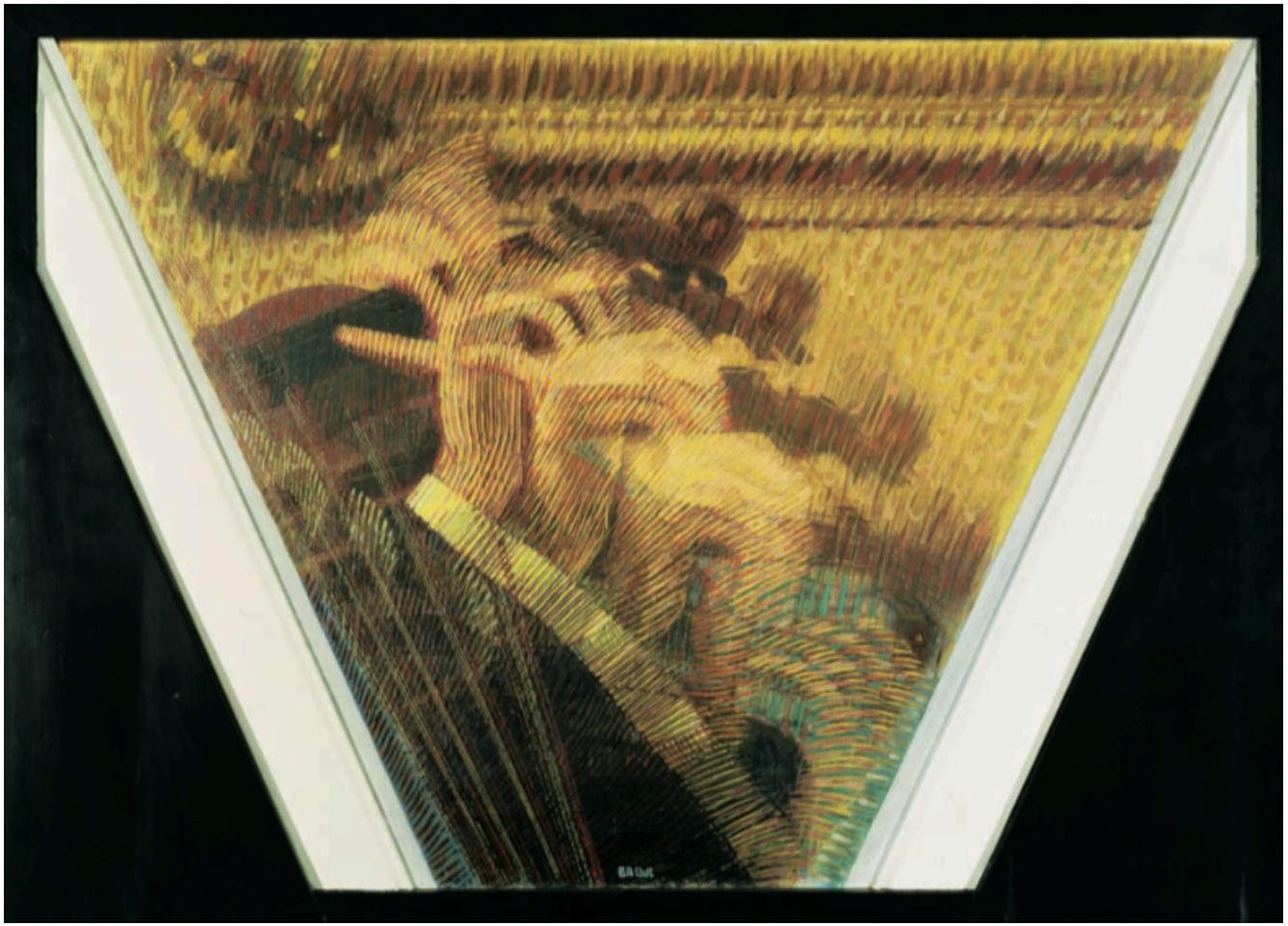
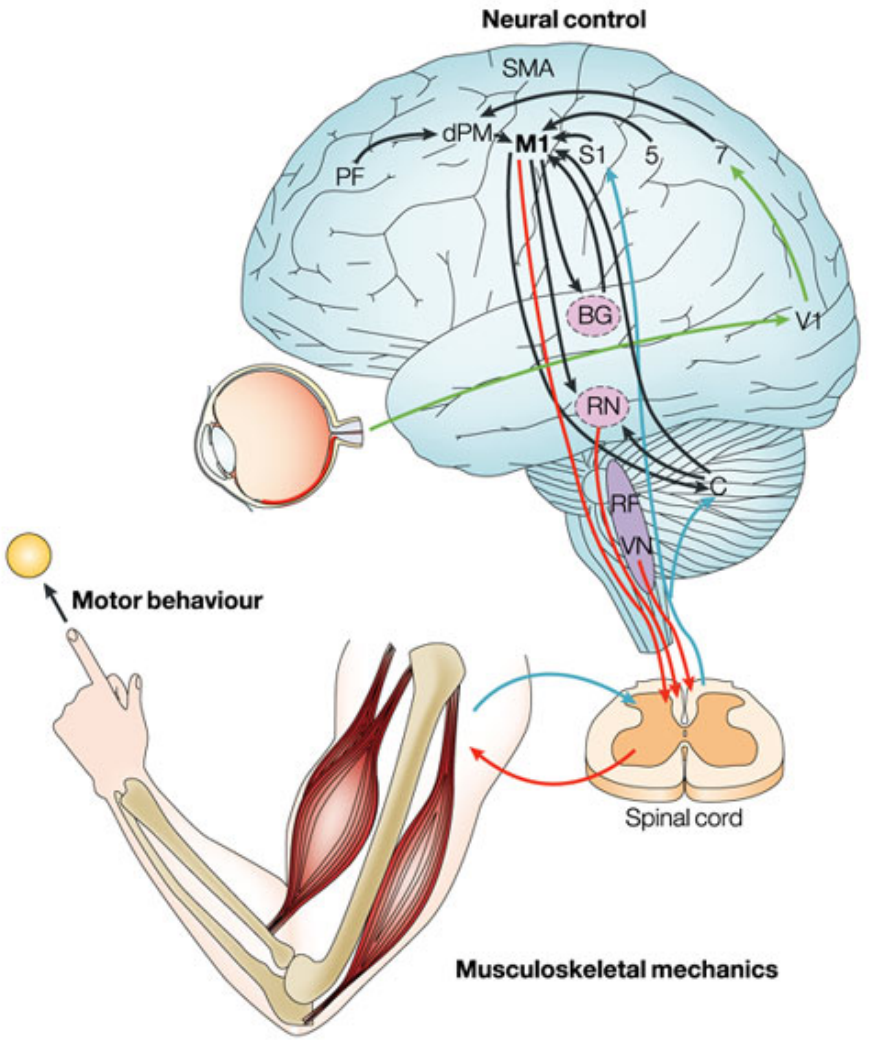
Movement



Brain areas involved in moving

Coordination of sensory information with desired movements

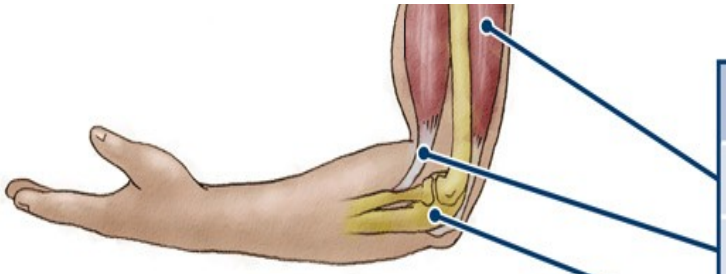
- SENSORIMOTOR



Scott, 2004

Nature Reviews | Neuroscience

Certain sensory receptors (proprioceptors) report movement and body location



Proprioception (body awareness)	Adaptation
Muscle spindles (muscle stretch)	Rapid
Golgi tendon organs (tendon stretch)	Rapid
Joint receptors (joint movement)	Rapid

Movements stretch the receptors to mechanically stimulate the dendrites within them to produce action potentials.

Kolb and Whishaw, 2005

Proprioception (body awareness)

- specialized receptors that give position of muscles, as well as tendon stretch and joint movement

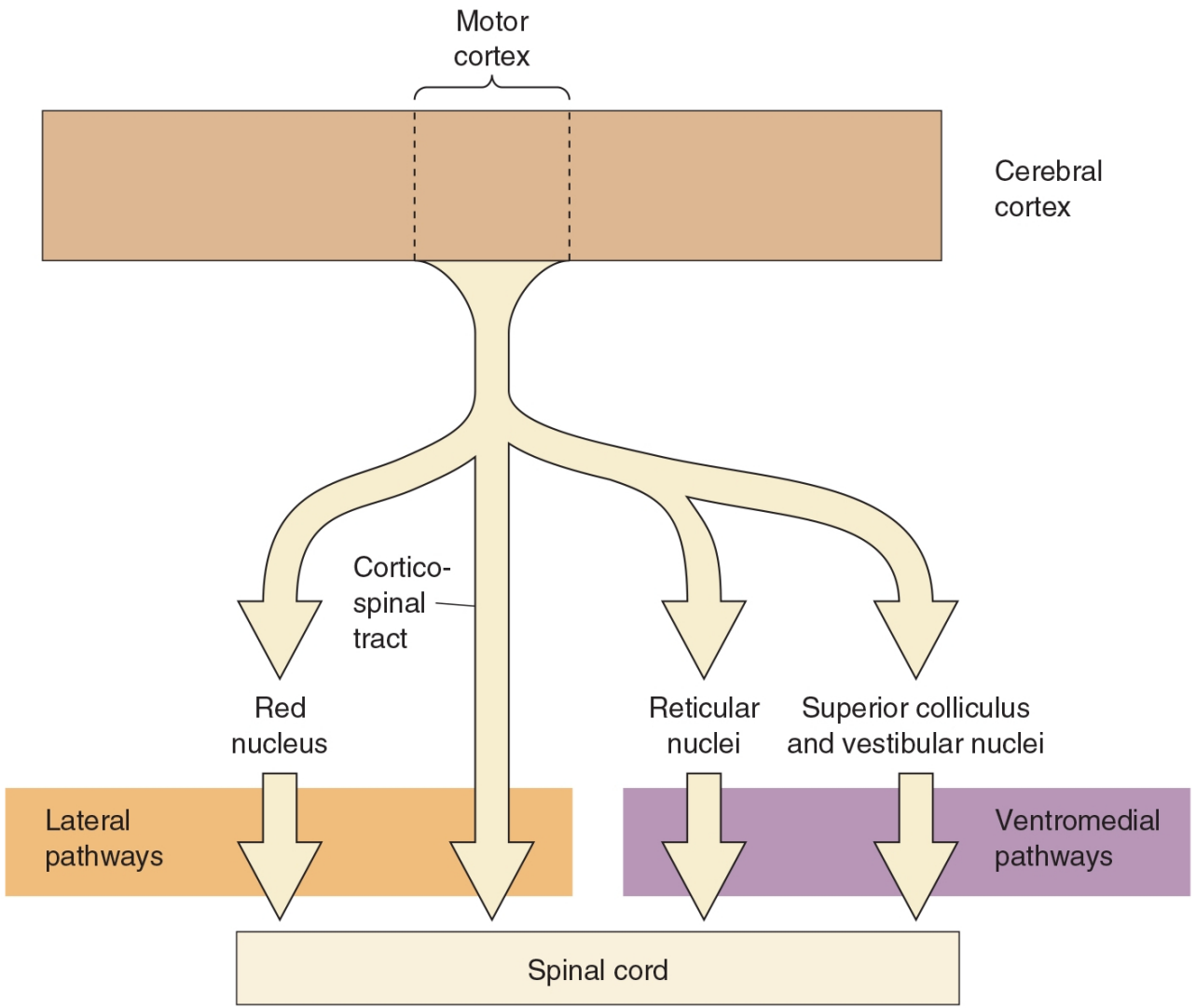
Critical when planning voluntary movements

- what position is my body in right now and what movements are possible?

The brain influences activity in the spinal cord to control movement in the periphery

Stage 1: Strategy --- “Ready”
Stage 2: Tactics --- “Set”
Stage 3: Execution --- “Go”

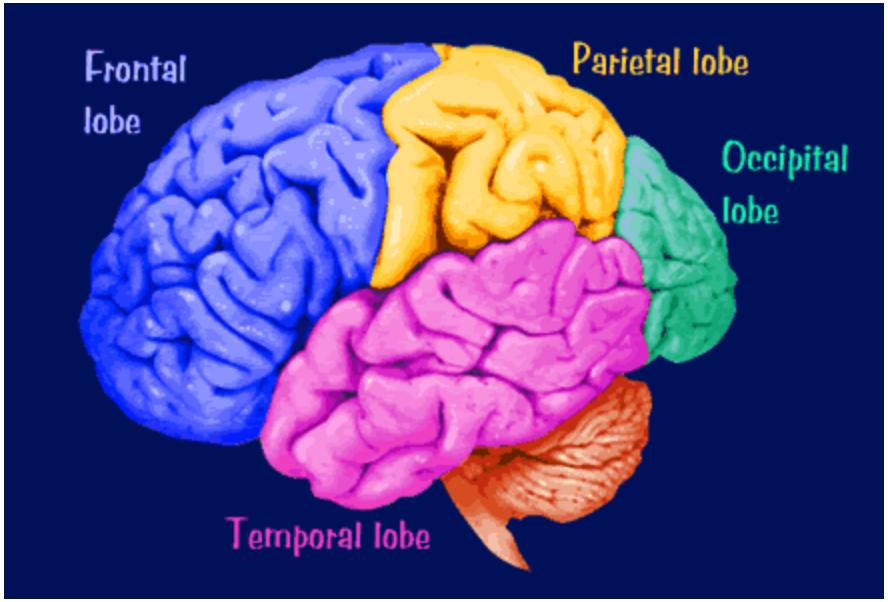
Motor Pathways
(from the brain to the spinal cord)



Cortical areas involved in movement

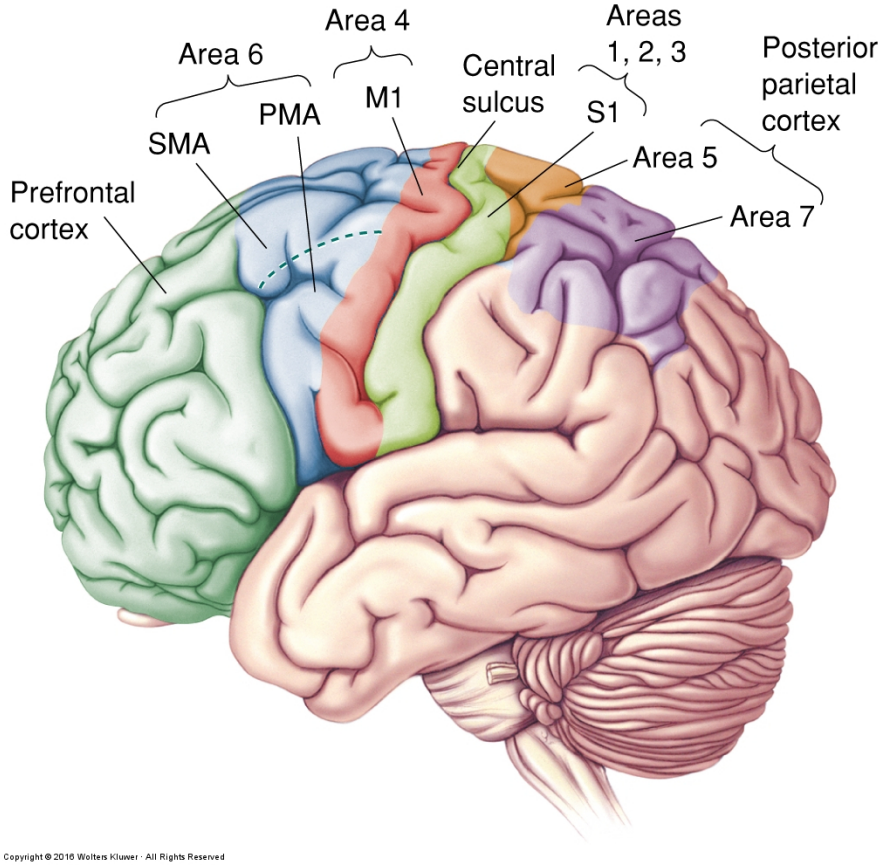
Voluntary control of movement engages just about every area of cortex

Movement depends on knowledge about body position, where it intends to go, selection/storage of a plan, the execution of the plan



Cortical areas involved in movement

- Posterior parietal cortex
  - Mental body image generated by sensory inputs into this area
  - Connects to the Prefrontal Cortex
- Prefrontal cortex
  - Abstract thought, decision making
- Together: Highest levels of motor control

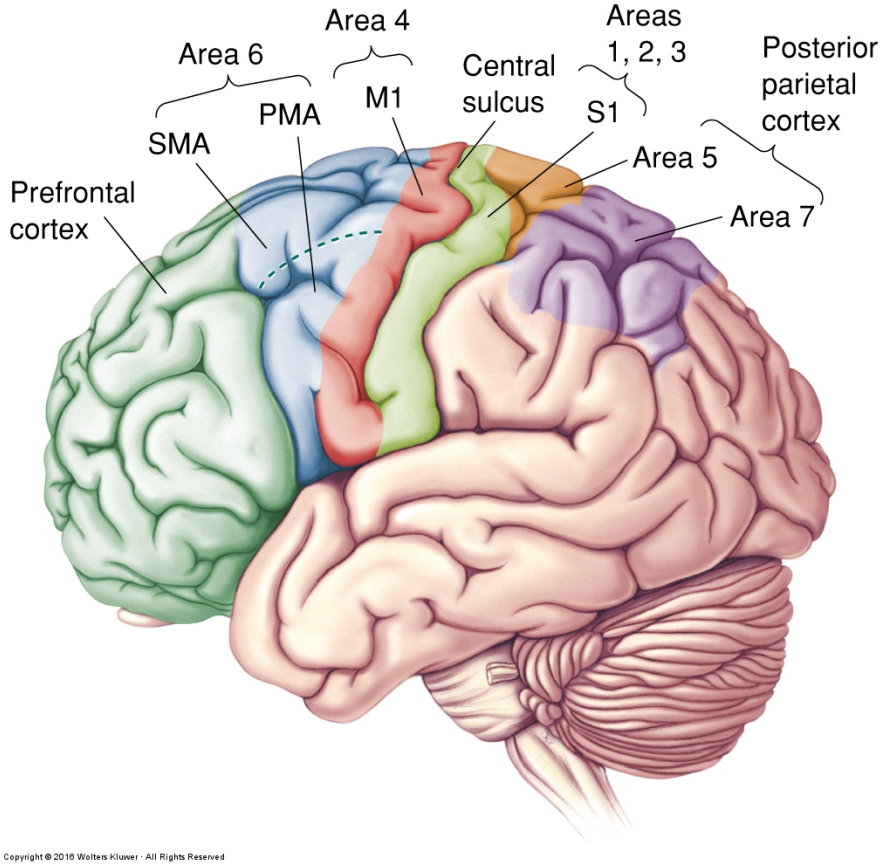


The "planners"

Cortical areas involved in movement

- Posterior parietal cortex & Prefronta cortex communicate with **Area 6** (premotor cortex)
  - Premotor area and supplementary mot area
  - Similar functions; different groups of muscles controlled

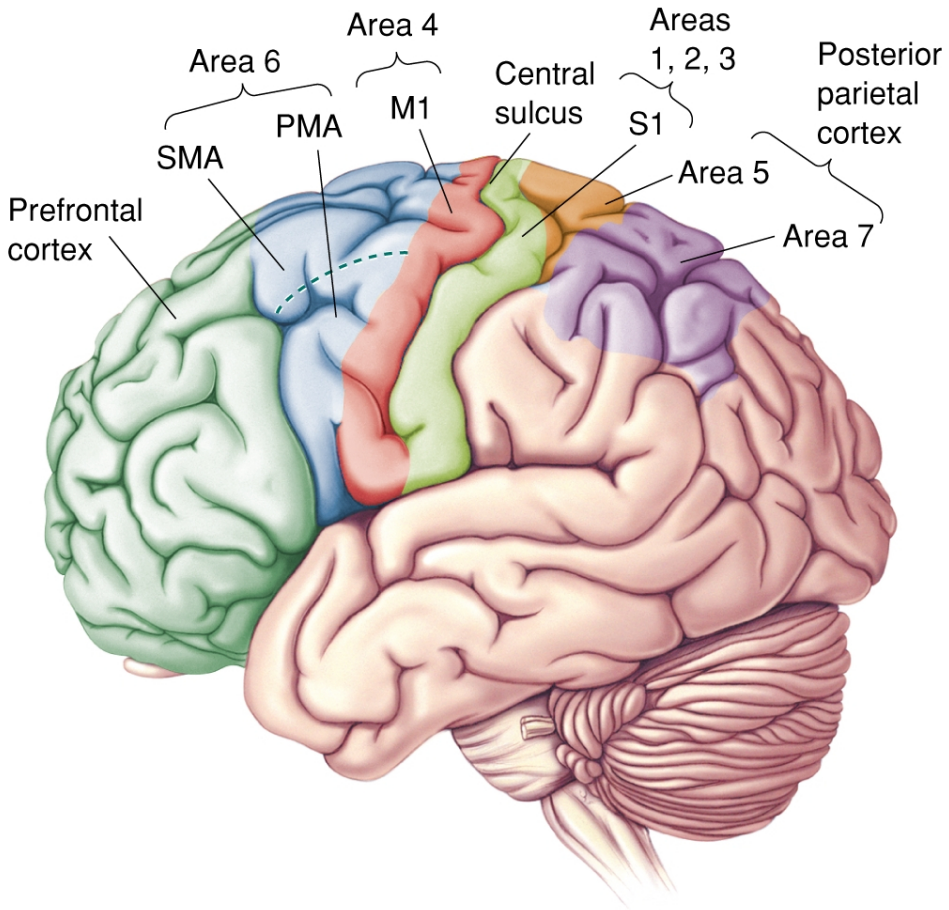
Area 6 is at the interface where desired action is converted into signals that specify **how** the action will be carried out.



The region calls up the "tactics"

Cortical areas involved in movement

Area 6 (pre-motor cortex) then communicates with area 4 (primary motor cortex = M1) of the frontal lobe

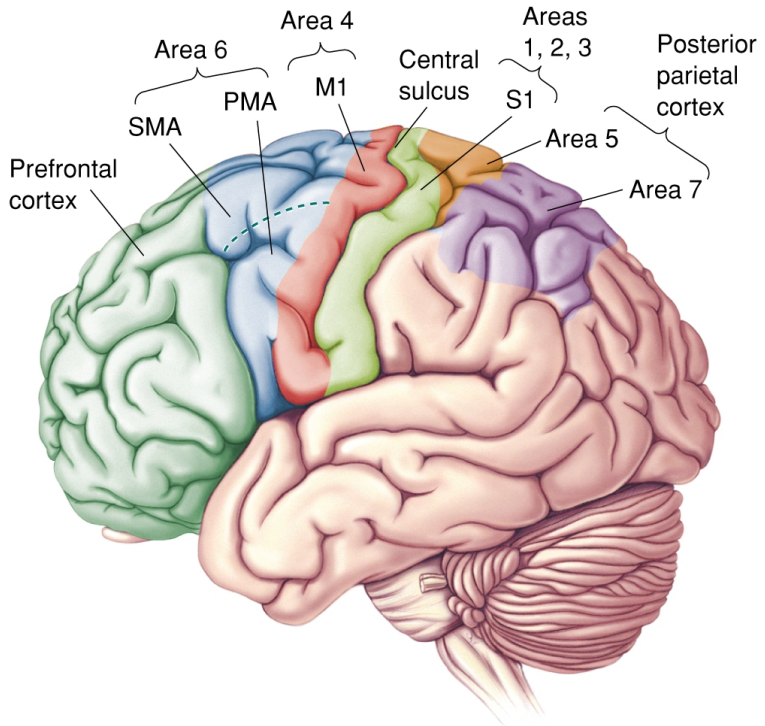


Primary motor cortex

Receives the motor selections from premotor cortex

Sends chosen movement commands to the appropriate levels of spinal cord

- most movements require both action commands and postural muscle changes



Summary: Cortical areas involved in movement

Prefrontal cortex (w/posterior parietal): ***plan*** (“ready”)

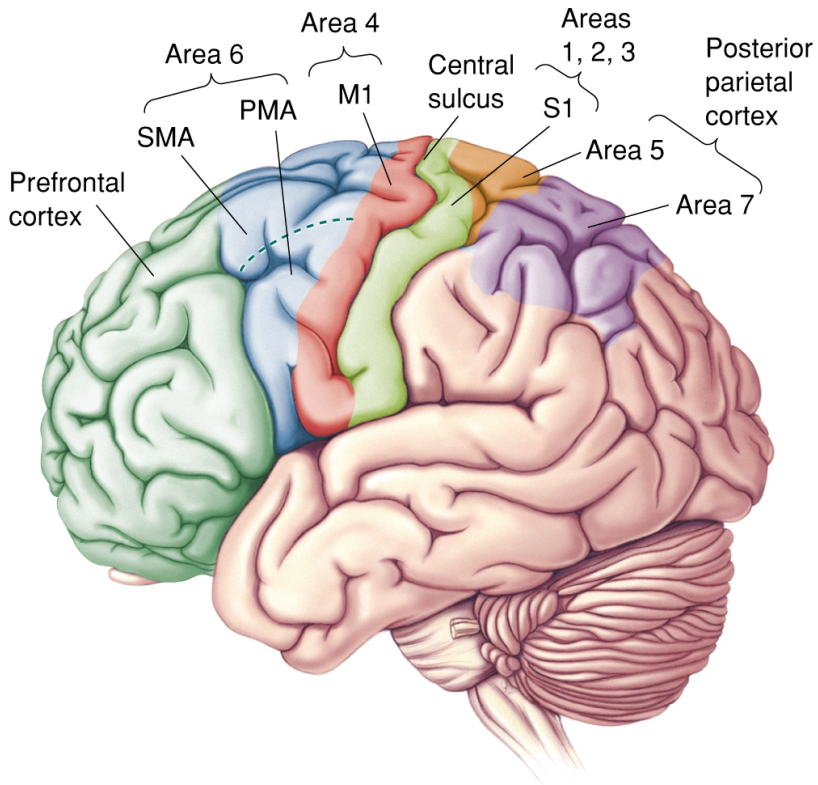
- the CEO with a goal

Premotor cortex (Area 6): ***sequence*** (“set”)

- the plant supervisor creates a strategy

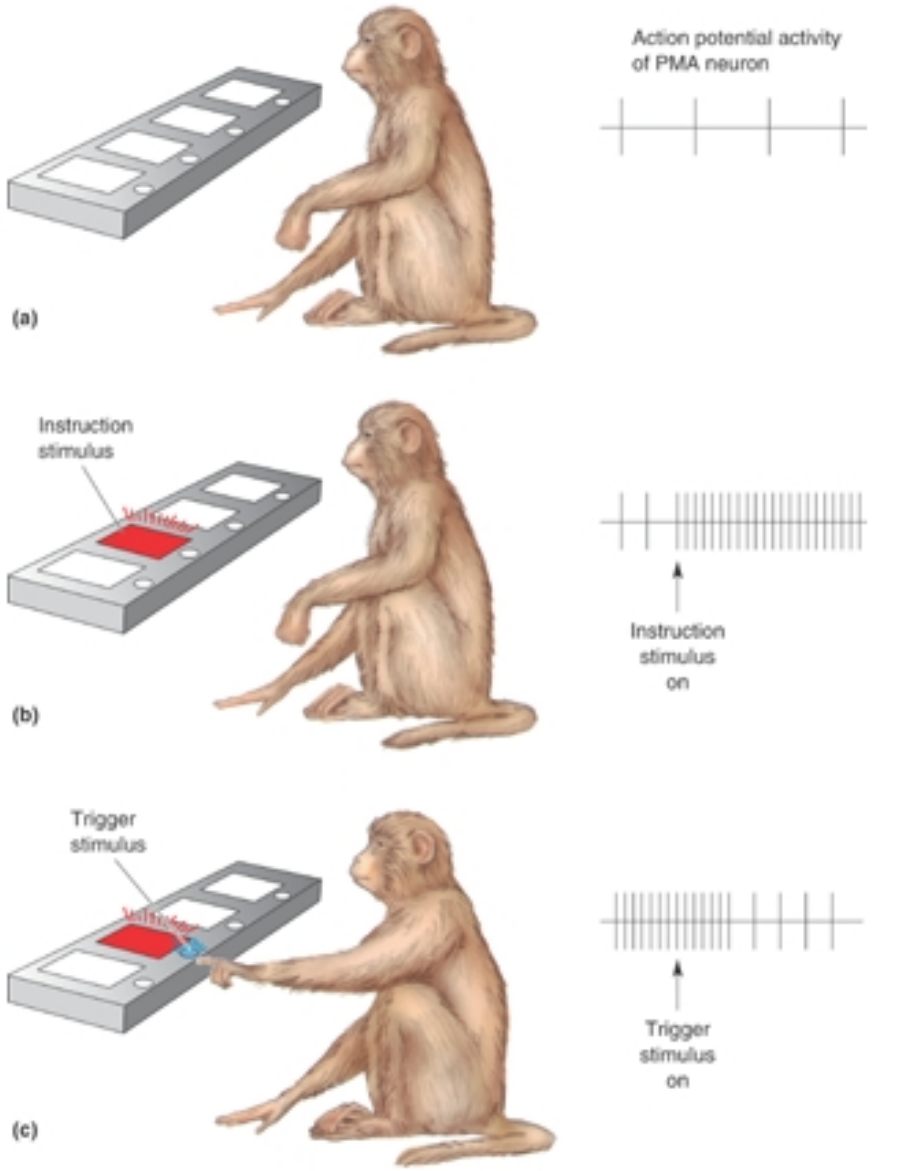
Motor cortex: ***execution*** (“go”)

- the assembly line workers create specific actions



Electrical recordings provide evidence for cortical involvement in movement

Firing in PMA before movement



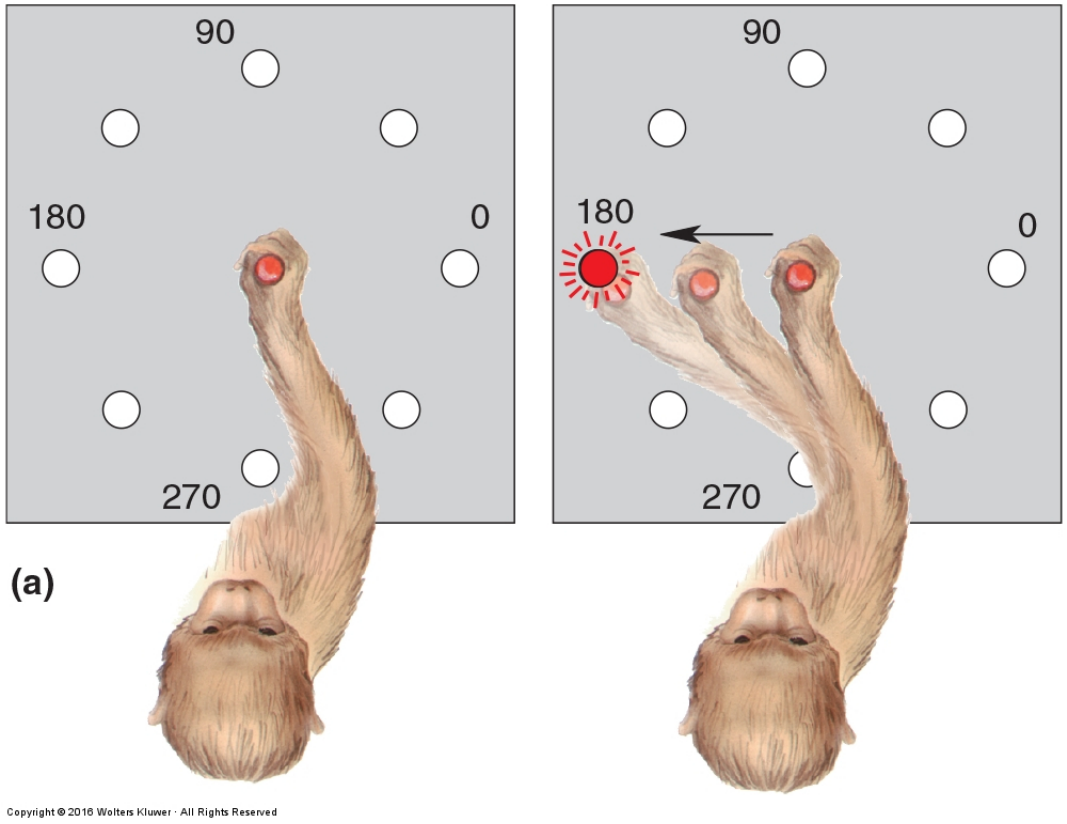
Can do similar experiments with M1 neurons

Neuronal firing of M1 neurons correlates with direction

Record from M1 arm neurons

Train monkey to move the lever in different directions

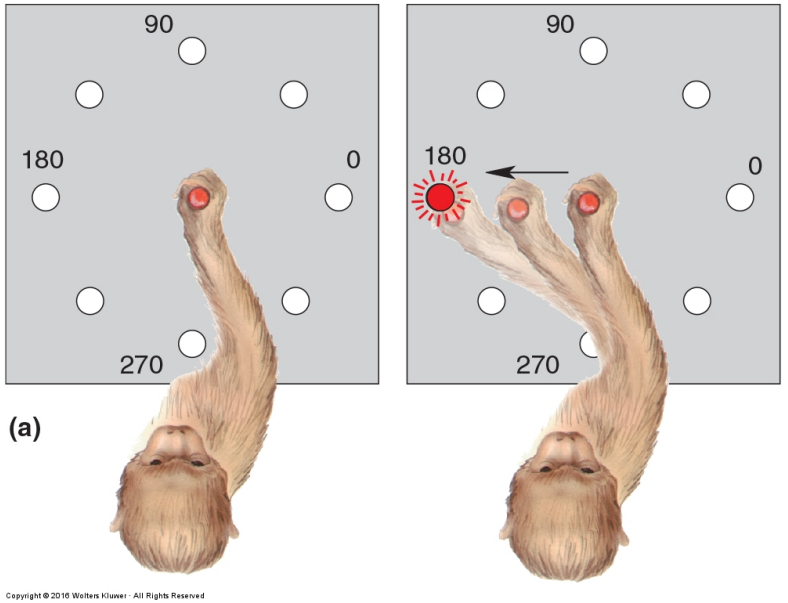
– does firing of M1 hand-sensitive neurons correlate to the direction of movement?

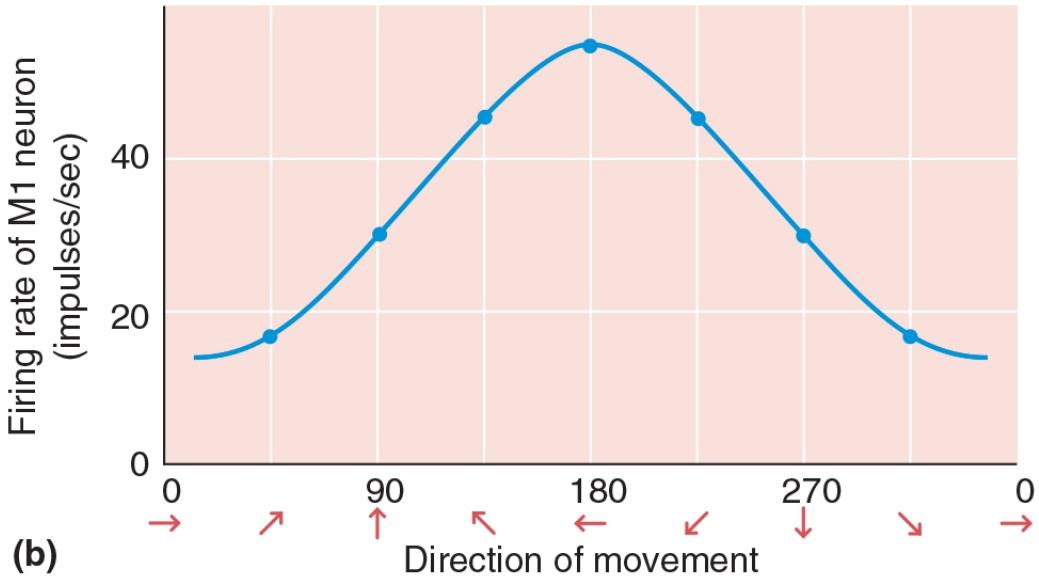


Direction sensitive M1 neurons

M1 neurons have direction preference

- here, neuronal firing is maximal when moving forward

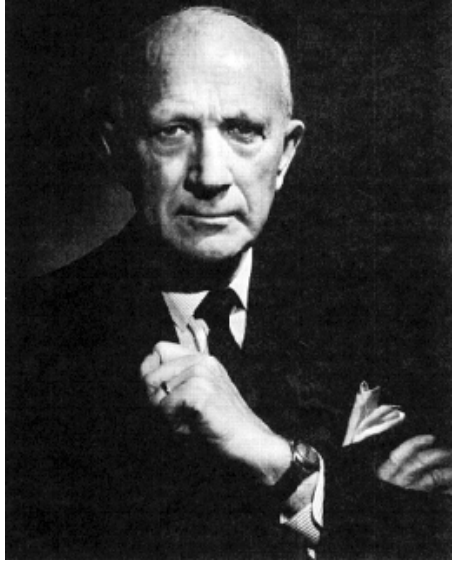




Cortical mapping

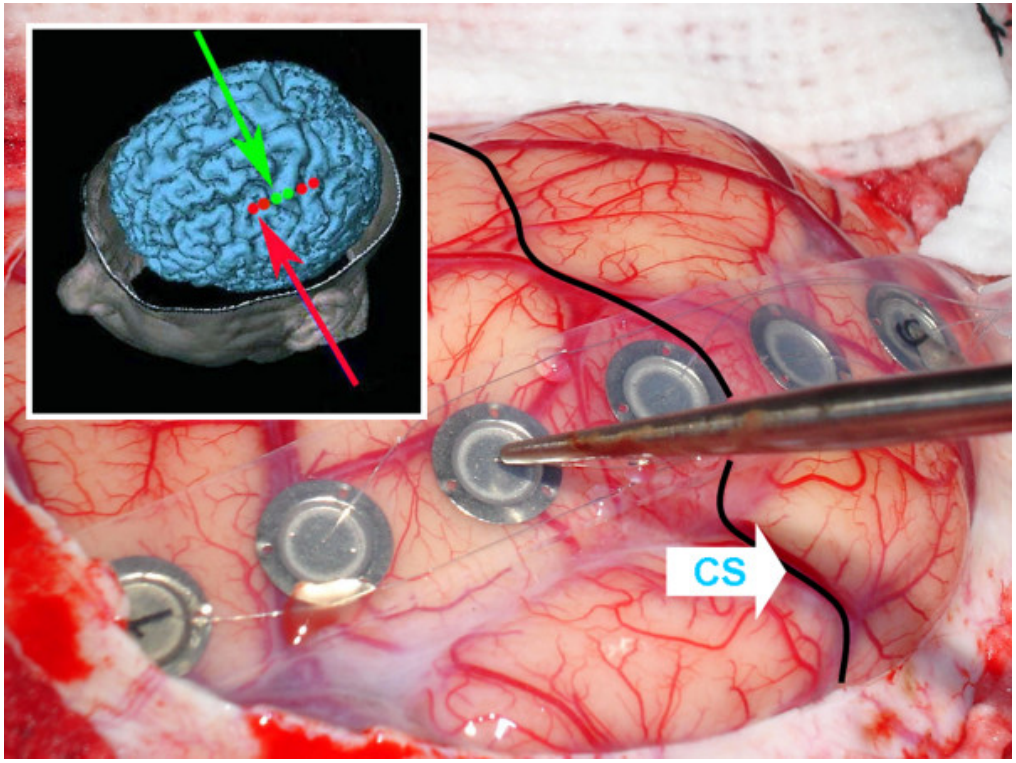
Electrical stimulation of small cortical areas

- Penfield mapped the motor and sensory cortices, as well as other functional areas

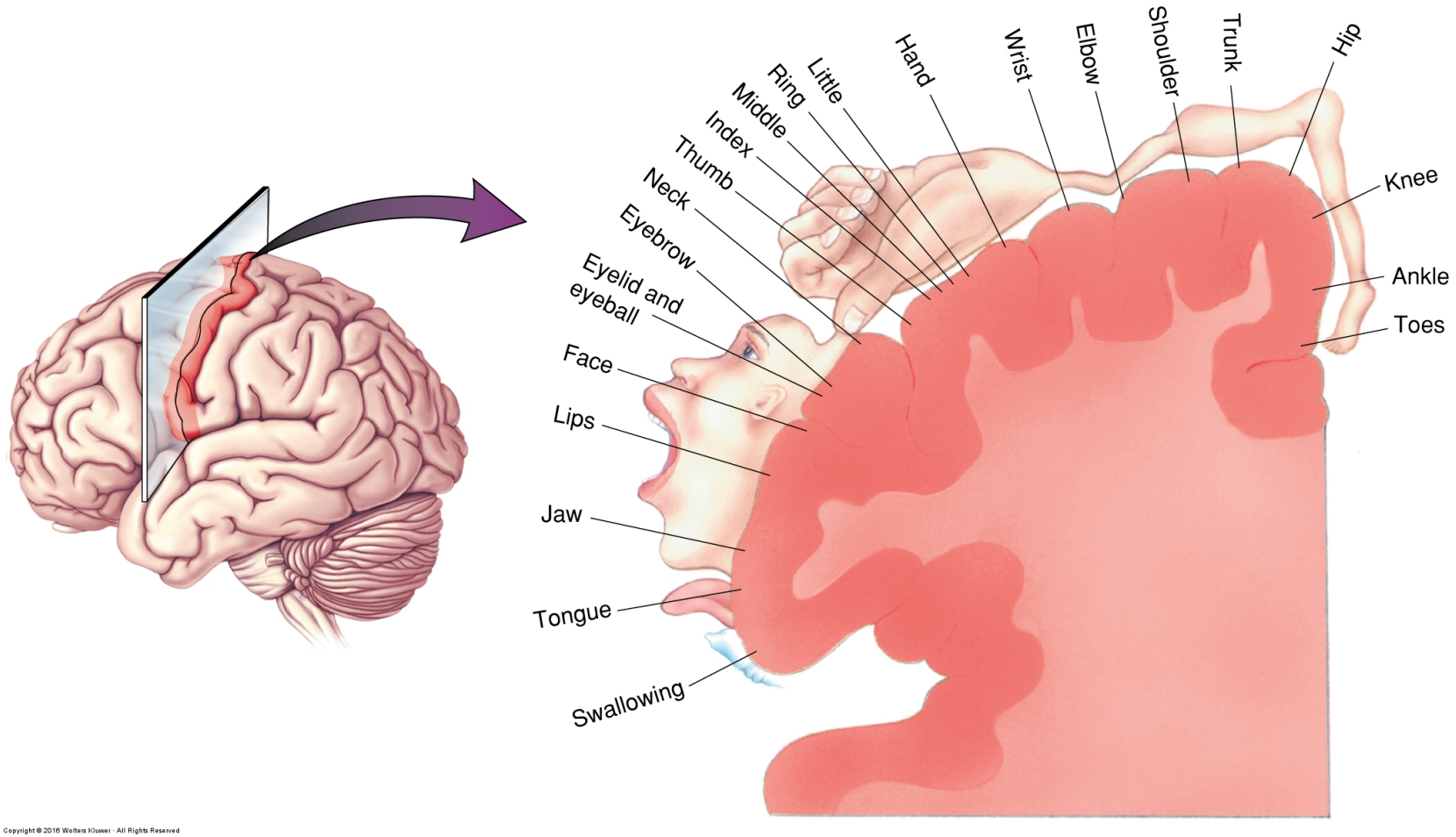


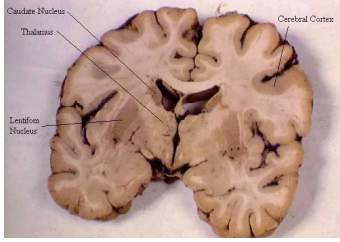
Wilder Penfield

Important for preserving areas from destruction during brain surgery

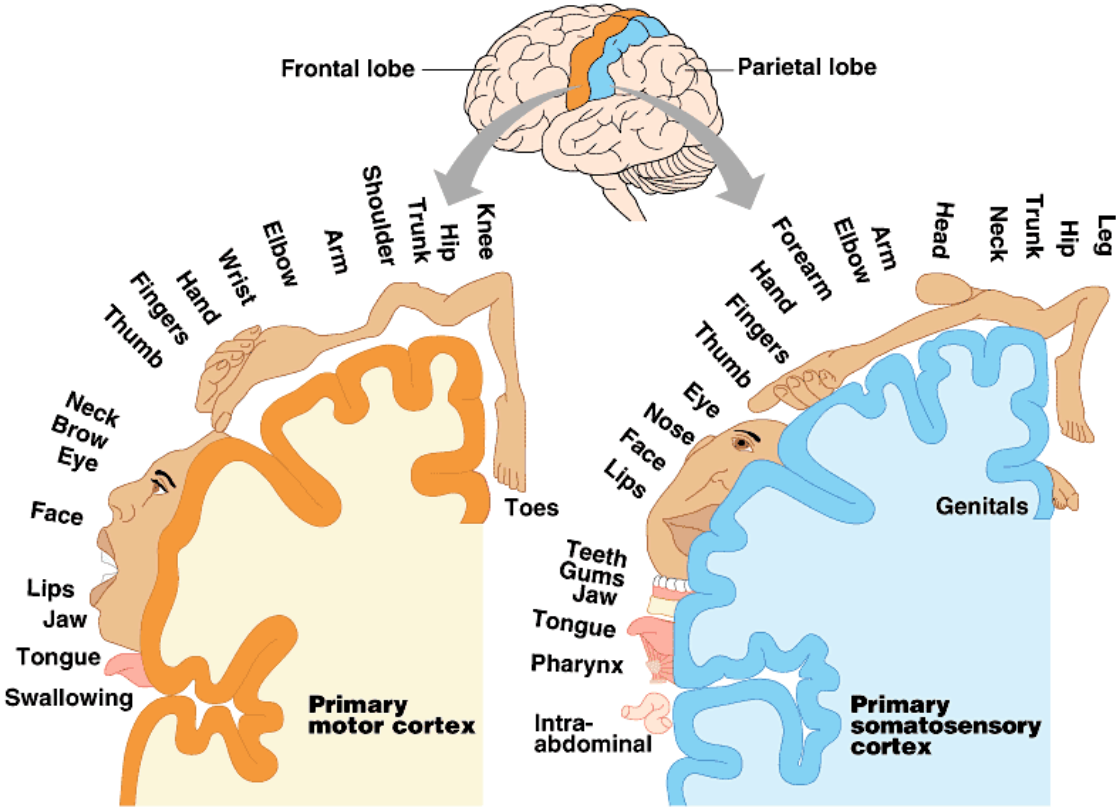


Motor homunculus





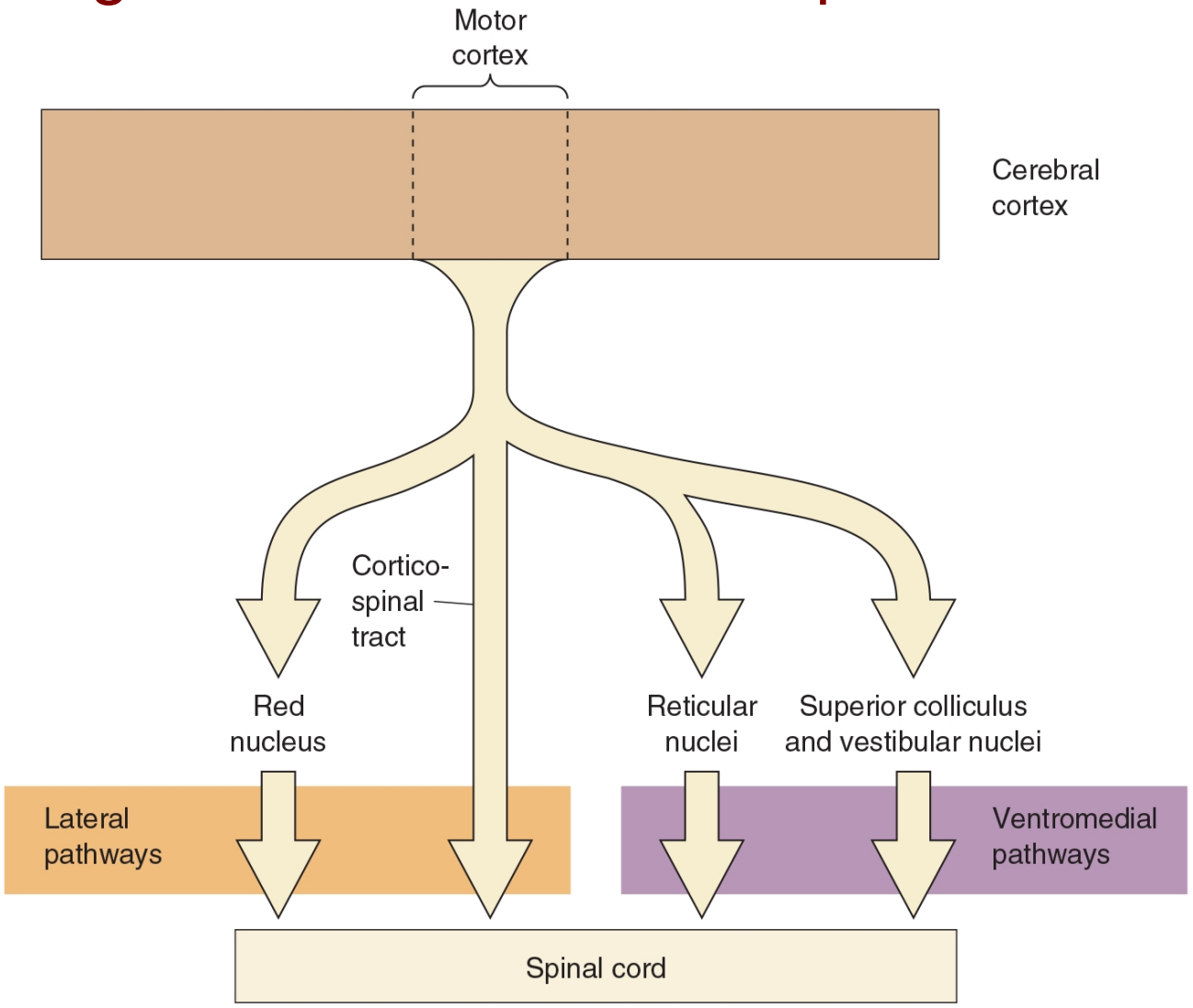
Comparing homunculi



SIMILARITIES: large face and hand (esp. finger) regions in both: small trunk regions

DIFFERENCES: sensation (teeth, organs) without voluntary muscles; motor (swallowing) without much sensory input

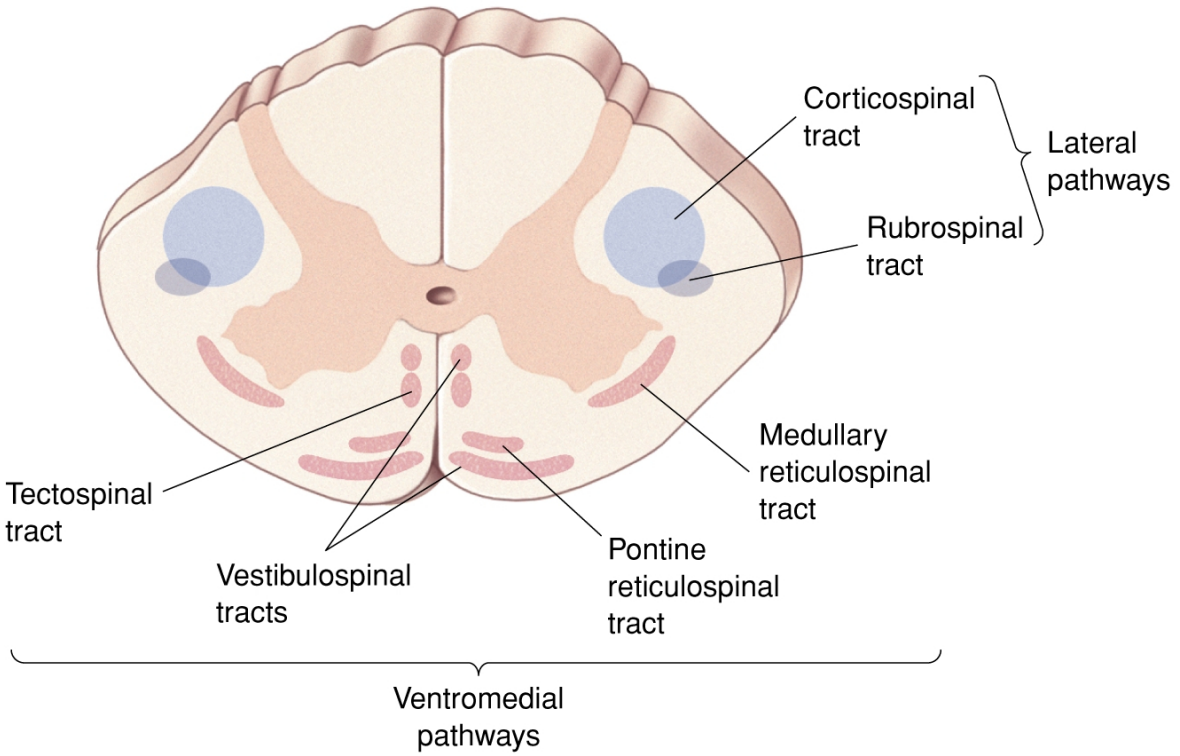
Going from the brain to the spinal cord



Lateral versus ventromedial pathways down the spinal cord

LATERAL PATHWAYS: control distal muscles

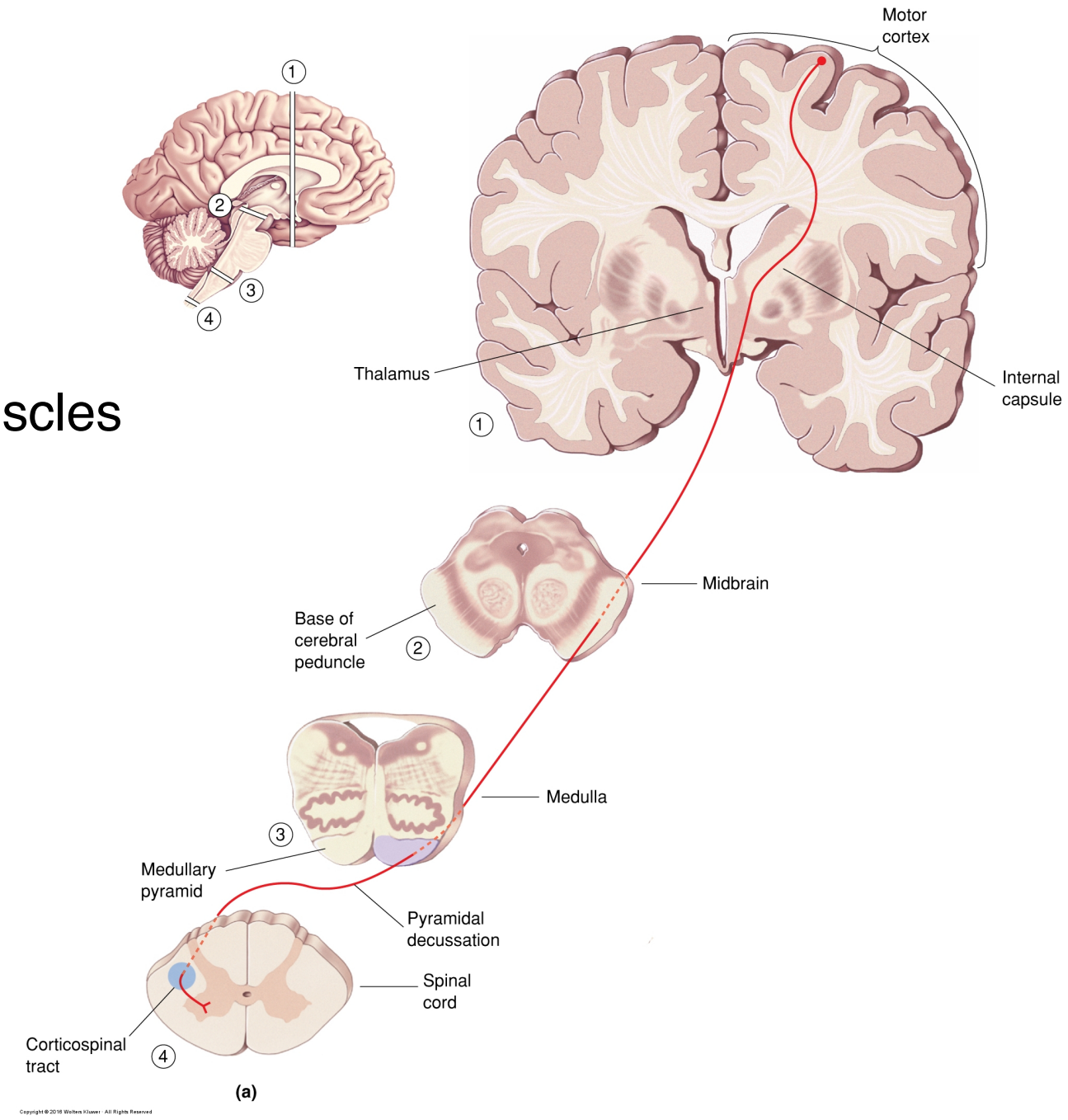
VENTROMEDIALPATHWAYS: control posture, midline



Lateral pathways

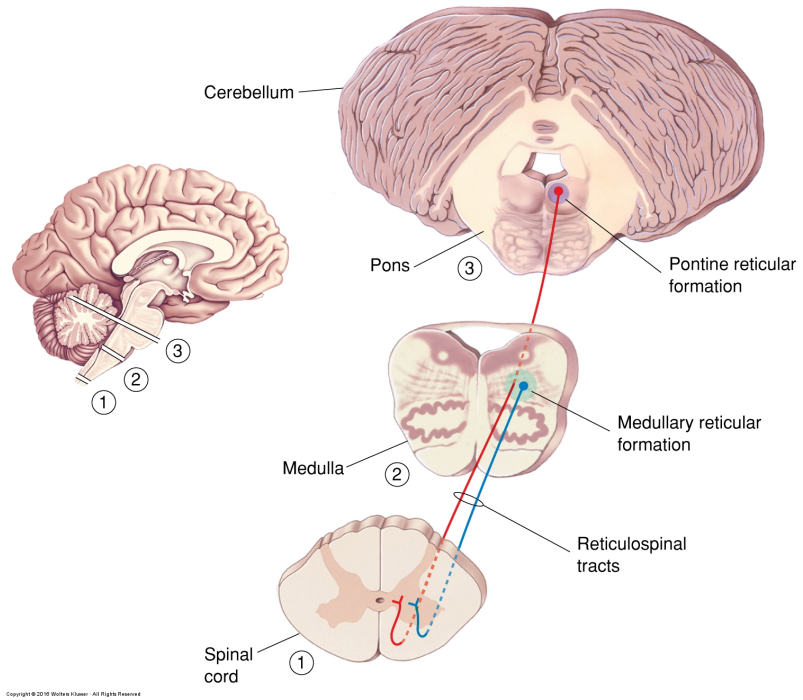
Controls distal muscles

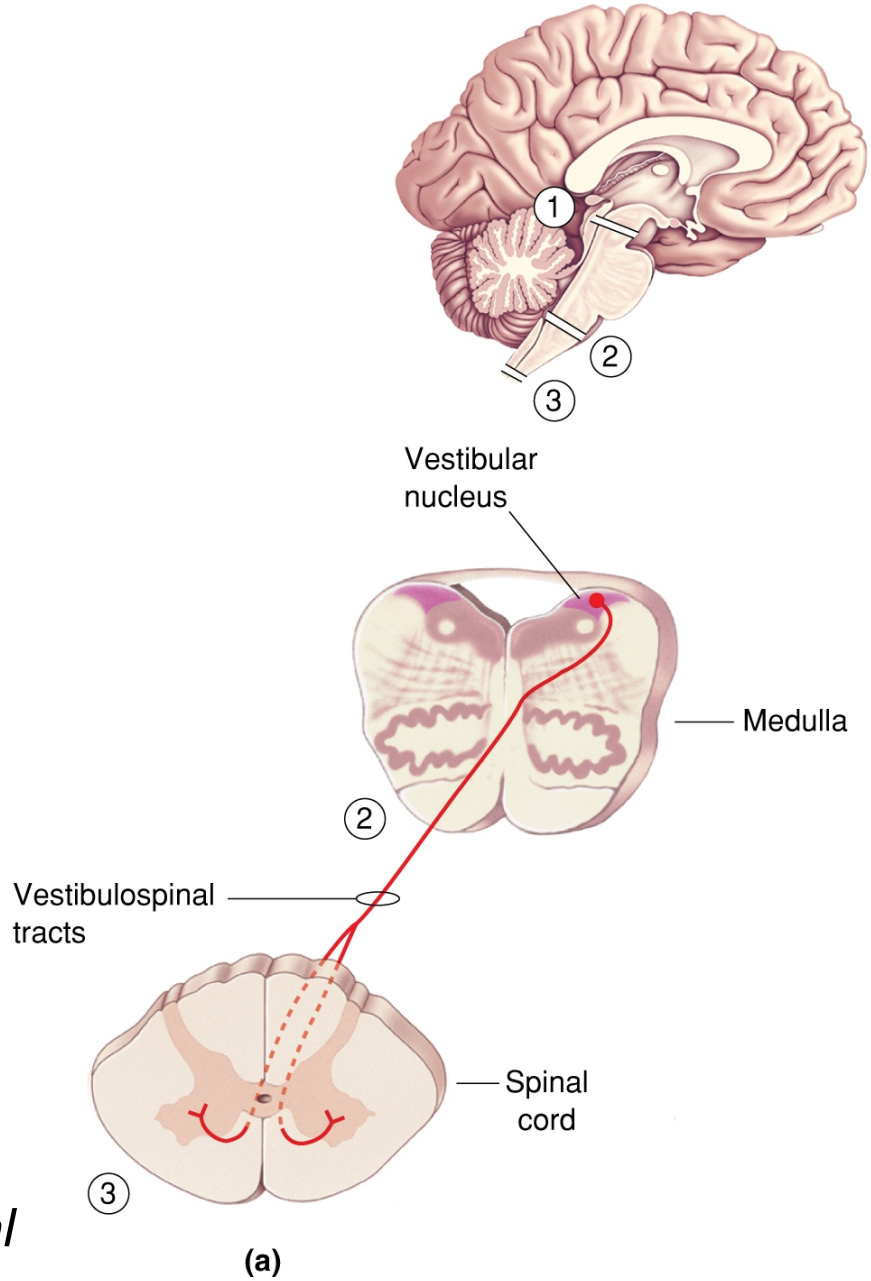
Notice that the information crosses over (contralateral)



Ventromedial pathways

Control posture, midline





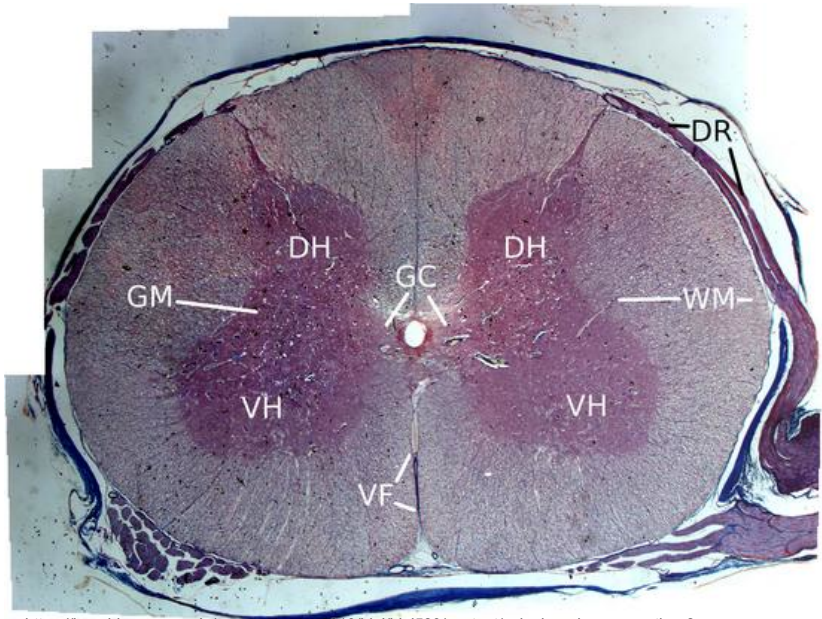
Different pathways control different muscle groups. Notice that some of the information crosses over to the contralateral side; some stays ipsilateral

Spinal motor neurons

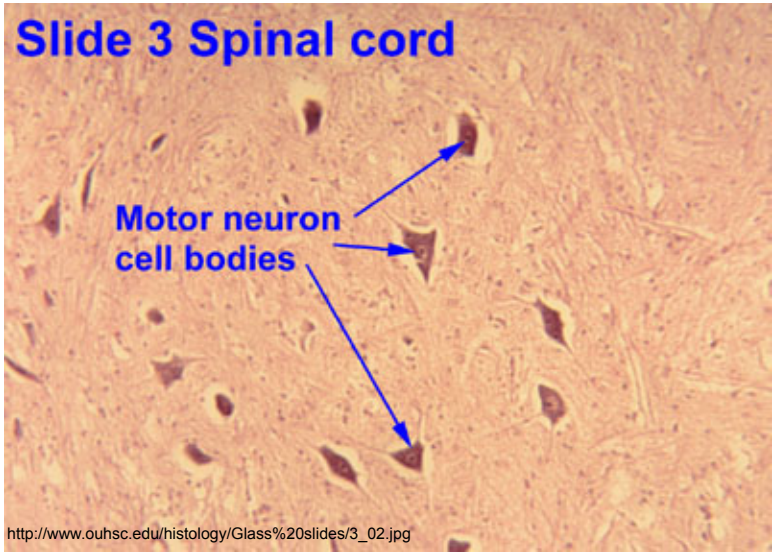
Motor neurons lie in the ventral horn (gray matter) of the spinal cord (VH in the image)

Motor neurons send their axons to muscle fibers forming the neuromuscular junction (NMJ)

- Motor neurons are some of the biggest neurons in the CNS (cell bodies ~70 μm)

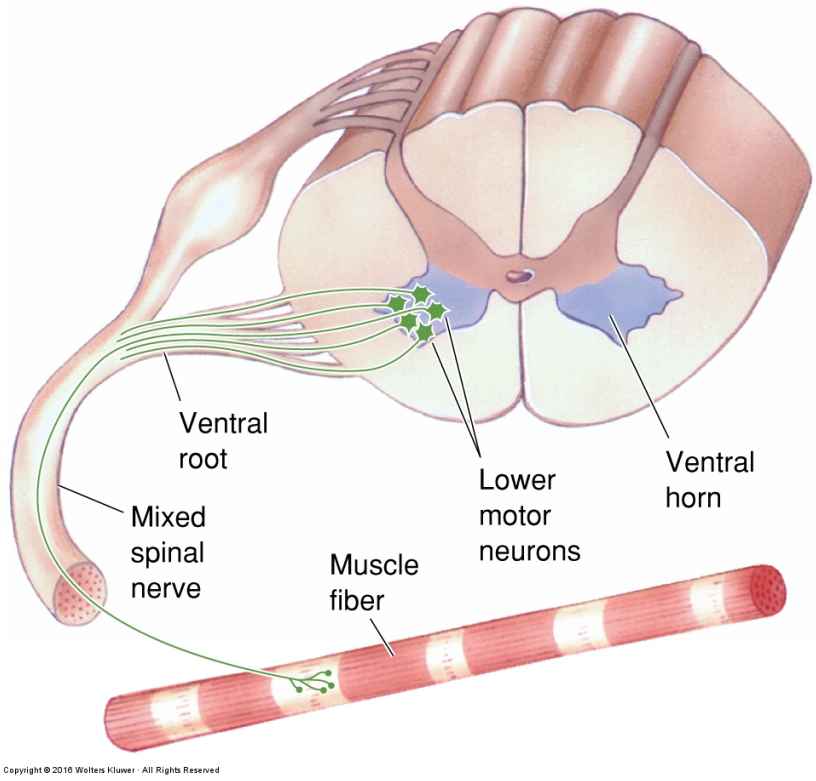


https://bcrc.bio.umass.edu/courses/spring2013/biol/biol523/content/spinal-cord-cross-section-2x

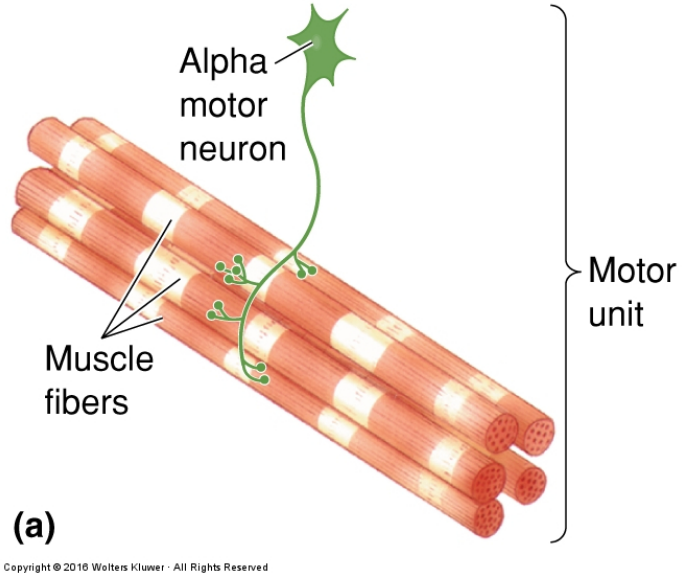


http://www.ouhsc.edu/histology/Glass%20slides/3_02.jpg

Motor neuronal control of muscles



www.nku.edu/~dempseyd/bio208pg8.htm



- Highly myelinated and large axons (fast connection from spinal cord to muscles)
- Release vesicles with ACh (acetylcholine) that causes the muscle fiber to contract
  - coordinated release from many neurons cause movements of the entire muscle

Neuromuscular junction (NMJ) is a cholinergic synapse

Acetylcholine (ACh)

- made from acetate & choline

One of the best studied transmitter system

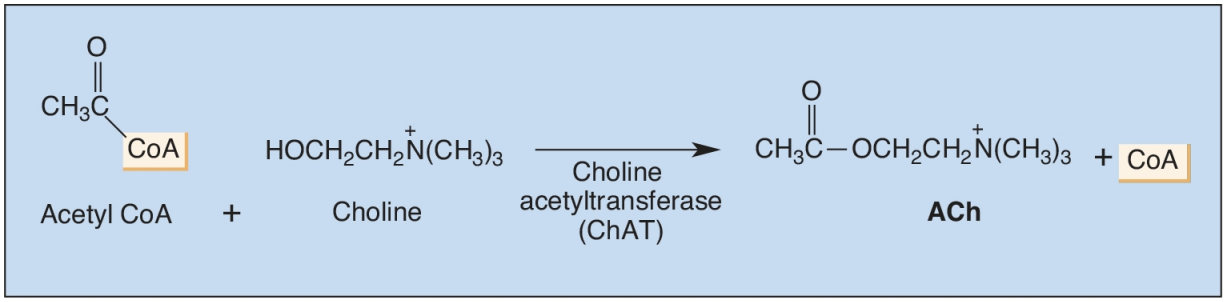
- at the neuromuscular junction (muscle contraction) and much of the ANS

Two receptor families

- nicotinic (ionotropic)
- muscarinic (metabotropic)

Making & breaking acetylcholine

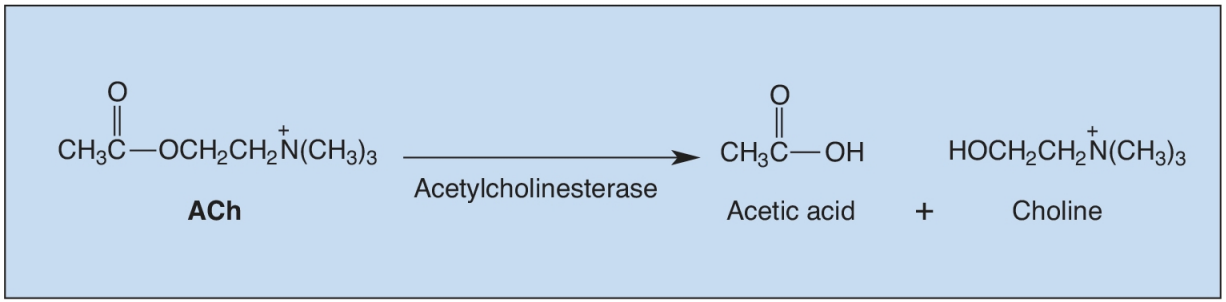
- Synthesizing ACh requires two enzymes
  - acetyl coenzyme A & choline acetyltransferase
- Breaking down ACh requires only one enzyme
  - Acetylcholinesterase



(a)

Synthesis takes place within neurons

Degradation takes place within synaptic cleft (acetic acid and choline can then be taken back into presynaptic cell for repackaging)



(b)

Acetylcholine (ACh) receptors

Nicotinic ACh receptors

- nicotine is an agonist
- ion channel opening is **excitatory**, non-selective cations
- on skeletal muscle (all voluntarily moved muscles)

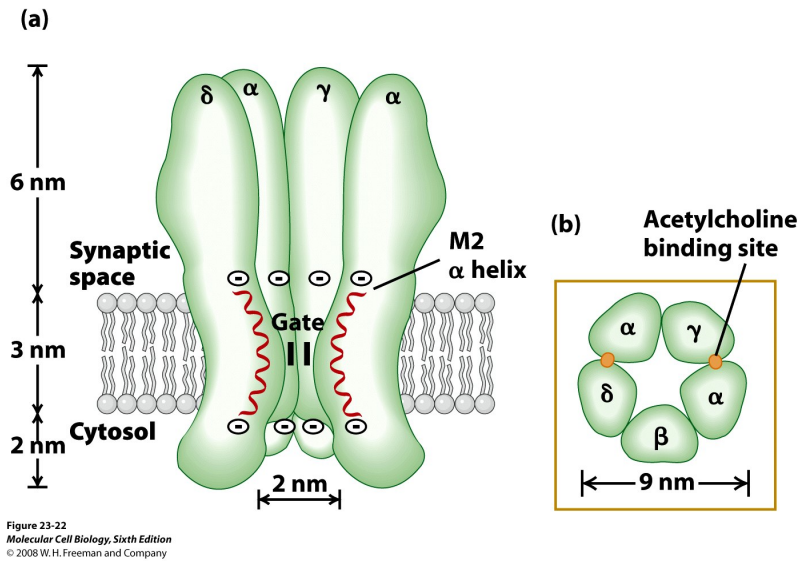


Figure 23-22
Molecular Cell Biology, Sixth Edition

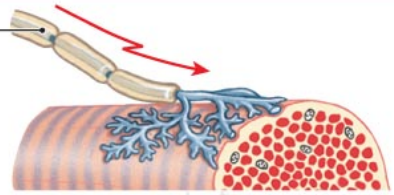
Muscarinic ACh receptors

- muscarine is an agonist
- G-protein coupled receptor to **inhibitory** currents (K^+ out or Cl^- in) or second-messengers
- on smooth muscle (heart, bladder, intestines, etc.)

The sequence of events in skeletal muscle contraction

Neural Control

A skeletal muscle fiber contracts when stimulated by a motor neuron at a neuromuscular junction. The stimulus arrives in the form of an action potential at the synaptic terminal.

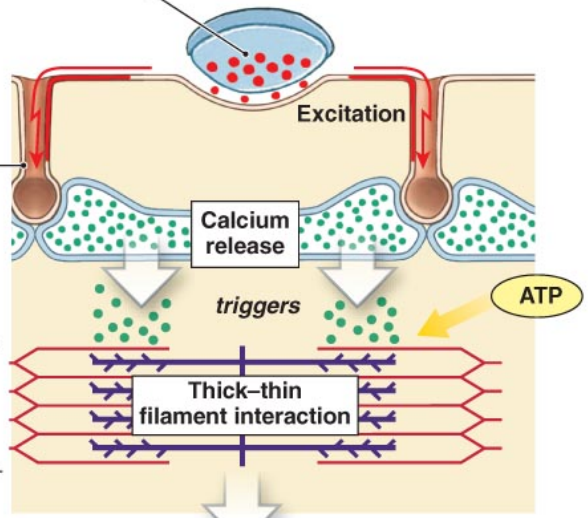


Excitation–contraction coupling

At the synaptic terminal, the action potential causes the release of ACh into the synaptic cleft. The ACh diffuses to the motor end plate, binds to receptors, and opens sodium ion channels, which leads to the production of an action potential in the sarcolemma.

The action potential in the sarcolemma travels along the T tubules to the triads, where it triggers the release of calcium ions from the terminal cisternae of the sarcoplasmic reticulum.

The contraction cycle then begins, and it will continue as long as ATP is available and action potentials are still produced at the motor end plate.



As the thick and thin filaments interact, the sarcomeres shorten, pulling the ends of the muscle fiber closer together.

leads to

During the contraction, the entire skeletal muscle shortens and produces a pull, or tension, on the tendons at either end.

Congenital myasthenic syndromes (CMSs)

Neuromuscular transmission disrupted

Commonly appear at birth or early in life

Often impairment at NMJ of ocular, cranial and limb muscles

Table 1 | **Classification of CMSs**

Site of defect	Index cases
Presynaptic defects (7%)	
CHAT deficiency‡	6
Paucity of synaptic vesicles and reduced quantal release	1
Lambert-Eaton syndrome like	1
Other presynaptic defects	4
Synaptic basal lamina-associated defects (14%)	
Endplate ACHE deficiency‡	26
Postsynaptic defects (79%)	
Kinetic abnormality of AChR with/without AChR deficiency‡	45
AChR deficiency with/without minor kinetic abnormality‡	83
RAPSYN deficiency‡	17
Plectin deficiency	1
Total (100%)	***185***

*Classification based on cohort of congenital myasthenic syndrome patients investigated at the Mayo Clinic between 1988 and 2003. ‡Gene defects identified.
ACHE, acetylcholinesterase; AChR, acetylcholine receptor; CHAT, choline acetyltransferase; CMSs, congenital myasthenic syndromes.

Andrew G. Engel, Kinji Ohno & Steven M. Sine
Nature Reviews Neuroscience 4, 339-352 (May 2003)

Myasthenia gravis

Autoimmune disease -
Antibodies develop against one's own AChR interfering with the normal function of ACh

http://www.myasthenia.org.au/assets/images/eyes2.jpg

Nature Reviews Immunology 2, 797-804 (October 2002) |
Timeline: Unravelling the pathogenesis of myasthenia gravis
Angela Vincent[1]

Loss of motor neurons leads to Amyotrophic lateral sclerosis (ALS)

Symptoms

- general weakness, often in limb, with problems swallowing
- later, speaking problems, and loss of motor control

Time course

- onset ranges, typically ~50 years old; death within 5 years of diagnosis

Baseball great Lou Gehrig retired because of his ALS. He died two years later.

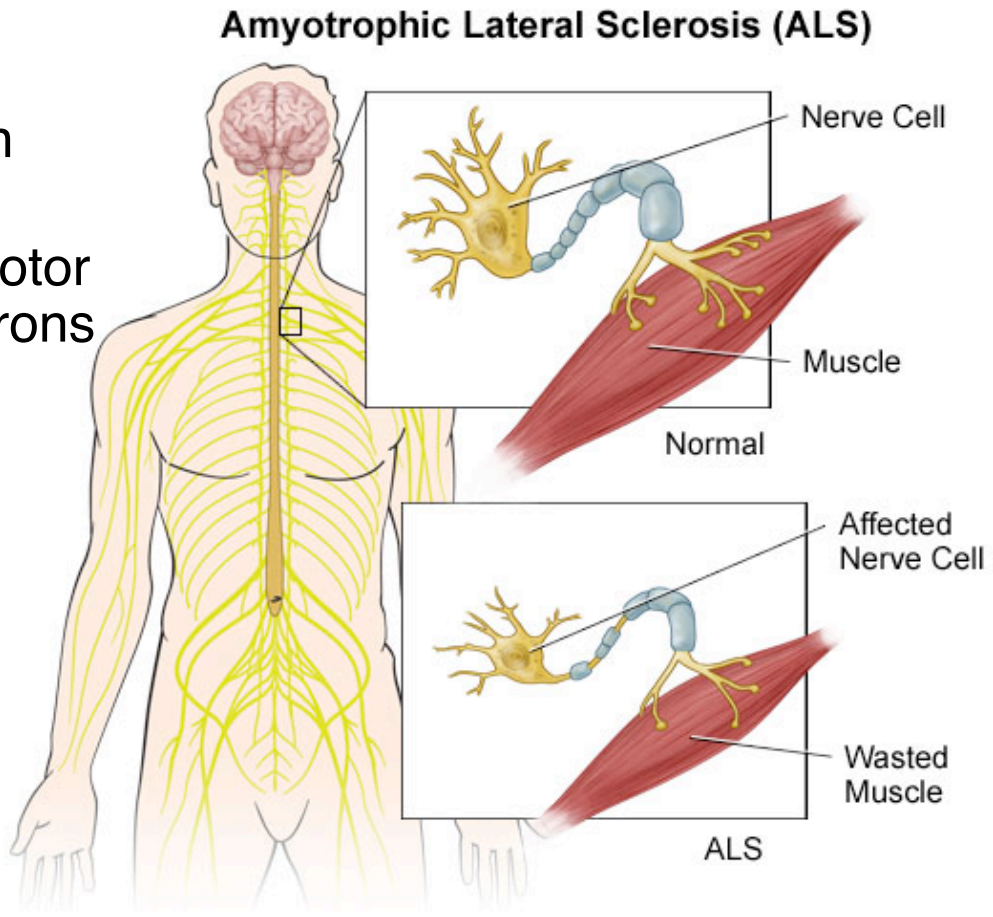
Amyotrophic lateral sclerosis

Cause

- unknown, multiple causes?
- one genetic cause (mutation in gene called *SOD1*) ~1-2%
- affects both primary cortical motor neurons *and* spinal motor neurons

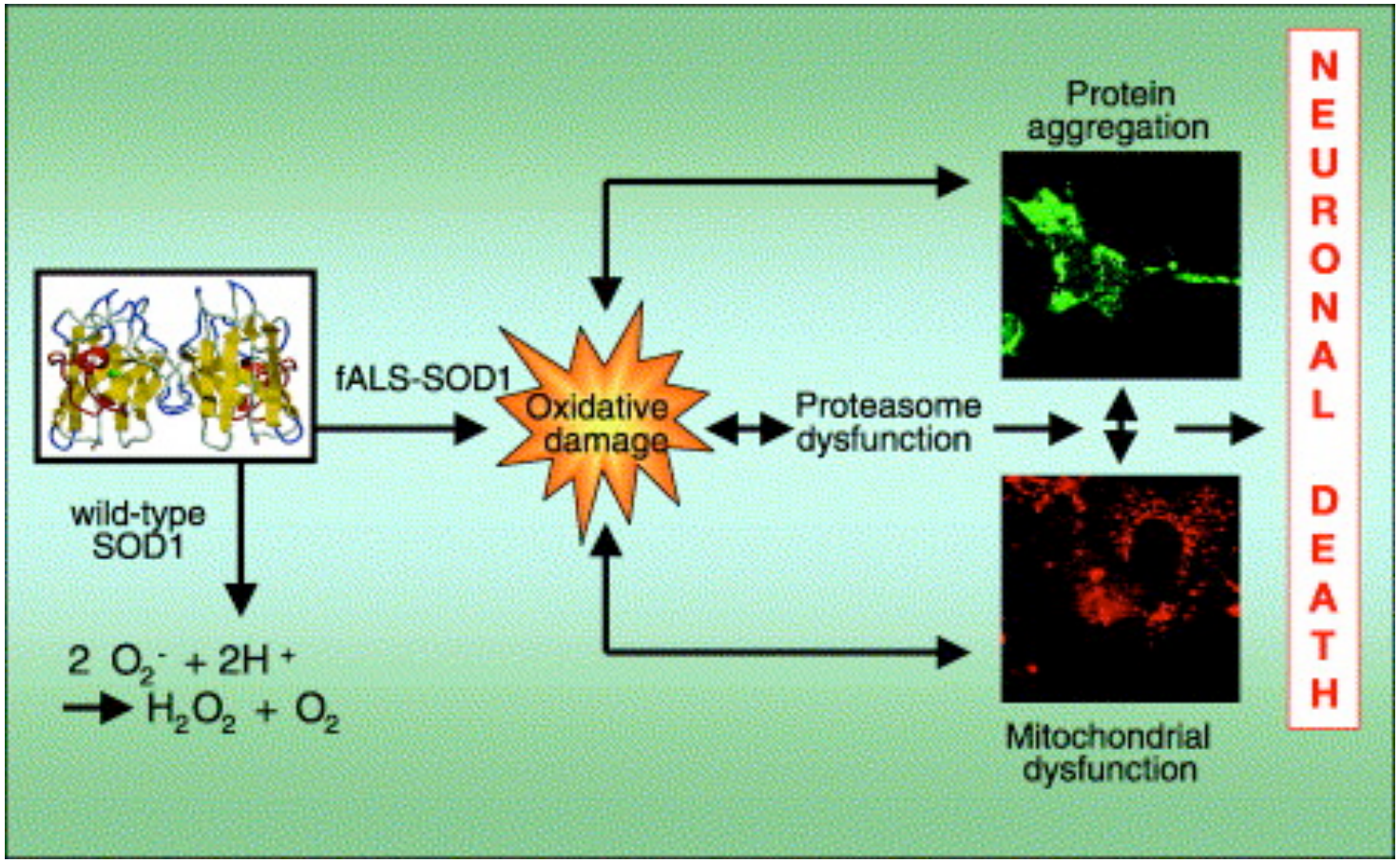
Treatment

- none currently, 90% of cases arise sporadically



http://www.yalemedicalgroup.org/stw/Page.asp?PageID=STW023404

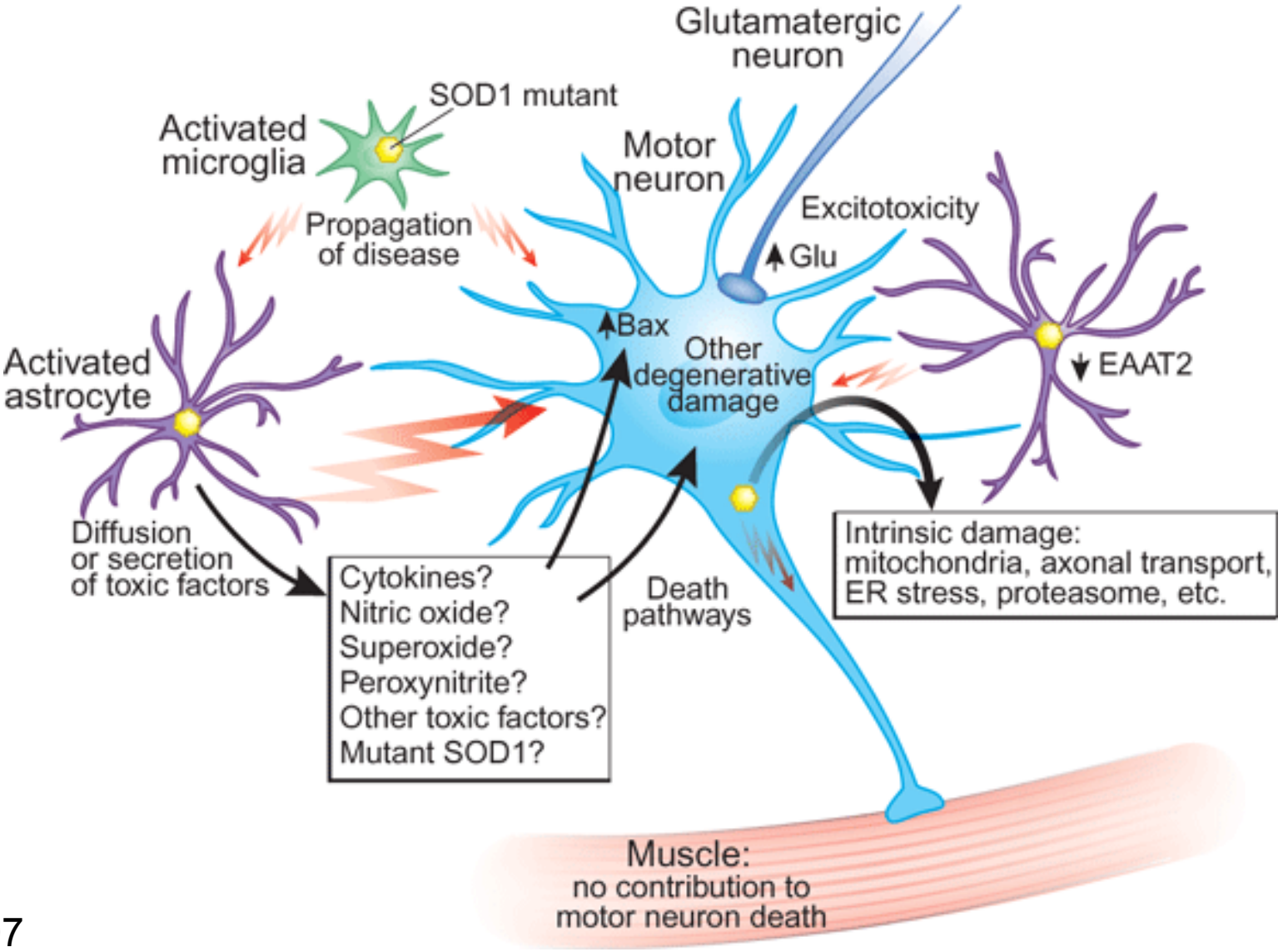
How mutant SOD1 leads to death of motor neurons is still not fully understood



SOD1 is an enzyme that metabolizes oxygen free radicals, helping to prevent oxidative damage

Carri et al., (2003) Brain Research Bulletin 4: 365-74

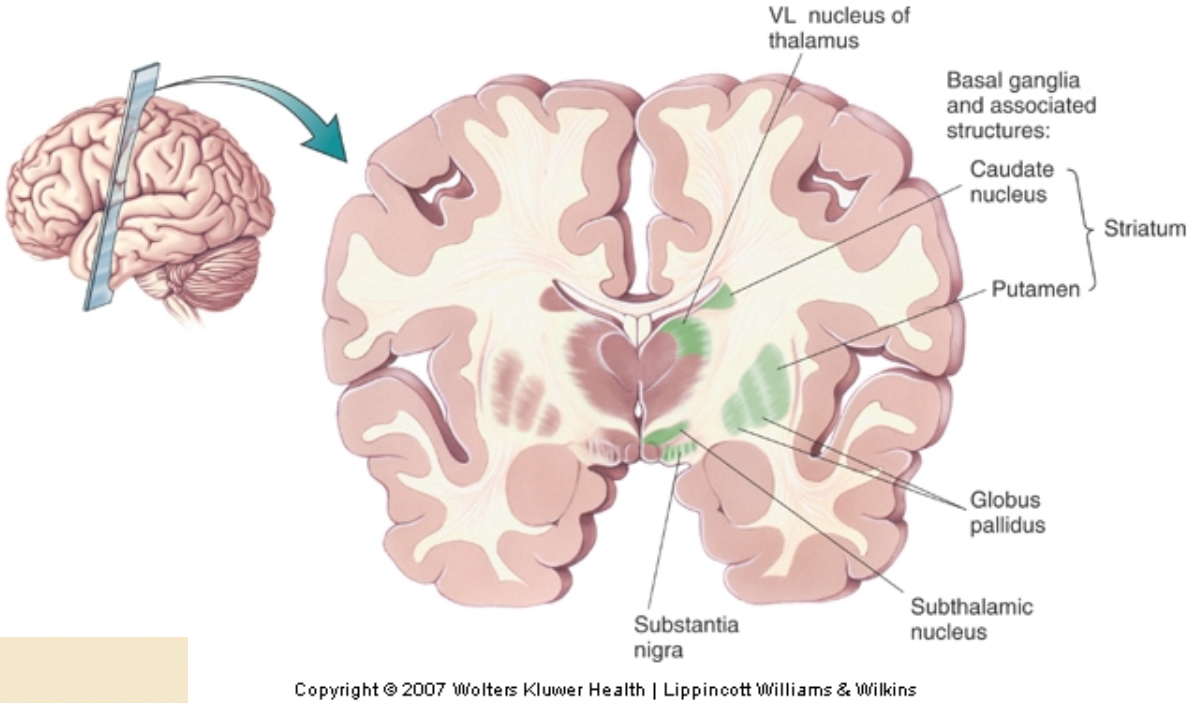
Multiple cellular mechanisms proposed to explain how mutant SOD1 leads to disease



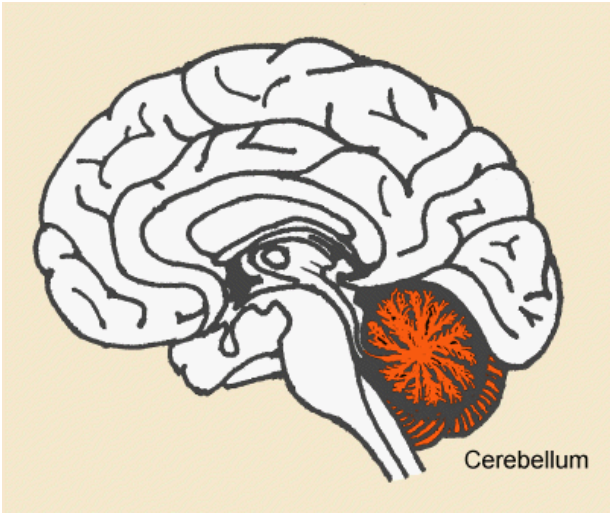
Julien, 2007

Other brain regions involved in movement

BASAL GANGLIA

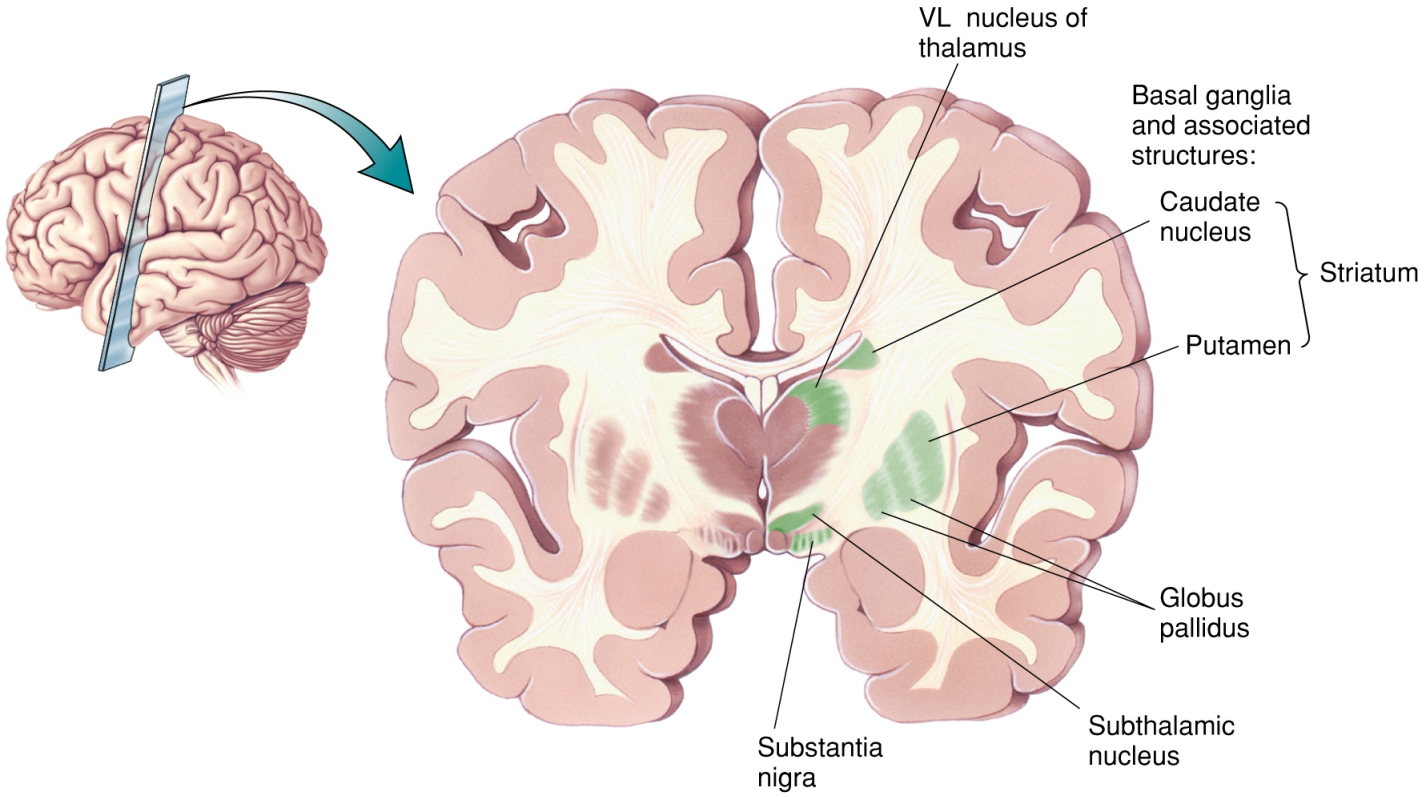


CEREBELLUM



Anatomy of the basal ganglia

Large group of distinct nuclei (includes the **striatum** (caudate nucleus + putamen), **globus pallidus**, and **subthalamus**)



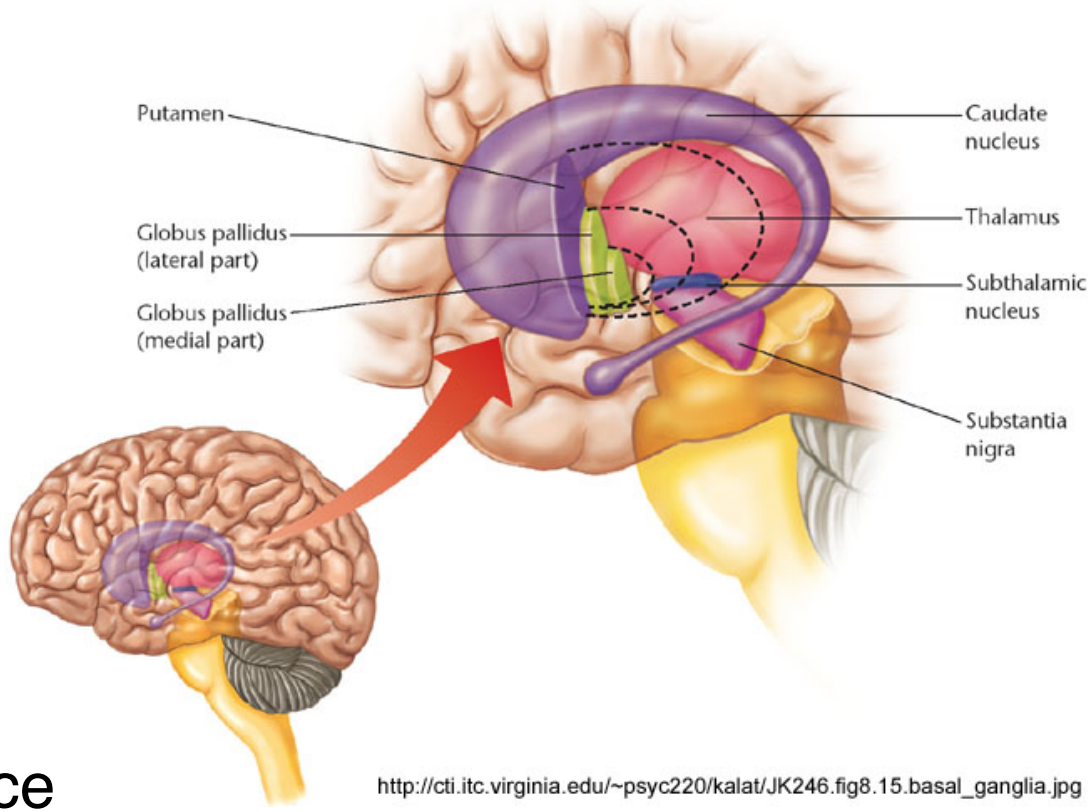
Basal ganglia

Damage causes many disorders

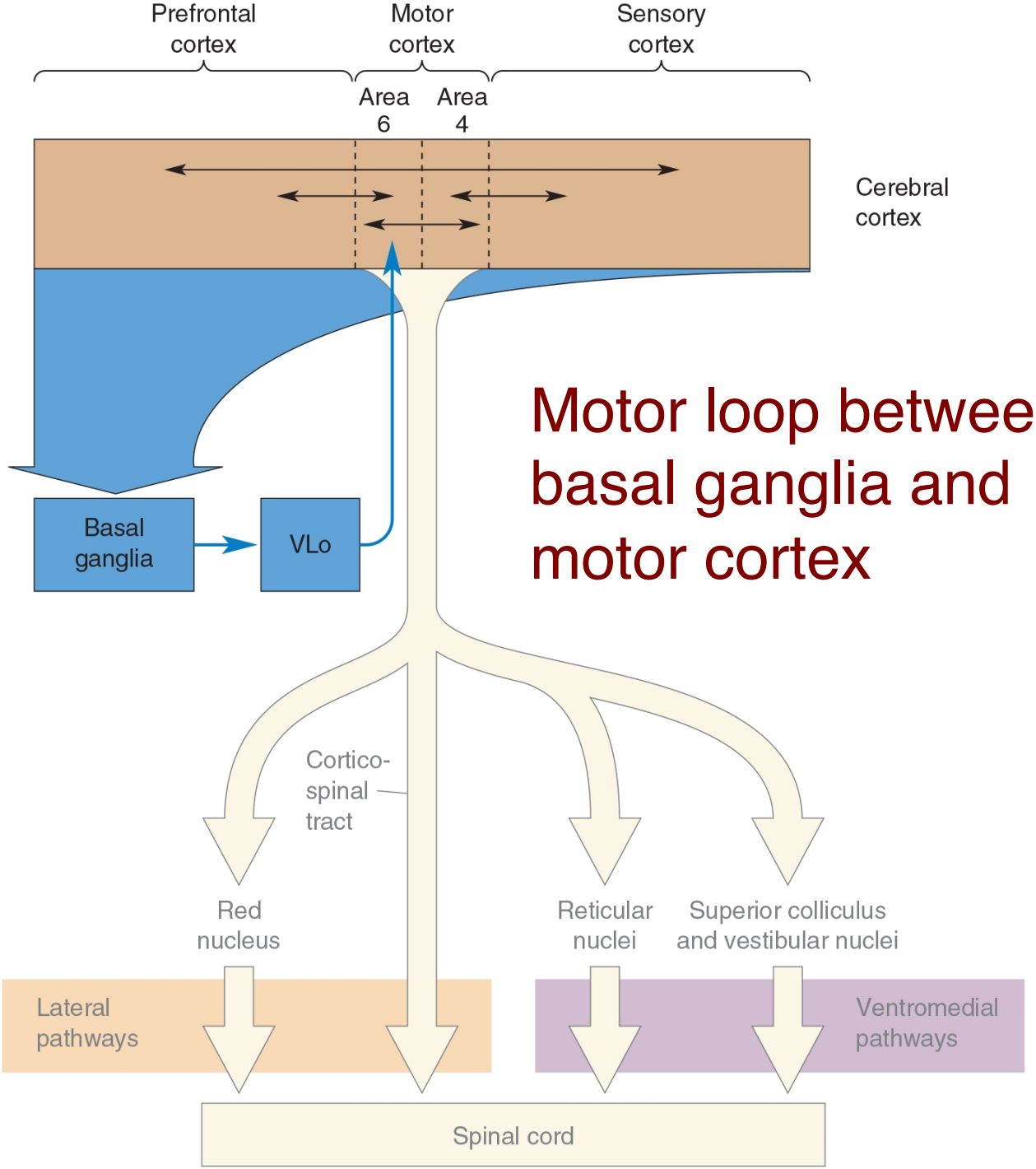
- hyperkinetic or involuntary movements
- hypokinetic or reduced movement ability

Suggests a role in the amount of movement force

- regulating excitatory and inhibitory signals



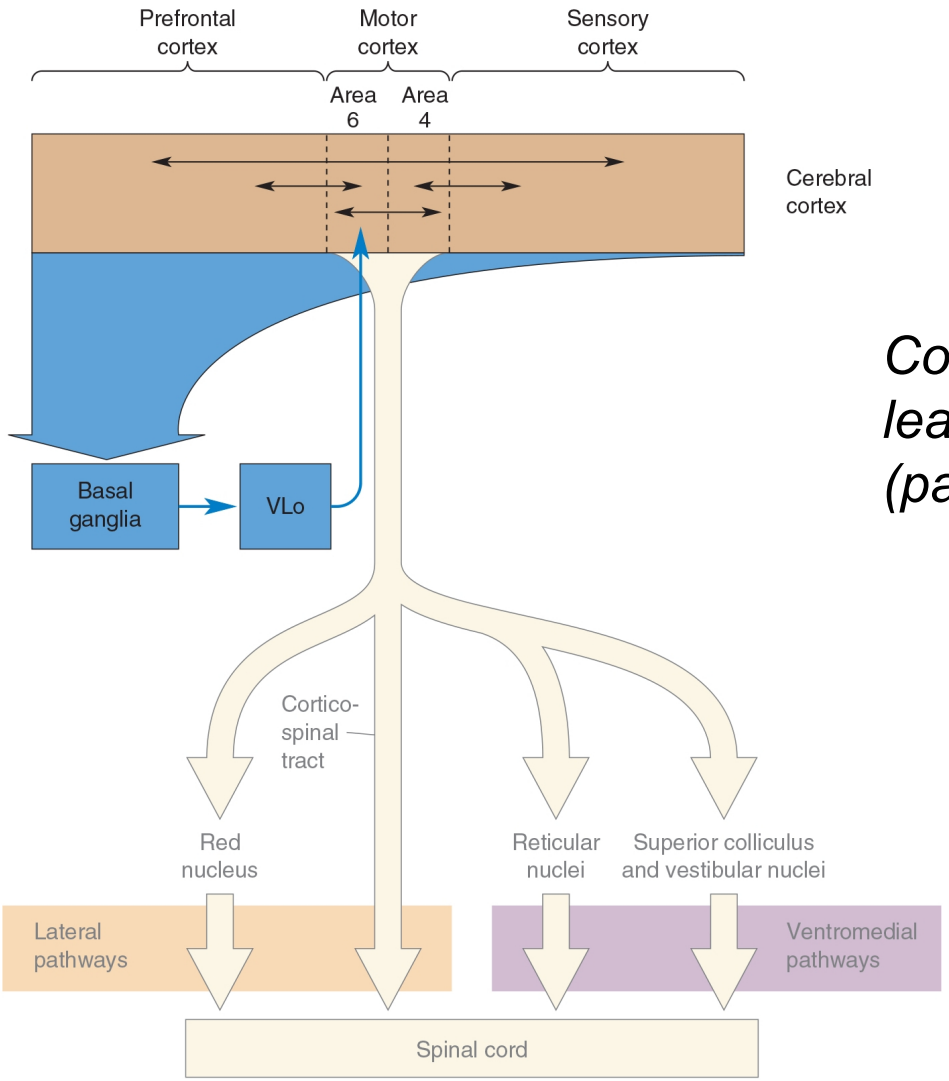
http://cti.itc.virginia.edu/~psyc220/kalat/JK246.fig8.15.basal_ganglia.jpg



Motor loop between basal ganglia and motor cortex

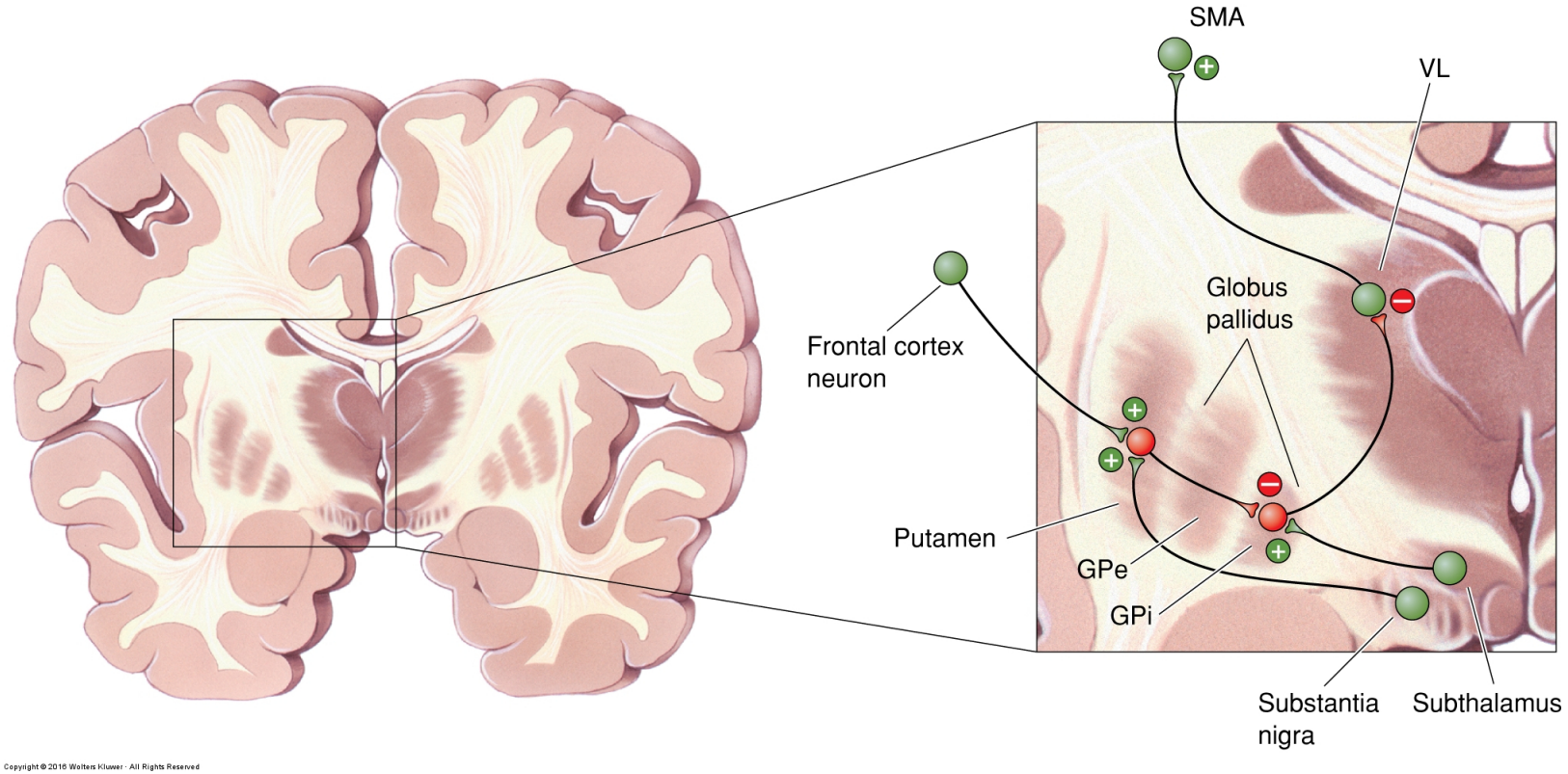
The motor loop

Cortex --- Striatum --- Globus Pallidus --- Vlo (thalamus) --- Cortex (SMA)



Cortical activation of the striatum leads to excitation of the SMA (part of Pre motor cortex – Area 6)

Basal ganglia motor loop



Inhibitory pathway and excitatory pathways

Relationship between excitatory versus inhibitory may allow for the adjustment of movement force

Disorders that involve the basal ganglia

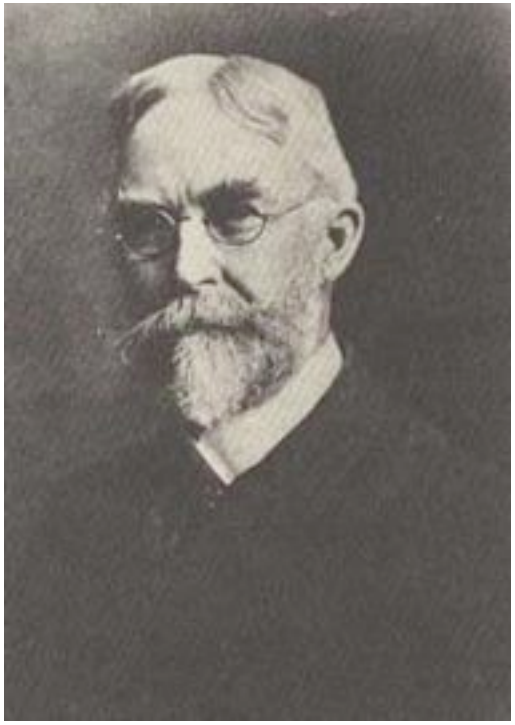
Huntington's disease

Symptoms

- cognitive (trouble learning, remembering old facts or skills)
- progresses to motor impairment (unsteady gait), & chorea (involuntary movements)

Time course

- onset ~30-45 years old, dead within 10-20 years; younger onset, quicker progression
- affects both sexes; high incidence in certain families (Venezuelan town has >700 cases)



George Huntington described the disease in 1872.

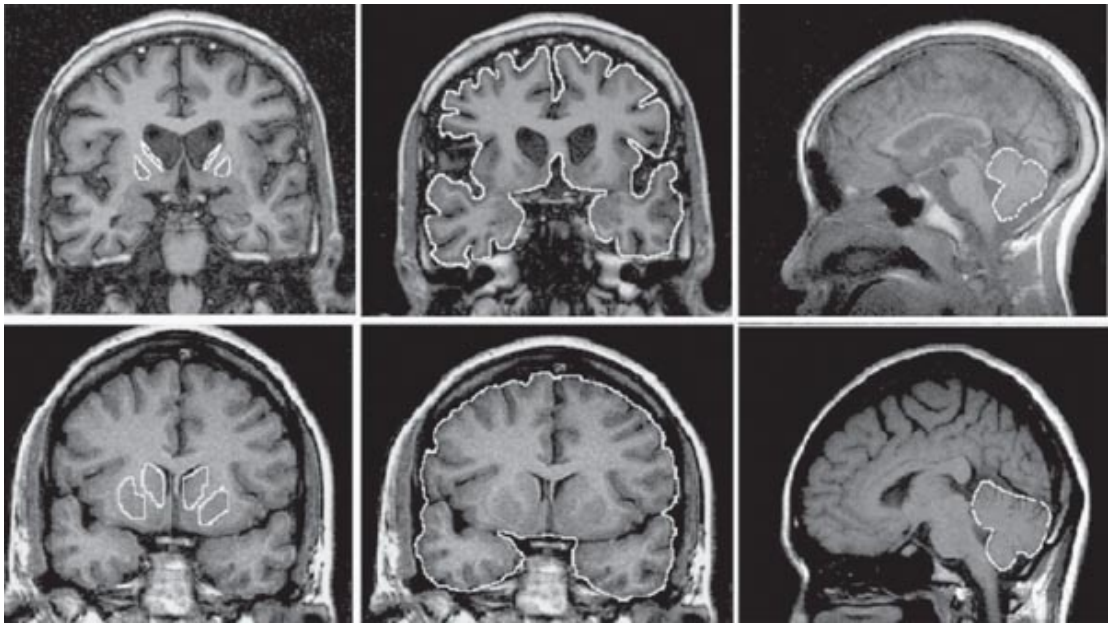
Huntington's disease

Cause

- genetic: the CAG repeat in the *huntingtin* gene
- CAG encodes a glutamine (amino acid), should be <30 in a row, in disease, from 40-100
- targets basal ganglia

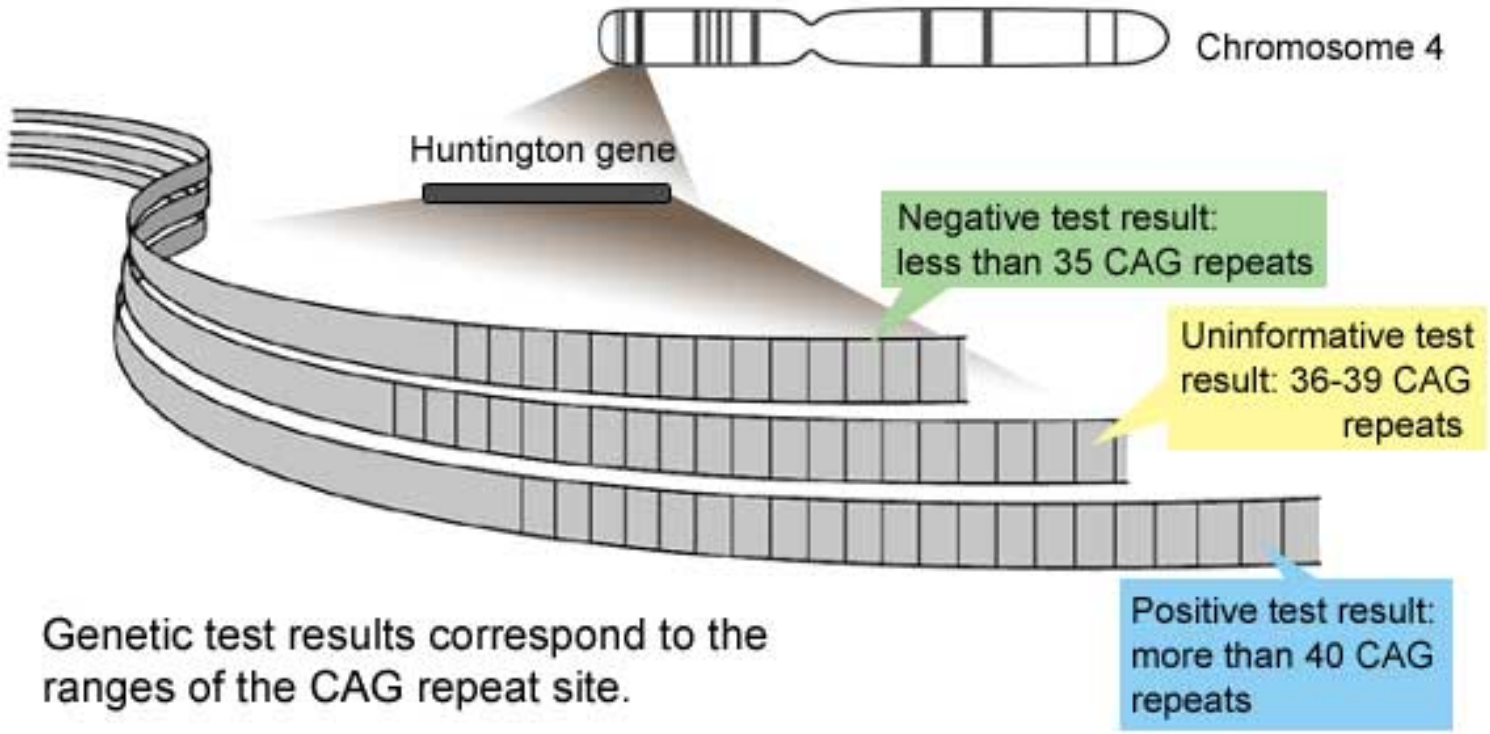
Treatment

- none currently; simple genetic test to determine risk



Braz J Med Biol Res
2006; 39: 1129-1136

Figure S-3: CAG Repeat Counts on the Huntington gene



Genetic test results correspond to the ranges of the CAG repeat site.

Expansion of CAG repeats in the *huntingtin* gene; CAG codes for glutamine in the huntingtin protein

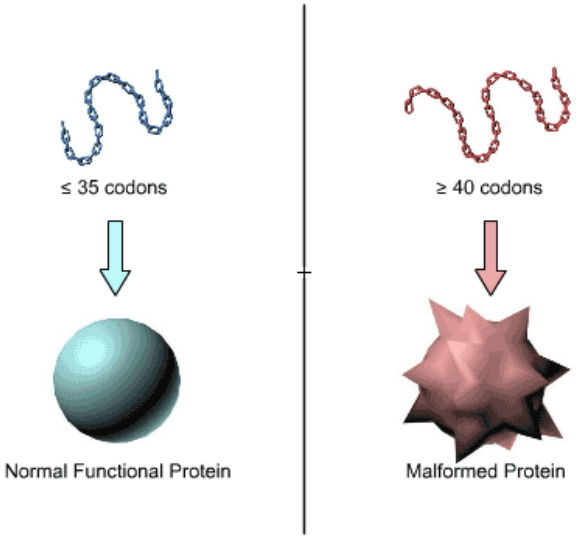
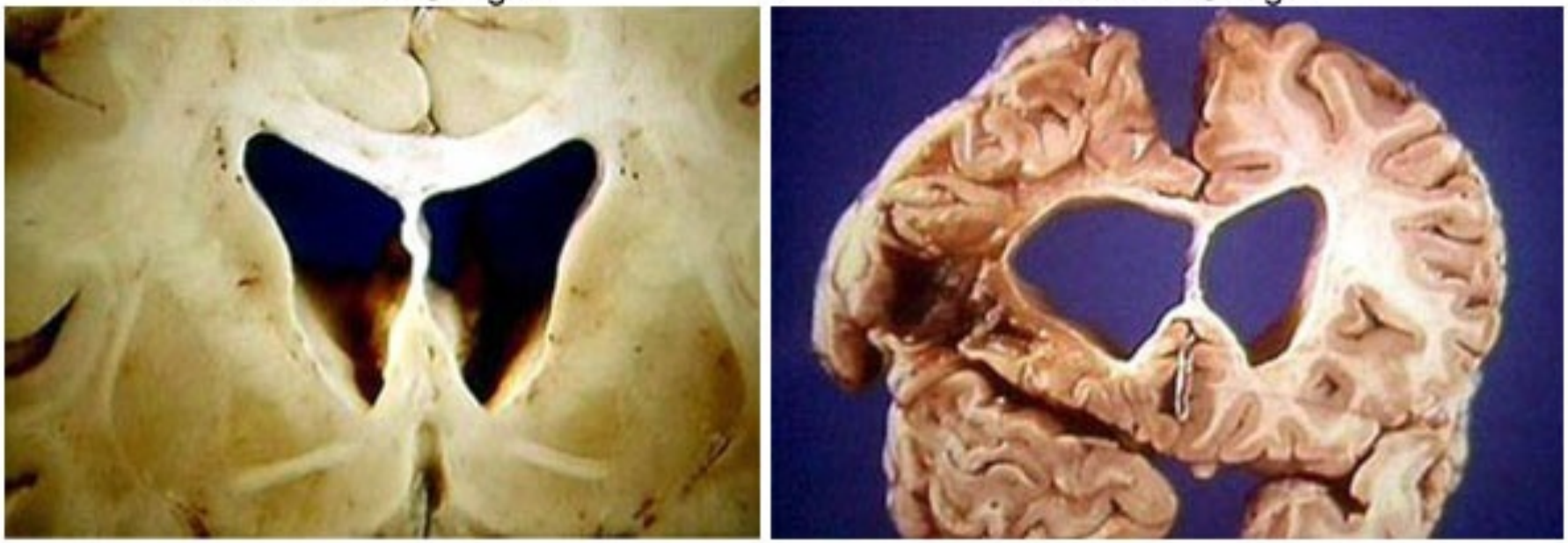


Figure D-4: Effect of HD on the Basal Ganglia

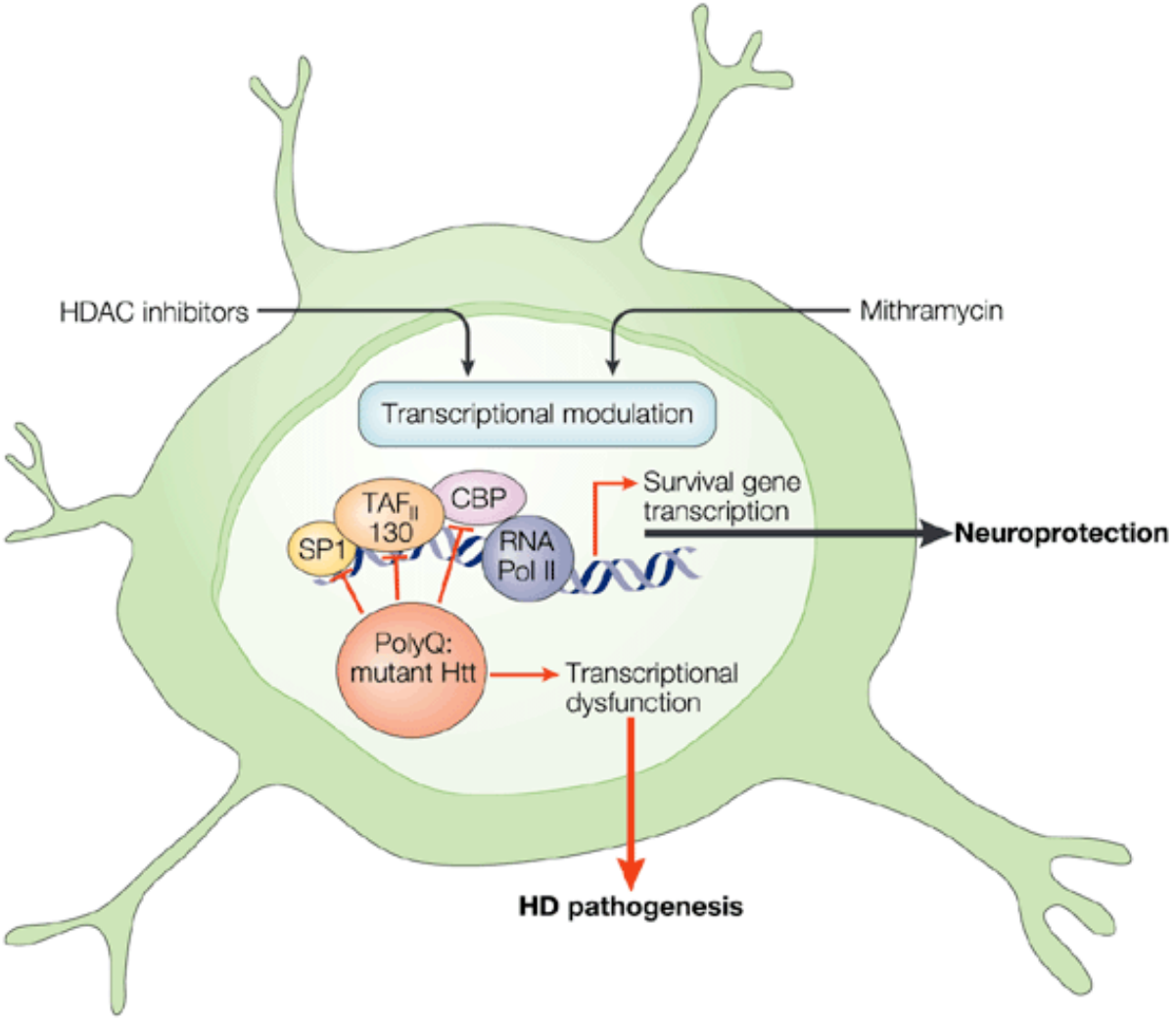
Normal Basal Ganglia vs. HD Basal Ganglia



The basal ganglia of the human brain, showing the impact of HD on brain structure in this region. Note especially that the brain of a person with HD has bigger openings due to the death of nerve cells in that region.

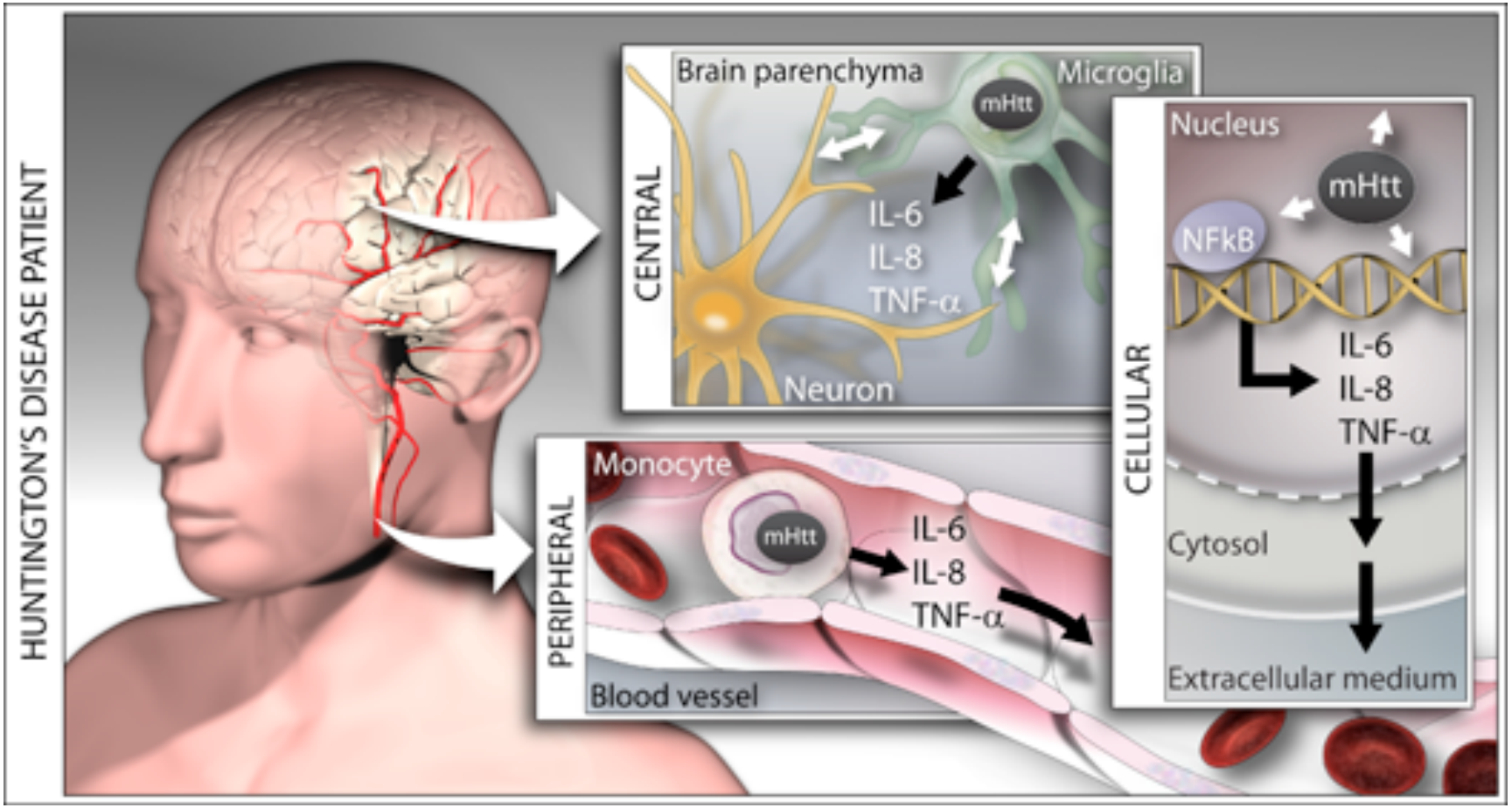
Source: Singer, Jonathan. Huntington's Disease. Online. Available at: http://ist-socrates.berkeley.edu/~jmp/HD.html

Mutant *huntingtin* may alter gene expression by affecting transcriptional regulation



Flint Beal M., Ferrante R.J. Experimental therapeutics in mouse models of Huntington's disease. *Nature Reviews Neuroscience*. 2004; 5: 373-84.22

Mutant *htt* may lead to increased expression of chemical signals involved in inflammation



http://hdresearch.ucl.ac.uk/our-results/inflammation/

Parkinson's disease

Symptoms

- four major symptoms: tremor, rigidity, slowness, & impaired balance
- leads to inability to do simple things
- cognitive loss over time

Time course

- onset: in most cases, well over 50 years old, though some genetic start younger

Michael J. Fox has early onset Parkinson's, Muhammad Ali had a related condition.

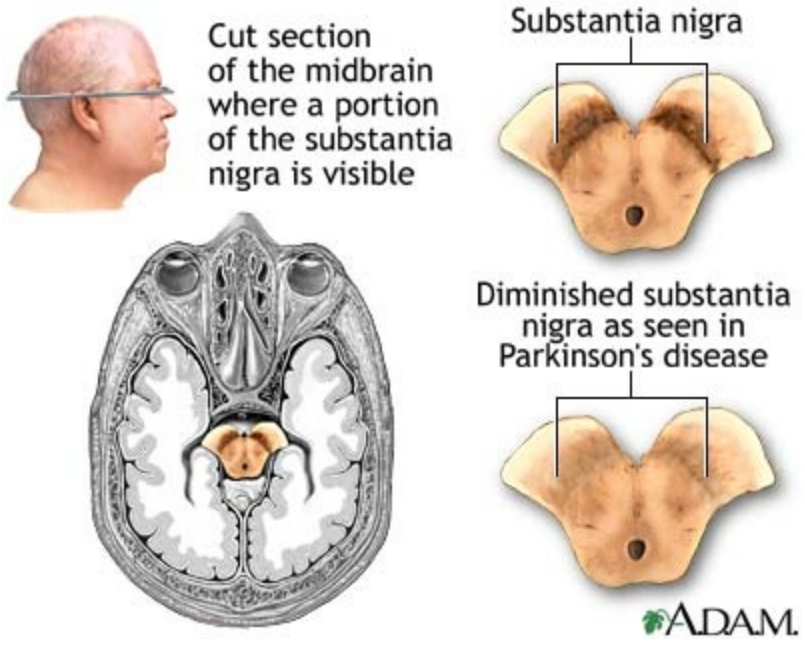
The underlying basis of Parkinson's disease involves loss of specific dopaminergic neurons

Cause

- loss of dopamine (DA) neurons in substantia nigra
- suggests that over life, these neurons are vulnerable

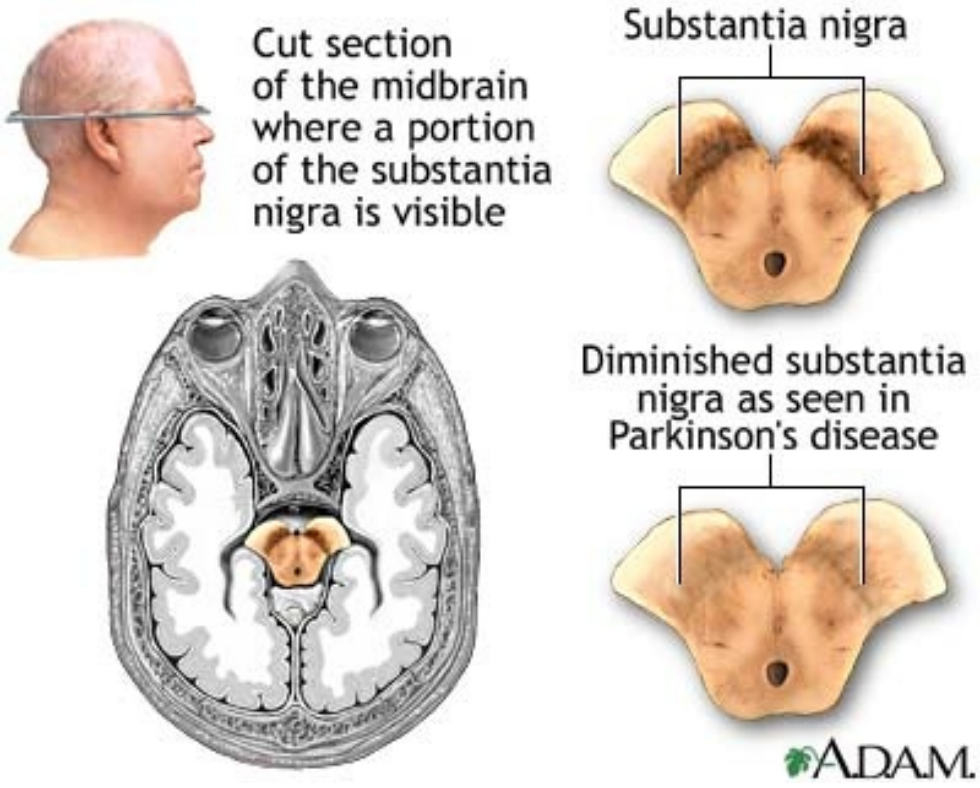
Treatment

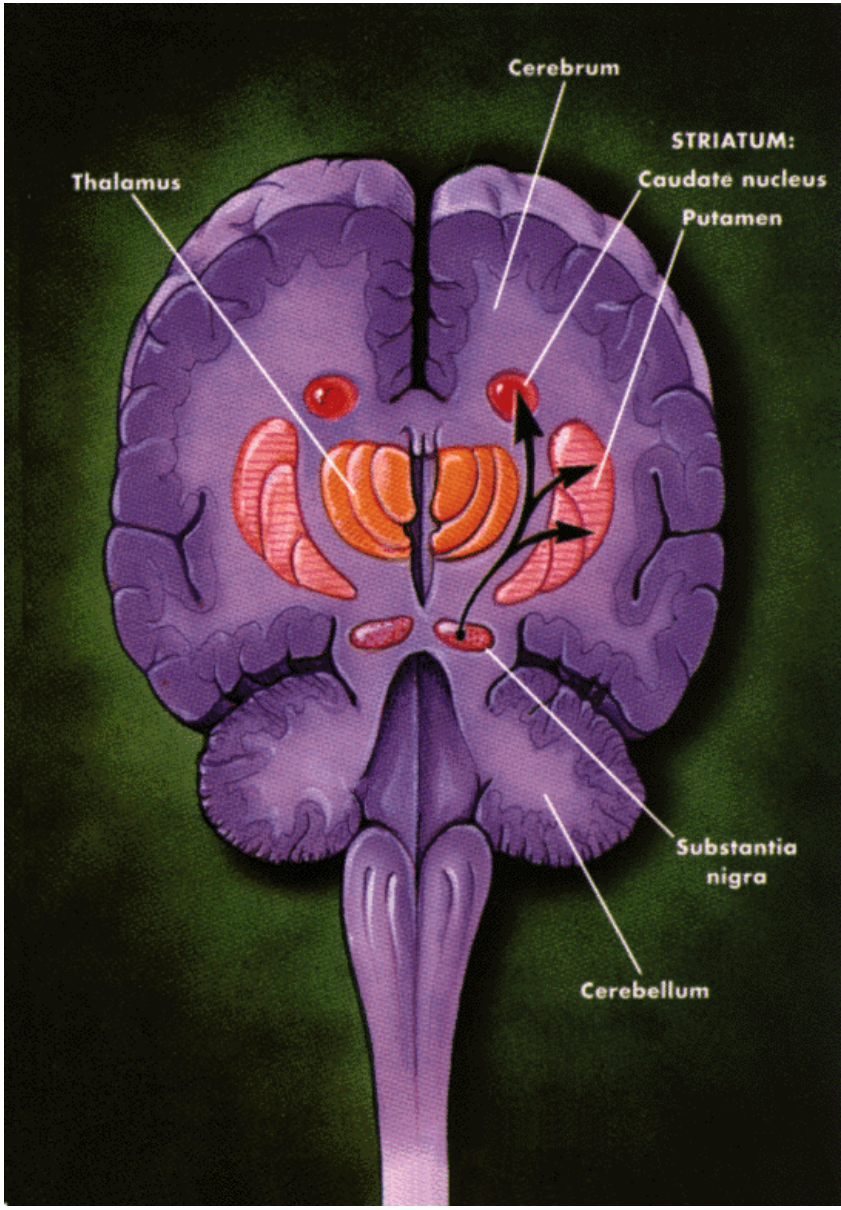
- no cure yet, but giving a DA precursor, L-DOPA, increases DA and motor functioning



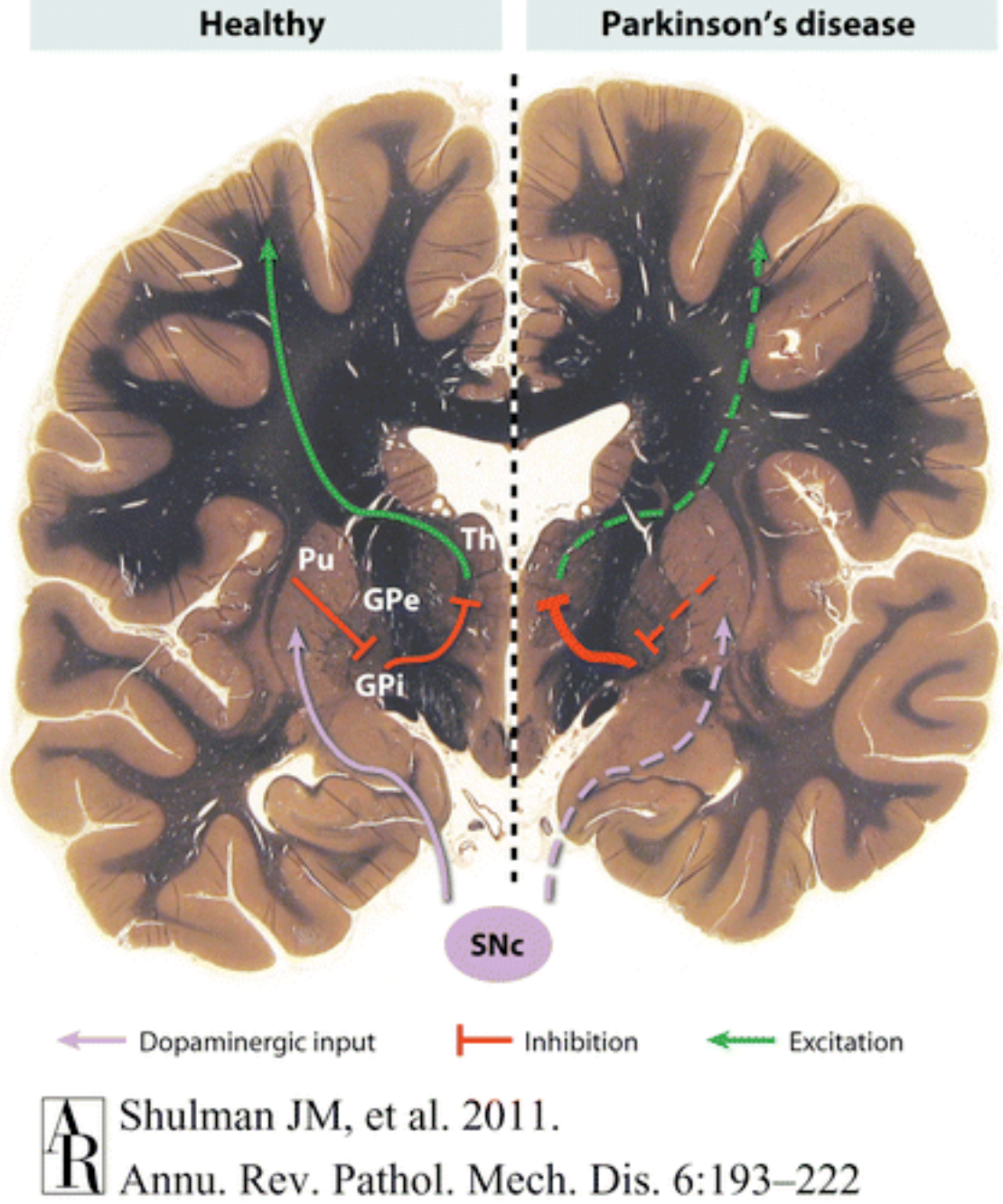
DA neurons from substantia nigra travel to the striatum in basal ganglia.

Dopaminergic neurons from the substantia nigra are lost in Parkinson's disease



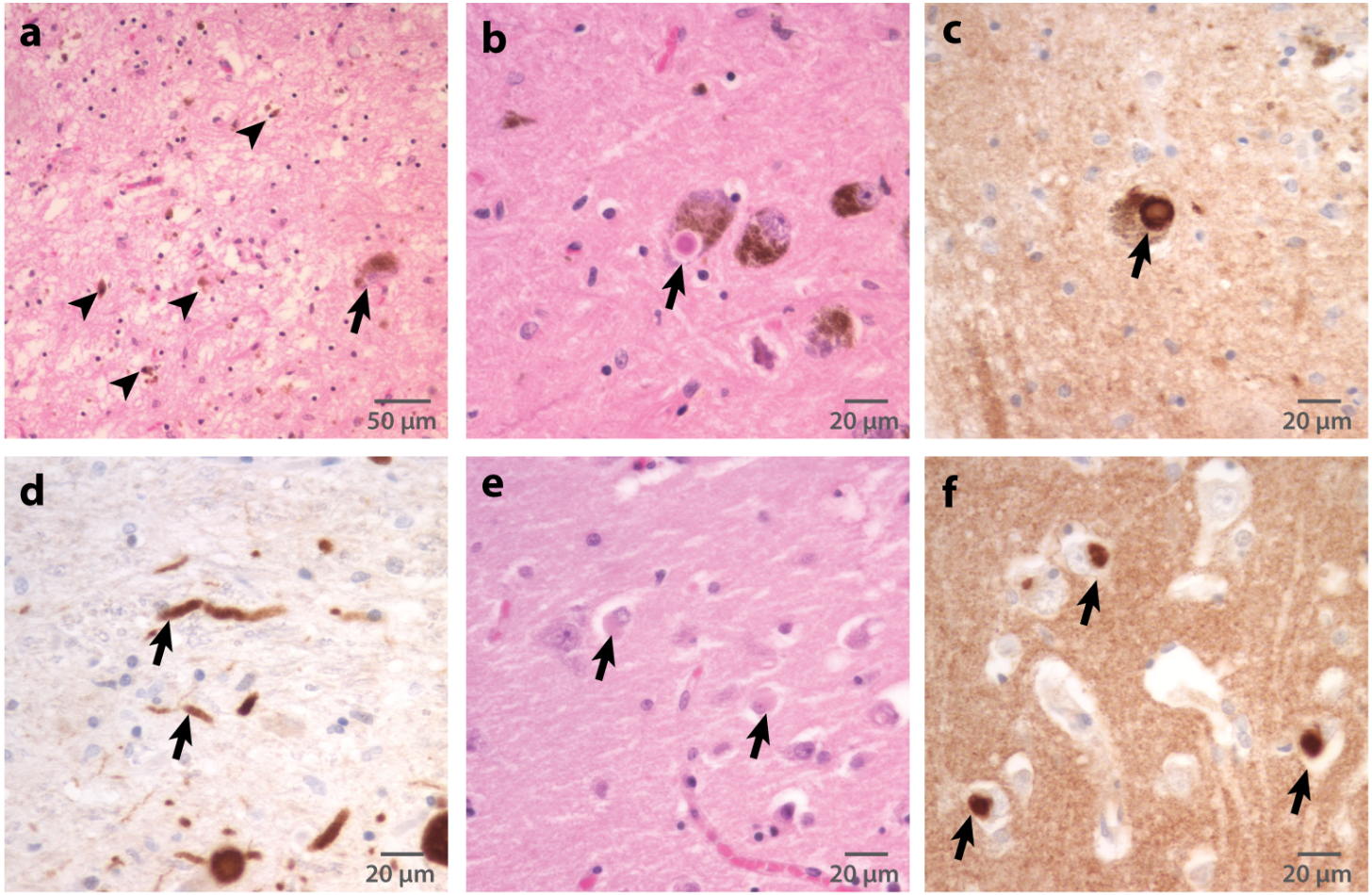


How loss of substantia nigral neurons affects the motor loop



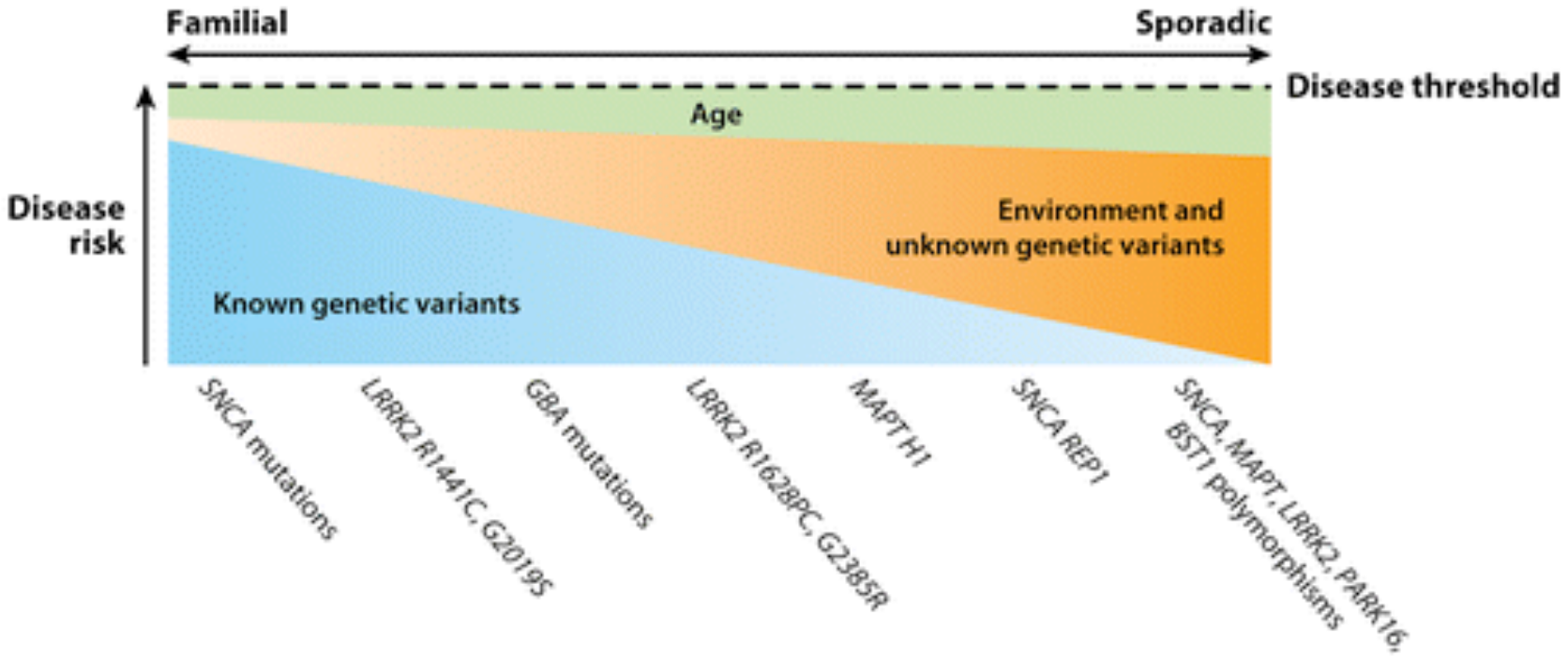
Shulman JM, et al. 2011.
Annu. Rev. Pathol. Mech. Dis. 6:193–222

Another characteristic of Parkinson's is the presence of Lewy bodies

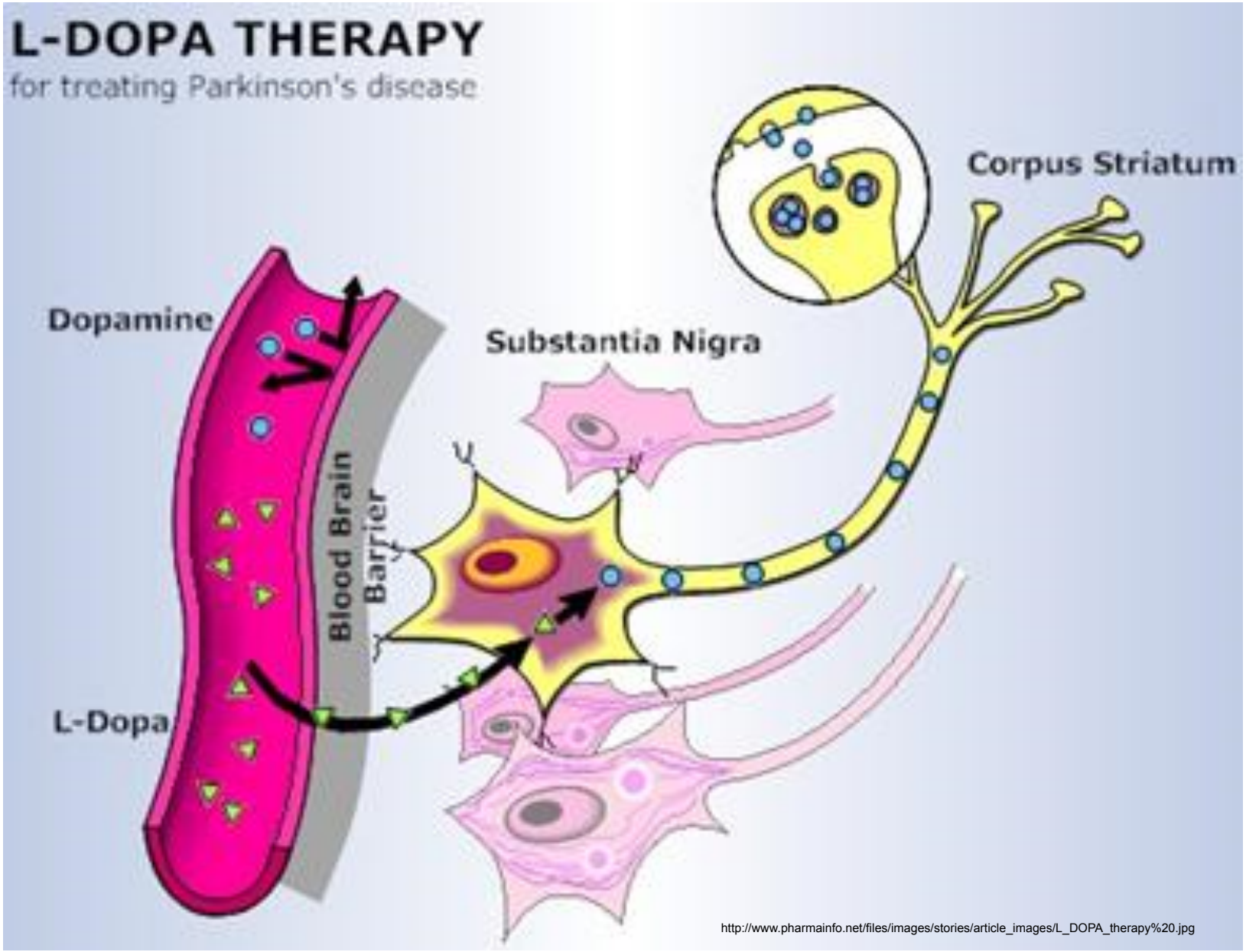


Shulman JM, et al. 2011.
Annu. Rev. Pathol. Mech. Dis. 6:193–222

Factors that affect PD risk



Shulman JM, et al. 2011.
Annu. Rev. Pathol. Mech. Dis. 6:193–222


L-DOPA THERAPY
for treating Parkinson's disease
Corpus Striatum
Dopamine
Substantia Nigra
Blood Brain Barrier
L-Dopa
http://www.pharmainfo.net/files/images/stories/article_images/L_DOPA_therapy%20.jpg

Tourette's syndrome

Symptoms

- motor (often facial) & vocal tics (grunting): can be simple (involving just a few muscle groups) or more complex
- spectrum disorder; different degrees of intensity

Time course

- onset between 2-15 years old (males 3-4 times more often); life-long, but normal expected lifespan

Tourette's syndrome

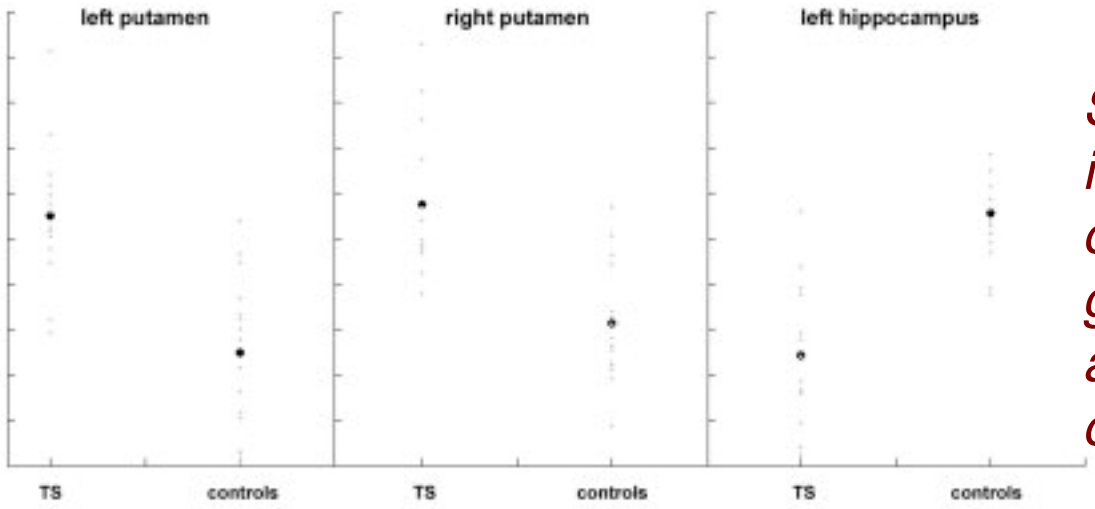
Affects basal ganglia and connecting circuits

Cause

- Largely unknown; both genetic & environmental factors implicated

Treatment

- most need none; many get better as they get older
- if frequent, medications are dopamine antagonists



Structural changes in different nuclei of the basal ganglia identified – affects regulation of motor force

Kusubeck et al., (2006)

Gray matter volumes in TS patients; higher volume in putamen

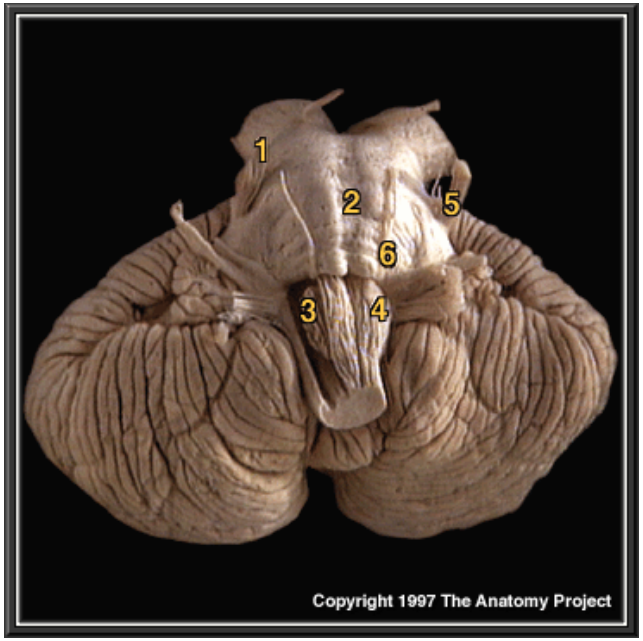
Cerebellum

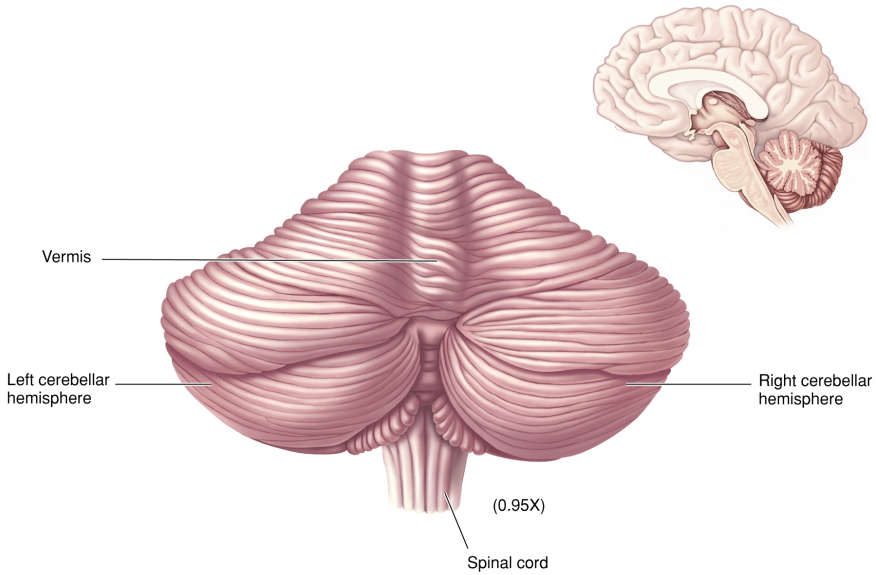
The ‘little brain’

- two hemisphere and the vermis (Latin for ‘worm’)

Important in acquisition and maintenance of motor skills

- motor timing
- error correction & movement adjustments



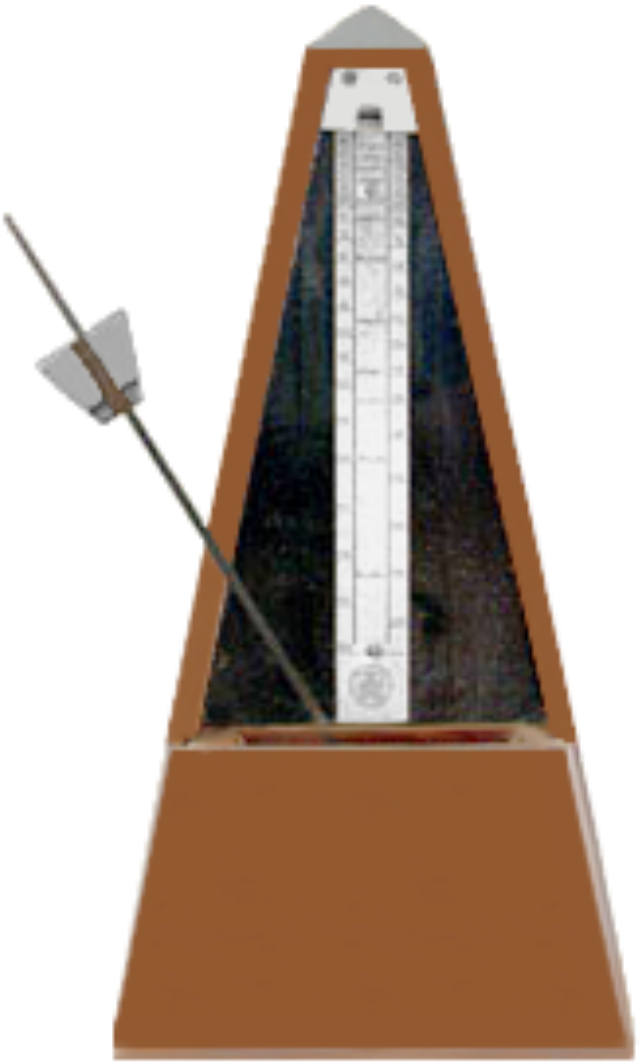


Cerebellum contributes to the control of movement timing

Cerebellum as timer

- tapping a finger in time with music requires a functional cerebellum
- anticipating length of time between stimuli

Possible that cerebellum times movement through coordination with neurons from the inferior olive in the medulla



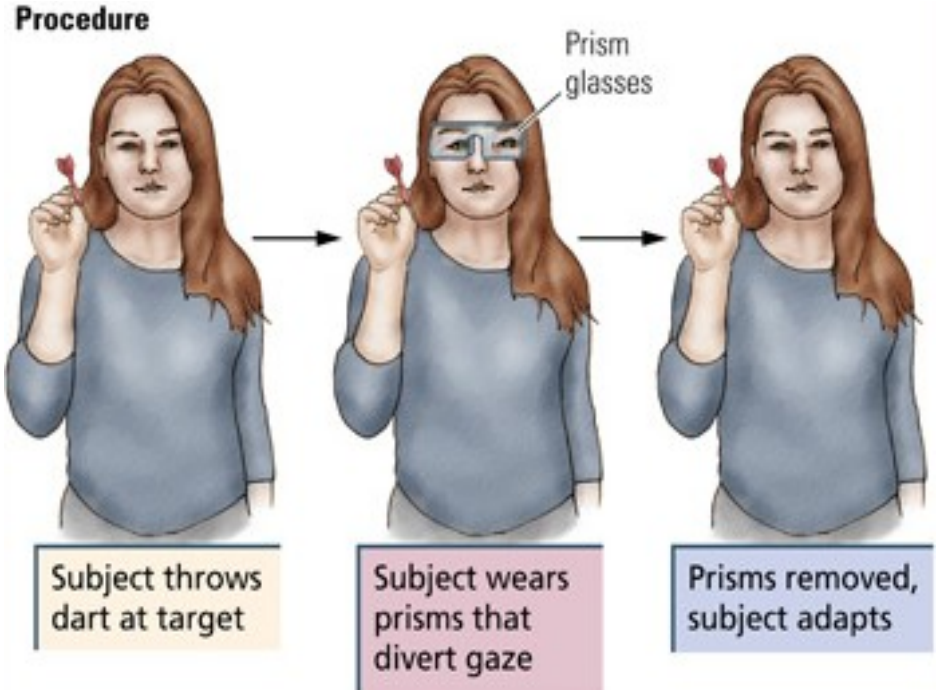
http://www.wpclipart.com/music/performance/metronome.png.html

Cerebellum also involved in adjusting movement to correct for errors

Throwing darts experiment

- wearing distorting prism glasses throws off visual perception
- control and cerebellar-damaged subjects

How does cerebellum affect this?



Kolb and Whishaw, 2005

Experimental results highlight the role of the cerebellum in error corrections

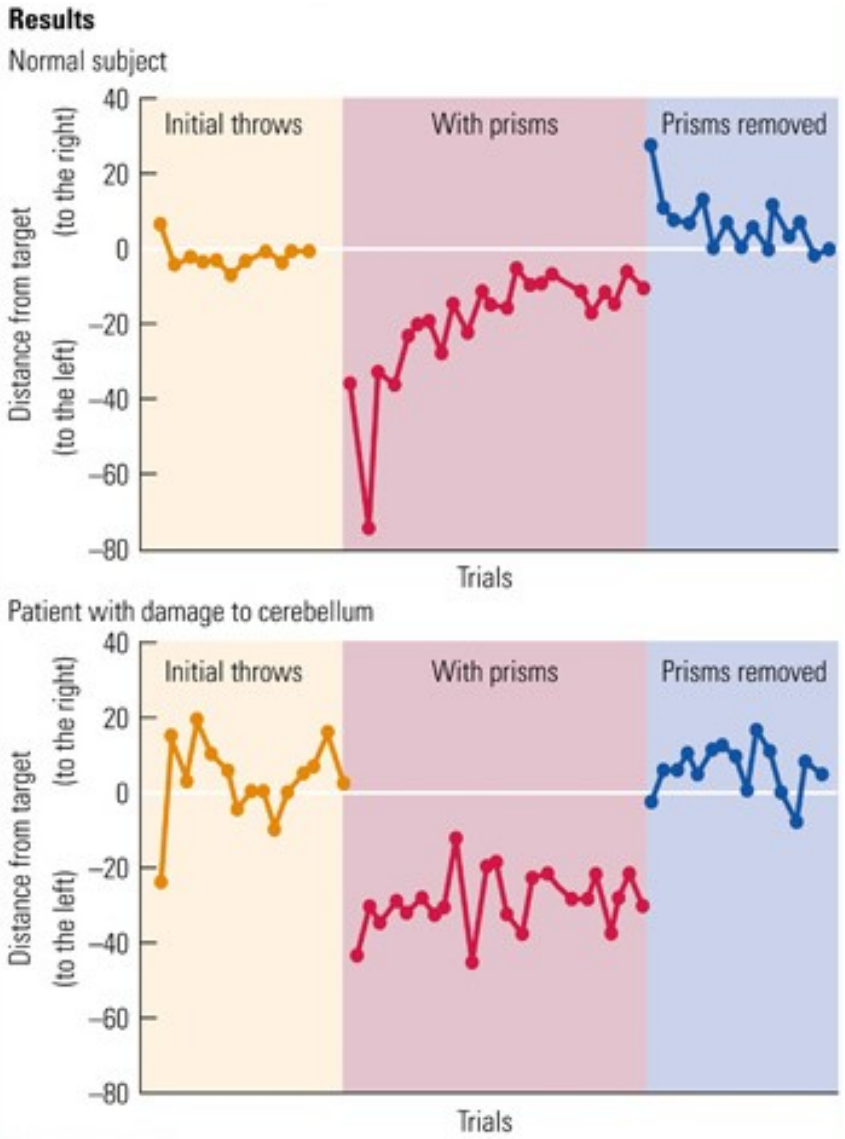
Put glasses on

- control: 1st throw way off, get better with each throw
- damage: can't fix

Take glasses back off

- control: miss badly, but fix
- damage: back to normal

'Error correction' by the cerebellum



Kolb and Whishaw, 2005

A neural circuit involved in error correction

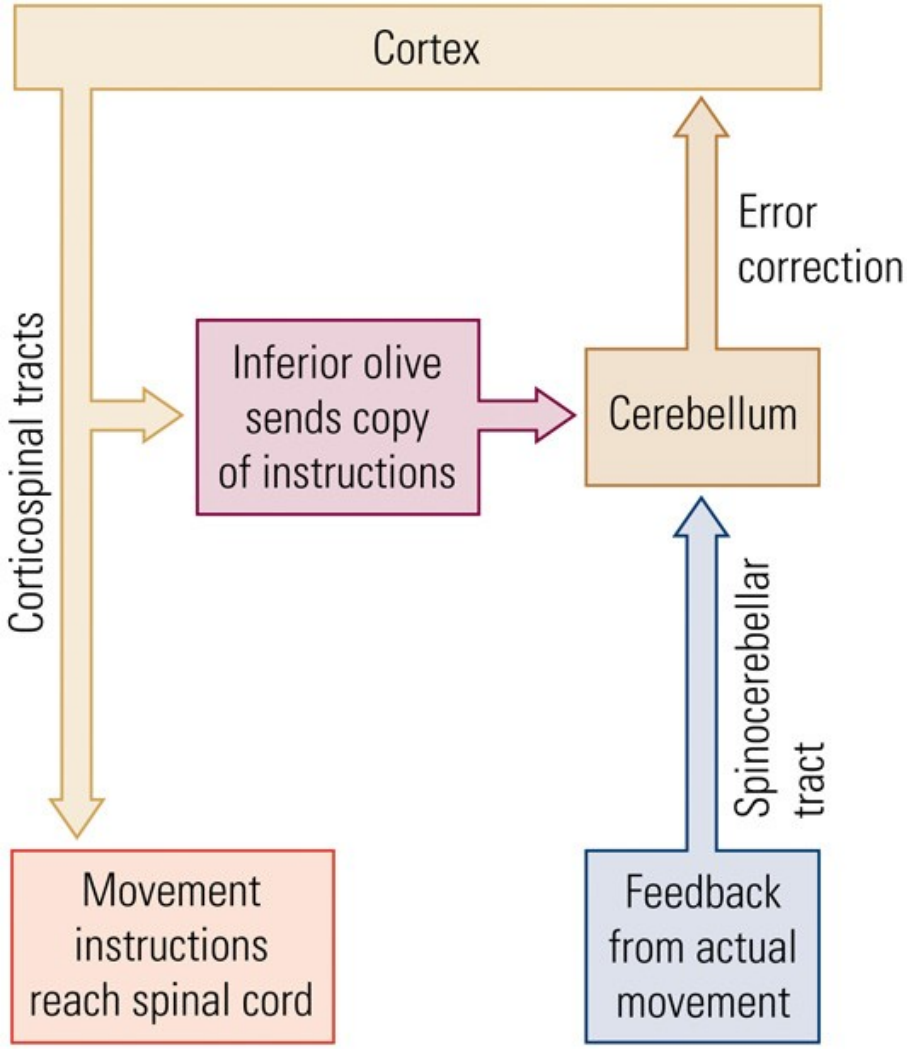
Motor cortex send signal to the spinal cord

- secondary copy sent to inferior olive (in medulla)

Cerebellum gets two signals

- inferior olive: the intended movement
- sensory input: the actual movement

Compare intended vs. actual movement



Kolb and Whishaw, 2005

Cerebellar ataxias

Symptoms

- slow, but progressive lack of coordination & gait, esp. hands, speech, and eye movements

Time course

- onset is usually >40 years old
- progression depends on particular type

The Ulas family in Turkey have a cerebellar ataxia and walk on all fours to compensate.

From BBC documentary 'The Family That Walks On All Fours'.

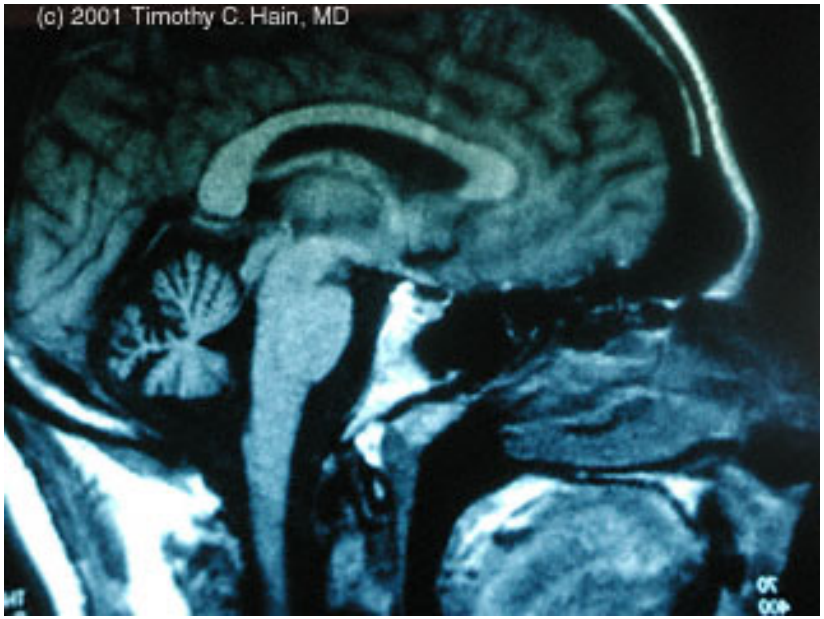
Cerebellar ataxias

Cause

- group of disorders
- both genetic and environmental
- genetic ones are often long, amino acid repeats (CAG/glutamine repeat; GAA/ glutamic acid repeat)
- loss of cerebellum neurons

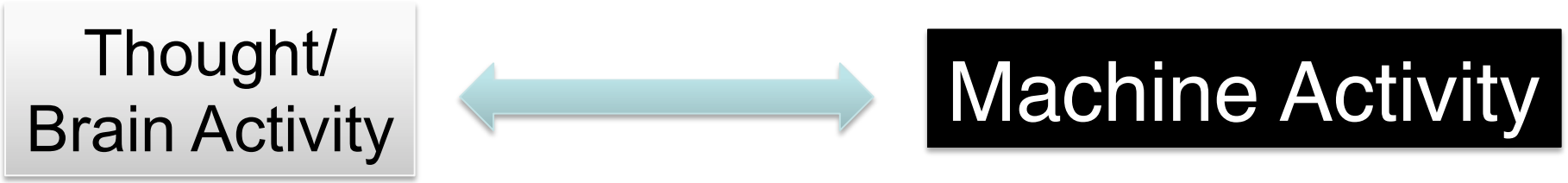
Treatment

- none currently



Degeneration of the cerebellum

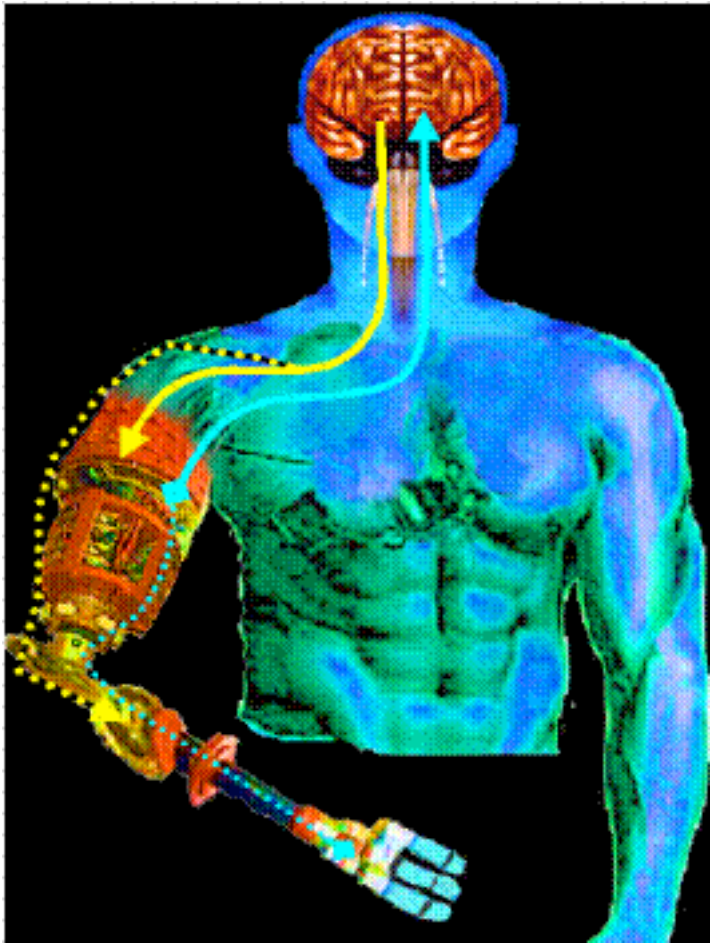
Brain-machine interfaces (BMI) or brain-computer interfaces (BCI)



Allows for communication and interaction with the external world without relying on peripheral nervous or muscular system activity.

Potentially useful for patients with severe brain damage, neurodegeneration, or spinal cord injury.

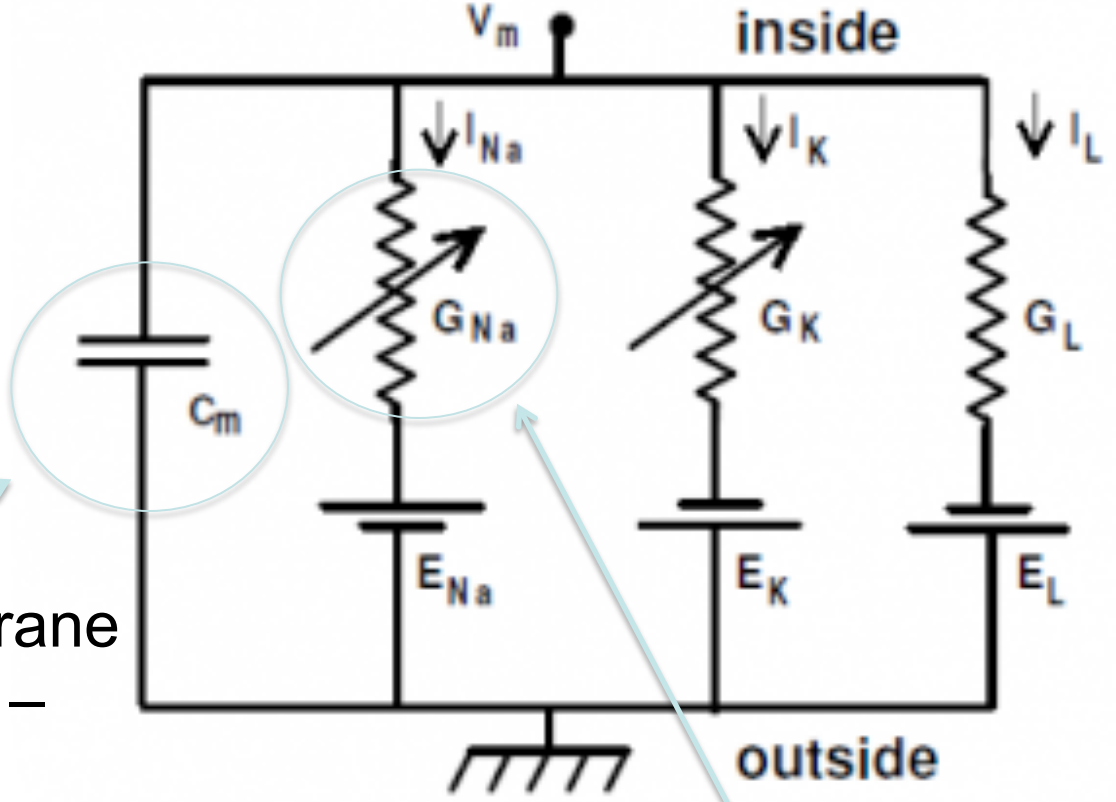
Neuroprosthetics



http://neurobio.drexelmed.edu/Research/NeuroEngineering/

Remember, neurons can be modeled as electrical circuits

So electrical circuits can be built to fill in gaps in neural pathways

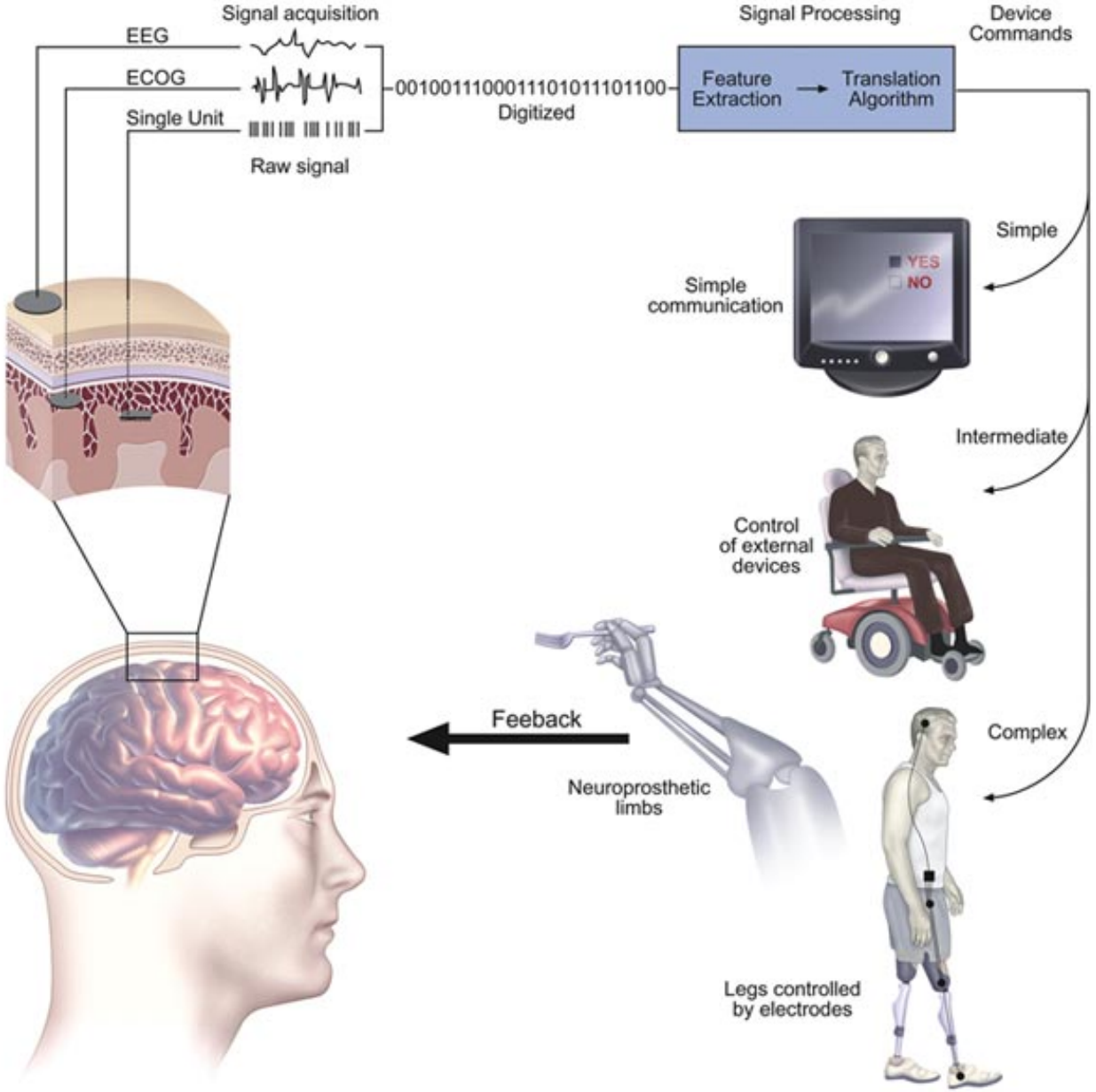


Neuron's membrane (acts a capacitor – stores charge)

Ion channels (act as variable resistors) affecting charge movement

http://neuronphysics.com/science/neuro/hh-neuron/

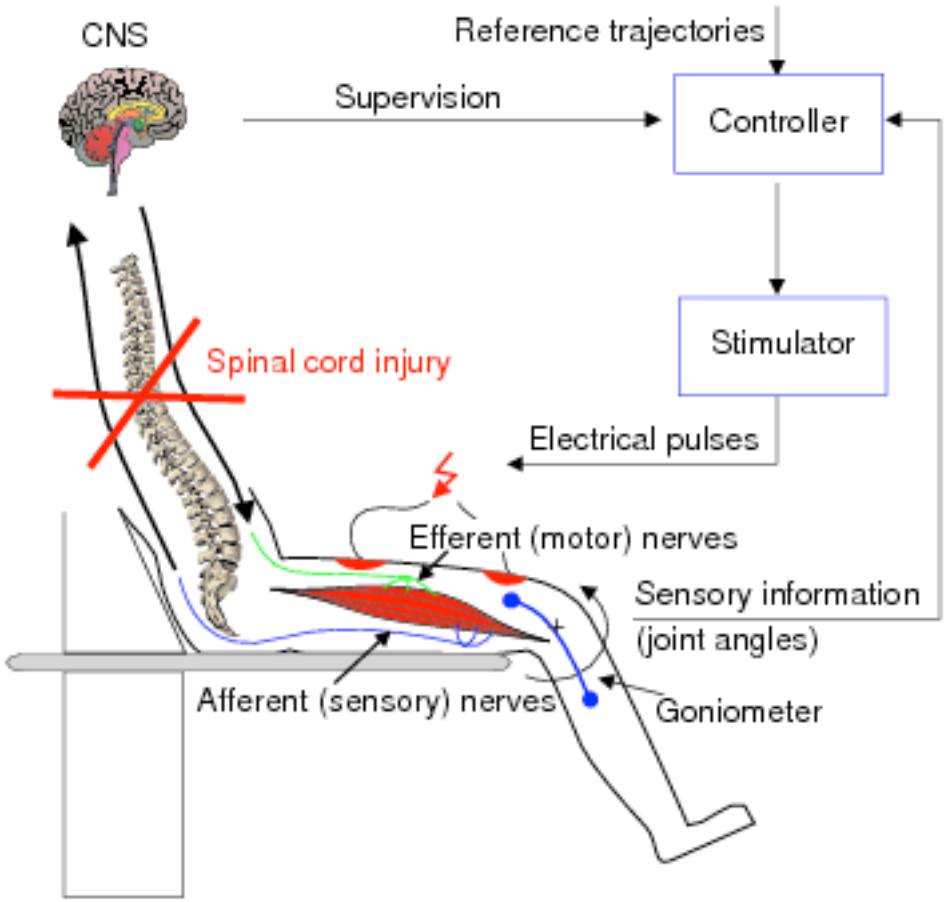
Signals recorded from the brain can be transformed into a signal that controls a device



http://cint.wustl.edu/graphics/assets/images/Projects/image353.jpg

Using BMI/BCI for motor restoration

FES = FUNCTIONAL ELECTRICAL STIMULATION: electrical currents generate action potentials in motor nerves that control muscles.



http://www.control.tu-berlin.de/
Controlled_Functional_Electric_Stimulation_for_Rehabilitation_Purposes

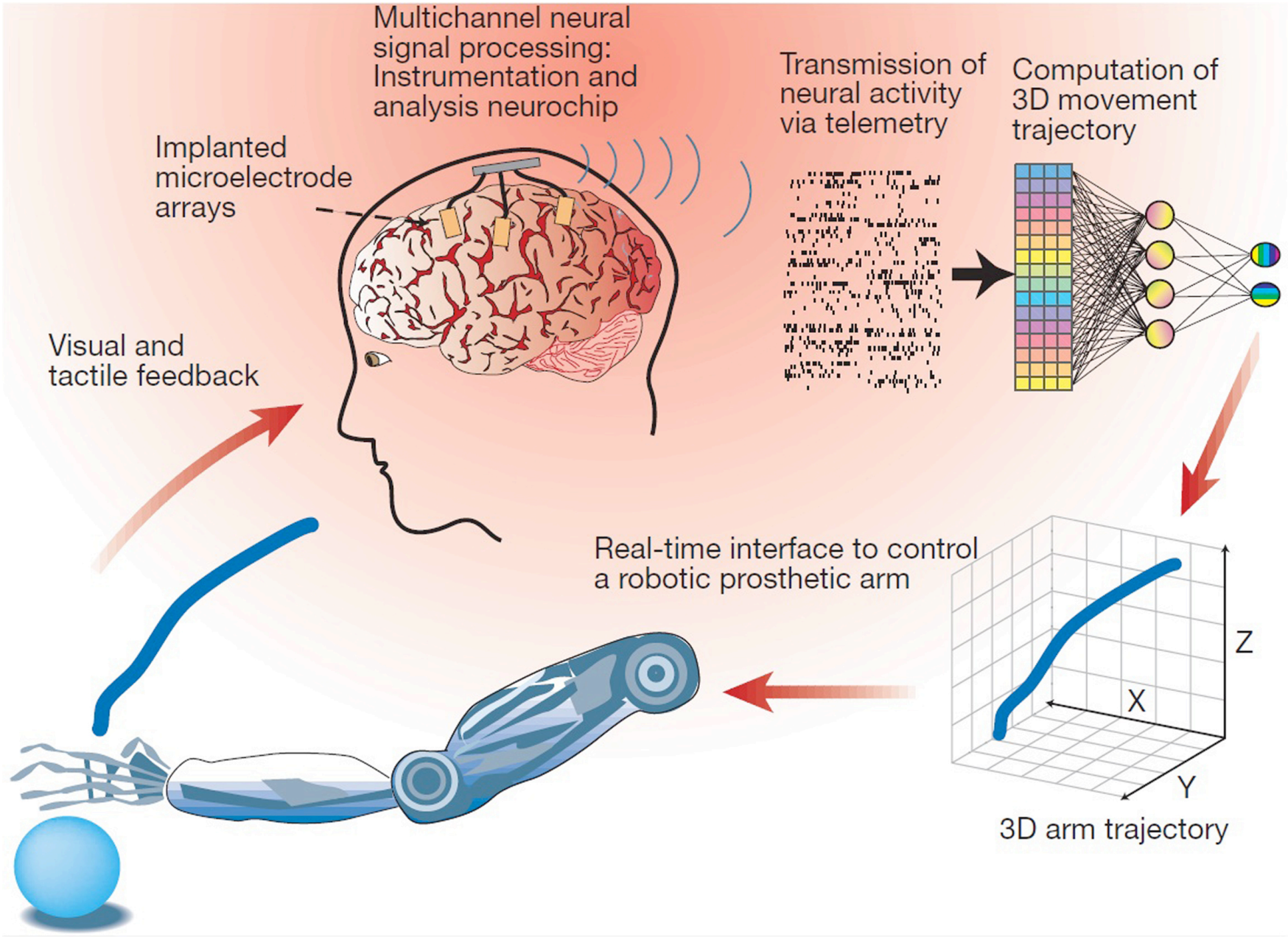
High-performance neuroprosthetic control by an individual with tetraplegia (Collinger et al., 2013)

Patient: 52 year old woman with spinocerebellar degeneration and tetraplegia. Had two intracortical microelectrode arrays implanted in left motor cortex

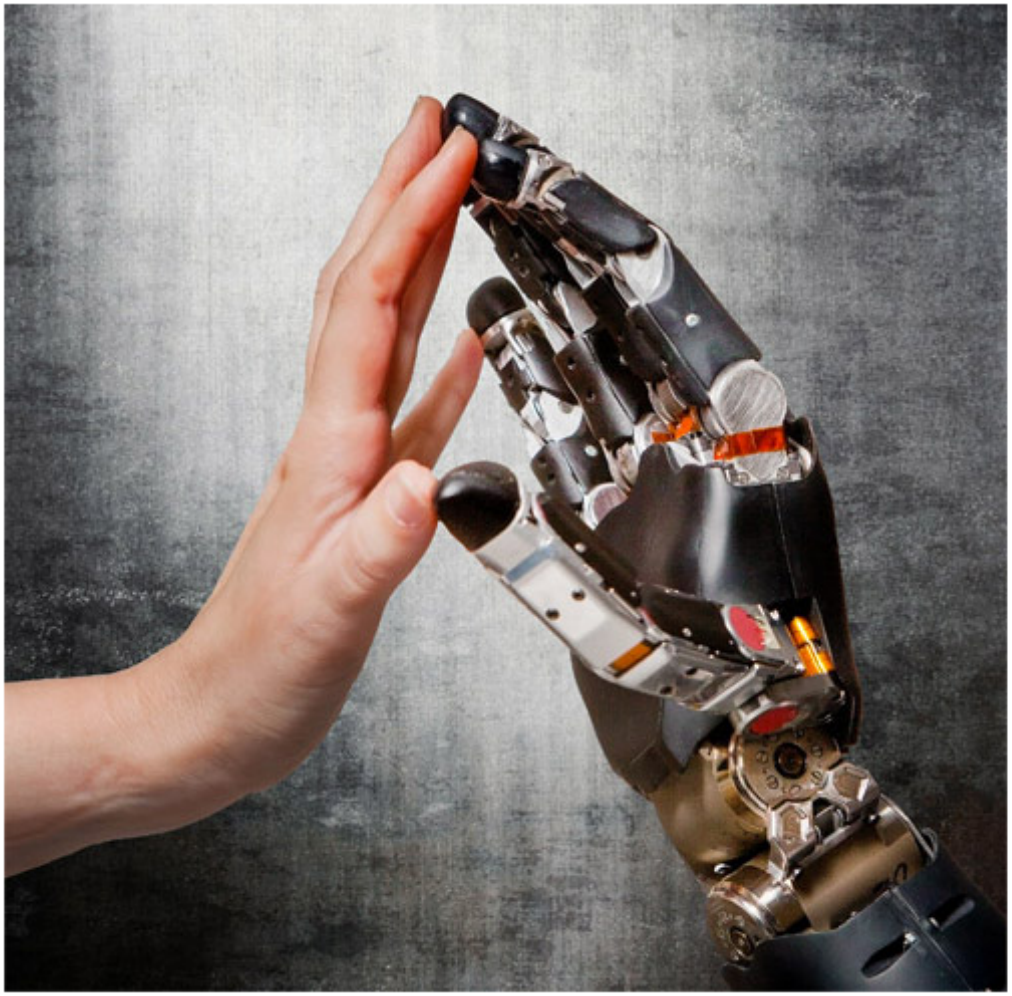
Two cables connected the array to the recording device (to measure signals in the brain) and another cable connected the device to a prosthetic arm

Neural decoder related neural firing rate to characteristics of movement (such as velocity) to control the arm

Collinger J.L., Wodlinger B., Downey J.E., Wang W., Tyler-Kabara E.C., Weber D.J., McMorland A.J.C., Vesllíste M., Boninger M.L., Schwartz A.B. High performance neuroprosthetic control by an individual with tetraplegia. Lancet. 2013; 381 (9866): 557-64.



http://www.frontiersin.org/Neuroengineering/10.3389/fneng.2010.00112/full



Neuroprosthetics

One approach to restoring sensorimotor function in amputees or tetraplegic patients consists in equipping them with anthropomorphic robotic arms that are interfaced directly with the nervous system.

To control these arms, not only must motor intention be translated into movements of the limb, but sensory signals must be transmitted from the limb to the patient. Indeed, without these signals, controlling the arm is very slow, clumsy, and effortful.

With this in mind, we develop approaches to convey meaningful and naturalistic sensations through stimulation of peripheral or cortical neurons, attempting to reproduce, to the extent possible, the patterns of neuronal activation that are relevant for basic object manipulation.

We anticipate that these studies will constitute an important step towards restoring touch to those who have lost it.

From Bensmaia lab website: http://bensmaialab.uchicago.edu/