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REVIEW

Acupuncture for Ischemic Stroke: A Critical Evaluation of Biological Mechanisms and Methodological Challenges

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Abstract: Ischemic stroke (IS) is a leading cause of long-term disability worldwide, creating an urgent need for effective adjunctive therapies to complement conventional treatments. Acupuncture has emerged as a widely investigated intervention for post-stroke recovery. This review provides a critical evaluation of the proposed biological mechanisms underlying acupuncture's effects in IS. We synthesize evidence from preclinical and clinical studies on its potential to promote the dynamic repair of the neurovascular unit (NVU), modulate intercellular communication, improve cerebral hemodynamics, enhance angiogenesis, and support neurorestoration. While a significant body of preclinical evidence suggests multifaceted benefits, we highlight a critical translational gap and the methodological limitations that currently temper clinical certainty. Key challenges include the heterogeneity of treatment protocols, the complexity of sham controls, and a frequent lack of objective biomarkers. Consequently, we conclude by outlining a clear agenda for future research, emphasizing the need for protocol standardization, rigorous large-scale randomized controlled trials (RCTs), and the integration of biomarkers to bridge the gap between proposed mechanisms and validated clinical outcomes. This critical perspective aims to guide future research toward definitively establishing acupuncture's role in the stroke care continuum.

Keywords: acupuncture, ischemic stroke, pathogenesis, neurovascular unit, recovery, angiogenesis

Introduction

Ischemic stroke (IS), caused by interrupted cerebral blood supply leading to brain cell death from oxygen and nutrient deprivation, is primarily due to thrombus or embolus blocking a cerebral artery.[1] As the most common stroke type, IS is a leading cause of long-term disability and a major global cause of death.[2] Symptoms vary with infarct size and location, potentially including sudden unilateral weakness, speech issues, vision problems, and balance difficulties.[3]

Timely treatment significantly improves prognosis. Current primary IS treatments, such as pharmacological thrombolysis and mechanical thrombectomy, focus on rapidly restoring cerebral blood flow to minimize neurological damage.[4] Proactive risk factor management and lifestyle modifications are crucial for reducing IS incidence and recurrence.[5]

Despite progress in acute IS management, many patients still face persistent neurological deficits, slow rehabilitation processes, and chronic complications, leading to a decline in long-term quality of life. This situation urgently requires innovative treatment strategies to enhance the effectiveness of conventional treatments. Among many alternative and adjuvant therapies, acupuncture, a key component of traditional medicine, has emerged as a widely investigated adjunctive therapy. While traditionally believed to regulate "qi" and "blood", modern scientific inquiry seeks to understand its biological underpinnings and clinical utility. A growing body of research explores its potential mechanisms of action and clinical efficacy, particularly in neurological rehabilitation. This review aims to critically evaluate the existing

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evidence for the mechanisms of acupuncture in IS treatment, highlight the strengths and limitations of current research, and provide a balanced perspective on its potential role in clinical practice.

Epidemiology

IS is a leading global cause of disability and death, with rising incidence and mortality, particularly in low- and middle-income countries, which bear 86% of the global stroke burden.[6] Annually, approximately 13.6 million new stroke cases occur worldwide, 87% of which are IS.[7] By 2019, global IS cases had risen significantly, with incidence, prevalence, and mortality rates reaching new highs; for instance, global stroke cases increased by 70% and deaths by 43% from 1990 to 2019.[8]

IS prevalence and mortality vary significantly by age, gender, and region. It predominantly affects the elderly, with global data consistently showing a higher incidence in older populations, especially with risk factors like hypertension and diabetes.[9]

While men generally have a higher IS incidence, women often experience more severe outcomes and higher mortality rates post-stroke, possibly due to increased susceptibility to depression and psychological issues during recovery.[10]

Clinical Manifestations

The clinical manifestations of IS vary with infarct size and location. Sudden unilateral limb weakness or numbness is a primary sign, affecting the face, arm, and leg on one side, leading to facial drooping, arm weakness, or difficulty walking. Sensory abnormalities like numbness are also common, resulting from disrupted blood supply to motor and sensory brain regions, causing hypoxia and neuronal functional loss.[11]

Language impairments stem from interrupted blood supply to language-processing brain areas. Common aphasias include expressive (Broca's area damage, fluent speech impaired but comprehension preserved), receptive (Wernicke's area damage, fluent but meaningless speech), conduction (arcuate fasciculus damage, impaired repetition), and anomia (difficulty naming objects due to angular gyrus damage). The type and severity depend on lesion location and extent, necessitating timely diagnosis for prognosis improvement.[12]

Patients may experience sudden blurred vision or complete vision loss in one or both eyes, often as homonymous hemianopia, caused by damage to the occipital lobe or visual cortex. Visual spatial neglect, an inability to perceive part of the visual field, can result from parietal lobe damage. Severity correlates with the affected brain region and extent of damage; eg, occipital lobe lesions can cause homonymous hemianopia, while inferior occipital lobe damage may lead to quadrant anopia.[13]

Balance and coordination difficulties primarily arise from interrupted blood supply to the cerebellum or other motor control regions. Cerebellar damage affects fine motor control and postural stability, causing unsteady gait, dizziness, and walking difficulties. Lesions in other areas like the brainstem and basal ganglia can lead to generalized motor impairments, affecting overall coordination and movement, such as rigidity, bradykinesia, or tremors from basal ganglia damage.[14]

Pathogenesis

Disruption of the Neurovascular Unit (NVU)

The neurovascular unit (NVU) - composed of neurons, glial cells, endothelial cells, pericytes, basement membrane, and extracellular matrix - is the foundation of brain function, maintaining blood-brain barrier (BBB) integrity, regulating cerebral blood flow, and supporting neuronal homeostasis.[15]

However, IS rapidly destroys this unit, exacerbating damage and hindering recovery.[16] The disruption of the BBB is an early key consequence: ischemia-reperfusion leads to endothelial cell dysfunction and death, reduces or redistributes tight junction proteins, and increases paracellular permeability.[17] Meanwhile, activated matrix metalloproteinases (MMPs), especially MMP-9, degrade the basement membrane, further disrupting the integrity of the BBB. This destruction allows neurotoxic blood components and peripheral immune cells to enter the brain parenchyma, exacerbating neuroinflammation and vascular edema.[18]

Furthermore, beyond increased permeability, endothelial cells become dysfunctional and activated. They upregulate adhesion molecules, facilitating leukocyte adhesion and transmigration into the brain tissue, thereby significantly contributing to post-ischemic inflammation. Endothelial cell swelling and apoptosis also worsen microvascular occlusion and perfusion deficits.[19] This disruption extends to pericytes, which are crucial regulators of capillary diameter and blood flow. Following IS, pericytes can constrict, contributing to the "no-reflow" phenomenon, or they may detach from the vessel wall and die, leading to further destabilization of the microvasculature and increased BBB permeability.[20]

Astrocytes undergo significant changes, with cytotoxic edema leading to swelling that can compress capillaries.[21] Reactive astrogliosis follows, potentially forming detrimental glial scars and dysregulating AQP4 water channels, contributing to edema.[22] Detachment of astrocyte endfeet further compromises BBB integrity and glymphatic clearance.[23] Simultaneously, microglia, the brain's resident immune cells, rapidly activate. While potentially protective initially, prolonged or excessive activation (often towards a pro-inflammatory M1 phenotype) releases cytotoxic mediators (ROS, NO, TNF-α, IL-1β, IL-6), directly injuring NVU components, perpetuating BBB damage, and recruiting more immune cells, creating a vicious cycle of neuroinflammation.[24]

Ultimately, while neurons are primary targets of ischemic injury due to energy failure and excitotoxicity, their demise is intricately linked to NVU failure. The resulting compromised microenvironment—with BBB leakage, inflammation, edema, and reduced perfusion—directly contributes to neuronal dysfunction and various death pathways.[25]

Hemodynamic Disorders

Hemodynamic failure, typically from cerebral artery stenosis or occlusion, critically reduces cerebral blood flow (CBF), initiating ischemic injury.[26] Major causes include acute disruptions from atherosclerosis or cardiogenic embolism,[27] progressive hypoperfusion from cerebral small vessel disease (CSVD) linked to chronic conditions like hypertension and diabetes,[28,29] and episodes of systemic hypoperfusion.[30]

Crucially, these diverse hemodynamic insults converge on the vascular endothelium, where altered shear stress and other mechanical forces trigger profound mechanotransduction events. This endothelial mechanosensing, alongside the release of damage-associated molecular patterns from stressed tissue, orchestrates the early neurovascular response. Key adaptive (and sometimes maladaptive) processes include the release of factors like SDF-1α[31] and HGF,[32] which attempt to drive neovascularization and endothelial repair in the ischemic penumbra. Concurrently, the local inflammatory milieu is shaped by cytokines such as IL-4[33] and chemokines like MIP-1β,[34] influencing immune cell dynamics.

The specific nature of the hemodynamic disturbance—whether it's the abrupt, severe flow cessation in large vessel occlusion versus the chronic, fluctuating hypoperfusion in CSVD—differentially activates these mechanosensitive pathways and dictates the subsequent molecular signature. Consequently, the intensity and profile of the immune and repair factor response vary significantly by stroke etiology.[35] For instance, acute IS studies reveal that etiologies like large artery atherosclerosis and cardiogenic embolism often induce more pronounced inflammatory responses, evidenced by higher plasma HGF and SDF-1α (reflecting both injury extent and repair attempts) and lower IL-4, when contrasted with conditions such as spontaneous carotid artery dissection which may present a distinct hemodynamic and inflammatory footprint.[36] This suggests that the initial "mechanical hit" to the vasculature not only defines the ischemic core but also primes the specific trajectory of neuroinflammation and repair. Understanding these etiology-specific, mechanotransduction-driven responses is key to tailoring future neuroprotective and restorative strategies.

Arterial Dissection

Arterial dissection is a significant cause of IS, particularly in younger individuals, involving a tear in the arterial intima that allows blood to enter the arterial wall.[37] This creates a false lumen, disrupting normal blood flow and often leading to vessel narrowing or complete occlusion, thereby reducing or blocking cerebral blood supply and causing IS.[38]

Cerebral arterial dissection is commonly linked to trauma, such as whiplash or head injuries. It can also occur in individuals with hereditary connective tissue disorders like Ehlers-Danlos or Marfan syndrome, which compromise vessel wall integrity.[39] Spontaneous dissection can also occur without obvious trauma or underlying disorder, though its precise cause is not fully understood; factors like sudden movements, increased arterial pressure, or pre-existing vascular abnormalities may contribute.

Diagnosing arterial dissection as an IS cause is often challenging due to its subtlety in initial imaging.[40] However, advanced techniques like MRA or high-resolution CT angiography can confirm it. Early diagnosis is crucial for prompt treatment, which may involve anticoagulants or antiplatelet agents to prevent thromboembolic complications, or in some cases, surgical or endovascular repair.[41]

Given the typically younger age of affected patients, the clinical course of dissection-related IS differs from strokes caused by atherosclerosis. Management requires a tailored approach considering the patient's overall health, underlying conditions, and the dissection's location and extent. Preventive measures, including trauma risk reduction and blood pressure management, are important for reducing recurrence, especially in those with connective tissue disorders.[42]

Excitotoxicity

Excitotoxicity is a critical mechanism in IS progression. When cerebral blood flow is interrupted, energy depletion prevents neurons from maintaining ion balance, leading to depolarization and excessive release of glutamate.[43]

Glutamate, the brain's main excitatory neurotransmitter, overactivates NMDA and AMPA receptors under ischemic conditions, causing a massive influx of calcium ions into neurons.[44] This calcium overload triggers a harmful intracellular cascade: it activates enzymes that degrade cellular structures and leads to mitochondrial dysfunction, increasing ROS and exacerbating oxidative stress.[45,46]

This cascade initiates neuronal death pathways, including apoptosis and necrosis. High calcium levels activate enzymes like calpain and protein kinase C, breaking down the cytoskeleton. NMDA receptor overactivation also generates large amounts of nitric oxide (NO), which forms potent oxidants like peroxynitrite, further damaging neurons.[47] Understanding these mechanisms informs targeted therapies like NMDA receptor antagonists, which reduce calcium overload and protect neurons from excitotoxic damage.[48,49]

Recent studies also highlight the crucial role of immune cells in IS excitotoxicity.[50] Natural killer (NK) cells, for example, are recruited to damaged brain tissue, where they exacerbate inflammation by releasing cytokines and cytotoxic substances. NK cell activity can disrupt the BBB and cause neuronal damage.[51] Their released pro-inflammatory cytokines, like IFN-γ and TNF-α, can activate neuronal NMDA and AMPA receptors, promoting further calcium influx and excessive excitatory responses. This not only directly harms neurons but also exacerbates secondary injuries like oxidative stress and apoptosis.[52–54] Other immune cells, such as macrophages and T cells, also contribute by secreting cytokines that regulate local immune responses and neuronal repair, potentially enhancing excitotoxicity and neuronal damage through increased neuronal depolarization and receptor activation.[55]

Oxidative Stress

When cerebral blood flow is interrupted, leading to hypoxia, the energy metabolism of cells is impaired, resulting in the generation of a large amount of ROS.[56] These ROS include superoxide anions, hydrogen peroxide, and hydroxyl radicals, which attack cell membrane lipids, triggering lipid peroxidation and producing harmful peroxidation products such as malondialdehyde and 4-hydroxynonenal. These products further compromise the integrity and function of cell membranes.[57]

In addition to lipid peroxidation, ROS causes oxidative modification of proteins, altering their structure and function. This includes enzyme inactivation, disruption of the cytoskeleton, and interference with signal transduction pathways, leading to cellular dysfunction. Oxidative modification of proteins can also result in the formation of insoluble aggregates that are difficult for the cell to degrade, potentially leading to apoptosis or necrosis.[46]

ROS-induced DNA damage is equally severe, involving DNA strand breaks, base modifications, and cross-linking. This damage activates cellular repair mechanisms such as base excision repair and nucleotide excision repair.[58] If repair is delayed or incomplete, it can result in genetic mutations or cell apoptosis. Severe DNA damage also activates apoptotic pathways involving p53, leading to cell death.[59]

Oxidative stress amplifies damage through the activation of various signaling pathways. For example, ROS can activate NF-κB, AP-1, and stress-activated protein kinases. Activation of these pathways induces the expression of numerous inflammatory factors such as TNF-α and interleukins.[60]

Additionally, ROS leads to mitochondrial dysfunction, further increasing ROS production and forming a self-amplifying feedback loop. The loss of mitochondrial membrane potential and reduced ATP production result in insufficient cellular energy supply, exacerbating cell damage and death. Mitochondrial damage also releases apoptotic inducing factor and cytochrome c, activating apoptotic pathways and leading to programmed neuronal death.[61]

Inflammatory Response

The inflammatory response is a critical determinant of IS outcomes, where dysregulated innate and adaptive immunity profoundly exacerbates brain damage and dictates long-term neurological deficits.[62]

Ischemia triggers rapid activation of resident microglia and astrocytes,[63] unleashing pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. This cytokine storm, amplified by platforms such as the NLRP3 inflammasome which is crucial for IL-1β maturation, is directly neurotoxic.[64] Early infiltrating neutrophils further fuel this onslaught with ROS and proteolytic enzymes,[65] causing extensive tissue degradation and promoting further leukocyte influx.[66,67] These initial events, driven by mediators like TNF-α and IL-1β, also rapidly compromise BBB integrity,[68] leading to vasogenic edema and secondary injury from extravasated components.[69]

Migrating monocytes differentiate into macrophages, and their phenotypic polarization into pro-inflammatory M1-like or reparative M2-like states critically influences the local environment; a sustained M1-like dominance perpetuates damage and impairs recovery.[70] Subsequently, BBB disruption exposes brain antigens, engaging adaptive immunity.[71] Antigen-specific T cells, particularly pro-inflammatory CD4+ Th1 and Th17 subtypes, and B cells can drive chronic neuroinflammation,[72] a phase often prolonged by deficient inflammation resolution mechanisms, including inadequate specialized pro-resolving mediator (SPM) production.[73]

This sustained neuroinflammation results in ongoing neuronal injury, demyelination, and synaptic dysfunction, leading to persistent neurological deficits,[74] often refractory to current treatments.[75] It also impairs endogenous repair, hindering neurogenesis and promoting an inhibitory glial scar that impedes axonal regeneration and functional restoration.[76,77]

The inflammatory cascade in IS is thus a dynamically detrimental process when uncontrolled.[78] Targeting specific molecular checkpoints—such as inflammasomes, promoting M2 polarization of microglia/macrophages, or augmenting SPM production—holds significant therapeutic promise for mitigating neuroinflammation and enhancing recovery post-stroke.[79]

Neuronal Apoptosis

Neuronal apoptosis is a critical mechanism in ischemia/reperfusion (I/R) injury, significantly contributing to nervous system damage. This programmed cell death occurs during both the hypoxic and reperfusion phases of I/R injury, each with distinct contributing mechanisms.[80]

In the hypoxic phase, reduced blood flow and oxygen activate the intrinsic apoptotic pathway. Hypoxia damages mitochondria, leading to the release of pro-apoptotic factors like cytochrome c into the cytoplasm.[81] Cytochrome c then forms an apoptosome complex with Apaf-1, activating caspase 9, an initiator caspase.[82] Activated caspase 9 subsequently activates caspase 3, the executioner caspase, which cleaves essential cellular components, driving the neuron to apoptosis and forming apoptotic bodies. This process results in cell death and loss of neuronal function, progressing ischemic brain injury.[83] The reperfusion phase, following ischemia, restores blood flow but also induces additional damage via reperfusion injury, mediated by oxidative stress, inflammation, and various apoptotic pathways.[84] This phase generates a large influx of inflammatory mediators like cytokines and ROS, exacerbating tissue injury. These mediators activate the extrinsic apoptotic pathway, triggered by death receptors (eg, Fas, TNFR1) on the cell membrane.[85] Their activation leads to a signaling cascade that activates caspase 8, which in turn activates caspase 3. Activation of caspase 3 in both intrinsic and extrinsic pathways ultimately leads to apoptotic body formation and further neuronal death.[86]

The interplay between the hypoxic and reperfusion phases exacerbates neuronal damage. Hypoxia-induced mitochondrial dysfunction activates the intrinsic pathway early on, while subsequent reperfusion triggers the extrinsic pathway through inflammatory mediators. This dual activation amplifies neuronal damage and neural tissue loss, impairing functional brain recovery.[87] The combination of oxidative stress, mitochondrial injury, and inflammatory responses

across both phases creates a vicious cycle sustaining neuronal apoptosis, making it a critical therapeutic target for IS and other forms of cerebral ischemia.[88]

Mechanisms of Acupuncture Treatment for IS

Acupuncture Promotes Dynamic Repair of the NVU

Acupuncture's therapeutic impact in IS transcends acute neuroprotection, extending to the sophisticated orchestration of dynamic Neurovascular Unit (NVU) repair.[89] This perspective suggests that acupuncture may act as a catalyst for a multi-phasic healing cascade within the NVU, which is pivotal for functional restoration. However, it is crucial to recognize that much of the direct evidence supporting this comprehensive role is derived from preclinical models, and its translation to clinical outcomes in humans requires further validation.

The proposed mechanisms involve several interconnected processes. First, preclinical studies suggest acupuncture may contribute to stabilizing the microenvironment by reinforcing the BBB.[90–92] Second, it is thought to guide glial contributions to repair, for instance, by potentially steering microglial polarization towards a pro-resolving M2-like phenotype.[93,94] While this M1/M2 paradigm is a useful heuristic, the actual complexity of microglial states is far greater, and the precise influence of acupuncture on this spectrum is still under investigation. Finally, the novel but more speculative hypothesis that acupuncture may mitigate cellular senescence[95] offers an exciting avenue for future research but currently lacks robust substantiation.

Acupuncture Modulates Intercellular Communication via Extracellular Vesicles (EVs)

An emerging and compelling hypothesis suggests that acupuncture may influence intercellular communication networks through extracellular vesicles (EVs), offering another layer to its proposed therapeutic mechanisms in IS.[96] EVs, encompassing exosomes and microvesicles, are nano-sized particles that serve as critical conveyors of bioactive cargo.[97] The central idea is that acupuncture stimulation could potentially alter the molecular cargo of EVs. For example, it is theorized that acupuncture might enrich EVs with specific neuroprotective miRNAs or anti-inflammatory cytokines, which could then be delivered to recipient cells within the damaged NVU.[98] The hypothesized functional consequences of such signaling could include promoting neuronal survival, enhancing angiogenesis, or guiding beneficial glial responses.[99] However, it is crucial to emphasize that this field is still in its infancy. The concept that acupuncture can systematically alter EV cargo for therapeutic benefit remains largely theoretical and requires rigorous experimental validation to move from correlation to causality. Investigating these potential EV signatures represents an innovative frontier in acupuncture research.

Improvement of Blood Flow

It has been proposed that acupuncture may improve cerebral blood flow (CBF) through multifactorial neurovascular modulation.[100,101] A primary hypothesized mechanism is the rebalancing of the autonomic nervous system (ANS). Preclinical studies suggest acupuncture may mitigate excessive sympathetic tone while promoting parasympathetic activity, potentially reducing vasoconstriction and improving perfusion.[102,103] For instance, some animal models show correlations between EA and increased vascular density or pro-angiogenic factors.[104] It is also suggested that acupuncture might influence key neurotransmitters and temper the vasoconstrictive effects of Ang II.[105–108]

Beyond vasomodulation, another proposed effect is the improvement of blood rheological properties, as some studies report that acupuncture can be associated with reduced blood viscosity.[109,110] However, the clinical significance and durability of these hemodynamic changes in human stroke patients remain to be firmly established.

Promotion of Angiogenesis and Collateral Circulation Reconstruction

Acupuncture is also investigated for its potential to promote angiogenesis and the reconstruction of collateral circulation. The underlying hypothesis is that by stimulating specific acupoints, acupuncture may help upregulate angiogenic factors like VEGF and bFGF, which could in turn support endothelial cell proliferation and new vessel formation.[111,112] Mechanistically, it is thought that acupuncture might influence ischemia-induced VEGF expression through autonomic

modulation or by affecting signaling pathways like PI3K/Akt.[113–115] Animal experiments have provided some support for these concepts. For instance, studies in rats with I/R injury have reported that EA was associated with improved regional cerebral blood flow and increased vascular density on histological analysis.[116] While these preclinical findings are encouraging, they must be interpreted with caution. A key challenge is determining whether the neovascularization observed in animal models is robust and stable enough to provide clinically meaningful perfusion benefits in the more complex human brain, and whether it directly contributes to long-term functional recovery.

Improvement of Cognitive Function and Memory Recovery

IS damages cognition-critical regions, impairing attention, learning, and memory.[117] Acupuncture is explored for its potential to aid in cognitive and memory recovery, with several integrated biological pathways being proposed. For instance, it is suggested that acupuncture may help regulate neurotransmitters (dopamine, serotonin) imbalanced by post-stroke anxiety and depression, thereby creating more favorable conditions for cognitive rehabilitation.[118,119]

Another proposed mechanism involves improving cerebral perfusion. Acupuncture is thought to modulate autonomic function to potentially enhance cerebral blood flow, which may support neuronal repair in vulnerable regions like the hippocampus.[120] Furthermore, it is hypothesized that acupuncture may influence neuroplasticity by promoting synaptic remodeling, upregulating neurotrophic factors like NGF, and activating endogenous neural stem cells.[119,121–126] While these proposed mechanisms are plausible and interconnected, they are primarily based on preclinical data. Robust clinical evidence is still needed to establish a definitive causal link between acupuncture and sustained cognitive improvements after IS.

Potential Neuroprotective and Neurorestorative Effects

A body of preclinical evidence suggests that acupuncture may orchestrate multifaceted neuroprotective and neurorestorative cascades following IS. In animal models, acupuncture has been shown to counter apoptosis by modulating the Bcl-2/Bax expression ratio and preserving mitochondrial integrity.[127] EA further refines this defense by epigenetically optimizing the expression of key survival and death genes, such as enhancing Bcl-2 and suppressing caspase-3 via targeted histone modifications, thereby substantially mitigating ischemic injury.[128]

Beyond immediate neuroprotection, it is hypothesized that acupuncture promotes neuroregeneration. Studies in rodents have reported that acupuncture can stimulate neural stem cell (NSC) proliferation and differentiation,[129] a process critically driven by activating the Wnt/β-catenin signaling pathway, a master regulator of NSC fate determination.[130] This regenerative drive appears to be linked to the upregulation of neurotrophic factors like BDNF. However, while elevated BDNF levels are consistently observed in animal studies, it remains a significant challenge to confirm whether these changes are of a sufficient magnitude to drive clinically meaningful neurogenesis and synaptic plasticity in human stroke patients. Furthermore, the link between acupuncture, NSC activation, and functional recovery is largely correlational, and a direct causal relationship in humans has not been established.[131] The concurrent augmentation of other neurotrophic factors like NGF and GDNF provides broad-spectrum support across diverse neuronal populations.[132,133]

Finally, acupuncture rebalances neurotransmitter systems, notably serotonin and dopamine, to improve mood, motor control, and cognitive functions.[134] This addresses debilitating post-stroke neuropsychiatric sequelae like depression and anxiety,[135] underscoring acupuncture's capacity for holistic neural restoration, which encompasses not only tissue salvage but also profound functional and psychological recovery.

Modulation of the Inflammatory Response Towards Resolution

Effective recovery from IS is increasingly understood to depend not on suppressing inflammation, but on orchestrating its active resolution.[136] Acupuncture is being investigated as a potential immunomodulator that may contribute to this process.

While many studies report that acupuncture can mitigate the initial surge of pro-inflammatory cytokines like TNF-α and IL-1β,[137] its more advanced, hypothesized role lies in facilitating the transition towards a pro-resolving immune state. For example, in preclinical models, acupuncture has been observed to guide glial cells towards phenotypes

associated with resolution and neuroregeneration.[138,139] However, the mechanisms governing this switch are highly complex and not fully understood. It is unclear whether acupuncture's effect is a primary directive action or secondary to other changes in the tissue microenvironment. Moreover, the promising concept of enhancing Specialized Pro-resolving Mediator (SPM) biosynthesis via acupuncture remains largely theoretical and requires direct experimental evidence.

Clinical Application and Future Directions

Positioning Acupuncture in the Stroke Care Continuum

The integration of acupuncture into the management of IS (IS) is not about replacing established first-line treatments but about strategically augmenting the entire care continuum. It is crucial to position acupuncture as a dynamic, phase-specific adjunctive therapy designed to complement conventional medicine, rather than an alternative to it. The cornerstone of modern IS treatment in the hyperacute phase remains rapid reperfusion via intravenous thrombolysis or endovascular thrombectomy. Acupuncture does not compete with these life-saving interventions; instead, its primary value lies in addressing their limitations, as even successful reperfusion often leaves patients with significant residual neurological deficits. Thus, acupuncture acts as a pro-restorative modality, working in concert with standard medical and rehabilitative care to enhance neuroplasticity, manage complications, and improve long-term functional outcomes. This positioning is implicitly supported by major clinical practice guidelines, such as those from the AHA/ASA, which emphasize comprehensive rehabilitation and are increasingly open to complementary approaches that can improve quality of life.[140]

The therapeutic goals and application of acupuncture evolve dynamically as a patient transitions through the different stages of stroke recovery. In the acute phase (0 to 7 days post-stroke), following primary life-saving measures and stabilization, the focus shifts to damage control. Here, acupuncture's role is primarily neuroprotective: aiming to limit infarct expansion, reduce cerebral edema, and inhibit the acute neuroinflammatory cascade, as consistently suggested by preclinical evidence.[141] It can be initiated at the bedside to create a more favorable microenvironment for recovery without interfering with standard care.

As the patient enters the subacute phase (1 week to 6 months post-stroke), which represents a "golden window" for neuroplasticity, acupuncture's goal transitions from neuroprotection to active neurorestoration. During this period, it demonstrates its most powerful synergistic potential when integrated with standard rehabilitation programs like physical (PT), occupational (OT), and speech therapy (ST). For instance, a well-timed acupuncture session before PT can reduce spasticity and "prime" the neuromuscular system for motor relearning. Similarly, numerous studies have shown that combining acupuncture with conventional rehabilitation is superior to conventional rehabilitation alone for improving motor function, managing dysphagia, and enhancing activities of daily living.[142,143]

Finally, in the chronic phase (>6 months post-stroke), when the potential for dramatic neurological recovery diminishes, acupuncture's focus shifts again. It becomes a valuable tool for managing persistent deficits and improving long-term quality of life. Key targets include chronic conditions often resistant to conventional treatments, such as Central Post-Stroke Pain (CPSP), resistant spasticity, and post-stroke depression (PSD).[144] In this capacity, acupuncture serves as a crucial non-pharmacological option within a multidisciplinary management plan, helping to reduce reliance on medications and their associated side effects, thereby offering sustained support for patients navigating the long-term journey of stroke recovery.

Methodological Challenges and Limitations in Current Research

Despite the promising mechanistic evidence and accumulating clinical data, the widespread adoption of acupuncture in mainstream stroke care is significantly hampered by persistent methodological challenges that undermine the reliability and reproducibility of research findings. A critical appraisal of these limitations is essential for guiding future high-quality research.

The most significant barrier is the profound heterogeneity in treatment protocols. Unlike pharmaceutical trials with standardized dosages, acupuncture studies vary widely in nearly every parameter. This includes the selection of acupoints, with little consensus on "core" versus "adjunctive" points for specific deficits; the method of stimulation

(manual needling, electroacupuncture, or scalp acupuncture); and the parameters of stimulation itself, such as the frequency and intensity of electroacupuncture or the specific manipulation techniques used. Furthermore, the dose of therapy—defined by treatment frequency (eg, daily vs three times weekly) and total duration—is often arbitrarily chosen, making it nearly impossible to compare outcomes across studies or determine an optimal therapeutic window. This lack of standardization is a primary reason why systematic reviews, despite often positive conclusions, frequently call for more methodologically robust trials. To overcome this, future research must prioritize the development of consensus-driven, standardized protocols, potentially through Delphi methods, and adhere rigorously to the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) guidelines to ensure transparency and reproducibility.[145]

A second major limitation is the lack of standardized and sensitive outcome measures. While common scales like the Fugl-Meyer Assessment (FMA) and the Barthel Index (BI) are frequently used, the selection of endpoints often varies, hindering effective meta-analysis. More importantly, these clinical scales may lack the sensitivity to detect subtle but meaningful changes, particularly in higher-level cognitive or fine motor functions. This issue is compounded by a near-universal absence of validated biomarkers in acupuncture trials. Without objective biological correlates—such as changes in neurotrophic factor levels, functional connectivity on fMRI, or specific inflammatory markers—it is difficult to link clinical improvements directly to the underlying neurorestorative mechanisms proposed in this review. The adoption of internationally recognized Core Outcome Sets (COS) for stroke rehabilitation is a crucial step forward, as is the integration of biomarker analysis into clinical trial design.[146]

Finally, the inherent nature of acupuncture presents a unique challenge in designing an appropriate placebo or sham control. This issue lies at the heart of the central and ongoing debate regarding acupuncture's efficacy beyond non-specific effects. Sham methods, such as non-penetrating needles or needling at non-acupoint locations, are not physiologically inert and can elicit their own therapeutic responses, making it difficult to isolate the "specific" effects of verum (real) acupuncture.

Consequently, critics argue that a significant portion of acupuncture's observed benefits in clinical trials may be attributable to powerful contextual factors, such as patient expectations, the therapeutic ritual, and patient-practitioner interaction, rather than the specific needling technique itself. While pragmatic trials comparing acupuncture plus standard care versus standard care alone are crucial for assessing real-world effectiveness, they cannot resolve this fundamental mechanistic question. Therefore, the field urgently needs innovative trial designs, such as three-arm trials (verum vs sham vs standard care) and the integration of objective biomarkers, to better dissect the specific contributions of acupuncture from its potent and clinically relevant non-specific effects.[147]

Together, these limitations underscore a critical need for a paradigm shift in acupuncture research towards greater methodological rigor, standardization, and a focus on bridging the gap between clinical outcomes and biological mechanisms.

Conclusion

This review synthesizes evidence suggesting that acupuncture may aid IS recovery through diverse mechanisms, including neuroprotection, angiogenesis, and inflammation resolution, positioning it as a promising adjunctive therapy. However, a critical translational gap exists, as these compelling findings are predominantly derived from preclinical models. Establishing the clinical significance and true impact of these mechanisms in human stroke patients remains a paramount challenge for the field.

To bridge this evidence gap, future research must pivot towards greater methodological rigor. The priorities are clear: standardizing treatment protocols to ensure reproducibility; conducting large-scale, high-quality RCTs with innovative sham-control designs to isolate specific effects; and integrating objective biomarkers to validate the proposed biological pathways. A focus on long-term functional outcomes will be essential to definitively establish acupuncture's role as an evidence-based therapy within the comprehensive stroke care continuum.

Abbreviations

AHA/ASA, American Heart Association/American Stroke Association; AMPA, Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Ang II, Angiotensin II; ANS, Autonomic nervous system; BI, Barthel Index; COS, Core Outcome

Sets; CPSP, Central Post-Stroke Pain; CT, Computed Tomography; EA, Electroacupuncture; FMA, Fugl-Meyer Assessment; fMRI, Functional magnetic resonance imaging; I/R, Ischemia/reperfusion; IS, Ischemic stroke; MRA, Magnetic resonance angiography; NK, Natural killer; NMDARs, NMDA receptors; NSCs, Neural stem cells; NVU, Neurovascular Unit; OT, Occupational therapy; PSD, Post-stroke depression; PT, Physical therapy; RCTs, Randomized controlled trials; ROS, Reactive oxygen species; ST, Speech therapy; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGpt-3.5 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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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