Modulatory effects on human sensorimotor cortex by whole-hand afferent electrical stimulation

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Abstract—*Objective:* To investigate the effect of electrical stimulation of the nerve afferents of the hand on cortical activity elicited by whole-hand subthreshold stimulation for sensation in healthy human subjects. *Methods:* Ten healthy volunteers were studied using BOLD-fMRI with 1) a test motor-task with finger-to-thumb tapping of the left hand, 2) a whole-hand afferent electrical stimulation of the left hand below the sensory level for sensation for 30 minutes, 3) a second fMRI run with the same paradigm as in the test motor-task immediately after electrical stimulation, and 4) a final identical fMRI run 2 hours post-stimulation to test the cortical changes induced by electrical stimulation. Experiments were carried out on a 1.5 T MR scanner and for fMRI echoplanar sequences were used. Data analysis was performed with SPM99. *Results:* An increase of movement-related responses was seen within the primary motor and primary somatosensory areas of both hemispheres when comparing the test motor-task with the motor-task after electrical stimulation relative to the baseline or sham stimulation. Two hours post-stimulation the modulatory effects of mesh-glove stimulation diminished to baseline level except within the contralateral primary motor region. *Conclusions:* The increased BOLD response spatially localized within the sensorimotor cortex reflects an increase in neuronal activity that may provide augmented neuronal excitability.

NEUROLOGY 2004;62:2262–2269

Impaired movement of the hand and arm and altered muscle tone of the affected side after hemispheric stroke lesions can be improved by using a wire mesh-glove to electrically stimulate the afferents of the hand below the conscious sensory threshold.[1-3] Subsensory mesh-glove stimulation generates synchronous tonic input to the brain, probably primarily due to depolarization of the large diameter group Ia and Ib afferents of the whole hand and to a lesser extent group II afferents, as is the case in functional and neuromuscular electrical stimulation.[4-7] Mesh-glove stimulation may act as a kinesthetic input to the posterior column nuclei, the (ventro-posterolateral) thalamus and cortical brain structures, especially Brodmann areas (BA) 3a and 2.[8-10]

fMRI, based upon the blood oxygen level dependent (BOLD) effect, allows the identification of physiologically activated brain areas by means of local and transient MR signal increases.[11] The most accepted explanation is that a local decrease in deoxyhemoglobin concentration within the venous microcirculation will result in an increase of the MR signal detected during brain activation.[11] We investigated whether changes of the BOLD signal could be demonstrated by fMRI after whole-hand afferent electrical stimulation below the level of consciousness and how long these changes would persist. Therefore, we applied fMRI to study cortical brain activity in 10 healthy right-handed volunteers during a volitional motor task before and after whole-hand mesh-glove stimulation. A preliminary fMRI study concerning this topic revealed a BOLD signal increase within the primary and secondary motor and somatosensory areas of both hemispheres immediately after the electrical stimulation.[12]

Patients and methods. The study was carried out in 10 healthy, right-handed volunteers (age 20 to 38 years, 6 men and 4 women), who signed the written consent form. The local Ethics Committee of the University of Innsbruck, where the experiments were performed and the data were analyzed, approved the study protocol.

We performed three fMRI runs with a conventional finger-to-thumb tapping paradigm of the left hand with epochs of movement and no movement. During the epochs of movement subjects performed a self-paced consecutive forward and backward tapping of the second to the fifth finger to the thumb with a frequency of approximately 2 Hz. The start and stop of the tapping sequence was indicated with an auditory cue ("go" and "stop"). Subjects' behavior was constant across the conditions as visually controlled by an investigator during the fMRI measurement. The tapping behavior (constancy of force of tapping, tapping frequency) of each subject was controlled by force transducers before and after each condition of the experiment and no differences between the begin-

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Supported by the Biomed2 Project PL 950870 of the European Community and by a grant from the Kent Waldrep National Paralysis Foundation, Dallas, TX.

Received July 17, 2003. Accepted in final form February 13, 2004.

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ning and the end of one condition and across the conditions could be lined out. Throughout the fMRI run subjects were instructed to position both hands relaxed on the abdomen, not to raise the left hand during tapping, and to keep their eyes closed during the fMRI recording. Further, they were instructed to remain relaxed supine without moving and without directing their attention specifically throughout the fMRI measurements. However, we did not attempt to control the level of alertness and attention.

Experimental setup. The experiment consisted of five experimental sequences: 1) a first baseline fMRI run, further referred to as test motor-task (TMT), 2) a mesh-glove stimulation of 30 minutes to the relaxed left hand outside the magnet with the subject lying relaxed supine upon the scanner board, 3) after exactly repositioning the scanner board in the bore of the magnet, a second fMRI run with the same motor paradigm as in TMT immediately after mesh-glove stimulation, in the following referred to as conditioned motor-task 1 (CMT1), 4) a 2-hour period outside the magnet with the subject lying relaxed supine upon the scanner board, and 5) after exactly repositioning the scanner board in the bore of the magnet a final fMRI run identical to CMT1 2 hours post mesh-glove stimulation (conditioned motor-task 2 [CMT2]). Furthermore, an identical study was performed with the same subjects but with sham stimulation, meaning that the subjects were not aware that electrical stimulation was not being applied. Sham stimulation was carried out on a different day to avoid any long lasting or conditioning effects of subsensory electrical stimulation.

In summary, our experimental design conforms to a two-by-three factorial design. The two factors were movement (rest vs self-paced finger opposition). The second factor was electrical stimulation with three levels (before, immediately after, and 2 hours later). We were particularly interested in the interaction between electrical stimulation and movement-related responses. We anticipated that the central correlates of electrical stimulation-induced motor-excitability would be expressed as an increase in motor-related responses following stimulation. In addition, we added a further factor to make a two-by-three-by-two design. This factor was simply replacing real electrical stimulation with sham stimulation. This enabled us to exclude non-specific time effects when making inferences about the stimulation x movement interaction.

Mesh-glove stimulation. The mesh-glove was connected to a two-channel stimulator (Schwa-Medico TENS Stem) with a common anode for output to the mesh-glove and a pair of separated surface electrodes as cathodes that were separately connected to 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 (figure 1). The mesh-glove is made of conductive, flexible wire and is easily slipped over the hand. Before fitting the hand with the mesh-glove, conductive jelly was applied over the whole hand. A train of 50 Hz stimuli with a pulse width of 250 μs was used for subthreshold stimulation. The subthreshold level of stimulation was defined by decreasing the stimulus strength to a level when the subject reported that tingling sensation had disappeared. The stimulus amplitude for the subthreshold stimulus was between 0.9 and 1 mA for each subject.

MRI. All experiments were performed on a 1.5 Tesla whole body scanner (Magnetom VISION, Siemens, Germany) with an echoplanar capable[13] gradient system (gradient ramp time 77 T/second, gradient strength 23 mT/m) and a circular polarized head coil (FoV = 250 mm). For fMRI, we employed T2*-weighted single shot echo-planar sequences (repetition time/echo time/α = 0.96 msec/66 msec/90°, matrix = 64×64, voxel dimension = $2.95 \times 2.95 \times 6.25$ mm). We acquired a whole brain scan (volume image) with 24 slices parallel to the bicommissural plane. Foam padding and a special helmet fixed to the head coil was used to restrict head motion. A series of 85 sequential volume images was acquired, consisting of epochs of five volume images during rest (R) alternating with five volume images during finger tapping (A) resulting in a time series of RARARARARARARARAR and a time resolution of 3 seconds.

Data analysis. Image analysis was performed using Matlab 5.3 and the statistical parametric mapping (SPM99) software (http://www.fil.ion.bpmf.ac.uk). The 85 volume images of each fMRI run were automatically coregistered and realigned to the first volume image of the TMT fMRI run to correct for head movements during the scans. The data were then normalized into the brain standard of the Montreal Neurologic Institute (MNI space).

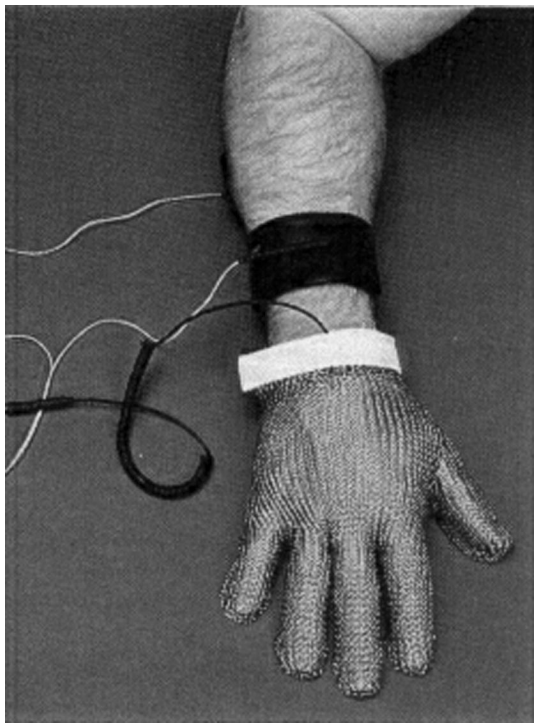

Figure 1. Mesh-glove: A two-channel stimulator delivers a train of 50 Hz stimuli (pulse width 250 μs) with the amplitude for subthreshold stimulation ranging from 0.9 to 1 mA. The mesh-glove acts as a common anode, the cathodes are placed over the tendons of the forearm flexors and extensors.

Anatomic localization of the activated brain areas was assigned with the aid of the atlas of Talairach[14] and the Talairach DAEMON software, which allows (based upon the original Talairach coordinates) an almost exact demarcation of the identifiable anatomic structures (e.g., BAs). Spatial smoothing was done with a Gaussian filter of FWHM = 6×6 x 12 mm. For the elimination of respiration and pulsation of cerebro-spinal fluid related motion artifacts, high (cut-off: 0.001 Hz) and low (cut-off: 0.1 Hz) pass filtering was used. We defined a design matrix comprising boxcar regressors convolved with a hemodynamic response function. These regressors modeled movement-related responses during the three levels of the stimulation factor (TMT, CMT1, and CMT2). By modeling movement-related effects independently for each of the three sessions we were able to model and test for interactions (differences in movement-related responses) using appropriate contrasts. Each contrast was tested with the appropriate T statistic and ensuing statistical parametric map. Only results that survived a correction for multiple comparisons at $p < 0.05$ (using the spatial extent k of suprathreshold clusters greater than 20 voxels) are reported. As significant interactions between the effects of stimulation and task were found, first the simple main effects of movement within each of the three stimulation conditions are reported. Then the interaction in terms of significant increases in motor responses when comparing CMT1 to TMT and, separately, CMT2 to TMT are characterized. It should be noted that all these analyses used a fixed-effect model because the interest lay in demonstrating electrically induced modulations of motor responses that could be measured in single subjects. The inferences about significant effects are therefore in relation to the precision with which these effects could be measured as opposed to inter-subject variability. In addition, a random effect analysis for the simple conditioning effects was performed, whereas the higher order contrasts (CMT1 vs TMT, CMT2 vs TMT, and CMT2 vs CMT1 and vice versa) survived only the first level.

Results. Figures 2 and 4 demonstrate the SPM of the TMT, CMT1, and CMT2 condition on a first and second

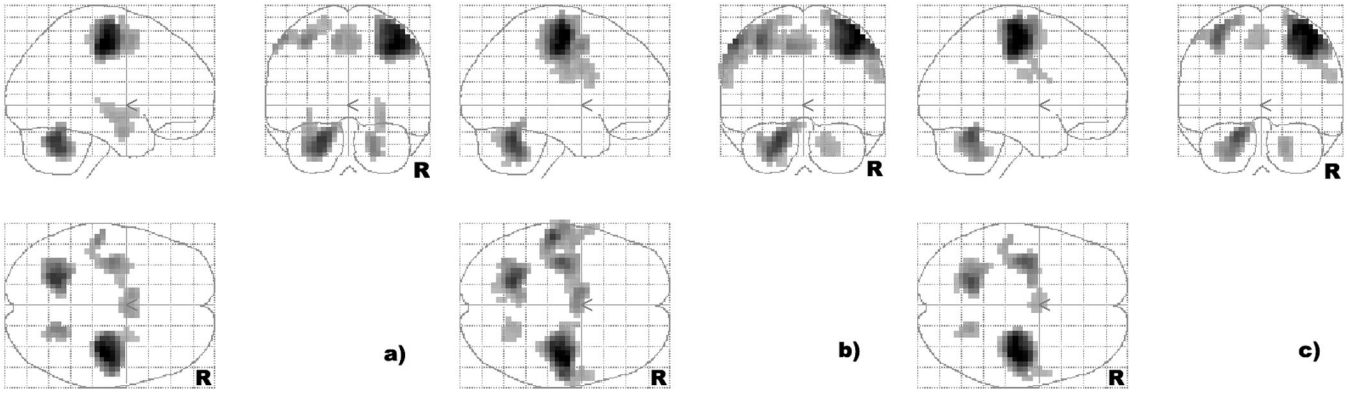

Figure 2. Within-condition analysis on a first level: a) blood oxygen level dependent (BOLD) response during test motor-task contra- and ipsilaterally within primary sensorimotor area (SM1), premotor area (PM), and supplementary motor area (SMA) as well as in both cerebellar hemispheres with a dominance of the left hemisphere ipsilaterally to the stimulated hand; b) increase of BOLD response during conditioned motor-task 1 of the contralateral hemisphere within SM1, PM, and inferior parietal lobule (IPL) and of the ipsilateral hemisphere within SM1, PM, IPL, SMA, and cingulate gyrus (GC); c) BOLD response 2 hours post stimulation with brain activation declining nearly to TMT level ($p < 0.05$*, cluster level* $k > 20$*, corrected for multiple comparisons; table 1).*

Table 1 *First level analysis within condition of TMT, CMT1, and CMT2. Poststimulation significant increase of cluster peak values and cluster voxels of activated foci within the contra- and ipsilateral SM/PM and the ipsilateral SMA/GC. Two hours poststimulation decrease within the contra- and ipsilateral SM/PM. No significant differences within the cerebellum (figures 2, 5;* $p < 0.05$*, cluster level* $k > 20$*, corrected for multiple comparisons).*

	First level analysis, peak value (*t*-value)		
	TMT	CMT1	CMT2
R SM/PM	17,24	21,38	20,64
MNI (x,y,z)	40, −16, 48	44, −12, 60	40, −20, 48
Brodmann area	4	4	4
Cluster voxels	245	365	317
L SM/PM	9,14	13,10	12,53
MNI (x,y,z)	−36, −12, 52	−36, −12, 52	−36, −12, 56
Brodmann area	6	6	6
Cluster voxels	88	371	112
L SMA/GC	7,07	9,76	8,47
MNI (x,y,z)	−8, −4, 52	−12, 0, 48	0, −4, 52
Brodmann area	24	24	6
Cluster voxels	76	371	44
R cerebellum	8,54	7,92	8,24
MNI (x,y,z)	20, −56, −36	20, −52, −36	20, −56, −36
Cluster voxels	46	38	36
L cerebellum	12,70	14,93	13,46
MNI (x,y,z)	−20, −56, −28	−20, −56, −28	−20, −56, −24
Cluster voxels	154	174	131

TMT = prestimulation; CMT1 = poststimulation; CMT2 = 2 hours poststimulation; SM = primary and secondary sensorimotor cortex (Brodmann area 4, 3a, 3b, 2, 1, 40); PM = premotor cortex; MNI (x,y,z) = coordinates that correspond to the brain standard of the Montreal Neurological Institute; SMA = supplementary motor area; GC = cingulate gyrus.

level analysis ($p < 0.05$, cluster level k > 20, corrected for multiple comparisons). With regard to first level analysis (figures 2 and 5), movement-related BOLD responses within the precentral (primary motor area [M1]), postcentral (primary somatosensory area [S1]), medial (premotor area [PM]), and superior frontal (supplementary motor area [SMA]) as well as the cingulate gyrus (GC) could be detected on both hemispheres. Additional activation on both cerebellar hemispheres with dominance of the left hemisphere ipsilateral to the stimulated hand was seen for all three conditions. During CMT1 BOLD response within the contra- and ipsilateral inferior parietal lobule (IPL) could also be recorded, brain activation that could not be verified during TMT and CMT2 (see figures 2 and 5, a and c). On a second level, during TMT movement-related BOLD responses contralaterally within SM1 and on the left cerebellar hemisphere, during CMT1 contra- and ipsilaterally within SM1 and on the left cerebellar hemisphere, and during CMT2 contra- and ipsilaterally within SM1 and on the left cerebellar hemisphere were delineated (see figure 4).

By comparing within- (see figure 2) and between- (see figure 5) condition analysis of the TMT, CMT1, and CMT2 condition on a first level, after 30 minutes of whole-hand afferent electrical stimulation subthreshold for sensory perception, an obvious difference of BOLD responses within the above mentioned brain areas was demonstrated. The average cluster peak values with their coordinates within the stereotactic space of the brain standard of the Montreal Neurological Institute (MNI coordinates) with corresponding BAs and volumes of activation for the three conditions are summarized in table 1.

Within-condition analysis on a first level. Comparing the TMT and CMT1 condition the group result yielded an increase of movement-related BOLD responses within the M1, S1, PM, and IPL on both hemispheres (figure 2, a and b). Furthermore, augmented BOLD response was seen within the SMA on the superior frontal gyrus as well as the cingulate gyrus of the left hemisphere. Brain activation on both cerebellar hemispheres did not show any sig-

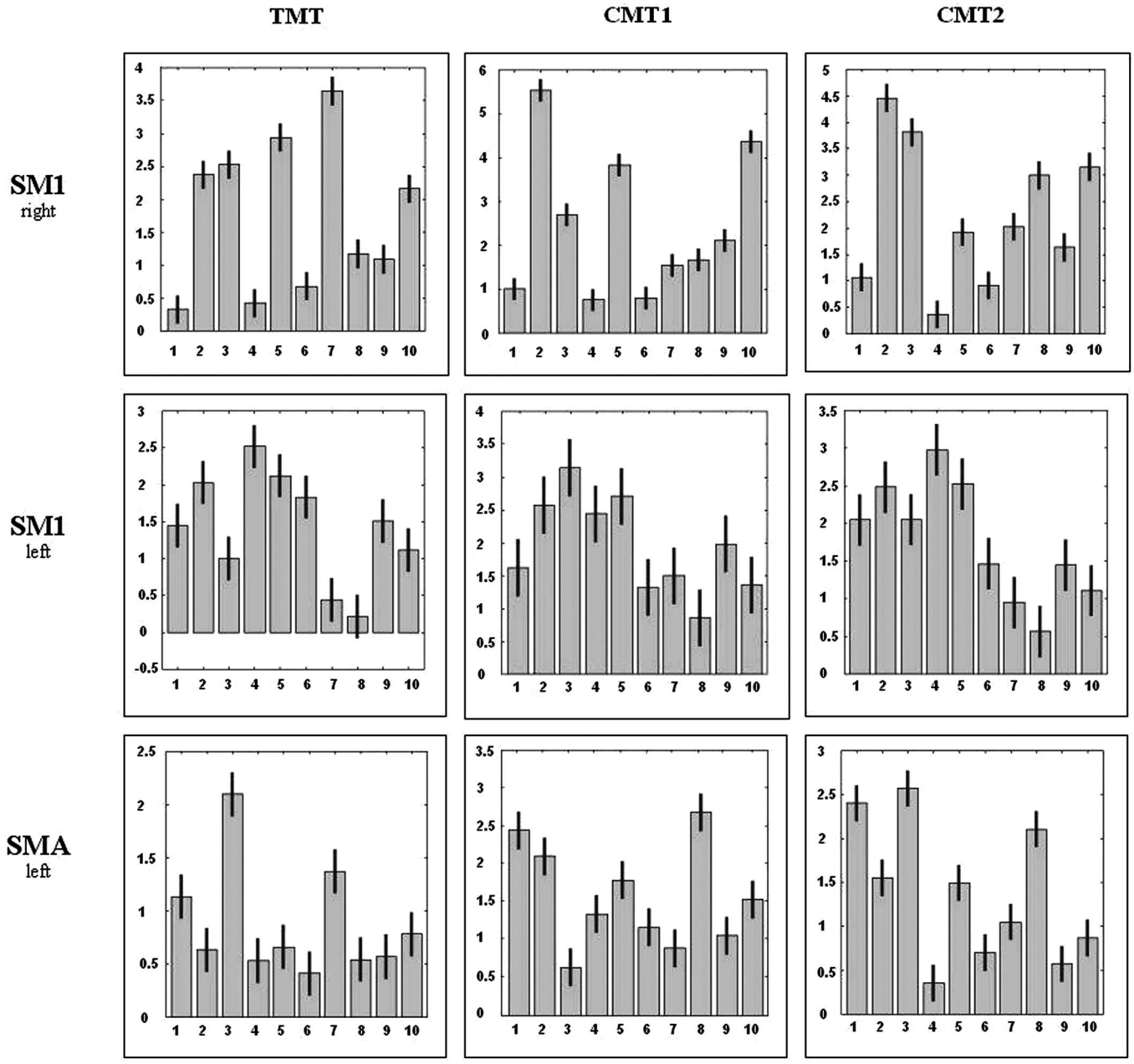

Figure 3. Bar chart showing the motor activation over the three levels of stimulation for voxels showing maximal interaction for parameter estimation on a first level analysis. Abscissa = number of subjects, ordinate = parameter estimation β for the main effect of the movement related responses under each of the three levels of stimulation (arbitrary units). TMT = test motor-task; CMT = conditioned motor-task; SM1 = primary somatosensory area; SMA = supplementary motor area.

nificant differences between the conditions but remained on a nearly constant level throughout the experiment (see figure 2 and table 1).

Within-condition analysis on a second level. Group analysis of TMT on a second level yields BOLD response contralaterally within SM1 and on the left cerebellar hemisphere, of CMT1 an increase of BOLD response on the contra- and ipsilateral hemisphere within SM1 and of CMT2 BOLD response on the contra- and ipsilateral hemisphere within SM1 with a slight decline of activation and activation on the left cerebellar hemisphere (see figure 4 and table 2).

Between-condition analysis on a first level. Group contrast of CMT1 vs TMT yielded an increase of brain activation bilaterally within SM1 (coactivation within M1 and S1), PM, and IPL and ipsilaterally within SMA and GC. There were no differences of cerebellar activation between conditions (see figure 4a). Group subtraction of CMT2 vs TMT solely yielded brain activation contralaterally to the stimulated hand within SM1 (see figure 4b). CMT1 vs CMT2 resulted in significant differences in BOLD signal within contra- and ipsilateral IPL and ipsilateral SM1 (see figure 4c).

Between-condition analysis on a second level. Between-condition analysis on a second level did not show any significant differences in movement-related responses.

Single-subject analysis. Single-subject analysis showed a consistent profile of changes of BOLD responses

Table 2 *Second level analysis within condition of TMT, CMT1, and CMT2. Increase (poststimulation) and decrease (2 hours poststimulation) of cluster peak values and cluster voxels of activated foci within the contra- and ipsilateral SM/PM and the left cerebellum without significance (figure 4; $p < 0.05$, cluster level $k > 20$, corrected for multiple comparisons).*

	Second level analysis, peak value (*t*-value)		
	TMT	CMT1	CMT2
R SM/PM	10, 90	12, 53	11, 11
MNI (x,y,z)	40, −16, 48	44, −12, 60	40, −20, 48
Brodmann area	4	4	4
Cluster voxels	84	112	99
L SM/PM	—	8, 17	7, 25
MNI (x,y,z)	—	−36, −12, 52	−36, −12, 56
Brodmann area	—	6	6
Cluster voxels	—	26	20
L cerebellum	6, 01	7, 04	6, 91
MNI (x,y,z)	−20, −56, −28	−20, −56, −28	−20, −56, −24
Cluster voxels	10	17	13

TMT = prestimulation; CMT1 = poststimulation; CMT2 = 2 hours poststimulation; SM = primary and secondary somatosensory cortex (Brodmann area 4, 3a, 3b, 2, 1, 40); PM = premotor cortex; MNI (x,y,z) = coordinates that correspond to the brain standard of the Montreal Neurological Institute.

as found in group analyses. Contralateral SM1 and PM was constantly activated in all of the 10 subjects and in each of the three conditions. TMT and CMT2 showed ipsilateral activation of the SM1 in six and of the PM in five subjects while CMT1 revealed activations within both anatomic regions in nine volunteers. SMA/GC uni- or bilaterally could be detected in TMT in seven, in CMT1 in nine, and in CMT2 in six subjects. Activation foci uni- or bilaterally within the inferior parietal lobule were only seen in CMT1. Singular activation spots within the superior parietal lobule (SPL) could be revealed in TMT, CMT1, and CMT2. To illustrate the consistency of the activations across the subjects within the right and left SM1 and the left SMA, bar charts showing parameter estimates for the size of the motor activations over the three stimulation levels for voxels showing a maximal interaction are presented (figure 5).

There was no evidence of a significant interaction between sham stimulation and movement-related responses when analyzing the sham time-series that were acquired on another day with the same protocol as verum stimulation but without electrical stimulation.

Discussion. During self-paced simple finger movements we found movement-related responses of several brain areas of the contra- and ipsilateral hemisphere within the pre- and postcentral gyrus, the medial and superior frontal gyrus, and on both cerebellar hemispheres with a dominance ipsilaterally to the active left hand. Neuronal activation within these areas was expected and has been reported by other investigators who studied the activity of human cortical motor areas during self-paced finger movements.[15-17] After 30 minutes of afferent electrical stimulation of the left whole-hand, an increase of brain activation on both hemispheres within the pre- and postcentral as well as the medial frontal gyrus could be detected. The left SMA showed augmented brain activation as well. The finding that an increase of movement- related responses were absent when the sham paradigm was applied further confirmed the validity of the presented results.

Whole-hand afferent electrical stimulation below the threshold for sensation is an active system, which depolarizes a certain population of kinesthetic afferents with cortical projections, especially group Ia and Ib fibers. There are definite experimental findings that confirm that sensory afferents of groups Ia (primary large muscle afferents), Ib (afferents from Golgi organs), and group II (slow and rapidly adapting skin afferents, secondary thin muscle

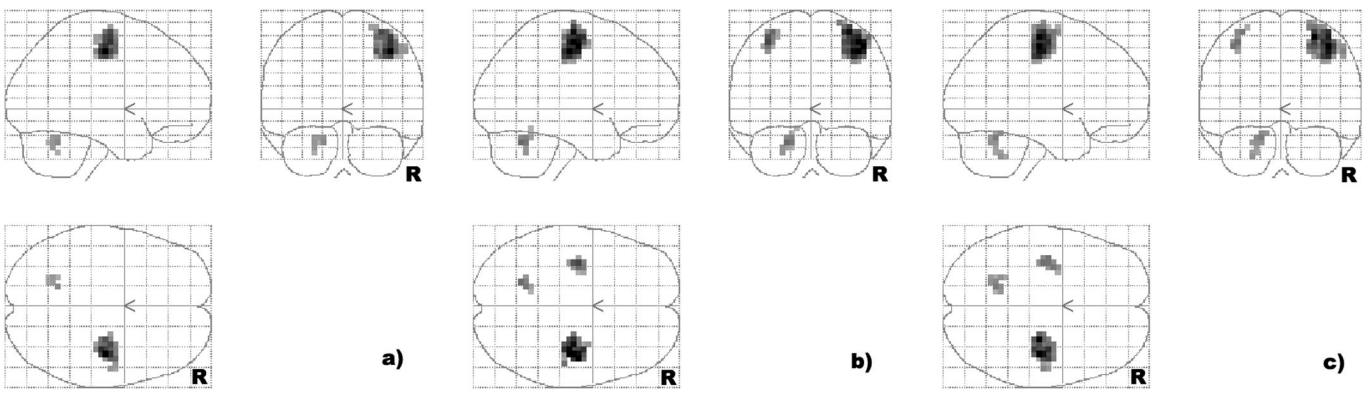

Figure 4. Within-condition analysis on a second level: a) blood oxygen level dependent (BOLD) response during test motor-task contralaterally within primary sensorimotor area (SM1) and on the left cerebellar hemisphere; b) increase of BOLD response during conditioned motor-task 1 on the contra- and ipsilateral hemisphere within SM1; c) BOLD response 2 hours post stimulation on the contra- and ipsilateral hemisphere within SM1 with a slight decline of activation and activation on the left cerebellar hemisphere ($p < 0.05$*, cluster level $k > 20$, corrected for multiple comparisons; table 2).*

Table 3 *Between-condition analysis on a first level for CMT1-TMT, CMT2-TMT, and CMT1-CMT2**

	First level analysis, peak value (*t*-value)		
	CMT1-TMT	CMT2-TMT	CMT1-CMT2
R SM/PM	5,94	5,39	3,95
MNI (x,y,z)	30, −20, 68	32, −16, 68	40, −36, 48
Brodmann area	6	6	40
Cluster voxels	144	38	28
L SM/PM	3,06	—	4,74
			3,76
MNI (x,y,z)	−40, −16, 56	—	−48, −20, 52
			−52, 40, 52
Brodmann area	4	—	3
			40
Cluster voxels	91	—	114
L SMA/GC	3,92	—	—
MNI (x,y,z)	−12, −4, 48	—	—
Brodmann area	24	—	—
Cluster voxels	45	—	—

* $p < 0.05$, cluster level $k > 20$, corrected for multiple comparisons. Between-condition analysis on a second level did not show any significant differences in movement-related BOLD signals (figure 5).

CMT1 = poststimulation; TMT = prestimulation; CMT2 = 2 hours poststimulation; SM = primary and secondary somatosensory cortex (Brodmann area 3a, 3b, 2, 1, 40); PM = premotor cortex; MNI (x,y,z) = coordinates that correspond to the brain standard of the Montreal Neurological Institute; SMA = supplementary motor area; GC = cingular gyrus.

afferents) have short-latency projections to the contralateral sensorimotor cortex, particularly BA 3a, 1, 2, and 4.[18-22] For the afferent route to the primary motor cortex M1 a projection from BA 3a is discussed.[23] In several PET and fMRI studies it was confirmed that vibration to the hand palm of healthy adult humans activates the contralateral SM1, the SMA, and the secondary somatosensory cortex S2 bilaterally.[24-26]

The hand can be a rich source of kinesthetic input to the brain via the afferents because the hand's intrinsic muscles have high-density muscle spindles,[27,28] there are a large number of joint receptors with corresponding large afferents, as well as Golgi tendon organs[29,30] with a portion of the tendons within the hand but belonging to the forearm muscles.[4] Further neurophysiologic research is necessary to determine the kind and size of the population of hand afferents depolarized under the experimental conditions and parameters of mesh-glove stimulation. However, regardless of which hand afferents mesh-glove stimulation depolarizes, it is certain that there are afferents, involved in proprioception, "which refer to the sensing of the body's own movement."[31]

The results of this study support the hypothesis that continuous whole-hand afferent electrical stimulation at the subthreshold level for conscious sensation involves neurophysiologic mechanisms that may be activated by externally controlled kinesthetic input and that can induce modulatory effects within the sensorimotor cortex. For the ipsilateral modulatory effects of the mesh-glove stimulation, direct cortical projections of the group Ia, b, and II afferents or transcallosal projections from the contralateral side can be discussed.[32,33] The detected increased BOLD responses spatially localized within the sensorimotor cortex reflect an increase in neuronal activity as a

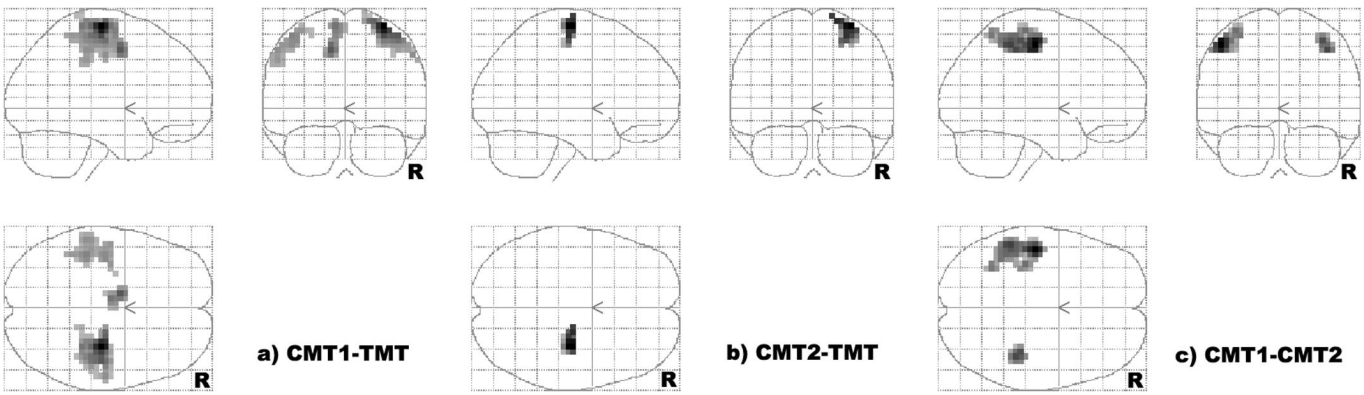

Figure 5. Between-condition analysis on a first level: a) conditioned motor-task 1 (CMT1) minus test motor-task shows an increase of movement-related blood oxygen level dependent (BOLD) responses within the contralateral primary sensorimotor area (SM1), premotor area (PM), and inferior parietal lobule (IPL) as well as the ipsilateral SM1, PM, IPL, supplementary motor area, and GC; b) CMT2-TMT leads to a residual BOLD response 2 hours post stimulation contralaterally within the SM1; and c) CMT1-CMT2 reveals three activity spots, one in the right parietal cortex (IPL, Brodmann area 40, table 3), one even more posterior in the left parietal cortex (IPL, Brodmann area 40; table 3), and one in the left primary sensory cortex (postcentral gyrus, Brodmann area 3a; table 3; $p < 0.05$, *cluster level* $k > 20$, *corrected for multiple comparisons, discussion see text).*

result of a dynamic interaction of various synaptic and cellular mechanisms due to the local processing of the augmented afferent kinesthetic input signals to the sensorimotor cortex.[34] From somatosensory evoked potential studies[35] it is known that electrical stimulation of group Ia and Ib afferents and their direct or transcallosal projections induce augmented local field potentials (LFP) within the sensorimotor cortex. The elevated LFP persist for at least several minutes and change intracortical excitability of motoneurons that can be recruited to a larger extent by a consecutively performed conditioned motor task. The applied mesh-glove stimulation should address especially group Ia and Ib and to a lesser extent group II afferents and thus should augment LFP within the sensorimotor cortex of both cerebral hemispheres. A strong correlation between spatially localized BOLD response and local field potentials has been shown recently.[34]

With regard to beneficial effects of mesh-glove subthreshold stimulation in stroke patients concerning improved motor performance after a daily mesh-glove training program over several weeks,[1-3] we suppose that mesh-glove stimulation may provide an increased toporegional motoneuron recruitment by augmented neuronal excitability, activity-dependent synaptic plasticity, and subsequent intracortical facilitation and unmasking of preexisting silent synapses.[36-41] Horizontal connections traversing the superficial layers of the motor cortex are capable of both increases and decreases in strength and synaptic efficacy.[42,43] It is important to consider that the enhanced motor recruitment is induced by a persistent high-frequency input, probably inducing intracortical synaptic modification through a long-term potentiation-like mechanism, and not by an active motor learning task, which then should have diminished the number of recruited motoneurons and thus cortical activity. Otherwise, as the changes persisted for 2 hours we also discard posttetanic potentiation-like phenomena.

Concerning the issue of augmented neuronal excitability, there is no direct evidence for its intracortical origin by the increased BOLD responses. However, in the literature,[32,44,45] there is evidence for a cortical origin of modulation of cortical motoneuron excitability by somatosensory peripheral input. The hypothesis that increased responsiveness of movement-related BOLD responses after electrical stimulation reflects increased motoneuron excitability has yet to be proven by further TMS studies, where we will especially concentrate on whether increased motoneuron excitability originates from a cortical, subcortical, or spinal level.

The parietal association cortex in the posterior parietal lobe consisting of the SPL and IPL is a mosaic of areas, each receiving a different specific type of sensory information and transforming it into information appropriate for action. The IPL is the site of convergence of proprioceptive or kinesthetic input containing premotor and visual information. During reaching and grasping with the hand, the parietal association cortex is involved in a series of sensorimotor transformations to convert the signal to the target location on the retina into a pattern of peripheral motor output signals to muscles, in order to move the hand to the target.[46,47] The information for these target movements will be processed primarily by the group Ia and Ib afferents, which are especially addressed by the mesh-glove stimulation. Thus, the IPL activity in CMT1 can give evidence for a direct input of mesh-glove stimulation uni- and bilaterally to the parietal association cortex, a brain region essential for the rehabilitation process after stroke, especially if somatosensory deficits or neglect are involved. The finding of increased activation within the IPL is therefore consistent with the described improvement of neglect that has been described after a daily mesh-glove stimulation program for 3 months in stroke patients.[1,2] Increased proprioceptive or kinesthetic input to the brain also has the potential of lowering muscle tone, which is in agreement with described beneficial effects of mesh-glove stimulation on spasticity.[1,2]

Further studies should focus on 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 hemispheric stroke lesions.[48] These and additional studies in the field of general neurology, neurophysiology, and neuroimaging should moreover particularly direct their investigatory efforts toward finding and developing new and potentially better or more accurate pretreatment instruments, methods, and procedures (best in a joint intra- and interdisciplinary neuroscientific approach), to precisely localize and define individual boundaries of postlesionally affected brain areas down to the last detailed anatomic structure. This information could help physicians planning the best rehabilitation treatment to decide on appropriate therapy. In any case it would be of interest to assess the potential of mesh-glove stimulation as a tool inducing metaplastic changes by up- or downregulating cortical reorganization processes after CNS lesions and possibly facilitating functional adaptive plasticity.

Acknowledgment

The authors thank Prof. Dr. Milan and Dr. Meta Dimitrijevic from the Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX, for support, and Dr. Klaus-Martin Stephan and Dr. Vicente González from the Department of Neurology, University Hospital Düsseldorf, Germany, for discussion.

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