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Vagus Nerve Stimulation in Ischemic Stroke

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Abstract

Purpose of Review—Vagus nerve stimulation (VNS) has emerged as a potential therapeutic approach for neurological and psychiatric disorders. In recent years, there has been increasing interest in VNS for treating ischemic stroke. This review discusses the evidence supporting VNS as a treatment option for ischemic stroke and elucidates its underlying mechanisms.

Recent Findings—Preclinical studies investigating VNS in stroke models have shown reduced infarct volumes and improved neurological deficits. Additionally, VNS has been found to reduce reperfusion injury. VNS may promote neuroprotection by reducing inflammation, enhancing

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Conflict of Interest Sasan Andalib, Cenk Ayata, Ethem Murat Arsava, Mehmet Akif Topcuoglu, Eder Leonardo Cáceres, Vinay Parikh, Masoom J Desai, Sara Girolami, and Mario Di Napoli each declare no potential conflicts of interest.

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cerebral blood flow, and modulating the release of neurotransmitters. Additionally, VNS may stimulate neuroplasticity, thereby facilitating post-stroke recovery.

Summary—The Food and Drug Administration has approved invasive VNS (iVNS) combined with rehabilitation for ischemic stroke patients with moderate to severe upper limb deficits. However, iVNS is not feasible in acute stroke due to its time-sensitive nature. Non-invasive VNS (nVNS) may be an alternative approach for treating ischemic stroke. While the evidence from preclinical studies and clinical trials of nVNS is promising, the mechanisms through which VNS exerts its beneficial effects on ischemic stroke are still being elucidated. Therefore, further research is needed to better understand the efficacy and underlying mechanisms of nVNS in ischemic stroke. Moreover, large-scale randomized clinical trials are necessary to determine the optimal nVNS protocols, assess its long-term effects on stroke recovery and outcomes, and identify the potential benefits of combining nVNS with other rehabilitation strategies.

Keywords

Non-invasive vagus nerve stimulation; Ischemic stroke; Stroke recovery; Blood–brain barrier; Neuroplasticity; Anti-inflammatory; Cortical spreading depolarization; Traumatic brain injury; Nucleus tractus solitarius; Locus coeruleus

Introduction

Stroke is a major global health concern, ranking as the second-leading cause of death and the third-leading cause of death and disability combined worldwide [1]. Since the approval of intravenous thrombolysis in 1996 [2], mechanical thrombectomy for large vessel occlusion has further expanded treatment options for acute ischemic stroke (AIS) [3]. However, even in the best-case scenario, only 24% of AIS cases receive thrombolytic therapy [4]. Furthermore, merely 3.1% of AIS patients undergo mechanical thrombectomy [5]. Many AIS patients are still not qualified for intravenous thrombolysis or mechanical thrombectomy; therefore, alternative and synergistic treatment options are warranted. Neuroprotective therapies for AIS have shown promise in preclinical studies but have been futile in clinical trials. One of the challenges of pharmacological agents is reaching the penumbra in the absence of reperfusion.

Neuromodulation is a rapidly evolving space in stroke—both as an acute treatment modality to mitigate against the deleterious effects of stroke and as a long-term tool to promote neuroplasticity and functional recovery in chronic settings. Vagus nerve stimulation (VNS) is a neuromodulation technique that delivers electrical signals to the vagus nerve. The technique was introduced by neurologist Corning more than a century ago [6]. Today, VNS via a surgically implanted device has been approved by the Food and Drug Administration (FDA) for the treatment of depression [7•], epilepsy [8•], and ischemic stroke [9]. Studies have shown VNS's potential for the treatment of various neurological disorders, such as Alzheimer's disease [10], Parkinson's disease [11•], traumatic brain injury (TBI) [12, 13•], tinnitus [14•], and sleep disorders [15]. Published literature suggests that VNS is a promising treatment in rat models of ischemic stroke via improved neurological function [16•]. However, implantable or invasive VNS (iVNS) requires surgery, so its use in acute clinical settings is not feasible. More recently, non-invasive VNS (nVNS) techniques have

been developed that can be used in acute settings. The FDA has already approved nVNS for treating cluster headaches [17]. A recent study evaluated its safety and feasibility in AIS [18], and ongoing clinical studies are testing its efficacy [19].

Vagus Nerve Anatomy and Function

The vagus nerve is the longest cranial nerve transmitting motor and sensory signals and is a major component of the parasympathetic nervous system. It contains motor, sensory, and parasympathetic nerve fibers, providing innervation to various organs and regulating physiological activities such as heart rate, blood pressure, gastrointestinal tract, stomach acid secretion, gall bladder, and biliary tract. In addition, the vagus nerve is a regulator of the cholinergic anti-inflammatory pathway, which can modulate the innate immune response [20].

Originating from the medulla oblongata in the brain stem, the vagus nerve exits the skull through the jugular foramen. From there, it extends through the carotid sheath in the neck and splits off into branches in the chest and the abdomen, ramifying to form the esophageal plexus and passing through the esophageal hiatus. These branches allow the vagus nerve to innervate various organs and tissues throughout the body. The vagus nerve has two main branches: the superior and inferior trunks that relay sensory information to the brainstem nuclei, where it is integrated and processed. The superior vagal trunk arises from the nucleus ambiguus in the medulla oblongata and innervates the larynx, pharynx, and upper esophagus. The inferior vagal trunk arises from the dorsal motor nucleus and innervates the heart, lungs, and gastrointestinal tract, excluding the spleen [21].

Within the vagus nerve, two distinct fiber tracts exist. The efferent fibers, including general visceral and special visceral fibers, carry signals from the brain to various organs and structures, which are critical in regulating their activities. The spleen is the primary source of inflammatory cytokines production, such as tumor necrosis factor (TNF), and is considered the main regulator of TNF production [22, 23]. Even though the vagus nerve does not directly innervate the spleen, efferent fibers terminate in celiac ganglia and superior mesenteric ganglion, which has led to different hypotheses of cholinergic anti-inflammatory pathway to inhibit pro-inflammatory cytokines by splenic macrophages [23–25].

The afferent fibers, constituting approximately 80% of the vagus nerve fibers, transmit sensory signals from the body back to the brain, terminating mainly in the nucleus tractus solitarius (NTS) in the brain stem [10] with some in the dorsal motor vagal nucleus and the area postrema, allowing for the control and coordination of gut function, as well as modulation of autonomic function and behavior in higher brain regions such as the prefrontal cortex, limbic system, and parietal cortex. The NTS has a direct, monosynaptic projection to the locus coeruleus (LC), a brain region that produces norepinephrine, allowing regulation of LC activity [26]. A further afferent branch, the auricular branch of the vagus nerve (ABVN), is located in the cymba concha of the outer ear.

Vagus nerve terminal branches innervate the gut wall, transmitting information about luminal contents and mechanosensory muscle activity. The sensory cell bodies are mainly

located in the nodose ganglia, which project centrally to the brain stem and peripherally to the organs they innervate. Therefore, the vagus nerve provides a bidirectional brain and body communication channel. This allows for the modulation of autonomic functions and integrating sensory information from the body with cognitive processes in the brain.

Invasive and Non-Invasive VNS

The anatomical pathway of the vagus nerve, particularly its extension through the neck, provides a suitable access point for stimulation that can influence a wide range of physiological processes regulated by the parasympathetic nervous system. This has led to exploring VNS as a potential treatment option for various neurological disorders.

In humans and large animals, the right vagus nerve is not recommended for stimulation as it regulates cardiac function. However, this is not an issue with rodents. For iVNS, the electrode is wrapped around the left vagus nerve and is tunneled subcutaneously to a pocket created in the left pectoral region for connecting to an implanted pulse generator [27••]. One of the main advantages of iVNS is its ability to provide continuous stimulation on a long-term basis. It has shown effectiveness in reducing seizure frequency and severity in epilepsy, improving mood in depression, and reducing chronic pain [7•, 8•].

The nVNS approach involves the delivery of electrical impulses using external devices that do not require surgical implantation. There are two nVNS devices: transcutaneous cervical VNS (tcVNS) and transcutaneous auricular VNS (taVNS). The electrodes for tcVNS are positioned on the neck overlying the vagus nerve using an electrolyte gel, while taVNS stimulates ABVN, which comprises thick myelinated axons of the Aβ class, albeit five to six times less numerous than those in the cervical vagus nerve [28]. Clinical studies have shown nVNS is safe and tolerable [29]. Two of the most widely used nVNS devices are gammaCore (tcVNS) and NEMOS (taVNS). The gammaCore device (electroCore, Rockaway, NJ, USA) [30] is FDA-approved for treating of headaches [18]. The NEMOS device (distributed by tVNS Technologies, previously Cerbomed) delivers signals to ABVN and has been approved for treating resistant epilepsy [30]. Figure 1 illustrates various types of VNS used in clinical settings.

Possible Mechanisms of VNS in Ischemic Stroke

Figure 2 depicts possible mechanisms of action of VNS. A deeper understanding of how VNS improves functional recovery following an ischemic stroke can broaden the scope of its applications in clinical settings. Moreover, identifying relevant biomarkers might enable adaptive trial designs with different stimulation protocols. Table 1 summarizes preclinical stroke studies conducted on the mechanistic role of VNS.

Enhanced Neuroplasticity

The engagement of neuromodulatory networks regulating synaptic plasticity offers a means through which VNS likely supports brain recovery. Activations of cholinergic, noradrenergic, and serotonergic systems make VNS-based rehabilitation promising for improving post-stroke motor deficits by promoting plasticity [31–33]. In a rat

model of middle cerebral artery occlusion (MCAo), VNS activated the brain-derived neurotrophic factor (BDNF)/cAMP/PKA/p-CREB pathway. It also enhanced axonal plasticity, regeneration reorganization, and improved neurobehavioral performance and functional recovery via the α7 nicotinic acetylcholine receptor (α7nAChR) [34]. Another preclinical stroke study illustrated that iVNS paired with rehabilitative supination training improved plasticity in corticospinal motor networks to increase synaptic connectivity to the musculature of the rehabilitated forelimb [35].

Anti-Inflammatory Effect

Neuroinflammation is an important mechanism affecting the outcome that starts a few hours after ischemic stroke and can persist as a delayed tissue reaction to injury. The vagus nerve, which connects the immune and central nervous systems, plays a significant role in regulating neuroinflammation [36]. The vagus nerve consists of highly myelinated A, lightly myelinated B, and unmyelinated C fibers. Vagus nerve A fibers may contribute to cytokine release regulation. The cholinergic anti-inflammatory pathway, mainly involving A fibers, has a low activation threshold and is involved in immune regulation. The neural pathways of the vagus nerve that detect inflammation are sensitive to lower concentrations of tissue inflammatory molecules, prompting a reaction even when these agents are not abundant enough to reach the brain via the bloodstream [37, 38].

VNS impedes the production of pro-inflammatory cytokines such as TNF, interleukin (IL)-1β, IL-6, and IL-18 [12, 39, 40]. The neuroprotective effect of iVNS after MCAo may be associated with inhibition of TNF-α and IL-6 expression [41•]. Experimental models have demonstrated that VNS inhibits TNF synthesis in the liver and prevents shock development in lethal endotoxemia [39]. In a rat model of MCAo, tcVNS decreased the number of Iba-1, CD68, and TNF-α positive cells and increased the number of high mobility group box 1-positive cells [42]. In a mouse model of MCAo, nVNS heightened microglial M2 polarization, shown by increased Arg-1 protein expression and Arg-1^{+} cells, while reducing levels of IL-17A protein expression [43]. Intranasal administration of recombinant IL-17A (rIL-17A) nullified the nVNS-induced microglial M2 polarization and its neuroprotective effect. In a rat MCAo model, tcVNS suppressed the injury cascade involving the MMPs/IL-1β signaling pathway in neurons through α7nAChR [40]. Others also have shown that VNS-induced neuroprotection after MCAo is likely related to the activation of the α 7nAchR/JAK2 anti-inflammatory pathway [44]. One study looking at the inflammatory markers among 20 healthy subjects treated with active or sham tcVNS indicated lower levels of IL-1β, IL-8, TNF, macrophage inflammatory protein-1α, and monocyte chemoattractant protein-1 in the active tcVNS arm [45]. In an MCAo model, taVNS promoted the secretion of acetylcholine, inhibited the secretion of IL-1β, IL-6, and TNF-α, and decreased connexin 43 phosphorylation in the ischemic penumbra and motor cortex [46]. Another study showed that iVNS upregulated peroxisome proliferator-activated receptor-gamma in ischemic penumbra and suppressed TNF-α, IL-1β, and immune cell activation [47].

Inhibition of Glutamate Release, Post-Reperfusion Hyperemia, Oxidative Stress, Apoptosis, and Autophagy

Excessive glutamate release after ischemia contributes to brain damage via free radicals or reactive oxygen species production [48]. A study showed that iVNS regulated malondialdehyde, glutathione, and superoxide dismutase levels in corticaland subcortical regions in a rat model of MCAo [49]. Additionally, it significantly attenuated both ischemia-induced glutamate release and transient increase of hippocampal blood flow during reperfusion [50]. Post-reperfusion hyperemia and excessive glutamate release are important factors in brain injury as they lead to the production of reactive oxygen species [50].

By activating neuronal and astrocytic α7nAChR, VNS inhibits apoptosis and oxidative stress responses, potentially by enhancing Akt phosphorylation and miR-210 expression, regulated by hypoxia-inducible factor and Akt-dependent pathways [51]. Using a rat model of stroke, another study showed that VNS suppresses inflammation and apoptosis by activating cholinergic and α7nAChR/Akt pathways, resulting in improved neurological outcomes, reduced infarct volume, decreased pro-inflammatory cytokine levels, and decreased cleaved caspase-3 protein levels [52]. Elsewhere, iVNS reduced neuronal apoptosis as shown by the reduced Bax and cleaved caspase-3 and increased Bcl-2 levels; the beneficial iVNS effects weakened following lipocalin-type prostaglandin D synthase (L-PGDS) down-regulation [53]. VNS also exhibits neuroprotective effects by inhibiting autophagy. In a rat stroke model, VNS downregulated autophagy-related proteins, including microtubule-associated protein 1 light chain 3 (LC3)-II and Beclin-1, and decreased cleaved caspase-3 protein levels [54].

Reduction of Blood–Brain Barrier Disruption

Stroke can lead to blood–brain barrier (BBB) dysfunction. VNS has been shown to recover BBB function post-stroke in preclinical studies [55]. In a rat model of MCAo, VNS produced neuroprotective effects by reducing infarct extent and IL-1β level in the ipsilateral hemisphere and by inhibiting MMP-2 and MMP-9 expressions in reactive astrocytes in the peri-infarct area [40]. Other studies have also confirmed that VNS reduces infarct size, improves neurological function, and reduces BBB disruption and brain edema after ischemic stroke in rats [42, 54–56, 57••]. Similar to preclinical stroke studies, VNS also decreased BBB permeability by reducing the up-regulation of aquaporin-4 and ipsilateral edema in preclinical TBI studies [13•, 58]. Of course, it is difficult to determine whether preserved BBB is due to the neuroprotective effect leading to milder injury (i.e., smaller infarcts) or via a direct effect on BBB.

Angiogenesis

In a rat MCAo model, taVNS improved neurobehavioral recovery and upregulated cerebral growth differentiation factor 11 (GDF11) [59]. GDF11 augments the proliferation of primary brain capillary endothelial cells, is involved in vascular remodeling, improves the volume of blood vessels, and restores age-related decline in neurogenesis [60].

Another preclinical stroke study [61] investigated the effect of taVNS on angiogenesis and explored potential molecular mechanisms. The study found that taVNS treatment

upregulated peroxisome proliferator-activated receptor-gamma (PPAR-γ) expression in the ischemic cortex, improved neurobehavioral recovery, reduced neuronal injury, decreased infarct volume, and increased angiogenesis. Moreover, VNS was shown to increase the expression of vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) in the ischemic hemisphere, which are key regulators of neuroplasticity [61]. In addition to the aforementioned beneficial effects, such as suppressing pro-inflammatory proteins, ta-VNS may improve dysphagia, possibly due to protecting ischemic white matter [62]. VNS also facilitated the growth of blood vessels and synapses in the ischemic hemisphere, ultimately improving functional outcomes [61, 63]. These findings highlight the VNS potential to promote both angiogenesis and neuroplasticity after stroke, contributing to improved recovery.

Cortical Spreading Depolarization

Following AIS, recurrent spreading depolarization (SD) waves are believed to worsen the outcomes. SD is an intense depolarization wave that originates in the ischemic penumbra and slowly propagates across the gray matter, constricting the arteries in the ischemic brain region and imposing a tremendous metabolic demand, thus increasing the supply–demand mismatch [64–66]. In a rat model of stroke, both iVNS and nVNS significantly decreased the frequency of SDs in the peri-infarct cortex compared with sham, without affecting relative blood flow changes, blood pressure, heart rate, or breathing rate [67]. Similar effects of VNS on the inhibition of SD were also observed in other experimental models that did not elicit cerebral ischemia [68, 69••]. The efficacy of VNS in suppressing SD is mediated through the activation of vagal visceral sensory afferents and their projections to subcortical neuromodulatory regions [69••]. Optimal VNS parameters for SD suppression are still under investigation, but it has been suggested that two 2-min sessions of tcVNS, spaced 5 min apart, yield the highest efficacy [70].

Gut-Brain Axis and Microbiome Regulation

The brain and the gastrointestinal tract keep a continuous and bidirectional communication through the gut-brain axis. The vagus nerve contains 80% of afferent fibers that can sense gut microbiota metabolites [71]. Some of these metabolites are neurotransmitters such as γ-aminobutyric acid, serotonin, dopamine, and acetylcholine, which act locally on the enteric nervous system but can also reach the brain through the vagus nerve [72, 73]. Other metabolites, such as short-chain fatty acids, could trigger the enteric nervous system and send signals through the terminals of the vagus nerve [74]. An imbalance in gut microbiota (dysbiosis) before stroke can indirectly contribute to an increased risk of stroke and negatively impact the outcome. Conversely, stroke can cause changes in gut motility, intestinal permeability, and dysbiosis [75], which leads to inflammation and oxidative stress, thereby worsening post-stroke outcomes and increasing the risk of pneumonia and cardiovascular and gastrointestinal complications [76, 77]. A cohort of elderly patients with acute cerebral infarction and healthy controls identified four bacterial pathways that might be related to the development of this disease, including methane metabolism, lipopolysaccharide synthesis, bacterial secretion, and flagellar assembly of the gut microbiota [78]. Also, there was a higher level of trimethylamine-N-oxide producing

bacteria and a decrease of butyrate-producing bacteria. Butyrate-producing bacteria might play a protective role against infections [78]. These findings might shed light on the modulation of gut microbiota and gut-brain axis through VNS as a potential for both preventive and therapeutic approaches for treating ischemic stroke. To address this void, future studies are needed.

VNS Treatment in Clinical Studies of Ischemic Stroke

Several lines of evidence indicate that VNS treatment can improve ischemic stroke outcomes. Table 2 outlines clinical VNS studies in the ensuing discussion.

Outcomes of iVNS in Ischemic Stroke

The effectiveness of iVNS on upper limb deficits in stroke patients has been investigated through several studies. Dawson et al. [27••] conducted a stroke trial in the UK with moderate to severe upper-limb impairment. The patients ($n = 20$) were randomized to receive either iVNS + rehabilitation or rehabilitation alone. While the intention-to-treat analysis showed no significant difference in Fugl–Meyer Assessment-Upper Extremity (FMA-UE) scores at 90 days, the per-protocol analysis demonstrated a significant difference favoring the iVNS + rehabilitation group. A case study also highlighted iVNS's potential for sensory recovery [79]. In another pilot study [80], stroke patients with upper-limb impairment were implanted with a VNS device and divided into active iVNS or sham iVNS groups. Clinically meaningful improvements were observed in the FMA-UE score at day 90 for the active iVNS group compared to the sham group.

Dawson et al. [81••] conducted a trial in the UK and the USA with stroke patients experiencing arm weakness. The group receiving 6 weeks of rehabilitation therapy followed by active iVNS showed a significant rise in FMA-UE scores compared to the sham group. A clinically meaningful response on the FMA-UE score was observed in a higher proportion of subjects in the iVNS group compared with the sham group at 90 days post-therapy. In 2021, the FDA approved the Vivistim® Paired VNS™ System for treating moderate to severe upper extremity motor deficits in stroke patients who undergo rehabilitation therapy [9]. Subsequent meta-analyses supported iVNS as a potential treatment option for improving motor function and daily activities in stroke patients [82–84].

Outcomes of nVNS in the Treatment of Ischemic Stroke

The use of iVNS devices, like Vivistim, is limited to a chronic setting. In contrast, nVNS can be employed in hyperacute, acute, and chronic stages. Notable studies on nVNS have been conducted across both the acute or subacute stroke stages [18, 85] and in chronic settings [86–88] demonstrating promise.

In a pilot study, stroke patients ($n = 14$) received robot-assisted therapy with either active or sham taVNS. Active taVNS significantly improved Fugl–Meyer Assessment (FMA) scores [86]. Another study by Redgrave et al. [87] involved stroke patients ($n = 13$) with residual upper limb weakness, receiving taVNS sessions along with rehabilitation. A substantial change in FMA-UE scores and sensory recovery was observed. In a post hoc analysis [88], eleven (92%) of the patients had a sensory loss at baseline, of whom 7 (64%) recovered

some sensation following the intervention (6 proprioception, 2 light touch, and 1 both modalities). In a randomized pilot study in China, subacute stroke patients (n = 21) with single upper limb motor function impairment underwent rehabilitation training with active or sham taVNS. The active taVNS group demonstrated significantly greater improvement in functional assessments at 12 weeks [85].

Regarding tcVNS, the TRanscutaneous cervical Vagus nErve stimulatioN as a treatment for acUte Stroke (TR-VENUS) trial showed the safety and feasibility in patients with AIS and intracerebral hemorrhage (ICH) [18]. In addition, there was a suggestion that high-dose tcVNS could significantly reduce infarct growth in patients with diffusion mismatch. The ongoing Non-invasive Vagus Nerve Stimulation in Acute Ischemic Stroke (NOVIS) trial (NCT04050501) randomizes patients to tcVNS combined with standard treatment or standard treatment alone within 12 h from symptom onset [19]. The primary endpoint is the infarct volume.

Effects on Cholinergic Neuromodulation and Cognitive Abilities

Cognitive impairments are commonly observed after stroke, affecting memory, attention, and executive functions. Studies have shown that the vagus nerve is crucial for the memory-enhancing effects of substances that stimulate peripheral receptors [89, 90••]. When combined with cognitive training, nVNS has been found to lead to greater improvements in attention and executive functions compared to cognitive training alone [91]. Vagotomy impairs these memory-enhancing effects, indicating the vagus nerve's role in relaying diverse peripheral information to impact memory [92–95]. Additionally, VNS causes the release of multiple neuromodulators throughout the brain, potentially enhancing sensory and cognitive processing [96, 97].

The activation of the basal forebrain (BF) cholinergic neurons and the synaptic release of acetylcholine from their target projections in the cortical and hippocampal areas is implicated in the regulation and maintenance of multiple cognitive functions, including attention and memory [98–100]. The electrical stimulation of the vagus nerve has been shown to activate BF cholinergic neurons and modulate cortical excitability through the activation of muscarinic receptors [101]. The effects of VNS on movement representation and plasticity of neurons in the primary motor cortex were abolished by either selective lesions or optogenetic inhibition of the BF cholinergic neurons [31, 102]. The cholinergic system is highly vulnerable to vascular damage in stroke, leading to cognitive impairments. Moreover, treatment with acetylcholinesterase inhibitors has shown efficacy in improving post-stroke cognitive impairments [103]. A recent study employing diffusion tractography and neuropsychological assessment reported that the structural status of the fornix, BF cholinergic region, and hippocampal subfields predicted spontaneous recovery and improvements in working and episodic memory in patients with stroke [104]. The available evidence suggests that the benefits of VNS in post-stroke cognitive functioning may partly involve central cholinergic neuromodulation. Given the evidence that VNS can also activate BF cholinergic neurons directly or indirectly via LC noradrenergic pathways resulting in cortical and behavioral activation [105], it is possible that the procognitive effects of VNS are driven in part by noradrenergic mechanism. Further studies are warranted to pars out

the contributions of cholinergic and LC-noradrenergic pathways in VNS-mediated cognition enhancement during post-stroke recovery.

Safety and Adverse Effects

The most serious complications of iVNS include infection and vocal cord palsy due to damage to the vagus nerve [106]. Regular maintenance, including battery replacement, is required, and the device and surgical procedure cost can be a limiting factor for some patients.

The nVNS approach appears to be well-tolerated and safe, with mild side effects [18, 29, 107–109]. Common side effects include transient hoarseness, throat discomfort, and mild skin irritation at the stimulation site [109]. Serious adverse events are rare, but further long-term safety studies are warranted to establish the full safety profile of nVNS in stroke patients.

Conclusions

VNS offers therapeutic potential for various neurological disorders. Experimental models have demonstrated that VNS can improve the outcome of stroke. The effect of VNS is exerted through its anti-inflammatory and neuromodulatory properties, to name a few. Clinical studies have also shown the safety and efficacy of VNS in improving neurological outcomes in stroke patients.

The iVNS method requires surgery that can only be applied in chronic settings. The advantage of nVNS is that the treatment can be applied in acute settings, even by paramedics in the field since VNS is safe for both ischemic and hemorrhagic strokes. Further research is needed to (1) determine the optimal stimulation parameters, intervention time from symptom onset, and treatment duration; (2) the mechanisms underlying the therapeutic effects of VNS need to be elucidated further to guide the development of personalized treatment strategies, and (3) most studies, so far, have relatively small sample sizes and variations in stimulation parameters and protocols, making it challenging to draw definitive conclusions. Therefore, future research should include larger-scale randomized clinical trials with standardized protocols to determine optimal stimulation parameters, treatment duration, and intervention time from symptom onset. Moreover, investigations into the long-term effects of VNS, including its potential for promoting neural plasticity and neuro-recovery and looking at a broader range of poststroke neurological deficits (e.g., dysphagia, cognition, sleep disturbance, urinary incontinence, and visual dysfunction) are warranted [110].

In addition, several emerging technologies may enhance the therapeutic potential of VNS in stroke recovery. For example, combining VNS with brain-computer interfaces (BCIs) may provide a more effective therapy. This emerging field has demonstrated the potential to revolutionize cognitive enhancement, epilepsy treatment, pain management, and stroke rehabilitation [111]. Harnessing the synergic power of neuromodulation and BCIs may pave the way for future innovative therapeutic strategies and personalized interventions.

Abbreviations

ABVN	Auricular branch of the vagus nerve
AIS	Acute ischemic stroke
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
CSD	Cortical spreading depolarization
FDA	Food and Drug Administration
GDF11	Growth differentiation factor 11
ICH	Intracerebral hemorrhage
LC	L ocus coeruleus
LC3	Light chain 3
L-PGDS	Lipocalin-type prostaglandin D synthase
IL	I nterleukin
MCAo	Middle cerebral artery occlusion
mRS	Modified Rankin scale
NIHSS	N ational Institute of Health stroke scale
NTS	Nucleus tractus solitarius
nVNS	Non-invasive vagus nerve stimulation
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
rIL-17A	Recombinant IL-17A
TBI	Traumatic brain injury
taVNS	Transcutaneous auricular vagus nerve stimulation
tcVNS	Transcutaneous cervical vagus nerve stimulation
VEGF	V ascular endothelial growth factor
VNS	Vagus nerve stimulation
α7nAChR	α7 Nicotinic acetylcholine receptor subunit

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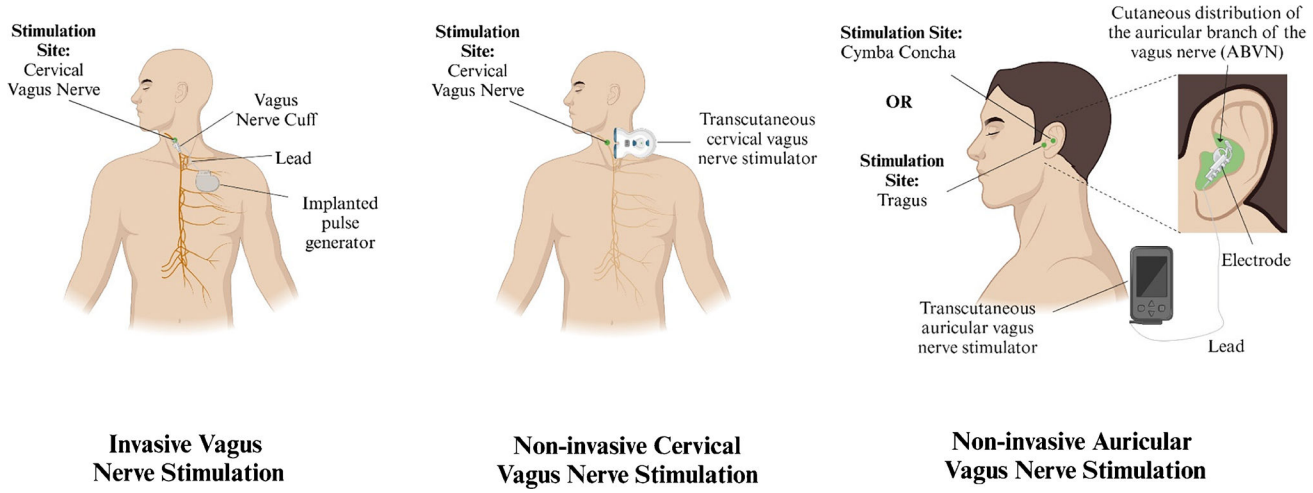

Fig. 1.

Vagus nerve stimulation methods used in clinical settings (created with BioRender.com)

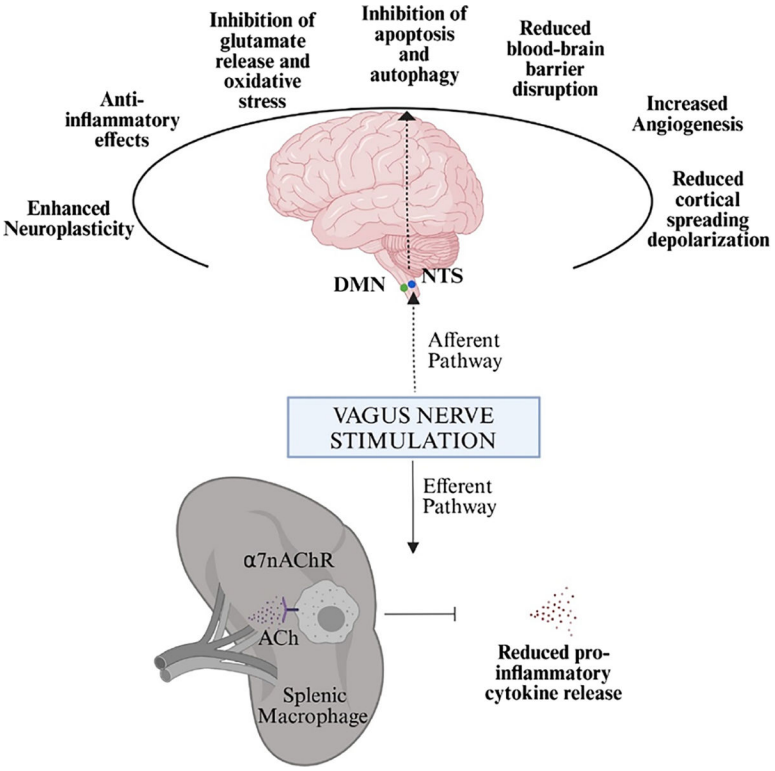

Fig. 2.

Mechanism of action of vagus nerve stimulation (VNS) (created with BioRender.com). Abbreviations: ACh, acetyl cholin; DMN, dorsal motor nucleus; NTS, nucleus tractus solitarius; α7nAChR, α7 nicotinic acetylcholine receptor subunit

Table 1

Summary of preclinical studies confirming the mechanistic role of VNS in stroke

Author, year	Preclinical stroke model	Intervention	Mechanism	Pathophysiological findings	Behavioral and neurological findings
Li et al., 2020 [34]	MCAo	taVNS	Neuroplasticity	α7nAChR is a potential mediator of taVNS neuroprotection in the acute phase of stroke, and its effect may be related to BDNF/cAMP/PKA/p-CREB pathway	NA
Myeres et al., 2018 [35]	Endothelin-1-induced ischemic lesions	iVNS paired with rehabilitative	Neuroplasticity	iVNS enhances plasticity in corticospinal motor networks to increase synaptic connectivity to the musculature of the rehabilitated forelimb	iVNS paired with rehabilitative supination training improves recovery of forelimb rotational function. VNS does not affect lesion size
Ay et al., 2016 [42]	MCAo	tcVNS	Anti-inflammatory effect	tcVNS decreased the number of Iba-1, CD68, and TNF-α positive cells and increased the number of high mobility group box 1-positive cells	nVNS reduced infarct size by 33% and improved neurological deficit
Zhao et al., 2022 [46]	MCAo	taVNS	Anti-inflammatory effect, changing the secretion of acetylcholine, and the phosphorylation of connexin 43	taVNS promoted the secretion of acetylcholine, inhibited the secretion of IL-1β, IL-6, and tumor necrosis factor-α, and decreased connexin 43 phosphorylation in the ischemic penumbra and motor cortex	taVNS improved neurological deficit
Zhao et al., 2019 [43]	MCAo	tcVNS	Anti-inflammatory effect	nVNS heightened microglial M2 polarization, shown by increased Arg-1 protein expression and Arg-1^{+} cells, while diminishing the increased levels of IL-17A protein expression; Intranasal administration of rIL-17A nullified the nVNS-induced microglial M2 polarization and abolished its neuroprotective effect	nVNS reduced infarct size and improved neurological deficit
Lu et al., 2017 [44]	MCAo	iVNS	Anti-inflammatory effect	Activation of the α 7nAchR/JAK2 pathway	iVNS reduced infarct size and improved neurological deficit
Xiang et al., 2015 [41•]	MCAo	iVNS	Anti-inflammatory effect	The neuroprotective effect of iVNS after MCAo may be associated with inhibition of TNF-α and IF-6 expression	iVNS reduced infarct size and improved neurological deficit
Yang et al., 2022 [40]	MCAo	tcVNS	Anti-inflammatory effect	tcVNS downregulates MMPs/IL-1β signaling pathways via a7nAChR	NA
Jiang et al. [47]	MCAo	iVNS	Anti-inflammatory effect through PPAR-γ upregulation	iVNS upregulated PPARγ in ischemic penumbra and suppressed TNF-α, IF-1β, and immune cell activation	iVNS reduced infarct size
Zhang et al., 2017 [53]	MCAo	iVNS	Decrease of apoptosis and L-PGDS mediation	iVNS reduced neuronal apoptosis as shown by the reduced Bax and cleaved caspase-3 and increased Bcl-2 levels. The beneficial iVNS effects weakened following L-PGDS down-regulation	iVNS reduced infarct size and improved neurological deficit
Ekici et al., 2013 [49]	MCAo	iVNS	Inhibition of glutamate release and oxidative stress	iVNS regulated malondialdehyde, glutathione, and superoxide dismutase levels in cortical and subcortical regions	iVNS reduced infarct size and improved neurological deficit
Miyamoto et al., 2003 [50]	CCAo	iVNS	Inhibition of glutamate release and hyperemia	iVNS attenuated both ischemia-induced glutamate release and transient increase of hippocampal blood flow during reperfusion	NA

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Author, year	Preclinical stroke model	Intervention	Mechanism	Pathophysiological findings	Behavioral and neurological findings
Jiang et al., 2015 [51]	MCAo	iVNS	Inhibition of inflammation, apoptosis, and oxidative stress	By activating neuronal and astrocytic α7nAChR, iVNS inhibits apoptosis and oxidative stress responses, potentially by enhancing Akt phosphorylation and miR-210 expression, regulated by hypoxia-inducible factor and Akt-dependent pathways	iVNS reduced infarct size and improved neurological deficit
Jiang et al., 2014 [52]	MCAo	iVNS	Suppressing inflammation and apoptosis	VNS suppresses inflammation and apoptosis by activating cholinergic and α7nAChR/Akt pathways	iVNS reduced infarct size and improved neurological deficit
Zhang et al., 2021 [54]	MCAo	iVNS	Inhibition of autophagy	iVNS downregulated autophagy-related proteins, including Microtubule-associated protein 1 LC3-II and Beclin-1, and decreased cleaved caspase-3 protein levels	iVNS reduced infarct size and improved neurological deficit
Yang et al., 2018 [55]	MCAo	nVNS	Reduction of BBB disruption	nVNS decreased BBB transfer rate (Ki map), lowered serum IgG leakage, visualized by IHC, protected vascular tight junction proteins from disruption in microvessels, and reduced expression of matrix metalloproteinases-2/9 in reactive astrocytes	nVNS reduced infarct size
Ma et al., 2016 [59]	MCAo	taVNS	Angiogenesis	taVNS upregulated cerebral GDF11, and downregulated splenic GDF11, an angiogenic factor that acts at least in part through ALK5	taVNS reduced infarct size and improved neurological deficit
Li et al., 2020 [61]	MCAo	taVNS	Angiogenesis	taVNS upregulated PPAR-γ expression in the ischemic cortex, reduced neuronal injury, and increased angiogenesis. Moreover, VNS increased the expression of VEGF and BDNF in the ischemic hemisphere	taVNS reduced infarct size and improved neurological deficit
Long et al., 2022 [62]	MCAo	taVNS	Angiogenesis	In addition to the effects of VNS on microglia and cortical neurons, taVNS increased capillary density and VEGF expression in white matter	taVNS promoted white matter repair and improved dysphagia symptoms
Jiang et al., 2016 [63]	MCAo	taVNS	Angiogenesis	taVNS promoted angiogenesis BDNF, eNOS, and VEGF were expressed at higher levels	taVNS improved functional recovery
Lindemann et al., 2020 [67]	MCAo	iVNS and tcVNS	SD	Both iVNS and tcVNS reduced cortical spreading depolarization	SD frequency was associated with decreased cortical stroke volume, whereas basal ganglia stroke volume remained unchanged. The beneficial effects on sensorimotor outcome were marginal

Abbreviations: *AIS*, acute ischemic stroke; *ALK5*, activin receptor-like kinase 5; *BBB*, blood–brain barrier; *BDNF*, brain-derived neurotrophic factor; *cAMP*, cyclic adenosine monophosphate; *CCAo*, common carotid artery occlusion; *eNOS*, endothelial nitric oxide synthase; *GDF11*, cerebral growth differentiation factor 11; *ICH*, intracerebral hemorrhage; *iVNS*, invasive vagus nerve stimulation; *JAK2*, Janus kinase 2; *LC3*, light chain 3; *IHC*, immunohistochemistry; *IgG*, immunoglobulin G; *IL*, interleukin; *MCAo*, middle cerebral artery occlusion; *NA*, not applicable; *p-CREB*, cAMP-response element binding protein; L-PGDS: lipocalin-type prostaglandin D synthase; *PKA*, protein kinase A; *PPAR-γ*, peroxisome proliferator-activated receptor-gamma; *rIL-17A*, recombinant IL-17A; *SD*, spreading polarization; *taVNS*, transcutaneous auricular vagus nerve stimulation; *tcVNS*, transcutaneous cervical vagus nerve stimulation; *TNF-α*, tumor necrosis factor- α; *VEGF*, vascular endothelial growth factor; *α7nAChR*, α7 nicotinic acetylcholine receptor subunit

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Table 2

Summary of the clinical stroke studies on the role of VNS

Author, year	Intervention	Study design	Sample size	Outcomes
Dawson et al., 2016 [27••]	iVNS + rehabilitation	The rehabilitation alone group received 6 weeks of 2-h rehabilitation sessions (each with more than 400 movement trials) 3 times a week. iVNS + rehabilitation group received the same rehabilitation protocol plus iVNS therapy	20 (9 in VNS + rehabilitation and 11 in rehabilitation-only groups)	There were no serious treatment adverse effects. The results showed no significant difference in the FMA-UE scores at 90 days follow-up in the intention-to-treat analysis. However, a significant difference was observed in the per-protocol analysis
Kimberley etal. 2018 [80]	iVNS	Stroke patients received 6-week in-clinic rehabilitation followed by a home exercise program while randomized. Assessments were performed on days 1, 30, and 90	17 (iVNS = 8 and sham = 9)	There were 3 serious adverse events related to surgery. The clinically meaningful response rate of FMA-UE at day 90 was 88% with the active iVNS and 33% with the sham iVNS ($P < 0.05$)
Dawson et al., 2021 [81••]	iVNS	Stroke patients with moderate-to-severe arm weakness, at least 9 months after stroke, were recruited. The patients were randomized to either 6 weeks of rehabilitation therapy followed by an exercise program at home	108 (iVNS = 53 and sham = 55)	A more significant improvement in mean FMA-UE was observed in the active iVNS group 24 h after completion of the therapy. A more significant number of iVNS subjects had improvement in the FMA-UE score at 90 days post-therapy
Capone et al., 2017 [86]	taVNS	In a sham-controlled pilot study, ischemic and hemorrhagic stroke patients were randomized to robot-assisted therapy + active or sham taVNS	12 (taVNS = 7 and sham = 5)	The FMA score improved significantly in the active taVNS group with no adverse events
Redgrave et al., 2018 [87]	taVNS	Patients with a history of stroke (more than 3 months) with residual upper limb weakness completed 18 1-h taVNS sessions over 6 weeks, along with rehabilitation	12 taVNS	Light-headedness was observed in 1 participant, and general tiredness and fatigue in 2. Only the former was considered to be attributed to the taVNS. A significant change in the FMA-UE score from the baseline was observed
Baig et al., 2019 [88]	taVNS	Post hoc analysis from [87]	12 taVNS	92% of the patients had a sensory loss at baseline, of whom 64% recovered some sensation following the intervention The maximal increase in UFM sensation score was seen in the patient with the greatest improvement in motor function
Wu et al., 2022 [85]	taVNS	Subacute ischemia stroke patients with single upper limb motor function impairment	21 (taVNS = 10 and sham = 11)	The FMA-UE, the WMFT, and the FIM scores were significantly higher than before treatment. A significantly greater improvement of those measurements was found in the taVNS group, in comparison with those in the sham-taVNS group
Arsava et al., 2022 [18]	tcVNS	Acute stroke patients were randomized into sham stimulation, standard-dose tcVNS, and high-dose tcVNS (standard-dose protocol repeated after 3 h)	68 (standard-dose tcVNS = 19, high-dose tcVNS = 25, and sham = 24,)	The composite safety outcome was achieved in 32.0% of sham and 47.7% of tcVNS groups. Treatment was initiated and completed in all but two patients. No significant difference was observed between the groups in NIHSS scores at 24 h. There was a statistically non-significant reduction in infarct growth in the high-dose nVNS group. In the subgroup of patients with clinical diffusion mismatch, infarct growth was significantly lower in the high-dose tcVNS group compared with the sham tcVNS

Abbreviations: *AIS*, acute ischemic stroke; *FMA-UE*, Fugl–Meyer Assessment-Upper Extremity; *FIM*, Functional Independence Measurement; *ICH*, intracerebral hemorrhage; *iVNS*, invasive vagus nerve stimulation; *NIFISS*, National Institute of Health stroke scale; *taVNS*, transcutaneous auricular vagus nerve stimulation; *tcVNS*, transcutaneous cervical vagus nerve stimulation; *WMFT*, Wolf motor function test