Changes in Cortical Excitability during and just before Motor Imagery

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Objective: Changes in cortical excitability during motor imagery were investigated in order to reveal the effect of hand dominance. During motor imagery, motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) muscle of the dominant hand using transcranial magnetic stimulation (TMS).
Methods: Twelve healthy right-handed subjects participated. Three motor imagery tasks (MITs) were provided; dominant hand grasping, non-dominant hand grasping, and ankle dorsiflexion ipsilateral to the dominant hand. MEPs were also recorded from the FDI muscle of the non-dominant hand during the same tasks.
Result: MEPs increased significantly in the dominant hand during MIT, just before MIT of the dominant hand, and prior to ankle dorsiflexion ipsilateral to the dominant hand. MEPs obtained from the FDI muscle of the dominant hand during MITs were greater than that obtained from the FDI muscle of the non-dominant hand. However, this difference was not significant.
Conclusion: The left primary motor cortex (M1) was more excited than M1 during MITs of the hand muscles. Cortical excitability increased just before MIT of the contralateral hand and leg muscles.

Key words: cortical excitability, motor imagery, transcranial magnetic stimulation, motor evoked potential, Lateralization

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a non-invasive tool for investigating the functioning of the human motor system. TMS over the primary motor cortex (M1), especially over the hand area, produces motor evoked potentials (MEP) in the corresponding skeletal muscles contralateral to the stimulated side [1, 2]. MEP amplitude reflects the level of cortical excitability.

Motor imagery in healthy subjects has been reported to increase cortical excitability [3]. MEP increases during motor imagery of the target muscle compared to no imagery (i.e., at rest). In studies of brain function imaging, it has been suggested that activity in the M1 area during a motor imagery task (MIT) is very similar to that observed during actual execution of the movement [4]. Recently, predominance of the left hemisphere has been indicated in many aspects of higher level motor planning [5, 6]. In addition, lateralization of motor imagery to the left hemisphere has important implications in rehabilitation [7].

Also, in several electroencephalogram (EEG) studies, change of EEG had been observed during not only motor execution but MIT. This phenomenon has been recognized as an event-related desynchronization (ERD), which indicates oscillations in cortical activation. Further, it suggested that this ERD may begin just before MIT [8]. In TMS study, Suzuki *et al.* reported that MEP amplitude at the beginning of imagery was assumed as resting condition [9]. But Kumru *et al.* noted that a significant increase of MEP amplitude was shown at 50ms before the beginning of MIT [10]. Moreover, there were no researches investigating the functional lateralization between left and right hemisphere just before MIT. So in this study, we investigated changes cortical excitability by use of TMS not only during MIT but also just before imagery, and considered the differences between the excitability of right and left hand area of M1 in healthy subjects.

MATERIALS AND METHODS

Subjects and Experimental set-up

Twelve healthy, normal right-handed subjects (7 men, 5 women; mean age: 35.8 ± 5.7 years, range: 23–54 years), with no known neurological disorders or contraindications to TMS [11] participated in this study. Dominant hand was determined by the Edinburgh Handedness Inventory [12]. The present study was approved by the Clinical Research Review Committee of the Tokai University School of Medicine and performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects.

Experiments were conducted in a quiet laboratory room at a controlled temperature of 25–27°C. Subjects sat in a comfortable reclining armchair with their eyes open facing a red light-emitting diode (LED) placed approximately 0.5 m in front of them at eye level. Arms and hands were at rest. Before the experiments began, subjects were required to keep their hands and fingers as relaxed as possible and to remain awake. An infrared heater was used to maintain hand and forearm skin temperatures at > 32°C.

To investigate cortical excitability of the left M1, all subjects were examined (i.e., the experiment in

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dominant M1). TMS was delivered over the left M1, and MEPs were recorded from right first dorsal interosseous (FDI) muscle. Also, to investigate changes in cortical excitability of the right M1 (i.e., the experiment in non-dominant M1), 6 of the 12 subjects were examined. Inversely to investigate in the dominant M1, TMS was delivered over the right M1 and MEPs were evoked from the left FDI.

TMS and electromyography (EMG) recording and motor imagery

The method and application of TMS procedures were similar to those described in a previous study [9]. TMS was performed using a Magnetic Stimulator SMN1200 with a maximal magnetic field strength of 2.2 Tesla (Nihon Kohden Co., Tokyo, Japan) equipped with a figure-eight coil 9 cm in mean diameter. The intersection of the coil was placed tangentially to the scalp, positioned approximately 2 cm to the left of the Cz according to the International 10−20 system, with the handle pointing backwards and laterally at 45º away from the midline. Stimulus intensity was initially set at 60% of the stimulator output. The coil was moved over the scalp in 1-cm steps to determine the hotspot. In the right hand experiment, TMS was applied over the hand motor area contralateral to the right hand to determine the hotspot and resting motor threshold (rMT). In the left hand experiment, TMS was applied over the hand motor area contralateral to the left hand. The position over which the magnetic stimulus elicited the largest and fastest MEP was considered to be the hotspot. MEPs were recorded from right and left FDIs using belly-tendon recording with surface Ag/AgCl disc electrodes (1 cm in diameter) with a bandpass of 5−2 kHz by a Neuropack MEB-2208 (Nihon Kohden Corporation, Japan). A disposable pre-gelled Ag/AgCl ground electrode was placed around the right hand.

EMG activities in the right FDI, left FDI, and right and left tibialis anterior (TA) muscles were monitored simultaneously to exclude the effects of voluntary movement. The sensitivity was set at 50 μV/div to check no contraction. rMT was defined as the lowest stimulus intensity to evoke at least 5 out of 10 MEPs with amplitudes of at least 50 μV. In all MITs, TMS intensity was then set at 120% of rMT. Control of TMS stimuli, lighting of LED and analysis of MEP data were performed using the LabVIEW 8.6 software (National Instruments Japan Corporation, Japan).

In each experiment, subjects were asked to do three independent imagery tasks (described as follows).

1) Right (dominant) hand grasping (RHG)
2) Left (non-dominant) hand grasping (LHG)
3) Right or Left ankle dorsiflexion (ADF).

At the experiment in dominant M1, MEPs were evoked from right FDI, subjects were requested to imagine their right ADF movement. On the other hand, at the experiment in non-dominant M1, they imagined their left one. In each experiment, the orders of these MITs were selected at random.

During these tasks, LED always lighted for 2s as the cues of the MIT. In each task, all subjects were instructed to imagine continuously while the LED was lighting. Turning off the LED light means the cues of finishing the imagery, so that subjects were required to stop imagery and keep all limbs relaxed (i.e., at rest). The LED lighted repetitively at the randomized intervals between 3 and 6 s.

In each MIT, TMS was delivered at one of four timings, 0, 1, 2, or 3s after the start of LED cue. We programmed that the order of those were selected automatically and randomly. TMS was also delivered at 3s after the cue (i.e., exactly 1s after the turning off the LED light). This MEP was measured at rest. We assumed this as evaluation at rest. First, the MEP amplitude at 0s was assumed evaluating the cortical excitability at just before the beginning of MIT. Thus, in the present study, we decided this as "just before MIT". Next, the MEP amplitude at 1 and 2s during motor imagery were considered for the evaluation of the excitability of the motor cortex and the length of the excitability change. Ten stimuli were delivered in each timing, and totally forty stimuli were delivered in all timings.

Data analysis

MEPs were recorded and measured as amplitudes from peak to peak determined by averaging 10 measurements in all of experiments. The amplitude of MEPs, which were recorded at rest, was compared between other three conditions in each experiment by conducting a Kendall rank correlation coefficient. MEPs at just before MIT and during MIT were expressed as a percentage of the average of the MEP at rest. Wilcoxon's signed-rank test was used for comparison. Differences were considered significant at a p value <0.05. The Statistical Packages for Social Sciences (SPSS 13.0J for Windows; SPSS Inc., Chicago, IL, USA) was used to conduct the statistical analysis.

RESULTS

Experiment in dominant M1

The mean amplitudes of MEPs at rest, which were measured in tasks of RHG, LHG, and right ADF were 1.40 ± 0.35 mV, 1.51 ± 0.39 mV, and 1.64 ± 0.28 mV, respectively. There were no significant differences between them. During the task in RHG, the mean amplitudes of MEPs just before MIT, 1s and 2s, were 2.50 ± 0.72 mV, 3.27 ± 0.99 mV, and 2.99 ± 0.82 mV, respectively. These percentage changes in MEPs increased significantly compared to those at rest ($p < 0.05$). Typical MEPs recorded during the different imagery tasks in one subject, are shown in Fig. 1. The percentage changes also increased significantly at just before MIT (Fig. 2A, $p < 0.05$). During the task in right ADF, the mean amplitudes of MEPs just before MIT, 1s and 2s, were 2.38 ± 0.54 mV, 2.16 ± 0.66 mV, and 1.96 ± 0.45 mV, respectively. Furthermore, in the task of right ADF, These percentage changes were increased significantly at just before MIT, but not at 1 and 2 s (Fig. 2B). In contrast, during the task of the LHG, MEP did not change significantly (Fig. 2C).

Experiment in non-dominant M1

The mean amplitudes of MEPs at rest, in tasks of LHG, RHG, and right ADF were 1.19 ± 0.31 mV, 1.26 ± 0.43 mV, and 1.54 ± 0.54 mV, respectively. There were no significant differences between them. During

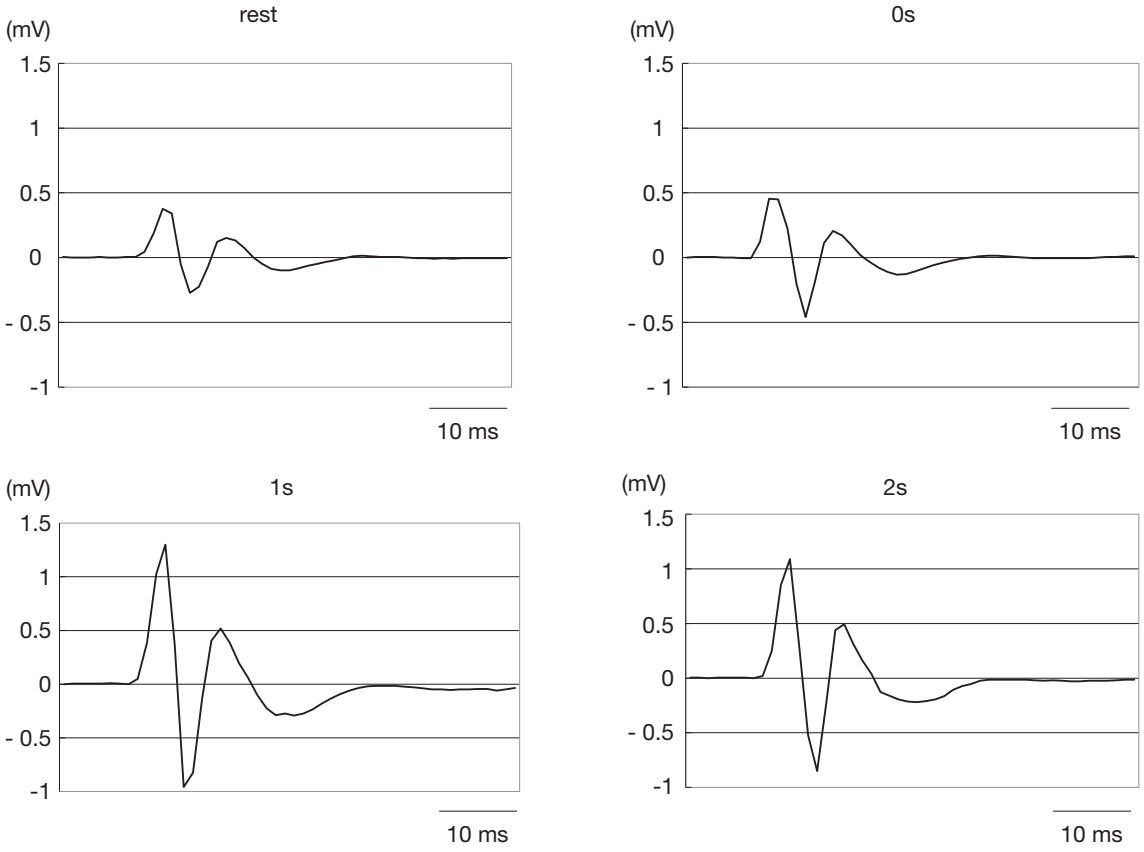

Fig. 1 A typical result from a single subject. Average motor evoked potentials (MEPs) in the first dorsal interosseous (FDI) during motor imagery task (MIT) (dominant hand). Note that MEPs increased significantly during MITs compared to that at rest. MEPs also increased just before MIT (i.e., 0 s)

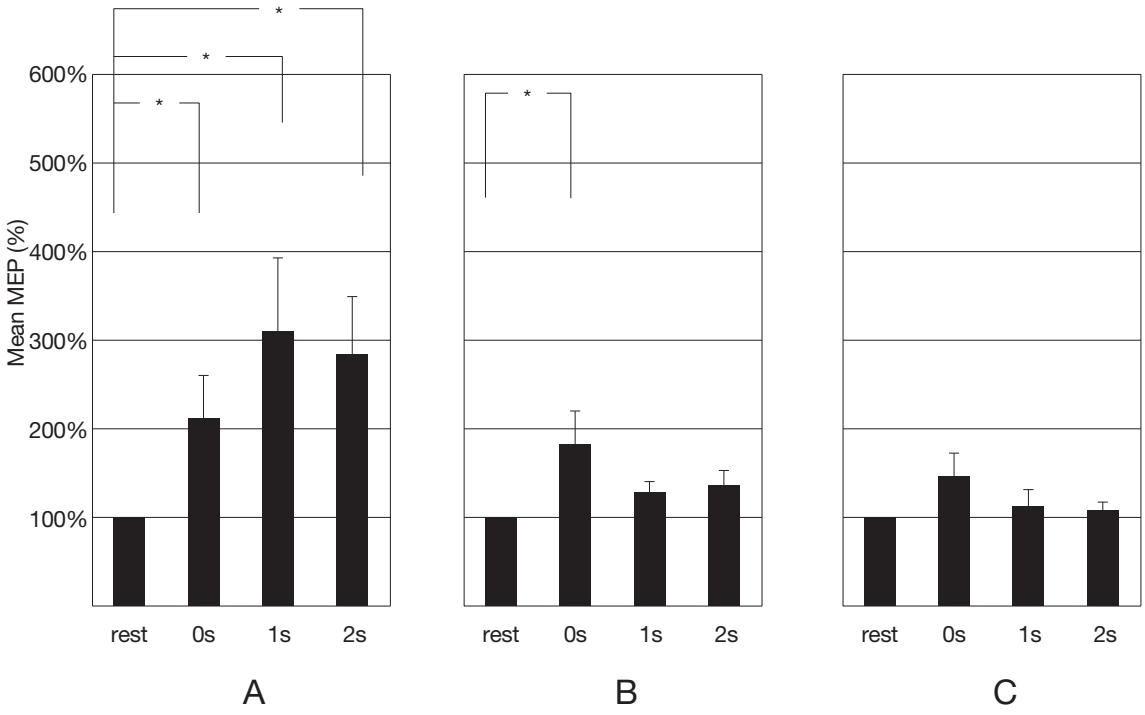

Fig. 2 MEP is expressed as a percentage of the mean MEP recorded over four time intervals (at rest, 0s, 1s, and 2s). **A** MIT of dominant hand. During motor imagery of dominant hand, MEP obtained during MIT increased significantly compared to that at rest. **B** MIT of ankle dorsiflexion (ADF) ipsilateral to dominant hand. Imagery of ADF ipsilateral to dominant hand tended to increase %MEP amplitude at the beginning and at 2s of MIT, but not at 1s. **C** MIT of non-dominant finger flexion. Finger flexion imaging of non-dominant hand did not increase %MEP amplitude during MIT. Results are expressed as means and standard errors (n = 12). * $p < 0.05$ (Wilcoxon's signed-rank test)

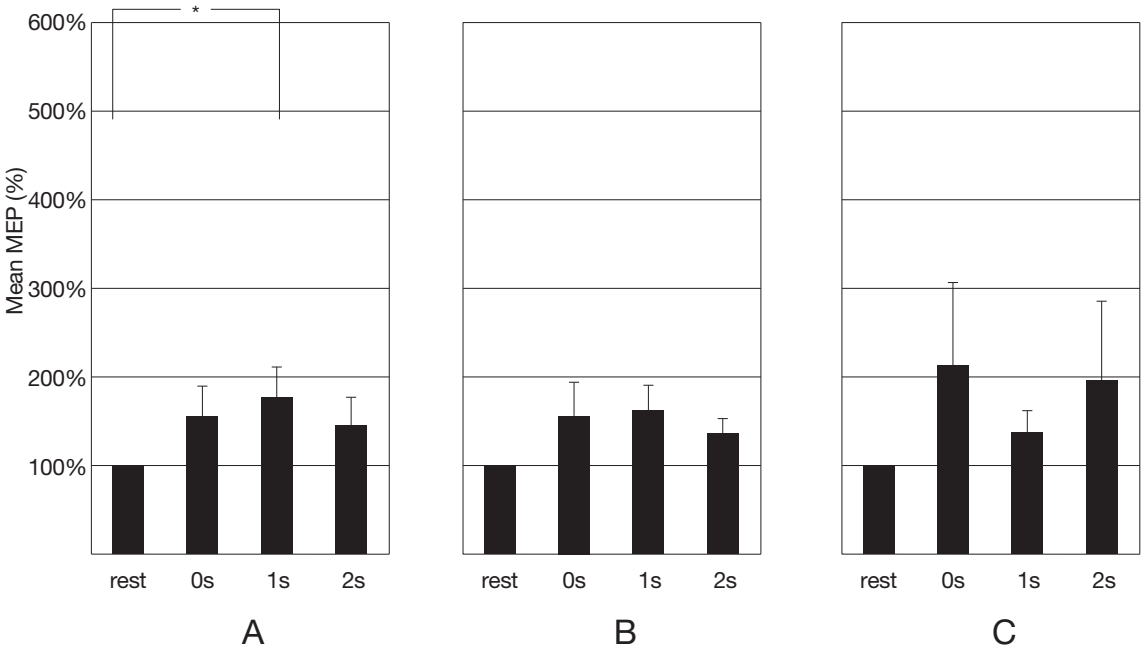

Fig. 3 MEPs of the non-dominant FDI recorded during MITs are expressed as a percentage of the MEPs over four time intervals (at rest, 0s, 1s, and 2s). **A** During motor imagery of the non-dominant hand, MEP increased 1s after LED cues compared to that at rest, but not at 0s and 2s. **B** No other changes in MIT were found during left ADF and **C** right hand grasping. Results are expressed as means and standard errors (n = 6). * $p < 0.05$ (Wilcoxon's signed-rank test)

the task in LHG, the mean amplitudes of MEPs just before MIT, 1s and 2s, were 1.33 ± 0.22 mV, 1.53 ± 0.25 mV, and 1.21 ± 0.16 mV, respectively. During the task of LHG, the percentage change in MEPs at only 1 s increased significantly compared to those at rest (Fig. 3A), but not at 0 and 2s. No other changes in MIT were found (i.e., left ADF and RHG; Fig. 3B and 3C, respectively).

Comparison between the experiment in dominant and non-dominant M1

There was no significant difference of MEP amplitude at rest between two experiments (i.e., in dominant and non-dominant M1). In dominant M1, Percentage changes in MEPs comparing 0s, 1s, and 2s with rest condition were 108%, 208% and 179%, respectively. Also Percentage changes at 0s, 1s, and 2s in MEPs in non-dominant M1 were 54%, 75% and 44%, respectively. This increase of MEP amplitude at each timings observed during RHG in the experiment in dominant M1 was larger than the one during LHG in non-dominant M1. But the difference between dominant M1 and non-dominant M1 was not significant.

DISCUSSION

In the present study, we investigated changes in cortical excitability of the M1 areas of the right and left hands during several motor imagery tasks. The findings of this study increased our understanding of temporal changes in the cortical excitability of M1 and asymmetrical functioning of the human brain during motor imagery.

Effect of MIT in the right hand on left M1

In the present study, the left M1 (i.e., dominant M1) was activated by motor imagery of right hand grasping. In a series of studies using TMS, motor imagery enhanced focal corticospinal excitability [13,14]. Our results showed similar increases in MEP amplitude during MIT. In a previous study, functional magnetic resonance imaging (fMRI) measurements showed an increase in signal intensity in the left M1 during motor imagery [15]. The left M1 is activated in a similar way during MIT in positron emission tomography (PET) [16].

MEPs amplitudes also increased significantly just before MIT. In TMS study, a gradual increase of cortical excitability starting approximately 100ms prior to simple reaction time response onset was found [17]. Therefore MIT onset was assumed as at just before the beginning of MIT. However, according to our data, MEP increased just before MIT in the right hand grasping task. This result might indicate that the change of activity in the left M1 starts before MIT. Kumru *et al.* reported that cortical excitability increased gradually over the 80−120 ms before EMG onset during reaction time tasks [10]. In their study, the decrease of short-inteval intracortical inhibition shortly preceded the MEP facilitation.

In this study, it is difficult to determine the onset of MIT, because of no EMGs. There might be differences between actual movement and MIT, but the almost same motor related areas might be activated. Therefore it is considered that the resting inhibitory state should be turned down, before increasing the excitability in the corticospinal motor tract. Intracortical inhibition may be involved in increase of MEP amplitude just before MIT, in a similar way as actual movement. In ERD studies, Morash *et al.* noted EEG changes in the 1s preceding MIT onset. Also they

suggested motor imagery preparation involved less M1 activity than does movement preparation [8]. Our results suggested that M1 excitability might increase just before MIT, so that "just before MIT" does not mean the rest condition.

In contrast, excitability of the left M1 did not increase during MIT of the left hand. The fMRI study mentioned earlier found that the left M1 is activated not only during motor imagery of the right hand grasping, but also of the left hand grasping [18]. MITs in this study were similar in their report; nevertheless, activation of the left M1 was not observed during MITs of the left hand in our study. Although fMRI has superior spatial resolution, its temporal resolution is inferior to that of TMS. Therefore, this difference might be due to different methods of assessing M1 excitability. Our results are in accord with those of previous reports on TMS. Facchini *et al.* [19] reported that the left M1 was not significantly activated during imagery of thumb movement ipsilateral to the left M1. They suggested that the imagery task used in that report was simple; so, the influence of motor imagery on the left M1 was clearly less than that with voluntary movement on the ipsilateral side.

MEP increased just before the onset of MIT in right ADF in the present study. Thus, MIT of right ADF might induce activation in the left M1 at MIT onset. In a study using MIT of ADF, Bakker *et al.* showed that MEPs from both the right TA and FDI increased during motor imagery [20]. They suggested that motor imagery of simple lower leg movements not only influences cortical excitability of the task-related muscle (TA, in this case), but also of the task-unrelated muscle (FDI). However, in this study, no change in cortical excitability of the FDI muscle was found during MIT of ADF. This discrepancy may be due to the method for determining the hot spot. In the study of Bakker *et al.*, the largest and fastest MEP in the TA was determined as the hotspot [20]. In this study, TMS was applied over the hand motor area contralateral to the right hand to determine the hotspot. In addition, TMS may have extended beyond the hand motor area to another proximal area when the M1 of the foot was stimulated. There are no previous reports about changes in activation of the hand motor area at the beginning of MITs of the foot. Before the cue, the subject might come to the ready state to the motor imagery. Therefore, the almost all area of M1 excitability might increase.

Effect of MIT in the left hand on right M1

MEPs obtained from the left FDI increased significantly during MITs of the left hand in this study. In the right M1 (i.e., non-dominant M1), Stinear *et al.* reported no change in cortical excitability during imagery of abducting and opposing the left thumb onto the tip of the left index finger [21]. In contrast, our results indicate an effect of MIT of the left hand on right M1. The different results might be caused by the difference in MITs. In addition, Stinear *et al.* suggested that to activate the right M1, imagery of a more forceful activity of the left hand may be necessary [21]. On the other hand, in a study using PET, Kawashima *et al.* found increased regional blood flow in the left M1 and premotor area during voluntary movement of both hands in right-handed subjects [22].

Some reports have suggested that more dexterous tasks are easier to imagine with the right hand than the left hand. These researches underline the common neural basis for actual and imagined movements [23, 24]. There is reason to believe that motor imagery is more difficult in the left hand than in the right. In these studies, MEP during MIT increased during motor imagery of the right hand, but not of the left hand. Regarding the right-left differences, Yahagi and Kasai demonstrated in their TMS study that MEP in the right FDI muscle was larger than in the left FDI muscle [6]. However, we found no significant difference in MEPs between the two hands during MIT, possibly because of the simplicity of MITs used in this study. Moreover, regarding changes in MEP amplitude during MIT of the left hand, right-handed subjects may have difficulty raising and maintaining excitability in the non-dominant M1 even for a few seconds. This phenomenon might represent a right-left difference in MIT that reinforces the left hemispheric dominance asserted in previous studies. In contrast to TMS study, there is the report to present stronger brain activity on non-dominant M1 during MIT of non-dominant hand in comparison with dominant M1 on functional MRI study [25]. In the other brain functional imaging study, brain activity is caught as spatial expanse, such as a premotor area and a supplementary motor area. In TMS study, because the MEPs reflect only cortical excitability in M1, it is difficult to evaluate activities of these areas. This difference might arise from the difference between functional study and TMS study.

Most studies on motor imagery suggest that its origin was supraspinal because the F-wave and H-reflex remained unchanged [26, 27]. Spinal excitability may be possible; however, the present study did not measure the F-wave and H-reflex. Further research is required to resolve this issue.

In conclusion, cortical excitability in the left M1 is stronger than in the right M1. A corresponding asymmetry in cortical motor organization occurs during MIT and cortical excitability increases just before MIT just as in actual motor execution. Furthermore, cortical excitability might be affected by motor imagery of the contralateral upper and lower limbs.

REFERENCES

1) Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. The Lancet 1985; 325: 1106–1107.
2) Izumi S, Findley TW, Ikai T, Andrews J, Daum M, Chino N. Facilitatory effect of thinking about movement on motor-evoked potentials to transcranial magnetic stimulation of the brain. Am J Phys Med Rehabil 1995; 74: 207–213.
3) Gandevia SC, Rothwell JC. Knowledge of motor commands and the recruitment of human motoneurons. Brain 1987; 110: 1117–1130.
4) Deiber M, Ibanez V, Honda M, Sadato N, Raman R, Hallett M. Cerebral Processes Related to Visuomotor Imagery and Generation of Simple Finger Movements Studied with Positron Emission Tomography. Neuroimage 1998; 7: 73–85.
5) Yahagi S, Kasai T. Motor evoked potentials induced by motor imagery reveal a functional asymmetry of cortical motor control in left- and right-handed human subjects. Neurosci Lett 1999; 276: 185–188.
6) Yahagi S, Kasai T. Facilitation of motor evoked potentials (MEPs) in first dorsal interosseous (FDI) muscle is dependent on different motor images. Electroencephalogr Clin Neurophysiol 1998;

109: 409–417.
7) Stinear CM, Fleming MK, Barber PA, Byblow WD. Lateralization of motor imagery following stroke. Clin Neurophysiol 2007; 118: 1794–1801.
8) Morash V, Bai O, Furlani S, Lin P, Hallett M. Classifying EEG signals preceding right hand, left hand, tongue, and right foot movements and motor imageries. Clinical Neurophysiology 2008; 119: 2570–2578.
9) Suzuki K, Tsuji T, Muraoka Y, Ota T, Masakado Y, Kimura A, *et al.* Facilitatory Effect of Motor Imagery in Patients with Hemiparetic Stroke. Jpn J Rehabil Med 2005; 42: 457–467.
10) Kumru H, Soto O, Casanova J, Valls-Sole J. Motor cortex excitability changes during imagery of simple reaction time. Exp Brain Res 2008; 189: 373–378.
11) Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998; 108: 1–16.
12) Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97–113.
13) Fadiga L, Buccino G, Craighero L, Fogassi L, Gallese V, Pavesi G. Corticospinal excitability is specifically modulated by motor imagery: a magnetic stimulation study. Neuropsychologia 1999; 37: 147–158.
14) Facchini S, Muellbacher W, Battaglia F, Boroojerdi B, Hallett M. Focal enhancement of motor cortex excitability during motor imagery: a transcranial magnetic stimulation study. Acta Neurol Scand 2002; 105: 146–151.
15) Kamijo K, Kawashima R, Yamazaki T. Functional MRI Measurement Movement-Imagery Task. Rinsho-nouha 2002; 44: 148–153. (in Japanese)
16) Kawashima R, Yamada K, Kinomura S, Yamaguchi T, Matsui H, Yoshioka S, *et al.* Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement. Brain Res 1993; 623: 33–40.
17) Hoshiyama M, Kitamura Y, Koyama S, Watanabe S, Shimojo M, Kakigi R. Reciprocal change of motor evoked potentials preceding voluntary movement in humans. Muscle and Nerve 1996; 19: 125–131.
18) Kamijo K, Kawashima R, Yamazaki T. Functional MRI Measurement during Movement-imagery Task. Rinsyo-noha 2002; 44: 148–153.
19) Facchini S, Muellbacher W, Battaglia F, Boroojerdi B, Hallet M. Focal enhancement of motor cotex excitability during motor imagety: a transcranial magnetic stimulation study. Acta Neurol Scand 2002; 105: 146–151.
20) Bakker M, Overeem S, Snijders AH, Borm G, van Elswijk G, Toni I, *et al.* Motor imagery of foot dorsiflexion and gait: effects on corticospinal excitability. Clin Neurophysiol 2008; 119: 2519–2527.
21) Stinear CM, Fleming MK, Byblow WD. Lateralization of unimanual and bimanual motor imagery. Brain Res 2006; 1095: 139–147.
22) Kawashima R, Inoue K, Sato K, Fukuda H. Functional asymmetry of cortical motor control in left-handed subjects. Neuroreport 1997; 8: 1729–1732.
23) Sirigu A, Cohen L, Duhamel JR, Pillon B, Dubois B, Agid Y, *et al.* Congruent unilateral impairments for real and imagined hand movements. Neuroreport 1995; 6: 997–1001.
24) Decety J. Do imagined and executed actions share the same neural substrate? Brain Res Cogn Brain Res 1996; 3: 87–93.
25) Kuhtz-Buschbeck JP, Mahnkof C, Holzknecht C, Siebner H, Ulmer S, Jansen O. Effector-independent representations simple and complec imagined finger movements: a combined fMRI and TMS stydy. European journal of Neuroscience 2003; 18: 3375–3387.
26) Hashimoto R, Rothwell JC. Dynamic changes in corticospinal excitability during motor imagery. Exp Brain Res 1999; 125: 75–81.
27) Liepert J, Neveling N. Motor excitability during imagination and observation of foot dorsiflexions. J Neural Transm 2009; 116: 1613–1619.