Exp Brain Res (2014) 232:1823–1832
DOI 10.1007/s00221-014-3874-4

RESEARCH ARTICLE

Unilateral imagined movement increases interhemispheric inhibition from the contralateral to ipsilateral motor cortex

Nan Liang · Kozo Funase · Makoto Takahashi · Kanji Matsukawa · Tatsuya Kasai

Received: 15 August 2013 / Accepted: 10 February 2014 / Published online: 22 February 2014

Abstract Whether a cortical drive to one limb modulates interhemispheric inhibition (IHI) from the active targeting to the non-active motor cortex (M1) remained unclear. The present study using a conditioning-test transcranial magnetic stimulation (TMS) paradigm aimed to directly demonstrate the modulation of IHI during unilateral voluntary or imagined movement in humans. Subjects were asked to actually perform right index-finger abduction (10–70 % of the maximum voluntary contraction) or to imagine the movement. Conditioning and test TMS with an interstimulus interval of 5, 10, and 15 ms were applied over the left and right M1, respectively, and the test motor evoked potential (MEP) was recorded from the left first dorsal interosseous (FDI) muscle. The conditioning TMS intensity was adjusted ranging from 0.6 to 1.4 (in 0.2 steps) times the resting motor threshold (rMT). With test TMS alone, MEP in the left FDI muscle significantly increased during voluntary or imagined movement of the right index-finger. MEP amplitude was significantly reduced in proportion to increments of the conditioning TMS intensity at rest (1.2 and 1.4 times the rMT, $P < 0.05$, respectively). Importantly, the MEP inhibition was markedly enhanced during voluntary or imagined movement in comparison with that at rest. The regression analysis revealed that IHI varied depending on the intensity of the impulses conveyed from left to right M1, but not on the corticospinal excitability of the active right hand. Our results suggest that IHI from the active to non-active M1 is enhanced during unilateral volitional motor activity.

Keywords Interhemispheric inhibition (IHI) · Voluntary drive · Motor imagery · Primary motor cortex (M1) · Transcranial magnetic stimulation (TMS) · Motor evoked potential (MEP)

N. Liang (✉) · K. Matsukawa · T. Kasai
Department of Integrative Physiology, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
e-mail: liangnan@hiroshima-u.ac.jp

K. Funase
Department of Human Sciences, Graduate School of Integrated Arts and Sciences, Hiroshima University, 1-7-1 Kagamiyama, Higashihiroshima 739-8521, Japan

M. Takahashi
Department of Biomechanics, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Introduction

Unilateral voluntary movement accompanies corticospinal activation not only on the contralateral but also on the ipsilateral side in humans (Hess et al. 1986; Kim et al. 1993; Liang et al. 2008, 2011; Stinear et al. 2001; Uehara et al. 2011). It has been revealed, using transcranial magnetic stimulation (TMS) techniques, that motor evoked potential (MEP) of the contralateral resting muscle was enhanced by ipsilateral homonymous muscle contraction without changes in the spinal motoneuron excitability (Liang et al. 2008; Morishita et al. 2011; Muellbacher et al. 2000; Stedman et al. 1998; Stinear et al. 2001). A supraspinal neural mechanism would therefore be operated for the enhancements of ipsilateral motor cortex (M1) excitability, while the details have not been fully defined.

We have recently shown that modulation of the cortico-cortical neural circuits may contribute to the enhancement of the ipsilateral M1 excitability (Liang et al. 2008; Morishita et al. 2011; Uehara et al. 2013) as well as that in the

contralateral M1 (Ridding et al. 1995). A release of short intracortical inhibition rather than changes in the intracortical facilitation seemed to be relevant. Interestingly, ipsilateral M1 excitability was enhanced not only during overt but also covert movement, i.e., unilateral imagined hand movement (Liang et al. 2008). These results suggested that the afferent inputs from the contracting muscle were not absolutely essential for the enhancement of ipsilateral M1 excitability. A central-originated interhemispheric modulation, which may be a result of motor outflows from the cortical drive for the contralateral limb, may play a role in the generation of ipsilateral facilitation.

The interhemispheric inhibition (IHI) through the corpus callosum, which contributes to the communications between bilateral M1, can be measured by single- or paired-pulse TMS. A single-pulse TMS applied over one M1 leads to inhibition of ongoing voluntary electromyographic (EMG) activity of the ipsilateral hand muscle, suggesting an inhibitory effect of TMS on the contralateral M1 (Ferbert et al. 1992; Giovannelli et al. 2009; Meyer et al. 1995). A paired-pulse TMS technique, by which a conditioning TMS is applied over the opposite M1 prior to the test TMS, reveals MEP inhibition (Di Lazzaro et al. 1999; Ferbert et al. 1992; Hanajima et al. 2001). During unilateral voluntary movement, it has been suggested that IHI is modulated bidirectionally (active to non-active hemisphere and vice versa) in healthy humans (Giovannelli et al. 2009; Hinder et al. 2010; Morishita et al. 2012; Murase et al. 2004; Nelson et al. 2009; Perez and Cohen 2008; Sattler et al. 2012). Since there is repeated evidence that the imagined movement shares neural structures with those underlying overt movement (Caldara et al. 2004; Gerardin et al. 2000; Kasai et al. 1997; Liang et al. 2006, 2007; Stinear and Byblow 2003, 2004; Yahagi et al. 1996), it is plausible to hypothesize that unilateral imagined movements accompany the modulation of IHI.

To test this hypothesis, we examined the modulations of IHI from the contralateral (active) toward the ipsilateral (non-active) M1 during unilateral imagined hand movement as well as voluntary movement. IHI was measured by applying the paired-pulse (conditioning and test) TMS over bilateral motor cortices. The force level of unilateral voluntary movement, the interstimulus interval (ISI) used to detect IHI, and the intensity of conditioning stimulus were adjusted to explore the differential effects of IHI.

Methods

Subjects

Eleven right-handed (Oldfield 1971) healthy volunteers (ten males and one female; age, 23 ± 1 years) participated in the present study after giving their written informed consent. Six of the subjects participated in the protocol 1 and 2, and all eleven participated in the protocol 3. The experimental procedures and protocols were performed in accordance with the Declaration of Helsinki and were approved by the Institutional Ethical Committee.

Experimental procedures

The subjects were seated comfortably in an armchair with both arms flexed at the elbow joint by 90° and relaxed on a horizontal plate attached to the armrests. Both arms were kept in a prone position throughout the experiment. At the beginning of the experiments, subjects were instructed to maximally perform the right index-finger abduction and the maximum force was measured as a standard reference. An immobile bar, to which a force sensor was affixed, was exteriorly attached to the distal interphalangeal joint of the right index-finger, and then the force signal was amplified by a strain gage amplifier (model 6M82, NEC San-ei Co. Ltd., Japan). The subjects were asked to perform voluntary movements with 10, 30, 50, and 70 % of the maximum voluntary contraction (MVC) by a visual feedback. An oscilloscope screen was presented in front of the subject, on which a horizontal beam line representing the target force was displayed. Another horizontal beam line representing the real force level generated by the subject was also displayed on the screen. The subjects were instructed to abduct the right index-finger and to keep the coincidence of the two beam lines for several seconds. Regarding the imagined movement, the subjects were asked to mentally simulate the identical right index-finger movement with their maximum effort, without any overt movements.

Electromyographic recordings

Surface electromyography (EMG) was recorded from the right and left first dorsal interosseous (FDI) muscles with 9-mm-diameter Ag–AgCl surface cup electrodes. The electrode was placed over the belly of the FDI muscle, and the reference electrode over the metacarpophalangeal joint. The EMG responses were amplified with a bandwidth filter of 5 Hz–3 kHz. All amplification procedures were controlled by a signal processor (7S12, NEC San-ei Co. Ltd., Japan). The analog signals were digitized at a sampling rate of 10 kHz (PowerLab system, AD Instruments Pty. Ltd., Australia) and were stored in a computer for off-line analysis (Scope).

TMS application

Two figure-of-eight-shaped coils (90 mm mean diameter) connected to two Magstim 200 stimulators (The Magstim

Table 1 Summary of the protocols

	Protocol 1	Protocol 2	Protocol 3
Number of subjects	6	6	11
Voluntary movement (%MVC)	Adjusted ranging 10–70	Fixed at 10	Fixed at 10
Paired-pulse TMS ISI (ms)	Fixed at 10	Adjusted ranging 5–15	Fixed at 10
Conditioning TMS intensity (×rMT)	Fixed at 1.2	Fixed at 1.2	Adjusted ranging 0.6–1.4

MVC maximum voluntary contraction, *TMS* transcranial magnetic stimulation, *ISI* interstimulus interval, *rMT* resting motor threshold

Company, UK), respectively, were used to deliver the conditioning and test TMS. The conditioning TMS was given over the left M1 and the test TMS over the right M1. Both coils were placed in a medial direction, and the extents of IHI were confirmed before the experiment by determining the MEP size in the left FDI muscle with or without conditioning TMS. The optimal site (motor hot spot) where stimulation of slight suprathreshold intensity consistently produced the largest MEPs in the contralateral FDI muscle was marked with a pen on the swimming cap-covered scalp. The resting motor threshold (rMT) was defined as the lowest stimulus intensity of TMS evoking MEP of above 50 μV in amplitude in more than half of the trials. The subjects were asked to voluntarily or mentally perform the abduction of the right index-finger after an auditory beep, and 2–3 s later test TMS (right M1) with or without conditioning TMS (left M1) was delivered for eliciting MEP in the left FDI muscle. At least ten trials were conducted in each condition. Great care was taken to relax the left hand during the experiment and off-line analysis. If any background EMG activity was detected in the left FDI muscle, the data were omitted from the analysis.

The three protocols are summarized in the Table 1. All protocols involved voluntary and imagined movements. In protocol 1, single- or paired-pulse TMS was applied when the subject was actually performing the abduction of the right index-finger with 10, 30, 50, and 70 % MVC in order to confirm the existence of ipsilateral M1 facilitation and IHI over a range of voluntary contraction levels. Also, an adequate force level (10 % MVC), with which the test MEP and conditioned MEP sizes were comparable with that during motor imagery, was determined and adopted in the main experiment (protocol 3). Test TMS with an intensity of 1.2–1.3 times the rMT was used to evoke a MEP with an amplitude of approximately 1.0 mV peak-to-peak in the left FDI muscle at rest. The stimulus intensity of conditioning TMS was fixed at 1.2 times the rMT, and the ISI was fixed at 10 ms. With the lateral–medial directed current, it has been assumed that both direct and indirect wave components are involved in MEP (Di Lazzaro et al. 1999; Hanajima et al. 2001). In addition, because the discharge area and subliminal fringe in the corticomotoneuronal cells during motor imagery and voluntary movement would be different from that at rest, the IHI or even if facilitation (Ugawa et al. 1993; Hanajima et al. 2001) might be varied by changing the IHI intervals (protocol 2) and conditioning intensities (protocol 3). In protocol 2, ISIs at 5, 10, and 15 ms were used to assess short IHI, which have been proposed as a means of investigating the IHI between the M1 (Ferbert et al. 1992; Ni et al. 2009). The stimulus intensity of conditioning TMS (×1.2 rMT) and voluntary movement (10 % MVC) was fixed in each subject, while that of test TMS was adjusted for matching the MEP size among the right-hand conditions (resting state, voluntary movement, and imagined movement). In protocol 3, the ISI (10 ms) and the intensity of voluntary movement (10 % MVC) were fixed, while both stimulus intensities of conditioning and test TMS were adjusted. The conditioning TMS with five different intensities (×0.6–1.4 rMT, in steps of 0.2 rMT) was applied, and the test TMS was adjusted in each subject for matching MEP size among the conditions.

Data and statistical analyses

The background EMG activities (with a 100-ms window) prior to the TMS trigger were calculated in all protocols. MEPs were measured as the peak-to-peak values.

For the data in protocol 1, test and conditioned MEPs among all right-hand conditions were analyzed using two-way analysis of variance (ANOVA) with repeated measures (factors; task and TMS pulse). The extents of MEP inhibition induced by the conditioning TMS were determined by normalizing the data as a ratio of the control (test TMS alone), and then one-way ANOVA with repeated measures was used to determine the difference in the MEP response ratio (conditioned/testing) among the conditions, followed by a Dunnett's post hoc test. For those in protocol 2 and 3, conditioned MEPs were normalized as a ratio of the control size (test TMS alone) and then grand mean ratios with standard error from pooled data were calculated. These data were analyzed using two-way ANOVA with repeated measures (factors; task and ISI or stimulus intensity of conditioning TMS), followed by a paired *t* test with Holm's sequential Bonferroni correction (Holm 1979). The

interaction between factors in two-way ANOVA was also determined with all three protocols. There was a fundamental question as to whether IHI from the active to non-active motor cortex varied depending on the corticospinal excitability of the active side. To address this issue, the correlation between MEP of the right FDI muscle and conditioned MEP of the left FDI muscle was examined by a linear regression analysis based on Pearson's coefficient analysis. The regression slope among all right-hand conditions was analyzed using one-way ANOVA with repeated measures, followed by a Dunnett's post hoc test. The level of statistical significance was defined as $P < 0.05$. The data values are expressed as mean ± SE.

Results

IHI during unilateral voluntary movement with different force levels (protocol 1)

There were no significant differences in EMG activities of the left FDI muscle among the conditions. MEP in the left FDI muscle was significantly reduced by the conditioning TMS ($F_{1,10} = 9.28$, $P < 0.05$) and was also significantly different among the right-hand conditions ($F_{5,50} = 4.98$, $P < 0.001$, Fig. 1a). No significant interaction was detected between the factors 'task' and 'TMS' ($F_{5,50} = 0.96$, $P = 0.453$), suggesting a general effect of IHI among the right-hand conditions. One-way ANOVA revealed a significant difference in the test MEP among the right-hand conditions ($F_{5,25} = 3.50$, $P < 0.05$), while that in the conditioned MEP showed no significant difference. The response ratio of the conditioned and test MEP which reflected the extents of IHI was significantly reduced by imagined movement and voluntary movements with 10–50 % MVC compared with that in the resting state ($F_{5,25} = 3.47$, $P < 0.05$, post hoc, $P < 0.05$, respectively, Fig. 1b), while that during voluntary movement at 70 % MVC tended to be significant ($P = 0.086$).

IHI with different ISIs (protocol 2)

Matching the test MEP size, conditioned MEPs during rest, motor imagery, and 10 % MVC among the ISIs used are shown in Fig. 2. The MEP response ratio was significantly different among the right-hand conditions ($F_{2,30} = 6.31$, $P < 0.01$; post hoc, rest and motor imagery, $P < 0.01$, rest and 10 % MVC, $P < 0.01$, motor imagery and 10 % MVC, $P > 0.05$). No significant interaction was detected between the factors 'task' and 'ISI' ($F_{2,30} = 0.25$, $P = 0.908$), suggesting the difference in MEP among right-hand conditions was independent of the ISIs. We therefore confirmed the effectiveness of ISIs used here for examining IHI, and that IHI became stronger during motor imagery and 10 % MVC compared with rest with the ISIs used.

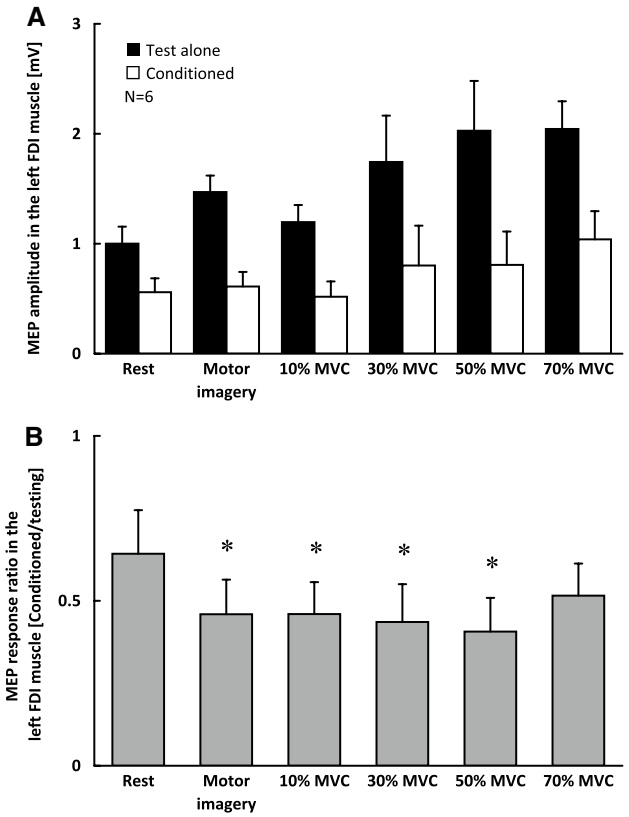

Fig. 1 MEPs of the left FDI muscle during resting state (rest), motor imagery, and voluntary movements (10–70 % MVC) of the right index-finger abduction with single- and paired-pulse TMS. The conditioning and test TMS were applied over the left and right motor cortex, respectively, and the stimulus intensity and interstimulus interval (10 ms) were fixed in each subject. **a** *Solid bars* indicate the MEPs with test TMS alone and *open bars* with conditioning TMS. **b** The response ratio of the conditioned and testing MEP among all right-hand conditions. *Significantly different from resting state, $P < 0.05$. *MVC* maximum voluntary contraction, *MEP* motor evoked potential, *FDI* first dorsal interosseous

IHI during unilateral imagined and voluntary movement (protocol 3)

The stimulus intensities and MEPs in the left FDI muscle during rest, motor imagery, and voluntary movement at 10 % MVC are summarized in Table 2. When the test TMS was delivered alone with fixed intensity (single-pulse TMS), MEP was significantly enhanced during imagined and voluntary movement as compared with that at rest ($F_{2,20} = 4.94$, $P < 0.05$, post hoc; $P < 0.05$, respectively). In the paired-pulse TMS paradigm, stimulus intensities of test TMS for matching MEP size among the conditions were significantly decreased during imagined

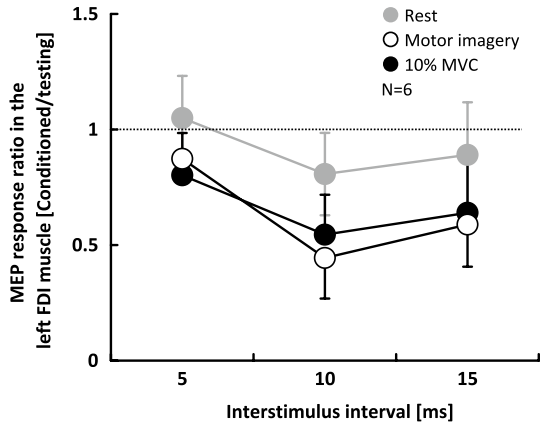

Fig. 2 MEPs of the left FDI muscle during resting state (rest), motor imagery, and 10 % MVC of the right index-finger abduction with paired-pulse TMS of which the interstimulus interval was adjusted to 5, 10, and 15 ms. Note that the MEPs were normalized to control size. *MVC* maximum voluntary contraction, *MEP* motor evoked potential, *FDI* first dorsal interosseous

Table 2 Test intensities and MEPs during single- and paired-pulse TMS paradigms

	Rest	MI	10 % MVC
Single-pulse TMS			
Test intensity (%MSO)	66.4 ± 3.5	66.4 ± 3.5	66.4 ± 3.5
MEP in the left FDI muscle (mV)	1.1 ± 0.1	1.5 ± 0.3	1.5 ± 0.2
Paired-pulse TMS			
Adjusted test intensity (%MSO)	66.4 ± 3.5	64.3 ± 3.2	64.1 ± 3.1
MEP in the left FDI muscle (mV)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1

MI motor imagery, *MVC* maximum voluntary contraction, *TMS* transcranial magnetic stimulation, *MSO* maximum stimulator output, *MEP* motor evoked potential, *FDI* first dorsal interosseous

and voluntary movement as compared with that at rest ($P < 0.05$, respectively).

Representative recordings of MEP of the left FDI muscle to test TMS with or without conditioning TMS are presented in Fig. 3a. MEPs were gradually reduced in association with increments of the conditioning stimulus intensity in all right-hand conditions. The extent of the inhibition of MEP was, especially with the higher intensity of conditioning TMS, greater during imagined or voluntary movement in comparison with that at rest. The means and SEs of the MEP response ratio are shown in Fig. 3b. With matched MEP size, the conditioned MEP were significantly decreased in proportion to increments of the stimulus intensity of the conditioning TMS ($F_{4,50} = 16.62$, $P < 0.0001$). Importantly, a significant difference in the MEPs among the right-hand conditions was detected ($F_{2,100} = 7.84$, $P < 0.001$). A significant interaction was also detected between the factors 'task' and 'conditioning TMS intensity' ($F_{2,100} = 2.33$, $P < 0.05$), suggesting a general effect of IHI among the right-hand conditions. A post hoc analysis showed that, during imagined or voluntary movement with 10 % MVC, conditioned MEP with higher intensities of the conditioning TMS was significantly smaller compared with that at rest (motor imagery; ×1.2 and 1.4 rMT, 10 % MVC; ×1.0, 1.2, and 1.4 rMT, $P < 0.05$, respectively). A slight but not significant facilitation of conditioned MEP was observed when the intensity of conditioning TMS was adjusted at ×0.6 rMT.

To explore whether MEP inhibition varied depending on the changes in the corticospinal excitability of the active hand, we assessed MEP in the right FDI muscle to conditioning TMS and its relation to the extent of MEP inhibition in the left FDI muscle (Fig. 4). The conditioning TMS over the left M1 elicited MEP inhibition of the left FDI muscle that was negatively correlated to the MEP of the right FDI muscle in all right-hand conditions ($P < 0.01$, respectively). Interestingly, the regression slope during motor imagery was not significantly different as compared with that at rest, while it was significantly decreased during 10 % MVC ($F_{2,20} = 5.91$, $P < 0.05$; post hoc, $P < 0.05$).

Discussion

A widely held notion regarding the transcallosal pathway to date is that the corpus callosum connecting homologous cortical areas operates to communications between the two hemispheres of the brain. In particular, the neurophysiological mechanism of IHI referring to an inhibitory effect of one hemisphere toward the opposite hemisphere is thought to play a crucial role in the motor system so as to prevent involuntary, mirrored movements during unilateral voluntary movements. Using a paired-pulse TMS technique, we have directly and explicitly demonstrated for the first time that a cortical drive increases IHI from the contralateral (active) to ipsilateral (non-active) M1. The novel findings here are that (1) IHI from active to non-active M1 was detected during rest, voluntary movement, and imagined movement when the conditioning TMS was adjusted above the rMT and when the ISIs were adjusted at 10 and 15 ms, (2) the extent of IHI was enhanced during voluntary and imagined movement as compared with that at rest, and (3) a negative correlation between MEP in the right (active) FDI muscle and conditioned MEP in the left (non-active) FDI muscle was observed in all right-hand conditions, while the slope of the regression line was not changed during imagined movement but blunted during voluntary movement as compared with that at rest. We have provided novel insights into the neural mechanisms that modulate IHI from the

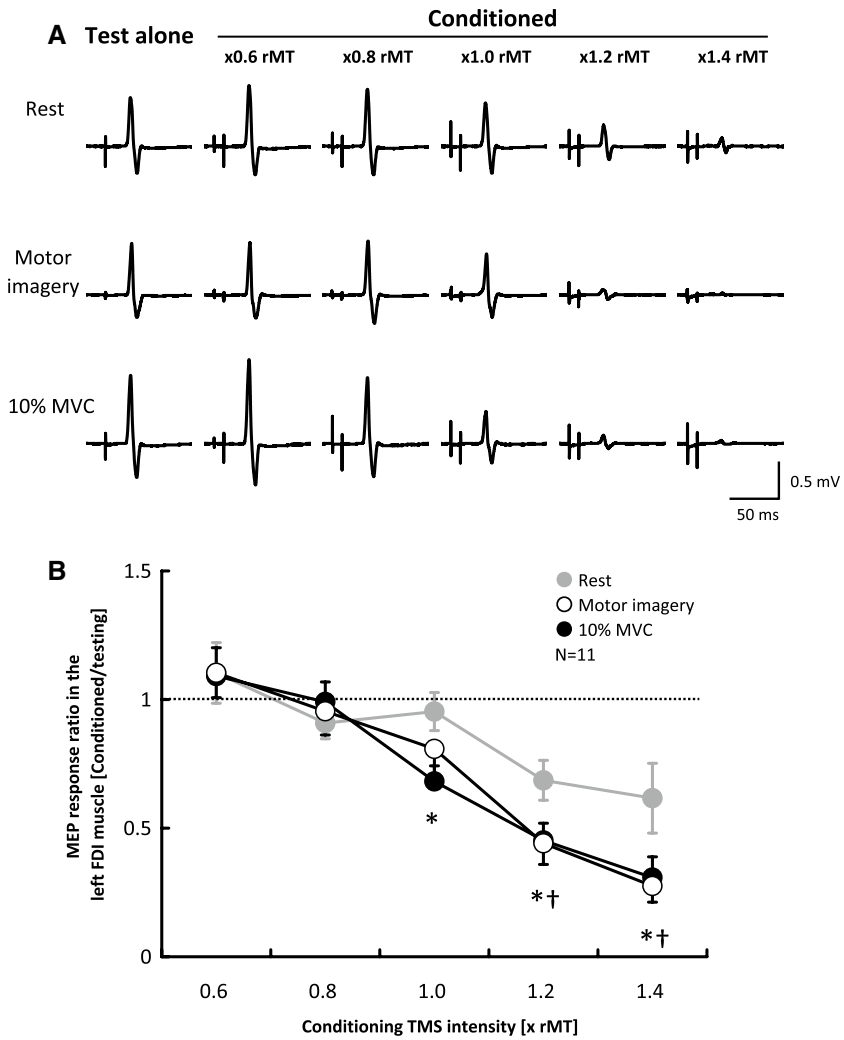

Fig. 3 MEPs of the left FDI muscle during resting state (rest), motor imagery, and 10 % MVC of the right index-finger abduction with single- (test alone) and paired-pulse TMS (conditioning intensity ranged from ×0.6 to ×1.4 rMT, interstimulus interval 10 ms). **a** Representative MEP recordings (averaged five trials) in all conditions. Note that the MEP test response size was matched among the conditions of rest, motor imagery, and 10 % MVC by adjusting the TMS intensity. **b** MEPs normalized to control size. Note the difference in MEPs between rest and motor imagery or 10 % MVC when the conditioning intensity was adjusted from ×1.0 to ×1.4 rMT. *Significant difference between rest and 10 % MVC, $P < 0.05$, †Significant difference between rest and MI, $P < 0.05$. *MVC* maximum voluntary contraction, *MEP* motor evoked potential, *FDI* first dorsal interosseous, *rMT* resting motor threshold

active to non-active M1 during unilateral volitional motor activity.

Modulations of ipsilateral M1 excitability and IHI during unilateral voluntary movement

Numerous studies have been conducted using neuroimaging and electrophysiological techniques to ascertain the excitability changes in the ipsilateral hemisphere accompanying unilateral voluntary movements (Chen et al. 1997; Duque et al. 2005; Kim et al. 1993; Morishita et al. 2011; Muellbacher et al. 2000; Stedman et al. 1998; Stinear et al. 2001; Tinazzi and Zanette 1998; Uehara et al. 2011; Verstynen et al. 2005). With a relatively low force level of voluntary movement (<50 % MVC), the increased corticospinal excitability was likely due to those occurred at the supraspinal level, for example, M1 (Liang et al. 2008; Muellbacher et al. 2000; Stedman et al. 1998; Stinear et al. 2001). The present study has confirmed the MEP facilitation in the resting left FDI muscle when the right FDI muscle was contracting at a force level of 10–70 % MVC (Fig. 1), while the extent of IHI tested by conditioning TMS was superficially weaker with 70 % MVC as compared with that during 10–50 % MVC or imagined movement (Fig. 1b). One explanation of this result is that the spinal motoneuron excitability corresponding to the non-active left FDI muscle would increase if the right FDI muscle contracted at such a higher force level of 70 % MVC (Liang et al. 2008; Muellbacher et al. 2000; Stedman et al. 1998). The increased excitability of spinal motoneuron pool would contribute to MEP facilitation to test TMS or MEP disinhibition to conditioning TMS, and therefore, it is difficult to identify the modulations of IHI during voluntary movement with a forceful muscle contraction.

Accumulating evidence regarding the changes in bilateral M1 excitability led the researchers in this field to focus on the contribution of the transcallosal neural pathway. IHI between homologous motor cortices, which can be studied by conditioning-test TMS paradigm (Ferbert et al. 1992), involves cortical inhibition (Di Lazzaro et al. 1999). The

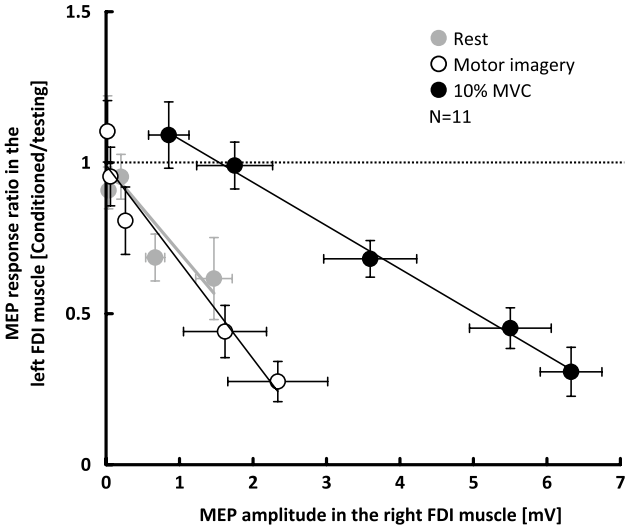

Fig. 4 Normalized MEPs of the left FDI muscle plot against the MEP elicited in the right FDI muscle. Each point presents the average data with one intensity of the conditioning TMS. Note that the regression slope was comparable between resting state ($y = -0.29x + 0.99$, $R^2 = 0.783$) and motor imagery ($y = -0.32x + 0.99$, $R^2 = 0.946$), while it was decreased during voluntary contraction with 10 % MVC ($y = -0.14x + 1.22$, $R^2 = 0.997$). *MVC* maximum voluntary contraction, *MEP* motor evoked potential, *FDI* first dorsal interosseous

inhibitory effects from non-active toward active M1 and vice versa have been shown to be modulated during unilateral movement (Hinder et al. 2010; Morishita et al. 2012; Murase et al. 2004; Nelson et al. 2009; Perez and Cohen 2008; Sattler et al. 2012). During unilateral static contraction, we have shown here that MEP in the contralateral resting muscle to single-pulse TMS increased in proportion to the output force of the moving hand, whereas no difference was detected in the conditioned MEP to paired-pulse TMS among all conditions, which led to an increment of IHI (Figs. 1, 2, 3). This finding was in line with a previous study in which the ipsilateral silent period of ongoing EMG to single-pulse TMS was enhanced during voluntary movements of the contralateral limb, suggesting that the activation of unilateral M1 by volitional motor activity of the contralateral limb increases IHI that toward the opposite M1 (Giovannelli et al. 2009). However, the forceful unilateral voluntary movement, which was applied so as to examine IHI by determining the silent period of EMG, was capable of affecting the corticospinal excitability at the cortical or spinal level (Liang et al. 2008; Muellbacher et al. 2000; Stedman et al. 1998; Stinear et al. 2001). The afferent activation from the contracting muscle is feasible to modulate the ipsilateral sensorimotor cortex excitability in this instance (Hadoush et al. 2010; Swayne et al. 2006) and, unintentionally, interacts with IHI. It is also revealed that ipsilateral silent period and IHI do not represent the same phenomenon, suggested that different populations of neurons are responsible for these two types of TMS (Chen et al. 2003). In consideration with our recent study showing that the facilitatory effect of unilateral imagined movement on the contralateral M1 excitability was reduced during voluntary movement of the opposite hand (Liang et al. 2011), ipsilateral EMG silent period study has limitation to investigate the sole modulation of IHI accompanying unilateral voluntary movement. Furthermore, whether unilateral imagined movement, a rehearsal of voluntary movement without any afferent input from the contracting muscle, modulates IHI has to be determined precisely.

Modulation of IHI by unilateral imagined movement

In the present study, the subjects were asked to solely perform unilateral imagined or voluntary movement, so as to exclude the contribution of the neural circuits responsible for bilateral movements to IHI if any. Because it has been suggested, at the behavioral and neuronal level, that partial but not complete overlap in the brain neural networks is involved in the unilateral and bilateral movements, although a unilateral movement appears to be similar in unilateral and bilateral movements (Donchin et al. 1998, 2001; Nozaki et al. 2006; Swinnen 2002). Several lines of evidence indicate that imagined movement shares neural structures with those during actual movement (Caldara et al. 2004; Gerardin et al. 2000; Kasai et al. 1997; Liang et al. 2006, 2007; Stinear and Byblow 2003, 2004; Yahagi et al. 1996). The fact that neither actual movement nor EMG activity was observed during imagined movement suggested no afferent input from the target muscle and, therefore, enabled us to purely explore the centrally originated mechanisms regarding IHI.

It is well known that the corticospinal excitability increased accompanying the contralateral imagined movement as well as voluntary movement (Kasai et al. 1997; Liang et al. 2006, 2007; Stinear and Byblow 2003, 2004; Yahagi et al. 1996). The enhancement of corticospinal excitability can be determined by an increase in the MEP amplitude and a decrease in the MT. In the present study, we confirmed MEP facilitation of the right FDI muscle to conditioning TMS during imagined or voluntary movement of the right index-finger. Several intensities of conditioning TMS including those with sub- and supra-MT (0.6–1.4 times the rMT) were utilized to determine the effects of increased corticospinal excitability on IHI toward the opposite M1. With voluntary movement, an inhibition of conditioned MEP in the left FDI muscle was observed with the conditioning TMS intensity at 1.0 times the rMT, with which conditioned MEP showed no significant changes at rest. The extent of inhibition became stronger by increasing the intensity, i.e., 1.2 and 1.4 times the rMT (Fig. 3). These observations suggested a decrease in the firing threshold

of the cortical neuron conveying activities to the opposite M1 through the transcallosal fibers during voluntary movement. However, such a threshold change, if any, was not likely occurred during motor imagery, because IHI started to emerge at 1.2 times the rMT (Fig. 3).

The increased corticospinal excitability for the right hand could also be represented in a decrease in MT. It was not surprising that MEP in the right FDI muscle could be detected with an intensity lower than the rMT (0.6 and 0.8 times the rMT in the present study, Fig. 4). This raised a fundamental question as to whether IHI could be modulated in a corticospinal excitability-dependent manner. If IHI increased depending on increments of the corticospinal excitability of the right hand, MEP enhancement in the right FDI muscle by imagined or voluntary movement would lead to stronger inhibition of the conditioned MEP in the left FDI muscle. In comparison with rest (Fig. 4), although the extents of IHI (ordinate) significantly increased during imagined or voluntary movement in proportion to the increments of MEP of the right FDI muscle (abscissa), the slope of regression line was not change during imagined movement and was decreased during voluntary movement. It is worthy to note that with a comparable size of MEP in the right FDI muscle (about 1–2 mV), there was no MEP inhibition in the left FDI muscle during 10 % MVC, while an obvious MEP inhibition was observed at rest or motor imagery. The marked increase in MEP of the right FDI muscle during voluntary movement with 10 % MVC would mainly represent the increased excitability of the spinal motoneuron pool, because it has been proposed that the majority of enhanced MEP during voluntary contraction is due to the increased excitability at the spinal level rather than that in the descending volleys (Di Lazzaro et al. 1998). This result suggested that the firing threshold of corticomotoneurons became lower than that of transcallosal neurons during voluntary movement, while those were comparable at rest or during motor imagery. Taken together, the present results suggested that the modulation of IHI during imagined or voluntary movement depends on the impulse conveyed from active to non-active M1 through the transcallosal pathways, but not on the corticospinal excitability corresponding to the voluntarily or imaginarily moving hand.

Possible mechanisms mediating the ipsilateral M1 excitability and IHI during unilateral imagined movement

The ipsilateral facilitation during unilateral voluntary and imagined movement which has been shown in the previous studies and also confirmed in the present study could not be explained by a release of IHI from active to non-active M1, because IHI was increased explicitly. The interaction between IHI and intracortical inhibition or facilitation during resting state and volitional motor activity remains unclear. Given that release of short intracortical inhibition contributes to the ipsilateral facilitation (Liang et al. 2008), and that conditioning TMS over the opposite M1 is capable of inducing a decrease in short intracortical inhibition (Daskalakis et al. 2002), one possible explanation for the neural mechanisms of ipsilateral facilitation is that an increased IHI directly suppresses the excitability of cortical output neurons and simultaneously makes a release of intracortical inhibition which indirectly enhances the excitability of cortical output neurons (Morishita et al. 2012). The competition of these inhibitory and facilitatory pathways exists at all times, and perhaps, the inhibition may be overwhelmed by the facilitation during unilateral volitional motor activity.

Except the M1, other motor-related cortical areas may also contribute to the increased IHI during motor imagery. Two distinct phase of IHI (10 and 40–50 ms, short and long IHI, respectively) could be detected using the conditioning-test TMS paradigm, both of which are due to cortical inhibition (Ni et al. 2009). It is assumed that the short IHI reflects the inhibition between M1, while the long IHI involves premotor cortex, somatosensory cortex, and prefrontal cortex (Ni et al. 2009), which are known as cortical areas engaging in volitional motor activity. During unilateral imagined movement in the present study, therefore, the ipsilateral M1 excitability may be modulated not only by contralateral M1 but also by other motor-related cortical areas. In this scenario, two possible pathways may be involved. The first is a pathway from the contralateral motor-related areas to the contralateral M1 and then passes through the transcallosal fibers to the ipsilateral M1. Second, a pathway from contralateral motor-related areas to the ipsilateral homologous ones and then to the targeted ipsilateral M1 is also possible, because the transcallosal fibers exist between homologous cortical areas other than M1s, e.g., bilateral premotor cortices (Mochizuki et al. 2007). According to the present results that increased IHI during motor imagery was observed when matching the test MEP size and when increasing the conditioning TMS intensity, it was likely the former case. Namely, the volitional motor activity-associated neuronal activities in the contralateral motor-related cortical areas may be integrated in the contralateral M1, which cause an inhibitory effect toward the ipsilateral M1 through the transcallosal fibers. It is of great interest to determine precisely the pathway contributing to the increased IHI during imagined or voluntary movement in further studies.

Limitations

Some potential limitations are involved in this study. First, both coils for delivering conditioning and test TMS over the left and right M1, respectively, were placed in a fixed,

medial direction in the present study. By changing the orientation of coil, i.e., the current direction applied in the brain, it has been proposed that different direct (D-) and/or indirect (I-) waves corresponding to different sets of cortical neurons could be recruited (Di Lazzaro et al. 2001; Kaneko et al. 1996; Sakai et al. 1997). The studies using cervical epidural electrodes that are capable of recording the corticospinal volleys to TMS have revealed that the first wave is D wave with the lateral–medial directed current (Di Lazzaro et al. 2001; Ni et al. 2011b), although the early and late I-wave components are also involved in the MEP induced in this way. The distinct difference in the MEP latency among lateral–medial, posterior–anterior, and anterior–posterior directed currents also supports this notion (Ni et al. 2011a). Moreover, the interhemispheric interactions between motor cortices have been shown to behave differently by I1- and I3 waves induced (Hanajima et al. 2001). Furthermore, enhancements of MEP to TMS during imagined movement varied depending on the current direction in the brain (Takahashi et al. 2004), i.e., I3 waves showed more MEP facilitation than that of I1 waves, suggesting different neural populations of corticomotoneuronal cells have differential sensitivities to imagined movement. Taking into consideration the previous studies, I1 waves may be preferentially induced in the present study. Given that MEP involving the contamination of D wave alone with I waves is less responsible for the intracortical neural circuits, the present protocol might be less sensitive than the traditional protocol using posterior–anterior directed current, especially in the case of the test pulse. Second, the ISIs of 5–15 ms used in the present study aimed to test the short IHI which has been shown to be mediated by direct transcallosal fibers between motor cortices (Daskalakis et al. 2002; Di Lazzaro et al. 1999; Ferbert et al. 1992; Hanajima et al. 2001; Murase et al. 2004; Perez and Cohen 2008). The long IHI with an ISI about 40–50 ms may have different physiological origins to those of short IHI as discussed above. The ipsilateral EMG silent period correlates with long IHI, but not with short IHI (Chen et al. 2003), suggesting that the populations of cortical neurons which mediates the long IHI are different from those activating short IHI. Future studies are needed to determine whether long IHI is also modulated during volitional motor activity.

Conclusion

The IHI from active to non-active M1 increases accompanying not only a unilateral voluntary movement but also a pure cortical drive of motor imagery.

Acknowledgments This study was supported, in part, by a Research Projects Grant-in-Aid for Young Scientists, Japan (N.L.).

Conflict of interest The authors declare that there is no conflict of interest.

References

Caldara R, Deiber MP, Andrey C, Michel CM, Thut G, Hauert CA (2004) Actual and mental motor preparation and execution: a spatiotemporal ERP study. Exp Brain Res 159:389–399

Chen R, Gerloff C, Hallett M, Cohen LG (1997) Involvement of the ipsilateral motor cortex in finger movements of different complexities. Ann Neurol 41:247–254

Chen R, Yung D, Li JY (2003) Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. J Neurophysiol 89:1256–1264

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R (2002) The mechanisms of interhemispheric inhibition in the human motor cortex. J Physiol (Lond) 543:317–326

Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P, Rothwell JC (1998) Effects of voluntary contraction on descending volleys evoked by transcranial stimulation in conscious humans. J Physiol (Lond) 508:625–633

Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, Rothwell JC (1999) Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. Exp Brain Res 124:520–524

Di Lazzaro V, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P, Profice P, Tonali P, Rothwell JC (2001) The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. Exp Brain Res 138:268–273

Donchin O, Gribova A, Steinberg O, Bergman H, Vaadia E (1998) Primary motor cortex is involved in bimanual coordination. Nature 395:274–278

Donchin O, Gribova A, Steinberg O, Bergman H, Cardoso de Oliveira S, Vaadia E (2001) Local field potentials related to bimanual movements in the primary and supplementary motor cortices. Exp Brain Res 140:46–55

Duque J, Mazzocchio R, Dambrosia J, Murase N, Olivier E, Cohen LG (2005) Kinematically specific interhemispheric inhibition operating in the process of generation of a voluntary movement. Cereb Cortex 15:588–593

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol (Lond) 453:525–546

Gerardin E, Sirigu A, Lehéricy S, Poline JB, Gaymard B, Marsault C, Agid Y, Le Bihan D (2000) Partially overlapping neural networks for real and imagined hand movements. Cereb Cortex 10:1093–1104

Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Viggiano MP, Cincotta M, Ziemann U (2009) Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. J Physiol (Lond) 587:5393–5410

Hadoush H, Inoue K, Nakanishi K, Kurumadani H, Sunagawa T, Ochi M (2010) Ipsilateral primary sensorimotor cortical response to mechanical tactile stimuli. NeuroReport 21:108–113

Hanajima R, Ugawa Y, Machii K, Mochizuki H, Terao Y, Enomoto H, Furubayashi T, Shiio Y, Uesugi H, Kanazawa I (2001) Interhemispheric facilitation of the hand motor area in humans. J Physiol (Lond) 531:849–859

Hess CW, Mills KR, Murray NM (1986) Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. Neurosci Lett 71:235–240

Hinder MR, Schmidt MW, Garry MI, Summers JJ (2010) Unilateral contractions modulate interhemispheric inhibition most strongly

and most adaptively in the homologous muscle of the contralateral limb. Exp Brain Res 205:423–433
Holm S (1979) A simple sequentially rejective multiple test procedure. Scand J Stat 6:65–70
Kaneko K, Kawai S, Fuchigami Y, Morita H, Ofuji A (1996) The effect of current direction induced by transcranial magnetic stimulation on the corticospinal excitability in human brain. Electroencephalogr Clin Neurophysiol 101:478–482
Kasai T, Kawai S, Kawanishi M, Yahagi S (1997) Evidence for facilitation of motor evoked potentials (MEPs) induced by motor imagery. Brain Res 744:147–150
Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Uğurbil K, Georgopoulos AP (1993) Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science 261:615–617
Liang N, Hayashi S, Takahashi M, Ni Z, Yamashita T, Yahagi S, Shimura K, Kasai T (2006) Further insight into excitability changes of intracortical inhibitory (ICI) and facilitatory (ICF) circuits in human hand motor area during motor imagery. Adv Exerc Sports Physiol 12:45–50
Liang N, Ni Z, Takahashi M, Murakami T, Yahagi S, Funase K, Kato T, Kasai T (2007) Effects of motor imagery are dependent on motor strategies. NeuroReport 18:1241–1245
Liang N, Murakami T, Funase K, Narita T, Kasai T (2008) Further evidence for excitability changes in human primary motor cortex during ipsilateral voluntary contractions. Neurosci Lett 433:135–140
Liang N, Funase K, Narita T, Takahashi M, Matsukawa K, Kasai T (2011) Effects of unilateral voluntary movement on motor imagery of the contralateral limb. Clin Neurophysiol 122:550–557
Meyer BU, Röricht S, Gräfin von Einsiedel H, Kruggel F, Weindl A (1995) Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain 118:429–440
Mochizuki H, Furubayashi T, Hanajima R, Terao Y, Mizuno Y, Okabe S, Ugawa Y (2007) Hemoglobin concentration changes in the contralateral hemisphere during and after theta burst stimulation of the human sensorimotor cortices. Exp Brain Res 180:667–675
Morishita T, Ninomiya M, Uehara K, Funase K (2011) Increased excitability and reduced intracortical inhibition in the ipsilateral primary motor cortex during a fine-motor manipulation task. Brain Res 1371:65–73
Morishita T, Uehara K, Funase K (2012) Changes in interhemispheric inhibition from active to resting primary motor cortex during a fine-motor manipulation task. J Neurophysiol 107:3086–3094
Muellbacher W, Facchini S, Boroojerdi B, Hallett M (2000) Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. Clin Neurophysiol 111:344–349
Murase N, Duque J, Mazzocchio R, Cohen LG (2004) Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol 55:400–409
Nelson AJ, Hoque T, Gunraj C, Ni Z, Chen R (2009) Bi-directional interhemispheric inhibition during unimanual sustained contractions. BMC Neurosci 10:31
Ni Z, Gunraj C, Nelson AJ, Yeh IJ, Castillo G, Hoque T, Chen R (2009) Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. Cereb Cortex 19:1654–1665
Ni Z, Charab S, Gunraj C, Nelson AJ, Udupa K, Yeh IJ, Chen R (2011a) Transcranial magnetic stimulation in different current directions activates separate cortical circuits. J Neurophysiol 105:749–756
Ni Z, Gunraj C, Wagle-Shukla A, Udupa K, Mazzella F, Lozano AM, Chen R (2011b) Direct demonstration of inhibitory interactions between long interval intracortical inhibition and short interval intracortical inhibition. J Physiol (Lond) 589:2955–2962
Nozaki D, Kurtzer I, Scott SH (2006) Limited transfer of learning between unimanual and bimanual skills within the same limb. Nat Neurosci 9:1364–1366
Oldfield R (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113
Perez MA, Cohen LG (2008) Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. J Neurosci 28:5631–5640
Ridding MC, Taylor JL, Rothwell JC (1995) The effect of voluntary contraction on corticocortical inhibition in human motor cortex. J Physiol (Lond) 487:541–548
Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I (1997) Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res 113:24–32
Sattler V, Dickler M, Michaud M, Simonetta-Moreau M (2012) Interhemispheric inhibition in human wrist muscles. Exp Brain Res 221:449–458
Stedman A, Davey NJ, Ellaway PH (1998) Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. Muscle Nerve 21:1033–1039
Stinear CM, Byblow WD (2003) Motor imagery of phasic thumb abduction temporally and spatially modulates corticospinal excitability. Clin Neurophysiol 114:909–914
Stinear CM, Byblow WD (2004) Modulation of corticospinal excitability and intracortical inhibition during motor imagery is task-dependent. Exp Brain Res 157:351–358
Stinear CM, Walker KS, Byblow WD (2001) Symmetric facilitation between motor cortices during contraction of ipsilateral hand muscles. Exp Brain Res 139:101–105
Swayne O, Rothwell J, Rosenkranz K (2006) Transcallosal sensorimotor integration: effects of sensory input on cortical projections to the contralateral hand. Clin Neurophysiol 117:855–863
Swinnen SP (2002) Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci 3:350–361
Takahashi M, Sugawara K, Hayashi S, Kasai T (2004) Excitability changes in human hand motor area dependent on afferent inputs induced by different motor tasks. Exp Brain Res 158:527–532
Tinazzi M, Zanette G (1998) Modulation of ipsilateral motor cortex in man during unimanual finger movements of different complexities. Neurosci Lett 244:121–124
Uehara K, Morishita T, Funase K (2011) Excitability changes in the ipsilateral primary motor cortex during rhythmic contraction of finger muscles. Neurosci Lett 488:22–25
Uehara K, Morishita T, Kubota S, Funase K (2013) Neural mechanisms underlying the changes in ipsilateral primary motor cortex excitability during unilateral rhythmic muscle contraction. Behav Brain Res 240:33–45
Ugawa Y, Hanajima R, Kanazawa I (1993) Interhemispheric facilitation of the hand area of the human motor cortex. Neurosci Lett 160:153–155
Verstynen T, Diedrichsen J, Albert N, Aparicio P, Ivry RB (2005) Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. J Neurophysiol 93:1209–1222
Yahagi S, Shimura K, Kasai T (1996) An increase in cortical excitability with no change in spinal excitability during motor imagery. Percept Mot Skills 83:288–290