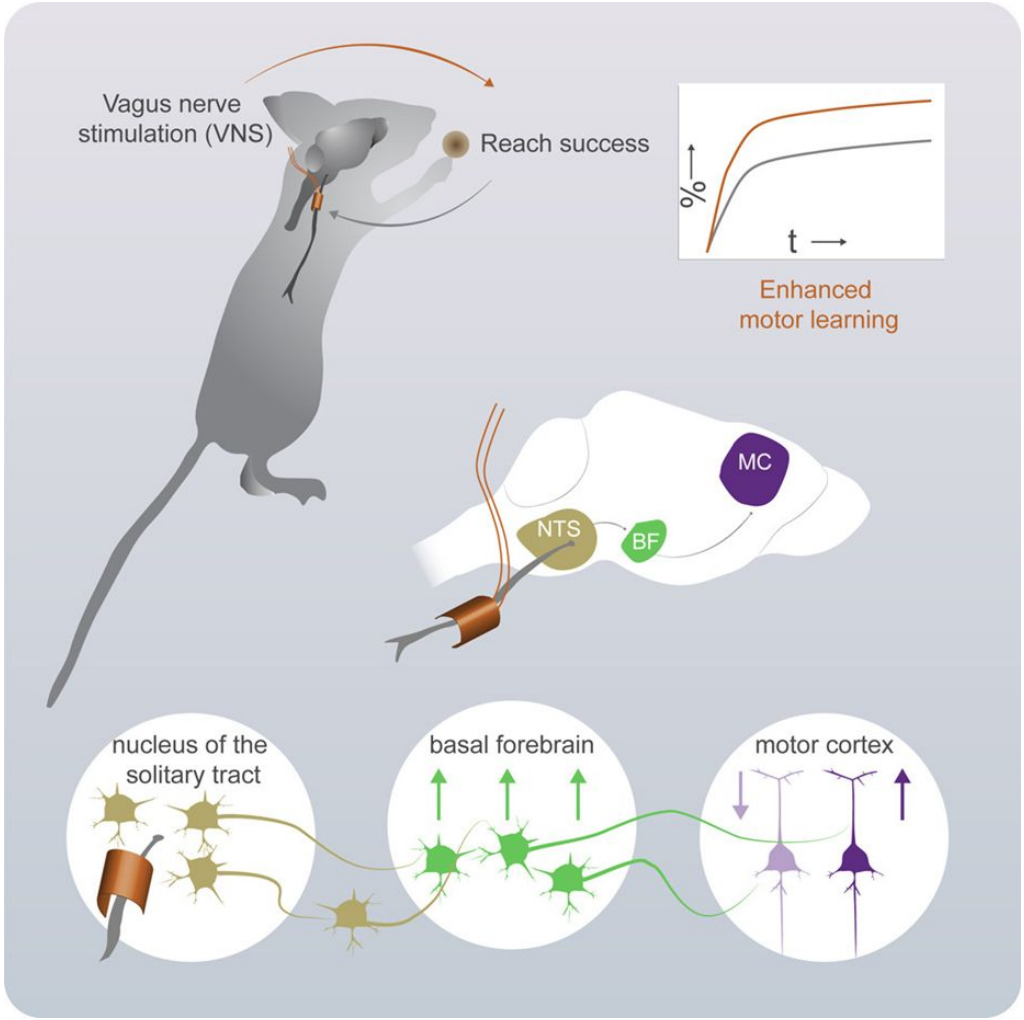
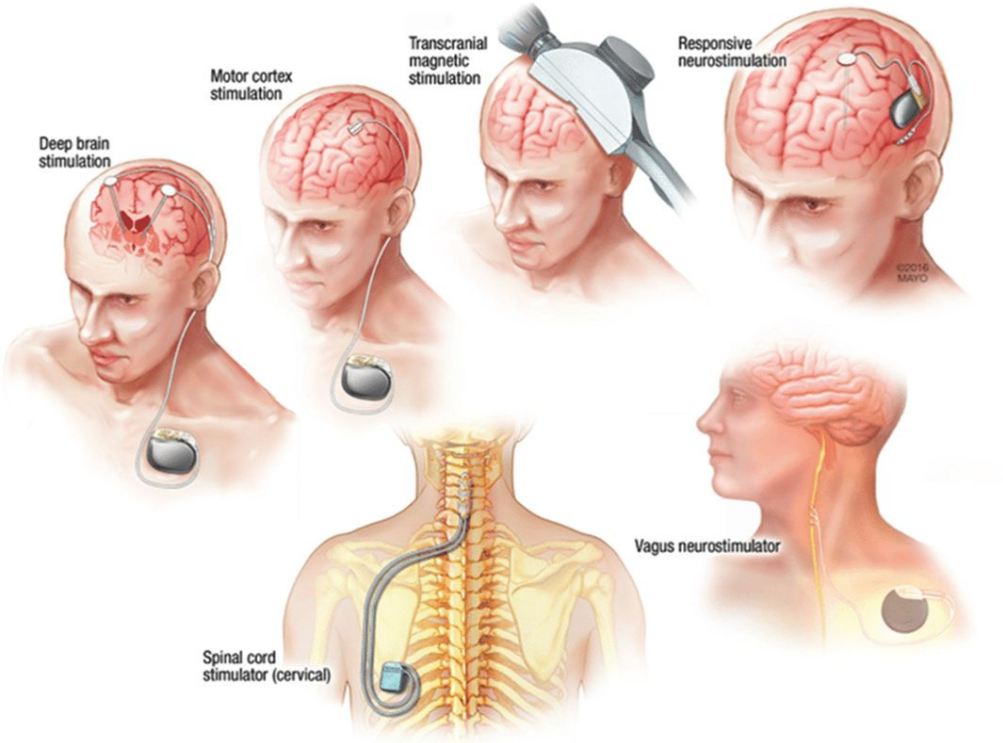


Section: Bowles et al. 2022

Background Recap:

Section W4

Neurostimulation devices can alter CNS activity across broad timescales



DBS for Parkinson's disease and essential tremor.

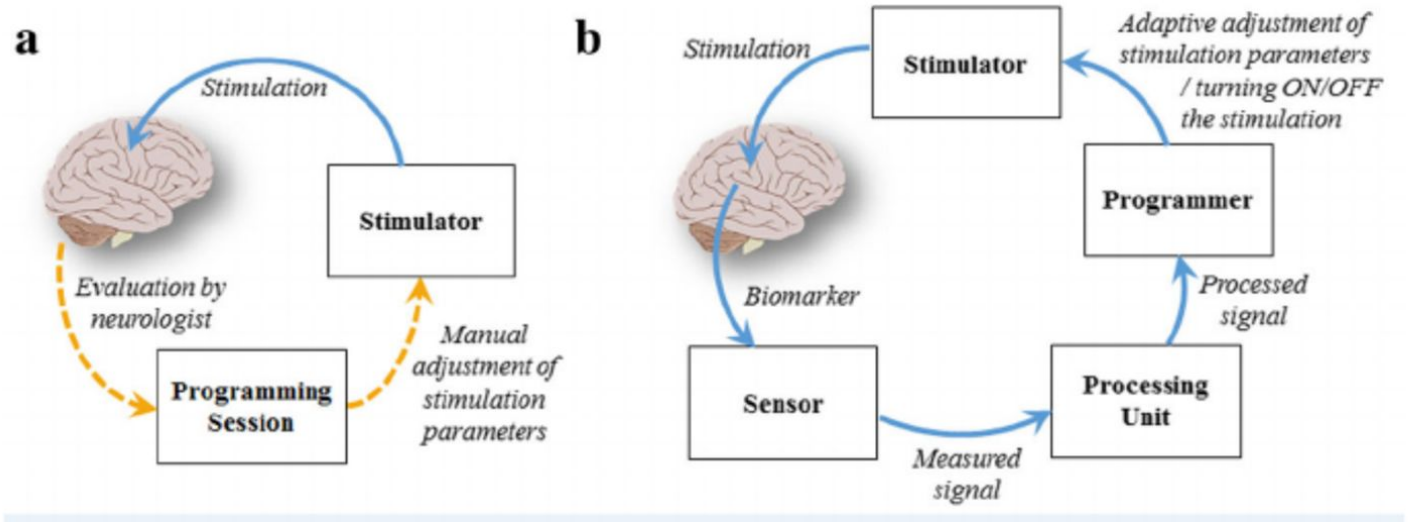
SCS for chronic pain.

TMS for depression, OCD, and migraines.

Closed-loop stimulation may increase neurostimulation efficacy and reduce side effects

Open-loop stimulation

Closed-loop stimulation



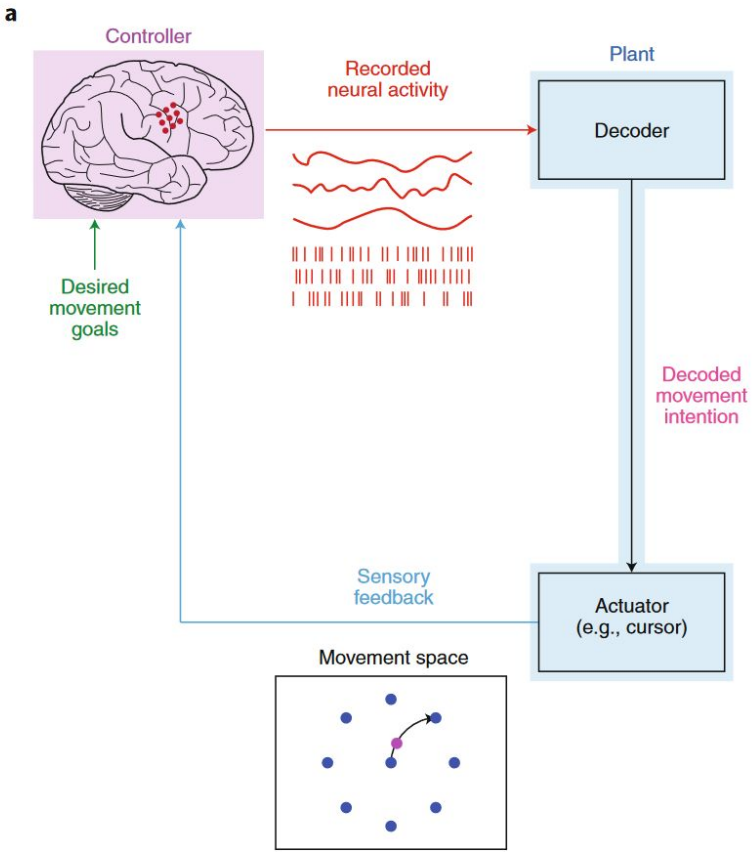
How can we develop relevant closed loop stimulation paradigms?

Closed-loop paradigms can be targeted towards many types of triggers:

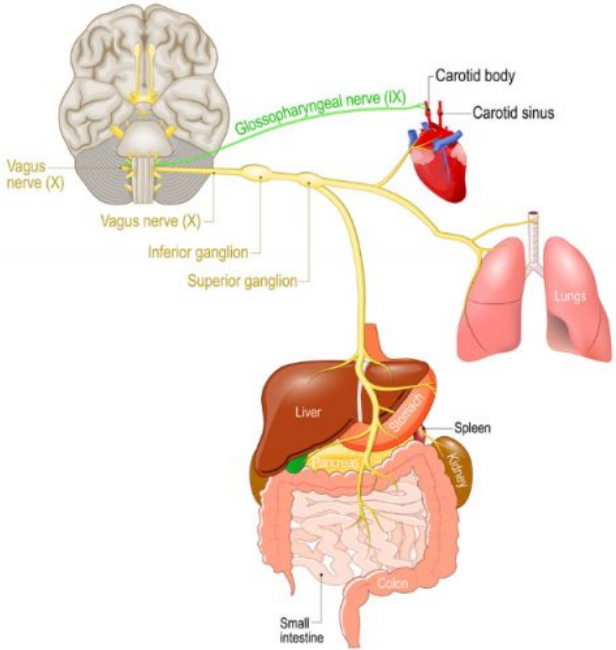
Environment triggers - tones, or task outcomes

Biomechanical triggers - certain movements, or tactile sensations

Physiological triggers - neural activity, muscle activity, hormones

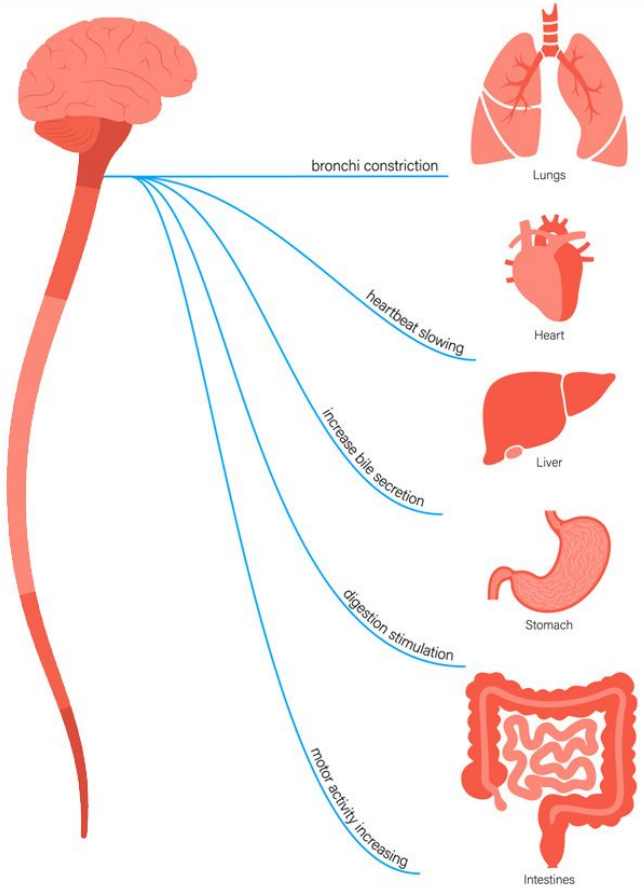


Vagus nerve function and anatomy

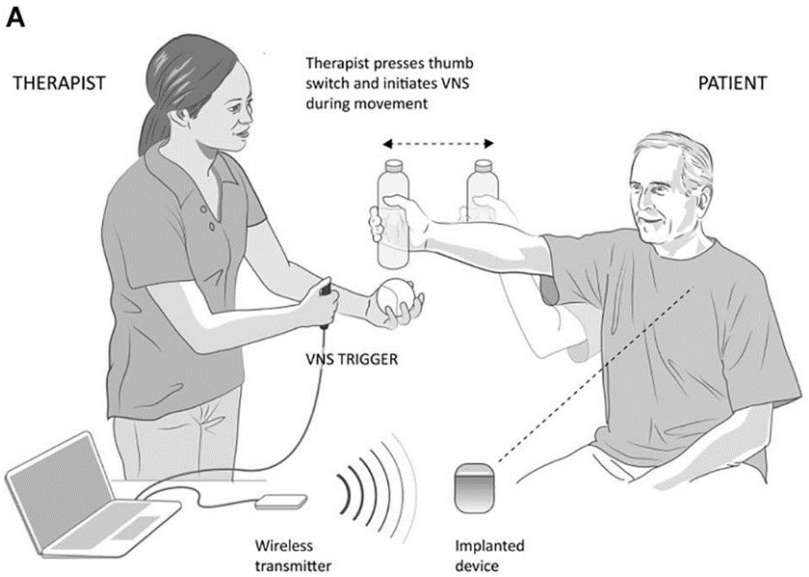


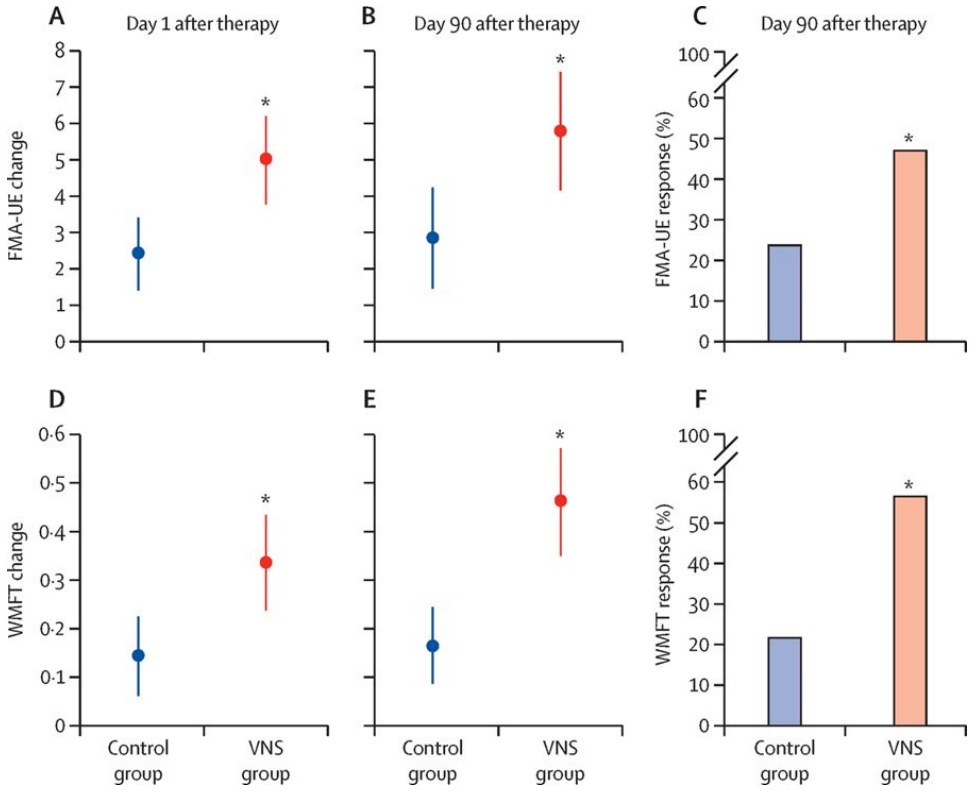
The VN innervates most visceral organs

Stimulating the VN activates the parasympathetic nervous system



VNS enhances stroke rehabilitation



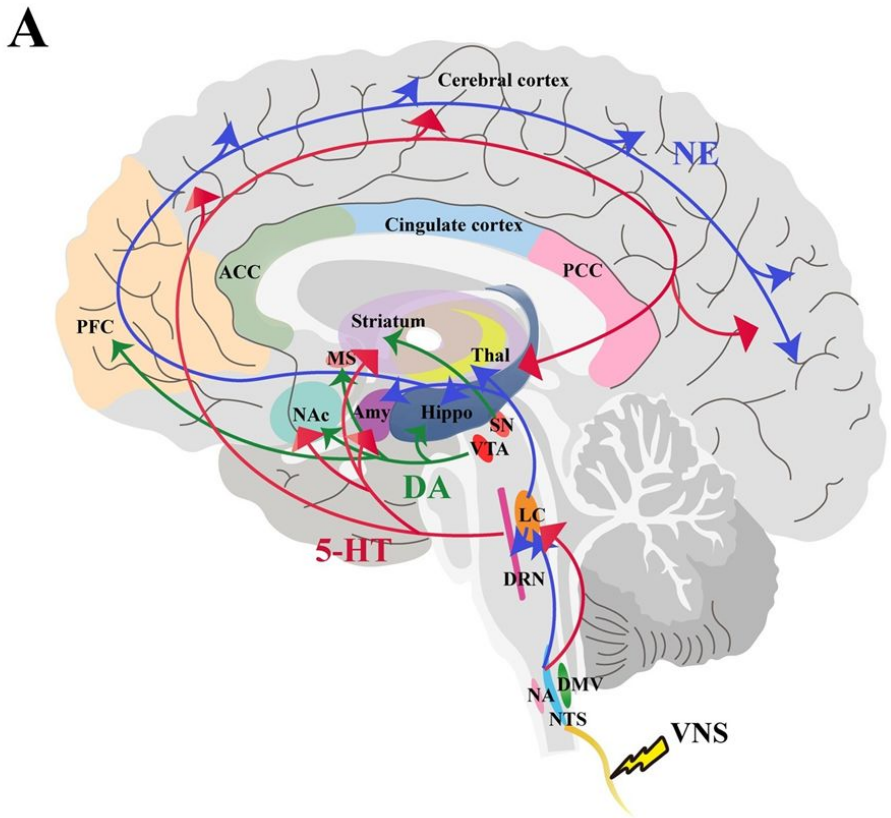


What are the mechanisms that underlie VNS-enhanced motor rehabilitation?

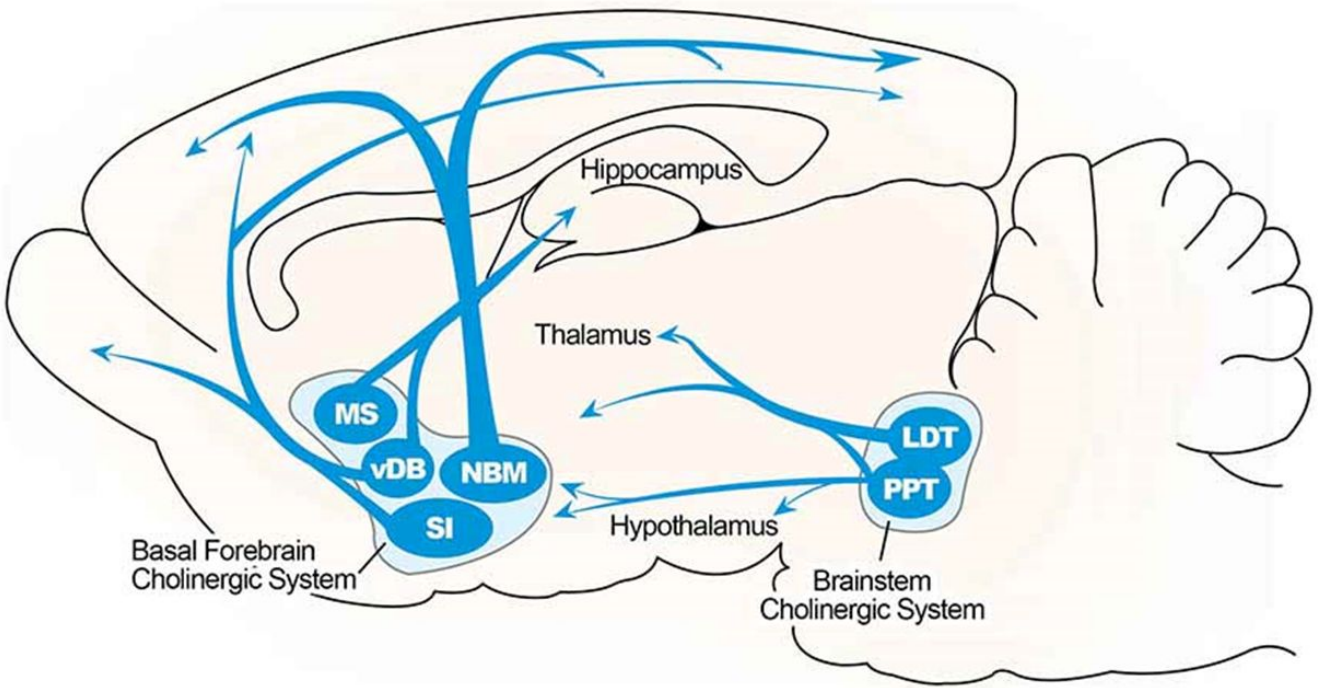
VNS activates multiple neuromodulatory systems

VNS is a “messy” stimulus:

- Serotonergic, dopaminergic, noradrenergic, and cholinergic systems are all activated.

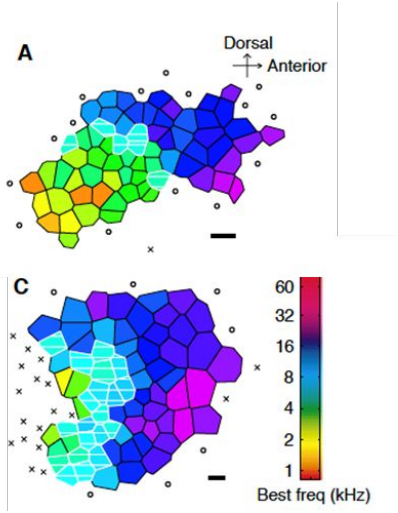


The cholinergic neuromodulatory system

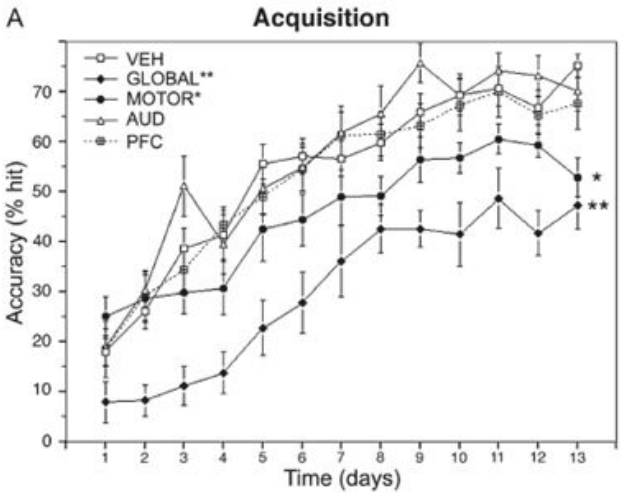


Cholinergic neuromodulation is closely linked with learning and plasticity

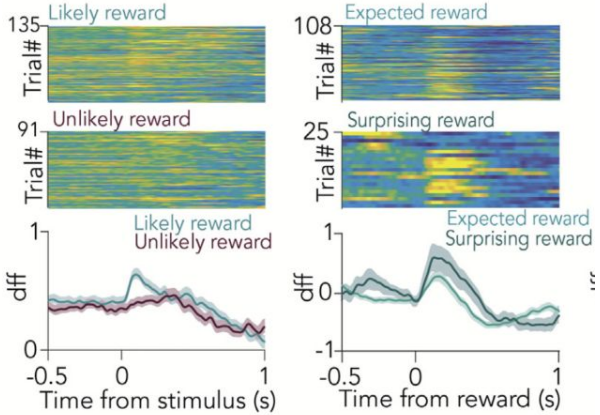
Cholinergic neuromodulation is a strong candidate for mediating VNS effects



Cholinergic stim. enhances plasticity



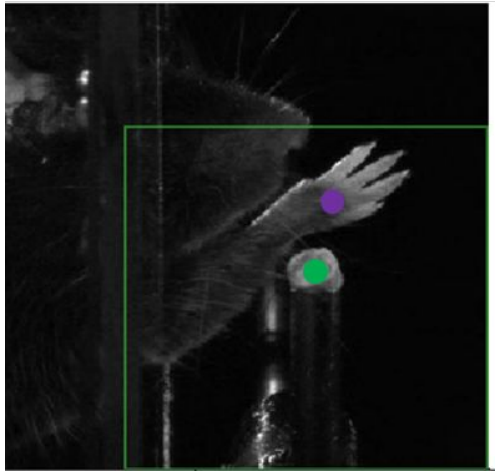
Cholinergic activity impacts motor learning

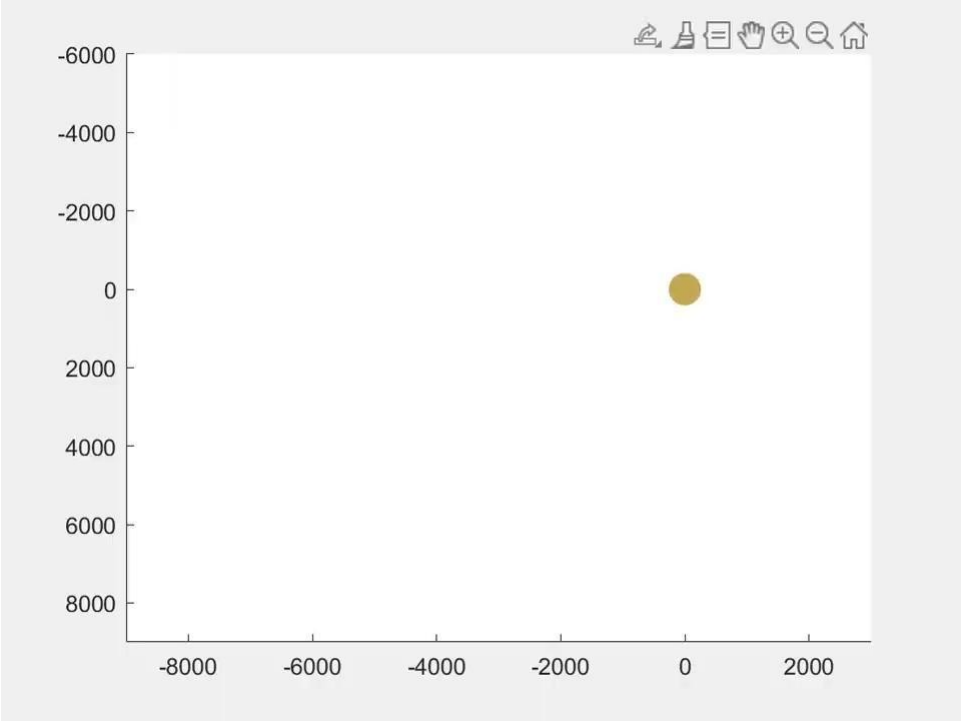


Cholinergic neurons encode cues and outcomes

Quantifying motor learning: expert reaches

Orientation

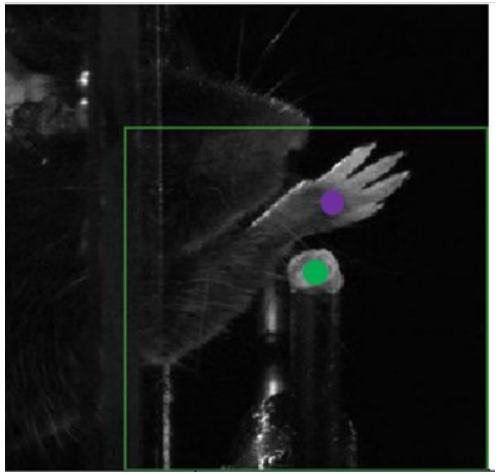


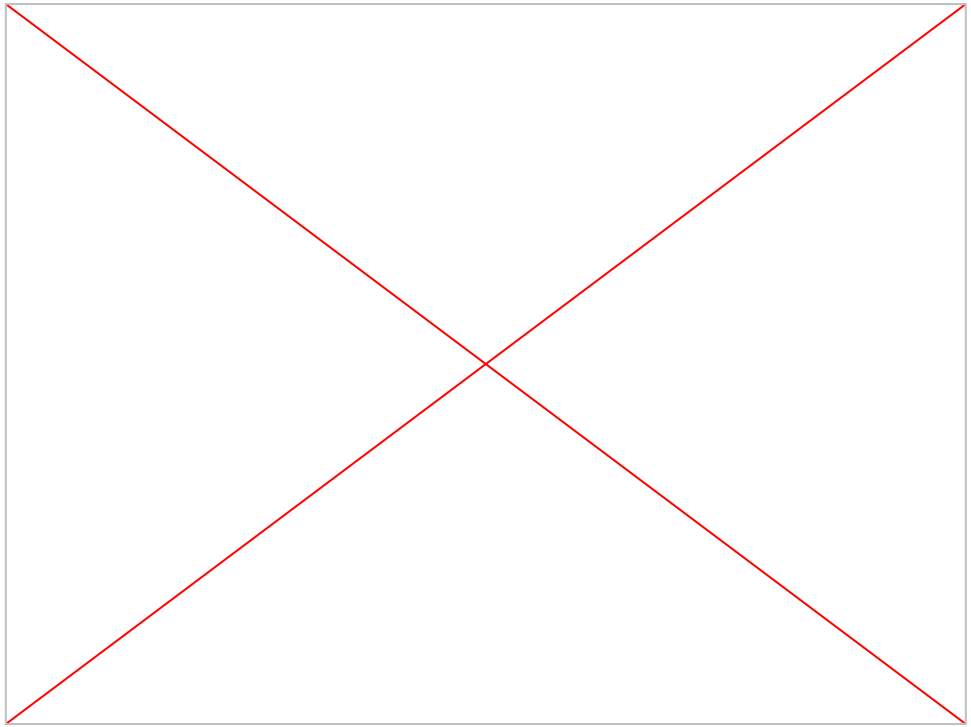


Success Reaches
Expert Template
Expert Reach
Non-Expert Reach

Quantifying motor learning: expert reaches

Orientation





Success Reaches
Expert Template
Expert Reach
Non-Expert Reach

What is the optimal closed-loop stimulation for VNS to enhance motor learning?

What are the endogenous systems that underlie VNS-enhanced motor rehabilitation?

Section Paper:

Vagus nerve stimulation drives selective circuit modulation through cholinergic reinforcement

Spencer Bowles [4] • Jordan Hickman [4] • Xiaoyu Peng [4] • ... Kayden Washington • Dane Donegan • Cristin G. Welle [5] • Show all authors • Show footnotes

Open Archive • Published: July 19, 2022 • DOI: https://doi.org/10.1016/j.neuron.2022.06.017 •

Vagus nerve stimulation (VNS) is a neuromodulation therapy for a broad and expanding set of neurologic conditions. However, **the mechanism through which VNS influences central nervous system circuitry is not well described, limiting therapeutic optimization**. VNS leads to widespread brain activation, but the effects on behavior are remarkably specific, indicating plasticity unique to behaviorally engaged neural circuits. To understand how VNS can lead to specific circuit modulation, we leveraged genetic tools including optogenetics and *in vivo* calcium imaging in mice learning a skilled reach task. We find that **VNS enhances skilled motor learning in healthy animals via a cholinergic reinforcement mechanism**, producing a rapid consolidation of an expert reach trajectory. **In primary motor cortex (M1), VNS drives precise temporal modulation of neurons that respond to behavioral outcome**. This suggests that VNS may accelerate motor refinement in M1 via cholinergic signaling, opening new avenues for optimizing VNS to target specific disease-relevant circuitry.

Figure 1. VNS modulates forelimb reach learning and requires temporally specific stimulation

What are the mechanisms of VNS influence on motor learning that the authors want to test?

- *Arousal and widespread cortical excitation: pseudo-random intervals.*
- *Spike-time dependent plasticity/attention: initiation of a subset of reach movements.*
- *Outcome reinforcement: after successful reach completion.*

What behavioral observation can they make (D:J)?

Paired VNS can enhance motor learning when happening after successful reaches, meaning that the mechanism is contingent on successful outcomes, likely ***reinforcement.***

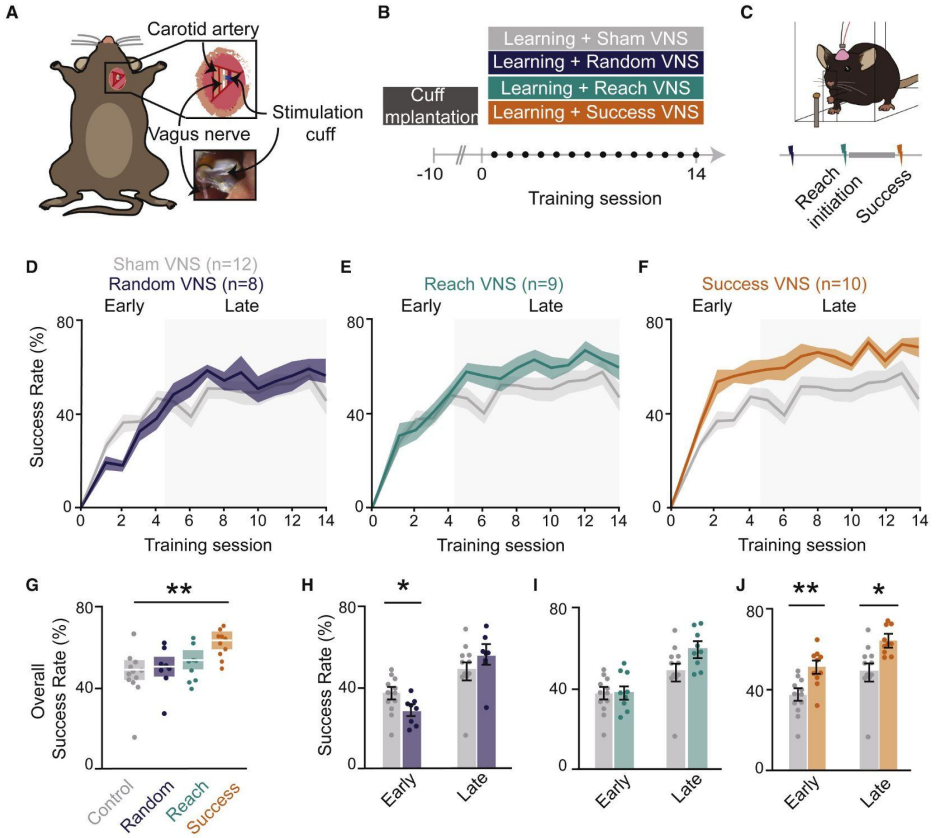


Figure 2. VNS improves success rate within sessions and in learned mouse during rehearsal of forelimb reach task

What are the central questions of the figure?

Are stimulation effects transient or persistent? Does this change base on stimulation type?

Panels (C:I): Which stimulation produces sustained effects?

Outcome-paired VNS has effects that last outside of stimulation.

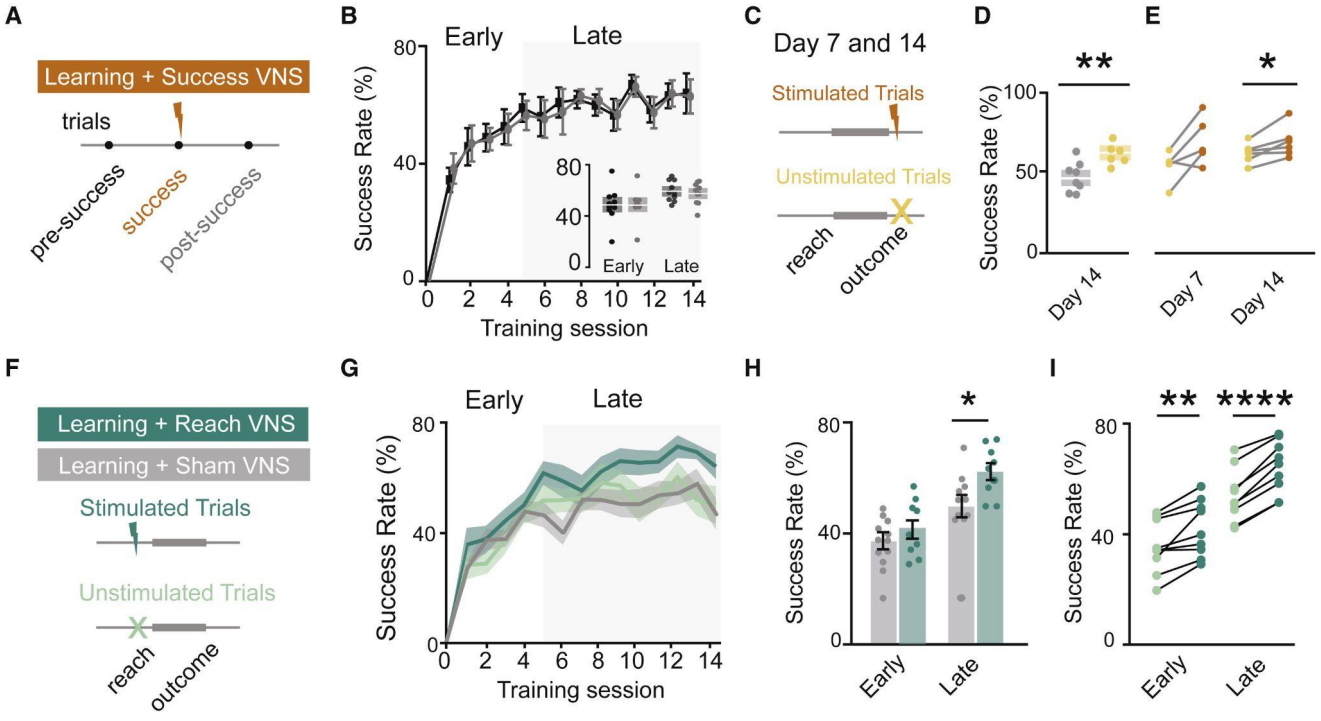


Figure 3. VNS drives BF neural activity in anesthetized and awake mice

Why are they looking at the basal ganglia?

*Area of the brains which project cholinergic neurons **to cortex** (because this behavior uses motor cortex).*

How do they show VNS modulation?

Significant change in z-scored firing rate between stimulation and baseline.

From what we know from previous weeks, what would you do next?

Opto-tagging of cholinergic neurons to identify them in the BG.

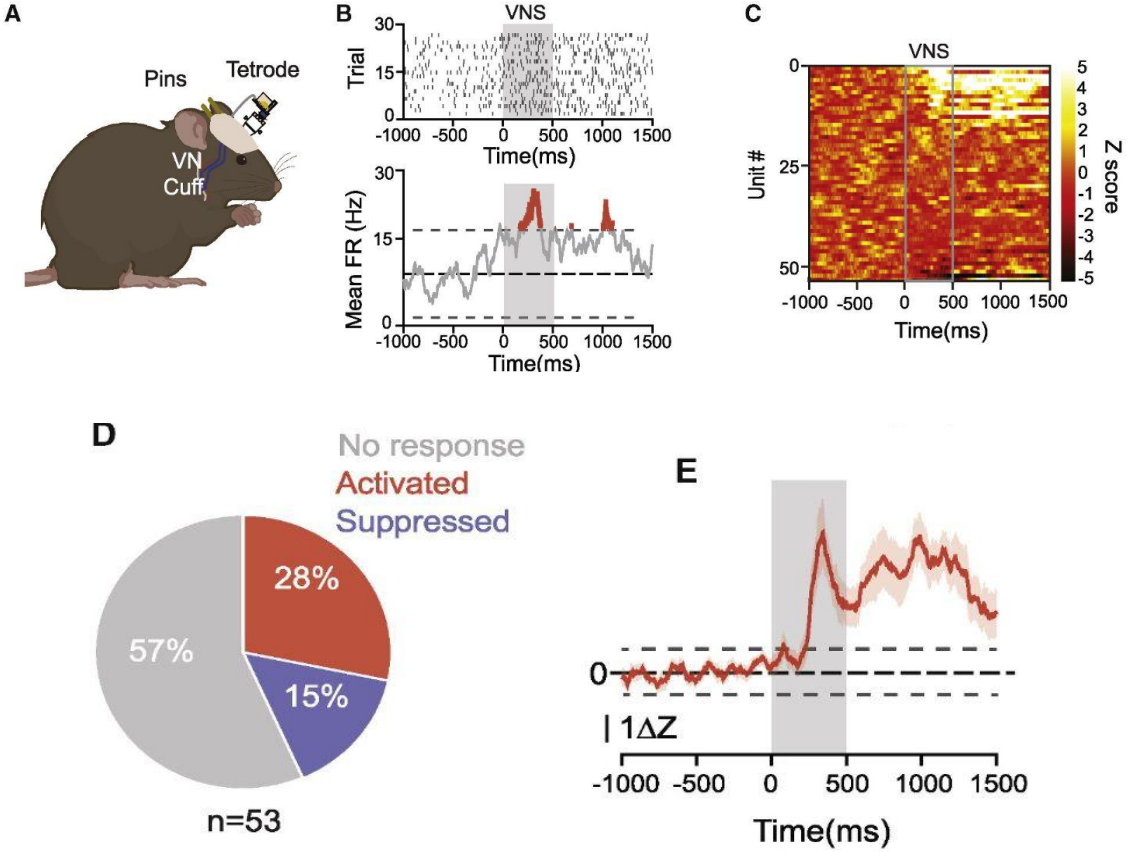
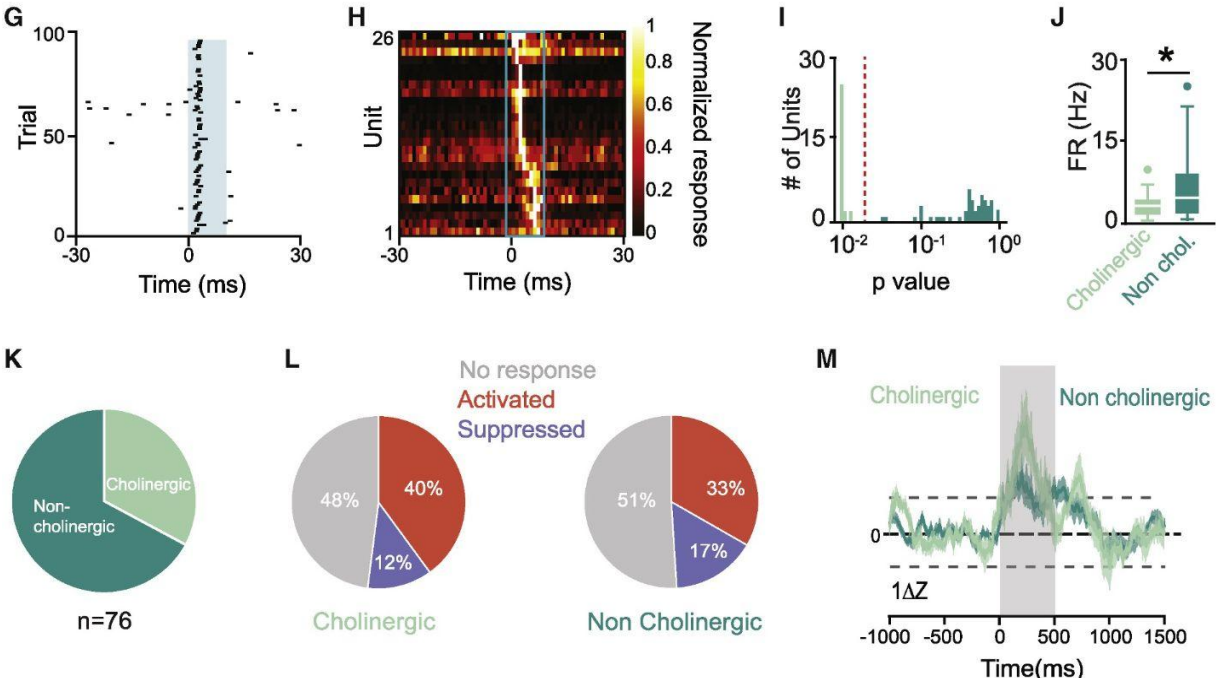
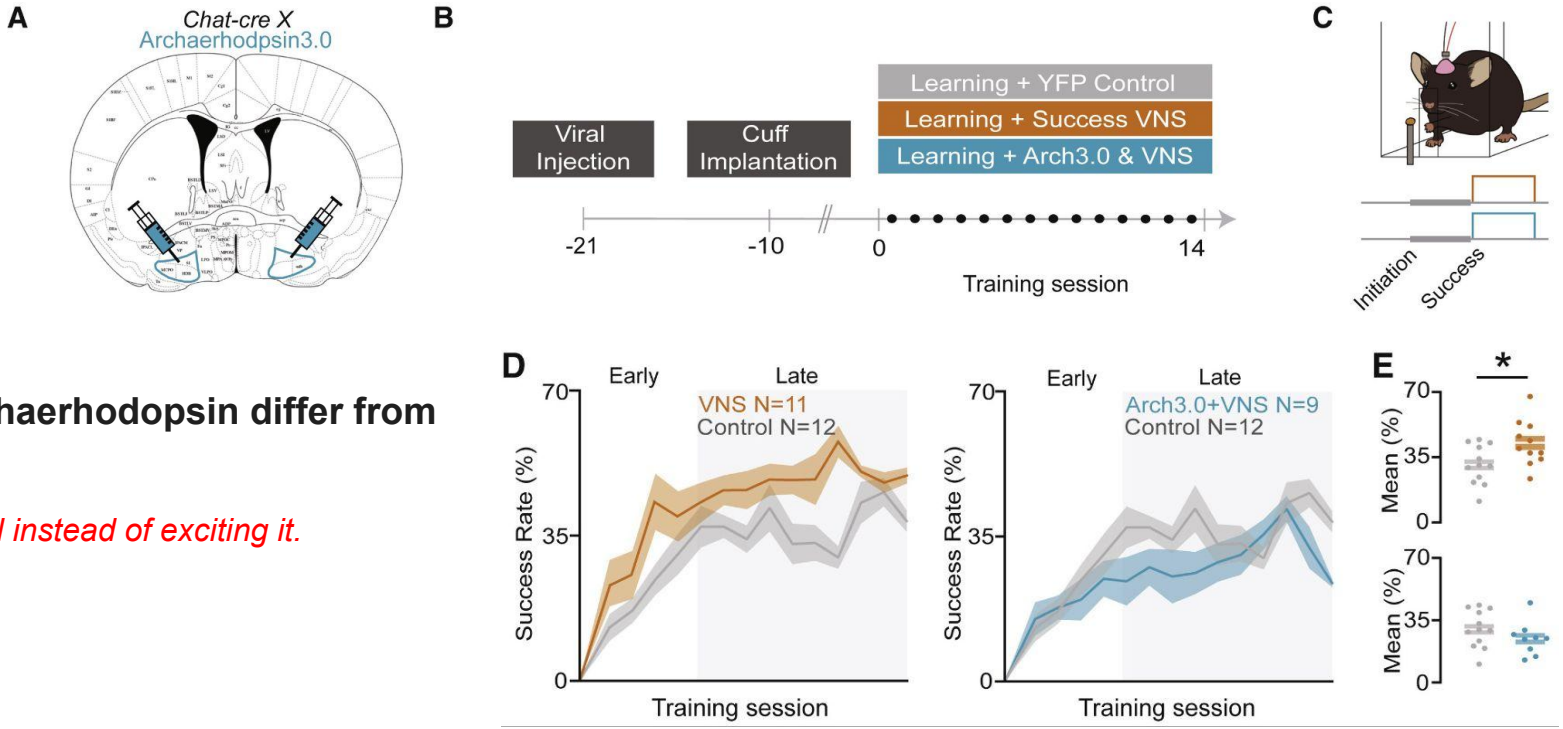


Figure 3. VNS drives BF neural activity in anesthetized and awake mice



So now we know that VNS can drive BF cholinergic neurons. But is it related to enhancing motor control?

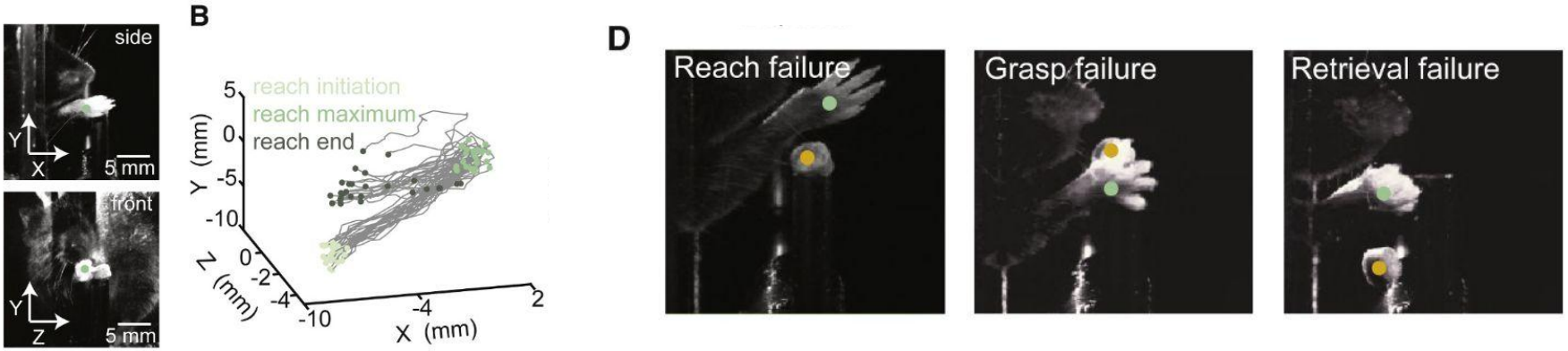
Figure 4. Success-paired VNS motor learning enhancement requires cholinergic neuromodulation



How does Archaerhodopsin differ from ChR2?

Arch inhibits a cell instead of exciting it.

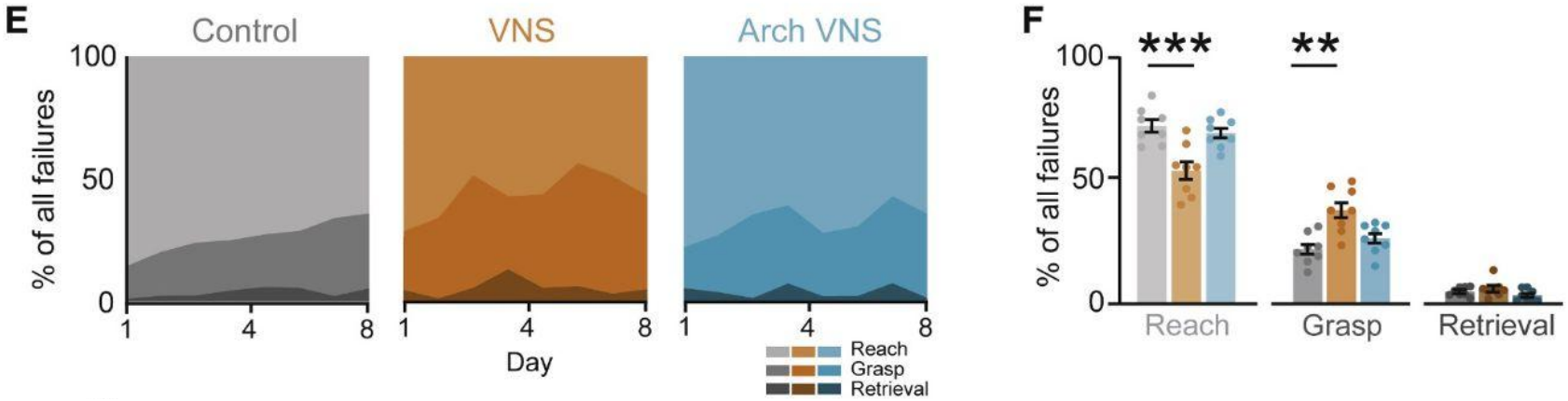
Figure 5. VNS improves performance through improved consolidation of reach trajectory



Are failure types categorized quantitatively or qualitatively?

Failure types are a qualitative categorizing.

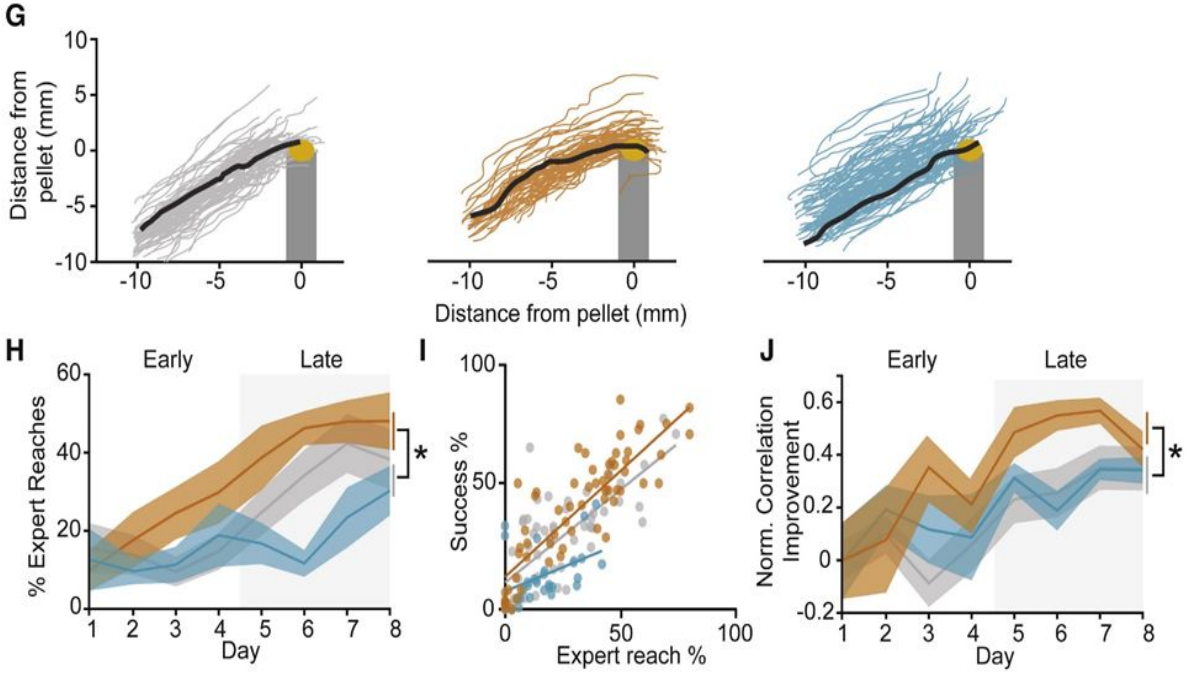
Figure 5. VNS improves performance through improved consolidation of reach trajectory



How might we interpret this change in failed attempts?

The reach failures represent the largest targeting errors of all attempt types, so the mice seem to be reducing their largest errors when Success-VNS → improved accuracy in reach trajectory.

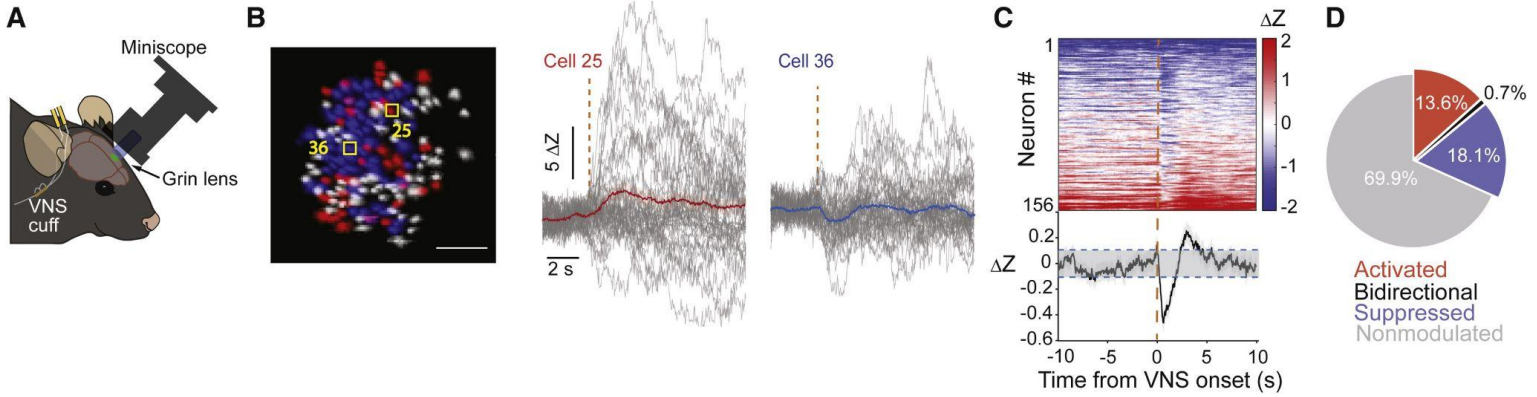
Figure 5. VNS improves performance through improved consolidation of reach trajectory



Why might a metric like an 'expert reach' be needed?

Each mouse may have a different kinematic strategy, making it difficult to compare between animals.

Figure 6/7. VNS drives acute neural suppression and activation in forelimb motor cortex



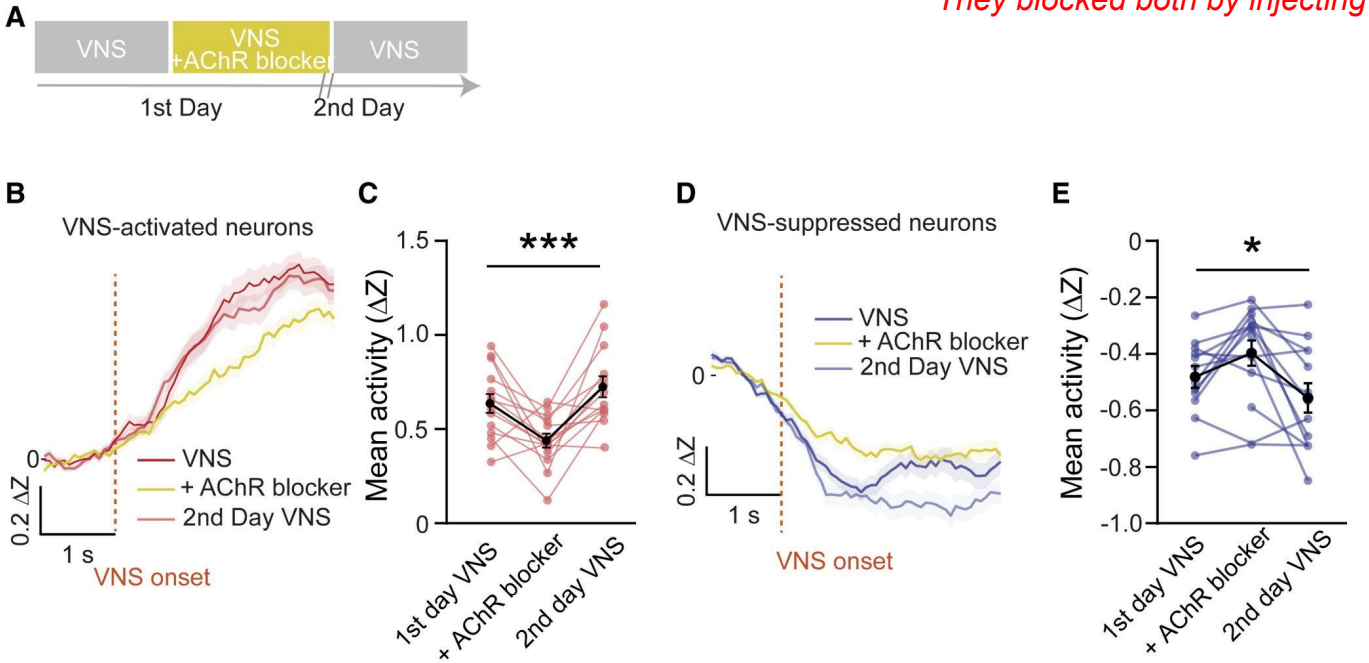
Why is it important that the researchers found VNS-responsive cells in motor cortex?

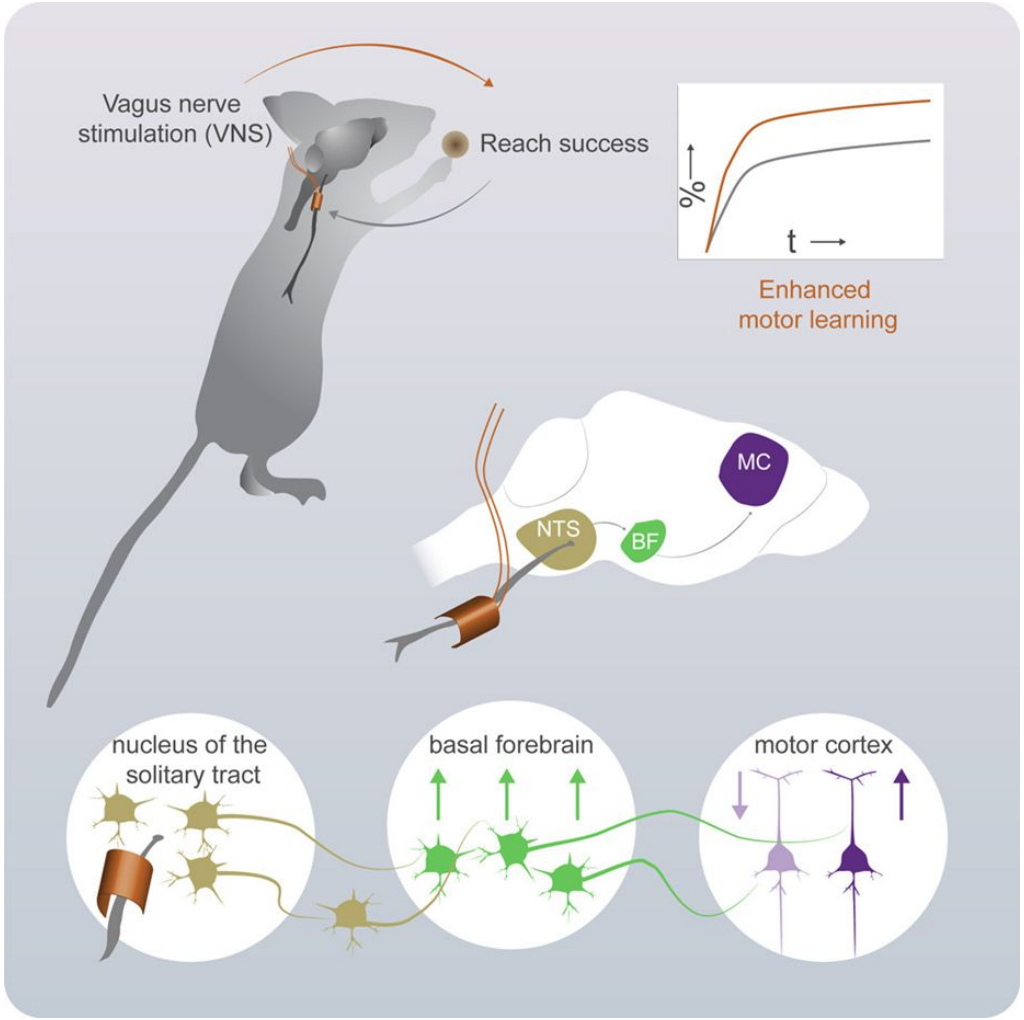
Cholinergic neurons do not drive motor behavior, so this helps complete the circuit model.

Figure 8. VNS-driven acute neural modulation is mediated through AChRs

Did the researchers block nicotinic or muscarinic ACh receptors?

They blocked both by injecting a cocktail of two drugs.





Summary

- VNS can enhance motor learning when paired with motor behavior.
  - Movement-paired stimulation produces short term effects, outcome-paired produces long term effects.
  - Motor learning improves because mice are better at selecting successful motor plans.
- VNS drives cholinergic activity in the basal forebrain.
  - Preventing cholinergic signalling is sufficient to prevent VNS-enhanced learning.
- VNS responsive neurons in motor cortex show reduced responses when ACh is blocked.

Paper round-up

- VNS paired with success enhances skilled motor learning in healthy animals
- Enhanced motor performance is due to accelerated consolidation of an expert motor plan
- Enhanced motor learning depends on cholinergic neural activity in the basal forebrain
- In primary motor cortex, VNS specifically modulates outcome-activated neurons

What did we learn? What questions do we have?

- **What points do they make in the discussion?**
- **Is anything unclear?**
- **What would you do next if you had to design an experiment?**
  - *Check other neuromodulators than Acetylcholine → can see that still doing something in Figure 8*
  - *Optogenetics on-off for Acetylcholine without the effect of VNS.*