

REVIEW

# Acupuncture on Post-Stroke Cognitive Impairment: A Systematic Review of Neuroimaging Studies

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**Background:** Post-stroke cognitive impairment (PSCI) is a severe central nervous system disorder for which acupuncture demonstrates therapeutic efficacy. Various neuroimaging studies have indicated that acupuncture may exert its effects through modulating central mechanisms. However, owing to the current lack of a systematic summary, this study aimed to integrate the existing evidence. **Methods:** Two independent reviewers conducted a search across eight databases and other sources, identifying potential neuroimaging trials on acupuncture for PSCI, spanning from the inception of the databases to August 25, 2024. Eligible studies were screened based on predefined inclusion and exclusion criteria, and their methodological quality was assessed.

**Results:** Twelve studies, including 671 participants, utilized manual acupuncture (n = 10), electroacupuncture (n = 1), or a combination of both (n = 1). Neuroimaging tools comprised functional magnetic resonance imaging (n = 7), electroencephalography (n = 2), magnetic resonance spectroscopy (n = 2), and functional near-infrared spectroscopy (n = 1). All studies consistently reported positive effects of acupuncture on patients suffering from PSCI. Changes in brain structure and function resulting from acupuncture are commonly observed in the cingulate cortex, parahippocampal gyrus, prefrontal cortex, and fusiform gyrus. Acupuncture appears to modulate cognition-related networks, including the default mode, central executive, frontoparietal, and salience networks, thereby influencing PSCI.

**Conclusion:** The therapeutic effects of acupuncture on PSCI may be mediated through the regulation of cognition-related brain networks. Yet, these studies remain at an exploratory stage, necessitating a combination of multiple imaging techniques and large, strictly designed multicenter RCTs to validate the neuroimaging findings.

Keywords: acupuncture, post-stroke cognitive impairment, systematic review, neuroimaging, mechanism

## Introduction

Stroke, recognized as the second leading cause of death by the World Health Organization, is a prevalent central neurological condition that frequently recurs and contributes significantly to both mortality and long-term disability. Post-stroke cognitive impairment (PSCI) is a prevalent complication subsequent to stroke, affecting 53.4% of stroke survivors. It encompasses PSCI with no dementia and post-stroke dementia (PSD), with a 1.5-year mortality rate of 50.0% in China for PSD. At Patients with PSCI may experience impairment in one or multiple cognitive domains, including orientation, memory, visuospatial function, executive function, and attention. According to previous reports, over 30% of patients with stroke show a noticeable decline in cognitive function within the first 3 months following their stroke. Furthermore, relevant literature indicates that nearly 7% of patients develop dementia within 12 months of a stroke. PSCI profoundly diminishes patients' quality of life, functional independence, treatment engagement, and

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imposes substantial societal and economic burdens.<sup>8,9</sup> Therefore, there is growing interest in finding effective treatments for PSCI.<sup>10</sup>

Currently, the mechanisms of PSCI remain incompletely understood, and no pharmacological treatment has been approved. Several studies have been conducted on cholinesterase inhibitors for the treatment of vascular dementia, <sup>11</sup> but only one has specifically focused on PSCI. <sup>12</sup> However, this study showed rivastigmine had no significant benefit over placebo on specified cognitive, functional, or behavioral outcomes at 24 weeks. Furthermore, this class of drugs is associated with significant adverse effects, such as bradycardia and syncope. <sup>13</sup> Hence, increasing attention is being given to non-pharmacological approaches for PSCI intervention.

Acupuncture, a non-pharmacological treatment commonly used in China, has been extensively adopted both domestically and internationally to address a wide array of health concerns. It is also employed to enhance cognition and memory and to address other forms of functional deterioration. Acupuncture possesses distinct features that differentiate it from other treatment modalities, incorporating meridian theory and acupoints to activate internal energy and thereby enhance patients' cognitive abilities. Many systematic reviews (SRs) and clinical studies 17–21 have demonstrated that acupuncture has the potential to improve cognitive function in patients with PSCI without evident side effects. However, the lack of a SR on neuroimaging studies of acupuncture for PSCI has hindered a comprehensive elucidation of its mechanisms in promoting cognitive recovery.

Cognitive function relies heavily on the normal operation of the central nervous system. Studies have demonstrated that a decline in cognitive ability is linked to changes in brain regions and networks.<sup>22,23</sup> Under certain circumstances, cognitive impairments observed in the initial stages following stroke may be reversible, possibly owing to the plasticity and adaptability of the human brain.<sup>24,25</sup> Research indicates that the modulation of brain plasticity can improve cognitive function.<sup>26</sup> Given the significance of brain plasticity in neural recovery and cognitive improvement, researchers are actively exploring the neural pathways underlying acupuncture-induced improvements in cognitive ability after PSCI. Rapid technological advancements have enabled the adoption of various non-invasive neuroimaging techniques, including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS), and magnetic resonance spectroscopy (MRS), to reveal changes in the neural characteristics in patients with PSCI following acupuncture therapy.<sup>27–30</sup> However, no SR has yet compiled neuroimaging findings related to the use of acupuncture in treating PSCI to systematically assess the mechanisms of acupuncture therapy and its effects on brain structure and function. Therefore, this SR aims to: (1) Characterize the main features of current neuroimaging studies on acupuncture for PSCI; (2) Synthesize evidence on acupuncture-induced alterations in brain structure, function, connectivity, and metabolism in PSCI patients; (3) Evaluate the efficacy and safety of acupuncture for PSCI based on the included studies; and (4) Identify future research trends and directions in this field. Given the exploratory stage of this research area and the primary goal of capturing neuroimaging evidence on brain changes, both randomized controlled trials (RCTs) and non-RCTs were included to provide a broader perspective.

#### Materials and Methods

This research was conducted with strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,<sup>31</sup> and the PICO framework, which comprised population (patients with PSCI), intervention (acupuncture therapy), control (healthy controls, standard treatment, training, or alternatives), and outcome (neuroimaging changes and cognitive outcomes). The registration of this SR has been completed on the PROSPERO platform (number CRD42024589542).

#### Selection Criteria for Inclusion and Exclusion

To ensure a more stringent selection process for literature review, the criteria for inclusion and exclusion in the screening were established beforehand. The inclusion criteria were as follows: (1) Chinese or English-language, peer-reviewed, original neuroimaging clinical research; (2) patients met the PSCI diagnostic standards; (3) the neuroimaging techniques utilized were fMRI, MRS, fNIRS, and EEG (4) the intervention group underwent acupuncture treatment, regardless of acupoints, acupuncture methods, or treatment duration; and (5) the control group comprised healthy controls, standard treatment, training, or alternatives.

The exclusion criteria were as follows: (1) duplicate or withdrawn articles; (2) SRs, protocols, letters, experimental research, and comments; or (3) insufficient/unavailable data.

## Strategies for Searching

Two independent reviewers (SY and ZY) conducted searches across the following electronic databases: Web of Science, PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, WanFang Database, VIP Database, Grey Literature Database, as well as additional resources (Chinese Clinical Trial Register [ChiCTR] and ClinicalTrials.gov) from database inception to August 25, 2024. A combination of subject terms and free terms was used, with the language limited to Chinese and English. These terms included "Stroke", "Post Stroke", "Apoplexy", "Cerebrovascular", "Cerebral Hemorrhage", "Cognitive Dysfunction", "Cognitive Impairment", "Age-Related Memory Disorders", "Cognitive Decline", "Mental Deterioration", "Acupuncture", "Acupuncture therapy", "Scalp Needle", "Warm Acupuncture", "Electroacupuncture", "Abdominal Needle", "Body Acupuncture", "Fire Acupuncture", "Neuroimaging", "Magnetic Resonance Imaging", "Magnetic Resonance Spectroscopy", "Functional Magnetic Resonance Imaging", "fMRI", and "Functional Near-Infrared Spectroscopy". Appendix 1 presents the electronic database search strategy used in this study.

## Study Selection and Data Extraction

After duplicates were eliminated, two separate reviewers assessed the titles and abstracts of the potentially relevant studies. The same reviewers then retrieved and examined the full-text versions of these articles to establish whether they met the inclusion criteria. In cases of disagreement, a third reviewer was consulted to mediate the discussion and ensure a unified decision.

Two independent reviewers (SY and QB) performed the data extraction process, utilizing a customized standardized form to gather pertinent information. Neuroimaging metrics were predefined as primary outcome measures. The extracted data encompassed identification details such as the first author's name, country of origin, and year of publication. Additionally, fundamental information including study design, sample size, diagnostic criteria, age range, and sex was collected. Further specifics included information on the intervention and control groups, assessment tools, clinical outcomes, adverse events and neuroimaging outcomes. To ensure comprehensive reporting of acupuncture interventions, we adhered to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)<sup>32</sup> and gathered exhaustive details on the acupuncture employed.

# **Quality Assessment**

To evaluate the risk of bias in the RCTs, we used the Cochrane risk-of-bias tool for randomized trials (RoB 2.0).<sup>33</sup> The RoB 2.0 tool evaluates five distinct domains for risk of bias assessment. The risk of bias for each domain was estimated and categorized separately as either "low", "some concerns", or "high". In accordance with RoB 2.0, we also determined the overall risk of bias (low, some concerns, high). To assess the risk of bias in non-RCTs, we used the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.<sup>34</sup> The RoB assessment includes the categories: critical, serious, moderate, low, and nonexistent. Methodological quality was evaluated by two authors. In cases of disagreement, a third researcher arbitrated the final decision.

# Data Analysis

Given the diversity of neuroimaging methods employed in the studies, a descriptive analytical approach was used to summarize and compare the primary characteristics and results. Narrative analysis was further applied to synthesize acupuncture-induced alterations in brain structure or function, with safety outcomes similarly described in narrative form due to limited reporting. This narrative synthesis adhered to the Synthesis Without Meta-analysis reporting guideline, which provides methodological standards for integrating heterogeneous quantitative evidence through structured grouping of studies, standardized presentation of outcomes, and transparent reporting of limitations.

## Neuroimaging Data Evaluation Criteria

The evaluation criteria for neuroimaging changes adhered to standardized statistical thresholds for significance testing, consistent with best practices in neuroimaging analysis. For fMRI studies, significance required combined voxel-level (typically p<0.001 uncorrected or p<0.05 corrected) and cluster-level thresholds (p<0.05 after Gaussian Random Field [GRF], False Discovery Rate [FDR], or Alpha Simulation [AlphaSim] correction). Graph theory analyses employed sparsity ranges to evaluate network properties across biologically plausible connection densities. EEG outcomes used established metrics, while MRS relied on metabolic ratios, both with significance set at p<0.05.

## **Assessment Tools**

Twelve assessment tools were used to evaluate the severity of PSCI. The tools for assessing overall cognitive function included the Montreal Cognitive Assessment (MoCA; n=9; 75%), Mini-Mental State Examination (MMSE; n=5; 41.67%), and Loewenstein Occupational Therapy Cognitive Assessment (LOTCA; n=1; 8.33%). Memory function was assessed using the Revised Wechsler Memory Scale-Chinese Version (WMS-RC; n=2; 16.67%), the Auditory Verbal Learning Test (n=1; 8.33%), and the Digit Span Test (DS; n=1; 8.33%). Executive function and attention were assessed using the Trail Making Test (TMT; n=2, 16.67%). The tools used to assess neurological deficits and motor function encompassed the National Institutes of Health Stroke Scale (n=2, 16.67%) and the Fugl-Meyer Assessment (n=1, 8.33%). Finally, the tools for assessing daily living abilities and functional independence included the Modified Barthel Index (MBI; n=1; 8.33%), the Activities of Daily Living Scale (ADL; n=1; 8.33%), and the Functional Independence Measure (FIM; n=1; 8.33%).

## **Results**

## Searching and Screening

The PRISMA flowchart, presented in Figure 1, outlines the methodical process of searching for and screening the appropriate literature. Overall, 131 articles were identified using the primary search strategy. After removing duplicates, 99 trials remained. Following initial screening, 17 studies were included in analysis. Upon conducting a second, more thorough examination of full-text articles, five studies were excluded based on the inclusion criteria: two lacked neuroimaging data, and three featured ineligible treatments. Therefore, 12 studies remained<sup>27,30,41–50</sup> for the final assessment. Appendix 2 contained the detailed rationale for excluding these five studies.

# Characteristics of Study

The summary of the characteristics of the selected studies is presented in Table 1. The studies were published between 2014 and 2023, with all trials conducted in China. One study (8.33%) was published in English, while the remaining eleven were published in Chinese.

The analysis encompassed nine RCTs and three non-RCTs. The number of participants ranged from 25 to 94. Ten trials aimed to explore whether acupuncture elicits cerebral responses, while two focused on investigating the impact of acupuncture on neural networks within the brain.

## Research Participants

Overall, the study included 582 patients diagnosed with PSCI and 57 healthy volunteers. Among those diagnosed with PSCI, 383 had ischemic stroke, and 41 had hemorrhagic stroke, and the stroke type for the remaining 158 patients was not specified or differentiated. Four neuroimaging trials used the classification for cerebral vascular disease, <sup>51</sup> three used the Chinese guidelines for cerebrovascular disease prevention and control, <sup>52</sup> and two used the expert consensus on the management of PSCI. <sup>53</sup> One study used a different criterion, whereas four omitted details on the diagnostic criteria. Three studies compared patients with PSCI with healthy participants, while the remaining studies solely focused on patients with PSCI. The age of the enrolled patients ranged from 53.15 to 70.1 years. Nine studies provided information on the sex of patients (265 males and 205 females). In the nine studies that only recruited patients with PSCI, the maximum and minimum sample sizes were 47 and 12 per group, respectively. In three studies that compared patients

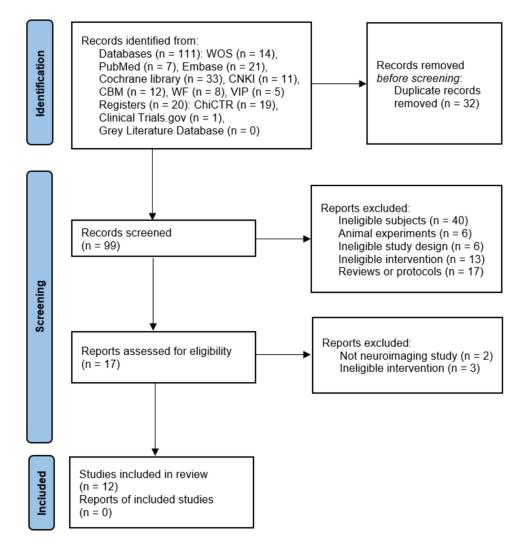


Figure I PRISMA flowchart. Systematic searches were performed across multiple electronic databases (Web of Science [WOS], PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure [CNKI], Chinese Biomedical Literature Database [CBM], WanFang [WF], VIP, Grey Literature Database) and trial registries (Chinese Clinical Trial Register [ChiCTR] and ClinicalTrials.gov) from inception to August 25, 2024.

with PSCI and healthy volunteers, the matched sample sizes for PSCI/healthy controls were 1/1, 11/7, and 10/9, respectively.

#### Acupuncture Details

Acupuncture-related information gathered from the studies is displayed in Table 2, following the STRICTA guidelines. Eleven studies (91.7%) mentioned rationale of acupuncture, including the types of acupuncture and the reasons for providing the treatment. Participants underwent between 1 and 56 needle insertions per session. The acupoints that were most frequently used were GV 20 (Baihui) and EX-HN1 (Sishencong). Acupuncture insertion depth was 7.5–37.5 mm. Four studies (33.3%) emphasized the needle sensation (deqi) during acupuncture stimulation. Ten studies (83.3%) used manual acupuncture, one study (8.3%) employed electroacupuncture, and one (8.3%) utilized both. The most commonly used needle diameters were 0.25, 0.30, and 0.35 millimeters, with the most frequently used lengths being 25 and 40 millimeters. The number of therapy sessions ranged from 10 to 72. Only four studies (33.3%) provided details on acupuncturists.

Table I Characteristics of Selected Studies

| Study                           | Country | Study<br>Design | N (A/B/C)         | Diagnostic<br>Criteria | Age (Year)                   | Gender<br>(M/F)          | Treatment<br>Courses | (A) Intervention Group     | (B)  Control  Group I                 | (C) Control Group II | Imaging<br>Modality | Scan<br>T | Assessment<br>Tools                  | Clinical Outcomes  | Adverse<br>Events | Analytical<br>Approaches  |
|---------------------------------|---------|-----------------|-------------------|------------------------|------------------------------|--------------------------|----------------------|----------------------------|---------------------------------------|----------------------|---------------------|-----------|--------------------------------------|--|-------------------|---|
| Li (2023) <sup>45</sup>         | China   | Non- RCT        | 46 (16 IS/16)     | ①<br>③<br>④            | A:60.5±12<br>B:61.5±12       | A: 12M/4F<br>B: 12M/4F   | 12weeks              | Acupuncture+<br>CM (NR)    | НС                                    | 1                    | rs-fMRI             | 3.0T      | MMSE,<br>MoCA, WMS-<br>RC            | (A): Post vs baseline:<br>Significant improvements<br>in MMSE, MoCA, WMS-<br>RC memory quotient,<br>long-term memory,<br>short-term memory, and<br>instantaneous memory<br>scores (p=0.05)     | None              | Amplitude of<br>low-<br>frequency<br>fluctuation,<br>Regional<br>homogeneity,<br>Degree<br>centrality       |
| Wang (2021) <sup>44</sup>       | China   | Non-RCT         | 36 (22 IS/14)     | <b>⑤</b>               | A:60.14±8.46<br>B:56.71±4.68 | A: 11M/11F<br>B: 4M/10F  | 2weeks               | Acupuncture                | нс                                    | 1                    | rs-fMRI             | 3.0T      | MMSE, MoCA                           | (A): Post vs baseline:<br>Significant improvements<br>in MMSE and MoCA<br>scores (p<0.001)   | NR                | Brain<br>topology<br>properties,<br>correlation<br>with MoCA  |
| Wang et al (2021) <sup>42</sup> | China   | RCT             | 80 (40 IS /40 IS) | <b>⑤</b>               | A:66±8<br>B:67±9             | A: 26M/14F<br>B: 24M/16  | 8weeks               | Acupuncture+<br>B          | Cognitive<br>training+CM<br>(NR)      | 1                    | rs-fMRI             | 3.0T      | NIHSS,<br>MMSE,<br>MoCA, FMA,<br>MBI | Between-group post-<br>treatment results:<br>Significant reduction in<br>NIHSS scores (p<0.05),<br>and significant<br>improvements in MMSE,<br>MoCA, FMA, and MBI<br>scores (p<0.05)           | NR                | Functional connectivity   |
| Na (2021) <sup>48</sup>         | China   | Non-RCT         | 25 (17)           | 1                      | 1                            | 1                        | 3weeks               | Acupuncture                | 1                                     | 1                    | rs-fMRI             | I.5T      | NIHSS,<br>MMSE, MoCA                 | (A): Post vs baseline: Significant reduction in NIHSS scores (p<0.01), and significant improvements in MMSE and MoCA scores (p<0.01)   | NR                | Amplitude of<br>low-<br>frequency<br>fluctuation,<br>Functional<br>connectivity,<br>Regional<br>homogeneity |
| Yu et al (2021) <sup>47</sup>   | China   | RCT             | 60 (30/30)        | 2                      | A:59±3<br>B:59±3             | A: 18M/12<br>B: 17M/13   | 4weeks               | Acupuncture+<br>B          | Rehabilitation<br>training+CM<br>(NR) | 1                    | rs-fMRI             | NR        | MoCA, TMT,<br>AVLT, DS               | Between-group post-<br>treatment results:<br>Significant improvements<br>in MoCA, AVLT and DS<br>scores (p<0.05); TMT<br>completion time<br>significantly lower than<br>control group (p<0.05) | NR                | Amplitude of low-<br>frequency<br>fluctuation   |
| Chen et al (2020) <sup>27</sup> | China   | RCT             | 56 (28/28)        | 1                      | A:65.3±6.8<br>B:64.5±7.2     | A: 16M/12F<br>B: 17M/11F | 24days               | Scalp<br>acupuncture<br>+B | CM (5mg /day<br>dose of<br>Donepezil) | /                    | fNIRS               | 1         | MoCA, ADL                            | Between-group post-<br>treatment results:<br>Significant improvements<br>in MoCA (p<0.001) and<br>ADL scores (p<0.0001)  | NR                | Cerebral<br>hemoglobin<br>levels,<br>correlation<br>with MoCA<br>and ADL                                    |

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| Zhang et al (2020) <sup>30</sup> China | RCT   | 60 (30 IS/30 IS)                      | 1                           | A:70.10±4.51 | A: 20M/10F   | 6weeks     | Scalp       | Rehabilitation  | 1   | MRS       | 3.0T    | MoCA | Between-group post- | NR  | Metabolic |   |
|--|-------|---------------------------------------|-----------------------------|--------------|--------------|------------|-------------|---|---|-----------|---------|------|---------------------|---|-----------|---|
|  |       |                                       |                             |              | B:69.03±4.70 | B: 18M/12F |             | acupuncture+B   | training+ Computer assisted cognitive system training + CM (NR)                                       |           |         |      |                     | treatment results: Significant improvement in MoCA, excluding abstract ability (p<0.05)   |           | Ration  |
| Guan (2019) <sup>41</sup>              | China | RCT                                   | 59 (15 IS/15 IS/27)         | 3, 5         | A:64.33±3.56 | A: IIM/9F  | 4weeks      | Acupuncture   | CM (5 mg/day  | НС        | rs-fMRI | 3.0T | MoCA                | Between-group post-   | NR        | Regional  |
|  |       |                                       |                             |              | B:63.93±3.22 | B: 10M/10F |             | +function<br>training+ B  | dose of<br>Donepezil; 15  |           |         |      |                     | treatment results: Significant improvements   |           | homogeneity,<br>Amplitude of  |
|  |       |                                       |                             |              | C:64.51±2.68 | C: 13M/14F |             |   | mg/day dose of folic acid; 1.5 mg/day dose of Mecobalamin; 30 mg/day dose of vitamin B <sub>6</sub> ) |           |         |      |                     | in MoCA, LOTCA and FIM scores (p<0.05); TMT completion time and error count significantly lower than control group (p<0.05)                               |           | low-<br>frequency<br>fluctuation,<br>Serum<br>biological<br>markers |
| Zhong (2018) <sup>43</sup>             | China | RCT                                   | 30 (12/13)                  | 1            | A:56.08±1.92 | A: IIM/4F  | 12weeks     | Acupuncture+  | Cognitive<br>Rehabilitation   | 1         | rs-fMRI | 3.0T | WMS-RC              | Between-group post-<br>treatment results:   | NR        | Amplitude of  |
|  |       |                                       |                             |              | B:53.15±1.39 | B: 10M/5F  |             |   | Training+ Basic treatment + CM (NR)   |           |         |      |                     | is improvements in WMS-RC total score, short-term memory and immediate memory (p<0.05); Other WMS-RC sub-scores showed no significant difference (p>0.05) |           | frequency<br>fluctuation  |
| Yang and Zhang<br>(2017) <sup>49</sup> | China | RCT                                   | 94 (47/44)<br>(50 IS/41 HS) | 1            | 1            | 1          | 4weeks      | Acupuncture+<br>B   | Rehabilitation<br>training+<br>Cognitive<br>Rehabilitation<br>Training+ CM<br>(NR)                    | 1         | EEG     | 1    | MMSE                | Between-group post-<br>treatment results:<br>Significant improvement<br>in MMSE (p<0.05)  | NR        | P300<br>potential,<br>Abnormal<br>rate of EEG                       |
| Zhang et al (2015) <sup>50</sup>       | China | RCT                                   | 65 (34 IS /31 IS)           | 1            | A:61.27±8.15 | A: 25M/9F  | 8weeks      | Scalp   | Rehabilitation  | 1         | EEG     | 1    | Picture             | Between-group post-   | NR        | N300  |
|  |       | l l l l l l l l l l l l l l l l l l l | training<br>+ CM (NR)       |              |              |            | recognition | treatment results: Significant improvement in picture recognition accuracy and shortening of reaction time (p<0.05) |   | potential |         |      |                     |   |           |   |
| Wang et al (2014) <sup>46</sup>        | China | RCT                                   | 60 (30 IS /30 IS)           | 1            | 1            | 1          | 12weeks     | Acupuncture+  | CM (90 mg/<br>day dose of<br>Nimodipine)  | 1         | MRS     | 3.0T | MoCA                | Between-group post-<br>treatment results:<br>Significant improvement<br>in MoCA (p<0.05)  | NR        | Metabolic<br>Ration   |

Notes: ①: Classification for cerebral vascular disease; ②: Guidelines for the Diagnosis and Treatment of Vascular Cognitive Impairment in China; ③: Expert Consensus on the Management of Post-stroke Cognitive Impairment; ④: Guidelines for the diagnosis and treatment of dementia and cognitive impairment in China; ⑤: Chinese guidelines for cerebrovascular disease prevention and control.

Abbreviations: RCT, randomized controlled trial; IS, ischemic stroke; HS, hemorrhagic stroke; HC, healthy control; CM, conventional medicine; Rtms, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; fNIRS, functional near-infrared spectroscopy; MRS, magnetic resonance spectroscopy; rs-MRI, resting-state cerebral functional magnetic resonance imaging; EEG, Electroencephalogram; MoCA, Montreal Cognitive Assessment Scale; NIHSS, National Institutes of Health Stroke Scale; DST, Double Support Time; MMSE, the Mini-Mental State Examination; WMS-RC, Wechsler Memory Scale-Revised in China; FMA, Fugl-Meyer assessment; MBI, Modified Barthel Index; TMT, Trail Making Test; AVLT, Auditory Verbal Learning Test; DS, Digital Span; ADL, Activity of Daily Living Scale; LOTCA, Loewenstein Occupational Therapy Cognitive Assessment; FIM, Function Independent Measure; NR, not recorded:

 Table 2 Acupuncture-Related Information Based on Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)

| Study                            |     | Acupuncture<br>Rationale |    | Deta      | Details of Needling   |                 |      |                             |   |  |    |                                      |    | Other Practitioner Components |    | Comparato |    |
|----------------------------------|-----|--------------------------|----|-----------|---|-----------------|------|-----------------------------|---|--|----|--------------------------------------|----|-------------------------------|----|-----------|----|
|                                  | la  | Ib                       | Ic | 2a        | 2b  | 2c              | 2d   | 2e                          | 2f  | 2g   | 3a | 3b                                   | 4a | 4b                            | 5  | 6a        | 6b |
| Li (2023) <sup>45</sup>          | TCM | Υ                        | NA | NR        | GV20, EX-HN1, GV26, ST2 (NR), GB20 (NR), GB12 (NR), BL10 (NR), PC6 (NR), HT7 (NR), ST40 (NR), SP6 (NR), LR3 (NR)  | 7.5–<br>37.5mm  | NR   | Manual                      | 30 minutes  | Diameter and<br>length:0.25and40mm                 | 36 | Frequency:<br>threetimes<br>per week | NA | NR                            | Y  | NA        | NA |
|                                  |     |                          |    |           |   |                 |      |                             |   | Needle Brand:Hwato                                 |    | Duration:12<br>weeks                 |    |                               |    |           |    |
| Wang (2021) <sup>44</sup>        | ТСМ | Υ                        | NA | 7         | PC6 (bilateral), GV20, EX-HNI   | 20-<br>25mm     | Deqi | Manual                      | 30 minutes  | Diameter and<br>length:0.35and50mm                 | 10 | Frequency:<br>fivetimes per<br>week  | NA | NR                            | NR | NA        | NA |
|                                  |     |                          |    |           |   |                 |      |                             |   | Needle Brand:NR                                    |    | Duration:2<br>weeks                  |    |                               |    |           |    |
| Wang et al (2021) <sup>42</sup>  | TCM | Υ                        | NA | 1         | GV20, HT7   | 20-<br>30mm     | NR   | Manual                      | 30 minutes  | Diameter and<br>length:0.35and25mm                 | 28 | Frequency:<br>every other<br>day     | NA | NR                            | NR | NR        | Y  |
|                                  |     |                          |    |           |   |                 |      |                             |   | Needle Brand:Hwato                                 |    | Duration:8<br>weeks                  |    |                               |    |           |    |
| Na (2021) <sup>48</sup>          | TCM | Y                        | NA | 4         | Frontal lobe group points (NR)  | NR              | NR   | Manual                      | 25 minutes  | NR   | 15 | Frequency:<br>fivetimes per<br>week  | NA | NR                            | Y  | NA        | NA |
|                                  |     |                          |    |           |   |                 |      |                             |   |  |    | Duration:3<br>weeks                  |    |                               |    |           |    |
| Yu et al (2021) <sup>47</sup>    | TCM | Y                        | NA | 17        | RN12, RN10, RN6, RN4, ST25 (bilateral), SP15 (bilateral), L14 (bilateral),<br>LR3 (bilateral), Upper Wind-Dampness Point (unilateral: affected side),<br>Upper Wind-Dampness Upper Point (unilateral: affected side), Upper Outer | NR              | NR   | Manual                      | 30 minutes  | NR   | 20 | Frequency:<br>five times<br>per week | NA | NR                            | NR | Υ         | Υ  |
|                                  |     |                          |    |           | Wind-Dampness Point (unilateral: affected side), Lower Wind-Dampness<br>Point (unilateral: affected side), Lower Wind-Dampness Lower Point<br>(unilateral: affected side)   |                 |      |                             |   |  |    | Duration:4<br>weeks                  |    |                               |    |           |    |
|                                  |     |                          |    |           |   |                 |      |                             |   | Needle Brand:Hwato                                 |    | Duration:12<br>weeks                 |    |                               |    |           |    |
| Chen et al (2020) <sup>27</sup>  | TCM | Υ                        | NA | 42-<br>56 | NR (divided into parietal, frontal, temporal, occipital, suboccipital, anterior parietal, and item regions)   | 12.7–<br>25.4mm | NR   | Manual                      | 30 minutes,<br>with one long-                             | Diameter and length:0.25and40mm                    | 48 | Frequency:<br>Twice a day            | NA | NR                            | NR | NR        | Υ  |
|                                  |     |                          |    |           |   | (0.5–1<br>inch) |      |                             | lasting needle<br>kept at each<br>acupoint for 6<br>hours | Needle Brand:<br>ANDE                              |    | Duration:<br>24 days                 |    |                               |    |           |    |
| Zhang et al (2020) <sup>30</sup> | тсм | Υ                        | NA | 5         | MS1, MS6 (bilateral)  | 15-<br>20mm     | NR   | Manual<br>and<br>Electronic | 30 minutes  | Diameter and<br>length:0.30and25mm;<br>0.25and40mm | 30 | Frequency:<br>fivetimes per<br>week  | NA | NR                            | NR | NR        | Υ  |
|                                  |     |                          |    |           |   |                 |      | Electionic                  |   | Needle Brand: Dongbang Electroacupuncture          |    | Duration:6                           |    |                               |    |           |    |
|                                  |     |                          |    |           |   |                 |      |                             |   | apparatus:<br>KWD-808I                             |    |                                      |    |                               |    |           |    |

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| Guan (2019) <sup>41</sup>              | TCM | Y  | NA | 13 | Yu's head acupoint division method - the seven zone division method includes the top zone, front top zone, and frontal zone. | 30mm          | NR   | Manual     | 6 hours    | Diameter and<br>length:0.35and40mm<br>Needle Brand:<br>ANDE                                    | 24 | Frequency:<br>sixtimes per<br>week<br>Duration:4<br>weeks   | NA | NR | NR | Y  | Y |
|--|-----|----|----|----|--|---------------|------|------------|------------|--|----|---|----|----|----|----|---|
| Zhong (2018) <sup>43</sup>             | ТСМ | Y  | NA | 2  | GV20, GV24   | 12.5-<br>20mm | Deqi | Manual     | 30 minutes | Diameter and<br>length:0.30and25mm<br>Needle Brand:<br>Hwato                                   | 60 | Frequency:<br>fivetimes per<br>week<br>Duration:12<br>weeks | NA | NR | Y  | Υ  | Y |
| Yang and Zhang<br>(2017) <sup>49</sup> | TCM | Y  | NA | 14 | MS1, GV20, EX-HN1, HT07 (bilateral), Sl03 (bilateral), Kl06 (bilateral), GB39 (bilateral)                                    | 7.5–<br>25mm  | Deqi | Manual     | 30 minutes | Diameter and<br>length:0.30and25mm;<br>0.30and40mm<br>Needle Brand:<br>Hwato                   | 24 | Frequency:<br>sixtimes per<br>week<br>Duration:4<br>weeks   | NA | NR | NR | NR | Y |
| Zhang et al (2015) <sup>50</sup>       | ТСМ | NR | NA | 6  | MSI, MSS, MS7 (bilateral)  | 30mm          | Deqi | Electronic | 30 minutes | Diameter and length: 0.25 and 40 mm Needle Brand: Hwato Electroacupuncture apparatus: KWD-808I | 40 | Frequency:<br>fivetimes per<br>week<br>Duration:8<br>weeks  | NA | NR | NR | NR | Y |
| Wang et al (2014)*6                    | TCM | Y  | NA | NR | GV20, GV24, EX-HN1, L14 (NR), LR3 (NR), SP6 (NR), ST40 (NR), RN12 (NR), ST36 (NR)  | NR            | NR   | Manual     | 30 minutes | NR   | 72 | Frequency:<br>six times per<br>week<br>Duration:12<br>weeks | NA | NR | Y  | NR | Y |

Notes: Ia: Style of acupuncture; Ib: Reasoning for treatment provided; Ic: Extent to which treatment was varied; 2a: Number of needle insertions per patient per session; 2b: Names of points used; 2c: Depth of insertion; 2d: Response sought; 2e: Needle stimulation; 2f: Needle retention time; 2g: Needle type; 3a: Number of treatment sessions; 3b: Frequency and duration of treatment sessions; 4a: Details of other interventions administered to the acupuncture group; 4b: Setting and context of treatment; 5: Description of participating acupuncturists; 6a: Rationale for the control or comparator; 6b: Precise description of the control or comparator.

Abbreviations: TCM, traditional Chinese medicine; NA, not applicable; NR, not recorded; Y, Yes; and, and.

#### Comparison

The 12 studies included the following four comparison types: three studies (25%) compared acupuncture with healthy volunteers, one study (8.3%) used a self-control design to compare before and after treatment, two studies (16.7%) contrasted acupuncture combined with conventional medicine against conventional medicine alone and six studies (50%) compared acupuncture plus conventional medicine and training to conventional medicine and training without acupuncture.

## Clinical Efficacy and Safety Outcomes

Among the 12 included studies, all 12 (100%) reported at least one clinical efficacy outcome. The most commonly used standardized cognitive measures were MoCA and MMSE. All 12 studies reported statistically significant improvements (p < 0.05) in primary clinical outcomes following acupuncture-based interventions. In RCTs, between-group comparisons demonstrated acupuncture's significant superiority over controls across multiple domains, including global cognition, functional independence and task-based neuropsychological measures. Notably, one study observed no significant between-group differences in specific secondary memory sub-scores (WMS-RC, p > 0.05) despite confirming efficacy in primary outcomes. <sup>43</sup> Due to substantial heterogeneity in study designs (eg, non-RCT vs RCT), interventions (eg, acupuncture alone vs combined with cognitive training), and outcome measures, a meta-analysis was not feasible. Results are summarized descriptively in Table 1.

Among the studies incorporated in this SR, only one article<sup>45</sup> explicitly documented the absence of acupuncturerelated adverse events during the intervention period. The remaining studies failed to report safety outcomes or adverse event monitoring data.

#### Imaging Techniques in PSCI Acupuncture Research

Studies utilized fMRI, fNIRS, EEG, and MRS to explore functional changes in the brain, event-related potentials, and metabolic ratios triggered by acupuncture in patients with PSCI. Among these, two articles specifically assessed metabolic ratios through MRS. One study used fNIRS for the evaluation of hemodynamic responses. Two studies analyzed event-related potentials (ERP) derived from EEG recordings to assess the neural responses associated with specific events. Ten trials assessed the functional alterations resulting from acupuncture. Seven studies utilized resting-state fMRI (rs-fMRI) to assess various aspects of brain activity patterns: two trials focused on functional connectivity (FC), three on regional homogeneity (ReHo), and five on the amplitude of low-frequency fluctuations (ALFF). Figure 2 displays the percentages of the various imaging tools.

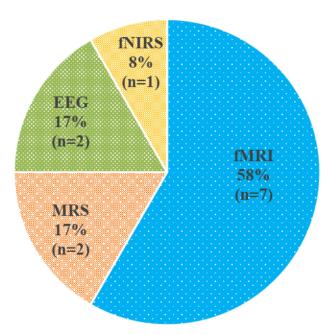


Figure 2 Percentages of various imaging tools. Distribution of imaging techniques used across the included studies (n = 12). Each study utilized only one technique.

## **Evaluation of Quality**

The methodological assessment's results are shown in Appendices 3 and 4.

Using the RoB 2 tool, a moderate RoB was identified across all nine RCTs. When evaluating the randomization process, six studies were assessed as low risk because they provided detailed randomization descriptions, while three were categorized as having some concern due to insufficient information. In terms of deviation from the intended intervention, one study had low bias, while eight studies had some concern owing to brief representations. Two studies had participant dropout but did not report the methods for handling missing data in detail, which raised several concerns. Other studies showed low bias. It is worth noting that all studies were deemed to have low bias regarding result measurements. However, concerns arose about selective reporting of outcomes in all RCTs, owing to the absence of detailed information on protocols and registrations.

Using the ROBINS-I tool, a moderate RoB was observed in all three non-RCTs. In terms of confounders, two studies exhibited low bias, while one showed moderate RoB due to a lack of information. Regarding missing data, one study had low bias, while two studies demonstrated moderate RoB due to dropouts. It is worth mentioning that all studies demonstrated low bias concerning participant recruitment, categorization of interventions, adherence to intended interventions, assessment of outcomes, and the choice of reported data.

# Results From Neuroimaging

#### Underlying Neural Mechanisms for Acupuncture

Evaluation criteria for neuroimaging outcomes, including statistical thresholds and correction methods, along with detailed results of acupuncture-induced brain alterations across all 12 predefined studies, are cataloged in <u>Appendix 5</u>. Brain alterations most frequently associated with repeated acupuncture in patients with PSCI are situated in the cingulate gyrus (a key node in the default mode network [DMN] and salience network [SN]; n=4), parahippocampal gyrus (a DMN-associated region; n=4), prefrontal cortex (a key node in the central executive network [CEN] and frontoparietal network [FPN]; n=4), and fusiform gyrus (a key region for visual processing and recognition; n=3). The DMN, CEN, FPN, and SN are crucial components formed by the brain areas mentioned in these trials. Except for the EEG results, all other observations were derived from resting-state conditions.

Using fNIRS, a study<sup>27</sup> demonstrated that repeated acupuncture enhanced the hemodynamic response in the prefrontal and motor cortices of both hemispheres in patients with PSCI. Furthermore, two MRS trials<sup>30,46</sup> demonstrated an increase in the ratio of N-acetylaspartate to creatine and a decrease in the ratios of choline to creatine and myo-inositol to creatine within the hippocampus (a DMN-associated region) and cerebral infarction areas of patients with PSCI, which could be attributed to routine acupuncture.

Two studies that used EEG in conjunction with ERP<sup>49,50</sup> revealed that repeated acupuncture can shorten the latency of the P300/N300 potential and prolong its amplitude in patients with PSCI. Specifically, the results revealed a significant shortening of the P300 component latency in the EEG recordings of these patients. This is a well-established indicator of enhanced cognitive processing speed and efficiency, primarily observed in the frontal lobe, parietal lobe, precentral gyrus, and postcentral gyrus for P300, and in the frontal lobe, precentral gyrus, postcentral gyrus, and fronto-central region for N300. Additionally, an increase in the amplitude of the P300/N300 complex was observed, suggesting that acupuncture stimulates neural activity within the brain regions corresponding to these EEG components.

Using fMRI trials, four neuroimaging studies documented increases or decreases in ReHo or ALFF across various brain regions following continuous acupuncture treatment. 41,45,47,48 In terms of ALFF, increases were observed in the parahippocampal gyrus, precuneus (a key node in the DMN), and middle temporal gyrus (a DMN-associated region) within the memory region; the superior parietal gyrus (a key node of the FPN) and fusiform gyrus within the visuospatial region; the cingulate gyrus, insula (a key node of the SN), and thalamus (a key node of the SN) within the emotional processing and cognitive function regions; and the inferior frontal gyrus (a key node of the FPN) and middle frontal gyrus (a key node of the FPN) within the language/executive function regions. However, decreases in ALFF were noted in the inferior temporal gyrus, fusiform gyrus, superior occipital gyrus, inferior occipital gyrus, and superior parietal lobule within the visuospatial region, and the superior frontal, inferior frontal, and middle temporal gyri within the

language/executive function regions. Regarding ReHo, increases were found in the parahippocampal gyrus, temporal pole, and precuneus within the memory region; the middle frontal gyrus within the language/executive function region; and the superior parietal gyrus within the visuospatial region. Nevertheless, decreases in ReHo were observed in the parahippocampal and middle temporal gyrus within the memory region, the lenticular and ventrolateral thalamic nuclei within the emotional processing and cognitive function regions, and the inferior frontal gyrus within the language/ executive function region. Furthermore, one study<sup>43</sup> compared the differences in ALFF values, revealing significant disparities in these changes within memory areas (eg right middle temporal gyrus), visuospatial areas (eg parietal lobule), cognitive function areas (eg cingulate gyrus) and emotional-affective processing, and language/executive function areas (eg frontal lobe, postcentral gyrus, and inferior frontal gyrus).

The ALFF and ReHo results indicated that acupuncture can exert extensive and complex effects on the functional brain regions of patients with PSCI, bidirectionally regulating activity disturbances in certain associated brain regions. It is noteworthy that following acupuncture treatment, changes in ALFF within the fusiform and inferior frontal gyri and changes in ReHo within the parahippocampal gyrus exhibited a dual nature. This duality may be associated with various factors, such as the specific parameters of acupuncture treatment, individual differences, and disease states. Additionally, increases or decreases in ALFF/ReHo do not necessarily imply an absolute enhancement or decline in function. Rather, they may represent a functional reorganization or optimization of the brain in response to acupuncture.

Moreover, one study<sup>44</sup> reported that nodal properties were mainly altered in patients with PSCI after acupuncture treatment. Graph theory analysis was employed to investigate these changes. The results indicated an increase in nodal centrality and local efficiency within brain areas related to cognitive functions, particularly in visuospatial areas (eg the fusiform gyrus, inferior occipital gyrus, and lingual gyrus) and memory areas (eg the precuneus and parahippocampal gyrus).

By performing an FC analysis, one study<sup>48</sup> demonstrated increased FC in the superior marginal gyrus, superior temporal gyrus, anterior cuneiform lobe, angular gyrus, superior occipital gyrus, inferior parietal lobe, posterior cingulate gyrus, and decreased FC in the middle occipital gyrus after acupuncture. Furthermore, employing FC analysis focused on specific regions of interest, another study<sup>44</sup> found that frequent acupuncture led to an enhancement in FC. Specifically, there was an increase in connectivity between the left hippocampus and regions, such as the middle frontal and right inferior gyri, as well as between the right hippocampus and areas including the left middle gyrus, inferior gyrus, parietal lobe, and superior frontal gyrus (a key node of the FPN).

The brain regions mentioned in previously conducted studies can generally be grouped according to their participation in four distinct neural pathways: DMN (eg. precuneus, anterior cingulate, parahippocampal gyrus, hippocampus, and middle temporal gyrus), CEN (eg, anterior cingulate, inferior parietal lobule, and superior dorsolateral frontal gyrus), FPN (eg, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and inferior parietal lobule), and SN (eg, parahippocampal gyrus, insula, anterior cingulate, and thalamus). The primary results from the consistent acupuncture are displayed in Figure 3.

#### The Relationship Between Neuroimaging Results and Clinical Outcomes

Three studies reported a relationship between the overall cognitive function and neuroimaging outcomes. Specifically, MoCA scores negatively correlated with degree centrality in the left inferior occipital gyrus of patients with PSCI after acupuncture treatment (r= -0.461, p= 0.031). However, MoCA scores are positively correlated with activity levels in the right frontal gyrus and inferior temporal gyrus (r= 0.365, p= 0.047; r= 0.387, p=0.035).41 Furthermore, LOTCA scores are positively correlated with activity levels in the right fusiform gyrus and right dorsolateral prefrontal cortex (r= 0.448, p=0.013; r=0.361, p=0.05). The study explored the relationship between neuroimaging outcomes and various memory function indicators. Total WMS-RC scores positively correlated with neural activity intensities in the right middle frontal gyrus and right inferior parietal lobule (r= 0.537, p=0.02; r = 0.505, p=0.02). Moreover, the neural activity intensity in the right middle frontal gyrus was positively correlated with short-term memory (r= 0.479, p= 0.048), whereas the neural activity intensity in the left posterior cingulate gyrus was positively correlated with long-term memory (r = -0.424, p = 0.035). As Regarding executive function indicators, TMT-A performance is negatively correlated with activity levels in the right inferior temporal gyrus (r= -0.394, p= 0.031). 41

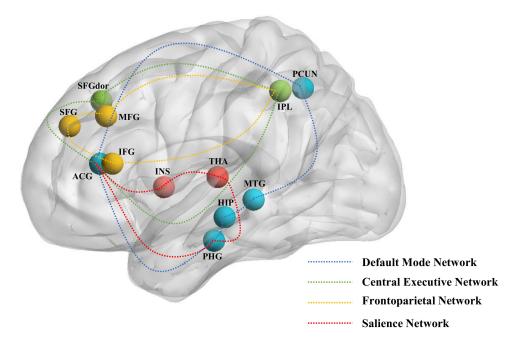


Figure 3 Results from consistent acupuncture. Lateral view of the left hemisphere. The reviewed studies indicated that sustained acupuncture primarily impacts specific brain regions and networks. Brain regions: ACG (anterior cingulate gyrus): Involved in emotion regulation, attention, and conflict monitoring; Hip (hippocampus): Critical for memory formation and spatial navigation; IFG (inferior frontal gyrus): A key node in the language network and also involved in cognitive control; IPL (inferior parietal lobule): Associated with sensory integration, mathematical cognition, and language processing; INS (insula): Plays a central role in interoceptive awareness, emotion, and pain processing; MFG (middle frontal gyrus): Implicated in working memory and executive functions; MTG (middle temporal gyrus): Involved in semantic memory and language comprehension; PCUN (precuneus): A key hub of the default mode network, associated with self-referential thought and consciousness; PHG (parahippocampal gyrus): Important for memory encoding and retrieval, and contextual association; SFG/SFGdor (superior frontal gyrus, dorsolateral): Primarily responsible for higher-order cognitive functions like planning, decision-making, and working memory; THA (thalamus): Acts as the central relay station for sensory and motor signals to the cerebral cortex. Brain networks: blue network, default mode network; green network, central executive network; yellow network, frontoparietal network; red network, salience network.

#### **Discussion**

To date, 12 articles measuring brain activity have been considered, providing visual evidence for a deeper understanding of the underlying central mechanisms of acupuncture in the treatment of PSCI. Subsequently, here, we discuss three essential areas: evaluating the current design and suggesting methodologies for improvement, assessing neuroimaging findings in PSCI after acupuncture, and outlining future research directions.

# Evaluating Current Design and Suggesting Methodologies for Improvement

This section evaluates methodological weaknesses and outlines key recommendations for improving the design of future acupuncture-neuroimaging studies in PSCI.

Our review of 12 neuroimaging research revealed that, in terms of design, three were non-RCTs, while nine were RCTs. However, none of these studies exhibited high methodological quality, primarily due to issues with result selection and biases from missing data. Therefore, to ensure the validity of neuroimaging trials investigating the effects of acupuncture in the treatment of PSCI, future research should adhere to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. <sup>54,55</sup> Notably, only two studies had sample sizes of 80 or larger, whereas 10 studies had sample sizes of 65 or smaller. In the field of neuroscience, the dependability and reproducibility of predicted outcomes may be jeopardized by limited sample sizes. <sup>56</sup> Therefore, increasing the sample size through standardized procedures is expected to improve the statistical significance of the research findings.

Variability in diagnostic criteria for PSCI was observed across studies. To enhance research quality, it is necessary to adopt a unified and stricter set of inclusion and exclusion criteria for defining PSCIs. Four studies employed the classification for cerebral vascular disease,<sup>51</sup> which are widely used for the clinical diagnosis of apoplexy. Three studies adopted the Chinese guidelines for cerebrovascular disease prevention and control.<sup>52</sup> However, the expert consensus on

the management of PSCI. 53 used by two studies for diagnosing PSCI, may offer a more specialized and comprehensive diagnostic approach than the general cerebrovascular criteria.

Although four comparison models were used, most studies focused solely on comparing acupuncture with other methods, without exploring factors such as variations in acupuncture insertion depth and other influences on efficacy. However, variations in acupuncturist qualifications, sensation of deqi, and the interval and length of treatments influenced outcomes. Hence, standardizing acupuncture protocols by establishing clear guidelines is crucial. Among the studies reviewed, only four provided descriptions of the acupuncturists involved, leaving information on the acupuncturists uncertain in other studies. Thus, to ensure consistency and reliability, it is recommended that each study use a single, skilled acupuncturist to conduct the treatments.

Despite the use of various assessment tools to comprehensively evaluate PCSI severity in the 12 studies, these tools have practical limitations that require further improvement. Specifically, regarding the assessment of overall cognitive function, the applicability of the MoCA is limited in illiterate and low-educated elderly individuals. To address this, the MOCA Basic, a revised version designed specifically for populations with low education or literacy levels, is recommended for future use in appropriate populations. To assess daily living abilities and functional independence, tools such as the MBI, ADL scale, and FIM provide comprehensive evaluations of patients' self-care abilities, social skills, and work capabilities. However, these instruments may overly rely on patient self-reports, neglecting the observations and judgments of assessors. Research indicates that self-report measurement methods may not fully reflect an individual's true capabilities, particularly when confronted with complex ADL tasks.<sup>57</sup> Consequently, future research should emphasize training and standardization of assessors to enhance the objectivity and accuracy of the assessments. Additionally, incorporating objective indicators, such as motion trajectory analysis, into the assessment system could offer a more comprehensive evaluation of patients' daily living abilities and functional independence.

Although all 12 studies unanimously reported statistically significant improvements in primary clinical outcomes (p < 0.05), limitations in safety reporting undermine the translational potential of these findings. Only one study explicitly documented the absence of acupuncture-related adverse events, 45 while the remaining 11 failed to report any safety monitoring data. This constitutes a methodological gap that contravenes CONSORT and STRICTA guidelines. 32,54 Future trials must prioritize safety documentation using standardized tools and report adverse events as a core outcome. Although acupuncture demonstrated statistically significant superiority in global cognition and functional independence compared to control groups, methodological heterogeneity across studies precluded quantitative data synthesis via metaanalysis, thereby compromising the interpretability of clinical implications. To address this limitation, future research should employ validated sham acupuncture controls and standardized acupoint regimens to ensure intervention consistency. Furthermore, variability in statistical thresholds and correction methods across studies (eg, GRF vs FDR vs AlphaSim) may affect the comparability of neuroimaging outcomes. Future consensus on standardized thresholds is critical for cross-study synthesis.

# Assessment of Neuroimaging Findings for PSCI After Acupuncture

This section synthesizes and interprets the key neuroimaging findings regarding the central mechanisms through which acupuncture may exert its therapeutic effects on PSCI.

The following neuroimaging techniques have been used to evaluate cerebral responses to acupuncture therapy for PSCI: fMRI, EEG, fNIRS, and MRS. fMRI was employed to detect alterations in the oxygenation levels of brain tissue, which reflect metabolic changes elicited by task-evoked neural activity or spontaneous neural fluctuations occurring in the absence of conscious cognition.<sup>58</sup> EEG, which directly detects electrical signals generated by neural activity in the cerebral cortex through electrodes, has been used to characterize post-stroke recovery mechanisms for motor, language, and cognitive deficits and to predict treatment responses to experimental therapies.<sup>59</sup> ERP, as a neuroelectrophysiological detection method with high temporal resolution, offers advantages such as real-time capability, objectivity, and broad accessibility, making it promising for diagnosing PSCI.<sup>60</sup> MRS measures neurotransmitter levels and examines changes in brain metabolites.<sup>61</sup> fNIRS monitors and assesses alterations in neuronal activity patterns by detecting optical absorption properties within cerebral tissue.<sup>62</sup>

Studies using fNIRS have demonstrated that acupuncture enhances cerebral hemodynamic responses in patients with PSCI, indicating it can improve brain function. Furthermore, MRS trials have revealed that acupuncture also positively impacts brain metabolism. Together, these findings provide mechanistic support for the potential use of acupuncture in treating PSCI. Studies employing task-state EEG, specifically analyzing ERPs associated with auditory and visual stimuli, have collectively revealed a significant positive impact of acupuncture on neural processing speed in patients with PSCI. In task-state EEG studies involving auditory stimuli, the P300 component has emerged as a crucial indicator of the brain's response speed and cognitive processing efficiency to auditory stimuli. As an ERP component closely associated with attention, memory, and decision-making processes, the shortened latency and increased amplitude of P300 reflect the enhanced auditory stimulus processing capabilities of the brain. In contrast, in task-state EEG studies involving visual stimuli, the N300 component serves as a key component for evaluating the brain's ability to process visual stimuli. Similar to the P300, the shortened latency and increased amplitude of the N300 are also indicative of accelerated visual stimulus processing speed and enhanced neural activity, suggesting that acupuncture not only improves auditory processing but also significantly enhances visual information recognition and processing efficiency.

The cingulate cortex (a key node in the DMN), parahippocampal gyrus, prefrontal cortex, and fusiform gyrus are among the common brain regions influenced by acupuncture in PSCI. These regions align with established pathological markers of post-stroke cognitive decline, as evidenced by neuroimaging findings demonstrating significantly reduced FC in the posterior cingulate cortex and altered FC patterns in the medial prefrontal cortex and hippocampus in stroke patients, especially those with PSCI, <sup>63</sup> while parahippocampal gyrus atrophy is linked to episodic memory deficits. <sup>64</sup> Our study found that patients with PSCI exhibit significantly reduced regional coherence in the anterior and posterior cingulate cortices, indicating impaired FC. This reduction in FC may affect cognitive functions such as attention, executive abilities, and memory, suggesting that cognitive impairments in patients with PSCI are associated with cingulate cortex dysfunction. 65 The parahippocampal gyrus, the central region of the medial temporal lobe, is vital for information storage and retrieval, and damage to this area may lead to memory impairment and other cognitive issues.<sup>66</sup> The prefrontal cortex is a crucial region of the brain responsible for higher-order cognitive functions, including executive function, attention, working memory, and decision-making.<sup>67</sup> One study has shown that patients with prefrontal cortex injuries may exhibit increased error rates and alterations in contrast perception thresholds during memory tasks.<sup>68</sup> Additionally, the interplay between the prefrontal cortex and basal nuclei constitutes a vital component of cognitive dysfunction following stroke. Research has demonstrated that supplementary connectivity routes within the neural framework, which govern effective communication between the prefrontal cortex and basal nuclei in patients with stroke, may aid in the recovery of cognitive impairments post-stroke.<sup>69</sup> The fusiform gyrus, the brain region vital for processing visual information and language comprehension, may experience impairments in visual memory and language processing following damage.<sup>70</sup> Therefore, these brain regions serve as primary targets for acupuncture in modulating PSCI.

Notably, neuroimaging analyses evaluating the neurological effects of acupuncture on PSCI have demonstrated the potential of acupuncture in modulating brain networks. The essential pathways implicated in acupuncture-induced improvement of PSCI can be outlined as follows: regions within the DMN (eg, precuneus, anterior cingulate, parahippocampal gyrus, hippocampus, and middle temporal gyrus), CEN (eg, anterior cingulate, inferior parietal lobule, and superior dorsolateral frontal gyrus), FPN (eg, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and inferior parietal lobule), and SN (eg, parahippocampal gyrus, insula, anterior cingulate, and thalamus) play pivotal roles in mediating the brain alterations observed in response to acupuncture-based interventions for PSCI. These brain networks, which align with the "triple-network model" (encompassing the DMN, CEN, and SN) implicated in cognitive processing across neurodegenerative conditions,<sup>71</sup> are closely associated with the pathological processes of PSCI. Altered connectivity within the DMN in patients with stroke may serve as the underlying basis for the reduction in episodic memory following stroke.<sup>72</sup> The DMN, associated with internalized cognitive processes,<sup>73</sup> plays a pivotal role in the neuropathophysiology of PSCI.<sup>65</sup> It is noteworthy that acupuncture's enhancement of DMN integrity parallels mechanisms observed in non-stroke cognitive disorders.<sup>74</sup> The CEN serves as a crucial executive control center in the brain and is responsible for a multitude of advanced cognitive functions, including working memory, attentional control, decision making, and emotional regulation.<sup>75</sup> The FPN is central to cognitive control and behavioral coordination, exhibiting

dynamic interactions with other functional brain networks. 76 One study indicated that patients with PSCI exhibit impaired FC centered on the FPN, suggesting that this incomplete FPN-centered connection may be the underlying pathological mechanism of PSCI, emphasizing the crucial significance of the FPN in cognitive control functions that are disrupted by stroke.<sup>77</sup> The SN dynamically coordinates the functions of other brain networks, ensuring effective allocation of attention and resources in response to internal and external challenges, thereby maintaining a balance between cognition and emotion.<sup>78</sup> Acupuncture exerts therapeutic effects on PSCI by targeting the DMN, CEN, FPN, and SN.

## Future Research Directions

This section outlines critical future research priorities to advance mechanistic understanding of acupuncture for PSCI.

The present investigation did not directly address the influence of acupuncture on specific cerebral regions in the context of PSCI. Hence, while research has explored acupuncture's general neurological effects, the precise mechanisms underlying its action in distinct brain areas remain elusive. Given the gaps in current research and the crucial role of specific brain regions, further studies are needed to clarify the neurological impacts of acupuncture on regions such as the cingulate cortex, parahippocampal gyrus, prefrontal cortex, and fusiform gyrus. These efforts will deepen our understanding of acupuncture's therapeutic mechanisms in PSCI, and may provide new perspectives on the effects of acupuncture on other neurodegenerative disorders or cognitive impairments.

Neuroimaging trials are crucial for elucidating brain function. Recent research has shown that acupuncture influences brain function, particularly within the triple-network model comprising the DMN, CEN, and SN, which are vital for cognitive processing and brain function.<sup>79-81</sup> However, no existing neuroimaging trials have specifically explored the impact of acupuncture on PSCI using this model. Therefore, designing specialized neuroimaging experiments to directly assess how acupuncture modulates triple-network activity in patients with PSCI will help reveal the specific neural mechanisms responsible for its beneficial effects.

Acupuncture has demonstrated efficacy in treating PSCI; however, the trials included in this SR focused solely on its sustained effects, without considering its immediate impact. Consequently, future studies should establish various time points (eg, immediately after acupuncture treatment, a few hours post-treatment, and a several days after treatment) to assess both immediate and sustained effects. This approach will provide a more comprehensive understanding of acupunctures' mechanisms and offer theoretical support for its clinical application.

Current neuroimaging studies have primarily focused on correlational relationships between acupuncture therapy and functional brain changes. 82,83 Most existing evidence relies on cross-sectional designs, which capture associations but cannot establish temporal or causal pathways. However, to gain deeper insights into how acupuncture therapy influences brain function, it is essential to determine whether these effects are directional or causal. Future studies should adopt longitudinal or interventional neuroimaging designs with repeated measurements to trace neuroplastic changes over time and better infer causality. This will enable more accurate assessment of the acupuncture's efficacy and provide a foundation for further exploration of its mechanisms. Furthermore, all 12 trials concentrated on structural or functional brain changes, using a single neuroimaging method. However, PSCI is a multifaceted disorder of the central nervous system, caused by stroke lesions that destroy the function of corresponding brain regions.<sup>84</sup> Therefore, integrating diverse methodologies is crucial. In particular, multimodal neuroimaging approaches are needed to capture the complexity of PSCI. Such approaches generate high-dimensional and complex datasets. To analyze these data effectively, machine learning algorithms play a particularly crucial role. These models are capable of extracting key features from vast amounts of multimodal data, which are related to both acupuncture treatment and changes in brain function. Through this process, underlying correlations and mechanisms can be revealed. 85,86 Accordingly, future research should not only collect and analyze multimodal data but also fully leverage machine learning to enhance data processing accuracy and efficiency, enabling more precise assessments of the mechanistic response to acupuncture treatment for PSCI.

# Strengths and Limitations

To our knowledge, this is the first SR focusing specifically on neuroimaging evidence for acupuncture in PSCI. Specifically, this SR highlights the brain regions and networks influenced by acupuncture, evaluates its effectiveness and safety, and analyzes correlations between clinical indicators and neuroimaging outcomes to provide practical insights for future clinical applications. However, this review had some limitations. First, despite extensive research efforts, the scarcity of studies meeting the inclusion criteria severely limits the scope and generalizability of our findings. Second, the use of varied analytical imaging methods in the included studies made it challenging to conduct a quantitative meta-analysis. Third, critical safety assessments were neglected. Fourth, heterogeneity restricted the synthesis to descriptive reporting rather than quantitative pooling, precluding effect size estimation. Finally, these studies focused solely on the effects of sustained acupuncture, neglecting its immediate impact, which limits our understanding of the comprehensive effects of acupuncture.

## **Conclusion**

Acupuncture for PSCI is effective, and its neural mechanisms may involve regulating cognition-related brain networks. However, to validate these findings beyond the limitations of current low-quality, small-sample studies, future research should integrate multi-modal imaging techniques within multicenter, large-sample, rigorously designed RCTs, while systematically collecting safety data.

## **Data Sharing Statement**

The original contributions presented in the study are included in the article/<u>Supplementary material</u>, further inquiries can be directed to the corresponding author, Zihan Yin.

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## **Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## **Disclosure**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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