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REVIEW

Resting-State fMRI Reveals the Neural Correlates of Acupuncture in the Treatment of Vascular Cognitive Impairment

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Abstract: Vascular cognitive impairment (VCI) represents a spectrum of cognitive deficits caused by cerebrovascular pathology, affecting multiple cognitive domains including memory, executive function, and attention. While pharmacological interventions for VCI remain limited, growing evidence supports acupuncture as an effective and safe therapeutic approach that improves both global cognition and activities of daily living in affected patients. Nevertheless, the neurobiological mechanisms underlying acupuncture's therapeutic effects require further elucidation. Resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as a powerful neuroimaging tool for investigating brain function in cognitive disorders. This technique detects blood oxygen level-dependent (BOLD) signals that reflect spontaneous neuronal activity during rest, providing insights into functional connectivity patterns and regional brain activity. In neurodegenerative conditions, rs-fMRI has successfully characterized alterations in functional networks and identified potential biomarkers of cognitive impairment. This review not only summarizes the existing evidence on the efficacy of acupuncture in treating VCI, but also synthesizes the current evidence from rs-fMRI studies to elucidate how acupuncture improves cognitive function in VCI patients through central mechanisms.

Keywords: vascular cognitive impairment, acupuncture, resting-state functional magnetic resonance, mechanism

Introduction

VCI represents a spectrum of cognitive disorders caused by diverse cerebrovascular pathologies, including atherosclerosis, white matter lesions, cerebral hypoperfusion, and ischemic or hemorrhagic stroke.[1] As an umbrella term, VCI encompasses conditions ranging from mild cognitive deficits to full dementia, predominantly resulting from vascular risk factors and cerebrovascular disease, either independently or in combination with neurodegenerative processes like Alzheimer's disease (AD). Globally, VCI accounts for 20–40% of dementia cases, ranking as the second most prevalent form after AD.[2] The clinical presentation typically involves progressive cognitive decline affecting memory, executive function, and visuospatial abilities, often accompanied by neuropsychiatric symptoms.[3] Notably, VCI is considered potentially reversible, particularly when identified early after stroke, making timely diagnosis and intervention crucial for potentially halting disease progression.[4,5] Current epidemiological data reveal the substantial global burden of dementia, with approximately 50 million cases worldwide in 2018 projected to surge to 152 million by 2050, posing significant challenges to healthcare systems globally.[1] Existing pharmacological treatments for dementia show limited effectiveness, providing mainly short-term symptomatic relief without modifying disease progression, while often causing adverse effects that compromise patients' quality of life.[5–7] The absence of clear molecular targets due to incomplete understanding of VCI's complex pathophysiology has hindered the development of effective treatments, creating urgent needs for therapies that can modify disease progression while improving patients' quality of life. Acupuncture, as a key component of Traditional Chinese Medicine (TCM), offers distinct advantages including safety, accessibility, clinical efficacy, and minimal side effects. Accumulating evidence demonstrates acupuncture's unique therapeutic benefits in managing VCI, with proven effectiveness in enhancing both cognitive function and daily living activities.[8–10] Numerous evidence-based studies have systematically validated both the

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clinical effectiveness and safety profile of acupuncture for VCI intervention,[8,10] though the precise molecular mechanisms underlying its therapeutic effects require further rigorous investigation.

Magnetic resonance imaging (MRI) is a conventional neuroimaging method that surpasses CT scans in detecting cerebral infarction, white matter high signal intensity, microhemorrhages, and brain atrophy, providing reliable support for clinical analysis.[11,12] Diagnostic outcomes of VCI imaging demonstrate that conventional MRI techniques offer advantages of speed and operational ease, leading to their extensive use in VCI research.[13,14] While conventional MRI excels at assessing disease extent and location, it faces challenges in establishing causal relationships between vascular lesions and cognitive impairment.[15] rs-fMRI, a specialized functional MRI technique, investigates the brain's resting-state networks by analyzing spontaneous BOLD signal fluctuations that reflect neuronal activity through neurovascular coupling mechanisms.[16,17] These BOLD signals originate from approximately 95% of the brain's energy consumption during neuronal activity, even at rest, and reveal synchronized oscillations among functionally connected brain regions. Rs-fMRI enables investigation of intrinsic brain networks and their functional organization during baseline states, without requiring specific tasks. This technique has become widely applied in studying neurological disorders, particularly for examining intrinsic brain activity and functional connectivity (temporal correlations between spatially remote neurophysiological events).[18,19] The advancement of rs-fMRI technology has significantly contributed to cognitive dysfunction neuropathology research, emerging as a key focus area.[20] This review examines rs-fMRI applications in acupuncture intervention for VCI, synthesizing existing literature to provide insights into acupuncture's neuropathological mechanisms in VCI treatment.

Application of Rs-fMRI Technique in VCI

General Imaging Characteristics of VCI

VCI demonstrates characteristic neuroimaging findings that are detectable through conventional MRI, including cerebral infarction, small vessel disease manifestations, hemorrhagic lesions, as well as white matter hyperintensities (WMHs) resulting from chronic ischemia or cerebral hypoperfusion.[7] Among these imaging markers, WMHs, patterns of brain atrophy, infarct burden, and hemorrhagic deposits have emerged as the most reliable diagnostic indicators for VCI.[1,21] Beyond structural abnormalities, advanced neuroimaging modalities can reveal functional alterations in VCI patients, such as disrupted resting-state functional connectivity, altered cerebral blood flow patterns, and metabolic changes in key cognitive networks, providing complementary pathophysiological insights.[22]

Common Clinical Indicators of Rs-fMRI

Common clinical indicators in rs-fMRI studies encompass diverse analytical approaches that primarily focus on functional differentiation and integration. These methods aim to identify distinctive functional changes occurring between different brain regions while providing imaging evidence of alterations spanning from localized brain areas to global network functionality. This facilitates deeper understanding of relevant neural network mechanisms. Key rs-fMRI indicators include regional homogeneity (ReHo), which measures local synchronization of spontaneous neural activity; functional connectivity (FC) that examines temporal correlations between spatially distinct regions; amplitude of low-frequency fluctuations (ALFF) quantifying spontaneous neural activity intensity; and degree centrality (DC) assessing network hub importance (Table 1). These metrics collectively serve as valuable tools for evaluating functional dynamics and interactions within brain networks, with demonstrated applications across various neurological conditions.

Regional Homogeneity (ReHo)

ReHo is a voxel-based metric that indirectly characterizes the synchronization of spontaneous neural activity within specific brain regions, demonstrating excellent test-retest reliability and high sensitivity in detecting spontaneous hemodynamic responses related to brain function.[34] Alterations in ReHo values can serve as neural markers to reveal the underlying pathogenesis of various conditions.[27,35] Notably, research has shown that acupuncture modulates ReHo values, increasing them in the anterior cingulate gyrus and left temporal gyrus while decreasing them in the left thalamus and right insula.[36] These brain regions significantly overlap with the default mode network, cognitive networks, and motor networks, suggesting acupuncture's central mechanism may involve coordinated modulation of neuronal activity across different brain network levels.[36] Studies have observed that mild cognitive impairment (MCI) is associated with abnormal ReHo values in relevant

Table 1 The Main Index Characteristics of Rs-fMRI (ALFF, ReHo, DC, FC) and Related Research Results

Index	Key Features	Key Findings	Limitations
ALFF	Measures spontaneous low-frequency fluctuations in BOLD signal; reflects intrinsic brain activity.	- The ALFF and fALFF may help detect the underlying pathological mechanism.[23] - Lower ALFF in the bilateral precuneus and higher ALFF in the bilateral anterior cingulate cortex, left insula and hippocampus.[24] -Increased PerAF in the right hippocampus and right thalamus.[25]	- Small sample sizes. - Heterogeneous preprocessing methods. - Limited longitudinal studies. -Vulnerable to head motion. - Requires large sample sizes for reliability. -Few studies on long-term effects. - Variability in thresholding methods. - Lack of standardization parameters.
ReHo	Assesses local synchronization of BOLD signals; indicates regional functional coherence.	- Reduced ReHo in posterior cingulate cortex and precuneus.[26] -High ReHo within temporo-limbic structures, low ReHo in frontal, parietal, posterior fusiform cortices, and caudate.[27] - ReHo in the left inferior parietal lobule was higher indicates the presence of a compensatory mechanism.[28]	
DC	Measures degree centrality of a voxel to the whole brain; reflects network hub activity.	-Lower DC values in the right middle frontal, precentral, and postcentral gyrus.[29] -Decreased DC in the left middle frontal cortex and bilateral middle cingulate cortex.[30] -Increased DC in the right middle frontal gyrus.[31]	
FC	Evaluates temporal correlations between brain regions; captures network-level connectivity.	-Decreased FC in the right inferior frontal gyrus, right middle frontal gyrus, bilateral pre-central gyrus, and right post-central /superior parietal lobules.[32] -Increased FC of the left supramarginal gyrus with right middle temporal gyrus, as well as brain-stem, cerebellum vermis with right middle frontal gyrus.[33]	

brain regions, making this metric valuable for understanding the condition.[26,28] For instance, Liu et al found MCI patients showed reduced ReHo in frontal, parahippocampal, and posterior cingulate areas compared to healthy subjects, while acupuncture increased ReHo in the precuneus and cingulate cortex, indicating acupuncture may modulate functional connectivity in specific brain regions to produce therapeutic effects.[37] Similarly, VCI patients exhibit significantly lower ReHo values in the superior and inferior frontal gyri, which correlate with poorer performance on cognitive assessments like Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), suggesting impairment in cognition-related brain regions.[38,39] Additionally, Orsolini et al observed significantly reduced ReHo values in the right insula, left superior frontal gyrus, and bilateral anterior cingulate gyrus among VCI patients compared to healthy controls, suggesting that cognitive decline in VCI may be associated with functional alterations in these brain regions.[40]

Functional Connections (FC)

FC serves as a powerful analytical method for assessing the strength of functional interactions between distinct brain regions by examining temporal correlations in BOLD signals. This approach captures global functional alterations in patients' brains and provides insights into neural mechanisms from a functional integration perspective, enabling the mapping of distant connections and detection of hemodynamic responses that may not be apparent through ReHo analysis.[38] Empirical research confirms the clinical relevance of FC in neurological interventions, as evidenced by Zhang et al's findings demonstrating enhanced connectivity between posterior and anterior cingulate gyri in post-stroke patients receiving acupuncture therapy, with observed neural patterns closely corresponding to Default Mode Network (DMN) regions known to be critical for memory consolidation and higher-order cognitive processing.[41,42] These findings suggest that acupuncture may enhance cognitive and motor functions by modulating DMN connectivity. Additional evidence shows increased FC values in the right middle temporal gyrus, brainstem, and right middle frontal gyrus post-acupuncture, with these changes significantly correlating with clinical improvements, indicating acupuncture's potential

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to stimulate somatosensory regions and enhance connectivity within sensory-motor and cognitive networks.[33] Notably, VCI research reveals significantly reduced FC between the right entorhinal cortex and frontal/precentral regions, with these FC values showing positive correlations with MoCA scores.[32] Such FC alterations may underlie the pathophysiology of cognitive impairment in VCI and could serve as early diagnostic markers for VCI. These collective findings highlight FC's utility in understanding network-level disruptions in neurological conditions and its potential as both a diagnostic tool and therapeutic target.

Amplitude of Low Frequency Fluctuations (ALFF)

The ALFF is a neuroimaging metric that quantifies the intensity of spontaneous brain activity during the resting state by calculating the square root of the power spectrum within a specific frequency range (typically 0.01–0.08 Hz). This measure directly reflects the strength of BOLD signals at the voxel level, providing an index of synchronized, spontaneous neuronal activity within regional brain areas.[43,44] Extensive research in both animal models and human studies has validated ALFF as a reliable tool for detecting alterations in regional spontaneous neuronal activity.[45–47] Decreased ALFF values in a given brain region often indicate functional impairment, whereas increased ALFF may reflect either dysfunction or compensatory neural activation.[48] Fundamentally, ALFF offers essential insights into regional neural activity dynamics, elucidating both normative and pathological brain functioning, thereby serving as a valuable tool for comprehending cerebral activity in healthy and diseased states. Further supporting its physiological relevance, studies have demonstrated that reduced BOLD signal intensity correlates with neuronal inhibition, linking ALFF directly to localized brain activity.[49,50] For instance, Yang et al's study demonstrated significantly elevated amplitude of ALFF in the left hippocampus of dementia patients, a region exhibiting substantial overlap with the DMN that is critically involved in memory consolidation and retrieval processes.[23] This finding suggests heightened spontaneous DMN activity as a potential mechanism for cognitive maintenance. Clinical studies in VCI have consistently identified ALFF abnormalities within DMN-associated regions. Yi et al reported decreased ALFF in the medial prefrontal cortex alongside increased ALFF in the right posterior cingulate cortex/precuneus in VCI patients compared to healthy controls.[51] Similarly, Li et al found significantly lower ALFF values in DMN hubs, including the bilateral precuneus, right angular gyrus, and right medial frontal gyrus, with these reductions independently correlating with lower MoCA scores.[52] Additionally, Liu et al documented elevated ALFF in the bilateral anterior cingulate cortex, left insula, and hippocampus among VCI patients, with insular ALFF showing a strong negative correlation with MoCA and MMSE scores.[24] Collectively, these findings implicate dysregulated spontaneous DMN activity as a potential biomarker and mechanistic contributor to cognitive decline in VCI.

To address the susceptibility of ALFF to physiological noise, Zou et al developed fractional amplitude of low-frequency fluctuations (fALFF), calculated as the ratio of ALFF to the total power within a specific low-frequency band.[43] While fALFF demonstrates improved sensitivity and specificity in detecting spontaneous brain activity by reducing interference from physiological signals like venous sinus and cerebrospinal fluid compared to ALFF,[23,53] it remains vulnerable to head motion artifacts.[43] Both metrics are complementary in investigating cognitive impairment mechanisms.[54] The more recent Percent amplitude of fluctuation (PerAF) quantifies BOLD signal fluctuations as a percentage of mean signal intensity per timepoint, showing superior test-retest reliability versus ALFF/fALFF.[55] PerAF effectively detects regional activity changes and is widely applied in cognitive impairment research.[56] Xu et al reported elevated PerAF in the right hippocampus/thalamus in cognitively impaired patients, with negative correlations between MMSE scores and PerAF in the right hippocampus/inferior temporal gyrus/left thalamus, suggesting compensatory neural mechanisms during early cognitive decline.[25] These findings collectively demonstrate that while fALFF improves upon ALFF's limitations regarding physiological noise, PerAF offers enhanced reliability for studying spontaneous brain activity alterations in conditions like Alzheimer's disease and mild cognitive impairment.

Degree Centrality (DC)

DC is a graph-theoretical method that evaluates diverse patterns of intrinsic brain connectivity by quantifying the importance of each node within the brain network at the voxel level. The fundamental principle of DC is that nodes with higher values represent more crucial network hubs, indicating greater information integration capacity.[57] Unlike ALFF which measures local neural activity, voxel-wise DC provides a comprehensive assessment of whole-brain functional connectivity during rest. DC also differs from ReHo approaches by revealing relationships between local activity and global network organization.[58] A key advantage of DC is its ability to analyze connectivity without requiring predefined regions of interest, enabling unbiased examination of network topology across the entire brain.[59–61] This characteristic makes DC particularly valuable for investigating disease-related alterations in brain network node.[62] DC has been widely applied to study neurobiological mechanisms in various conditions, with reported abnormalities in AD, Parkinson's disease, and other neurodegenerative disorders.[29,31,63,64] For instance, studies have shown DC reductions in frontal and cingulate regions in mild cognitive impairment patients, with values increasing following treatment.[30] Similarly, decreased DC in default mode network regions like the angular gyrus and precuneus has been associated with cognitive decline in vascular cognitive impairment.[52] These findings demonstrate DC's utility as a sensitive biomarker for understanding network-level dysfunction in cognitive disorders. The method's ability to map whole-brain connectivity patterns at high spatial resolution continues to provide important insights into the pathophysiology of neurological and psychiatric conditions.

Neuroimaging Performance of VCI in Rs-fMRI

rs-fMRI proves valuable for both mapping intrinsic brain function in healthy individuals and detecting disease-related alterations, providing crucial insights into functional connectivity patterns.[65–67] This technique enables investigation of neuromodulation mechanisms in clinical treatments,[68–70] while demonstrating particular sensitivity in identifying neuronal activity abnormalities across neurodegenerative disorders.[71] Given the established correlation between VCI neuroimaging markers and cognitive deficits, rs-fMRI has been successfully applied to both early VCI diagnosis and mechanistic studies of its central pathways.[32,72] Furthermore, rs-fMRI assessments of local brain function (ALFF/ReHo) and network connectivity serve as valuable biomarkers for predicting cognitive impairment progression in VCI patients. Studies demonstrate distinct functional alterations in VCI, including: 1) reduced ALFF in parietal/prefrontal regions with concurrent increases in anterior cingulate and middle frontal gyri; 2) elevated ReHo in posterior cerebellum and supra-parietal/occipital regions; 3) progressive network connectivity disruption correlating with cognitive decline severity. Notably, ReHo abnormalities in cingulate cortex show significant associations with MoCA scores and executive dysfunction, revealing region-specific neural correlates of cognitive impairment in VCI.[73,74] These findings collectively highlight rs-fMRI's utility in characterizing functional brain changes underlying VCI progression.[75,76] Another rs-fMRI study revealed significant differences in ALFF values between VCI patients and healthy controls. Specifically, ALFF values were decreased in the posterior cingulate cortex/precuneus but increased in the temporal region. Notably, executive function scores in VCI patients positively correlated with ALFF values in the left prefrontal lobe, suggesting a link between regional functional impairment and clinical manifestations that could aid in VCI screening.[77] Chen et al further demonstrated that VCI patients exhibited reduced BOLD signals in the left anterior cingulate cortex and right parahippocampal gyrus, alongside increased signals in the left caudate nucleus, right frontal lobe, and superior temporal/parietal gyri.[78] These DMN-related BOLD signal changes may provide neuroimaging markers for VCI identification and help differentiate it from amnestic mild cognitive impairment.[78]

In summary, this study highlights the utility of rs-fMRI in identifying functional connectivity patterns associated with cognitive impairment in VCI patients. The technique reveals distinct neural activity signatures while providing mechanistic insights into VCI pathophysiology through brain network analysis.

Application of Acupuncture Therapy in VCI

Acupuncture therapy has emerged as a significant intervention for VCI, with growing clinical and preclinical evidence supporting its efficacy. As a safe, non-pharmacological intervention without toxic side effects, acupuncture represents an important complementary treatment option for VCI spectrum disorders ranging from mild impairment to vascular dementia.[79]

Acupuncture demonstrates significant therapeutic potential for VCI, with multiple studies confirming its efficacy in improving cognitive function.[80] Systematic reviews reveal that acupuncture interventions, particularly when combined with conventional therapies, show superior outcomes in improving MMSE and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) scores compared to pharmacological treatments alone.[81] The therapeutic mechanisms appear multifaceted, involving enhanced cerebral blood flow, modulation of oxidative stress pathways, and improved synaptic plasticity. Importantly, meta-analyses have consistently established the safety profile of acupuncture for VCI treatment while demonstrating its capacity to stimulate neural pathways and optimize cerebral metabolic responses.[82] These findings collectively suggest acupuncture represents both an effective and safe intervention for cognitive improvement in VCI patients. Furthermore, a randomized controlled multicenter trial demonstrated that patients with VCI showed significantly greater reductions in ADAS-Cog scores after 3 months of acupuncture treatment compared to those receiving pharmacotherapy alone.[9] The mean change from baseline to 6 months further highlighted the superior benefits of acupuncture intervention. These results indicate that acupuncture may serve as an effective complementary and alternative treatment for VCI, potentially offering comparable or even better outcomes in improving cognitive function and daily living activities. Randomized controlled trials demonstrate acupuncture's efficacy in improving cognitive function in VCI patients. Studies show cognitive improvements emerge by 4–8 weeks of treatment, with benefits persisting up to 16 weeks.[83] The therapeutic effects appear to diminish by 32 weeks, suggesting extended treatment may be necessary for sustained benefits. In another study by Zeng et al, VCI patients showed notable increases in Fugl-Meyer assessment, Barthel index, and MoCA scores after 4 and 8 weeks of acupuncture.[84] By 8 weeks, their Barthel index and MoCA scores exceeded those of controls, indicating enhanced cognitive function, daily mobility, and quality of life.[84] These findings highlight acupuncture's potential as an adjunct therapy for VCI management.

Animal studies have provided crucial insights into acupuncture's mechanisms for treating VCI. Research demonstrates that acupuncture improves cognitive function by protecting hippocampal long-term potentiation (LTP), reducing neuroinflammatory markers, and enhancing glucose metabolism in the hippocampus.[85–87] Electroacupuncture specifically shows neuroprotective effects by modulating inflammatory pathways and improving synaptic plasticity in VCI models.[88] These findings collectively suggest acupuncture's multifactorial action in alleviating VCI through neuroprotection, anti-inflammatory effects, and metabolic regulation.

In conclusion, acupuncture serves as a beneficial adjunct to standard therapies, offering a safe, well-tolerated, and side-effect-free option for patients. It shows promise as a complementary and alternative treatment for drug-intolerant VCI cases. Critically, earlier intervention correlates with greater potential for cognitive recovery, underscoring the importance of timely implementation for optimal therapeutic outcomes in VCI management.[89]

Exploring the Central Mechanism of Acupuncture by Rs-fMRI Technology

Neuroimaging has become an indispensable tool for investigating the central mechanisms of acupuncture, offering systematic insights into its precise mode of action and acupoint specificity. Current neuroimaging research in acupuncture primarily examines four key aspects: 1) brain responses to acupoint stimulation; 2) neural pathways mediating acupuncture effects; 3) visualization of acupuncture-brain connectivity; and 4) objective assessment of therapeutic outcomes.[90–92] Among available neuroimaging modalities, rs-fMRI has emerged as particularly valuable due to its non-invasive nature, excellent safety profile, high spatial-temporal resolution, and strong reproducibility. This technique enables novel investigations of acupuncture's influence on functional brain networks and interregional communication, providing revolutionary quantitative methods to characterize how acupuncture modulates neural connectivity patterns.[93,94]

The Proposed Central Mechanism of Acupuncture Effect

Acupuncture exerts its therapeutic effects by amplifying localized stimuli through specific acupoints, which are then transmitted via the body's meridian system to regulate systemic networks. This process involves complex signal transduction and modulation across multiple physiological networks, ultimately activating functional networks at various targets to restore homeostasis.[95] The therapeutic outcome manifests as counteracting disease networks, thereby achieving preventive and symptomatic relief effects.[95] Neuroimaging studies, particularly rs-fMRI, have demonstrated that acupuncture's effects are primarily mediated through central nervous system modulation.[96,97] The central nervous system coordinates neural activity across extensive cortico-subcortical networks, with notable involvement of limbic-bilateral cortical regions, subcortical structures, and the hippocampus.[98–100] Key regions implicated in acupuncture's mechanism include the posterior limbic system and subcortical areas.[101] Meta-analyses of rs-fMRI data reveal that acupuncture stimulation typically activates sensory-motor cortical networks, particularly the insula, thalamus, and anterior cingulate gyrus.[102] The limbic-parabrachial neocortical network (LPNN), including the medial prefrontal cortex, caudate nucleus, amygdala, and posterior cingulate gyrus, typically exhibits deactivation patterns.[102] These differential activation patterns reflect acupuncture's multidimensional modulation of cognitive, emotional, and pain processing networks. Further investigations demonstrate that acupuncture influences neural activity across diverse brain regions including the cerebellum, while modulating functional connectivity patterns.[103] Characteristic changes include reduced connectivity in the DMN alongside increased connectivity in the right posterior cerebellar lobe, left parahippocampal gyrus, thalamus, and motor areas.[103] These findings collectively suggest that acupuncture engages intrinsic brain networks to produce its multifaceted regulatory effects, with particularly pronounced effects observed in individuals with existing pathological imbalances. The hemodynamic responses induced by acupuncture reveal its capacity to modulate the LPNN, while also exerting regulatory effects on the hippocampus, somatosensory cortex, hypothalamus, insula, and brainstem. This comprehensive neuromodulation underscores acupuncture's potential to restore physiological balance through central nervous system mechanisms.[104–106]

Research has demonstrated that acupuncture may have more pronounced effects in individuals with pathological imbalance compared to healthy subjects.[107,108] Studies have shown acupuncture can enhance functional connectivity in disease-affected brain regions like the precuneus and cingulate cortex in MCI patients, potentially restoring their functionality.[37] The therapeutic effects of acupuncture appear related to its ability to maintain neural equilibrium, suggesting a mechanism for its intervention in MCI.[37] Neuroimaging evidence indicates acupuncture activates specific brain regions (hippocampus, caudate nucleus, cerebellum) that correlate with cognitive function in AD patients.[109] These regions overlap with areas affected by AD pathology, suggesting acupuncture may provide therapeutic benefits by modulating these neural circuits. Furthermore, different acupoint combinations appear to selectively activate distinct brain regions, highlighting the importance of optimal acupoint selection for AD treatment.[109] rs- fMRI studies reveal acupuncture modulates key networks involved in dementia pathophysiology, including the prefrontal cortex and medial prefrontal regions.[110] Acupuncture enhances connectivity within cognitive-related networks while also influencing sensorimotor and limbic networks.[111,112] These findings suggest acupuncture's therapeutic effects may stem from its ability to regulate neuroplasticity across multiple functional brain networks.[113]

In summary, acupuncture modulates brain functional networks in cortical and subcortical limbic structures through multi-target and multi-level coordination. This network regulation underlies acupuncture's therapeutic effects on cognitive function in VCI. Therefore, studies highlight its ability to modulate brain functional networks, particularly in the hippocampus and DMN, which are critical for cognitive function.[114,115] For instance, rs-fMRI studies reveal that acupuncture can improve the cognitive function of vascular cognitive impairment by increasing the functional connectivity of the DMN and enhancing cerebral blood flow.[9,89] These findings support acupuncture's inclusion in multimodal clinical protocols for VCI, especially as a non-pharmacological adjunct. In addition, by identifying target brain regions, rs-fMRI may guide precision acupuncture protocols, such as selecting specific acupoints for patients with distinct neural signatures.[79,115] However, rs-fMRI research on VCI remains preliminary, with clinical translation challenges. More rigorous studies are needed to validate these neuroimaging findings and establish clinical efficacy. Thereby promoting the combination of acupuncture's neuromodulatory effects with rs-fMRI biomarkers to optimize VCI management.

Limitations

According to the contents of Tables 1 and 2 and the reports in the existing literature, there may be several major limitations in the current rs-fMRI research on acupuncture treatment for VCI: 1) Sample size issues: Most studies suffer from small sample sizes without reporting sample consistency. 2) Methodological variability: Significant inconsistencies exist in stimulation protocols (points/positions), patient conditions, rs-fMRI parameters, acquisition sequences, and analysis methods. Head motion artifacts during scanning notably confound FC measurements by introducing spatiotemporal noise and reducing signal quality. The technique's inherent limitations include low sampling frequencies restricting high-frequency neural dynamics detection, spatial-temporal resolution trade-offs, and inability to discern causal interactions from correlational FC. 3) Unreported acupuncture experience: Studies frequently fail to document subjects' prior acupuncture exposure, potentially affecting treatment response variability. These constraints render existing findings preliminary, necessitating: larger multi-center RCTs with standardized protocols, advanced motion correction, multimodal imaging integration, and longitudinal designs tracking network evolution. Future research should prioritize sample

Table 2 Current Important Studies on the Application of fMRI in Vascular Cognitive Impairment

Study	Study Type, MRI Method, Sample Size	Limitations	Results
[89] Electroacupuncture improves vascular cognitive impairment no dementia: A Randomized Clinical Trial	Randomized Clinical Trial (Interventional); fMRI functional connectivity analysis; 140	Short follow-up period; lack of sham acupuncture control group	Acupuncture improved cognitive function, increased functional connectivity in DMN, and enhanced cerebral blood flow in VCI patients.
[116] Differential Abnormality in Regional Brain Spontaneous Activity and Functional Connectivity in Patients of Non-Acute Subcortical Stroke With Versus Without Global Cognitive Functional Impairment	Observational study; fMRI identifies regional brain spontaneous activity and functional connectivity; 62	Small sample size; cross-sectional design; lack of longitudinal follow-up	Unique patterns of brain activity and connectivity in patients with cognitive impairment, shedding light on potential neural mechanisms; the left gyrus rectus may be a potential neural regulatory stimulus target in clinical applications.
[117] Effects of computerized cognitive training on functional brain networks in patients with vascular cognitive impairment and no dementia	Randomized controlled trial (Interventional); fMRI identifies the changes in brain functional networks; 60	The relatively short follow-up period; small sample size	Decreased FC within the default mode network; increased functional coupling between the DMN and sensorimotor network and between the language network and executive control network.
[118] Frequency-dependent white-matter functional network changes associated with cognitive deficits in subcortical vascular cognitive impairment.	Observational study; rs-fMRI with frequency-dependent white-matter functional connectivity analysis; 36	Cross-sectional design; potential confounding factors not fully controlled; small sample size	Frequency-specific white-matter functional network disruptions; specific white-matter tracts or networks may show altered connectivity in relation to different cognitive domains.
[119] Concurrent brain structural and functional alterations related to cognition in patients with cerebral small vessel disease	Observational cross-sectional study; rs-fMRI to calculate ALFF; 65	Cross-sectional design limits causal inferences; Limited information about clinical assessment methods	Specific correlations between imaging changes and cognitive deficits; Functional network alterations.
[120] Cortical structural degeneration and functional network connectivity changes in patients with subcortical vascular cognitive impairment.	Observational study; functional network connectivity analysis of rs-fMRI; 46	Cross-sectional design limits causal interpretation; Limited sample size	Lower network connectivity between the visual network and sensorimotor network, positively correlated with information processing speed.
[52] Aberrant Amplitude of Low-Frequency Fluctuation and Degree Centrality within the Default Mode Network in Patients with Vascular Mild Cognitive Impairment.	Observational case-control study; rs-fMRI analyzing ALFF and DC; 31	Cross-sectional design limits causal interpretation; small sample size; confounding factors of age, gender, comorbidities, lifestyle, and genetic were not considered	Decreased brain activity within the DMN, including the bilateral precuneus, angular gyrus, and medial frontal gyrus; the decreased ALFF was independently associated with lower MoCA scores; aberrant spontaneous brain activity in the DMN might subserve as a potential biomarker.
[121] Altered Neurovascular Coupling in Subcortical Ischemic Vascular Disease	Observational case-control study; combined ReHo and CBF; 54	Lack of longitudinal data to assess progression; does not comprehensively consider other aspects of brain function and structure	Decreased global ReHo-CBF coupling in the left insula, right middle temporal gyrus, right precuneus, left precentral gyrus, and left inferior parietal lobule.

(*Continued*)

Table 2 (Continued).

Study	Study Type, MRI Method, Sample Size	Limitations	Results
[122] Altered static and dynamic indices of intrinsic brain activity in patients with subcortical ischemic vascular disease: a resting-state functional magnetic resonance imaging analysis	Observational case-control study; rs-fMRI analyzing ALFF and dALFF; 58	Potential motion artifacts in dynamic analysis; Lack of longitudinal follow-up data	Increased ALFF in right superior frontal gyrus; decreased dALFF in right precuneus and left dorsal anterior cingulate cortex; ALFF value in left ANG of was correlated with the score of delayed memory scale.

sizes adequate for detecting small-medium effects, controlled acupuncture administration, and clinical correlation analyses to establish acupuncture as personalized VCI therapy.

In fact, most acupuncture research originating from China faces several important limitations. First, significant genetic and ethnic differences exist across populations. Diverse ethnic groups have distinct genetic backgrounds that can affect physiological responses and neural plasticity. Since existing studies primarily involve Chinese populations, their findings may not generalize to other ethnic groups. This reduces external validity, as the neural mechanisms of acupuncture's effects on VCI may vary by genetic background. Second, cultural and healthcare system differences substantially influence outcomes. As a core component of TCM, acupuncture is deeply embedded in China's cultural and medical practices. There, it enjoys widespread acceptance within the healthcare system, with unique clinical protocols, acupoint selection methods, and needle techniques. These culturally specific elements, including TCM's meridian theory that guides acupoint selection, differ from western medical paradigms. Consequently, the therapeutic effects and neural responses observed in Chinese studies may not translate to other cultural and healthcare contexts. Finally, the geographical concentration of studies in China limits opportunities for cross-validation. Replicating findings across diverse populations and regions is crucial for verifying scientific conclusions. Future research should prioritize international collaboration and include more diverse populations to address these limitations and strengthen the evidence base.

Conclusion and Perspective

VCI is intricately associated with multiple pathophysiological processes including inflammation, coagulation cascade activation, endothelial dysfunction, and neurovascular unit impairment.[123] These processes interact dynamically during disease progression, contributing to heterogeneous clinical presentations that highlight the need for personalized therapeutic approaches. rs-fMRI has emerged as a powerful tool for investigating brain functional alterations in VCI, enabling the detection of spontaneous neural activity across microscopic, mesoscopic and whole-brain levels.[124,125] This technique not only reveals functional activities in the brain affected by VCI but also provides a new approach to explore the mechanisms of acupuncture intervention. Acupuncture may modulate multiple central nervous system pathways to improve neurovascular coupling, enhance brain function, and promote neuroplasticity.[9,126] The neuroimaging biomarkers derived from rs-fMRI could reflect injury patterns resulting from complex interactions among various pathophysiological processes. Importantly, acupuncture's therapeutic effects on VCI may involve modifications across multiple biological processes along the VCI pathophysiological cascade, emphasizing the need to identify key biological pathways and prognostic biomarkers for optimizing acupuncture treatment strategies.

Current functional imaging research on VCI remains in its nascent phase, with no comprehensive rs-fMRI studies elucidating acupuncture's therapeutic mechanisms for VCI. The lack of disease-modifying treatments may stem not only from therapeutic protocol limitations but also from insufficient methodological rigor in clinical trial design. Future research should integrate advanced experimental models with standardized methodologies, incorporate precision neuroimaging techniques to identify disease progression biomarkers, and employ machine learning approaches to elucidate the central mechanisms underlying acupuncture's therapeutic effects. These developments should substantially improve our ability to identify effective VCI treatments and advance toward personalized acupuncture therapy approaches.

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Author Contributions

All authors read and approved the final manuscript. 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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