Optical Illusion alters M1 Excitability after Mirror Therapy – a TMS Study

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Abbreviated title for the running head: Optical Illusion alters M1 Excitability after MT

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Summary

Introduction: The contralesional 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 contralesional M1 via the transcallosal interhemispheric inhibition (IHI) is still unclear. The present study investigated the change of IHI as well as the intracortical inhibition and the intracortical facilitation of both M1 induced by training in a mirror with the use of the transcranial magnetic stimulation (TMS).

Methods: In this 2x2 factorial design (time x 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 both hands. Before and after training the TMS was applied along with training tests of both hands. Tests were the same motor skills daily exercised by both groups.

Results: Test 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 both investigation time points and groups.

Conclusion: The current study confirms previous suggestion of the involvement of the “contralesional”-left-sided (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.

Keywords: stroke rehabilitation, mirror therapy, TMS, excitability, optical illusion, visual feedback
**Introduction**

During the last years the Mirror Therapy (MT) is increasingly used in stroke patients (4) (31). 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 arises the affected limb is being moved.

Ramachandran and colleagues first described the use of a mirror in arm amputees for phantom pain reduction (21) (20) and then suggested the benefit of MT in hand recovery after stroke (1).

Ramachandran and Altschuler supposed that the ipsilateral-(contralesional) corticospinal tracts from the primary motor cortex (M1) play a role in the recovery process after MT (20). Recently, the benefit involvement of the ipsilateral projections from M1 to muscles has been described in motor recovery after stroke (23). But, 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 (14). The shift of activation from one M1 to the other M1 might be based by the restoration of an altered interhemispheric inhibition (IHI) between both M1 (15). A balance between both M1 can be affected after stroke and its re-modulation improves paretic hand function (16). Therefore, it is of interest whether MT has influence on the IHI between both M1.

We were interested in the "training-induced plasticity" by 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 (5) (13) or transcranial magnetic stimulation (TMS) (6) (7) (8). Therefore, in this 2x2 factorial design with the factors time (before and after a training procedure) and group (mirror-group and control-group) TMS was used to evaluate IHI between both M1 (12). Furthermore the resting motor threshold (RMT), the intracortical inhibition (ICI) and the
intracortical facilitation (ICF) before and after the 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 years). 12 females and 12 males were divided in two groups. One group trained with their right dominant hand in a mirror (the "mirror-group", MG) and the control-group (CG) trained the same motor skills with their right dominant hand, but a board instead of a mirror was positioned between both hands. All subjects were right-handed according to the Edinburgh Handedness Inventory (18). Four subjects (two in each group) have 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 affection 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 20 min standardized exercises daily with their right hand over four days. They practiced five training skills each lasting 2 min (moving marbles with a spoon; putting a stick in whole like the Nine-Hole-Peg-Test; sorting of spillikins; putting elastic bands over a glass and moving playing cards from a predefined position). These skills were repeated after a break of 3 min. Training skills were standardized by definition of its procedure. 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
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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 (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 starting training (baseline), after daily training session and after the four day training period (post) (these tests were termed as "test"). The same skills used during the training session were tested (tests lasted 10 min and included five 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 starting training (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 received by audio feedback and visual inspection of electro myography (EMG) sweeps. Magnetic stimuli were delivered using a MagVenture MagPro X100 stimulator discharging via a figure-of-eight-shaped slight bended coil (MagVenture MC-B70, for specifications see: http://www.magventure.com) placed over the scalp overlying the motor cortex about 7 cm lateral to the vertex. For evaluation of interhemispheric inhibition (IHI) two Magstim figure-of-eight-shaped flat coils (outer diameter 95 mm) and two Magstim 200 Monopulse stimulators were used (The Magstim
Company Limited, UK). 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 M. interosseus dorsalis I (FDI) (30) (22). Recordings were obtained using 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 off-line evaluated (Signal® software, version 3.07). Parameters analysed were: the resting motor threshold (RMT), the intracortical inhibition (ICI) with an interstimulus Intervall (ISI) of 2 and 3 ms, the intracortical facilitation (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% out of ten stimulations did evoke MEP amplitudes of more than 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 rest motor threshold (RMT), the test stimulus had an intensity of 120% of the 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% 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. Hereby, the ICI values were calculated as the mean values of ISI 2 and 3 ms and the ICF values were evaluated as the mean values of ISI 10 and 15 ms. Data are given as mean and standard deviation. Statistical evaluation was performed using the
two-sided t-test for paired probes for sets of data acquired before and after training. Intergroup effects were tested with the two-sided t-test of the post values in relation to baseline (post/baseline MG value vs. post/baseline CG value). Differences were regarded 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).

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).

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

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 both groups regarding daily training. This excludes the argumentation that the superior test effect of MG could be based on less training of CG.

Figure 1 insert here

TMS data (for normalized MEPs see table 1)

RMT

MG: RMT $M1_{\text{left}}$ was at time point post significantly lower than before (p = 0.04).

CG: Post RMT on $M1_{\text{left}}$ was significantly lower (p = 0.02).

Between MG and CG there were no differences, neither in $M1_{\text{left}}$ nor in $M1_{\text{right}}$.

ICI and ICF
MG: ICI of M1_{left} at post was stronger than at baseline (p = 0.01). ICI of M1_{right} was significantly lower than at baseline (p = 0.04).

CG: The ICF of M1_{left} was significantly stronger at post than at baseline (p = 0.02).

Between MG and CG an intergroup difference of ICI changes in M1_{left} was evident (post/baseline MG = 0.75 vs. post/baseline CG = 1.21; p = 0.03). There were no other differences either in M1_{left} nor in M1_{right}.

IHI

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

Insert Figure 2 and 3 and Table 1 here

Correlation between test of the untrained left hand with RMT, ICI, ICF and IHI

The change of MG's tests results of the left untrained hand at time point post (as percentage to 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 M1_{left} 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 current study the interhemispheric inhibition (IHI) by conditioning stimulus of one M1 and test stimulus of other M1 did not change over the mirror training time. But, both groups showed a training induced excitability change in different direction. In CG the excitability of M1_{left} increased, while in MG the excitability decreased (for more clarification contralesional or M1_{left} is ipsilateral to the untrained hand behind the mirror/board). For the M1_{right} the excitability did not change in CG while in MG a disinhibition was evident (see Figure 3). Considering the course of test results, MG demonstrated more increase in comparison to CG.
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with the test results of d2. 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 d4 and post, therefore an increase of test results in MG in comparison to CG for the untrained left hand could be based on the influence of different underlying plasticity, alternatively a less motivation could be assumed in CG, but the test results of the trained right hand was comparable between CG and MG. Furthermore, the change of MG's tests results of the untrained left hand at time point post was close correlated with ICI change of M1_left.

Information of M1_left from recent TMS studies are lacking. Previous TMS studies investigated the excitability of M1_right (6) (7) (8). They found an increase of excitability of M1_right by an amplitude increase of MEP which is in accordance to our finding. Furthermore, we extent previous findings. The reported excitability increase within M1_right 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 observation of motor training in association with physical practice has been shown to increase excitability of M1 in young (25-26) and old healthy volunteers (3). The formation of motor memory in M1 as the effect of additional observation of hand movement could be based on the involvement of action observation network (25-26). In MT the affected hand is also immobilized while patients are observing the movement of the unaffected hand in the mirror. According to previous findings (25-26) (3) 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 MT and CG. Both lateral premotor cortex showed an increased functional interaction with the supplementary motor area (SMA), which in turn showed an increased functional coupling with the SMC_left (ipsilateral to hand
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behind the mirror; the untrained left hand) (10). The close correlation between test results of
the untrained left hand in the current study with excitability decrease of the M1\textsubscript{left} supports the
suggestion of the involvement of the left (contralesional) SMC in MT in stroke patients (20),
as has been shown in a recent fMRI study (10). But, they found that the network involved in
training induced plasticity of MT goes beyond the action observation network (10).

The role of the ipsi- and contralesional primary sensorimotor cortex (SMC) in the motor
recovery after stroke is controversially discussed. The motor training of the affected hand
induced plasticity changes within the ipsilesional SMC (9, 11), which can be forced by local
repetitive TMS in a certain patient group (2). While Ramachandran and Altschuler supposed
the involvement of the contralesional SMC in MT (20), an fMRI activation shift toward
ipsilesional M1 after MT (14) might be caused by a change of an interplay between both M1
after MT. The fMRI activation shift toward affected (ipsilesional) SMC after six weeks home-
based MT was contrasted to a smaller activation shift of a control-group (14). A less
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 (14) 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 (27) to allow distinction
between activation changes induced by neuroplasticity and those induced by accelerated hand
movement. However, the translation of the current findings obtained in young healthy
subjects into elderly stroke patients must be done with caution, because age related functional
changes have previously been described (28) (29). Additionally, a reduced intracortical
paired-pulse inhibition has been found in elder population (19), therefore training effects
could be different in studies investigating different age population. But increased ICI in M1\textsubscript{left}
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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 which affected the hand paresis (24). Furthermore inducing an inhibition of the left (contralesional) M1 by low frequency repetitive TMS improves hand function (17) explained by an altered balance between the contra- and ipsilesional M1 after stroke (16).

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.
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References


Figure legends

Figure 1
The mirror-group (MG) and the control-group (CG) exercised standardized motor skills with their right dominant hand 20min daily over four 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.

a) Tests results of the trained right and b) untrained left 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 significant greater improvement in MG in comparison to CG (p < 0.02).

Figure 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 MEP of ICI of M1_left in MG was post significantly reduced (p = 0.01). Consequently, at post the ICI of M1_left is stronger in MG, thus a decrease of excitability of M1_left appeared in MG.

b) The M1_right ICI showed a significant increase of the normalized MEP after training in MG (p = 0.04). Consequently, a disinhibition appeared over the M1_right in MG.

c) The intracortical facilitation of M1_left in CG demonstrated a significant increase of the normalized MEP at time point post (p = 0.02). Therefore, M1_left showed an increase of facilitation in CG. Bars indicate standard deviation, asterisk indicates significance.
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 way. This could be the consequence of different visual information in MG in contrast to CG (View from above; left side = left).
Figure 1

Mirror-Group (MG)  Control-Group (CG)

(a) Trained right hand

(b) Untrained left hand
Figure 2

a. Intracortical inhibition left M1 MG

b. Intracortical inhibition right M1 MG

c. Intracortical facilitation left M1 CG
Figure 3

<table>
<thead>
<tr>
<th>Mirror-Group (MG)</th>
<th>Control-Group (CG)</th>
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<tbody>
<tr>
<td>ICI</td>
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<td>ICF</td>
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ICI left

M1_left

M1_right
Table 1: MEPs (in µV) of RMT and normalized MEPs of ICI, ICF and IHI at different time points (baseline, post) in MG (mirror-group) and CG (control-group).

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<th>M1&lt;sub&gt;right&lt;/sub&gt;</th>
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