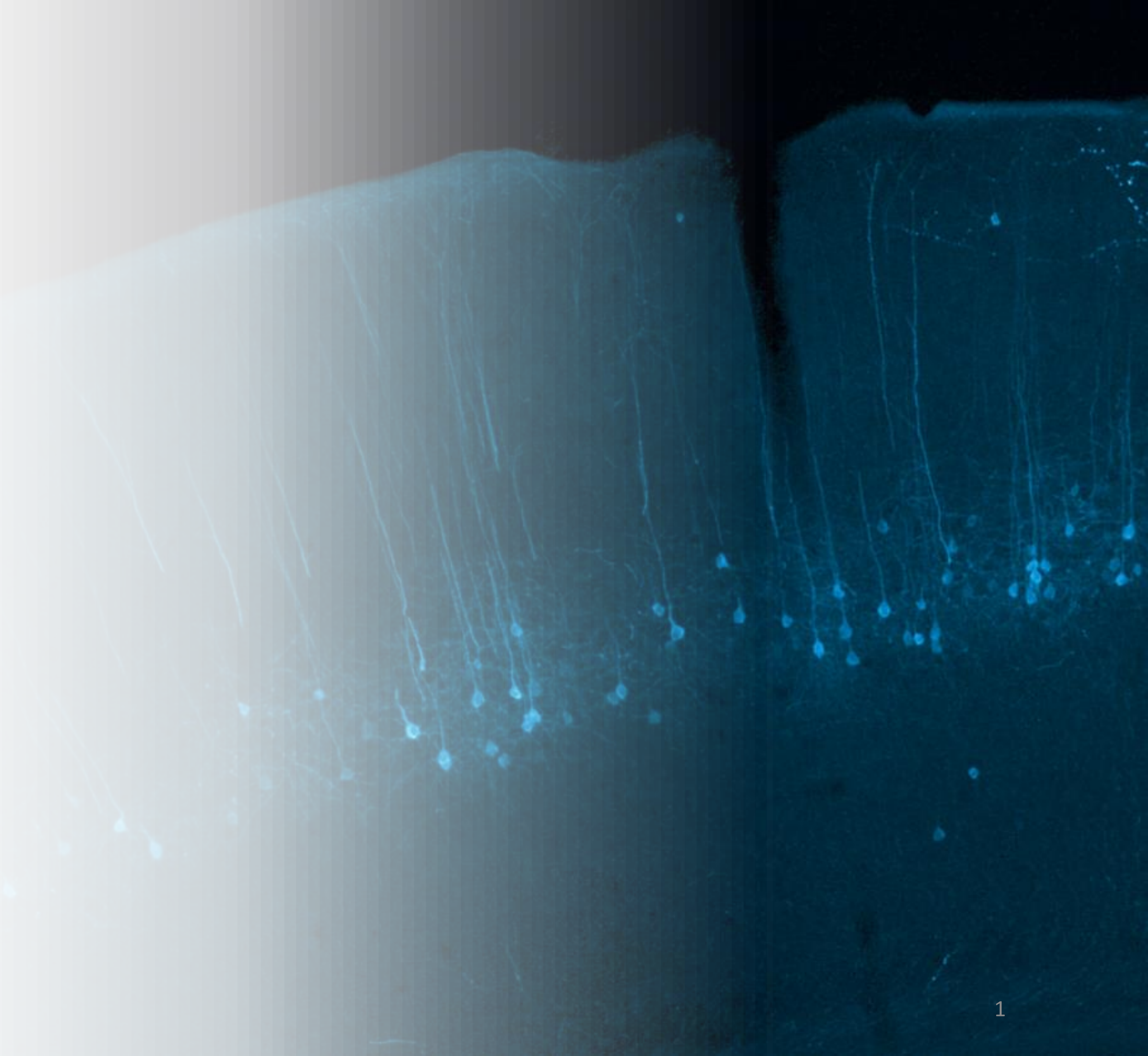
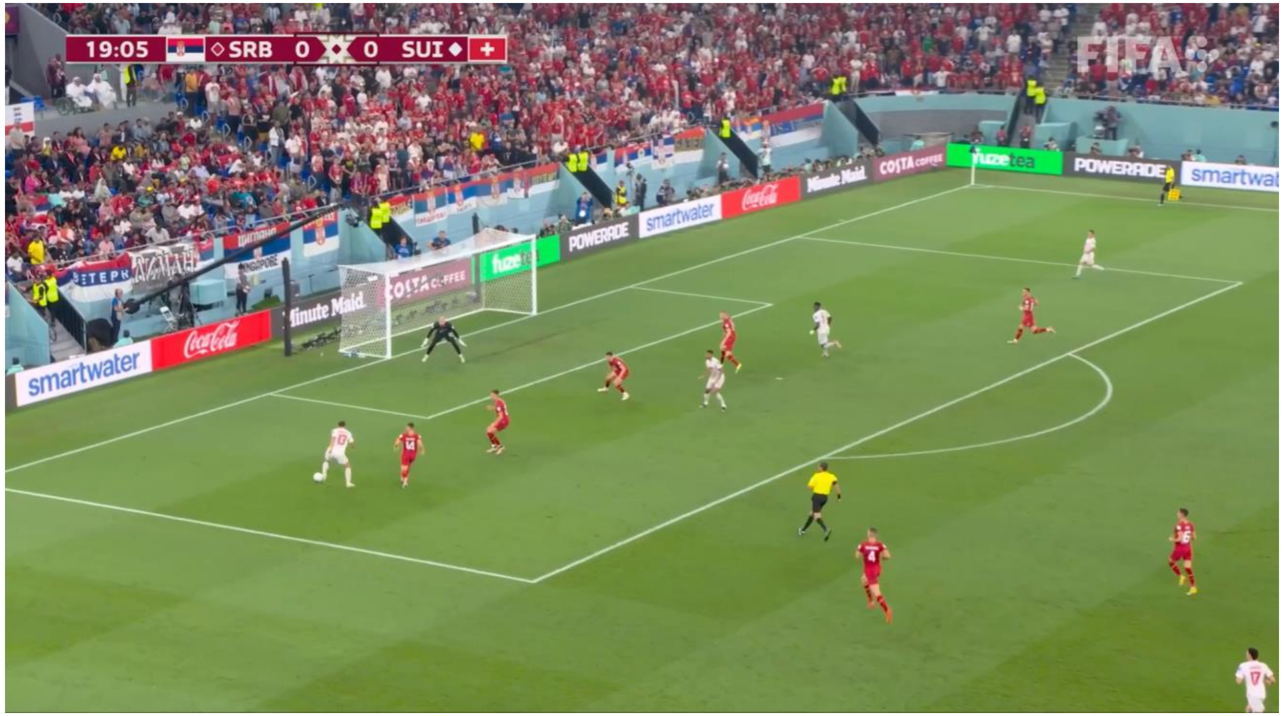
Motor learning & neuro-modulation

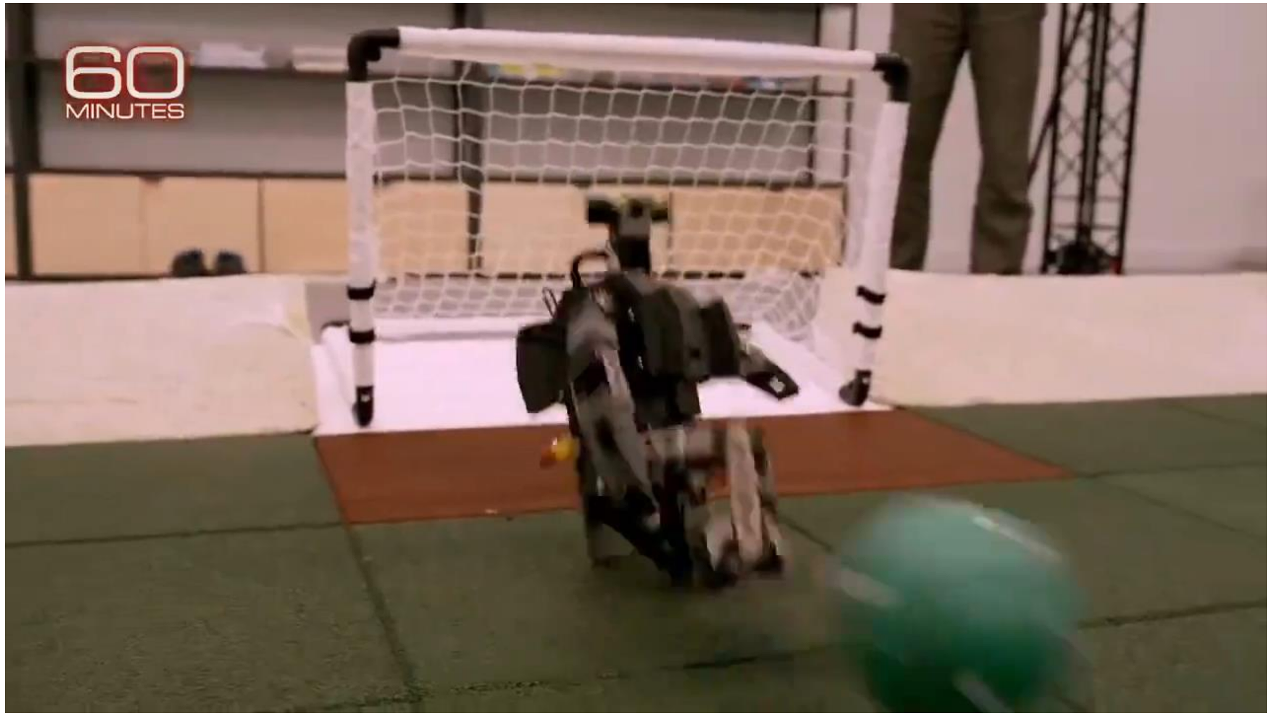
NX-435 Mackenzie Mathis, PhD



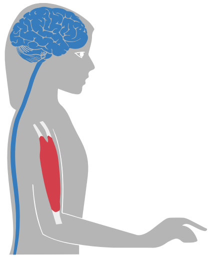
Biological Intelligence

Artificial Intelligence

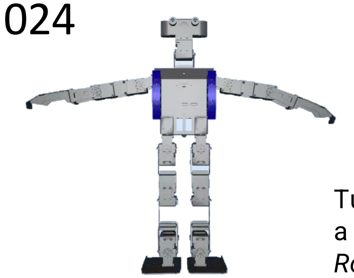




World Cup 2022 CH



DeepMind 2024



Tuomas Haarnoja *et al*. Learning agile soccer skills for a bipedal robot with deep reinforcement learning. *Sci. Robotics* (2024).

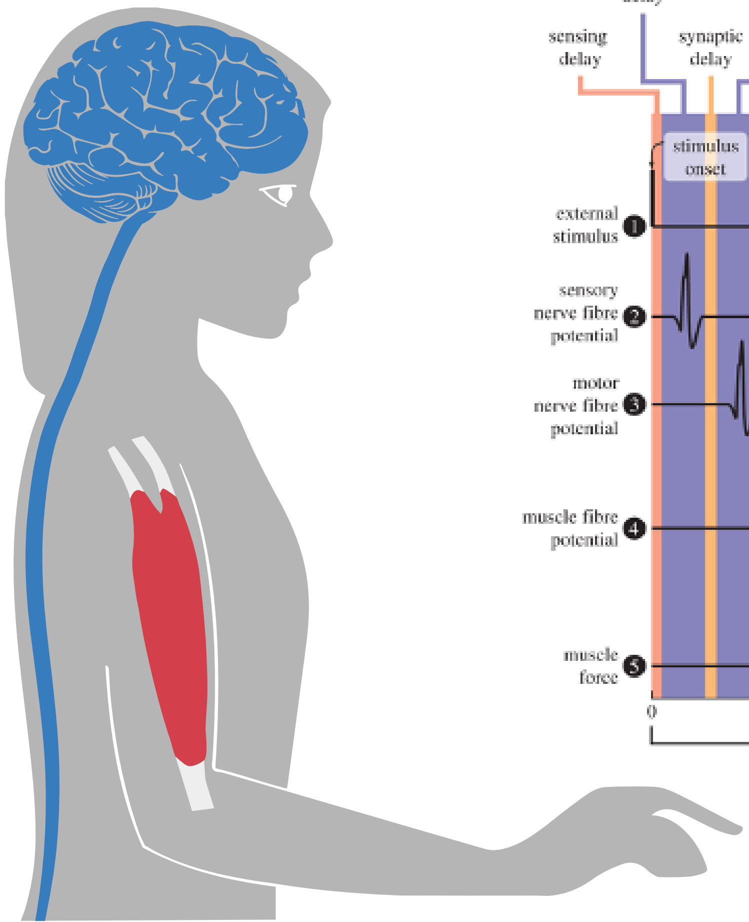
Boston Dynamics

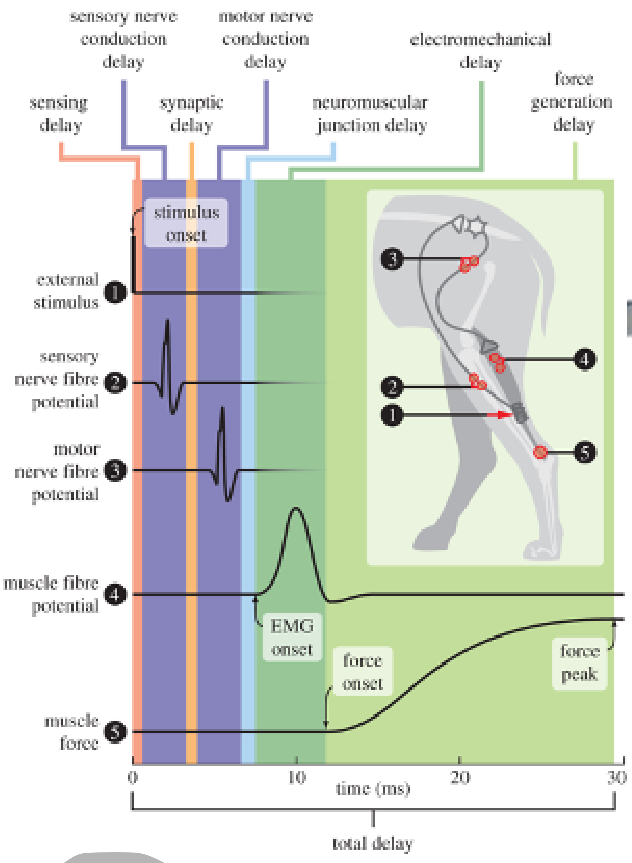
Biological Intelligence

Artificial Intelligence

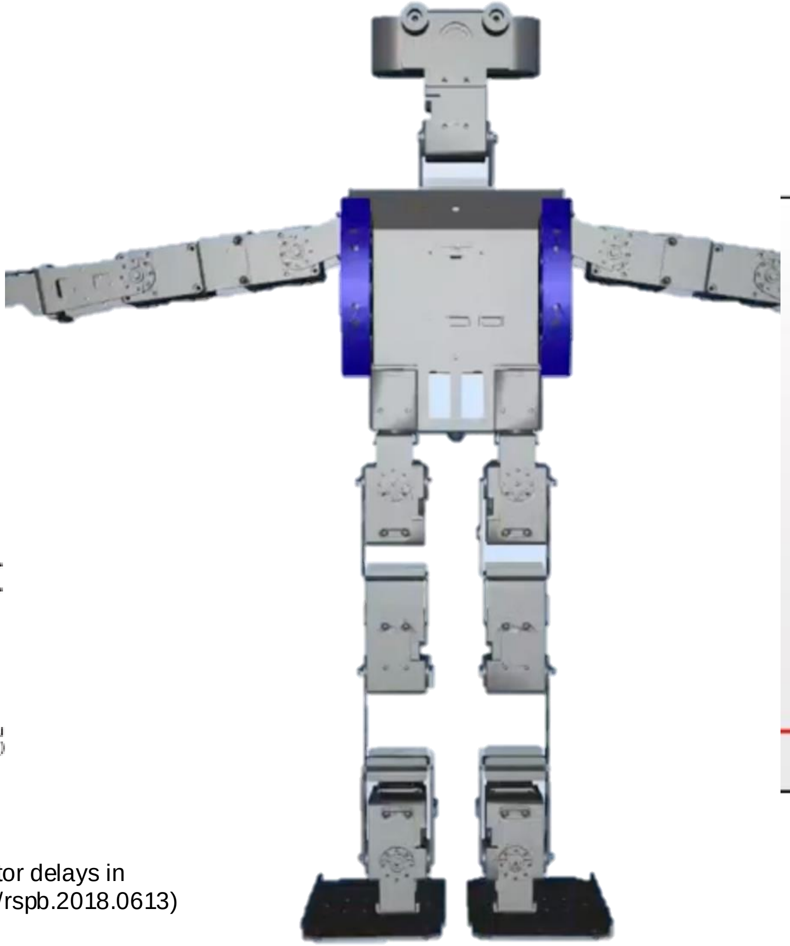
our nervous system is slow!

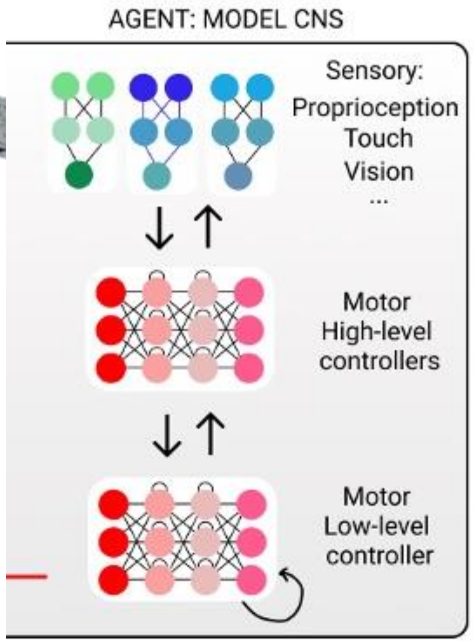
electronics are fast!





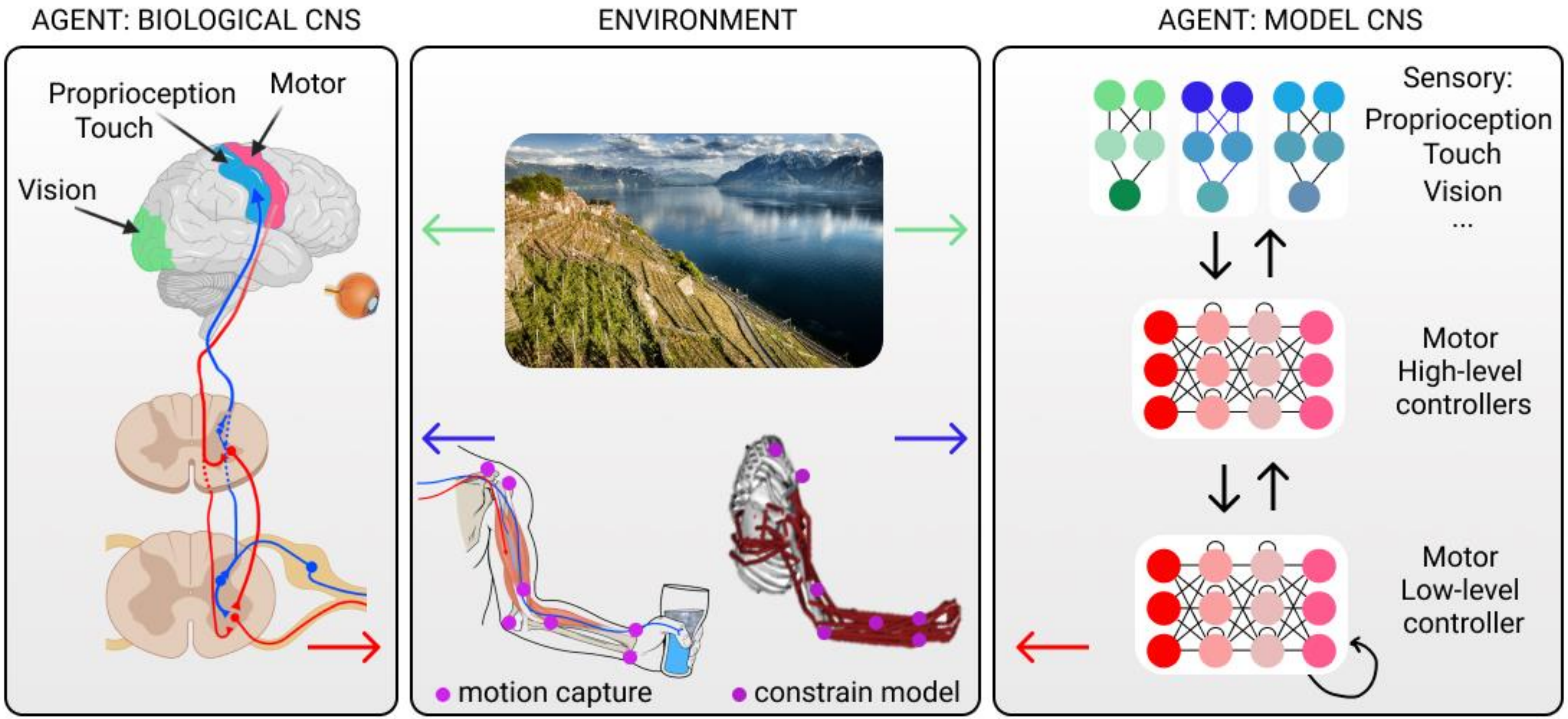
Adapted from Scaling of sensorimotor delays in terrestrial mammals. DOI: (10.1098/rspb.2018.0613)





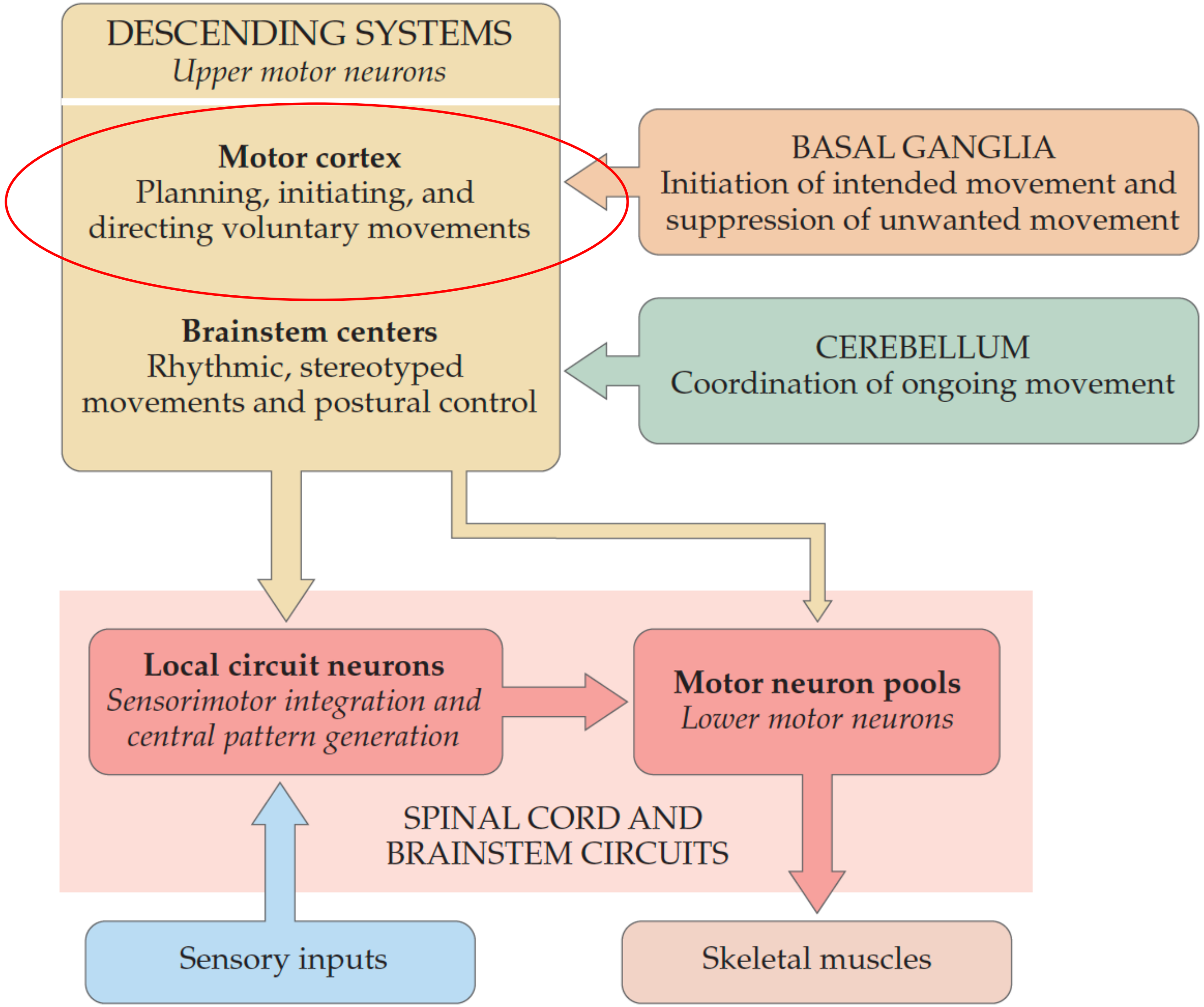
Adapted from Hausmann … Mathis 2021

Reverse engineering adaptive behavior



Hausmann et al. Current Opinion in Neurobiology 2021

The neural control of movement



Purves, Figure 16.1

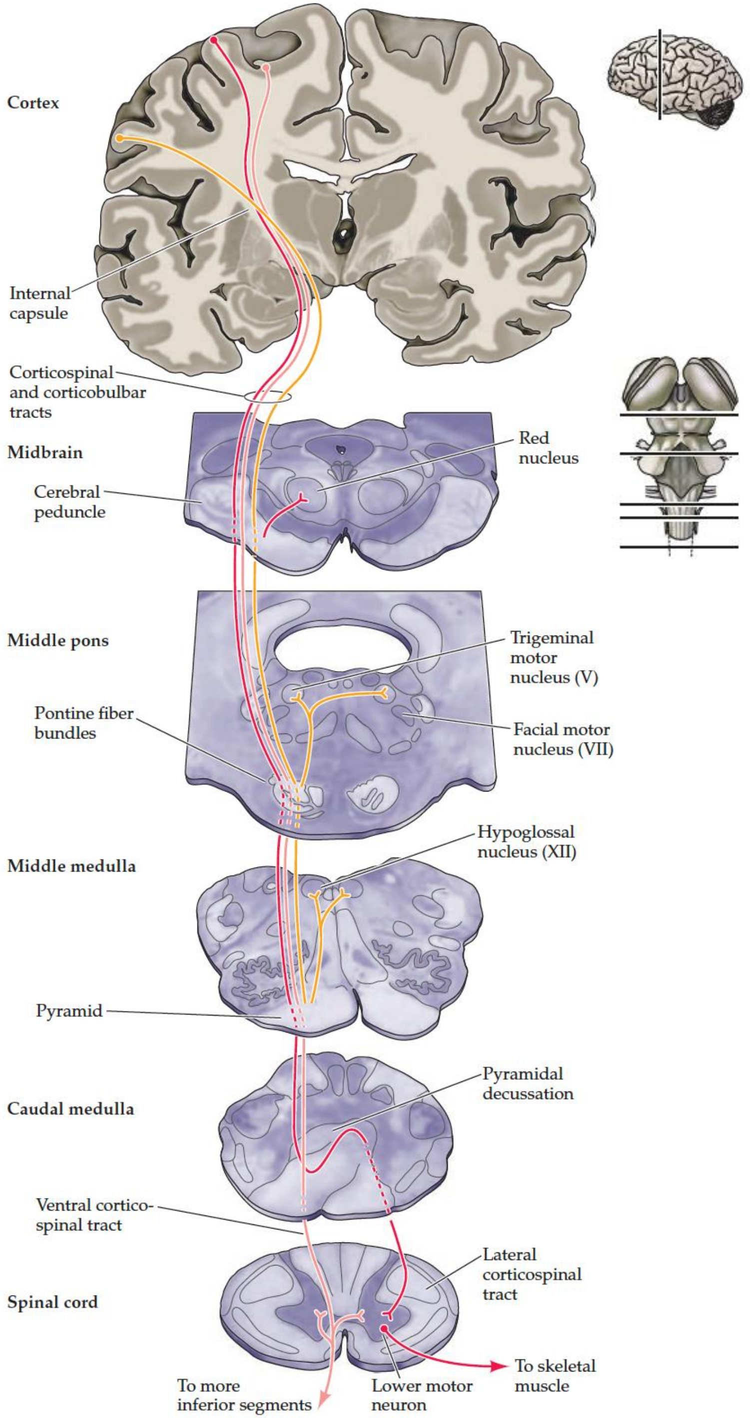
Four systems make essential and distinct contributions to motor control:

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

The corticospinal tract

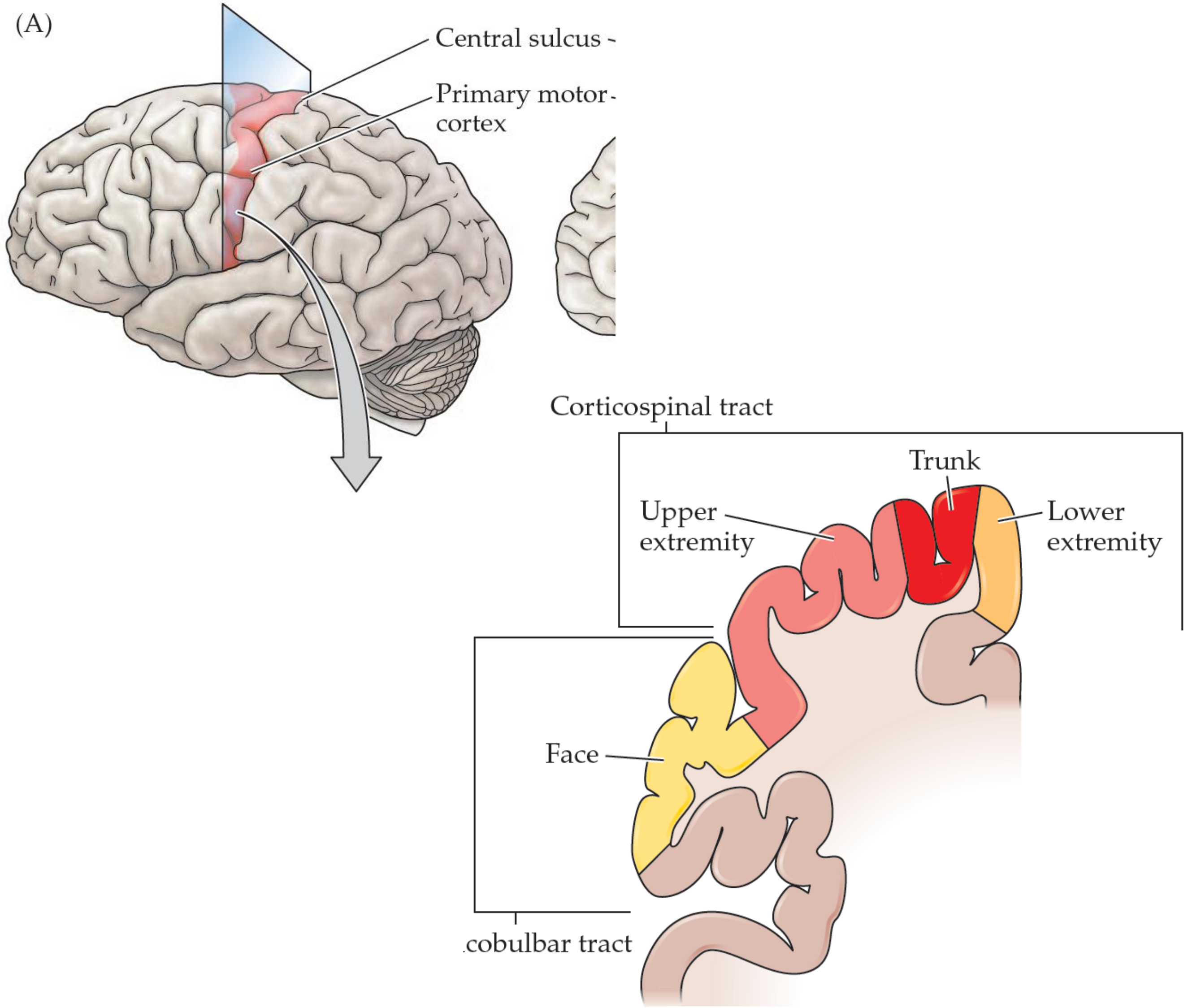
The corticospinal tract (red):

- 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



Purves, Figure 17.4

Motor maps in motor cortex



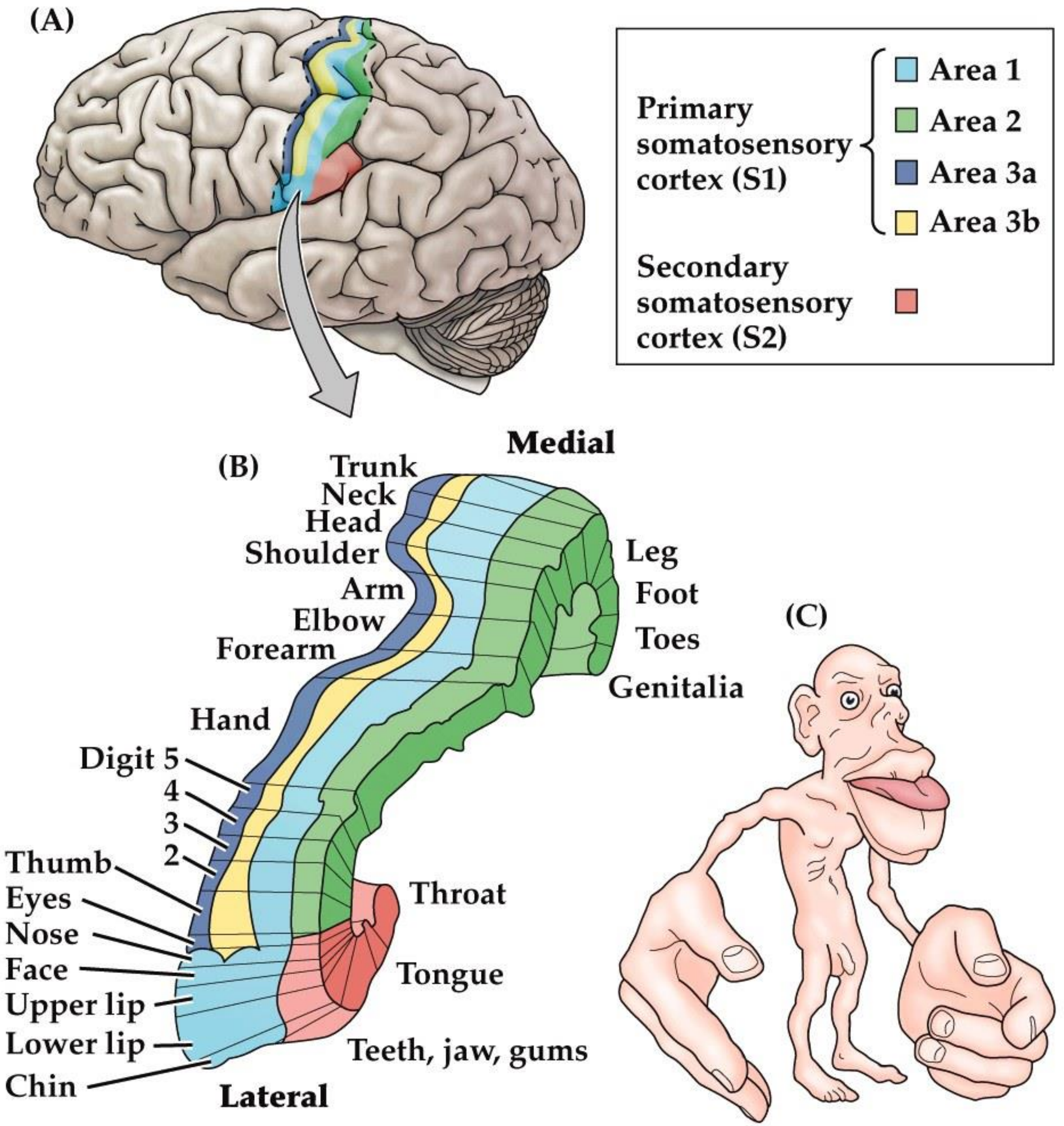
- A “motor map“ was suggested by the systematic “march“ of **seizures** from
  one body part to another

- 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

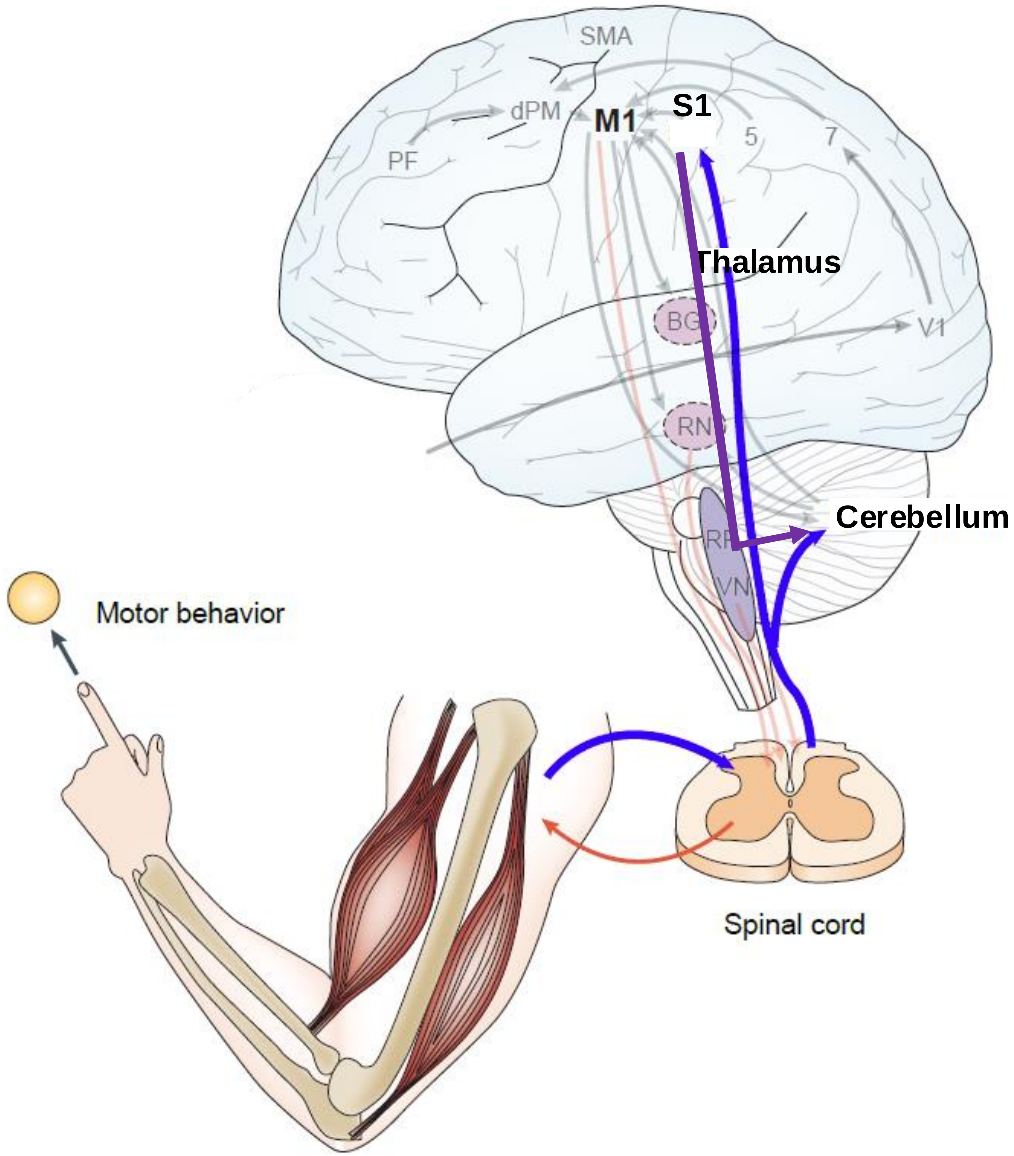
Purves, Figure 17.5

Somatotopic order in the human primary somatosensory cortex

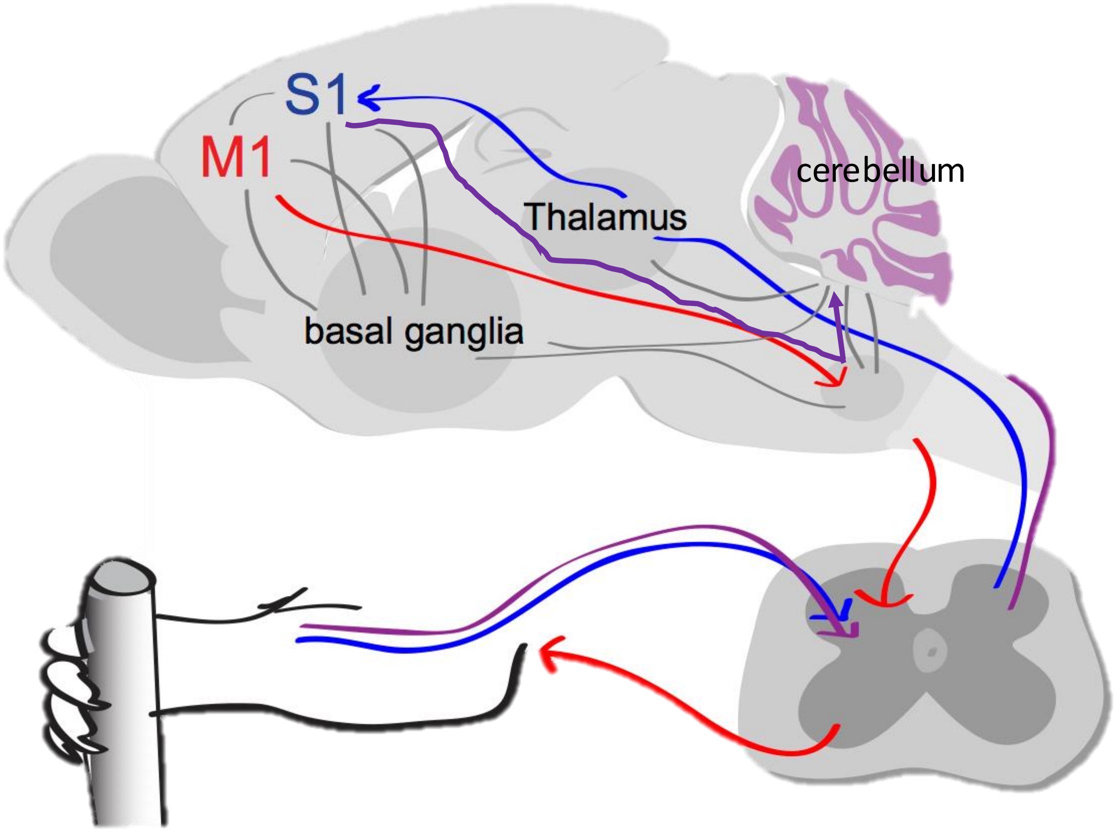


Purves Chapter 9, 9.11

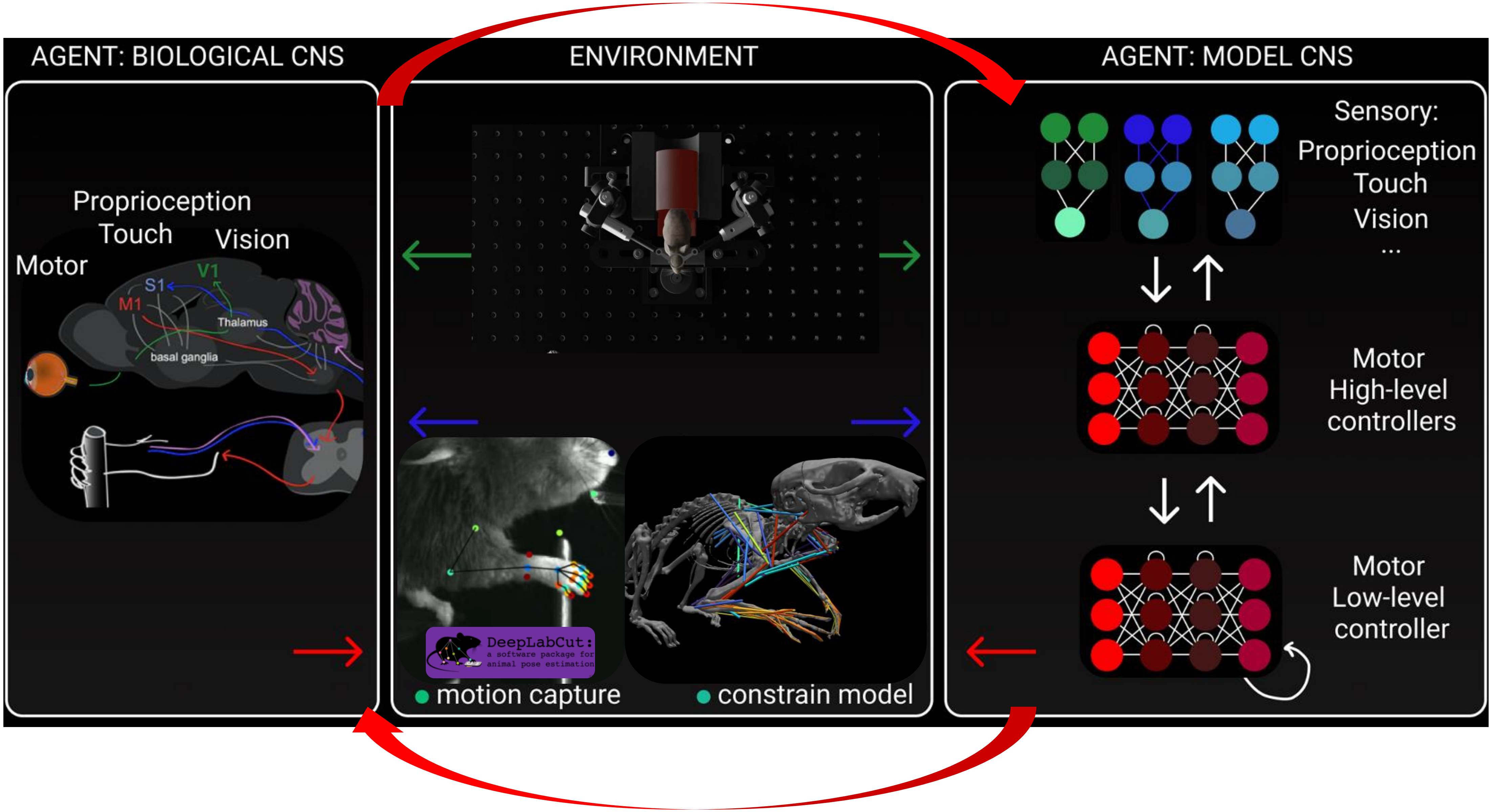
Integrative sensorimotor control



Adapted from Scott, 2004



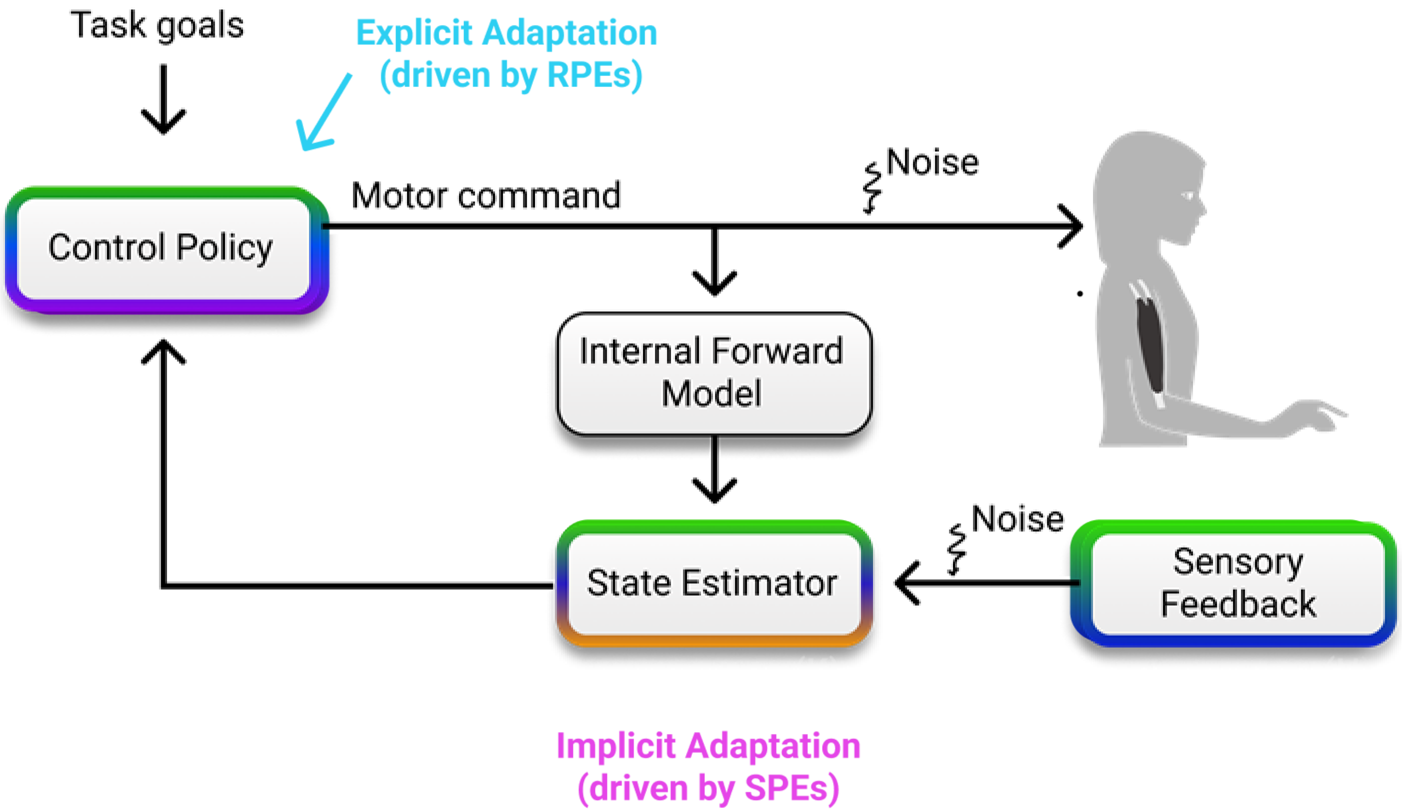
Reverse engineering adaptive motor control



Adapted from Hausmann, Marin Vargas, A. Mathis & M. Mathis Current Opinion in Neurobiology 2021

Motor learning (adaptation) within a “session”

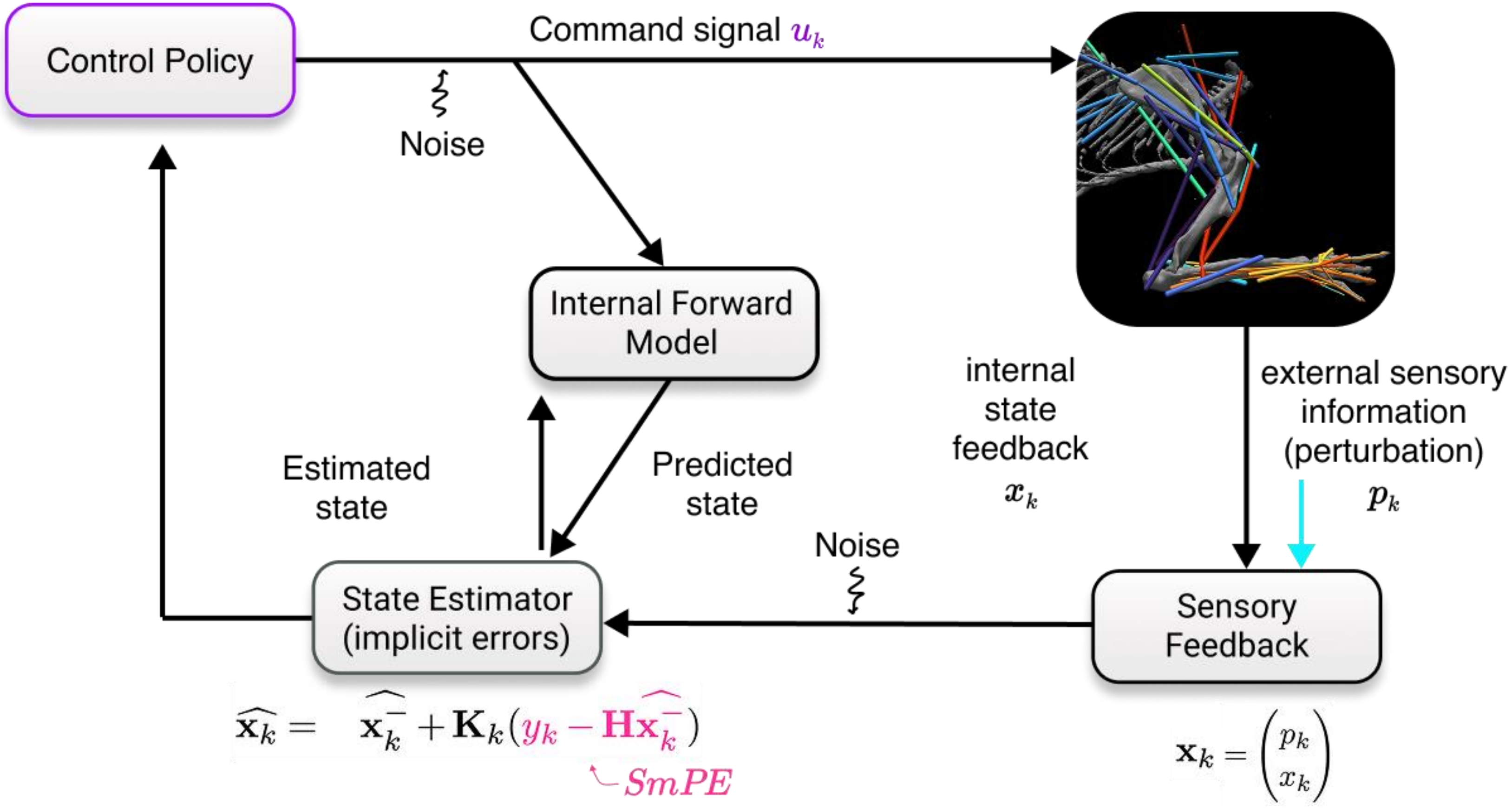
How do animals (and agents) learn to adapt?



Wolpert et al. Science 1995, Todorov & Jordan 2002
Izawa & Shadmehr 2011, Kawato & Gomi 1992, …, Scott 2004

Theory-guided framework for studying motor learning

across trial (k) learning model



Wolpert et al. Science 1995, Todorov & Jordan 2002
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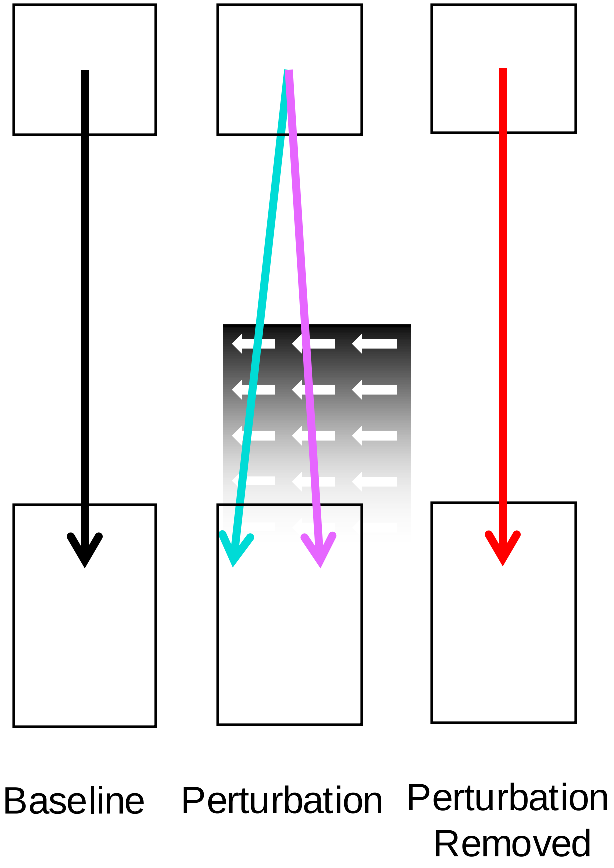
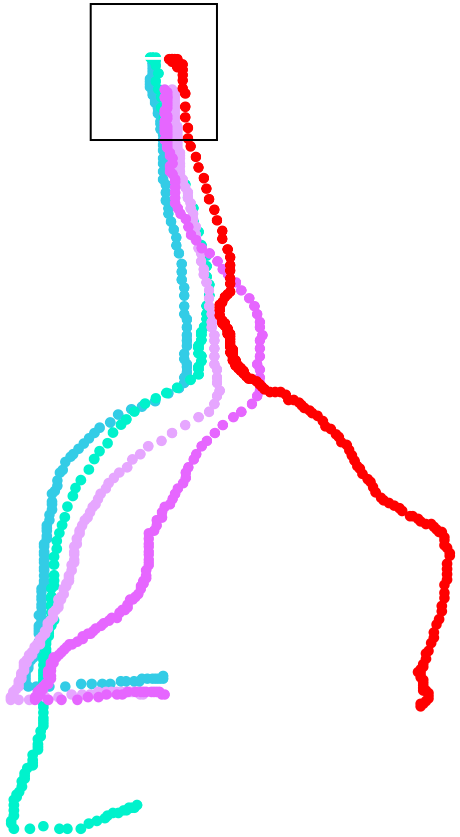
Motor learning (adaptation) within a session





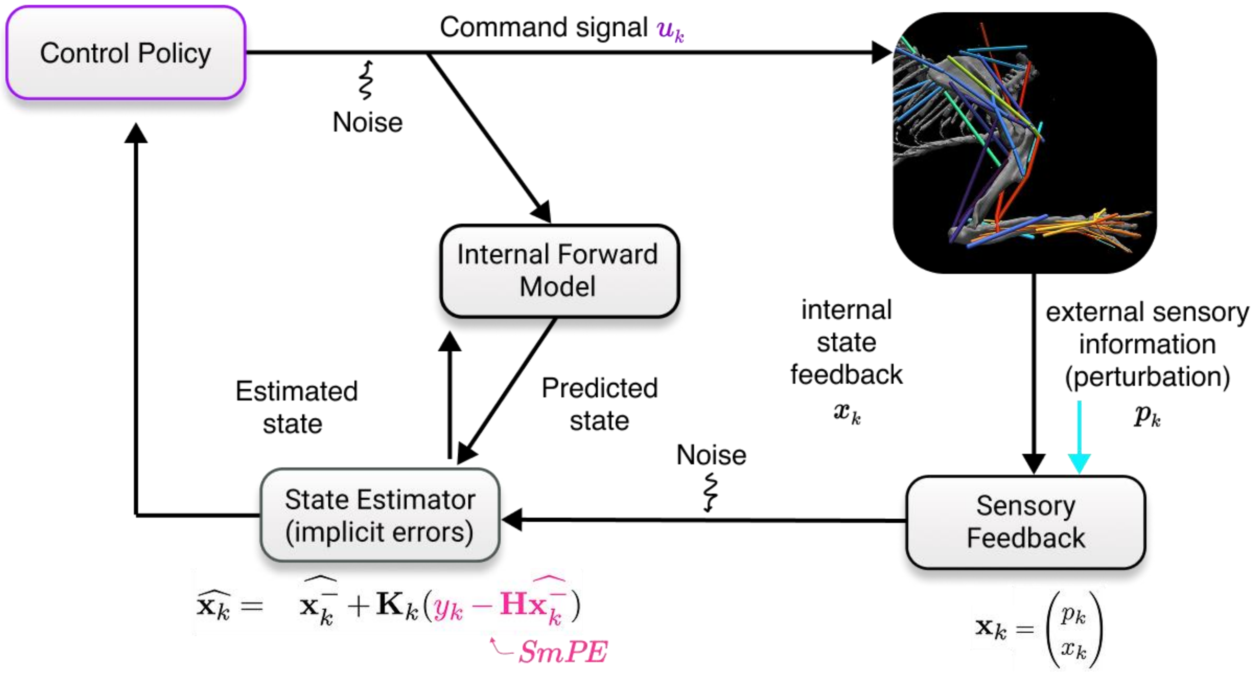
Mathis, Mathis, Uchida 2017 Neuron

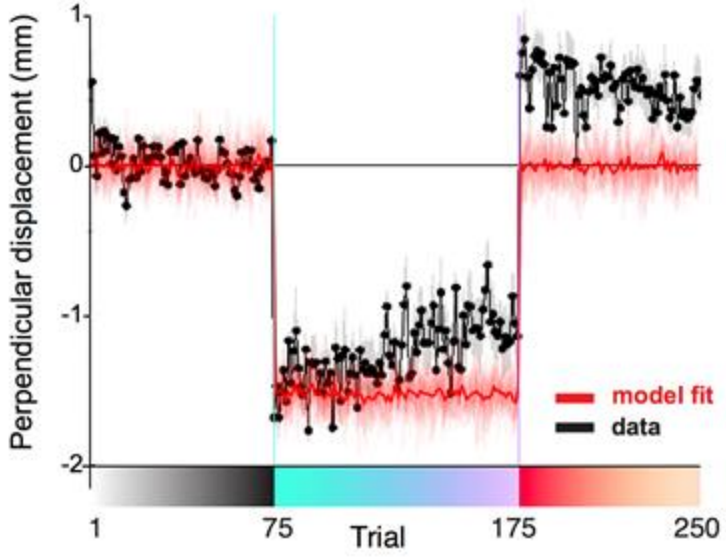
Forelimb motor adaptation is driven by sensory prediction errors

$\delta(t) = r(t) + \gamma * \hat{V}(t+1) - \hat{V}(t)$

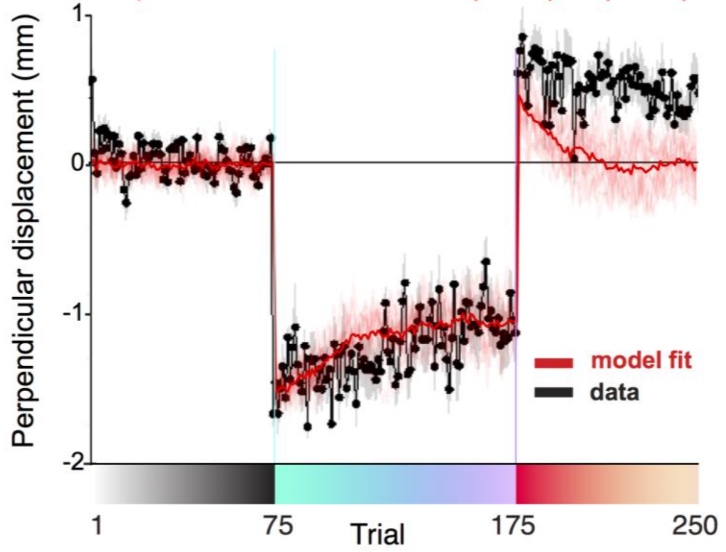
Model with TD learning (RPE) only

across trial (k) learning model





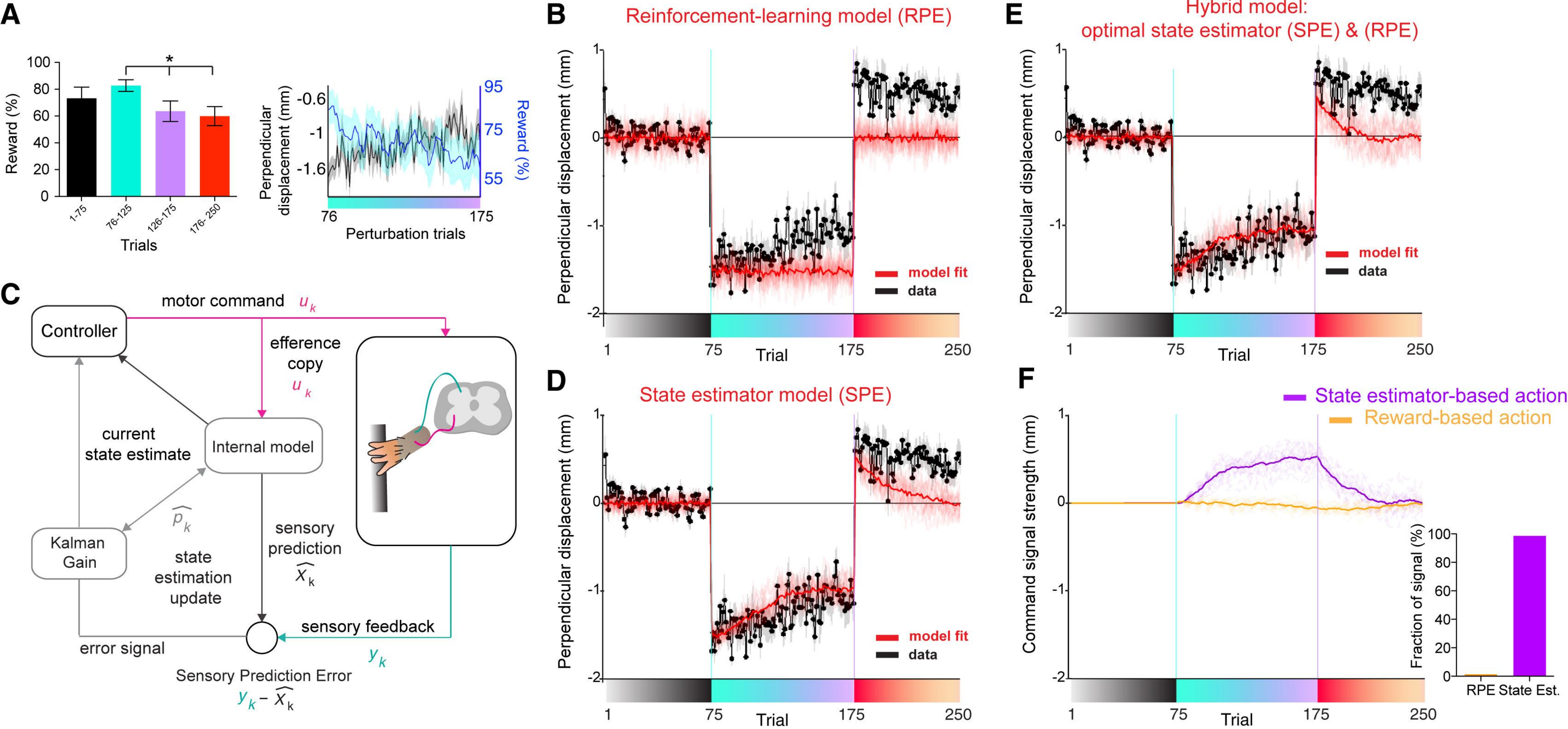
Hybrid model:
optimal state estimator (SPE) & (RPE)



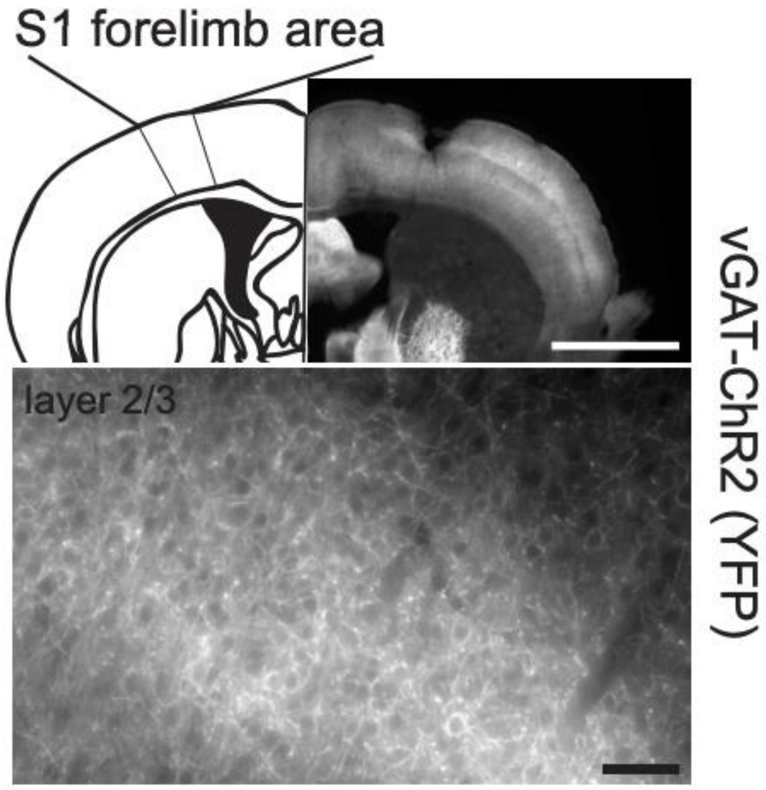
State estimator (SPE) model drives fit

Mathis, Mathis, Uchida 2017 Neuron

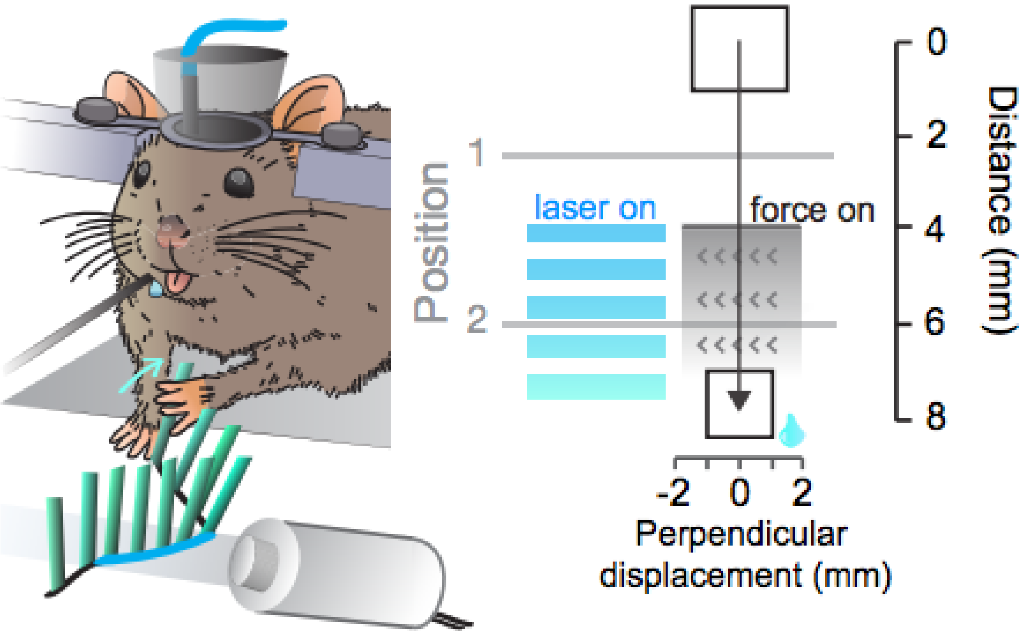
Forelimb motor adaptation is driven by sensory prediction errors



Perturbing sensory circuits: testing the role of S1 in adaptation



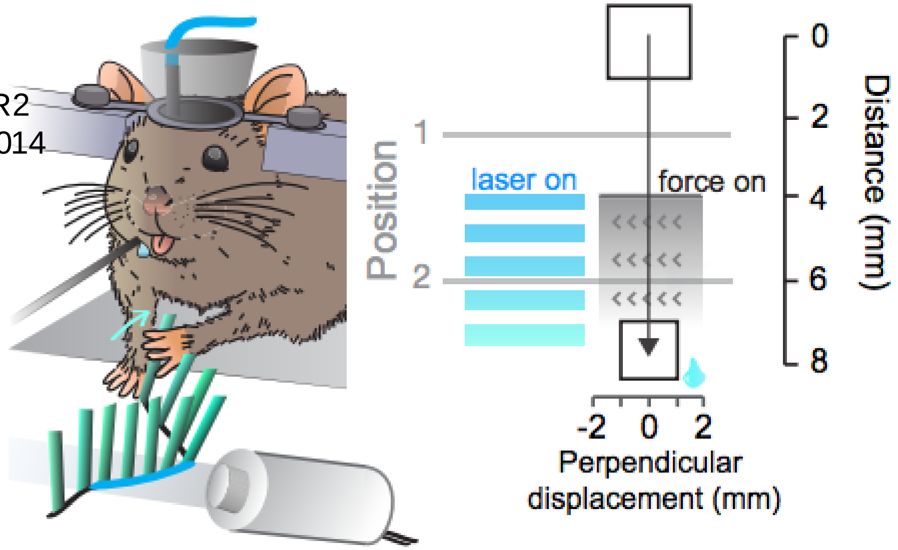
VGAT-ChR2
Guo et al 2014

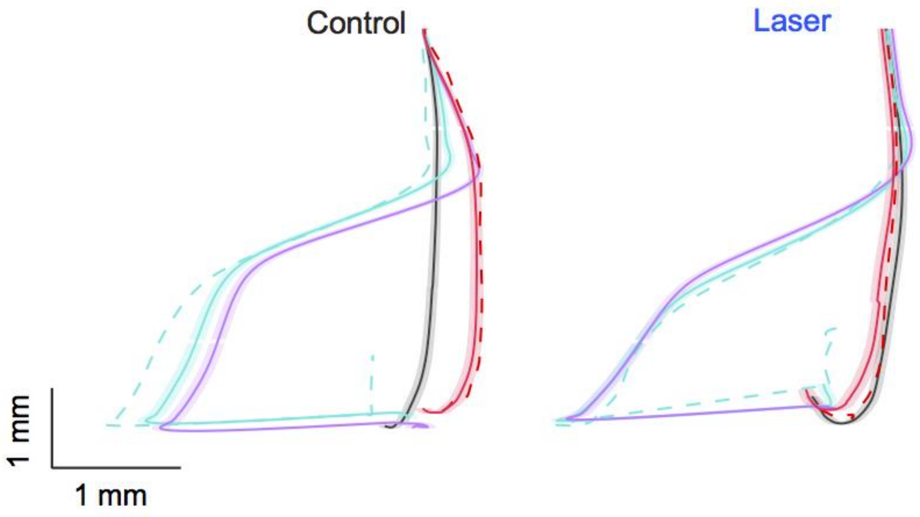


100 ms laser delivered in 5 ms pulses at 50 Hz

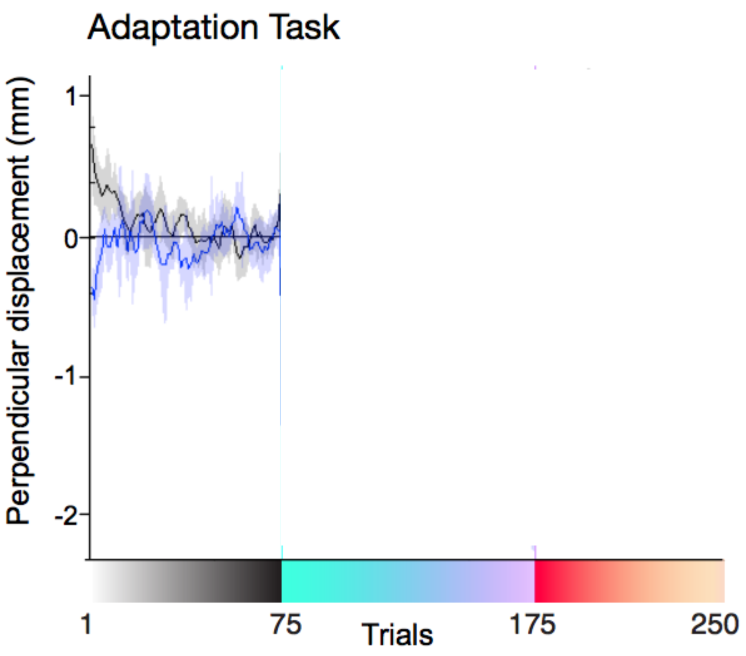
Perturbing sensory circuits: testing the role of S1 in adaptation

VGAT-ChR2
Guo et al 2014





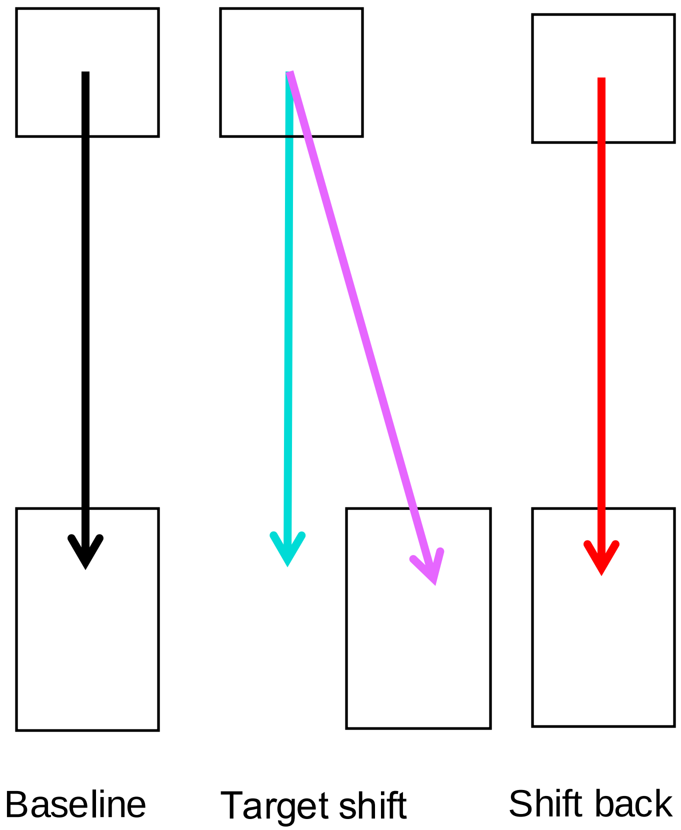
Laser sessions
Control sessions

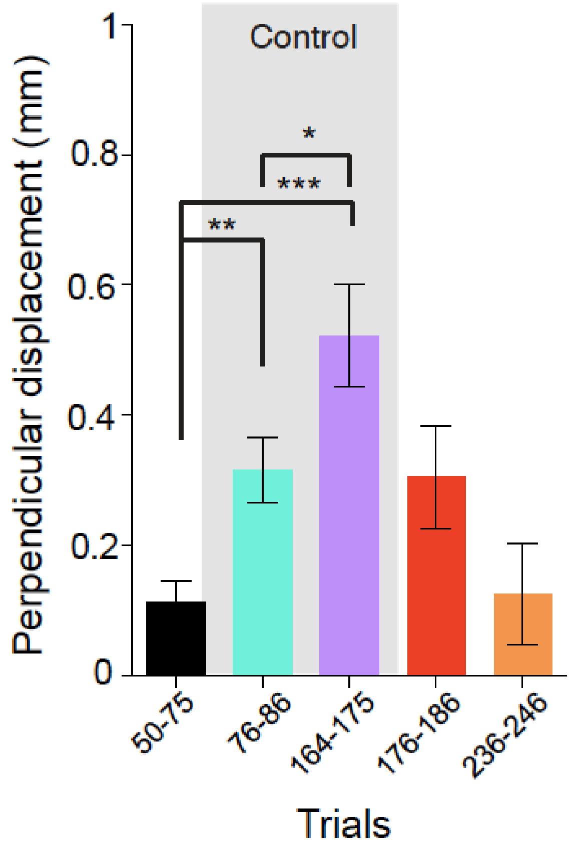


(*n* = 12 sessions control, *n* = 17 laser; 3 mice)

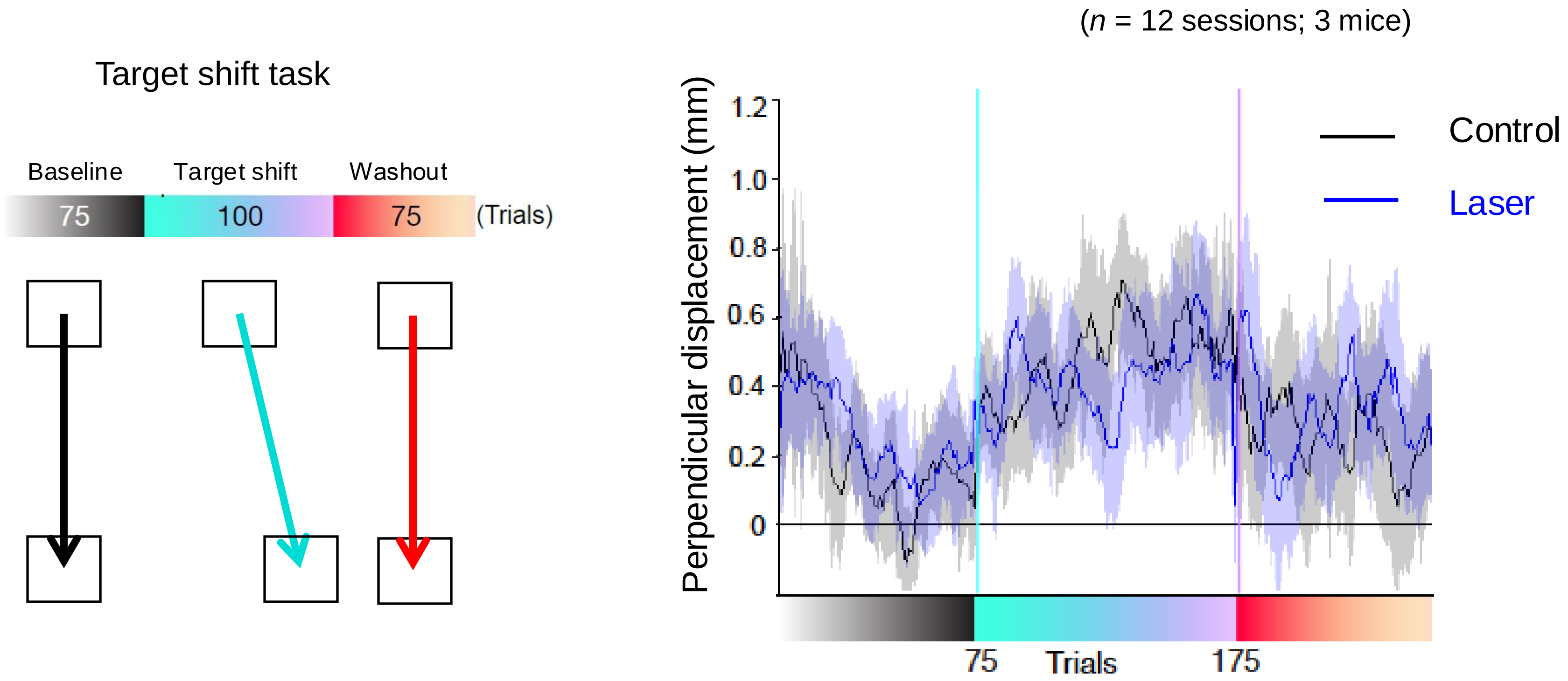
Mathis et al, 2017 Neuron

Motor learning within a session driven by RL





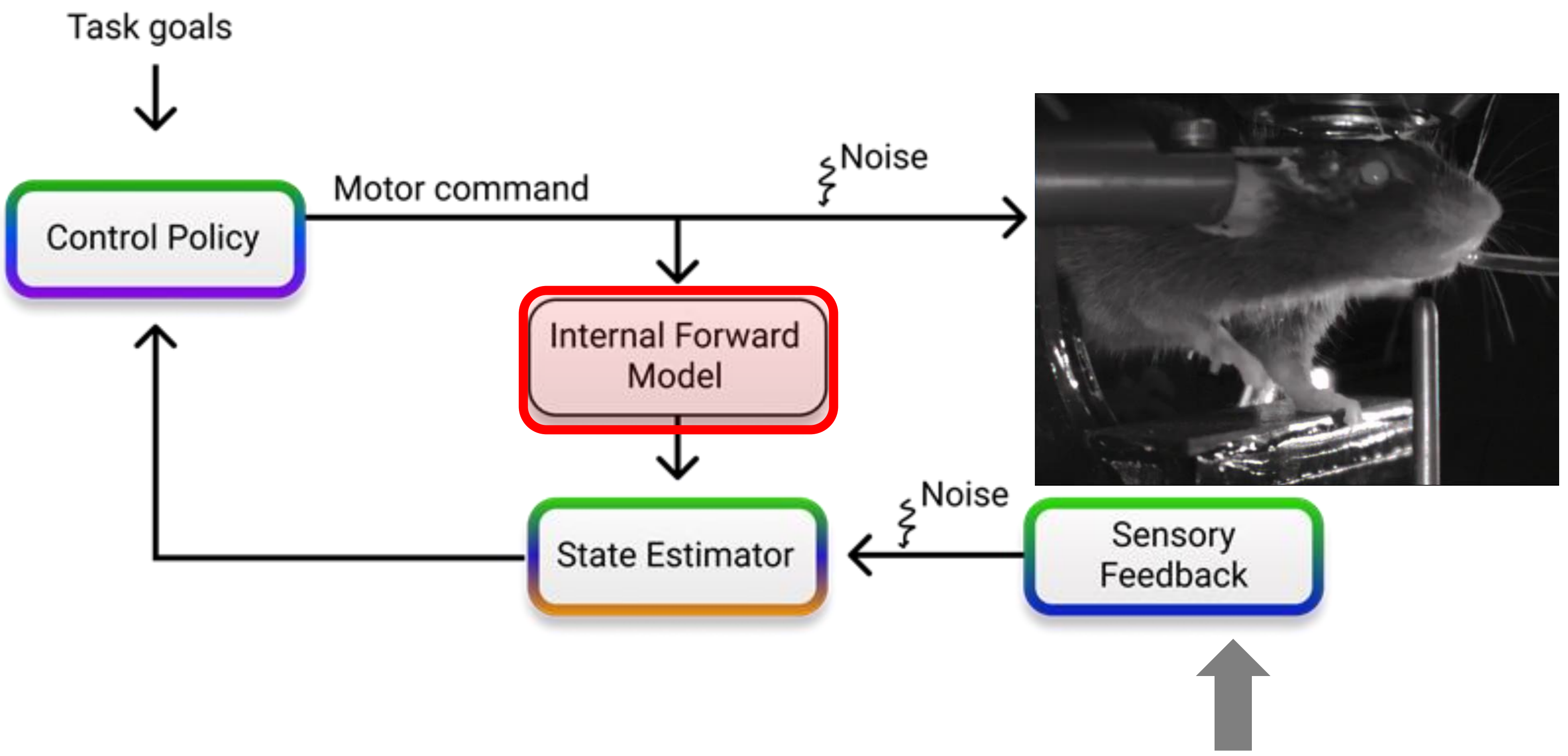
S1 inactivation does not affect reward-based learning



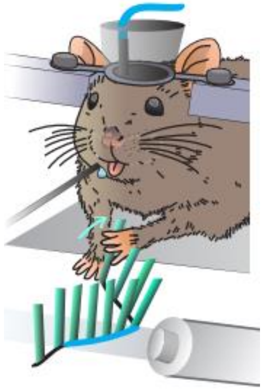
The role of S1 in adaptation

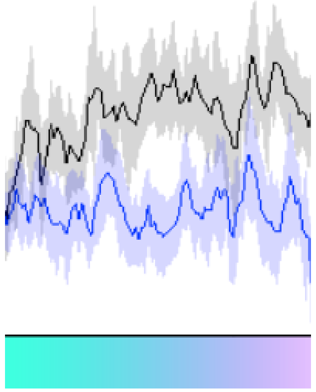
1 — Did inactivation block **acquisition?**

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



Sensory feedback about force field perturbation





Perturbation block

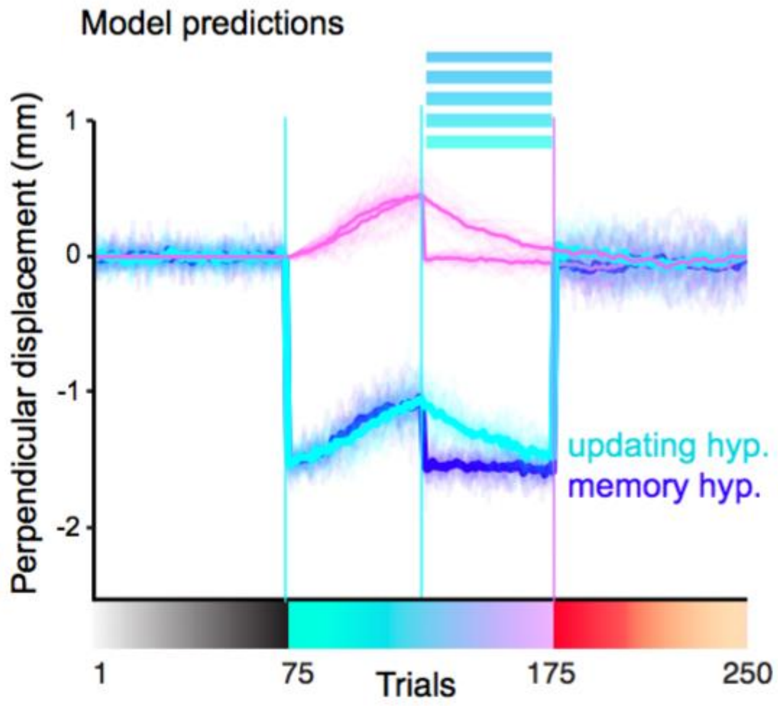
Sensory prediction error

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

$\widehat{m}_k$: "= 0" (memory hyp.)

$K_k (s - \hat{s})$: "= 0" (updating hyp.)

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

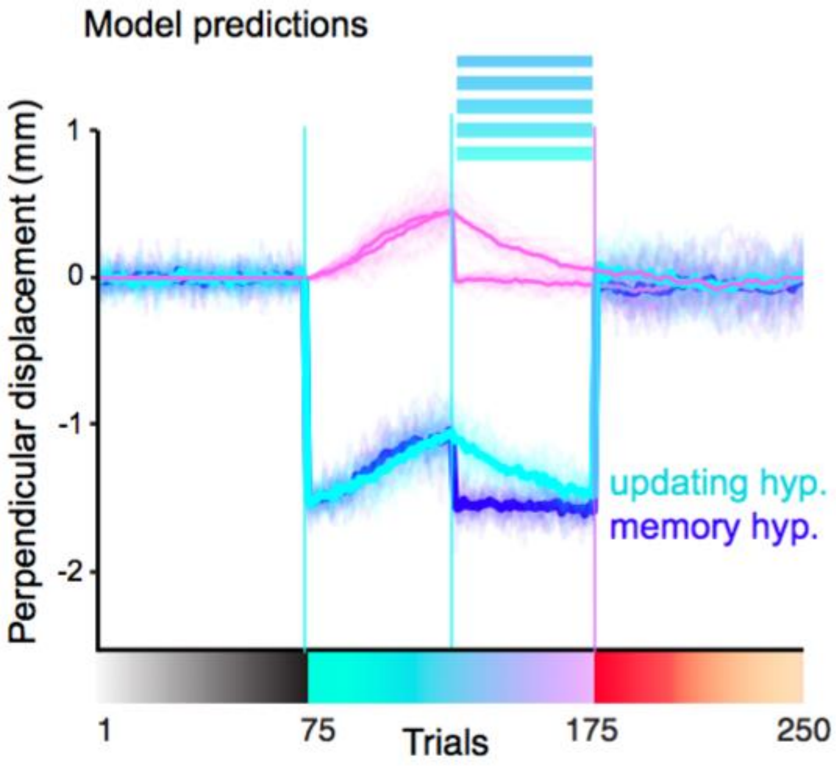


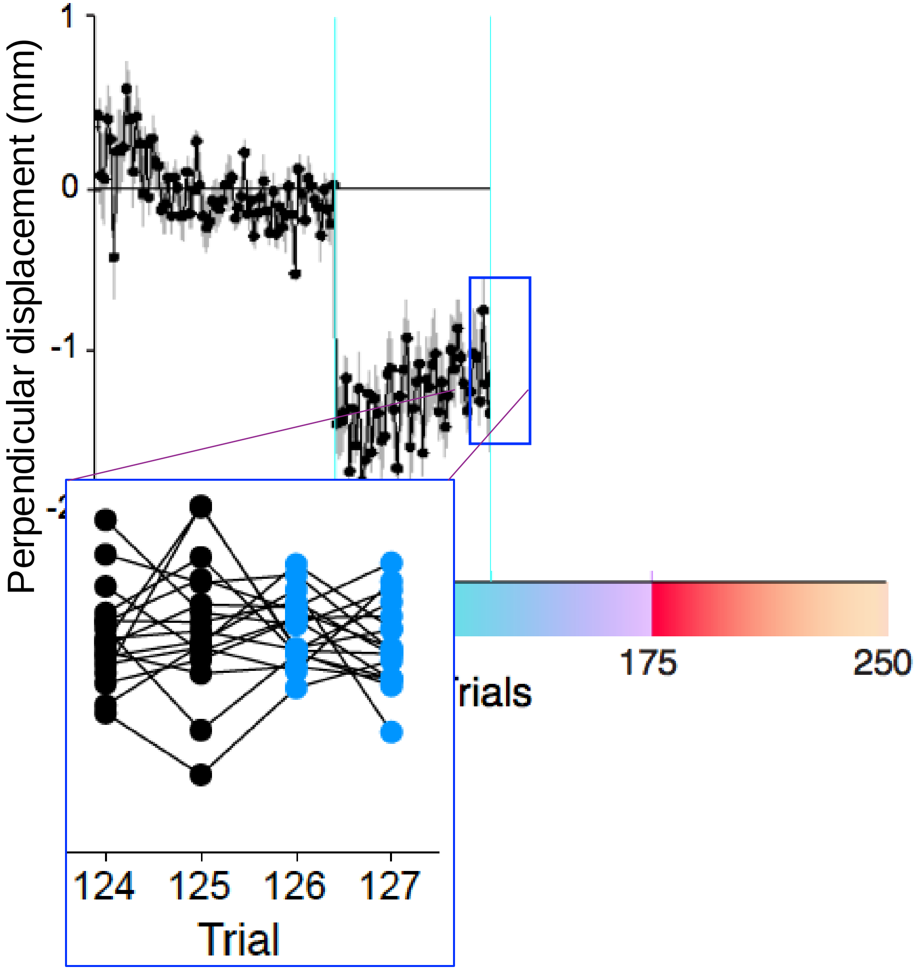
$$m_{k+1} = \widehat{m_k} + K_k\,(s - \hat{s})$$

"= 0" (memory hyp.)

"= 0" (updating hyp.)

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





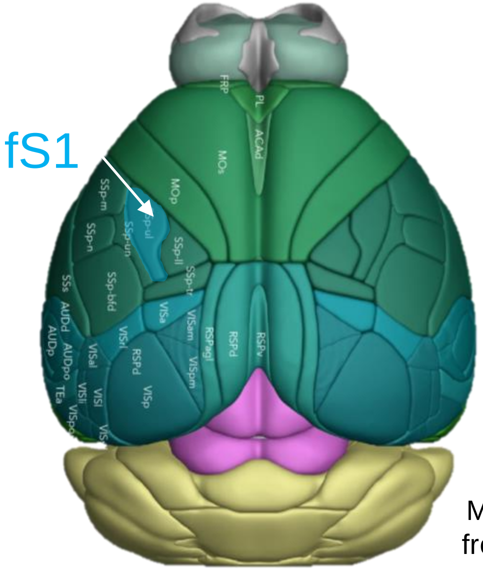
Part 1 conclusions

- **Mice can learn to rapidly learn a new sensorimotor mapping (motor adaptation)**

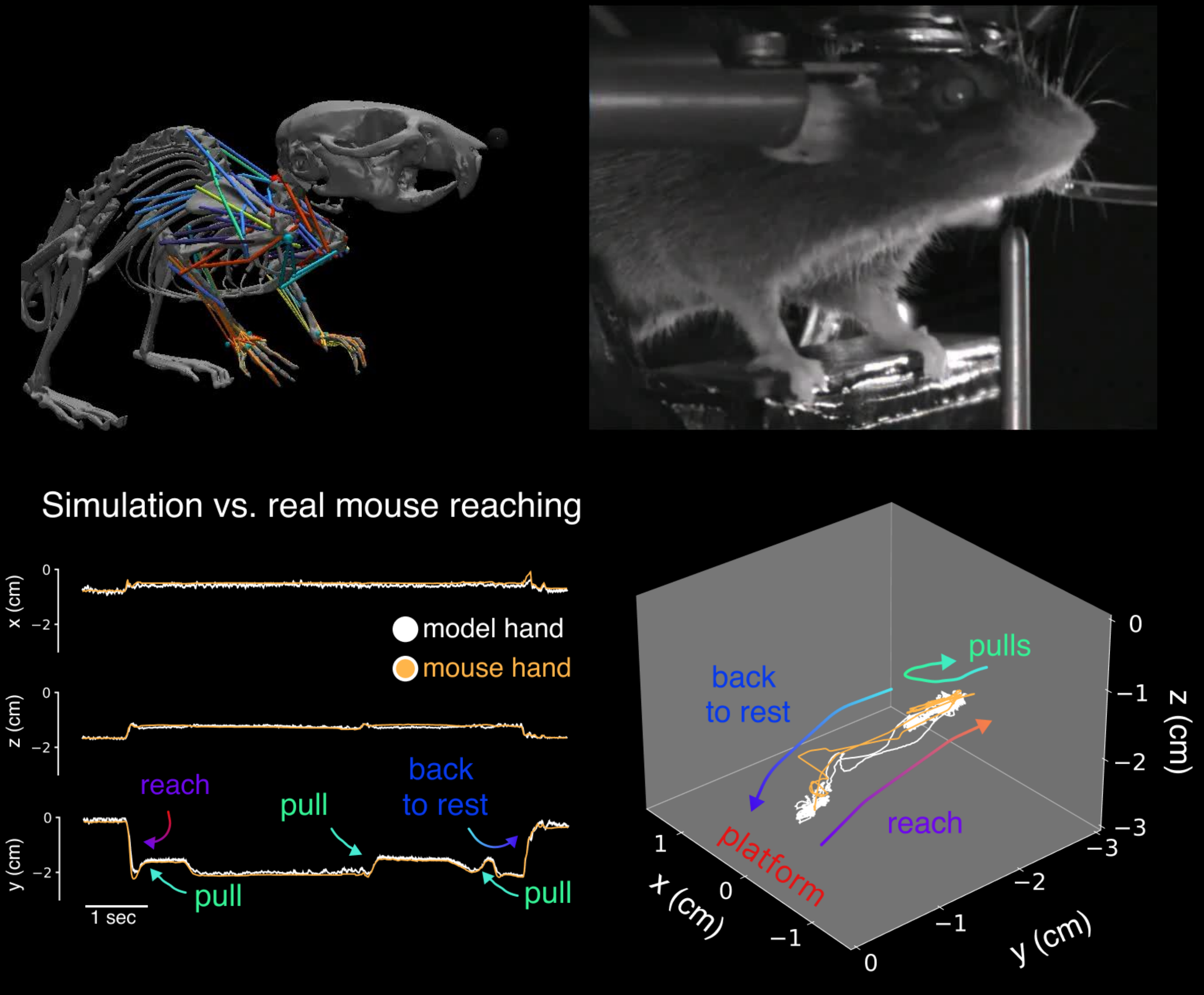
- **Forelimb S1 is essential to** adaptation (in this task), but inactivation of S1 did not effect motor control

- 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 …

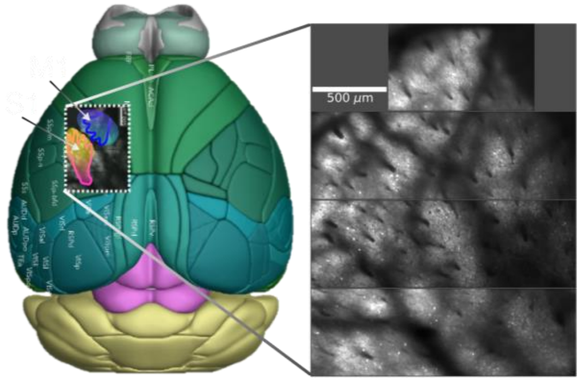


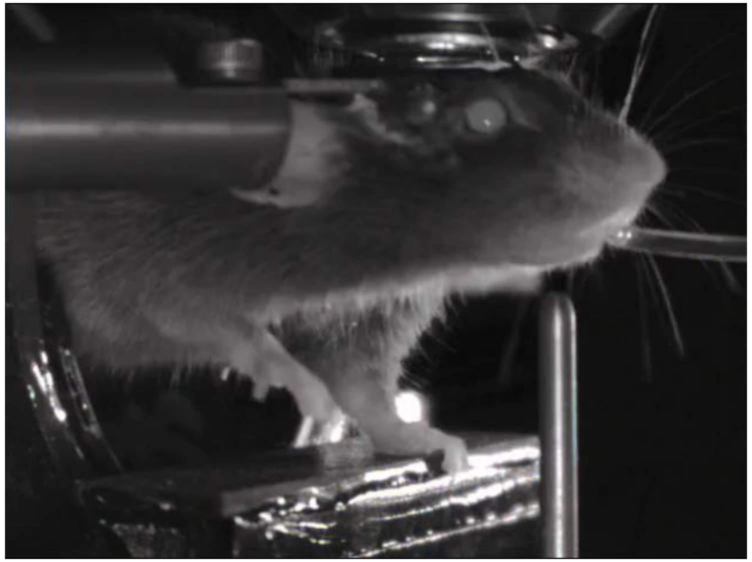
Mouse brain diagram
from the Allen Institute



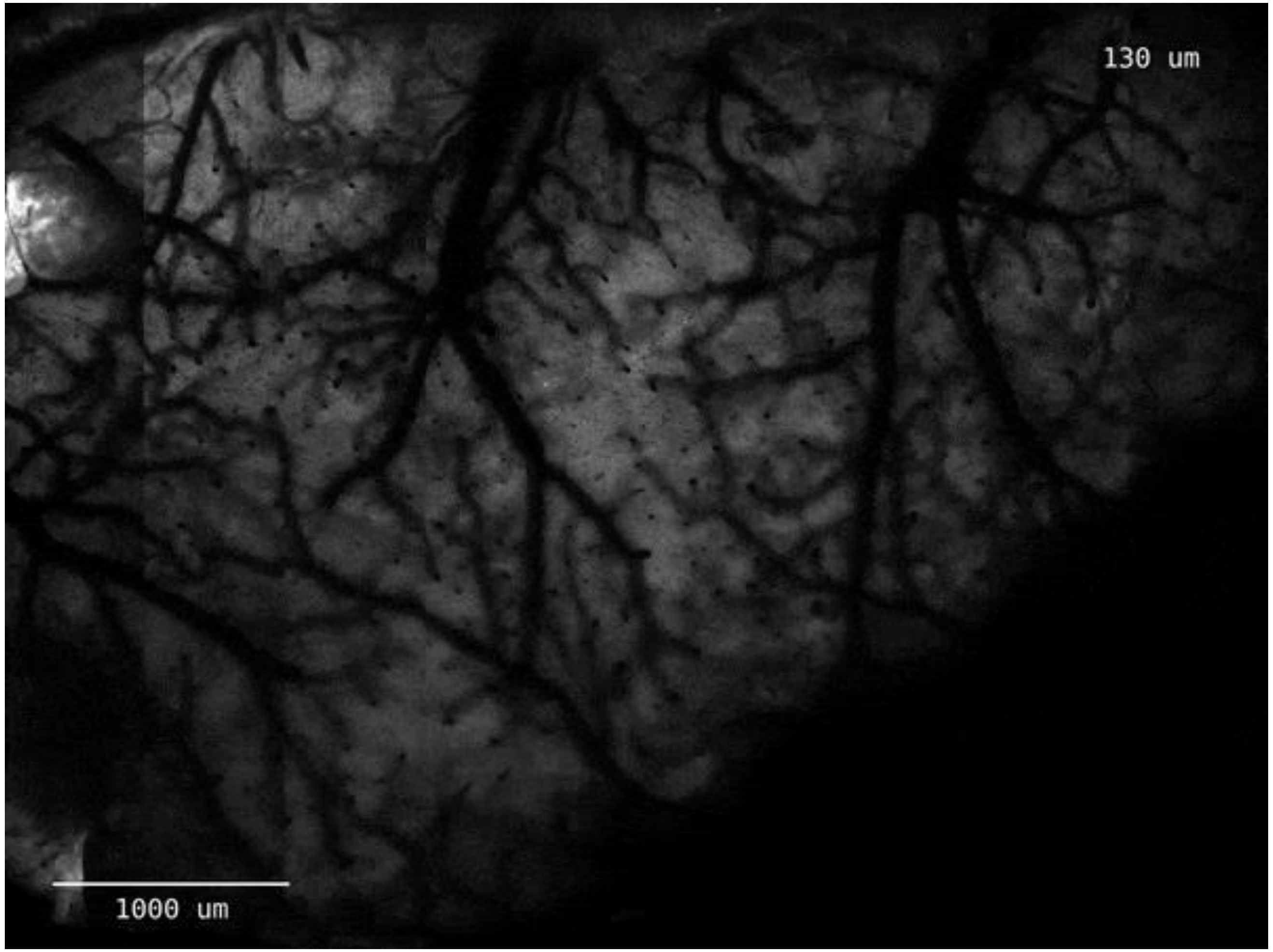
Our in silico model can mimic the 3D kinematics of the mice

Measuring internal models in the brain (of mice)



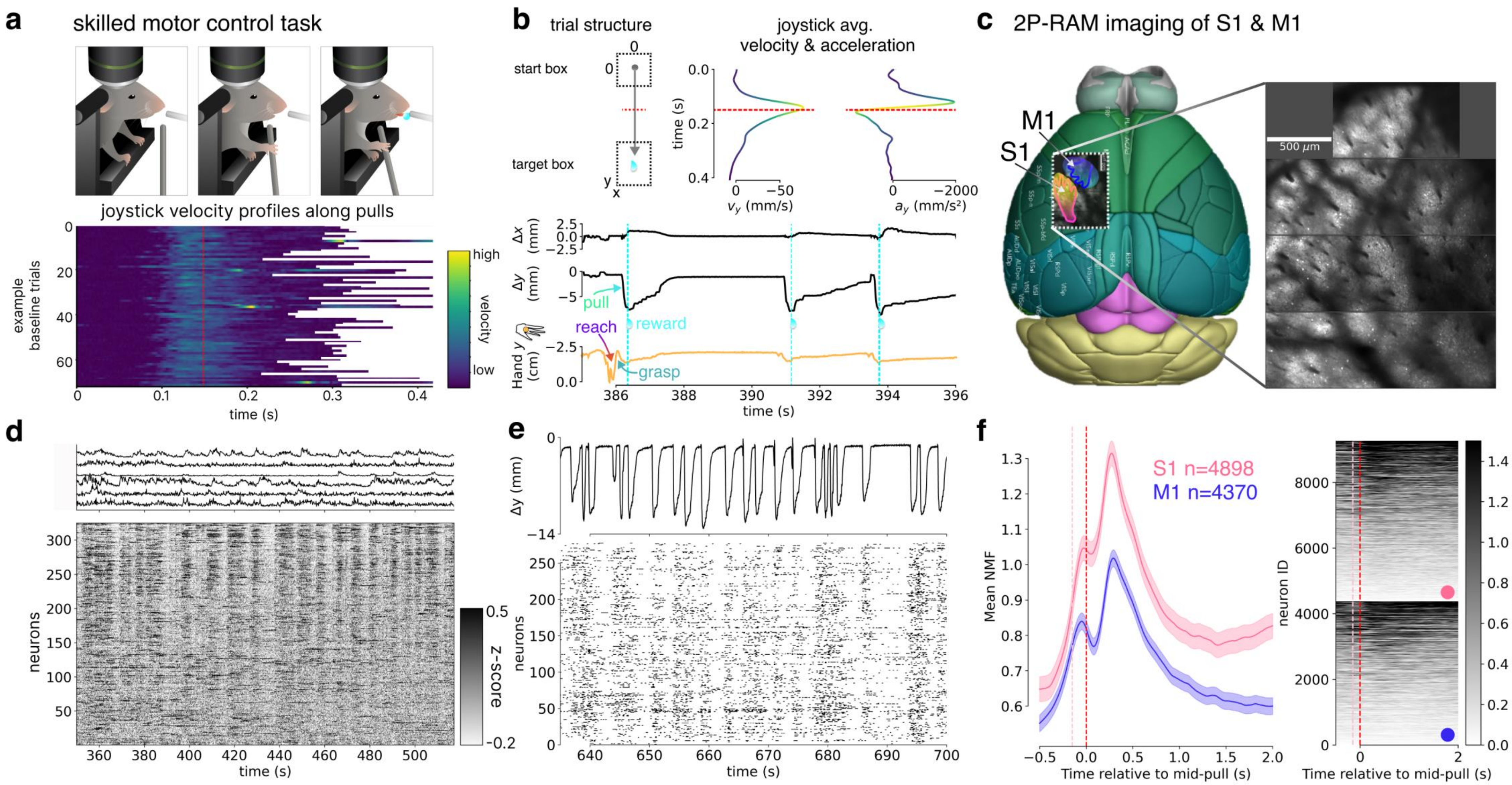


DeWolf, Schnieder et al. 2024 bioXiv



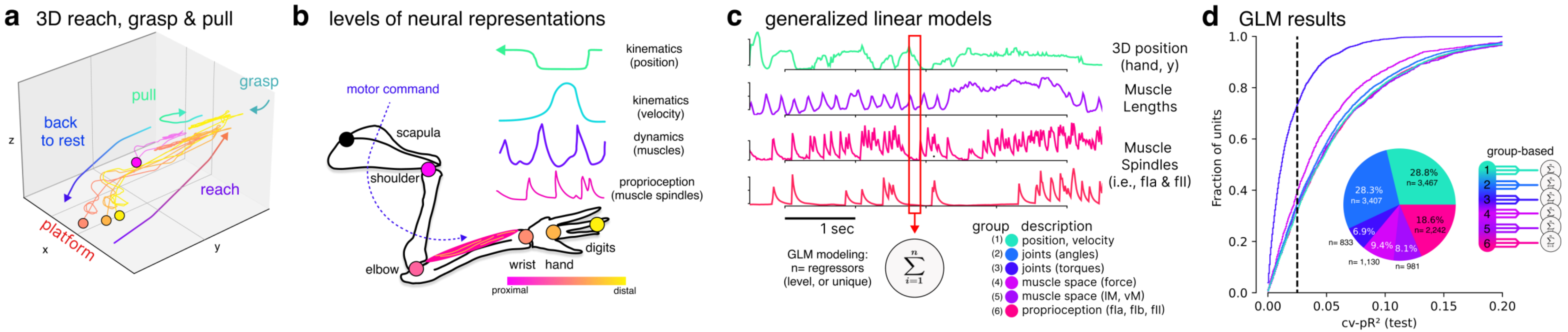
Sofroniew et al 2016 eLife

M1 and S1 encode movement-related features



DeWolf, Schnieder et al. 2024 bioXiv

M1 and S1 encode abstract & muscle-level features



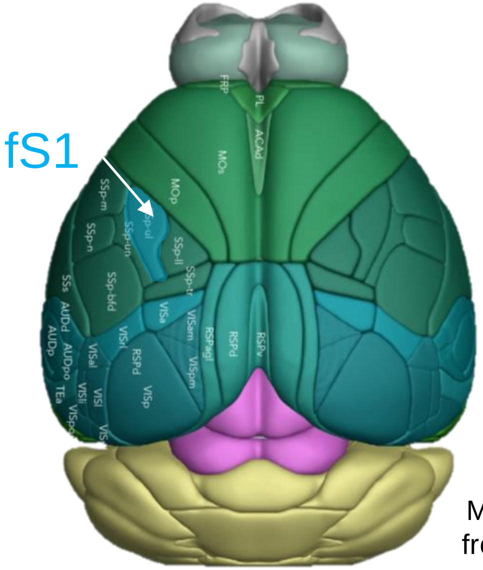
- in the neural & behavioral analysis lecture(s)

You will learn to do pose estimation & GLMs!

DeWolf, Schnieder et al. 2024 bioXiv

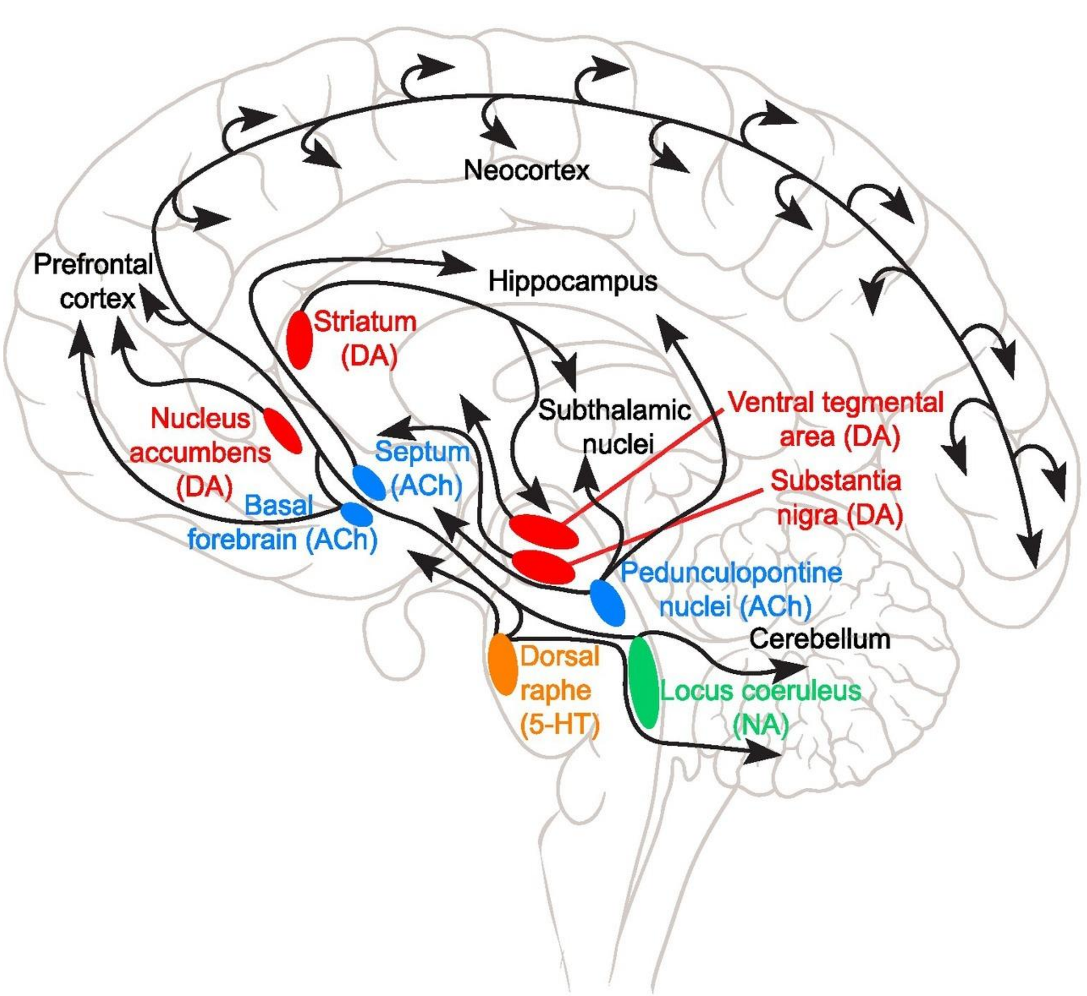
Part 1 conclusions

- **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 … muscles, 3D position, …



Mouse brain diagram from the Allen Institute

What other systems are can modulate motor learning?



Neuromodulatory systems

Spencer Bowles, PhD

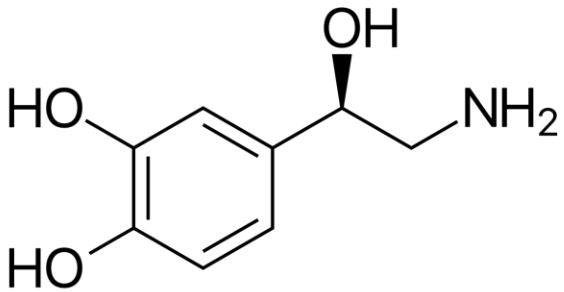
What are neuromodulators?

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

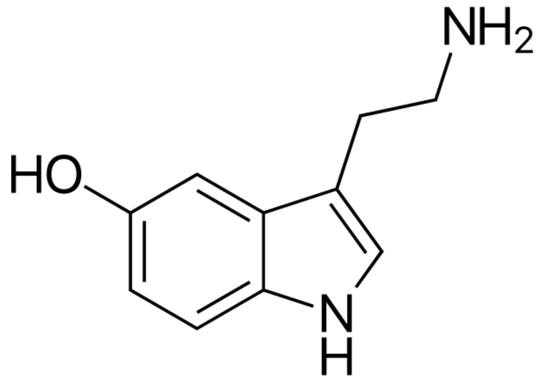
Glutamate and GABA are the most common NTs, accounting for approximately 90% of all neurons!

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

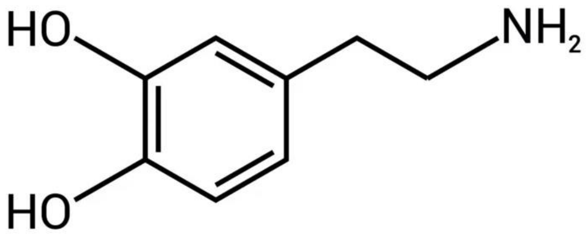
Noradrenaline



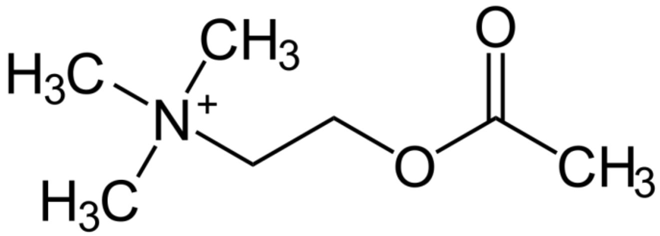
Serotonin



Dopamine



Acetylcholine

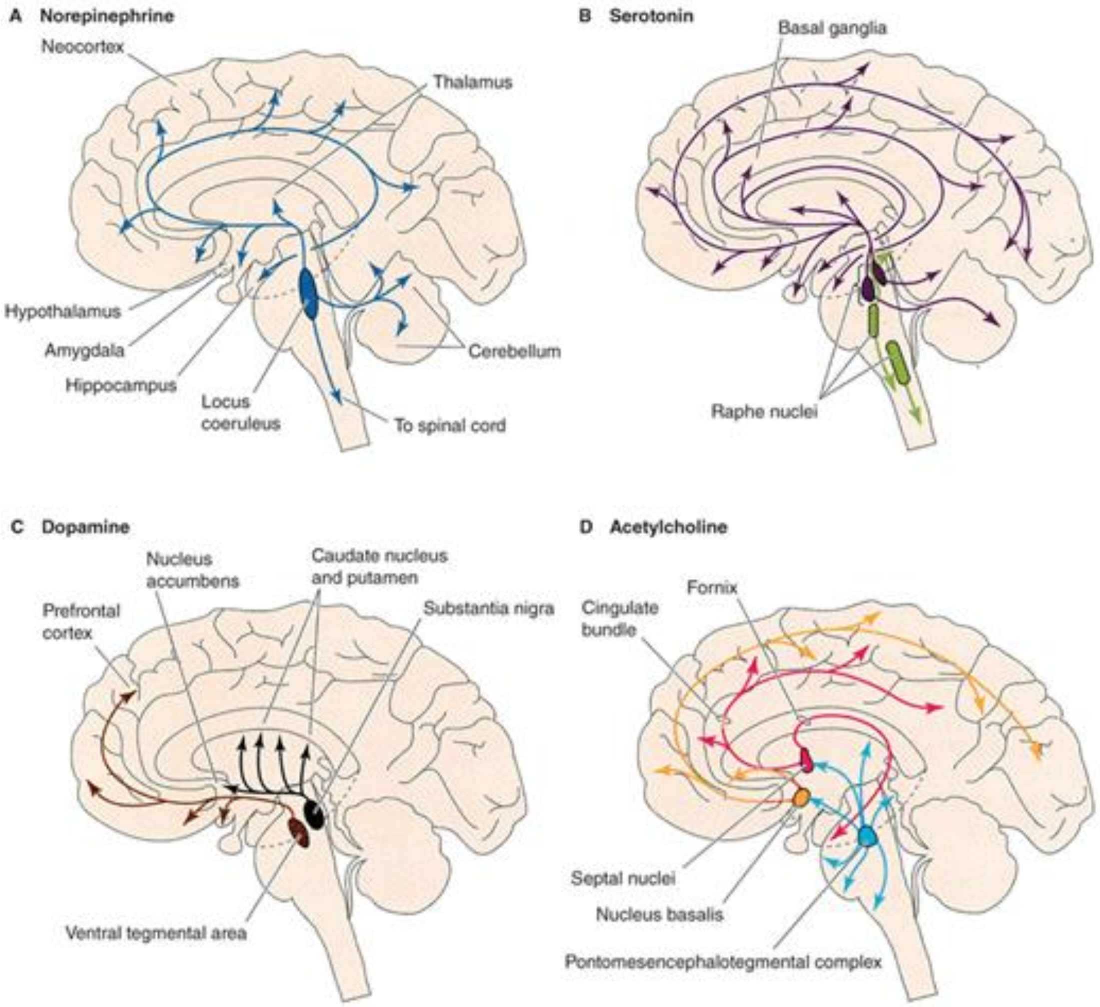


Avery & Krichmar, 2017

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 Boitano, Heddwen L. Brooks: Ganong's Review of Medical Physiology, 25th Ed.
www.accessmedicine.com

What are neuromodulators?

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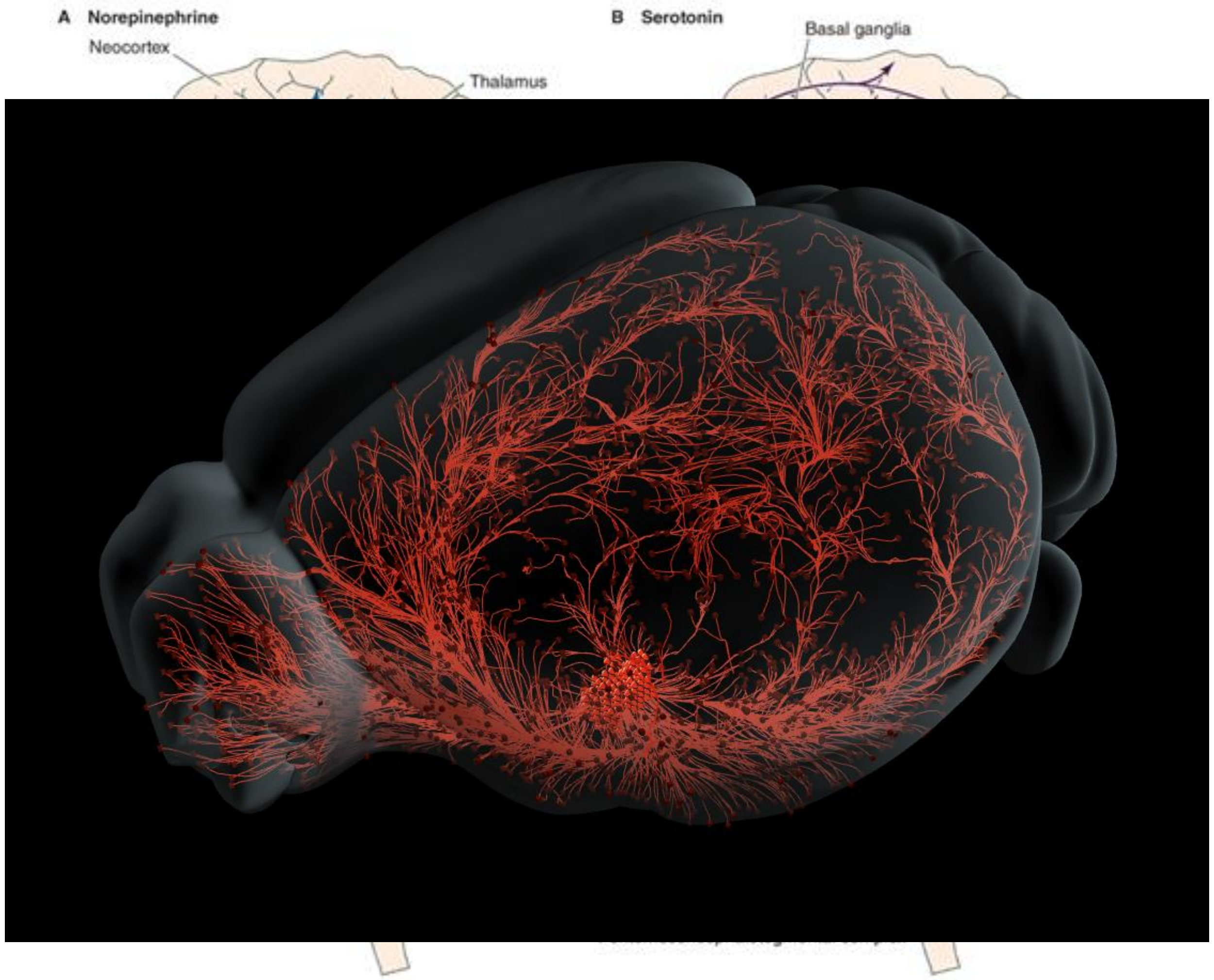
These neurons send wide-ranging projections that target diverse subsets of other regions.

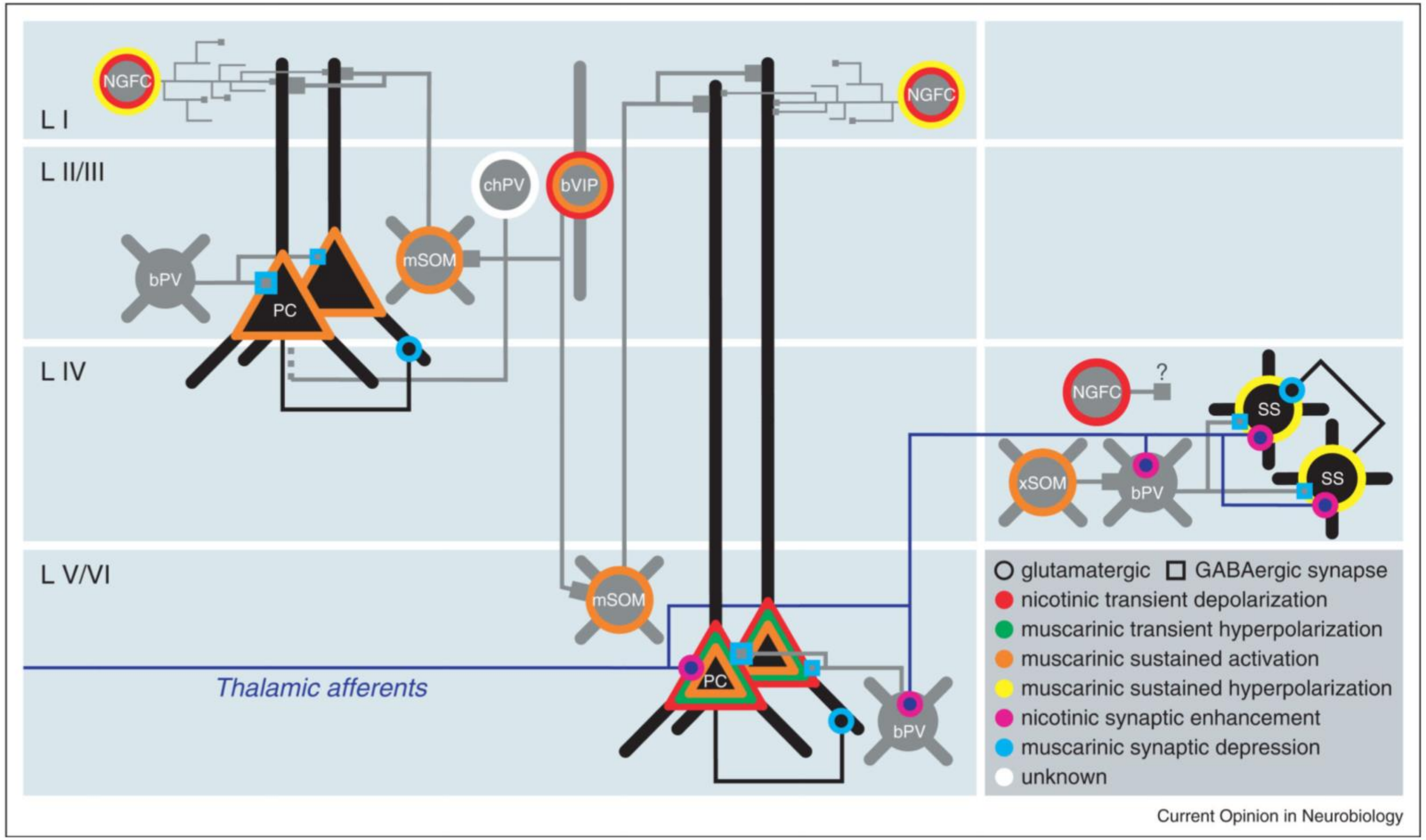
NMs can act over varying timescales, from milliseconds to hours.



Source: Kim E. Barrett, Susan M. Barman, Scott Boitano, Heddwen L. Brooks: Ganong's Review of Medical Physiology, 25th Ed.
www.accessmedicine.com

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.

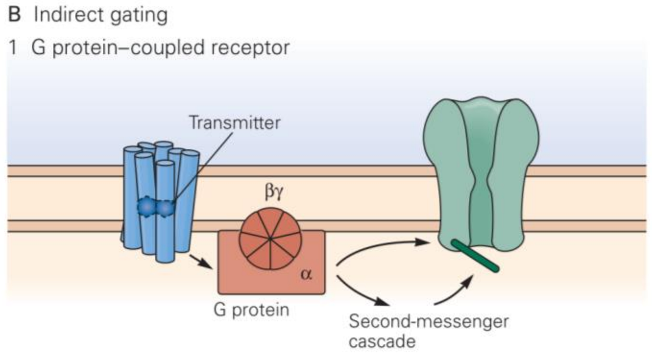


Munoz & Rudy 2014

G protein-coupled receptors (GPCRs)

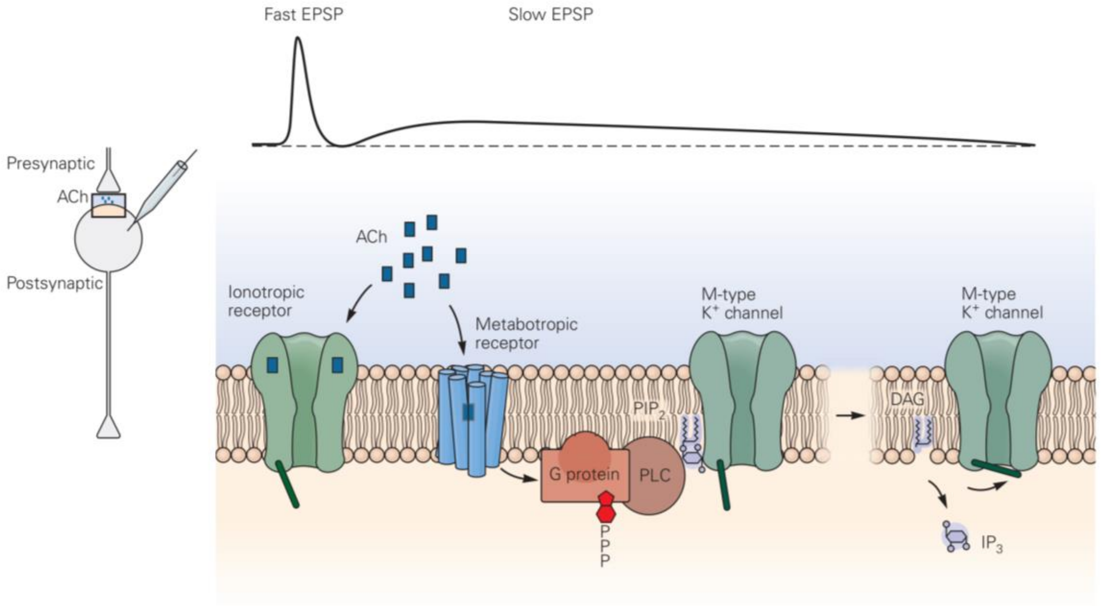
The G protein complex is activated when a neuromodulator binds to a GPCR

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



Cascades can produce a variety of effects including:

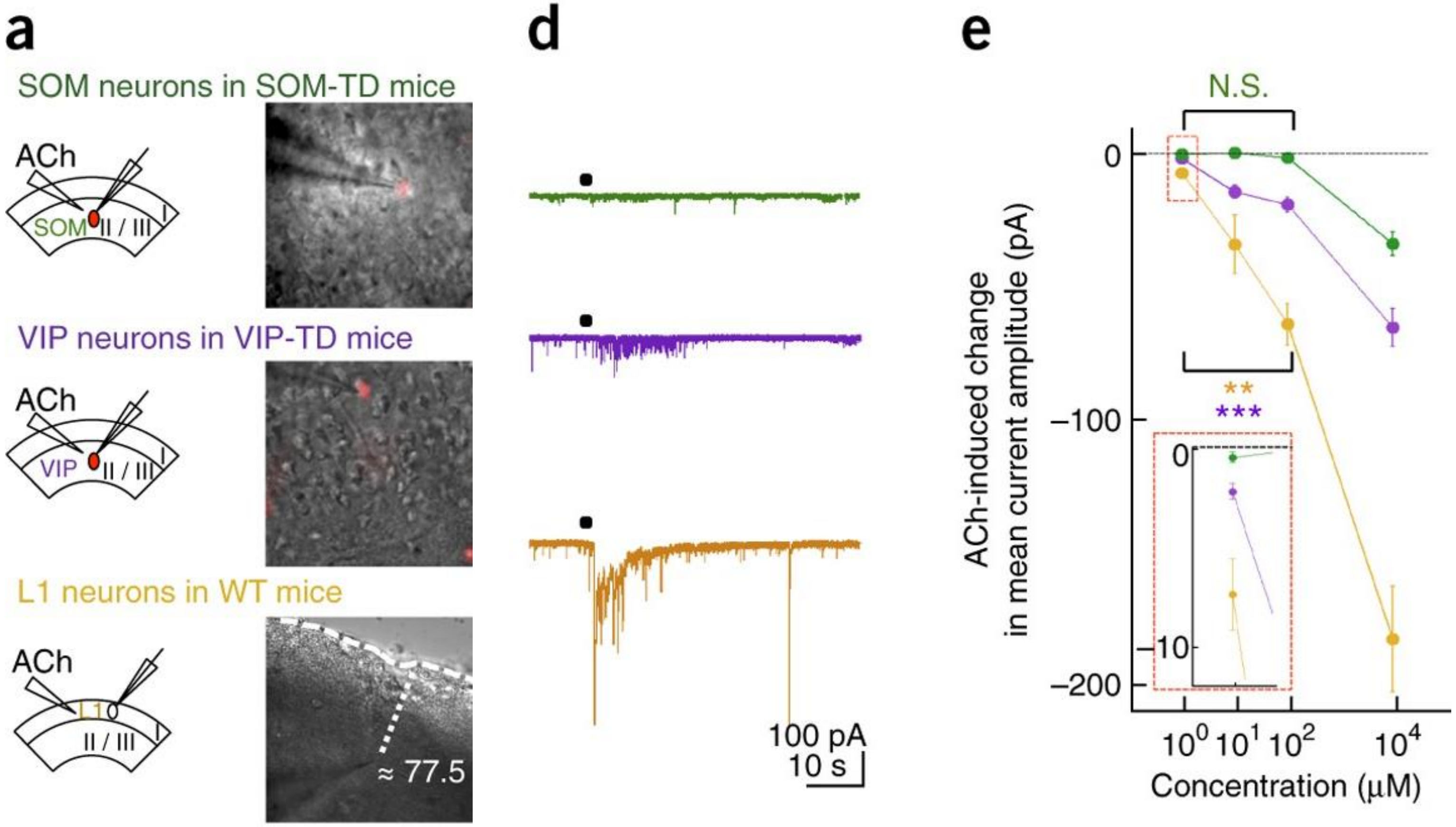
- Presynaptic facilitation, Long-term potentiation, slow excitation/inhibition, and protein translation.



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.

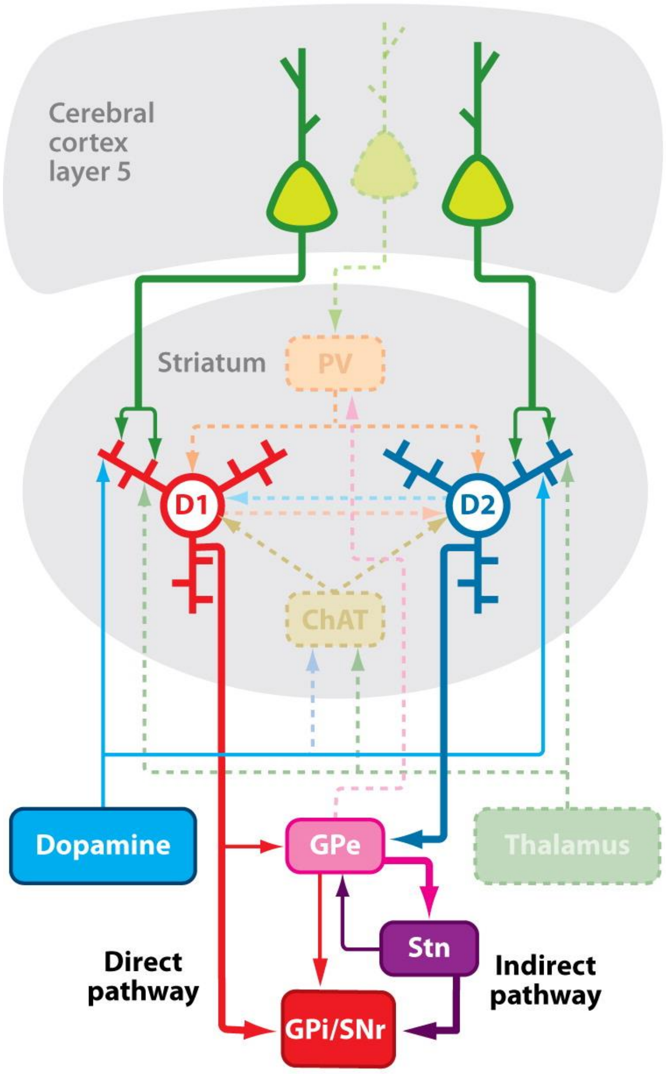


Chen Sugihara & Sur. 2015

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

a



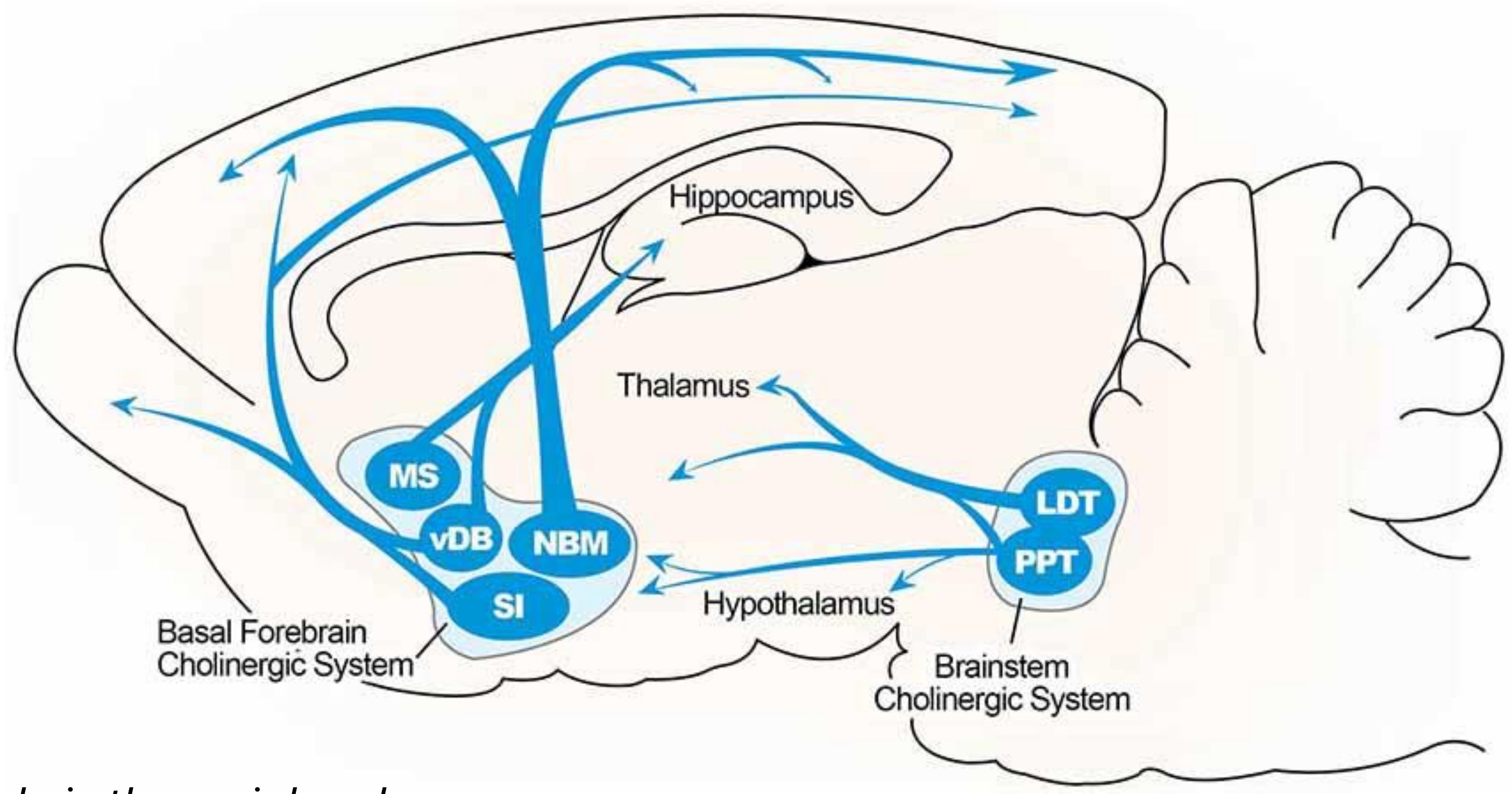
Corticostriatal and direct/indirect pathway canonical striatal microcircuits

Gerfen CR, Surmeier DJ. 2011. Annu. Rev. Neurosci. 34:441–66

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

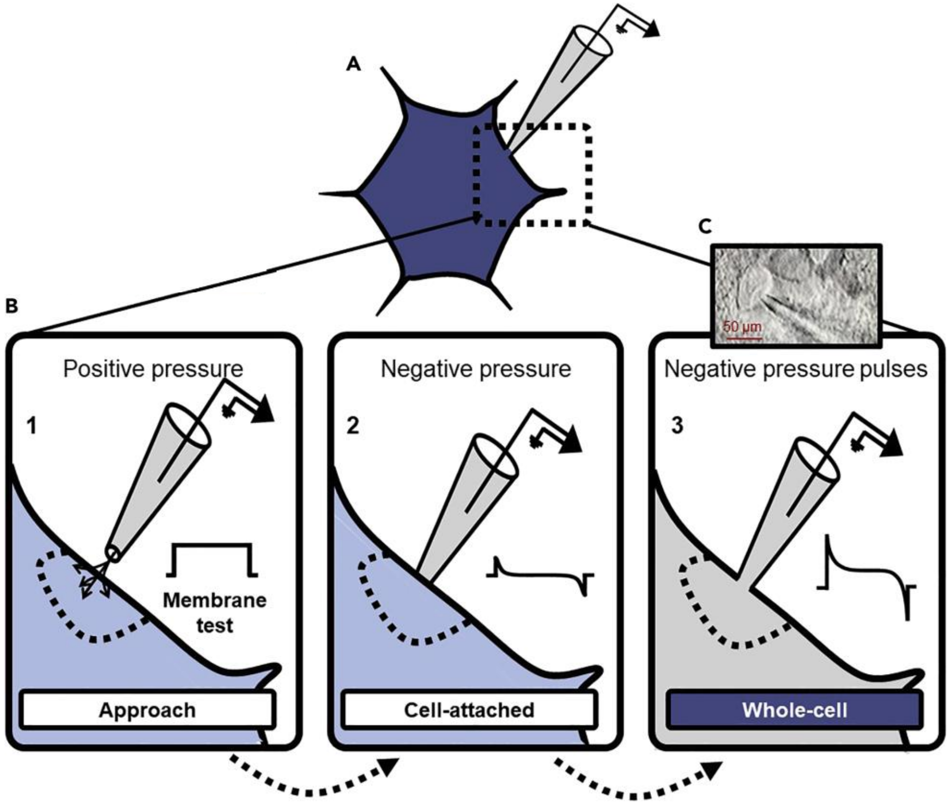
Making history, discovering the first neurotransmitter

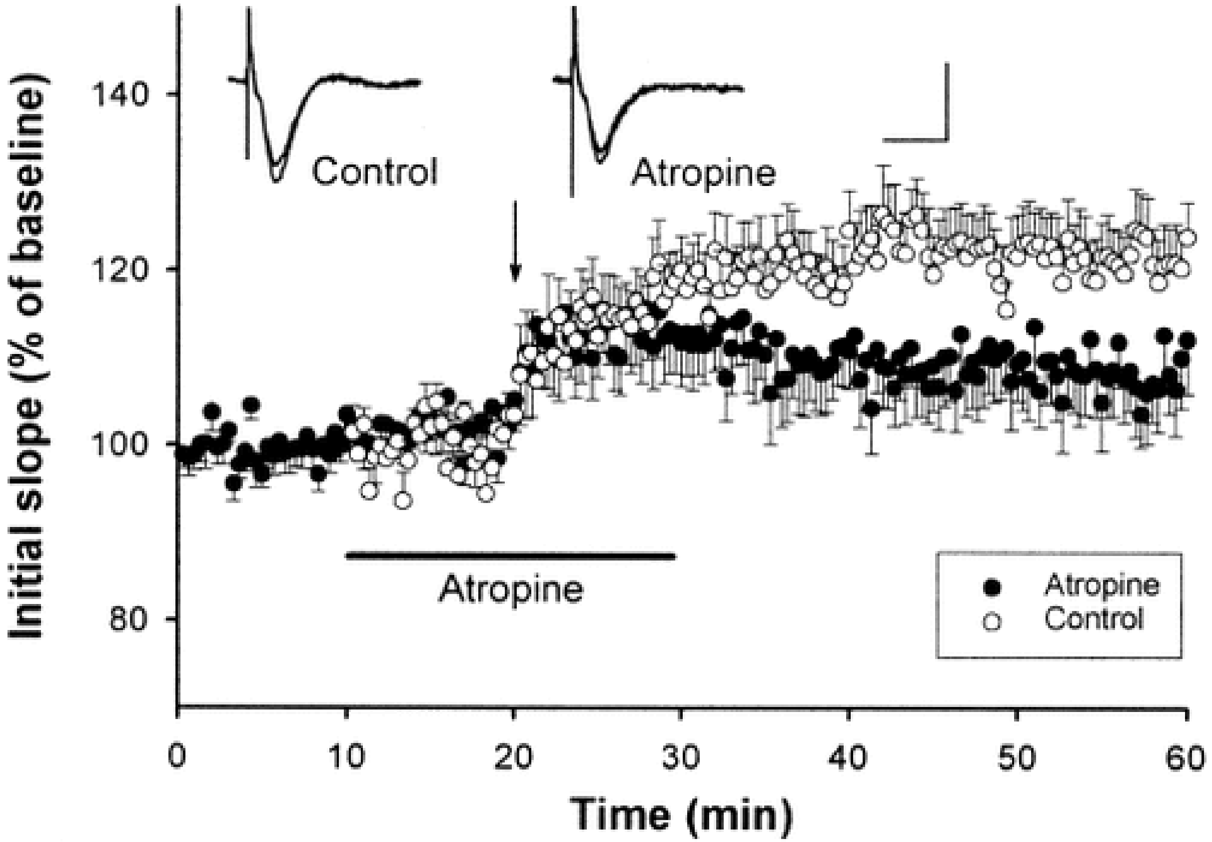
Otto Loewi

Acetylcholine was first isolated as a neurochemical in 1915

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

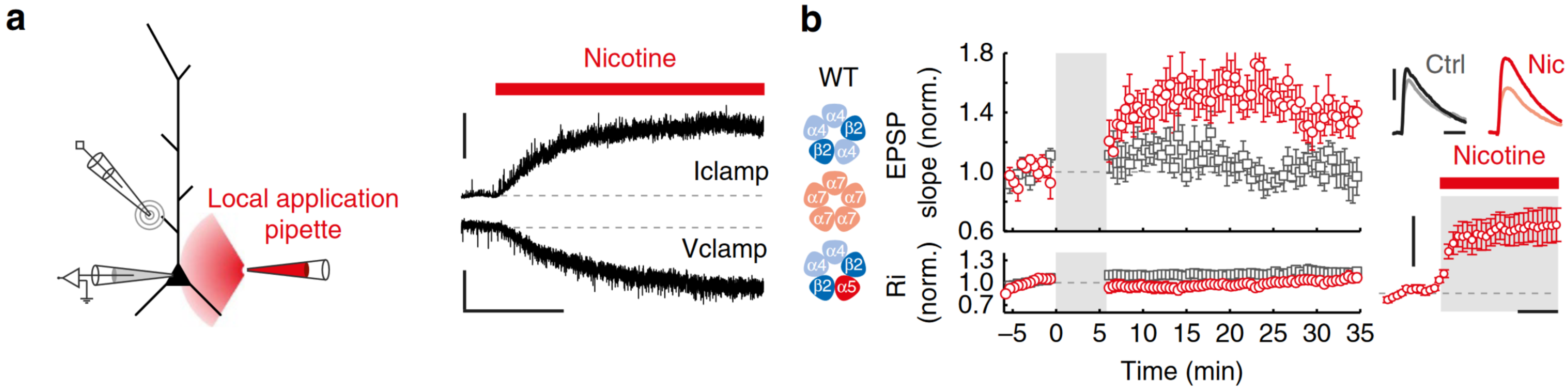
Acetylcholine facilitates long term potentiation





Cheong et al., 2001

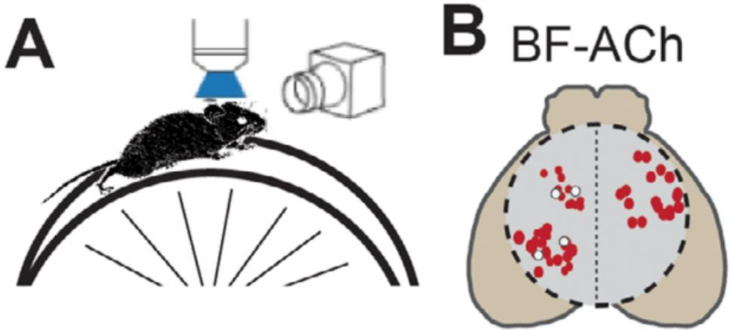
Acetylcholine facilitates long term potentiation



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

Verhoog et al., 2016

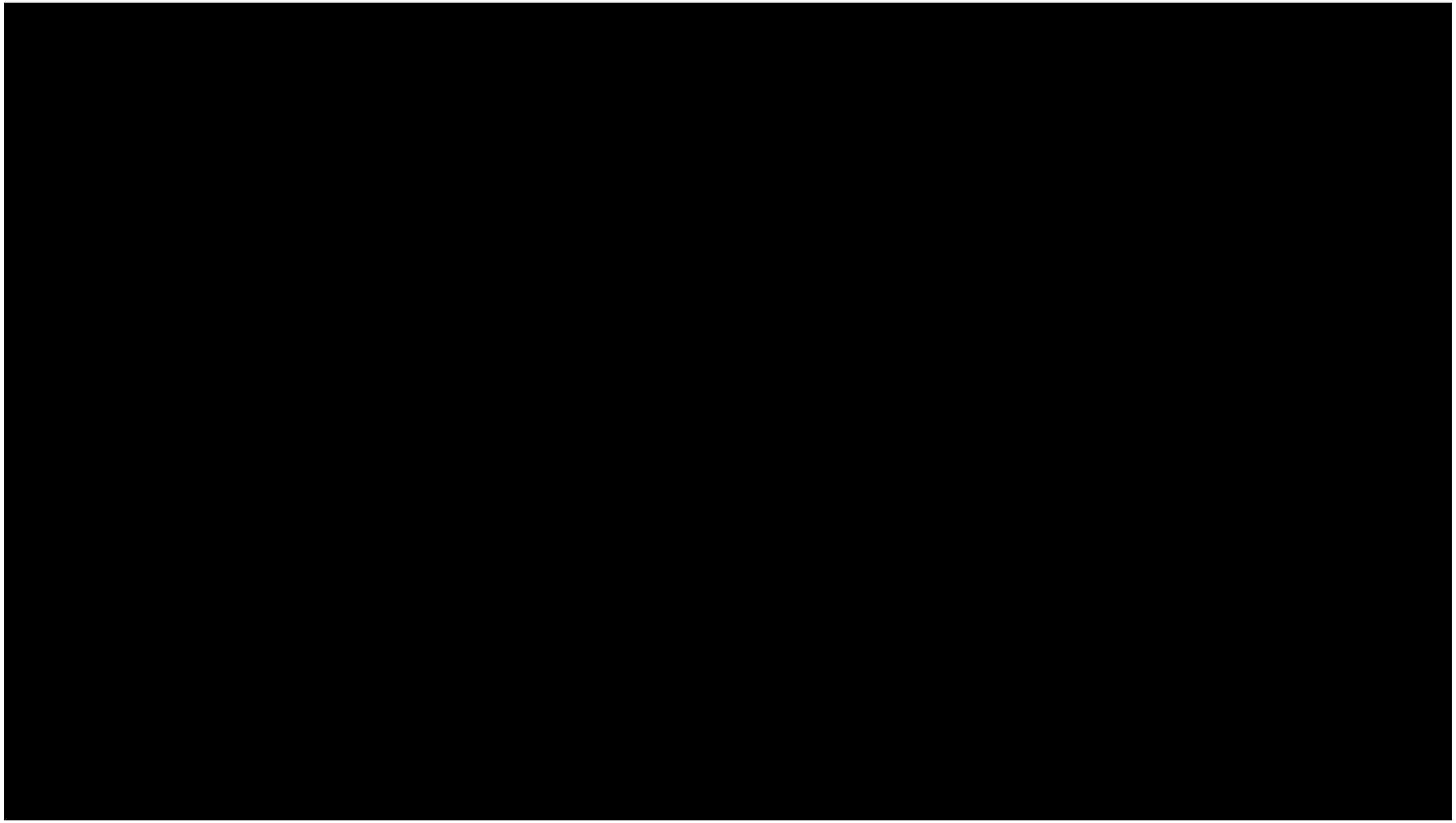
Cholinergic signaling mediates arousal and attention



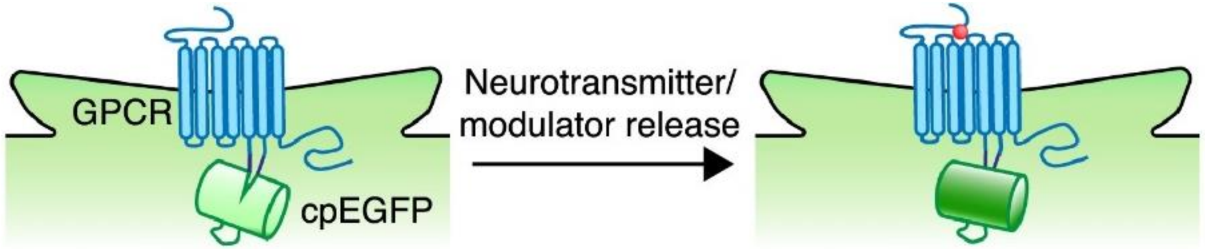
How do researchers detect neuromodulator activity if it does not always directly produce spiking?

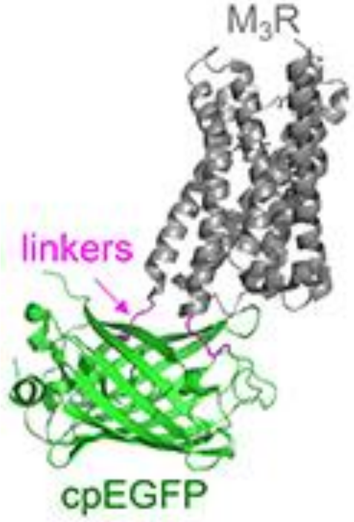
Reimer et al., 2016
Collins et al., 2023

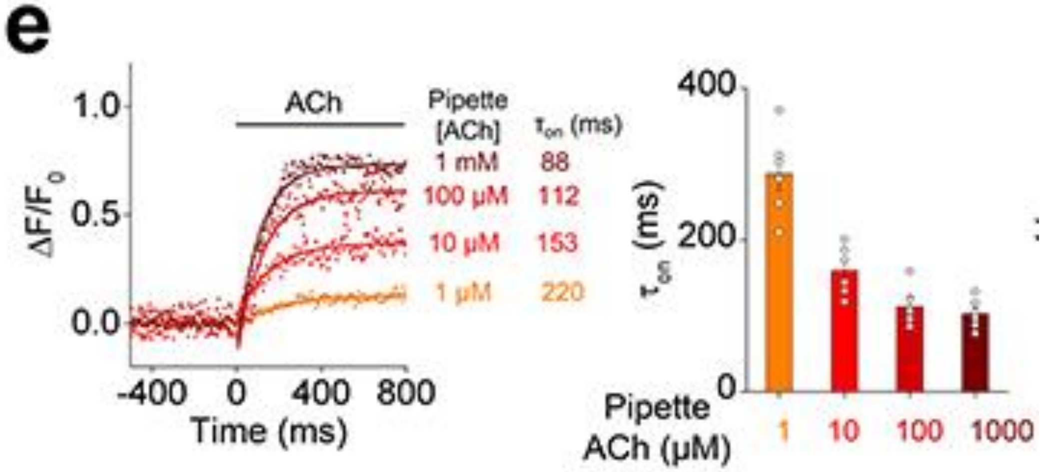
Measuring neuromodulator activity *in vivo*

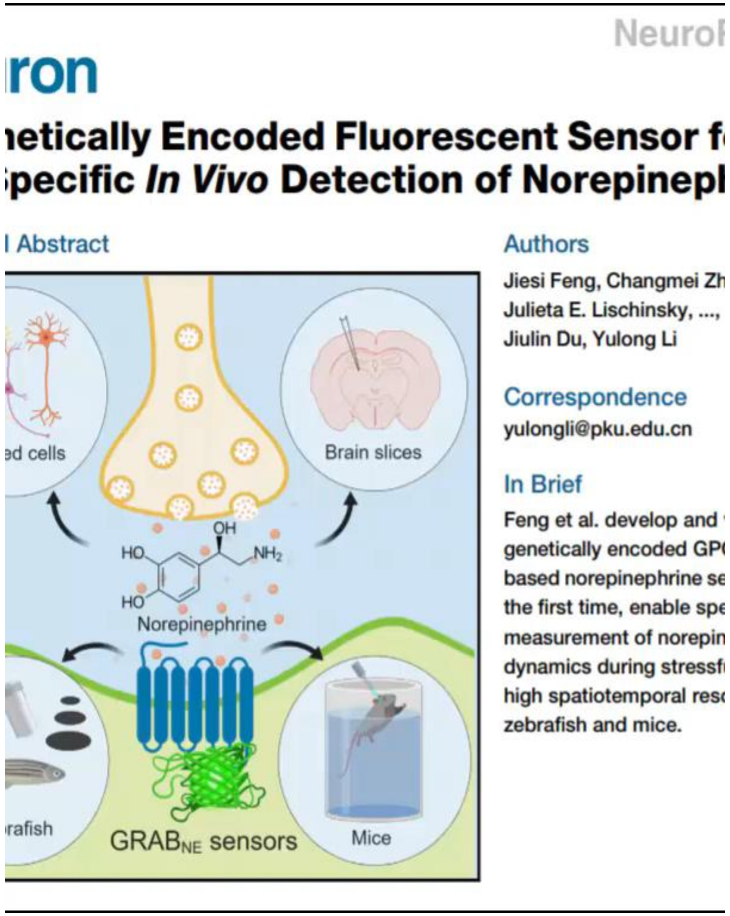


Measuring neuromodulator activity *in vivo*





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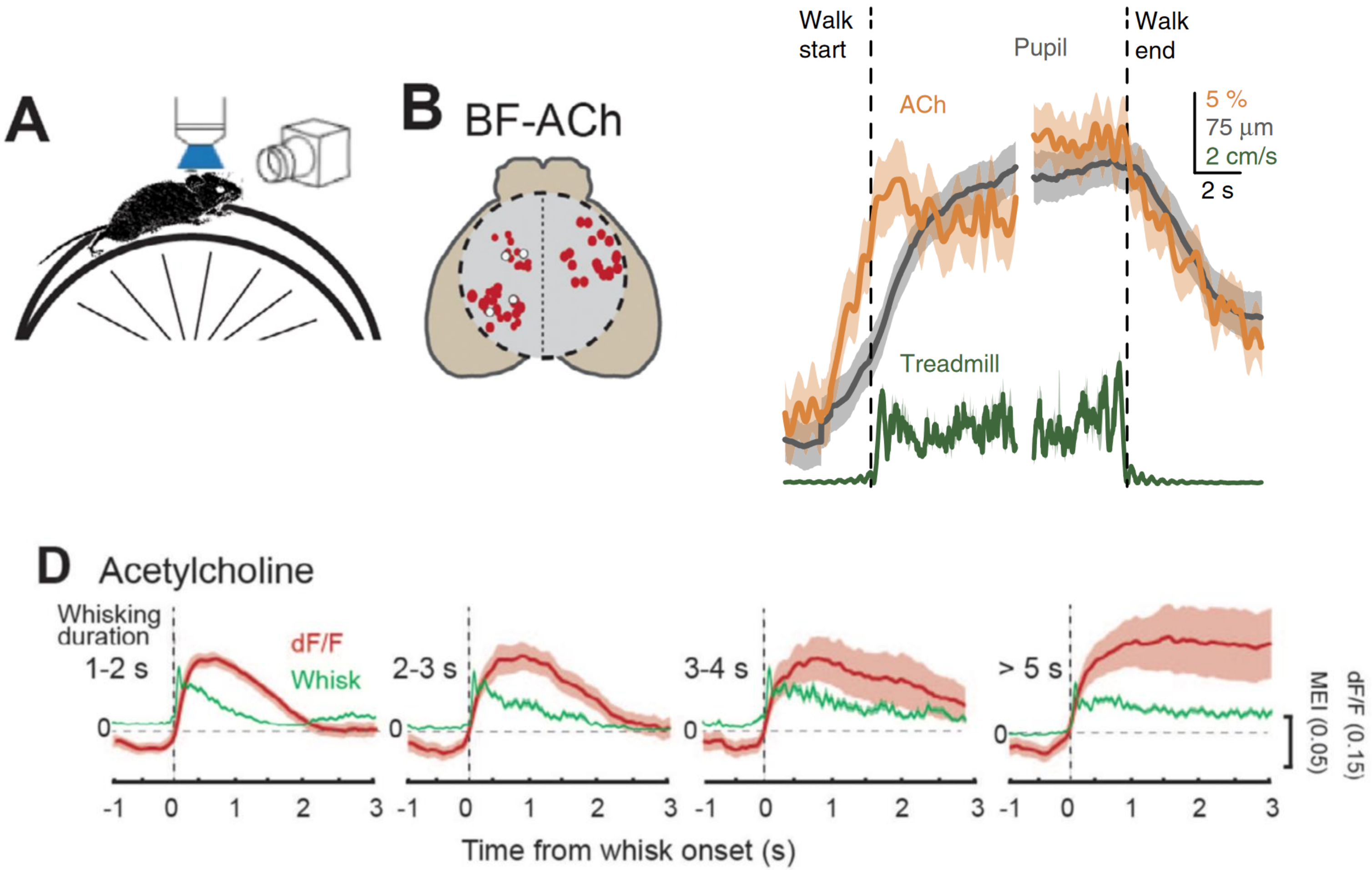
netically Encoded Fluorescent Sensor f
pecific *In Vivo* Detection of Norepinepl
Abstract

Authors
Jiesi Feng, Changmei Zh
Julieta E. Lischinsky, ...,
Jiulin Du, Yulong Li
Correspondence
yulongli@pku.edu.cn
In Brief
Feng et al. develop and
genetically encoded GP
based norepinephrine se
the first time, enable spe
measurement of norepin
dynamics during stressf
high spatiotemporal reso
zebrafish and mice.

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

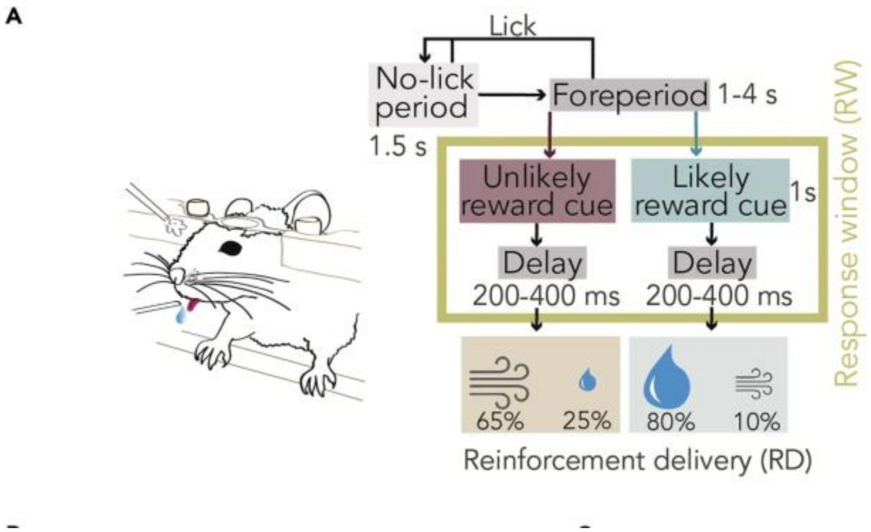
Cholinergic signaling mediates arousal and attention

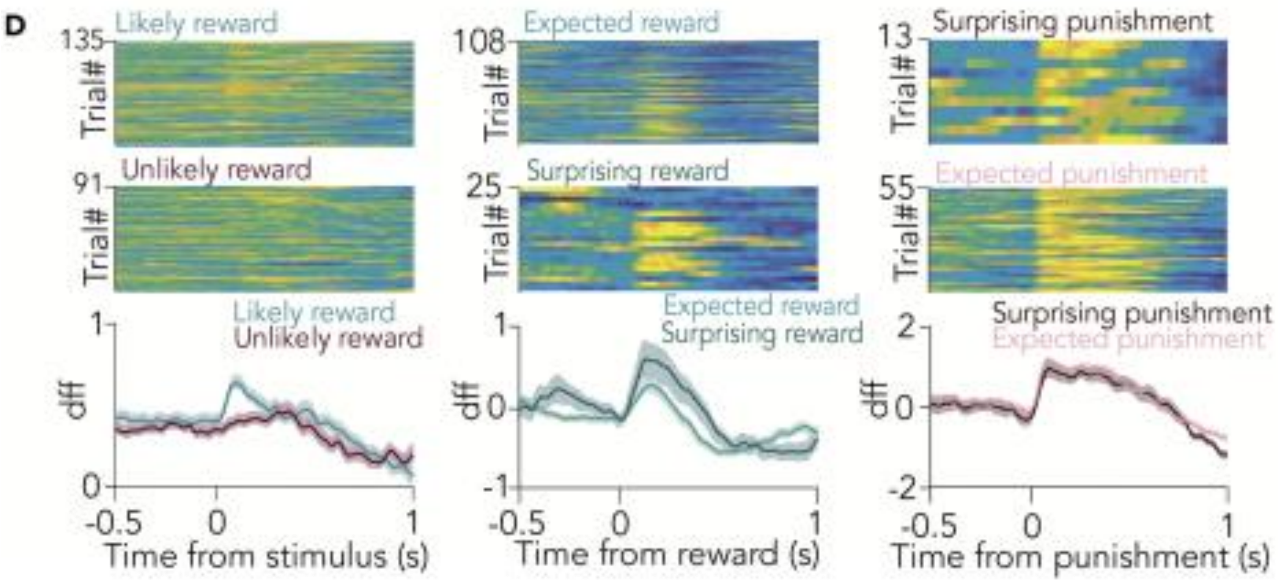


Cholinergic activity also fluctuates closely with certain motor behaviors, especially those related to exploration of the environment.

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

Cholinergic neurons encode cues, rewards and punishments





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

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

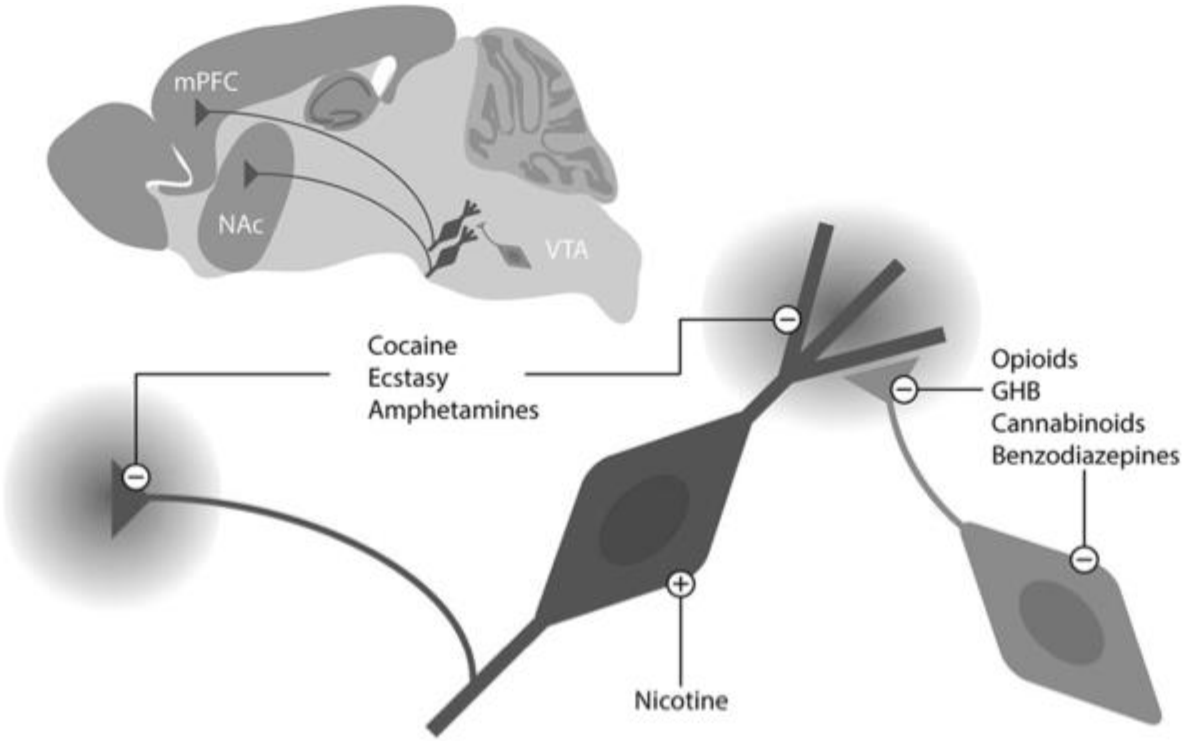
Hegedüs et al., 2023

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.

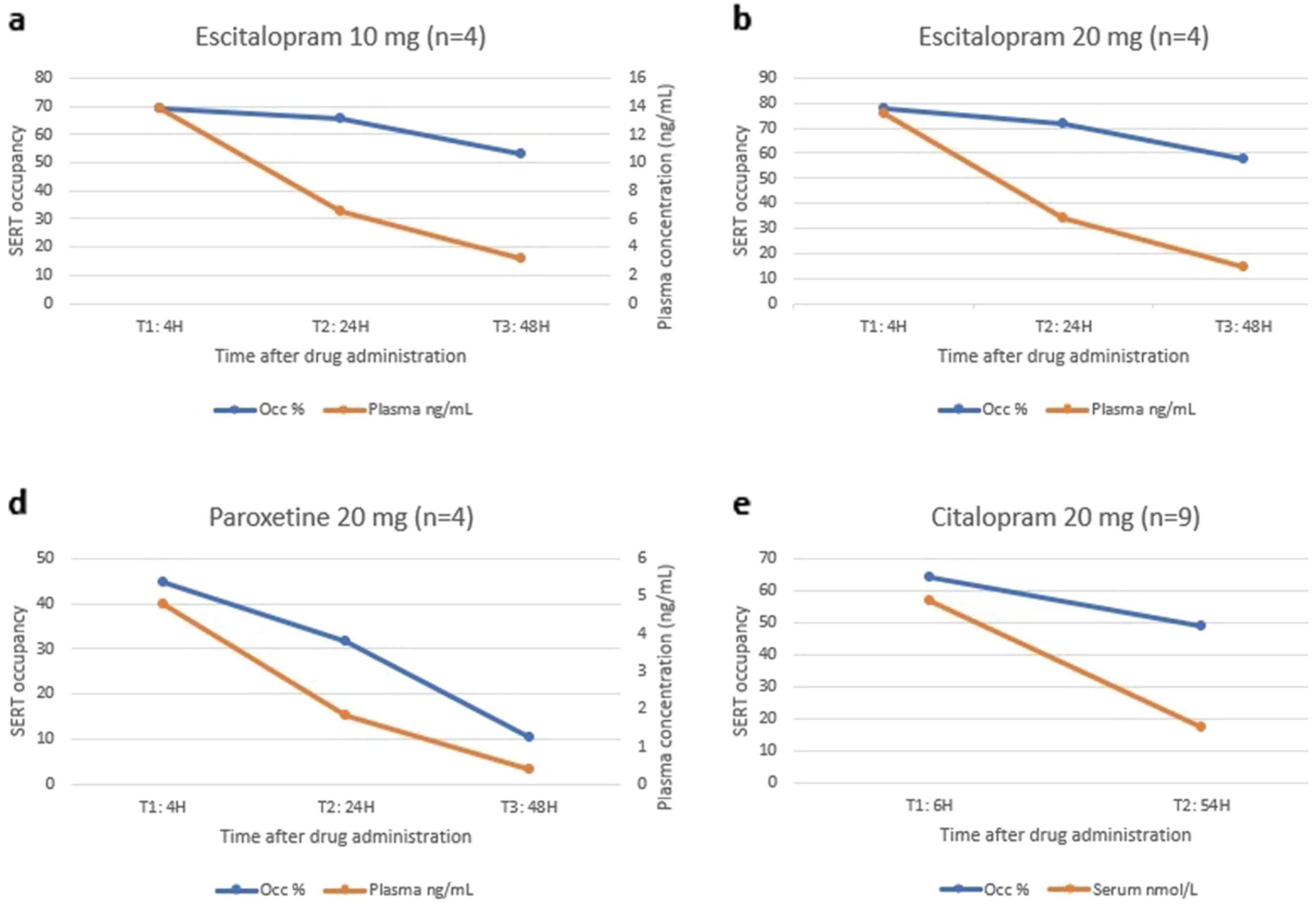


Luscher, 2013

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.

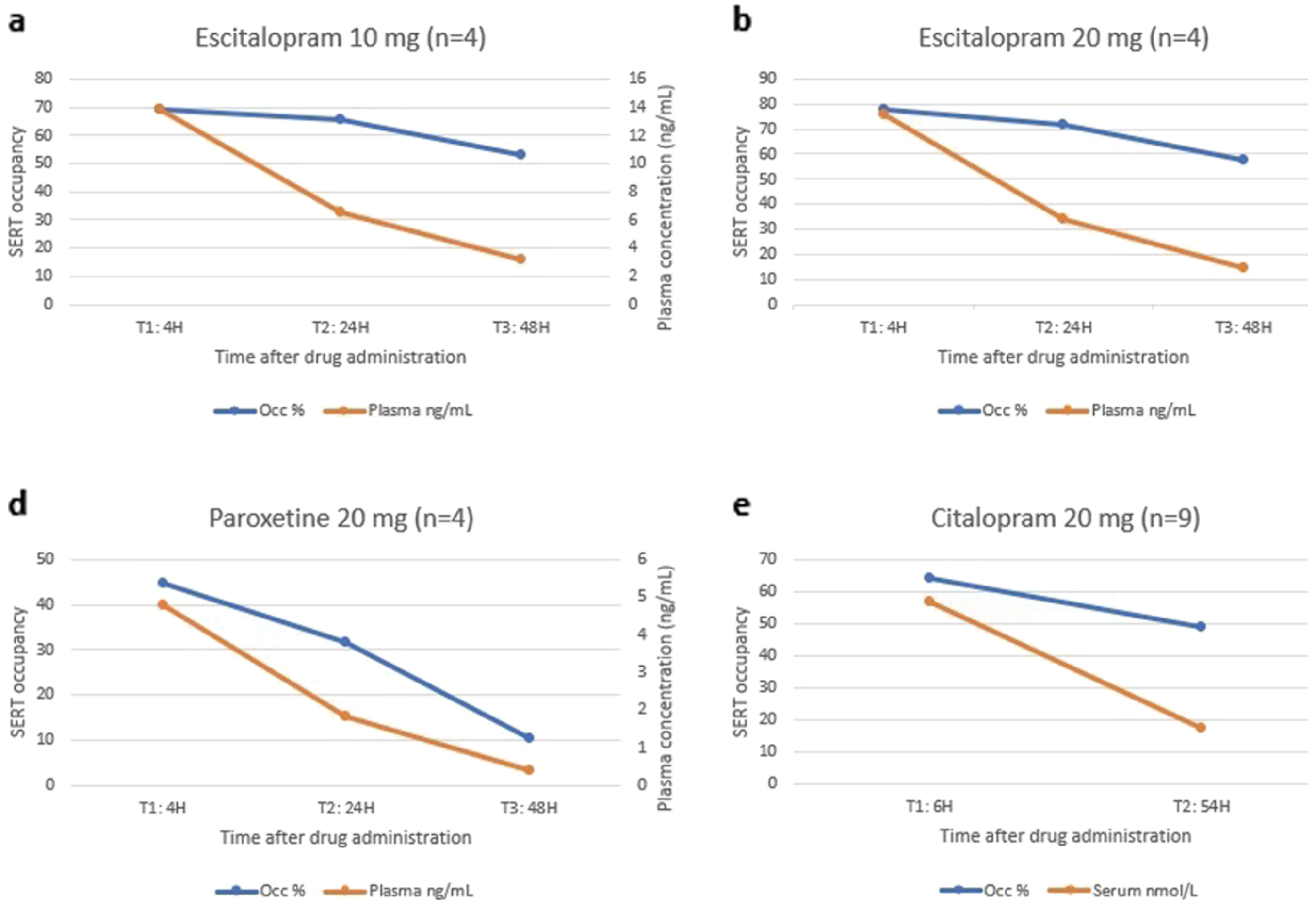


Sørensen, Ruhé & Munkholm 2022

Manipulating neuromodulatory circuits

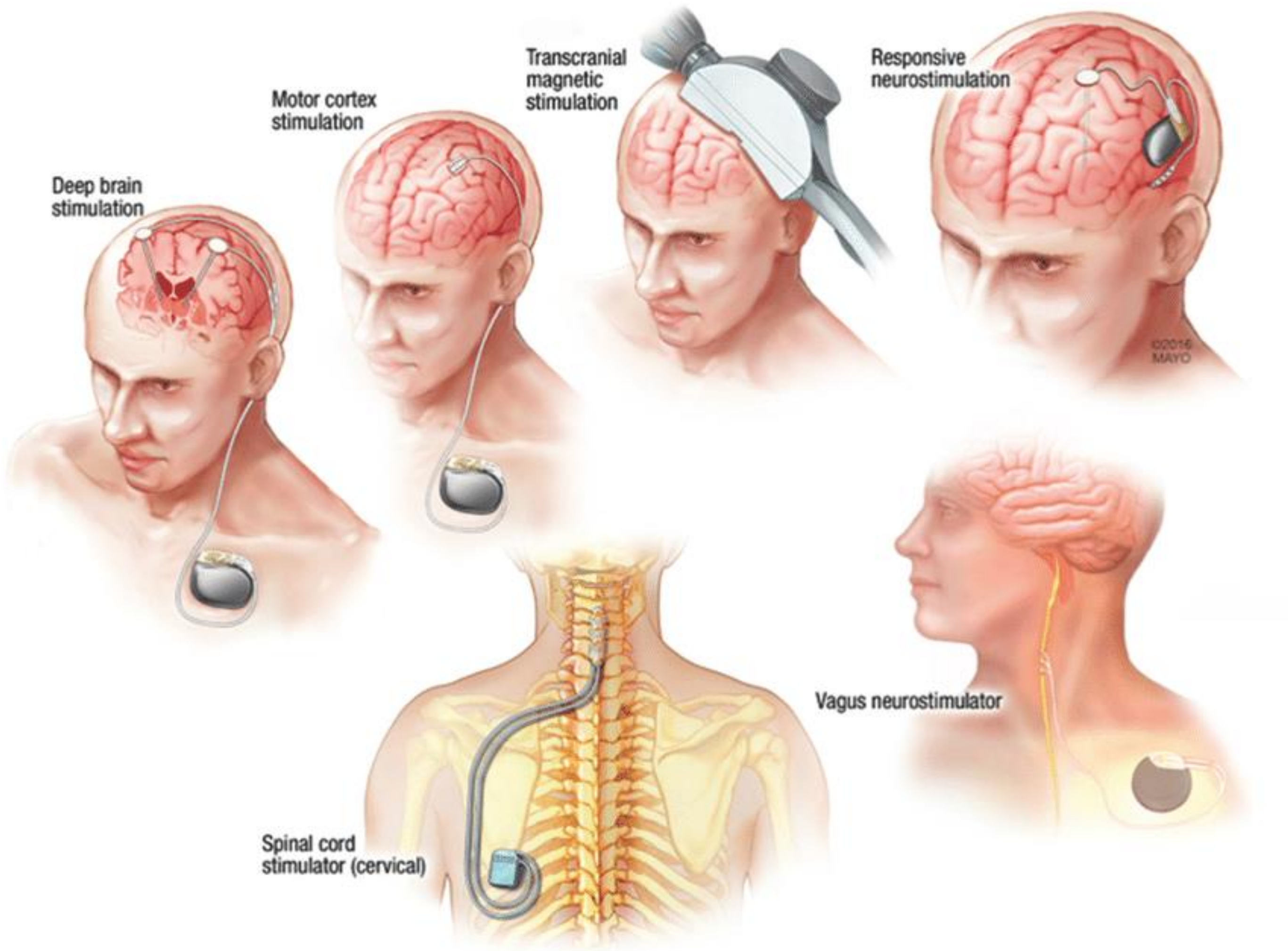
While great for making long-lasting changes to NM systems, altering NMs more rapidly can be challenging.

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



Sørensen, Ruhé & Munkholm 2022

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.

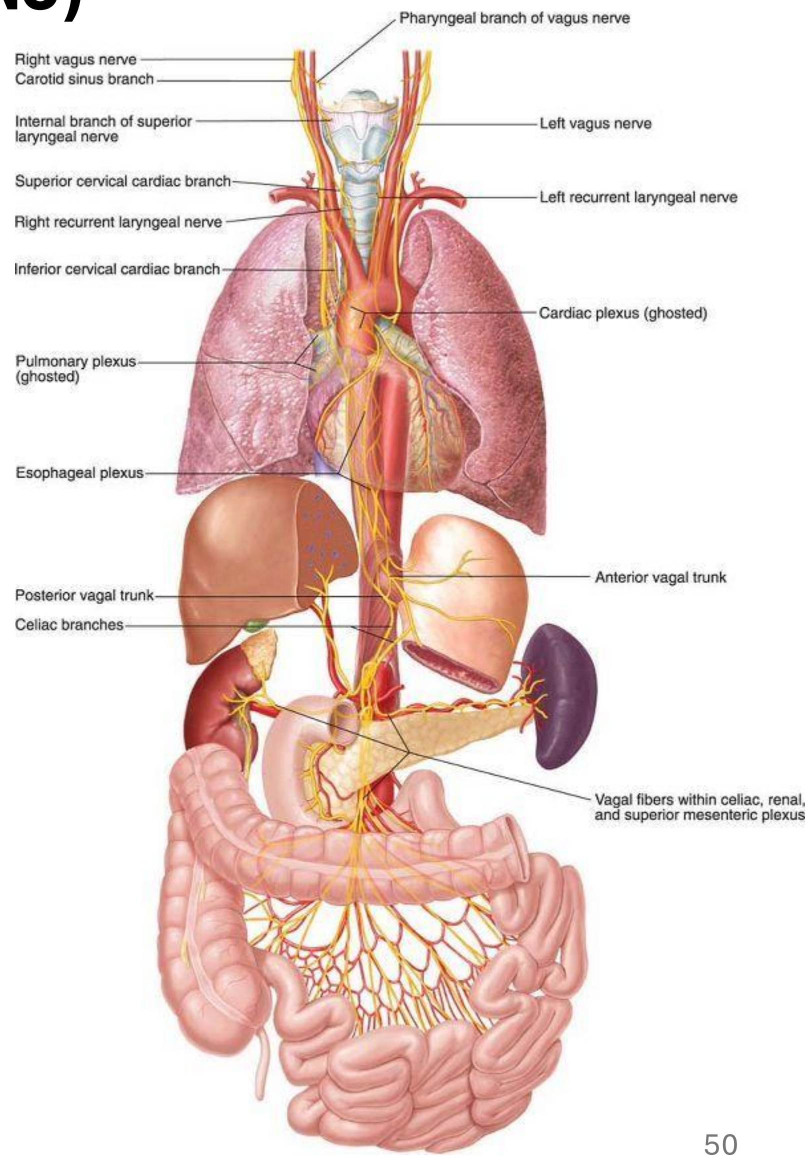
Vagus Nerve Stimulation (VNS)

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

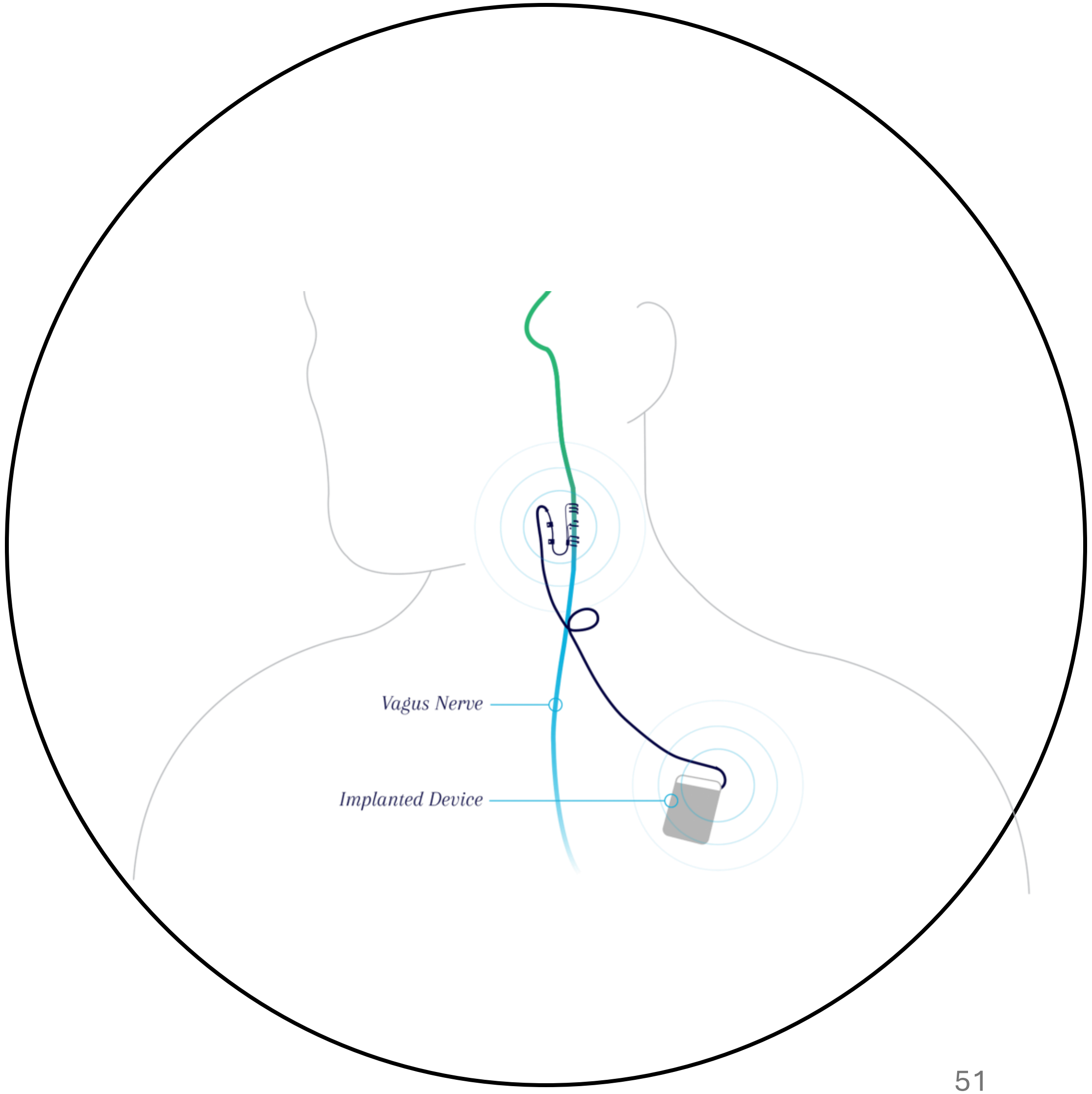


Vagus Nerve Stimulation (VNS)

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.

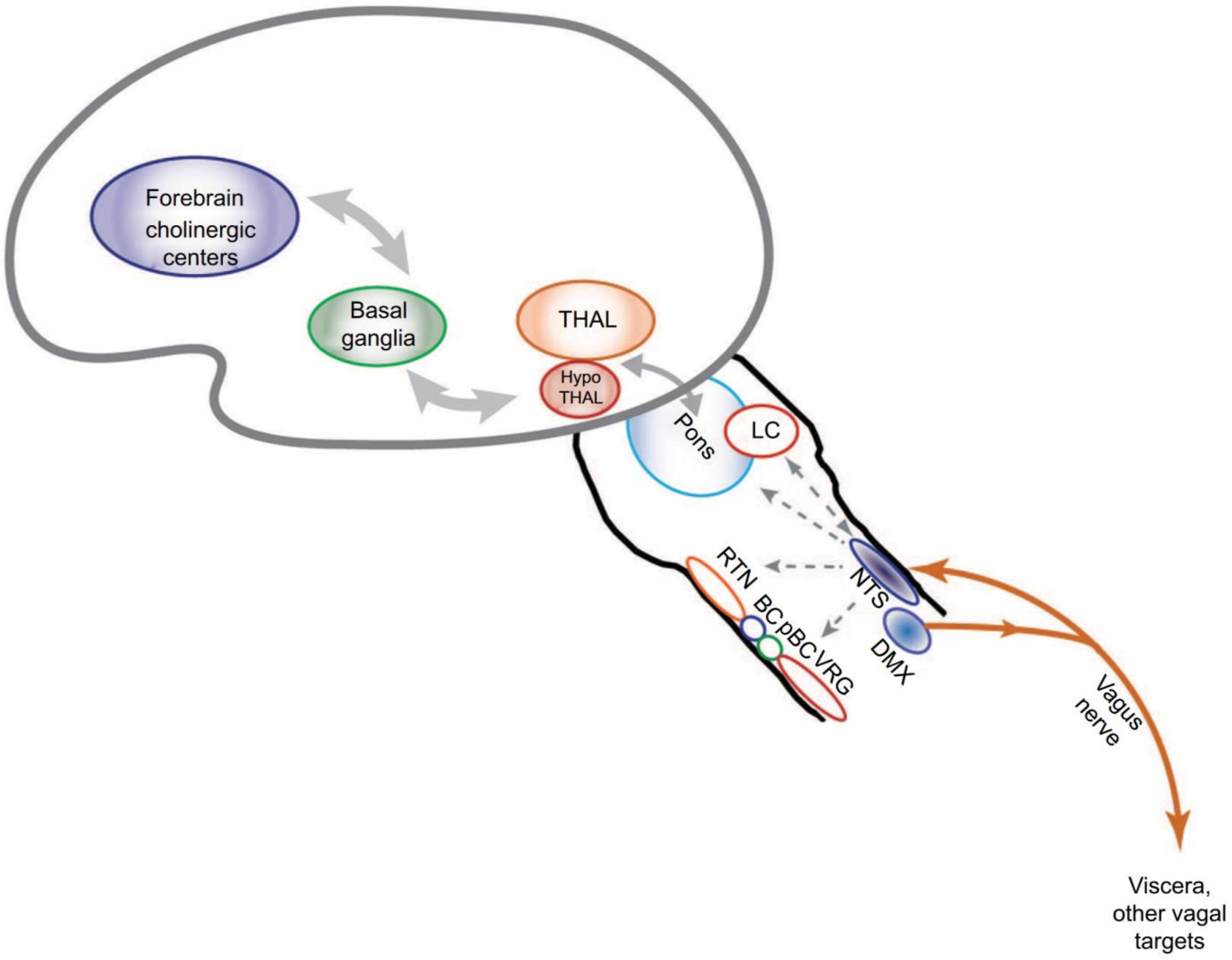


VNS activates several CNS modulatory systems

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

Stimulation of this NTS drives activity in several neuromodulatory centers.

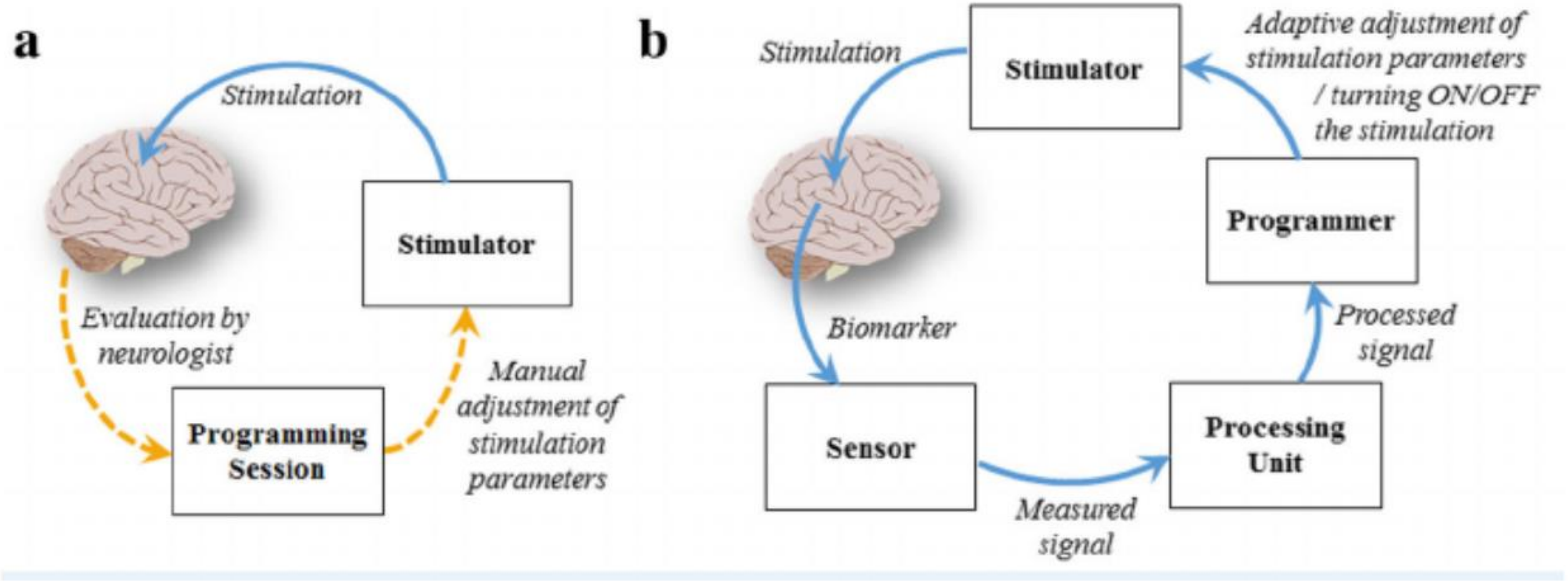
What are some potential issues with broad NM activation?



Key Concept: Open-loop vs closed-loop stimulation

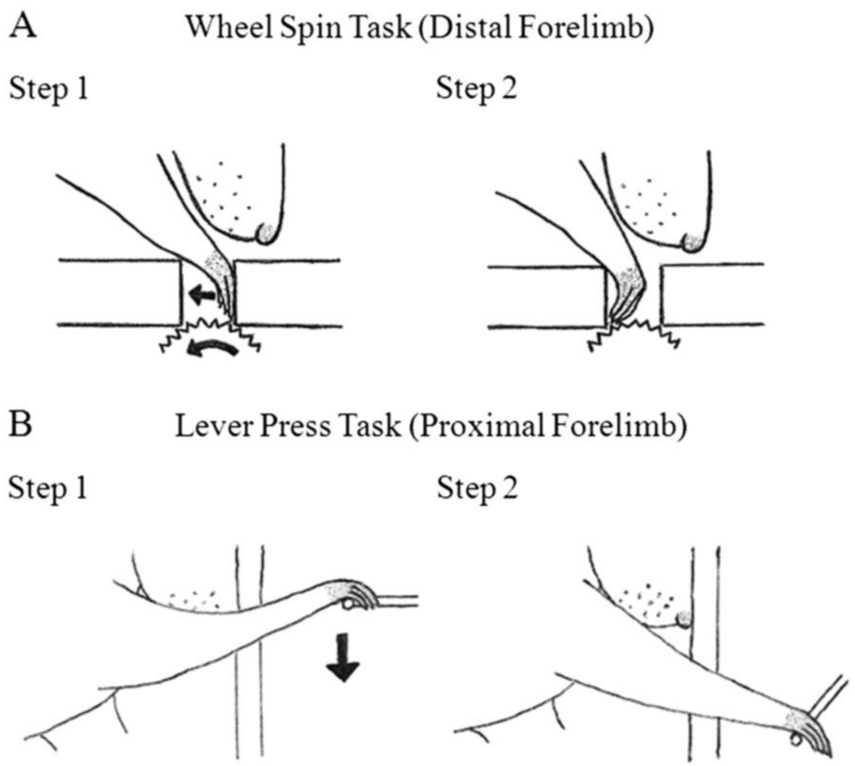
Open-loop stimulation is given at a set interval, and is unrelated to biomarkers

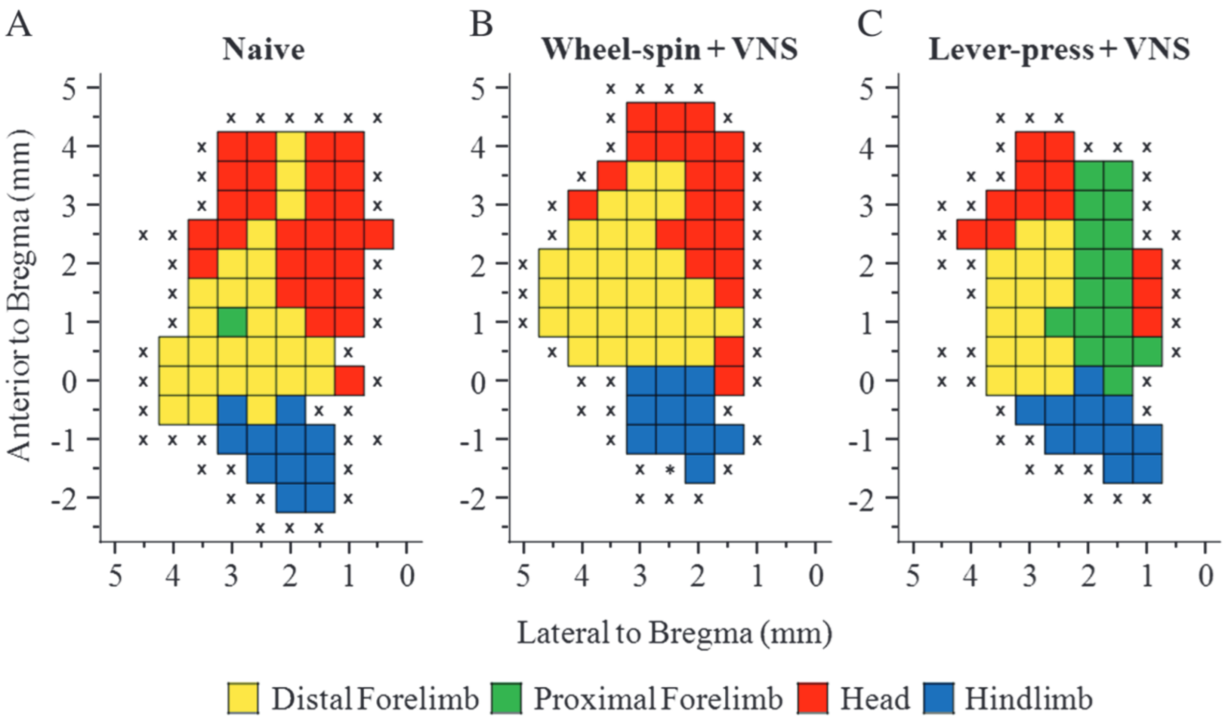
Closed-loop stimulation uses biomarkers as a signal to start or stop stimulation



Parastarfeizabadi & Kouzani, 2017

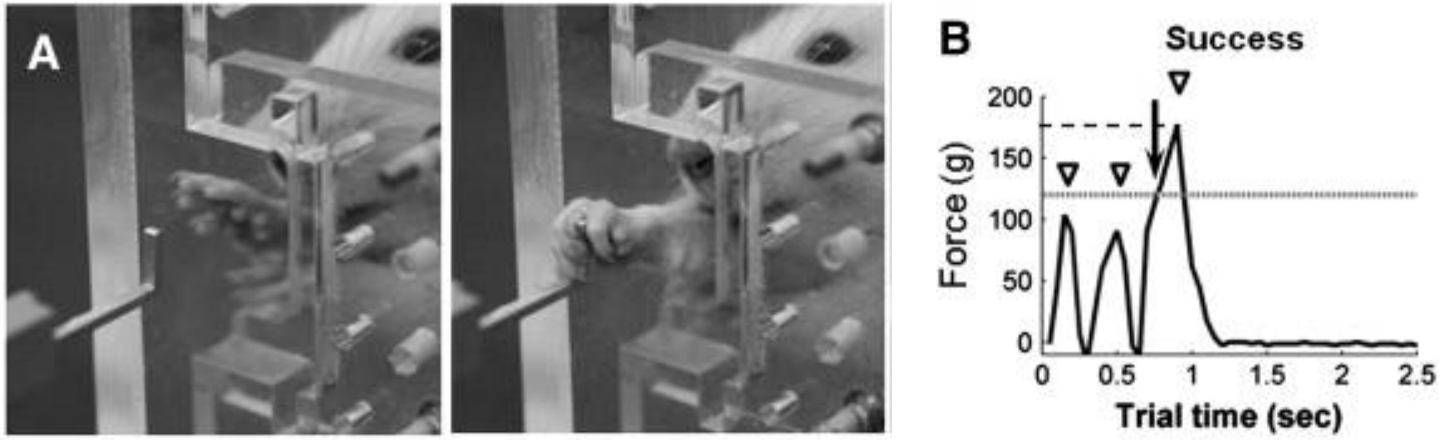
Closed- loop VNS can enhance cortical plasticity





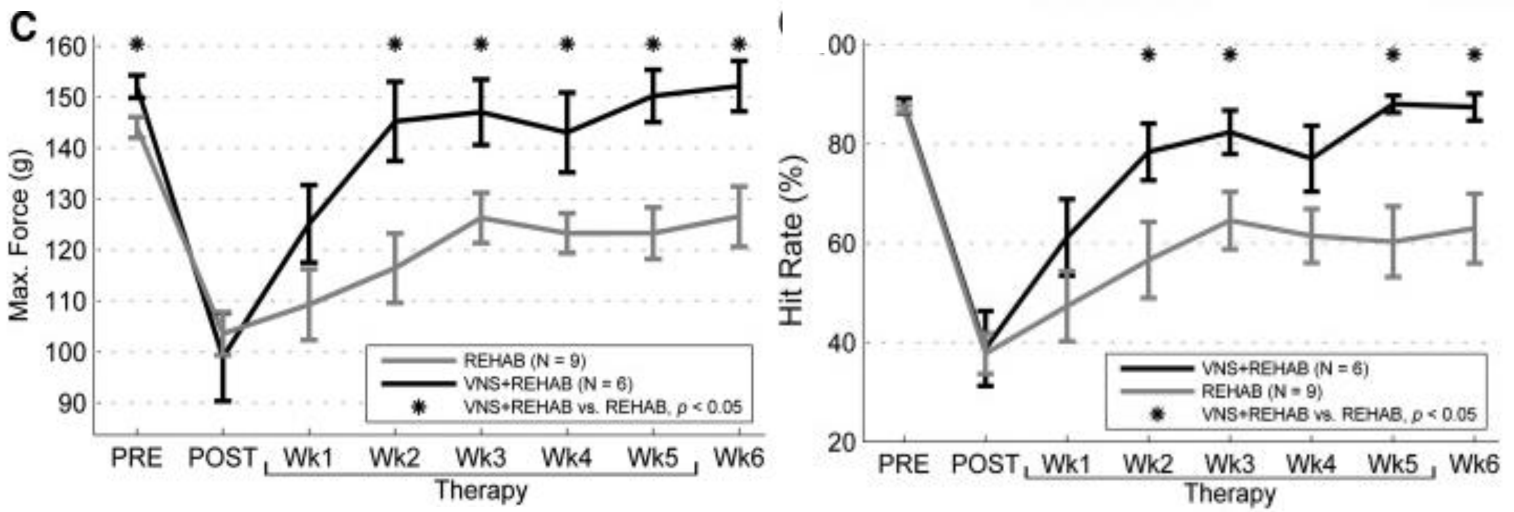
Porter et al., 2011

VNS can enhance stroke rehabilitation



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

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



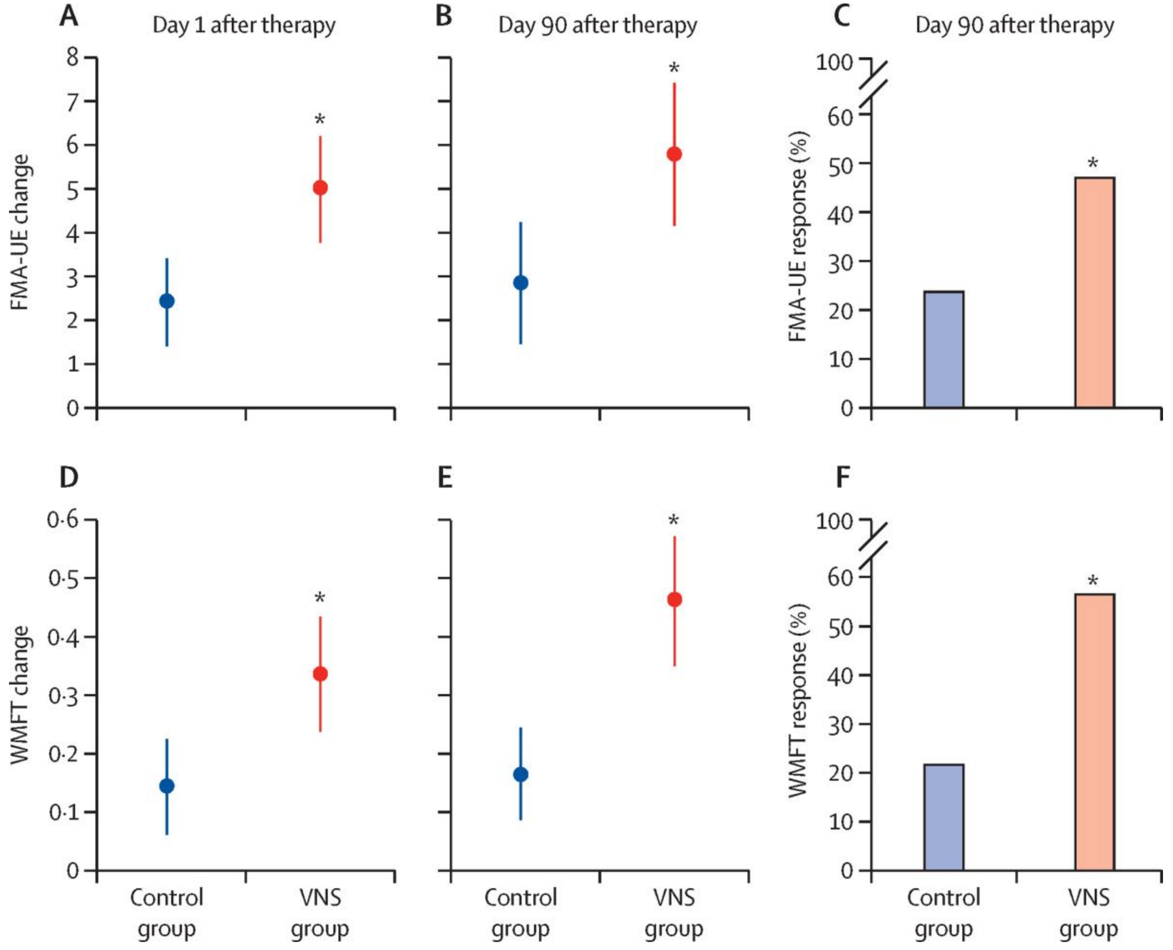
Khodaparast et al., 2013

VNS can enhance stroke rehabilitation

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

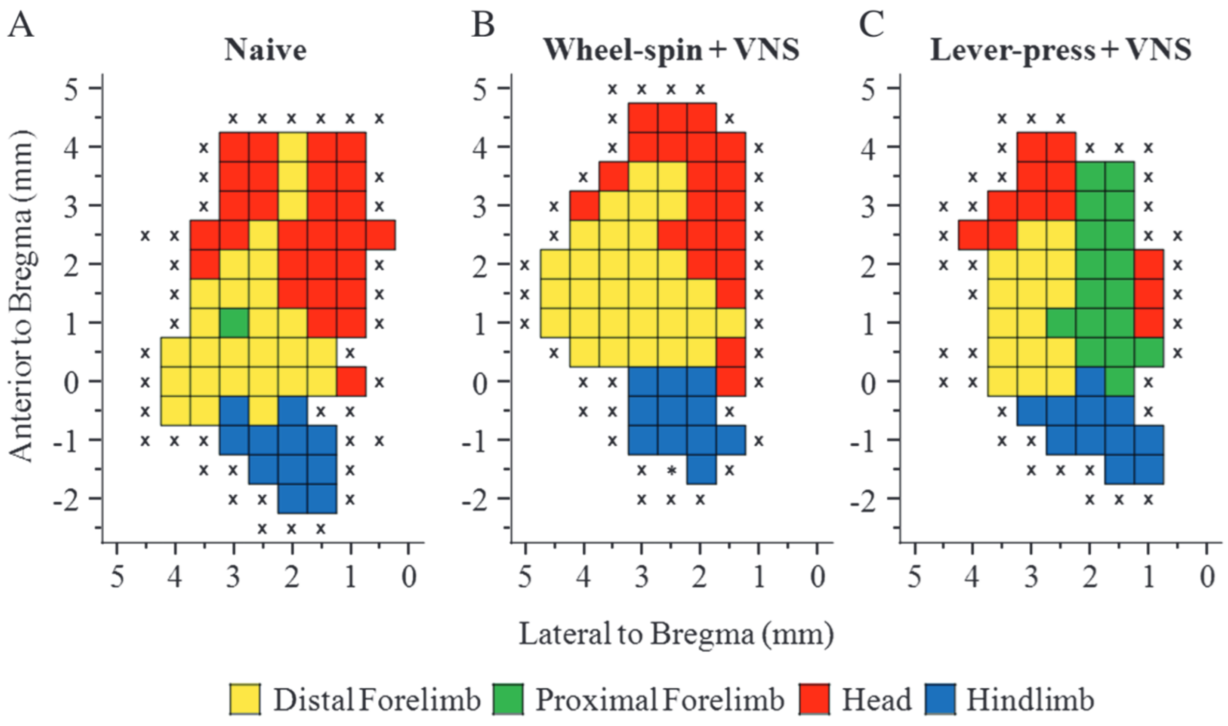
- VNS was approved as a stroke rehabilitation treatment in 2021.

What are the mechanisms that underly VNS-enhanced plasticity?

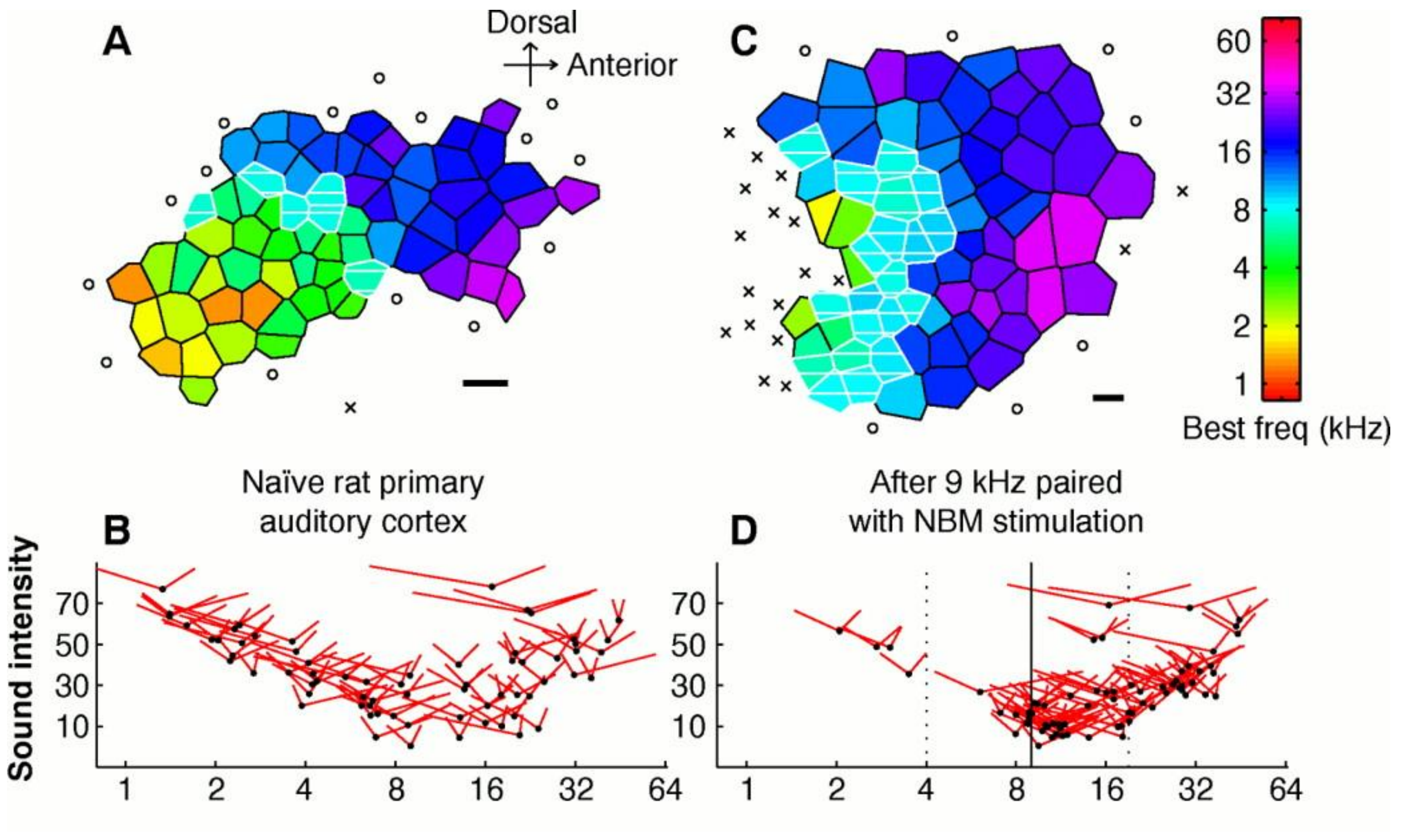


Dawson et al., 2021

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



Does directly stimulating the target system produce the same outcomes?



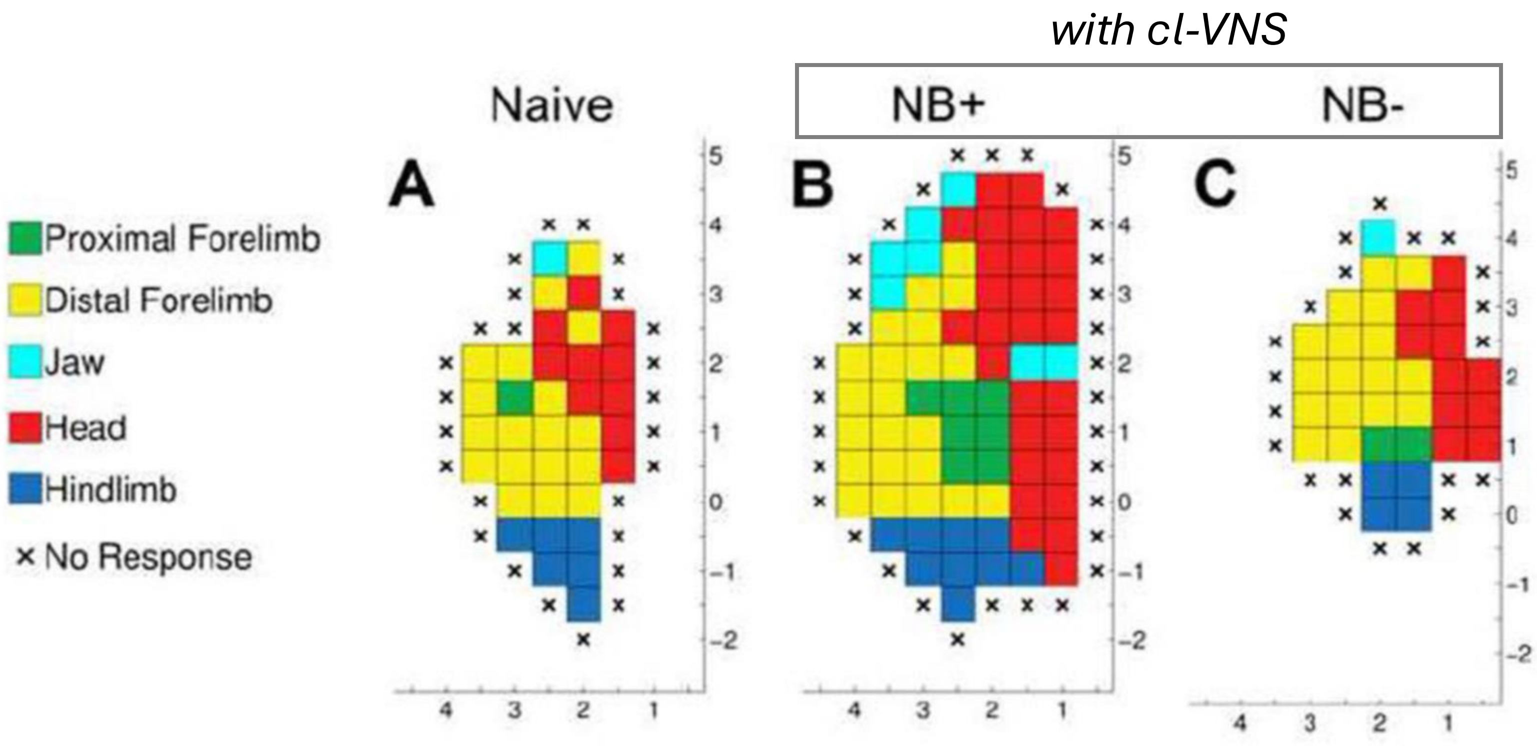
Cholinergic basal forebrain stimulation paired with a tone drives plasticity in auditory cortex

Kilgard and Merzenich, Science 1998

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

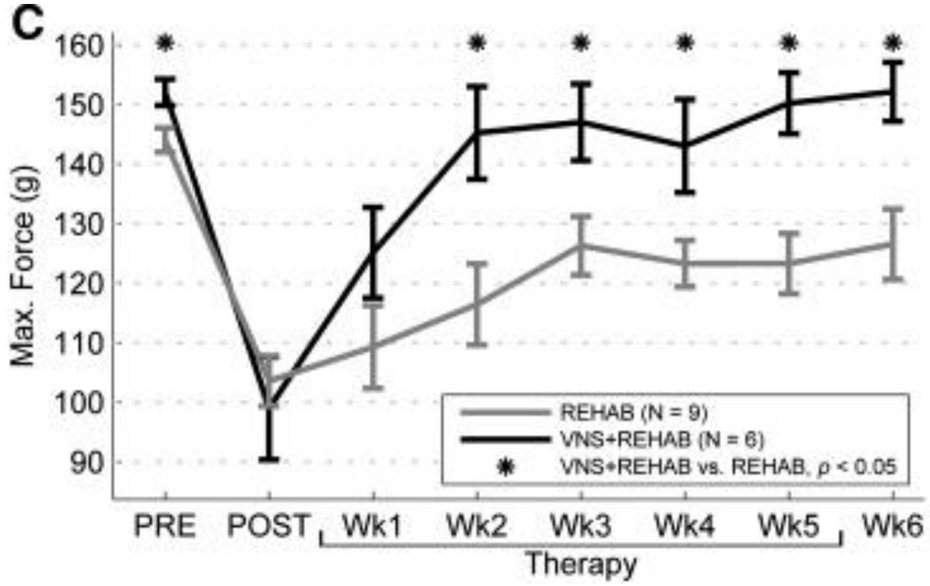
Chemical lesions of cholinergic neurons prevent VNS-driven remapping of motor cortex.

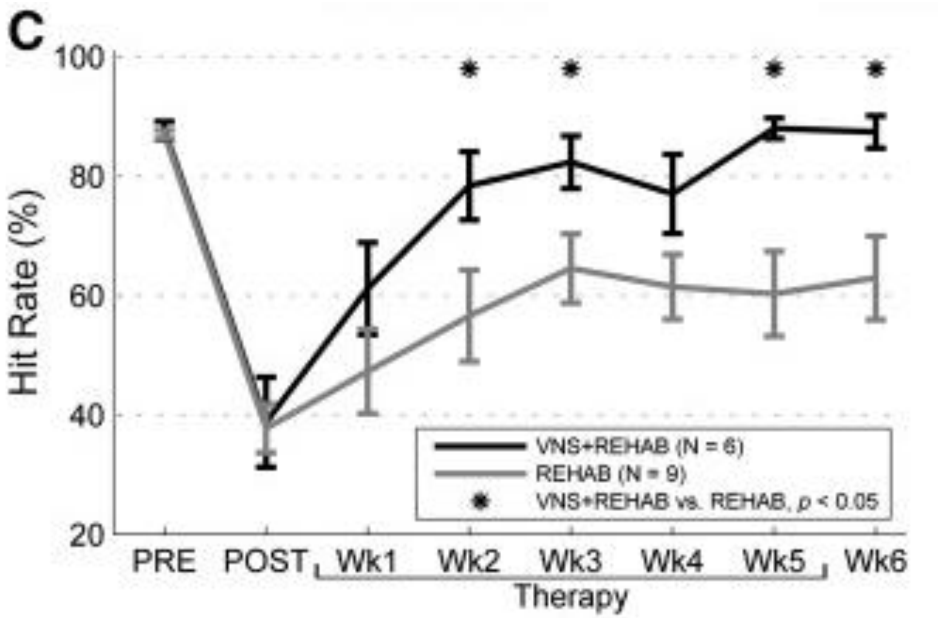
Note: NB refers to the nucleus basalis of Meynert, one of the primary nuclei in the basal forebrain.



Hulsey et al., 2016

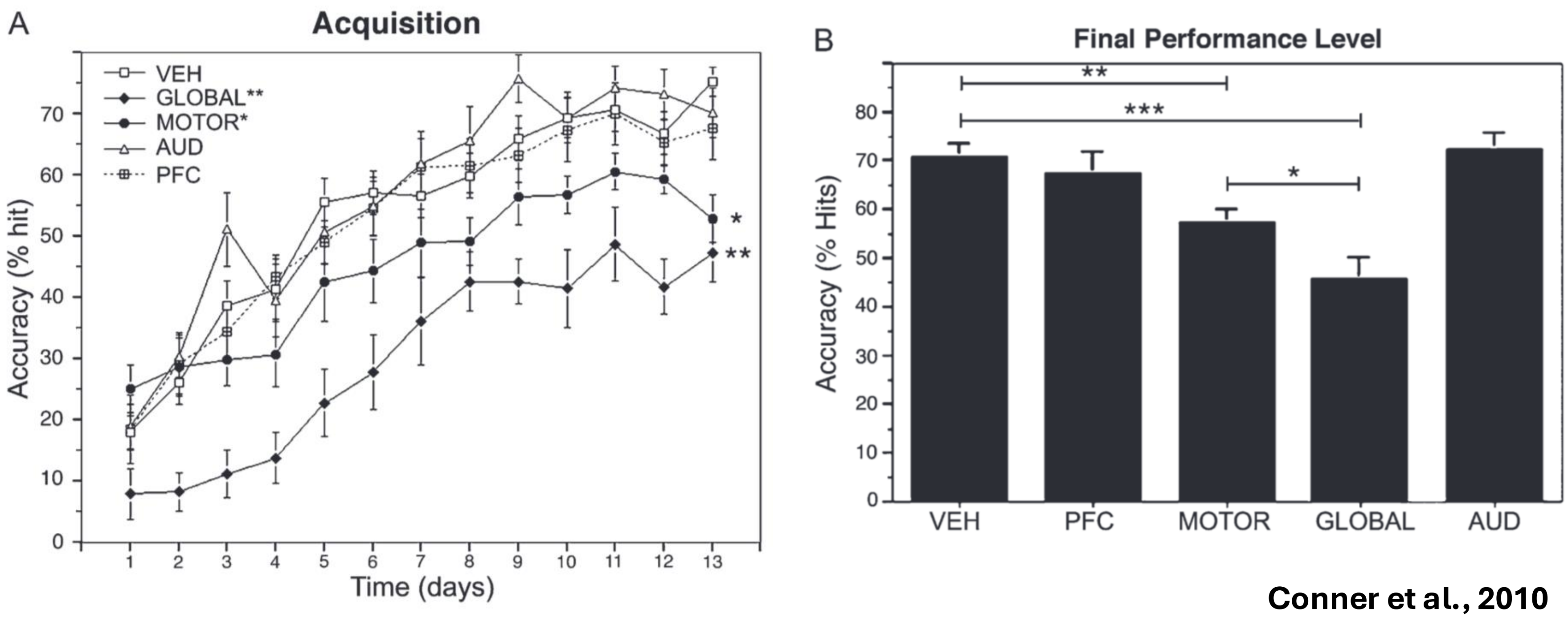
Is the target system naturally involved in the behavior your device treats?





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



Conner et al., 2010

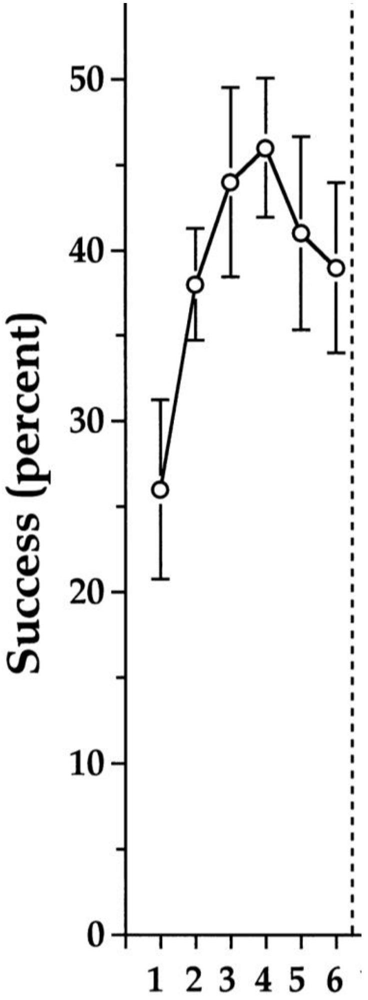
The cholinergic system is a strong candidate mediating VNS effects

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.



Gonzalez et al., 2004

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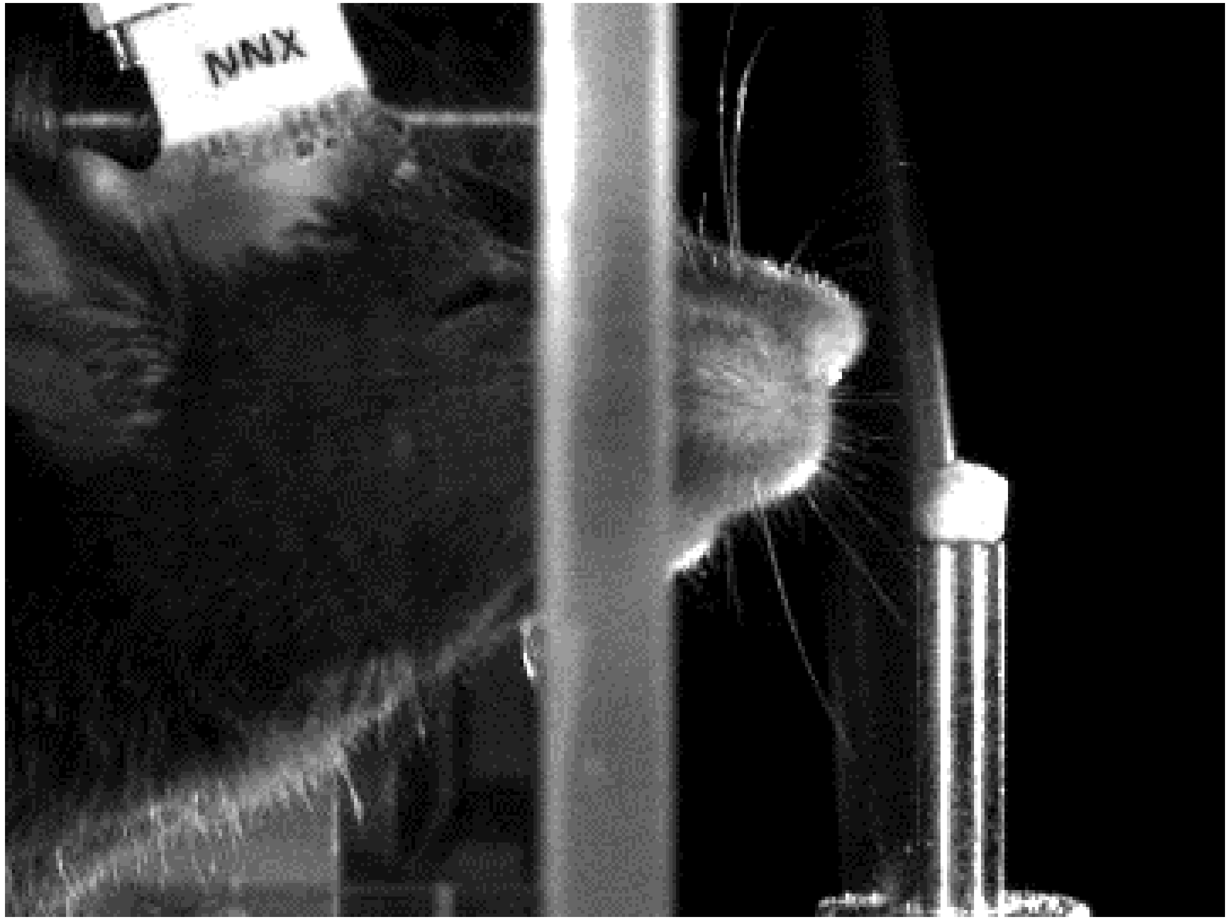


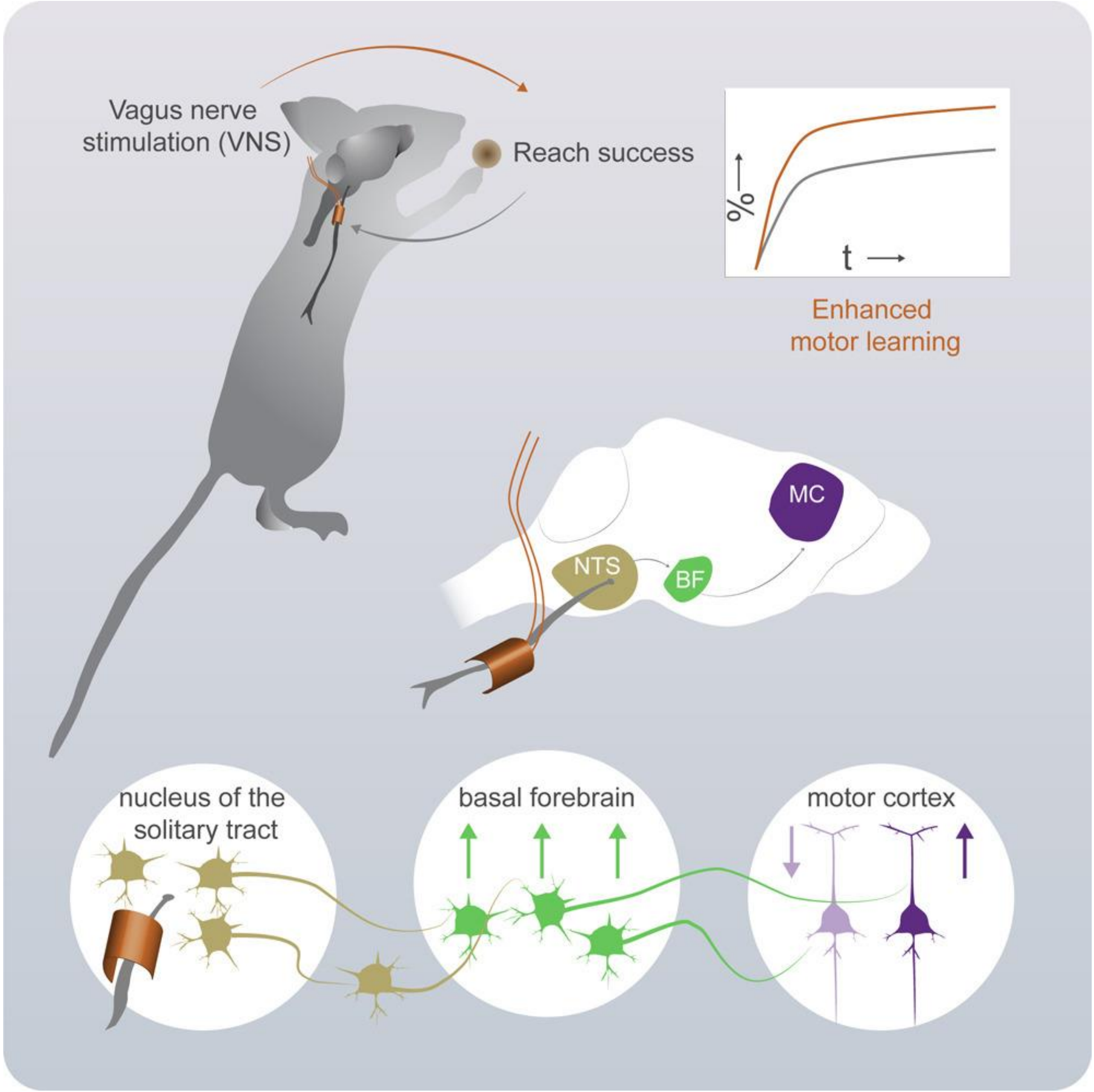
Neuron

Volume 110, Issue 17, 7 September 2022, Pages 2867-2885.e7

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 Williamson [3], 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 though 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.