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Increased motor cortical excitability after whole-hand electrical stimulation: A TMS study

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ABSTRACT

Objective: To examine the neuromodulatory effect of whole-hand mesh-glove (MG) stimulation on motor cortical pathways, we explored motor cortical excitability before and after suprathreshold whole-hand MG stimulation using transcranial magnetic stimulation (TMS).
Methods: Twenty-eight healthy volunteers (14 controls) were studied at baseline, immediately post and 1 h post-MG stimulation for 30 min. Motor thresholds (MTs), motor evoked potentials (MEPs) recruitment curve, short intracortical inhibition (SICI) and intracortical facilitation (ICF) after paired magnetic stimuli were evaluated.
Results: After MG stimulation the MTs were significantly reduced and slope of MEP recruitment curve significantly increased; furthermore, the stimulation led to a sustained decrease of SICI and increase of ICF in the contralateral motor cortex. These effects lasted for at least 60 min and were stronger 1 h post-stimulation compared with testing immediately after stimulation. A sham group did not show any differences before and after MG stimulation.
Conclusions: We provide a first demonstration that MG whole-hand stimulation induces increases in motor cortical excitability lasting at least 1 h. Both the strength of the corticospinal projections and the inhibitory and facilitatory intracortical mechanisms are involved. Synaptic modifications such as long-term potentiation mechanisms may underlie this stimulation-induced cortical plasticity changes.
Significance: Present results prove the MG stimulation to be a promising tool in neurorehabilitation.

1. Introduction

A number of different neurorehabilitation strategies include manipulation of the somatosensory system. It has been previously reported that impaired movement of the hand and arm and altered muscle tone of the affected side after hemispherical stroke lesions can be improved by using a subthreshold mesh-glove (MG) stimulation of the afferents of the hand below the conscious sensory threshold (Dimitrijevic and Soroker, 1994; Dimitrijevic, 1994; Peurala et al., 2002). Subsensory MG stimulation generates synchronous tonic input to the brain due to depolarization of large diameter group Ia and Ib afferents and to a lesser extent group II afferents of the whole hand. MG stimulation acts as a kinesthetic input to the posterior column nuclei, the ventro-posterolateral thalamus and cortical brain structures, especially Brodmann areas 3a, 2, and 4 (Phillips et al., 1971; Wiesendanger and Miles, 1982; Mariorenzi et al., 1991; Bodegard et al., 2003).

Previous fMRI studies based upon the blood oxygen level dependent (BOLD) effect have shown an increase of BOLD response after a period of 30 min of whole-hand afferent electrical MG stimulation within the primary and secondary sensorimotor cortex (Golaszewski et al., 1999, 2004). Obviously, neuromodulatory effects of MG stimulation can change motor cortex representation bilaterally within the primary and secondary sensorimotor cortex

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and consequently have the potential to induce neuroplasticity in post-stroke neurorehabilitation. The nature of the increased BOLD response is not completely understood. It may be due to a vascular response of the precapillary microvasculature or to reduced thresholds of the sensorimotor networks, thus leading to an increased motoneuron recruitment in a consecutive volitional motor task. It has been recently demonstrated that the median nerve stimulation elicited an enduring increase in task-related perfusion and BOLD responses in the thumb representation in the absence of changes in baseline blood flow (Wu et al., 2005). It could therefore be hypothesized that the increased BOLD response may be due to an increased cortical excitability. However, the mechanism of fMRI activation changes in the affected primary motor cortex is still unclear in electrophysiological terms.

Transcranial magnetic stimulation (TMS) allows studying the excitatory and inhibitory circuits of the human motor cortex non-invasively. A large number of studies have used TMS methods to examine the effect of afferent sensory input from the hand on the excitability of human motor cortex. Using a paired-pulse protocol the main effect following digital and mixed nerve stimulation is a reduction of short interval intracortical inhibition SICI (Ridding and Rothwell, 1999; Sailer et al., 2002). Motor evoked potentials (MEPs) are affected by a preceding electrical stimulus to mixed or cutaneous nerve (Deuschl et al., 1991; Rossini et al., 1996; Ridding and Rothwell, 1999; Tokimura et al., 2000). However, studies of conditioning mixed or cutaneous nerve stimulation in the upper extremities have yielded conflicting results, showing either no effect on MEP amplitudes, MEP amplitude facilitation, MEP amplitude inhibition or both (Troni et al., 1988; Delwaide and Olivier, 1990; Mariorenzi et al., 1991; Uncini et al., 1991; Komori et al., 1992; Ohki et al., 1994; Clouston et al., 1995; Inghilleri et al., 1995; Kaneko et al., 1998; Manconi et al., 1998), depending on the parameters used (Palmer and Ashby, 1992; Maertens de Noordhout et al., 1992; Manganotti et al., 1997; Kofler et al., 1998), on disparate effects of stimuli on different motoneuron pools, on different experimental settings (e.g. single pulses versus stimulus trains, various stimulus intensities, relaxed versus contracted target muscles), and on different stimulation and recording sites. Low amplitude vibration of a muscle was found to increase the amplitude of MEPs evoked in that muscle and at the same time to decrease the effectiveness of SICI (Rosenkranz et al., 2003; Rosenkranz and Rothwell, 2003).

It has recently been demonstrated that BOLD signal intensity changes within affected primary sensorimotor cortex before and after constraint-induced movement therapy showed a close correlation with SICI and intracortical facilitation (ICF) measured with TMS via paired-pulse stimulation (Hamzei et al., 2006). The use of complementary methods may give the opportunity to interpret cortical reorganization from different perspectives. The aim of the study was to investigate the effects of whole-hand afferent electrical stimulation on the motor system, and how long possible changes would persist. We used TMS applied in single- and paired-pulse paradigms to measure basic parameters of motor cortex excitability. Results allow conclusions about the physiological basis of mesh-glove fMRI effects. In case of a specific vascular response of the precapillary microvasculature independent from neuronal effects, TMS parameters should not change after mesh-glove stimulation.

2. Materials and methods

2.1. Subjects and experimental design

The study was carried out in 28 healthy, right-handed volunteers (age 20–45 years, 12 males and 16 females) without any neurological deficits. Half of the subjects were assigned to the verum group and half to the control group. The verum group underwent MG stimulation and the control group sham stimulation. Informed consent was obtained from all subjects after the experimental nature had been fully explained and the study protocol was approved from the local Ethics Committee.

Subjects were seated in a comfortable reclining chair during TMS measurements, MG stimulation, and at rest. Both hands were placed relaxed on soft supports beside the body. The study design included a first TMS examination through which the baseline profile of intracortical activity was achieved (T0). The subjects underwent a second examination with TMS immediately after a MG stimulation for 30 min (T1) to the relaxed left hand with the subject lying relaxed in the reclining chair, and a final TMS examination after a 1 h resting period (T2).

2.2. TMS assessments

TMS was performed using two Magstim 200 magnetic stimulators (Magstim Co., Whitland, Dyfed, UK) connected to a Bistim module throughout all experiments to preserve identical stimulator output during the single- and paired-pulse TMS measurements. A figure-of-eight coil (external loop diameter 90 mm) was held over the left motor cortex at the optimum scalp position to elicit motor responses in the right first dorsal interosseus (FDI) muscle at the lowest motor threshold (MT).

The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline to induce postero-anterior current flow. Surface muscle responses were obtained via two 9 mm diameter Ag–AgCl electrodes with the active electrode applied over the motor point of the muscle and the reference on the metacarpophalangeal joint of the index finger. Muscle responses were amplified and filtered (bandwidth 8–2000 Hz) by D150 amplifiers (Digitimer, Welwyn Garden City, Herfordshire, UK), and recorded on disc (DasyLab 8.0 software package) for off-line analysis. Resting motor threshold (MT) was defined as the minimum stimulus intensity that produced an MEP at rest of 50 μV in 5 of 10 trials. We evaluated the amplitude of the MEPs produced by a single TMS pulse at increasing stimulus intensities (MEP recruitment curve). The TMS intensities were 90%, 100%, 110%, 120%, 130%, 140%, 150%, and 160% of the MT, determined for each subject. These intensities remained the same in T0-, T1- and T2-measurements. The MEP recruitment curve was determined at rest. Eight pulses were delivered for each stimulus intensity, with stimulus intensities administered randomly. To avoid collecting startle and reflex responses, we excluded the first MEP for each trial from the analysis. SICI and ICF were studied using the technique of paired magnetic stimulation (Kujirai et al., 1993). The conditioning and the test stimuli were set at 80% and 120% of MT, respectively. Inhibitory interstimulus intervals (ISI) of 3 ms and facilitatory ISIs of 13 ms were used. Eight stimuli were delivered at each ISI. During TMS assessments subjects were given audiovisual feedback at high gain to assist in maintaining complete relaxation. The presentation of conditioned and unconditioned trials was randomized. In case of changed MT after T0 for the paired-pulse measurements the stimulus intensity was adjusted to the corresponding MT in T1 and T2. The actual amplitudes after correction relate to those before mesh-glove stimulation in the same subjects.

2.3. F-wave measurements

To test the spinal networks contribution effect to global neuromodulatory changes, F-wave assessments were employed in the same experimental session. Supramaximal electric stimulation on the ulnar nerve at the wrist was delivered transcutaneously using

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surface electrodes. Stimulus intensity was adjusted to produce a maximal M-wave in the adjacent muscle. F-waves were recorded in relaxed FDI. The peak-to-peak amplitude and persistence of F-waves (average, 80 trials) were determined before and after MG stimulation.

2.4. Mesh-glove stimulation

The mesh-glove (Prizm Medical Inc., Oakwood, USA) was connected to a two-channel stimulator (TENS Stem, Schwa-Medico, Ehringshausen, Germany) with a common anode for output to the MG and a pair of separated surface electrodes as cathodes that were separately connected to a 4×3 cm karaya-padded carbon rubber electrodes placed over the tendons of the extensors and flexors on the dorsal and volar surfaces of the forearm just proximal to the wrist (Fig. 1). The MG is made of conductive, flexible wire and is easily slipped over the hand. Before fitting the hand with the MG, conductive jelly was applied over the whole hand. A train of 50 Hz stimuli with a pulse width of 300 μs was used for stimulation. The conscious sensory threshold was defined by the subject as a feeling of tingling both on palmar and dorsal site of the hand. The amplitude for the threshold stimulus ranged between 2.0 and 3.0 mA among the subjects. The suprathreshold stimulation level was defined individually by increasing the stimulus intensity to 120% of the conscious sensory threshold. The sham stimulation was carried out identically but the stimulator strength was set to 0 mA. Subjects were informed that they will receive current stimulation below their consciousness of sensation.

2.5. Data analysis and statistics

MEP amplitudes were measured off-line. Separate one-way ANOVAs (analysis of variance) were used to assess the effect of MG stimulation on MT (expressed as percentage of maximum stimulator output). For the MEP recruitment curve the amplitudes were calculated as percentage of the maximum mean MEP at baseline (T0) – which was usually at 160% of MT intensity – for each subject individually. The MEP amplitudes were then analyzed using a repeated measures ANOVA with the within-subject factors "stimulus intensity" (eight levels: starting from 90% to 160%) and "time" (three levels: T0, T1 and T2) and the between-subject factor "group" (two levels: MG stimulation and sham stimulation). If a significant interaction with group in the three-factorial ANOVA was found, follow-up two-factorial ANOVAs for each group separately with within-subject factors "stimulus intensity" and "time" were conducted.

For the conditioned MEP responses (SICI and ICF) the amplitudes were calculated as percentage of the single-pulse MEP for each subject individually. Then a repeated measures ANOVA was used to assess the effect of MG stimulation on conditioned MEP amplitudes with the within-subject factors "ISI" (two levels: inhibitory/3 ms and facilitatory/13 ms) and "time" (three levels: T0, T1 and T2) and the between-subject factor "group" (two levels: MG stimulation and sham stimulation). If a significant interaction with "group" in the three-factorial ANOVA was found, follow-up two-factorial ANOVAs for each group separately with within-subject factors "stimulus intensity", "ISI" and "time" were conducted.

A two-factorial ANOVA with the within-subject factor time (three levels: T0, T1 and T2) and the between-subject factor "group" (two levels: MG stimulation and sham stimulation) was performed to test changes in F-wave amplitude and persistence.

In all statistical tests a significance level of .05 was used with Greenhouse–Geisser correction when appropriate. Further, where of interest, Bonferroni corrected post-hoc comparisons were conducted.

3. Results

3.1. Motor threshold

MT measured at baseline varied between 37% and 45% of maximum stimulator output among subjects. As shown in Fig. 2 MG stimulation had a significant effect on MT as shown by the reliable ANOVA interaction effect between "group" and "time" ($F_{(2,52)} = 5.99$, $p < .01$). The ANOVA also revealed a main effect of "time" ($F_{(2,52)} = 5.99$, $p < .01$) but this effect is obviously related to the strong effect of MG stimulation since the control group did not show any differences in MT. No main effect of "group" was found. Post-hoc comparisons showed reliable MT decreases immediately after and 1 h after stimulation ($ps < .001$, Bonferroni corrected).

3.2. MEP recruitment curves

Fig. 3 presents the effect of MG stimulation on MEP recruitment curves measured at T0, T1 and T2. The three-factorial ANOVA revealed a reliable interaction of "group" and "time" ($F_{(2,52)} = 3.30$, $p < .05$) indicating a significant effect of MG stimulation. Besides this interaction, significant main effects of "stimulus intensity" ($F_{(7,182)} = 333.17$, $p < .001$) and of "group" ($F_{(1,26)} = 8.67$, $p < .01$)

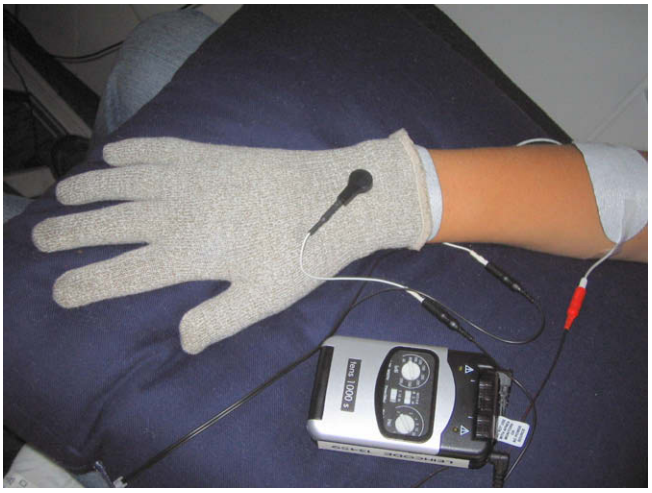

Fig. 1. *Mesh-glove:* a two-channel stimulator delivers a train of 50 Hz stimuli (pulse width 300 μs) with the amplitude above the threshold for sensation (ranging from 2.4 to 3.6 mA). The mesh-glove acts as a common anode, the cathodes are placed over the tendons of the forearm flexors and extensors.

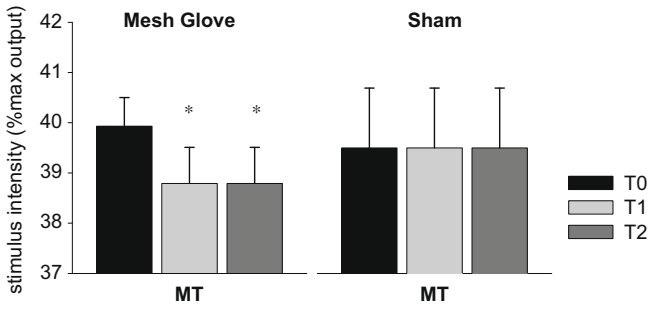

Fig. 2. (A) Mean (SE) of resting motor threshold (MT) expressed as percentage of maximum stimulator output for the FDI muscle before (T0), immediately after (T1), and 1 h after (T2) MG stimulation (right panel) and sham stimulation (left panel). (B) Mean (SE) of MEP amplitude at MT before (T0), immediately after (T1), and 1 h after (T2) MG stimulation (right panel) and sham stimulation (left panel). Asterisk (*) indicates significant difference ($p < .05$) from T0.

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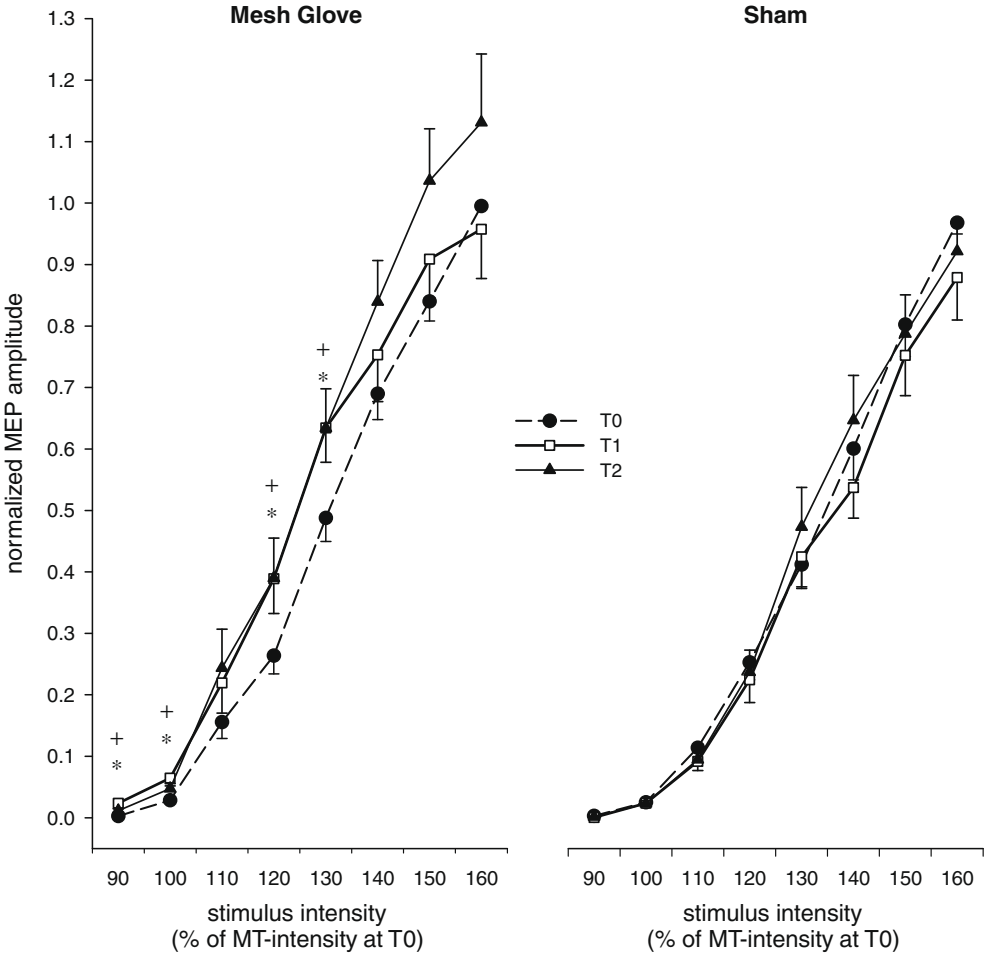

Fig. 3. MEP recruitment curve before (T0), immediately after (T1), and 1 h after (T2) MG stimulation (right panel) and sham stimulation (left panel). MEP is normalized to the maximum mean MEP in T0 for each subject individually and then pooled for all subjects in each group separately. For each stimulus intensity mean (SE) of the normalized MEP amplitude is plotted. Asterisk (∗) indicates significant difference ($p < .05$) of T1 from T0. Plus (+) indicates significant difference ($p < .05$) of T2 from T0.

were revealed. No other effects were found reliable. The follow-up ANOVAs for each group separately revealed for both groups a main effect of "stimulus intensity" ($F_{(7,91)} = 193.10$, $p < .001$ and $F_{(7,91)} = 159.84$, $p < .001$) for control and stimulation group, respectively. However, whereas the control group did not show any effects on amplitudes after time and no interaction effects of "stimulus intensity" and "time" (Fs < 1), the group which received real MG stimulation showed the important reliable main effect of "time" ($F_{(2,26)} = 4.38$, $p < .05$) with increased amplitudes after MG stimulation. The interaction effect did not reach significance ($F_{(2,26)} < 2$). In both post-stimulation conditions (T1 and T2) the recruitment curve was increased compared to T0. Post-hoc comparisons at each intensity revealed that at lower and midrange intensities MEP increases were significant both in T1 and T2 compared to T0 (ps < .05, Bonferroni corrected). At higher stimulus intensities (140–160% of MT_{T0} intensity) these tendency was partly kept although not reaching significance level (see Fig. 3). Additionally, post-hoc group comparisons at each intensity were conducted and showed reliable differences between MG stimulation and sham stimulation at T1 and T2. To evaluate possible T0 differences between the group which received MG stimulation and the group which received sham stimulation a two-factorial ANOVA with factors "group" and "stimulus intensity" was conducted which apart from an inherent main effect of "stimulus intensity" ($F_{(7,182)} = 366.43$, $p < .001$) did not reveal any effects indicating that groups did not differ at T0.

3.3. Paired-pulse stimulation

Fig. 4 shows the effect of MG stimulation on SICI and ICF. Here apart from the inherent effect of "ISI" ($F_{(1,26)} = 98.21$, $p < .001$) the three-factorial ANOVA revealed also a main effect of "time" ($F_{(2,52)} = 3.22$, $p < .05$) and an interaction effect between "time" and "group" ($F_{(2,52)} = 5.77$, $p < .01$). No other effects were found reliable. Follow-up ANOVAs for each group separately confirmed the effect of "ISI" ($F_{(1,13)} = 92.54$, $p < .001$ and $F_{(1,13)} = 31.66$, $p < .001$) for controls and MG stimulation group, respectively, but found a reliable effect of "time" only for the group which received real MG stimulation ($F_{(2,26)} = 7.58$, $p < .01$). Other effects were not found reliable. Generally, in the group which received real MG stimulation in both post-stimulation conditions (T1 and T2) the MEP inhibition at short ISIs of 3 ms was reduced and the facilitation at longer ISIs of 13 ms was increased compared to T0. However, as post-hoc comparisons revealed, these changes in inhibition and facilitation did not reach significance level for T1 but did so for T2 ($p < .05$, Bonferroni corrected). To evaluate possible T0 differences between the group which received MG stimulation and the group which received sham stimulation a two-factorial ANOVA with factors "group" and "ISI" was conducted which apart from the main effect of "ISI" ($F_{(1,26)} = 52.83$, $p < .001$) did not reveal any effects indicating that groups did not differ at T0.

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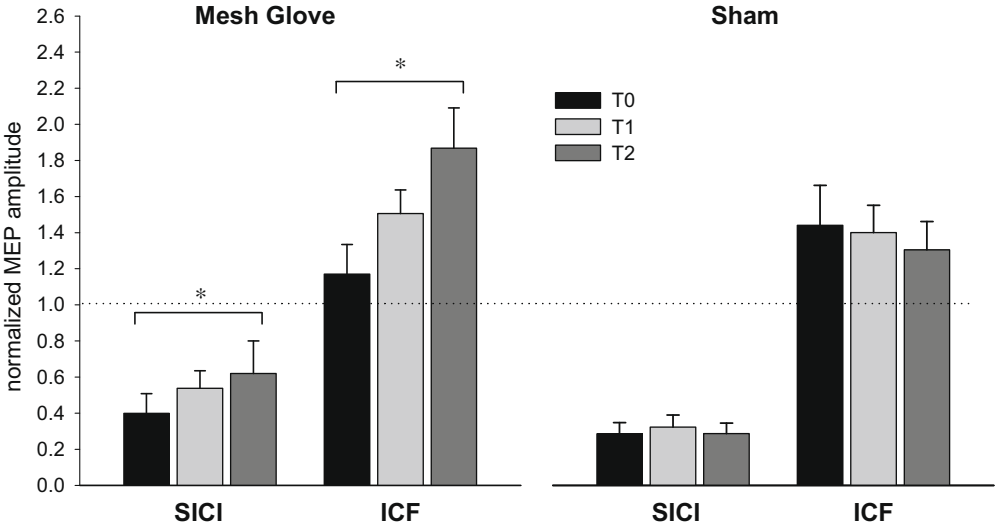

Fig. 4. Paired-pulse stimulation before (T0), immediately after (T1), and 1 h after (T2) MG stimulation (right panel) and sham stimulation (left panel). The values for intracortical inhibition (SICI) and intracortical facilitation (ICF) are normalized for each subject to their corresponding values in single-pulse stimulation for each condition and then plotted as mean (SE). Asterisk (*) indicates significant difference ($p < .05$) from T0.

3.4. F-waves

The two-factorial ANOVAs did not reveal any significant effects for F-wave persistence ("time": $F_{(2,52)} = 0.08$, $p = .84$; "group": $F_{(1,26)} = 0.45$, $p = .51$; interaction of factor "time" with factor "group": $F_{(2,52)} = 0.29$, $p = .65$) nor F-wave amplitude ("time": $F_{(2,52)} = 0.47$, $p = .59$; "group": $F_{(1,26)} = 0.12$, $p = .73$; interaction of factor "time" with factor "group": $F_{(2,52)} = 0.44$, $p = .61$).

4. Discussion

The present study demonstrates that whole-hand electrical stimulation modulates corticospinal excitability as well as intracortical inhibitory and excitatory circuits. MT is thought to reflect the neuronal membrane excitability because it is increased by drugs that block voltage-gated sodium channels (Ziemann et al., 1996b) but not by drugs influencing neuronal synaptic transmission. Compared to MT the MEP recruitment curve assess neurons that are intrinsically less excitable or spatially further from the center of activation by TMS (Hallett, 1999).

Since the paired-pulse technique gives access to the motor cortex independently of spinal or peripheral mechanisms, it allows the evaluation of the intracortical circuits. There is good evidence that the interaction between a subthreshold conditioning stimulus and a suprathreshold test stimulus at short ISIs (1–5 ms) relies on activation of γ-aminobutyric acid (GABA) – in particular $GABA_A$ – circuits in the motor cortex (Ziemann et al., 1996a,b; Hanajima et al., 1998). The circuit underlying intracortical facilitation is less well understood, and is thought to be mediated by glutamate (Liepert et al., 1997). Moreover, the down regulation of inhibitory neural circuits seems to play also a critical role in strengthening excitatory synapses (Hess and Donoghue, 1994). Our findings suggest that MG stimulation also had a direct effect on the excitability of the intracortical circuits responsible for SICI and ICF at a cortical level. Conversely, no changes in spinal motor excitability (amplitude and persistence of F-waves) were observed. The increased motor cortical excitability may represent the electrophysiological correlate of increased effectiveness of movement-related BOLD responses after electrical stimulation. The increased BOLD responses within the sensorimotor cortex appear thus to be due to interactions at cortical level. It would be interesting to determine in future studies if subthreshold whole-hand stimulation also elicits changes in motor cortex excitability similar to those elicited by suprathreshold stimulation.

One salient finding of our study is that the changes in motor cortex excitability outlast the actual somatosensory stimulation by at least 1 h. Moreover, intracortical excitability was significantly enhanced 1 h after MG stimulation while it was not significantly increased immediately after stimulation. The reasons for the late excitability enhancement remain unclear. The delayed facilitation we observed may be a functional evidence of intracortical synaptic reorganization. The neuronal basis of these long-lasting effects may involve long-term potentiation (LTP) mechanisms. Synaptic modifications such as LTP could be a crucial mechanism underlying this stimulation-induced cortical plasticity. Since its discovery in the early 1970s, LTP, as well as long-term depression (LTD) of synaptic transmission, had been suggested to be crucial factors for activity-dependent changes in the strength of synaptic connections and efficiency of synaptic signal transduction (Keller et al., 1990). Many studies demonstrated that these pathways play an important role in cortical synaptic plasticity. However, it is difficult to study the outcome of synaptic modifications on behavioural changes induced by stimuli that drive LTP or LTD-like processes in human subjects. Repeated activation of excitatory synapses in the central nervous system induces both short-term potentiation and LTP (Keller et al., 1990). Both types of synaptic potentiation affect N-methyl-D-aspartate glutamate receptors leading to the formation of new synapses or the unmasking of other excitatory amino acid receptors on motor neurons (Ghirardi et al., 1995). Remote modulations of motor cortex excitability may also be involved which could be accomplished by other cortical areas as well as subcortical structures connected with the primary motor cortex.

This increased excitability localized within the sensorimotor cortex may reflect an increase in neuronal activity as a result of a dynamic interaction of various synaptic and cellular mechanisms due to the local processing of the augmented afferent kinesthetic input to the sensorimotor cortex (Bütefisch et al., 2003). It is known from somatosensory evoked potential studies (Liepert et al., 2000), that electrical stimulation of group Ia and Ib afferents and their direct or transcallosal projections induce augmented local field potentials within the sensorimotor cortex. The elevated local field potentials persist for at least several minutes and change

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intracortical excitability of motoneurons that can be recruited to a larger extent by a consecutive motor task. The applied MG stimulation involves especially group Ia, Ib and group II afferents (Phillips et al., 1971; Veale et al., 1973; Wiesendanger and Miles, 1982; Panizza et al., 1989, 1992) and thus may increase local field potentials within the sensorimotor cortex of both cerebral hemispheres. Fibres carrying different afferent quality have different activation thresholds. With the applied stimulation parameters all the above mentioned fibres were effectively stimulated.

Sensory afferents of groups Ia, Ib, and group II have short latency projections to the contralateral sensorimotor cortex, particularly BA 3a, 1, 2, and 4 (Phillips et al., 1971; Strick and Preston, 1982a; Sanes et al., 1995). For the afferent route to the primary motor cortex M1 a projection from BA 3a has been discussed (Strick and Preston, 1982b). In several PET and fMRI studies it was confirmed that vibration to the hand palm of healthy adult humans activates the contralateral sensorimotor cortex SM1, the supplementary motor cortex SMA, and the secondary somatosensory cortex S2 bilaterally (Francis et al., 2000; Golaszewski et al., 2002). The hand is a rich source of kinesthetic input to the brain because of its high density of muscle spindles (Pons et al., 1992) there are a large number of joint receptors with corresponding large afferents, as well as Golgi tendon organs (Jami, 1992; Lafleur et al., 1992). The results of this study support the hypothesis that continuous whole-hand afferent electrical stimulation involves neurophysiological mechanisms that may be activated by externally controlled kinesthetic input and that can induce modulatory effects within the sensorimotor cortex. A strong correlation between a spatially localized BOLD response and local field potentials has been recently shown (Logothetis et al., 2001). With regard to beneficial effects of MG stimulation in stroke patients concerning improved motor performance after a daily MG training program over several weeks (Dimitrijevic and Soroker, 1994; Dimitrijevic, 1994; Peurala et al., 2002), we suppose that MG stimulation may provide an increased toporegional motoneuron recruitment by augmented neuronal excitability, activity-dependent synaptic plasticity, and subsequent intracortical facilitation and unmasking of pre-existing silent synapses (Jacobs and Donoghue, 1991; Pascual-Leone and Torres, 1993; Hess and Donoghue, 1994). Horizontal connections traversing the superficial layers of the motor cortex are capable of both increases and decreases in strength and synaptic efficacy (Hirsch and Gilbert, 1993; Kaelin-Lang et al., 2002). This enhanced motoneuron recruitment is likely induced by a persistent high-frequency input, probably inducing intracortical synaptic modification through a LTP mechanism rather than by an active motor learning task, which then should have diminished the number of recruited motoneurons and thus cortical activity; otherwise, as the effects persisted for at least 1 h we also discard posttetanic potentiation-like phenomena.

In conclusion, the increased cortical excitability leads to an extension of neuronal activity (increased BOLD signal). The time course of neurophysiological effects, as measured by TMS, suggests a prolonged clinical efficacy of MG stimulation. Further studies should focus on the issue whether more specialized stimulation protocols can prolong the modulatory effects on the sensorimotor cortex through plastic changes in synaptic efficacy and thus can subserve a long-term rehabilitation process of impaired motor functions of the hand after hemispherical stroke lesions. This finding of increased motor cortical excitability after MG stimulation can help to develop new rehabilitation strategies in combination with physical and occupational therapy.

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References

Bodegard A, Geyer S, Herath P, Grefkes C, Zilles K, Roland PE. Somatosensory areas engaged during discrimination of steady pressure, spring strength, and kinesthesia. Hum Brain Mapp 2003;20:103–15.

Bütefisch CM, Netz J, Wessling M, Seitz RJ, Hömberg V. Remote changes in cortical excitability after stroke. Brain 2003;126:470–81.

Clouston PD, Kiers L, Menkes D, Sander H, Chiappa K, Cros D. Modulation of motor activity by cutaneous input: inhibition of the magnetic motor evoked potential by digital electrical stimulation. Electroencephalogr Clin Neurophysiol 1995;97:114–25.

Delwaide PJ, Olivier E. Conditioning transcranial cortical stimulation (TCCS) by exteroceptive stimulation in parkinsonian patients. Adv Neurol 1990;53:175–81.

Deuschl G, Michels R, Berardelli A, Schenck E, Inghilleri M, Lücking CH. Effects of electric and magnetic transcranial stimulation on long latency reflexes. Exp Brain Res 1991;83:403–10.

Dimitrijevic MM. Mesh-glove. 1. A method for whole-hand electrical stimulation in upper motor neuron dysfunction. Scand J Rehabil Med 1994;26:183–6.

Dimitrijevic MM, Soroker N. Mesh-glove. 2. Modulation of residual upper limb motor control after stroke with whole-hand electric stimulation. Scand J Rehabil Med 1994;26:187–90.

Francis ST, Kelly EF, Bowtell R, Dunseath WJ, Folger SE, McGlone F. FMRI of the responses to vibratory stimulation of digit tips. Neuroimage 2000;11:188–202.

Ghirardi M, Montarolo PG, Kandel ER. A novel intermediate stage in the transition between short- and long-term facilitation in the sensory to motor neuron synapse of aplysia. Neuron 1995;14:413–20.

Golaszewski S, Kremser C, Wagner M, Felber S, Aichner F, Dimitrijevic MM. Functional magnetic resonance imaging of the human motor cortex before and after whole-hand afferent electrical stimulation. Scand J Rehabil Med 1999;31:165–73.

Golaszewski SM, Siedentopf CM, Baldauf E, Koppelstaetter F, Eisner W, Unterrainer J, et al. Functional magnetic resonance imaging of the human sensorimotor cortex using a novel vibrotactile stimulator. Neuroimage 2002;17:421–30.

Golaszewski SM, Siedentopf CM, Koppelstaetter F, Rhomberg P, Guendisch GM, Schlager A, et al. Modulatory effects on human sensorimotor cortex by whole-hand afferent electrical stimulation. Neurology 2004;62:2262–9.

Hallett M. Motor cortex plasticity. Electroencephalogr Clin Neurophysiol Suppl 1999;50:85–91.

Hamzei F, Liepert J, Dettmers C, Weiller C, Rijntjes M. Two different reorganization patterns after rehabilitative therapy: an exploratory study with fMRI and TMS. Neuroimage 2006;31:710–20.

Hanajima R, Ugawa Y, Terao Y, Sakai K, Furubayashi T, Machii K, et al. Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. J Physiol 1998;509(Pt 2):607–18.

Hess G, Donoghue JP. Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. J Neurophysiol 1994;71:2543–7.

Hirsch JA, Gilbert CD. Long-term changes in synaptic strength along specific intrinsic pathways in the cat visual cortex. J Physiol 1993;461:247–62.

Inghilleri M, Berardelli A, Cruccu G, Manfredi M, Priori A, Rothwell JC. Inhibition of hand muscle motoneurones by peripheral nerve stimulation in the relaxed human subject. Antidromic versus orthodromic input. Electroencephalogr Clin Neurophysiol 1995;97:63–8.

Jacobs KM, Donoghue JP. Reshaping the cortical motor map by unmasking latent intracortical connections. Science 1991;251:944–7.

Jami L. Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. Physiol Rev 1992;72:623–66.

Kaelin-Lang A, Luft AR, Sawaki L, Burstein AH, Sohn YH, Cohen LG. Modulation of human corticomotor excitability by somatosensory input. J Physiol 2002;540:623–33.

Kaneko K, Kawai S, Taguchi T, Fuchigami Y, Yonemura H, Fujimoto H. Cortical motor neuron excitability during cutaneous silent period. Electroencephalogr Clin Neurophysiol 1998;109:364–8.

Keller A, Pavlides C, Asanuma H. Long-term potentiation in the cat somatosensory cortex. Neuroreport 1990;1:49–52.

Kofler M, Glocker FX, Leis AA, Seifert C, Wissel J, Kronenberg MF, et al. Modulation of upper extremity motoneurone excitability following noxious finger tip stimulation in man: a study with transcranial magnetic stimulation. Neurosci Lett 1998;246:97–100.

Komori T, Watson BV, Brown WF. Influence of peripheral afferents on cortical and spinal motoneuron excitability. Muscle Nerve 1992;15:48–51.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol 1993;471:501–19.

Lafleur J, Zytnicki D, Horcholle-Bossavit G, Jami L. Depolarization of Ib afferent axons in the cat spinal cord during homonymous muscle contraction. J Physiol 1992;445:345–54.

Liepert J, Schwenkreis P, Tegenthoff M, Malin JP. The glutamate antagonist riluzole suppresses intracortical facilitation. J Neural Transm 1997;104:1207–14.

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Liepert J, Hamzei F, Weiller C. Motor cortex disinhibition of the unaffected hemisphere after acute stroke. Muscle Nerve 2000;23:1761–3.
Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature 2001;412:150–7.
Maertens de Noordhout A, Rothwell JC, Day BL, Dressler D, Nakashima K, Thompson PD, et al. Effect of digital nerve stimuli on responses to electrical or magnetic stimulation of the human brain. J Physiol 1992;447:535–48.
Manconi FM, Syed NA, Floeter MK. Mechanisms underlying spinal motor neuron excitability during the cutaneous silent period in humans. Muscle Nerve 1998;21:1256–64.
Manganotti P, Zanette G, Bonato C, Tinazzi M, Polo A, Fiaschi A. Crossed and direct effects of digital nerves stimulation on motor evoked potential: a study with magnetic brain stimulation. Electroencephalogr Clin Neurophysiol 1997;105:280–9.
Mariorenzi R, Zarola F, Caramia MD, Paradiso C, Rossini PM. Non-invasive evaluation of central motor tract excitability changes following peripheral nerve stimulation in healthy humans. Electroencephalogr Clin Neurophysiol 1991;81:90–101.
Ohki Y, Suzuki T, Ugawa Y, Uesaka Y, Sakai K, Kanazawa I. Excitation of the motor cortex associated with the E2 phase of cutaneous reflexes in man. Brain Res 1994;633:343–7.
Palmer E, Ashby P. The transcortical nature of the late reflex responses in human small hand muscle to digital nerve stimulation. Exp Brain Res 1992;91:320–6.
Panizza M, Nilsson J, Hallett M. Optimal stimulus duration for the H reflex. Muscle Nerve 1989;12:576–9.
Panizza M, Nilsson J, Roth BJ, Basser PJ, Hallett M. Relevance of stimulus duration for activation of motor and sensory fibers: implications for the study of H-reflexes and magnetic stimulation. Electroencephalogr Clin Neurophysiol 1992;85:22–9.
Pascual-Leone A, Torres F. Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain 1993;116:39–52.
Peurala SH, Pitkanen K, Sivenius J, Tarkka IM. Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. Clin Rehabil 2002;16:709–16.
Phillips CG, Powell TP, Wiesendanger M. Projection from low-threshold muscle afferents of hand and forearm to area 3a of baboon's cortex. J Physiol 1971;217:419–46.
Pons TP, Garraghty PE, Mishkin M. Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. J Neurophysiol 1992;68:518–27.
Ridding MC, Rothwell JC. Afferent input and cortical organisation: a study with magnetic stimulation. Exp Brain Res 1999;126:536–44.
Rosenkranz K, Rothwell JC. Differential effect of muscle vibration on intracortical inhibitory circuits in humans. J Physiol 2003;551:649–60.
Rosenkranz K, Pesenti A, Paulus W, Tergau F. Focal reduction of intracortical inhibition in the motor cortex by selective proprioceptive stimulation. Exp Brain Res 2003;149:9–16.
Rossini PM, Tecchio F, Sabato A, Finazzi-Agro A, Pasqualetti P, Rossi S. The role of cutaneous inputs during magnetic transcranial stimulation. Muscle Nerve 1996;19:1302–9.
Sailer A, Molnar GF, Cunic DI, Chen R. Effects of peripheral sensory input on cortical inhibition in humans. J Physiol 2002;544:617–29.
Sanes JN, Donoghue JP, Thangaraj V, Edelman RR, Warach S. Shared neural substrates controlling hand movements in human motor cortex. Science 1995;268:1775–7.
Strick PL, Preston JB. Two representations of the hand in area 4 of a primate. I. Motor output organization. J Neurophysiol 1982a;48:139–49.
Strick PL, Preston JB. Two representations of the hand in area 4 of a primate. II. Somatosensory input organization. J Neurophysiol 1982b;48:150–9.
Tokimura H, Di Lazzaro V, Tokimura Y, Oliviero A, Profice P, Insola A, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol 2000;523(Pt 2):503–13.
Troni W, Cantello R, De Mattei M, Bergamini L. Muscle responses elicited by cortical stimulation in the human hand: differential conditioning by activation of the proprioceptive and exteroceptive fibers of the median nerve. In: Rossini PM, Marsden CD, editors. Non-invasive stimulation of the brain and spinal cord: fundamentals and clinical application. New York: Alan R. Liss; 1988.
Uncini A, Kujirai T, Gluck B, Pullman S. Silent period induced by cutaneous stimulation. Electroencephalogr Clin Neurophysiol 1991;81:344–52.
Veale JL, Mark RF, Rees S. Differential sensitivity of motor and sensory fibres in human ulnar nerve. J Neurol Neurosurg Psychiatry 1973;36:75–86.
Wiesendanger M, Miles TS. Ascending pathway of low-threshold muscle afferents to the cerebral cortex and its possible role in motor control. Physiol Rev 1982;62:1234–70.
Wu CW, van Gelderen P, Hanakawa T, Yaseen Z, Cohen LG. Enduring representational plasticity after somatosensory stimulation. Neuroimage 2005;27:872–84.
Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res 1996a;109:127–35.
Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W. Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 1996b;40:367–78.

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