Optical illusion alters M1 excitability after mirror therapy: a TMS study

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Läppchen CH, Ringer T, Blessin J, Seidel G, Grieshammer S, Lange R, Hamzei F. Optical illusion alters M1 excitability after mirror therapy: a TMS study. J Neurophysiol 108: 2857–2861, 2012. First published September 12, 2012; doi:10.1152/jn.00321.2012.—The contralateral primary motor cortex (M1) has been suggested to be involved in the motor recovery after mirror therapy, but whether the ipsilesional M1 is influenced by the contralateral M1 via transcallosal interhemispheric inhibition (IHI) is still unclear. The present study investigated the change of IHI as well as the intracortical inhibition and intracortical facilitation of both M1 induced by training in a mirror with the use of transcranial magnetic stimulation (TMS). In this 2 × 2 factorial design (time × group), healthy subjects exercised standardized motor skills with their right hand on four consecutive days. Either a mirror (mirror group) or a board (control group) was positioned between their hands. Before and after training TMS was applied along with training tests of both hands. Tests were the same motor skills exercised daily by both groups. Tests of the untrained left hand improved significantly more in the mirror group than in the control group after training (P = 0.02) and showed a close correlation with an increase of intracortical inhibition of M1 left. IHI did not show any difference between investigation time points and groups. The present study confirms the previous suggestion of the involvement of the “contralateral” left-side (ipsilateral to the hand behind the mirror) M1 after mirror therapy, which is not mediated by IHI. Even with the same motor skill training (both groups performed same motor skills) but with different visual information, different networks are involved in training-induced plasticity.

stroke rehabilitation; mirror therapy; transcranial magnetic stimulation; excitability; optical illusion; visual feedback

DURING RECENT YEARS mirror therapy (MT) has been used increasingly in stroke patients (Dohle et al. 2009; Yavuzer et al. 2008). A mirror is positioned orthogonally in front of the patient, who performs motor exercises with the unaffected arm. While patients observe the unaffected arm in the mirror, the illusion is created that the affected limb is being moved.

Ramachandran and colleagues first described the use of a mirror in arm amputees for phantom pain reduction (Ramachandran and Altschuler 2009; Ramachandran et al. 1995) and then suggested the benefit of MT in hand recovery after stroke (Altschuler et al. 1999).

Ramachandran and Altschuler supposed that the ipsilateral (contralateral) corticospinal tracts from the primary motor cortex (M1) play a role in the recovery process after MT (Ramachandran and Altschuler 2009). Recently, the benefit of involvement of the ipsilateral projections from M1 to muscles has been described in motor recovery after stroke (Schwerin et al. 2008). However, a recent functional MRI (fMRI) study in chronic stroke patients demonstrated an activation shift toward the ipsilesional M1 after MT, in contrast to a control group (Michielsen et al. 2011). The shift of activation from one M1 to the other might be based on the restoration of an altered interhemispheric inhibition (IHI) between both M1 (Murase et al. 2004). Balance between both M1 can be affected after stroke, and its remodulation improves paretic hand function (Nowak et al. 2009). Therefore, whether MT has influence on the IHI between both M1 is of interest.

We were interested in the “training-induced plasticity” of training with a mirror rather than the direct effect of observing one’s hand in the mirror, as was investigated with the use of fMRI (Fink et al. 1999; Matthys et al. 2009) or transcranial magnetic stimulation (TMS) (Fukumura et al. 2007; Funase et al. 2007; Garry et al. 2005). Therefore, in this 2 × 2 factorial design with the factors time (before and after a training procedure) and group (mirror and control groups) TMS was used to evaluate IHI between both M1 (Läppchen et al. 2011). Furthermore, the resting motor threshold (RMT), intracortical inhibition (ICI), and intracortical facilitation (ICF) before and after training in both groups were investigated. This study was performed in healthy subjects to provide evidence in a healthy network before investigating stroke patients.

METHODS

Subjects

The study group consisted of 24 healthy subjects (mean age 24.1 yr). Twelve women and twelve men were divided into two groups. One group trained with their dominant right hand in a mirror (the “mirror group,” MG), and the control group (CG) trained the same motor skills with their dominant right hand, but a board instead of a mirror was positioned between the hands. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971). Four subjects (2 in each group) had to be excluded because they did not complete the tests.

The exclusion criteria were pregnancy, cardiac pacemaker, ferromagnetic intracranial pieces, inner ear prosthesis, hearing aid, epilepsy, depression, head trauma, stroke, or other affliction of the central nervous system. The study was approved by the ethics committee of the university hospital, and all subjects gave their written informed consent.

Training Procedure

Subjects in both groups trained with 20-min standardized exercises daily with their right hand over 4 days. They practiced five training skills each lasting 2 min (moving marbles with a spoon; putting a stick in a hole like the nine-hole peg test; sorting of spillikins; putting elastic bands over a glass; and moving playing cards from a pre-
defined position). These skills were repeated after a break of 3 min. Training skills were standardized by definition of their procedures. Subjects were encouraged to execute quickly and to stay focused on the task while an instructor sat beside them. The MG practiced the training skills with a mirror positioned orthogonally in front of the subjects, and they continually looked in the mirror. A board of the same dimension was positioned in place of the mirror in the CG (see Fig. 1). During training, both the MG and the CG could not see their untrained left hand; they did not move their left hand while training with their right hand. Both hands were tested before training started (baseline), after daily training sessions, and after the 4-day training period (post) (these tests were termed “test”). The same skills used during the training session were tested (tests lasted 10 min and included 5 trained skills for 2 min each). For the tests, the mirror in the MG and the board in the CG were removed. The five trained tasks were tested. The number of successful trials was counted for each skill during the 2-min testing period, e.g., the number of marbles moved from one bowl to another. The number of successful trials for each of the five skills was averaged for each day and for each hand.

TMS

TMS was performed before training started (baseline) and after the training session (post), always in late afternoon. Subjects sat on a comfortable chair with their heads fixed with a universal framework, a head band, and a chin forehead rest, allowing only minimal movements (http://www.localite.de). Eyes were open and fixed on a small black cross on a white board. The hands rested on a pillow on their knees. Complete relaxation of both first dorsal interosseus muscles (FDI) was perceived by audio feedback and visual inspection of electromyography (EMG) sweeps. Magnetic stimuli were delivered with a MagVenture MagPro X100 stimulator discharging via a figure eight-shaped slightly bended coil (MagVenture MC-B70; for specifications see http://www.magventure.com) placed over the scalp overlaying the motor cortex approximately 7 cm lateral to the vertex. For evaluation of IHI, two Magstim figure eight-shaped flat coils (outer diameter 95 mm) and two Magstim 200 Monopulse stimulators were used (Magstim). Coils were positioned at an angle of 45° from the midline with the handles pointing backward and laterally and adjusted to the hot spot where the largest compound motor evoked potential (MEP) could be evoked constantly in the contralateral muscle interosseus dorsalis I (FDI) (Rossini et al. 1994; Werhahn et al. 1994). Recordings were obtained with silver surface electrodes fixed over FDI in a tendon belly arrangement of both hands. The raw EMG signal was filtered (high-cut filter of 8 kHz and low-cut filter of 10 Hz), amplified, converted via a CED micro 1401 laboratory interface (Cambridge Electronic Design, Cambridge, UK), electronically stored, and evaluated off-line (Signal software, version 3.07). Parameters analyzed were RMT, ICI with an interstimulus interval (ISI) of 2 and 3 ms, ICF with an ISI of 10 and 15 ms, and IHI with an ISI of 8 ms. RMT was defined as the intensity at which at least 50% of 10 stimulations evoked MEP amplitudes of >50 μV and was determined by stepwise decreasing stimulator output by 1% for both sides independently. Paired pulse stimuli for ICI and ICF at ISI of 2, 3, 10, and 15 ms were applied at rest in a randomized order of 58 test stimuli (2, 3, 10, 15 ms 10 times each, single test pulse 18 times). The conditioning stimulus had an intensity of 80% of RMT; the test stimulus had an intensity of 120% of RMT of the related side. Paired magnetic stimuli for IHI with ISI of 8 ms were applied at rest in a randomized order of 20 test stimuli. For IHI, new RMT were determined. The conditioning and test stimulus intensity were 120% of RMT of the related side. At baseline and post, RMT were separately measured. Data evaluation was performed off-line. Data of paired-pulse stimulation were evaluated regarding changes in normalized MEP amplitudes. The ICI values were calculated as the mean values for ISI of 2 and 3 ms, and the ICF values were evaluated as the mean values for ISI of 10 and 15 ms. Data are given as means and SD. Statistical evaluation was performed with the two-sided t-test for paired probes for sets of data acquired before and after training. Intergroup effects were tested with two-sided t-test of the post values in relation to baseline (post/baseline MG value vs. post/baseline CG value). Differences were regarded as significant when P < 0.05, corrected for multiple comparisons (Bonferroni correction).

RESULTS

Tests

MG subjects showed a significant improvement of tests of the trained right hand (paired t-test; P < 0.001) and of the untrained left hand (P < 0.001) (Fig. 1).

CG subjects also showed a significant improvement of tests of the trained right hand (P < 0.001) and of the untrained left hand (P < 0.001) (Fig. 1).

There were no differences between groups concerning the trained right hand. The left hand test results improved significantly more in MG than in CG (P < 0.02) (Fig. 1).

The average training performance of five skills was retrospectively analyzed between MG and CG (Student t-test; P < 0.05). There was no difference between the groups regarding daily training. This excludes the argument that the superior test effect of MG could be based on less training of CG.

TMS Data

For normalized MEPs see Table 1.

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Fig. 1. The mirror group (MG) and the control group (CG) exercised standardized motor skills with their right dominant hand for 20 min daily over 4 days. Either a mirror (MG) or a board (CG) was positioned orthogonally in front of them. Both hands were tested (“tests”) before (“baseline”) and after (“post”) the training procedure and at the end of each training day (d). A and B: test results of the trained right (A) and untrained left (B) hand. Test results in MG and in CG improved significantly from baseline to post. While for the test results of the trained right hand there was no significant difference between groups, test results of the untrained left hand showed a significantly greater improvement in MG compared with CG (P < 0.02).
Table 1. MEPs of RMT and normalized MEPs of ICI, ICF, and IHI at different time points in MG and CG

<table>
<thead>
<tr>
<th></th>
<th>M1_left</th>
<th>M1_right</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Post</td>
</tr>
<tr>
<td>RMT MG</td>
<td>45 ± 5</td>
<td>44 ± 4</td>
</tr>
<tr>
<td>RMT CG</td>
<td>47 ± 7</td>
<td>46 ± 8</td>
</tr>
<tr>
<td>ICI MG</td>
<td>0.36 ± 0.16</td>
<td>0.26 ± 0.12</td>
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<tr>
<td>ICI CG</td>
<td>0.34 ± 0.19</td>
<td>0.40 ± 0.19</td>
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<tr>
<td>ICF MG</td>
<td>1.35 ± 0.29</td>
<td>1.29 ± 0.36</td>
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<tr>
<td>ICF CG</td>
<td>1.43 ± 0.46</td>
<td>1.82 ± 0.50</td>
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<tr>
<td>IHI MG</td>
<td>0.91 ± 0.16</td>
<td>0.95 ± 0.25</td>
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<tr>
<td>IHI CG</td>
<td>0.98 ± 0.12</td>
<td>0.99 ± 0.28</td>
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Values (in μV) are means ± SD. MEP, motor evoked potential; RMT, resting motor threshold; ICI, intracortical inhibition; ICF, intracortical facilitation; IHI, interhemispheric inhibition; M1, primary motor cortex; baseline, before starting training; post, after training period; MG, mirror group; CG, control group.

RMT. For MG, RMT M1left was significantly lower at post than before (P = 0.04).

For CG, RMT on M1 left was significantly lower at post (P = 0.02).

Between MG and CG there were no differences, either in M1left or in M1right.

ICI and ICF. For MG, ICI of M1left at post was stronger than at baseline (P = 0.01); ICF of M1right was significantly lower than at baseline (P = 0.04) (Fig. 2).

For CG, ICF of M1left was significantly stronger at post than at baseline (P = 0.02) (Fig. 2).

Between MG and CG an intergroup difference of ICI changes in M1left was evident (post/baseline MG = 0.75 vs. post/baseline CG = 1.21; P = 0.03). There were no other differences either in M1left or in M1right.

IHI. No significant changes in IHI between groups and hemispheres were evident.

Correlation Between Test of Untrained Left Hand with RMT, ICI, ICF, and IHI

The change of MG’s test results of the left untrained hand at time point post (as percentage of baseline) was correlated with percent change of normalized MEP of RMT, ICI, ICF, and IHI (post in relation to baseline). Only the ICI change of M1left showed a close correlation with the improvement of test of the untrained left hand (Pearson correlation coefficient r = 0.6, P < 0.001).

DISCUSSION

In the present study the IHI by conditioning stimulus of one M1 and test stimulus of the other M1 did not change over the mirror training time. However, both groups showed a training-induced excitability change, in different directions. In CG the excitability of M1left increased, while in MG the excitability decreased (for more clarification, contralesional or M1left is ipsilateral to the untrained hand behind the mirror/board). For M1right, the excitability did not change in CG, while in MG a disinhibition was evident (see Fig. 3). Considering the course of test results, MG demonstrated more increase compared with CG with the test results of day 2. At post, CG demonstrated a decrease of test results of the untrained left hand, while MG test results further increased. There was no training session between day 4 and post; therefore an increase of test results in MG compared with CG for the untrained left hand could be based on the influence of different underlying plasticity. Alternatively, a lower motivation could be assumed in CG, but the test results of the trained right hand were comparable between CG and MG. Furthermore, the change of MG’s test results of the untrained left hand at time point post was closely correlated with the ICI change of M1left.

Information on M1left from recent TMS studies is lacking. Previous TMS studies investigated the excitability of M1right (Fukumura et al. 2007; Funase et al. 2007; Garry et al. 2005). They found an increase of excitability of M1right by an amplitude increase of MEP, which is in accordance with our findings. Furthermore, we extend previous findings. The reported excitability increase within M1right is mediated through a decrease of ICI. The contrasting excitability changes of both groups support the suggestion of the involvement of different networks even when the same motor skills were trained but with different visual information. For example, an additional

Fig. 2. Evaluation of the intracortical inhibition (ICI) and the intracortical facilitation before (baseline) and after (post) training procedure in MG and CG. A: the normalized motor evoked potential (MEP) of ICI of M1left in MG was significantly reduced at post (P = 0.01). Consequently, at post the ICI of M1left was stronger in MG; thus a decrease of excitability of M1left appeared in MG. B: the M1right ICI showed a significant increase of the normalized MEP after training in MG (P = 0.04). Consequently, a disinhibition appeared over the M1right in MG. C: the intracortical facilitation (ICF) of M1left in CG demonstrated a significant increase of the normalized MEP at post (P = 0.02). Therefore, M1left showed an increase of facilitation in CG. Bars indicate standard deviation. Asterisks indicate significance.
observation of motor training in association with physical practice has been shown to increase excitability of M1 in young (Stefan et al. 2005, 2008) and old (Celnik et al. 2006) healthy volunteers. The formation of motor memory in M1 as the effect of additional observation of hand movement could be based on the involvement of the action observation network (Stefan et al. 2005, 2008). In MT the affected hand is also immobilized while patients are observing the movement of the unaffected hand in the mirror. In light of previous findings (Celnik et al. 2006; Stefan et al. 2005, 2008), we suggest that different excitability changes of M1 between MG and CG are also mediated by the action observation network. A recent fMRI study in healthy subjects provided evidence for different network involvement in MG and CG. Both lateral premotor cortices showed an increased functional interaction with the supplementary motor area (SMA), which in turn showed an increased functional coupling with the left primary sensorimotor cortex (SMC) (ipsilateral to hand behind the mirror; the untrained left hand) (Hamzei et al. 2012). The close correlation between test results of the untrained left hand in the present study with excitability decrease of M1<sub>left</sub> supports the suggestion of the involvement of the left (contralesional) SMC in MT in stroke patients (Ramachandran and Altschuler 2009), as has been shown in a recent fMRI study (Hamzei et al. 2012). However, they found that the network involved in training-induced plasticity of MT goes beyond the action observation network (Hamzei et al. 2012).

The role of the ipsi- and contralesional SMC in the motor recovery after stroke is controversial. The motor training of the affected hand induced plasticity changes within the ipsilesional SMC (Hamzei et al. 2006, 2008), which can be forced by local repetitive TMS in a certain patient group (Ameli et al. 2009). While Ramachandran and Altschuler (2009) supposed the involvement of the contralesional SMC in MT, an fMRI activation shift toward ipsilesional M1 after MT (Michielsen et al. 2011) might be caused by a change of an interplay between both M1 after MT. The fMRI activation shift toward affected (ipsilesional) SMC after 6-wk home-based MT was contrasted to a smaller activation shift of a control group (Michielsen et al. 2011). A lower activation shift of the control group might be based on an increase of unaffected SMC activation as a consequence of bimanual therapy. Furthermore, the recent fMRI study (Michielsen et al. 2011) did not consider that along with hand function improvement after MT the use of active hand movement in fMRI (which is compared to baseline investigation) needs to be constant in both performance and effort through the following scanning periods (Ward et al. 2003) to allow distinction between activation changes induced by neuroplasticity and those induced by accelerated hand movement. However, translation of the present findings obtained in young healthy subjects into elderly stroke patients must be done with caution, because age-related functional changes have been described previously (Ward et al. 2003, 2008). Additionally, a reduced intracortical paired-pulse inhibition has been found in an elder population (Peinemann et al. 2001); therefore training effects could be different in studies investigating different age populations. However, increased ICI in M1<sub>left</sub> after MT is a promising explanatory model for the recovery process of stroke patients, because a disinhibition of the (contralesional) left M1 was described after stroke that affected hand paresis (Shimizu et al. 2002). Furthermore, inducing an inhibition of the left (contralesional) M1 by low-frequency repetitive TMS improves hand function (Nowak et al. 2008) explained by an altered balance between the contra- and ipsilesional M1 after stroke (Nowak et al. 2009).

In summary, a goal-directed movement is based on the integration of sensory information into a motor format. Different excitability changes within M1 were evident even with the same motor training procedure but with different visual feedback. This supports the involvement of different networks in relation to visual information leading to the functional coupling of both hands in one M1 ipsilateral to the hand behind the mirror.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


Fig. 3. A schema of ICI and ICF changes after training in MG and CG. With the same motor skill training procedure the ICI and ICF changed in different ways. This could be the consequence of different visual information in MG in contrast to CG (view from above; left side = left).


