Enhanced Motor Cortex Excitability During Ipsilateral Voluntary Hand Activation in Healthy Subjects and Stroke Patients

Hartwig Woldag, PhD; Sven Lukhaup, MD; Caroline Renner; Horst Hummelsheim

Background and Purpose—It is still a matter of debate whether the ipsilateral voluntary hand activation has a facilitatory or inhibitory effect on the nondominant or affected hemisphere. To give an answer to this question is of great importance for the rehabilitation of stroke patients, because they often use the unaffected hand for compensation.

Methods—Ten healthy volunteers and 11 stroke patients were investigated using transcranial magnetic stimulation (TMS). TMS was applied to the dominant/unaffected hemisphere during performance of different tasks (simple index finger abduction, pinch grip, and power grip) at various force levels (5%, 10%, 50%, and 100% maximal voluntary contraction) with the ipsilateral hand. Peak-to-peak amplitudes of motor-evoked potentials were used as measure for motor cortex excitability.

Results—Both simple and complex tasks led to a facilitation of the contralateral corticospinal system at all levels of applied force. Not only the facilitatory effect in general but also the slope of the relationship between force level and MEP amplitude were significantly lower in stroke patients indicating that both the general activation level of the impaired motor system and the bandwidth of possible activation levels are diminished.

Conclusion—Voluntary activation of the hand does not exert an inhibitory effect on the excitability of the ipsilateral hemisphere in healthy volunteers or in stroke patients. (Stroke. 2004;35:2556-2559.)

Key Words: evoked potentials, motor 

Loss of motor skill in the affected hand is one of the most frequent sequelae of stroke. Despite the therapeutic goal to achieve functional improvements of the affected hand, patients have to maintain their independence by using the unaffected hand in the activities of daily living.

Transcranial magnetic stimulation (TMS) has introduced the possibility to examine the excitability of the motor cortex in humans. Voluntary contraction of a respective target muscle enhances the motor-evoked potential (MEP) amplitude. The strongest facilitation occurs at contraction forces between 2% and 6% of maximal surface electromyogram (sEMG). According to Datta et al, the facilitatory effect of voluntary contraction is task-dependent. The simple abduction of the index finger resulted in larger MEPs of the first dorsal interosseous muscle (FDI) than in a power grip. Yet Flament et al found larger MEPs of the FDI during several complex tasks compared with a simple index finger abduction. In both studies, the activation of the FDI was kept constant in all conditions by monitoring the sEMG. In a more recent study, Hasegawa et al described a lower TMS threshold and larger MEP amplitudes in the FDI during the precision grip compared with the power grip.

MEPs of the relaxed FDI of the nondominant hand increase during voluntary contraction of the FDI of the dominant hand in a range between 10% and 70% of maximal voluntary contraction (MVC). Ziemann and Hallett found a stronger facilitation of the nontask hand while performing complex finger sequences with the task hand than during a mild tonic contraction (5% MVC) of the task hand. It has been suggested that the facilitation of motoneurons of limb muscles during voluntary contraction of contralateral muscles might involve transcallosal pathways. However, Meyer et al argued that this facilitation is mediated on a spinal level rather than via transcallosal fibers, because the facilitatory effect of strong voluntary contraction of one hand on the MEPs of the opposite hand is still present in patients with agenesis of corpus callosum.

Beyond the presumed facilitatory connections there is evidence for inhibitory transcallosal pathways: a conditioning TMS pulse over the motor cortex of one hemisphere 10 to 15 ms before a test stimulus over the opposite hemisphere diminishes the MEP amplitude of the test stimulus.

Tonic voluntary activation of hand muscles is transiently suppressed by stimulation of the ipsilateral hemisphere. This inhibition is lacking in patients with agenesis of the anterior half of the corpus callosum. In healthy volunteers, Liepert et al found an inhibitory effect of phasic pinch grips at low forces (1%...
TABLE 1. Data of Stroke Patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Weeks Since Infarction</th>
<th>Affected Hemisphere</th>
<th>RMA Score</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>7</td>
<td>R</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>8</td>
<td>R</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>6</td>
<td>L</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>9</td>
<td>R</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>10</td>
<td>L</td>
<td>9</td>
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<td>59</td>
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<td>R</td>
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<td>5</td>
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<td>9</td>
<td>70</td>
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<td>L</td>
<td>2</td>
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<tr>
<td>10</td>
<td>81</td>
<td>6</td>
<td>L</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
<td>11</td>
<td>L</td>
<td>10</td>
</tr>
</tbody>
</table>

R indicates right; L, left; RMA, Rivermead Motor Assessment, arm section (range 0–15).

and 2% of MVC) on the MEPs of the nontask hand, whereas tonic contractions at 20% and 40% MVC enhanced the MEPs of the nontask hand.

For the rehabilitation of stroke patients, it is of great importance to know whether the compensatory use of the unaffected hand exerts an inhibitory or a facilitatory influence on the affected hemisphere. In the present study, we tested the influence of voluntary activation of the dominant/unaffected hand performing various tasks at various strengths on the nondominant/centrally paretic hand of healthy volunteers and stroke patients.

Subjects and Methods

Subjects

Ten healthy right-hand dominant (Edinburgh Inventory of Handedness) volunteers (mean age 26; range, 24 to 34; 5 women, 5 men) and 11 stroke patients with a central hemiparesis (mean age, 62.7; range, 43 to 81; 7 women, 4 men) participated in the study. The patients had a subcortical infarction in the territory of the medial cerebral artery confirmed by cranial computed tomography (CT). The mean latency between stroke and enrollment into the study was 7.8 weeks. For functional assessment, we used the arm section of the Rivermead Motor Assessment. Patient data are summarized in Table 1. All patients and volunteers gave their written informed consent. The study protocol had been approved by the local ethics committee.

Experimental Protocol

Subjects had to perform 3 different tasks with the dominant or the unaffected hand (task hand): (1) simple tonic abduction of the index finger; (2) pinch grip; and (3) power grip. The order was pseudo-randomized. Tasks had to be executed at different force levels measured by sEMG of the FDI. The sEMG recording allowed a selective measurement of the voluntary activation of the FDI during tasks of different complexity. Subjects were asked to perform with 5%, 10%, 50%, and 100% of their maximum sEMG, which was recorded using Ag/AgCl electrodes (Medtronic L0202) mounted in a belly-tendon fashion over the FDI. The sEMG signals were amplified (programmable 4-channel amplifier; Jaeger/Toennies), rectified, integrated, and displayed on a monitor as an envelope curve for visual feedback (MP 100A; Biopac Systems Inc). Subjects were asked to fully relax the nontask hand. sEMG of the FDI of the nondominant/affected hand (nontask hand) was used for acoustic control of relaxation and for MEP recordings.

Transcranial magnetic stimuli were applied by means of a focal figure-of-8 coil connected to a Magstim 200 magnetic stimulator (Magstim Company Ltd). The coil was positioned tangentially to the scalp with the handle backwards 45° away from the midline as has been proved to be the optimal position for activation of the hand motor field. The coil was moved in small steps over the hand area until a maximum MEP in the contralateral FDI (nontask hand) was elicited. This position was maintained by fastening the coil on a waistcoat frame set, which additionally stabilized the head position. Stimulus intensity was adjusted at 120% of motor threshold, which was defined as the minimum stimulus intensity-eliciting MEPs of >50 μV in at least 5 of 10 consecutive stimuli with the hand at rest.

For each force level of each task, 10 consecutive stimuli were applied. MEP signals were amplified, band pass-filtered (20 Hz to 2 kHz) (programmable 4-channel amplifier), and stored on hard disk for offline analysis. After visual inspection to exclude MEPs contaminated by artifacts or by previous voluntary EMG activity, MEPs were averaged and the peak-to-peak amplitude was measured (MP 100A; Biopac Systems Inc).

For each subject the average MEP amplitude during full relaxation of both hands was set to 100% and the individual changes during the tasks were expressed as percentage ratios. A 2-way ANOVA for repeated measures was calculated separately for healthy volunteers and patients, with task and force as the main effects on the MEPs. In cases of significant differences, a Holm–Sidak post hoc analysis for all pairwise multiple comparisons was added. The comparison of the facilitatory effect of different force levels between patients and volunteers was performed by t test. For a non-normal distribution, the rank sum test was used. To compare the relationships between force level and MEP amplitude, a regression analysis followed by a t test for intercept and slope was calculated. Alpha risk was set at 0.05.

Results

In patients and in healthy volunteers, the main effect on MEP amplitudes derived from the force level (P<0.001). All levels of tonic voluntary activation led to a facilitation of the contralateral motor system. This holds true for simple and for complex tasks (Table 2). Multiple comparisons among healthy subjects showed significant differences between all force levels, except between 5% and 10%, whereas in patients

TABLE 2. Motor-Evoked Potential Amplitudes at Different Force Levels and Tasks

<table>
<thead>
<tr>
<th>Force, %</th>
<th>Healthy Volunteers</th>
<th>Stroke Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple</td>
<td>Pinch</td>
</tr>
<tr>
<td>5</td>
<td>216.5±115.4</td>
<td>170.9±118.9</td>
</tr>
<tr>
<td>10</td>
<td>209.5±66.5</td>
<td>173.7±105.4</td>
</tr>
<tr>
<td>50</td>
<td>274.9±137.9</td>
<td>269.5±175.6</td>
</tr>
<tr>
<td>100</td>
<td>502.5±289.0</td>
<td>411.2±257.4</td>
</tr>
</tbody>
</table>

Force levels measured as % ratios of maximal surface-EMG. MEP amplitudes expressed as % ratios of relaxation. Simple indicates simple index finger abduction; pinch, pinch grip; power, power grip.
The facilitatory effect of voluntary contraction of the task hand on the nontask hand was significantly lower in patients ($P<0.03$). Additionally, regression analysis of the relationship between force level and MEP amplitude revealed that the slope is significantly ($P<0.05$) lower in patients (MEP amplitude $=108.975+1.710 \times$ force level) compared with healthy volunteers (MEP amplitude $=159.726+2.692 \times$ force level).

In both groups we did not find a significant effect of the task on the MEP amplitude. Significant differences between the tasks were only detected in patients between pinch and power grip, in which the power grip resulted in the smallest amount of facilitation ($P=0.004$).

**Discussion**

The present study was designed to evaluate the effect of voluntary hand activities on the ipsilateral motor cortex in healthy volunteers and in stroke patients, particularly considering the possibility of transcallosal inhibition.

In accordance with earlier studies with healthy subjects, we revealed exclusively facilitatory effects in healthy subjects and in patients irrespective of the force level and the motor task. Generating low forces at 1% or 2% MVC during phasic pinch grip, an inhibition of the nontask hand had been described by Liepert et al. Because most of the patients in our study were not able to generate and hold such a low force continuously, we decided to start with a force of 5% of maximal voluntary sEMG. Furthermore, in a context of functional motor rehabilitation, forces of 1% or 2% MVC appear to be of minor relevance.

The increase of MEP amplitudes of the nontask hand during voluntary activation of the ipsilateral hemisphere was lower in stroke patients than in healthy volunteers. Furthermore, regression analysis and the comparison between the regression lines showed a slope that was less steep in patients. Therefore, the facilitatory effect was not only reduced on the whole, but also per force level produced by the nonaffected hand. Thus, the general activation level of the impaired motor system and the bandwidth of possible activation levels are diminished.

The largest MEPs were elicited while activating the target muscle between 2% and 6% of maximal sEMG. Beyond these levels, no further significant changes were observed. Our study, however, showed an increase even between 50% and 100% of maximal sEMG of the homologues nontarget muscle in both groups and in all tasks. Stinear et al also found a larger MEP during activation of the nontarget muscle (abductor pollicis brevis) with 100% than with 62.5% MVC. This could be interpreted as a more continuous modulatory effect on the contralateral motor cortex by the active motor cortex.

Whether the ipsilateral facilitation is mediated at a spinal or supraspinal level is still a matter of debate. The present study has not been primarily designed to answer this question. Nevertheless, F-wave amplitude is regarded as a measure of excitability of the spinal motoneurone pool. The fact that the F-wave amplitudes were not modulated by contraction of homologues contralateral muscles makes it doubtful that facilitation takes place at the spinal level.

Even though data are conflicting, facilitatory effects on the task hand and on the nontask hand seemed to be task-dependent. Only in patients did we find differences between various tasks, and we observed a lower facilitatory effect of the power grip compared with the pinch grip in patients, also. This is in accordance with the results of Hasegawa et al, who found a stronger facilitation of the task hand in healthy volunteers while performing a precision grip compared with a power grip. In healthy subjects, Ziemann and Hallett demonstrated a stronger facilitation of the nontask hand during complex finger movements (finger tapping sequence) by the task hand compared with simple movements. The fact that in our study this effect was limited to patients could be a statistical rather than a real physiological phenomenon.

In terms of neurological rehabilitation, the principal message of the present study is that during occupational or physiotherapy using simple and complex movements by the unaffected hand to compensate for the functional loss of the affected hand, do not exert an inhibitory impact on the excitability of the motor cortex of the affected side. This is in accordance with studies in chronic stroke patients showing a functional improvement of the upper extremity after bilateral arm training. Nevertheless, it must be kept in mind that the strongest facilitation occurs during voluntary activation of the impaired motor system and that, particularly in the presence of extinction and/or neglect phenomena, occupational and physiotherapy have to eagerly focus on the affected extremity.
References


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