Cerebral function imaging of acupuncture treatment for stroke: A protocol for systematic review and meta-analysis

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Abstract

Background: Stroke is one of the most common causes of death and is the main cause of persistent and acquired disability in adults worldwide. Acupuncture is recommended as an alternative and complementary strategy for stroke treatment by the World Health Organization as it can significantly improve patients' quality of life. However, the central nervous system (CNS) mechanism of acupuncture treatment of stroke is unclear. The aim of this study is explore the effective pathway and action mechanism of acupuncture treatment for stroke on the CNS.

Methods: The following databases will be searched by electronic methods: PubMed; Medline; Embase; Cochrane Library; Chinese National Knowledge Infrastructure; VIP Database; Wan-fang Data; Chinese Biomedical Database. All of them will be retrieved from the establishment date of the electronic database to December 2020, all included studies will be evaluated risk of bias by the Cochrane Handbook. Spatial coordinates of the Montreal Neurological Institute of activated brain regions will be the primary outcome. The systematic review will be conducted with the use of SDM v5.141 software for voxel meta-analysis in this study.

Results: This study will obtain the correlation between the activated brain regions of acupuncture treatment for stroke.

Conclusion: This study will explore the effective pathway and action mechanism of acupuncture, and provide a reliable scientific basis for the treatment of stroke by acupuncture.

PROSPERO registration number: CRD42021231329.

1. Introduction

Stroke is defined as an acute focal injury of the central nervous system (CNS) arising from a vascular cause such as cerebral infarction, or intracerebral hemorrhage, or subarachnoid hemorrhage[1]. It is one of the most common causes of death and is the main cause of persistent and acquired disability in adults worldwide. The World Health Organization (WHO) refers to stroke as the incoming epidemic of the 21st century, and it is expected to increasingly affect younger patients. In Europe, stroke cause over 1 million deaths, and worldwide, stroke cause 6.5 million deaths[2]. According to a report published in The Lancet, stroke has become the leading cause of death in China since 2017, and stroke burden in China has increased over the past 30 years, especially remains particularly high in rural areas[3, 4]. However, it has been estimated that over 90% of the burden of stroke is attributable to modifiable factors[5]. Among these, interventions targeting modifiable factors have shown their significant impact in reducing the incidence and mortality of stroke[6].

Acupuncture is one of the oldest and most studied techniques in Chinese medicine, the mode of operation is insertion of a fine needle into the skin or deeper tissues at acupoints of the body, which is recommended as an alternative and complementary strategy for stroke treatment by the WHO[7, 8]. This

needling involving manipulated manually, electrically, or by heat. In the CNS, endogenous opioids are the principal biological mediators of the therapeutic actions of this ancient technique[7]. Clinical trials have shown that acupuncture can enhance balance[9], reduce spasticity[10], and increase muscle strength[11]. A systematic review and meta-analysis of randomized trials conducted in 2010 has indicated that acupuncture may be effective in improving post-stroke impairment, as measured by its motor rehabilitation, increased perfusion within peri-infarcts, and the stimulation of neuronal reorganization, amongst other findings[12]. However, the poor study quality and publication bias hinder the strength of this recommendation.

Functional magnetic resonance image (fMRI) is nonpolluting, noninvasive, and has high temporal and spatial resolution, neuronal activity was measured by monitoring the hemodynamic response. It can objectively and visually evaluate different cerebral functional areas activated by acupuncture under physiological and pathological conditions[13]. It has become a reliable technique to reveal the CNS mechanism of acupuncture because of high repeatability and reliability[13, 14].

In recent years, researchers have study the CNS mechanism of acupuncture in the treatment of stroke by fMRI, and show that acupuncture can activate several relevant regions in the brain. However, the activation regions found in various studies are not completely consistent, and the exact mechanisms underlying the beneficial effects of acupuncture in the treatment of stroke remain unclear. At present, there is no systematic review to conduct statistical analysis on the studies in this area. Therefore, the aim of this study is collected clinical research with cerebral function image as primary outcome, comparison the influence of acupuncture treatment for stroke on the CNS, in order to understand the role of acupuncture in the central level, and explore the effective pathway and action mechanism of acupuncture treatment for stroke.

2. Methods

2.1 Study registration

This protocol has been registered on the International Prospective Register of Systematic Reviews in PROSPERO (registration number is CRD42021231329), and was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis protocol (PRISMA-P)[15].

2.2 Inclusion criteria

2.2.1 Study type. All Clinical randomized controlled trials (RCTs), semi-randomized controlled trials, observational studies will be included, without restrictions on country but language will be limited on English and Chinese.

2.2.2 Participants. This study will include participants with stroke. Regardless of gender, age, occupation, education, etiology, and severity, etc.

2.2.3 Type of intervention. Studies using acupuncture in experimental groups will be included,acupuncture may be manipulated manually, electrically or by heat.

2.2.4 Type of outcome measures.

2.2.4.1 Primary outcome. Spatial coordinates of the Montreal Neurological Institute (MNI)[16] of activated brain regions will be the primary outcome.

2.2.4.2 Secondary outcome. Secondary outcomes mainly include the following aspects: effective rate, associated symptoms, quality of life, adverse events incidence.

2.3 Exclusion criteria

- The exclusion criteria contain the following items:
- ·Participants with the unclear diagnosis;
- ·The intervention combined with any complementary therapy such as Chinese herb;
- ·reviews, animal experiments, theory discussion, case reports, conference articles, and other non-RCTs study;
- ·Incomplete data or information;
- ·Repeatedly checked or published literature.

2.4 Search strategy

We plan to search the following databases: PubMed; Medline; Embase; Cochrane Library; Chinese National Knowledge Infrastructure (CNKI); VIP Database; Wan-fang Data; Chinese Biomedical Database (CBM). All of them will be retrieved from the establishment date of the electronic database to December 2020. The retrieval mode used will be a combination of medical subject words and free words, including “strokes”, “apoplexy”, “cerebral infarction”, “cerebral stroke”, “cerebrovascular accident”, “brain vascular accident”, “acupuncture”, “needle”, “electroacupuncture”, “scalp acupuncture”, “manual acupuncture”, “warm needle”, “temperature needle”, “magnetic resonance imaging”, “magnetic resonance image”, “NMR imaging”, “zeugmatography”, “MRI scans”, “functional MRI”, “fMRI”, “spin echo imaging”, “randomized controlled trial”, “random allocation”, “semi-randomized controlled trials”, “allocation, random”, “RCT randomized controlled”, “randomized, controlled”, “clinical trial”. The search strategy takes PubMed as an example, and shown in Table 1.

Table 1
The search strategy for PubMed.

Order	strategy
#1	Search: “Stroke”[Mesh] Sort by: Publication Date
#2	Search: ((((apoplexy[Title/Abstract]) OR (cerebral infarction[Title/Abstract])) OR (cerebral stroke[Title/Abstract])) OR (cerebrovascular accident[Title/Abstract])) OR (brain vascular accident[Title/Abstract]) Sort by: Publication Date
#3	#1 OR #2
#4	Search: “Acupuncture”[Mesh] Sort by: Publication Date
#5	Search: ((((((acupuncture[Title/Abstract]) OR (needle[Title/Abstract])) OR (electroacupuncture[Title/Abstract])) OR (scalp acupuncture[Title/Abstract])) OR (manual acupuncture[Title/Abstract])) OR (warm needle[Title/Abstract])) OR (temperature needle[Title/Abstract]) Sort by: Publication Date
#6	#4 OR #5
#7	Search: “magnetic resonance imaging”[MeSH] Sort by: Publication Date
#8	Search: ((((((magnetic resonance image) OR (NMR imaging)) OR (zeugmatography)) OR (MRI scans)) OR (functional MRI)) OR (fMRI)) OR (spin echo imaging) Sort by: Publication Date
#9	#7 OR #8
#10	Search: ((((((randomized controlled trial[Publication Type]) OR (semi-randomized controlled trials[Publication Type])) OR (RCT randomized controlled[Publication Type])) OR (random allocation[Title/Abstract])) OR (allocation, random[Title/Abstract])) OR (randomized, controlled[Title/Abstract])) OR (clinical trial[Title/Abstract]) Sort by: Publication Date
#11	Search (humans[MeSH Terms]) NOT animals[MeSH Terms] Sort by: Publication Date
#12	#10 AND #11
#13	#3 AND #6 AND #9 AND #12

2.5 Data collection

2.5.1 Study selection

We plan to conduct a systematic review between March 30, 2021 and December 30, 2022. The selection of study, which includes literature screening, data extraction, management and examination, will be conducted by 2 reviewers. They will independently screen the titles, abstracts, and keywords of all retrieved studies and determine which trials meet the inclusion criteria, full texts of all possible relevant studies will be obtained for further evaluation. Any disagreements will be resolved by discussion between the 2 reviewers and the third author. The details of the selection process are shown in Fig. 1.

2.5.2 Data extraction and management

The two data managers independently extracted the relevant data included in the study according to a unified data extraction table. The data extraction table mainly includes: (1) the basic information of the study (name of the researcher, type of study, year of publication, country, language, publication status); (2) study characteristics (sample size, source of cases, age, course of disease, diagnostic criteria, inclusion and exclusion criteria); (3) intervention and control measures (acupoints, manipulation); (4) research methodology (generation of random scheme, allocation concealment, blind method, baseline comparability, loss of follow-up, intentionality analysis); (5) measurement data of outcome indicators. Any divergences will be discussed and resolved between the data managers, and further differences will be arbitrated by the third manager.

2.5.3 Assessment of risk of bias in included studies

All included studies will be evaluated risk of bias by the Cochrane Handbook, the judgment of risks will be evaluated and described from the following 6 items, including generation of random sequences, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. Risk will be divided into 3 levels: “low risk of bias”, “high risk of bias” and “unclear risk of bias”.

2.5.4 Dealing with missing data

If trial data is insufficient or missing, the corresponding author will be contacted by telephone or email. If missing data is not be available or the author cannot be contacted, these studies will be excluded. We will conduct a limited analysis based on available data and discuss the potential impact of missing data.

2.6 Statistical analysis

The systematic review will be conducted with the use of SDM v5.141 (Seed-based D Mapping)[17, 18] software for voxel meta-analysis in this study. Data analysis shall be carried out in MNI spatial coordinates. If the research results are not reported in MNI spatial coordinates, Lancaster conversion method shall be used to convert them into MNI space coordinates. The statistical analysis threshold of this voxel meta-analysis was $P < 0.005$, $Z > 1$, clustering degree ≥ 10; this corresponds to a corrected $P < 0.05$.

2.6.1 Heterogeneity assessment

We will use I^2 to evaluate statistical heterogeneity between trials. If the $I^2 < 50\%$, there was little or no heterogeneity in the evidence for the combined outcome, while heterogeneity was evaluated as significant ($I^2 \geq 50\%$) and the trials included were sufficient, we will conduct a subgroup analysis to explore the potential source of the heterogeneity.

2.6.2 Subgroup analysis

If there are a large number of subgroup studies, a subgroup analysis is performed to determine heterogeneity. It may be includes the method of intervention, the choice of acupoints, the improvement of concomitant symptoms, the duration and severity of the disease, etc.

2.6.3 Sensitivity analysis

We will conduct a sensitivity analysis to verify the robustness of the preliminary results by a revaluation of risk of bias, methodological quality, missing data or other possible factors. If there is a large difference, sensitivity analysis will be employed careful interpretation.

2.6.4 Publication bias

If more than 10 studies are included in the meta-analysis, we will evaluate the publication bias by EGGER regression test, and the evaluation will be presented in the form of funnel plots.

2.7 Grading the quality of evidence

We will evaluate the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[19]. It is divided into four grades: high, moderate, low, very low.

2.8 Ethics and dissemination

Ethical approval is not necessary because our study is not linked to individual patient data. The study findings will be published in a peer reviewed journal or conference presentations to explore the effective pathway and action mechanism of acupuncture treatment for stroke on the CNS.

3. Discussion

Stroke is a major chronic non-infectious disease that seriously endangers health. It has five characteristics: high morbidity, high disability rate, high mortality rate, high recurrence rate and high economic burden[20]. With the acceleration of social aging and urbanization, the popularity of unhealthy lifestyles of residents, and risk factors of cerebrovascular diseases are extensive exposure, the stroke burden has an explosive growth trend characterizing by rapid growth of low-income groups, obvious gender and regional differences, and younger trend[21]. At present, the standardized incidence of the first stroke among residents with 40 to 74 years old in China has increased by an annual rate of 8.3%[20]. Acupuncture, as an alternative and complementary strategy for stroke treatment recommended by the WHO[8], has been promoted and applied as it can significantly improve the life quality of patients. This could not only provide effective alternative therapies for patients, but also reduce the burden on public health.

A basic study indicated that the mechanism of acupuncture in the treatment of ischemic cerebrovascular diseases may be related to neurovascular units including blood-brain barrier, astrocytes, microglia cells, neurons[22]. Another clinical study showed that acupuncture can promote the remodeling of white matter function after stroke and thus improve motor dysfunction[23]. Despite this, there is still a lack of high-quality research evidence on acupuncture treatment of stroke, and the CNS mechanism of acupuncture treatment of stroke is not clear. Therefore, this study conducted a systematic review and meta-analysis of cerebral functional imaging in acupuncture treatment for stroke based on the existing literature, and will obtain the correlation between the activated brain regions of acupuncture, so as to explore the effective

pathway and action mechanism of acupuncture, and provide a reliable scientific basis for the treatment of stroke by acupuncture.

Abbreviations

CNS=central nervous system; WHO=World Health Organization; fMRI=functional magnetic resonance image; PRISMA-P=Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; RCTs=randomized controlled trials; MNI=Montreal Neurological Institute; CNKI=Chinese National Knowledge Infrastructure; CBM=Chinese Biomedical Database; GRADE=Grading of Recommendations Assessment, Development and Evaluation.

Declarations

Ethics approval and consent to participate: Ethical approval is not necessary because our study is not linked to individual patient data.

Disclaimer: The funders' and authors' institutions are not responsible for its content.

Competing interests: The authors declare no conflicts of interest.

Consent for publication: All authors have read and approved the publication of the protocol.

Data availability statement: No additional data are available.

Declaration of Competing Interest: The authors declare no conflicts of interest.

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Contributors: Yihao Zhou and Jing Shi contributed equally to this work and should be considered as co-first authors. Jing Shi provided study conception and funding support. Yihao Zhou assisted with the design, drafting the protocol and registered the protocol in the PROSPERO database. Gan Huang developed the search strategy, with input from Zhilin Huang, Chunhong Luo, Anhong Dai and Xuelian Zhang. Sifeng Feng, Guangzhi Yang, Xiaoqing Zhao and Min Wang critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

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References

1. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.
2. Rochemont DR, Mimeau E, Misslin-Tritsch C, et al. The epidemiology and management of stroke in French Guiana. BMC Neurol. 2020;20(1):109.
3. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019;394(10204):1145-1158.
4. Wang W, Jiang B, Sun H, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480687 Adults. Circulation. 2017;135(8):759-771.
5. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016;15(9):913-924.
6. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-254.
7. Chavez LM, Huang SS, MacDonald I, et al. Mechanisms of Acupuncture Therapy in Ischemic Stroke Rehabilitation: A Literature Review of Basic Studies. Int J Mol Sci. 2017;18(11):2270.
8. Li X, Wang Q. Acupuncture therapy for stroke patients. Int Rev Neurobiol. 2013;111:159-179.
9. Liu SY, Hsieh CL, Wei TS, et al. Acupuncture stimulation improves balance function in stroke patients: a single-blinded controlled, randomized study. Am J Chin Med. 2009;37(3):483-494.
10. Zhao JG, Cao CH, Liu CZ, et al. Effect of acupuncture treatment on spastic states of stroke patients. J Neurol Sci. 2009;276(1-2):143-147.
11. Yan T, Hui-Chan CW. Transcutaneous electrical stimulation on acupuncture points improves muscle function in subjects after acute stroke: a randomized controlled trial. J Rehabil Med. 2009;41(5):312-316.
12. Wu P, Mills E, Moher D, et al. Acupuncture in poststroke rehabilitation: a systematic review and meta-analysis of randomized trials. Stroke. 2010;41(4):e171-e179.
13. Liu can, Zhou Zhigen, He Xiaoting, et al. Progress in the central mechanism of acupuncture with fMRI. Lishizhen Med Mater Med Res. 2017,28(03):686-688.
14. Bian Wenjin, Zhen Junping, Jin Bo, et al. A preliminary study on the central analgesic mechanism of acupuncturing the stomach meridian foot-Yangming by fMRI. Chin J Magn Reson Imaging. 2020,11(11):979-984.
15. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
16. Evans AC, Collins DL, Mills SR, et al. 3D statistical neuroanatomical models from 305 MRI volumes. Nuclear Science Symposium and Medical Imaging Conference. 1993;1813-1817

17. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br J Psychiatry. 2009;195(5):393-402.
18. Tahmasian M, Eickhoff SB, Giehl K, et al. Resting-state functional reorganization in Parkinson's disease: An activation likelihood estimation meta-analysis. Cortex. 2017;92:119-138.
19. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-406.
20. Report on stroke prevention and treatment in China writing group. Brief report on stroke prevention and treatment in China, 2019. Chin J Cerebrovasc Dis. 2020;17(05):272-281.
21. Wang Yongjun, Li Zixiao, Gu Hongqiu, et al. Chinese Stroke Report 2019. Chin J Stroke. 2020;15(10):1037-1043.
22. Li Guangda, Han Yongsheng. Research advances in neurovascular unit mechanism in acupuncture treatment of ischemic stroke. Acupuncture Research. 2019;44(12):863-866.
23. Fang Jiliang, Rong Peijing, Liu Bo. Modern fMRI exploring the neuromechanism of traditional acupuncture. Chin J Magn Reson Imaging. 2020;11(02):81-83.

Figures

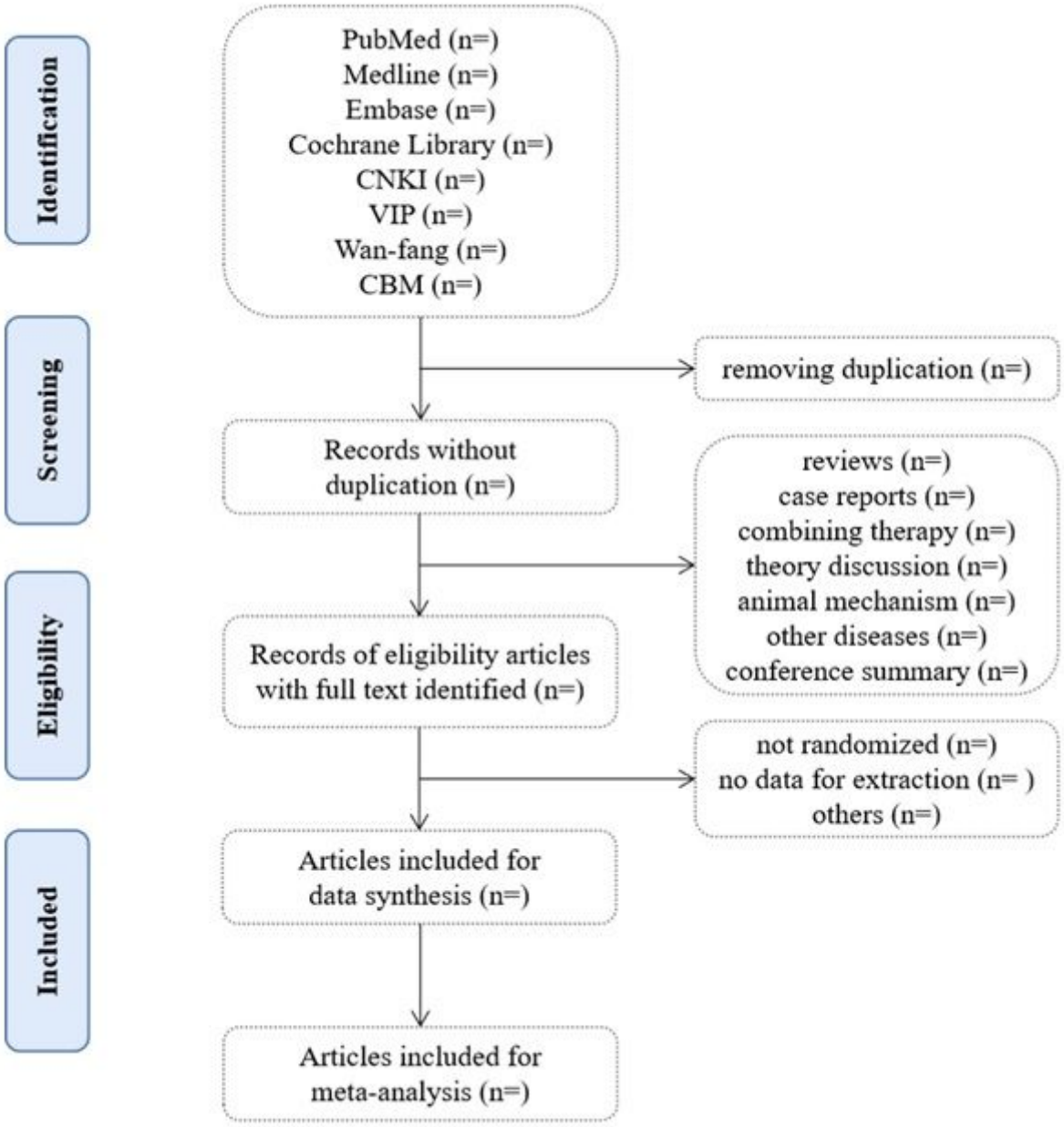

Figure 1

Flowchart of literature selection.