Changes in interhemispheric inhibition from active to resting primary motor cortex during a fine-motor manipulation task

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Morishita T, Uehara K, Funase K. Changes in interhemispheric inhibition from active to resting primary motor cortex during a fine-motor manipulation task. J Neurophysiol 107: 3086–3094, 2012. First published March 14, 2012; doi:10.1152/jn.00888.2011.—The effect of performance of a sensorimotor task on the interhemispheric inhibition (IHI) induced from the active primary motor cortex (M1) to the resting M1 was examined in 10 right-handed subjects. Transcranial magnetic stimulation (TMS) was performed to produce motor evoked potentials (MEP) in the resting right (Rt)-first dorsal interosseous (FDI). For the paired-TMS paradigm, a conditioning stimulus (CS) was delivered to the Rt-M1, and its intensity was adjusted from 0.6 to 1.4 times the resting motor threshold of the MEP in the left (Lt)-FDI in 0.2 steps. The test stimulus was delivered to the Lt-M1, and its intensity was adjusted to evoke similar MEP amplitudes in the Rt-FDI among the task conditions. The interstimulus interval was fixed at 10 ms. As a sensorimotor task, a fine-motor manipulation (FM) task (using chopsticks to pick up, transport, and release glass balls) was adopted. In addition, an isometric abduction (IA) task was also performed as a control task. These tasks were carried out with the left hand. The IHI from the active to the resting M1 observed during the FM task was markedly increased compared with that induced during the IA task, and this effect was not dependent on the MEP amplitude evoked in the active Lt-FDI by the CS. The present findings suggest that the increased IHI from the active to the resting M1 observed during the FM task was linked to reductions in the activity of the ipsilateral intracortical inhibitory circuit, as we reported previously.

ipsilateral primary motor cortex excitability; transcranial magnetic stimulation

IN PREVIOUS transcranial magnetic stimulation (TMS) studies, unilateral hand motor tasks, and especially fine-motor tasks, activated the ipsilateral primary motor cortex (ipsi-M1) innervating the contralateral homologous hand muscles during the resting state (Morishita et al. 2011; Muellbacher et al. 2000; Stedman et al. 1998; Tinazzi and Zanette 1998; Ziemann and Hallett 2001). In addition, a brain imaging study demonstrated the same phenomenon during unilateral hand motor tasks (Kim et al. 1993). Furthermore, a number of TMS studies have suggested that the activation of the ipsi-M1 during the performance of a unilateral hand motor task is mediated by transcallosal pathways (Stedman et al. 1998; Tinazzi and Zanette 1998), and a brain imaging study showed increased blood oxygen level-dependent (BOLD) signal activity in the ipsi-M1 and the corpus callosum during a unilateral hand motor task (Kobayashi et al. 2003). Therefore, it is considered that unilateral hand motor tasks lead to the activation of the ipsi-M1 via transcallosal pathways.

The paired-TMS paradigm can be used to study the neural mechanisms of the corpus callosum, which is involved in interhemispheric inhibition (IHI). IHI can be measured by applying a conditioning stimulus (CS) to one hemisphere, which inhibits the size of the motor evoked potentials (MEP) evoked by the application of a test stimulus (TS) to the opposite hemisphere at interstimulus intervals (ISI) of between 6 and 50 ms (Ferbert et al. 1992; Ni et al. 2009). A number of studies have provided evidence that IHI is predominantly mediated through the corpus callosum (Di Lazzaro et al. 1999; Ferbert et al. 1992). It is considered that IHI might play a crucial role in suppressing involuntary contralateral activity and assist in the coordination of bimanual hand motor tasks (Duque et al. 2005, 2007; Hubers et al. 2008). In accordance with this view, several studies have investigated the effects of performance of unilateral hand motor tasks on the IHI induced from the active to the resting M1, and it was found that unilateral hand motor tasks moderately increase the IHI induced from the active to the resting M1 (Ferbert et al. 1992; Hinder et al. 2010; Talelli et al. 2008; Vercauteren et al. 2008).

In a recent study (Morishita et al. 2011), we reported that performing a fine-motor manipulation (FM) task, as a sensorimotor task, markedly increased ipsi-M1 excitability. In addition, we also detected decreased short-interval intracortical inhibition (SICI), i.e., disinhibition of the ipsi-M1 during the FM task. Taking these findings into account, we hypothesized that the enhanced ipsi-M1 excitability produced during the FM task was mediated by transcallosal inputs from the active to the resting M1, in other words, from the contralateral M1 (contra-M1) to the ipsi-M1. However, the effects of performing such a sensorimotor task on interhemispheric neural mechanisms have not been examined in detail. To explore this hypothesis, we examined the changes in IHI from the active to the resting M1 during the performance of an FM task and compared them with those produced during a simple voluntary contraction task.

METHODS

Subjects. Ten right (Rt)-handed subjects (5 men and 5 women; age range 20–27 yr) gave their informed written consent to participate in the experiment. The handedness of each subject was evaluated with the Edinburgh Handedness Inventory (Oldfield 1971). The subjects were comfortably seated on a reclined chair and were instructed to put both of their hands on a horizontal plate attached to the chair’s armrests. While performing the motor tasks with their left (Lt)-hand, the subjects were asked to completely relax their Rt-hand. All experimental procedures were carried out in accordance with the Declara-
tion of Helsinki and were approved by the ethics committee of Hiroshima University.

**EMG recording.** Surface electromyography (EMG) recordings were taken from the first dorsal interosseous (FDI) muscles of both hands with Ag/AgCl surface electrodes with a diameter of 9 mm. All EMG recordings were amplified at a bandwidth of 5 Hz–3 kHz, and all amplification procedures were controlled with a signal processor (7512; NEC San-ei). The analog outputs from the signal processor were digitized at a sampling rate of 10 kHz and then transferred to a computer for off-line analysis (PowerLab system, ADInstruments). Supramaximal electrical stimuli, 1-ms square pulses, were delivered via paired bar-type electrodes at 1-s intervals to the ulnar nerve in the Lt-wrist to evoke the maximum M responses (M\text{max}). Recordings of the integrated EMG (iEMG) of the FDI in the task-performing hand for the 100 ms prior to the TMS trigger were made with the Integral Abs, Scope (version 3.7.6), PowerLab system.

**TMS.** Two figure-of-eight coils with an external diameter of 90 mm were separately connected to a MagStim200 stimulator (Magstim).

The TS was applied to the Lt-M1, and the CS was applied to the Rt-M1. Both coils were placed perpendicular to the mid sagittal line to prevent them from overlapping. The optimal position for evoking MEP from the contralateral FDI was determined and marked on a nylon mesh swimming cap worn by the subjects with a soft-tip pen to ensure reliable coil placement between trials. The resting motor threshold (rMT) of the contralateral FDI was defined as the minimum TMS intensity required to evoke MEP of >50 μV in at least 5 of 10 trials in each M1. Special attention was paid to the involuntary EMG activity of the resting Rt-FDI during the performance of the hand motor tasks with the Lt-hand. EMG activity was monitored by auditory feedback. If EMG activity of >25 μV was detected in the resting FDI, the data were omitted from the subsequent analyses (Mullbacher et al. 2000). We also analyzed iEMG of the FDI in the resting hand. As a result, 94.23% of trials were used for the subsequent analyses. The peak-to-peak MEP amplitudes were measured off-line.

**Hand motor tasks.** All subjects performed two types of unilateral hand motor task. The FM task involved the repetitive picking up, transporting, and release of glass balls (diameter 15 mm, weight 5.6 g) from one box (150 × 220 × 60 mm) to another, as accurately and quickly as possible for 2–3 min with wooden chopsticks (length 240 mm). The subjects were instructed to match their force output to the target force level of the TMS triggering signal was set so that the TMS was manually triggered, regardless of the movement phase of the FM task, with careful attention paid to ensure that the TMS was not delivered during a certain movement phase, i.e., the TMS triggers were randomly dispersed without regard for the movement phase of the FM task. We have previously confirmed that there is no significant correlation between the iEMG (∼10% of MVC) in the active FDI during the FM task and the MEP amplitude in the resting FDI, indicating that at relatively low EMG activity levels the EMG activity in the task-performing hand does not affect ipsi-M1 excitability (Morishita et al. 2011).

**Experimental procedure.** First, we examined the effects of performing the FM task and the IA task on ipsi-M1 excitability, using the single-TMS paradigm. We carried out the experiment in the following three conditions: resting conditions in both hands, performing the FM task with the Lt-hand, and performing the IA task with the Lt-hand. During the single-TMS paradigm, the TMS intensity was set to 20% above the rMT for the MEP in the resting Lt-FDI. The three conditions for the single-TMS paradigm were randomized between subjects, although the FM task was always performed prior to the IA task so that the muscle activity observed during the IA task could be defined in relation to that induced during the FM task. We then examined the changes in IHI from the active to the resting M1 during the FM and IA tasks, using the paired-TMS paradigm. The three conditions for the paired-TMS paradigm were also randomized between subjects. The ISI between the CS and TS was set to 10 ms. For the paired-TMS paradigm, five CS intensities, increasing in 0.2 steps from 0.6 to 1.4 times the rMT of the MEP in the Lt-FDI, were tested. The TS intensity was adjusted to evoke a control MEP of ∼1 mV in each condition. It has been reported that MEP with different amplitudes are subjected to different degrees of inhibition from transcortical inputs (Daskalakis et al. 2002; Ferbert et al. 1992; Kukawadwa et al. 2005). Each condition consisted of five randomly selected CS intensities and the TS alone, and the test order was randomized between subjects. Ten TMS trials were performed for each CS intensity and the TS alone for both the at-rest and hand motor task conditions. The stimuli were delivered at intervals of at least 6 s.

**Additional experiments.** In a recent study (Morishita et al. 2011), we detected no significant correlation between the iEMG in the active FDI and the MEP amplitude in the resting FDI, which indicates that ipsi-M1 excitability is not dependent on the movement phase of the task being performed, at least at relatively low EMG activity levels. However, it is possible that the movement phase of a task influences the excitability of the transcortical pathways affecting IHI. To examine this, we performed the following additional experiments in three of the subjects who participated in the present study.

First, we examined the relationship between the test MEP amplitude in the resting Rt-FDI, which was considered to be an indicator of the degree of IHI, and the MEP amplitude in the activeLt-FDI during the IA task. We used the paired-TMS paradigm. The TS and CS intensities were set to 20% above the rMT for the MEP in the Rt- and Lt-FDI, respectively. Fifty MEP were simultaneously evoked in the resting Rt-FDI and the activeLt-FDI during the FM task.

Second, we examined the effect of movement phase on MEP amplitude in the resting Rt-FDI during the FM task. During the FM task, the TMS was triggered automatically in response to the force signal from a custom-made chopstick, which was attached to a foil strain gauge (type N11-FA-5-120-11-VSE3; NEC San-ei Instruments). The force signal was amplified by a strain amplifier (model 6M82; NEC San-ei), which was connected to the force sensor. A beam line indicating the force level generated by each subject was displayed on an oscilloscope monitor. Another beam line representing the target force, which was defined as the mean iEMG measured in the FM task, was also displayed on the monitor. The iEMG values obtained during the IA task were defined as a percentage of the maximum voluntary contraction (MVC) value for the 100 ms prior to the TMS trigger relative to the mean iEMG measured during the FM task in each subject. The monitor was placed ∼1 m in front of the subject, and the subject was instructed to match his/her force output to the target beam line. During the FM task, the TMS was manually triggered, regardless of the movement phase of the FM task, with careful attention paid to ensure that the TMS was not delivered during a certain movement phase, i.e., the TMS triggers were randomly dispersed without regard for the movement phase of the FM task. We have previously confirmed that there is no significant correlation between the iEMG (∼10% of MVC) in the active FDI during the FM task and the MEP amplitude in the resting FDI, indicating that at relatively low EMG activity levels the EMG activity in the task...
Fig. 1. A: typical averaged motor evoked potential (MEP) waveforms \((n = 5)\) recorded in the resting right ( Rt)-first dorsal interosseous (FDI) and the full-wave rectified, averaged EMG recorded in the active left (Lt)-FDI in 1 subject in each condition [rest, fine-motor manipulation (FM) task, and isometric abduction (IA) task]. B: group mean MEP amplitude values \((n = 10, \pm SE)\) recorded in the resting Rt-FDI in each condition (rest, FM task, and IA task). \(*P < 0.05, **P < 0.01\).

Conditions. Two-way ANOVA with repeated measures was used to analyze the effect of IHI in the paired-TMS paradigm \((task \times CS\) intensity). If a significant main effect was found, post hoc tests for multiple comparisons [Fisher’s protected least significant difference (PLSD) test] were performed at each CS intensity. One-way ANOVA with repeated measures was also used for analyses of the mean MEP amplitudes evoked in the active Lt-FDI by the different CS intensities among the task conditions (rest, FM task, and IA task) and the effect of IHI on the resting Rt-FDI in the paired-TMS paradigm. The correlations between the MEP amplitudes in the resting Rt-FDI and the MEP amplitudes in the active Lt-FDI, as well as those between the mean MEP amplitudes in the active Lt-FDI and the iEMG in the active Lt-FDI were tested with Pearson product-moment correlation coefficients. The threshold for significance was set at \(P < 0.05\).

RESULTS

Effects of unilateral hand motor task on MEP amplitude in contralateral resting FDI. The rMT \((mean \pm SD, n = 10\) for the Lt- and Rt-M1 for all subjects were \(45.6 \pm 4.4\%\) and \(47.5 \pm 4.9\%\) of maximum stimulator output. Figure 1A shows the typical averaged MEP waveforms \((n = 5)\) recorded in the resting Rt-FDI and the full-wave rectified, averaged EMG recorded in the active Lt-FDI in one subject at rest and during the performance of each task, i.e., the FM and IA tasks, with the Lt-hand. The group mean MEP amplitude values obtained in these conditions \((n = 10, \pm SE)\) are shown in Fig. 1B. The mean MEP amplitude was \(0.76 \pm 0.31\ mV\) at rest, \(1.71 \pm 0.81\ mV\) during the FM task, and \(0.99 \pm 0.56\ mV\) during the IA task. A significant main effect was detected \([F_{(2,18)} = 6.851, P < 0.01]\). In the post hoc tests, significant differences between rest and the FM task \((P < 0.01)\) and between the FM task and the IA task \((P < 0.05)\) were detected. The mean iEMG of the FDI in the task-performing hand was \(10.15 \pm 3.11\%\) of MVC during the FM task and \(11.26 \pm 5.24\%\) of MVC during the IA task. There was no significant difference in iEMG between the tasks \((t = 0.993, P = 0.347)\). The mean iEMG of the FDI in the resting hand was \(1.18 \pm 0.30\ mV\)-ms during the rest condition, \(1.23 \pm 0.26\ mV\)-ms during the FM task, and \(1.31 \pm 0.19\ mV\)-ms during the IA task. There was no significant difference in iEMG of the FDI in the resting hand \([F_{(2,18)} = 0.711, P = 0.50]\).

Changes in IHI induced from active contra-M1 to resting ipsi-M1 during hand motor task. Figure 2A shows typical examples of the averaged MEP waveforms \((n = 5)\) recorded in the resting Rt-FDI of one subject in response to the TS alone and under each CS. Those shown in Fig. 2A, left, center, and right, were recorded at rest, during the FM task, and during the IA task, respectively. The group mean IHI values \((n = 10, \pm SE)\) recorded in the resting Rt-FDI at rest and during the performance of each task with the Lt-hand are shown in Fig. 2B. MEP amplitude is expressed as a percentage of the mean MEP amplitude evoked by the TS alone. The mean TS intensity \((\%\) of Lt-M1 rMT) was \(139.48 \pm 12.66\%\) at rest, \(115.10 \pm 12.66\%\) during the FM task, and \(105.37 \pm 12.66\%\) during the IA task.
6.32% during the FM task, and 129.71 ± 13.96% during the IA task, and the mean MEP amplitudes evoked by the TS alone were 1.29 ± 0.38 mV at rest, 1.23 ± 0.28 mV during the FM task, and 1.19 ± 0.43 mV during the IA task. The MEP amplitudes evoked by the TS alone were almost the same size, and there were no significant differences between the MEP amplitudes evoked by the TS alone among the task conditions \( [F_{(2,18)} = 0.225, P = 0.80] \), indicating that the adjustment of the TS intensity was appropriate in each condition. Under the well-controlled MEP amplitudes evoked by the TS alone, a significant main effect of CS intensity was found, and a significant difference was also detected between the tasks. In the post hoc tests, significant differences between the at-rest and FM task conditions and between the FM task and the IA task were detected. In addition, there were no significant differences between the at-rest and IA task conditions (Table 1 and Table 2). These results indicate that IHI from the active to the resting M1 was increased during the FM task compared with those observed at rest and during the IA task.

**MEP amplitude evoked by CS during hand motor tasks.** We also analyzed the MEP amplitude evoked by the CS in the active Lt-FDI. Figure 3A shows typical averaged MEP waveforms \((n = 5)\) recorded in the active Lt-FDI and the resting Rt-FDI of one subject during the performance of each task at a set CS intensity \((1.2 \times \text{rMT of the MEP in the Lt-FDI})\). The MEP amplitudes evoked by the CS in the active Lt-FDI were almost the same (Fig. 3A, left), whereas there were marked differences in the IHI recorded in the resting Rt-FDI between the FM task and the IA task, as shown in Fig. 3A, right. Figure 3B shows the group mean MEP amplitude values evoked by the CS \((n = 10, \pm \text{SE})\), MEP amplitude is expressed as a percentage of the mean MEP amplitude of \(M_{\text{max}}\). The MEP amplitude increased with CS intensity \( [F_{(4,18)} = 92.03, P < 0.01] \). Additionally, both tasks resulted in higher MEP amplitudes than the at-rest condition \( [F_{(2,18)} = 21.373, P < 0.01] \). In the post hoc tests, significant differences between the at-rest condition and the tasks were detected at all CS intensities \((P < 0.01)\), and no significant differences between the FM task and the IA task were found at any CS intensity \((P > 0.05)\).

We further analyzed the relationship between the MEP amplitudes evoked by the CS in the active Lt-FDI and the effect of IHI in the resting Rt-FDI from a different point of view. Figure 4A shows the typical averaged MEP waveforms \((n = 5)\) recorded in one subject in the resting Rt-FDI showing the degree of IHI at rest and during the performance of each task, and those observed in the active Lt-FDI, which were almost the same size at each CS intensity. The group mean MEP amplitude values \((n = 10, \pm \text{SE})\) evoked in the active Lt-FDI by the different CS intensities are shown in Fig. 4B. There were no significant differences among the task conditions \( [F_{(2,18)} = 0.367, P = 0.70] \). Figure 4C reveals the group mean MEP amplitude values \((n = 10, \pm \text{SE})\) in the resting Rt-FDI indicating the degree of IHI, induced by the same CS intensities as shown in Fig. 4B. ANOVA showed a trend toward differences among the task conditions \( [F_{(2,18)} = 2.852, P = 0.08] \).

**MEP amplitude in resting Rt-FDI was not dependent on movement phase in active Lt-FDI during FM task.** Figure 5, top, shows the relationships between the MEP amplitude in the active Lt-FDI and the test MEP amplitude in the resting Rt-FDI showing the degree of IHI during the FM task observed in three subjects. There were no significant correlations between them. In contrast, Fig. 5, bottom, shows the relationships between the MEP amplitude in the active Lt-FDI during the FM task and the iEMG in the active Lt-FDI for the 100 ms prior to the TMS trigger for the same three individual subjects. Significant correlations were found between these parameters, as we reported previously (Morishita et al. 2011).

Figure 6A shows examples of the single-TMS paradigm (Fig. 6A, left) and the paired-TMS paradigm (Fig. 6A, right) in which the subject performed the FM task with his/her Lt-hand. The TMS was automatically triggered when the force signal from the chopstick reached the triggering level during the FM task. Figure 6B shows the time courses of the mean MEP amplitude values \((\pm \text{SD})\) recorded in the resting Rt-FDI from three subjects when the TMS was triggered at different times, indicating MEP amplitude evoked by the TS alone and the test MEP amplitude showing the degree of IHI. In these three subjects, the timing of the TMS trigger did not affect the MEP amplitude. These results indicate that the movement phase of the task being performed does not affect the excitability of the transcallosal pathways, at least at relatively low EMG activity levels.

**DISCUSSION**

The main findings of the present study were as follows: 1) Performance of the FM task with the Lt-hand significantly increased the MEP amplitude in the resting Rt-FDI; 2) significantly increased IHI from the active to the resting M1 was observed during the FM task; 3) although MEP with similar amplitudes were evoked in the active Lt-FDI at each CS intensity during the FM and IA tasks, increased IHI was observed during the FM task; and 4) the changes in the MEP amplitude in the resting Rt-FDI, which was considered to be an indicator of the degree of IHI, were not related to a particular movement phase of the task being performed by the active Lt-hand during the FM task.

**Increased ipsi-M1 excitability during FM task.** A number of studies have shown that performing unilateral hand motor tasks...
facilitates ipsi-M1 excitability without affecting spinal motoneuron excitability, and this facilitation is probably produced by transcallosal inputs from the active M1 that innervate unilateral hand motor tasks (Stedman et al. 1998; Tinazzi and Zanette 1998). In the present study, we compared the effects of performing an FM task and an IA task (as a simple voluntary contraction task) on ipsi-M1 excitability. As reported previously, a significant facilitation of ipsi-M1 excitability was observed during the FM task (Morishita et al. 2011). This result was consistent with the findings of previous studies (Ghacibeh et al. 2007; Ziemann and Hallett 2001). In contrast, performing the IA task did not increase ipsi-M1 excitability. This result is also in agreement with the findings of previous studies, in which relatively low EMG activity did not affect ipsi-M1 excitability or spinal motoneuron excitability (Muellbacher et al. 2000; Stedman et al. 1998). The EMG activity levels generated during the FM and IA tasks were similar (~10% of MVC), suggesting that the enhancement of ipsi-M1 excitability during the FM task was due to the properties of the task, i.e., it was a fine-motor manipulation task rather than a simple voluntary contraction task.

**Increase in IHI from active contra-M1 to resting ipsi-M1 during FM task.** To the best of our knowledge, our study is the first to investigate the effect of performing a sensorimotor task, such as the FM task, on IHI from the active to the resting M1. As mentioned in the introduction, a number of studies have shown the effect of performing a unilateral simple voluntary contraction on IHI from the active to the resting M1 (Ferbert et

![Fig. 3. A: typical averaged MEP waveforms (n = 5) recorded in the active Lt-FDI in each condition (FM task and IA task) and the resting Rt-FDI in 1 subject. CS intensity was fixed at 1.2x the rMT of the MEP in the Lt-FDI. B: recruitment curves of the amplitude of the MEP evoked in the active Lt-FDI by the CS (n = 10, ±SE) [% of maximum M (Mmax)] in each condition (rest, FM task, and IA task). x-Axis indicates CS intensity (ratio to the rMT of the MEP in the Lt-FDI).](image)

![Fig. 4. A: typical averaged MEP waveforms (n = 5) recorded in the active Lt-FDI in each condition (rest, FM task, and IA task) and the resting Rt-FDI in 1 subject, showing that MEP with similar amplitudes were evoked by different CS intensities. CS intensity was 1.2x rMT at rest and 0.8x rMT during the FM task and the IA task. B: group mean MEP amplitude values (n = 10, ±SE) recorded in the active Lt-FDI in each condition (rest, FM task, and IA task). C: group mean MEP amplitude values (n = 10, ±SE) recorded in the resting Rt-FDI in each condition (rest, FM task, and IA task).](image)
al. 1992; Hinder et al. 2010; Talelli et al. 2008). Ferbert et al. (1992) first reported that unilateral simple voluntary contraction of the Lt-FDI resulted in weakly, but significantly, increased IHI from the active to the resting M1. However, we did not detect a significant increase in IHI from the active to the resting M1 during the IA task. Talelli et al. (2008) found that the effect of a unilateral simple voluntary contraction on IHI from the active to the resting M1 was very variable. Therefore, the fact that we did not detect significant increases in the IHI induced from the active to the resting M1 during the IA task might simply have been due to substantial intersubject variability. Meanwhile, it has also been reported that marked IHI was evident when a CS was applied to the dominant M1 innervating the dominant hand during the resting state (Baumer et al. 2007). Hinder et al. (2010) and Vercauteren et al. (2008) evaluated the IHI of the Lt-hand during the performance of a simple voluntary contraction task with the dominant Rt-hand (opposite to the conditions studied here). Thus there is a possibility that hemispheric asymmetry affects the degree of IHI during the active state. Furthermore, the degree of IHI could be affected by differences in the target muscles (Harris-Love et al. 2007). Vercauteren et al. (2008) reported an increase in IHI from the active to the resting M1 during the performance of a unilateral simple voluntary contraction with the dominant upper limb. In their study, IHI was evaluated in the left extensor carpi radialis longus muscle and the flexor carpi radialis muscle. Therefore, no consensus exists regarding the degree of IHI from the active to the resting M1 during the performance of a unilateral simple hand motor task. Further investigations are required to examine whether the degree of IHI is dependent on hemispheric asymmetry and/or the target muscle during the performance of unilateral simple hand motor tasks.

On the other hand, we detected a marked increase in IHI from the active to the resting M1 during the FM task. It has been suggested that such increases in IHI from the active to the resting M1 are used to suppress excessive ipsi-M1 excitability (Duque et al. 2007). Complex unilateral hand motor tasks, such as the FM task, might generate involuntary mirror movements in the contralateral resting homologous muscle. In fact, we occasionally observed involuntary EMG activity in the resting Rt-FDI during the performance of the FM task with the nondominant Lt-hand. Thus, in order to suppress excessive ipsi-M1 excitability, which could generate involuntary mirror movements, the IHI from the active to the resting M1 has to be increased (Kobayashi et al. 2003). Alternatively, Daskalakis et al. (2002) reported that IHI inhibits SICI in the target hemisphere during the resting state. Therefore, the increased IHI observed during the FM task could be the neural mechanism responsible for reducing SICI in the ipsi-M1, i.e., disinhibition, during the FM task (a sensorimotor task), as we reported previously (Morishita et al. 2011). As a result, decreased SICI in the ipsi-M1 leads to increased ipsi-M1 excitability during the FM task. However, it should be kept in mind that although there is evidence that IHI is mediated via transcallosal pathways (Di Lazzaro et al. 1999; Ferbert et al. 1992; Ni et al. 2009), some subcortical mechanisms might also be involved (Gerloff et al. 1998). In addition, complex unilateral hand motor tasks could lead to higher activity in various brain regions, including the cerebellum (Tsuda et al. 2009). Thus we cannot state that the effects induced by the FM task in the present study were mediated by the transcallosal pathways between the two M1 regions alone. Further investigation is required to confirm the explanations described above.

Different neuronal populations mediate IHI and corticospinal output. As described above, several studies have investigated the effect of performing unilateral hand motor tasks on IHI from the active to the resting M1. However, these studies had methodological issues, i.e., some of them adjusted the CS intensity to evoke the same MEP amplitude in
the active muscle (Nelson et al. 2009, 2010; Perez and Cohen 2008) whereas others did not (Ferbert et al. 1992; Hinder et al. 2010; Talelli et al. 2008; Vercauteren et al. 2008). Perez and Cohen (2008) reported that the IHI from the active to the resting M1 was reduced during simple unilateral hand motor tasks at force levels ranging from 10% to 70% of MVC when the CS intensity was adjusted. On the other hand, Vercauteren et al. (2008) reported that the IHI from the active to the resting M1 was increased when it was examined without CS intensity adjustment. These findings support the assertion that IHI is positively correlated with suprathreshold CS intensity, i.e., IHI is generally weaker at lower CS intensities (Ferbert et al. 1992; Ni et al. 2009). Nevertheless, it is possible that the induction of strong IHI from the active to the resting M1 is mediated by increased contralateral corticospinal output. Therefore, the methodological issues regarding the adjustment of the CS intensity in IHI experiments cannot be ignored. Several studies have discussed this issue. Although a number of studies have shown that MEP amplitude was altered by the use of various current directions (Di Lazzaro et al. 2001; Sakai et al. 1997; Werhahn et al. 1994), Chen et al. (2003) and Ni et al. (2009) showed that the current direction of the CS did not affect the degree of IHI. If the contralateral corticospinal output affects the degree of IHI, different degrees of IHI would be detected during the use of various CS current directions. In addition, a triple-TMS study reported that intracortical facilitation (ICF) did not facilitate IHI in the originating hemisphere (Lee et al. 2007). Generally, it is considered that ICF leads to an increase in contralateral corticospinal excitability, which is represented by an increased MEP amplitude. However, despite this increased MEP amplitude, the degree of IHI in the originating hemisphere is not affected. If the transcallosal and corticospinal tract projections are closely related, ICF should influence the degree of IHI. Finally, an animal study suggested that the transcallosal and

Fig. 6. A: examples of single transcranial magnetic stimulation (TMS) (left) and paired TMS (right) during the FM task: typical averaged MEP waveforms (n = 5) recorded in the resting Rt-FDI during the FM task. Left: MEP amplitude evoked by the TS alone. Right: MEP amplitude recorded after the application of both the CS and the TS, which was considered to indicate the degree of IHI. Force curves measured by a foil strain gauge attached to a chopstick during the FM task are shown. Horizontal dotted lines indicate the triggering level (−0.3 N). CS and TS were triggered when the force reached the triggering level. Vertical dashed lines indicate the timing of the trigger. Six intervals between the triggering level being reached and the initiation of the TMS trigger were tested (0, 100, 200, 300, 400, and 500 ms). B: time courses of the mean (±SD) MEP amplitude values observed in different TMS trigger timing conditions recorded from 3 subjects. y-Axis indicates the MEP amplitude recorded in the resting Rt-FDI, and x-axis indicates the different timings of TMS trigger. ○, MEP amplitude evoked by the TS alone; ●, MEP amplitude recorded after the application of both the CS and the TS, indicating the degree of IHI.
corticospinal projecting cells are distinct (Catsman-Beerevoets et al. 1980). These studies strongly suggest that the transcallosal and corticospinal projections are distinct. Our present results clearly show that the MEP amplitudes evoked by the CS during the FM and IA tasks were almost the same, while marked differences in the IHI from the active to the resting M1 were observed between these tasks. Also, we analyzed the MEP, amplitudes in the resting Rt-FDI showing the degree of IHI, and found that MEP with similar amplitudes were evoked by CS with different intensities. Although the CS intensity was weak, a trend toward greater inhibition during the performance of the FM task was observed. In addition, we clearly demonstrated the independence of the MEP amplitude in the resting Rt-FDI, which was considered to be an indicator of the degree of IHI, from the MEP amplitude in the active Lt-FDI during the FM task. During the FM task, which was developed as a task with various movement phases, the MEP amplitude in the active Lt-FDI was strongly dependent on the iEMG produced during the 100 ms prior to the TMS trigger in the active Lt-FDI. However, the movement phase of the task did not affect the excitability of the transcallosal pathways. Finally, we also demonstrated the relationship between the MEP amplitude and the timing of the TMS trigger related to the force of the signal during the FM task. It should be kept in mind that although the timing of the TMS trigger did not affect the excitability of the transcallosal pathways, there might be still movement phase effects on transcallosal pathways. The TMS timing was somewhat varied at later timing of the TMS trigger because the task speed depends on the subjects, but Fig. 6 shows that the timing of the TMS trigger did not affect the degree of IHI including at later timing of the TMS trigger. If we controlled movement phase of the task exactly, the property of the task as a fine-motor manipulation task must have vanished. Therefore, despite this limitation, our present results also support the assertion that the projections from the transcallosal and the corticospinal pathways are distinct, as mentioned above, and we conclude that our procedures for measuring IHI were appropriate and reliable.

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DISCLOSURES
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AUTHOR CONTRIBUTIONS
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