NERVOUS SYSTEM

2ND SEMESTER/CC/PHYA

PHYSIOLOGY HONOURS (CBCS) SEMESTER-II
(MODULE-CC-4)

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Computed Tomography Scan (CT scan)

A **CT scan** or **computed tomography scan** (formerly known as computed axial tomography or CAT scan) is a **medical imaging technique** used in radiology to get detailed images of the body noninvasively for diagnostic purposes.

The first clinical CT scan was performed in 1971 using a scanner invented by Sir Godfrey Hounsfield. **Sir Godfrey Newbold Hounsfield** (28 August 1919–12 August 2004) was an English electrical engineer who shared the **1979 Nobel Prize for Physiology** or Medicine with Allan MacLeod Cormack for his part in developing the diagnostic technique of X-ray computed tomography (CT).

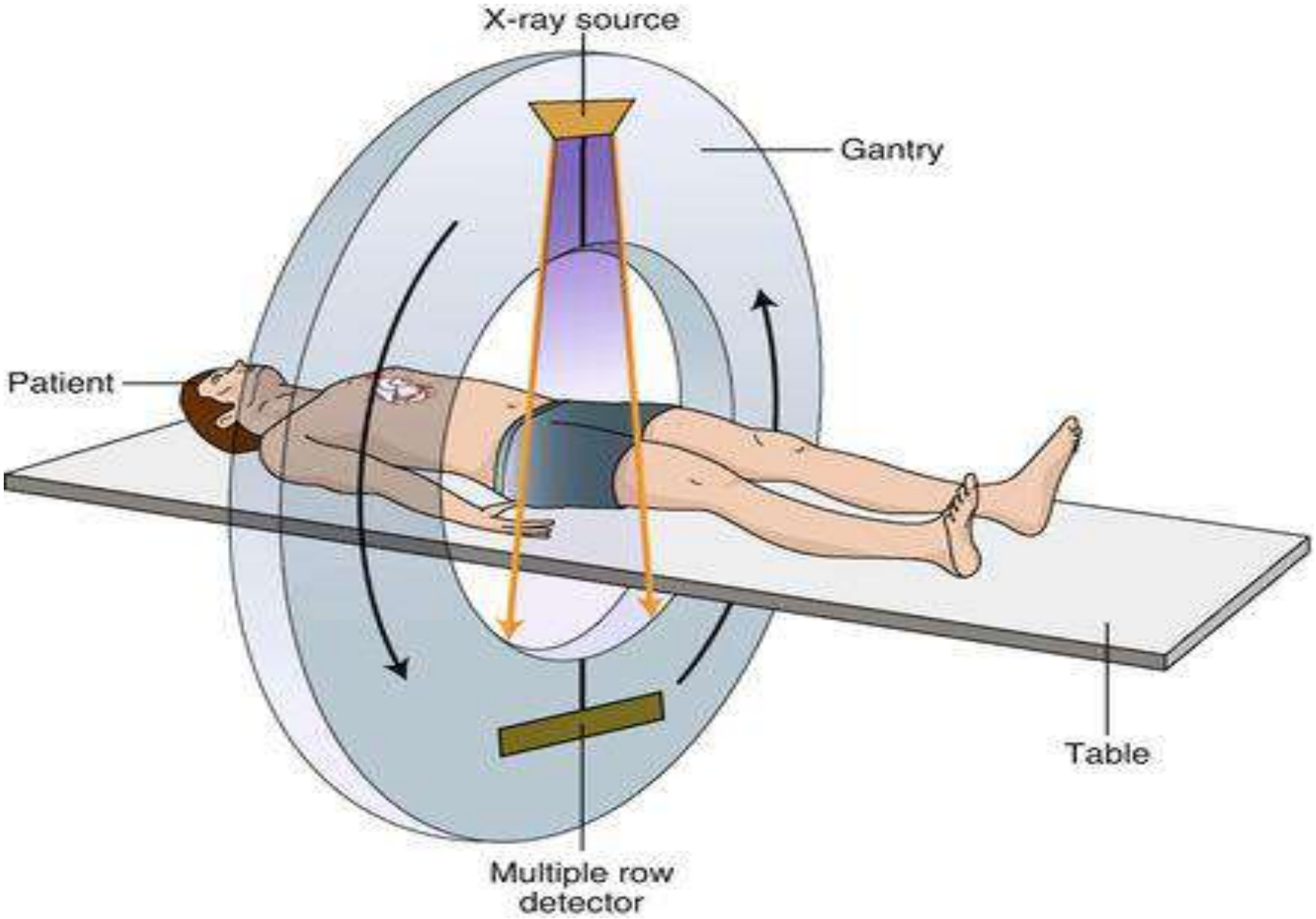
Principle

1. The word *tomography* is derived from **Ancient Greek 'tomos' = slice; 'graphein' = to write.** It is a method of imaging of an object by analyzing its slices.

2. The term "computed tomography", or CT, refers to a **computerized x-ray imaging procedure** in which a narrow beam of x-rays is aimed at a patient and quickly rotated around the body, producing signals that are processed by the machine's computer to generate **cross-sectional images—or "slices"**—of the body. These slices are called **tomographic images**.

3. Unlike a conventional x-ray—which uses a fixed x-ray tube—a CT scanner uses a **motorized x-ray source** that rotates around the circular opening of a donut-shaped structure called a **gantry**. During a CT scan, the patient lies on a bed that slowly moves through the gantry while the x-ray tube rotates around the patient, shooting narrow beams of x-rays through the body.

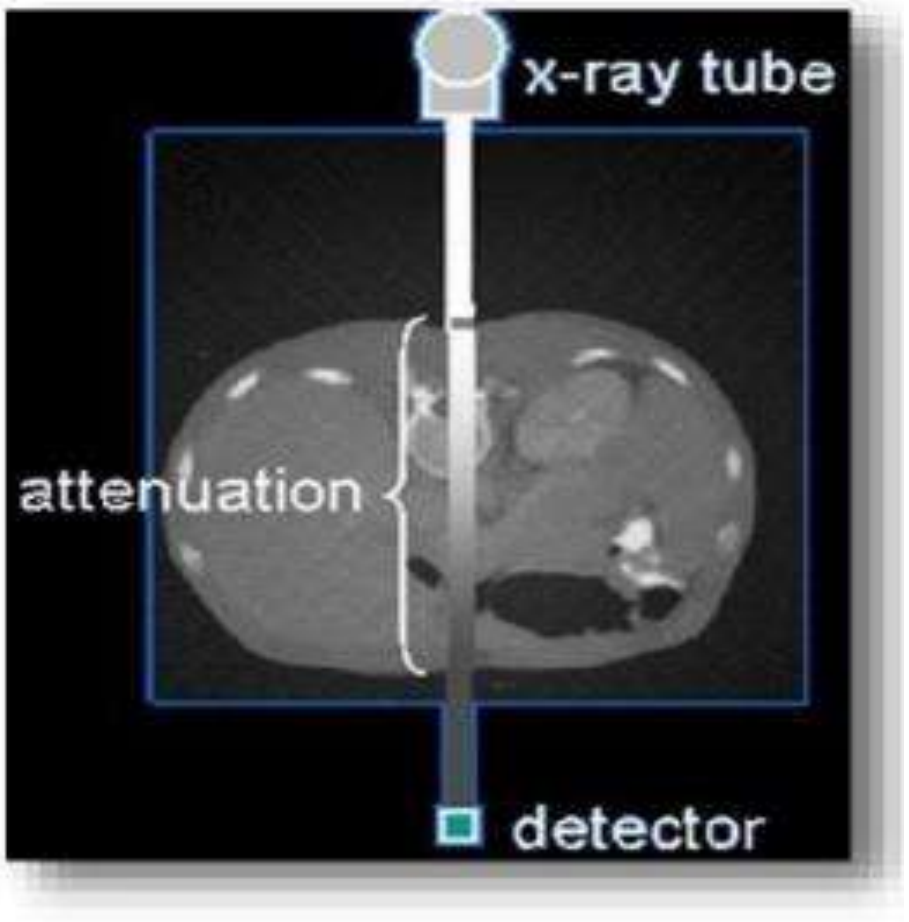
4. **As the X-rays pass through the patient, they are attenuated differently by various tissues according to the tissue density**.


X-ray source
Gantry
Patient
Table
Multiple row detector

What are we measuring?

The average linear attenuation coefficient (μ), between tube and detectors

Attenuation coefficient reflects the degree to which the X-ray intensity is reduced by a material

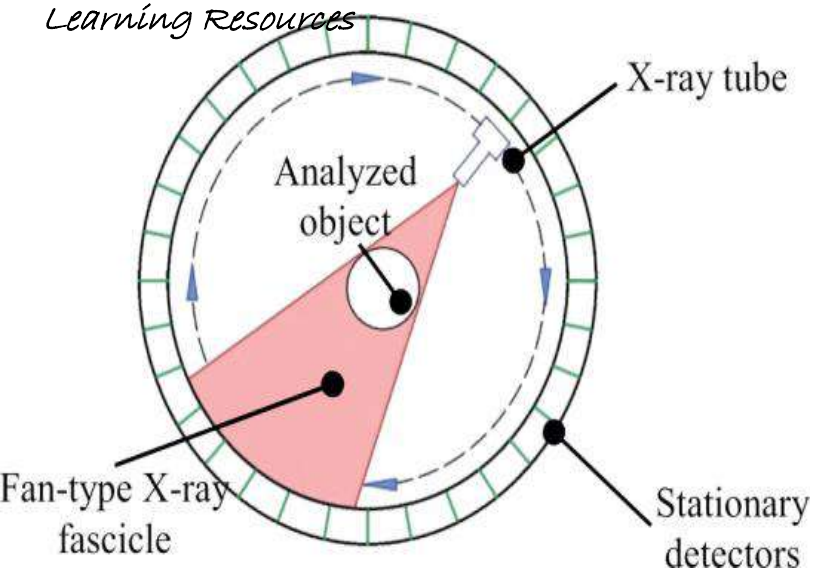


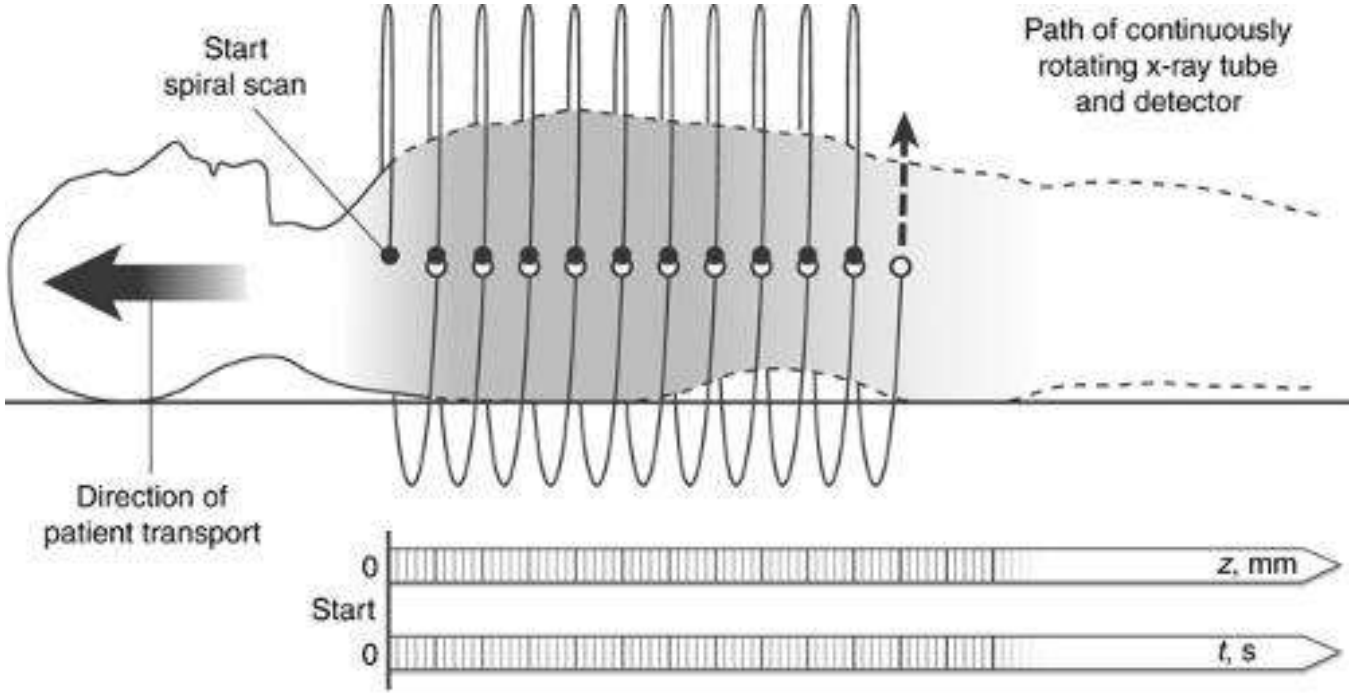
As the X-rays pass through the patient, they are attenuated differently by various tissues according to the tissue density.

5. **Each time the x-ray source completes one full rotation, the CT computer uses sophisticated mathematical techniques to construct** a **2D image slice** of the patient. The thickness of the tissue represented in each image slice can vary depending on the CT machine used, but usually ranges from **1-10 millimeters**. When a full slice is completed, the image is stored and the motorized bed is moved forward incrementally into the gantry. The x-ray scanning process is then repeated to produce another image slice. This process continues until the desired number of slices is collected.

6. Once a number of successive slices are collected by the machine's computer, they can be digitally "stacked" together to form a **3D IMAGE** of the patient .

7. The values that are assigned to the pixels in a CT image are associated with the **average linear attenuation coefficient μ** (m-1) of the tissue represented within that pixel. **As an X ray beam is transmitted through the patient, different tissues are encountered with different linear attenuation coefficients**. A CT image is composed of a matrix of pixels representing the average linear attenuation co-efficient in the associated volume elements (voxels).


X-ray tube
Analyzed object
Fan-type X-ray fascicle
Stationary detectors


Start spiral scan
Path of continuously rotating x-ray tube and detector
Direction of patient transport
0
Start
0
z, mm
t, s

74526_01_005

Uses

1. CT scanning is perfectly suited for **3D imaging** and used in, for example, brain, cardiac, musculoskeletal, and whole body CT imaging.

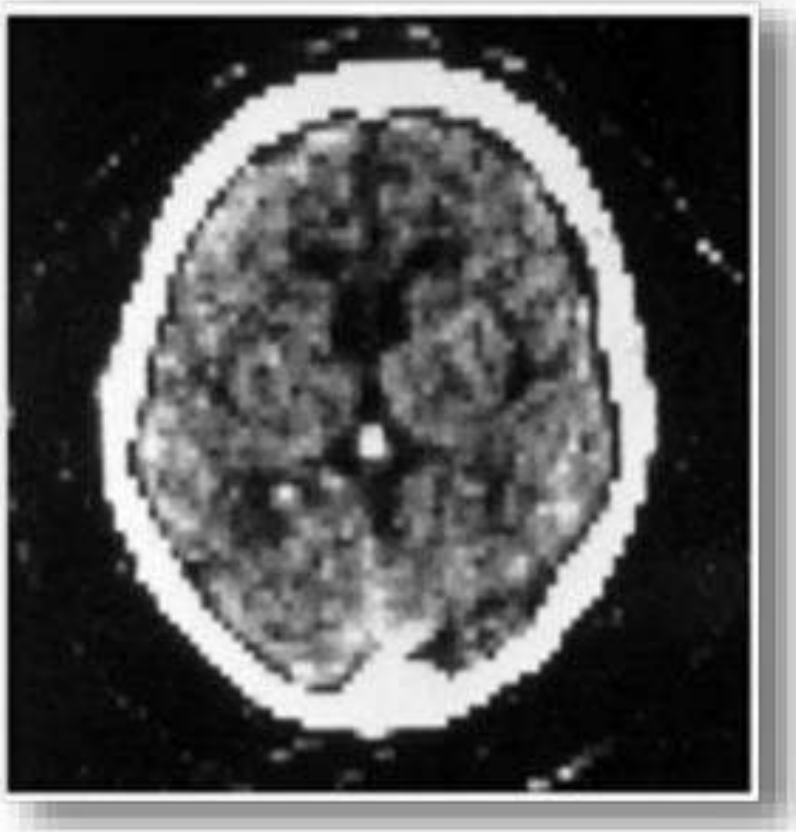
2. A CT scan is particularly useful when imaging **complex bone fractures, severely eroded joints, or bone tumors**. Fractures, ligamentous injuries, and dislocations can easily be recognized with a 0.2 mm resolution.

3. CT can also be used to image the **head** in order to locate injuries, tumors, clots leading to stroke, hemorrhage, and other conditions. CT scanning of the head is typically used to detect **infarction (stroke), tumors, calcifications, haemorrhage, and bone trauma**. Of the above, hypodense (dark) structures can indicate edema and infarction, hyperdense (bright) structures indicate calcifications and haemorrhage and bone trauma can be seen as disjunction in bone windows.

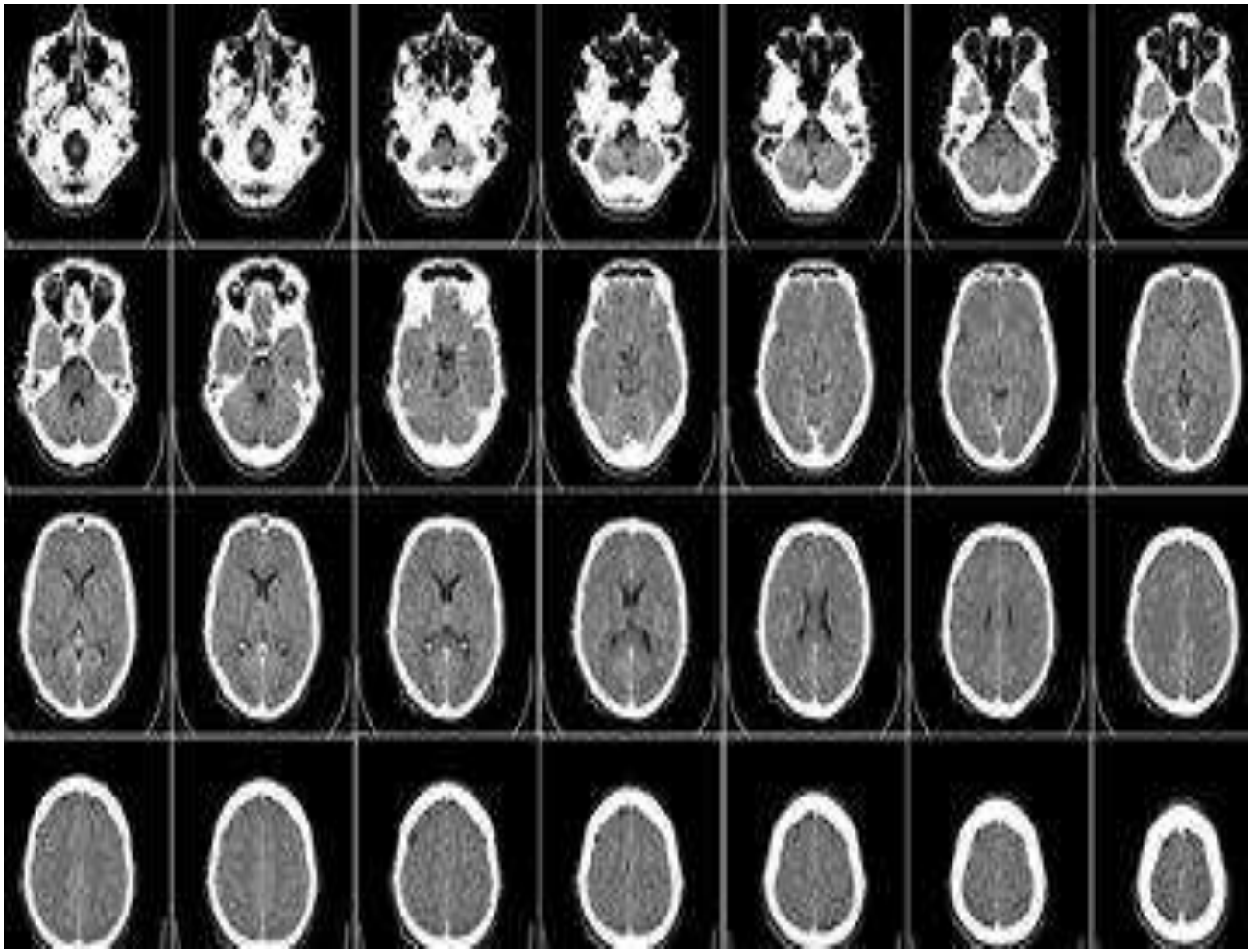
4. CT scans can be used to identify **disease or injury within various regions** of the body. For example, CT has become a useful screening tool for detecting possible tumors or lesions within the **abdomen**.

5. A CT scan of the **heart** may be ordered when various types of heart disease or abnormalities are suspected.

6. It can image the **lungs** in order to reveal the presence of tumors, pulmonary embolisms (blood clots), excess fluid, and other conditions such as emphysema or pneumonia.



This is the first CT image taken by first generation CT.



Computed tomography of human brain, from base of the skull to top.
Taken with intravenous contrast medium.

Advantages

CT scanning has several advantages over traditional two dimensional medical radiography.

1. **First,** CT eliminates the superimposition of images of structures outside the area of interest.

2. **Second**, CT scans have **greater image resolution**, enabling examination of finer details. CT can distinguish between tissues that differ in radiographic density by 1% or less.

3. **Third,** CT scanning enables **multi-planar** reformatted imaging: scan data can be visualized in the transverse (or axial), coronal, or sagittal plane, depending on the diagnostic task.

4. CT scan is **quick, non invasive, painless and less expensive** than MRI.

5. The improved resolution of CT has permitted the development of **new investigations**. For example, **CT angiography** avoids the invasive insertion of a catheter.

6. CT scanning can perform a **virtual colonoscopy** with greater accuracy and less discomfort for the patient than a traditional colonoscopy. Virtual colonography is far more accurate than a barium enema for detection of tumors and uses a lower radiation dose.

Disadvantages:

1. CT scans use x-rays, and all x-rays produce **ionizing radiation**. Ionizing radiation has the potential to cause biological effects in living tissue. The radiation used in CT scans can damage body cells, including DNA molecules, which can lead to **radiation-induced cancer.** Compared to the lowest dose x-ray techniques, CT scans can have 100 to 1,000 times higher dose than conventional X-rays.

2. A CT scan in a **pregnant woman poses risks to the baby** if imaging of the abdomen and pelvis is needed. Doctors prefer to use exams that do not use radiation, such as MRI or ultrasound.

3. In some patients, **contrast agents may cause allergic reactions**, or in rare cases, temporary **kidney failure**. The most common reaction from these agents is mild, including **nausea, vomiting, and an itching ra**sh.

MAGNETIC RESONANCE IMAGING (MRI)

1. The development of magnetic resonance imaging (MRI) for use in medical investigation has provided a huge forward leap in the field of diagnosis, particularly with avoidance of exposure to potentially dangerous ionizing radiation. MRI is a **non-invasive imaging technology that produces three dimensional (3D) detailed anatomical images.** It is often used for disease detection, diagnosis, and treatment monitoring

2. The nuclear magnetic resonance (NMR) phenomenon was first described experimentally by both **Bloch and Purcell in 1946**, for which they were both awarded the **Nobel Prize for Physics in 1952**. The first clinical magnetic resonance images were produced in Nottingham and Aberdeen in **1980,** and magnetic resonance imaging (MRI) is now a widely available, powerful clinical tool.

PRINCIPLE:

1. The human body is mostly water. Water molecules (H_2O) contain hydrogen nuclei (protons), which become aligned in a magnetic field. The basis of MRI is the directional magnetic field, or ***moment*****,** associated with charged particles in motion. Because nuclei are charged particles, this precession produces a small magnetic moment.
2. **When a human body is placed in a large magnetic field (BO), many of the free hydrogen nuclei align themselves with the direction of the magnetic field.** To obtain an MR image of an object, the object is placed in a uniform magnetic field of between 0.5 to 1.5 Tesla. As a result, the object's hydrogen nuclei align with the magnetic field and create a **net magnetic moment, M**, parallel to **B0**

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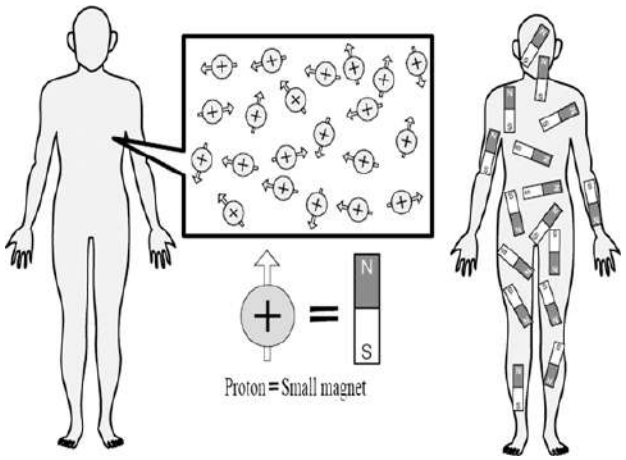
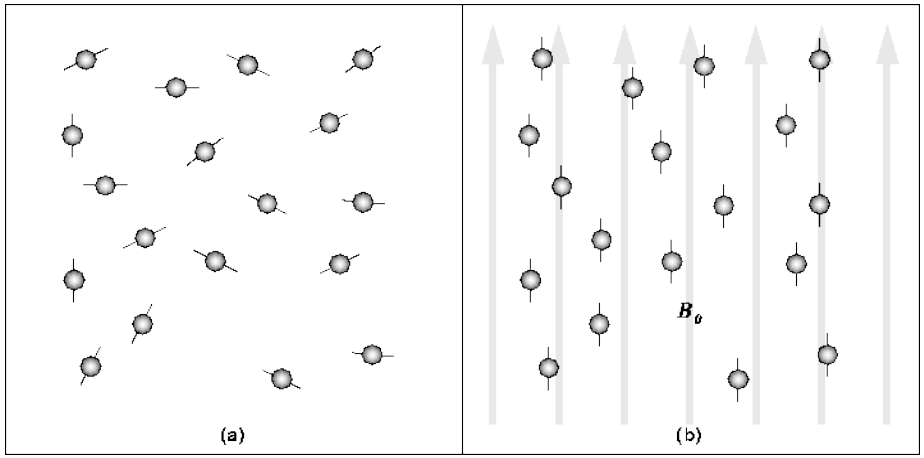
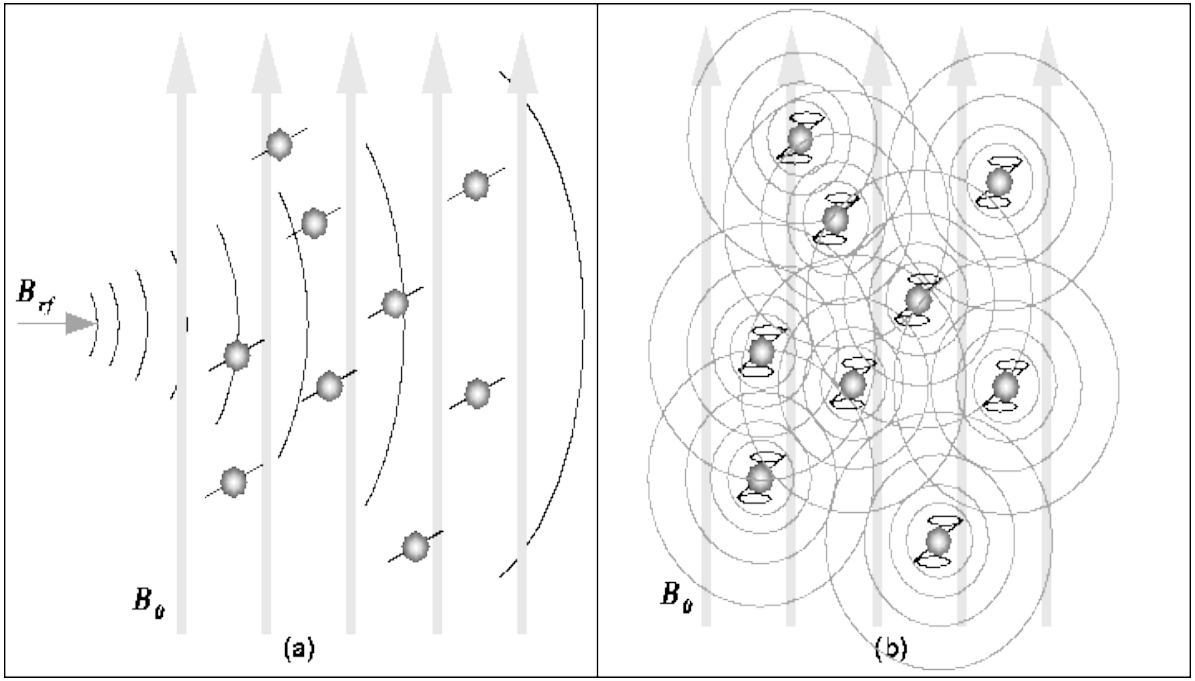




(a). in the absence of a strong magnetic field, hydrogen nuclei are randomly aligned. (b)When the strong magnetic field, is applied, the hydrogen nuclei 'precess' about the direction of the field.

Next, a **radio-frequency (RF) pulse, Brf** , is applied perpendicular to Bo. This pulse, causes **M to tilt away from Bo** as in the following Figure.

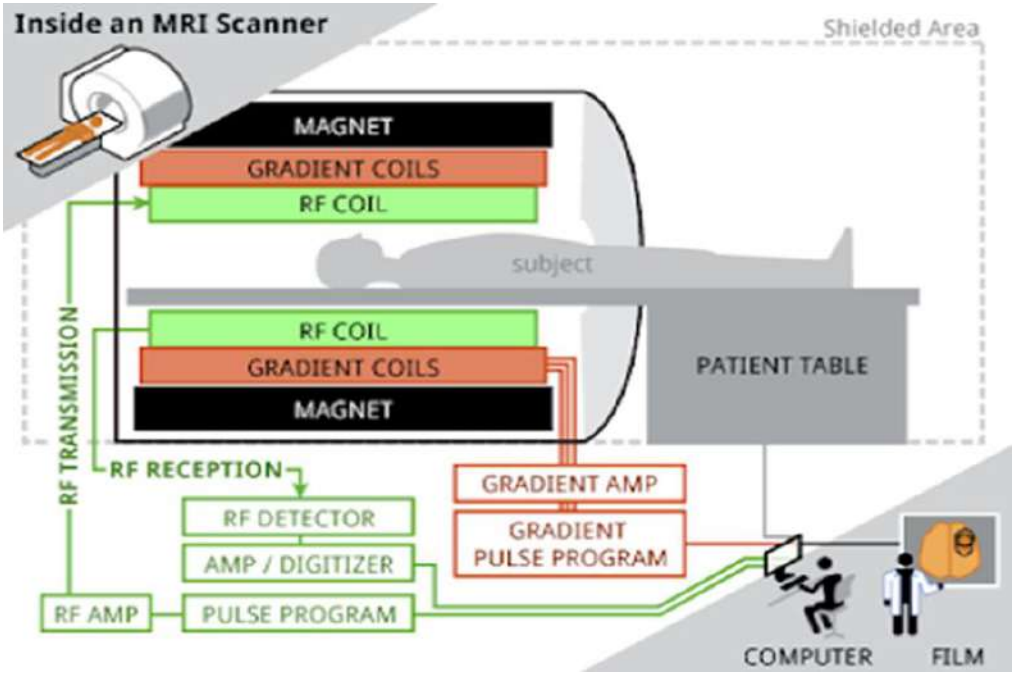


(a) The RF pulse, Brf, causes the net magnetic moment of the nuclei, M , to tilt away from Bo.
(b) When the RF pulse stops, the nuclei return to equilibrium such that M is again parallel to Bo. During realignment, the nuclei lose energy and a measurable RF signal.

3. Once the RF signal is removed, the nuclei realign themselves such that their net magnetic moment, M, is again parallel with Bo . This return to equilibrium is referred to as ***relaxation*****.** During relaxation, the nuclei lose energy by emitting their own RF signal. This signal is referred to as the ***free-induction decay* (FID) response** signal. The FID response signal is measured by a **conductive field coil** placed around the object being imaged. This measurement is processed or *reconstructed* to obtain **3D grey-scale MR images**.

4. The **time it takes for the protons to realign with the magnetic field**, as well as the **amount of energy released**, changes depending on the environment and the chemical nature of the molecules. Physicians are able to tell the difference between various types of tissues based on these magnetic properties.

5. To obtain an MRI image, a patient is placed inside a large magnet and must remain very still during the imaging process in order not to blur the image. Contrast agents (often containing the element **Gadolinium**) may be given to a patient intravenously before or during the MRI to increase the speed at which protons realign with the magnetic field. The faster the protons realign, the brighter the image.



Precaution:

1. The MRI unit is an extremely strong magnet, so patients should **avoid wearing jewelry and other accessories** because they could interfere with the machine's magnetic field. Some items are **not** allowed to enter the exam room-Jewelry, watches, credit cards, and hearing aids (all can be damaged), Pins, hairpins, metal zippers, and similar metallic items (can alter images taken), Removable dental work, Pens, pocketknives, eyeglasses.

2. Most of the time, MRI is safe for patients who have implants made of metal. However, the technologist should know if the patient has **medical/electronic devices in his/her body including:** artificial heart valves, implanted drug infusion ports, implanted electronic devices, artificial limbs or metallic joint prostheses, implanted nerve stimulators, metal screws, plates, or surgical staples etc. If there is any doubt about the presence of metal in the patient's body, an x-ray should be taken.

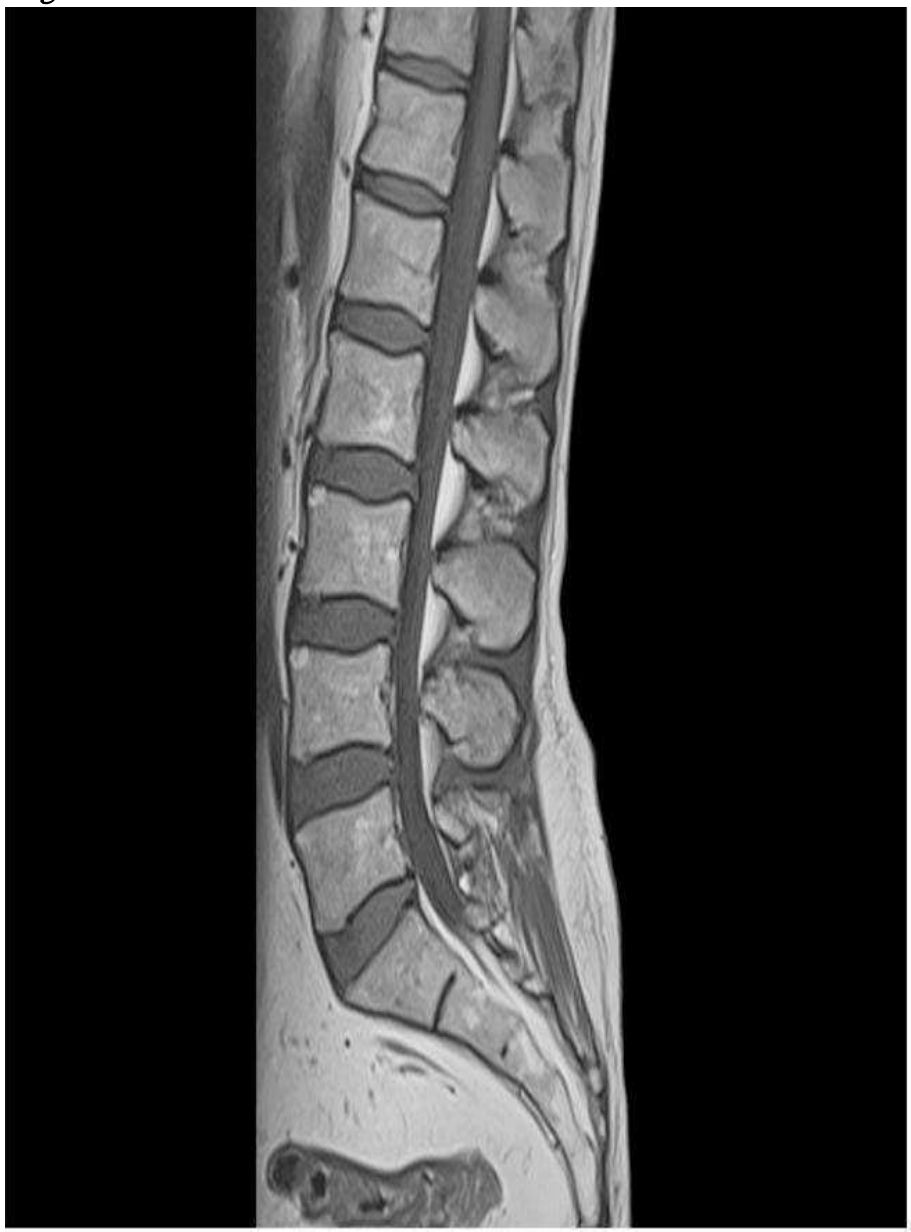
USES of MRI:

1. Magnetic resonance imaging can produce highly sophisticated and highly detailed images of the human body. Generally speaking, MRI scanning is **excellent for visualising soft tissue, the non-bony parts of the body.** Without contrast agent an MRI can show-the **shape, size, appearance, and location of organs, bones, and joints, the presence of abnormal growths, signs of inflammation or infection**. When contrast agent is used MRI can show-**size and location of benign or malignant growths, enlarged lymph nodes, changes in blood flow and extracellular volume.**

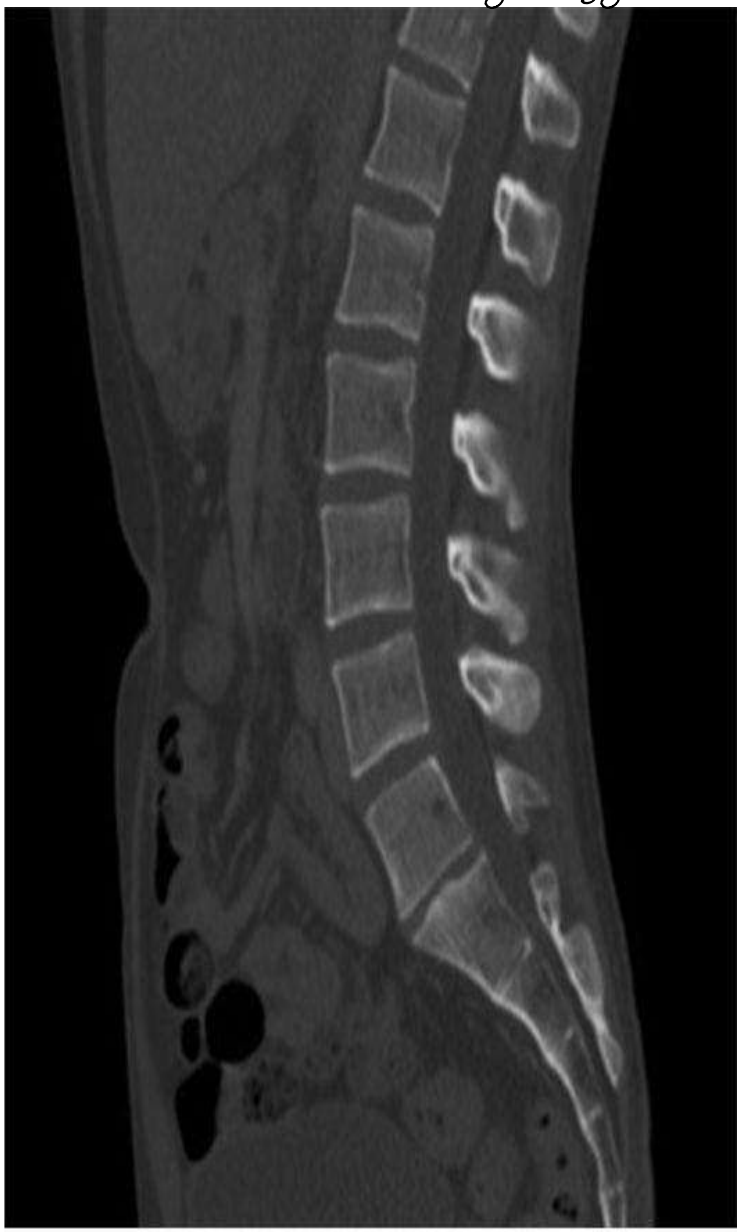
2. In the **brain,** MRI can differentiate between white matter and grey matter and can also be used to diagnose aneurysms and tumors. One kind of specialized MRI is **functional Magnetic Resonance Imaging** (fMRI.) This is used to observe brain structures and determine which areas of the brain "activate" (consume more oxygen) during various cognitive tasks.

3. Magnetic resonance imaging helps identify **tumors** by magnifying the differences in water content and blood flow between tissues. Contrast material highlights this concentration of blood vessels to help pinpoint **malignant growths**.

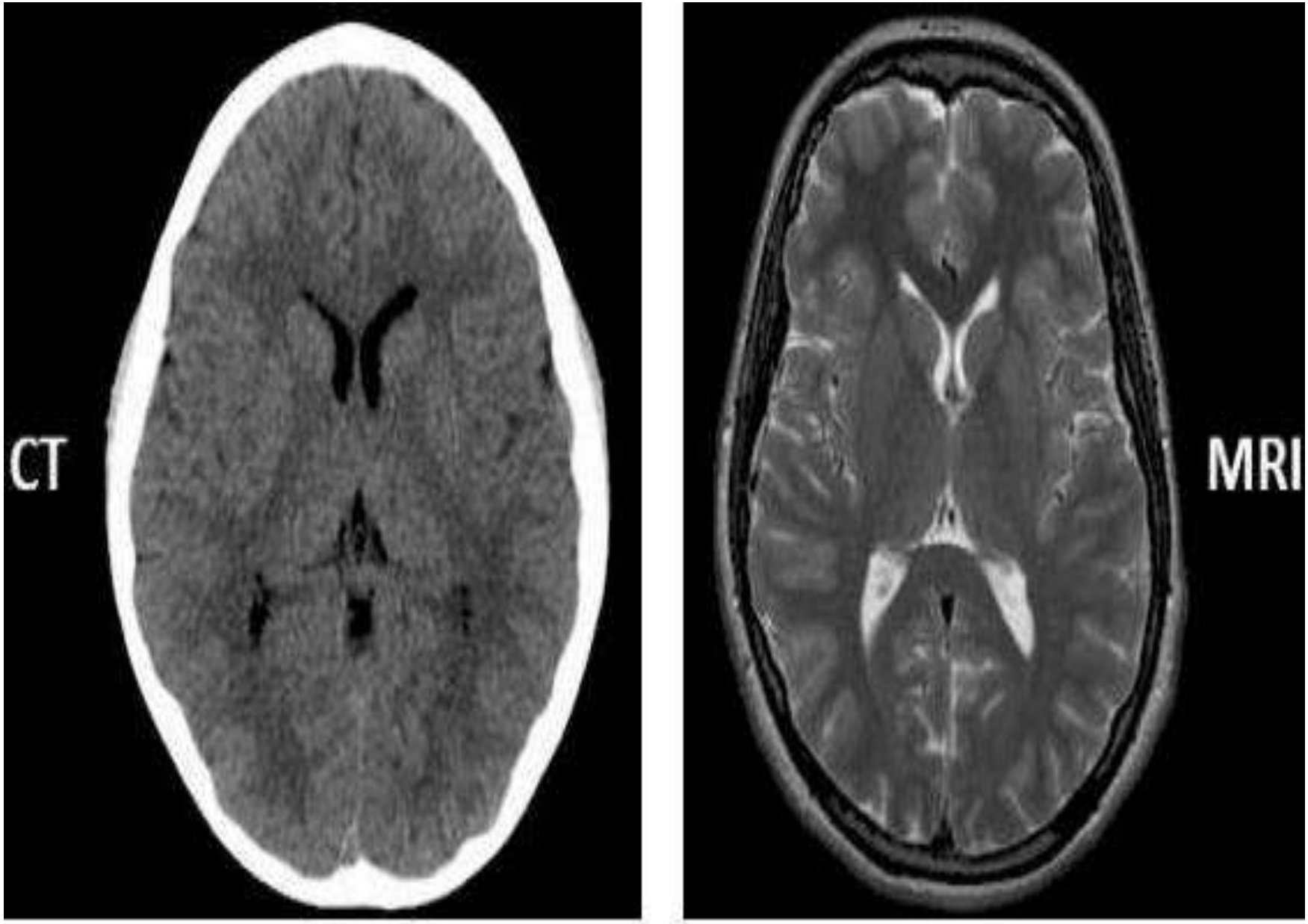
4. It can provide information about how the blood moves through certain organs and blood vessels, allowing problems with **blood circulation, such as blockages**, to be identified.



MRI Scan Image



CT Scan Image


CT
MRI
a
b

ADVANTAGES:

1. MRI gives **extremely clear, detailed images of soft-tissue** structures that other imaging techniques cannot achieve.
2. An MRI scanner can be used to take images of **any part of the body** (e.g., head, joints, abdomen, legs, etc.), in any imaging direction. It is particularly useful for showing soft tissue structures.
3. It **does not cause any radiation exposure** to the patient. So they can be safely used in people who might be particularly vulnerable to the effects of radiation, such as pregnant women and babies
4. MRI provides **better soft tissue c**ontrast than CT and can differentiate better between fat, water, muscle, and other soft tissue than CT (CT is usually better at imaging bones).
5. MRI is **non-invasive**.
6. MRI contrasting agent is **less likely to produce an allergic reaction** that may occur when iodine-based substances are used for x-rays and CT scans.
7. Unlike techniques that examine small parts of the body (i.e. ultrasound or mammography) MRI exams **can cover large portions** of the body
8. MRI can determine if a **cancer has spread**, and help determine the best treatment.

DISADVANTAGES:

1. MRI is **time consuming** – averaging approximately 35-45 minutes to complete. This limits their use in trauma and emergency situations, where CT scanning is often preferred.
2. They are also by far **the most expensive** of all the imaging modalities available.
3. MRI safety has recently become a major focus in hospital and outpatient environments due to the **potential attraction to ferromagnetic objects** and devices. Some medical and implantable devices are considered contraindications for MRI evaluation – such as cardiac pacemakers, heart monitors, defibrillators and other battery-operated devices.
4. **Loud noise** commonly referred to as clicking and beeping, as well as sound intensity up to 120 decibels in certain MR scanners, may require special ear protection.
5. Nerve Stimulation—a twitching sensation sometimes results from the rapidly switched fields in the MRI.
6. Contrast agents—patients with severe renal failure who require dialysis may risk a rare but serious illness called **nephrogenic systemic fibrosis** that may be linked to the use of certain **gadolinium-containing agents**.
7. it is recommended that MRI scans be avoided as a precaution especially in the first trimester of pregnancy when the fetus' organs are being formed and contrast agents, if used, could enter the fetal bloodstream.
8. **Claustrophobi**a—people with even mild claustrophobia may find it difficult to tolerate long scan-times inside the machine.
9. The radiofrequency energy used during the MRI scan could lead to **heating of the body**.. It may cause heating of the implanted medical device and the surrounding tissue, which could lead to burns.
10. To produce good quality images, patients must generally **remain very still** throughout the entire MRI procedure. Infants, small children, and other patients who are unable to lay still may need to be **sedated or anesthetized** for the procedure.

Advantages & Disadvantages

Advantages

1. Excellent soft tissue contrast resolution
2. Ability to obtain direct transverse, sagittal, coronal and oblique images
3. Does not use ionizing radiation
4. Does not produce bone/air artefacts

Disadvantages

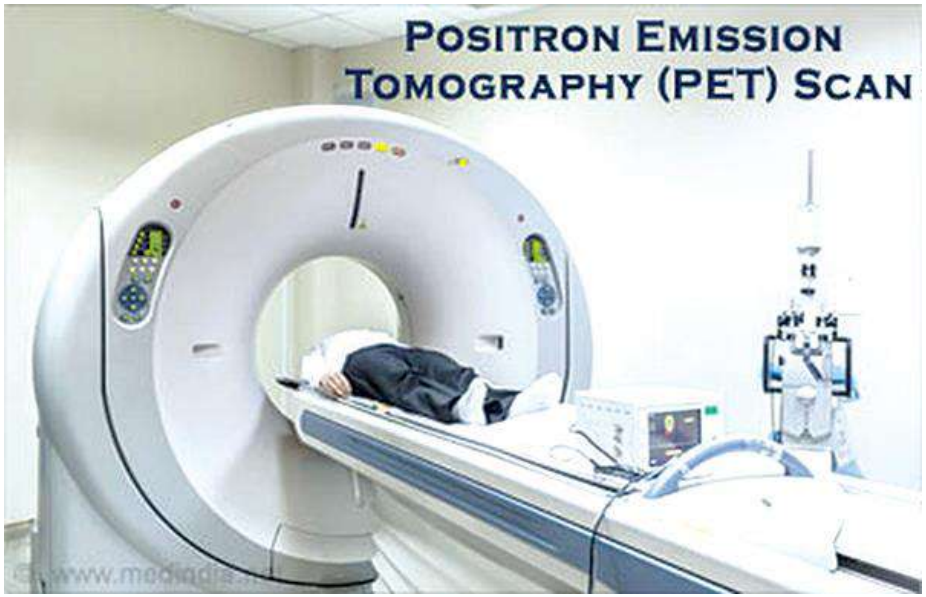
1. Longer imaging time
2. Complexity of the equipment and scan acquisition
3. High Cost
4. Inability to demonstrate calcification or cortical bone details
5. Bullet shrapnel and metallic fragments may move and become projectile (Contraindicated for patients with Cardiac pacemakers, dental implants, heart valve prosthesis and aneurysm clips)

	CT Scans	MRI
Principle	Uses multiple X-rays, taken at different angles to produce cross-sectional images	Uses powerful magnetic fields and radiofrequency pulses to produce detailed images
Radiation	Minimal	None
Uses	Excellent for observing bone and very good for soft tissue, especially with the use of intravenous contrast dye	Excellent for detecting very slight differences in soft tissue
Cost	Usually less expensive than MRI	Often more expensive than CT scans
Time taken	Very quick, taking only about 5 min, depending on the area being scanned	Depends on the part of the body being examined and can range from 15 min–2 h
Application	Produces a general image of an area such as internal organs, fractures, or head trauma	Produces more detailed images of soft tissue, ligaments, and organs
Benefits	Faster and can provide images of tissue, organs, and skeletal structure	Produces more detailed images
Risks	• Harmful for unborn babies • A very small dose of radiation • A potential reaction to the use of dyes	• Possible reactions to metals due to magnets (e.g., artificial joints, eye implants, intrauterine devices, pacemakers) • Loud noises from the machine can cause hearing issues • Increase in body temperature during long MRIs • Claustrophobia

What is the difference between an MRI and a CT Scan?

MRI Scan	CT Scan
Designed for looking at soft tissues, tendons, ligaments, spinal cords, and the brain	Better suited for imaging injuries from trauma, staging cancer, and diagnosing conditions in blood vessels
Bony structures less detailed compared to CT Scan	Bony structures are more clear and detailed
Powered by strong magnetic fields	Powered by low doses of radiation
Being inside an MRI is like being inside a large tube. This causes some people to experience claustrophobia or anxiety due to the length of the exam.	Most people are comfortable with a CT scan, as the machine is donut-shaped and not fully enclosed.
Lasts at least 30 minutes	Lasts 5 - 10 minutes
MRI machines make loud noises, so you will receive headphones or earplugs	CT machines make soft, whirring noises and have flashing lights
You may be asked to hold your breath from time to time	Holding breath is not required as much
Patients with metal or certain medical implants are not able to undergo MRIs due to the magnetic field pulses	CT scan can be performed with no risk to medical implants or metal

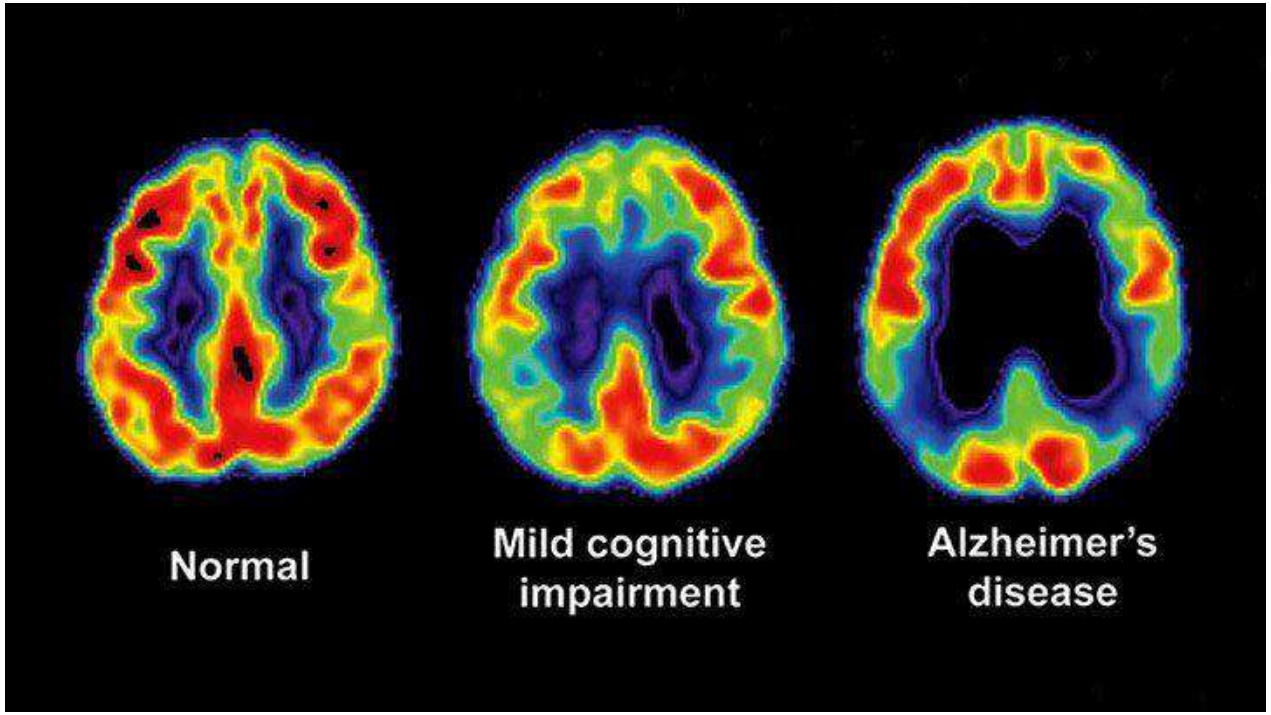
PET SCAN



1.Positron emission tomography (PET) uses small amounts of **radioactive materials** called **radiotracers** or radiopharmaceuticals, a special camera and a computer to evaluate organ and tissue functions.

2. The most common radiotracer is **F-18 fluorodeoxyglucose (FDG),** a molecule similar to glucose. They accumulate in tumors or regions of inflammation. Cancer cells are more metabolically active and may absorb glucose at a higher rate.

3. A patient usually receives the radiotracer in an injection, or by swallowing or inhalation, It accumulates in the area under examination. A special camera detects **gamma ray emissions from the radiotracer**. The camera and a computer produce pictures.



USE:

1.A PET scan measures important body functions, such as metabolism. It assesses **tissue metabolism and viability.**

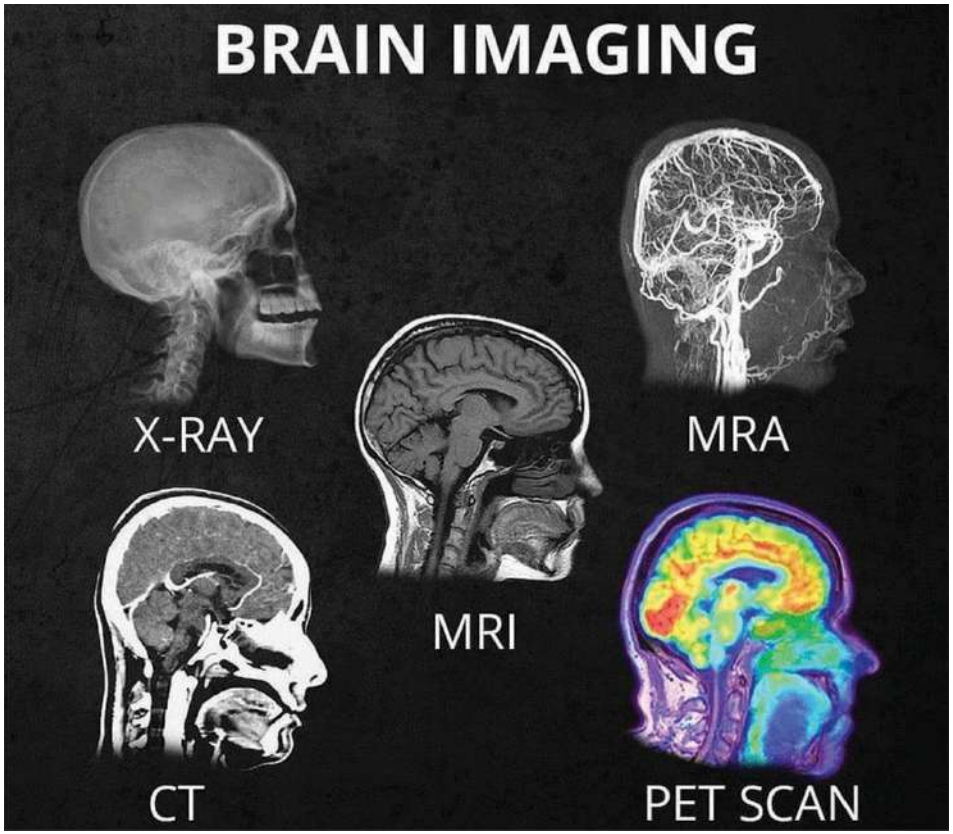
2.**Detect cancer** and make a diagnosis. Because of this high level of chemical activity, cancer cells often show up as bright spots on PET scans.

3.Determine whether a **cancer has spread** in the body.

4.Determine if a **cancer has returned** after treatment.

5.Determine the effects of a heart attack (myocardial infarction) on areas of the heart.

7.Evaluate brain abnormalities. Glucose is the main fuel of the brain. By detecting radioactive glucose, the PET scan can show which areas of the brain are using glucose at the highest rates. PET scans are used to help diagnose and manage many CNS disorders, including: **Alzheimer's disease, depression, epilepsy, head trauma, Parkinson's disease** etc.



ADVANTAGE:

1. Nuclear medicine is **non-invasive.**
2. Except for intravenous injections, it is **usually painless.**
3. Since it studies metabolic functions of a patient, PET imaging can be used as an **alternative to biopsy** and also other exploratory surgeries conducted to determine how far a disease has spread.
4. It can **differentiate between non-cancerous and cancerous tumours.** PET scans are the most precise medical tools to help minimize the number of unnecessary surgeries done because of wrong staging data and diagnosis in cancer.

DISADVANTAGE:

1. Nuclear medicine has a **low radiation risk,** particularly for pregnant or lactating women.
2. **Allergic reactions** to radiotracers are rare and usually mild.
3. Slow-growing, less active tumours may not absorb much tracer. **Small tumours** (less than 7mm) may not be detectable.
4. Since it is a new procedure, it is quite **expensive** compared to other forms of medical imaging. They also require a cyclotron which is an expensive machine used to create radioisotopes.

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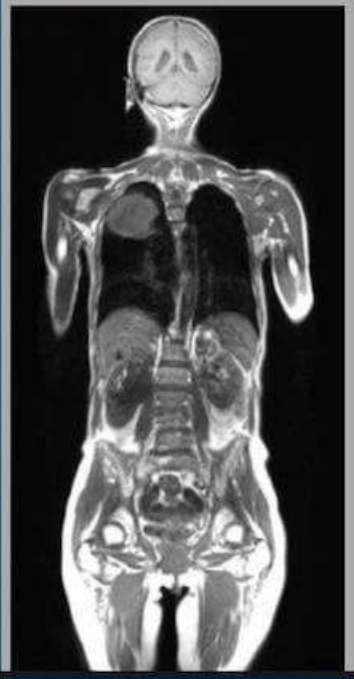
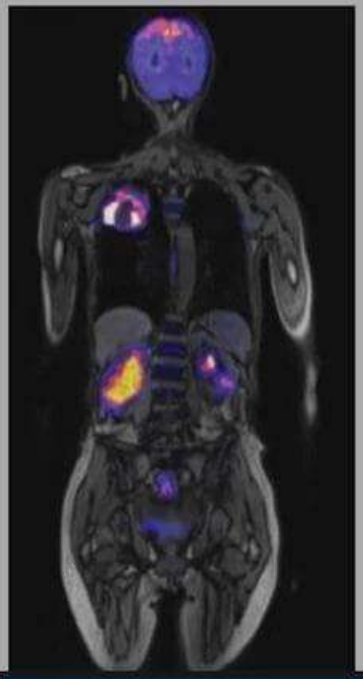
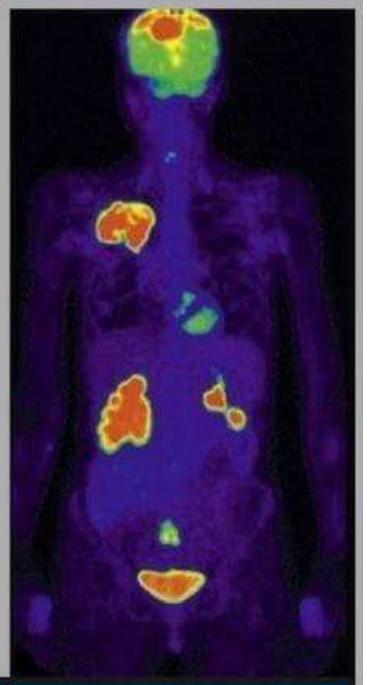
	MRI	CT	PET
			
Tech	Magnets + radio waves	X-rays (3D)	Radiation traces with CT Scan
Detect	Soft Tissue, Tendon, Ligament Brain	Bony structure and blood vessels	Cancer Heart Brain
Procedure Time	30 min	5 - 10 Min	60 - 90 Min

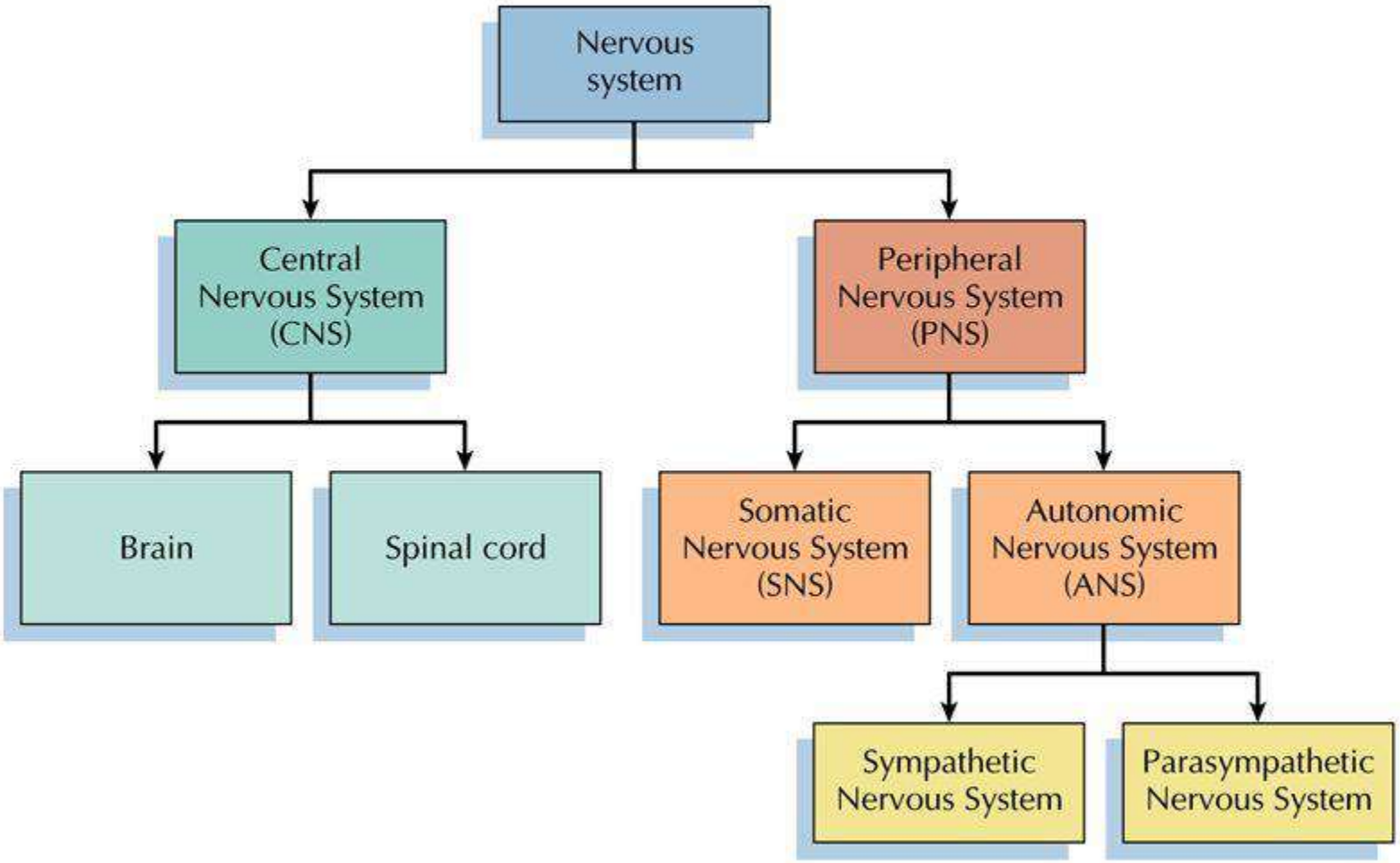
Questions:

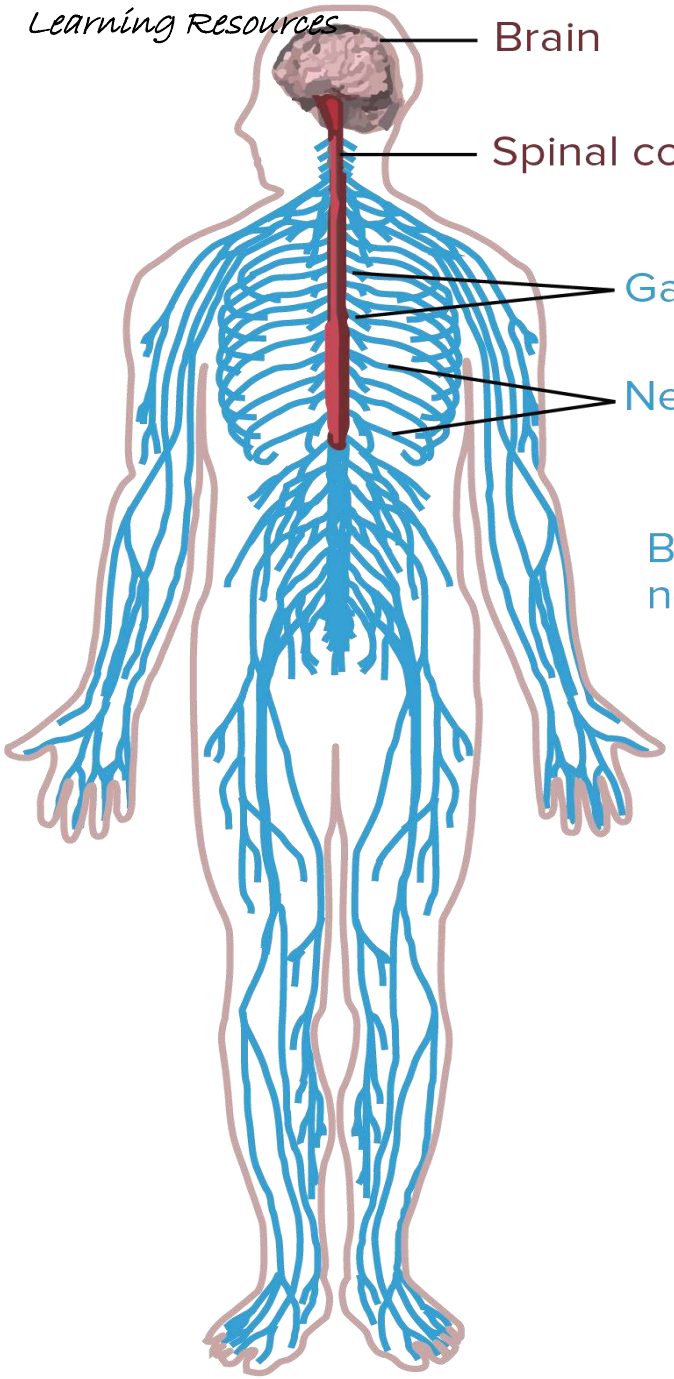
1. Discuss the principle and uses of MRI.
2. Discuss the principle and uses of CT scan.
3. Discuss the principle and uses of PET scan.
4. State any two advantages and disadvantages of each of MRI, CT scan and PET scan.

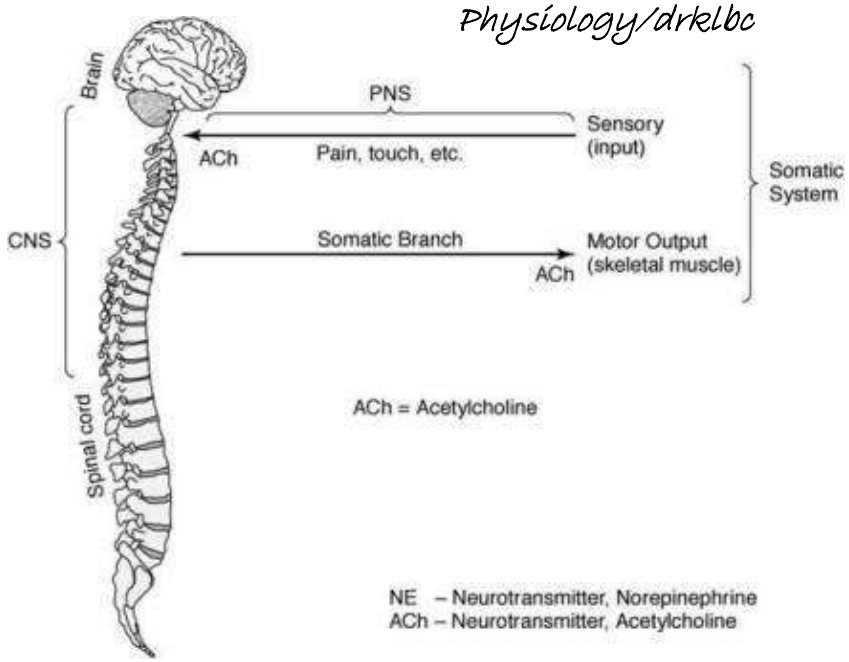
STRUCTURAL ORGANIZATION OF BRAIN AND SPINAL CORD

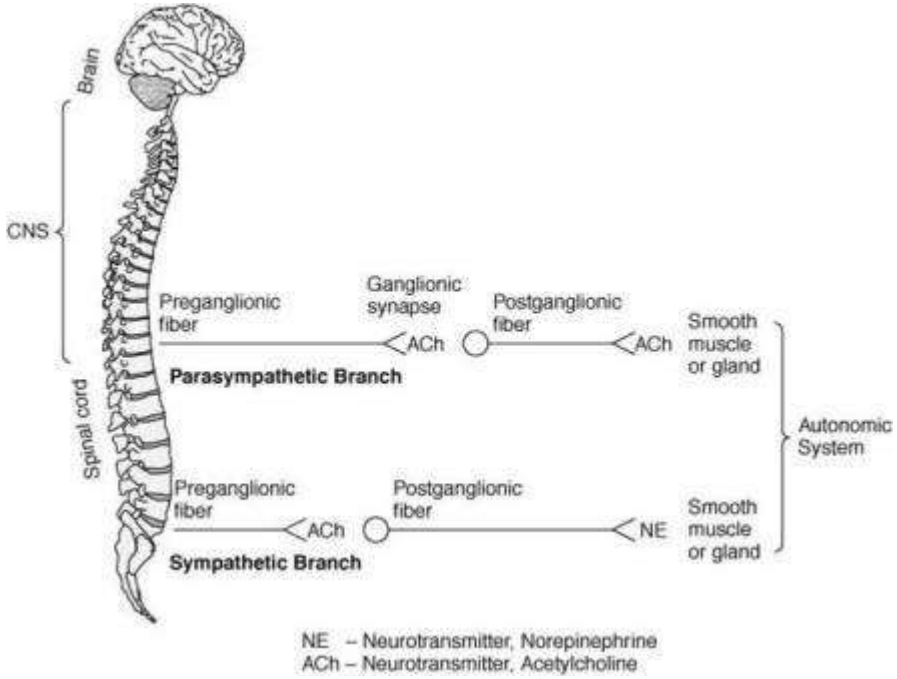
CC4 THEORY

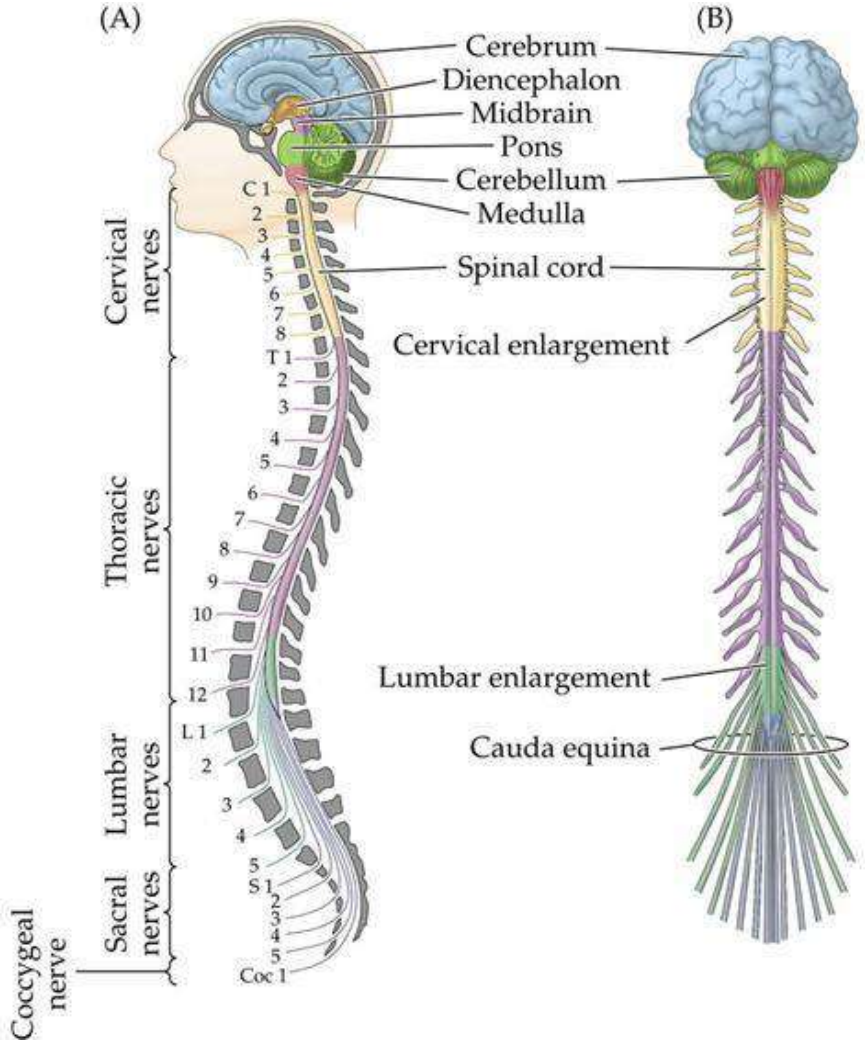
The Nervous System



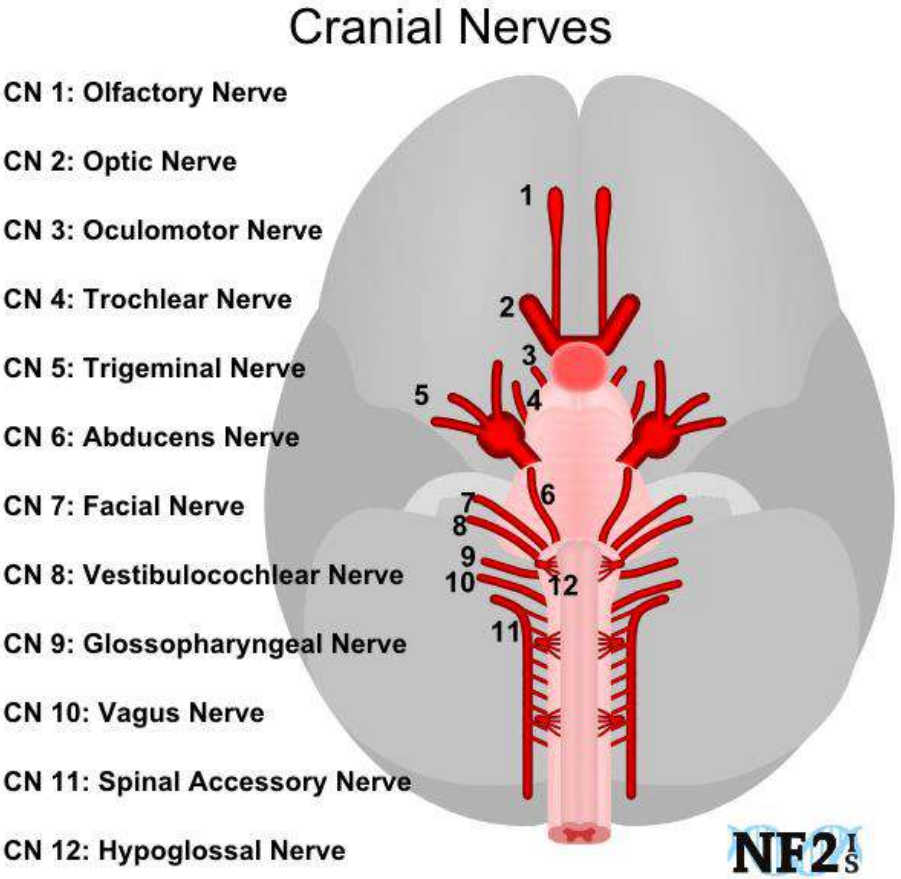

Brain
Spinal cord
Central nervous system
Ganglia
Nerves
Blue = peripheral nervous system


Brain
PNS
Sensory (input)
ACh
Pain, touch, etc.
Somatic System
CNS
Somatic Branch
Motor Output (skeletal muscle)
ACh
Spinal cord
ACh = Acetylcholine
NE – Neurotransmitter, Norepinephrine
ACh – Neurotransmitter, Acetylcholine


Brain
CNS
Preganglionic fiber
Ganglionic synapse
Postganglionic fiber
ACh
ACh
Smooth muscle or gland
Parasympathetic Branch
Spinal cord
Autonomic System
Preganglionic fiber
Postganglionic fiber
ACh
NE
Smooth muscle or gland
Sympathetic Branch
NE – Neurotransmitter, Norepinephrine
ACh – Neurotransmitter, Acetylcholine



SPINAL NERVES

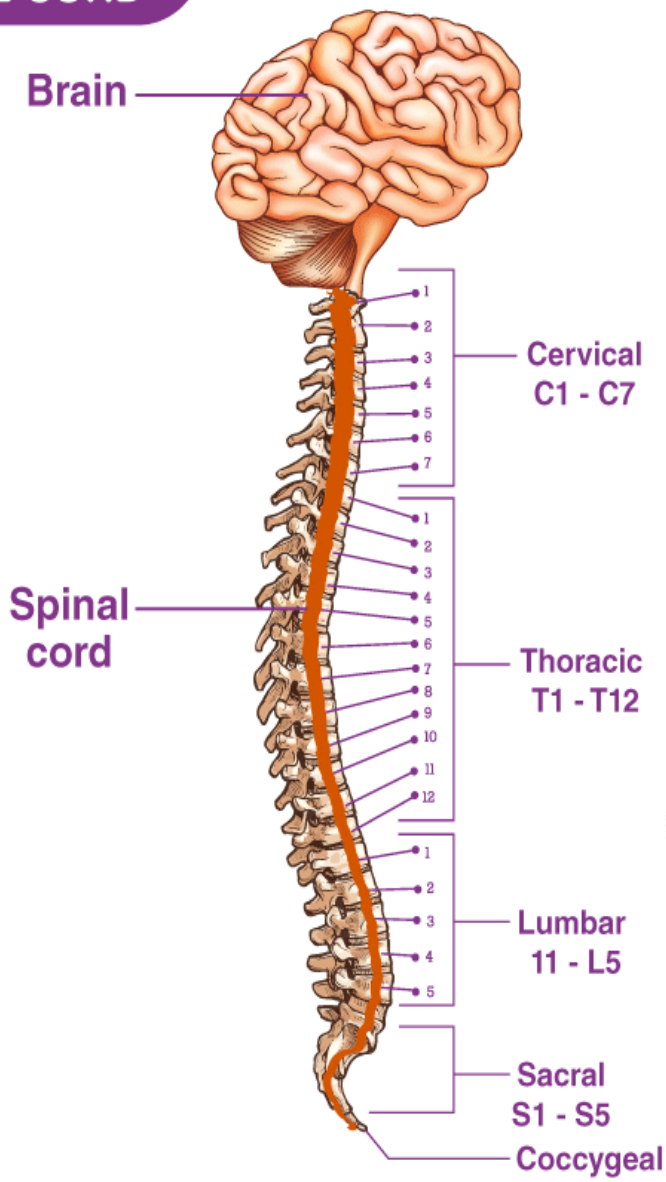


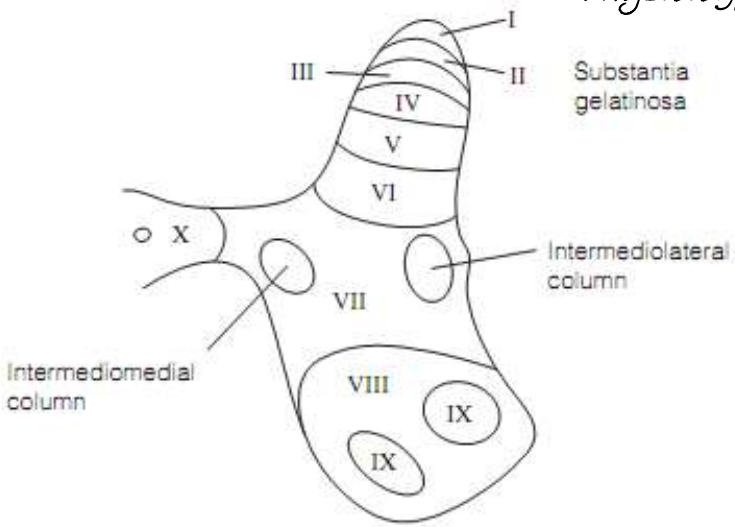
Cranial Nerves: There are twelve pairs of cranial nerves arising from the brain. These nerves are named after the parts they come from and the functions they perform.

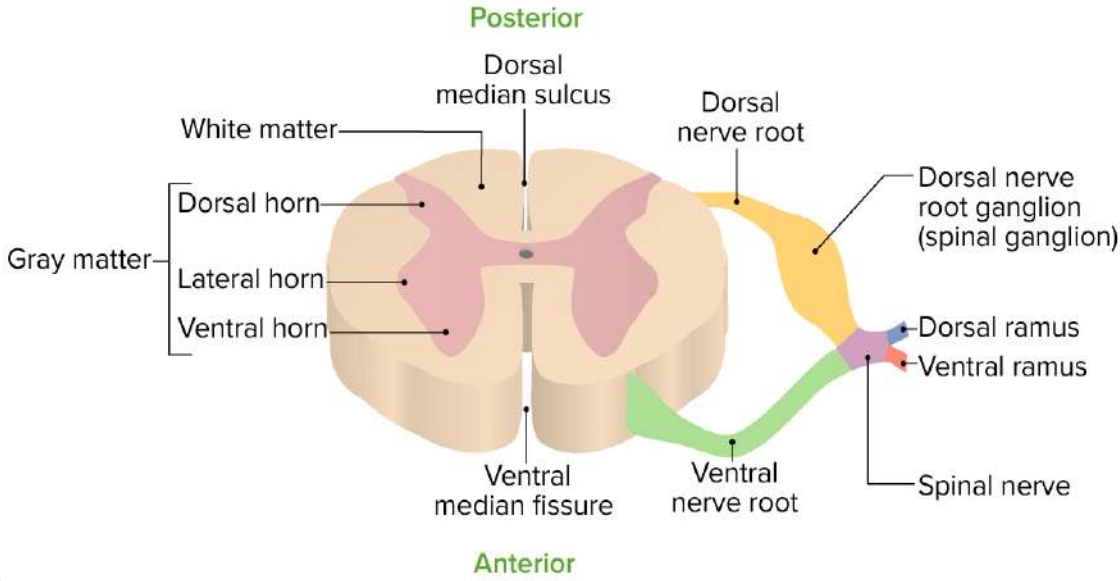
Cranial Nerves - Nature and functions

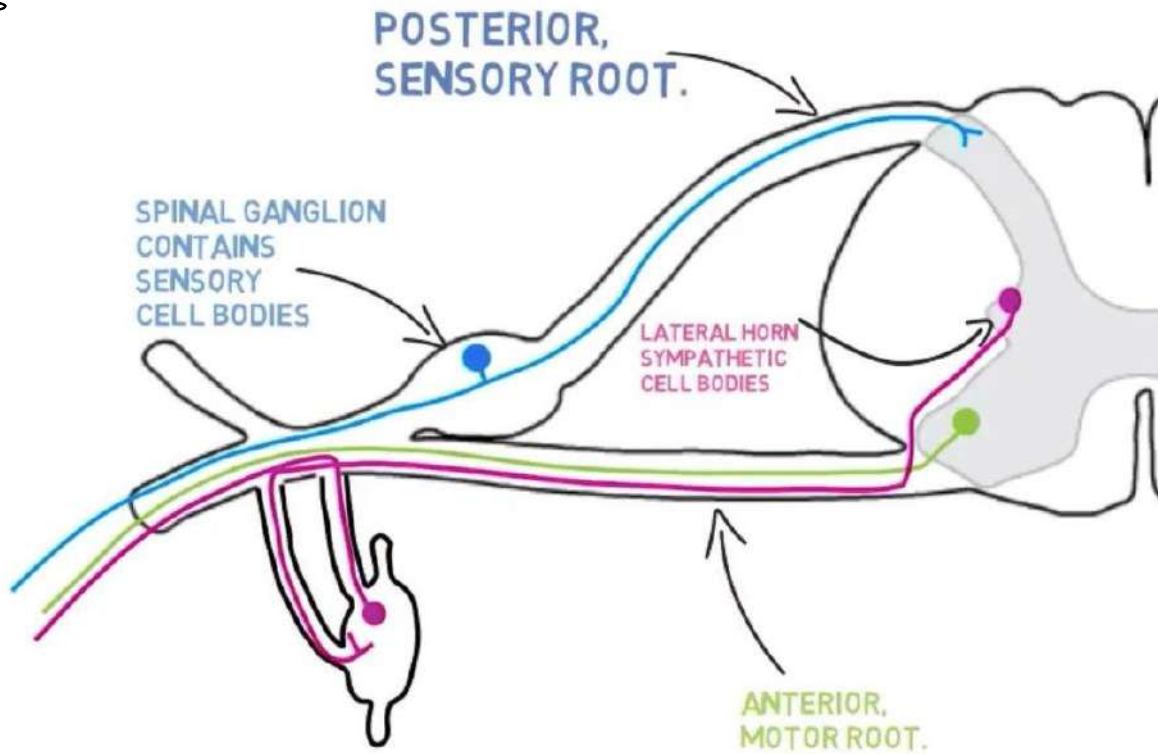
Sr. No.	Name	Origin	Distribution	Nature	Functions
I	Olfactory	Olfactory lobes	Olfactory epithelium in nasal cavity	Sensory	Smell
II	Optic	Optic lobe on midbrain	Retina of eye	Sensory	Light
III	Occulomotor	Floor of midbrain	Eye, 4 muscles of eyeball	Motor	Movements of eyeball
IV	Trochlear/Pathetic	Floor of midbrain	Eye (superior oblique muscles of eyeball)	Motor	Rotation of eyeball
V	Trigeminal (Dentist nerve) (a) ophthalmic (b) maxillary (c) mandibular	Anterior medulla oblongata	Head, face, jaws, teeth	Mixed Sensory sensory mixed	Sensation of touch, taste, jaw movement tooth.
VI	Abducens	Side of medulla	Lateral rectus muscle of eyeball	Motor	Movement of eye
VII	Facial	Side of Pons varolii	Muscles of face, neck, taste buds or salivary glands.	Mixed	Facial expression, movement of neck, tongue, saliva secretion
VIII	Auditory vestibulo cochlear	Side of medulla	Organ of Corti in cochlea, Semicircular canals	Sensory	Hearing, Equilibrium
IX	Glossopharyngeal	Lateral side of medulla	Muscles of mucosa of pharynx, tongue, parotid salivary glands	Mixed	Taste and pharyngeal contraction, saliva secretion.
X	Vagus	Lateral side of medulla	Larynx, trachea, pharynx, Oesophagus, heart, stomach, lungs, intestine	Mixed	Vocal cords, lungs, respiratory reflexes, peristaltic movements, speech, swallowing, secretion of gastric glands, inhibition of heart beat
XI	Spinal accessory	Lateral and posterior side of medulla	Muscles of pharynx, larynx, neck, shoulder	Motor	Muscles of pharynx, larynx, neck, shoulder movements
XII	Hypoglossal	Ventral side of medulla	Muscles of tongue	Motor	Movements of tongue

SPINAL CORD


Brain
Spinal cord
Cervical C1 - C7
Thoracic T1 - T12
Lumbar 11 - L5
Sacral S1 - S5
Coccygeal


I
II
III
IV
V
VI
VII
VIII
IX
IX
X
Substantia gelatinosa
Intermediolateral column
Intermediomedial column

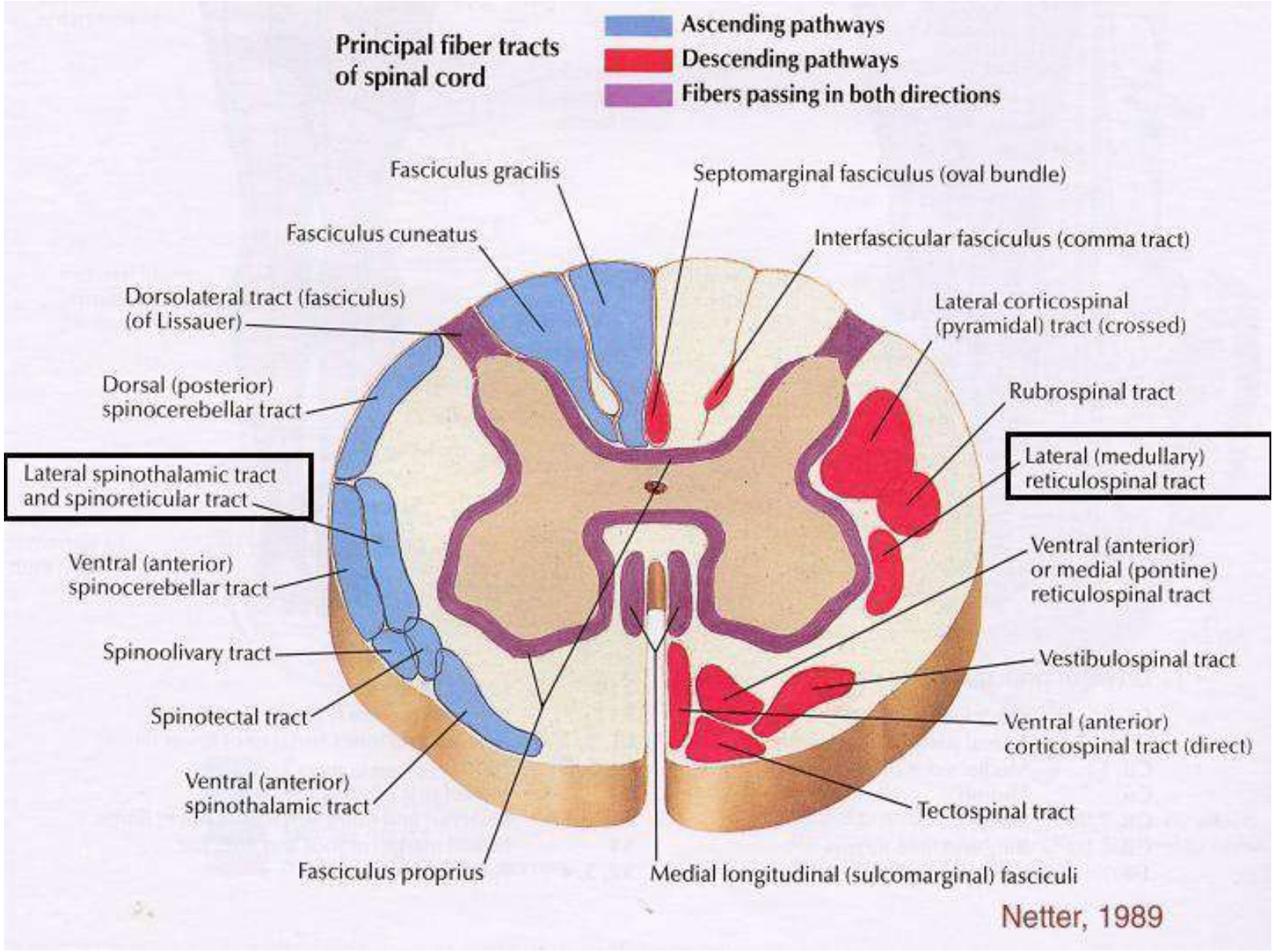

Posterior
Dorsal median sulcus
White matter
Dorsal nerve root
Dorsal nerve root ganglion (spinal ganglion)
Dorsal horn
Gray matter
Lateral horn
Ventral horn
Dorsal ramus
Ventral ramus
Spinal nerve
Ventral median fissure
Ventral nerve root
Anterior



Bell-Magendie law

- The principle that in the spinal cord the dorsal roots are sensory and the ventral roots are motor is known as the **Bell-Magendie law**

Law discovered by **Sir Charles Bell** (an anatomist) and **Sir Francois Magendie** (a Pathophysiology and Physiology professor)



Ascending and Descending tracts of spinal cord

Reflex

- Reflex is involuntary reaction to a stimulus. It is an automatic response.

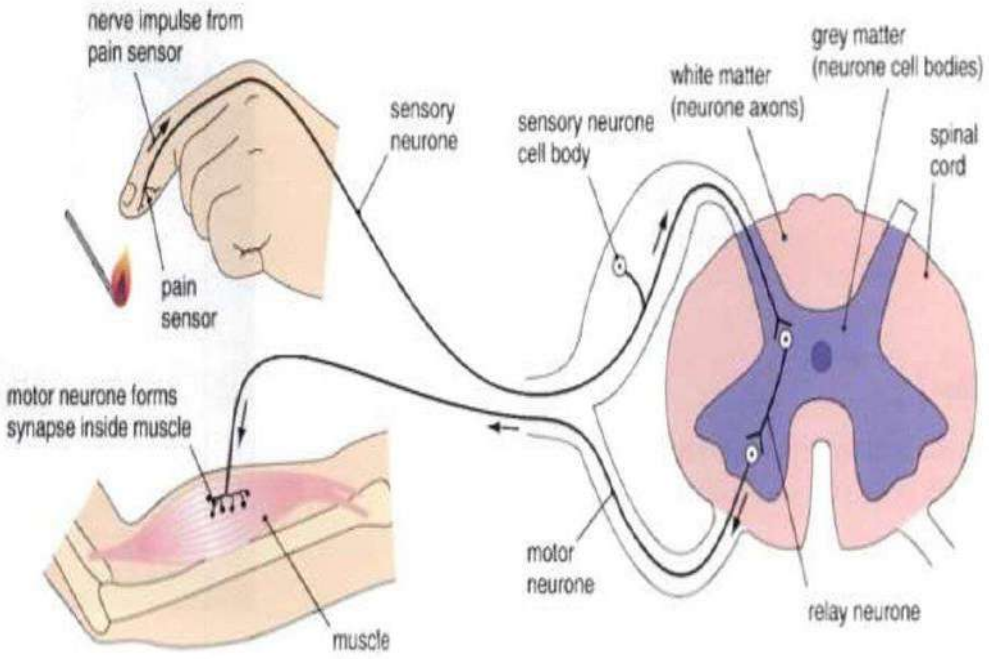
Stimulus	Reflex
A delicious food	salivation
Spoiled food	nausea
An object reaching to your eye	blinking
When light becomes brighter	Pupils get smaller
Knee is hit by a hard substance	Knee jerk reflex

Reflex is an involuntary and sudden response to stimuli.

The reflex arc is a neural pathway that mediates or controls the reflex reaction of the body.

Reflex arc

- **Reflex arc** is when nerve signal move through neural pathway
- Components of a reflex arc are:
- 1. **Receptor** which detects stimulus
- 2. **Sensory neuron** carries information to the spinal cord
- 3. **Motor neuron** carries information to an effector
- 4. **Interneuron**, which is located in the spinal cord. It connects sensory neuron to motor neuron
- 5. **Effector**, which is a muscle or other organ that produce the reflex action



CLASSIFICATION OF REFLEX ACTION

1) Depending upon Effector response:

a) **Autonomic reflexes**: control actions of internal organs (glands, heart, visceral smooth muscle etc.)
b) **Somatic reflexes**: control skeletal muscles. Eg., stretch reflex and other superficial reflexes.

2) Depending upon number of Synapses:

a) **Asynaptic**- no synapse. E.g., axon reflex.
b) **Monosynaptic** - reflex arc consists of only 2 neurons, 1 synapse, Eg., stretch reflex
c) Polysynaptic – 1 sensory, 1 motor neuron, interconnected by 2 or more interneurons, and more than 2 synapses. Eg., withdrawal reflex, crossed extensor reflex.

3) Depending upon the Type of sensory receptor;

a) **Exteroceptive: E**xtero-receptor receives stimuli from external environment
b) Interoceptive: Intero-receptor receives stimuli from internal environment
c) Proprioceptive: Proprioceptor receives stimuli about position of body parts

4) According to clinical classification:

a) Superficial reflex- It is initiated by stimulating appropriate receptors of skin or mucous membrane, usually polysynaptic and usually involve moving away from stimulus . E.g. plantar response, corneal and conjunctival reflexes etc.
b) **Deep reflex-** It is initiated by stimulating receptors deep in muscles (Spindles & Golgi Tendon Organs), also called tendon reflexes . E.g. knee jerk, ankle jerk etc.
c) Visceral reflex-At least one part of the reflex arc is autonomic nerve, stimulation receptors in viscera. E.g, pupillary reflex, carotid sinus reflex.
d) **Pathological reflexes-** present only during abnormal conditions.

5) Anatomical classification:

a) **Segmental reflex** –End of afferent neuron and beginning of efferent neuron are in the same segment of spinal cord

b) **Intersegmental reflexes** End of afferent neuron and beginning of efferent neuron are in different segment of spinal cord

c) **Supra segmental reflexes-** centre for this reflex lies above the spinal cord

6) Depending upon development:

a) **Un-conditioned /Innate reflex-**Present from birth, genetically determined
b) **Conditioned/Acquired reflex-** learned later in life.

7) Depending upon processing site:

a) **Spinal reflex-** processing in spinal cord
b) **Cranial reflex-** processing in brain

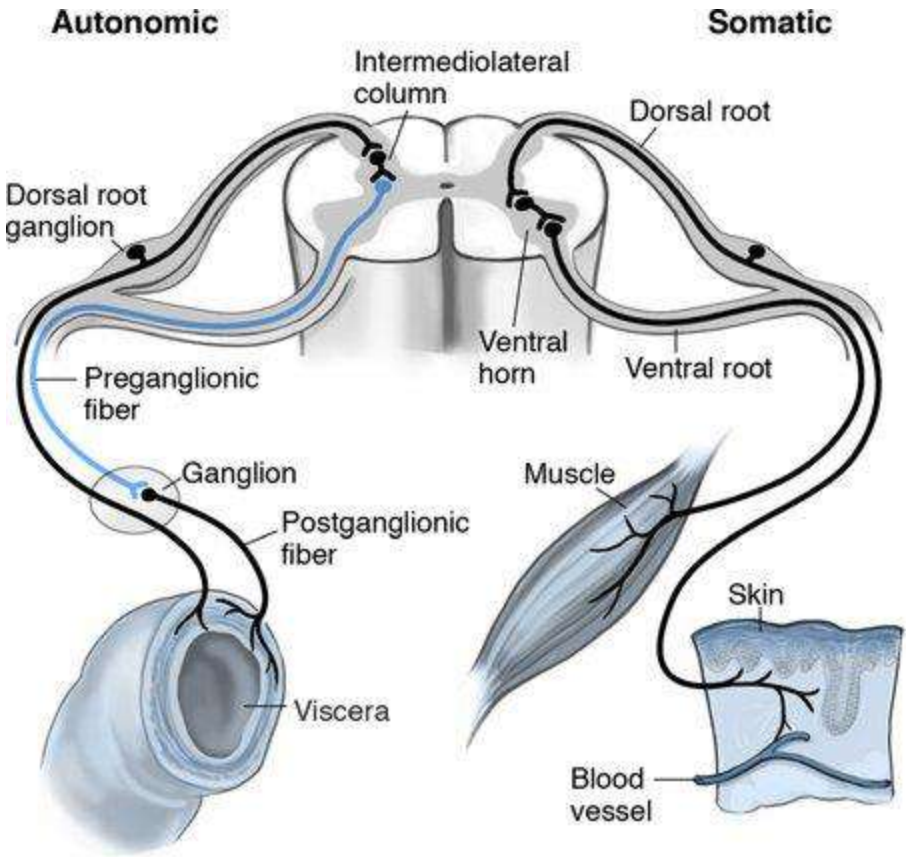
8) Functional classification:

a) **Flexor reflex-**
b) **Extensor reflex**
c) **Righting reflex**
d) **Postural reflex**
e) **Withdrawal reflex**

1) Depending upon Effector response:

a) **Autonomic reflexes**: control actions of internal visceral organs (glands, heart, visceral smooth muscle etc.)

b) **Somatic reflexes**: control skeletal muscles. E.g., stretch reflex and other superficial reflexes.



2) Depending upon number of Synapses:

a) **Asynaptic**- No synapse. E.g., axon reflex.

b) **Monosynaptic** - 1 synapse, E.g., stretch reflex

c) Polysynaptic – 2 or more synapses. E.g., withdrawal reflex, crossed extensor reflex.

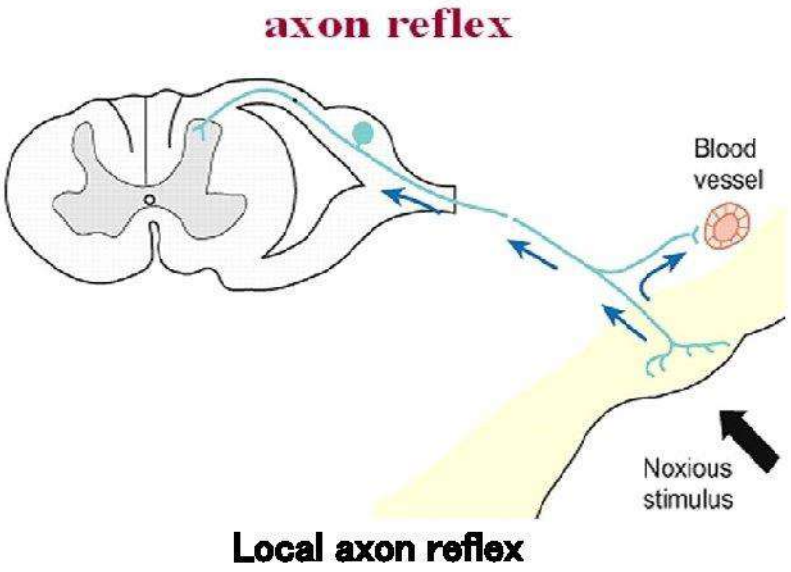
Asynaptic reflex:

It is a reflex resulting from a stimulus applied to one branch of a nerve, which sets up an impulse that moves centrally to the point of division of the nerve, where it is reflected down the other branch to the effector organ.

Transmitting a signal from one end of a nerve to another end is a type of **antidromic** transmission

Example: **Axon reflex or triple response by Lewis.**

Axon reflexes are important in a lot of physiological and physio-pathological processes from regulation of skin blood flow and sweating to inflammation and pain, from itch to asthma and allergic rhinitis.

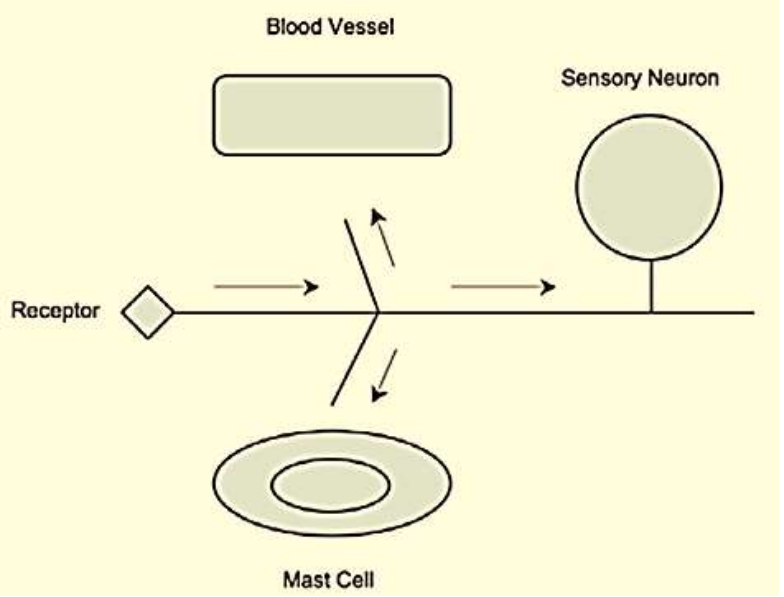


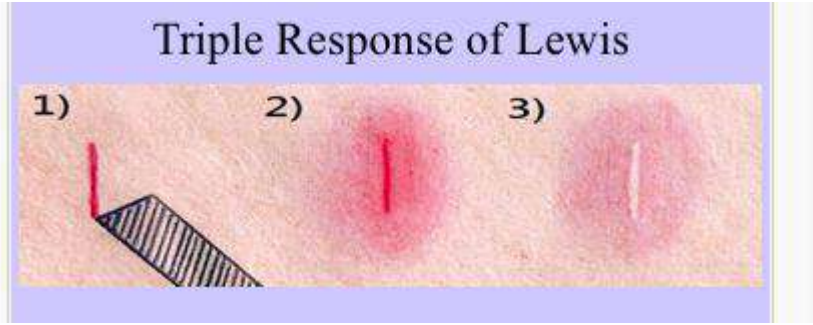
Axon reflex (TRIPLE RESPONSE):

1. A reflex response to scratching of the skin with a sharp object: a **red line** appears within seconds, followed by a **red flare** in the surrounding skin, and finally a **white weal**, these phenomena constituting the *triple response*.

2. The weal and flare result from the activity of **pain receptors** that transmit impulses along their axons not only in the normal orthodromic direction towards the central nervous system but also in the **antidromic direction** from axon forking nodes into the neighboring skin, where the **free nerve endings respond by releasing substance P**.

3. P substance binds to **artery walls** causing them to dilate and to produce the flare response, and which also binds to **mast cells** and stimulates them to release histamine, resulting in the accumulation of fluid that constitutes the weal response.



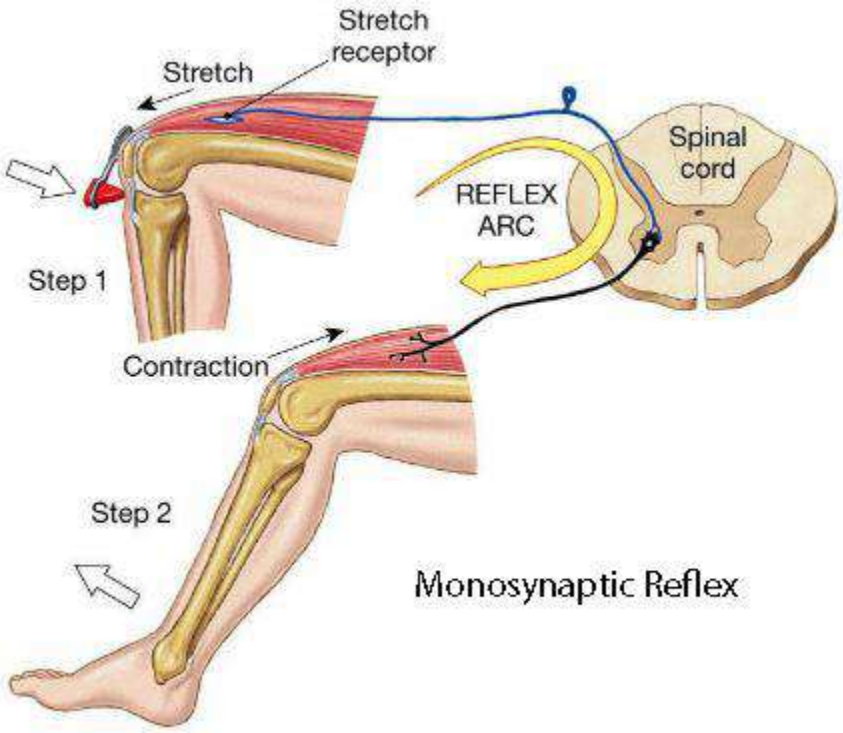


Red line | Spread of redness | Localized oedema

Monosynaptic reflex:
A reflex arc that provides a direct communication between sensory and motor neurons via a **single synapse.**

Example: The monosynaptic stretch reflex like **knee jerk reflex**

1. This reflex begins inside the **muscle spindle** receptor of the muscle, which detects both the amount and rate of muscle stretch.
2. When the muscle experiences a stretch stimulus, **sensory impulses** are transmitted from the muscle spindle via Ia afferent fibers to the dorsal root of the spinal cord.
3. Once in the dorsal horn of the gray matter of the spinal cord, the fiber **synapses** on the corresponding **alpha motor neuron** in the ventral horn of the spinal cord.
4. This alpha **efferent fiber** then exits through the ventral root to the neuromuscular junction of the original muscle to cause contraction.



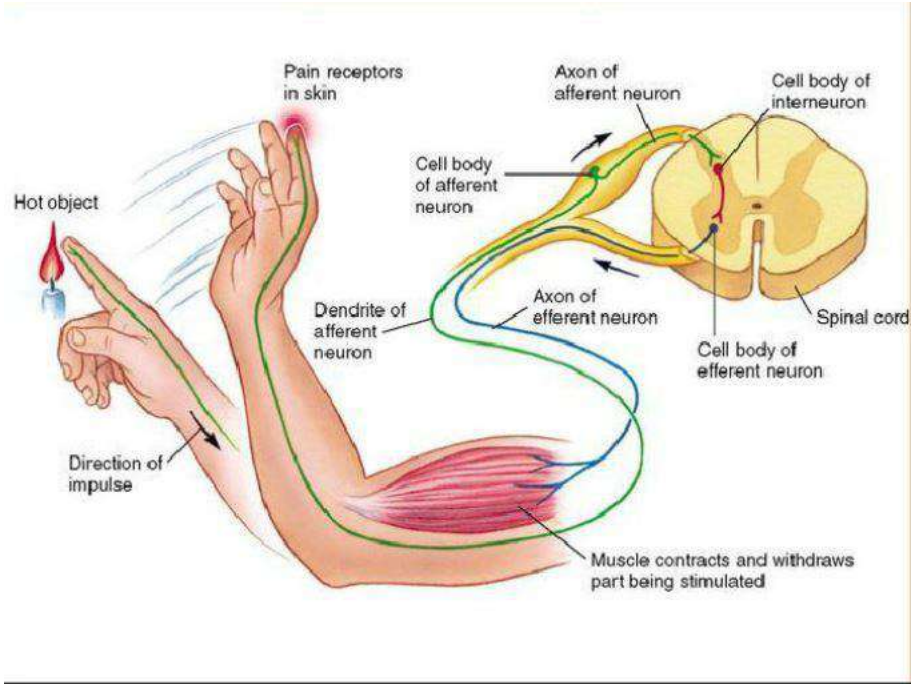
Polysynaptic reflex:

Polysynaptic reflexes involve **at least two to several synapses** involving one or more interneurons.

Examples: For example, the **withdrawal reflex** (nociceptive or flexor withdrawal reflex) is a spinal reflex that causes **automatic withdrawal of a limb from a painful stimulus.**

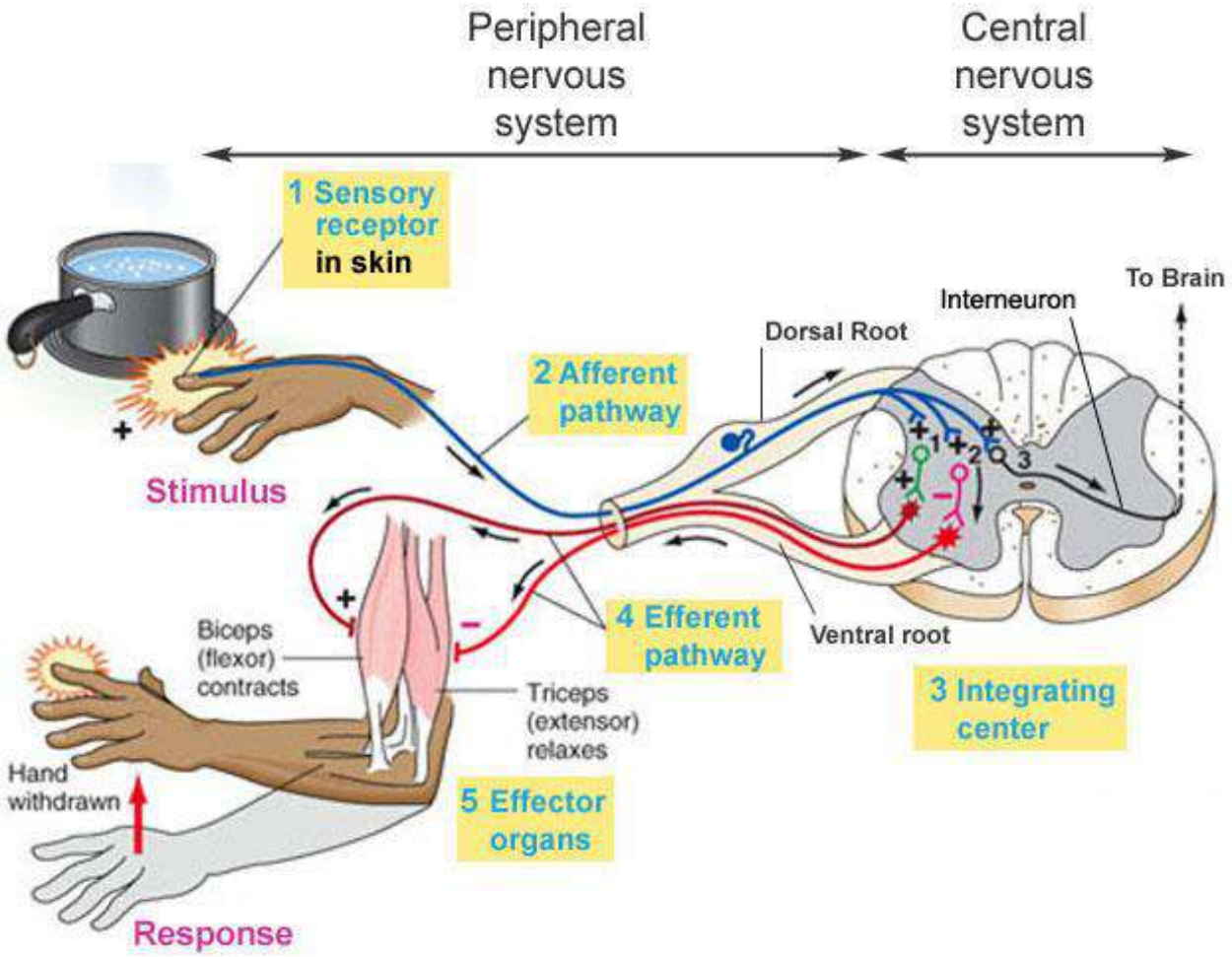
.

1. Noxious stimulus excites the sensory **nociceptor**/pain receptor.
2. Signal travels through a **primary sensory neuron** to enters the dorsal horn of the spinal cord
3. The neuron synapses with **an interneuron**
4. The interneuron synapses with an alpha **motor neuron**
5. The motor command leaves via the ventral horn to excites **the ipsilateral (same side) flexor muscle.**



During the withdrawal reflex there is **contraction of flexor** muscle of the limb which comes into contact with the noxious stimuli; At the same time it also **inhibition of the extensor muscle** of that same limb. ThisIt is called ***reciprocal inhibition*.**

This is due to motor neurons that supply the **ipsilateral extensor muscle** receive signals from an inhibitory interneuron .



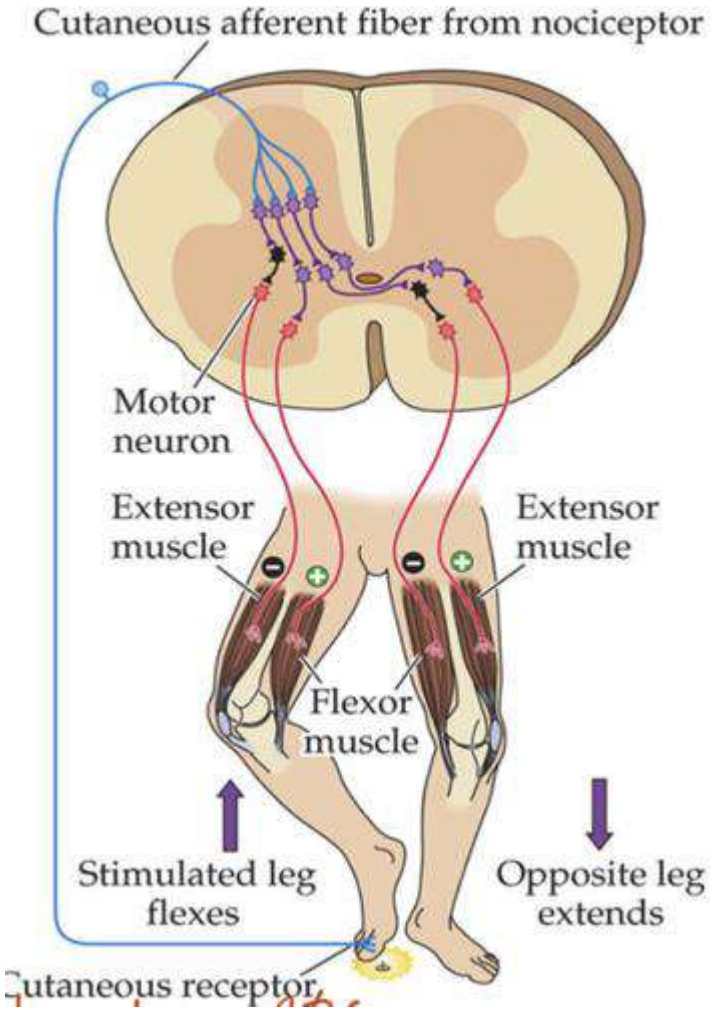
Crossed extensor reflex

The crossed extensor reflex is a **part of the withdrawal reflex** in which the contralateral limb compensates for loss of support when the ipsilateral limb withdraws from painful stimulus in a withdrawal reflex.

During a withdrawal reflex, the flexors in the withdrawing limb contract and the extensors relax, while in the other limb, the opposite occurs. **(flexor relax and extensor contracts).**

An example of this is when a person steps on a nail: The leg that is stepping on the nail pulls away, while the other leg takes the weight of the whole body.

On the contralateral side (the one that bears all the weight), the flexors relax and the extensors contract to stiffen the leg since it must **suddenly support the entire weight of the body.** At the same time, signals travel up the spinal cord and cause **contraction of the contralateral muscles of the hip and abdomen** to shift the body's center of gravity over the extended leg.



4) According to clinical classification:

a)**Superficial reflex-** initiated by receptors of skin.

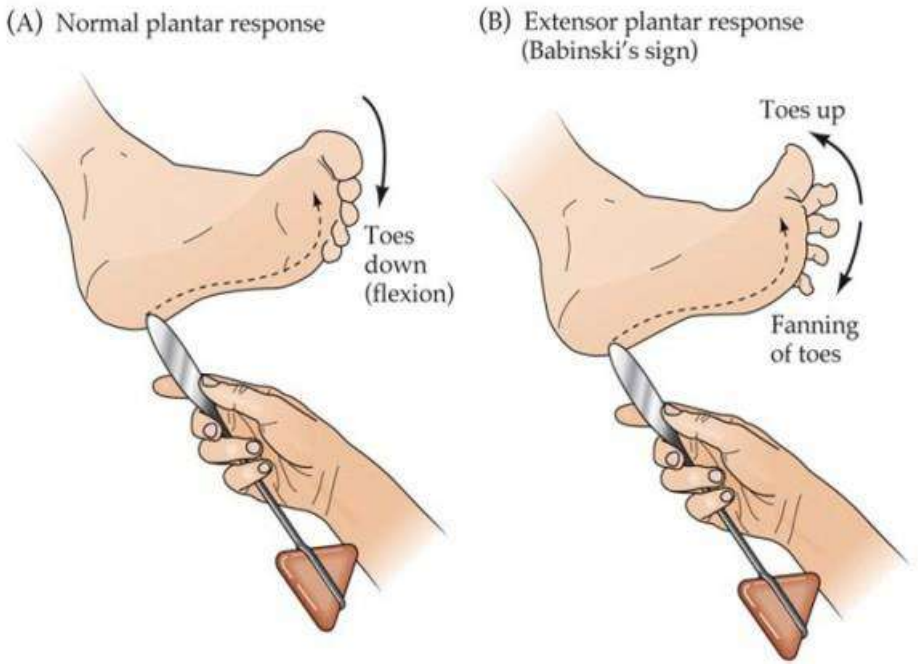
b)**Deep reflex-** It is initiated by stimulating receptors deep in muscles (Spindles & Golgi Tendon Organs), also called tendon reflexes. E.g. knee jerk, ankle jerk etc.

c) Visceral reflex- At least one part of the reflex arc is autonomic nerve, stimulation of receptors in viscera. E.g, pupillary reflex, carotid sinus reflex.

d) **Pathological reflexes-** present only during abnormal conditions.

a) Superficial reflex:

It is initiated by stimulating **receptors of skin or mucous membrane,** usually polysynaptic and usually involve moving away from stimulus . E.g. **plantar response, corneal and conjunctival reflexes etc.**

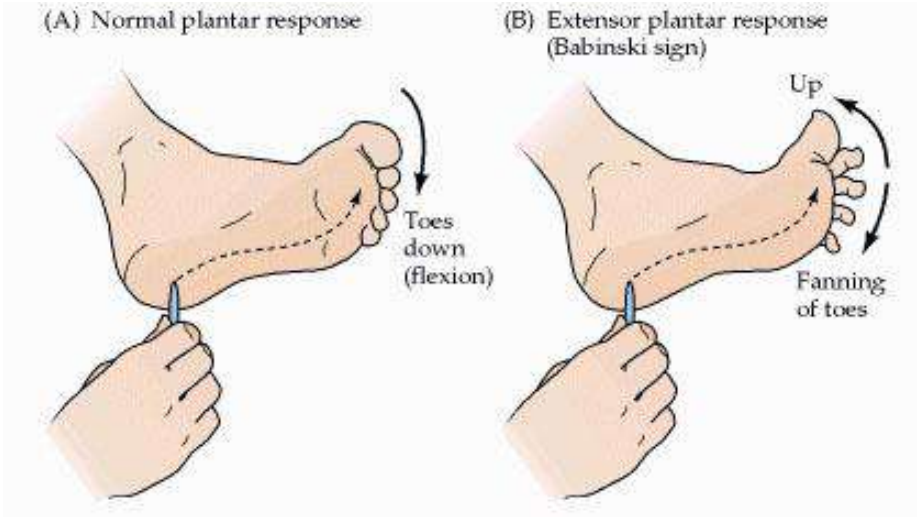


Plantar reflex: Stroking the lateral part of the sole of the foot with a fairly sharp object produces **plantar flexion of the big toe;** often there is also flexion and adduction of the other toes. This normal response is termed the *flexor plantar reflex*. The plantar reflex is the most common superficial reflex examined.

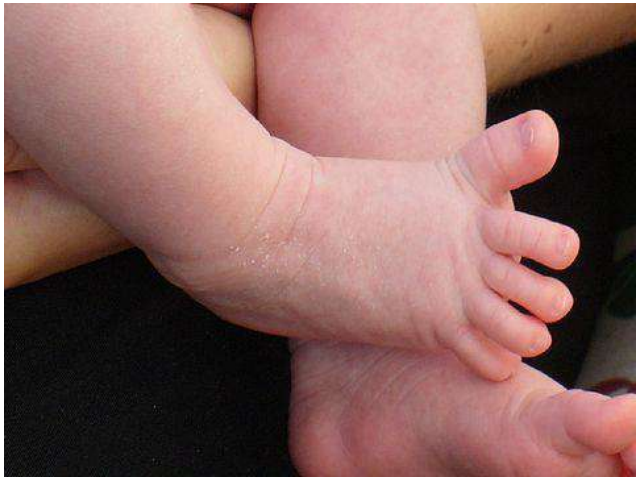
Babinski sign:

Babinski sign occurs when stimulation of the lateral plantar aspect of the foot leads to **extension (dorsiflexion or upward movement) of the big toe**. Also, there may be fanning of the other toes.
The Babinski reflex (plantar reflex) was described by the neurologist Joseph Babinski in 1899. Since that time, it has been incorporated into the standard neurological examination.

The Babinski reflex tests the integrity of the corticospinal tract (CST). Damage anywhere along the CST can result in the presence of a Babinski sign.



New born

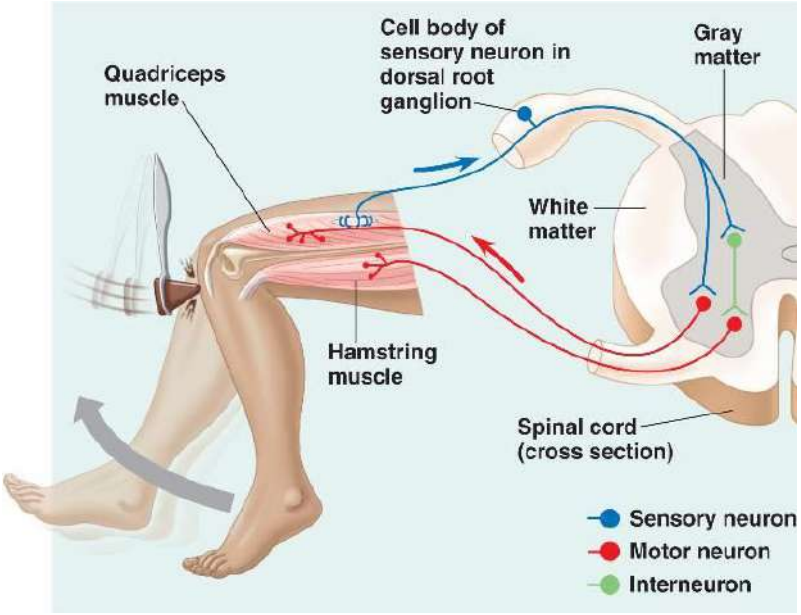


This positive Babinski reflex happens naturally in babies and young children until they're about 6 months to 2 years old. It is one of the normal reflexes in infants. Their CST

b)**Deep reflex-** It is initiated by stimulating receptors deep in muscles (Spindles & Golgi Tendon Organs), also called tendon reflexes. E.g. **knee jerk, ankle jerk** etc.

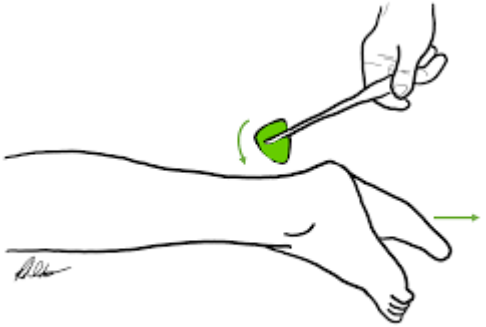
Knee-jerk reflex

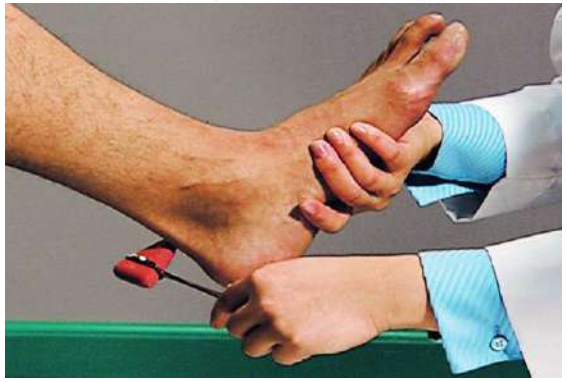
Also called **patellar reflex**, sudden kicking movement of the lower leg in response to a sharp tap on the **patellar tendon,**



Ankle jerk reflex

The **ankle jerk reflex**, also known as the **Achilles reflex**, occurs when the **Achilles tendon** is tapped while the foot is dorsiflexed. A positive result would be the jerking of the foot towards its plantar surface (plantar flexion).






ACHILLES
DEEP
TENDON
REFLEX EXAM

FOR MEDICAL & PARAMEDICAL STUDENTS

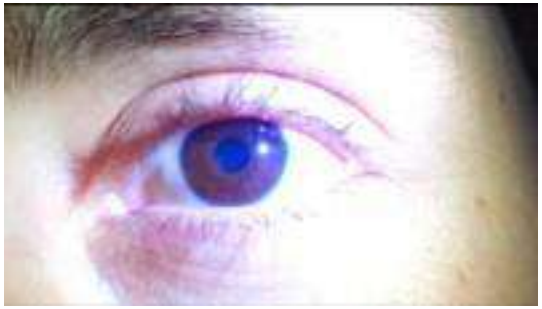
PLANTAR REFLEX

BABINSKI SIGN

c) Visceral reflex-

At least one part of the reflex arc is autonomic nerve, stimulation of receptors in viscera. E.g, **pupillary reflex, carotid sinus reflex.**

The pupillary light reflex is an **autonomic reflex** that **constricts the pupil in response to light**, thereby adjusting the amount of light that reaches the retina. Pupillary constriction occurs via innervation of the iris sphincter muscle, which is controlled by the parasympathetic system.



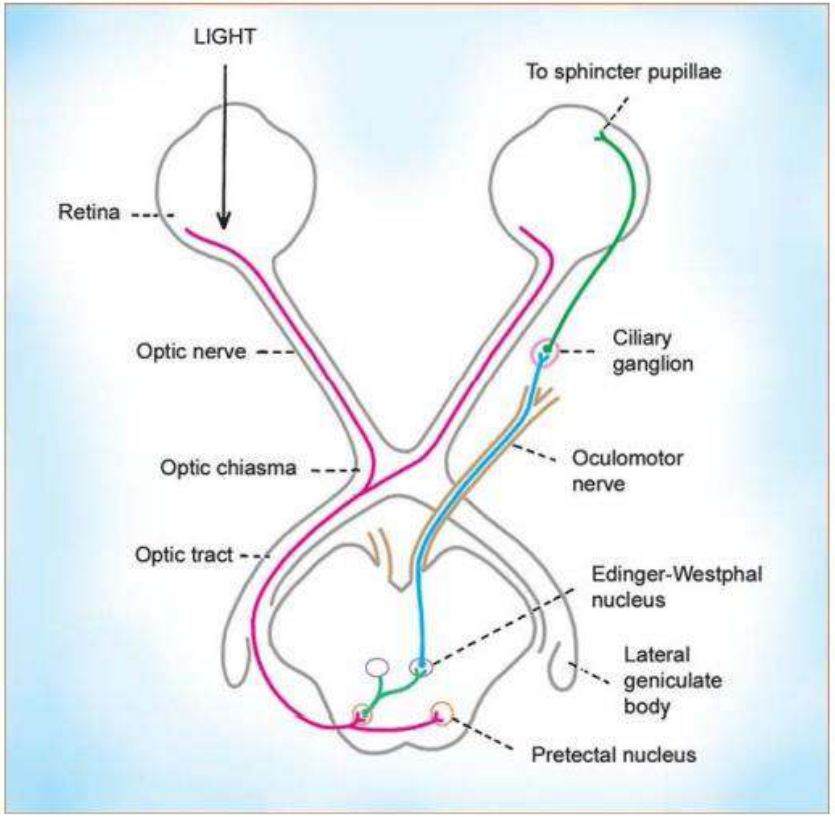
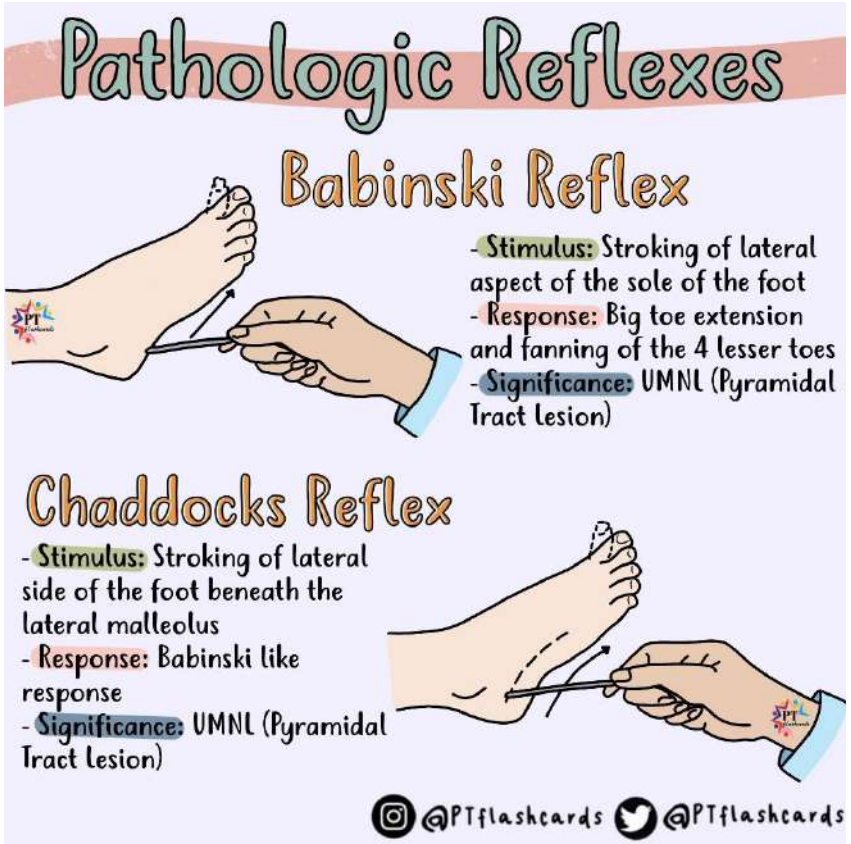
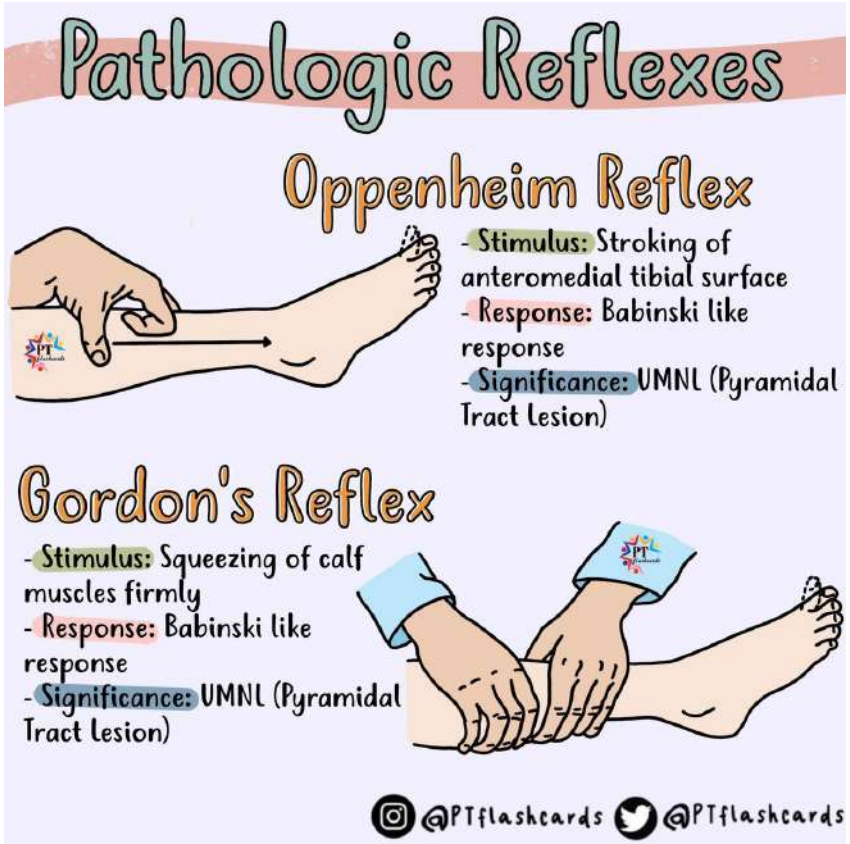


Fig. 18.4. Pathway for the light reflex. Note that all structures shown are bilateral. Some of them are shown only on one side for sake of clarity.

d) Pathological reflexes- present only during abnormal conditions like in injury or disease (which causes release of primitive reflexes from natural inhibition of supraspinal centres.)

A typical pathological reflex is the extensor plantar reflex like **Babinski sign** and **Chaddock sign** in adults**.**





a) Segmental reflex:

A reflex in which afferent impulses enter the cord in the same segment or segments from which the efferent impulses emerge.

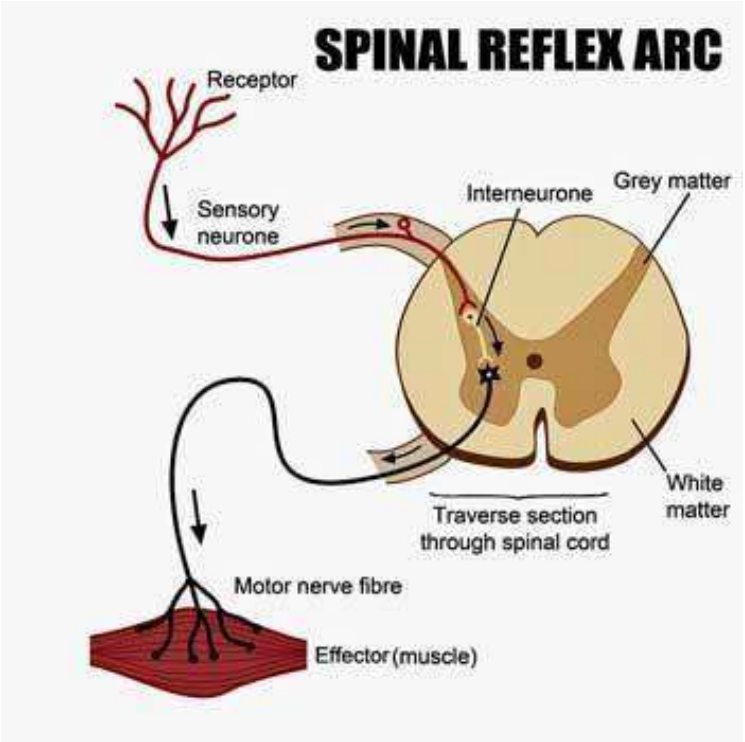
Example: **Knee jerk reflex (stretch reflex)**

5) Anatomical classification:

a) **Segmental reflex** –End of afferent neuron and beginning of efferent neuron are in the same segment of spinal cord

b) **Intersegmental reflexes** End of afferent neuron and beginning of efferent neuron are in different segment of spinal cord

c) **Supra segmental reflexes-** centre for this reflex lies above the spinal cord

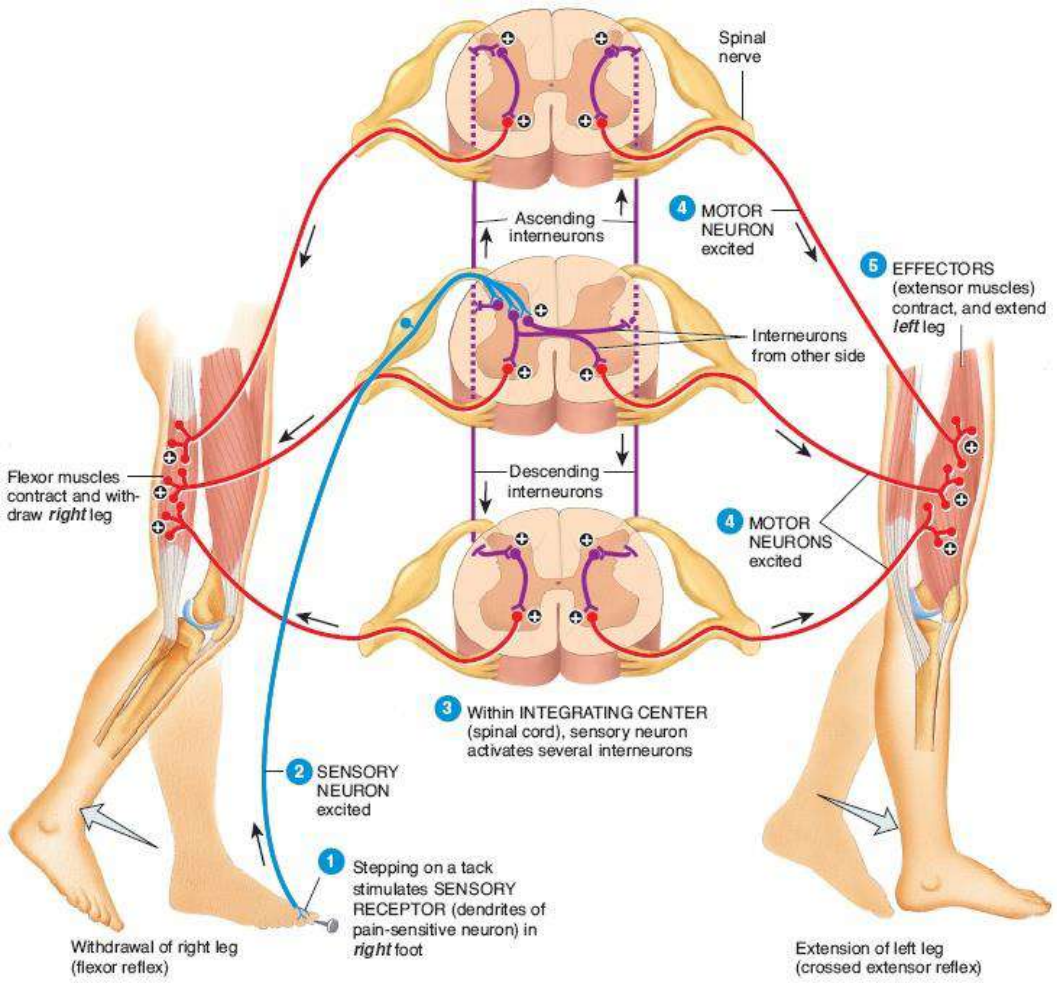


b) Intersegmental reflex:

It is a reflex arc formed by fibers of sensory neurons or interneurons that travel from **one spinal segment to another segment** to communicate with motor neurons, so, the input and the output occur at different levels of the spinal cord.

for example **withdrawal reflex is an intersegmental reflex arc**, It mediates the flexion of the limb that comes into contact with the noxious stimuli; it also inhibits the extensors of that same limb. It also accompanied by crossed extensor reflex.

The reflex involves motor neurons from multiple levels of the spinal cord. Sometimes the pain to the foot causes **contractions of abdominal and hip muscle higher up the body.**



c) SUPRA SEGMENTAL REFLEX:

Centers for such reflexes lies above the spinal cord.
Example- **postural reflex of head and limbs.**

Cerebral cortex centre:

1. Optical righting reflex
2. Placing reaction
3. Hopping reaction

Midbrain righting reflexes:

1. Labyrinthine reflex
2. Neck reflex
3. Body on head
4. Body on body

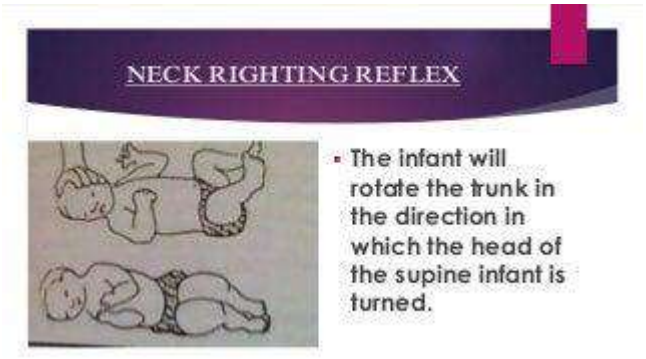
Medullary reflex:

1. Tonic labyrinthine reflex
2. Tonic neck reflex

Hopping reaction
- lateral displacement while standing
- cause animal to hop to maintain balance

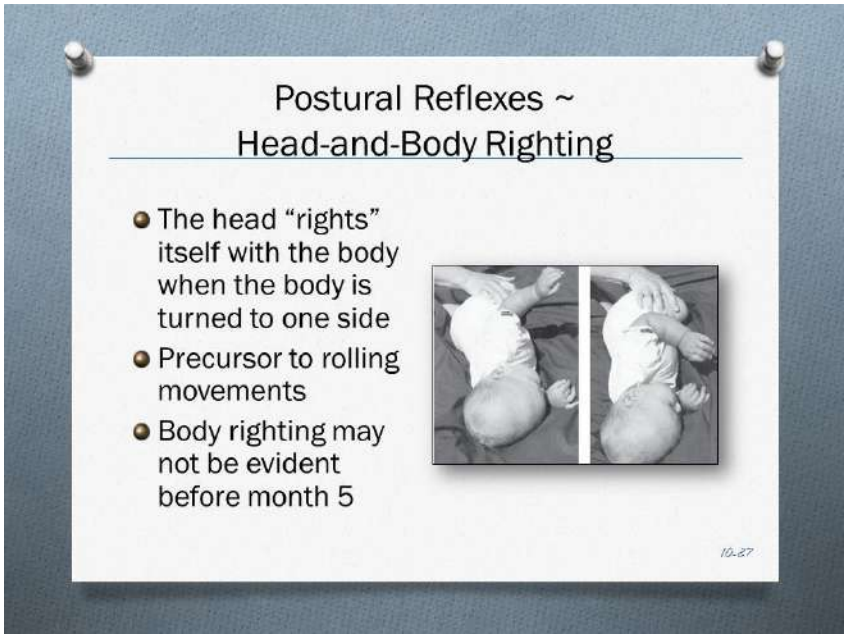
- Placing reflex : when the infant is held erect and the dorsum of the foot is drawn along the under edge of a table top → flexion followed by extension of the leg
- Appears by 4 days in the newborn

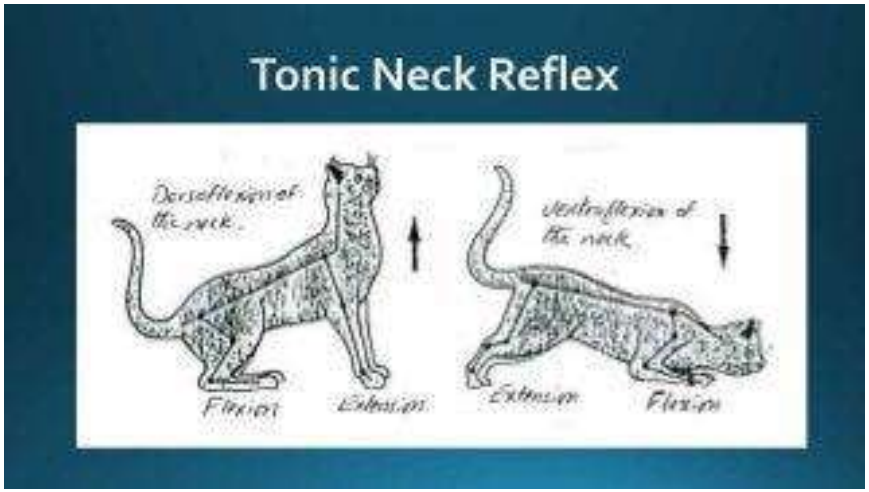
- Stepping Reflex
- When feet touch the ground , the infant appears to take some steps
- Stepping reflex disappears before walking :



Tonic neck reflex

When your baby is lying down and their head is turned to the right or left, the corresponding arm extends while the other arm bends next to their head. This makes them look like they're about to start fencing.





Depending upon development:

a) **Un-conditioned /Innate reflex-**Present from birth, genetically determined

b) **Conditioned/Acquired reflex-** learned later in life.

a) Unconditional reflexes:

- It is the one in which **no previous experience or learning is required.**
- Unconditioned reflexes are usually performed through the spinal cord and lower parts of the brain. Unconditional reflexes are a substrate for **lower nervous activity.**

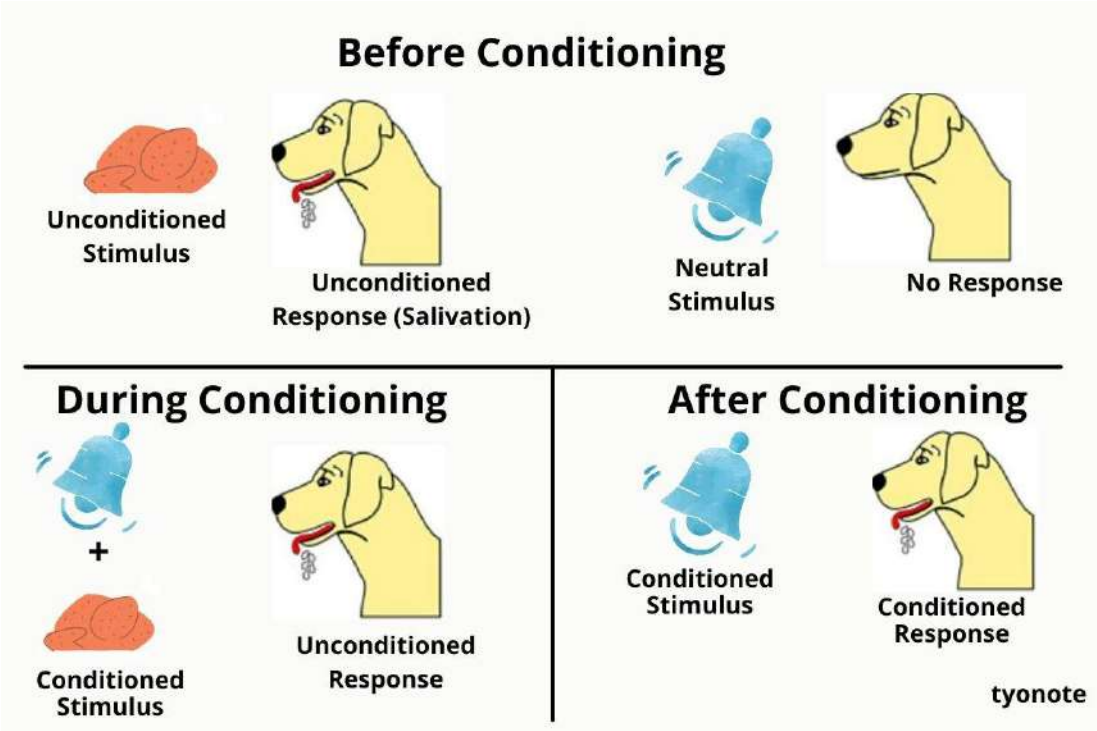
- Examples:
  - **Apetitive reflex**: sucking reflex, food intake, respiratory reflex etc. for preservation of life.
  - **Protective reflex:** Escape reflex, cough etc to protect from injury.
  - **Orientation reflex:**
  - **Sexual reflex:** reproductive reflex for preservation of species etc.
  - **Emotive behavior and instinct** -Fear, rage in response to danger etc.

Examples of unconditional reflexes

Unconditional Stimulus	Unconditional Response
Puff of air to the eye	Eye blink
Food in the mouth	Salivation
Cold Temperature	Shivering
High Temperature	Perspiration
Foreign matter in nose	Sneezing
Foreign matter in throat	Coughing
Spoiled food	Sickness, vomiting

b) Conditioned reflex:

- A conditioned reflex is a reaction that the body **acquires during its life** and due to experience or learning.
- In humans and higher animals, conditioned reflexes are developed through the formation of **temporary connections in the cerebral cortex** and serve as mechanisms for adaption to the complex changing environmental conditions.
- Conditioned reflexes are the basic physiological mechanism for **higher nervous activity**
- They are made but also **inhibited, strengthened and attenuated** in the dependence on needs of current relations of organism to the external environment.
- Examples: Learning of **dancing, cycling, singing, swimming and driving** are conditioned reflexes.



CLASSICAL CONDITIONING:

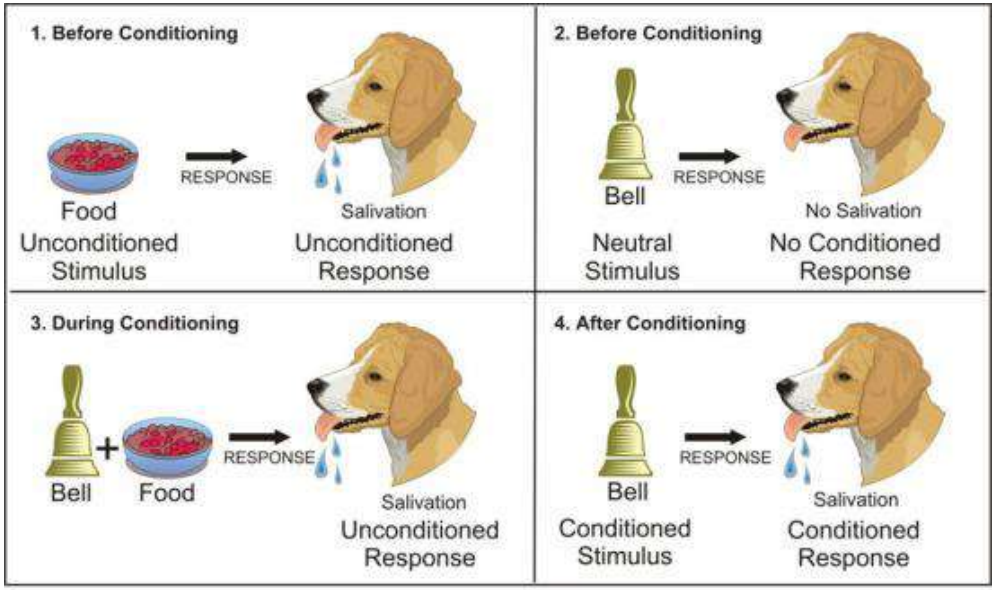
Up until Ivan Pavlov's experiments that led to the discovery of classical conditioning. **Pavlov, a Russian physiologist,** set out to study dogs' digestive systems.

While it was natural for a dog to salivate when food was put in its mouth, if the food was paired with something else, like a light turning on or a bell ringing, the **animal would soon associate the bell with the food as well.** Once a connection between the food and the light or bell was made, even if food wasn't present, the dog would salivate to the light or the bell by itself. This process is called classical conditioning.

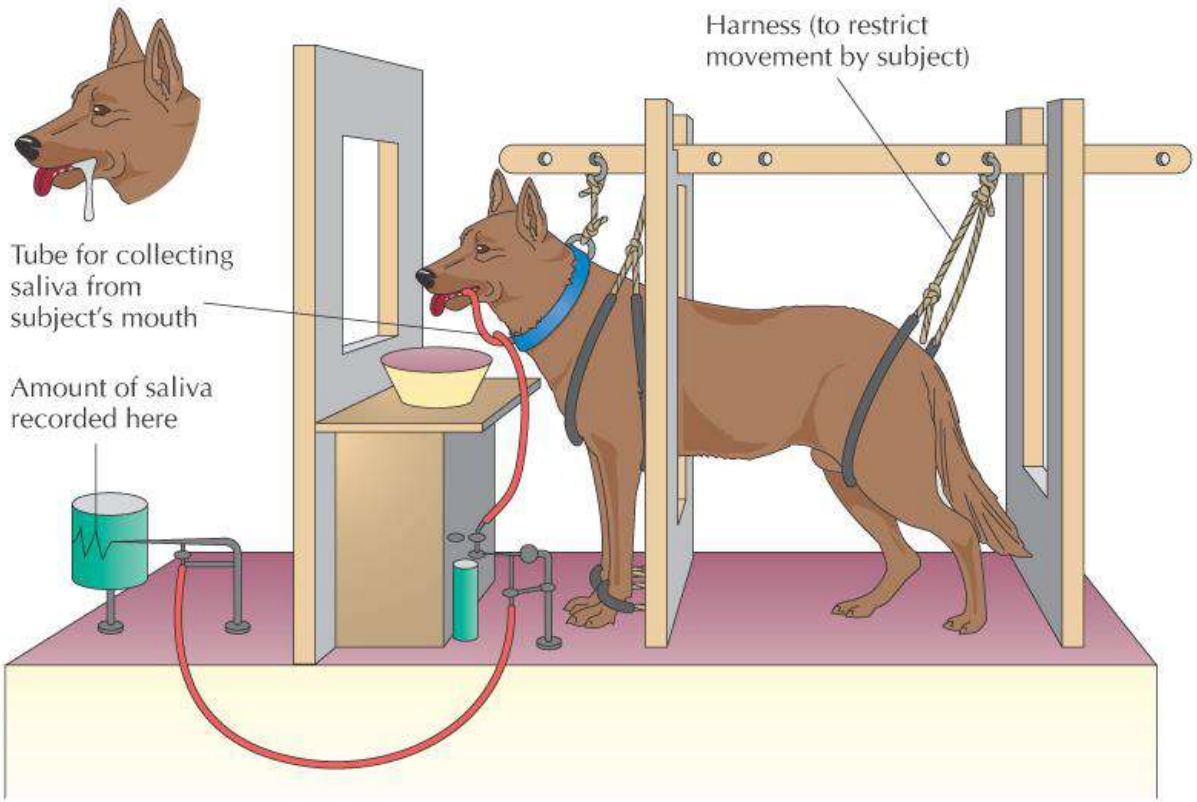
It hinges on **pairing an unconditioned stimulus with a neutral stimulus**.

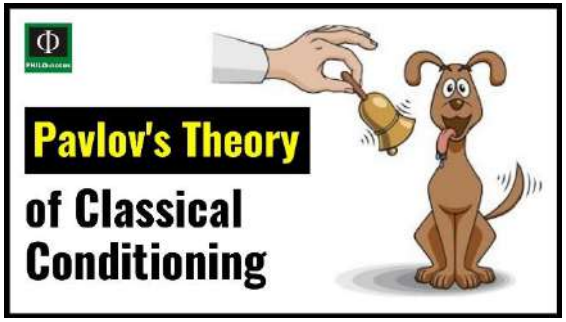
Pairing the unconditional stimulus and neutral stimulus causes the **neutral stimulus to become a conditioned stimulus**. If these stimuli always occur together, the unconditioned stimulus will become associated with the conditioned stimulus.

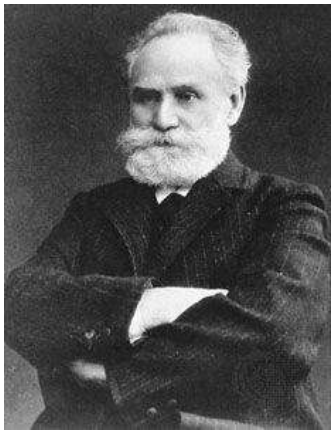
So in the scenario with Pavlov's dogs, **the food is the unconditioned stimulus,** salivation is the unconditioned response, the light or **bell is the conditioned stimulus,** and salivation in response the light or bell is the conditioned response.



Classical Conditioning


Harness (to restrict movement by subject)
Tube for collecting saliva from subject's mouth
Amount of saliva recorded here


Pavlov's Theory
of Classical Conditioning



Unconditioned vs. conditioned

- Inborn, inherited
- Stable, constant
- Activity of low nerve centers
- Adequate stimulation only
- Specific (for species)
- Based on the certain reflex arch
- Give certain adaptation

- Acquired during life
- May be established or abolished
- Activity of cortical (higher) centers
- Any stimulus may be conditioned
- Individual
- Based on temporary connection of neurons
- Give better adaptation

Characteristics of reflexes

- Irradiation
- Delay
- Summation
- Occlusion
- Subliminal fringe
- Facilitation
- Recruitment
- After discharge
- Fatigue
- Fractionation
- Reciprocal innervation
- Rebound phenomenon

PROPERTIES OF REFLEX ACTION

1. Adequate stimulus :

Reflex activity is stereotype and specific(in term of both stimulus and response). Receptor responds maximally only when appropriate stimulus is applied. So the stimulus that produces a reflex is very precise , know as adequate stimulus for a particular reflex.

2. Irradiation

If Too Strong a stimulus, It Spreads to neighboring neurons in centre producing a wider response.
Mechanism –Transmission through many collaterals. For example: Withdrawal response Crossed extensor response.

3. Habituation/Sensitization:

Reflexes Modified by experience. If stimulus (non injurious) repeated at frequent intervals, response declines and disappear. This is called habituation. If injurious stimulus applied next time, it causes intensification of response, this is called sensitization. Neurotransmitters is reduced in habituation and augmented in sensitization.

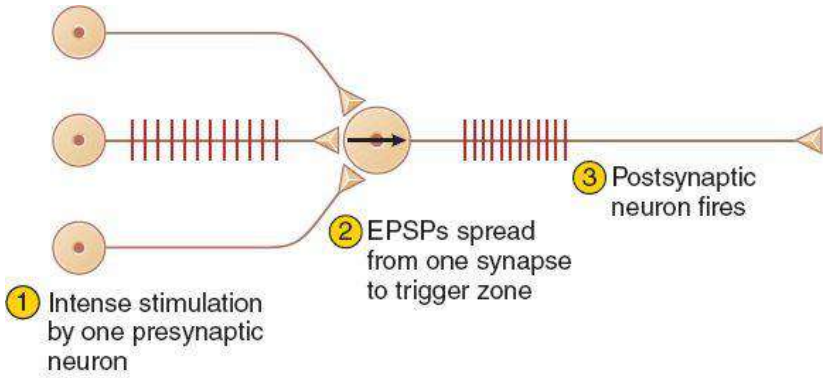
4. Reflex delay:

Time interval present between application of stimulus and beginning of response. Mechanism – due to synapse.

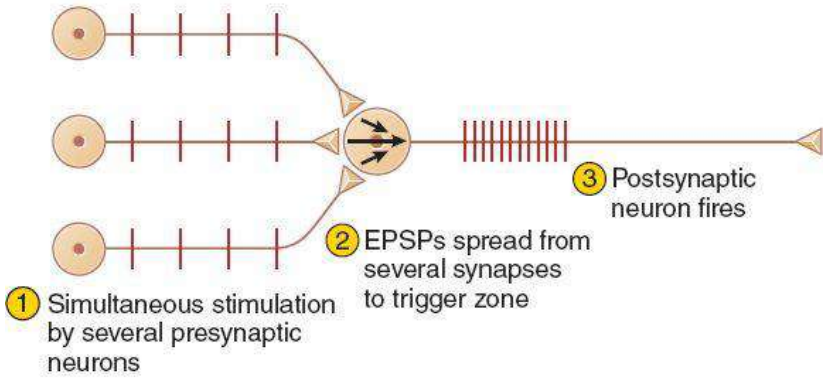
5. Summation:

If Subliminal stimuli applied– there is no or insufficient response.

If the subliminal stimuli undergo **Spatial summation** – (applied simultaneously) or **Temporal summation** (in series) it produce response. Mechanism – persistence of excitability in the path of reflex arc, which summates with the next.



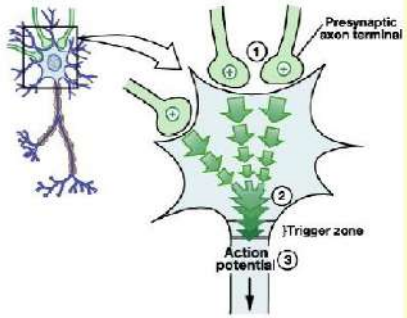
(a) Temporal summation

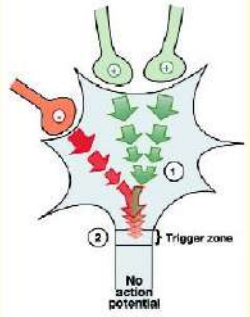


(b) Spatial summation

3. Summation of excitation

a). Spatial (as a result of integrative function of neuron) **the summing of the synaptic inputs from different neurons upon the dendrites and cell body of one neuron**





6. Occlusion:

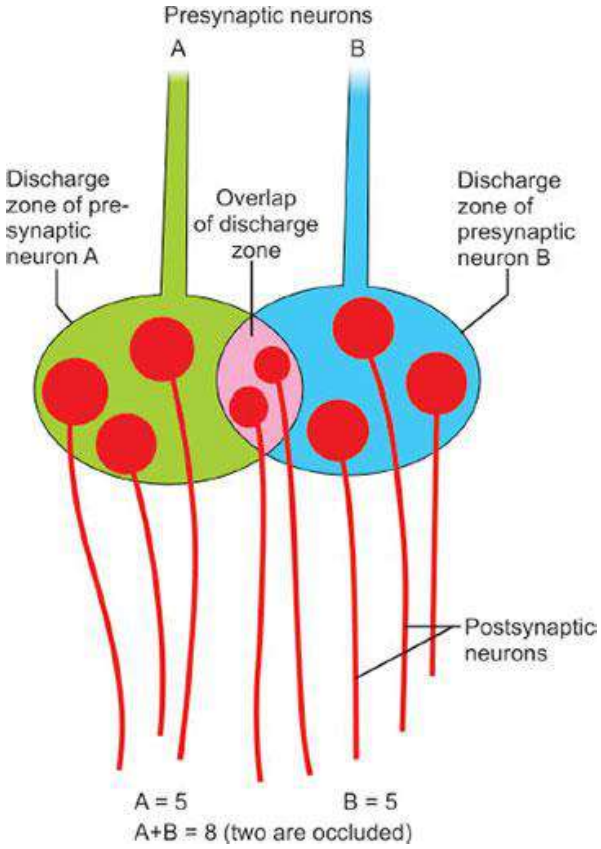
Tension produced by simultaneous stimulation of 2 afferents is less.

t1 : by afferent 1

t2 : by afferent 2

Then, T < t1 + t2

Mechanism : due to common motor nerves shared by both afferents.

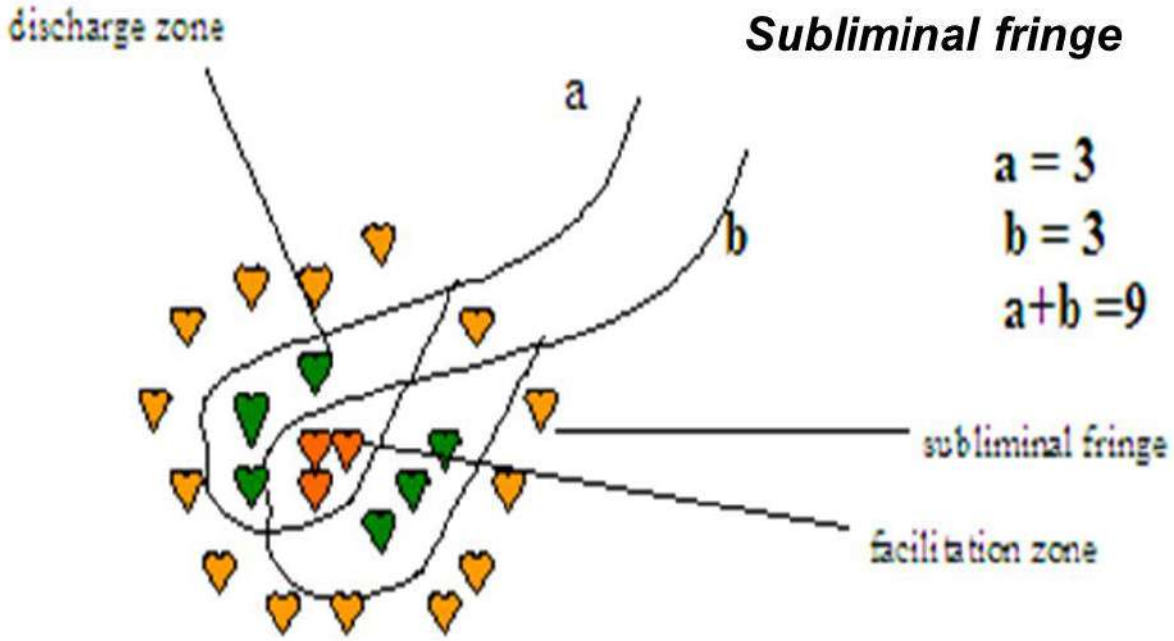


7. Subliminal Fringe:

Reverse of occlusion:

T > t 1 + t 2

Mechanism: when separate stimuli applied , inadequate for some motor neurons (subliminal) when simultaneous stimuli applied – these subliminal ones get summated.



8. Facilitation:

If reflex is elicited repeatedly at proper intervals, the response becomes progressively higher for first few occasions.

Mechanism : passage of 1st impulse facilitates the transmission of next one – by decreasing synaptic resistance , the next subliminal stimulus becomes liminal. (facilitation)

9. After discharge:

After a continuous reflex contraction , if stimulus discontinued – contraction continues for some time . relaxes gradually (not at once)

Mechanism – interneuron go on discharging . And also impulse takes longer time to reach muscle through interneurons.

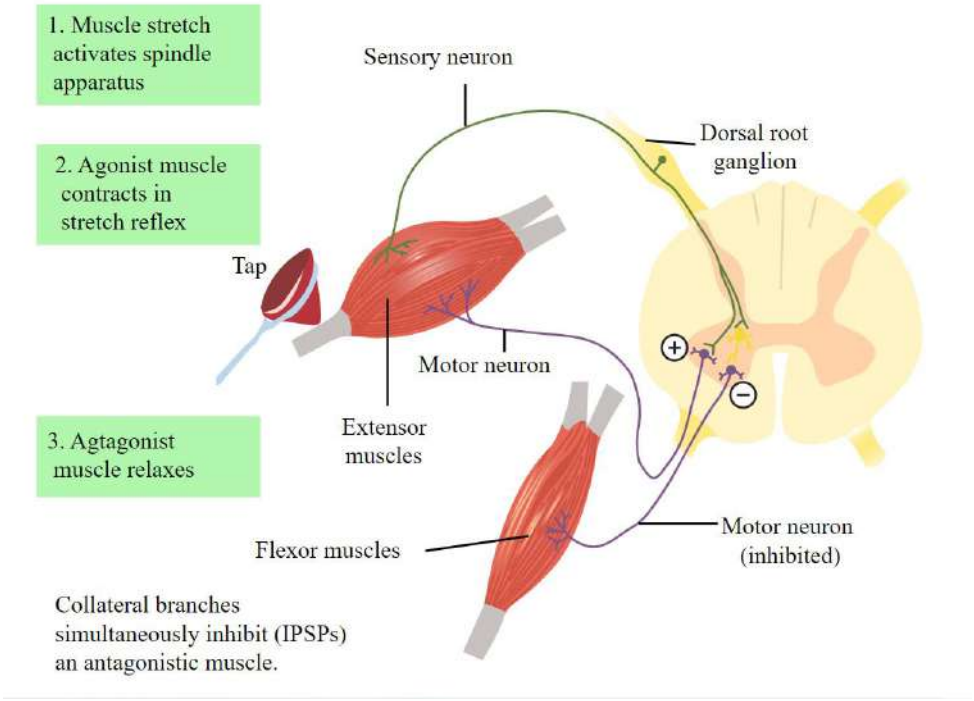
10. Fatigue:

If a reflex is elicited repeatedly, it becomes feebler and disappear.

Mechanism – seat of fatigue is CNS (synapse)- Synapse > motor end plate > muscle.

11. Reciprocal innervation:

Bell, in 1826, and Sherrington in 1893, clearly demonstrated reciprocal innervation in their experimental animals. Sherrington's law: Increased innervation to a muscle is accompanied by decreased innervation to its antagonist. **when a stretch reflex excites one muscle, it often simultaneously inhibits the antagonist muscles.** This is the phenomenon of *reciprocal inhibition,* and the neuronal circuit that causes this reciprocal relation is called *reciprocal innervation.* Likewise, reciprocal relations often exist between the muscles on the two sides of the body, as exemplified by the flexor and extensor muscle reflexes. **One muscle group (agonists) must relax to allow another group (antagonists) to contract. This is called reciprocal inhibition.**



12. Fractionation:

Supramaximal stimulation of any of the sensory nerve of the from a limb never produces as strong contraction of the flexor muscle as elicited by **direct stimulation of the muscle itself.** This is because the afferent input fractionate the motor neuronal pool. Therefore direct motor nerve stimulation causes higher amount of contraction than reflexly through afferent neuron. Mechanism- strength of impulse lost while crossing synapse. So only a part of (fraction of) motor pool is stimulated.

13. Recruitment:

some reflexes, called recruiting reflexes, can hardly be evoked by a single stimulus. Instead, they require **increasing stimulation to induce a response**. The reflex contraction of the bladder, for example, requires an increasing amount of urine to stretch the muscle and to obtain muscular contraction. If repetitive stimulus is maintained the strength of reflex contraction slowly increases to final level. This slow build up is due to gradual activation of more motor neurons

14. Rebound Phenomenon:

This is **exaggeration of reflex after a temporary period of inhibition.** For example a flexor withdrawal reflex in one limb involves stimulation of flexors and inhibition of extensors. If it is followed by another reflex which involves stimulation of extensor of the same limb, the extensor response will be greatly exaggerated. Rebound is one of the important mechanism for coordinating the rhythmic to and fro movement required in **walking and running**. When the inhibition is over the reflex reappears and become more powerful.

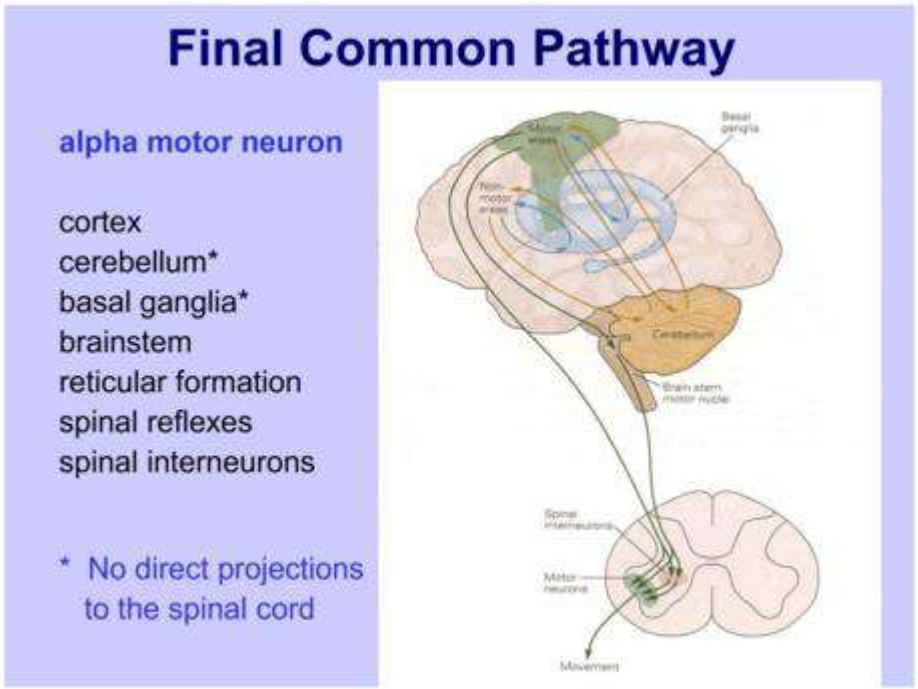
15. Final common path:

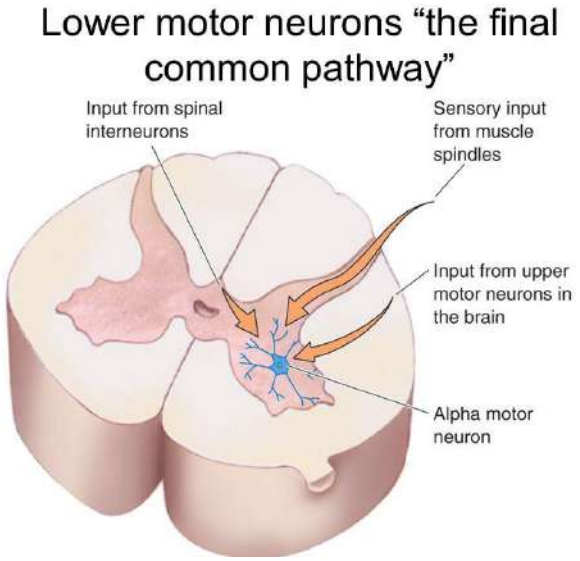
The **alpha motor neurons** that supply the extra fusal fibres in skeletal muscle are the efferent sides of many reflex arcs. All neural influences affecting muscle contraction ultimately funnel through them to the muscles. Therefore they are called the final common path.

Numerous neural inputs converge on them. **Surface of average motor neurons and its dendrites accommodates about 10,000 synaptic knobs.**

There are at least 5 signal inputs from the same spinal segment.

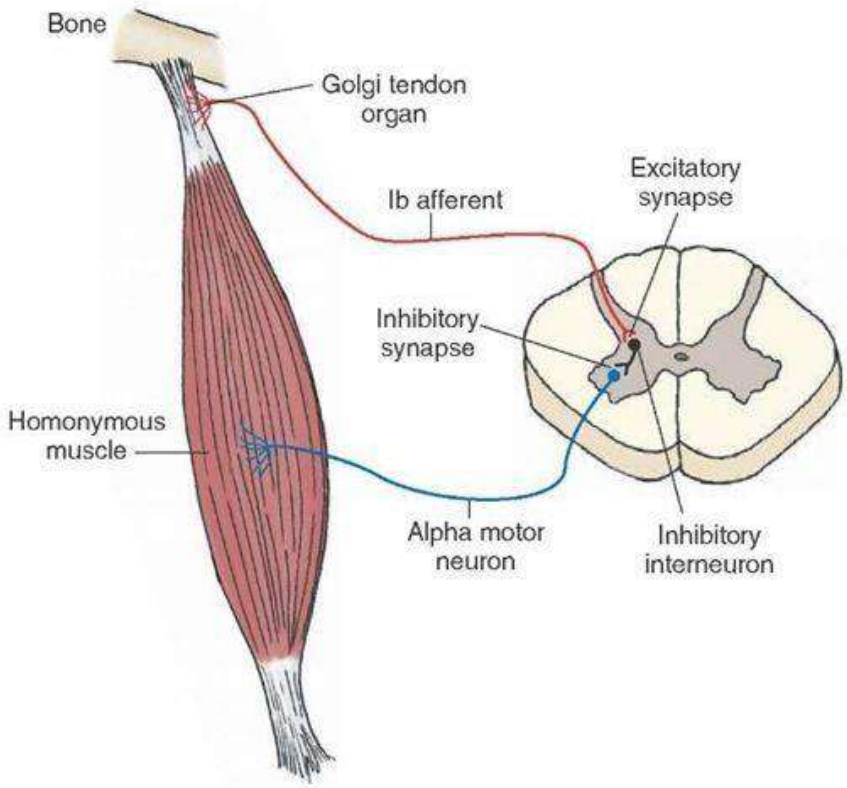
In addition to that there are excitatory and inhibitory interneuron inputs from other levels of spinal cords and long descending tracts from brain. All these input converge on them and determine the activity in the final common paths.





INVERSE STRETCH REFLEX

Excessive tension on a muscle (either by passive stretch of tendon or active muscle contraction) **cause relaxation of the muscle.** The receptors are golgi-tendon organs. When stimulated it causes excitation of inhibitory interneurons in spinal cord supplying alpha motor neurons. The reflex produces immediate relaxation of the muscle. The reflex, also known as golgi tendon reflex, protects muscle from rupture.



OPERANT CONDITIONING

1. The term *operant conditioning*[1] was coined by **B. F. Skinner in 1937** in the context of reflex physiology.

2. Operant conditioning, sometimes referred to as instrumental conditioning, is a **method of learning that employs rewards and punishments for behavior.**

3. Through operant conditioning, an association is made between a behavior and a consequence (whether negative or positive) for that behavior

4. Operant conditioning relies on a fairly simple premise: **Actions that are followed by reinforcement will be strengthened** and more likely to occur again in the future.
5.
6. Conversely, **actions that result in punishment or undesirable consequences will be weakened** and less likely to occur again in the future.

Reinforcement in Operant Conditioning

Reinforcement is any event that **strengthens or increases the behavior** it follows. There are two kinds of reinforcers. In both of these cases of reinforcement, the behavior increases.

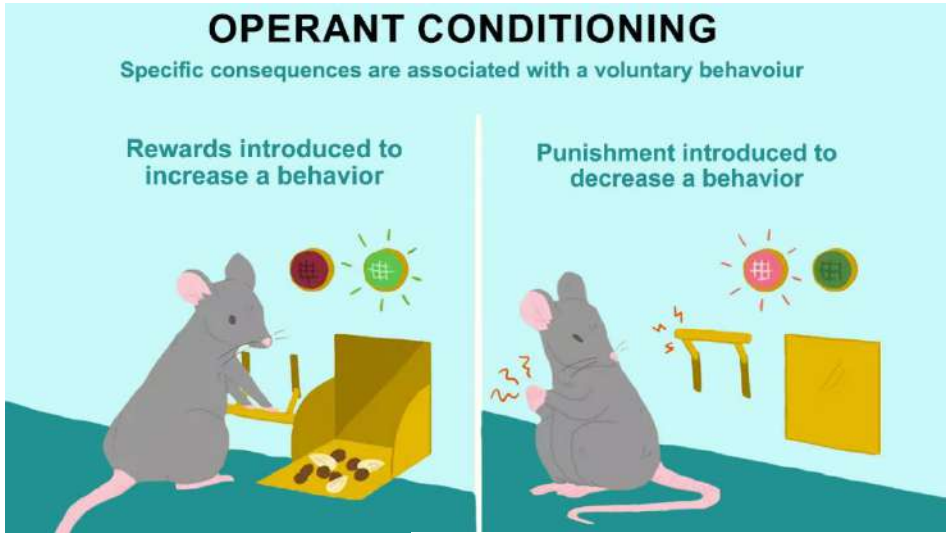
1.**Positive reinforcers** are favorable events or outcomes that are presented after the behavior. In positive reinforcement situations, a response or behavior is strengthened by the addition of praise or a direct reward. If you do a good job at work and your manager gives you a bonus, that bonus is a positive reinforcer.

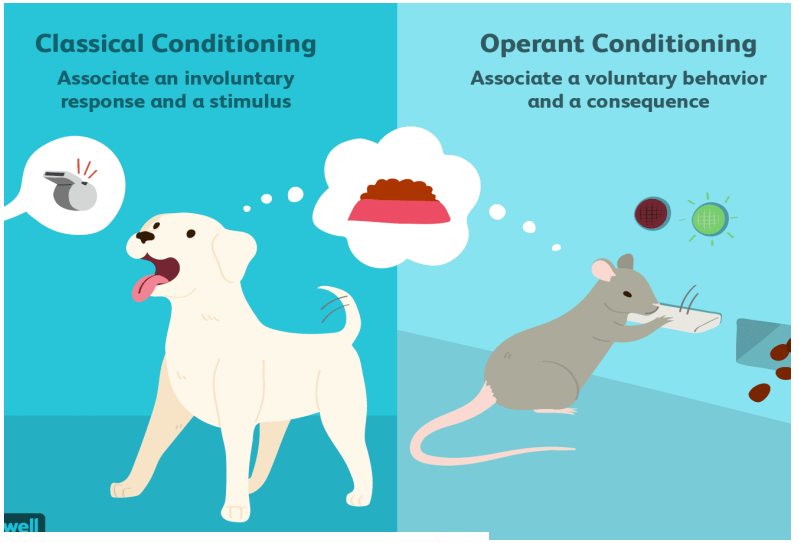
2.**Negative reinforcers** involve the removal of an unfavorable events or outcomes after the display of a behavior. In these situations, a response is strengthened by the removal of something considered unpleasant. For example, if your child starts to scream in the middle of a restaurant, but stops once you hand them a treat, your action led to the removal of the unpleasant condition, negatively reinforcing your behavior (not your child's).

Punishment is the presentation of an adverse event or outcome that causes a **decrease in the behavior** it follows. There are two kinds of punishment. In both of these cases, the behavior decreases.

1.**Positive punishment**, sometimes referred to as punishment by application, presents an unfavorable event or outcome in order to weaken the response it follows. Spanking for misbehavior is an example of punishment by application.

2.**Negative punishment**, also known as punishment by removal, occurs when a favorable event or outcome is removed after a behavior occurs. Taking away a child's video game following misbehavior is an example of negative punishment.





2) Operant Conditioning

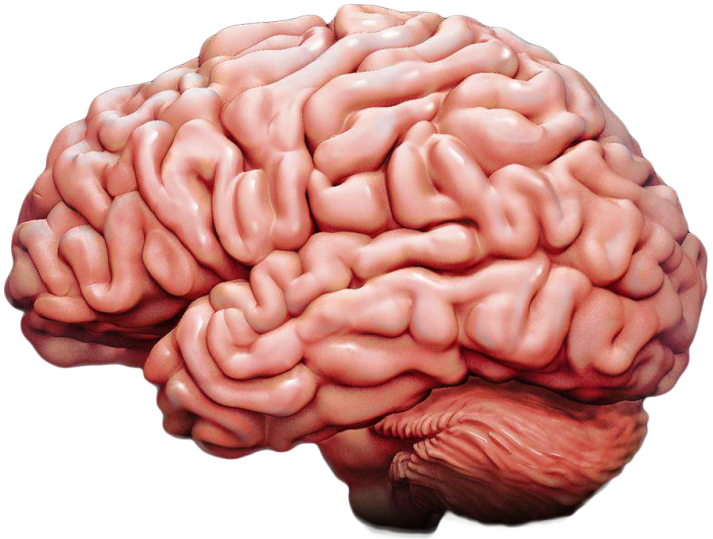
Classical Conditioning vs. Operant Conditioning

1. Bhvr is involuntary	1. Bhvr. is voluntary
2. Organism is passive	2. Organism is active
3. R+ comes BEFORE	3. R+ comes AFTER
4. Learn through associating 2 stimuli	4. Learn from consequences of behavior

Reflex action: (Questions from previous years)

1. Compare the structure of autonomic and somatic reflex arc.(5/2013) (5/2007) (4/2016)
2. Explain the following properties of reflex action. Summation, Occlusion and sub-liminal fringe. (2+2/2012) (5/2017)
3. Are occlusion and subliminal fringe in reflex action are opposite to reach other? Explain your answer. (5/2014)
4. What is reflex action? (4/2006)
5. Discuss the following properties of reflex action: Recruitment, Inhibition, Reciprocal Innervation and after discharge. (4+4+4+4/2006)
6. Discuss the ‘after discharge’ and ‘fractionation’ in reflex action. (2+2/2015)
7. What do you mean by spatial and temporal summation? (2+2/2015)
8. short notes: operant conditioning.(5/2006)
9. Short notes: conditioned reflex. (5/2005)
10. What is reflex arc? Describe different types of reflex arc? (2+8)/2004)
11. Short notes; Axon reflex. (5/2004) (2/2014)
12. what do you mean by superficial and deep reflexes? (2/2015)

BRAIN



1. On average, an adult brain weighs between 1.0 kg – 1.5 kg.

2. In terms of length, the average brain is around 15 centimeters long.

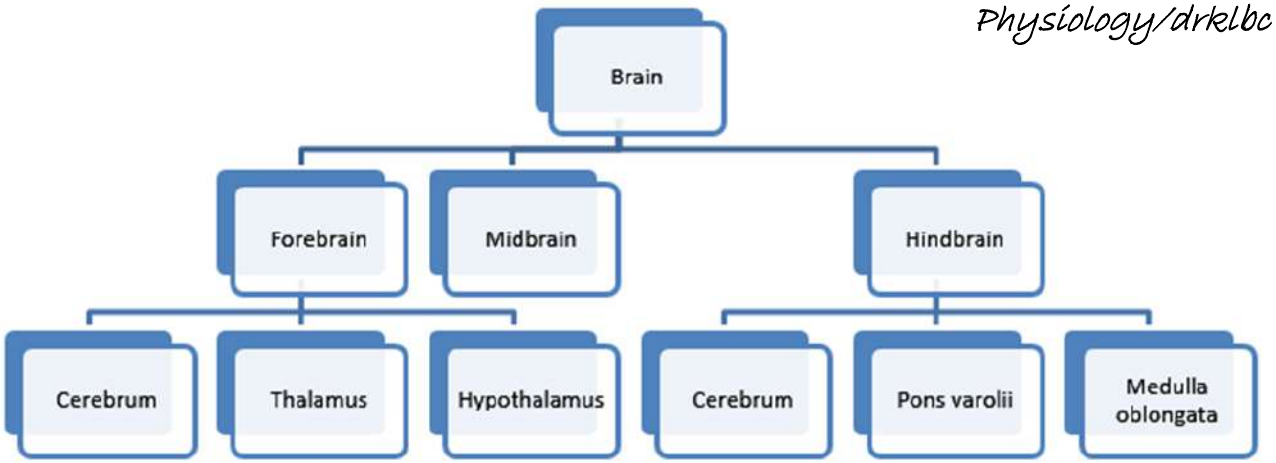
3. Anatomically, the brain is contained within the cranium and is surrounded by the cerebrospinal fluid.

4. The brain is one of the largest and most complex organs in the human body. It is made up of more than 100 billion nerves that communicate in trillions of connections called synapses

5. Uniqueness of the human brain is its relatively large cerebral cortex, which accounts for 82% of brain mass.

6. The brain can be divided into three basic units: the forebrain, the midbrain, and the hindbrain.

Parts of Brain:



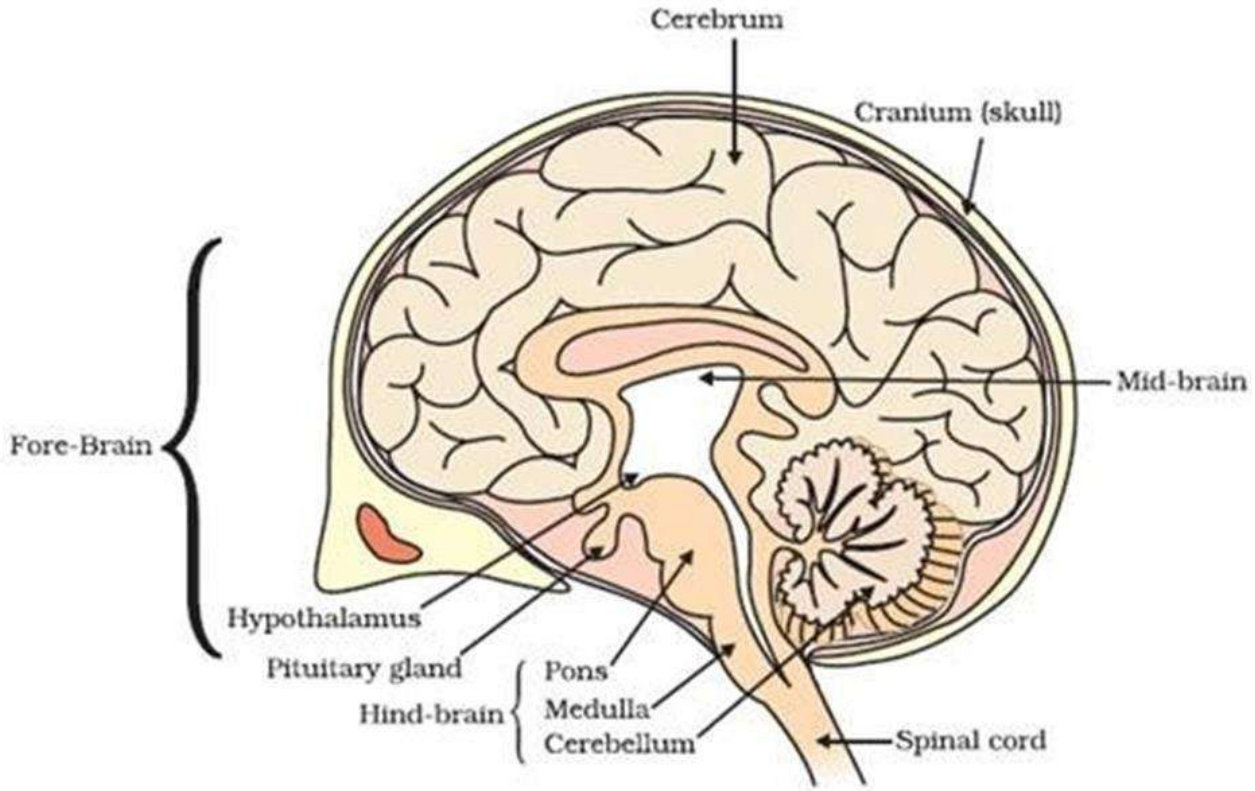


Figure 7.3 *Human brain*

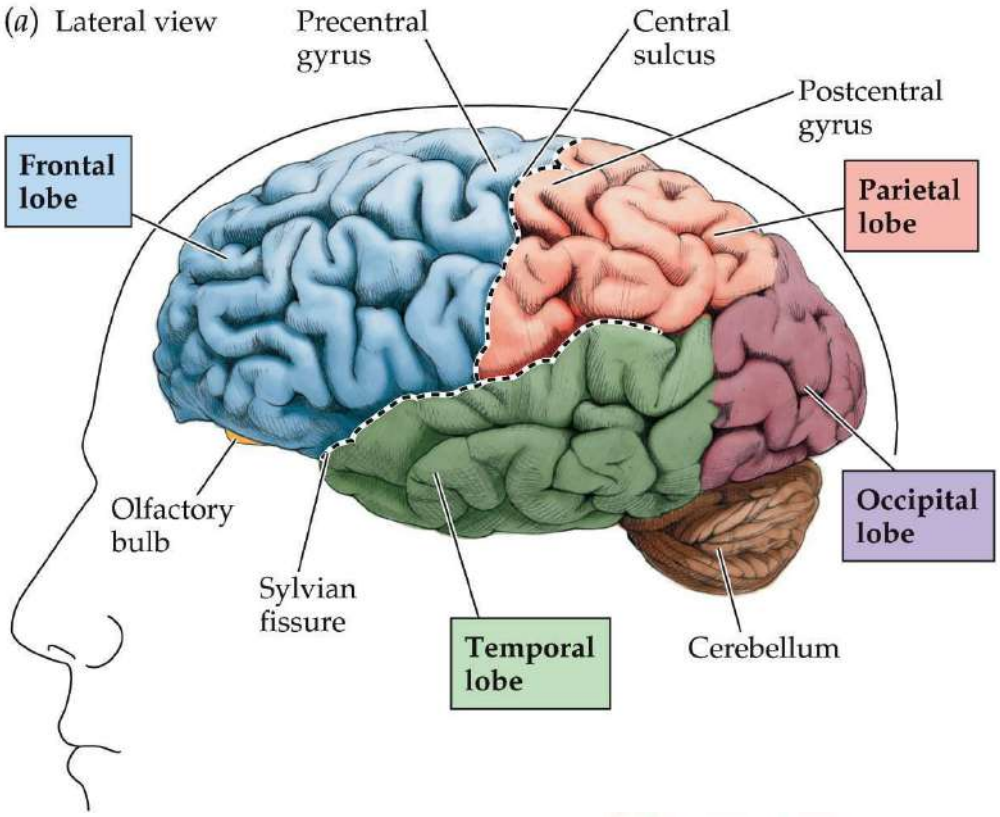
CEREBRUM OR CEREBRAL CORTEX:

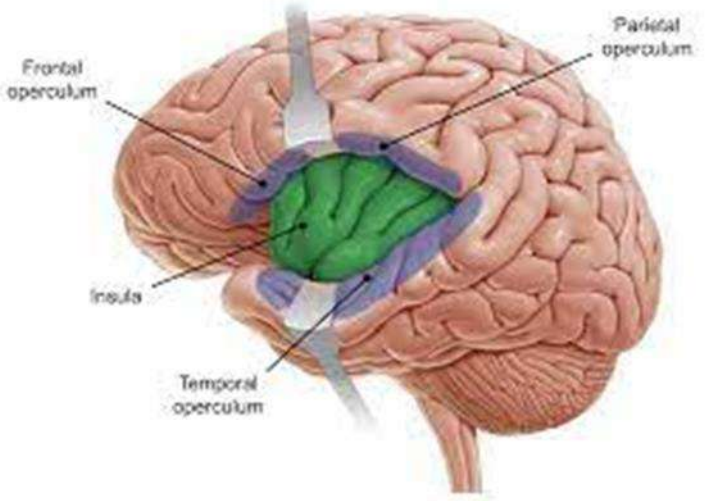
1. It is the uppermost and largest part of the brain and is divided into left and right hemispheres, which are joined by and communicated through the corpus callosum.

2. Each cerebral hemisphere is divided into five lobes, the **frontal lobe, the parietal lobe, the occipital lobe, and the temporal lobe.** A fifth lobe, the **insula** or Island of Reil, lies deep within the lateral sulcus.

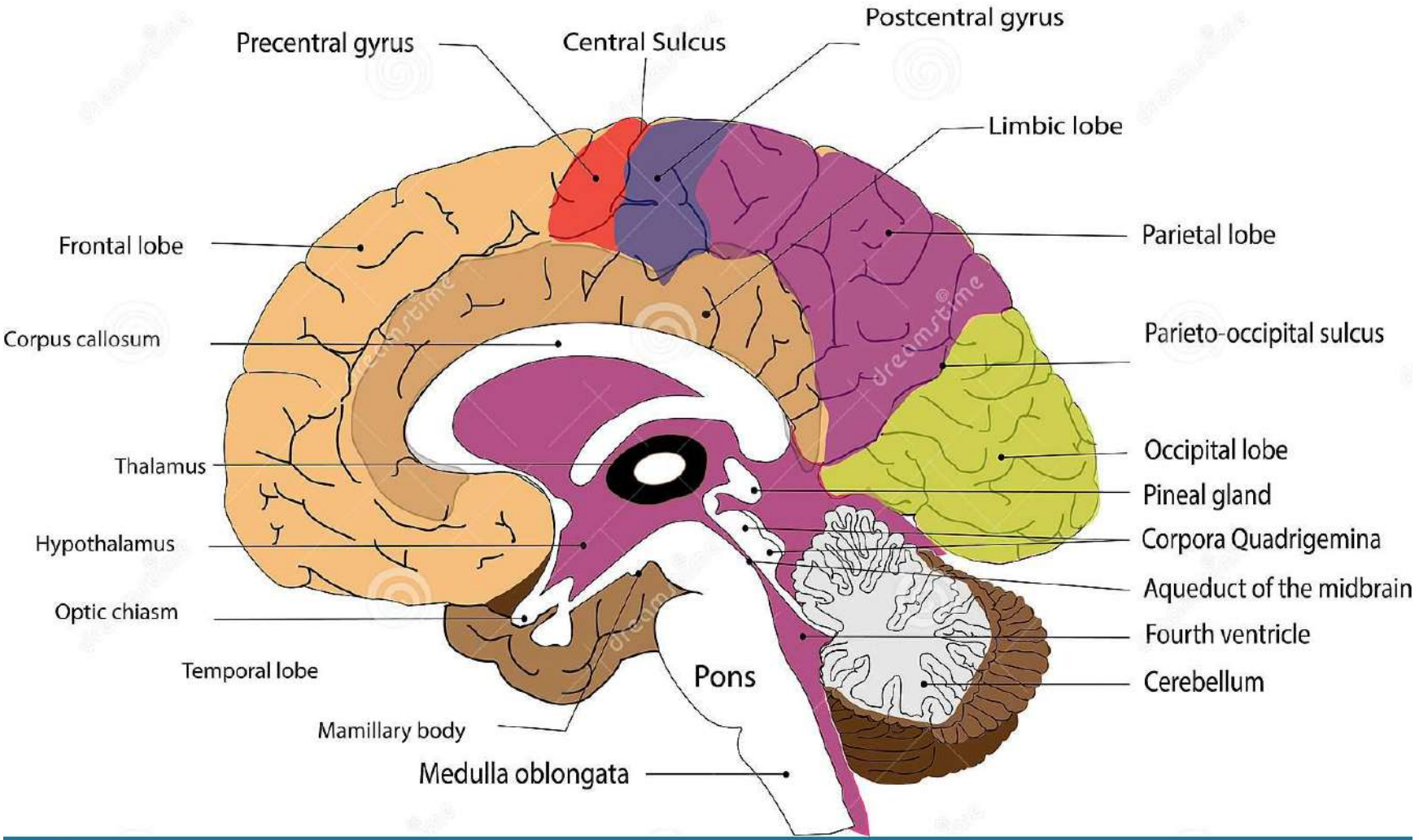
3. The limbic system is a primitive brain structures buried under the cortex. (sometimes termed as limbic lobe)

4. In humans, the lobes of the brain are divided by a number of bumps and grooves. These are known as **gyri** (bumps) and **sulci** (groves or fissures). The folding of the brain, increases its surface area and enables more cerebral cortex matter to fit inside the skull.





A midsagittal view showing the inner boundaries of the lobes of the cerebral cortex



BRODMANN AREA:

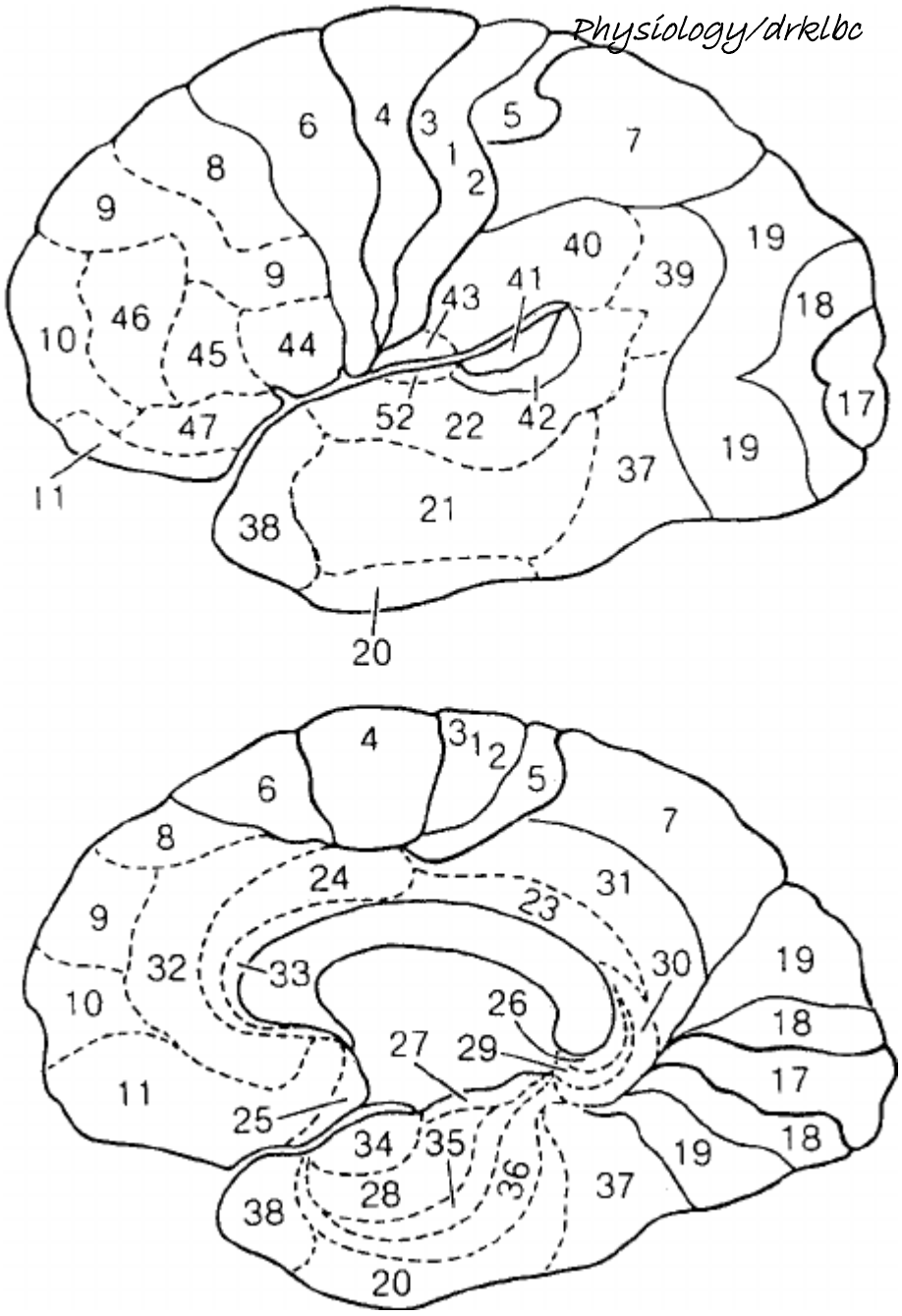
1. The Brodmann areas are a way of **mapping** the cortex pioneered by **Korbinian Brodmann**.(1868-1918).

2. Brodmann (1909) made a detailed study of the cortex, observing the way its layers, tissues, neurons, and other cells varied in structure and size.

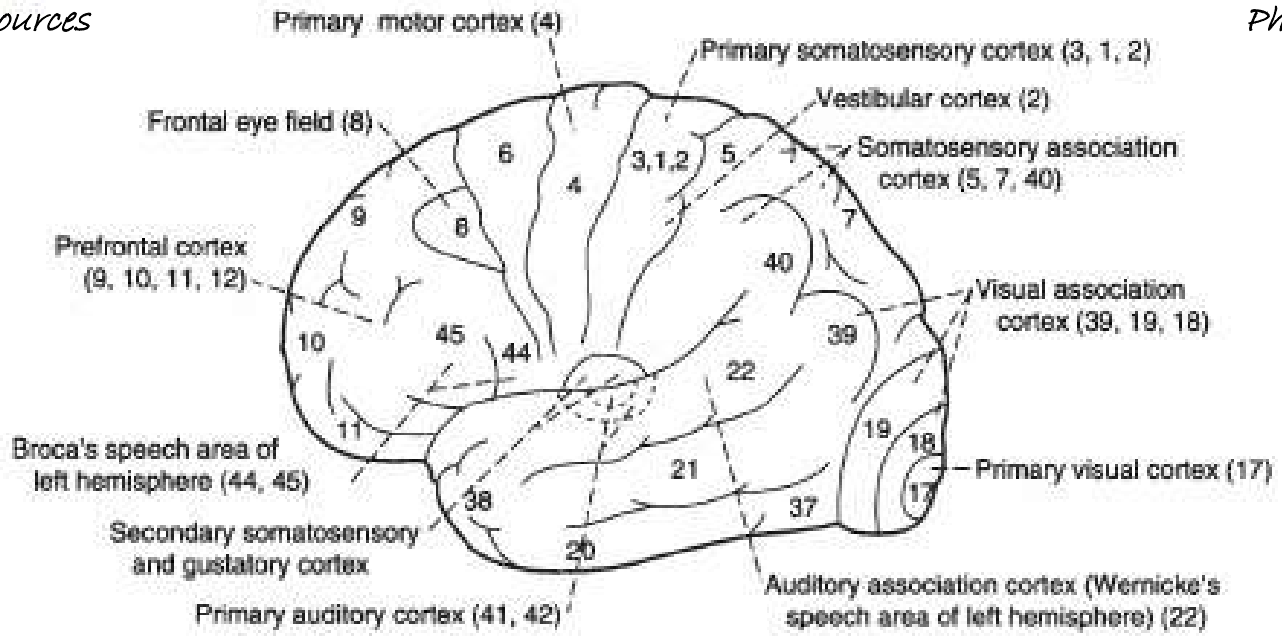
3. Through using Brodmann's areas, the cortex of the brain can be divided into **52 areas** which are numbered sequentially.

4. These areas are distinguished by microscopic anatomy through the shapes and types of cells and their connections.

5. Despite controversy Brodmann's areas are still widely used today



A



B

Lobe	Number	Other names
Frontal	4	Primary motor area (M1)
	6	Premotor, supplemental motor areas
	8	Frontal eye fields
	44, 45	Broca's area
	46	Epicenter of working memory
Parietal	3,1,2	Primary somatosensory area (S1)
	5, 7	Somatosensory association (7 is multimodal)
	39, 40	Inferior parietal lobule (angular & supramarginal gyri)
Occipital	17	Primary visual area (V1); striate cortex
	18, 19	Visual association areas; extrastriate cortex
Temporal	41, 42	Primary & secondary auditory areas (A1 & A2)
	20, 21 & 22	Temporal association areas (Wernicke's area in

Somatosensory area I and somatosensory area II
(1,2,3, 5.7)

Primary motor area and other area.
(4,6,8,44,45,46)

Visual area
(17,18,19)

Auditory area
(41,42)

PHYLOGENETIC TYPES OF CORTEX

Since the evolution took a long time to shape the human brain in a way we know it today, there are different cortical areas that can be categorized based on their phylogenetic age:

1. **The allocortex (subdivided into Archicortex & Paleocortex)**
2. **The meso-cortex (also known as Juxtallocortex)**
3. **Isocortex (neo cortex)**

1. Allocortex

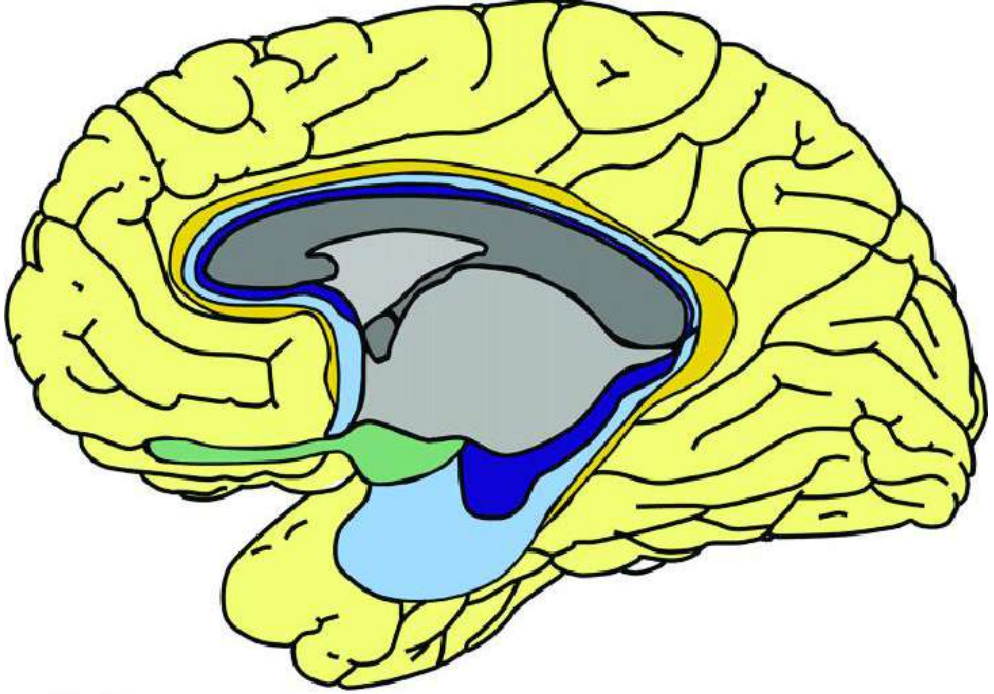
- This cortex contains **most ancient** phylogenetically structures. Subdivided into archi and paleocortex.
- The **archicortex** consists of only three cellular layers: polymorphic, pyramidal and the molecular layer. It is associated with the limbic system, specifically with the hippocampal formation, meaning it is involved with emotional expression and memory.
- The **paleocortex** contains three to five layers of cells. It is located within the para-hippocampal gyrus (entorhinal cortex), uncus (piriform cortex) and lateral olfactory gyrus, meaning it mediates the sense of smell.

2. Mesocortex

- Also known as Juxtallocortex, it is actually the transitional form between the allocortex and neocortex. It contains three to six layers and is found in the insula and cingulate gyrus. Subdivided into peri-archicortex and pro-isocortex.

3. Isocortex (neocortex):

- Isocortex is the **most recent** cortical portion and makes up to 90% of the human cortex. It includes all of the lobes except for the limbic. It consists of **six layers of cells** marked with Roman numbers I to VI, going from the most superficial layer to the deepest.
- The first four layers (I-IV) are input stations that receive corticopetal fibers.
- Layers V and VI are output stations that give rise to corticofugal projection fibers.



paleocortex

archicortex

periarchicortex

isocortex

proisocortex

Isocortex (neocortex)	6 layers	90% of cerebral hemisphere (sensory, motor and association areas)
Mesocortex (periallocortex, proisocortex)	3–6 layers	Majority of limbic lobe (e.g. cingulate/parahippocampal gyri)
Allocortex	3 layers	Hippocampal formation (archicortex) Primary olfactory areas (paleocortex)

HISTOLOGICAL STRUCTURE OF THE CEREBRAL CORTEX (NEOCORTEX)

Neuroscientists discovered that the neurons in neocortex are organized in layers, or laminas, parallel to the surface of the brain. There are 6 layers.

1.Molecular (Plexiform) layer I: consists of apical dendritic tufts of the pyramidal neurons, horizontally organized axons, Cajal cells and glial cells.

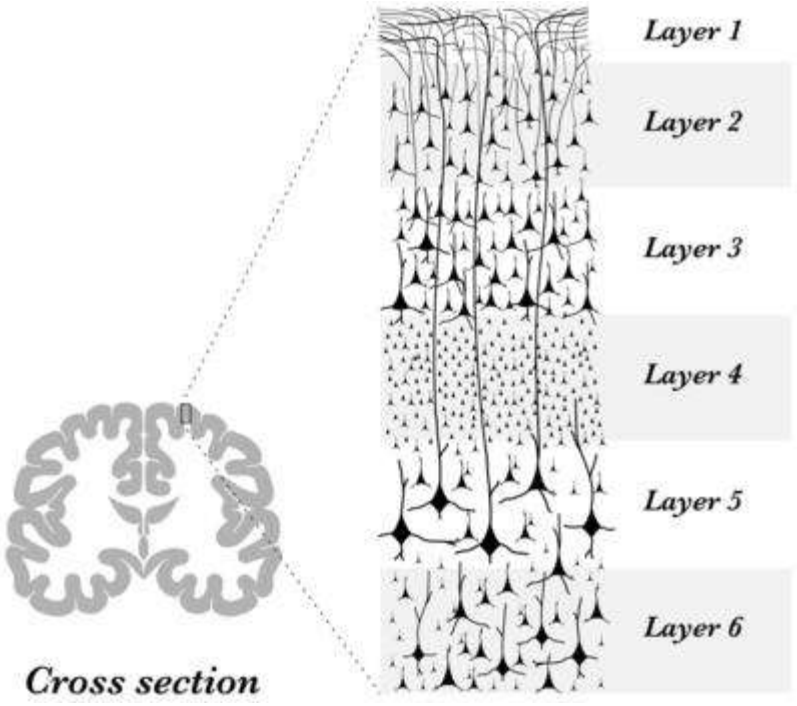
2.External granular layer II: consist of mainly granular cells and small pyramidal cells.

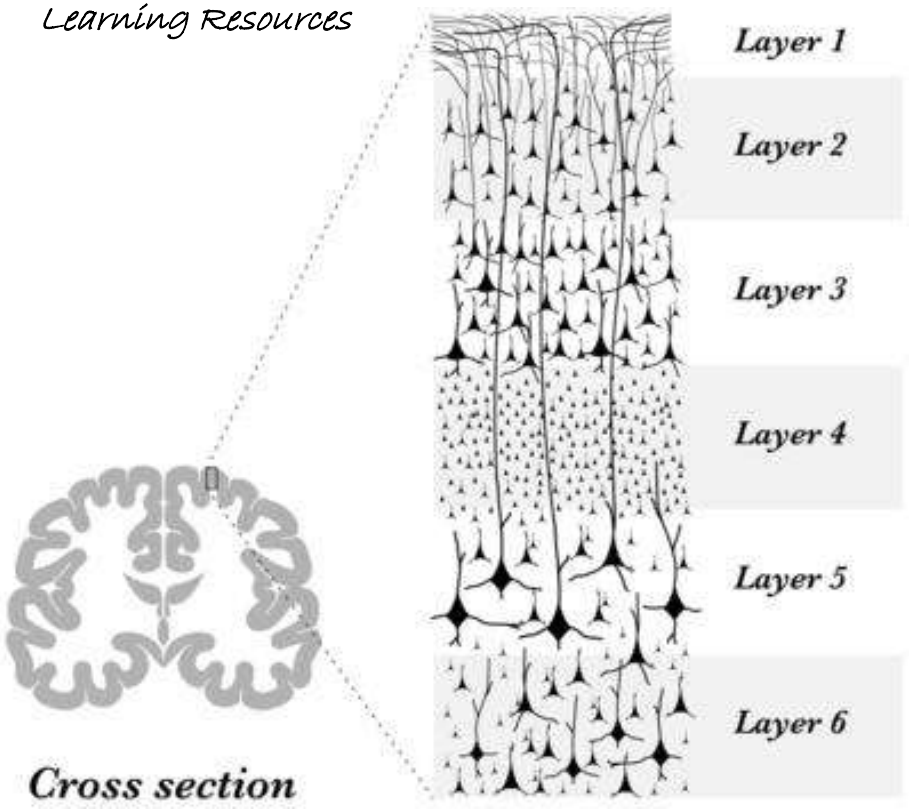
3.External pyramidal layer III: consists of small and medium-sized pyramidal cells. Horizontally running myelinated fibers makes the band of Baillarger stripe.

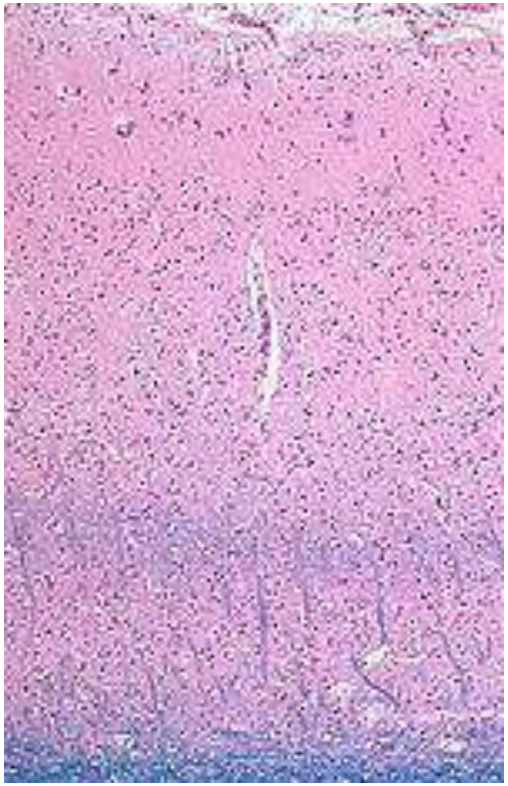
4.Internal granular layer IV: contains small round granular cells (spiny stellate cells, spiny interneurons) and small pyramidal cells.

5.Internal pyramidal layer V: contains the largest pyramidal cells. Axons of the pyramidal cells leave the cortex and reach subcortical areas. Layer V is subdivided into Va, Vb and Vc sublayers. The inner band of Baillarger is observed in layer V in myelin-stained sections.

6.Multiform (Polymorphous) layer VI: Excitatory cells like spiny stellate cells, pyramidal cells, inverted pyramidal neurons, bipolar/fusiform cells, are present in layer VI. It also contains inhibitory interneurons.







Band of Baillarger: The band of Baillarger consist of two bundles of myelinated fibers, located in the internal granular layer of layer IV and internal pyramidal layer of layer V. At a microscopic level, the lines of Baillarger can be found throughout the cortex.

The stria of Gennari: It is a band of highly myelinated fibers that runs tangentially to the gray matter surface in primary visual cortex, at the level of layer IV. Due to its presence, the primary visual cortex is also known as the striate cortex. This structure is visible to the naked eye on macroscopic examination of the brain and represents a special case of the outer band of the lines of Baillarger.

CEREBRAL DOMINANT HEMISPHERE

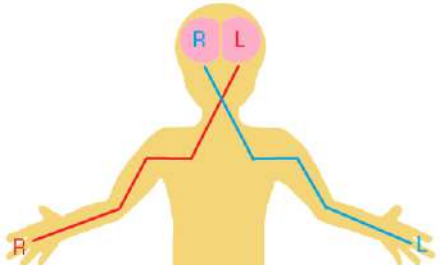
Although the left and right cerebral hemispheres look alike in shape, size, and dimensions, they differ in their neuronal activities and functional areas Some established functional differences have been identified among the right and left cerebral hemispheres

1. **Dominant cerebral hemisphere** The cerebral hemisphere controlling the **language** is considered as a dominant cerebral hemisphere. In all right-handed people and almost half of the left-handed people, language is processed in the left hemisphere and therefore, the left hemisphere is the dominant hemisphere in 90–95% of the population. The dominant hemisphere is more proficient in **handedness**, language, mathematical and analytical processes.
2. **Non-dominant hemisphere:** The opposite hemisphere is Known as non-dominant hemisphere. It is more proficient in creative arts, music, spatial comprehension, geometrical and fa

Hemisphere Functions

Dominant Hemisphere	Non-dominant Hemisphere
•Language-related activities: reading, writing, speaking	Nonverbal functions: 1. Motor tasks requiring orientation of body in space
•Complex intellectual functions requiring verbal, analytical, and computational skills	2. Recognition and understanding of musical patterns 3. Nonverbal visual experiences

HANDEDNESS



Cerebral Dominance

- 90-95% right handed people = left hemisphere dominance
- 65-75% left handed people = left hemisphere dominance
- True ambidextrous people
  - 60% left dominance
  - 30% right dominance
  - 10% equal dominance
- Handedness is not a 100% accurate assessment of cerebral dominance
  - Wada testing

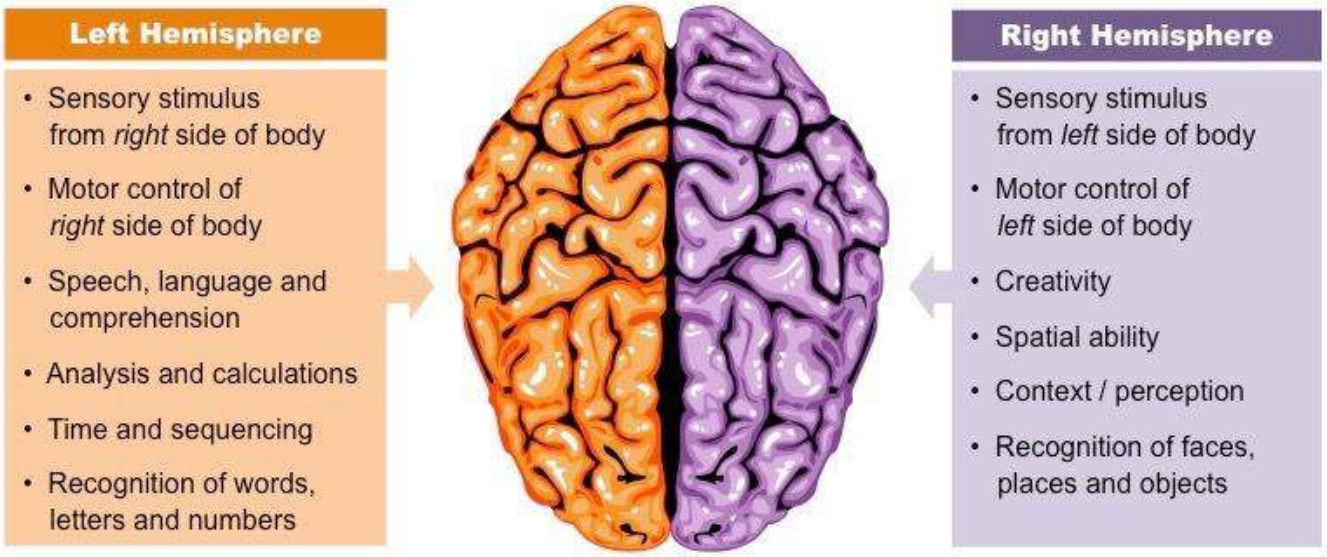
CATEGORICAL AND REPRESENTATIONAL HEMISPHERE:

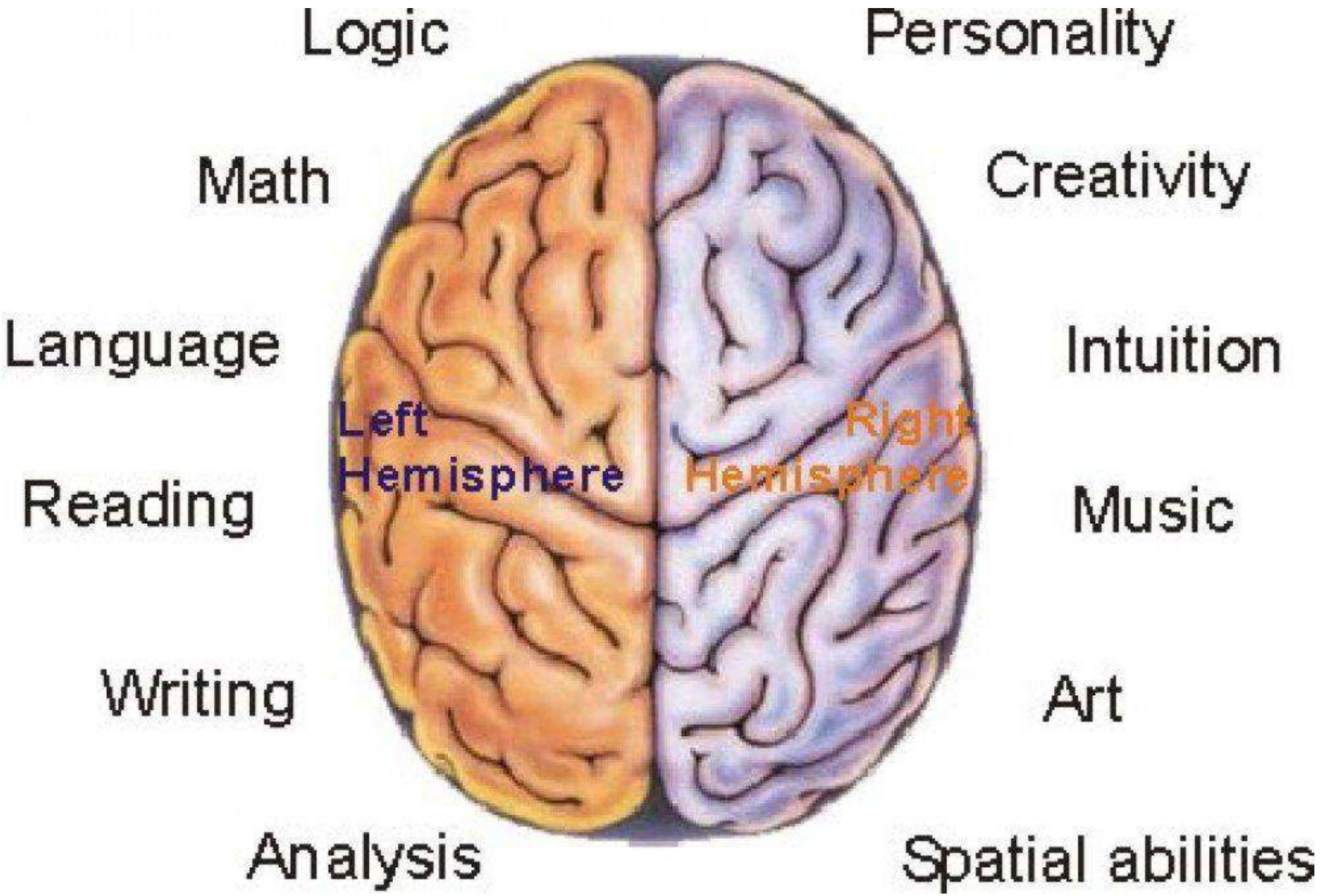
1. Human brain is not symmetrical. In humans, the left and right sides process information differently and control different patterns of behavior. This is known as **brain lateralization (cerebral asymmetry).** The right and left sides of the brain are specialized for certain skills.

2. It is said that brain's capacity and efficiency may be increased by not duplicating all functions on the left and right sides. In this way , brain can increase its cognitive capacity without increasing brain size.

3. **Categorical hemisphere (dominant hemisphere):** In almost 97% of the people, Left hemisphere is specialized for language and analytical ability, and is also called categorical hemisphere. Hemispheric specialization is related to handedness. In 96% of right-handed individuals, who constitute 91% of the human population, the left hemisphere is the dominant or categorical hemisphere. Lesions in the categorical hemisphere produce language disorders like fluent, non-fluent, and global aphasias.

4. **Representational hemisphere:** The right hemisphere specialized for visuo-spatial ability is the representational hemisphere . Lesions in the representational hemisphere produce astereognosis and agnosia—the inability to identify objects by feeling them.




Logic
Personality
Math
Creativity
Language
Intuition
Left Hemisphere
Right Hemisphere
Reading
Music
Writing
Art
Analysis
Spatial abilities

THE PREFRONTAL ASSOCIATION CORTEX:

1. The prefrontal association cortex (PFC) is a cortical region in the anterior part of the cerebrum. The PFC is regarded as the center of higher cortical functions. **The PFC contains the Brodmann areas 8, 9, 10, 11, 12, 13, 14, 24, 25, 32, 44, 45, 46, and 47.**
2. In humans PFC occupies a far larger percentage of the brain than in any other animal. And it is theorized that, as the brain has tripled in size over five million years of human evolution, the prefrontal cortex has increased in size sixfold.

3. FUNCTIONS:

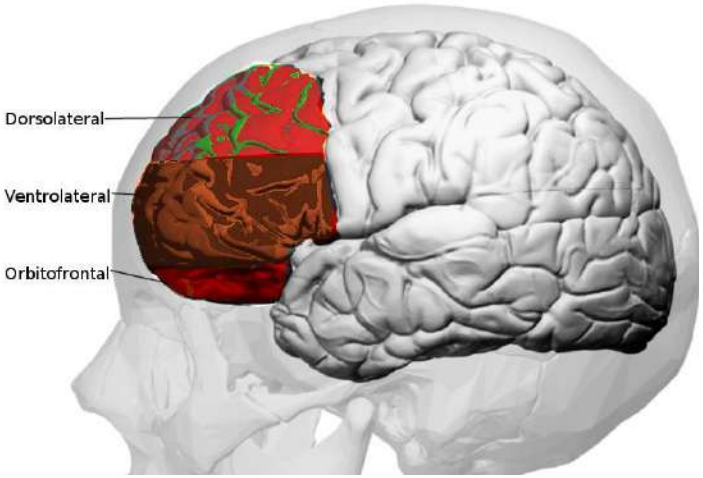
- PFC controls the **executive functions** of the brain: planning, insight, foresight, and many of the most basic aspects of personality. The PFC is involved in memory formation, planning, execution, higher-order information processing, and suppression of unwanted behaviors.

- **Dorsolateral prefrontal cortex** plays a critical role in **working memory,** the ability to keep "in mind" recent events or the moment-to-moment results of mental processing.

- Left **ventrolateral prefrontal cortex** is vital in the **processing of words and sentences. It** has been implicated in speech production, language comprehension, and response planning before speaking In contrast,

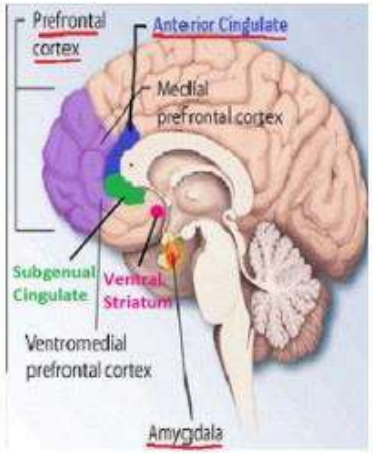
- **ventromedial prefrontal cortex** is interconnected more with limbic structures such as the amygdala, Patients with damage here are impulsive and have trouble **suppressing inappropriate responses and emotional reactions**

- Several studies on sleep physiology have demonstrated that the PFC is an area of origin for **slow waves during the non-REM sleep cycle** as evidenced by the decreased regional cerebral blood flow to prefrontal areas during non-REM sleep

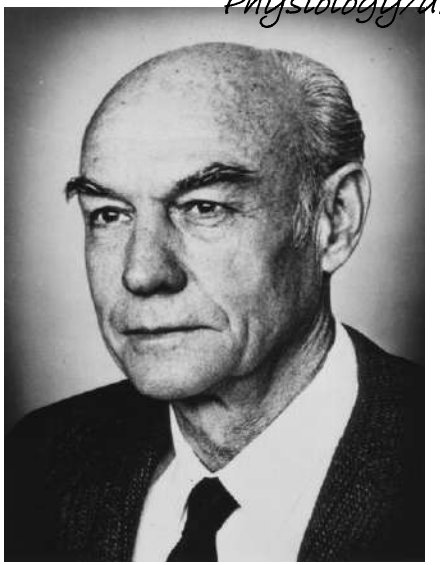


Executive Functions – prefrontal cortex

- Planning
- Organization
- Time management
- Task initiation
- Working memory
- Metacognition
- Self-Control
- Attention
- Perserverance
- Flexibility

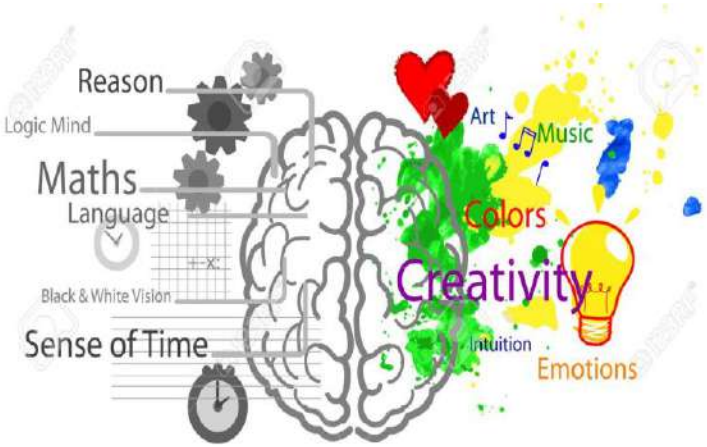


SPLIT BRAIN:



1. The term "split-brain" refers to patients in whom the corpus callosum has been cut to reduce the spread of epileptic foci between the cerebral hemispheres. **Roger Sperry,** who initiated split-brain research and supervised the experiments on commisurotomy in humans, received a Nobel prize for this work in 1981.

2. Split-brain patients provide a unique window into functional specialization of each cerebral hemisphere. Left brain was characterized as linear, logical, and rational, and the right as holistic, creative, intuitive, and emotional.



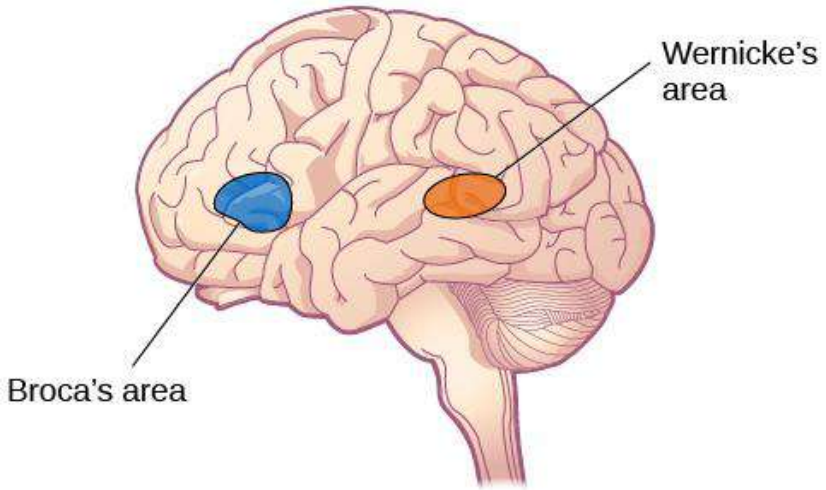
3. **Symptoms:** Patients with split-brain syndrome retain intact memory and social skills. They maintain motor skills which were learned before the onset of their condition; examples include walking, swimming, and biking. They can also learn new tasks that involve either parallel or mirrored movements of their fingers or hands. They cannot, however, learn to perform new tasks that require interdependent movement of each hand, such as learning to play the piano etc. Split-brain patient may remain conscious following commissurotomy because the connections between the cortex and thalamus in each hemisphere remain

Cerebral cortex:

1. Write short notes on histological structure of cerebral cortex. (3/2018)
2. What is bands of Baillarger? (1/2018)
3. What do you mean by somatosensory area I and somatosensory area II. (2/2018)
4. What is somatotopic organization in cerebral cortex? (1/2018)
5. What is meant by complimentary specialization of cerebral hemispheres? discuss the asymmetric functions of cerebral hemispheres. (1+3/2018)
6. What do you mean by categorical and representational hemisphere? (4/2010)
7. What are juxtallo-cortex and allocortex? (4/2011)
8. What is split brain? (2/2015)
9. What do you mean by isolated cortex? (1/2018)
10. Write short notes on pre-frontal association cortex. Mention any two important functions (4+2/2016)
11. Describe the functions of different locations of frontal and parietal lobes of cerebrum. (3/2018)- Khurana/CC Chatterjee.

Broca's and Wernicke's areas (Language and speech)

1. **Broca's** and **Wernicke's areas** are cortical areas specialized for production and comprehension of human language. Broca's area is found in the left inferior **frontal** gyrus and Wernicke's area is located in the left posterior superior **temporal** gyrus.



Discovery:

1. In 1861, when **Paul Broca**, a French neurosurgeon, examined the brain of a recently deceased patient. Though he had been able to understand spoken language, he could neither speak a complete sentence nor express his thoughts in writing. Broca found a sizable lesion in the left inferior frontal cortex. (His famous statement that "we speak with the left hemisphere" came after this discovery). This area is involved in **production of speech and articulation.**

2. Ten years later, **Carl Wernicke**, a German neurologist, discovered another part of the brain, this one involved in **understanding language**, in the posterior portion of the left temporal lobe. People who had a lesion at this location could speak, but their speech was often incoherent and made no sense.

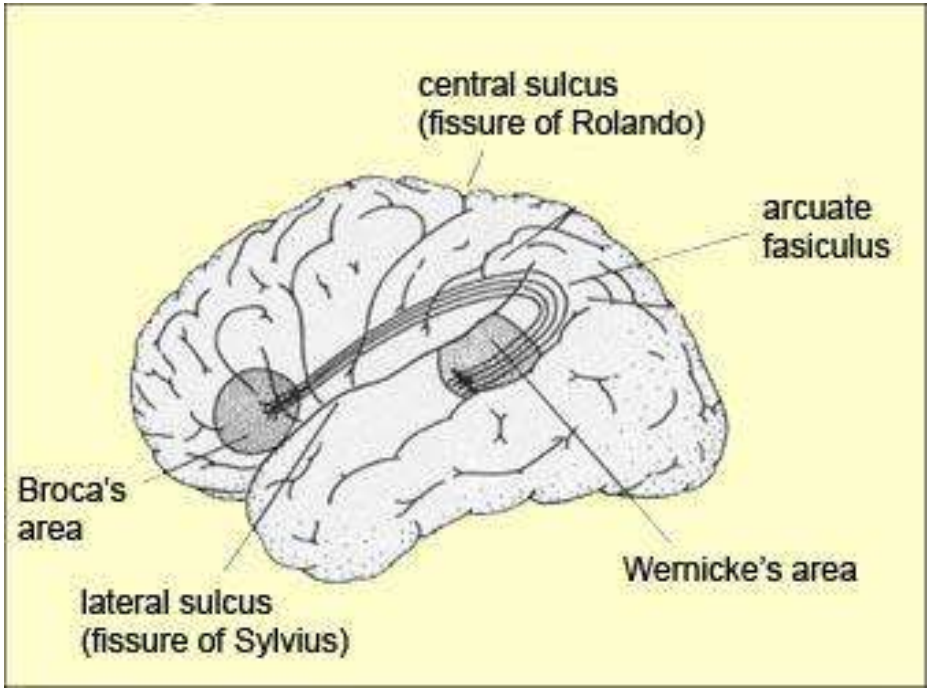
3. There is a third area known as **angular gyrus** which allows us to associate a perceived word with different images.

THE LANGUAGE LOOP IN BRAIN:

Neuroscientists now agree that there is a neural loop that runs around the lateral sulcus (also known as the fissure of Sylvius) in the **left hemisphere** of the brain, which is involved both in understanding and in producing spoken language.

1. At the frontal lobe end of this loop, lies **Broca's area**, which is usually associated with the production of language. At the other end (in the posterior temporal lobe), lies **Wernicke's area**, which is associated with the processing of words that we hear or any language inputs. Broca's area and Wernicke's area are connected by a large bundle of nerve fibers called the **arcuate fasciculus.**
2. This language loop is found in the **left hemisphere** in about 90% of right-handed persons and 70% of left-handed persons, language being one of the functions that is performed asymmetrically in the brain.

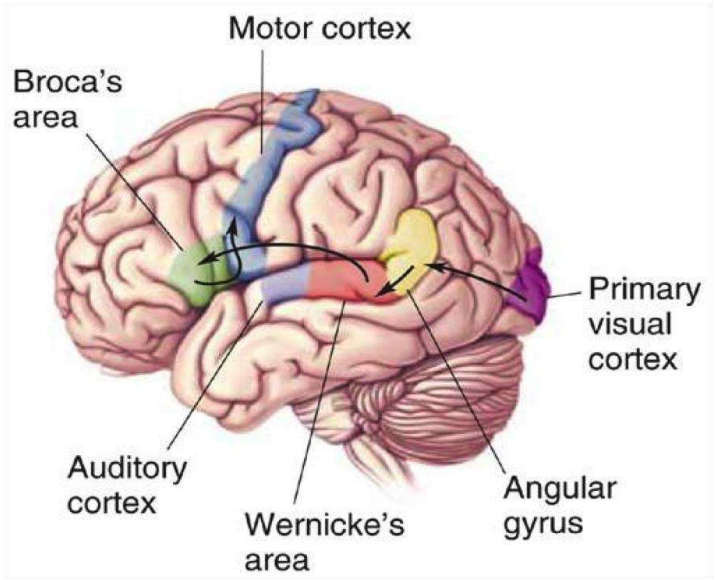
3. Surprisingly, this loop is also found at the same location in deaf persons who use sign language.

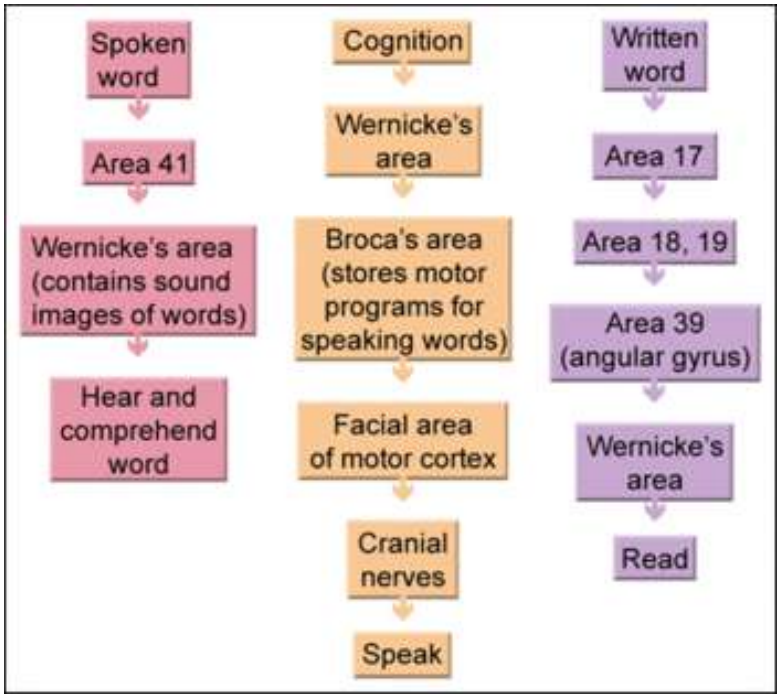


Geschwind-Wernicke model (Language model):

1. According to this model, **each of the various characteristics of language (perception, comprehension, production, etc.) is managed by a distinct functional module in the brain**, and each of these modules is linked to the others by a very specific set of serial connections.

1. According to this model, when **we hear a word spoken**, this auditory signal is processed first in our brain's **primary auditory cortex**, which then sends it on to the neighboring **Wernicke's area.** Wernicke's area associates the structure of this signal with the representation of a word stored in your memory, thus enabling you to retrieve the meaning of the particular word.
2. In contrast, **when we read a word out loud**, the information is perceived first by our **visual cortex**, which then transfers it to the **angular gyrus**, from which it is sent on to Wernicke's area. Then, this information is transmitted to **Broca's area** via the arcuate fasciculus. Broca's area plans the pronunciation process. Lastly, this information is forwarded to the motor cortex, which controls the muscles that we use to pronounce the word. Language disorders arise from breakdowns in this network of connections between these modules.





APHASIA:

Aphasias are **abnormalities of language functions** that are not due to defects of vision or hearing or to motor paralysis. They are caused by lesions in the categorical hemisphere. The most common cause of aphasia is embolism or thrombosis of a cerebral blood vessel.

Types:

1. **Non-fluent aphasia (Broca's aphasia):** In this type, the lesion is in Broca's area. Speech is slow, and words are hard to come by. Patients with severe damage to this area are limited to two or three words with which to express the whole range of meaning and emotion.

2. **Fluent aphasia (Wernicke's aphasia):** In this type, the lesion is in Wernicke's area. Posterior superior temporal gyrus in the dominant hemisphere becomes damaged or destroyed . The patient is capable of understanding either the spoken word or the written word but are unable to interpret the thought that is expressed. In this condition, speech itself is normal and sometimes the patients talk excessively. However, what they say makes little sense. The patient also fails to comprehend the meaning of spoken or written words.

3. **Global Aphasia:** It is found when the lesion in Wernicke's area is widespread and extends (1) backward into the angular gyrus region, (2) inferiorly into the lower areas of the temporal lobe, and (3) superiorly into the superior border of the sylvian fissure. Person with global aphasia can neither read nor write. There is a combined defect of both receptive and expressive language.

4. **Dyslexia:.** If the angular gyrus is destroyed, then the stream of visual stimuli passing from the visual cortex into Wernicke's area is blocked. Therefore, the person may be able to see words and even know that they are words but not be able to interpret their meanings. This is the condition called dyslexia, or word blindness.

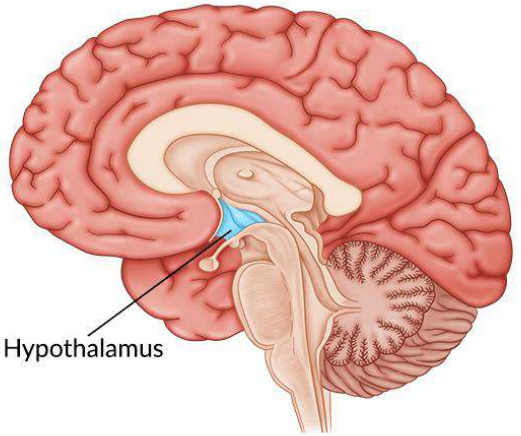
Language and Speech:

1. What are Broca's area and Wernicke's area? (1/2018)
2. State the location and function of Wernicke's area (2/2022)
3. Mention the impairments of functions due to the separate lesions of these areas. (2/2018)
4. What is Aphasia? Classify different types of Aphasia. (2+4/2019/2021)
5. What is fluent and non-fluent aphasia? (5/2022)
6. State the location of sensory and motor speech area. (4/2019)

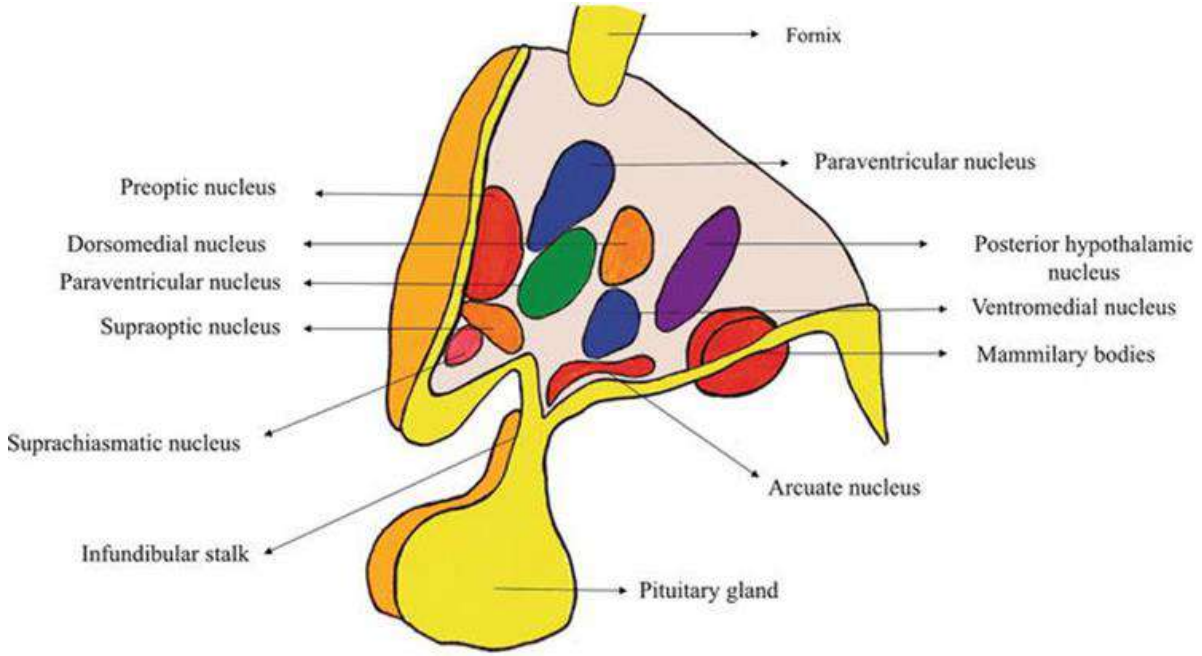
HYPOTHALAMUS

1. The hypothalamus is a small conglomerate of nuclear bodies lying below the thalamus and making up the floor of the third cerebral ventricle.

2. Speaking broadly, the hypothalamus is a high-level sensory integration and motor output area that maintains homeostasis by controlling endocrine, autonomic, and somatic behavior.



3. There are 11 unique nuclei within hypothalamus.
   - Paraventricular nucleus
   - Preoptic nucleus
   - Supraoptic nucleus
   - Suprachiasmatic nucleus
   - Anterior nucleus
   - Posterior nucleus
   - Ventromedial nucleus
   - Dorsomedial nucleus
   - Arcuate nucleus
   - Mamillary nucleus/ bodies



FUNCTIONS OF HYPOTHALAMUS (cont)

- Functions are

1. Controls body temperature
2. Controls thirst and urine output
3. Controls food intake(Hunger and Satiety center)
4. Controls anterior pituitary hormone secretion
5. Produces posterior pituitary hormones
6. Controls uterine contraction and milk ejection
7. Serves as major ANS coordinating center
8. Plays role in emotional and behavioral pattern
9. Participates in the sleep – wake cycle

ROLE OF HYPOTHALAMUS IN FOOD INTAKE

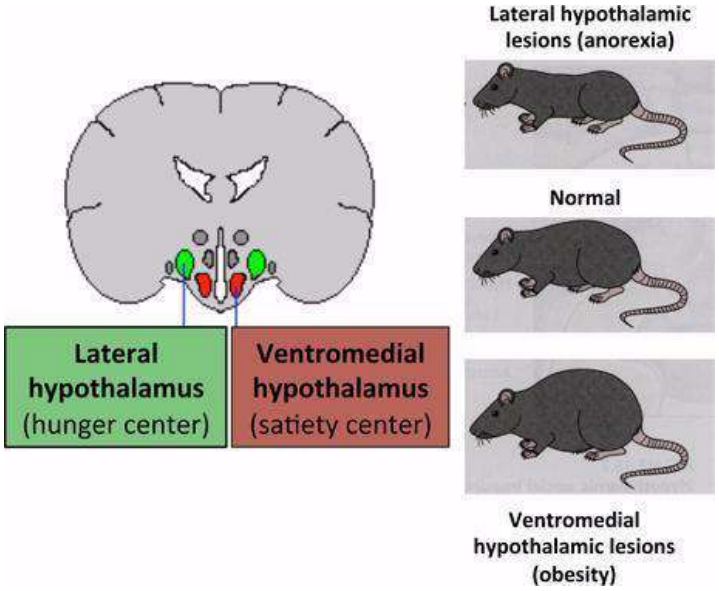
The old concept: Hypothalamic Hunger and Satiety Center:

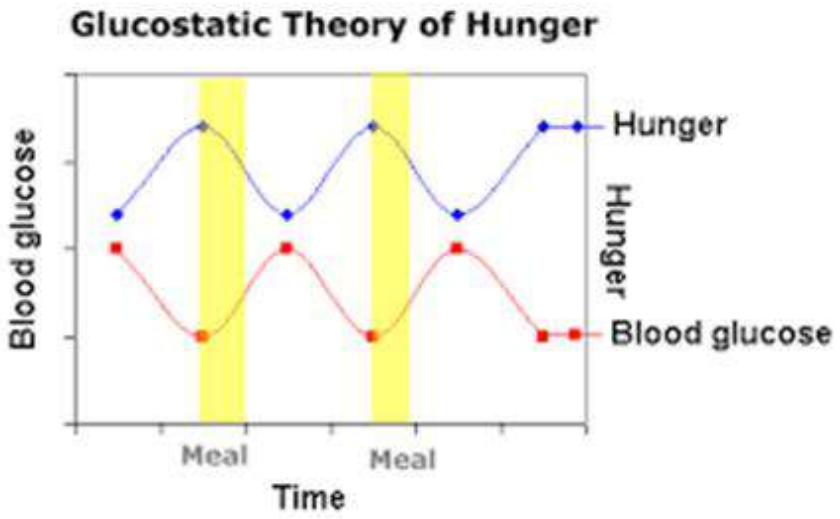
In the 1950s, experiments on rats seemed to suggest that eating behavior is controlled by two different regions of the hypothalamus:

1. **FEEDING CENTRE(LH)** : In 1951, Anand and Brobeck reported that bilateral electrolytic lesions to the lateral hypothalamus produce aphagia—a complete cessation of eating. So LH was considered to be the feeding centre.

2. **SATIETY CENTRE (VMH):** In 1940, it was discovered that large bilateral electrolytic lesions to the ventromedial hypothalamus produce hyperphagia (excessive eating) and extreme obesity. So VMH was considered as satiety centre.

Glucostatic hypothesis: 1950's that Mayer put forward the glucostatic theory. **Glucose** was thought of as a likely satiety factor. According to Glucostatic Theory, hunger and the initiation of eating occurs as a result of a decline in blood glucose. When the plasma glucose concentration rises after a meal it can be sensed by "Gluco-receptor" neurons in the hypothalamus to signal termination of feeding.





However, recent evidence suggests that this concept is not enough to explain food intake behaviors. There are many other nuclei within the hypothalamus which influence hunger and satiety.

ROLE OF HYPOTHALAMUS IN FOOD INTAKE (NEW CONCEPT)

Five hypothalamic nuclei have been associated to food intake regulation: the **Lateral, Ventromedial, Dorsomedial, PVN and Arcuate nuclei** .

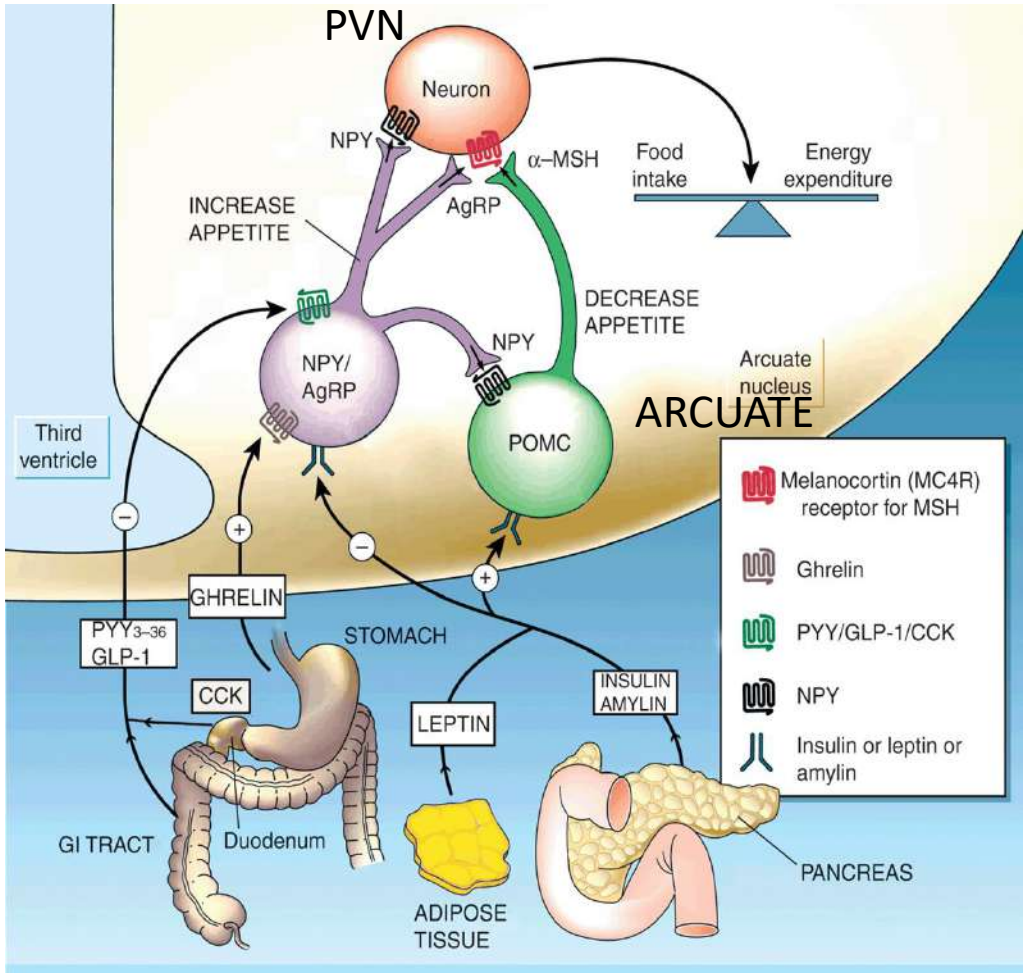
1. **1st order neuron:** The **arcuate nuclei hosts first order neurons**. It is located adjacent to the median eminence, a circumventricular organ. Thus, circulating hormones and nutrients can access the this nucleus without passing the Blood brain barrier.

   - Some neurons in arcuate nucleus expresses **orexigenic peptide** (stimulate hunger) like neuropeptide Y (NPY) and neuropeptide agouti-gene related peptide (AgRP) which project to second order neurons localized in the PVN to stimulate food intake.

   - Other population of neurons in arcuate nucleus expresses **anorexigenic neuropeptides** (produces satiety) like proopiomelanocortin (POMC) and CART which also project to second order neurons in PVN and LHA in order to inhibit food intake and produce satiety**.** The α-melanocyte-stimulating hormone (α-MSH), an anorexigenic neuropeptide, released from POMC neurons binds to PVN to inhibit food intake and promote satiety.

2. 2nd order neuron: The **PVN neurons are the 2nd order neurons** which synthesize and secrete **neuropeptides** (CRH, TRH, somatostatin, vasopressin, and oxytocin) that have a net catabolic action. In addition, PVN sends sympathetic outflow to the peripheral metabolic organs, including **liver and adipose tissue**, resulting in increased fatty acid oxidation and lipolysis.

Many peripheral metabolic signals **(like ghrelin, leptin, intestinal peptide, insulin etc.)** can influence these hormones in hypothalamus.



1. **GHRELIN:** Ghrelin is an orexigenic peptide, primarily secreted from the stomach. Plasma ghrelin concentrations have been shown to increase before meals. Ghrelin increases food intake by stimulating (NPY) and (AgRP) in hypothalamus. Intravenous infusion or subcutaneous injection of ghrelin in humans increases both subjective hunger and food intake.

2. **LEPTIN** : Leptin is an anorexigenic hormone exclusively produced by white adipocytes. Plasma leptin concentration increases when lipid reserves are high, Circulating leptin enters the brain through BBB and activate POMC/CART neurons in hypothalamus. At the same time it also inhibits the activity of NPY/AgRP neurons, resulting in reduced food intake and satiety. Leptin deficiency in humans results in profound hyperphagia.

3. **INSULIN:** After a meal, insulin secretion rises and exercises an anorexigenic effect.

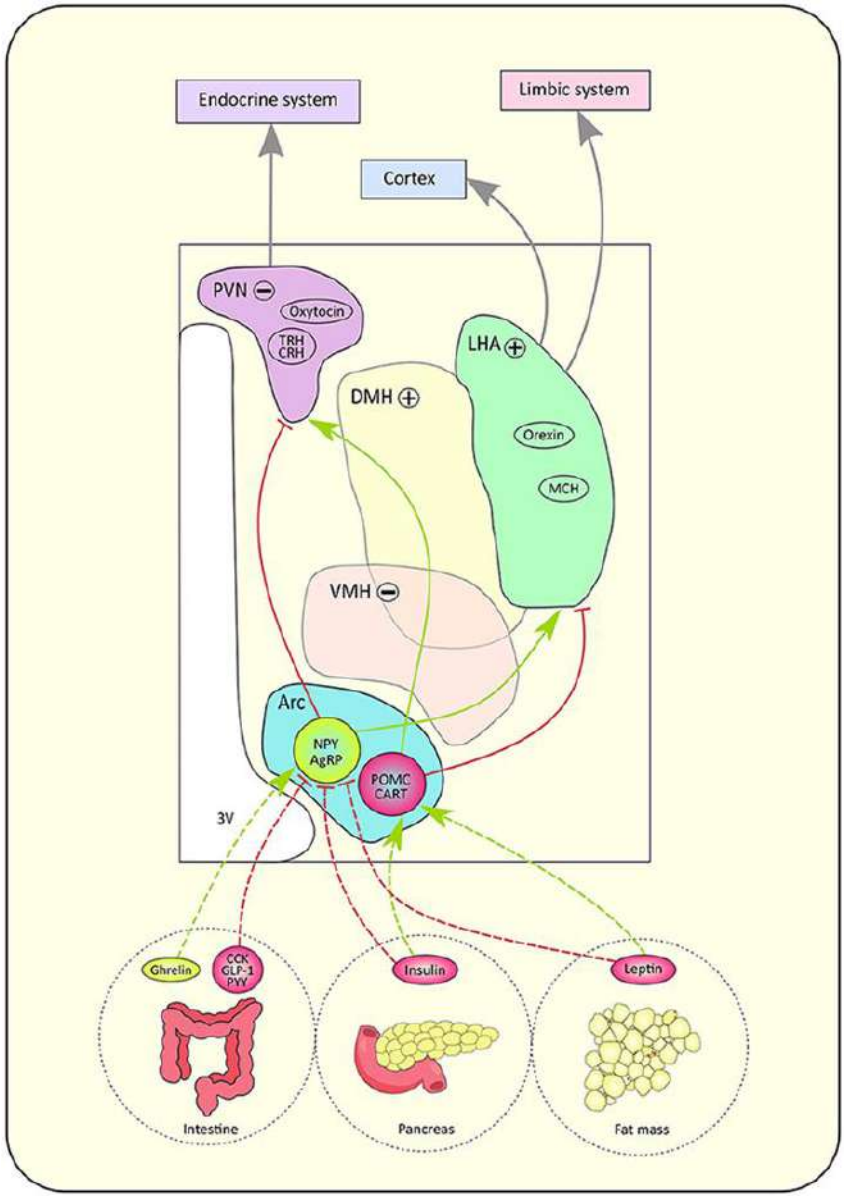
4. **INTESTINAL PEPTIDES** like cholecystokinin (CCK), and glucagon-like peptide-1 (GLP-1) stimulate satiety. Intravenously infused CCK within a physiological range has been shown to significantly decrease food intake in both lean and obese individuals

2. Ventromedial nucleus (VMN): The VMN mainly receives neuronal projections from the Arcuate nucleus, and projects their axons to the DMN and LHA. The VMN contains neurons that can sense glucose and leptin. **Destruction of the VMN caused hyperphagia and obesity**. Thus, the VMN is regarded as a pivotal area in generating **satiety.**

3. Dorsomedial nucleus (DMN): The DMN contains a high level of NPY terminals and α-MSH terminals originating from the Arcuate nucleus. . **Destruction of DMN also results in hyperphagia and obesity.**

4. Lateral hypothalamus: Destruction of LHA leads to hypophagia and weight loss. Therefore, **LHA has been considered to be a feeding center**. LHA produces orexigenic neuropeptides, the melanin concentrating hormone **(MCH) and orexin**, also called hypocretin.

***Orexin** are neurotransmitter hormones, synthesized in neurons of lateral Hypothalamus. Orexin-producing neurons are involved in glucose sensing and promote food intake. Orexin are inhibited by leptin and activated by Ghrelin and Hypoglycemia.



ROLE OF HYPOTHALAMUS IN THIRST

Thirst is "the physiological urge to drink water". In studies, it is recognized when subjects report the conscious sensation of a desire to drink.

1. The 4 major stimuli to thirst are:

   - **Hypertonicity:** Cellular dehydration acts via an osmoreceptor mechanism in the hypothalamus.
   - **Hypovolaemia:** Low blood volume is sensed via the low pressure baroreceptors in the great veins and RA.
   - **Hypotension:** The high pressure baroreceptors in carotid sinus & aorta provide the sensors
   - **Angiotensin II**: This is produced consequent to the release of renin by the kidney (eg., in response to renal hypotension)

2. **Thirst leads to drinking**. Drinking stimulates mechanoreceptors in the mouth and pharynx. These peripheral receptors provide input to the hypothalamus and the sensation of thirst is attenuated.

THIRST CENTRES IN BRAIN:

- The subfornical organ (SFO)
- Organum vasculosum of the lamina terminalis (OVLT) and
- Median preoptic nucleus (Mn PO)

All these 3 regions are part of 'circumventricular organs(CVOs) '.

Circumventricular organ

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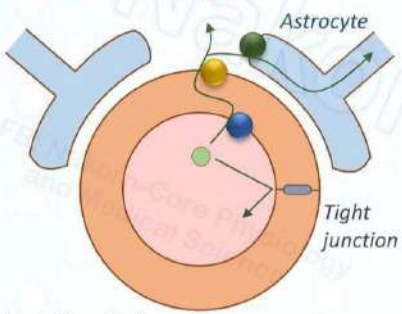
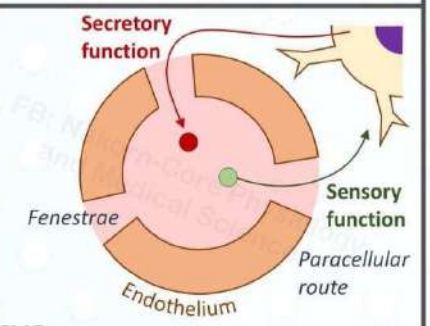
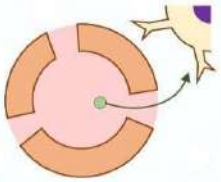


Blood brain barrier

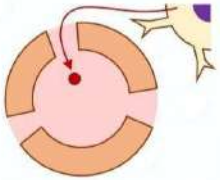


CVOs



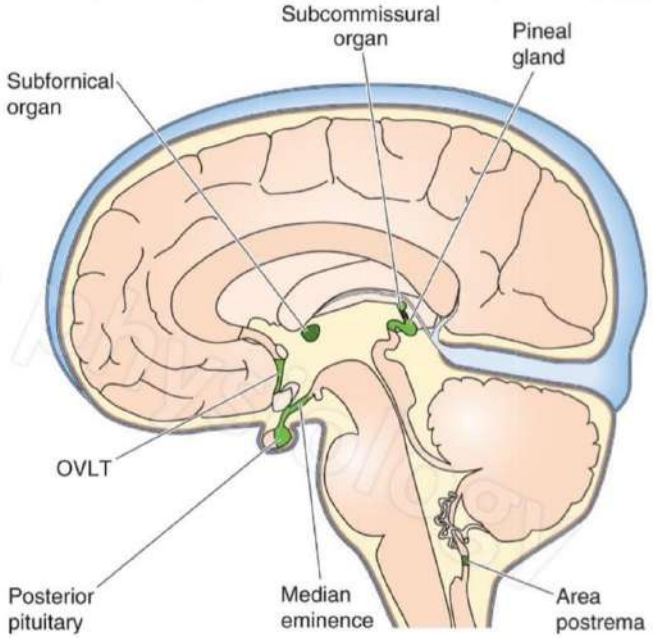
Sensory CVOs

1. OVLT
2. Subfornical organ
3. Area postrema



Secretory CVOs

1. Pineal gland
2. Median eminence
3. Posterior pituitary
4. Subcomissural organ



Circumventricular organs

- Posterior pituitary.
- Area postrema.
- Organum vasculosum of the lamina terminalis (OVLT).
- Subfornical organ (SFO).

These areas are outside the blood brain barrier. They have fenestrated capillaries .

Functions:

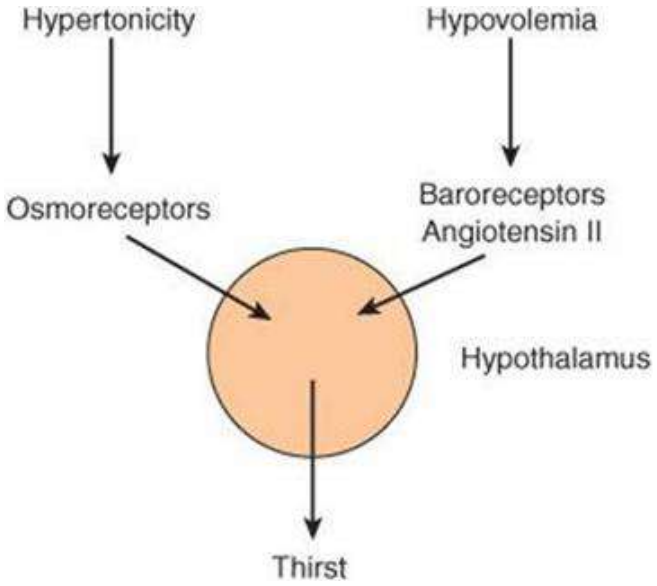
- Chemoreceptor trigger zone. As area postrema that trigger vomiting & cardiovascular control.
- Ang II acts on SFO and OVLT to increase H_2O intake.
- IL2 induce fever by (+) circumventricular organs.

STIMULATION OF OSMORECEPTORS IN BRAIN:

The **central osmoreceptors** are primarily present in two of the circumventricular organs named the organum vasculosum laminae terminalis **(OVLT)** and the subfornical organ **(SFO).**

If plasma osmolarity rises above 290 mOsmol/kg, water moves out of the osmoreceptor cell due to osmosis, causing the osmoreceptor to shrink in size. stretch inactivated cation channels (SICs) or TRPV open and allow positively charged ions, such as Na+ and K+ ions to enter the cell. This causes initial depolarization of the osmoreceptor and activates voltage-gated sodium channel, leading to an action potential and initiate the sensation of thirst.

In addition, these osmoreceptors cells of SFO and OVLT are sensitive to angiotensin II (AT1R). They also receive signals from peripheral arterial baroreceptors. Thus, SFO/OVLT neurons sense plasma osmolality, volume, and pressure to control thirst.



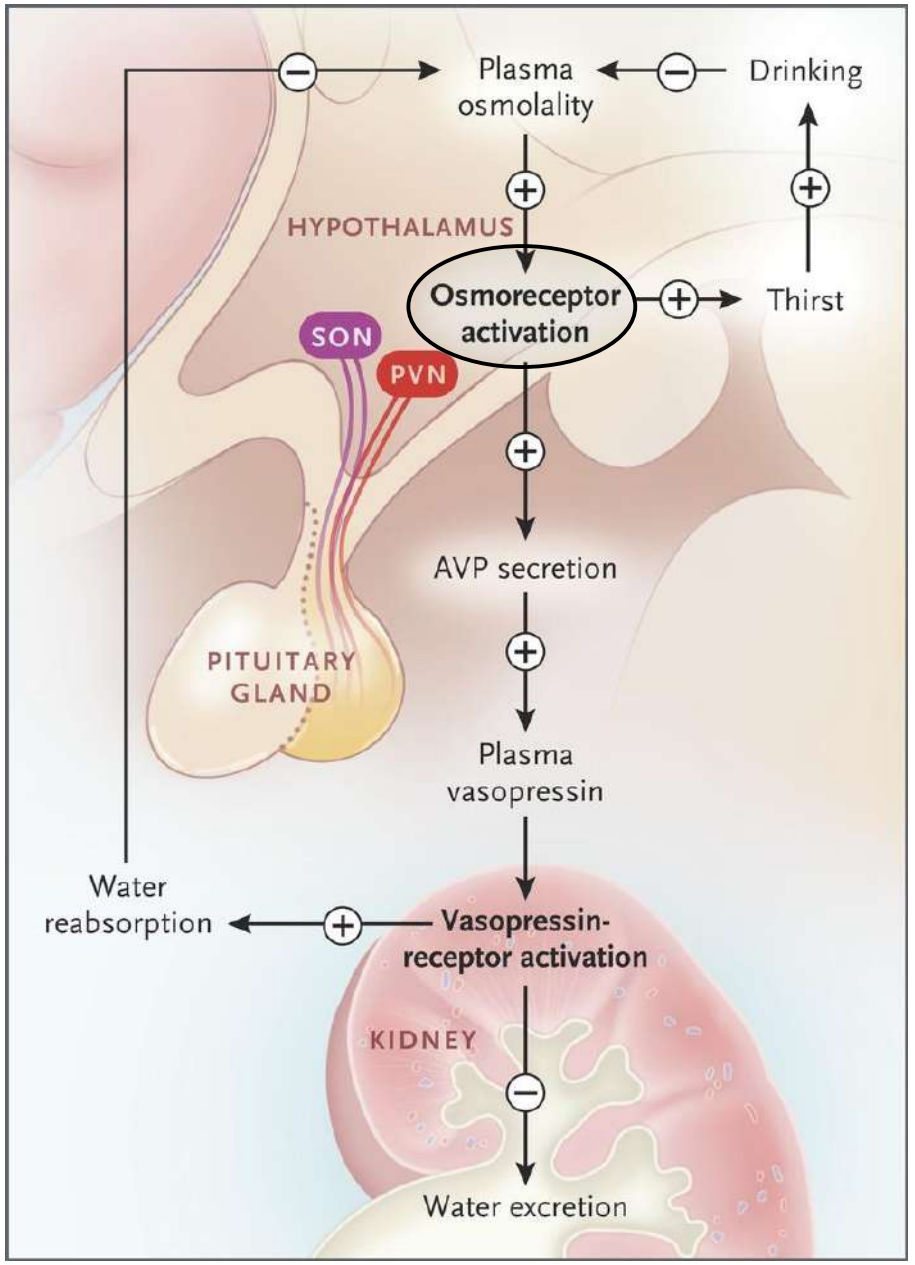
What happens when osmoreceptors are stimulated?

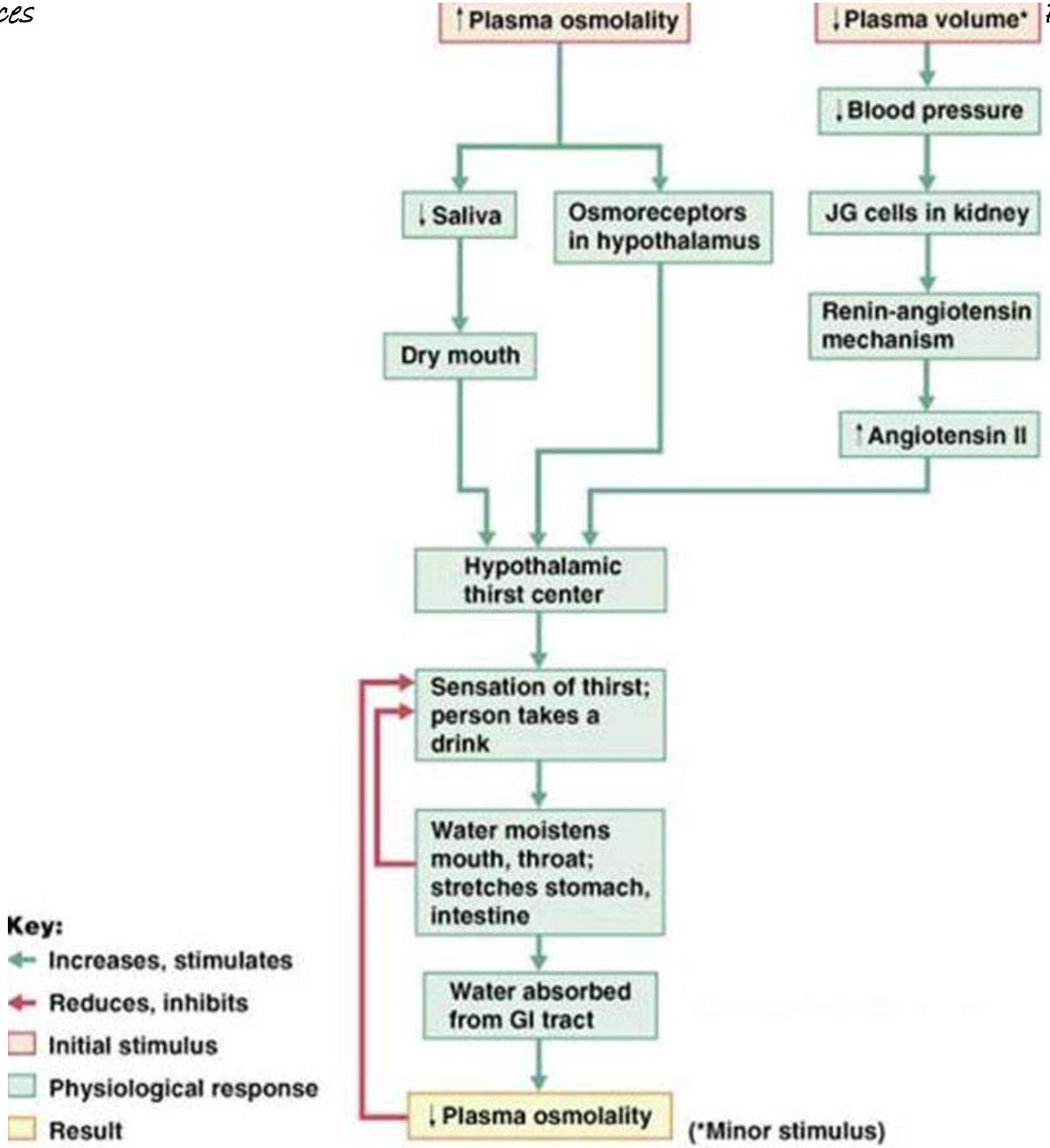
1. When the **SFO and OVLT** neurons (osmoreceptors) sense an increase in the serum osmolality above the permissible levels, **they relay this signal to the insula and cingulate cortex** via the paraventricular, dorsomedial and lateral nuclei of hypothalamus.

2. The cortex perceives these stimuli as thirst, and further invokes emotional and behavioral responses to quench thirst. As a result, **the individual becomes conscious of the demand for water. Upon drinking, this emotion is satisfied by the effect of water on the tongue and the buccal mucosa.**

3. At the same time, AVP (ADH) is produced by magnocellular neurons in the PVN and SON of hypothalamus. **AVP promotes the reabsorption of water from the collecting duct in kidney.** When the individual drinks water, both the thirst and AVP release ceases.

4. Another important responses to hypovolemia and hypotension is **generation of angiotensin II**. The SFO is the principal site in the brain where ANGII acts to promote drinking behavior. **It also promote water reuptake by the kidneys.**




↑Plasma osmolality
↓Plasma volume*
↓Blood pressure
↓Saliva
Osmoreceptors in hypothalamus
JG cells in kidney
Renin-angiotensin mechanism
Dry mouth
↑Angiotensin II
Hypothalamic thirst center
Sensation of thirst; person takes a drink
Water moistens mouth, throat; stretches stomach, intestine
Water absorbed from GI tract
↓Plasma osmolality
(*Minor stimulus)
Key:
Increases, stimulates
Reduces, inhibits
Initial stimulus
Physiological response
Result

Hypothalamic obesity :

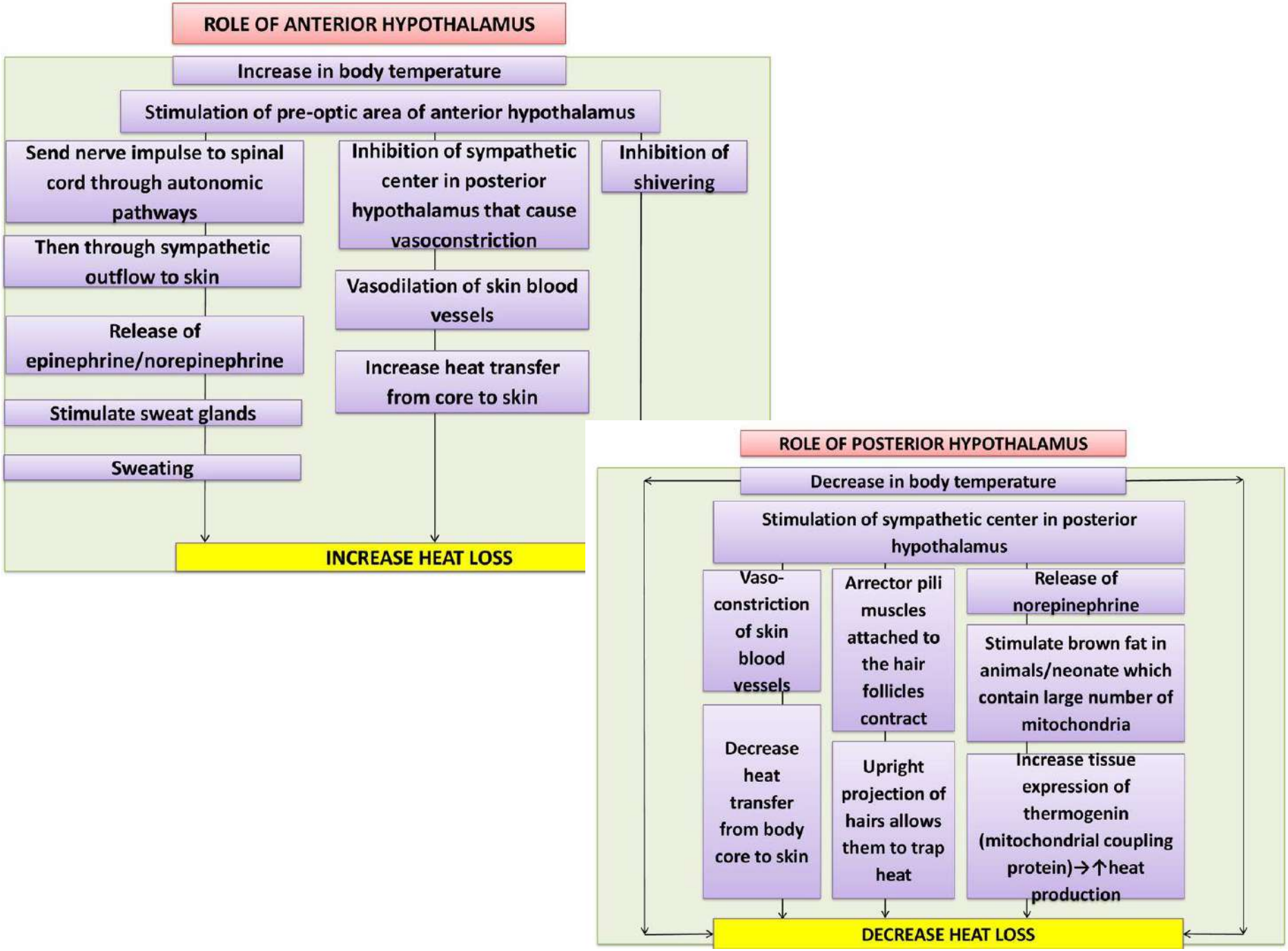
Hypothalamic obesity refers to obesity that is caused by physical or inborn damage to the hypothalamus. This condition most often occurs because of injury to the hypothalamus due to a tumor, swelling in the brain, brain surgery, or head trauma. In general, the clinical picture of hypothalamic obesity is characterized by rapid weight gain, extreme obesity, hyperphagia, decreased resting energy expenditure, and reduced physical activity.

Mamillary body:

The mammillary bodies are round, paired structures that lie in the inferior hypothalamus. They are a relay in the Papez circuit . There are 2 mammillary bodies on either side of the midline.

The primary function associated with the mammillary bodies is **recollective memory**. Mammillary bodies, and their projections to the anterior thalamus via the mammillo-thalamic tract, are important for recollective memory. The damage of medial mammillary nucleus leads to spatial memory deficit.

ROLE OF HYPOTHALAMUS IN BODY TEMPERATURE REGULATION

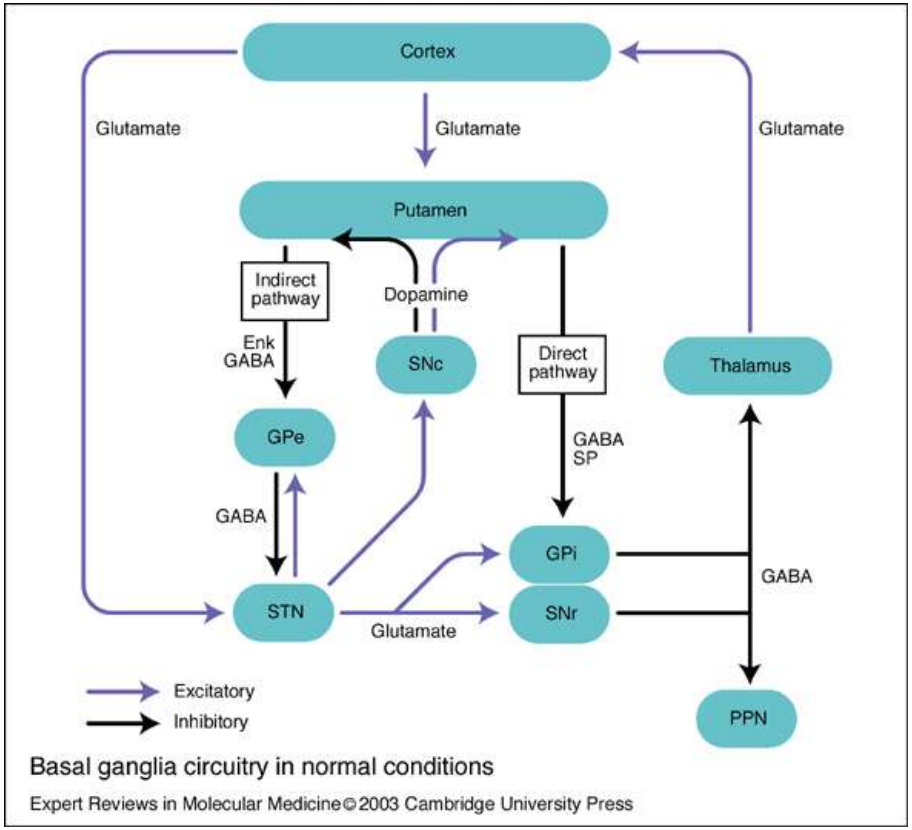

ROLE OF ANTERIOR HYPOTHALAMUS
Increase in body temperature
Stimulation of pre-optic area of anterior hypothalamus
Send nerve impulse to spinal cord through autonomic pathways
Then through sympathetic outflow to skin
Release of epinephrine/norepinephrine
Stimulate sweat glands
Sweating
Inhibition of sympathetic center in posterior hypothalamus that cause vasoconstriction
Vasodilation of skin blood vessels
Increase heat transfer from core to skin
Inhibition of shivering
INCREASE HEAT LOSS
ROLE OF POSTERIOR HYPOTHALAMUS
Decrease in body temperature
Stimulation of sympathetic center in posterior hypothalamus
Vaso-constriction of skin blood vessels
Decrease heat transfer from body core to skin
Arrector pili muscles attached to the hair follicles contract
Upright projection of hairs allows them to trap heat
Release of norepinephrine
Stimulate brown fat in animals/neonate which contain large number of mitochondria
Increase tissue expression of thermogenin (mitochondrial coupling protein)→↑heat production
DECREASE HEAT LOSS

Hypothalamus:

1. Discuss the role of hypothalamus in body temperature regulation. (8/2021)
2. Discuss the role of hypothalamus in hunger and satiety. (8/2022)
3. Discuss the role of hypothalamus in thirst. (3/2012/2009)
4. What do you mean by circumventricular organs? (2/2021)
5. What is hypothalamic obesity? (3/2009)
6. What is mammillary body?

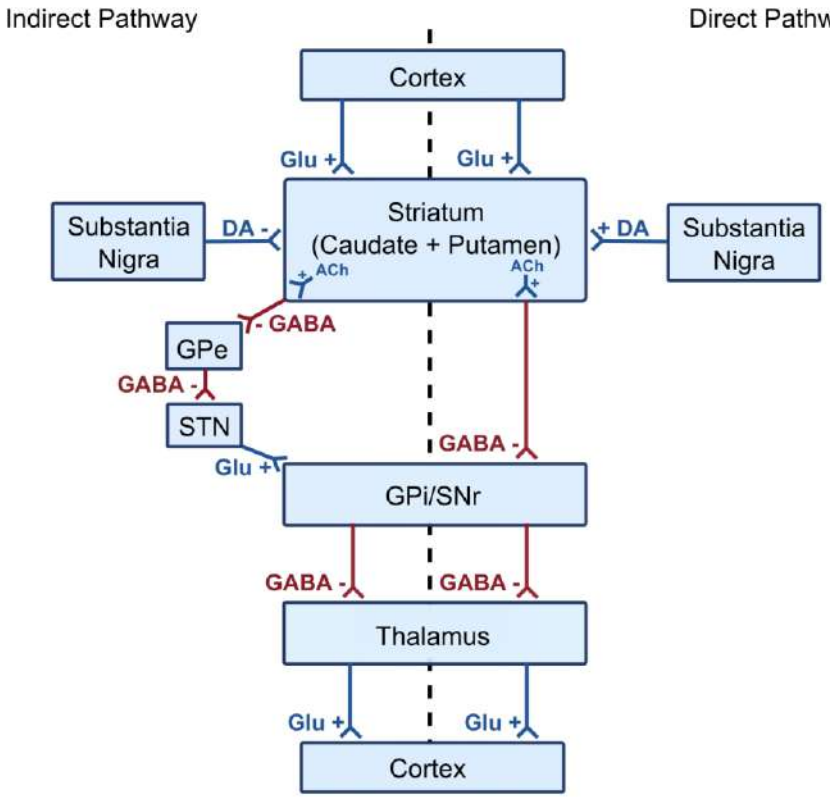
Thalamus:

1. Name the different nuclei of thalamus. (3/2012)(5/2010)
2. What is thalamic animal?(3/2021)
3. What do you mean by specific and non specific thalamic nuclei?(2/2008)
4. Discuss the functions of thalamus.(8/2008)
5. What is recruiting response? (2/2010)
6. Mention the function of mammillo-thalamic tract. (2/2021)
7. Why thalamus is called the “Gateway to the Cerebral Cortex”? (2/2021)



Basal ganglia circuitry in normal conditions

Basal Ganglia



Moises Dominguez

Basal ganglia:

1. Describe the neural circuits of basal ganglia and mentioning the neurotransmitters present in the neurons. (7+2/2016)
2. Which neuronal circuit in the basal ganglia is responsible for smooth transition of one motor programme from another? (2/2021)
3. What are ataxia and cog-wheel rigidity? (2+3/2021)
4. What is intention tremor? (2/2021)
5. What is Huntington's chorea? (5/2008)
6. Name the components of basal ganglia. (4/2009)
7. Discuss the functions of basal ganglia. (7/2009)
8. Mention the degenerative changes in brain in Parkinson's disease/. (2/2006)

Limbic system:

1. What are the components of limbic system? Describe the neural connections within different nodal points of limbic system. (2+3/2018)

2. Describe Papez Circuit and discuss its role in the regulation of emotions. (3+4/2021)

3. What is Kluver-Bucy syndrome? (2/2022)

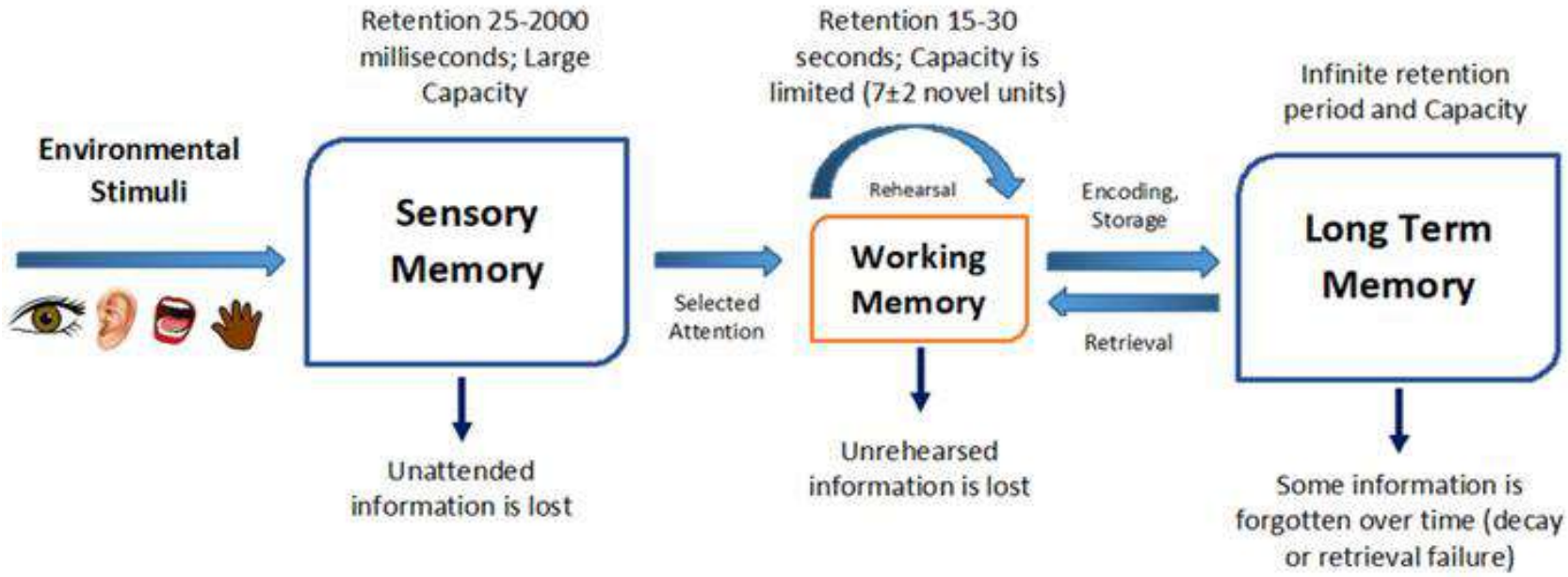
LEARNING AND MEMORY

Memory and learning are so **closely connected** that people often confuse them with each other. But the specialists who study them consider them two distinct phenomena.

1. **Learning is 'acquisition of the information' and memory is the 'retention and storage of that information'.**

2. **Memory is essential to all learning** because it lets you store and retrieve the information that you learn. Memory is basically nothing more than the record left by a learning process.

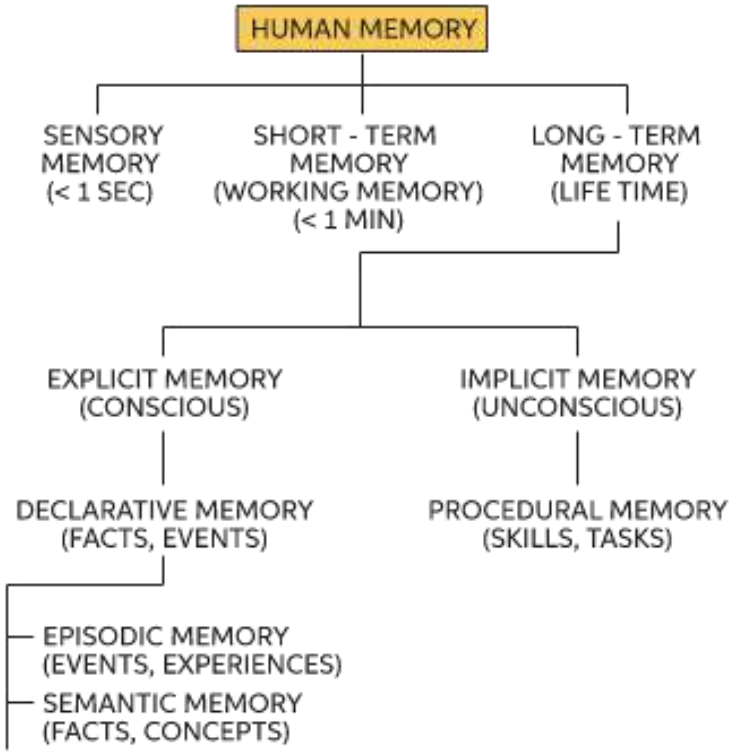
Furthermore, memories shape our identity: we are who we are because of our memories, which guide our thoughts and decisions, and influence our emotional reactions.



Common classification of memories:

On the basis of their duration:

1) **Short-term memory (STM):** It includes memories that last for seconds or at most minutes unless they are converted into longer- term memories. The prefrontal cortex (PFC) receives highly processed information from all sensory areas as well as emotional and memory areas. And responsible for working memory.
2) **Intermediate long-term memories (ITM):** It last for days to weeks but then fade away.
3) **Long-term memory (LTM):** which, once stored, can be recalled up to years or even a lifetime later.



According to their behavioral manifestation, which reflect the use of distinct underlying networks,

1) **Declarative memory or Explicit memory:** It Is associated with consciousness (can be consciously recalled) and is dependent on the **hippocampus** and other parts of the **medial temporal lobes** of the brain for its retention. Example- Events and facts. Two types- episodic and semantic memory.

2) **Non-declarative memory or Implicit Memory:** Does not involve awareness, and its retention does not usually involve processing in the hippocampus. Procedural memories that store information about skills, for example, driving a car, riding a bike or playing piano etc. Procedural memories critically recruit the **cerebellum and basal ganglia,**

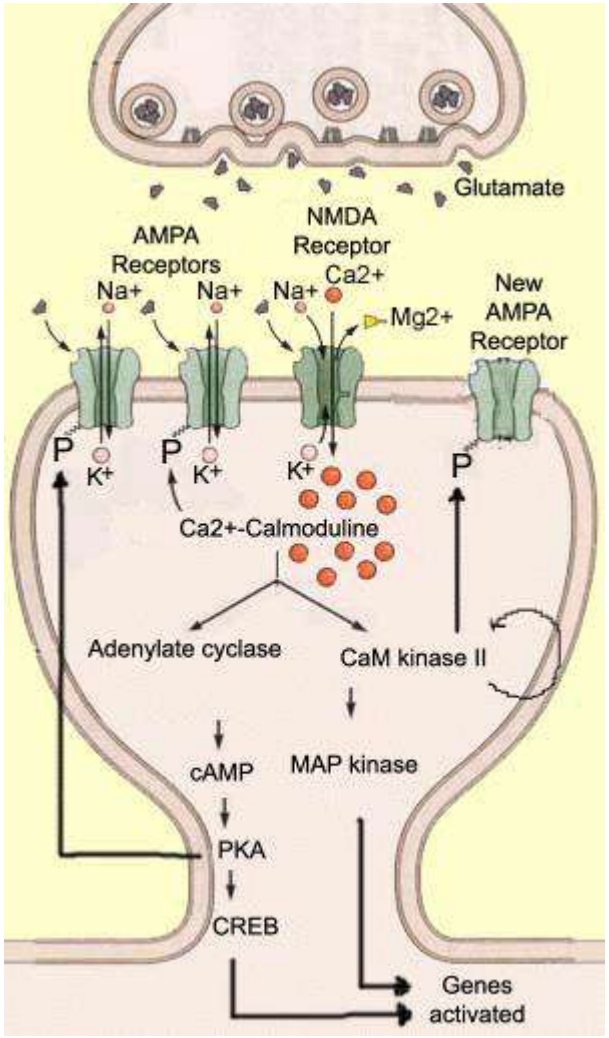
Semantic and Episodic memory

1. Semantic memory is a type of long-term declarative memory that refers to facts, concepts and ideas which we have accumulated over the course of our lives. commonly regarded as general knowledge.

2. An episodic memory is a memory of a specific event. Because each person has a different perspective and experience of an event, episodic memories of that event are unique to each person. Closely related to this is autobiographical memory—memories of your own life history.

PHYSICAL AND CHEMICAL CHANGES TAKE PLACE WHEN SHORT TERM MEMORY IS TRANSFORMED INTO LONG TERM MEMORY:

1. **Long-term potentiation (LTP): It** is a rapidly developing **persistent enhancement of the postsynaptic potential (PSP) response to pre-synaptic stimulation** after a brief period of rapidly repeated stimulation of the presynaptic neuron. It occurs in many parts of the nervous system but has been studied in greatest detail in the hippocampus.
***(Explained in Glutamate neurotransmitter Signaling)



2. **Structural Changes Occur in Synapses**
   - Increase in vesicle release sites for secretion of transmitter substance .
   - Increase in number of neurotransmitter vesicles ‘
   - Increase in number of presynaptic terminals
   - Changes in structures of the dendritic spines that permit transmission of stronger signals
   - Change s in number of neurons and their connectivities

Soon after birth, there is a principle of "use it or lose it" that governs the final number of neurons and their connectivities in respective parts of the human nervous system. This is a type of learning.

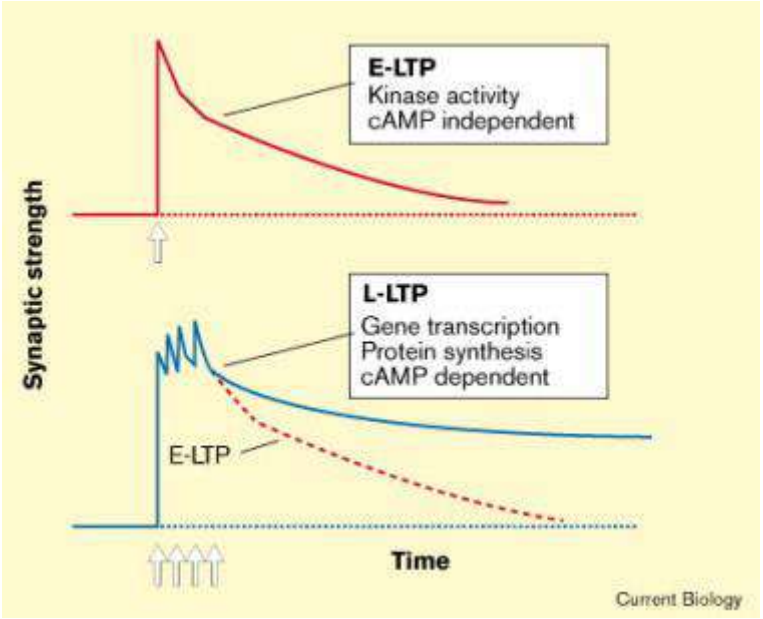
(For example, if one eye of a newborn animal is covered for many weeks after birth, visual cortex neurons, normally connected to the covered eye, will degenerate, and the covered eye will remain either partially or totally blind for the remainder of life.)

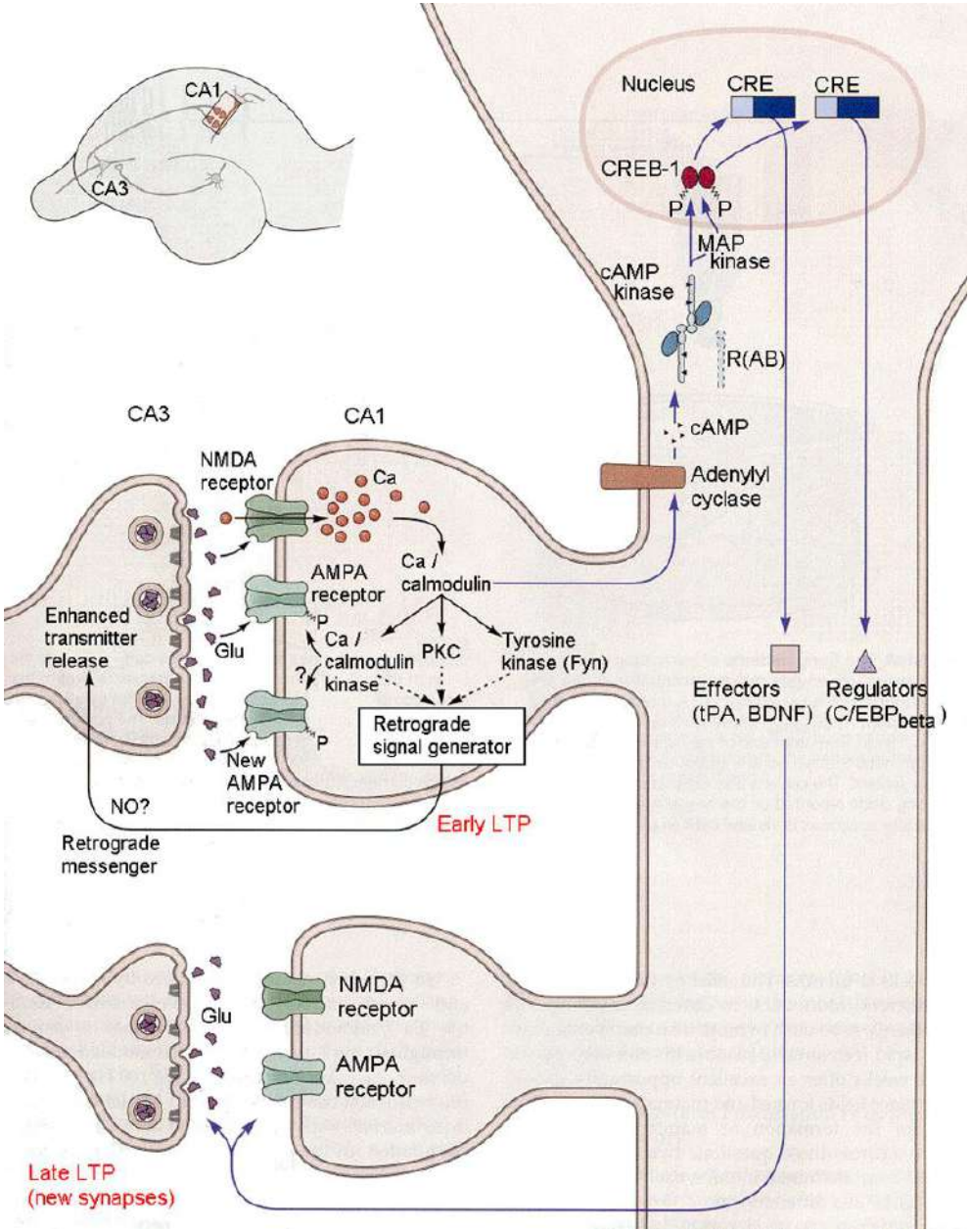
EARLY AND LATE LTP:

LTP is the most intensively studied cellular model of the memory and generally divided at least two distinct phases as early and late.

1. Early LTP requires activation of CaMKII that initiates biochemical events and trafficking of proteins, which eventually potentiate synaptic transmission, and is **independent of de novo protein synthesis.**

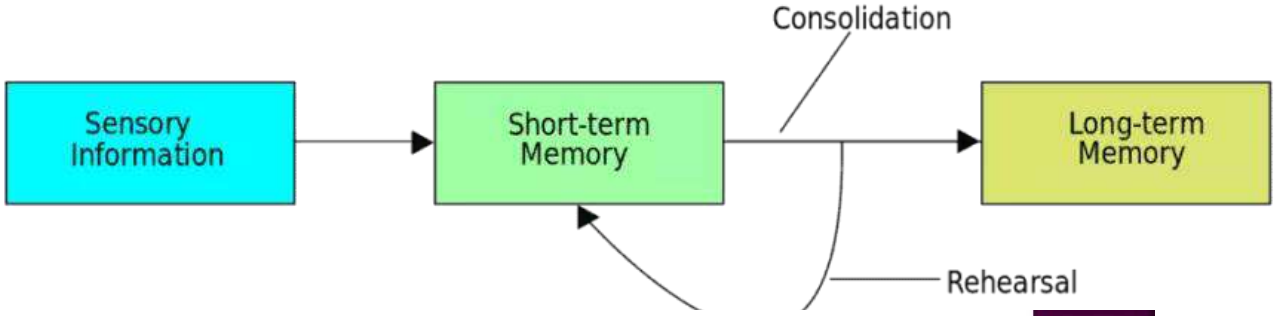
2. In contrast, Late-LTP **requires gene expression and local protein synthesis** regulated via TrkB receptor- and functional prions CPEB2-3-mediated translation.





Memory consolidation:

One general feature of long-term memory formation is that a newly encoded memory initially exists in a **fragile state** and can be disrupted very easily by several types of interferences (pharmacological, molecular or behavioral). With time, the memory becomes stronger and resilient to disruption. This process of **strengthening and stabilization of memory** is known as memory consolidation



Consolidation Theory

- Information that is transferred from STM to LTM needs a period of time to be properly and permanently encoded and stored – ('consolidated' or set - think concrete!)
- The consolidation theory suggests that there are structural/physical changes to the neurons (long-term potentiation & axon growth) as new memories are formed.
- These changes take time (consolidation phase) and the memory can be interfered with (changed) or erased (lost permanently) during this time.
- The new memory is vulnerable for at least 30 minutes *after* being experienced.
- The hippocampus and medial temporal lobe play an important role in consolidation
- Reconsolidation is the process of returning information back to LTM after it has been retrieved and used – the memory may be altered in this time.

PERFORANT PATHWAY:

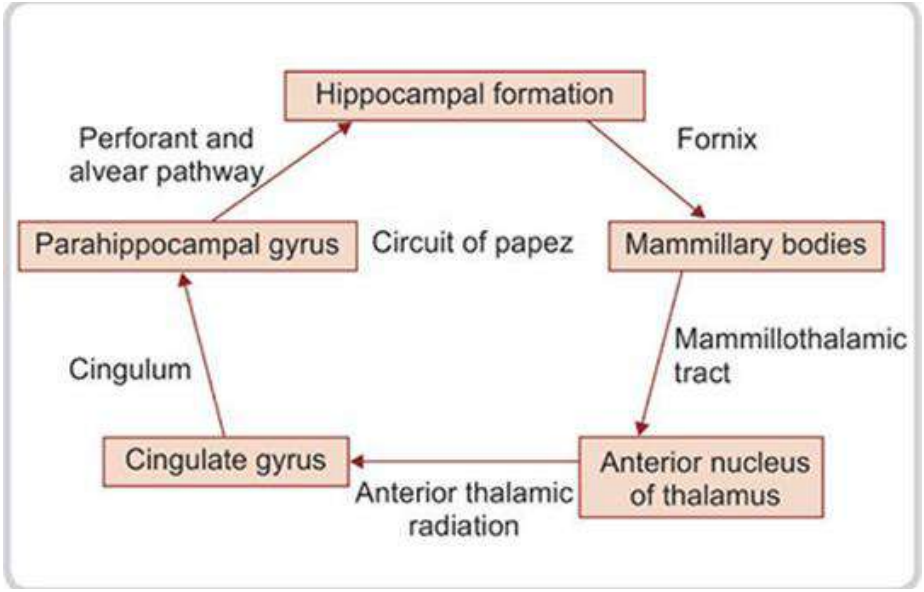
Perforant pathway is the neural pathway in brain (hippocampus) where **LTP** was first discovered. It is a major site of **synaptic plasticity** and **memory formation.**
This pathway declines in old age.

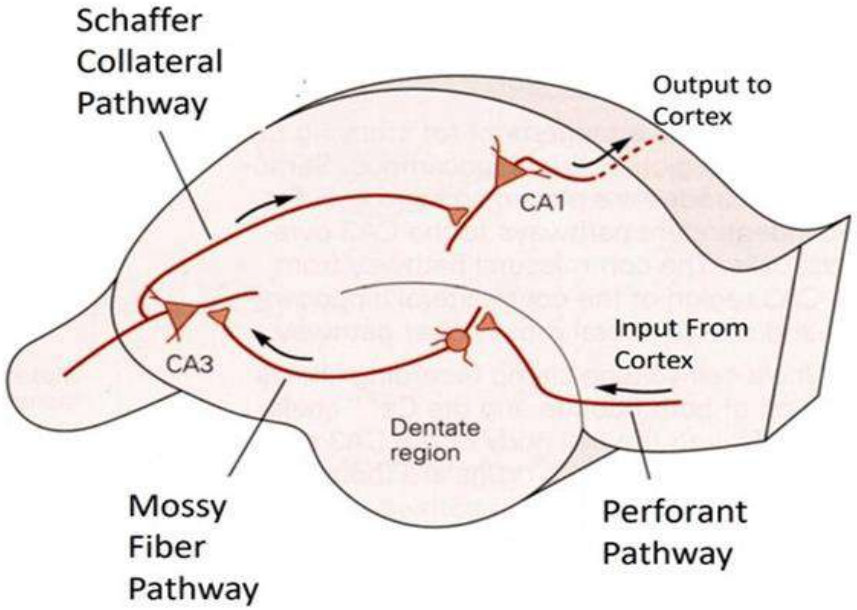
1. The perforant path is the **major input to the hippocampus.** The axons of the perforant path arise principally in **entorhinal cortex** (EC). Theses axons primarily project to the granule cells of the **dentate gyrus** (DG) (Few also projects to the CA3 and CA1 region and the subiculum directly).

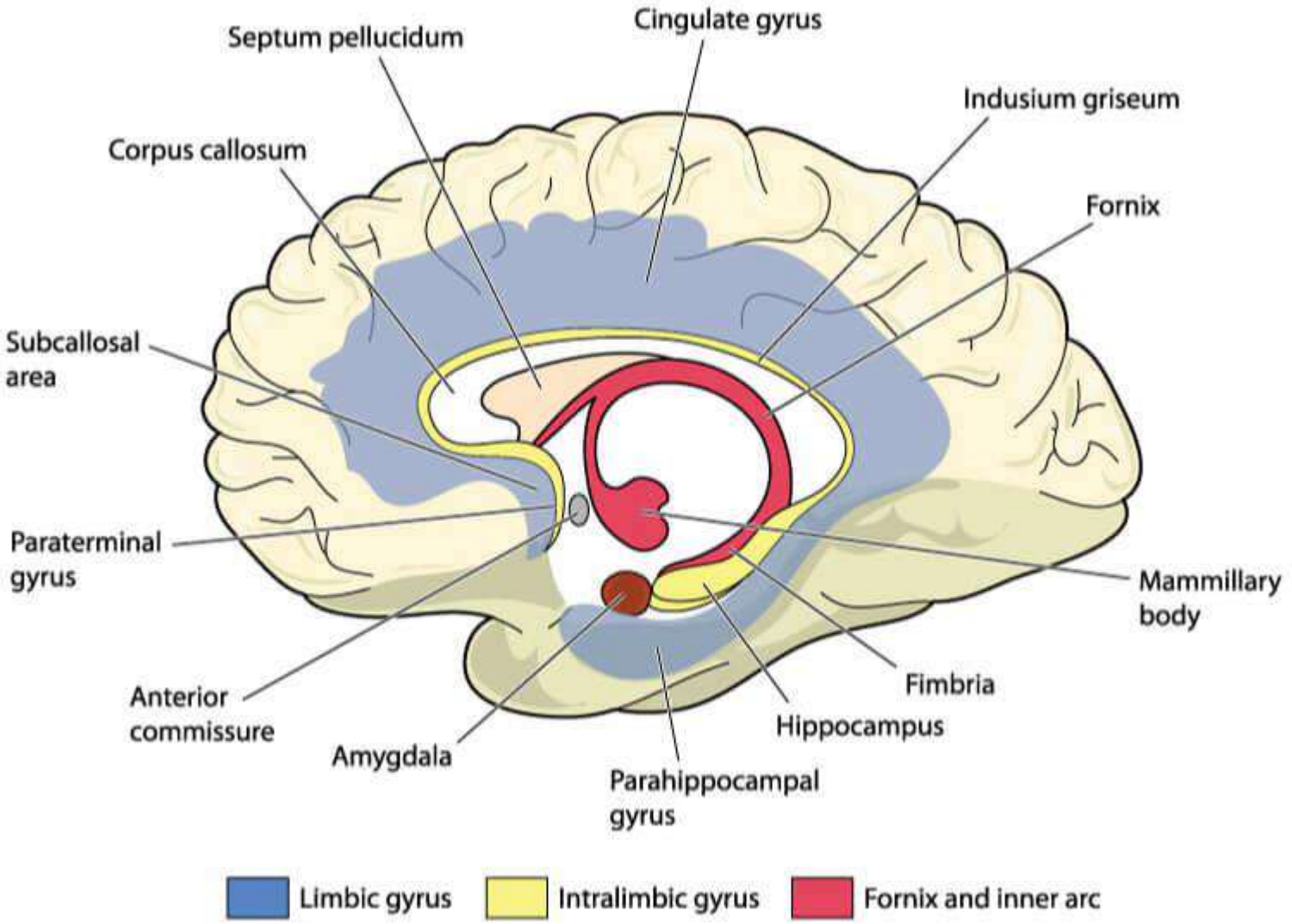
2. The **mossy fibres** are the axons of DG granule cells. They extend from the dendate gyrus to CA3 pyramidal cells.

3. Schaffer collateral pathway is derived from the CA3 region and projects into CA1 region.

4. The pathway from CA1 to Subiculum (Sb) and on to the entorhinal cortex forms the principal output from the hippocampus.






Septum pellucidum
Cingulate gyrus
Indusium griseum
Corpus callosum
Fornix
Subcallosal area
Paraterminal gyrus
Mammillary body
Fimbria
Anterior commissure
Hippocampus
Amygdala
Parahippocampal gyrus
Limbic gyrus
Intralimbic gyrus
Fornix and inner arc

‘Multiple trace theory’ for memory consolidation:

1) Memories are encoded in **hippocampal–cortical** networks.
2) **Connections between the cortex and the hippocampus are initially strong but weaken as connections within the cortex are established.**
3) Traces in the cortex are context-free (or semantic) in nature. Traces in the hippocampus provide spatial and temporal context (episodic).
4) Retrieval of contextually rich episodic memories always depends on hippocampal–cortical networks. Retrieval of remote semantic memories is possible in the absence of a functional hippocampus.

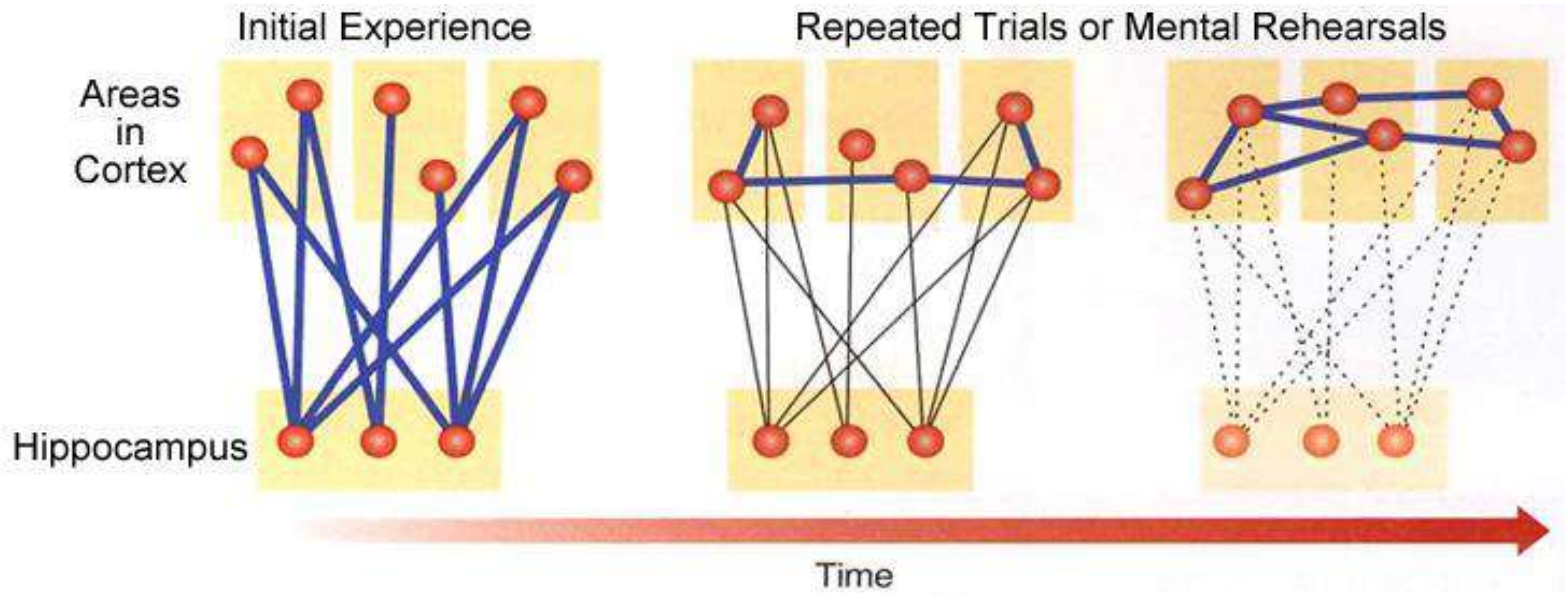


FIGURE 7.21 Sequence of events that occur in consolidation. Connections between the cortex and the hippocampus are initially strong but weaken as connections within the cortex are established. (Adapted from Frankland & Bontempi, 2005.)

WHAT IS LEARNING? **Learning is a specific change or modification of behaviour** as a result of experience with an external event in an individuals life. Learning is the **strengthening of existing responses or formation of new responses** to existing stimuli that occurs because of practice or repetition.

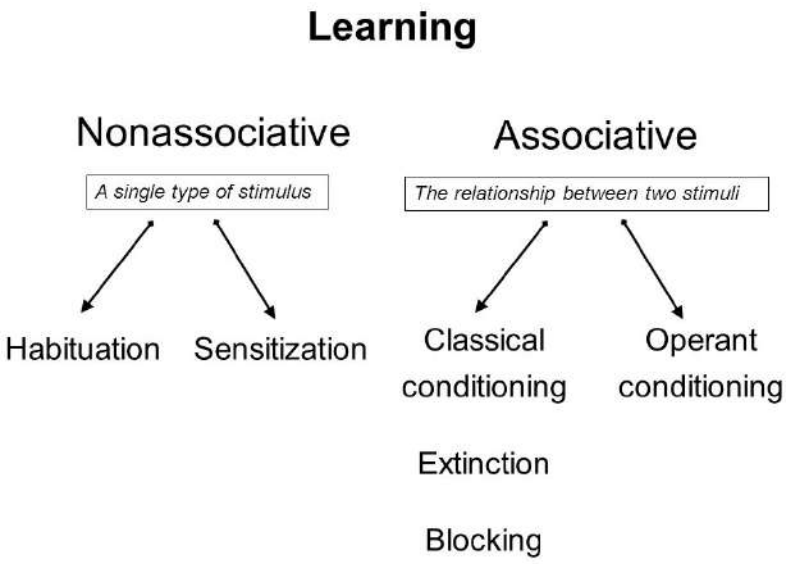
Types:

a. Non-associative learning: In this type of learning,, an organism's behavior (magnitude of response) toward a certain stimulus changes over time. It occurs in response to a single stimulus, without any positive or negative reinforcement. **Habituation and sensitization** constitute the two major forms of non-associative learning and are opposite to each other.

Examples: we get habituated to a sound or get sensitized to a painful stimulus.

b. Associative leaning: Associative learning occurs through the association of two previously unrelated stimuli. Two types.

- **Classical conditioning**: It involves pairing a neutral stimulus with an unconditioned stimulus. Eventually, the neutral stimulus becomes the conditioned stimulus. **Pavlov wherein his dogs started to salivate when he rang a bell.** This is the best-known example of classical conditioning,
- **Operant conditioning:** By contrast, Operant conditioning is a method of learning that occurs through rewards and punishments for behavior. The behavior is more likely to happen again if it is followed by a reinforcement, and it's less likely to occur if followed by punishment **A dog might learn that, by sitting and staying, it will earn a treat.** The dog then gets better at sitting and staying in order to receive the treat.



HABITUATION:

The response decreases over time to repeated stimulus

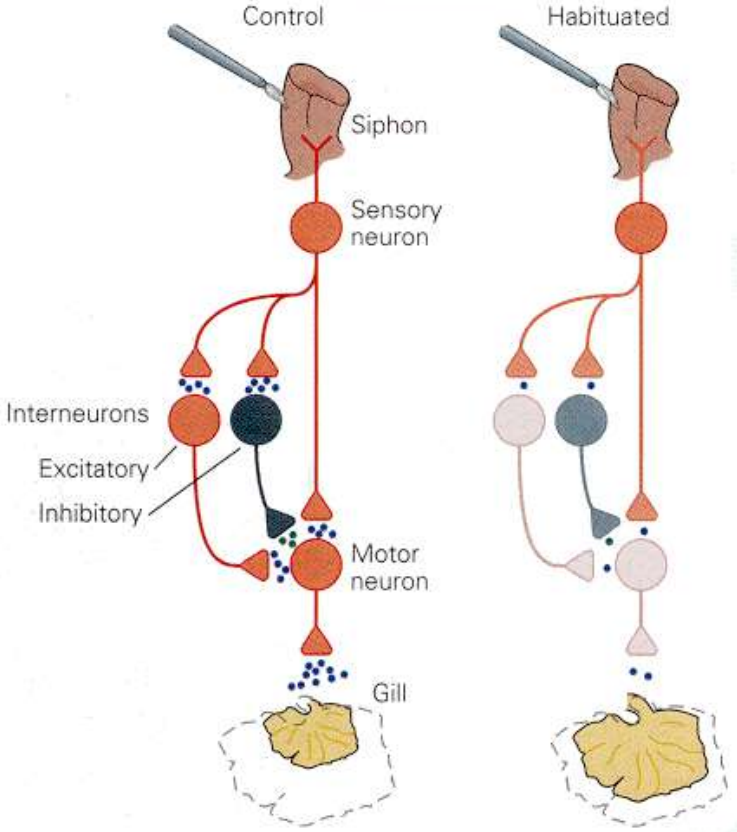
(Eg., We don't hear sound of AC or airplane after a while. Gill withdrawal reflex decreases in aplysia etc.)

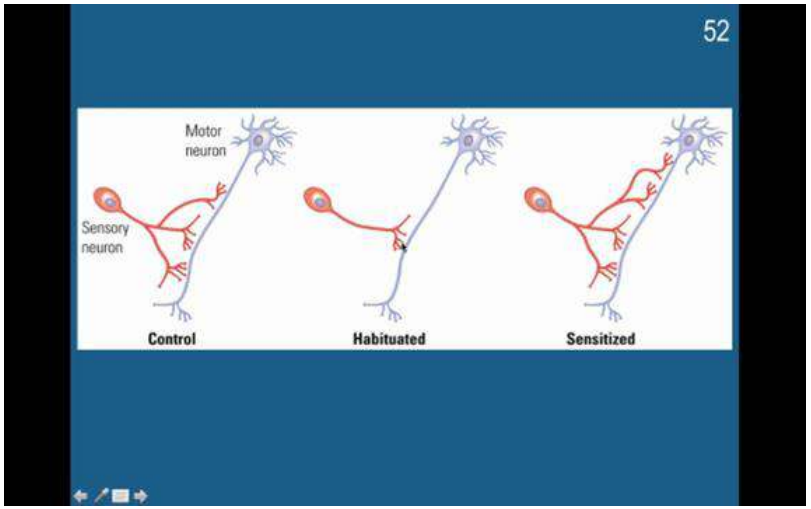
Experiments performed in **Aplysia californica**, the sea slug. **If the siphon of the animal is stimulated mechanically the animal withdraws the gill.** This is a simple reflex circuit. With repeated stimulation, the response decreases (habituated).

- With repeated activation, the stimulus leads to a **decrease in the number of dopamine-containing vesicles in presynaptic neuron** (sensory neuron). There appears to be no change in the sensitivity of postsynaptic NMDA or non-NMDA receptors.

- Long term changes also follow. Normal aplysia has 1300 terminals of sensory neuron on the surface of motor neuron. **It decreases to 800 after habituation.**

It is presumed that habituation in vertebrates, including man, occurs by a similar process.

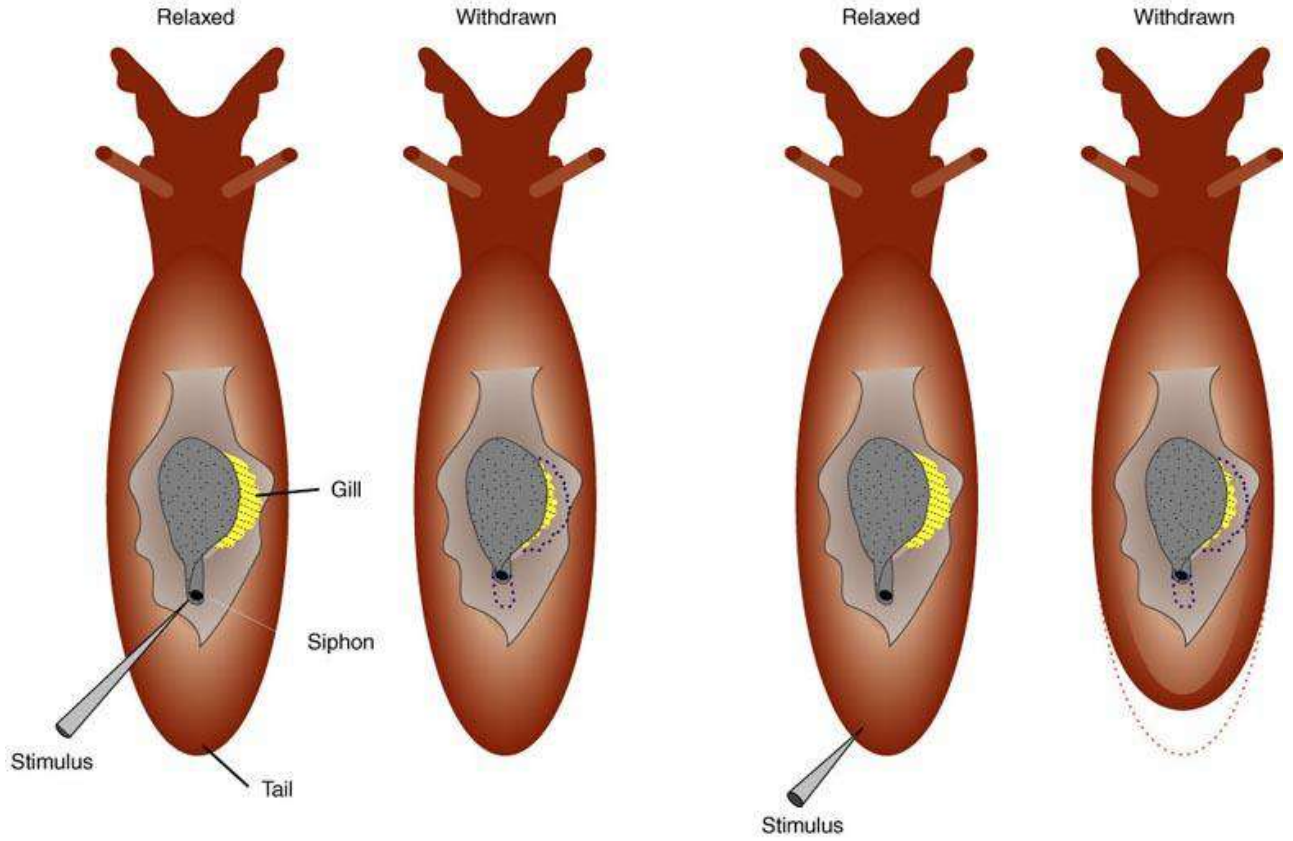




APLYSIA (SEA SLUG)

NORMAL GILL-SIPHON REFLEX

SENSITIZATION-
TAIL SIPHON REFLEX



SENSITIZATION:

Sensitization is the strengthening of a neurological response to a stimulus due to the response to a secondary stimulus.

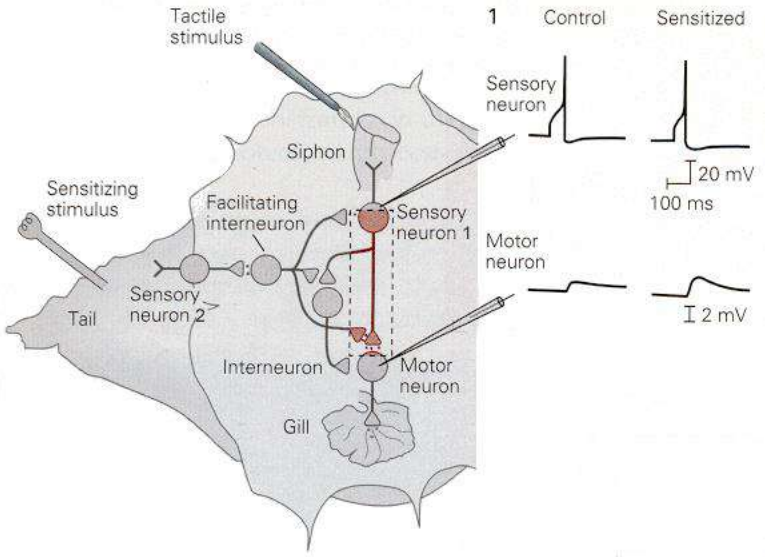
(For eg., if a loud sound is suddenly heard, an individual may startle at that sound. If a shock is given following the sound, then the next time the sound occurs, the individual will subsequently react even more strongly to the sound.

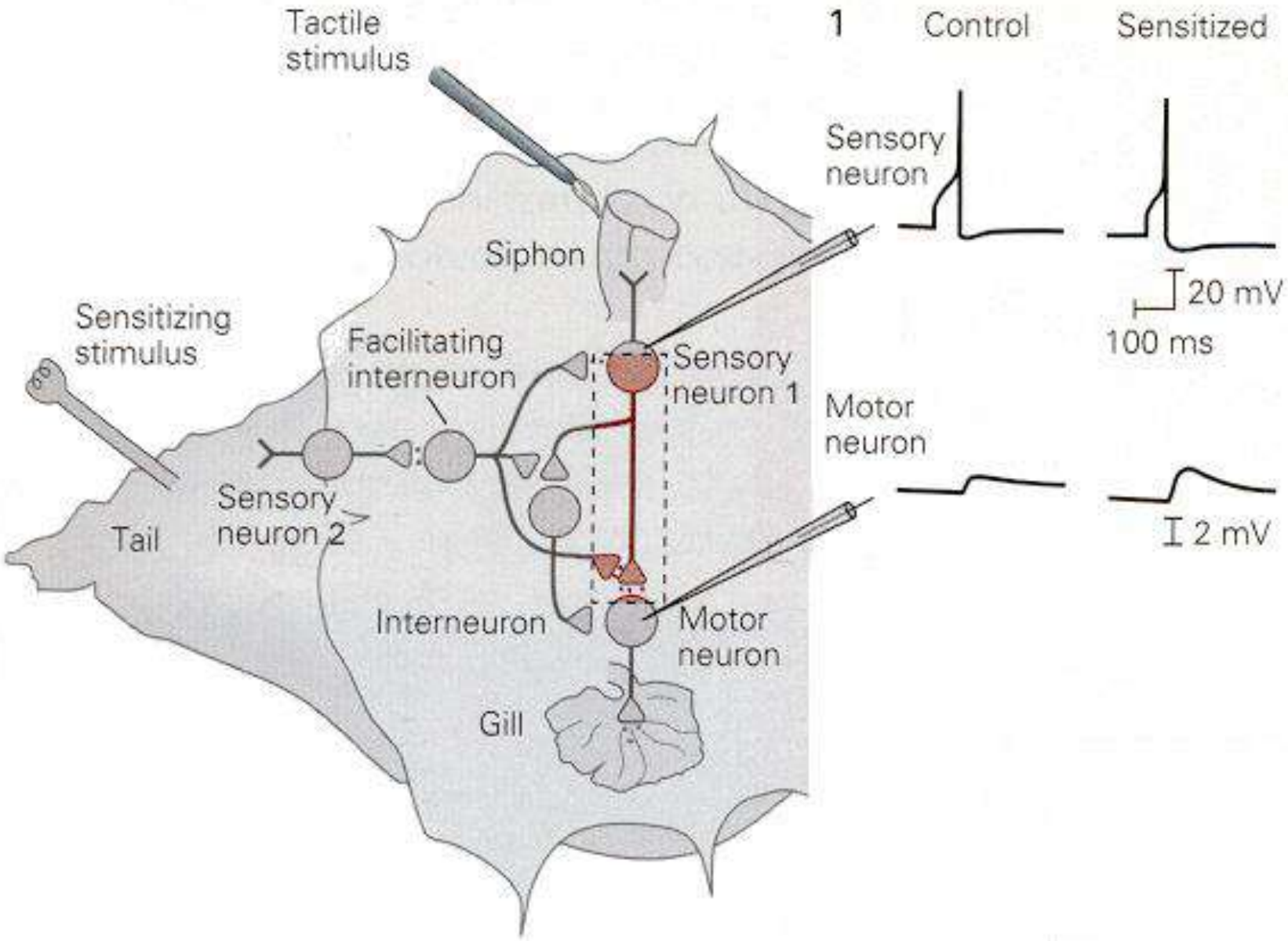
In aplysia, **if the tail is stimulated just before the syphon, the withdrawal become more forceful and quicker**.

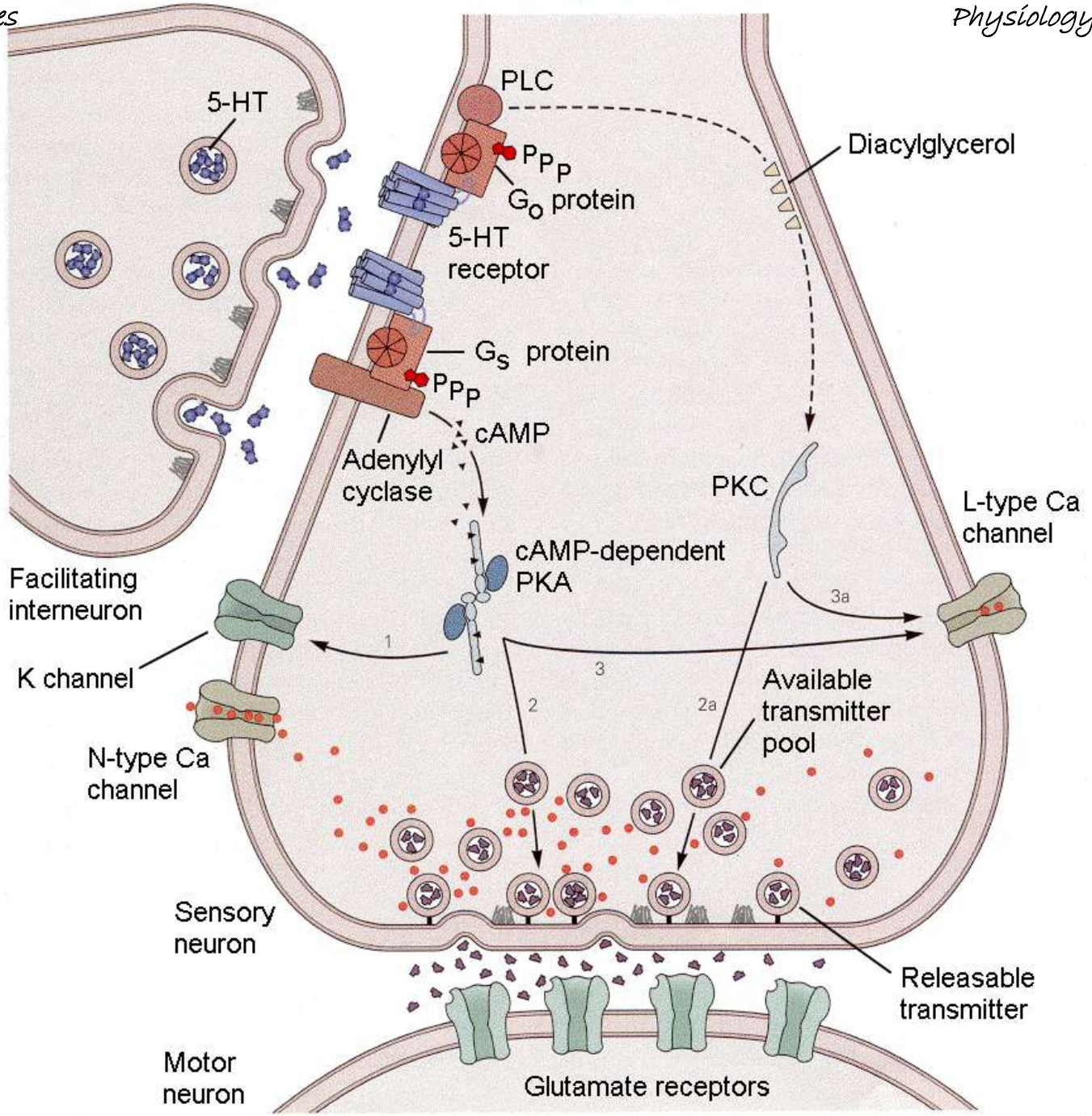
- Activation of the sensory receptors in the tail activates sensory neuron-2 to excite a facilitating interneuron, which, in turn, finally excites the sensory neuron-1 in the reflex pathway. The mechanism of this appears to involve **serotoninergic, axo-axonic synapses.**

- **Serotonin** (5HT) is released by the presynaptic (interneuron) where it binds to receptors on the postsynaptic (sensory-neuron-1) and activates a G protein dependent signaling to **close K channels, opens Ca channels and mobilizes vesicles for exocytosis in sensory neuron-1**. This results in larger EPSP in motor neuron and a more forceful response by the gill.

- Long term changes also follow. Normal aplysia has 1300 terminals of sensory neuron on motor neuron. **It increases to 2800 after sensitization.**




Tactile stimulus
Siphon
Sensitizing stimulus
Facilitating interneuron
Sensory neuron 1
Sensory neuron 2
Tail
Interneuron
Motor neuron
Gill
1
Control
Sensitized
Sensory neuron
20 mV
100 ms
Motor neuron
2 mV


5-HT
PLC
Diacylglycerol
P P P
G_o protein
5-HT receptor
G_s protein
P P P
cAMP
Adenylyl cyclase
PKC
L-type Ca channel
cAMP-dependent PKA
Facilitating interneuron
3a
1
3
2
2a
K channel
Available transmitter pool
N-type Ca channel
Sensory neuron
Releasable transmitter
Motor neuron
Glutamate receptors

AMNESIA:

Amnesia is when a person can no longer recall information that is stored in their memory. It is a very rare condition. Damage to brain structures that form the limbic system, such as the hippocampus and thalamus, can lead to amnesia.

The most common types of amnesia are:

1. **Anterograde amnesia:** A person with anterograde amnesia cannot remember new information. This usually results from brain trauma, such as a blow to the head that causes brain damage. The person will have their full memory from the time before the injury.
2. **Retrograde amnesia:** In some ways the opposite of anterograde amnesia, retrograde amnesia is when a person cannot remember events that occurred before their trauma, but they can remember what happened after it.
3. **Transient global amnesia:** This is a temporary loss of all memory and, in severe cases, difficulty forming new memories. This is very rare and more likely in older adults with vascular (blood vessel) disease.
4. **Traumatic amnesia:** This refers to memory loss resulting from a hard blow to the head, for instance, in a car accident. The person may experience a brief loss of consciousness or coma. This type of amnesia is usually temporary, but its duration often depends on the severity of the injury.
5. **Fugue or dissociative amnesia:** Rarely, a person can forget both their past and their identity. They may wake up and suddenly have no sense of who they are. The trigger is usually a traumatic event.
6. **Prosopamnesia:** The person cannot remember faces. People can either acquire or be born with it.

MEDICAL CAUSES:

Amnesia may result from brain injury or damage. Possible causes include-stroke, encephalitis, or brain inflammation, oxygen deprivation, respiratory distress, or carbon monoxide poisoning, subarachnoid hemorrhage, brain tumor, some seizure disorders, head injuries, surgery and anesthesia.

Memory:

1. How do you classify memory based on information stored? (3/2021)
2. Distinguish between explicit and implicit memory. (5/2019/2021)
3. What are episodic and semantic memory? (2/2018)
4. What do you mean by declarative and non-declarative memory? (2+2/2010)
5. Discuss the physiological basis of habituation and sensitization in aplysia. (5/2018)
6. Discuss the process of long-term potentiation (LTP). (6/2022) What are early and late LTP? (4/2008)
7. What is long term depression? (2/2022)
8. What is perforant pathway? (2/2010)
9. Describe the neural circuitry in hippocampus involved in memory consolidation. (6/2010)
10. What is meant by "Consolidation of Memory"? (2/2019)
11. What is operant conditioning? (2/2014)
12. What is classical conditioning? (4/2008)
13. What do you mean by anterograde and retrograde amnesia? (3/2014)

SLEEP

DEFINITION:

1. Sleep, a normal, reversible, recurrent state of reduced responsiveness to external stimulation.
2. Sleep is different from states of coma, hibernation and death by the fact that it can be rapidly reversed.

WHY WE NEED SLEEP?

It is essential for survival.

1. Neural maturation
2. Facilitation of learning or memory
3. Targeted erasure of synapses to "forget" unimportant information that might clutter the synaptic network
4. Cognition
5. Clearance of metabolic waste products generated by neural activity in the awake brain
6. Conservation of metabolic energy.

SLEEP PHASES:

The human body cycles through two phases of sleep,

1. **Rapid eye movement (REM)** and
2. **Non-rapid eye movement (NREM)** sleep, which is further divided into three stages, **N1-N3.**
3. The body cycles through all these stages approx. 4 to 6 times each night, averaging 90 minutes for each cycle.

Sleep Stages	Type of Sleep	Other Names	Normal Length
Stage 1	NREM	N1	1-5 minutes
Stage 2	NREM	N2	10-60 minutes
Stage 3	NREM	N3, Slow-Wave Sleep (SWS), Deep Sleep	20-40 minutes
Stage 4	REM	REM Sleep	10-60 minutes

NON-REM SLEEP:

N1 (Stage 1) /Light Sleep (5%)

- This is the lightest stage of sleep and begins when more than 50% of the alpha waves are replaced with low-amplitude mixed-frequency (LAMF) activity in EEG.
- Muscle tone is present in the skeletal muscle, and breathing tends to occur at a regular rate.
- This stage lasts around 1 to 5 minutes, consisting of 5% of total sleep time.

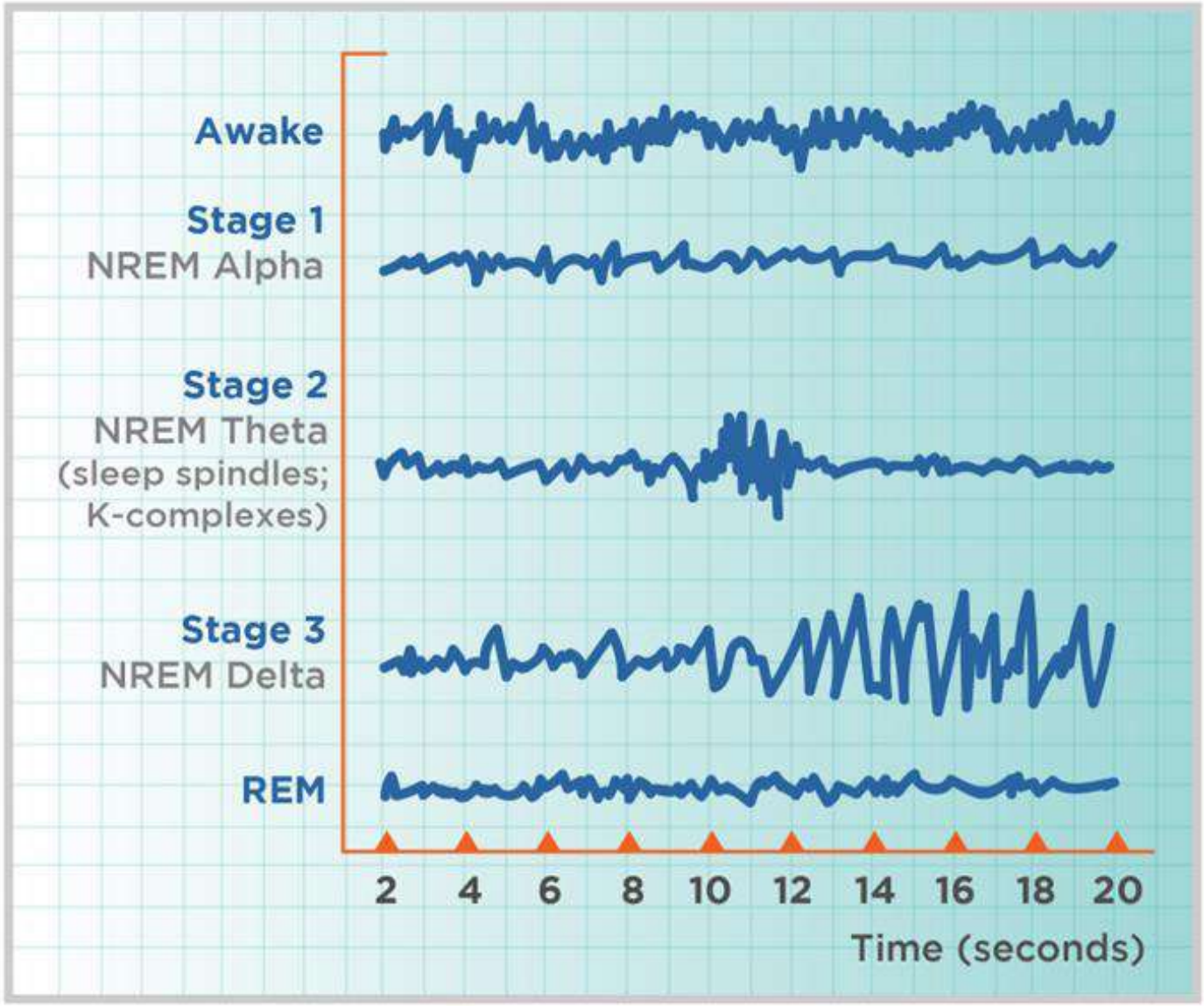
N2 (Stage 2) / Deeper Sleep (45%)

- This stage represents deeper sleep as your heart rate and body temperate drop.
- It is characterized by the presence of sleep spindles, K-complexes, or both. Sleep spindles are brief, powerful bursts of neuronal firing This mechanism is believed to be integral to synaptic plasticity.
- Numerous studies suggest that both sleep spindles and K complex play an important role in memory consolidation, specifically procedural and declarative memory.
- Stage 2 sleep lasts around 25 minutes in the first cycle and lengthens with each successive cycle, eventually consisting of about 45% of total sleep.
- This stage of sleep is when bruxism (teeth grinding) occurs.

N3 (Stage 3)/Deep Sleep (25%):

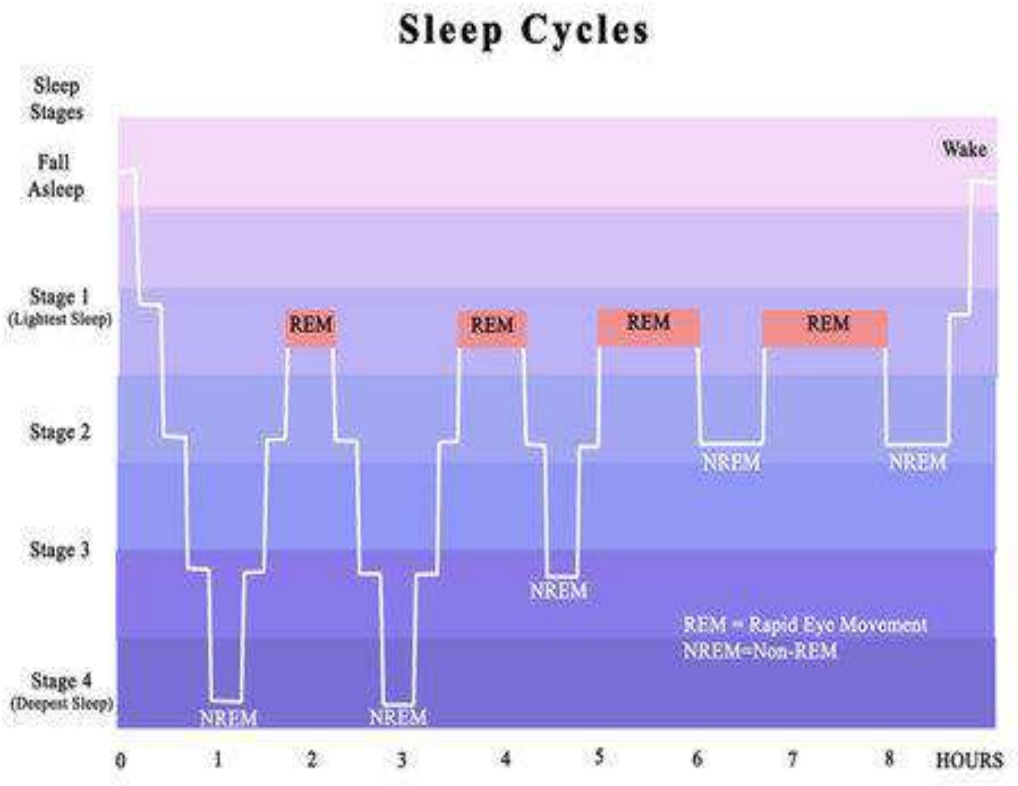
- N3 is also known as slow-wave sleep (SWS).
- This is considered the deepest stage of sleep and
- EEG is characterized by delta waves with much lower frequencies and higher amplitudes
- This stage is the most difficult to awaken from, and, for some people, even loud noises (> 100 decibels) will not awaken them.
- As people age, they tend to spend less time in this slow, delta wave sleep and more time in stage N2 sleep. Although this stage has the greatest arousal threshold, if someone is awoken during this stage, they will have a transient phase of mental fogginess, known as sleep inertia.
- Cognitive testing shows that individuals awakened during this stage tend to have moderately impaired mental performance for 30 minutes to an hour.
- This is the stage when the body repairs and regrows tissues, builds bone and muscle and strengthens the immune system.
- This is also the stage when sleepwalking, night terrors, and bedwetting occurs.

EEG RECORDINGS DURING SLEEP



REM (rapid-eye movement sleep)/ (25%)

- REM is associated with dreaming and irregular muscle movements as well as rapid movements of the eyes
- It is not considered a restful sleep stage.
- The EEG is similar to an awake individual. The EEG recording shows beta waves - similar to brain waves during wakefulness. The brain is highly active throughout REM sleep, increasing brain metabolism by up to 20%.
- But skeletal muscles are atonic and without movement, except for the eyes and breathing rate becomes more erratic and irregular. That's why it is known as paradoxical sleep.
- This stage usually starts 90 minutes after you fall asleep, with each of your REM cycles getting longer throughout the night. The first period typically lasts 10 minutes, with the final one lasting up to an hour.
- REM is when dreaming, nightmares occur.



Reticular Formation and Sleep & wakefulness:

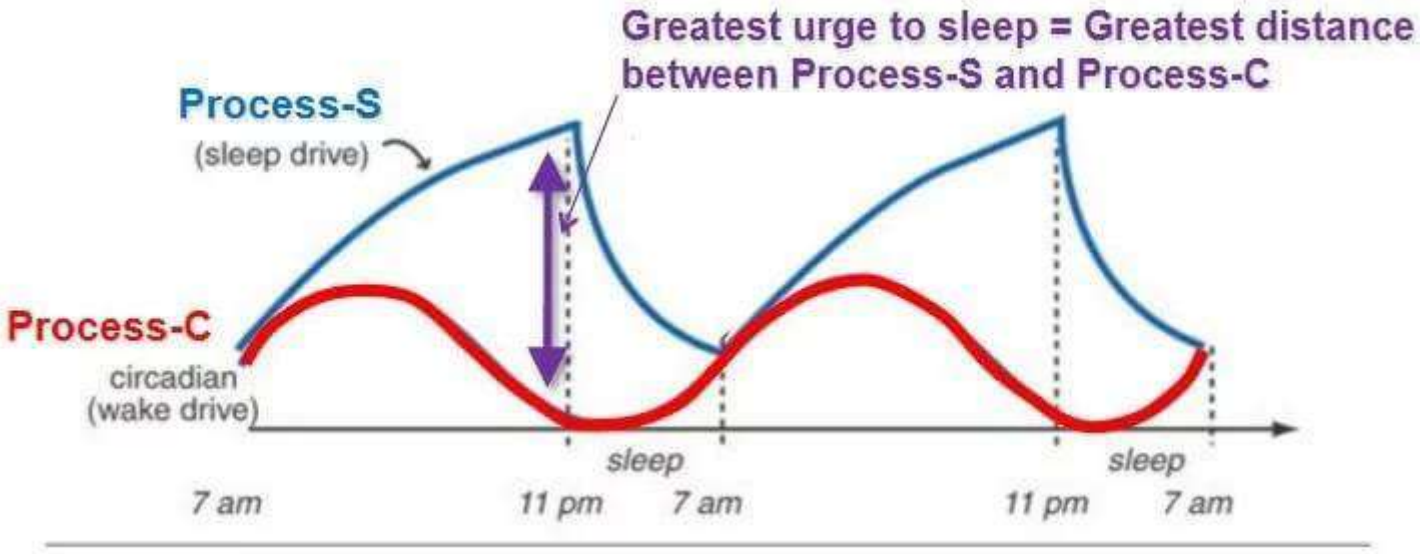
1. Differentiate between REM and NREM sleep. (4/2019)
2. Why REM sleep is known as paradoxical sleep? (2/2022)
3. Mention the characteristic features of REM sleep. (3/2014)
4. Describe the EEG pattern in different stages from wakefulness to sleep. (5/2021)
5. Explain the neurological basis of EEG. (5/2019)
6. Describe the role of reticular activating system in induction of sleep. (5/2012)
7. What is *cerveau isole* preparation? Discuss briefly the active and passive theories of sleep. (2+6/2011)
8. What is PGO spike? (2/2012) What is k-complex? (2/2011)

SLEEP-WAKE REGULATION:

The established, widely accepted two-process model of sleep wake regulation (Fig.5) was postulated by the internationally well-known sleep researcher Alexander Borbély in 1982. The sleep-wake system is thought to be regulated by the interplay of two major processes, one that promotes sleep (process S) and one that maintains wakefulness (process C).

Process S is the homeostatic drive for sleep. The need for sleep (process S) accumulates across the day, peaks just before bedtime at night and dissipates throughout the night.

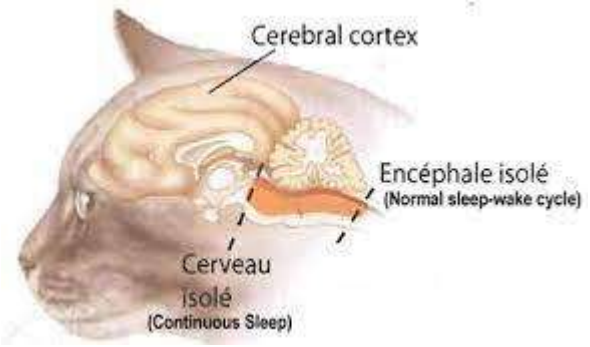
Process C is wake promoting and is regulated by the circadian system. Process C builds across the day, serving to counteract process S and promote wakefulness and alertness. The process C is guided endogenously via the suprachiasmatic nucleus (SCN) in the hypothalamus However, this wake-promoting system begins to decline at bedtime.



THEORIES OF SLEEP:

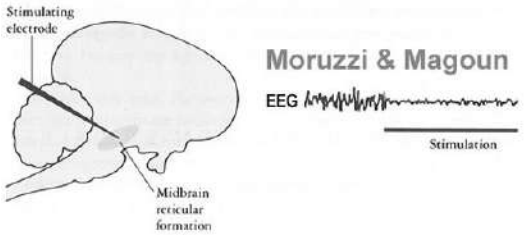
1. **Sleep is a passive process**: According to traditional belief, prolonged activity of the brain during the day is followed by rest/inactivity of brain at night in the form of sleep. Sleep was considered as a passive process till the 1950s.

2. **Sleep is an active process:** This passive theory of sleep was replaced by the active sleep genesis concept, mainly after the realization that brain activity is only slightly reduced during sleep. Employing various modern techniques, discrete areas were demarked by various scientists who assigned them the roles in the regulation of NREM and REM sleep.

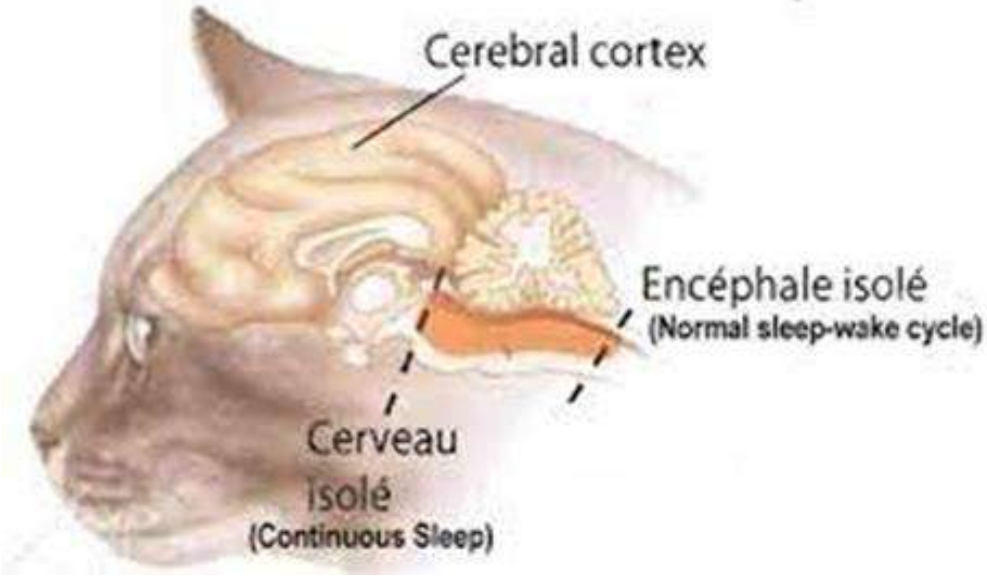


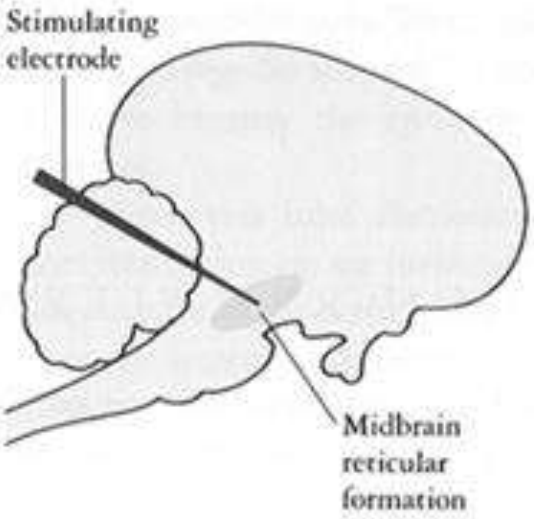
3. **Bremer's experiment:**
   - **Cerveau isole preparation:** Frederic Bremer found that transection of the brain of cats at the mid-collicular level led to "**sleeplike**" behavior and slow waves in the cortex.
   - **Encephale isole preparation:** In contrast, transection at the junction of the brain stem and spinal cord **did not alter the normal cyclic alternation of sleep-wake states** and demonstrated that sensory input from the spinal cord was not necessary for wakefulness to occur.

4. **Moruzzi and Horace Magoun experiment:** Moruzzi and Horace Magoun showed that electrical stimulation of the **midbrain reticular formation** in anesthetized cats caused **wakefulness** and the appearance of an "activated" EEG similar to that seen during waking.



Together these findings led to the important concept of the **"ascending reticular activating system (ARAS),"** a network (reticulum) of nerve fibers ascending from the brain stem, which activates forebrain during waking and REM sleep.





Moruzzi & Magoun

EEG

Stimulation

ASCENDING ACTIVATIONG SYSTEM(AAS)

The ascending arousal system (AAS) controls arousal and mental alertness. The AAS was originally referred to as ascending reticular activating system (ARAS) 70 years ago (Moruzzi and Magoun, 1949).

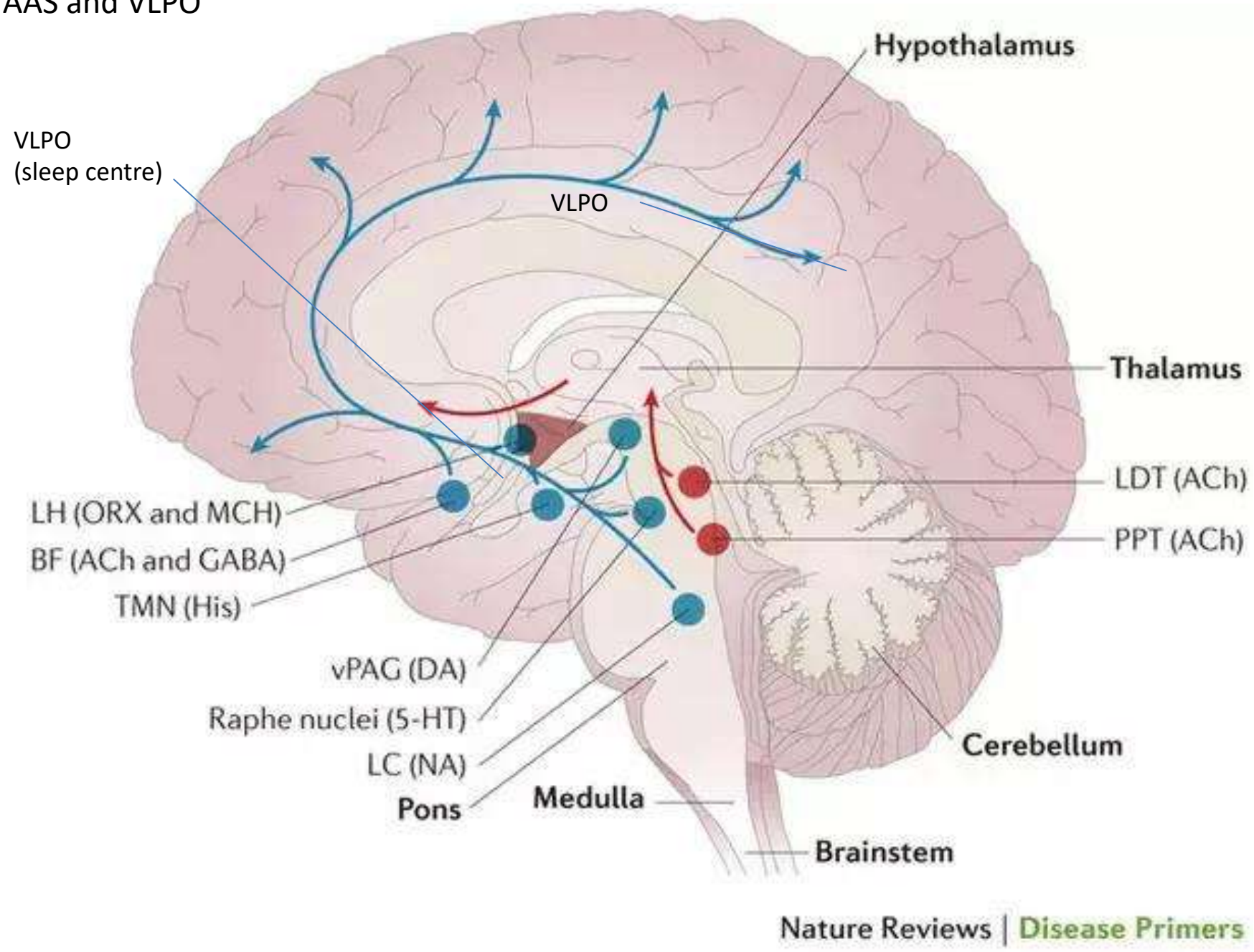
AAS originates in the brainstem and basal forebrain (BF), runs through the midbrain reticular formation (RF) and innervates the thalamus and cortex..

There are two pathways of the AAS:

1) The Dorsal Pathway: The two main regions in the dorsal pathway are the pedunculopontine (PPT) and latero-dorsal tegmental nuclei (LDT) which project with mainly cholinergic cells to the thalamus. which project to the "nonspecific" intralaminar and midline thalamic nuclei which diffusely innervate many areas of the cerebral cortex as The activation of the thalamus by the PPT and LDT facilitates further thalamocortical transmission. PPT/LDT neurons are most active during wakefulness and rapid eye movement (REM) sleep

2) The ventral pathway: It arises from several regions in the brainstem and caudal hypothalamus, bypasses the thalamus and projects to the BF and the cerebral cortex. These regions contain monoaminergic cell groups and include the locus coeruleus (LC, noradrenalin), the raphe nucleus (RN, serotonin), and the tubero-mamillary nucleus (TMN, histamine). The ventral pathway is further activated by lateral hypothalamic nucleus, which contain orexin(hypocretin), and basal forebrain nuclei, which contain acetylcholine or GABA. All of these systems project to and activate the neocortex

AAS and VLPO


Hypothalamus
VLPO
(sleep centre)
VLPO
Thalamus
LDT (ACh)
PPT (ACh)
LH (ORX and MCH)
BF (ACh and GABA)
TMN (His)
vPAG (DA)
Raphe nuclei (5-HT)
LC (NA)
Pons
Medulla
Cerebellum
Brainstem
Nature Reviews | Disease Primers

FLIP-FLOP switch model of Sleep and Wakefulness:

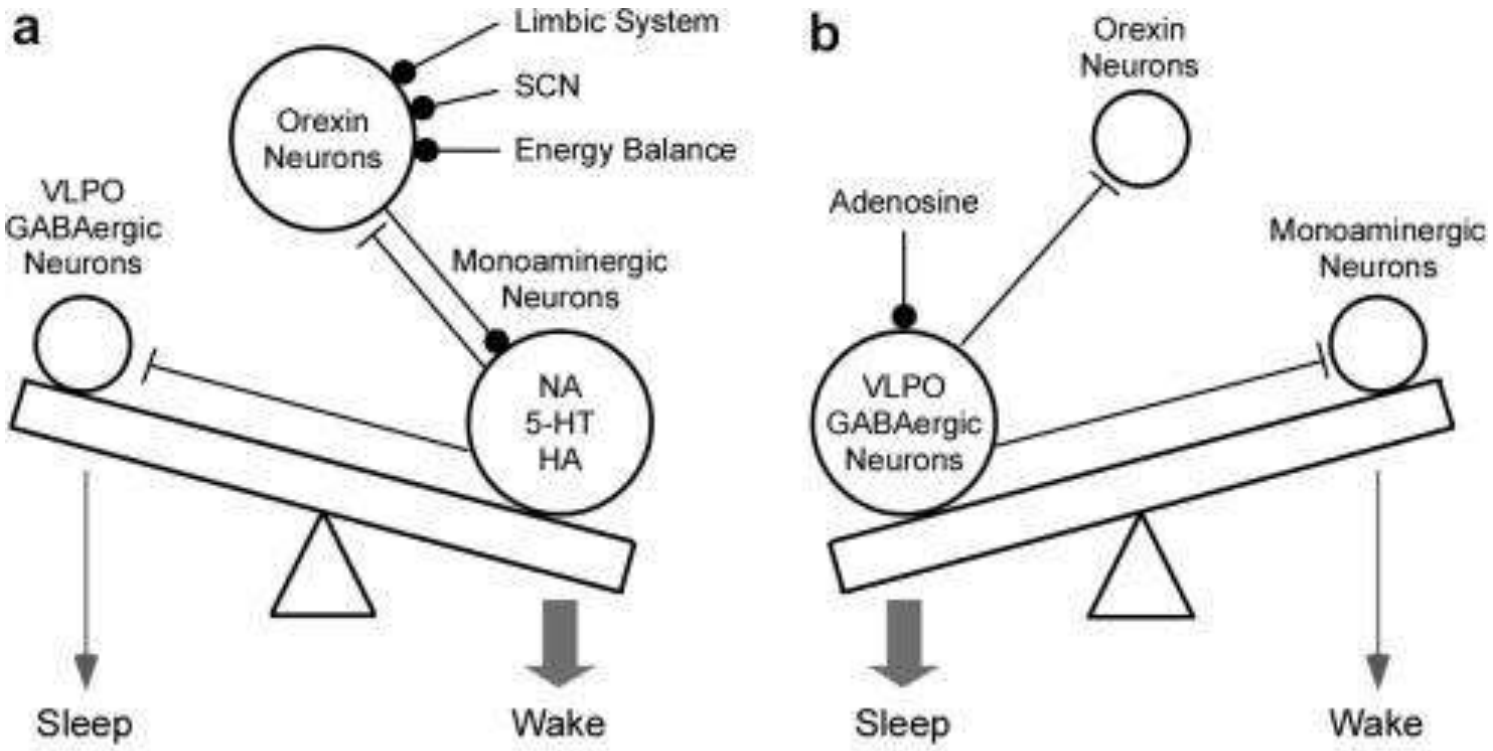
The 'flip-flop switch' model of sleep and wakefulness claims that wake and sleep are two distinct and consecutive vigilance states. There are two components which play an important role in the state of wakefulness and sleep: AAS and VLPO. when monoamine nuclei discharge intensively during wakefulness, they inhibit the VLPO, and when VLPO fire rapidly during sleep, block the discharge of the monoamine cell groups [98]. This relationship is described as a bistable, "flip-flop" circuit, in which the two halves of the circuit strongly inhibit each other to produce two stable discharge patterns – on or off

Wakefulness is primarily initiated and stabilized by monoaminergic and cholinergic neurotransmission in the upper brain stem. The ventrolateral preoptic nucleus (VLPO) plays a key role in this model. quieting the ascending monoaminergic arousal system during sleep. projected heavily to nuclei of the ARAS, especially the histaminergic tuberomammillary nucleusIts action is either suppressed by the TMN, LC, and RN – with the effect of wakefulness – or, in contrast, the VLPO is highly active and suppresses these regions, resulting in the state of sleep. Like VLPO neurons, MnPO neurons project to and inhibit wake-promoting neurons of the ARAS

During wakefulness (upper panel), the monoaminergic nuclei (red) inhibit the ventrolateral preoptic nucleus (VLPO; purple), thereby relieving the inhibition of the monoaminergic cells, and that of the orexin (ORX) neurons (green), and the cholinergic pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT; yellow). Because the VLPO neurons do not have orexin receptors, the orexin neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibit the VLPO on their own. orexins stabilize behavioral state via their strong excitatory actions on wake-promoting neurons. Analysis of orexin knockout mice revealed that they have many more transitions between wake, NREM, and REM states

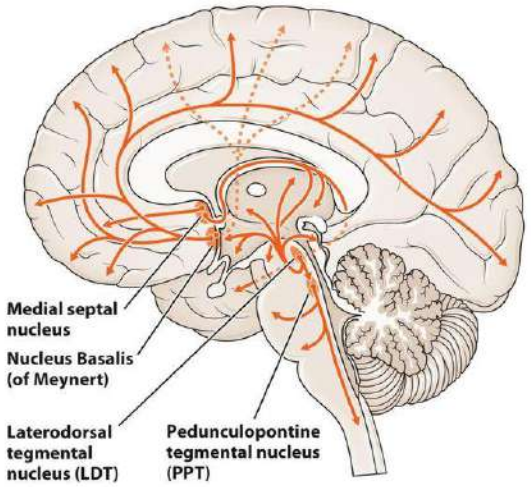
During sleep (lower panel), The ventrolateral preoptic nucleus contains gamma-aminobutyric acid (GABA) and galanin, and when triggered, initiates the onset of sleep via circadian input from SCN and endogenous chemical signals (example, adenosine), which accumulate in proportion to time spent awake. the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition. This also allows it to inhibit the orexin neurons, further preventing monoaminergic activation that might interrupt sleep. The direct mutual inhibition between the VLPO and the monoaminergic cell groups forms a classic flip-flop switch, which produces sharp transitions in state, but is relatively unstable. The addition of the orexin neurons stabilizes the switch. As an individual falls asleep, the electroencephalogram (EEG) primarily changes from a state of high frequency and low voltage waves in the waking state to higher voltage and slower waves signifying NREM sleep. In contrast, melatonin-concentrating neurons, which play an important role in REM homeostasis, are strongly active during REM sleep [119], and cholinergic neurons of the basal forebrain discharge at maximal rates during both REM sleep and active waking

During wakefulness (a), the monoaminergic nuclei (red) inhibit the ventrolateral preoptic nucleus (VLPO; purple), thereby relieving the inhibition of the monoaminergic cells, and that of the orexin (ORX) neurons (green), and the cholinergic pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT; yellow). Because the VLPO neurons do not have orexin receptors, theorexin neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibiting the VLPO on their own. During sleep (b), the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition. This also allows it to inhibit the orexin neurons, further preventing monoaminergic activation that might interrupt sleep. The direct mutual inhibition between the VLPO and the monoaminergic cell groups forms a classic flip-flop switch, which produces sharp transitions in state, but is relatively unstable. The addition of theorexin neurons stabilizes the switch



A circuit containing mutually inhibitory elements sets up a selfreinforcing loop, where activity in one of the competing sides shuts down inhibitory inputs from the other side, and therefore disinhibits its own action. Such a circuit is called a 'flip-flop switch' by electrical engineers,Rapid sleep-wake cycling also is common in the elderly [6], who have fewer VLPO neurons Adenosine also may excite VLPO neurons by disinhibiting GABAergic inputs [16]. Therefore, by inhibiting the basal forebrain arousal system

The Brain during REM Sleep



his area corresponds to the rostral part of the subcoeruleus area as defined by Paxinos and Watson in the rat (160). REM-on neurons in this area are primarily glutamatergic, as indicated by vGLUT2 in situ hybridization and Fos immunohistochemistry (248). Other nearby reticular formation areas containing glutamatergic neurons such as the nucleus pontis oralis (PnO) and nucleus pontis caudalis (PnC) play a role in particular aspects of REM sleep such as theta rhythm generation or rapid eye movements. These neurons may be involved in phasic phenomena of REM sleep such as PGO waves.

Synchronized electrical field potentials in the pons, lateral geniculate nucleus, and occipital cortex (PGO waves) occur singly at high amplitude in the period immediately preceding the onset of REM sleep (transitional REM period; 30–90 s) and in bursts of lower amplitude during REM sleep itself (98, 146, 274, 580, 584, 1228). They are considered the source of dreaming episodes and visual imagery during REM sleep

During REM sleep, descending pontine subcoeruleus (SubC) glutamatergic projections excite diffusely organized glycinergic neurons of the bulbar reticular formation, including the medullary ventral gigantocellular nucleus (GiV). GABAergic/glycinergic output from the GiV inhibits spinal motoneurons, producing muscle atonia.

REM sleep control, originally proposed by McCarley and Hobson (819). A: the original reciprocal interaction model demonstrates increased REM activity as positive feedback of REM-on neuronal populations occurs. This activity leads to excitation of REM-off neuronal populations, which then inhibit REM-on activity. REM-off activity is self-inhibiting, and eventually wanes, releasing REM-on neurons as REM sleep again occurs. The REM-off and REM-on neuronal populations in the mesopontine tegmentum are also configured in a mutually inhibitory circuit **Rapid eye movement (REM) sleep consists of a dreaming state in which there is activation of the cortical and hippocampal electroencephalogram (EEG) rapid eye movements, and loss of muscle tone. Although REM sleep was discovered more than 50 years ago, the neuronal circuits responsible for switching between REM and non-REM (NREM) sleep remain poorly understood. Here we propose a brainstem flip-flop switch, consisting of mutually inhibitory REM-off and REM-on areas in the mesopontine tegmentum. Each side contains GABA ([gamma]-aminobutyric acid)-ergic neurons that heavily innervate the other. The REM-on area also contains two populations of glutamatergic neurons. One set projects to the basal forebrain and regulates EEG components of REM sleep, whereas the other projects to the medulla and spinal cord and regulates atonia during REM sleep. The mutually inhibitory interactions of the REM-on and REM-off areas may form a flip-flop switch that sharpens state transitions The REM-off and REM-on areas are mutually inhibitory.**

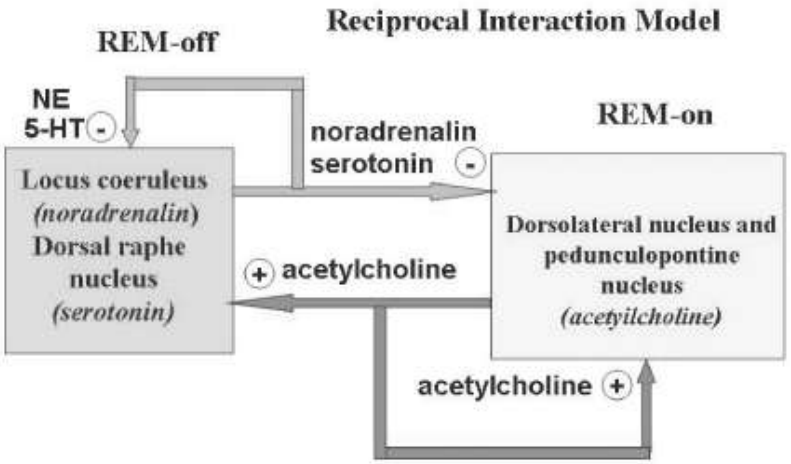
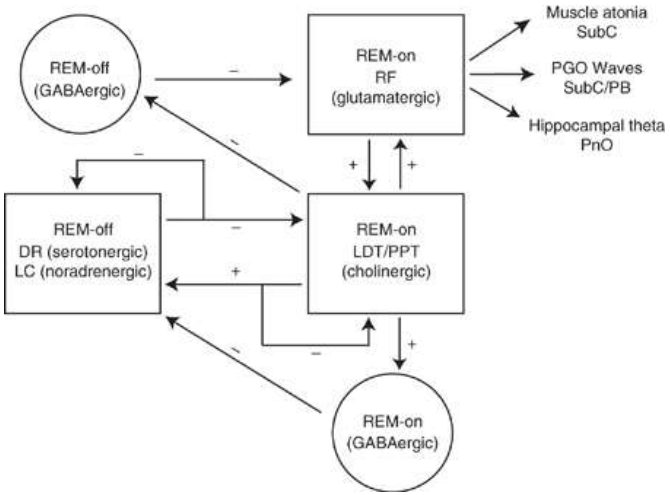


Figure 2 - Reciprocal Interaction Model
Cholinergic REM-on cells and serotoninergic-noradrenergic REM-off cells. During wakefulness, aminergic REM-off system is tonically activated, causing EEG desynchronization and inhibiting cholinergic REM-on cells. During REM sleep, aminergic REM-off cells are silenced and the cholinergic system, free from inhibitory influences, reaches its peak.



Orexins

Orexin, also known as hypocretin, is a neuropeptide that regulates arousal, wakefulness, and appetite.consolidate wakefulness (increase the duration of long waking bouts), suppress REM sleep (sect. IV), and enhance wakefulness in periods of starvation

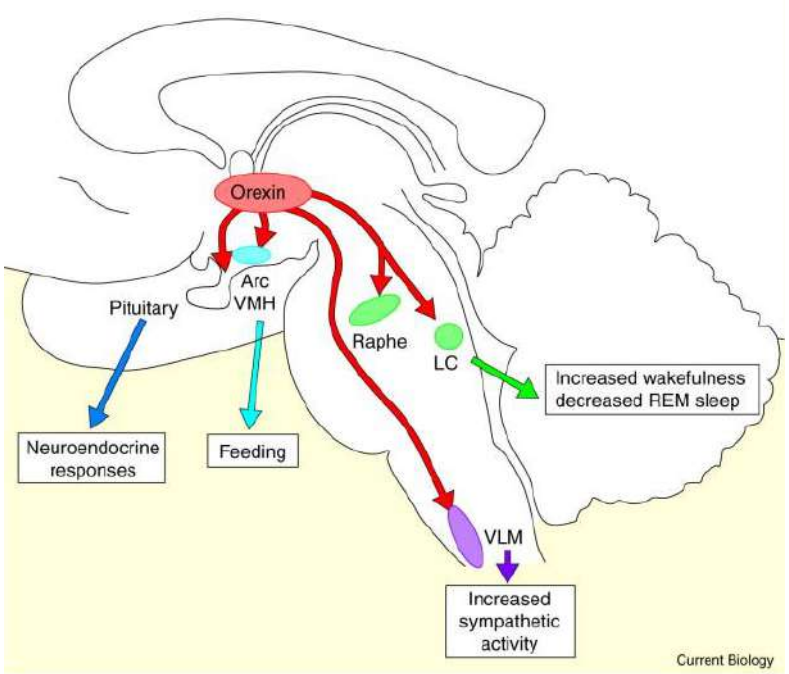
Orexins (also called hypocretins) are neurotransmitters produced in small neuronal populations within the lateral (LH) and perifornical (PFA) areas of the hypothalamus. The name orexin originated from the Greek root word for appetite, orexis

The receptors for these neuropeptides (Hcrtr1 [Orxr1] and Hcrtr2 [Orxr2]) have been identified as G-protein coupled receptors

Early work showed that intracerebroventricular application of orexin A dose-dependently increases wakefulness in rats

Orexin neurons respond to a wide variety of peripheral and central signals indicating nutritional state (164, 268, 393, 1048, 1452). Several metabolic signals which increase with feeding, such as glucose, leptin, and neuropeptide Y, inhibit orexin neurons in vitro (164, 393, 1452). In contrast, orexin neurons are activated by fasting in non-human primates

It was proposed that orexins exert their wake-promoting action through stimulation of the histamine system



Vestibular apparatus:

1. Describe the structure of vestibular apparatus with a neat diagram. (6/2010)
2. Discuss the histological structure of crystal ampullaris and macula. (4+2/2015)
3. What is otokonia? (2/2010)(2/2008)
4. What do you mean by otolithic organ? (2/2008)
5. Hoe the receptor in crista ampullaris are stimulated in physiological conditions? (6/2010)(4/2008)
6. Describe the transduction mechanism in vestibular hair cells. 98/2008)
7. Discuss the postural reflexes originated in vestibular receptor.(4/2008)
8. What do you mean by optokinetic and rotatory nystagmus ? (2=2/2010)

CEREBELLUM:

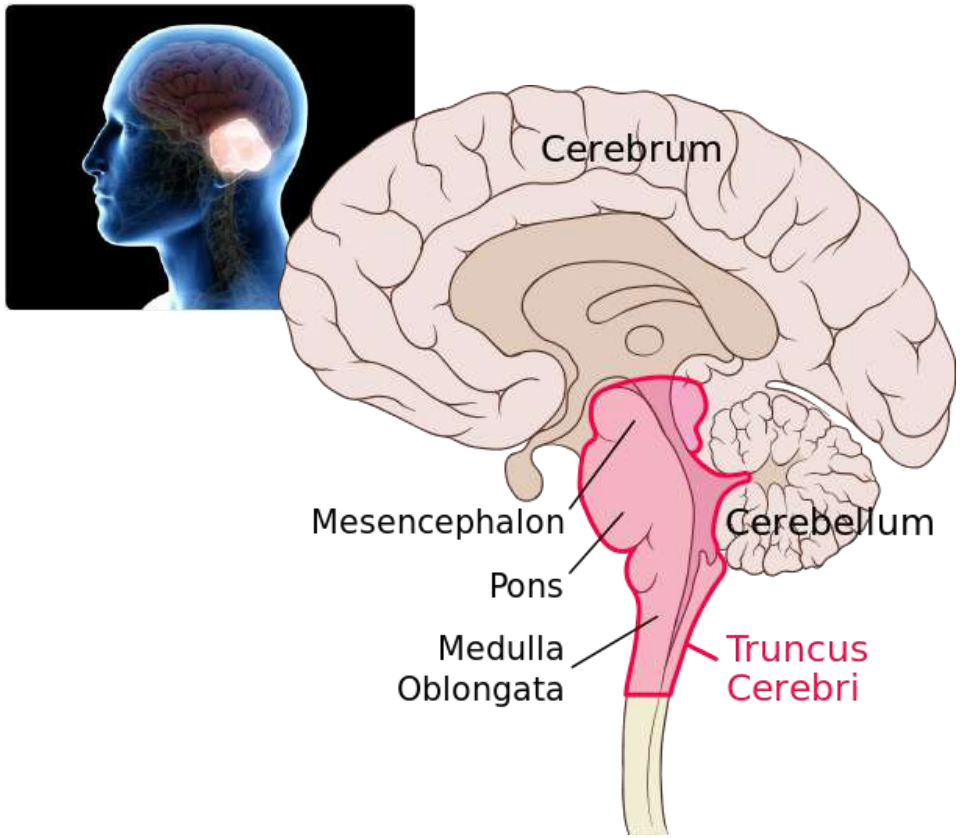
1. The cerebellum is a vital component in the human brain as it plays a role in **motor movement and balance control.** The cerebellum coordinates gait and maintains posture, controls muscle tone and voluntary muscle activity but is unable to initiate muscle contraction. Damage to this area in humans results in a loss in the ability to control fine movements, maintain posture, and motor learning.

2. Cerebellum is a Latin word meaning '**little brain**'. It is the **largest part of the hind brain** and weighs about 150 g. It is located immediately inferior to the occipital and temporal lobes, Cerebellum is separated from the pons and medulla by the cavity of fourth ventricle.

Anatomy:

The cerebellum consists of two hemispheres which are connected by the **vermis. T**he cerebellum consists of grey matter and white matter:

•**Grey matter** – located on the surface of the cerebellum. It is tightly folded, forming the cerebellar cortex.
•**White matter** – located underneath the cerebellar cortex. Embedded in the white matter are the four cerebellar nuclei (the dentate, emboliform, globose, and fastigi nuclei).



There are three ways that the cerebellum can be subdivided –

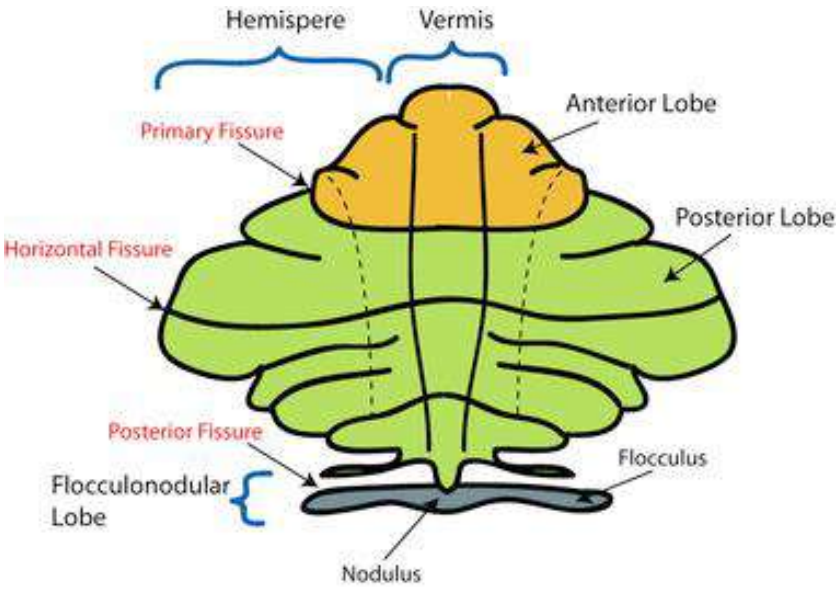
1. Anatomical subdivision,
2. Zonal division
3. Phylogenetic division
4. Functional division

1. Anatomical Division:

There are three anatomical lobes that can be distinguished in the cerebellum;

1. **The anterior lobe,**
2. **The posterior lobe and**
3. **The flocculo-nodular lobe.**

These lobes are divided by two fissures – the primary fissure and posterolateral fissure. The V-shaped **primary fissure** separates the anterior and posterior lobe, while the **posterolateral fissure** separates the posterior and flocculo-nodular lobes.

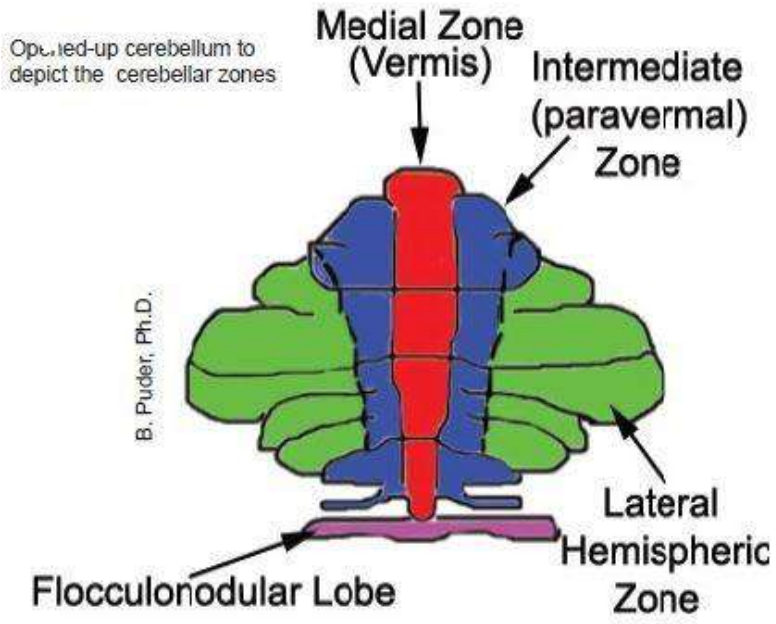


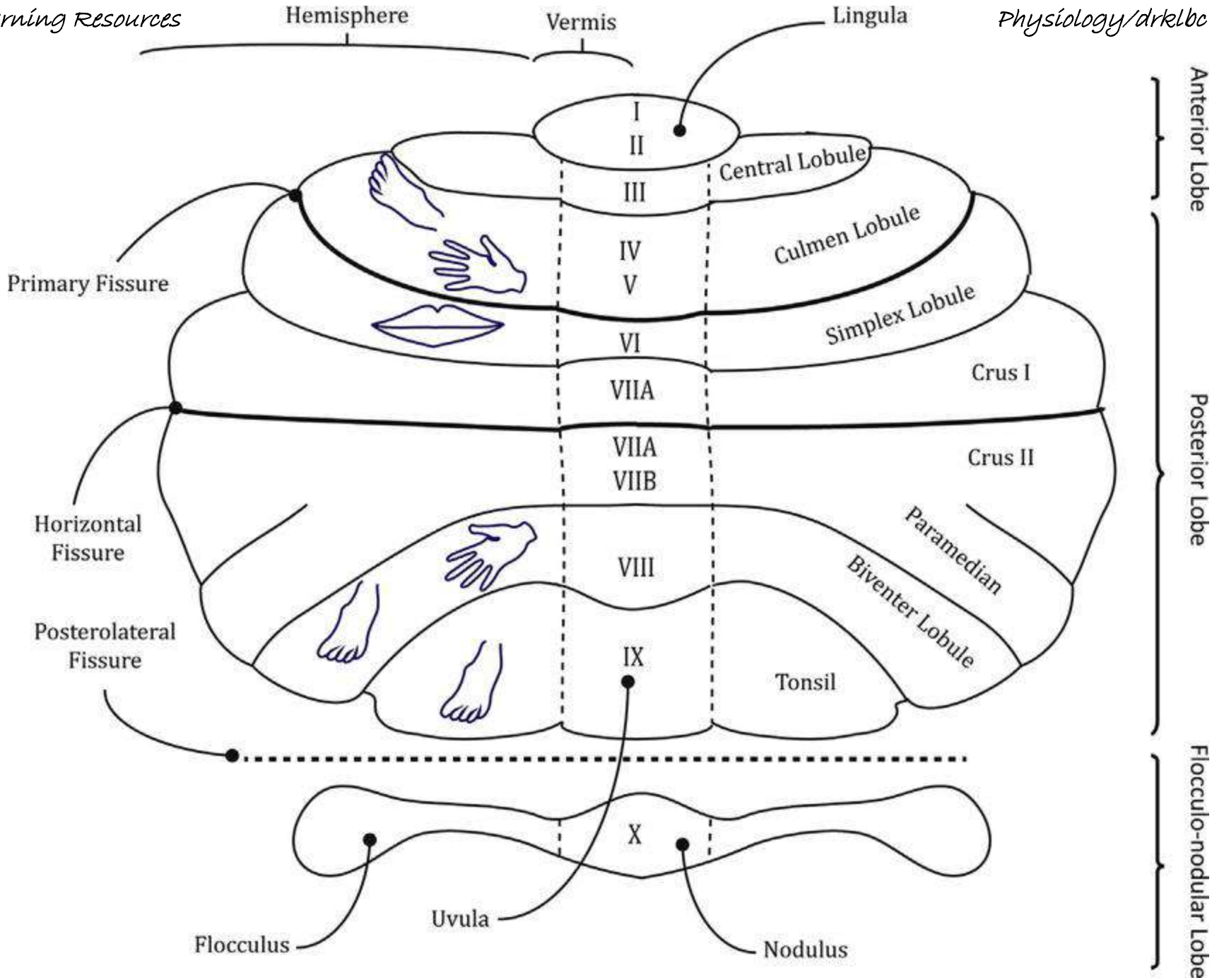
2. Zonal (longitudinal) division:

There are three cerebellar zones.

- In the midline of the cerebellum is the **vermis.**
- Either side of the vermis is the **intermediate zone.**
- Lateral to the intermediate zone are the **lateral hemispheres.**

There is no difference in gross structure between the lateral hemispheres and intermediate zones




Hemisphere
Vermis
Lingula
I
II
III
IV
V
VI
VIIA
VIIA
VIIB
VIII
IX
X
Central Lobule
Culmen Lobule
Simplex Lobule
Crus I
Crus II
Paramedian
Biventer Lobule
Tonsil
Primary Fissure
Horizontal Fissure
Posterolateral Fissure
Flocculus
Uvula
Nodulus
Anterior Lobe
Posterior Lobe
Flocculo-nodular Lobe

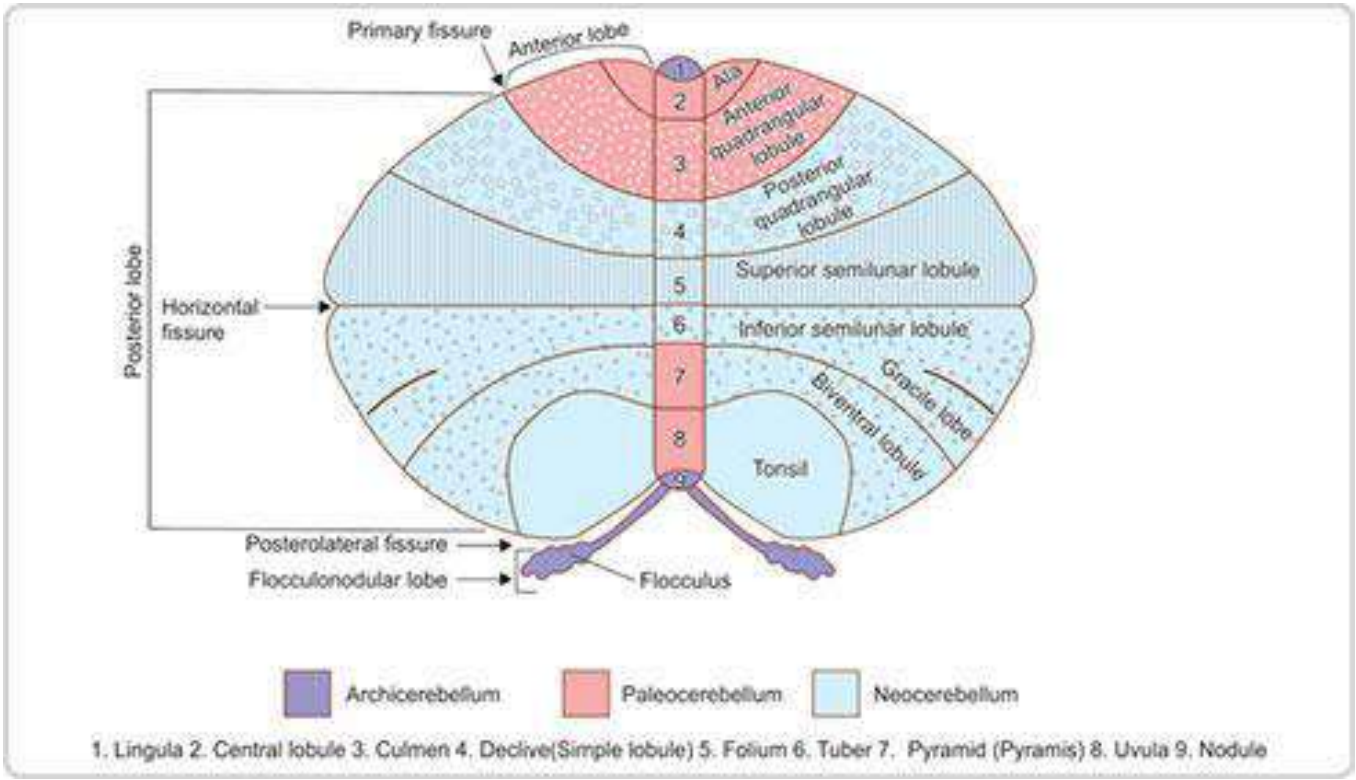
C. PHYLOGENETIC SUB-DIVISION:

Phylogenetically cerebellum is divided into three subdivisions:

1. **Archicerebellum (vestibular cerebellum):** it is the oldest part of cerebellum and first to appear in aquatic vertebrates. Fishes and lower amphibians possess only this component of the cerebellum. Archicerebellum comprises of **flocculo-nodular lobe and lingula.** It maintains equilibrium, tone and posture of trunk muscles.

2. **Paleocerebellum (spinal cerebellum):** It appears next in terrestrial vertebrates with the appearance of limbs. It includes **anterior lobe except lingula** and **pyramid and uvula.** It is concerned with spinocerebellar connections and responsible for tone, posture and crude movements of the limbs.

3. **Neocerebellum (cerebral cerebellum):** It is the most recent part of cerebellum to develop. It develops in primates and associated with the enlargement of cerebral cortex. It is very prominent in higher mammals. Neocerebellum includes **posterior lobe except pyramid and uvula.** It is mainly **'cortico-ponto-cerebellar'** connections and is concerned with smooth performance of skilled voluntary movements .



1. Lingula 2. Central lobule 3. Culmen 4. Declive(Simple lobule) 5. Folium 6. Tuber 7. Pyramid (Pyramis) 8. Uvula 9. Nodule

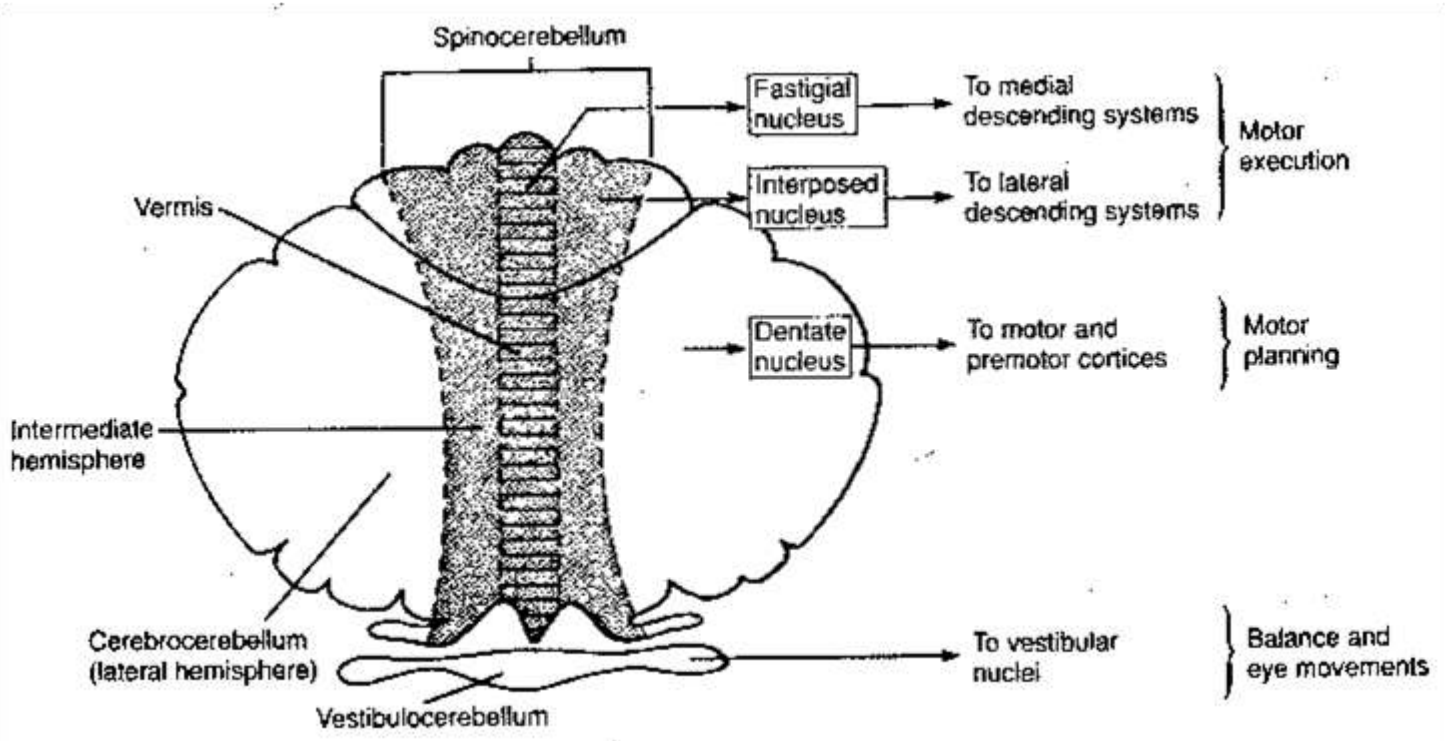
4. Functional Divisions:

The cerebellum can also be divided by function. There are three functional areas of the cerebellum –

1. **Cerebro-cerebellum** – the largest division, formed by the **lateral hemispheres**. It is involved in planning movements and motor learning. It receives inputs from the cerebral cortex and pontine nuclei, and sends outputs to the thalamus and red nucleus. This area also regulates coordination of muscle activation and is important in visually guided movements.

2. **Spino-cerebellum** – It comprised of the **vermis and intermediate zone** of the cerebellar hemispheres. It is involved in regulating body movements by allowing for error correction. It also receives proprioceptive information.

3. **Vestibulo-cerebellum** – the functional equivalent to the **flocculo-nodular lobe**. It is involved in controlling balance and ocular reflexes, mainly fixation on a target. It receives inputs from the vestibular system, and sends outputs back to the vestibular nuclei.



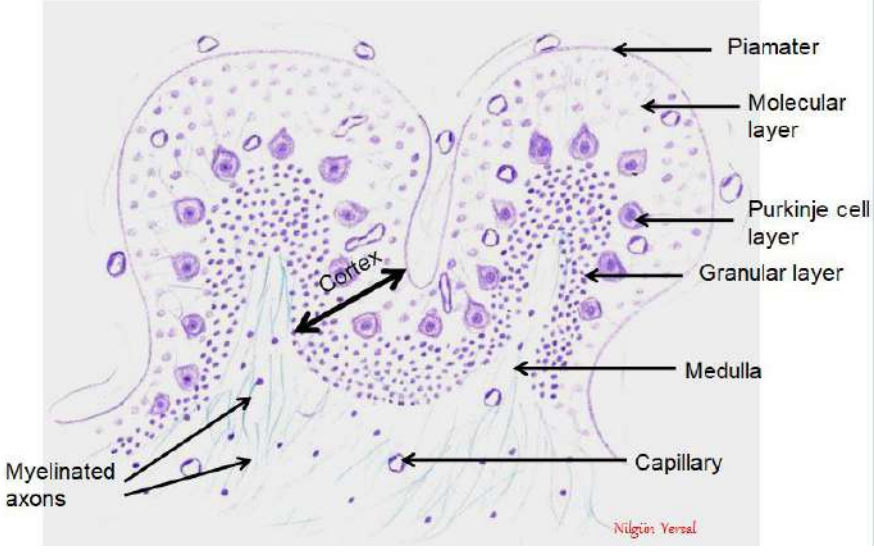
CYROARCHITECTURE (HISTOLOGY) OF CEREBELLAR CORTEX:

1. Cerebellum consists of outer layer of grey matter (the cerebellar cortex) and inner layer of white matter.
2. The cerebellar cortex is a folded sheet-like structure (folia).
3. Each folium consists of central core of white matter surrounded by thin layer of grey matter.
4. Central core of white matter is arranged in the form of the branching tree so called 'arbor vitae cerebelli'.
5. The **gray matter** of the cortex divides into three layers:
   - **An external molecular layer**
   - **A middle Purkinje cell layer**
   - **An internal - the granular layer.**

Molecular layer: This layer consists of unmyelinated nerve fibers derived from axons of granule, stellate and basket cells, dendrites of Purkinje and Golgi cells. The axons of stellate and basket cells follow transverse course parallel to the cortical surface and synapse with dendrites of Purkinje cells.

Purkinje cell layer: Purkinje cell layer consists of single layer of flask shaped Purkinje cells. Dendrites of these cells travel upwards into the molecular layer. Axons of Purkinje cells travel through granular layer into white matter where they form synaptic connections with intracerebellar (deep) nuclei.

Inner granular layer: The inner granular layer composed of numerous granule cells and few Golgi cells. Axons of these cells enter into molecular layer where they bifurcates and pass parallel to the long axis of cerebellar folium. These fibres are known as parallel fibres.



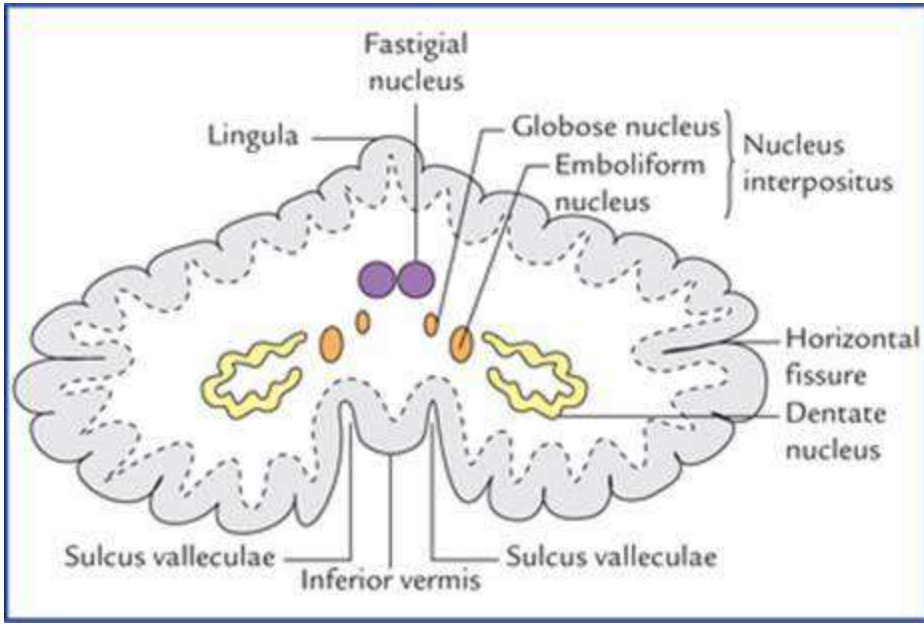
Intracerebellar nuclei (deep cerebellar nuclei):

Intracerebellar nuclei also known as central nuclei are collection of grey matter embedded in white matter.

As these are situated close to roof of IV ventricle on each side of midline hence also referred as roof nuclei.

From lateral to medial side, these are

(1) **Dentate nucleus,**
(2) **Emboliform nucleus,**
(3) **Globose nucleus, and**
(4) **Fastigial nucleus.**



Dentate nucleus

It is the most prominent cerebellar nucleus and largest in primates including human beings. It belongs to neocerebellum and receives afferent from it.

Emboliform nucleus

It is oval shaped and located medial to dentate nucleus. It belongs to paleocerebellum.

Globose nucleus

It is rounded in shape and situated between emboliform and fastigial nuclei. It has similar connections as emboliform nucleus. Emboliform and globose nuclei together are known as nucleus interpositus.

Fastigial nucleus

This nucleus is situated in the midline in the vermis and smaller than dentate nucleus but larger than nucleus interpositus. It belongs to archicerebellum

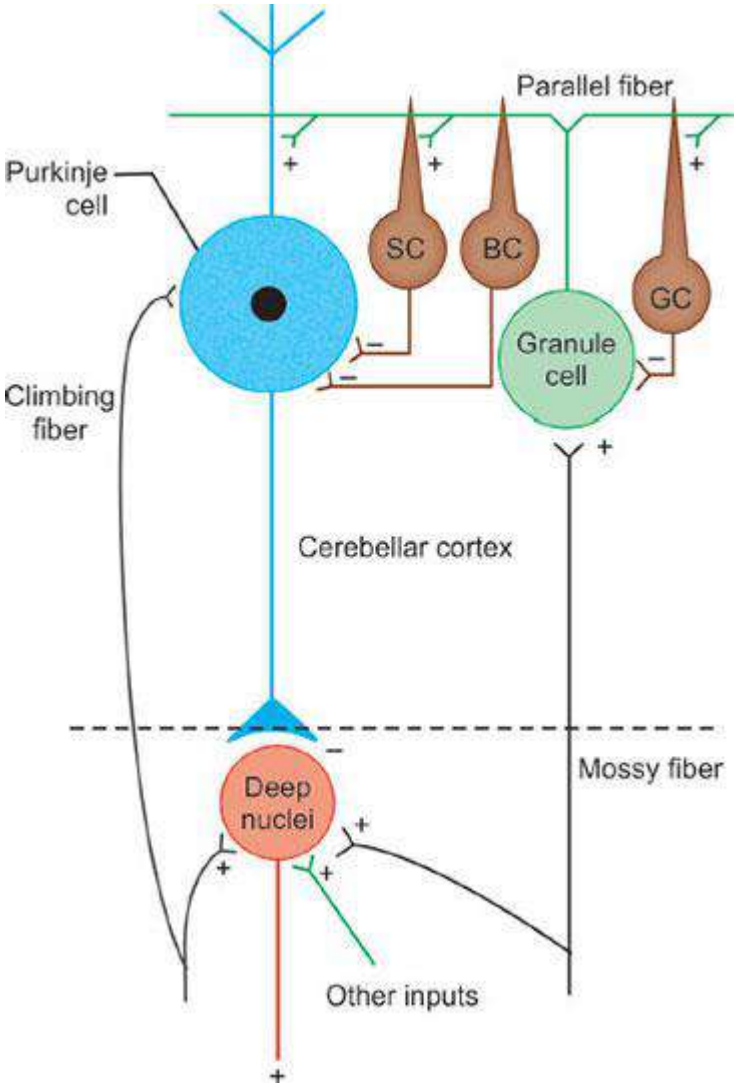
INTRINSIC CEREBELLAR CIRCUITRY:

1. Afferent fibres reaching the cerebellum are of two types: (a) climbing fibres and (b) mossy fibres.

2. **Climbing fibres** arises in the inferior olivary nucleus and each fibre after giving a collateral to the intracerebellar (deep) nuclei synapses with the Purkinje cell. The climbing fibers are named so because they travel in the cortex like vine branches on a tree. climbing fibers use aspartate as their main excitatory neurotransmitter

3. **Mossy fibres** are the main afferent fibres of cerebellum, and each mossy synapses with dendrites of granule cells and axons of Golgi cells. Axons of granule cells form the parallel fibre in cortex. Mossy fibres also excite the Purkinje cells through granule cells which excites stellate and basket cell. Basket and stellate cells in turn inhibit the Purkinje cells. Mossy fibers use glutamate as main excitatory neurotransmitter.

4. Purkinje cells finally inhibit **intracerebellar (deep) nuclei** which in turn control muscular activity through motor areas of brainstem and cerebral cortex.



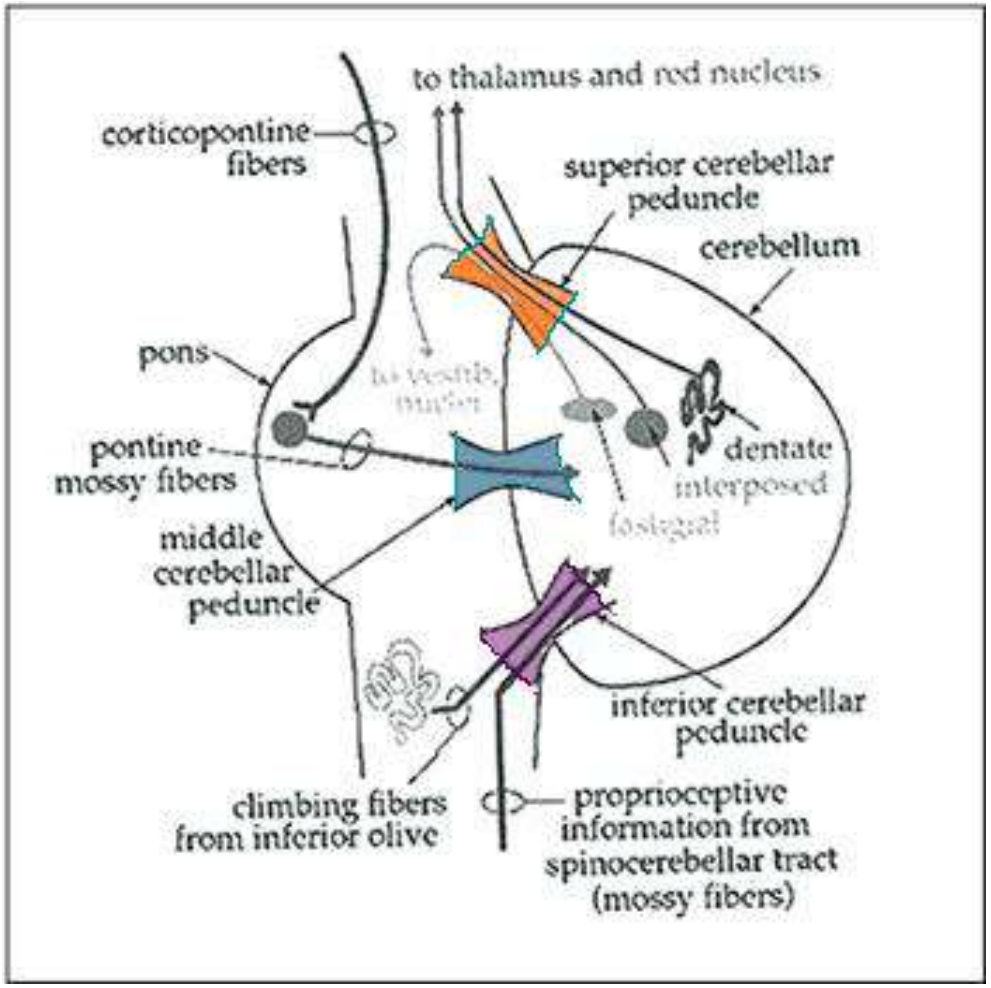
CEREBELLAR PEDUNCLE:

The cerebellum is connected to the brainstem by three large bands of nerve fibers known as cerebellar peduncles:

1) **Inferior cerebellar peduncle (ICP)** (known as **restiform body**): The ICP includes afferent fibers from the lateral cuneate nucleus , dorsal spinocerebellar tract, vestibular nuclei and olivary nucleus (climbing fibers). The Efferent fibers arises from **fastigial nucleus** which goes to reticular formation and vestibular nuclei.

2) **Middle cerebellar peduncle (MCP)** (or brachium pontis): The middle peduncle is entirely afferent. The fibers come from neurons of pontine nuclei.

3) **Superior cerebellar peduncle (SCP)** (or brachium conjunctivum). The only afferents in the peduncle are from ventral spinocerebellar tract. E*fferent fibers* arise from the **interpositus nucleus** which synapse in the red nucleus to influence activity in the rubrospinal tract. Axons from the **dentate nucleus** synapse in the contralateral thalamus, which projects to motor areas of cerebral cortex.

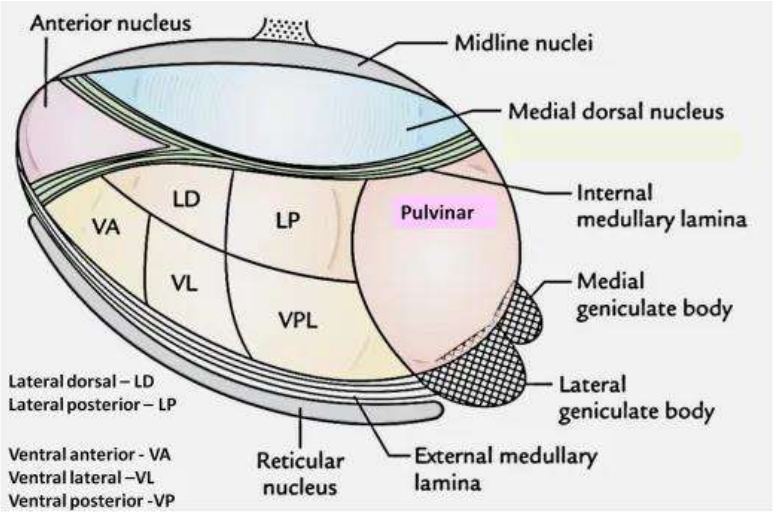


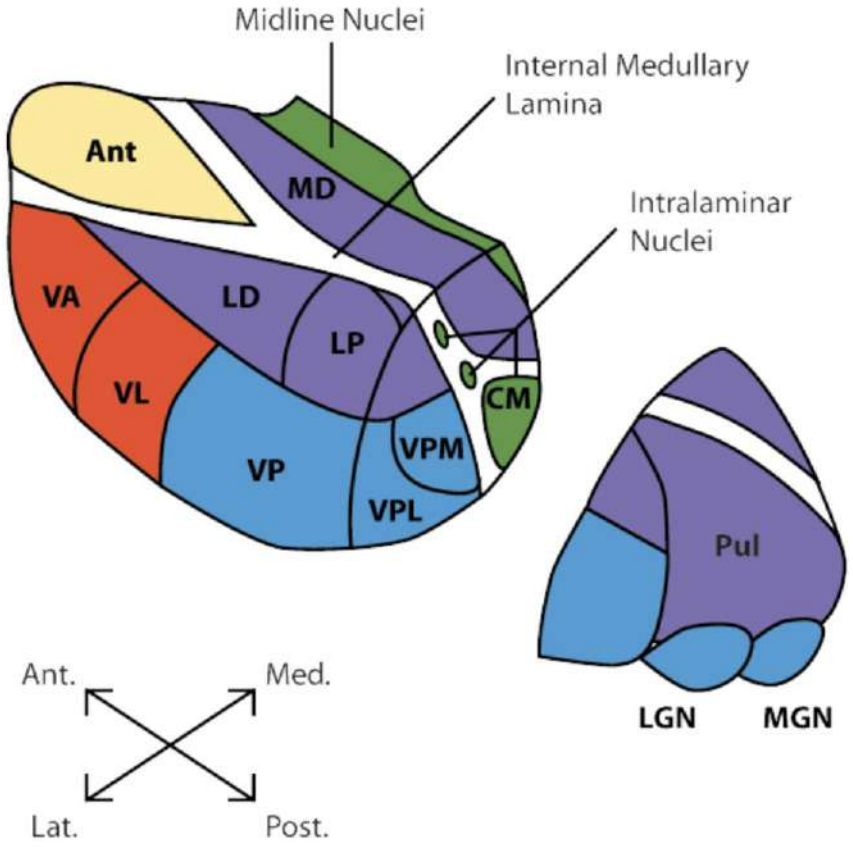
Cerebellum:

1. Describe the neural circuitry in cerebellar cortex mentioning the neurotransmitter involved therein. (3+1/2018)
2. What are meant by feed-back and feed-forward inhibition in cerebellar cortical circuitry. (1/2018)
3. What do you mean by archicerebellum and paleocerebellum? (4/2007)
4. What are climbing and mossy fibres? (2/2019)
5. What is restiform body? (1/2014)
6. Name the deep cerebellar nuclei. (2/2007)
7. Describe the role of cerebellum in the control of muscle tone, posture, and equilibrium. (7+3/2021)
8. How cerebellum helps in the act of locomotion. (6/2019)
9. Discuss the functions of cerebellum on accurate and precise voluntary movements. (5/2018)

CEREBRAL CIRCULATION AND STROKE

1. Mention any four properties of cerebral circulation. (4/2014)
2. What is circle of Willis? (2/2011) State the significance of circle of Willis. (2/2013)
3. What is aneurism? (2/2014)
4. What is a cerebrovascular stroke (CVA)?
5. What are 3 types of strokes?





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- Based on their connection with the cerebral cortex, the thalamic nuclei are divided into:
  - Specific nuclei
  - Nonspecific nuclei

Specific nuclei:

- Have well-defined sensory and motor functions
- Have highly organized point-to-point connection with sensory & motor regions of cerebral cortex
- Lie within the ventral group of the lateral nuclear group

Non-specific Nuclei:

- Receive less functionally distinct afferent input
- Connect with wider area of cortex, including associative and limbic regions
- Include nuclei of the dorsal tier of lateral group, and whole of the anterior and medial group