https://doi.org/10.1016/j.mehy.2020.109590

Title page

Does task complexity influence motor facilitation and visuo-motor memory during mirror therapy in post-stroke patients?

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Key words: Stroke, Mirror therapy, Primary motor cortex, Precuneus, Functional near infrared spectroscopy

Number of pages: 23

References: 58

Tables: 1

Figures: 4

Conflict of interest: The team of authors report no conflict of interest.

Acknowledgements: The work of UMB is supported by The Hong Kong Polytechnic University PhD scholarship. The authors acknowledge all the participants and our research assistant, Ms Sze Man Fung for her assistance and support.

ABSTRACT

Stroke is one of the most common causes of mortality and reduced disability-adjusted life years worldwide. Hemiparesis due to reduced skeletal-muscle power is an effect of brain lesions. Mirror therapy can significantly improve motor performance among post-stroke patients. To determine if altering the complexity of the mirror task in the mirror therapy paradigm would enhance top-down motor facilitation and visuo-motor memory demand, we conducted a pilot study on four post-stroke patients. Our preliminary results showed that performing complex finger tapping task resulted in enhanced activities in the primary motor cortex and precuneus, ipsilateral to the moving hand in the mirror therapy paradigm. We hypothesise the following: (a) complex finger tapping would result in stronger top-down motor facilitation and higher demand on visuo-motor memory than simple finger tapping in the mirror therapy paradigm, and (b) observing a blurred mirror image would result in increased top-down motor facilitation and higher demand on visuo-motor memory than a clear mirror image. To confirm these hypotheses, we propose a cross-sectional observational study on a large sample of post-stroke patients. This paper reports the findings of the pilot study, the rationale for testing the hypotheses, the experimental set-up, the task design and the assessment protocol for functional near-infrared spectroscopy.

Keywords: Stroke, Mirror therapy, Primary motor cortex, Precuneus, Functional near infrared spectroscopy

Does task complexity influence motor facilitation and visuo-motor memory during mirror therapy in post-stroke patients?

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BACKGROUND

Stroke is among the most prevailing causes of death and the most common causes of decline in disability-adjusted life-years globally [1,2]. The cases of stroke-induced disability across all gender and age groups have increased over the years [3]. Hemiparesis, a common cause of disability in people with stroke, is reported in approximately 50% of cases and results in reduced muscle efficiency [4]. Rehabilitation modalities that can facilitate motor recovery following stroke include exercise therapy [5], non-invasive brain stimulation [6], robotic systems [7], sensory cueing [8], virtual reality therapy [9] and mirror therapy [10]. Mirror therapy is a cost-effective and patient-centred approach that requires minimal or no assistance from a physical therapist once the treatment technique is learned [11,12].

Mirror therapy paradigm

Systematic reviews with meta-analyses provide moderate evidence for the use of mirror therapy for motor functional improvement of the upper and lower limbs among people with stroke [11-13]. During the therapy, the user places his/her paretic limb behind the mirror and the unaffected limb stays in front of the reflecting surface of the mirror [14]. A plane mirror is placed in an erect position, which corresponds to the body midline of the user so the paretic limb is hidden from the view of the user [14]. Observation of the visuo-motor image of the unaffected limb generates an illusion of moving the hidden affected limb. The generated mirror illusion is associated with motor, cognitive and perceptual processes [10,15] in line with the reported activations of various neural substrates, including the primary motor cortex (M1), precuneus, premotor cortex, primary somatosensory cortex, dorsolateral prefrontal cortex, superior temporal gyrus and posterior cingulate cortex [10]. The training effects of mirror therapy leads to up-regulation of activity in ipsilesional M1 and is associated with upper-limb functional improvement among people with chronic stroke [16]. This effect may also be attributed to the proprioceptive afferent signals from the static limb and the transcallosal effect of movement execution in the ipsilateral hemisphere [17-19]. Similarly, the effect of the mirror illusion on the precuneus has been well documented [20-23]. Interestingly, the interhemispheric activation shift towards the ipsilesional hemisphere in the precuneus has been associated with the likelihood of functional regain after mirror therapy [23]. The role of precuneus in the provision of spatial information about mental images during motor imagery [24] makes it a marker that explains the role of motor imagery in the mirror therapy paradigm [10].

The mirror creates a visual feedback of an imagined action (motor imagery) due to the observation of movements similar to that of individual's own movements [25,26]. Various mirror tasks [10] result in the mental generation of the imagined action and depict the movement of the hidden limb in the mirror therapy paradigm [17,18]. Studies of motor imagery have been conducted to ascertain the effect of manipulating the imagined motor task on the extent of activations in various neural substrates [27], such as motor imagery of different motor sequences (often simple vs. complex series of finger movements) [28] or using varied motor imagery modalities (visual or kinaesthetic motor imagery) [29]. Kinaesthetic motor imagery of a complex finger movement task has shown significantly greater activations in the premotor cortex, posterior parietal and cerebellar region and increased motor-evoked potential values in comparison with the imagery of a simple finger movement task [28].

Rationale for the study

The attributes of mirror tasks may exert varied excitatory effect on M1 ipsilateral to the moving limb by altering the content of the mirror images [30-32]. All the previous studies that manipulated mirror attributes were conducted on healthy participants [30-32]. None of the studies assessed the effect of task complexity on the extent of activations in ipsilateral M1 and precuneus. Therefore, the present study aims to further explore the instant effect of manipulating finger task complexity and mirror image clarity on the extent of activations in ipsilesional M1 and precuneus by using functional near-infrared spectroscopy (fNIRS) to determine the most suitable mirror therapy paradigm for best functional recovery among people with stroke. We hypothesise that:

Hypothesis 1: Complex finger tapping will result in stronger top-down motor facilitation and higher demand on visuo-motor memory than simple finger tapping in the mirror therapy paradigm.

Hypothesis 2: Observing a blurred mirror image will result in increased top-down motor facilitation and higher demand on visuo-motor memory in comparison with a clear mirror image.

Findings of our pilot study

We conducted a pilot study to assess the influence of simple and complex finger tapping tasks on ipsilesional M1 and precuneus activations in the mirror therapy paradigm by using fNIRS among four participants with chronic stroke. A cross-sectional design with a plane mirror set-up was utilised. The complex finger tapping task generated stronger activations in the ipsilesional M1 (mean difference between complex finger tapping and control condition = 0.0154 µmol/l) compared with simple finger tapping (-0.0048 µmol/l). The activation in the precuneus was also stronger during the complex finger tapping (0.0745 µmol/l) compared with that under simple finger tapping condition (0.0582 μmol/l). These findings support our hypotheses (See raw data file).

Scientific premise for testing the proposed hypotheses

Hypothesis 1: Motor imagery is described as a strategy of mirror therapy [25] and is associated with a mental rehearsal of the displayed movement, depicting the limb behind the mirror [26]. Previous studies suggested that mirror therapy is a form of visually guided motor imagery, and both rehabilitation modalities share some underlying neural processes [10,30,33]. Moreover, kinaesthetic motor imagery of the complex finger tapping task generated stronger motor-evoked potential amplitude than that of the simple finger tapping task [28]. Therefore, we propose that visual observation of complex finger tapping task in the mirror would trigger stronger top-down motor facilitation in M1 ipsilateral to the moving hand and higher demand on visuo-motor working memory through kinaesthetic motor imagery processes among healthy and stroke participants.

Hypothesis 2: A high degree of visual impoverishment of the mirror image in mirror therapy paradigm degrades the kinaesthetic mirror illusion [34]. Therefore, we propose lowering the vividness of the mirror image to require more effort to internally generate movement sensation through imagery processes, leading to higher demand on the top-down motor system and the visuo-motor working memory among healthy and stroke participants.

STUDY PROTOCOL

We planned to conduct a cross-sectional observational study involving 36 participants (18 healthy individuals and 18 patients who suffer from stroke). Community-dwelling post-stroke patients will be invited for the study by using advertisement flyers. Age-matched healthy volunteers working at Hong Kong Polytechnic University will be invited and serve as the control group.

Sample size calculation

G-power software (http://www.gpower.hhu.de/) was used to calculate the sample size for the study. Assuming 80% power, 5% type I error and moderate partial eta-squared (η^2) of 0.06 [http://www.mormonsandscience.com/gpower-guide.html], 18 post-stroke patients and 18 healthy volunteers will be needed to detect significant between- and within-group differences by using repeated ANOVA on the change in oxygenated haemoglobin concentration in the M1 and precuneus regions of interests (ROIs) based on fNIRS method.

Participants

The inclusion criteria of the post-stroke participants are (1) male or female aged 40–75 years with normal or corrected-to-normal vision and hearing; and (2) without history of severe deficits in memory, communication and understanding of verbal instructions [Mini-Mental State Examination [35] of > 24 points] [36]. The exclusion criteria are recurrent stroke and/or any trauma that affects voluntary movement of the unaffected upper extremity. For age-matched healthy volunteers, the inclusion criteria are: (1) right-handed adults, (2) 40-75 years old with normal or corrected-to-normal vision and hearing and (3) without history of psychiatric or neurological disorders.

Participant recruitment and ethical consideration

Ethical approval for this study will be obtained from the Human Subjects Ethics Sub-committee of Hong Kong Polytechnic University before the study commences. The study will be registered with the Hong Kong University Clinical Trial Registry (HKUCTR). We will use purposive sampling to recruit participants with stroke and age-matched healthy volunteers.

Experimental setup

The experiment will be conducted in a well-lighted and quiet room by using the plane mirror set-up, which was used in previously published studies [25,30,37-39]. Each participant will be seated comfortably at a table facing an erect plane mirror (30 inches × 24 inches) positioned perpendicularly to the table surface that corresponds to the mid-sagittal plane of the participant. A completely clear mirror or 35% blurred mirror (using a mesh) will be used in the study. The extent of blurriness of the mirror was assessed during our pilot study. Participants will place their unaffected or right (for healthy volunteers) forearms/hands and the affected or left forearm/hands on the table, each 15 cm lateral to the reflecting and non-reflecting surfaces of the clear or blurred mirror, respectively. These distances will be labelled on the table by using an adhesive tape to ensure that all participants place their forearms/hands at precise positions during the experiment. This arrangement is in line with previous findings that mirror illusion is more intense when the position of the mirror image coincides with that of the static hidden hand behind the mirror [18]. Furthermore, participants will be instructed to perform finger tapping strokes by using a wireless keyboard (Mofii X210, Shenzhen SQT Electronics Co., Ltd.) with the index, middle and ring fingers of the unaffected or right hand, while observing the mirror-inverted visuo-motor image depicting the paretic or left hand hidden behind the mirror. Finger tapping will be paced using an auditory metronome at a frequency of 1.5 Hz (90 b/m). A foam board will be placed at the coronal plane between the participant's trunk and the unaffected forearm to prevent gazing at the moving hand and implement unilateral viewing condition [40]. Participants will also be instructed to imagine the displayed hand in the mirror as the hidden affected or left hand [38,39], while also internally generating movement sensation (kinaesthesia) associated with the displayed hand.

Task design

The study design will involve the manipulation of finger tapping complexity (simple or complex) and clarity of the mirror image (clear or blurred) (Figure 1 or 2), resulting in four finger-tapping conditions. Each of the four conditions will have a separate control condition involving the direct view of the active hand (Figure 3 & 4) to control minimal ipsilateral excitations during movement execution in the mirror therapy paradigm [40]. Overall, the experiment will comprise of eight conditions, which will be performed in a block design. Table 1 illustrates the eight conditions to be tested during the experiment.

Each of the conditions will be performed in 10 similar experimental blocks [41], with each block lasting 20 s, followed by an inter-block rest period of 20 s [42]. Figure 5 illustrates the layout of the experimental blocks. Participants will commence and terminate each block upon hearing a sound from E-prime software. The inter-trial rest period after each of the four experimental conditions will be set as 3 min to allow the participants to rest and fill the vividness of kinaesthetic mirror illusion and the internal generation of a movement sensation questionnaire [modified from the methods of Diers et al. [43] and Roberts et al. [44]] (Appendix 1). In addition, 1.5 min will be provided after each of the four control conditions for the participants to rest because the questionnaire will not be filled after the completion of these conditions. E-prime software will be set to randomise the finger tapping conditions among the participants to minimise the order effect [42]. Overall, the participants will perform 80 blocks of finger tapping movements which will be completed in approximately 74 min (Figure 4).

During the simple finger tapping tasks, the participants will be instructed to perform repeated rhythmical finger tapping sequences with the index, middle and ring fingers on the keyboard with three coloured keys (red, pink and green). In the complex finger tapping task, longer randomised sequence will be performed using the same number of fingers (Table 1). Surface electromyography will be used to continuously record and monitor the motor activity of the extensor digitorum muscle during the experiment to ensure the relaxation of the hidden upper extremity located behind the mirror [45].

Table 1: Finger tapping conditions

Task label	Condition	Task complexity	Nature of task (all finger tapping self-paced at 1.5Hz)
A	Clear (MVF) + simple	Simple finger tapping movement	Repeated tapping of colored keys with the index, middle and ring fingers + clear mirror visual feedback
B	Clear (DVAH) + simple (CONTROL CONDITION)	Simple finger tapping movement	Repeated tapping of colored keys with the index, middle and ring fingers + direct view of clear actively moved hand
C	Clear (MVF) + complex	Complex finger tapping movement	Tapping sequence: ring × 2, index × 2, middle × 2, ring × 1, middle × 1 & index × 1 on colored keys + clear mirror visual feedback
D	Clear (DVAH) + complex (CONTROL CONDITION)	Complex finger tapping movement	Tapping sequence: ring × 2, index × 2, middle × 2, ring × 1, middle × 1 & index × 1 on colored keys + direct view of clear actively moved hand
E	Blurred (MVF) + simple	Simple finger tapping movement	Repeated tapping of colored keys with the index, middle and ring fingers + blurred mirror visual feedback
F	Blurred (DVAH) + simple (CONTROL CONDITION)	Simple finger tapping movement	Repeated tapping of colored keys with the index, middle and ring fingers + direct view of blurred actively moved hand

G	Blurred (MVF) + complex	Complex finger tapping movement	Tapping sequence: ring × 2, index × 2, middle × 2, ring × 1, middle × 1 & index × 1 on colored keys + blurred mirror visual feedback
H	Blurred (DVAH) + complex (CONTROL CONDITION)	Complex finger tapping movement	Tapping sequence: ring × 2, index × 2, middle × 2, ring × 1, middle × 1 & index × 1 on colored keys + direct view of blurred actively moved hand

Abbreviations: Mirror visual feedback, MVF; Direct view of active hand, DVAH.

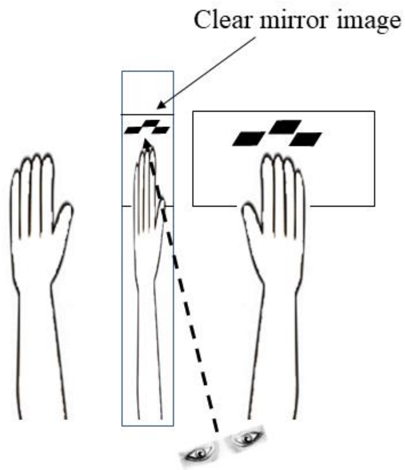

Figure 1: Clear (MVF)

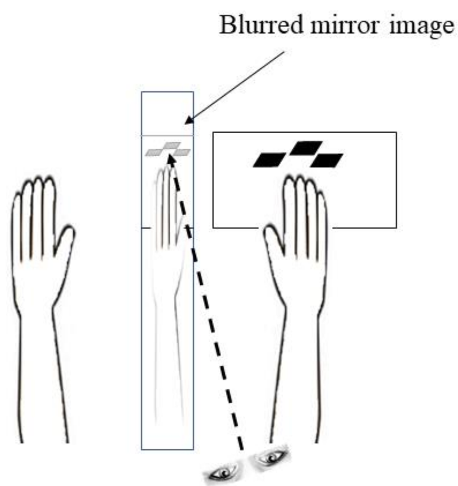

Figure 2: Blurred (MVF)

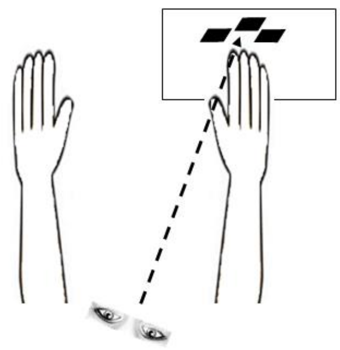

Figure 3: Clear (Direct view of active hand) (CONTROL CONDITION)

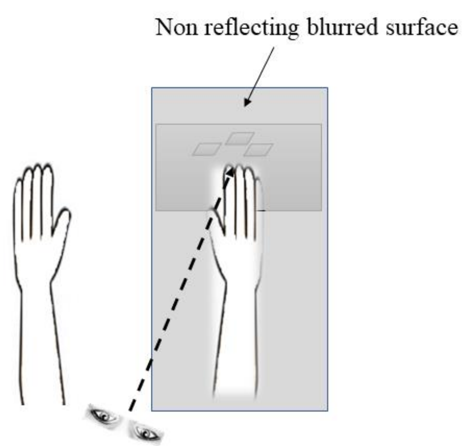

Figure 4: Blurred (Direct view of active hand) (CONTROL CONDITION)

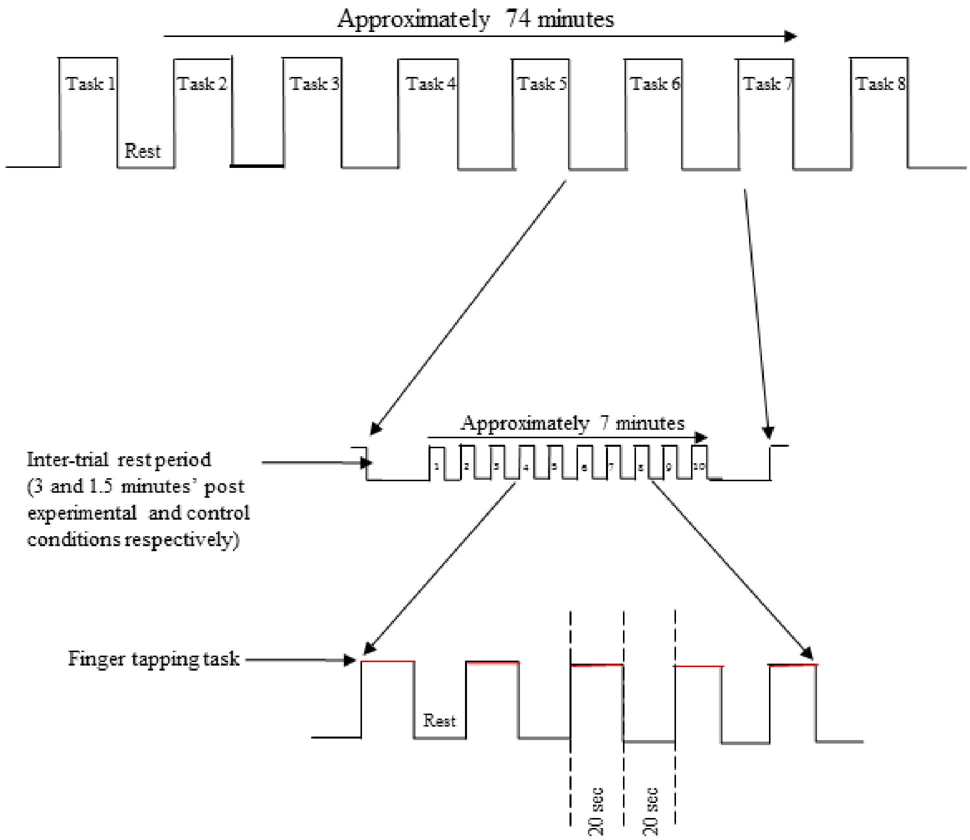

Figure 5: Task design (8 finger tapping conditions, each with 10 finger-tapping blocks)

FINGER TAPPING TRAINING

A practice session of 1 h will be performed prior to the brain scan [46] to ensure that the participants can perform simple and complex finger-tapping tasks properly with ease and requiring considerable attentional demands [47]. During the practice session, keyboard strokes will be paced at a frequency of 1.5 Hz by using an auditory metronome. Participants will be instructed to synchronize each finger tapping stroke with the beat of the metronome until they can perform the task accurately.

BEHAVIOURAL ASSESSMENT

The wireless keyboard will be synchronised with a laptop to record the number of correct and wrong finger tapping strokes during each condition. Finger tapping error rates will be calculated as follows: 'total number of errors/total number of finger taps', where an error is defined as any finger tap occurring outside the prescribed sequences [48]. After completing every finger tapping task, a follow-up question on the colour of the first or last key stroked will be asked to assess participant's engagement in the finger tapping. Similarly, questions on the vividness of kinaesthetic mirror illusion and the effort in generating the movement sensation will be asked using the illusion questionnaire.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (FNIRS) RECORDINGS

fNIRS will be used to assess neurovascular changes (blood oxygenation) bilaterally in the M1 and precuneus during the experiment. fNIRS has been adopted in several previous mirror therapy studies [20,23,49]. The optical brain imaging device has been validated for testing cortical changes in experimental conditions with varied finger tapping complexities [42]. fNIRS is safe, relatively less expensive when compared to functional magnetic resonance imaging (fMRI), easy to use and most importantly, this tool also allows for more reliable measurements in different postures and environments without requiring an individual to lie within the scanner as in the case of fMRI [50].

DATA ACQUISITION AND LOCATING THE REGION OF INTERESTS (ROIs)

We will use the fNIRS device with an optical topography system (ETG-4000, Hitachi Medical Co., Tokyo, Japan) comprising 18 emitters and 16 detectors. We will follow the standard practice for acquiring data by using fNIRS, which is in line with the method adopted previously [20]. Briefly, the optode positions will be selected to cover the M1 (precentral area) of the participant's head, providing a total area of four crucial channels bilaterally, where the emitters and detectors will be placed 3 cm from each other [20]. M1-ROI will be defined as channels around electroencephalogram (EEG) positions C3 and C4, known to cover the left and right M1, respectively [51]. Precuneus-ROI will be defined as a region slightly below the Pz region, yielding a total area of three crucial channels bilaterally [20]. Furthermore, locating the Cz, C3, C4 and Pz positions on the surface of the skull will be carried out based on the guideline provided by Jurcak et al. (2007) [52]. An EEG cap will be used to secure the optodes during the experiment.

FNIRS DATA PRE-PROCESSING

Data processing will be performed using MATLAB toolbox HomER2 [53]. Firstly, the optical density changes will be generated from the raw intensity data [54], and the motion artifacts will then be corrected using the Spline interpolation algorithm [55]. Secondly, a band-path filter of 0.01 Hz to 0.3 Hz will be used to further process the optical density changes [54]. Thirdly, the optical density will then be converted to concentration changes of oxygenated and deoxygenated haemoglobin at different time points using the Beer-Lambert law [54]. Finally, channel-by-channel processing involving the normalisation of concentration changes to zero mean and unit variance (z-score) will be performed [56,57]. The averages of oxygenated and deoxygenated haemoglobin will be calculated for all the participants of the two groups under the experimental conditions (participants with stroke and the healthy volunteers). Data analysis will be conducted using oxygenated haemoglobin signals due to its reported higher sensitivity in detecting cortical regional blood flow [58]. Baseline-corrected time courses will be calculated and averaged across subjects and smoothed (moving window of 20 s) for all the finger tapping conditions [20].

STATISTICAL ANALYSIS

A between-within subjects' ANOVA will be used to compare the concentration change of oxygenated haemoglobin in M1-ROI and precuneus-ROI (ipsilateral to the moving side/right hand) between the groups and within the experimental conditions. If the ANOVA shows significant differences, then post-hoc analysis will be performed using Tukey-Kramer's honestly significant difference test for multiple comparisons. Changes in the oxygenated haemoglobin concentrations in the ROIs for each experimental condition will be compared with the changes due to the associated control condition among the two groups (for instance, tasks 'A & B', 'C & D', 'E & F' and 'G & H'; Table 1). The level of statistical significance for this study will be set at $p \geq 0.05$.

Hypothesis 1 will be supported if there is significantly higher mean difference in the concentration change in the oxygenated haemoglobin level in M1-ROI and precuneus-ROI during complex finger tapping (tasks C & D) than that during simple finger tapping (task A & B).

Hypothesis 2 will be supported if there is a significantly higher mean differences in the concentration change in the oxygenated haemoglobin level in M1-ROI and precuneus-ROI when viewing blurred mirror images (tasks 'E & F'; 'G & H') than when observing clear mirror images (tasks 'A & B'; 'C & D').

CONSEQUENCES OF HYPOTHESES

If the hypotheses are true, then the findings of this research will provide a scientific premise for treatment progression in mirror therapy regimen. Increasing the complexity of the mirror task and the blurriness of the mirror image will increase the top-down motor facilitation and the demand on visuo-motor working memory.

CONCLUSION

Stroke is associated with a spectrum of functional limitations and is one of the most disabling neurological conditions. Mirror therapy has been found to positively influence motor recovery among people with stroke. Although previous studies tested the significance of manipulating the task on motor facilitation during mirror therapy among healthy volunteers, experiments among people with stroke are not available. This study will help determine the benefits of manipulating the complexity of task and the clarity of mirror reflection on the facilitation of the involved M1 and precuneus. Determining the means to increase and enhance stronger cortical excitation will be a breakthrough in stroke rehabilitation. We consider this study novel and worthwhile.

CONFLICT OF INTEREST

The team of authors report no conflict of interest.

ACKNOWLEDGEMENTS

The work of UMB is supported by The Hong Kong Polytechnic University PhD Studentships. The authors acknowledge all the participants and our research assistant, Ms Sze Man Fung for her assistance and support.

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