

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

#### Title (Provisional)

The effect of intermittent theta burst stimulation combined with acoustic startle priming motor training on upper limb motor function and neural plasticity in stroke individuals : study protocol for a randomized controlled proof-of-concept trial

#### Authors

Chen, Yu; Xia, Nan; Li, Jinghong; Liang, Weiqiang; Yin, Yangyang; Zhai, Linhan; Wang, Mingzhu; Wang, Qiuxia; Zhang, Jing

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### VERSION 1 - REVIEW

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Reviewer	1
Name	Serrada, Ines
Affiliation	University of South Australia, Physiotherapy
Date	23-Jul-2024
COI	Nil.

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Thank you for your submission, this is an interesting proof of concept trial. A minor revision is required to clarify a few comments. Please see below:

Page 3 Abstract

-introduction line 31 'enters the vision of the rehabilitation field'. What does this mean?

-introduction- need to mention ASP

-abstract methods and analysis. All abbreviations need to be in full iTBS, ASP, FMA-UE, MAS, DTI, fMRI

-abstract methods and analysis. Clarify the 'four phases'.

Page 4 introduction

-line 21. Approximately two-thirds. Of how many? What is the population number?

Page 7

-line 28 use term ASP so we can relate the term and 'using a loud sound...' This needs to be clearer.

## Page 8 Methods. Table 1.

- spelling error - 'basic information'
- have you thought about including a quality of life outcome measure too?
- the heading before/after the first treatment. Is this before AND after or before OR after?  
Make this clear it's the former AND.

## Page 9 Participants

- line 15- why limit to 70 years old?
- line 16- within 3 months so acute participants? Are they still in the acute hospital setting?  
Please clarify.
- line 18- spelling of Fugl-Meyer
- line 19- are you assessing both upper and lower limb FMA for inclusion criteria? Please explain why? How did you arrive at 85 and 38 points?
- line 23- cognitive learning ability- will you test cognition for inclusion criteria? Will there be a cut-off? E.g. MOCA or MMSE?
- lines 31-50 exclusion criteria. This is very broad, what is your reasoning for excluding so many potential participants?
- line 56- spelling error. 'Obtain'

## Page 10 Procedure

- line 24 full stop required '... speech and swallowing training. This rehabilitation program will be...'
- line 26. 4-6 hours per day, 5 days per week. Is this usual practice?
- line 32- 'will be provided before the daily rehabilitation intervention' 5 days per week for 3 weeks? Clarify. Please include duration of time pre-session? How long will the TBS/ASP training take? Will patients be able to tolerate this amount of therapy in addition to 4-6 hours per day?
- line 35- 'as well as 3 weeks'. And 7 weeks? Relate to Table 1.
- line 48- spelling error Fugl-Meyer
- lines 47-52 suggest adding a QoL Outcome measure

## Page 11

- line 35- tenses - intervention for subjects will be applied on the...
- lines 36-43 - add evidence/reference for the sham protocol.

## Page 12

-line 22- 'at least 40 times' - have you considered fatigue? Will this limit your inclusion criteria if participants can't achieve this?

-line 51 '10 consecutive trials' - again will this amount be manageable or tolerable for the participant? Please explain.

-outcome measures- recommend adding a QoL measure

Page 15

-line 36 spelling error? 'Correct any current distortions...'

Page 16

-sample size calculation- what will be the duration of recruitment for this study?

Page 19- summary

-Perhaps add 'and aim to improve UL function'. Make sure to return to the functional purpose of your study.

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<b>Reviewer</b>	<b>2</b>
<b>Name</b>	<b>Bernardo-Filho, Mario</b>
<b>Affiliation</b>	<b>Universidade do Estado do Rio de Janeiro</b>
<b>Date</b>	<b>23-Sep-2024</b>
<b>COI</b>	<b>I understand. I have no conflicts of interest. I consent to put my name as a reviewer of this manuscript.</b>

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Congratulations. The subject of this study is highly relevant, but its presentation must be improved. Please, see in the attached file my suggestions.

**\*\*\*\* The reviewer provided a marked copy with additional comments. Please contact the publisher for full details. \*\*\*\***

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## VERSION 1 - AUTHOR RESPONSE

**Dear Dr. Ines Serrada:**

Thank you for your positive comments on this research paper. We have made corresponding supplements and modifications as required and hope to satisfy you. we have provided the point-to-point response to the questions that you raised as below:

Page 3 Abstract

- Respond to comment: -introduction line 31 'enters the vision of the rehabilitation field'. What does this mean?  
Thank you for raising this issue. This sentence means that 'attracts attention in the field of rehabilitation', the whole sentence has been revised to 'Among these, the cortico-reticulospinal tract (CRST) has gained attention in rehabilitation due to its unique ascending and descending

- structural features...’.
2. Respond to comment: -introduction- need to mention ASP.  
 Thank you very much for your suggestion. The sentence ‘Acoustic startle priming (ASP) training and intermittent theta burst stimulation (iTBS) are emerging as potential methods to regulate CRST function.’ has been added to section ‘**Introduction**’.
  3. Respond to comment: -abstract methods and analysis. All abbreviations need to be in full iTBS, ASP, FMA-UE, MAS, DTI, fMRI  
 Thank you for the advice, all abbreviations in this part has been revised.
  4. Respond to comment: -abstract methods and analysis. Clarify the ‘four phases’.  
 Thank you for raising this issue. Four phases include: baseline assessment, post-first intervention assessment, assessment after intervention for 3 weeks and assessment after 4-weeks follow up.
  5. Respond to comment: -line 21. Approximately two-thirds. Of how many? What is the population number?  
 Thank you for raising this issue. The sentence should be: ‘Stroke is the leading cause of disability in adults, affecting over 1 million individuals annually in Europe. About two-thirds of stroke patients experience persistent upper limb motor dysfunction and nearly 64% are unable to walk independently.’. The references are the article by Doumas et al. ‘*Serious games for upper limb rehabilitation after stroke: a meta-analysis*’ and the the article ‘*Ipsilateral Motor Pathways and Transcallosal Inhibition During Lower Limb Movement After Stroke*’ by Cleland et al.
  6. Respond to comment: -line 28 use term ASP so we can relate the term and ‘using a loud sound...’  
 This needs to be clearer.  
 The sentence has been revised to ‘In addition, as proposed earlier regarding acoustic startle priming (ASP)’.
  7. Respond to comment: -spelling error - ‘basic information’.  
 I sincerely apologize for the mistake; the spelling error has been corrected.
  8. Respond to comment: -have you thought about including a quality of life outcome measure too?  
 Thank you for the valuable suggestion. Thank you very much for your valuable suggestions. As our primary focus was on the improvement of motor function, we had not previously included the QoL scale. The QoL scale has now been added to the manuscript in section ‘**Clinical assessments**’
  9. Respond to comment: -the heading before/after the first treatment. Is this before AND after or before OR after? Make this clear it’s the former AND.  
 Thank you for raising this issue. It should be "before and after," as the immediate effects of brain activity changes might be observed after the first treatment. The original text has been revised to "before and after."
  10. Respond to comment: -line 15- why limit to 70 years old?  
 Thank you for your comments. The highest age of stroke patients is limited to 80 years old in articles ‘*Effectiveness of theta and gamma electroacupuncture for post-stroke patients on working memory and electrophysiology: study protocol for a double-center, randomized, patient- and assessor-blinded, sham-controlled, parallel, clinical trial*’ by Xu et al. and ‘*Startle Increases the Incidence of Anticipatory Muscle Activations but Does Not Change the Task-Specific Muscle Onset for Patients After Subacute Stroke*’ by Xia et al. The max age limit is lowered to 70 because patients in this study protocol needed to be instructed to stay focus during acoustic startle priming training and to undergo a longer MRI scan - about 25 minutes per session.
  11. Respond to comment: -line 16- within 3 months so acute participants? Are they still in the acute hospital setting? Please clarify.  
 The volunteers we recruited should be patients who have stabilized after the onset of their

- condition and are admitted for rehabilitation treatment. Patients are not in the acute hospital setting.
12. Respond to comment: -line 18- spelling of Fugl-Meyer  
I sincerely apologize for the mistake; the spelling error has been corrected.
  13. Respond to comment: -line 19- are you assessing both upper and lower limb FMA for inclusion criteria? Please explain why? How did you arrive at 85 and 38 points?  
Thank you for your feedback. This section has been revised to 'The patient has severe upper limb motor impairment, with a Fugl-Meyer Assessment of Upper Extremity score of 0–35.' The reference is '*Rudimentary Dexterity Corresponds With Reduced Ability to Move in Synergy After Stroke: Evidence of Competition Between Corticoreticulospinal and Corticospinal Tracts*' by Senesh et al. The study found that the patients whose FMA-UE score is below 35 rely more on CRST.
  14. Respond to comment: -line 23- cognitive learning ability- will you test cognition for inclusion criteria? Will there be a cut-off? E.g. MOCA or MMSE?  
Thank you for raising this issue. We will assess the patients, and those with a Mini-Mental State Examination (MMSE) score of  $\geq 22$  and who comply with the intervention will be included. The original text has been revised accordingly. The reference is the article by Wei et al. '*Immediate and short-term effects of continuous theta burst transcranial magnetic stimulation over contralesional premotor area on post-stroke spasticity in patients with severe hemiplegia: Study protocol for a randomized controlled trial*'.
  15. Respond to comment: -lines 31-50 exclusion criteria. This is very broad, what is your reasoning for excluding so many potential participants?  
Items 2, 3, and 5 are to ensure that other diseases do not affect the patients' motor function, while items 4 and 6 are to ensure that patients can successfully complete the trial. Item 1 is to exclude the influence of a prior stroke history on the recovery of motor function. Thank you for your suggestions; I have reorganized the exclusion criteria, which has now been revised to: (1) A history of multiple strokes or bilateral strokes. (2) Severe upper/lower limb spasticity, with a Modified Ashworth Scale (MAS) grade of 3 or higher, or other conditions affecting upper and lower limb function, such as joint muscle contractures, severe frozen shoulder, surgical history, rheumatic diseases, etc. (3) Severe cognitive impairment, inability to effectively communicate with medical personnel. (4) Other conditions deemed unsuitable for participation by the researcher, which may lead to adverse consequences, such as severe hypertension, coronary heart disease, claustrophobia, etc.
  16. Respond to comment: -line 56- spelling error. 'Obtain'  
I sincerely apologize; the spelling error has been corrected.
  17. Respond to comment: -line 24 full stop required '... speech and swallowing training. This rehabilitation program will be...'  
Thank you very much for your feedback; the original text has been corrected.
  18. Respond to comment: -line 26. 4-6 hours per day, 5 days per week. Is this usual practice?  
Yes, this is usual rehabilitation training.
  19. Respond to comment: -line 32- 'will be provided before the daily rehabilitation intervention' 5 days per week for 3 weeks? Clarify. Please include duration of time pre-session? How long will the TBS/ASP training take? Will patients be able to tolerate this amount of therapy in addition to 4-6 hours per day?  
Yes, iTBS, ASP trainings will be applied five days a week for a total of three weeks. A single session of iTBS and ASP training lasts approximately 190 seconds and 30 minutes, respectively. Thank you for your feedback. The original text has been revised to 'The iTBS, sham iTBS, ASP,

or non-ASP training involved in this study will be provided before the daily rehabilitation intervention, five days per week for a total of three weeks. A single session of iTBS and ASP training lasts approximately 190 seconds and 30 minutes, respectively.' Regarding the patients' tolerance, we will obtain informed consent from the patients in advance and provide psychological reassurance before the procedure. If patients cannot tolerate it, they will not be included in the final study.

20. Respond to comment: -line 35- 'as well as 3 weeks'. And 7 weeks? Relate to Table 1.  
I sincerely apologize, and thank you for your suggestions; the original text has been revised to 'Resting-state MRI scans will be conducted before and immediately after the subject's first intervention, 3 weeks after the intervention, and during the follow-up at week seven.'
21. Respond to comment: -line 48- spelling error Fugl-Meyer  
I sincerely apologize, thank you for your advice, the spelling error has been revised.
22. Respond to comment: -lines 47-52 suggest adding a QoL Outcome measure  
Thank you very much for your valuable suggestions. The QoL measurement has been added to the existing research protocol.
23. Respond to comment: -line 35- tenses - intervention for subjects will be applied on the...  
Thank you very much for your valuable suggestions, the tense has been corrected.
24. Respond to comment: -lines 36-43 - add evidence/reference for the sham protocol.  
Thanks for your advice, the reference is an article '*Immediate and short-term effects of continuous theta burst transcranial magnetic stimulation over contralesional premotor area on post-stroke spasticity in patients with severe hemiplegia: Study protocol for a randomized controlled trial*' written by Wei et al. This reference is added in the first paragraph of part 'Study design'
25. Respond to comment: -line 22- 'at least 40 times' - have you considered fatigue? Will this limit your inclusion criteria if participants can't achieve this?  
To avoid this situation, we will add different lengths of intervals between the two stimulations to prevent fatigue and instruct the patients to focus in advance.
26. Respond to comment: -line 51 '10 consecutive trials' - again will this amount be manageable or tolerable for the participant? Please explain.  
Thank you for raising this issue. Each of the 10 trials includes 10 sound stimuli. We will inquire about and test the patients' tolerance in advance to ensure they can complete the entire process. Additionally, different lengths of intervals will be added between the two stimulations, and each patient will experience varying numbers of stimuli, ranging from 40 to 60, to avoid anticipation and fatigue.
27. Respond to comment: -outcome measures- recommend adding a QoL measure  
Thank you for your valuable suggestions; the measurement QoL has been added to the current research protocol in section '**Clinical assessments**'.
28. Respond to comment: -line 36 spelling error? 'Correct any current distortions...'  
Thank you for your advice, this sentence means that using FSL tools to correct distortions caused by eddy current.
29. Respond to comment: -sample size calculation- what will be the duration of recruitment for this study?  
The study will begin recruiting patients after obtaining ethical approval, with an expected enrollment of 36 patients over a period of 2 to 3 years.
30. Respond to comment: -Perhaps add 'and aim to improve UL function'. Make sure to return to the functional purpose of your study.  
Thank you for your suggestions; we will keep in mind that the original intention of our research is



to enhance patient well-being. The first item of 'Strengths and Limitations' has been revised to 'Combining novel treatment methods, this study is the first to integrate ASPT with iTBS to improve UL function.'

**Dear Dr. Mario Bernardo-Filho**

Thank you for your pertinent evaluation of this research manuscript. We have made corresponding supplements and modifications as required, and used AI to improve the expression of our manuscript. We hope to satisfy you.

We have provided the point-to-point response to the questions that you raised as below:

1. Page2 Line4: Respond to comment: -I suggest avoiding abbreviation in the title.  
Thank you for your valuable advice, it has been revised to 'intermittent theta burst stimulation'.
2. Page3 Line37: Respond to comment: -Add a clear aim.  
Thank you for your advice, the sentence 'This study aims to investigate the feasibility of segmentally modulating the cortico-reticular and reticulospinal tracts through ASP and iTBS, while evaluating the resulting therapeutic effects.' has been added.
3. Page3 Line46: Respond to comment: Define all the abbreviations in the first time, here and throughout the manuscript.  
Thank you so much for your suggestion. Abbreviations that first appear have their full names indicated.
4. Page4 Line26: Respond to comment: I suggest adding sentences about the lower extremity motor dysfunction that limit the practice of physical activities.  
Thanks for your valuable suggestion, the first sentence has added 'About two-thirds of stroke patients experience persistent upper limb motor dysfunction and nearly 64% are unable to walk independently'. The reference is an article by Cleland et al. '*Ipsilateral Motor Pathways and Transcallosal Inhibition During Lower Limb Movement After Stroke*'.
5. Page4 Line38: Respond to comment: Add references with some strategies at the end of this sentence.  
Thanks for your advice, references have been added.
6. Page5 Line31: Respond to comment: imaging  
Thanks for your valuable advice. Spelling error has been corrected.
7. Page6 Line21: Respond to comment: clarify....I suggest repeating ...Chen et al 28  
Thank you for your valuable advice, the sentence has been revised to 'The study of Chen et al. on SE...'
8. Page6 Line41: Respond to comment: A  
I sincerely apologize for this mistake. The grammar error has been corrected.
9. Page11 Line25: Respond to comment: It is not necessary. iTBS was already defined.  
Thank you for your suggestion, the sentence has been revised to 'The iTBS paradigm involves a burst-pulse consisting of three pulses at 50 Hz'.
10. Page16 Line38: Respond to comment: will be  
Thank you for your valuable advice, the tense error has been revised.