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Hemispheric asymmetry of ipsilateral motor cortex activation during unimanual motor tasks: further evidence for motor dominance

Ulf Ziemann[a,*], Mark Hallett[b]

[a]*Clinic of Neurology, J.W. Goethe-University, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany*
[b]*Human Motor Control Section, NINDS, NIH, Bethesda, MD 20892, USA*

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Abstract

Objectives: To test to which extent the increase in ipsilateral motor cortex excitability during unimanual motor tasks shows hemispheric asymmetry.

Methods: Six right-handed healthy subjects performed one of several motor tasks of different complexity (including rest) with one hand (task hand) while the other hand (non-task hand) was relaxed. Focal transcranial magnetic stimulation was applied to the motor cortex ipsilateral to the task hand and the amplitude of the motor evoked potential (MEP) in the non-task hand was measured. In one session, the task hand was the right hand, in the other session it was the left hand. The effects of motor task and side of the task hand were analyzed. Spinal motoneuron excitability was assessed using F-wave measurements.

Results: Motor tasks, in particular complex finger sequences, resulted in an increase in MEP amplitude in the non-task hand. This increase was significantly less when the right hand rather than the left hand was the task hand. This difference was seen only in muscles homologous to primary task muscles. The asymmetry could not be explained by changes in F-wave amplitudes.

Conclusions: Hemispheric asymmetry of ipsilateral motor cortex activation either supports the idea that, in right handers, the left motor cortex is more active in ipsilateral hand movements, or alternatively, that the left motor cortex exerts more effective inhibitory control over the right motor cortex than vice versa. We suggest that hemispheric asymmetry of ipsilateral motor cortex activation is one property of motor dominance of the left motor cortex.

Keywords: Ipsilateral motor cortex; Inter-hemispheric inhibition; Motor dominance; Transcranial magnetic stimulation; Motor evoked potentials

1. Introduction

Unilateral hand motor tasks may lead to activation of the ipsilateral motor cortex in the absence of overt electromyographic activity in the voluntarily relaxed homologous muscle of the contralateral hand. Specifically, transcranial electrical stimulation (TES) or transcranial magnetic stimulation (TMS) may reveal facilitation of motor evoked potentials (MEPs) in a relaxed contralateral hand muscle during contraction of the ipsilateral homologous muscle (Hess et al., 1986; Muellbacher et al., 2000; Rossini et al., 1987; Stedman et al., 1998; Tinazzi and Zanette, 1998; Zwarts, 1992). While part of this facilitation may occur at the spinal level, a contribution from the ipsilateral motor cortex was demonstrated by paired-pulse TMS experiments (Muellbacher et al., 2000) and by the absence of increases in MEP amplitude, if transcranial electrical stimulation of the motor cortex or brain stem stimulation were used instead of TMS to probe spinal excitability (Stedman et al., 1998; Tinazzi and Zanette, 1998). Functional magnetic resonance imaging (fMRI) studies also showed that unilateral finger movements often resulted in activation of the ipsilateral motor cortex (Kim et al., 1993; Rao et al., 1993). The nature of these activations is unclear. It may reflect subthreshold mirror activity which spreads from the primarily active motor cortex contralateral to the task hand into the ipsilateral motor cortex. Alternatively, it may result from activation of ipsilaterally or bilaterally distributed motor pathways whose existence in man has been demonstrated recently using TMS (Wassermann et al., 1994; Ziemann et al., 1999).

One important question has not been addressed yet. Does this activation of the motor cortex ipsilateral to the task hand occur symmetrically for both hands, or is there significant hemispheric asymmetry? One fMRI study showed that, in right handers, ipsilateral motor cortex activation appeared predominantly in the left motor cortex (Kim et al., 1993). Another study demonstrated that inter-hemispheric inhibi-

* Corresponding author. Tel.: +49-69-6301-5739; fax: +49-69-6301-6842.
E-mail address: u.ziemann@em.uni-frankfurt.de (U. Ziemann).

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tion using paired conditioning test TMS of both motor cortexes (Ferbert et al., 1992) in right handers was more prominent from left to right motor cortex than vice versa (Netz et al., 1995). Finally, unimanual simple reaction time tasks lead to an increase of MEP size in the response hand, starting some 80–100 ms before response onset, paralleled by a decrease in MEP size in the non-response hand. In right handers, this inhibition was more prominent when the dominant hand was the response hand (Leocani et al., 2000). All these data point towards the left motor cortex being more prominently activated or less inhibited during motor tasks of the ipsilateral left hand.

In this TMS study, we further explored this issue by specifically addressing the following questions: (1) can the more prominent activation of left compared to right motor cortex during motor tasks of the ipsilateral hand be confirmed with MEP measurements in the voluntarily relaxed contralateral non-task muscle?; (2) if so, is this hemispheric asymmetry dependent on task complexity?; (3) is the hemispheric asymmetry restricted to a primary task muscle, or does it also occur in a muscle not directly involved in the motor task?; (4) to which extent do changes in excitability at the level of the spinal motoneuron explain the asymmetry of changes in MEP amplitude?

2. Methods

2.1. Subjects

Six healthy volunteers (mean age 33.3 ± 5.4 years, one woman, 5 men) participated in the study after written informed consent was obtained. All were right-handers according to the Edinburgh Inventory of handedness (Oldfield, 1971). The study was approved by the NINDS Institutional Review Board.

2.2. Experimental protocol

Each subject was tested twice in separate sessions. In one session, the right hand was the task hand, in the other session it was the left hand. The order (left vs. right) was pseudo-randomized and balanced across subjects. Five different motor tasks were compared. The task hand was either fully relaxed (‘Rest’), or performed a moderate tonic isometric contraction (approximately 5% of maximum voluntary contraction) with thumb-to-middle finger opposition (‘Tonic’), or a simple thumb-to-middle finger opposition-abduction sequence (‘Simple’), or a complex sequence of 4 elements, with the thumb touching the index, middle, ring and little finger in that order (‘Cpx-4’), or a complex thumb-to-finger opposition-abduction sequence of 16 elements (‘Cpx-16’, for the full sequence, see (Sadato et al., 1996). All subjects received detailed instructions on how to perform the different motor tasks. In particular, they were asked to practice the Cpx-4 and Cpx-16 sequences until they were able to run the sequences smoothly and without errors. The sequences were performed self-paced at a rate of about two movements every second. Throughout all motor tasks, subjects were asked to voluntarily relax the non-task hand. Muscle activity was recorded with surface EMG from the opponens pollicis (OPP, primary task muscle) and the abductor digiti minimi muscle (ADM, hand muscle not primarily involved in the motor tasks) of both hands, using a 4-channel Dantec Counterpoint electromyograph (Dantec, Skovlunde, Denmark). The EMG was band-pass filtered (50 Hz–2 kHz), digitized at a rate of 5 kHz and stored for off-line analysis on an IBM-compatible 486 AT lab computer.

For transcranial magnetic stimulation (TMS), a focal figure-of-eight coil (diameter of each wing, 70 mm) and a Magstim 200 magnetic stimulator (Magstim, Spring Gardens, Whitland, Carmarthenshire, UK) were used. The coil was held tangentially to the scalp with the handle pointing backwards and 45° away from the midline. Thus, the induced current in the brain ran from posterior to anterior, approximately perpendicular to the line of the central sulcus. This is the optimal direction for trans-synaptic activation of the cortico-motoneuronal projection to hand muscles (Brasil-Neto et al., 1992; Kaneko et al., 1996). The coil was moved in small steps over the hand area of the motor cortex until maximum motor evoked potentials (MEPs) were elicited in the contralateral OPP. This optimal position was marked with a pen on the scalp to ensure constant coil placement throughout the experiment. Resting motor threshold of the contralateral OPP was determined to the nearest 1% of maximum stimulator output and defined as the minimum stimulus intensity which produced small MEPs >50 μV in at least 5 out of 10 consecutive trials (Rossini et al., 1994). Stimulus intensity was then adjusted to produce MEPs of 0.5–1 mV in peak-to-peak amplitude in the contralateral OPP when both hands were at rest.

In addition to the MEP measurements, spinal motoneuron excitability of the non-task hand was tested by F-wave measurements, using supramaximal electrical stimulation of the median nerve at the wrist.

The EMG levels produced by the OPP and ADM of the task hand were quantified (in mV) in the rectified single trials during a 20 ms epoch directly before the stimulus. EMG levels were averaged according to task and side of task hand.

During each experimental session, 15 blocks were run, each consisting of 20 trials. The 15 blocks were assigned to 3 repetitions of each of the 5 motor tasks (see above). The order of task was pseudo-randomized and balanced across sessions and subjects. In each block, in 10 trials TMS was applied to the motor cortex ipsilateral to the task hand, and F-waves were elicited in the other 10 trials. The order of TMS and F-wave trials was pseudo-randomized. During the tasks ‘Rest’ and ‘Tonic’, stimulation occurred at a variable inter-trial interval of 4–6 s. During the sequence tasks (‘Simple’, ‘Cpx-4’ and ‘Cpx-16’), stimulation was triggered by a force sensing resistor (Interlink Electronics, Santa

Barbara, CA), which was firmly attached to the tip of the middle finger of the task hand. Opposition of the thumb against the middle finger resulted in touching the force sensing resistor and triggered the stimulus, provided that an internal delay of at least 5 s had passed since the last trial.

2.3. Statistical analysis

For each subject, MEP and F-wave amplitudes of the non-task hand were analyzed on a single trial basis. Any trial was discarded from analysis if the EMG revealed that the non-task hand was not fully relaxed. MEP and F-wave amplitudes were then averaged according to task. For each subject, changes in amplitudes during the active tasks were then expressed as ratios of active task over 'Rest', with values >1 indicating task-induced facilitation. For MEPs, the main effects of task ('Tonic', 'Simple', 'Cpx-4', 'Cpx-16'), Muscle (OPP, ADM) and task hand (left, right) were then analyzed in a 3-way ANOVA model for repeated measures. F-Waves were analyzed similarly in a two-way ANOVA with task and task hand as the main effects. Muscle was not a factor because only the OPP was tested. Conditional on a significant F-value, post-hoc *t* tests were applied for paired comparisons. Significance was assumed if $P < 0.05$.

3. Results

3.1. Motor threshold, stimulus intensity, EMG level of task hand

Resting motor threshold and applied stimulus intensities were not different between the left and right non-task hand muscles (motor threshold for left vs. right OPP: 44.7 ± 6.7 vs. $47.0 \pm 8.4\%$; motor threshold for left vs. right ADM: 45.0 ± 6.3 vs. $47.3 \pm 8.8\%$; stimulus intensity left vs. right non-task hand: 63.8 ± 13.5 vs. $64.3 \pm 12.3\%$). In addition, there was no left versus right difference between the EMG levels produced by the task hand (Fig. 1). Therefore, left versus right differences in cortico-motoneuronal excitability, physical stimulus parameters or EMG level produced during the different motor tasks cannot account for the following effects.

3.2. MEP amplitudes

Motor task had a significant effect on MEP amplitudes ($F = 6.82$, d.f. = 3; $P = 0.004$). While 'Tonic' and 'Simple' resulted in only small changes in MEP amplitude in the non-task hand, the complex sequences ('Cpx-4' and 'Cpx-16') led to a clear increase (Fig. 2A).

The main effects of muscle and task hand were not significant, but there was a significant interaction between these two effects ($F = 17.05$, d.f. = 1, $P = 0.009$). This interaction was explained by a stronger task-induced MEP facilitation in the OPP if the left hand was the task hand, while a trend towards the opposite was true for the ADM (Fig. 2A). Post-hoc paired *t* tests showed that this left-right difference was statistically significant for the OPP ($P = 0.008$), while the difference did not reach statistical significance in the ADM ($P = 0.13$). It should be noted that the 'Tonic' and 'Simple' tasks resulted even in slight MEP inhibition in the OPP of the non-task hand, if the task was performed with the dominant right hand (Fig. 2A).

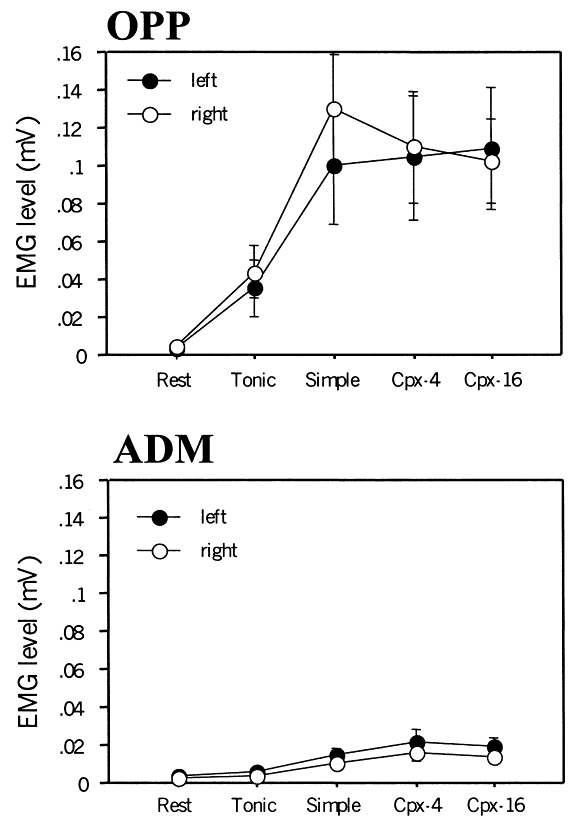

Fig. 1. Mean EMG level (±SD) in the task hand of 6 subjects as a function of motor task and task hand (open circles, right hand; closed circles, left hand) for two different muscles (upper, opponens pollicis muscle (OPP), primary task muscle; lower, abductor digiti minimi muscle (ADM), hand muscle not directly involved in the task). Cpx-4 and Cpx-16, complex thumb-to-finger opposition sequences, consisting of 4 and 16 elements (for further details, see text).

3.3. F-Waves

The significant left-right difference of task-induced changes in MEP amplitude in the OPP could not be explained by changes in spinal excitability as measured by F-waves (Fig. 2B). The effects of task, task hand and their interaction were not significant ($P = 0.80$, $P = 0.19$ and $P = 0.60$, respectively).

4. Discussion

The principal result of this study in right-handed healthy subjects is a hemispheric asymmetry of ipsilateral motor

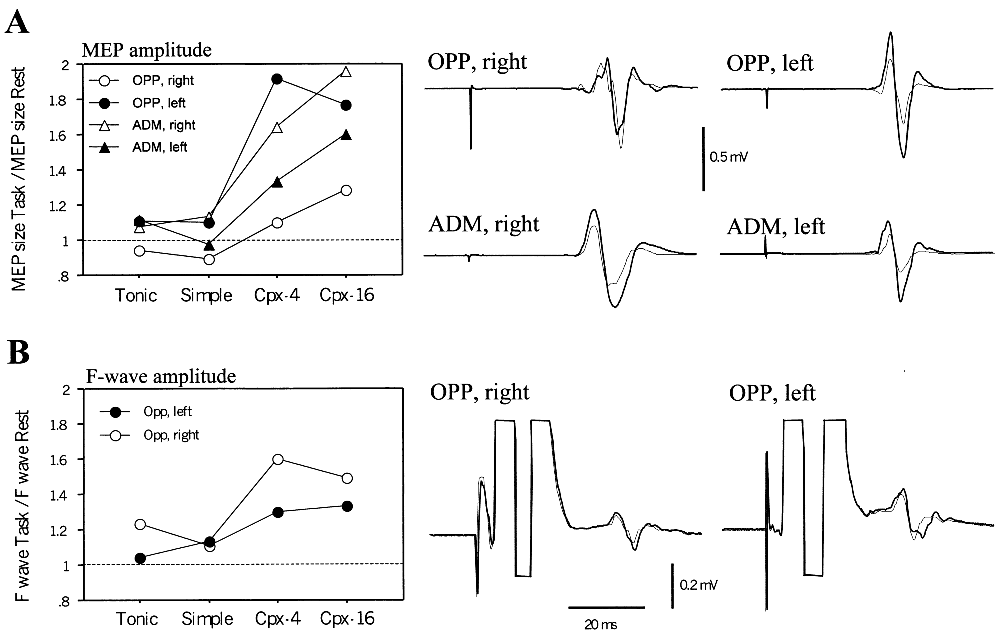

Fig. 2. Changes in MEP amplitude (A) and F-wave amplitude (B) of the voluntarily relaxed non-task hand induced by 4 different motor tasks performed by the task hand. Left panels show means of all 6 subjects. Symbols refer to the side of the task hand (open symbols, right hand; closed symbols, left hand) and the muscle (circles, opponens pollicis (OPP); triangles, abductor digiti minimi (ADM)). Task-induced changes in MEP and F-wave amplitude are compared to amplitudes measured when the task hand was at rest, and are given as amplitude ratios of 'Task'/'Rest'. Right panels demonstrate MEP and F-wave recordings from one representative subjects while the task hand was either at rest (thin traces) or while performing the complex thumb-to-finger opposition-abduction sequence containing 4 elements (Cpx-4, thick traces). Each trace is the average of 10 single trials. Note that the MEPs in the OPP of the non-task hand showed almost no change if the task was performed with the dominant right hand (A, OPP right), but were clearly facilitated, if the same task was done with the left hand (A, OPP, left). The ADM exhibited a similar facilitation, no matter which hand was the task hand (A, ADM right, ADM left). Finally, the F-waves measured in the OPP showed slight facilitation, which again showed no effect by task hand (B, OPP right, OPP left). The large truncated potential prior to the F-waves is the maximum direct muscle responses (M wave).

cortex activation during unimanual motor tasks: MEP amplitudes in the voluntarily relaxed contralateral non-task hand are significantly less facilitated if the task is performed with the dominant right hand rather than with the non-dominant left hand. This asymmetry was observed only in a primary task muscle (OPP), but not in another hand muscle not directly involved in the motor task (ADM) and could not be explained by changes in excitability at the level of the spinal motoneuron (F-wave measurements).

4.1. Site of action

Previous studies have demonstrated already that at least part of the MEP facilitation in muscles of the contralateral hand during unilateral activation of homologous ipsilateral hand muscles occurs at the level of the motor cortex. The facilitation was not seen, if anodal TES instead of TMS was used (Tinazzi and Zanette, 1998). TES can activate the corticomotoneuronal system directly compared to the largely trans-synaptic activation by TMS (Day et al., 1989; Di Lazzaro et al., 1998). Hence, TES bypasses to some extent changes in excitability at the level of the motor cortex. MEP facilitation was also not observed, if the descending cortico-spinal tract was stimulated directly at the level of the cervical cord, using high-voltage transcutaneous electrical stimulation (Stedman et al., 1998). Finally, exploration of motor cortex excitability by paired-pulse TMS (Kujirai et al., 1993; Ziemann et al., 1996) showed a decrease of intracortical inhibition in the motor cortex ipsilateral to the task hand (Muellbacher et al., 2000). This technique of paired-pulse TMS measures the excitability of inhibitory and excitatory cortico-cortical circuits which in turn control the excitability of the cortico-motoneurons in the motor cortex (Kujirai et al., 1993; Ziemann, 1999; Ziemann et al., 1996). Therefore, a task-related decrease in intracortical inhibition points to a reduction in the activity of inhibitory mechanisms directly at the level of the motor cortex.

However, F-wave studies have provided evidence that, in addition to an increase in cortical excitability, MEP facilitation may be accompanied by an increase in excitability of the spinal motoneuron (Muellbacher et al., 2000; Sica et al., 1976). In agreement with those studies, we showed that F-wave amplitudes in the voluntarily relaxed non-task OPP increased during motor tasks performed by the task hand. This effect was very small with the 'Tonic' and 'Simple' tasks, but more conspicuous with the complex thumb-to-finger opposition-abduction sequences (Fig. 2B). The crucial point is that the hemispheric asymmetry of MEP facilitation (significantly stronger facilitation if the left hand was the task hand) was not reflected by the F-wave measurements (no significant difference related to task hand). We conclude, therefore, that the observed asymmetry of MEP facilitation takes place at a supra-spinal site, most likely in the motor cortex ipsilateral to the task hand.

4.2. Concepts of motor dominance

Two fundamentally different, although not mutually exclusive models have been proposed to explain functional differences of the cerebral hemispheres of man. One model assumes that both motor cortexes have large capabilities controlling motor function of the contralateral hand, but asymmetrical motor performance is a consequence of intrinsic hemispheric specialization. Such asymmetries between the two motor cortexes were reported by a number of studies. In vivo magnetic resonance imaging morphometric studies revealed that the intrasulcal length of the precentral gyrus in right-handed normal subjects showed a pronounced left-larger-than-right asymmetry (Amunts et al., 1997; Foundas et al., 1998), indicating a larger size of the dominant left motor cortex. Movement-related neuromagnetic field recording demonstrated a greater segregation of the neuronal dipole generators subserving different finger and hand movements in the dominant motor cortex (Volkmann et al., 1998). The degree of this expansion of motor cortex in the dominant hemisphere was related to the asymmetry of hand performance in a standardized handedness test and may provide extra space for encoding of a greater motor skill repertoire of the preferred hand (Volkmann et al., 1998). TMS mapping studies provided evidence for a slightly larger representation of hand muscles in the dominant motor cortex of healthy subjects at rest (Byrnes et al., 1999; Triggs et al., 1999; Wassermann et al., 1992), while such a hemispheric difference was not seen when TMS was applied during slight tonic contraction of the target hand muscle (Wilson et al., 1993). This evidence for a larger representation of the hand in the dominant motor cortex was supported by one functional magnetic resonance study which showed a greater volume of activation in contralateral motor cortex during movement of the dominant compared to the non-dominant hand (Dassonville et al., 1997). The degree of this lateralization was related to the degree of handedness.

When tested with a non-focal concentric stimulating coil, motor threshold of a hand muscle was slightly lower for the dominant hand (Cantello et al., 1991; Macdonell et al., 1991; Triggs et al., 1994) and the degree of asymmetry correlated with inter-hand differences in finger tapping speed and performance in a peg-board dexterity test (Triggs et al., 1997). This may indicate either greater excitability of the dominant motor cortex, or larger motor representation, or both. However, the hemispheric difference in motor threshold disappeared when tested with a focal stimulating coil (present experiments; Cicinelli et al., 1997). This suggests that the excitability of the 'core' of the motor cortex representation as tested with focal TMS at threshold intensity is not different between hemispheres. Finally, measurements of the cortical silent period showed a shorter duration in a muscle of the dominant hand (Priori et al., 1999). The cortical silent period is very likely mediated by long-lasting GABA-B receptor dependent cortical inhibitory mechanisms (Werhahn et al., 1999). The reported hemispheric asymmetry may therefore indicate less cortical inhibition, and hence greater excitability in the dominant motor cortex.

In addition to this motor cortex dominance for the contralateral hand, this model of hemispheric specialization may include a stronger involvement of the dominant motor cortex in ipsilateral hand movements. Our data are fully compatible with this view. The stronger increase of MEPs in the dominant non-task hand (while the non-dominant hand performed the task) may be a consequence of a stronger increase in excitability of the dominant motor cortex during ipsilateral hand movement, which 'spills over' to the representation of the non-task hand in the same motor cortex. The idea of a more prominent involvement of the dominant motor cortex in ipsilateral hand movement is supported by the effects of repetitive TMS (rTMS) on the performance of ipsilateral finger sequences. In right-handed subjects, left motor cortex rTMS resulted in significantly more errors than right motor cortex rTMS (Chen et al., 1997). Furthermore, behavioral studies revealed more ipsilateral deficits in stroke patients with left hemispheric damage than those with right hemispheric damage (Haaland and Harrington, 1994; Haaland et al., 1987; Kimura, 1977; Wyke, 1971).

The other model of cerebral dominance proposes that both motor cortexes have identical motor capabilities in controlling the contralateral hands, but hemispheric differences occur due to asymmetric inhibitory interaction between the two motor cortexes. Paired TMS studies provided evidence for clear inter-hemispheric facilitatory (Ugawa et al., 1993) and inhibitory effects (Ferbert et al., 1992). At least some of these inter-hemispheric effects are mediated via the corpus callosum (Di Lazzaro et al., 1999). The trans-callosal inhibition seems to play a crucial role in suppressing mirror activation of the ipsilateral motor cortex during intended unilateral hand motor tasks (Nass, 1985). This idea is supported by the disappearance of physiological mirror movements during adolescence which is paralleled by the maturation of the transcallosal inhibitory system (Müller et al., 1997). It was shown previously that the trans-callosal inhibition is asymmetric in right-handers with a stronger inhibition from left-to-right motor cortex than vice versa (Netz et al., 1995). The present results are in good agreement with those findings. If the mutual inter-hemispheric inhibitory control is asymmetric with stronger inhibition from left-to-right motor cortex, it can be predicted that a unimanual motor task will result in less MEP facilitation of the non-task hand if the task is performed with the dominant right hand. Further evidence for asymmetry of inter-hemispheric inhibition came from EMG recordings during simple reaction time experiments, which showed a higher probability of mirror activity in the non-response hand, if the response hand was the non-dominant hand (Leocani et al., 2000). Furthermore, simple reaction time tasks led to an increase of MEP size in the response hand, starting some 80–100 ms before response onset, paralleled by a decrease in MEP amplitude in the non-response hand. This MEP inhibition was more prominent, when the dominant right hand was the response hand (Leocani et al., 2000).

Both models of hemispheric dominance (asymmetry of ipsilateral 'interest' versus asymmetry of inter-hemispheric inhibition) apply also to brain regions outside the motor cortexes and therefore seem to constitute a general property of hemispheric specialization. One other prominent example is the dominance of right parietal cortex for attention to peri-personal space, which may be explained either by representation of both contralateral and ipsilateral peri-personal space in the right parietal cortex but representation of contralateral space only in left parietal cortex (Oliveri et al., 1999) or more prominent inter-hemispheric inhibition from right to left parietal cortex (Seyal et al., 1995).

Another important extension of previous knowledge is the finding that this asymmetry of MEP facilitation occurred only in a primary task muscle (OPP), whereas another muscle not directly involved in the motor task (ADM) did not show significant asymmetry. However, there was a non-significant trend in the ADM towards more MEP facilitation if the right hand was the task hand (cf. Fig. 2A). This was opposite to the OPP (more facilitation if the left hand was the task hand). The EMG level in the ADM of the task hand was very low and not different between right and left task hand (cf. Fig. 1). This indicates that the ADM was not a primary task muscle. Furthermore, side differences in EMG level cannot account for the trend towards a side difference in MEP facilitation. Therefore, the MEP facilitation in the ADM can be best interpreted as unspecific co-activation, which is partly 'filtered out', either by less activation in the motor dominant ipsilateral cortex, or by more activation in the non-dominant cortex via less inter-hemispheric inhibition from the dominant to the non-dominant motor cortex. Taken together, the OPP and ADM data suggest that motor dominance is specific for the task muscle and, in addition, shows a trend towards suppression of co-activated adjacent motor cortex representations not primarily involved in the task.

In conclusion, we provide evidence for hemispheric asymmetry of ipsilateral motor cortex activation during unilateral hand movement. This asymmetry may either indicate more prominent ipsilateral activation of the dominant motor cortex, or stronger inter-hemispheric inhibition of the non-dominant motor cortex, or both. While motor cortex dominance traditionally has been related to the contralateral hand, we propose here that the asymmetry of ipsilateral motor cortex activation constitutes another property of motor dominance.

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