in transcallosal inhibition explain their findings.[5-7,11] In rats, acute cortical lesions lead to an increase in excitability of homotopic areas of the contralateral hemisphere[50] and facilitation of motor skill learning with the unaffected forelimb.[26] In humans, the cortical excitability in the unaffected motor cortex can increase after lesions or transient suppression of cortical excitability, such as hemispherectomy and transection of the corpus callosum,[51] unilateral cortical strokes,[8-11] or ischemic nerve block of one hand leading to a reduction in its sensorimotor representation.[42] Intracortical excitability measures with paired-pulse TMS may be more sensitive than the MEP size to changes in transcallosal interactions. Patients with hemispheric strokes have abnormally decreased intracortical inhibition in the healthy hemisphere, presumably because of the impaired transcallosal inhibition.[11] In agreement with these past findings, in Experiment 4, we demonstrated a change in right M1 intracortical inhibition and facilitation after left rTMS but failed to show a significant change in the size of MEPs induced in the left FDI (by right-sided stimulation) after rTMS of the left M1.

Several functional imaging and TMS studies have demonstrated that the functional central anatomy of the control of overlearned sequential unimanual finger movements includes bilateral primary motor (M1) and premotor cortices, supplementary motor area, and parietal lobes (somatosensory cortices and Brodmann's area 7 or 40).[52-59] Activity in these areas

increases with task complexity. For example, disruption of ipsilateral M1 by high-frequency rTMS (15 Hz, 120% MT intensity) results in timing errors while playing complex sequences of piano keys with four fingers but not during simple sequences.[52] However, some studies find an increase in activity in the ipsilateral M1 in relationship to sequence complexity,[54,60] but others do not.[55,58,59] This may depend on the specific task and movement requirements. The sequential movement used in our experiments was an overlearned, single-digit repetitive task without external pacing that would not appear to demand prominent support from the ipsilateral M1. The ipsilateral M1, especially the left M1 during left-handed movements, appears engaged in the execution of complex motor sequences,[52,61] perhaps exerting an inhibitory control over the contralateral hemisphere to prevent overflow movements.

Index finger tapping speed with either hand is reportedly not changed after 0.9-Hz rTMS of the left motor cortex.[17] Our results appear to be at odds with these findings. However, several methodologic differences, such as the different task, a longer duration of assessment, mechanically different counter, or amount of practice, may all account for these discrepant results. In the earlier study, subjects tapped 50 to 60 times/min,[17] whereas our subjects did so 48 times in 9 to 15 seconds. Fatigue during their longer testing interval (1 minute) may have masked subtle rTMS effects. Most importantly, the intensity of stimulation (115% of MT, higher than in our study) may play a critical role in determining the relative influence of rTMS on inhibitory vs excitatory circuits and hence the resulting behavioral consequences.[62]

The premotor area was also targeted as a control site given the tight coupling of premotor and motor cortex[33,34] and existence of commissural fibers between premotor cortices that occupy a large part of the corpus callosum.[35] Our results indicate that rTMS of the premotor area has an effect similar to, but weaker than, rTMS of M1. Possibly the effects observed after rTMS of the premotor area may be the result from the spread of rTMS to M1.

A concern regarding our experimental design is the effect of motor learning. Several stages are known to be involved in the acquisition of motor skills: "fast learning" with an initial within-session improvement, followed by a "consolidation" phase of several hours and a "slow learning" phase lasting for a few weeks.[63] A learning plateau may be observed after as little as 2 hours of practice of a simple task.[21] Our study used a relatively simple task, and all subjects had learned and extensively practiced the motor task at least 1 day before the experiment. Although we observed daily decreases of baseline execution times indicating a possible "slow" motor learning confounder, this effect was minimal as compared with the size of the rTMS-related behavioral impact. The order of the targeted areas was varied across subjects and successfully abolished differences among the baseline execution times across rTMS conditions. Additionally, some subjects, who participated in more than one experiment and had overlearned the task, still showed improvement in their motor behavior after rTMS of the ipsilateral M1 but never after rTMS of other sites (see figures 2 and 3).

Nevertheless, we cannot exclude the possibility that our observation may reflect the promotion of motor learning by facilitating intrinsic circuits of the motor area contralateral to rTMS. M1 is engaged during the early stages of motor learning,[21] and facilitation of motor skill learning has been observed after unilateral lesions of sensorimotor cortex in a recent animal experiment.[26] To fully rule out an effect of rTMS on motor learning, a further study would be necessary with subjects who have practiced the task for more than 1 month.[63] Conversely, the potential beneficial effect of rTMS on motor learning is an intriguing possibility also worth pursuing.

Our results show that rTMS of one M1 can lead to a behavioral gain for the performance of a simple motor task with the ipsilateral hand, without obvious adverse effects. Although it may seem paradoxical that promoting inhibition in one motor cortex may result in improved motor function, it has been suggested in animal and human studies that direct or indirect "damage" to specific areas in the CNS may result in facilitation of behavior.[5] rTMS provides an ideal tool to systematically study the possibility of such functional facilitation and offers the possibility of engaging it for therapeutic purposes.

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