

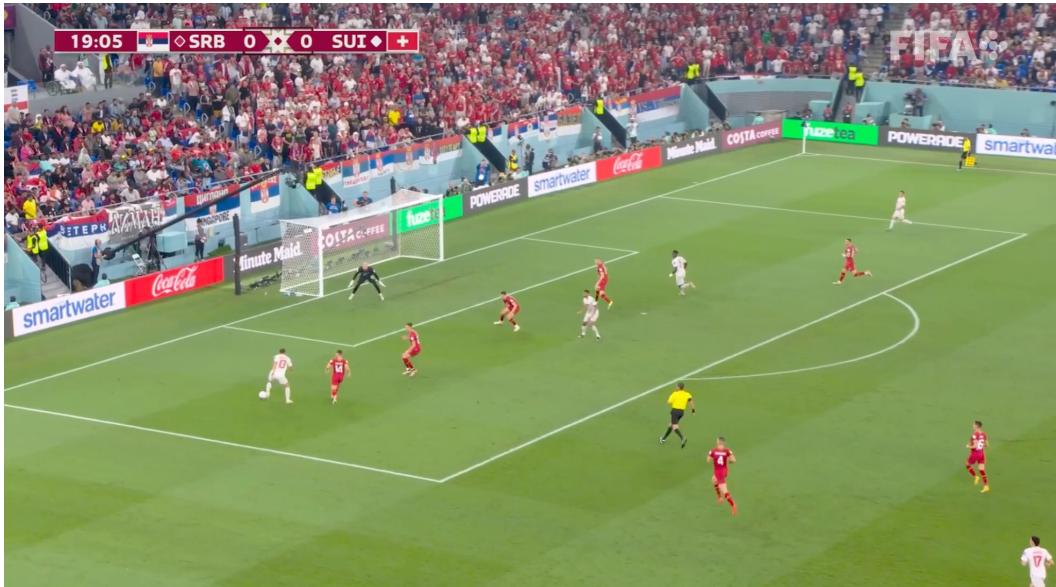


Motor learning & neuro-modulation

Spencer Bowles, PhD

& Mackenzie Mathis, PhD

Biological Intelligence



World Cup 2022

Artificial Intelligence

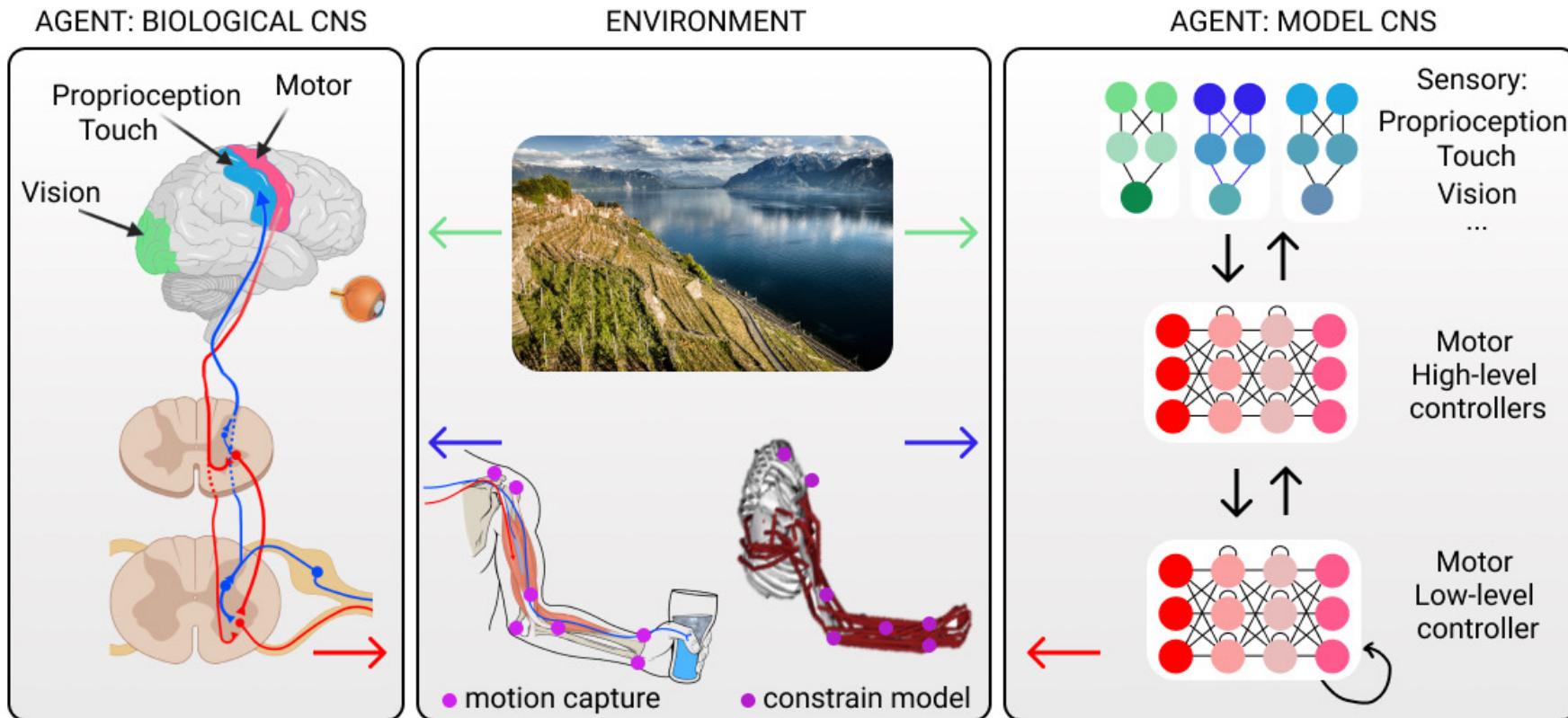
adaptability of our intelligence



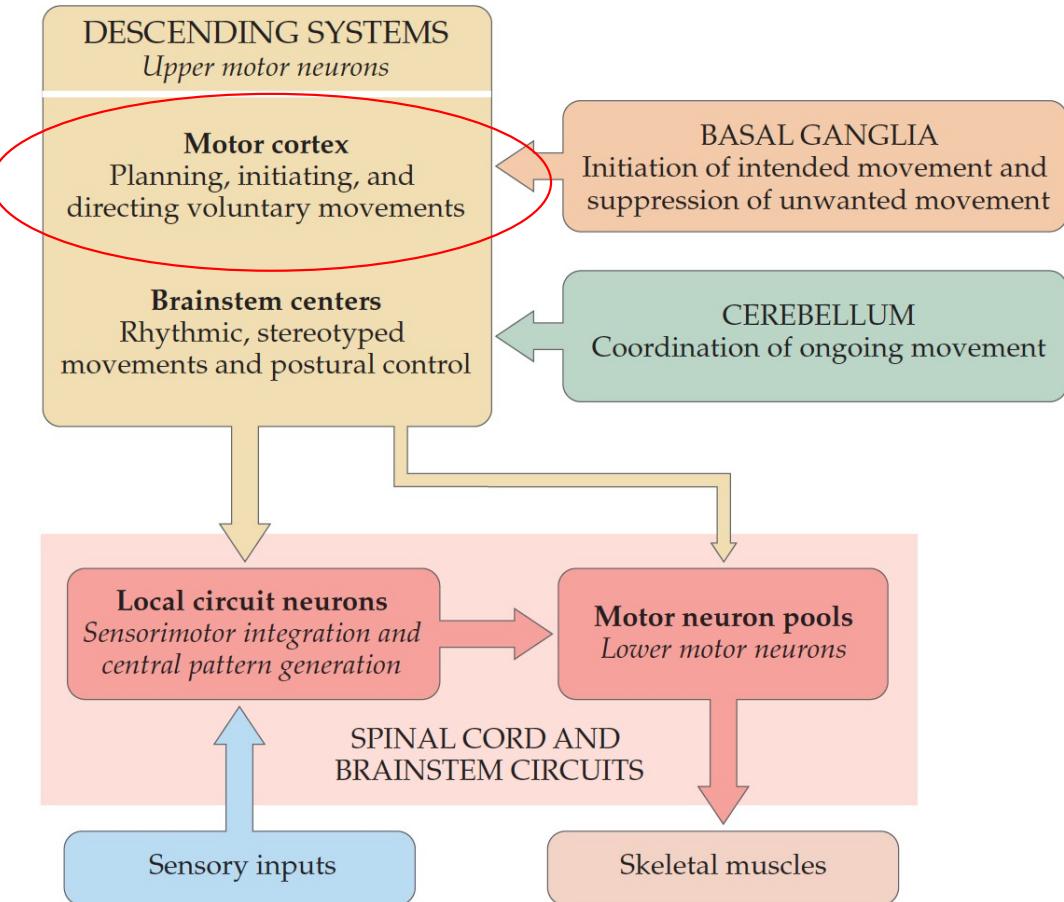
DeepMind 2023

This is still a large gap in our ability to build adaptive systems

Reverse engineering adaptive behavior



The neural control of movement



movement
↑
SUPPRESS
↓
most releases here, 70 b/g

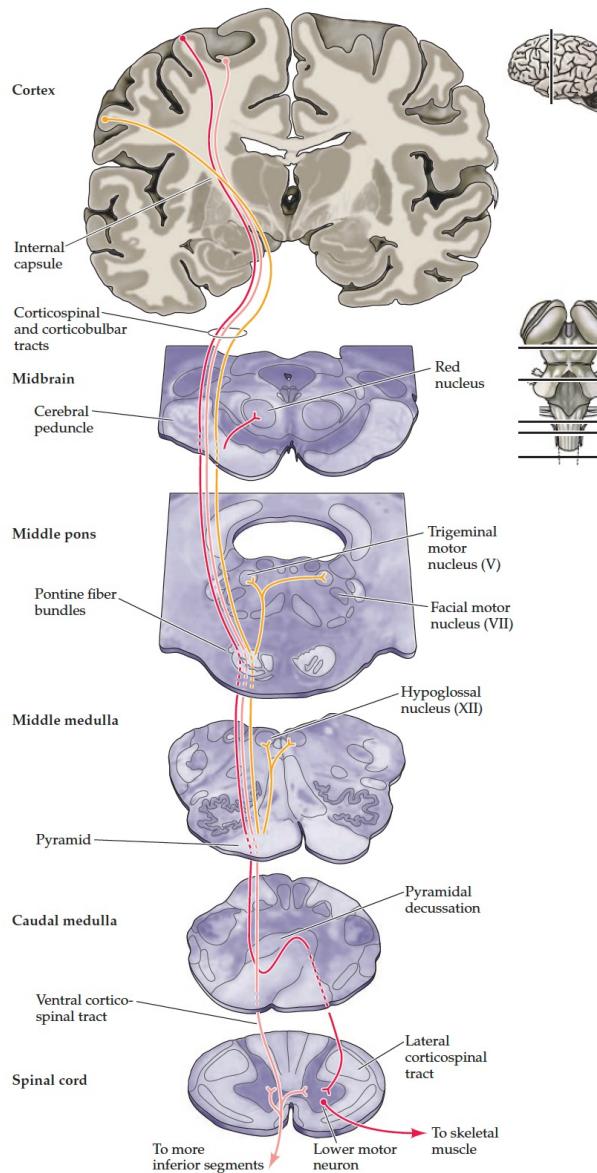
Four systems make essential and distinct contributions to motor control:

- The **spinal cord** (and brainstem circuits)
- The **cerebellum**
- Descending control centers in the cerebral cortex and brainstem
- The basal ganglia

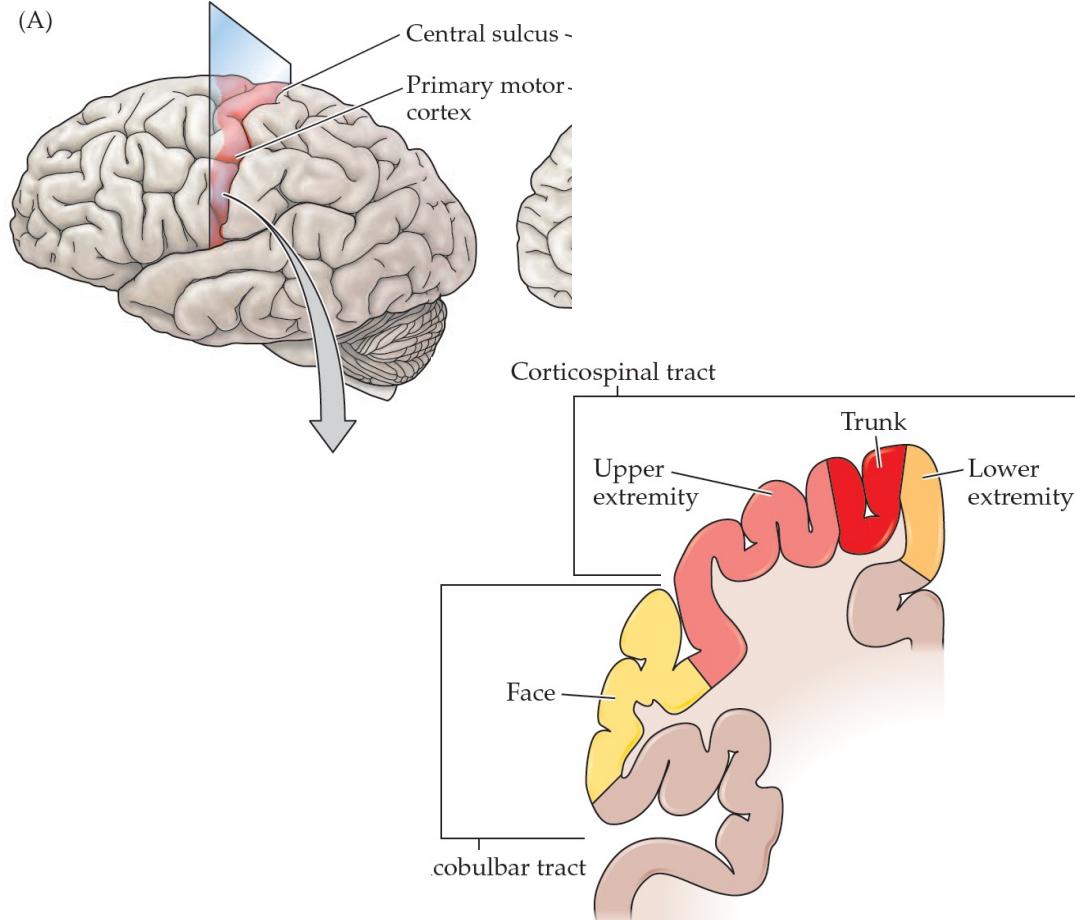
The corticospinal tract

The corticospinal tract (red):

- Distinct from "corticobulbar" tract (gold) that descends to the brainstem ("bulbar").
- Axons cross-over to other body side at "pyramidal decussation"
- Some axons directly contact *motor* neurons in the ventral horn to control distal extremities
- Most contact local circuits

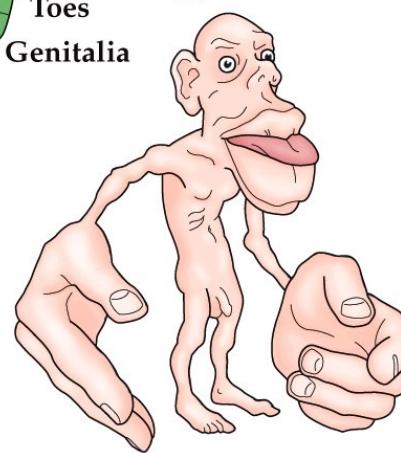
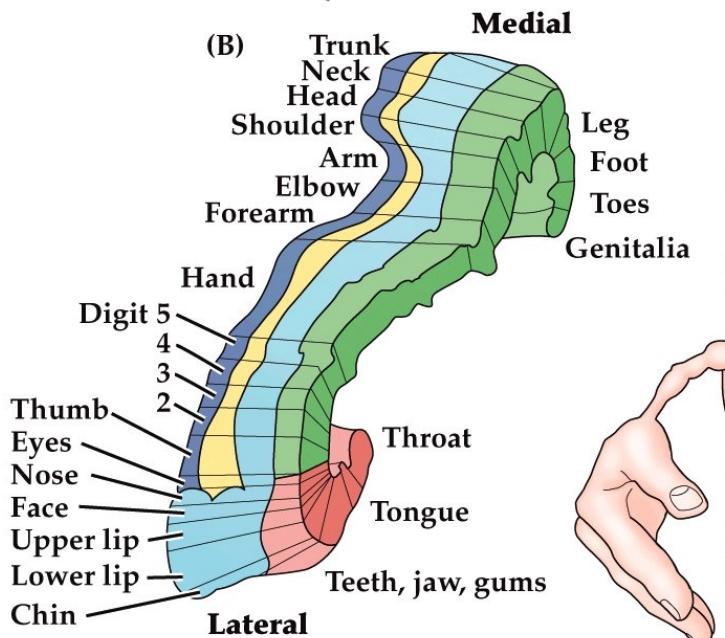
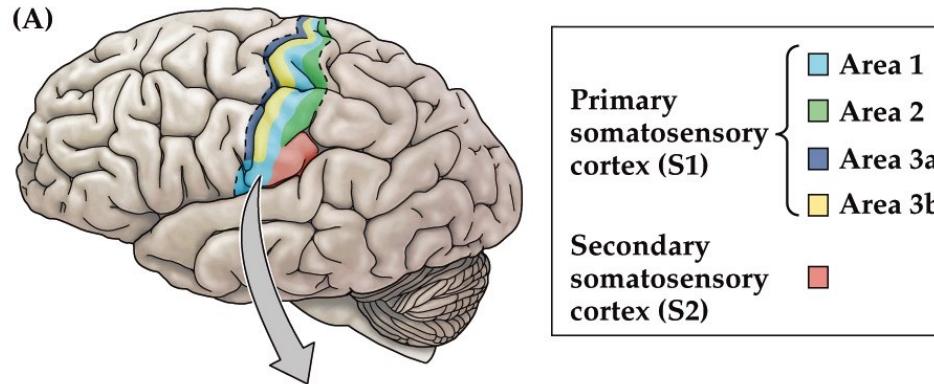


Motor maps in motor cortex



- A "motor map" was suggested by the systematic "march" of **seizures** from one body part to another
- The "motor map" was confirmed from **microstimulation** of motor cortex in **awake patients** (Wilder Penfield ~1950)
- Note: the "motor map" is **congruent with** the map of primary sensory cortex, which is just posterior to M1, posterior to central sulcus

Somatotopic order in the human primary somatosensory cortex



homoetus

two pencils

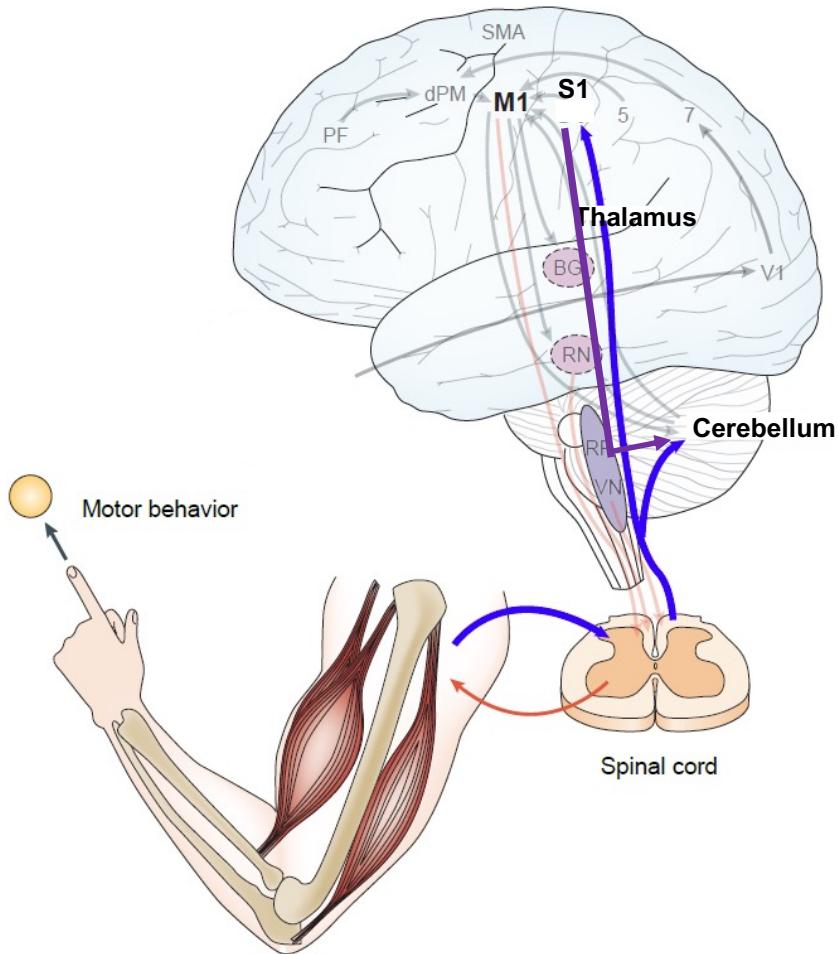
experiment

→ people think

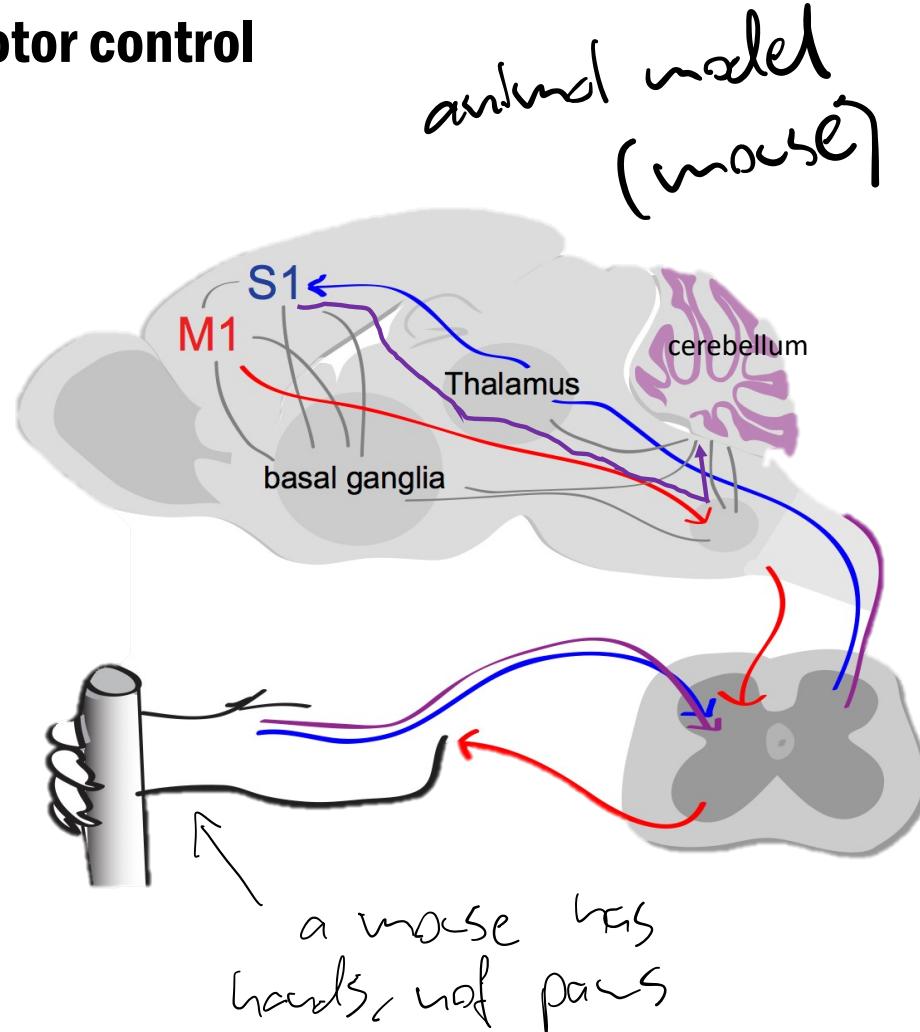
that we are

pencil

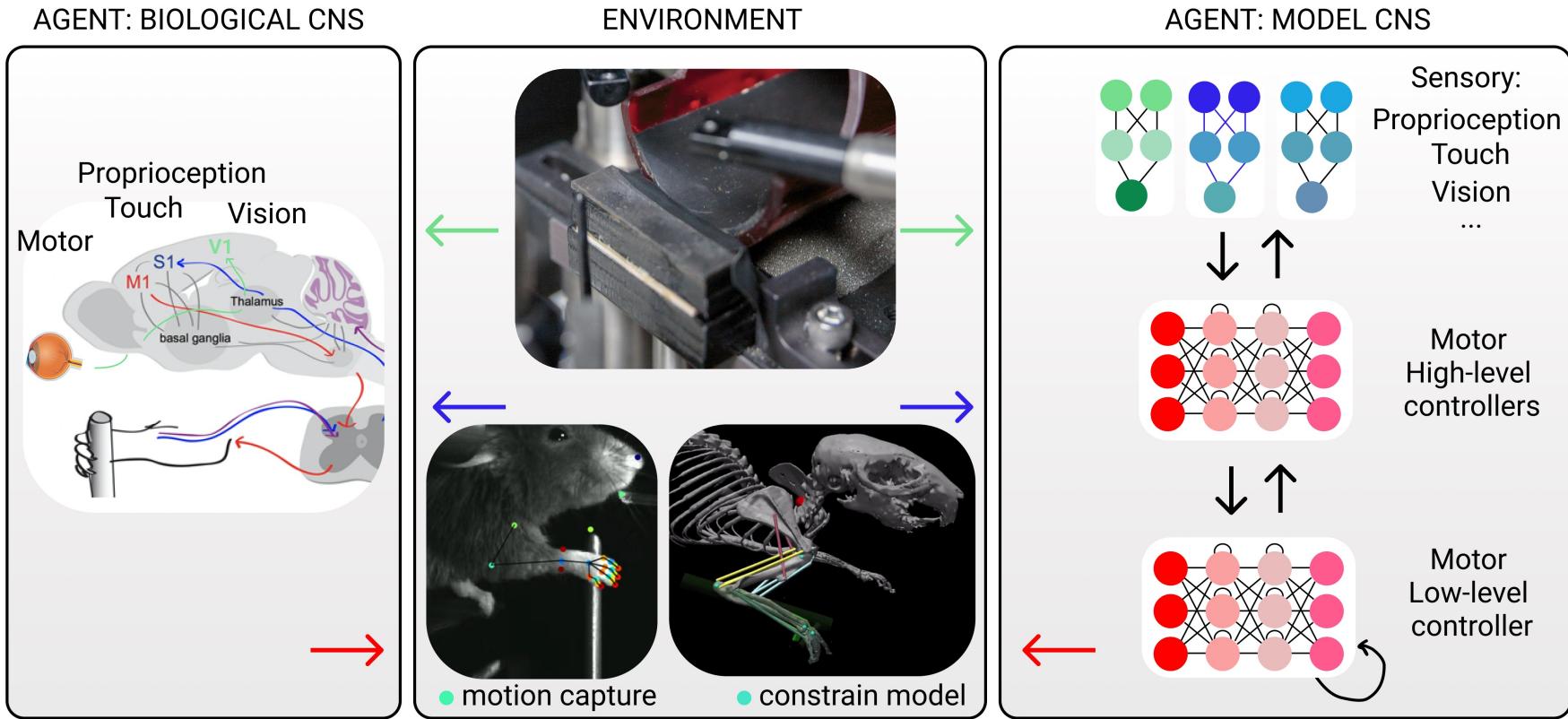
Integrative sensorimotor control



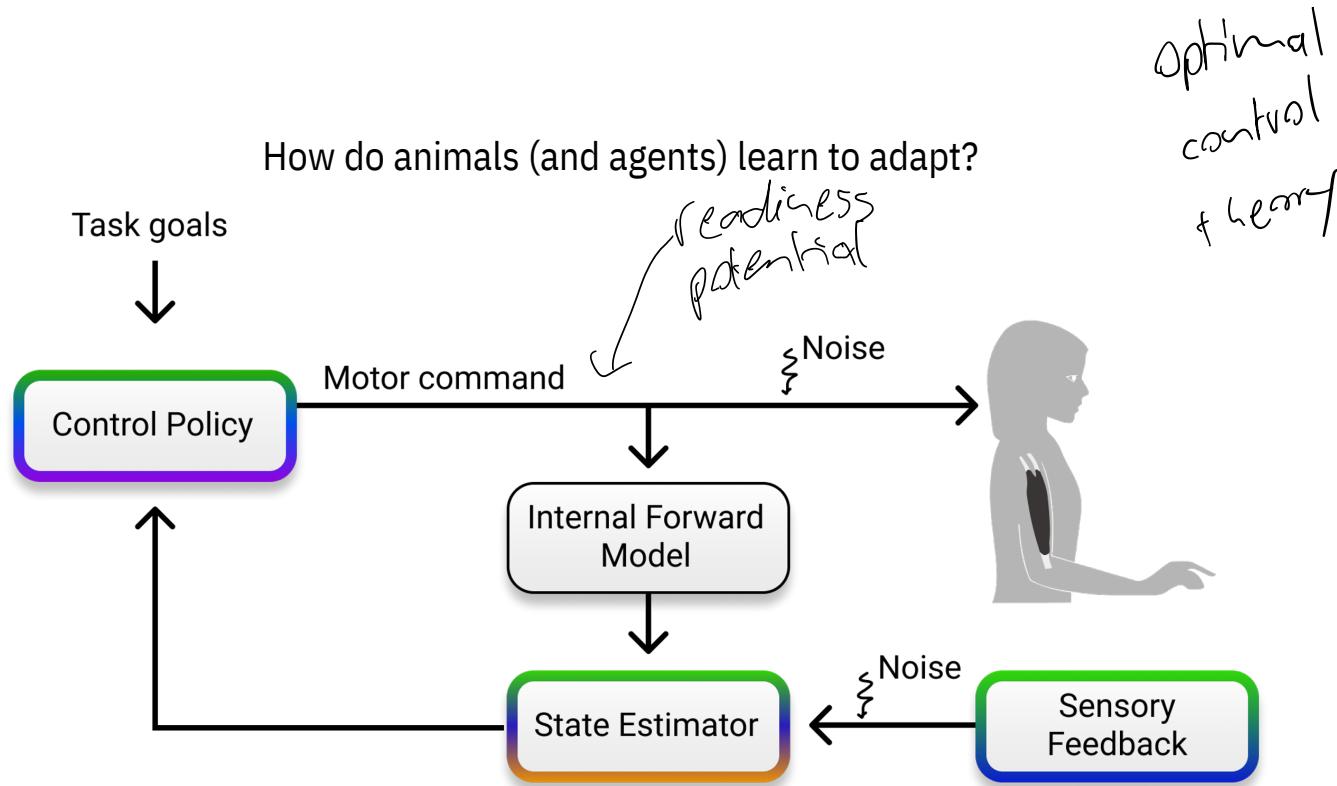
Adapted from Scott, 2004



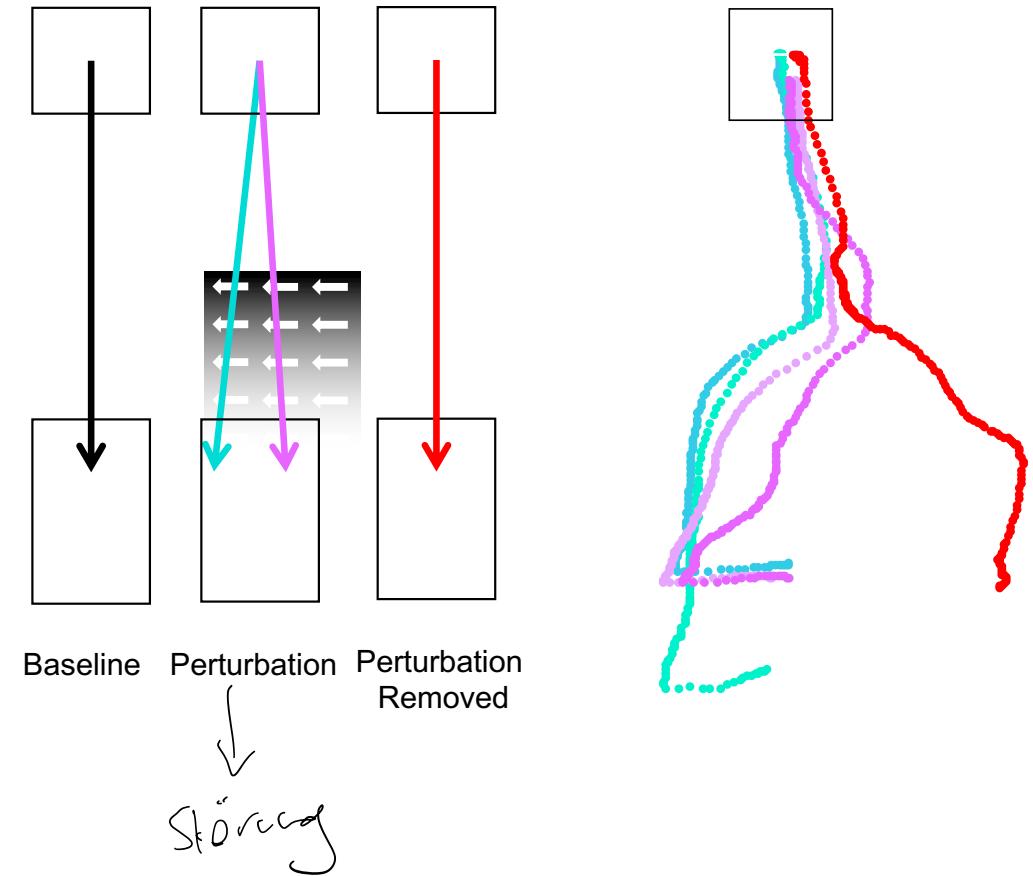
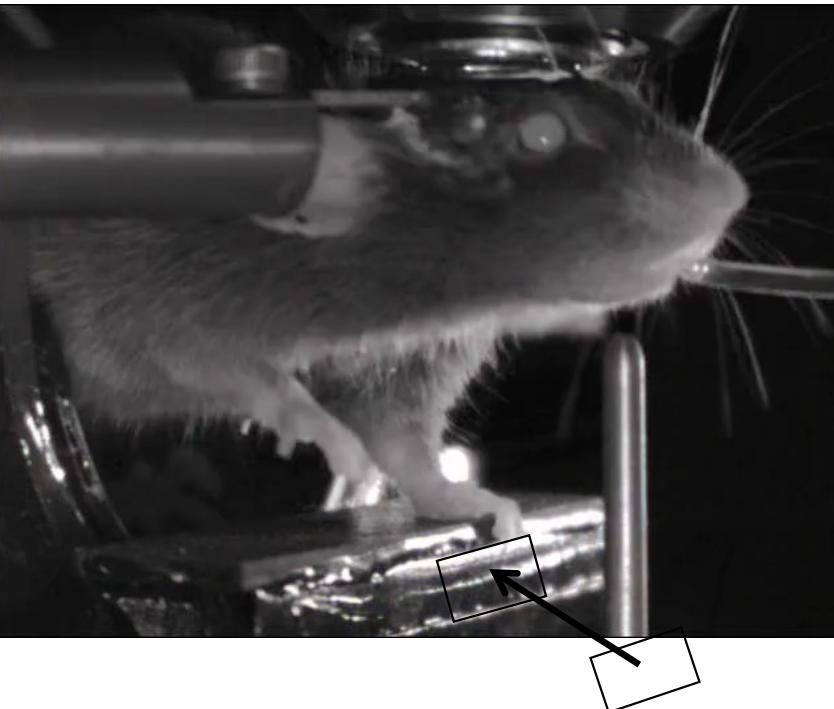
Reverse engineering adaptive behavior



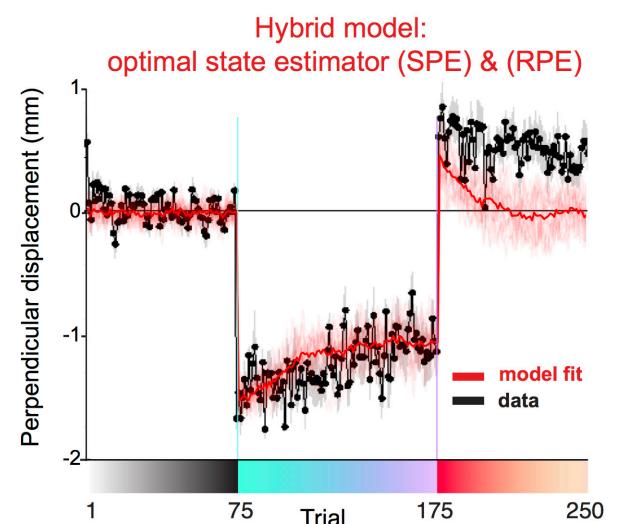
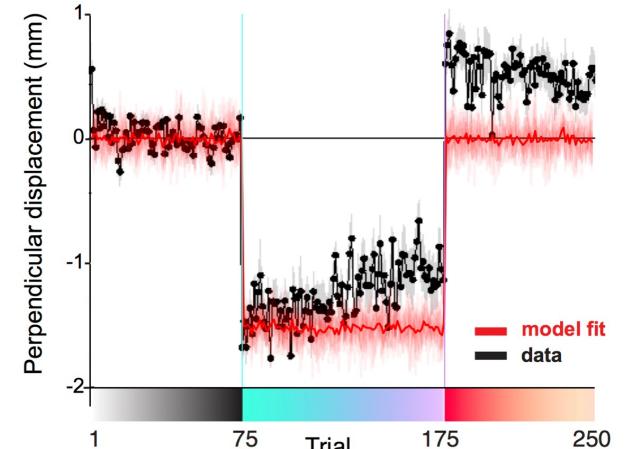
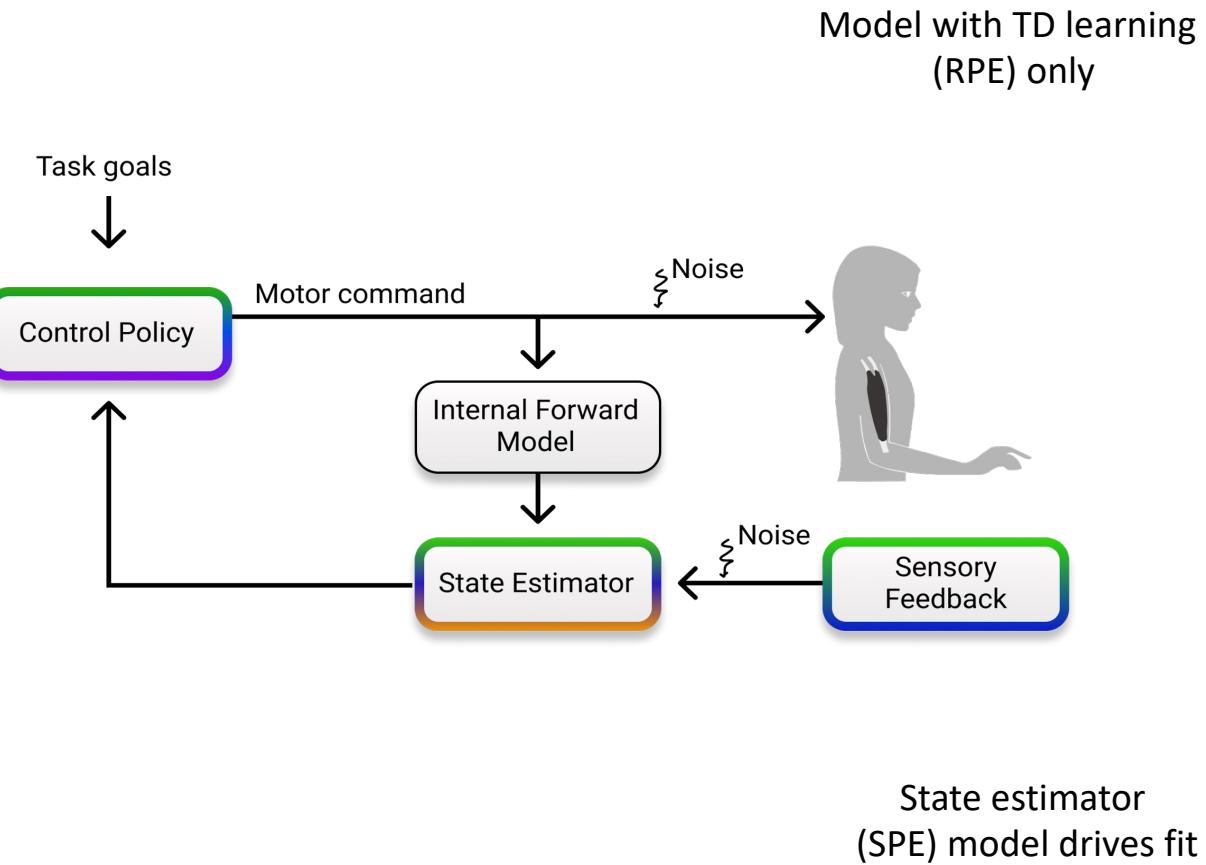
Theory-guided framework for studying motor learning



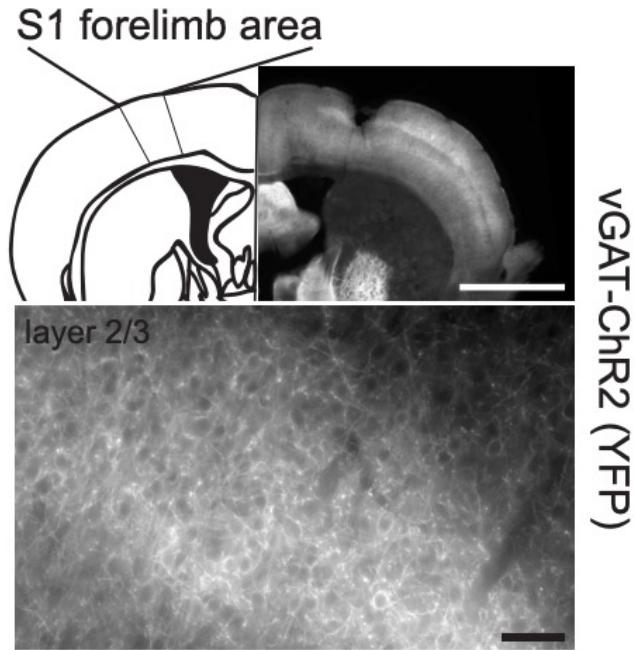
Motor learning (adaptation) within a session



Forelimb motor adaptation is driven by sensory prediction errors

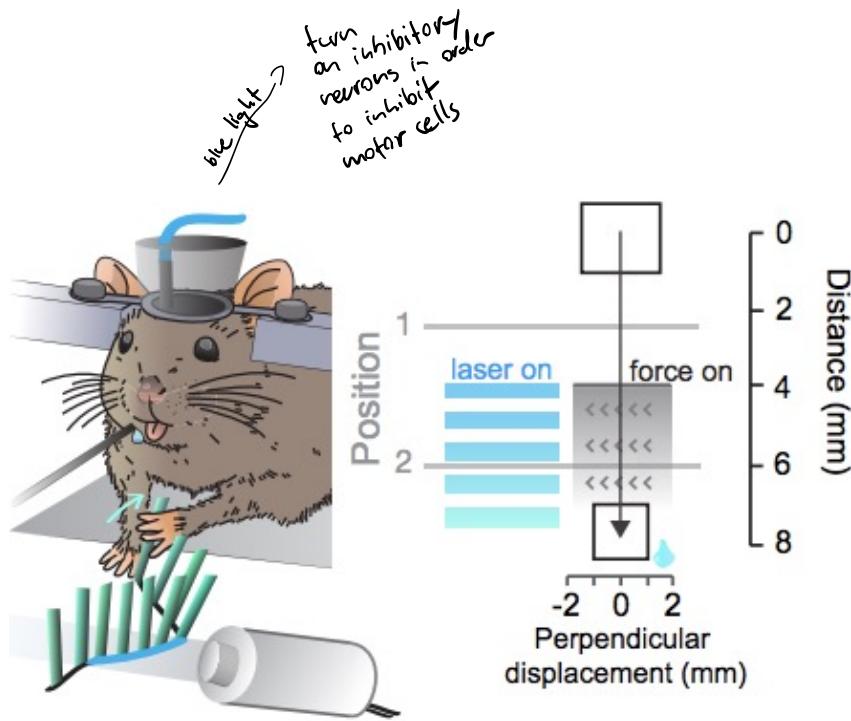


Perturbing sensory circuits: testing the role of S1 in adaptation



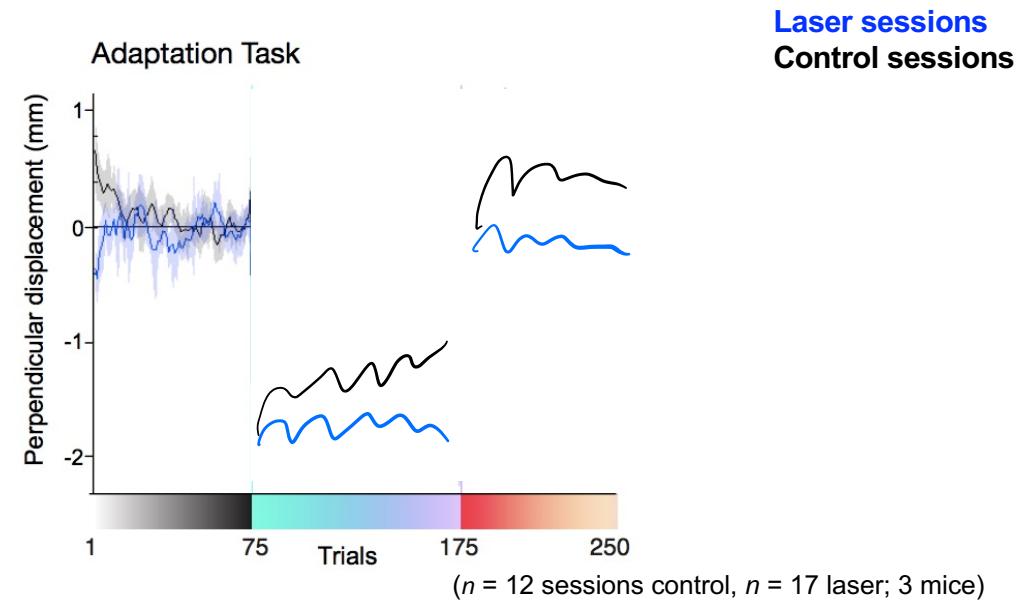
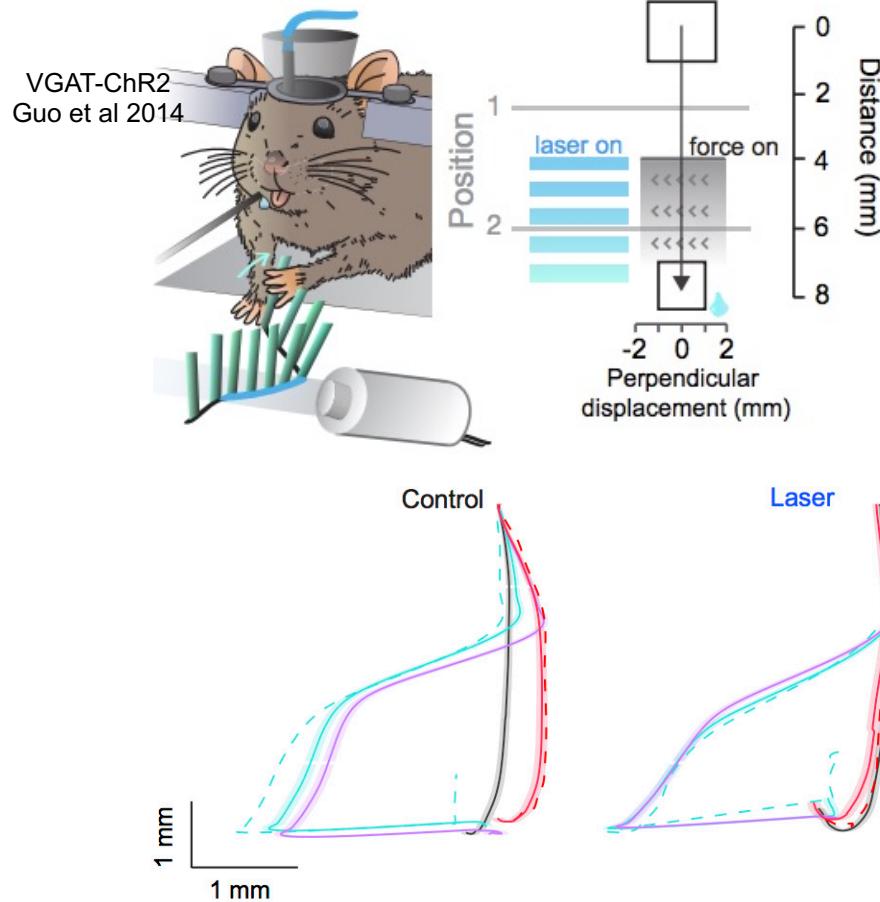
VGAT-ChR2
Guo et al 2014

optogenetic
control
of S1 neurons

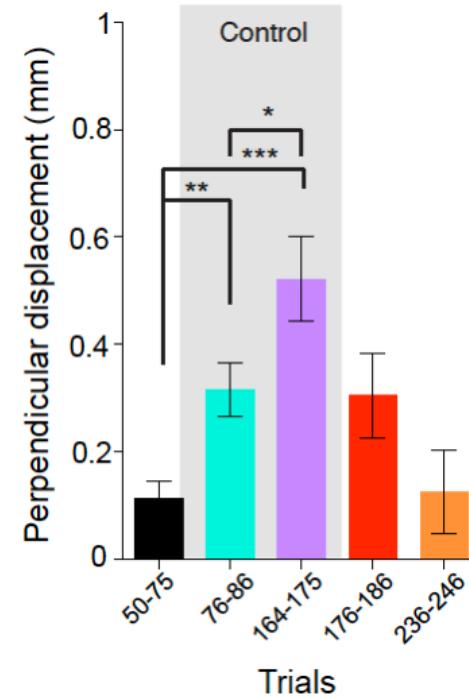
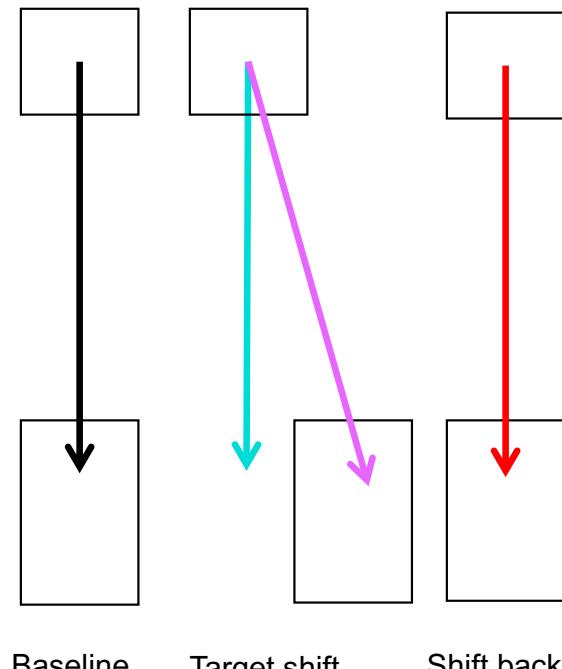


100 ms laser delivered in 5 ms pulses at 50 Hz

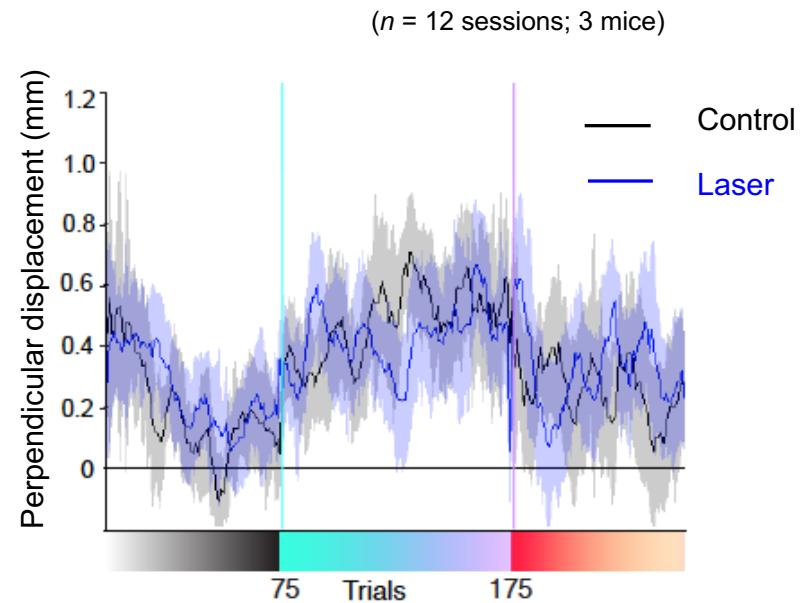
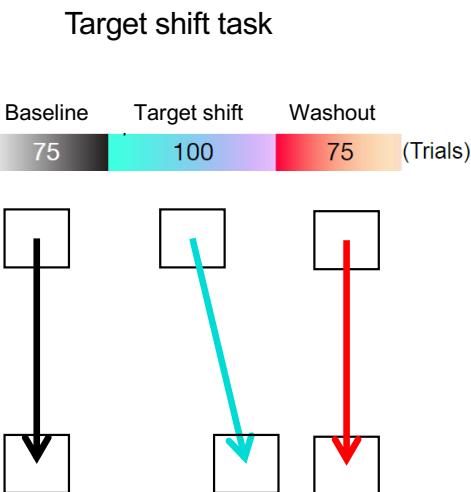
Perturbing sensory circuits: testing the role of S1 in adaptation



Motor learning within a session driven by RL



S1 inactivation does not affect reward-based learning



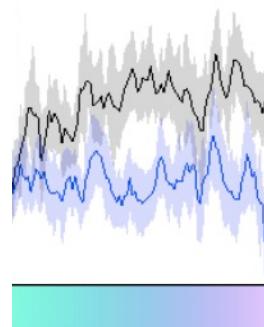
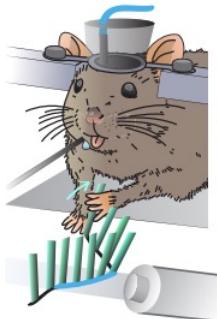
The role of S1 in adaptation

1

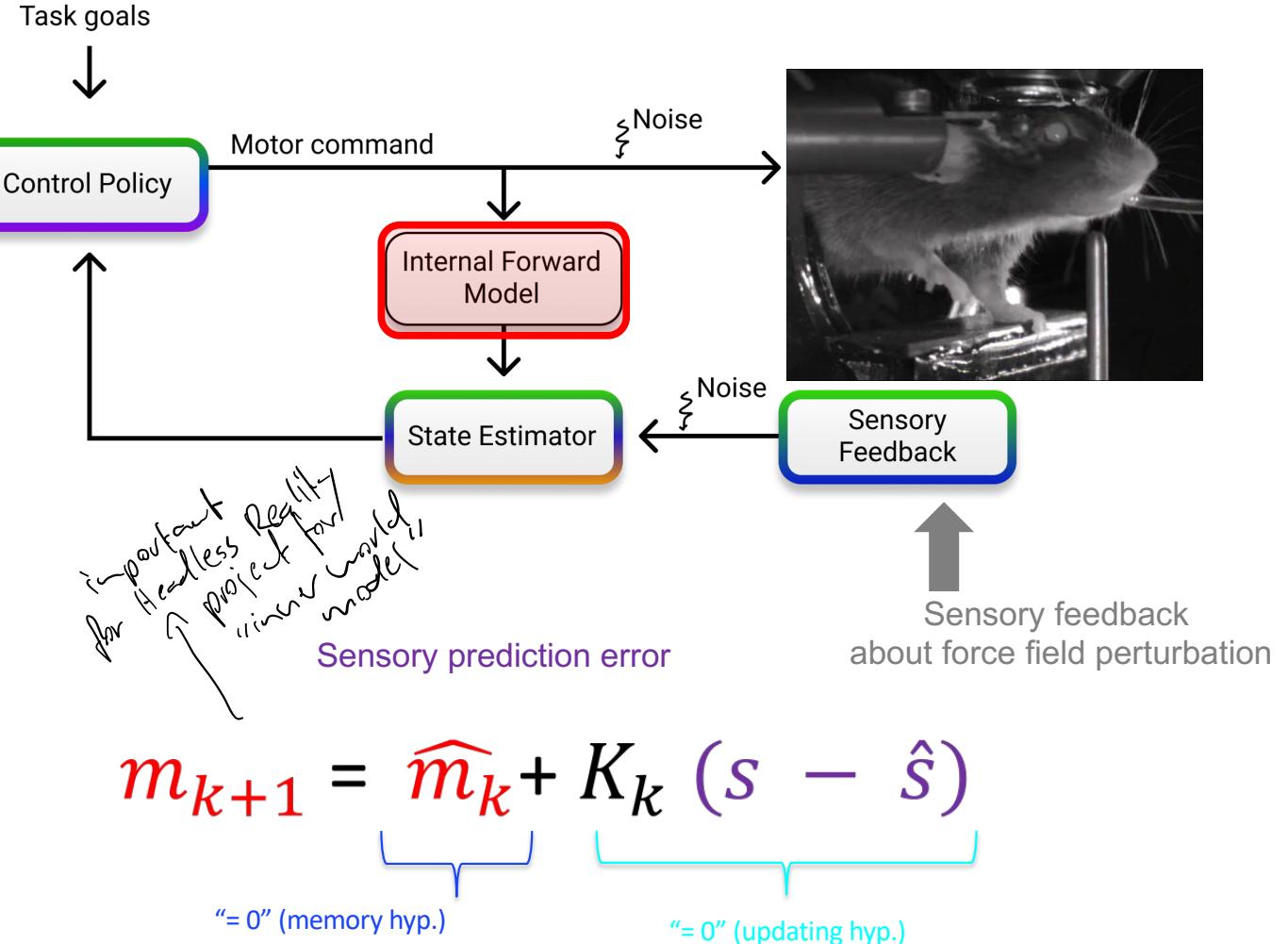
Did inactivation block **acquisition**?

2

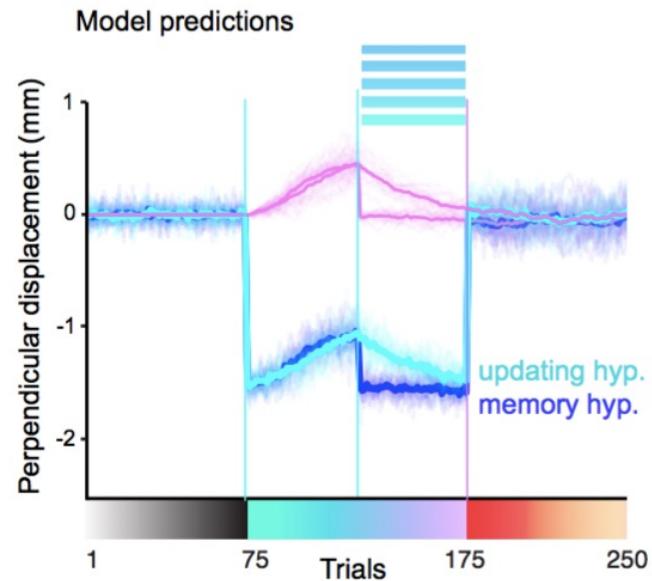
Or block **expression** of an adapted motor command via internal model?



Perturbation block



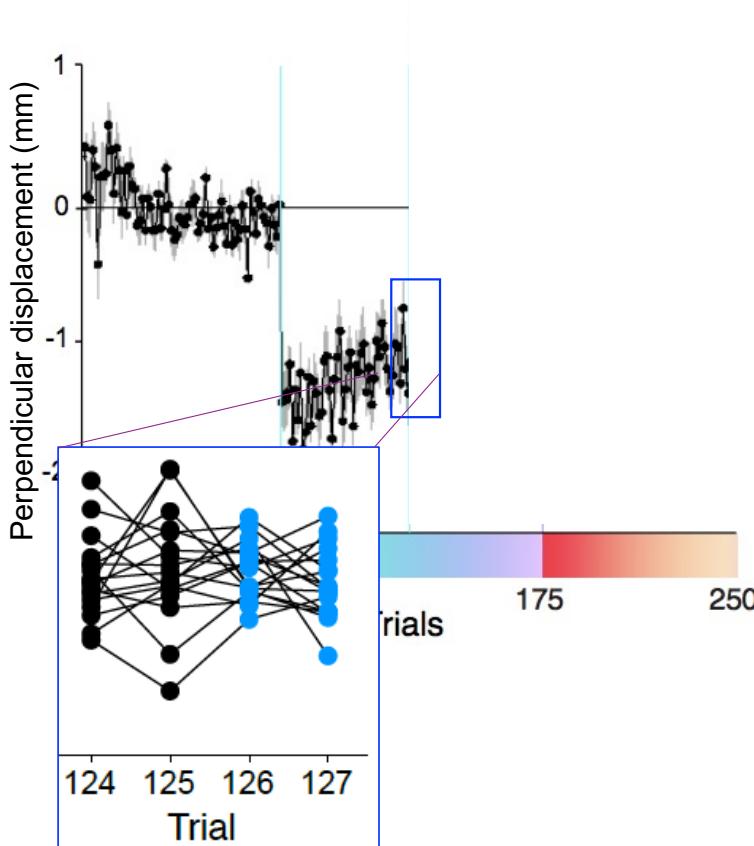
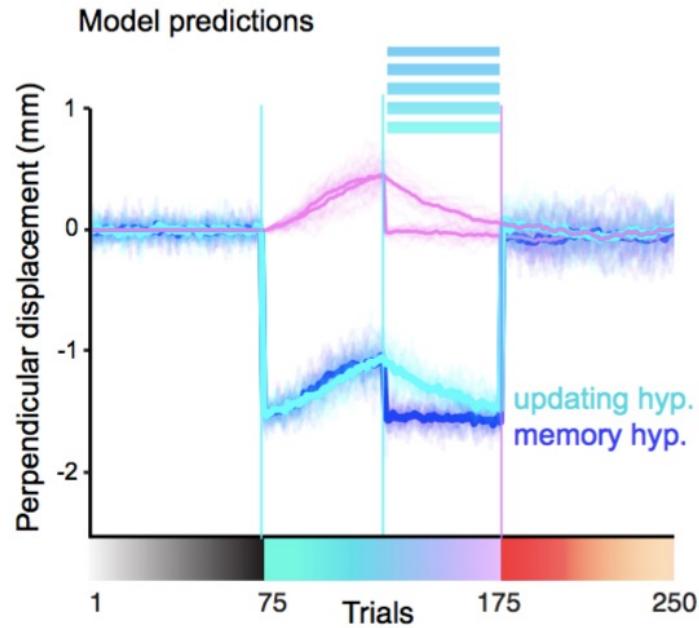
Could S1 be updating or housing a memory of the perturbation?



$$m_{k+1} = \widehat{m}_k + K_k (s - \hat{s})$$

= 0" (memory hyp.) = 0" (updating hyp.)

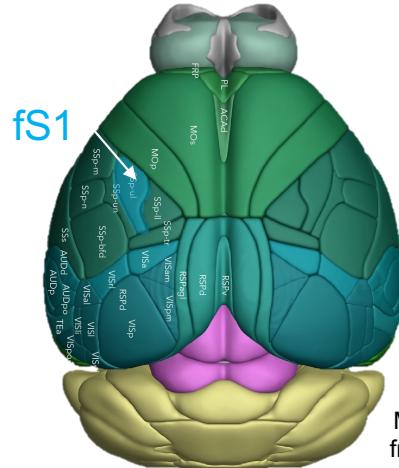
S1 inactivation after adaptation: S1 does not exclusively house the model (memory) of the perturbation



Part 1 conclusions

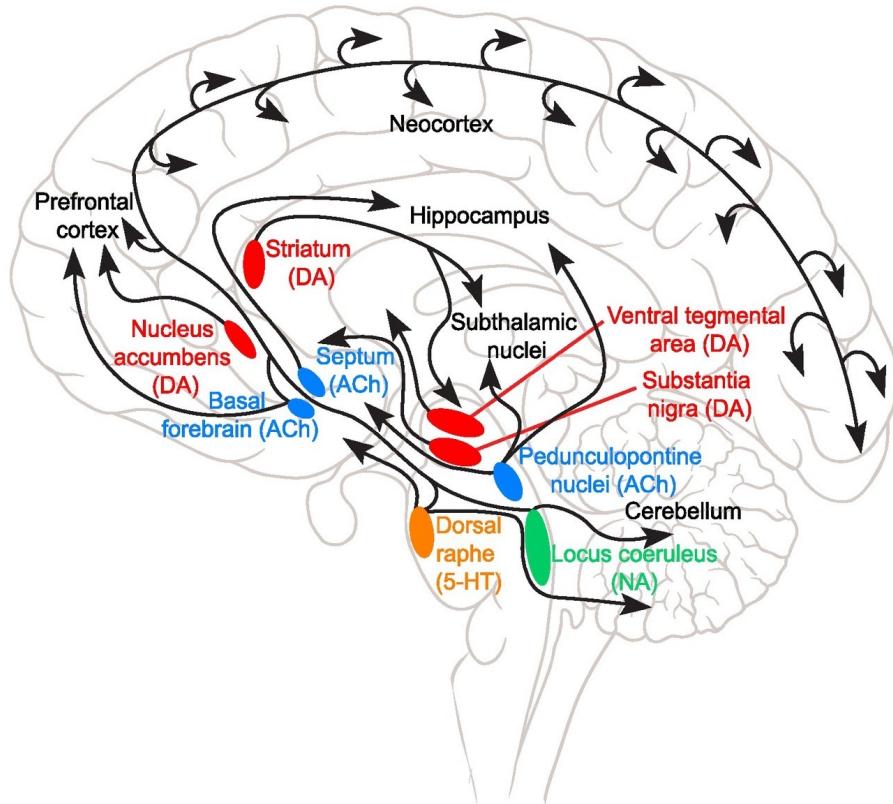
- Mice can learn to rapidly learn a new sensorimotor mapping (motor adaptation)
 - Forelimb S1 is essential to adaptation (in this task), but inactivation of S1 did not effect motor control
 - Theory-guided experiments suggest S1 does not exclusively house an internal model, and sensory prediction errors (vs. reward prediction errors) drive learning
 - Ongoing work: what are neurons in S1 encoding ...

7 doesn't hold the inner word model



Mouse brain diagram from the Allen Institute

What other systems are can modulate motor learning?



Neuromodulatory systems

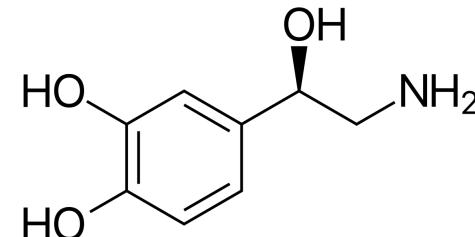
What are neuromodulators?

Neurotransmitters (NTs) refer to any chemical released from neurons that activate receptors on other neurons.

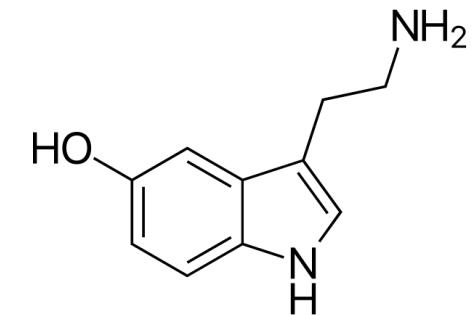
Glutamate and GABA are the most common NTs, accounting for approximately 90% of all neurons!

Neuromodulators (NMs) refer to a subset of NTs that do not directly activate ion-channel receptors, but instead alter neural responses to excitation and inhibition.

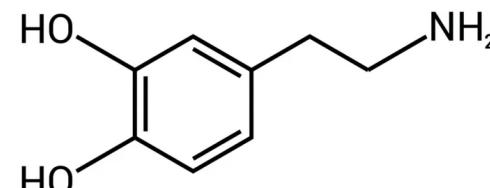
Noradrenaline



Serotonin

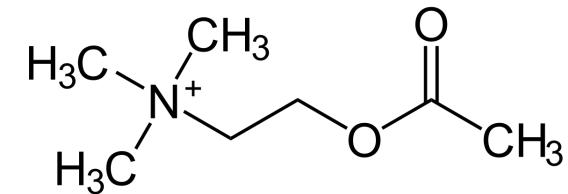


Dopamine



g-protein

Acetylcholine

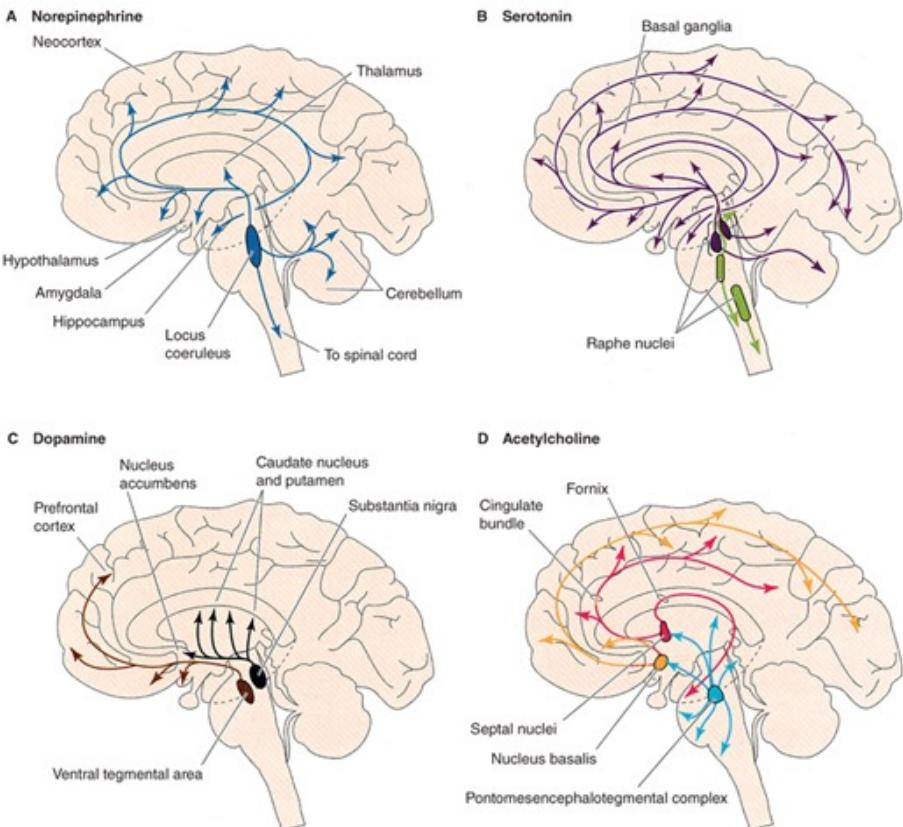


Avery & Krichmar, 2017

What are neuromodulators?

NM systems are generally clustered in a few small nuclei.

These neurons send wide-ranging projections that target diverse subsets of other regions.



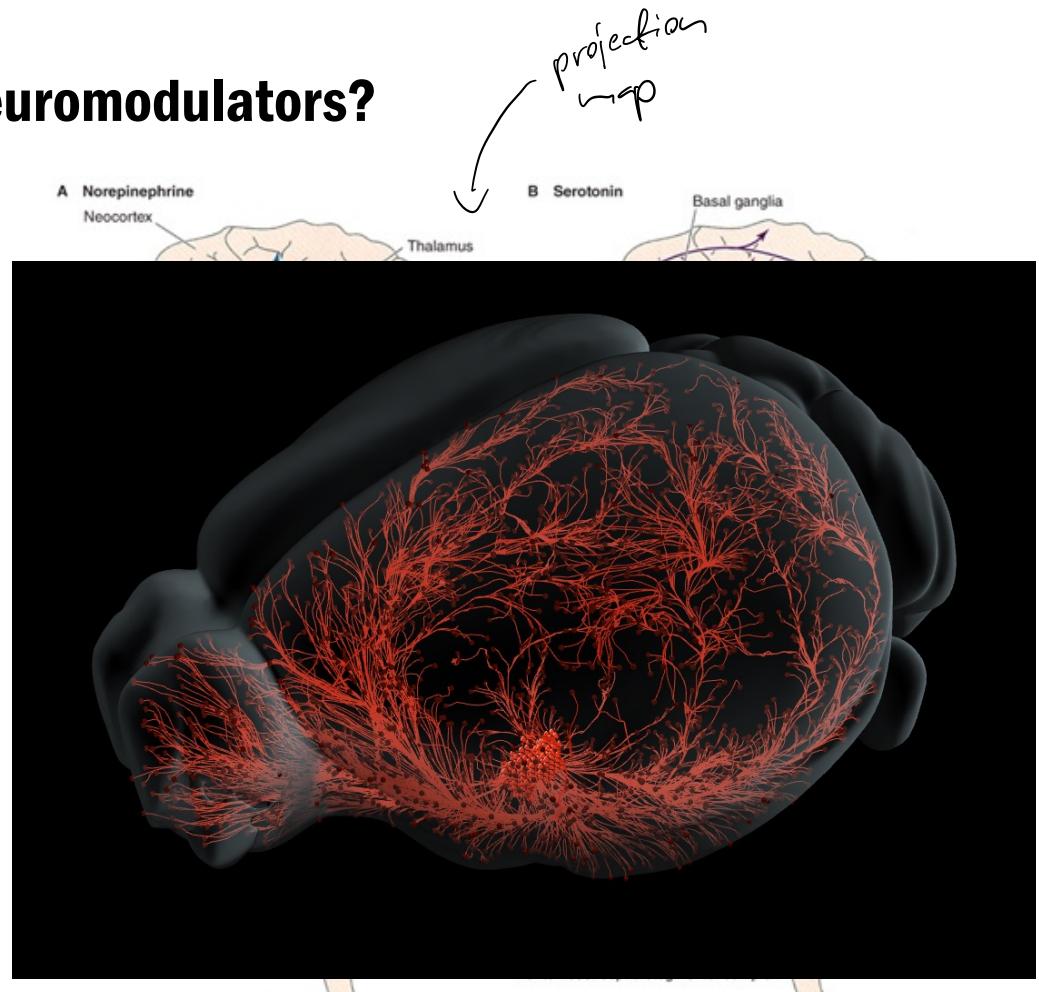
Source: Kim E. Barrett, Susan M. Barman, Scott Boltano, Hedden L. Brooks: Ganong's Review of Medical Physiology, 25th Ed.
www.accessmedicine.com
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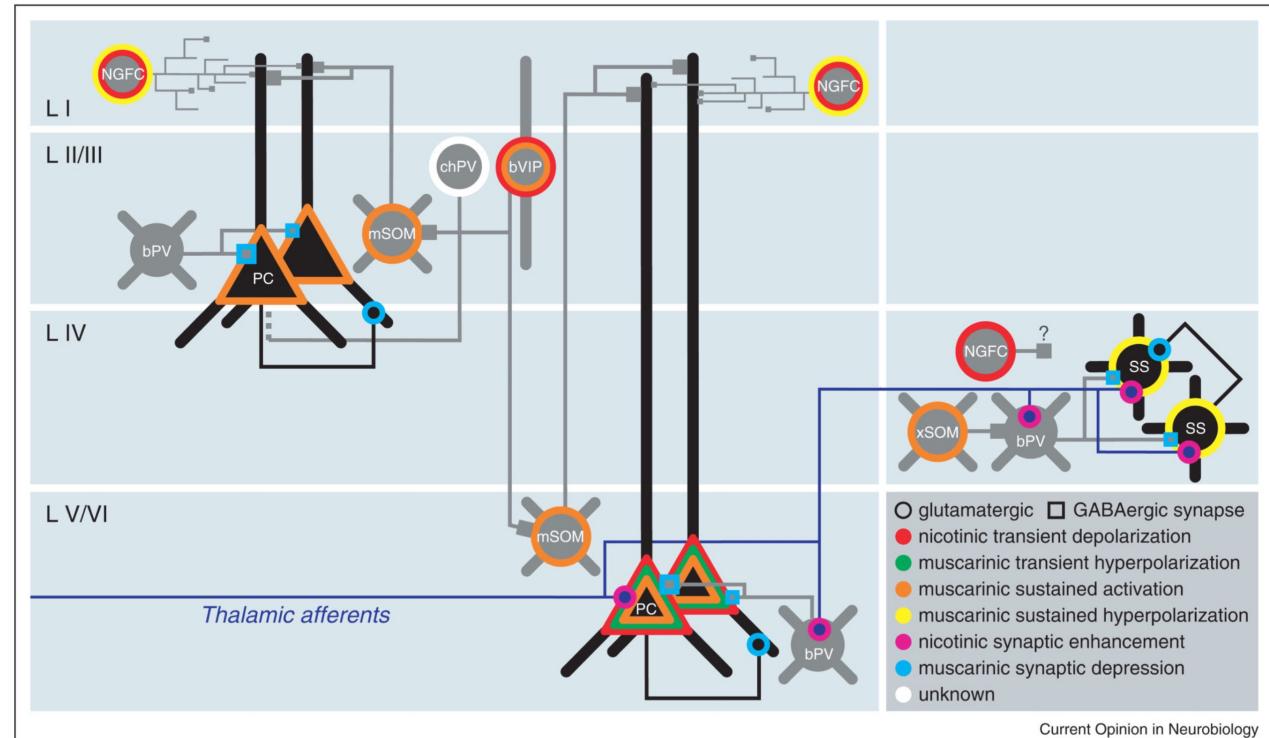
These neurons send wide-ranging projections that target diverse subsets of other regions.

NMs can act over varying timescales, from milliseconds to hours.



Neuromodulators have multiple receptor subtypes with diverse effects

NMs do sometimes have ligand-gated receptors (such as nicotinic receptors), but primarily act through G-protein coupled receptors.



Current Opinion in Neurobiology

Munoz & Rudy 2014

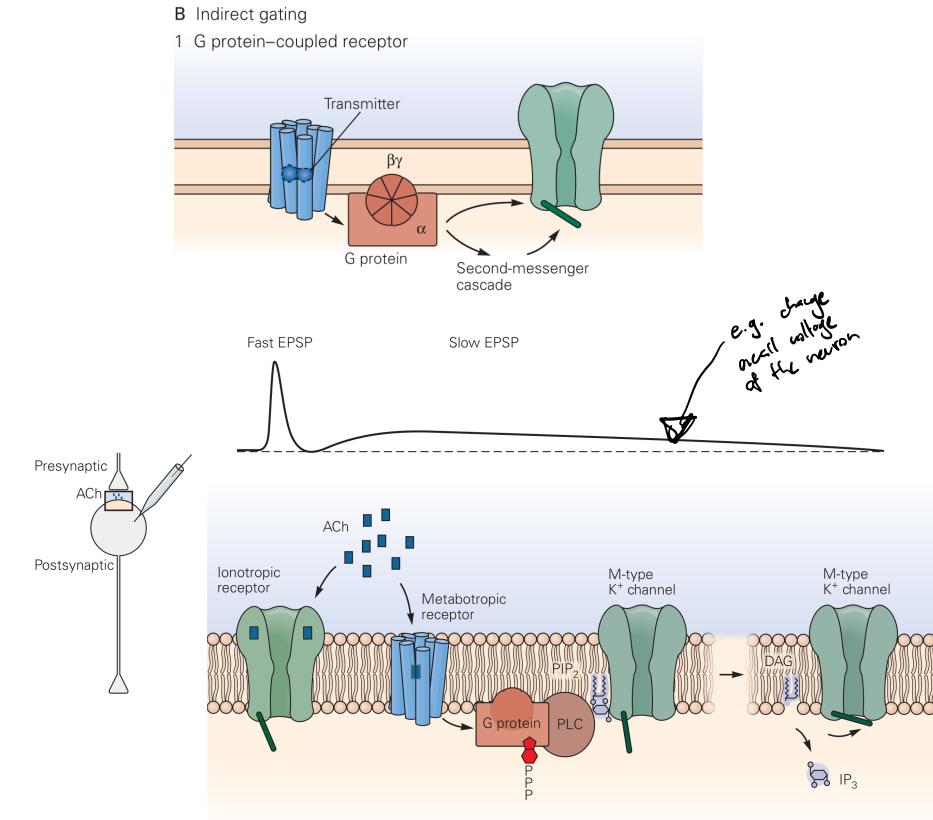
G protein-coupled receptors (GPCRs)

The G protein complex is activated when a neuromodulator binds to a GPCR

- A subunit of the complex then breaks off and starts a second messenger cascade

Cascades can produce a variety of effects including:

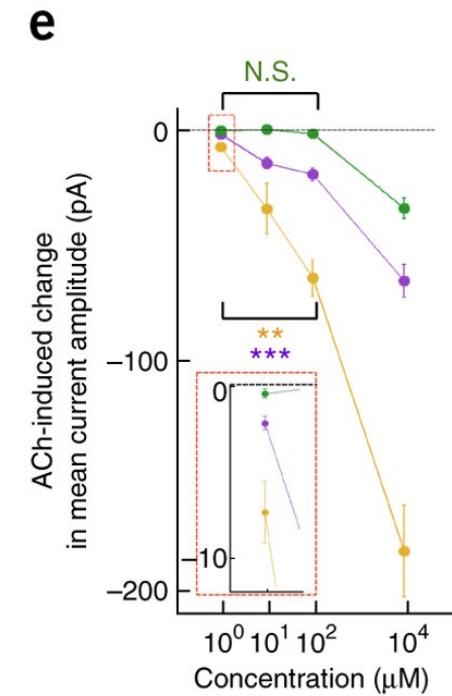
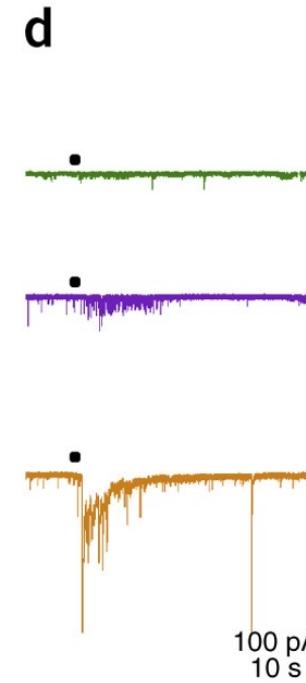
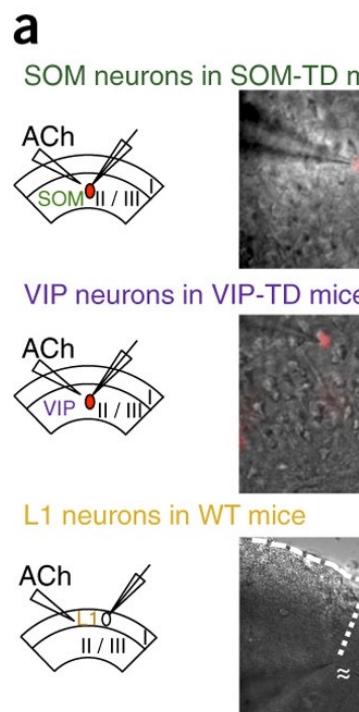
- Presynaptic facilitation, Long-term potentiation, slow excitation/inhibition, and protein translation.



Neuromodulators have multiple receptor subtypes with diverse effects

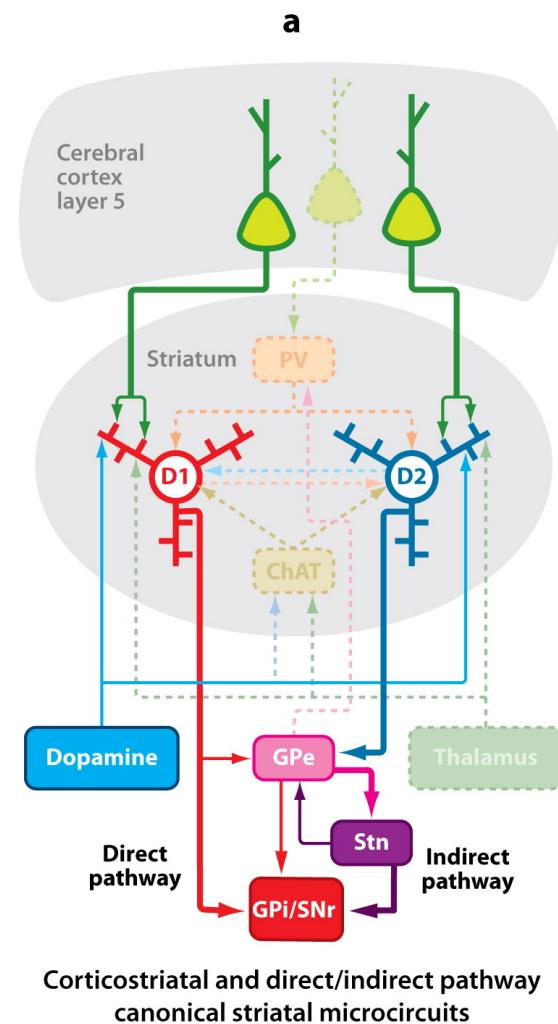
NMs do sometimes have ligand-gated receptors (such as nicotinic receptors), but primarily act through G-protein coupled receptors.

NM volume and duration can preferentially engage different receptor subtypes.



Section callback: where do dopamine signals go after the VTA?

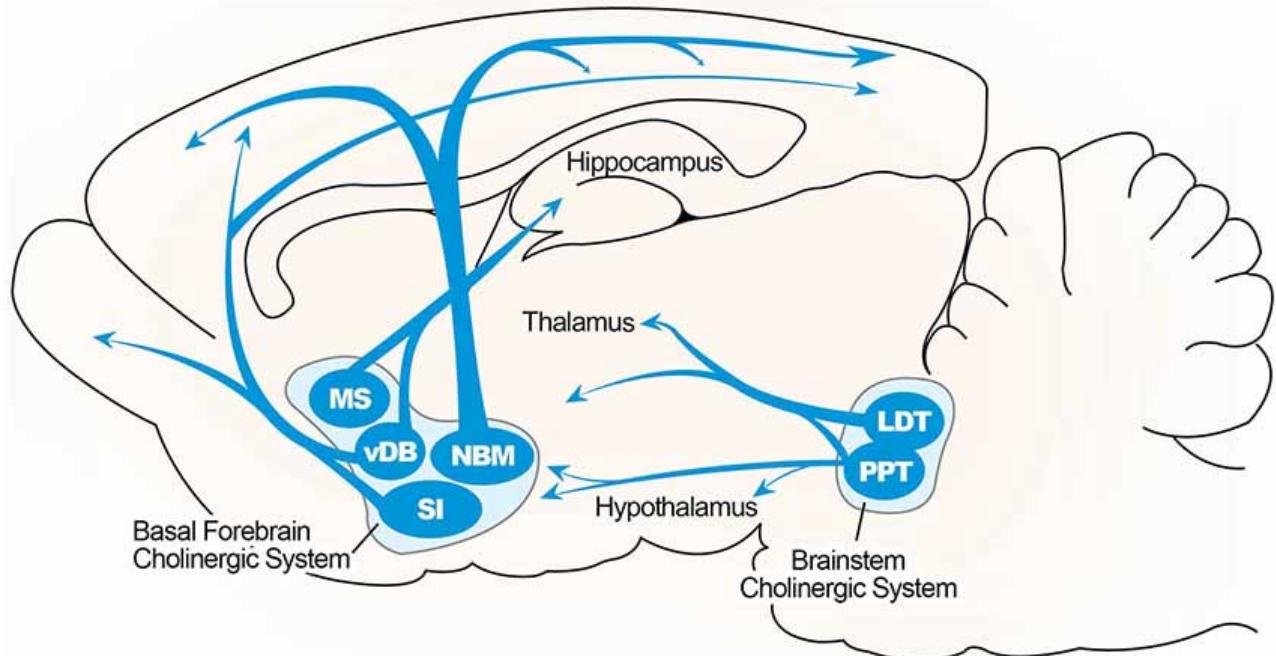
- Dopamine (DA) neurons project broadly, but one well studied projection connects to the basal ganglia.
 - In this circuit, DA neurons primarily target inhibitory cells called medium spiny neurons (MSNs), which preferentially produce either D1-like, or D2-like DA receptors.
 - D1-like receptors are excitatory
 - D2-like receptors are inhibitory
 - The two types MSNs contribute to the direct and indirect striatal circuits respectively



The cholinergic neuromodulatory system

Acetylcholine (ACh) is classically called the “learning” neurotransmitter.

The first neurotransmitter ever discovered!



Note: ACh plays a very different role in the peripheral nervous system as the main neurotransmitter at the neuromuscular junction

Saswati et al., 2015

Making history, discovering the first neurotransmitter



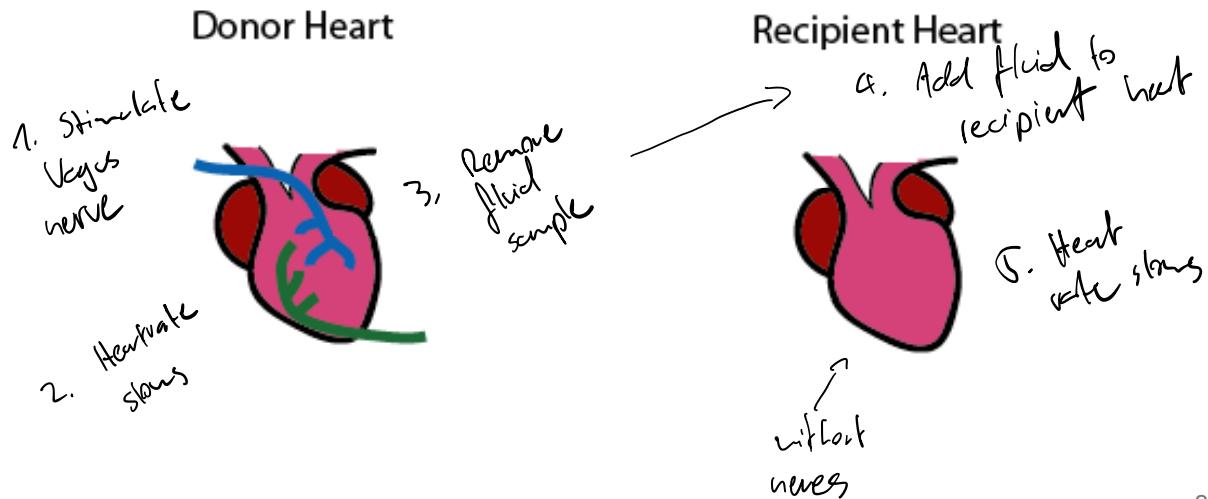
Otto Loewi

Acetylcholine was first isolated as a neurochemical in 1915

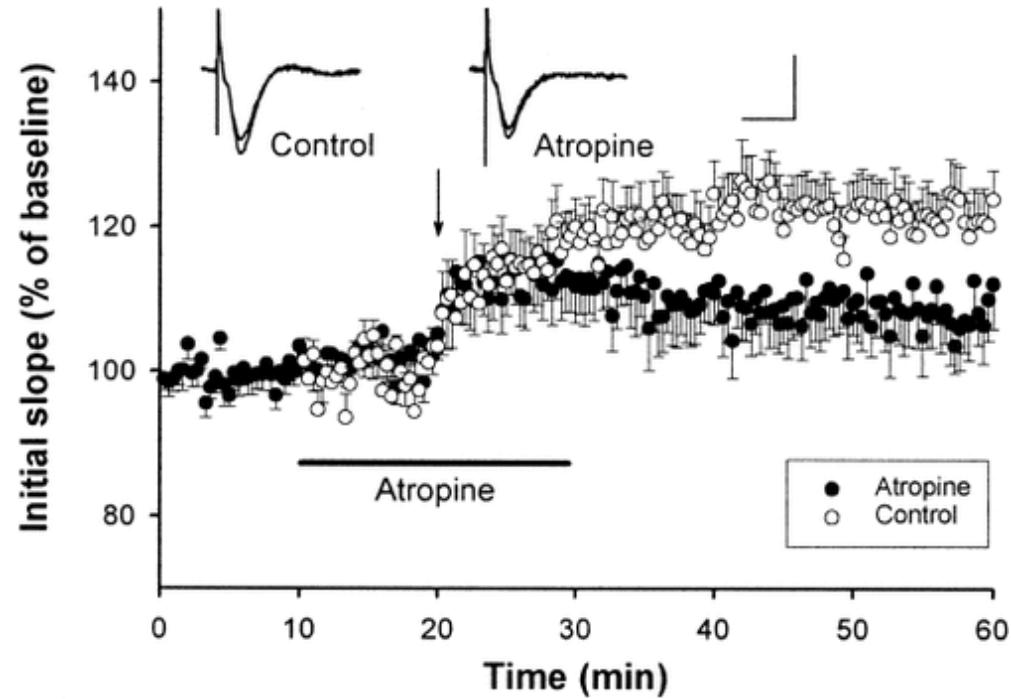
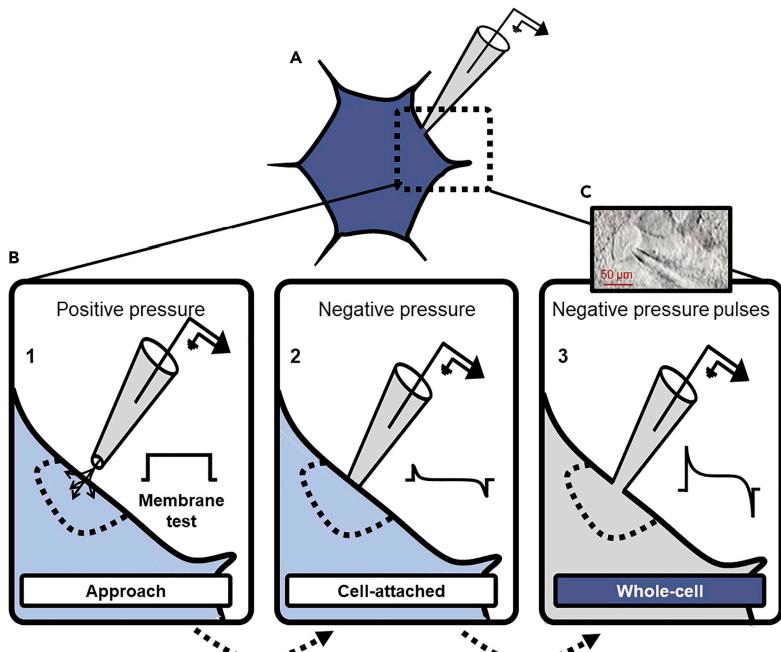
two debates
had various
communicate
with each
other

1. purely electrical
2. purely chemical

Otto Loewi claims to have thought of the following experiment in a dream.

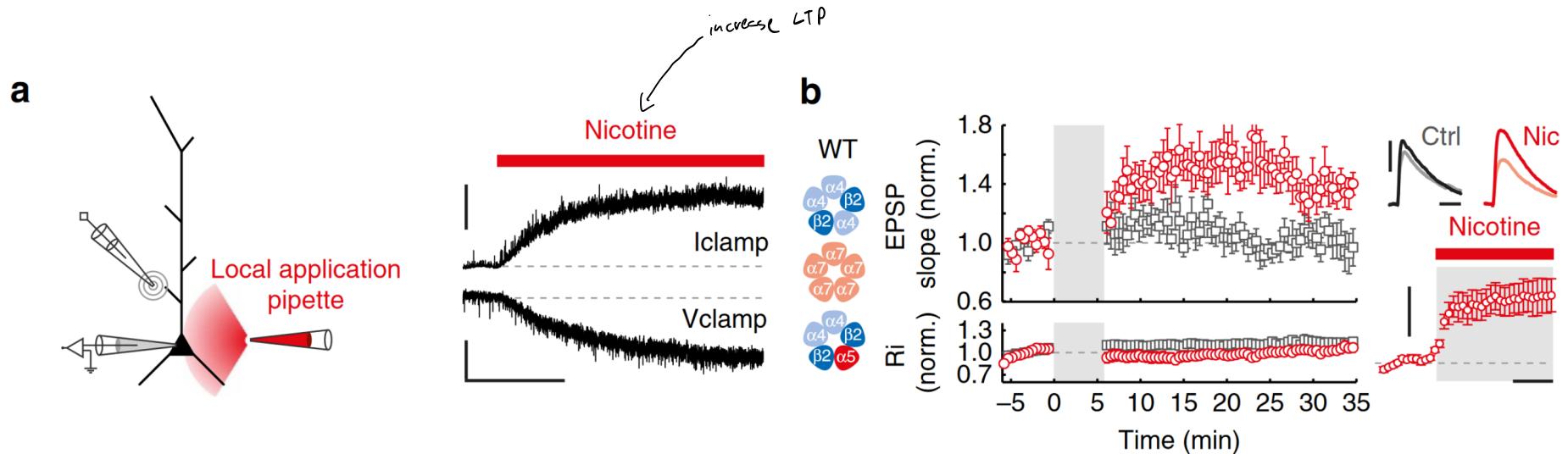


Acetylcholine facilitates long term potentiation



Cheong et al., 2001

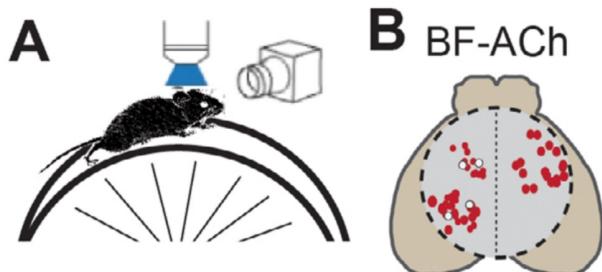
Acetylcholine facilitates long term potentiation (LTP)



Cholinergic dysfunction has also been strongly associated with age-related cognitive decline.

Verhoog et al., 2016

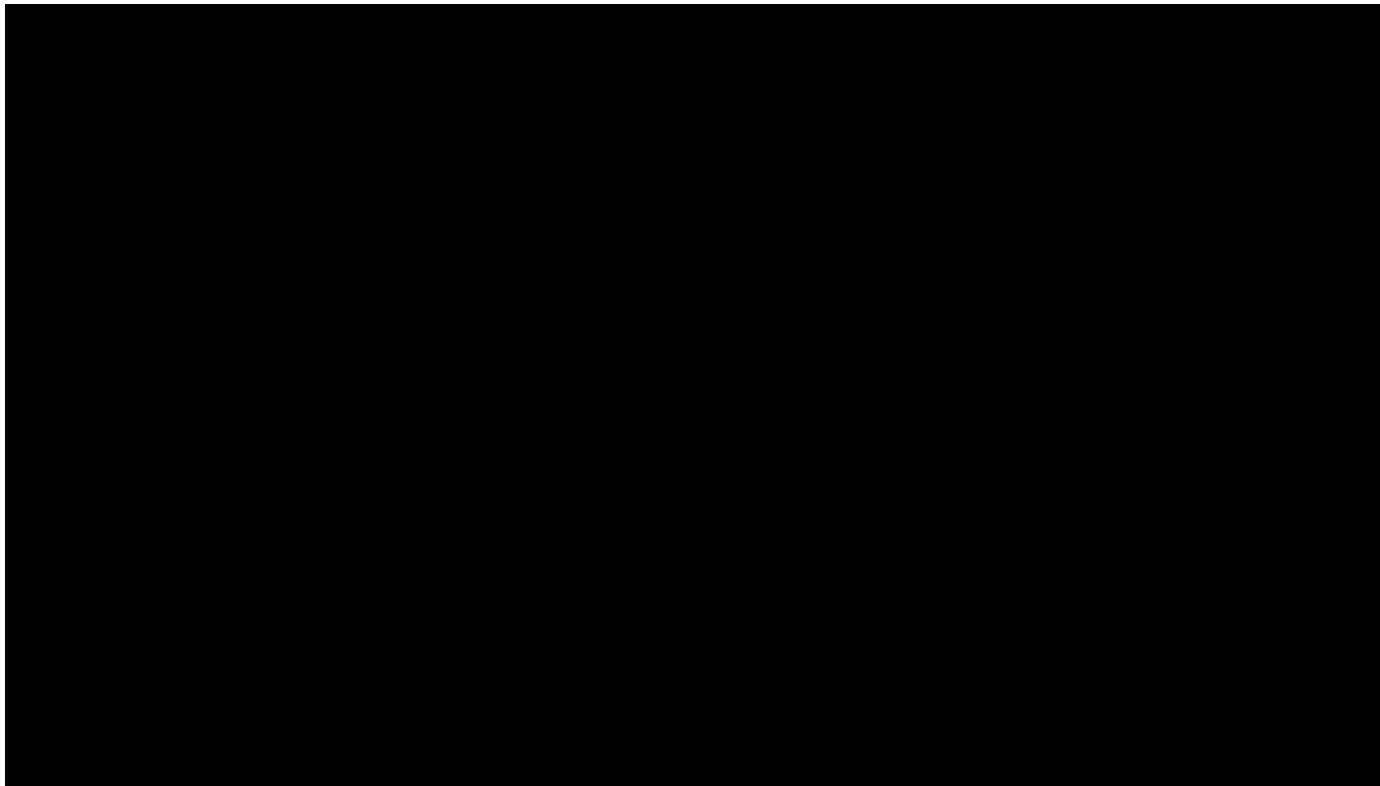
Cholinergic signaling mediates arousal and attention



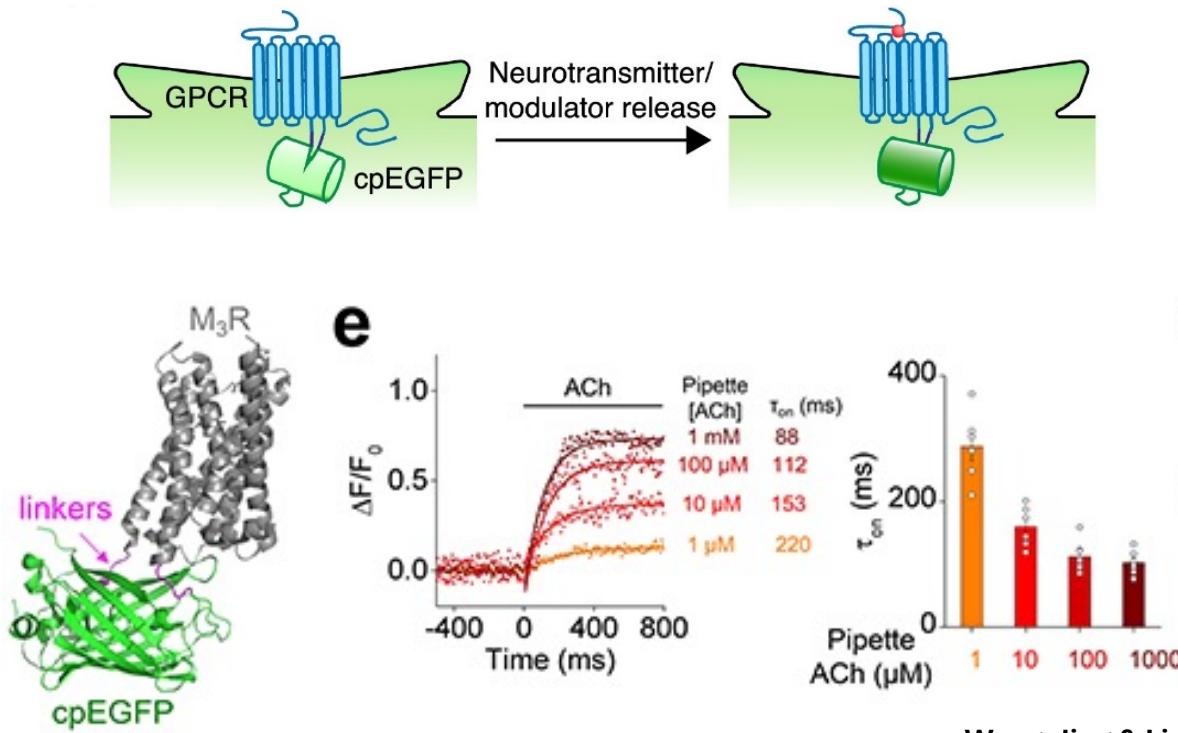
How do researchers detect neuromodulator activity if it does not always directly produce spiking?

Reimer et al., 2016
Collins et al., 2023

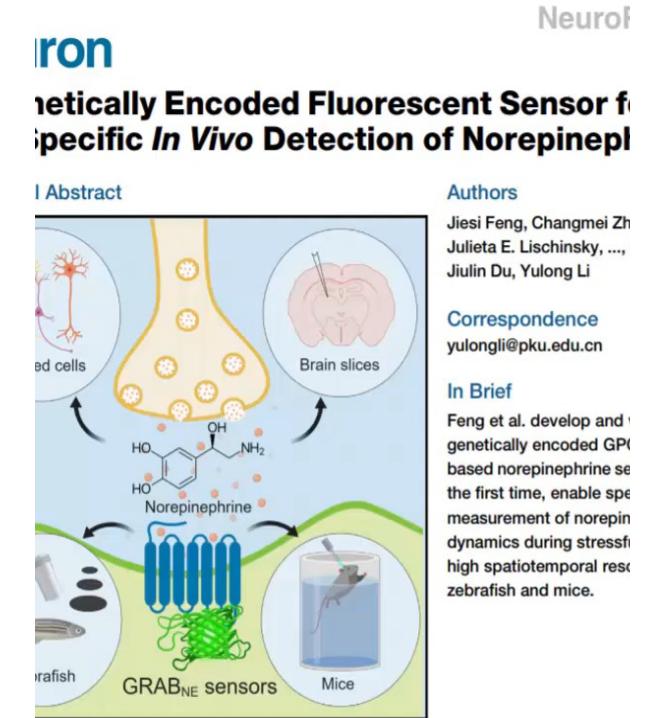
Measuring neuromodulator activity *in vivo*



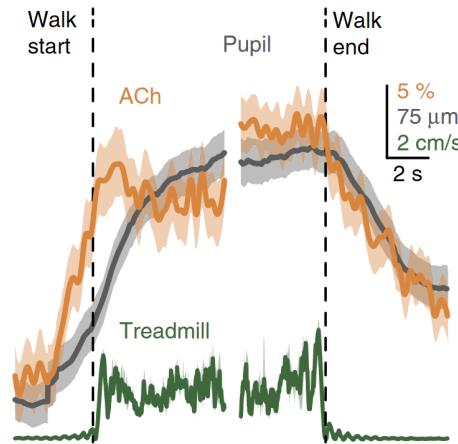
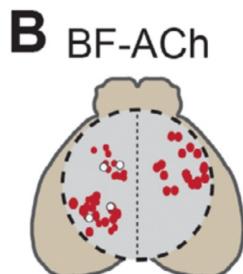
Measuring neuromodulator activity *in vivo*



Wang, Jing & Li, 2018
Jing et al., 2021

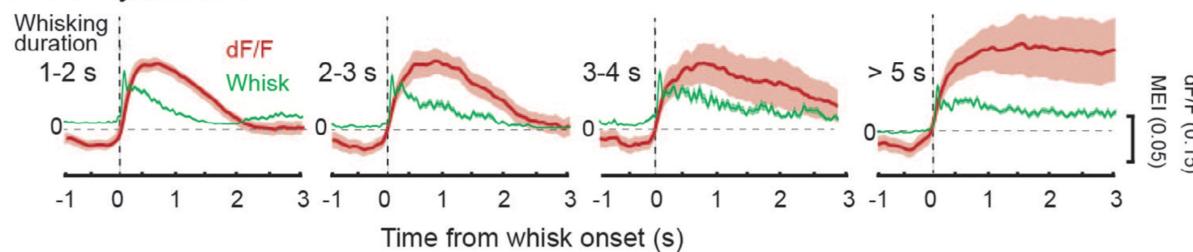


Cholinergic signaling mediates arousal and attention



Cholinergic activity also fluctuates closely with certain motor behaviors, especially those related to exploration of the environment.

D Acetylcholine

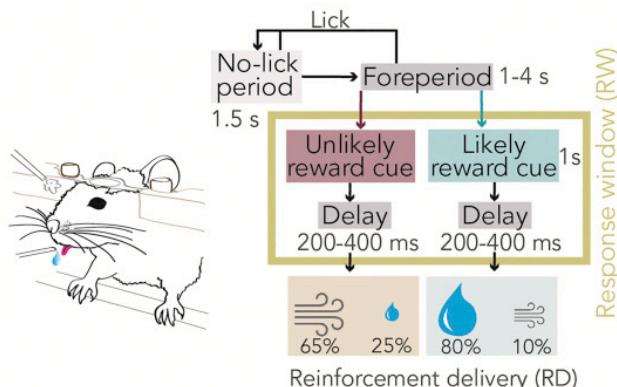


Reimer et al., 2016
Collins et al., 2023

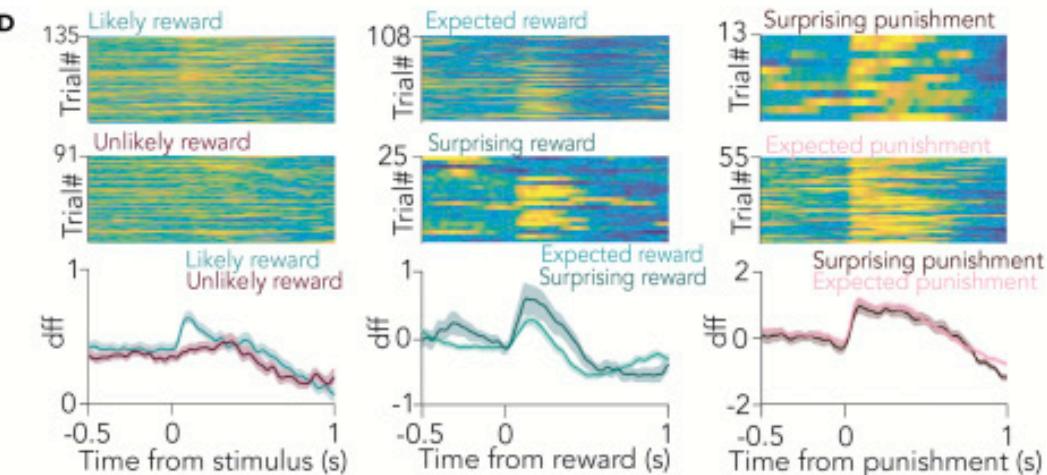
Cholinergic neurons encode cues, rewards and punishments

then why do we use dopamine?

A



D



Encoding strength is often linked to the *certainty* of a cue or outcome.

Punishments are the exception;; they are always strongly encoded.

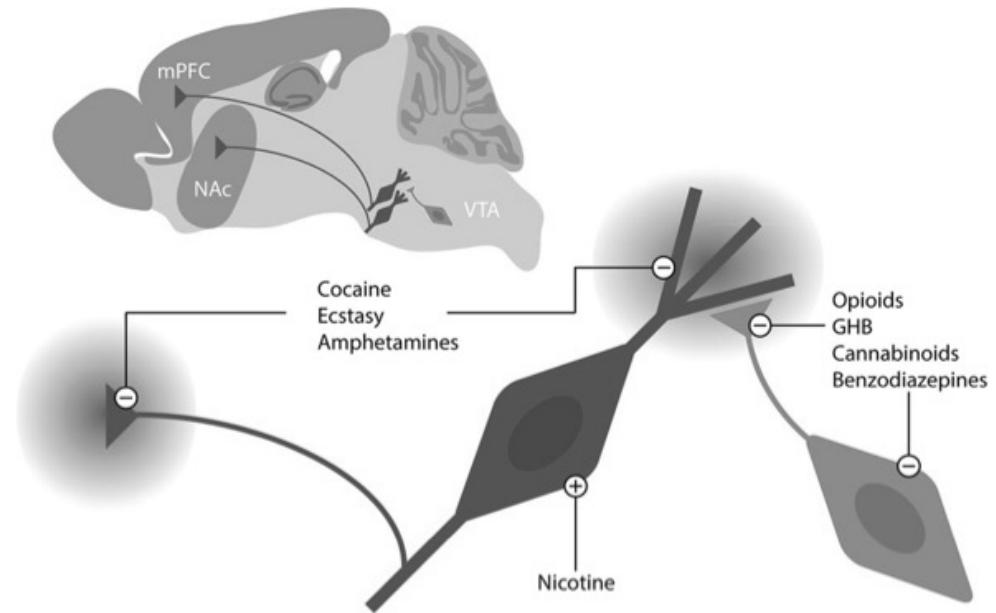
Manipulating neuromodulatory circuits

Neuromodulatory systems are often the targets of pharmaceutical products, both clinical and recreational.

A few examples of clinical drugs targeting NM circuits:

- SSRIs and SNRIs for depression and anxiety disorders.
- L-DOPA for Parkinson's disease.

↓
helps synthesize
dopamine

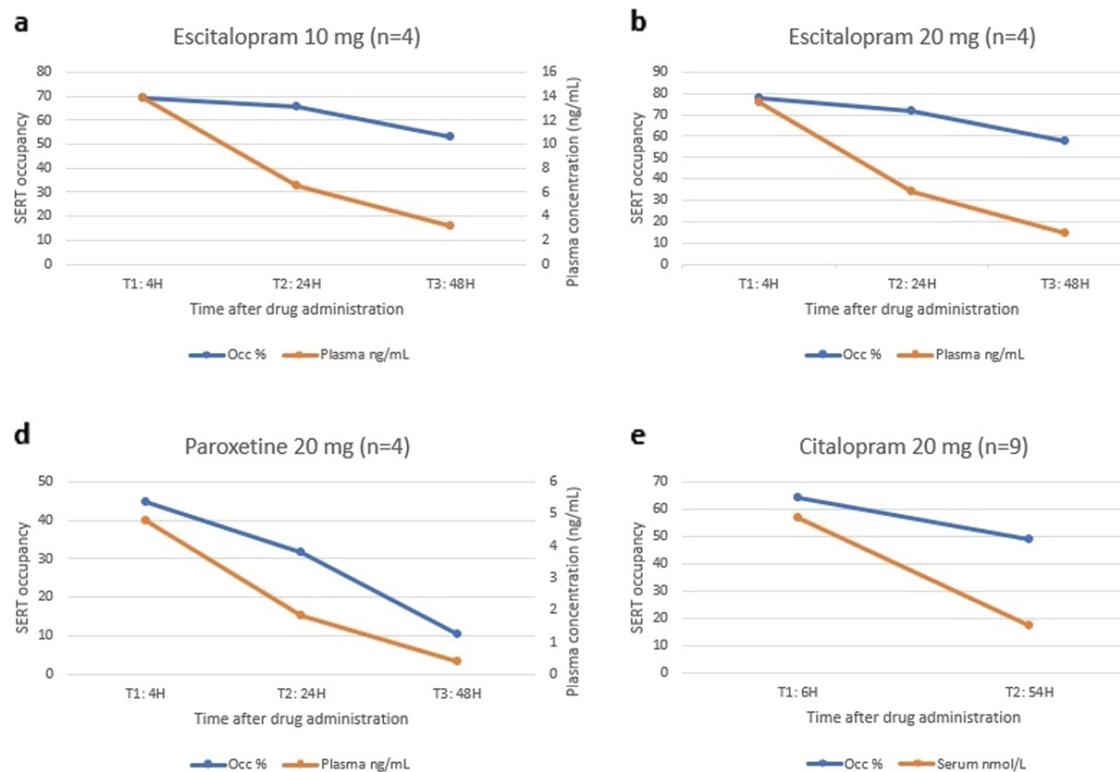


Luscher, 2013

Manipulating neuromodulatory circuits

While great for making long-lasting changes to NM systems, altering NMs more rapidly can be challenging.

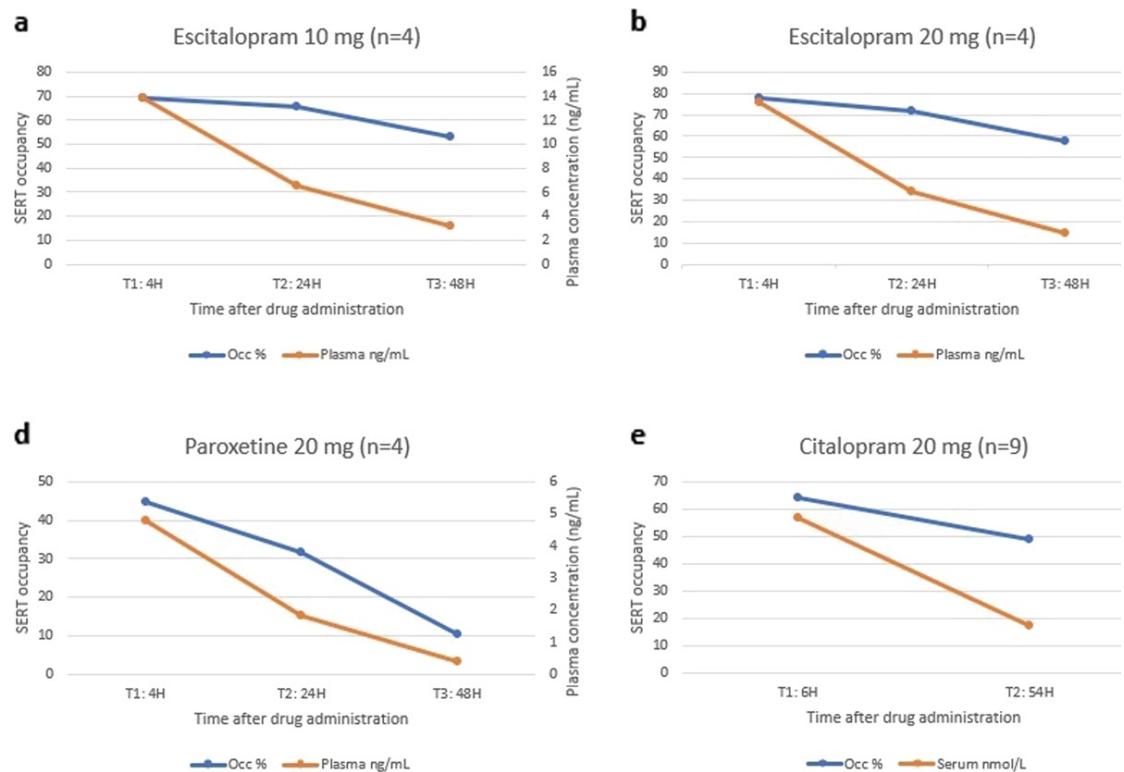
NOTE: drug treatments are slow acting partially by design. It is easier to take one pill a day instead of one pill and hour.



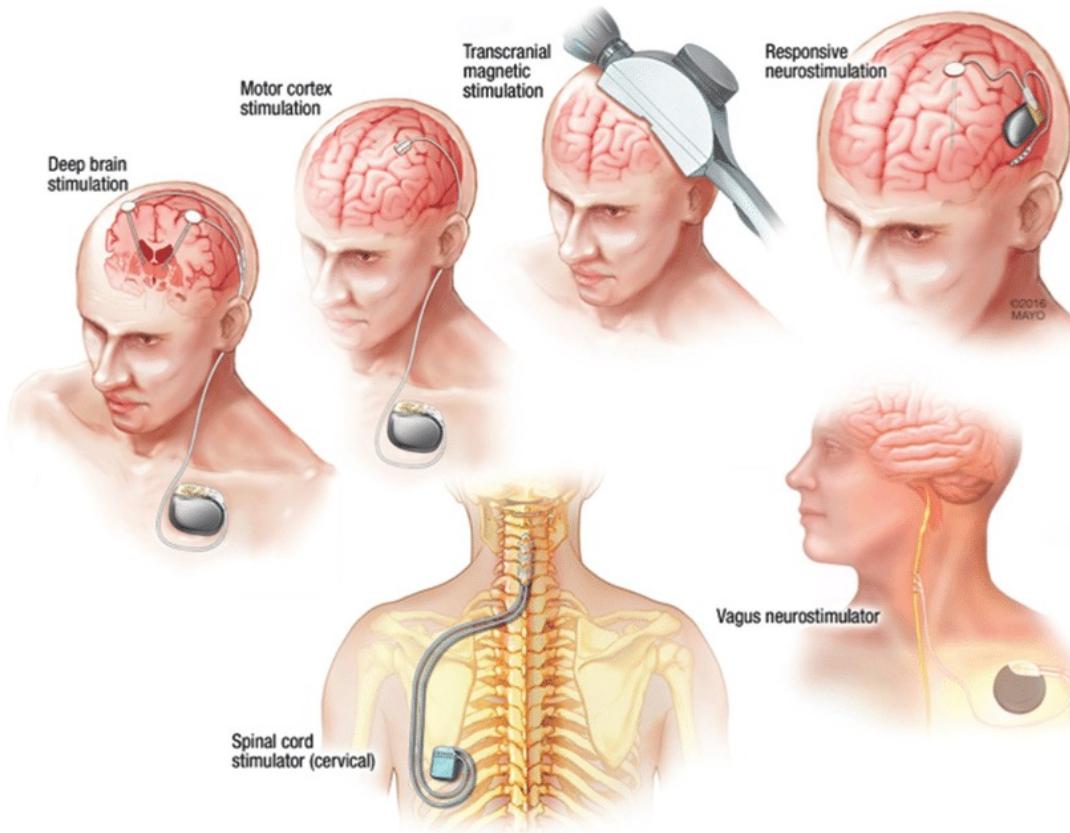
Manipulating neuromodulatory circuits

While great for making long-lasting changes to NM systems, altering NMs more rapidly can be challenging.

What are some tools that could allow rapid manipulation of neuromodulators?



Neurostimulation Devices for the Treatment of Neurologic Disorders



Edwards et al., 2017

Neurostimulation devices interface with the nervous system directly by delivering **electrical stimulation to target circuits.**

The majority of these devices are invasive, but research into noninvasive stimulation is growing.

most
of
the
time
patient
have
several
problems
to
justify
surgery

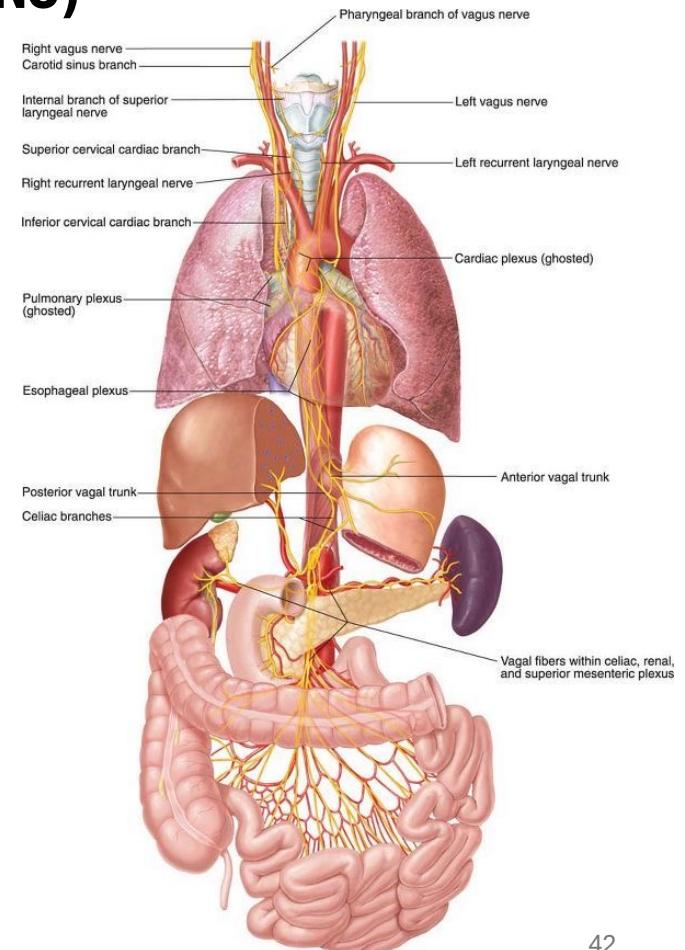
Vagus Nerve Stimulation (VNS)

The vagus nerve (VN) is the 10th cranial nerve

It innervates many visceral organs, as well as the heart and the lungs.

The “gut-brain-axis” signals through the VN.

- Stimulating the VN can activate the parasympathetic nervous system, and this is the source of the ‘vagal nerve reset’ trends currently common in social media

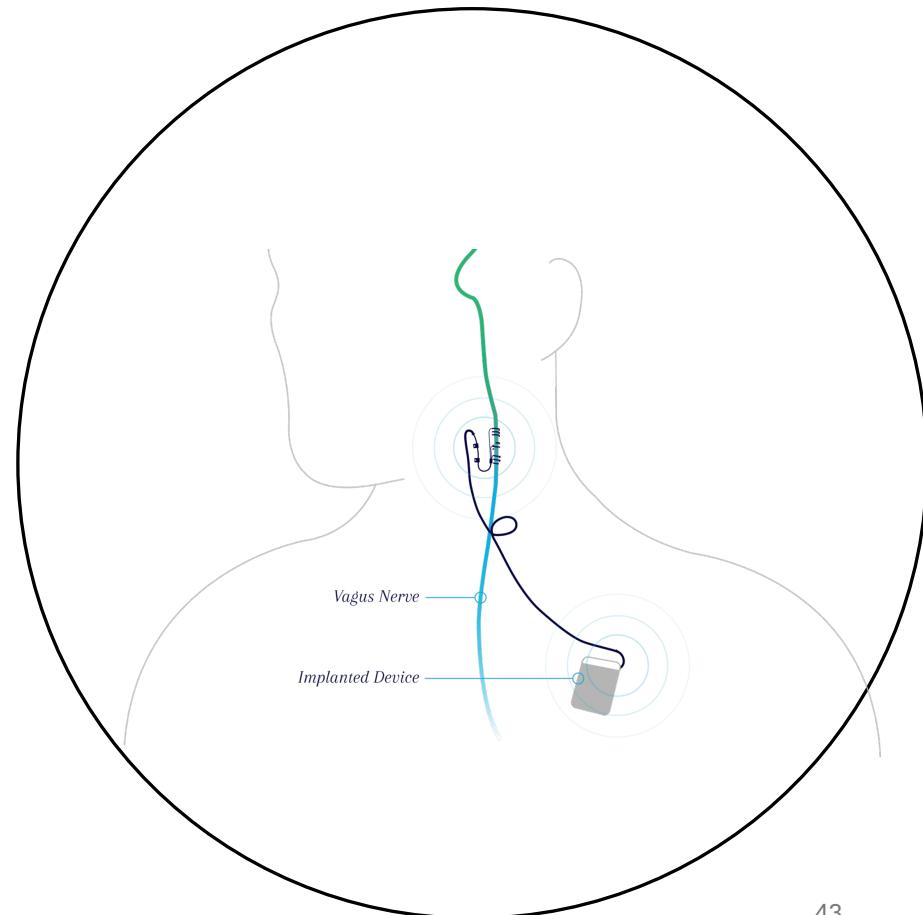


Vagus Nerve Stimulation (VNS)

VNS is a clinical treatment where a stimulating electrode cuff is placed on the cervical branch of the vagus nerve.

VNS has been used as a clinical treatment for depression and epilepsy for two decades.

- There are about 100,000 implanted patients in the US today.

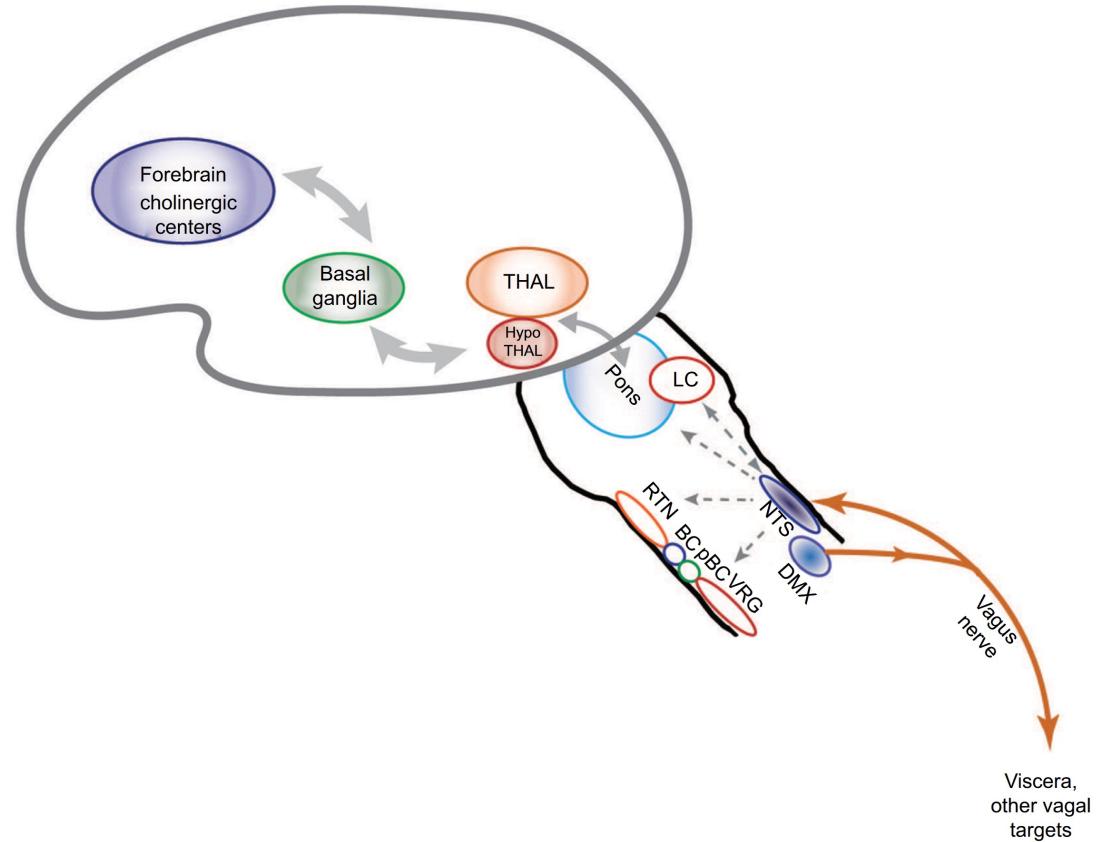


VNS activates several CNS modulatory systems

The VN terminates in the nucleus of the stria terminalis (NTS).

Stimulation of this NTS drives activity in several neuromodulatory centers.

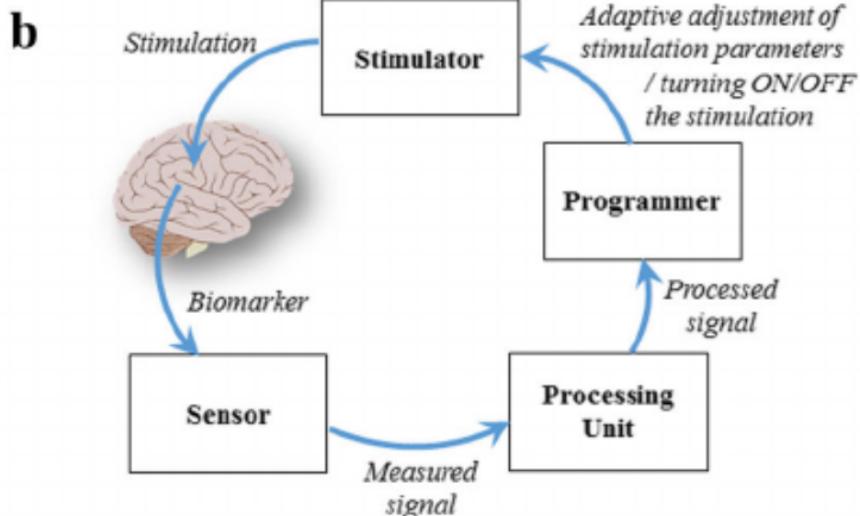
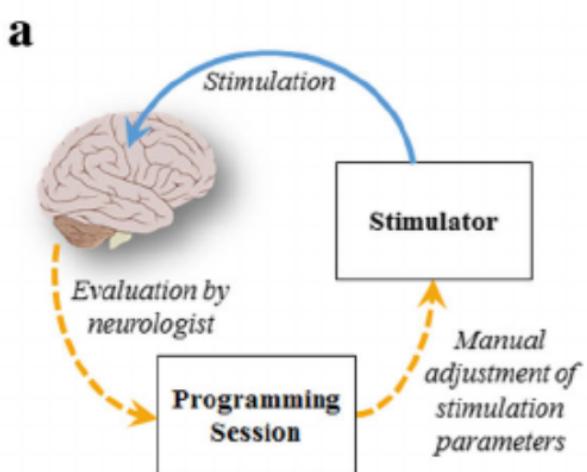
What are some potential issues with broad NM activation?



Key Concept: Open-loop vs closed-loop stimulation

Open-loop stimulation is given at a set interval, and is unrelated to biomarkers

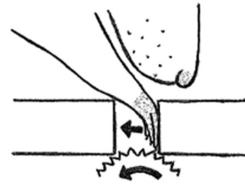
Closed-loop stimulation uses biomarkers as a signal to start or stop stimulation



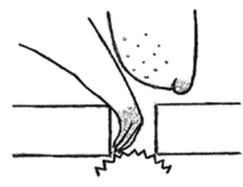
Closed-loop VNS can enhance cortical plasticity

A Wheel Spin Task (Distal Forelimb)

Step 1

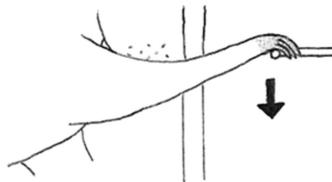


Step 2



B Lever Press Task (Proximal Forelimb)

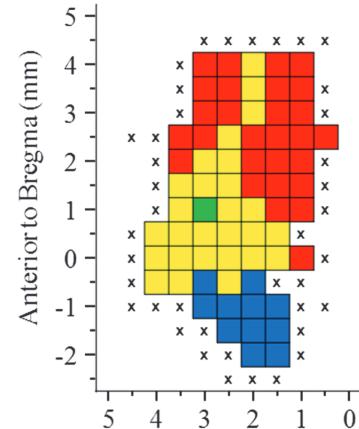
Step 1



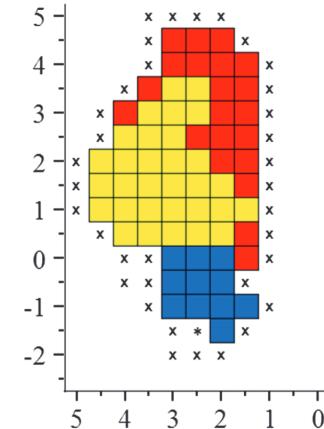
Step 2



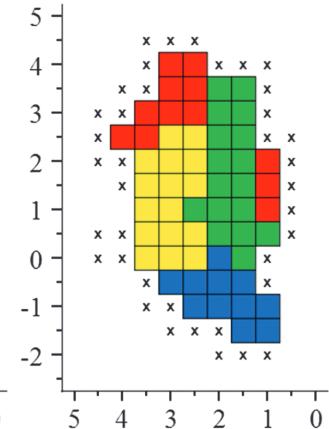
A Naive



B Wheel-spin + VNS



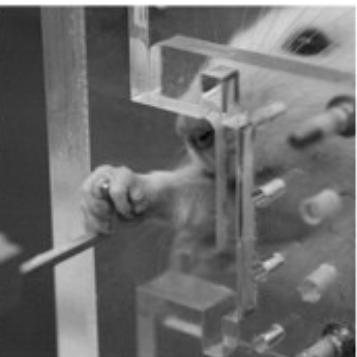
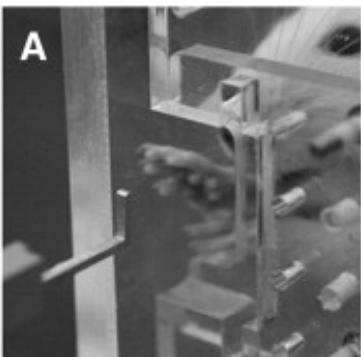
C Lever-press + VNS



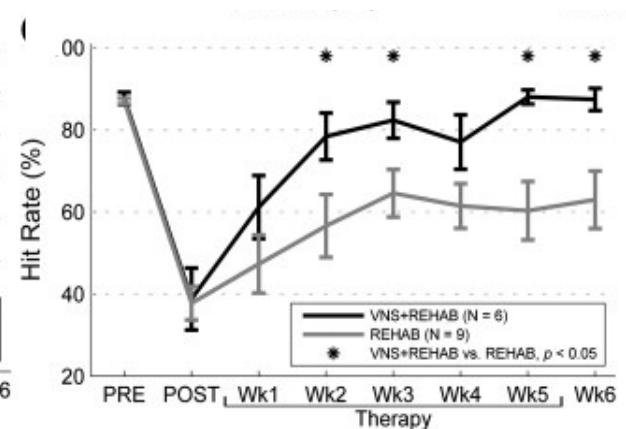
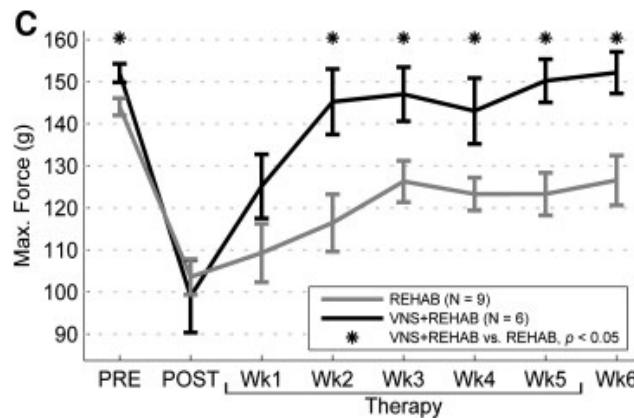
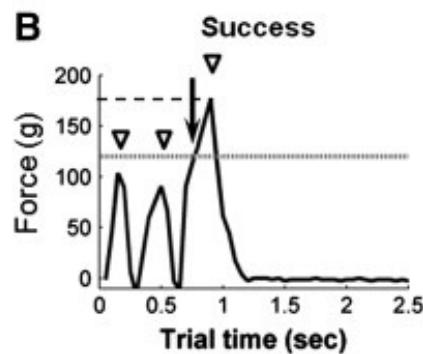
■ Distal Forelimb ■ Proximal Forelimb ■ Head ■ Hindlimb

Porter et al., 2011

VNS can enhance stroke rehabilitation



Mice who had been trained on a lever pull task were given ischemic strokes.



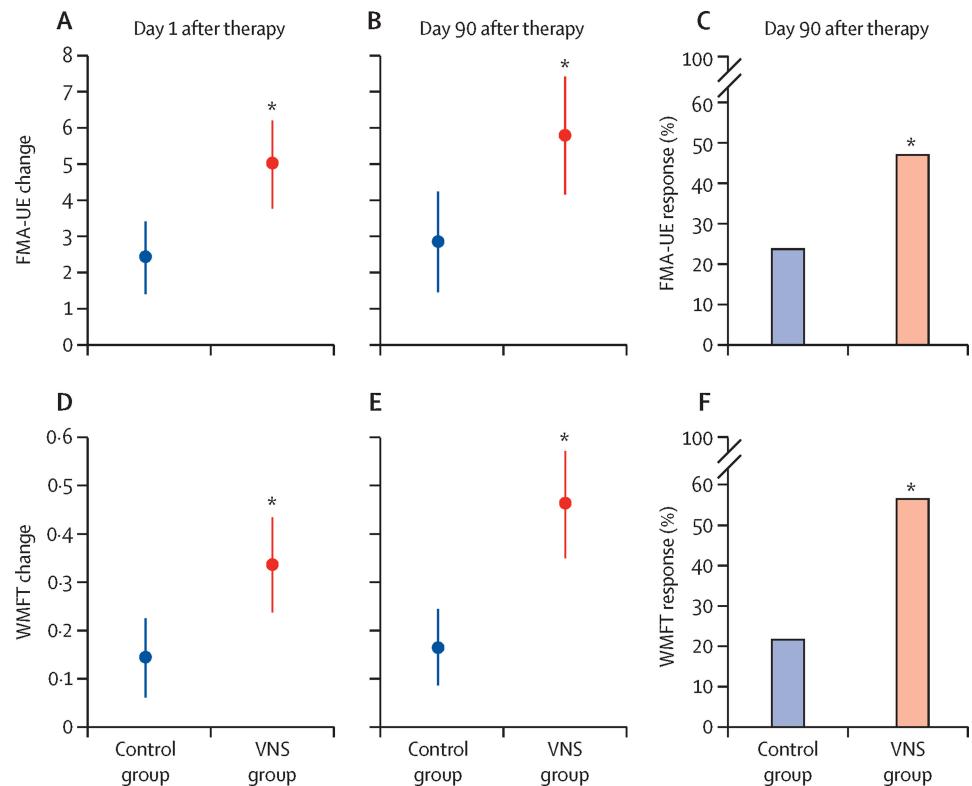
They were then retrained on the task while receiving cl-VNS.

VNS can enhance stroke rehabilitation

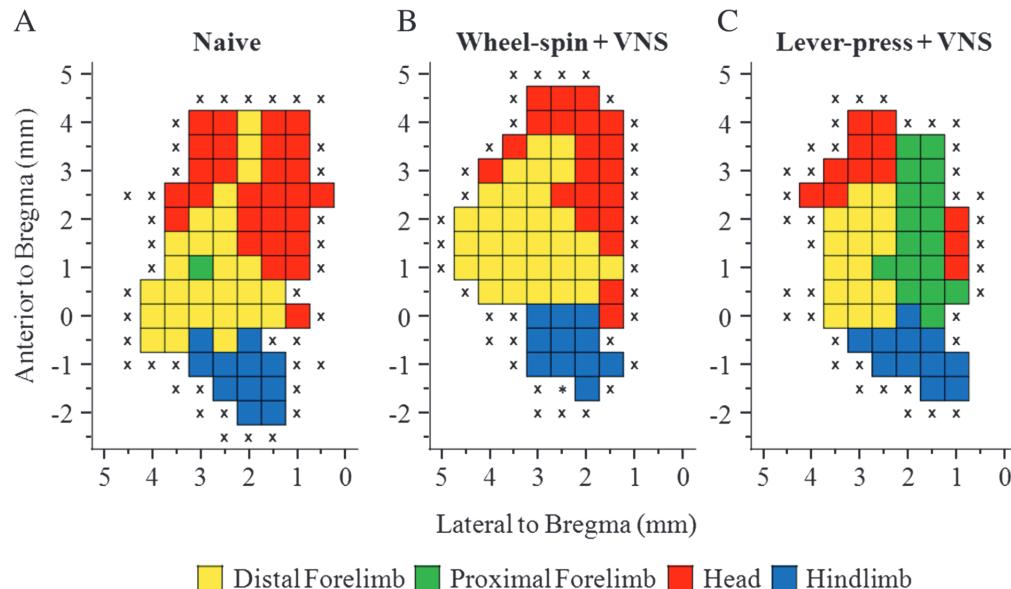
A similar protocol was implemented in clinic with stroke patients, with similar results.

- VNS was approved as a stroke rehabilitation treatment in 2021.

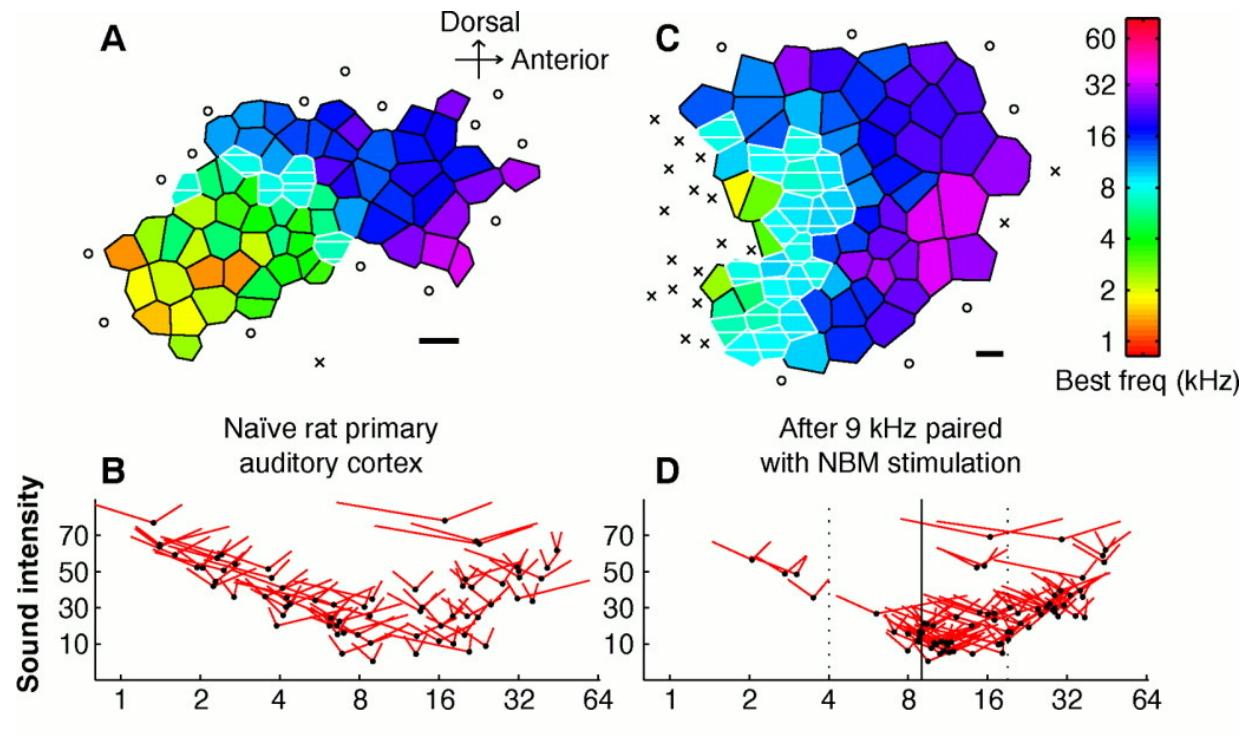
What are the mechanisms that underly VNS-enhanced plasticity?



How do you identify the target system of a neurostimulation device?



Does directly stimulating the target system produce the same outcomes?



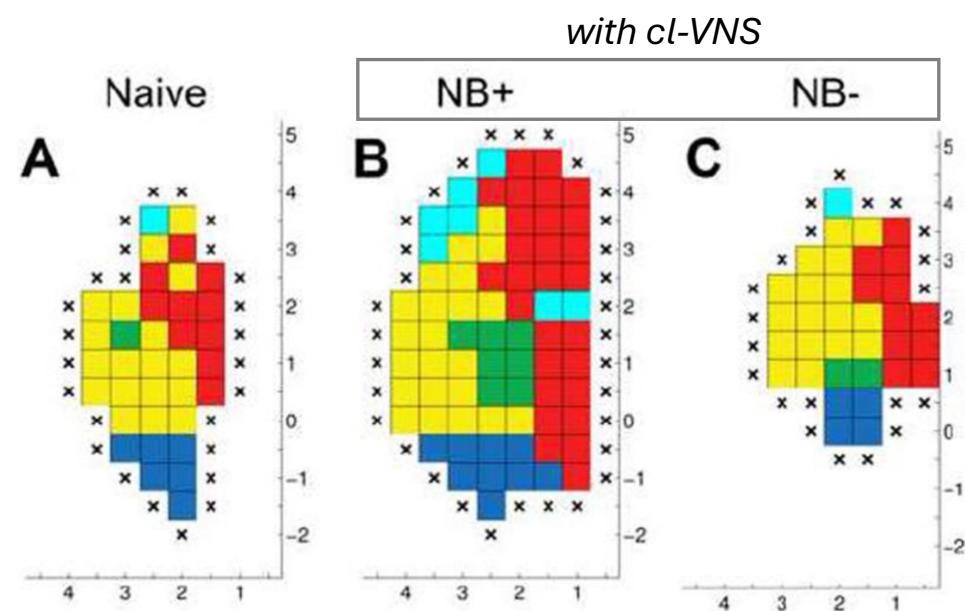
Cholinergic basal forebrain stimulation paired with a tone drives plasticity in auditory cortex

Does lesioning your target system impact the performance of your device?

Chemical lesions of cholinergic neurons prevent VNS-driven remapping of motor cortex.

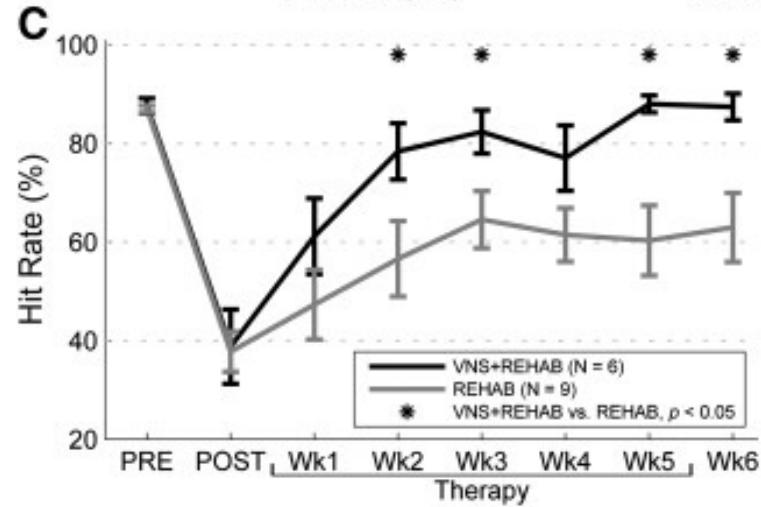
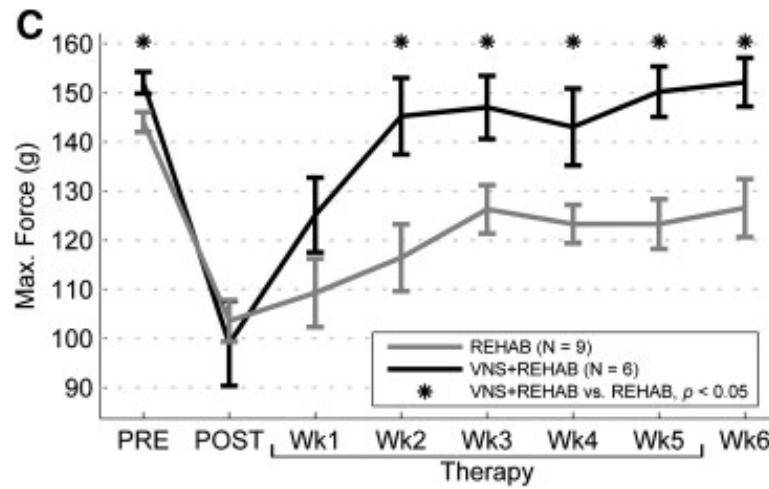
Note: NB refers to the *nucleus basalis of Meynert*, one of the primary nuclei in the basal forebrain.

- Proximal Forelimb
- Distal Forelimb
- Jaw
- Head
- Hindlimb
- ✖ No Response



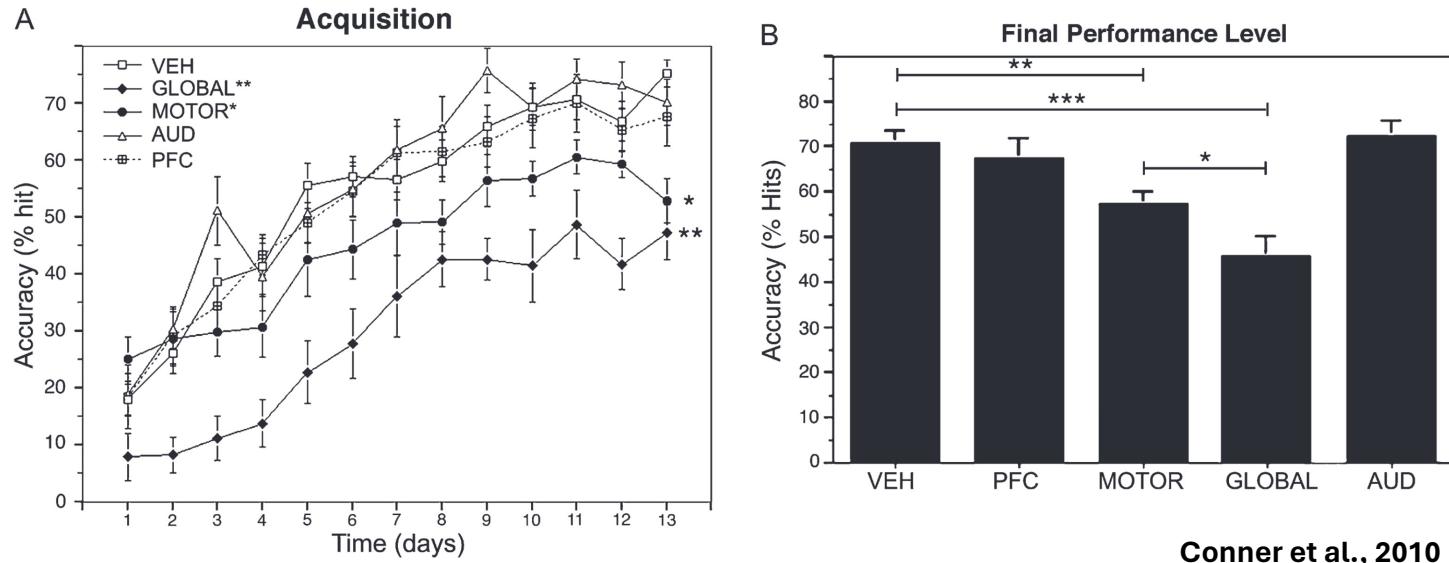
Hulsey et al., 2016

Is the target system naturally involved in the behavior your device treats?



Is the target system naturally involved in the behavior your device treats?

Chemical lesions of cholinergic neurons negatively impact learning in a skilled motor task



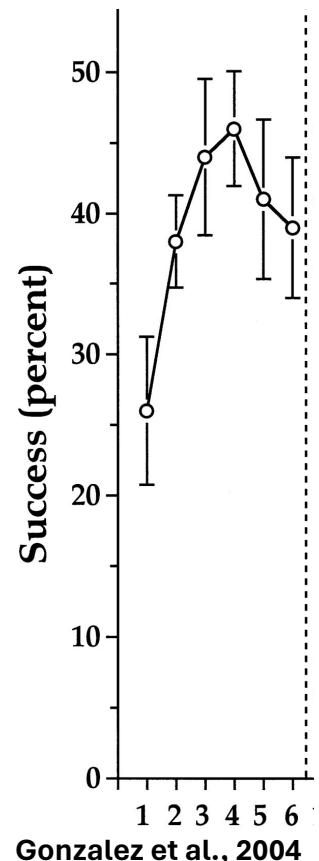
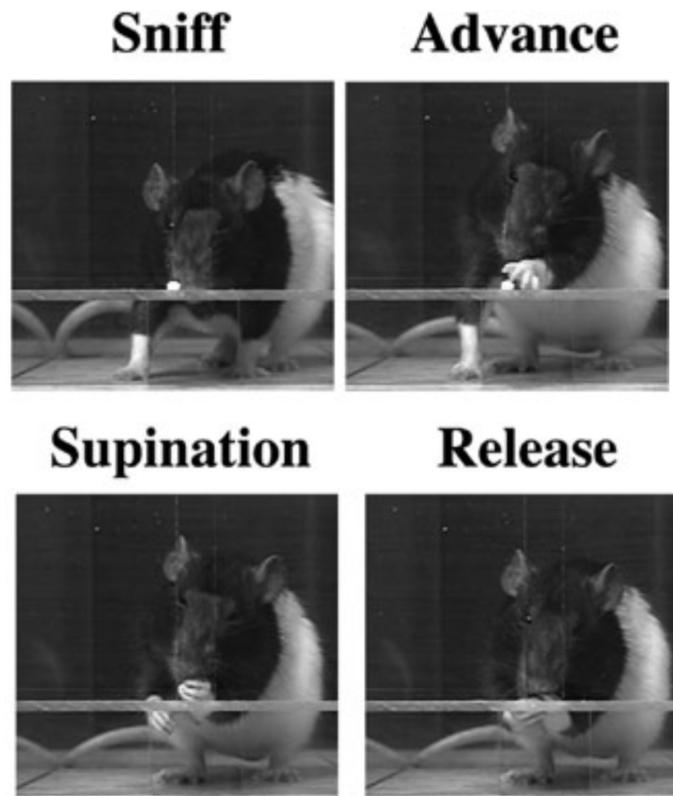
The cholinergic system is a strong candidate mediating VNS effects

Skilled reaching behavior in rodents

Rodents are can be a good model for skilled motor control because they have hands, not paws.

The skilled reach task has been used to study motor control in rodents for several decades.

- In this task, rodents reach for a food pellet with a single paw, and must return it to the cage without dropping it.

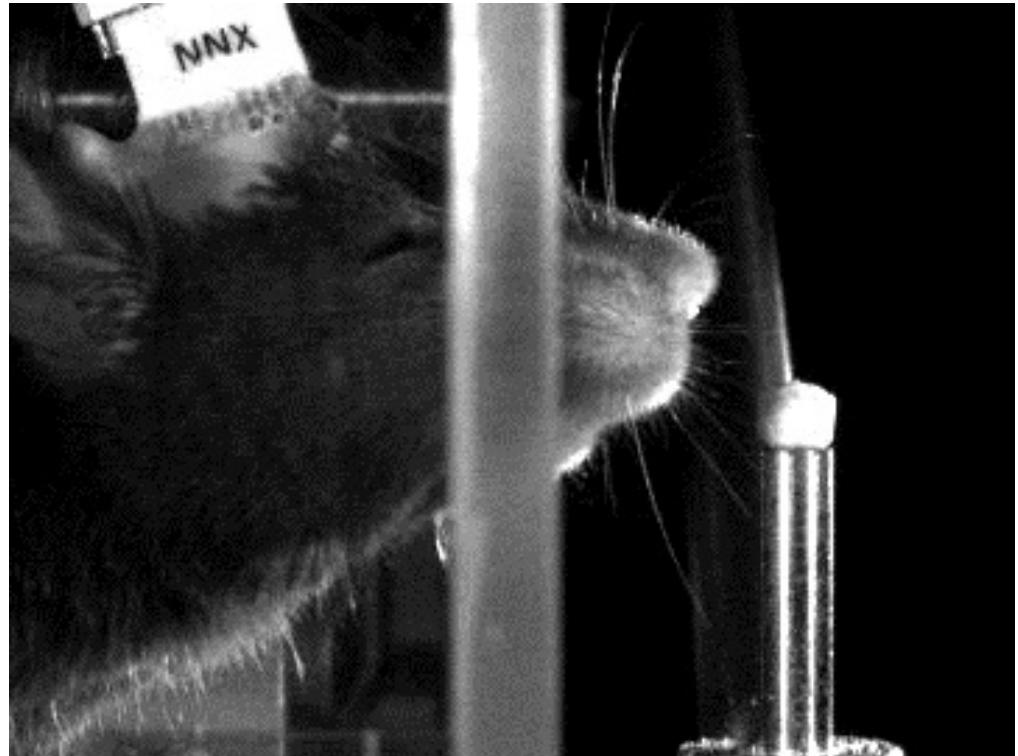


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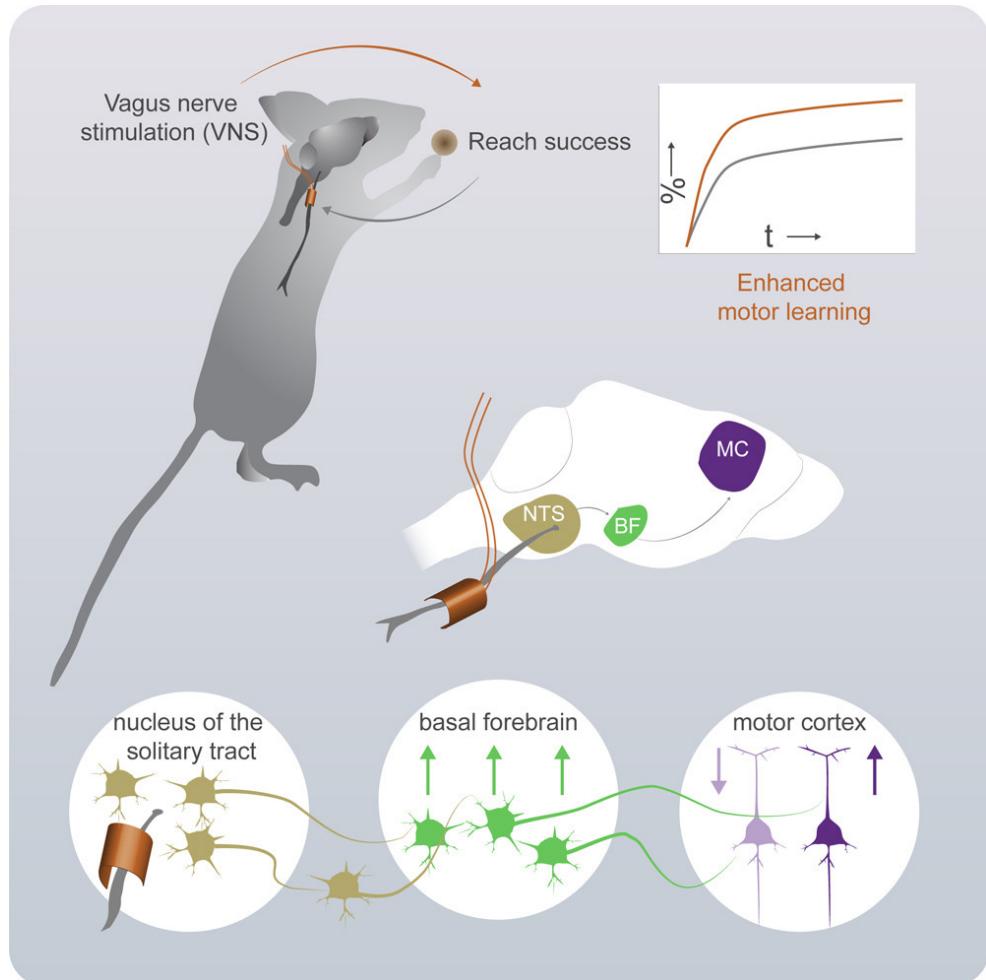
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Article

Vagus nerve stimulation drives selective circuit modulation through cholinergic reinforcement

Spencer Bowles^{1 2 4}, Jordan Hickman^{1 4}, Xiaoyu Peng^{1 2 4}, W. Ryan Williamson³,
Rongchen Huang^{1 2}, Kayden Washington^{1 2}, Dane Donegan^{1 2}, Cristin G. Welle^{1 2 5}  



Summary Part 2

- Neuromodulators refer to neurotransmitters that act primarily through G-protein couple receptors, rather than ligand-gated excitation and inhibition.
 - Neuromodulators can have diverse effects due to the variety of their receptors.
- Acetylcholine is one commonly studied NM.
 - It is associated with mediating plasticity and arousal, as well as encoding cues and outcomes.
- Bioelectric interfaces are a tool for manipulating NMs that can act on a more rapid timescale than pharmaceuticals.
 - They also have high potential for targeted treatment due to closed-looping.
- VNS is a BMI that can enhance rehabilitation after stroke through closed-loop stimulation.
 - There is evidence that this effect is mediated, in part, by activating cholinergic neuromodulation.