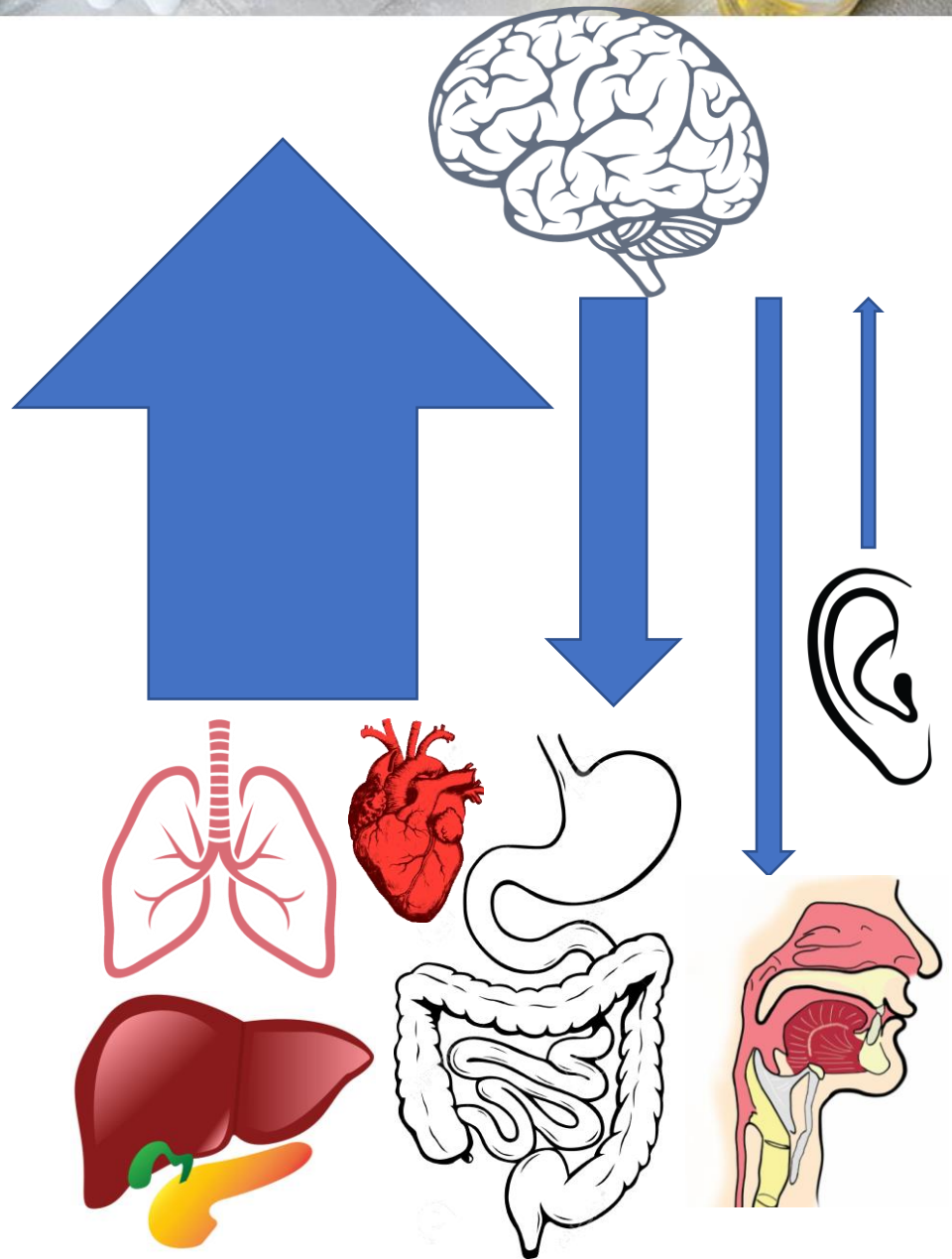
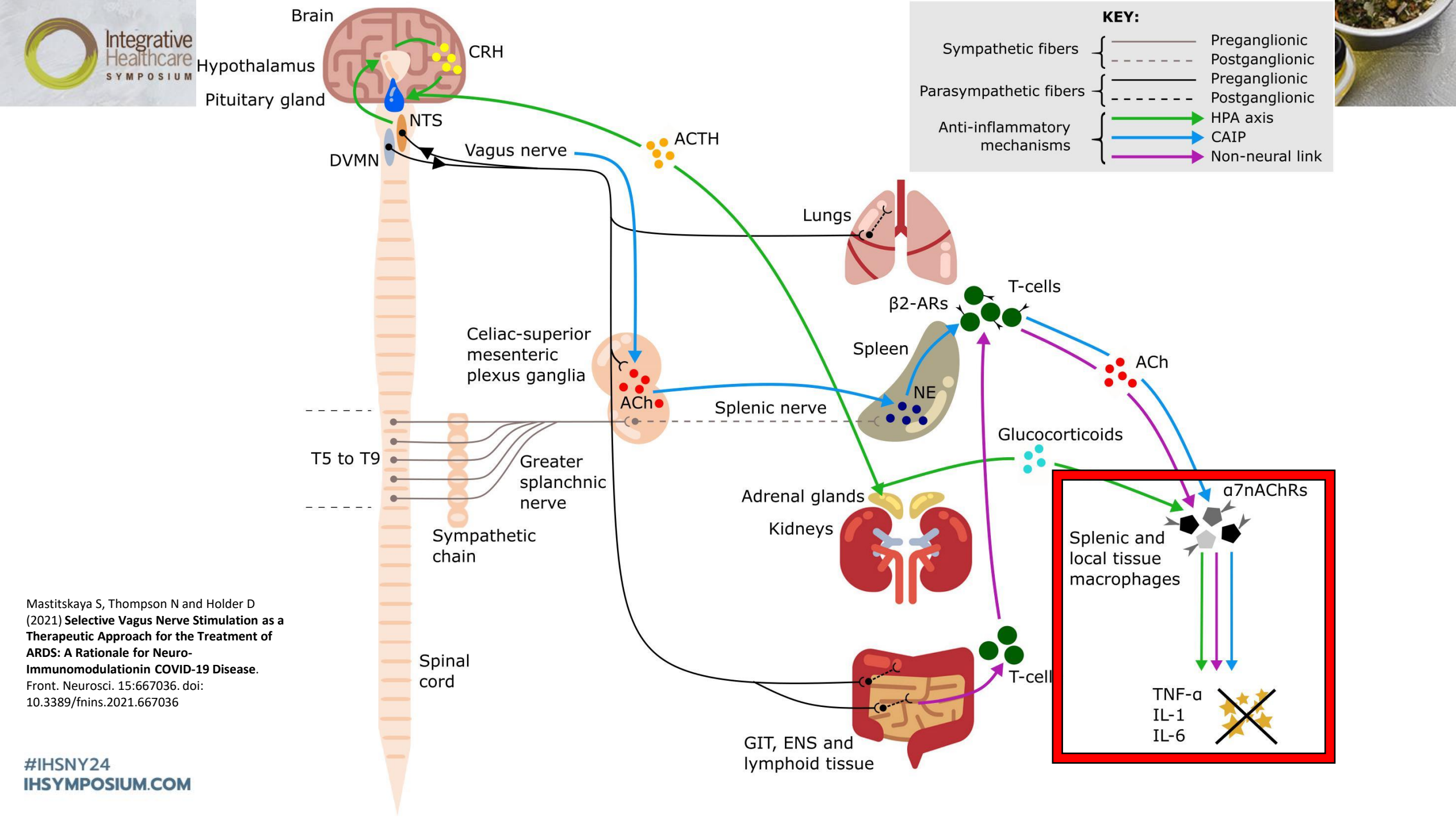
Vagus Nerve Stimulation:
Inflammatory Control to Improved Cognition

Navaz Habib DC, AFMCP, AcuP

What Happens in Vagus…

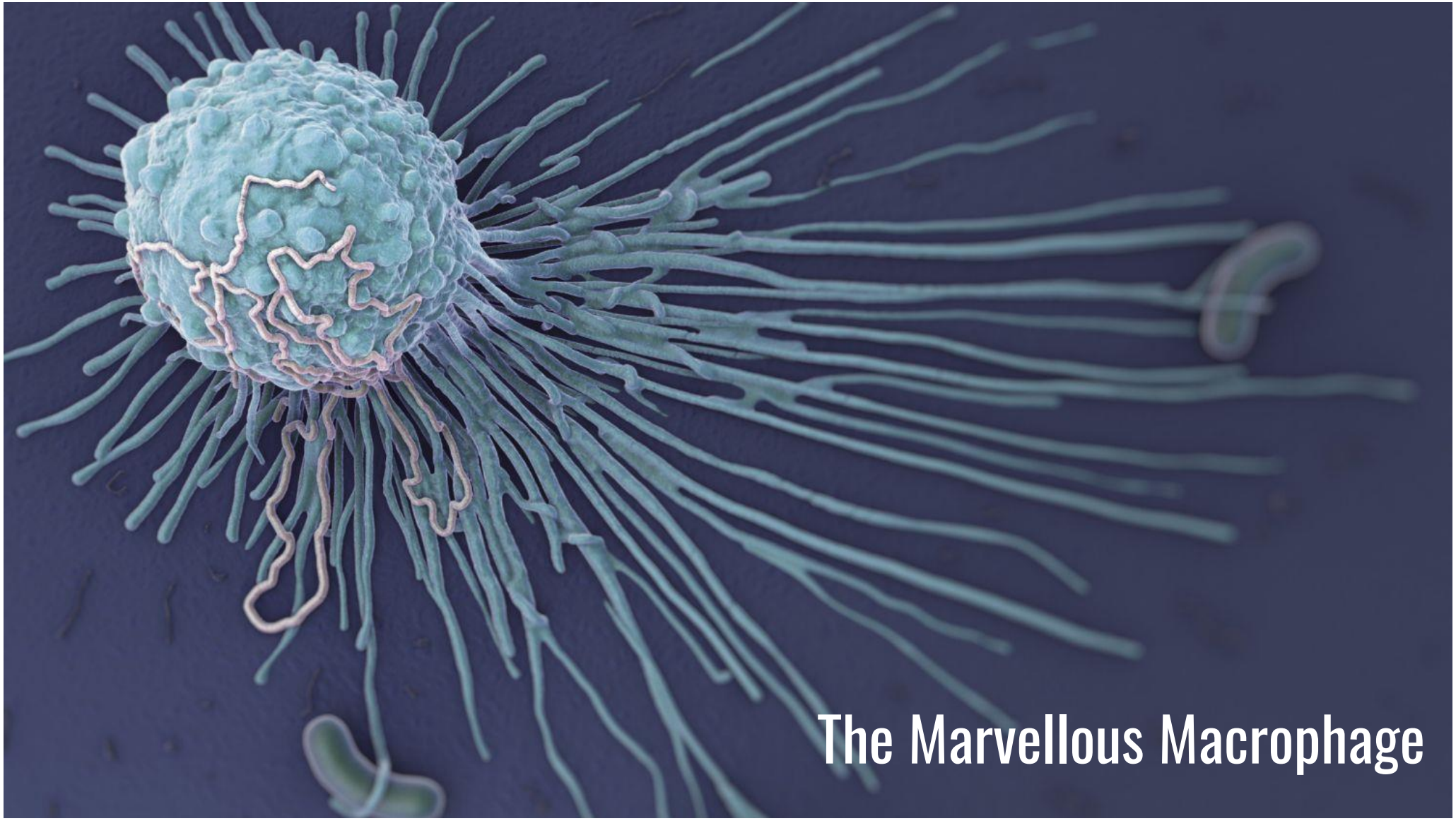
- 80% Parasympathetic Afferent
  - Status Information from viscera to the brain
- 15% Parasympathetic Efferent
  - Rest/digest information from brain to organs
  - Inflammatory control via CAIP
- 4% Motor
  - To the pharyngeal and laryngeal muscles
- 1% Sensory
  - From the skin of the auricle (ear)





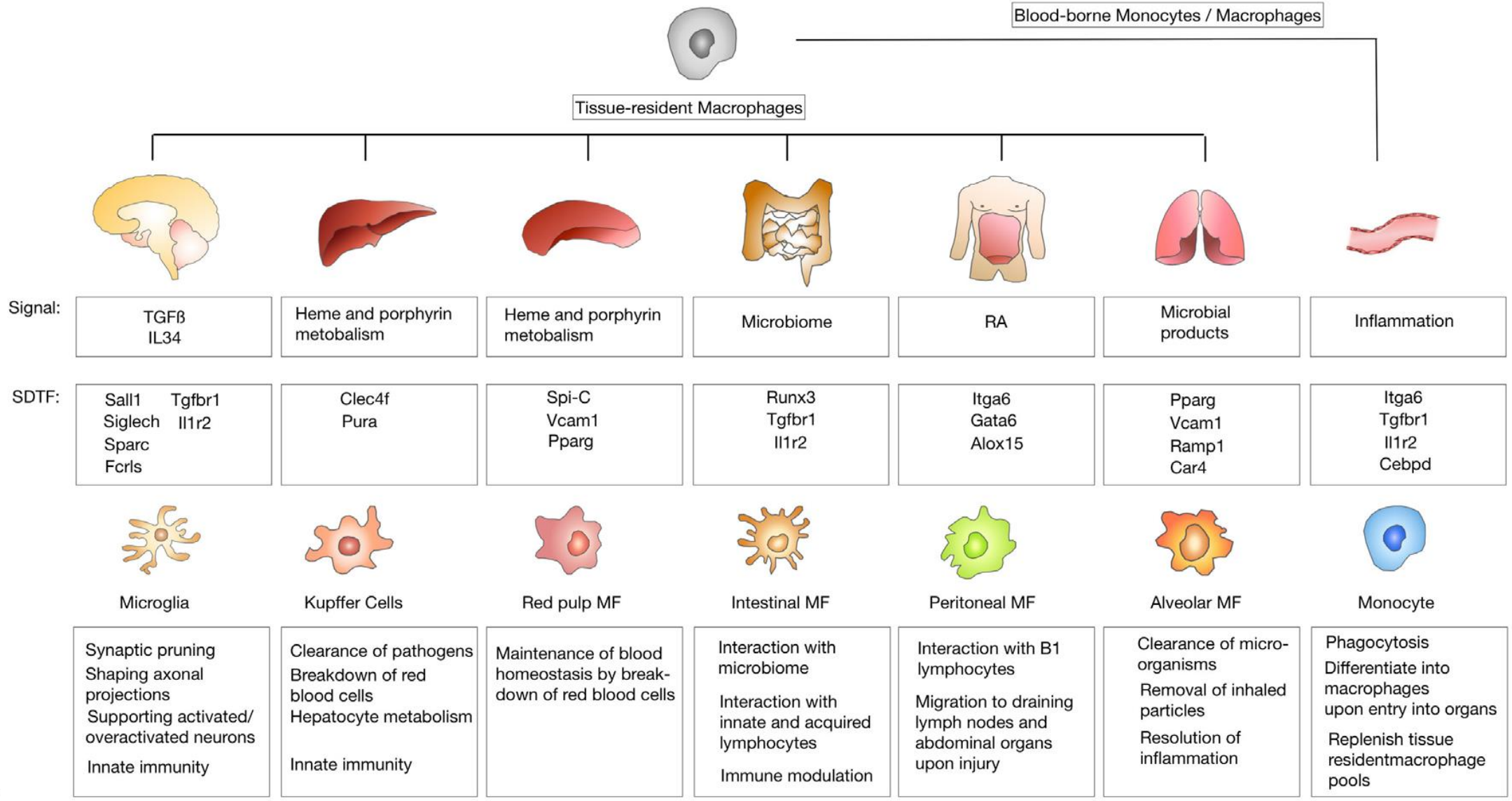
Mastitskaya S, Thompson N and Holder D (2021) **Selective Vagus Nerve Stimulation as a Therapeutic Approach for the Treatment of ARDS: A Rationale for Neuro-Immunomodulationin COVID-19 Disease**. Front. Neurosci. 15:667036. doi: 10.3389/fnins.2021.667036

Integrative Healthcare SYMPOSIUM



The Marvellous Macrophage

#IHSNY24
IHSYMPOSIUM.COM

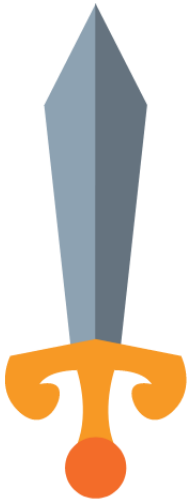


Brain-Resident Microglia and Blood-Borne Macrophages Orchestrate Central Nervous System Inflammation in Neurodegenerative Disorders and Brain Cancer
April 2018 Frontiers in Immunology

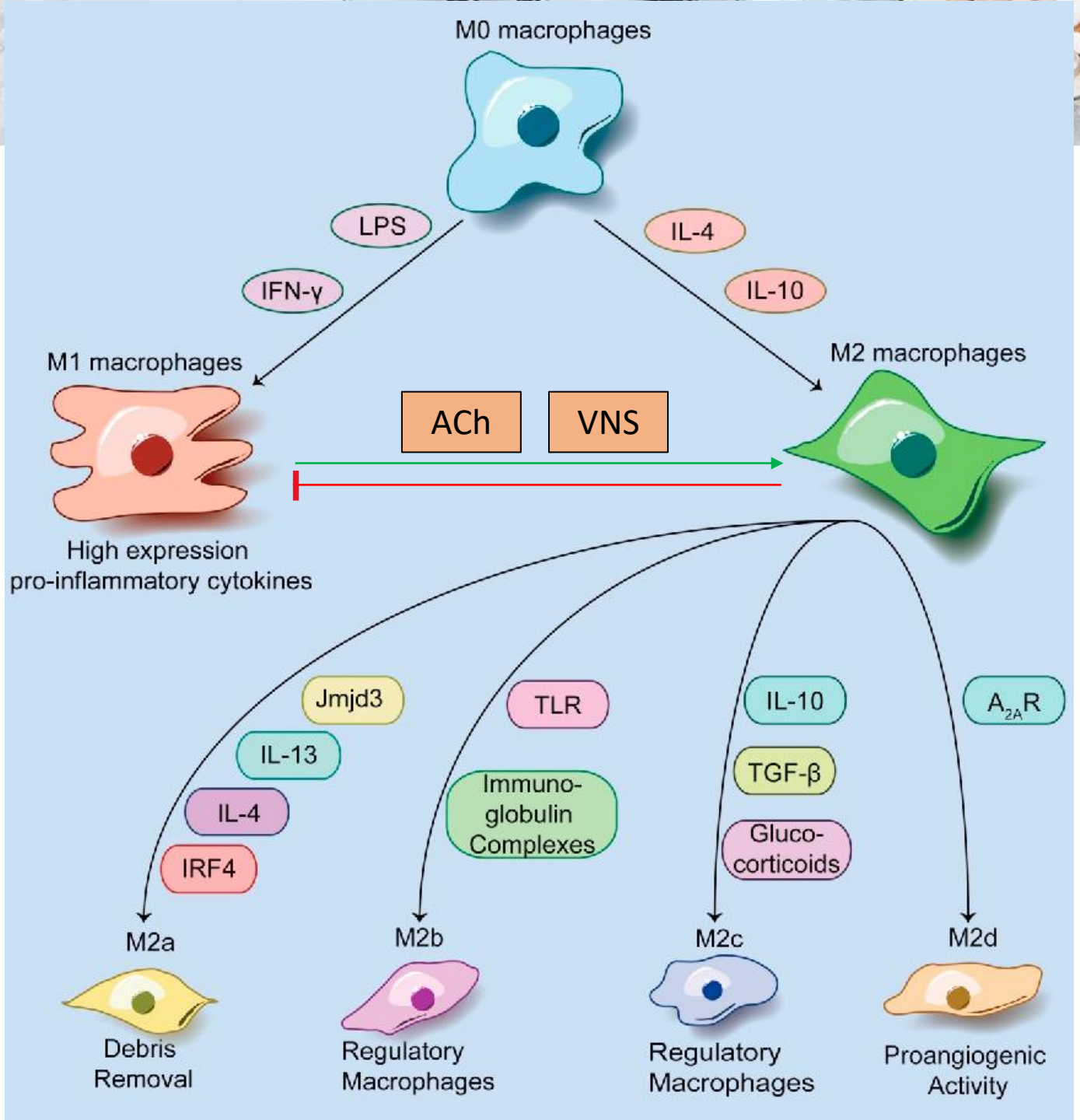
The Target Cells of Vagus Nerve CAIP

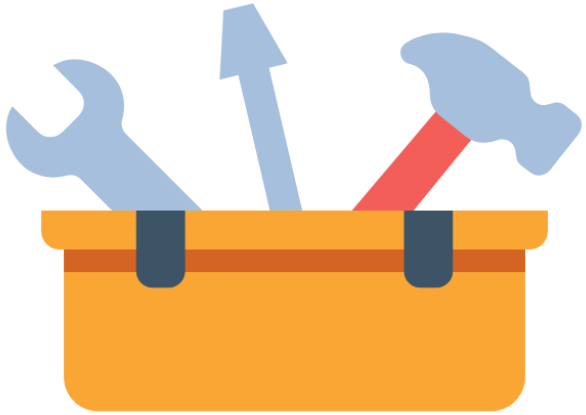
- Directly Innervated Tissue Resident Macrophages
  - CNS - Microglia, Perivascular and Meningeal Macrophages
  - Blood Vessels – Vascular Macrophages
  - Lungs - Alveolar Macrophages
  - Liver - Kupffer Cells and Motile Macrophages
  - Gut – Intestinal Macrophages
  - Spleen (via Splenic Ganglion) – Red Pulp Macrophages and Circulating Monocytes

- Indirectly via Splenic Amplification of ACh
  - Skin – Langerhans Cells and Dermal Macrophages
  - Serosa – Peritoneal and Pleural Macrophages
  - Muscle – Skeletal Muscle Macrophages
  - Adipose Tissue – Adipose Associated Macrophages
  - Bone - Osteoclasts



FIGHT

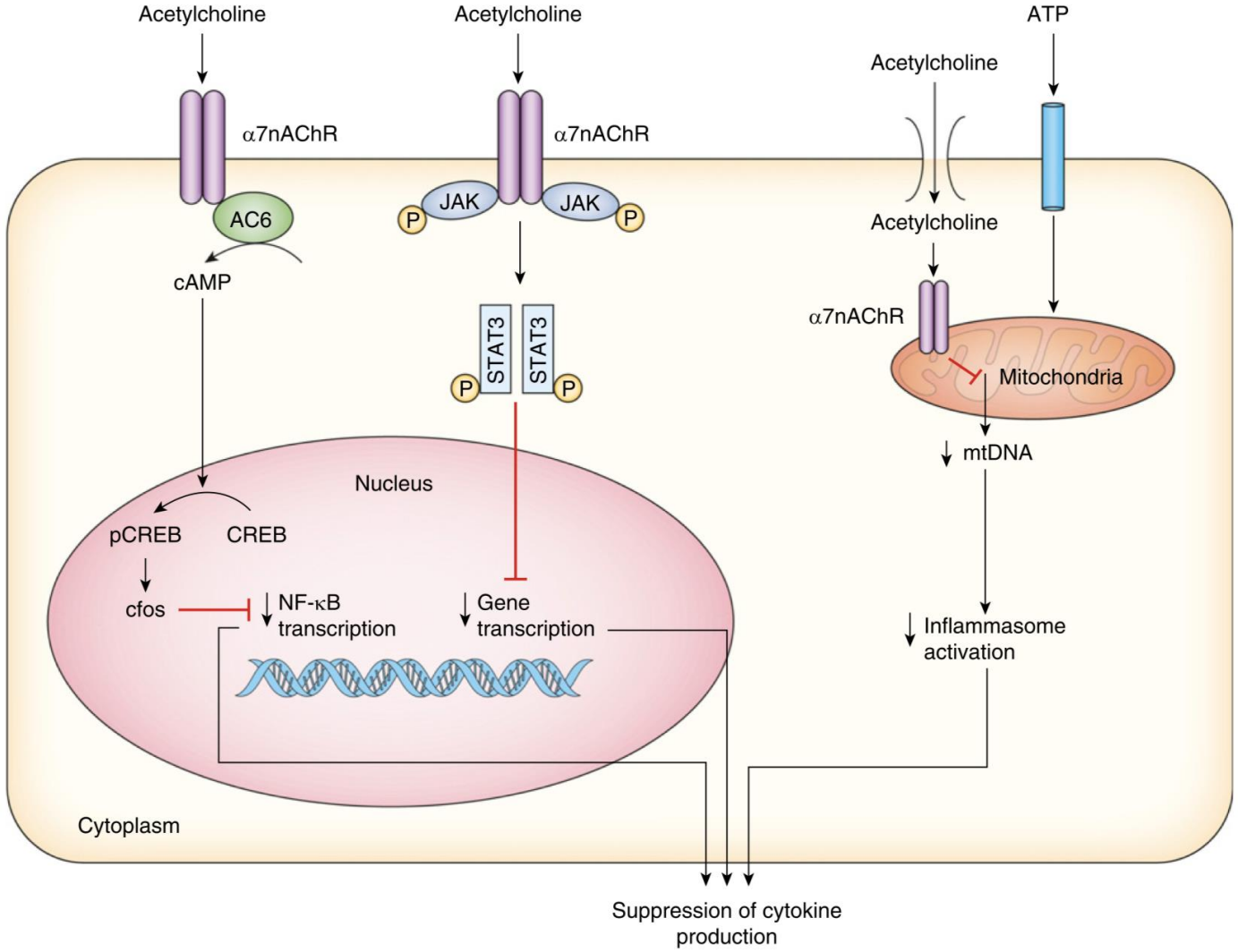




FIX

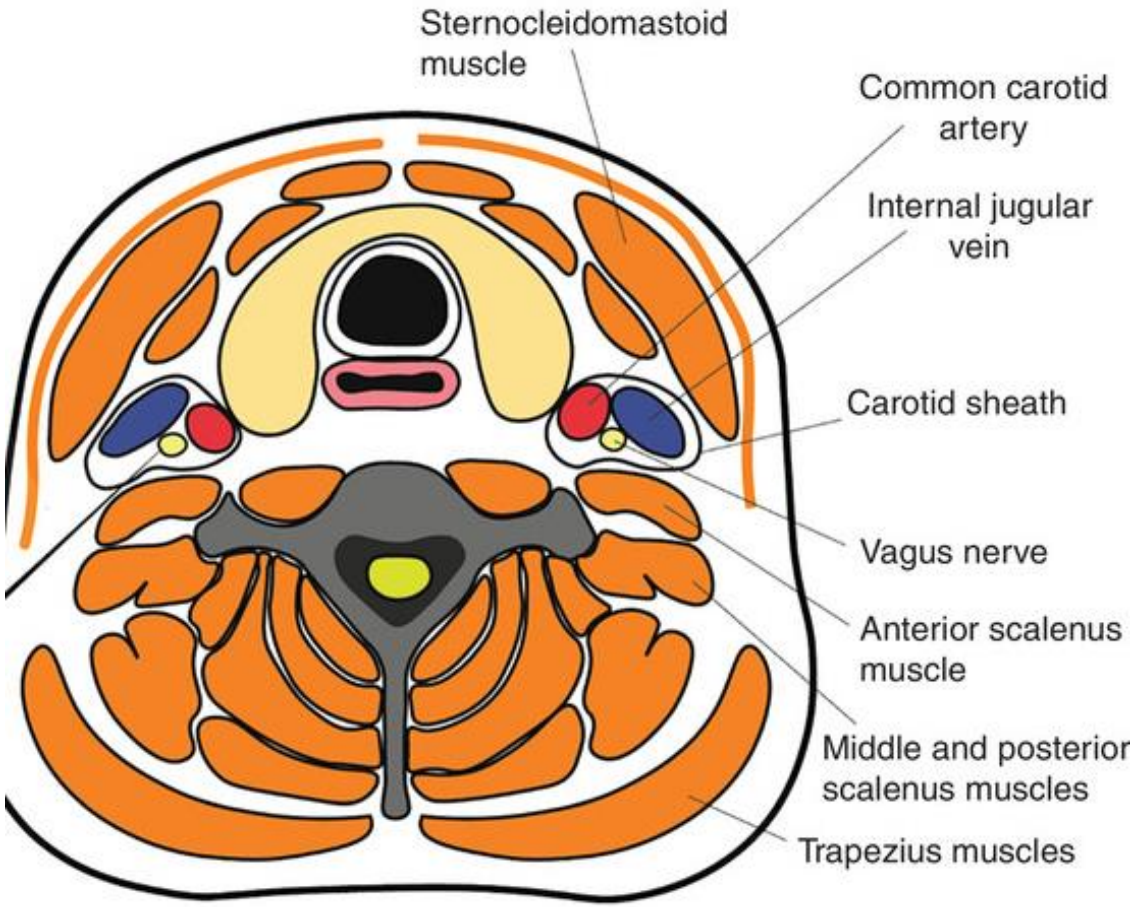
Wang, Youhan et al. **"M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds."** *International Immunopharmacology* 70 (2019): 459–466.

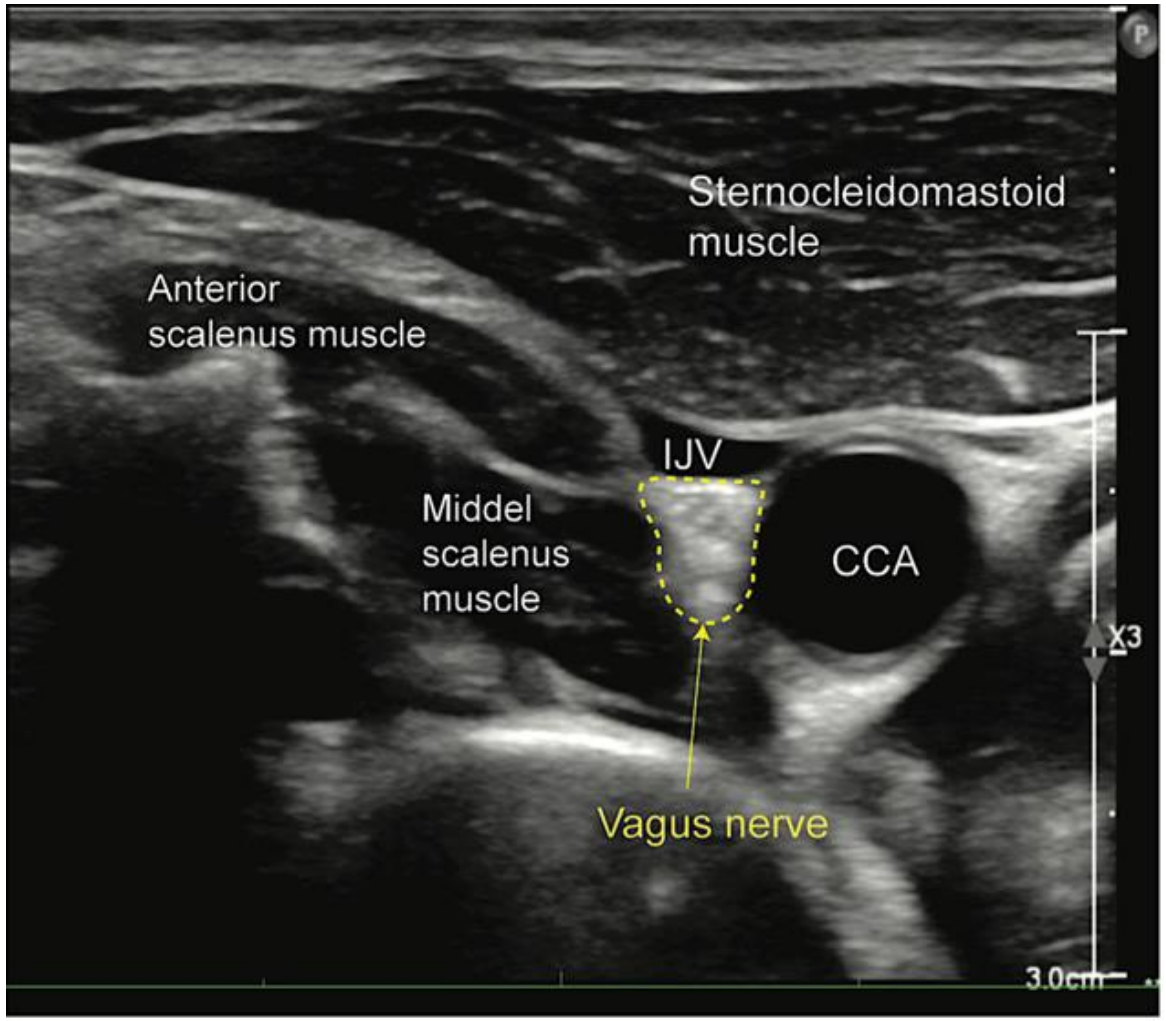
Cellular Effects of CAIP



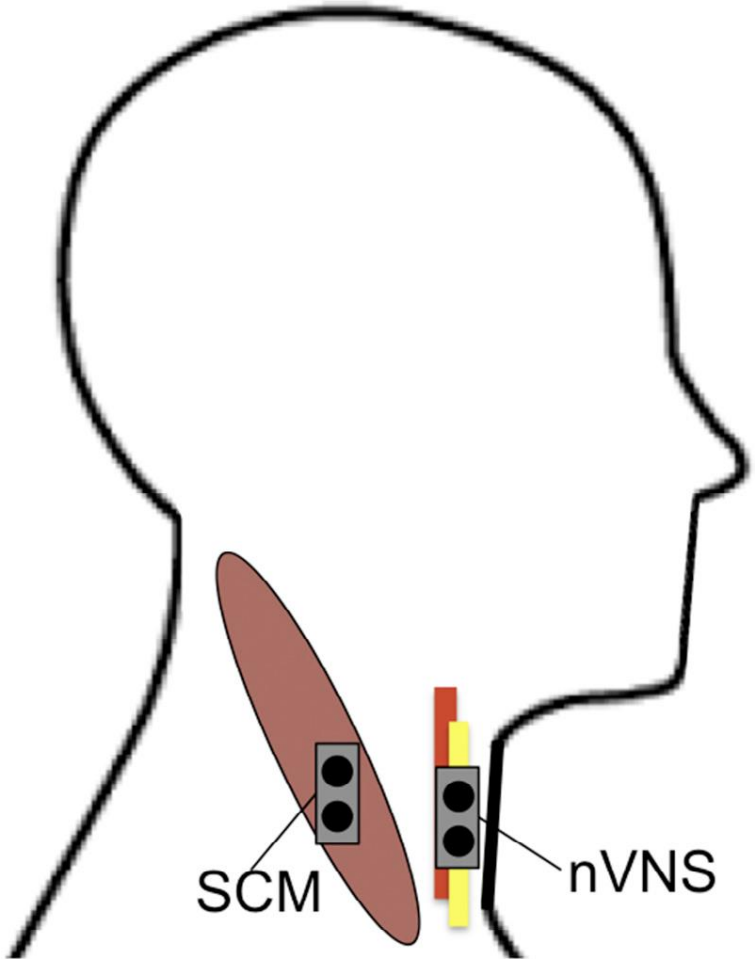
FIX THIS
Wang, Youhan et al. **"M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds."** *International Immunopharmacology* 70 (2019): 459–466.

Where is Vagus (Nerve, not City)





How does nVNS Work?

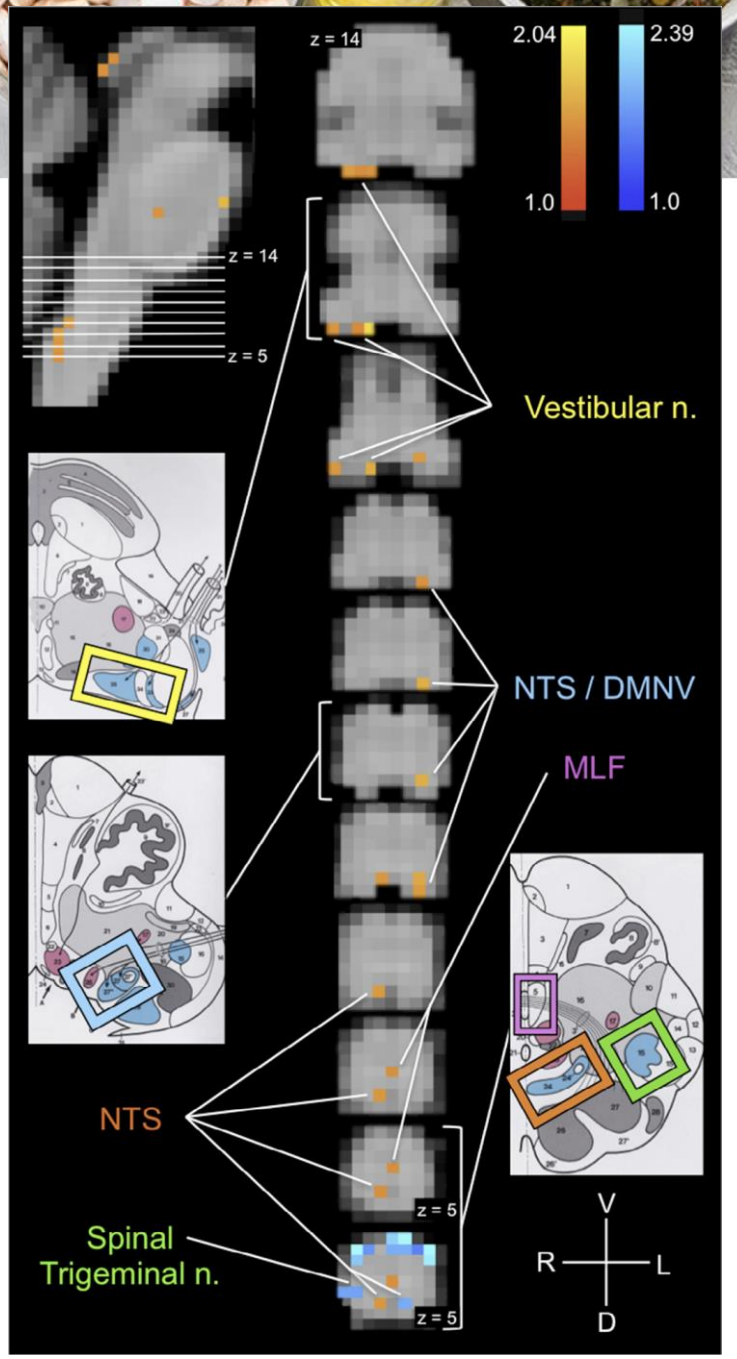


Activation of Brainstem Nuclei:

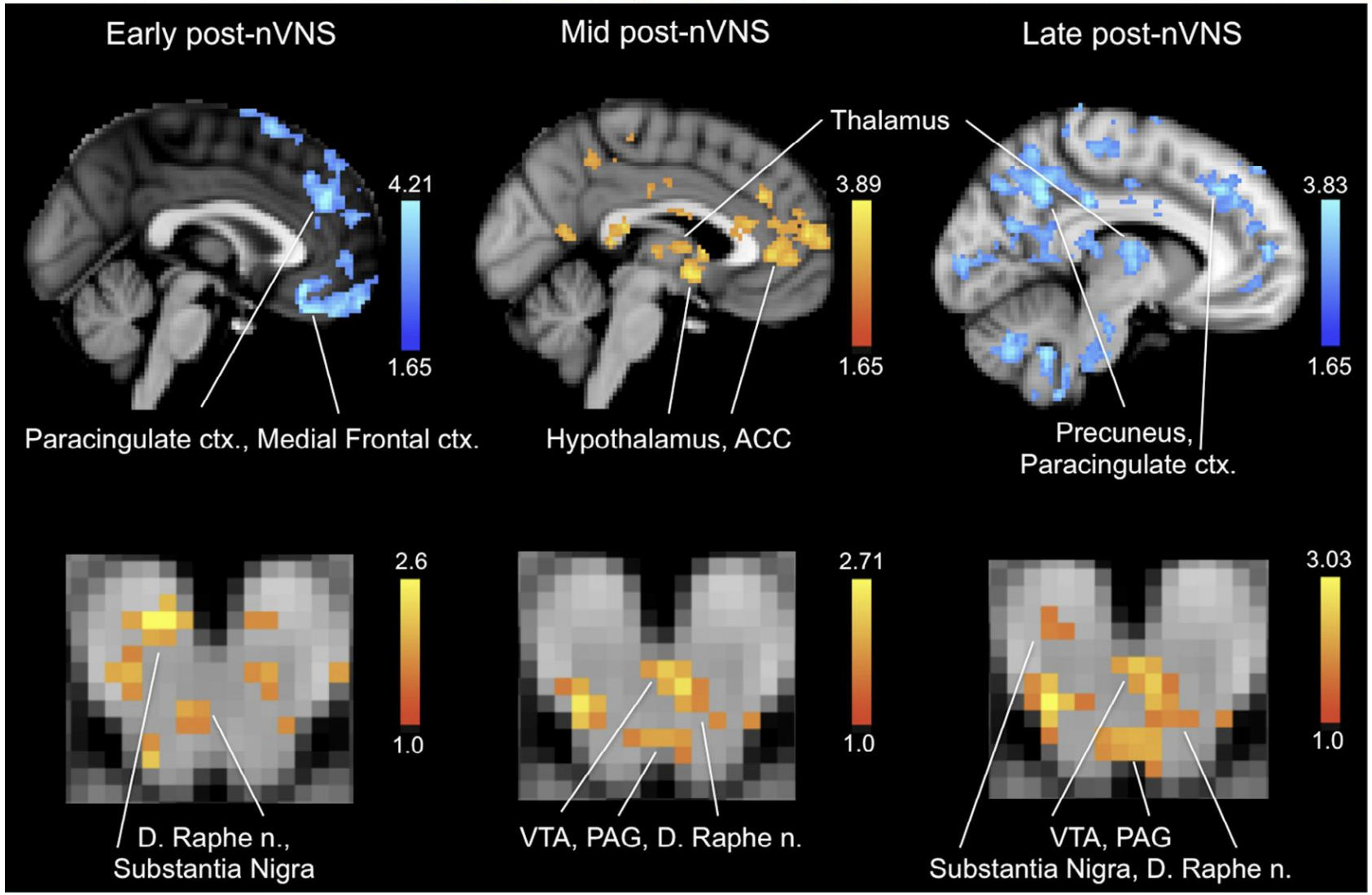
- **Nucleus of the Solitary Tract**
- **Dorsal Motor Nucleus of Vagus**
- Vestibular Nuclei
- Medial Longitudinal Fasciculus

Inhibition of Brainstem Nuclei:

- Spinal Trigeminal Nucleus

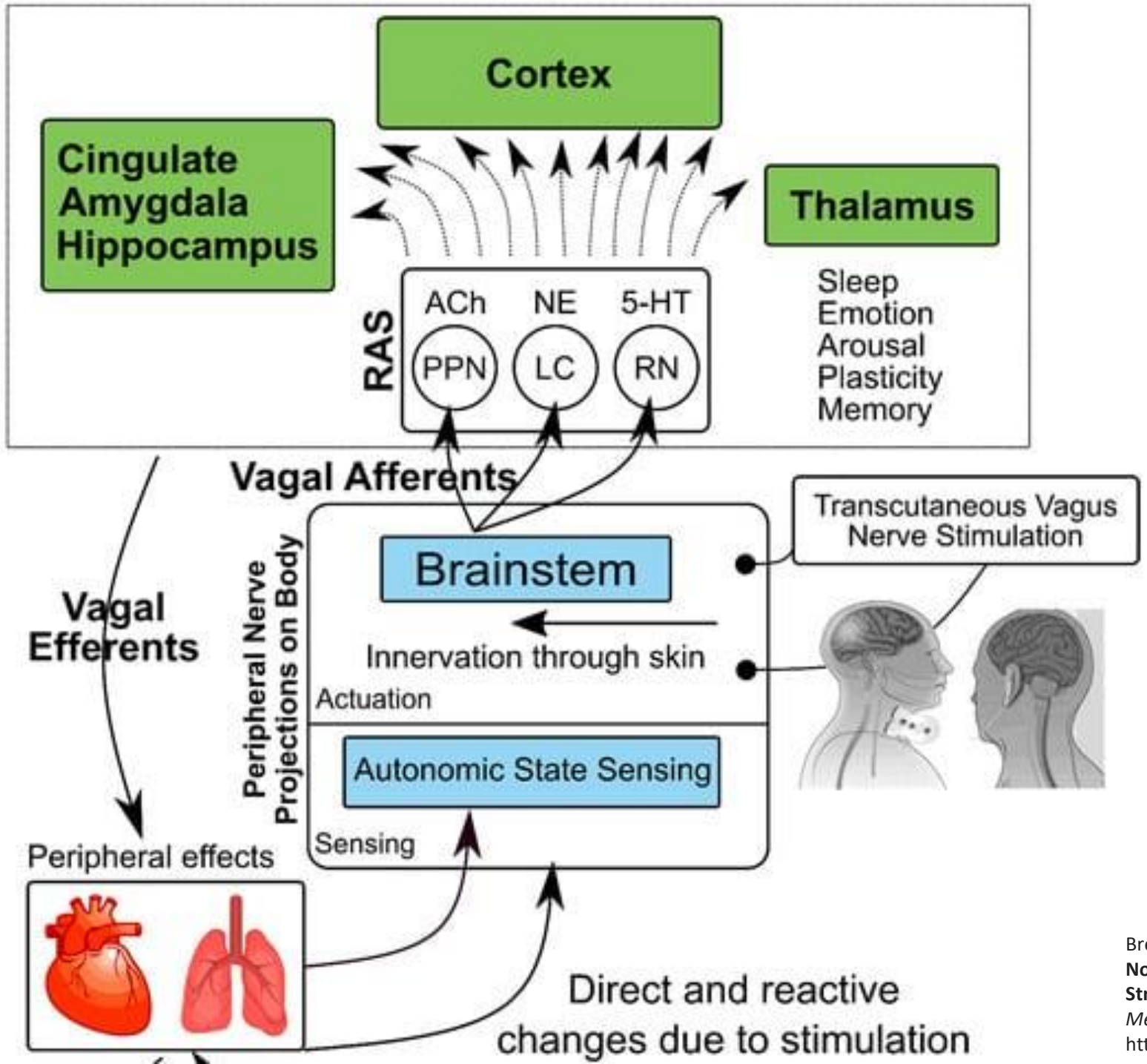


Access to Vagal Projections via Cutaneous Electrical Stimulation of the Neck: fMRI Evidence in Healthy Humans.
Frangos, E. Komisaruk, B. Brain Stimulation. DOI: 10.1016/j.brs.2016.10.008



Early Phase (3-5 mins) Mid Phase (7-9 mins) Late Phase (13-15 mins)

Access to Vagal Projections via Cutaneous Electrical Stimulation of the Neck: fMRI Evidence in Healthy Humans.
Frangos E, Komisaruk B. Brain Stimulation. DOI: 10.1016/j.brs.2016.10.008



Bremner, J.D. et al. **Application of Noninvasive Vagal Nerve Stimulation to Stress-Related Psychiatric Disorders**. *J. Pers. Med.* **2020**, *10*, 119. https://doi.org/10.3390/jpm10030119

VNS Facilitates a STATE SHIFT

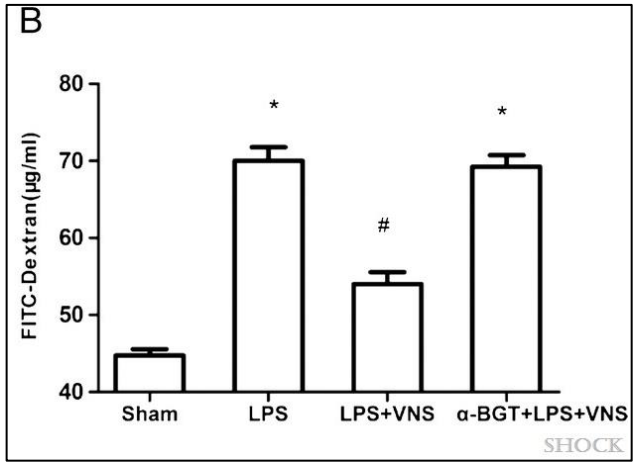
Inflammatory	→	Anti-Inflammatory
Sympathetic	→	Parasympathetic
Fight/Flight	→	Rest/Digest/Recover

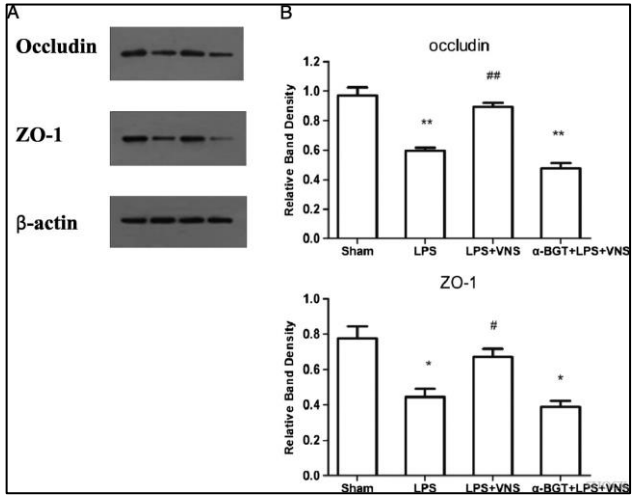
VNS and Intestinal Hyperpermeability

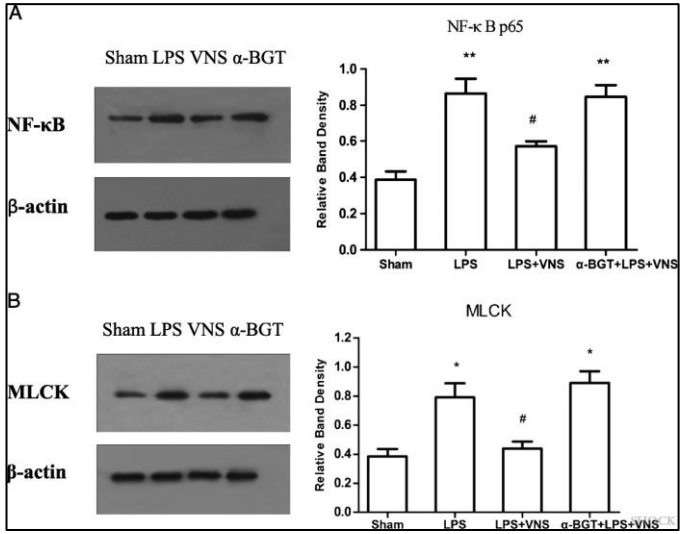
VNS prevented ultrastructure injury in endotoxemic mice.

Stimulation of vagus nerve improves intestinal tight junction protein expression.

VNS inhibits MLCK and NF-κB, the molecules responsible for intestinal tight junction breakdown.







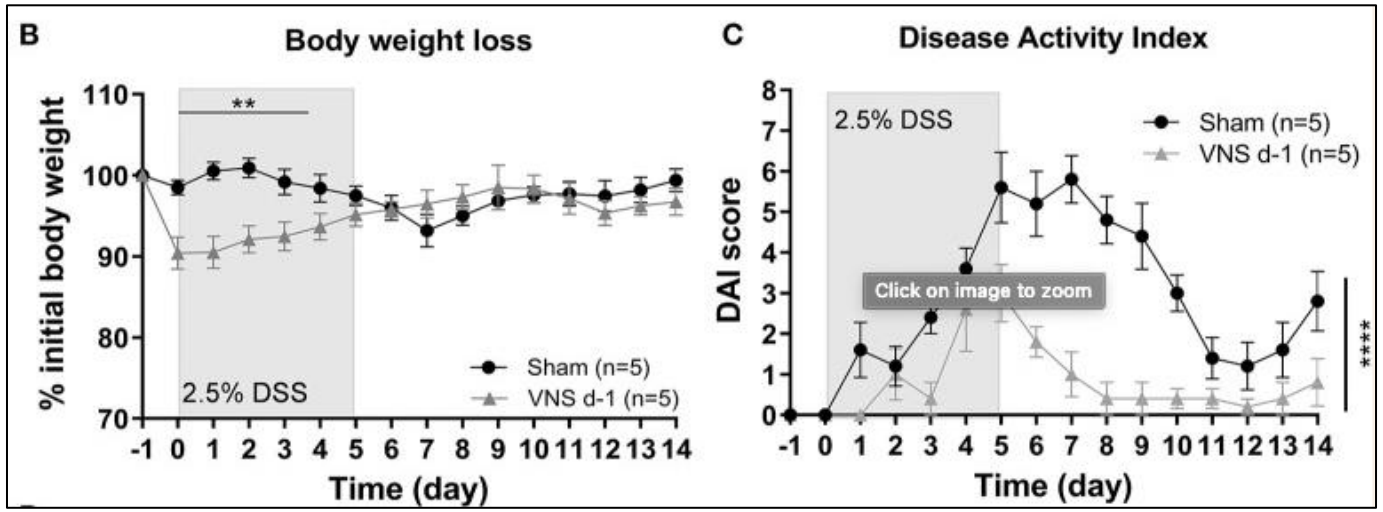
Vagus Nerve Stimulation Attenuates Intestinal Epithelial Tight Junctions Disruption in Endotoxemic Mice Through α7 Nicotinic Acetylcholine Receptors Zhou, Hui; Liang, Hui; Li, Zhi-Feng; Xiang, Hui; Liu, Wei; Li, Jian-Guo. Shock40(2):144-151, August 2013. doi: 10.1097/SHK.0b013e318299e9c0

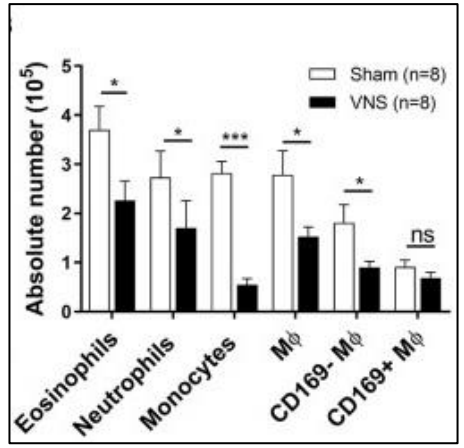
VNS in Inflammatory Bowel Disease

VNS prior to DSS exposure improves colitis by reducing apoptosis and promoting epithelial cell proliferation.

VNS treatment during DSS-induced colitis improves body weight and disease activity.

VNS during DSS-induced colitis controls innate immune cell influx into inflamed colon tissue and dampens the immune response.



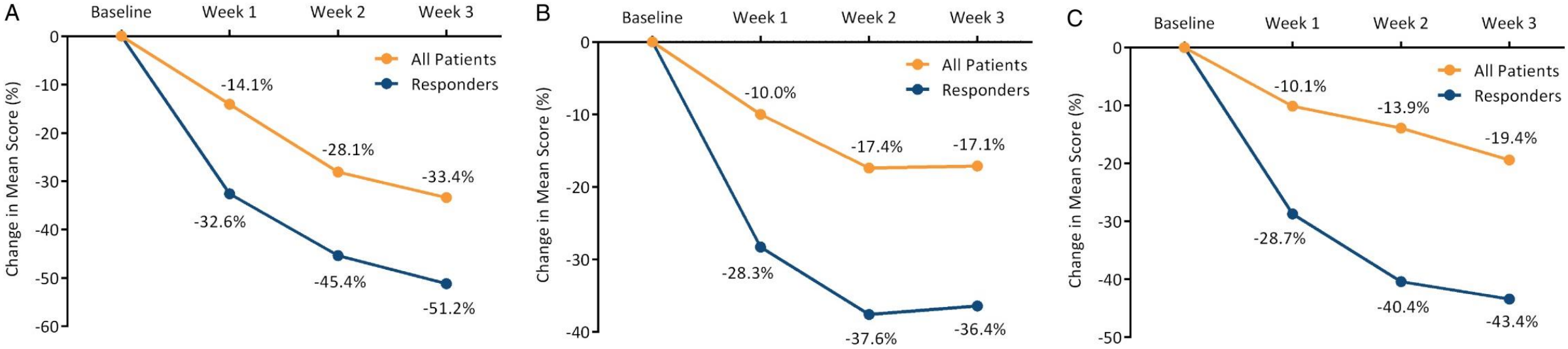


Meroni et al. **Vagus Nerve Stimulation Promotes Epithelial Proliferation and Controls Colon Monocyte Infiltration During DSS-Induced Colitis.** Front Med (Lausanne). 2021 Jul 7;8:694268. doi: 10.3389/fmed.2021.694268.

nVNS in Gastroparesis

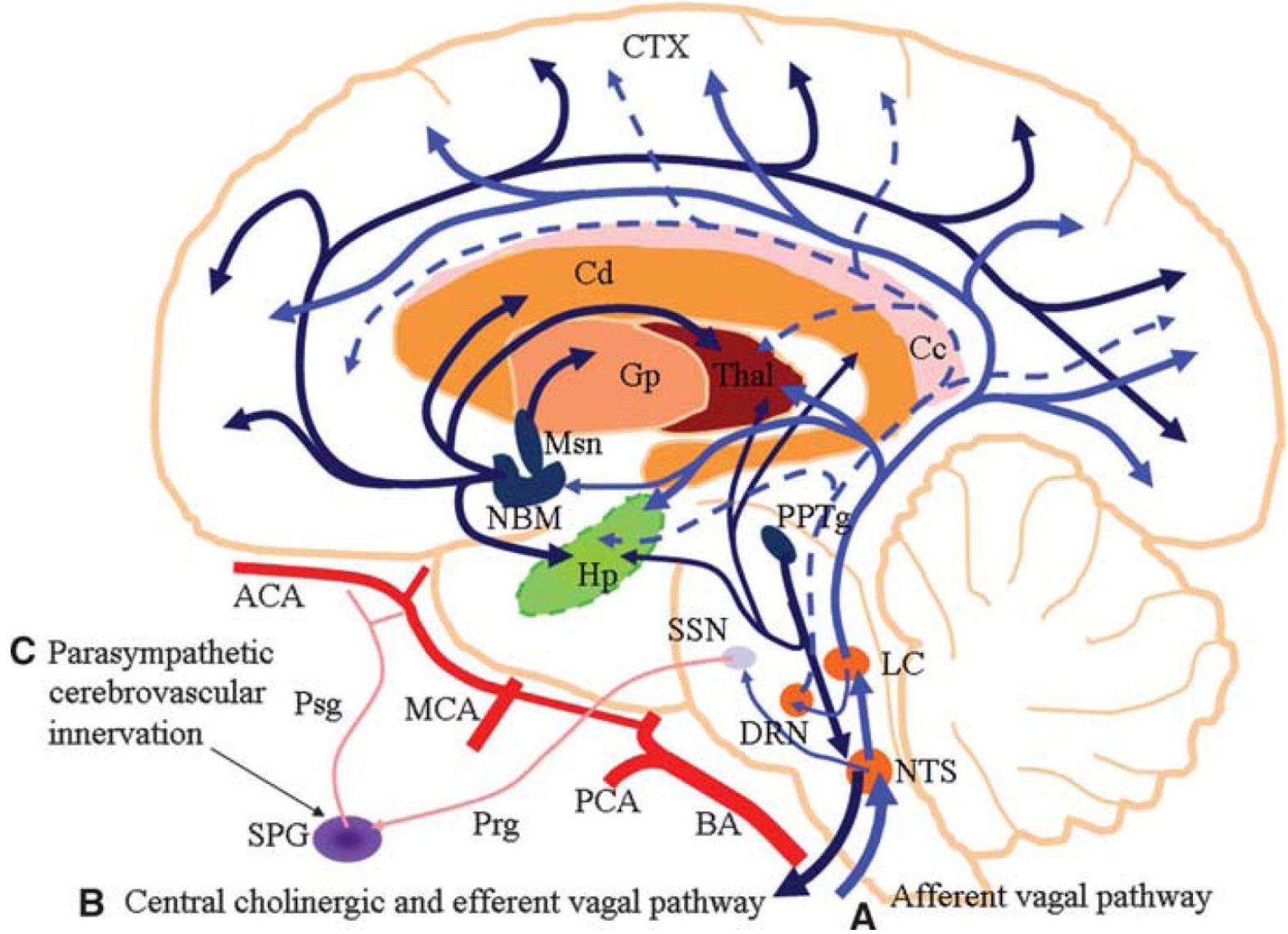
Short-term treatment with nVNS alleviates the cardinal symptoms of gastroparesis in a 3-week proof of concept study

- Improvement in nausea/vomiting (figure A)
- Improvement in post-prandial fullness/early satiety (figure B)
- Improvement in bloating (figure C)



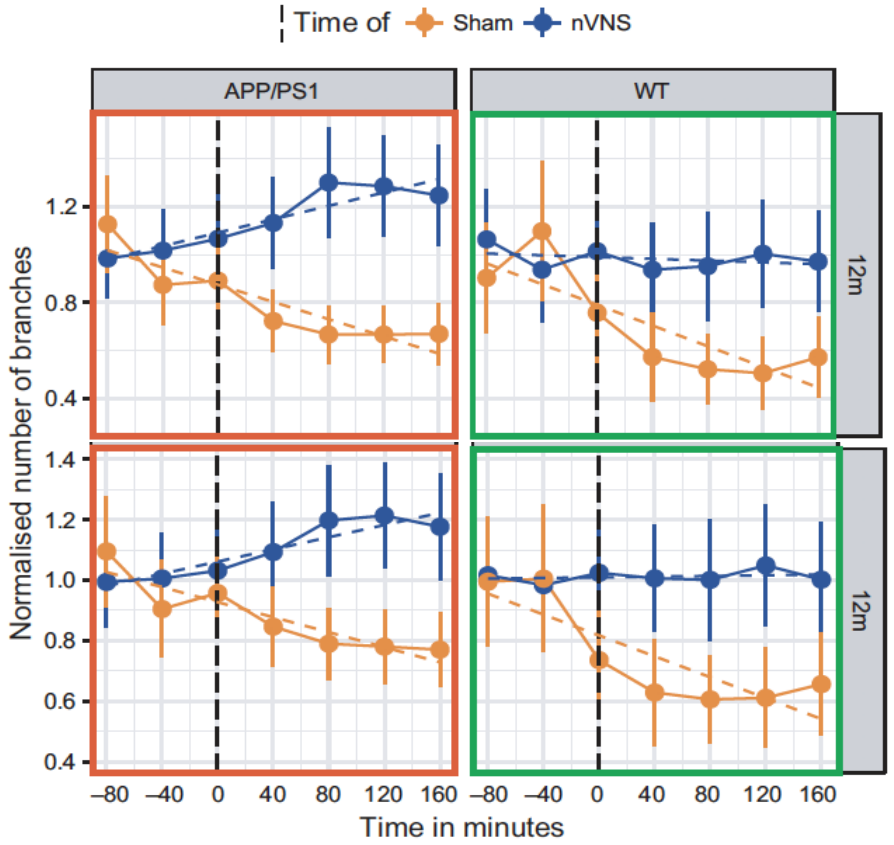
Paulon E et al. **Short-term non-invasive cervical vagus nerve stimulation in patients with drug-refractory gastroparesis**. Frontline Gastroenterol. 2017 Oct;8(4):325-330. doi: 10.1136/flgastro-2017-1008091

Acetylcholine in the CNS



Cheyuo C, Jacob A, Wu R, Zhou M, Coppa GF, Wang P. **The Parasympathetic Nervous System in the Quest for Stroke Therapeutics**. *Journal of Cerebral Blood Flow & Metabolism*. 2011;31(5):1187-1195. doi:10.1038/jcbfm.2011.24

VNS Alters Microglia Morphology



"VNS can promote M2 microglia polarization and inhibit M1 microglia polarization to alleviate brain injury via inhibition of the TLR4/MyD88/NF-κB pathway in microglia"[1]

VNS promotes microglial M2 polarization through upregulating α7nAChR to reduce neuroinflammation … VNS could significantly decrease the concentrations of the pro-inflammatory cytokines and elevate the concentrations of the anti-inflammatory cytokines."[2]

"Our data show for the first time that morphological changes in activated microglia may be directly reversed by nVNS."[3]

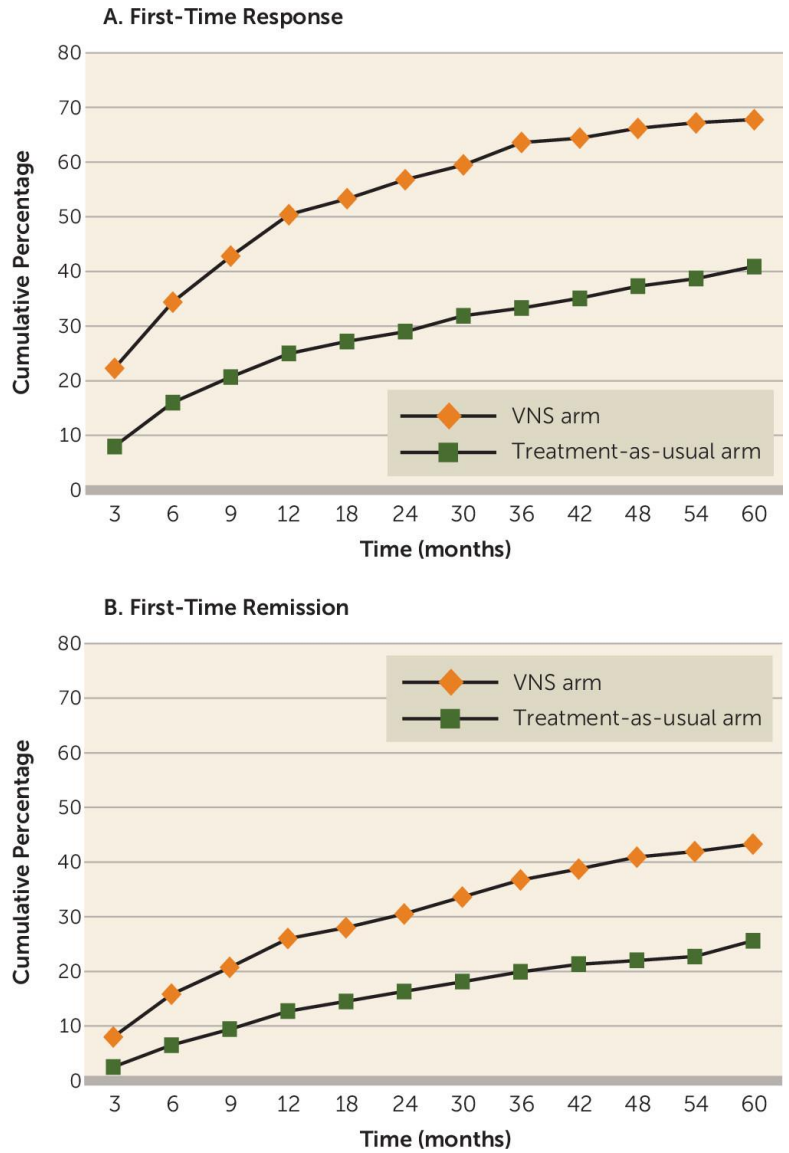
[1]Zhang, et al., **Vagus nerve stimulation promotes the M1-to-M2 transition via inhibition of TLR4/NF-κB in microglia to rescue the reperfusion injury**, *Journal of Stroke and Cerebrovascular Diseases*, Vol. 31, Iss. 9, (2022)
[2]Chen, et al**., Vagus Nerve Stimulation Reduces Neuroinflammation Through Microglia Polarization Regulation to Improve Functional Recovery After Spinal Cord Injury**, *Frontiers in Neuroscience*, Vol. 16, 813472 (2022)
[3]Kaczmarczyk, et al., **Microglia modulation through external vagus nerve stimulation in a murine model of Alzheimer's disease**, Journal of Neurochemistry, Vol. 10, 1111 (2018)

VNS in Major Depression

"The cumulative percentage of first-time responders in the VNS arm was approximately double that in the treatment-as-usual arm at all postbaseline time points."

"Analysis of cumulative remission (based on a MADRS total score ≤9 at any postbaseline visit) demonstrated that over time, patients in the VNS arm were significantly more likely to experience remission than those in the treatment-as-usual arm."

"The patients in the VNS arm had significantly more positive outcomes in response rate, time to response, and duration of response, while also experiencing reduced mortality and suicidality, as evident in both the clinician-rated and the patient-rated scales."



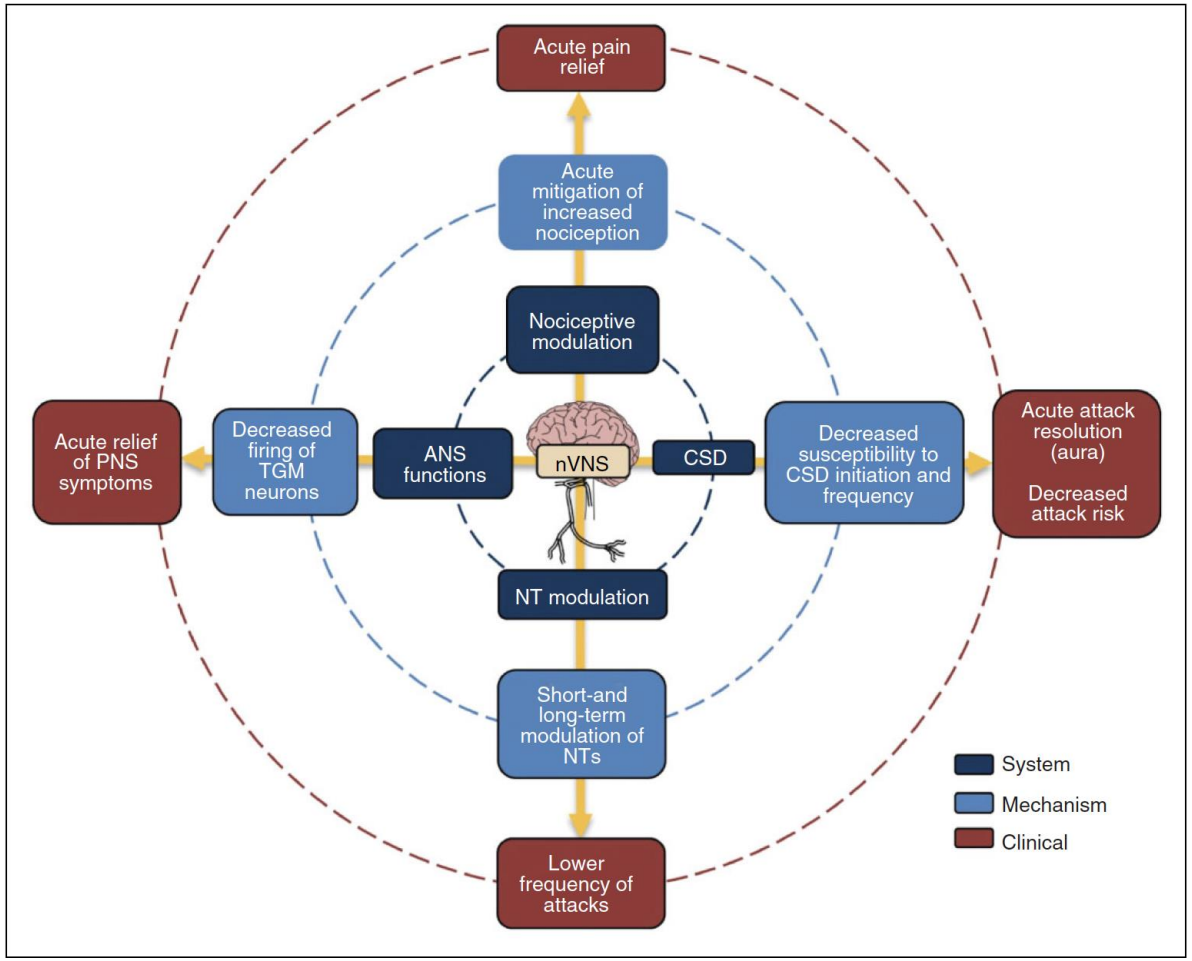
A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. Aaronson et al. American Journal of Psychiatry. Mar 31 2017 https://doi.org/10.1176/appi.ajp.2017.16010034

nVNS in Migraine and Cluster Headache

Cluster headache showed 42% therapeutic gain in acute attacks and 3.9 fewer attacks/week with nVNS

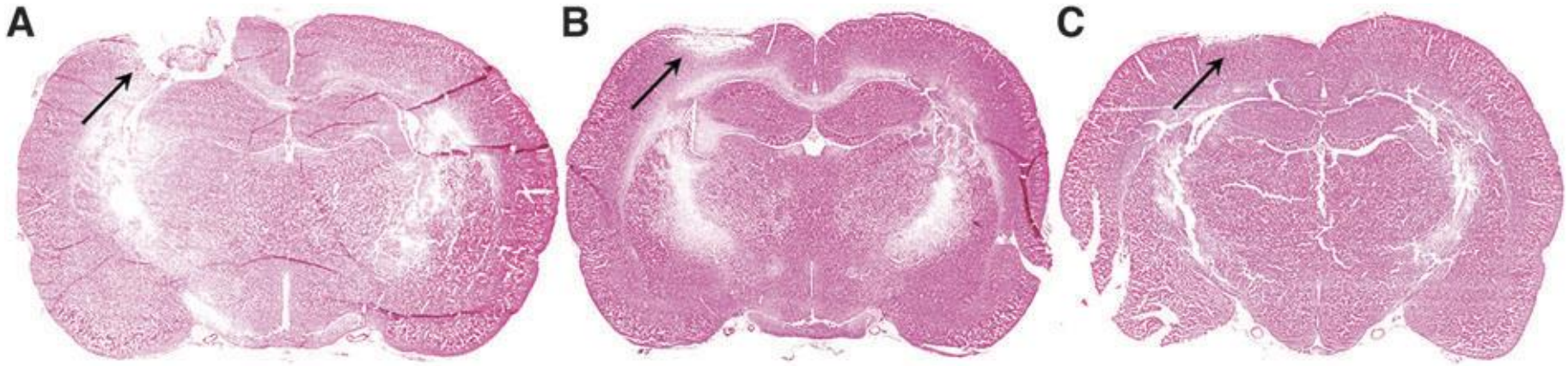
Migraine patients showed 10.7% therapeutic gain after a single therapeutic event, and a significant reduction in migraine days per month of 1.2

Migraine patients had significantly lower use of medication for pain relief with use of nVNS (7.2 to 2.8, and 17.3 to 6.5)



Silberstein SD, et al. **Non-invasive vagus nerve stimulation for primary headache: A clinical update**. Cephalalgia. 2020 Oct;40(12):1370-1384. doi: 10.1177/0333102420941864.

Acute Anti-Inflammatory Effects of nVNS



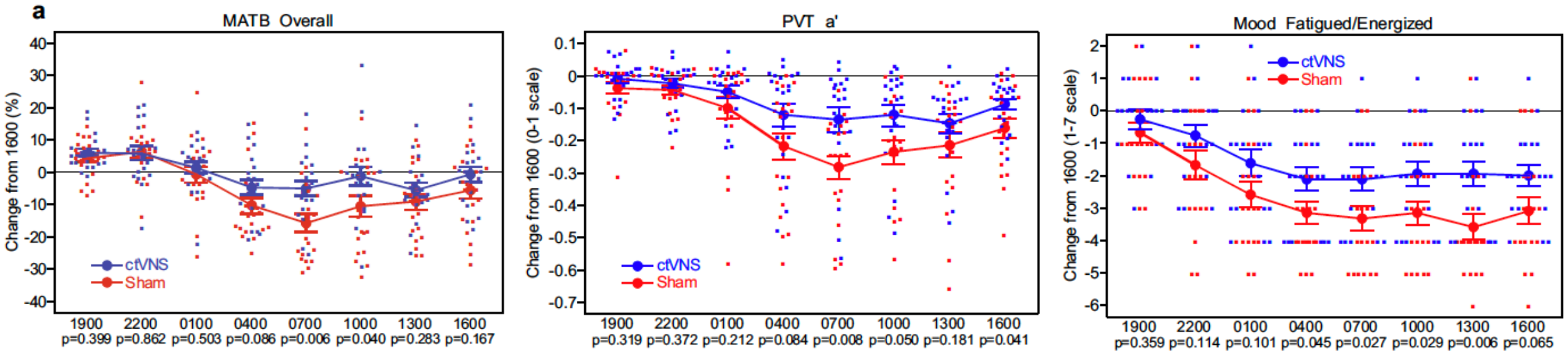
Control | Five 2-min stimulations | Five 2x2-min stimulations

Observed a statistically significant reduction in post-TBI lesion volume among both nVNS groups (2-min and 2 x 2-min).

The brain damage reduction in the higher dose (2 x 2-min) nVNS group was large enough to translate into a significant improvement in the neurobehavioral outcome measures (motor function and anxiety).

Divani, A. et al. **Non-Invasive Vagus Nerve Stimulation Improves Brain Lesion Volume and Neurobehavioral Outcomes in a Rat Model of Traumatic Brain Injury**. *Journal of neurotrauma*, *40*(13-14), 1481–1494. https://doi.org/10.1089/neu.2022.0153

tcVNS Improves Cognitive Performance Under Sleep Deprivation Stress



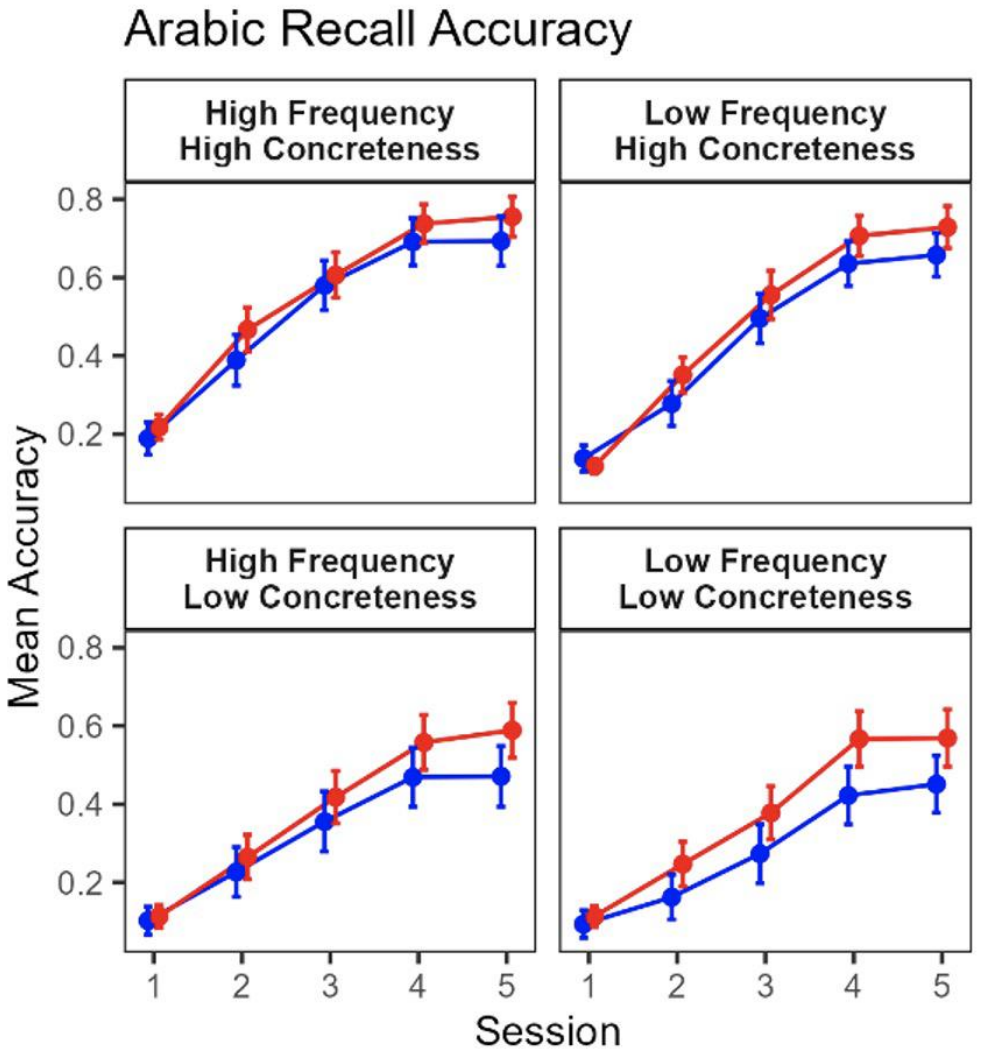
The ctVNS group performed significantly better on arousal, multi-tasking, and reported significantly lower fatigue ratings compared to sham for the duration of the study. ctVNS could be a powerful fatigue countermeasure tool that is easy to administer, long-lasting, and has fewer side-effects compared to common pharmacological interventions.

McIntrre, L.K. et al. (2021). **Cervical transcutaneous vagal nerve stimulation (ctVNS) improves human cognitive performance under sleep deprivation stress.** *Communications biology*, *4*(1), 634. https://doi.org/10.1038/s42003-021-02145-7

tcVNS Improves Language Recall Accuracy

The study showed a signicant positive effect of tcVNS over sham (p=0.025) on language recall, thereby suggesting tcVNS ability to significantly improve the recall of a foreign language compared to sham.

The improvement achieved through tcVNS treatment on days 2-4 was maintained on day 5 demonstrating that the recall advantage that emerged during training was sustained after the completion of treatment.

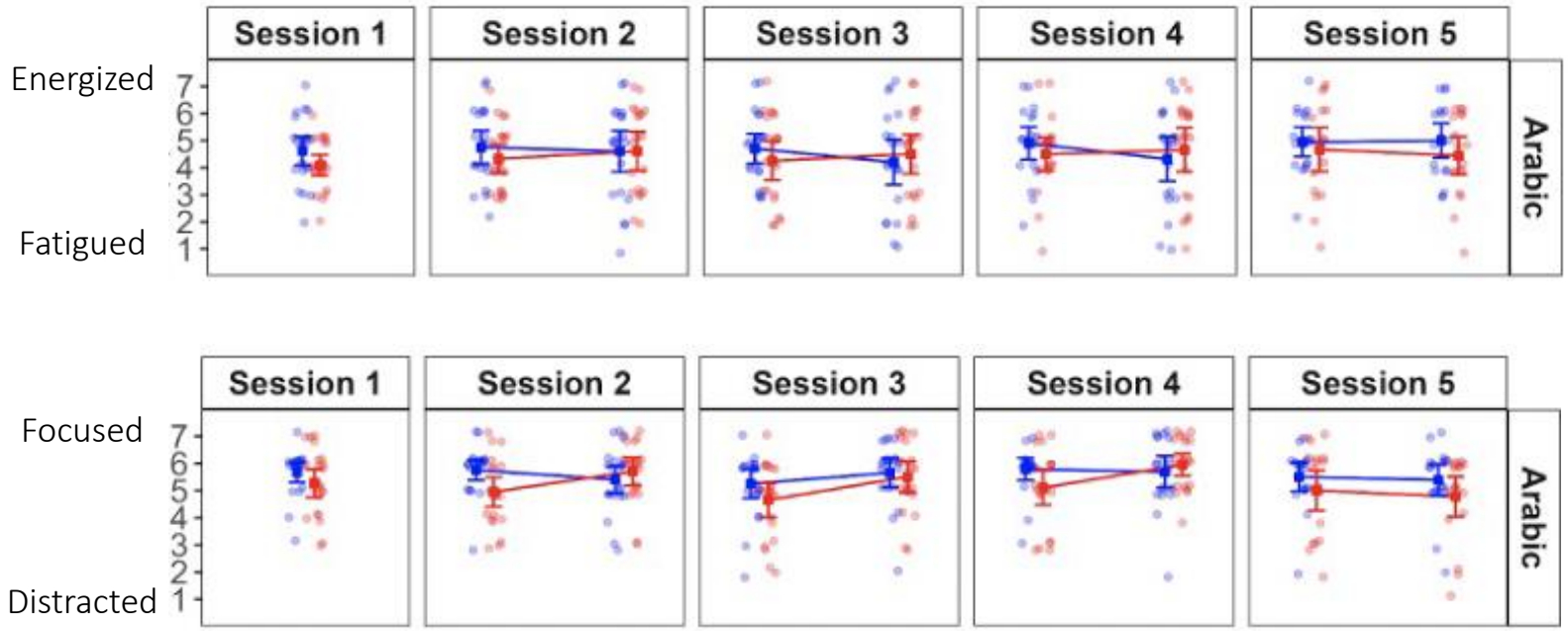


Miyatsu T. et al. **Transcutaneous Cervical Vagus Nerve Stimulation Enhances Second-Language Vocabulary Acquisition while Simultaneously Mitigating Fatigue and Promoting Focus.** Poster Presented at: American Academy of Neurology 75th Annual Meeting; April 2023; Boston MA.

tcVNS promotes Energy and Focus

Equally impressive were the improvements in the subject's energy and mood despite the rigors of the training program.

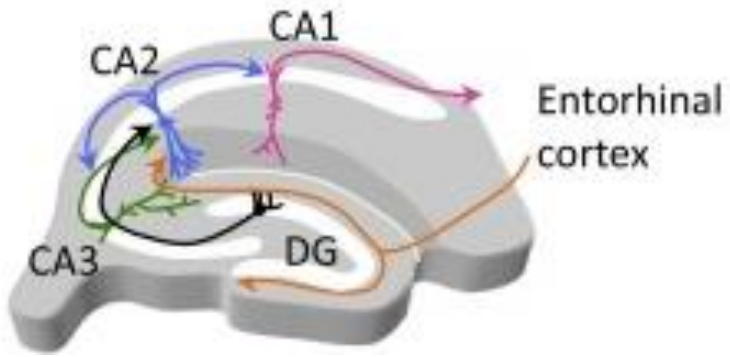
This study compliments our findings that suggest tcVNS could be a valuable tool to enhance war fighter training and resilience in a range of areas.

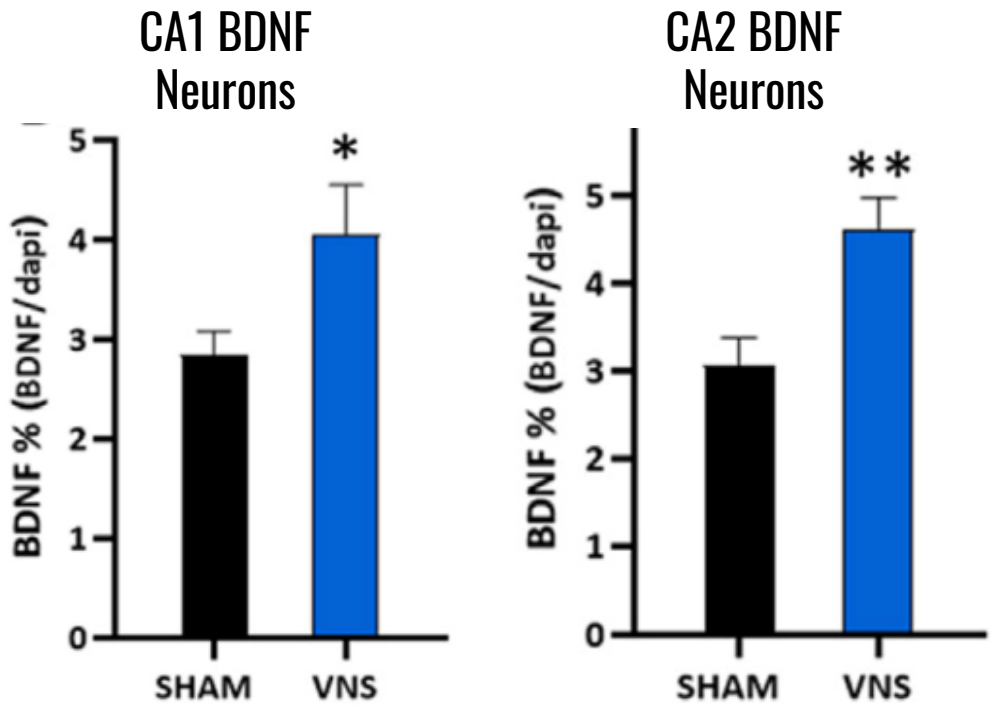


Miyatsu T. et al. **Transcutaneous Cervical Vagus Nerve Stimulation Enhances Second-Language Vocabulary Acquisition while Simultaneously Mitigating Fatigue and Promoting Focus.** Poster Presented at: American Academy of Neurology 75th Annual Meeting; April 2023; Boston MA.

VNS Induced Hippocampal Neuroplasticity and Cognitive Enhancement

BDNF Expression in the CA1 and CA2 regions of the Hippocampus are increased after VNS. IHC staining identified a higher number of BDNF positive cells in the CA1 and CA2 regions of the hippocampus of stimulated rats compared to unstimulated rats.





Olsen, L. K., Moore, R. J., Bechmann, N. A., Ethridge, V. T., Gargas, N. M., Cunningham, S. D., Kuang, Z., Whicker, J. K., Rohan, J. G., & Hatcher-Solis, C. N. (2022). **Vagus nerve stimulation-induced cognitive enhancement: Hippocampal neuroplasticity in healthy male rats.** *Brain stimulation*, *15*(5), 1101–1110. https://doi.org/10.1016/j.brs.2022.08.001

nVNS for Cognitive Enhancement

"[C]hronic VNS produces sustained clinical and cognitive improvements in TRD patients … Vagus nerve stimulation seems a very promising adjunctive therapy for TRD patients with cognitive impairment"[1]

"Immediate recall and delayed recognition scores were significantly improved after 6 weeks of VNS … improved verbal memory performance was seen after 6 weeks of VNS treatment"[2]

"The ctVNS group performed significantly better on arousal, multi-tasking, and reported significantly lower fatigue ratings compared to sham for the duration of the study …"[3]

"Transcutaneous vagus nerve stimulation … may be a potential treatment for improving cognitive dysfunction … The present study showed that tcVNS had beneficial effects on cognitive performance, mainly improving memory and language skills and attention."[4]

[1]Jodoin, et al., Long-term Sustained Cognitive Benefits of Vagus Nerve Stimulation in Refractory Depression, *Journal of ECT*, (2018)
[2]Mertens, et al., The potential of invasive and non-invasive vagus nerve stimulation to improve verbal memory performance in epilepsy patients, *Scientific Reports*, Vol. 12, Art. No. 1984 (2022)
[3]McIntire, et al., Cervical transcutaneous vagal nerve stimulation (ctVNS) improves human cognitive performance under sleep deprivation stress, *Communications Biology*, Vol. 4, 634 (2021)
[4]Zhang, et al., Cognitive function and brain activation before and after transcutaneous cervical vagus nerve stimulation in healthy adults: A concurrent tcVNS-fMRI study, *Frontiers in Psychology*, Vol, 13, 1003411 (2022)

Vagus Nerve Stimulation is NOT A CURE, it is a tool to facilitate a STATE SHIFT!

Thursday 2:45pm – 3:45pm

Vagus Nerve Stimulation - Inflammatory Control to Improved Cognition

Please scan this QR code on you mobile

or tablet device to access the session feedback survey

Vagus Nerve Stimulation - Inflammatory
Control to Improved Cognition