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## Excitability changes in human hand motor area dependent on afferent inputs induced by different motor tasks

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**Abstract** Using the technique of transcranial magnetic stimulation (TMS) with a figure-of-eight-shaped coil in 16 normal volunteers, we studied the extents of motor evoked potentials (MEPs) induced by remote facilitation of voluntary teeth clenching (VTC) and by motor imagery (MI). In particular, we examined whether different excitability changes in the primary motor cortex (M1) induced by both facilitation methods occur between early (I1 and I2) and late (I3 and I4) components of I-waves elicited from a first dorsal interosseous (FDI) muscle. Both components of I-waves were induced by anterior-medially (AM) directed currents or posterior-laterally (PL) directed currents. Our hypothesis was that facilitatory effects of VTC and MI on M1 differ because the neural pathways of these afferent inputs differ. The present results indicate that during MI MEP amplitudes of late components are significantly larger than those of early ones, although both MEP amplitudes are enhanced. On the other hand, during VTC MEP amplitudes of early components are significantly enhanced, but those of late ones are rather depressed. We conclude that recruitment of early and late components of I-waves differ depending on the afferent inputs to the motor cortex.

**Keywords** Transcranial magnetic stimulation · Motor-evoked potential · Motor imagery · Voluntary teeth clenching · Early and late I-waves · Current directions · Primary motor cortex · First dorsal interosseous muscle · Humans

### Introduction

It has been established on the basis of histological and neurophysiological studies that the primary motor cortex (M1) of primates receives both corticocortical and thalamocortical afferent inputs (Aizawa and Tanji 1994). Despite the wealth of anatomical studies only little is known about the functional roles of individual afferent inputs to M1. It is not well known, for example, how these afferent inputs influence on human M1 functions (Kaneko et al. 1994). In the present study we addressed this question using transcranial magnetic stimulation (TMS) for eliciting excitability changes in M1 during motor imagery (MI) and remote facilitation of voluntary teeth clenching (VTC).

It is well known that motor imagery (MI) is activated according to the intended movement, and that specifically internal motor commands can precisely activate M1 with no change in the spinal level without recourse to afferent feedback (Gandevia and Rothwell 1987; see also Kasai et al. 1997; Yahagi et al. 1996). In addition, the amount of corticomotoneuronal cell activity is affected by different motor imageries using the same muscle (Yahagi and Kasai 1998), and there is hemispheric asymmetry in right- and left-handed individuals (Yahagi and Kasai 1999). Taken together, MI plays an important role in developing a preparatory type of activity in M1, whereas the thalamocortical pathway provides substantial inputs. On the other hand, remote effects by means of VTC on cortical and spinal sites were shown using as indicators of H-reflex and MEP simultaneously recordings from the same flexor carpi radialis muscle (Sugawara and Kasai 2002). Based on the results of this report, remote facilitation induced by VTC seems to occur at both levels, i.e., one is a release of

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presynaptic inhibition at the spinal level (see Zehr and Stein 1999), and the other is a temporally unmasking of lateral excitatory projections at the cortical level. In addition, concerning excitability changes in the cortical level, more recently it has been demonstrated that MEP facilitation during VTC occurs just after the electromyographic (EMG) onset of the masseter muscle in the hand motor area at the early phase of VTC (intervals shorter than 50 ms) in M1 (Furubayashi et al. 2003). Based on the early facilitation of the time course of VTC the hand motor area in M1 must be finely regulated by substantial inputs provided via somatosensory cortex.

The modulations of M1 excitability are probably based on the intracortical networks underlying the inhibitory or excitatory interneurons by which TMS can preferentially affect these interneurons. These modulations would be detected by identifying different I-waves induced by different current directions (anterior-medially, AM; posterior-laterally, PL), at which early (I1) and late (I3) waves are recognizable especially by their latencies (Hanajima et al. 1998; Sakai et al. 1997). The exact nature of the generation of I-waves is still unclear, but there is convincing evidence that they originate in M1, mainly through activation of corticocortical projections onto cortical neurons. However, little is known about what kind of information or afferent inputs are provided to M1 circuits. Thus, the present investigation was to address different input effects between MI and VTC on termination of cortical excitability. We therefore carried out the following single magnetic stimulation study investigating whether different effects of MI and VTC occur on early and late I-wave components in M1 neural circuits.

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## Materials and methods

The two experiments included 16 healthy volunteers (11 men, 5 women; aged 24–45 years) who provided informed consent. Experiments were performed in accordance with the Declaration of Helsinki (1964) and approved by the local ethics committee of Hiroshima University. In the first experiment we examined excitability changes in M1 during MI. Of the 16 subjects 8 participated in this set of experiment. It is conceivable that the excitability changes in M1 during MI depend on the instructions given to the subject. For example, the instruction to image the sensation of moving might produce desynchronization over motor cortical areas, while the instruction to visualize movement might produce desynchronization over visual cortical areas (Pfurtscheller and Berghold 1989). In the present study subjects were therefore simply asked to image maximum contraction of the index finger abduction. This instruction seems comparable to image the sensation of moving, and this is supported by the finding that MI was predominantly associated with desynchronization over M1 (Yahagi and Kasai 1998). In addition, during MI under the relaxed muscle conditions great care was taken to check the EMG activity, and TMS was always delivered without background EMG activity in the first

dorsal interosseous (FDI) muscle, i.e., during experiments we checked and monitored whether there was definitely an absence of background EMG activity using a digital oscilloscope at high gain with a pretriggering facility (Kasai et al. 1997).

In the second experiment of VTC the other 8 subjects practiced VTC, and all of them were able to perform VTC sufficiently well within 200 ms. For recording MEPs within 50 ms after the EMG onset of the masseter muscle (Furubayashi et al. 2003) TMS were delivered by the triggered pulse by the EMG onset of masseter muscle. In one session, at least five trials were tested and four or five sessions were repeated with each subject. Intertrial intervals were randomly set at 10–15 s, and the “go” signal (experimenter’s voice “go”) was given to the subject. After this signal the subject made VTC at any time once she/he was ready. This is therefore is not a reaction time task but a kind of self-paced teeth clenching.

In both experiments we chose two current directions induced in the brain while in a relaxed muscle condition. A figure-of-eight shaped coil with 9 cm mean diameter (Magstim, UK), was placed over the hand motor area and held at different orientations to determine the current directions at which early and late components of I-waves could be preferentially elicited. We found that AM-directed current preferentially elicited early components of I-waves, and that PL-directed current elicited late components of I-waves in all subjects. Judging from MEP latencies, in relaxed muscles MEPs to AM currents seem likely to be produced by combination of I1 and I2 waves or early waves. Those to PL currents are probably generated by I3 and I4 waves or other late waves. It is well known that onset latencies were consistent with I1 and I3 waves and stable in active muscle (Sakai et al. 1997). Indeed in our most recent study during slight voluntary contraction of the FDI muscle VTC enhanced MEP responses in AM, whereas it reduced the response size in PL. In addition, the onset latency of MEP in AM was shorter than that in PL and was consistent with I1 wave latency, and that in PL was consistent with I3 waves. Furthermore, these onset latencies were unaffected by VTC (Sugawara et al. 2004). Thus effects of VTC and MI may reflect summation of different I-waves. However, in active muscles it is impossible to perform MI and is also difficult to decide the cause of changes in MEP amplitude dependent on task differences or on background EMG activities. Additionally, in the present study we must compare effects of MI with those of VTC under the same muscle condition. Thus we examined effects of MI and VTC on MEP amplitudes in relaxed muscles.

We defined the threshold (1.0xth) as the lowest intensity that evoked a small MEP (about 50  $\mu$ V) in at least 50% of successive trials. With both current directions TMS intensities of 1.1 or 1.2xth were used for each subject. At least ten trials were collected each TMS intensity with each subject, and trial intervals were given every 10–15 s. TMS was always delivered with the optimal timing during MI of the maximum index finger abduction by checking the self-reports of subjects. In the VTC experiment control

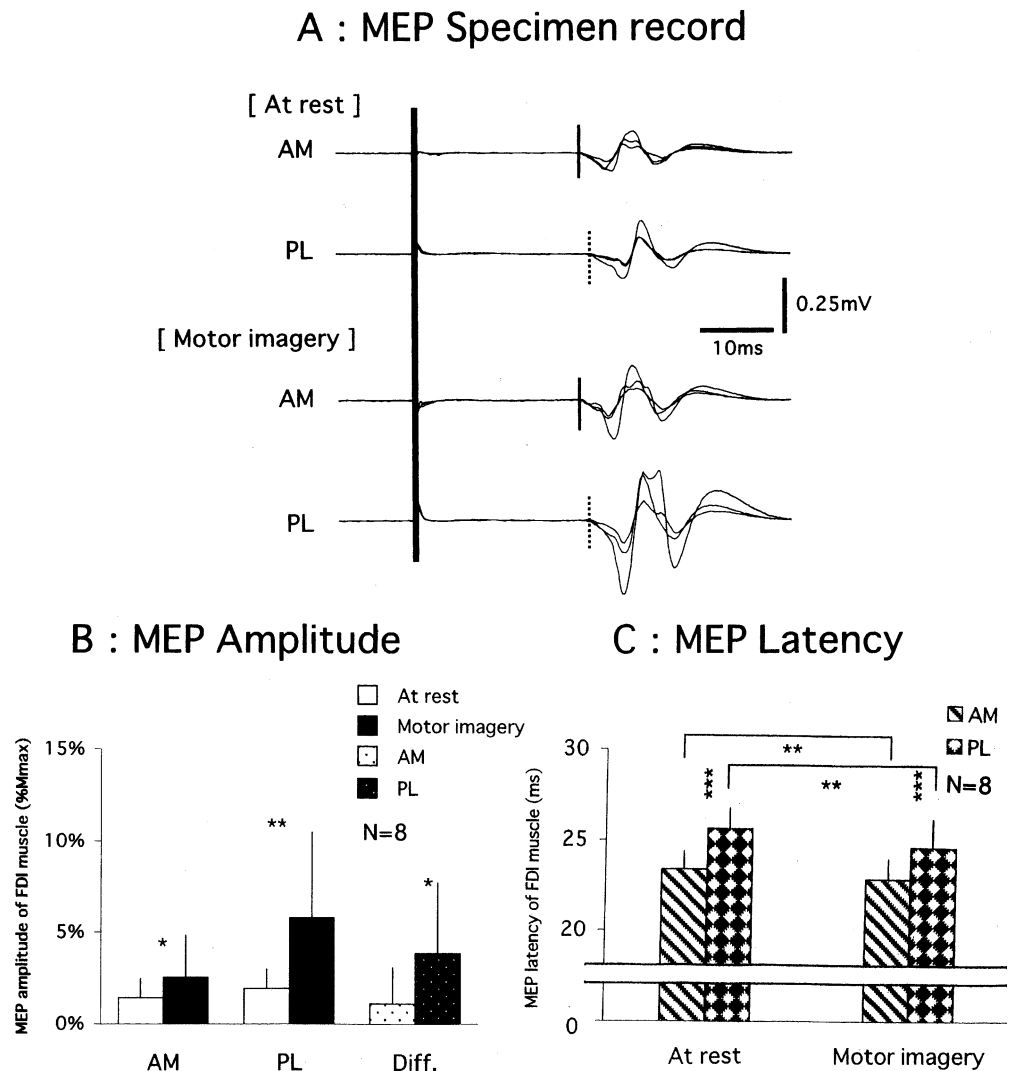
(without VTC) and conditioned (with VTC) trials should be randomly intermixed in the same session. In our experiments, however, such randomization could not be carried out because the masseter muscle contraction triggered the stimulation in conditional trials, and teeth clenching should not be performed in control trials. Because the amplitudes of those control responses before different sessions were not significantly different in the same subject, we used all control responses (30–40 responses) as one group of control conditions in the analysis.

Subjects were seated in a comfortable chair and the EMG activity was recorded from the right FDI muscle using Ag-AgCl surface electrodes (1.0 cm diameter) placed over the muscle belly, with the reference over the metacarpophalangeal joint. The EMG signals were amplified, using a channel with gain ( $\times 0.5$ ), filtered (bandwidth 5–2000 Hz), digitized by an analog-to-digital interface at a sampling rate of 5 kHz for further analysis and recorded on a computer. Each recorded interval lasted 500 ms, of which the first 100 ms preceded the stimulus. As a control procedure with each subject in both

experiments the right ulnar nerve with each subject was electrically stimulated at supramaximal intensity, and the amplitudes of the resulting compound motor action potentials (M response) of the FDI muscle were measured using the same electrode as used for the MEP recordings. This allowed a comparison to be made between the M response and the responses evoked by TMS. In this study therefore changes in the peak-to-peak amplitudes of the EMG responses were expressed as a percentage of the maximum M response (proportion of Mmax). Since some parts of the MEP amplitudes may largely reflect changes in the muscle fiber electrophysiological properties, it is important to compare the changes in MEP size with those of the maximum M response.

We compared the MEP amplitudes of the FDI muscle between at rest and MI or VTC at AM and PL current directions. Analysis of variance of two factors and post-hoc analysis were used to assess the significance of MI or VTC on MEP amplitudes at AM and PL. Post hoc comparison was performed using the paired two-tailed Student's *t* test. The same procedure was followed for

**Fig. 1 A** Specimen records of MEPs (superimposed three trials) at rest and during motor imagery (MI) under different current directions (AM and PL). **B** Means and standard deviations of MEP amplitudes obtained from eight subjects at each condition in AM and PL current directions, respectively. **C** Means and standard deviations of MEP latencies obtained from all subjects tested ( $n=8$ ) at each condition in AM and PL current directions. \* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$



MEP latency. The statistical significant level was set at 5%.

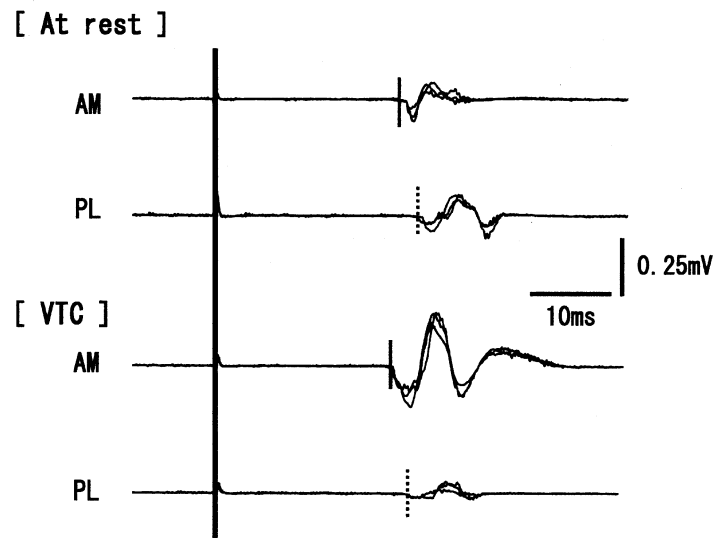
**Results**

Figure 1A shows examples of MEP recordings (superimposed three trials) during MI in a single subject. These MEP records were induced by an optimal TMS intensity (1.2xth) in AM- and PL-directed currents without (at rest) and with (during) MI. MEP amplitudes were enhanced with MI for both directed currents and these results were obtained from all subjects tested ( $n=8$ ) with no exceptions in spite of different individual values across the subjects. Figure 1B shows means and standard deviations of MEP

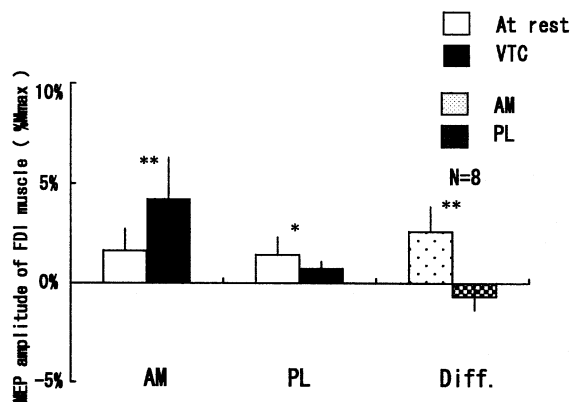
amplitudes obtained from all subjects. A significant interaction effect on MEP amplitudes (AM or PL and with or without MI) was found ( $F_{(1,28)}=6.50, P<0.05$ ). Thus post hoc comparisons of enhanced MEP amplitudes in both PL and AM were significantly larger with MI than those without MI (AM:  $t=2.49, df=7, P<0.05$ ; PL:  $t=4.59, df=7, P<0.01$ ). Furthermore, amount of enhanced MEP amplitude in PL was larger than that in AM (difference in Fig. 1B;  $t=2.38, df=7, P<0.05$ ).

With regard to MEP latencies a significant interaction of conditions was also found ( $F_{(1,28)}=12.75, P<0.01$ ). Thus post hoc comparisons of MEP latencies in AM were always shorter than those in PL (at rest:  $t=7.75, df=7, P<0.001$ ; MI:  $t=6.33, df=7, P<0.001$ ), and MEP latencies in both current directions during MI were also shorter than

**A:MEP Specimen record**



**B : MEP Amplitude**



**C : MEP Latency**

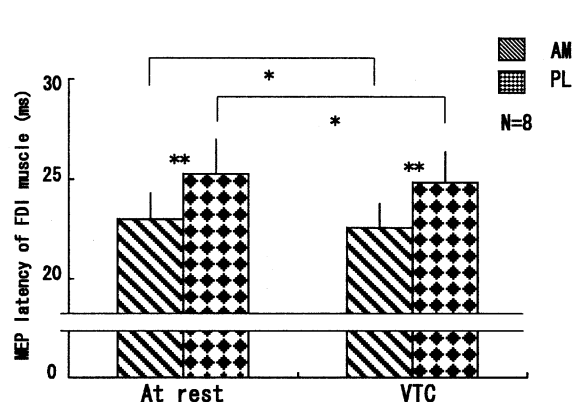


Fig. 2 A Specimen records of MEPs (superimposed three trials) during voluntary teeth clenching (VTC) under different current directions (AM and PL). B Means and standard deviations of MEP amplitudes obtained from all subjects tested ( $n=8$ ) at each condition

in AM and PL current directions, respectively. C Means and standard deviations of MEP latencies obtained from all subjects tested ( $n=8$ ) at each condition in AM and PL current directions. \* $P<0.05$ , \*\* $P<0.01$

those at rest (AM:  $t=3.91$ ,  $df=7$ ,  $P<0.01$ ; PL:  $t=3.31$ ,  $df=7$ ,  $P<0.01$ ).

Figure 2A shows examples of MEP recordings (superimposed three trials) during VTC in a single subject and the same representations as Fig. 1A. MEP amplitudes in AM were enhanced during VTC, but these in PL were slightly depressed. These results were obtained from all subjects tested ( $n=8$ ) with no exceptions in spite of different individual values across the subjects. Figure 2B shows means and standard deviations of MEP amplitudes obtained from all subjects tested ( $n=8$ ) and the same representations as Fig. 1B. A significant interaction effect on MEP amplitudes (current directions and with or without VTC) was found ( $F_{(1,28)}=11.70$ ,  $P<0.01$ ). Thus, post hoc comparisons of enhanced MEP amplitudes with VTC were significantly larger in AM than that at rest ( $t=3.49$ ,  $df=7$ ,  $P<0.01$ ), but surprisingly MEP amplitude with VTC was smaller in PL than that at rest ( $t=2.36$ ,  $df=7$ ,  $P<0.05$ ). Thus the amount of different MEP amplitudes between at rest and VTC in PL was significantly smaller than that in AM (difference in Fig. 2B;  $t=3.38$ ,  $df=7$ ,  $P<0.01$ ).

With regard to MEP latencies a significant interaction of conditions was statistically significant ( $F_{(1,28)}=6.61$ ,  $P<0.05$ ). Thus, post hoc comparisons of MEP latencies in AM were shorter than those in PL (at rest:  $t=4.75$ ,  $df=7$ ,  $P<0.01$ ; VTC:  $t=4.33$ ,  $df=7$ ,  $P<0.01$ ), and in both current directions MEP latencies during VTC were shorter than those at rest (AM:  $t=3.91$ ,  $df=7$ ,  $P<0.05$ ; PL:  $t=3.31$ ,  $df=7$ ,  $P<0.05$ ).

## Discussion

Low-intensity TMS excites corticospinal neurons indirectly via interneurons that activate a series of indirect or I-waves in a descending volley, and higher intensities of stimulation evoke not only I-waves but also a D-wave that arises from direct activation of the corticospinal tract (Day et al. 1989; Di Lazzaro et al. 1998b; Rothwell et al. 1991). At TMS intensities near the resting motor threshold therefore the temporal summation of I-waves at motoneuronal cell bodies must be an important determinant of MEP level, i.e., MEP amplitude is highly dependent on the level of excitability of interneurons in the motor cortex (Mills 1991; Rothwell et al. 1991). Additionally, the I-waves are believed to arise by transsynaptic activation of corticospinal neurons following TMS activation of intracortical interneurons or corticocortical association fibers (Sakai et al. 1997). Up to four waves (I1–I4) can be observed, each separated by about 1.5 ms. There is evidence that separate neural I-wave elements are produced in descending corticospinal volleys by TMS, as they are differentially sensitive to the direction of current flow in the coil (Day et al. 1989; Di Lazzaro et al. 2001; Hanajima et al. 1998; Sakai et al. 1997).

The difference in MEP latencies between AM and PL current directions in the present study is likely explained by different current directions activating cortical elements

at a variety of different sites as described above. That is, different neural subpopulations of corticospinal neurons with different spinal targets could be recruited by the two forms of stimulation (Di Lazzaro et al. 1998a; AP and PA in their terms). These recruited neurons had different conduction velocities and induced different EPSPs in motor cortical pyramidal cells, and consequently in motoneurons these might contribute to the latency differences between them. Thus in enhanced MEP amplitudes by MI, early and late I-wave components could separately activate different populations of cortical neurons in M1. On the other hand, in changes of MEP amplitudes by VTC, early I-wave components produced by AM were enhanced whereas late I-wave components produced by PL were not affected or reduced. This indicates that I-waves recorded at the same latency (such as late I-waves) were not completely the same between those produced by AM and PL directed currents. Because of these combinations of responsible volleys in relaxed muscles, effects of VTC may reflect summation of effects on different later I waves in this conditions. Judging from the deduction of MEP amplitude with shortened its latencies elicited by PL, we consider that this additional complexity masks the inhibitory effects on I3 waves so that later I-wave (I4) components are temporally unmasked for MEP amplitudes in the relaxed muscle. From these all arguments we conclude that MI affected M1 circuits activated by AM and PL directed currents in spite of different amount of values between them, and that VTC affected M1 circuits activated by AM and PL directed currents differentially: it facilitates the one and inhibits the others.

It has been established on the basis of histological and neurophysiological studies that the M1 of primates receives both corticocortical and thalamocortical afferent inputs as described above (Kaneko et al. 1994). In the present study we assumed that MI activate M1 by input drive via the thalamocortical pathway because it is agreed that MI is the same as motor preparation, and its neural pathways are the same as in real movement (Porro et al. 1996). On the other hand, VTC also activated M1 but inputs to M1 are processed in a different manner, i.e., afferent inputs coming from the muscle spindles in the remote muscle via somatosensory cortex. Interestingly, in the present results these afferent inputs via different neural pathways have different effects on early (I1) and late (I3) M1 neural circuits. That is, inputs of MI have facilitatory effect on both M1 neural circuits, and those of VTC have separate effects, i.e., facilitatory on early (I1) M1 neural circuits as the same as MI and inhibitory on late (I3) M1 neural circuits.

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