INPLASY PROTOCOL

To cite: Li et al. Comparative Efficacy of 5 non-pharmaceutical Therapies For Adults With Post-stroke Cognitive Impairment: Protocol For A Bayesian Network Analysis Based on 55 Randomized Controlled Trials. Inplasy protocol 202260036. doi: 10.37766/inplasy2022.6.0036

Received: 08 June 2022

Published: 08 June 2022

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Support: **None.**

Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
None declared.

Comparative Efficacy of 5 non-pharmaceutical Therapies For Adults With Post-stroke Cognitive Impairment: Protocol For A Bayesian Network Analysis Based on 55 Randomized Controlled Trials

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Review question / Objective: **This study will provide evidence-based references for the efficacy of 5 different non-pharmaceutical therapies in the treatment of post-stroke cognitive impairment(PSCI). 1. Types of studies. Only randomized controlled trials (RCTs) of Transcranial Magnetic Stimulation(TMS), Transcranial Direct Current Stimulation(tDCS), Acupuncture, Virtual Reality Exposure Therapy(VR) and Computer-assisted cognitive rehabilitation(CA) for PSCI will be recruited. Additionally, Studies should be available in full papers as well as peer reviewed and the original data should be clear and adequate. 2. Types of participants. All adults with a recent or previous history of ischaemic or hemorrhagic stroke and diagnosed according to clearly defined or internationally recognized diagnostic criteria, regardless of nationality, race, sex, age, or educational background. 3.Types of interventions and controls. The control group takes non-acupuncture treatment, including conventional rehabilitation or in combination with symptomatic support therapy. The experimental group should be treated with acupuncture on basis of the control group. 4.The interventions of the experimental groups were Transcranial Magnetic Stimulation(TMS), Transcranial Direct Current Stimulation(tDCS), Acupuncture, Virtual Reality Exposure Therapy(VR) or Computer-assisted cognitive rehabilitation(CA), and the interventions of the control group takes routine rehabilitation and cognition training or other therapies mentioned above that were different from the intervention group. 5.Types of outcomes. The primary outcomes are measured with The Mini-Mental State Examination (MMSE) and/or The Montreal Cognitive Assessment Scale (MoCA), which have been widely used to evaluate the cognitive abilities. The secondary outcome indicator was the Barthel Index (BI) to assess independence in activities of daily living (ADLs).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 June 2022 and was last updated on 08 June 2022 (registration number INPLASY202260036).

INTRODUCTION

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Current Stimulation(tDCS), Acupuncture, Virtual Reality Exposure Therapy(VR) and Computer-assisted cognitive rehabilitation(CA) for PSCI will be recruited. Additionally, Studies should be available in full papers as well as peer reviewed and the original data should be clear and adequate. 2. Types of participants. All adults with a recent or previous history of ischaemic or hemorrhagic stroke and diagnosed according to clearly defined or internationally recognized diagnostic criteria, regardless of nationality, race, sex, age, or educational background. 3.Types of interventions and controls. The control group takes non-acupuncture treatment, including conventional rehabilitation or in combination with symptomatic support therapy. The experimental group should be treated with acupuncture on basis of the control group. 4.The interventions of the experimental groups were Transcranial Magnetic Stimulation(TMS), Transcranial Direct Current Stimulation(tDCS), Acupuncture, Virtual Reality Exposure Therapy(VR) or Computer-assisted cognitive rehabilitation(CA), and the interventions of the control group takes routine rehabilitation and cognition training or other therapies mentioned above that were different from the intervention group. 5.Types of outcomes. The primary outcomes are measured with The Mini-Mental State Examination (MMSE) and/or The Montreal Cognitive Assessment Scale (MoCA), which have been widely used to evaluate the cognitive abilities. The secondary outcome indicator was the Barthel Index (BI) to assess independence in activities of daily living (ADLs).

Rationale: Network meta-analysis extends pairwise meta-analyses to enable the pooling of data from many clinical trials, comparing at least two treatments. Inferences regarding the relative efficacy of each treatment are thus reinforced by the inclusion of both direct and indirect information. A network meta-analysis based on Bayes' theorem of existing datasets provides a framework for comprehensive evaluation of different acupuncture interventions' time-point efficacy and safety.

Condition being studied: Among all stroke sequelae, post-stroke cognitive impairment (PSCI) is common, affecting 17.6% to 83% of stroke survivors, which not only lead to disability, dependence, and low quality of life but also associated closely with the high risk of recurrent ischemic stroke and the reduction in five-year survival. As the tremendous burden of stroke continues to rise, PSCI has become a mounting public healthcare challenge that needs to be addressed urgently. At present, the treatments for PSCI mainly include oral drug interventions, physical therapy, cognitive training, and so on. Compared with oral drug therapy for PSCI, non-pharmaceutical interventions were more effective with fewer side effects. Transcranial Magnetic Stimulation(TMS), Transcranial Direct Current Stimulation(tDCS), Acupuncture, Virtual Reality Exposure Therapy(VR) and Computer-assisted cognitive rehabilitation(CA) are widely used non-pharmaceutical interventions in the clinical treatment of PSCI and has shown good efficacy. However, differences of these therapies in the form, duration, and applicable population are existing. It is unclear which therapy is more efficacy for PSCI patients. Therefore, this study aims to compare and rank the 5 non-pharmaceutical therapies using a variety of different outcomes through a network meta-analysis, and to analyze their impacts on activities of daily living, so as to obtain the optimal treatment plan for PSCI patients and provide a basis for clinical treatments decision-making.

METHODS

Search strategy: Electronic databases including Web of Science, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wangfang database, China Science and Technology Journal Database(VIP), and Chinese Biomedical Medicine (CBM). Search strategy based on MeSH terms combining with free text words was applied in English databases, while counterpart terms in Chinese were used in Chinese

databases. A sample search of Pubmed is as follows: #1:("Stroke"[Mesh]) OR ("Brain Ischemia"[Mesh]) OR ("Cerebral Hemorrhage"[Mesh]) OR (Stroke*[Title/Abstract]) OR (Cerebrovascular Accident*[Title/Abstract]) OR (Brain Vascular Accident*[Title/Abstract]) OR (Apoplexy[Title/Abstract]) OR (Brain Infarct*[Title/Abstract]) OR (Cerebral Infarct*[Title/Abstract]) OR (Brain Stem Infarct*[Title/Abstract]) OR (Subcortical Infarction*[Title/Abstract]) OR (Brain Venous Infarction*[Title/Abstract]) OR (Cerebral Artery Stroke[Title/Abstract]) OR (Cerebral Artery Infarction[Title/Abstract]) OR (Cerebral Circulation Infarction[Title/Abstract]) OR (Circulation Brain Infarction[Title/Abstract]) OR (Choroidal Artery Infarction[Title/Abstract]) OR (CVA[Title/Abstract]) OR (CVAs[Title/Abstract]) OR (Brain Ischemia*[Title/Abstract]) OR (Ischemic Encephalopath*[Title/Abstract]) OR (Cerebral Ischemia*[Title/Abstract]) OR (Brain Hypoxia Ischemia*[Title/Abstract]) OR (Cerebral Anoxia Ischemia*[Title/Abstract]) OR (Cerebral Hemorrhage*[Title/Abstract]) OR (Cerebral Brain Hemorrhage*[Title/Abstract]) OR (Cerebral Parenchymal Hemorrhage*[Title/Abstract]) OR (Cerebrum Hemorrhage*[Title/Abstract]) OR (Intracerebral Hemorrhage*[Title/Abstract]) OR (Basal Ganglia Hemorrhage[Title/Abstract]) OR (Subarachnoid Hemorrhage*[Title/Abstract]) OR (Cerebral Hypertensive Hemorrhage*[Title/Abstract]) #2: (Cognition Disorders[MeSH Terms]) OR (Dementia, Vascular[MeSH Terms]) OR (Cognition Disorder*[Title/Abstract]) OR (Vascular Dementia*[Title/Abstract]) OR (Cognitive Dysfunction*[Title/Abstract]) OR (Cognitive Impairment*[Title/Abstract]) OR (Mild Neurocognitive Disorder*[Title/Abstract]) OR (Cognitive Decline*[Title/Abstract]) OR (Mental Deterioration*[Title/Abstract]) OR (cognitive defect[Title/Abstract]) OR (Multi-Infarct Dementia*[Title/Abstract]) OR (Lacunar Dementia*[Title/Abstract]) OR (Arteriosclerotic Dementia*[Title/Abstract]) OR (Chronic Progressive Subcortical Encephalopathy[Title/Abstract]) OR (Subcortical Leukoencephalopathies[Title/Abstract]) OR (cognitive disorder* after stroke[Title/Abstract]) OR (cognitive impairment* after stroke[Title/Abstract]) OR (cognitive Dysfunction* after stroke[Title/Abstract]) OR (Cognitive Decline* after stroke[Title/Abstract]). #3: (Transcranial Magnetic Stimulation[MeSH Terms]) OR (Transcranial Direct Current Stimulation[MeSH Terms]) OR (Acupuncture[MeSH Terms]) OR (Acupuncture Therapy[MeSH Terms]) OR (Electroacupuncture[MeSH Terms]) OR (Virtual Reality[MeSH Terms]) OR (Virtual Reality Exposure Therapy[MeSH Terms]) OR (Transcranial Magnetic Stimulation*[Title/Abstract]) OR (TMS[Title/Abstract]) OR (tDCS[Title/Abstract]) OR (Transcranial Direct Current Stimulation*[Title/Abstract]) OR (Cathodal Stimulation tDCS*[Title/Abstract]) OR (Transcranial Random Noise Stimulation[Title/Abstract]) OR (Transcranial Alternating Current Stimulation[Title/Abstract]) OR (Transcranial Electrical Stimulation*[Title/Abstract]) OR (Anodal Stimulation tDCS*[Title/Abstract]) OR (Pharmacopuncture[Title/Abstract]) OR (Acupuncture[Title/Abstract]) OR (Acupuncture Therapy[Title/Abstract]) OR (Acupuncture Treatment*[Title/Abstract]) OR (Pharmacoacupuncture Treatment[Title/Abstract]) OR (Pharmacoacupuncture Therapy[Title/Abstract]) OR (Acupotomy[Title/Abstract]) OR (Acupotomies[Title/Abstract]) OR (Electroacupuncture[Title/Abstract]) OR (Virtual Reality[Title/Abstract]) OR (VR[Title/Abstract]) OR (Virtual Reality Exposure Therapy[Title/Abstract]) OR (Virtual Reality Immersion Therapy[Title/Abstract]) OR (Virtual Reality Therapy[Title/Abstract]) OR (Virtual Reality Therapies[Title/Abstract]) OR (computer-assisted cognitive rehabilitation[Title/Abstract]) OR (((cognitive[Title/Abstract]) OR (cognition[Title/Abstract])) AND (computer*[Title/Abstract])). #4: Randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR placebo[Title/Abstract]. #5: #1 AND #2 AND #3 AND #4.

Participant or population: Patients with cognitive impairment after stroke.

Intervention: Transcranial Magnetic Stimulation(TMS), Transcranial Direct Current Stimulation(tDCS), Acupuncture, Virtual Reality Exposure Therapy(VR) and Computer-assisted cognitive rehabilitation(CA).

Comparator: Conventional rehabilitation and cognition training.

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: 1.Types of studies. Only randomized controlled trials (RCTs) will be recruited and regardless of population characteristics, blind method, and duration of trials. However, the language is limited to English or Chinese. We will remove Non-RCTs such as meeting abstracts, clinical experience, case reports, system reviews, animal trails, duplications meeting abstracts. Additionally, Studies should be available in full papers as well as peer-reviewed and the original data should be clear and adequate.2.Types of participants. All adults with a recent or previous history of ischaemic or hemorrhagic stroke and diagnosed according to clearly defined or internationally recognized diagnostic criteria(e.g. confirmed by CT or MRI scan), regardless of nationality, race, sex, age, or educational background. However, the patients who are not medically stable or unable to follow basic commands will be excluded.3.Types of interventions and controls. The interventions of the experimental group were non-pharmaceutical therapies including Transcranial Magnetic Stimulation(TMS), Transcranial Direct Current Stimulation(tDCS), Acupuncture, Virtual Reality Exposure Therapy(VR) or Computer-assisted cognitive rehabilitation(CA). The interventions of the control group were conventional rehabilitation and cognition training or other therapies mentioned above that were different from the intervention group. However studies in which the intervention or control modality was unclear or combined with medications that could improve cognitive dysfunction or combined two or more non-pharmacological interventions mentioned above were excluded.4.Types of outcomes. The primary outcomes were the Mini-Mental State Examination (MMSE) and/or the Montreal Cognitive Assessment Scale (MoCA), which have been widely used to evaluate the cognitive abilities. The Barthel Index (BI) was used as a secondary outcome indicator to assess independence in activities of daily living (ADLs).

Information sources: An all-round online search for published related studies will be conducted in the following academic databases from their inception throughout Dec 2021: Web of Science, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wangfang database, China Science and Technology Journal Database(VIP), and Chinese Biomedical Medicine (CBM). Search strategy based on MeSH terms combining with free text words was applied in English databases, while counterpart terms in Chinese were used in Chinese databases. In addition, relevant references will also be checked carefully under the guidelines of the snowball strategy.

Main outcome(s): The primary outcome indicator was the assessment of cognitive function, and the RCTs included at least either the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment(MoCA).

Additional outcome(s): The Barthel Index (BI) was used as a secondary outcome indicator to assess independence in activities of daily living (ADLs).

Data management: 1.Data collection and export. Two independent reviewers will search and screen the literature according to inclusion and exclusion criteria respectively. Firstly, duplicates will be removed by endnote software, then suitable literature, including potential references, will be identified by reading the title and abstract, and finally eligible literature will be assessed by reading the text content. Any objections will be discussed and resolved by experienced reviewers. 2.Data extraction and analysis.

Two reviewers will independently extract data. The following data will be extracted: (1)General characteristics: first author, the year of publication, and nationality. (2)The characteristic of participants: sample size, average age, sex, the progression of disease. (3)The characteristics of intervention: intervention type, control interventions, the time of each intervention, total treatment duration, follow-up time. (4)Outcomes: primary outcomes and secondary outcomes, adverse events. If necessary, the authors will be contacted for more information to supplement the missing data.

Quality assessment / Risk of bias analysis: The assessment of the risk bias will be conducted According to the Cochrane Collaboration's tool provided by Cochrane Handbook for Systematic Reviews. The assessment will be conducted by two independent authors, with any disagreements to be settled by an experienced reviewer.

Strategy of data synthesis: The pairwise meta-analyses of direct evidence will be performed using review manager 5.4. Mean Difference (MD) and 95% Confidence Intervals (CIs) will be calculated for continuous data. The statistical heterogeneity across different trials will also be assessed using the I2 statistics. In case that the p value is ≥0.1 and I2 ≤50%, MD will be combined with fixed effects model (FEM). In case that the p value is<0.1 and I2＞50%, the random effects model(REM) will be applied. The Markov Chain Monte Carlo (MCMC) in OpenBUGS3.2.3 will be employed to perform network meta-analysis on PSCI patients under a Bayesian framework. To assess the consistency of the NMA, the node-split method will be used to locate the inconsistency between direct and indirect effects of treatment. In addition, the surface under the cumulative ranking curve(SUCRA) will be estimated for the effectiveness of each intervention, and then funnel plots will be drawn to analyze publication bias. SUCRA has a value of 0 to 1. The closer it is to 1, the more effective the intervention is considered.

Subgroup analysis: If necessary, age, the types of stroke, and the treatment of duration will be carried out as subgroup analysis to assess the heterogeneity of the study.

Sensitivity analysis: In addition, sensitivity analysis will be conducted to exclude those studies of lower quality and to determine the robustness and consistence of the combined results.

Language: The language is limited to English or Chinese.

Country(ies) involved: China.

Keywords: Network Analysis; PSCI; Non-pharmacological Therapies; Protocol.

Dissemination plans: The result of this study will be submitted to a peer-reviewed journal for publication.

Contributions of each author:

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