VAGAL NERVE STIMULATION AIDED STROKE RECOVERY: VIVISTIM TECHNOLOGY

Introduction:

Stroke is a condition manifested by rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer. This malady can include ischemic and hemorrhagic infarction, intracerebral hemorrhage, and subarachnoid hemorrhage (SAH). In adults, 80-85% of strokes are ischemic while in children, 55% of strokes are ischemic. Ischemic stroke is the number one cause of disability among adults in the United States with 795,000 Americans affected per year (1 stroke every 40 seconds). Stroke is a major cause of death with 128,000 mortalities per year.

When considering morbidity, upper limb disability represents one of the most common stroke symptoms with 60% of individuals displaying upper limb deficits >6 months after injury. Because upper limb dysfunction is associated with poor post stroke quality of life (QOL), any treatments that improve function will translate into a better QOL for afflicted individuals

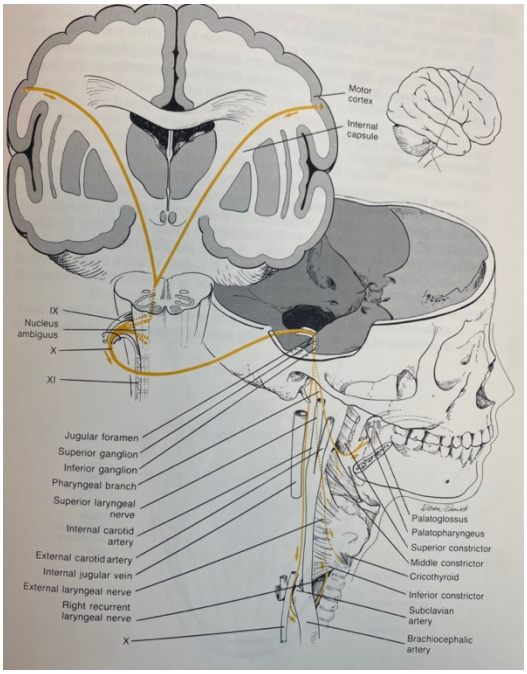
Neural Plasticity:

The term *neural plasticity (NP)* "refers to the capacity of the nervous system to modify itself, functionally and structurally, in response to experience and injury" (von Bernhardi R, *et al*. What is neural plasticity? Adv Exp Med Biol. 2017;1015:1-15. Doi: 10.1007/978-3-319-6217-2_1). Following ischemic brain injury (Ischemic Stroke; IS) and resultant brain dysfunction, NP is believed to support functional recovery from brain damage (Khodaparast N, *et al*. Vagus nerve stimulation delivered during motor rehabilitation improves recovery in a rat model of stroke. Neurorehabil Neural Repair. 2014 Sep; 28(7):698-706). Over the last decade, researchers have investigated methods to improve NP in stroke victims in an attempt to enhance recovery of neurologic function beyond what can be achieved by physical rehabilitation alone.

Vagal/Vagus Nerve (VN):

The right and left VN (Cranial Nerve 10), the longest cranial nerves in the body, arise from the medulla oblongota section of the brainstem. This nerve:

1. Carries parasympathetic nervous system impulses to the internal organs thus regulating digestion, heart rate, respiratory rate, blood pressure, coughing, sneezing, and vomiting.
2. Innervates muscles of the throat and tongue
3. Innervates muscles of the thoracic and abdominal organs
4. Innervates stretch and chemoreceptors in the aortic arch and carotid artery
5. Provides sensation to the portions of the ear and throat



MOTOR STRIP
IN THE BRAIN

VAGAL NERVE

ORGANS, MUSCLES

SENSORY STRIP
IN THE BRAIN

VAGAL NERVE

ORGANS, RECEPTORS

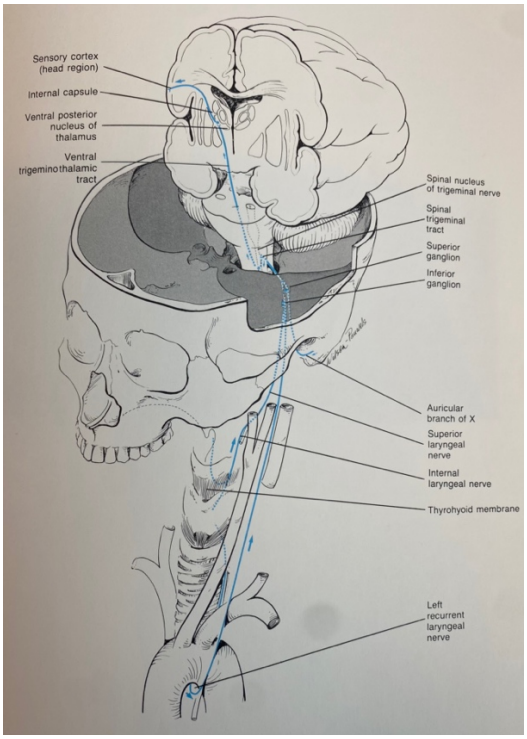


Figure 1: Left sided drawing shows the vagus nerve (VN) arising from the medulla. The descending yellow line shows the VN traveling down towards the throat and organs. The VN receives signals from the motor strip section of the brain (yellow lines). The right sided drawing shows the sensory portion of the VN. The blue lines travel from the organs to the VN

in the medulla. Connections then run from the VN to the sensory strip in the brain. The arrows on the right show a schematic of the motor and sensory VN fibers and connections to the brain.

Vagal Nerve Stimulation:

Vagal nerve stimulation (VNS) entails sending painless, regular, mild pulses of electrical energy to the brain via the vagus nerve (VN; Cranial Nerve 10). This stimulation is achieved by surgically implanting electrodes around the VN in the neck. These electrodes are attached to a small battery that is placed under the skin of the chest. The battery sends electrical impulses to the vagus nerve which in turn causes neurotransmitters released in the brain to. Stimulate the brain's motor cortex which controls muscle movements (Figure 2). For a more in-depth explanation refer to VNS Mechanism of Action section below.

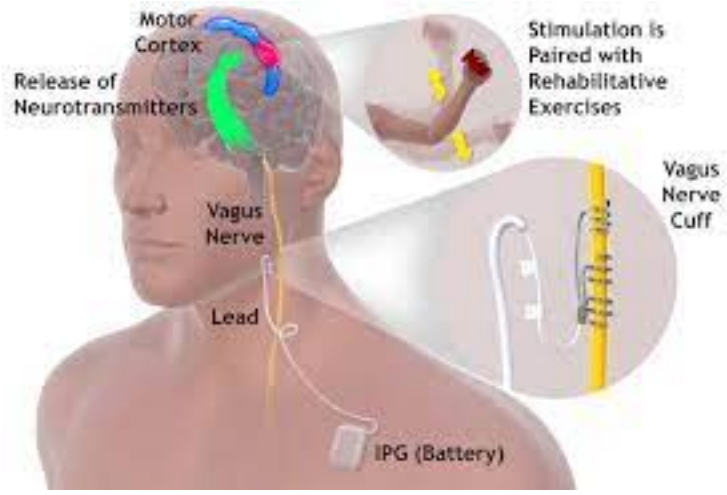


Figure 2: This figure shows the battery implanted under the skin of the chest. The battery is connected to an electrode lead that is placed in contact with the VN in the neck. Electrical stimulation from the battery travels to the VN in the neck with impulses then traveling up the VN to the brain. Neurotransmitters that are released alter the structure of the motor center of the brain (motor cortex).

VNS is currently used under FDA approval or in investigational studies to treat epilepsy, depression, anxiety, and dementia (Groves DA, *et al*. Vagal nerve stimulation: A review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev. 2005 May; 29(3):493-500. Doi: 10.1016/j.neubiorev.205.01.004). In 2021, VNS was `approved by the FDA to improve functional recovery following ischemic stroke.

VNS and Stroke Rehabilitation: Vivistim System:

Animal and Human Studies:

In 2014, Khodaparast, et al. published their initial results testing VGS is rats suffering from experimentally induced acute strokes that disabled a right or left forelimb (Khodaparast N, *et al*. Vagus nerve stimulation delivered during motor rehabilitation improves recovery in a rat model of stroke. Neurorehabil Neural Repair. 2014 Sep; 28(7):698-706). Animals were divided into three groups. Group 1 underwent VPS during rehabilitation, Group 2 underwent VPS after rehabilitation and Group 3 underwent rehabilitation alone. Results from this study indicated that VPS during rehabilitation yielded full forelimb recovery while VPS after rehabilitation and rehabilitation alone yielded partial and no recovery, respectively. The authors had proof of concept demonstrating the benefits of VPS in stroke recovery when used during rehabilitation.

To next investigate the effects of VPS in the setting of chronic stroke, in 2015, Khodaparast *et a*l. published the effects of VPS in stroked rats who were treated six weeks after injury (Khodaparast N, et al. Vagus nerve stimulation during rehabilitative training improves forelimb recovery after chronic ischemic stroke in rats. Neurorehabil Neural Repair. 2016 Aug; 30(7):676-684). Once again three groups were studied. Six weeks after stroke Group 1 underwent VNS during rehabilitation, Group 2 underwent VNS two hours after daily rehabilitative training, and Group 3 underwent rehabilitation without VPS. Results from this study indicated that VPS during rehabilitation yielded 86% recovery of forelimb strength, while VPS after rehabilitation and rehabilitation alone yielded 47% and 42% recovery, respectively. The authors had proof of concept demonstrating the benefits of VPS in chronic stroke recovery when used during rehabilitation.

Based on the above animal studies, Dawson *et al*. studied the effects of VPS > 6 months after stroke in 20 patients with moderate to severe upper limb weakness. Two groups were randomized. Group 1 underwent rehabilitation alone (three 2-hr sessions a week for six weeks). Group 2 underwent 0.5 second VNS simultaneously paired with rehabilitation movements. Results from this study suggested benefits from VPS with no serious adverse events.

In 2018, Kimberley *et al*. published results from a blinded and randomized trial investigating the benefits of VPS after chronic stroke in human subjects who experienced injury 4 months to 5 years prior to study initiation (Kimberley TJ, *et al*. Vagus nerve stimulation paired with upper limb rehabilitation after chronic stroke. Stroke. 2018; 49:2789-2792). Ninety days following treatment investigators found that VNS treated patients had 88% meaningful improvement in upper extremity function while rehabilitation patients alone demonstrated 33% meaningful recovery. Proof of concept showed that VPS during rehabilitation sessions was beneficial when compared to rehabilitation alone.

In 2021, Dawson *et al*. published a 19 center, 108 patient randomized and blinded VNS-Rehabilitation post stroke study (Dawson J, et al. Vagus nerve stimulation paired with

rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): A randomized, blinded, pivotal device trial. 2021 Apr 24;397(10284):1545-1553). Ninety days following treatments the authors noted meaningful improvement in 47% of the VNS-Rehab group as compared to 24% in the Rehab group that had not received VNS.

Based upon the above series of studies, in 2021 the U.S. Food and Drug Administration approved the MicroTransponder Vivistim Paired VNS System (Vivistim System) for the treatment of moderate to severe upper extremity motor weakness associated with chronic ischemic stroke (https://www.fda.gov/news-events/press-annpuncements/fda-approves-first-its-kind-stroke-rahabilitation-system).

VNS Mechanism of Action:

Rehabilitation therapy following cortical injury improves functional outcome through promotion of neuroplasticity. VNS simultaneously paired with rehabilitation is felt to further promote rehabilitation induced neuroplasticity by increasing the release of neuromodulators (acetylcholine and norepinephrine; Ach and NE) from the nucleus basalis (NB) (ACh releasing) and the locus coeruleus (LC) (NE releasing) throughout the cortical layers of the brain (Figure 3). These biochemicals appear to help reorganize motor system synaptic connections and recruit motor neurons which results in improved forelimb function (Engineer ND, et al. Targeted vagus nerve stimulation for rehabilitation after stroke. Front Neurosci. 2019; 13 280. Doi: 10.3389/fnins.2019.00280). Support for the above hypothesis is provided by experiments that have shown than damage to the LC and NB inhibit neuroplasticity. Other experiments have shown that VNS in rats that is simultaneously administered with an auditory tone causes the rat auditory cortex to increase in size while electrical stimulation of the trigeminal nucleus simultaneous with an auditory tone had no effect on the rat's auditory cortex size. Similarly, VNS during sensory stimulation increases the plasticity of the sensory cortex.

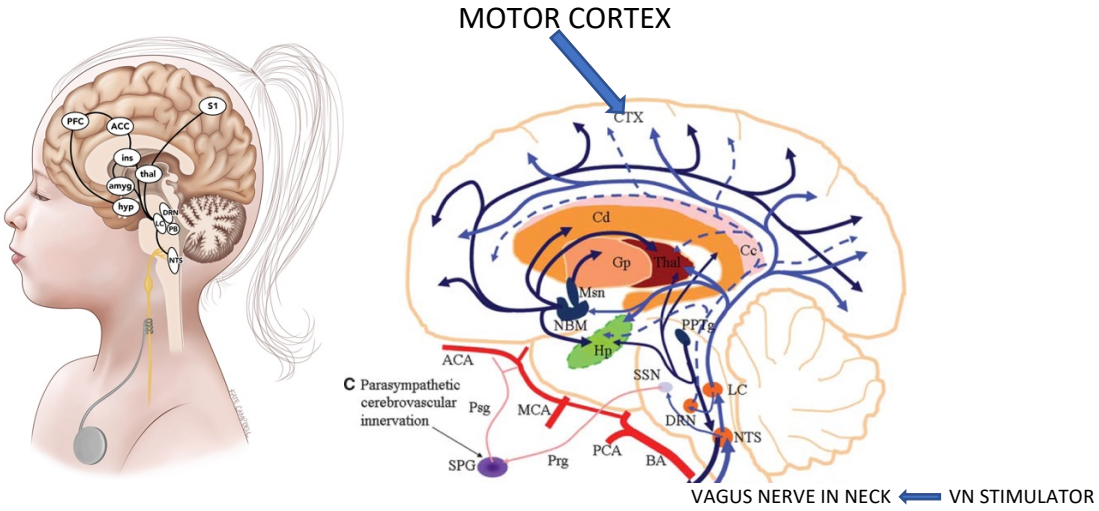


Figure 3: These images show the pathway by which the VN stimulation in the neck sends signals to the motor cortex which increase NE and Ach concentrations and increase neuroplasticity in the motor cortex of previously stroked patients

In summary, therefore, VNS stimulation that is provided simultaneously with a particular stimulus (motor activity) will cause the cortical region that subserves that activity to change/augment. This explains why animal and human upper limb functional improvement was seen only when rehabilitative movements were performed at the same time as the delivery of VN stimuli. Improvements were not seen when VN were delivered after a rehabilitative session was completed.

Patient Selection, Surgical Procedure, and Post-Surgical Rehabilitation:

The Vivistem System is intended to be used to stimulate the vagus nerve during rehabilitation therapy in order to reduce upper extremity motor deficits and improve function in chronic ischemic stroke patients with moderate to severe arm weakness.

In order for an individual to be eligible for Vivistim implantation they must meet the following inclusion and exclusion critieria:

Inclusion:

- Unilateral cortical ischemic stroke > 9 months and < 10 years before time of implantation
- Age >22 years and <80 years
- Fugl-Meyer Assessment of the upper extremity $\geq$20 and $\leq$50
- Ability to communicate, understand, follow two step commands
- Right or left side upper extremity weakness
- Ability to flex and extend the wrist, abduct and extend the thumb and at least two other fingers

Exclusion:

- History of hemorrhagic stroke
- Ongoing dysphagia or aspiration
- Medications that may interfere with VNS
- Prior vagus nerve injury such as during carotid endarterectomy
- Depression (Beck Score >29)
- High surgical risk
- Current use of a stimulation device (pacemaker, neurostimulator)
- Psychological instability, substance abuse
- Pregnancy
- Recent Botox injections to extremity
- Severe spasticity (Ashworth $\geq$3)
- Significant sensory loss

While risks of surgery include major permanent morbidity and mortality, the most common risks (>5% risk) of Vivistem implantation include mild to moderate:

- Local pain
- Bruising
- Hoarseness
- Depression
- Muscle pain
- Throat irritation
- Infection
- Headache

Most of the above events resolve within 1-2 after surgery although vocal cord injury may take 12-18 months to resolve.

Rehabilitation therapy usually begins two weeks after surgery. The rehabilitation protocol involves:

- 6 weeks
- 3 sessions per week
- Each session is 90 minutes long

Once the 6-week sessions are completed, patients continue with a daily 30-minute, home based, self-directed therapy program. The VNS is activated at home by the patient using a handheld magnet.

Conclusion:

VNS combined with rehabilitation therapy using the Vivistim system has been shown to significantly improve upper extremity function in patients who have suffered ischemic strokes. Implantation of the device may be carried out 9 months to 9 years following stroke in patients aged 22 - 80. While the procedure is not risk free, complication rates are low with most post-surgical untoward events resolving within 2 weeks of the procedure.