EPFL

Neuro X Institute

Neuromodulation of the autonomous nervous system : Vagal nerve stimulation (VNS)

Nx-436

'Advanced methods for human neuromodulation'

Prof. Friedhelm Hummel

Defitech Chair for Clinical Neuroengineering,
Neuro-X Institute (INX) & Brain Mind Institute (BMI)
Ecole Federale Polytechnique de Lausanne (EPFL)

Department of Clinical Neuroscience, University Hospital of Geneva

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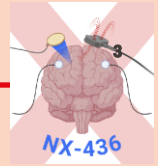
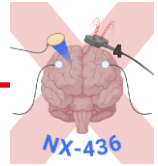
15/11/2023

Objectives

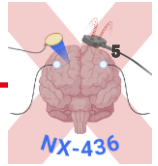


- Understand the autonomous nervous system (ANS) incl. the Vagal nerve
- Concept of Vagal Nerve Stimulation (VNS)
- Translational approaches of VNS



Brain

Storming



NERVOUS SYSTEM

CENTRAL NERVOUS SYSTEM

BRAIN

SPINAL CORD

PERIPHERAL NERVOUS SYSTEM

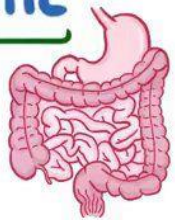
SOMATIC

Voluntary movement of skeletal muscle

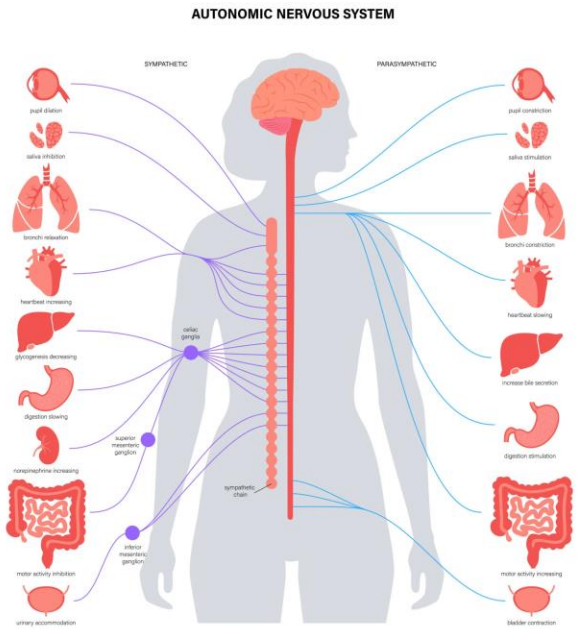
AUTONOMIC

SYMPATHETIC PARASYMPATHETIC

Involuntary movement of
* Smooth muscles
* Glands of organs



The autonomic nervous system (ANS)



https://www.simplypsychology.org

- ANS controls **vital functions** such as heartbeat, breathing, and digestion
- ANS involved in the **acute stress response**, works with the endocrine system to prepare the body to **fight-or-flight** and **rest-and-digest**
- ANS transmits **information** from and to the internal body organs
- ANS operates **automatically** (not under voluntary control)
- ANS **always** active

Two main divisions:

Sympathetic nervous system:

system is responsible for your body's "**fight-or-flight**" response.

Parasympathetic nervous system:

opposite of the sympathetic nervous system; responsible for the "**rest-and-digest**" body processes.

Hypothalamus

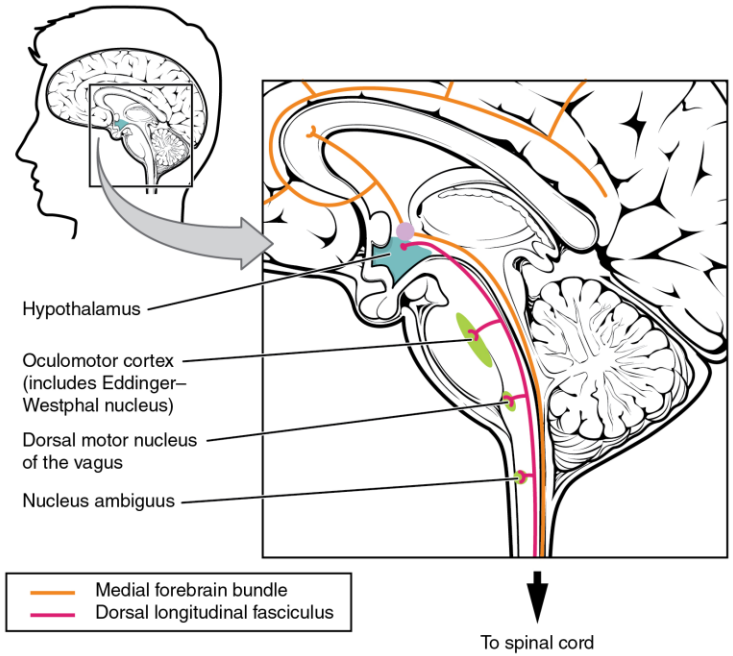


Image credit: "Fiber Tracts of the Central Autonomic System" by OpenStax

Hypothalamus regulates both ANS and endocrine functions by three main neurotransmitters

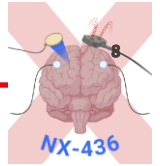
Acetylcholine
parasympathetic nervous system, inhibiting effect.

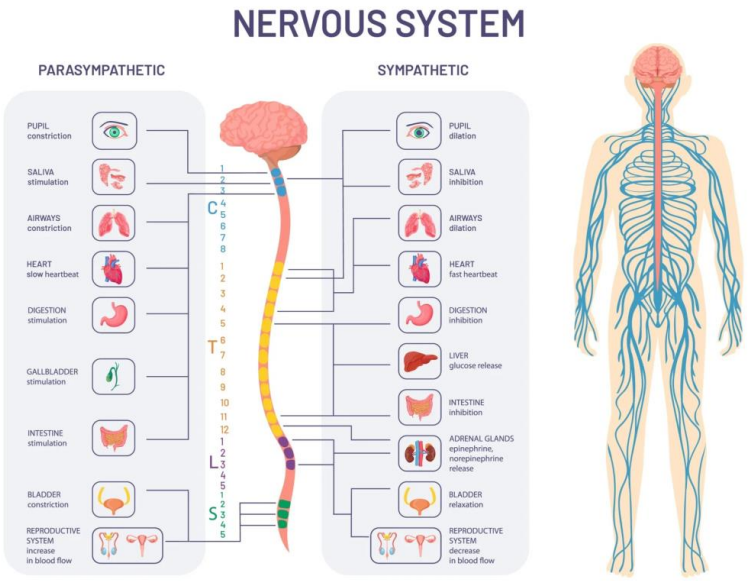
Epinephrine/Adrenaline
sympathetic nervous system, stimulating effect.

Norepinephrine/Noradrenaline
sympathetic nervous system and has also a stimulating effect.

Well connected to the limbic system

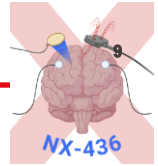
The autonomic nervous system





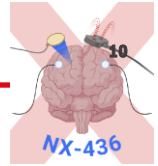
https://my.clevelandclinic.org/

- **Eyes**: width of pupils and eye muscles for focus.
- **Lacrimal** (eyes), nasopharyngeal (nose) and salivary (mouth) glands:
- **Skin**: ability to sweat and muscles that cause hair to stand up (. “goosebumps”)
- **Heart** and **circulatory system**: heart rate, blood pressure and width of blood vessels..
- **Immune System:** parasympathetic nervous system can trigger reactions of immune system.
- **Lungs** width of your airway and the network of passages for air
- **Intestines:** manages the digestion process.
- **Liver, Pancreas:** regulates release of insulin and other hormones from the pancreas liver.
- **Urinary tract**: Your autonomic nervous system manages bladder muscles
- **Reproductive system**: autonomic system plays a key role in your body’s sexual functions



Conditions and disorders affecting the autonomic nervous system (neuropathy)

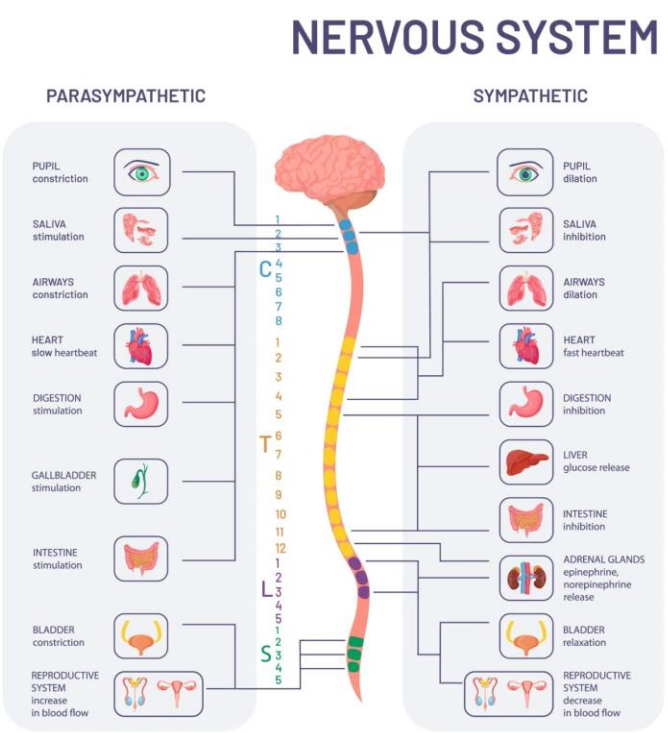
- **Diabetes**
- **Amyloidosis**
- **Autoimmune and inflammatory conditions**
- **Congenital and genetic conditions** (e.g., Baroreflex Failure Syndrome, Hereditary Sensory and Autonomic Neuropathies (HSAN), Familial Dysautonomia)
- **Infections:** damage due to e.g., viruses (e.g. HIV, Lyme disease)
- **Neurodegenerative disorder**, e.g. Multi System Atrophy (MSA)
- **Toxins**: e.g., mercury.
- **Trauma**. only the case with injuries to spinal cord that damage or cut off autonomic connections farther down.
- **Tumors**

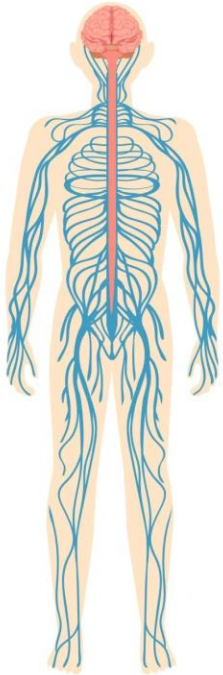


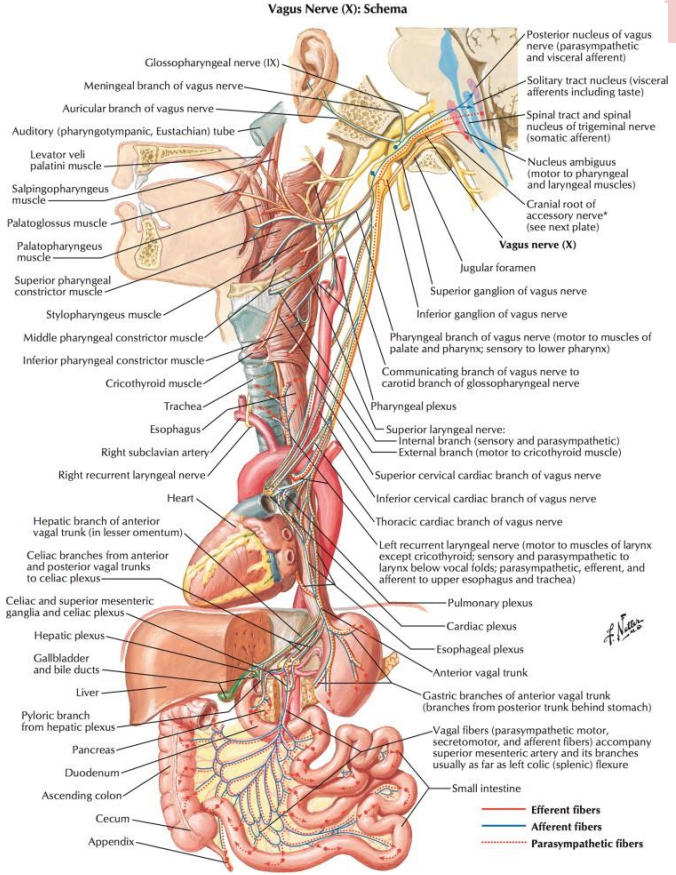
The symptoms of autonomic nervous system conditions, e.g.

- Heart rhythm problems (including arrhythmias).
- Dizziness or passing out when standing up.
- Trouble swallowing (dysphagia).
- Trouble digesting food (including gastroparesis).
- Constipation.
- Incontinence (bladder or bowel).
- Sexual dysfunction.
- Sweating too much (hyperhidrosis) or not sweating enough (anhidrosis).
- Problems tolerating hot temperatures.

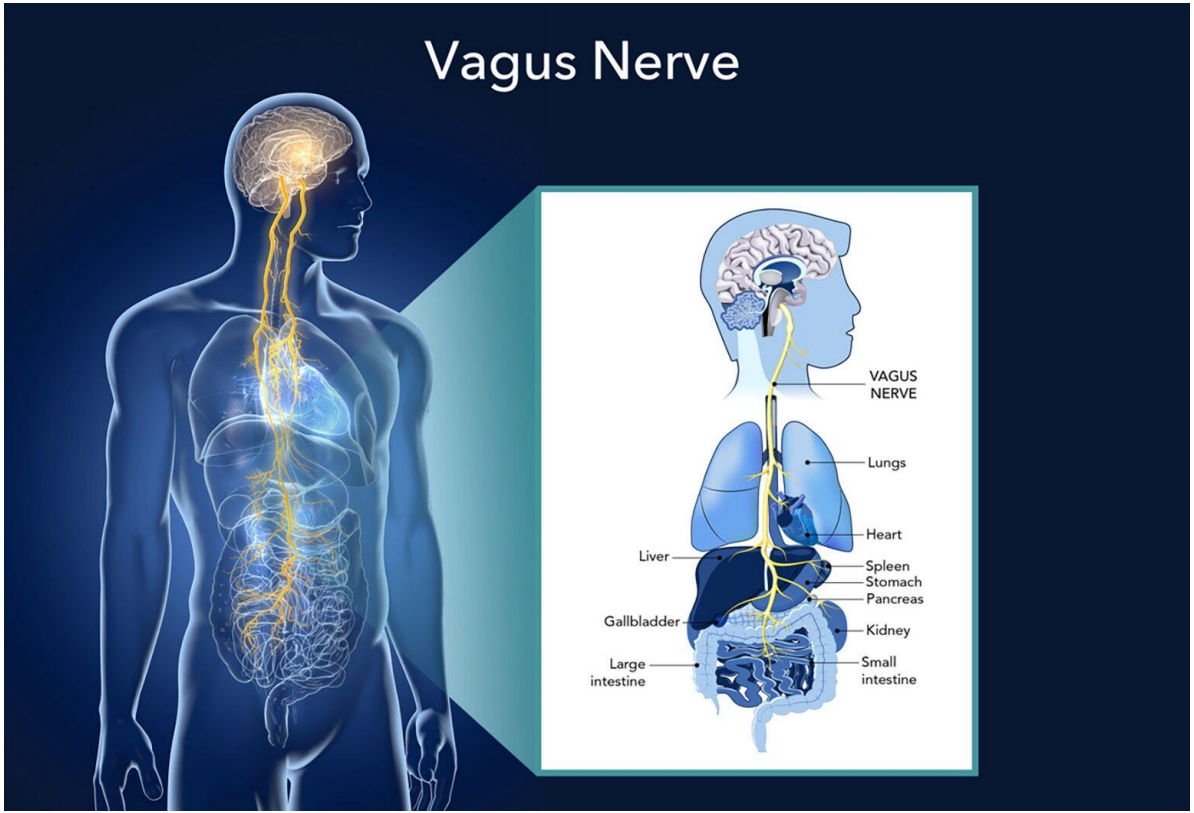
The autonomic nervous system







How to perform vagal nerve stimulation?



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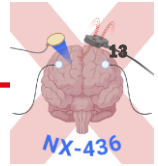
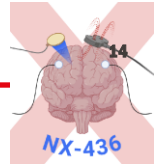


Vagus Nerve Stimulation (**VNS**) is a therapeutic technique where **electrical** impulses are delivered to the vagus nerve to treat conditions like epilepsy, depression, and more recently, disorders related to the autonomic nervous system.

Several types of **electrode systems** have been developed for VNS, with differences in design, placement, stimulation parameters, and intended use. Here's an overview of the different electrode systems used for VNS:

How to perform vagal nerve stimulation?



1. Cervical (Traditional) Vagus Nerve Stimulation

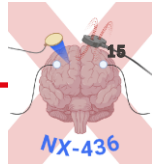
- **Electrode Type**: Implantable cuff electrode
- **Placement**: Around the vagus nerve in the neck (cervical vagus nerve).
- **System Overview**:

  This is the most commonly used system in clinical practice.
  A helical cuff electrode is surgically implanted around the left vagus nerve in the neck.
  The cuff is connected to a pulse generator implanted subcutaneously in the chest, similar to a pacemaker.
  The system delivers electrical pulses to the vagus nerve on a regular schedule or can be manually activated by the patient using a magnet.

2. Transcutaneous Vagus Nerve Stimulation (tVNS)

- **Electrode Type**: Non-invasive surface electrodes
- **Placement**: On the skin, either over the auricular branch of the vagus nerve (ear-based tVNS) or the cervical vagus nerve (neck-based tVNS).
- **System Overview**:

  This system uses electrodes placed on the skin to stimulate the vagus nerve non-invasively.
  For **auricular tVNS (aVNS)**, electrodes are placed on the ear, targeting the auricular branch of the vagus nerve.
  For **cervical tVNS**, electrodes are placed on the skin over the vagus nerve in the neck.
  This system is portable and does not require surgery.



3. Implantable Selective Vagus Nerve Stimulation (sVNS)

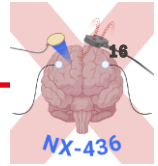
- **Electrode Type**: Multi-contact cuff electrode
- **Placement**: Around the cervical vagus nerve, similar to traditional VNS, but with multiple contacts for selective stimulation.
- **System Overview**:

  Unlike traditional VNS systems that use a simple helical cuff electrode, sVNS systems use multi-contact cuff electrodes that allow for **selective stimulation** of different fibers within the vagus nerve.
  This selectivity can target either afferent (sensory) or efferent (motor) fibers, which can improve therapeutic outcomes and reduce side effects.

4. Endovascular Vagus Nerve Stimulation (eVNS)

- **Electrode Type**: Endovascular electrodes (inside a blood vessel)
- **Placement**: Electrodes are threaded through a blood vessel, usually the jugular vein, to stimulate the vagus nerve from inside the vessel.
- **System Overview**:

  This system represents a novel, **minimally invasive** approach to stimulating the vagus nerve.
  Electrodes are delivered through the jugular vein and positioned near the vagus nerve, allowing for **direct electrical stimulation** without the need for open surgery.
  It's still largely experimental but offers the potential for less invasive procedures compared to traditional implantable VNS systems. on brain activity.



5. Laparoscopic Vagus Nerve Stimulation

- **Electrode Type**: **Cuff electrodes** placed on the vagus nerve in the abdomen.
- **Placement**: Around the vagus nerve in the abdomen (abdominal vagus nerve stimulation).
- **System Overview**:

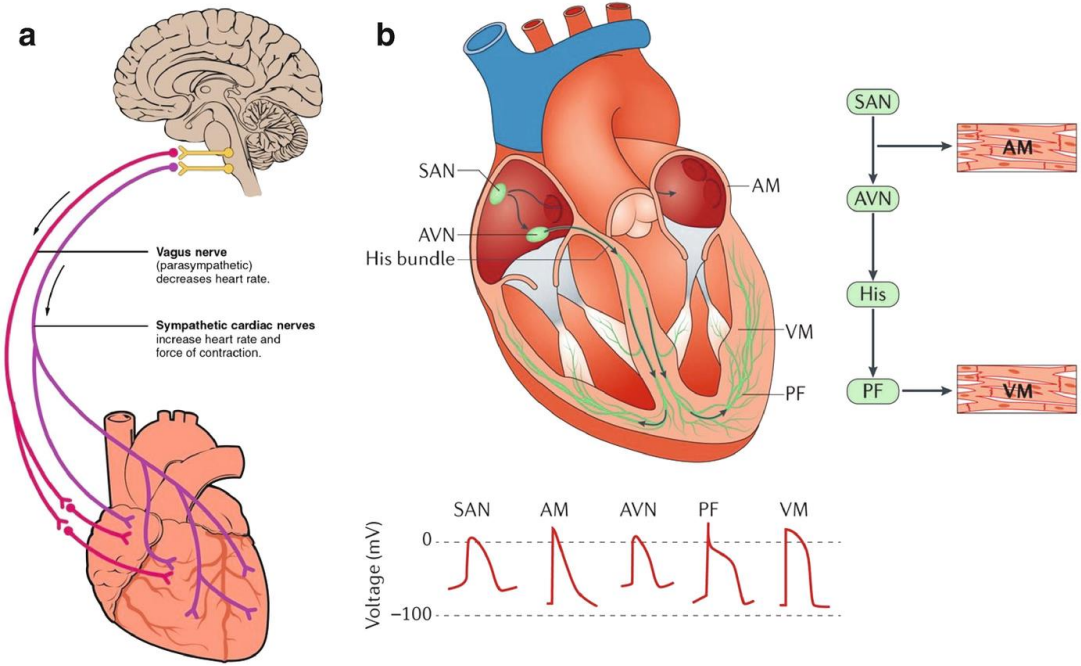
  This system involves laparoscopic surgery to place electrodes on the vagus nerve near the **stomach**.
  It's primarily used in studies and trials related to treating **obesity**, **diabetes**, and **gastrointestinal disorders**.
  Abdominal VNS aims to modify the vagal signals related to **hunger** and **satiety**.

6. Closed-Loop Vagus Nerve Stimulation

- **Electrode Type**: Implantable cuff electrodes with feedback sensors.
- **Placement**: Around the cervical vagus nerve, similar to traditional systems, but with added sensors for feedback.
- **System Overview**:

  Closed-loop systems adjust stimulation parameters in real-time based on the body's physiological responses.
  Sensors can detect heart rate, brain activity (e.g., from EEG), or other signals and adjust the electrical stimulation to optimize therapy.
  This can lead to more precise and effective stimulation, reducing unnecessary stimulation and minimizing side effects.

How to perform vagal nerve stimulation?



Cardiac innervation and physiology. (**a**) Paired cardioinhibitory and cardioaccelerator functions of vagus and sympathetic cardiac nerves. (**b**) In a balanced cardiac conduction system cardiac impulse (arrows) travels from the sinoatrial node (SAN) across the atrial myocardium (AM), and moves through the atrioventricular node (AVN) toward left and right bundle branches. Their simultaneous activation provides synchronized activation of the ventricular myocardium (VM). C. Distinct action potential morphologies at respective levels of the cardiac conduction system. PF: Purkinje fibers.

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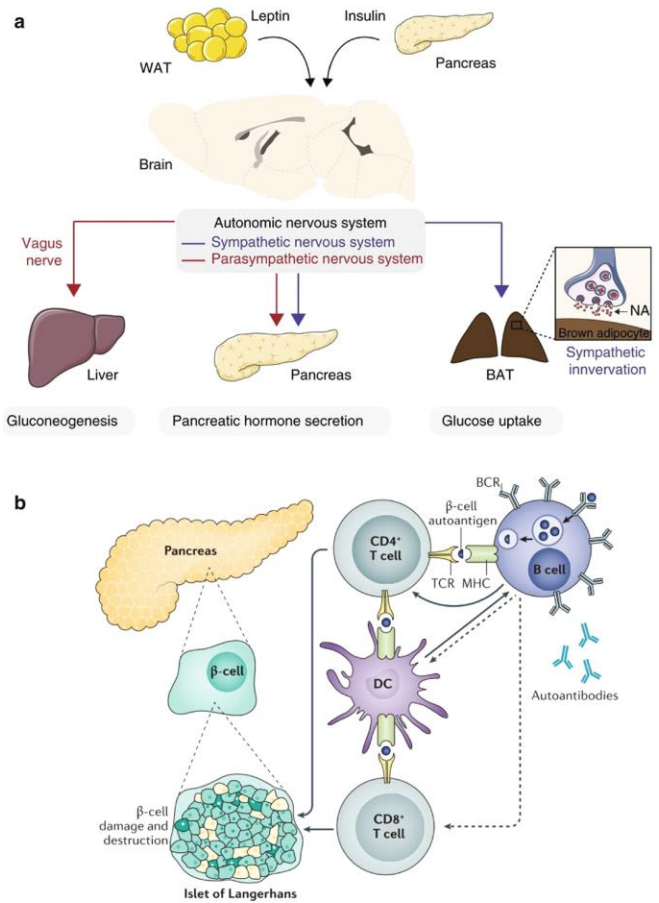
How to perform vagal nerve stimulation?



Type 1 diabetes mellitus pathogenesis. (**a**) Neural pathways involved in the control of glucose homeostasis. Leptin and insulin act on specific brain regions that modulate glucose utilization and production in peripheral tissue via the autonomic nervous system. WAT white adipose tissue, NA noradrenaline. (**b**) T1DM is an immune-mediated disease. Activated B cells interact with CD4+, CD8+ T cells, and dendritic cells (DCs). Antigen presentation by B cells and DCs leads to β-cell damage and destruction. Dashed arrows indicate the potential interactions between the cells. BCR B cell receptor, TCR T cell receptor. (**c**) T1DM causes very little or no insulin being produced by the pancreas, which results in high blood sugar levels.

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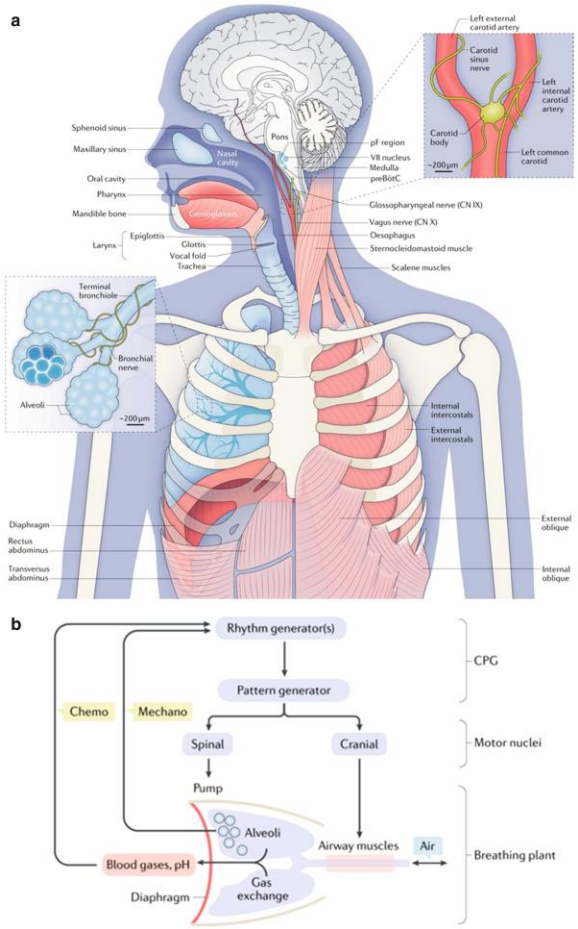
How to perform vagal nerve stimulation?



Key elements for generating breathing pattern. (**a**) The anatomy and physiology of respiration. (**b**) Central pattern generator (CPG) is composed of rhythm- and pattern-generating microcircuits with spinal and cranial motor nuclei innervating pump and airway muscles, respectively. The inspiratory cycle can be measured via electrical recordings from the phrenic nerve, a branch of the vagus nerve (cranial nerve (CN) X) innervating laryngeal adductor muscles, the hypoglossal nerve (CN XII) innervating the tongue protrude, and diaphragmatic EMG.

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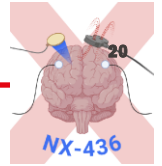
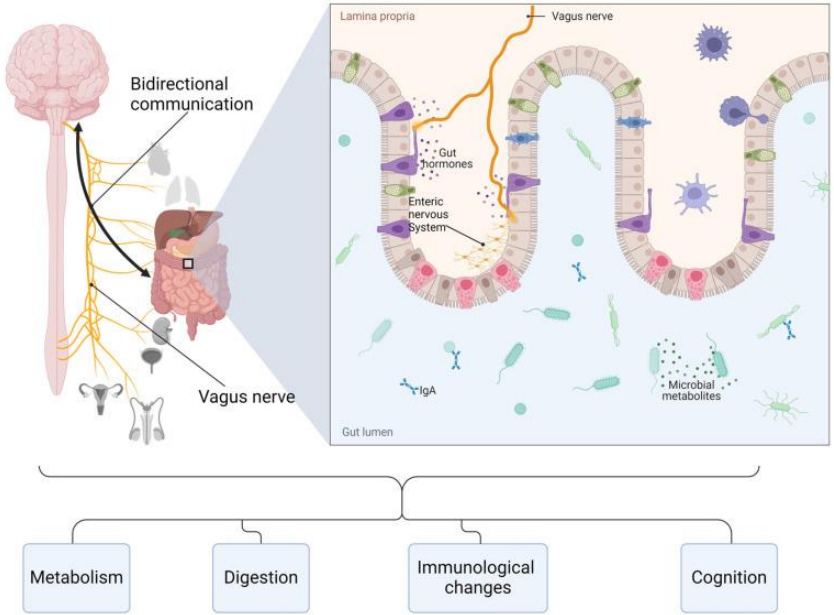
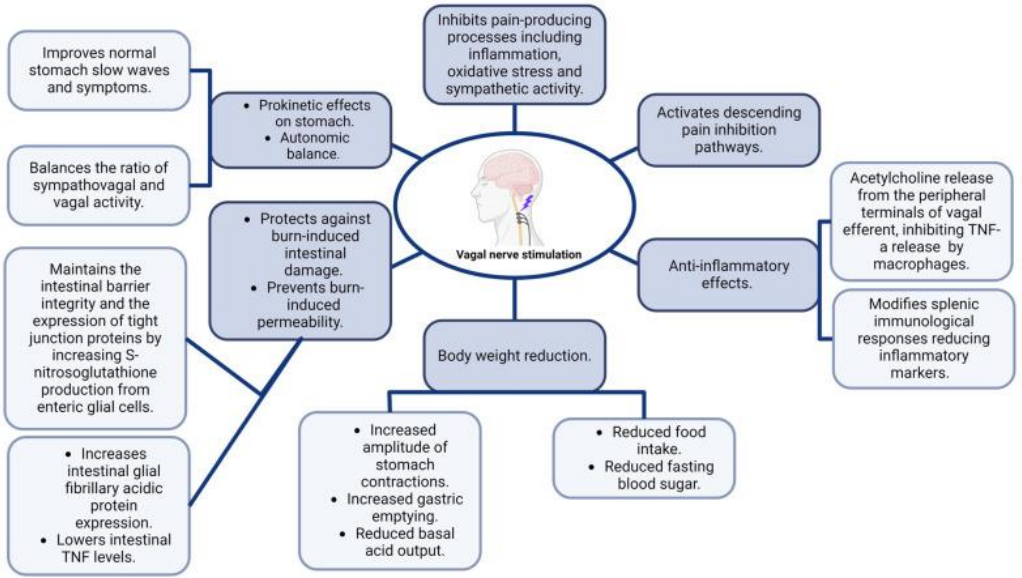


Key components and functions of the gut–brain axis

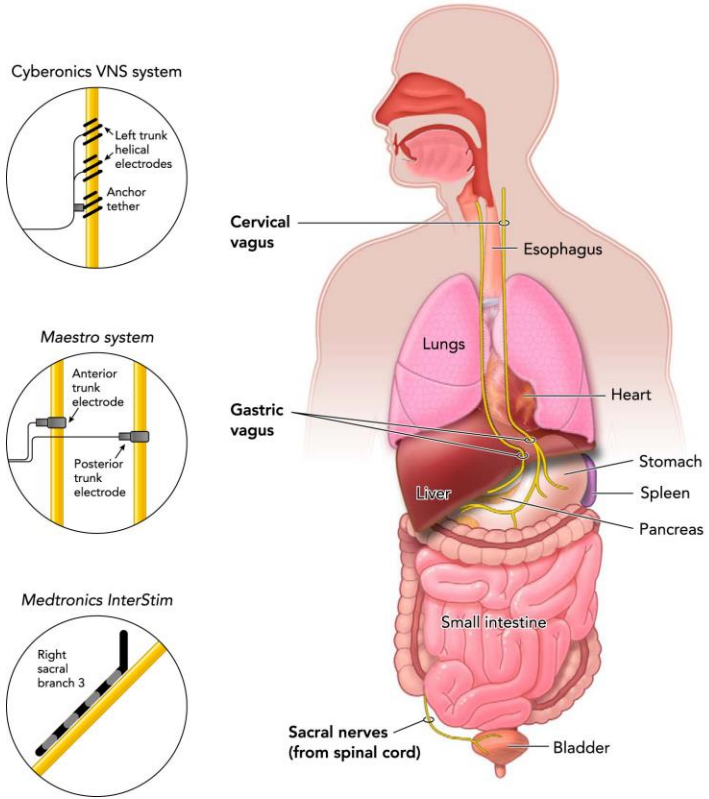


Summary of VNS effects on gut–brain-physiology.



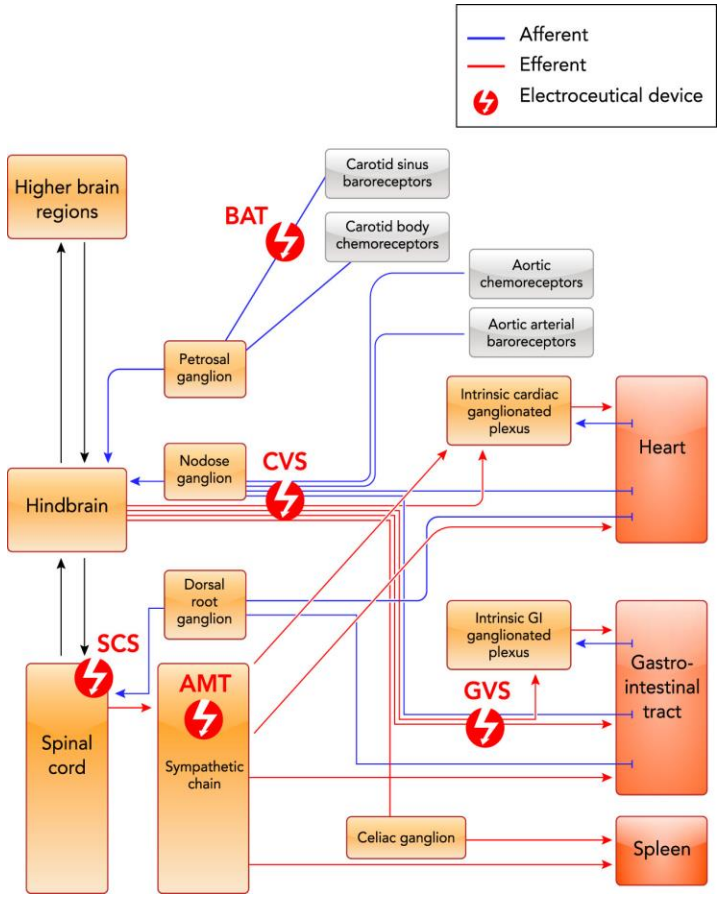
Aljeradat et al. 2024 Pathophysiology

How to perform vagal nerve stimulation?



Horn et al. 2019

How to perform vagal nerve stimulation?



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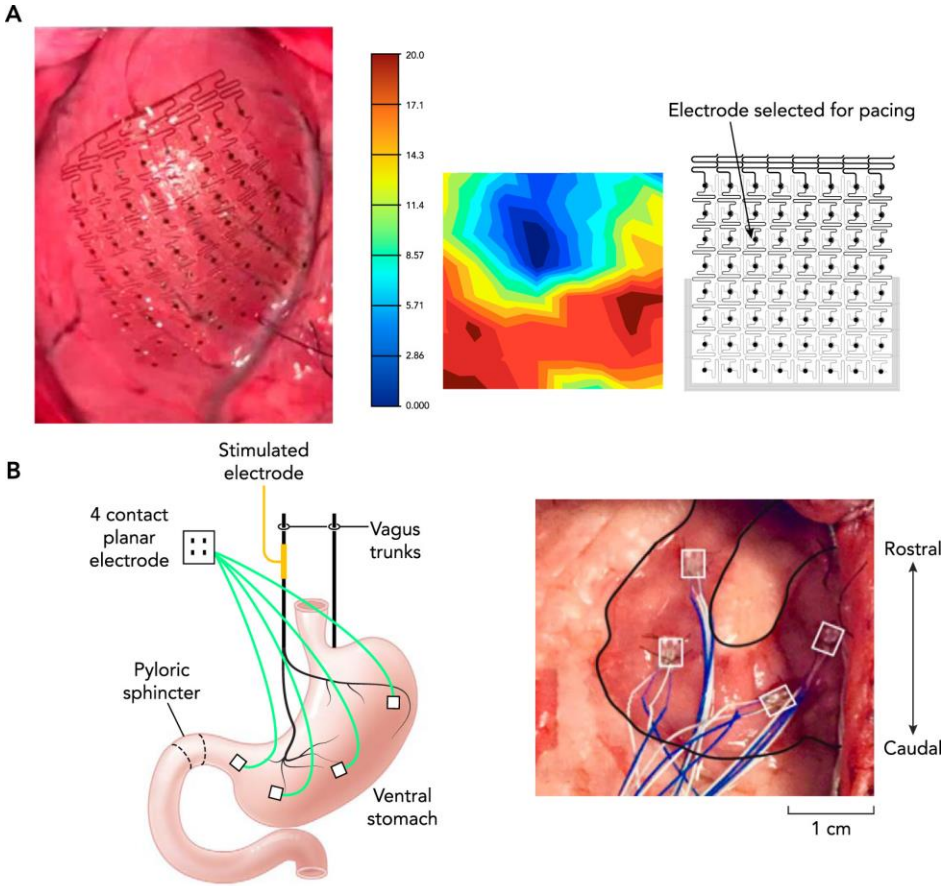
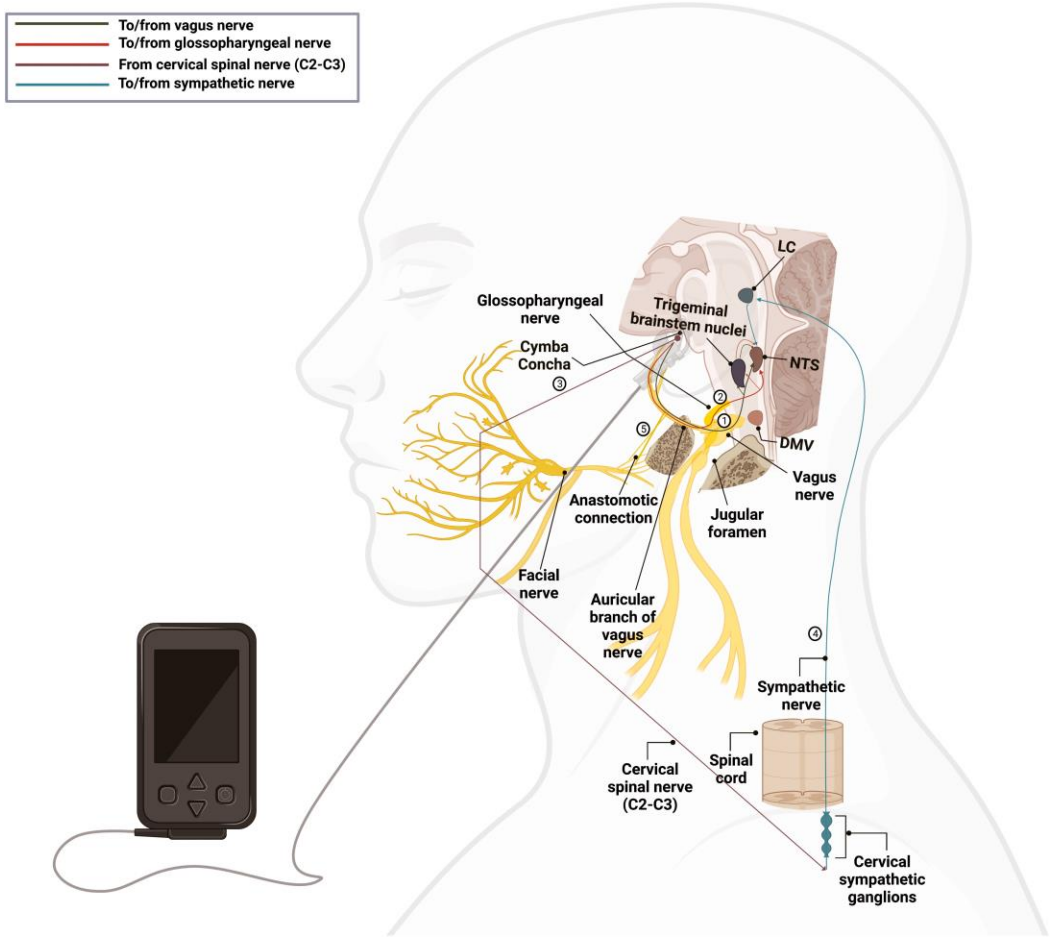


Horn et al. 2019

How to perform tVNS?

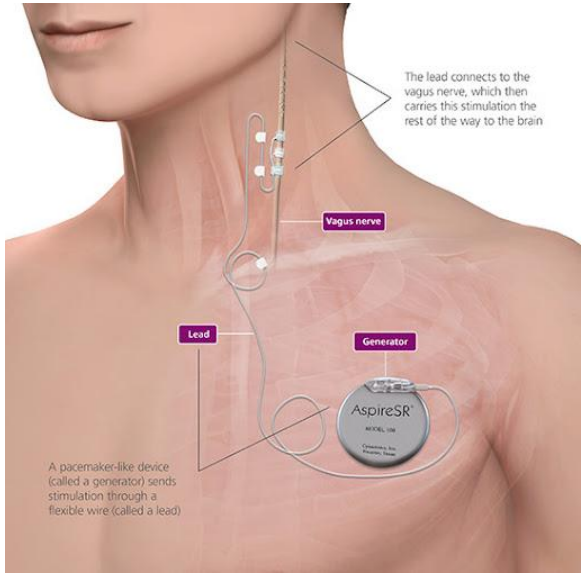


Stimulating the cymba concha of the external ears activates

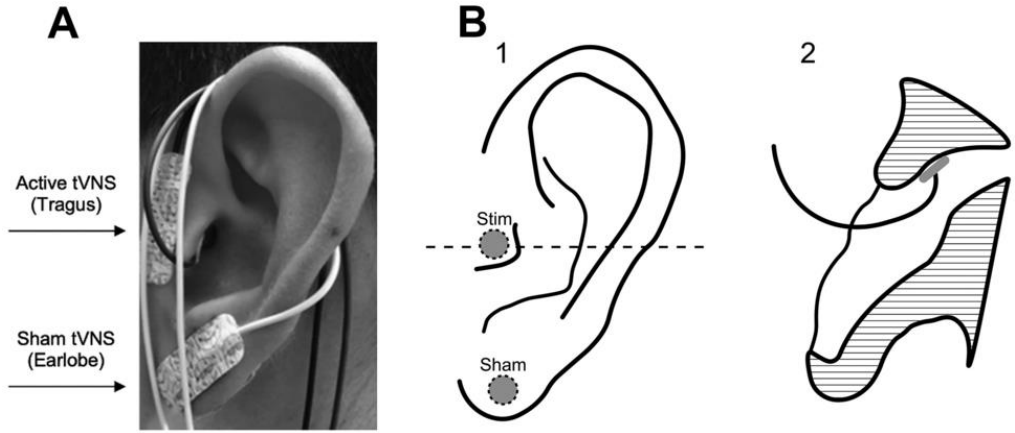
(1) the auricular branch of the VN activating the Nucl. Tractur solitarius (NTS)
(2) Nonvagal nerves projecting on NTS
(3) Cervical spinal nerves (C2, C3)
(4) Sympathetic nerves activating Locus coeruleus (LC) and NTS
(5) Facial nerves connection to auricular VN

Hesampour et al. 2023

How to perform VNS?

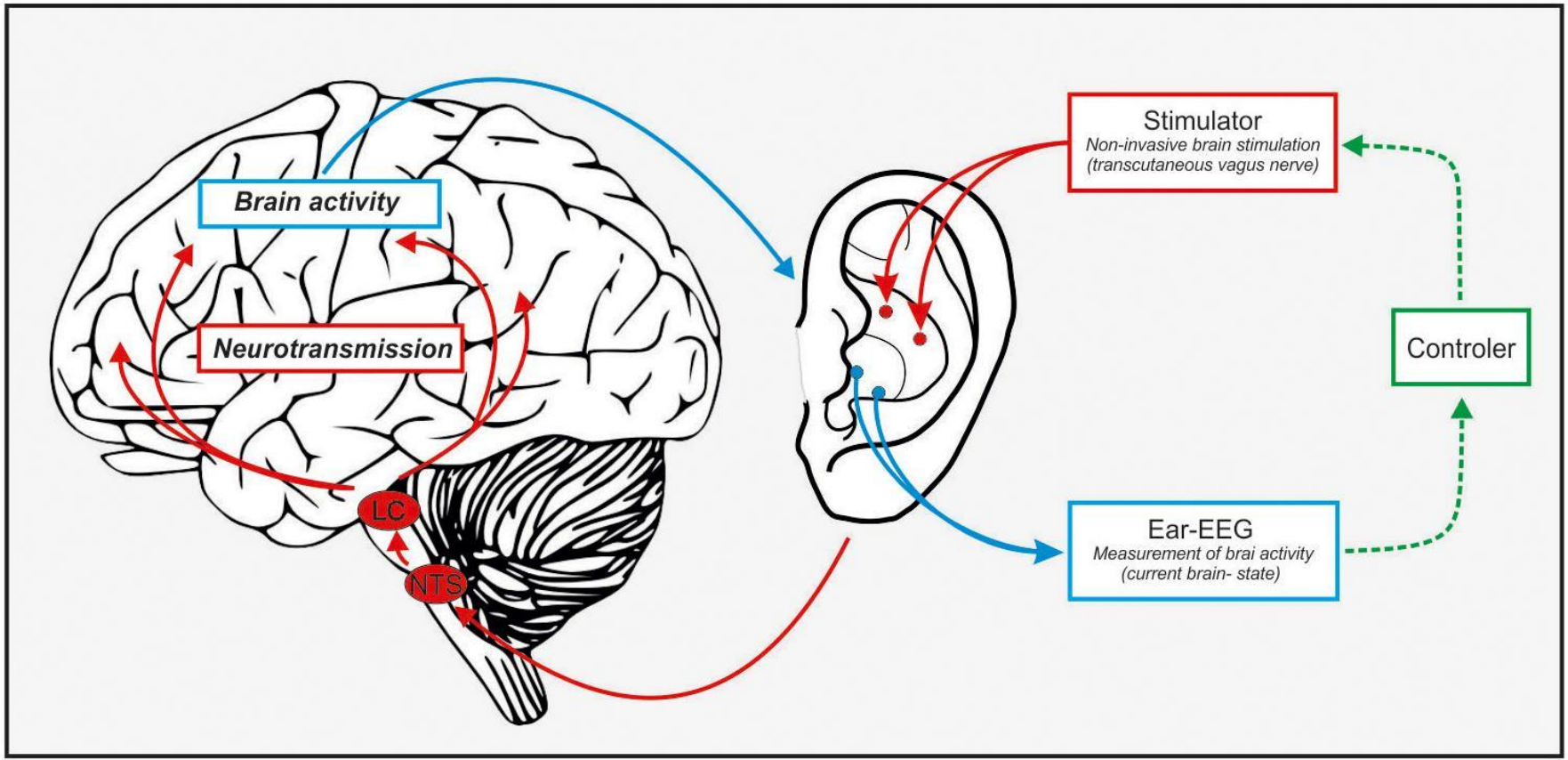


https://www.rch.org.au/

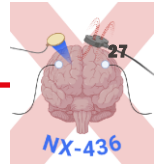


Murphy et al. 2022

Non-invasive closed-loop approaches

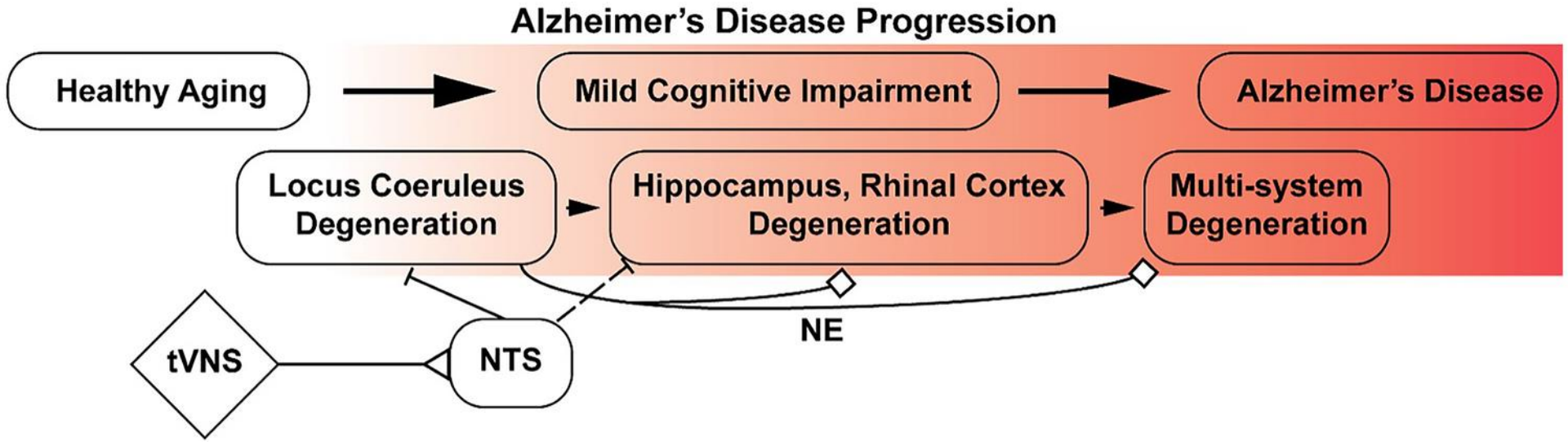


Ruhnau, Zaehle 2021



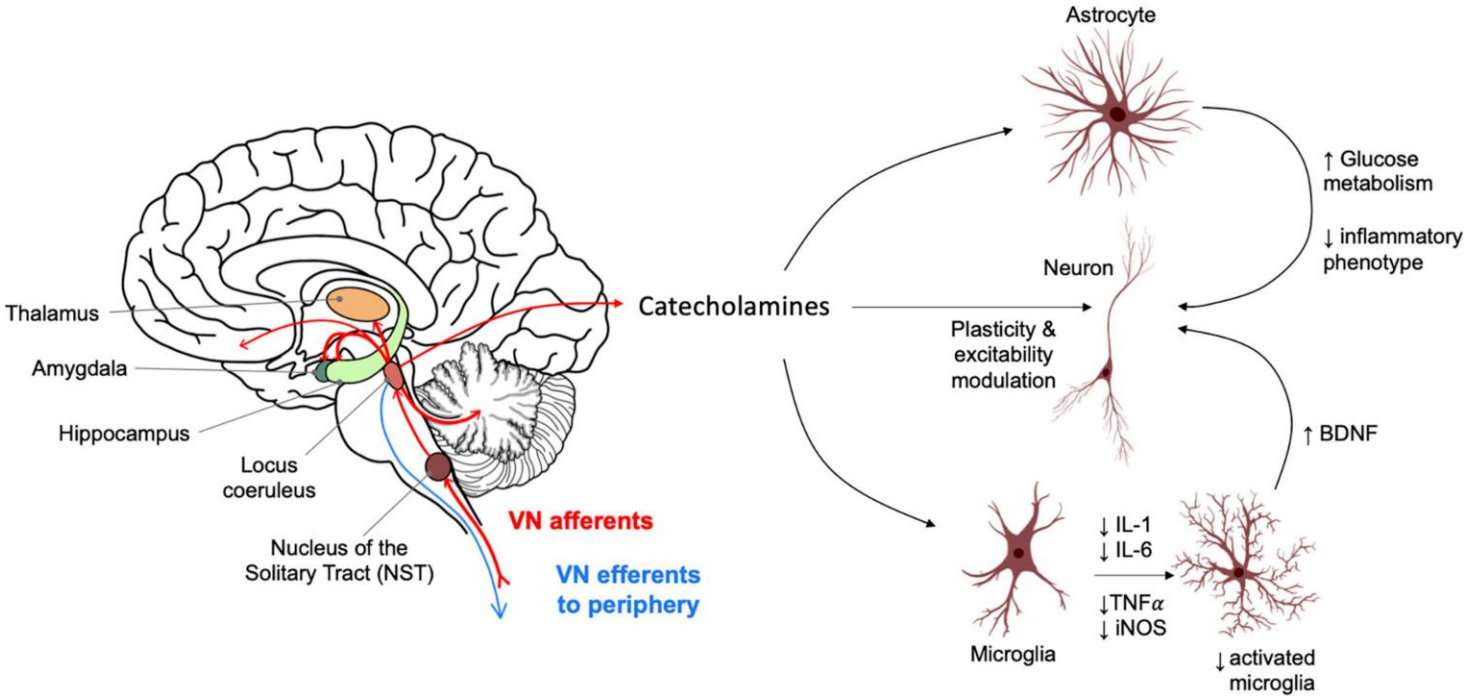
Clinical Translation

VNS and cognitive deficits



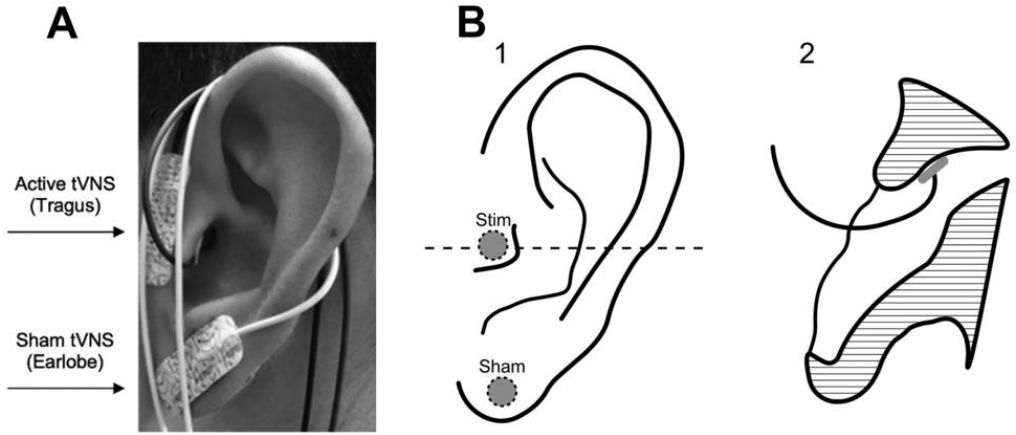
Murphy et al. 2022

VNS and cognitive deficits



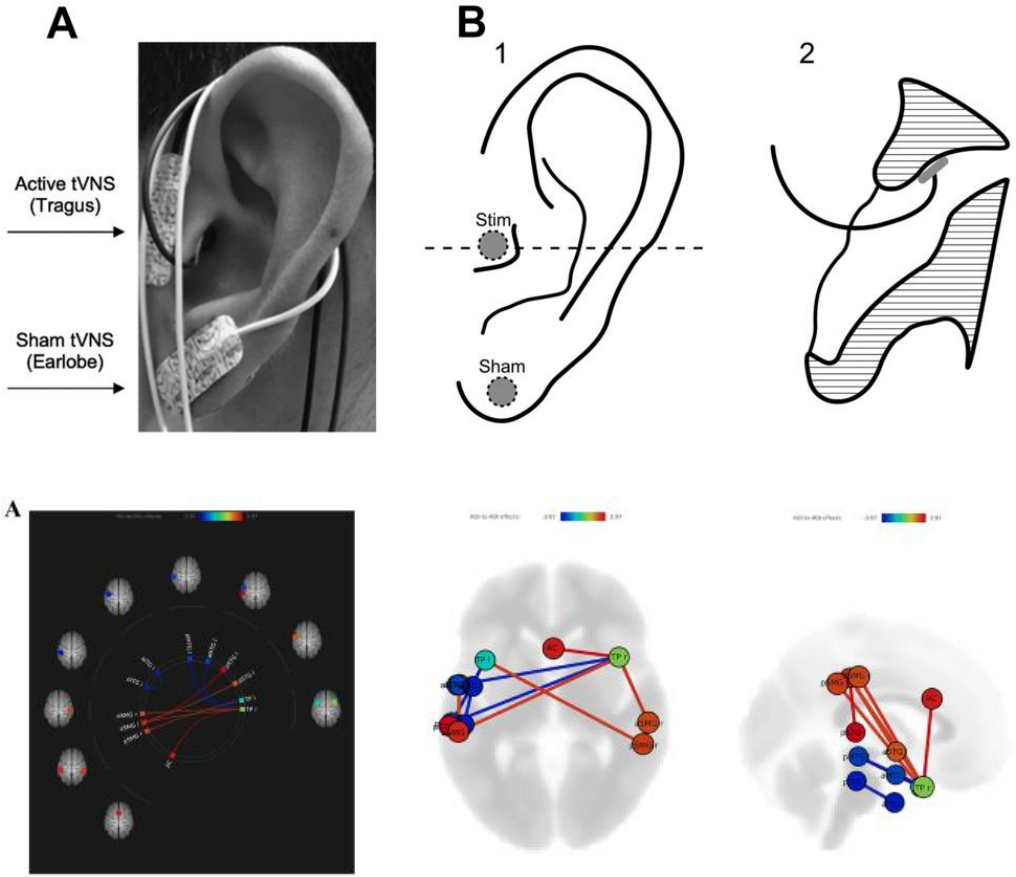
Vargas-Caballero et al. 2022

VNS and cognitive deficits



Murphy et al. 2022

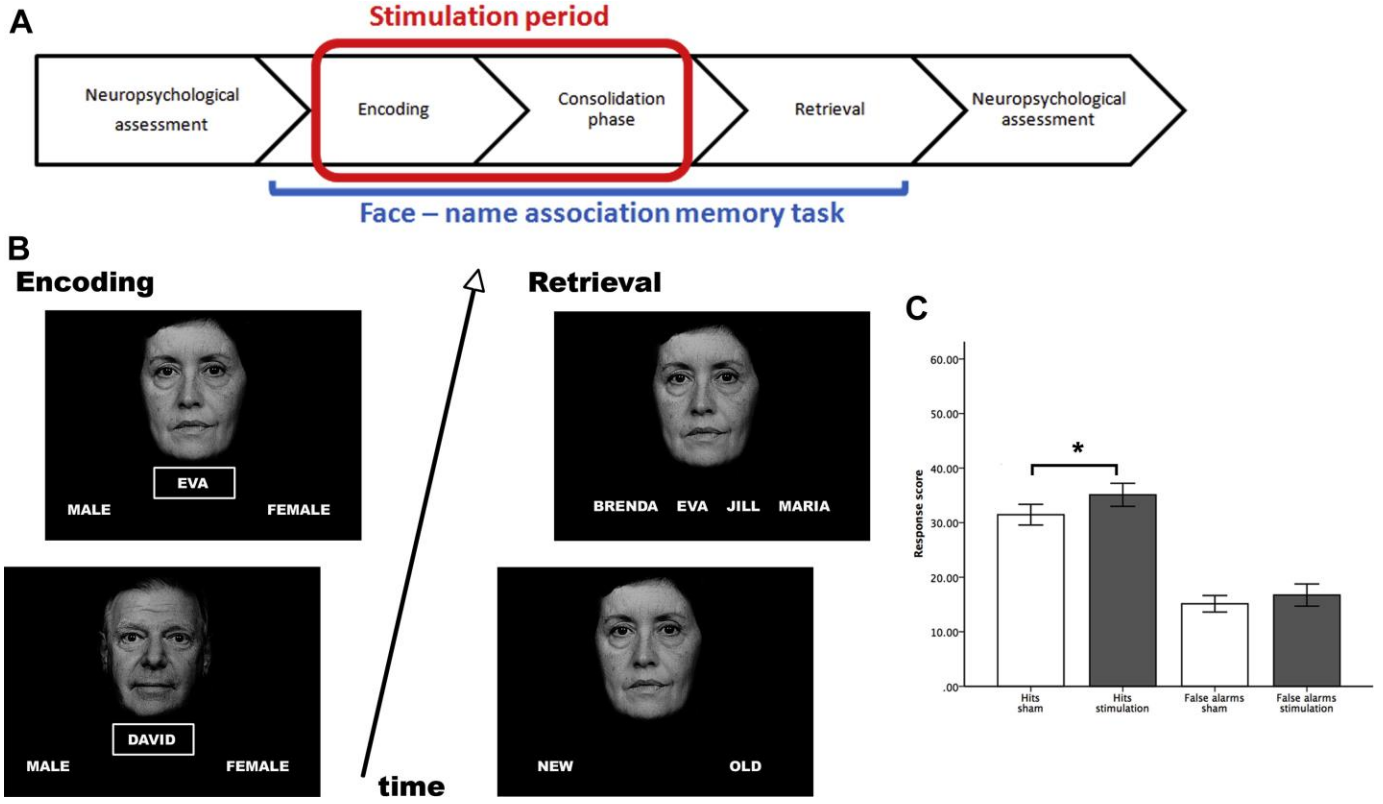
VNS and cognitive deficits



Change in connectivity was observed between semantically relevant regions

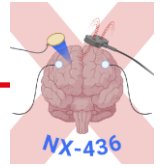
Murphy et al. 2022

VNS and cognitive deficits



Jacobs et al. 2015

VNS and cognitive deficits

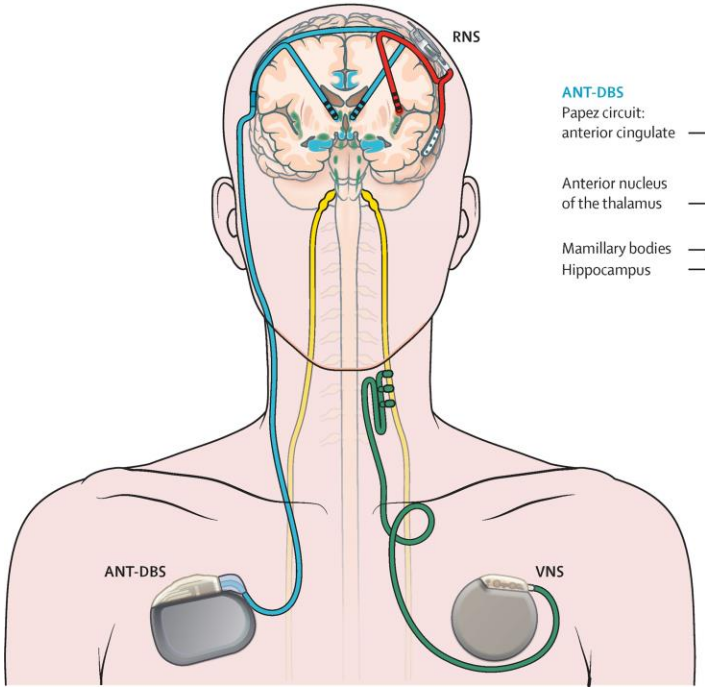


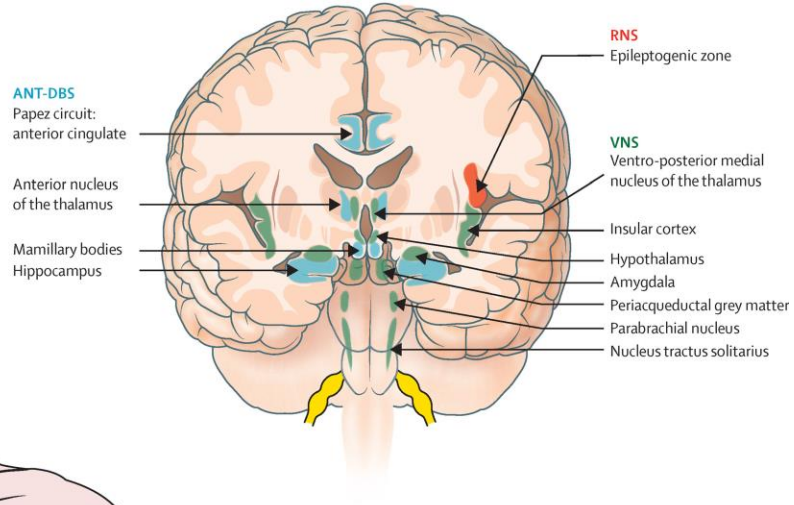
Trial name/ Number	Patient population	Stimulation type	Outcome measures	Start/End
The wandering nerve: gateway to boost Alzheimer's disease: https://ClinicalTrials.gov/show/NCT04908358	Older, healthy individuals *N* = 35	Active tVNS respiratory-gated 4 week Sham arm	Face-name association task up to 25 weeks after treatment Inflammatory blood biomarkers	August 2021/April 2026
The locus coeruleus and memory https://ClinicalTrials.gov/show/NCT02363504	Healthy older individuals and prodromal AD 60–85 years *N* = 35	Tesla magnetic resonance imaging (MRI) with memory task and tVNS	BOLD response during memory task Memory task performance (acute) NE levels	February 2017/December 2020 (overdue)
Modulating the locus coeruleus function https://ClinicalTrials.gov/show/NCT04877782	Healthy individuals 60–80 years *N* = 30	Auricular tVNS	Pupillometry BOLD response Memory task performance up to 10 days after tVNS	October 2021/January 2024
Treatment of mild cognitive impairment with transcutaneous vagal nerve stimulation (TVNS MCI) https://clinicaltrials.gov/ct2/show/NCT03359902	MCI patients, healthy older controls *N* = 125	Auricular tVNS	Delayed recall assessment	January 2018/May 2022

N numbers represent per group.

Vargas-Caballero et al. 2022

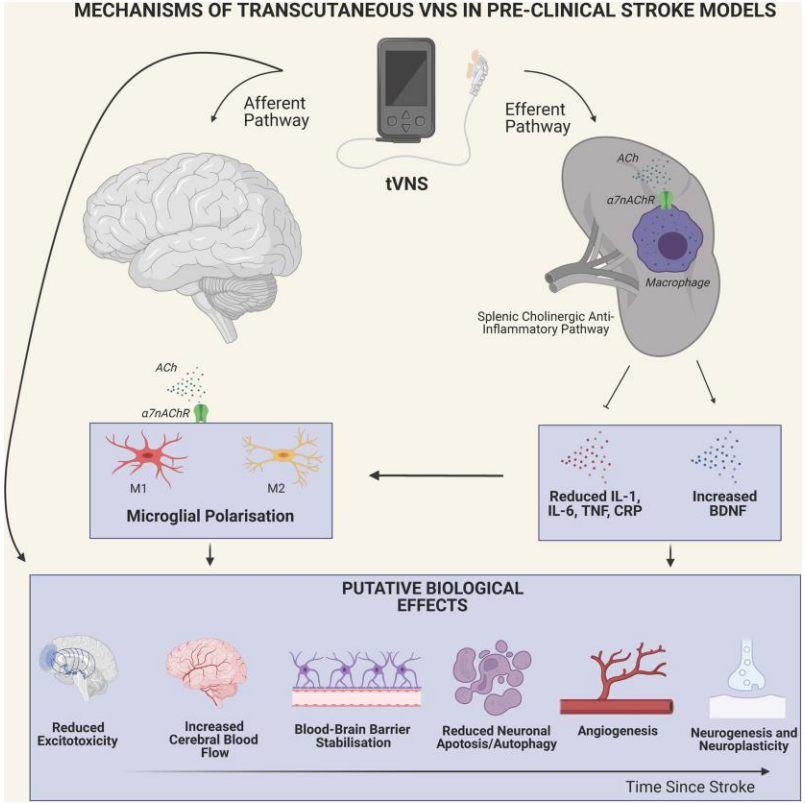
VNS and Epilepsy





Rifflin et al. 2021

VNS and Stroke recovery



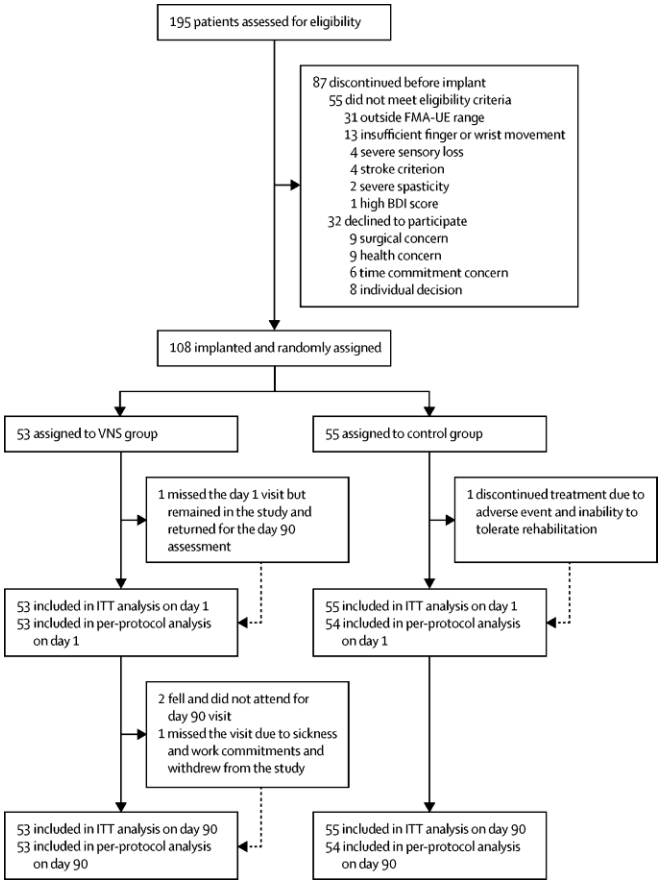
Sheharyar et al. 2023

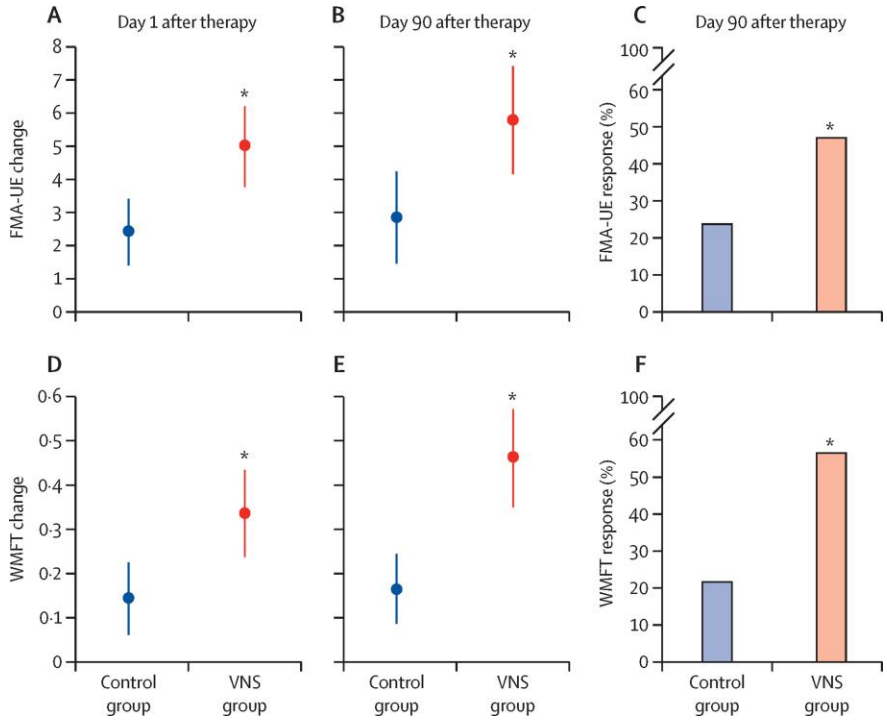
Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial

Jesse Dawson, Charles Y Liu, Gerard E Francisco, Steven C Cramer, Steven L Wolf, Anand Dixit, Jen Alexander, Rushna Ali, Benjamin L Brown, Wuwei Feng, Louis DeMark, Leigh R Hochberg, Steven A Kautz, Arshad Majid, Michael W O'Dell, David Pierce, Cecília N Prudente, Jessica Redgrave, Duncan L Turner, Navzer D Engineer, Teresa J Kimberley

www.thelancet.com **Vol 397 April 24, 2021**

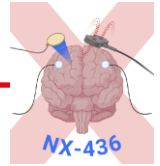
VNS and Stroke recovery

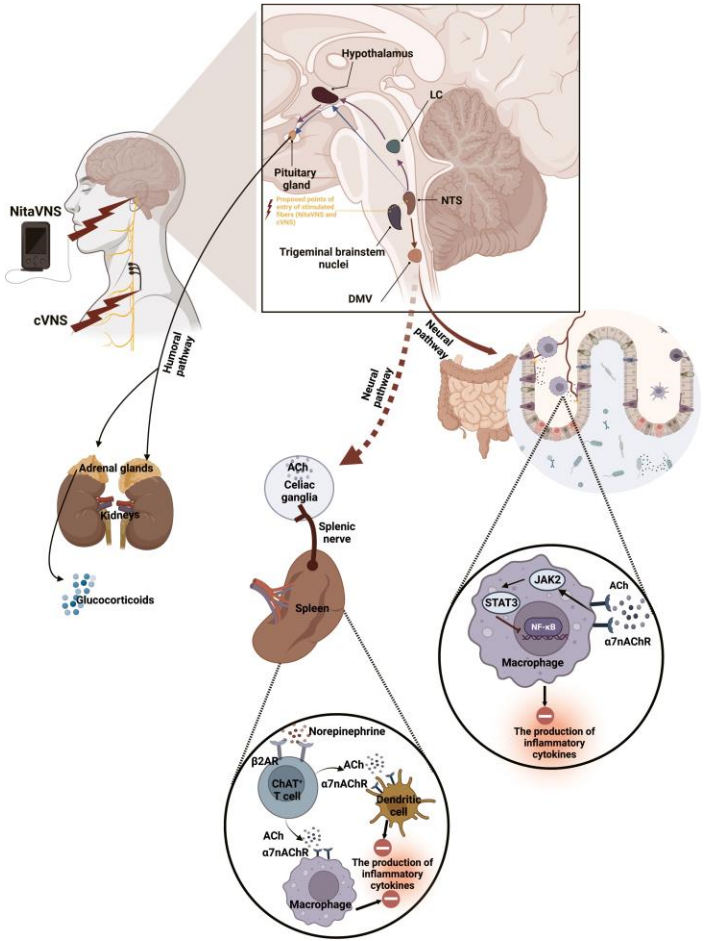




Dawson et al. 2021

VNS and anti-inflammatory effects





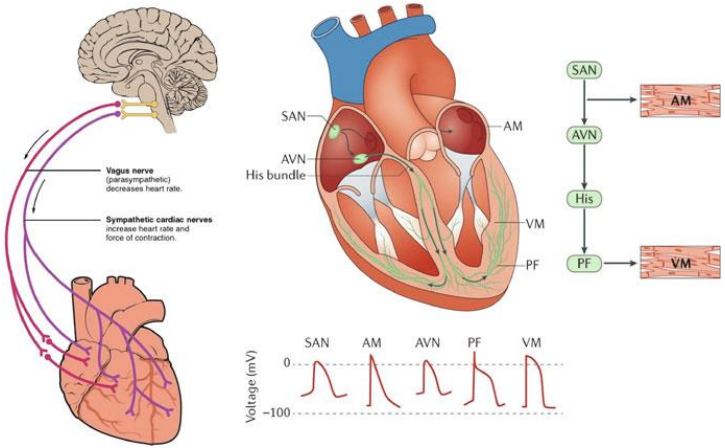
Brain-Gut-axis

VNS can lead to an anti-inflammatory effect by different mechanims

Impact on Inflammatory bowel disease (IBD)

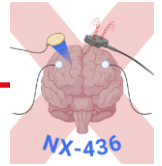
Hesampour et al. 2023

Cardiac innervation and physiology

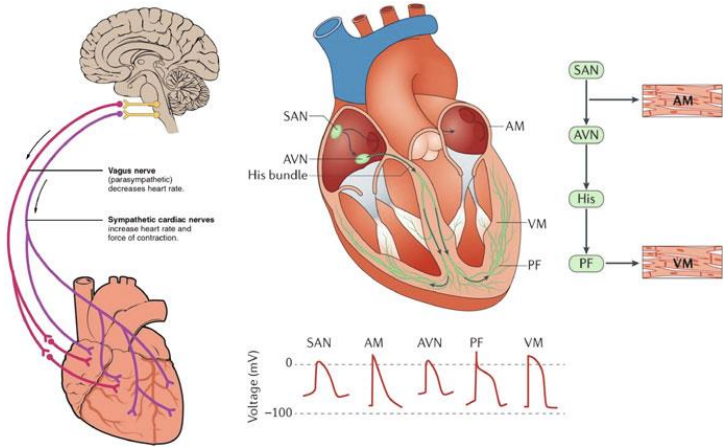


Handbook of Neuroengineering

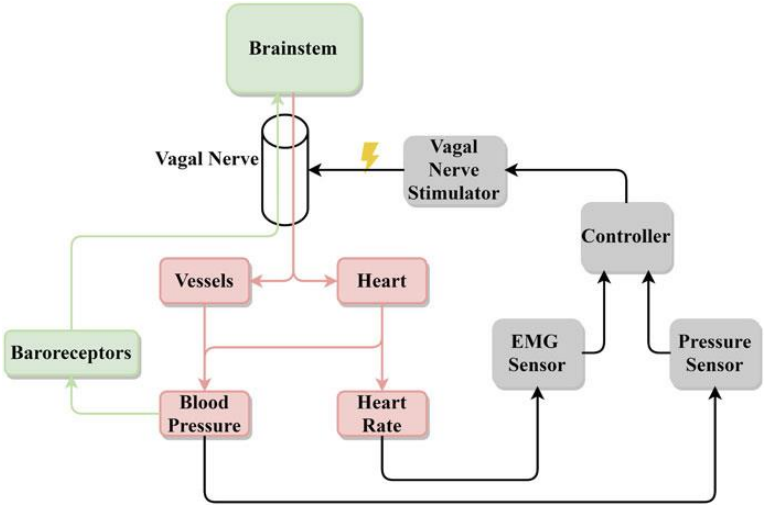
VNS and cardiac functions



Cardiac innervation and physiology

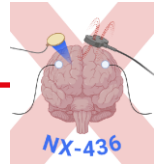


Closed–loop system

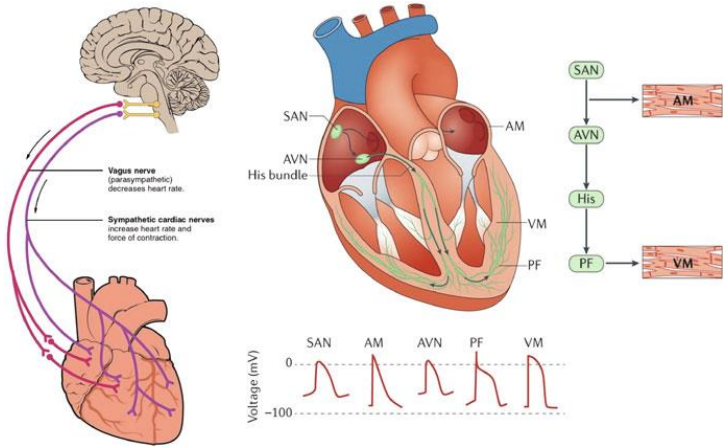


Handbook of Neuroengineering

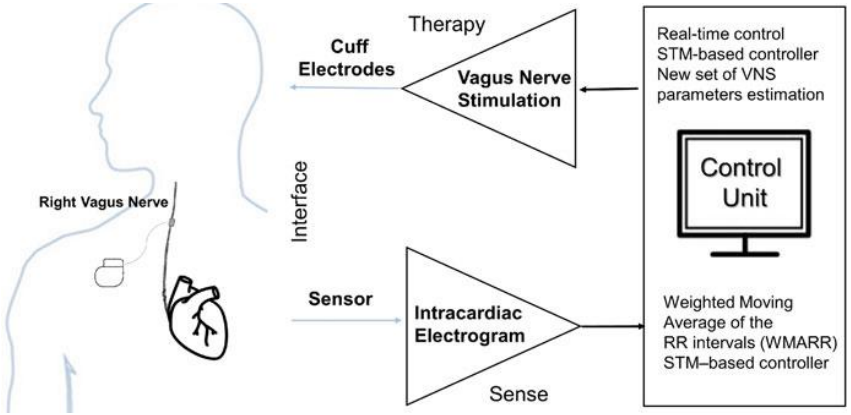
VNS and cardiac functions



Cardiac innervation and physiology

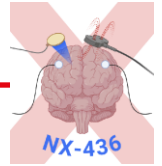


Closed–loop system – heart failure

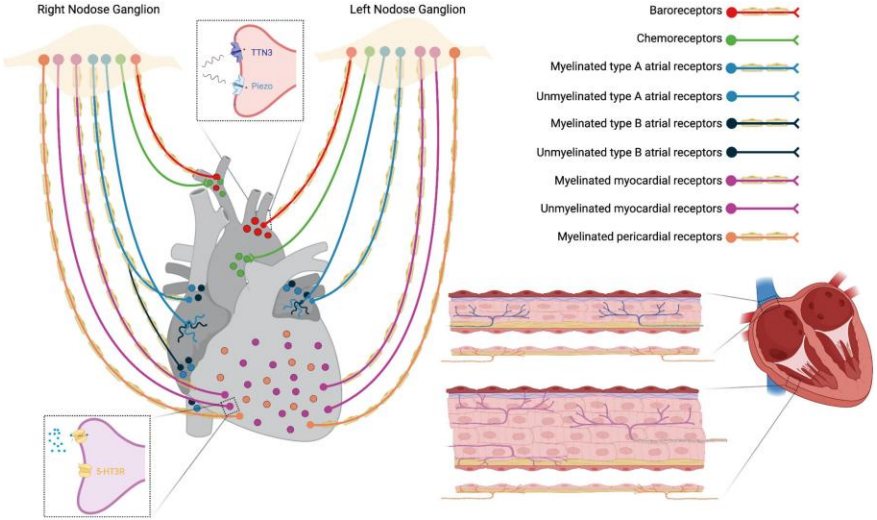


Handbook of Neuroengineering

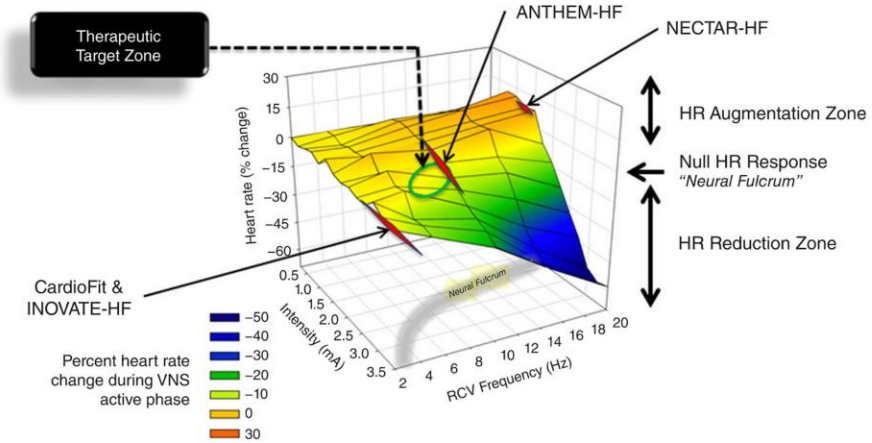
VNS and cardiac functions



Cardiac innervation and physiology



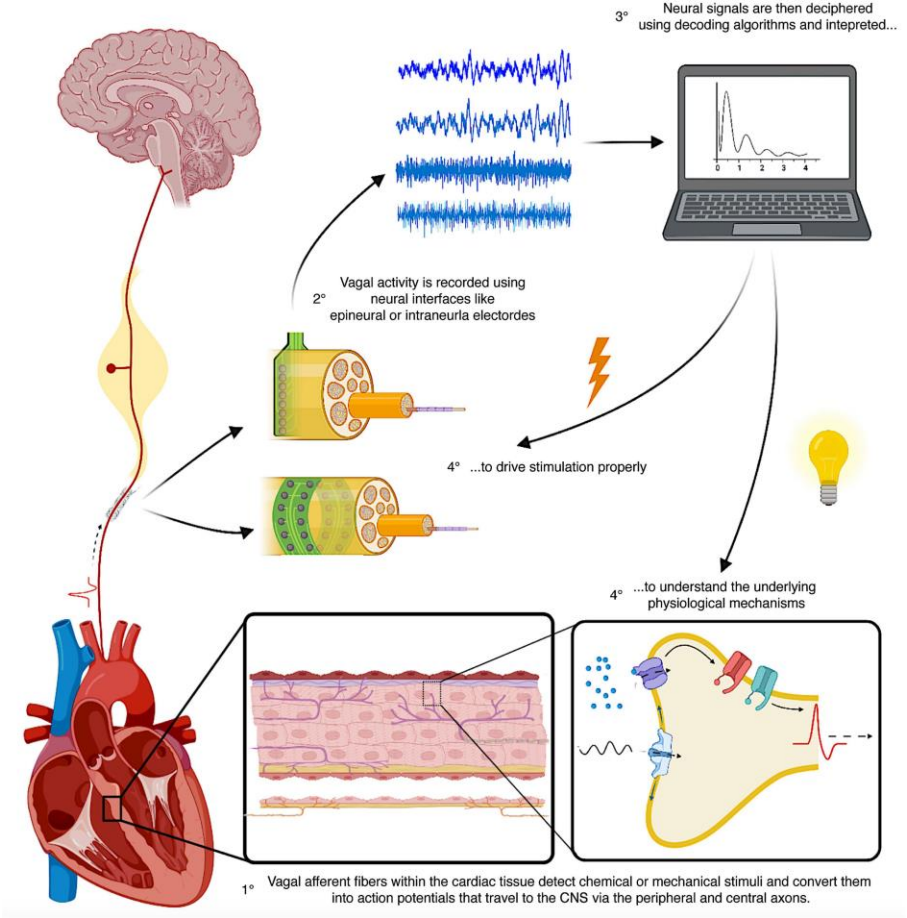
Stimulation parameters



Ottaviani et al. 2022

VNS and cardiac functions

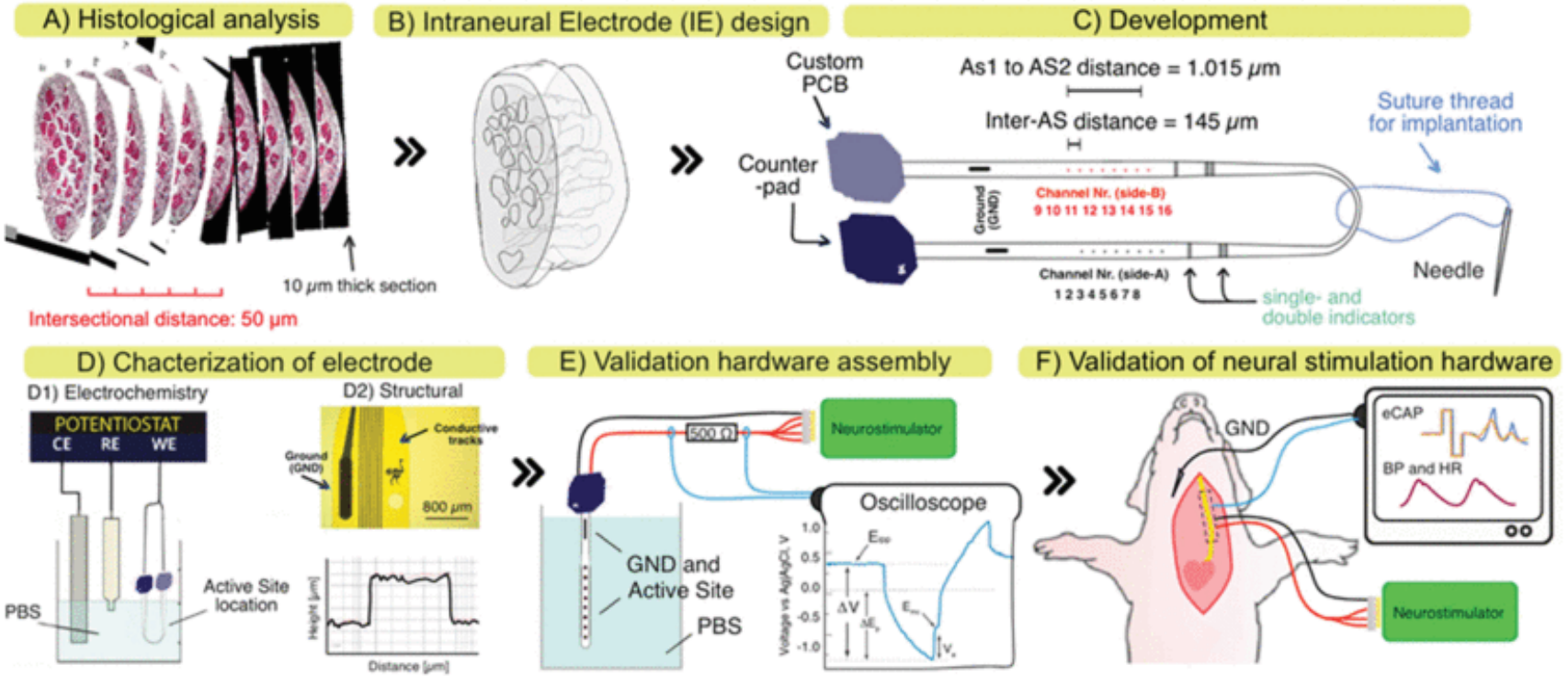
Closed-loop VNS



Ottaviani et al. 2022

Further development –intraneural electrodes

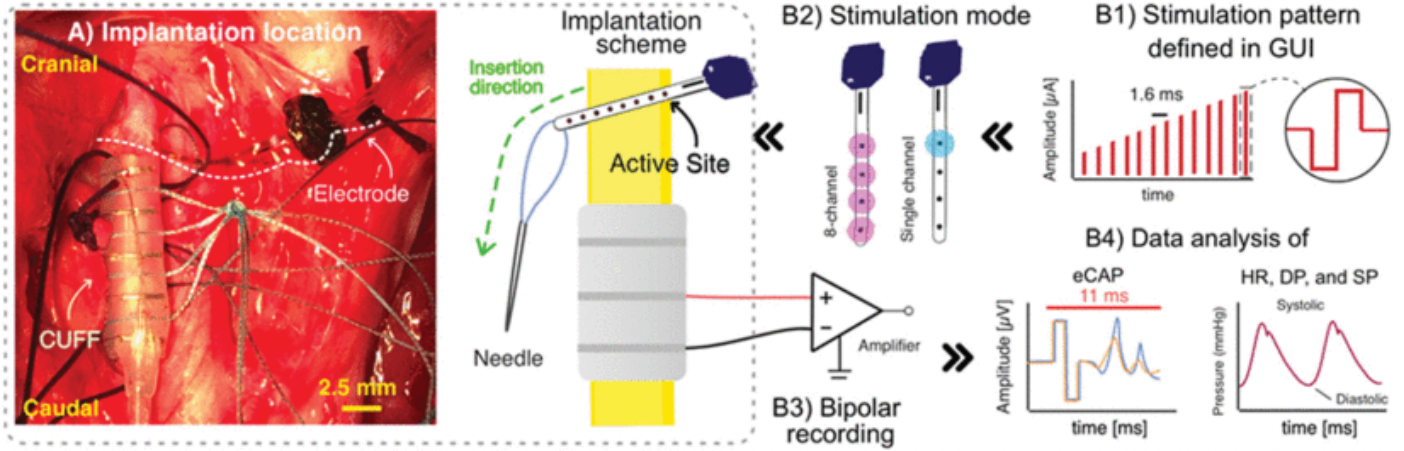
Workflow for the development and validation of neural stimulation hardware to selectively modulate the vagus nerve.

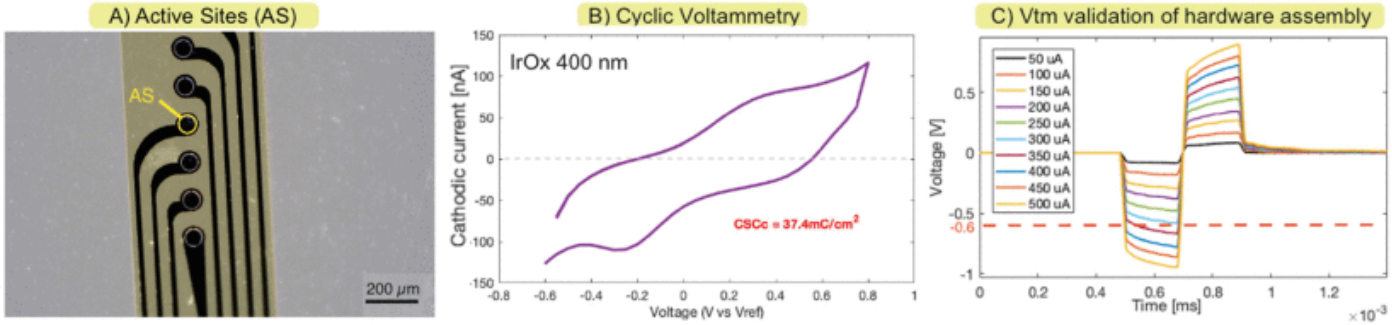


Strauss et al. 2023 IEEE

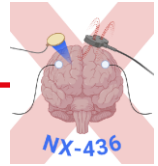
Further development –intraneural electrodes

Overview of the experimental setup to validate the selectivity of neural stimulation hardware.



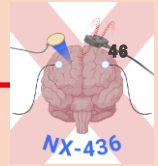


Strauss et al. 2023 IEEE

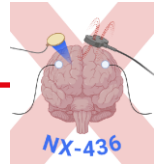


- Vagus nerve stimulation (VNS) can be performed invasively (cuff) or non-invasively (transauricular)
- Allows to modulate the vegetative systems, e.g.
  - cardiac functions
  - Brain-gut axis
- With clinical application in
  - Epilepsy
  - Stroke recovery
  - Heart failure
  - Inflammatory Bowl disease
  - Dementia
- Closed-loop applications

Take home message



- Understand the autonomous nervous system (ANS) incl. the Vagal nerve
- Concept of Vagal Nerve Stimulation (VNS)
- Different stimulation options (non-invasive, invasive)
- Translational approaches of VNS



Questions?