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RECEIVED 22 October 2024

ACCEPTED 14 April 2025

PUBLISHED 28 April 2025

CITATION

Yang X, Li B, Wu L and Cui Y (2025)
Acupuncture treatment of vascular cognitive
impairment through peripheral nerve
stimulation pathway: a scoping review.
Front. Aging Neurosci. 17:1515327.
doi: 10.3389/fnagi.2025.1515327

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Acupuncture treatment of vascular cognitive impairment through peripheral nerve stimulation pathway: a scoping review

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Objective: This study aims to explore the central effects of acupuncture on vascular cognitive impairment (VCI) through peripheral nerve stimulation.

Methods: This scoping review followed the methodological framework proposed by Arksey and O'Malley and the PRISMA-ScR guidelines. A comprehensive search of databases, including PubMed, Web of Science, MEDLINE, and Embase, was conducted, including 79 studies on acupuncture interventions for VCI. Acupoints and their underlying anatomical structures related to peripheral nerves were summarized, and the potential pathways of acupuncture effects via different peripheral nerves were explored.

Results: The results showed that acupuncture, by stimulating specific acupoints on the head, face, torso, and limbs, significantly affects peripheral nerve networks, including the cervical, lumbar, and sacral plexuses, thoracic nerves, vagus nerve, trigeminal nerve and its branches. The nerve stimulation effects of acupuncture can enhance the regulation of cerebral blood flow, modulate neuroimmune responses, improve brain function, and promote neuroplasticity through multiple central nervous system pathways, ultimately improving cognitive function and treating VCI.

Conclusion: Acupuncture is a treatment modality that influences the central nervous system through peripheral nerve stimulation to treat VCI. A deeper understanding of the central effects induced by acupuncture-triggered neural reflexes can contribute to the improvement of existing therapies and help elucidate the scientific principles underlying acupuncture's therapeutic effects.

KEYWORDS

vascular cognitive impairment, peripheral nerve stimulation, central nervous system modulation, acupuncture, electroacupuncture

1 Introduction

Vascular Cognitive Impairment (VCI) primarily arises from cerebrovascular diseases (van der Flier et al., 2018; Corriveau et al., 2016), manifesting as mild cognitive impairments (MCI) or a combination of ischemic or hemorrhagic cerebral vascular factors. It can also co-occur with vascular dementia (VD) linked to Alzheimer's disease (AD) (Zhang et al., 2019). Studies predict that around 2050, the global number of individuals affected by VCI will reach 150

million, incurring substantial financial costs (Alzheimers Disease International, 2018). The ongoing global aging population has exacerbated the occurrence of vascular risk factors and intensified the prevalence among the expanding elderly population (Fitzpatrick et al., 2004). In the future, approximately one-third of individuals aged 65 and above may experience a stroke or dementia (Wolf, 2012). Factors such as cerebral vascular narrowing, reduced blood flow, microbleeds, impaired neural circuits, and brain structural damage may contribute to the onset of VCI. Hypoxia, increased blood–brain barrier (BBB) permeability, endothelial dysfunction, systemic inflammation, and the inflammation-associated aging clock (iAge) represent other potential mechanisms (Zlokovic et al., 2020). Multiple infarctions can cause neurodegenerative changes, thus impacting cognitive function (Biesbroek et al., 2013). Risk factors for VCI encompass hypertension (Reitz et al., 2007), obesity (Pedditzi et al., 2016), hyperglycemia (Saczynski et al., 2008), hyperlipidemia (van de Rest et al., 2008; Dangour et al., 2010; Stough et al., 2012), elevated homocysteine (Nalder et al., 2021), and smoking. Symptomatic treatment for VCI often involves using acetylcholinesterase inhibitors and NMDA receptor antagonists to improve cognition. However, drugs like donepezil and galantamine show limited clinical efficacy, providing only mild enhancements in cognitive function, often with no statistically significant difference compared to a placebo (Battle et al., 2021). Hence, continued exploration of pharmaceuticals and other clinical interventions remains necessary.

Neural or peripheral nerve stimulation is an adjunctive alternative therapy for treating cognitive impairments or cerebrovascular diseases, aiming to regulate the central nervous system through peripheral stimulation. For example, ear and Vagus nerve stimulation (VNS) have been repeatedly reported to enhance and improve cognitive function (Wang et al., 2022; Choi et al., 2022). Damage to the autonomic nervous system leads to dysregulation of neural control, resulting in reduced cerebral blood flow (CBF), often associated with a range of nonspecific neurological symptoms (Ratan and Schiff, 2018). The activation of relevant brain areas after brain injury plays an enhanced role in neuroplasticity. Transcranial direct current stimulation affects synaptic plasticity, brain network connectivity, and CBF regulation (Bikson et al., 2016). The underlying principle is to induce changes in transmembrane potentials of neurons through stimulation, thereby affecting neuronal excitatory and inhibitory responses (Nitsche et al., 2012). It can also activate activity in relevant brain areas, aiding in alleviating central sensitization (Esposito et al., 2019). Simultaneously, it modulates vascular constriction and dilation through the vascular neurocoupling mechanism (Sdrulla et al., 2018). Multiple pathways demonstrate the close connection between the peripheral and central nervous systems. The intrinsic mechanisms activated through neural stimulation hold significant therapeutic implications for VCI.

Acupuncture is the most widely used traditional medical complementary and alternative therapy. According to the World Health Organization's 2019 report, acupuncture is utilized in 113 out of 120 countries surveyed (Zhang et al., 2019). Countries like China, the United States, the United Kingdom, Australia, Japan, South Korea, and Malaysia have established clinical practice guidelines for acupuncture (Wu et al., 2021; Yang et al., 2017). Several high-quality clinical randomized controlled trials have demonstrated the effectiveness of acupuncture in managing various diseases such as obesity, facial paralysis, different types of pain, ischemic stroke, irritable bowel syndrome, depression, and hypertension (Wen et al., 2021; Zhong et al.,

2022). With the advancement of modern science and technology, scientists have been continually exploring the physiological mechanisms through which acupuncture operates. Acupuncture therapy, by stimulating acupoints, mobilizes the body's intrinsic systems and self-regulatory potential, playing a role in disease prevention and treatment. Acupoints serve as the initial response sites to acupuncture stimulation and are the starting point for acupuncture effectiveness (Zhou and Benharash, 2014). In the 1970s, domestically and internationally researchers began investigating the anatomical structure of acupoints. Currently, studies have revealed (Zhou and Benharash, 2014; Cho et al., 2022) that in the trunk region, there are four nerve plexuses of the spinal nerves that reach the skin of the neck, back, waist, abdomen, and sacrum. The subcutaneous area of acupoints corresponds to the same or nearby spinal segments and nerve branches of visceral organs. Subcutaneous tissues in the upper limb acupoint areas are mostly related to the radial nerve, median nerve, and ulnar nerve. They are commonly used to treat diseases of the head, face, chest, and segmental nerve distribution areas. In the lower limb acupoint areas, subcutaneous nerve tissues are mostly related to the sciatic nerve and femoral nerve and their branches (such as the peroneal nerve and tibial nerve) and are commonly used to treat diseases of the lower limbs, abdomen, or pelvic area. Studies have shown (Gong et al., 2020; Torres-Rosas et al., 2014) that acupuncture, as a form of mechanical stimulation, induces biophysical changes in the subcutaneous tissues of the acupoint area. This stimulation excites local nerve receptors and mechanosensitive ion channels (MSCs) in nerve cells and nerve terminals of the acupoint area, leading to their activation and release of relevant chemicals that act on corresponding receptors in nerve terminals. This process transforms mechanical force signals into electrochemical signals, thus exerting the effects of acupuncture. Moreover, acupuncture can also activate MSCs on non-neuronal cells like macrophages, granulocytes, mast cells, and T cells in the acupoint area (Li et al., 2021; Wu et al., 2014; Huang et al., 2018), triggering the release of chemical substances that act on surrounding nerve cells or receptors in nerve terminals. This activation initiates neuroimmune regulation in the acupoint area, converting the physical signal of acupuncture into a biochemical signal and generating subsequent biological effects. This article mainly explores related Neurostimulation therapy of VCI, attempting to summarize the central effects of acupuncture on peripheral nerve stimulation, reveal the mechanism of acupuncture treatment for VCI, and the theory of acupuncture's neural effects.

2 Methods

This scoping review followed the methodological framework proposed by Arksey and O'Malley (2005), which includes identifying the research question, searching for relevant studies, selecting studies, charting the data, and summarizing, synthesizing, and reporting the results based on the PRISMA-ScR (Tricco et al., 2018) (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines.

2.1 Research question of this review

The main focus of this review is to summarize the peripheral nerves involved in acupoint stimulation based on studies related to

acupuncture interventions for VCI. The aim is to explore the potential peripheral nerve pathways that may be involved in acupuncture treatment for VCI.

2.2 Search strategy

We searched English-language databases, including PubMed, Web of Science, MEDLINE, and Embase. The search terms included subject headings and related terms such as “acupuncture,” “electroacupuncture,” and keywords like “vascular cognitive impairment.” The two sets of keywords were connected using the logical operator “AND.” The search covered the period from the inception of each database up to March 27, 2024, and included all publicly available journal publications. [Supplementary Table 1](#) provides detailed information on the PubMed search strategy.

2.3 Research inclusion and exclusion criteria

Articles involving acupuncture and related therapies were eligible, provided that the intervention subjects met the established criteria for VCI. Eligible study types included clinical randomized controlled trials, animal studies, systematic reviews, meta-analyses, and case reports. Studies that did not pertain to acupuncture interventions specifically aimed at VCI were systematically excluded. The criteria ensured that only those studies with a clear focus on the intervention and target population were retained.

2.4 Screening and selection of studies

The screening and selection process commenced with the use of EndNote X9 to manage the retrieved literature. Initially, the built-in duplication tool was utilized to eliminate duplicate records, followed by manual checks to remove any remaining duplicates not detected by the software. Subsequently, a thorough review of titles and abstracts was conducted to exclude studies unrelated to acupuncture interventions for VCI. The remaining studies were then subjected to a blinded evaluation by two independent reviewers. Any discrepancies or disagreements encountered during the review process were resolved through consultation with a senior researcher, whose expertise ensured that the final selection was both accurate and consistent.

2.5 Extraction of effective data and evidence synthesis

We primarily extracted acupoint information from these studies and compiled it into a table. Additionally, we reclassified the acupoints mentioned in these articles based on the nerves within the anatomical structures underlying each acupoint. The neuroanatomical correlations of the acupuncture points will be referenced from the Chinese higher education “14th Five-Year Plan” textbook *Acupoint Anatomy* (Shao, 2023) and the *Interactive Medical Acupuncture Anatomy* (Teton NewMedia, USA, 2016) (Robinson, 2016). Finally,

we categorized and summarized the research progress on acupuncture treatment for VCI based on classifying peripheral nerves and explored the underlying mechanisms involved in these pathways.

3 Results

3.1 Screening and selection of studies

Through a search of English-language databases, including PubMed, Embase, MEDLINE, and Web of Science, a total of 233 articles were identified (PubMed = 31, Embase = 36, MEDLINE = 58, Web of Science = 108). After removing duplicates, 124 articles remained for the initial screening phase. Of these, 40 articles were excluded based on screening titles and abstracts, leaving 79 articles for full-text evaluation. During the full-text review, two conference abstracts were excluded, resulting in 79 articles that were ultimately included in this review ([Figure 1](#)).

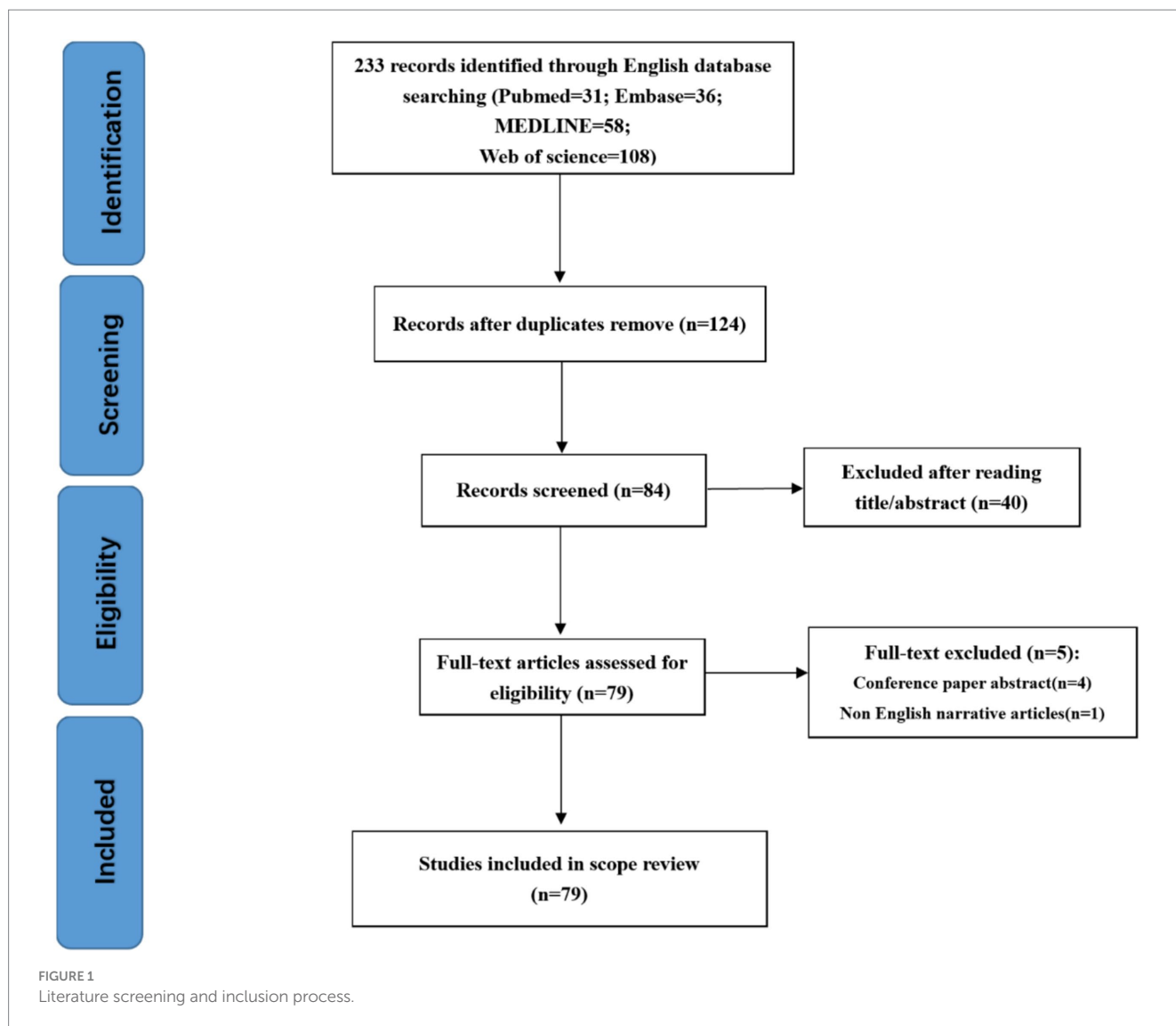
3.2 Basic characteristics of articles

The reviewed articles cover a timeline from 2005 to 2024, providing a comprehensive overview of research on acupuncture and its effects on VCI and related conditions. The body of research was composed of 32 experimental animal studies, 14 clinical studies (including 12 randomized controlled trials and 2 non-randomized trials), and 33 literature-based investigations. The animal studies were conducted to explore the mechanisms underlying acupuncture's effects on cognitive function, often employing rat models of multi-infarct dementia or VD to mimic clinical conditions.

On the clinical side, the randomized controlled trials focused on evaluating the efficacy of acupuncture in improving cognitive function in patients with VCI or other forms of cognitive decline. Furthermore, a substantial portion of the literature consists of comprehensive reviews and syntheses of existing data. Among the 33 literature investigations, 31 are systematic reviews, with 13 of these incorporating meta-analyses to quantitatively assess the efficacy of acupuncture. In addition to these rigorous analyses, there is one narrative review that offers a succinct overview of the field, as well as one Delphi consensus study that gathers expert opinions to guide future research directions. Specific information of all literatures can be found in [Supplementary Table 2](#).

3.3 Common acupoints and nerves involved

Based on the statistical analysis of acupoints that appeared across all the included studies, we have summarized the acupoints incorporated across all studies under consideration. All fourteen meridians are represented, including extra nerve acupoints and scalp acupoints. As illustrated in [Figure 2](#), The most commonly involved acupoints are often located in the Taiyang Bladder Meridian, followed by the Foot Shaoyang Gallbladder Meridian and the Governor Vessel. We have categorized the acupoints according to the involved nerves, dividing them into groups that encompass acupoints related to upper limb neural networks and their branches, as well as those pertaining to the lower limbs and sacral



region innervated by the lumbosacral plexus and its branches. Other categories include acupoints related to the lower limbs and lumbar-dorsal areas innervated by the lumbar plexus and its branches, as well as back-shu points associated with the thoracic nerve plexus and its branches, neck and occipital acupoints connected to the cervical plexus and its branches, facial and cranial acupoints linked to cranial nerves and their branches, and acupoints distributed along the autonomic nervous system. Notably, cranial nerves, lumbosacral plexus, and cervical plexus acupoints are the most prevalent (Figure 3), with specific acupoints and their corresponding neural affiliations detailed in the Table 1.

Our examination of acupoints, categorized by meridians and associated neural networks, reveals their predominant distribution around the peripheral nerves of the limbs, cranial nerves, spinal nerves, and the autonomic nervous system. In 1971, Jiao creatively established sixteen stimulation areas on the scalp. Some studies suggest that scalp acupuncture in specific zones can treat injuries to the corresponding brain regions and even induce molecular changes (Sun et al., 2020). Scalp acupoints predominantly project onto cranial and cervical nerves (Dorsher and Chiang, 2018). Additionally, a subset of the summarized acupoints involves the autonomic nervous system.

It is established that acupuncture significantly influences the central autonomic regulatory center, a controller of the autonomic nervous system, as demonstrated by a wealth of animal studies (Li et al., 2022; Ohsawa et al., 1995; Uchida et al., 2010; Sato et al., 1993). Acupuncture's impact on the autonomic nervous system follows a segmental distribution pattern, with the ability to modulate sympathetic/parasympathetic output. Acupuncture engages in diverse neural regulations, and the following sections will categorize them by different neural systems, exploring the pathways and mechanisms through which acupuncture exerts its effects on VCI (Figure 4).

3.4 Acupuncture and brachial plexus stimulation

Peripheral nerves are richly distributed in the body's meridians and acupoints, and the involvement of the peripheral nervous system is essential for the efficacy of acupuncture. Acupuncture can improve cognitive function by stimulating the brachial plexus nerve, typically through the synergistic action of multiple nerve branches. Acupoints

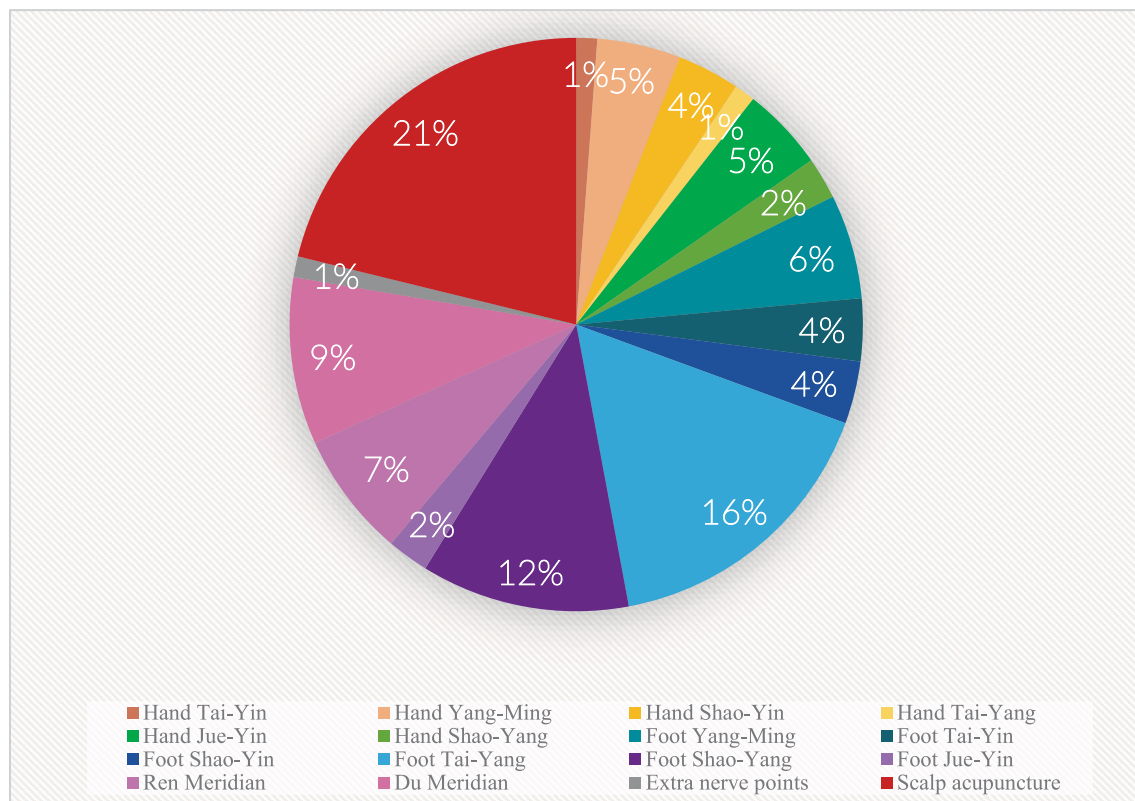


FIGURE 2
Number of different meridian acupoints.

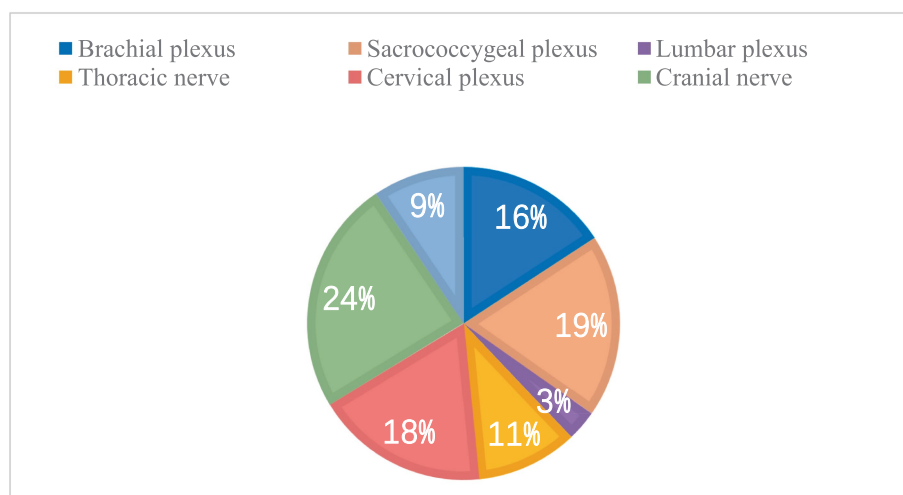


FIGURE 3
Number of acupoints involved in different nerves.

commonly used in VCI acupuncture interventions include LI4 (Hegu), PC5 (Jianshi), PC6 (Neiguan), and Waiguan, traversed by the radial nerve, ulnar nerve, median nerve, and musculocutaneous nerve, respectively. The brachial plexus nerve constitutes a complex anatomical nerve network, including branches such as the musculocutaneous nerve, radial nerve, ulnar nerve, median nerve, axillary nerve, thoracodorsal nerve, and long thoracic nerve, primarily

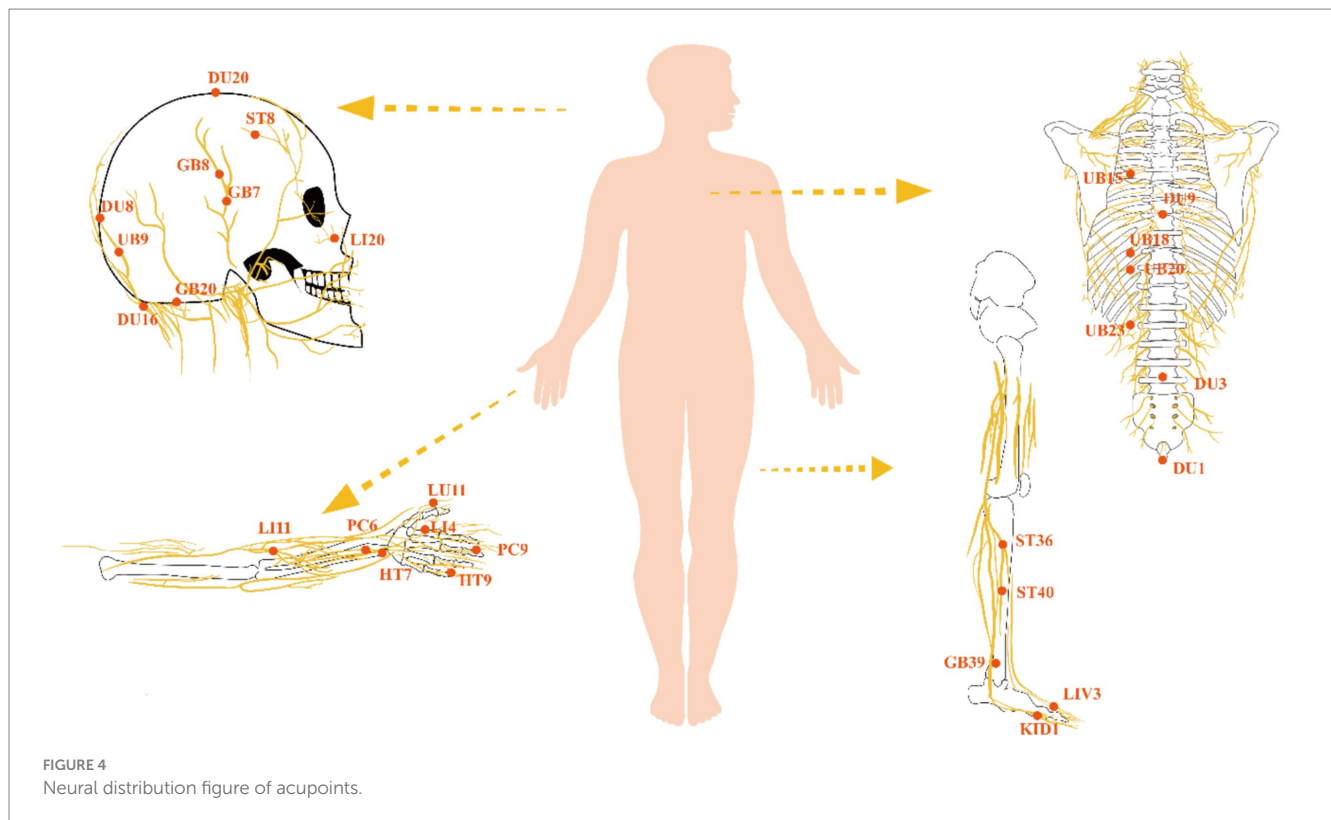
supplying the upper limbs (Kattan and Borschel, 2011; Orebaugh and Williams, 2009). An interaction exists between the brachial plexus nerve and cognitive function. The hippocampus, an essential limbic system component, is believed to play a significant role in brain memory and emotional formation processes. Preclinical evidence suggests that chronic peripheral nerve injuries reduce neurogenesis in the adult hippocampus's granule cell layer of the dentate gyrus (DG)

TABLE 1 Commonly used acupoints and their related peripheral nerves.

Main neural stems and origins involved	Branching nerve	Involving acupoints
Brachial plexus	Musculocutaneous nerve	LU11 (ShaoShang), LI11 (Quchi), HT7 (ShenMen), HT5 (TongLi), PC6 (NeiGuan), PC5 (JianShi), SJ5 (WaiGuan)
	Radial nerve	LU11 (ShaoShang), LI1 (ShangYang), LI4 (Hegu), SJ5 (WaiGuan), LI11 (QuChi)
	Ulnar nerve	HT7 (ShenMen), HT5 (TongLi), HT9 (ShaoChong), SJ1 (GuanChong), SI1 (ShaoZe)
	Median nerve	PC6 (NeiGuan), PC5 (JianShi), PC7 (DaLing), LU11 (ShaoShang), LI1 (ShangYang), LI4 (Hegu), PC9 (ZhongCong)
Sacrococcygeal plexus	Sciatic/tibial nerve branches	SP6 (ShanYinJiao), KID3 (TaiXi), KID4 (DaZhong), KID6 (ZhaoHai), ST36 (ZuSanLi), GB44 (ZuQiaoYin), KID1 (YongQuan), UB67 (ZhiYin), GB30 (HuanTiao)
	Sciatic nerve/common peroneal nerve branch	ST36 (ZuSanLi), GB39 (XuanZhong), LIV3 (TaiChong), LIV1 (DaDun), ST45 (LiDui), SP1 (YinBai), ST40 (FengLong), GB30 (HuanTiao)
	Coccygeal nerve	DU1 (ChangQiang)
Lumbar plexus	Femoral nerve	SP10 (XueHai)
	L3 ~ L4	UB23 (ShenShu), DU3 (YaoYangGuan)
Thoracic plexus	T4	REN17 (DanZhong)
	T5 ~ T6	UB15 (XinShu), DU9 (ZhiYang), UB45 (YiXi), DU9 (ZhiYang)
	T7 ~ T8	REN12 (ZhongWan)
	T9 ~ T10	UB18 (GanShu)
	T11 ~ T12	UB20 (PiShu), REN4 (GuanYuan), REN6 (QiHai)
Cervical plexus	Cervical nerve	DU16 (FengFu), DU14 (DaZhui), DU15 (YaMen), Occipital scalp needle, Temporal scalp needle
	Greater occipital nerve	DU16 (FengFu), UB9 (YuZhen), UB10 (TianZhu), GB20 (FengChi), GB8 (ShaiGu), DU20 (BaiHui), DU15 (YaMen), DU17 (NaoHu), DU18 (QiangJian), EX-HN1 (SiShenCong)
	Lesser occipital nerve	GB20 (FengChi), GB12 (WanGu), EX-HN13 (YiMing)
Cranial nerve	Trigeminal nerve	ST8 (TouWei), GB8 (ShuaiGu), GB7 (QuBing), EX-HN1 (SiShenCong), DU23 (ShangXing), DU24 (ShenTing), GB14 (YangBai), UB4 (QuChai), DU20 (BaiHui), EX-HN03 (YinTang), LI20 (YingXiang), GB13 (BenShen), GB15 (TouLinQi), Top forehead scalp needle
	Facial nerve	LI20 (YingXiang)
	Auditory nerve	EX-HN13 (YiMing)
	Accessory nerve	EX-HN13 (YiMing)
	Vagus	EX-HN13 (YiMing), Auricular acupoint
Autonomic nerve	Sympathetic nerve	UB23 (ShenShu), DU3 (YaoYangGuan), UB15 (XinShu), DU9 (ZhiYang), UB45 (YiXi), UB18 (GanShu), UB20 (PiShu)
	Parasympathetic nerve	EX-HN13 (YiMing), Auricular acupoint

(Vania et al., 2016; Xia et al., 2020). Clinical studies have found activation of the medial-hypothalamic pathway following brachial plexus nerve injury (BPI), a critical structure for pain processing integration (Wang et al., 2019). Changes occur in other brain regions related to cognitive functions post-brachial plexus nerve injury (p-BPI), with decreased functional connectivity within the primary motor cortex (M1) (Fraiman et al., 2016). Cognitive functions participate in the sensory (Mahmoudaliloo et al., 2011) and functional (De Azevedo et al., 2018) recovery processes of the hand after upper limb peripheral nerve injury, where patients with BPI exhibit dynamic changes in the resting-state brain networks (RSNs) during treatment. Patients with improved muscle strength show significantly increased connectivity in the sensorimotor network (SMN) and salience network (SN) post-treatment. In contrast, all patients exhibit a trend of decreased connectivity in the default mode network (DMN) postoperatively, indicating the role of brain plasticity and

compensatory mechanisms in the recovery process of peripheral nerve injury (Bhat et al., 2017). Research analyzing the conduction function of peripheral nerves in elderly individuals with different cognitive levels has found that the conduction velocity of the median motor nerve and the peroneal motor nerve differs significantly (Qian et al., 2022), suggesting damage to fast-conducting fibers related to movement in cognitive impairment patients, with a decline in motor conduction ability. Additionally, the motor conduction velocity of the median and peroneal nerve is positively correlated with the ideographic part of the Montreal Cognitive Assessment (MoCA) and verbal fluency task (VFT) (Amira et al., 2024). Magnetic stimulation of PC6 (Neiguan) and PC (Daling) in healthy subjects shows increased functional connectivity of brain areas associated with higher cognitive functions such as emotion, memory, and language (Dai et al., 2019), with activation of brain regions closely related to cognitive and emotional processes, such as the frontal lobe and temporal lobe (Haili



et al., 2022), and significant improvement in information transmission efficiency in the brain cortex during stimulation. Acupuncture at LI4 (Hegu) has been shown to modulate frontal and temporal lobe activity in patients with AD and MCI, while enhancing the connectivity between the hippocampus and the motor cortex (Zheng et al., 2018; Wang et al., 2012). Functional magnetic resonance imaging (fMRI) scans of 24 healthy individuals show that cerebellar activation is typically only observed during acupuncture at the Waiguan acupoint (Wik et al., 2016). Traditionally associated with motor coordination and balance, the cerebellum plays a crucial role in various aspects of higher functions, with emerging research revealing its broader contributions to cognition, emotion, and reward processes (Buckner, 2013; Schmahmann, 2019; Wagner and Luo, 2020). Electrical stimulation of the ulnar nerve at an α frequency (10 Hz) in Brain-Computer Interface (BCI) subjects increases the classification accuracy of left and right-hand motor imagery from 66.41 to 81.57%, with effects lasting for at least two days (Zhang et al., 2020). Stimulation of the ulnar nerve was considered that can improve motor imagery classification accuracy, enhancing the neural function of cognitive impairment patients.

3.5 Acupuncture and lumbo/sacral plexus stimulation

The lumbosacral plexus, originating from L1-S3 spinal nerve roots, controls lower limb sensation and motor function (Di Benedetto et al., 2005). Anatomically, it consists of the “upper” lumbar plexus and the “lower” sacral plexus (Laughlin and Dyck, 2013). The lumbar plexus is located within the psoas major muscle and comprises the anterior branches of the T12 to L4 nerve roots. The nerve branches of

the lumbar plexus mainly include the iliohypogastric nerve, ilioinguinal nerve, genitofemoral nerve, lateral femoral cutaneous nerve, obturator nerve, and femoral nerve. The sacral plexus comprises the lumbosacral trunk (L4, L5), all sacral nerves, and the anterior branches of the coccygeal nerve, which originate from the ventral edges of the L4 to S4 nerve roots. The nerve branches of the sacral plexus mainly include the lumbosacral trunk, superior gluteal nerve, inferior gluteal nerve, sciatic trunk/nerve, and pudendal nerve. More research is needed on the relationship between sciatic nerve injury and cognitive impairment among the sacral plexus nerves. A cross-sectional study from China found that as a branch of the sciatic nerve, the peroneal nerve exhibits decreased nerve conduction velocity in patients with MCI and AD, and the conduction velocity of the peroneal nerve is significantly correlated with the diagnosis of AD (Qian et al., 2022; Qian and Xiao, 2020). In addition, sciatic nerve injury can lead to neuropathic pain (Jones et al., 2018), and patients with neuropathic pain often report adverse emotional and cognitive consequences (Mendes et al., 2008; Begoña et al., 2018), such as anxiety, depression, sleep disorders (Radat et al., 2013; Attal et al., 2011), attention deficits, memory difficulties, and decreased decision-making ability (María and Rosa, 2005; Mccracken and Iverson, 2001).

Currently, cognitive function is clinically improved by stimulating the nerve branches of the lumbosacral plexus, which is still in the exploratory stage (Qu et al., 2016; Yamada et al., 2004). However, acupuncture at acupoints where the lumbosacral plexus nerves are distributed can improve cognitive function, usually through the synergistic action of multiple nerve branches. The sciatic nerve is the most commonly involved pathway. Acupoints such as SP6 (Sanyinjiao), KID3 (Taixi), KI1 (Yongquan), and GB30 (Huantiao) are mainly innervated by the branches of the sciatic nerve. Acupoints such as ST36 (Zusanli), LR3 (Taichong), and GB34 (Yanglingquan) are

associated with the branches of the sciatic nerve. Evidence suggests that long-term acupoint massage (6 months) can improve cognitive function and activities of daily living in patients with mild to moderate dementia (Liang Ooi et al., 2023), with SP6 being a commonly used acupoint for intervention.

3.5.1 Neural plasticity

Animal experiments have shown that electroacupuncture (EA) at SP6 improves spatial learning ability in rats with daytime cognitive dysfunction after insomnia, possibly related to the upregulation of brain-derived neurotrophic factor (BDNF)/Tropomyosin receptor kinase B (TrkB) signaling and inhibition of neuronal apoptosis after EA (Lina et al., 2023). When acupuncture was applied to rats with ketamine-induced cognitive impairment (Miao et al., 2023), it was found that the rats' neurological and behavioral symptoms improved, and the neurodegeneration of the locus coeruleus (LC) was alleviated, possibly due to EA regulating the Calmodulin-Dependent Protein Kinase II (CAMKII)/cAMP Response Element-Binding Protein (CREB) pathway, thus mitigating the adverse effects mentioned above. When mice experience cognitive changes due to social isolation, stress-induced increases in neurotrophic factors such as nerve growth factor (NGF) or BDNF occur (Aloe et al., 2002; Alleva et al., 1996), and EA can reverse these changes (Manni et al., 2009). Acupuncture at ST36 significantly reduces the escape latency of VD rats (Li et al., 2015), improves impaired hippocampus-dependent memory in animals, and is associated with regulating energy metabolism in astrocytes, increasing neuron counts, and upregulating synaptic plasticity (Li et al., 2015). Acupuncture at ST36 can enhance calcium signals in pyramidal neurons and astrocytes in the somatosensory cortex, leading to delayed calcium transients in astrocytes, activating neurons and astrocytes (Chang et al., 2022).

3.5.2 Changes in EEG mechanism and brain functional connectivity

Acupuncture at ST36 (Zusanli) modulates both periodic (delta, alpha) and aperiodic (slope, offset) electroencephalogram (EEG) features, reflecting neural entrainment and network changes (Yu et al., 2024; Yu et al., 2018; Yu et al., 2024). Graph theory and machine learning reveal that varied acupuncture techniques produce distinct connectivity patterns, enabling precise classification (Yu et al., 2019; Rao et al., 2025). Resting-state fMRI studies have shown that acupuncture at KI3 (Taixi) not only activates brain regions associated with perception, movement, cognition, association, hearing, and vision in healthy young adults, healthy elderly individuals, and patients with MCI, but also enhances connectivity between the dorsolateral/medial prefrontal cortex and the posterior temporal lobe (Zhu et al., 2015; Chen et al., 2014). Notably, compared with healthy individuals, acupuncture at KI3 (Taixi) in MCI patients can modulate additional cognition-related brain regions: it not only reduces the amplitude of low-frequency fluctuations (ALFF) in areas such as the posterior cingulate gyrus, right frontal lobe, and cerebellum, but also increases ALFF values in the left precuneus, thereby exerting a more significant therapeutic effect under pathological conditions (Jia et al., 2015). Meanwhile, acupuncture at GB34 can regulate local homogeneity in areas including the anterior insula as well as the frontal and temporal lobes (Chen et al., 2012; Feng et al., 2012; Liu et al., 2018). Moreover, fMRI research has found that acupuncture at LR3 primarily activates brain functional networks associated with vision, association, and

emotional cognition (Zheng et al., 2016). Further experiments indicate that simultaneous needling of LR3 and KI3 (Taixi) in healthy volunteers activates brain regions related to vision, emotion, and cognition while inhibiting areas linked to emotion, attention, speech semantics, and memory (Zhang et al., 2015).

3.6 Acupuncture and cervical plexus stimulation

The cervical plexus comprises the anterior branches of the first to fourth cervical nerves, situated deep to the upper part of the sternocleidomastoid muscle, anterior to the origins of the scalene muscles and levator scapulae muscle (Usui et al., 2010). The primary cutaneous branches of the cervical plexus are (I) the lesser occipital nerve, originating from the C2 spinal nerve, distributed over the posterior aspect of the scalp and ear, providing skin sensation; (II) the transverse nerve of the neck. Composed of branches from C2 and C3, distributed over the anterior neck skin, providing skin sensation; (III) the supraclavicular nerve, formed by the combination of branches from C3 and C4, primarily distributed over the lower lateral neck, upper chest wall, and shoulder skin; (IV) the greater occipital nerve, composed of branches from C2 and C3, distributed over the scalp and adjacent skin. All of these nerves are cutaneous nerves. In addition, the cervical plexus gives off some muscular branches to supply the muscles of the neck region and diaphragm. The phrenic nerve, a motor branch of the cervical plexus, originates from the anterior branches of C3–C5 and provides motor innervation to the diaphragm (Waxenbaum et al., 2024; Kim et al., 2018; Paraskevas et al., 2014). Skin electrodes target the greater occipital nerve, establishing a communication gateway from the periphery to the brain via specific afferent fibers that project to the brainstem and synapse with the nucleus tractus solitarius (NTS) (Luckey et al., 2023; Adair et al., 2020), further activating the LC noradrenergic system of the brainstem, projecting to both the primary cortex and subcortical areas (Berridge and Waterhouse, 2003).

Branches of the cervical nerve, greater occipital nerve, and lesser occipital nerve are distributed under the acupoint of GB20 (Fengchi). Clinical studies have shown that massage of GB20 (Fengchi) and similar acupoints for 6 months can improve cognitive function and activities of daily living in patients with mild to moderate dementia (Liang Ooi et al., 2023). There is also a tiny occipital nerve distributed under the GB12 (Wangu) acupoint. Stimulation of this acupoint significantly improved learning ability in rats compared to the VD model group, with decreased mRNA expression levels of TNF- α , IL-6, and IL-1 β (Fang and Sui, 2016). Animal experiments with laser acupuncture at DU20 (Baihui) have shown a significant increase in neuronal density in the CA1 and CA3 regions, increased activity of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), decreased IL-6 and β -amyloid density ratio, exerting antioxidant and anti-inflammatory effects, thereby alleviating cognitive impairment in focal ischemic rats (Jittiwat, 2019). EA at DU20 (Baihui) and DU14 (Dazhui) enhances learning and memory abilities in rats, downregulating levels of inflammatory factors such as IL-1 β , JAK2, and TNF- α (Han et al., 2017), alleviating hippocampal synaptic plasticity damage (Zheng et al., 2016), upregulating mRNA expression of BDNF and vascular endothelial growth factor

(VEGF) (Kim et al., 2014), increasing regional cerebral blood flow (rCBF) (Han et al., 2017), promoting the regeneration of oligodendrocytes (Ahn et al., 2016), and increasing the number of proliferating cells and differentiated cells in the hippocampus and subventricular zone (Kim et al., 2014). Neuroimaging evidence indicates that EA at DU20 (Baihui) induces an increase in regional homogeneity (ReHo) in multiple areas, including the orbitofrontal cortex (OFC), midcingulate cortex (MCC), precentral cortex, and precuneus. It decreases ReHo values in the anterior cingulate cortex (ACC), supplementary motor area, thalamus, and cerebellum and decreases ReHo values in the precentral gyrus (preCUN) (Yu et al., 2019). Acupuncture at DU20 (Baihui), GB20 (Fengchi), and the Chorea-Tremor Controlled Zone reduced PD tremor by modulating the cerebello-thalamo-cortical circuit (decreased DC/ReHo and increased ALFF) and altering cognitive networks (DMN, visual areas, insula, PFC) (Li et al., 2018).

3.7 Acupuncture and thoracic plexus stimulation

Thoracic nerves originate from the thoracic spinal cord. After exiting through the intervertebral foramen, they divide into anterior, posterior, meningeal, and communicating branches. Except for the first and parts of the twelfth pair, the anterior branches do not form plexuses and maintain segmental characteristics. The first to eleventh pairs are intercostal nerves, while the twelfth pair forms the subcostal nerves (Cramer, 2014).

Acupuncture or moxibustion at single or multiple points corresponding to the distribution of thoracic nerves can improve cognitive function. The location of the CV4 (Guanyuan) acupoint corresponds to the peripheral nerves of the T11-T12 segments. Studies have shown that moxibustion at CV4 (Guanyuan) and moxa smoke exposure both ameliorated cognitive deficits in APP/PS1 mice by normalizing tricarboxylic acid cycle flux and unsaturated fatty acid metabolism (Ha et al., 2019). Before the decline in cognitive abilities, there is a significant decrease in cerebral glucose metabolism (Shoshan-Barmatz et al., 2018). Neuronal functional activity requires a lot of energy, which is mainly provided by mitochondria. Mitochondrial defects can lead to synaptic dysfunction, neuroinflammation, and neuronal death (Arnold and Finley, 2023). Peripheral nerves from the T7-T8 segments innervate CV12 (Zhongwan). Using resting-state fMRI, researchers observed brain function changes during EA at CV4 (Guanyuan) and CV12 (Zhongwan) in 21 healthy volunteers. Stimulation significantly enhanced local connectivity in the ventromedial prefrontal cortex network, including the medial orbitofrontal and ventral anterior cingulate cortices, compared to the resting state (Fang et al., 2012).

3.8 Acupuncture and trigeminal nerve stimulation

The trigeminal nerve, the fifth cranial nerve, is located on the ventrolateral surface of the brainstem at the midpoint level. It comprises a thicker sensory root and a thinner motor root. Originating from the petrous part of the temporal bone, it terminates in the principal and spinal nuclei within the brainstem. The trigeminal nerve

has three main branches—ophthalmic, maxillary, and mandibular—extensively distributed across the eye, forehead, nose, upper jaw, oral cavity, and cheek, and it innervates facial sensation and transmits sensory information from the dura mater (Kumada et al., 1977). It connects to the vasomotor center of the brainstem, including the lateral tegmental area, and is easily stimulated percutaneously (Goadsby et al., 1996; DeGiorgio et al., 2011).

Acupuncture at certain head and facial acupoints often coincide with the trigeminal nerve distribution. For example, ST7 (Xiaguan) is located at the branches of the facial and auriculotemporal nerves, with the mandibular nerve, including the inferior alveolar and lingual nerves. Other points like GB14 (Yangbai) and BL2 (Zanzhu) are distributed with the supraorbital and frontal nerves. According to meridian theory, the trigeminal nerve's branches partial consistency with the routes of the three yang meridians of the hand and foot. The therapeutic effects of acupuncture at head acupoints seem to be associated with more inputs from the trigeminal nerve and the unique roles of the TG and trigeminal spinal nucleus (STN) in regulating meningeal function (Moskowitz et al., 1998). It is well-known that endogenous substances change after acupuncture. As a neuroregulatory therapy, trigeminal nerve stimulation is believed to treat VCI by increasing dopamine release in the hippocampus through the TG - corticotropin-releasing hormone (CRH) - dopamine transporter (DAT) - hippocampus (HPC) pathway, thereby enhancing hippocampal-dependent memory (Xu et al., 2023). Electrical acupuncture has been repeatedly shown to have effects on neuroprotection (Liu et al., 2017; Shi et al., 2018), synaptic plasticity (Gerrow and Triller, 2010), and regulation of neural cross-talk (Tu et al., 2019; Chang et al., 2018).

3.8.1 Neural plasticity

Following electrical acupuncture stimulation of the trigeminal nerve branches EX-HN3 (Yintang) and DU20 (Baihui), there was a reversal of ischemia-reperfusion injury, with increased expression of BDNF, tyrosine kinase B, N-methyl-D-aspartate receptor 1, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, gamma-aminobutyric acid A receptor, Ca²⁺/calmodulin-dependent protein kinase II, and synaptic density protein 95 in the prefrontal cortex and hippocampus, leading to improved spatial and cognitive memory in rats (Zheng et al., 2020).

3.8.2 Regulation of cerebral blood flow and cerebral perfusion

Stimulation of the trigeminal nerve has a relevant effect on the cerebral arterial vascular system, increasing CBF through retrograde evoked potentials, trigeminal parasympathetic reflex, and other central pathways (White et al., 2021). Long-term changes in CBF and perfusion are among the causes of VCI. A study found that EA at GB15 (Toulingqi) significantly increased CBF in rats, suggesting a trigeminal nerve-meninges-cerebrospinal fluid pathway as a potential shortcut for brain regulation and treatment (Wang et al., 2017). Electrical stimulation of the trigeminal nerve can balance disturbances in cerebral perfusion (Shiflett et al., 2015; Chiluwal et al., 2017), which is associated with activation of the parasympathetic nervous system (Branston, 1995) and release of related vascular active molecules such as acetylcholine (Ach), vasoactive intestinal peptide (VIP), and nitric oxide (NO) (Shelukhina et al., 2017; Goadsby and Shelley, 1990; Jones et al., 2001). A study found that 100 Hz trigeminal EA enhances

parasympathetic tone, upregulates eNOS-derived NO and acetylcholine vasodilation, and improves prefrontal cortical perfusion (Waki et al., 2017). A recent study implanted a neuromodulatory device into the pterygopalatine ganglion located deep beneath the ST7 (Xiaguan) acupoint in patients with acute ischemic stroke (Bornstein et al., 2019). This device stimulation increased CBF and perfusion within 24 h, improving cortical involvement. The effect within 3 h was comparable to intravenous alteplase and exceeded alteplase between 3–4.5 h.

3.8.3 Changes in brain functional connectivity

International standard scalp acupuncture involving the distribution of the trigeminal nerve has been shown to enhance the regional homogeneity of the anterior cingulate cortex and medial prefrontal gyrus in healthy elderly individuals (Chung et al., 2019). Moreover, studies have demonstrated that EA at GV24 (Shenting) and ST8 (Touwei) enhances the functional connectivity of the executive control, sensorimotor, and attention networks, while reducing the connectivity of the DMN (Chen et al., 2023). In addition, among acute ischemic stroke (AIS) patients with high-risk factors for VCI, those who received scalp acupuncture showed significant improvements in NIHSS scores and increased functional connectivity measures (VMHC, ALFF, ReHo) in regions responsible for sensory integration, language processing, and motor coordination (Liu et al., 2021).

3.9 Acupuncture and Vagus nerve stimulation

The vagus nerve (VN) is the tenth cranial nerve, with extensive distribution throughout the body, making it the longest and most widely distributed nerve among the cranial nerves. It originates from the medulla oblongata of the brainstem, passes through the jugular foramen into the carotid sheath, travels along the posterior groove between the carotid artery or internal carotid artery and internal jugular vein to reach the root of the neck, and then extends to the thorax and abdomen (Foley and DuBois, 1937). It comprises approximately 20% efferent fibers and 80% afferent fibers. Efferent or motor visceral pathways innervate organs below the neck, including the heart, lungs, and gastrointestinal tract, with the brain receiving information from the afferent projections of the vagus nerve. Afferent fibers project to the NTS and LC within the brainstem (Nomura and Mizuno, 1984), then directly or indirectly project to many brain areas, such as the midbrain, hypothalamus, amygdala, hippocampus, and frontal lobe (Lange et al., 2011; Carreno and Frazer, 2016). The auricular branch of the VN is the only afferent branch located on the body surface, innervating the skin around the external auditory meatus, inner ear pinna, and earlobe (Butt et al., 2020; Kiyokawa et al., 2014; Peuker and Filler, 2002). Moreover, the earlobe is entirely innervated by the auricular branch of the vagus nerve (Peuker and Filler, 2002). It contains approximately 80% of afferent fibers that transmit sensory information to the central nervous system, while the remaining fibers transmit motor information. A recent systematic review suggests (Robinson et al., 2012) that the auricular branch of the vagus nerve projects to the NTS, which further connects with other brain regions such as LC, lateral hypothalamus, amygdala, anterior cingulate cortex, insular cortex, and ventral tegmental area.

The EX-HN13 (YiMing) acupoint and auricular acupoint are commonly used acupoints in clinical practice for treating VCI. Stimulating these acupoints may activate pathways related to the vagus nerve. The EX-HN13 (YiMing) acupoint is located 1 cun posterior to TB-17 (YiFeng) at the inferior border of the mastoid process. The YiMing acupoint's deep needling can stimulate the vagus nerve's trunk. Some ear acupoints, such as heart (concha, CO15) and kidney (CO10), are widely distributed with the auricular vagus nerve. It is well-known that electrical stimulation of the vagus nerve and transcutaneous electrical stimulation of the auricular vagus nerve (taVNS) are two therapies that are quite similar in principle and mechanism of action. taVNS likely originated in China, with traditional Chinese medicine theory considering the relationship between "ear acupoints" and "disease" based on meridian theory and holistic concepts (Pj et al., 2015). In 1990, the World Health Organization recognized ear acupuncture as a microsystem of acupuncture that can positively affect systemic function regulation (World Health Organization, 1990).

3.9.1 Neural plasticity

The occurrence of VCI is closely related to central nervous system damage caused by ischemia and hemorrhage, and neuroplasticity is important for the recovery of cognitive function. VNS can upregulate the expression of BDNF and dendritic spines in the hippocampus (Biggio et al., 2009) and can activate serotonergic neurons in the hippocampus (Manta et al., 2009). Neurotransmitters associated with VNS, such as norepinephrine released from the LC that activates adrenergic receptors, play a crucial role in enhancing attention, reactivity, and other cognitive functions (Cheng et al., 2022). Ach supports memory formation and gamma-aminobutyric acid (GABA) not only inhibits but also coordinates excitatory activity, both playing key roles in cognitive enhancement (Trifilio et al., 2023). Electrical current pulses at a certain frequency for ear stimulation can upregulate the activation of the locus coeruleus-norepinephrine pathway, and upregulate the release of acetylcholine and GABA (Trifilio et al., 2023).

3.9.2 Anti-inflammation mechanism

Neuroinflammation is an immune cascade reaction mediated by glial cells in the central nervous system where innate immunity resides. Various destructive events, including hypoxia, ischemia, and infection, can trigger inflammatory responses. Long-term chronic hypoperfusion-induced ischemia and hypoxia can over-activate neuroinflammation, leading to pathological changes such as cell apoptosis and BBB damage, exacerbating the occurrence and development of cognitive impairment (Tian et al., 2022). The parasympathetic ganglia in the vagus nerve express receptors for interleukin IL-1 (Sternberg, 2006), and communication between the afferent and efferent branches of the vagus nerve in the NTS constitutes a connection between somatic immunity and the central nervous system (Thayer and Sternberg, 2010). The NTS projects to the dorsal motor nucleus of the vagus nerve (DMV) and nucleus ambiguus (NA), where these signals regulate many immune organs such as the spleen, liver, and gastrointestinal tract, while acetylcholine released by the vagus nerve can regulate immune responses by modulating various cell receptors such as NF- κ B's α 7 nicotinic acetylcholine receptor (α 7nAChR) (Ma et al., 2019), these parasympathetic neural pathways together constitute the so-called "cholinergic anti-inflammatory pathway."

Furthermore, the regulation of microglia by the vagus nerve is also considered relevant to cognition, as degeneration of the LC and downregulation of norepinephrine levels in the projection area can lead to increased activation of microglia and astrocytes (Kaczmarczyk et al., 2017). The chronic activation and polarization of microglia can activate inflammatory responses. VNS can restore microglia to a healthy state by upregulating norepinephrine through the LC, and changes in microglial expression can regulate neurotrophic factors such as BDNF and bFGF, as well as anti-inflammatory cytokines such as IL-4, IL-10, and TGF- β , thereby adjusting the tendency of neuroinflammation (Clancy et al., 2014).

3.9.3 Regulations of cerebrospinal fluid circulation, cerebral blood flow, and perfusion

Cerebrospinal fluid circulation dysfunction is associated with cognitive impairment, and patients with cognitive impairment may experience cerebrospinal fluid circulation disorders, which correlate with symptoms' severity (Attier-Zmudka et al., 2019). A study on the relationship between VNS and cerebrospinal fluid circulation reported that VNS after stroke-induced VCI can enhance cerebrospinal fluid circulation (Cheng et al., 2020), which is beneficial for the metabolism and excretion of toxic metabolites in the brain substance during the progression of ischemic stroke, such as amyloid-beta and Nogo-A. Reduced CBF leading to brain damage is also an important condition for the onset of VCI, and vascular remodeling is crucial in the course of stroke and cerebral small vessel disease. The establishment of collateral circulation and angiogenesis are the main reasons for increasing cerebral blood volume (Liu et al., 2014). VNS has been shown to increase microvascular density and endothelial cell proliferation around the ischemic area (Jiang et al., 2016), and upregulate the expression of BDNF, VEGF (Jiang et al., 2016), and GDF11 (Katsimpardi et al., 2014), which can promote angiogenesis and increase the proliferative capacity of brain capillary endothelial cells (ECs). Other studies have also shown that VNS may act by increasing CBF in the bilateral thalamus, hypothalamus, cerebellar hemisphere, right postcentral gyrus, frontal lobe cortex, and cingulate cortex (Conway et al., 2006).

3.9.4 Changes in brain functional connectivity

With the development of functional magnetic resonance imaging, brain functional connectivity is another major approach to treating VCI. VNS transmits signals to important brain areas, such as the LC and NTS, through electrical pulse conduction (Schachter and Saper, 1998). These structures relay signals to higher structures such as the hippocampus, insula, frontal lobe cortex, and motor cortex (Dolphin et al., 2022). The LC, as the noradrenergic (NE) center, is believed to play an important role in cognitive function, with its LC-NE system associated with attention, executive function, memory, and emotion recognition (Aston-Jones and Cohen, 2005). VNS is believed to be associated with this (Naparstek et al., 2023). Another theory suggests that cognitive aging and reduced cerebral hemisphere activity, such as in the frontal lobe cortex (Dolcos et al., 2002), to some extent exacerbate this barrier. VNS as an additional neural circuit can be a compensatory neural resource to enhance cognitive function (Reuter-Lorenz and Cappell, 2008).

3.9.5 Other effects

Some studies have also proposed that VNS can reduce BBB permeability and protect its integrity. During the onset of VCI, the integrity of the BBB is beneficial for preventing harmful fluids, chemicals, and blood-derived cells from entering the brain parenchyma, thereby reducing the incidence of inflammatory reactions (Jiang et al., 2018). Additionally, during ischemia-reperfusion injury, VNS can downregulate the levels of TUNEL-positive cells and cleaved caspase-3 protein in the ischemic penumbra and upregulate p-Akt to inhibit the occurrence of cell apoptosis (Jiang et al., 2014). VNS can also affect cognition through the brain-gut axis pathway, which is related to the autonomic regulation function of the vagus nerve (Carabotti et al., 2015). The enteric nervous system (ENS) can produce more than 30 neurotransmitters, which can be released into the bloodstream through the BBB. Communication between the vagus nerve and ENS is mainly mediated by cholinergic activation, serving as a flow of information between the gut and the vagus nerve and central nervous system (Carabotti et al., 2015; Schemann, 2005).

3.10 Acupuncture and other nerves stimulation

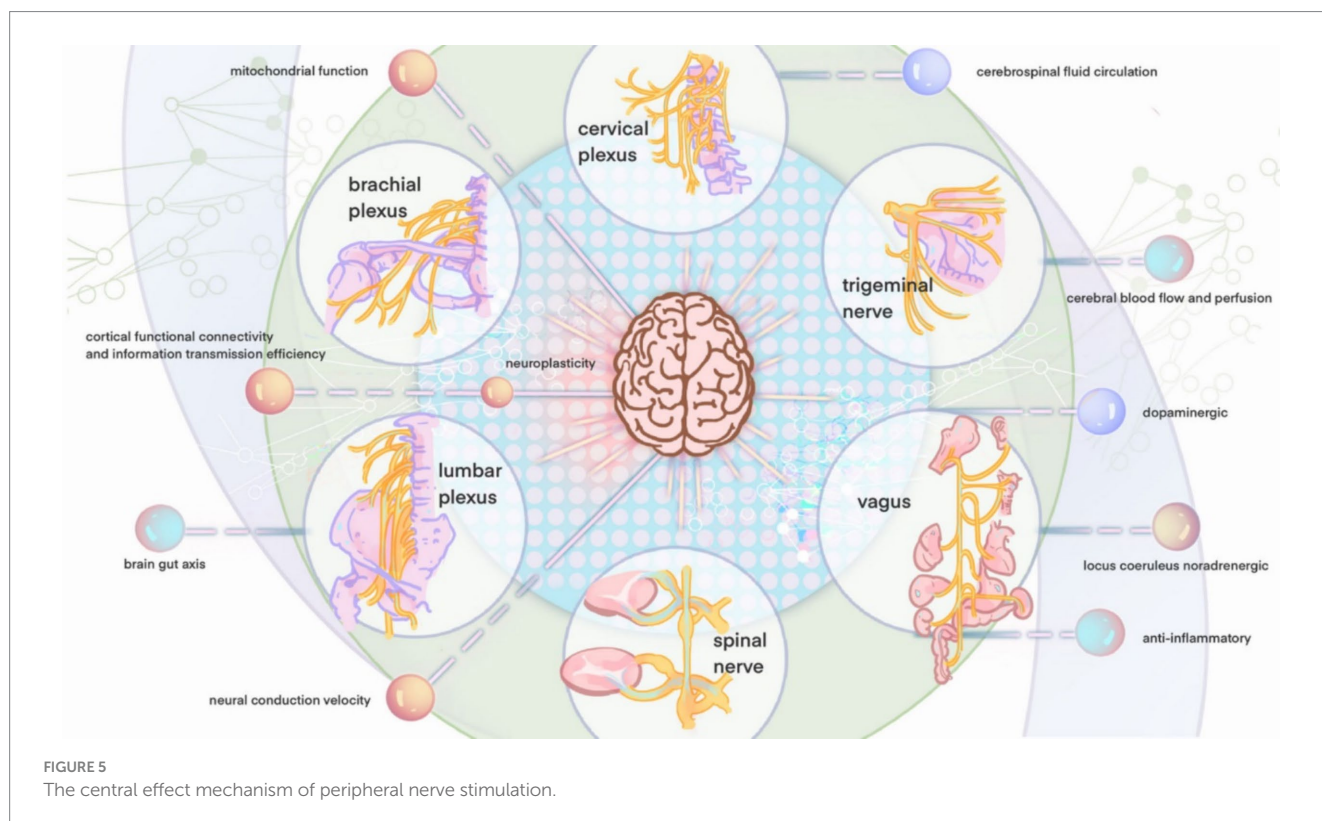
Several potential acupuncture mechanisms involve other cranial nerves, such as the facial, optic, and olfactory nerves. Multiple facial acupoints involve the distribution of the facial nerve, such as ST7 (Xiaguan), which distributes the zygomaticotemporal branch of the facial nerve and fiber projections from the facial nerve nucleus. Facial nerve stimulation has been studied for increasing CBF in ischemic stroke (Borsody et al., 2013; Borsody et al., 2014). A study explored the minimum stimulation parameters for increasing CBF with facial nerve magnetic stimulation in Yorkshire pigs and tested safety, tolerability, and efficacy in healthy volunteers (Sanchez et al., 2018). The results indicated that continuous stimulation of the facial nerve at 1.6–1.8 Tesla power for approximately 10 min resulted in an average CBF of $32 \pm 6\%$, with a $\geq 25\%$ increase observed in 10 out of 31 volunteers. Some other cranial nerve pathways are gradually being discovered, such as the optic nerve and olfactory nerve. There is an association between the optic nerve and MCI, as retinal imaging through fundus photographs or optical coherence tomography (OCT) observes changes in the optic nerve head to identify early cognitive impairment (Gao et al., 2023). MCI patients exhibit significant progressive tau pathology and deposition of amyloid plaques in the olfactory area (CAm), with signal changes from the olfactory nerve possibly predicting the development of dementia (Bathini et al., 2019). Neural stimulation not only affects a series of changes in the peripheral and central systems but also heralds changes in the function of higher centers with changes in peripheral nerve signals. The nervous system operates like a precise, tightly linked network, where changes in any link may lead to effects on the periphery or even central nervous system changes. Many nerves, such as the optic nerve and olfactory nerve, cannot be stimulated through acupuncture, suggesting that improvements or new inventions are anticipated.

4 Discussion

The neural pathway is one of the main avenues for achieving acupuncture effects, especially in treating peripheral and central nervous system diseases. Stimulating different nerve trunks may have different effects, as the types of nerve fibers contained in nerve trunks vary, with a bundle of nerves potentially containing up to seven different types of nerve fibers. These nerve fibers include somatic afferent and efferent nerve fibers and autonomic nerve fibers. Stimulation of a certain nerve trunk may evoke multiple and diverse nerve reflex effects, and with the varying number and complexity of different nerve fibers, the effects and pathways become even more intricate. For central nervous system diseases such as VCI, cerebrovascular accidents, and AD, neural stimulation therapy may be an effective and direct approach, as it circumvents the restrictive effects of the BBB on certain drugs. Unraveling the mechanisms underlying the central effects induced by nerve stimulation reflexes is conducive to advancing the renewal of existing therapies. And it holds significant importance in revealing the mechanisms of acupuncture.

When attempting to unravel the complex neural effects of acupuncture on central nervous system diseases such as VCI based on different nerve types, it is found that the differences in acupuncture effects based on acupoints are indeed related to anatomical and neural structural variations. For instance, somatic afferent and efferent nerve stimulation pathways are more closely associated with central nervous system plasticity and brain functional connectivity. In contrast, the autonomic nervous pathway is more relevant to anti-inflammatory responses and CBF regulation (Figure 5). The brachial plexus via LI4 (Hegu) and

PC6 (Neiguan) enhances cognitive function by modulating hippocampal connectivity, increasing motor cortex activity, and improving motor imagery accuracy through median and ulnar nerve stimulation. EA at PC6 (Neiguan) upregulates BDNF while suppressing axon-growth inhibitors, thereby promoting neuronal sprouting and synaptogenesis (Mu et al., 2023). Lumbosacral plexus stimulation at SP6 and Zusanli (ST36) improves spatial learning, alleviates neuropathic pain, and boosts mitochondrial function via BDNF/TrkB signaling. Zusanli also increases VEGF, activating PI3K/ERK pathways to foster neurogenesis and cortical angiogenesis and translating into enhanced synaptic plasticity and functional recovery (Mu et al., 2023). Cervical plexus activation at GB20 (Fengchi) and Baihui (DU20) reduces inflammation, enhances antioxidant activity, and modulates both sensorimotor and default mode networks. Stimulation of Baihui elevates BDNF and VEGF in ischemic brain tissue and improves cerebral perfusion and repair through angiogenesis-driven mechanisms (Li et al., 2022). Thoracic nerve stimulation at CV4 (Guanyuan) and CV12 (Zhongwan) enhances prefrontal connectivity and cerebral glucose metabolism. Trigeminal nerve activation at EX-HN3 (Yintang) and GB15 (Toulingqi) increases CBF, upregulates synaptic proteins such as BDNF, and combats ischemia–reperfusion injury. VNS at EX-HN3 (Yintang) and auricular points promotes anti-inflammatory responses via the cholinergic pathway in which vagal efferents act on macrophage $\alpha 7$ nicotinic acetylcholine receptors to reduce systemic inflammation (Oh and Kim, 2022). This stimulation also upregulates neurotransmitters including norepinephrine and acetylcholine and enhances both angiogenesis and cerebrospinal fluid circulation. Emerging evidence suggests that facial and optic



nerve stimulation may influence cerebral perfusion and serve as early biomarkers of cognitive change. Together these neuroplastic and anti-inflammatory mechanisms provide a coherent basis for acupuncture's therapeutic effects on cognitive function.

However, there are some limitations in our review. First, our literature search used limited search terms and databases, potentially missing relevant studies. This incomplete retrieval could bias our conclusions by overlooking contradictory or supportive evidence. Second, we did not perform a meta-analysis or quantitative synthesis, limiting our ability to accurately estimate effect sizes or consistency across studies; thus, our findings remain qualitative. Third, attributing specific mechanisms to individual acupoints is based largely on indirect evidence, inferred from general findings or animal studies rather than confirmed by direct experimental data. Fourth, many reviewed studies employed combined acupoint protocols rather than testing single points separately. Finally, research on somatic nerve involvement in cognitive impairment remains limited, restricting our understanding of how sensory or motor signal deficits may contribute to neuronal loss and cognitive decline. Therefore, targeted studies exploring isolated acupoint mechanisms and somatic nerve roles in cognitive disorders are needed.

Future research should address these gaps by focusing on specific acupoint mechanisms through targeted single-acupoint studies. This approach could clarify the unique molecular pathways associated with each acupoint. Additionally, integrating multimodal methods such as functional MRI or EEG combined with molecular biomarkers (e.g., BDNF, inflammatory cytokines) would enhance our understanding of how acupuncture-induced neural changes correlate with therapeutic outcomes. Further systematic exploration of EA parameters, including frequency and intensity, could optimize therapeutic efficacy by identifying conditions that specifically activate desired neural pathways. Finally, translating these findings into rigorously designed clinical trials is essential to validate mechanisms observed in animal models. Long-term human studies could assess whether acupuncture confers sustained neuroplastic or disease-modifying benefits, thereby advancing its evidence-based clinical application. Of course, as unknown territories emerge, the principles of acupuncture, an “ancient therapy,” and the scientific connotations of meridians and acupoint theories will be further revealed.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding authors.

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XY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. BL: Conceptualization, Data curation, Funding acquisition, Resources, Writing – original draft, Writing – review & editing. LW: Conceptualization, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. YC: Project administration, Validation, Writing – original draft.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Open Project of National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion (Grant No. NCRCP2023009).

Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnagi.2025.1515327/full#supplementary-material>

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