PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and safety of Brain-computer interface technology in the treatment of post-stroke motor disorders: A protocol for systematic review and meta-analysis
AUTHORS	Zhang, Xiaolin; Cao, Di; Liu, Junnan; Zhang, Qi; Liu, Mingjun

VERSION 1 – REVIEW

REVIEWER	stephanie Lefebvre university of Bern Switzerland
REVIEW RETURNED	31-Jul-2020

GENERAL COMMENTS	In this study protocol, the authors described the goals and the methods of a future meta-analysis on the use of brain-computer interface technology to enhance motor recovery in patients after a stroke. The described methods sound correct however the global protocol is not well written and not well explained. The language needs to be checked. (tense (too many different tenses are used in this manuscript), typos, grammar mistakes…). There are also a lot of typos or dashes in the middle of words or multiple spaces between words. In the middle of the words. In the abstract, the abbreviations need to be consistent. Either, the abbreviations need to be explained or we should refer to the abbreviations list but one way needs to be picked. In the abstract, there is a mistake, it should be Bartel index, not Battel. In the abstracts, what are the sports functions? What it is referring too, this expression is mentioned only one time and never explain. The strengths and limitations section is unclear. Especially the second and the last point need to be re-written. A rationale for the different measures and techniques is missing in the introduction. For example. BCI technique is not described. Similarly, the rationale for the interest in BCI is missing. The introduction needs to be rethought, for example, Page 5 = too long sentence, Page 1, 2nd sentence is useless. Be careful with some wording: naming BCI a brain stimulation can be misleading. It is a Neuromodulation technique that would include VR, BCI, Brain stimulation, neurofeedback etc… The discussion needs to be different from the introduction.

REVIEWER	Raquel Carvalho CESPU - IPSN- Portugal
REVIEW RETURNED	16-Aug-2020

GENERAL COMMENTS	General comments

	The authors propose to do a systematic review in order to understand the efficacy and safety of BCI in post-stroke disorders. The paper reflects a valid and pertinent issue. During the review process, I identified a number of concerns related to the manuscript, which should be addressed. Please revise grammar, structure and redundancy. Abstract Please consider to change the sentence “to enhance the effectiveness”. To enhance or to assess? The intervention could be more precisely described at abstract. Will you include all types of BCI? Virtual reality, robotics,… Which control condition will be used? Conventional treatment, no treatment at all,… Which will be your expected results? Which are your exclusion criteria? You aim to assess the improvement of sports function and quality of life; however, your primary and secondary outcome measure not assess this dimension… Consider to clarify or modify. Moreover, you have a different aim in the introduction I suggest keywords different from title to facilitate the search (e.g. brain-machine interface…) Introduction The introduction reviewed some studies with the same theme and well establish the relevance of this study. Page 4 line 37-41 - strange reference in this more epidemiological report? Page 4 line 54 – “At present, it is known that high-intensity, high-dose and repeated related training tasks are the key factors of post-stroke rehabilitation treatment.” Miss the reference Page 5 line 3 – “The training process is boring” Please explain if you want to mention the long process instead of boring… That will depend of the rehabilitation team… Methods Page 5 line 45 - Consider to use FMA to determine patient’s severity at baseline Page 6 line 3 - Will you include all types of BCI? Virtual reality, robotics,… Please clarify.. Page 6 line 6 - Will you consider no rehabilitation treatment as control condition? Please consider to add it Page 6 line 37 – consider to use neurofeedback in search strategy Page 8 line 39 – The quality of the studies will be divided into 3 levels: “low risk of bias,” “high risk of bias,” and “unclear risk of bias.”. Please add reference Discussion Your discussion in drive through the BCI benefits however, as mentioned it is not clear if the source of motor recovery derives from conventional therapy, the motor imagery by itself, neurofeedback from BCI, or the combination of these… You may consider this possibility… Minor issues Please had the information about full name of BCIT, PSMD and ASH at abstract Please consider to use only BCI since it is more common Please consider to remove the abbreviations FMA, MBI, MAS, MMT of from de abstract, since you used it only once. Please had corrections to Abbreviations: “The Fugl Meyer motor

	function (FMA) score will be used as primary outcome,Modified battel index (MBI), modified ASH - worth score (MAS) and upper extremity freehand muscle strength assessment (MMT)". Do you want to mean FMA= Fugl Meyer motor function… Page 5 Line 9 and line 28 – is the first time you mention BCIT and PSMD in full text please had full name before Page 5 line 22 – did you want to mention central nerve system? Please consider to add system… Page 7 line 55 "The fifinal selection" – please correct Page 8 line 39 - TThe quality of the studies – please correct Page 8 line 54 - if We cann't wait for a valid reply – please correct Page 9 line 19 - we will per-forme. Please correct Reference 4. Are different from the all the rest

REVIEWER	David J. Lin Massachusetts General Hospital, USA
REVIEW RETURNED	31-Aug-2020

GENERAL COMMENTS	This is a protocol for a review and meta-analysis of brain computer interface technology for post-stroke motor disorders. The main issue is that - I am unclear as to the significance of this. If the goal is to conduct a systematic review and meta-analysis, they should indeed do this and write up the findings. No primary data collection is necessary for this. The end result, even if based of other studies, may be worthy of publication. However, a protocol describing how a future systematic review and meta-analysis will be undertaken has limited significance. Furthermore, the protocol itself as written has a number of spelling and grammatical errors and has limited contextual significance for the field. The introduction is not adequate background for the subject. Brain-computer interfaces (BCIs) are a novel technology and many clinicians are not familiar with them. If a clinician was searching in BMJ for studies evaluating the effectiveness and safety of new stroke rehab options, this introduction would not provide that clinician with sufficient background on BCIs. What is it? What are the components? What types are there? The introduction also lacks details on various methods of recording brain signals, as well as the numerous types of effectors. These are critical information to consider when factoring in a patient populations and locale constraints. Furthermore, the introduction briefly discusses upper extremity functionality but, nowhere else does it state that this study is exclusively looking at upper extremity function, except in section 2.2.2. Types of patients. In that section, it states that the investigators are evaluating patients with moderate to severe upper extremity and hand dysfunction. Lastly, the introduction contains conclusive claims of effectiveness and safety for BCIs. If there is already evidence for the effectiveness and safety of BCIs, why is the study needed? In addition, if BCIs have been deemed effective and safe, why aren't they being used as a standard of care? In Methods, how will moderate - severe upper extremity function across studies be defined? What statistical methods will be used to aggregate different study populations? Bayesian modeling could be considered here. The discussion has limited scope. Together, the introduction and

	discussion do not set the stage or provide adequate framework for even why a review and meta-analysis such as this should be performed at this time.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name
stephanie lefebvre

Institution and Country
university of Bern
Switzerland

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
In this study protocol, the authors described the goals and the methods of a future meta-analysis on the use of brain-computer interface technology to enhance motor recovery in patients after a stroke.
The described methods sound correct however the global protocol is not well written and not well explained.
The language needs to be checked. (tense (too many different tenses are used in this manuscript), typos, grammar mistakes…). There are also a lot of typos or dashes in the middle of words or multiple spaces between words.
In the middle of the words. In the abstract, the abbreviations need to be consistent. Either, the abbreviations need to be explained or we should refer to the abbreviations list but one way needs to be picked.
In the abstract, there is a mistake, it should be Bartel index, not Battel.
In the abstracts, what are the sports functions? What it is referring too, this expression is mentioned only one time and never explain.
The strengths and limitations section is unclear. Especially the second and the last point need to be re-written.
A rationale for the different measures and techniques is missing in the introduction. For example. BCI technique is not described. Similarly, the rationale for the interest in BCI is missing.
The introduction needs to be rethought, for example, Page 5 = too long sentence, Page 1, 2nd sentence is useless.
Be careful with some wording: naming BCI a brain stimulation can be misleading. It is a Neuromodulation technique that would include VR, BCI, Brain stimulation, neurofeedback etc…
The discussion needs to be different from the introduction.

Reviewer: 2
Reviewer Name
Raquel Carvalho

Institution and Country
CESPU - IPSN- Portugal

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
General comments
The authors propose to do a systematic review in order to understand the efficacy and safety of BCI in post-stroke disorders.
The paper reflects a valid and pertinent issue.
During the review process, I identified a number of concerns related to the manuscript, which should be addressed.
Please revise grammar, structure and redundancy.

Abstract
Please consider to change the sentence “to enhance the effectiveness”. To enhance or to assess?
The intervention could be more precisely described at abstract. Will you include all types of BCI? Virtual reality, robotics,… Which control condition will be used? Conventional treatment, no treatment at all,… Which will be your expected results?
Which are your exclusion criteria?
You aim to assess the improvement of sports function and quality of life; however, your primary and secondary outcome measure not assess this dimension… Consider to clarify or modify. Moreover, you have a different aim in the introduction
I suggest keywords different from title to facilitate the search (e.g. brain-machine interface…)

Introduction
The introduction reviewed some studies with the same theme and well establish the relevance of this study.
Page 4 line 37-41 - strange reference in this more epidemiological report?
Page 4 line 54 – “At present, it is known that high-intensity, high-dose and repeated related training tasks are the key factors of post-stroke rehabilitation treatment.” Miss the reference
Page 5 line 3 – “The training process is boring” Please explain if you want to mention the long process instead of boring… That will depend of the rehabilitation team…

Methods
Page 5 line 45 - Consider to use FMA to determine patient’s severity at baseline
Page 6 line 3 - Will you include all types of BCI? Virtual reality, robotics,… Please clarify..
Page 6 line 6 - Will you consider no rehabilitation treatment as control condition? Please consider to add it
Page 6 line 37 – consider to use neurofeedback in search strategy
Page 8 line 39 – The quality of the studies will be divided into 3 levels: “low risk of bias,” “high risk of bias,” and “unclear risk of bias.”. Please add reference

Discussion
Your discussion in drive through the BCI benefits however, as mentioned it is not clear if the source of motor recovery derives from conventional therapy, the motor imagery by itself, neurofeedback from BCI, or the combination of these… You may consider this possibility…

Minor issues
Please had the information about full name of BCIT, PSMD and ASH at abstract
Please consider to use only BCI since it is more common
Please consider to remove the abbreviations FMA, MBI, MAS, MMT of from de abstract, since you used it only once.

Please had corrections to Abbreviations: “The Fugl Meyer motor function (FMA) score will be used as primary outcome,Modified battel index (MBI), modified ASH - worth score (MAS) and upper extremity freehand muscle strength assessment (MMT)”. Do you want to mean FMA= Fugl Meyer motor function…
Page 5 Line 9 and line 28 – is the first time you mention BCIT and PSMD in full text please had full name before
Page 5 line 22 – did you want to mention central nerve system? Please consider to add system…
Page 7 line 55 “The fifinal selection” – please correct
Page 8 line 39 - TThe quality of the studies – please correct
Page 8 line 54 - if We cann't wait for a valid reply – please correct
Page 9 line 19 - we will per-forme. Please correct
Reference 4. Are different from the all the rest

Reviewer: 3
Reviewer Name
David J. Lin

Institution and Country
Massachusetts General Hospital, USA

Please state any competing interests or state ‘None declared’:
None

Please leave your comments for the authors below
This is a protocol for a review and meta-analysis of brain computer interface technology for post-stroke motor disorders.

The main issue is that - I am unclear as to the significance of this. If the goal is to conduct a systematic review and meta-analysis, they should indeed do this and write up the findings. No primary data collection is necessary for this. The end result, even if based of other studies, may be worthy of publication. However, a protocol describing how a future systematic review and meta-analysis will be undertaken has limited significance.

Furthermore, the protocol itself as written has a number of spelling and grammatical errors and has limited contextual significance for the field.

The introduction is not adequate background for the subject. Brain-computer interfaces (BCIs) are a novel technology and many clinicians are not familiar with them. If a clinician was searching in BMJ for studies evaluating the effectiveness and safety of new stroke rehab options, this introduction would not provide that clinician with sufficient background on BCIs. What is it? What are the components? What types are there? The introduction also lacks details on various methods of recording brain signals, as well as the numerous types of effectors. These are critical information to consider when factoring in a patient populations and locale constraints. Furthermore, the introduction briefly discusses upper extremity functionality but, nowhere else does it state that this study is exclusively looking at upper extremity function, except in section 2.2.2. Types of patients. In that section, it states that the investigators are evaluating patients with moderate to severe upper extremity and hand dysfunction. Lastly, the introduction contains conclusive claims of effectiveness and safety for BCIs. If there is already evidence for the effectiveness and safety of BCIs, why is the study needed? In addition, if BCIs have been deemed effective and safe, why aren’t they being used as a standard of care?

In Methods, how will moderate - severe upper extremity function across studies be defined? What statistical methods will be used to aggregate different study populations? Bayesian modeling could be considered here.

The discussion has limited scope. Together, the introduction and discussion do not set the stage or provide adequate framework for even why a review and meta-analysis such as this should be performed at this time.

AUTHOR RESPONSE:

Responds to the reviewer's comments:
Reviewer #1:
1. Response to comment: (Please state any competing interests or state 'None declared')
Response:we have stated the competition interests in the "2.1. Patient and public involvement" section and the end of the article.
2. Response to comment: (……In the abstract, there is a mistake, it should be Bartel index, not Battel…….)
Response:We are very sorry for our incorrect writing and have made the correction according to the Reviewer's comments.
Reviewer #2:
1. Response to comment: (Please revise grammar, structure and redundancy)
Response:we are very lucky to meet such a careful and conscientious reviewer, and very grateful for helping us put forward such detailed and specific suggestions for revision. We have revised and proofread one by one according to your suggestions.

Special thanks to you for your good comments.

Reviewer #3:
1. Response to comment: (The significance of this study)
Response:Stroke has a high incidence rate, high recurrence, high disability, and high mortality. About 85% of survivors have upper extremity dysfunction,and more than 60% still have hand dysfunction and cannot live independently after treatment. placing a heavy burden on the family and society. Evidence based medicine has shown that stroke rehabilitation is the most effective way to reduce disability, In addition to traditional rehabilitation therapy, which relies on rehabilitation physiotherapists to train patients, auxiliary training with the help of a rehabilitation robot is also available. However the training process can be boring and it is difficult to mobilize patients to participate in training, and the clinical evidence-based evidence proves that the treatment effect is limited.
brain-computer interface technology (BCIT), a neuromodulation technique that includes VR, BCI, brain stimulation, neurofeedback etc., is a cutting-edge, popular, non-invasive new method of central nervous system intervention that involves brain stimulation, and has been studied and applied in clinical treatment.Some independent studies have proved that it has better rehabilitation effect and is more interesting than traditional rehabilitation because of its novelty .

So that it is significance to synthesize results from randomized controlled trials to assess the effectiveness and safety of brain-computer interface technology in the treatment of post-stroke motor disorders.

VERSION 2 – REVIEW

REVIEWER	Stéphanie Lefebvre university of Bern, Switzerland
REVIEW RETURNED	13-Nov-2020

GENERAL COMMENTS	I appreciated the efforts of the authors to comply with the reviewers comments and to clarify the different issues. But in its current form the protocol is not suitable for publication. The points mentioned in the previous revision have not been fully address. Abstract it is still written "Modified Battel Index", which is not the correct name of the test. the correct name should be Modified Barthel Index. (same in the abbreviation list) Fugl-Meyer needs the -. Introduction The introduction is still not clear, not well written. the added paragraphs are confusing. "brain-computer interface technology (BCIT), a neuromodulation technique that includes VR, BCI, brain stimulation, neurofeedback etc., is a cutting-edge, popular, non-invasive new method of central nervous system intervention that involves brain stimulation, and has been studied and applied in clinical treatment" this is too long for a sentence, and again, as stated in my first review, the authors should not define BCI as a brain stimulation technique it is confusing and incorrect. you can combine it with brain stimulation but by it self it is not brain stimulation. all that point need to be clarified. the whole introduction need a complete rewriting, like the first sentence "Stroke, or cerebrovascular accident, has a high incidence rate, high recurrence, high disability, and high mortality", this is not well written, 4 high in 16 words it is quite indigest. Page 18 line 36-43. this is not well explained. its sounds like the authors are saying that all BCI should involve all of these techniques. The whole new insertion need to be reorganized. In the Methods 2.3.3 the authors can not state that the BCI intervention could be brain stimulation, or there is real need to explain what the authors mean by brain stimulation.

REVIEWER	Raquel Carvalho CESPU - Portugal
REVIEW RETURNED	18-Nov-2020

GENERAL COMMENTS	This version of manuscript was improved so I recommend the acceptance; however, there are small aspects that should be corrected before. Page 4 line 11 - “is a cutting-edge, popular, non-invasive new method of central nervous system intervention that involves brain stimulation, and has been studied and applied in clinical treatment.” Since, could induce misperception with deep brain stimulation, please consider to use the term neuroplasticity instead. Page 4 line 28-29 “It detects brain signals that convey intention and

	converts them into executable output through machines, making it "a direct connection between living nerve tissue and artificial devices, establishing a communication channel between the computer and the brain". Add reference Page 4 line 36 . “and decodes its meaning, and “writing” to the brain to manipulate the activity of a specific area and influence function.” Instead of writing please consider to use “, back to the brain in feedback manner, in order to manipulate…

VERSION 2 – AUTHOR RESPONSE

Responds to the reviewer’s comments:

Reviewer #1:

1. Response to comment: (……the correct name should be Modified Barthel Index.Fugl-Meyer needs the -.……)

Response: We are very sorry for our incorrect writing of Modified Barthel Index, and negligence of ugl-Meyer needs the "-",We checked the spelling and details again, We should be more rigorous and conscientiously.

We are very sorry for our negligence of

2. Response to comment: (……The introduction is still not clear, not well written. the added paragraphs are confusing.……)

Response: Combined with clinical practice, we have consulted more frontier literatures and re-written this part according to the Reviewer’s suggestion.

3. Response to comment: (……In the Methods 2.3.3 the authors can not state that the BCI intervention could be brain stimulation, or there is……)

Response:With the continuous development and enrichment of brain computer interface technology, there are more and more intervention methods. VR, BCI, brain stimulation, and nerve feedback have appeared in published articles, which should not be all. Of course, not all brain computer interface technologies contain these contents. Most of them only contain one or two of them.

Special thanks to you for your advice and help us improve the accuracy of the article.

Reviewer #2:

1. Response to comment: (……Page 4 line 11 - “is a cutting-edge, popular…….)

Response:It is really true as Reviewer suggested that "neuroplasticity" is more specific and accurate.

2.Response to comment: (……Page 4 line 28-29 “It detects.....puter and the brain". Add reference)

Response: We are very sorry for our negligence of the reference.

3.Response to comment: (……Page 4 line 36 . “and decodes its meaning, and “writing”)

Response: We have made the correction according to the Reviewer’s comments.

Special thanks to you for your good comments.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

VERSION 3 – REVIEW

REVIEWER	Lefebvre Stephanie University of Bern, Switzerland
REVIEW RETURNED	09-Dec-2020

GENERAL COMMENTS	the authors addressed my comments.