Perspective

Acupuncture and Herbal Medicine

Rewiring central sensitization: neuroimmune and autonomic effects of acupuncture

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Central sensitivity syndrome (CSS), which includes long COVID or post-acute sequelae of SARS-CoV-2 (PASC), fibromyalgia (FM), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and postural orthostatic tachycardia syndrome (POTS), is characterized by a state of hyperexcitability and dysregulation in the central nervous system. This group of disorders shares overlapping multisystem symptoms, such as widespread pain, fatigue, cognitive dysfunction, autonomic instability, and poor sleep quality. In addition, these disorders share overlapping mechanisms, including autonomic imbalance, neuroinflammation, impaired descending inhibition, and central sensitization. Current treatments are focused only on symptom relief, with no disease-modifying therapies available, and some patients worsen with pharmacological treatments, particularly with long-term opioid use. These limitations highlight the need for safe, non-pharmacological interventions that can address CSS symptoms without worsening the underlying dysfunction. Notably, the US Department of Veterans Affairs and the US Department of Defense Clinical Practice Guidelines already recommend offering acupuncture as part of the management of chronic multisystem illness and symptoms consistent with fibromyalgia, noting that its improvements in quality of life outweigh the risk of adverse events, which tend to be minor and uncommon[1]. In this perspective, we propose that acupuncture may represent a promising adjunctive approach for the management of CSS.

Neuroimmune modulation

Acupuncture has been reported to modulate excitatory neurotransmission by suppressing spinal glutamate levels, N-methyl-D-aspartate (NMDA) receptors, P2X purinergic receptors, substance P, calcitonin gene–related peptide, and ion channels, such as transient receptor potential vanilloid 1 (TRPV1) and hyperpolarization-activated cyclic nucleotide-gated channels (HCN). Acupuncture was also reported to increase endogenous opioid peptides (β-endorphin and enkephalins), upregulate μ-opioid receptors, and enhance γ-aminobutyric acid (GABA) activity[2]. Low-frequency electroacupuncture has been shown to alleviate neuropathic pain by stimulating spinal microglial expression of interleukin-10 (IL-10), which activates β-endorphin production through opioid receptor–dependent pathways.

In addition to its effects on neurotransmitter levels, acupuncture has been reported to modulate synaptic plasticity in the spinal dorsal horn by inhibiting long-term potentiation (LTP) of C-fiber synapses and suppressing wide dynamic range (WDR) neuronal activity[3]. These effects are mediated by NMDA receptor–dependent postsynaptic calcium influx and downstream phosphorylation of extracellular signal-regulated kinase (ERK) and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB). Together, these processes are key mediators of central sensitization.

Acupuncture has been demonstrated to affect neuroglial crosstalk. Acupuncture has been shown to modulate chemokines and their receptors, such as CX3CL1/CX3CR1, CXCL12/CXCR4, CCL2/CCR2, and CXCL1/CXCR2. Recently, acupuncture was shown to suppress the CXCL12/CXCR4-ERK/NF-κB signaling axis in the spinal dorsal horn, thereby inhibiting glial activation and downstream neuroinflammation in a sciatic neuropathic pain model. Acupuncture also downregulates pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, through modulation of the janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), phosphoinositide 3-kinase/mechanistic target of rapamycin (PI3K/mTOR), toll-like receptor 4/nuclear factor kappa-light-chain-enhancer of activated B cells (TLR4/NF-κB), and mitogen-activated protein kinase (MAPK) signaling pathways, thereby reducing microglial and astrocytic activation[4].

At the supraspinal and neural circuit level, animal studies have identified various brain nuclei affected by acupuncture, including the periaqueductal gray (PAG), lateral habenula (LHb), medial prefrontal cortex (mPFC), and anterior cingulate cortex (ACC).

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Specifically, acupuncture has been reported to play an analgesic role and improve synaptic plasticity in these regions by regulating synapse-related protein expression, inhibiting overactive glial cells and pro-inflammatory mediators, maintaining the balance of excitatory and inhibitory neurons, and maintaining glucose metabolic homeostasis and functional metabolic connectivity. A recent meta-analysis further demonstrated that acupuncture significantly modulated connectivity in the ACC, insula, primary somatosensory cortex, thalamus, and default mode network in chronic pain patients[5]. These changes implicate acupuncture not only in alleviating clinical pain but also in modulating brain networks involved in central pain processing[5]. Acupuncture has also been reported to increase vagal activity and parasympathetic tone, thereby improving autonomic balance as reflected by increases in heart rate variability (HRV).

Overall, these findings demonstrate that acupuncture affects multiple levels of the neuraxis implicated in the pathophysiology of CSS. This multilevel interaction distinguishes acupuncture from pharmacological approaches that typically target a single pathway and provides a mechanistic rationale for its potential as an intervention for CSS (Figure 1).

Clinical implications

Across CSS conditions, clinical studies have suggested that acupuncture is associated with improvements in pain severity, fatigue, sleep quality, mood, and autonomic symptoms. Multiple systematic reviews and meta-analyses have evaluated the efficacy of acupuncture for the treatment of FM. In a systematic review of 12 randomized controlled trials (RCTs), Zhang et al.[6] found that acupuncture was significantly superior to sham acupuncture in relieving pain and improving quality of life, with low- to moderate-quality evidence[6]. Zheng and Zhou[7] confirmed these findings in a subsequent meta-analysis of 13 RCTs, reporting moderate-quality evidence that acupuncture reduces pain and improves well-being. However, no evidence was found to support improvements in fatigue, sleep quality, or stiffness. Recently, Ye et al.[8] pooled 17 RCTs encompassing 1,066 patients with FM and found significant improvements in visual analogue scale (VAS) pain scores, fibromyalgia impact questionnaire (FIQ) scores, depression, and fatigue. However, similar to the findings of Zheng and Zhou[7], no significant improvement in sleep was observed[8]. Jin et al.[9] also conducted a meta-analysis, including 773 patients with FM, and reported significant improvements in pain and stiffness over both the short and long term. In addition, a subgroup analysis showed that electroacupuncture provided additional benefits for fatigue and tender points. Benefits in quality of life, mental health, work ability, anxiety, depression, and energy were only observed in the short term (≤8 weeks)[9]. However, the overall evidence quality ranged from very low to moderate, highlighting the need for larger, well-designed RCTs.

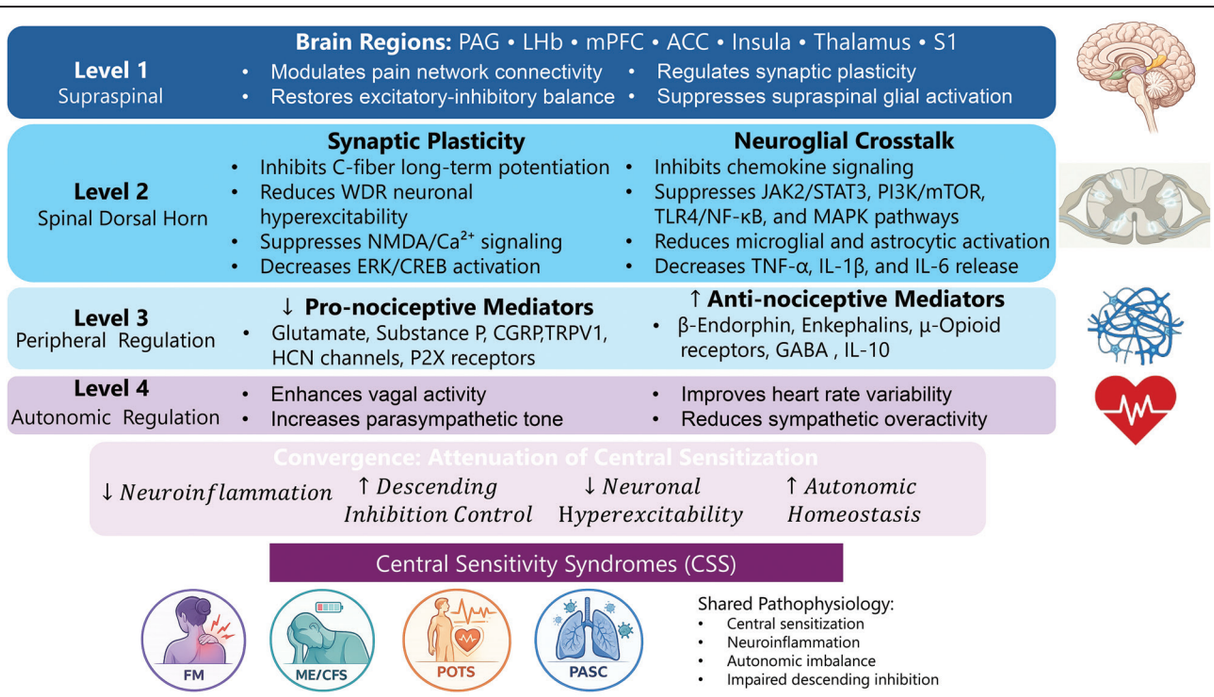


Figure 1. Multilevel mechanisms by which acupuncture modulates the neuraxis to attenuate central sensitization in central sensitivity syndromes (CSS). The figure is organized into four hierarchical levels. Acupuncture influences supraspinal (level 1), spinal dorsal horn (level 2), peripheral neuromodulatory (level 3), and autonomic (level 4) pathways. Collectively, these mechanisms reduce neuroinflammation and neuronal hyperexcitability while restoring descending inhibitory control and autonomic homeostasis. These convergent effects target the shared pathophysiology of fibromyalgia (FM), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), and post-acute sequelae of SARS-CoV-2 (PASC). ACC: Anterior cingulate cortex; CGRP: Calcitonin gene–related peptide; CREB: cAMP response element-binding protein; ERK: Extracellular signal–regulated kinase; HCN: Hyperpolarization-activated cyclic nucleotide-gated channels; LHb: Lateral habenula; MAPK: Mitogen-activated protein kinase; mPFC: Medial prefrontal cortex; NMDA: N-methyl-D-aspartate; PAG: Periaqueductal gray; S1: Primary somatosensory cortex; TLR4/NF-κB: Toll-like receptor 4/nuclear factor-κ B; TRPV1: Transient receptor potential vanilloid 1; WDR: Wide dynamic range.

HM9_V6N3.indb 299 26-Sep-26 15:37:58

Overall, current evidence consistently supports the use of acupuncture for pain reduction in patients with FM, with some evidence suggesting improvements in fatigue, depression, and quality of life. However, the current evidence is derived from RCTs with small sample sizes, and the overall quality remains low to moderate. Future studies should investigate beyond symptom reports by including endoplasmic reticulum stress markers before and after treatment, which have been identified as contributing factors to FM. In addition, neural connectivity assessments with functional magnetic resonance imaging (fMRI) should be utilized to objectively assess the efficacy of acupuncture for FM.

Several systematic reviews and meta-analyses have evaluated the efficacy of acupuncture in the treatment of ME/CFS. Fang et al.[10] conducted a meta-analysis of 51 RCTs including 3,473 patients and reported that acupuncture and moxibustion, a traditional Chinese medicine therapy consisting of burning dried mugwort, were significantly more effective than other treatments for CFS. However, the overall rating of Grading of Recommendations Assessment, Development and Evaluation (GRADE) was low quality[10]. Feng et al.[11] conducted a meta-analysis and reported that acupuncture improved fatigue, especially when combined with rehabilitation. However, similar to prior studies, the authors cautioned that the strength of the conclusions was limited due to study heterogeneity and the inclusion of low-quality trials[11]. Kim et al.[12] also conducted a broader review of 55 RCTs for CFS/ME and identified acupuncture as one of only five non-pharmacological interventions showing statistical significance for fatigue-related symptoms. However, no intervention demonstrated definitive efficacy across the included studies[12]. At the individual trial level, Chen et al.[13] evaluated the effects of acupuncture on mental and somatic fatigue in a randomized cohort of 60 patients with CFS. Patients treated with acupuncture reported significant improvements in both mental and physical fatigue (an effectiveness rate of 86.67%) according to the FS-14 and significant reductions in depression, anxiety, and interpersonal sensitivity according to the SCL-90[13]. Ng et al.[14] also reported significant improvements in mental and physical fatigue among patients with ME/CFS undergoing acupuncture therapy. Additionally, Kim et al.[15] investigated the effects of acupuncture in a larger cohort of 150 patients, reporting a significant reduction in overall fatigue in the acupuncture group compared with the control group. Overall, the current evidence suggests that acupuncture may be effective in reducing fatigue and improving associated somatic and psychological symptoms, including anxiety and depression, in patients with ME/CFS. However, the overall quality of the evidence remains low, limiting the ability to make definitive recommendations. Future studies should investigate beyond symptom reports and include metabolite testing and inflammatory markers before and after treatment to more rigorously evaluate the efficacy of acupuncture in patients with ME/CFS.

Evidence for the efficacy of acupuncture in POTS is limited owing to the small size of the trials. In a systematic review, Diedrich et al.[16] demonstrated a decrease in dysautonomia symptoms, including gastrointestinal function, orthostatic tolerance, and total scores on the Composite Autonomic Symptom Score (COMPASS-31) questionnaire after four 1-hour sessions of transcutaneous auricular vagal nerve stimulation (taVNS) administered daily for 14 days. This study also showed a smaller increase in heart rate after standing, although this finding was not statistically significant. In a sham-controlled, double-blind RCT involving 26 patients with POTS, Stavrakis et al.[17] analyzed the effects of taVNS delivered to the tragus of the ear. Two months after taVNS, the increase in heart rate during the postural test was significantly lower in patients who received active treatment. Serum TNF-α levels were also significantly decreased in individuals receiving active taVNS, suggesting an anti-inflammatory effect. Among the symptoms included in the COMPASS-31, secretomotor function was the only symptom that showed significant improvement[17]. Likewise, Shiffer et al.[18] reported that 14-day tVNS enhanced cardiovagal modulation, reduced sympathetic activity, and improved orthostatic symptoms in 22 patients with hyperadrenergic POTS (Hyper-POTS). The optimal stimulation parameters, including frequency and pulse width for taVNS, remain undetermined for patients with POTS and continue to be evaluated. Overall, taVNS shows promise for POTS by modulating autonomic balance and reducing inflammation. However, all current evidence is derived from small pilot trials, and larger RCTs with standardized stimulation methodologies are needed to determine the optimal protocols.

Nearly one-third of patients with PASC also experience neurological and neuropsychiatric symptoms such as fatigue, cognitive dysfunction, sleep disturbances, headache, depression, and anxiety[19]. Lam et al.[20] analyzed 110 randomized controlled trials utilizing acupuncture for common symptoms reported in PASC. This study reported significant improvements in chronic fatigue, pain symptoms, depression, cognitive impairment, insomnia, daytime sleepiness, and reductions in intensity, although not headache frequency, of headaches related to PASC. However, the included trials were not conducted specifically in PASC populations, and the authors concluded that well-designed clinical trials in patients with PASC are needed to validate their findings[20]. One pilot study conducted in 2022 evaluated the effects of taVNS on PASC symptoms over a 4-week period, during which participants received 48 1-hour sessions. Treated patients reported significantly decreased mental fatigue, providing preliminary evidence that taVNS may be a potential therapy for PASC-related neuropsychiatric symptoms[21]. Zheng et al.[22] also conducted a pilot study of 24 female patients with PASC and reported that 10-day tVNS significantly improved cognitive function, anxiety, depression, and sleep quality, with fatigue improvements reaching significance at 1 month. More recently, Azabou et al.[23] reported that 8 weeks of taVNS significantly improved autonomic symptoms, post-traumatic stress disorder symptoms, and cognitive performance in 17 patients with PASC. Kraft et al.[24] also reported significant improvements in fatigue, physical performance, and exertional dyspnea in 79 patients with PASC who were treated with traditional Chinese medicine, of whom 85% received acupuncture.

HM9_V6N3.indb 300 26-Sep-26 15:37:58

Overall, while the indirect evidence from Lam et al.[20] suggests that acupuncture may address many symptoms associated with PASC, the emerging direct evidence from pilot studies is consistent with these findings. However, most of the direct evidence has been derived from small, heterogeneous pilot studies. Consistent with the other CSS conditions discussed above, larger, well-designed RCTs incorporating biomarkers or neuroimaging are required to establish the efficacy of acupuncture in PASC populations.

Safety of acupuncture

Acupuncture is generally considered safe, with an incidence of adverse events ranging from 6.71% to 8.6%; the incidence of serious adverse events is approximately 0.001%[25].

Future research

The mechanistic evidence discussed here was predominantly derived from animal models, and its translation to human CSS populations requires validation. Clinically, the included studies were heterogeneous in their acupuncture protocols and study methodologies, including varying treatment modalities, needle types, point selection, stimulation parameters, and session frequency. In addition, the sample sizes were small, and the outcome measures were primarily subjective. The quality of evidence across conditions also limits the strength of clinical recommendations, as the quality ranges from very low to moderate. Future research should prioritize large-scale, well-designed studies that directly compare acupuncture modalities with current pharmacological therapies or appropriate control groups. Future studies should incorporate objective biomarkers, such as cytokine assays, alongside validated symptoms and quality-of-life (QOL) measures. Additionally, trials should evaluate the optimal treatment frequency and duration required to achieve meaningful clinical benefits. Studies should include diverse patient populations to facilitate a more direct comparison of the effects of acupuncture across CSS conditions. Such studies will allow more definitive recommendations regarding the integration of acupuncture therapy into the management of these complex disorders.

Overall, acupuncture may represent a clinically safe adjunctive therapy for CSS by modulating neuroimmune inflammation and autonomic imbalance. Current evidence suggests that acupuncture improves fatigue, pain, sleep quality, mood, cognition, and autonomic function.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Zachary L. Morcos and Jacqueline Junco conceived the study. Zachary L. Morcos performed the initial comprehensive literature search, synthesized the evidence, wrote the introduction, safety of acupuncture, and conclusion sections, and revised the manuscript for submission. Kaley Sloan and Rohan Reddy conducted additional literature searches for their respective sections and authored the sections on post-acute sequelae of SARS-CoV-2 infection and postural orthostatic tachycardia syndrome (Kaley Sloan) and fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (Rohan Reddy). All sectional contributions by Kaley Sloan and Rohan Reddy were edited and integrated by Zachary L. Morcos and Jacqueline Junco. Jacqueline Junco provided methodological and conceptual guidance, supervised the project, and revised the manuscript for intellectual content. All authors reviewed and approved the final version of the manuscript.

Ethical approval of studies and informed consent

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Data availability

Not applicable.

Declaration of generative AI in scientific writing

The authors declare that no generative artificial intelligence (AI) technologies were used in the conception, drafting, or revision of this manuscript. All work was performed solely by the human authors.

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HM9_V6N3.indb 301 26-Sep-26 15:37:58

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HM9_V6N3.indb 302 26-Sep-26 15:37:58