PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for patients with subacute stroke: a randomized controlled trial protocol
AUTHORS	Chen, Yi; Su, Wei; Gui, Chen-Fan; Guo, Qi-Fan; Tan, Hui-Xin; He, Lin; Jiang, Han-Hong; Wei, Qing-Chuan; Gao, Qiang

VERSION 1 – REVIEW

REVIEWER	Agarwal, Smriti Cambridge University Hospitals NHS Foundation Trust
REVIEW RETURNED	23-Aug-2022

GENERAL COMMENTS	This study examines an interesting hypothesis as to whether stimulating the cerebellar vermis improves balance and gait after subacute stroke. The study hypothesis is reasonably clearly laid out and methods are appropriately described. The study protocol adheres to the SPIRIT 13 statement for clinical trial design. I have a few comments for the authors to consider. It would be worth providing some more detail on physiological mechanisms underlying the role of the cerebellar vermis in gait recovery after stroke. Previous neurostimulation studies targeting the ipsilateral cerebellum have demonstrated a positive effect on gait and balance recovery in chronic stroke. The authors may wish to contextualise the current trial with these previous studies. The time window of upto 6 months after stroke is somewhat generous for subacute stroke. While there is no strict definition, I would recommend a period of 90 days as the cut off for inclusion in the study. Exclusion criteria mention pre-existing neurological diseases and cognitive impairment. Patients on CNS modulating drugs (antidepressants, benzodiazepines, antiepileptics etc) should be excluded. Naturally, there will be some overlap between patients on centrally acting drugs and pre-existing neurological diseases. While a cut off for Fugl-Meyer is appropriately incorporated into the inclusion criteria for severity of impairment, the outcome measures should also include the Fugl-Meyer score as an overall index of motor function. I would recommend using gait/locomotion analysis as a secondary outcome measure (Ferrarello et al 2013 https://doi.org/10.2522/ptj.20120344).

	The authors would need to explain more clearly why a 3-week time point is used for outcome measures. Would longer follow up be helpful? Why do the authors choose active motor threshold rather than resting motor threshold? There will be a proportion of patients where a motor threshold may not be obtainable from the affected hemisphere. What would be the authors' approach in this scenario?

REVIEWER	He , Weijia
REVIEW RETURNED	28-Oct-2022

GENERAL COMMENTS	Thanks a lot for sharing your research protocol in BMJ open, allowing more scholars to know more about iTBS for post-stroke rehabilitation. There are mainly two questions about the inclusion criteria listed in your manuscript, which I am looking forward to your further information on. 1. In your proposal, patients with different types of stroke (ischemic stroke or hemorrhagic stroke) are combined together. Could you please offer more information to support the reason that there is no need to distinguish one from the other , for the rehabilitation of balance function? 2. For the period of follow-up , "3 weeks" is chosen, rather than several months. Are there any researches to support it's a better choice for looking into long-term treatment effects?

VERSION 1 – AUTHOR RESPONSE

Reviewer **1**:

Q1：It would be worth providing some more detail on physiological mechanisms underlying the role of the cerebellar vermis in gait recovery after stroke. Previous neurostimulation studies targeting the ipsilateral cerebellum have demonstrated a positive effect on gait and balance recovery in chronic stroke. The authors may wish to contextualise the current trial with these previous studies.

Response: Thank you for your suggestions. In 2019, Koch's research published in *JAMA Neurology* revealed that iTBS over the cerebellar hemisphere could promote gait and balance recovery in patients with ischemic chronic stroke.[1] Additionally, our research group also did a lot of work to explore the effect of iTBS over the cerebellar hemisphere on tone[2], balance[3], and locomotion[4] in post-stroke patients. However, based on the results of our previous studies, we focused on the trunk control and balance function in stroke patients in this study. Therefore, we provide more detailed discussions about the physiological mechanisms underlying the role of the cerebellar vermis in balance after stroke. Of course, there is no denying that balance is closely related to gait performance. Consequently, after comprehensive consideration, according to your valuable

comments, we have expanded the background on previous studies in the introduction part on Pages 4-5 Lines 84-85 and Lines 88-92, and appropriately added relevant contents of physiological mechanisms underlying the role of the cerebellar vermis in gait performance in the discussion part on Page 19 Lines 404-406. Changes were highlighted in “Main Document - marked copy”.

Q2：The time window of up to 6 months after stroke is somewhat generous for subacute stroke. While there is no strict definition, I would recommend a period of 90 days as the cut off for inclusion in the study.

Response: Thank you for your suggestions. The specific reasons for our choice of the 2 weeks to 6 months as the time windows of subacute stroke are as follows:

1. In 2017, the Stroke Rehabilitation and Recovery Roundtable taskforce defined the recovery epochs of stroke[5], which reported that: hyperacute,≤24-hours post-stroke; acute, >24-hours but≤7-days post-stroke; early subacute, >7-days but≤3-months post-stroke, and late subacute, >3-months (>90-days) but≤6-months (≤180-days) post-stroke. It is also used as allocation criteria in a systematic review published in *Stroke* in 2021.[6] In this study, we included both early subacute and late subacute stroke patients.
2. A diffusion MRI study in subacute stroke confirmed that the chronic stage begins around 6 months after stroke onset, which published in *Neurology* in 2020.[7]
3. Consider the patient tolerance and the safety of iTBS in clinical practice, the stimulation will be applied after 2 weeks after stroke onset when the patient’s condition is completely stable.

After all the authors discussed it together, we did not change the inclusion criteria of the course of disease. However, we updated the references with more authoritative evidence in the revised manuscript.

Q3：Exclusion criteria mention pre-existing neurological diseases and cognitive impairment. Patients on CNS modulating drugs (antidepressants, benzodiazepines, antiepileptics etc) should be excluded. Naturally, there will be some overlap between patients on centrally acting drugs and pre-existing neurological diseases.

Response: We do agree with your comment and have added this exclusion criterion on Page 7 Line 151. We also updated the information in the Chinese Clinical Trial Registry.

Q4：While a cut off for Fugl-Meyer is appropriately incorporated into the inclusion criteria for severity of impairment, the outcome measures should also include the Fugl-Meyer score as an overall index of motor function.

Response: Thank you for your suggestions. We have included the Fugl-Meyer assessment scale score for lower extremities (FMA-LE) on Page 15 Lines 297-300 in our original manuscript.

Q5：I would recommend using gait/locomotion analysis as a secondary outcome measure (Ferrarello et al 2013 https://doi.org/10.2522/ptj.20120344).

Response: Dear reviewer, thank you for your suggestions again. Due to we focused on the trunk control and balance function in stroke patients in this study, all the outcome measures were chosen to comprehensively assess the trunk control and balance function. After all the authors discussed it together,e haven't added the gait/locomotion analysis to outcome measures. Of course, there is no denying that balance is closely related to gait performance. Consequently, we appropriately added relevant content in the discussion part on Page 19 Lines 404-406.

Q6：The authors would need to explain more clearly why a 3-week time point is used for outcome measures. Would longer follow up be helpful?

Response: There are limited studies reported the long-term effects of iTBS in stroke patients. Among them, the representative studies are as follows: the research published in *JAMA Neurology* in 2019 showed that cerebellar iTBS promotes gait and balance recovery in patients with stroke by acting on cerebello-cortical plasticity. Significant changes were observed both at T1 (after 3 weeks of treatment) and T2 (3 weeks follow-up after the end of treatment).[1] Another research published in *Stroke* in 2022 revealed 10-session iTBS yielded a superior effect compared with sham stimulation for improving motor functions in stroke participants. However, the superiority was diminished at follow-up (ie, at day 15 after the completion of the 10-session training). Therefore, based on the previous researches, we decided to choose three weeks as the follow-up period.[8]

Q7：Why do the authors choose active motor threshold rather than resting motor threshold?

Response: As the *Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines* published in 2021 reported[9]: the majority of TBS papers have used the parameters originally described by Huang et al (50 Hz bursts of 3 pulses repeated at 5 Hz; stimulus intensity of 80% AMT) (Huang et al., 2005). To the best of our knowledge, there has only been one seizure reported using these parameters (Lenoir et al., 2018). The other seizures reported using TBS have used parameters that exceed these levels. Therefore, the iTBS stimulation intensity of 80% active motor threshold is safer than the 80% resting motor threshold. Additionally, most studies on the cerebellar iTBS in stroke patients selected 80% active motor threshold as the stimulation intensity[1-4 10] considering patient tolerance.

Q8：There will be a proportion of patients where a motor threshold may not be obtainable from the affected hemisphere. What would be the authors' approach in this scenario?

Response: If the participant cannot elicit motor-evoked potentials or cannot tolerate the preset standard stimulus intensity, the stimulator output intensity is set to the participant's maximum tolerated intensity.[11] We have modified the description in the method part on Page 8 Lines 176.

Reviewer **2**:

Q1：In your proposal, patients with different types of stroke (ischemic stroke or hemorrhagic stroke) are combined together. Could you please offer more information to support the reason that there is no need to distinguish one from the other, for the rehabilitation of balance function?

Response: Thank you for your valuable suggestions. After the relevant researches were retrieved, we revised the inclusion criteria to only include ischemic stroke patients according to the study published in *JAMA Neurology*.[1] We also updated the information in the Chinese Clinical Trial Registry. Changes were highlighted on Page 6 Lines 137 and 140 in "Main Document - marked copy".

Q2：For the period of follow-up, "3 weeks" is chosen, rather than several months. Are there any researches to support it's a better choice for looking into long-term treatment effects？

Response: There are limited studies reported the long-term effects of iTBS in stroke patients. Among them, the representative studies are as follows: the research published in *JAMA Neurology* in 2019 showed that cerebellar iTBS promotes gait and balance recovery in patients with stroke by acting on cerebello-cortical plasticity. Significant changes were observed both at T1 (after 3 weeks of treatment) and T2 (3 weeks follow-up after the end of treatment).[1] Another research published in *Stroke* in 2022 revealed 10-session iTBS yielded a superior effect compared with sham stimulation for improving motor functions in stroke participants. However, the superiority was diminished at follow-up (ie, at day 15 after the completion of the 10-session training). Therefore, based on the previous researches, we decided to choose three weeks as the follow-up period.[8]

References:

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VERSION 2 – REVIEW

REVIEWER	Agarwal, Smriti Cambridge University Hospitals NHS Foundation Trust
REVIEW RETURNED	23-Nov-2022

GENERAL COMMENTS	The authors have addressed the issues raised in reviewer comments satisfactorily.