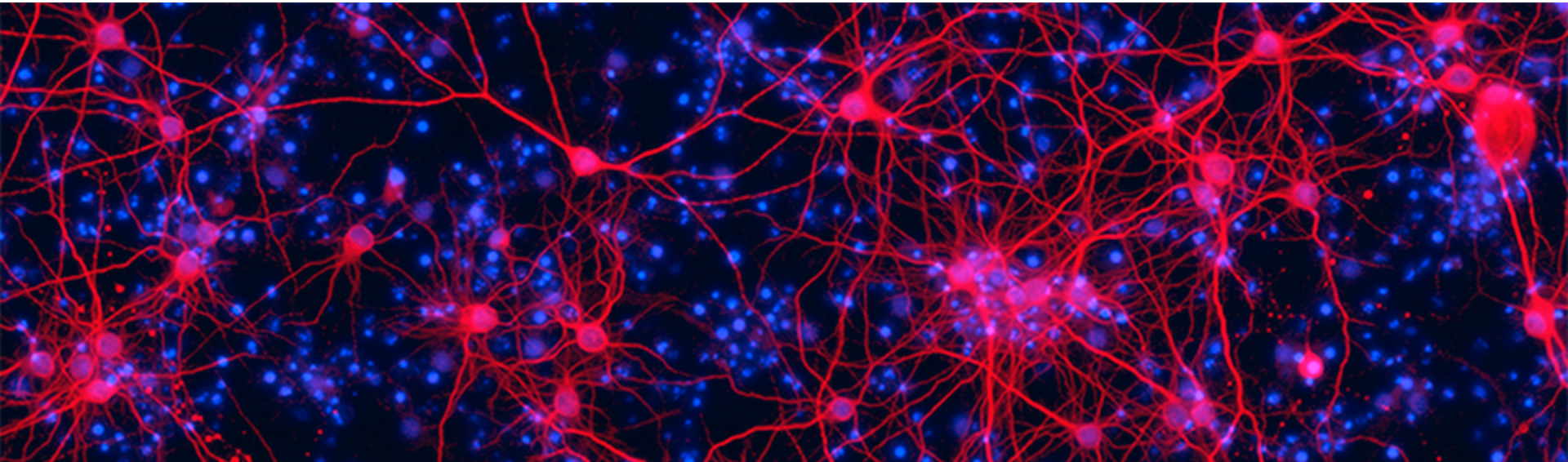
Applied Neuroscience

Columbia Science Honors Program

Fall 2016

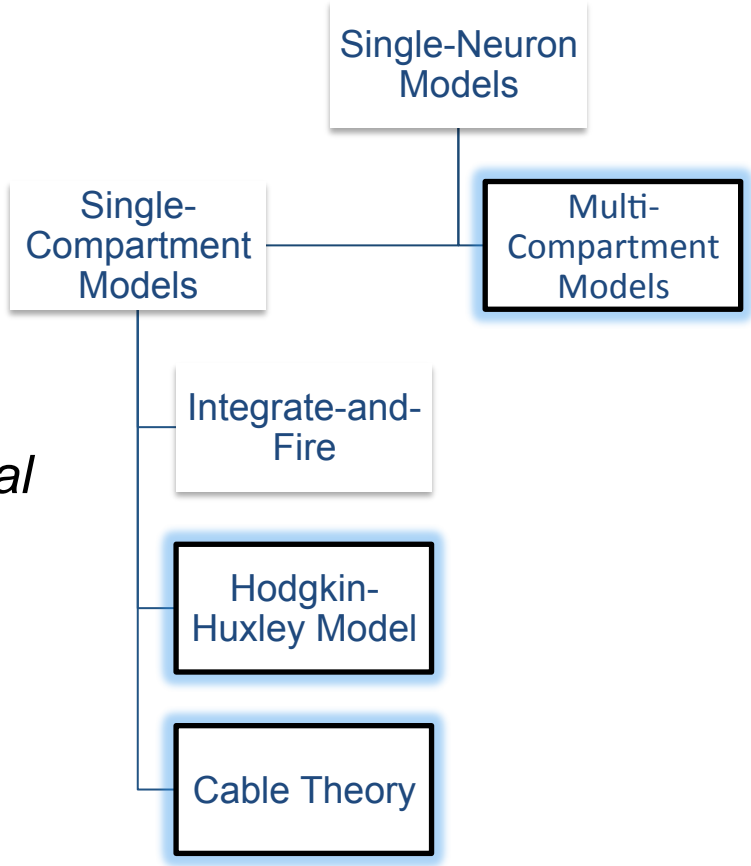
Computational Models of Neurotransmission and Motor Systems



Neurotransmission and Multi-Compartment Models

To Model a Neuron:

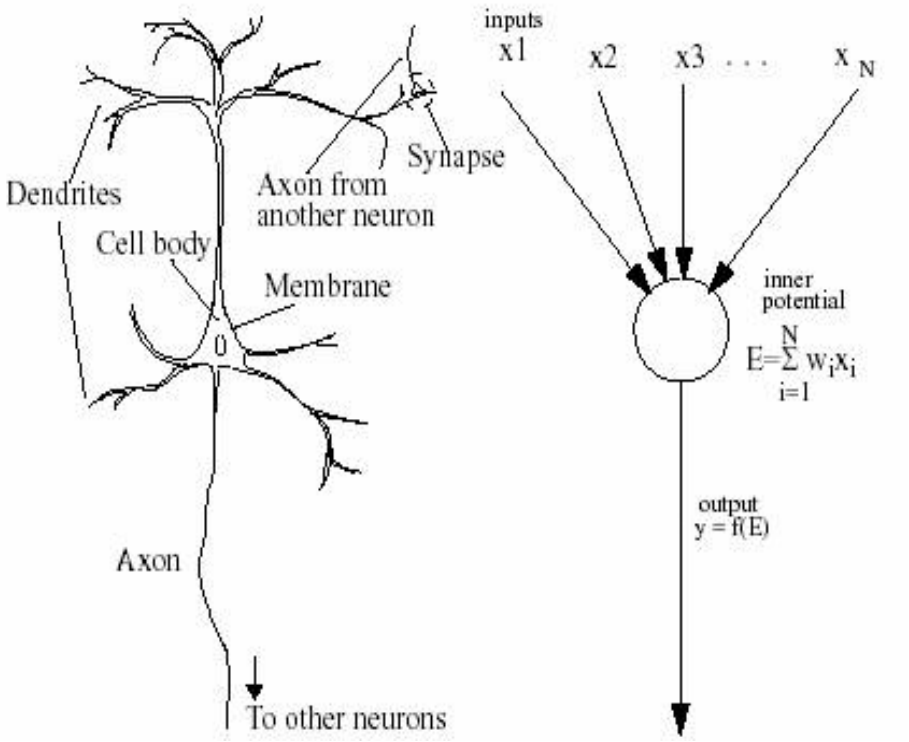
1. Intrinsic properties of cell membrane
2. Morphology



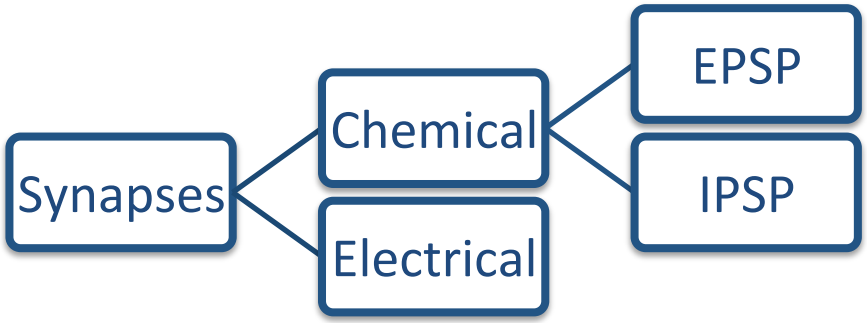
Single-Compartment Models
describe the membrane potential of a single neuron by a single variable and ignore spatial variables

Multi-Compartment Models
describe how variables are transmitted among the compartments of a system

Simulation of a Neuron



Neuronal Structure	Analogy
Dendritic Tree	Input (sums output signals received from surrounding neurons in the form of electric potential)
Soma	Processing
Axon	Output



Input to Neuron:
Continuous Variable

Output to Neuron:
Discrete Variable

Man V. Machine in Information Processing

Features	Human Brain	Von Neumann Computer
Data Representation	Analog	Digital
Memory Localization	Distributed	Localized
Control	Distributed	Localized
Processing	Parallel	Sequential
Skill Acquisition	Learning	Programming

Computational Models of Neurotransmission

Objective: Model the transformation from input to output spikes

Last Time:

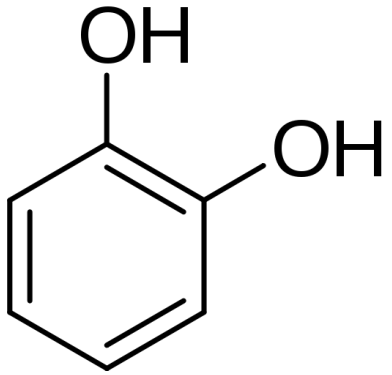
1. Model how the membrane potential changes with inputs
   Passive RC Membrane Model
2. Model the entire neuron as one component
   Integrate-and-Fire Model
3. Model the effects of inputs from synapses

Agenda:

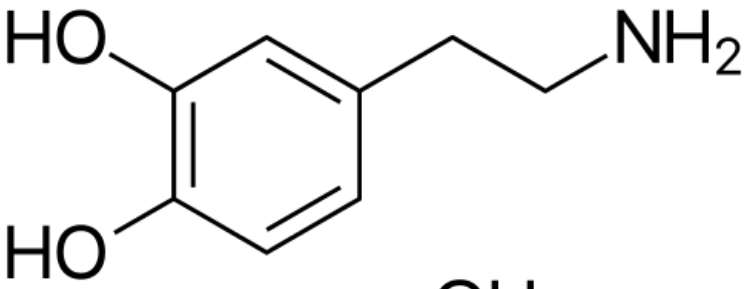
4. Chemistry of Neurotransmission
5. Model active membrane
   Hodgkin-Huxley Model
6. Motor Systems
   Primate Case Study

Catecholamines

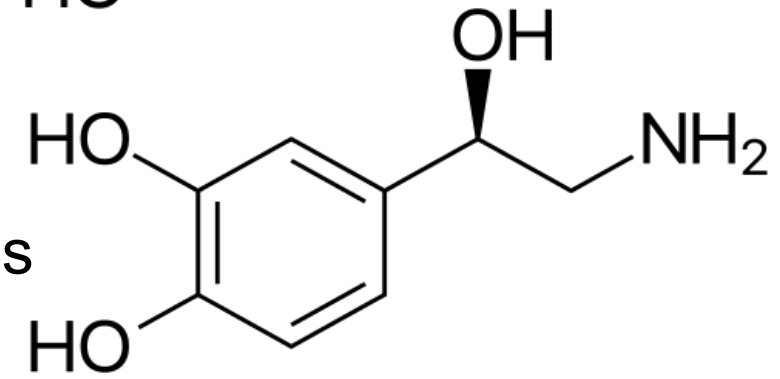
Catecholamine: a monoamine that has a **catechol** (benzene with two hydroxyl groups at carbons 1 and 2 and a side-chain anime)



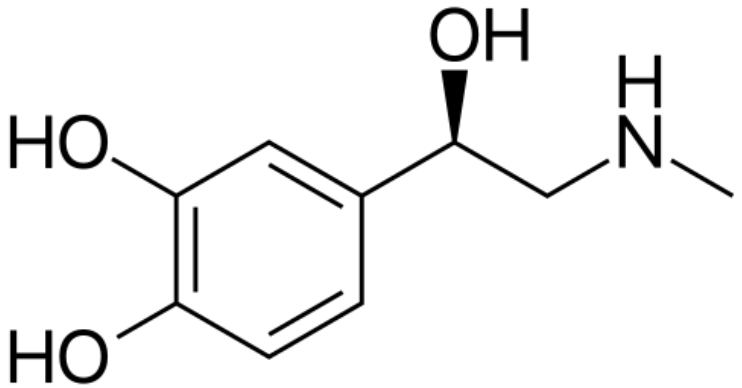
Dopamine (DA): important neurotransmitter involved in reward-motivated behavior and motor control



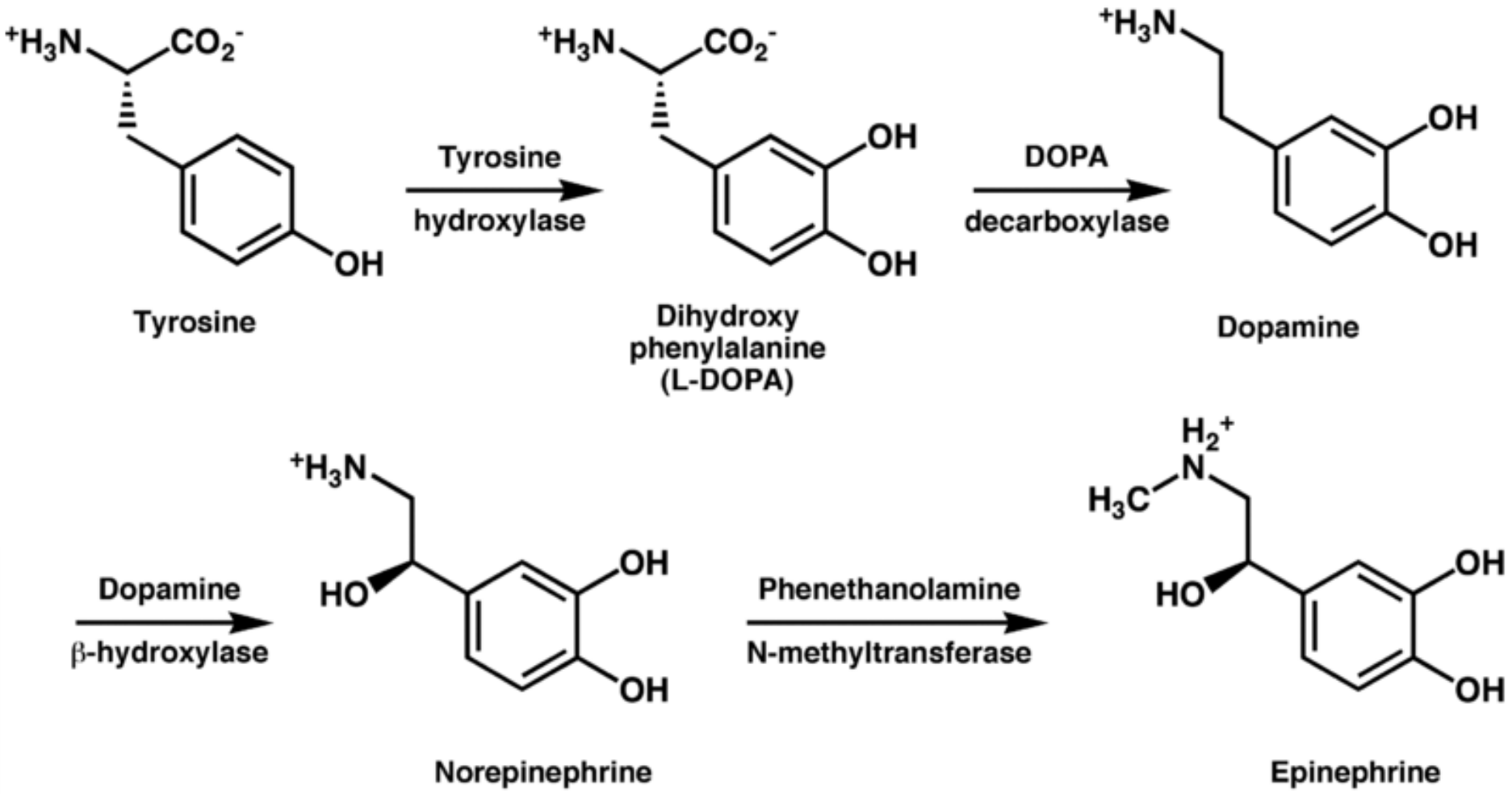
Norepinephrine (NE): functions to mobilize the brain and body for action as part of fight-or-flight response



Epinephrine (EPI): (adrenaline) medication for anaphylaxis and cardiac arrest, hormone in fight-or-flight response

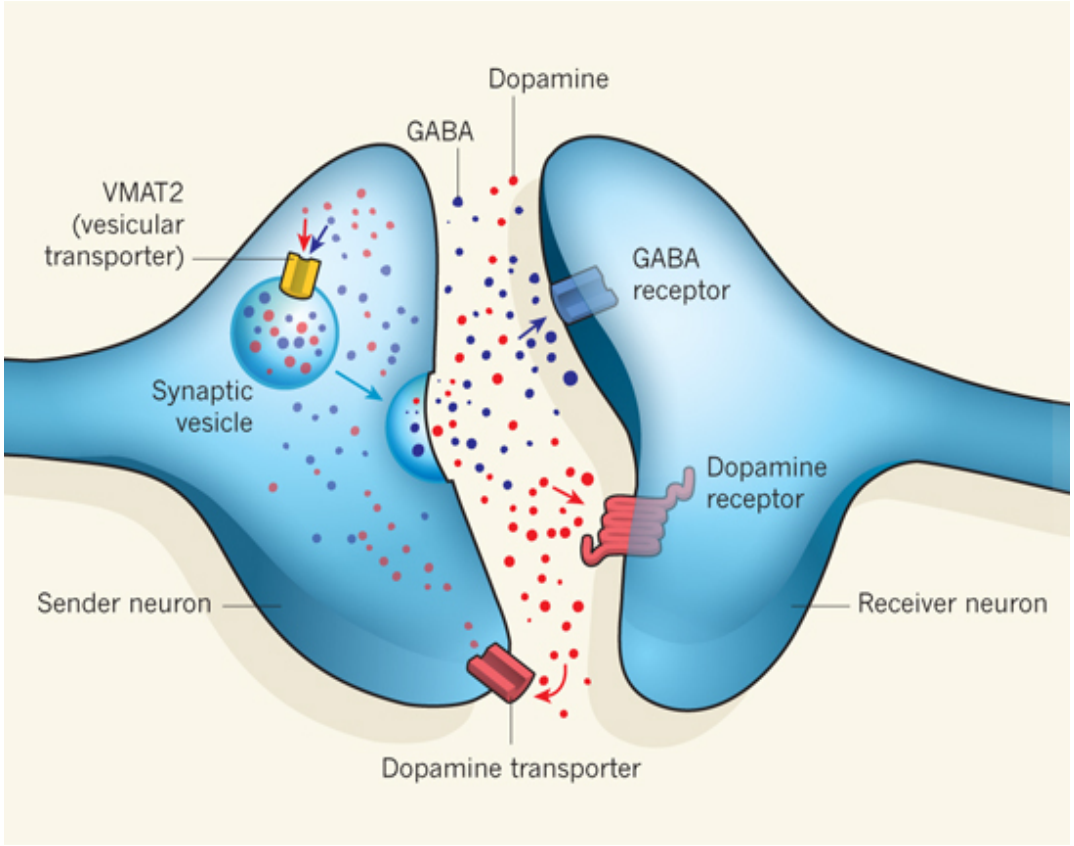


Catecholamine Synthesis



The rate-limiting enzyme is **tyrosine hydroxylase**, which is regulated by the product (feedback) and by stress (up-regulation)

Dopamine Vesicular Release



1. In sender neuron, vesicular transporters (proteins) pack neurotransmitters (dopamine) into vesicles.
2. When cell is activated, synaptic vesicles are discharged into synaptic cleft.
3. Neurotransmitters bind to receptors on the surface of the receiver neuron, triggering changes in the cell's activity.

Two Messages in One Parcel

Tritsch et al illustrate that dopamine-releasing neurons use VMAT2 to store dopamine and GABA in the same vesicles. Co-release allows dopamine-releasing neurons to modulate activity.

Modulation of Catecholamines

1. Modulation of Release

Release of catecholamines is dependent on neuronal cell firing.

Some drugs induce the release independently from nerve cell firing.

In animal models, an increase in catecholamine release produces increased loco-motor activity and stereotyped behavior.

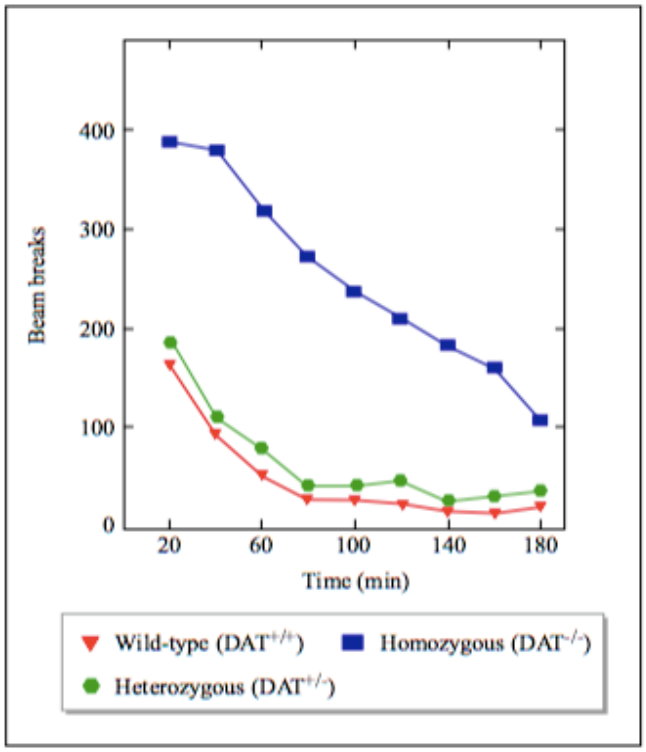
Psycho-stimulants such as **amphetamine** and **methamphetamine** in humans result in increased alertness, euphoria, and insomnia.

2. Modulation of Auto-Receptors

Stimulation of auto-receptors inhibits catecholamine release.

Auto-receptor antagonists increase catecholamine release.

Transgenic Animals



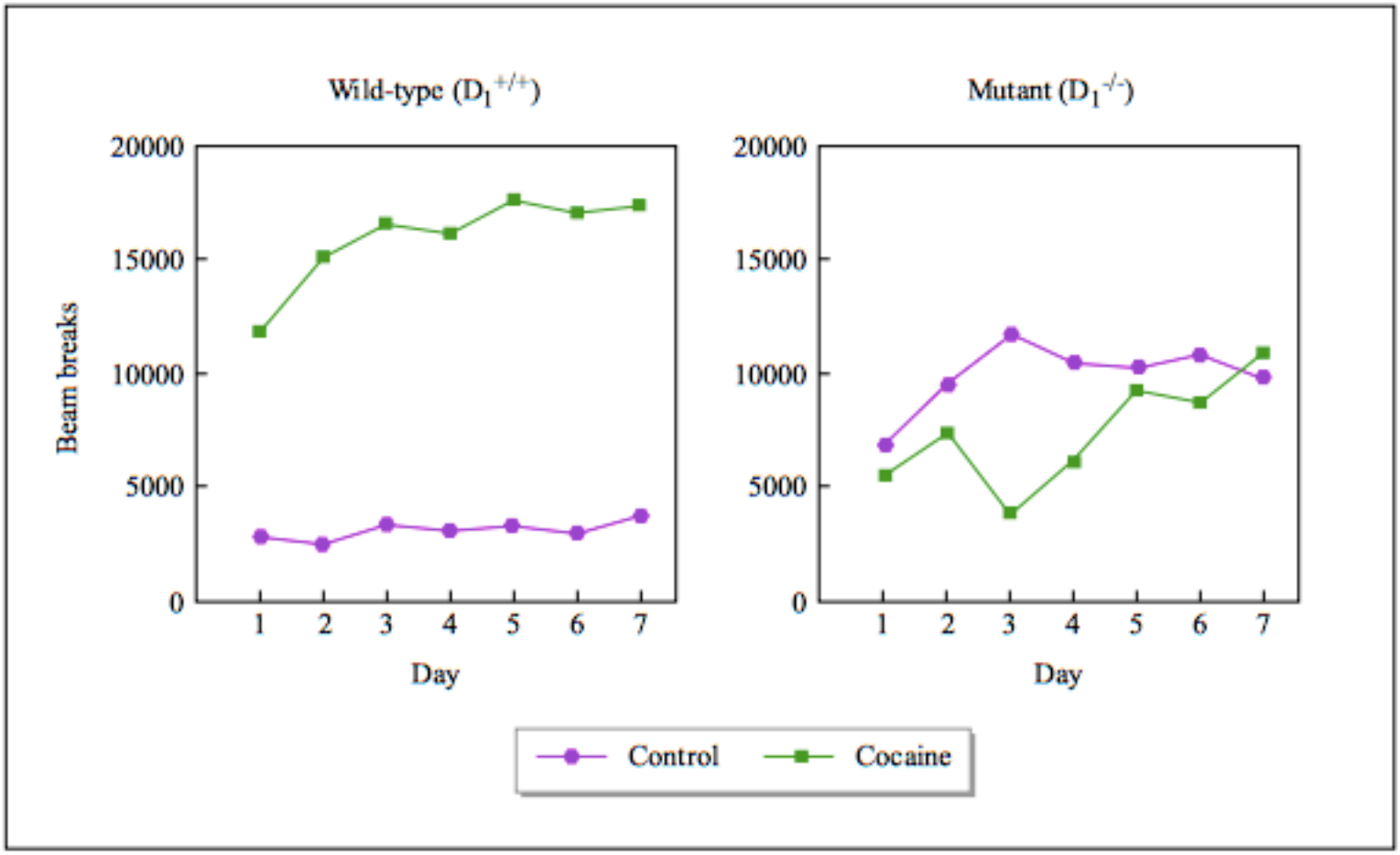
Transgenic Animal: Animal that has a foreign gene inserted into its genome

Transgenic animals are useful for the characterization of neurotransmitter action

Dopamine Transporter (DAT): membrane-spanning protein that pumps dopamine out of the synapse back into the cytosol

Figure illustrates that mutant mice lacking the dopamine transporter (DAT) show an increase in loco-motor activity.

Effects of Cocaine on Dopamine



Mice that lack dopamine receptors are insensitive to loco-motor stimulating effects induced by cocaine.

Cocaine: Acts as an Inhibitor of Catecholamine Reuptake

Dopaminergic Pathways

1. Nigro-striatal Tract

Cells from the substantia nigra project to the striatum in the forebrain that functions in control of movement
*Affected in **Parkinson Disease***

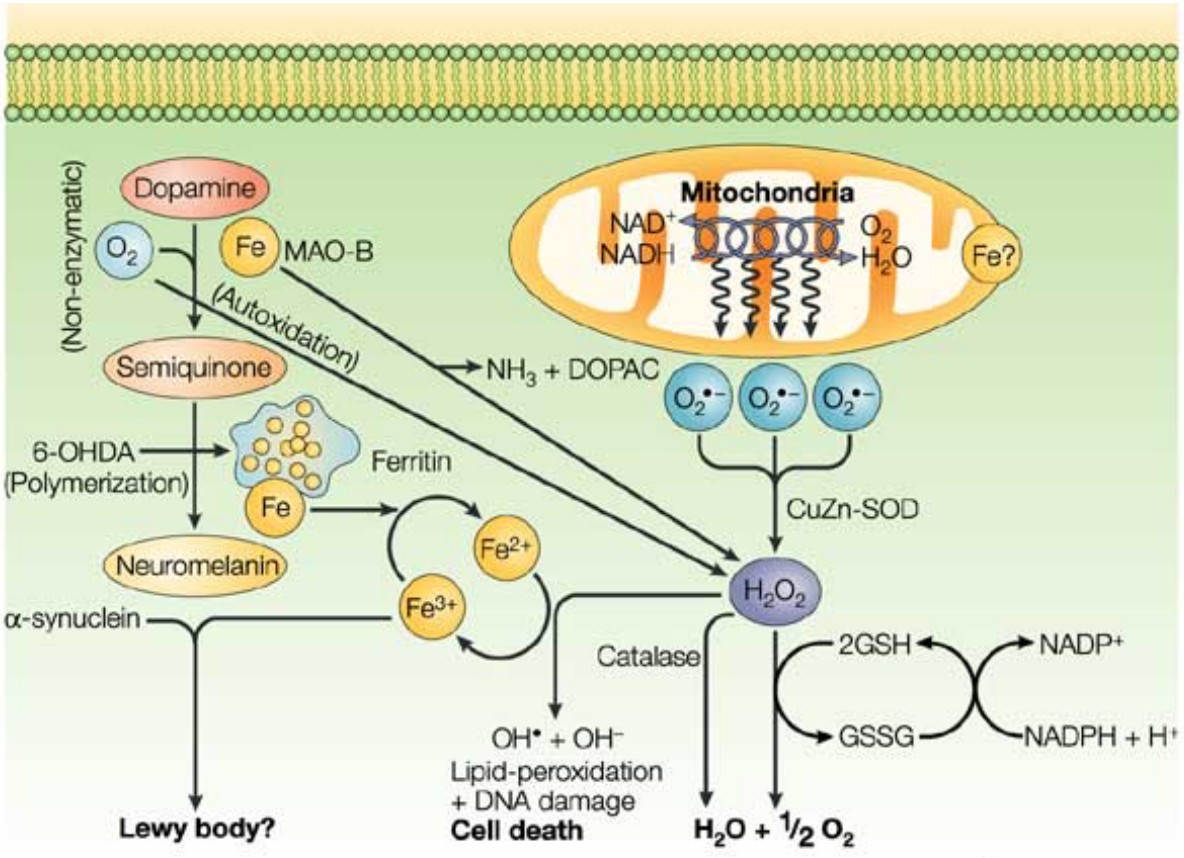
2. Meso-limbic Dopamine Pathway

Dopaminergic neurons in the Ventral Tegmental Area (VTA) in the mesencephalon. Projects to structures of the limbic system: *nucleus accumbens, septum, amygdala, and hippocampus*
*Affected in **Drug Abuse and Schizophrenia***

3. Meso-cortical Dopamine Pathway

Dopaminergic neurons in the Ventral Tegmental Area (VTA) in the mesencephalon project to the cerebral cortex.
*Affected in **Drug Abuse and Schizophrenia***

Parkinson Disease



Iron and Oxidative Stress Hypothesis

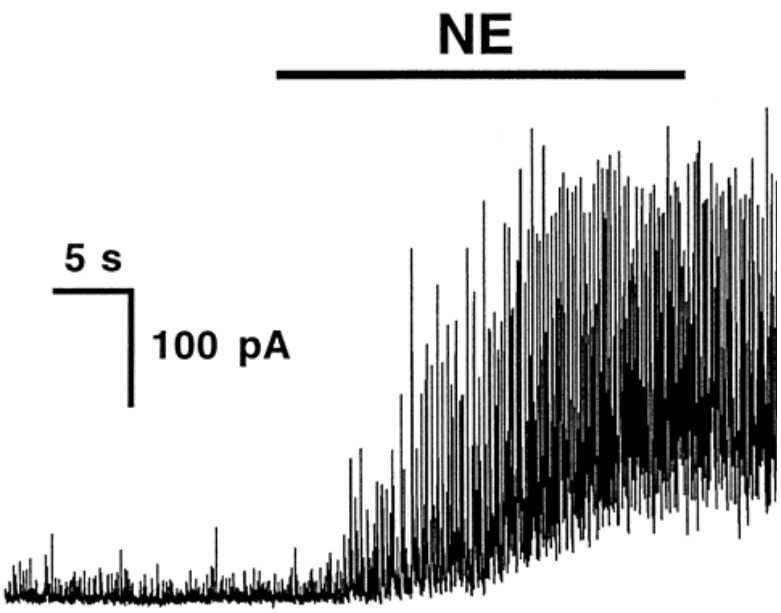
Mechanisms of cell-death based on post-mortem findings shown above, which indicate reduced mitochondrial complex I activity, loss of reduced glutathione (GSHP), and increased iron and oxidative stress levels in ***substantia nigra***.

Major Symptoms:
Motor Deficits
Cognitive Dysfunction

Cause:
Death of Dopaminergic Neurons in the ***substantia nigra***

Possible cause for Dopamine Loss:
Oxyradical-induced oxidative stress that damages and kills DA neurons

Norepinephrine



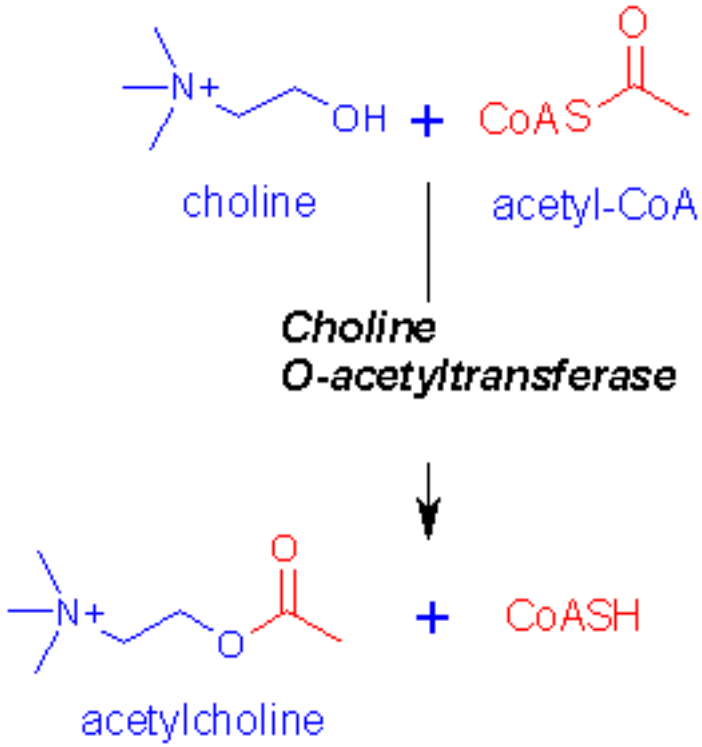
In the figure above, norepinephrine increases the frequency of post-synaptic currents.

Norepinephrine neurons in the **locus coeruleus (LC)** play an important role in the state of vigilance: being alert to external stimuli

Norepinephrine modulates:

1. Vigilance
2. Anxiety
3. Pain
4. Hunger and Eating Behavior

Acetylcholine



Acetylcholine is an ester of acetic acid and choline. It is synthesized from choline and acetyl-CoA in certain neurons.

Acetylcholine is a neurotransmitter in:

1. Neuro-muscular Junctions
2. Peripheral Nervous System
3. Central Nervous System

Factors that regulate acetylcholine synthesis:

1. Availability of reagents
2. Firing Rates

Factors that Modulate Acetylcholine Release

1. Toxin in Venom of Black Widow Spider

Induce a massive release of acetylcholine, thereby causing:

tremors, pain, vomiting, salivation, and sweating

2. Botulinum Toxins

Block acetylcholine release, thereby causing:

blurred vision, difficulty speaking and swallowing, and muscle weakness

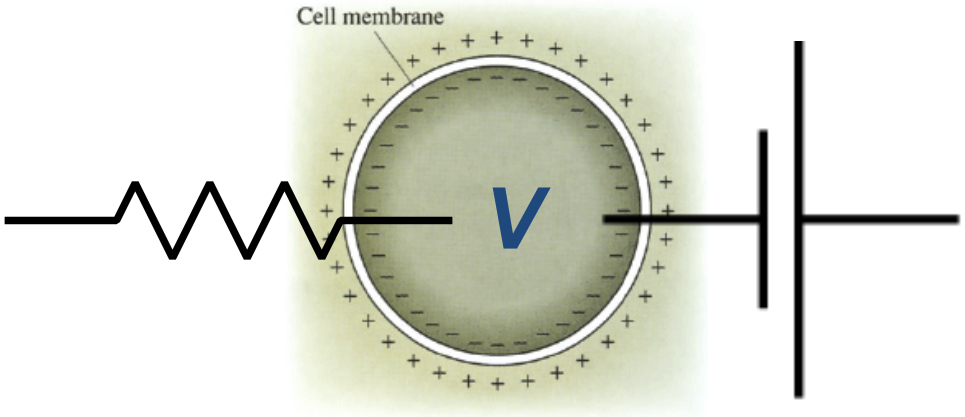
Toxins are picked up by cholinergic neurons at the neuro-muscular junction, resulting in muscle paralysis.

Low Dose of Botox can be used for therapeutic purposes:

*1. Relieve **dystonia:** permanent muscle contraction*

2. Reduce Wrinkles

Modeling Neural Membranes



Membrane Current due to Ions ("Leak Current")

$$-i_m = c_m \frac{dV}{dt} = \frac{dQ}{dt}$$

$R_m = r_m / A$
$r_m \sim 1\ M\Omega\ mm^2$
(Specific Membrane Resistance)

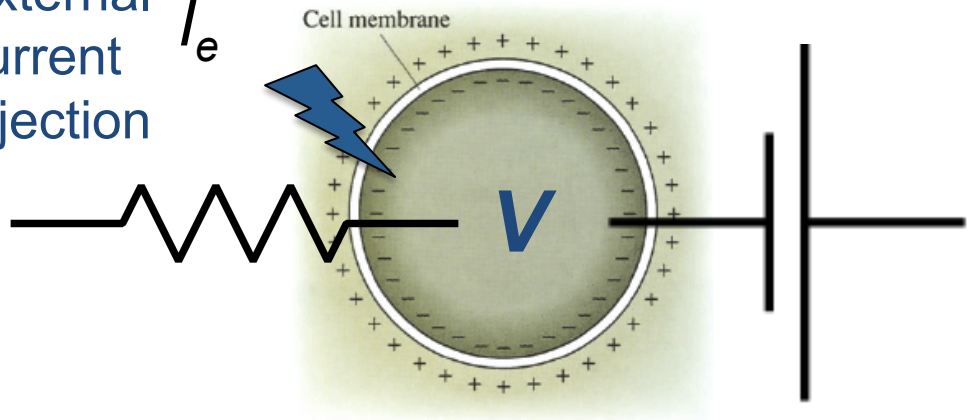
$Q = C_m V$
$C_m = c_m A$
$c_m \sim 10\ nF / mm^2$
(Specific Membrane Capacitance)

Membrane Current with Leak Conductance Term

$$i_m = \sum_i g_i (V - E_i) = g_L (V - E_L) = \frac{(V - E_L)}{r_m}$$

Compartment Membrane Model

External current injection I_e



Membrane Time Constant

$\tau_m = r_m c_m$

$$c_m \frac{dV}{dt} = -\frac{(V - E_L)}{r_m} + \frac{I_e}{A}$$

$R_m = r_m / A$

$r_m \sim 1\ M\Omega\ mm^2$

(Specific Membrane Resistance)

$Q = C_m V$

$C_m = c_m A$

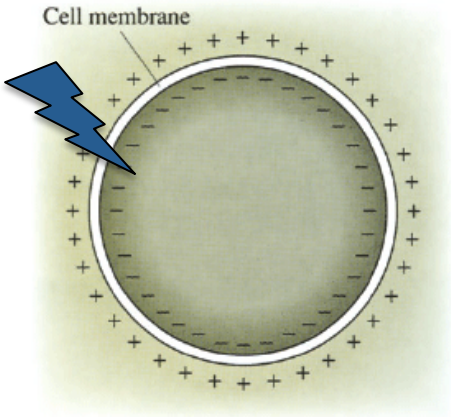
$c_m \sim 10\ nF / mm^2$

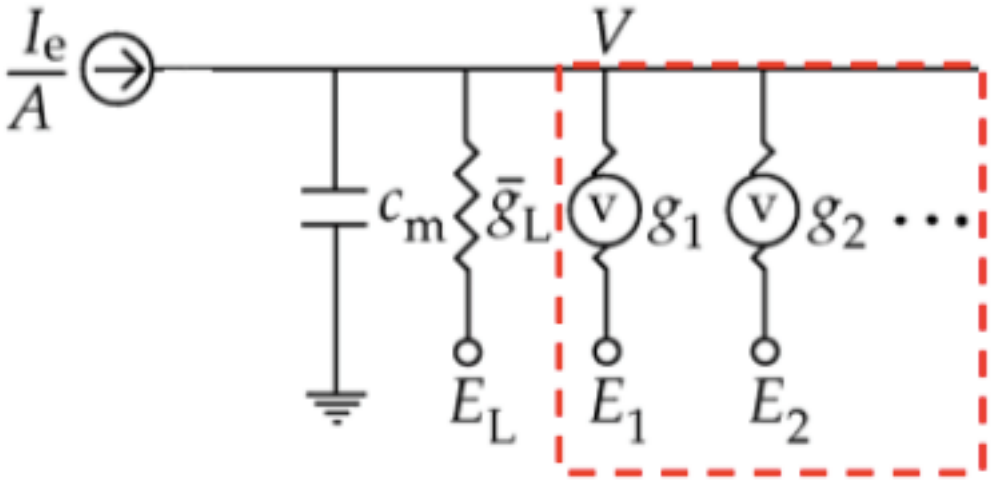
(Specific Membrane Capacitance)

$$\tau_m \frac{dV}{dt} = -(V - E_L) + I_e R_m$$

Modeling Active Membranes

External current injection I_e





$$\tau_m \frac{dV}{dt} = -(V - E_L) - r_m g_1 (V - E_1) \ldots + I_e R_m$$

$$g_1 = g_{1,\max} P_1$$

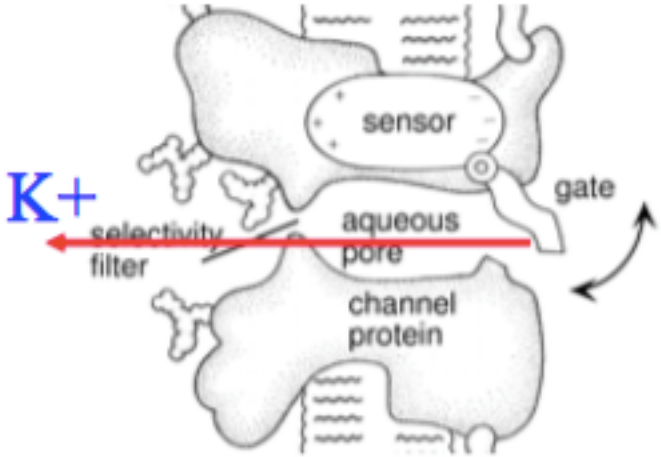
$g_{1,max}$ represents maximum possible conductance

P_1 represents the fraction of ion channels open

Example 1: Delayed-Rectifier K^+ Channel

$$g_K = g_{K,\max} P_K$$

$$P_K = n^4$$



4 **=** indicates 4 independent subunits are necessary for K^+ channel to open

$$\frac{dn}{dt} = \alpha_n(V_1)(1-n) - \beta_n(V_2)n$$

V_1 **=** opening rate
n **=** fraction of channels open
1 – n **=** fraction of channels closed
V_2 **=** closing rate

Example 2: Transient Na^+ Channel

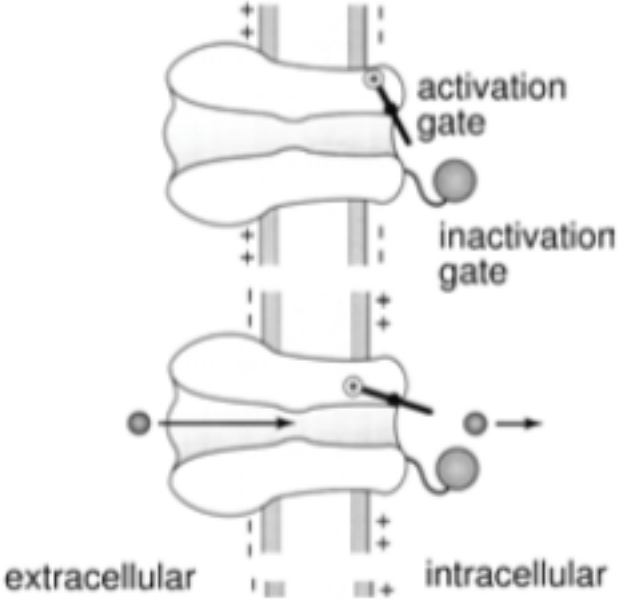
$$g_{Na} = g_{Na,\max} P_{Na}$$

$$P_{Na} = m^3 h$$

***m* =** Activation

***3* =** indicates 3 independent subunits are necessary for Na^+ channel to be activated

***h* =** Inactivation

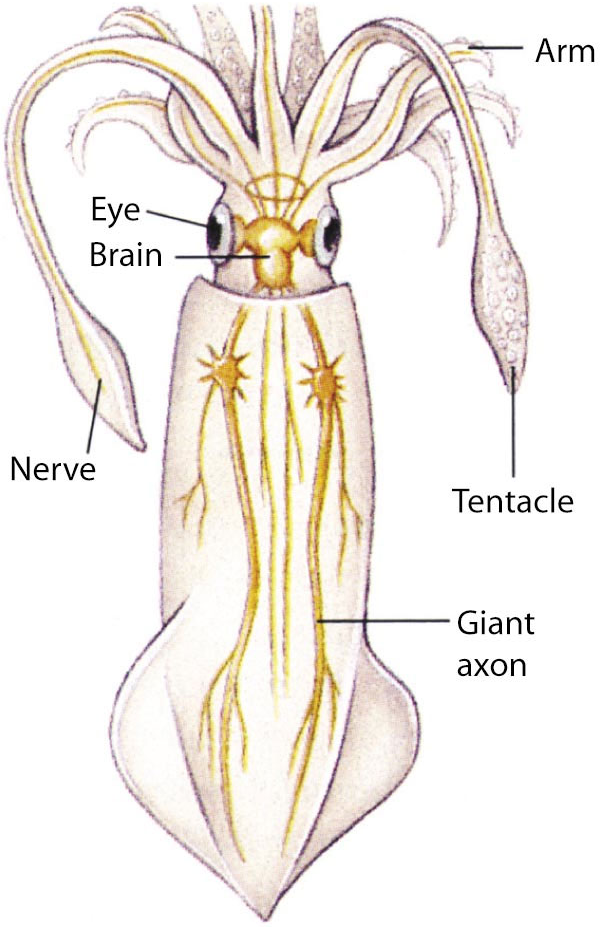


$$\frac{dm}{dt} = -(\alpha_m + \beta_m)m + \alpha_m$$

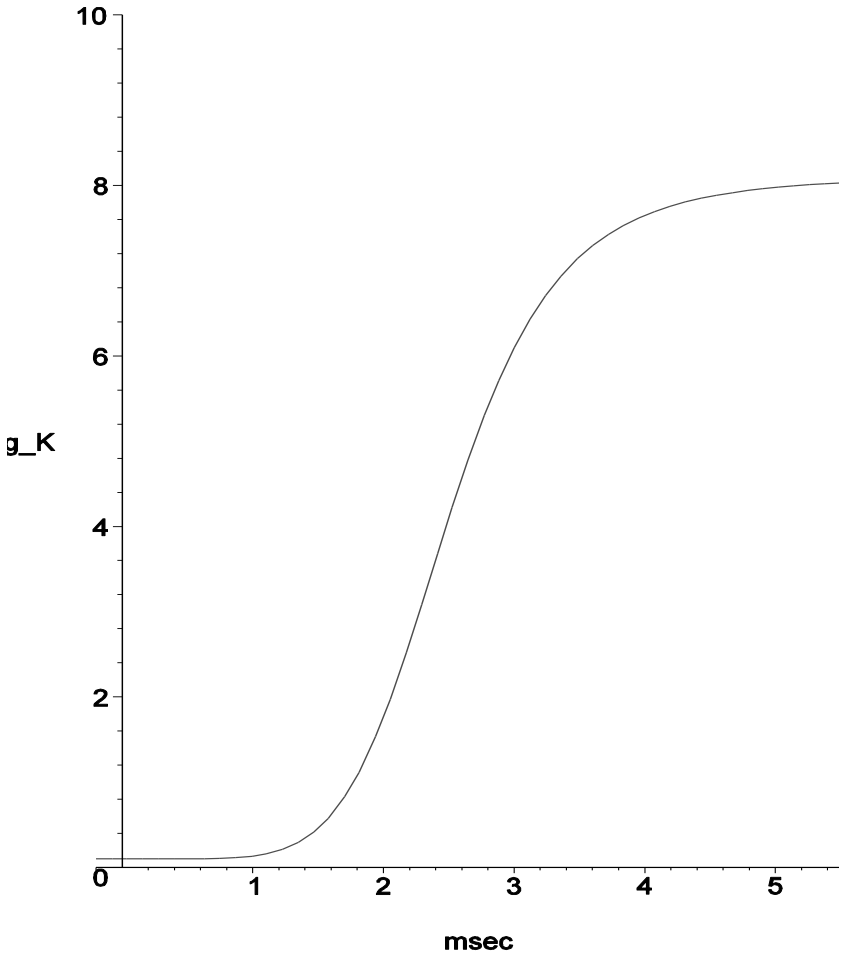
$$\frac{dh}{dt} = -(\alpha_h + \beta_h)h + \alpha_h$$

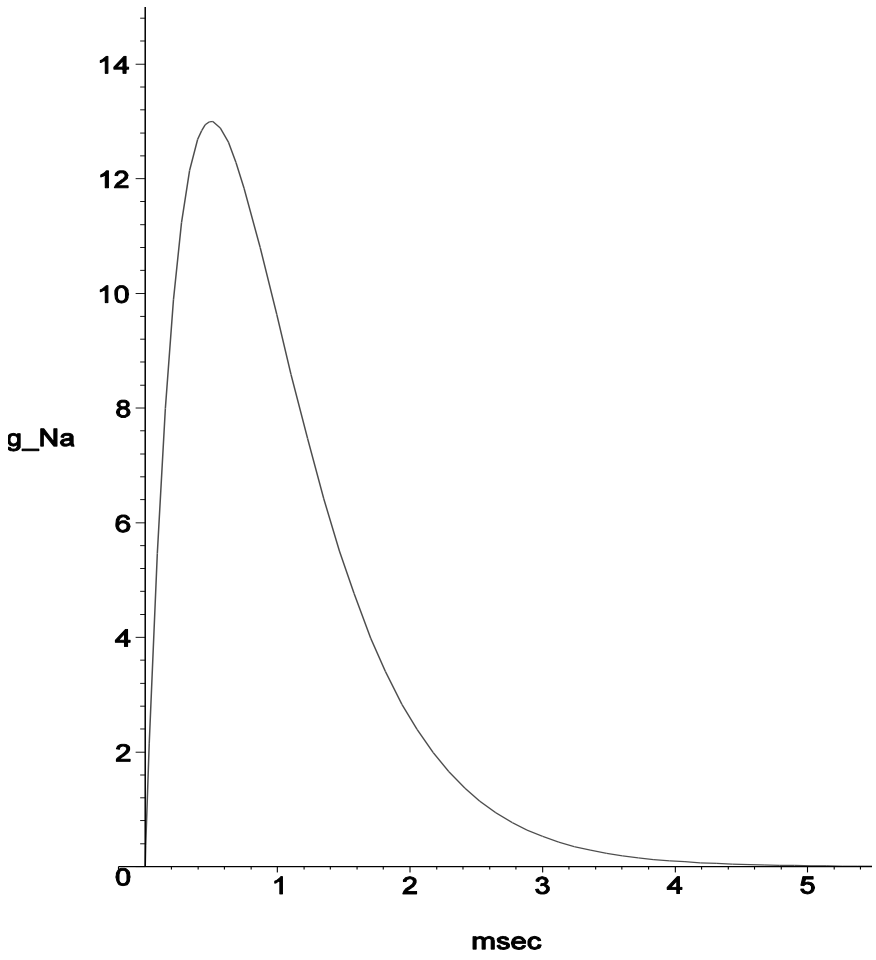
Hodgkin-Huxley Model

Alan Hodgkin, Andrew Huxley, John Eccles
Nobel Prize in Physiology (1963) for discovery of mechanisms of the giant squid neuron cell membrane



Variable Conductance

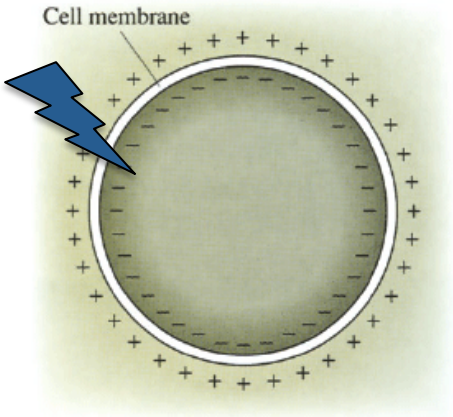


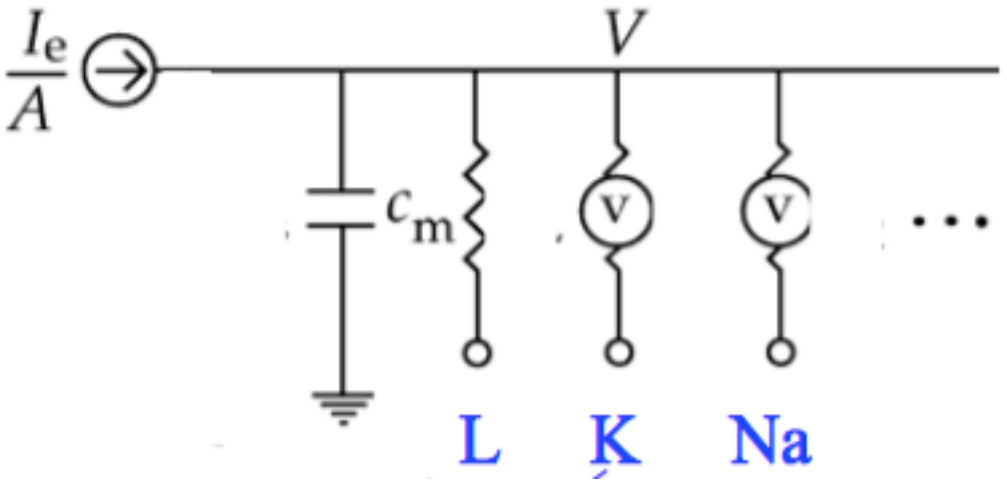


Experiments illustrated that g_K and g_{Na} varied with time *t* and voltage *V*. After stimulus, Na responds much more rapidly than K.

Hodgkin-Huxley Model

External current injection I_e



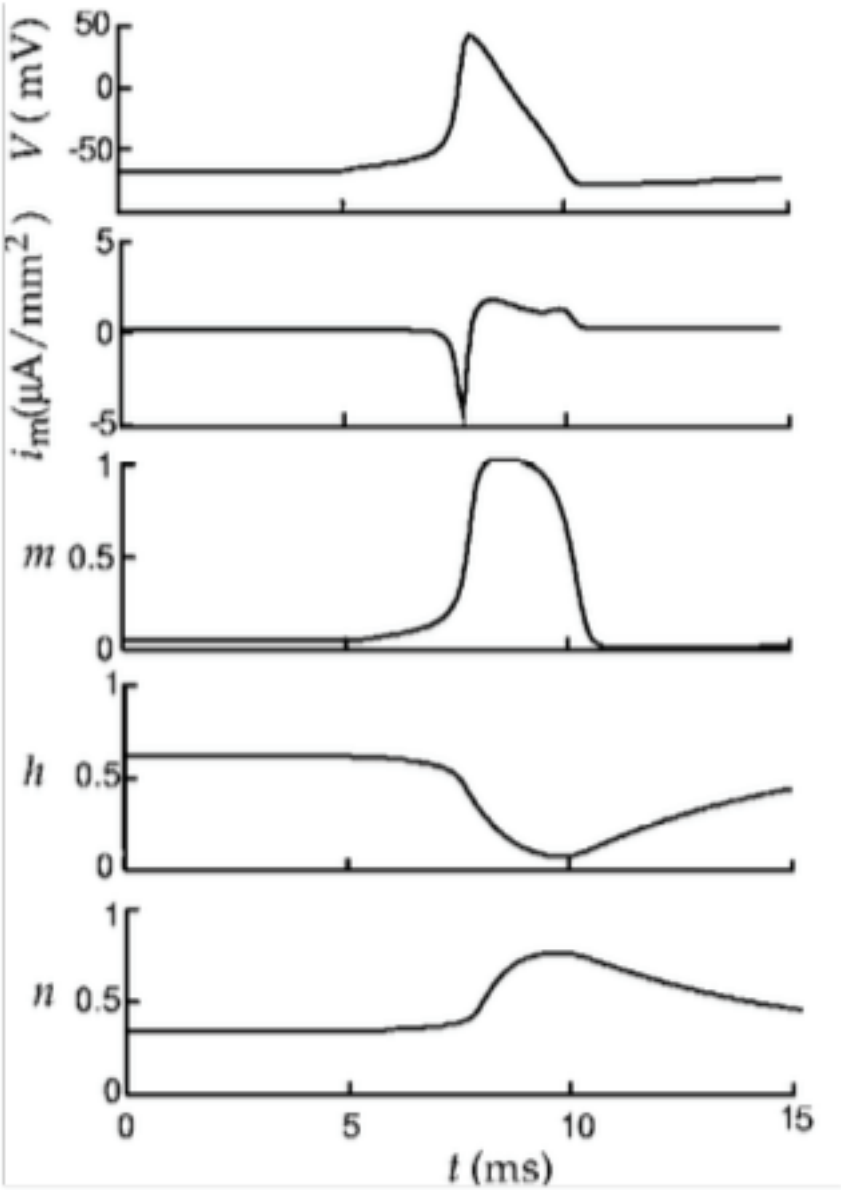


$$c_m \frac{dV}{dt} = -i_m + \frac{I_e}{A}$$

$$i_m = g_{L,\max}(V - E_L) + g_{K,\max} n^4 (V - E_K) + g_{Na,\max} m^3 h (V - E_{Na})$$

E_L = -54 mV
E_K = -77 mV
E_{Na} = +50 mV

Hodgkin-Huxley Model Dissected



Action Potential (Spike)

Membrane Current

Na^+ Activation (m)

Na^+ Inactivation (h)

K^+ Activation (n)

Motor Systems

Objective: Understand a computational model of motor control

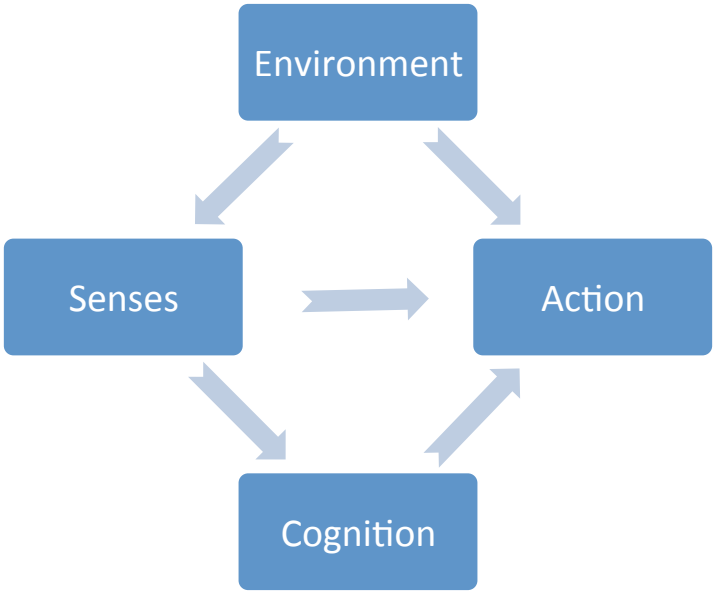
Agenda:

1. Motor control
2. Motor cortex

- ❖ Primate case study
- ❖ Spiker Boxes

Motor control

1. Through our senses, we perceive our world and relation to it.
2. But this processing is useless if we didn't have a way to act upon the environment we are sensing.
   i.e. running from a predator; searching for food when hungry
3. Sometimes, the relationship between sensory input and motor output is simple. Other times it isn't.
   i.e. touching a hot stove and moving your hand
4. Final output is a set of commands to muscles in our body to exert force.

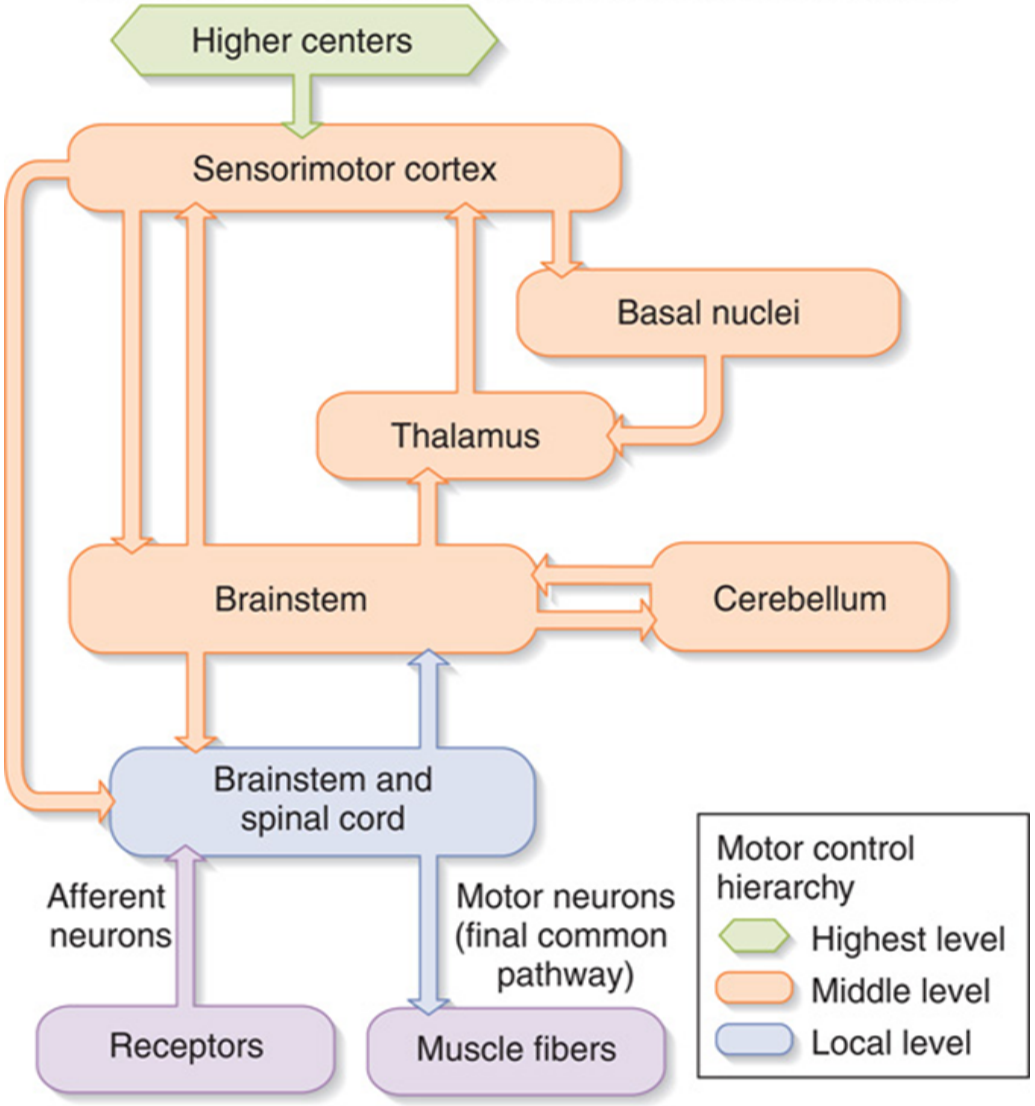


Components of motor control

1. Volition
2. Coordination of signals to many muscle groups
3. Proprioception
4. Postural adjustments
5. Sensory feedback
6. Compensation for the physical characteristics of the body and muscles
7. Unconscious processing
8. Adaptability

These components let us perform complex movements, easily. The brain has evolved complex mechanisms to perform these tasks.

Motor control hierarchy



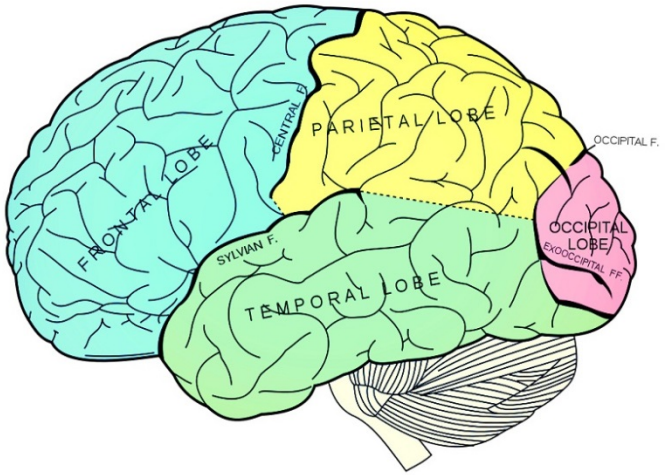
Motor cortex

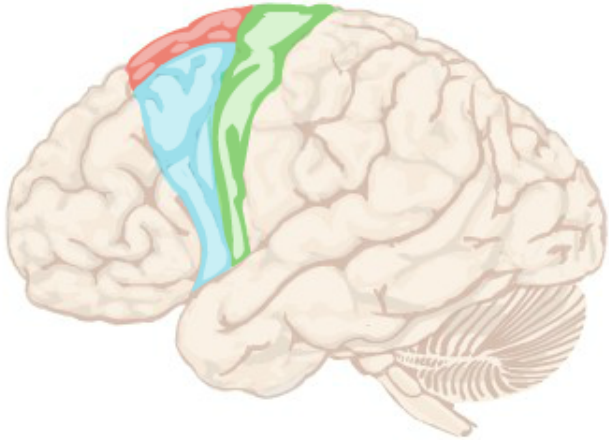
Contains three areas of the frontal lobe

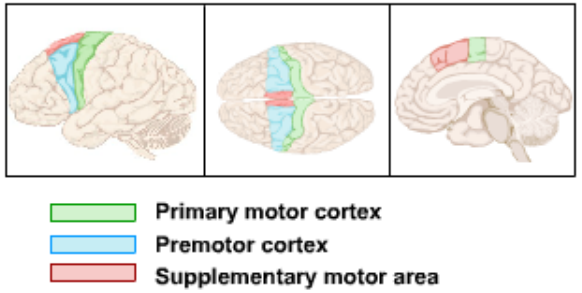
- Primary motor cortex
- Premotor cortex
- Supplementary motor area

Electrical stimulation of these areas causes movements of certain body parts.

Primary motor cortex requires the least amount of electrical current to elicit movement.



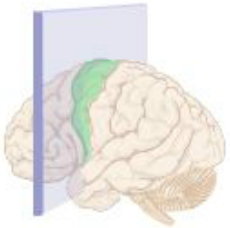


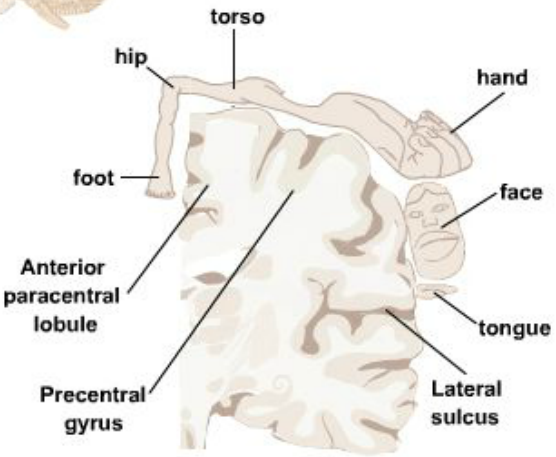


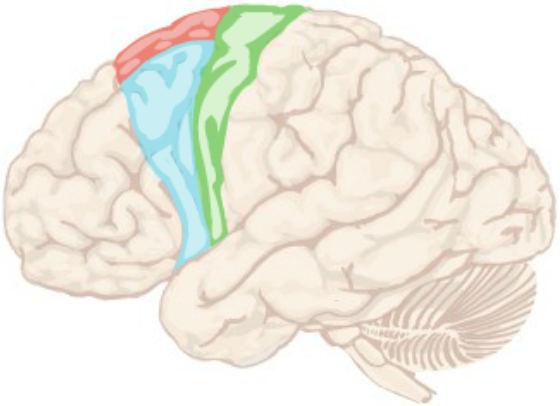
Primary motor cortex

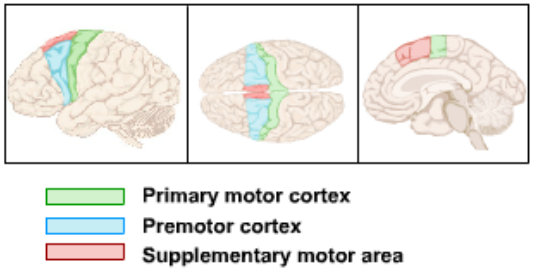
It is somatotopically organized.

Homonculus
'the little man'









Representations of body parts that perform precise movements are disproportionately large compared to body parts that do coarse movements.

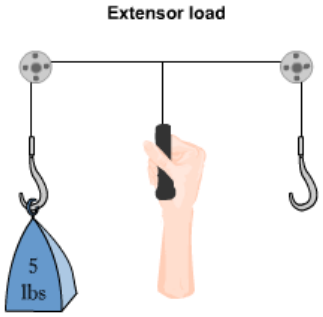
Premotor cortex and supplementary motor area also contain somatotopic maps.

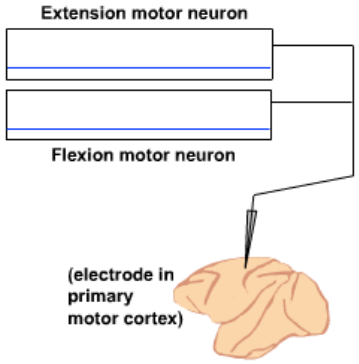
Encoding of movement by motor cortex

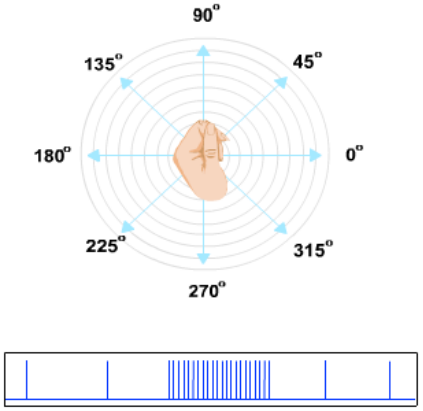
Primary motor cortex:
Controls individual movements that require the activity of multiple muscle groups.

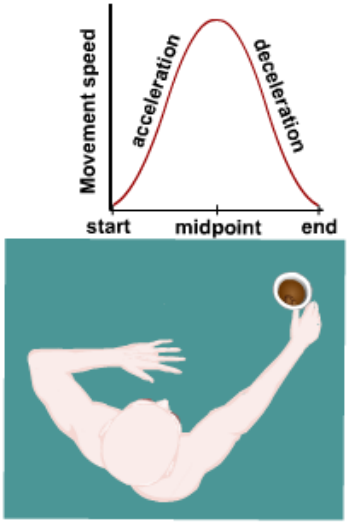
Encodes the parameters that define individual movements or sequences:

1. Neurons fire 5-100 msec before onset of movement
2. Force of a movement
3. Direction of movement
4. Extent of movement
5. Speed of movement





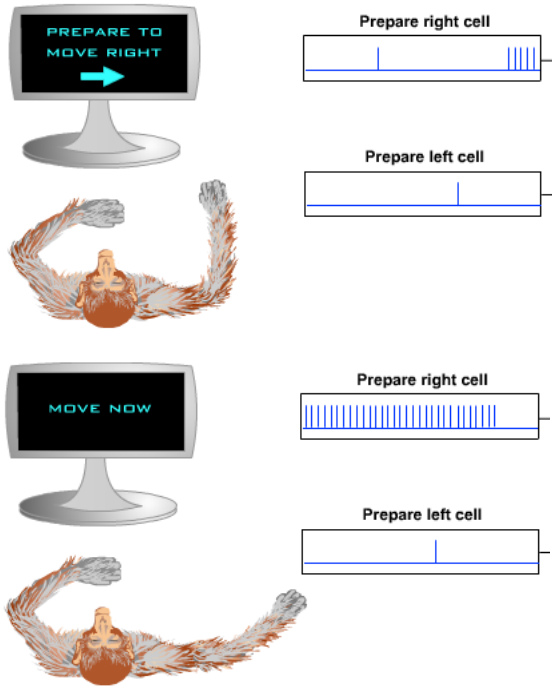


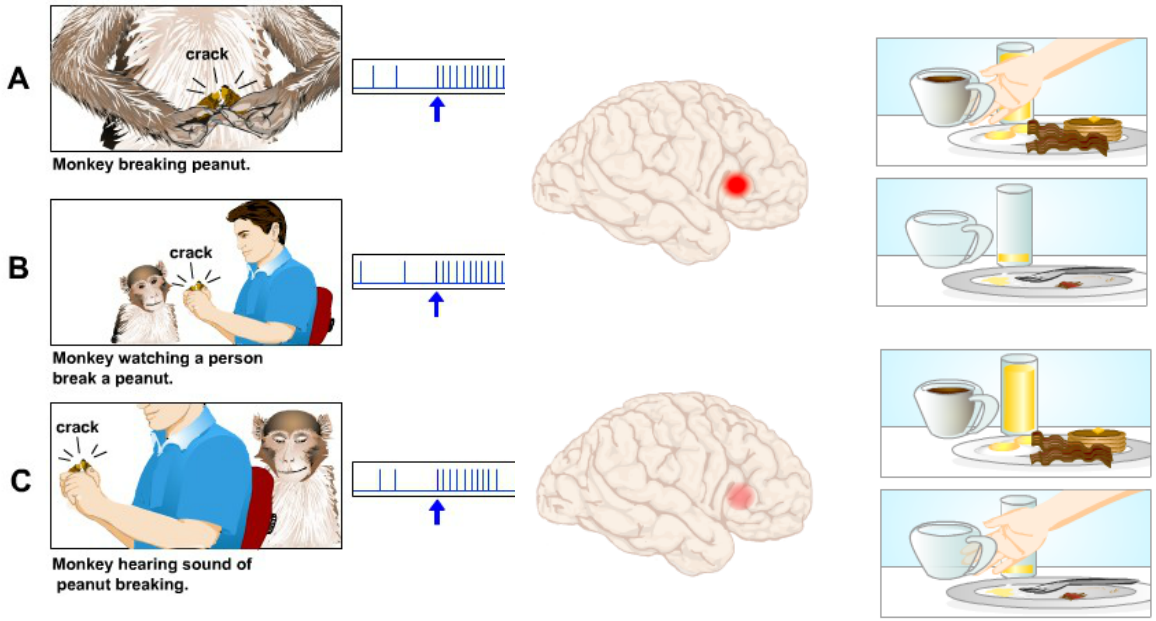


Encoding of movement by motor cortex

Premotor cortex:
Performs more complex, task-related processing than primary motor cortex.

Involved in selection of appropriate motor plans for voluntary movements:
1. Signal the preparation for movement
2. Signal various sensory aspects associated with particular motor acts
3. Sensitive to behavioral context of a particular movement
4. Signals correct and incorrect actions



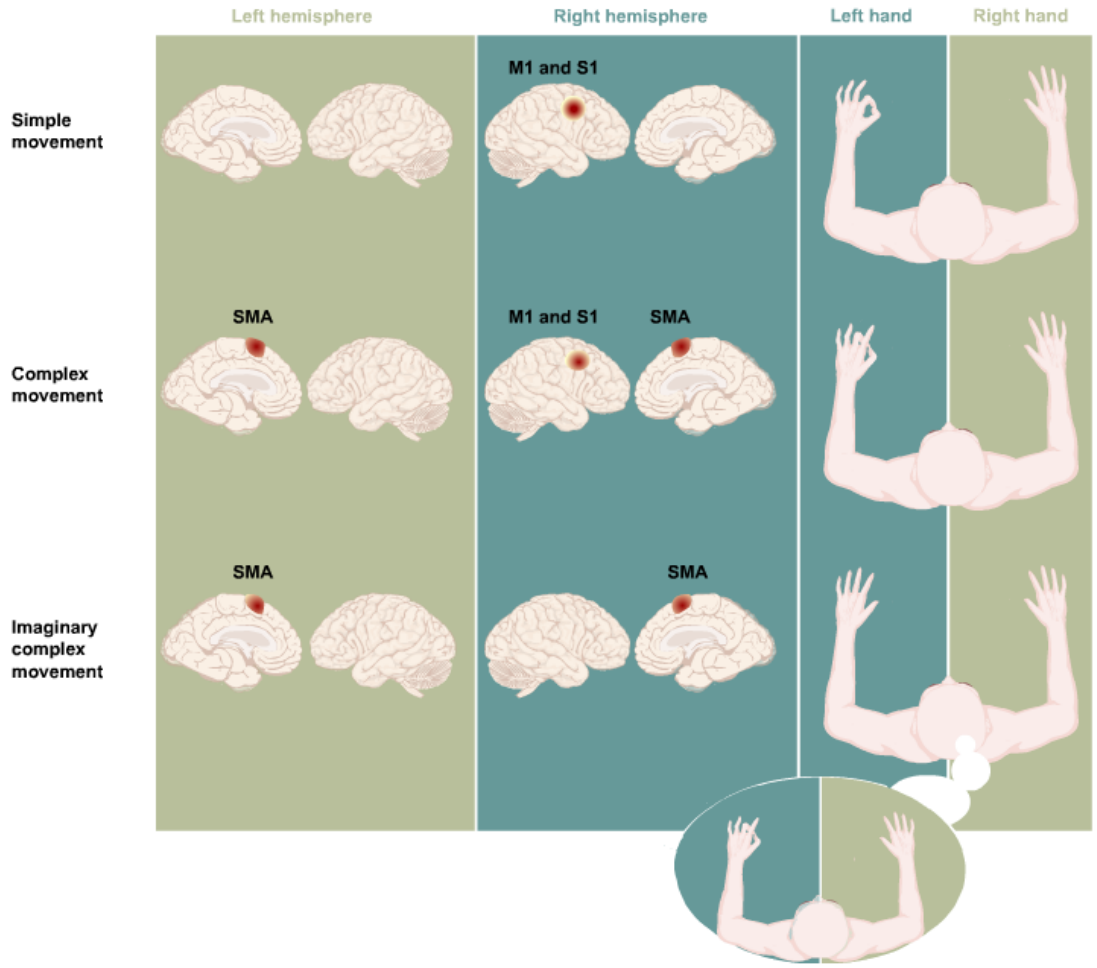


Encoding of movement by motor cortex

Supplementary motor area (SMA):
Involved in programming complex sequences of movements and coordinating bilateral movements.

Involved in selecting movements based on remembered sequences of movements:

1. Responds to sequences of movements and to rehearsal of sequences of movements
2. Transformation of kinematic to dynamic information

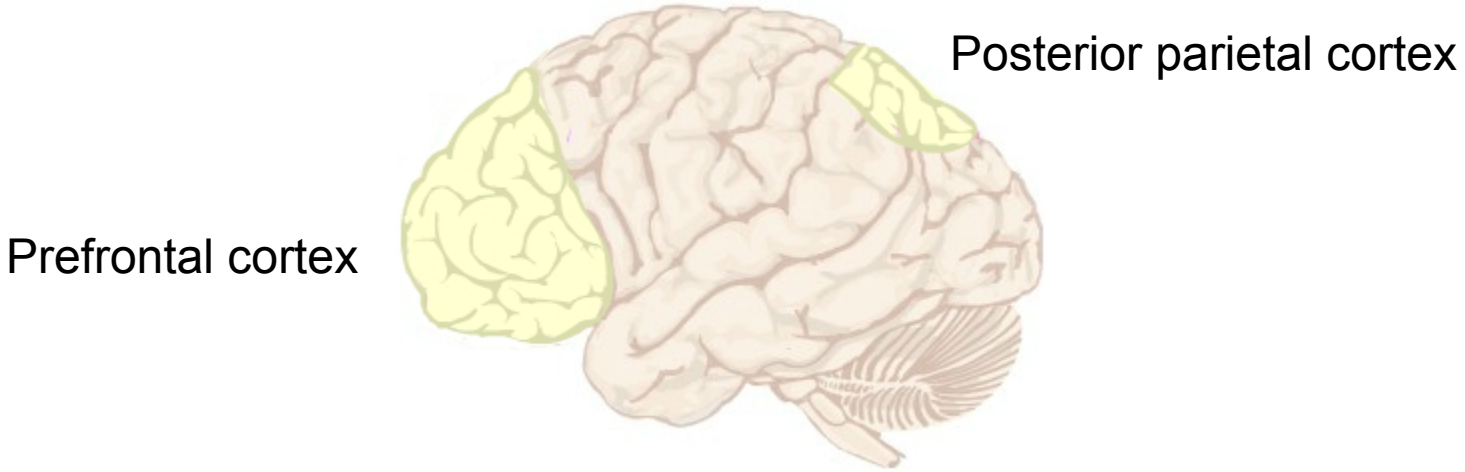


Encoding of movement by non-motor areas

Association cortex:
Made up of prefrontal cortex and posterior parietal cortex.

Not motor areas, but they are necessary to ensure that movements are adaptive to needs of the organism and appropriate for behavioral context:

1. *Posterior parietal cortex*: Involved in ensuring that movements are targeted accurately to objects in external space.
2. *Prefrontal cortex*: Involved in the selection of appropriate actions for a particular behavioral context.



Primate case study

Rhesus macaque (*Macaca mulatta)*

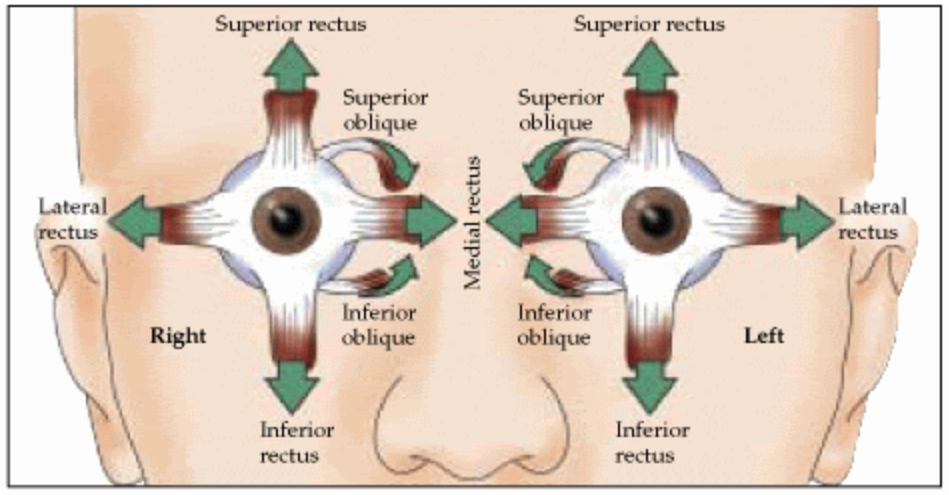
Important primate model organism – similarities to humans genetically, physiologically and metabolically

Investigation of complex cognitive functions are only possible in species who have behavior similar to humans: non-human primates

Will look at two common studies: saccade and reach tasks

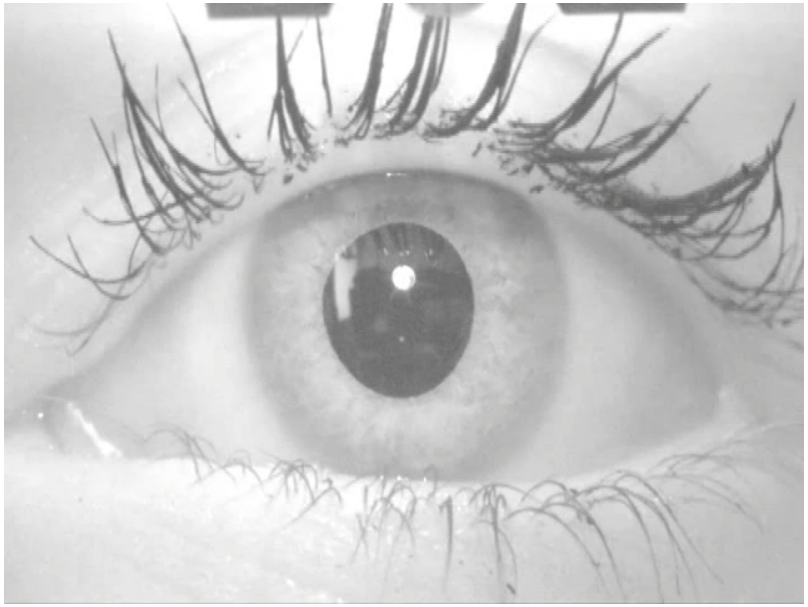
Eye movements are controlled by six muscles

1. There are one pair of muscles for each:
   - Horizontal
   - Vertical
   - Torsional
2. Extraocular motor neurons are located in the brainstem



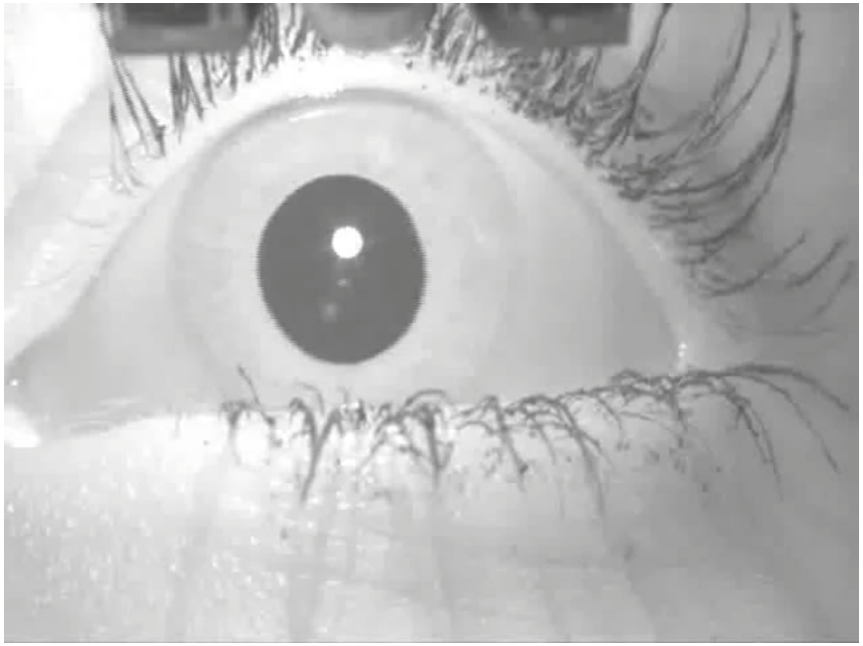
Eye movements fall into two categories

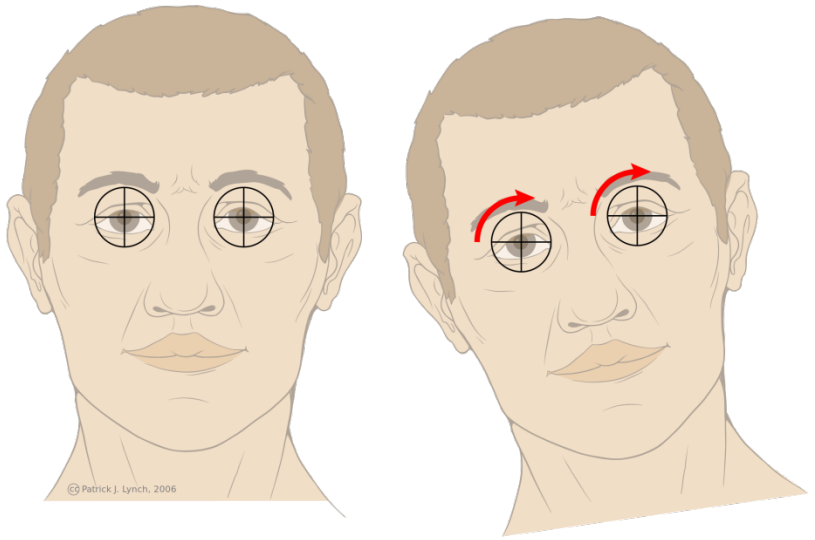
1. Gaze-shifting (foveating):
   - Saccades – involves the superior colliculus
   - Smooth pursuit



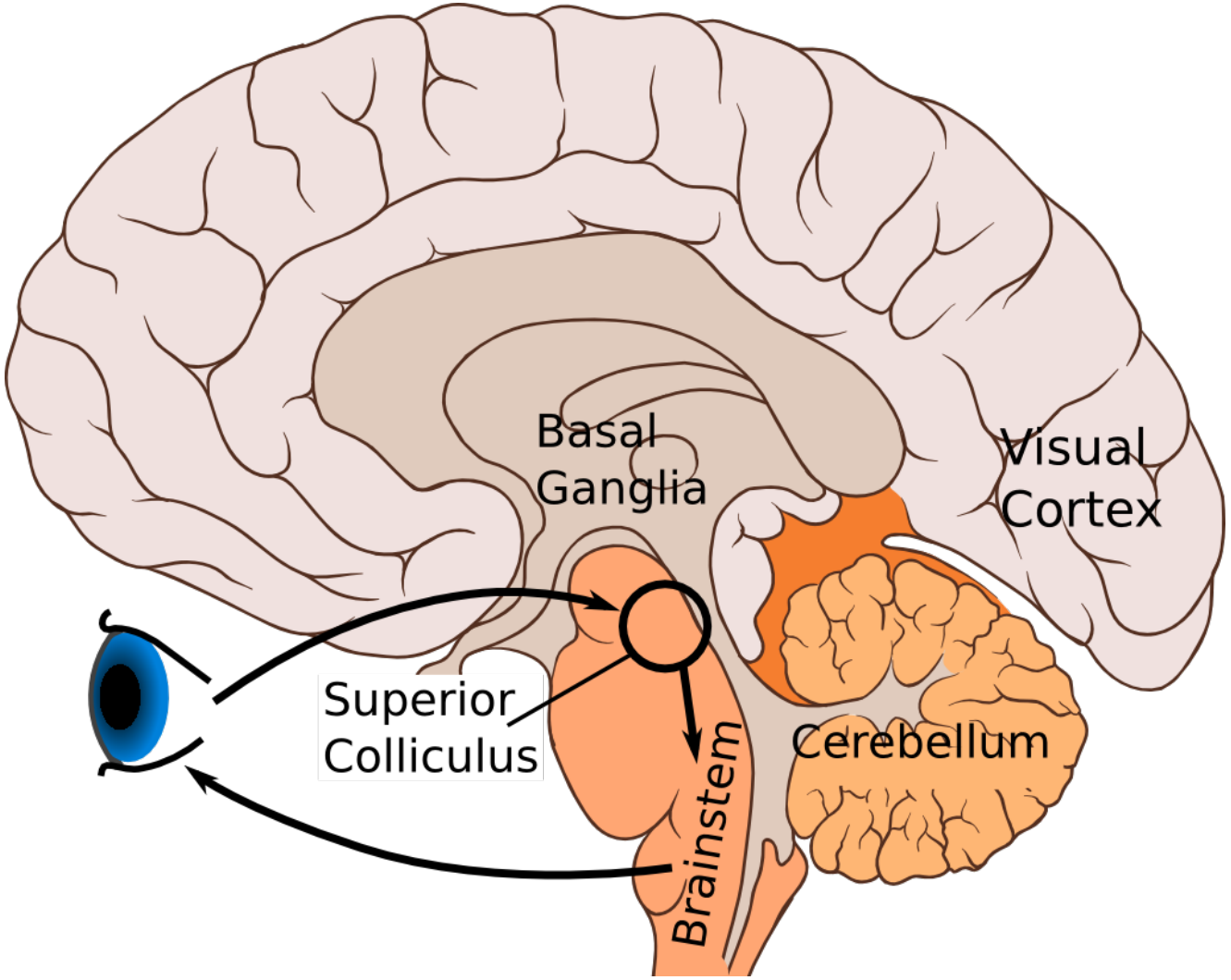
Eye movements fall into two categories

1. Gaze-shifting (foveating):
   - Saccades – involves the superior colliculus
   - Smooth pursuit
2. Gaze-stabilizing (fixating):
   - Optokinetic reflex
   - Vestibulo-ocular reflex

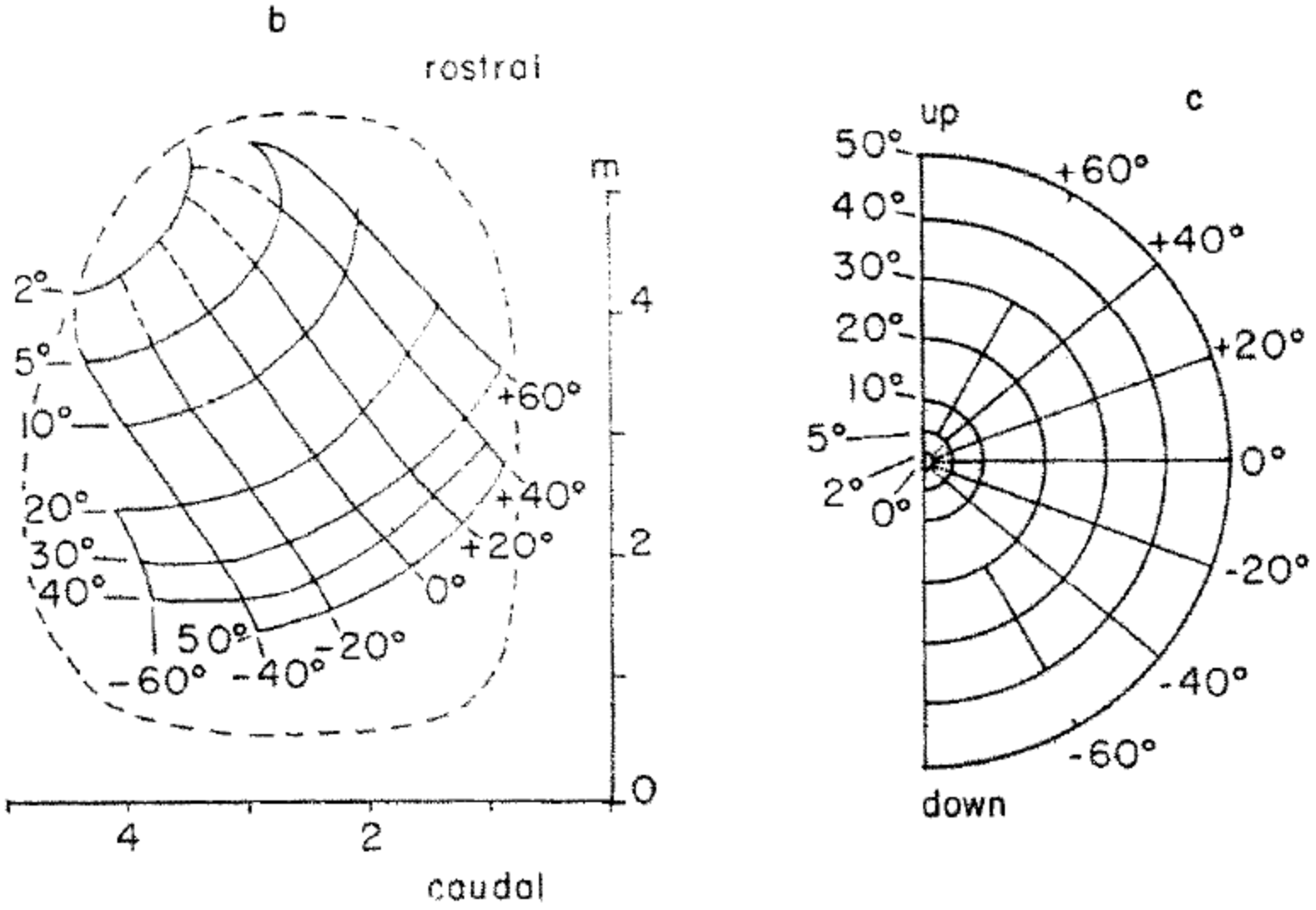




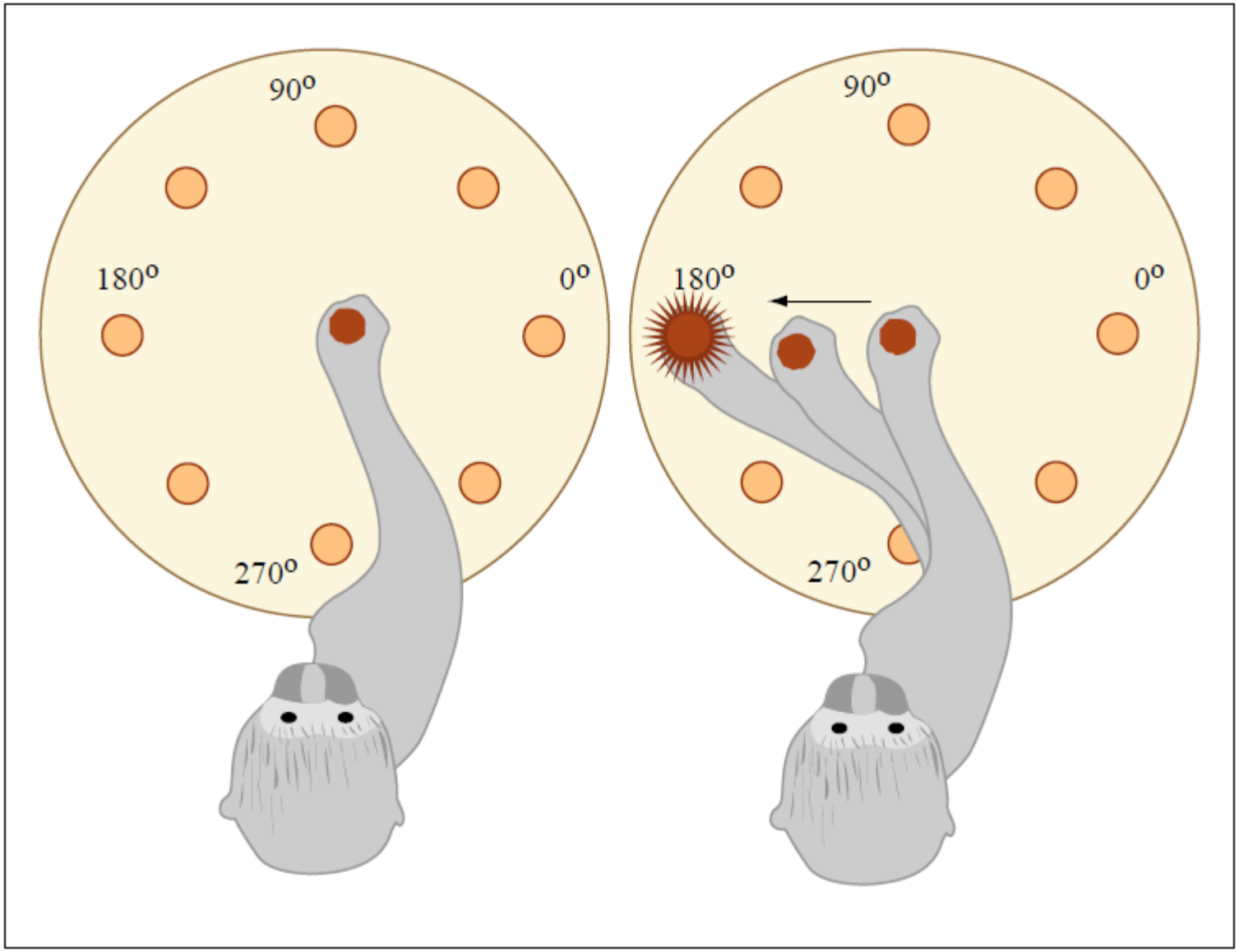
Superior colliculus



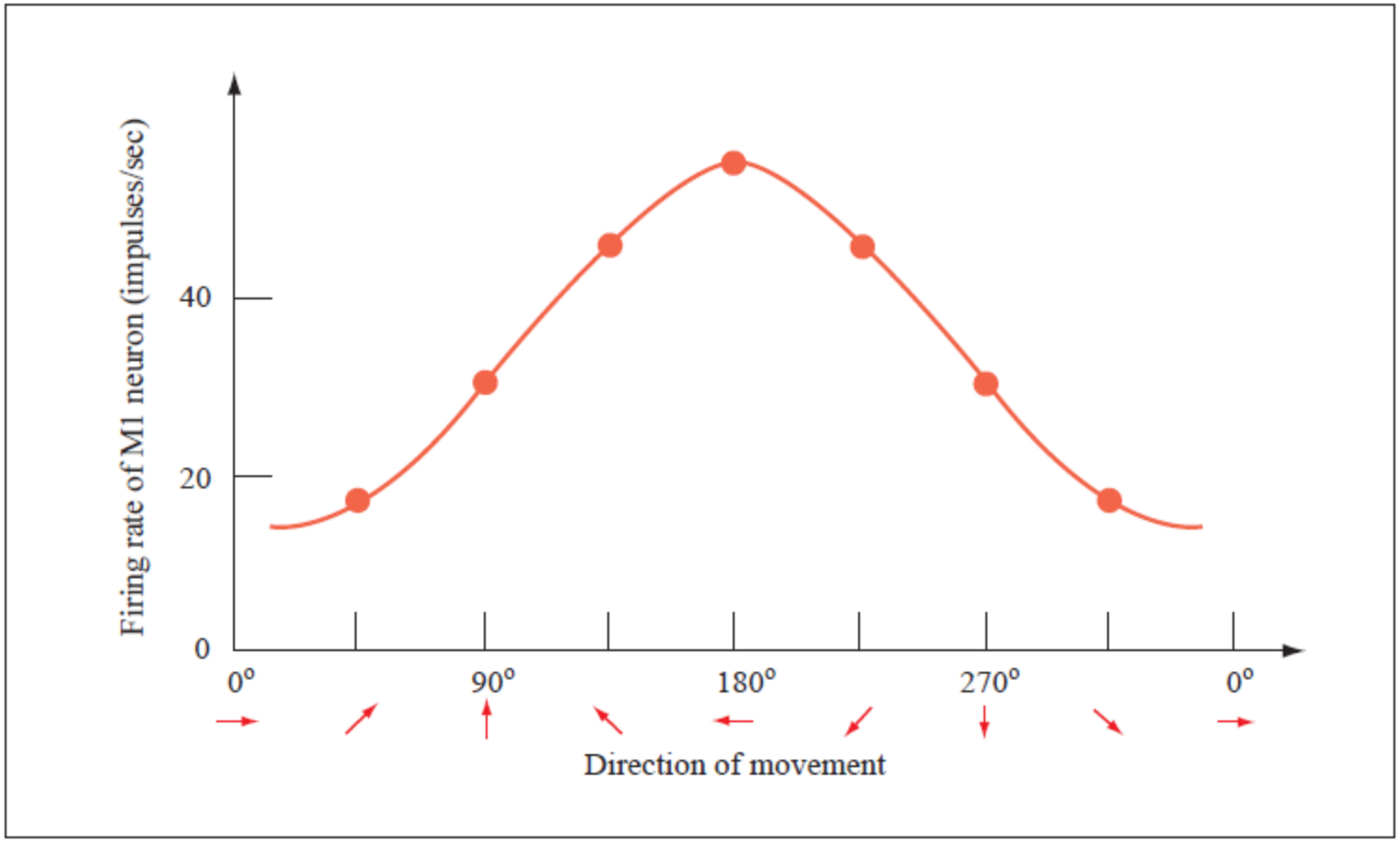
Saccade vectors in the superior colliculus



Reaching task



Primary motor cortex cells are broadly tuned to reaching direction



Spiker Boxes

Can be used to detect the EMG signal of muscles non-invasively.

Electromyography (EMG) signal: a technique used to evaluate and record the electrical activity produced by skeletal muscles.

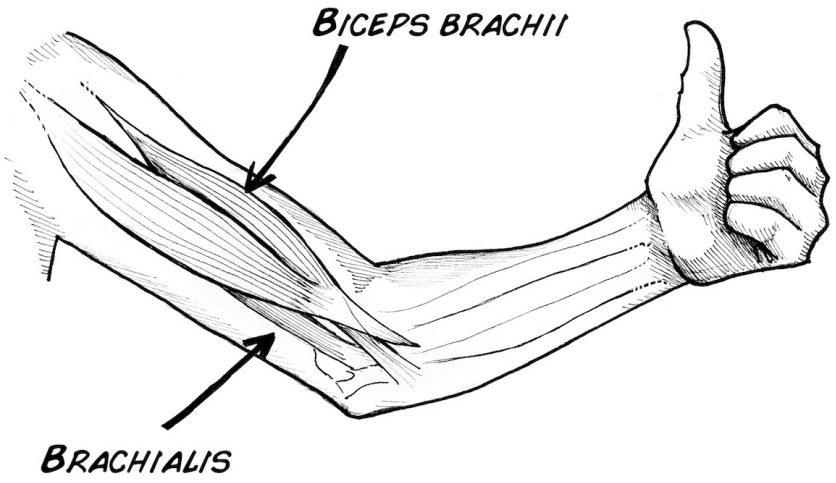
It detects the electric potential generated by muscle cells when the cells are electrically or neurologically activated.

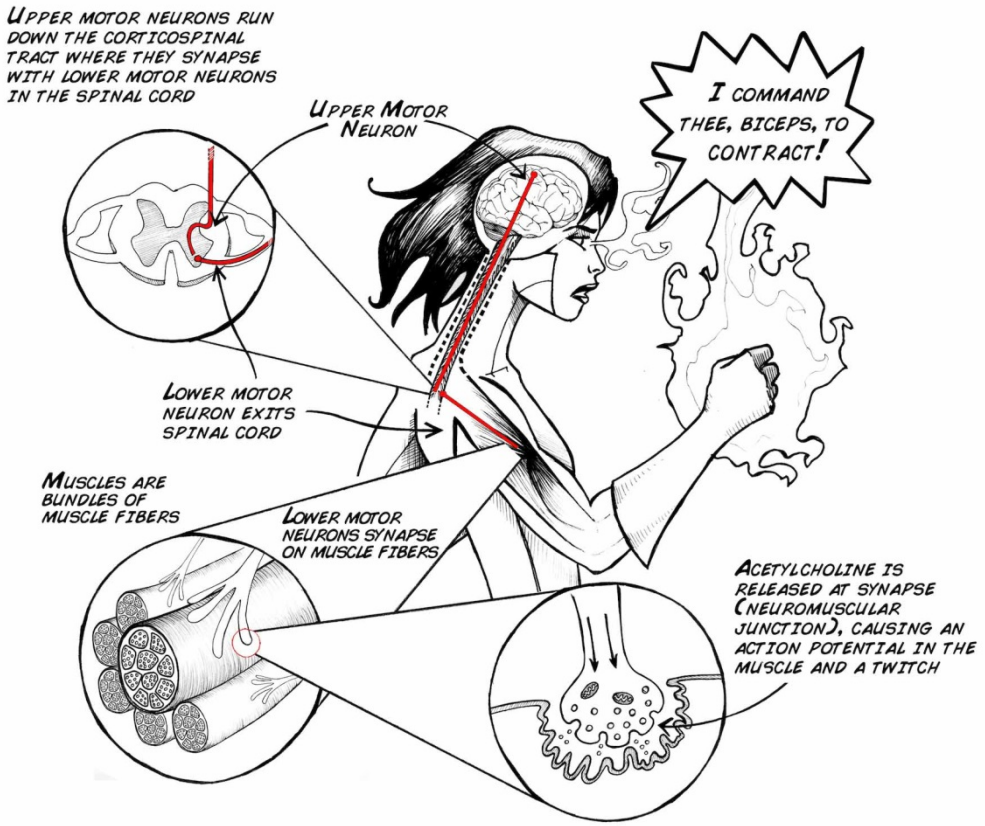
Experiment 1: Record electricity from your muscles

What will you learn?

You will learn about muscle physiology through EMGs.

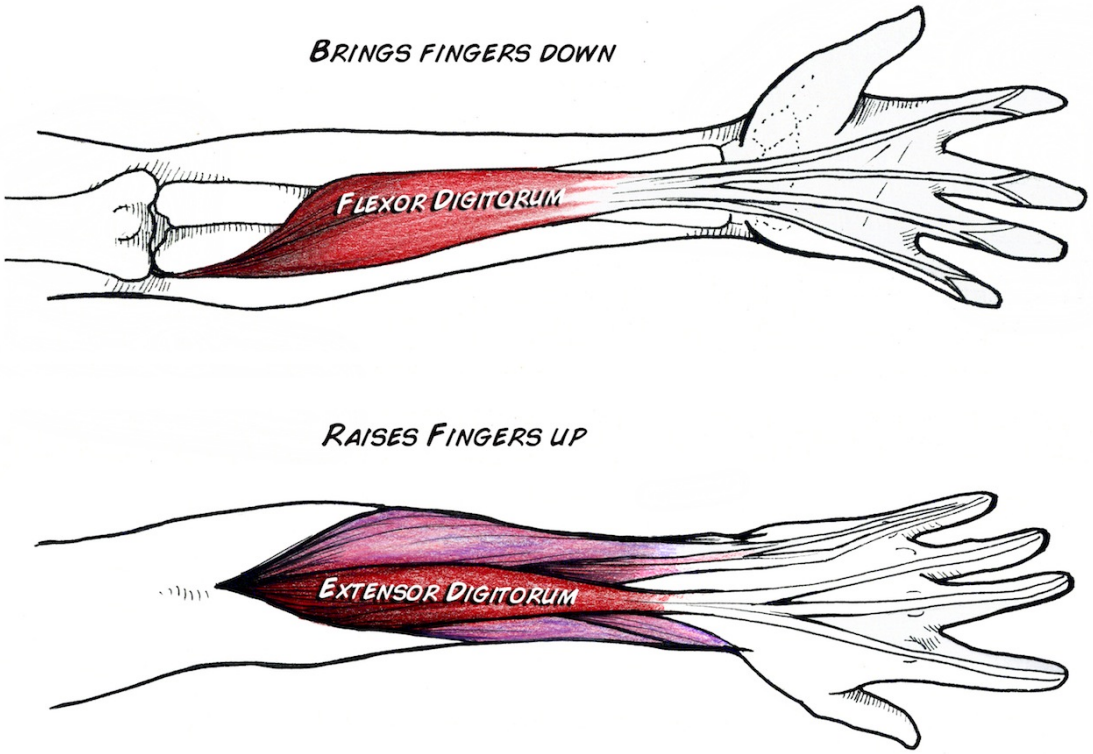
You will listen to the electrical impulses of muscles at rest and during contraction.

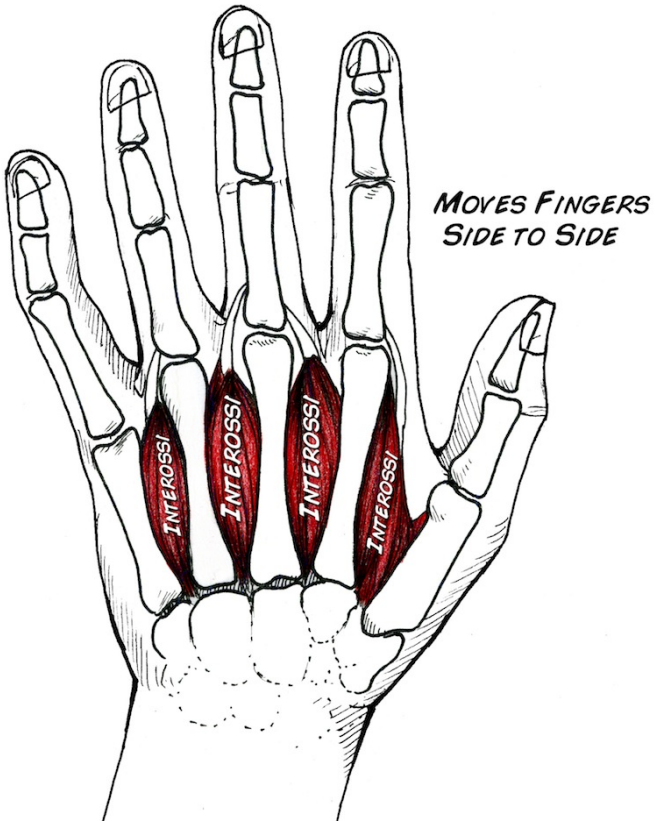




Experiment 2: Muscle action potentials

What will you learn?
You will learn how to record neural activity from the small interosseous muscles in your hand.





Experiment 2: Muscle action potentials

How to do this experiment