influx into the neurons, resulting in induction of LTD-like plasticity. However, neither SICI nor LICI was altered by priming over SMA, thus leading to the tentative conclusion that it is much less likely that the priming effects arise as a consequence of the alteration of intracortical inhibitory circuits.

Another possible explanation is related to several human studies in which voluntary contraction influences rTMS-induced plasticity (Fujiwara & Rothwell, 2004; Gentner *et al.* 2008; Huang *et al.* 2008). The after-effects of rTMS depend on the state of the cortex at the time the stimulation is applied. Thus, the effect of 5 Hz rTMS on SICI was reversed by muscle contraction during rTMS (Fujiwara & Rothwell, 2004). More recently, voluntary contraction during TBS abolished TBS-induced plasticity (Huang *et al.* 2008). Huang *et al.* (2008) proposed two possibilities to account for such state-dependent effects. First, the voluntary contraction perhaps changes the membrane potential or Ca^{2+} concentration of pyramidal neurons, directly affecting TBS-induced plasticity. 'Busy line' effects are another possible explanation; given that synapses stimulated by TBS are the same as those activated by voluntary contraction, extra activation of those synapses by TBS is negligible (Huang *et al.* 2008). Yet another study showed that voluntary contraction of sufficient duration changes the direction of TBS-induced plasticity; the authors contrastingly interpret their findings within the framework of metaplasticity theory (Gentner *et al.* 2008). Perhaps it is still an open question regarding the mechanism of effects of voluntary contraction on TBS-induced plasticity. In any case, SMA priming which produced changes in SICF might be a sign of some sort of baseline difference in the state of motor cortex independent of metaplasticity, resulting in alteration of subsequent QPS-induced plasticity.

SMA–M1 interplay and metaplasticity

Experimental observations of metaplasticity are considered to represent a major form of homeostatic mechanism of synaptic plasticity that prevents neuronal circuits from becoming destabilized and that maintains them within a dynamic range of modifiability (Abbott & Nelson, 2000; Abraham, 2008). Our findings might therefore highlight a homeostatic (or metaplastic) regulation of synaptic plasticity within excitatory circuits of M1 by input from SMA. Since SMA is implicated in higher motor control and the learning process (Luppino *et al.* 1993; Tanji & Shima, 1994; Tanji, 1996; Hikosaka *et al.* 1999; Nachev *et al.* 2008), the present results further raise the intriguing possibility that a preceding period of learning which entails a change in neuronal activity of SMA may regulate subsequent learning that is handled by neuronal circuits of M1 (Hikosaka *et al.* 1999; Sane & Donoghue, 2000). Since this study was not designed to test this hypothesis, future studies would be needed to shed light on possible metaplastic interplay between SMA and M1 during motor learning.

Finally, the shortcoming of the present study is that the lack of direct recording of synaptic responses in conscious humans renders any hypothesis about the precise neuronal mechanisms underlying QPS-induced plasticity or metaplasticity speculative (Cooke & Bliss, 2006). However, although the interpretation of the present data is inferential, the present study does suggest strongly that there may be important interactions between M1 and SMA in terms of metaplasticity.

Conclusions

Preceding stimulation over SMA elicited bidirectional shifts of the crossover point of the stimulus–response function of subsequent motor cortical plasticity. SMA priming transiently altered the synaptic efficiencies of excitatory circuits within M1. The data support the view that the homeostatic changes are mediated via mechanisms of metaplasticity. These findings highlight an important interplay between M1 and SMA regarding metaplasticity which might underpin learning and memory processes.

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Author contributions

M.H. and Y.U. contributed to the conception and design of the experiments. M.H. performed the experiments and analysed the data. All authors participated in data interpretation. M.H., Y.T. and Y.U. wrote the manuscript. All authors revised the manuscript and approved the final manuscript. The experiments were performed at Department of Neurology, the University of Tokyo, Japan.

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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

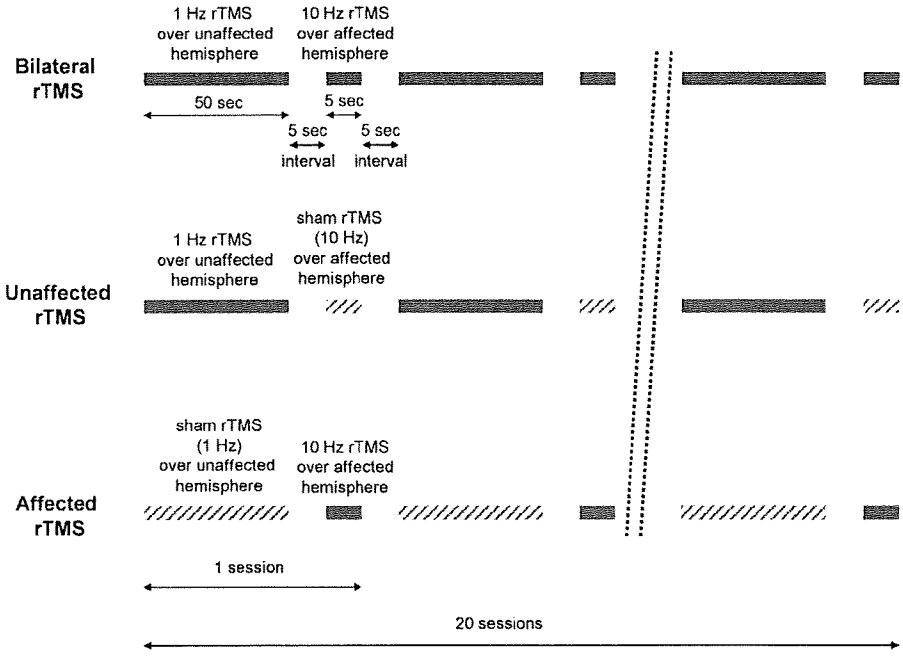

Fig. 1. The protocol of repetitive transcranial magnetic stimulation (rTMS). In the bilateral rTMS group, the patients were stimulated at 1 Hz and 50 sec train duration over the unaffected hemisphere, alternating with 10 Hz and 5 sec train duration over the affected hemisphere, with an interval of 5 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.

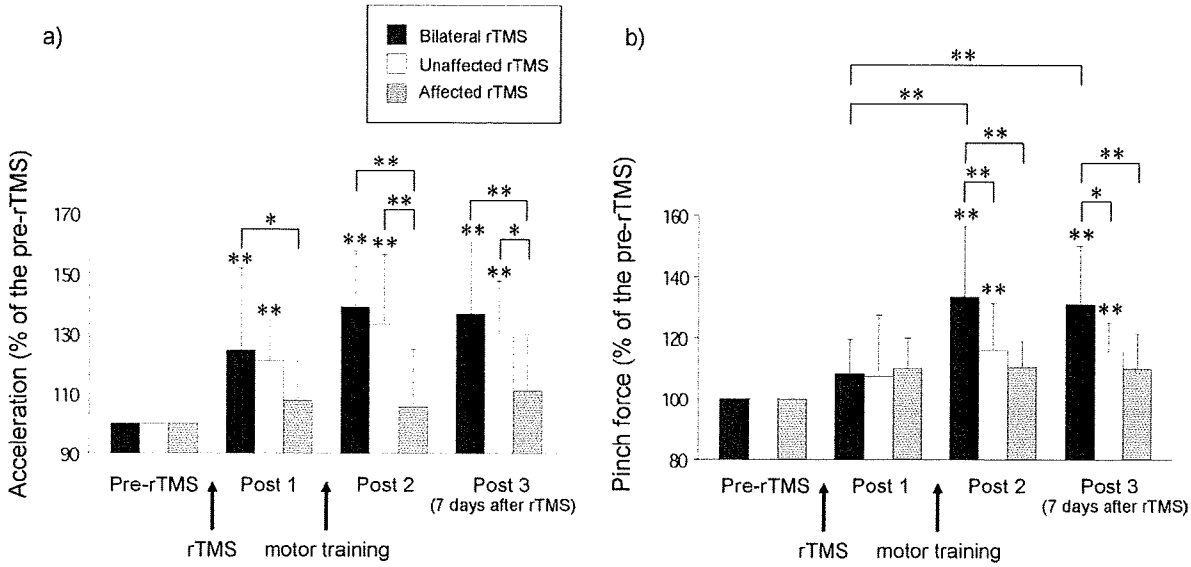

Fig. 2. The effects of repetitive transcranial magnetic stimulation (rTMS) and motor training; (a) acceleration; (b) pinch force. Bilateral and unaffected rTMS improved the acceleration of the paretic hand (pre-TMS vs Post 1: bilateral, $p=0.002$; unaffected, $p=0.008$) and this improvement in acceleration 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 ($p<0.001$)

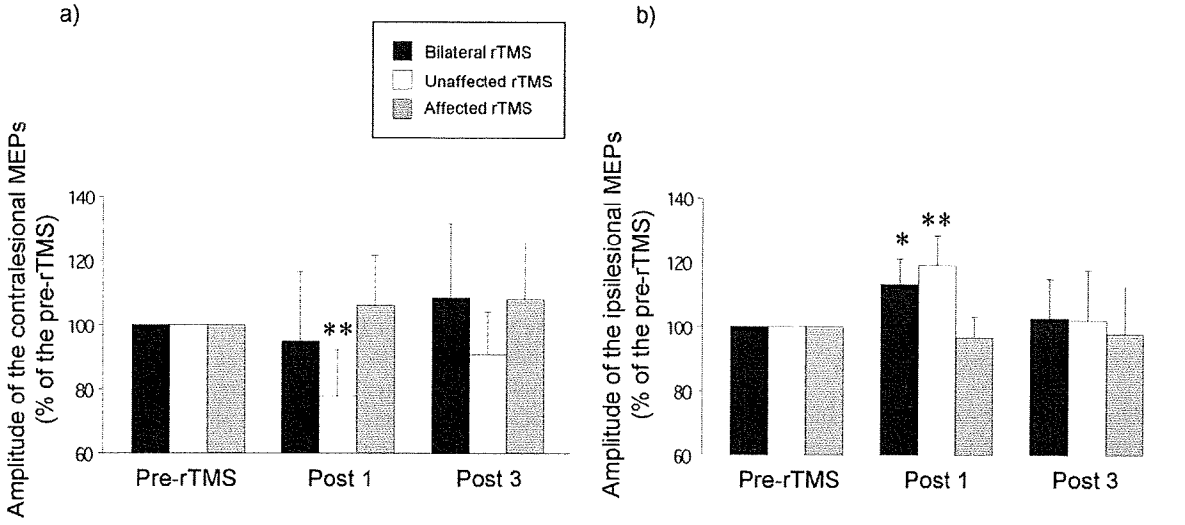

Fig. 3. The change in the corticospinal excitability after repetitive transcranial magnetic stimulation (rTMS). (a) Amplitude of the contralesional MEPs. (b) Amplitude of the ipsilesional motor evoked potentials (MEPs). Unaffected rTMS decreased the amplitude of contralesional MEPs (pre-rTMS vs Post 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.

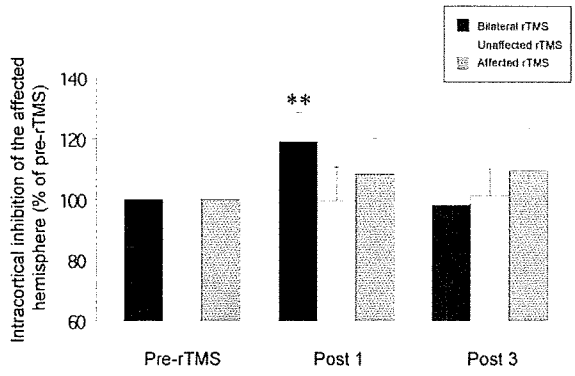

Fig. 4. The change in the intracortical inhibition after repetitive transcranial magnetic stimulation (rTMS). A decreased intracortical inhibition of the affected hemisphere was produced by bilateral rTMS (pre-rTMS vs Post 1: $p=0.002$). However, the change induced by rTMS was observed to be diminished 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.

ACKNOWLEDGEMENTS

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磁気刺激による治療*

竹内直行[1)]　生駒一憲[1)]

Key Words：磁気刺激，脳卒中

はじめに

反復経頭蓋磁気刺激（repetitive transcranial magnetic stimulation；rTMS）は刺激強度，刺激頻度，刺激回数を変化させることによって大脳皮質の興奮性を変化させることが可能である．神経系の分析・評価だけでなく，興奮性，抑制性に働いたりする複雑なネットワークを呈する大脳で，刺激方法の組み合わせによりさまざまな中枢性疾患への応用が期待されている．今回，脳卒中に対するrTMS治療法について，他の神経疾患に対する治療報告を交えながら紹介する．

脳卒中後遺症（図）

1．脳卒中運動麻痺（表1）

左右半球の対立モデルから，脳卒中患者の運動麻痺は障害側運動野からの出力減少，および健側運動野からの過剰な脳梁抑制によるものと考えられている[1,2)]．そのため，脳卒中後の麻痺側機能の改善の戦略として，障害側運動野の興奮性増加，健側運動野の興奮性低下を引き起こすことが重要である．上記の理由からrTMSを用いて健側運動野を抑制，障害側運動野を興奮させて麻痺側機能を改善させる方法が報告されている．障害側運動野への高頻度rTMSおよび健側運動野への低頻度rTMSは，障害側運動野の興奮性を増加させ，錐体路機能の活性化および大脳皮質の可塑性を増大させるため，運動訓練効果が増大すると考えられている[3)]．

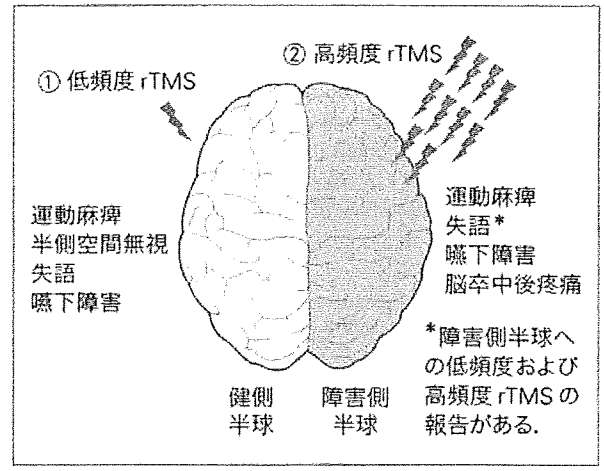

図　脳卒中後遺症に対するrTMS治療
① 低頻度rTMSによって健側半球の機能を低下させ，脳梁抑制を介し，障害側半球の活性化を引き起こす．
② 高頻度rTMSによって直接，障害側半球の活性化を引き起こす．

2．半側空間無視（表2）

片側半球障害によって引き起こされた半側空間無視は運動麻痺と同じメカニズムで，健側半球（主に左）からの過剰な脳梁抑制によって障害半球機能が低下すると考えられる．そのため，健側半球へ低頻度rTMSを行い，障害側半球を活性化させる報告が多い．

* Application of neurophysiology for rehabilitation：therapy using transcranial magnetic stimulation.

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表 1　脳卒中後麻痺に対する rTMS 治療報告

報告者	患者人数	障害部位	発症からの期間	刺激部位	刺激方法	刺激回数
Mansur CG, et al *Neurology*, 2005	8 人 rTMS 8 人 シャム刺激 8 人	皮質，皮質下梗塞	12 か月以上	健側運動野	1 Hz 100% rMT (健側)	600 stimuli
Khedr EM, et al *Neurology*, 2005	52 人 rTMS 26 人 シャム刺激 26 人	皮質下，皮質梗塞 (MCA 領域)	5〜10 日	障害側運動野	3 Hz 120% rMT (健側)	10 trains of 10s ×10 sessions
Takeuchi N, et al *Stroke*, 2005	20 人 rTMS 10 人 シャム刺激 10 人	皮質下梗塞	6〜60 か月	健側運動野	1 Hz 90% rMT (健側)	1,500 stimuli
Kim YH, et al *Stroke*, 2006	15 人 rTMS 15 人 シャム刺激 15 人	皮質下，皮質病変 (脳出血，脳梗塞)	6〜41 か月	障害側運動野	10 Hz 80% rMT (障害側)	8 trains of 2s
Fregni F, et al *Stroke*, 2006	15 人 rTMS 10 人 シャム刺激 5 人	皮質下，皮質梗塞	12〜126 か月	健側運動野	1 Hz 100% rMT (健側)	1,200 stimuli ×5 sessions
Talelli P, et al *Clin Neuropysiol* 2007	6 人 rTMS 6 人 シャム刺激 6 人	皮質下，皮質梗塞	12〜108 か月	障害側運動野	intermittent TBS 80% aMT (障害側)	20 trains of 10 bursts (5 Hz)
Kirton A, et al *Lancet Neruol* 2008[13]	10 人 (7 歳以上の小児) rTMS 5 人 シャム刺激 5 人	皮質下梗塞	28〜160 か月	健側運動野	1 Hz 100% rMT (健側)	1,200 stimuli ×8 sessions
Izumi S, et al *J Rehabil Med* 2008[17]	9 人 rTMS 5 人 シャム刺激 4 人	皮質下，皮質梗塞	9〜122 か月	障害側運動野	0.1 Hz 100% rMT* (障害側)	100 stimuli ×4 sessions

TBS：Theta Burst Stimulation（1 burst：50 Hz，3 stimuli），*麻痺側随意収縮中に実施

表 2　運動機能以外の症状に対する rTMS の応用の報告

報告者	障害名	患者人数	発症からの期間	刺激部位	刺激方法	刺激回数
Oliveri M, et al *Neurology*, 2001	半側空間無視	7 人 rTMS 7 人 シャム刺激 7 人	1〜48 週間	P5 or P6 (健側半球)	25 Hz 115% rMT (健側)	10 stimuli
Brighina F, et al *Neurosci Lett*, 2003	半側空間無視	3 人 コントロールなし	3〜5 か月	P5 (健側半球)	1 Hz 90% rMT (健側)	900 stimuli ×7 sessions
Shindo K, et al *J Rehabil Med*, 2006	半側空間無視	2 人 コントロールなし	6 か月	P5 (健側半球)	0.9 Hz 95% rMT (健側)	900 stimuli ×6 sessions
Naeser MA, et al *Brain Lang*, 2005	失語	4 人 コントロールなし	5〜11 年	右ブローカ部位 (健側半球)	1 Hz 90% rMT (健側)	1,200 stimuli ×10 sessions
Khedr EM, et al *Acta Neurol Scand*, 2009[5]	嚥下障害	26 人 rTMS 14 人 シャム刺激 12 人	5〜10 日	障害側運動野	3 Hz 120% rMT (健側)	10 trains of 10s ×5 sessions
Verin E, et al *Dysphagia*, 2009[6]	嚥下障害	7 人 コントロールなし	11〜132 か月	健側運動野	1 Hz 120% rMT (健側)	120 stimuli ×5 sessions
Khedr EM, et al *J Neurol Neurosug Psychiatry*, 2005	脳卒中後疼痛	24 人 rTMS 14 人 シャム刺激 10 人	18±17 か月	障害側運動野	20 Hz 80% rMT (障害側)	10 trains of 10s ×5 sessions
Andre-Obadia N, et al *Clin Neuropysiol*, 2006	脳卒中後疼痛	10 人 rTMS 10 人 シャム刺激 10 人	6.9±4.0 年	障害側運動野	20 Hz 90% rMT (障害側)	20 trains of 4s
Hirayama A, et al *Pain*, 2006	脳卒中後疼痛	12 人 rTMS 12 人 シャム刺激 12 人	1.3〜16 年	障害側運動野	5 Hz 90% rMT (障害側)	10 trains of 10s
Goto T, et al *Pain*, 2008	脳卒中後疼痛	17 人 コントロールなし	1.0〜8.8 年	障害側運動野	5 Hz 90% rMT (障害側)	10 trains of 10s

3．失　語（表2）

左半球言語領域周囲または右半球の病巣対側部位など，患者間によって機能代償部位が異なるため，個々の症例に合わせて刺激部位を決定する必要がある．安保[4]は言語タスク時の機能画像を利用し，賦活部位の対側半球に低頻度 rTMS を行い，言語機能の回復が得られたと報告している．

4．嚥下障害（表2）

障害側半球への高頻度 rTMS[5]，および健側半球への低頻度 rTMS[6]の報告がある．急性期および慢性期ともに報告を認めるが，急性期においては自然回復の可能性（コントロール群よりは改善を認めているが）の問題点がある．また，嚥下機能は両側支配の報告が多いため，健側半球機能を低下させることにより嚥下機能が悪化する可能性も否定できない．

5．脳卒中後疼痛（表2）

障害側運動野へ高頻度 rTMS を行う報告が多い．疼痛改善のメカニズムは不明であるが，以前より大脳皮質電気刺激によって除痛が得られた報告があり，共通のメカニズムが推測されている．一つの仮説としては，脳卒中後の慢性疼痛は障害側運動野での脱抑制に関連があると考えられており，それを rTMS で是正することによって除痛効果が得られる可能性がある[7]．

rTMS 実施における注意点

rTMS の副作用としては，てんかん誘発が一番の問題点である．rTMS 実施には，Wassermann[8]，Chen ら[9]および日本臨床神経生理学会[10]から公表されている rTMS の安全性に関するガイドラインに従って行うことが望ましい．大脳皮質の興奮性の目安として筋電図をモニターすることが行われるが，可能であれば脳波もモニターすることが望ましい．

一般的に rTMS の禁忌として，頭蓋内の金属，心臓ペースメーカー，てんかんが挙げられる．コイル近くの金属製の物体は TMS により加熱されるため，一般的に口以外の頭部金属の存在は TMS に禁忌である．その一方で，低頻度 rTMS は GABA 受容体などの大脳皮質レベルでの抑制機構の機能亢進を誘導できる可能性から，低頻度 rTMS がてんかんの治療に有効であるとの論文が報告されている[11,12]．

今後の可能性と問題点

1．小児脳卒中患者に対する rTMS

成人脳卒中患者の報告が主であったが，2008 年に小児脳卒中患者での検討が初めて報告された[13]．ただし，この報告は 7 歳以上の症例を対象としている．6～7 歳以下の小児は脳梁が未発達であるため，過剰な脳梁抑制を低下させる健側 rTMS 療法は効果が少ないと考えられている．

2．運動療法との併用

強制使用は，麻痺のためあまり使用していない麻痺側上肢を強制的に使用することによって運動機能を改善させる方法であるが，健側上肢を抑制することによって健側半球興奮性を低下させる側面をもつ[14]．そのため，強制使用は障害側運動野を活性化させ，健側運動野の興奮性を低下させる rTMS 治療法と共通点がある．障害側 rTMS と強制使用の併用に追加効果はなかったが[15]，健側 rTMS と強制使用の組み合わせには，有効な可能性が示唆されている[16]．さらに，麻痺側運動中に障害側運動野へ rTMS を実施することで麻痺が改善したとの報告がある[17]．

3．健側機能に与える問題点

低頻度 rTMS によって健側機能の低下は認めない報告が多いが[18]，脳卒中患者において健側運動野は，麻痺側運動に対する高次機能につき関連が指摘されているため[19]，健側運動野の抑制は健側上肢機能を悪化させる可能性がある．ただし，障害側半球への高頻度 rTMS もてんかんのリスクを増大させる可能性がある[20]．

4．追加刺激

rTMS の効果として，加速度，反応時間，ペグボードタスクの改善が報告されており，単回の rTMS によって得られる改善率は 10～30%程度である．障害側への 3 Hz rTMS を 10 日間実施することによって刺激後も効果が 10 日間持続し[21]，健側運動野へ低頻度 rTMS を 5 日間実施することによって運動機能の改善が 2 週間持続したことが報告されている[22]．しかし，麻痺のステージが改善するなど，日常生活レベルでの改善はいまだに難

表 3　その他の中枢性疾患に対する rTMS の応用の報告

報告者	障害名	患者人数	刺激部位	刺激方法	刺激回数
Siebner HR, et al *NeuroReport*, 1999	パーキンソン病	12 人 rTMS 12 人 シャム刺激 12 人	運動野 （症状のより強い部位の対側）	5 Hz 90% rMT	15 trains of 30s
Koch G, et al *Neurology*, 2005	パーキンソン病	8 人 rTMS 8 人 シャム刺激 8 人	補足運動野	1 Hz 90% rMT	900 stimuli
Hamada M, et al *Mov Disord*, 2008	パーキンソン病	98 人 rTMS 55 人 シャム刺激 43 人	補足運動野	5 Hz 110% aMT	20 trains of 10s ×8 sessions
Terugau F, et al *Lancet*, 1999[11]	てんかん	9 人 コントロールなし	円形コイルの中央部を頭頂部に設置*	0.33 Hz 刺激強度の記載なし	1,000 stimuli ×5 sessions
Kinoshita M, et al *Seizure*, 2005[12]	てんかん	7 人	F3，F4，P3**	0.9 Hz 90% rMT or 100% aMT	2 trains of 15 min ×5 sessions
Siebner HR, et al *Neulogy*, 1999	ジストニア	16 人 rTMS 16 人 シャム刺激 10 人	左運動野 （右手が罹患部位）	1 Hz 90% rMT	1,800 stimuli
Murase CG, et al *Brain*, 2005	ジストニア	9 人 rTMS 9 人 シャム刺激 9 人	運動野，運動前野 補足運動野	0.2 Hz 85% rMT	250 stimuli

*円形コイルのため特定の刺激部位ではないが，両側運動野が刺激されていると考えられる．
**10/20 EEG system に基づく．

表 4　rTMS による治療報告

- 脳卒中
- パーキンソン病
- うつ病
- ジストニア
- 耳鳴り
- 神経因性疼痛
- てんかん
- 筋萎縮性側索硬化症
- 統合失調症
- 強迫性障害
- トゥレット症候群

しいのが現状である．

5．患者背景

われわれの検討では，年齢，発症からの期間などによる rTMS 効果の差は認めなかった[23]．rTMS の効果は，健側運動野刺激および障害側運動野刺激ともに，障害側運動野の活性化を目的とするため，運動野に病巣がある症例に対する効果は小さいと考えられる．麻痺側が共同運動レベルである症例には rTMS の効果が少ないことを経験しており，効果がある症例は錐体路機能がある程度保たれている必要がある．

おわりに

磁気刺激による治療は，パーキンソン病，てんかん，ジストニアなどの中枢性疾患への応用も報告されている（**表 3**）[24]．rTMS による治療報告のある主な疾患を**表 4** に示したので参照していただきたい．

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ニュース News

肢体不自由児に音楽教材を
CD ブック製作

三重県立度会特別支援学校の小学部音楽グループが，肢体不自由児のための CD ブック「イキイキたいそう」を自費製作した．肢体不自由児を対象にした音楽教材はほとんどなく，現場から生まれた教材として関係者から注目を集めそうだ．

それまでは，現場に即した教材がなく，幼児や一般向けの教材をアレンジして使っていた．だが，障害の度合いによっては，テンポが速すぎたり，動きが難しすぎるなど，使い勝手が悪かった．

CD ブックは，約 70 分の音楽と A4 判 94 頁の冊子のセット．冊子は 1 曲ずつ見開きで動作説明，動かし方・援助の仕方，演奏のコツ，楽譜などを写真やイラスト入りで分かりやすく紹介．子どもたちの障害の度合いに合わせて活用できるよう，現場ならではの細やかな配慮が随所にちりばめられている．

CD ブックは無料（送料 1 冊 290 円）で配布している．問い合わせと申し込みは氏名，所属先，電話番号，郵送先住所を記入し，ファクス（0596-62-0002）で三重県立度会特別支援学校の小学部音楽グループへ．（小沢由紀）

（毎日新聞・三重　2009 年 6 月 5 日）

経頭蓋磁気刺激療法

竹内直行　生駒一憲

はじめに

1985年イギリスのBarkerらが中枢神経を安全に刺激できる経頭蓋磁気刺激(transcranial magnetic stimulation；TMS)をLancetに紹介後[1]，1991年Pascual-Leoneらが連続的にTMSを行う反復経頭蓋磁気刺激法(repetitive transcranial magnetic stimulation；rTMS)をはじめてヒトに応用した[2]．それ以降様々な中枢神経疾患の評価および治療に応用されている．今回TMSのメカニズム，rTMSの臨床応用の報告について記載する．

TMSの作用

TMSのメカニズムとして頭蓋上においたコイルに高電流高電圧をパルスで流し，それにより生じる磁束が，頭蓋骨に平行な大脳の良導体部分に渦電流を引きおこすことにより，平行に走行する大脳介在ニューロンが主として興奮し，介在ニューロンに接続する皮質脊髄ニューロンが間接的に興奮することによって，最終的に筋発射がおこると考えられている(図1)[3,4]．rTMSは刺激強度，刺激頻度，刺激回数を変化させることによって大脳皮質の興奮性を変化させることが可能で，刺激方法の組み合わせにより様々な中枢性疾患への応用が期待されている．1 Hz以下の低頻度rTMSは刺激部位に抑制性に作用し[5]，5 Hz以上の高頻度rTMSは興奮性の作用を持つ[6]．

rTMS実施における注意点

rTMSの副作用としてはてんかん誘発が一番の問題点であり，rTMS実施には，Wassermann[7]，Chenら[8]から公表されているrTMSの安全性に関するガイドラインに従っ

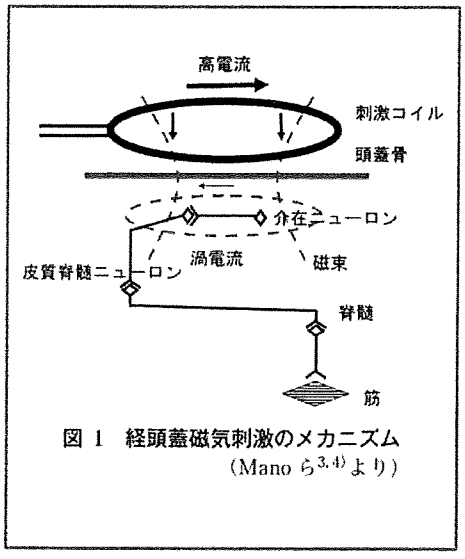

図1　経頭蓋磁気刺激のメカニズム
(Manoら[3,4]より)

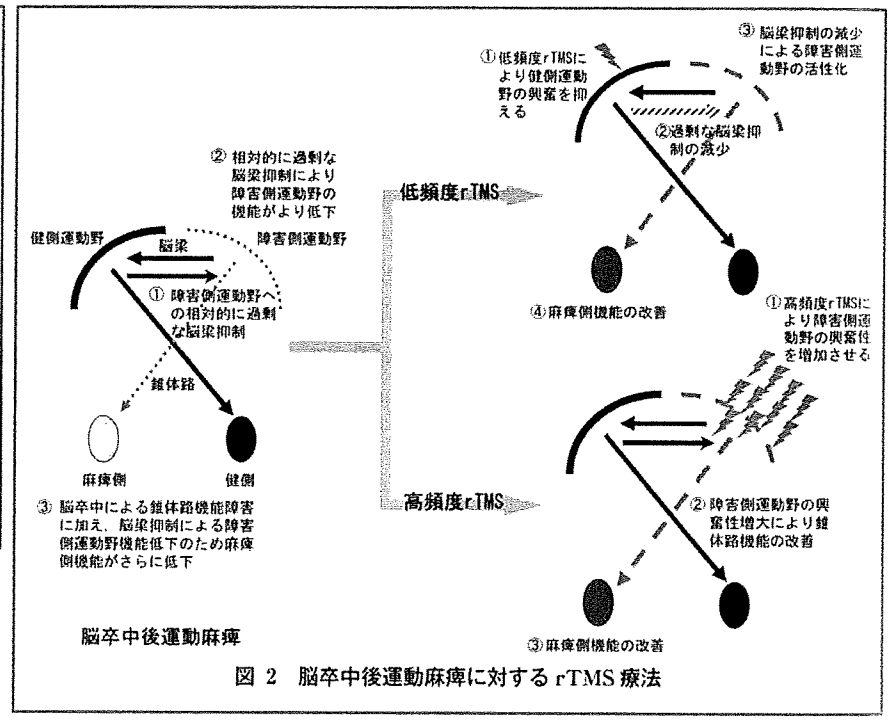

図2　脳卒中後運動麻痺に対するrTMS療法

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いこま かつのり　同 教授

0289-0585/09/¥500/論文/JCOPY

て行うことが望ましい．大脳皮質の興奮性の目安として筋電図をモニターすることが行われるが，可能であれば脳波をモニターすることが望ましい．一般的にrTMSの禁忌として頭蓋内の金属，心臓ペースメーカー，てんかんの家系があげられる．コイル近くに金属製の物体があるとTMSにより加熱されるため，口以外の頭部金属の存在は一般的にTMSに禁忌である．しかしながら低頻度rTMSは抑制効果があり，GABA受容体などの大脳皮質レベルでの抑制機構の機能亢進を誘導できる可能性から，低頻度rTMSがてんかんの治療に有効であるとの論文が報告されている[9,10]．

臨床応用

様々な疾患に対する治療結果が報告されているが，リハビリテーションの対象となる脳卒中患者への応用が期待されている．左右半球の対立モデルから，脳卒中患者の運動麻痺は障害側運動野からの出力減少，および健側運動野からの過剰な脳梁抑制によるものと考えられている（図2左）[11,12]．そのため脳卒中後麻痺側機能の改善の戦略として，障害側運動野興奮性の増加，健側運動野興奮性の低下

表1 脳卒中後麻痺に対するrTMS治療報告

報告者	患者人数(人)	障害部位	発症からの期間	刺激部位	刺激方法	刺激回数
Mansur et al. 2005 Neurology	8 rTMS 8，シャム刺激 8	皮質，皮質下梗塞	12カ月以上	健側運動野	1 Hz 100% rMT(健側)	600 stimuli
Khedr et al. 2005 Neurology	52 rTMS 26，シャム刺激 26	皮質下，皮質梗塞 (MCA 領域)	5-10 日	障害側運動野	3 Hz 120% rMT(健側)	10 trains of 10 s ×10 sessions
Takeuchi et al. 2005 Stroke	20 rTMS 10，シャム刺激 10	皮質下梗塞	6-60カ月	健側運動野	1 Hz 90% rMT(健側)	1500 stimuli
Kim et al. 2006 Stroke	15 rTMS 15，シャム刺激 15	皮質下，皮質病変 (脳出血，脳梗塞)	6-41カ月	障害側運動野	10 Hz 80% rMT(障害側)	8 trains of 2 s
Fregni et al. 2006 Stroke	15 rTMS 10，シャム刺激 5	皮質下，皮質梗塞	12-126カ月	健側運動野	1 Hz 100% rMT(健側)	1200 stimuli ×5 sessions
Talelli et al. 2007 Clin Neurophysiol	6 rTMS 6，シャム刺激 6	皮質下，皮質梗塞	12-108カ月	障害側運動野	intermittent TBS 80% aMT(障害側)	20 trains of 10 bursts (5 Hz)
Kirton et al. 2008 Lancet Neurol	10 (7歳以上の小児) rTMS 5，シャム刺激 5	皮質下梗塞	28-160カ月	健側運動野	1 Hz 100% rMT(健側)	1200 stimuli ×8 sessions
Izumi et al. 2008 J Rehabil Med	9 rTMS 5，シャム刺激 4	皮質下，皮質梗塞	9-122カ月	障害側運動野 (麻痺側随意収縮中に実施)	0.1 Hz >100% rMT(障害側)	100 stimuli ×4 sessions

TBS：Theta Burst Stimulation
(1 burst：50 Hz，3 stimuli)

表2 運動機能以外の症状に対するrTMSの応用

報告者	障害名	患者人数(人)	発症からの期間	刺激部位	刺激方法	刺激回数
Oliveri et al. 2001 Neurology	半側空間無視	7 rTMS 7，シャム刺激 7	1-48 週間	P5 or P6 (健側半球)	25 Hz 115% rMT(健側)	10 stimuli
Brighina et al. 2003 Neurosci Lett	半側空間無視	3 コントロールなし	3-5カ月	P5 (健側半球)	1 Hz 90% rMT(健側)	900 stimuli ×7 sessions
Shindo et al. 2006 J Rehabil Med	半側空間無視	2 コントロールなし	6カ月	P5 (健側半球)	0.9 Hz 95% rMT(健側)	900 stimuli ×6 sessions
Naeser et al. 2005 Brain Lang	失語	4 コントロールなし	5-11 年	右 Broca 部位 (健側半球)	1 Hz 90% rMT(健側)	1200 stimuli ×10 sessions
Khedr et al. 2009 Acta Neurol Scand	嚥下障害	26 rTMS 14，シャム刺激 12	5-10 日	障害側運動野	3 Hz 120% rMT(健側)	10 trains of 10 s ×5 sessions
Verin et al. 2009 Dysphagia	嚥下障害	7 コントロールなし	11-132カ月	健側運動野	1 Hz 120% rMT(健側)	120 stimuli ×5 sessions
Khedr et al. 2005 J Neurol Neurosurg Psychiatry	脳卒中後疼痛	24 rTMS 14，シャム刺激 10	18±17カ月	障害側運動野	20 Hz 80% rMT(障害側)	10 trains of 10 s ×5 sessions
Andre-Obadia et al. 2006 Clin Neurophysiol	脳卒中後疼痛	10 rTMS 10，シャム刺激 10	6.9±4.0 年	障害側運動野	20 Hz 90% rMT(障害側)	20 trains of 4 s
Hirayama et al. 2006 Pain	脳卒中後疼痛	12 rTMS 12，シャム刺激 12	1.3-16 年	障害側運動野	5 Hz 90% rMT(障害側)	10 trains of 10 s
Goto et al. 2008 Pain	脳卒中後疼痛	17 コントロールなし	1.0-8.8 年	障害側運動野	5 Hz 90% rMT(障害側)	10 trains of 10 s

表 3　その他の中枢性疾患に対する rTMS の応用

報告者	障害名	患者人数(人)	刺激部位	刺激方法	刺激回数
Siebner et al. 1999 NeuroReport	パーキンソン病	12 rTMS 12，シャム刺激 12	運動野 (症状のより強い部位の対側)	5 Hz 90% rMT	15 trains of 30 s
Koch et al. 2005 Neurology	パーキンソン病	8 rTMS 8，シャム刺激 8	補足運動野	1 Hz 90% rMT	900 stimuli
Hamada et al. 2008 Mov Disord	パーキンソン病	98 rTMS 55，シャム刺激 43	補足運動野	5 Hz 110% aMT	20 trains of 10 s ×8 sessions
Terugau et al. 1999 Lancet	てんかん	9 コントロールなし	円形コイルの中央部を 頭頂部に設置*	0. 33 Hz 刺激強度の記載なし	1000 stimuli ×5 sessions
Kinoshita et al. 2005 Seizure	てんかん	7	F 3，F 4，P 3**	0. 9 Hz 90% rMT or 100% aMT	2 trains of 15 min ×5 sessions
Siebner et al. 1999 Neurology	ジストニア	16 rTMS 16，シャム刺激 10	左運動野 (右手が罹患部位)	1 Hz 90% rMT	1800 stimuli
Murase et al. 2005 Brain	ジストニア	9 rTMS 9，シャム刺激 9	運動野，運動前野 補足運動野	0. 2 Hz 85% rMT	250 stimuli

*円形コイルのため特定の刺激部位ではないが，両側運動野が刺激されていると考えられる．
**accoding to 10/20 EEG system

を引きおこすことが重要である．上記の理由から rTMS を用い健側運動野を抑制，障害側運動野を興奮させ，麻痺側機能を改善させる方法が報告されている(表 1)(図 2 右)[13~15]．運動機能障害以外にも脳卒中後疼痛，失語，半側空間無視，嚥下障害への応用が報告されている(表 2)．

その他の疾患に対する rTMS の臨床応用として，パーキンソン病，てんかん，ジストニア(表 3)，うつ病，耳鳴り，筋萎縮性側索硬化症，統合失調症，強迫性障害，疼痛と多岐にわたり報告されている[16]．

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Tobacco Smoking Can Potentiate C-fiber Evoked Potentials in Human Brain

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Abstract: The effects of smoking and nicotine on ultralate laser evoked potentials (LEPs), the EEG responses to C-fiber stimulation by a laser beam, were investigated in humans. Ultralate LEPs were repeatedly measured in two sessions, one after smoking, and the other in abstinence from smoking. The dominant frequency of the background EEG alpha activity, heart rate and venous plasma nicotine concentration were also measured. The peak-to-peak amplitude of the two major components (N2 and P2) of ultralate LEPs was significantly correlated both with the plasma nicotine concentration and with the background alpha frequency. The results suggest an arousal effect of nicotine on C-fiber mediated pain. The effect of nicotine on C-fiber LEPs was in the opposite direction of that on Aδ fiber LEPs. The difference between C and Aδ fibers might indicate a difference in effects of nicotine on first and second pain responses.

Keywords: Electroencephalography, pain, unmyelinated nerve fibers, tobacco smoking, event related potentials, nicotine.

INTRODUCTION

Numerous studies have explored effects of smoking and nicotine on event related potentials (ERPs) [1, 2], including selected ERP components [3] and the P300 [4]. Most of these studies reported increased amplitudes and/or decreased latencies supporting the hypothesis that nicotine generally enhances brain processing. On the contrary, we recently found that Aδ fiber pain-related laser evoked potentials (LEPs) were reduced by smoking (Miyazaki *et al.*, submitted 2009). Since the degree of the amplitude reduction was in parallel with the plasma concentration of nicotine, the finding was in line with previous studies showing antinociceptive effects of nicotine in animals [5, 6] and humans [7, 8].

Noxious stimuli applied to the skin, however, activate two discrete nociceptive pathways. The sharp or first pain is mediated by thinly-myelinated Aδ fibers while the dull or second pain by unmyelinated C fibers. The sharp pain is considered to facilitate avoidance behaviors while the dull pain is thought to be related to more prolonged pain as in inflammation. Since the peripheral conduction velocity is markedly different between the two fibers (10 to 20 versus 0.5 to 2.0 m/s), evoked potentials due to Aδ and C-fibers can be clearly differentiated [9]. Special stimulating paradigms enable one to activate C-fibers exclusively [10]. This is the first report on the effects of tobacco smoking and nicotine on pain-related brain activities after selective C fiber stimulation.

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MATERIALS AND METHODS

Subjects

Ten healthy male volunteers who had a smoking habit participated in the study. Since no clear cortical responses were evoked by laser stimulation in two subjects, probably due to a small signal-to-noise ratio when recording ultralate LEPs, data from eight subjects aged 24 to 43 (mean ± SD: 32.9 ± 6.6) years were used. The mean number of years that the subjects have smoked was 11.2 ± 8.3 years. The mean number of cigarettes they were smoking per day was 10.3 ± 5.1. The subjects had no history of psychiatric or neurological disorders, or substance abuse, which were confirmed by the authors; psychiatrists (T.M. and K.I) and a neurologist (R.K.). The study was approved in advance by the Ethics Committee of the National Institute for Physiological Sciences, Okazaki, Japan. Written consent was obtained from all the subjects.

Stimulation and Recordings

A Tm:YAG laser (BLM1000S, Carl Baasel Lasertechnik, Starnberg, Germany) was used for noxious stimulation. The laser pulses were 2000 nm in wavelength, 1 ms in duration, and 3 mm in diameter. A low intensity laser beam was applied to a tiny area of subjects' skin using a thin aluminum plate with numerous fine holes as a spatial filter, to selectively stimulate unmyelinated C fibers without activating Aδ fibers as described previously [10, 11]. The beam was applied to the dorsum of the right hand between the first and second metacarpal bones. The stimulation intensity was adjusted to a level at which stimulation produced a clear pricking Aδ mediated pain without the spatial filter (156.3 ± 9.5 mJ). The laser energy was kept constant throughout the experiment for each session of each

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subject. To avoid tissue damage, the irradiated points were moved slightly for each stimulus.

LEPs were recorded using a scalp electrode placed at Cz referred to the linked earlobes (A1+A2) according to the International 10/20 system. The EEG signals were recorded with a bandpass filter of 0.1 to 100 Hz at a sampling rate of 1000 Hz, and then digitally filtered with a 50 Hz low-pass filter. The window of analysis was from 100 ms before to 1200 ms after the stimulus onset, and the prestimulus period was used as the DC baseline. For the analysis of the dominant alpha frequency of background EEG activity, electrodes were placed on O1 and O2. The impedance of the electrodes was kept below 5 kohm. A pair of electrodes on the supra- and infra-orbit of the right eye was used to reject blink artifacts. An electrocardiogram was used to measure the heart rate, using a pair of disk electrodes placed on each forearm.

Procedures

The experiments were conducted in two sessions, Smoking and Control, on a separate day starting at either 9 am or 1 pm. The starting time was counterbalanced between subjects and between sessions. The procedures of the experiment were the same for the two sessions, except that subjects did not smoke a cigarette in the Control session. For each session, subjects were required to be abstinent from smoking for at least twelve hours before the experiment. To confirm this, CO concentration in end-tidal expired air was measured at first. Subjects were asked to exhale into an analyzer (Micro CO, Micro Medical Ltd., Rochester, UK). Subjects were seated in an armchair in a quiet electrically shielded room with temperature controlled at 24 to 26°C. An indwelling catheter for collecting venous blood samples was placed in the left cephalic vein. There were five runs of recordings at different times: before smoking (Pre), and 5, 20, 35 and 60 minutes after smoking. Just before each run, venous blood was collected for measurements of plasma nicotine concentration (PNC), and an electrocardiogram and EEGs were recorded for at least 20 s for heart rate and alpha frequency calculation, respectively.

The peak frequency of the background alpha activity was determined using fast Fourier transform (FFT). In each run, twelve stimuli were applied and LEPs were recorded. The inter-stimulus interval was varied at random between 14 and 19 sec. In the Smoking session, subjects smoked a cigarette with 1.0 mg of nicotine for five minutes just after Pre, and then the remaining four runs followed. The Control session was conducted 5 to 20 (mean 11.2) days after the Smoking session for each subject. The plasma nicotine concentrations were measured using gas chromatography-mass spectrometry. The method was similar to that used previously to analyze urinary cotinine concentrations [12] with the addition of a solid phase extraction step carried out on an MCX column (Water Corporation, Milford, MA). The MCX column was prepared and the sample eluted as described previously [13]. The blood samples were from the same subjects that participated in our previous study (Miyazaki *et al.*, submitted 2009). Since the sensation that the subjects perceived after laser stimulation varied from a mild pressure to burning pain as we previously reported [11], we did not measure subjective pain ratings in this study.

Data Analysis

For each run of LEP recordings, five artifact-free epochs with a clear response were averaged. The peak latency of N2 and P2, and the peak-to-peak amplitude of the N2/P2 complex were calculated using time frames with latency periods of 650 to 1000 ms and 700 to 1150 ms for N2 and P2, respectively. The effects of Smoking (the Smoking session versus the Control session) and Run were assessed by two-way analysis of variance (ANOVA). Changes in the N2/P2 amplitude and in the frequency of the background alpha-band EEG activity relative to those of Pre were calculated. The correlations between the N2/P2 amplitude and dominant alpha frequency, and between the N2/P2 amplitude and PNC were assessed by a coefficient, r. Data were expressed by the mean ± standard deviation.

RESULTS

The expiratory CO concentration was 0 to 6 (mean ± SD: 2.9 ± 1.0) and 0 to 9 (3.5 ± 0.9) ppm for the Smoking and Control sessions, respectively, indicating the instruction to be abstinent from smoking was followed by the subjects. The PNC, mean heart rate and dominant frequency of the alpha activity for each run are listed in Table **1**. The PNC, heart rate and alpha frequency for Pre were not different between the Control and Smoking sessions ($p = 0.20$, $p = 0.69$ and $p = 0.20$, respectively, paired-t test). In the Smoking session, the heart rate, alpha frequency and PNC increased 5 min after smoking and gradually decreased (Fig. **1**). Results of a two-way (Smoking and Run) ANOVA indicated that Smoking was a significant factor to determine PNC ($F(1, 70) = 33.6$, $p < 0.0001$), heart rate ($F(1, 70) = 12.3$, $p = 0.0008$) and background alpha frequency ($F(1, 70) = 17.4$, $p < 0.0001$). A significant interaction between Smoking and Run was also found for all of PNC ($F(4, 70) = 4.6$, $p = 0.0022$), heart rate ($F(4, 70) = 2.52$, $p = 0.049$) and alpha frequency ($F(4, 70) = 2.7$, $p = 0.04$). The mean PNC, heart rate and background alpha rhythm were largest for the 5 min run.

The N2 and P2 components of LEPs were observed at 775 ± 66 and 892 ± 70 ms after the onset of stimulation, respectively (Fig. **2A**). The peak latencies of the N2 and P2 components and the N2/P2 peak-to-peak amplitude are listed in Table **1**. A two-way (Smoking and Run) ANOVA indicated that the N2 latency did not differ significantly between the two sessions ($p = 0.11$) or among five runs ($p = 0.34$). Smoking and Run were also not a significant factor to determine the P2 latency ($p = 0.20$ and 0.22, respectively). On the other hand, a two-way ANOVA showed that the N2/P2 amplitude was significantly different among five runs ($F(4, 70) = 5.1$, $p = 0.0012$), but not between the Control and Smoking sessions ($p = 0.74$). Grand-averages of ultralate LEPs across subjects for each run are shown in Fig. (**2A**).

As shown in Fig. (**2B**), the behavior of the N2/P2 amplitude over the Runs for the Smoking session was similar to that of the dominant alpha frequency. To support this, the N2/P2 amplitude had a significant positive correlation with the dominant frequency of the background alpha rhythm in the Smoking session ($r = 0.44$, $p = 0.0047$, Fig. **3B**). This positive correlation was also found in the Control session ($r = 0.33$, $p = 0.037$, Fig. **3A**). Both the dominant alpha frequency ($r = 0.58$, $p < 0.0001$) and N2/P2 amplitude ($r =$