

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of camera-based mirror visual feedback therapy for stroke patients and the neural mechanisms involved: Protocol of a multicentre randomized control study
AUTHORS	Ding, Li; Wang, Xu; Guo, Xiaoli; Chen, Shugeng; Wang, Hewei; Cui, Xiao; Rong, Jifeng; Jia, Jie

VERSION 1 – REVIEW

REVIEWER	Dr Kenneth Monaghan Institute of Technology (IT) Sligo, Ireland
REVIEW RETURNED	11-Apr-2018

GENERAL COMMENTS	<p>TITLE Seems appropriate.</p> <p>ABSTRACT Appears to be an appropriate account of the protocol.</p> <p>INTRODUCTION Overall good rationale provided for the need to have this study, with an appropriate literature provided. Specific comments Authors may need to be careful with language in second sentence. I am certain there are more than 3 evidence based treatments for upper extremity recovery, but they focus on just 3. Can they clarify what 'single fixed training mode' means? The authors mention that the feasibility of camera based MVF has been studied before. Could some of the data from these studies be included to put in context the range of improvements that were achieved. As mentioned below in the methods section, should the authors refer to the potential ability of MVF to influence balance/lower limb function when used primarily in the upper limb. The secondary outcomes chosen would suggest that this is possible so perhaps some mention of examples from the literature would be useful for the reader. Generally, it is assumed that we choose outcome measures based on an obvious link between the intervention and that particular outcome but I cannot see the obvious potential of upper limb Mirror Therapy to improve balance or walking speed/velocity.</p> <p>METHODS Specific Comments Will it be possible to recruit a large enough sample of > 6 months since stroke population of 'Inpatients' as is suggested?</p>
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	<p>'all these interventions are in addition to their routine treatments in the hospital'. Is it possible that the routine treatments in the hospital could influence the recovery rather than the actual MVF etc. Can the authors define the routine treatments in hospital in terms of how many minutes' therapy patients are likely to receive, and is this different for the < 6 months/> 6 months' patient groups? Why are the outcomes assessed after 2 weeks of treatments rather than just at baseline and end of the 4 weeks?</p> <p>Regarding the outcome measures chosen, can I query why so many secondary outcomes were chosen. I think a justification for so many might be needed, and can each outcome state what exactly is being measured e.g. the MAS is reported to measure spasticity but almost all reviewers of my papers have queried the fact that MAS measures muscle tone rather than spasticity. Can the authors be more specific? In particular, I am interested to know;</p> <ul style="list-style-type: none"> • Is the Wolf Motor Function required when the Fugl Meyer is already the primary outcome scale? • What instrument for the Grip Strength Test? • Why the Berg Balance Scale when the upper limb is being targeted by the therapy. Perhaps more reference to the potential effects of Mirror Therapy with balance need to be introduced in the Introduction. • Again, why the 10MWT when upper body therapy being applied. If the authors feel that there is a logical potential for upper limb therapy to influence lower limb function, then it would be important for all readers to see this mentioned in the Introduction. <p>Can the issue of blinding be addressed? It is not specified who undertakes the outcome assessments. I would advise that it is an independent clinician because although it is easy to randomise and not allow a member of your team know what group a participant has been in, for relative subjective assessments e.g. MAS, there is always the chance that all groups can be given a higher value in re-assessments and this can potentially bias the findings.</p> <p>Can allocation of patients to each group be discussed in methods and how authors intend to minimise allocation bias?</p>
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REVIEWER	Floriana Pichiorri Fondazione Santa Lucia, IRCCS, Rome, Italy
REVIEW RETURNED	05-Jun-2018

GENERAL COMMENTS	<p>The paper presents a study protocol to investigate the effects of camera based mirror therapy for upper limb motor rehabilitation after stroke. Although the study design is clear, as well as the general/main objective (to demonstrate a better outcome in the target group), I have several concerns regarding specific objectives and the lack of sufficient details on the study methods.</p> <ol style="list-style-type: none"> 1. I recommend English revision (typos, and a random use of present and future tenses makes the reading challenging). 2. What are the specific objectives: eg which mechanisms underlie the expected improved outcome with the proposed training, what do you expect to see in the hand laterality task and in the eeg evaluation (page 4) 3. the instruction given to the patients in the camera based MVF intervention is not clear: I believe it is motor attempt with both
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	<p>hands but then what is the relation with motor imagery (page 5 lines 38-40)</p> <p>4. The sham MVF is even less clear, what will the patient do? again motor attempt or imagery? did you refer to previous literature to implement the sham condition? (page 5 lines 48-53)</p> <p>5. page 4 line 50 you say you mean to compare eeg signals in the two conditions, do you mean during the training session or before/after the training period? this is not clear</p> <p>6. EEG evaluation: from page 6 lines 27-44 I understand that EEG will be recorded during the hand laterality task, is this correct?; it is not sufficiently clear how this data will be analyzed and what measures will be taken into consideration (and also what are the hypotheses for choosing these measures): brain network is definitely too general.</p> <p>Altogether I believe that, for a protocol description to be worth reading (and publishing) there is need for:</p> <ul style="list-style-type: none"> - clearer general and specific objectives and hypotheses (which could be confirmed by the results or confuted) - definitely better explanation of the methods and I refer particularly to: a) intervention protocol and sham protocol (how was it implemented and why so) b) analyses to be performed on accompanying outcome measures: hand laterality task and eeg, with specific hypotheses and expectations.
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REVIEWER	Michel Guerraz University Savoie Mont Blanc
REVIEW RETURNED	27-Aug-2018

GENERAL COMMENTS	<p>The manuscript reports a planned study already approved by the by Huashan Hospital Institutional Review Boards on 15th March 2017. Except that date of approval, there is no clear timetable for the study</p> <p>The present project is of great interest and likely useful for the neuro-rehabilitation community. The purpose is to test the effect of Mirror Visual Feedback (and more specifically camera based MVF) on motor rehabilitation following stroke but also on brain plasticity with a rather large sample of stroke participants (90 participants divided in three groups of 30). The procedure is clear and the study well controlled.</p> <p>Minor correction Line 27 : functional magnetic resonance imaging instead of functional magnetic imagine</p>
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VERSION 1 – AUTHOR RESPONSE

Response to the reviewers' comments

Reviewer #1:

Reviewer Name: Dr Kenneth Monaghan

Institution and Country: Institute of Technology (IT) Sligo, Ireland

Please state any competing interests or state 'None declared': None declared.

General comments:

TITLE: Seems appropriate. ABSTRACT: Appears to be an appropriate account of the protocol. INTRODUCTION: Overall good rationale provided for the need to have this study, with an appropriate literature provided.

Specific comments:

1. *Authors may need to be careful with language in second sentence. I am certain there are more than 3 evidence based treatments for upper extremity recovery, but they focus on just 3.*

Response: Thanks for the comment, and our apologies for unclear statements. As the reviewer suggested, in the revision, a more careful statements were added. The part was revised as the following:

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

2. *Can they clarify what 'single fixed training mode' means?*

Response: Thanks for the comment. There are some disadvantages of conventional mirror therapy via a real mirror. One of them is undiversified training program, which we called "single fixed training mode". A real mirror can only present regular mirror visual feedback and therapists usually provide repeated, monotonous exercise, which limits the application of mirror therapy. Thus, in the manuscript, "single fixed training mode" meant undiversified training program. In order to make it clearer, this was rewritten as following:

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}

3. *The authors mention that the feasibility of camera based MVF has been studied before. Could some of the data from these studies be included to put in context the range of improvements that were achieved.*

Response: We thank the reviewer for this comment. The populations of studies on the feasibility of camera-based MVF vary, including healthy subjects and patients; moreover, the protocols of these studies are also different from each other. So we chose one of our previous study on camera-based MVF (cited as #16) to clarify the feasibility of it. This part was revised as following:

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 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 was employed in the present study for better training posture, more systematic training procedure, and manipulatable visual feedback.

- 4. As mentioned below in the methods section, should the authors refer to the potential ability of MVF to influence balance/lower limb function when used primarily in the upper limb. The secondary outcomes chosen would suggest that this is possible so perhaps some mention of examples from the literature would be useful for the reader. Generally, it is assumed that we choose outcome measures based on an obvious link between the intervention and that particular outcome but I cannot see the obvious potential of upper limb Mirror Therapy to improve balance or walking speed/velocity.*

Response: We thank the reviewer for this suggestion and comments. From the perspective of whole body function, there are interactions between lower and upper limbs. For example, the improvement of motor control of upper limb (such as arm swinging) might contribute to the balance control or ambulation. Moreover, some studies also reported that patients with better function of upper limb could have better balance control and ability of ambulation. Thus, we hypothesized that upper limb MT could improve lower limb function, although there is no obvious link between the present intervention and outcomes. As suggested by the reviewer, this was added and explained in the Introduction section as following:

As suggested by previous study, stroke patients with better upper limb motor function had 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} Thus, we proposed 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.

- 5. Will it be possible to recruit a large enough sample of > 6 months since stroke population of 'Inpatients' as is suggested?*

Response: Thanks for the comment. The majority of medical resources distributed mainly in general hospitals in China. Therefore, many patients would choose to stay in the hospital to receive treatment rather than in the community health care centre or at home, even if they are in chronic stage. Moreover, we recruited 79 patients in our previous study, where 24 of them were in chronic stage. So, it is possible to recruit enough sample in the present study.

- 6. 'all these interventions are in addition to their routine treatments in the hospital'. Is it possible that the routine treatments in the hospital could influence the recovery rather than the actual MVF etc.*

Can the authors define the routine treatments in hospital in terms of how many minutes' therapy patients are likely to receive, and is this different for the < 6 months/> 6 months' patient groups?

Response: We thank the reviewer for this insightful comment. In the present study, all the eligible patients of the three groups (MG, Sham-MG, and CG), who met the inclusion criteria will receive the routine treatments. Similar routine programs will be provided based on the comparable baseline characteristics of each patient. Thus, from the perspective of analysis, it is comparable among each group for the routine treatments. In our hospital, patients receive the routine treatments focusing on motor functions for around 2 hours every day, mainly including physical therapy and occupational therapy, such as passive movement training, neurodevelopmental approaches, strength training, massage, stretching, traditional Chinese medicine, occupational therapy and so on. No special or interventional methods will be conducted. The routine treatments might vary from patient to patient according to the motor deficit severity, but they are not dependent on the time after stroke in our hospital. As suggested by the reviewer, this point was clarified in the Method section as the following:

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.

7. *Why are the outcomes assessed after 2 weeks of treatments rather than just at baseline and end of the 4 weeks?*

Response: We appreciate this comment. In order to investigate the optimal treatment time for camMVF, we plan to conduct the second assessments after 2-weeks intervention to observe the tendency of therapeutic effectiveness.

8. *Regarding the outcome measures chosen, can I query why so many secondary outcomes were chosen. I think a justification for so many might be needed, and can each outcome state what exactly is being measured e.g. the MAS is reported to measure spasticity but almost all reviewers of my papers have queried the fact that MAS measures muscle tone rather than spasticity. Can the authors be more specific? In particular, I am interested to know;*

- 1) *Is the Wolf Motor Function required when the Fugl Meyer is already the primary outcome scale?*
- 2) *What instrument for the Grip Strength Test?*
- 3) *Why the Berg Balance Scale when the upper limb is being targeted by the therapy. Perhaps more reference to the potential effects of Mirror Therapy with balance need to be introduced in the Introduction.*
- 4) *Again, why the 10MWT when upper body therapy being applied. If the authors feel that there is a logical potential for upper limb therapy to influence lower limb function, then it would be important for all readers to see this mentioned in the Introduction.*

Response: Thank the reviewer for the comments. The objective of the present study emphasized on the effectiveness of camMVF, especially for the improvements on motor function, and the

potential neuromechanism. Moreover, in order to investigate the possible aspects of treatment benefits of camMVF, these secondary assessments were chosen. In our study, we use MAS to investigate the spasticity as an inclusion criterion prior to the intervention. As reported, MAS is used to assess the spasticity, which is a velocity-dependent increase in muscle tone in response to passive movement. From my point of view, it is better to use some devices to measure the muscle tone, stiffness, and elasticity, like Myoton-3.

- 1) The Wolf Motor Function Test (WMFT) was removed as suggested by the reviewer.
- 2) A hydraulic hand dynamometer (Exacta™) was employed.
- 3) and 4) These two points were explained above.

9. *Can the issue of blinding be addressed? It is not specified who undertakes the outcome assessments. I would advise that it is an independent clinician because although it is easy to randomise and not allow a member of your team know what group a participant has been in, for relative subjective assessments e.g. MAS, there is always the chance that all groups can be given a higher value in re-assessments and this can potentially bias the findings.*

Response: Thank the reviewer for the comment and suggestion. This is a single-blinded trial, where the assessor is blinded. This point was clarified in the study outcomes, Method section.

The primary outcome and clinical assessments will be administered at baseline, after 2 weeks and 4 weeks of treatment by an independent researcher.

10. *Can allocation of patients to each group be discussed in methods and how authors intend to minimise allocation bias?*

Response: Thank the reviewer for the comment. The allocation sequence was based on a computer-generated random-number table. An envelope was extracted for random grouping when an eligible patient was recruited. In order to minimise the allocation bias, the randomization program and all the assignments were conducted by an independent researcher. We further clarified this point in the Method section as the following:

The allocation sequence is based on the computer-generated random number table. Randomization program and all the assignments are conducted by an independent researcher.

Response to the reviewers' comments

Reviewer #2:

Reviewer Name: Floriana Pichiorri

Institution and Country: Fondazione Santa Lucia, IRCCS, Rome, Italy

Please state any competing interests or state 'None declared': None declared

General comments:

The paper presents a study protocol to investigate the effects of camera based mirror therapy for upper limb motor rehabilitation after stroke. Although the study design is clear, as well as the general/main objective (to demonstrate a better outcome in the target group), I have several concerns regarding specific objectives and the lack of sufficient details on the study methods.

1. *I recommend English revision (typos, and a random use of present and future tenses makes the reading challenging).*

Response: We appreciate the suggestion. The English language was carefully checked and refined.

2. *What are the specific objectives: eg which mechanisms underlie the expected improved outcome with the proposed training, what do you expect to see in the hand laterality task and in the eeg evaluation (page 4)*

Response: We thank the reviewer for the valuable comment. These points were clarified as following in the Introduction section:

Thus, 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.

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).

3. *the instruction given to the patients in the camera based MVF intervention is not clear: I believe it is motor attempt with both hands but then what is the relation with motor imagery (page 5 lines 38-40)*

Response: Thank the reviewer for this insightful comment. Given that mirror therapy is one type of graded motor imagery, which is a visual guided motor imagery. During training, the therapist will give necessary instructions to help patients focus on the screen and persuaded them to imagine that the two moving hands on the screen are his/her own hands. We recognise it as perception of ownership or experience of embodiment rather than motor imagery. An additional instruction to patients was added, following the suggestion from the reviewer.

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.

4. *The sham MVF is even less clear, what will the patient do? again motor attempt or imagery? did you refer to previous literature to implement the sham condition? (page 5 lines 48-53)*

Response: Thanks for this comment. Patients of the sham-MG will receive same training as MG, including training protocol, intensity, and duration. The sham condition is based on the protocol of one previous study (cited as #33). During the sham-MG, patients are required to conduct motor attempt and also imagine their both hands moving. Because of the shielded reflection, there is no visual feedback from the affected side, where mirror illusion does not exist. We revised this part as following:

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.

5. *page 4 line 50 you say you mean to compare eeg signals in the two conditions, do you mean during the training session or before/after the training period? this is not clear*

Response: We thank the reviewer for this comment. We will compare the alterations of EEG signals before and after the intervention between groups. This point was clarified as following:

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

6. *EEG evaluation: from page 6 lines 27-44 I understand that EEG will be recorded during the hand laterality task, is this correct?; it is not sufficiently clear how this data will be analyzed and what measures will be taken into consideration (and also what are the hypotheses for choosing these measures): brain network is definitely too general.*

Response: Thanks the reviewer for this valuable comment. The EEG will be recorded during the hand laterality task, and the data will be analysed from the perspective of performance of laterality judgement (reaction time and accuracy), event related potentials (ERP), and properties of brain network. In our previous pilot study, we found the segregation of global clustering coefficient was improved after MVF intervention, which suggested the improved local efficiency of a network communication. Therefore, according to the theory of graded motor imagery, we hypothesize that it can modulate the brain network involved in motor imagery and visual perception. Global and nodal clustering coefficient, and characteristic path length will be computed in this study to quantify the small-world properties of a network. Moreover, given that mirror visual feedback is a visual guided motor imagery, MVF can modulate the motor preparation/planning as motor imagery. Thus, ERPs

of the hand laterality task will be compared among groups to assess the ability of mental rotation, which is recognized as a classic protocol to evaluate motor execution and preparation. We further clarified this part as following:

The EEG signals are collected from a 64-channel Ag/AgCl EasyCap™ (Brain Products GmbH, Munich, Germany) and recorded during the hand laterality task. All electrodes are referenced to FCz and with impedance 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. ERP and network properties (including clustering coefficient and characteristic path length) will be analysed and compared among groups to investigate the underlying mechanism of camMVF.

7. *Altogether I believe that, for a protocol description to be worth reading (and publishing) there is need for:*

- clearer general and specific objectives and hypotheses (which could be confirmed by the results or confuted)

- definitely better explanation of the methods and I refer particularly to: a) intervention protocol and sham protocol (how was it implemented and why so) b) analyses to be performed on accompanying outcome measures: hand laterality task and eeg, with specific hypotheses and expectations.

Response: Thanks the reviewer for the comment and suggestion. As the reviewer suggested, clearer objectives and more detailed explanations of methods/protocols were added in the Introduction and Method section, respectively. Moreover, we have explained the analyses of outcome measures and expectations, including the EEG signals and hand laterality task, in the Introduction and Method section.

Response to the reviewers' comments

Reviewer #3:

Reviewer Name: Michel Guerraz

Institution and Country: University Savoie Mont Blanc

Please state any competing interests or state 'None declared': no competing interests

General comments:

The manuscript reports a planned study already approved by the by Huashan Hospital Institutional Review Boards on 15th March 2017. Except that date of approval, there is no clear timetable for the study. The present project is of great interest and likely useful for the neuro-rehabilitation community. The purpose is to test the effect of Mirror Visual Feedback (and more specifically camera based MVF) on motor rehabilitation following stroke but also on brain plasticity with a rather large sample of stroke

participants (90 participants divided in three groups of 30). The procedure is clear and the study well controlled.

Response: We appreciate the comment from the reviewer. As suggested by the reviewer, a recruitment period for the study was added:

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.

1. *Line 27 : functional magnetic resonance imaging instead of functional magnetic imagine*

Response: Thanks for the suggestion. The phrase “functional magnetic imagine” has been changed to “functional magnetic resonance imaging”.

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 (fNIRS) techniques.

Response to the comments from editorial office

1. *Please provide another copy of your figures with better qualities and please ensure that figures are of better quality or not pixelated when zooming in and make sure that they have a resolution of at least 300 dpi.*

Response: Thanks for the suggestion. High resolution figures have been submitted.

2. *Authors must include a statement in the Methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions:*

- *How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?*
- *How did you involve patients in the design of this study?*
- *Were patients involved in the recruitment to and conduct of the study?*
- *How will the results be disseminated to study participants?*
- *For randomised controlled trials, was the burden of the intervention assessed by patients themselves?*

Response: Thanks for the comment. This part was added as following in the Method section:

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. 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.

3. *Patient advisers should also be thanked in the contributorship statement/acknowledgements. If patients and or public were not involved please state this.*

Response: We appreciate this suggestion. The following part was added:

Acknowledgements

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

VERSION 2 – REVIEW

REVIEWER	Dr Kenneth Monaghan Institute of Technology (IT) Sligo, Ireland
REVIEW RETURNED	24-Nov-2018

GENERAL COMMENTS	The authors have addressed all of my comments in a very Professional and appropriate fashion and have made this a very detailed Protocol document. I commend the Authors on the detail they have included and the fashion with which they have addressed all 3 reviewer comments. I look forward to reading about the trial results when completed.
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REVIEWER	Floriana Pichiorri Fondazione Santa Lucia, IRCCS, ROME, Italy
REVIEW RETURNED	06-Nov-2018

GENERAL COMMENTS	The authors have addressed my comments. However, I still find the English form inadequate. I suggest to ask for a certified English revision.
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