

Vagus Nerve Stimulation (VNS) - current and 21 century indications -



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Vagus Nerve Stimulation (VNS) - current and 21 century indications –

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Disclosures

▶ Ekkehart's direct research funding / travel grants / speaker fees / accommodation funding (in alphabetical order):

- ▶ **ABBOTT Lab. (UK)**
- ▶ **David Lewis Centre for Epilepsy (DLC,UK)**
- ▶ **EISAI (Japan)**
- ▶ **Eli Lilly (UK)**
- ▶ **Epilepsy Research Foundation (now Research Epilepsy UK)**
- ▶ **Glaxo-Smith-Kline (UK)**
- ▶ **GW Pharmaceuticals (UK, NHS licenced Epidyolex manufacturer)**
- ▶ **UK Home Office Research Unit (ASM / AED prescribing in Cat A, Cat B HMP Services, and SHSA)**
- ▶ **LivaNova plc (U.S.); VNS manufacturer**
 - ▶ Including Project funds / CORE_VNS Study (past and forthcoming)
- ▶ **NIHR (x3)**
- ▶ **Sanofi (France)**
- ▶ **SK BioPharmaceuticals (Canada)**
- ▶ **Wellcome Trust (Fellowship post)**

Vagus nerve – SAFE – current and future indications

▶ The VAGUS NERVE (CN X)

▶ **Functional Neuroanatomy**

- ▶ Functional neurology / neuroplasticity / neuro-chemistry

▶ **Current, (NICE) licenced therapeutic indications**

- ▶ **DRE (Drug – resistant Epilepsies)**

- ▶ Neurodevelopmental esp. ASD indications (IPG – Interventional Procedures Guidelines)

- ▶ **Depression**

- ▶ NICE (NG 222, 29 June 2022, amended May 2024 – structural change only)

▶ **Future (NICE) – licenced therapeutic indications (~5-10 years, max)**

- ▶ **Dementiae**

- ▶ **Immunotherapy**

- ▶ Exploratory research with NRP – Quadram Institute for Biosciences – GI tract

- ▶ **Headache syndromes**

- ▶ Chronic cluster headache

- ▶ Migraine – chronic, with or without aura and photosensitivity

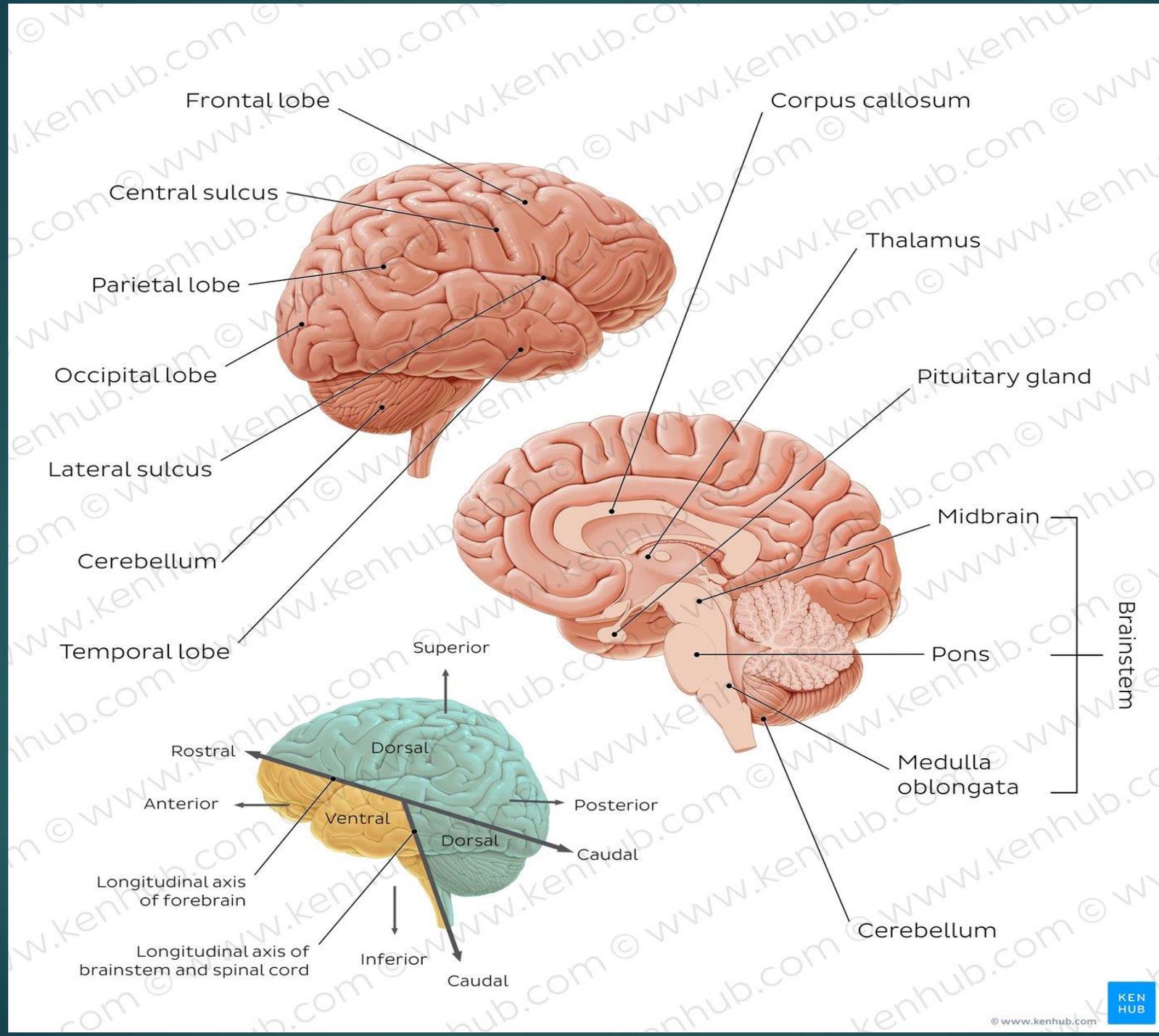
▶ **Innovation - research areas**

- ▶ **Biomes' role in GI – CNS axis in ASD research**

- ▶ **New Scientist**

- ▶ **Epilepsy with Autism (NIHR and large LivaNova / NIHR x62 international multi-centre study)**

- ▶ ASD without epilepsy



Cranial nerve I (olfactory nerve)

Cranial nerve II (optic nerve)

Cranial nerves III, IV, and VI (oculomotor, trochlear, and abducens nerve)

Cranial nerve V (trigeminal nerve)

Cranial nerve VII (facial nerve)

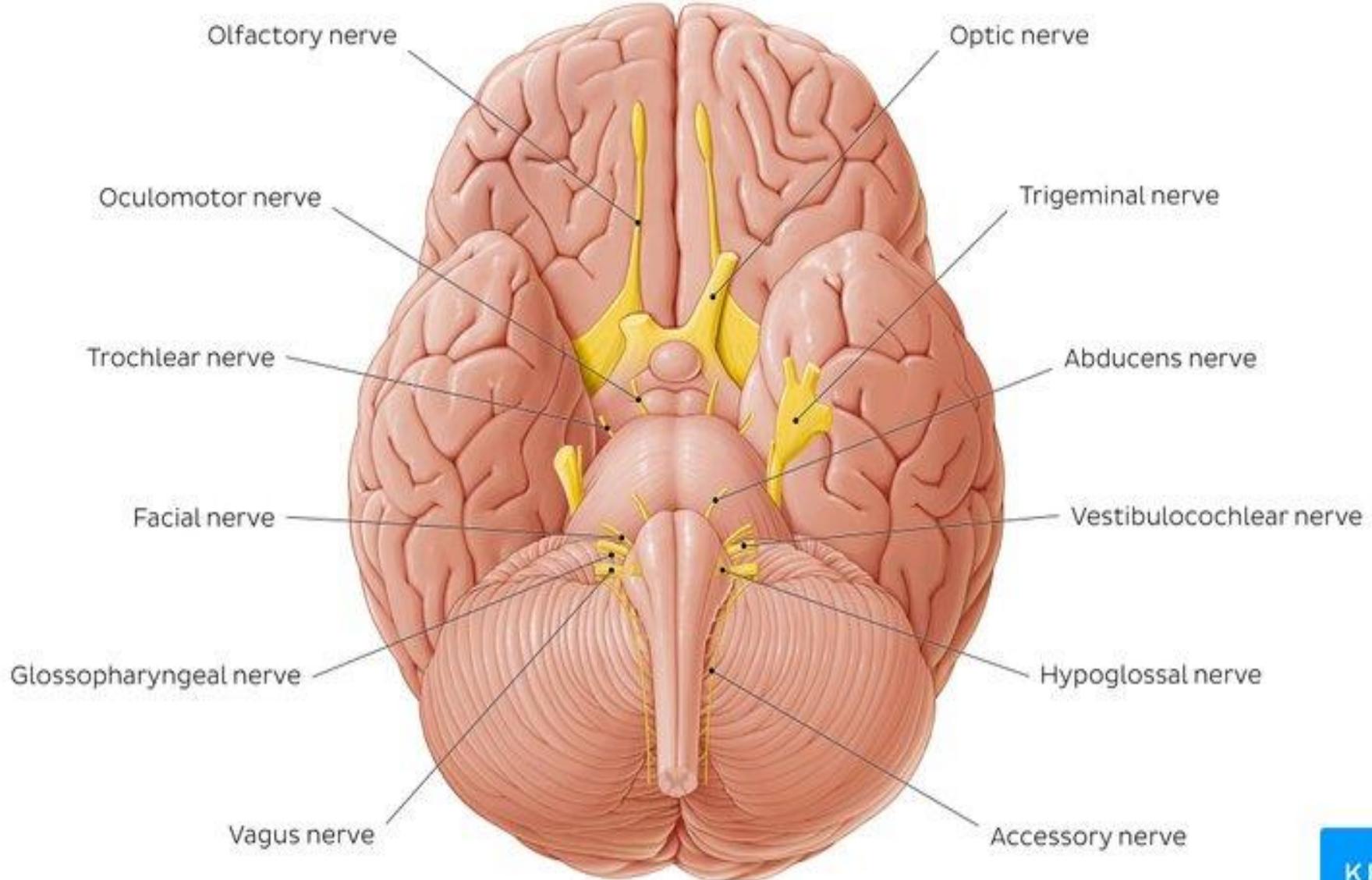
Cranial nerve VIII (vestibulocochlear nerve)

Cranial nerve IX (glossopharyngeal nerve)

Cranial nerve X (vagus nerve)

Cranial nerve XI (Accessory nerve)

Cranial nerve XII (Hypoglossal nerve)



Vagus Nerve CN X

Functional Neuroanatomy

- ▶ **CN X is**
 - ▶ longest cranial nerve (motor / sensory / autonomic functions)
 - ▶ R CNX ~75%-85% efferent
 - ▶ L CNX ~75%-85% afferents (cardiac - , and recurrent laryngeal branches)
- ▶ **Pathway**
 - ▶ Exit Medulla oblongata (bilaterally) – f. jugularis – x2 ganglia (superior and inferior) – etc
- ▶ **Functional CN X**
 - ▶ **RIGHT side**
 - ▶ all peripheral organs, especially digestive system, including autonomic / neurovegetative, sensory and motor branches
 - ▶ **LEFT**
 - ▶ See next slide – afferents via Nc tractus solitarius

Left Vagus Nerve CN X – cerebral ramifications

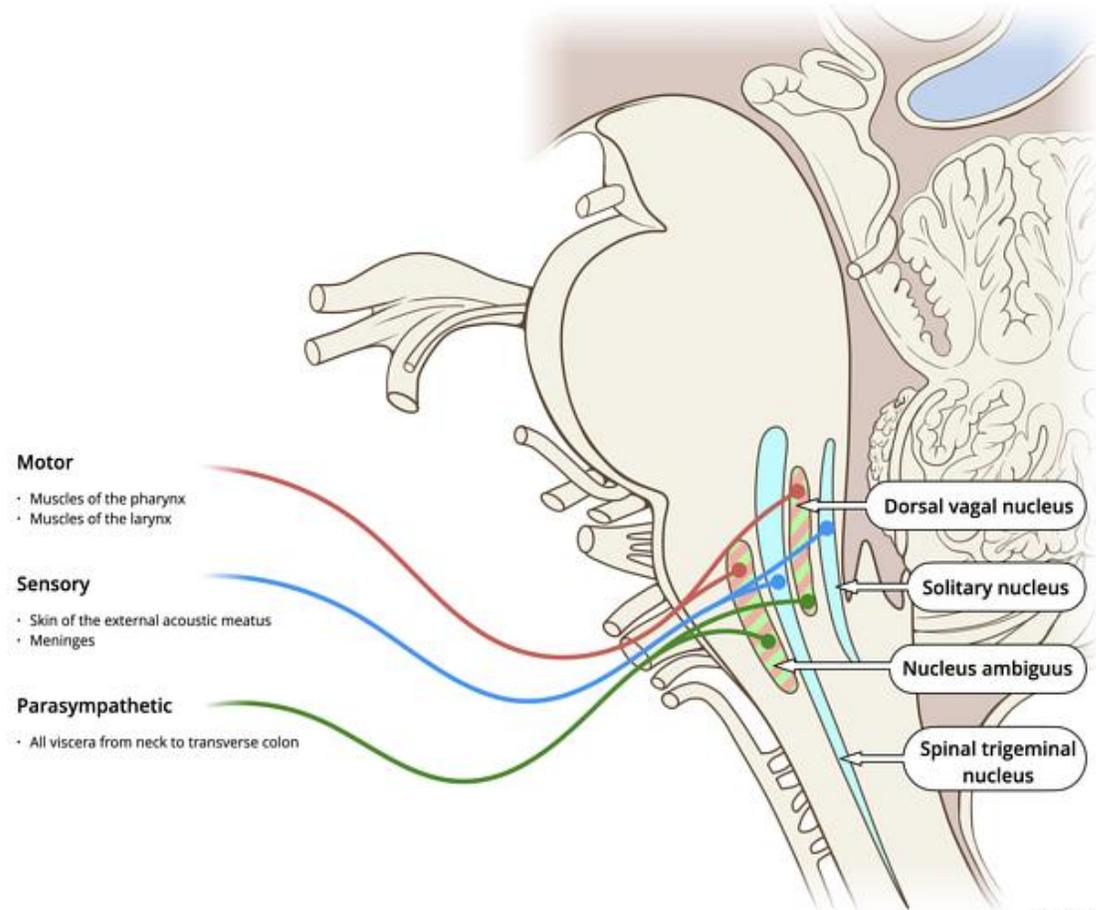
Nc tractus solitarius

Cooper Cm, Farrand AQ, et al. J Physiol. 2021 Dec;599(23):5261-5279. doi: 10.1113/JP282064. Epub 2021 Nov 17.

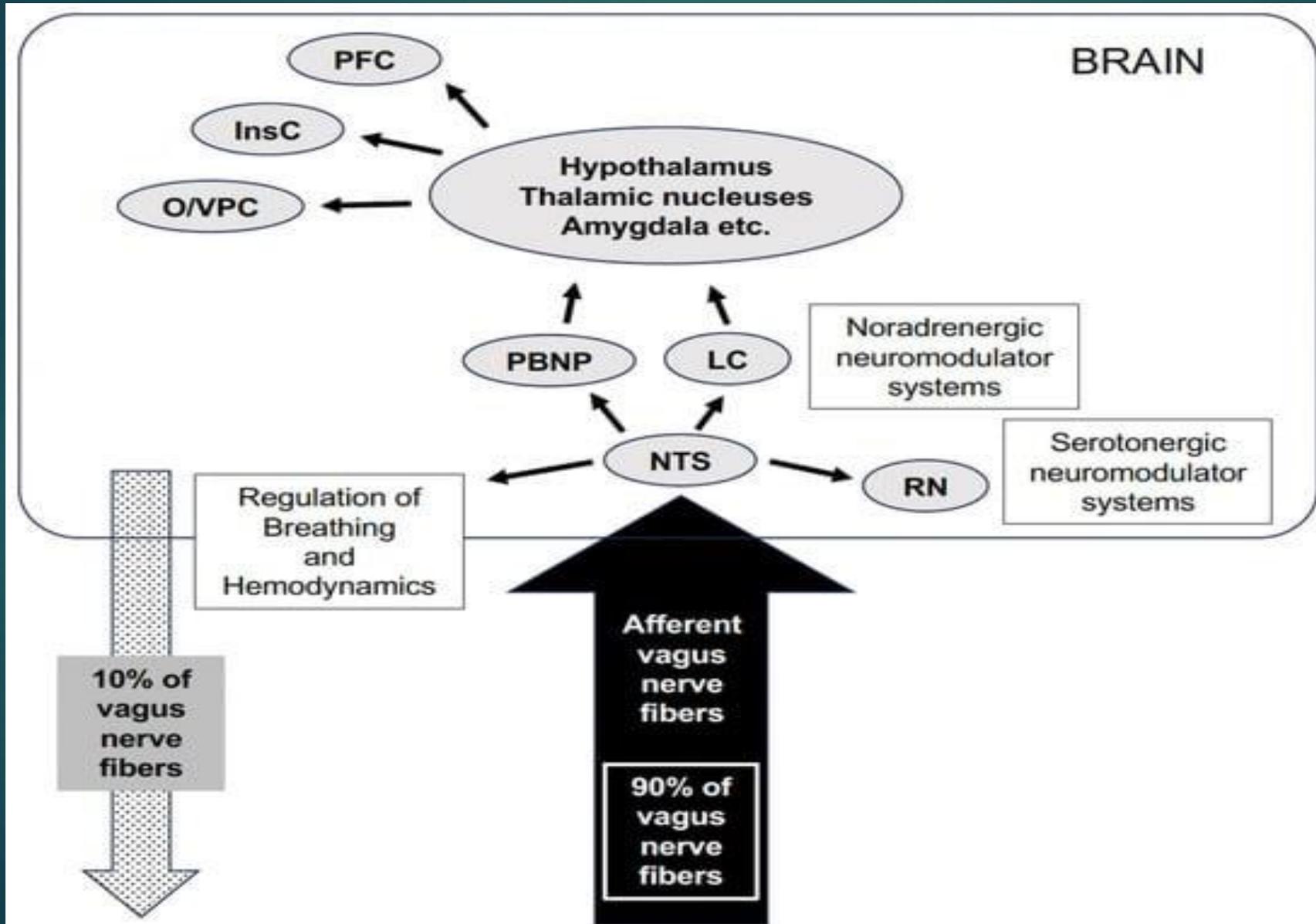
Vagus nerve stimulation activates nucleus of solitary tract neurons via supramedullary pathways PMID: 34676533 DOI: 10.1113/JP282064

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28/06/2024

Vagus nerve



Vagus Nerve – intracerebral connectivity – Neural circuitries



Vagus Nerve – main functional significance

▶ Parasympathetic Actions

- ▶ CN X is the main parasympathetic **BI-DIRECTIONAL** communication highway between all peripheral organs, their functional status and the brain

▶ Gut Brain Axis - Paradigm shift in last 5 years in research of brain-gut axis.

- ▶ The microbiota (micro-biomes) – communication vehicles for GI- BRAIN axis a BI-DIRECTIONAL ANS involving way
- ▶ L 80% afferent fibres
 - ▶ A mixed afferent, efferent, and motor components
 - ▶ The main autonomic reciprocal network connection between CNS – periphery

▶ Anti-inflammatory [ACh mediated] pathway - able to dampen peripheral inflammation and to decrease intestinal permeability, thus very probably modulating microbiota composition.

- ▶ Stress inhibits the VN and has deleterious effects on the gastrointestinal tract and on the microbiota - IBS, Crohn's disease, other anti-inflammatory bowel disease (BDI), both characterised by a dysbiosis second to low vagal tone; RA (incl Still's Disease)
- ▶ the bidirectional interactions between the gut microbiome and the brain suggests integration of CNS – GI tract – immune system [now status of an 'organ'] – CYTOKINES AS MODULATORS – VNS treatment increases vagal tone – reduces pro-inflammatory Cytokines [NB involved in epileptic encephalopathies, schizophrenia etc, also]
- ▶ Stroke Neuro-rehabilitation

▶ VNS therapy

- ▶ an alternative non-pharmacological therapy to conventional treatment / combined with conventional tx
 - ▶ Main indications (1998 EU approved, 2002, UK NICE: DRE as adjunctive therapy
- ▶ SYMPATHO-VAGAL FUNCTIONAL IMBALANCE modulated by VNS bio-electrostimulation
- ▶ Rodent Models – **GLIAL NEUROGENESIS** at 10 years established GABA-ergic seizure-genic neural networks
- ▶ Resilience
 - ▶ Monoamine-ergic (NE/NA – Adrenaline) imbalance in
 - ▶ Mood disorders, anxiety disorders - VNS treatment has capacity to regulate imbalance (The New Scientist Oct / Nov 2023)
- ▶ NB Infant data – CN X stimulation in ASD

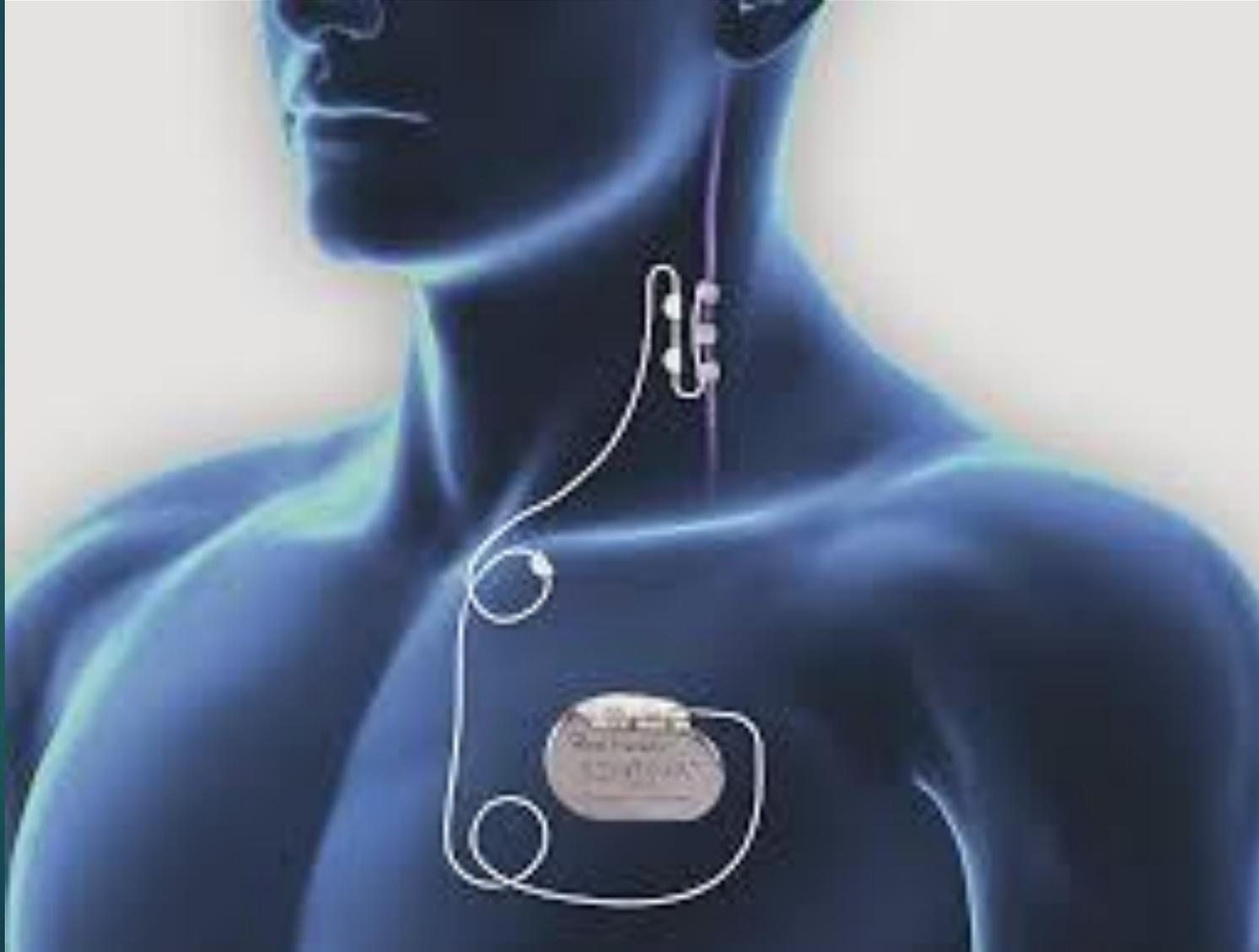
▶ FDA (Food and Drug Administration) investigates autoimmune and chronic inflammatory disorders

- ▶ etc etc

Vagus Nerve Stimulation (VNS)

- ▶ **1994 CE marque for treatment recalcitrant seizures**
 - ▶ 2000 – 2004 EU VNS Exec Ref Group, then NICE (UK) VNS ERG – both Michael Trimble (Chair)
 - ▶ 1996 FDA (US) Approval
 - ▶ 2004 NICE licenced in NHS for tx of seizure and ‘treatment recalcitrant epilepsies / seizures.....and epilepsies not amenable to epileptogenic foci / epileptogenic zone resection (neurosurgery)
 - ▶ 2002 SUDEP – Epilepsy Deaths in the Shadows (Hannah M, Brown St, Chadwick D., Fish D., Lei Sanders, et al)
 - ▶ Has significantly improved therapeutic prognosis of otherwise treatment non-responsive patients with high risk of SUDEP variables
 - ▶ 2014 – 2016
 - ▶ NICE development of ASD / neurodevelopmental epilepsy patient pathways (IPG; Internventional Procedures Guidelines) due to under-referrals

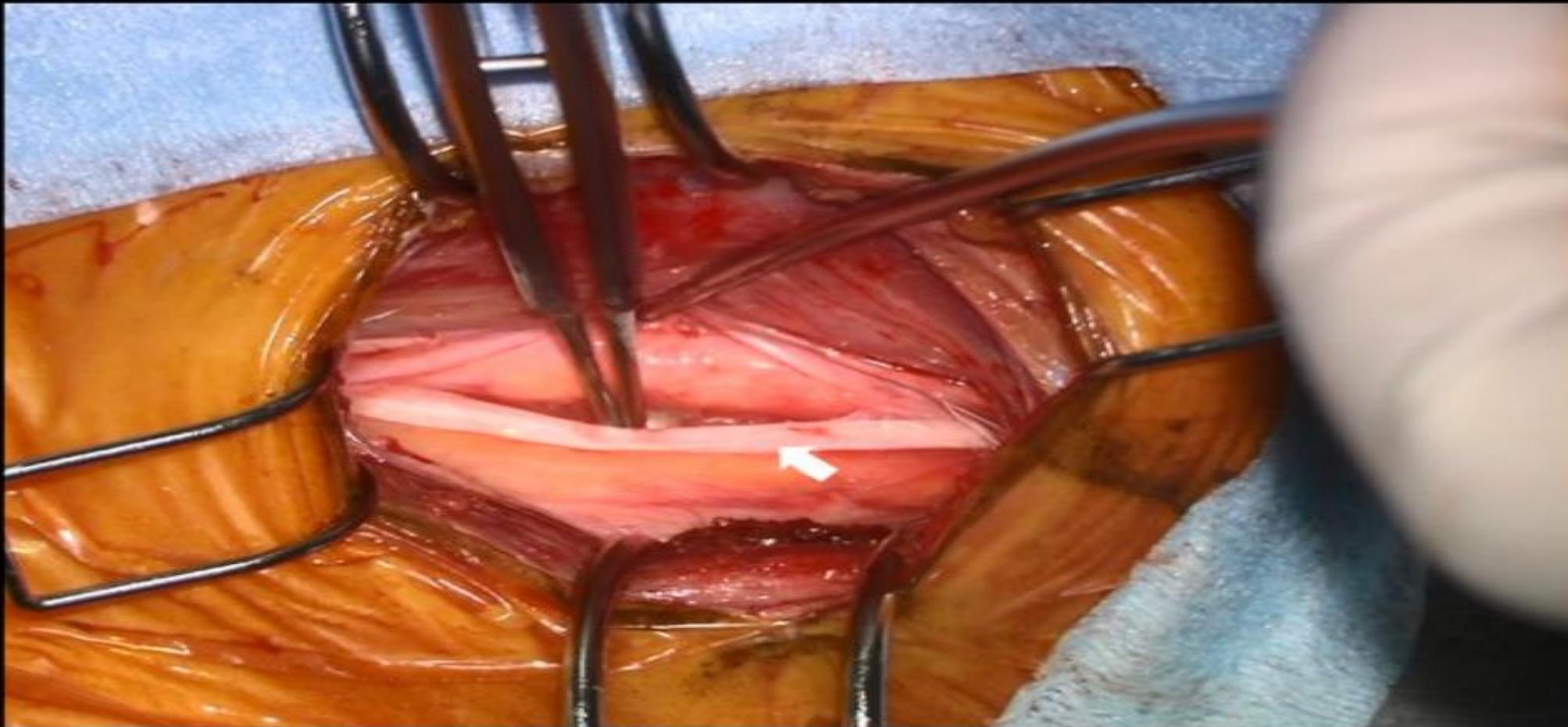
Current Model SenTiva 1000M



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NNUH FT VNS Centre Programme x5 world 'Firsts'

– incl. NECK Surgery Lead Implantation Surgeon -
(Paul Montgomery, now Andy Bath)



Clinical Monitoring - Stimulation Parameters @ Ramping Schedule

Modern VNS



AutoStim: Closed-loop therapy that responds to heart rate increases that may be associated with seizures



Guided Programming: On-touch programming that simplifies dosing towards achieving the targeted therapeutic level



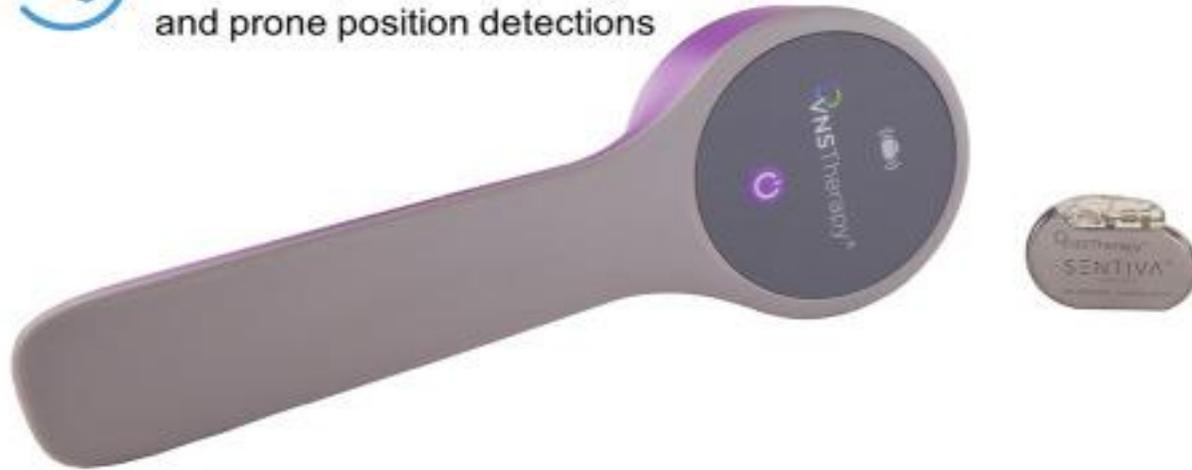
Scheduled Programming: Pre-program a schedule for VNS to auto-titrate without the need for an office visit



Day-Night Programming: Customize and program two separate therapies within a 24-hour period



Events & Trends: Track and display the amount of tachycardia detections, AutoStims, magnet use, low heart rate detections and prone position detections



Stimulation Parametres (time)

Table 2 Duty cycles for various ON and OFF times

| ON time (sec) | Duty cycles (% ON time) | | | | | | | | |
|---------------|-------------------------|-----|-----|-----|-----|-----|----|----|----|
| | OFF time (min) | | | | | | | | |
| | 0.2 | 0.3 | 0.5 | 0.8 | 1.1 | 1.8 | 3 | 5 | 10 |
| 7 | 58% | 44% | 30% | 20% | 15% | 10% | 6% | 4% | 2% |
| 14 | 69 | 56 | 41 | 29 | 23 | 15 | 9 | 6 | 3 |
| 21 | 76 | 64 | 49 | 36 | 29 | 19 | 12 | 8 | 4 |
| 30 | 81 | 71 | 57 | 44 | 35 | 25 | 16 | 10 | 5 |
| 60 | 89 | 82 | 71 | 59 | 51 | 38 | 27 | 18 | 10 |

Not recommended.

Courtesy of Cyberonics, Inc. and Nihon Kohden.

Ramping Schedule – Tablet data

| Stimulation | C 1 | C 2 | C 3 | C 4 | C 5 | C 6 | C 7 | C 8 | C 9 |
|--------------------|------|------|------|------|------|------|------|------|--|
| | | | | | | | | | 3 / 6 / 12 / 24 / months [rodent histo-pathology data at 10y] |
| Output (mA) | 0.25 | 0.50 | 0.75 | 1.0 | 1.25 | 1.50 | 1.75 | 2.0 | 2.25 |
| Frequency (Hz) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Pulse Width (msec) | .250 | .250 | .250 | .250 | .250 | .250 | .250 | .250 | .250 |
| On Time (seconds) | 30` | 30` | 30` | 30` | 30` | 30` | 30` | 30` | 30` |
| OFF Time (minutes) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Duty Cycle (10% +) | Y | Y | Y | Y | Y | Y | Y | Y | |
| 8 other | | | | | | | | | |

Vagus Nerve Stimulation (VNS) side-effect profile

- ▶ 3 months >> 6 months > / none at 9 months
 - ▶ Hoarseness / change in voice N.B. only for the 30 (60sec) stimulus
 - ▶ Sore throat
 - ▶ Shortness of breath
 - ▶ Prickling feeling in the skin (m. plathysmalis – CN VII @ nc cervicalis transversalis)
 - ▶ Coughing (L n recurrens laryngii)
 - ▶ Sleep apnoea
 - ▶ now no longer a BNF contraindication, 'just a caution' – LivaNova worked very hard on this – I remain cautious

Mayo - / Cleveland Clinic (Ohio) advice

- ▶ Whilst pregnant
- ▶ Significant respiratory compromise asthma, sleep apnea, COPD, chronic lung diseases and disorders.
- ▶ Peptic ulcers Have active peptic ulcer disease.
- ▶ Type 2 DM
- ▶ CN X abnormalities (single CN X)
- ▶ Dysautonomia - abnormal functioning of your autonomic nervous system.
- ▶ Other forms of brain stimulation due to conduction risks
- ▶ Established cardiac pathologies
- ▶ H.O ICD-11 (Jan 2022) SMI, including
 - ▶ Schizophrenia - schizoaffective -, delusional disorders spectrum, and
 - ▶ BPD2 [e.g. with 4+ cycles or manic episodes]

NICE NG 217 / IPG50 – habitual non-compliance by 2nd tier epilepsy services

▶ Drug Resistant Epilepsy (DRE)

▶ ILAE (April 2017) Definition:

- ▶ ‘...ongoing seizure activity after 3 + anti-seizure medications’ [ASMs]...**to be referred to a specialist VNS assessment and tx centre**

▶ **At East Coast (part of BRC Hub application)**

- ▶ NRP NNUH FT Neuroscience Division, Dual Diagnosis Epilepsy, Neurodevelopmental VNS Programme Centre - **a tertiary, supra-regional commissioned plus case by case from NHNN, King’s, South coast, up to Humber bridge referrals**

REF:

- Epilepsia (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies
- Patrick Kwan 1, Alexis Arzimanoglou, Anne T Berg, Martin J Brodie, W Allen Hauser, Gary Mathern, Solomon L Moshé, Emilio Perucca, Samuel Wiebe, Jacqueline French. 2009, Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. PMID: 19889013 DOI: 10.1111/j.1528-1167.2009.02397.x

30 - year follow-up study – confirmed DRE as effective threshold diagnosis

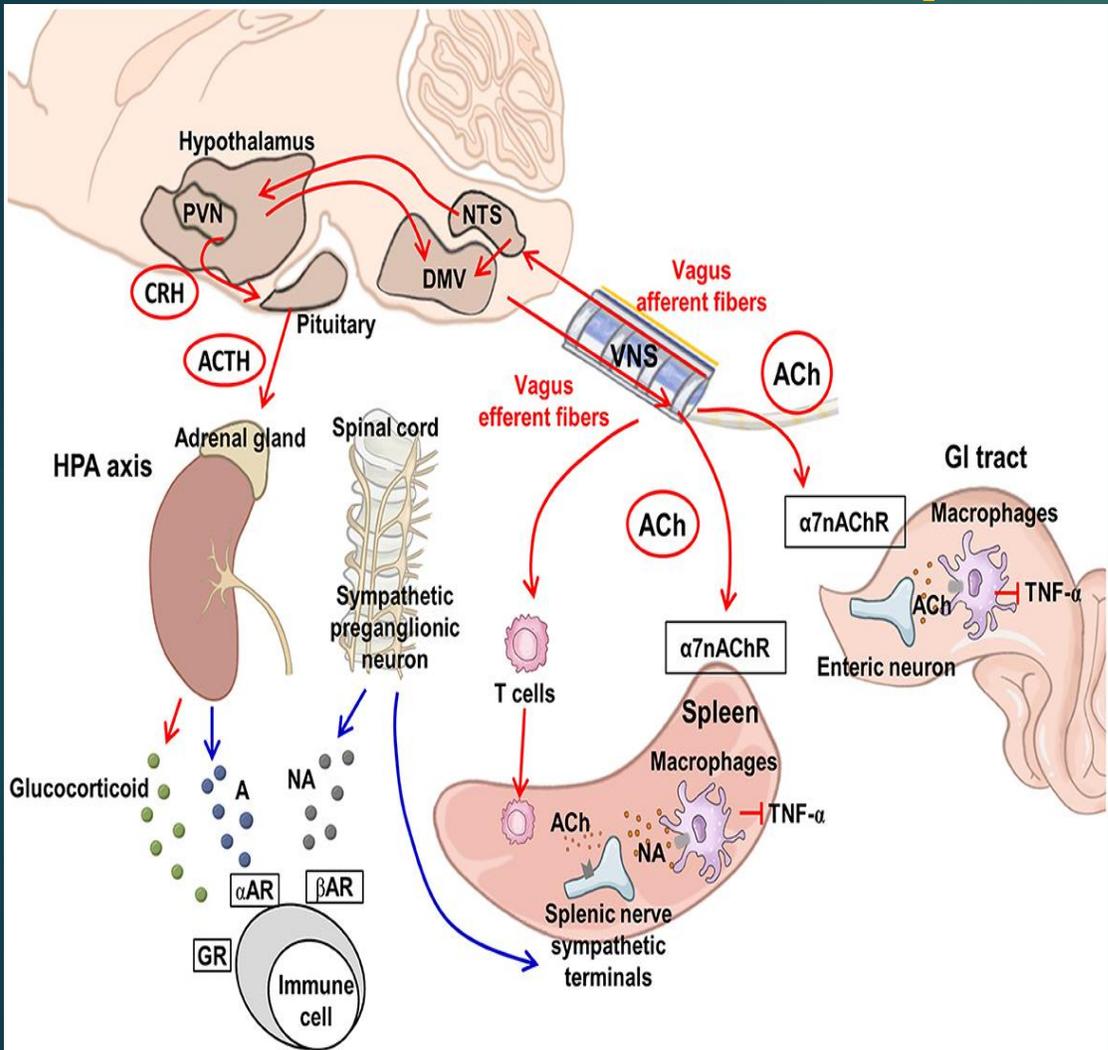
- **NICE Evidence review 14, April 2022: Vagus nerve stimulation (VNS). Epilepsies in children, young people and adults: diagnosis and management.** NICE Guideline, No. 217 & NICE Guideline, No 50 (VNS) National Guideline Centre (UK). London: National Institute for Health and Care Excellence (NICE); ISBN-13: 978-1-4731-4513-9

Current trends, novel frontiers *under investigation

- ▶ Vagal neuromodulation in
 - ▶ immunological* / auto-immune diseases*
 - ▶ GI* - biomes, RA* (Still's), Psoriasis*, Lupus erythematosus, Epileptic Encephalopathies (RS, LGS, Dravet's S amongst others), Limbic encephalitis*
 - ▶ Tinnitus
 - ▶ Sleep research in VNS
 - ▶ Neurodevelopmental disorders
 - ▶ Recent NIHR call
 - ▶ NRP (CI) – Cambs et al team withdrew application due to ethical concerns for the RCT design drafted by non-VNS or Epileptology based design and methodology.
 - ▶ Adopted studies NIHR – LivaNova – Oxford University
 - ▶ CORE_VNS STUDY (n=642; 26 study sites, closed) – UEA / Norwich Research Park / NNUH PI site for EoE
 - ▶ Subanalysis 30 Sept 2024 NNUH NRP (CI site)– Oxford – LivaNova – proposal
 - ▶ Paediatric cohort infant / childhood studies
 - ▶ **NAUTE-Qv1 (Norwich Autism Outcome Evaluation Questionnaire version 1)** – Audits and Cohort studies - submitted
 - ▶ First such structured tool, interviewer or informant-based ICD-11 WHO 6A02.0 – 6A02.Z and SCAN3 (WHO, CUP; 2024/5)

Neuroinflammation – VNS activation – anti-inflammatory neuroplasticity - dementiae

2/06/2024



- ▶ immunomodulatory functions through vagal efferent fibers mediated by the CAP and vagal afferent circuits mediated by the HPA axis. Therefore
- ▶ VNS enhances vagus nerve-mediated anti-inflammatory effects and is
- ▶ Indicated in treatment of multiple diseases with underlying inflammatory etiologies (Kelly et al., 2022; the New Scientist).
- ▶ VNS exerts its immunomodulating effects via the CAP to reduce pro-inflammatory cytokines, activate microglia and macrophages, and alter the consequences of neuroinflammation (Figure 1).
- ▶ VNS increases CN X [ACh] - binds to the $\alpha 7nAChR$ in cytokine-producing immune cells - inhibits the production of inflammatory cytokines. Wang et al. (2003) found TNF synthesis was inhibited in wild-type mice treated with VNS; however, this inhibition was diminished in $\alpha 7$ -deficient mice, suggesting that the anti-inflammatory action of VNS is mediated via ACh and the $\alpha 7nAChR$ (Wang et al.,

REVIEW article
 Front. Aging Neurosci., 06 July 2023
 Sec. Neuroinflammation and Neuropathy
 Volume 15 - 2023 | <https://doi.org/10.3389/fnagi.2023.1173987>

Neuroimmunomodulation of vagus nerve stimulation and the therapeutic implications

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