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Further evidence for excitability changes in human primary motor cortex during ipsilateral voluntary contractions

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Abstract

The present study aimed to further investigate whether the intracortical neural circuits within the primary motor cortex (M1) are modulated during voluntary contractions of ipsilateral muscle without the excitability changes at the spinal level. Single- and paired-pulse (interstimulus intervals, ISIs; 3ms and 12 ms) transcranial magnetic stimulations of the left M1 were applied to elicit motor evoked potential (MEP) in the right first dorsal interosseous (Rt-FDI) muscle during voluntary contractions of the left FDI (Lt-FDI) muscle (10% and 30%MVC). F-waves of Rt-FDI muscle were recorded under these left index-finger conditions for ensuring that the excitability changes occur at the supra-spinal level. MEPs were also recorded during motor imagery of the left index-finger abduction instead of overt movement. The results showed that, in single-pulse TMS paradigm, MEPs in Rt-FDI muscle were markedly enhanced during voluntary contractions of Lt-FDI muscle compared with the complete resting state. In paired-pulse TMS paradigm, the short intracortical inhibition was significantly reduced in proportion to increments of ipsilateral muscle contraction, whereas the intracortical facilitation had no change. F-wave of Rt-FDI muscle was unchanged under these conditions, while MEP in Rt-FDI muscle was also enhanced during motor imagery of left index-finger abduction. Based on the present results, it is suggested that in the transition from rest to activity of ipsilateral homonymous muscle, the intracortical inhibitory neural circuits may be independently modulated. The excitability changes in M1 might be induced by overflows of voluntary drive given to the ipsilateral limb, probably via the transcallosal pathway. (246/ 250 words)

*Keywords (6)**:*** Short intracortical inhibition (SICI); Intracortical facilitation (ICF); Motor imagery; Primary motor cortex; Motor evoked potential (MEP); Transcranial magnetic stimulation (TMS)

Introduction

Motor evoked potential (MEP) induced by transcranial magnetic stimulation (TMS) is widely used to assess the corticospinal excitability in humans non-invasively. When applying TMS over one primary motor cortex (M1), MEP elicited in the contralateral targeted muscle can be enhanced not only during contractions of itself but also during contractions of ipsilateral homonymous muscle (Hess et al., 1986; Stedman et al., 1998; Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Ziemann and Hallett, 2001; Stinear et al., 2001; Ghacibeh et al., 2007). The MEP enhancements reflect that the excitability of corticospinal tract correspondent with the targeted muscle is increased, while the underlying mechanism seems differently between these two conditions.

There are two possible mechanisms responsible for MEP enhancement: excitability changes at the cortical level and the spinal level. During contractions of targeted muscle itself, both the reduced intracortical inhibition within contralateral M1 (Ridding et al. 1995) and the increased excitability of spinal motoneurons owing to the descending volleys are contributory to the MEP enhancements (Di Lazzaro et al. 1998). In this case, it has been proposed that the majority of enhanced MEP size is due to the increased excitability at the spinal level rather than that in the descending volleys (Di Lazzaro et al. 1998). On the other hand, MEP enhancement in the resting muscle during contractions of contralateral homonymous muscle is likely mainly due to the excitability changes in the M1 (Stedman et al., 1998; Muellbacher et al., 2000; Stinear et al., 2001), at least during relatively low force levels (<50% maximum voluntary contraction; MVC). Thus, it is suggested that proprioceptive input induced by active muscle play no dominant role in enhancing MEP in the resting muscle. During voluntary contractions at low force levels, therefore, it seems possible that the intracortical neural circuits within ipsilateral M1 are modulated without excitability changes at the spinal level. Moreover, there is also a possibility that a covert movement, instead of overt movement, also modulates ipsilateral M1 excitability, probably via the transcallosal pathway.

To test the possibility of these issues, in the present study we used single- and paired-pulse

TMS of the dominant M1 and recorded MEP from the right first dorsal interosseous (Rt-FDI) muscle during voluntary contractions (10%, and 30%MVC) of the left FDI (Lt-FDI) muscle. We recorded F-wave of Rt-FDI muscle to confirm that the excitability of spinal motoneuron pool is unchanged under these conditions. In addition, to examine whether the excitability changes in dominant M1 are induced by motor overflows from non-dominant M1 rather than afferent inflows, we recorded MEPs during motor imagery of the left index-finger abduction instead of overt movements. We hypothesized that the intracortical circuits within M1 are modulated in the transition from rest to activity of ipsilateral muscle, and the effects of motor overflow can also be observed during motor imagery of ipsilateral limb.

Materials and methods

Subjects

Eight healthy volunteers (six males and two females; mean age 26.3 years; range 21-34 years) participated in the present study after giving their written informed consent. All subjects were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The experimental procedures were in accordance with the Declaration of Helsinki and with the approval of the Local Ethics Committee of Hiroshima University.

Experimental procedures

The subject was seated comfortably in an armchair with the upper limbs relaxed on a horizontal plate attached to the armrests. All experimental protocols were undertaken with both the left and right arms in the prone position. At the beginning of the experiment, we measured the maximum force of the left index-finger abduction as a standard reference in each individual. An immobile bar of which a force sensor was fixed, was exteriorly attached to the left index-finger. The force signal was amplified by a strain gage amplifier (model AS1302, Nihondenkisanei, Tokyo,

Japan) which was connected to the force sensor. A beam line indicating real force level generated by the individual, was displayed on an oscilloscope monitor. Another beam line was also displayed on the monitor representing the target force (10% or 30%MVC). The subject was instructed to abduct the left index-finger and to keep the coincidence of two beam lines for several seconds. The right index-finger was at complete rest throughout the experiment.

EMG recordings

Surface EMG recordings were taken from the Rt-FDI and Lt-FDI muscles with 9mm diameter Ag-AgCl surface cup electrodes. The active electrodes were placed over the muscle bellies and the reference electrodes over the metacarpophalangeal joints of the right and left index-fingers, respectively. EMG responses were amplified at a bandwidth of 5 Hz- 3 kHz, and all amplification procedures were controlled by a signal processor (7S12, NEC San-ei Co. Ltd., Japan). Analog outputs from the signal processor were digitized at a sampling rate of 10 kHz and then fed to a computer for off-line analysis (PowerLab system, AD Instruments Pty. Ltd., Australia). Special attention was paid to the background EMG activities of Rt-FDI muscle throughout the experiment and the off-line analysis. If any background EMG activities were detected, the data were omitted from the analysis.

TMS application

A figure-of-eight shaped coil with external diameter of wings 90 mm connected to a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK) was placed over the left motor cortex in the antero-medial direction. TMS through the coil was applied to evoke MEP form the Rt-FDI muscle. We determined the optimal position for activation of the Rt-FDI muscle by moving the coil in 0.5-cm steps around the presumed hand motor area in the left M1. The site at which stimulation of slight suprathreshold TMS intensity consistently evoked the largest MEP in the right FDI muscle,

was regarded as the motor hot-spot and was marked with a pen on the scalp of which a swimming cap was covered. The resting motor threshold (rMT) was defined as the lowest stimulus intensity evoking MEP in the Rt-FDI muscle with amplitude of at least 50μV in at least four out of eight trials. During the single-pulse paradigm, TMS intensity was fixed to evoke MEP with a peak-to-peak amplitude of approximately 0.5-1.0mV in Rt-FDI muscle during complete resting state. During the paired-pulse TMS paradigm (Kujirai et al. 1993), the conditioning and test stimuli were given through the same coil by connecting two Magstim 200 stimulators via a Bistim module (Magstim, Whitland, Dyfed, UK). The intensity of the conditioning stimulus was 10% below the rMT, at which we confirmed that MEP could never be identified under all conditions of the left index-finger. The intensity of the test stimulus was adjusted for eliciting MEP with a peak-to-peak amplitude of 0.5-1.0mV in all left index-finger conditions. We selected two interstimulus intervals (ISIs), i.e., 3ms and 12ms, which could be used to investigate the SICI and ICF circuits, respectively (Kujirai et al., 1993; Ziemann et al., 1996).

During control condition (rest), MEPs were recorded when subject was looking at a small round mark (1cm in diameter) instead of the oscilloscope monitor. During performing the left index-finger abductions (10% and 30%MVC), TMS pulse was delivered when subject was maintaining the targeted force levels without oscillations. At least 10 MEPs were recorded in each condition and in single- and paried-pulse TMS paradigms, respectively. The order of single- and paired-pulse TMS, and that of ISIs (3ms and 12ms), was intermixed randomly.

F-wave recordings

The excitability of the spinal motoneuron pool can be assessed by testing the magnitude of F-wave, which is generated by a recurrent discharge of antidromically activated spinal motoneuron pool (Mayer and Feldman, 1967). To clarify whether changes in MEP are due to excitability changes at the spinal level or at the supraspinal level, we applied supra-maximum electrical stimulations on

the ulnar nerve at the right wrist, for eliciting F-waves of Rt-FDI muscle during all left index-finger conditions. F-waves were successfully recorded in seven of eight subjects, and 10 trials were recorded in each condition.

Motor imagery task

It has been proposed that the dynamic patterns of excitability changes in M1 during motor imagery are as the same spatio-temporal characteristics as those during overt movements (Hashimoto and Rothwell, 1999; Stinear and Byblow, 2003; Caldara et al., 2004; Yahagi and Kasai, 1998; Liang et al., 2007). During covert movements, therefore, the ipsilateral M1 excitability might also be modulated as same as during overt movements. If motor imagery of unilateral limb has effects on the ipsilateral M1 excitability, the excitability changes in ipsilateral M1 probably represent an interhemispheric transfer between homologous cortical areas on either hemisphere via the neural pathway of the corpus callosum rather than interactions at the spinal level. To address this possibility, we encouraged subjects to perform maximum mental effort of the left index-finger abduction after a beep sound. Several (2-3) seconds later, a TMS pulse was delivered. The coil was placed over the left or right M1 for eliciting MEP in Rt-FDI or Lt-FDI muscle, respectively. Under this condition we used the single-pulse TMS paradigm as described above. At least 10 MEPs were recorded in each condition.

Data and statistical analyses

The Background EMGs (with a 100-ms window prior to the TMS trigger) of Rt-FDI muscle between the left index-finger conditions were analyzed using one-way repeated-measure ANOVA. MEPs were measured as the peak-to-peak values. Between the left index-finger conditions, MEPs of Rt-FDI muscle in the single-pulse TMS paradigm, TMS intensities and adjusted MEPs of Rt-FDI muscle in the paired-pulse TMS paradigm, were separately analyzed using one-way

repeated-measure ANOVA. If a significant effect was obtained, Post-hoc analyses were done using a paired *t*-test with Holm's sequential Bonferroni correction (Holm, 1979). In order to investigate the effects of left index-finger contraction on SICI and ICF circuits within ipsilateral M1, MEPs induced by paired-pulse TMS were normalized as a ratio of the adjusted MEP size for each subject, and then grand mean ratio with standard error from pooled data were calculated. These data were analyzed using two-way repeated-measure ANOVA (factors; left index-finger condition and ISI). If a significant effect was obtained, post-hoc analyses were done using a paired *t*-test with Holm's sequential Bonferroni correction. Also calculated and analyzed was F-wave amplitude in Rt-FDI muscle between the left index-finger conditions, using one-way repeated-measure ANOVA. Regarding motor imagery task, the differences in MEPs between the control and motor imagery conditions in both hands were compared by a paired *t*-test with Holm's sequential Bonferroni correction. The level of statistical significance was defined as $P<0.05$. The data values are expressed as means± SE.

Results

The background EMG activities of Lt-FDI muscle were expectedly different between the index-finger conditions (0.09±0.00%MVC for rest, 10.50±0.01%MVC for 10%Force, 30.00±0.02%MVC for 30%Force), while those of Rt-FDI muscle remained unchanged under these conditions. The test intensities and MEPs of Rt-FDI muscle in the single- and paired-pulse TMS paradigms under all left index-finger conditions are summarized in Table 1. When TMS intensity was fixed, MEPs induced by single-pulse TMS were significantly enhanced in proportion to increments of left index-finger abduction force level ($F_{2,14}=17.23$, $P<0.001$; post-hoc: rest and 10%Force; $P<0.01$, rest and 30%Force; $P<0.01$, 10% and 30%Force; $P<0.01$). Regarding the paired-pulse TMS, test intensities for adjusting MEPs were significantly decreased in proportion to increments of left index-finger abduction force level ($F_{2,14}=28.78$, $P<0.0001$; post-hoc: rest and

10%Force; P<0.001, rest and 30%Force; P<0.001, 10% and 30%Force; P<0.01).

Insert Table 1 near here

Fig. 1A shows EMG specimen recordings of Rt-FDI and Lt-FDI muscles during resting state and left index-finger abductions with the force levels of 10% and 30%MVC. Although MEPs to single-pulse TMS were adjusted and had no change between the left index-finger conditions, there were definite differences in MEPs accompanying increased force levels of left index-finger abduction with ISI of 3ms, whereas those with ISI of 12ms were less changed. Means and SEs of MEPs obtained from all subjects (n=8) are shown in Fig. 1B. A significant difference was found in factor 'ISI' ($F_{1,14}$=24.94, P<0.001) and in factor 'left index-finger condition' ($F_{2,14}$=4.76, P<0.05). Post-hoc analysis showed that MEPs between the ISI 3ms and 12ms were significantly different under all left index-finger conditions (rest; P<0.001, 10%Force; P<0.01, 30%Force; P<0.05). More importantly, with ISI of 3ms MEPs were definitely increased accompanying increments of left index-finger abduction force (rest and 10%Force; P<0.01, rest and 30%Force; P<0.01, 10% and 30%Force; P<0.01), whereas MEPs with ISI of 12ms were unchanged. That is, SICI and ICF circuits were separately modulated accompanying ipsilateral muscle contractions. Additionally, F-waves obtained from the subjects tested (n=7) were unchanged under the left index-finger conditions but were definitely facilitated during MVC (Fig. 1C), suggesting that during 10% and 30%MVC of left index-finger abduction MEP enhancements were not due to the excitability changes at the spinal level.

Insert Fig. 1 near here

Fig. 2A shows EMG specimen recordings of Rt-FDI and Lt-FDI muscles during motor

imagery of the left index-finger abduction instead of overt movements. Means and SEs of MEPs in Rt-FDI (upper) and Lt-FDI (lower) muscles obtained from all subjects (n=8) are shown in Fig. 2B. These MEP were induced by TMS with the coil placed over the left and right M1, respectively. MEPs in Lt-FDI muscle were significantly enhanced (P<0.01), and surprisingly, MEPs in Rt-FDI muscle were also enhanced (P<0.001). The phenomena indicated that unilateral M1 excitability is modulated by ipsilateral covert movements as similar to overt movements.

Insert Fig. 2 near here

Discussion

The present results provide additional evidence that during relatively weak voluntary contractions of ipsilateral muscle SICI within M1 could be modulated without the excitability changes at the spinal level. Moreover, M1 excitability was modulated not only during ipsilateral overt movements but also during covert movements, i.e., motor imagery of ipsilateral limb, suggesting that the excitability changes in M1 are induced by motor overflow of voluntary drives given to the ipsilateral limb.

In the present study, we showed that corticospinal excitability does increase in proportion to increments of ipsilateral hand muscle contractions in keeping with previous studies (Hess et al., 1986; Stedman et al., 1998; Muellbacher et al., 2000; Stinear et al., 2001). Although the previous studies have emphasized factors of force level and TMS intensity in ipsilateral enhancement (Chiappa et al., 1991; Samii et al., 1997), in the present study MEPs of Rt-FDI muscle were markedly enhanced during left index-finger abduction, suggesting that the ipsilateral force levels (10% and 30% MVC) and TMS intensities were sufficient for inducing changes in corticospinal excitability. Any changes in MEP may depend on excitability changes in both the M1 and spinal motoneuron pool. The former determines the amplitude and number of I-waves that are recruited,

and the latter determines how many motoneurons are recruited by a given descending input. In the present study, the changes in MEP could not be explained by changes in F-wave. Moreover, motor imagery of ipsilateral limb, which involves excitability changes in the contralateral M1 rather than those at the spinal level (Yahagi et al., 1996; Kasai et al., 1997; Kiers et al., 1997; Abbruzzese et al., 1999), also modulated the corticospinal excitability. Therefore, it reveals that afferent inflows are unnecessary to ipsilateral motor control, and suggests that the changes in corticospinal excitability during relatively weak voluntary contractions of ipsilateral muscle are mainly due to excitability changes at the supra-spinal level.

The present results of the reduced SICI during ipsilateral voluntary contractions are in line with this view. Since it is general consensus that SICI occurs at the cortex rather than subcortical structures (Kujirai et al., 1993; Ziemann et al., 1996; Di Lazzaro et al., 1998), our results suggested that the intracortical network within M1 was modulated. Reduction in SICI serves to ‘‘release’’ cortical representations from inhibition (Ridding et al., 1995; Floeter and Rothwell, 1999), and it is found to be reduced not only during voluntary contractions of contralateral muscle (Ridding et al., 1995), but also during forceful voluntary contractions of ipsilateral homonymous muscle (Muellbacher et al., 2000). Based on the present results, it is suggested that in the transition from rest to activity of ipsilateral muscle, MEP facilitation of contralateral resting muscle is mainly due to the excitability changes in M1, probably mediated via the transcallosal pathway connecting homologous cortical areas on either hemisphere. When increasing the ipsilateral force levels, increased excitability at the spinal motoneuron pool may also additionally contribute to the MEP facilitation, which is evidenced by the previous results in healthy humans (Hess et al., 1986; Stedman et al., 1998; Muellbacher et al., 2000) and patients with callosal agenesis (Meyer et al., 1995).

We therefore conclude that during relatively weak contractions of ipsilateral homonymous muscle, MEP facilitation of the contralateral resting muscle is mainly due to the modulations of intracortical neural network that would be independently occurred without the excitability changes at

the spinal level. The excitability changes in M1 can also be observed during covert movements of ipsilateral limb, suggesting that the facilitatory effects might be induced by a voluntary drive given to the ipsilateral limb, probably via the transcallosal pathway. Additionally, since there is a possibility that the left hemisphere might play a relatively greater role in ipsilateral motor control than the right hemisphere (Ziemann and Hallett, 2001), and that the modulations of intracortical neural circuit are dependent on muscle properties (Takahashi et al., 2005, 2006), it is also possible that the ipsilateral facilitatory effect might be different depending on hemispheric dominance and muscle property. Focus on these issues, further studies using TMS protocols of interhemispheric inhibition and SICI and ICF are needed to test the possibility.

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Figure legends

Fig. 1. (A) Electromyography (EMG) specimen recordings (average of five trials) of right and left first dorsal interosseous (Rt-FDI and Lt-FDI) muscles during resting state and left index-finger abductions with 10% and 30%Force. Note that with the single-pulse TMS (upper) MEPs of Rt-FDI muscle represent the adjusted ones in all left index-finger conditions. With the paired-pulse TMS, the recordings with interstimulus intervals (ISIs) of 3ms (middle) and 12ms (lower) are respectively shown. **(B)** Means and SEs (n=8) of normalized MEP (%Control) at each left index-finger condition with ISIs of 3ms and 12ms. **(C)** Means and SEs (n=7) of F-wave under each left index-finger condition and during maximum voluntary contraction. *P <0.01

Fig. 2. (A) Electromyography (EMG) specimen recordings (average of five trials) of right and left first dorsal interosseous (Rt-FDI and Lt-FDI) muscles during complete resting state and during motor imagery of left index-finger abduction. **(B)** Means and SEs (n=8) of MEP in the Rt-FDI muscle (upper) and Lt-FDI muscle (lower). *P <0.01, **P <0.001

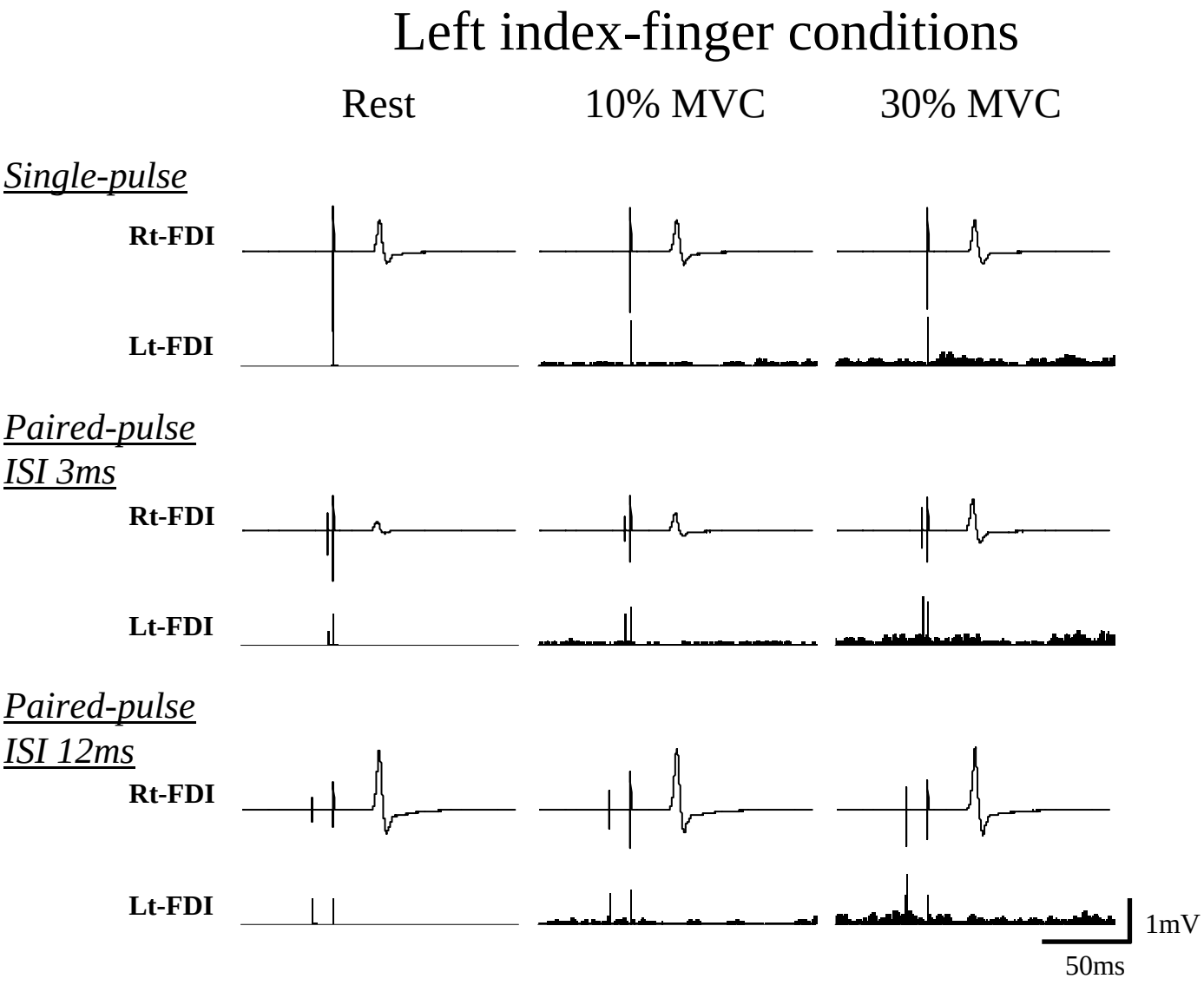
Table 1 Test intensities and MEPs during single- and paired-pulse TMS paradigms

	Left index-finger conditions		
	Rest	**10% MVC**	**30% MVC**
Single-pulse TMS			
Test intensity [%MSO]	65.6±5.7	65.6±5.7	65.6±5.7
MEP in Rt-FDI muscle [mV]	0.7±0.0	1.3±0.2	1.9±0.3
Paired-pulse TMS			
Adjusted test intensity [%MSO]	65.6±5.7	63.6±5.7	62.1±5.5
MEP in Rt-FDI muscle [mV]	0.7±0.1	0.7±0.0	0.7±0.1

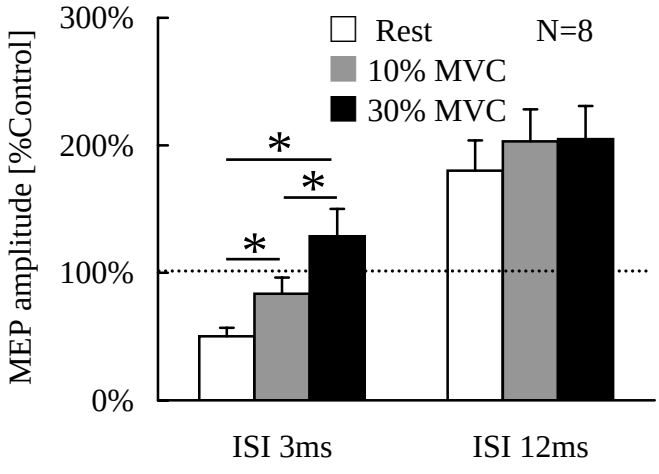
Values are mean± SE

MEPs motor evoked potentials, *TMS* transcranial magnetic stimulation,
MVC maximum voluntary contraction, *MSO* maximum stimulator output
Rt-FDI right first dorsal interosseous

A


Left index-finger conditions
Rest
10% MVC
30% MVC
Single-pulse
Rt-FDI
Lt-FDI
Paired-pulse
ISI 3ms
Rt-FDI
Lt-FDI
Paired-pulse
ISI 12ms
Rt-FDI
Lt-FDI
1mV
50ms

B


MEP amplitude [%Control]
300%
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Rest
10% MVC
30% MVC
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ISI 12ms

C

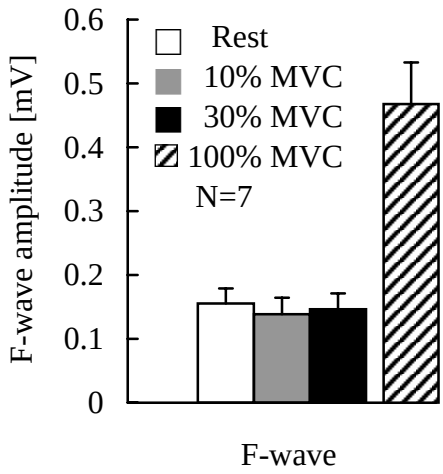
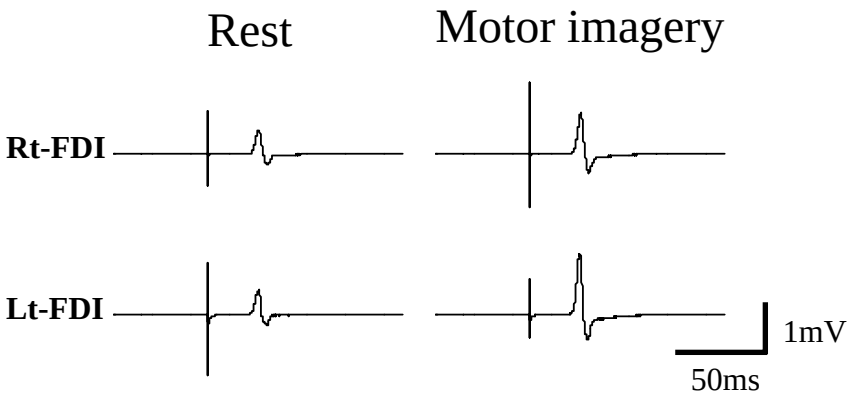

F-wave amplitude [mV]
0.6
0.5
0.4
0.3
0.2
0.1
0
Rest
10% MVC
30% MVC
100% MVC
N=7
F-wave

Figure 1

A


Rest
Motor imagery
Rt-FDI
Lt-FDI
1mV
50ms

B

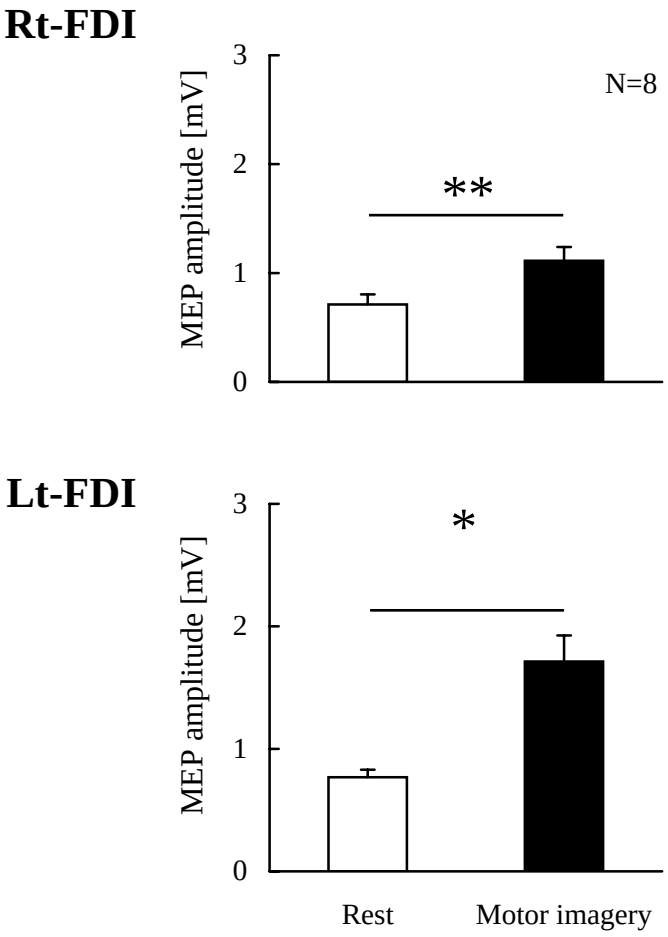

Rt-FDI
MEP amplitude [mV]
N=8
**
Lt-FDI
MEP amplitude [mV]
*
Rest
Motor imagery

Figure 2