Introduction to the Nervous System

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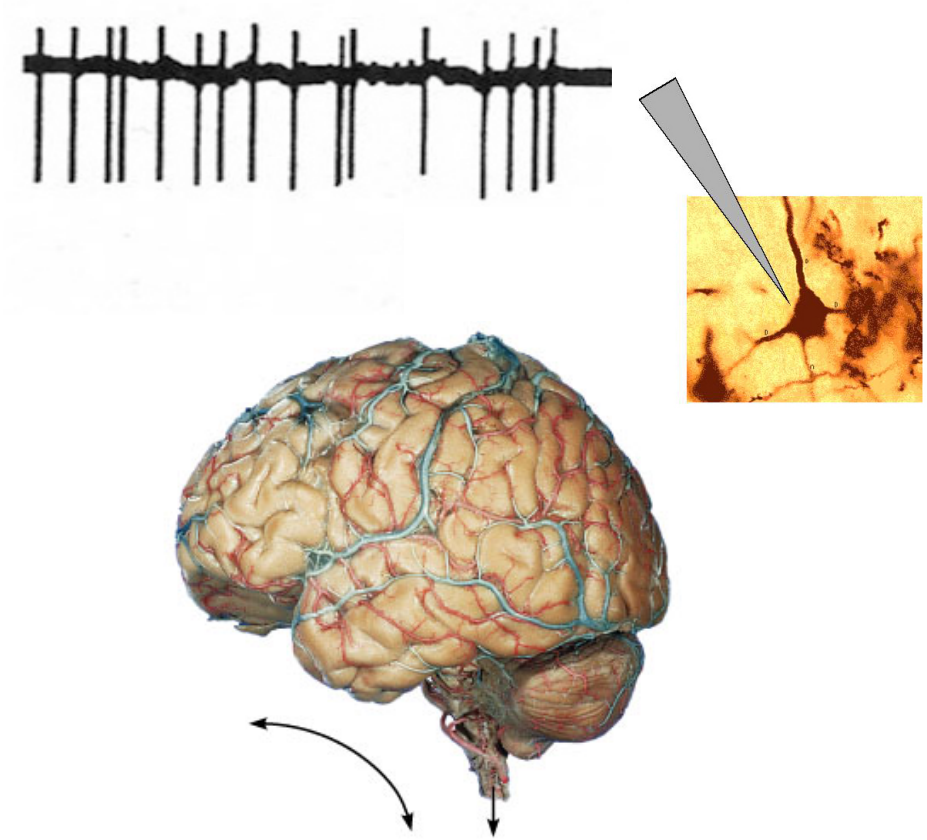


Why study the brain?

Basic Science – understanding “how the brain works” – from ***molecules*** to ***mind***

Being an engineer – we are always attracted by real world applications

Medical point of view
Autism, Schizophrenia, Parkinson’s, Alzheimer’s, Epilepsy, Cerebral Palsy – Disease and Cure

Engineer’s point of view
Neural Prostheses: Cochlear Implants, Hearing Aids, Artificial Retina, Sensor Development, Brain Computer Interface, Robotics, Artificial Intelligence

The brain is unparalleled as a computer - an unique machine
Brain based Algorithms: “Pattern” Recognition and “Pattern” Learning
“Pattern” – can be in any one or combinations of sensory space(s) – generalizes to even cognitive space?

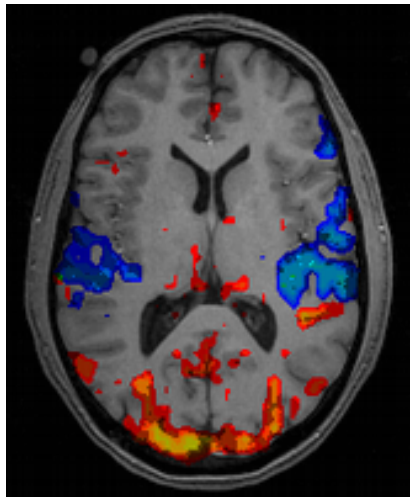
Architecture – Rules of connectivity (Recognition) and Rules of Changes in Connectivity (Learning) – It is the nature of connections and how they adapt is what determines the function

Ways to measure “activity” in the brain

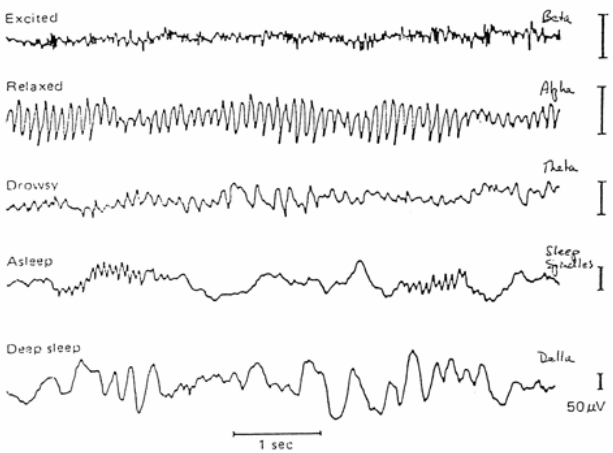
Activity:
What is activity – membrane potential, spike trains (series of action potentials) Hodgkin-Huxley described the process mathematically

Direct and Indirect Measures -
EEG, fMRI, BOLD-signal, single unit, multi-channel, patch-clamp, Ca-imaging – high resolution

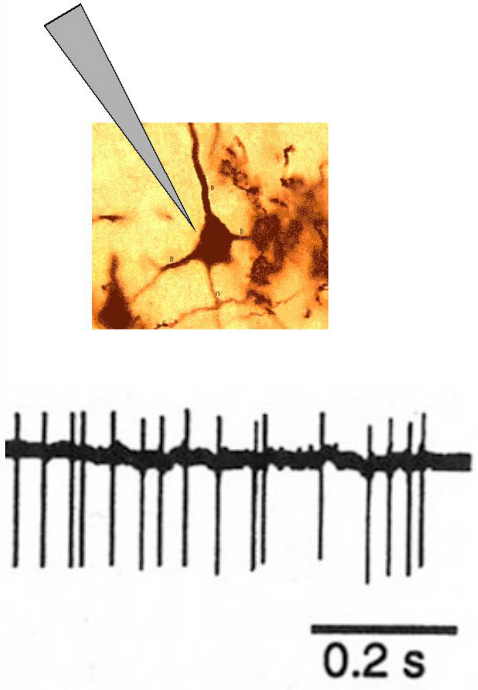
FMRI



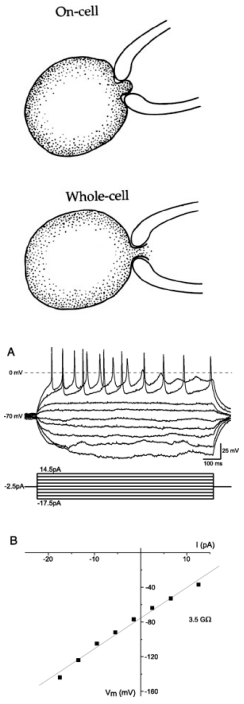
EEG



SINGLE UNIT

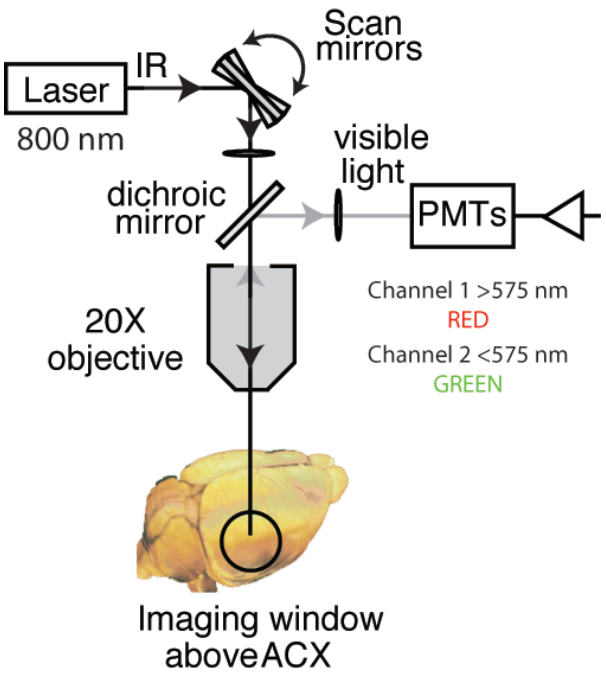


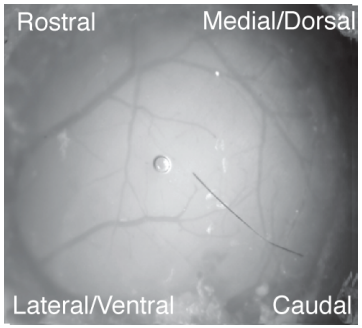
WHOLE CELL

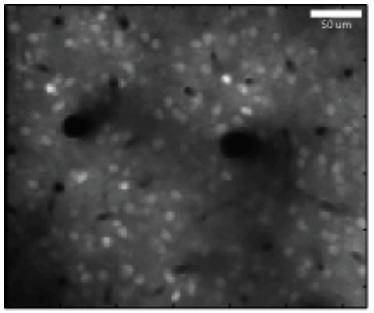


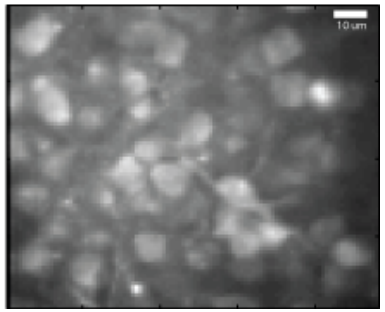
Ways to measure “activity” in the brain

In-vivo 2-photon Calcium Imaging



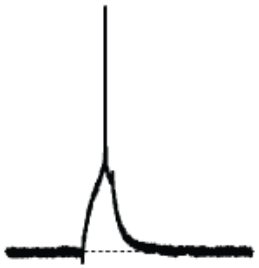




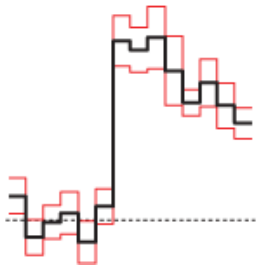


Whole Cell Recording

Voltage Trace



ΔF/F (Fluorescence Trace)

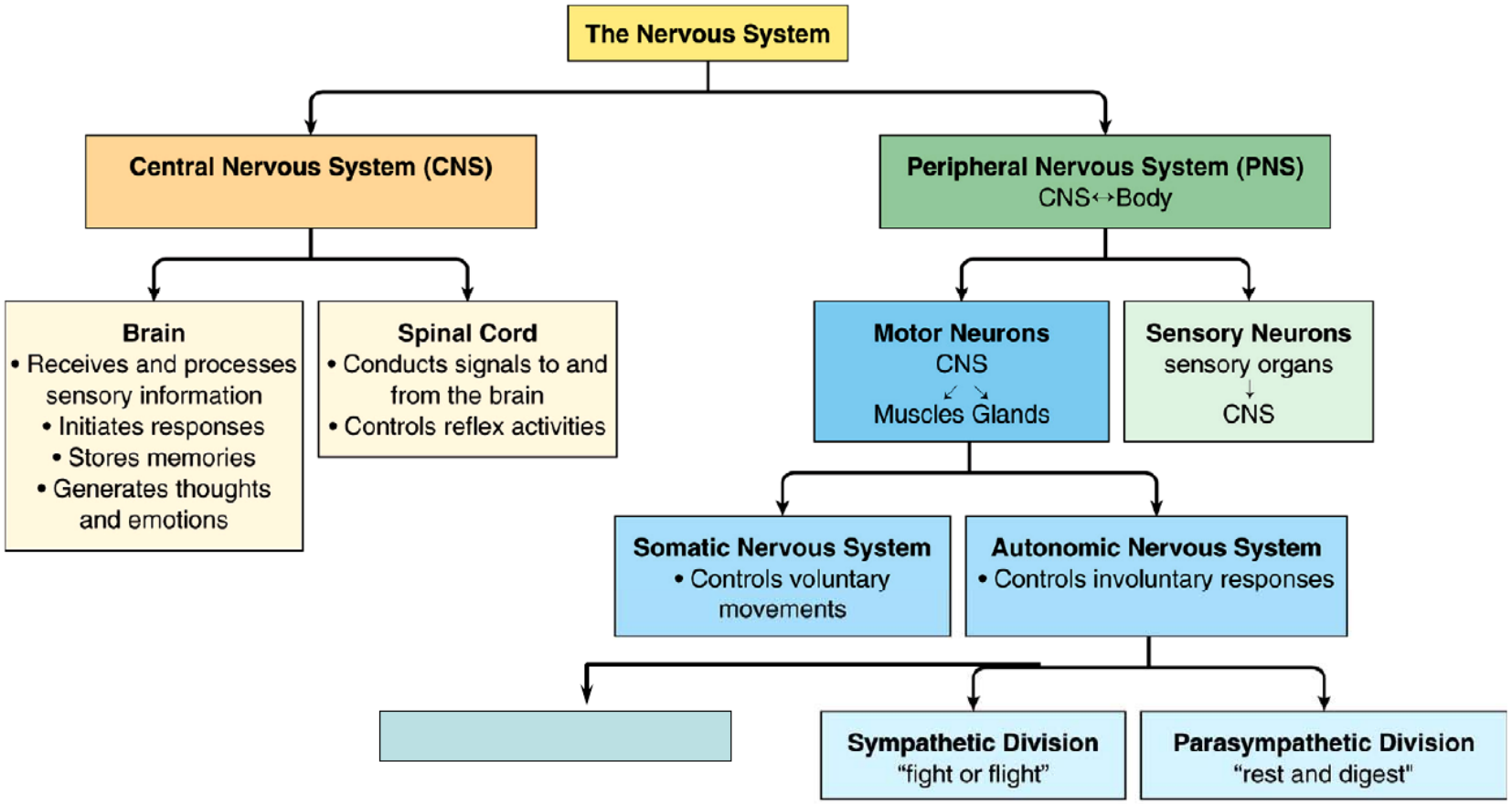


Basic Divisions of the Nervous System

- Central nervous system (“CNS”) – occupies cranium and vertebral column
  - Brain
  - Spinal cord

- Peripheral nervous system (“PNS”)
  - Cranial nerves
  - Spinal nerves
  - Ganglia (clusters of cell bodies)

Basic Divisions of the Nervous System



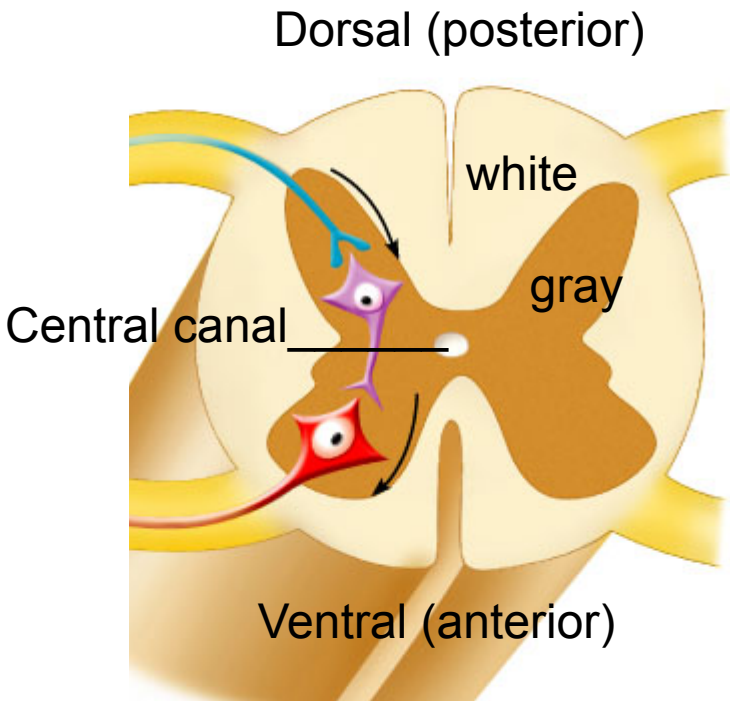
The Spinal Cord

- Foramen magnum to L1 or L2
- Runs through the vertebral canal of the vertebral column

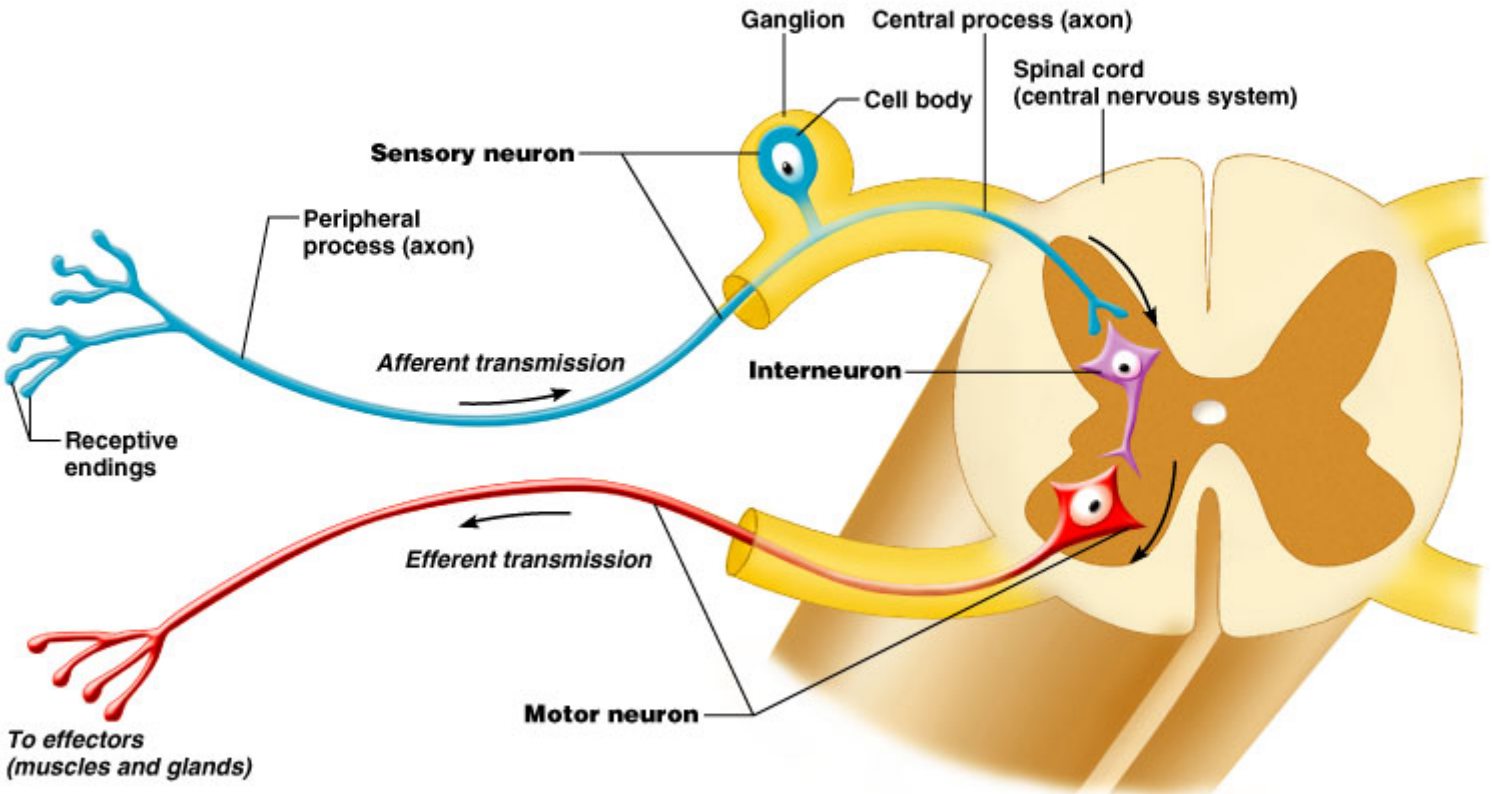
- Functions
  1. ***Sensory and motor innervation*** of entire body inferior to the head through the ***spinal nerves***
  2. ***Two-way conduction pathway*** between the body and the brain
  3. ***Major center for reflexes***

The Spinal Cord: Gray/White in spinal cord

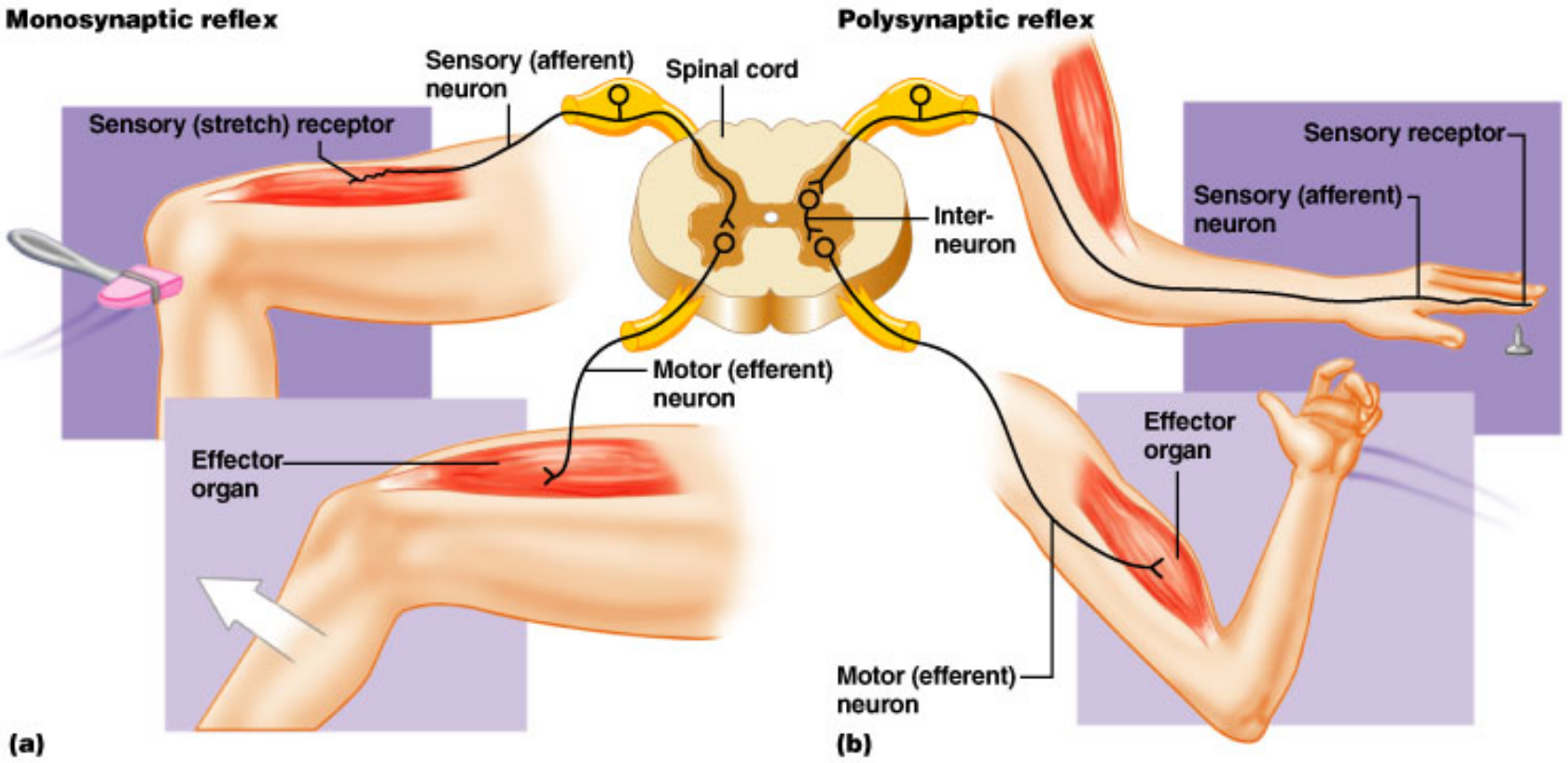
- Hollow central cavity (“central canal”)
- Gray matter surrounds cavity
- White matter surrounds gray matter (white: ascending and descending tracts of axons)
- “H” shaped on cross section
- Dorsal half of “H”: cell bodies of interneurons
- Ventral half of “H”: cell bodies of motor neurons
- No cortex (as in brain)



The Spinal Cord



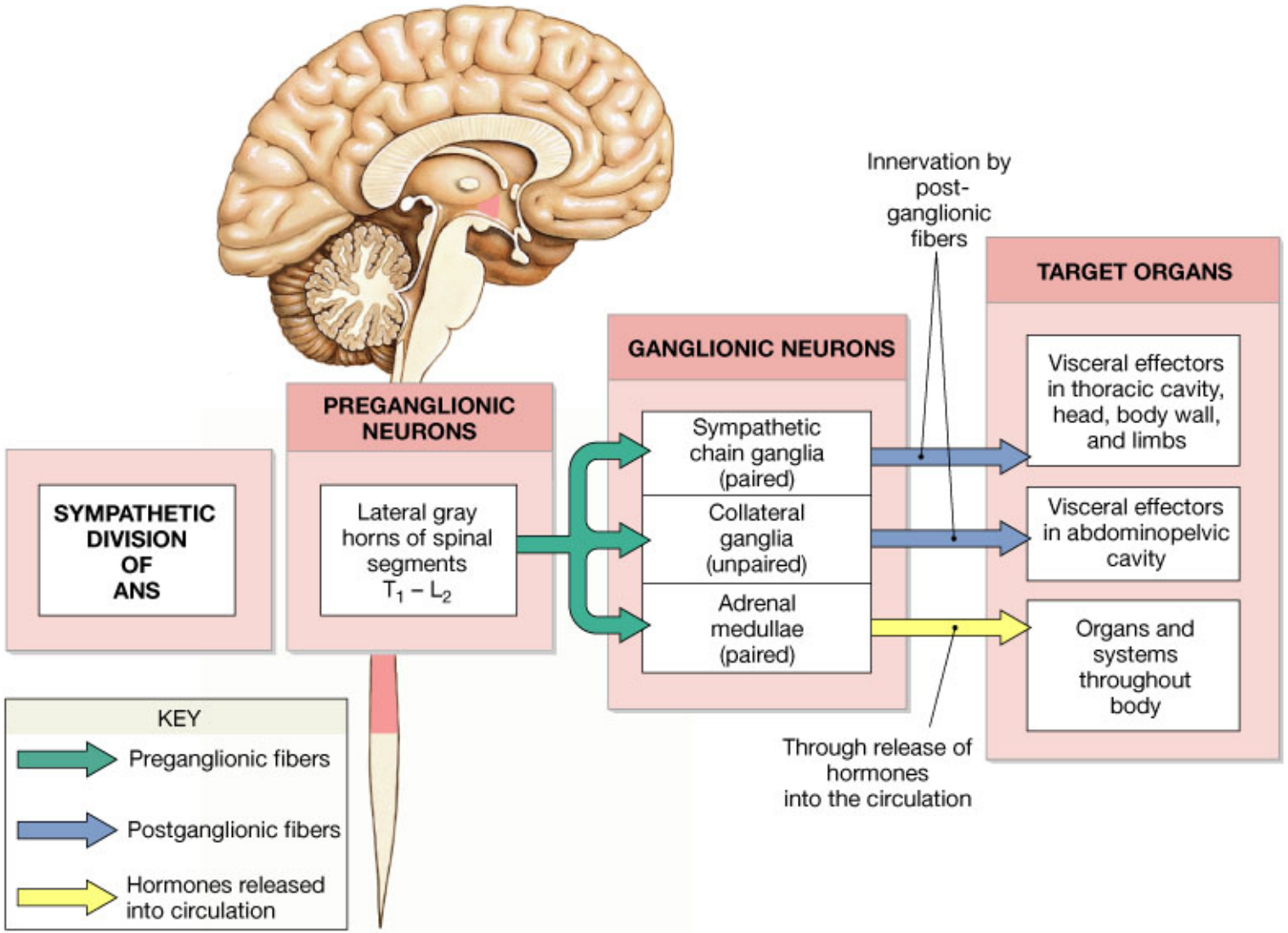
Spinal Cord: Reflex arcs - monosynaptic or polysynaptic



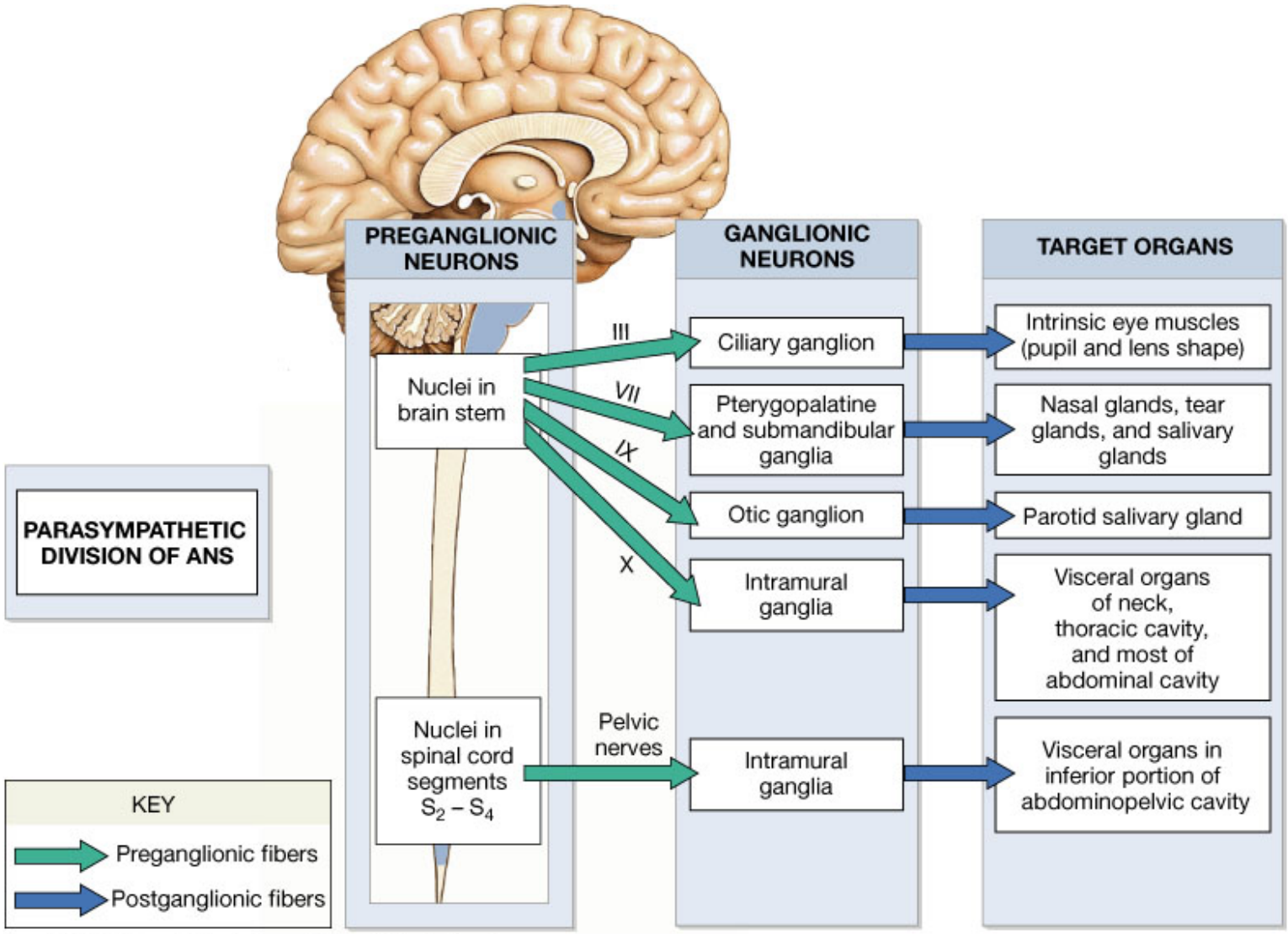
White matter of the spinal cord
(myelinated and unmyelinated axons)

- ***Ascending*** fibers: sensory information from sensory neurons of body up to brain
- ***Descending*** fibers: motor instructions from brain to spinal cord
  - Stimulates contraction of body's muscles
  - Stimumulates secretion from body's glands
- ***Commissural*** fibers: white-matter fibers crossing from one side of cord to the other
- Most pathways cross (or ***decussate***) at some point
- Most synapse two or three times along the way, e.g. in brain stem, thalamus or other

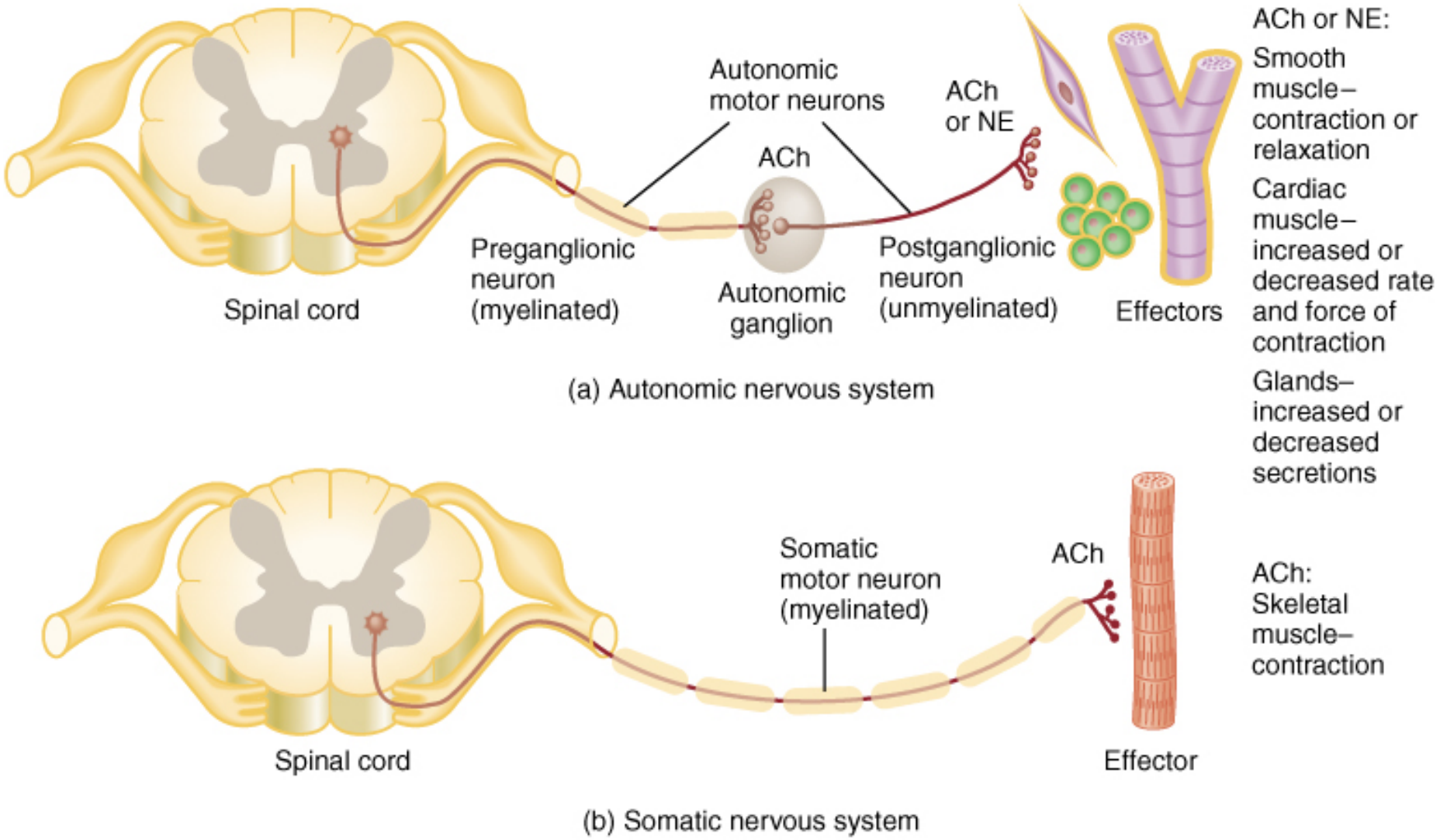
The Organization of the Sympathetic Division of the ANS



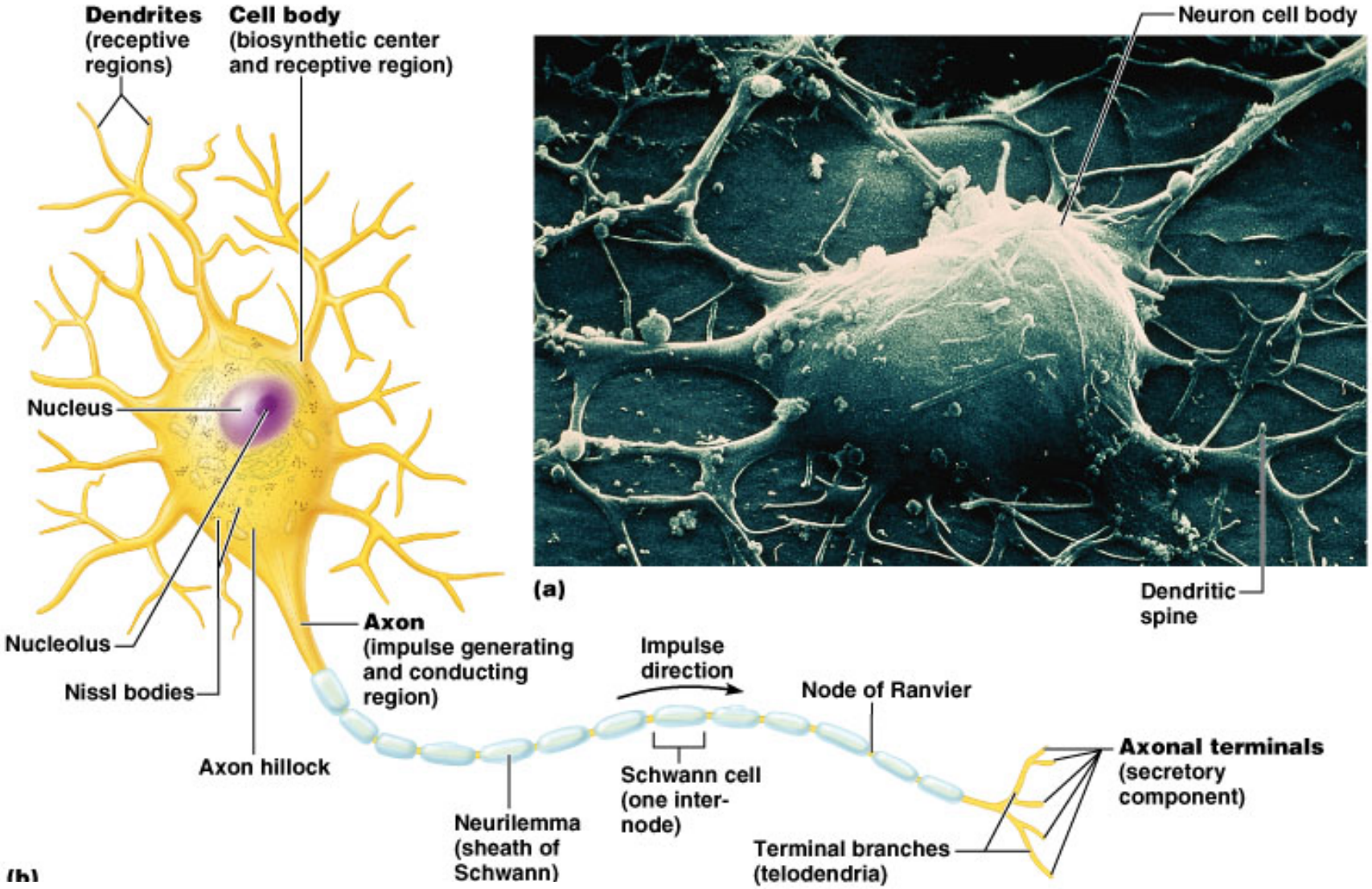
The Organization of the Parasympathetic Division of the ANS



The Organization of the Somatic Nervous System



Neurons: The Basic Functional and Computational Units



GLIA: “Supporting” cells

- Neuroglia usually refers to CNS ones
- Just “glia” to both
- Divide throughout life
- Smaller and darker than neurons
- Outnumber neurons 10 to 1

Astrocytes
: Star shaped; the most numerous
: Involved in metabolism & synapse formation

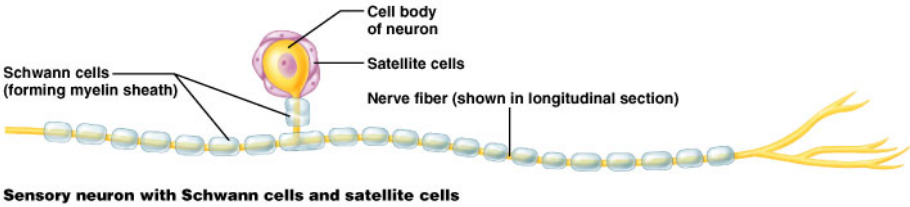
Microglia
: Phagocytes

Ependymal cells
: Line the cavities of CNS and spinal cord; cilia

Oligodendrocytes
: Produce myelin sheaths in CNS (see later slide)

In the PNS:

- Satellite cells
  - Surround neuron cell body
- Schwann cells
  - Form myelin in PNS



Sensory neuron with Schwann cells and satellite cells

Physiological Processes in the Neuron

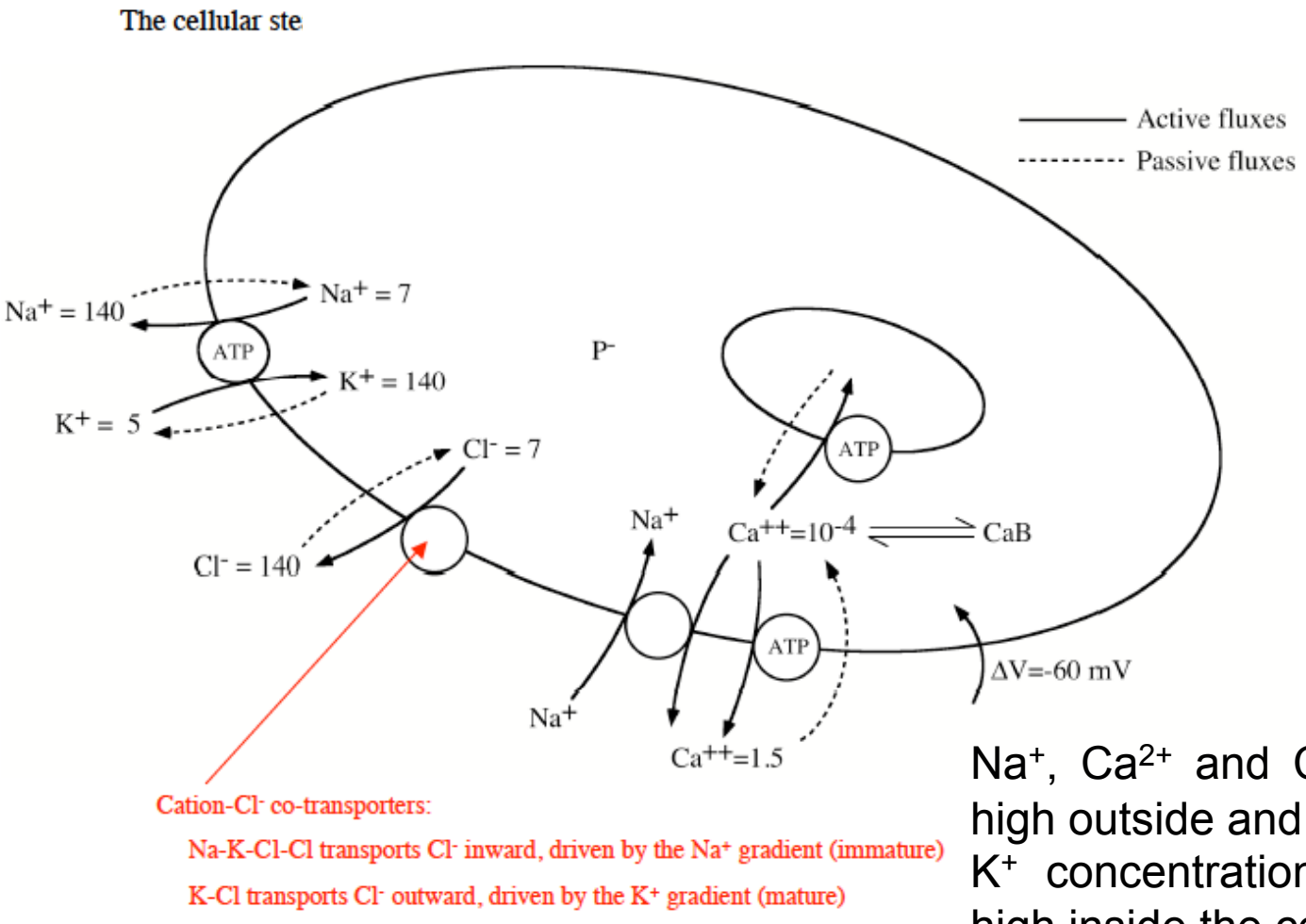
How do neurons integrate (compute) and transmit information

so that we function in a seamless manner

in a rapidly changing dynamic environment –

- by perceiving information
and
- taking appropriate actions

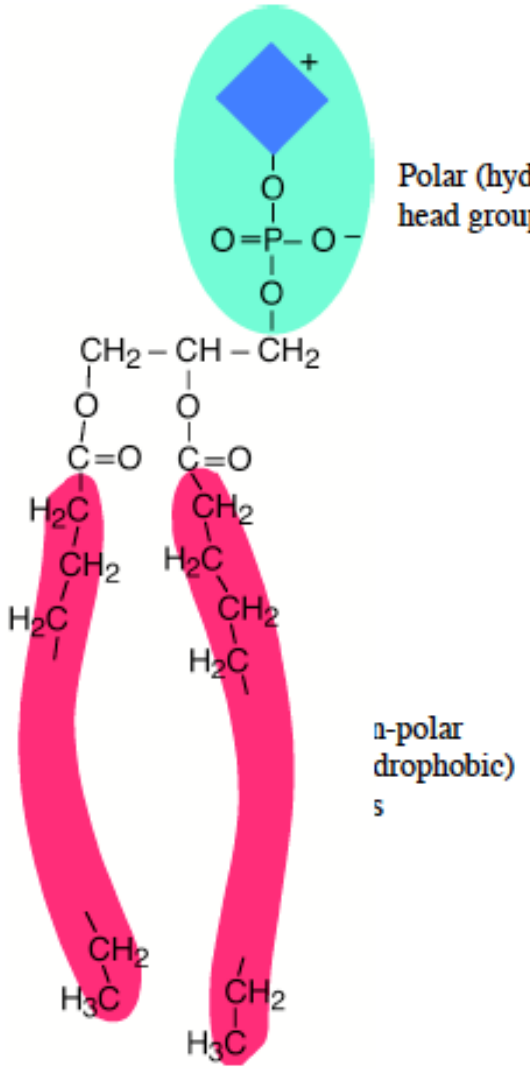
Cellular Steady State



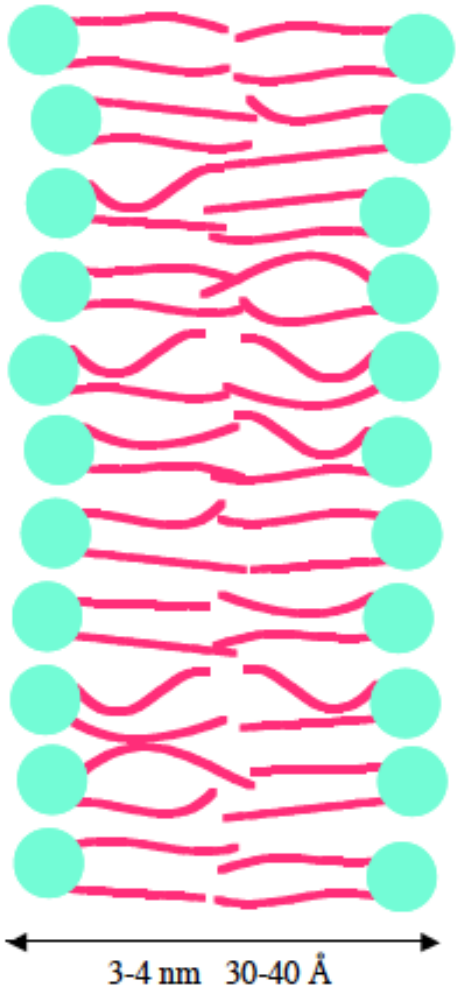
Na^+, Ca^{2+} and Cl^- concentrations are high outside and low inside the cell

K^+ concentration is low outside and high inside the cell

Membrane: Lipid Bilayer

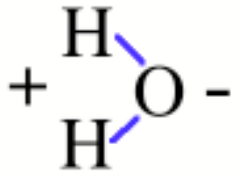


The lipid bilayer structure of membrane:

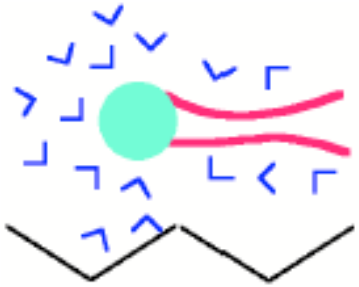


Membrane: Lipid Bilayer

Membranes are stabilized and ions are unable to permeate membranes in significant numbers because of **hydrogen bonding** in aqueous solutions.



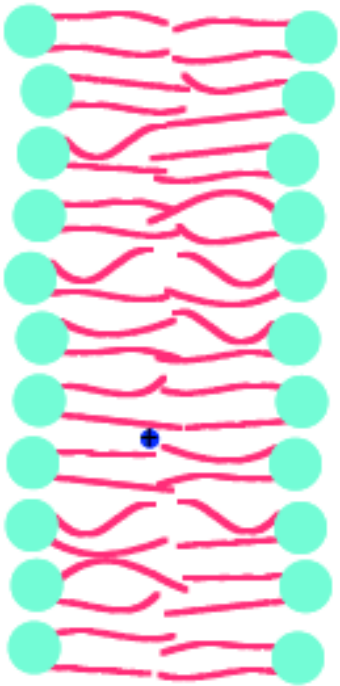
Water molecule dipole



H-bonded head region

Tail region not H-bonded, **energetically unfavorable!**

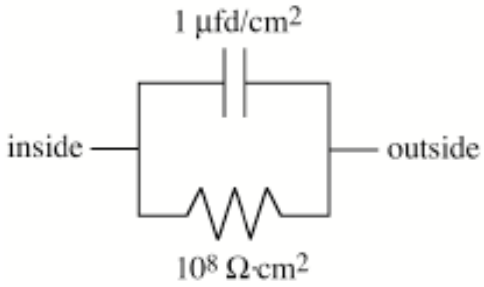
Sodium ion stabilized in solution by H-bonds (176 RT bond energy/ mole)



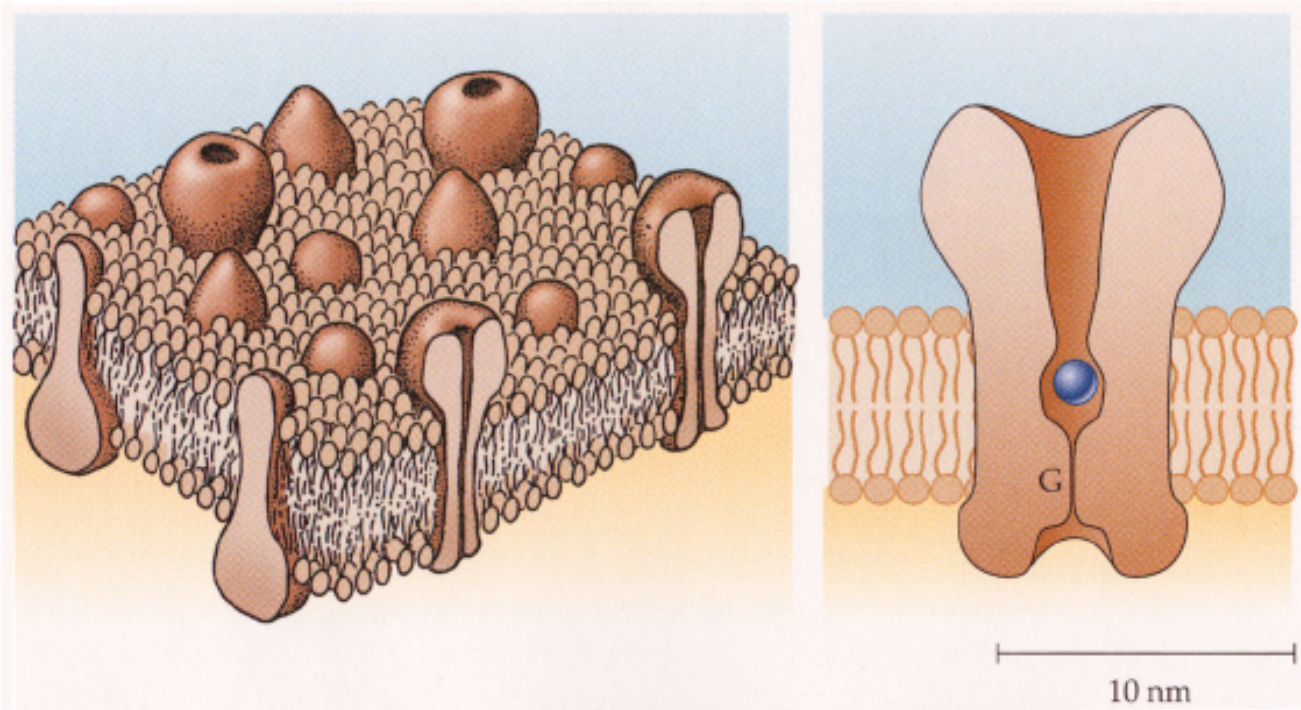
Same ion in membrane interior, no H-bonds. A high-energy state.

Membrane: Lipid Bilayer

Pure lipid bilayers can be created artificially and have electrical characteristics like the circuit at right. The capacitance is about the same as for real nerve membrane, but real nerve membrane has a resistance several orders of magnitude smaller, about 10^3 - 10^5 Ω·cm^2



The reason for the difference, of course, is that membrane contains **ion channels**, proteins that provide specialized ionic conduction pathways through the membrane.



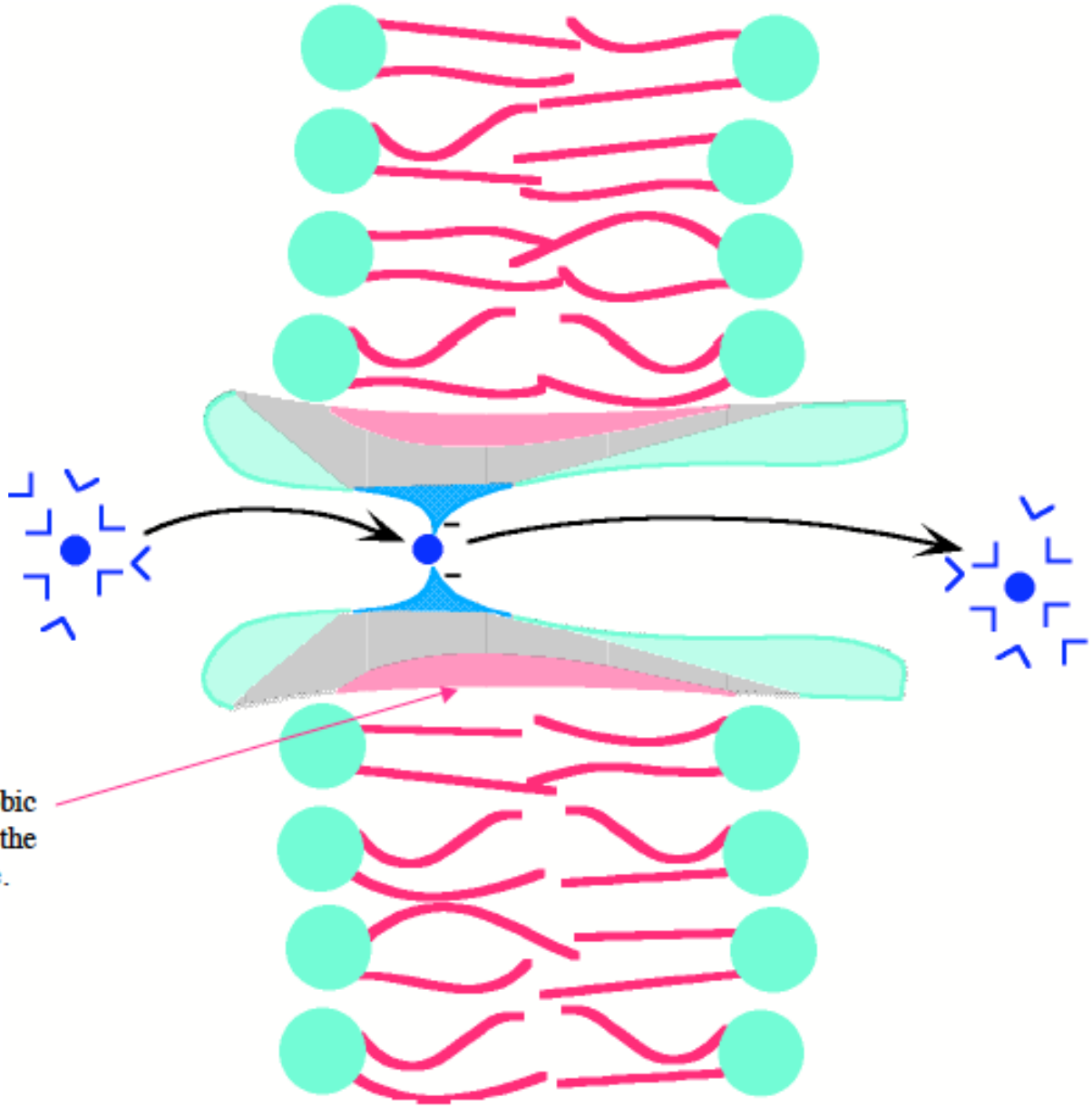
Nicholls et al., 2001

Membrane: Ion Channels

The function of the ion channel is to provide a **hydrophylic pore** inside the membrane. In the simplest model, we can imagine a two-step process:

1. Dehydration of the ion and binding to a polarized negatively charged site in the channel pore
2. Rehydration of the ion in the opposite solution

The energy of dehydration of the ion is provided by the binding energy to the site in the channel.

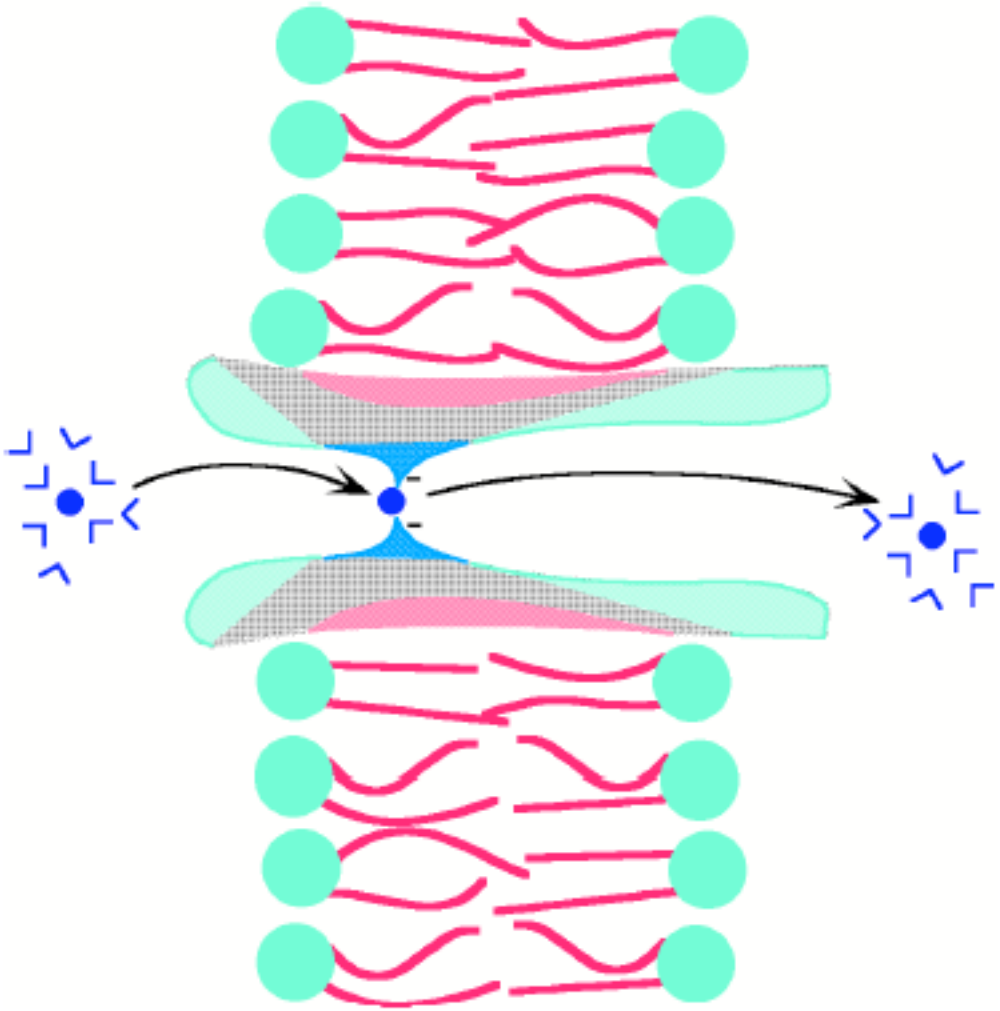


Note that the channel molecule has a hydrophobic exterior which stabilizes the channel in the membrane.

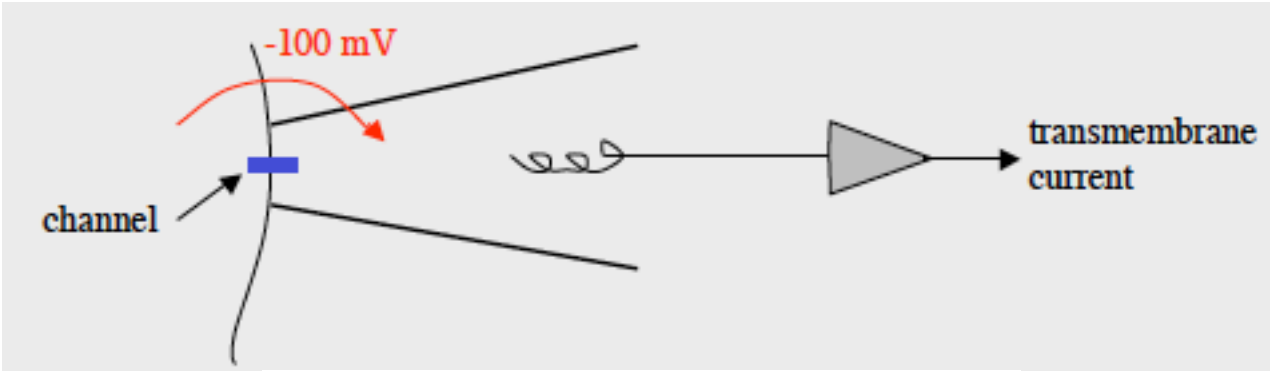
Membrane: Ion Channels

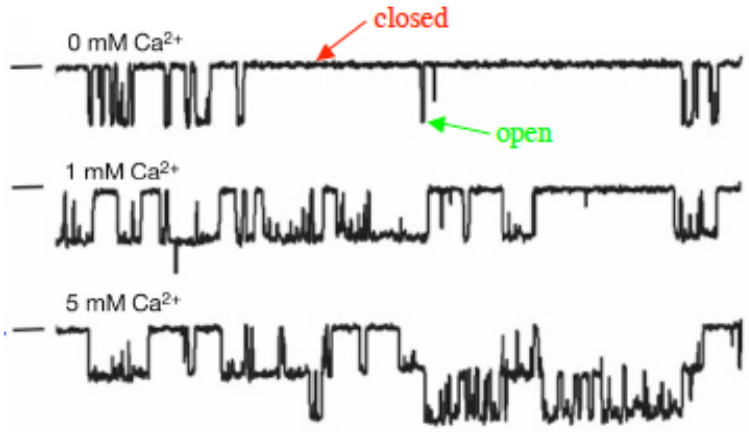
The channel is shown to have a narrow spot where an ion might be found with high probability, almost a binding site. This spot serves as the **selectivity filter**, determining the selectivity of the channel for particular ions.

Note that the ion cannot really *bind* to the selectivity filter, because that would slow propagation through the channel. Conductance through an open channel is about the same as through an aqueous pore of similar size (see Hille, p. 294).



Gating of Ion Channels



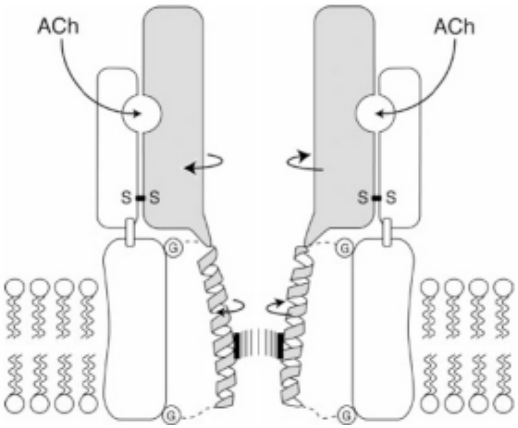


Gating refers to the fact that channels change their conductance state, from open to closed or closed to open. The transitions occur sharply over very fast time scales. Generally gating is influenced by membrane potential (voltage gated) or by some ligand (ligand gated). In the above example the channel is more likely open as the Ca^{2+} concentration increases

Membrane: Ion Channels (Ligand Gated, Voltage Gated)

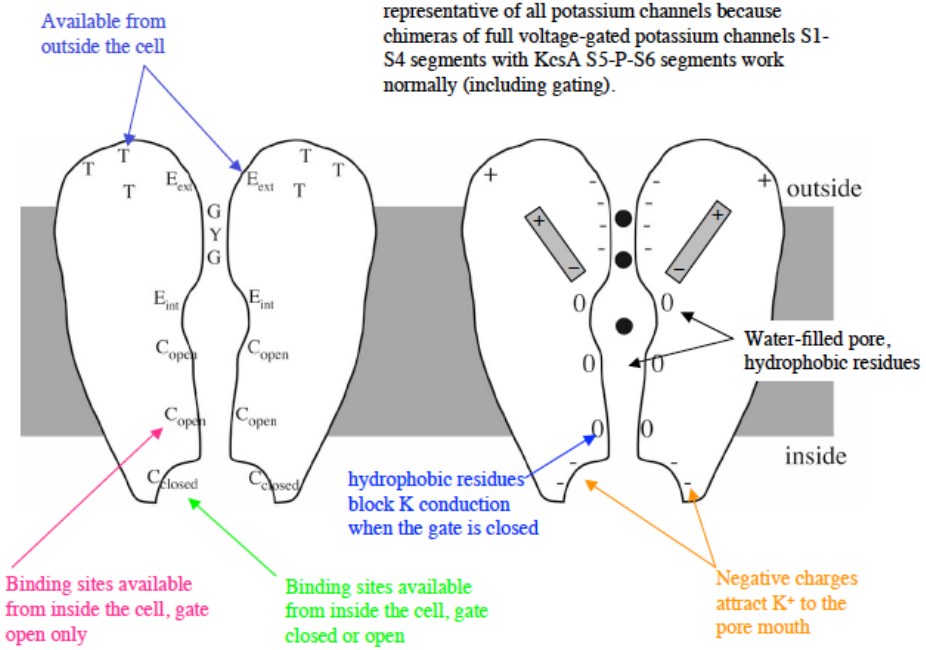
Ligand Gated

Model for gating of the NAChR. Binding of ACh causes the gray part of the extracellular domain to rotate as drawn, producing a rotation and realignment of the M2 segments increasing or decreasing the size of the pore in the vicinity of V255 and L251.

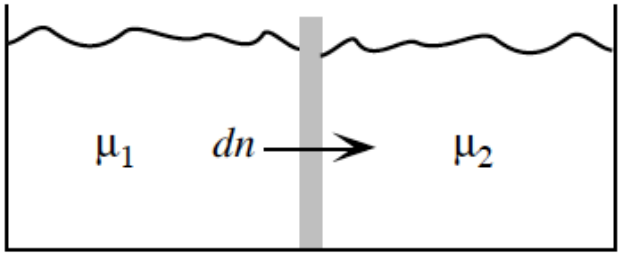


Voltage Gated

The structure of the KcsA channel is believed to be representative of all potassium channels because chimeras of full voltage-gated potassium channels S1-S4 segments with KcsA S5-P-S6 segments work normally (including gating).



Electrochemical Potential

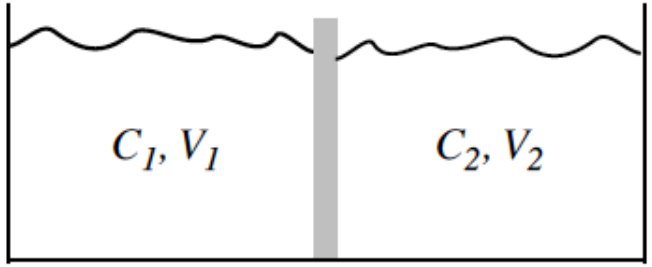


$$dG = -\mu_1 dn + \mu_2 dn \leq 0$$

$$\mu_i = \mu_i^0 + RT \ln C_i + z_i F V + \cdots$$

At Equilibrium

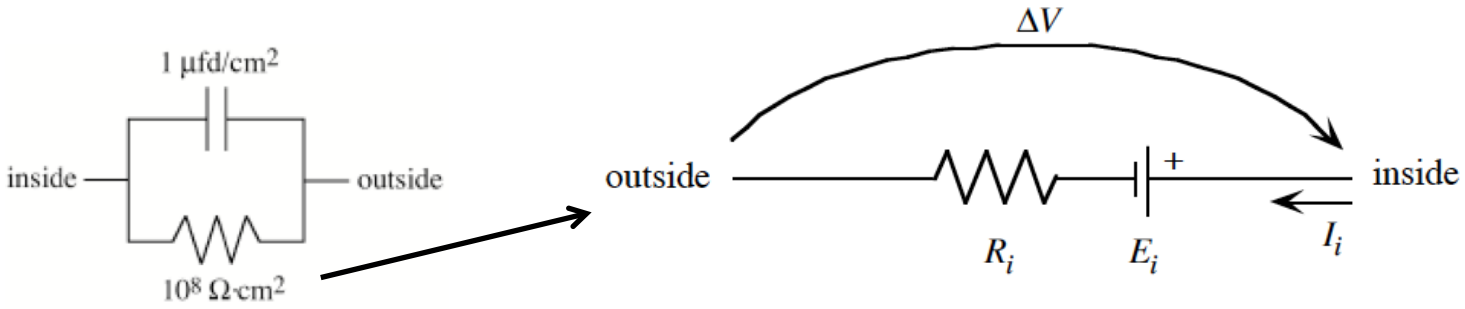
$$\mu_i^0 + RT \ln C_1 + z_i F V_1 = \mu_i^0 + RT \ln C_2 + z_i F V_2$$



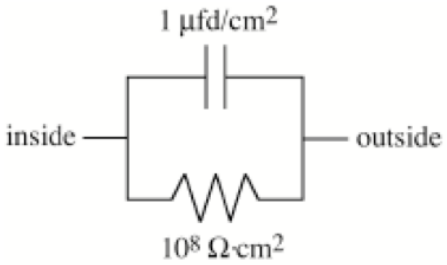
Equilibrium: Nernst Equation

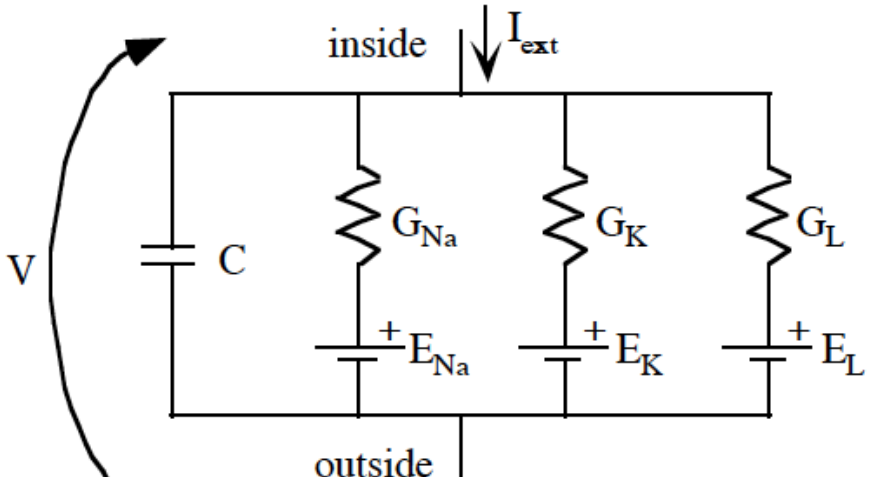
$$V_2 - V_1 = E_i = \frac{RT}{z_i F} \ln \frac{C_1}{C_2}$$

Equivalent Electrical Circuit



Hodgkin Huxley Model: Spiking of Neurons





$$C\frac{dV}{dt} = I_{ext} - G_{Na}(V - E_{Na}) - G_{K1}(V - E_K) - G_L(V - E_L)$$

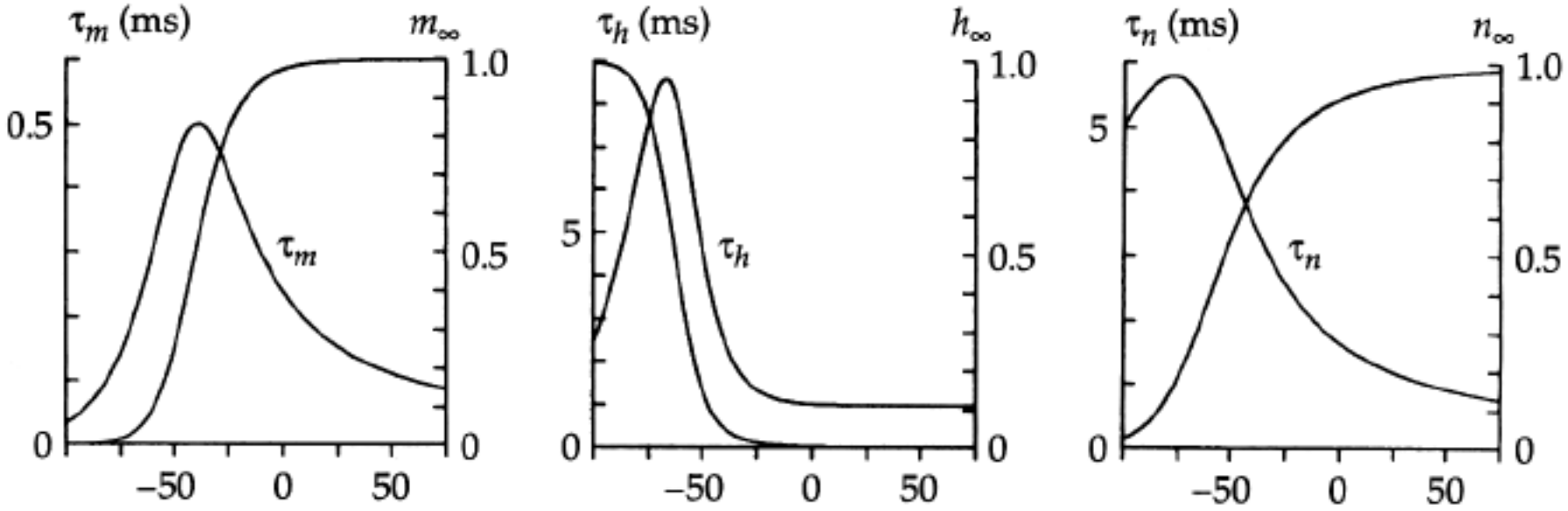
$$G_{Na} = \overline{G}_{Na} m^3 h \qquad \frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)}$$

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$

$$G_K = \overline{G}_K n^4 \qquad \frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)}$$

m_{inf}, h_{inf},and n_{inf} values give the steady state values at a particular V and time Constants quantify how fast the steady state value is reached.

Hodgkin Huxley Model: Spiking of Neurons



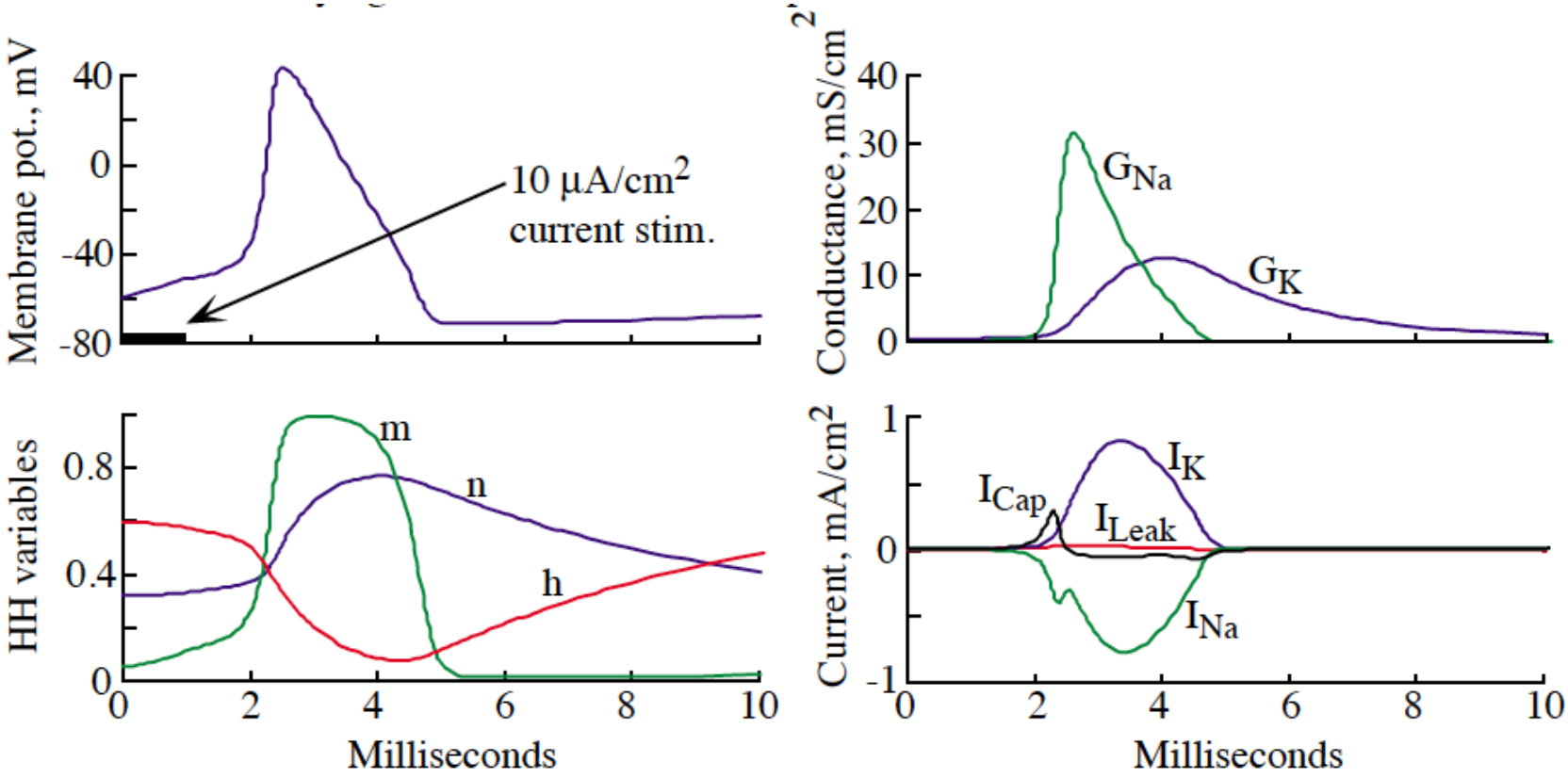
Note the differences in the scales of the time constants for *m*, *h* and *n*; also the differences in m_{inf} and h_{inf} functions.

m and *h* are the activation and inactivation variables for Na^+ channels and *n* is the activation variable for K^+ channels.

Na^+ channels allow Na-ions to flow into the cell and hence depolarize the cell (increase the potential inside from resting state)

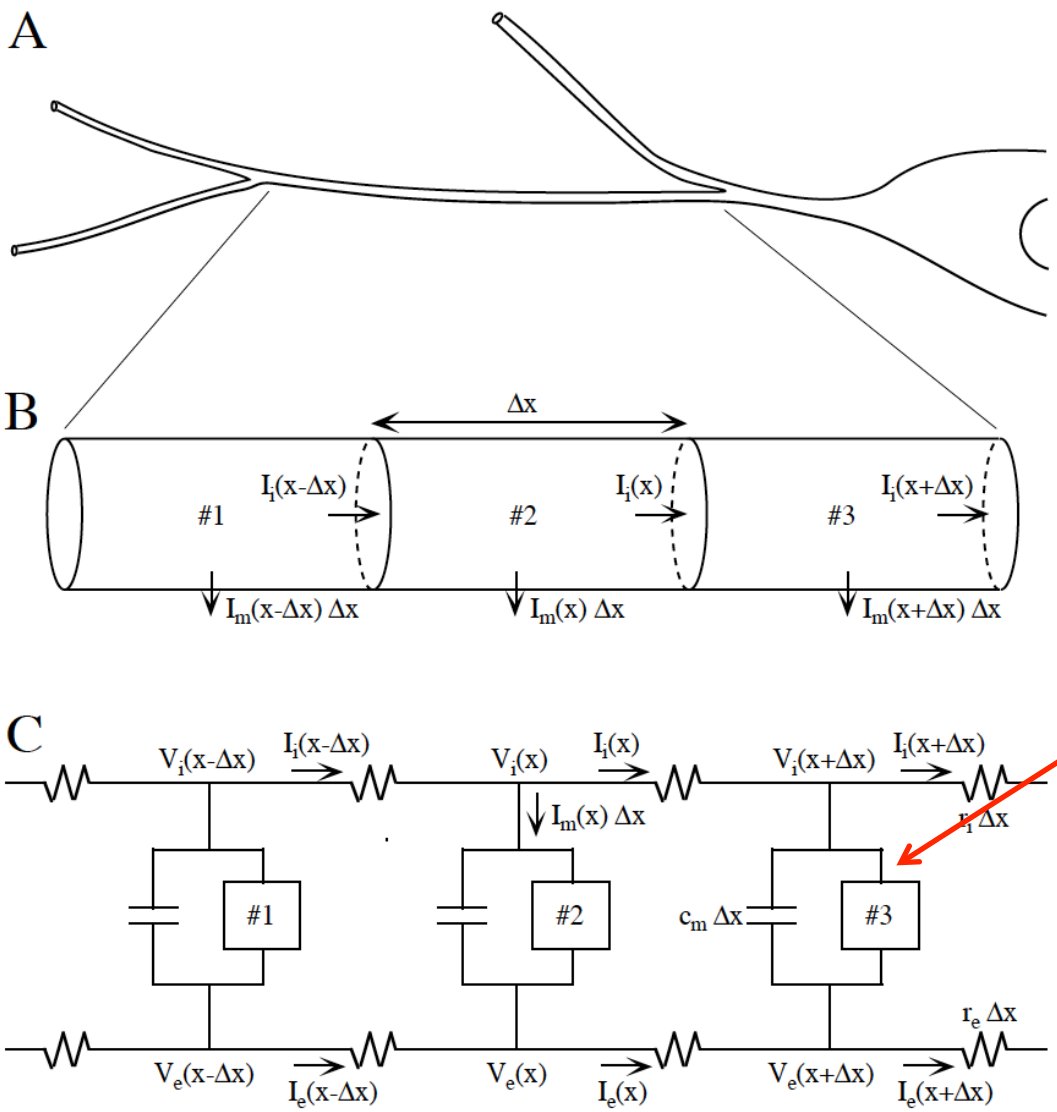
K^+ channels allow K-ions to flow out of the cell and hence hyperpolarize the cell (lower the potential inside from resting state)

Hodgkin Huxley Model: Spiking of Neurons



Rising phase of the action potential is from opening of Na^+ channels - increases in inside potential – further increases in Na^+ channels … and so on.
Until inactivation of Na^+ channels start – which reduces opening of Na^+
and
Opening of K^+ channel which repolarizes the cell.

Transmission through Dendrites (Passive)



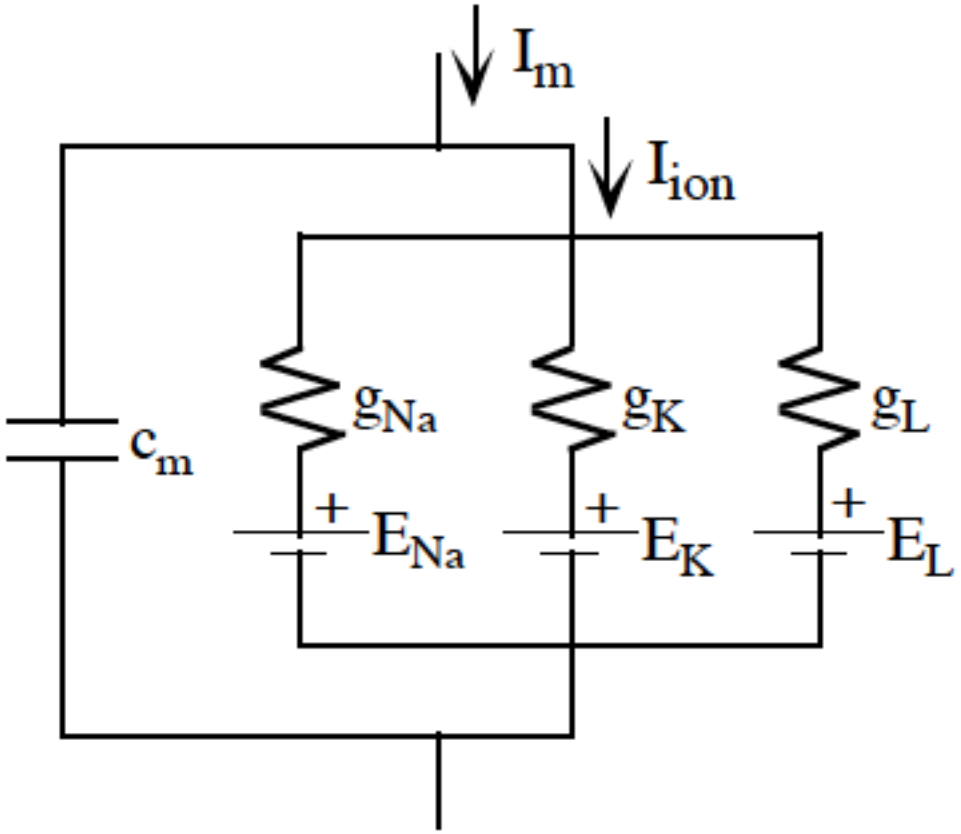
The description of voltage as a function of space/position (x) and time (t)

$$\frac{1}{r_i + r_e}\frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + I_{ion}$$

Injection of current at a certain location (synaptic input) on the dendrite induces a change in membrane potential V (increase or decrease = Excitatory or Inhibitory postsynaptic potential, EPSP or IPSP) – the equation when solved with the boundary condition of current injection then shows how the change propagates through the dendrite (x) over time (t).

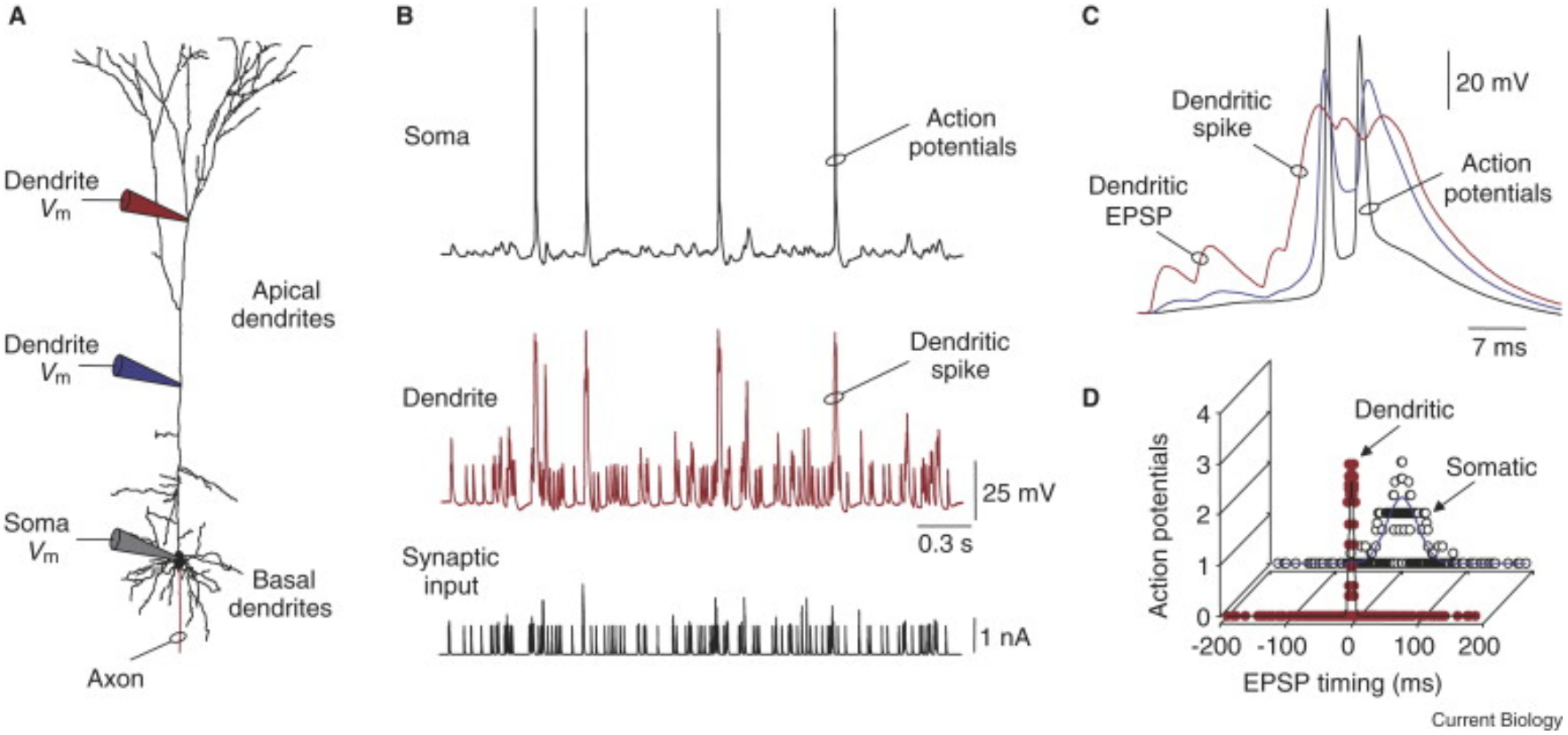
For passive flow along dendrite (without ion channels) the current across the membrane is simply through fixed conductance ($I_{ion}=gV$)

Transmission through Dendrites (Active)



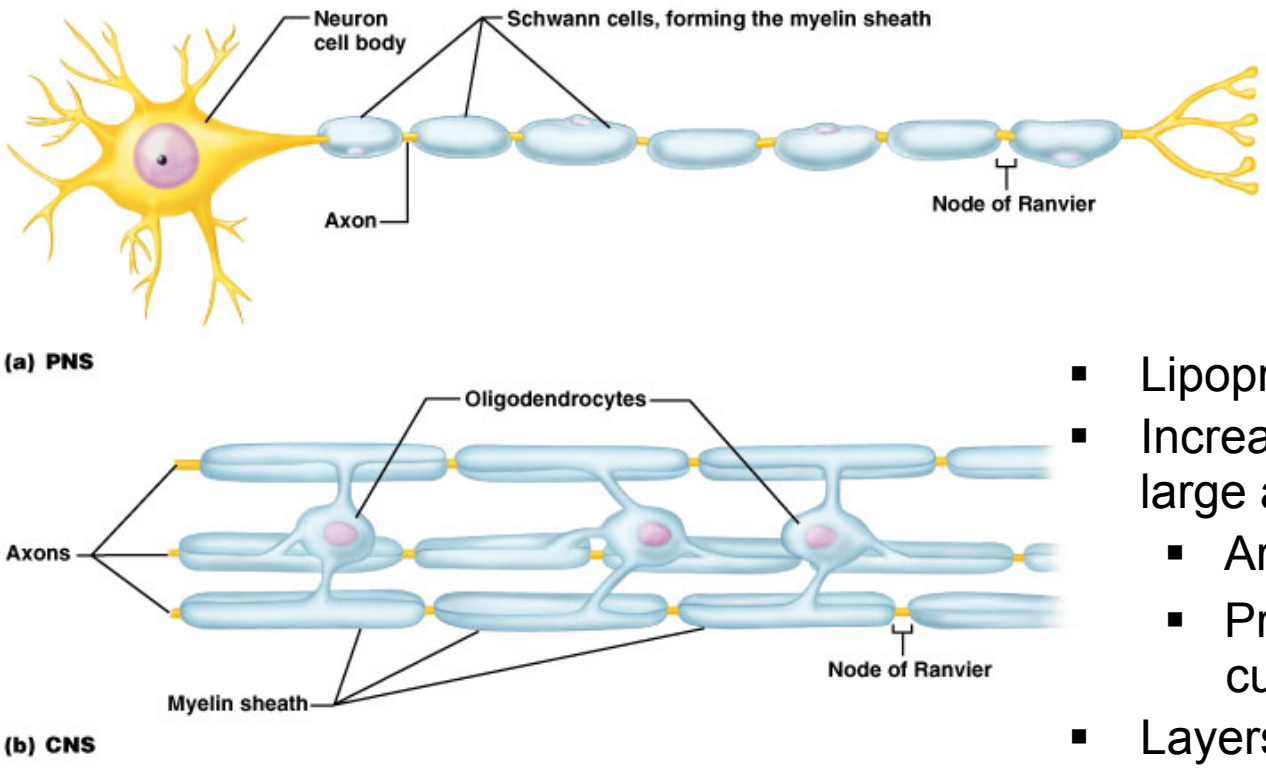
For active flow along dendrite (with ion channels) the current across the membrane is again modeled in the same way with incorporation of voltage or ligand gated ion channels with conductances that vary based on properties of the ion channels.

Dendritic Integration to Spiking Output



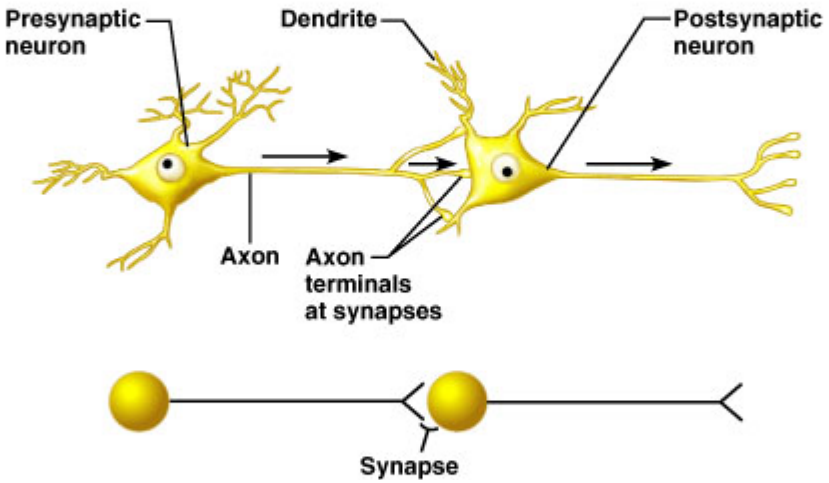
Numerous synaptic inputs of different types coming in to different locations in the dendrites (spines or even cell body) of a neuron. The net effect of all such inputs after propagation to the cell body determines whether a neuron will spike in response to such inputs or not.

Transmission through Axons
Myelin



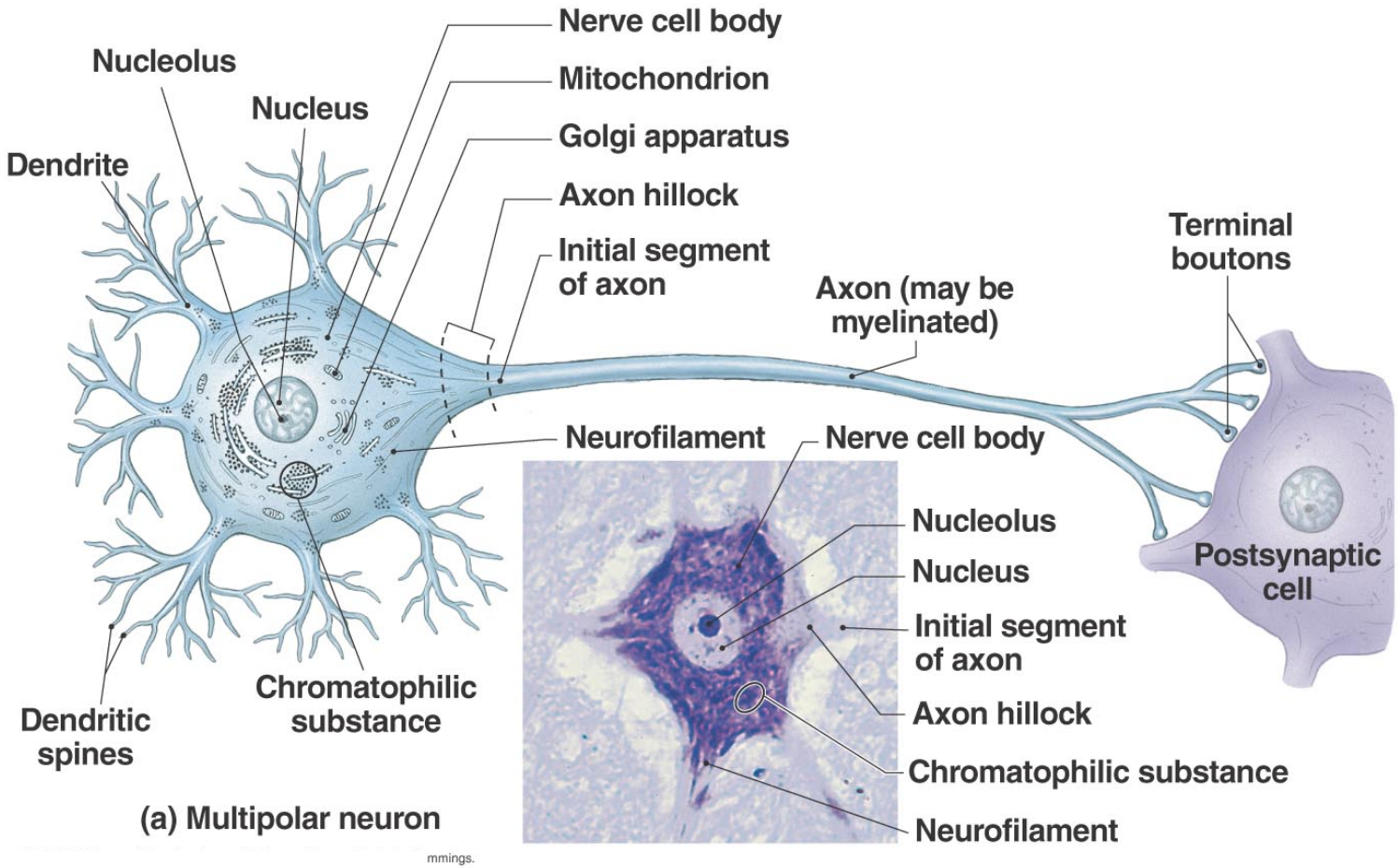
- Lipoprotein
- Increases speed of conduction, large axons
  - Are “insulation”
  - Prevent leakage of electric current
- Layers with spaces (nodes of Ranvier) between cells
- Impulse “jumps” from node to node
- “Unmyelinated” axons – smaller, slower

Synapses



- Junctions between neurons
- Information is passed (usually chemically)
- Unidirectional
- Presynaptic (*toward* synapse) vs postsynaptic (*away from* synapse): most neurons function as both
- Synaptic cleft (tiny gap)
- Often synapses form on tiny mushroom like bodies on dendrites called spines

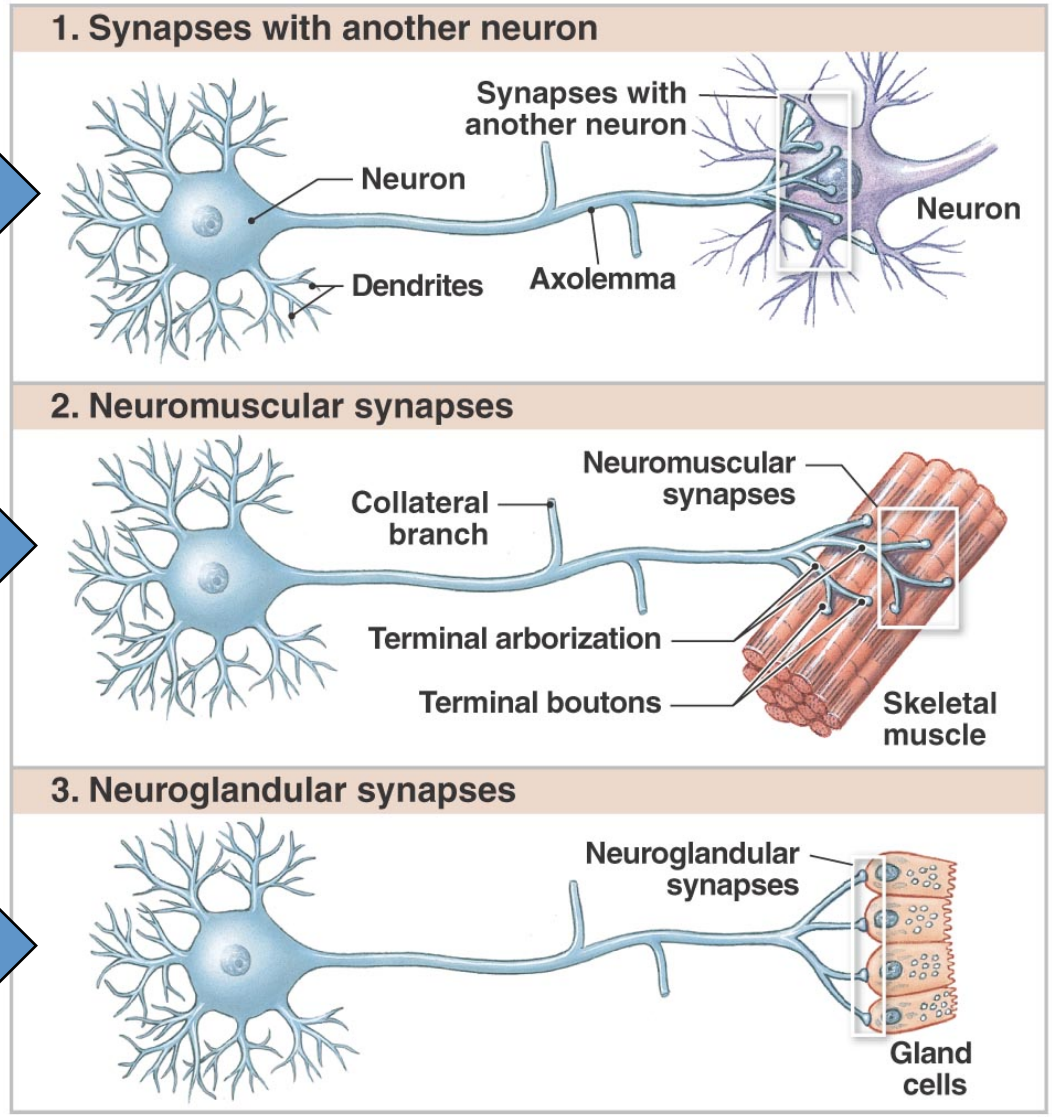
Synapses


Nerve cell body
Mitochondrion
Golgi apparatus
Axon hillock
Initial segment of axon
Nucleolus
Nucleus
Dendrite
Axon (may be myelinated)
Terminal boutons
Neurofilament
Nerve cell body
Nucleolus
Nucleus
Initial segment of axon
Axon hillock
Chromatophilic substance
Neurofilament
Postsynaptic cell
Chromatophilic substance
Dendritic spines
(a) Multipolar neuron

Synapses

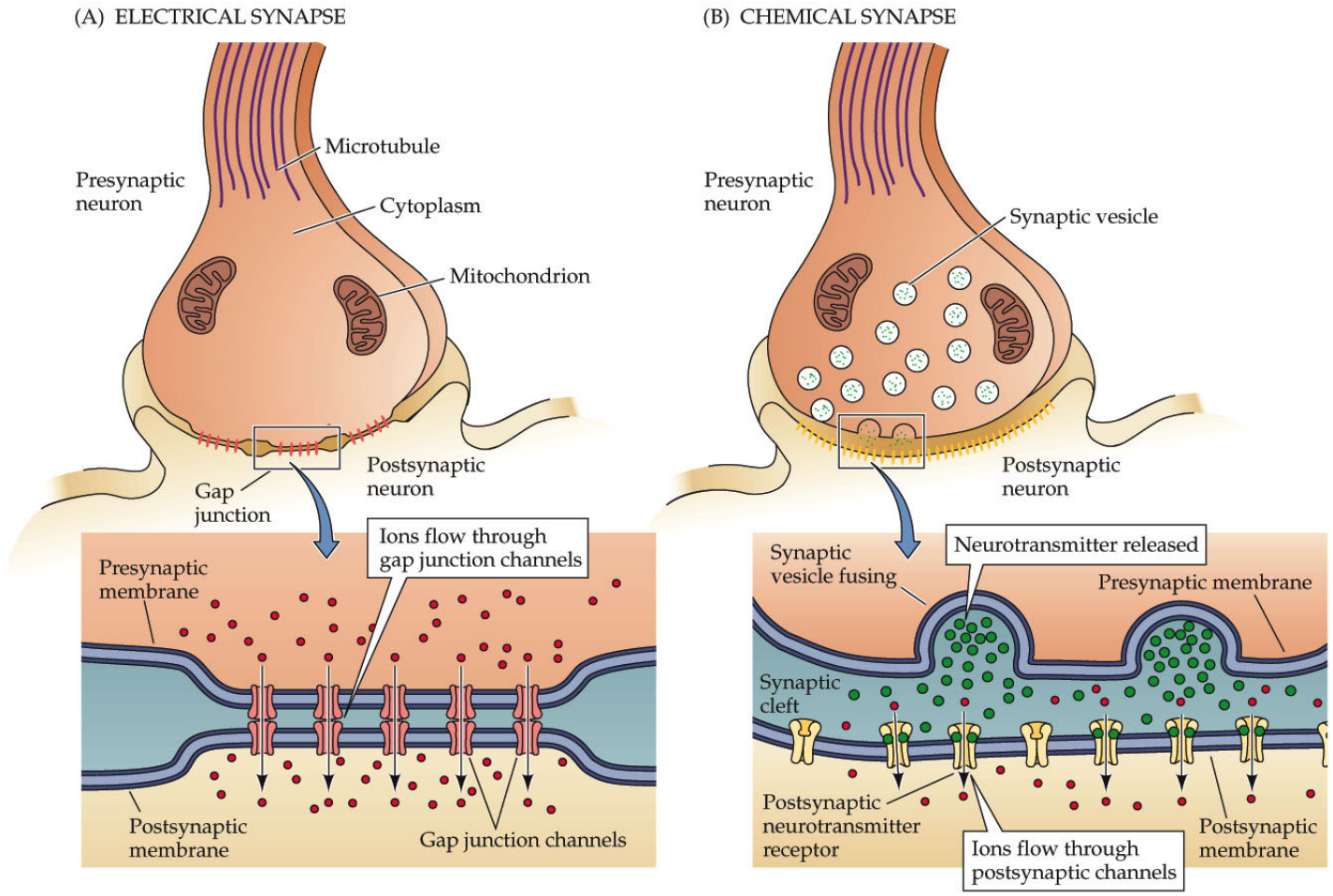
Neurons can synapse with:

1. Neurons
2. Muscle
3. Glands

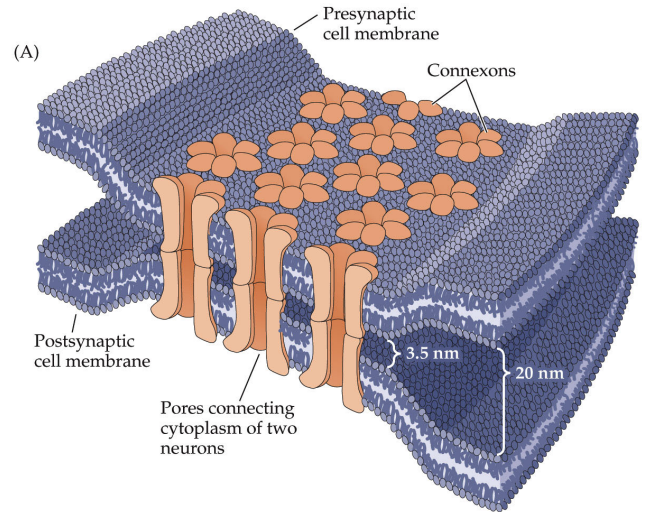


Synapses

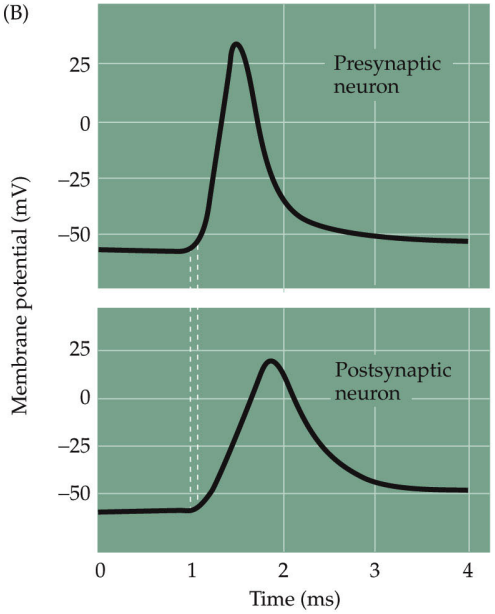
Two principal kinds of synapses: electrical and chemical

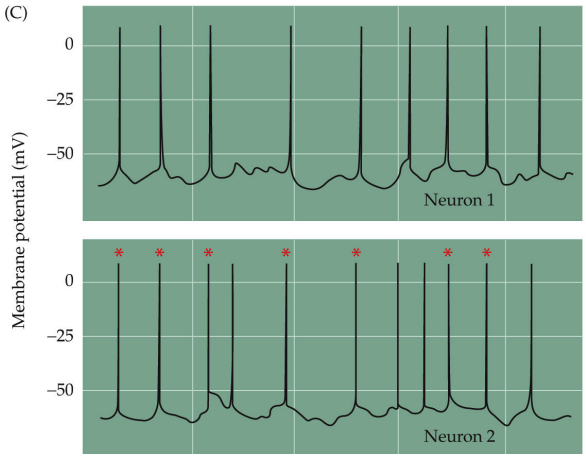


Gap junctions are formed where hexameric pores called connexons connect with one between cells



Electrical synapses are built for speed

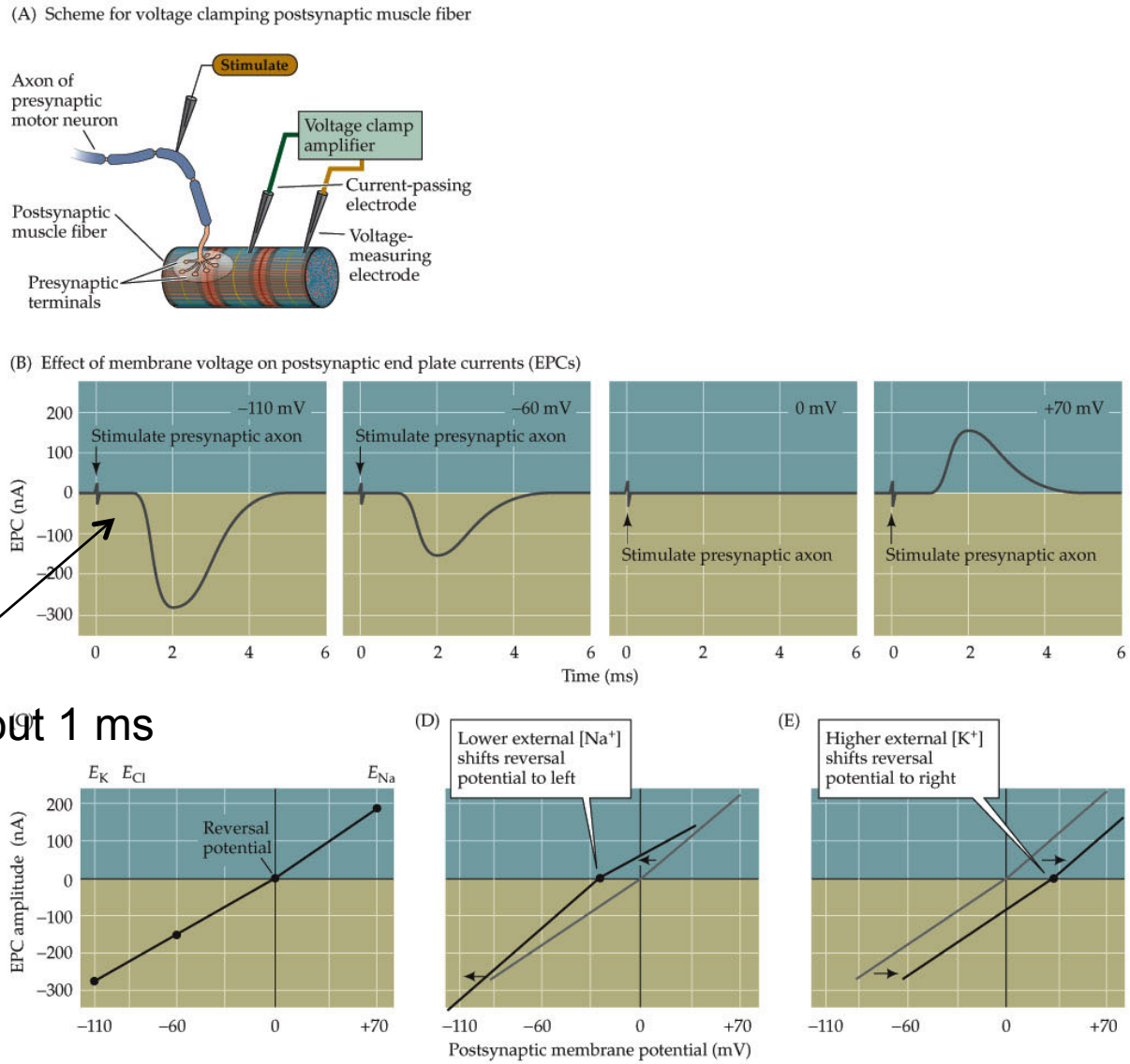




***NEUROSCIENCE, Fourth Edition,* Figure 5.2 (Part 2)**

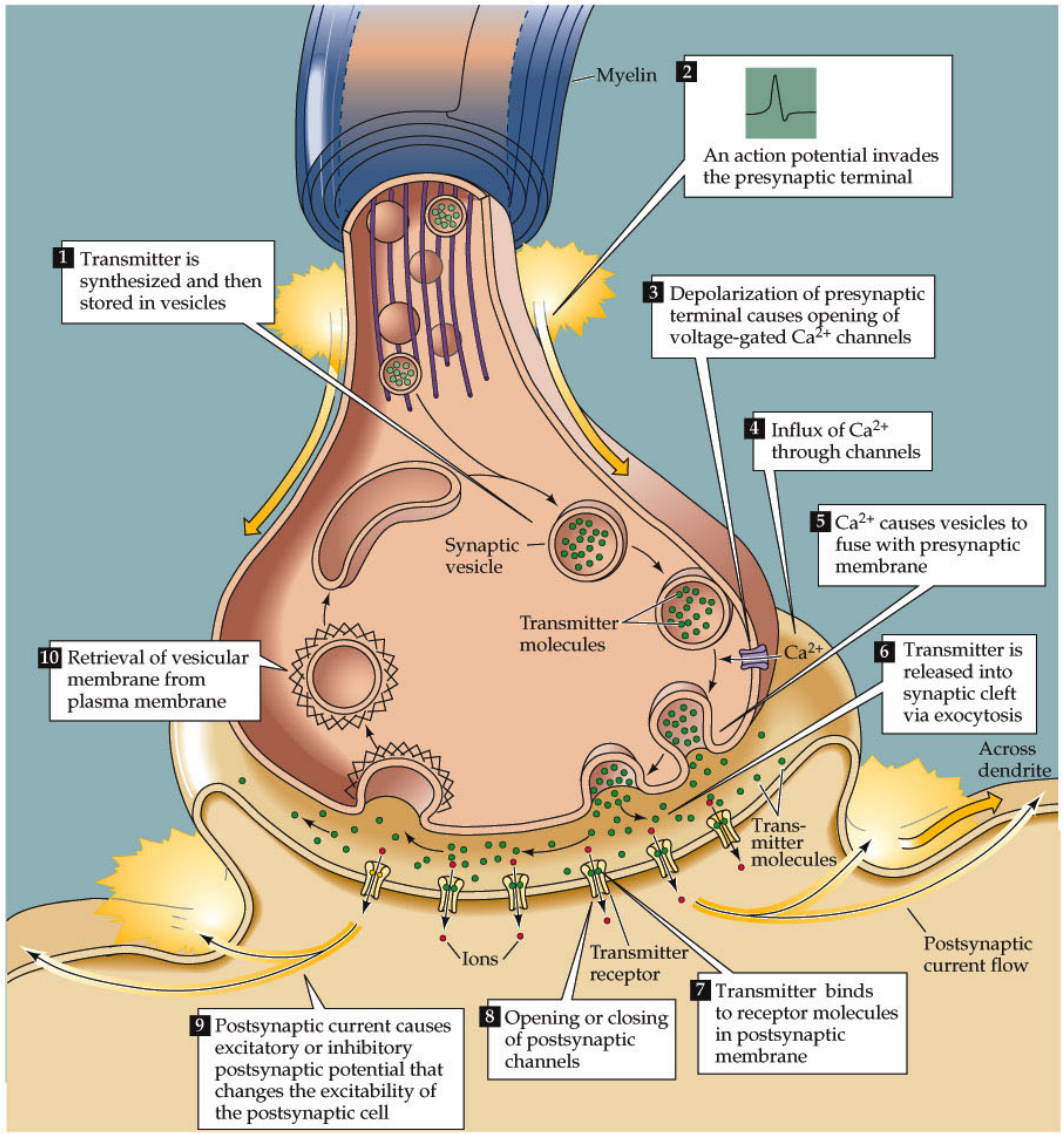
Electrical coupling is a way to synchronize neurons with one another

Contrast with chemical synapse

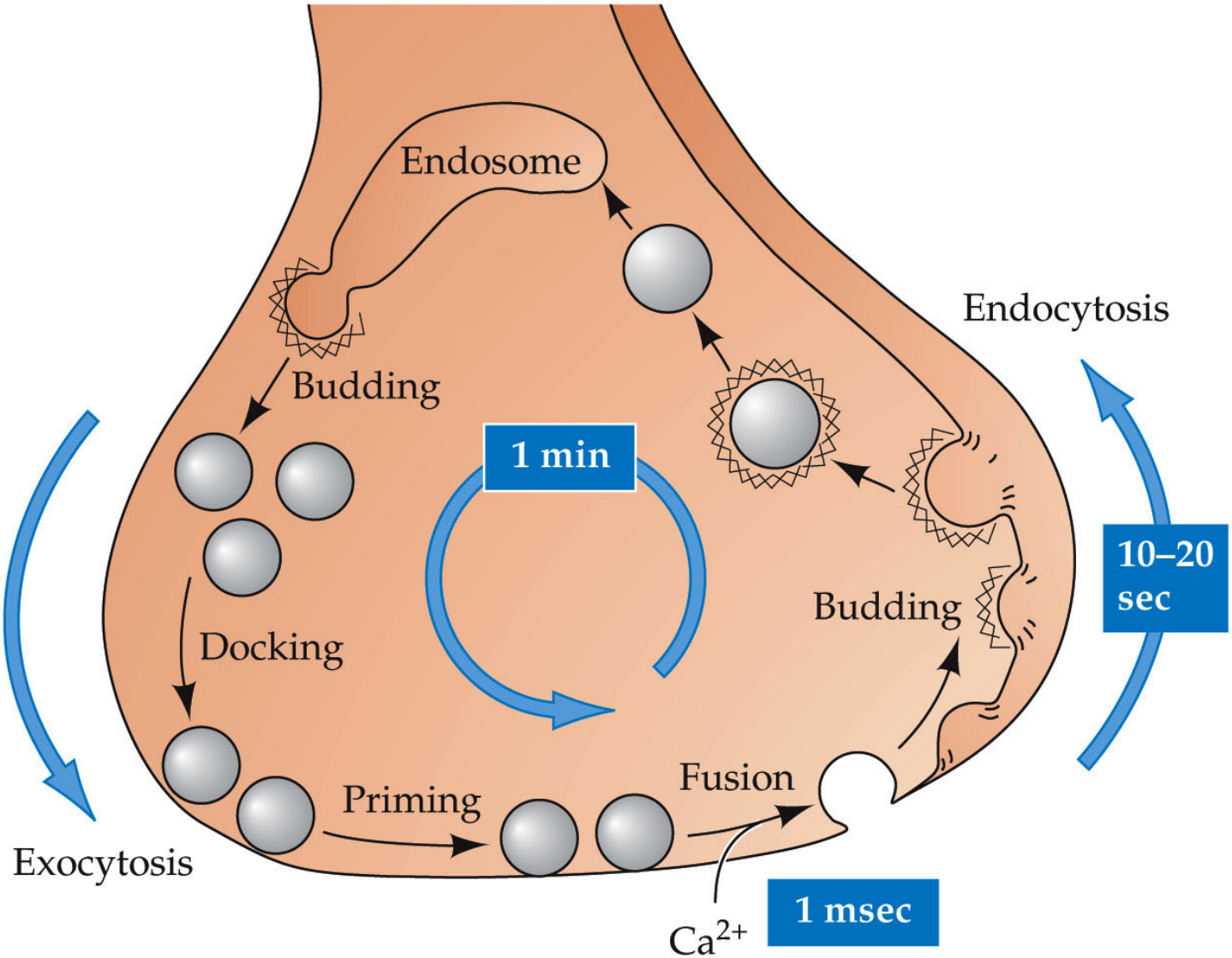


Delay of about 1 ms

Chemical synapses: the predominant means of communication between neurons



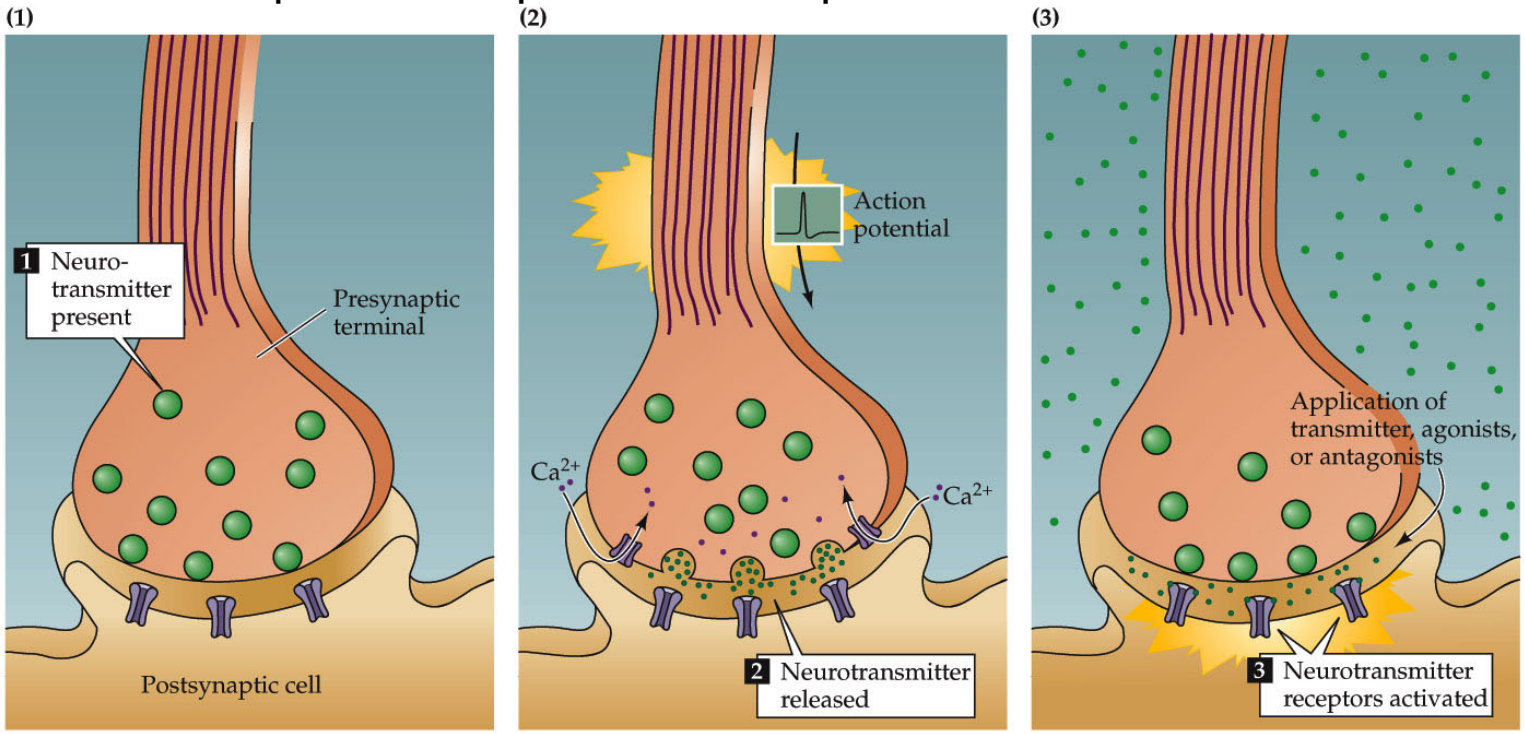
The Synaptic Vesicle Cycle



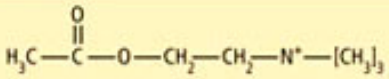
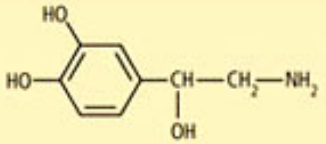
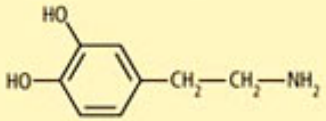
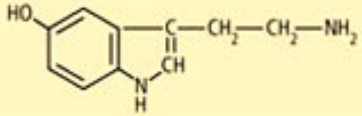
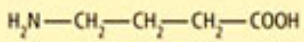
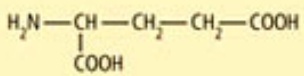
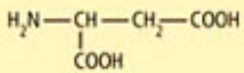
Neurotransmitters

Criteria that define a neurotransmitter:

1. Must be present at presynaptic terminal
2. Must be released by depolarization, Ca^{++}-dependent
3. Specific receptors must be present



Neurotransmitters

Neurotransmitter	Structure	Functional Class	Secretion Sites
Acetylcholine		Excitatory to vertebrate skeletal muscles; excitatory or inhibitory at other sites	CNS; PNS; vertebrate neuromuscular junction
Biogenic Amines			
Norepinephrine		Excitatory or inhibitory	CNS; PNS
Dopamine		Generally excitatory; may be inhibitory at some sites	CNS; PNS
Serotonin		Generally inhibitory	CNS
Amino Acids			
GABA (gamma aminobutyric acid)		Inhibitory	CNS; invertebrate neuromuscular junction
Glycine		Inhibitory	CNS
Glutamate		Excitatory	CNS; invertebrate neuromuscular junction
Aspartate		Excitatory	CNS
Neuropeptides (a very diverse group, only two of which are shown)			
Substance P	Arg—Pro—Lys—Pro—Gln—Gln—Phe—Phe—Gly—Leu—Met	Excitatory	CNS; PNS
Met-enkephalin (an endorphin)	Tyr—Gly—Gly—Phe—Met	Generally inhibitory	CNS

Neurotransmitters: Glutamate Receptors

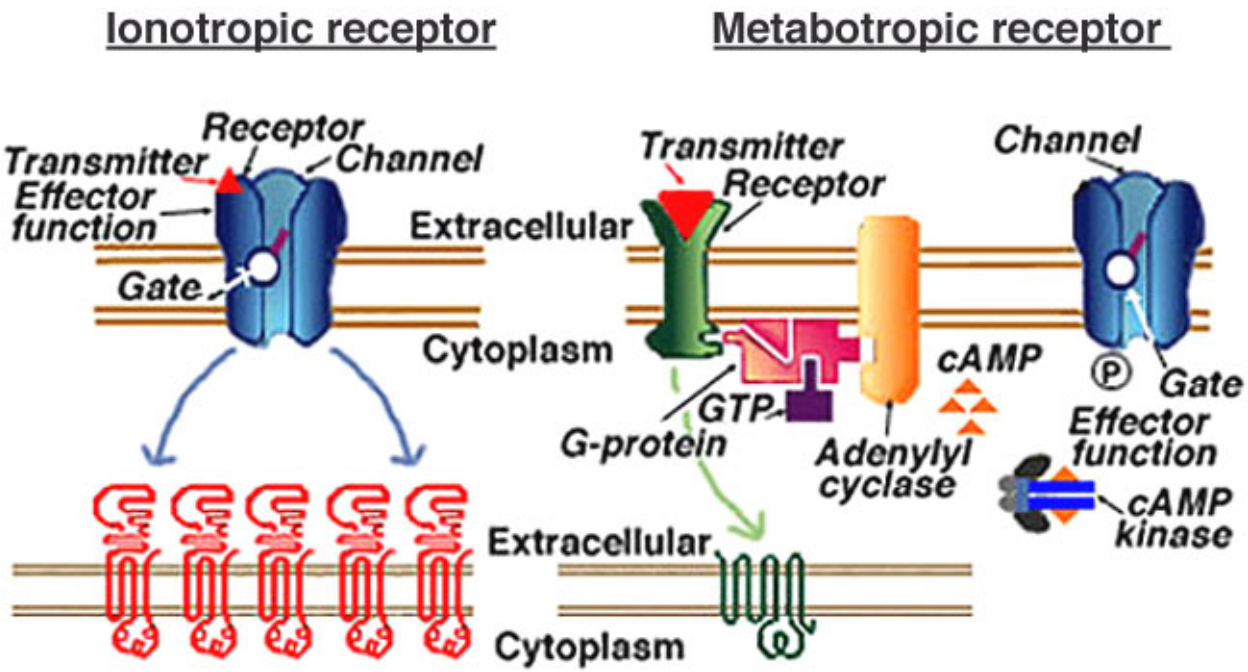
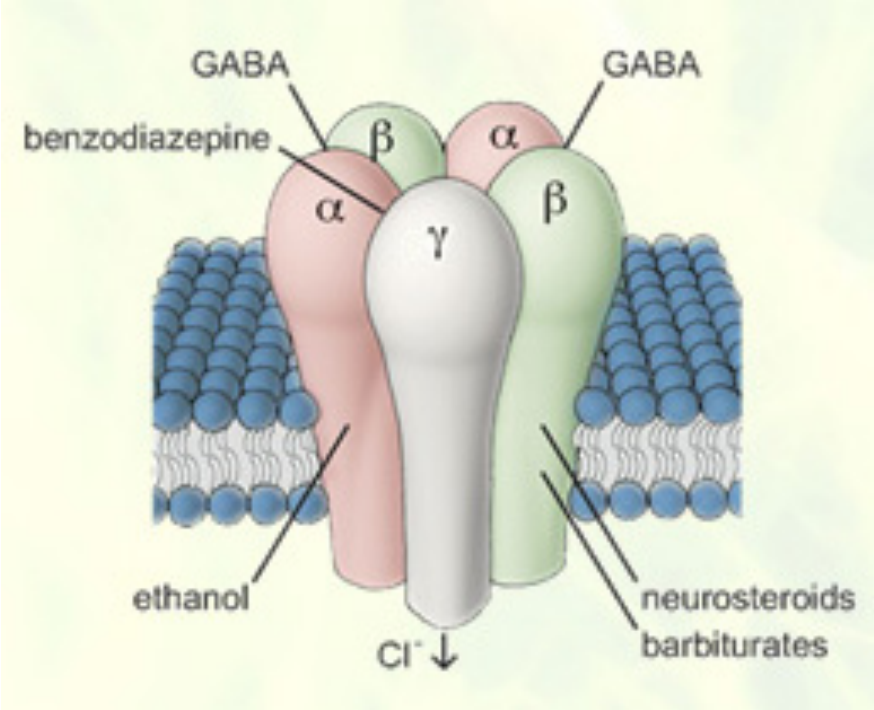


Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (

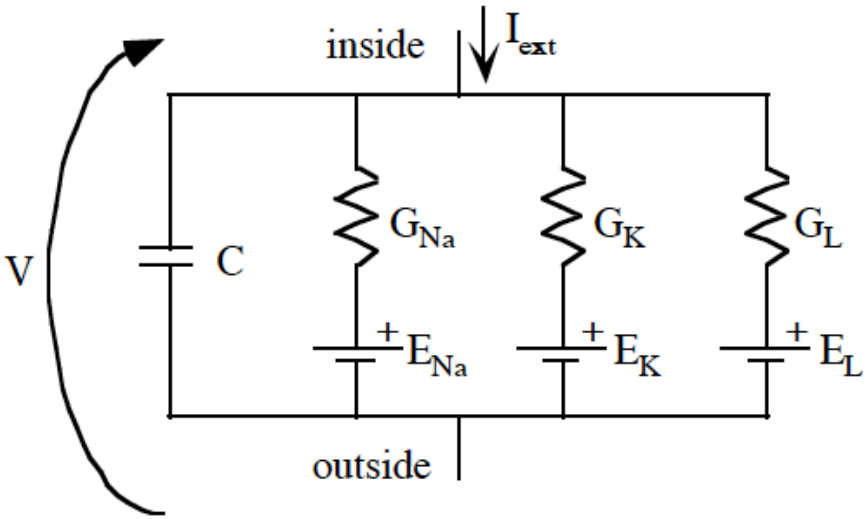
Fig. 5b. Metabotropic receptors are coupled to their associated ion channels by a second messenger cascade (top). Each mGluR is composed of one polypeptide, which is coupled to a G-protein

Neurotransmitters:
GABA Receptors

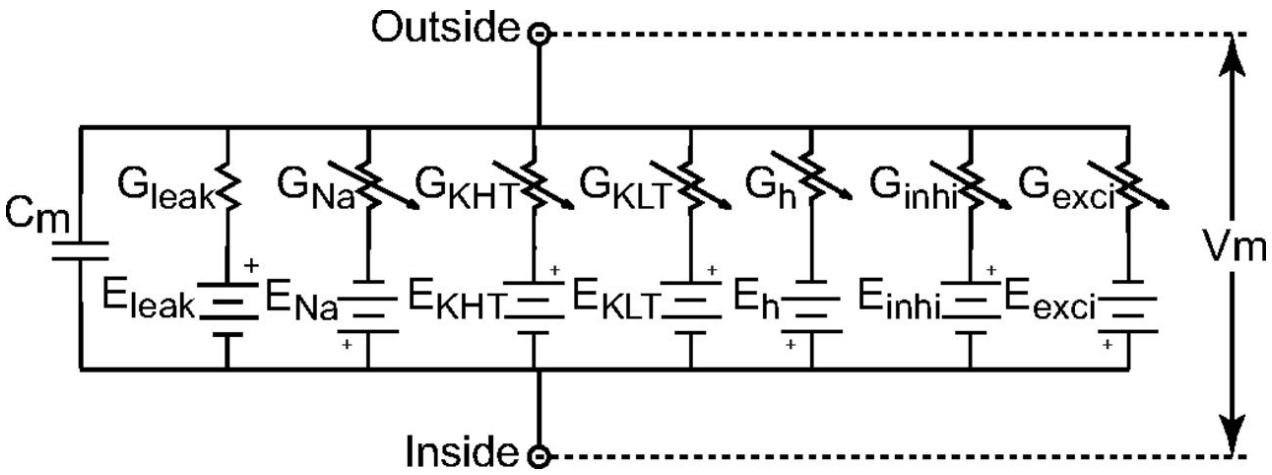


GABA receptor are essentially chloride channels. There are binding sites on the outside region of the receptor. When GABA binds to the receptor, the protein structure in the inside go through a conformational change to open up and allow Cl^- to flow into the cell down an electrochemical gradient. Cl^- flow into the cell hyperpolarizes the cell and hence has an inhibitory effect

Equivalent Circuit Model with Synapses

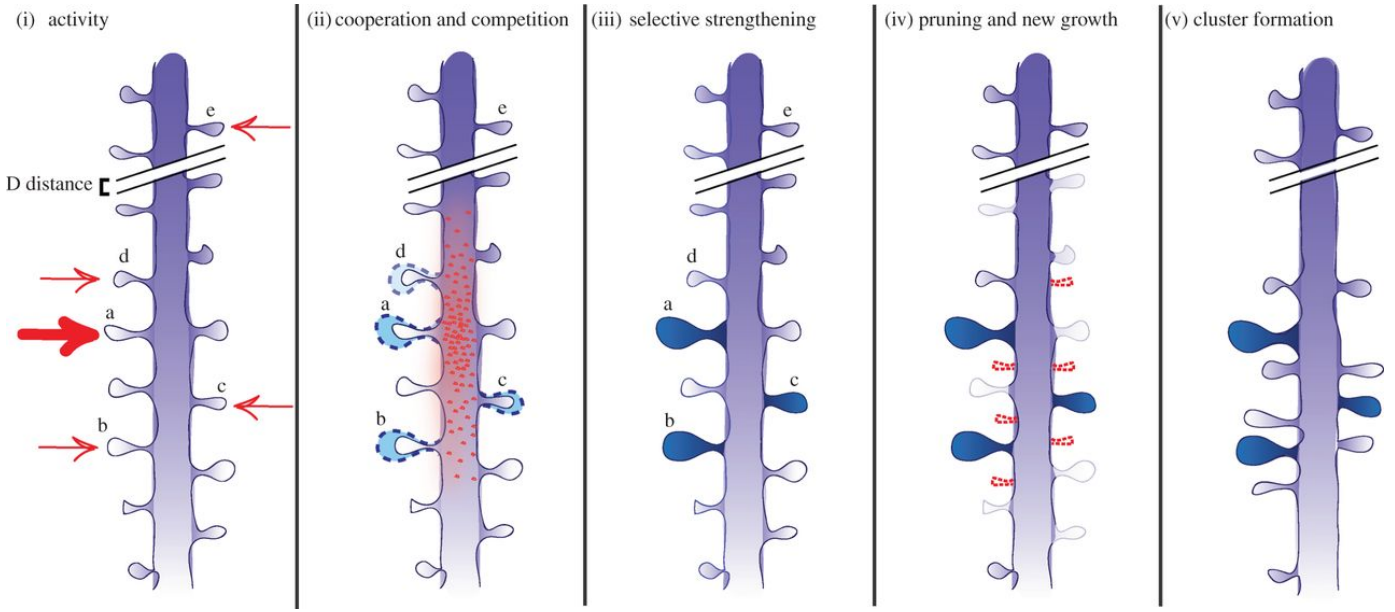


Inclusion of synaptic inputs on to a neuron can be modeled as additional currents (new trans-membrane current branches) that have synaptic conductances which change based on the membrane potential or ligand concentration and are activated when there is a pre-synaptic action potential.

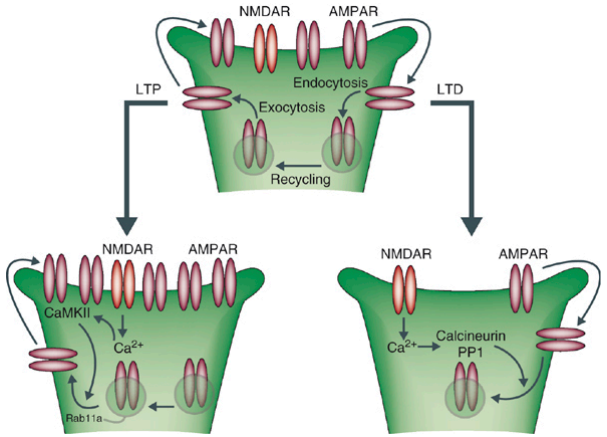


Adaptation – the KEY
Plasticity and Different Time scales of plasticity

Adaptation – the KEY
Plasticity and Different Time scales of plasticity

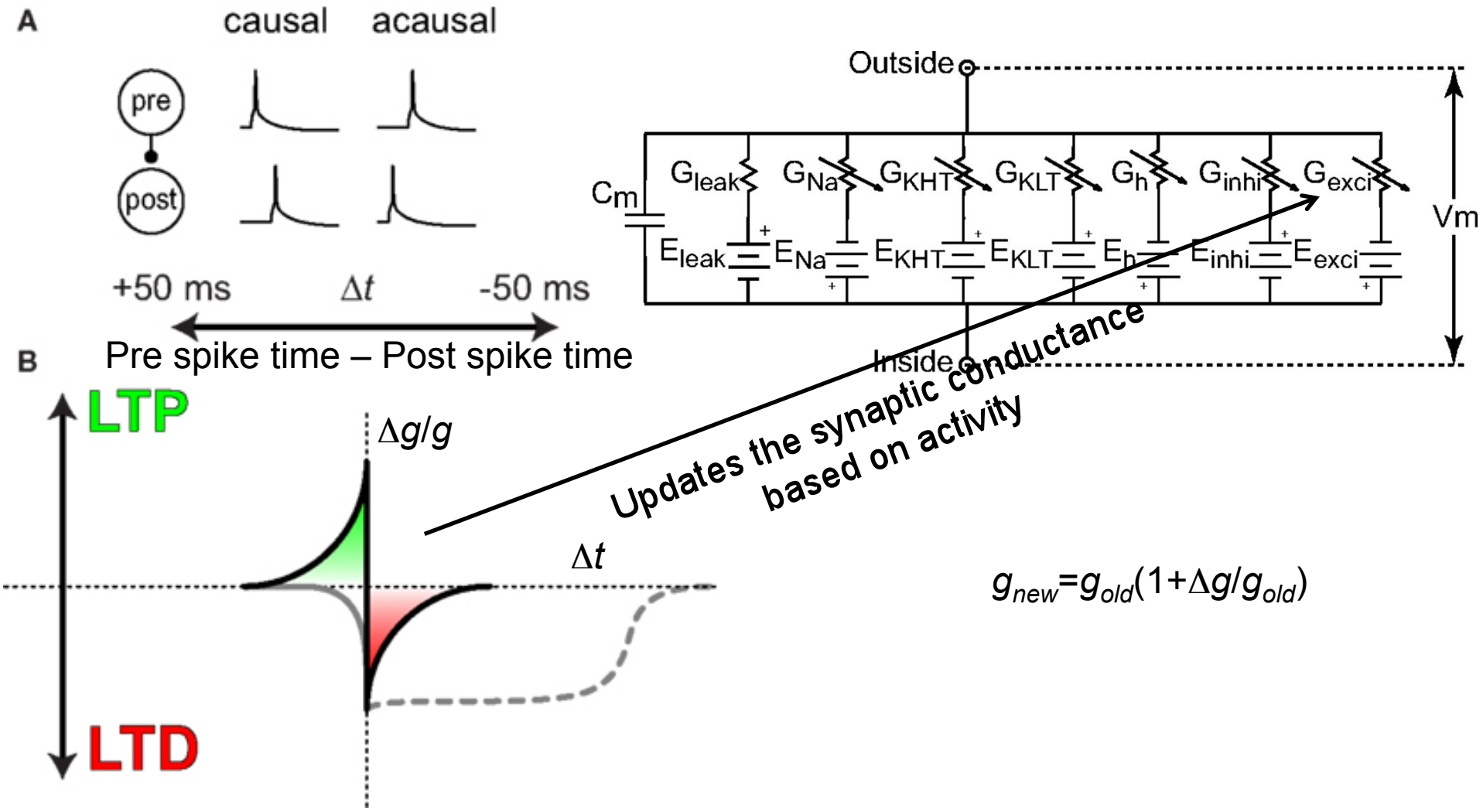


Variety of changes and variety of time scales: size of spines, number spines, location of spines, removal and reduction of spines. All these make change in synaptic connections between neurons possible



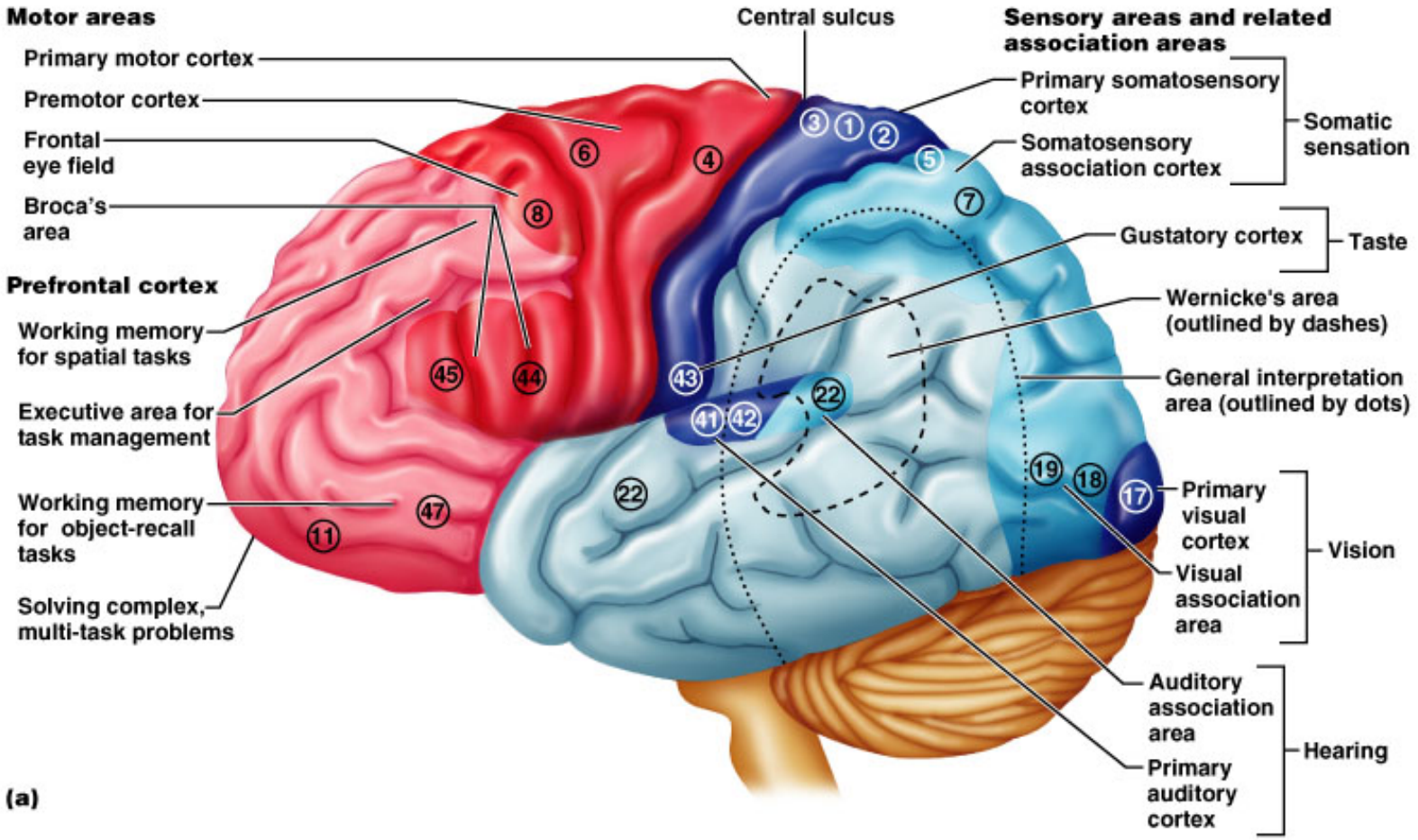
Increases or decreases in concentration of neurotransmitter receptors can also occur at fast time scales allowing change in synaptic strength

Adaptation – the KEY
Plasticity and Different Time scales of plasticity
Activity Regulated Spike Timing Dependent Plasticity



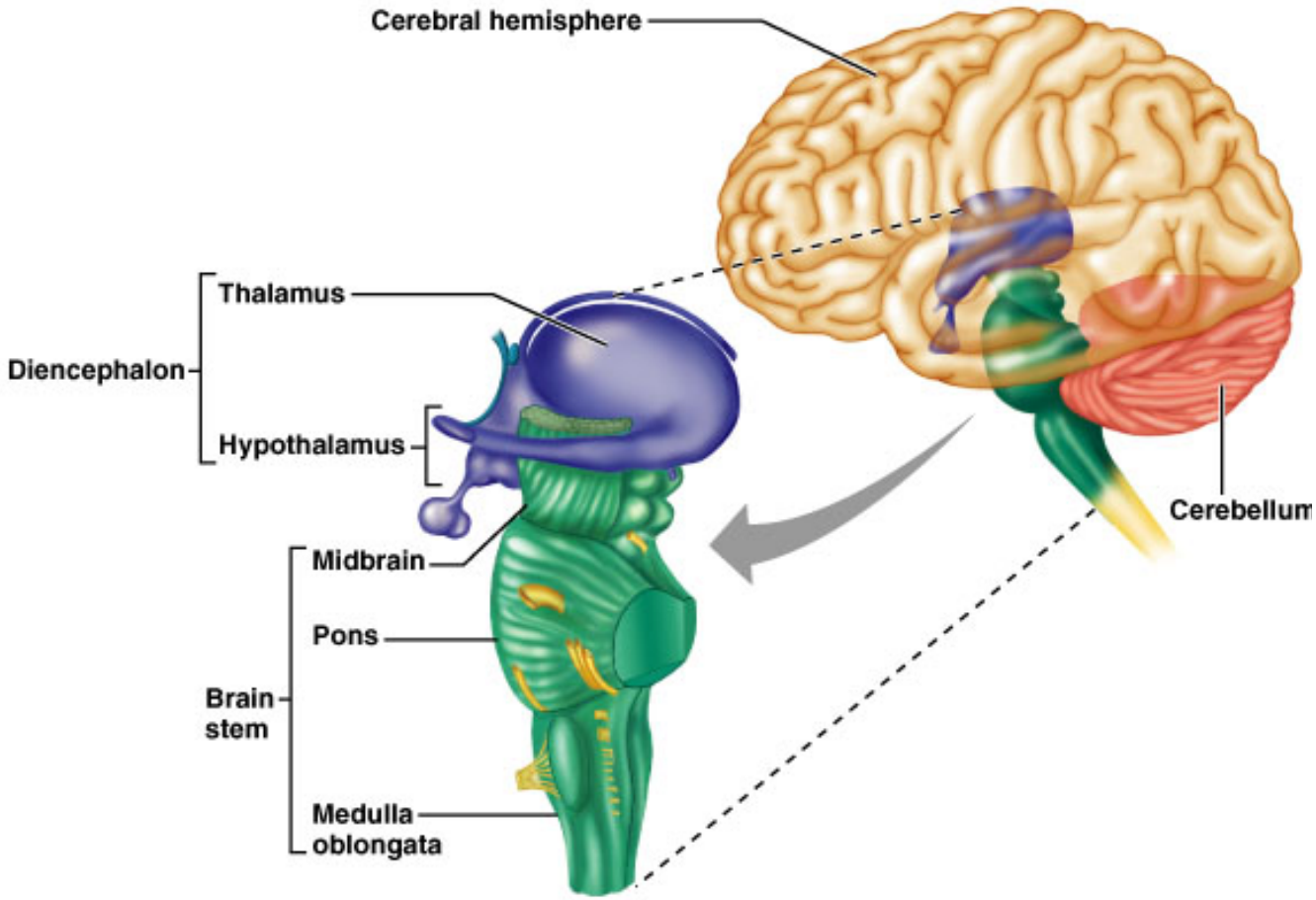
$g_{new}=g_{old}(1+\Delta g/g_{old})$

Basic Neural Systems: How is it all put together?
Organization of the Brain – Different Systems



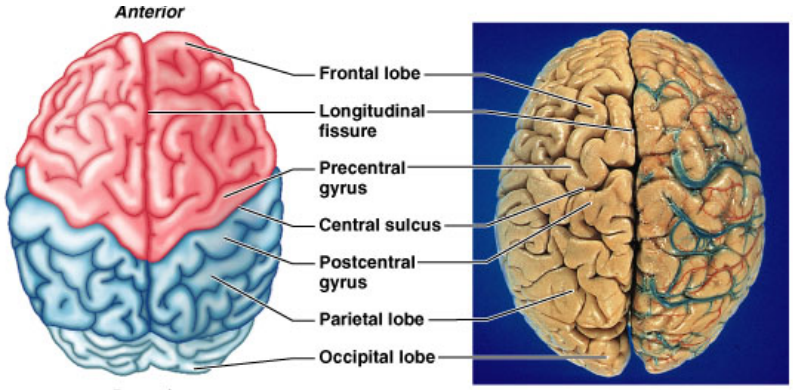
Parts of Brain

(d) Adult brain structures
Cerebrum: Cerebral hemispheres (cortex, white matter, basal nuclei)
Diencephalon (thalamus, hypothalamus, epithalamus)
Brain stem: midbrain
Brain stem: pons
Cerebellum
Brain stem: medulla oblongata
Spinal cord

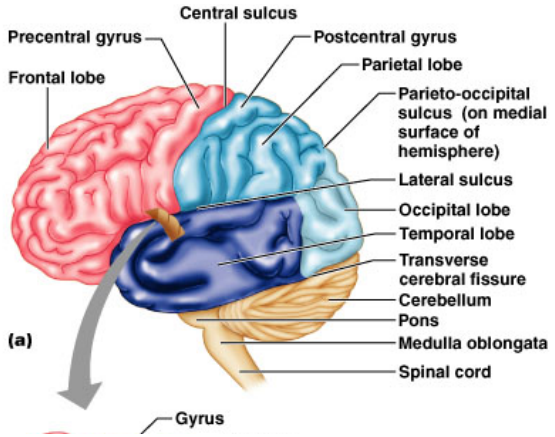


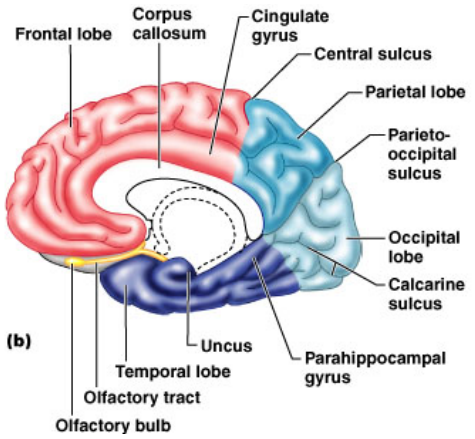
Cerebral hemispheres and lobes

- Divided by ***longitudinal fissure*** into right & left sides
- ***Central sulcus*** divides frontal from parietal lobes



- ***Lateral sulcus*** separates temporal lobe from parietal lobe
- ***Parieto-occipital sulcus*** divides occipital and parietal lobes (not seen from outside)
- ***Transverse cerebral fissure*** separates cerebral hemispheres from cerebellum

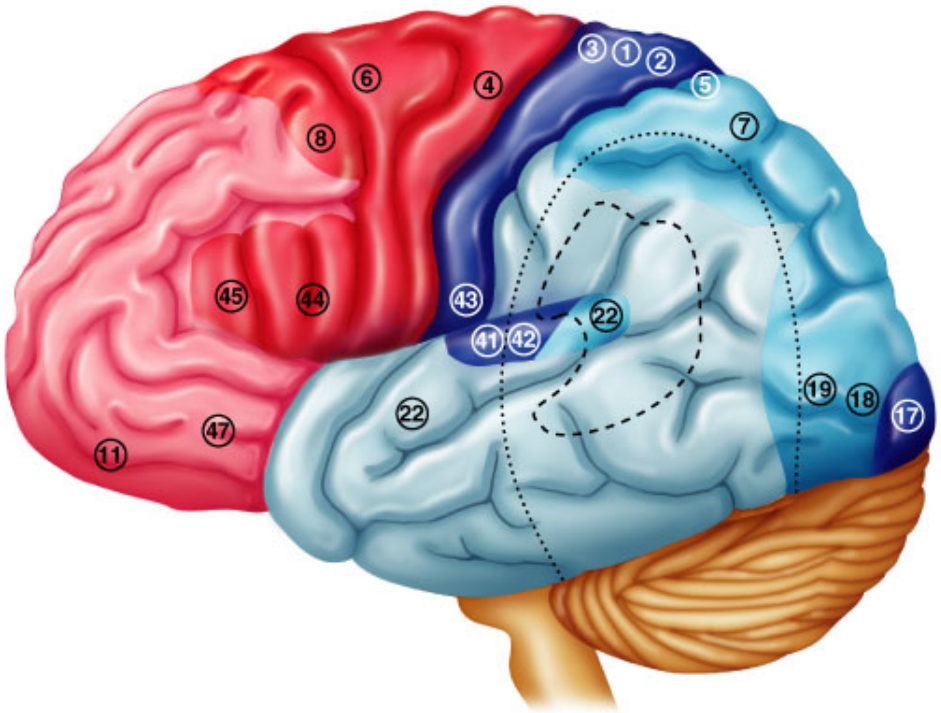




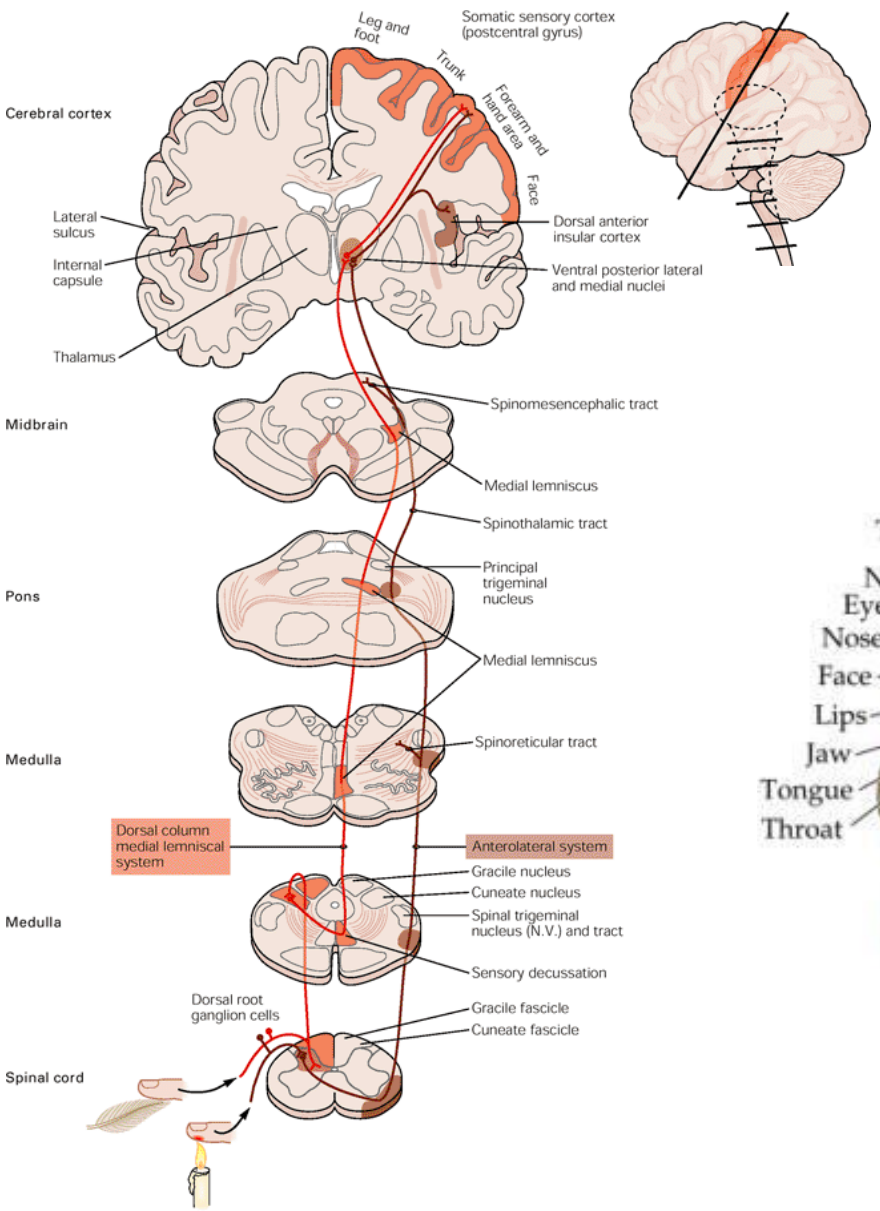
Sensory areas
Posterior to central sulcus

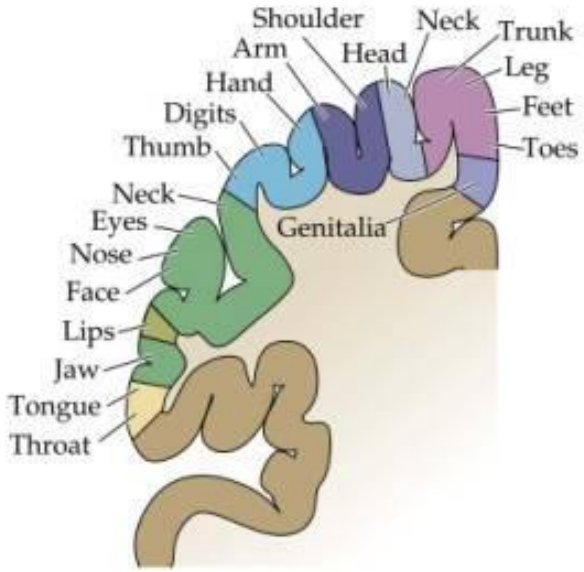
- Primary somatosensory cortex: postcentral gyrus of parietal lobe (allows conscious awareness of sensation and the ability to localize it: *where* the sensation is from)

- Somatosensory association area: behind it (understanding of what is being felt: the *meaning* of it)



Sensory Areas: Somatosensory Pathway and Receptive Fields

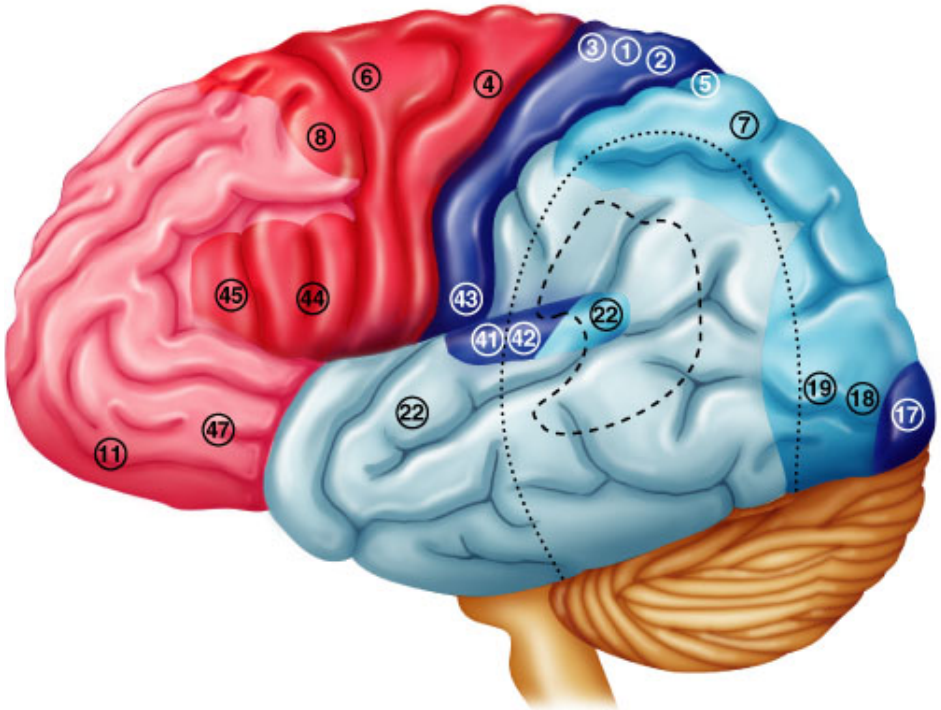




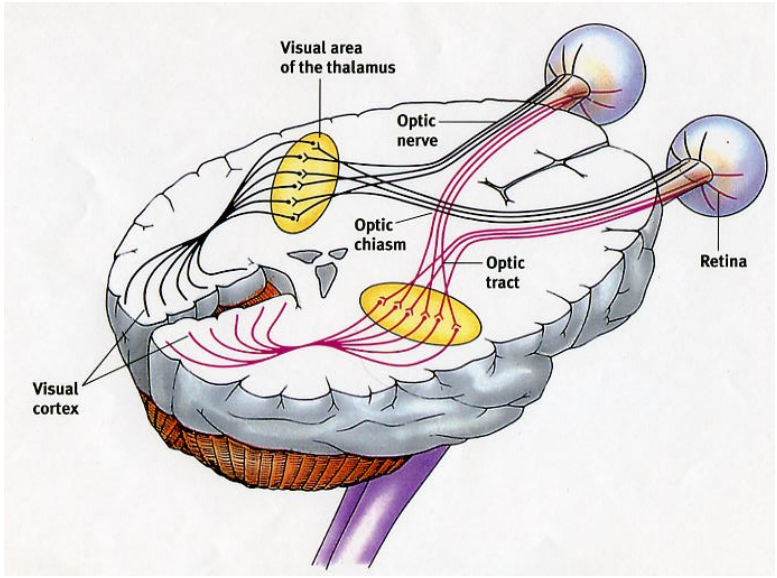
Sensory areas
Posterior to central sulcus

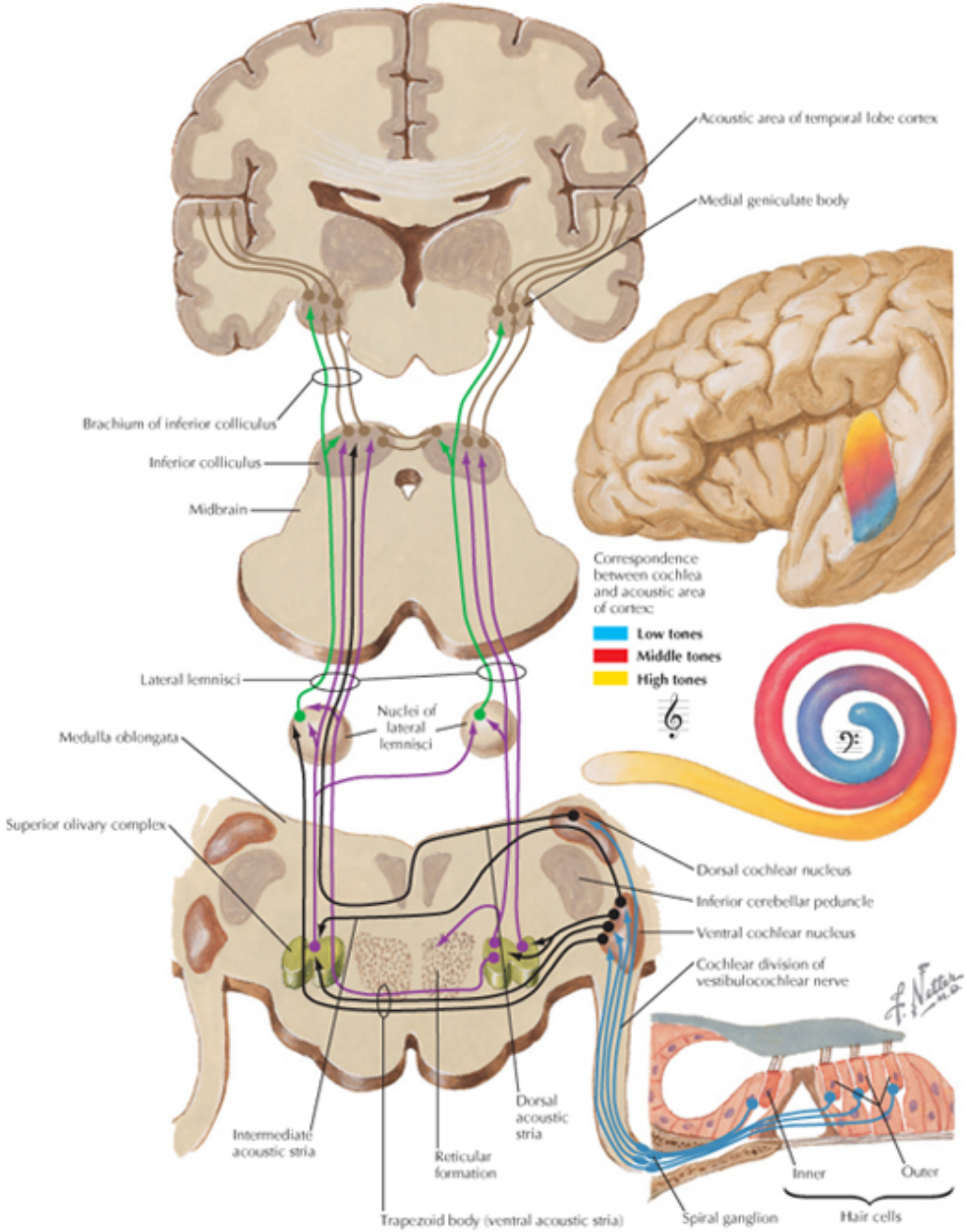
- Sight: occipital lobe
  - Primary visual cortex (17)
    - Handles info from contralateral retina (right ½ of visual field is on left side)
    - Map of visual space
    - If damaged: functionally blind because no conscious awareness of sight
  - Visual association area (18 & 19)
    - Face recognition is usually on the right side

- Hearing: temporal lobe
  - Primary auditory area (41)
  - Auditory association area (22)



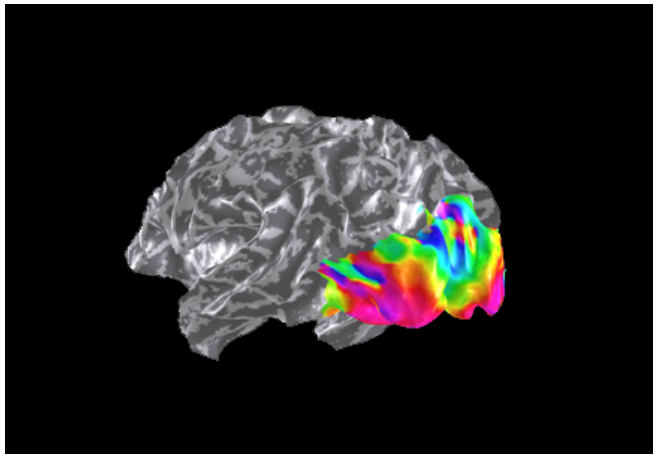
Sensory Areas: Auditory and Visual Pathways





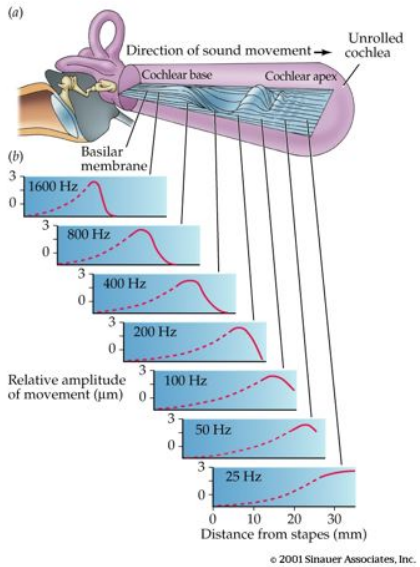
Sensory Areas: Auditory and Visual Receptive Fields

Retinotopy



Tonotopy

Frequency tuning



Orientation Tuning

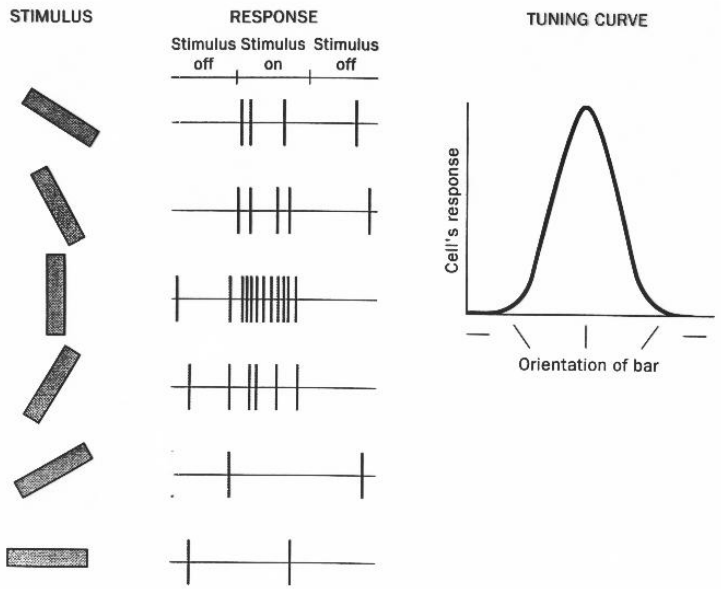
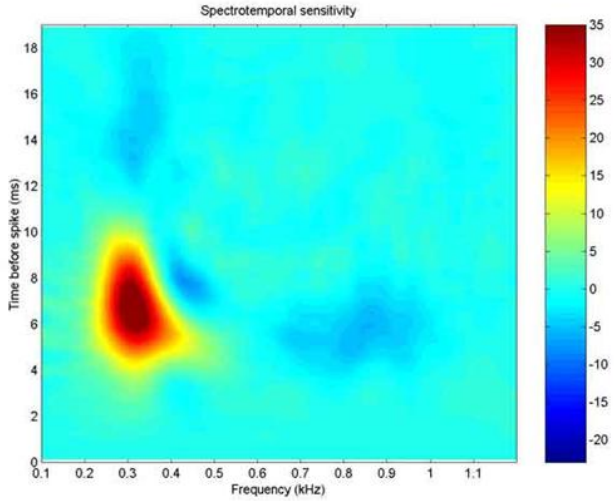


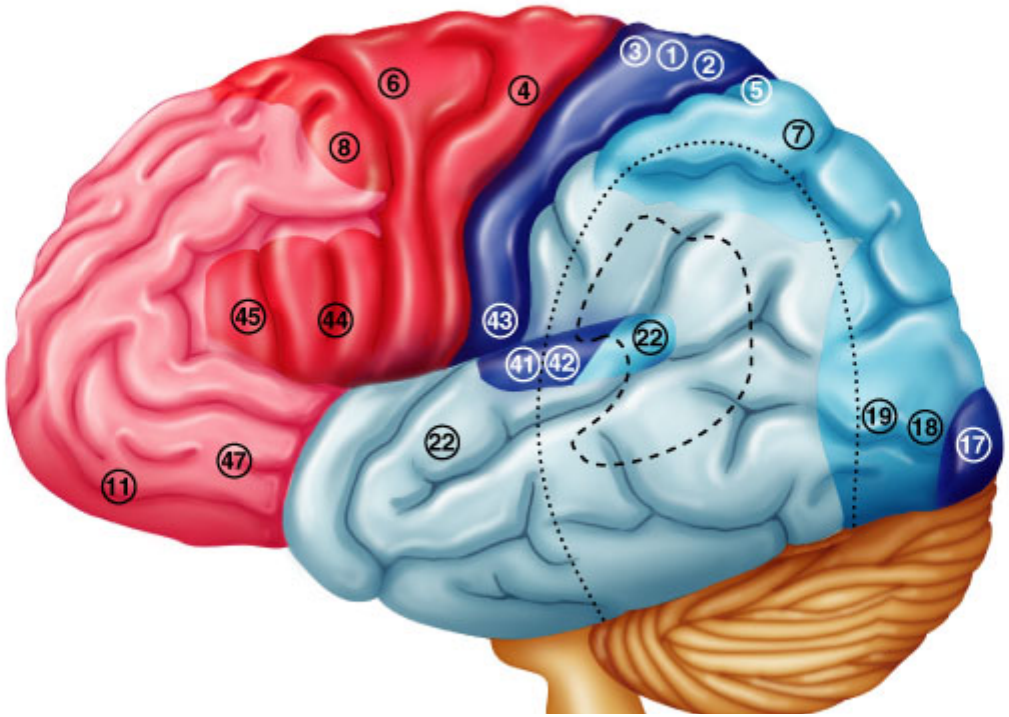
FIGURE 4.8 Response of a single cortical cell to bars presented at various orientations.

Spectrotemporal Tuning



Motor areas
Anterior to central sulcus

- Primary motor area
  - Precentral gyrus of frontal lobe (4)
  - Conscious or voluntary movement of skeletal muscles

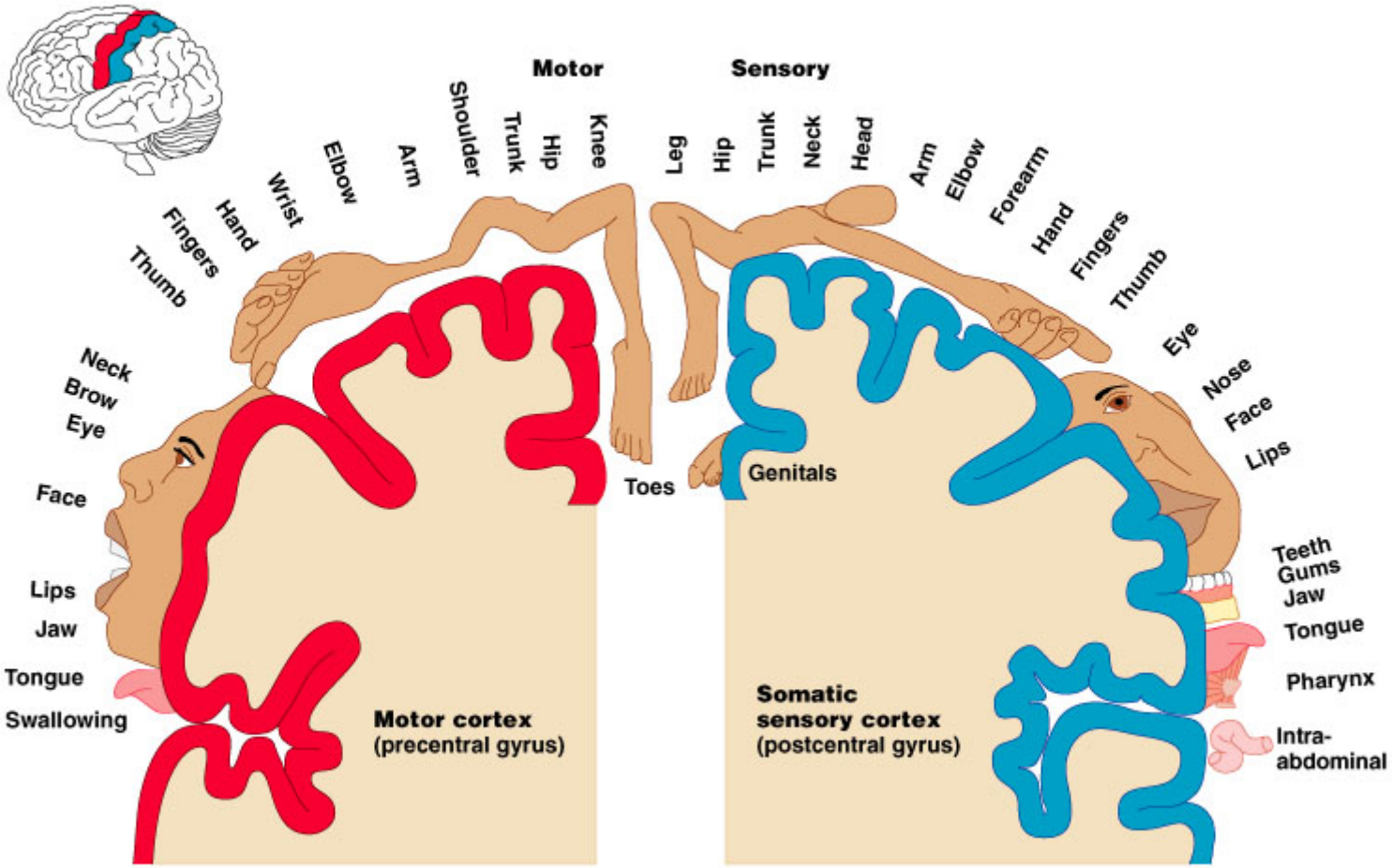


Motor areas
Anterior to central sulcus

- Primary motor area continued
  - Precentral gyrus of frontal lobe
  - Precise, conscious or voluntary movement of skeletal muscles
  - Large neurons called ***pyramidal cells***
  - Their axons: form massive ***pyramidal*** or ***corticospinal tracts***
    - Decend through brain stem and spinal cord
    - **Cross to contralateral (the other) side** in brainstem
    - Therefore: ***right side of the brain controls the left side of the body, and the left side of the brain controls the right side of the body***

Homunculus – “little man”

- Body map: human body spatially represented
  - Where on cortex; upside down

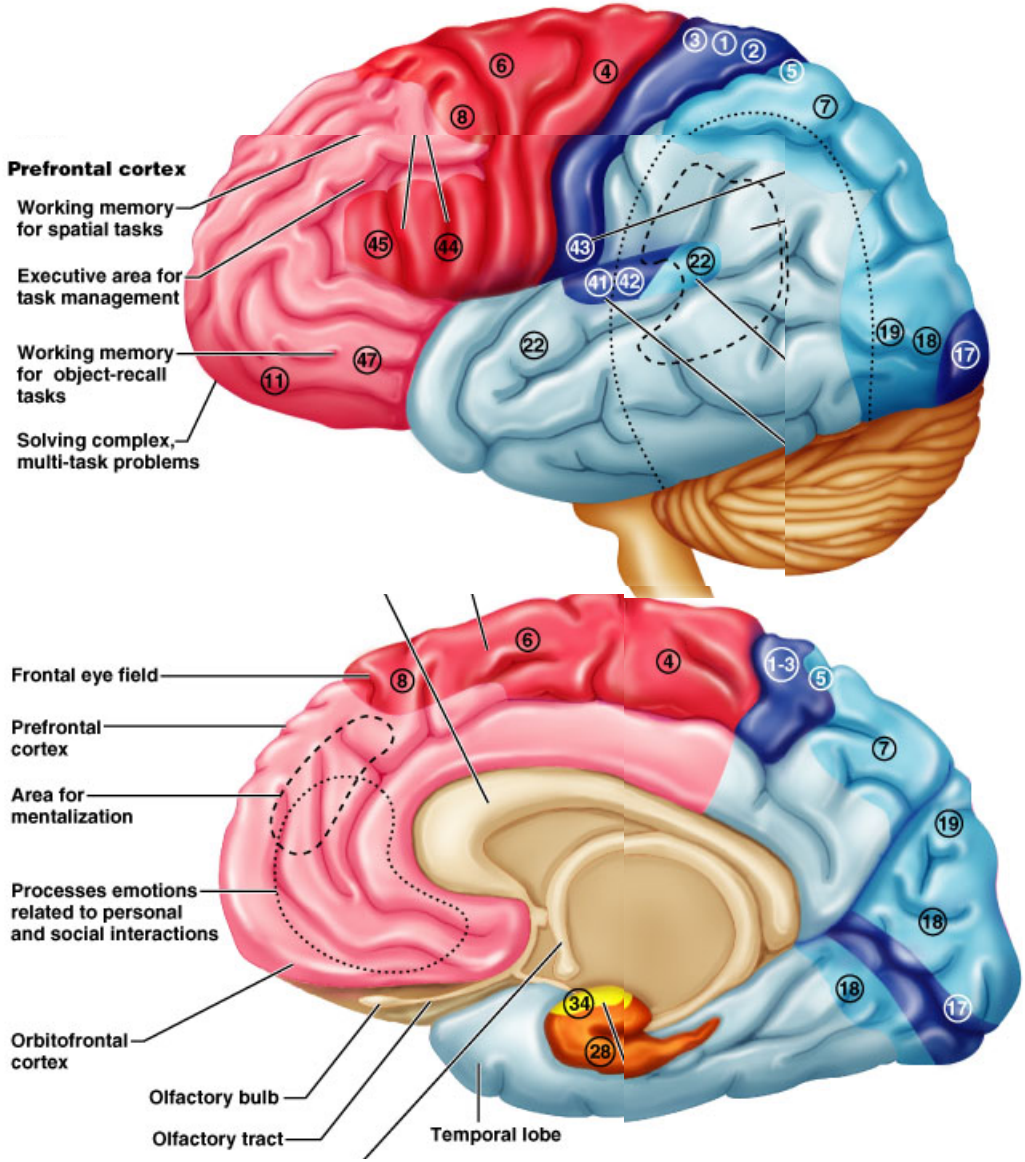


Prefrontal cortex: cognition

This area is remodeled during adolescence until the age of 25 and is very important for well-being; it coordinates the brain/body and inter-personal world as a whole

Intellect
Abstract ideas
Judgment
Personality
Impulse control
Persistence
Complex
Reasoning
Long-term planning

Social skills
Appreciating
humor
Conscience
Mood
Mental flexibility
Empathy



Executive functioning

e.g. multiple step problem solving requiring temporary storage of info (working memory)

Association Areas

Association areas: everything else

- Tie together different kinds of sensory input
- Associate new input with memories
- Is to be renamed ***"higher-order processing" areas***