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# Research Progress and Mechanisms of Acupuncture Combined with Transcutaneous Vagal Nerve Stimulation in the Treatment of Cognitive Impairment after Stroke

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**Abstract:** Cognitive impairment is a common complication after stroke, which not only affects the rehabilitation process of patients but also increases the family and socio-economic burden. Finding an effective treatment for cognitive impairment after stroke is urgent. Acupuncture can effectively activate blood circulation, dredge collaterals, tonify qi and blood, and regulate yin and yang. It is an effective method for the treatment of cognitive impairment after stroke. Recent studies have shown that acupuncture combined with various modern rehabilitation techniques, such as transcutaneous vagus nerve stimulation, has better clinical effects than either acupuncture or rehabilitation therapy alone. This article reviews the clinical research and basic mechanisms in this field by searching Chinese and English literature from the past 20 years, aiming to provide research ideas for future studies on the combined treatment of post-stroke cognitive impairment and related mechanisms.

**Keywords:** Percutaneous vagal nerve stimulation; Cognitive impairment after stroke; Stroke; Acupuncture

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## 1. Introduction

Post-stroke cognitive impairment (PSCI) is a clinical phenomenon secondary to stroke, characterized by cognitive decline lasting less than six months. This condition encompasses cognitive impairment caused by various types of stroke, including multiple infarctions, key brain area infarctions, subcortical infarctions, and cerebral hemorrhage [1].

In recent years, population aging has become increasingly prominent in China, with stroke emerging as the leading cause of mortality among Chinese residents [2]. As the incidence of stroke continues to rise annually, its high disability, mortality, and recurrence rates have resulted in a growing number of patients experiencing cognitive impairment after stroke. Reports indicate that up to 69.8% of stroke patients in Asian countries experience cognitive decline within three months [3], and stroke increases the risk of dementia by 4 to 12 times [4]. Severe cases can significantly impact patients' quality of life and social activities, imposing a substantial burden on families and society. Therefore, early intervention and treatment of PSCI are crucial for preventing and managing cognitive impairment after stroke.

Currently, the main treatment methods for PSCI patients include drug therapy, management of mental and behavioral symptoms, and rehabilitation treatments combining traditional Chinese and Western medicine [5,6]. Studies suggest that rehabilitation techniques, such as percutaneous vagal nerve stimulation, also have certain clinical effects [7].

With advancements in medicine, exploring ways to combine traditional Chinese and Western rehabilitation therapies holds significance for improving the efficacy of PSCI treatment. Percutaneous vagal nerve stimulation is a rehabilitation technique that regulates the vagus nerve network. The various branches of the vagus nerve govern functional structures involved in memory processing, and studies have shown that vagus nerve stimulation (VNS) can promote cognitive recovery [8,9].

Acupuncture combined with percutaneous vagal nerve stimulation can effectively improve cognitive impairment after stroke and delay its progression. Therefore, the primary aim of this study is to summarize clinical research on acupuncture combined with percutaneous vagal nerve stimulation in treating PSCI. This aims to provide new and more effective treatment methods and ideas for PSCI and offer clinical evidence for the application of acupuncture combined with percutaneous vagal nerve stimulation in PSCI management.

## 2. PSCI overview

### 2.1. Clinical manifestations

Stroke imposes a significant burden in China. In 2020, the prevalence and incidence of stroke in China were 2.6% and 50.52 million, respectively [10]. Approximately one in three stroke patients develop post-stroke cognitive impairment (PSCI) [11]. PSCI is characterized by cognitive impairment that occurs within six months after a stroke and persists for more than three months. The occurrence of a stroke is a prerequisite for the diagnosis of PSCI, with ischemic stroke being the most common type, although hemorrhagic stroke is also included. The primary clinical manifestation is mild cognitive impairment, with daily life and work abilities being normal or only slightly affected.

### 2.2. Epidemiological data of PSCI

Epidemiological data on PSCI have been widely reported, but significant variability exists among studies. Differences arise due to the selection of study populations, research timelines, sampling periods, research contexts, cognitive tests used, and cutoff values [12]. Recent studies have reported that many stroke patients develop cognitive impairment following stroke events [13,14]. The incidence of PSCI ranges from 11% to 42%, while the proportion of PSCI without dementia varies from 14% to 29% [15]. To date, no large-scale study on the incidence of PSCI has been conducted in China. The prevalence of related conditions has increased significantly, with the growing incidence of PSCI posing substantial challenges to patients' quality of life, mental health, family caregiving, and economic resources.

## 2.3. The pathogenesis of PSCI

The pathogenesis of PSCI is not fully understood in modern medicine. It is highly complex and influenced by multiple factors, with considerable variability among studies. The pathogenesis encompasses neuroanatomical and pathological changes, cerebral microvascular lesions, neurodegenerative diseases, genetic factors, and molecular mechanisms [7]. Molecular mechanisms involve nerve cell apoptosis, oxidative stress-induced nerve cell damage, neuroinflammatory injury, white matter damage, neural pathway disruptions, blood-brain barrier dysfunction, synaptic plasticity impairment, amyloid-β protein deposition in the brain, cholinergic system dysfunction, excitatory amino acid cytotoxicity, and oxygen free radical damage mechanisms [7].

# 3. Acupuncture treatment of PSCI

Acupuncture treatment for PSCI does not have a direct counterpart in terms of disease nomenclature. However, based on its clinical manifestations, PSCI corresponds to traditional Chinese medicine (TCM) diseases such as "dementia," "forgetfulness," and related conditions. Ye Tianshi stated in *Clinical Guide Medical Records* from the Qing Dynasty: "At the beginning of apoplexy, diuresis is obvious in the elderly," suggesting that cognitive impairment may manifest in the early stages of stroke [16,17]. Therefore, PSCI is secondary to stroke, with its pathological basis rooted in the brain. TCM considers the disease's origin in the kidney, while it is also closely related to the heart, liver, spleen, and other organs. The etiology and pathogenesis are complex. Physicians across generations have believed that the disease is centered in the brain, with turbid phlegm and blood stasis as primary pathological factors. Its therapeutic mechanisms may involve promoting neuron regeneration and repair, regulating the balance of qi and blood, and harmonizing the functions of the internal organs.

Currently, PSCI is treated through drug therapy, management of mental and behavioral symptoms, and TCM and Western rehabilitation techniques. Acupuncture has gained increasing attention due to its multi-target, multi-mechanism, safe, and effective characteristics, including scalp acupuncture, ear acupuncture, buccal acupuncture, and body acupuncture.

## 3.1. Scalp acupuncture selection

The pathology of cognitive impairment after stroke is located in the brain. Shao Tongzhen stated in *The Doctor is Easy to Manage the Brain*: "The brain is the master of the body, also known as the residence of the soul. The body can perceive movement, remember ancient and modern times, and process all things due to the brain's power." The brain, considered the sea of marrow, governs emotion and perception. Regulating brain meridians is thus a critical aspect of achieving therapeutic effects.

Zhang and Li [18] used Baihui as the central point and alternately needled three groups of Bagua points in eight directions around Baihui. After analyzing scale data and homocysteine levels post-treatment, it was concluded that this therapy improves various aspects of patients' cognitive abilities. Cai *et al.* [19] utilized scalp acupuncture combined with back Shu points, targeting Sishen Cong, Baihui, Shenting, Shenshu, Ganshu, Pishu, Feishu, and Xinshu (bilateral points). Statistically significant improvements in MoCA, MBI, and SF-36 scores indicated that scalp acupuncture combined with back Shu acupuncture is effective for mild to moderate cognitive impairment after stroke.

Zhang [20] applied the Tongdu Tiaoshen acupuncture method, combined with cognitive training, on points such as Baihui, Shenting, Yintang, Shuigou, Chengzhu, and Lianquan. Analysis of MoCA scores post-treatment demonstrated improvements in cognitive function and daily living abilities in PSCIND patients. Zhou *et al.* [21] employed scalp acupuncture (parietal line, frontal line, frontal line 1, and frontal line 2) combined with donepezil hydrochloride. Serum levels of Aβ, Smur100β, and BDNF, along with MoCA and MMSE scale scores, were analyzed. Results showed that scalp acupuncture inhibits the expression of Aβ and Smur100β, increases serum BDNF protein, and improves cognitive dysfunction.

Zhai *et al.* [22], through a review of domestic core periodical literature from the past 10 years, concluded that head, neck, and face points, particularly Baihui, Sishen Cong, Shenting, and Fengchi, are primary for treating post-stroke cognitive impairment. For example, Baihui, located at the intersection of the hand and foot Yang meridians with the Governor meridian, is believed to regulate qi and blood flow to the brain, thereby nourishing the marrow and improving cognitive function. Clinical studies suggest that acupuncture at Baihui enhances memory in stroke patients by strengthening brain network connections between the hippocampus, frontal lobe, and parietal lobe [23].

### 3.2. Body needle selection

Body acupuncture is a traditional method for treating stroke sequelae and has a long history. The *An and B Classic of Acupuncture and Moxibustion* states: "Loss of wisdom is the domain of Neiguan." Acupoint selection varies among practitioners based on individual patient differences and clinical presentation. Acupuncture enhances cerebral blood flow (CBF) and metabolism, thereby improving cognitive function [24].

Wang *et al.* [25] identified Baihui, Shenting, Sishen Cong, Sanyinjiao, Zusanli, and Neiguan as the most frequently used points for treating PSCI in clinical trials published in Chinese and English journals over the past 15 years. Wang [26] divided patients into three groups: basic treatment, routine acupuncture, and abdominal acupuncture (targeting Zhongwan, Xiawan, Qihai, Guanyuan, and Daheng). Scores for MoCA, LOTCA, and improved Barthel were significantly better in the treatment group compared to controls. Gao *et al.* [27] utilized data mining to analyze effective acupoints for PSCI, identifying points such as Neiguan, Sanyinjiao, Zusanli, Taixi, Shenmen, Taichong, Fenglong, and Xuehai.

## 4. Study on the mechanism of percutaneous vagal stimulation in the treatment of PSCI

"The ear is the gathering place of the clan pulse" and "the ear is connected to the brain" indicate that the "ear" is closely linked to the meridians and the brain. The twelve meridians extend throughout the body, reaching the brain, which is considered the Abode of the Spirit. This suggests that stimulation of the ear can regulate mental functions. Modern anatomical studies have also revealed that the ear connects to the brain through the vagus nerve, glossopharyngeal nerve, facial nerve, and ototemporal nerve.

The vagus nerve, the longest and most widely distributed cranial nerve, extends from the brain to the ear, neck, chest, and abdominal organs. It comprises general visceral motor and sensory fibers, general somatosensory fibers, and special visceral motor fibers. A percutaneous vagal nerve stimulator is a physiotherapeutic tool developed in recent years for treating certain intractable conditions. Since the vagus nerve in the neck, chest, and abdomen is located deep within the body and difficult to access directly, the exposed auricular region, which contains vagus nerve afferent fibers, offers a direct pathway to the central nervous system.

### 4.1. Regulation of cerebral blood flow

Numerous studies have demonstrated that transcutaneous vagus nerve stimulation (tVNS) can regulate and increase cerebral blood flow [28-30]. This effect may result from the stimulation of the vagus nerve, which dilates cerebral blood vessels through a neural reflex mechanism, thereby improving the blood supply to brain tissue [31,32]. Enhanced cerebral blood flow supports improved neuronal metabolism and function, reducing damage to neurons caused by ischemia and hypoxia. This mechanism provides a therapeutic effect on PSCI [33].

### 4.2. Regulation of the neurotransmitter system

Transcutaneous vagus nerve stimulation can also modulate the brain's neurotransmitter system, increasing the release of key neurotransmitters such as acetylcholine and dopamine [34]. Acetylcholine plays a crucial role in cognitive processes like learning and memory [35]. Dopamine, involved in the regulation of the reward system and motivational behavior, also affects cognitive function [36]. By promoting the release of these neurotransmitters, tVNS enhances neuronal signal transmission and synaptic plasticity, thereby improving cognitive function.

### 4.3. Inhibition of neuroinflammatory response

Transcutaneous vagus nerve stimulation can inhibit neuroinflammatory responses and reduce the levels of inflammatory factors [37]. This effect may be due to the tVNS stimulation of the vagus nerve, which activates the cholinergic anti-inflammatory pathway through a neural reflex mechanism, thereby suppressing the release of inflammatory factors [38]. Reducing inflammatory responses not only mitigates neuronal injury and death but also enhances the neurotransmitter system and neural plasticity, contributing to the therapeutic effects of tVNS on PSCI [39].

Wang *et al.* [40] employed tVNS to stimulate the ear cavity and auricular concha, targeting ear acupoints associated with the vagus nerve (e.g., liver, spleen, kidney, pancreas, heart, lung, trachea, Sanjiao, endocrine). Data showed that serum levels of TNF-α, IL-6, and IL-1β were significantly lower in the tVNS group on days 1 and 3 post-operation compared to sham stimulation and control groups. Theoretically, percutaneous vagus nerve stimulation activates efferent vagus nerve impulses in the concha region, thereby initiating the cholinergic anti-inflammatory pathway and suppressing the inflammatory response [41].

Inflammatory responses in the nervous system are major contributors to PSCI. Following ischemic damage, activated stromal cells and inflammatory mediators lead to immune cell infiltration, blood-brain barrier dysfunction, cellular edema, neuronal destruction, and apoptosis [42]. Studies suggest that serum markers and elevated levels of inflammatory factors like C-reactive protein, IL-6, and IL-12 in cerebrospinal fluid are associated with PSCI pathogenesis [43,44].

Qi *et al.* [45] conducted a study on 98 patients undergoing knee or hip arthroplasty. In this study, the stimulation group received electrical vagus nerve stimulation after anesthesia induction, while the control group did not. Cognitive impairment incidence was observed on day 7, before discharge, and two months post-operation. Results indicated that the tVNS significantly reduced cognitive impairment on day 7 and before discharge but had no significant effect two months post-operation. Furthermore, the stimulation group exhibited lower white blood cell counts on the first post-operative day, suggesting that the mechanism of tVNS in reducing cognitive impairment may involve suppression of the postoperative inflammatory response.

In a water maze experiment on epileptic rats, VNS intervention significantly improved spatial learning and memory [46]. VNS reduced IBA-1 protein expression in the hippocampus, a marker of microglia activation. Microglia-mediated central inflammatory responses are critical contributors to hippocampal neuron damage and cognitive impairment in epilepsy [47,48]. Decreased levels of TNF-α, IL-6, and IL-1β further suggested that VNS may reduce hippocampal inflammation by inhibiting microglia activation and promoting anti-inflammatory effects. Therefore, percutaneous vagus nerve stimulation can potentially treat cognitive impairment by alleviating inflammation.

### 4.4. Promotion of neuroplasticity

Transcutaneous vagus nerve stimulation promotes neuroplasticity by enhancing neuronal regeneration and synaptic formation. This effect may occur because tVNS stimulation of the vagus nerve regulates the expression of neurotrophic and growth factors in the brain [49]. Increased neuroplasticity facilitates cognitive function recovery, making it a beneficial therapeutic approach for PSCI [50,51].

## 5. Acupuncture combined with transcutaneous vagus nerve stimulation in the treatment of PSCI

Acupuncture and tVNS operate through distinct mechanisms. Acupuncture primarily regulates meridian qi, blood flow, and visceral function, while tVNS modulates cerebral nerve activity and immune system functions. When used together, these approaches can exert synergistic effects, enhancing therapeutic efficacy.

Both acupuncture and tVNS are relatively safe treatments with minimal side effects. Acupuncture may occasionally cause localized pain, minor bleeding, or bruising, whereas tVNS may lead to skin allergies, irritation, or discomfort. Combining these treatments could potentially mitigate the occurrence of such adverse effects by balancing their individual risks.

Overall, the combination of acupuncture and tVNS represents a promising integrative approach for the treatment of cognitive impairment following stroke, leveraging their complementary mechanisms to achieve better clinical outcomes.

## 6. Summary

Acupuncture has increasingly been shown to be a promising intervention for the treatment of PSCI, demonstrating positive effects on patients' cognitive function [52]. Data mining has revealed that the top five acupoints for PSCI treatment are Baihui, Shenting, Sishencong, Fengchi, and Neiguan, with the primary meridians involved being the Governor Vessel, Gallbladder Meridian, Spleen Meridian, and Stomach Meridian [53].

The disease primarily affects the brain and is associated with kidney essence deficiency, brain loss, phlegm, and blood stasis that obstruct the orifices, leading to cognitive dysfunction. Acupuncture targeting key points such as Baihui, Shenting, and Sishencong can clear the orifices, stimulate the brain, and improve cognitive impairment. Acupoints like Neiguan and Shenmen on the upper limbs and Zusanli, Sanyinjiao, and Taichong on the lower limbs can address limb dysfunction by dispelling wind, nourishing blood, invigorating circulation, and unblocking the meridians and collaterals [54].

The Governor Vessel, which connects to the brain, is central to these treatments as it regulates the marrow sea, clears brain pathways, and aligns with the brain's association with the kidneys [55]. Research has shown that acupuncture significantly improves cognition, memory, orientation, and daily living activities [56,57]. According to TCM, acupuncture balances qi and blood, reduces stroke sequelae, and effectively treats cognitive impairment [58].

The pathogenesis of PSCI is not fully understood but may involve inflammatory responses. Stroke-induced activation of macrophages and the release of inflammatory mediators can breach the blood-brain barrier, leading to nerve damage and cognitive decline [59]. While VNS typically requires implanting electrodes around the cervical vagus nerve, it reduces systemic inflammation and neuroinflammation, thereby improving cognitive function. However, its invasive nature makes it less acceptable to patients. In contrast, tVNS is non-invasive, portable, and well-tolerated, making it a more practical option [60].

The effects of VNS on cognitive impairment after stroke depend on the recovery stage. In the chronic phase, VNS promotes brain function recovery and neuroplasticity, whereas in the acute phase, it provides neuroprotection, facilitates neuroregeneration and angiogenesis, and enhances neuroplasticity [61-63].

Acupuncture combined with tVNS offers significant improvements in PSCI symptoms by leveraging their complementary mechanisms [64]. However, limitations in current research, including study quality, sample size, and potential language bias, highlight the need for large-scale, multicenter, high-quality randomized controlled trials. These trials will better establish the safety, long-term efficacy, and scientific foundation for integrating acupuncture and tVNS into post-stroke rehabilitation. Such efforts could pave the way for innovative therapeutic strategies to slow cognitive impairment progression.

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