ISRC-CN³ Autumn School 2023

Introductory Neuroscience

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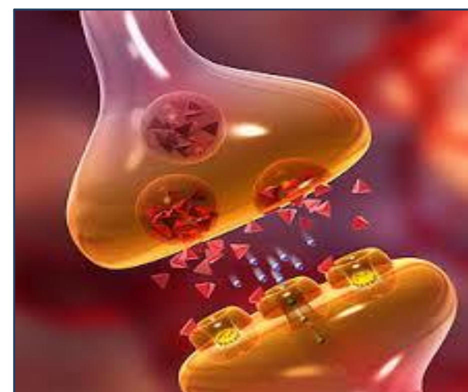
Lecture Outline

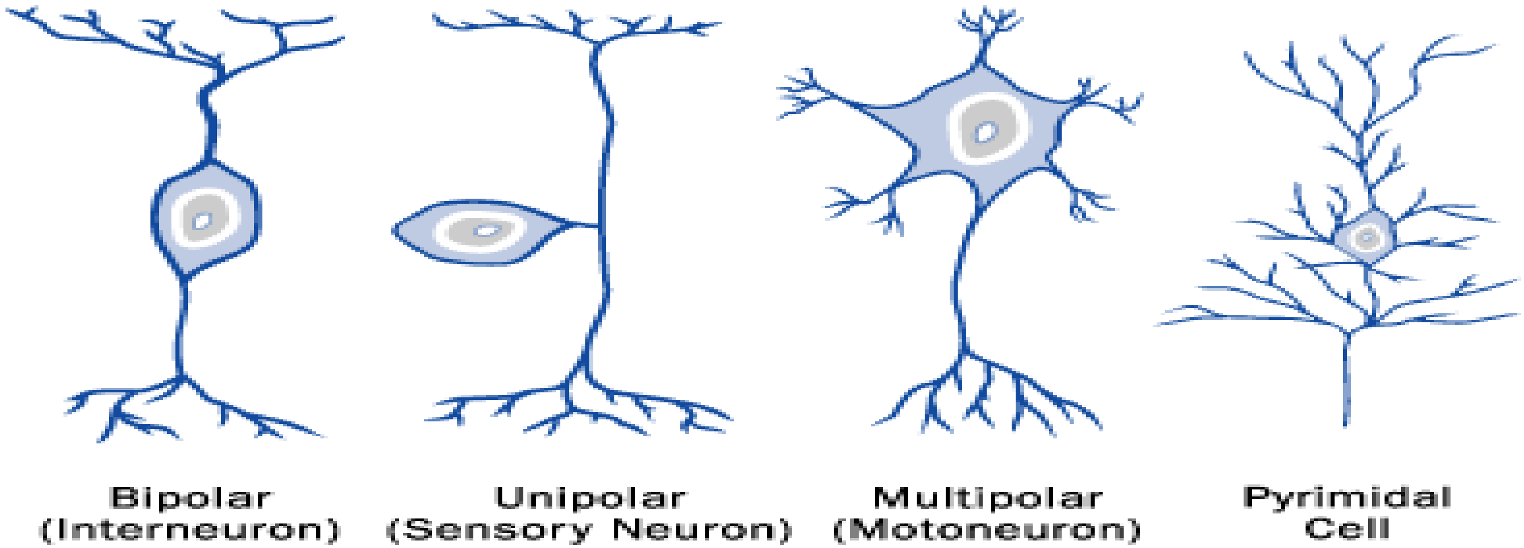
1. Structure of the nervous system
2. Functional overview of the Central Nervous System
3. Neuronal Signalling
4. Synaptic Transmission



Cells of the Nervous System

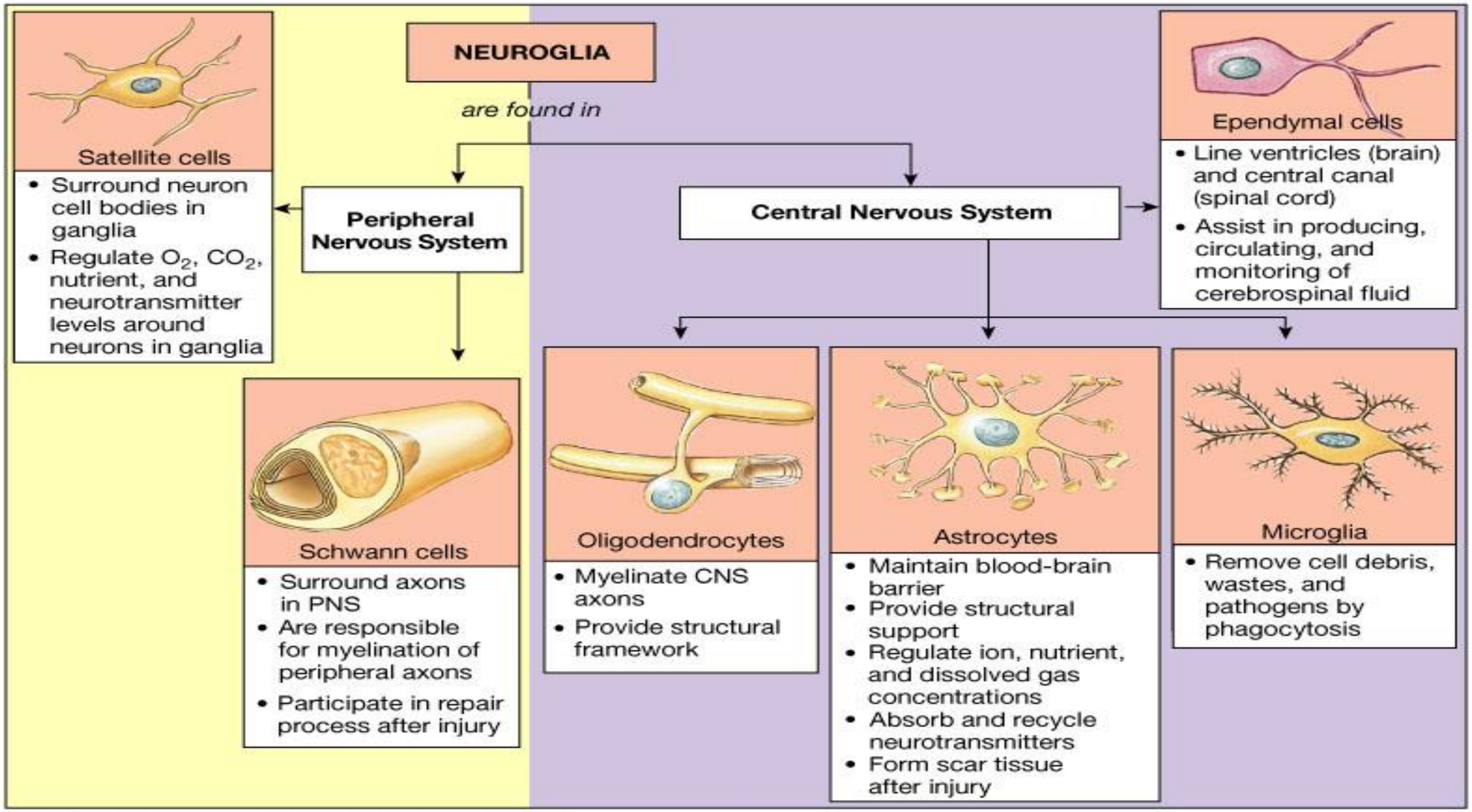
- Two primary cell types in the nervous system: Neurons and Glia

Neurons: Basic *information processing* structures of the nervous system

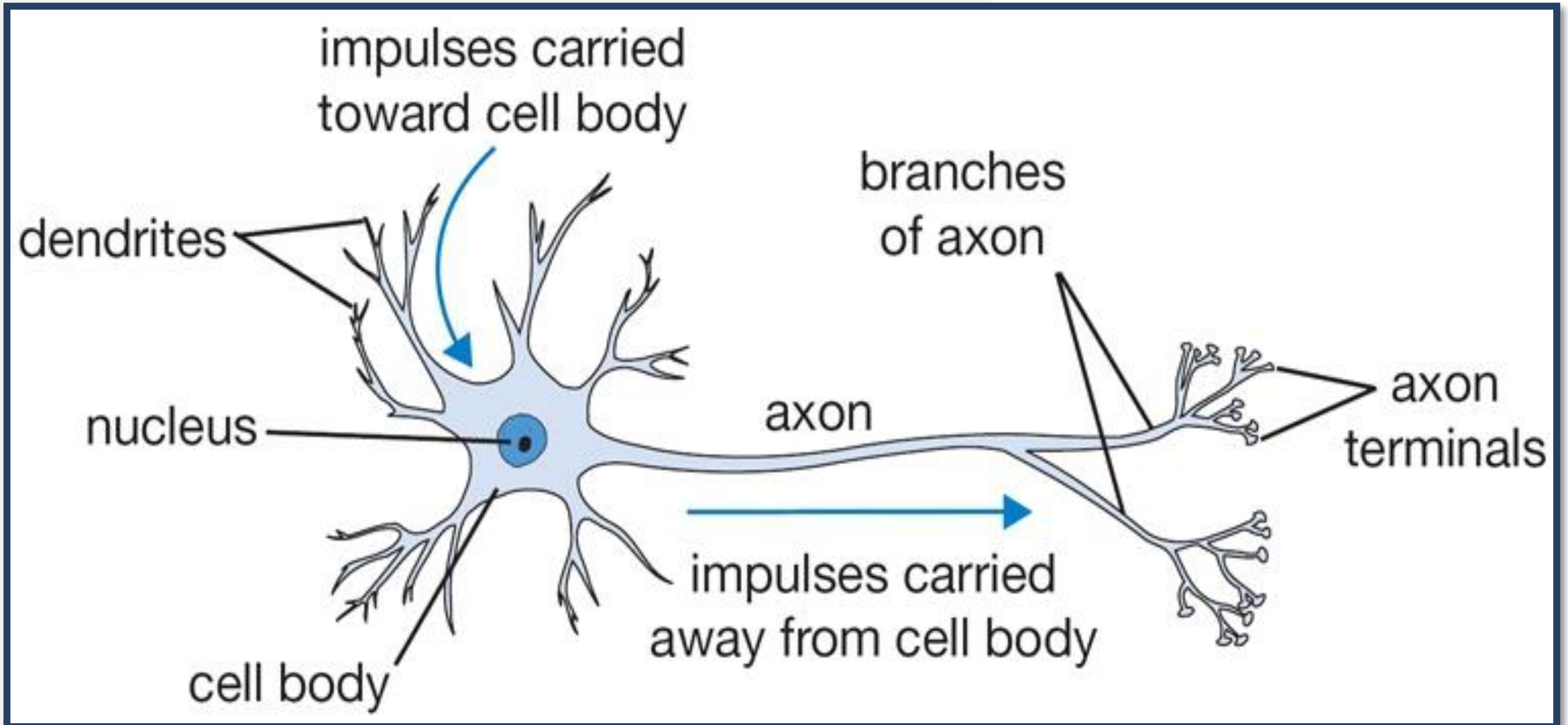


Cells of the Nervous System

Glia: Provide *support* to neurons; physical support, maintain the chemical environment and provide immunological function.



Basic Neuron Structure



Basic Neuron Structure

- **Soma** (cell body) – contains the nucleus and other organelles that maintain cell metabolic function.
- **Dendrites** – treelike projections from the soma that receive information from other cells.
- **Axon** is the elongated fiber that extends from the cell body to the terminal endings and transmits the neural signal.

Structure of the Nervous System

Central Nervous System

Brain and spinal cord

Peripheral Nervous System

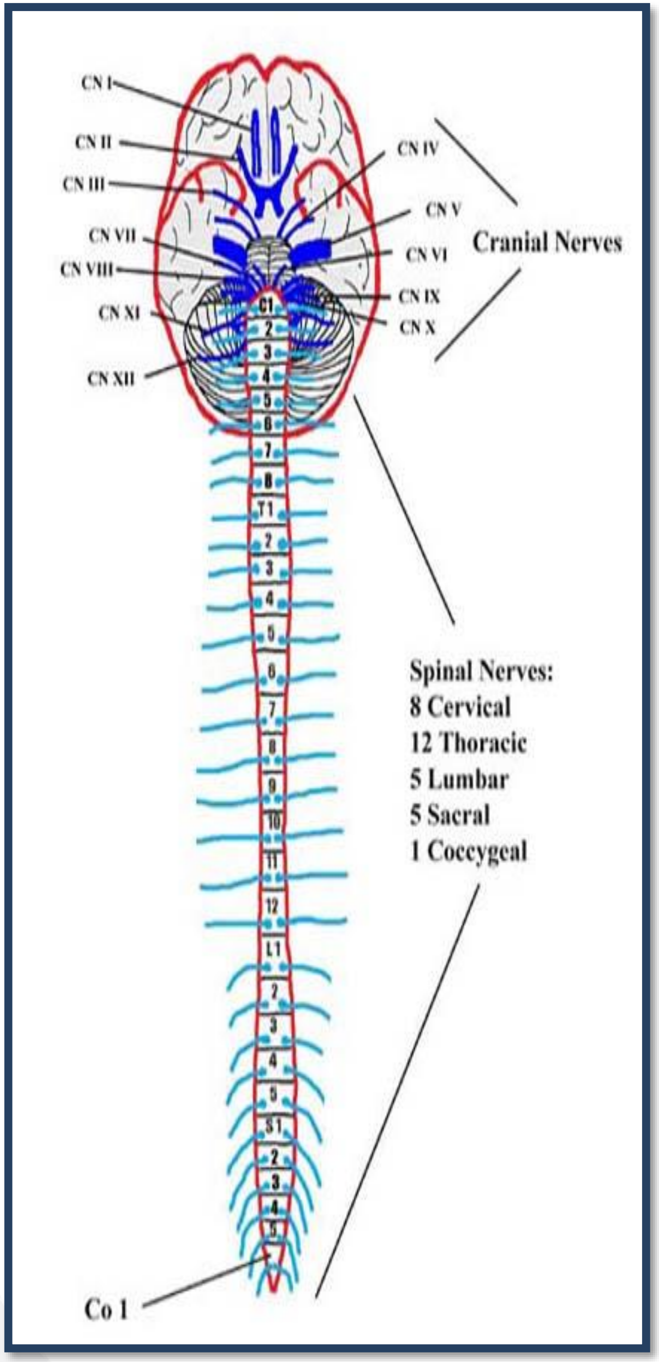
All nerves outside the brain and spinal cord

PNS further sub-divided into:

1. ***Somatic system*** ***– controls voluntary muscles with both spinal and cranial nerves***
2. ***Autonomic nervous system*** ***– consists of autonomic nerves and some cranial nerves and controls the function of organs and gland***

Somatic Nervous System

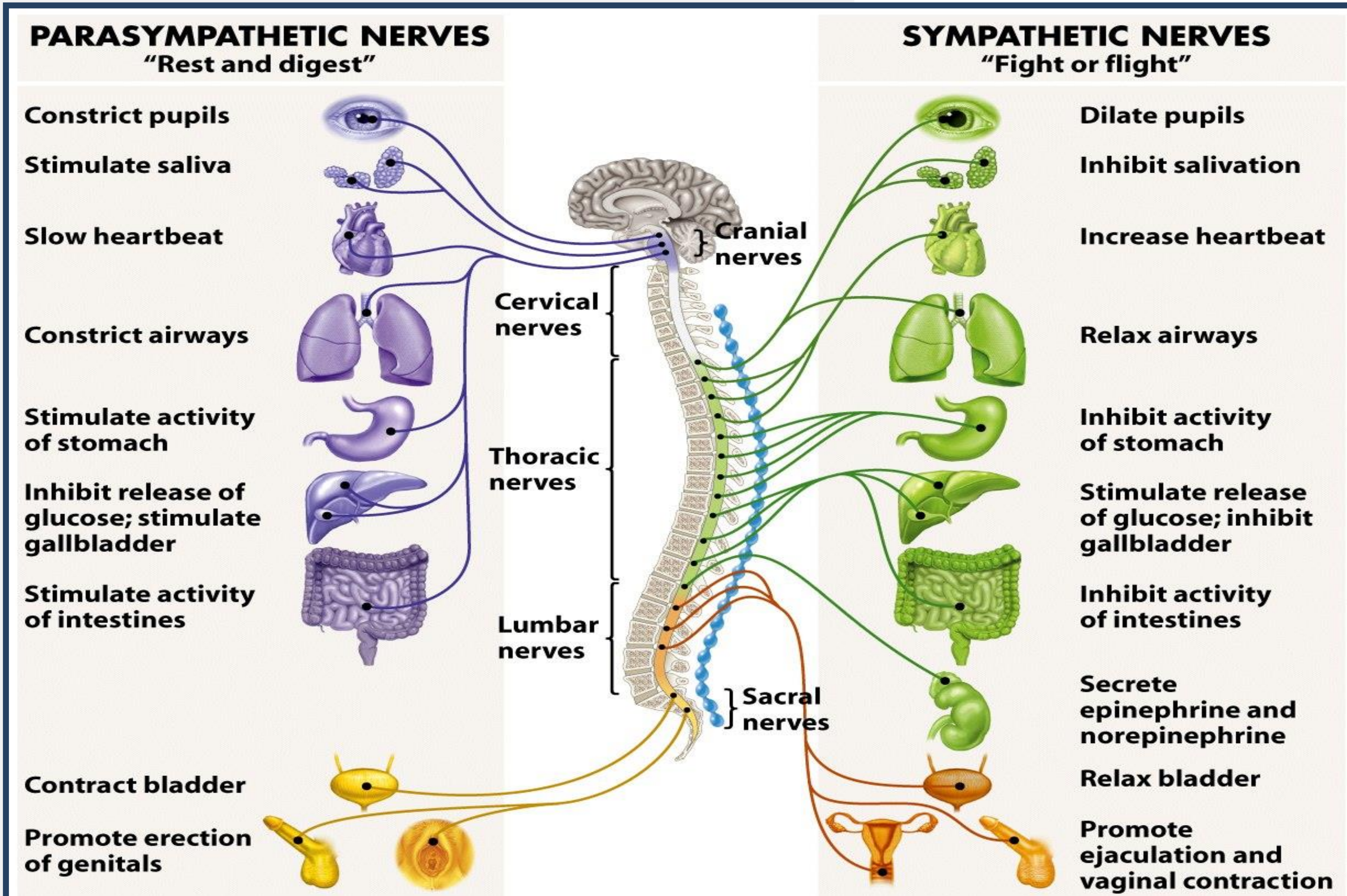
- **Spinal nerves (mixed nerves) - consist of many neurons some of which carry sensory information and some carry motor information**
- **Sensory afferents – neurons that carry sensory information from the surface of the body and from muscles into the spinal cord; cell bodies in dorsal root ganglia**
- **Motor efferents – neurons responsible for voluntary movements; begin in the spinal cord and end in ventral horn of spinal cord and end on skeletal muscles**
- **Cranial nerves – provide functions similar to spinal nerves but primarily serve the head and neck. Not all mixed nerves; several have only motor ot sensory function**



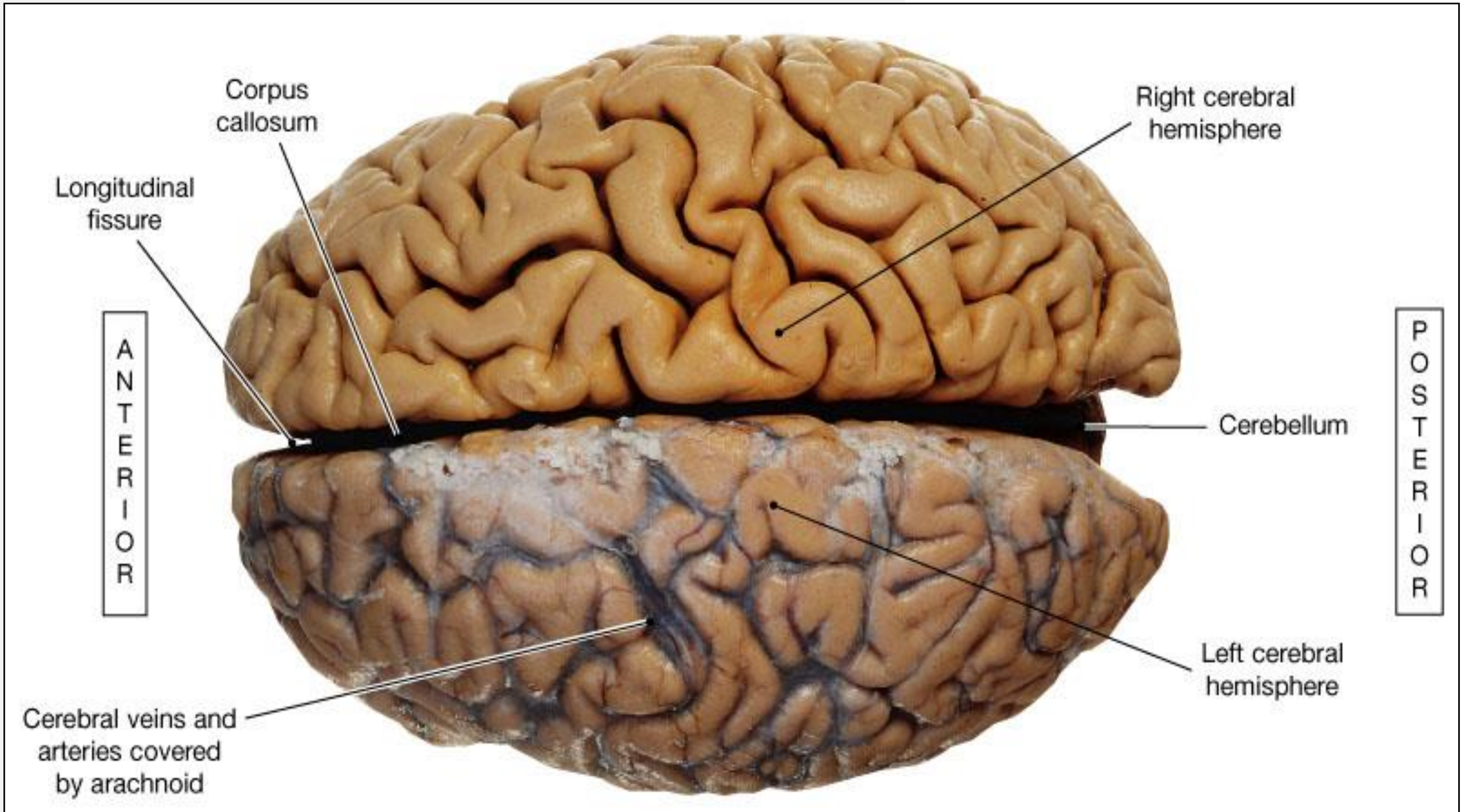
Autonomic Nervous System

- **Autonomic nervous system regulate the internal environment smooth muscles and glands such as:**
  - **Intestine**
  - **Urinary bladder**
  - **Cardiac muscle**
  - **Adrenal and salivary glands**
- **The purpose of the ANS is to control important bodily functions**
- **Divided into sympathetic and parasympathetic divisions whose functions generally work in opposition to one another**
- ***Sympathetic nervous system*** **('fight or flight') – predominates when energy expenditure is necessary e.g. during times of stress, excitement or exertion**
- ***Parasympathetic nervous system ('rest and digest')*** **– predominates when energy can be conserved and stored for later use**

Autonomic Nervous System

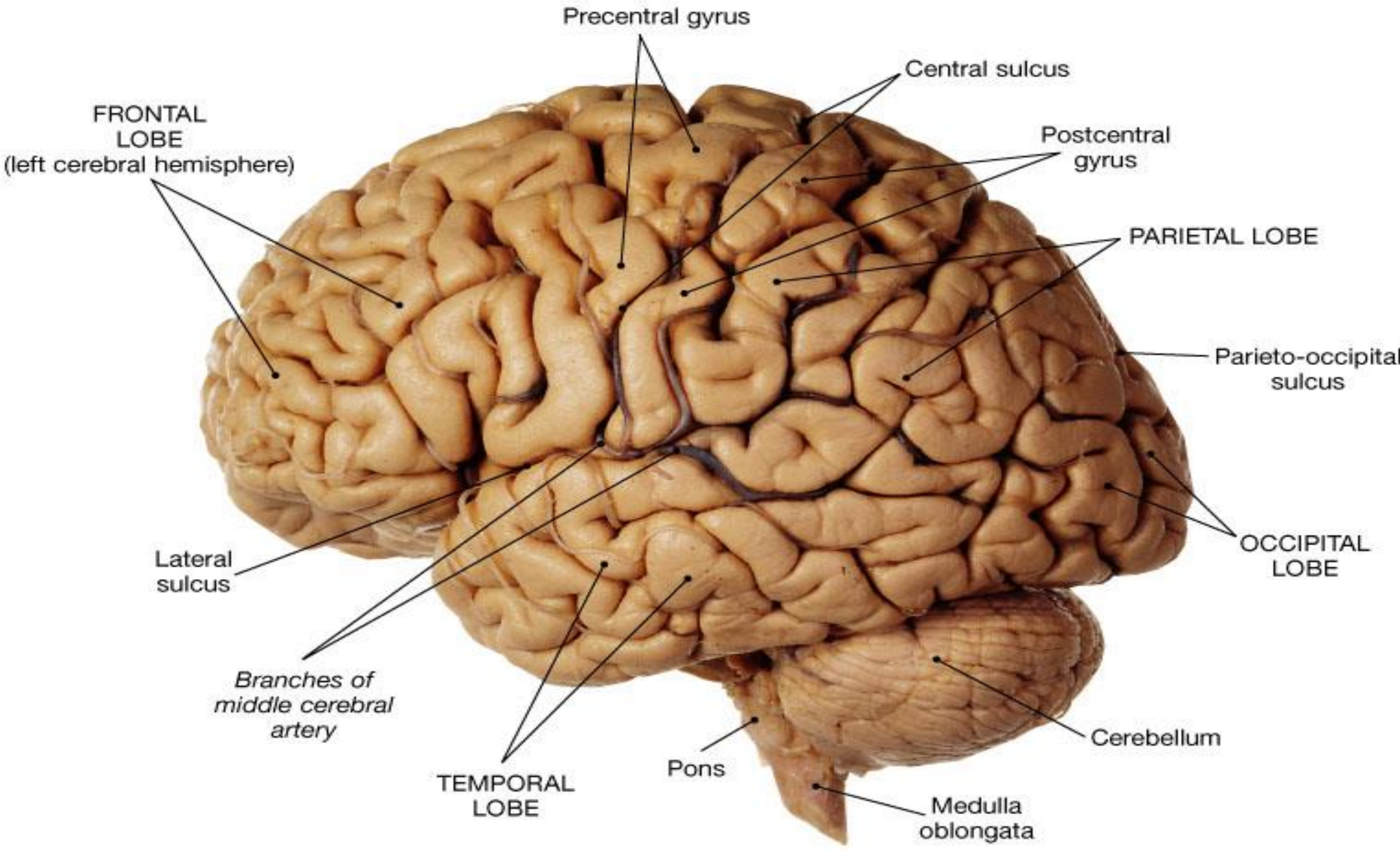


External surface of the brain



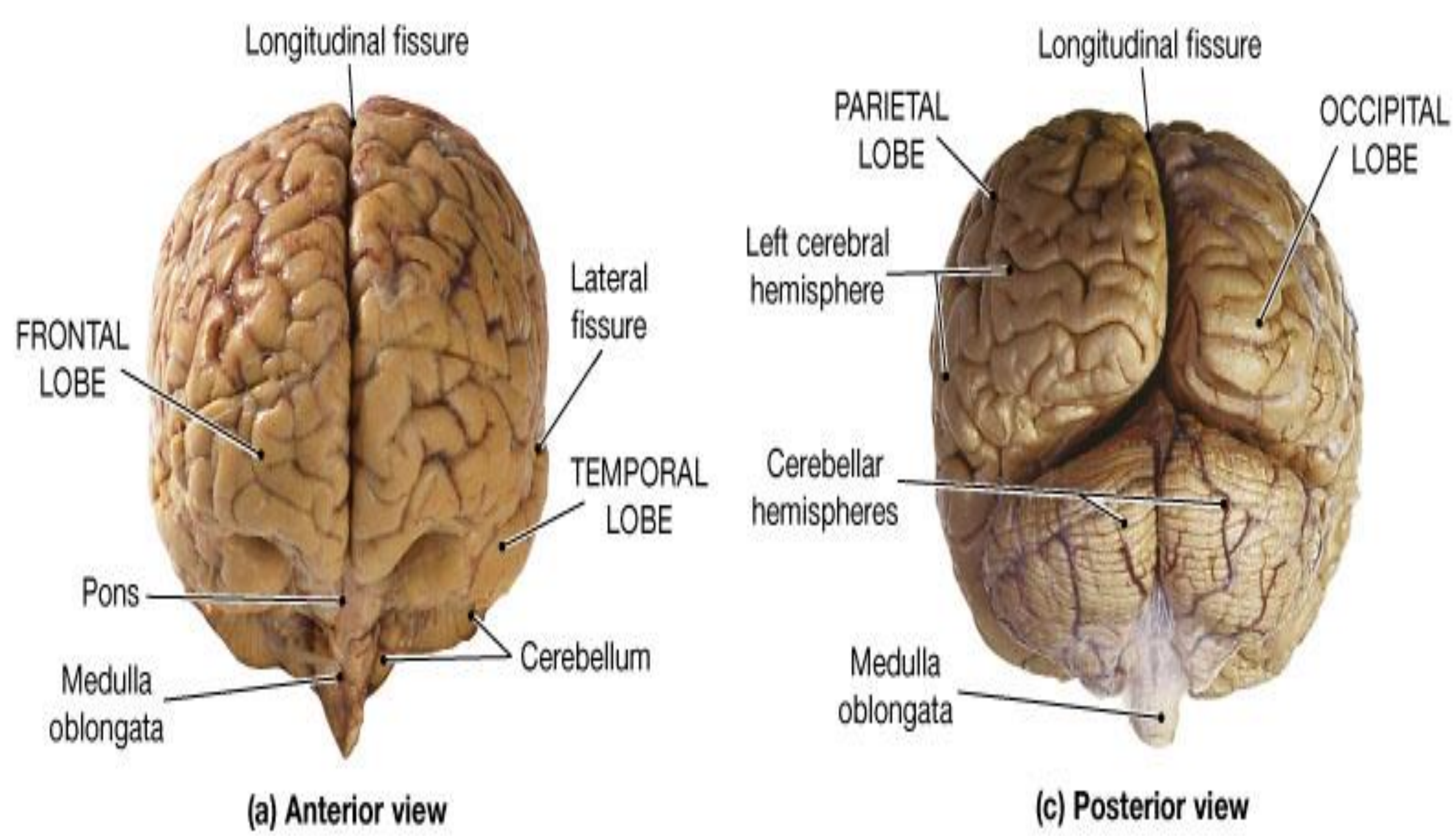
(b) Superior view

External surface of the brain

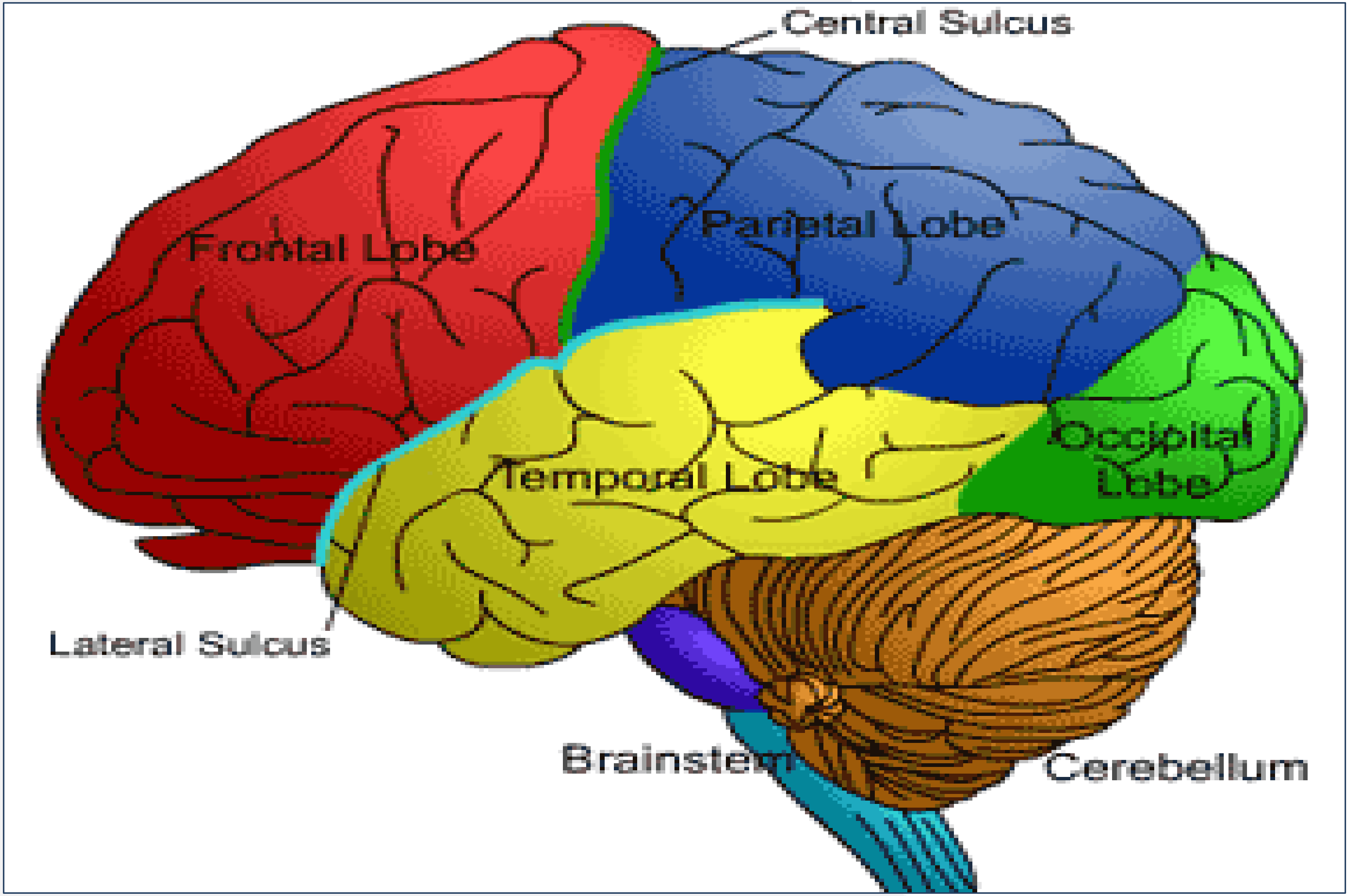


(d) Lateral view

External surface of the brain



External surface of the brain



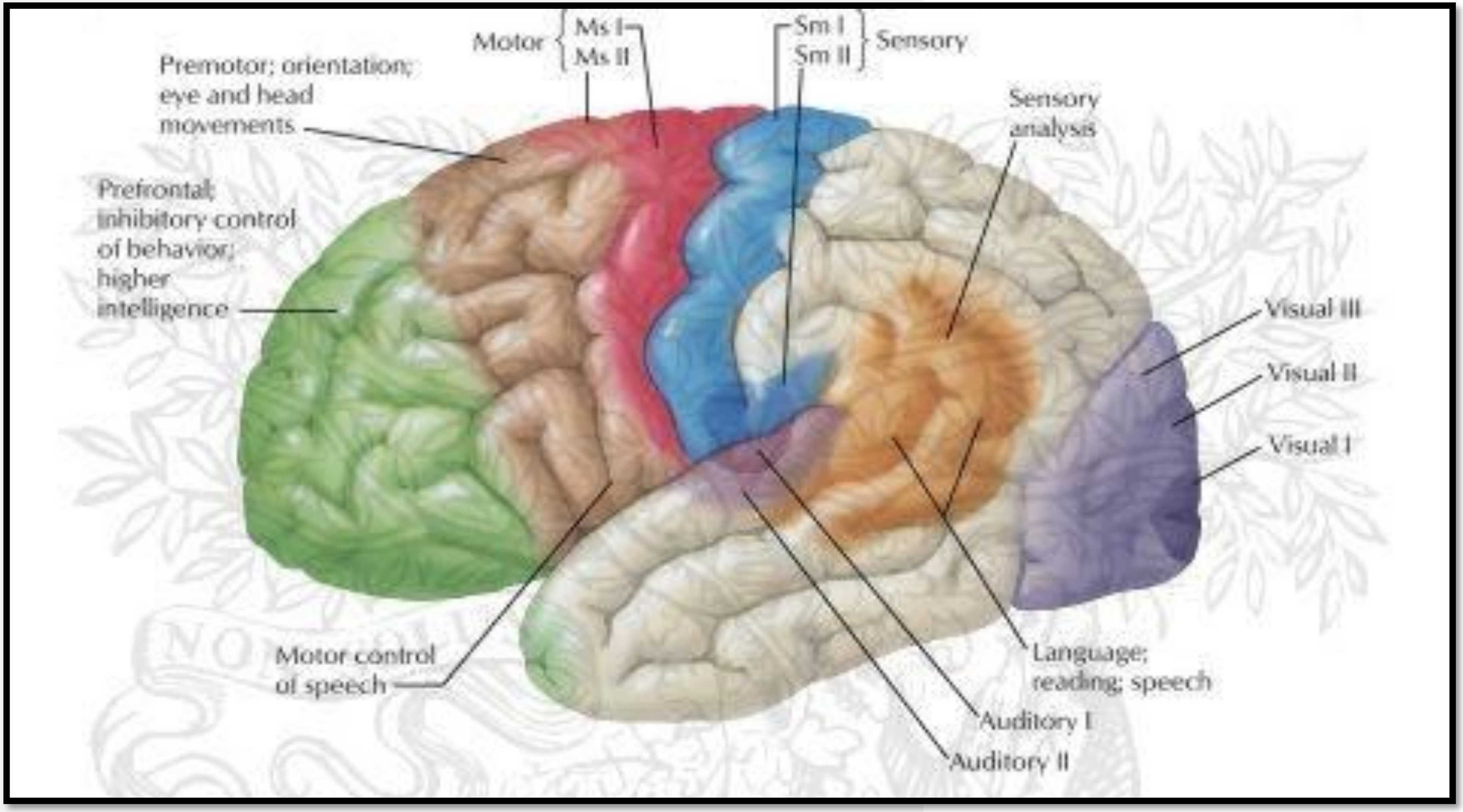
Cerebral Cortex

Cerebral cortex – two *hemispheres* connected by the *corpus callosum*

Divided into four lobes based on function:

1. ***Frontal lobe*** **- associated with reasoning, planning, parts of speech, movement, emotions, and problem solving**
2. ***Parietal lobe*** **- associated with movement, orientation, recognition, perception of stimuli**
3. ***Occipital lobe*** **- associated with visual processing**
4. ***Temporal lobe*** **- associated with perception and recognition of auditory stimuli, memory, and speech**

Cerebral Cortex



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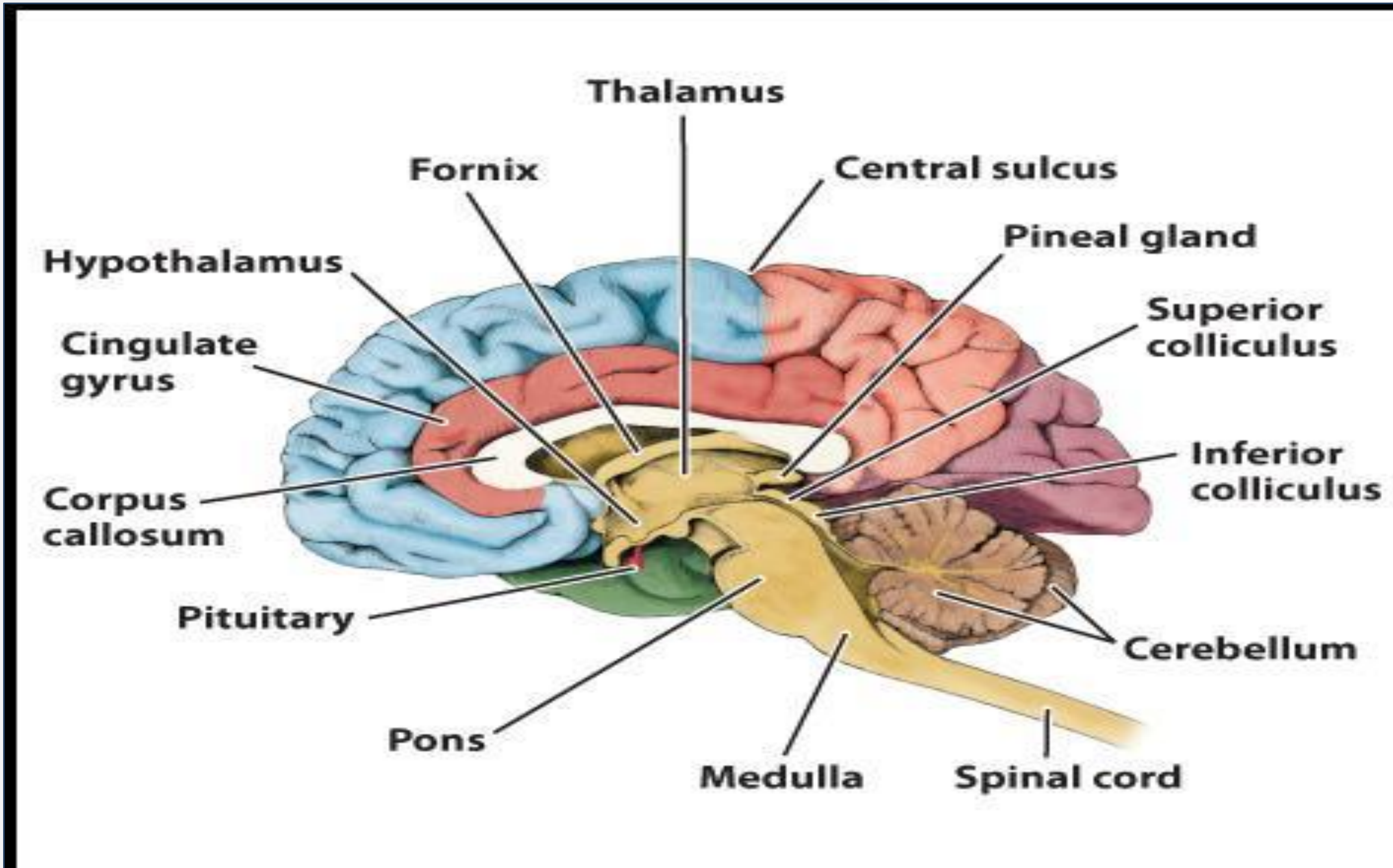
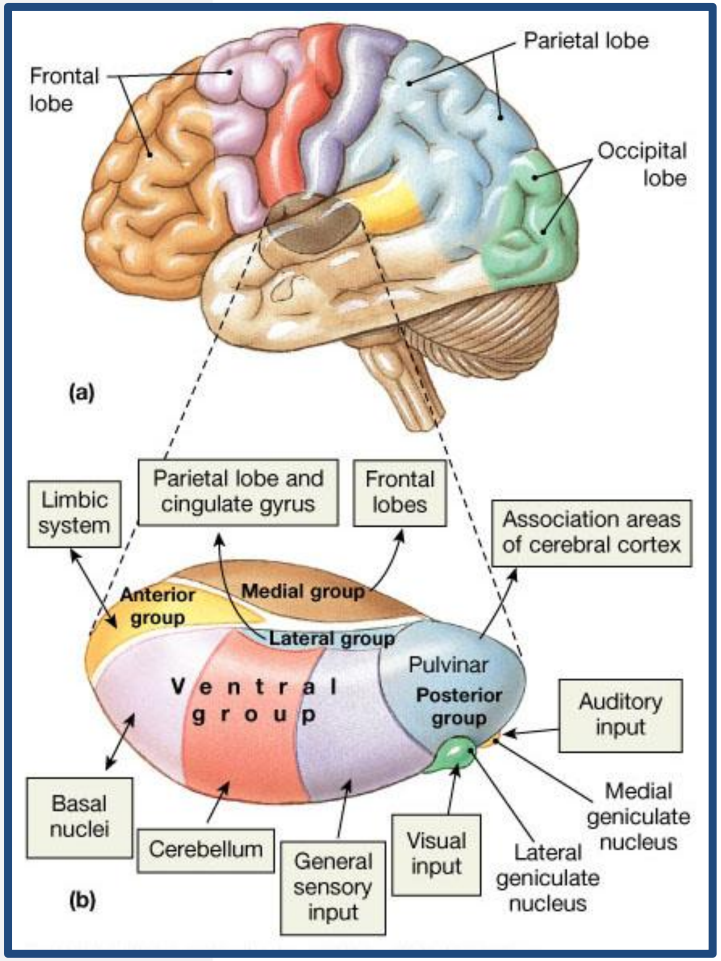
Mid-sagittal View



Thalamus

- Final relay point for ascending sensory information
- Coordinates the activities of the cerebral cortex and basal nuclei
- Domain-specific information processing



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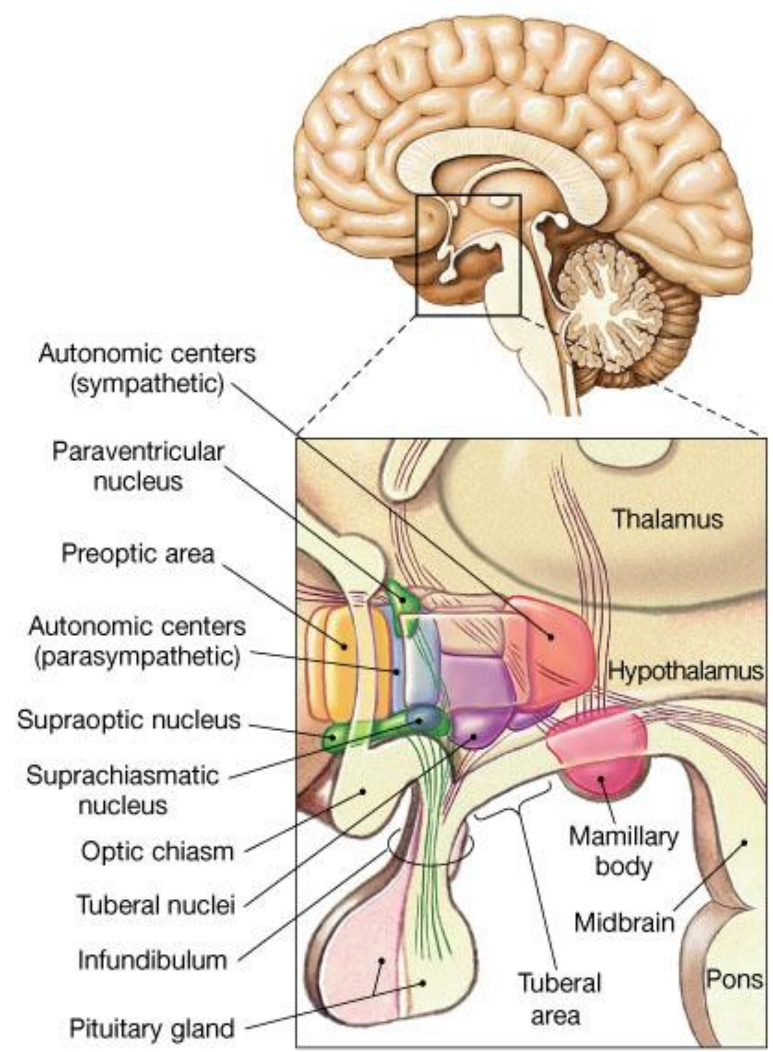
Hypothalamus

- Controls somatic motor activities at the subconscious level
- Controls autonomic function
- Coordinates activities of the endocrine & nervous systems
- Secretes hormones
- Produces emotions and behavioral drives
- Regulates body temperature
- Coordinates circadian cycles of activity
- Feeding, fighting, fleeing, and reproductive behavior

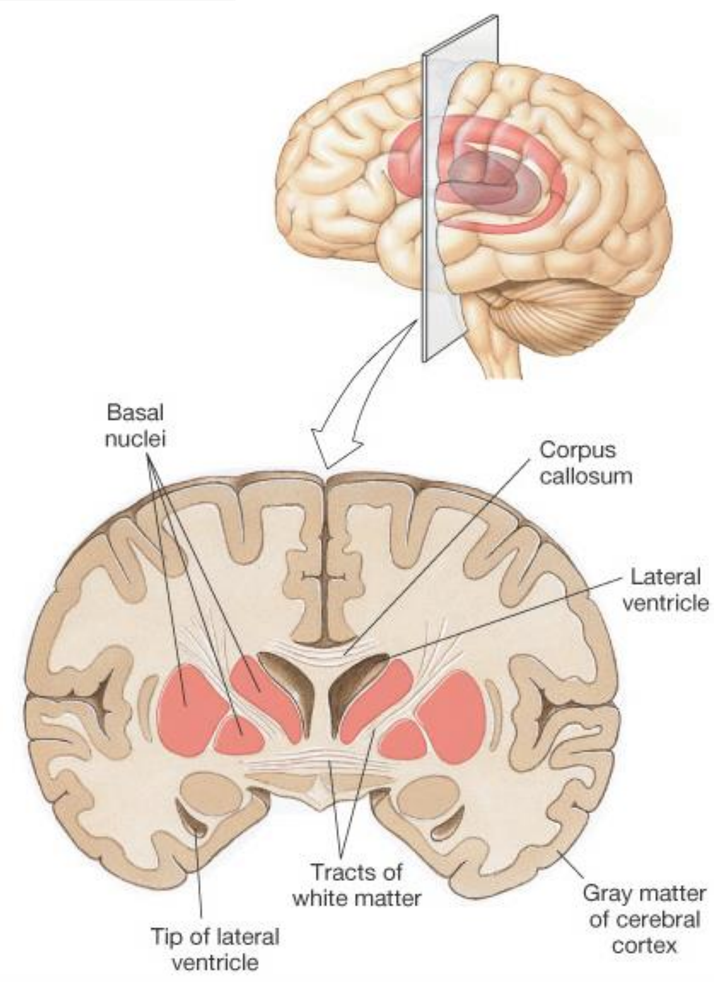


(a)

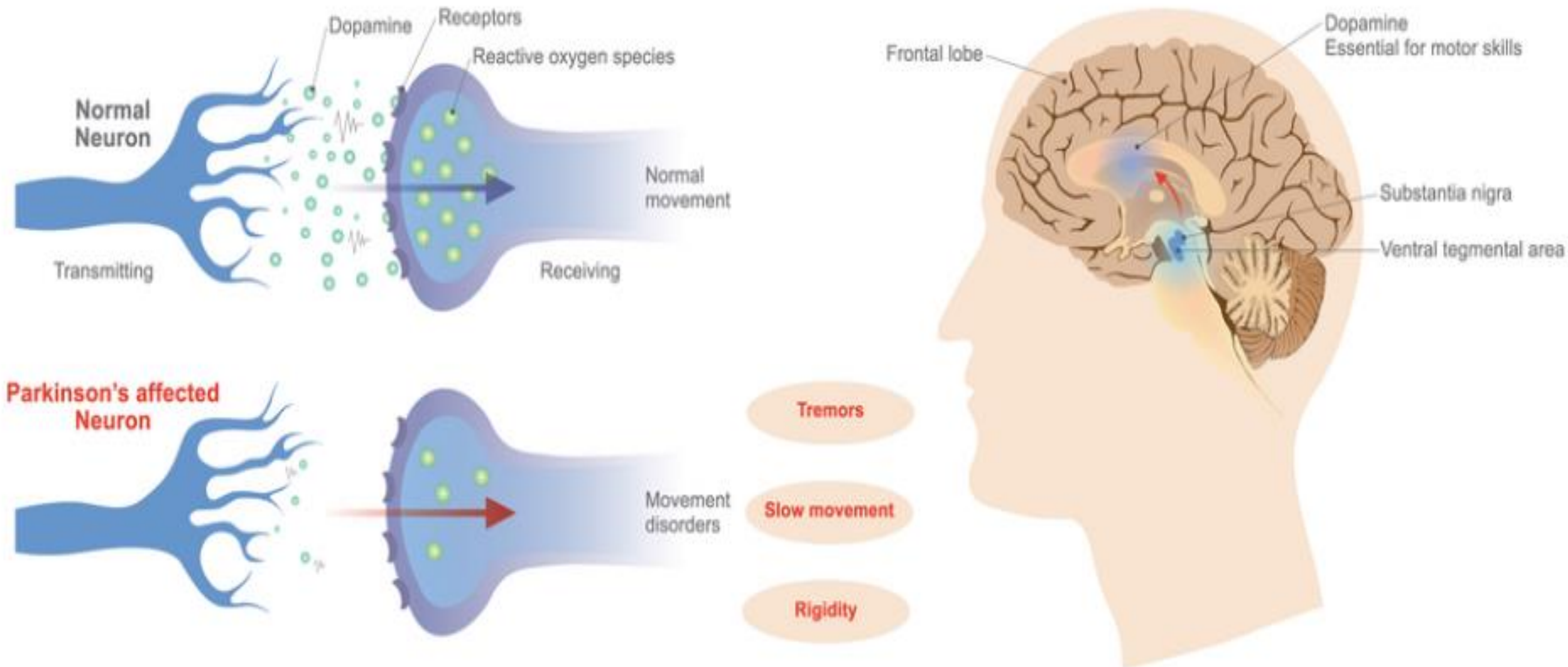
Basal Ganglia

Primary functions

- Regulate muscle tone throughout the body
- Initiate and maintain voluntary movements while suppressing involuntary movements
- Maintenance of posture and balance

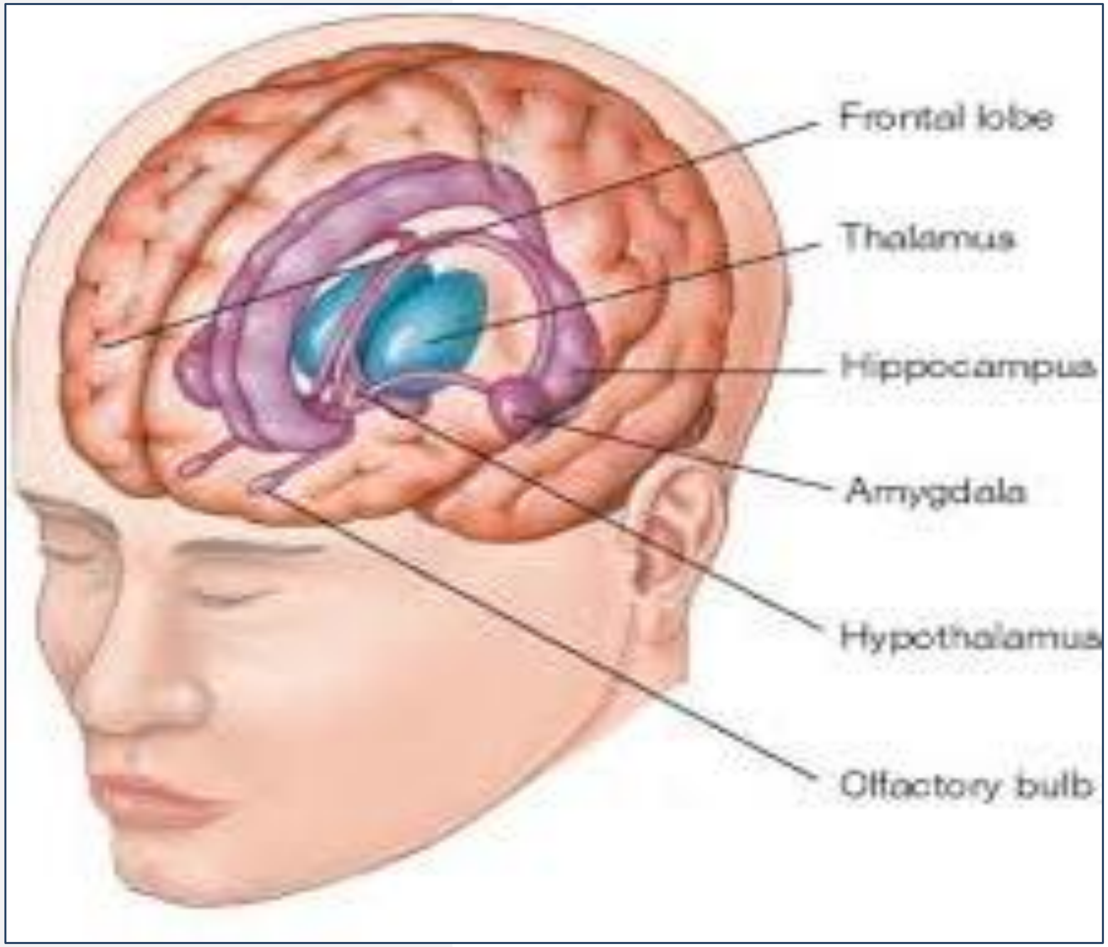


Parkinson's disease



The Limbic System

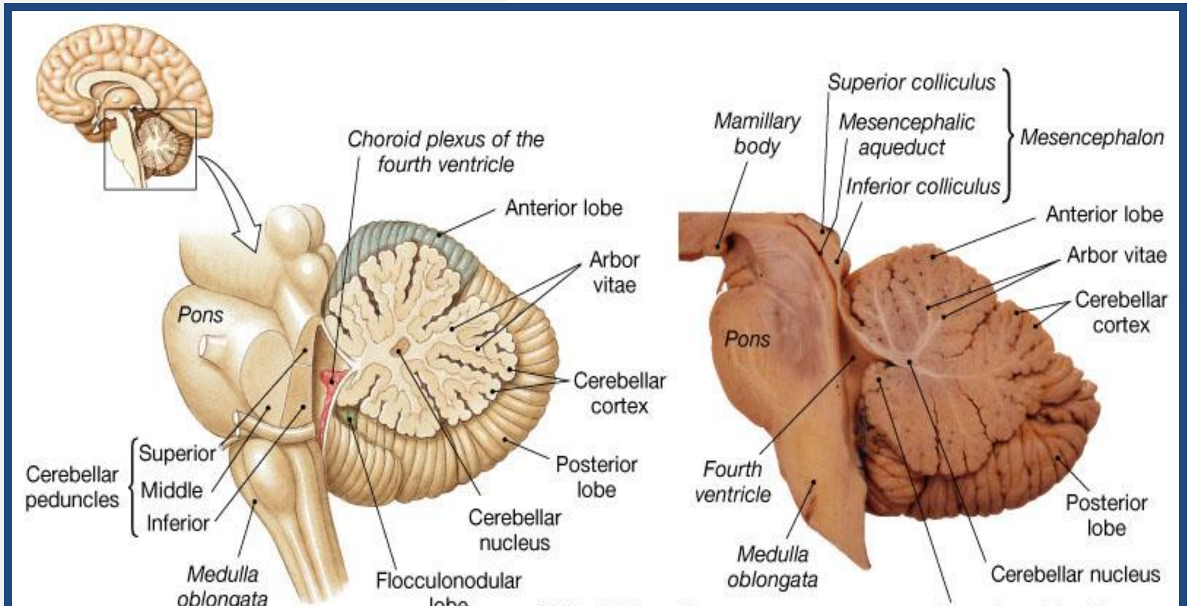
- The limbic system is responsible for controlling various functions in the body.
- Some of these functions include interpreting emotional responses, storing memories, and regulating hormones.
- The limbic system is also involved with sensory perception, motor function, and olfaction.



Cerebellum

It controls:

- Posture
- Balance
- Voluntary movements



(b) Sagittal section

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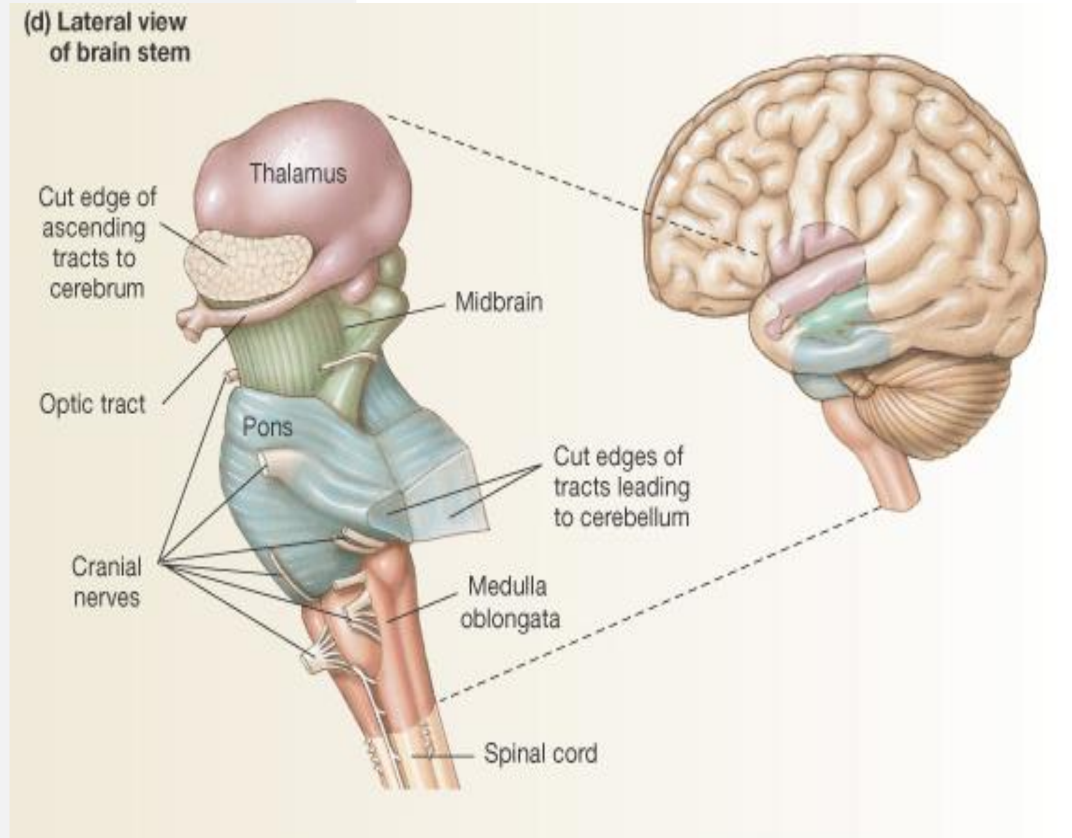
Brain Stem: Midbrain, Pons & Medulla

- An important link between spinal cord and higher brain levels, relays motor and sensory impulses between other “higher” parts of the brain and spinal cord
- Midbrain – eye movement control
- Pons/Medulla - Signal relay & Involuntary functions

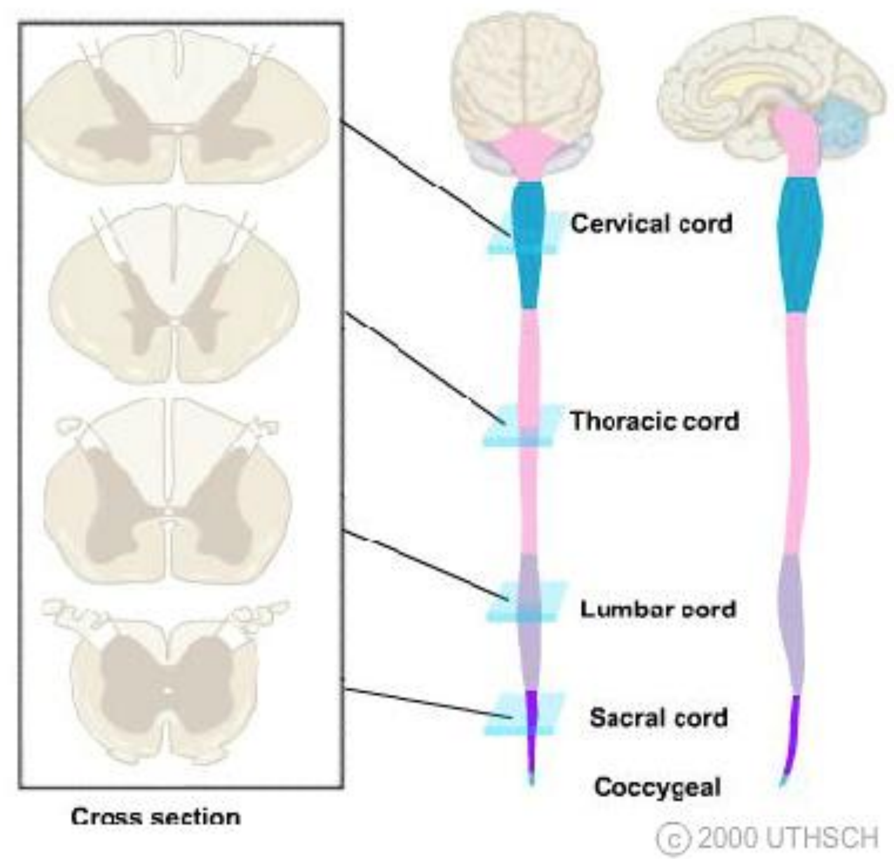


Spinal Cord

The spinal cord is a cylindrical structure of nervous tissue composed of white and gray matter, is uniformly organized and is divided into four regions:

- cervical (C),
- thoracic (T),
- lumbar (L) and
- sacral (S),

each of which is comprised of several segments



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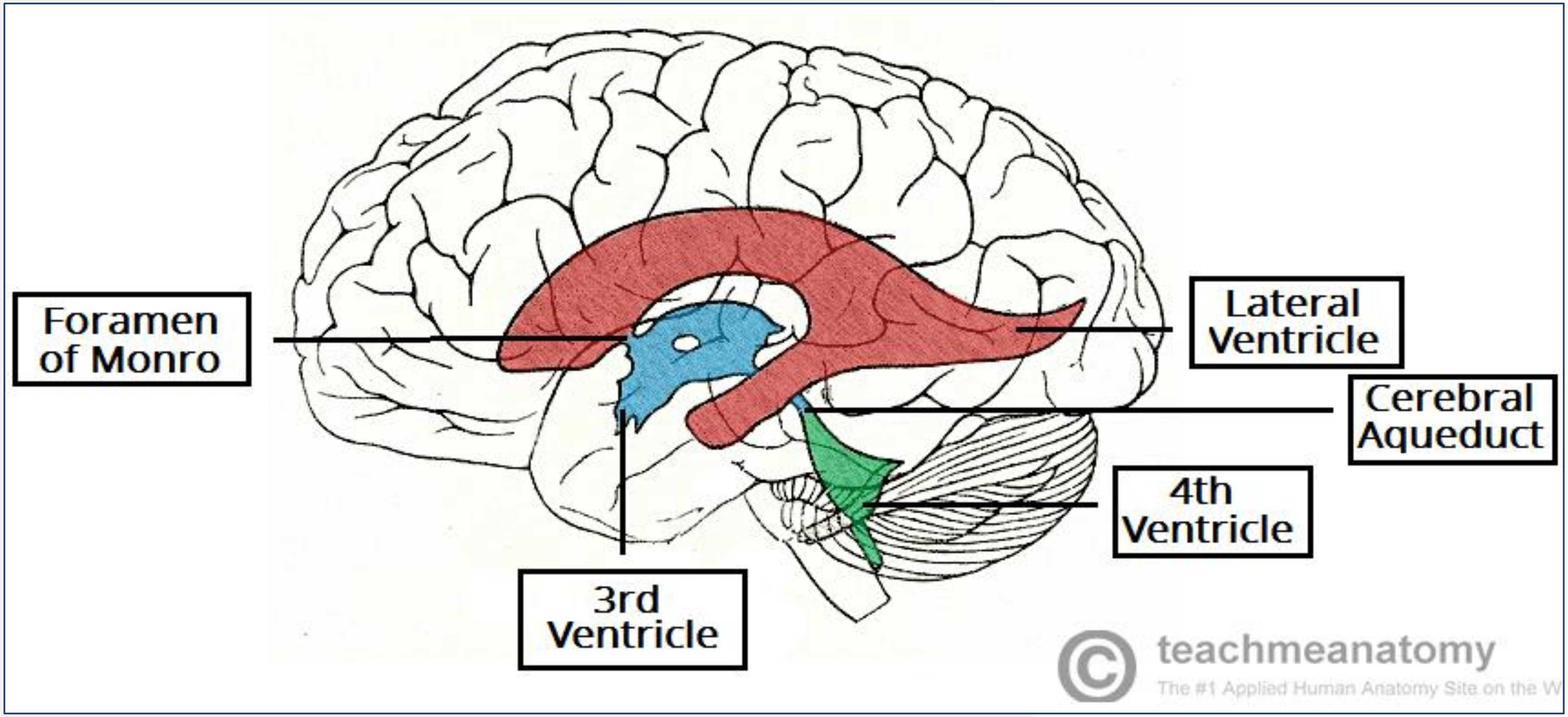
Cerebrospinal Fluid (CSF)

CSF surrounds the brain and spinal cord and has three main functions:

1. **Protection - acts as a cushion for the brain, limiting neural damage in cranial injuries**
2. **Buoyancy - By being immersed in CSF, the net weight of the brain is reduced to approximately 25 grams. This prevents excessive pressure on the base of the brain.**
3. **Chemical Stability - The CSF creates an environment to allow for proper functioning of the brain. E.g. Maintaining low extracellular K+ for synaptic transmission.**

Ventricular System

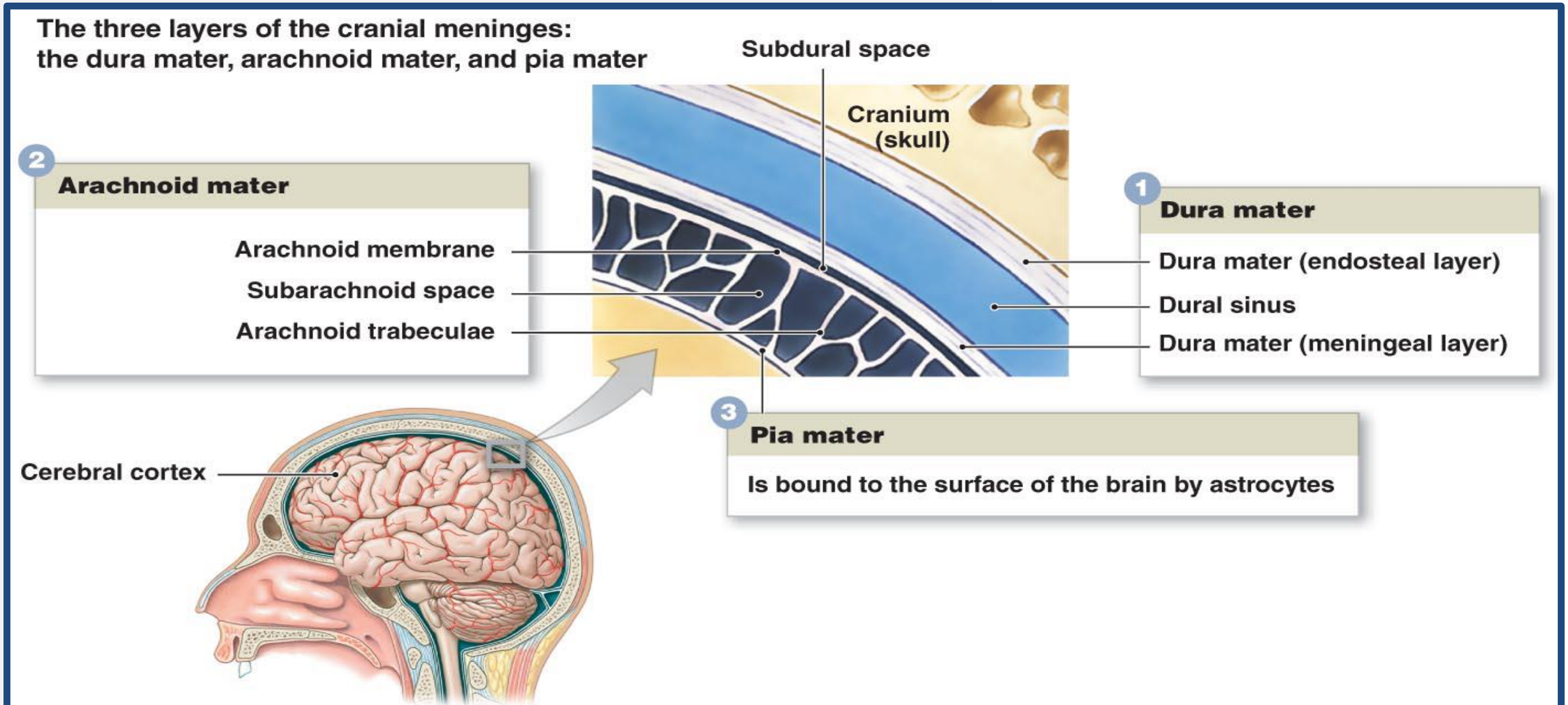
- Ventricles are structures that produce and circulate CSF around the brain
- Lined by ependymal cells that form a structure called the choroid plexus which is where CSF is produced



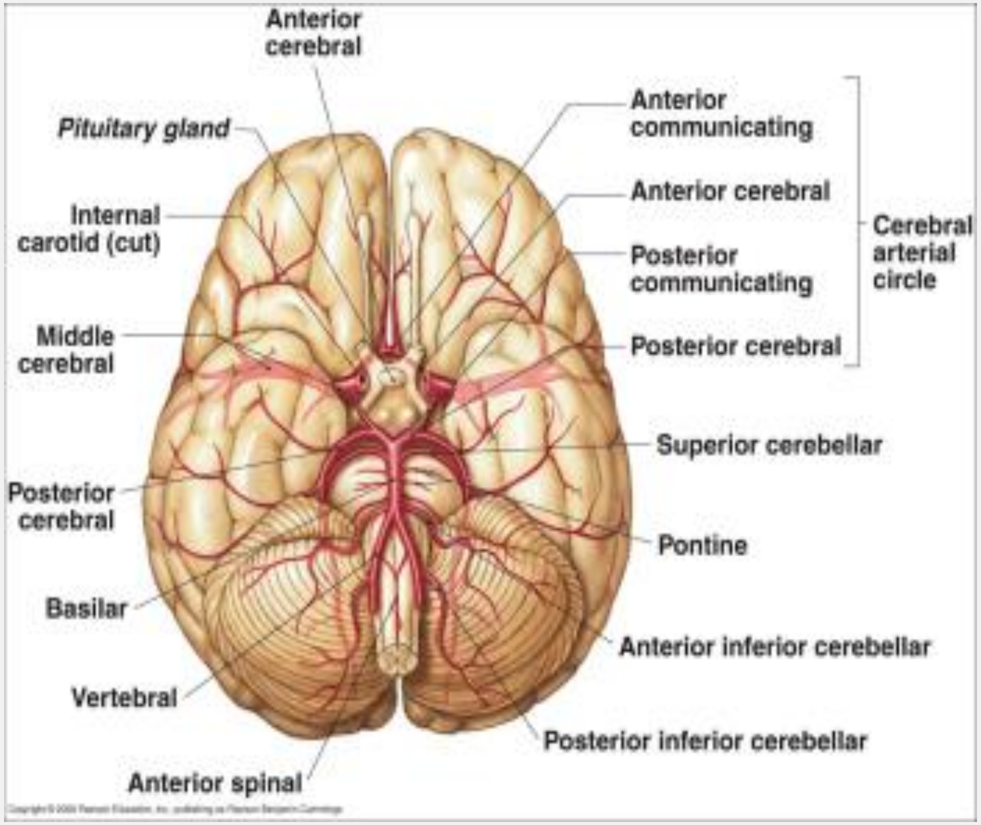
Meninges

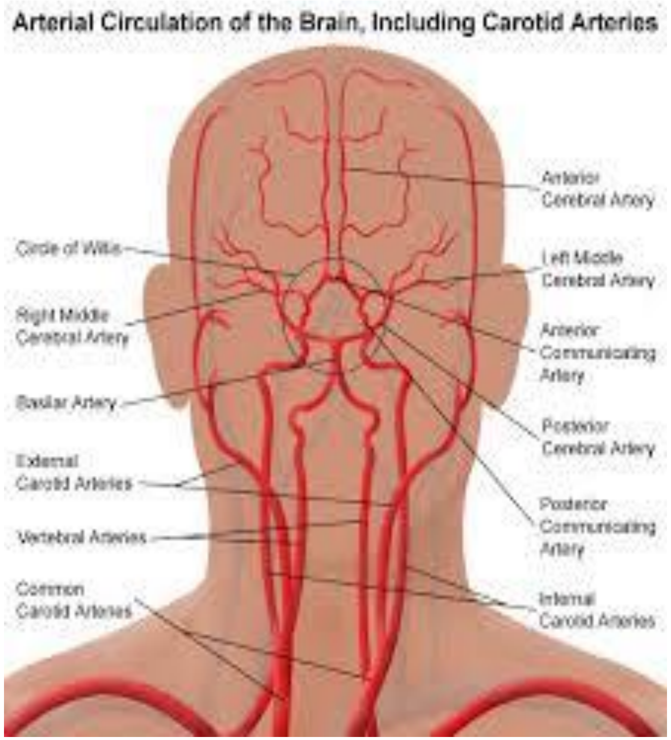
The main functions of the meninges are:

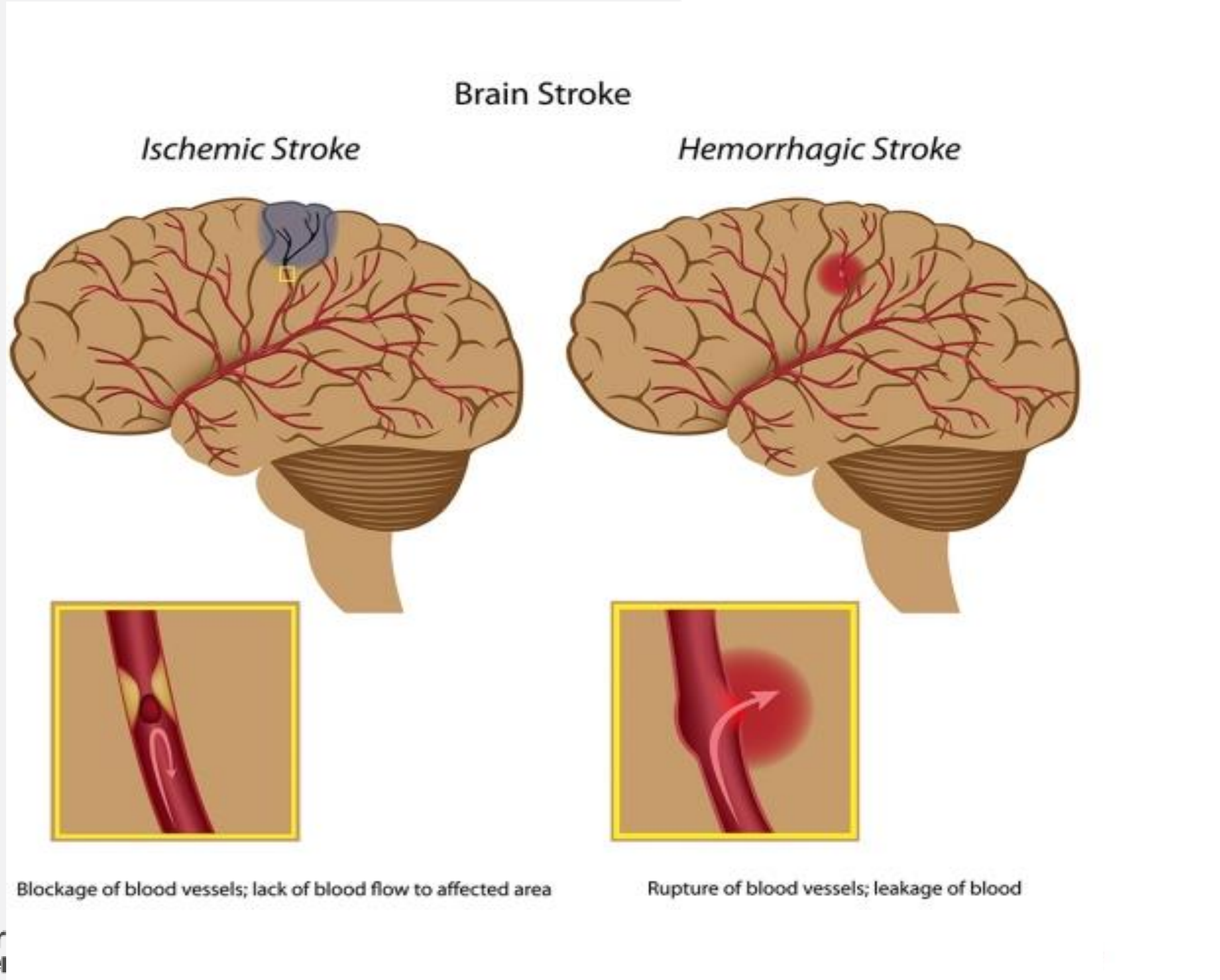
1. **Protecting the brain and spinal cord from *mechanical injury***
2. **Providing *blood supply* to the skull and to the hemispheres**
3. **Providing a space for the *flow of cerebrospinal fluid*.**



Blood Supply to the Brain





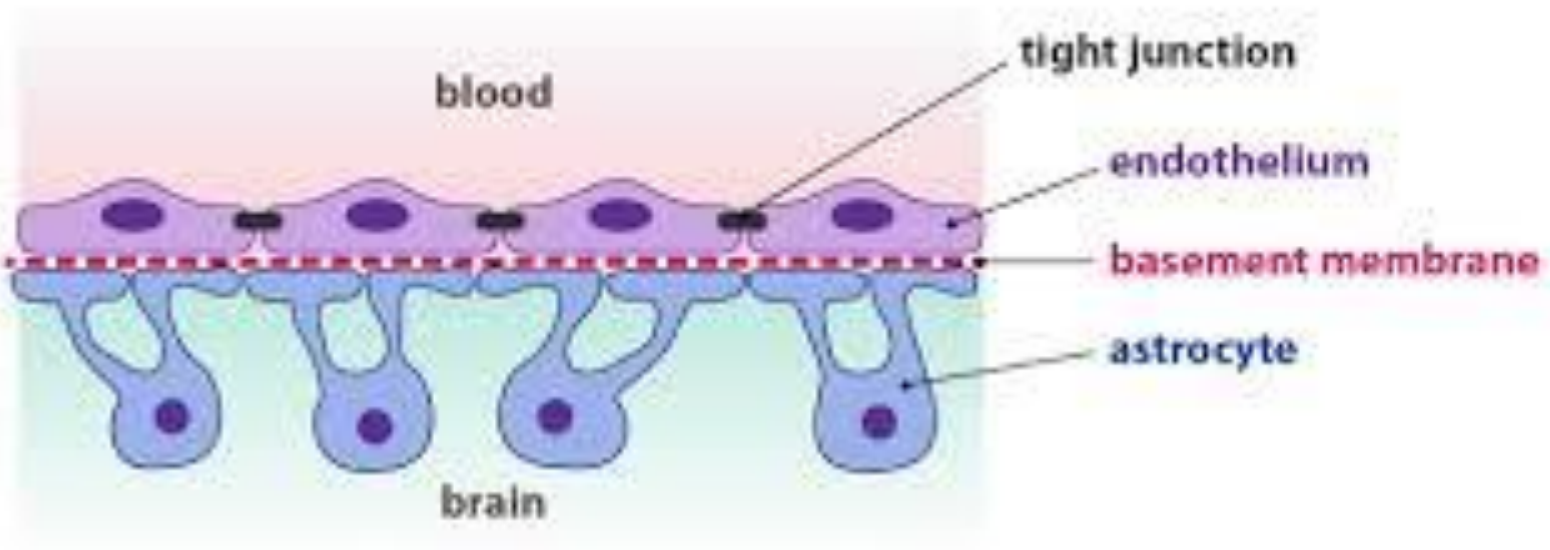

Brain Stroke
Ischemic Stroke
Hemorrhagic Stroke
Blockage of blood vessels; lack of blood flow to affected area
Rupture of blood vessels; leakage of blood

Blood-brain Barrier

- **A semipermeable membrane separating the blood from the cerebrospinal fluid,**
- **Allows the passage of water and some small molecules like amino acids**
- **Prevents larger lipophilic molecules and potential neurotoxins from entering the brain**
- **A small number of regions in the brain, including the circumventricular organs (CVOs), do not have a blood–brain barrier.**
- **Distinct morphology of capillaries, adjoining edges of endothelial cells are fused forming tight junctions.**
- **Protects the brain but also makes drug delivery to the brain difficult.**

tion

Blood-brain Barrier



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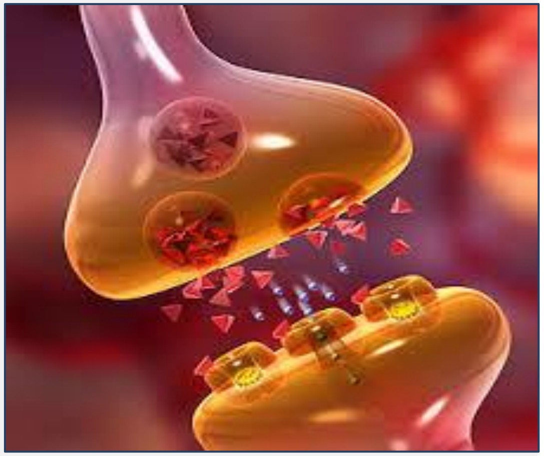
Overview of Signaling in the nervous system.



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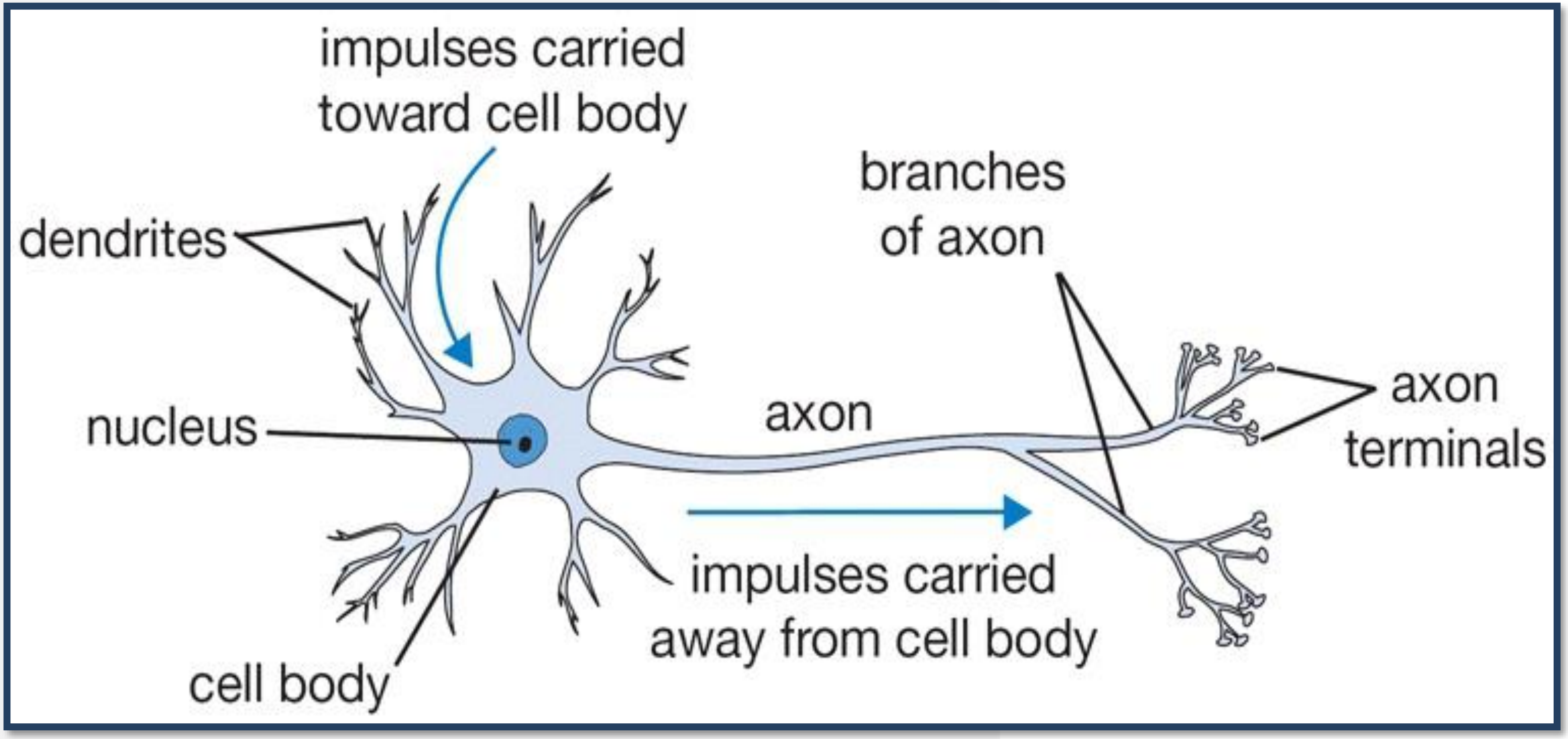
Basic Neuron Structure



https://www.youtube.com/watch?v=6qS83wD29PY

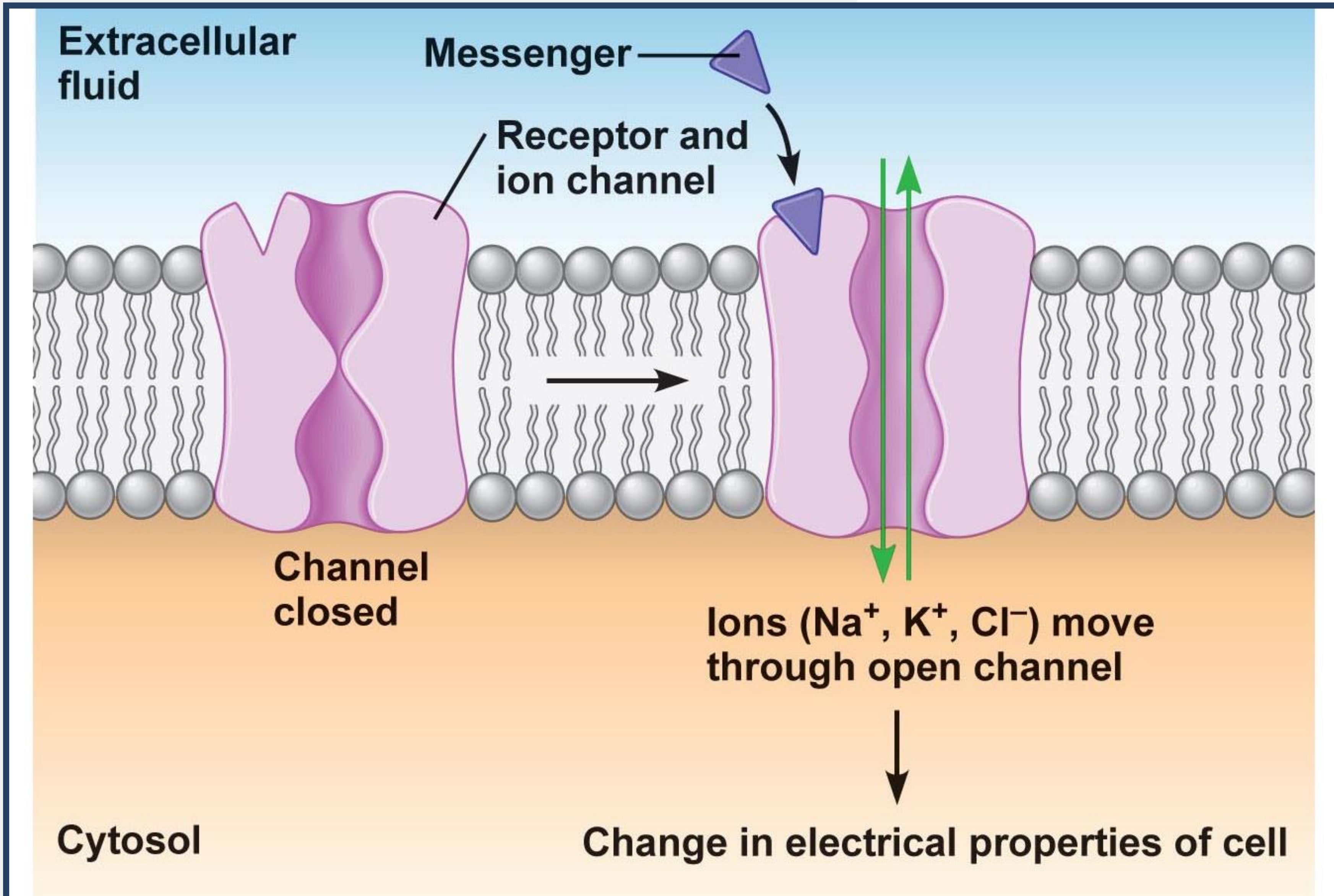
Ion Channels

- Present on cell membrane of neurons
- Present on membrane to allow transport of charged particles such as potassium (K^+), sodium (Na^+), chloride (Cl^-), and calcium (Ca^{2+}) through the membrane
- Protein molecules that penetrate through the membrane and have water-filled pore through which ions pass
- Relatively specific for a particular ion, although some do allow more than one type of ion to pass through

Ion Channels

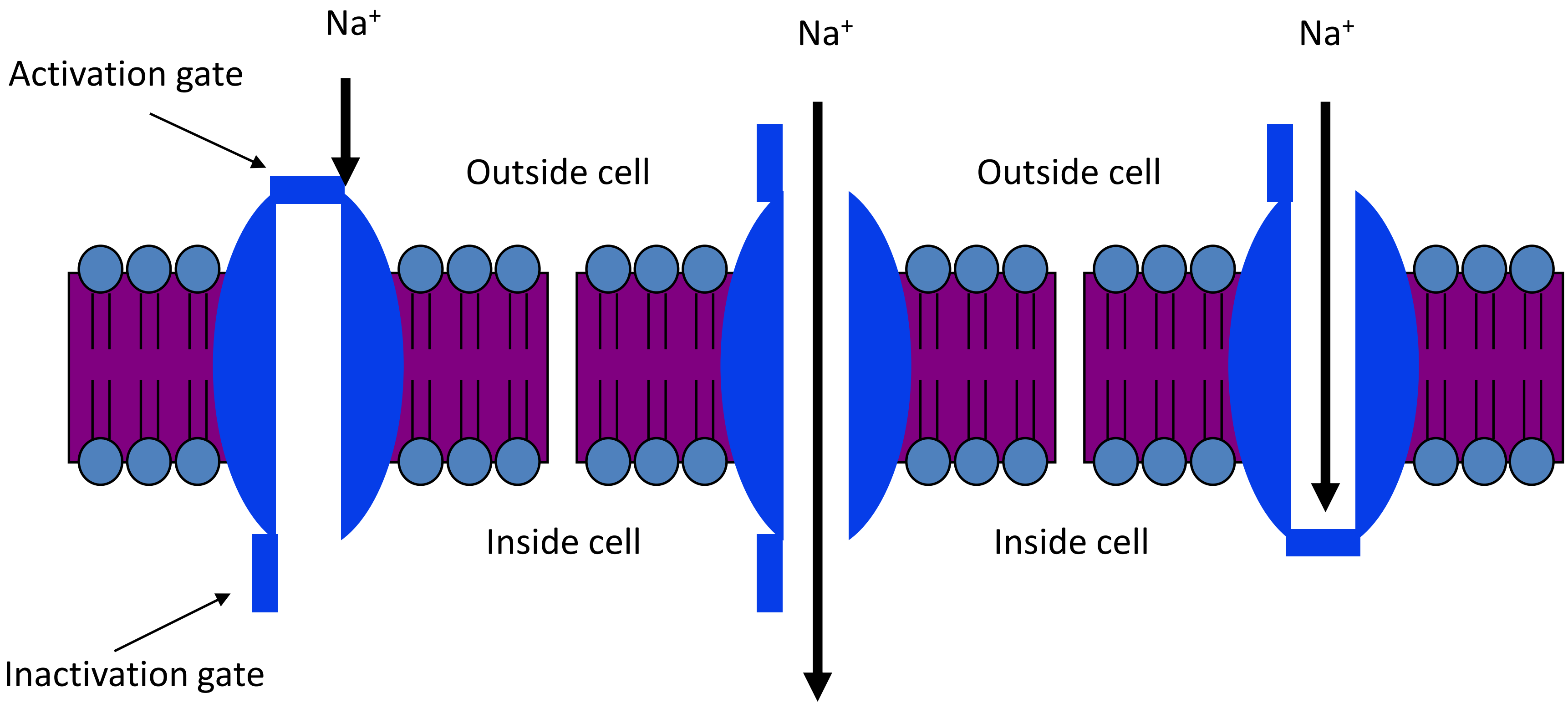
- **Gated channels** - **normally in a closed configuration but open momentarily in response to specific stimuli to allow passage of ions**
- **Ligand-gated channels – channel protein changes shape and opens, allowing flow of an ion, following a ligand (e.g. neurotransmitter, hormone or drug) binding to a receptor that recognizes the ligand.**
- **Voltage-gated channels - channel opened by a small electrical charge to the membrane surrounding the channel**
- ***Direction which an ion flows*** **is determined by relative concentration; always travels from high to low concentration (Na+, Cl-, Ca2+ out; K+ in)**
- **Open only briefly and then closes again, limiting total ion flux**

Ligand-gated Ion Channel



Voltage-gated Ion Channel

Voltage-regulated (voltage-gated) sodium channel



Resting (-70 mV)	Activated (-60 to +30 mV)	Inactivated (+30 mV, delayed)

Electrical Transmission within a Neuron

- **Transmission of information within a single neuron is an electrical process**

Incoming signal from another cell

↓

Threshold reached

↓

Action Potential
(Electrical signal)

↓

Conveys message along
axon to axon terminals

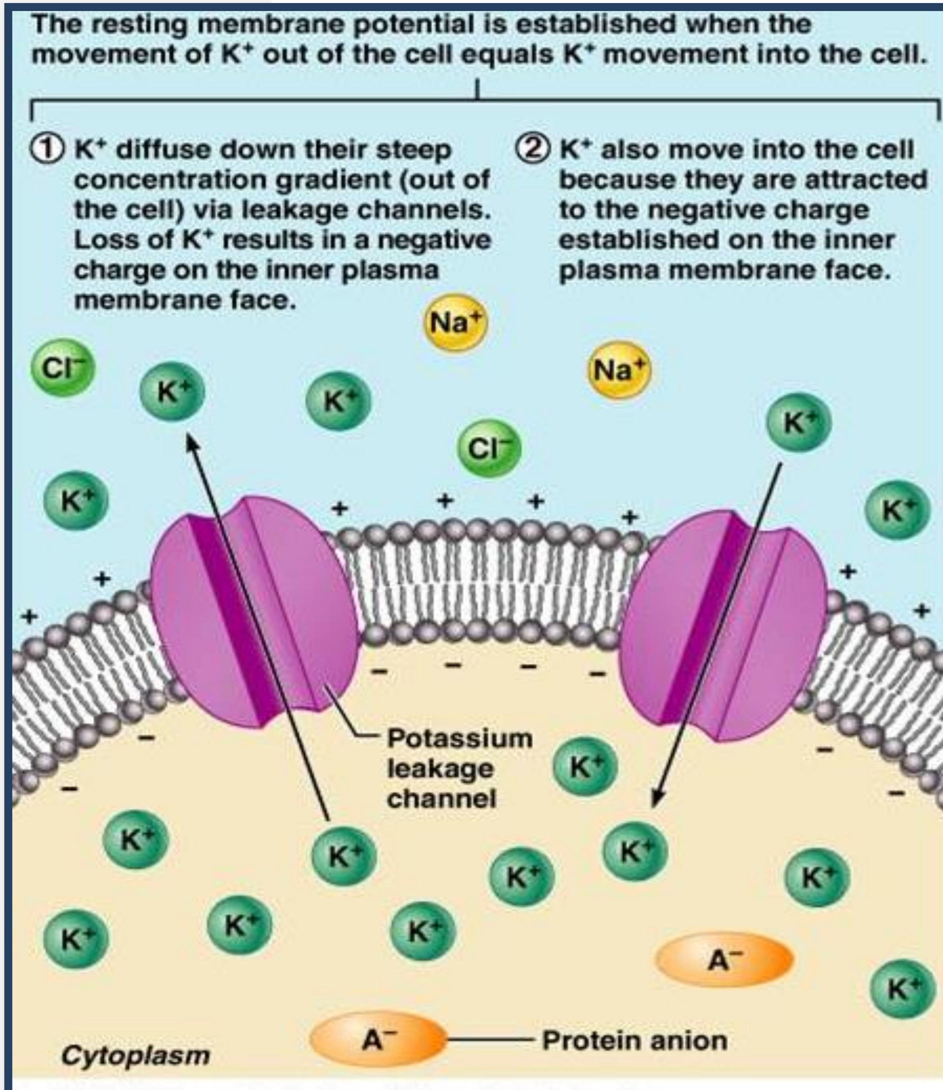
Resting Potential

- Resting membrane potential – difference in electrical charge inside the cell compared with outside the cell
- The inside of a neuron is more negative than the outside of a neuron
- Difference is roughly -70mV
- Neurons are polarized in their resting state, meaning there is ‘potential’ for current to flow
- Membrane potential caused by:
    - Selective permeability of the membrane
    - Uneven distribution of ions inside and outside the cell
    - More negatively charged ions inside the cell
    - More positively charged ions outside

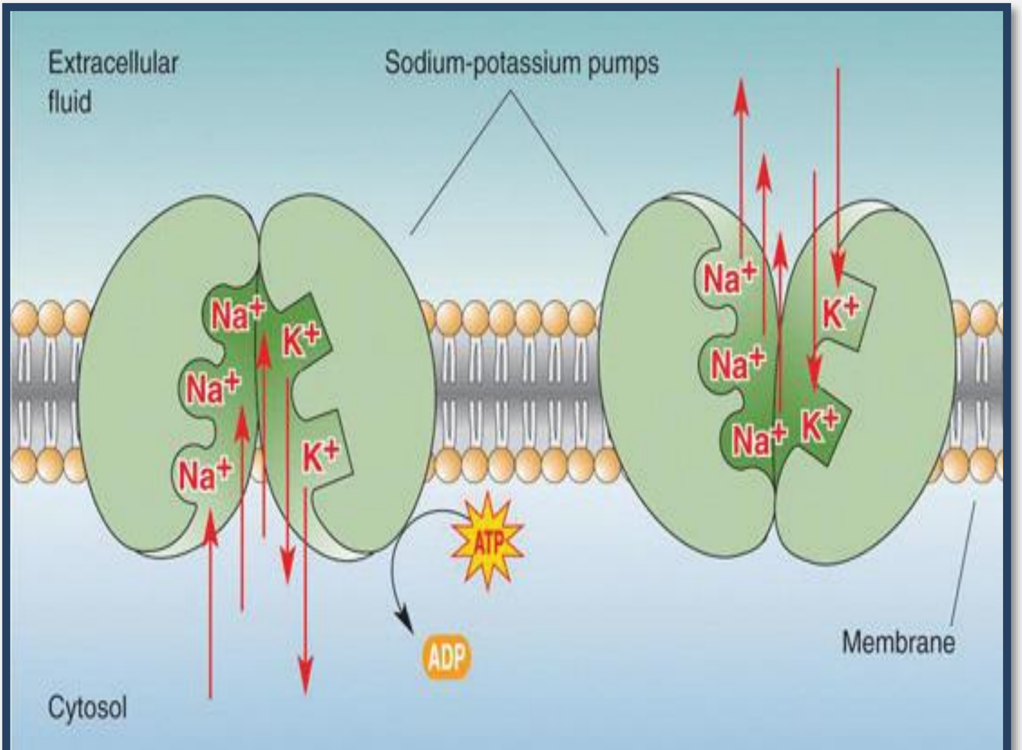
Distribution of ions inside and outside a neuron at resting potential

Differences in ionic makeup

- Inside the neuron has *lower* concentration of Na^+ and Cl^- than outside
- Inside has *higher* concentration of K^+ and negatively charged proteins (A^-) than outside



Resting Membrane Potential



- Negative interior of the cell is due to much greater diffusion of K^+ out of the cell than Na^+ diffusion into the cell
- *Sodium-potassium pump* stabilizes the resting membrane potential by maintaining the concentration gradients for Na^+ and K^+
- For every 3 Na+ ions that are pumped out, 2 K+ are pumped in, keeping the inside of the cell negative

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Changes in membrane potential

- **Membrane potential changes when:**
  - Ion concentrations on two sides change
  - Permeability of membrane to ions changes

- **Changes in membrane potential are signals used to receive, integrate and send information**

Types of membrane potential difference

Resting potential

- Membrane potential of neurons in resting state.

Action potential

- Brief, stereotyped ("all-or-none") change of membrane potential in the positive direction during excitation of cells.
- Amplitude: around 100 mV.
- Duration: nerve cells around 1.5 ms

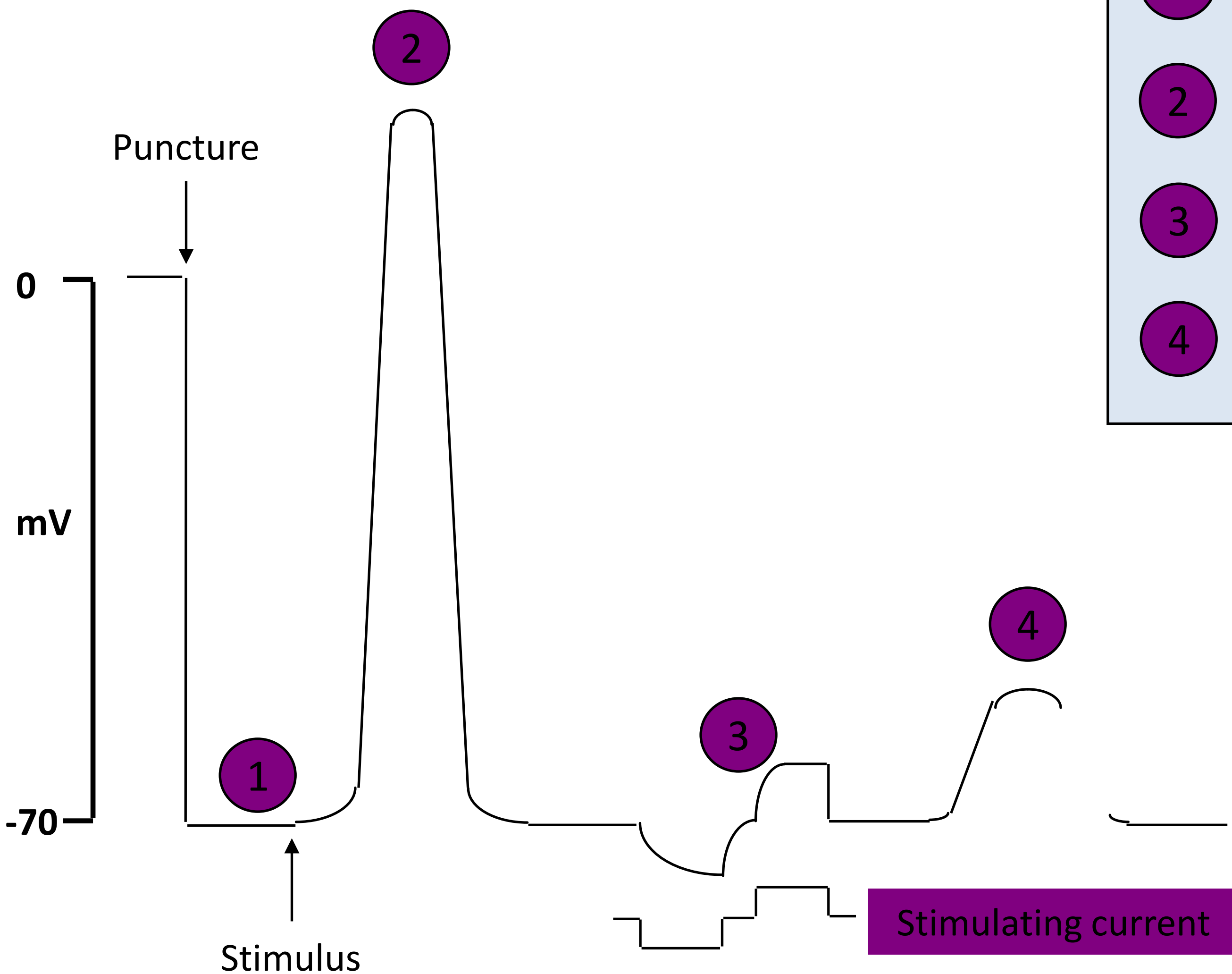
Electrotonic potential

- Positive (depolarizing) or negative (hyperpolarizing) departure from resting potential due to flow of current across membrane.
- Depolarizing current acts as a stimulus (i.e. triggers an action potential when a threshold is reached).

Synaptic potential

- Depolarizing (excitatory) or hyperpolarizing (inhibitory) departure from resting potential due to activation of excitatory or inhibitory synapses.

Changes in membrane potential



1. Resting potential
2. Action potential
3. Electrotonic potential
4. Synaptic potential

Changes in membrane potential

Depolarization

- A ***reduction*** in membrane potential (toward zero)
- Inside of the membrane becomes ***less negative*** than the resting potential
- ***Increases*** the probability of producing a nerve impulse

Hyperpolarization

- An ***increase*** in membrane potential (away from zero)
- Inside of the membrane becomes ***more negative*** than the resting potential
- ***Reduces*** the probability of producing a nerve impulse

Membrane Potentials That Act as Signals

Two types of signals:

- **Graded potentials**
  - Incoming short-distance signals
- **Action potentials**
  - Long-distance signals of axons

Graded Potentials

- Occur when a stimulus causes ***gated ion channels*** to open
  - E.g., receptor potentials, generator potentials, postsynaptic potentials
- Magnitude varies directly (graded) with stimulus strength
- Decrease in magnitude with distance as ions flow and diffuse through leakage channels
- Short-distance signals

Action Potentials

- Brief reversal of membrane potential with a total amplitude of ~100 mV
- Occurs in muscle cells and axons of neurons
- Does ***NOT*** decrease in magnitude over distance
- Principal means of long-distance neural communication

Graded Potentials vs. Action Potentials

Graded Potential

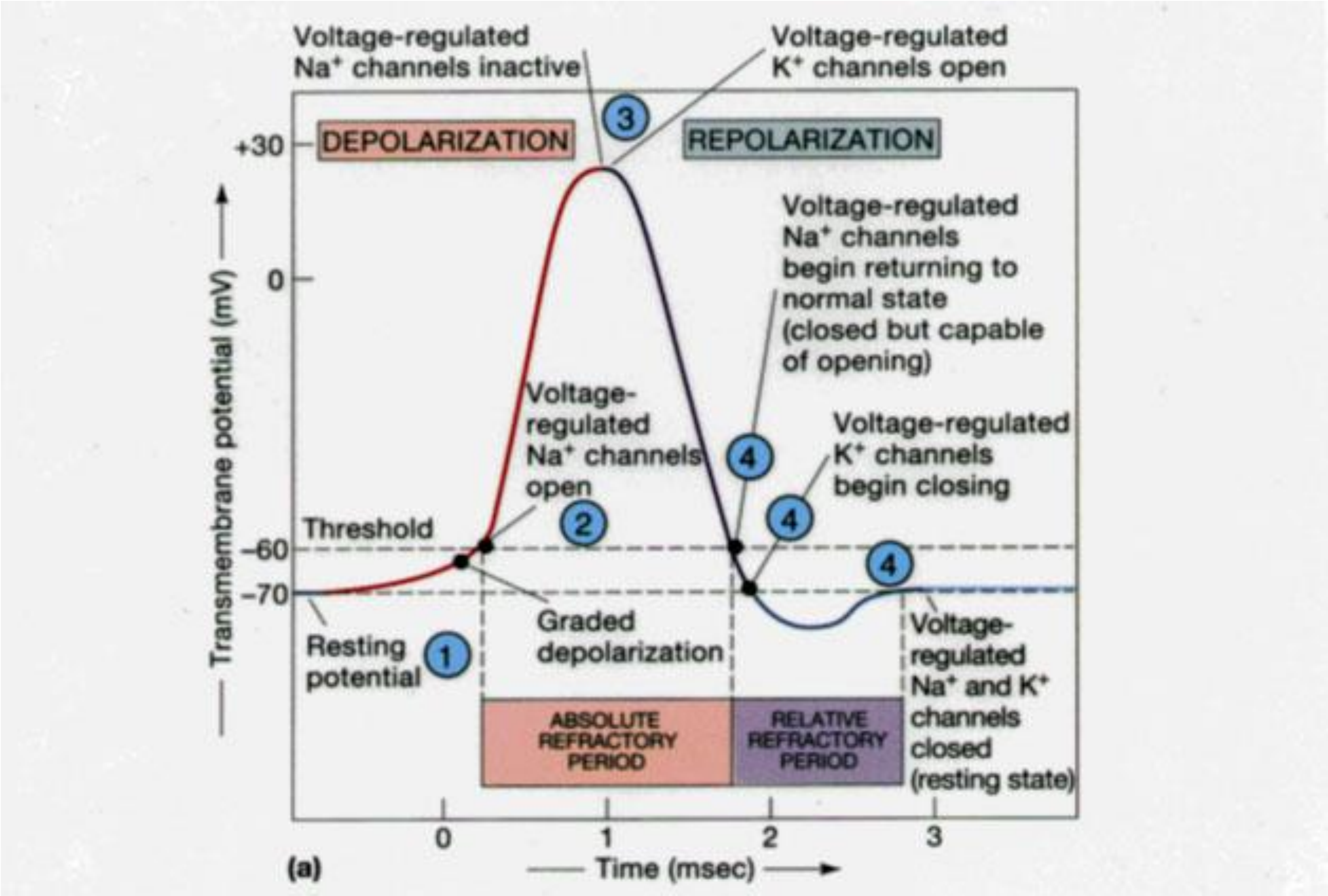
- Chemically gated ion channels
- Stimulus is related to the strength
- Die out with increasing distance
  - Due to leakage of the charge
- Short distance travel

Action Potential

- Voltage gated ion channels
- Stimulus is consistent
- Do not decrease with distance
- Long distance travel

*****Graded Potentials can cause Action Potentials***

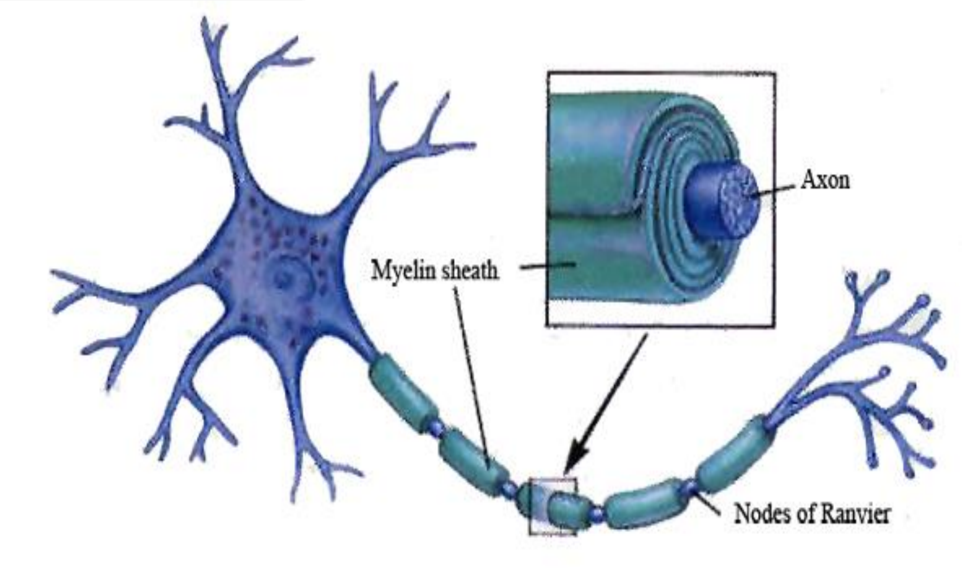
Changes during an action potential

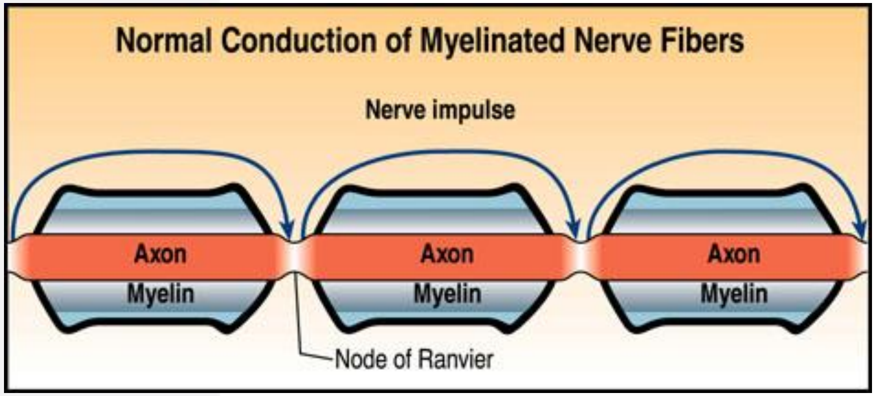


Myelination

- Myelin is produced by specific types of glial cells (oligodendrocytes- CNS; Schwann cells – PNS)

- Layers of myelin wrap around axons and provide electrical insulation to the neuron.





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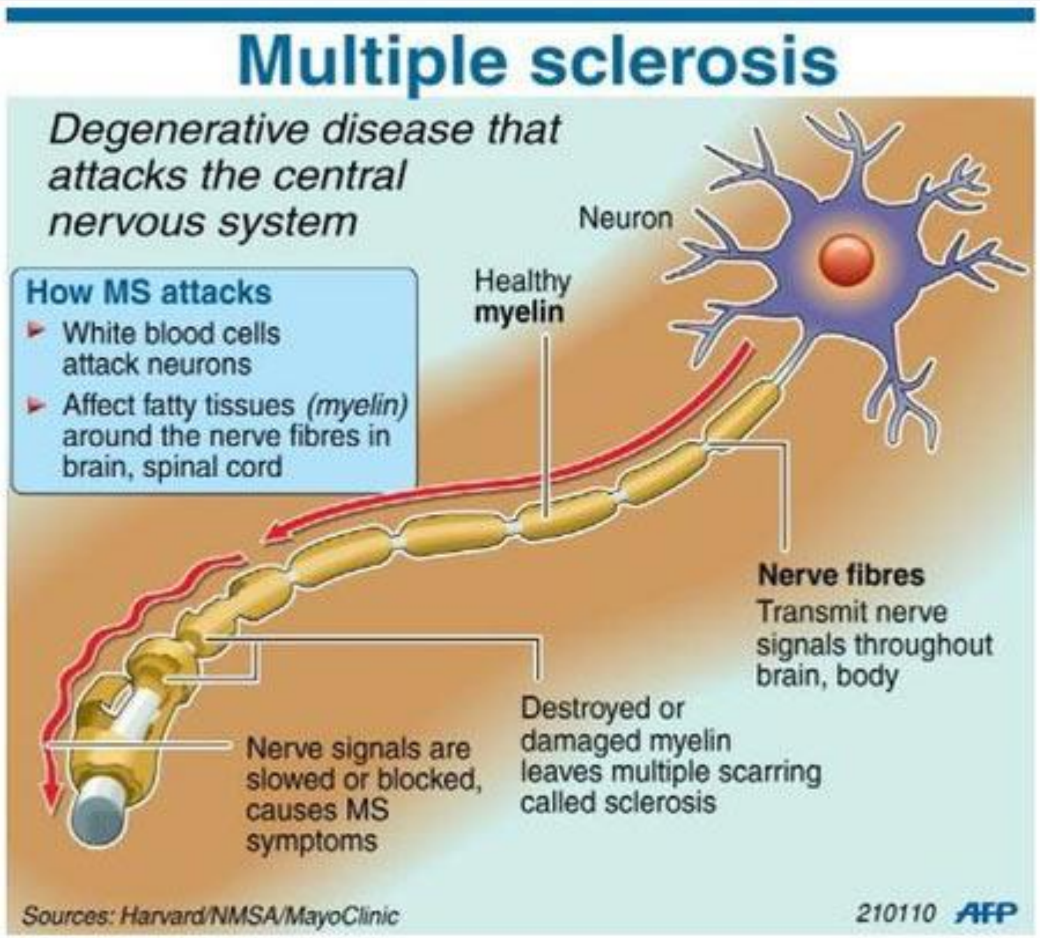
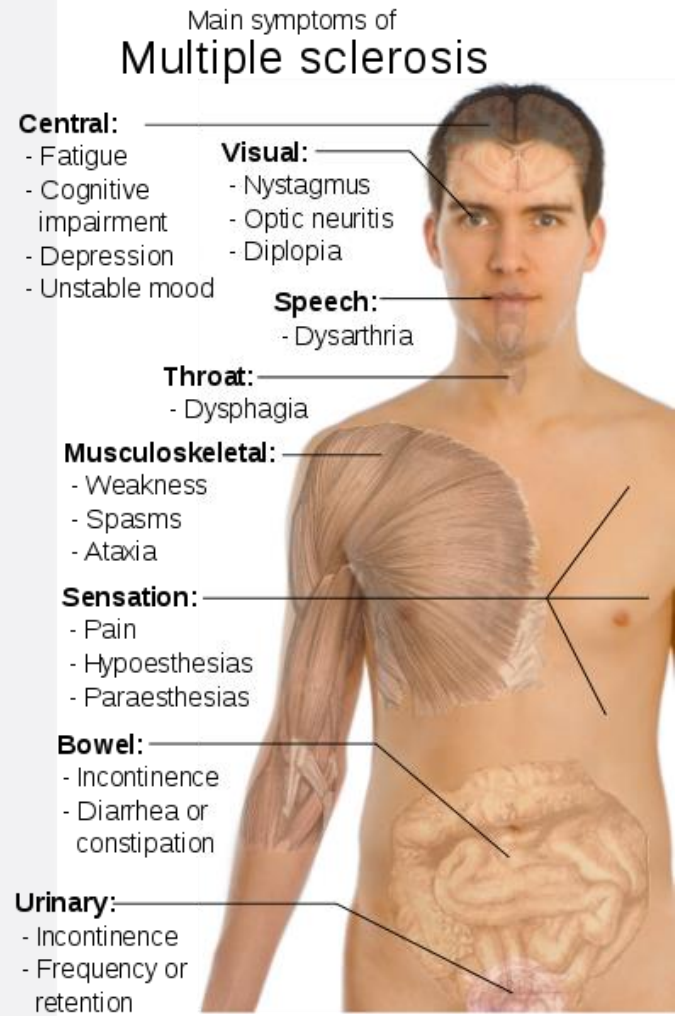
Myelination

CONTINUOUS PROPAGATION (UNMYELINATED AXONS)	SALTATORY PROPAGATION (MYELINATED AXONS)
In continuous propagation an action potential:	***In saltatory propagation an action potential:***
Is propagated along the axon.	Cannot move by continuous propagation because myelin sheath blocks movement of ions across membrane.
Always moves forward not backward as previous segment of axon is still in absolute refractory period.	Can only occur where myelin is interrupted (i.e. at nodes of Ranvier).
Appears to move as sequence of tiny (1.5 ms) steps.	Is propagated by "jumping" from node to node.
Moves at 1 metre/second (around 2 m.p.h.).	Moves more rapidly than in unmyelinated axons.

Demyelinating Disease





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The Synapse

What is a synapse?

- **A synapse is a specialized junction through which impulses pass from a presynaptic neuron to another (postsynaptic) cell (*synaptic transmission*).**
- **Or, in more basic terms, a place where two membranes can communicate.**
- **May be *electrical*, relying on direct physical contact, or *chemical*, relying on the actions of a neurotransmitter.**

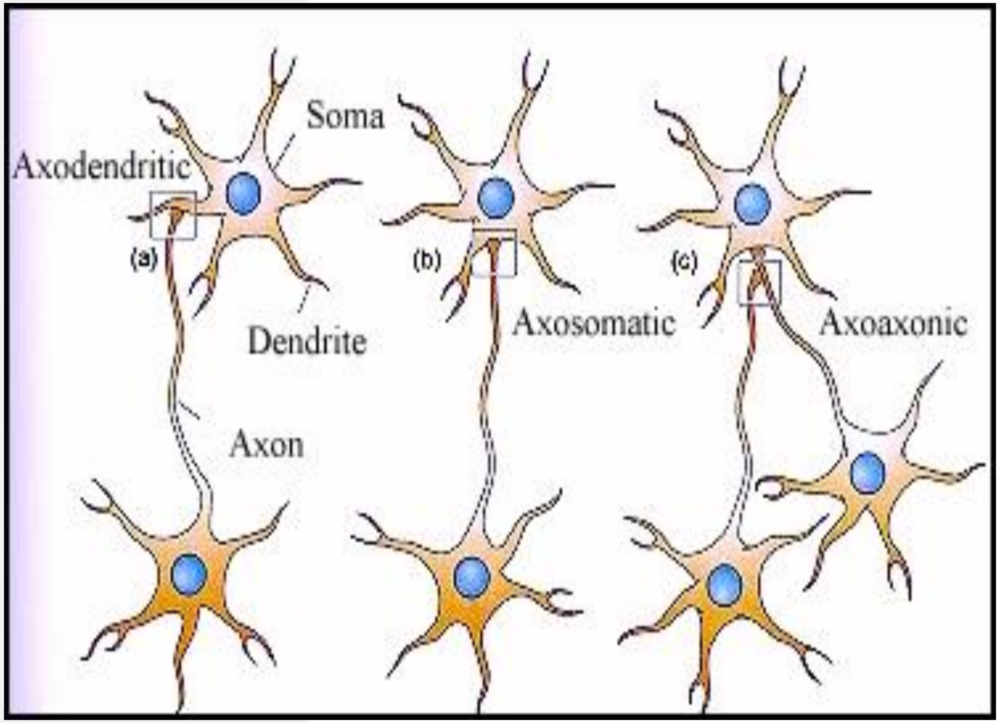
Types of Synapses

Axodendritic

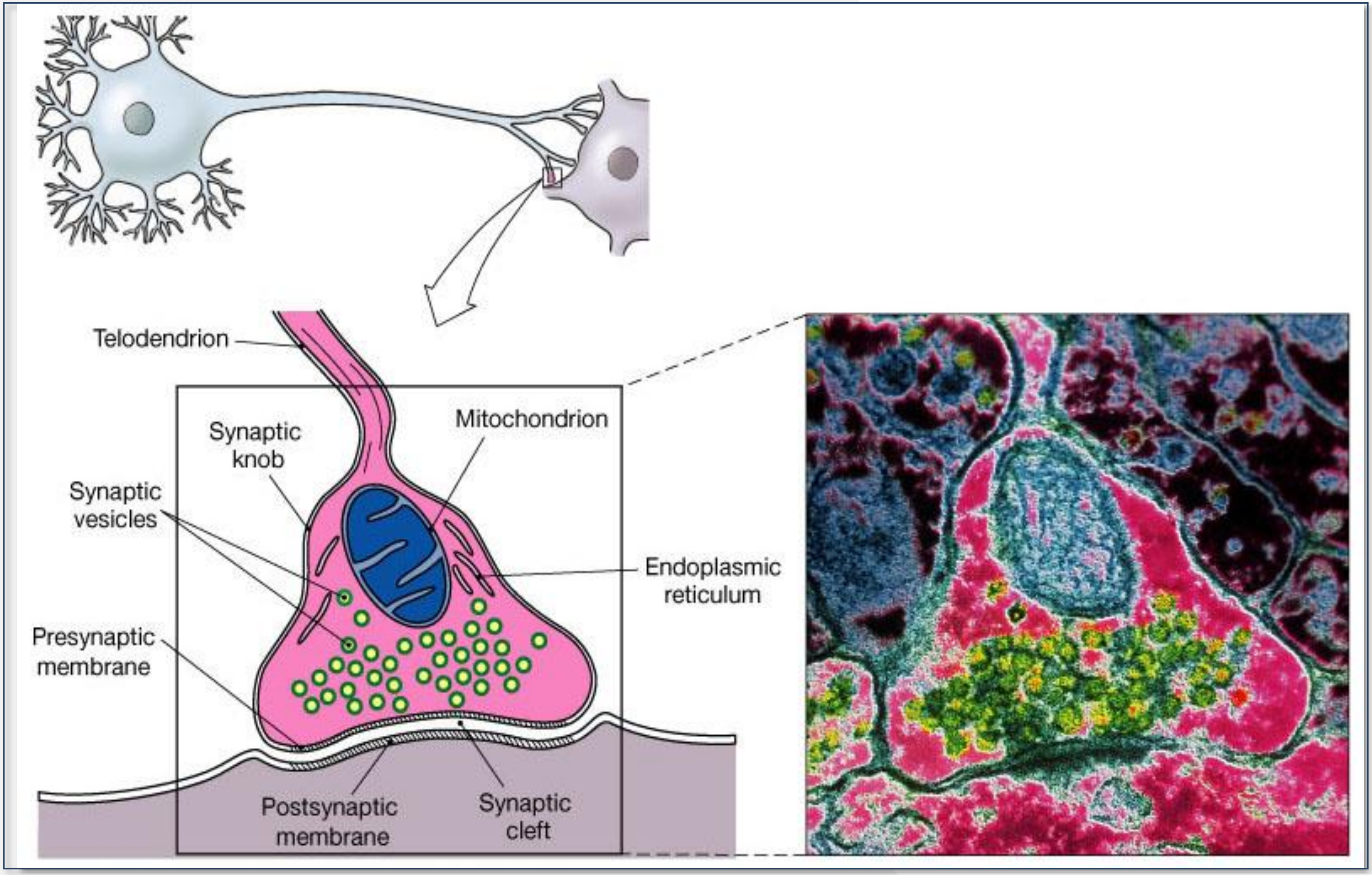
- Between the axon of one neuron and the dendrite of another

Axosomatic

- Between the axon of one neuron and the soma of another



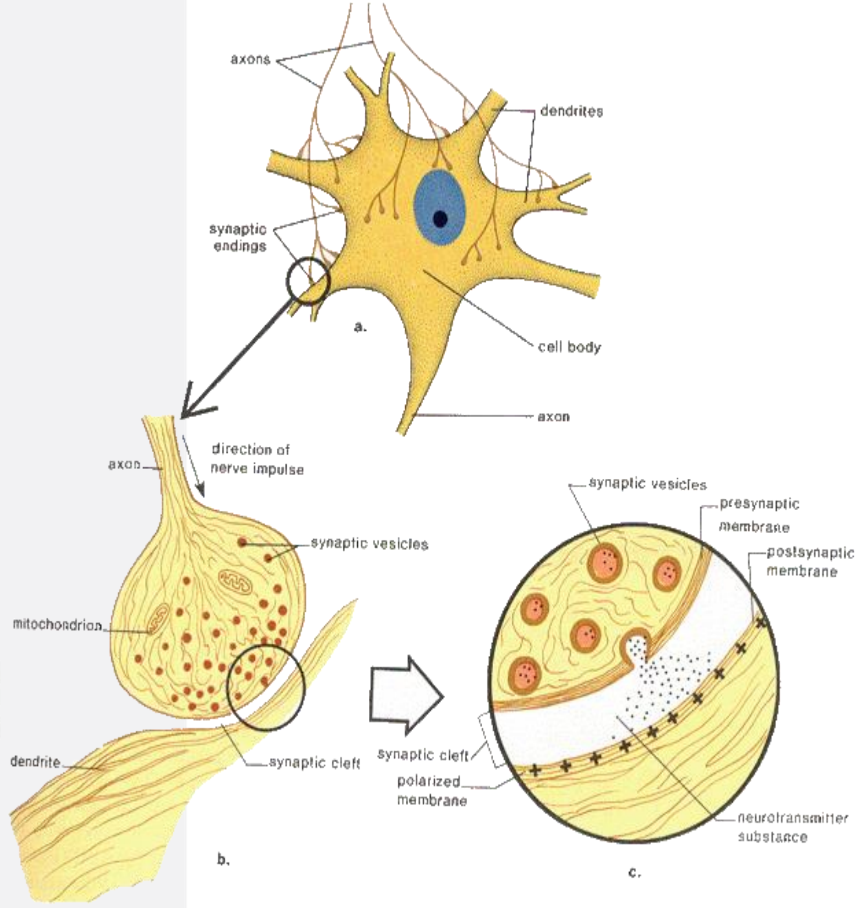
Chemical Synapse



Synaptic Cleft

Transmission across the synaptic cleft:

- Is a chemical event (as opposed to an electrical one)
- Involves release, diffusion, and binding of neurotransmitters
- Ensures unidirectional communication between neurons

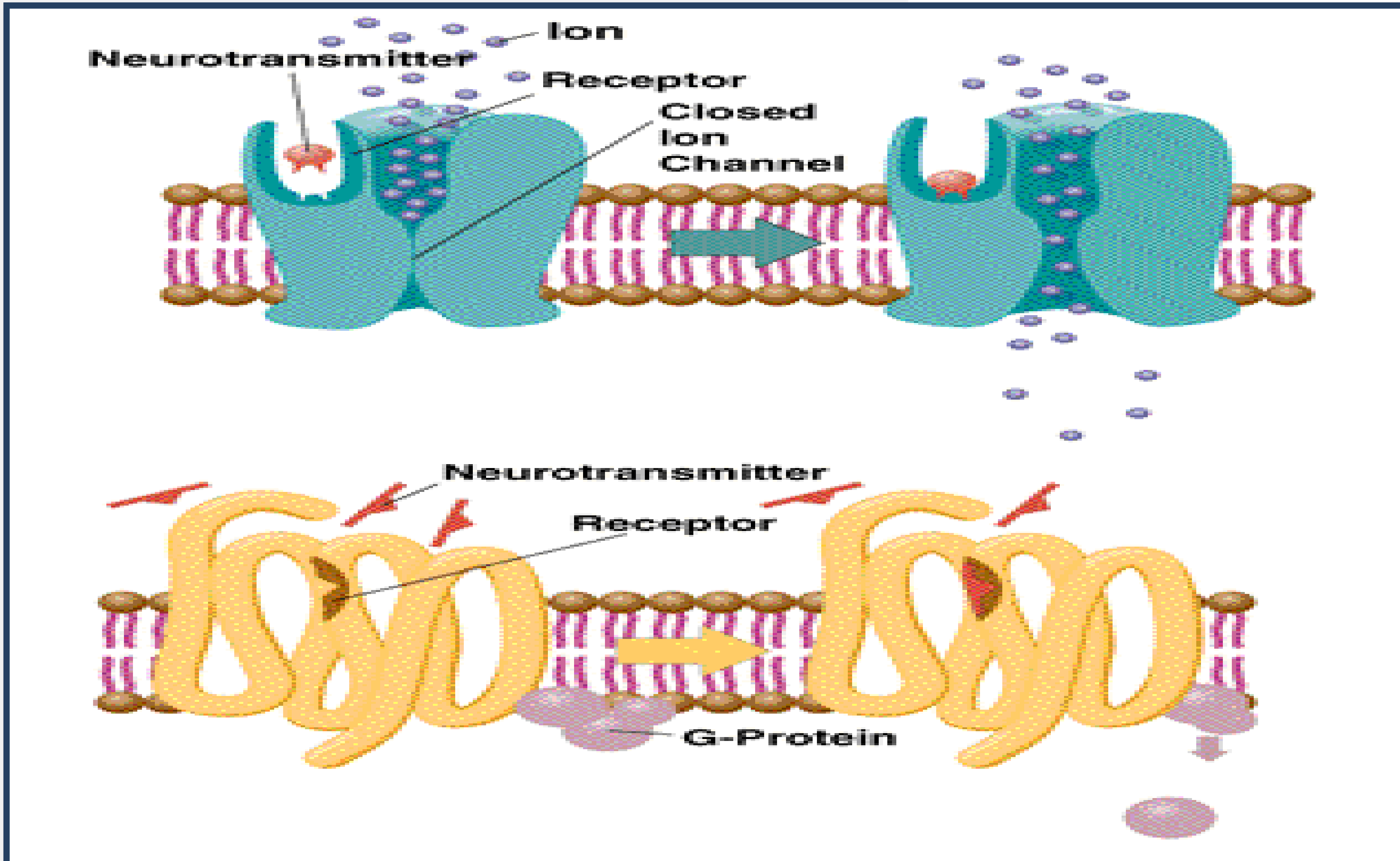


Ion channel-linked receptor and G-protein coupled receptors

- **The binding of the neurotransmitter to its receptors can influence the postsynaptic neuron in one of two fundamentally different ways:**

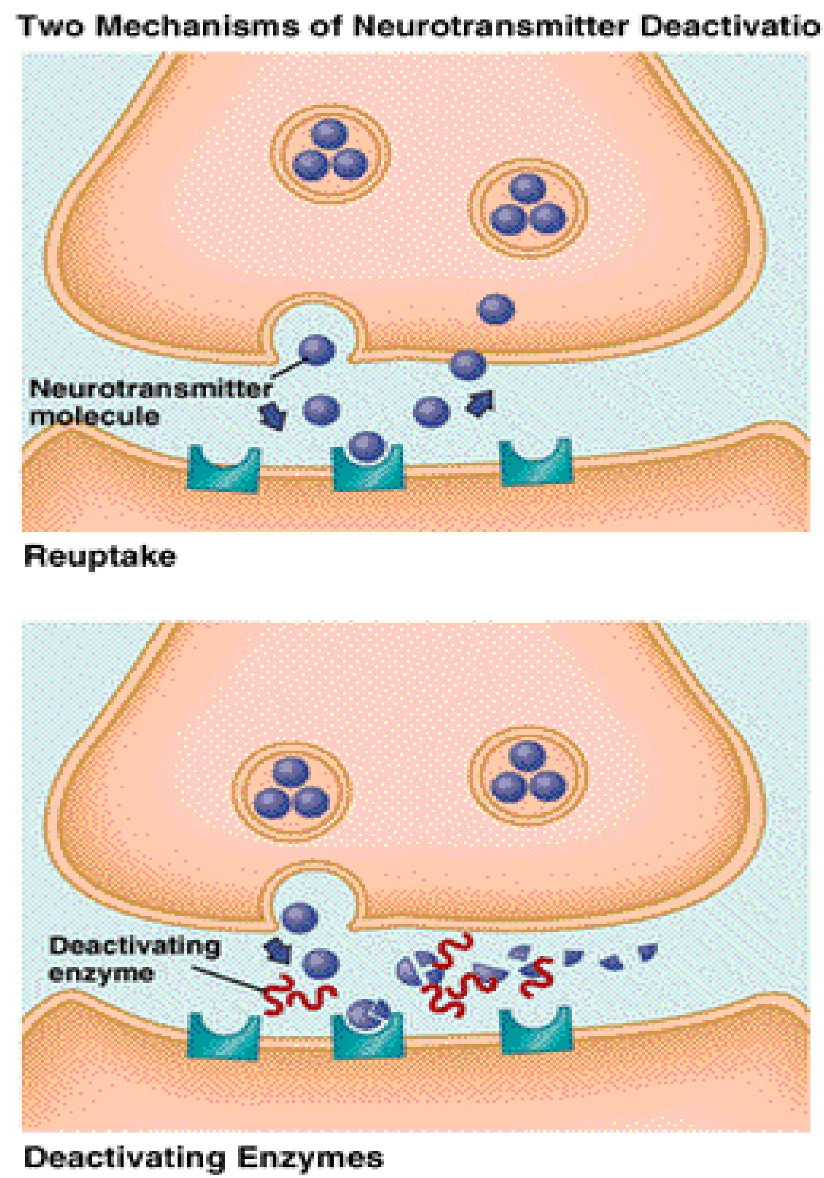
  1. **It can directly influence chemical-gated channels in the postsynaptic membrane and induce brief EPSPs or IPSPs; or**
  2. **It can trigger chemical reactions in the cytoplasm of the postsynaptic neuron that lead to the production of chemicals, called secondary messengers (e.g., cyclic AMP), which can have more enduring and far-reaching effects on the sensitivity of the neuron**

Ion channel-linked receptor and G-protein coupled receptors



Termination of Neurotransmitter Effects

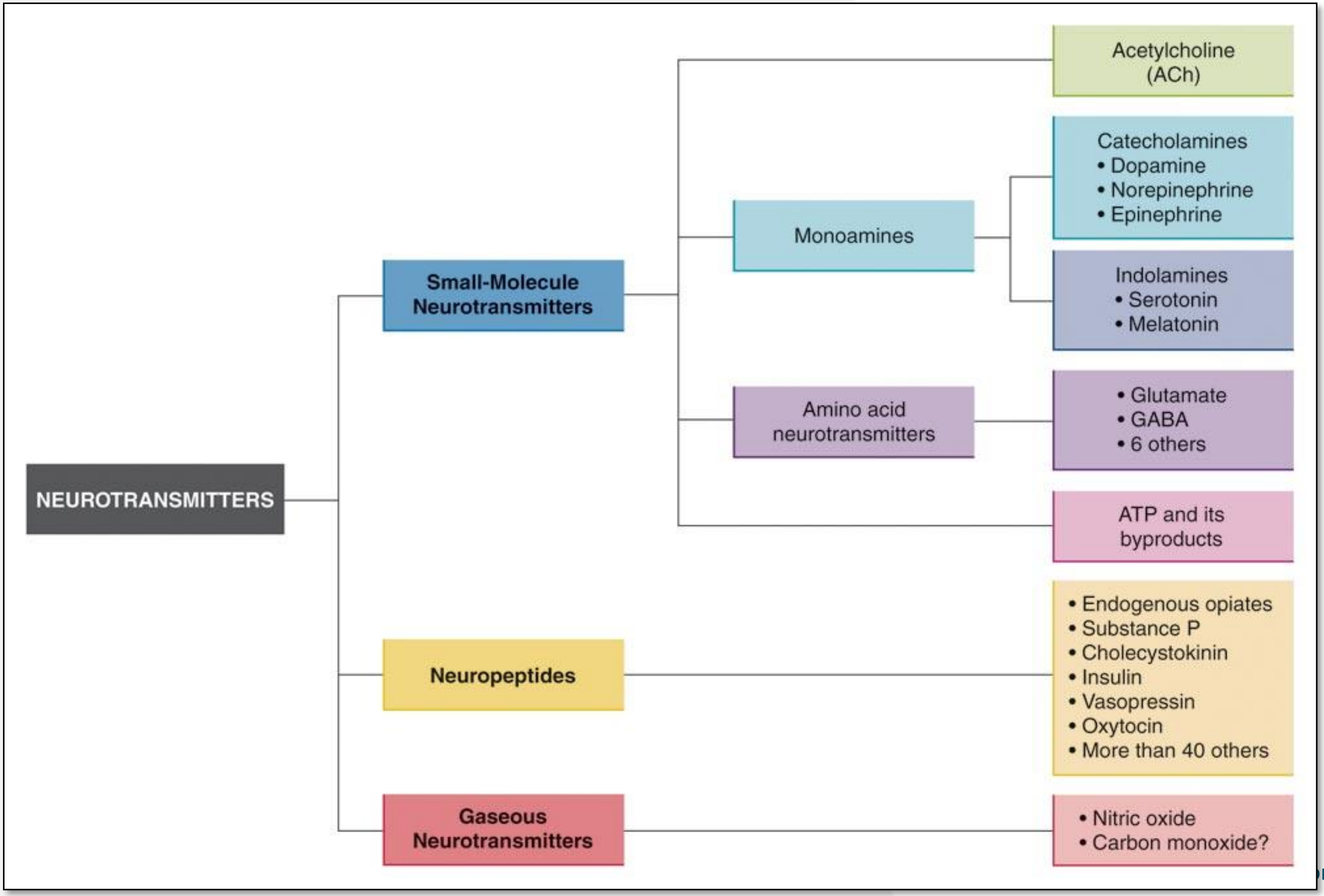
- **Within a few milliseconds, the neurotransmitter effect is terminated**
  - Degradation by enzymes
  - Reuptake by astrocytes or axon terminal
  - Diffusion away from the synaptic cleft



Neurotransmitters

- Most neurons make two or more neurotransmitters, which are released at different stimulation frequencies
- 50 or more neurotransmitters have been identified
- Classified by chemical structure and by function

Neurotransmitter Families



Neurotransmitters – Functional Classification

- **Excitatory and inhibitory neurotransmitters are present in both central and peripheral nervous systems.**
- **Sometimes same neurotransmitter is excitatory in one location but inhibitory in another, therefore response is dependent on receptor.**

Excitatory neurotransmitters

- **Glutamate (brain, brain stem).**
- **Aspartate (spinal cord).**

Inhibitory neurotransmitters

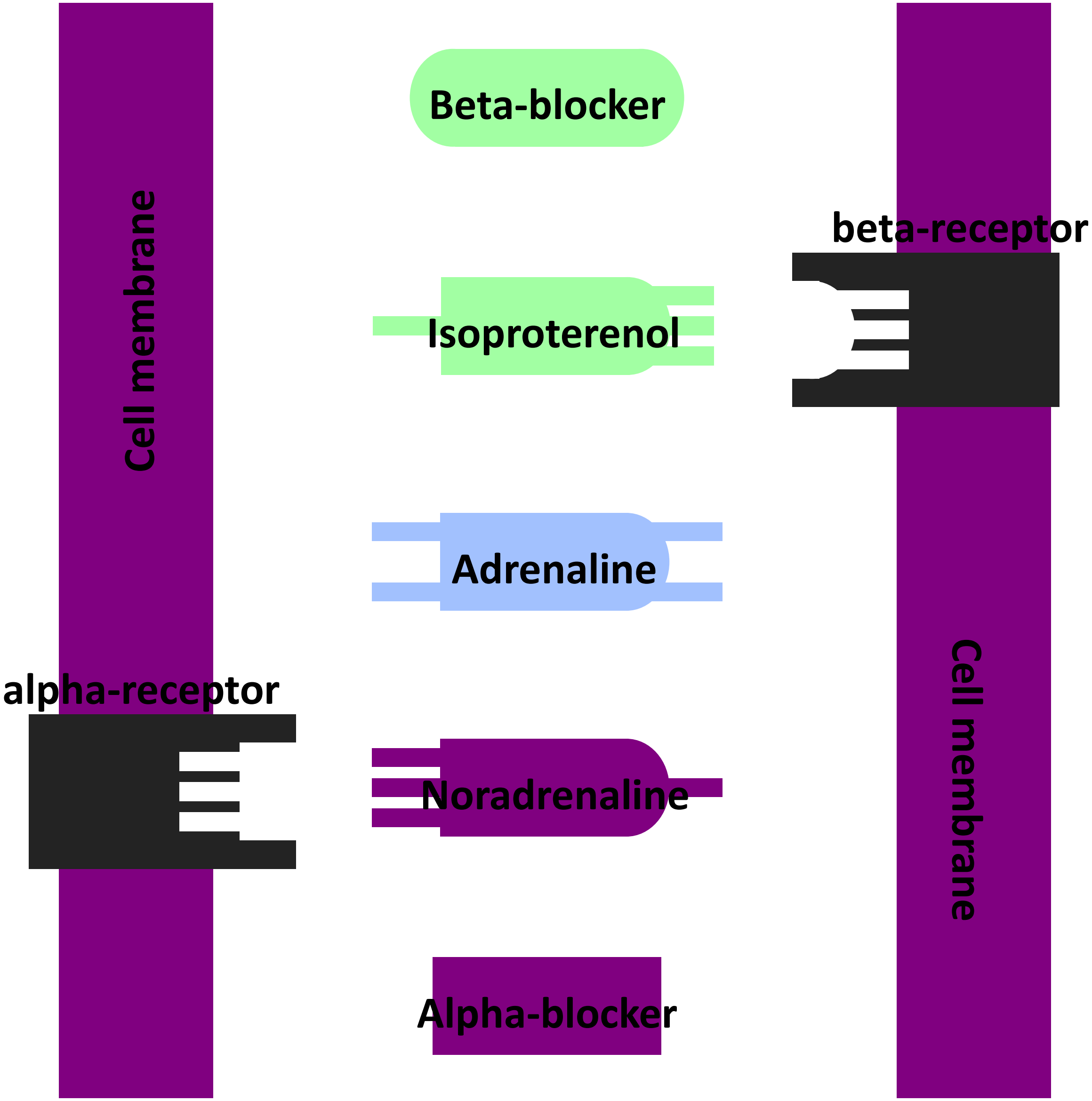
- **Gamma-aminobutyric acid, or GABA (brain).**
- **Glycine (primarily spinal cord, brain).**

Conditions and agents altering impulse conduction

- Chemical and physical environment of neuron influences impulse conduction and synaptic transmission.

Alkalosis	Defined as an increase in pH above 7.45. Increases excitability of neurons, giving rise to inappropriate impulses. Range of effects from light-headedness right through to convulsions.
Acidosis	Defined as decrease of pH below 7.35. Results in progressive depression of neuronal activity. Range of effects from apathy through to coma.
Excessive pressure	If nerve is subjected to excessive or prolonged pressure, impulse conduction can be blocked.
Agonist	Agent that enhances synaptic transmission or mimics effect of natural neurotransmitter.
Antagonist	Agent that blocks the action of a neurotransmitter.

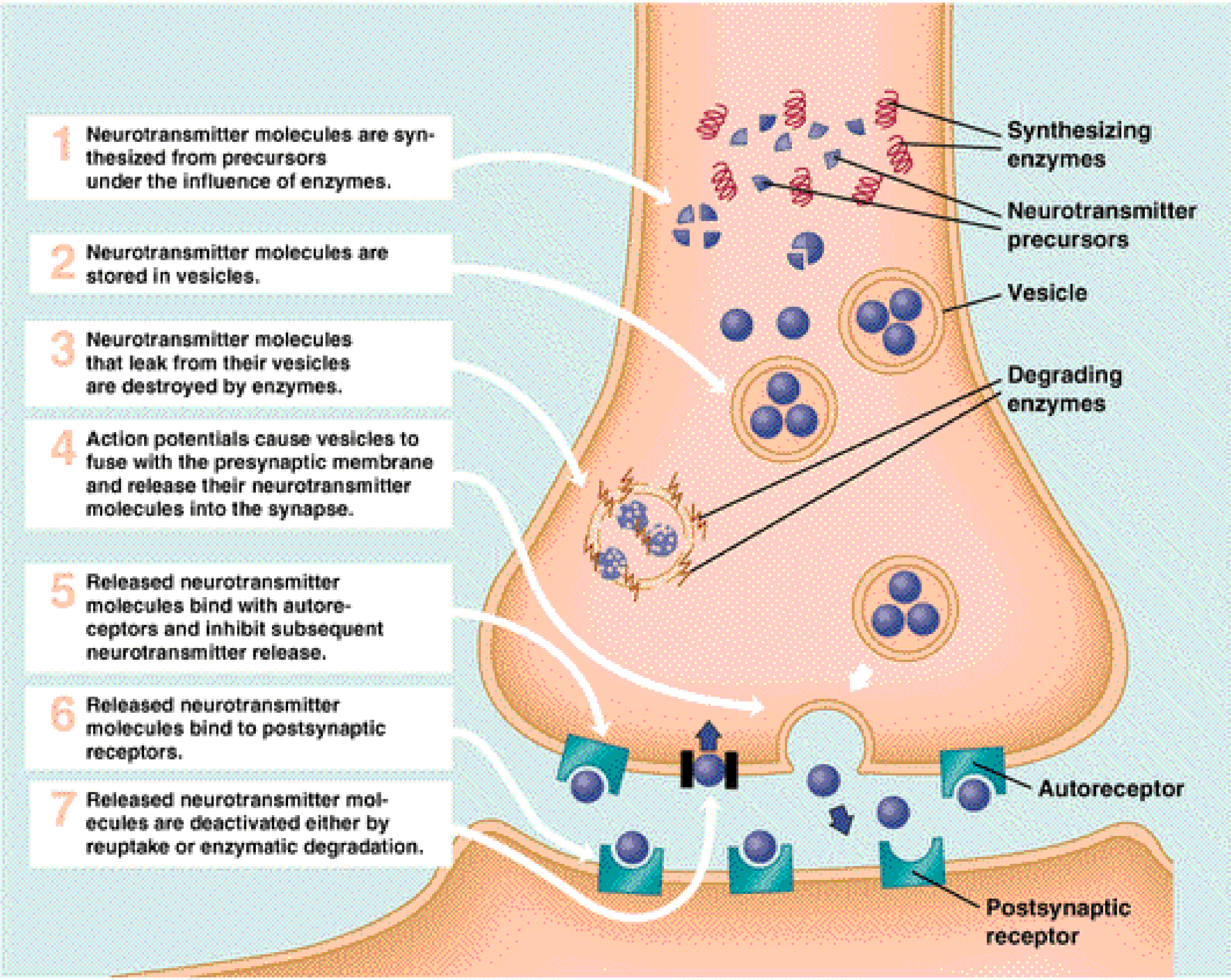
Agonist and antagonist binding



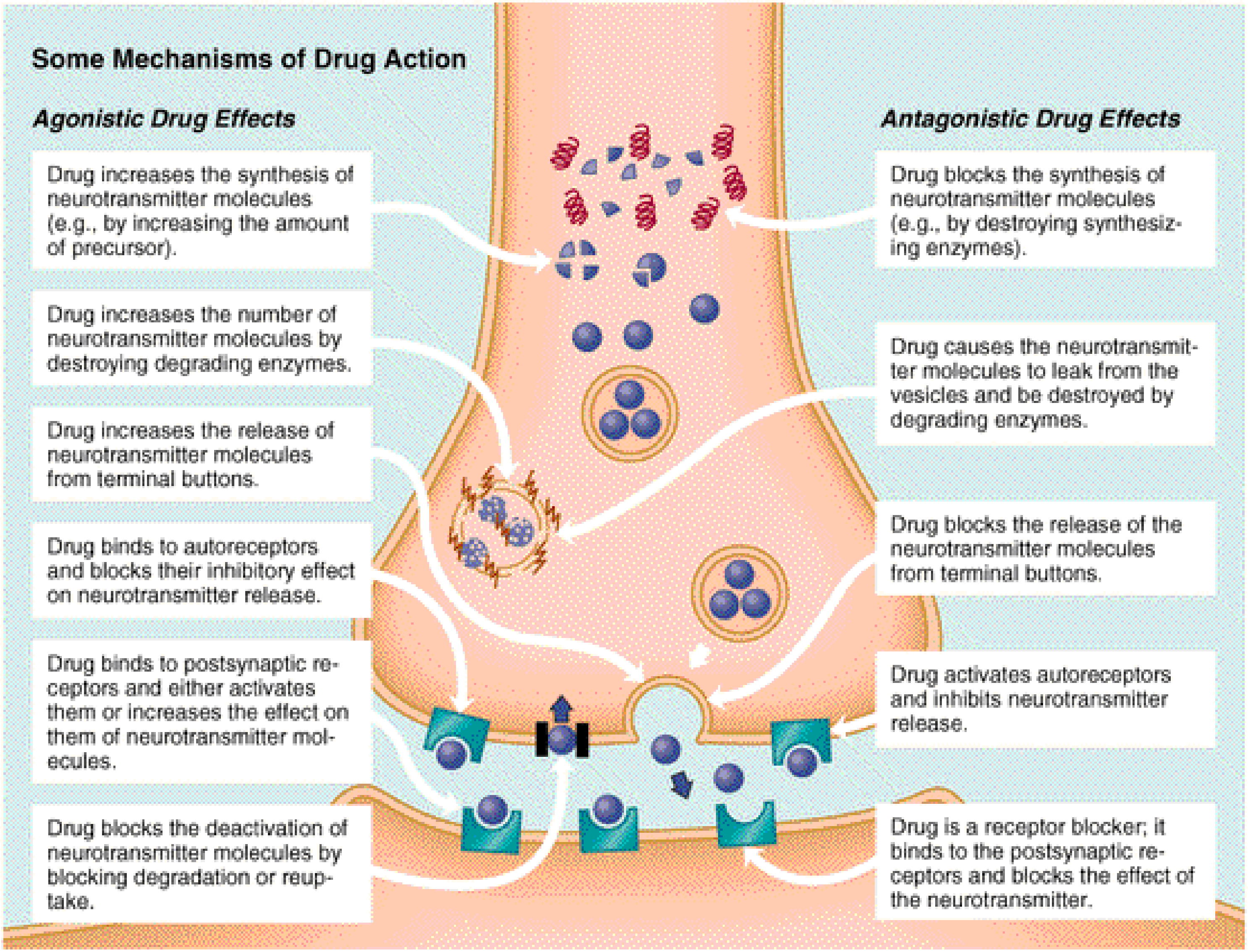
Lock-and-key concept

- Binding of the ‘key’ (messenger substance) to the ‘lock’ receptor transmits information.
- Each communication system uses somewhat different ‘keys’ and ‘locks’.

► Seven Processes in Neurotransmitter Action



► Mechanisms of Drug Effects



Disorders associated with neurotransmitter imbalances

Condition	Main symptoms	Imbalance of neurotransmitter in brain
Alzheimer's disease	Memory loss, dementia	Deficient acetylcholine
Clinical depression	Debilitating inexplicable sadness	Deficient noradrenaline and/or serotonin
Epilepsy	Seizures, loss of consciousness	Excess GABA leads to excess noradrenaline and dopamine
Huntington's disease	Personality changes, uncontrollable movements	Deficient GABA
Insomnia	Inability to sleep	Excess noradrenaline
Myasthenia gravis	Progressive muscular weakness	Deficient acetylcholine receptors at neuromuscular junctions
Parkinson's disease	Tremors of hands, slowed movements, muscle rigidity	Deficient dopamine
Schizophrenia	Inappropriate emotional responses, hallucinations	Deficient GABA leads to excess dopamine

Drugs that alter neurotransmitter levels

Drug	Neurotransmitter affected	Mechanism of action	Effect
Curare	Acetylcholine	Decreases neurotransmitter in synaptic cleft	Muscle paralysis
Reserpine	Noradrenaline	Packaging neurotransmitter into vesicles	Limb tremors
Cocaine	Noradrenaline	Blocks reuptake	Euphoria
Monoamine oxidase inhibitors	Noradrenaline	Blocks enzymatic degradation of neurotransmitter in presynaptic cell	Mood elevation
Tryptophan	Serotonin	Simulates neurotransmitter synthesis	Sleepiness
Prozac and related drugs	Serotonin	Blocks reuptake	Mood elevation
Valium	GABA	Enhances receptor binding	Decreases anxiety