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Conflict of Interest declaration

None of the authors have potential conflicts of interest to be disclosed. The authors alone are responsible for the content and writing of this paper.

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ABSTRACT

Introduction

As a combination of visual stimulation and motor imagery, mirror visual feedback (MVF) is an effective treatment for motor impairment after stroke. However, few studies have investigated the effect of MVF on involved cognition, like visual perception and motor imagery. Camera-based mirror visual feedback (camMVF) which overcomes intrinsic limitations and disadvantages of real mirror is recognized as an optimized setup. This study aims to investigate the effect of camMVF as an adjunct treatment for stroke patients comparing with conventional therapy, and the possible neural mechanisms of MVF on involved cognition and brain network.

Methods and analysis

This is a multicentre, single-blinded, randomized controlled trial including 90 patients randomized into camMVF group (MG=30), sham-MVF group (sham-MG=30) and conventional group (CG=30). Patients will receive 60 minutes corresponding intervention in each group for 5 days per week, lasting 4 weeks. The primary outcome is the Fugl-Meyer Assessment Upper Limb subscale (FMA-UL). Secondary outcomes include the Wolf Motor Function Test, modified Ashworth Scale, Grip strength test, Purdue Pegboard Test, and modified Barthel Index, the Functional Independence Measure, the Berg Balance Scale, 10-meter walking test, hand laterality task and EEG signals.

Ethics and dissemination

Ethics approval was granted by Huashan Hospital Institutional Review Boards on 15th March 2017, (KY2017-230) in Shanghai, China. We plan to submit a manuscript of the results to a peer-reviewed journal, and present results at conferences, rehabilitation forums and the general public.

Trial registration number Chinese Clinical Trial Register, ID: ChiCTR-INR-17013644. Registered on 2 December, 2017.

Strengths and limitations of this study

- This is the first randomised controlled trial investigating the effect of camera-based MVF on stroke patients, and the underlying neuro-mechanism on involved cognition and brain network.
- Our findings could have the benefits of improving the technique and developing novel interface of MVF based on EEG results.
- This study presents a method of providing systematic procedure of mirror therapy.
- Comparisons of camera-based MVF and real mirror based MVF are still needed in the future studies.

INTRODUCTION

Upper extremity motor impairment is a specific consequence following stroke.[1] Approximately 65% of patients with hemisphere stroke would live with a paretic upper extremity,[2] especially for the hand, which seriously affects motor performance and limits the quality of daily life. There are some evidence-based treatments to promote the recovery of upper extremity and hand, such as constraint-induced movement therapy, robot-assisted therapy and mirror therapy (MT). [3–5] MT, which has been in wide use in the rehabilitation of upper extremity and hand, is a less labour intensive and more convenient method.[6–8] During MT, a plain mirror is employed to provide the reflection of the unaffected hand movements. The reflection (mirror visual feedback, MVF) would provide a misperception of ownership, which is recognized as mirror illusion. However, the real mirror used in MT has some disadvantages including balance control, postural pressure, weight shifting and single fixed training mode, which limit the application in clinic.[9,10] To the best of our knowledge, numerous studies have proposed various technological strategies to create new interface of MVF to overcome the disadvantages.[10–14] As one of them, the feasibility of camera-based MVF in rehabilitation has been investigated by some previous studies.[9,13,15] In order to optimize MT, a camera-based MVF setup was employed in the present study for better training posture, more systematic training procedure and manipulatable visual feedback.

As a plasticity-based approach, the reversion of learned non-use and the activation and modulation of central nervous are general theory of MT.[16–19] Compared with real mirrors, the camera-based MVF would also have the same therapeutic theory. Studies in amputees or healthy controls suggested that the camera-based MVF can increase the cortical activation of sensorimotor cortex, parietal and middle temporal cortex, using electroencephalogram (EEG), functional magnetic imagine (fMRI) and functional near-infrared spectroscopy (fNIS) techniques.[10,11,15,20] However, the effect of MVF on brain reorganization of stroke patients remains unexplored. MVF is recognized as one component of graded motor imagery combined with visual stimulation.[21–23] It is possible that MVF could promote the recovery of motor imagery ability, enhance visual perception of the affected limb, and reorganize the corresponding brain network. Brain network involved in motor imagery, especially the extended motor network, plays an important role in the motor process before execution, like motor preparation and planning.[24–26] An abnormal extended motor network has been found even in stroke patients with good functional recovery, and the abnormalities were correlated with residual functional impairment.[24]

We hypothesize that the camera-based MVF would be an effective adjunct treatment for stroke patients with the underlying mechanism on visual perception, motor imagery and brain network reorganization. A hand laterality task, which involves visual processing and mental rotation of hands,[27] provides a good paradigm to study motor imagery and visual perception of hands. Using clinical assessments, the hand laterality task and EEG analyses, we aim to explore the effects of camera-based procedural MVF on stroke patients comparing with conventional treatment, and the underlying central mechanism.

METHODS AND ANALYSIS

Design

This is a multicentre, single-blinded, randomized controlled trial (as part of the camera-based MVF study, the register number: ChiCTR-INR-17013644). A study flow is shown in Figure 1.

Patient population

Each centre is expected to randomize 30 stroke inpatients who meet the clinical criteria (Table 1).

Randomization

Patients are stratified using motor deficit severity (according to the Fugl-Meyer Upper Extremity (FMA-UE) score, more impaired ≤ 35 and less impaired ≥ 36)[28,29] and days from onset (early < 6 months and late ≥ 6 months). The eligible patients who are informed about and consent for the study will receive a baseline assessment, and then be randomly allocated into one of the groups. Patients in each group are treated separately without knowing the allocation during the whole study. The randomization assignment is generated through the Matlab (The MathWorks, Inc.) by an independent researcher.

Intervention

Patients are randomly assigned into camera-based MVF group (MG), sham-MVF group (sham-MG) or conventional group (CG). All inpatients will receive 60-minute treatment per day, 5 days per week, and lasting for 4 weeks (20 sessions) during their hospitalization. Muscle stretch and massage are also administered for patients before and after treatments for relaxation purpose and all these interventions are in addition to their routine treatments in the hospital.

Camera-based MVF intervention

In this trial, we use a camera-based MVF box (1200 mm×940 mm×702 mm) to present manipulable visual feedback (mirrored, shielded, delayed and amplified), instead of a real plane mirror. Two mounted cameras are used to capture the hand motion, and a 23.8-inch LED screen (1920×1080 pixels) is used to present the visual feedback. During treatment, patients are seated in front of the LED screen with a comfortable height and placed their hands in the box, which blocks the real visual feedback of both hands. The reflection and mirrored reflection of the unaffected hand are presented on the screen as the similar size of real hands during MG intervention (Figure 2). The camera-based MVF provide systematic procedure of MT, which contains basic and functional movement training items and verbal instructions with standard motion guide videos.

In the basic part, 25 items focusing on hand, wrist, and forearm are included, such as grasp, finger-to-finger, wrist extension/flexion, forearm supination/pronation and so on. Tool-based items, like bottle grasping and wooden cube picking, are included in the functional part. Therapists can choose any item to make a training plan according to the motor impairments. Moreover, in order to make the training more self-disciplinary and less labour intensive, there are verbal instructions/orders during the whole treatment and motion guiding videos at the initial of training.

During the camera-based MVF intervention, patients are asked to conduct the training motions symmetrically as possible and synchronously and perceive the ownership change through the reflection and mirror illusion. Experienced therapist will make the training plan and adjust the difficulties of items to avoid global synkinesis of the affected limb and provide appropriate assistance. In this trial, every patient will receive 60-minute training per session including four to five items (include 3-4 basic items and 1-2 functional items), and each item repeats 60 times per session.

Sham-MVF intervention

The camera-based MVF box is still used for sham-MVF intervention, where the reflection of the affected side is shielded but motion imagining of the affect hand is still required (Figure 2). We will compare the differences of clinical measurements and EEG signals between MVF and sham-MVF to explore the effect of MVF.[30] In sham-MG, patients will receive similar training protocol based on the motor impairments and same intensity and duration as patients in MG.

Conventional intervention

Conventional intervention contains dosage-equivalent treatments of physiotherapy and/or occupational therapy focused on hands, wrist and forearm. The training principle and items are similar with MG and sham-MG.

Study outcomes

The primary outcome and clinical assessments will be administrated at baseline, after 2 weeks and 4 weeks of treatment. Hand laterality task and EEG recording will be administrated before and after the intervention.

Primary

The Fugl-Meyer Assessment Upper Limb subscale (FMA-UL) will be employed to assess the motor impairment as primary outcome.

Secondary

Clinical assessment

Clinical measurements contain the Wolf Motor Function Test (WMFT), modified Ashworth Scale (mAS), Grip strength test, Purdue Pegboard Test, modified Barthel Index, the Functional Independence Measure (FIM), the Berg Balance Scale (BBS) and 10-meter walking test (10-MWT). And these measurements focus on the evaluation of motor impairment, motor function, tone and strength of muscle, dexterity of hands (mild to moderate impaired patients), mobility and daily function.

Hand laterality task and EEG recording protocol

The hand laterality task is used to assess the visual perception and motor imagery of hands.[27] The patients are seated in front of a portable computer and judge the laterality of the hand pictures presented on the display (13 inches). The whole experiment consists of 4 blocks after 1 training block. There is a 3 min inter-block break. In each block, there are 96 trials. In each trial, a black cross is displayed for 800 ms, and then stimulus pictures (9 cm × 9 cm) of the left or right back-view hand at 6 different angles (0°, 60°, 120°, 180°, 240° and 300°, in total of 2 × 6 types stimulus pictures) are presented randomly with equal probability. Patients are requested to make hand laterality judgment as quickly and accurately as possible by pressing corresponding button using their unaffected hands. The hand pictures are presented until the patients respond. Stimuli are controlled by E-prime 2.0 (Psychology Software Tools, Inc, Pittsburgh, USA).

The EEG signals during the hand laterality task are recorded to study the brain network involved in visual perception and motor imagery. The EEG signals are collected from a 64-channel Ag/AgCl EasyCap™ (Brain Products GmbH, Munich, Germany). All electrodes are referenced to FCz and with impendence below 20 kΩ. The EEG signals are amplified by BrainAmp MR Plus amplifier (Brain Products GmbH, Munich, Germany) and recorded continuously using Vision Recorder (Version 1.03, Brain Products GmbH, Munich, Germany) at sample rate of 1000 Hz.

Statistical methods

Sample Size

We performed sample size estimation to detect difference of group × time interaction on clinical outcome (FMA-UL). An effect size (f) of 0.27 to 0.3 is expected based on previous MVF studies.[11,31] With the expected effect size, sample size in total of 75 to 90 is required in repeated ANOVA given a power of 0.8 and a two-sided type-I error of 0.01. We therefore plan to recruit 90 patients (30 in each group) in this study.

Statistical analyses

The primary analysis will be performed using the intention-to-treat principle. The treatment effects will be compared using two-ways repeated measures analysis of variance (ANOVA) for clinical measurements, taking TIME (three levels: before intervention, 2 and 4 weeks after intervention) as within-subject factor and GROUP (three levels: MG, sham-MG and CG) as between-subject factor. Three-ways repeated ANOVA will be used to test the behaviour during the hand laterality task (response time and accuracy), taking TIME (two levels: before intervention and after intervention) and HAND (two levels: affected and unaffected) as within-subject factors and GROUP (three levels: MG, sham-MG and CG) as between-subject factor. A p-value < 0.05 will be set as indicating statistical significance for all analyses.

ETHICS AND DISSEMINATION

This study has been approved by Huashan Hospital Institutional Review Boards on 15th March 2017, (KY2017-230) in Shanghai, China. And this trial has been registered on 2nd December 2017 as ChiCTR-INR-17013644. The institutional review board of Huashan Hospital will receive the study reports at the middle and end of the study and monitor the study implementation and data collection. Any modifications to the protocol will also be agreed by the review board. All the study data will be preserved as case report forms. Huashan Hospital is sponsor for the study. Patients will be recruited from Huashan Hospital Fudan University Jing'an Branch, the first Rehabilitation Hospital of Shanghai and Shanghai Changning Tianshan Traditional Medicine Hospital and receive intervention there. This study protocol was written in line with the SPIRIT checklist.[32] The study weill eventually be published in a peer-reviewed journal, and findings will be presented at conferences, rehabilitation forums and the general public.

DISCUSSION

MT is a plasticity-based approach which has shown significant results on motor impairment in RCTs.[3,6,7] But the real mirror has some technological limitations and disadvantages, such as weight shifting and postural pressure,[9,10] which could be overcame by the camera-based MVF. The present study is aimed to test the effectiveness of camera-based MVF therapy, comparing with conventional treatment in stroke rehabilitation and investigate underlying neural mechanism from aspects of involved cognition and brain network. Our study will indicate future implementation of novel manipulable MVF and systematic procedure and suggest better understanding of central mechanism in motor control that will improve the effectiveness of MT.

MVF is a visual stimulation combined with motor imagery.[21–23] This special reflection can enhance the perception of affected limbs and sense of ownership; besides, with the activation of cognitive cortex, MVF can eventually activate the primary motor cortex and restore motor execution.[33,34] Stroke disrupted both corticospinal output, like motor execution and motor processes more upstream, such as attention, motor preparation, or planning.[26] Recognized as one component of graded motor imagery,[21,23] MVF might have the potential to improve motor imagery and visual perception of the affected hand, mediate motor cognitive process, and reorganize the motor network. According to the results of clinical measurements and EEG analysis of the MG, sham-MG and CG, the study is aimed to explore the neural mechanism of MVF, which will be the supplementary evidence on reversal of cortical reorganization and plasticity of MVF.

Contributors

All the authors were involved in the conception and design of research. LD and XW are principal investigator; SC and HW advised the design of the camMVF system and treatment procedure; XC, JR, and JJ are responsible for the different study centre; JJ is the lead researcher and study manager. LD wrote the first draft and all the authors contributed to the final version.

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Competing interests

None declared.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
• From 25 to 75 years old	• Medical conditions deteriorate
• Diagnosed as unilateral stroke by CT or MRI between two weeks and one year following stroke onset	• A history of epilepsy and serious heart, lung, liver and kidney function failure
• Ability of following the instructions (MMSE ≥ 25)	• Other problems that hinder the study implementation
• Muscle tension (mAS ≤ 2)	
• Ability of identify the laterality of the hands	

CT: Computed Tomography; MRI: Magnetic Resonance Imaging; MMSE: The Mini–Mental State Examination; mAS: modified Ashworth Scale.

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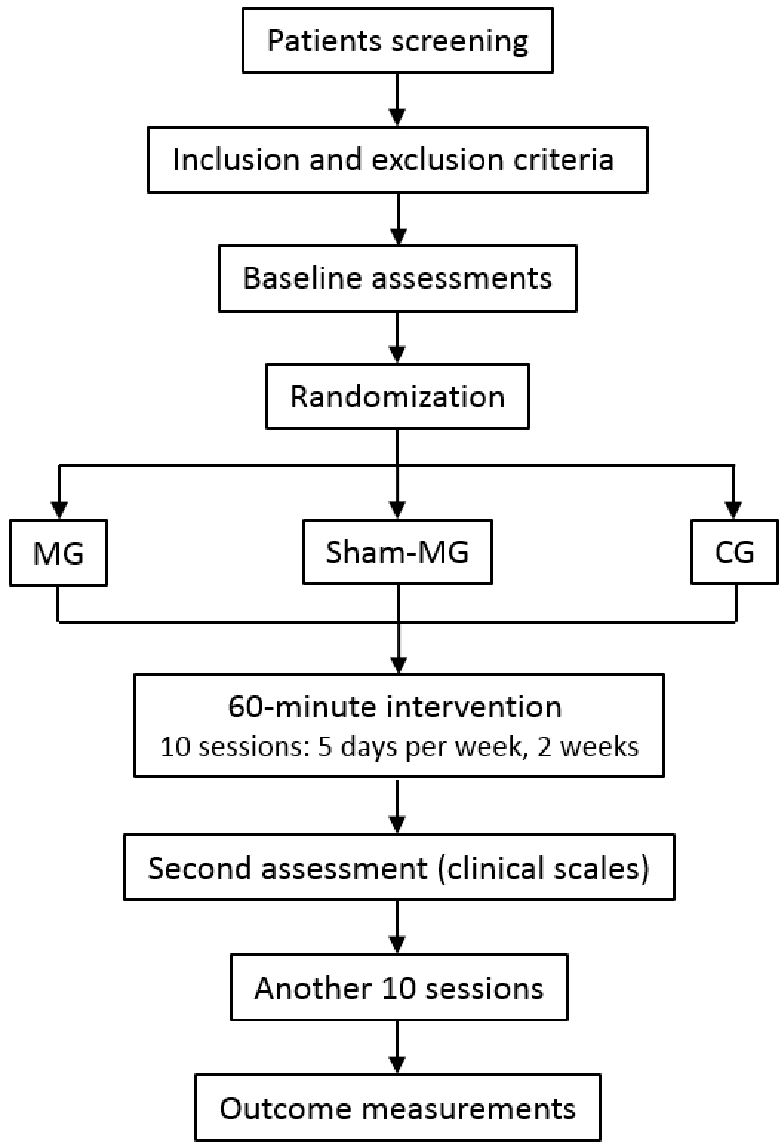

Figure 1. Trial flow chart. MG: camera-based mirror visual feedback intervention group; Sham-MG: shielded mirror visual feedback intervention group; CG: conventional intervention group.

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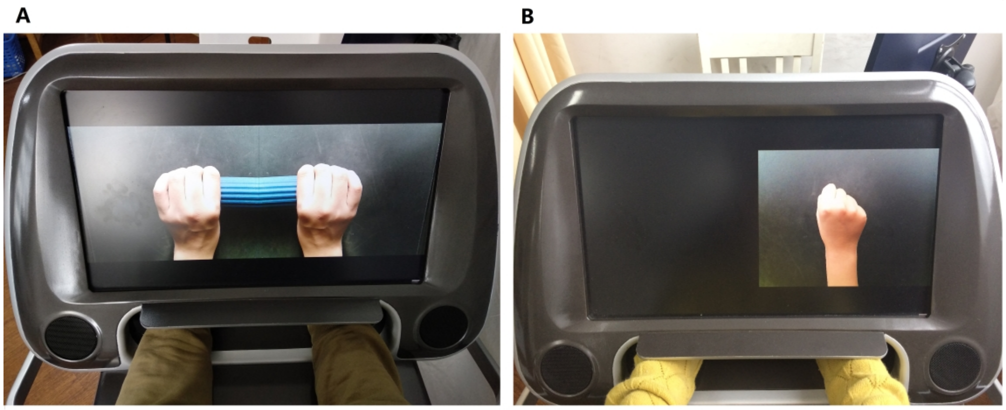

Figure 2. The camera-based Mirror Visual Feedback (MVF) system in the present study. A: normal MVF of bar grasping for patients in MG; B: shielded MVF of making a fist for patients in sham-MVF.

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Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	6
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	6
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	See note 1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	4

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	4
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See note 2
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	See note 3
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	See note 4
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	See note 5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	See note 6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	See note 7
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	See note 8

Author notes

1. 6, name and grant number were provided
2. n/a, no other analyses are included
3. n/a, analyses will be conducted at the end of the study
4. n/a, the study protocol has been approved by ethical boards, and adverse events were limited in this study.
5. n/a, no ancillary studies included
6. n/a, review board has approved the safety and feasibility of the study
7. n/a, the data (case report form) will be preserved by review board of Huashan Hospital and data disclose has been described during the clinical trial registration.

8. n/a, no biological specimens in the study

 This checklist was completed on 08. March 2018 using http://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Effects of Camera-based Mirror Visual Feedback Therapy for Stroke Patients and Neural Mechanisms: Study protocol of a multicentre randomized control study

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Effects of Camera-based Mirror Visual Feedback Therapy for Stroke Patients and Neural Mechanisms: Study protocol of a multicentre randomized control study

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None of the authors have potential conflicts of interest to be disclosed. The authors alone are responsible for the content and writing of this paper.

Effects of Camera-based Mirror Visual Feedback Therapy for Stroke Patients and Neural Mechanisms: Study protocol of a multicentre randomized control study

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ABSTRACT

Introduction

As a combination of visual stimulation and motor imagery, mirror visual feedback (MVF) is an effective treatment for motor impairment after stroke. However, few studies have investigated the effect of MVF on involved cognition, like visual perception and motor imagery. Camera-based mirror visual feedback (camMVF) which overcomes intrinsic limitations and disadvantages of real mirror is recognized as an optimized setup. This study aims to investigate the effect of camMVF as an adjunct treatment for stroke patients comparing with conventional therapy, and the possible neural mechanisms of MVF on involved cognition and brain network.

Methods and analysis

This is a multicentre, single-blinded, randomized controlled trial including 90 patients randomized into camMVF group (MG=30), sham-MVF group (sham-MG=30) and conventional group (CG=30). Patients will receive 60 minutes corresponding intervention in each group for 5 days per week, lasting 4 weeks. The primary outcome is the Fugl-Meyer Assessment Upper Limb subscale (FMA-UL). Secondary outcomes include modified Ashworth Scale, Grip strength test, Purdue Pegboard Test, and modified Barthel Index, the Functional Independence Measure, the Berg Balance Scale, 10-meter walking test, hand laterality task and EEG signals.

Ethics and dissemination

Ethics approval was granted by Huashan Hospital Institutional Review Boards on 15th March 2017, (KY2017-230) in Shanghai, China. We plan to submit a manuscript of the results to a peer-reviewed journal, and present results at conferences, rehabilitation forums and the general public.

Trial registration number Chinese Clinical Trial Register, ID: ChiCTR-INR-17013644. Registered on 2 December, 2017.

Strengths and limitations of this study

- This is the first randomised controlled trial investigating the effect of camera-based MVF on stroke patients, and the underlying neuro-mechanism on involved cognition and brain network.
- Our findings could have the benefits of improving the technique and developing novel interface of MVF based on EEG results.
- This study presents a method of providing systematic procedure of mirror therapy.
- Comparisons of camera-based MVF and real mirror based MVF are still needed in the future studies.

INTRODUCTION

Upper extremity motor impairment is a specific consequence following stroke.[1] Approximately 65% of patients with hemisphere stroke live with a paretic upper extremity,[2] especially for the hand, which seriously affects motor performance and limits the quality of daily life. There are some evidence-based treatments to promote the recovery of upper extremity and hand, such as constraint-induced movement therapy, robot-assisted therapy, mirror therapy (MT) and so on. [3–5] MT, which is in wide use in the rehabilitation of upper extremity and hand, is a less labour intensive and more convenient method.[6–8] During MT, a plain mirror is employed to provide the reflection of the unaffected hand movements. The reflection (mirror visual feedback, MVF) can provide a misperception of ownership, which is recognized as mirror illusion. However, the real mirror used in MT has some disadvantages including balance control, postural pressure, weight shifting and undiversified training program, which limit the application in clinic.[9,10] To the best of our knowledge, numerous studies have proposed various technological strategies to create new interface of MVF to overcome these disadvantages.[10–14] As one of them, the feasibility of camera-based MVF in rehabilitation has been investigated by some previous studies.[9,13,15,16] Our previous study also showed that camera-based MVF could improve the motor function of upper limb and the ability of mental rotation for stroke patients.[16] In order to optimize MT, the camera-based MVF setup is employed in the present study for better training posture, more systematic training procedure, and manipulatable visual feedback. As suggested by previous study, stroke patients with better upper limb motor function have better balance control.[17] Moreover, the improved upper limb motor function might reduce the assistance during transfer and ambulation, and elicit an interlimb reflex response, which contribute to the improvements of lower limb function indirectly.[17,18] Therefore, we propose a hypothesis that camMVF could have the potential to improve the motor function of upper limb, similar with conventional MT, and might improve the ability of daily activity, balance control, and ambulation.

As a plasticity-based approach, the reversion of learned non-use and the activation of central nervous are general theory of MT.[19–22] Compared with real mirrors, the camera-based MVF also has the same therapeutic theory. Studies in amputees or healthy controls suggested that the camera-based MVF could increase the cortical activation of sensorimotor cortex, parietal and middle temporal cortex, using electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIS) techniques.[10,11,15,23] However, the effect of MVF on brain reorganization of stroke patients remains unexplored. MVF is recognized as one component of graded motor imagery combined with visual stimulation.[24–26] It is possible that MVF could promote the recovery of motor imagery ability, enhance visual perception of the affected limb, and reorganize the corresponding brain network. Brain network involved in motor imagery, especially the extended motor network, plays an important role in the motor process before execution, like motor preparation and planning.[27–29] An abnormal extended motor network has been found even in stroke patients with good functional recovery, and the abnormalities are correlated with residual functional impairment.[27] In our study, EEG recording combined with a hand laterality task, which involves visual processing and mental rotation of hands,[30] provides a good paradigm to study motor imagery and visual perception of hands. According to the result of our previous study,[16] we hypothesize that the improved efficiency of brain network communication can contribute to the performance of hand laterality task (reaction time and accuracy) after the intervention of camera-based MVF training. Moreover, relying on the reorganization of network, camera-based MVF training can also lead to different manifestations of event related potentials (ERP).

METHODS AND ANALYSIS

Design

This is a multicentre, single-blinded, randomized controlled trial (as part of the camera-based MVF study, the register number: ChiCTR-INR-17013644). A study flow is shown in Figure 1.

Patient population

Each centre is expected to randomize 30 stroke inpatients who meet the clinical criteria (Table 1).

Randomization

Patients are stratified using motor deficit severity (according to the Fugl-Meyer Upper Extremity (FMA-UE) score, more impaired ≤ 35 and less impaired ≥ 36)[31,32] and days from onset (early < 6 months and late ≥ 6 months). The eligible patients who are informed about and consent for the study will receive a baseline assessment, and then be randomly allocated into one of the groups. Patients in each group are treated separately without knowing the allocation during the whole study. The randomization assignment is generated through the Matlab (The MathWorks, Inc.) by an independent researcher.

Intervention

Patients are randomly assigned into camera-based MVF group (MG), sham-MVF group (sham-MG) or conventional group (CG). The allocation sequence is based on the computer-generated random number table. Randomization program and all the assignments are conducted by an independent researcher. All inpatients will receive 60-minute treatment per day, 5 days per week, and lasting for 4 weeks (20 sessions) during their hospitalization. Subsequent 30-minute hand function rehabilitation will be conducted for all patients after each treatment. Muscle stretch and massage are also administered for patients before and after treatments for relaxation purpose and all these interventions are in addition to their routine treatments (2 hours per day) in the hospital.

Camera-based MVF intervention

In this trial, we use a camera-based MVF box (1200 mm×940 mm×702 mm) to present manipulable visual feedback (mirrored, shielded, delayed and amplified), instead of a real plane mirror. Two mounted cameras are used to capture the hand motion, and a 23.8-inch LED screen (1920×1080 pixels) is used to present the visual feedback. During treatment, patients are seated in front of the LED screen with a comfortable height and place their hands in the box, which blocks the real visual feedback of both hands. The reflection and mirrored reflection of the unaffected hand are presented on the screen as the similar size of real hands during MG intervention (Figure 2). The camera-based MVF provides systematic procedure of MT, which contains basic and functional movement training items and verbal instructions with standard motion guide videos.

In the basic part, 25 items focusing on hand, wrist, and forearm are included, such as grasp, finger-to-finger, wrist extension/flexion, forearm supination/pronation and so on. Tool-based items, like bottle grasping and wooden cube picking, are included in the functional part. Therapists can choose any item to make a training plan according to the motor impairments. Moreover, in order to make the training more self-disciplinary and less labour intensive, there are verbal instructions/orders during the whole treatment and motion guiding videos at the initial of training.

During the camera-based MVF intervention, patients are asked to conduct the training motions symmetrically as possible and synchronously, and persuade themselves to imagine the moving hands on the screen are their own hands. Experienced therapist will make the training plan and adjust the difficulties of items to avoid global synkinesis of the affected limb and provide appropriate assistance. In this trial, every patient will receive 60-minute training per session including four to five items (include 3-4 basic items and 1-2 functional items), and each item repeats 60 times per session.

Sham-MVF intervention

The camera-based MVF box is still used for sham-MVF intervention, where the reflection of the affected side is shielded (Figure 2).[33] In sham-MG, patients are required to perform the same exercise as MG, including the training protocol, intensity, and duration. During the training, symmetrical motor attempt and imagining of both hands moving are required. We will compare the differences of clinical measurements and alterations of EEG signals before and after interventions between two groups to explore the effect of MVF.[34]

Conventional intervention

Conventional intervention contains dosage-equivalent treatments of physiotherapy and/or occupational therapy focused on hands, wrist and forearm (same exercise programs without MVF). The training principle and items are similar with MG and sham-MG.

Study outcomes

The primary outcome and clinical assessments will be administrated at baseline, after 2 weeks and 4 weeks of treatment by an independent researcher. Hand laterality task and EEG recording will be administrated before and after the intervention by another researcher.

Primary

The Fugl-Meyer Assessment Upper Limb subscale (FMA-UL) will be employed to assess the motor impairment as primary outcome.

Secondary

Clinical assessment

Clinical measurements contain modified Ashworth Scale (mAS), Grip strength test (hydraulic hand dynamometer, Exacta^{TM}), Purdue Pegboard Test, modified Barthel Index, the Functional Independence Measure (FIM), the Berg Balance Scale (BBS) and 10-meter walking test (10-MWT). And these measurements focus on the evaluation of motor impairment, motor function, tone and strength of muscle, dexterity of hands (mild to moderate impaired patients), mobility and daily function.

Hand laterality task and EEG recording protocol

The hand laterality task is used to assess the visual perception and motor imagery of hands, and the reaction time and accuracy of the task will be measured.[30] The patients are seated in front of a portable computer and judge the laterality of the hand pictures presented on the display (13 inches). The whole experiment consists of 4 blocks after 1 training block. There is a 3 min inter-block break. In each block, there are 96 trials. In each trial, a black cross is displayed for 800 ms, and then stimulus pictures (9 cm × 9 cm) of the left or right back-view hand at 6 different angles (0°, 60°, 120°, 180°, 240° and 300°, in total of 2 × 6 types stimulus pictures) are presented randomly with equal probability. Patients are requested to make hand laterality judgment as quickly and accurately as possible by pressing corresponding button using their unaffected hands. The hand pictures are presented until the patients respond. Stimuli are controlled by E-prime 2.0 (Psychology Software Tools, Inc, Pittsburgh, USA).

The EEG signals are collected from a 64-channel Ag/AgCl EasyCapTM (Brain Products GmbH, Munich, Germany) and recorded during the hand laterality task. All electrodes are referenced to FCz and with impendence below 20 kΩ. The EEG signals are amplified by BrainAmp MR Plus amplifier (Brain Products GmbH, Munich, Germany) and recorded continuously using Vision Recorder (Version 1.03, Brain Products GmbH, Munich, Germany) at sample rate of 1000 Hz. ERPs and network properties (including clustering coefficient and characteristic path length) will be analysed and compared among groups to investigate the underlying mechanism of camMVF.

Statistical methods

Sample Size

We perform sample size estimation to detect difference of group × time interaction on clinical outcome (FMA-UL). An effect size (f) of 0.27 to 0.3 is expected based on previous MVF studies.[11,35] With the expected effect size, sample size in total of 75 to 90 is required in repeated ANOVA given a power of 0.8 and a two-sided type-I error of 0.01. We therefore plan to recruit 90 patients (30 in each group) in this study.

Statistical analyses

The primary analysis will be performed using the intention-to-treat principle. The treatment effects will be compared using two-ways repeated measures analysis of variance (ANOVA) for clinical measurements, taking TIME (three levels: before intervention, 2 and 4 weeks after intervention) as within-subject factor and GROUP (three levels: MG, sham-MG and CG) as between-subject factor. Three-ways repeated ANOVA will be used to test the behaviour during the hand laterality task (response time and accuracy), taking TIME (two levels: before intervention and after intervention) and HAND (two levels: affected and unaffected) as within-subject factors and GROUP (three levels: MG, sham-MG and CG) as between-subject factor. A p-value < 0.05 will be set as indicating statistical significance for all analyses.

Patient and public involvement

Development of the research question and the intervention content were based on stroke patients who received MT via camMVF and gained motor improvements in our previous pilot study. The training protocols were iteratively improved based on feedbacks from participants since July, 2014. We assessed the participant burden of the intervention and research measures through group interviews and informal feedback in our previous pilot study. Patients will not be involved in recruitment of participants or conduct of the study. We will send a summary of results to all study participants.

ETHICS AND DISSEMINATION

This study has been approved by Huashan Hospital Institutional Review Boards on 15th March 2017, (KY2017-230) in Shanghai, China. And this trial has been registered on 2nd December 2017 as ChiCTR-INR-17013644. Patient recruitment begins from 10th Dec. 2017 to 31th Dec. 2018 and primary data analysis will begin in October 2018. The institutional review board of Huashan Hospital will receive the study reports at the middle and end of the study and monitor the study implementation and data collection. Any modifications to the protocol will also be agreed by the review board. All the study data will be preserved as case report forms. Huashan Hospital is sponsor for the study. Patients will be recruited from Huashan Hospital Fudan University Jing'an Branch, the first Rehabilitation Hospital of Shanghai and Shanghai Changning Tianshan Traditional Medicine Hospital and receive intervention there. This study protocol was written in line with the SPIRIT checklist.[36] The study weill eventually be published in a peer-reviewed journal, and findings will be presented at conferences, rehabilitation forums and the general public.

DISCUSSION

MT is a plasticity-based approach which has shown significant results on motor impairment in RCTs.[3,6,7] But the real mirror has some technological limitations and disadvantages, such as weight shifting and postural pressure,[9,10] which could be overcame by the camera-based MVF. The present study is aimed to test the effectiveness of camera-based MVF therapy, comparing with conventional treatment in stroke rehabilitation and investigate underlying neural mechanism from aspects of involved cognition and brain network. Our study will indicate future implementation of novel manipulable MVF and systematic procedure and suggest better understanding of central mechanism in motor control that will improve the effectiveness of MT.

MVF is a visual stimulation combined with motor imagery.[24–26] This special reflection can enhance the perception of affected limbs and sense of ownership; besides, with the activation of cognitive cortex, MVF can eventually activate the primary motor cortex and restore motor execution.[37,38] Stroke disrupted both corticospinal output, like motor execution and motor processes more upstream, such as attention, motor preparation, or planning.[29] Recognized as one component of graded motor imagery,[24,26] MVF might have the potential to improve motor imagery and visual perception of the affected hand, mediate motor cognitive process, and reorganize the motor network eventually. According to the results of clinical measurements and EEG analysis of the MG, sham-MG and CG, the study is aimed to explore the neural mechanism of MVF, which will be the supplementary evidence on reversal of cortical reorganization and plasticity of MVF.

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Contributors

All the authors were involved in the conception and design of research. L Ding and X Wang are principal investigator; XL Guo is responsible for the EEG recording and analyses; SC Chen and HW Wang advised the design of the camMVF system and treatment procedure; X Cui, JF Rong and J Jia are responsible for the different study centre; J Jia is the lead researcher and study manager. L Ding wrote the first draft and all the authors contributed to the final version.

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Competing interests

None declared.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
• From 25 to 75 years old	• Medical conditions deteriorate
• Diagnosed as unilateral stroke by CT or MRI between two weeks and one year following stroke onset	• A history of epilepsy and serious heart, lung, liver and kidney function failure
• Ability of following the instructions (MMSE ≥ 25)	• Other problems that hinder the study implementation
• Muscle tension (mAS ≤ 2)	
• Ability of identify the laterality of the hands	

CT: Computed Tomography; MRI: Magnetic Resonance Imaging; MMSE: The Mini–Mental State Examination; mAS: modified Ashworth Scale.

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Figure Legends

Figure 1. Trial flow chart. MG: camera-based mirror visual feedback intervention group; Sham-MG: shielded mirror visual feedback intervention group; CG: conventional intervention group.

Figure 2. The camera-based Mirror Visual Feedback (MVF) system in the present study. **A:** normal MVF of bar grasping for patients in MG; **B:** shielded MVF of making a fist for patients in sham-MVF.

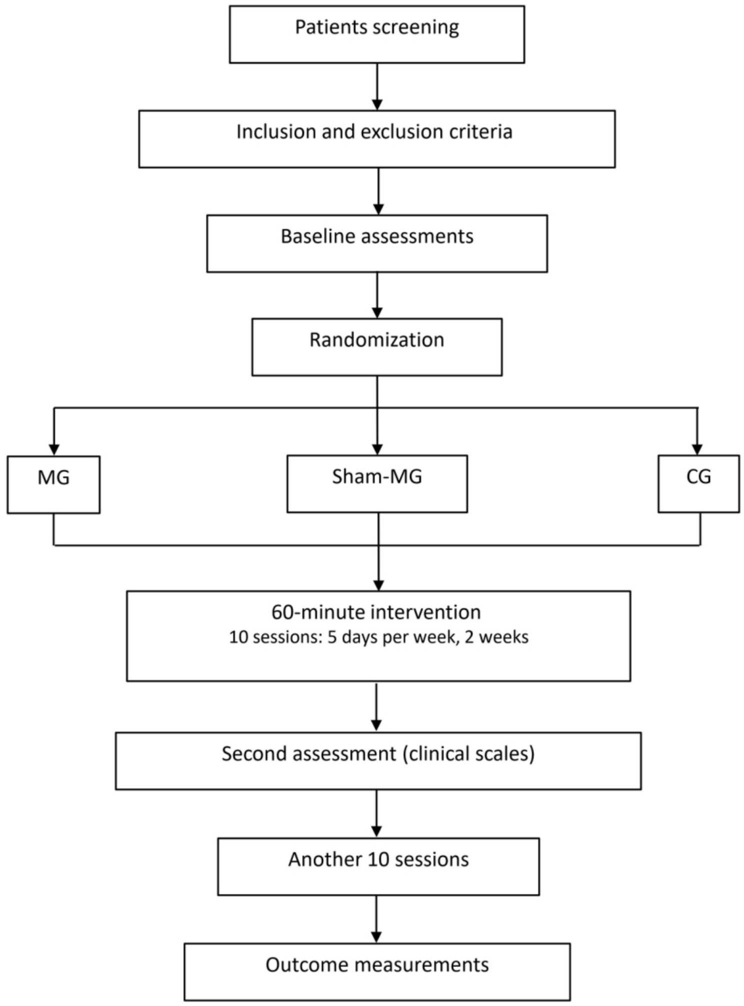

Figure 1. Trial flow chart. MG: camera-based mirror visual feedback intervention group; Sham-MG: shielded mirror visual feedback intervention group; CG: conventional intervention group.

149x156mm (300 x 300 DPI)

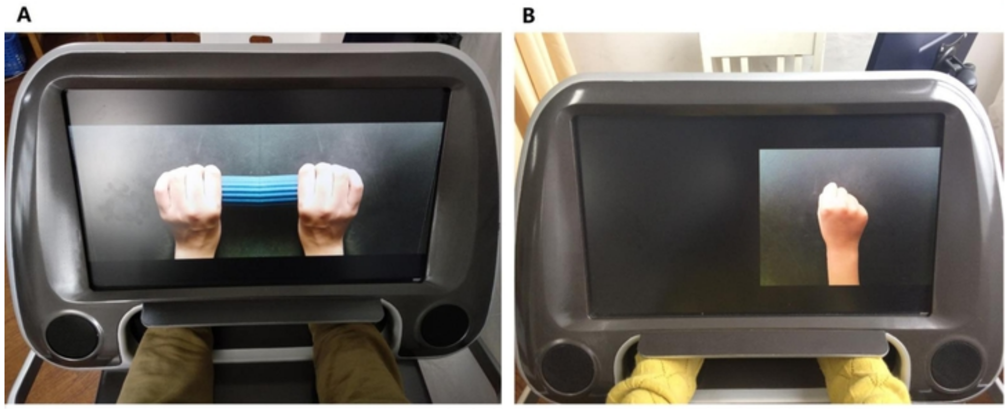

Figure 2. The camera-based Mirror Visual Feedback (MVF) system in the present study. A: normal MVF of bar grasping for patients in MG; B: shielded MVF of making a fist for patients in sham-MVF.

61x25mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	6
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	6
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	See note 1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	4

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	4
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See note 2
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	See note 3
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	See note 4
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	See note 5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	See note 6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	See note 7
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	See note 8

Author notes

1. 6, name and grant number were provided
2. n/a, no other analyses are included
3. n/a, analyses will be conducted at the end of the study
4. n/a, the study protocol has been approved by ethical boards, and adverse events were limited in this study.
5. n/a, no ancillary studies included
6. n/a, review board has approved the safety and feasibility of the study
7. n/a, the data (case report form) will be preserved by review board of Huashan Hospital and data disclose has been described during the clinical trial registration.

8. n/a, no biological specimens in the study

 This checklist was completed on 08. March 2018 using http://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Effects of camera-based mirror visual feedback therapy for stroke patients and the neural mechanisms involved: Protocol of a multicentre randomized control study

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Effects of camera-based mirror visual feedback therapy for stroke patients and the neural mechanisms involved: Protocol of a multicentre randomized control study

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Effects of camera-based mirror visual feedback therapy for stroke patients and the neural mechanisms involved: Protocol of a multicentre randomized control study

Li Ding[1], Xu Wang[2], Xiaoli Guo[2], Shugeng Chen[1], Hewei Wang[1], Xiao Cui[3], Jifeng Rong[4], Jie Jia[1,5,6]

ABSTRACT

Introduction

As a combination of visual stimulation and motor imagery, mirror visual feedback (MVF) is an effective treatment for motor impairment after stroke; however, few studies have investigated its effects on relevant cognitive processes such as visual perception and motor imagery. Camera-based MVF (camMVF) overcomes the intrinsic limitations of real mirrors and is recognized as an optimal setup. This study aims to investigate the effects of camMVF as an adjunct treatment for stroke patients, compare camMVF outcomes with those of conventional therapy, and elucidate neural mechanisms through which MVF influences cognition and brain networks.

Methods and analysis

This will be a multicentre, single-blinded, randomized controlled trial including 90 patients randomized into three groups: camMVF (MG = 30), sham-MVF (sham-MG = 30), and conventional (CG = 30). Patients in each group will receive a 60-min intervention 5 days per week over 4 weeks. The primary outcome will be the Fugl-Meyer Assessment Upper Limb subscale (FMA-UL) measurement. Secondary outcomes include the modified Ashworth Scale, Grip strength test, modified Barthel Index, Functional Independence Measure, Berg Balance Scale, 10-meter walking test, hand laterality task, and electroencephalography (EEG).

Ethics and dissemination

Ethics approval was granted by Huashan Hospital Institutional Review Boards on March 15, 2017 (KY2017-230). We plan to submit the results to a peer-reviewed journal and present them at conferences, rehabilitation forums, and to the general public.

Trial registration number Chinese Clinical Trial Re, ID: ChiCTR-INR-17013644. Registered on December 2, 2017.

Strengths and limitations of this study

- This is the first randomised controlled trial investigating the effect of camera-based MVF on stroke patients and the underlying neural mechanisms.
- Our findings could help improve camera-based MVF techniques and facilitate development of a novel MVF interface, based on EEG results.
- This study presents a method for developing a systematic procedure for mirror therapy.
- Future studies including comparisons of camera- and real mirror-based MVF are required.

INTRODUCTION

Upper extremity motor impairment is a specific consequence of stroke.[1] Approximately 65% of patients with hemisphere stroke live with paretic upper extremities,[2] particularly the hands, which seriously affects motor performance and decreases quality of life. Some evidence-based treatments promote the recovery of the upper extremities and hands, such as constraint-induced movement therapy, robot-assisted therapy, and mirror therapy (MT), among others. [3–5] MT, which is widely used during rehabilitation of the upper extremities and hands, is less labour intensive and more convenient than other methods.[6–8] During MT, a plain mirror is employed to provide reflection of the unaffected hand movements. The reflection (referred to as mirror visual feedback, MVF) can generate a misperception of ownership, which is recognized as a mirror illusion; however, the real mirror used in MT has some disadvantages including lacking balance control, postural pressure, and weight shifting, and it provides an undiversified training program, all of which limit its clinical application.[9,10] Numerous studies have proposed various technological approaches to create a new MVF interface to overcome these disadvantages.[10–14] The feasibility of one such strategy for rehabilitation, camera-based MVF (camMVF), has been investigated in previous studies.[9,13,15,16] Our prior research demonstrated that camMVF can improve upper limb motor function and mental rotation ability in stroke patients.[16] To optimize MT, a camMVF setup was employed in the present study to improve training posture, provide a more systematic training procedure, and manipulable visual feedback. A previous report suggested that stroke patients with superior upper limb motor function have better balance control.[17] Moreover, improved upper limb motor function may reduce the assistance required during transfer and ambulation, and elicit an interlimb reflex response, which can indirectly contribute to improvements in lower limb function.[17,18] Therefore, we hypothesise that camMVF could improve upper limb motor function, in a similar way to conventional MT, and has potential to improve the ability of patients to achieve daily activities, balance control, and ambulation.

As a plasticity-based approach, the reversion of learned non-use and activation of the central nervous system are the theoretical bases of MT.[19–22] Compared with real mirrors, camMVF is, in theory, therapeutically identical. Electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIS) studies of amputees or healthy controls have suggested that camMVF can increase cortical activation of the sensorimotor cortex, along with the parietal and middle temporal cortices.[10,11,15,23] However, the effects of MVF on brain reorganization in stroke patients remain unexplored. MVF is recognized as one component of graded motor imagery, combined with visual stimulation.[24–26] It is possible that MVF could promote the recovery of motor imagery ability, enhance visual perception of the affected limb, and reorganize the corresponding brain network. Brain networks involved in motor imagery, particularly the extended motor network, are important for the motor processes that precede execution, such as motor preparation and planning.[27–29] An abnormal extended motor network has even been found in stroke patients with good functional recovery, and such abnormalities correlate with residual functional impairment.[27] In our study, EEG recording combined with a hand laterality task, which involves visual processing and mental rotation of hands,[30] provides a good paradigm by which to study motor imagery and visual perception of the hands. Based on the results of our previous study,[16] we hypothesised that improved brain network communication efficiency can contribute to performance in the hand laterality task (reaction time and accuracy) following camMVF training intervention. Moreover, relying on network reorganization, camMVF training can also lead to different manifestations of event-related potentials (ERPs).

METHODS AND ANALYSIS

Design

This is a multicentre, single-blinded, randomized controlled trial (part of the camMVF study, registration number: ChiCTR-INR-17013644). A study flow diagram is presented in Figure 1.

Patient population

Each centre is expected to randomize 30 stroke inpatients who meet the clinical criteria (Table 1).

Randomization

Patients will be stratified based on motor deficit severity, according to the Fugl-Meyer Upper Limb (FMA-UL) score, where patients with scores ≤35 are classified as more impaired and those with scores ≥36 as less impaired, [31,32] and days from onset (early <6 months and late ≥6 months). Eligible patients who are informed about and consent to participate in the study will receive a baseline assessment, and then be randomly allocated into one of the groups. Patients in each group will be treated separately without knowing their allocation throughout the entire study. Randomization assignment will be generated using MATLAB (The MathWorks, Inc.) by an independent researcher.

Intervention

Patients will be randomly assigned into one of three groups: camMVF (MG), sham-MVF (sham-MG), or conventional treatment (CG). The allocation sequence will be based on a computer-generated random number table. The randomization program and all assignments will be conducted by an independent researcher. During their hospitalization, all inpatients will receive 60 min of treatment per day, for 5 days a week, lasting for 4 weeks (20 sessions). Hand function rehabilitation (30 min) will be conducted for all patients following each treatment. Muscle stretch and massage will also be administered to patients before and after treatments for relaxation purposes, and all of these interventions will be in addition to their routine hospital treatments (2 h per day).

CamMVF intervention

In this trial, we will use a camMVF box (1200 × 940 × 702 mm) to present manipulable visual feedback (mirrored, shielded, delayed, and amplified), in place of a real plane mirror. Two mounted cameras will be used to capture hand motions, and visual feedback will be presented using a 23.8-inch LED screen (1920 × 1080 pixels). During treatment, patients will be seated in front of the LED screen at a comfortable height and place their hands in the box, which will block real visual feedback from both hands. The reflection and mirrored reflection of the unaffected hand will be presented on the screen at a similar size to real hands during the MG intervention (Figure 2). CamMVF provides a systematic procedure for MT, which contains basic and functional movement training items and verbal instructions with standard motion guide videos.

The basic part comprises 25 items that focus on the hand, wrist, and forearm, such as grasp, finger-to-finger, wrist extension/flexion, and forearm supination/pronation. The functional part will include tool-based items, such as bottle grasping and wooden cube picking. Therapists can choose any item to design a training plan, according to the patient's motor impairments. Moreover, to make the training more self-guided and less labour intensive, there are verbal instructions/orders during the whole treatment, along with motion guiding videos during the initial training.

During the camMVF intervention, patients will be asked to conduct the training motions as symmetrically and synchronously as possible, and to persuade themselves to imagine the moving hands on the screen are their own. An experienced therapist will design the training plan and adjust item difficulty to avoid global synkinesis of the affected limb and provide appropriate assistance. In this trial, every patient will receive a 60-min training session, including 4 to 5 items (with 3–4 basic items and 1–2 functional items), and each item will be repeated 60 times per session.

Sham-MVF intervention

The camMVF box will also be used for the sham-MVF intervention; however, the reflection of the affected side will be shielded (Figure 2).[33] In the sham-MG group, patients will be required to perform the same exercises as those in the MG group, including the training protocol, intensity, and duration. During training, patients will be required to attempt symmetrical movement and imagine that both hands are moving. We will compare the differences in clinical measurements and alterations in EEG signals before and after interventions between the two groups to explore the effects of MVF.[34]

Conventional intervention

Conventional intervention will comprise dosage-equivalent treatments of physiotherapy and/or occupational therapy focused on the hands, wrists, and forearms (i.e., the same exercise programs without MVF). The training principle and items will be similar to those applied for the MG and sham-MG groups.

Study outcomes

The primary outcome and clinical assessments will be measured by an independent researcher at baseline, and after 2 and 4 weeks of treatment. The hand laterality task and EEG recording will be administered before and after the intervention by another researcher.

Primary

The FMA-UL subscale will be used to assess motor impairment as the primary outcome.

Secondary

Clinical assessment

Clinical measurements will include the modified Ashworth Scale (mAS), grip strength test (hydraulic hand dynamometer, Exacta^{TM}), modified Barthel Index, functional independence measure (FIM), Berg balance scale (BBS), and 10-meter walking test (10-MWT). These measurements focus on the evaluation of motor impairment, motor function, muscle tone and strength, hand dexterity (mild to moderately impaired patients), mobility, and daily function.

Hand laterality task and EEG recording protocol

The hand laterality task is used to assess visual perception and motor imagery of the hands, and the reaction time and accuracy of the task will be measured.[30] The patients will be seated in front of a laptop and asked to judge the laterality of hand images presented on the 13-inch display. The whole experiment consists of four blocks, following a single training block. There will be 3-min inter-block breaks. In each block, there will be 96 trials. In each trial, a black cross is displayed for 800 ms, and then stimulus images (9 × 9 cm) of the back-view of the left or right hand at six different angles (0°, 60°, 120°, 180°, 240°, and 300°), giving a total of 2 × 6 types of stimulus image, will be presented randomly with equal probability. Patients will be instructed to make hand laterality judgments as quickly and accurately as possible by pressing a corresponding button using their unaffected hand. Images will be presented until the patient responds. Stimuli will be controlled using E-prime 2.0 (Psychology Software Tools, Inc, Pittsburgh, PA, USA).

EEG signals will be collected from a 64-channel Ag/AgCl EasyCap^{TM} (Brain Products GmbH, Munich, Germany) and recorded during the hand laterality task. All electrodes will be referenced to FCz and have impendence <20 kΩ. EEG signals will be amplified using a BrainAmp MR Plus amplifier (Brain Products GmbH, Munich, Germany) and recorded continuously using Vision Recorder (Version 1.03) at sample rate of 1000 Hz. ERPs and network properties (including clustering coefficient and characteristic path length) will be analysed and compared among groups to investigate the mechanism underlying camMVF.

Statistical methods

Sample Size

We estimated the sample size required to detect differences in the effects of group × time interactions on clinical outcome (FMA-UL). An effect size (f) of 0.27 to 0.3 is expected, based on previous MVF studies.[11,16,35] Given the expected effect size, a total sample size of 75 to 90 will be required for repeated analysis of variance (ANOVA) with a power of 0.8 and a two-sided type-I error of 0.01. Therefore, we plan to recruit 90 patients (30 per group).

Statistical analyses

Primary analysis will be performed using the intention-to-treat principle. Treatment effects will be compared using a two-way repeated ANOVA for clinical measurements, taking TIME (three levels: before intervention, and 2 and 4 weeks after intervention) as a within-subject factor and GROUP (three levels: MG, sham-MG, and CG) as a between-subject factor. A three-way repeated ANOVA will be used to test behaviour during the hand laterality task (response time and accuracy), taking TIME (two levels: before and after intervention) and HAND (two levels: affected and unaffected) as within-subject factors and GROUP (three levels: MG, sham-MG, and CG) as a between-subject factor. A p-value < 0.05 will indicate statistical significance for all analyses.

Patient and public involvement

Development of the research question and intervention content was based on data from stroke patients in our previous pilot study who received MT via camMVF and achieved motor improvements. Training protocols were iteratively improved based on feedback from participants since July 2014. We assessed the participant burden of the intervention and research measures using group interviews and informal feedback in our previous pilot study. Patients will not be involved in participant recruitment or study conduct. We will send a summary of the study results to all participants.

ETHICS AND DISSEMINATION

This study was approved by Huashan Hospital Institutional Review Board on March 15, 2017, (KY2017-230) in Shanghai, China. This trial was registered on December 2, 2017 (ChiCTR-INR-17013644). Patient recruitment began December 10, 2017 and will continue to December 31, 2018. Primary data analysis began in October 2018. The institutional review board of Huashan Hospital will receive study reports at the middle and end of the study and monitor the study implementation and data collection. Any modifications to the protocol will also be agreed by the review board. All study data will be preserved as case report forms. Huashan Hospital is the sponsor for the study. Patients will be recruited from Huashan Hospital Fudan University Jing'an Branch, the first Rehabilitation Hospital of Shanghai, and Shanghai Changning Tianshan Traditional Medicine Hospital and receive interventions at these hospitals. This study protocol was written according to the SPIRIT checklist.[36] The study will eventually be published in a peer-reviewed journal, and the findings will be presented at conferences, rehabilitation forums, and to the general public.

DISCUSSION

MT is a plasticity-based approach shown to have significant effects on motor impairment in RCTs;[3,6,7] however, real mirrors have some technological limitations and disadvantages, including weight shifting and postural pressure,[9,10] which may be overcome using camMVF. The present study is aimed to test the effectiveness of camMVF therapy, compare it with conventional treatment for stroke rehabilitation, and investigate the underlying neural mechanisms for involved aspects of cognition and brain networks. Our study will identify methods and systematic procedures for future implementation of the novel, manipulable camMVF method and facilitate better understanding of the central mechanisms involved in motor control, which will improve MT effectiveness.

MVF is a visual stimulation combined with motor imagery.[24–26] This special type of reflection can enhance the perception of affected limbs and increase the patient's sense of ownership. In addition, by activating the cognitive cortex, MVF can eventually activate the primary motor cortex and improve motor execution.[37,38] Stroke disrupts both corticospinal output (e.g. upstream motor execution) and motor processes (e.g. attention, motor preparation, and planning).[29] Recognized as contributing to graded motor imagery,[24,26] camMVF may have the potential to improve motor imagery and visual perception of the affected hand, mediate motor cognitive processes, and eventually reorganize the motor network. According to the results of clinical measurements and EEG analysis of the MG, sham-MG, and CG groups, the study aims to explore the neural mechanisms underlying camMVF, which will provide supplementary evidence of how this therapy can promote cortical reorganization and plasticity.

Acknowledgements

The authors would like to thank the participants of our previous pilot investigation for contributing to the study design by providing feedback about their experiences and preferences.

Contributors

All the authors were involved in the conception and design of the research. L Ding and X Wang are the principal investigators. XL Guo will be responsible for EEG recording and analyses. SC Chen and HW Wang advised on the design of the camMVF system and treatment procedure. X Cui, JF Rong, and J Jia are responsible for the different study centres. J Jia is the lead researcher and study manager. L Ding wrote the first draft, and all the authors contributed to the final version of this protocol.

Funding

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Competing interests

None declared.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
• Age, 25 to 75 years old • Diagnosed with unilateral stroke by CT or MRI between 2 weeks and 1 year following stroke onset • Ability to follow the instructions (MMSE ≥ 25) • Muscle tension (mAS ≤2) • Ability to identify hand laterality	• Deteriorating medical condition • A history of epilepsy or serious heart, lung, liver, or kidney function failure • Other problems that hinder study implementation

CT, computed tomography; mAS, modified Ashworth scale; MRI, magnetic resonance imaging; MMSE, mini-mental state examination.

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Figure Legends

Figure 1. Trial flow chart. MG, camera-based mirror visual feedback intervention group; Sham-MG, shielded mirror visual feedback intervention group; CG, conventional intervention group.

Figure 2. The camera-based mirror visual feedback (MVF) system used in the present study. **A:** Normal MVF of bar grasping for patients in the MG group. **B:** Shielded MVF of making a fist for patients in the sham-MVF group.

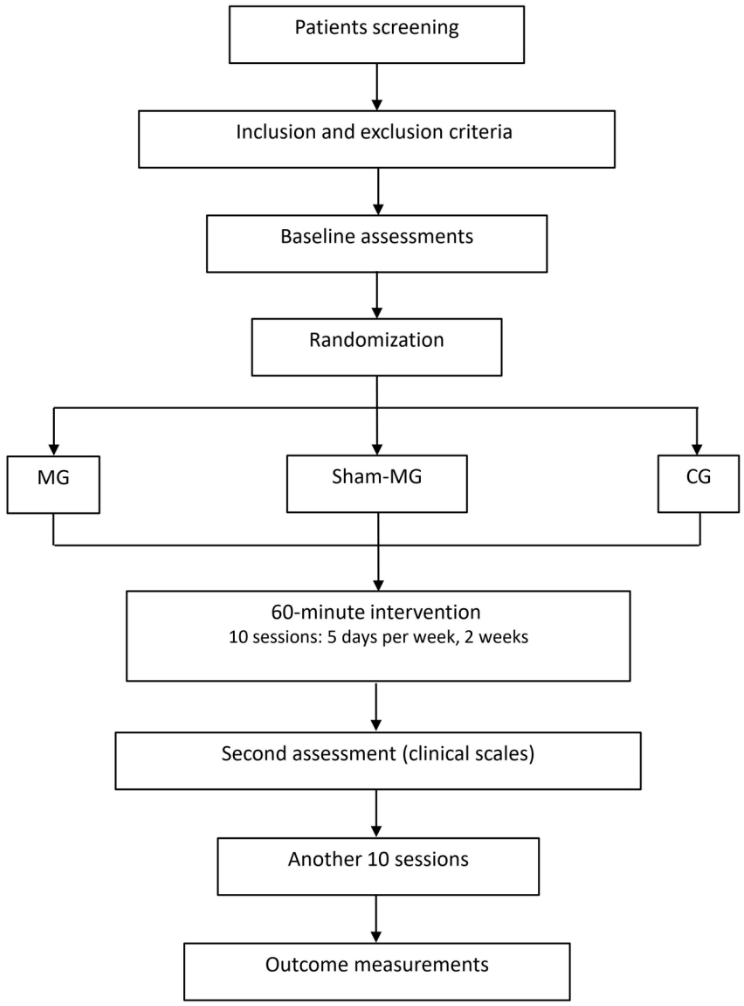

Figure 1. Trial flow chart. MG: camera-based mirror visual feedback intervention group; Sham-MG: shielded mirror visual feedback intervention group; CG: conventional intervention group.

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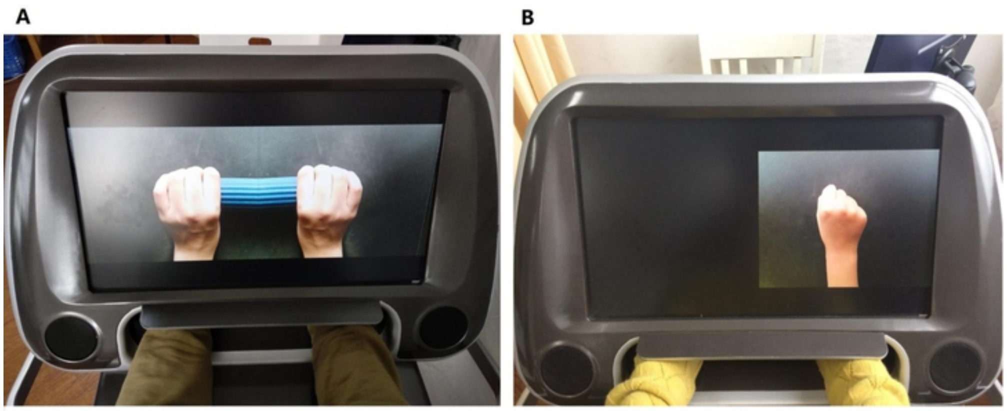

Figure 2. The camera-based Mirror Visual Feedback (MVF) system in the present study. A: normal MVF of bar grasping for patients in MG; B: shielded MVF of making a fist for patients in sham-MVF.

61x25mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	6
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	6
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	See note 1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	3
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	4

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	4
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	See note 2
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	See note 3
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	See note 4
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	6
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	See note 5
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Data access	#29	Statement of who will have access to the final trial dataset,	n/a

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	See note 6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	See note 7
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	See note 8

Author notes

1. 6, name and grant number were provided
2. n/a, no other analyses are included
3. n/a, analyses will be conducted at the end of the study
4. n/a, the study protocol has been approved by ethical boards, and adverse events were limited in this study.
5. n/a, no ancillary studies included
6. n/a, review board has approved the safety and feasibility of the study
7. n/a, the data (case report form) will be preserved by review board of Huashan Hospital and data disclose has been described during the clinical trial registration.

8. n/a, no biological specimens in the study

 This checklist was completed on 08. March 2018 using http://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai