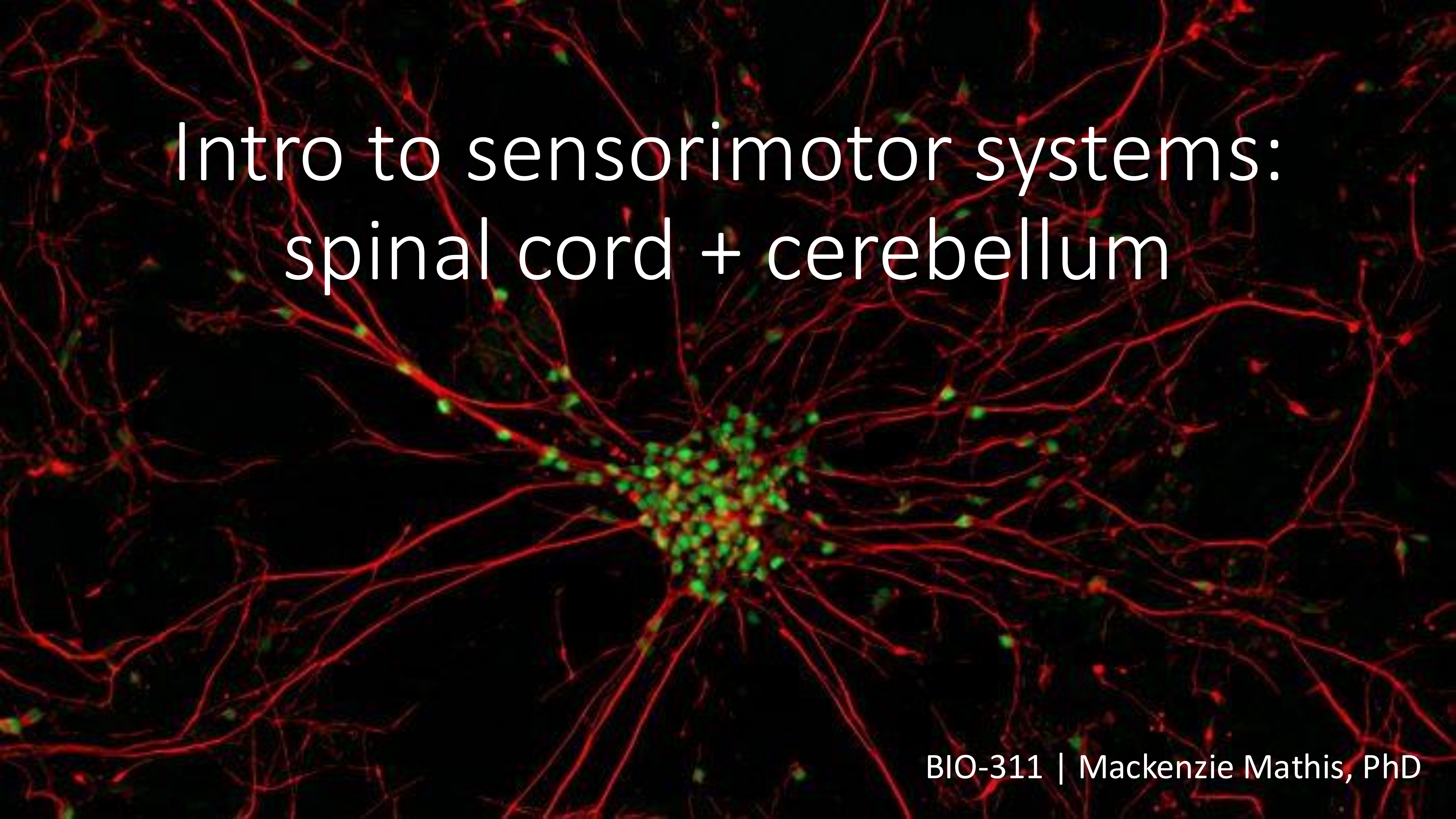
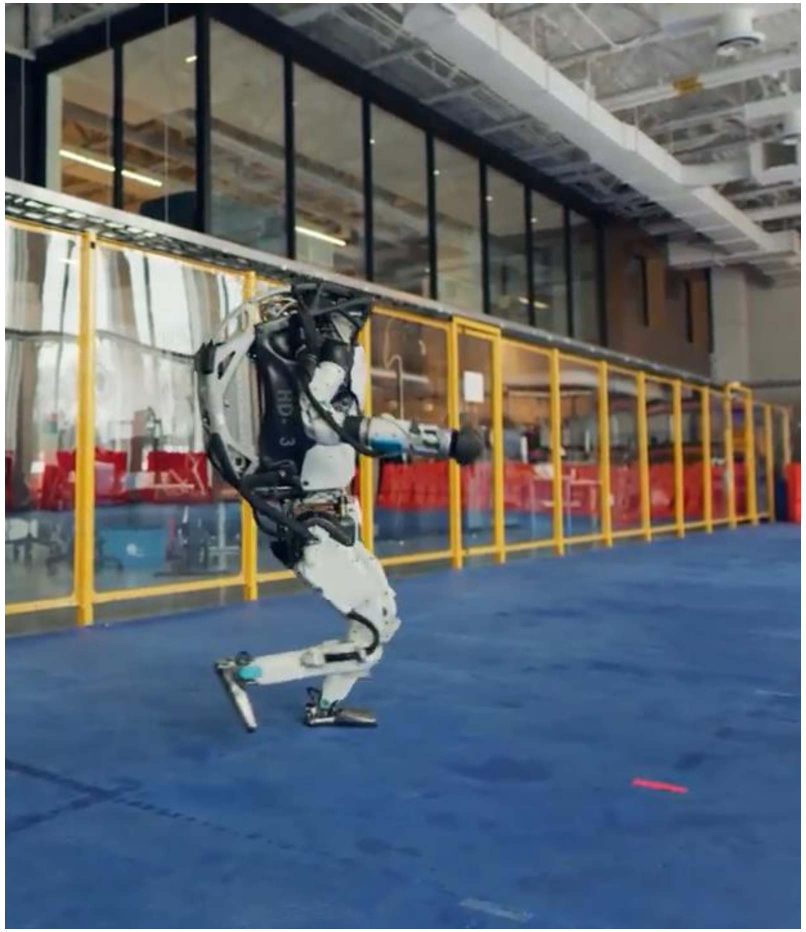


Intro to sensorimotor systems: spinal cord + cerebellum

BIO-311 | Mackenzie Mathis, PhD

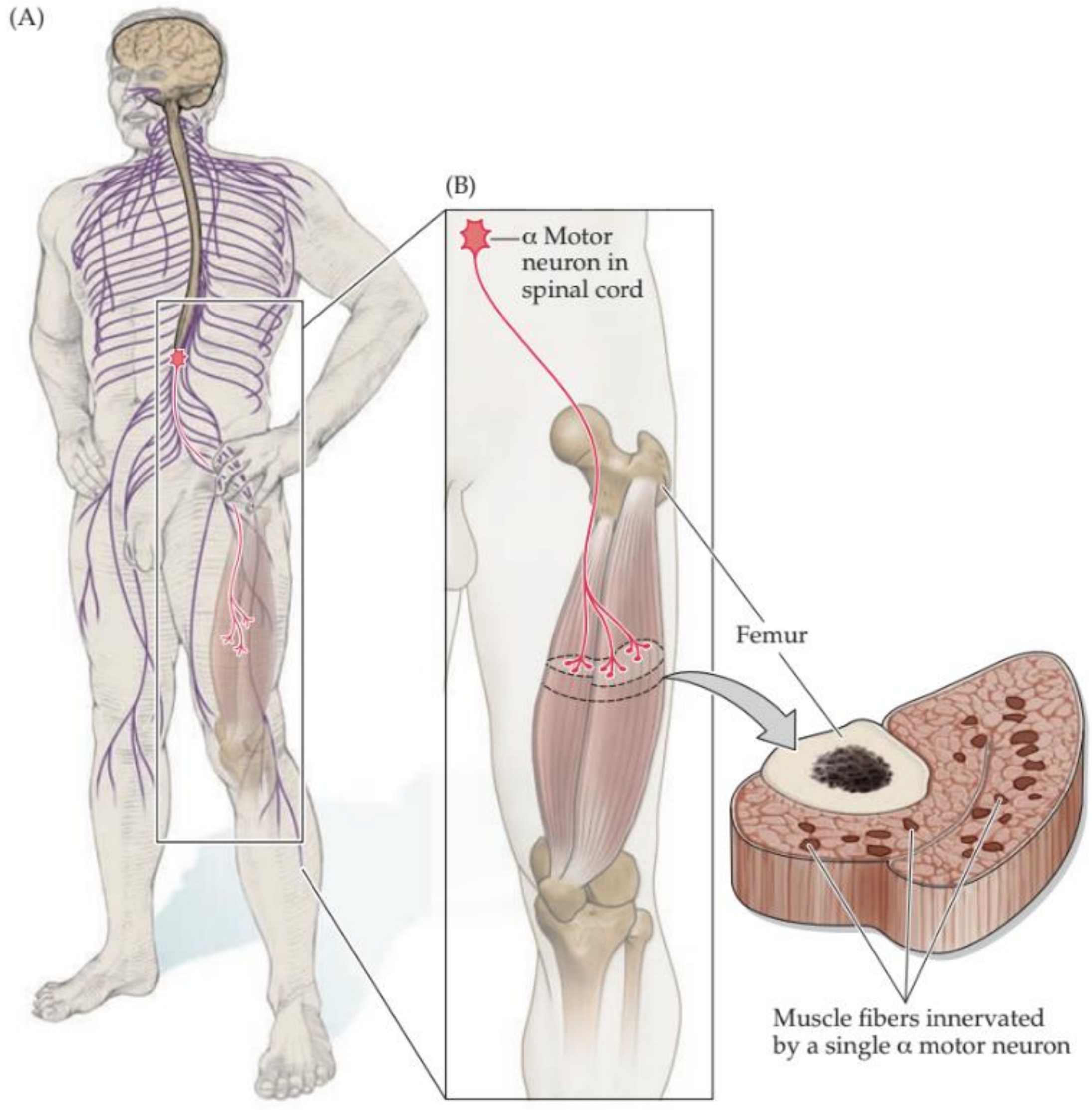
The neural control of movement: “easy” in biological agents and yet still very hard to engineer in AI or robotics!

Simone Biles All Around 2021 GK U.S Classic



Boston Dynamics

The neural control of movement: sensorimotor system

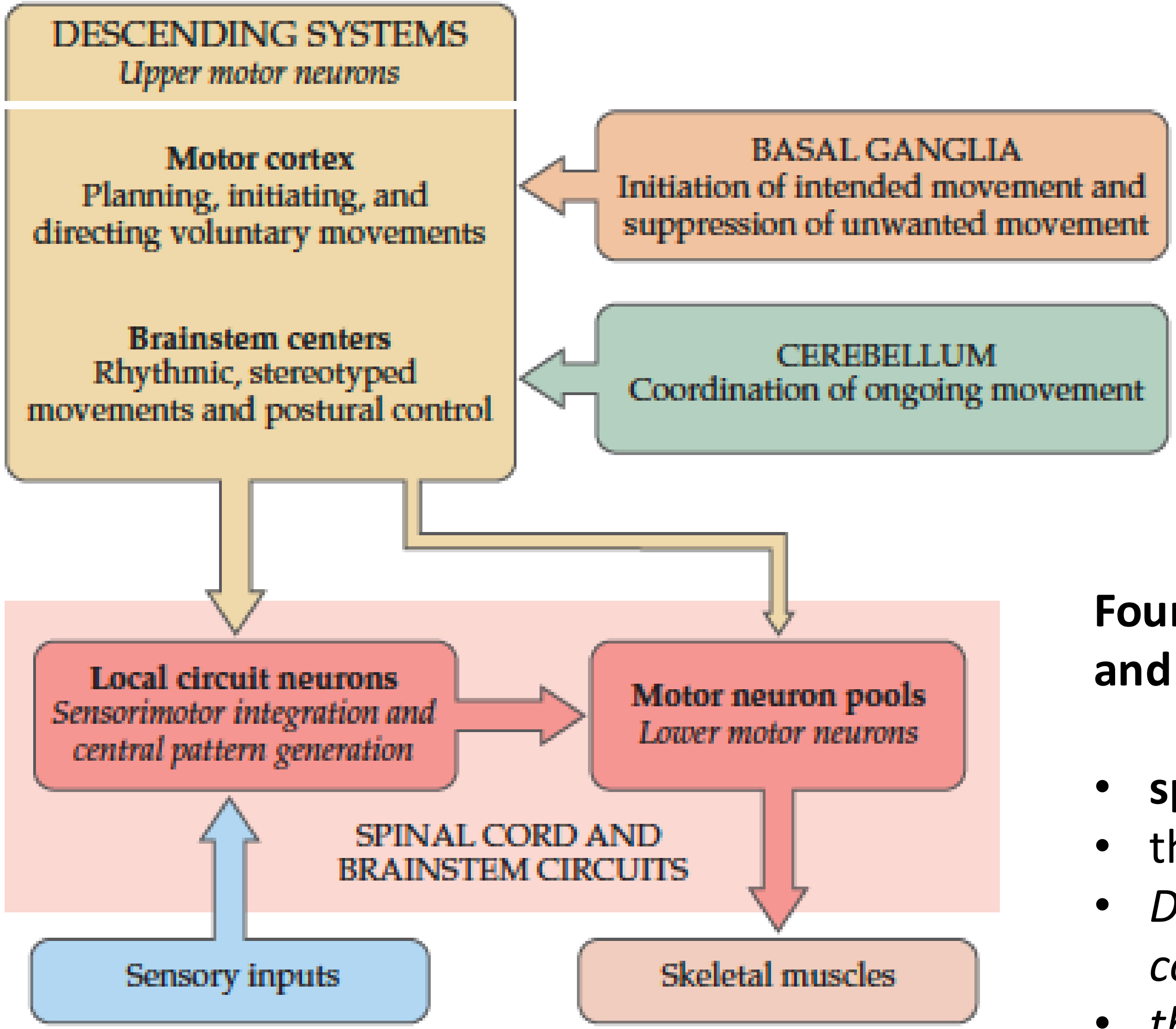


MOVEMENTS, WHETHER VOLUNTARY or involuntary, are produced by spatial and temporal patterns of muscular contractions orchestrated by neural circuits in the brain and spinal cord.

Mini TL;DR:

- Neuroanatomy is a key to functional understanding: upper sensorimotor areas, lower motor areas
- The Motor Unit
- Brainstem & spinal cord are essential for reflexes
- Cerebellum for smooth movements

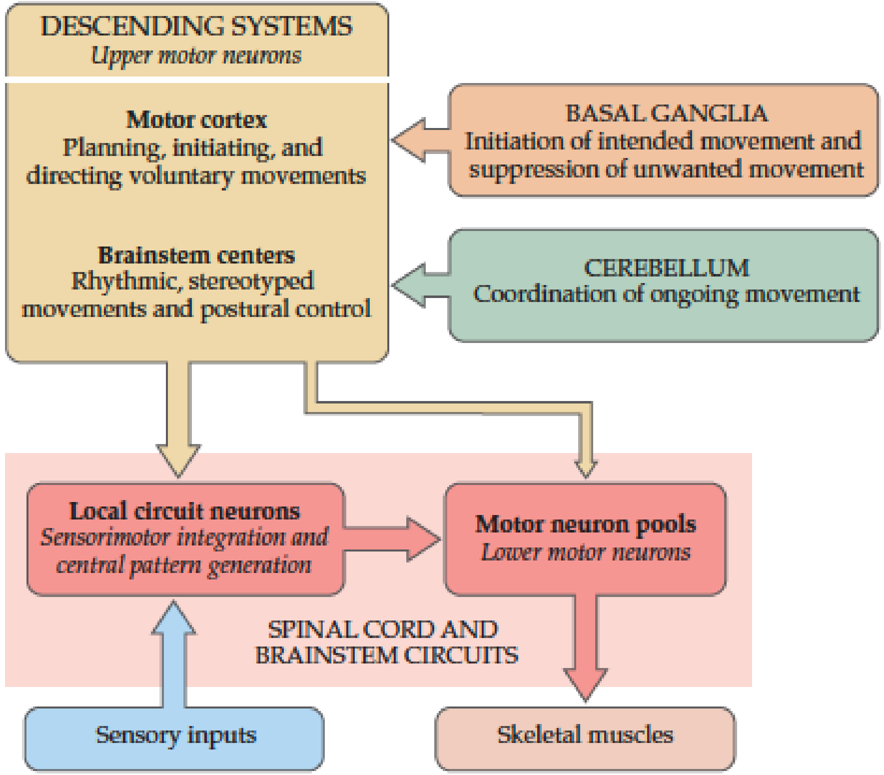
The neural control of movement: sensorimotor system

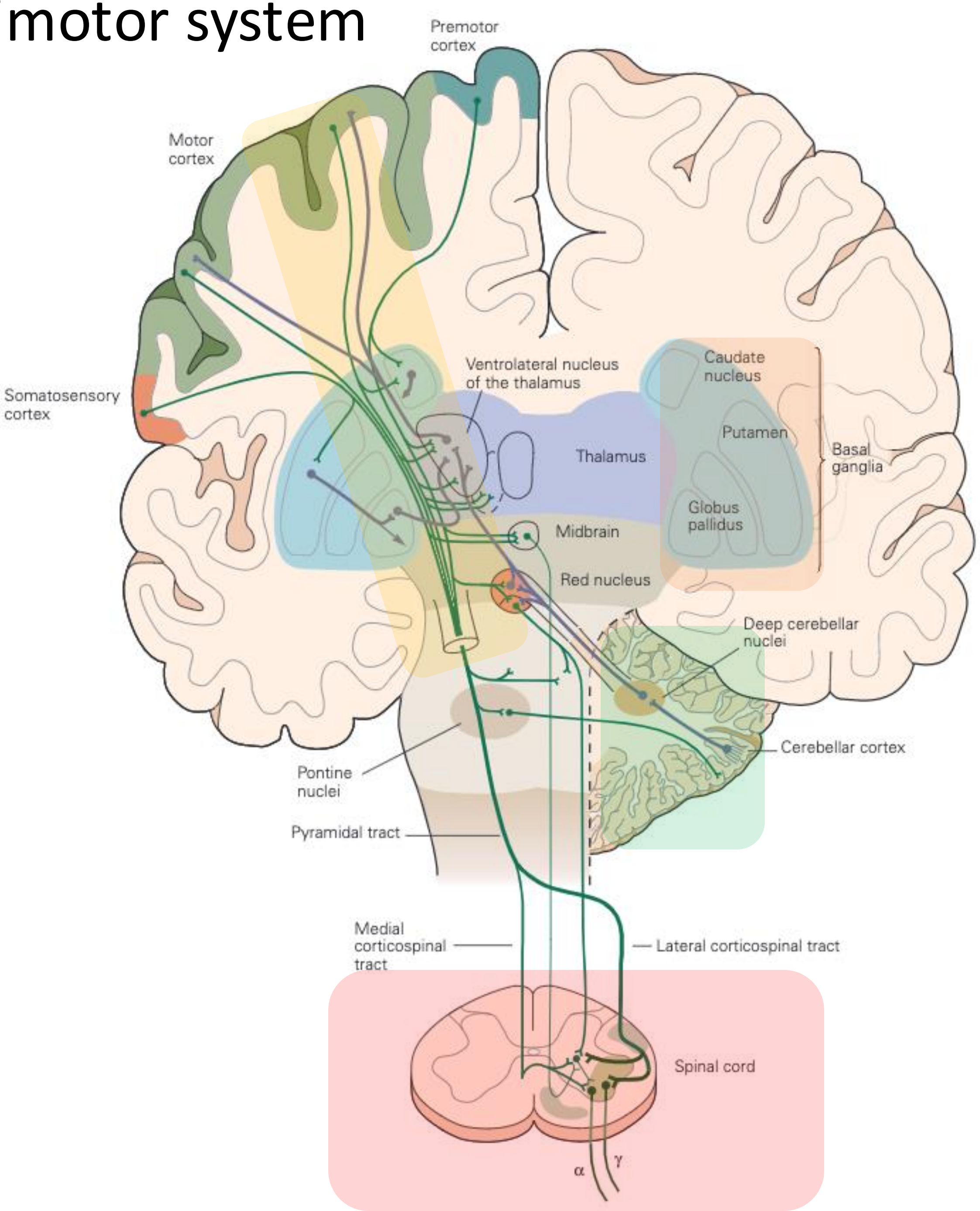


Four systems make essential and distinct contributions to motor control:

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

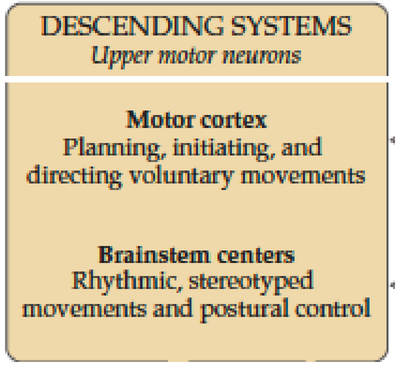
The neural control of movement: sensorimotor system

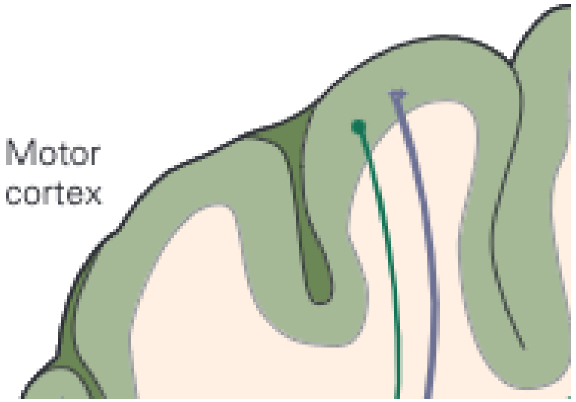


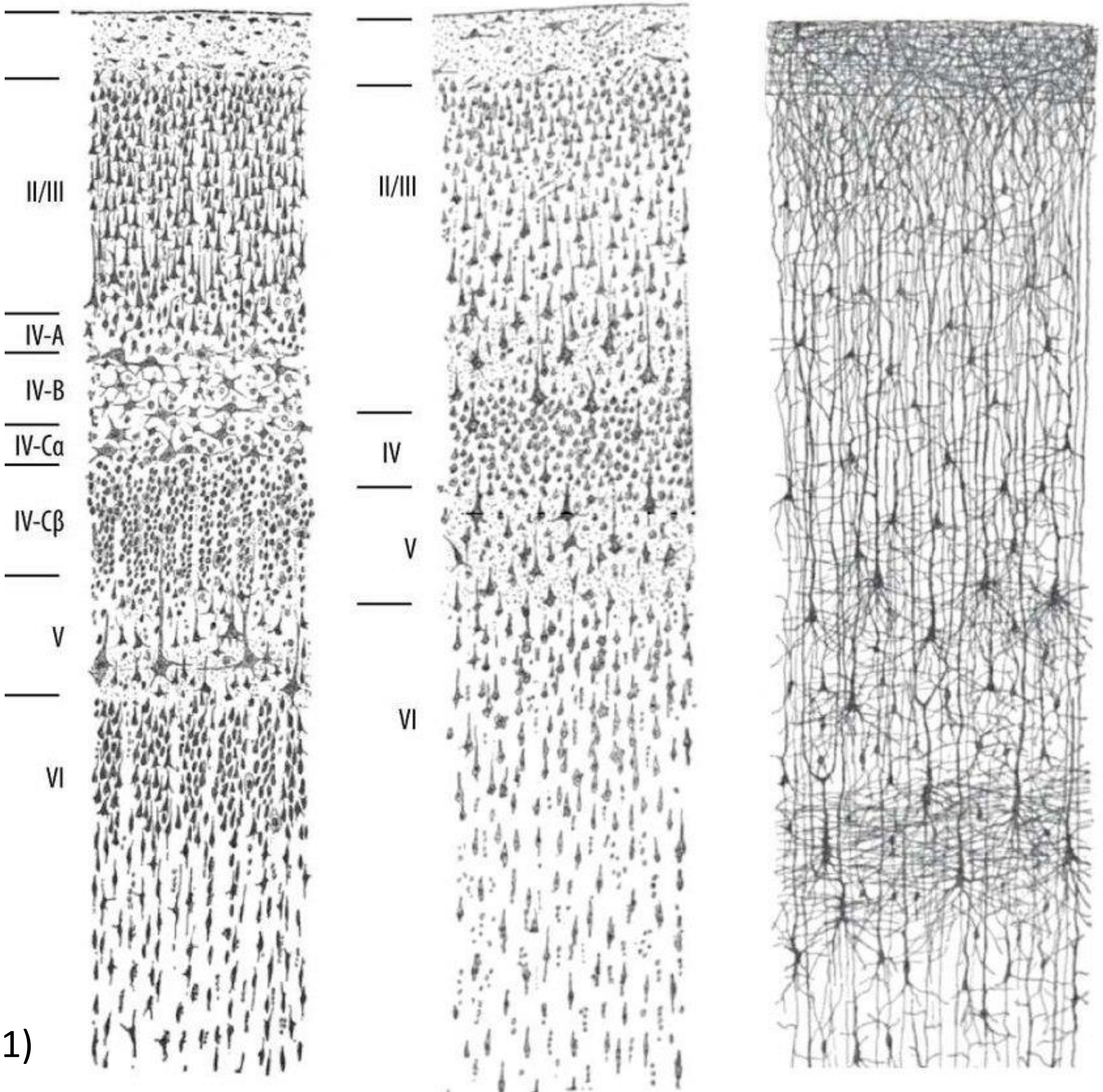


Kandel et al, 2013, Principles of Neural Science, 5e

The neural control of movement: sensorimotor system



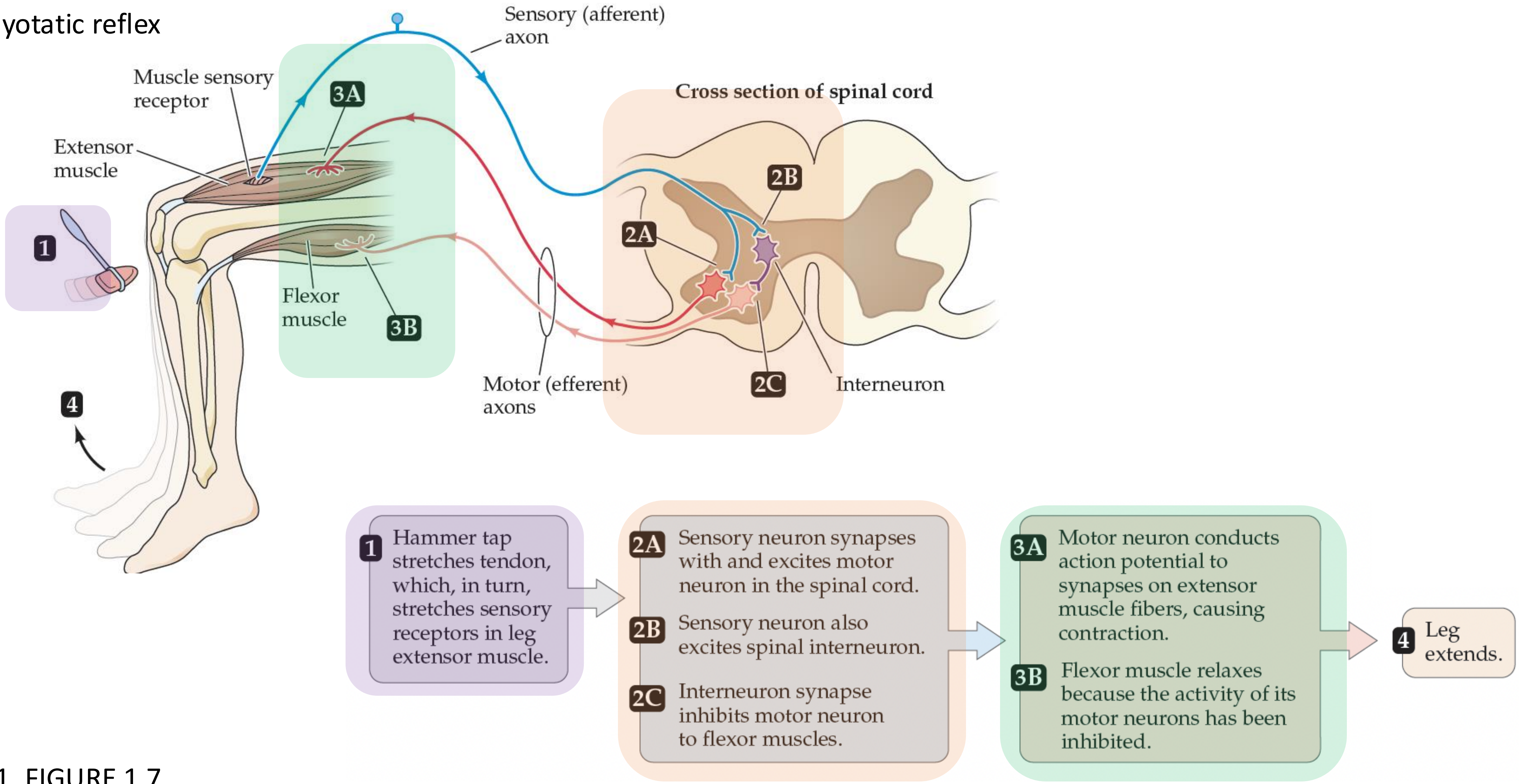




Ramon y Cajal (1911)

Reminder: reflex behavior in order to study a simple "circuit"

Myotatic reflex

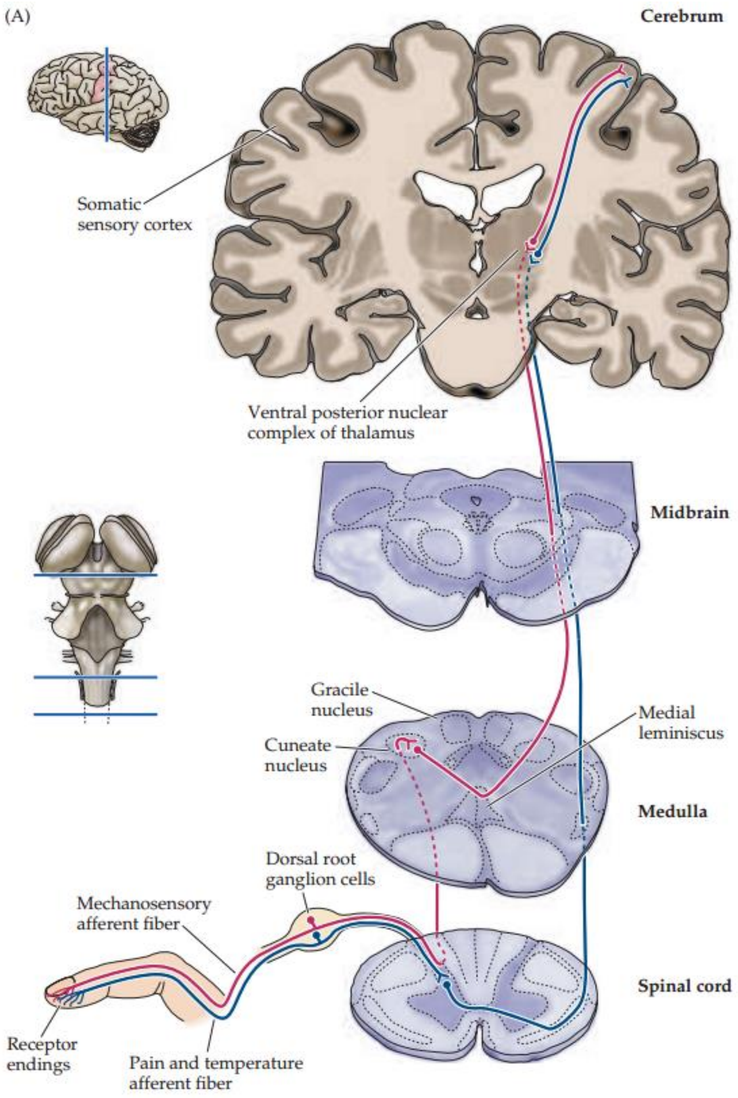


CH 1, FIGURE 1.7

Reminder: somatosensory feedback

afferent fiber:
Information is carried *from* periphery *to* the CNS

efferent fiber:
carries information *from* the CNS *towards* the periphery (makes an effect in the p.)



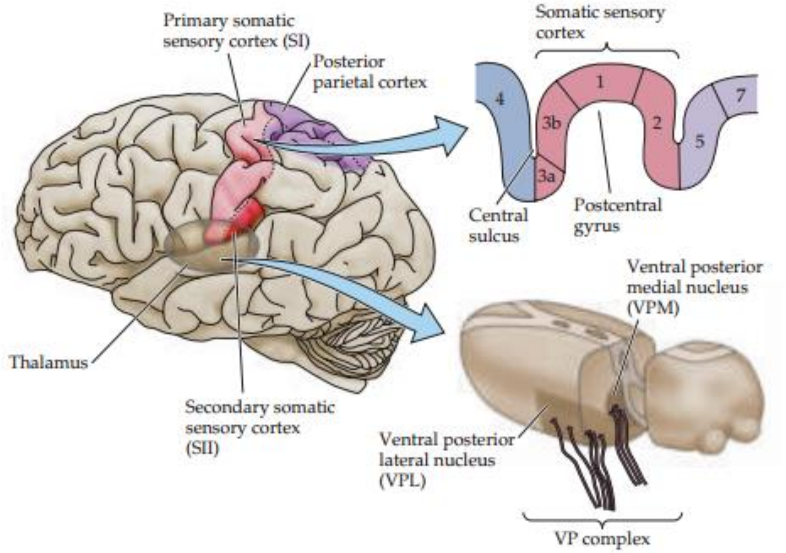
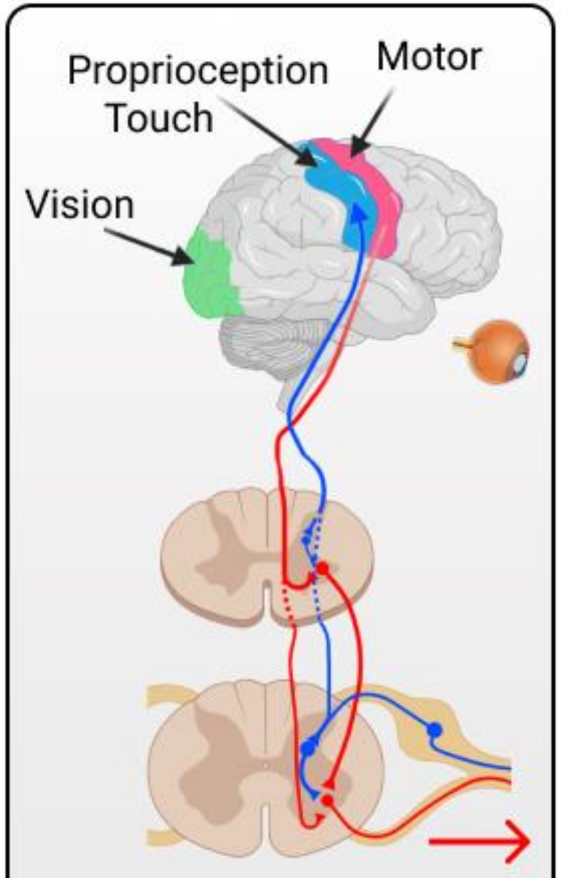


Figure 8.7 Diagram of the somatic sensory portions of the thalamus and their cortical targets in the postcentral gyrus. The ventral posterior nuclear complex comprises the VPM, which relays somatic sensory information carried by the trigeminal system from the face, and the VPL, which relays somatic sensory information from the rest of the body. Inset above shows organization of the primary somatosensory cortex in the postcentral gyrus, shown here in a section cutting across the gyrus from anterior to posterior. (After Brodal, 1992, and Jones et al., 1982.)

Upper motor neurons synapse onto lower motor neurons (in humans)

efferent fiber:
carries information *from* the CNS *towards* the periphery (makes an effect in the p.)



Hausmann et al 2021

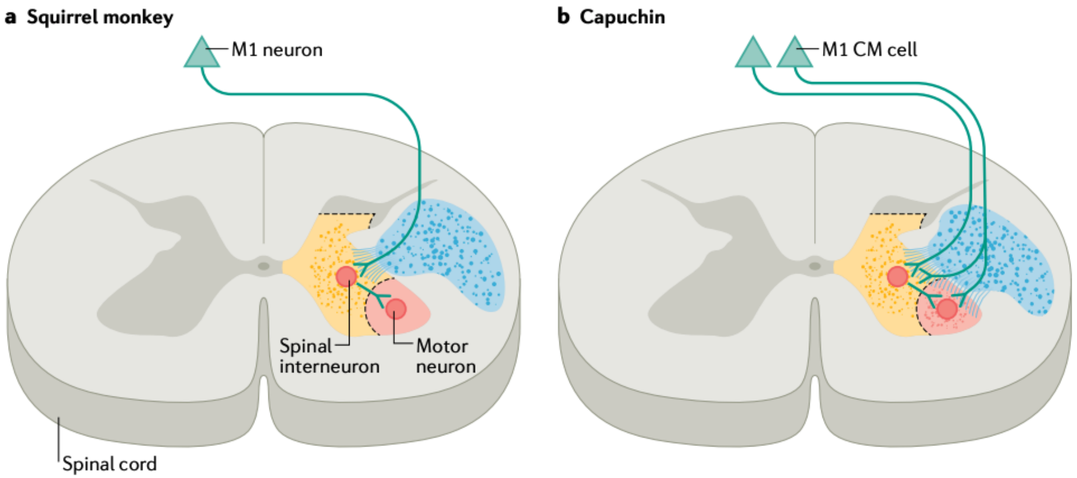
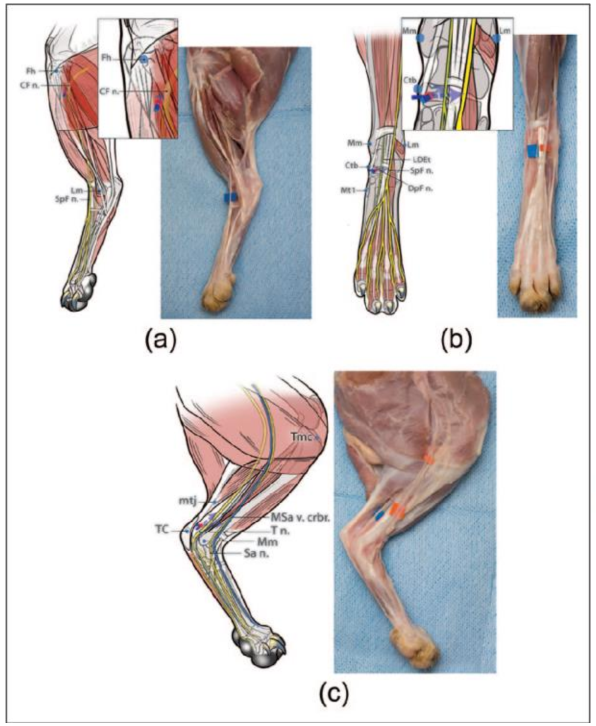


Fig. 2 | **Direct and indirect pathways from the cortex to the muscles.** Traced axons (dots) from the primary motor cortex at the C8 level of the spinal cord. **a** | Such tracing has revealed that, in squirrel monkeys, neurons from the primary motor cortex (M1) project via the pyramidal tracts (blue region) to spinal interneurons (located in the yellow region), which in turn project to motor neurons (located in the red region). **b** | In capuchins, M1 sends direct projections to motor neurons in addition to indirect projections through spinal interneurons. Presumably owing in part to this direct pathway, capuchins are more dexterous than squirrel monkeys. CM, corticomotoneuronal. Adapted with permission from REF.[204], Copyright 1993 Society for Neuroscience.

Bensmaia 2021

- **lower motor neurons** send their axons out of the brainstem and spinal cord to innervate the skeletal muscles of the head and body, respectively

Spinal Cord Neuroanatomy Basics



Enomoto, M., Lascelles, B.D., & Gerar
M.P. (2017). *Journal of Feline Medicine and Surgery, 19*, 1215 - 1223

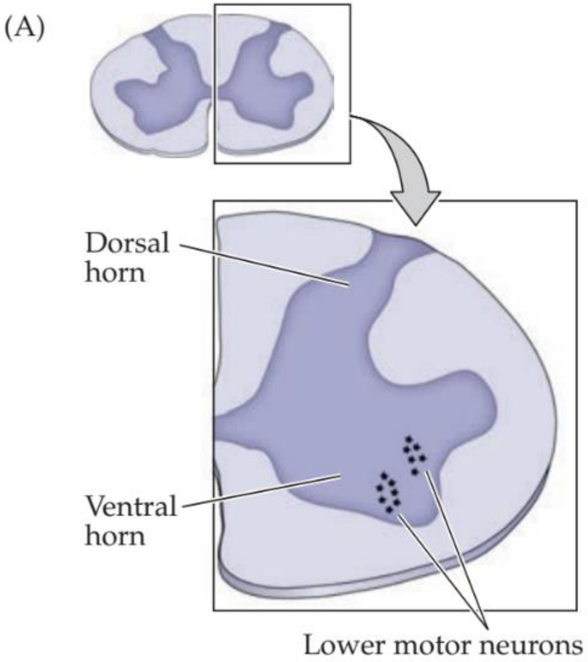
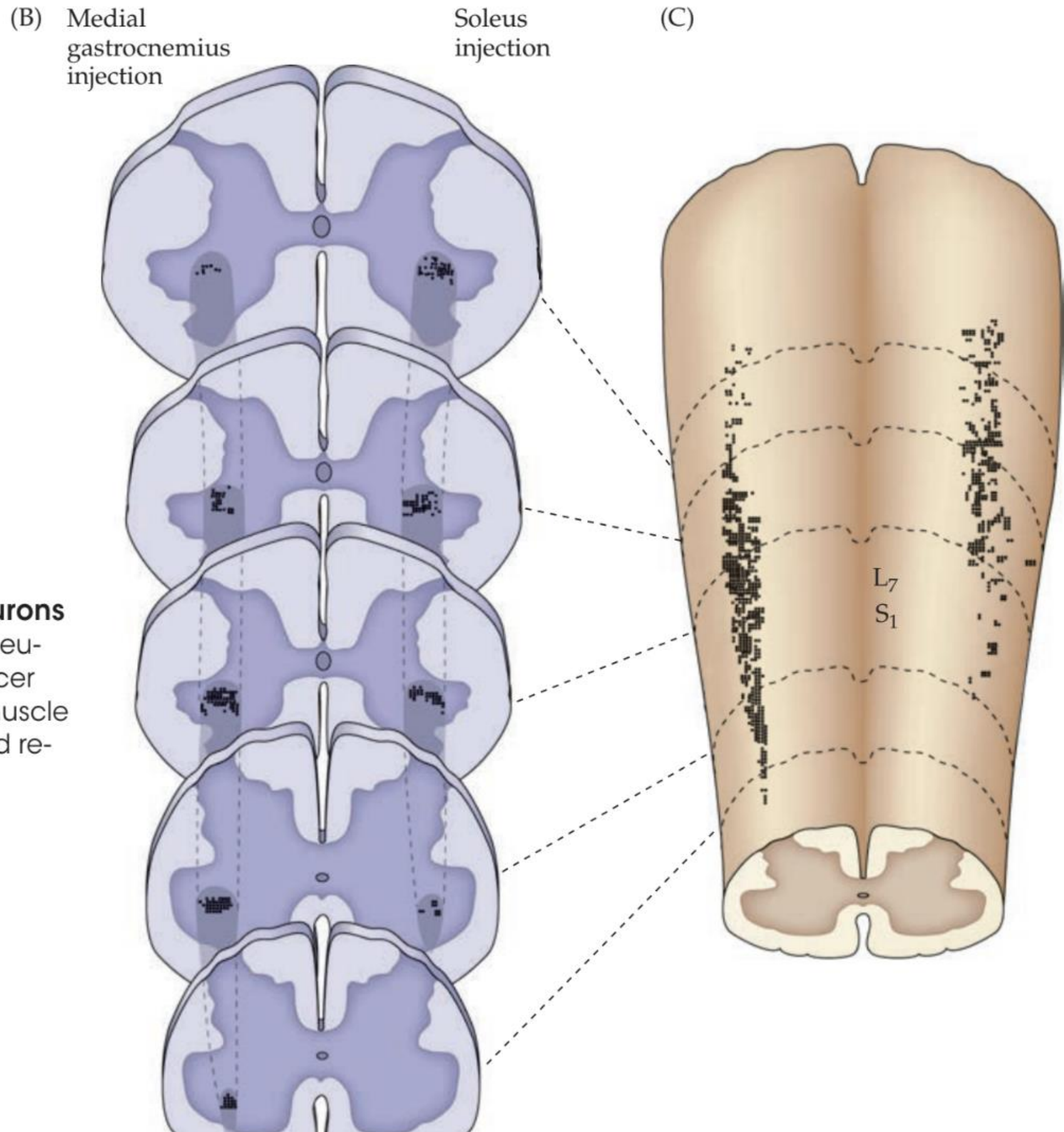
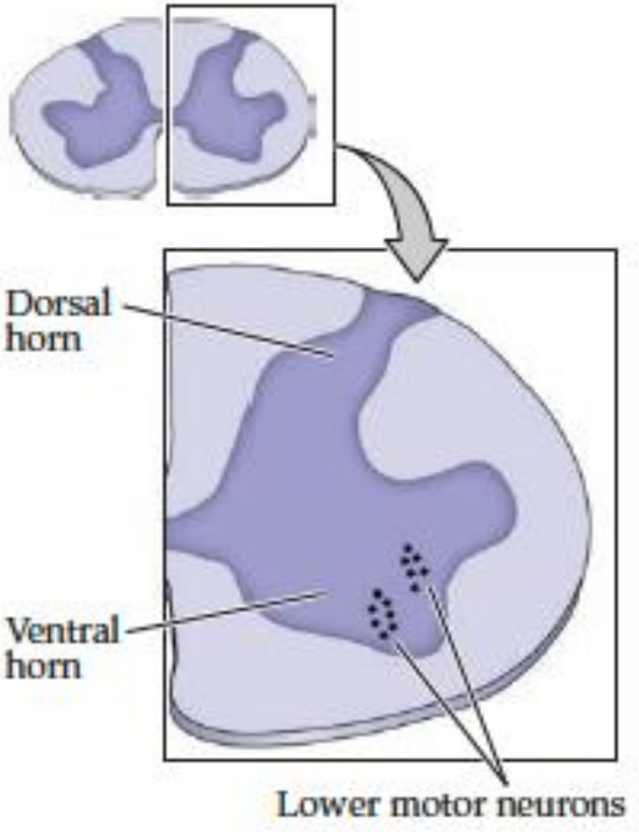
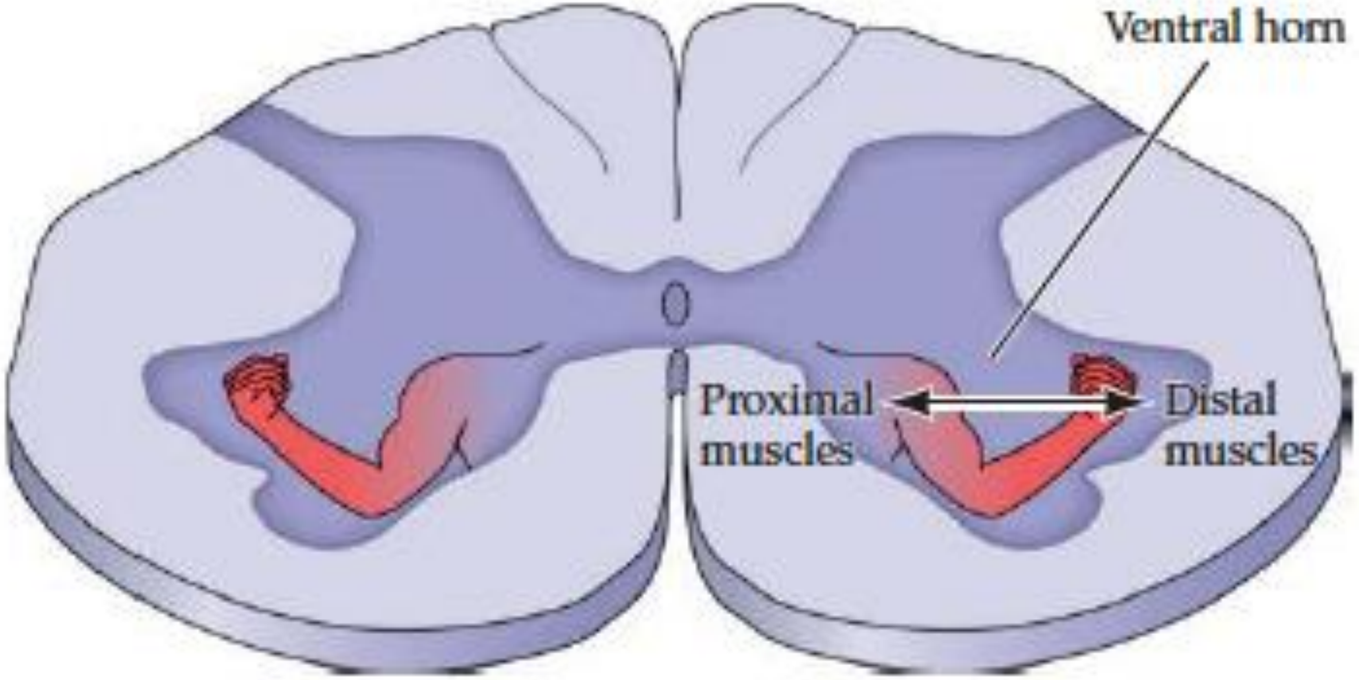


FIGURE 16.2 Distribution of lower motor neurons in the ventral horn of the spinal cord. Motor neurons were identified by injecting a retrograde tracer into either the medial gastrocnemius or soleus muscle of the cat, thus labeling neuronal cell bodies and revealing their spatial distribution.

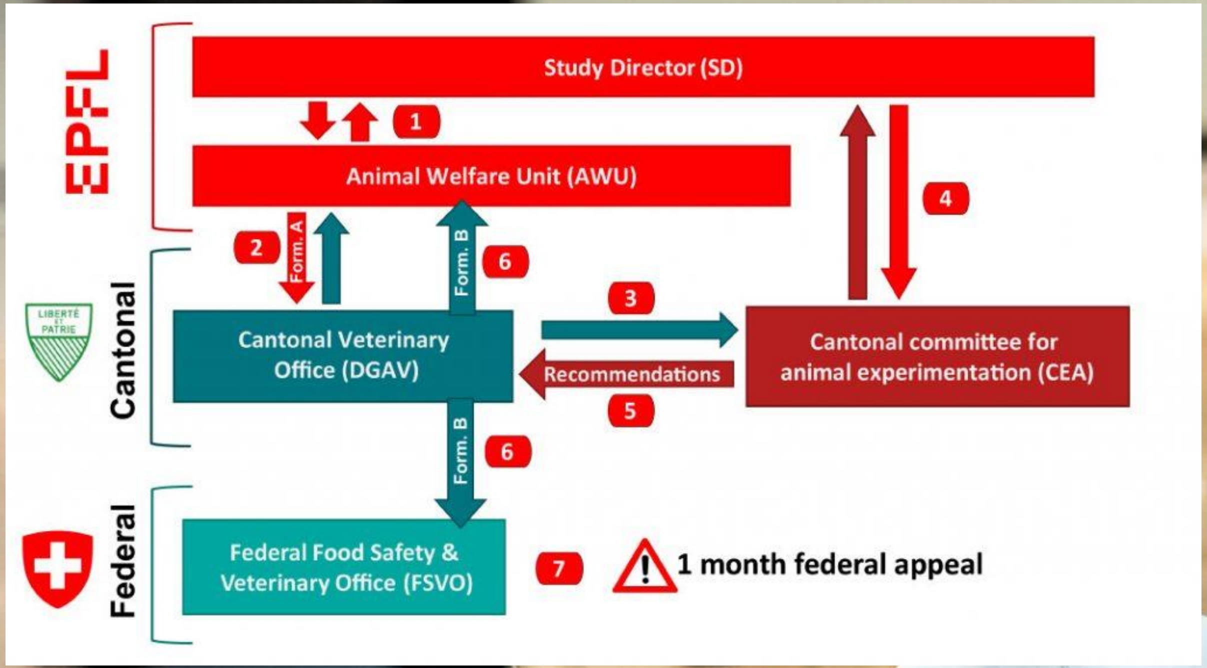


Spinal Cord Neuroanatomy Basics



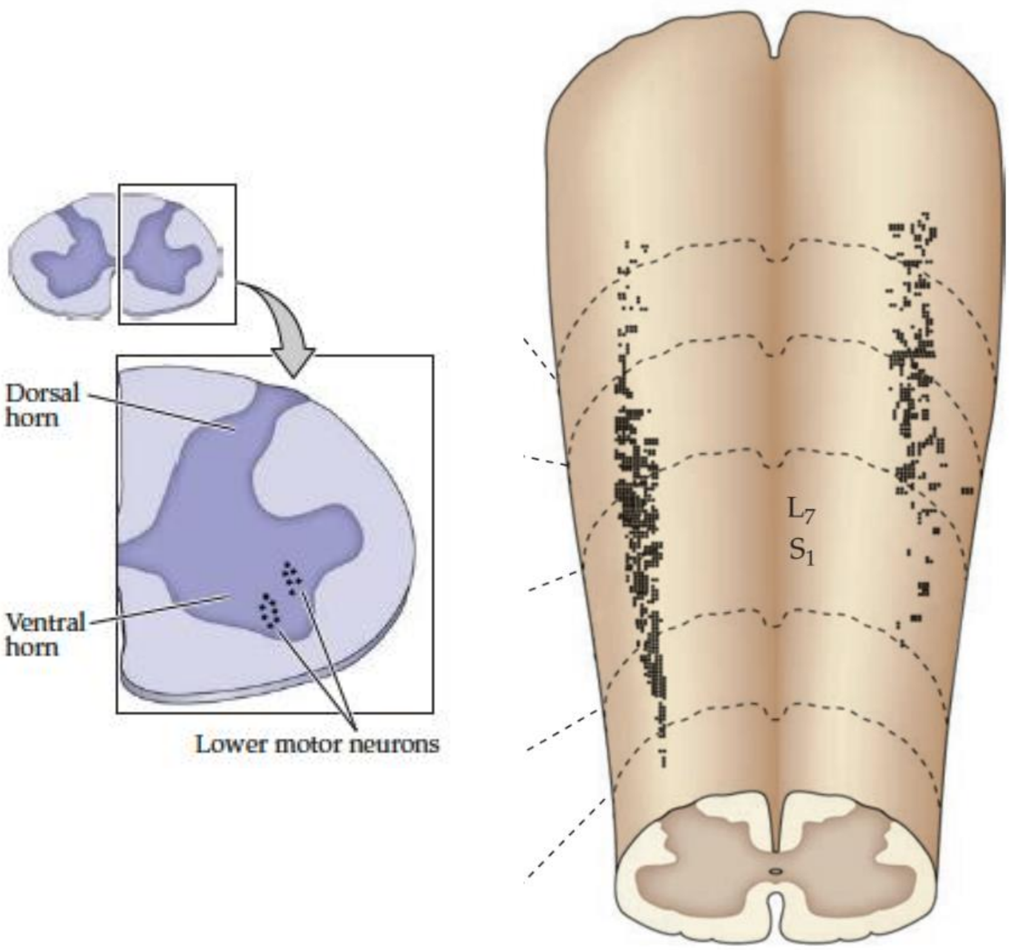


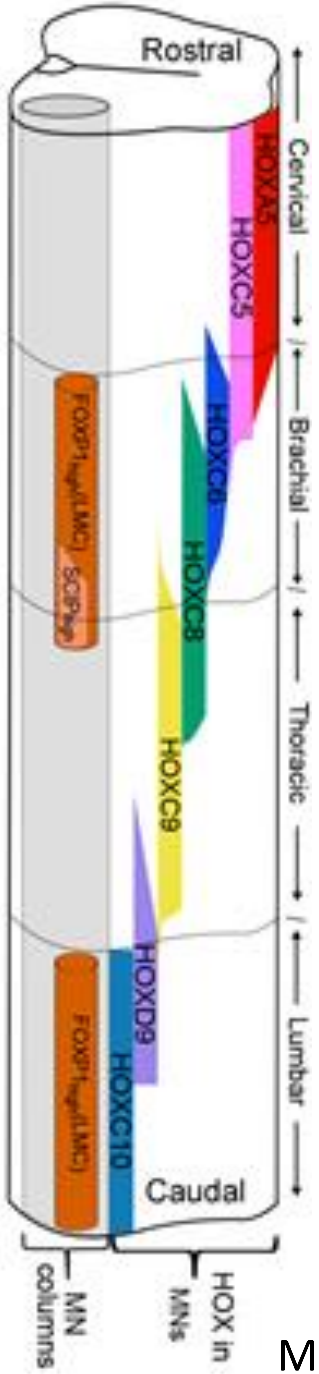
- lower motor neurons **send their axons out of the brainstem and spinal cord to innervate the skeletal muscles** of the head and body, respectively



https://www.epfl.ch/research/experimentation-research-with-animals/how-do-we-work-with-animals/

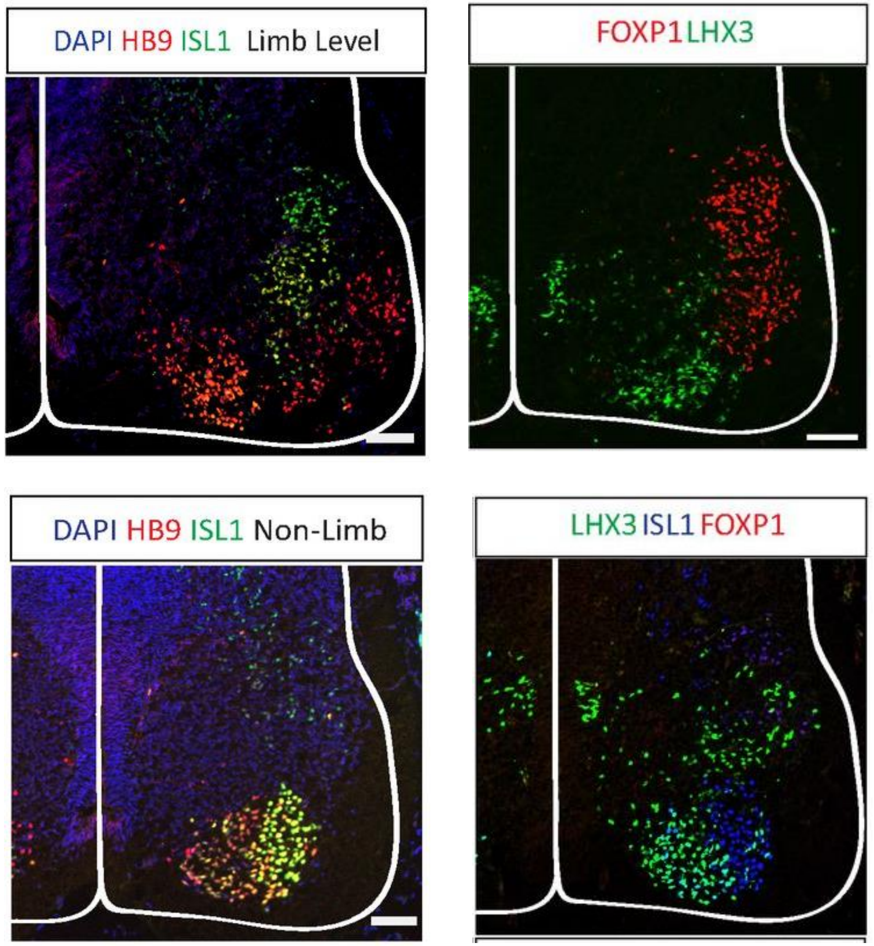
Spinal Cord Neuroanatomy Basics





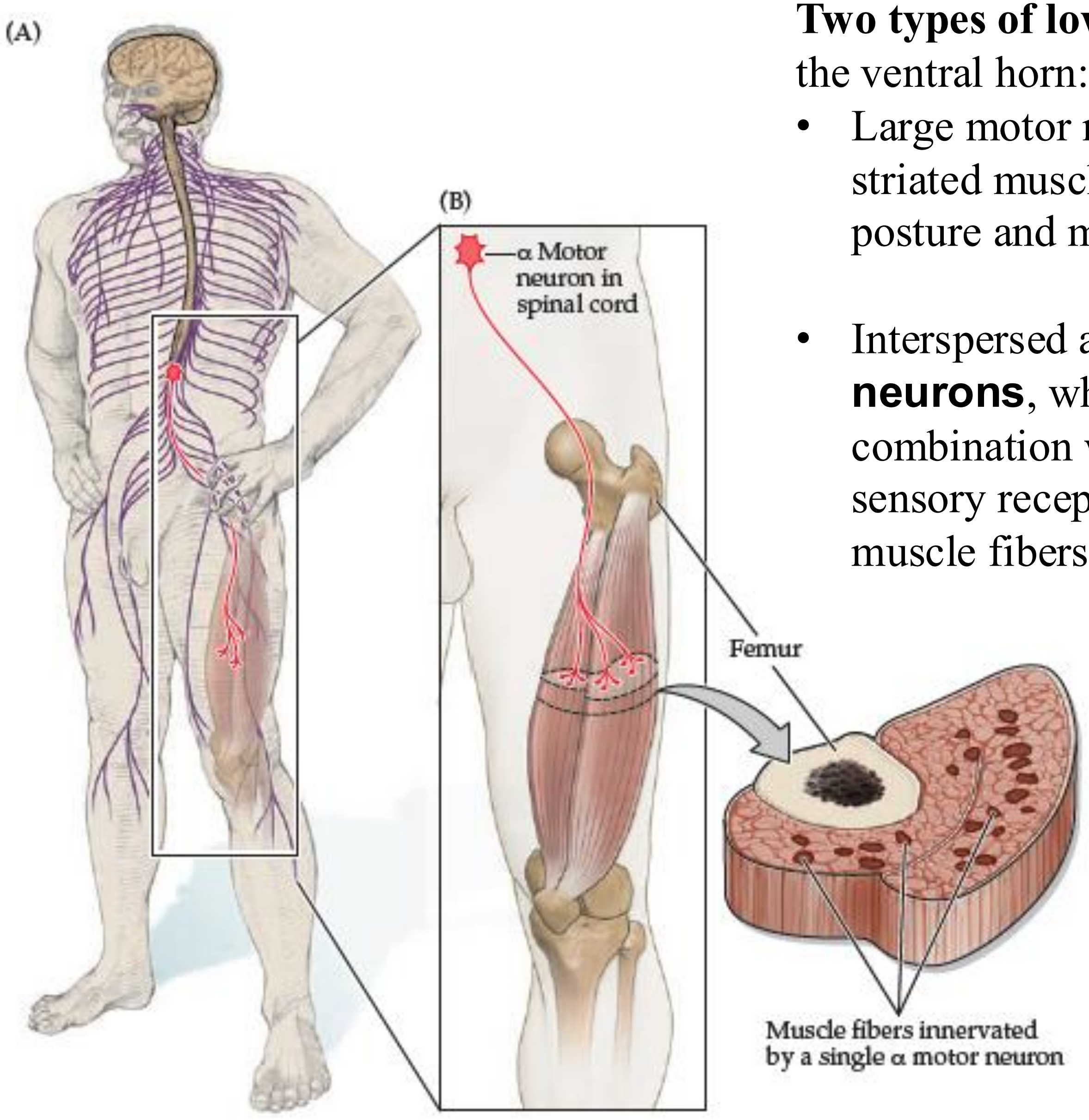
Mouilleau 2021

Genes regulate sub-types of motor neurons



Mathis* et al 2013

The Motor Unit



Two types of lower motor neurons are found in the motor neuron pools of the ventral horn:

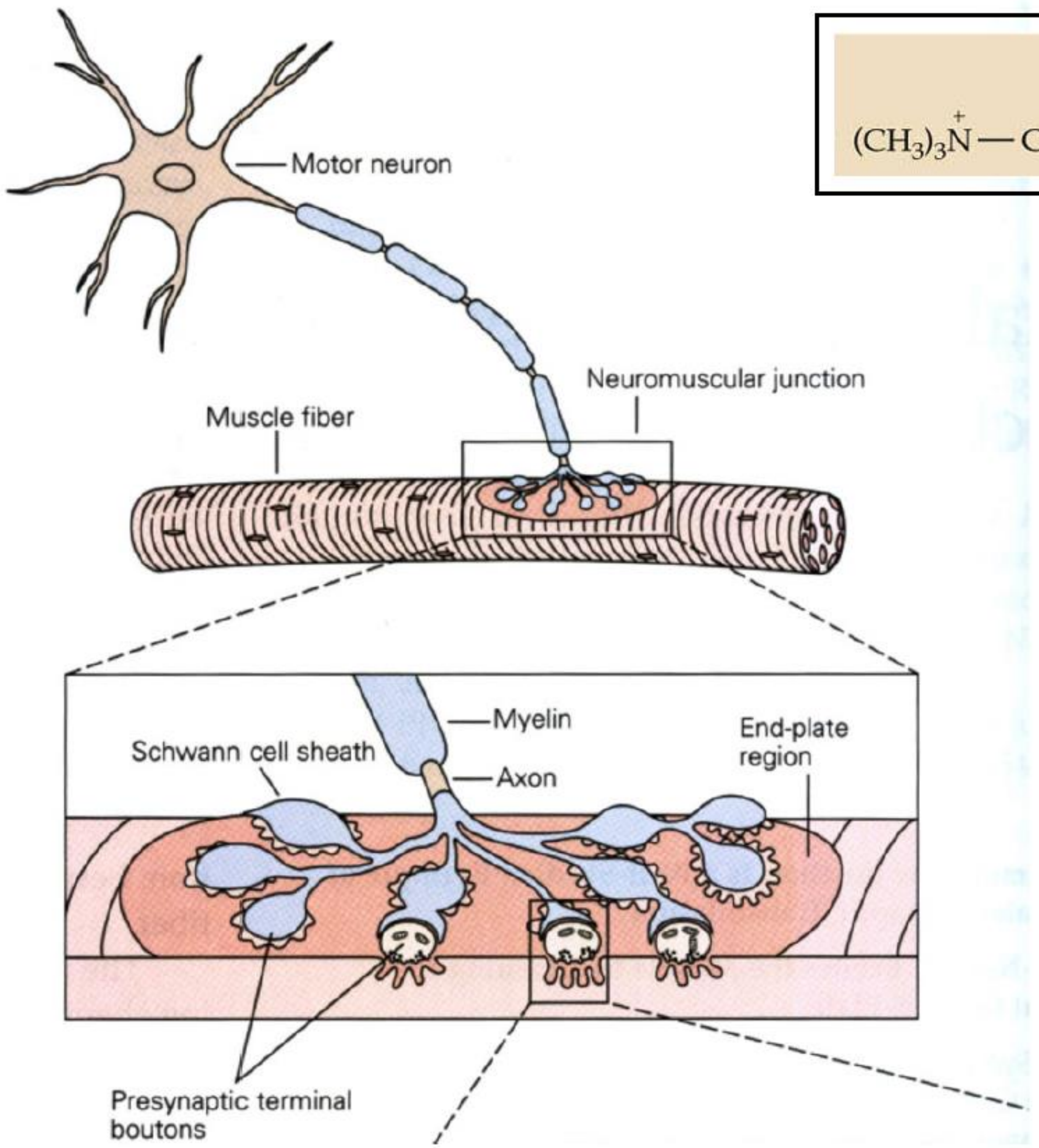
- Large motor neurons are called **α motor neurons**; they innervate the striated muscle fibers that actually generate the forces needed for posture and movement.

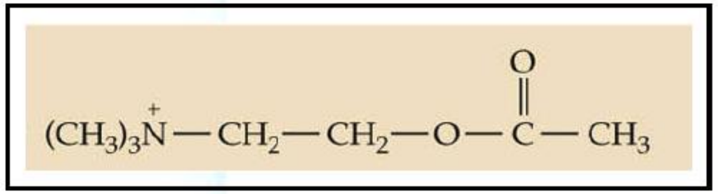
- Interspersed among the α-motor neurons are smaller **γ motor neurons**, which innervate specialized muscle fibers that, in combination with the nerve fibers that innervate them, are actually sensory receptors arranged in parallel with the force-generating striated muscle fibers.

Motor unit: All muscle fibers innervated by a single motor neuron
(~ 3 – 500 muscle fibers)

extrafusal skeletal muscle fibers in mature mammals are innervated by only a **single α motor neuron!**

The nerve - muscle synapse, or neuromuscular junction



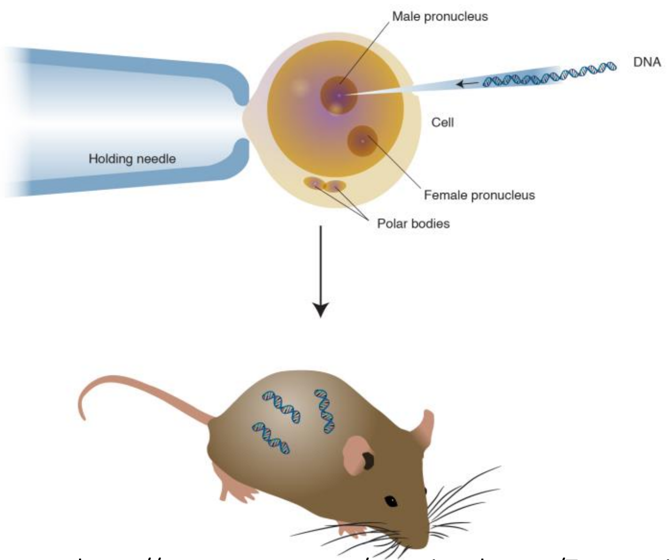


Acetylcholine

Acetylcholine is the neurotransmitter used at the neuromuscular junction
—in other words, it is the chemical that motor neurons of the nervous system release in order to activate muscles.

Kandel, Fig. 11.1

Transgenic mice to study neuroanatomy



https://www.genome.gov/genetics-glossary/Transgenic

Transgenic means that one or more DNA sequences from another species have been introduced by artificial means.

Imaging Neuronal Subsets in Transgenic Mice Expressing Multiple Spectral Variants of GFP

Joshua R Sanes, Harvard University

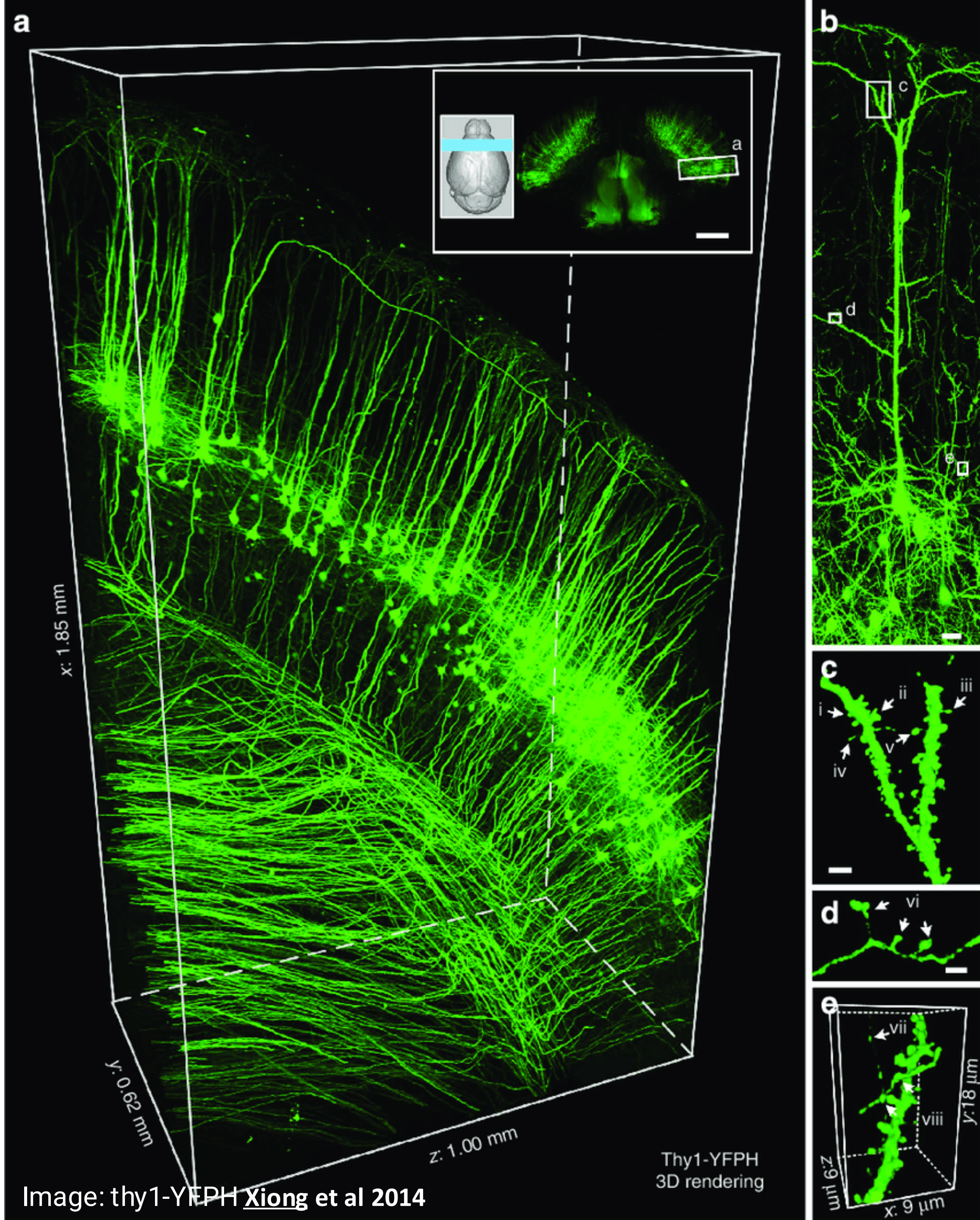
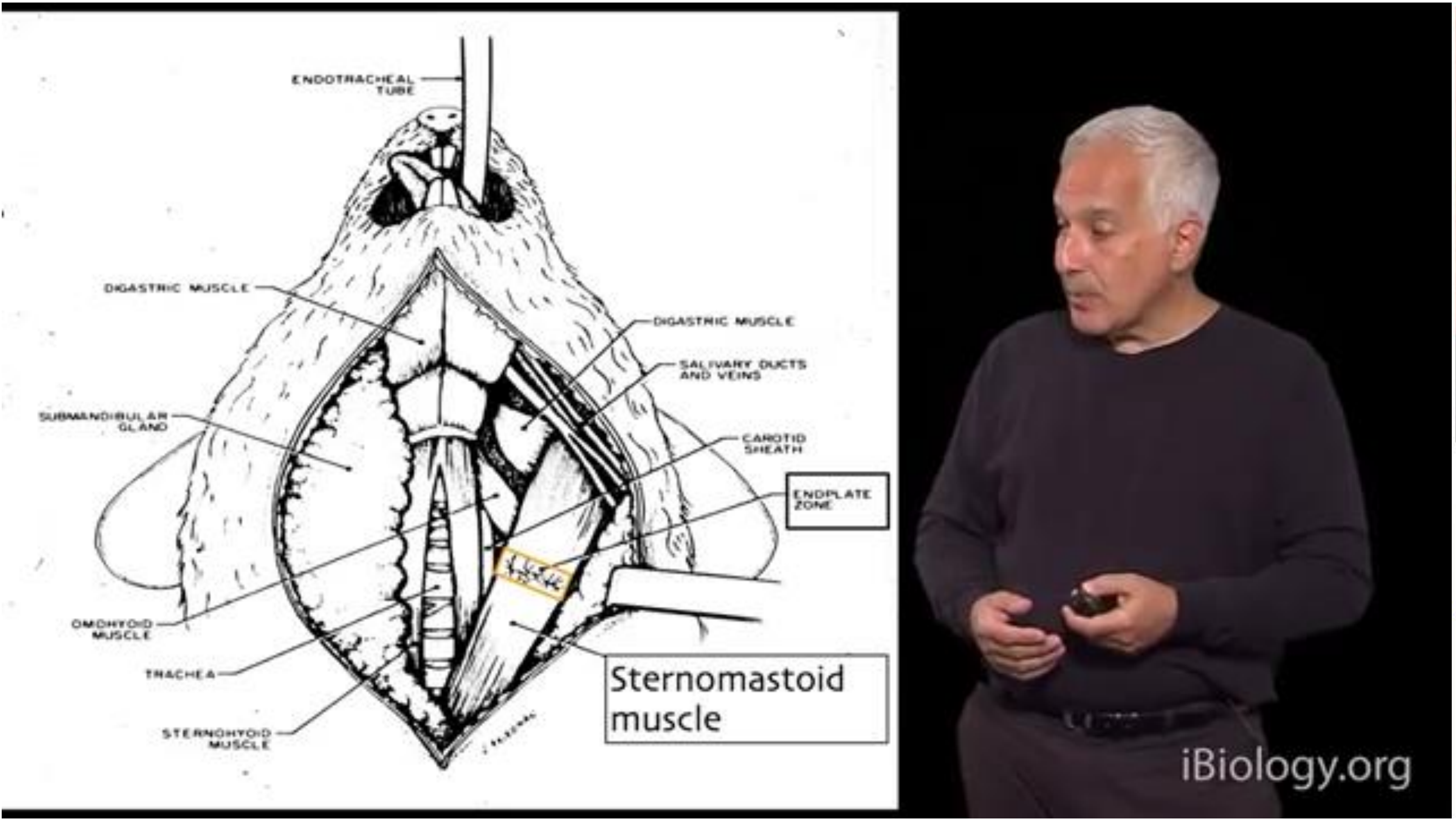
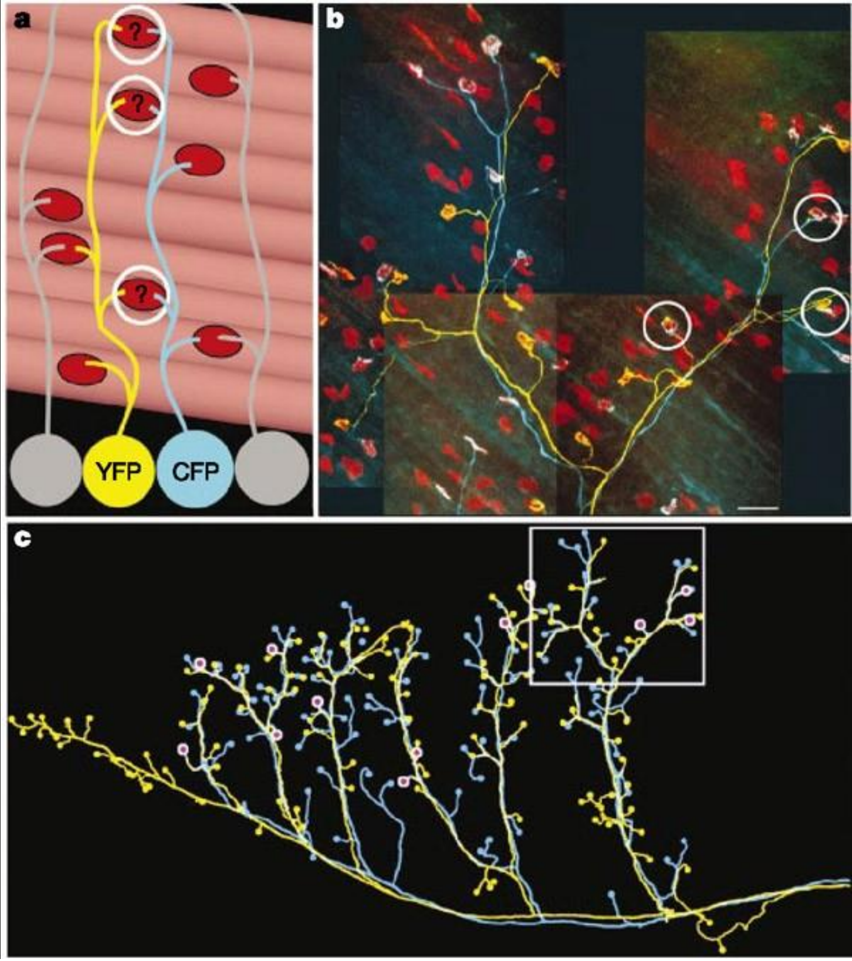


Image: thy1-YFPH **Xiong et al 2014**

Transgenic mice to study neuroanatomy: the neuro-muscular junction





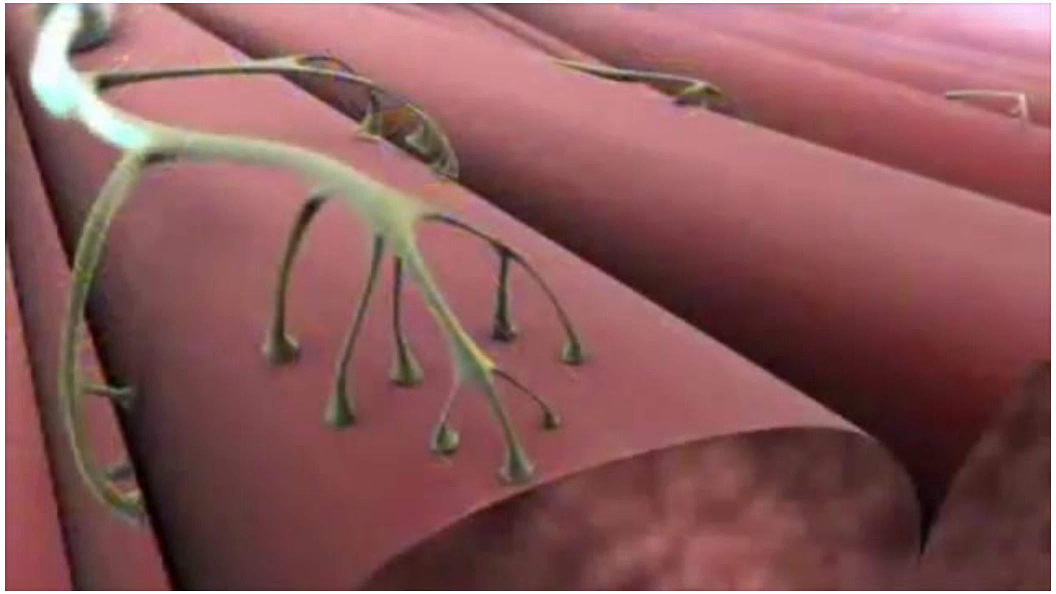
https://www.youtube.com/watch?v=r1qwQ3Qrzhs

Prof. Jeff Litchman

The role of neuronal identity in synaptic competition

Narayanan Kasthuri & Jeff W. Lichtman

Alpha Motor neurons & **The Motor Unit**



Because an **action potential** generated by a **motor neuron** typically brings to contraction threshold all of the muscle fibers the neuron contacts, the **single α motor neuron** and its associated muscle fibers constitute the smallest unit of force that can be activated by the muscle.

Sherrington was the first to recognize this fundamental relationship between an α motor neuron and the muscle fibers it innervates, for which he coined the term **motor unit.**

The Motor Unit: 3 different types

- fast fatigable
- fast fatigue resistant
- slow

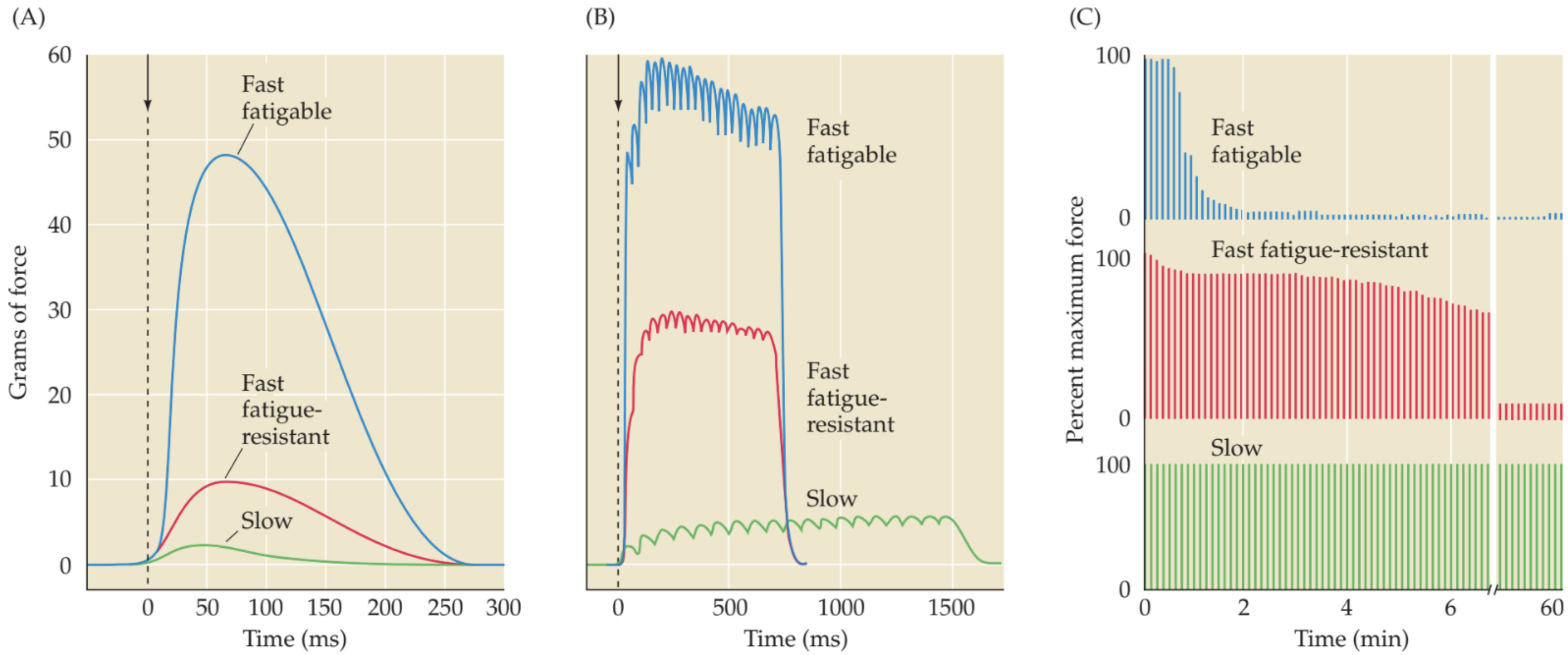
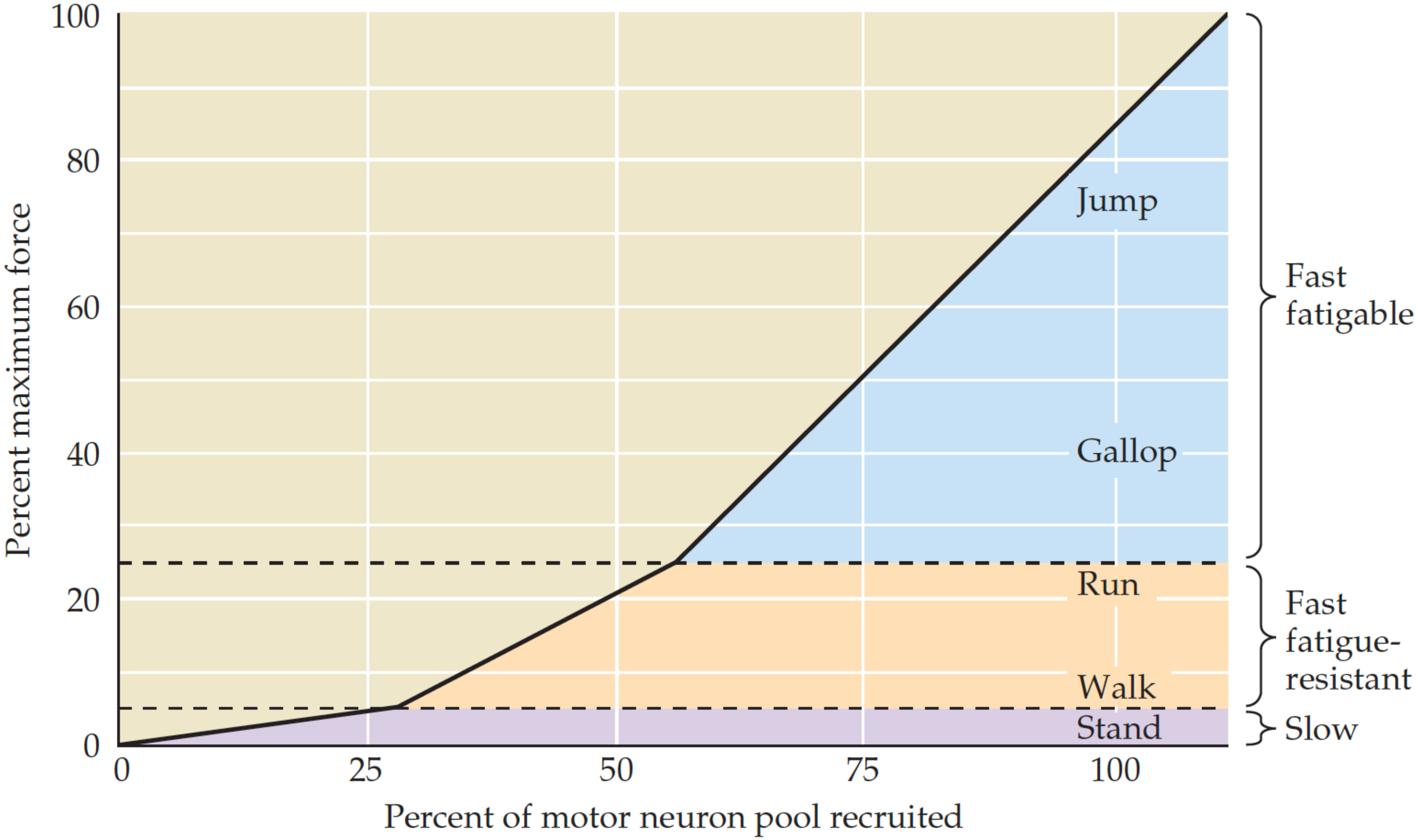


FIGURE 16.6 Force and fatigability of the three different types of motor units. In each case, the response reflects stimulation of a single α motor neuron. (A) Change in muscle tension in response to a single action potential. (B) Tension in response to repetitive stimulation of each type of motor unit. (C) Response to repeated stimulation at a level that initially evokes maximum tension. The ordinate represents the force generated by each stimulus. Note the different time scales in the three panels and the strikingly different tensions generated and fatigue rates among motor units. (After Burke et al., 1973.)

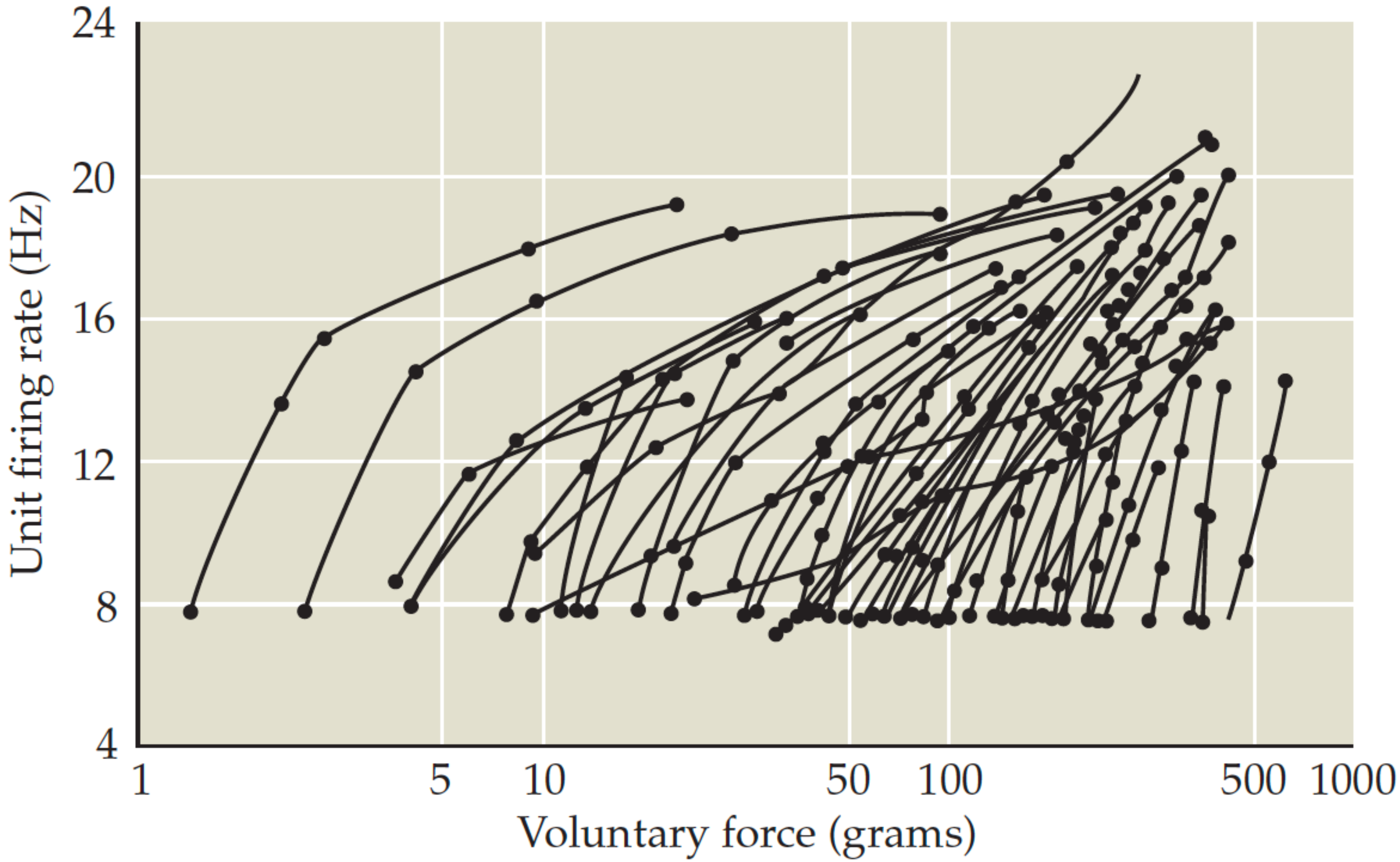
Motor neuron recruitment in the cat medial gastrocnemius muscle under different behavioral conditions



Henneman's Size Principle: Weak input drives smallest motor units (low threshold). Then progressively larger ones recruited with larger input to motor pool.

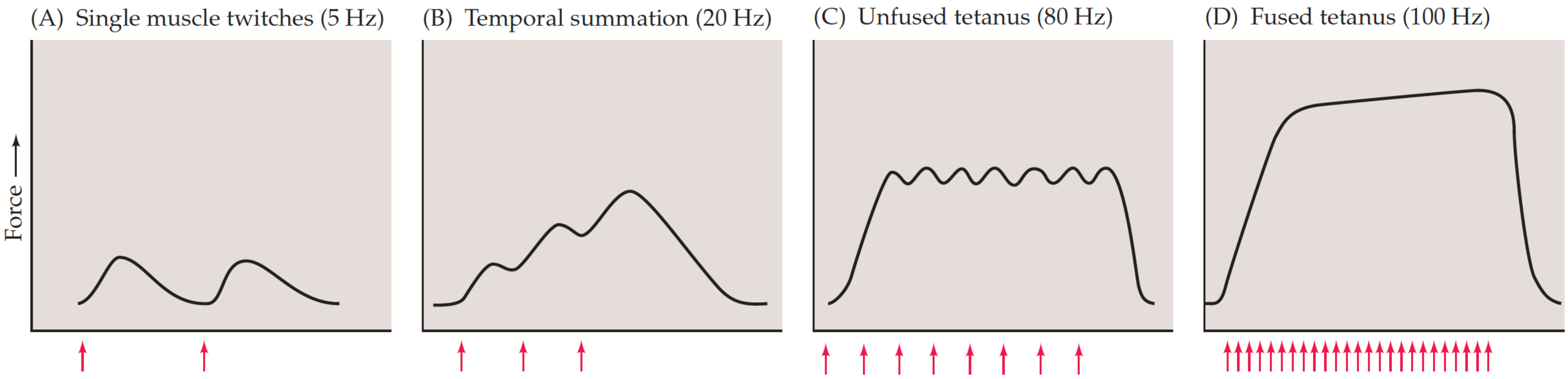
Purves, Figure 16.7

The number of active motor units and their rate of firing both increase with voluntary force



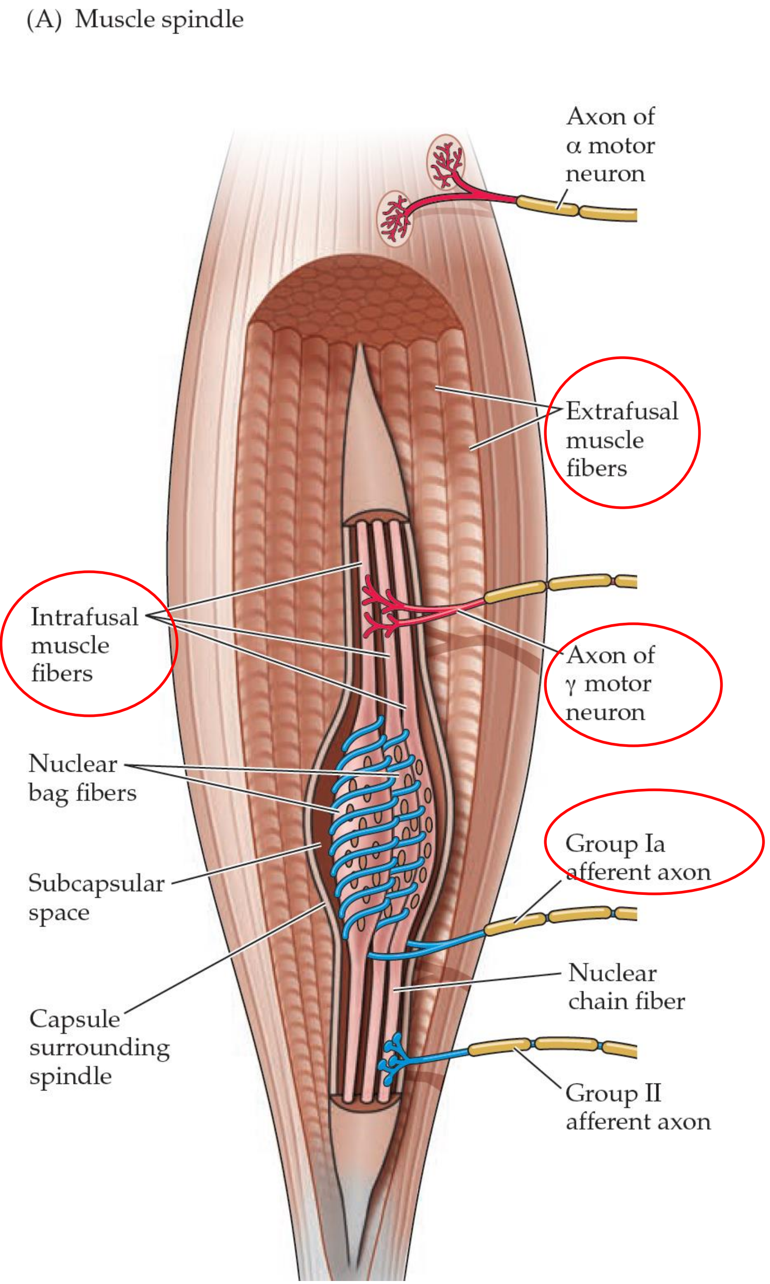
Purves, Figure 16.9

Effect of stimulation rate on muscle tension



Purves, Figure 16.8

Stretch reflex circuitry



Purves, Figure 16.10

<u>Important terminology:</u>

- **extrafusal** muscle fibers = the "working“ muscle fibers

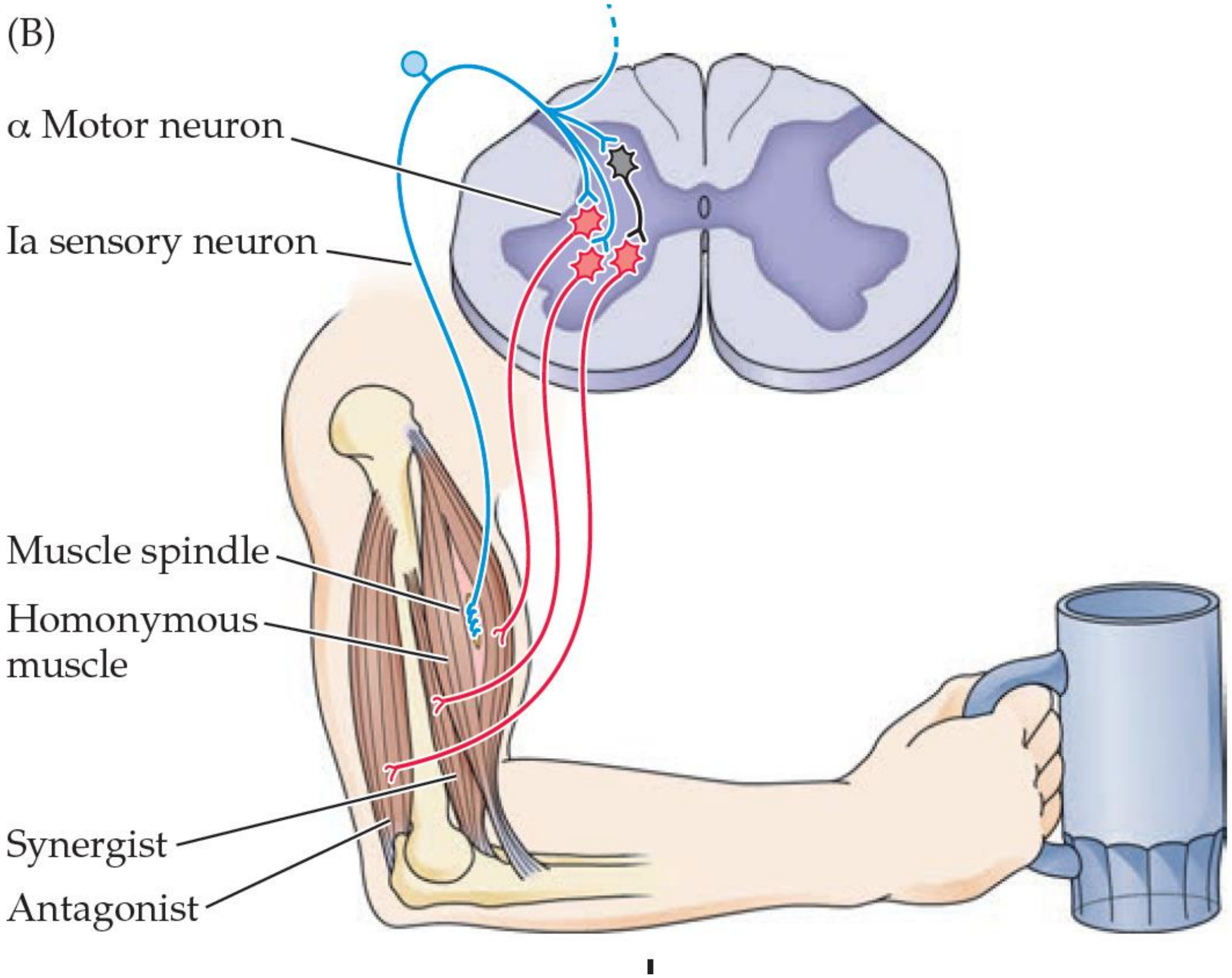
- **intrafusal** muscle fibers = -they "measure“ muscle length

- **α-motor neurons**: innervate "working muscle fibers"

- **γ-motor neurons**: innervate intrafusal fibers and modulate their „pre-tension"

- afferent axons: sensory axons conducting the signal towards the CNS

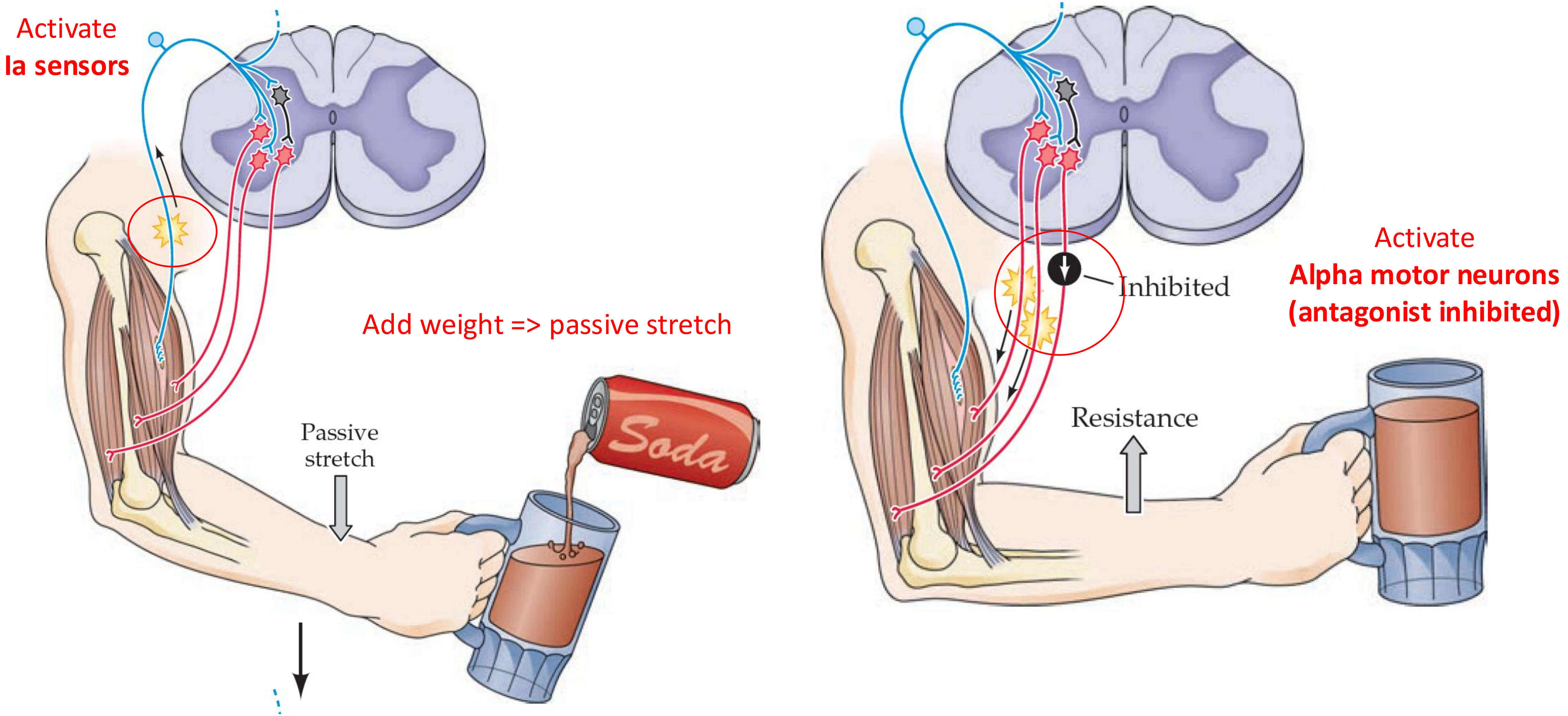
Stretch reflex circuitry



Negative feedback loop involving the **intrafusal muscle** and **Ia sensors (spindle receptor)**

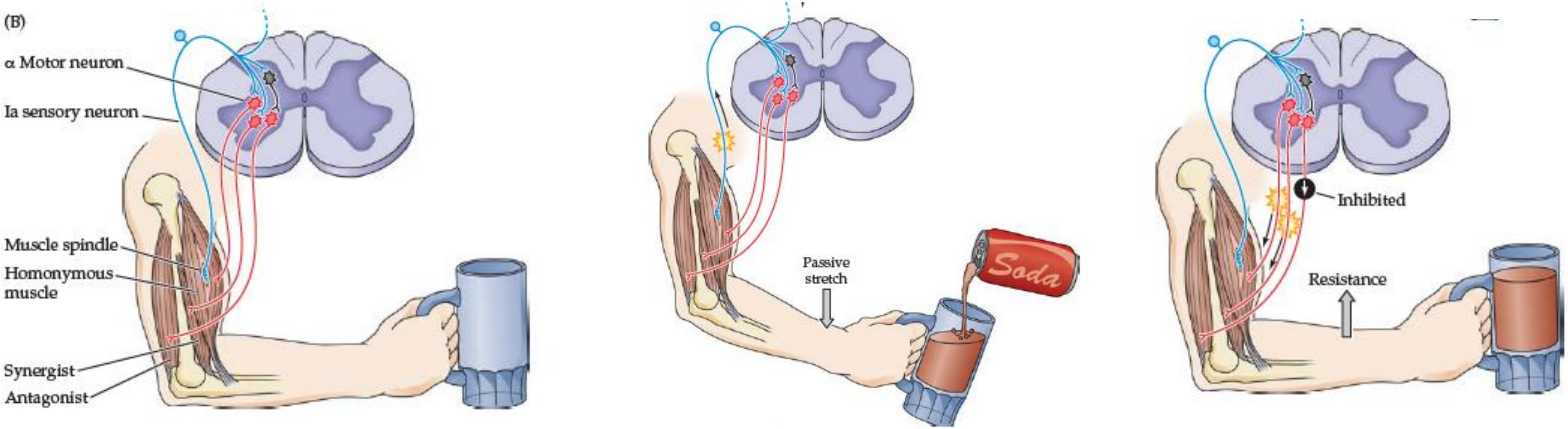
Purves, Figure 16.10

Stretch reflex circuitry



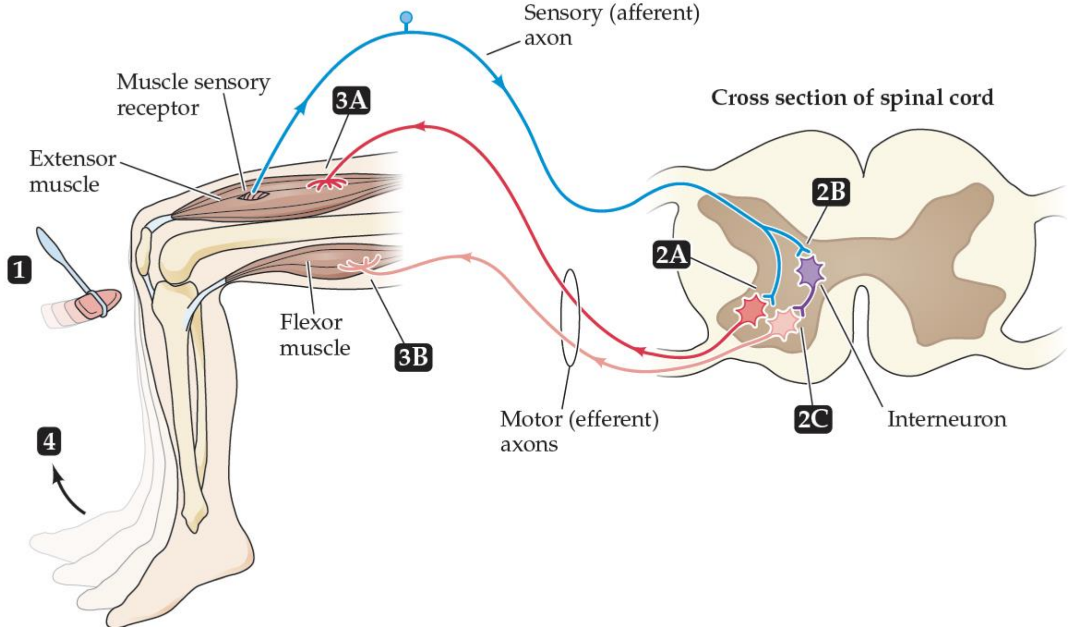
Purves, Figure 16.10

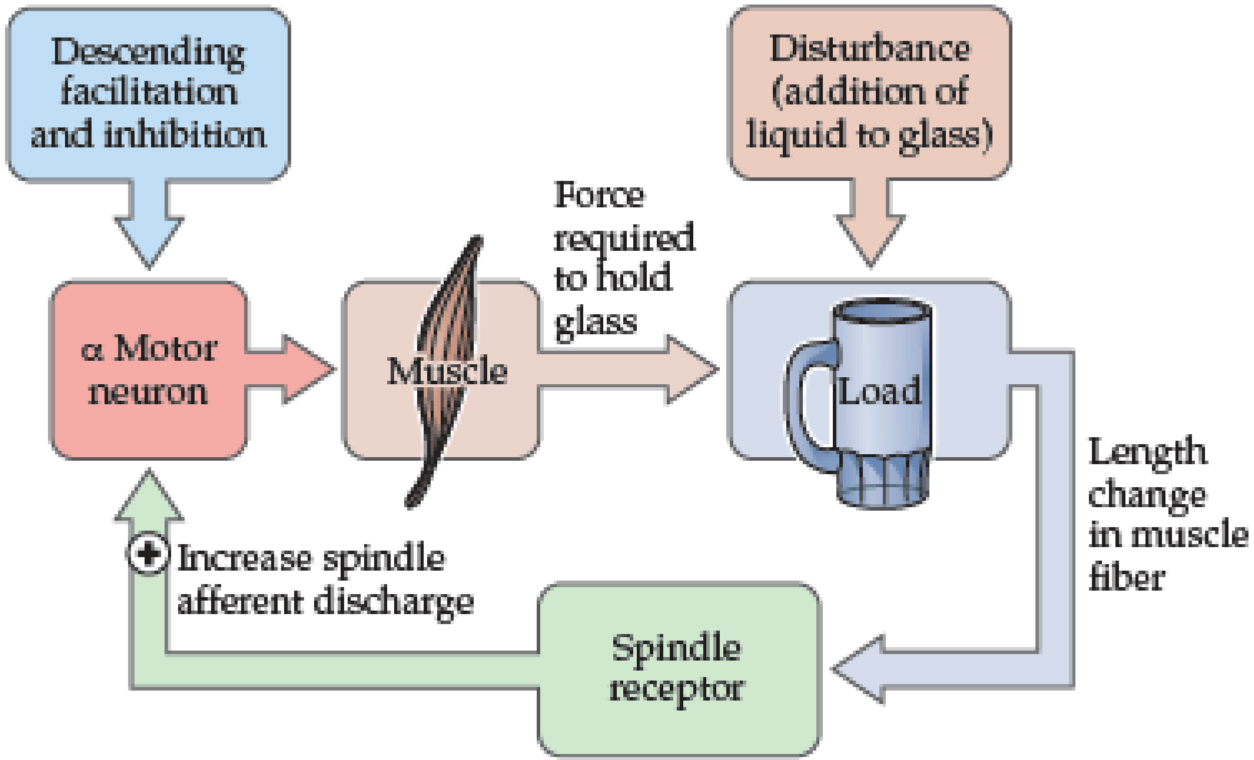
The Spinal Cord Circuitry Underlying Muscle Stretch Reflexes



Each lower motor neuron innervates many muscle fibers within a single muscle

The Spinal Cord Circuitry Underlying Muscle Stretch Reflexes



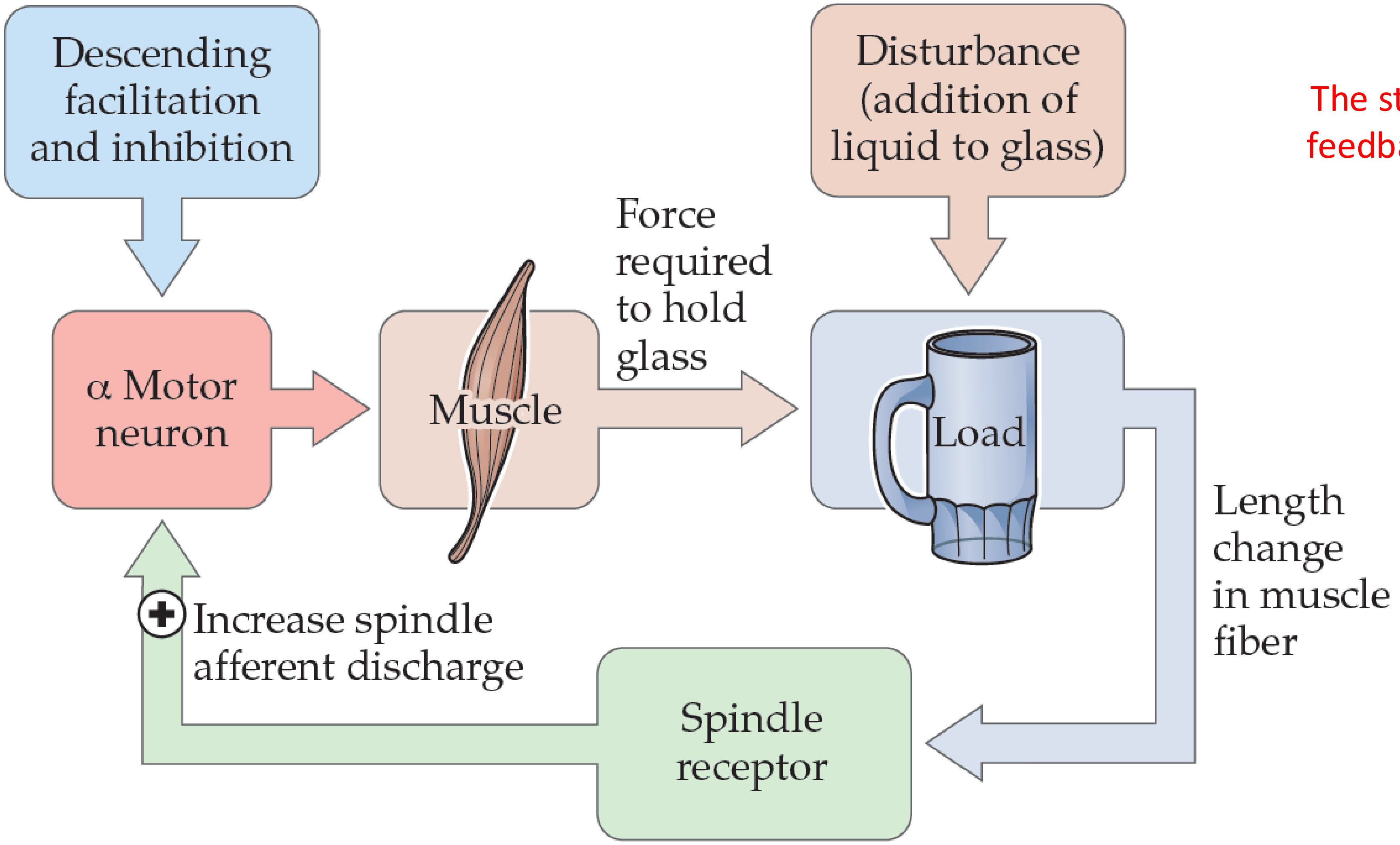


The stretch reflex operates as a negative feedback loop to regulate muscle length.

CH 1, FIGURE 1.7

CH 16, FIGURE 10

Stretch reflex circuitry

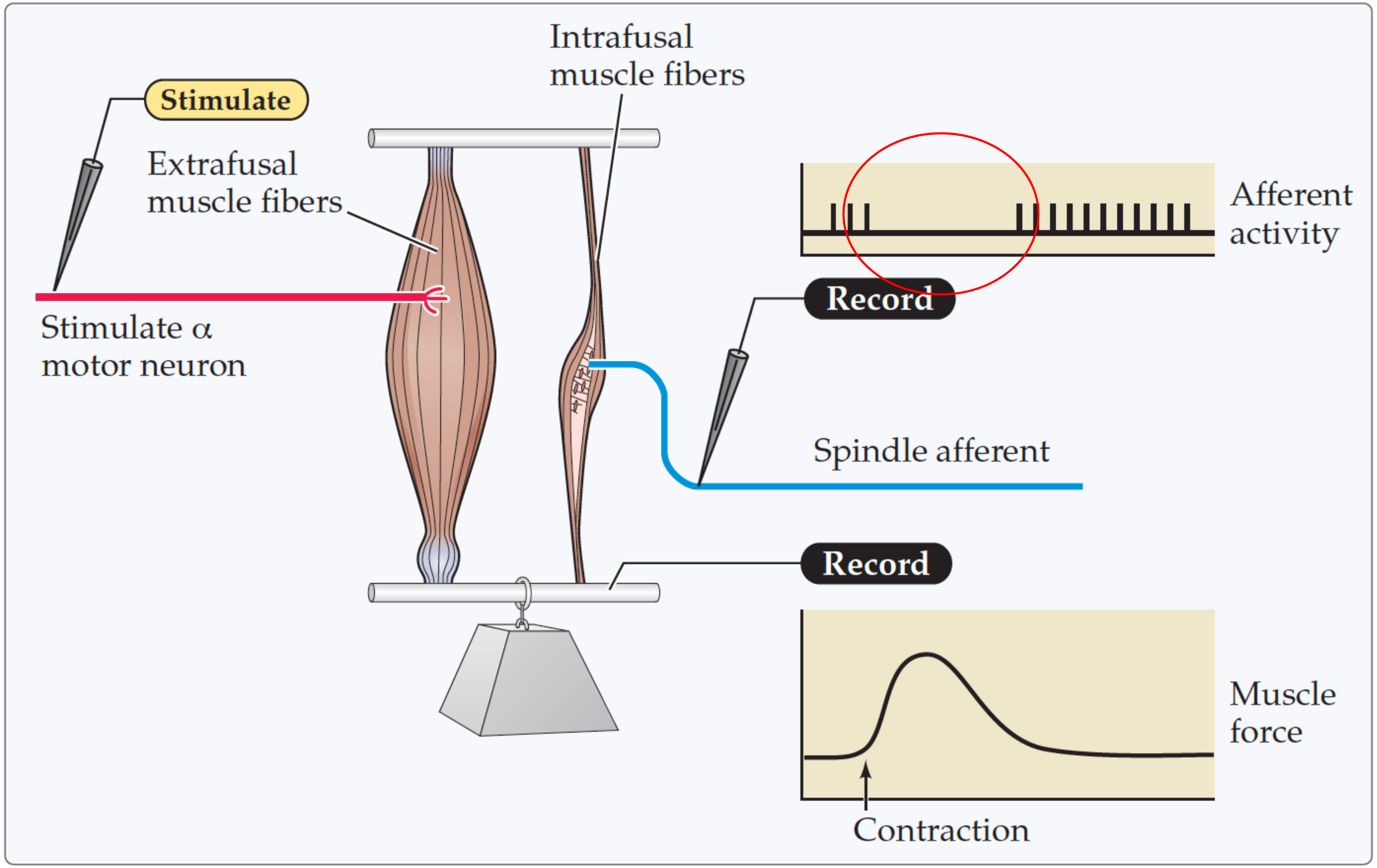


The stretch reflex operates as a negative feedback loop to regulate muscle length.

Purves, Figure 16.10

The role of γ motor neurons in regulating muscle spindle responses

(A) α Motor neuron activation without γ

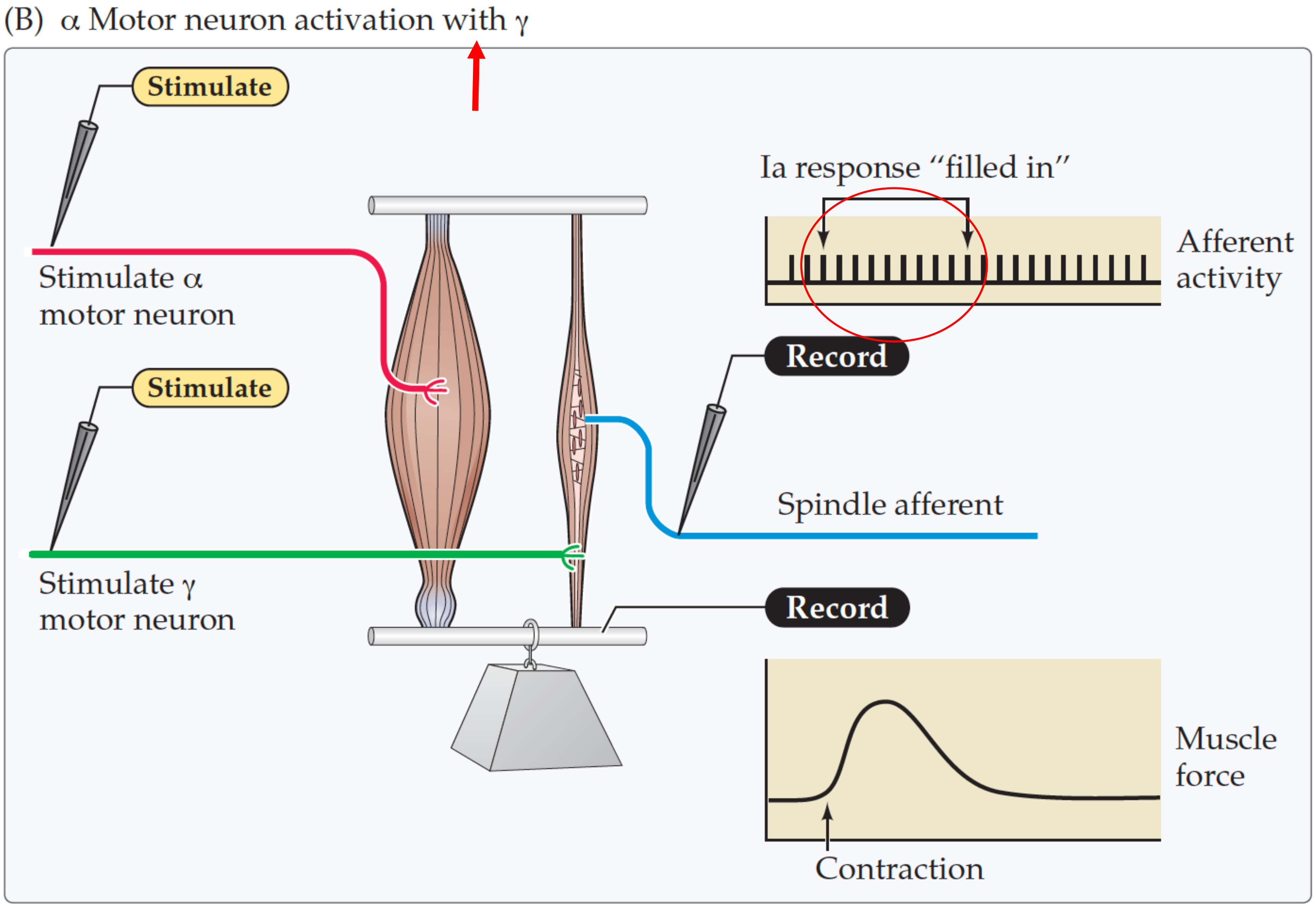


Purves, Figure 16.11

The role of γ motor neurons in regulating muscle spindle responses

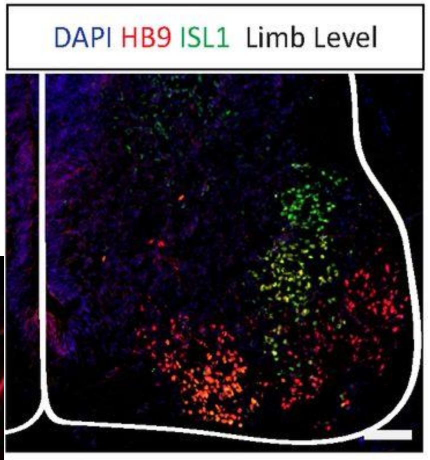
α motor neurons, and γ-motor neurons are usually activated together!

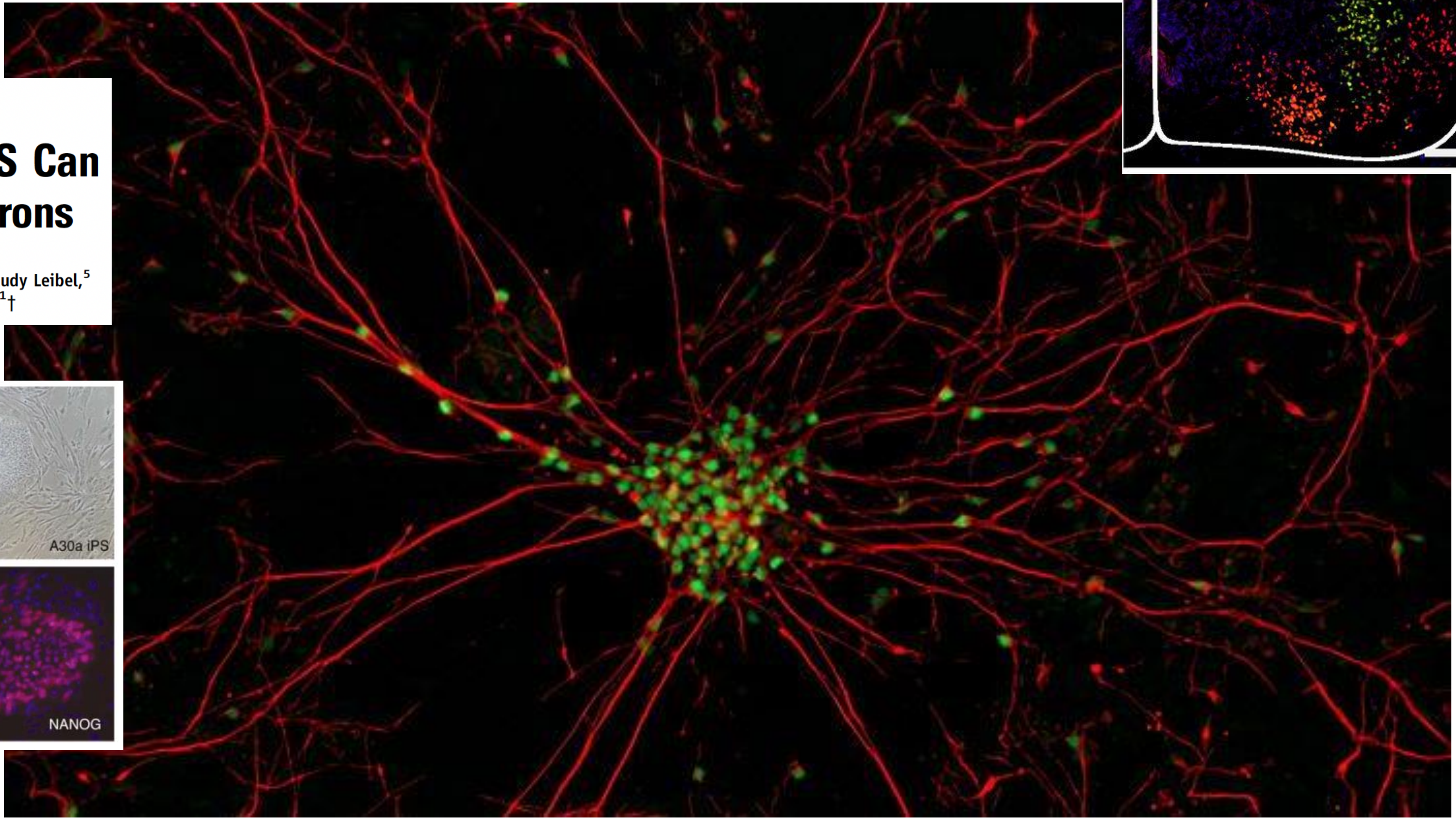
… so that γ-MN can prevent passive relaxation of intrafusal fiber



Purves, Figure 16.11

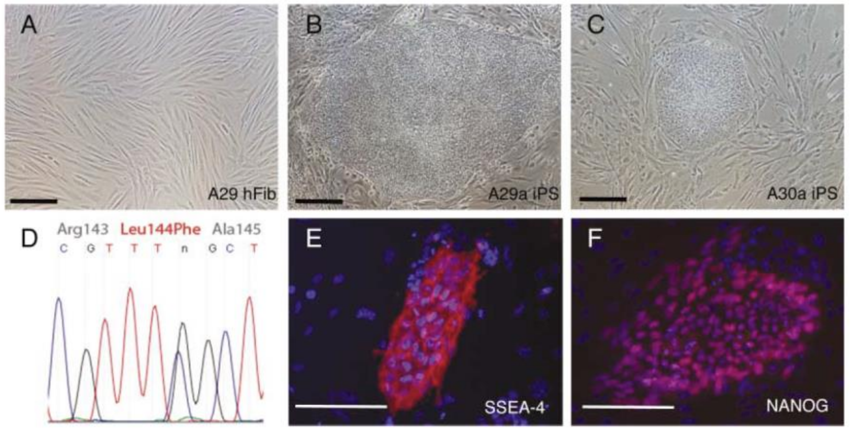
Studying motor neurons in vivo is very difficult: scientists developed new assays to grow motor neurons in a dish





Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons

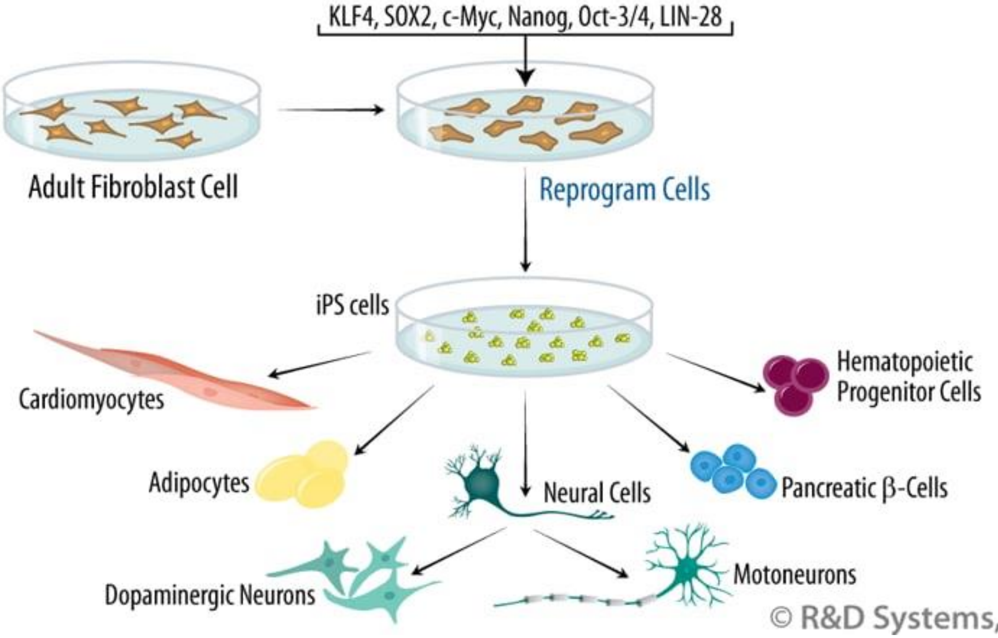
John T. Dimos,[1*] Kit T. Rodolfa,[1,2*] Kathy K. Niakan,[1] Laurin M. Weisenthal,[1] Hiroshi Mitsumoto,[3,4] Wendy Chung,[4,5] Gist F. Croft,[4,6] Genevieve Saphier,[1] Rudy Leibel,[5] Robin Goland,[7] Hynek Wichterle,[4,6] Christopher E. Henderson,[4,6] Kevin Eggan[1]†



New opportunities for bioengineering:
stem cells for growing cell-type specific neurons

Shinya Yamanaka

Discovered four transcription factors (Oct4, Sox2, cMyc, Klf4) that could make adult cells pluripotent

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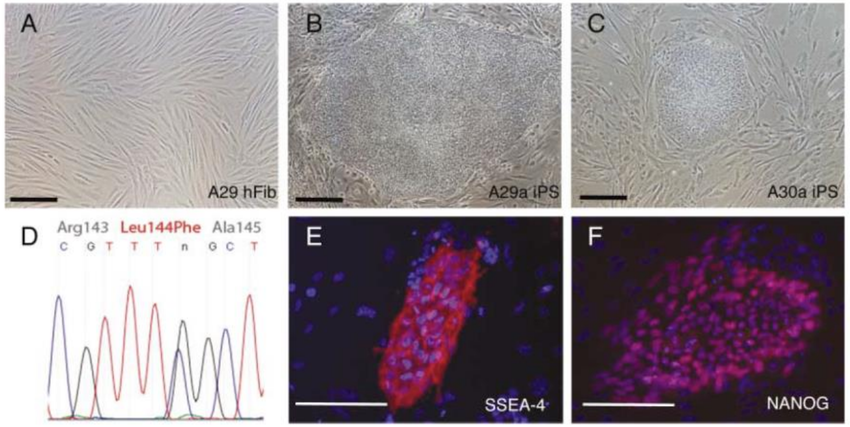

New opportunities for bioengineering:
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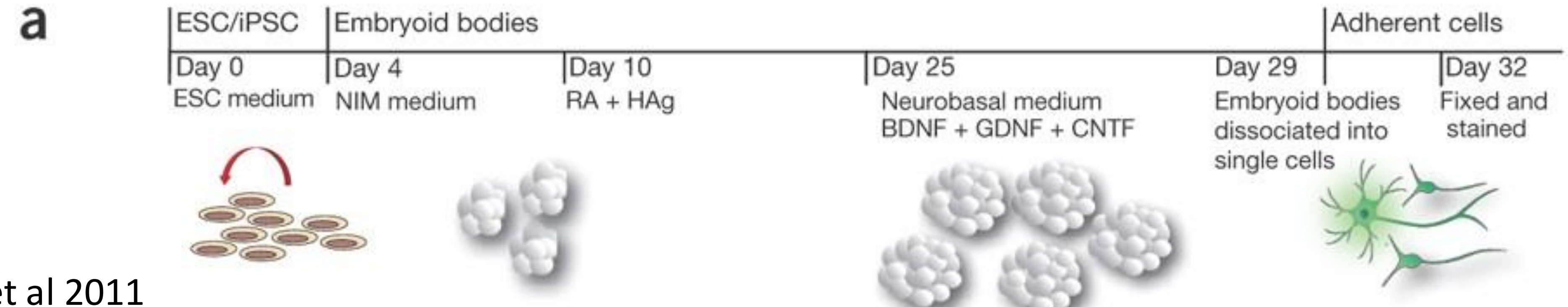
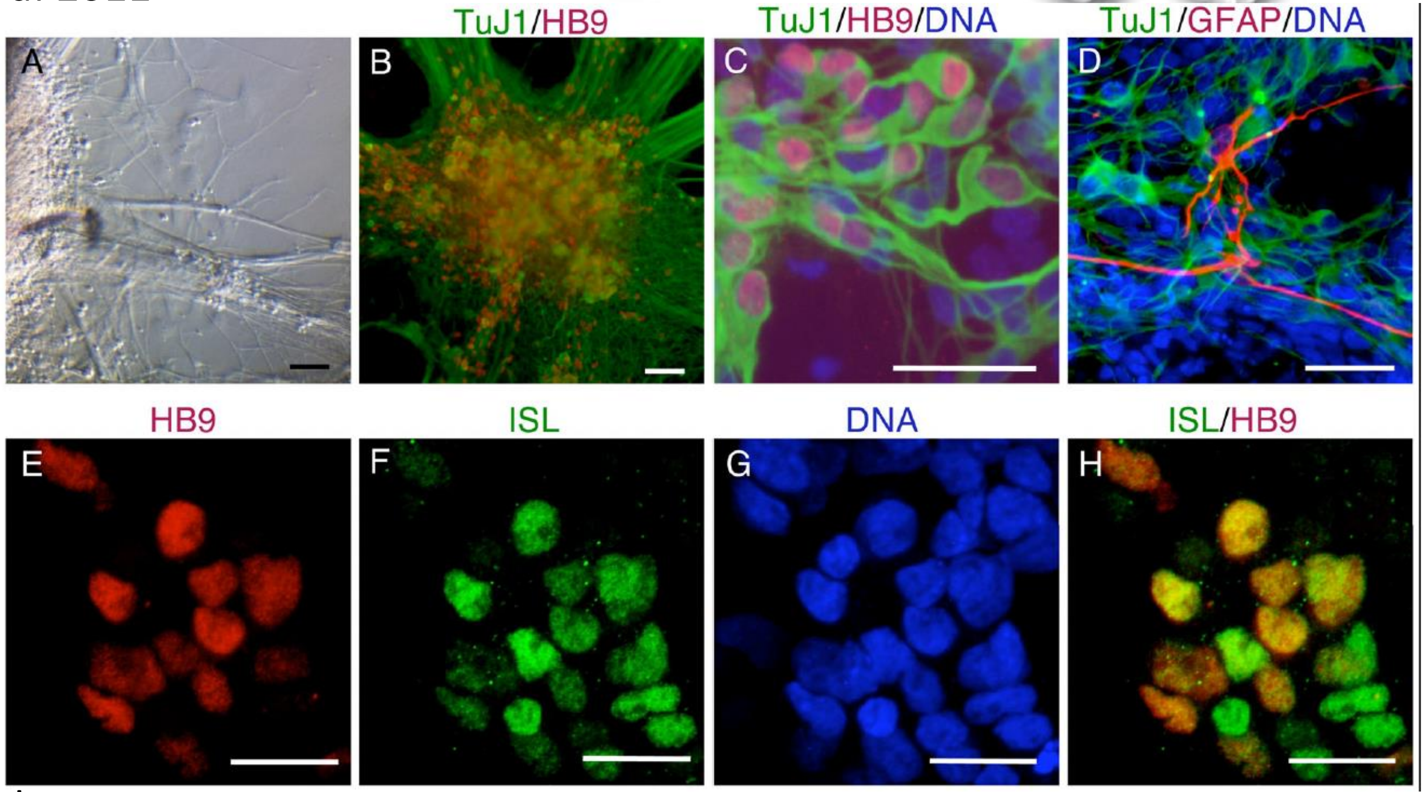


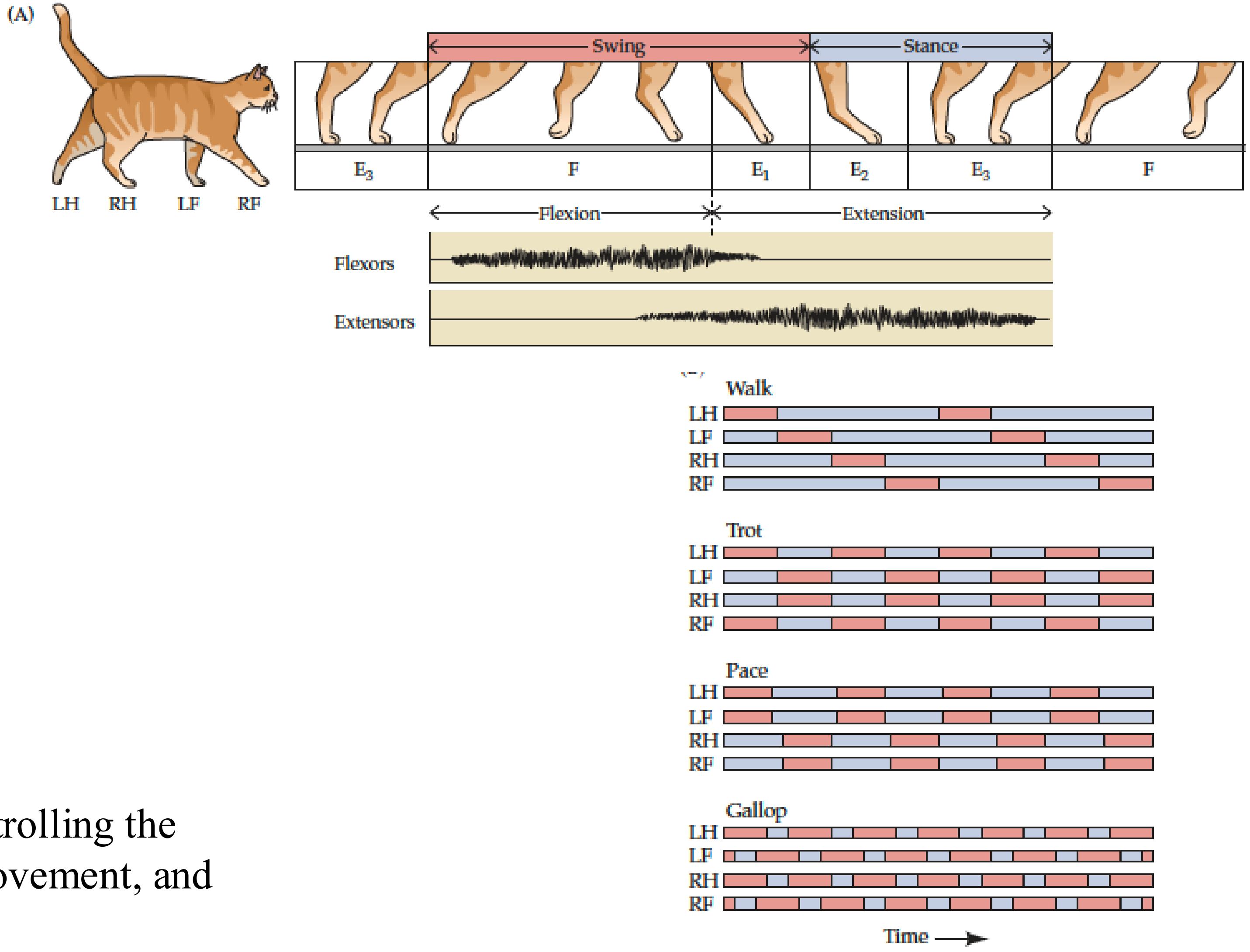
Boulting et al 2011



Dimos et al 2008

iPSC-based drug discovery is a promising technology for developing novel therapeutics for neurodegenerative diseases lacking useful disease models, such as amyotrophic lateral sclerosis (ALS).

The mammalian cycle of locomotion is organized by **central pattern generators** in the spinal cord.

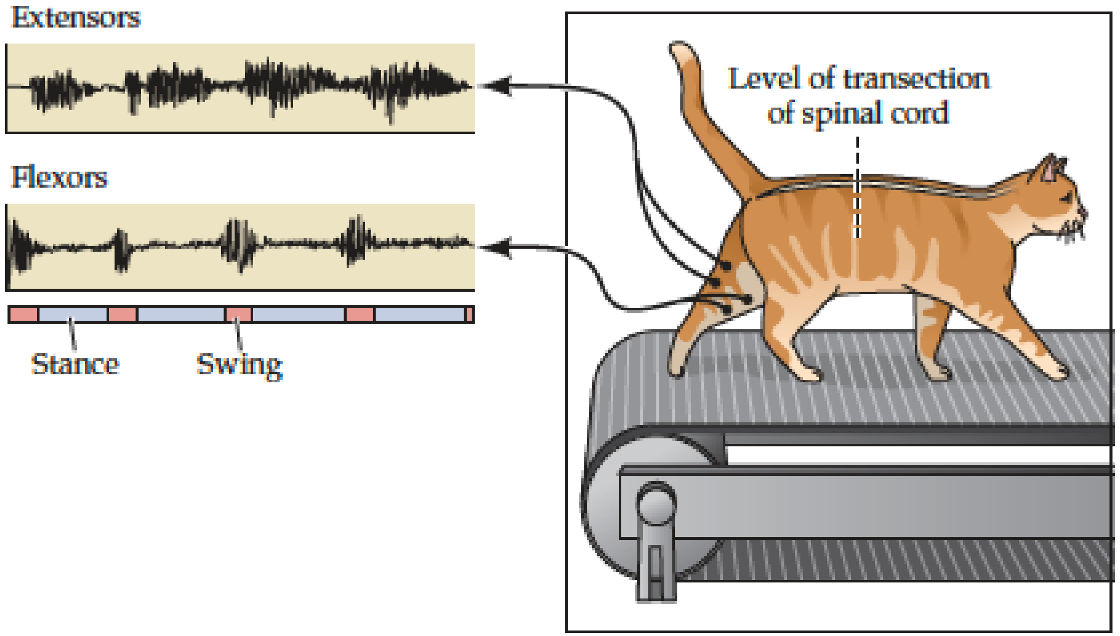


central pattern generators are fully capable of controlling the timing and coordination of such complex patterns of movement, and of adjusting them in response to altered circumstances.

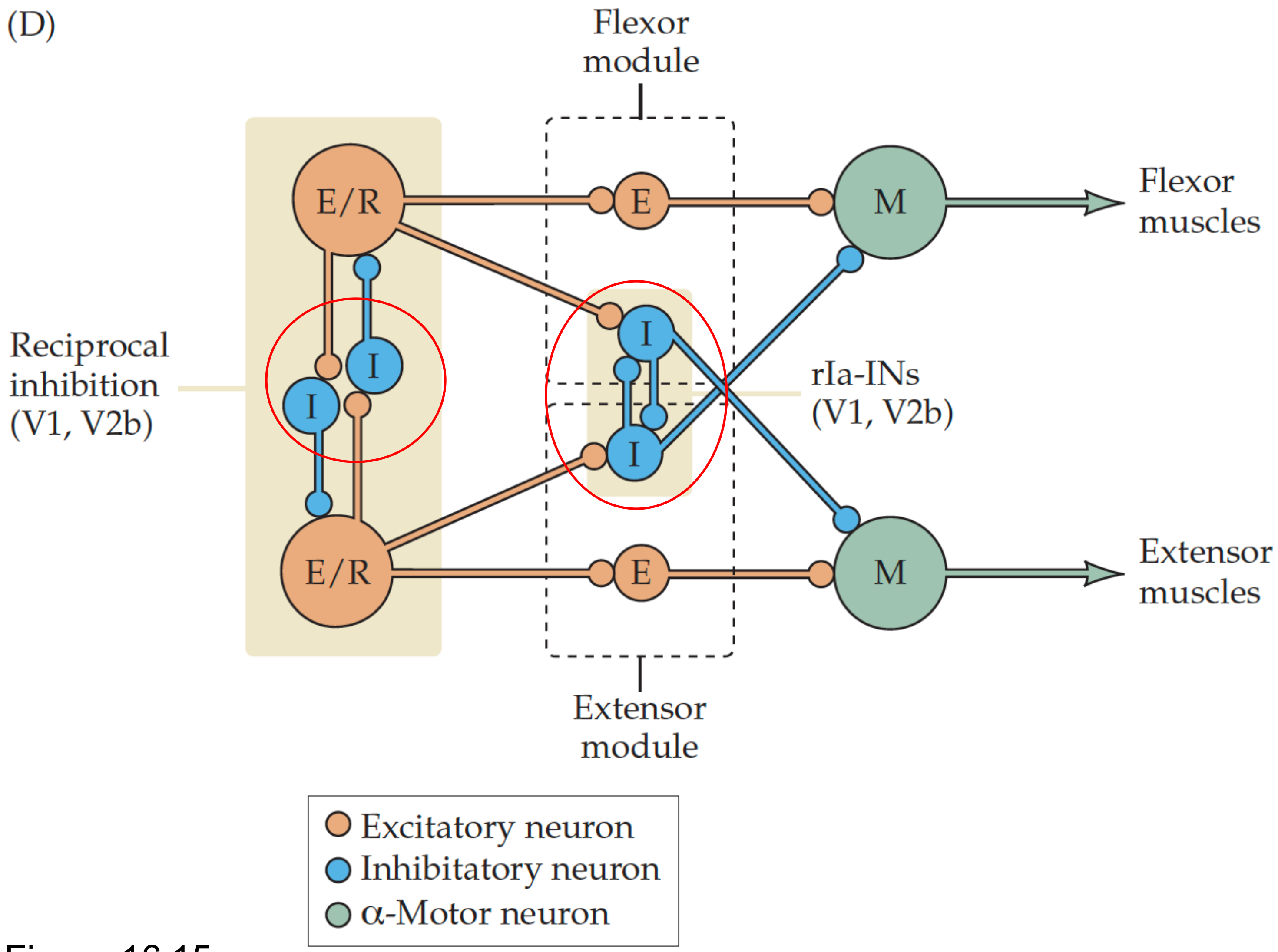
The mammalian cycle of locomotion is organized by **central pattern generators** in the spinal cord.

- Following transection of the spinal cord at the thoracic level, a cat's hindlimbs will still make coordinated locomotor movements if the animal is supported and placed on a moving treadmill
→ this suggests a reflex-like response to treadmill movement ...

- Can even walk after cutting dorsal root (no sensory inputs) if apply L-DOPA (although the speed of walking is slowed and the movements are less coordinated than under normal conditions)



The mammalian cycle of locomotion is organized by central pattern generators in the spinal cord

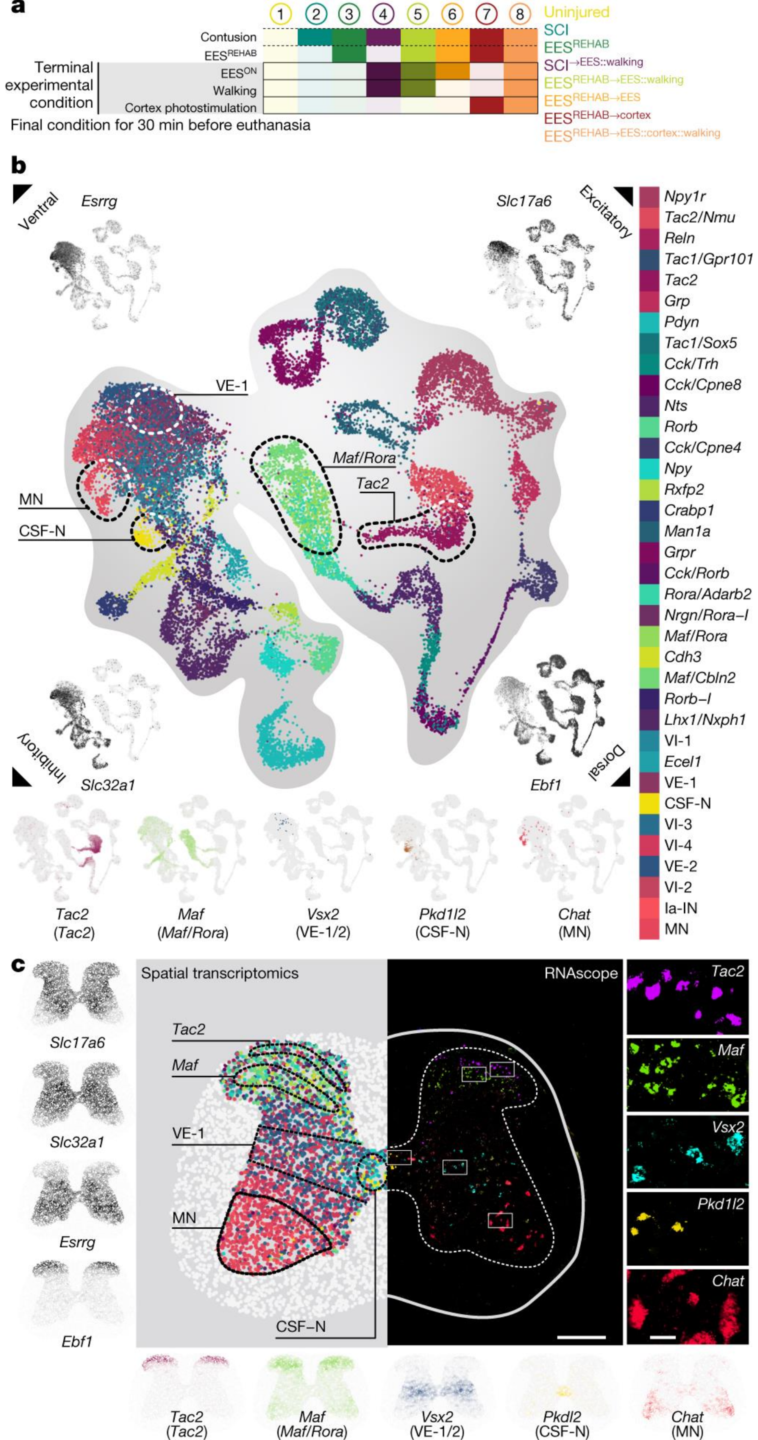


Note **reciprocal inhibition** of antagonistic muscles at multiple sites (interneurons, Motor neurons)!

Purves, Figure 16.15


Gregoire Courtine
Jocelyne bloch
1 June 2012
Science
R. van den Brand*, J. Heutschi*, Q. Barraud, J. DiGiovanna, K. Bartholdi, M. Huerlimann, L. Friedli, I. Vollenweider, E.M. Moraud, S. Duis, N. Dominici, S. Micera, P. Musienko, G. Courtine, **Restoring voluntary control of locomotion after paralyzing spinal cord injury,** *Science (2012).*


nature
31 October 2018
F. Wagner*, J.-B. Mignardot*, C. Le Goff-Mignardot*, R. Demesmaeker, S. Komi, M. Cap
so, A. Rowald, I. Seáñez, M. Caban, E. Pirondini, M. Vat, L. McCracken, R. Heimgar
Fodor, A. Watrin, P. Seguin, E. Paoles, K. Van Den Keybus, G. Eberle, B. Schurch, E. Pr
F. Becce, J. Prior, N. Buse, R. Buschman, E. Neufeld, N. Kuster, S. Carda, J. von Zitzev
Delattre, T. Denison, H. Lambert, K. Minassian†, J. Bloch†, G. Courtine†, **Targeted neur**
nology restores walking in humans with spinal cord injury, *Nature (2018).*

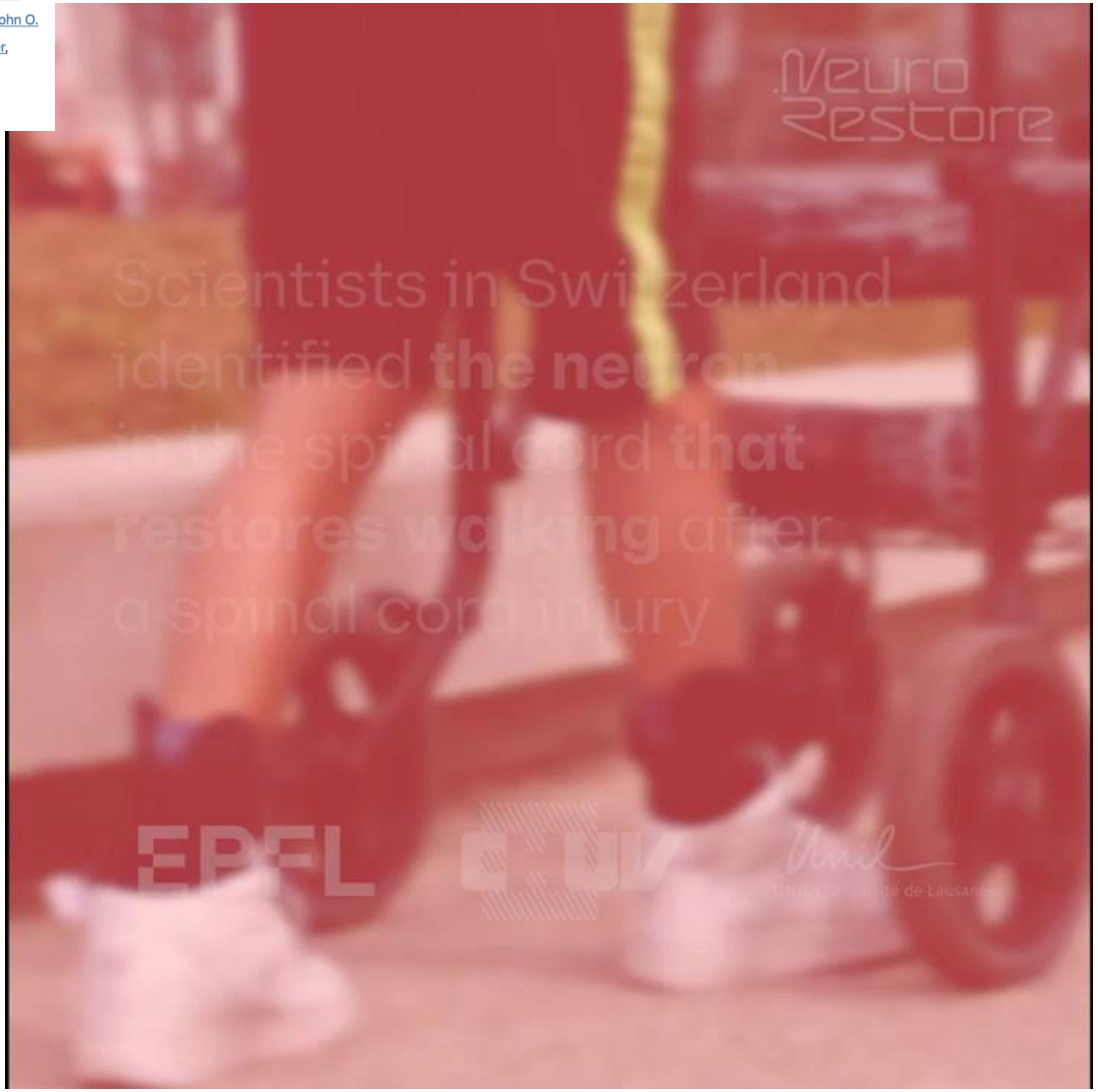


Article | Open Access | Published: 09 November 2022

The neurons that restore walking after paralysis

Claudia Kathe, Michael A. Skinnider, Thomas H. Hutson, Nicola Regazzi, Matthieu Gautier, Robin Demesmaeker, Salif Komi, Steven Ceto, Nicholas D. James, Newton Cho, Laetitia Baud, Katia Galan, Kaya J. E. Matson, Andreas Rowald, Kyungjin Kim, Ruijia Wang, Karen Minassian, John O. Prior, Leonie Asboth, Quentin Barraud, Stéphanie P. Lacour, Ariel J. Levine, Fabien Wagner, Jocelyne Bloch, ... Grégoire Courtine + Show authors

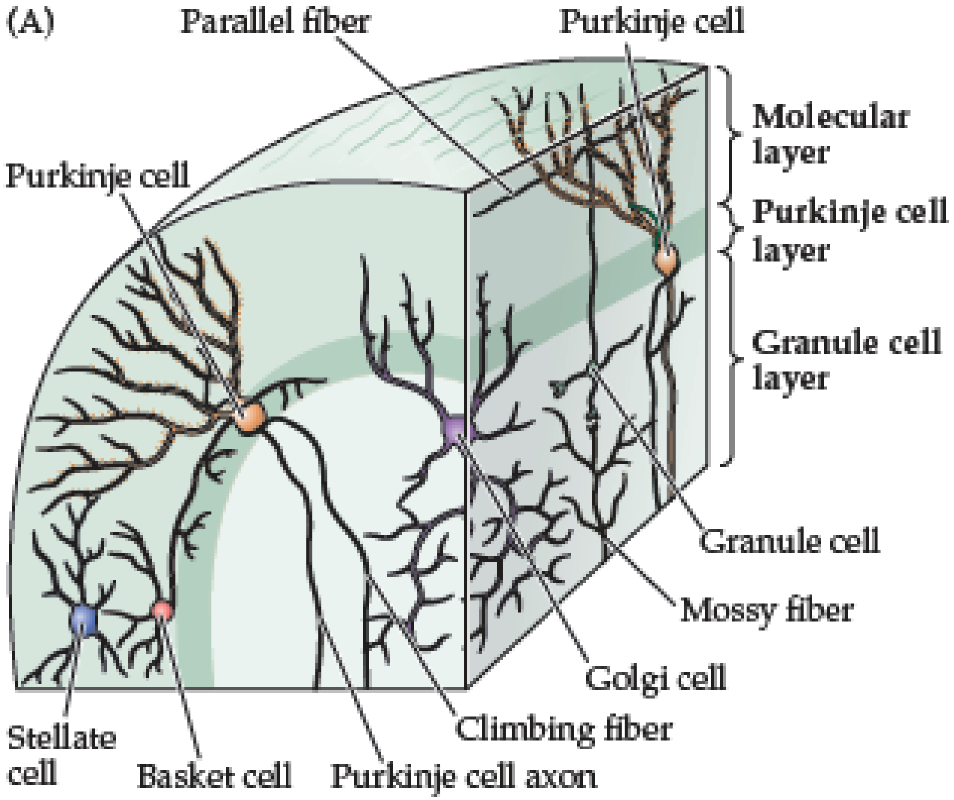
Nature 611, 540–547 (2022) | Cite this article



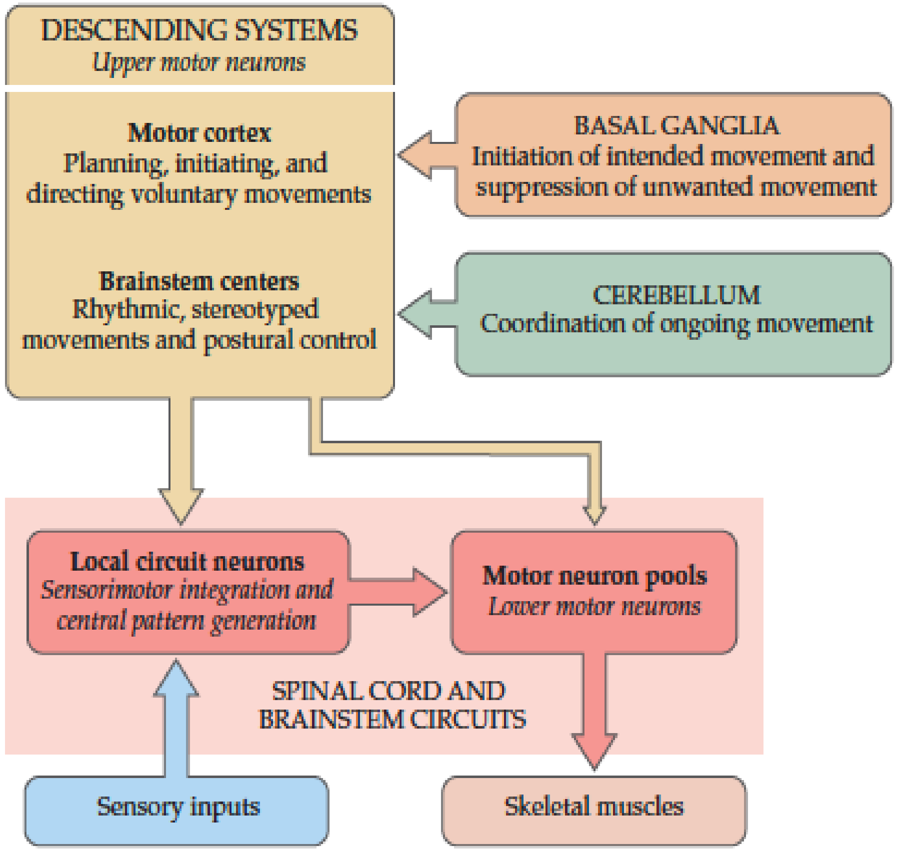
https://actu.epfl.ch/news/scientists-identify-neurons-that-restore-walking-2/

Part 2:
the **cerebellum**

BIO-311 | Mackenzie Mathis, PhD



The neural control of movement: sensorimotor system



Four systems make essential and distinct contributions to motor control:

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

Cerebellar damage impairs motor learning & control in humans

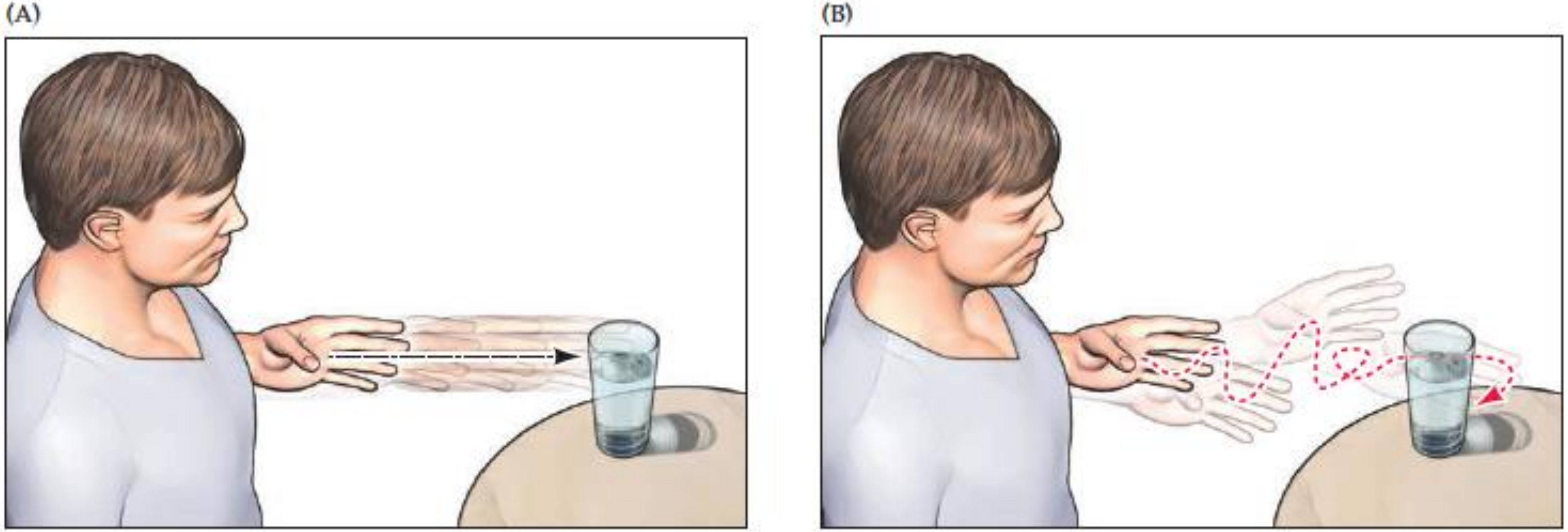
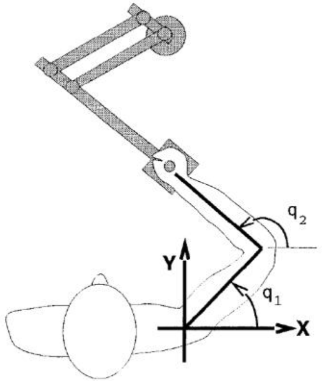


FIGURE 19.16 Illustration of appendicular ataxia with cerebellar damage.

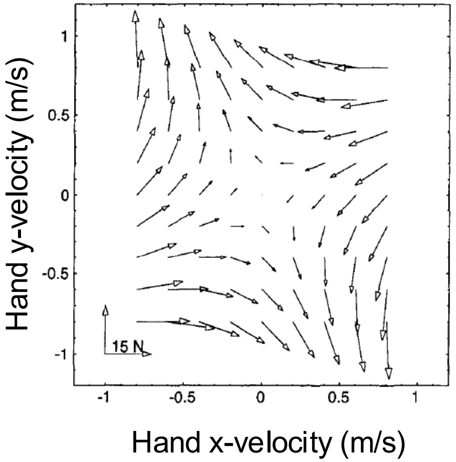
Cerebellar damage impairs motor learning & control in humans

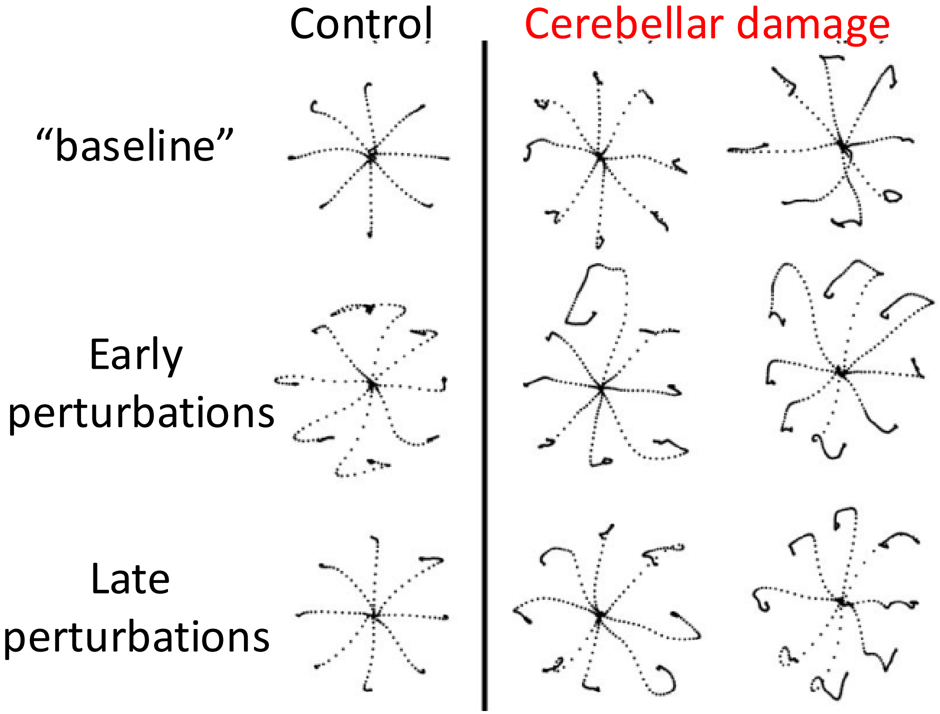
https://www.youtube.com/watch?v=Txlvuu2byUY

Cerebellar ataxia
affects ~4 in 100,000 people



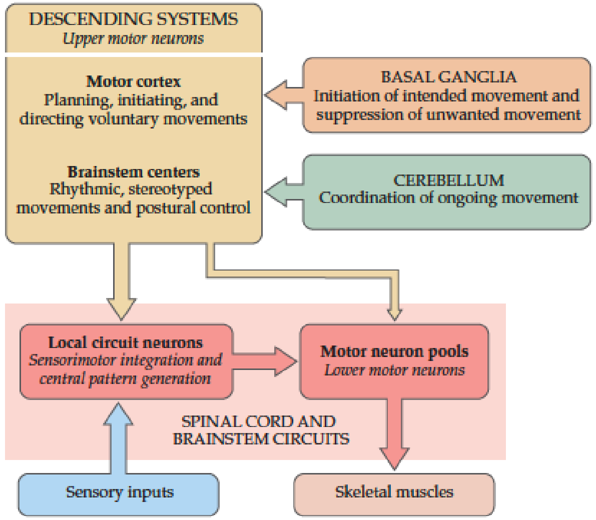
Shadmehr & Mussa-Ivaldi, 1994

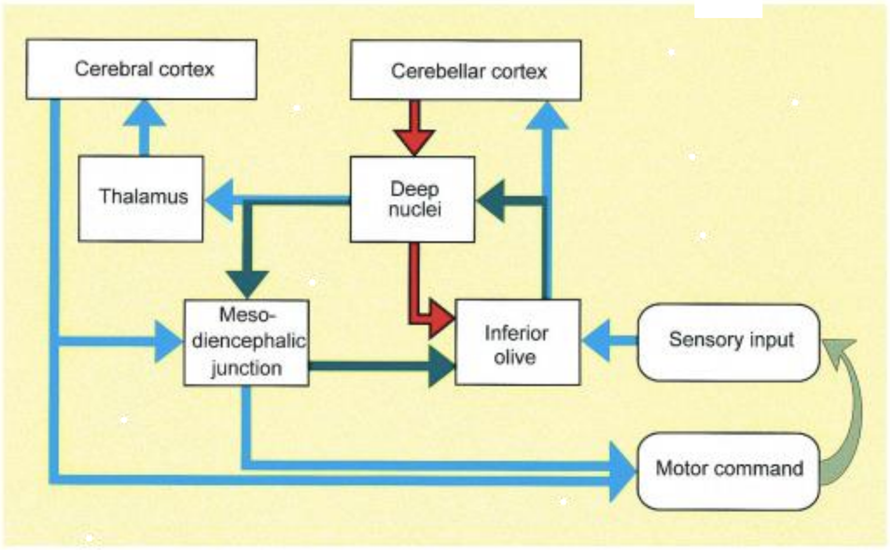


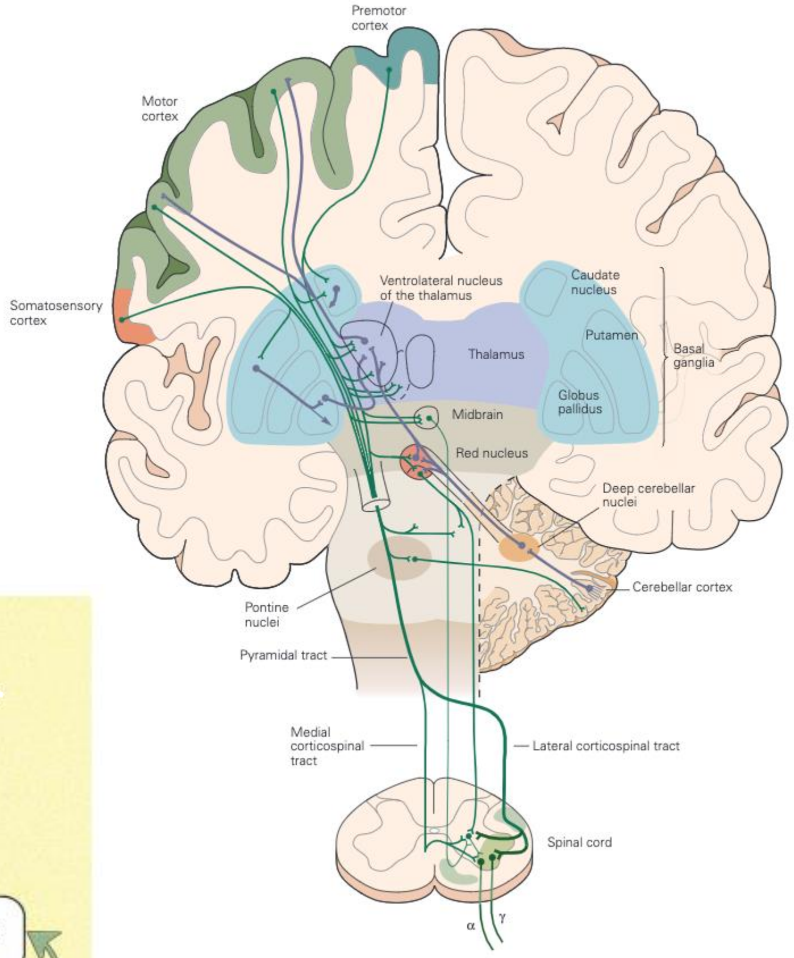


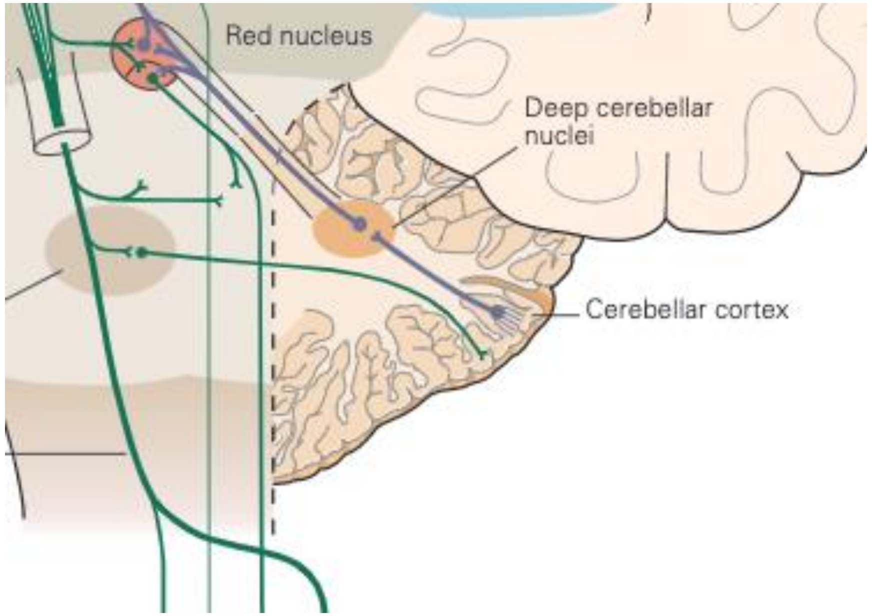
Smith & Shadmehr, 2005

The cerebellum: systems perspective









De Zeeuw et al, 1998

The cerebellum: functional organization

cortex

brainstem

spinal cord sensory feedback

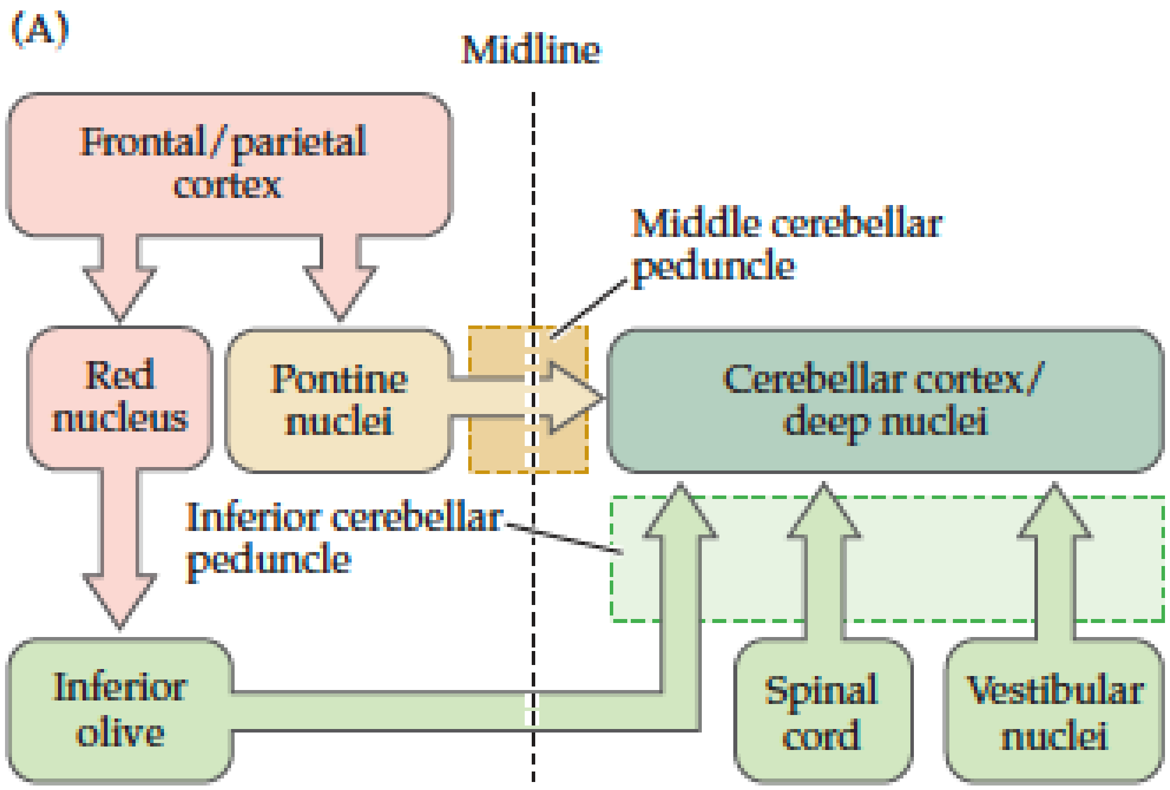
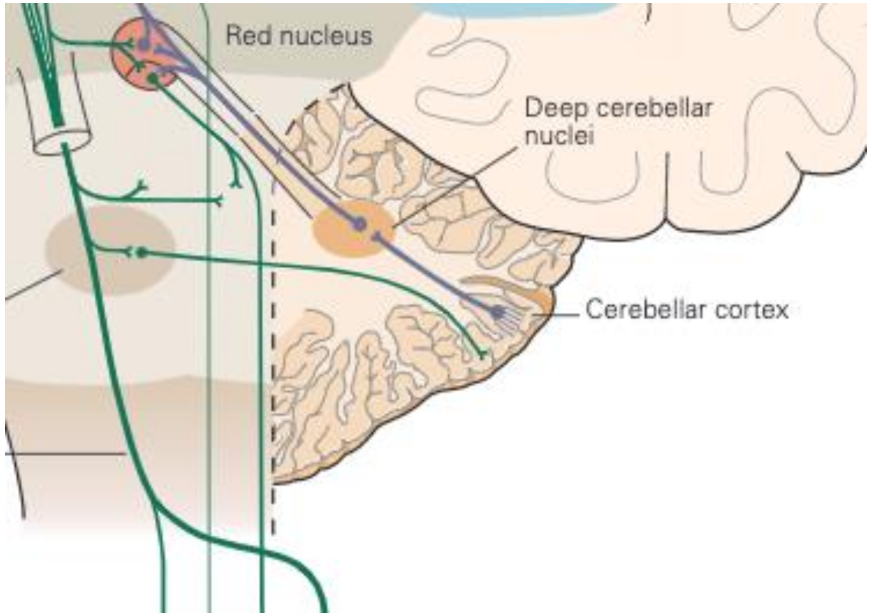
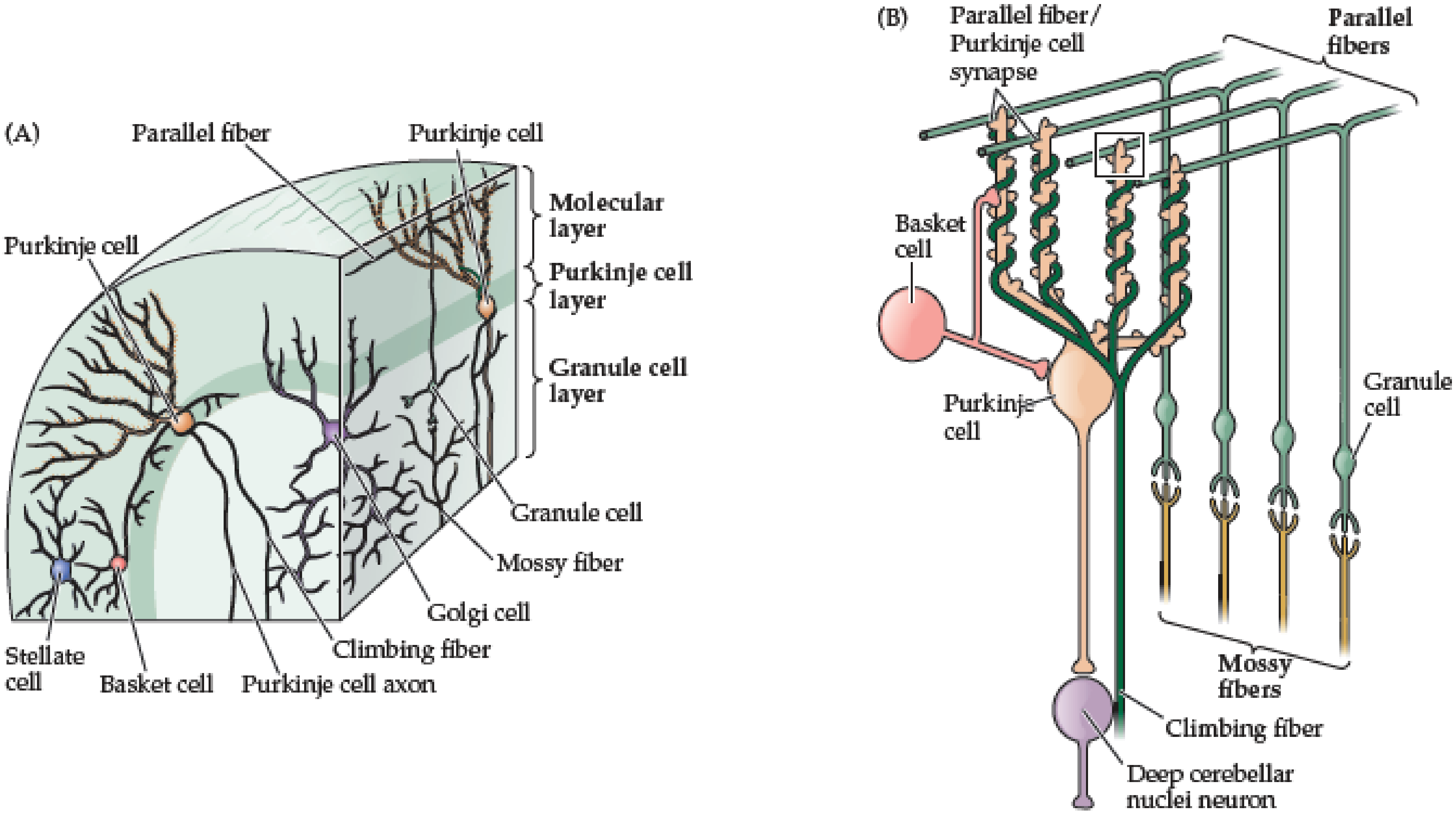


FIGURE 19.3 Functional organization of the inputs to the cerebellum.

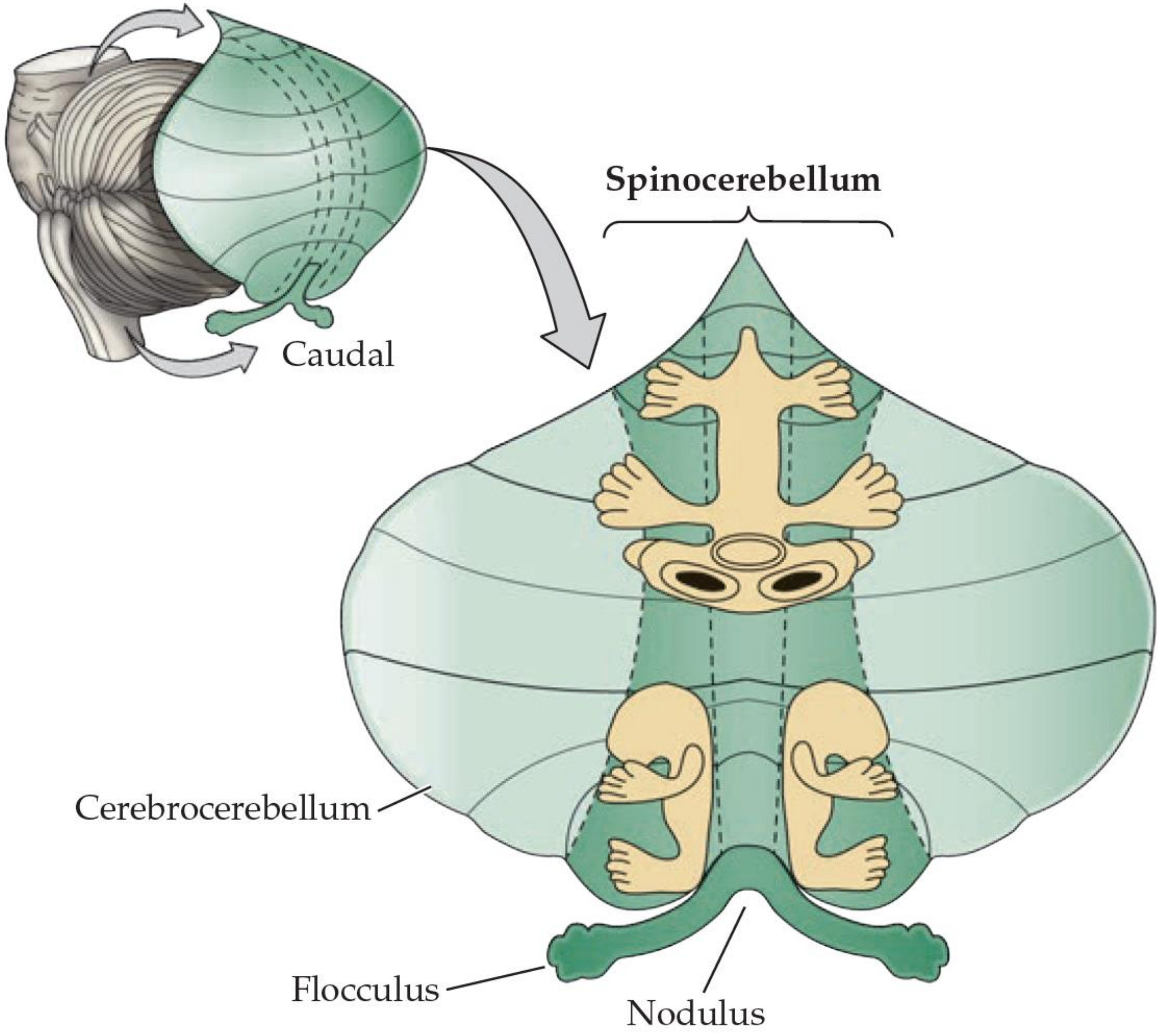


The cerebellum: functional organization



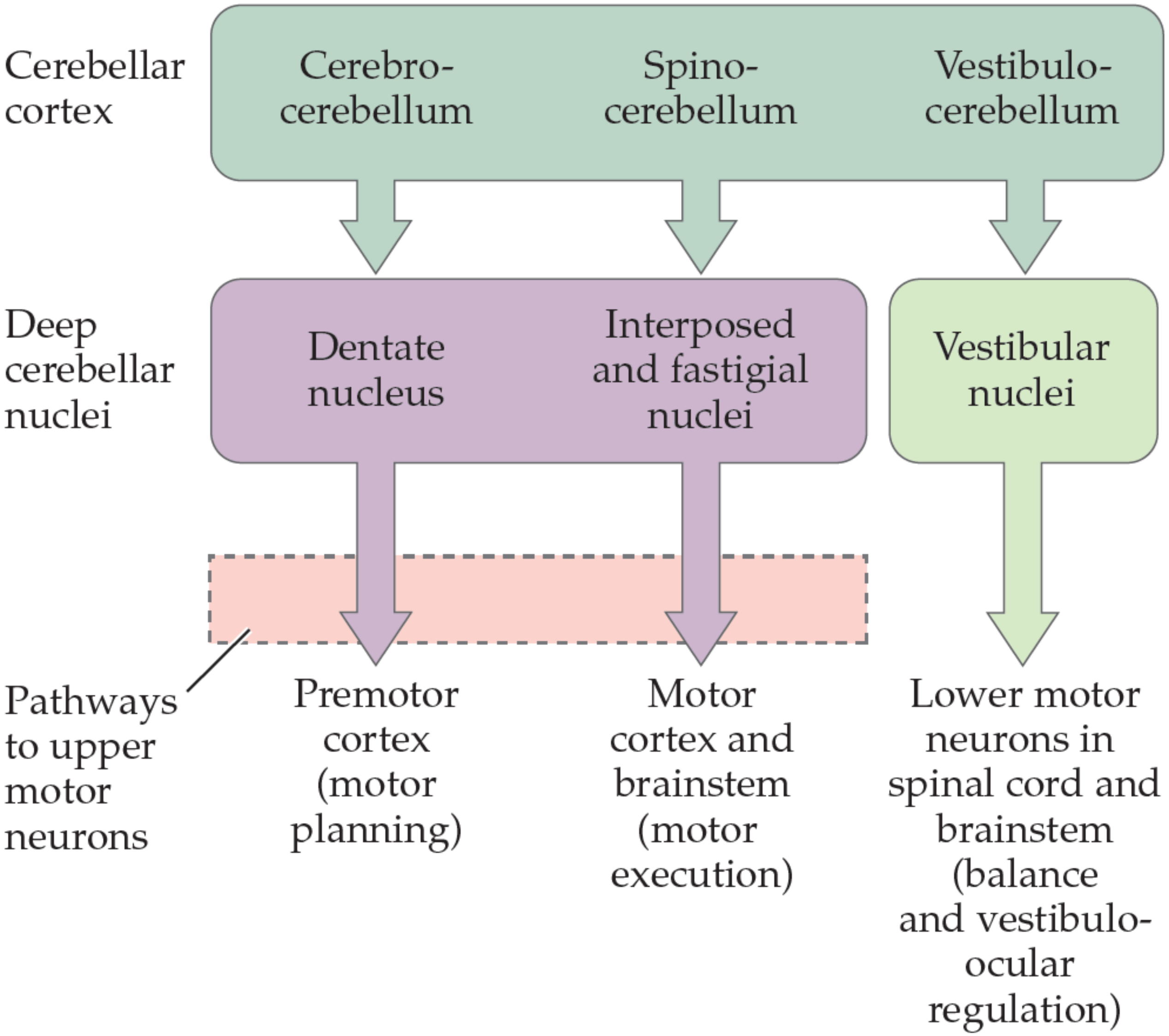
Purkinje Neuron: principle output cell of the cerebellum

Somatotopic maps of the body surface in the cerebellum



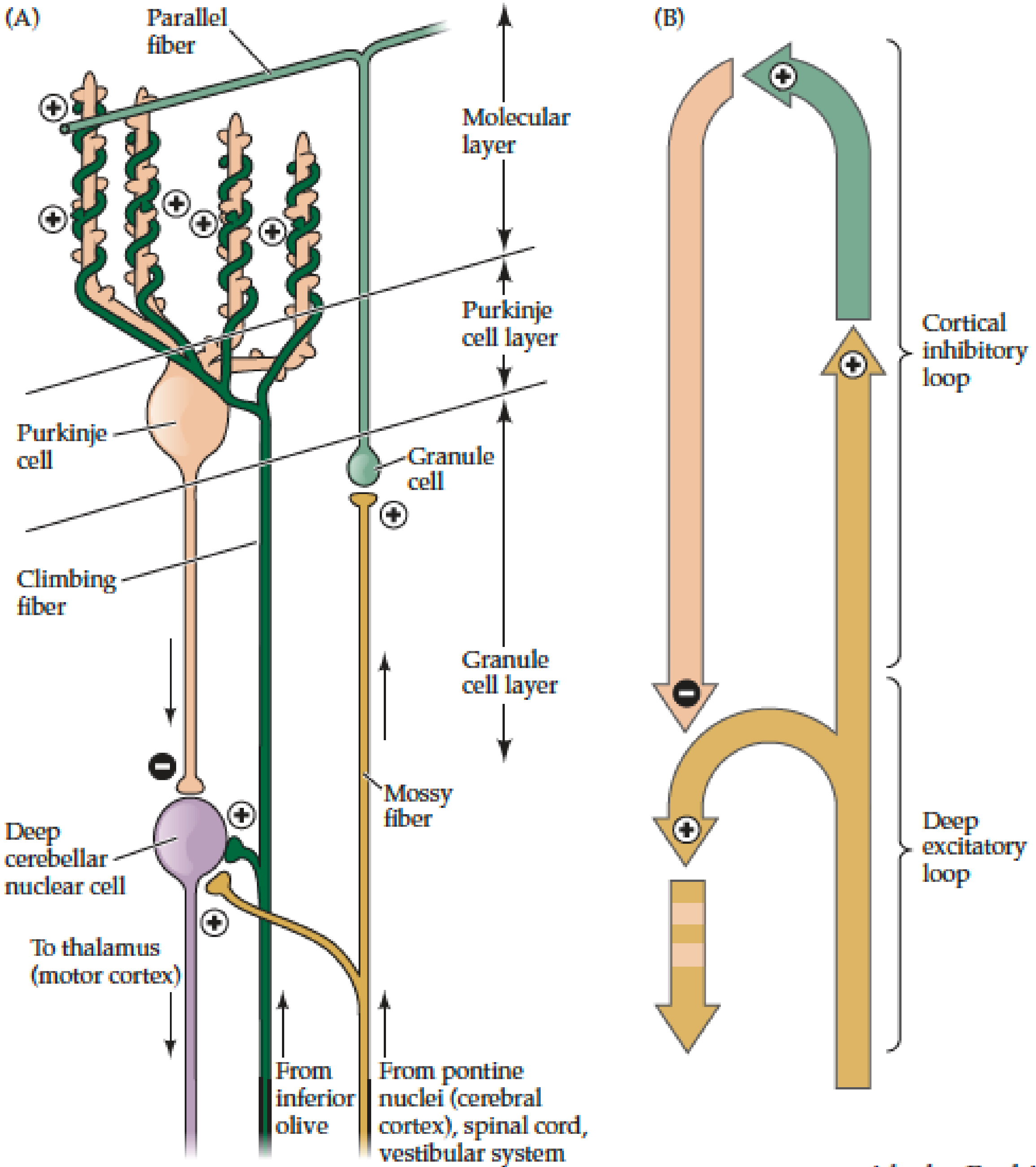
Purves, Figure 19.4

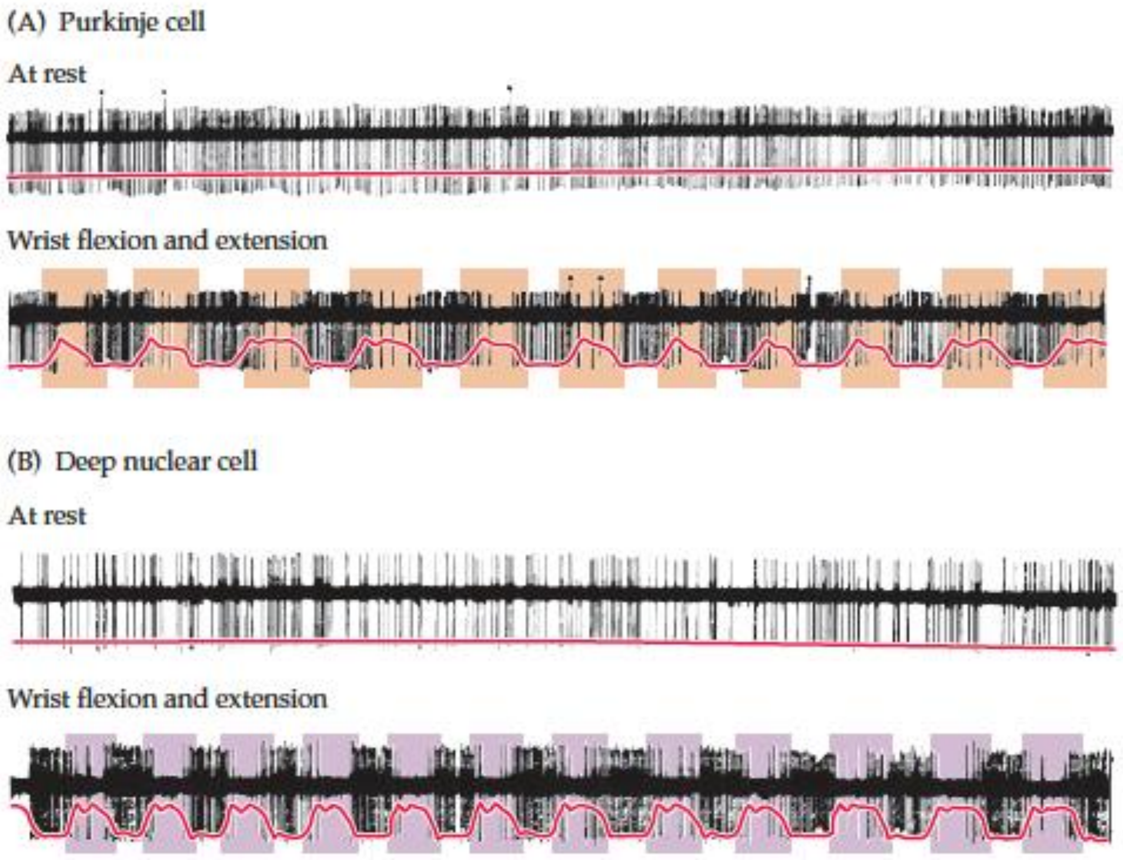
Functional organization of cerebellar outputs



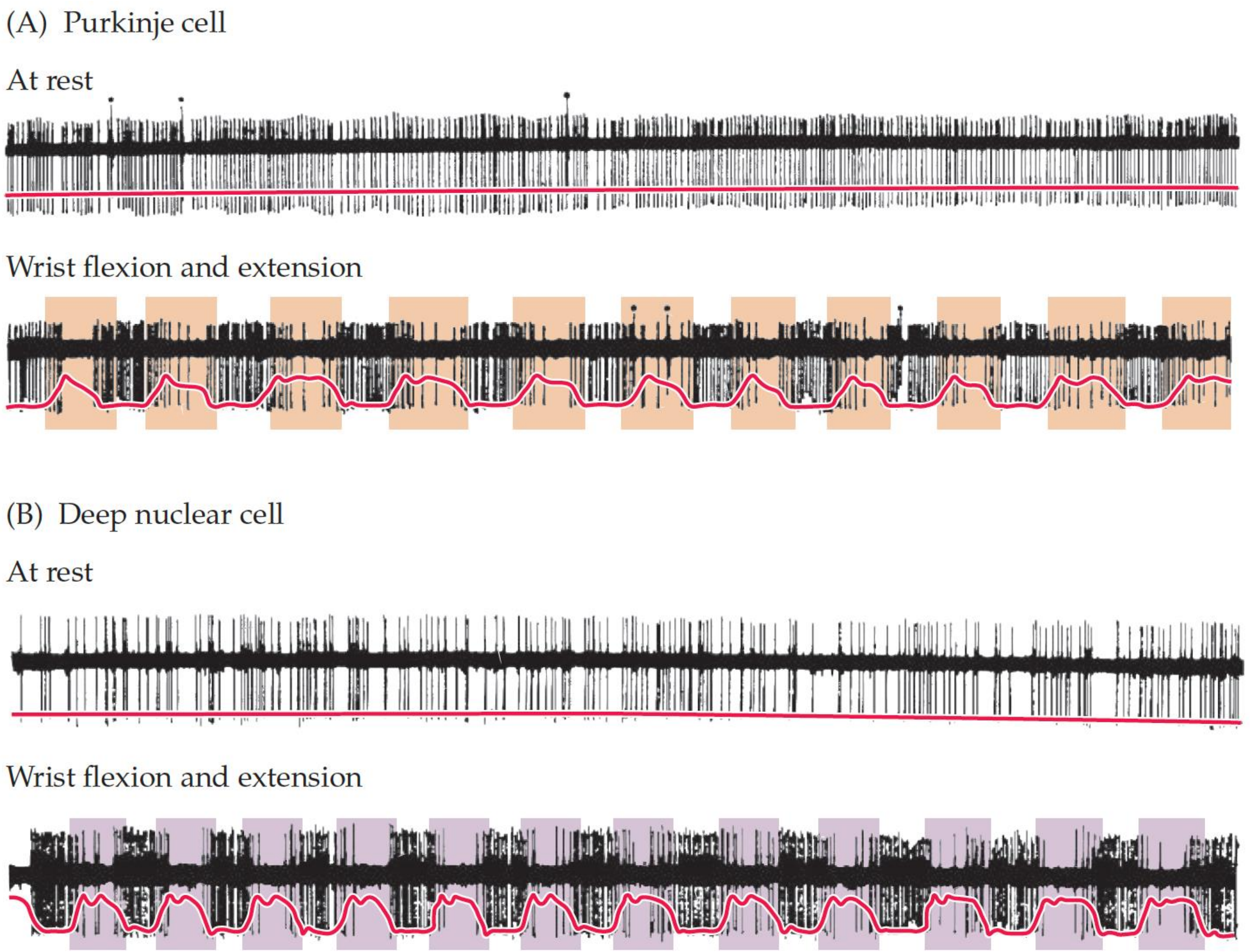
Purves, Figure 19.5

The cerebellum: functional organization



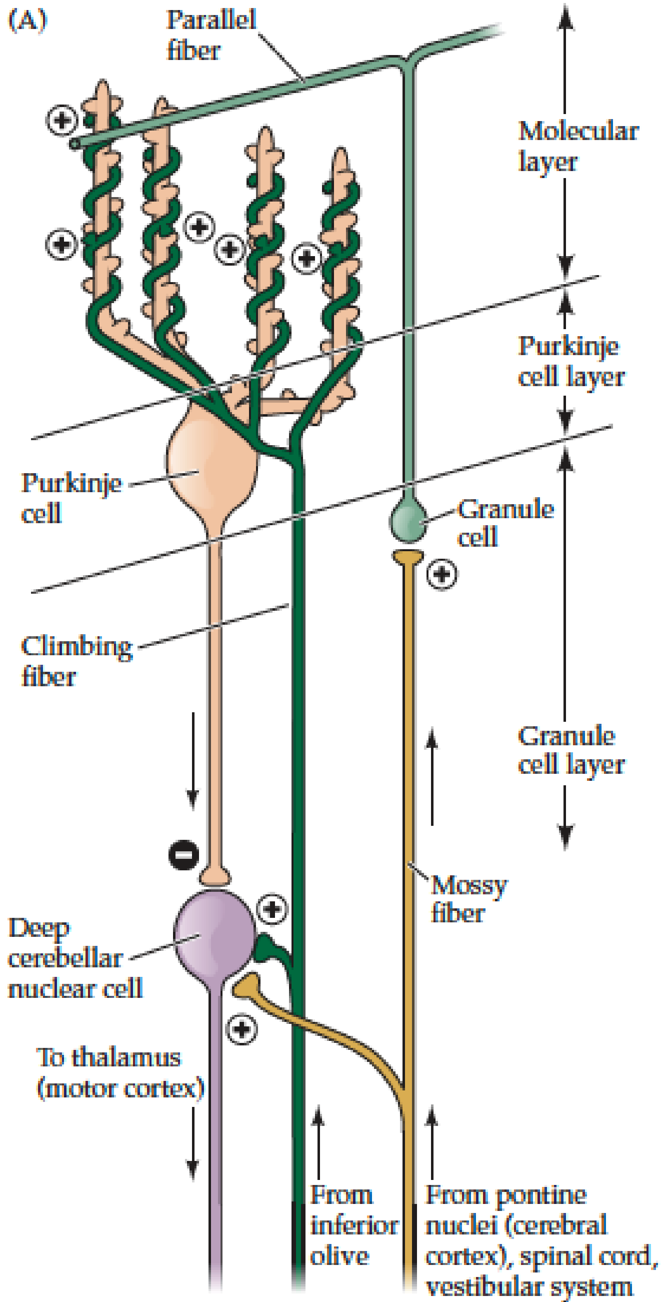


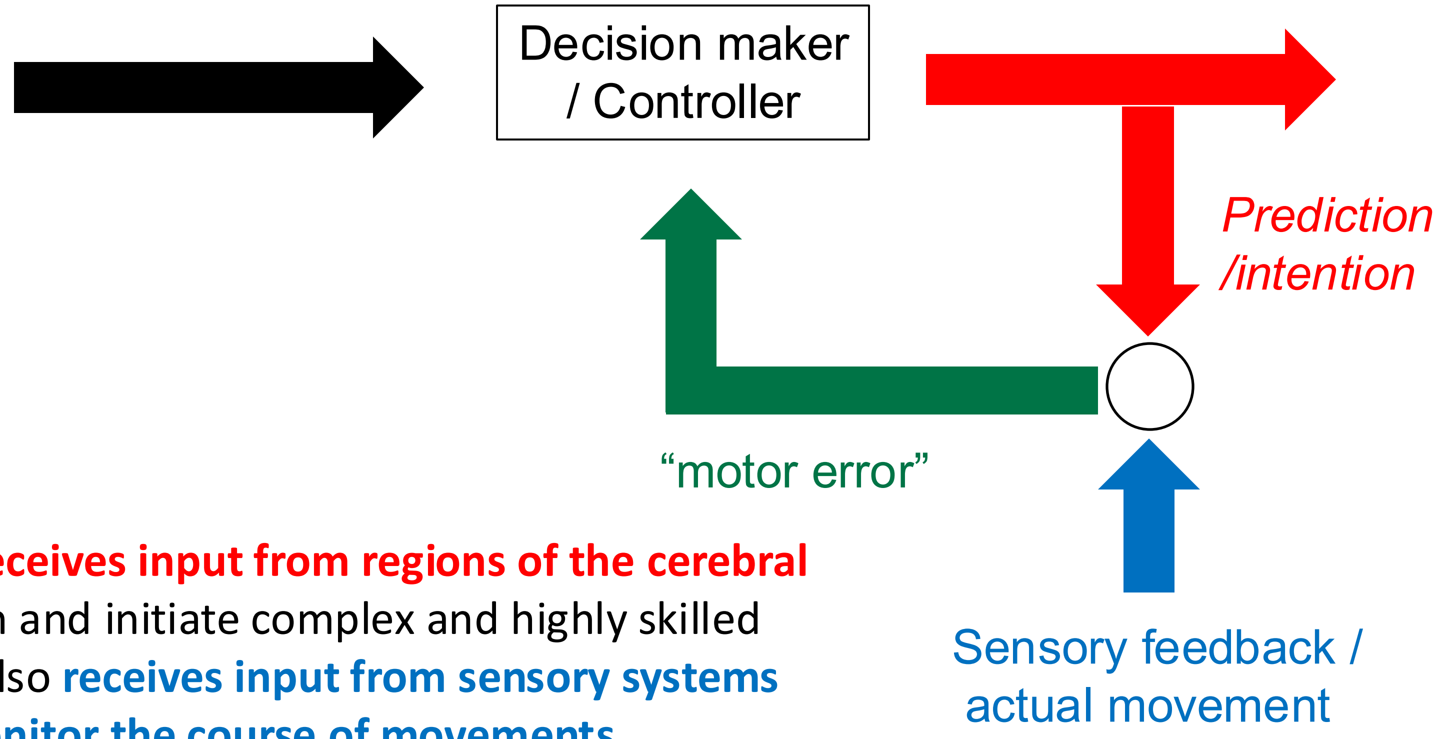
Activity of Purkinje cells and cells of the deep cerebellar nuclei reflect ongoing movements



Purves, Figure 19.12

The cerebellum: a circuit for motor-error based learning

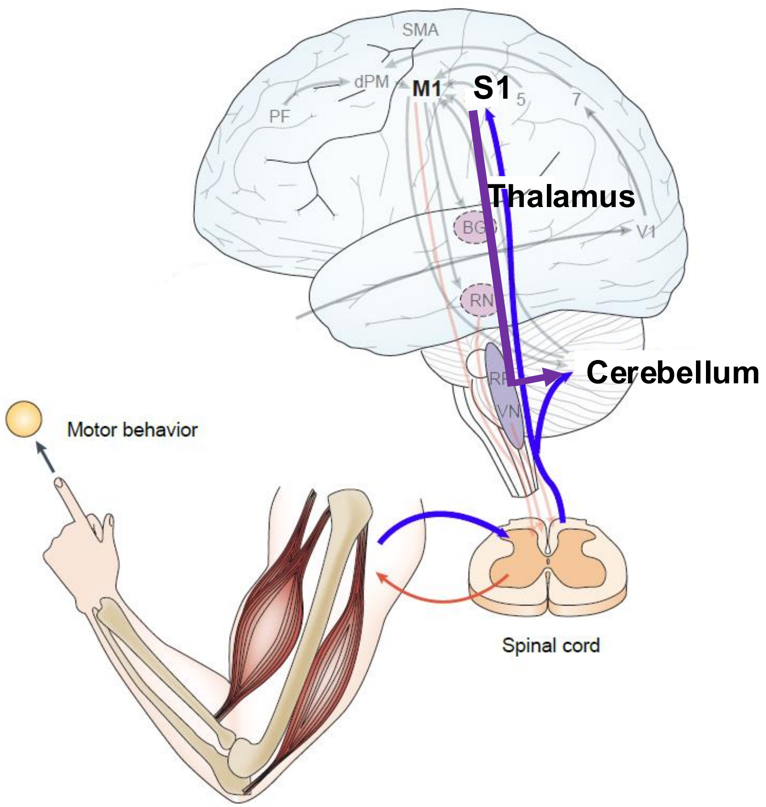




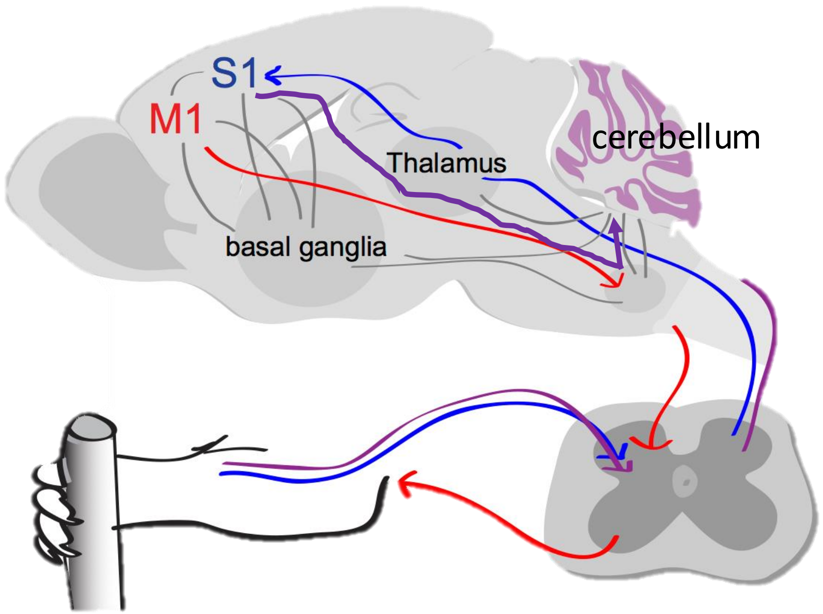
The cerebellum **receives input from regions of the cerebral cortex** that plan and initiate complex and highly skilled movements; it also **receives input from sensory systems that monitor the course of movements**

This arrangement enables a comparison of **an intended movement** with the **actual movement** and a reduction in the difference, or **"motor error."**

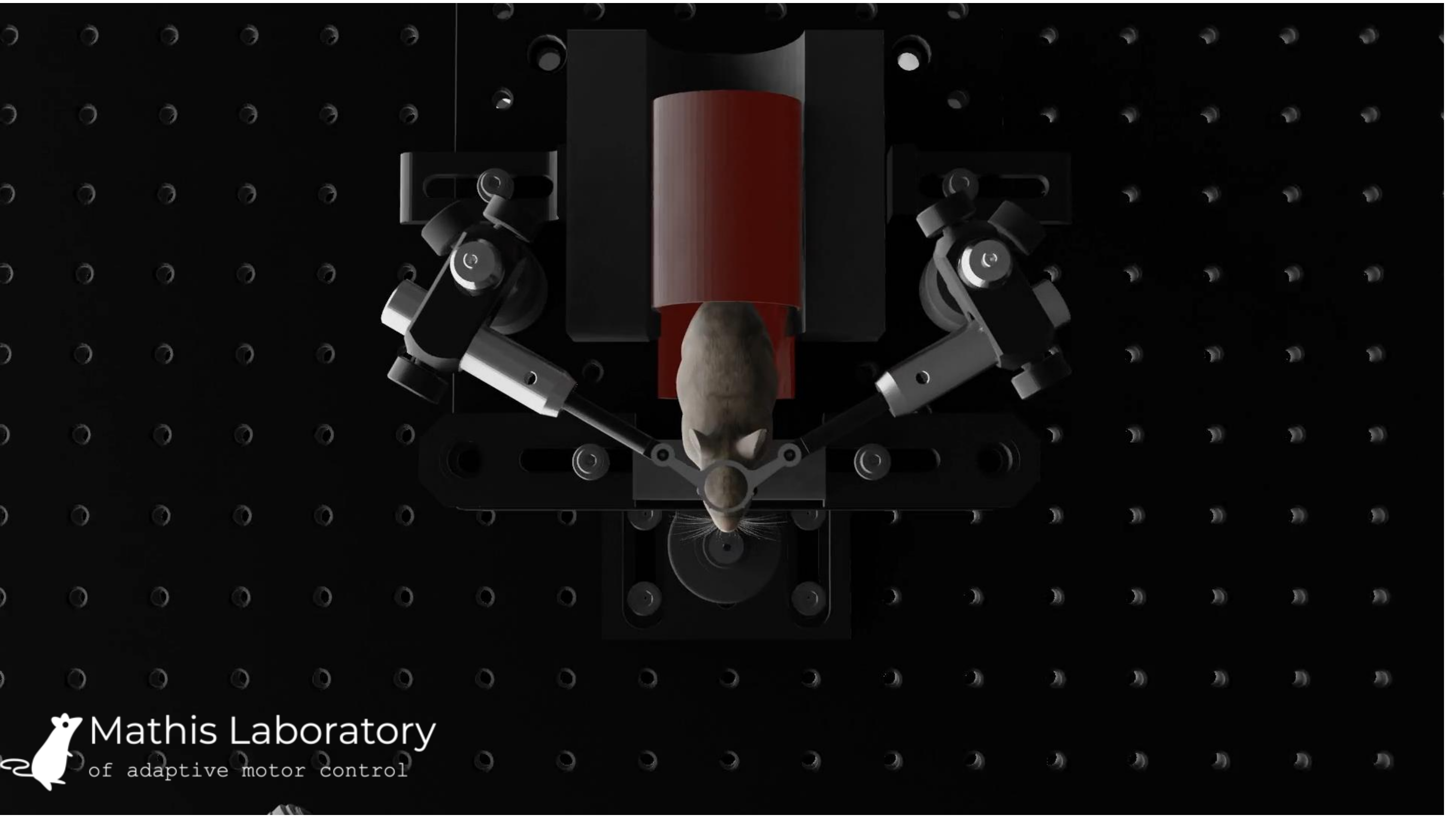
Interactions from cortex to the cerebellum: implications for motor learning



Adapted from Scott, 2004

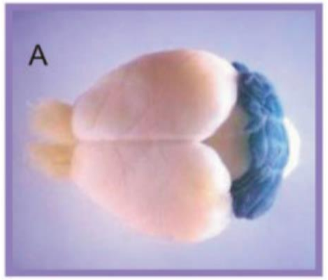


cerebellar inactivation impairs motor adaptation & control **in mice**

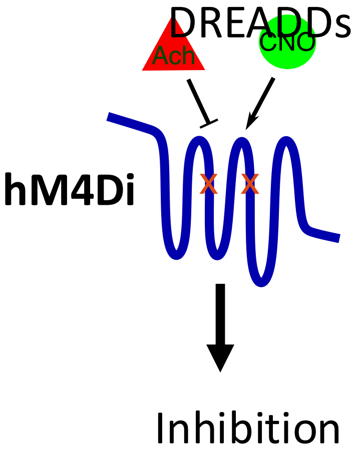


Mathis 2017

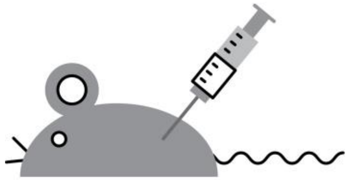
cerebellar inactivation impairs motor control **in mice**



Zhang et al, 2004

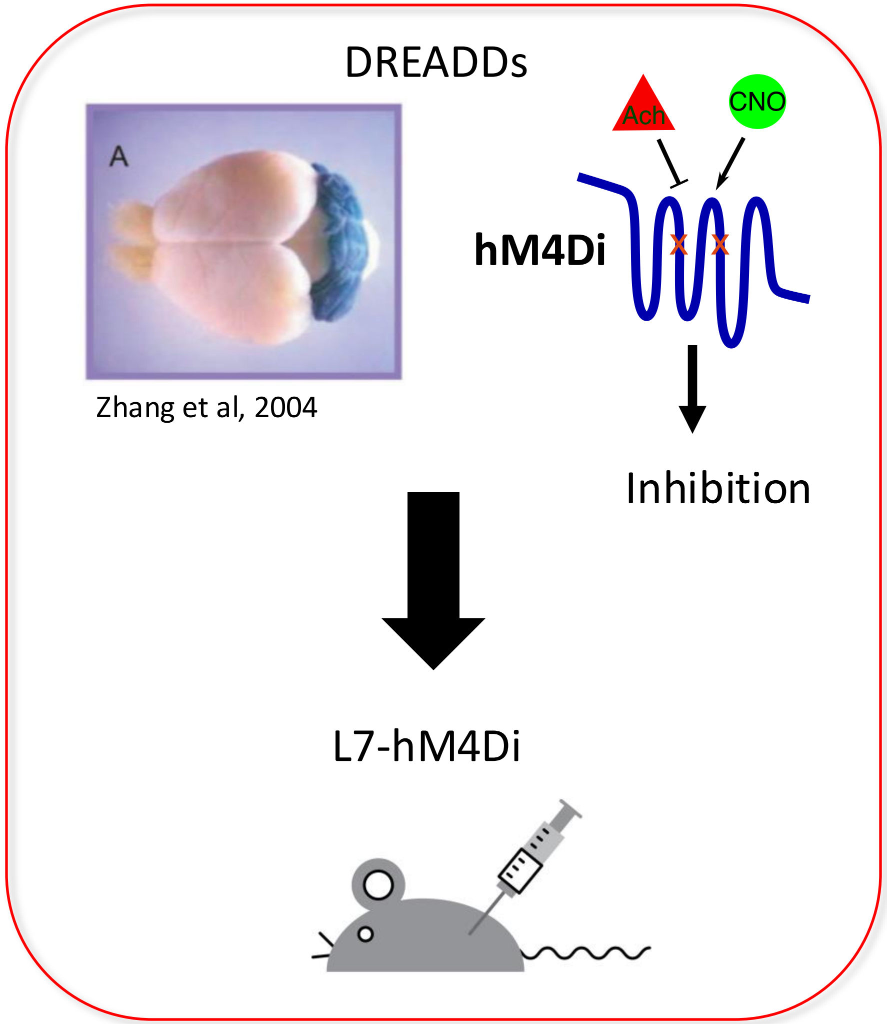


L7-hM4Di

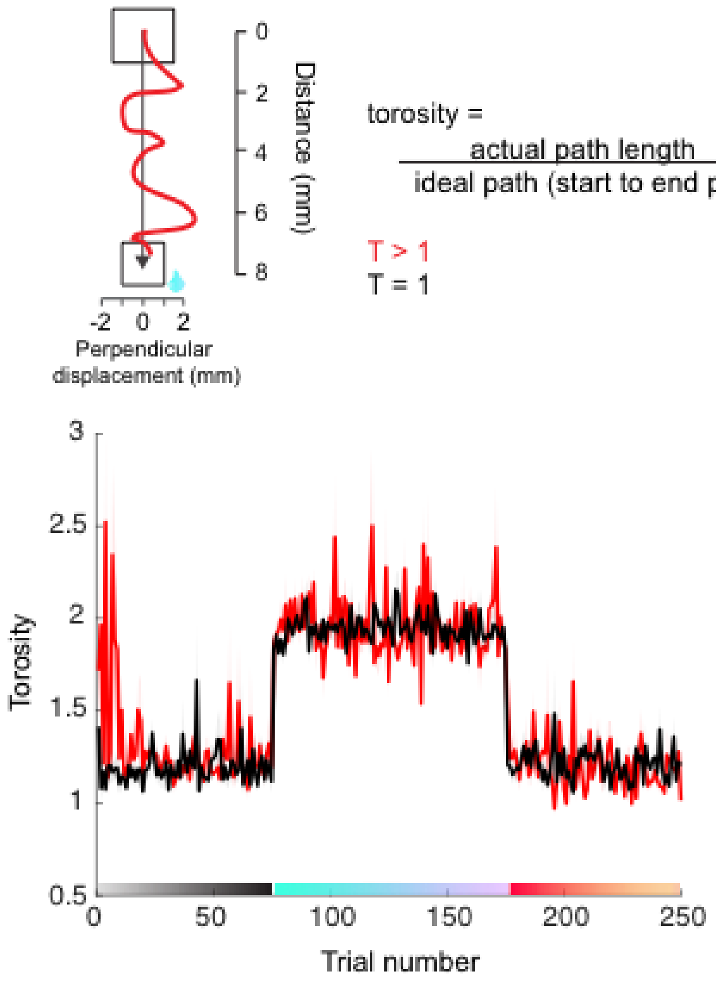


Credit: [THOMAS DEERINCK, NCMIR / SCIENCE PHOTO LIBRARY]

cerebellar inactivation impairs motor control **in mice**



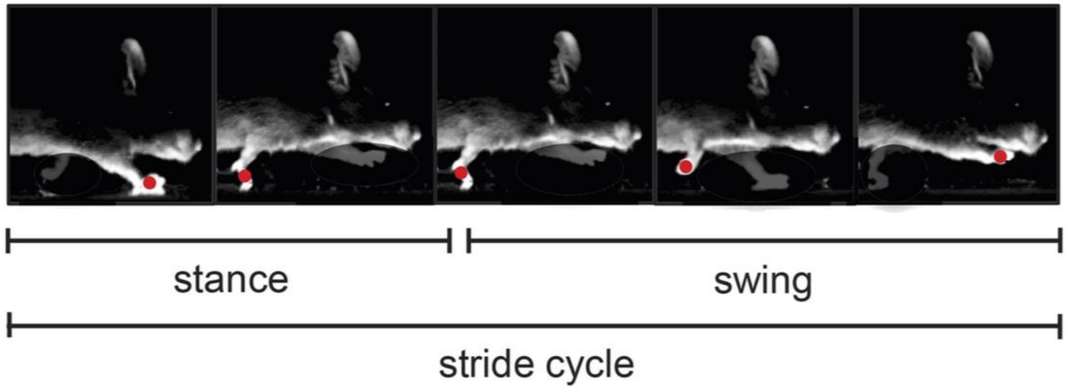
Motor Control

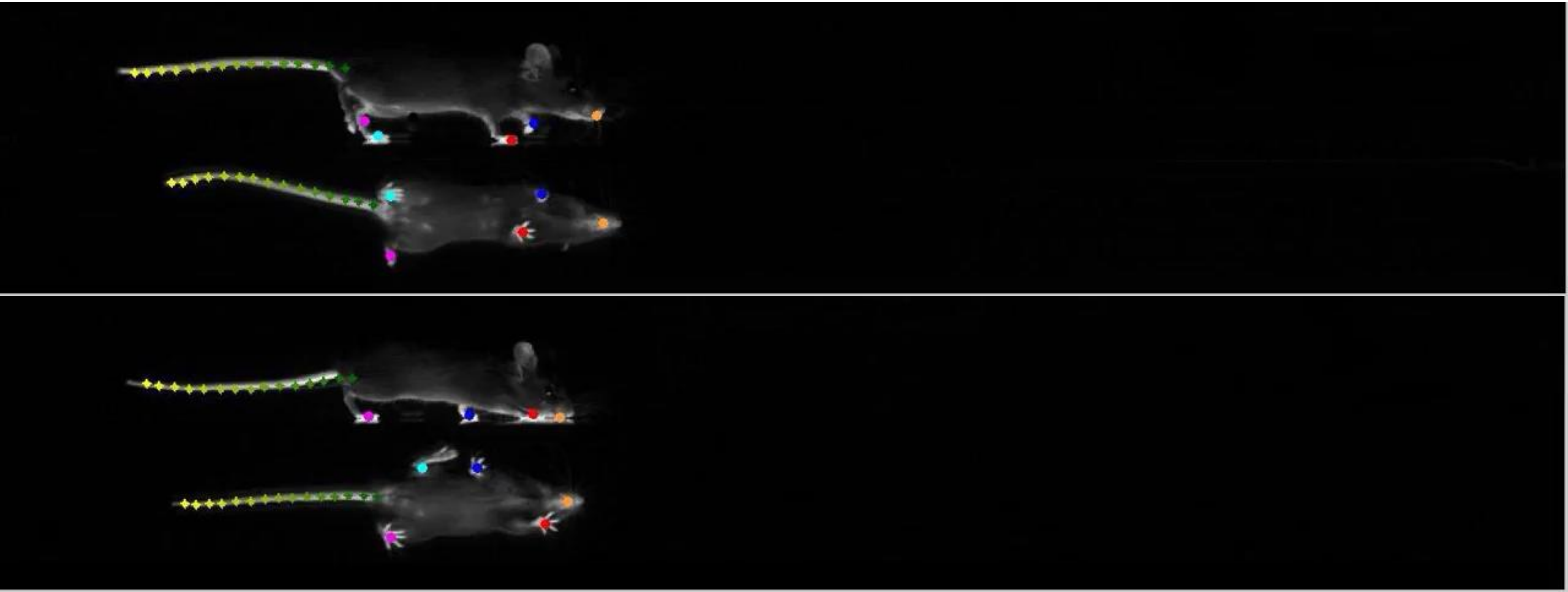


Mathis 2017

A quantitative framework for whole-body coordination reveals specific deficits in freely walking ataxic mice

Ana S Machado, Dana M Darmohray, João Fayad, Hugo G Marques, Megan R Carey





The cerebellum: identified genetic mutations that cause damage

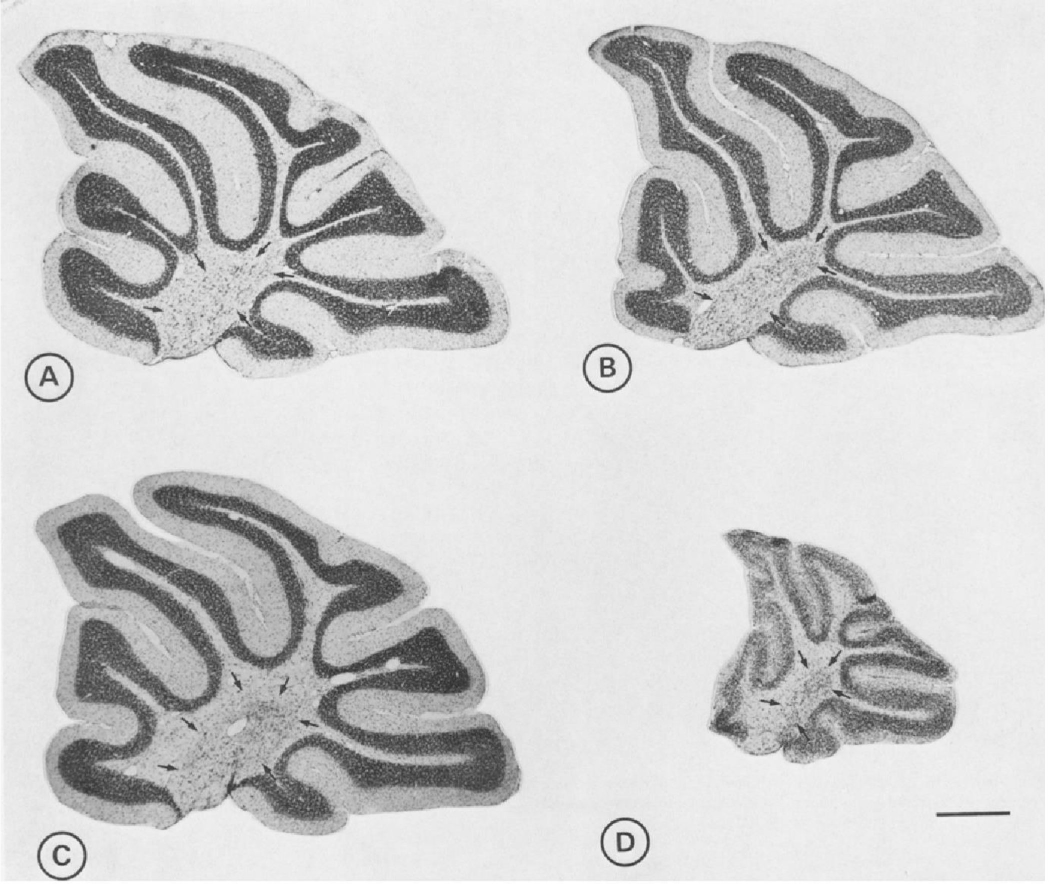


Fig. 3A–D. Low power light micrographs of the left cerebellar hemisphere cut parasagittally at 240 um from the medial beginning of the

A 23-day-old control, B 23-day-old mutant, C 300-day-old control, D 300-day-old mutant. Notice the severe cerebellar atrophy in the 300-day-old mutant.

Motor Mutations in Mice

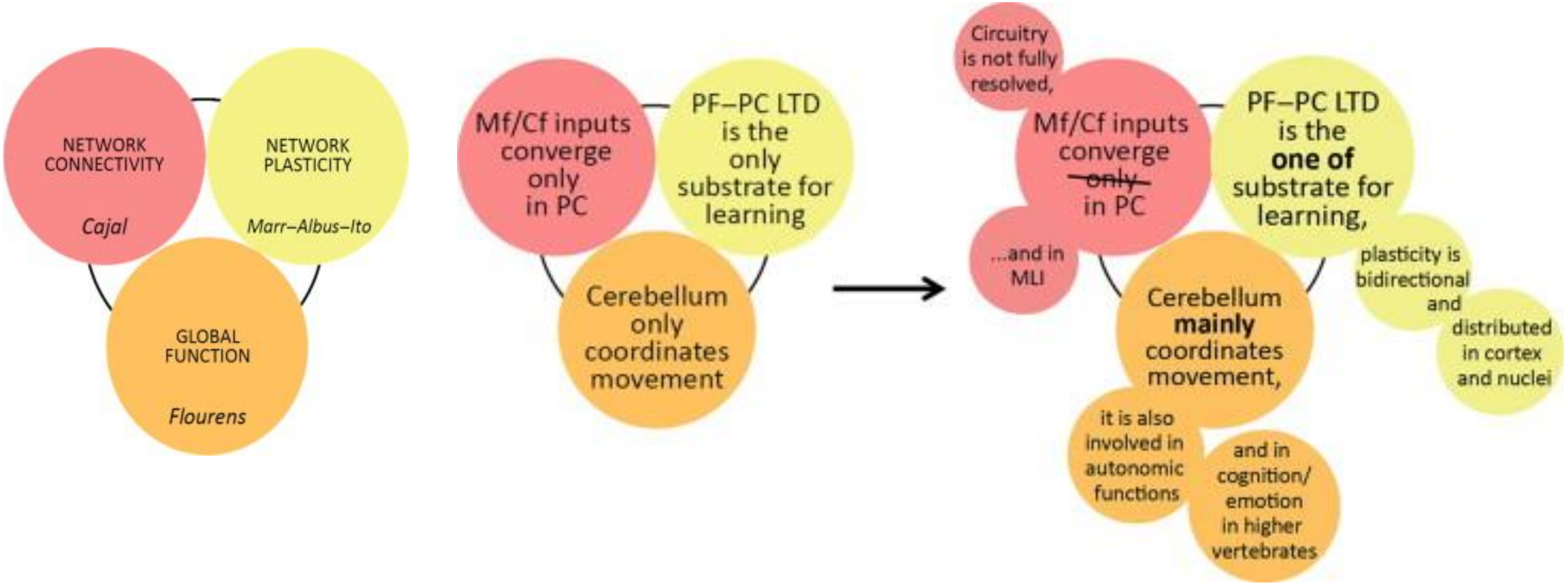
Mutation	Inheritance	Chromosome affected	Behavioral and morphological characteristics
reeler (rl)	Autosomal recessive	5	Reeling ataxia of gait, dystonic postures, and tremors. Systematic malposition of neuron classes in the forebrain and cerebellum. Small cerebellum, reduced number of granule cells.
weaver (wv)	Autosomal recessive	?	Ataxia, hypotonia, and tremor. Cerebellar cortex reduced in volume. Most cells of external granular layer degenerate prior to migration.
leaner (tg1a)	Autosomal recessive	8	Ataxia and hypotonia. Degeneration of granule cells, particularly in the anterior and nodular lobes of the cerebellum. Degeneration of a few Purkinje cells.
lurcher (lr)	Autosomal semi-dominant	6	Homozygote dies. Heterozygote is ataxic with hesitant, lurching gait and has seizures. Cerebellum half normal size; Purkinje cells degenerate; granule cells reduced in number.
nervous (nr)	Autosomal recessive	8	Hyperactivity and ataxia. Ninety percent of Purkinje cells die between 3 and 6 weeks of age.
Purkinje cell degeneration (pcd)	Autosomal recessive	13	Moderate ataxia. All Purkinje cells degenerate between the fifteenth embryonic day and third month of age.
staggerer (sg)	Autosomal recessive	9	Ataxia with tremors. Dendritic arbors of Purkinje cells are simple (few spines). No synapses of Purkinje cells with parallel fibers. Granule cells eventually degenerate.

Adapted from Caviness and Rakic, 1978.

Anterograde transsynaptic degeneration in the deep cerebellar nuclei of Purkinje cell degeneration (pcd) mutant mice

- L. Triarhou, J. Norton, B. Ghetti
- Published 2004

The cerebellum: an evolving understanding of it's role in the brain



Questioning the Cerebellar Doctrine

ElisaGalliano*[1] Chris I.De Zeeuw*[†]

Why do we have a brain?

Daniel Wolpert · Movement expert

https://www.ted.com/talks/daniel_wolpert_the_real_reason_for_brains?language=en

Take homes:

- Neuroanatomy from cortex to spinal cord
- Four systems make essential and distinct contributions to motor control
- Spinal cord: dorsal, ventral, rostral caudal → proximal vs. distal innervation: also "home" to central pattern generator circuit
- Motor pools and genetic diversity of motor neuron types
- neuro-muscular junction: acetylcholine
- Alpha, gamma motor neurons
- The motor Unit! one alpha MN→ the muscle fibers it innervates. Three types!

Consider how this whole system is involved in lifting a glass of water … (could you draw and explain this?)

- The cerebellum receives input from regions of the cerebral cortex that plan and initiate complex and highly skilled movements; ***it also receives input from sensory systems that monitor the course of movements.***
- Cerebellar damage or genetic mutations cause ataxia, other movement disorders
- Purkinje neuron is principle output neuron of the cerebellum
- Motor errors are a critical role for this circuit: from learning to rapid adaptation
- Organization of the cerebellar circuit: the 4 big ones: granule cell, Purkinje cell, parallel fibers, basket cell
- Many open questions still remain!