# Original Article
# Mirror therapy versus action observation therapy: effects on excitability of the cerebral cortex in patients after strokes

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Abstract: As rehabilitation therapies based on the mirror neuron theory, both mirror therapy and action observation therapy can activate the mirror neuron system. Activation is critical for the recovery of limb function in patients with strokes. However, it is unclear if any differences exist between the two interventions concerning cortical excitability in humans. The current study aimed to compare the effects of the two interventions on motor cortical excitability in patients with strokes via transcranial magnetic stimulation (TMS). Twenty-one ischemic stroke patients completed four experimental protocols described by the 2×2 cross-over design, including mirror therapy with target [MT (+)], mirror therapy without target [MT (-)], action observation therapy with target [AT (+)], and action observation therapy without target [AT (-)]. Each experiment included 4 modules, in which TMS was employed to stimulate the M1 area of the contralateral cerebral cortex. Amplitude and latency levels of abductor pollicis brevis muscles were measured before the first module (B0) and after each module (B1-B4), respectively. Only the MT (+) group had significantly increased amplitude ($P<0.05$). No significant changes in latency were found between the 4 groups (all $P>0.05$). Amplitude in the MT (+) group was elevated gradually, along with the extension of intervention times. The B4 value approached 1.8-fold of the B0 base value ($P<0.05$). In conclusion, it was found that mirror therapy with targets is more likely to increase the excitability of the M1 area of the cerebral cortex, compared with mirror therapy without targets and action observation therapy, in patients with strokes. This excitability increases significantly when there is an extension of intervention times.

Keywords: Mirror neuron, cerebral cortex, transcranial magnetic stimulation, abductor pollicis brevis muscle

## Introduction

A special type of neurons, mirror neurons are excited not only when an individual performs specific actions, but also when an individual observes the same or similar actions from others of the same kind [1]. Mirror neurons that spread in different brain areas form a mirror neuron system [2-4]. This system acts following an "observation and execution matching mechanism" [5]. This can unify action, perception and execution. Accumulating evidence has indicated that the "observation and execution matching mechanism" plays an important role in action understanding, action imitation, motor imagery and motor learning, as well as other

crucial neurophysiological processes [6-9]. These processes happen to be an important theoretical basis of action observation therapy and mirror therapy in the neurorehabilitation field [10, 11].

Proposed by Ramachandran et al. in 1995, mirror therapy is also known as mirror visual feedback (MVF) or plane mirror therapy [12]. It was originally applied to treat phantom limb pain. It is now used in patients with post-stroke dyskinesia [13]. In mirror treatment, patients move the affected side limb, improving motor function by observing the imaging of uninjured limbs formed in the mirror. Mirror therapy integrates action observation, motor imagery, imita-

**Table 1.** Participant characteristics. All non-categorical values are presented as mean ± inter-subject standard deviation

| Characteristics | Value (s) |
|---|---|
| Gender | 12 F/9 M |
| Paretic leg | 21 L |
| Age (yrs) | 52.4 ± 10 |
| Time since stroke (mos) | 3.6 ± 0.2 |
| Height (cm) | 168.2 ± 12 |
| Mass (kg) | 62.2 ± 14 |
| Brunnstrom stage | 15 IV/6 V |
| Classification of Stroke | 10 cerebral infarction/11 cerebral hemorrhage |

tion learning, and other processes to promote the recovery of motor function [14, 15]. Mirror therapy has been found to significantly improve hand function, Brunnstrom's staging, and functional independence measure (FIM) scores in patients [16, 17]. Other independent studies have confirmed its curative effects [18-20].

Action observation therapy requires patients to observe action processes carefully, trying their best to imitate it. The action process includes video clips of action, movements of uninjured side limbs, or demonstrations from a therapist. Observed content could be simple physical exercise or complex daily life activities, which varies from person to person in ways and content. It is helpful for early intervention of rehabilitation training when the therapy is used in patients with acute stages of brain injuries. It is also helpful in improving curative effects, as well as reducing fatigue, when used in the recovery period [21]. Action observation therapy integrates action observation, imitation learning, and other processes to achieve therapeutic effects [11, 22]. Ertelt et al. applied this therapy in patients with chronic cerebral infarction for the first time. It was found that upper limb function of patients was significantly improved [23]. Buccino G et al. further confirmed the effects of Action Observation Therapy in subsequent experiments [10].

Mirror therapy and action observation therapy have evidently beneficial effects on limb function recovery in patients with strokes. They have been widely used for the recovery of hemiplegic upper limb function in clinical settings. While mirror therapy requires more motor imagery, action observation therapy requires more imitation learning. At the nerve mechanism level, both therapies promote plasticity chang-

es and functional reorganization in the brain through activating the mirror neuron system to promote the recovery of motor function. However, it remains unclear whether these two interventions differ in the ability to excite the M1 area of the contralateral cerebral cortex in humans. Hence, the current study aimed to compare the effects of these interventions on motor cortical excitability in patients with strokes receiving transcranial magnetic stimulation (TMS).

## Material and methods

### Study subjects

Twenty-one ischemic stroke patients were selected to participate in this experiment, with general characteristics listed in **Table 1**. All subjects were dextro-manual, as confirmed by Edinburgh questionnaires [24]. All participants met the criteria for inclusion and exclusion of TMS [25]. Each subject completed four experimental protocols described by the 2×2 crossover design, including mirror therapy with target [MT (+)], mirror therapy without target [MT (-)], action observation therapy with target [AT (+)], and action observation therapy without target [AT (-)] (**Figure 1A**). The interval between the two experiments was about 1 hour, which allowed for full relaxation of the participants. Written informed consent was obtained from all participants. All experiments involving human subjects were approved by the Ethics Committee of the Affiliated Hospital of Qingdao University.

### Mirror therapy (MT)

Participants sat on the chair in front of the table with feet separated to shoulder width. Hip joints, knee joints, and ankle joints flexed to 90 degree. A 30 cm * 30 cm mirror facing the right upper limb was put on the table in parallel to the midline of the participant, as previously described [17]. The participants were asked to use the right hand to grasp a 1 cm * 1 cm * 1 cm red square block. They were asked to look in the mirror and imagine that they were grasping the block with the left hand. Each grasp and

drop took about 6 seconds and each module consisted of 20 times of grasp and drop, lasting about 2 minutes. After each module, motor cortical excitability was measured, taking about 1 minute. Subsequently, the next module began and cortical excitability was measured again. The task ended until when all 4 modules were completed. The experiment with participants grasping and dropping a real red square block was referred to mirror therapy with target [MT (+)], while the experiment with the right hands performing only the action of grasping and dropping without targeted objects was referred to mirror therapy without target [MT (-)].

*Action observation therapy (AT)*

Participants sat on the chair in front of the table with feet separated to shoulder width. Hip joints, knee joints, and ankle joints flexed to 90 degree. A computer with a video playing was put on the table. While watching the video, in which a 1 cm * 1 cm * 1 cm red square block was grasped and dropped by left hand, the participants were required to imitate the action with the left hand. Each grasp and drop took about 6 seconds and each module consisted of 20 times of grasping and dropping, lasting about 2 minutes. After each module, motor cortical excitability was measured, which took about 1 minute. Subsequently, the next module began and cortical excitability was measured again. The task ended until when all 4 modules were completed. The experiment with participants watching video of grasping and dropping a real red square block was referred to action observation therapy with target [AT (+)], while the experiment with the participants watching a video of performing only the action of grasping and dropping without targeted objects was referred to action observation therapy without target [AT (-)].

*Measurement and data collection*

YRDCCY transcranial magnetic stimulator (manufactured by Wuhan Yiruide Medical Equipment New Technology Co., Ltd) was adopted for this experiment. The instrument had a maximum magnetic field output intensity of 2.5 T, a stimulation beat generated from one type "8" coil, and one side coil with an inner diameter of 10 mm and outer diameter of 50 mm. These two coils were not on the same surface, but with an angle roughly corresponding to the con-

vex face of the skull. The wire was 1.3 m in length. A Keypoint 4C EMG/evoked potential instrument was adopted as the recording response device, recording electromyography.

Testing was carried out in a quiet and sound insulation environment. The participants sat on an armchair, fully relaxed. A surface electrode was placed on the abductor pollicis brevis muscle of participants and electromyographic activity was recorded. The reference electrode was placed at the muscle tendon and the ground line was connected to the wrist. The coil was placed on right hand representative area, which was near the international 10~20 system C3 point [26] (**Figure 1B**). The TMS coil was put close to the scalp surface of participants, making sure that the intersection point of the two coil magnetic lines could be placed at center of the stimulation point. The handle was vertical to the occipital side of the participants.

Rest motor threshold (RMT) was defined as the minimum magnetic stimulation intensity. The patients maintained a relaxed state and stimulated the marked point of abductor pollicis brevis muscle to produce a motor evoked potential. Under RMT conditions, in every 10 stimuli, 5 of them could produce motor evoked potential with an amplitude >50 µV to abductor pollicis brevis muscle in a resting state [27]. Within 1 minute, amplitude and latency levels of motor evoked potential were recorded 15 times, in total, by stimulating the cortex with 110% RMT with about 4 seconds each time. For each task, measurements were made before the first module (B0) and after each module. Measurement results of 4 continuous modules in each task were denoted as B1, B2, B3, and B4, respectively (**Figure 1C**).

*Statistical analysis*

Data is presented as mean ± standard deviation and was analyzed by SPSS18.0 statistical software package. Effects comparisons between the two interventions were conducted based on analysis of variance of repeated measured data for single samples. First, Mauchly tests were used to test spherical data. Non-spherical data were corrected by Greenhouse-Geisser. When F-values were significant, comparisons between before-and-after indexes of each intervention were paired tested by post-
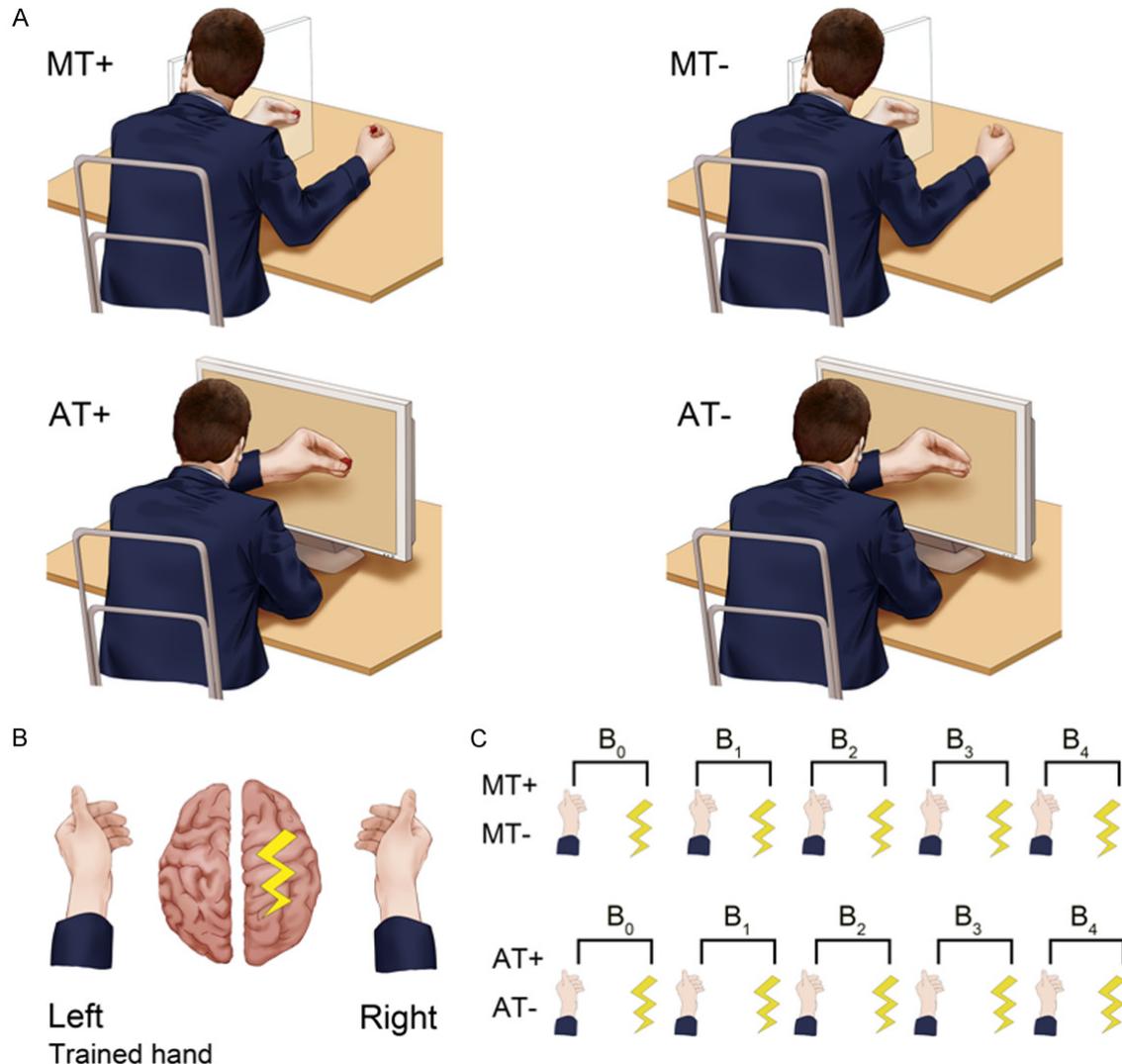
Figure 1. A. Four experimental protocols were used, including mirror therapy with target [MT (+)], mirror therapy without target [MT (-)], action observation therapy with target [AT (+)], and action observation therapy without target [AT (-)]; B. Transcranial magnetic stimulation (TMS) was delivered to the right motor cortex (M1) and motor evoked potential levels (MEPs) were recorded in the trained (left) hand; C. Prior to and following training, participants underwent TMS assessment of corticospinal excitability (CSE). Training was divided into four blocks (B1-4), each followed by TMS assessment.

hoc tests. $P<0.05$ indicates statistical significance.

## Results

*Comparison of amplitude and latency of motor evoked potential in brain M1 area before and after intervention in the 4 groups*

First, this study analyzed the effects of intervention within each single group by comparing amplitude and latency values before (B0) and after therapy (expressed as Bn+, which averaged B1, B2, B3, and B4). No evident statistical differences in basal amplitude and latency levels of the four groups before intervention (B0) were found. A series of interventions induced significant changes in amplitude (Bn+ versus B0, $P<0.05$) only in the MT (+) group, but not in MT (-), AT (+), and AT (-) groups (**Figure 2A**). None of the interventions elicited significant changes in latency of the 4 groups (Bn+ versus B0, all $P>0.05$) (**Figure 2B**).

Next, this study compared the effects of the 4 interventions by focusing only on amplitude and latency values after therapy (Bn+ versus Bn+). As shown in **Figure 2A**, compared to any
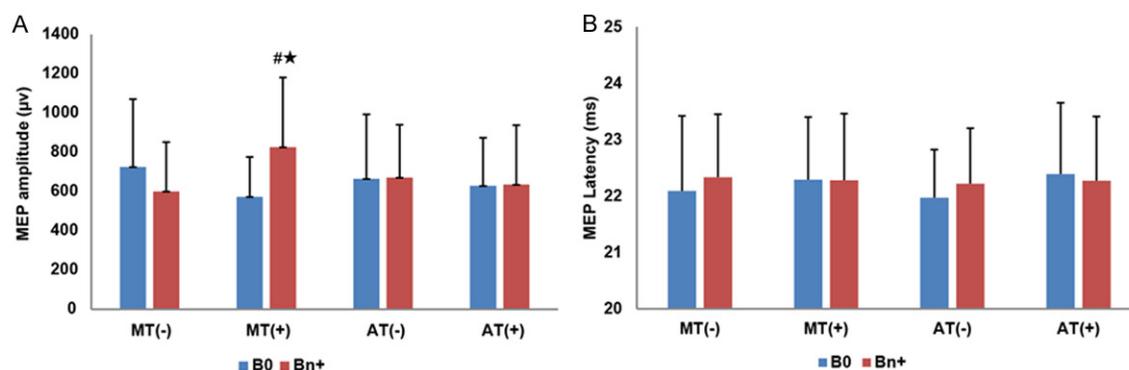
Figure 2. Comparisons of amplitude and latency of motor evoked potential in the brain M1 area before and after intervention. A. Summary of the amplitude values in the 4 groups before (B0) and after intervention (Bn+, which averaged B1, B2, B3, and B4). The MT (+) group had a significantly elevated amplitude after intervention (*P<0.05, Bn+ versus B0). Compared to any of the other 3 groups, The MT (+) group had a significantly elevated amplitude value (#P<0.05, Bn+ versus Bn+), while any other two groups did not show statistically significant changes (all P>0.05); B. Summary of latency values in the 4 groups before (B0) and after intervention. There were no significant changes in latency between any two groups of the four groups before and after intervention (all P>0.05).

of the other 3 groups, the MT (+) group had a significantly elevated amplitude value, while the other two groups did not show statistically significant changes (all *P*>0.05). In terms of latency after intervention, there were no significant changes between any two of the 4 groups (**Figure 2B**).

*Comparison of variation trends for amplitude and latency of motor evoked potential in brain M1 area after intervention in the 4 groups*

As shown in **Figure 3A** and **Table 2**, the amplitude of the MT (+) group gradually increased, along with the extension of intervention times. Notably, the amplitude value at B4 reached to 1.85-fold of the base value (B4 versus B0, *P*<0.05). While the amplitude at B4 in the AT (+) group was slightly higher than that at baseline, the MT (-) group and AT (-) group had slightly decreased amplitude values, compared with baseline. However, these changes were not statistically significant (B4 versus B0, *P*>0.05).

Comparisons between the same modules (after same times of intervention) between different intervention groups showed that the MT (+) group differed from the other groups in amplitude. As shown in **Figure 3B**, the amplitude of the MT (+) group increased significantly in B2, B3, and B4 modules, compared with the MT (-) group (★*P*<0.05). It increased significantly in the B4 module, compared with the AT (-) group (°*P*<0.05) and increased significantly in

B3 and B4 modules, compared with the AT (+) group (°*P*<0.05). No significant differences were found from comparisons between the other groups.

Latency for both the MT (-) group and AT (-) group was slightly prolonged, along with the extension of intervention times. The MT (+) group and AT (+) group had slightly shortened latency after intervention (**Figure 3C**). However, no statistical significance was found in these comparisons (all *P*>0.05).

Discussion

Activation of the mirror neuron system plays an important role in action observation, action imitation, and motor imagery. These three neurophysiological processes have a great influence on motor learning processes. Therefore, the mirror neuron system is also an important neural mechanism of motor learning [2, 4, 28]. Action observation therapy realizes action learning through observation, while mirror therapy involves action observation, motor imagery, imitation learning, and many other processes. This study compared the amplitude and latency of motor evoked potential in the brain M1 area under different modules in four groups, including mirror therapy with target [MT (+)], mirror therapy without target [MT (-)], action observation therapy with target [AT (+)], and action observation therapy without target [AT (-)]. Motor cortical excitability under mirror therapy
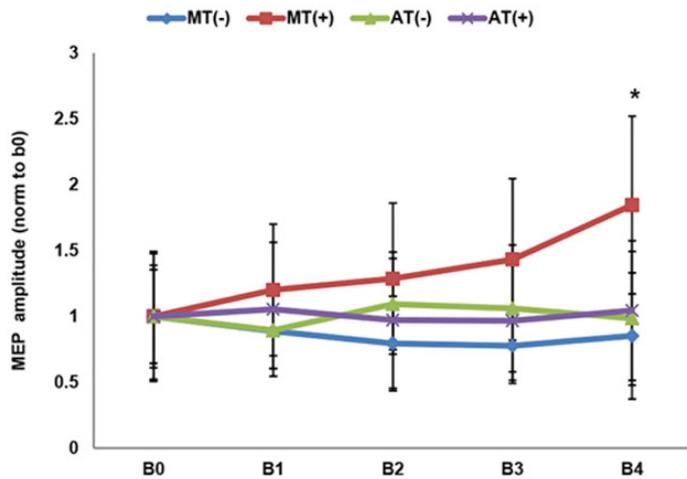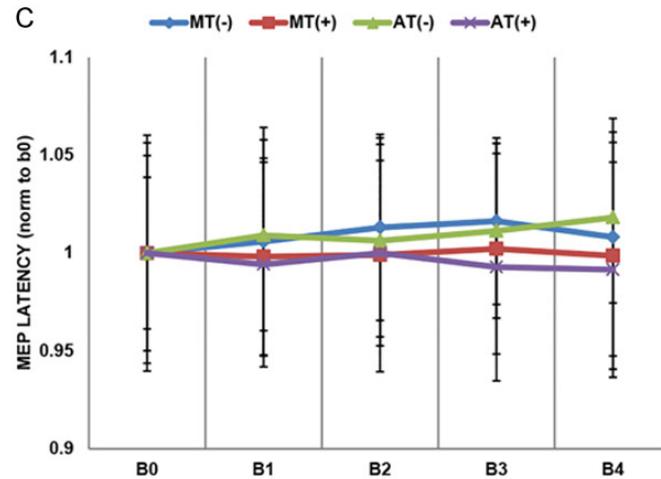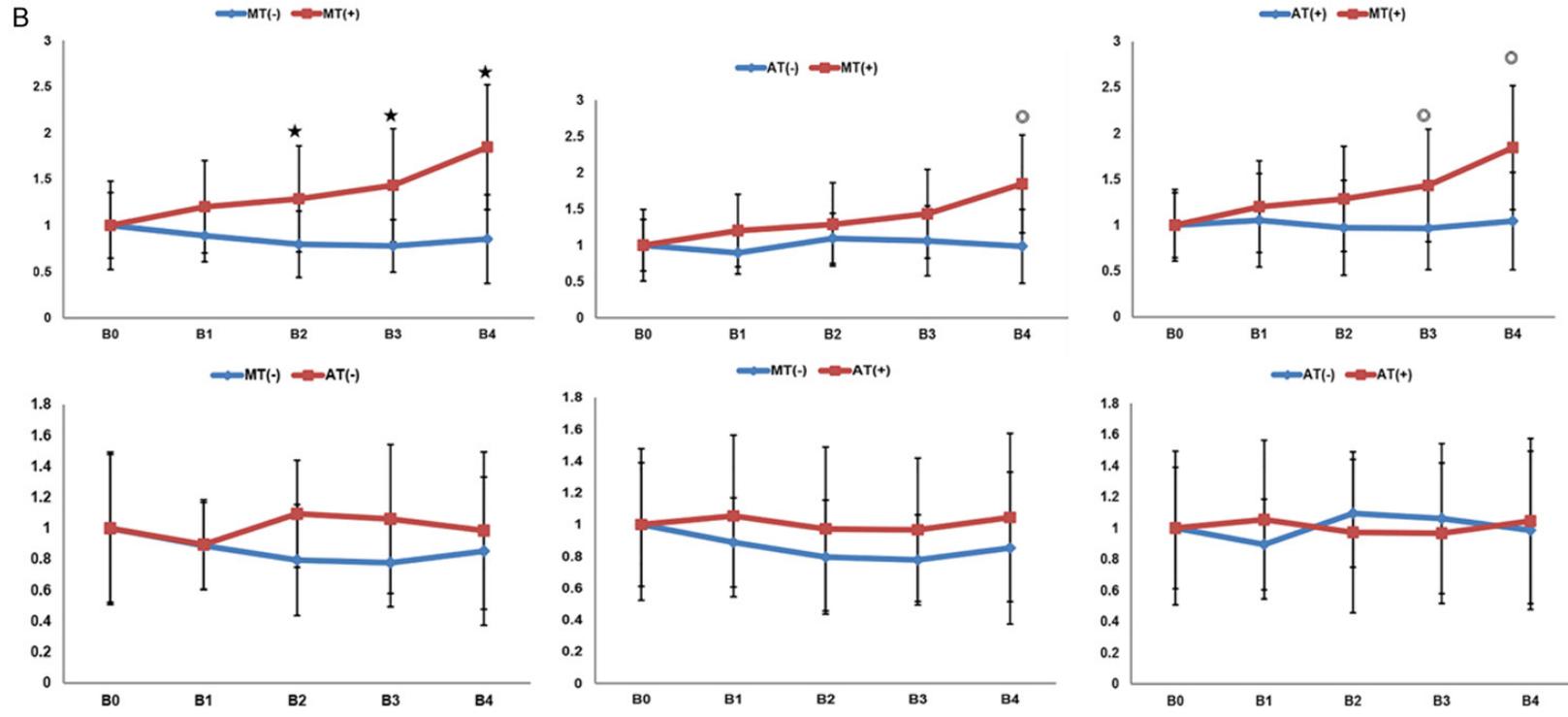
**Figure 3.** The variation trends of amplitude and latency of motor evoked potential in the brain M1 area under different modules in four experiments. A. The amplitude of the MT (+) group increased along with the extension of intervention times and B4 reached to 1.85-folds of the base value (B4 versus B0, *$P<0.05$); B. Comparisons between the same modules among different intervention groups showed that the amplitude of the MT (+) group increased significantly in B2, B3, and B4 modules, compared with the MT (-) group (★indicate $P<0.05$); The amplitude of the MT (+) group increased significantly in the B4 module, compared with AT (-) group (○indicate $P<0.05$). Amplitude of the MT (+) group increased significantly in B3 and B4 modules, compared with the AT (+) group (◎indicate $P<0.05$); C. There were no significant changes in latency under different modules in the four experiments ($P>0.05$).

**Table 2.** The amplitude and latency variation trend of motor evoked potential in brain M1 area under different modules in four experiments

| | | B0 | B1 | B2 | B3 | B4 |
|---|---|---|---|---|---|---|
| MT (-) | Amplitude (uv) | 724.23 ± 345.79 | 642.93 ± 203.50 | 575.83 ± 259.66 | 563.19 ± 205.91 | 617.19 ± 346.99 |
| | Latency (ms) | 22.09 ± 1.33 | 22.22 ± 1.29 | 22.38 ± 1.05 | 22.45 ± 0.94 | 22.27 ± 1.34 |
| MT (+) | Amplitude (uv) | 572.54 ± 203.16 | 687.79 ± 285.86 | 736.67 ± 328.16* | 820.52 ± 350.40*,◎ | 1056.65 ± 386.54*,★,◎,○ |
| | Latency (ms) | 22.29 ± 1.11 | 22.25 ± 1.12 | 22.27 ± 1.33 | 22.34 ± 1.20 | 22.26 ± 1.29 |
| AT (-) | Amplitude (uv) | 664.67 ± 327.65 | 594.71 ± 193.00 | 727.21 ± 229.76 | 704.96 ± 319.72 | 655.13 ± 337.60 |
| | Latency (ms) | 21.97 ± 0.85 | 22.17 ± 1.07 | 22.11 ± 1.08 | 22.22 ± 0.98 | 22.37 ± 0.96 |
| AT (+) | Amplitude (uv) | 628.81 ± 244.61 | 662.87 ± 319.68 | 611.38 ± 324.38 | 608.00 ± 283.58 | 657.04 ± 333.15 |
| | Latency (ms) | 22.39 ± 1.26 | 22.26 ± 1.17 | 22.39 ± 1.06 | 22.23 ± 1.30 | 22.20 ± 1.23 |

The amplitude of MT (+) group increased with the extension of intervention, B4 reached to 1.85 times of the base value, all this were significantly meaningful in statistics (*indicate $P<0.05$); Comparison between the same modules among different intervention groups showed that the amplitude of MT (+) group increased significantly in B2, B3, and B4 module compared with MT (-) group (★indicate $P<0.05$); the amplitude of MT (+) group increased significantly in B4 module compared with AT (-) group (○indicate $P<0.05$); the amplitude of MT (+) group increased significantly in B3 and B4 module compared with AT (+) group (◎indicate $P<0.05$). There was no significant changes in latency under different modules in four experiments ($P>0.05$).

with a target [MT (+)] was the highest, gradually increasing with extension of intervention times. There may be multiple reasons that explain present results, detailed below.

*Differences in activated area*

In 2007, Ertelt et al. first applied action observation therapy to chronic stroke patients with middle cerebral artery blood-supply area infarction (attacked period >6 months) [23]. Functional magnetic resonance imaging (fMRI) tests showed that the excitability of the bilateral ventral premotor cortex, bilateral superior temporal sulcus cortex, bilateral supplementary motor cortex, and supramarginal gyrus increased. Hamzei et al. also found that, after application of mirror therapy, hand function levels of patients were improved significantly [16]. Distribution of the mirror neuron system in the premotor cortex and supplementary motor cortex was significantly activated. Both therapies can activate the mirror neuron system. However, there are no comparative studies concerning specific activation time sequences and network connections. The present study suggests that mirror therapy can activate the area of the mirror neuron system that is more responsible for motor function.

*Differences in activation degrees*

When participants observed or imitated the up-warp forefinger or middle finger, Iacoboni et al. observed the signal intensity. This verified the results of fMRIs in the blood oxygen level dependent (BOLD) in the BA44 area [29]. They found that signals in two areas, the lower frontal cortex (BA44) and tip of the posterior parietal cortex (PPC), increased during motor observation. The signal became higher during motor execution and was the highest during action imitation. Action observation therapy includes observation and imitation of action. Besides observation and imitation, mirror therapy also includes motor imagery. The current study found that the cortical excitability of the M1 area under mirror therapy with a target was the highest, consistent with results found by Garry and Nojima et al. [15, 30]. They found that mirror visual feedback was helpful in promoting excitability of the M1 area of the motor cerebral cortex in the same side. In recent studies, Yarossi et al. also found that mirror therapy can improve ipsilateral cortical excitability and that cortex excitability did not greatly increase during observation of hand movements [31]. It remains uncertain whether this is due to the neural mechanism of mirror therapy, in which

motor imagery, in addition to observation and imitation, is required.

*Differences in action understanding*

Umiltà et al. [32] found that the mirror neuron system would be activated when participants were informed of the existence of a target, no matter if it was blocked or not. The mirror neuron system would not be activated when there was no target, no matter if it was blocked or not. In studies of fMRIs made by Iacoboni et al., the same action was put into different scenes [29]. Participants were required to observe and pick up a cup from a tidy and cluttered table (different purpose of picking up cups were given, drinking water and cleaning the table). Although participants observed the same action (picking up the cup), the excitability of mirror neurons was different under different scenes and behavioral intentions (drinking and cleaning). This indicated that mirror neurons play a role in understanding behavioral intentions. The current study also helps to draw the same conclusions, suggesting that cortical excitability increases in mirror therapy with a target, compared to that with no target. Subsequent studies have found that excitability of the cerebral cortex decreased significantly when there was no target [32-34]. Consistently, the current study confirmed that excitability of cerebral cortex under mirror therapy with a target was higher than that without a target. This means that excitability of the cerebral cortex could be highly improved when participants know the action intention. Therefore, during mirror therapy, making the patients fully understand the intention of action execution might be more beneficial in improving recovery.

*Differences in the degree of concentration*

Debnath [35] and Praamstra et al. [36] found that the effects of mirror therapy on cortical excitability were affected by concentration of attention. Cortical excitability increased greatly when more attention was required. Cortical excitability decreased when less attention was required. A study from Yarossi et al. also suggested that mirror therapy could enhance motor cortical excitability of the same side [31], which was increased greatly when a target was provided. This might be because more attention was needed. Verstynen [37] and van den Berg et al. [38] found that task load and complexity could also affect excitability of the cere-

bral cortex, which might be because more attention is paid to a complicated task. The current study found that the cortical excitability under mirror therapy with a target was the highest. This might also be due to more attention paid. In action observation therapy, participants are easily distracted, which might cause a decrease in cortical excitability.

*Experiment limitations*

The current investigation had several limitations. First, the repeated application of TMS to cortical excitability testing may have affected cortex excitability. In this study, the magnetic stimulation interval frequency was only 4 seconds. This might be too low and may have caused inhibition of the cortex activity. Second, interaction effects may occur when the same participant executed different experimental modules. To avoid this, this study adopted a random ordering method and extended the interval between different modules as much as possible. Third, the sample size of this study was too small. Subjects included in this study were drawn from a single area. Thus, they were subjected to race and region bias. Fourth, it was difficult to avoid the impact of wash over effects.

**Conclusion**

Mirror therapy with a target is more likely to increase excitability of the M1 area of the cerebral cortex, compared with mirror therapy without a target and action observation therapy, in patients with strokes. Excitability increases significantly when there is an extension of intervention times.

**Disclosure of conflict of interest**

None.

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