Vagus nerve stimulation may enhance motor learning through modulation of cholinergic basal forebrain

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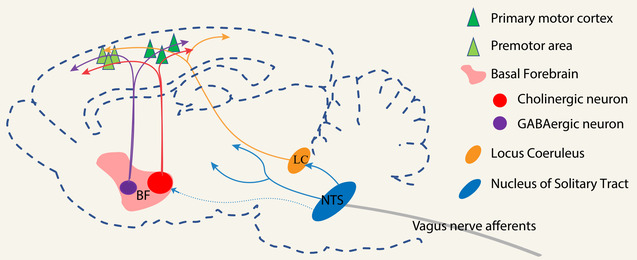
Brain Interfaces • Optics • Electrophysiology

Background

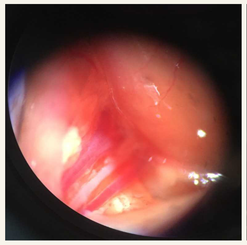
Vagus nerve stimulation (VNS) is currently used to treat drug-resistant epilepsy and depression. There are results indicating that VNS may also be useful in treating a wide range of autoimmune, metabolic, and neurologic disorders. Preclinical studies show that VNS can induce cortical plasticity and improve rehabilitation after stroke of SCI. Albeit showing tremendous potential, the underlying mechanism of VNS remains ambiguous.

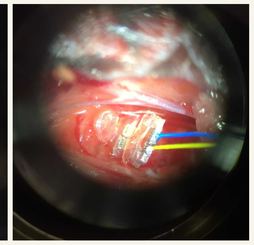
There is evidence to indicate that VNS activates locus coreleus, an important neuromodulatory center. Futher, recent evidence suggest that basal forebrain may mediate VNS-induced cortical map plasticity.

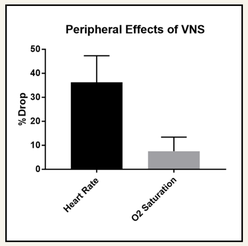


We aim to tease apart the specific circuitry that underlies VNS-induced cortical plasticity in a healthy mouse model. Identifying these specific anatomic pathways will help guide future research on the use of VNS in patients with motor deficits and may illuminate the mechanims of other therapeutic benefits.

Methods



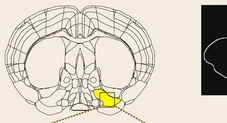




- Model: We used a healthy mouse model to explore VNS neural circuitry
- VNS: mice were implanted with a stimulating cuff electrode and the nerve was stimulated, which was confirmed by heart rate drop and oxygen saturation drop
- Immunohistochemistry: using a cFos-eGFP mouse line, we either preformed VNS, as described above, or kept a mouse under anesthesia for a comparable amount of time. Then, we stained basal forebrain with an anti-ChAT antibody and an anti-GFP antibody and stained locus coeruleus with an anti-tyrosine hydroxylase (TH) antibody and an anti-GFP antibody
- Electrophysiology: using a ChAT-Chr2 mouse line, which expressed channel rhodopsin in cholinergic neurons only, we implanted an optical fiber and recording electrode in Basal Forebrain. Then, we measured the response of both cholinergic and non-cholinergic cells to VNS

Histology

Cholinergic Basal Forebrain



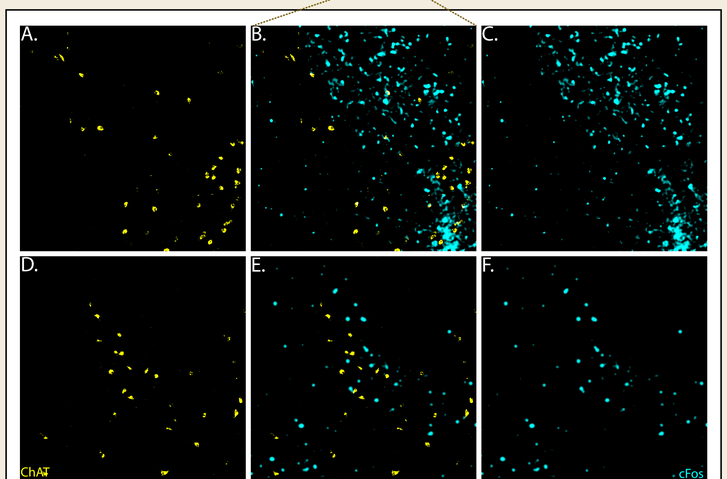
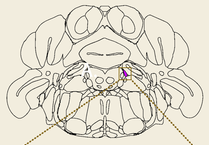


Figure 2: A/D) ChAT expression in BF following acute VNS (A) or no surgery (D). B/E) ChAT and cFos-driven GFP expression in BF following acute VNS (B) or no surgery (E). C/F) cFos-driven GFP expression following acute VNS (C) or no surgery (F).

Noradrenergic Locus Coeruleus



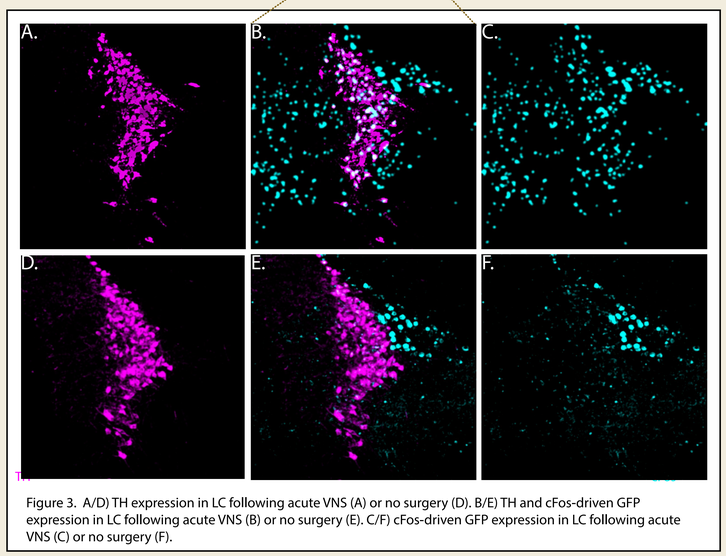
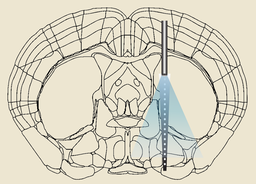


Figure 3. A/D) TH expression in LC following acute VNS (A) or no surgery (D). B/E) TH and cFos-driven GFP expression in LC following acute VNS (B) or no surgery (E). C/F) cFos-driven GFP expression in LC following acute VNS (C) or no surgery (F).

Electrophysiology



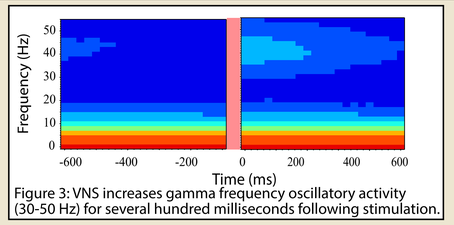


Figure 3: VNS increases gamma frequency oscillatory activity (30-50 Hz) for several hundred milliseconds following stimulation.

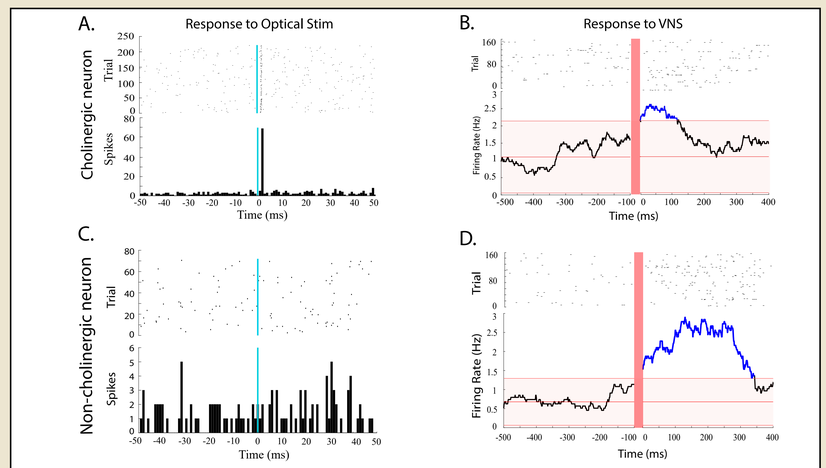


Figure 4: A/B) Cholinergic neurons respond to light (A) and a sample of them respond to VNS (B). C/D) Non-cholinergic neurons do not respond to light (C), but a sample of them respond to VNS (D).

Conclusions and Future Work

These results indicate that the enhancement of motor learning may be mediated by the excitation of basal forebrain, a neuromodulatory nuclei that widely projects to cortex. The projections from vagus nerve to the basal forebrain are still not fully defined, and may be mediated through locus coeruleus. To further dissect this, we are working on employing tracing experiments using a retrograde tracer in basal forebrain and an anterograde tracer in to the nerve itself and in to Nucleus of Solitary Tract, where vagal affarents terminate.

We have begun by doing a pilot AAV1 viral tracing injections (results below) in vagus nerve show tracing to NTS. Future viral injections will be with polysynaptic viral constructs.

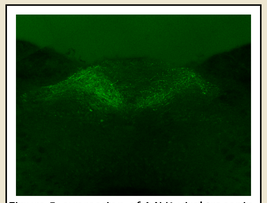
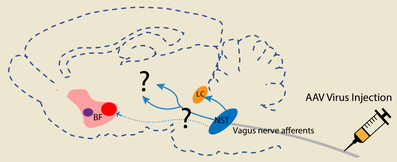


Figure 5: expression of AAV1 viral tracer in NTS after injection into the vagus nerve



Acknowledgements

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