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Effectiveness and safety of brain computer interface technology in the treatment of post-stroke motor disorders: A protocol for systematic review and meta-analysis

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Effectiveness and safety of brain computer interface technology in the treatment of post-stroke motor disorders: A protocol for systematic review and meta-analysis

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Abstract

Methods:A searching strategy will be carried out mainly in eight databases in English and Chinese, China National Knowledge Infrastructure, the Chinese Scientific Journal Database, the Wanfang database, China Doctoral Dissertations Full-text Database, and China Master's Theses Full-text Database，Cochrane Central Register of Controlled Trials, PubMed, Embase.In addition, Manual retrieval of papers, conference papers, ongoing experiments, internal reports, etc. to supplement electronic retrieval.Select all eligible studies published by June 8, 2020. Only randomized controlled trials related to BCIT for PSMD will be included to enhance the effectiveness. 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) will be assessed as secondary outcome. Side effects and adverse events will be used as safety evaluations. To ensure the quality of the systematic evaluation, study selection, data extraction, and quality assessment will be independently performed by 2 authors, and the third author will deal with any disagreement. The Review Manager V.5.3.3 and STATA15.1 will be used to perform the data synthesis and subgroup analysis.
Results:In this systematic review and meta-analysis, we will synthesize the studies to assess the improvement of sports function and quality of life in patients with PSMD, and to evaluate the safety of BCIT.
Conclusion: This study will provide strong evidence for evaluating whether BCIT therapy is effective and safe for PSMD patients.
PROSPERO registration number:ID190868
(URLhttps://www.crd.york.ac.uk/prospero/#recordDetails)

Strengths and limitations of this study

- This systematic review and meta-analysis provid-ed a broad review of the efficacy and safety of brain computer interface technology in the treatment of

post-stroke motor disorders.

- Randomised controlled trials comparing brain computer interface technology combined with Routine rehabilitation treatment to Routine rehabilitation treatment were included to avoid potential risk of bias that may exaggerate the estimated effect of brain computer interface.
- The search strategy was comprehensive, over 11 Chinese and English databases will be detected.
- Subgroup analysis was carried out to exclude the differences caused by the location of the study and the length of treatment.
- Overall, Brain computer interface technology and related virtual reality technology as a new science and technology, the introduction of rehabilitation medicine time is relatively short, the relevant randomized controlled trials have been completed, resulting in limited number of studies. The results may have some limitations.In addition, due to the differences in the level of rehabilitation practitioners in different regions, the conventional rehabilitation treatment may have a little bias on the research results.

Abbreviations: 95% CIs = 95% confidence intervals, BCIT = brain computer interface technology, PSMD = post-stroke motor disorders, 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)

Keywords: brain computer interface technology, post-stroke motor disorders, effect, safety

1. Introduction

Stroke, also known as cerebrovascular accident, is a major disease that endangers human health. It has the characteristics of high incidence rate, high recurrence rate, high disability rate and high mortality. About 85% of survivors have upper extremity dysfunction.[1] More than 60% of the patients still have hand dysfunction and can not live independently after treatment.[2] It places a heavy burden on the family and society.

Although the level of clinical diagnosis and treatment of stroke has been improved in recent years, most of the surviving patients are left with motor, sensory, cognitive, language and mental disorders.[3] Evidence based medicine has proved that stroke rehabilitation is the most effective way to reduce the disability rate, and it is also an indispensable key link in the organizational management mode of stroke.[4] Effective rehabilitation treatment can not only restore the residual function of patients, but also mobilize their own potential, and create conditions for improving their ability to live independently and return to society.[5]At present, it is known that high-intensity, high-dose and repeated related training tasks are the key factors of post-stroke rehabilitation treatment. In addition to the traditional rehabilitation therapy which relies on the rehabilitation physiotherapist to train the hand handle of patients, there are also some auxiliary training with the help of rehabilitation robot. The training

process is boring and it is difficult to mobilize the autonomy of patients to participate in the training, which affects the treatment effect.[6]

In recent years, with the continuous integration, promotion and development of rehabilitation medicine, biomedical engineering, computer science, artificial intelligence and other disciplines and fields, BCIT, as a cutting-edge, popular, non-invasive new method of brain stimulation central nervous intervention, has been continuously studied and applied in clinical treatment.[7] It combines with peripheral nerve intervention,[8] such as functional stimulation, vibration stimulation, sensory stimulation, exoskeleton and even combined with other central nervous interventions such as transcranial magnetic stimulation and transcranial electrical stimulation.[9] At present, BCI has been proved to be effective in hand function rehabilitation of stroke patients.[10-15] The application of BCIT in the rehabilitation of upper limb and hand function of stroke patients with hemiplegia not only saves manpower and is more safe, but also enables patients to participate in rehabilitation training actively and promote the remodeling of the central nerve.[16] Not only can the hand function recover effectively, but also can improve the patients' ability of daily life.[17] It provides a new rehabilitation technology for the rehabilitation of upper limb and hand function of stroke hemiplegic patients in rehabilitation institutions.

Therefore,our study aim to synthesize the randomized controlled trials (RCTs) and access the effectiveness and safety of BCIT in the treatment of PSMD.

2. Methods

2.1. Design and registration of the review

This systematic review and meta-analysis protocol has been registered at nternational Prospective Register of Systematic Reviews PROSPERO. The registration number is CRD42019137399. This systematic review protocol is structured in accordance with the guideline of Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P).[18]

2.2. Inclusion criteria for study selection

2.2.1. Types of studies. Randomized controlled trials (RCTs) that published or registered before June 8, 2020 are the only study type to be included. Quasi-RCTs, review articles,case reports, and other studies that do not meet the requirements will be excluded.

2.2.2. Types of patients. The patients, The age is 18~75 years old, In line with the diagnostic criteria of stroke in the classification of cerebrovascular diseases in China in 2015, For the first stroke confirmed by CT or MRI, 1 month≤course≤6 months,With moderate and severe upper extremity and hand dysfunction,With moderate and severe hand Dysfunction [grade 2≤Brunnstrom grade 4, improved Ashworth Spasm scale (MAS) < Level 3] will be included, regardless of the limitation of gender and nationality. Patients with other diseases that serious cognitive and speech disorders, cannot understand and complete the therapist's instructions (MMSE < 21 points); history of drug and alcohol dependence, serious liver and kidney function diseases or other diseases that may affect brain structure and function, and other mental disorders will be excluded.

2.2.3. Types of interventions. We will include studies in which intervention group

applying BCIT alone or in combination with Routine rehabilitation treatment as the intervention, such as manual therapy, exercise therapy and electronic biofeedback, etc, the control group undergoing Routine rehabilitation treatment treatment.

2.2.4. Types of outcome measures

2.2.4.1. Primary outcome. The primary outcome is the Fugl Meyer motor function (FMA) score.

2.2.4.2. Secondary outcomes. Secondary outcomes include the Modified battel index (MBI), modified ASH - worth score (MAS) and upper extremity freehand muscle strength assessment (MMT) .

In the subgroup analysis, the treatment times of improvement of motor function and the therapeutic method that BCIT combined with other treatments would be expounded.

2.2.5. Exclusion criteria. The studies with the following situation will be excluded: the participants were diagnosed with secondary stroke; duplicated data or the data cannot be extracted. Observational studies, retrospective studies,nonrandomized trials, quasiexperimental studies, and animal studies were excluded. Additionally, the studies with in-sufficient data or lacking effective sort were also not included.

2.3. Search methods for the identification of studies

A searching strategy will be carried out mainly in eight databases in English and Chinese, China National Knowledge Infrastructure, the Chinese Scientific Journal Database, the Wanfang database, China Doctoral Dissertations Full-text Database, and China Masters Theses Full-text Database， Cochrane Central Register of Controlled Trials, PubMed, Embase. In addition, Manual retrieval of papers, conference papers, ongoing experiments, internal reports, etc. to supplement electronic retrieval.Select all eligible studies published by June 8, 2020.

2.4. Search strategy

The search strategy is created on the basis of the Cochrane handbook guidelines (5.1.0). We formulated search strategies for each database used the keywords such as “post-stroke”,“ motor disorders”, “brain computer interface”, and “RCT”. Subsequent databases searches used MeSH headings, including as “post-stroke”,“motor disorders” and “brain computer interface” , in addition to keywords from the initial retrieval. And other article searches were conducted by reviewing the literature lists of relevant research articles. Used PubMed as an example, the search strategy for PubMed is summarized in Table 1.

Table 1 Search strategy for PubMed.

Number	Search terms
1	brain computer interface.ti,mesh.
2	direct neural interface..ti,ab.
3	brain-machine interface.ti,ab.
4	Or 1-3

5	post-stroke. ti,ab.
6	after stroke. ti,ab.
7	Or 5-6
8	motor disorders. ti,mesh.
9	dyskinesias. ti,ab.
10	Or 8-9
11	Randomized controlled trial.pt.
12	Controlled clinical trial.pt.
13	Randomized.ab.
14	Randomly.ab.
15	trial.ab.
16	or 11-15
17	exp animals/not humans.sh.
18	16 not 17
19	4 and 7 and 10and 18

2.5. Data extraction

2.5.1. Selection of studies. Records from databases and other resources will be uploaded to a database created by EndNote9.7 software. The abstracts of all studies will be independently screened by the review authors (XLZ and JNL). The full text of articles potentially suitable for the review will be obtained for further assessing eligibility based on the inclusion criteria or/and exclusion criteria. The studies that do not fulfill the inclusion criteria will be excluded and listed with reasons for their exclusion. Any disagreement will be resolved by consensus or discussion with a 3rd authors (MJL).The fifinal selection procedure is indicated in Figure 1 abide by the PRISMA guidelines.[19]

2.5.2. Data extraction and management. Two reviewers (XLZ and QZ) will assess the eligibility of the studies retrieved during the searches independently using the

inclusion and exclusion criteria. The following data will then be extracted from the studies selected for inclusion using a data collection form, and recorded onto an Excel file: first author and year, study design, sample, intervention, type of measures, risk of bias assessment and findings. The results will be cross-checked by the two reviewers, and any disagreements will be resolved by consensus, with any ongoing differences in opinion being arbitrated by a third reviewer (DC).

We may also contact the original authors to provide additional relevant information, if necessary.

The data extraction form will include the following items:

1). general information: title, authors, year of publication, and Study area, average age, average course of disease and treatment time;

2). trial characteristics: design, duration of follow-up, method of randomization, allocation concealment, incomplete outcome data, blinding (patients, people administering treatment,outcome assessors);

3). intervention(s): intervention(s) (The form of BCIT, Routine rehabilitation treatment, Application time，duration of session),comparison intervention(s) (Routine rehabilitation treatment, Application time，duration of session);

4). patients: total number and number in both groups, baseline characteristics, diagnostic criteria, withdrawals and losses to follow-up (reasons, description);

5). outcomes: outcomes specified above, Adverse drug reactions and adverse time，length of follow-up,quality of reporting of outcomes.

2.5.3. Assessment of risk of bias in included studies.

The bias tool of Cochrane Handbook for Systematic Reviews of Interventions[20] will be used for evaluating the risk of bias, which will be independently evaluated by 2 reviewers(ZXL and DC). The risk of bias will be assessed in 6 dimensions: random sequence generation; allocation concealment; blinding method for patients,researchers and outcome evaluators; incomplete result data; selective reporting; and other issues.TThe quality of the studies will be divided into 3 levels: “low risk of bias,” “high risk of bias,” and “unclear risk of bias.”. Any discrepancies will be resolved through discussions with the third author. When a consensus cannot be reached by discussion, the third reviewer(MJL) will make the decision.

2.5.4. Measures of treatment effect.

Methods vary depending on the type of data. For the dichotomous variables outcomes, the total effective rate and adverse events, we will analyze the rate ratio. The mean difference will be used to evaluate the continuous variables data. The 95% confidence interval will be presented for both dichotomous outcomes and continuous outcomes.

2.5.5. Management of missing data.

We will contact the original author for the missing or incomplete data.the waiting time defaults to 1 month after an email is sent. The incomplete data will be dislodged if We cann't wait for a valid reply.

2.5.6. Assessment of heterogeneity.

Statistical heterogeneitywill be assessed with the I-square (I2) statistic.[21] The I2statisticof less than 50% indicates a low level of statistical heterogeneity,and that of 50% or more will be considered substantial statisticalheterogeneity. If substantial

heterogeneity is identified, we will report it and explore possible causes using sensitivity analysis and subgroup analysis.

2.5.7. Assessment of reporting biases.

We will apply the funnel plots to evaluate the reporting biases if the included studies are more than ten trials. Otherwise, the STATA15.1 software will be conducted to perform the Egger test.

2.5.8. Subgroup analysis.

We plan to carry out the followingsubgroup analyses if possible: The study area is different, different routine rehabilitation methods,the average course of disease is different, and the length of treatment is different. We will use the formal test for subgroup interactions in Review Manager 5.3.

2.5.9. Sensitivity analysis.

we will per-forme the Sensitivity analysis to explore the effects of trial risk of bias on primary outcomes if possible. In the analysis, we will exclude lowerquality trials and repeat the meta-analyses to access the quality and robustness when the significant statistical heterogeneity arose according to sample size and insufficient data.

2.6. Grading the quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[22] will be used to assess the quality of the evidence and risk of bias with on-line GRADE(https://www.gradeworkinggroup.org/). The assessment will be adjudicated into 4 levels:high, moderate, low, or very low.

2.7.Ethics and dissemination

This systemic review will evaluate the efficacy and safety of BCIT combined with Routine rehabilitation treatment in the treatment of PSMD. Since all the data included are published, the systematic review does not need ethical approval.This systematic review and meta-analysis will bepublished in a peer-reviewed journal.

3. Discussion

With the aging of the world population and the influence of living habits and environmental changes, stroke has a high incidence rate, high disability rate, low cure rate and so on.[23] However, there are many dysfunction after stroke, the most common one is motor dysfunction.Especially the motor dysfunction of the upper limbs and hands, because of its long treatment cycle and poor prognosis, has always been the clinical focus and difficulty. [24]At present, most of the conventional treatment techniques of upper limb and hand function after stroke are focused on peripheral treatment, including various facilitation techniques, functional electrical stimulation, etc., but these methods are different from direct intervention on patients' brain, and the effect is not significant. [25,26]

With the development of rehabilitation medicine technology and artificial intelligence technology, [27] BCIT realizes the use of control signals generated by EEG activities, so that human beings can interact with the surrounding environment without the influence of peripheral nerves and muscles.This can not only effectively make up for

the limitations of traditional rehabilitation methods, increase the interest of treatment, but also benefit the rehabilitation treatment of upper limb and hand function. The unique function of BCIT makes it applied in the rehabilitation of motor disorders after stroke, which not only saves manpower and is more safe, but also enables patients to participate in rehabilitation training actively and promote the remodeling of the central nerve.[28] It is a promising treatment which not only can the hand function recover effectively, but also can improve the patients' ability of daily life [29].

This systematic review and meta-analysis will provide patients,clinicians, and health decision makers with a deeper understanding of the efficacy and safety of BCIT in the treatment of PSMD.

The PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist of this protocol is presented in PRISMA-P checklist

Statement
It is not necessary for ethical approval because this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. The protocol will be disseminated in a peer-reviewed journal or presented at a relevant conference.

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Competing interests None declared.
Patient consent for publication Not required.
Provenance and peer review Not commissioned; externally peer reviewed.
Data sharing statement Data extracted from original studies and data used for meta-analysis are available on request.

Author contributions
XLZ conceived of the study, and perform this review.The manuscript was drafted by XLZ and MJL. DC and QZ developed the search strategy. XLZ and QZ will independently screen the potential studies and extract data. XLZ and DC will assess the risk of bias and perform data synthesis. MJL will arbitrate any disagreement and ensure that no errors occur during the review. All review authors critically reviewed, revised and approved the subsequent and final version of the protocol.
Conceptualization:Mingjun Liu .
Data curation: Xiaolin Zhang, Di Cao,Qi Zhang,Junnan Liu.
Methodology:Xiaolin Zhang.
Project administration: Xiaolin Zhang.
Supervision: Mingjun Liu.
Writing – original draft: Xiaolin Zhang, Di Cao.
Writing – review & editing: Xiaolin Zhang.

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Fig.1 PRISMA flow diagram of study and exclusion

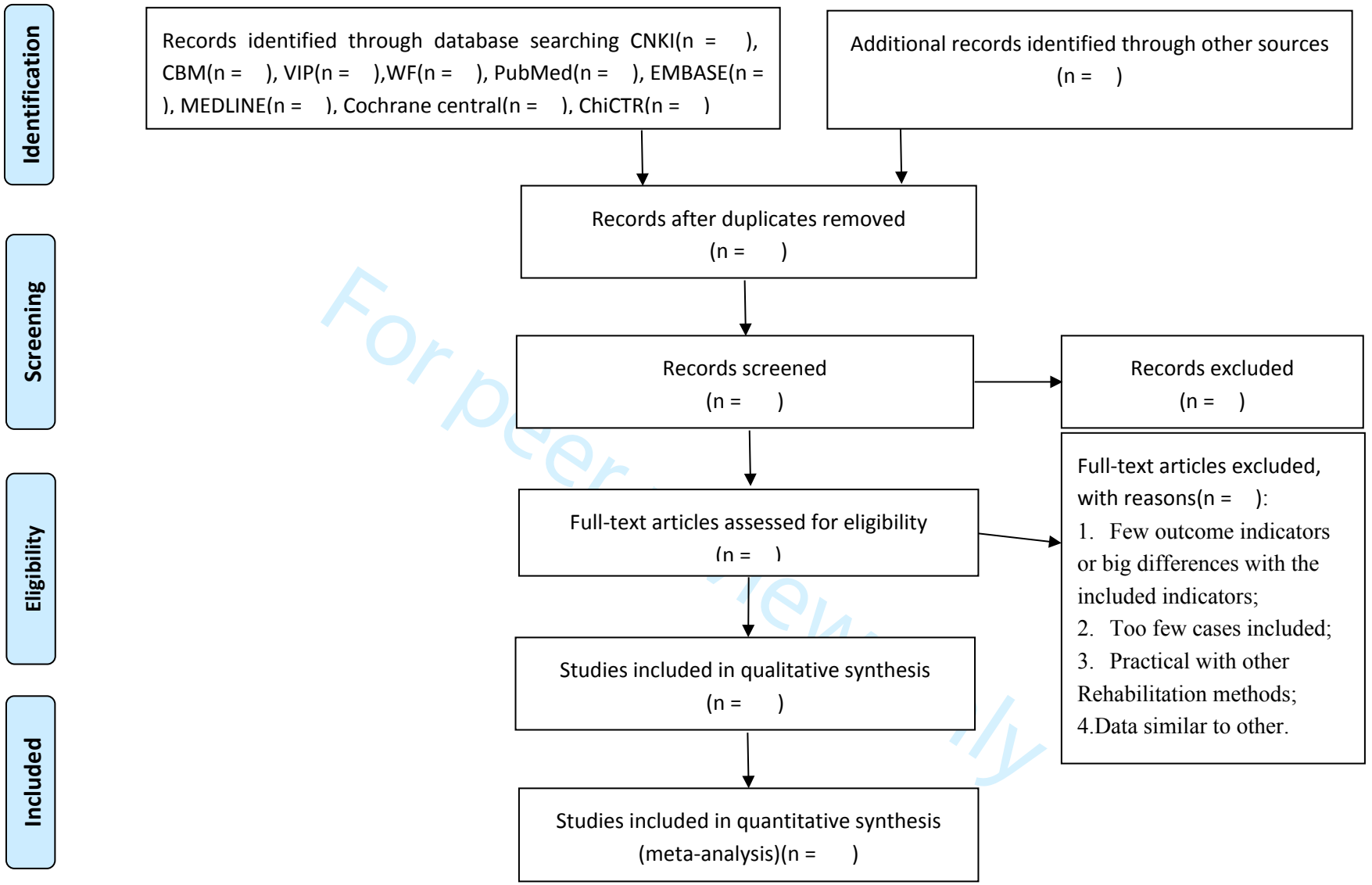

Fig.1 PRISMA flow diagram of study and exclusion

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	3-4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Effectiveness and safety of Brain computer interface technology in the treatment of post-stroke motor disorders: A protocol for systematic review and meta-analysis

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Abstract

Introduction: The high incidence rate of stroke, coupled with its high recurrence, disability, and mortality rates places a heavy burden on society and on the families of individuals who experience stroke. About 85% of stroke survivors have upper extremity dysfunction, and more than 60% have continuing hand dysfunction and cannot live independently after treatment. Our study aims 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.
Methods: English and Chinese searching strategies will be conducted in eight databases: the China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, China Doctoral Dissertations Full-Text Database, China Master's Theses Full-Text Database, Cochrane Central Register of Controlled Trials, PubMed, and Embase. In addition, manual retrieval of research papers, conference papers, ongoing experiments, internal reports, etc. will supplement electronic retrieval. The searches will select all eligible studies published on or before June 8, 2020. To enhance the effectiveness of the study, only randomized controlled trials related to brain-computer interface technology for post-stroke motor disorders will be included. **Analysis:** The Fugl Meyer Motor Function score will be the primary outcome measure; the Modified Battel Index, Modified Ashworth Score, and the upper extremity freehand muscle strength assessment will be secondary outcomes. Side effects and adverse events will be included as safety evaluations. To ensure the quality of the systematic evaluation, study selection, data extraction, and quality assessment will be independently performed by two authors, and the third author will handle any disagreement. Review Manager V.5.3.3 and STATA15.1 will be used to perform the data synthesis and subgroup analysis.
Ethics and Dissemination: This systemic review will evaluate the efficacy and safety of BCIT combined with routine rehabilitation treatment for treatment of PSMD. Since

all included data will be obtained from published articles,it does not require ethical approval,and will be published in a peer-reviewed journal.
PROSPERO registration number:CRD42020190868

Strengths and limitations of this study

- This systematic review and meta-analysis will provide a broad review of the efficacy and safety of brain-computer interface technology in the treatment of post-stroke motor disorders.
- Randomised controlled trials comparing brain computer interface technology combined with routine rehabilitation treatment to routine rehabilitation treatment, alone have not yet discovered whether the source of motor recovery derives from conventional therapy, the motor imagery by itself, neurofeedback from BCI, or a combination of these.
- The search strategy will be comprehensive, covering eight Chinese and English databases.
- Subgroup analysis will be conducted to exclude differences related to the study location or length of treatment.
- Overall, Brain-computer interface technology is a new sciencethat was only recently introduced into rehabilitation medicine so there are a limited number of studies,which may limit the study results. Also, evidence produced by some studies may be of moderate to very low quality because of unspecified or unclear randomisation procedures or substantial heterogeneity in the outcome measures.

Abbreviations: 95% CIs=95% confidence intervals, BCIT=brain computer interface technology, PSMD=post-stroke motor disorders, FMA=The Fugl Meyer motor function score ,MBI=Modified battel index , MAS=modified ASH - worth score, MMT=upper extremity freehand muscle strength assessment

Keywords: Brain-machine interface，Brain stimulation，post-stroke motor disorders, effect, safety

1. Introduction

Stroke, or cerebrovascular accident, has a high incidence rate, high recurrence, high disability, and high mortality. About 85% of survivors have upper extremity dysfunction,[1]and more than 60% still have hand dysfunction and cannot live independently after treatment.[2] placing a heavy burden on the family and society. Although clinical diagnosis and treatment of stroke has improved in recent years, most surviving patients are left with motor, sensory, cognitive, language, and mental disorders.[3] Evidence based medicine has shown that stroke rehabilitation is the most effective way to reduce disability, and is also a key link in the organizational management mode of stroke.[4] Effective rehabilitation treatment can both restore the patients' residual function, and mobilize their potential, improving their ability to live independently and return to society.[5]High-intensity, high-dose, and repeated related training tasks are key factors in post-stroke rehabilitation treatment.[3] 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.[6]

With the continuous integration, promotion, and development of rehabilitation medicine, biomedical engineering, computer science, artificial intelligence and other disciplines, 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.[7] It can be combined with peripheral nerve intervention,[8] such as functional stimulation, vibration stimulation, sensory stimulation, and exoskeleton stimulation, and can even be combined with other central nervous system interventions, such as transcranial magnetic stimulation and transcranial electrical stimulation.Some independent studies have proved that it has better rehabilitation effect and is more interesting than traditional rehabilitation because of its novelty.[9] BCIT can be regarded as an auxiliary technology for people who are unable to communicate or are paralyzed (e.g., patients with post-stroke limb dyskinesia, amyotrophic lateral sclerosis, or spinal cord injury). 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". Unlike related devices, brain computer interface involves two-way feedback between the user and the system to produce body changes, restoring some function for those who have lost limbs, suffered from massive paralysis, or have severe neurological damage. Interface technology includes "reading" the brain, which records brain activity and decodes its meaning, and “writing” to the brain to manipulate the activity of a specific area and influence function.BCIs use three methods to record brain signals: (1) non-invasive methods record signals from the scalp (electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), and near infrared spectroscopy (NIRS)); (2) invasive methods record signals from the surface of the cortex by ECoG, and with the aid of a microelectrode array, signals can be recorded from the inner cortex, which is more invasive, but the signal-to-noise ratio is also improved.Because of its security, portability, cost-effectiveness, and high resolution, non-invasive BCI is widely used.[10-15] Applying BCIT to rehabilitate upper limb and hand function in stroke patients with hemiplegia is safer, less labour intense, and allows patients to actively participate in rehabilitation training to promote central nervous system remodelling.[16] This both facilitates effective recovery of hand function and improves the patients' ability to perform normal daily activities.[17]

The proposed date for completing the study is:March 12, 2021

2. Methods and analysis

2.1. Patient and public involvement

This article is based on previously conducted studies and does not involve any patient

and public involvement or new studies of human or animal subjects performed by any of the authors.

2.2. Design and registration of the review

This systematic review and meta-analysis protocol is registered with the international Prospective Register of Systematic Reviews PROSPERO, registration number is CRD42020190868. The protocol is structured in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P).[18]

2.3. Inclusion criteria for study selection

2.3.1. Types of studies. Only Randomized controlled trials (RCTs) that published or registered before June 8, 2020 will be included. Quasi-RCTs, review articles, case reports, and other studies that do not meet the requirements will be excluded.

2.3.2. Types of patients. Patients' age will be between 18 and 75 years. In line with China's 2015 diagnostic criteria for classifying cerebrovascular diseases, the first stroke confirmed by CT or MRI with a course greater than one month and less than or equal to six months, with moderate to severe upper extremity and hand dysfunction meeting the criteria (Brunnstrom grade 2-4, FMA score < 20, improved Ashworth spasm scale (MAS) less than level 3) will be included, regardless of gender and nationality. Patient exclusion criteria: presence of other diseases resulting in serious cognitive and speech disorders; patients who could not understand and complete the therapist's instructions (MMSE < 21 points); history of drug or alcohol dependence; serious liver or kidney disease; other diseases that may affect brain structure and function; and other mental disorders.

2.3.3. Interventions types . We will include studies where the intervention group received BCIT（includes one or more of VR, BCI, brain stimulation, nerve feedback ,etc),alone or in combination with routine rehabilitation treatmen(manual therapy, exercise therapy and electronic biofeedback, etc.)where the control group received only conventional rehabilitation treatment.

2.3.4. Outcome measures

2.3.4.1. Primary outcome. The primary outcome Measure will be the Fugl Meyer Motor Function (FMA) score.

2.3.4.2. Secondary outcomes. Secondary outcomes will include the Modified Battel Index (MBI), Modified Ashworth Score (MAS) and The upper extremity freehand muscle strength assessment (MMT) .

In the subgroup analysis, times to improvement of motor function and the type of therapeutic intervention combined with BCIT will be analysed.

2.3.5. Article exclusion criteria. Studies with the following situations will be excluded: participants were diagnosed with secondary stroke; duplicated data or data cannot be extracted;observational studies;retrospective studies;non-randomized

trials;quasi-experimental studies; and animal studies. Additionally, studies with insufficient data or lacking effective sort will also not be included.

2.4. Search methods for the identifying of studies

English and Chinese search strategies will be conducted on eight databases: the China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, China Doctoral Dissertations Full-Text Database, and China Masters Theses Full-Text Database, Cochrane Central Register of Controlled Trials, PubMed, and Embase. In addition, we will conduct manual retrieval of papers, conference papers, ongoing experiments, internal reports, etc. to supplement electronic retrieval. We will select all eligible studies published on or before June 8, 2020.

2.5. Search strategy

The search strategy will be based on the Cochrane handbook guidelines (5.1.0) including keywords such as “post-stroke”, “ motor disorders”, “brain computer interface” or “neurofeedback”, and “RCT”. Subsequent searches will use MeSH headings, including “post-stroke”, “motor disorders”, and “brain computer interface”, in addition to keywords from the initial retrieval. Additional article searches will review the reference lists of relevant research articles. As an example, the search strategy for PubMed is summarized in Table 1.

Table 1 Search strategy for PubMed.

Number	Search terms
1	brain computer interface.ti,mesh.
2	direct neural interface.ti,ab.
3	neurofeedback.ti,ab.
4	brain-machine interface.ti,ab.
5	Or 1-4
6	post-stroke. ti,ab.
7	after stroke. ti,ab.
8	Or 6-7
9	motor disorders. ti,mesh.
10	dyskinesias. ti,ab.
11	Or 9-10

12	Randomized controlled trial.pt.
13	Controlled clinical trial.pt.
14	Randomized.ab.
15	Randomly.ab.
16	trial.ab.
17	or 12-16
18	exp animals/not humans.sh.
19	17 not 18
20	5 and 8and 10and 19

2.6. Data extraction

2.6.1. Studies selection. Records from databases and other resources will be uploaded to a database created in EndNote, version 9.7. All extracted abstracts will be independently screened by the review authors (XLZ and JNL). We will obtain the full text of all potentially suitable articles to further assess eligibility based on the inclusion/exclusion criteria. Studies that do not meet the inclusion criteria will be excluded and the reason for exclusion will be recorded. Any disagreement will be resolved by consensus or discussion with a third author (MJL). The final selection procedure will abide by the PRISMA guidelines,[19] and is presented in Figure 1.

2.6.2. Data extraction and management. Two reviewers (XLZ and QZ) will independently apply the inclusion and exclusion criteria to assess each retrieved study's eligibility. The following data will then be extracted from the selected studies for inclusion using a data collection form, and recorded in Excel file: first author and publication year, study design, sample, intervention, types of measures, risk of bias assessment, and findings. The results will be cross-checked by the two reviewers, and disagreements will be resolved by consensus, with any ongoing differences in opinion arbitrated by a third reviewer (DC). We may also contact the original authors to provide additional relevant information, if necessary.

The data extraction form will include the following items:

1) General information: title, authors, publication year, and study area, average patient age, average disease course, and treatment time.
2) Trial characteristics: design, follow-up duration, randomization method, allocation concealment, incomplete outcome data, blinding (patients, people administering treatment, outcome assessors).

3) Intervention: primary intervention (BCIT type, routine rehabilitation treatment, application time, session duration); comparison interventions (routine rehabilitation treatment, application time. session duration).
4) Patients: total number and number in each group, baseline characteristics, diagnostic criteria, withdrawals, and losses to follow-up (reasons, description).
5) Outcomes: primary outcomes, adverse drug reactions, adverse time, follow-up length, quality of outcomes reporting.

2.6.3. Risk of bias in assessment. Two reviewers (ZXL and DC) will independently apply the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions [20]to evaluate the risk of bias in each selected study. Six dimensions will be assessed: random sequence generation; allocation concealment; blinding method for patients, researchers, and outcome evaluators; incomplete results data; selective reporting; and other issues. The studies will be categorized into three quality levels: low risk of bias, high risk of bias, and unclear risk of bias.[18] Any discrepancies will be resolved through discussions with the third author. When a consensus cannot be reached by discussion, the third reviewer (MJL) will decide.

2.6.4. Treatment effect measures. Methods will vary by data type. For dichotomous variables, total effective rate and adverse events, we will analyse the rate ratio; for continuous variables, we will analyse mean differences. The 95% confidence interval will be presented for both dichotomous and continuous outcomes.

2.6.5. Missing data management. We will contact the original author to obtain the missing or incomplete data and will wait one month after an email is sent to receive a reply. If we are unable to obtain the missing data, the incomplete data will be excluded from the analysis

2.6.6. Heterogeneity assessment. Statistical heterogeneity will be assessed with the I-square (I^2) statistic.[21] An I2 statistic of less than 50% indicates a low level of statistical heterogeneity; 50% or more will be considered substantial statistical heterogeneity. If substantial heterogeneity is identified, we will report it and explore possible causes using sensitivity analysis and subgroup analysis.

2.6.7. Reporting biases assessment. We will construct funnel plots to evaluate reporting bias if the included studies include more than ten trials. Otherwise, STATA15.1 software will be used to perform the Egger test.

2.6.8. Subgroup analysis. We plan to carry out the following subgroup analyses, if possible: study area differences, differences in routine rehabilitation methods, average course of disease differences, and length of treatment differences. We will use the formal test for subgroup interactions in Review Manager 5.3.

2.6.9. Sensitivity analysis. When possible, we will perform sensitivity analysis to

explore the effects of the trial's bias risk on primary outcomes. These analyses will exclude lower quality trials and repeat the meta-analyses to assess quality and robustness when significant statistical heterogeneity arises, according to sample size and insufficient data.

2.7. Grading the quality of evidence

The online version of the Grading of Recommendations Assessment, Development, and Evaluation methodology (GRADE; https://www.gradeworkinggroup.org/) [22] will be used to assess the quality of the evidence and risk of bias, categorized into four levels: high, moderate, low, or very low.

3. Discussion

With the aging of the world population and the influence of living habits and environmental changes, stroke has become a major global health issue.[23] Motor dysfunction of the upper limbs and hands following stroke is especially important in clinical settings because of its long treatment cycle and poor prognosis.[24] Currently, most conventional upper limb and hand function rehabilitation techniques following stroke focus on peripheral treatment, such as facilitation techniques, functional electrical stimulation, etc., but these methods often result in low treatment effectiveness, so they are insufficient.[25,26]

Recent developments in rehabilitation medicine and artificial intelligence technology have focused on more direct brain-based interventions.[27] BCIT employs control signals generated by EEG activities, allowing patients to interact with the surrounding environment without the influence of peripheral nerves and muscles. This can effectively overcome the limitations of traditional rehabilitation methods, increase patients' interest in treatment, and benefit upper limb and hand function rehabilitation. BCIT applied in the rehabilitation of motor disorders after stroke is safer, requires less time and work for clinicians, and allows patients to actively participate in rehabilitation training that promotes remodelling of the central nervous system.[28] BCIT is a promising treatment for recovering hand function following stroke, which will facilitate patients' ability to perform activities of daily life [29].

However, the specific BCIT mechanisms that facilitate rehabilitation of post-stroke limb disorders needs further research, because it is not clear whether the source of motor recovery derives from conventional therapy, motor imagery by itself, neurofeedback from BCI, or a combination of these mechanisms. This systematic review and meta-analysis will provide patients, clinicians, and healthcare policy makers with a deeper understanding of BCIT's efficacy and safety in the treatment of PSMD.The PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist of this protocol is presented in PRISMA-P checklist

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Competing interests The authors declare that they have no competing interests.
Patient consent for publication Not required.
Provenance and peer review Not commissioned; externally peer reviewed.
Data sharing statement All data relevant to the study are included in the article,Subject to publication.

Author contributions
XLZ conceived of the study, and perform this review.The manuscript was drafted by XLZ and MJL. DC and QZ developed the search strategy. XLZ and QZ will independently screen the potential studies and extract data. XLZ and DC will assess the risk of bias and perform data synthesis. MJL will arbitrate any disagreement and ensure that no errors occur during the review. All review authors critically reviewed, revised and approved the subsequent and final version of the protocol.
Conceptualization:Mingjun Liu .
Data curation: Xiaolin Zhang, Di Cao,Qi Zhang,Junnan Liu.
Methodology:Xiaolin Zhang.
Project administration: Xiaolin Zhang.
Supervision: Mingjun Liu.
Writing – original draft: Xiaolin Zhang, Di Cao.
Writing – review & editing: Xiaolin Zhang.

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Fig.1 PRISMA flow diagram of study and exclusion

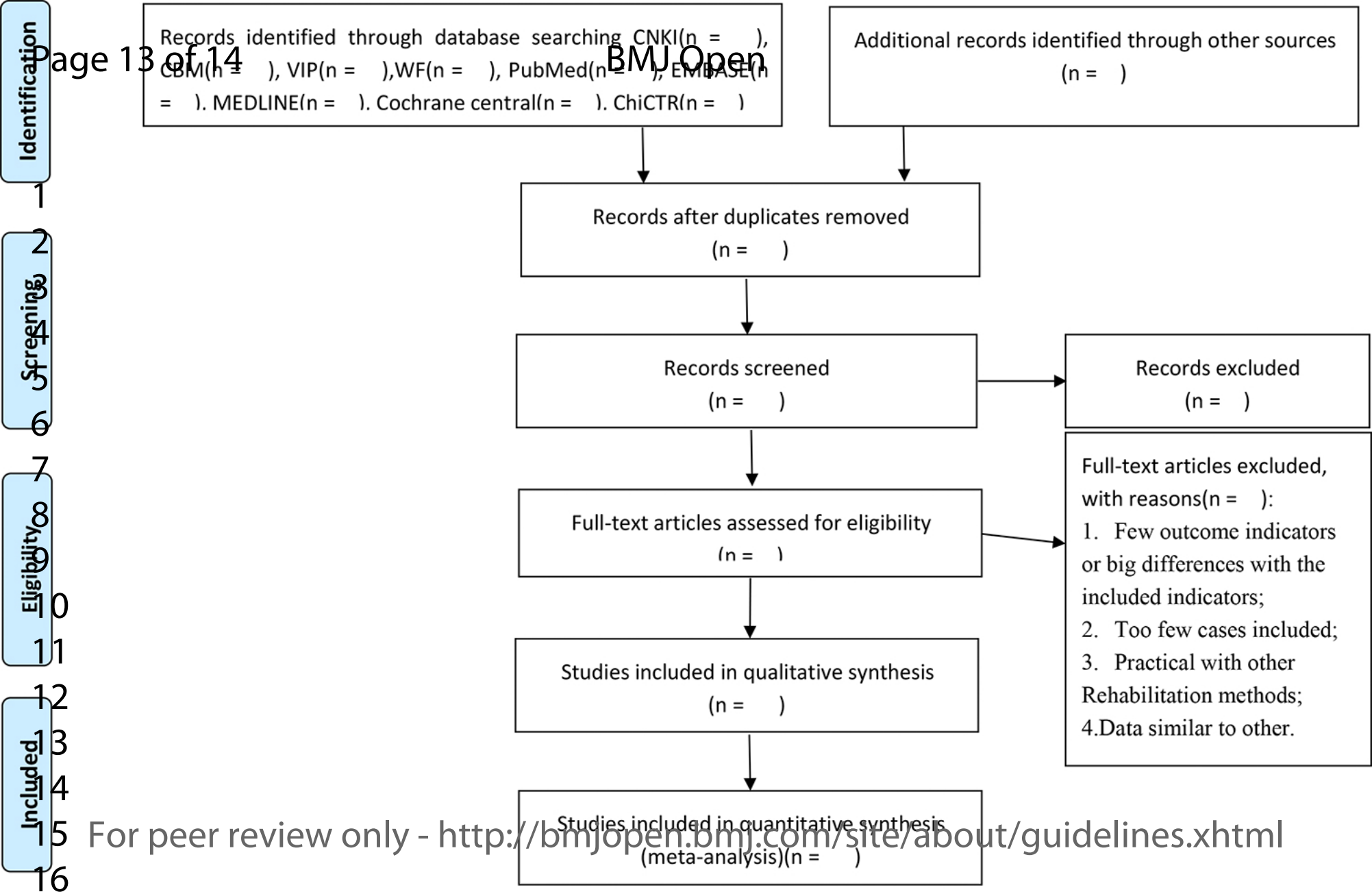

Fig.1 PRISMA flow diagram of study and exclusion

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	3-4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Effectiveness and safety of Brain-computer interface technology in the treatment of post-stroke motor disorders: A protocol for systematic review and meta-analysis

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ABSTRACT

Introduction: About 85% of stroke survivors have upper extremity dysfunction, and more than 60% have continuing hand dysfunction and cannot live independently after treatment. Numerous recent publications have explored Brain Computer Interfaces technology as rehabilitation tools to help subacute and chronic stroke patients recover upper extremity movement. Our study aims to synthesise results from randomised controlled trials to assess the effectiveness and safety of brain-computer interface technology in the treatment of post-stroke motor disorders.

Methods and analysis: English and Chinese search strategies will be conducted in eight databases: the China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, China Doctoral Dissertations Full-Text Database, China Master's Theses Full-Text Database, Cochrane Central Register of Controlled Trials, PubMed, and Embase. In addition, manual retrieval of research papers, conference papers, ongoing experiments, and internal reports, among others,will supplement electronic retrieval. The searches will select all eligible studies published on or before June 8, 2020. To enhance the effectiveness of the study, only randomised controlled trials related to brain-computer interface technology for post-stroke motor disorders will be included. The Fugl-Meyer Motor Function score will be the primary outcome measure; the Modified Barthel Index, Modified Ashworth Score, and the upper extremity freehand muscle strength assessment will be secondary outcomes. Side effects and adverse events will be included as safety evaluations. To ensure the quality of the systematic evaluation, study selection, data extraction, and quality assessment will be independently performed by two authors, and a third author will handle any disagreement. Review Manager V.5.3.3 and STATA15.1 will be used to perform the data synthesis and subgroup analysis.

Ethics and dissemination: This systemic review will evaluate the efficacy and safety of brain-computer interface technology combined with routine rehabilitation treatment

for treatment of post-stroke motor disorders. Since all included data will be obtained from published articles,the review does not require ethical approval. The review will be published in a peer-reviewed journal.
Trial registration number:CRD42020190868

Strengths and limitations of this study

- Include randomised controlled trials to discover whether the source of motor recovery derives from conventional therapy, the motor imagery by itself, neurofeedback from BCI, or a combination of these.
- Language and publication date will not be restricted.
- Conduct the sensitivity analysis to test whether the conclusions are robust.
- Different types of Brain-computer interface technology may lead to a large degree of heterogeneity.
- Subgroup analysis will be conducted to exclude differences related to the study location or length of treatment.

Abbreviations: 95% CIs=95% Confidence Intervals, BCIT=brain-computer interface technology, PSMD=post-stroke motor disorders, FMA=The Fugl-Meyer Motor Function score ,MBI=Modified Barthel Index , MAS=modified ASH - worth score, MMT=upper extremity freehand muscle strength assessment, RCT=randomised control trial; VR=virtual reality

INTRODUCTION

Stroke or cerebrovascular accident is the second leading cause of death and disability in the world ; [1]In China, the incidence rate is the first, the number of new cases is over 2.5 million every year, the death toll is over 1.5 million, and the cost of treatment is as high as 40 billion every year..[2] About 85% of survivors have upper extremity dysfunction[3],and more than 60% still have hand dysfunction and cannot live independently after treatment.[4] Such problems place a heavy burden on the family and society.

Although clinical diagnosis and treatment of stroke have improved in recent years, most surviving patients are left with motor, sensory, cognitive, language, and mental disorders.[5] Evidence based medicine has shown that stroke rehabilitation is the most effective way to reduce disability, and is also a key link in the organisational management mode of stroke.[6] Effective rehabilitation treatment can both restore the patients' residual function, and mobilise their potential, improving their ability to live independently and return to normallife.[7] High-intensity, high-dose medicine, and repeated related training tasks are key factors in post-stroke rehabilitation treatment.[5] 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 mobilise patients to participate in training, and the clinical evidence-based evidence indicates that the treatment effect is limited.[8]

With the continuous integration, promotion, and development of rehabilitation

medicine, biomedical engineering, computer science, artificial intelligence and other disciplines, BCIT have successfully been used for motor recovery training in stroke patients. BCIT, a neuromodulation technique that includes virtual reality (VR), brain-computer interface (BCI), brain stimulation, and neurofeedback, among other techniques, is a cutting-edge, popular, and non-invasive new method of central nervous system intervention .It involves neuroplasticity, and has been studied and applied in clinical treatment.[9,10] Some independent studies have shown that BCIT has better rehabilitation effects and is more interesting for patients than traditional rehabilitation because of its novelty.[11] BCIT can be regarded as an auxiliary technology for people who are unable to communicate or are paralysed (e.g. patients with post-stroke limb dyskinesia, amyotrophic lateral sclerosis, or spinal cord injury). 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". [12] Unlike related devices, BCIT involves two-way feedback between the user and the system to produce body changes, restoring some function for those who have lost limbs, suffered from massive paralysis, or have severe neurological damage. Interface technology includes ‘reading’ the brain, which records brain activity and back to the brain in feedback manner, in order to manipulate the activity of a specific area and influence function.BCIT essentially involves translating human brain activity into external action by sending neural commands to external devices.[12-17] Applying BCIT to rehabilitate upper limb and hand function in stroke patients with hemiplegia is safer, less labour intense, and allows patients to actively participate in rehabilitation training to promote central nervous system remodelling.[18] This both facilitates effective recovery of hand function and improves the patients' ability to perform normal daily activities.[19]

The proposed date for completing the study is:March 12, 2021.

METHODS AND ANALYSIS

Design and registration of the review

This systematic review and meta-analysis protocol is registered with the international Prospective Register of Systematic Reviews PROSPERO: the registration number is CRD42020190868. The protocol is structured in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P).[20]

Inclusion criteria for study selection

Types of studies

Only randomised controlled trials (RCTs) that were published or registered before June 8, 2020 will be included. Quasi-RCTs, review articles, case reports, and other studies that do not meet the requirements will be excluded.

Types of patients

Patients' age will be between 18 and 75 years. In line with China's 2015 diagnostic criteria for classifying cerebrovascular diseases, the first stroke confirmed by CT or MRI with a course greater than one month and less than or equal to six months, with moderate to severe upper extremity and hand dysfunction meeting the criteria (Brunnstrom grade 2-4, the Fugl Meyer Motor Function score (FMA)< 20, improved Ashworth spasm scale (MAS) less than level 3) will be included, regardless of gender and nationality. Patient exclusion criteria will include: presence of other diseases resulting in serious cognitive or speech disorders; patients who could not understand and complete the therapist's instructions (Mini-mental state examination(MMSE) < 21 points); history of drug or alcohol dependence; serious liver or kidney disease; other diseases that may affect brain structure and function; and other mental disorders.

Interventions types

We will include studies where the intervention group received BCIT（Including one or more of VR, BCI, brain stimulation,and nerve feedback, among others),alone or in combination with routine rehabilitation treatment (manual therapy, exercise therapy, and electronic biofeedback, among others), while the control group received only conventional rehabilitation treatment.

Outcome measures

Primary outcome

The primary outcome measure will be the Fugl-Meyer Motor Function (FMA) score.

Secondary outcomes

Secondary outcomes will include the Modified Barthel Index (MBI), Modified Ashworth Score (MAS) and the upper extremity freehand muscle strength assessment (MMT).

In the subgroup analyses, times to improvement of motor function and the type of therapeutic intervention combined with BCIT will be analysed.

Article exclusion criteria

Studies with the following situations will be excluded: participants were diagnosed with secondary stroke; duplicated data or data that cannot be extracted;observational studies;retrospective studies;non-randomised trials;quasi-experimental studies; and animal studies. Additionally, studies with insufficient data or lacking effective sort will also not be included.

Search methods for the identifying of studies

English and Chinese search strategies will be conducted on eight databases: the China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, China Doctoral Dissertations Full-Text Database, and China Master's Theses Full-Text Database, Cochrane Central Register of Controlled Trials, PubMed, and Embase. In addition, we will conduct manual retrieval of papers,

conference papers, ongoing experiments, and internal reports, among others, to supplement electronic retrieval. We will select all eligible studies published on or before June 8, 2020.

Search strategy

The search strategy will be based on the Cochrane handbook guidelines (5.1.0) including keywords such as ‘post-stroke’, ‘motor disorders’, ‘brain computer interface’ or ‘neurofeedback’, and ‘RCT’. Subsequent searches will use MeSH headings, including ‘post-stroke’, ‘motor disorders’, and ‘brain computer interface’,, in addition to keywords from the initial retrieval. Additional article searches will review the reference lists of relevant research articles. As an example, the search strategy for PubMed is summarised in Table 1.

Table 1 Search strategy for PubMed.

Number	Search terms
1	brain computer interface.ti,mesh.
2	direct neural interface.ti,ab.
3	neurofeedback.ti,ab.
4	brain-machine interface.ti,ab.
5	or 1-4
6	post-stroke. ti,ab.
7	after stroke. ti,ab.
8	or 6-7
9	motor disorders. ti,mesh.
10	dyskinesias. ti,ab.
11	or 9-10
12	randomised controlled trial.pt.
13	Controlled clinical trial.pt.
14	randomised.ab.
15	Randomly.ab.

16	trial.ab.
17	or 12-16
18	exp animals/not humans.sh.
19	17 not 18
20	5 and 8and 10and 19

Data extraction

Study selection

Records from databases and other resources will be uploaded to a database created in EndNote, version 9.7. All extracted abstracts will be independently screened by the review authors (XLZ and JNL). We will obtain the full text of all potentially suitable articles to further assess eligibility based on the inclusion/exclusion criteria. Studies that do not meet the inclusion criteria will be excluded and the reason for exclusion will be recorded. Any disagreement will be resolved by consensus or discussion with a third author (MJL). The final selection procedure will follow the PRISMA guidelines[21], and is presented in Figure 1.

Data extraction and management

Two reviewers (XLZ and QZ) will independently apply the inclusion and exclusion criteria to assess each retrieved study's eligibility. The following data will then be extracted from the selected studies for inclusion using a data collection form, and recorded in an Excel file: first author and publication year, study design, sample, intervention, types of measures, risk of bias assessment, and findings. The results will be cross-checked by the two reviewers, and disagreements will be resolved by consensus, with any ongoing differences in opinion arbitrated by a third reviewer (DC). We may also contact the original authors to provide additional relevant information, if necessary.

The data extraction form will include the following items:

1) General information: title, authors, publication year, and study area, average patient age, average disease course, and treatment time.
2) Trial characteristics: design, follow-up duration, randomisation method, allocation concealment, incomplete outcome data, blinding (patients, people administering treatment, outcome assessors).
3) Intervention: primary intervention (BCIT type, routine rehabilitation treatment, application time, session duration); comparison interventions (routine rehabilitation treatment, application time. session duration).
4) Patients: total number and number in each group, baseline characteristics, diagnostic criteria, withdrawals, and losses to follow-up (reasons, description).
5) Outcomes: primary outcomes, adverse drug reactions, adverse time, follow-up

length, quality of outcomes reporting.

Risk of bias in assessment

Two reviewers (XLZ and DC) will independently apply the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions [22] to evaluate the risk of bias in each selected study. Six dimensions will be assessed: random sequence generation; allocation concealment; blinding method for patients, researchers, and outcome evaluators; incomplete results data; selective reporting; and other issues. The studies will be categorised into three quality levels: low risk of bias, high risk of bias, and unclear risk of bias.[20] Any discrepancies will be resolved through discussions with the third author. When a consensus cannot be reached by discussion, the third reviewer (MJL) will decide.

Treatment effect measures

Methods will vary by data type. For dichotomous variables, total effective rate and adverse events, we will analyse the rate ratio; for continuous variables, we will analyse mean differences. The 95% confidence interval will be presented for both dichotomous and continuous outcomes.

Missing data management

We will contact the original author to obtain the missing or incomplete data and will wait one month after an email is sent to receive a reply. If we are unable to obtain the missing data, the incomplete data will be excluded from the analysis

Heterogeneity assessment

Statistical heterogeneity will be assessed with the I-square (I^2) statistic.[23] An I^2 statistic of less than 50% indicates a low level of statistical heterogeneity; 50% or more will be considered substantial statistical heterogeneity. If substantial heterogeneity is identified, we will report it and explore possible causes using sensitivity analysis and subgroup analysis.

Reporting biases assessment

We will construct funnel plots to evaluate reporting bias if the included studies include more than ten trials. Otherwise, STATA15.1 software will be used to perform the Egger test.

Subgroup analysis

We plan to carry out the following subgroup analyses, if possible: study area differences, differences in routine rehabilitation methods, average course of disease differences, and length of treatment differences. We will use the formal test for subgroup interactions in Review Manager 5.3.

Sensitivity analysis

When possible, we will perform sensitivity analysis to explore the effects of the

trial's bias risk on primary outcomes. These analyses will exclude lower quality trials and repeat the meta-analyses to assess quality and robustness when significant statistical heterogeneity arises, according to sample size and insufficient data.

Grading the quality of evidence

The online version of the Grading of Recommendations Assessment, Development, and Evaluation methodology (GRADE; https://www.gradeworkinggroup.org/) [24] will be used to assess the quality of the evidence and risk of bias, categorised into four levels: high, moderate, low, or very low.

Ethics and dissemination

This systemic review will evaluate the efficacy and safety of BCIT combined with routine rehabilitation for treatment of PSMD. Since all included data will be obtained from published articles,it does not require ethical approval,and will be published in a peer-reviewed journal.Due to the lack of relevant systematic reviews in this field, this study will combine relevant RCTs to better explore evidence on BCIT combined with routine rehabilitation for treatment of PSMD and guide clinical practice and BCIT researches.

Patient and public involvement

This article is based on previously conducted studies and does not involve any patient and public involvement or new studies of human subjects performed by any of the authors.

DISCUSSION

With the aging of the world population and the influence of living habits and environmental changes, stroke has become a major global health issue.[25] Motor dysfunction of the upper limbs and hands following stroke is especially important in clinical settings because of its long treatment cycle and poor prognosis.[26] Currently, most conventional upper limb and hand function rehabilitation techniques following stroke focus on peripheral treatment, such as facilitation techniques, functional electrical stimulation, etc., but these methods often result in low treatment effectiveness, so they are insufficient.[27,28]

Recent developments in rehabilitation medicine and artificial intelligence technology have focused on more direct brain-based interventions.[29] BCIT employs control signals generated by EEG activities, allowing patients to interact with the surrounding environment without the influence of peripheral nerves and muscles. This can effectively overcome the limitations of traditional rehabilitation methods, increase patients' interest in treatment, and benefit upper limb and hand function rehabilitation. BCIT applied in the rehabilitation of motor disorders after stroke is safer, requires less time and work for clinicians, and allows patients to actively participate in rehabilitation training that promotes remodelling of the central nervous

system.[30] BCIT is a promising treatment for recovering hand function following stroke, which will facilitate patients' ability to perform activities of daily life [31].

However, the specific BCIT mechanisms that facilitate rehabilitation of post-stroke limb disorders needs further research, because it is not clear whether the source of motor recovery derives from conventional therapy, motor imagery by itself, neurofeedback from BCI, or a combination of these mechanisms. This systematic review and meta-analysis will provide patients, clinicians, and healthcare policy makers with a deeper understanding of BCIT’ s efficacy and safety in the treatment of PSMD.The PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist of this protocol is presented in PRISMA-P checklis.

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Contributors XLZ(Xiaolin Zhang) conceived the study and provided general guidance to the drafting of the protocol. XLZ and DC(Di Cao) drafted the protocol. QZ designed the search strategy. XLZ, DC, JNL(Junnan Liu), QZ and CZ drafted the manuscript. MJL(Mingjun Liu) and XLZ reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.
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Competing interests We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests..
Patient consent for publication Not required.
Provenance and peer review Not commissioned; externally peer reviewed.

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Fig.1 PRISMA flow diagram of study and exclusion

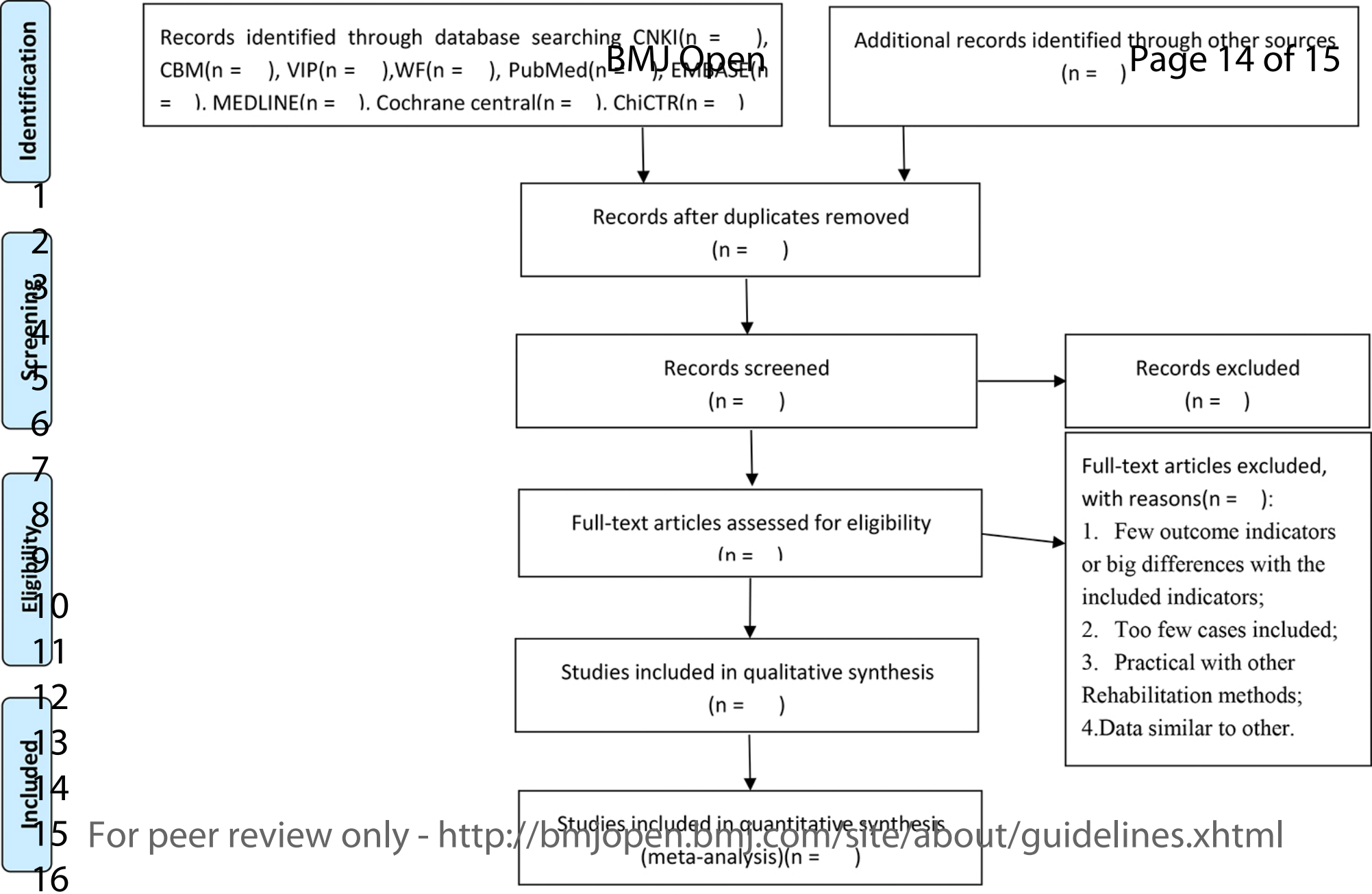

Fig.1 PRISMA flow diagram of study and exclusion

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	3-4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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