



## Review

# Vagus Nerve Stimulation in Stroke Management: Brief Review of Evolution and Present Applications Paired with Rehabilitation

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**Abstract:** Cerebrovascular accident (CVA) or stroke is a devastating neurological condition with dismal prognosis associated with recurrent episodes that further damage the neuronal networks, thus disabling neuronal plasticity. Vagus nerve stimulation (VNS) has been used in clinical practice to treat epilepsy for several decades and is well accepted as a safe procedure devoid of serious adverse events. Bailey and Bremer demonstrated that VNS has the capabilities to stimulate neuronal pathways that enhance the recovery of damaged cerebral function. Further studies have strengthened these observations, while technology has improved the tolerability of implants, resulting in VNS applications for epilepsy. Several animal models on neural plasticity have improved our understanding of VNS and its ability to provide neuromodulation to improve recovery in stroke patients. The closed-loop stimulation of the vagus nerve with individualized stimulation parameters combined with physical therapy appears to be an attractive option today. VNS is also being tested as a noninvasive trans-cutaneous modality to further improve patient acceptance and tolerability. However, the implantation of VNS is yielding desirable outcomes and appears to be a more reliable treatment for stroke rehabilitation in clinical trials.



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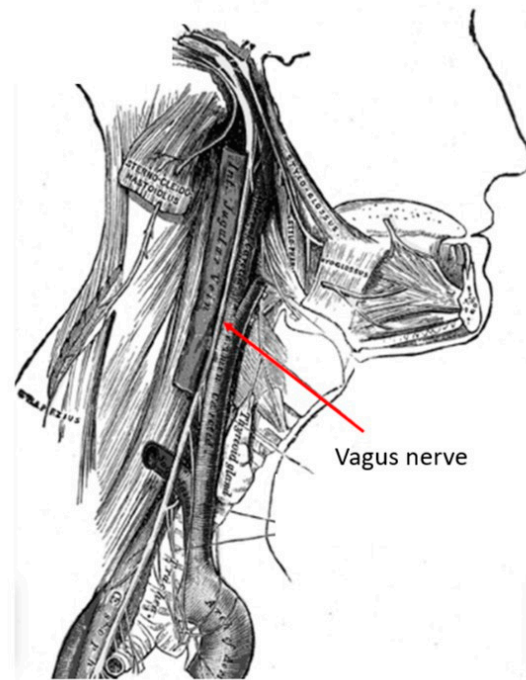
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**Keywords:** stroke; paralysis; vagus nerve; VNS; physical therapy

## 1. Introduction

The vagus nerve is the longest cranial nerve, providing bilateral parasympathetic innervation to the viscera. It is located in the posterior layer of the carotid sheath within the cervical deep fascia of the neck (Figure 1). Its extensive clinical utility became evident following electrical stimulation studies by Bailey and Bremer in 1938 in Chicago, IL, USA [1]. Their observations were later reproduced by Dell and Olson, whose feline studies on vagal nerve projections to the sensory cortex, thalamus and cerebellum demonstrated the potential of vagus nerve stimulation (VNS) in synchronizing cortical activity [2]. A detailed examination with recent technology has named these network connections as the “vagus afferent network”, part of connectomics. These extensive vagus nerve afferents include neurotransmitter centers like the nucleus tractus solitarius, locus coeruleus, dorsal raphe nucleus, parabrachial nucleus, thalamocortical connections, limbic system circuits of amygdala, hippocampus, hypothalamus and cerebellum [3].



**Figure 1.** Anatomy of the vagus nerve in the neck within the carotid sheath. This anatomy is very familiar to neurosurgeons who perform anterior cervical spine surgery. (Courtesy: creative commons).

## 2. Vagus Nerve as a Neuromodulation Target

### 2.1. Anatomy of Vagus Nerve and Neuromodulatory Projections

The vagus nerve provides the primary parasympathetic supply to the body, encompassing both sensory and motor innervation. In the neck, it primarily consists of ascending fibers that enable access to the cortical centers via electrical stimulation through the nuclei of the solitary tract, the locus coeruleus, raphe nuclei, and nucleus basalis—key sources for neuromodulatory chemicals like acetyl choline, norepinephrine, and serotonin [4–7].

These nuclei have extensive connections throughout the central nervous system, with preferential supply to certain brain regions. The locus coeruleus (LC) supplies adrenergic fibers to the prefrontal, motor and sensory cortices [8], while the raphe nuclei (RN) provide serotonergic innervation to the visual cortex and other primary sensory cortices [9].

Additionally, the limbic system receives cholinergic input from the nucleus basalis (NB) [10], whereas spinal cord interneurons receive serotonergic and adrenergic input from the LC and RN [11]. Consequently, given these widespread connections, the vagus nerve has the unique ability to control or modulate these extensive areas of the nervous system [12,13].

### 2.2. Neural Mechanisms of Paired VNS

Neuromodulation by VNS combined with physical rehabilitation is better known as paired VNS. The aforementioned neurotransmitters affect both the acute excitability and neuroplasticity of the CNS [14,15]. Inhibiting the release of these neurotransmitters prevented paired VNS-induced cortical reorganization in animal models [16,17], resulting in behavioral alterations [18]. Multiple studies have illustrated the potential of paired VNS-induced neuromodulation to enhance neuronal plasticity and regeneration in clinical populations including chronic stroke [19]. Many neurotransmitters, especially dopamine, encourage learning patterns to remodel behavior in a positive direction. This reinforcement is considered a key mechanism for initiating neurorehabilitation [20,21]. Evidence from animal studies suggests that VNS delivered after training provides targeted reinforcement, whereas stimulation alone results in the diffuse activation of neuronal output. In rats, Engineer et al. (2011) demonstrated that combining vagus nerve stimulation with training

yielded increased responses in the auditory cortex [22], similar to findings from studies involving the motor activity of the forelimbs [17,23]. However, timing is crucial when combining stimulations to match synaptic activity at the neuronal level for optimal results in stroke rehabilitation [24].

Several studies emphasized the importance of precise timing in paired VNS since delays in reinforcement can dampen its effectiveness [16,23]. VNS may also play a role in reducing inflammatory responses and blood–brain barrier (BBB) permeability; however, in a chronic stroke patient set for rehabilitation, these acute mechanisms may not be relevant [25].

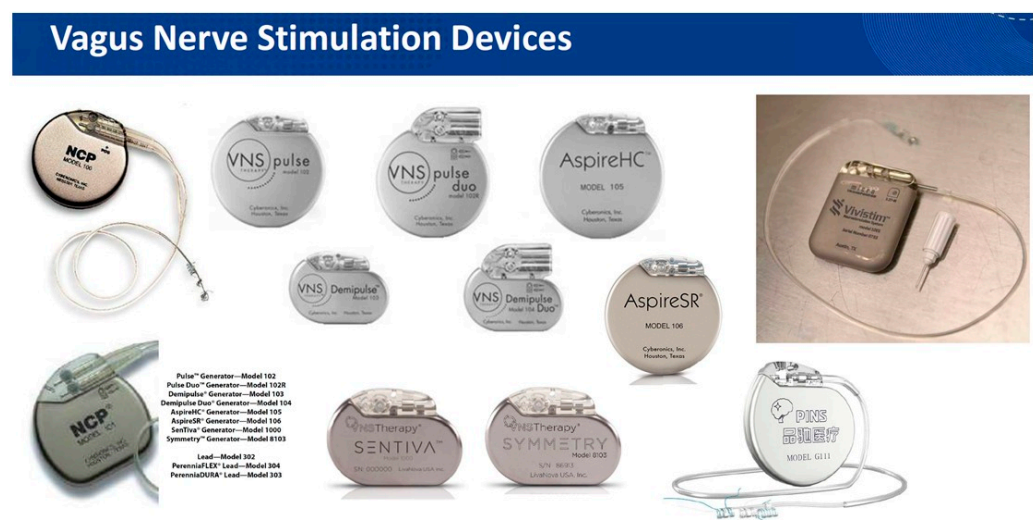
### 2.3. Vagus Nerve and Clinical Neuromodulation

Indications for VNS in clinical settings have existed in the field of epilepsy and later in refractory cases of depression, while more recently, its potential has expanded to stroke rehabilitation, obesity treatment and various neuropsychiatric diseases [26,27].

Future indications for VNS may include pain, migraine, cardiovascular disease, and inflammatory/autoimmune diseases [28–30]. These novel applications for VNS are being actively investigated, driven by advancements in less invasive devices, improved surgical techniques of implantation [31], and recently developed closed-loop systems [32].

### 2.4. The VNS Equipment

Zabara et al. have been credited with introducing the modern VNS system, which consists of a pulse generator connected by a wire to the electrode wrapped around the vagus nerve within the carotid sheath in the neck [33]. After implantation, the system is typically activated after surgical trauma subsides, 2 weeks postoperatively, and then the stimulation parameters are adjusted to optimize clinical outcomes and patient comfort [34]. While the electrode design has remained unchanged over the years, the generator (Figure 2) has undergone several updates, becoming more sophisticated and miniaturized. These advancements have reduced surgical trauma and hospitalization while improving patient acceptance without compromising treatment efficacy. Noninvasive VNS alternatives include the transcutaneous stimulation of the main trunk of the vagus nerve in the neck (tcVNS) or the auricular branch of the vagus nerve (ABVN) by keeping electrodes on the earlobe (taVNS).



**Figure 2.** Various commercially available VNS equipment versions. Note the recognizable difference in the appearance of VNS devices used for epilepsy and depression and the dedicated device (last on the right) for post-stroke rehabilitation.

### 2.5. Mechanisms of VNS

The vagus nerve is a major component of the parasympathetic innervation of the viscera, predominantly consisting of afferent fibers. Hence, its stimulation has yielded various therapeutic effects across a variety of disorders [28,35]. Zabara demonstrated the antiepileptic influence of VNS in canines, while Krahel et al. proposed that the inhibition or lesioning of the LC may be responsible for the suppression of seizure activity [33,36]. It has also been postulated that the noninvasive percutaneous technique mimics the standard implanted version of VNS.

### 2.6. Neural Substrate

The locus coeruleus, the brain's primary noradrenergic center, receives projections from the vagus nerve, and its ablation reduces seizure activity, similar to VNS [36]. In addition, VNS modulates monoaminergic activity by increasing both serotonin and norepinephrine concentrations in CSF [37]. Moreover, in rats, VNS enhances the electrical activity of monoaminergic neurons, a major event in depression management [38]. Neuroimaging studies indicate that VNS influences the prefrontal cortex and limbic system, suggesting a role in mood regulation. Additionally, VNS has been shown to increase brain-derived neurotrophic factor (BDNF) expression, which plays a crucial role in alleviating depression and facilitating post-stroke motor activity as an essential component in enhancing learning and memory [39–41]. Driskill et al. studied drug-seeking rat models to demonstrate that VNS increased BDNF in the infralimbic cortex to regulate synaptic activity for neuronal plasticity [42].

## 3. Clinical Applications

### 3.1. Neuromodulation in Stroke Rehabilitation

Cerebrovascular accidents or strokes remain a major burden on health care, ranking among the leading causes of mortality and morbidity [43]. Surviving stroke patients struggle to regain the functional use of their paralyzed body parts, and motor rehabilitation serves a critical role in improving their quality of life. Zhi et al. (2022) found neuromodulation most efficient among four motor rehabilitation treatments (neuromodulation, training, technological and pharmacological intervention) to improve function post-stroke [44]. Despite their initial promise, current neuromodulatory options have been insufficient to improve motor function following a stroke. Following the initial study by Bailey and Bremer [1], the stimulation of the vagus nerve has been investigated in several animal models of stroke to evaluate recovery patterns. Utilizing motor as well as non-motor tasks, experimental results have been promising, demonstrating that pairing VNS with the concerned activity (motor or auditory tasks) enhances cortical reorganization and improves the plasticity in the relevant cortical areas [45,46]. Additionally, VNS modulates immune responses and has shown to improve outcomes not only in stroke recovery but also in post-traumatic stress disorder (PTSD) therapy [47,48].

### 3.2. Implanted VNS and Paired Motor Rehabilitation Therapy

Patients in trials receiving physical rehabilitation with or without VNS (uniform stimulation parameters of, 0.8 mA current amplitude, 0.1 ms pulse width, 30 Hz frequency, and 0.5 s duration, delivered along with simultaneous motor movements) exhibited meaningful arm recovery favoring stimulation in several trials [27,49,50]. As recently as 2021, the FDA approved the Vivistim Paired VNS system by MicroTransponder (Vivistim, MicroTransponder Inc., Austin, TX, USA) for the treatment of moderate to severe upper extremity motor deficits associated with chronic ischemic stroke. Several ongoing multicenter studies are being conducted to continue investigating its efficacy.



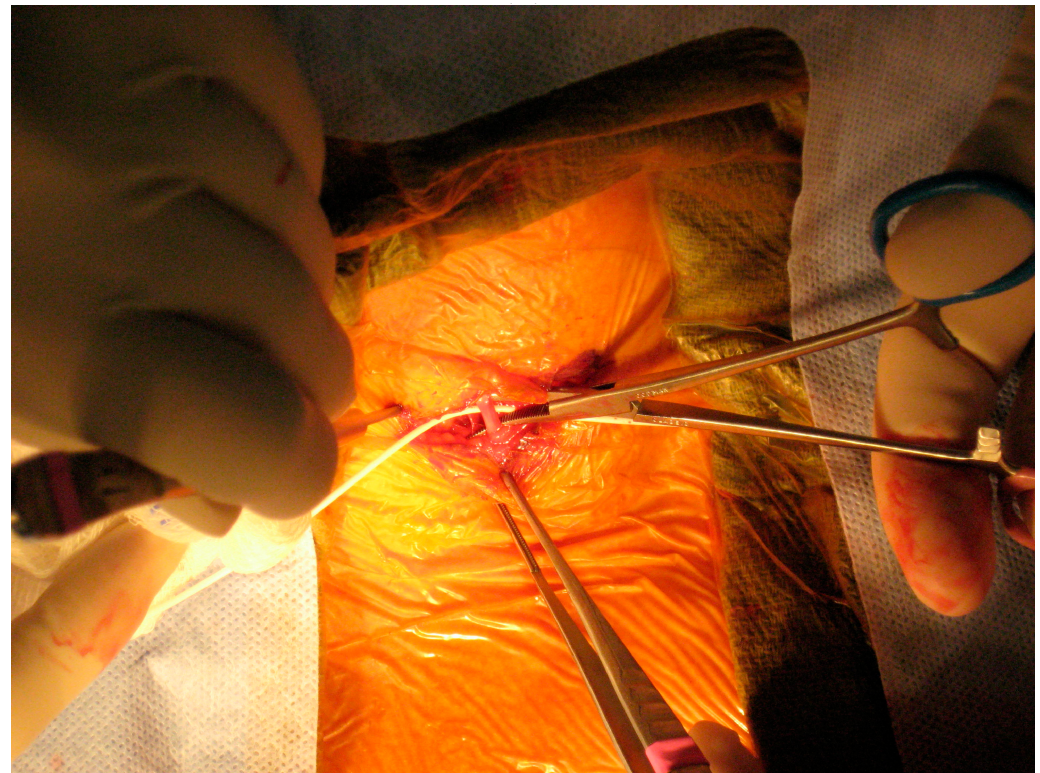
### 3.3. Technique of VNS Implantation

Today, VNS implantation is a standardized procedure following the routine approach for epilepsy surgery. It is performed on the left side only. After opening the skin and platysma, a carotid triangle is dissected to reach the posterior layer of the carotid sheath where the vagus nerve is located. The nerve is freed along its longitudinal extent to wrap the spring electrode around it (Figure 3). This electrode has extensions for the implantable pulse generator (IPG). A separate incision is given in the infraclavicular region to accommodate the IPG and a subcutaneous tunnel is made to connect both the incisions and bring down the electrode extensions. The battery is placed in the infraclavicular region and connected to these electrodes. Incisions are closed in layers after ensuring a favorable signal from the remote operator.

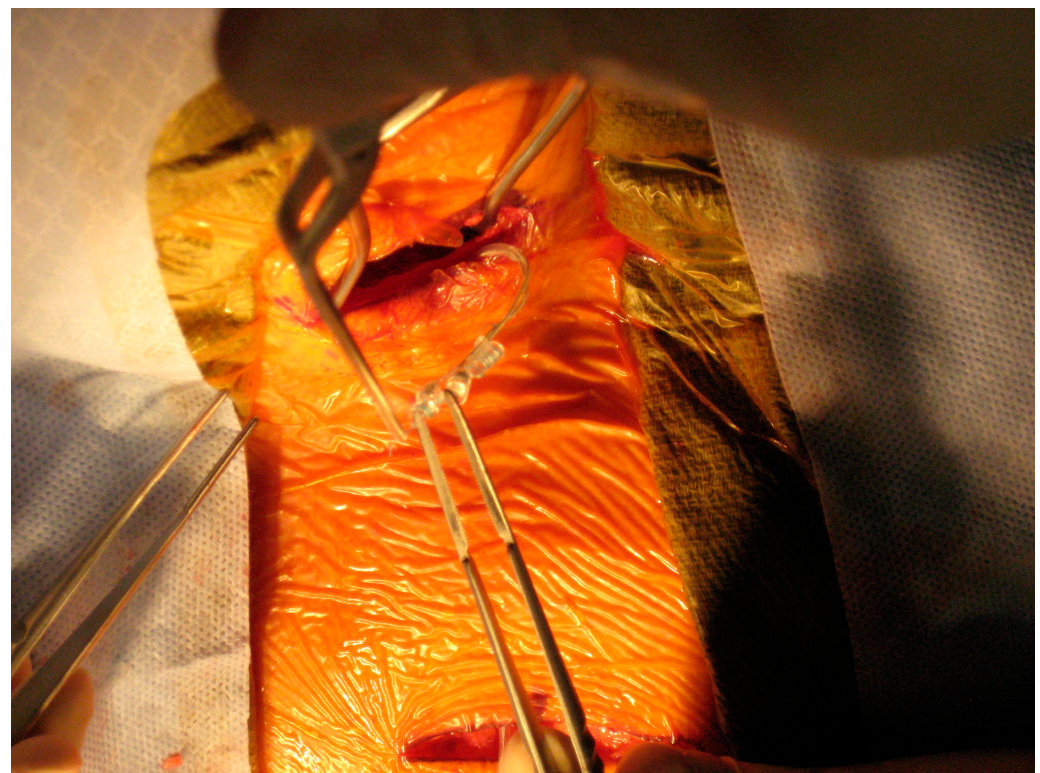


(A)

**Figure 3.** *Cont.*



(B)

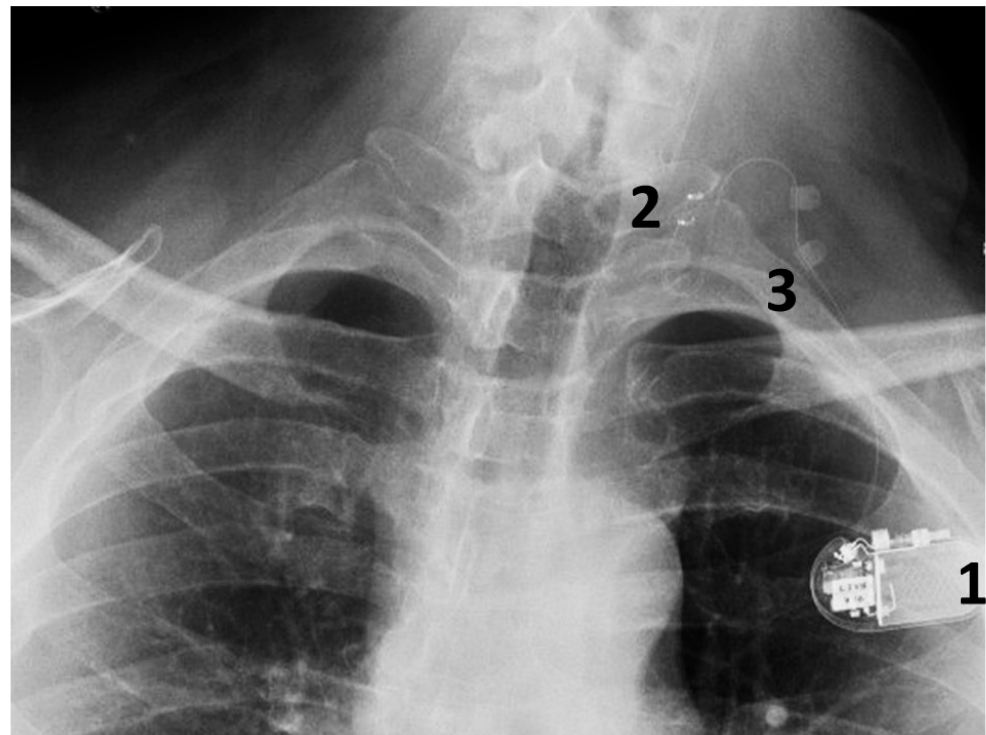


(C)

**Figure 3.** Implantation steps of the VNS system: (A) the marking of skin incisions in the neck and infraclavicular region; (B) the dissection of the vagus nerve in the cervical region; (C) the handling of the VNS electrode prior to the implantation.

This is conducted under general anesthesia, and the patient is kept under observation for a day. The surgical procedure is safe and serious complications are rare (Figure 4).





**Figure 4.** A chest radiograph showing the components of the implanted VNS system: 1. The implantable pulse generator; 2. the electrode contacts on the left vagus nerve; 3. silicone anchors to stabilize the electrode in place.

In a long-term follow-up review of 497 procedures, the team of Ben-Menachem reported an overall complication rate of 8.6% for all implantation procedures and 3.7% were hardware-related complications. Postoperative hematoma and infection were the most common complications; others included infection, vocal cord palsy, facial weakness, pain and the disconnection of the leads [51].

### 3.4. Noninvasive VNS

Noninvasive VNS, specifically taVNS, has been explored in stroke rehabilitation using slightly differing stimulation parameters [52–54]. Targeting cymba concha or acoustic meatus on the left side, one of these studies yielded significant improvements in upper extremity motor function [53]. Redgrave et al. utilized 18 sessions of 1 h each applying 25 Hz stimulation and 100 s pulse width for taVNS in post-stroke patients [53]. Baig et al. employing a similar technique in chronic stroke patients obtained promising recovery in sensory loss too [55]. Other trials also had encouraging outcomes favoring stimulation over sham stimulation [52,54]. Capone et al. combined robotic-assisted physical therapy with taVNS for rehabilitation of their post-stroke patients to document that noninvasive VNS resulted in significantly greater motor recovery compared to physical rehabilitation alone [52].

In a pilot study, motor-activated auricular vagus nerve stimulation (MAAVNS) was encouraging in its outcomes. In an individualized closed-looped stimulation study, MAAVNS was used to improve upper extremity motor function, utilizing surface electromyography (EMG) for the stimulation delivery feedback [33]; in this pilot study on 16 patients, Badran et al. came up with encouraging results showing noninvasive tcVNS treatment to be comparable to the implanted VNS [33].

Peng et al. utilized neuroimaging (fMRI) to evaluate ipsilateral versus contralateral ear stimulation by measuring blood oxygenation level-dependent (BOLD) signals [56]. The study demonstrated that the same side ear stimulation (ipsilateral neuromodulation)

provided a greater excitation of the ipsilateral cortex and stronger activation of task-related motor areas compared to contralateral neuromodulation.

#### 4. Discussion

Current estimates reveal that 7.6 million adults are struggling with stroke in the US, while an additional 3.4 million will join this group in ten years [57]. The majority of these patients suffer from sustained upper extremity motor dysfunction, curtailing their activities of daily living (ADLs) and quality of life [58–60]. Over the past decade, physical therapy and rehabilitation techniques have evolved with some promise but remain time-intensive and require specialized environments with certain equipment [61–63]. However, neuromodulation by VNS combined with physical rehabilitation (paired VNS) appears to be a more efficient treatment option [64].

Chicago neurosurgeon Percival Bailey conducted extensive laboratory studies on cerebral localization and functional neurosurgery. Animal experiments by Bailey and Bremer revealed that the stimulation of the vagus nerve enhanced memory via afferent projections to the brainstem [1]. Subsequent experimental and preclinical studies further suggested the role of VNS in promoting neuronal plasticity following neurological injury [19,65]. Study groups in stroke models demonstrated consistent improvements compared to control groups when VNS was applied simultaneously with physical therapy [65].

Translational studies have established possible pathways through which paired VNS activity improves the paralyzed upper extremity in humans: the descending ipsilateral corticospinal tract and the contralateral cortico-reticulospinal tract [66]. Meyers et al. demonstrated that paired VNS significantly improved upper limb function in paretic rats compared to sham stimulation [18,67]. It is also possible that other motor pathway regions may contribute to improving neural plasticity following paired VNS.

##### 4.1. VNS and the Stimulation Parameters in Human Stroke Rehabilitation

The vagus nerve is stimulated on the left side for VNS and the parameters need to be tailored to patient comfort rather than the elicitation of the desirable response. The increasing intensity may improve the stimulation of the nerve, but the patient's tolerance should take the priority as discomfort can cause disproportionate impedance. Here, the pulse width requires attention along with its interaction with stimulation intensity. Increasing the pulse width can achieve better VNS results, keeping the intensity stable [68]. There is still scope for exploring the interactions between stimulation and pulse width.

Ben-Menachem et al. recommended a biologically active frequency between 20 and 30 Hz for both implantation and transcutaneous VNS for optimum behavior results, pending a further search for acceptable frequency levels [69]. Other investigators also concede the need to study the ranges of frequencies as well as the on/off periods to prevent damage to the nerve and prolong the IPG duration of life without compromising the neural plasticity effects of the therapy [70].

##### 4.2. The Noninvasive Transcutaneous Stimulation of the Vagus Nerve

Transcutaneous stimulation methods differ significantly from the implanted VNS systems in both their neuromodulation pathways and stimulation responses [71].

The noninvasive methodology predominantly elicits responses mediated by a cutaneous sensation and may not even reach the vagus nerve fibers within the carotid sheath. Understandably, the percutaneous stimulation tends to fail in eliciting physiological activity comparable to standard VNS. Bucksot et al. demonstrated that tcVNS may achieve responses similar to implanted VNS, but only at much higher stimulation intensities—potentially exceeding clinical tolerability to a great extent [72]. Additionally, tcVNS may

not provide adequate stimulation consistency to yield the desired clinical results. Thus, stimulation intensity must be modulated to moderate intensities in order to be clinically efficient and tolerable [19]. One possible reason for this failure is the anatomical variability of the vagus nerve at stimulation sites, which may contribute to inconsistent effects [73,74].

#### *4.3. Safety and Feasibility of VNS*

VNS has been in clinical use for several decades and has proven to be safe and well tolerated, especially in epilepsy patients. In stroke patients, so far, it has been reported to be safe without serious adverse events related to the procedure or the implant [75]. Its utility as a combination therapy in stroke rehabilitation is another encouraging feature since it may reduce the number of required visits and allow for personalized device monitoring. Multicenter clinical trials have been approved by the FDA to further evaluate the efficacy of paired VNS in motor rehabilitation for stroke patients.

#### *4.4. Other Promising Indications for Paired VNS*

Beyond the motor improvements observed in stroke patients, paired VNS shows potential for broader neuromodulation applications, including incomplete cervical spinal cord injury, lower extremity paralysis, dysphagia and sphincter dysfunctions [76,77].

### **5. Summary**

Paired VNS therapy used in stroke rehabilitation is a safe and promising modality, with encouraging outcomes from multiple multi-institutional studies supporting its clinical use. Combining rehabilitation-aimed motor activity and neuromodulation appears to be a better approach for improving motor function than the passive physical therapy of a paralyzed extremity alone [63] while also reducing compensatory movements [78]. Based on robust supporting preclinical models, VNS for stroke rehabilitation is tailored to the requirements of the paralyzed extremity, the upper extremity as of now, especially when delivered through an individualized closed loop of short bursts of stimulation synchronized with physical therapy movements [79]. This therapy is supported by the observations that paired VNS activates several neuromodulation pathways engaging noradrenergic, cholinergic and serotonergic networks to improve neuronal plasticity [19]. While noninvasive VNS might be appealing to the patients, its mechanism may differ from that of implanted neuromodulatory systems. At this point in time, there is no consensus on the possible best parameter for VNS therapy, considering the multiple variables at play during the rehabilitation of the stroke patients. Hopefully, a wide range of stimulation frequencies, pulse widths, current intensities and durations will be narrowed down to contribute to the long-lasting outcomes in VNS treatment in human neurological ailments.

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## Abbreviations

The following abbreviations are used in this manuscript:

CVA	Cerebrovascular accident
VNS	Vagal nerve stimulation
CNS	Central nervous system
LC	Locus coeruleus
RN	Raphe nuclei
tcVNS	Transcutaneous VNS
ABVN	Auricular branch of the vagus nerve
taVNS	Transauricular VNS
CSF	Cerebrospinal fluid
BDNF	Brain-derived neurotrophic factor
PTSD	Post-traumatic stress disorder
MAAVNS	Motor-activated auricular VNS
fMRI	Functional magnetic resonance imaging
BOLD	Blood oxygenation level-dependent
ADL	Activity of daily living

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