The Central Nervous System Physiology

Mustansiriyah College of Medicine
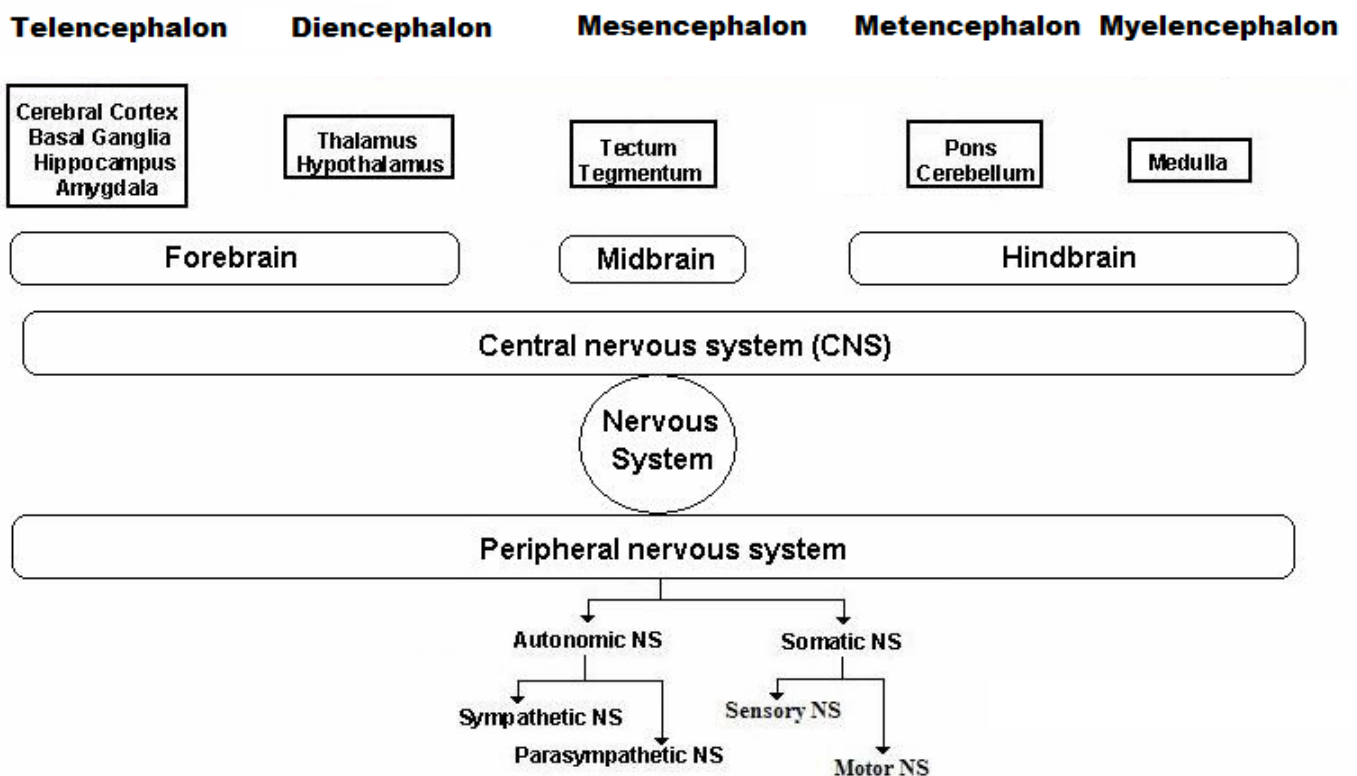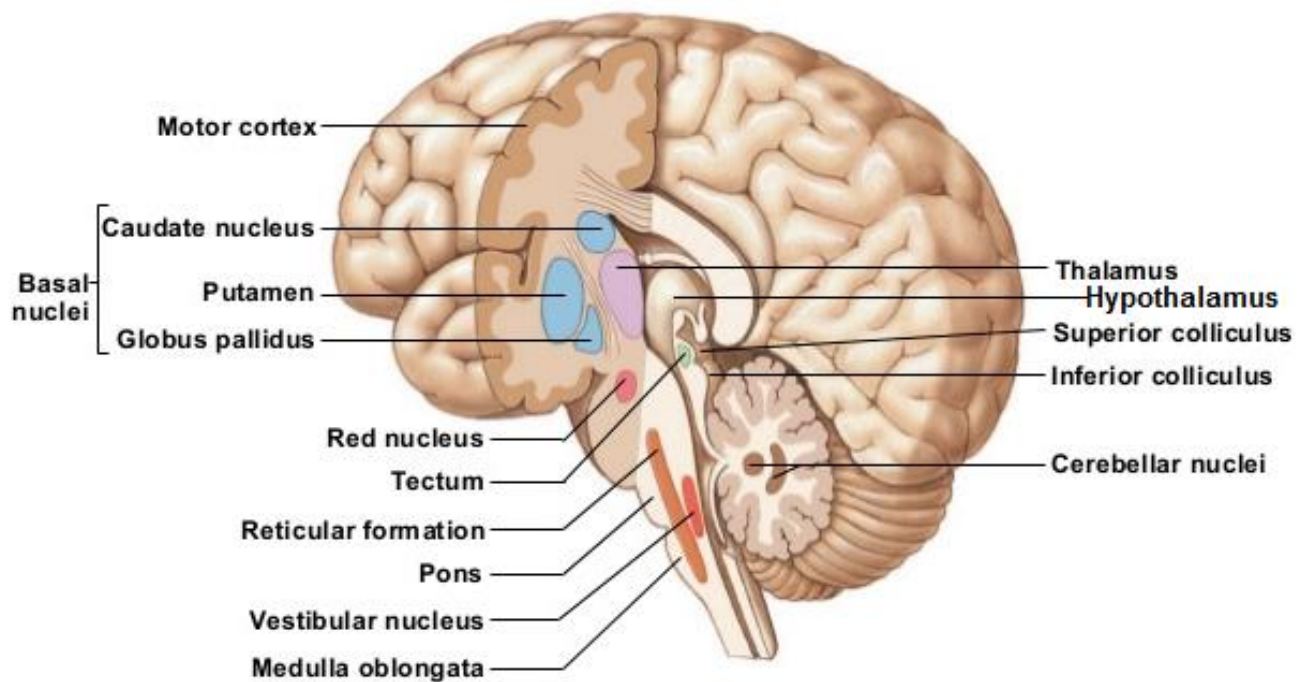
Nervous System Functions:

[1]. **Coordinate the activities of other systems** (along with the endocrine system) through senses and responses to internal and external events; therefore, it maintains homeostasis of the body. This is achieved via the **sensory** and **motor** functions of the CNS.

[2]. **Store experiences (memory)** and **establishes patterns of response** based on prior experiences (learning).

IMPORTANT PARTS OF NERVOUS SYSTEM

The functional levels of CNS: The intercommunication between the external environment and the CNS is mediated by the **sensory-somatic peripheral nervous system,** while the intercommunication between the internal environment and the CNS is mediated by **autonomic peripheral nervous system**. The CNS can be divided into three functional levels:
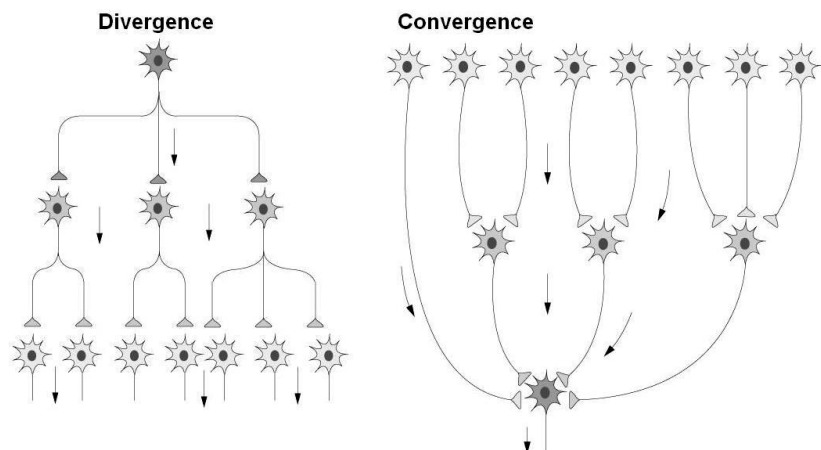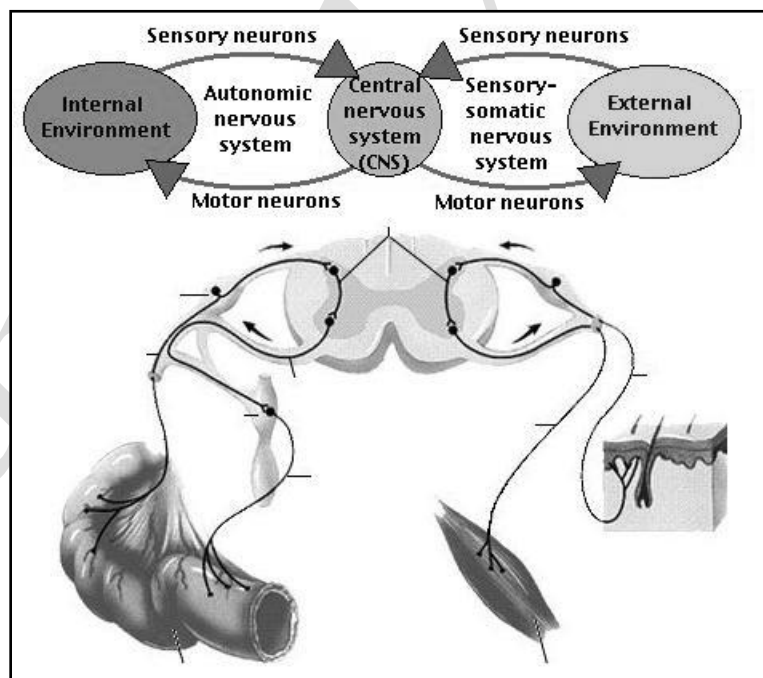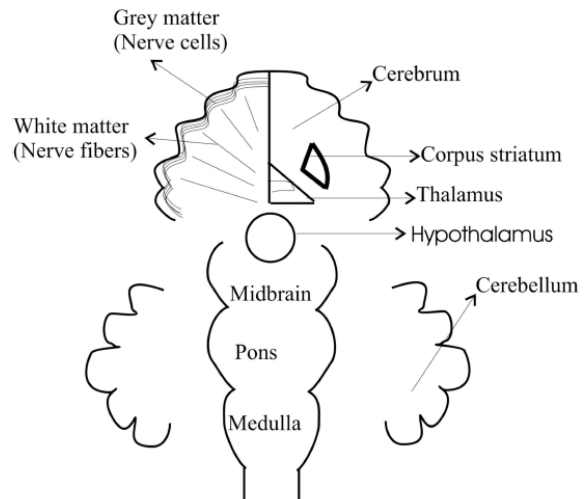
1- Spinal cord level: Spinal cord acts (a) as a conduit for signals from the periphery of the body to the brain or in opposite direction from the brain back to the body. In addition to this function (b) many reflex control centers are located in the spinal cord, which are in turn controlled by higher levels of CNS.

2- The lower brain level (subcortical level): Most of the subconscious activities of the body are controlled in the lower areas of the brain, i.e. medulla, pons, epencephalon, hypothalamus, thalamus, cerebellum, basal ganglia. Such of these activities are control of arterial pressure, respiration, control of equilibrium, feeding reflexes, many emotional patterns such as anger, excitement, sexual activities, reaction to pain, reaction to pleasure.

3- The higher brain level (cortical level): Cerebral cortex converts the lower CNS function into very determinative precise operations. In addition, the cerebral cortex is a very large memory storehouse and it is essential for most of our thought processes in association with the lower CNS centers.

The neuronal pools: Neuronal pool (or nuclei or centers) is a collection of intercommunicated neurons. Each pool has its own special characteristics of organization which


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cause it to process signals in its own special way. The examples of such pools are basal ganglia, specific nuclei in the thalamus, and cerebellum etc. The CNS is made up of thousands of separate neuronal pools. Each pool has fiber tracts coming to it (afferent fibers) and other leaving it (efferent fibers). The input signals to the neuronal pool may excite, inhibit, or facilitate the neurons within the pool.

The neuronal pool may allow the incoming signals to pass sequentially (**serial processing**), to allow the same incoming signal to pass simultaneously (**parallel processing**), or amplifies the input signal (**amplification**) and transmit these amplified signals to one or different directions (**divergence**). Sometimes an incoming signal to a neuronal pool causes an output excitatory signal going in one direction and at the same time an inhibitory signal going elsewhere. The center may summate the effects of multiple incoming signals that converge on the same pool (**convergence**). And, sometimes a signal entering a pool causes a prolonged output discharge (called **after-discharge**), even after the incoming signal is over. The mechanisms by which after - discharge occurs are the following:

[a] Synaptic after-discharge: When excitatory synapses discharge on the surface of postsynaptic neuron a long-acting synaptic transmitter substances.

[b] Parallel circuit for after-discharge: When the input signal spreads through a series of neurons in the neuronal pool and from many of these neurons impulses keep converging on an output neuron.
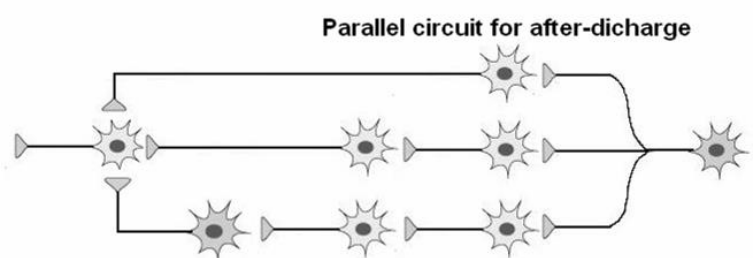
[c] Reverberatory circuit for after-discharge: When excitatory signal stimulate a neuron in a neuronal pool, the excited neuron in the pool feeds back to re-excite itself. Examples of reverberatory system are those which occur during respiration in which the inspiratory neuronal pool in the medulla become excited for about 2 sec

Parallel circuit for after-dicharge

Reverberatory circuit for after-discharge

during each respiratory cycle. Also one theory of wakefulness is that continual reverberation occurs somewhere within the brain stem to keep a wakefulness area excited during the waking hours.
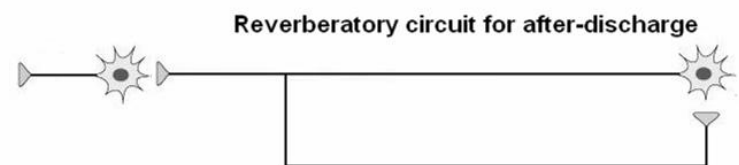
Some neuronal pools emit output signals continuously even without excitatory input signals. This occurs probably due to the rhythmical property of the neurons within the pool or due to the reverberating circuits.

Stabilization of neuronal circuits by inhibitory mechanisms: Without the stabilization of the neuronal circuits of the brain, any excitatory signal entering any part of the brain would set off a continuous cycle of re-excitation of all other parts and therefore, the brain would be busy by a mass of uncontrolled signals that would be transmitting no information. Such an effect actually occurs in widespread areas of the brain during epileptic convulsions. The NS prevents this from happening all the time by inhibiting the signal transmission. Some neuronal pools exert gross inhibitory control over widespread areas of the brain such as many of the basal ganglia which exert inhibitory influences throughout the motor control system.

Physiologically, the inhibitory mechanisms within the CNS are of two types:
(1) Presynaptic inhibitory mechanism: In which the inhibition occur at the presynaptic neuron before the signal reaches the synapse itself. Presynaptic inhibition can be achieved by two different mechanisms:

(A) Opening Cl and K ion channels at the presynaptic terminal: In which an inhibitory neuron

synapses an adjacent neuron at its axon or terminals and secretes an inhibitory transmitter substance (mostly **GABA**) which opens Cl and K ion channels at the axon or the terminal of the presynaptic neuron. The opening of Cl and K channels allows Cl ions to diffuse into the terminal fibril and K ions to diffuse out of the terminal fibril (causing a state of local hyperpolarization) and cancel much of the excitatory effect of the positively charged Na ions that enter the terminal fibril when an action potential arrives. Consequently, this will lead to reduce the voltage of the action potential that reaches the synaptic membrane of the terminal. And consequently decreases the amount of Ca ions that enter the terminal and therefore also the amount of transmitter released by the terminal. Therefore, the degree of excitation of the postsynaptic neuron is greatly suppressed or inhibited.

(B) Blocking Ca channels: Some of the inhibitory neurons secrete an inhibitory neurotransmitter (such as **enkephalin**) at the membrane of the terminal buttons of the presynaptic neurons that block Ca channels in the membrane of the nerve terminal and consequently decreases the amount of Ca ions that enter the terminal and therefore also the amount of transmitter released by the terminal.

(2) Postsynaptic inhibitory mechanism: This type of inhibition can be due to the generation of IPSP at the postsynaptic membrane or the occurrence of the synaptic fatigue in which the signal becomes progressively weaker with the more prolonged period of excitation. Other form of synaptic inhibition is the presence of refractory period at the postsynaptic neuron.

Anatomically, the inhibition of an informational pathway within the CNS can occurred at two different locations and these are:

[I] Lateral inhibition: In which the nerve fibers of a pathway give off collateral fibers that synapse with an inhibitory neuron. The inhibitory interneuron then send its nerve fiber to synapse at the axon or the terminal of the adjacent less excited neurons in the signal pathway preventing signals in an informational pathway from spreading diffusely everywhere.

[II] Recurrent inhibition (inhibitory feedback circuits): In which a collateral terminal return from the pathway back to excite an inhibitory interneuron which in turn send its fiber to the initial excitatory neuron of the same pathway and lead to inhibition of it.

Adjustment of the pathway sensitivity: The nervous system can adjust the sensitivity of an informational pathway by two mechanisms:

1- The fatigue mechanism for automatic short-term adjustment: In which the overused pathways usually become fatigue so that their sensitivities will reduced. On the other hand, those that are underused will become rested and their sensitivities will increase.

2- Downgrading or upgrading of synaptic receptors for automatic long-term adjustment: In which over usage of a circuit will lead to gradually decreasing sensitivity of the synapses because of decreased receptor proteins (downgrading), while under usage will cause increase in sensitivity because of increased receptor proteins (upgrading).
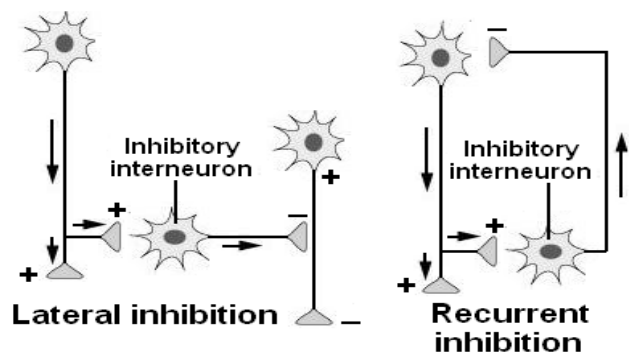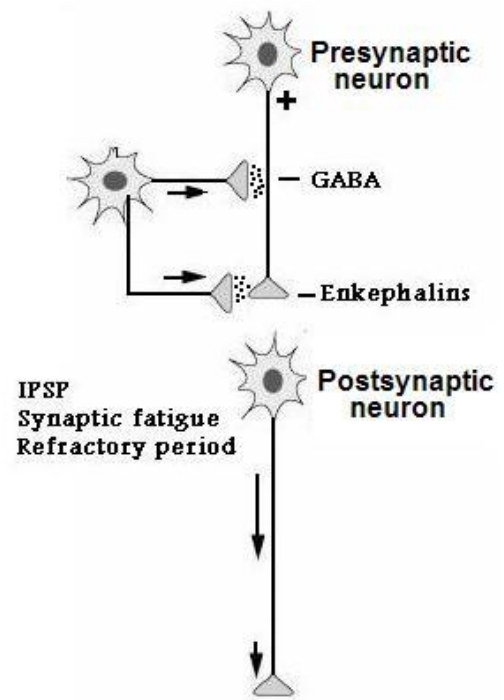
Somatosensory functions of the CNS
Sensory receptors and their basic mechanisms of action

Somatosensory system is defined as the sensory system associated with different parts of the body. Input to the NS is provided by the **sensory receptors** that detect sensory stimuli. Sensory receptors are specialized cells or neurons that transduce environmental signals (mechanical forces, light, sound, chemicals, and temperature) into neural signals (action potential) in neuron attached to it.

According to the type of energy or stimulus that stimulates receptors, there are five different types of sensory receptors:

[1] **Mechanoreceptors**, which detect mechanical deformation of the receptor or of cells adjacent to the receptor which include <u>tactile sensations</u> (touch, pressure, vibration, tickles, itch, stereognosis), <u>hearing</u>, <u>equilibrium</u>, and the <u>position sense</u> (or proprioceptive). Proprioceptors monitor the position of joints, the tension in tendons and ligaments, and the state of muscular contraction. There are three major groups of proprioceptors: Muscle Spindles, Golgi Tendon Organs, & Receptors in Joint Capsules (that detect pressure, tension, and movement at the joint.).

[2] **Thermoreceptors,** which detect changes in temperature, some receptors detecting cold and others warmth.

[3] **Pain receptors (nociceptors),** which detect damage in the tissues, whether it is a physical damage or chemical damage.

[4] **Electromagnetic receptors (photoreceptors),** such as rods and cones which detect light on the retina of the eye.

[5] **Chemoreceptors,** which detect taste in the mouth (taste receptors), smell in the nose (olfactory receptors), O_2 and CO_2 concentrations in the blood (carotid body receptors), osmolality of body fluids (osmoreceptors), and perhaps other factors that make up the chemistry of the body.

In general, clinically, senses can be classified into three types:

[A] **Somatic senses** are the sensations arising from skin, muscles, tendons and joints. These sensations have **specific receptors,** which respond to a particular type of stimulus. That include;

1. Tactile sensations, that include **touch**, **pressure**, **tickling**, **itch**, the **vibratory** and **stereognosis** sensations (stereognosis is the ability to determine what an object is just by using the modality of touch).

2. Position (or proprioceptive) sensation.

3. Pain sensation.

4. Thermal sensation.

[B] **Special senses:** Special sensations are the complex sensations for which the body has some **specialized sense organs**. They include vision, smell, taste, hearing, and equilibrium sensations (rotational and linear acceleration).

[C] **Visceral sensations:** Which are those concerned with perception of the internal environment such as those receptors which detect the changes in the osmolarity of the plasma (osmoreceptors), the pH, and other body fluids chemistry and pressure (chemoreceptors, baroreceptors).

Sensory Receptors — Hair shaft; Merkel disk (light touch); Meissner's corpuscle (light touch); Pacinian corpuscle (deep pressure); Ruffini ending (pressure); Free nerve endings (pain, heat, cold); Free nerve endings (sense changing position of hairs)

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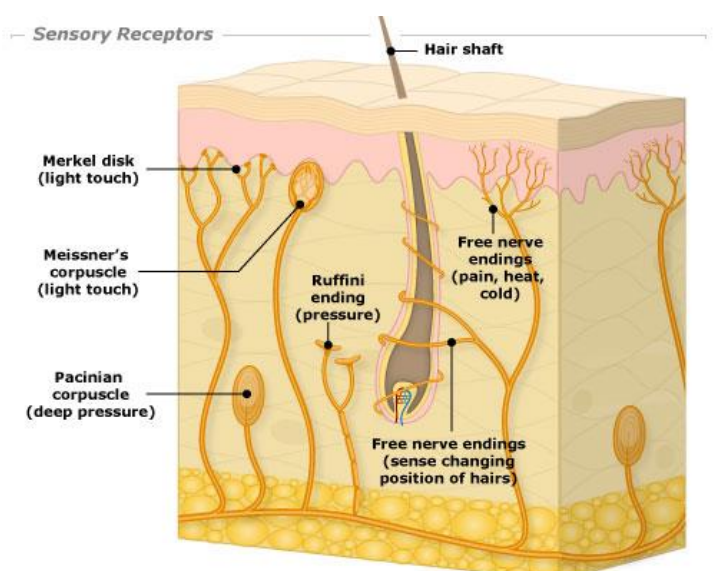
General properties of receptors:

1. The sensitivity of receptors: Each type of receptor is very highly sensitive to one type of stimulus (or particular type of energy) for which it is designed. A sensory receptor can be activated by variety of stimuli but the threshold for each of these stimuli varies considerably. The stimulus or the energy for which a sensory receptor is most sensitive (lowest threshold for detection) is called the **adequate stimulus**.

2. The specificity of the nerve fiber attached to the receptor: Each nerve fiber is specialized to transmit only one modality of sensation (a labeled line). Each nerve tract terminates at a specific point in the CNS, and the type and the site of sensation felt when a nerve fiber is stimulated is determined by this point in the CNS to which the fiber leads no matter how or where along the pathway the activity is initiated.
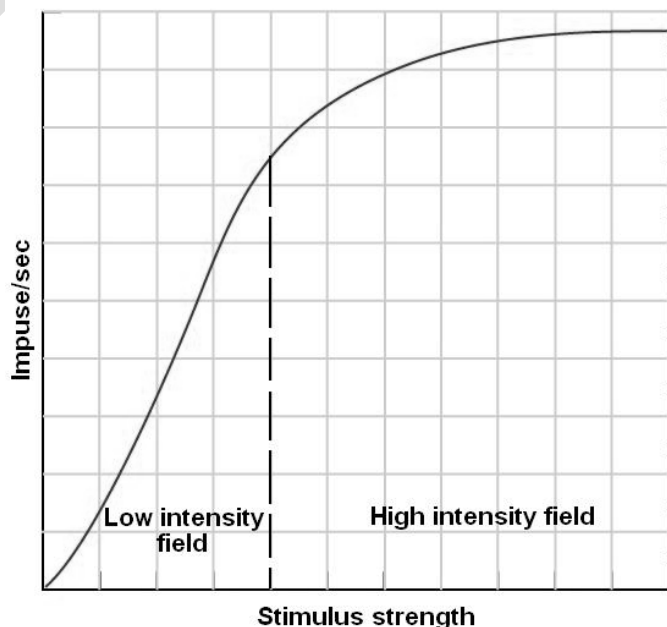
An example is seen in patients with amputated limb who may complain of pain and other sorts of sensations in the absent limb a condition called phantom limb. The ends of the nerves cut at the time of amputation often form nerve tangles called neuromas. These may discharge spontaneously or when pressure is put on them. The impulses that are generated are in nerve fibers that previously came from sense organs in the amputated limb, and the sensations evoked are projected to where the receptors used to be.

3. The ability to generate a receptor potential (generator potential): The mechanism used by the receptor to produce the receptor potential varies depending on the type of receptor. The stimulus that excites the receptor:

[A] May activate second messenger systems (such as Ca ions, cAMP, or cGMP) or,

[B] It may increase or decrease the permeability of the receptor membrane to ions such as Na and K ions without involvement of a second messenger.

All these mechanisms change the transmembrane potential. This local graded change in the membrane potential of the receptor is called **receptor potential** or **generator potential (depolarization)** except in the photoreceptors where the light causes hyperpolarization. When receptor potential rises at or above the threshold level, action potential starts to be elicited and propagated along the nerve fiber attached to the receptor. As the stimulus intensity increases, the receptor potential increases, and as the receptor potential increases, the impulse rate in the nerve fiber (the frequency of action potentials) increases. Therefore, the impulse rate is proportional to the stimulus intensity. However, the impulse rate in the nerve fiber is directly proportional to the low intensities of the applied stimuli (at low intensity field) and less steep when the intensities of the applied stimuli are high (at high intensity field).   The brain can recognize the intensity of the stimulus that is transmitted to it by:

[A] Variation in the frequency of the action potential generated by the activity in a given receptor (called **temporal summation, or frequency coding**) and

[B] By variation in the number of receptor activated (called **spatial summation or population coding**).

4. Adaptation or desensitization of receptors: It is a progressive decrease of receptor response to the continuous application of a constant sensory stimulus. When a continuous sensory stimulus is applied, the receptors respond at first with a very high impulse rate, and then at a progressively lower rate until finally many of them no longer respond at all. The time for adaptation is quite variable in different types of receptors ranging from few thousandths of a second to few days. According to the period for adaptation, sensory receptors can be divided into:

    A. Tonic receptors: They are slowly and incompletely adapting receptors. These types of receptors continue transmitting impulses to the brain as long as the stimulus is present or at least for many minutes or hours. Therefore, they keep the brain constantly appraised of the status of the body and its relation to its surroundings. Examples of such receptors are the joint capsule receptors, muscle spindles, Golgi tendon apparatuses, the receptors of the macula in the vestibular apparatus, the pain receptors, and baroreceptors of the arterial tree, the chemoreceptors of the carotid and aortic bodies, and some of the tactile receptors.

    B. Phasic receptors: They are rapidly and completely adapting receptors. These receptors are stimulated only when the stimulus intensity changes. Furthermore, the number of impulses transmitted is directly related to the rate at which the change takes place. For instance, in the case of pressure receptors, sudden pressure applied to the skin excites this receptor for a few milliseconds, and then its excitation is over even though the pressure continues. But then it transmits a signal again when the pressure is released.

5. Sensory unit: A single sensory axon with its branches forms the sensory unit. When a stimulus is applied, a response is produced from the region of the area that is stimulated. This is called receptive field. As the stimulus intensity is increased, more and more sensory units are activated and this is called recruitment of sensory units. It should be remembered that a sensory unit of one type of receptor could overlap with the sensory units of other types of receptors in the skin. This overlapping of sensory units from other receptors will also be stimulated when the intensity of stimulus is increased.

[1] Tactile sensations: Mechanoreceptors specialized to receive tactile Information. Four major types of encapsulated mechanoreceptors are specialized to provide information to the central nervous system about touch, pressure, itch, tickle, vibration, and stereognosis: Meissner's corpuscles, Pacinian corpuscles, Merkel's disks, and Ruffini's corpuscles. These receptors are referred to collectively as low-threshold (or high-sensitivity) mechanoreceptors because even weak mechanical stimulation of the skin induces them to produce action potentials. They are frequently classified as separate sensations but they are all detected by the same type receptors which may differ histologically.

    Touch and pressure: Pressure is sustained touch. Touch receptors are most numerous in the skin of the fingers and lips and relatively scarce in the skin of the trunk, and they are found around hair follicles in addition to the subcutaneous tissues of hairless areas. Touch sensation is carried by type A and C nerve fibers.

    Itch and tickle: Relatively mild stimulation of the skin, eyes, and certain mucous membranes produces itch and tickle sensations carried by type C nerve fibers. Scratching relieves itching because it activates afferent fibers that block transmission (through lateral inhibition) of the itch carrying fibers at the dorsal horn of the spinal cord. Itching can be produced by repeated local mechanical stimulation of the skin and by variety of chemical agents such as bile salts, histamine, and kinins.

    Vibratory sensation: All the different tactile receptors are involved in detection of vibration between 60 up to 700 cycles/sec. Vibratory sensation is conducted by type A nerve fibers. Vibratory and proprioceptive sensations are closely related, when one is depressed, so is the other.

    Stereognosis: The sense of touch that is essential for perception of form, shape, and spatial nature of objects. Tactile sensors are located predominantly in the palm, especially in the fingertips, and

in the tongue and oral cavity. <u>Stereognostic perception of an object requires that the CNS integrate signals from adjacent receptors into a spatial pattern and coordinate them with tactile motor function</u>. **Synthetic senses** are the sensations synthesized at cortical level, by integration of impulses of basic sensations. Two or more basic sensations are combined in some of the synthetic senses. Best examples of synthetic senses are <u>vibratory sensation</u>, <u>stereognosis</u> and <u>two-point discrimination</u>.

[2] The position (or proprioceptive) sense:

[2] The position (or proprioceptive) sense: Proprioceptive (or position) sensations are the sensations of the physical state of the body, including position and movement sensations. It is carried by <u>type A</u> nerve fiber. They involve the sensory signals from the tendons, muscles, the joint capsules, ligaments, skin, deep tissues near the joints, pressure sensations from the bottom of the feet, and even the sensation of equilibrium (vestibular system). Proprioceptive sensation is either <u>conscious</u> and is carried by lemniscal pathway or <u>subconscious</u> and is carried by spinocerebral tract (as will described later). It can be divided into two subtypes:

   1. Static proprioceptive sensation, which means conscious recognition of the orientation of the different parts of the body with respect to each other and,

   2. Dynamic proprioceptive sensation (Kinesthesia), which means conscious recognition of movements and the rates of movement of the different parts of the body.

[3] Pain sensation

[3] Pain sensation: An unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is a protective mechanism for the body and protects your body from injury (or further injury if you have already hurt yourself). Pain also helps healing...because an injury hurts, you rest. It occurs whenever any tissues are being damaged, and it causes the individual to react to remove the pain stimulus. There are two types of pain; **acute pain** (sharp or pricking or fast or electrical pain) as in cut finger and **chronic pain** (burning or aching or throbbing or nauseous or slow pain) as in sunburn. Acute pain often results from tissue damage, such as a skin burn or broken bone. Acute pain can also be associated with headaches or muscle cramps. This type of pain usually goes away as the injury heals or the cause of the pain (stimulus) is removed. Chronic pain refers to pain that persists after an injury heals, cancer pain, pain related to a persistent or degenerative disease, and long-term pain from an unidentifiable cause, for example, the stimulus cannot be identified in as many as 85% of individuals suffering lower back pain..

There are some people who are born WITHOUT the sense of pain. These people have a rare condition called "congenital insensitivity to pain". Their nervous systems are not equipped to detect painful information. You may think this is a good thing....it is NOT. Without the ability to detect painful events, you would continue to cause injury to yourself. For example, if you broke a bone in your arm, you might continue using the arm because it did not hurt. You could cause further injury to your arm. People with congenital insensitivity to pain usually have many injuries like pressure sores, damaged joints and even missing or damaged fingers!

Acute (fast) pain	Chronic (slow) pain
[1] Occurs within about 0.1 sec after a pain stimulus is applied. Often results from tissue damage, such as a skin burn or broken bone. This type of pain usually goes away as the injury heals or the cause of the pain (stimulus) is removed.	Occurs after a sec or more and then increases slowly over a period of many sec and sometimes even minutes. Chronic pain persists after an injury heals, cancer pain, pain related to a persistent or degenerative disease and long-term pain from an unidentifiable cause.
[2] It is felt in the skin and can be highly	It is felt both in the skin and in almost any internal tissue and it is very grossly localized (deep pain)

localized (superficial pain).	
[3] It transmitted through type **Aδ** pain fibers which can be blocked by moderate compression of the nerve fiber.	It transmitted through type **C** pain fibers which can be blocked by low concentrations of local anesthetic.
[4] Glutamate is the probable neurotransmitter	**Substance P** is the probable neurotransmitter. Inhibition of the release of substance P is the basis for pain relief by opioids.
[5] 1st order neurons terminate mainly in **lamina I** at the dorsal horn and these excite second order neurons	1st order neurons terminate almost entirely in **lamina II and III** of dorsal horns of spinal cord, together called as substantia gelatinosa.
[6] The 2nd order neuron is **terminated in the thalamus**.	The 2nd order neuron is **terminated in the thalamus** but gives collateral to **reticular formation**, **periaqueductal gray** area, and **hypothalamus**.
[7] It evokes a withdrawal reflex and a sympathetic response, including an increase in blood pressure and a mobilization of body energy supplies.	It produces nausea, profuse sweating, a lowering of blood pressure, and a generalized reduction in skeletal muscle tone.

Because of this double system of pain innervation, a sudden onset of painful stimulus gives a double pain sensation: a fast sharp pain followed a second or so later by a slow burning pain. The sharp pain apprises the person very rapidly of a damaging influence and making the person to react immediately to remove himself from the stimulus. On the other hand, the slow pain sensation tends to become more and more painful over a period of time.

Types of pain receptors: The pain receptors (nociceptors) are all <u>free nerve endings</u> and are of <u>tonic type</u>. Pain receptors can be classified into 3 types according to the type of stimulus that excite them and these are:

1. Mechanosensitive pain receptors: They are excited almost entirely by excessive mechanical stress or damage to the tissues.

2. Thermosensitive pain receptors: They are sensitive to extreme of heat or cold.

3. Chemosensitive pain receptors: They are sensitive to various chemical substances released at sites of injury and cause direct extreme stimulation of pain nerve fibers without necessarily damaging them such as <u>Substance P</u>, <u>lactic acid</u>, <u>bradykinin</u>, <u>serotonin</u> (or 5HT from platelets), <u>histamine</u> (from mast cells), <u>potassium ions</u> (from damaged Cells), acids, <u>prostaglandins</u> (from arachidonic acid released from damaged cells), <u>acetylcholine</u>. <u>Proteolytic enzymes</u> are actually cause direct damage to the pain nerve endings. Aspirin and other non-steroidal anti-inflammatory drugs (like voltaren, ponstan, and brufen) prevent the formation of prostaglandins. Since prostaglandins play a role in sensitization of pain nerve fibers and without them, the nociceptors are less likely to become sensitized and therefore less pain impulses will be transmitted.

Ischemia can cause pain due to [l] accumulation of large amounts of lactic acids in the tissues and [2] due to the production of other chemical agents from the tissues as a result of the cell damage.

Muscle spasm can cause pain either [l] directly due to stimulation of mechanosensitive pain receptors and [2] indirectly by causing ischemia (by compression the blood vessels and diminishes blood flow and by increasing the metabolic rate in the muscle tissue at the same time) and thereby stimulating chemosensitive pain receptors.

Referred pain: <u>That is the pain felt in a part of the body considerably remote from the tissues causing the pain.</u> Usually the pain is initiated in one of the visceral organs and referred to an area on the body surface or deep area of the body not exactly coincident with the location of the viscus producing the pain. The best known example is referral of cardiac pain to the inner aspect of the left arm. Other

examples include pain in the tip of the shoulder owing to irritation of the central portion of the diaphragm and pain in the testicle due to distortion of the ureter.

The mechanism of the referred pain is as follow: *The visceral pain fibers enter the spinal cord and synapse with second order neuron that also receives pain fiber from the skin. When the visceral pain fibers are stimulated, pain signals from the viscera are then conducted through the same spinal neurons that conduct pain signals from the skin, and person has the feeling that the sensations actually originate in the skin itself.*

The rules that determine the areas to which the pain is referred are:

1. Dermatomal rule: In which the pain is usually referred to a structure that developed from the same embryonic segment or dermatome in which the pain originates. For example, during embryonic development, the diaphragm migrates from the neck region to its adult location in the abdomen and takes its nerve supply, the phrenic nerve, with it. The afferent fibers of the phrenic nerve enter the spinal cord at the level of the second to fourth cervical segments, the same location at which afferents from the tip of shoulder enter.

2. Brain interpretation rule: Pain signals from visceral structure may converge on the same spinothalamic tract that receives sensory somatic signals from the peripheral structures. Since somatic pain is much more common than visceral pain, the brain has learned that activity arriving in a given pathway is caused by a pain stimulus In a particular somatic area.

3. Facilitation effects rule: In which the incoming impulse from visceral structures lower the threshold of spinothalamic neurons receiving afferent from somatic areas, so that minor activity in the pain pathways from the somatic areas passes on to the brain.

Visceral pain: It is the pain from different viscera of the abdomen and chest. The true visceral pain is transmitted through type C nerve fibers that run in the sympathetic or parasympathetic nerves. **The viscera have somatic receptors for pain sensation only**. Because there are relatively few pain receptors in the viscera, visceral pain is poorly localized. Visceral pain is different from surface pain and that is a highly localized types of damage to the viscera rarely cause pain. On the other hand, any stimulus that causes diffuse stimulation of pain nerve endings throughout a viscus causes pain that can be extremely severe. Such stimuli include ischemia of visceral tissue, chemical damage to the surface of the viscera, spasm of the smooth muscle in a hollow viscus, distention of a hollow viscus, or stretching of the ligaments. The brain, the parenchyma of the liver and the alveoli of the lungs are almost entirely insensitive to pain of any type. Yet, the liver capsule, the bile ducts, the bronchi, the parietal pleura, parietal peritoneum, and pericardium are very sensitive to pain. This is because these structures are supplied with extensive innervation from the spinal nerves.

There is evidence that some of the 1st order neuron of the visceral pain fiber terminate the intermediate gray region of the spinal cord near the central canal. These neurons, in turn, synapse with the 2nd order neuron that send their axons not through the anterolateral white matter of the spinal cord
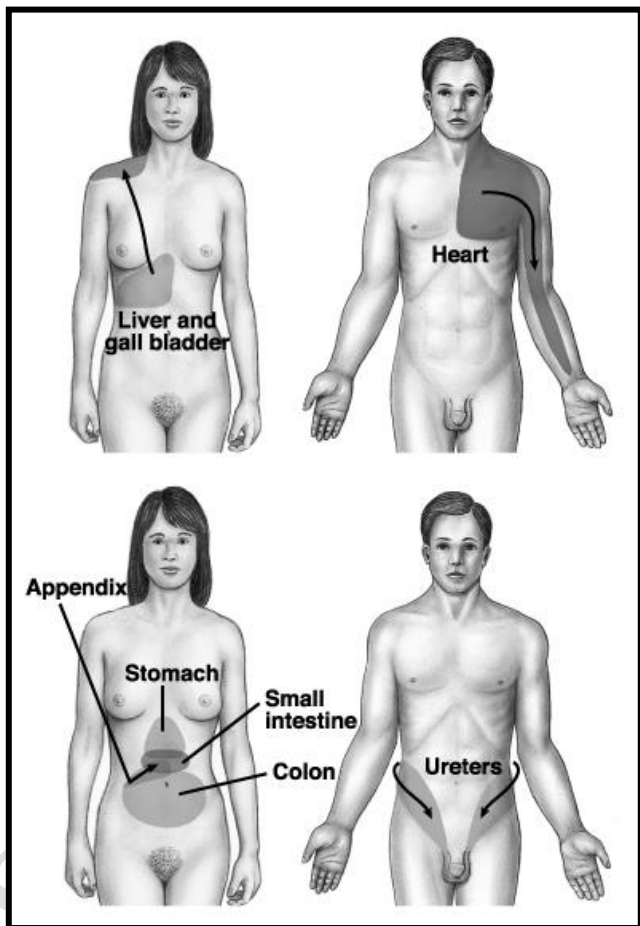
(as might be expected for a pain pathway) but through the dorsal columns ipsilaterally in a position very near the midline. These second order axons then synapse in the gracilis nucleus of the medulla, where the third-order neurons give rise to fibers that form the contralateral medial lemniscus and eventually synapse at diffuse nuclei of thalamus. From the thalamus, a fourth-order neuron projects to cerebral cortex.

Central inhibition of pain: Pain perception is affected by a variety of psychological factors such as mood and emotional motivational state. For example, under "fight and flight" condition, the threshold for pain increases such that stimuli that usually produce pain are not perceived as painful. Opposite phenomenon also occurs. For example, when a subject is anxious, a non-painful stimulus may perceive as painful. The degree to which each person reacts to pain varies tremendously. There is individual variation in response to pain, which is influenced by genetic makeup, cultural background, age and gender. The variation of patient`s reaction to pain is due to partly from the capability of the brain itself to control the degree of input of pain signals to the NS by activation of a pain control system, called analgesia system and partly by stimulation of large sensory fibers from the peripheral tactile receptors.

1- Analgesia system: It consists of three major components and these are:

[A] The neurons of **periaqueductal gray area.**

[B] Neurons of **raphe magnus nucleus.**

[C] **Pain inhibitory complex** located in the dorsal horns of the spinal cord, the areas called **marginal nucleus (MN, or layer I) for fast pain (acute) and substantia gelatinosa (SG, or layers II, III, IV) for slow pain (chronic)**.

[D] plus other **accessory components** (such as periventricular nuclei around the third ventricle and medial forebrain bundle in the hypothalamus). In the reticular formation, **noradrenergic neurons** projected from the locus ceruleus and **dopaminergic neurons** projected from the ventral tegmental area also appear to be involved to suppress incoming pain signals at the spinal level.

The neurons of periaqueductal gray area (which secrete **enkephalin** as neurotransmitter) can be stimulated or inhibited via thalamus by the limbic system and prefrontal cortex of the brain. The neurons of periaqueductal gray area send their signals to neurons of raphe magnus nucleus. Those fibers originating in this nucleus descend in both lateral
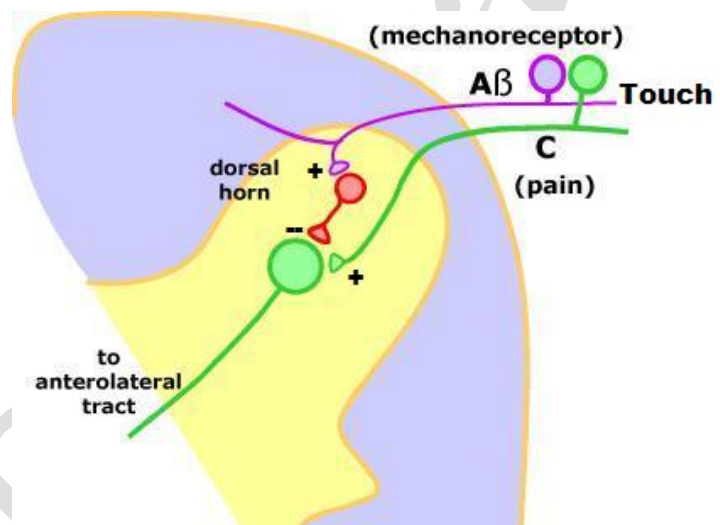

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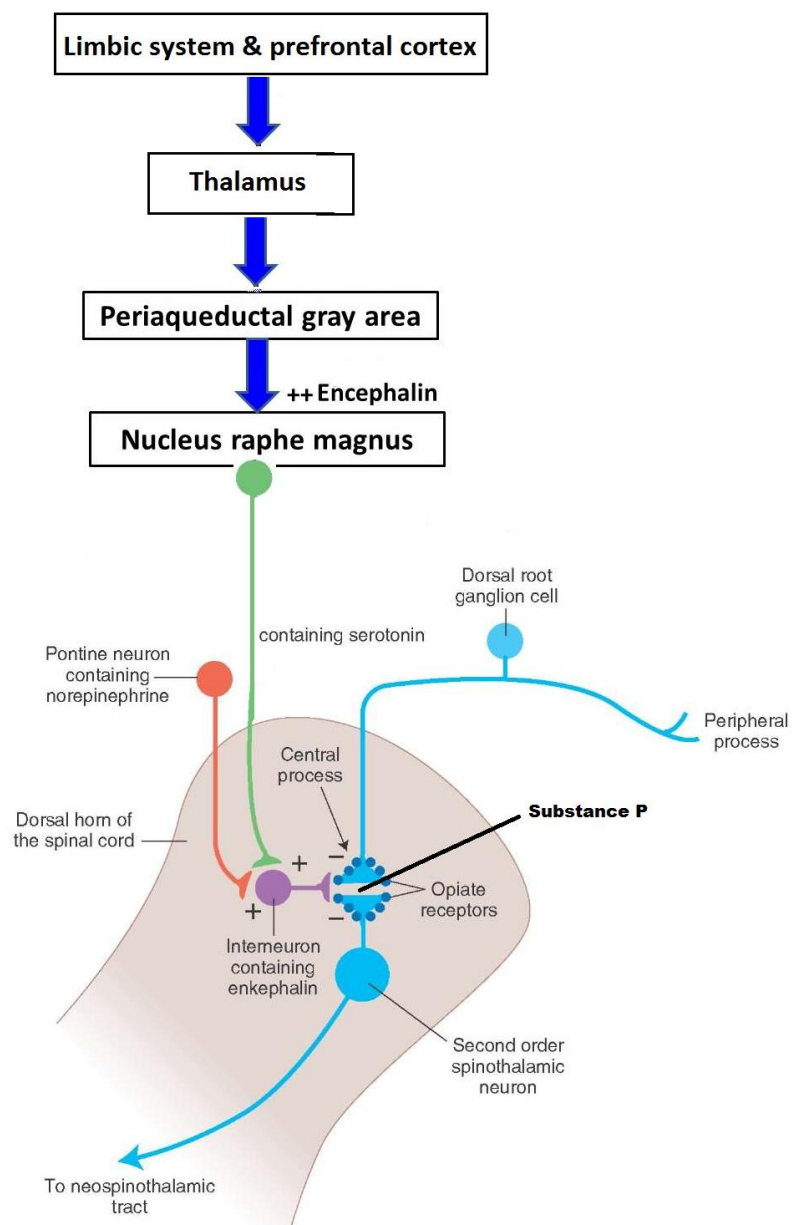
and ventral columns and terminate in the interneurons of the pain inhibitory complex of the spinal cord secrete **serotonin** at their endings which stimulate these interneurons to secrete **enkephalin**. The enkephalin, in some way is believed to cause presynaptic and postsynaptic inhibition of the incoming pain fibers in the dorsal horns. At this point the pain signals can be blocked before they are relayed on to the brain. Presynaptic Inhibition probably achieved by blocking Ca channels in the membranes of the nerve terminal.

It was found that these areas of the analgesia system have opiate receptors which interact with morphine (an opiate substance) and with some morphine-like neurotransmitters that is naturally secreted in the brain such as beta-endorphin which is found in hypothalamus and pituitary gland, met- and leu- enkephalin which are found in analgesia system, and dynorphin which is present in only minute quantities in nervous tissue, but having 200 times as much pain-killing effect as morphine when injected directly into the analgesia system. In addition, multiple areas of the brain have been shown to have opiate receptors.

2- Stimulation of peripheral sensory fiber (gate control theory): Cells in substantia gelatinosa (SG) act as the "**gate**". Stimulation from large fibres (A fibers) causes the gate to close due to stimulation of inhibitory interneuron that inhibits the pain incoming nerve fiber (cells in SG are stimulated, decrease pain signal). Stimulation from small fibers (C fibers) opens gate due to inhibition of inhibitory interneuron (cells in SG are inhibited, increase pain signal). Stimulation of large sensory fibers from the peripheral tactile receptors (such as massage or acupuncture) depresses the transmission of

pain signals either from the same area of the body or even from areas sometimes located many segments away. As these sensory tactile fibers enter the dorsal column of the spinal cord give collateral fibers to the dorsal horn of the cord. Impulses in these collateral or interneurons on which they end inhibit transmission from the dorsal root pain fibers to the spinothalamic neurons.

[4] Thermal Sensations: Thermal sensations are detected by two different types of subcutaneous sensory receptors. Therefore, the subcutaneous temperature actually determines the responses. There are two types of thermal receptors and these are:

[1] The cold receptors which respond maximally to temperature slightly below body temperature. This will be seen until the temperature reaches 45o C. Temperature beyond this will not stimulate the thermoreceptors, but stimulates the nociceptors which give pain sensation.

[2] The warmth receptors which respond maximally to temperature slightly above body temperature. The fall in body temperature below 30o C stimulates only the cold receptors and the warm receptors remain inactive. Temperature below 10° C will stimulate the nociceptors and give pain sensation.

The cold sensation is carried by the Aδ and C, whereas, the warm is carried by only C fibers. In most areas of the body there are three to ten times as many cold receptors as warmth receptors. The person determines the different gradations of thermal sensations by the relative degrees of stimulation of the different types of receptors. Because the number of cold or warmth receptors in any one surface area of the body is very slight, it is difficult to judge gradations of temperature when small areas are stimulated. The judgment of gradation is increased as the stimulated surface area increases.

The thermal receptors respond markedly to changes in temperature in addition to being able to respond to steady states of temperature (i.e. they are tonic and at the same time phasic type of

receptors). This means that when the temperature of skin is actively falling, a person feels much colder than when the temperature remains at the same level. Conversely, if the temperature is actively rising the person feels much warmer than he would at the same temperature if it was constant.

Almost all the afferent sensory somatic information of the body enters the spinal cord through the dorsal roots of the spinal nerves or the brain stem via the cranial nerves. On entering the spinal cord the sensory signals are carried to the brain by three sensory pathways:

1. The dorsal column pathway (medial lemniscal system): In which:
[A] First order neurons (dorsal root sensory fibers) enter the dorsal column of the spinal cord and then pass up on the same side of its entrance in the spinal cord to the medulla, where they synapse in the cuneate and gracile nuclei.
[B] From the cuneate and gracile nuclei the second order neurons are originated and decussate immediately to the opposite side and then pass upward to the thalamus through medial leminisci pathways which is joined by additional decussated fibers from the sensory nucleus of the trigeminal nerve.
[C] From thalamus, third order neurons project mainly to the somatic sensory area located at postcentral gyrus and occupy the cerebral cortex of the anterior portion of the parietal lobe.

The dorsal column carries the following sensations: **fine touch** and **pressure** (including weight, shape, Size, texture)**, vibration, stereognosis, and conscious proprioception (sense of position and movements of different parts of body).**

2. The anterolateral pathways (spinothalamic pathway): In which:
[A] First order neurons (dorsal root sensory fibers) enter the dorsal horns of the spinal cord and synapse with the second order neurons.

[B] The second order neurons cross to the opposite anterolateral white column where they turn upward toward the thalamus through anterior and lateral spinothalamic tracts. Some of the second order neurons of the anterolateral system, which carry signals from slow C pain fibers, give collateral fibers to **reticular formation**, **periaqueductal gray area,** and **hypothalamus**.
[C] From thalamus, third order neurons project mainly to the somatic sensory area of the cortex along with the neurons of the dorsal column.

The anterolateral system carries the following sensations: **crude touch** and **pressure, pain, thermal, tickle, itch, and sexual sensations.**
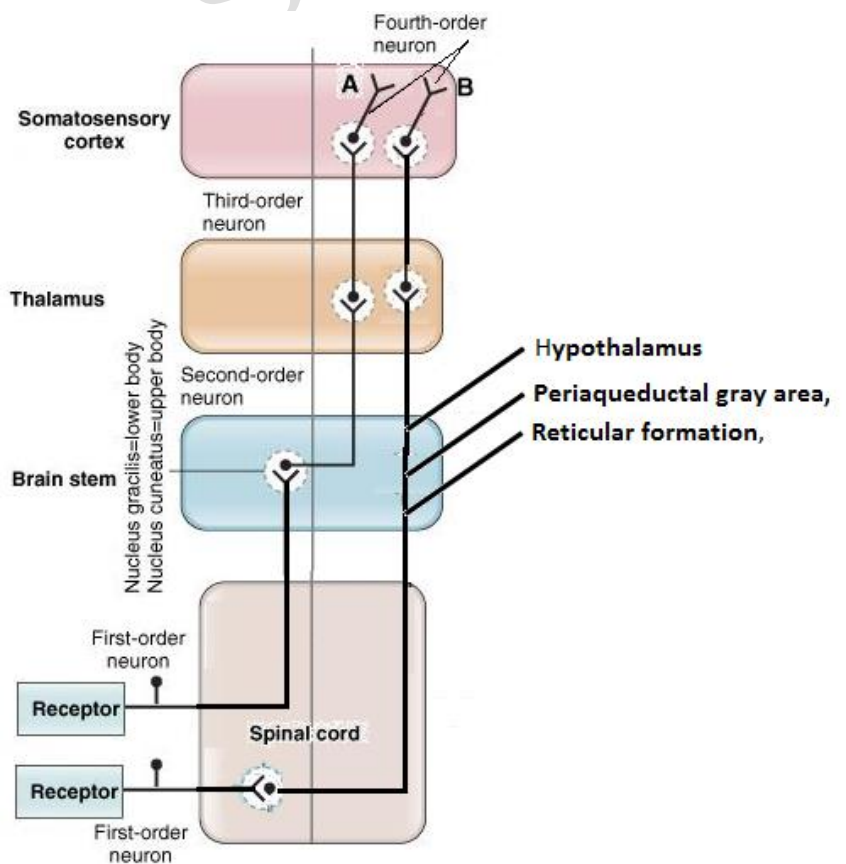
The course of the somatic sensations through the spinal cord. A= The dorsal column pathway. B = The anterolateral pathways.

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*In general, the sensations that **transmitted rapidly**, and with **fine gradations** of intensity and **highly localized** to exact points in the body are transmitted in the dorsal system. While those sensations which do not transmit rapidly, and lack of fine gradations, and poorly localized to exact points in the body are transmitted in the anterolateral system.*

Ascending tracts
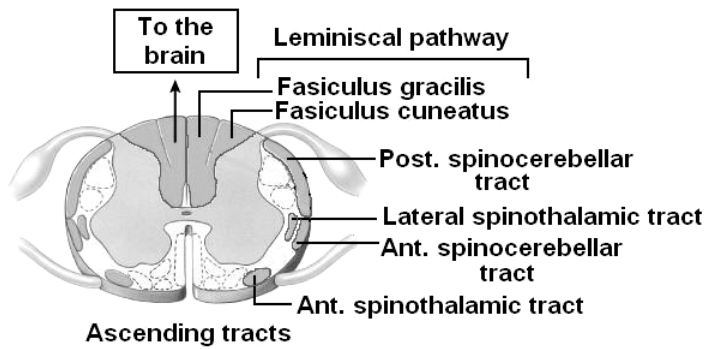
Signs of lesions of the central sensory pathways:
[1] *A lesion confined to the **posterior column of the spinal cord** will cause:*

❖ *Loss of position and vibration sense on the same side, but the sensation of pain, touch, temperature will be preserved*.

❖ *The loss of the sense of the position causes sensory ataxia (muscle incoordination) and the patient has difficulty on standing in upright balanced position with the feet close together without swaying **(Romberg's test)** due to loss of proprioceptive sensations. This type of ataxia is more marked when the eyes are closed. The same symptoms will be found if the first order neurons of the proprioceptive nerve fiber are damaged peripherally but they will then be associated with other signs of peripheral nerve disease.*

[2] *Lesions of the **spinothalamic tracts** cause impairment of the ability to appreciate pain and temperature on the contralateral side of the body below the level of the lesion. Touch is usually modified (it feels different) but not abolished because of its alternative pathway in the posterior columns.*

[3] *In the brain stem, the spinothalamic tract and medial lemniscus run close together. Therefore, lesion of the **upper brain stem** usually affects all forms of sensation on the contralateral side of the body.*

[4] *Lesions of the main sensory nuclei of the **thalamus** may cause:*

❖ *Loss of various modalities of sensation on the opposite side of the body.*

❖ *And spontaneous pain of most unpleasant quality in the opposite side of the body which often causes considerable emotional reaction.*

3. The spinocerebellar pathways: They carry proprioceptive information from Golgi tendon organs and muscle spindles. All of these first order neurons have their cell bodies in the dorsal root ganglion. They pass through the dorsal horn to form synapses with second order neurons. Second order neurons pass through the spinal cord as:

- **Dorsal spinocerebellar tract:** Axons of second order neurons reach lateral column of same side (**ipsilateral**). Then, these fibers ascend through other spinal segments and reach medulla oblongata. From here, the fibers reach cerebellum through inferior cerebellar peduncle. *Lesion of this tract causes unilateral loss of the subconscious kinesthetic sensation occurs in lesion of this tract on the same side, as this tract has uncrossed fibers.*

- **Ventral spinocerebellar tract:** Ventral spinocerebellar tract contains both **crossed** and **uncrossed** fibers. Majority of the fibers of second order neurons cross the midline and ascend in lateral white column of opposite side. Some fibers ascend in the lateral white column of the same side also. Finally, the fibers reach the cerebellum through the superior cerebellar peduncle. *Lesion of this tract leads to loss of subconscious kinesthetic sensation in the opposite side.*

In general, the same principles apply to transmission in the anterolateral pathway as in the dorsal column-medial lemniscal system, except for the following differences: **(1) the velocities of transmission** are only one-third to one-half those in the dorsal column-medial lemniscal system, ranging between 8 and 40 m/sec; **(2) the degree of spatial localization of signals is poor; (3) the gradations of intensities**

are also far less accurate, most of the sensations being recognized in 10 to 20 gradations of strength, rather than as many as 100 gradations for the dorsal column system; and **(4) the ability to transmit rapidly changing or rapidly repetitive signals is poor**.

NOTE: PROPRIOCEPTIVE SENSATION IS EITHER <u>CONSCIOUS</u> AND IS CARRIED BY LEMNISCAL PATHWAY OR <u>SUBCONSCIOUS</u> AND IS CARRIED BY SPINOCEREBRAL TRACT.

Layers of the cerebral cortex: The cerebral cortex contains six separate layers of neurons, beginning with layer I next to the surface and extending progressively deeper to layer VI. Each layer performs functions different from those in other layer. For examples:
The cerebral cortex contains six layers of neurons, beginning with layer I next to the brain surface and extending progressively deeper to layer VI. As would be expected, the neurons in each layer perform functions different from those in other layers. Some of these functions are:

1. The incoming sensory signal excites neuronal layer IV first; then the signal spreads toward the surface of the cortex and also toward deeper layers.
2. Layers I and II receive diffuse, nonspecific input signals from lower brain centers that facilitate specific regions of the cortex (ARAS). This input mainly controls the overall level of excitability of the respective regions stimulated.
3. The neurons in layers II and III send axons to related portions of the cerebral cortex on the opposite side of the brain through the corpus callosum.
4. The neurons in layers V and VI send axons to the deeper parts of the nervous system. Those in layer V are generally larger and project to more distant areas, such as to the basal ganglia, brain stem, and spinal cord, where they control signal transmission. From layer VI, especially large numbers of axons extend to the thalamus, providing signals from the cerebral cortex that interact with and help to control the excitatory levels of incoming sensory signals entering the thalamus.

Functionally, the neurons of the somatic sensory cortex are arranged in vertical columns extending all the way through the six layers of the cortex. Each of these columns serves a single specific sensory modality, some responding to stretch receptors around Joints, some responding to tactile stimulation, etc. Furthermore, the columns for the different modalities are interspersed among each other to allow the beginning of analysis of the meanings of the sensory signals.

The corpus callosum plays an essential role in integrating the activity of the two cerebral hemispheres:

Sensory information from the right half of the body is represented in the somatosensory cortex of the left hemisphere and vice versa. Equally, the left motor cortex controls the motor activity of the right side of the body. Despite this apparent segregation, the brain acts as a whole, integrating all aspects of neural function. This is possible because, although the primary motor and sensory pathways are crossed, there are many cross-connections between the two halves of the brain, known as commissures. As a result, each side of the brain is constantly informed of the activities of the other. The largest of the commissures is the vast number of fibers that connect the two cerebral hemispheres, known as the corpus callosum. Experimental work has shown that most of the nerve fibers that traverse the corpus callosum project to comparable functional areas on the contralateral side. It was subsequently found that epileptic discharges can spread from one hemisphere to the other via the corpus callosum and that major epileptic attacks can involve both sides of the brain. In a search for a cure for the severe bilateral epilepsy experienced by some patients, their corpus callosum was cut by the human split-brain operation. This had the desired end result in a reduction in the frequency and severity of the epileptic attacks. It also offered the opportunity of careful and detailed study of the functions of the two hemispheres of the human brain.

Higher interpretation of sensory signals: This is achieved by the cerebral cortex in the following areas:
    [1] Primary sensory areas.
    [2] Sensory association areas.
    [3] Wernicke's area.

[1] Primary sensory areas: They include:
- **Primary somatic sensory area.**
- **Primary visual sensory area.**
- **Primary auditory sensory area.**

They are the areas of the cerebral cortex to which the respective sensory signals are projected. They have spatial localization of signals from peripheral receptors. These areas analyze only the simple
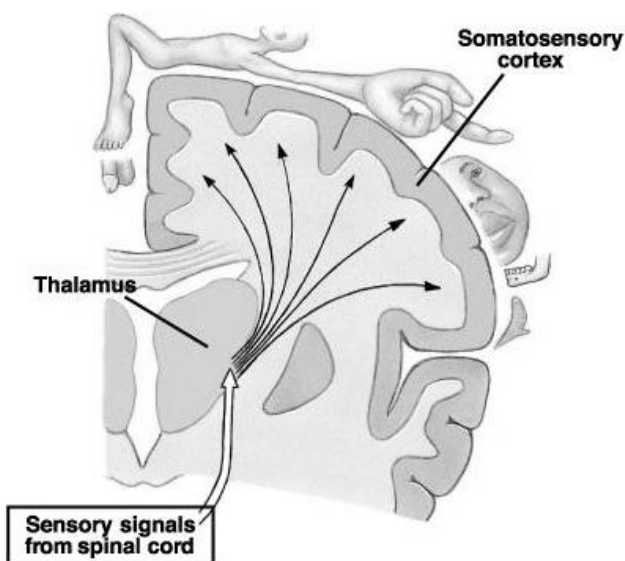

aspects of sensations and that is to inform the brain that a sensory signal is actually arrived to the cerebral cortex but they are not able of complete analysis of complicated sensory patterns. Despite the inability of the primary sensory areas to analyze the incoming sensations fully, when these primary areas are destroyed the ability of the person to utilize the respective sensations usually suffers drastically.

In the primary somatic sensory area **the spatial orientation of the different parts of the opposite side of body were represented**. The size of the area of representation is directly proportional to the number of specialized sensory receptors in each respective peripheral area of the body. For instances, the lips are by far the greatest of all, followed by the face and thumb, whereas the entire trunk and lower part of the body are represented by relatively small areas.

Yet, cortical lesions do not abolish somatic sensation. Thus, perception may occur at subcortical level and it is possible in the absence of the cortex. Therefore, wide spread excision of primary somatic sensory area may lead to the following signs:

    ☐ *The person is unable to localize*

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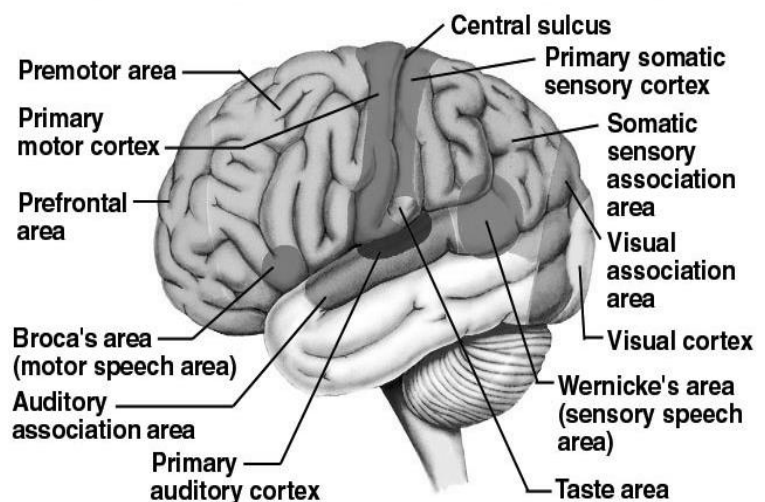
discretely the different sensations in the different parts of the body.
☐ *He is unable to judge exactly the degrees of pressure against his body.*
☐ *He is unable to judge exactly the weights of objects.*
☐ *He is unable to judge shapes or forms of objects.*
☐ *He is unable to judge texture of materials.*

[2] Sensory association areas: That include:
- **Somatic sensory association area.**
- **Visual sensory association area.**
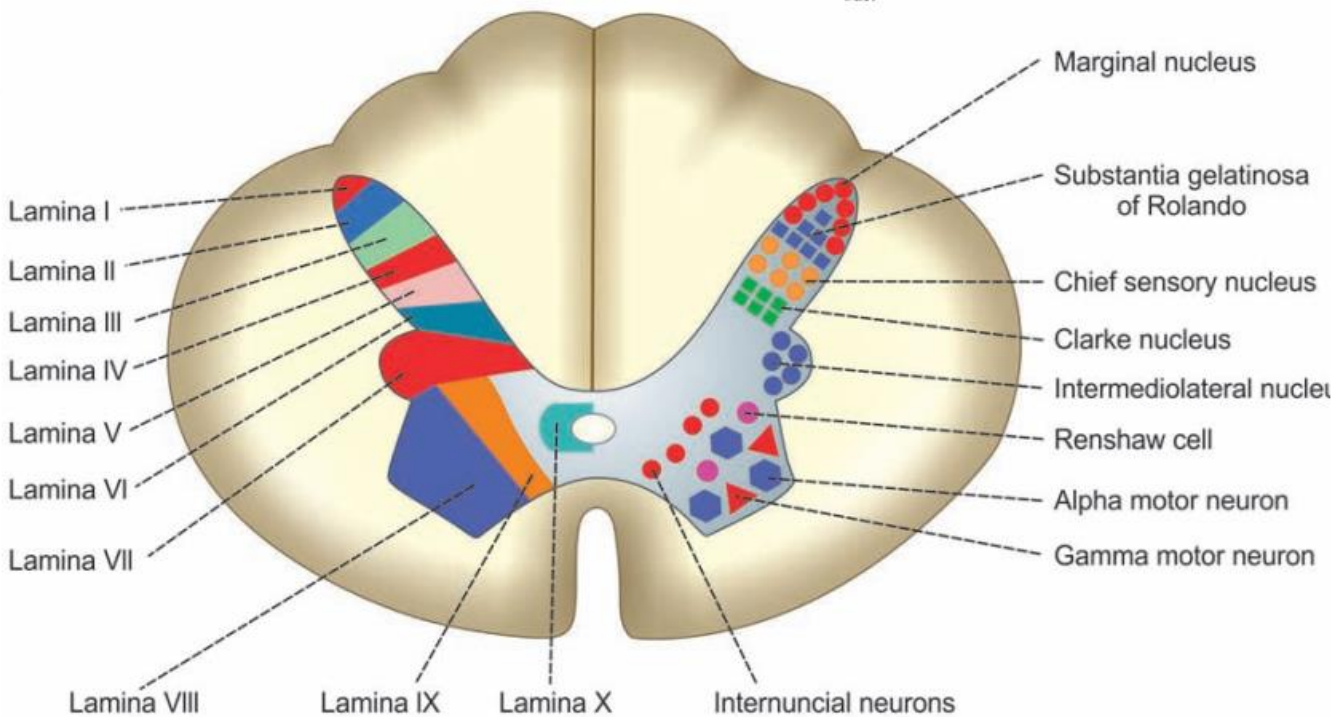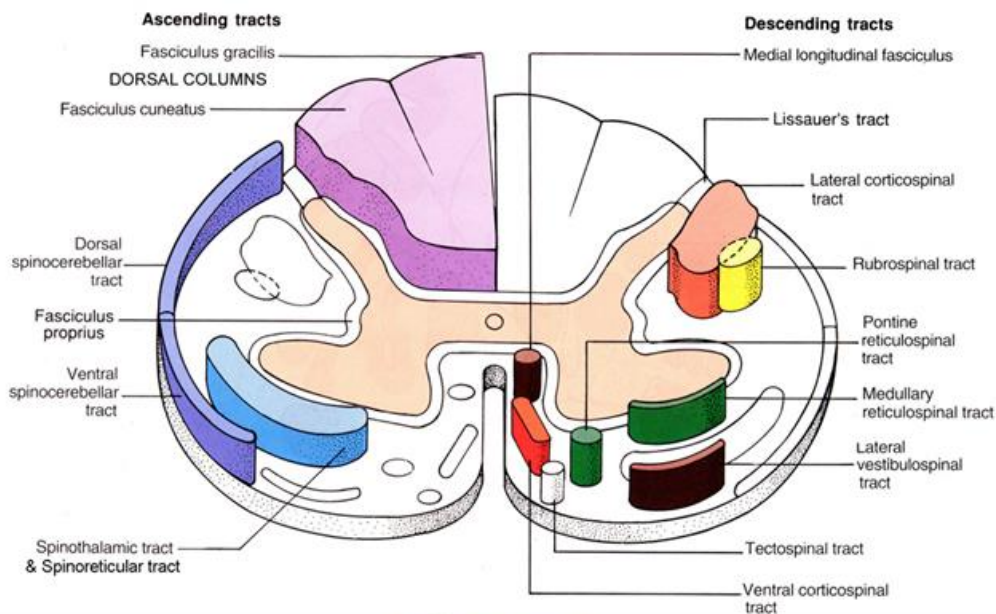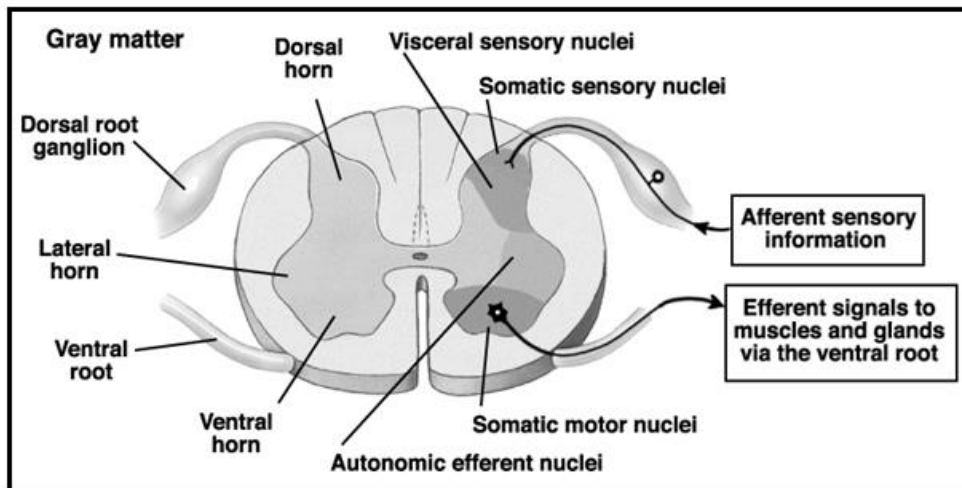- **Auditory sensory association area.**

Around the borders of the primary sensory areas are regions called sensory association areas. The general function of the sensory association areas is to provide a higher level of interpretation of the sensory signals. <u>In these areas, interpretation of the sensory signals is achieved by giving the brain the simplest meaning and characteristic of the sensory signal</u>. Destruction of the sensory association area greatly reduces the capability of the brain to analyze and interpretate different characteristics of sensory experiences. *Damage to the sensory association area is associated with specific deficits known as **agnosias**.*

Sensory somatic association area is located in the parietal cortex behind primary somatic sensory area. It plays important roles in deciphering the sensory information that enters the primary somatic sensory area by combining information from multiple points in the primary somatic sensory area to decipher its meaning.

*Damage can affect the ability to recognize objects even though the objects can be felt (**tactile agnosia**). Loses the ability to recognize complex objects and complex forms by the process of feeling them is called **astereognosis**, even though there is no specific sensory deficit. Stereognosis is the ability to determine what an object is just by using the modality of touch.*

[3] Wernicke's area: It is the area where the sensory association areas all meet one another in the posterior part of the temporal lobe where temporal, parietal, and occipital lobes all come together. This area is called Wernicke's area which converge the different sensory interpretative areas. It is highly developed in the dominant side of the brain (left side) and <u>plays the greatest role in interpretation of the complicated meanings of different sensory experiences.</u>

Somatomotor functions of the CNS

Gray matter

- Dorsal horn
- Visceral sensory nuclei
- Somatic sensory nuclei
- Dorsal root ganglion
- Lateral horn
- Ventral root
- Ventral horn
- Somatic motor nuclei
- Autonomic efferent nuclei

Afferent sensory information

Efferent signals to muscles and glands via the ventral root

Ascending tracts
- Fasciculus gracilis
- DORSAL COLUMNS
- Fasciculus cuneatus
- Dorsal spinocerebellar tract
- Fasciculus proprius
- Ventral spinocerebellar tract
- Spinothalamic tract & Spinoreticular tract

Descending tracts
- Medial longitudinal fasciculus
- Lissauer's tract
- Lateral corticospinal tract
- Rubrospinal tract
- Pontine reticulospinal tract
- Medullary reticulospinal tract
- Lateral vestibulospinal tract
- Tectospinal tract
- Ventral corticospinal tract

- Lamina I
- Lamina II
- Lamina III
- Lamina IV
- Lamina V
- Lamina VI
- Lamina VII
- Lamina VIII
- Lamina IX
- Lamina X
- Internuncial neurons

- Marginal nucleus
- Substantia gelatinosa of Rolando
- Chief sensory nucleus
- Clarke nucleus
- Intermediolateral nuclei
- Renshaw cell
- Alpha motor neuron
- Gamma motor neuron

Neurons in gray horn of spinal cord: thoracic segment

Descending pathways involved in motor control

The brain communicates with the spinal motor circuitry through two major groups of descending pathways, named according to their location in the spinal white matter.

1. The lateral pathways are <u>concerned with voluntary movement of the distal muscles (e.g., muscles of the arm and hand)</u>. There are two major pathways in this group, the corticospinal tract and the rubrospinal tract.

> **[A] The lateral corticospinal tract,**
> **[B] The rubrospinal tract,**
> **[C] The lateral medullary reticulospinal tracts,**
> **[D] The lateral vestibulospinal tract,**

2. The ventromedial pathways originate in the brainstem and <u>innervate the proximal and axial muscles to help maintain head position</u> and <u>posture</u>, <u>muscle tone</u> and <u>gross movements of the neck</u>, <u>trunk</u>, and <u>proximal limb muscles</u>. Sensory information about the body position and balance is derived from the visual and vestibular systems and is conveyed via three major tracts:

> **[A] The anterior corticospinal tract,**
> **[B] The tectospinal tract,**
> **[C] The medial pontine reticulospinal tracts,**
> **[D] The medial longitudinal fasciculus**

NOTE: The medial longitudinal fasciculus links the three main nerves which control eye movements, i.e. the oculomotor, trochlear and the abducent nerves, as well as the vestibulocochlear nerve. The purpose of the medial longitudinal fasciculus is to integrate movement of the eyes and head movements.

The motor functions of the CNS can be divided into:

- Movement, There are three classes of movements:

  [a] Reflexes which are involuntary, rapid, stereotyped movement such as eye-blink, coughing, knee jerk and graded control by eliciting stimulus.

  [b] Voluntary movement which is complex actions such as reading, writing, playing piano. They are purposeful, goal-oriented and learned type of activity which can be improved with practice.

  [c] Mixed pattern which combine voluntary & reflexive acts such as chewing, walking, running. It is initiated and terminated voluntarily, but once initiated it become repeatitive and reflexive.

- Posture and balance,
- Communication.

Reflexes: The basic unit of reflexes is the **reflex arc**. The arc consists of a <u>sense organ (receptor)</u>, <u>an afferent neuron, one or more synapses in a central integrating station or sympathetic ganglion</u>, <u>an efferent neuron, and an effector.</u> The connection between the afferent and efferent neurons is generally in the brain or spinal cord. The afferent neurons enter via the dorsal roots or cranial nerves and have their cell bodies in the dorsal root ganglia or in the homologous ganglia on the cranial nerves. The efferent fibers leave via the ventral roots or corresponding motor cranial nerve. The connection between the afferent and the efferent neurons is usually in the central nervous system and activity in the reflex arc is modified by multiple inputs converging on them from higher motor control centers.

The spinal cord reflexes: Sensory signals enter the cord through the sensory roots. After entering the cord, every sensory signal travels to two separate destinations:

1. The sensory nerve or its collateral terminate in the gray matter of the cord and elicit local segmental motor responses.

2. The signals travel to higher and lower segmental levels of the cord itself or to the brain stem or even to the cerebral cortex.

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Each segment of the spinal cord has several millions neurons in its gray matter and these are:

A. The posterior sensory neurons that we discussed previously.

B. The anterior motor neurons: These gives rise to the nerve fibers that leave the cord via the anterior roots and innervate the effector such as skeletal muscle fibers. The cells of the anterior horn of spinal cord or motor cranial nuclei and their efferent fibers that run to motor units are also called the <u>lower motor neurons</u> to distinguish them from the upper motor neurons of the higher motor control centers. Thus the lower motor neuron is the **final common path** for all efferent impulses directed at the muscle.

The anterior motor neurons are of three types:

1. The alpha motor neurons or alpha efferent neurons: Which give off large nerve fibers (type A alpha nerve fiber) that innervate the large skeletal muscle fibers (**extrafusal muscle fibers**) forming the motor units.

2. The gamma motor neurons or gamma efferent neurons: Which give off nerves fibers (type A gamma nerve fiber) that innervate very small special skeletal muscle fibers called **intrafusal fibers** which are part of the muscle spindle.

3. The interneurons: These are small neurons that have many interconnections one with the other. Most of the incoming sensory signals from the spinal nerves are transmitted first through interneurons where they are appropriately processed and then terminate on the anterior motor neurons.

Some of the anterior motor neurons immediately after the motor axons leave the soma give collateral branches to innervate adjacent interneurons called **Renshaw cells** which are located in the ventral horn of the spinal cord. These cells in turn are inhibitory cells that transmit inhibitory signals to the same motoneuron (recurrent inhibition) or to the nearby motor neurons (lateral inhibition).

❖ The recurrent inhibition is important to allow only the initial impulses arriving at a motoneuron to pass through easily while the late impulses will find the anterior horn cells partially inhibited and will therefore produce a smaller motor discharge than the initial excitatory impulses. This makes what is called a "negative feedback" circuit, and presumably protects the body from accidental over activity of the motor neuron concerned, and therefore damage to the muscle it is connected to.

❖ The lateral inhibition is to focus or sharpen the signals, i.e. to allow transmission of the primary signal while suppressing the tendency for signals to spread to adjacent neurons.
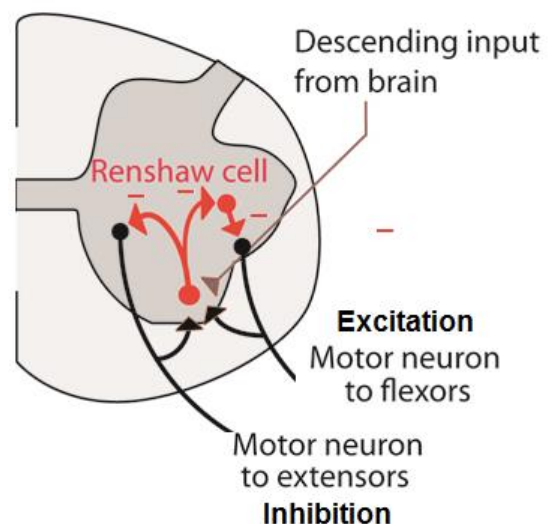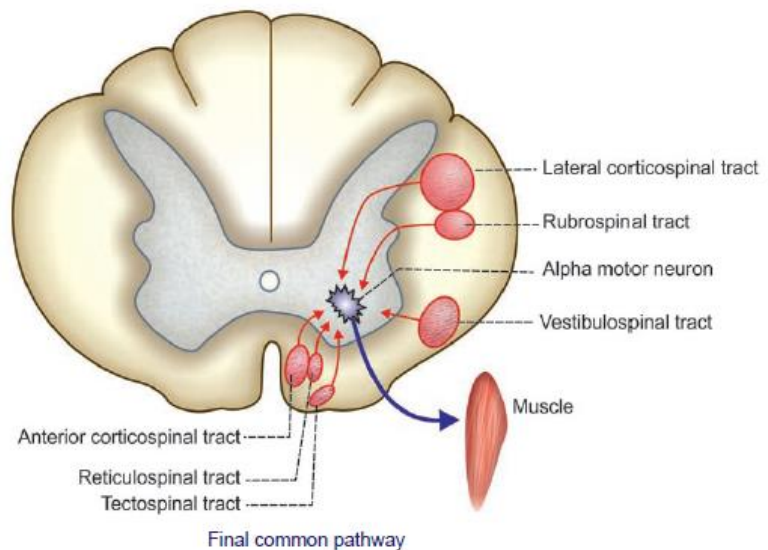
The muscle receptors and their roles in muscle control: Proper control of muscle requires not only excitation of the muscle by the anterior motor neurons but also continuous feedback of information from each muscle to the nervous system which is achieved by two special types of sensory receptors

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and these are:

 1. Muscle spindles: They are distributed throughout the belly of muscle and send information to the NS about the muscle length and the rate of change of its length.

2. Golgi tendon organs: They are located among the fascicles of a tendon between it and the muscle itself and which send information about tension or rate of change of tension.

Muscle spindle: Each muscle spindle consists of 3—10 specialized muscle fibers enclosed in a connective tissue capsule. These fibers are called **intrafusal muscle fibers** to distinguish them from the **extrafusal muscle fibers** which are the regular contractile units of the muscle. The intrafusal fibers are in parallel with the rest of the muscle fibers but not for the entire length of the muscle. The central region of each of the intrafusal fibers does not contract while the ends do. The central non contractile portion of the fiber functions as a **sensory receptor.**

   There are two types of intrafusal fibers and these are **nuclear chain fibers** (which detect the changes in muscle length, i.e. static changes) and **nuclear bag fiber** (which detect the rate of change in muscle length, i.e. dynamic changes).

        The receptor portion of the muscle spindle is stimulated by stretch of the midportion of the spindle. This can occur as a result of:

        1. Lengthening the whole muscle which will in turn stretch the mid-portions of the spindle and therefore excite the receptor.

        2. Contraction of the end-portions of the intrafusal fibers by increase stimulation of gamma motor neurons that will stretch the mid-portions of the spindle and therefore excite the receptor and increases the rate of firing while shortening the mid-portion of the muscle spindle by inhibition of gamma motor fibers decreases this rate of firing.

        The number of impulses transmitted from the muscle spindles increases directly in proportion to the degree of stretch and the rate of change of its length and continues for as long as the receptor itself remains stretched. Normally, there is a slight amount of continuous gamma motor excitation, consequently, the mid-portion of the muscle spindles emit sensory nerve impulses continuously.

        The neurons involved in various reflex arcs (both alpha and gamma motor neurons) normally receive a basal level of **excitatory stimulation** from the brain through the following descending tracts:

- **Corticospinal tract**, the activation of α motor neuron during voluntary action co-activates γ efferents also, in order to maintain muscle length when extrafusal fibers contract.
- **Lateral vestibulospinal tracts** to stimulate extensor (antigravity) muscles, and inhibit flexors.
- **Pontine reticulospinal tract**.
- **Rubrospinal tract** (excites flexors alpha and gamma motor neurons to the distal muscles).

        These excitatory pathways are held in check directly or indirectly by **inhibitory descending pathways** on gamma motor neurons by:

- **Medullary reticulospinal tract** (inhibitory to both alpha and gamma motor neurons).
- **Rubrospinal tract** (inhibits extensor alpha and gamma motor neurons to the distal muscles).

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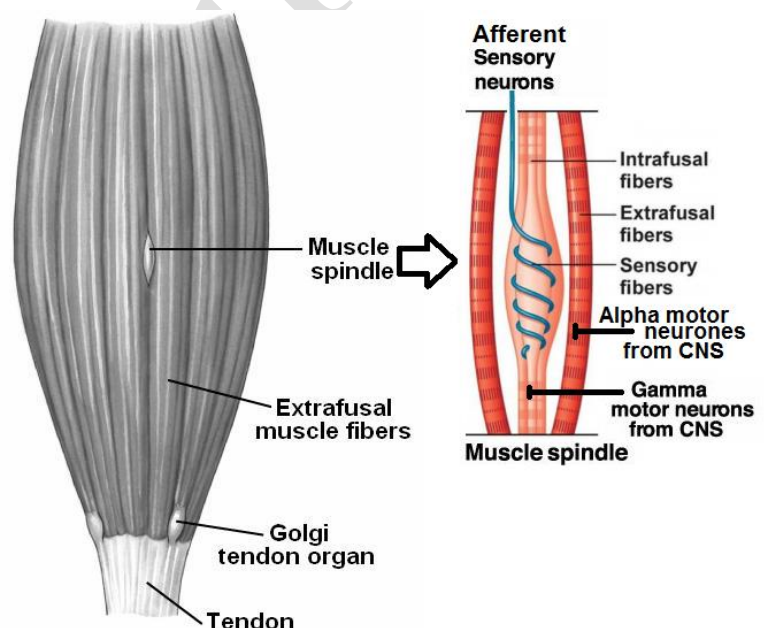
Therefore, the sensitivity of muscle spindles (and consequently all the spinal cord reflexes) can be modified through the increase (excitation) or decrease (inhibition) of gamma motor neurons which leads to increase or decrease the response of the muscle spindles to stretch.

Other areas of the brain are also involved in the regulation of gamma motor neurons **indirectly** through their effect on the descending tracts such as basal ganglia (**inhibitory**) and cerebellum (**excitatory** or **inhibitory**).

❖ The activity of the gamma motor neurons are also affected by **anxiety** which causes an increase in gamma neurons discharge.

❖ In addition, stimulation of the skin, especially by **noxious agents**, increases gamma efferent discharge to ipsilateral flexor muscle spindles while decreasing that to extensors and produces the opposite pattern in the opposite limb.

❖ It is well known that trying to pull the hands apart when the flexed fingers are hooked together facilitates the knee jerk reflex (**Jendrassik's maneuver** or **reinforcement**) and this may be due to increased gamma efferent discharge initiated by afferent impulses from the hands.

❖ When Corticospinal and corticoreticular projections are damaged with an intact of the vestibular nuclei and vestibulospinal tract are intact, gamma neurons discharge is increased. This is due to:

- Unopposed activity of vestibulospinal tracts (excitatory) and,
- Continuous activity of pontine reticular formation (excitatory) on the gamma motor neurons by strong stimulation of cerebellum, vestibular nuclei, and signals from peripheral somatosensory receptors..

❖ When only corticospinal fibers are damaged with an intact of corticoreticular and reticulospinal projections, no change in gamma neurons discharge was observed. This is due to the existence of both pontine (a tonic excitatory structure) and medullary (inhibitor) reticulospinal tract.
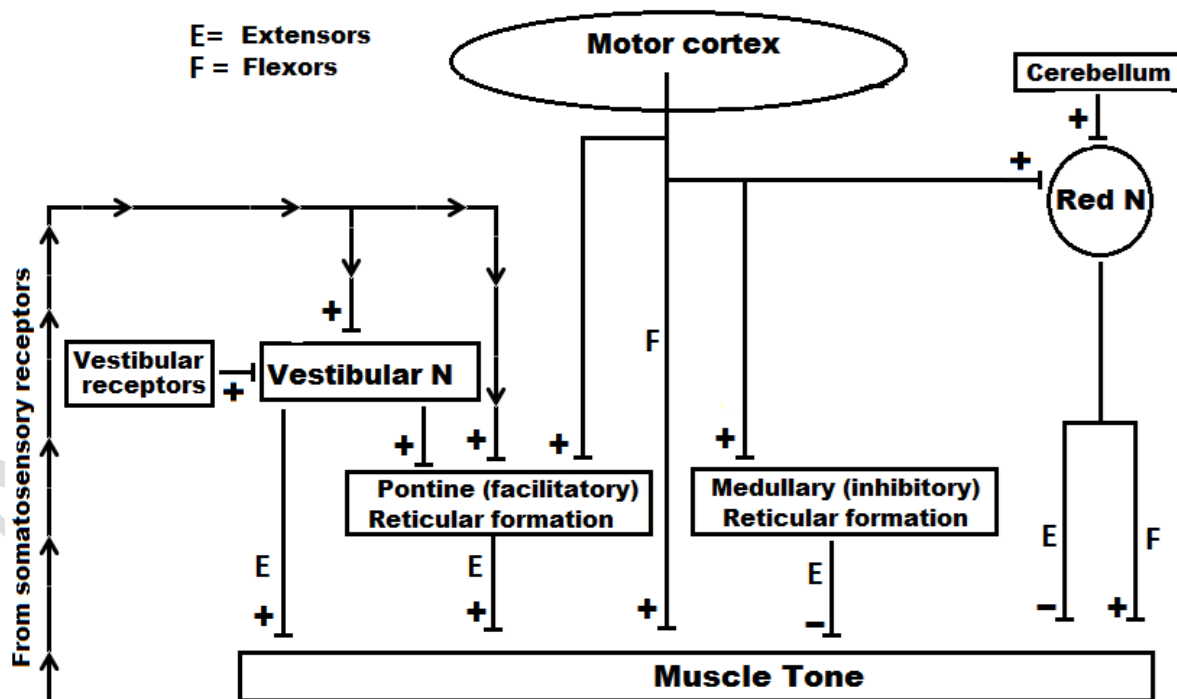
❖ **Spinal cord transection and spinal shock**: When the spinal cord is suddenly transected, essentially all cord functions immediately become depressed, a reaction called **spinal shock**. The results are paraplegia (loss of voluntary movements below the level of the lesion due to interruption of the descending pathway from the motor centers in the brain stem and higher centers), loss of conscious

sensation below the level of the lesion, and initial loss of reflexes. The reason for this initial loss of reflexes is that normal activity of the cord neurons depends to a great extent on continual excitatory tonic discharges from higher centers, particularly discharges transmitted through the corticospinal tracts, pontine reticulospinal tracts and vestibulospinal tracts. After a few hours or a few days or weeks of spinal shock, the spinal neurons gradually regain their excitability and may become relatively hyperactive. The recovery of reflex excitability may possibly be due to the development of **denervation hypersensitivity** to the mediators released by the remaining spinal excitatory endings. Another possibility for which there is some evidence is the **sprouting of collaterals** from existing neurons, with the formation of additional excitatory endings on interneurons and motor neurons. If the lesion is at C7, there will be loss of sympathetic tone to the heart. As a result, heart rate and arterial pressure will decrease. If the lesion is at C3, breathing will stop because the respiratory muscles have been disconnected from control centers in the brain stem. If the lesion is at C1 (e.g., as a result of hanging), death occurs.

The stretch reflex (also called **tendon reflex** or **deep reflex):** It is a reflex mediated by the muscle spindles. When a skeletal muscle with an intact nerve supply is stretched, it contract. This is called a stretch reflex. It is the only monosynaptic reflex in the body in which a single synapse is present in the reflex arc located between the afferent and the efferent neurons. The nerve fiber originating in a muscle spindle enters the dorsal root of the spinal cord and then it passes directly to the anterior horn of the cord gray matter and synapses directly with anterior alpha motor neurons that send nerve fibers back to the same muscle from where the muscle spindle fiber originated. Via changes in the sensitivity of the muscle spindles the threshold of the stretch reflex in various parts of the body can be adjusted and shifted to meet the needs of postural control. The time between the application of the stimulus (the stretch) and the response (muscle contraction) is called **the reaction time**. The spinal cord conduction time through this reflex arc is called the **central delay**. When a stretch reflex occurs, the muscles that antagonize the action of the muscle involved (antagonists) relax. This phenomenon is called **reciprocal inhibition (or innervation)**.

The pathway mediating this effect appears to be bi-synaptic in which a collateral branch from the afferent neuron passes in the spinal cord to an inhibitory interneuron that synapses directly on one of the motor neurons supplying the antagonist muscles. In addition, when stretch reflex occurs, the other muscles that perform, or help in perform the same set of joint motion as the agonists (synergist muscles) are also stimulated.
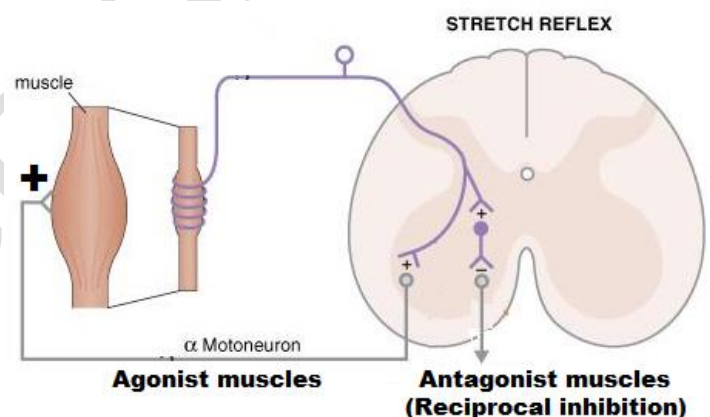
The clinical applications of the stretch reflex are the knee-jerk and other muscle jerks. In knee-jerk, tapping the patellar tendon elicits the jerk, a stretch reflex of the quadriceps femoris muscle, because the tap on the tendon stretches the muscle.

The main functions of the stretch (tendon) reflex are:
 [A] **The establishment of muscle tone**. As there is a slight amount of continuous tonic gamma motor excitation, consequently the mid-portion of the muscle spindles are continuously slightly stretched and emit sensory nerve impulses continuously, and completing the stretch reflex arc. Through this reflex arc, muscle tone is established which can be defined as a residual amount of muscle contraction even the muscle is at rest or inactivity. This residual amount of muscle contraction (muscle tone) tends to maintain the same length of the muscle by resisting stretch (the change in its length). The primary

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purpose of muscle tone is to keep your muscles primed and ready for action. The always activated state of partial contraction maintains balance and posture, and it also functions as a safety mechanism that allows for a quick, unconscious muscle reflex reaction to any sudden muscle fiber stretch.

A. If the motor nerve to a muscle is cut, the muscle offers very little resistance to stretch and is said to be **flaccid** because of the cutting of the reflex arc.

B. A **hypotonic muscle** is one in which the resistance to stretch is low due to low gamma efferent discharge.

C. A **hypertonic or spastic muscle** is one in which the resistance to stretch is high due to high gamma efferent discharge.

[B] Stabilization of body position during tense motor action: Any time a person must perform a muscle function that requires a high degree of delicate and exact positioning, excitation of the appropriate muscle spindles (through the excitation of gamma motor neuron) by signals from the facilitatory pontine reticular formation stabilizes the positions of the major joints. To do this the facilitatory pontine reticular formation transmits excitatory signals through the gamma nerve fibers to the intrafusal muscle fibers of the muscle spindles on both sides of the joint. This shortens the ends of the spindles and stretches the central receptor regions, thus increasing their signal output. As the spindles on both sides of each joint are activated at the same time, reflex excitation of the skeletal muscles on both sides of the joint also increases, producing tight, tense muscles opposing each other at the same joint. The net effect is that the position of the joint becomes strongly stabilized, and any force that tends to move the joint from its current position is opposed by the highly sensitized stretch reflex.

[C] Damping or smoothing function of the stretch reflex against unsmoothed motor signals: Signals from the spinal cord are often transmitted to a muscle in an unsmooth form, increasing in intensity for a few milliseconds, and then decreasing in intensity, then changing to another intensity level, and so forth. When the muscle spindle apparatus is not functioning satisfactorily, the muscle contraction is jerky during the course of such a signal. The stretch reflex prevents oscillation and jerkiness of the body movements induced by the unsmoothed signals from other parts of the NS. When the muscle spindle is not functioning, the muscle contraction becomes very jerky during the course of such signals.

[D] Enhancement of extrafusal muscle fiber contraction (gamma loop servo system): Stretch reflex increases the degree of excitation of the extrafusal fibers. When a muscle should contract against a great load, both the alpha and gamma motor neurons are stimulated simultaneously. However, the extrafusal muscle fibers might contract less than the intrafusal fibers. This mismatch in contraction would stretch the receptor portions of the spindles and, therefore, elicit a stretch reflex that would provide extra excitation of the extrafusal fibers.

The Golgi tendon organ: They are encapsulated sensory receptors and are stimulated by the tension produced by the muscle fibers. These receptors have both a dynamic and static response as those found in muscle spindles. Signals from the tendon organ are transmitted through nerve fibers to local areas of the cord, to cerebellum and to cerebral cortex.
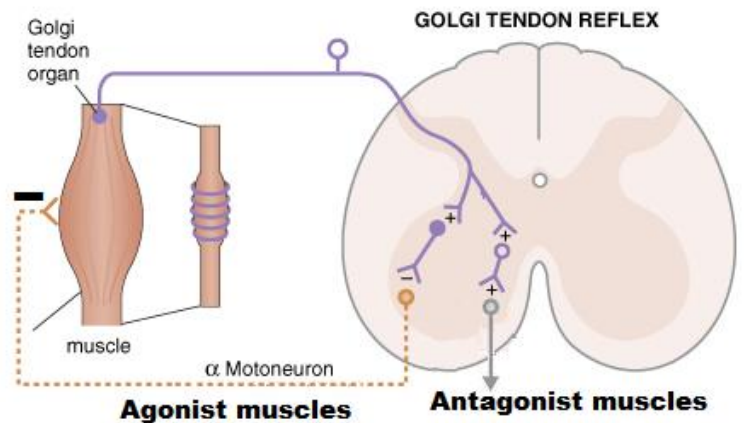
The Golgi tendon reflex (inverse stretch reflex): It is a reflex mediated by Golgi tendon organs. When the Golgi tendon organs of a muscle are stimulated by increased muscle tension due to active muscle contraction (or to much less extent passively by stretching the muscle), signals are transmitted into the spinal cord and excite inhibitory interneurons that in turn inhibit the anterior alpha motor neurons innervated the same muscle from which signals were originated. This brings about relaxation of a muscle in response to strong stretch is called the **inverse stretch reflex**. On the other hand, if the tension becomes too little, impulses from the tendon organ cease, and the resulting loss of inhibition allows the alpha motor neurons to become active again, thus increasing muscle tension back toward a higher level.

Thus, this reflex provides a <u>negative feedback mechanism</u> that:

❖ Prevents the development of too much tension on the muscle and sometimes leads to sudden relaxation of the entire muscle preventing tearing of the muscle or avulsion of tendon from its attachments to the bone.

❖ Another function of the Golgi tendon reflex is to equalize the contractile forces of the separate muscle fibers. That is, those fibers that exert excess tension become inhibited by the reflex, whereas those that exert too little tension become more excited because of the absence of reflex inhibition. This would spread the muscle load over all the fibers and especially would prevent damage in isolated areas of a muscle where small numbers of fibers might be overloaded.

Control of Golgi tendon reflex: The sensitivity of this inhibitory reflex is regulated by higher centers in the brain which adjust the set-point for muscle tension. The brain sends signals to the target muscle through alpha motor neurons to cause muscle contraction at a required tension and at the same time sends signals to the inhibitory interneurons of the cord to apprise them of the tension required in each given muscle. Then, as the degree of contraction approaches the tension required (as detected by the feedback from the Golgi tendon organs), the inhibitory interneurons automatically inhibit the muscle contraction to prevent additional tension. In this way, the tension becomes adjusted to the set-point dictated by the brain.

The withdrawal (flexor) reflex: It is an example of polysynaptic reflex in which one or more interneurons are interposed between the afferent end efferent neurons. Almost any type of cutaneous sensory stimulus (especially painful stimulus) on a limb is likely to cause the flexor muscles of the limb to contract (or contraction of other muscles), thereby withdrawing the limb from the stimulus. This is called the flexor or withdrawal reflex. The reflex arc is as follow: the painful stimulus pass into a pool of interneurons and then to the anterior motor neurons. In the interneuron pool, the signals will stimulate the following circuits:

1. Diverging circuits to spread the reflex to the necessary muscles for withdrawal.

2. Circuits to excite the ipsilateral flexor (agonist) muscles for withdrawing the limb.

3. Circuits to inhibit the ipsilateral extensor (antagonist) muscles called **reciprocal inhibition circuits**.

4. Circuits to cause a prolonged repetitive **after-discharge** even after the stimulus is over which occurs especially in very strong pain stimulus.

5. Circuits to cause crossing of the signals to the other side of the cord with reciprocal innervation (inhibition

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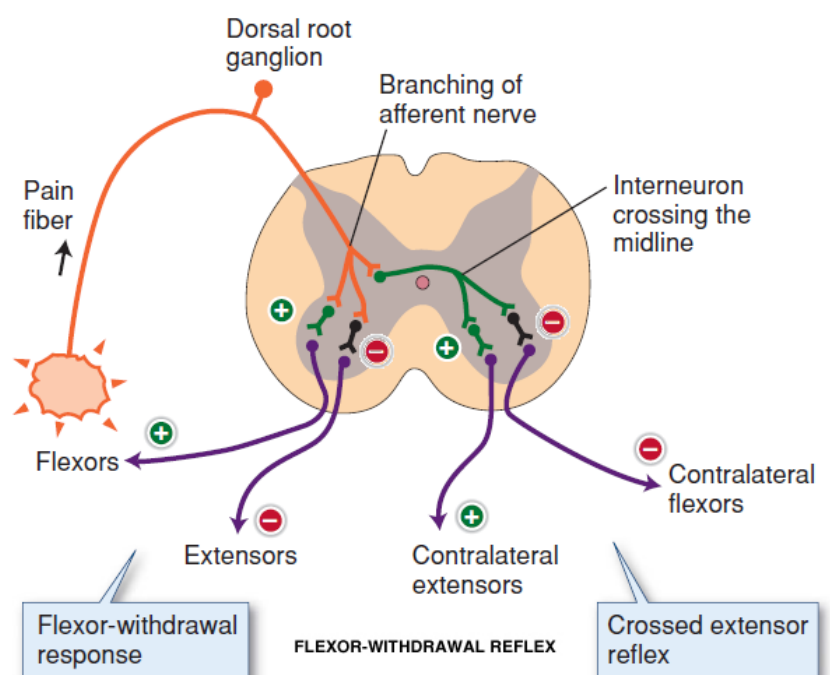
of the contralateral flexor muscles and excitation of the contralateral extensor muscles) to cause exactly opposite reactions to those that cause the flexor reflex. This type of reflex is called the **crossed extensor reflex** in which the opposite limb begins to extend and pushing the entire body away from the object causing the painful stimulus.

The clinical applications of such a reflex are abdominal reflex, cremasteric reflexes, all of them are forms of withdrawal reflex.

The higher motor control systems: The higher motor control systems involve the structures that control all motor activities executed at the brainstem level and spinal cord and these are:

1. The pyramidal system.

2. The extrapyramidal system.

Note: The pyramidal and extrapyramidal systems are often called **upper motor neurons**.

Through descending spinal tracts of the upper motor neurons (mainly the pyramidal tracts, vestibulospinal tract, and reticulospinal tracts) and the activities of the basal ganglia and cerebellum, all influence directly or indirectly:

[1]. The cells of the anterior horn of spinal cord or motor cranial nuclei from which the lower motor neuron runs to motor unit*.* Therefore, the lower motor neuron is the final common path for all efferent impulses directed at the muscle. The inputs converging on the motor neurons bring about voluntary activity, adjust body posture to provide a stable background for movement, and coordinate the action of various muscle to make movements smooth and precise.

[2]. the transmission of neuronal impulses through spinal reflex arcs. There are two mechanisms by which descending projections may control transmission through segmental reflex arcs:

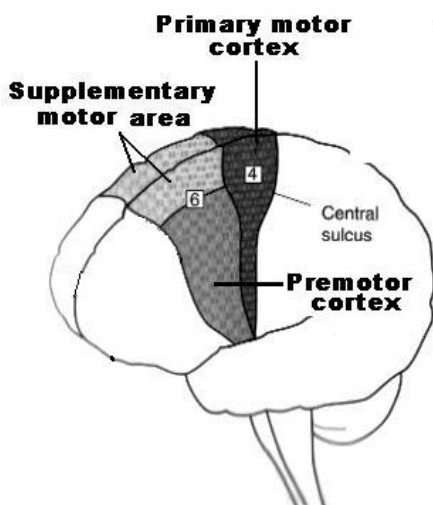[A] By their excitatory or inhibitory action on the neurons involved in the spinal reflex arc.

[B] By their inhibitory action on the terminal part of afferent sensory fibers before their synapse with the next neuron (presynaptic inhibition).

The pyramidal system: Which consists of the **motor cortex** and **pyramidal (corticospinal and corticobulbar) tracts.**

A: The motor cortex is the area of the cerebral cortex concerned with control of body movement and it is located directly in front of the central sulcus and occupying approximately the posterior one half of the frontal lobes. The motor cortex has extensive connections with other areas of cerebral cortex and with subcortical structures (caudate nucleus, thalamus, red nucleus, pontine nuclei, olive, and lateral reticular nucleus) through its efferent fibers and also with cerebellum. The motor cortex divided into three separate divisions:
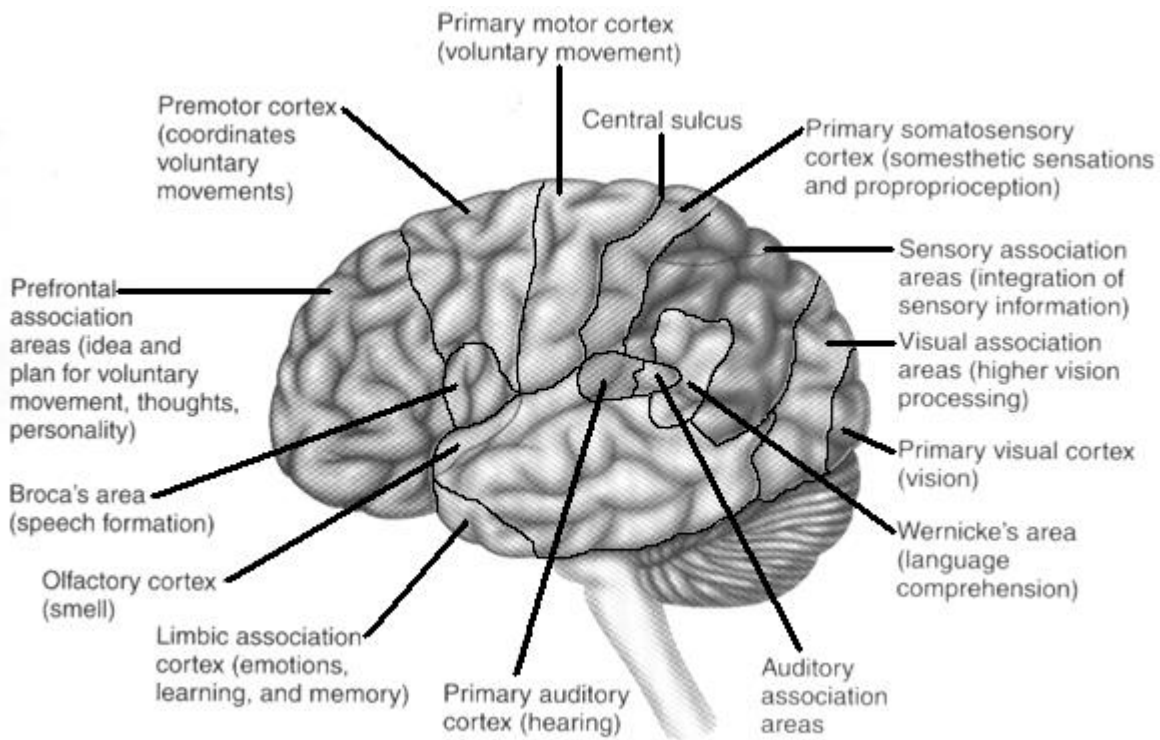
[1] **The primary motor cortex**
[2] **The supplementary motor cortex**
[3] **The premotor cortex**
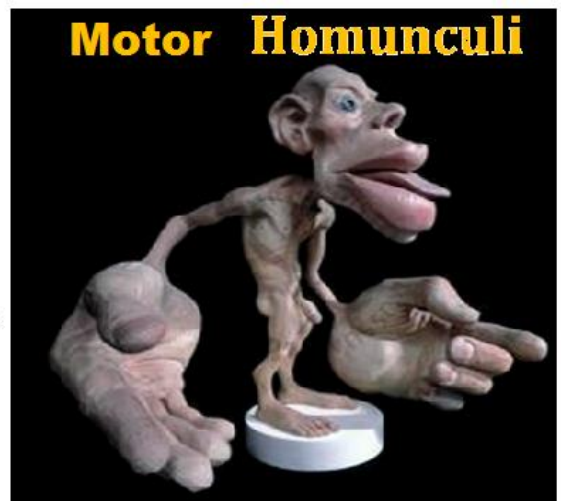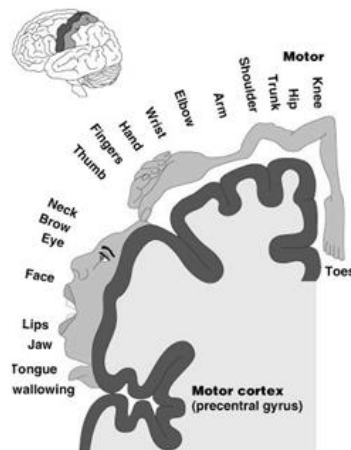
[1] **The primary motor cortex:** This is located directly in front of the central sulcus in the precentral gyrus. From the primary motor area pyramidal motor neurons originated and send their fibers directly or indirectly to the anterior motor neurons of the spinal cord through the corticospinal tract and to the brain stem through corticobulbar tract. The spatial orientation of different muscles of the opposite side of the body is represented in this area (except for the lower two thirds of the face which is represented bilaterally). The extremities of the opposite side of the body are represented in this, with the feet at the top of the gyrus and the face at the bottom. The surface area of representation of each muscle is proportional to the skill with which the part is used in fine voluntary movement. The areas involved in speech and hand movements are especially large in the cortex. The area of motor cortex is divided into columns, each represents a movement –not a muscle- and it is crossed.

Functions of the primary motor cortex: It is responsible for the execution of movement.

- More than one half of the entire primary motor cortex is concerned with controlling of conscious voluntary fine, precise, discrete (separate) skilled movements of the hands and the muscles of speech which are highly developed in human being.
- This area increases muscle tone by facilitation of stretch reflex. The primary motor cortex normally exerts a continual tonic stimulatory effect on the motor neurons of the spinal cord; when this stimulatory effect is removed, hypotonia results. Most lesions of the motor cortex, especially those caused by a stroke, involve not only the primary motor cortex but also adjacent parts of the brain such as the basal ganglia. In these instances, muscle spasm almost invariably occurs in the afflicted muscle areas on the opposite side of the body (because the motor pathways cross to the opposite side). This spasm results mainly from damage to accessory pathways from the non-pyramidal portions of the motor cortex. These pathways normally inhibit the vestibular and reticular brain stem motor nuclei. When these nuclei cease their state of inhibition (i.e., are "disinhibited"), they become spontaneously active and cause excessive spastic tone in the involved muscles, as we discuss more fully later in the chapter. This is the spasticity that normally accompanies a "stroke" in a human being.

Damage to this area causes lack of patient's fingers coordination and patient cannot precisely contract just one digit or a particular group of digits.

Clinical application:

The **middle cerebral artery** supplies the majority of the lateral surface of the cortex, including the section of primary motor cortex (and primary sensory cortex) responsible for movement (and sensation) of the face and upper extremities. An occlusion of the middle cerebral artery will cause contralateral spastic paresis (and impaired sensation) of the face and upper extremities. The area responsible for the lower extremities is supplied by the **anterior cerebral artery**; an occlusion of the anterior cerebral artery will have similar effects of the lower extremities.

[2] The supplementary motor cortex: This is located on medial surface of the frontal lobe slightly anterior to the primary motor cortex. It is responsible for generating mental planning of complex sequence of events of a motor act that need bimanual coordination (for example tying shoe laces) and sends these instructions to the premotor Area. Example: When you try to tie your shoe laces, you may sit down on a chair, then you may bend your back forward, then use your both hands to hold the ends of lace, then stretch the lace firmly, then make a node. Such mental planning of the sequence of events of a motor act is achieved by the supplementary motor cortex. It is important in movements that require both hands e.g. tying one's shoe laces.

Damage to this area leads to the following: Patient cannot tie shoe laces because of impaired selection of a particular movement sequence.

[3] The premotor cortex: This is located anterior to primary motor area and below the supplementary motor area on the lateral side of the hemisphere. It assembles the details of the mental planning of a motor act received from the supplementary motor area. In another words, this area instructs the primary motor area of how to do the motor act by constructing the details of the muscles involved in each event of a motor act and arrange the muscle contractions in order. This area is active during "mental rehearsal" for a movement. With repetition, the proper pattern of stimulation becomes stored in your premotor cortex as a ready-made program (also called **engram**).

Damage to premotor cortex area leads to the following:
- ☐ *Patient cannot initiate the movement the patient wishes to make.*
- ☐ *Patient exhibits **motor apraxia** (defect in motor performance without paralysis) because the selection of a particular movement is impaired.*

- □ *Reappearance of grasping reflex. E.g. when you have a patient in coma and you try to put a thing in his hand, he grasps it. Grasp reflex: happens when you put something the baby's hand, he will just grasp it, and this is before the age of 2 years, normally after 2 years, the area 6 is well developed and this reflex will be inhibited.*
- □ *Loss of bimanual coordination.*

Within the premotor cortex the following areas are present:

 1. **Broca's area** (Brodmann's area 44 and 45) for speech: This is the ward formation area. In most people (97%), both Broca's area and Wernicke's area are found in only the left hemisphere of the brain. *Damage to it (Broca's aphasia or non-fluent aphasia) does not prevent a person from vocalizing, but it does make it impossible for the person to speak whole words rather than uncoordinate utterances or an occasional simple words such as "no" or "yes".*

2. **The voluntary eye movement area** (Brodmann area 8 & 9) for controlling eye and eyelid movements such as blinking. It is part of the frontal cortex in the human brain. Situated just anterior to the premotor cortex (BA6), it includes the frontal eye fields (so-named because they are believed to play an important role in the control of eye movements).

Damage to this area prevents a person from voluntarily moving the eyes toward different objects. Instead, the eyes tend to lock on specific objects, an effect controlled by signals from the occipital region. Damage to this area, by stroke, trauma or infection, causes tonic deviation of the eyes towards the side of the injury. This finding occurs during the first few hours of an acute event such as cerebrovascular infarct (stroke) or hemorrhage (bleeding).This area also controls eyelid movements such as blinking.

3. **Head rotation area:** Stimulation this area will elicit head rotation. This area is closely associated with the eye movement field and presumably related to directing the head toward different objects.

4. **Area for hand skills**: *Damage to this area causes the hand movements become incoordinate and nonpurposeful, a condition called* **motor apraxia.**

B: Pyramidal tract (corticospinal and corticobulbar tracts): This tract originates about <u>40% from the primary motor cortex,</u> few of them from **giant pyramidal cells**, also called **Betz cells**, <u>40% from premotor cortex,</u> and <u>20% from the somatic sensory areas at the parietal lobe</u>. The pyramidal tracts include both the corticospinal and corticobulbar tracts (go to the motor nuclei of cranial nerves, in many cases bilaterally). These upper motor neuron nerve fibers travel from the cerebral cortex and terminate either in the brainstem (corticobulbar) or spinal cord (corticospinal) and are involved in control of motor functions of the body. Through their travel, they send collateral fibers to many subcortical structures.

The afferent nerve fibers that travel from the **somatic sensory cortex** are terminated at sensory cell groups in the dorsal horn of the spinal cord and in the dorsal column nuclei to keep them at a certain degree of excitation or inhibition thus helping to control the faithfulness of sensory signal transmission from incoming somatosensory pathways. This is achieved by controlling the amount of information being passed on to the brain and probably they instruct the sensory nuclei at the spinal cord that a movement is about to take place.

Regardless of the location of their cell bodies, pyramidal tract fibers (**direct corticospinal tract**) begin their descent from the cortex as a corona radiata (radiating crown) before forming the internal capsule. At the level of medulla, the majority of the pyramidal fibers (80%, originated mainly from
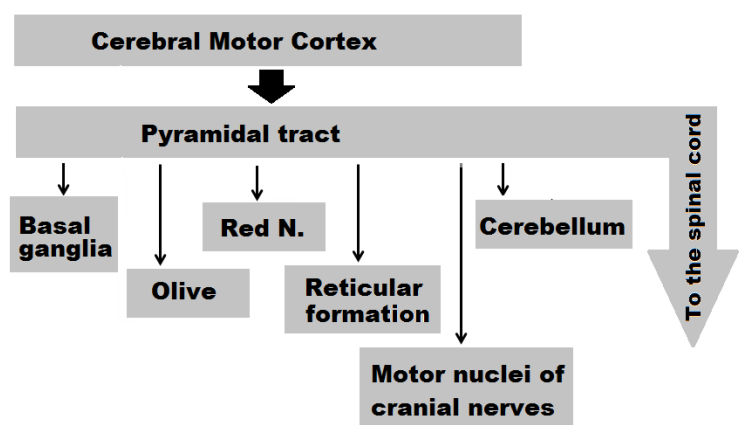
primary motor area) then crosses to the opposite side and descends in **the lateral corticospinal tracts** of the cord. Finally, these fibers terminate either directly or indirectly through interneuron (excitatory for the agonist muscles or inhibitory for antagonist muscles) that in turn synapse with anterior motor neurons. These fibers are concerned with contralateral distal limb muscles and hence with skilled movements especially of the hands and fingers. The pyramidal tract is a major controller of muscle activity for finger movements for performance of voluntary, purposeful activity such as writing, typing, tying knots, fastening buttons and playing musical instruments. However, some of the fibers terminate directly on the anterior motor neurons. A few of the fibers (20%, originated mainly from premotor area) do not cross to the opposite side in medulla but pass ipsilaterally down the cord through the reticular formation as **ventral (anterior) corticospinal tracts**, but before termination, majority of the fibers of this anterior corticospinal tract cross to the opposite side at different levels of spinal cord either directly or through interneurons to synapse with anterior motor neurons. These fibers are concerned with axial and proximal limb (girdle) muscle contraction. The neurotransmitter of the pyramidal system is **glutamate** and/or **aspartate.**

Figure 13.7 Stephen Hawking (1942–), Lucasian Professor of Mathematics at Cambridge University.

The cerebral cortex itself and subcortical structures (basal ganglia, brainstem reticular formation, Olive, Red nucleus, and cerebellum) all receive simultaneously strong signals from the pyramidal tract every time a signal is transmitted down the spinal cord to cause a motor activity.

*A highly selective damage to lateral corticospinal tract is associated with deficit with **fine skilled movements of hand and fingers**. On the other hand, lesion of ventral corticospinal tract causes difficulty with **balance**, **walking**, and **climbing**.*

Clinical application:
Poliomyelitis *and* ***amyotrophic lateral sclerosis (ALS)*** *are two diseases that involve destruction of motor neurons. In both diseases, the skeletal muscles atrophy from lack of innervation. Poliomyelitis is caused by the poliovirus, which destroys motor neurons in the brainstem and ventral horn of the spinal cord.*

ALS is also known as Lou Gehrig disease after the baseball player who contracted it. It is marked not only by the degeneration of motor neurons and atrophy of the muscles, but also sclerosis of the lateral regions of the spinal cord—hence its name. In most cases of ALS, neurons are destroyed by an inability of astrocytes to reabsorb glutamate from the tissue fluid, allowing this neurotransmitter to accumulate to a toxic level. The early signs of ALS include muscular weakness and difficulty in speaking, swallowing, and using the hands. Sensory and intellectual functions remain unaffected, as evidenced by the accomplishments of astrophysicist and best-selling author Stephen Hawking, who was stricken with ALS while he was in college. Despite near-total paralysis, he remains highly productive and communicates with the aid of a speech synthesizer and computer. Tragically, many people are quick to assume that those who have lost most of their ability to communicate their ideas and feelings have no ideas and feelings to communicate. To a victim, this may be more unbearable than the loss of motor function itself.

The extrapyramidal system: <u>Which includes all those portions of the brain and brain stem and their fibers that contribute to motor control but that are not part of the pyramidal system</u>. This system is concerned mainly with:

- **Postural control and stability,**
- **Inhibits unwanted muscular activity,**
- **Maintains muscle tone,**
- **It is responsible for facial expression such as sadness, irony and happiness and swallowing.**

Extrapyramidal system includes:

1. **Basal ganglia,**
2. **Reticular formation,**
3. **Vestibular nuclei,**
4. **Red nuclei,**
5. **Tectum (superior colliculi),**
6. **Olivary nucleus,**
7. **Cerebellum.**

   The descending spinal extrapyramidal tracts are crossed lateral pathway except vestibular nucleus which has in addition crossed and uncrossed ventromedial pathways to the cervical segments of the spinal cord.

   The main spinal **extrapyramidal tracts** (**indirect corticospinal tract**) include:

- **Tectospinal tract** (from the superior colliculus of the tectum and is involved in the control contralateral neck muscles),
- **Vestibulospinal tract** (from vestibular nuclei),
- **Reticulospinal tracts** (from pontine and medullary reticular formation),
- **Rubrospinal tract** (from the red nucleus).

The red nucleus: A distinctive oval nucleus (pink in fresh specimens because of an iron-containing pigment in many of the cells) centrally placed in the upper mesencephalic reticular formation of the brain stem. It receives fibers from the <u>cerebellum</u>, <u>cerebral cortex</u>, and from <u>basal ganglia</u> and the most important efferent projection of the red nucleus is to the contralateral spinal cord. It operates in close association with the pyramidal tract. Although often pictured in illustrations of human anatomy, they are almost nonexistent in humans and have little functional importance. This nucleus gives rise the rubrospinal tract that crosses to the opposite side in the lower brain stem and follows a course parallel to the lateral corticospinal tract and terminate directly or indirectly (through interneuron) on the anterior motor neurons.

   The red nucleus has a somatotopical representation of all the muscle of the body similar to the motor cortex but far less developed fineness of representation. The corticorubral pathway serves as an accessory route for the transmission of discrete signals from the motor cortex to the spinal cord. <u>The rubrospinal</u>
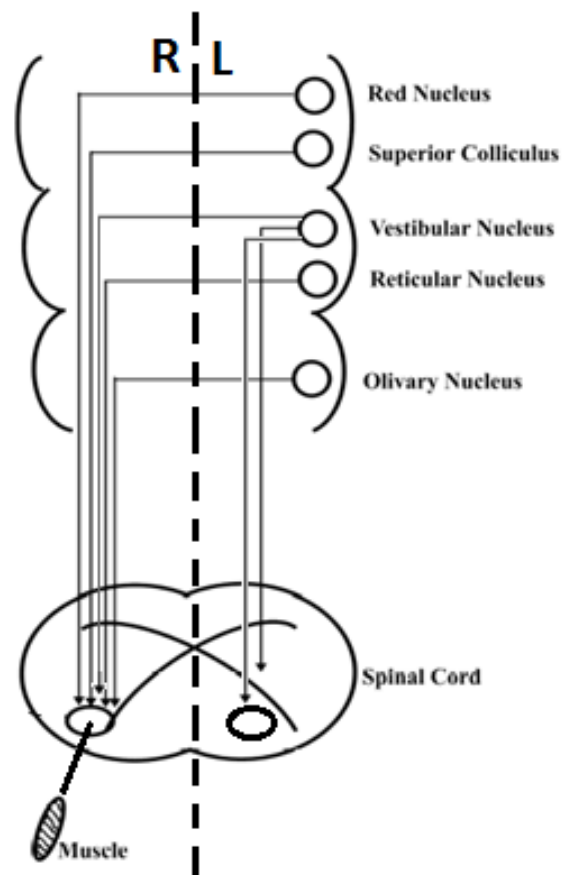
tract is involved in large movements of proximal musculature of the limbs. **It inhibits activity of extensors (alpha and gamma motoneuron), and increases activity of flexors (alpha and gamma motoneuron).** There are no clinical case studies involving a lesion limited to the red nucleus.

The reticular formation: Reticular formation is a diffused mass of neurons and nerve fibers, which form an ill-defined meshwork of reticulum in central portion of the brainstem. Reticular formation is situated in brainstem. It extends downwards into spinal cord and upwards up to thalamus and subthalamus. The Reticular Formation represents a rostral extension of the inter-neuronal network in the intermediate gray matter of the spinal cord. Although it appears as a loosely organized collection of cells, the reticular formation is highly organized and differentiated, consisting of distinct neuronal populations with specific functions. The neurons of the reticular formation receive collateral nerve ending from the spinal cord (touch, pain, proprioception, vibratory, and temperature receptors), from eye and ears, from cortex (collateral from pyramidal tract), from the thalamus, hypothalamus, basal ganglia and from cerebellum. In addition, the reticular formation provides multiple efferent fibers that pass both upward and downward in the axis of the NS that play important roles in the adjustment of endocrine secretion, regulation of sensory input and consciousness.
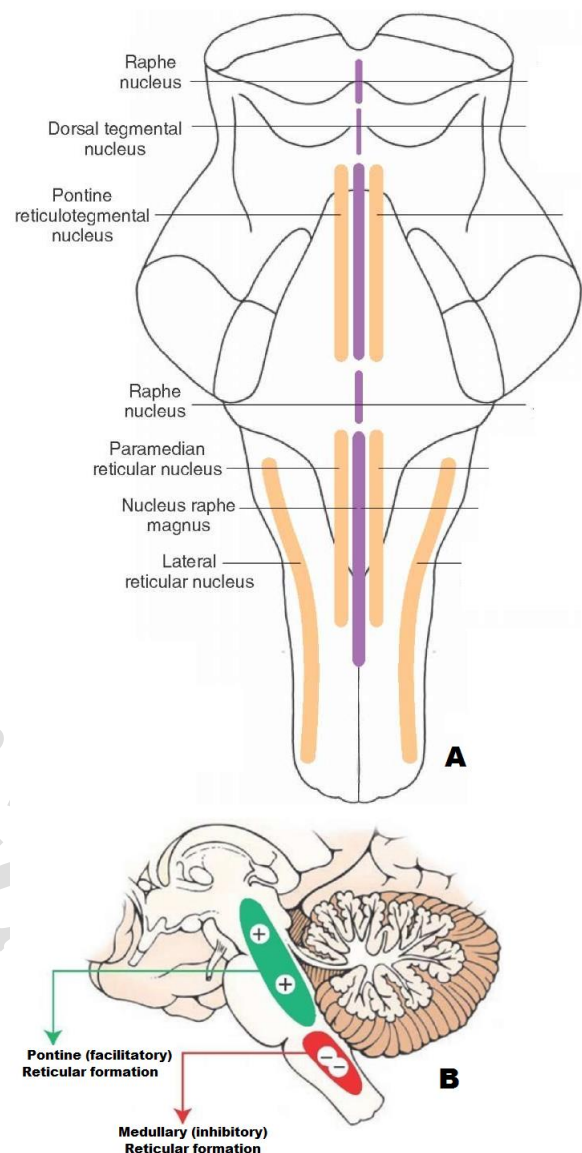
How is the reticular formation organized? Traditionally the nuclei are divided into three columns

- In the **median column – the raphe nuclei,** they secrete serotonin (5-hydroxytryptamine, 5-HT), which is an inhibitory neurotransmitter.
- In the **medial column – magnocellular or gigantocellular reticular nuclei** (because of larger size of the cells). It forms the major output of the reticular formation and send fibers to the hypothalamus, thalamus and spinal cord. These nuclei are associated with **motor functions.**
- In the **lateral column – parvocellular nuclei** (because of smaller size of the cells). Neurons of these nuclei receive sensory signals from the cranial nerves, cerebellum and spinal cord.

Within the reticular formation, there are functional neuronal aggregates such as Cardiac centers, respiratory centers, vasomotor centers, salivatory centers, chemoreceptors neurons.

Reticular formation is divided into three divisions based on the location in brainstem. Each division of reticular formation has its own collection of nuclei.

- A. Medullary reticular formation
- B. Pontine reticular formation
- C. Midbrain reticular formation.

The afferent and efferent connections of reticular formation are shown in figures.

Based on functions, reticular formation along with its connections is divided into two systems:
A. Descending reticular system.
B. Ascending reticular activating system.

A. Descending reticular system: With respect to descending reticular system, its motor functions, the reticular formation can be divided into **pontine (facilitatory)** and **medullary (inhibitory areas)**.

- The **facilitatory area** extends from about middle of the pons up through the mesencephalic tegmentum. Stimulation has a general **stimulatory effect on both extensors and flexors, with the predominant effect on extensors** (**antigravity muscles**) (through **pontine reticulospinal tract**). It receives excitatory input from:

Cortex	Cerebellum	Vestibular nuclei	Sensory pathways (general or special sensations)

- The **inhibitory area** comprises the caudal portion of the medulla. Stimulation has a general **inhibitory effect on both extensors and flexors**, **with the predominant effect on extensors**. The inhibitory area tends to **inhibit the extensors** (through **medullary reticulospinal tract**). It receives strong input from the:

Cortex	Cerebellum	Red nucleus	Other motor pathways

A. Functions of the descending reticular system:
The ascending projections of the reticular formation are involved in 4 different types of functions:
• The regulation of posture
• The control of muscle tone
• The modulation of pain sensation
• The coordination of autonomic functions

1. The regulation of posture: The reticulospinal tracts are two long descending pathways associated with the control of movements and posture. The medial (pontine) reticulospinal tract enhances the extensor tone, whereas the lateral (medullary) reticulospinal tract inhibits extensors. In the spinal cord, both of these motor tracts terminate in the ventral horn of the spinal cord. A balance between the activities of these pathways facilitates fine control of posture through actions on the extensor muscles of the lower limb. Standing posture can be maintained because the reticular formation sends impulses to the extensor muscles of the upper and lower limbs to stiffen and control the position of the body's center of gravity and to maintain the gravity line within the base of support. To support the body against gravity and maintain that position over an extended period of time with minimal muscular effort, the gravity line will fall between the feet in front of the talus bone. Any slight departure from that specific position will increase the general tone in the extensor muscles.

2. The control of muscle tone: The reticulospinal tract is involved in the influence of muscle spindles, making them more or less sensitive, and hence altering muscle reflexes. The reticulospinal tract is also involved in the control of sympathetic and sacral parasympathetic outflow by the hypothalamus.

3. The modulation of pain sensation: The sensation of pain is modulated at the level of spinal cord by descending projections that inhibit nociceptive neurons through direct and indirect connections in the superficial layers of the dorsal horn. These descending projections are:

- **Serotoninergic** projections from raphe magnus nucleus.
- **Noradrenergic** Noradrenergic neurons projected from the locus ceruleus and dopaminergic neurons projected from the ventral tegmental area also appear to be involved to suppress incoming pain signals at spinal level.

4. The coordination of autonomic functions: Centers controlling inspiration, expiration, the normal rhythm of breathing, heart rate and blood pressure, gastrointestinal activities, and ocular (pupillary) reflexes have been identified in the medulla and pontine reticular formation. Neurons in the reticular formation are important for coordinating a variety of stereotyped behaviors such as:

• Gastrointestinal responses such as swallowing, vomiting, chewing, lip movements, and movements of the tongue.
• Respiratory activities (respiratory rhythm, coughing, hiccuping, sneezing)
• Cardiovascular responses (baroceptor reflexes and responses to cerebral ischemia and hypoxia)
• The horizontal and vertical eye movements.
• Organizing emotional facial expressions (smiling and crying).

B. Ascending reticular activating system: The mesencephalic and upper pontine portions (facilitatory) of the reticular formation is giving an ascending **monoaminergic (NE, 5-HT)** and **cholinergic** projections to the cerebral cortex and thalamus to increase wakefulness as well as the responsiveness to sensory stimuli, a state known as arousal and provide intrinsic activation of large areas of the brain. This portion of the reticular formation is also called **reticular activating system (RAS).** From RAS multiple diffuse pathways terminate in almost all areas of both diencephalon and the cerebrum. These pathways control the overall degree of activity of the cortex, and other subcortical nuclei. Ascending projections from the rostral reticular formation to the cerebral cortex and thalamus increase wakefulness as well as the responsiveness to sensory stimuli, a state known as **arousa**l. These pathways form an ascending reticular activating system (ARAS). Tumor or lesion in ARAS leads to sleeping sickness or coma. The impact of head injury on ARAS also causes coma.

RAS is subject to excitation and therefore subject to increased levels of activation. Two basic types of stimuli are especially likely to increase the activity of the RAS and these are:
1. Sensory stimuli: All the sensory pathways send collaterals to ARAS, which is a multisynaptic relay system. These collaterals project in diffused areas of ARAS. So, the sensory impulses transmitted via the collaterals reach different parts of ARAS. It also receives afferents from spinal cord directly in the form of spinoreticular tract. These sensory signals on entering the reticular formation may activate the RAS and awaken the subject immediately. This is called arousal reaction.
2. Retrograde stimuli from almost all parts of the cerebrum especially from motor regions to the reticular formation via direct fiber pathways. This may explain the importance of moving around when one wishes to remain awake.

RAS is subject to inhibition and therefore subject to decrease levels of activation, which can lead to sleep. This can be achieved by the areas of reticular formation in the brain stem below the midlevel of the pons and throughout the medulla oblongata which is inhibitory to the spinal cord segmental activities through inhibitory reticulospinal tracts and can be inhibitory to RAS that may lead to sleep. Damage to this area causes the cerebrum to become active and to remain active indefinitely as if it remains continuously awake.

A confined damage to the RAS or their pathways causes the cerebrum to become inactive that is to go into **coma,** during which some electrical activity of the brain can be recorded. Coma is distinct from sleep in that a person cannot be aroused from coma. In some comatose patients, all parts
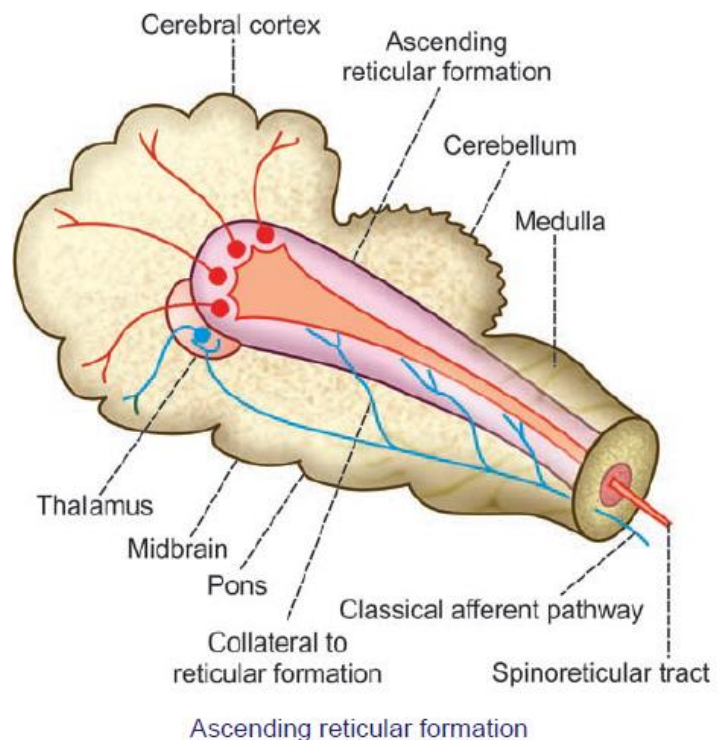
of the brain are inactivated, not just the RAS. In this case all electrical activity of the brain ceases, that is the brain waves are said to be flat. This is the condition called **brain death** and the person can then remain alive only by being sustained on artificial respiration, administration of nutrition by stomach tube or intravenously, etc.

Tectum: The tectum is located in the dorsal region of the mesencephalon (mid brain). It consists of four nuclei that form four mounds on the dorsal surface, collectively called **Corpor (Bodies) Quadrigemina (Four Twins)**. Each mound is called a Colliculus (Hill); there are two superior colliculi and two inferior colliculi. The tectum is responsible for auditory and visual reflexes. the tectospinal tract is a nerve pathway that coordinates head and eye movements. To be specific, the tectospinal tract connects the midbrain tectum and cervical regions of the spinal cord. It is responsible for motor impulses that arise from one side of the midbrain to muscles on the opposite side of the body (Contralateral). The function of the tectospinal tract is to mediate reflex postural movements of the head in response to visual and auditory stimuli. The portion of the midbrain from where this tract originates is the superior colliculus, each **superior colliculus** receives visual inputs from the visual cortex through the thalamus on that side. Each **inferior colliculus** receives auditory input from nuclei in the medulla oblongata and pons. Some of this information may be forwarded to the medial geniculate nucleus of the thalamus on the same side. The superior colliculi control the reflex movements of the eyes, head, and neck in response to visual stimuli, such as a bright light and thus can be involved in responses to stimuli faster than cortical processing would allow and mediating contralateral movements of the head, neck, and eyes in response to visual stimuli. The inferior colliculi control reflex movements of the head, neck, and trunk in response to auditory stimuli, such as a loud noise. The inferior colliculi are responsible for **auditory (Startle) reflex**. A reflex is seen in normal infants in response to a loud noise. The infant with make a sudden body movement, the arms fling out sideways with the palms up and the thumbs flexed.

Tegmentum: The tegmentum (tegmentum, Latin for covering) refers to the ventral part of the midbrain. In addition to the reticular formation, the tegmentum contains three colorful structures- the periaqueductal gray, the substantia nigra, and the red nucleus. **It is rich in dopamine and serotonin neurons**. The tegmentum is considered to be part of the **pleasure system**, or **reward circuit**, one of the major sources of incentive and behavioural motivation. Activities that produce pleasure tend to activate the tegmentum. The reward system is short circuited by addictive drugs, including cocaine, amphetamines, alcohol, nicotine, and opiates, which all increase dopaminergic transmission in the tegmentum. Hence, it is widely implicated in neurobiological theories of addiction. It is also shown to process various types of **emotion and security motivation**, where it may also play a role in **avoidance** and **fear-conditioning**.

Vestibular Nuclei: The vestibular nuclei control balance. The vestibular nuclei (located at the border of the pons and medulla). They are synaptically linked to the extrapyramidal system. So that persons with extrapyramidal disorders frequently also have problems with balance and they may experience frequent falls. The main sensory organ is semicircular canals of the vestibular apparatus in the internal ear that monitor the position and movement of the head. There are three semicircular canals which represent all three spatial planes. The sensory receptors of the semicircular canals project polysynaptically to the vestibular nuclei which are located in the medulla adjacent to the floor of the fourth ventricle. These nuclei in turn have two ways traffic of axons (via the inferior cerebellar peduncle) to the cerebellum to maintain equilibrium. The major tracts and functions of the vestibular system include:

1. Maintain the body, neck and the head in an upright balanced position:

This is achieved by excitation of antigravity muscles especially related to movements of the head through:

- Uncrossed descending pathways known as the <u>lateral vestibulospinal tracts</u>,
- Crossed <u>medial vestibulospinal tracts</u> and
- Two-ways traffic with the cerebellum (<u>reflex of equilibrium)</u>. which gives cerebellum the information it needs to adjust any motor skills it happens to be controlling at the time.

Lesions involving the vestibular nerve, nuclei, and descending pathways will result in problems such as <u>stumbling or falling towards the side of the lesion</u>. This is because in normal conditions, the two lateral vestibulospinal tracts usually counteract each other functionally. Therefore, if you have a patient with a lesion that has destroyed the <u>left vestibular nerve</u>, then the left vestibular nuclei and the left lateral vestibulospinal tract are "tuned" down. Meanwhile, the normal right nerve, nucleus, and the right lateral vestibulospinal tract are in good shape, and now the right side takes over. The end result is stumbling and falling to the weak side, in this case to the left. Again, here Romberg sign is positive while the eyes are closed.
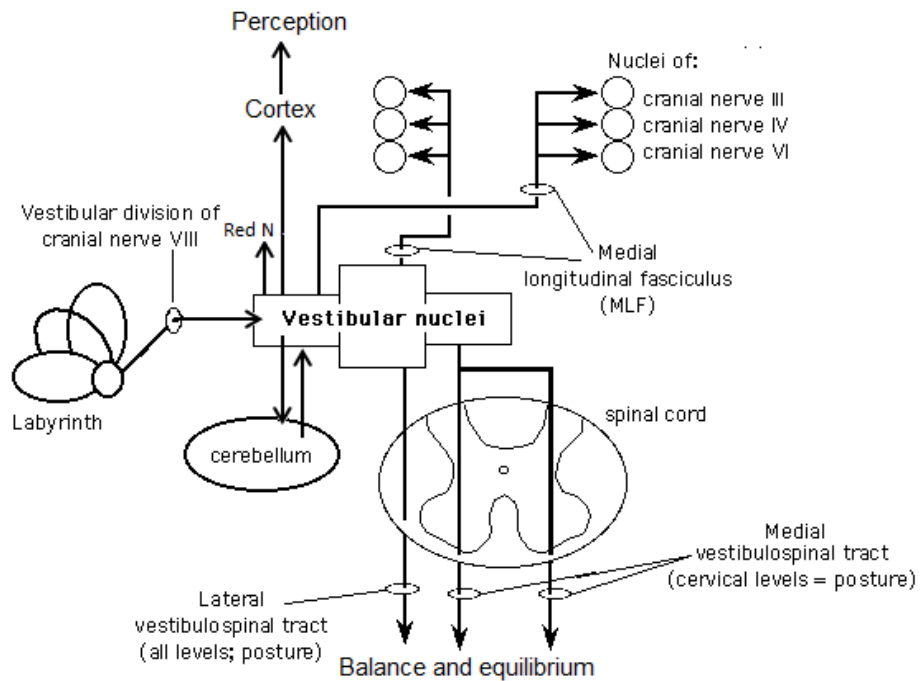
2. Maintain the retinal image while the head is moving:

❖ The vestibular nucleus in association with cranial nerves III (oculomotor N), IV (troclear N.), VI (abducent N.), and XI (accessary N.), controlling the head, neck, and eye muscles forming **vestibulo-ocular reflex**. The vestibule-ocular reflex helps maintain fixation of the eyes (fovea of the retina) on an object of interest with movement of the head. Therefore, eye movements induced by the vestibular apparatus are compensatory, that is, they oppose head movements or changes in head position. For example, a quick turn (or push) of your head to the RIGHT will result in a compensatory reflex turning of the two eyes to the LEFT. The first order neurons are vestibular afferents from semicircular canals which terminate in the vestibular nuclei. The second order neurons project from vestibular nuclei to oculomotor nuclei. The third order neurons project from oculomotor nuclei to extraocular muscles.

❖ The vestibule-ocular tract which controls saccadic eye movements (voluntarily turning both of our eyes horizontally to the left or right in order to see a new object of interest).

3. Conscious awareness of balance:
The vestibule-cortical tract through the thalamus to the inferior parietal gyrus of cerebral cortex provides awareness of balance or not (dizziness).

The practical implications are that diseases of the inner ear cause loss of equilibrium, dizziness and saccadic eye movements when the head is turned.

The basal ganglia: The Basal ganglia are a group of functionally related nuclei located bilaterally in the inferior cerebrum, diencephalon and midbrain.

- The basal ganglia do not make any direct sensory or motor connections with the spinal cord, their contribution to the control of movement is made indirectly through the sensory and motor cortex (see figure).
- Physiologically, the basal ganglia composed of the following nuclei:

1. Caudate nucleus

**2. Globus pallidus** (Globus pallidus interna and Globus pallidus externa) (GP, GPi, GPe)

3. Putamen

4. Substantial nigra (pars reticulata and pars compacta) (SN, SNr, SNc)

5. Subthalamic nuclei (STN) (body of Luys)

The caudate nucleus and putamen together form the neostriatum which represents the input door of the basal ganglia neuronal circuit. Caudate nucleus and lentiform nucleus together are called corpus striatum. The putamen and the globus pallidus together are called the lentiform (lenticular) nucleus.

- These structures have high oxygen consumption. They suffer rapidly from hypoxia or ischemia. The copper content of the substantia nigra and the nearby locus ceruleus is particularly high. Excess copper in the plasma is bound to a protein made in the liver called ceruloplasmin until it is excreted in bile. In **Wilson disease**, there is failure, of ceraloplasmin formation and inability to excrete copper in bile. Consequently, serum copper level rises which leads to copper intoxication. Large amounts of copper accumulate in the cells of the liver and the lentiform nucleus of the basal ganglia which lead finally to hepatolenticular degeneration.
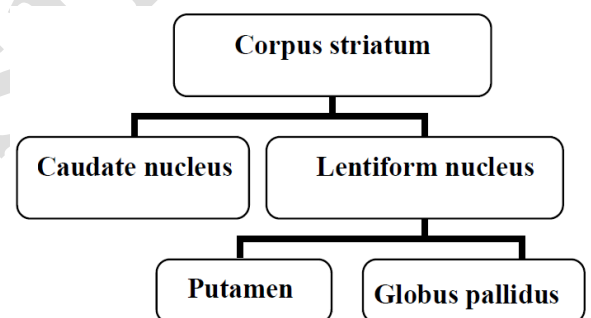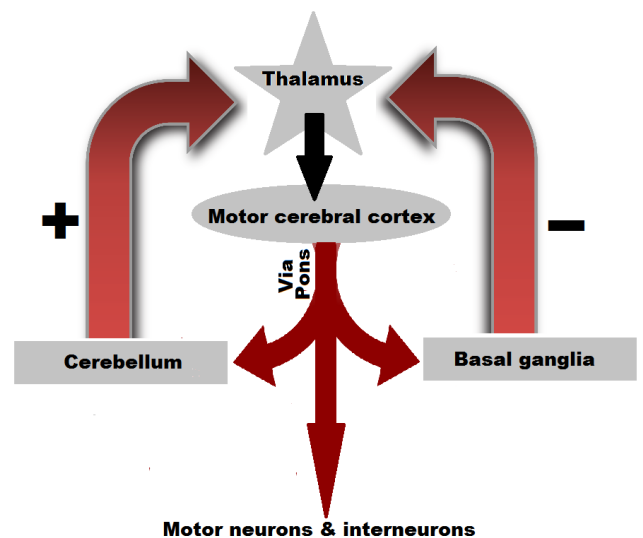
- There are two neuronal circuit in basal ganglia:
- There are two neuronal circuit in basal ganglia:
  1. Direct Excitatory pathway (Stimulates motor cortex by <u>decreasing the inhibition</u> on the thalamus, thus Promotes Movement
  2. Indirect Inhibitory pathway (Inhibits motor cortex) by <u>increasing the inhibition</u> on the thalamus, thus Inhibits Movement
- Basal ganglia neurotransmitters are:
  1. Dopamine: It selectively excites the direct pathway and inhibits the indirect pathway, thus promotes movement.
  2. Acetylcholine: It inhibits the direct pathway and excites the indirect pathway, thus inhibits movement
  3. GABA, is inhibitory in the neuronal circuit
  4. Glutamate, is excitatory in the neuronal circuit

NOTES: Overactivity in the indirect pathway is a major factor in Parkinsonian signs, while underactivity in the indirect pathway is a major factor in hyperkinetic disorders such as hemiballism (violent involuntary throwing movements of the limb after a lesion in the contralateral subthalamic nucleus), Huntington disease (which is an autosomal dominant hyperkinetic disorder characterized by chorea, dementia and behavioral disturbance). Therefore the effect of depletion of these dopaminergic

projections to the striatum, as occurs in Parkinson's disease, can now be predicted. **Dopamine selectively excites the direct pathway and inhibits the indirect pathway**, thus determining those signals that are reinforced and those that are suppressed.

Overactivity in the indirect pathway is a major factor in Parkinsonian signs (due to dopamine depletion), while underactivity in the indirect pathway is a major factor in hyperkinetic disorders such as hemiballism (violent involuntary throwing movements of the limb after a lesion in the contralateral subthalamic nucleus), Huntington disease (which is an autosomal dominant hyperkinetic disorder characterized by chorea, dementia and behavioral disturbance).

It is important to note that almost all the motor and sensory fibers connecting the cerebral cortex and spinal cord pass between the caudate nucleus and putamen. This mass of nerve fibers is called the **internal capsule** of the brain. Many of the synaptic connections are inhibitory and use GABA as their neurotransmitter.

The main functions of basal ganglia are:
[1] Shared in control the learned complex pattern motor activity: Basal ganglia in association with the motor and sensory cortex and cerebellum responsible for **planning, programming** and **timing** of the learned complex pattern of motor activity such as writing a letters of alphabet, cutting paper with scissors, hammering nails, shooting basketball through a hoop, passing a football, throwing a baseball, the movements of shoveling dirt, when dressing, and virtually any other of our skilled movements. The basal ganglia in association with the cerebellum nuclei modify movement on a minute-to-minute basis. Motor cortex sends information to basal ganglia and cerebellum, and both structures send information right back to cortex via the
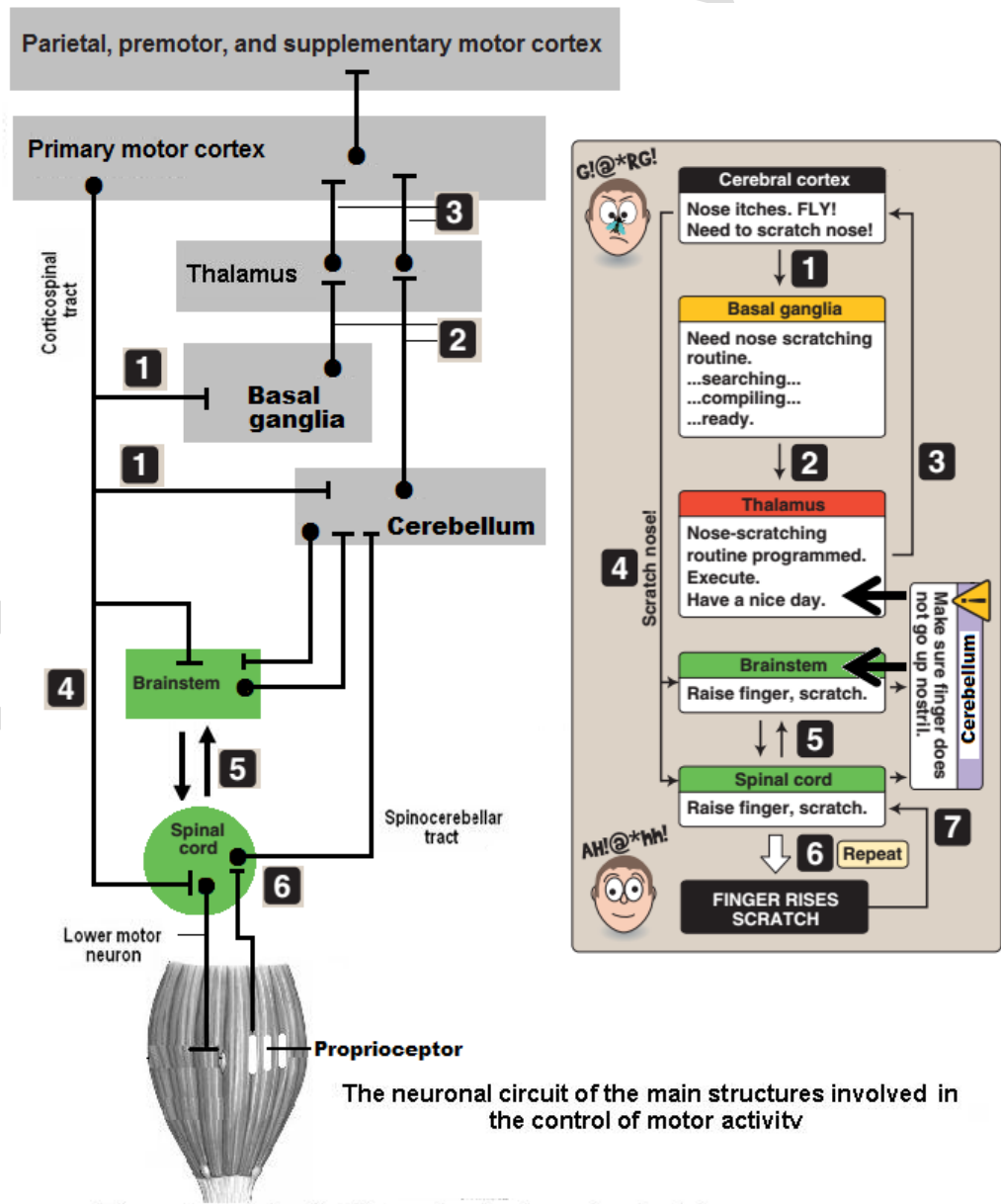

Figure: The hierarchical organization of the motor system.

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thalamus (remember, to get to cortex you must go through thalamus). The output of the cerebellum is excitatory, while the basal ganglia are inhibitory. The balance between these two systems allows for smooth, coordinated movement executed by motor cortex, and a disturbance in either system will show up as movement disorders. Therefore, basal ganglia in association with the cerebellum select and accentuate the wanted patterns of movement and suppress useless or unwanted patterns of movement.

[2] Control the instinctive cognition of the sequences of motor response: Cognition means the thinking processes of the brain, using both sensory inputs to the brain plus information already stored in memory. Most of our motor actions occur as a consequence of cognition or thinking process (thought) generated in the brain. Some of the basic instinctive cognitions and their motor responses need to be executed without thinking for too long time, to respond quickly and appropriately. The basal ganglia plays major role in this instinctive cognitive control of the sequence of motor response. A good example of this would be for a person to see a lion approach and then respond instantaneously and automatically by [a] turning away from the lion, [b] beginning to run, and [c] even attempting to climb a tree. Without the cognitive functions, the person might not have the instinctive knowledge, without thinking for too long time, to respond quickly and appropriately.

[3] Control the speed of movement and the scale of movements: For instance, one may write a small "a" on a piece of paper or a large letter "a" on a chalkboard. Regardless of his choices, the proportional characteristics of the letter remain the same. Patients with severe lesions of the basal ganglia, these speed and scaling functions are poor or even not existent. In addition, patients lacking left basal ganglia might draw the face of another human being, providing proper proportions for the right side of the face but almost ignoring the left side (which is in his left field of vision). Such patients will try always to avoid using their right arms, right hand, or other portions of their bodies for the performance of tasks, almost not knowing that these parts of their bodies exist.

[4] Control the posture: The basal ganglia in association with other structures help to control the axial and girdle movements of the body (i.e. control of posture). These movements provide the background positioning of the body and proximal limbs so that the more discrete motor functions of the hands and feet can then be performed. Lesions of the basal ganglia seriously interfere with the attitudinal movements that are necessary to position the hand and therefore, make it difficult or impossible for one to use the hand for discrete activities.

[5] Inhibit muscle tone throughout body: The feedback loops from the cortex through the basal ganglia and then back to the cortex make virtually all these loops negative feedback loops. This effect results inhibitory signals transmitted from the basal ganglia to cerebral cortex. Therefore, widespread destruction of the basal ganglia underline causes muscle rigidity throughout the body.

Disorders of Function: Clinical signs in basal ganglia lesion are contralateral to the side of lesion. This is because: Basal ganglia circuit doesn't cross but, the corticospinal tract crosses to the contralateral side and Basal ganglia modulate the motor cortex.

A. Hypokinetic disorders – Lesions of Direct Pathway: Parkinsonism Disease:
*Degeneration of Dopaminergic neurons of Substantia nigra and accumulation as Lewy bodies Also, ongoing unopposed ACh activity leading to activation of inhibitory pathway Inhibition of motor cortex and movement Accompanied by: TRAP **T**remor (Resting pill-rolling) **R**igidity (Lead-pipe and cog-wheel) **A**kinesia **P**osture (Stooped).*

B. Hyperkinetic disorders – Lesions of Indirect Pathway:
*1. **Hemiballismus:** Violent projectile movement of limb seen contralateral to the lesion.*
*2. **Chorea:** Rapid, involuntary and purposeless jerks of irregular and variable location on the body.*

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3. Athetosis: *Spontaneous and often continuous writhing movements of a hand, an arm, the neck, or the face.*

4. Wilson's Disease (Hepatolenticular degeneration): *Dystonia and Tremor.*

5. Dystonia: *Increased/sustained muscle contractions, twisting of the trunk or extremities, and abnormal postures.*

The cerebellum

The little brain, also termed the motor autopilot, helps regulate movements and posture, influences muscle tone, eye movements and balance. <u>The cerebellum is especially vital to the control of very rapid muscular activities such as running, typing, playing the piano, and talking. Loss of this area of the brain can cause almost total incoordination of these activities even though its loss causes no paralysis of any muscle.</u> Cerebellum has wide interconnections with various parts of the NS and with the peripheral sensory receptors.

The cerebellum receives information from **spinal cord** (through the dorsal spinocerebellar tracts and the ventral spinocerebellar tract), **eyes** and **ears** (through tectocerebellar tract from colliculi), **cerebral cortex** (through cortico-ponto-cerebellar tract), **olivary nucleus** (through olivocerebellar), **cuneate nucleus** (through cuneocerebellar tract), and **vestibular nucleus** (through vestibulocerebellar tract).

The ingoing pathways to the cerebellum arranged into two main input fibers that pass to the cerebellar cortex and these are **climbing fibers** (originated from inferior olive of the medulla) and **mossy fibers** (originated from many centers in the brain stem and spinal cord). <u>Both are excitatory fibers which send collaterals to the deep cerebellar nuclei and pass to the cortex.</u>

The cerebellum has two important structures:

External cerebellar cortex (which contains only 5 types of neurons; Purkinje, Granule, Basket, Stellete, and Golgi cells) and **Deep cerebellar nuclei** (which are dentate, Globose, Emboliform, and Fastigiel nuclei). Deep nuclei receive excitatory inputs from the mossy and climbing fibers and inhibitory inputs from Purkinje cells. Many of the cells of the

Neuronal connections in cerebellum

cerebellum are constantly active (tonic discharge), and the deep nuclear cells continually send tonic excitatory output signals to the other areas of the motor system. Therefore, a decrease of the nuclear cell-firing rate is considered an inhibitory output signal from the cerebellum, while an increase in firing rate is considered an excitatory output signal.

The main functions of cerebellum

1. Cerebellum is planning, programming and **timing** of sequential pattern of the motor activities. Cerebellum in association with motor and sensory cortex and basal ganglia are planning, programming and timing for the next movement at the same time that the present movement is occurring. *In cerebellar dysfunction, this capability is seriously disturbed especially for rapid movements, which can lead to extreme incoordination and failure of progression of the purposeful movements of the hands, fingers, and feet, a condition called <u>dysdiadochokinesia.</u> In which jumbled movements occur instead of the normal coordinate movements. In addition, speech is affected, a condition called <u>dysarthria.</u>*

2. Cerebellum monitors (assesses), compares, and makes corrective adjustments in the motor activities elicited by other parts of the brain. During rapid movement, the motor cortex transmits signals
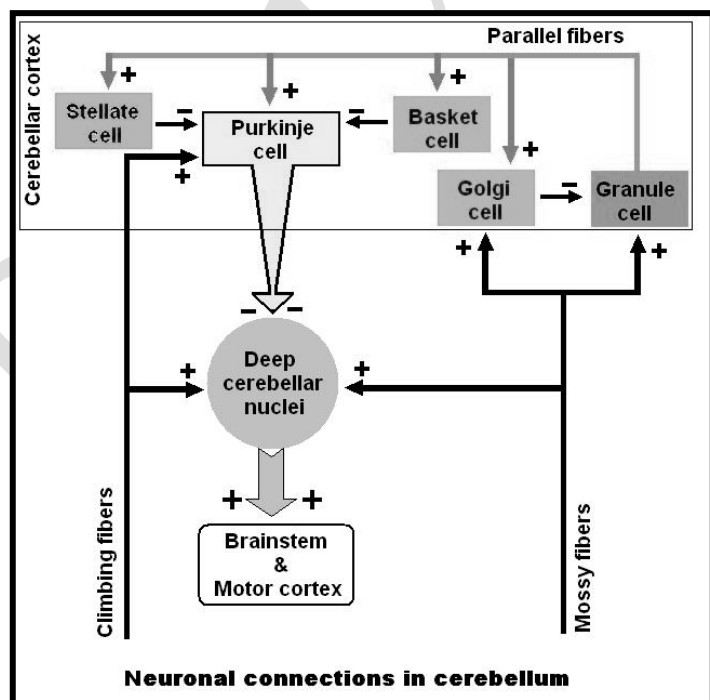
to the respective muscles to perform the intended movement. The cerebellum assesses the strength of these signals and compares it with the actual strength that reaches the anterior motor neuron and the rate of movement. The cerebellum then calculates the length of time that will require reaching the point of intention. If the comparison between the intention of the motor system and the actual motor response is unfavorable, then appropriate corrective signals are transmitted instantaneously back into the motor system to increase or decrease the levels of activation of the specific muscles (corrective adjustment function) and to stop the movement precisely at the intended point, thereby preventing the overshoot. Prevention of overshooting by the cerebellum is called the damping function of the cerebellum.

In cerebellar dysfunction, overshooting does occur (the effect is called <u>dysmetria or past pointing</u>), the conscious centers of cerebral cortex recognize this and initiate a movement in the opposite direction to bring the arm to its intended position. But again the arm, because of its momentum, overshoots, and appropriate corrective signals must again be instituted by the cerebral cortex. Thus they are oscillates back and forth past its intended point for several cycles before it finally fixes on its mark. This effect is called an action or <u>intention tremor</u>.

3. Predictive function of cerebellum: The cerebellum functions with the spinal cord and brain stem to control postural and equilibrium during movements. This is achieved by predictive function of cerebellum. Cerebellum is especially important in controlling the balance between agonist and antagonist muscle contractions during rapid changes in body positions as dictated by the vestibular apparatuses. This is achieved by the predictive function (**efference copy**) of the cerebellum who analyzes the information dictated from peripheral sensory receptors (especially from the muscles, joints, and skin surface) and vestibular nuclei about the rate and direction of movement of each part of the body and compute these information to predict the position of these parts of the body within the next 15-20 msec and therefore, provide almost instantaneous correction of postural motor signals as necessary for maintaining equilibrium even during extremely rapid motion, including rapidly changing directions of motion. Besides movements of the body, cerebellum also plays a role in predicting other events. For instance, the rates of progression of both auditory and visual phenomena can be predicted. An example, a person can predict from the changing visual scene how rapidly he is approaching an object.

Cerebellar dysfunction causes extreme disturbance of equilibrium during performance of rapid motions than during stasis.

4. Cerebellar control of the muscle spindles: Cerebellum receives extreme amount of information from the muscle spindles via the dorsal spinocerebellar tracts. In turn, from cerebellum, signals are transmitted into the brain stem (pontine and medullary reticular formation) and motor cortex to stimulate the gamma efferent fibers that innervate the muscle spindles themselves. This pattern of arrangement forms a **cerebellar stretch reflex** or **negative stretch reflex**. When the muscle is already contracted, any sudden release of the load on the muscle that allows it to shorten will elicit reflex muscle inhibition rather than reflex excitation to oppose the shortening of the muscle in the same way that the positive stretch reflex opposes lengthening of the muscle.

Loss of the cerebellar component of the stretch reflex will result to an effect called <u>rebound</u> in which, if a person with cerebellar disease is asked to pull upward strongly on an arm while the physician holds it back at first and then lets go, the arm will fly back until it strikes the face instead of being automatically stopped. In normal state, the cerebellum instantaneously and powerfully sensitizes this stretch reflex mechanism whenever a portion of the body begins to move unexpectedly in an unwilled direction. In addition, <u>hypotonia</u> is occurred in cerebellar dysfunction which results from loss of facilitation of the motor cortex and brain stem nuclei by the tonic discharge of the deep cerebellar nuclei.

5. Control of ballistic movements. Many rapid movements of the body, such as the movements of the fingers in typing, the movements of the eyes when reading or when looking at successive points

along a road when a person is moving in a car, where the eyes jump from one position to the next. These movements occur so rapidly that it is not possible to receive feedback information either from the periphery to the cerebellum or from the cerebellum back to the motor cortex before the movements are over. These movements are called ballistic movements. Without cerebellum, this movement becomes very difficult to perform.
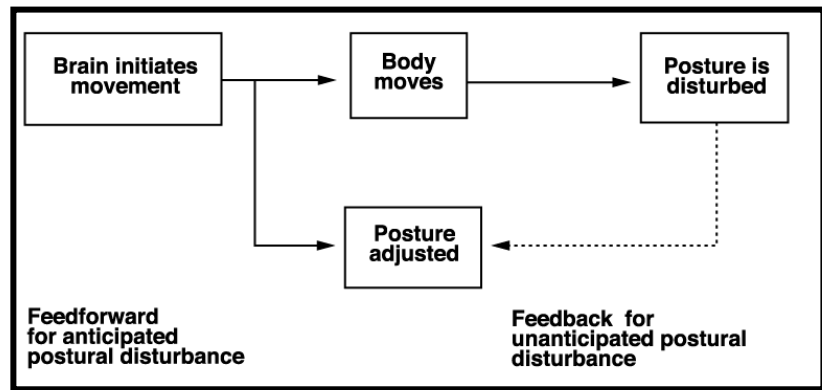
Control of equilibrium (or postural reflexes)

Control of equilibrium (or postural reflexes): Posture serves 3 main behavioral functions:

1. To support head and body against gravity through antigravity reflexes. These reflexes maintain the body in an upright balanced position against the gravity. Therefore, there should be a background contraction of the trunk and neck musculature and proximal portions of the limbs to provide support of the body against gravity and therefore, to maintain the body in an upright balanced position. This is achieved by controlling the muscles tone. The mechanism in the maintenance of muscle tone forms the static postural reflex. This reflex provides stable postural backgrounds for the axial and girdle movements so that the more discrete motor functions of the hands and feet can then be performed.
2. To align the body with center of gravity to maintain center of body's mass over center of support.
3. To provide a stable background for movement and to stabilize supporting parts of body while other parts move. These reflexes maintain the body in balance during the movement of the body. The mechanism, which maintains balance during voluntary action, forms the phasic postural reflex.

Reflex Arc of Postural Reflex:
- ☐ Afferent Pathway- comes from the muscle spindles and Golgi tendon organ, eyes, the vestibular apparatus, the pressure receptors on the bottom of feet and on body wall and proprioceptors.
- ☐ Integrating Centers- are formed by neuronal network in the brain stem and spinal cord.
- ☐ Efferent Pathway- α-motor neurons supplying the various skeletal muscles i.e. the effector organ.

Motion sickness is a disturbance of the inner ear's sensation of balance. Nine out of ten people have experienced this nausea and vomiting, usually when riding in a car or on a boat. Although the cause of motion sickness is not known, one theory is that it results when visual information contradicts the inner ear's sensation that one is motionless. Consider a woman riding in a car. Her inner ears tell her that she is not moving, but the passing scenery tells her eyes that she is moving. The problem is compounded if she tries to read. The brain reacts to these seemingly contradictory sensations by signaling a "vomiting center" in the medulla oblongata.

Signs of lesion of the upper motor neuron (pyramidal and extrapyramidal systems): Damage to the motor cortex or the pyramidal and extrapyramidal systems tracts due to interruption of blood supply to it is called **stroke**.

The signs of upper motor neuron lesion are:
[1] Weakness in corticospinal distribution, i.e. shoulder abduction and finger movements, hip flexion

and toe dorsiflexion.
[2] Spastic increase in muscle tone.
[3] Increased stretch reflexes.
[4] Extensor planter response (positive Babinski sign).
[5] Little or no atrophy.

Signs of lesion of the lower motor neuron:
[1] Weakness or paralysis of the involved muscles.
[2] Loss of tone on passive movement (flaccidity).
[3] Absence of reflexes in the involved muscles.
[4] A normal flexor planter response unless the neurons of this reflex are damaged.
[5] Muscle atrophy.
[6] Abnormal electrical excitability of the peripheral nerves and muscle in association with fibrillation and fasciculation of the involved muscles.

Signs of lesion of the extrapyramidal system only (without pyramidal system lesion):
[I] No paralysis of the muscle but rather a slowness of movements in association with changes in facial expression and loss on the opposite side of some stereotyped movements associated with postural adjustment such as swinging the arm when walking.
[2] The muscle tone may be increased or decreased. Hypertonia of extrapyramidal type affects both the gravity and antigravity muscles by the same degree (rigidity).
*[3] The presence of involuntary movements such tremor, choreiform movements, and athetosis.*

The prefrontal cortex (frontal association cortex)

These areas are located in the frontal lobe anterior to the motor regions. The functions of these areas are:

1. To control the types of behavior that should be followed for each social or physical situation.
2. These areas prevent distractibility (inability to concentrate) from a sequence of thoughts.
3. Elaboration of thought, i.e. an increase in depth and abstractness of the different thoughts. Elaboration of thought is important to:
   - A. Prognosticates.
   - B. Plan for the future.
   - C. Delay action in response to incoming sensory signals so that the sensory information can be weighed until the best course of response is decided.
   - D. Consider the consequences of motor action even before these are performed.
   - E. Solve complicated mathematical, legal, or philosophical problems.
   - F. Correlate all avenues of information in diagnosing rare disease.
   - G. Control one's activities in accord with moral laws.
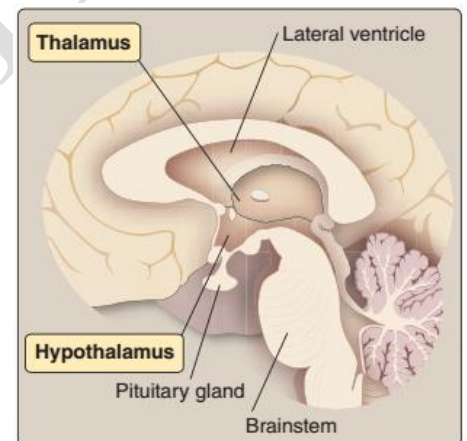
The thalamus

Thalamus is a large ovoid mass of gray matter, situated bilaterally in diencephalon. Various nuclear groups of the thalamus are freely interconnected by short intermediary neurons.

Thalamus receives **afferents** from cortex, subcortical structures, spinal cord. It sends **efferents** to whole cerebral cortex, hypothalamus, basal ganglia, and limbic system. The connecting fibers between the thalamus and the cortex are collectively called **thalamic radiation** that is the collection of nerve

fibers connecting thalamus and cerebral cortex. It contains both **thalamocortical** and **corticothalamic** fibers. All these fibers between thalamus and cerebral cortex pass through internal capsule.

Functions of the thalamus:
Thalamus is primarily concerned with **somatic functions** and it plays little role in the visceral functions. Following are the various functions of thalamus:

1. Anatomical and functional gateway for cerebral cortex: Impulses of almost all the sensations (with the exception of the olfactory system) reach the thalamic nuclei. After being processed in the thalamus, i.e. i.e. integrated and modified, the impulses are carried to specific areas of cerebral cortex through thalamocortical fibers.

2. Center for determining quality of sensations: Thalamus is also the center for determining the quality of sensations, i.e. to recognize the type, location and other details of sensations, and also to determine whether a sensation is pleasant or unpleasant and agreeable or disagreeable. This is done in collaboration with the cerebral cortex, the limbic system and hypothalamus.

3. Role in arousal and alertness reactions: Because of its connections with nuclei of reticular formation, thalamus plays an important role in arousal and alertness reactions. It facilitates the cerebral cortex by raising its excitability up to the level necessary to do all cerebral functions. Without the thalamus, the cerebral cortical functions are markedly depressed.

4. Center for reflex activity: Since the sensory fibers relay here, thalamus forms the center for many reflex activities.

5. Center for integration of motor activity: Through the connections with cerebellum and basal ganglia, thalamus serves a gateway for these structures to the cerebral cortex.

The Limbic System

It is the entire basal system of the brain that mainly controls the person's emotional behavior and drive (instinctual behavior) but also many higher mental functions, such as learning and formation of memories. The limbic system comprises a collection of functionally related structures (shown in figure) that strongly influence autonomic activity via connections to the hypothalamus and reticular formation. The primary structures within the limbic system include the amygdala, hippocampus, hypothalamus, basal ganglia, and cingulate gyrus. **The hypothalamus is a major output pathway of the limbic system and has communicating pathways with all levels of this system**. Hypothalamus and its allied structures send output signals in three directions:

1. Downward to the reticular formation and then to the autonomic nervous system.
2. Upward toward many higher areas of the diencephalon and cerebrum.
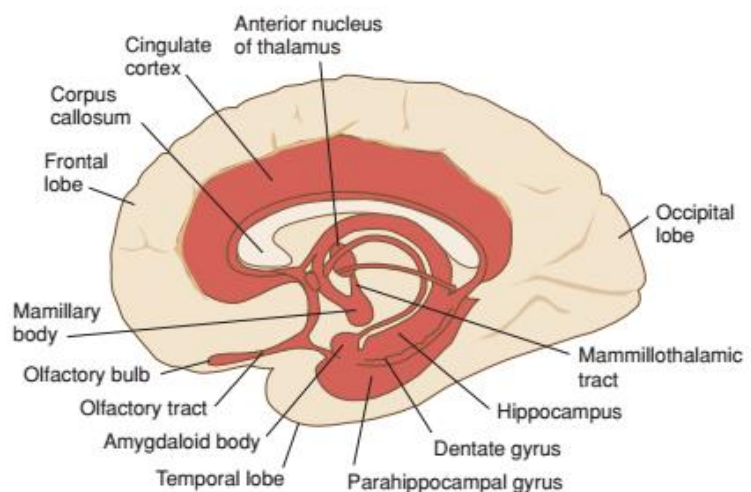
Major anatomic structures forming the limbic system.

Papez circuit
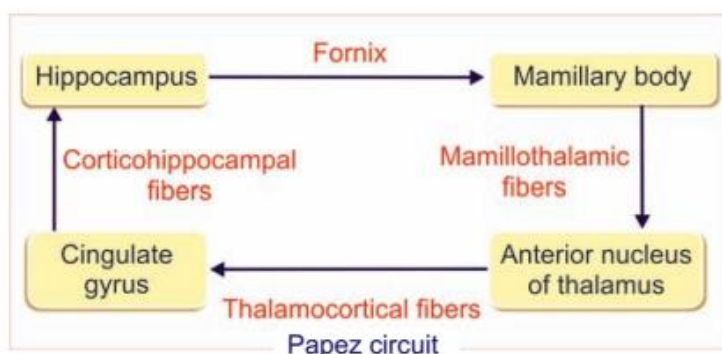
3. To the infundibulum to control most of the secretary functions of pituitary gland.
This system is a functional grouping rather than an anatomical one.

Functions of the limbic system include:
1. The limbic system in humans is a center for basic emotional drives. There are few synaptic connections between the cerebral cortex and the structures of the limbic system especially amygdala (which is the emotion center of the brain), that perhaps helps to explain why we have so little conscious control over our emotions. The cingulate gyrus coordinates smells, sights, and pleasant memories, and induces an emotional reaction to pain, and helps regulate aggressive behavior. There is a closed circuit of information flow between the limbic system and the thalamus and hypothalamus called the **Papez circuit**. In the Papez circuit, a fiber tract, the fornix, connects the hippocampus to the mammillary bodies of the hypothalamus, which in turn project to the anterior nuclei of the thalamus. The thalamic nuclei, in turn, send fibers to the cingulate gyrus, which then completes the circuit by sending fibers to the hippocampus. Through these interconnections, the limbic system and the hypothalamus appear to cooperate in the neural basis of emotional states.
2. Linking the conscious intellectual functions of the cerebral cortex with the unconscious autonomic functions of the brain stem; and
3. Facilitating memory storage and retrieval. The hippocampus plays an essential role in the formation of new memories and recalls the old one. It is extremely sensitive to hypoxia.
4. Motivation: The sensory cortex, motor cortex, and association areas of the cerebral cortex enable you to perform complex tasks, but it is largely the limbic system that makes you want to do them. For this reason, the limbic system is also known as the motivational system.
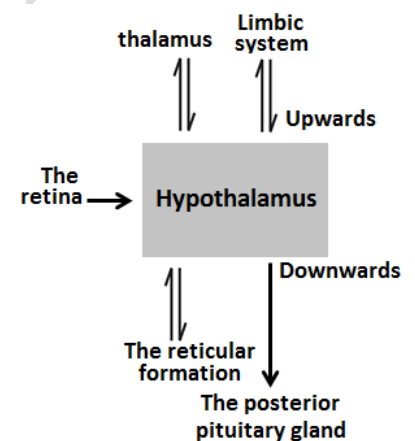
Hypothalamus

The hypothalamus is the part of the diencephalon which forms the floor and part of the lateral wall of the third ventricle. In humans; it is the size of an almond. It is connected to the pituitary gland by the pituitary stalk (hypophysial stalk). The **hypothalamus is a major central component of the limbic system.**

The afferent and efferent connections of hypothalamus are shown in figure. **The main hypothalamic centers are:**

- Sympathetic center
- Endocrinal center
- Food intake center
- Thermoregulation center
- Water balance center
- Salt appetite center
- Biological clock center
- Reward and punishment center
- Fear, Rage, Placidity centers
- Sexual behavior

**Functions of the hypothalamus:**
[I] Autonomic function: The hypothalamus is considered as a "**sympathetic center**" which responds to emotions by generalized sympathetic activation (the alarm response). The sympathetic center includes adrenaline and noradrenalin secretion centers which selectively control the secretion of these

catecholamines from the adrenal medulla in different conditions. Hypothalamus has very limited control over parasympathetic activities. *Autonomic disturbances can be the result of hypothalamic lesion, e.g. Lack of response to emergency situations. Increase or decrease in catecholamine release, excessive sweating, spontaneous vasodilation (hot flushes) or vasoconstriction.*


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[II] Endocrinal function: The hypothalamus controls the secretion of hormones from the anterior and the posterior pituitary glands. Hypothalamus produces **releasing** or **inhibiting hormones**. These hormones stimulate or inhibit the release of hormones from the anterior pituitary gland. The axons of the neurons of the supraoptic nucleus terminate in the median eminence, which is the basal part of the hypothalamus, just behind the optic chiasma. The releasing and inhibiting hormones move inside the hypothalamic neurons by axoplasmic flow to their terminals in the median eminence where they are released. From the median eminence, they reach the anterior pituitary via the blood in the **hypothalamo-hypophysial portal circulation**. The paraventricular nuclei of the hypothalamus are connected to the posterior pituitary through the **hypothalamo-hypophysial tract**. These nuclei synthesize the hormones **oxytocin** and **antidiuretic hormone (ADH).** These hormones flow down in the axoplasm of the neurosecretory cells to the axon terminals in the posterior pituitary where they remain stored in secretary vesicles inside the nerve terminals. The hormones are released on the arrival of the proper nerve signals from the supraoptic and paraventricular nuclei. The hormones then diffuse through the walls of the capillaries of the posterior pituitary into the blood stream.

Hypothalamus also regulates uterine contractility and milk ejection by the breast. The neurons of certain nuclei in hypothalamus secrete **oxytocin** through pituitary gland which causes increased contractility of the uterus and also contraction of the myoepithelial cells that surround the alveoli of the breasts causing the alveoli to empty the milk through the nipples.

[III] Control of food intake: The hypothalamus contains a "**food intake controlling system"** which controls the appetite for food. Food intake controlling system is under the influence of limbic system. In addition, the limbic system determines the type and quality of food that is eaten. Food intake controlling system consists of two centers; an "**appetite** or **feeding center**" which stimulates the appetite, and a "**satiety center**" which inhibits the appetite. The satiety center acts by inhibiting the inherent tonic activity of the feeding center. The damage of the satiety center leads to hyperphagia. Damage to the feeding center leads to severe anorexia which

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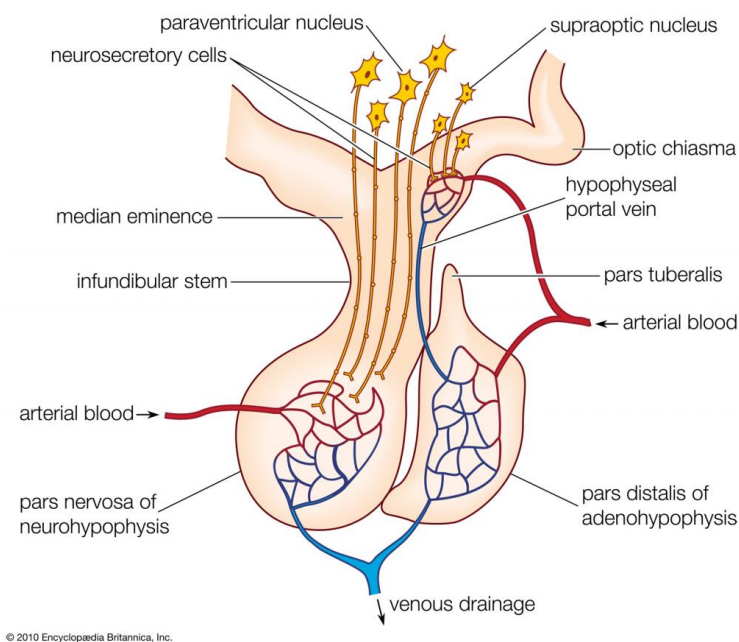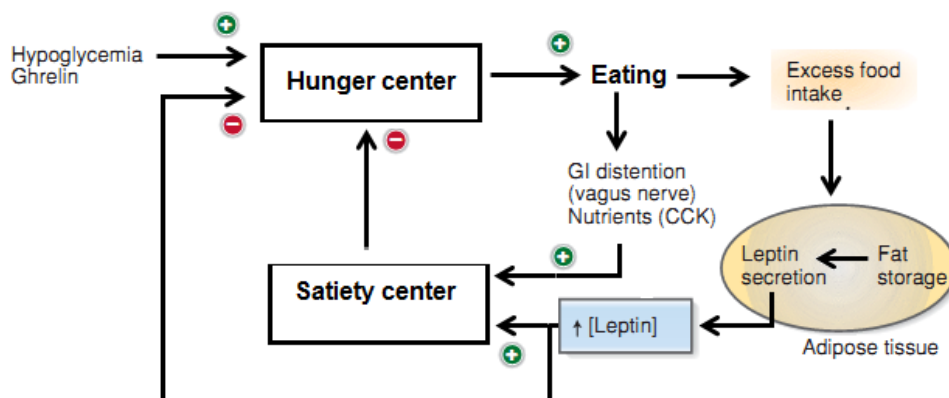
could be fatal. The hypothalamic food intake controlling system is adjusted to a "set point" to maintain a specific body weight for each individual. If a person is starved for some time, then left free to eat afterwards, he eats only enough to restore his pre-starvation weight. Also if a person is overfed for some time and left free to eat afterwards, he eats too little until he regains his previous weight.

The drive to eat is influenced by both short-term factors related to the daily pattern of meals and by long-term factors related to the energy stores in adipose tissue.

- In the short term, hunger is induced by **hypoglycemia** and by the gastrointestinal peptide hormone **ghrelin**. After a meal is consumed, the sensation of satiety is mediated via the **vagus nerve**, due to distention of the stomach and by the release of the gastrointestinal hormone, cholecystokinin.

- The major long-term regulator of eating is **leptin**, a polypeptide hormone released by adipocytes, which stimulates the satiety center and inhibit hunger center, thereby inhibiting eating. Plasma leptin concentration reflects the size of the total body fat store; there is a feedback loop in which high levels of body fat should increase leptin levels and decrease feeding. Patients who are obese are poorly responsive to leptin, which may contribute to the development and maintenance of overeating.

Bilateral destruction of amygdala causes psychic blindness in the choice of foods that the subject eats regarding its type and quality.

Hyperphagia or anorexia can be produced by lesions in the hypothalamic appestat. This leads to either hypothalamic obesity or severe emaciation.

[IV] Thermoregulation: The **hypothalamic thermostat** consists of a "**heat loss center**" in the anterior "hypothalamus and a "**heat gain center**" in the posterior hypothalamus. Both centers are interconnected and work in a reciprocal manner.

- Stimulation of the heat loss center leads to cutaneous vasodilation and profuse sweating. The heat loss center is sensitive to any change in blood temperature (± 0.02°C) which is an indicator of the body core temperature (through central thermoreceptors located in hypothalamus, spinal cord, abdominal organs and other internal location). It responds mainly to any increase in core temperature to prevent hyperthermia.

- Stimulation of the heat gain center leads to cutaneous vasoconstriction, increased muscle tone, shivering and stimulation of catecholamine secretion. The heat gain center responds to input signals coming from cutaneous thermoreceptors which monitor the surface temperature (through skin peripheral thermoreceptors). It responds mainly to cooling of the skin to prevent hypothermia.

Hyperthermia or hypothermia may be produced by lesions in the hypothalamic thermostat.

[V] Control of water balance: Hypothalamus regulates body water by **creating the sensation of thirst through thirst center and conserve water.** Thirst center is found in the lateral hypothalamus. It receives stimulatory input signals from different sources:

1. from osmoreceptors in the hypothalamus, in the liver, and other brain areas located outside
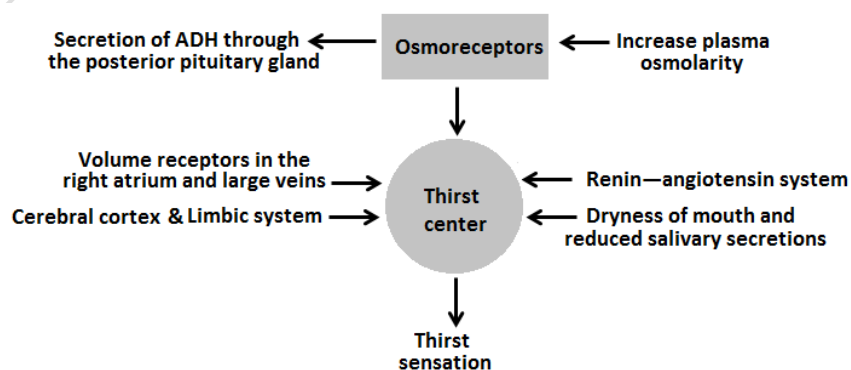
blood-brain barrier. When the electrolytes inside the neurons of this center or in the allied areas of hypothalamus become too concentrated, the subject develops an intense desire to drink water until the

electrolyte concentration of the osmoreceptors neurons return to normal. Therefore, the neurons of this osmoreceptors are stimulated by an increased osmotic pressure of the body fluids to initiate thirst and drinking. In addition, stimulation of the osmoreceptor cells stimulates the **paraventricular nuclei** to secrete **ADH** through the posterior pituitary gland. This hormone is absorbed into the blood and acts on the collecting ducts of the kidneys to cause massive reabsorption of water, thereby decreasing the loss of water into the urine.

      2. **Decrease of the ECF volume:** A decrease in ECF volume also stimulates thirst by a pathway, which is independent of the osmolality of the plasma. The effect of ECF volume depletion on thirst is mediated in part via renin—angiotensin system in which angiotensin II acts on a specialized receptor area in hypothalamus to stimulate the neural areas concerned with thirst.

      3. from the limbic system and cerebral cortex. Psychic and emotional stimuli can produce or modify thirst sensation.

      4. from the mouth and pharynx such as dryness of mouth and reduced salivary secretions: These are the most common signals. For example, eating a very dry food produces the desire to drink water because salivary secretion is not adequate to keep the mouth moist.

[VI] Control of salt appetite: There is a "salt appetite center" in the anterior hypothalamus very close to the osmoreceptors. Its cells are sensitive to changes in plasma osmolality, as well as the level of sodium in the plasma (osmosodium receptors). They are stimulated by hyponatremia, hypotonicity or hypovolemia to increase the appetite for salt (craving for salt).

[VII] Control of cyclical phenomena (biological clock) by suprachiasmatic nucleus: Circadian rhythm occurs in more than 100 parameters of human organs and functions. E.g. body temperature is lowest in the early morning and highest in the evening, so is the heart rate. Corticotropin-releasing hormone (CRH), Adrenocorticotropic hormone (ACTH) and cortisol secretions are highest at 8 AM and lowest at midnight. Melatonin secretion from the pineal gland is increased by night a suprachiasmatic nucleus and decreases in daylight. Darkness probably stimulates melatonin secretion by the pineal gland, which inhibits the secretion of gonadotropic hormones from the anterior pituitary, and thus reduces sexual drive. The menstrual cycle in adult females is an example of a physiological monthly rhythm. Whenever body is exposed to a new pattern of daylight or darkness rhythm, the biological clock is reset, provided the new pattern is regular. Accordingly, the circadian rhythm also changes. The pacemaker of the circadian rhythm is found in the **suprachiasmatic nucleus** of hypothalamus which plays an important role in setting the biological clock by its connection with retina via retino-hypothalamic fibers. Through the efferent fibers, it sends circadian signals to different hypothalamic nuclei, the pineal gland, and the reticular formation to maintain the circadian rhythm of sleep, hormonal secretion, thirst, hunger, appetite, etc.

      Disruption to rhythms usually has a negative effect in the short term. Many travelers have experienced the condition known as jet lag, with its associated symptoms of fatigue, disorientation and insomnia.

[VIII] Role in learning and memory: The hypothalamus contains a **reward center**. When stimulated, it gives a sense of reward; i.e. relaxation, pleasure and satisfaction. In addition, there is a **punishment center**, when stimulated it gives a sense of punishment; displeasure fear and terror. Less potent reward and punishment centers are found in the amygdala, the hippocampus and other areas of the brain. These centers constitute important components of the reward and punishment systems which are very important for emotions, motivation, memory and learning. To keep any experience in the long term memory, it needs either of two mechanisms; to stimulate the reward and punishment system or to be practiced repeatedly. Otherwise, the experience is easily forgotten and will not add to the memory

stores of the individual. The hypothalamus is also a relay station in the neuronal circuit which is concerned with short term memory.

Disturbances in memory and learning ability can be the result of hypothalamic lesion. This is due to interruption of the limbic system which is concerned with short term memory. Lesions in the punishment or reward centers depress the ability to develop long term memory for important events.

[IX] Control of motor responses to emotions: The motor responses to emotions are controlled by complex mechanisms that involve the hypothalamus, amygdala, and association areas of the limbic system.

➔ Amygdala is located in the temporal lobe.

➔Within the hypothalamus, fear center, rages area, placidity area are located.

Stimulation or damage of some hypothalamic areas produces certain emotions with specific motor responses as follows:

Fear: Fear is an unpleasant emotional state which involves a sense of insecurity because of impending danger or evil. It is produced by stimulation of the **fear center** in the hypothalamus. Reactions to fear include cowering, avoidance, and sweating, pupillary dilation, turning the head from side to side to seek escape and flee. **Amygdaloid nuclei** in the temporal lobes activate the fear center in the hypothalamus. Bilateral temporal lobectomy abolishes fear sensation. In this case, the subject cannot evaluate dangers and proceeds towards them without precautions; e.g. handling dangerous animals as scorpions or snakes, or crossing roads full of rapidly going vehicles.

Rage: Rage is violent anger. It is produced by stimulation of a certain area of the lateral hypothalamus (**rage area**). This area is **tonically** inhibited by the **placidity area** of the hypothalamus, and the **limbic system**. Lesions in the placidity area or the limbic association area produce rage. Reactions in rage include taking the attack position, generalized sympathetic stimulation and fighting. In cats there is hissing, spitting, growling and well directed biting and clawing.

Placidity: Placidity means calmness with little or no response to provocation. It is produced by stimulation of the placidity area of the hypothalamus. The amygdaloid nuclei facilitate the rage area and inhibit the placidity area. Bilateral amygdaloid lesions would then inhibit the rage area and facilitate the placidity area. If the placidity area is subsequently damaged, placidity changes into rage because the rage area would be released from the inhibitory influence of the placidity area. Bilateral destruction of the amygdaloid nuclei was made in Japan on agitated, violent, aggressive mental patients. The patients turned placid and manageable, without any sign of hypersexuality.

Emotional disturbances can be the result of hypothalamic lesion, e.g. fear, rage, or placidity due to irritation or damage of different hypothalamic regions.

[X] Sexual behavior: Libido and sexual activity is mainly under the control of the **cerebral cortex** and **limbic system** which are sensitive to sex hormones. However, hypothalamus is involved in the following way:

1. The hypophysiotropic area controls the release of the pituitary gonadotropins, which in turn control the release of sex hormones from the gonads.
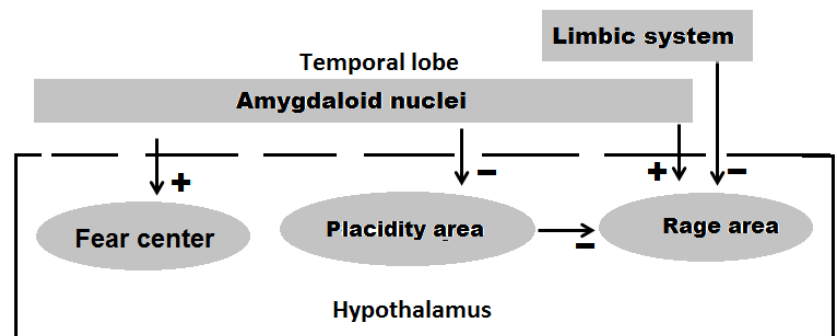
2. The anterior hypothalamus in the female contains estrogen sensitive neurons. When stimulated, these neurons increase the sexual desire and initiate the heat of sexual behavior. The female seeks out the male (the enticement reaction). Lesions in this area abolish this behavior.

3. Stimulation of parts of the lateral hypothalamus produces sexual excitement and penile erection in male monkeys.

In humans, the sexual functions have become extensively encephalized and conditioned by social and psychic factors. However, hormones play small role in the sexual behavior in humans (for example testosterone and estrogen increase libido, i.e. sexual interest and drive, in males). This is because of the greater degree of encephalization of sexual functions in humans.

Specific Functions of Other Parts of the Limbic System

Functions of the Hippocampus: It has numerous but mainly indirect connections with many portions of the cerebral cortex, as well as with the basal structures of the limbic system—the amygdala, hypothalamus, septum, and mamillary bodies. Almost any type of sensory experience causes activation of at least some part of the hippocampus, and the hippocampus in turn distributes many outgoing signals to the anterior thalamus, hypothalamus, and other parts of the limbic system, especially through the fornix, a major communicating pathway. Thus, the hippocampus is an additional channel through which incoming sensory signals can initiate behavioral reactions for different purposes. As in other limbic structures, stimulation of different areas in the hippocampus can cause almost any of the different behavioral patterns such as pleasure, rage, passivity, or excess sex drive. Another feature of the hippocampus is that it can become hyper-excitable. For instance, weak electrical stimuli can cause focal epileptic seizures in small areas of the hippocampi. These often persist for many seconds after the stimulation is over, suggesting that the hippocampi can perhaps give off prolonged output signals even under normal functioning conditions. During hippocampal seizures, the person experiences various psychomotor effects, including olfactory, visual, auditory, tactile, and other types of hallucinations that cannot be suppressed as long as the seizure persists, even though the person has not lost consciousness and knows these hallucinations to be unreal. Probably one of the reasons for this hyper-excitability of the hippocampi is that they have a different type of cortex from that elsewhere in the cerebrum, with only three nerve cell layers in some of its areas instead of the six layers found elsewhere.

The theoretical function of the hippocampus in learning: The hippocampus originated as part of the olfactory cortex. In many lower animals, this cortex plays essential roles in determining whether the animal will eat a particular food, whether the smell of a particular object suggests danger, or whether the odor is sexually inviting, thus making decisions that are of life-or-death importance. Very early in evolutionary development of the brain, the hippocampus presumably became a critical decision-making neuronal mechanism, determining the importance of the incoming sensory signals. Once this critical decision making capability had been established, presumably the remainder of the brain also began to call on the hippocampus for decision making. Therefore, if the hippocampus signals that a neuronal input is important, the information is likely to be committed to memory. It has been suggested that the hippocampus provides the drive that causes translation of short-term memory into long-term memory—that is, the hippocampus transmits some signal or signals that seem to make the mind *rehearse over and over* the new information until permanent storage takes place. Whatever the mechanism, without the hippocampi, *consolidation* of long-term memories of the verbal or symbolic thinking type is poor or does not take place.

Functions of the Amygdala: The amygdala has abundant bidirectional connections with the hypothalamus, as well as with other areas of the limbic system. In lower animals, the amygdala is concerned to a great extent with olfactory stimuli and their interrelations with the limbic brain. The amygdala receives neuronal signals from all portions of the limbic cortex, as well as from the neocortex

of the temporal, parietal, and occipital lobes—especially from the auditory and visual association areas. Because of these multiple connections, the amygdala has been called the "window" through which the limbic system sees the place of the person in the world. In turn, the amygdala transmits signals (1) back into these same cortical areas, (2) into the hippocampus, (3) into the septum, (4) into the thalamus, and (5) especially into the hypothalamus.
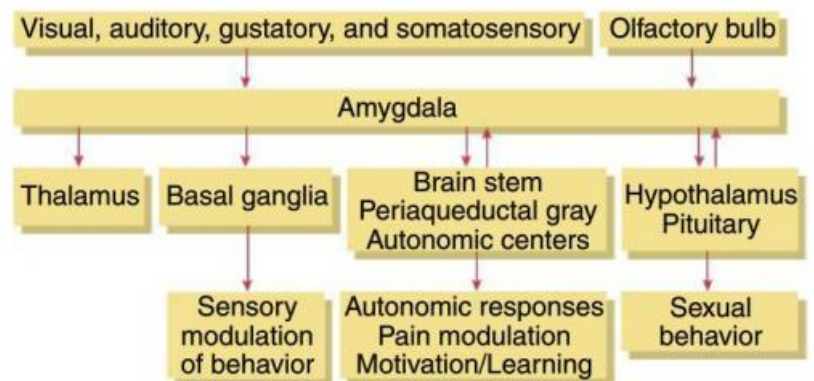

Figure: Amygdala connections and functions.

Effects of stimulating the Amygdala:

A. In general, stimulation in the amygdala can cause almost all the same effects as those elicited by direct stimulation of the hypothalamus, plus other effects. Effects initiated from the amygdala and then sent through the hypothalamus include:

- Increases or decreases in arterial pressure;
- Increases or decreases in heart rate;
- Increases or decreases in gastrointestinal motility and secretion;
- Defecation or micturition;
- Pupillary dilation or, rarely, constriction;
- Pilo-erection; and
- Secretion of various anterior pituitary hormones, especially the gonadotropins and adrenocorticotropic hormone.

B. Aside from these effects mediated through the hypothalamus, amygdala stimulation can also cause several types of involuntary movement. These include:

- Tonic movements, such as raising the head or bending the body;
- Circling movements;
- Occasionally clonic, rhythmical movements; and
- Different types of movements associated with olfaction and eating, such as licking, chewing, and swallowing.

C. In addition, stimulation of certain amygdaloid nuclei can cause a pattern of rage, escape, punishment, severe pain, and fear similar to the rage pattern elicited from the hypothalamus, as described earlier.

D. Stimulation of other amygdaloid nuclei can give reactions of reward and pleasure.

E. Finally, excitation of still other portions of the amygdala can cause sexual activities that include erection, copulatory movements, ejaculation, ovulation, uterine activity, and premature labor.

Effects of bilateral ablation of the amygdala— the Klüver-Bucy Syndrome: When the anterior parts of both temporal lobes are destroyed in a monkey, this removes not only portions of temporal cortex but also of the amygdalas that lie inside these parts of the temporal lobes. This causes changes in behavior called the Klüver-Bucy syndrome, which is demonstrated by an animal that (1) is not afraid of anything, (2) has extreme curiosity about everything, (3) forgets rapidly, (4) has a tendency to place everything in its mouth and sometimes even tries to eat solid objects, and (5) often has a sex drive so strong that it attempts to copulate with immature animals, animals of the wrong sex, or even animals of a different species. Although similar lesions in human beings are rare, afflicted people respond in a manner not too different from that of the monkey.

<u>Overall Function of the Amygdalas:</u> The amygdalas seem to be behavioral awareness areas that operate at a semiconscious level. They also seem to project into the limbic system one's current status in relation to both surroundings and thoughts. On the basis of this information, the amygdala is believed to make the person's behavioral response appropriate for each occasion. Figure summarizes some of these roles of the amygdala.

Higher functions of cortex

This section concerns such brain functions as **sleep**, **memory**, **cognition**, **emotion**, **learning** and **language**. These are associated especially with the cerebral cortex, but not exclusively; they involve interactions between the cerebral cortex and such areas as the cerebellum, basal nuclei, limbic system, hypothalamus, and reticular formation.

Emotion

Feelings and our emotional memories form in the **hypothalamus** and **amygdala**. The **prefrontal cortex** is the seat of <u>judgment</u>, <u>intent</u>, and <u>control over the expression of our emotions</u>. **It is by prefrontal cortex that we decide the appropriate way to show our feelings.**

The **amygdala** also seems to be involved in a broad range of functions including many important aspects of personality which depend on an intact, functional amygdala and hypothalamus. When specific regions of the amygdala or hypothalamus are destroyed or artificially stimulated, humans and other animals exhibit blunted or exaggerated expressions of anger, fear, aggression, self-defense, pleasure, pain, love, sexuality, and parental affection, as well.

The psychosomatic effects of the behavioral system: Abnormal function of the CNS can frequently lead to serious dysfunction of the different somatic organs of the body. The mechanisms by which stimulatory affects in the brain can affect the peripheral organs occur through three routes:
1. through the motor nerves to the skeletal muscles throughout the body.
2. through the autonomic nerves to the different internal organs of the body.
3. through the hormones secreted by the pituitary gland in response to nervous activity in the hypothalamus.

The memory

It is the capacity of the brain to store what is learned, and subsequently recalls information. The storage capacity of the human brain is limited. So, the information that flow into the brain is classified. The most important ones (less than 1%) are selected and stored, but all the rest are neglected and forgotten. Physiologically, <u>memories are caused by the formation of</u> **memory traces.** <u>Memory traces are new pathways or facilitated pathways (which are changes in the capability of synaptic transmission of signals from one neuron to the next through the neural circuit of the brain as a result of previous neural activity)</u>. In other words, synapses are not fixed for life; in response to experience, they can be added, taken away, or modified to make transmission easier or harder. This ability of synapses to change is called **synaptic plasticity**. These changes are mainly located in the cerebral cortex. These facilitated or new pathways once they established, the thinking could activate them to reproduce the memories. All degree of memory occur, some memories lasting a few sec and others lasting up to years. A basic and generally accepted classification of memory is based on the duration of memory retention, and identifies four distinct types of memory:
1. Sensory memory (immediate memory).
2. Short-term memory.
3. Intermediate-term memory.
4. Long-term memory.

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1. Sensory memory: It is the ability to retain sensory signals in the sensory areas of the brain for a **very short interval of time** (a sec or less) following the actual sensory experience and replaced by new sensory signals in less than one sec. During this time it can be used for further processing. Accumulation of Ca^{2+} in the presynaptic terminals with each signal possibly causes prolonged release of neurotransmitter at the synapse (**presynaptic potentiation**).

2. Short-term memory (STM or, primary memory) (or working memory): It is the memory of facts, words, numbers, letters, or other information for a **few sec to a few minutes at a time** but lasting only as long as the person continues to think about the numbers or facts. For instance, one can memorize the digits of a telephone number for a short period of time after looking up the number in the telephone directory. One of the most important characteristics of primary memory is that the information in this memory store is instantaneously available so that the person does not have to search through his or her mind for it as one does for information that has been put away in the secondary memory stores, However, new bits of information are replaced the old one. STM serves as a sort of temporary holding bin for data that we may or may not want to retain. Short-term memory involves synaptic changes. The possible mechanisms for primary memory are:
- **Reverberating circuit theory**.
- **Presynaptic facilitation or inhibition.**

3. Intermediate-term memory, that last for many **minutes** or even **weeks**. They will eventually be lost unless the memory traces are activated enough to become more permanent; then they are classified as long-term memories. One of its characteristics is that one must search through the memory stores for seconds to minutes before it is possible to recall the memory. The possible mechanism for such memory is **chemical changes in the presynaptic terminal** or **the postsynaptic membrane** (post-tetanic potentiation) causing the memory paths to become facilitated for days or weeks thereafter.

4. Long-term memory that lasts for **years**. The secondary long-term memory is the storage in the brain of highly overlearned information as one's own name and address. The information transformation from the intermediate-term memory to long-term memory is enhanced by the following factors:
- **Excitation, stimulation of the reward or punishment systems.** We learn best when we are alert, motivated, surprised, and aroused. For example, when we witness shocking events, consolidation is almost immediate. Norepinephrine, a neurotransmitter involved in memory processing of emotionally charged events, is released when we are excited which helps to explain this phenomenon. In addition, we remember and learn best when the event induces a reward or punishment response rather than indifference.
- **Repeated practice or rehearsal of the experience.** Rehearsal or repetition of the material
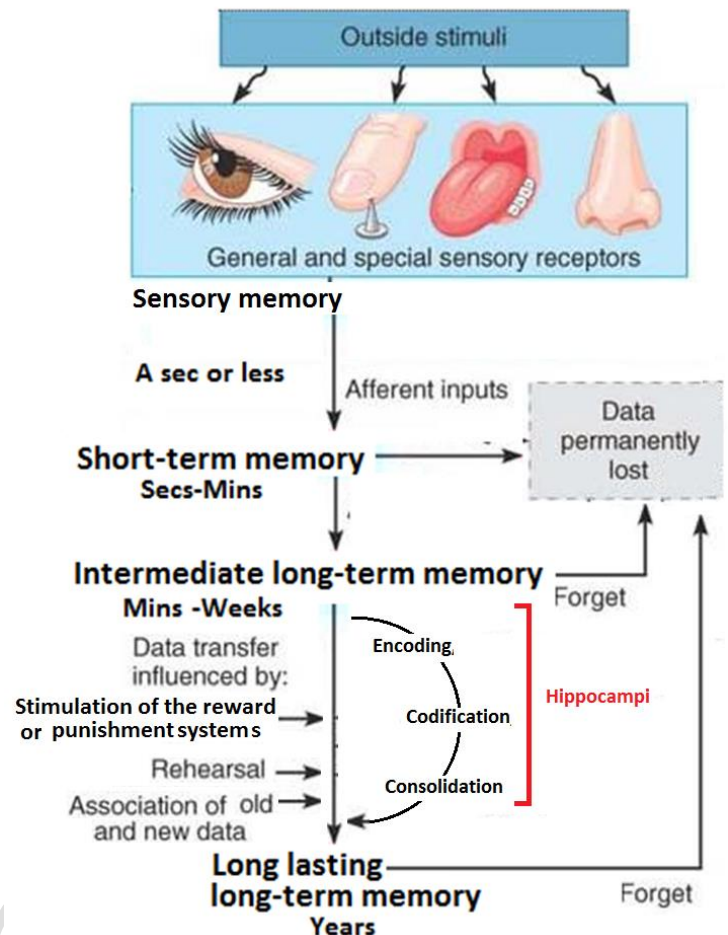
enhances memory. Rehearsal of the same information again and again accelerates and potentiates the process of consolidation of STM into LTM.

- **Association of old and new data.** Tying "new" information to "old" information already stored in LTM appears to be important in remembering facts. In order to encode incoming information, or an event, into long-term memory, the best way to do this is to link, associate or connect the incoming information with something already in your memory in order to make it meaningful. You can retrieve the memory, because you have an actual means to recall it, due to associating, linking or connecting the incoming information with something already in your memory.

This memory is difficult to disrupt, and it is seldom affected in retrograde amnesia. Information in the long-term memory comes from the intermediate-term memory by years of practice, which strongly consolidates the memory. The stored information in the long-term memory remains available for retrieval even if information in other memories is erased by brain injury or disease. This is because information in the long-term memory occupies large areas of the brain and more than one "copy" of the information is stored in different regions of the brain. The access to the long-term memory is very rapid, e.g. one immediately remembers his name if he is asked about it.

The possible mechanism for such memory is **anatomical or physical changes in the synapses** causes fixation of memories in the brain, such changes perhaps changes in numbers of presynaptic terminals, perhaps in sizes of the terminals, or perhaps in the sizes of the dendrites. Such anatomical changes could allow signals to pass through the circuits with more ease the more often the memory trace is used. The cellular mechanism of long-term memory is **activation of genes** that lead to synthesis of specific proteins that remain in the cell nucleus and permanently enhance synaptic transmission.

Stages in the formation and retrieval of memory: The main stages in the **memory formation** (Encoding, codified, and consolidate) achieved by the activity of hippocampus (involved in learning and formation of recent memory and **retrieval of memory** are:

A. Encoding: When information comes into our memory system (from sensory input), it needs to be changed into a form that the system can cope with, so that it can be stored. Think of this as similar to pressing of letter "A" on a keyboard of a computer, this letter will be transformed (changed, or encoded) to a different format (binary code, i.e. series of zeros and ones) in the computer memory (RAM of the computer). The sensory information, visual (picture), acoustic (sound), and semantic (meaning) can be stored if they are changed (encoded) into different formats. You can think of the process of storing memories in your mind to be similar to that of a computer that utilizes RAM (Random Access Memory) for the temporary storage of information before being placed in long-term storage on the hard drive.

B. Codification: Again, think of this as similar to computer, if you want to save file, the computer will ask you to name the file (**codified**, in English means arrange [laws or rules] into a systematic code) and the site to save this file, and normally you **save the file into a folder in direct association with other memories of the same type of information** (in computer`s term as if storing different files according to their types).

C. Storage or **consolidation** of memory (creation of a permanent record of the encoded information): It is something like the "Paste" function in computer`s term. The computer term "Paste" is analogue to "consolidation" in memory language. For the short-term memory to be converted into intermediate and long-term memory it must become **consolidated**, i.e. the synapses must become permanently facilitated. Therefore, the process of memory consolidation apparently involves fitting new facts into the various categories of knowledge already stored in the cerebral cortex. The process of consolidation requires 5-10 minutes for minimal consolidation and an hour or more for maximal consolidation.

C. Retrieval calling back the stored information in response to some cue for use in some process or activity.

Brain areas such as the **mammillary bodies, the amygdala, temporal lobes**, **thalamus**, and

hippocampus are thought to be involved in memory. It has been demonstrated that damage to these structures can result in impaired performance on certain memory tasks. In contrast to the rest of the brain, new neurons are produced in the hippocampus throughout life. They arise from a pool of stem cells in brain, and newly-formed neurons are particularly sensitive to the induction of LTP.

Hippocampi and **amygdala** are responsible for the establishment of the long-term memory. Patients with bilateral hippocampal damage are unable to establish new long-term memories of those types of information (verbal and symbolic types) that are the basis of intelligence. This is called **anterograde amnesia**. Damage to the hippocampus and surrounding medial temporal lobe structures on either side may result in only slight memory loss.

Thalamic nuclei and parts of the **parahippocampal gyrus** play a role in helping the person to search the memory storehouse and thus be able to read out the memories. Therefore, lesions in these parts of the brain result in inability of the patient to recall memories from the past, which is from the long-term memory storage bins, even though the memories are known to be still there. This condition is called **retrograde amnesia**. In this condition, the degree of amnesia for recent events is likely to be much greater than for events of the distant past. The reason for this difference is probably that the distant memories have been rehearsed so many times that elements of these memories are stored in widespread areas of the brain.

People with hippocampal lesions usually do not have difficulty in learning physical skills that do not involve verbalization or symbolic types of intelligence.

There are two forms of long-term memory:
A. Explicit or declarative and procedural: It is the retention of events and facts that you can put into words—numbers, names, dates, and so forth. It is about 'what/where/when/why', i.e. facts and events. Explicit memory can be expressed, or declared, as a statement, such as 'India achieved independence on 15 August 1947'. The distinction is important because in patients having bilateral lesions of the temporal lobe, only explicit memory is lost. Implicit memory largely depends on subcortical structures.

B. Implicit (or non-declarative) or procedural memory: It is the retention of motor skills—how to tie your shoes, play a musical instrument, or type on a keyboard. These forms of memory involve different regions of the brain but are probably similar at the cellular level. Implicit memory largely depends on subcortical structures.   Implicit (or non-declarative) memory is about 'how to', i.e. perceptual and motor skills, e.g. cycling, swimming, or solving a puzzle. Implicit memory largely depends on subcortical structures.   There are three types of non-declarative memory:
■ The ability to learn a skill or procedure (e.g., riding a bicycle) is called procedural memory.
■ The ability to form emotional associations in the memory is called learned emotion.
■ Conditioned reflexes are a simple form of memory; for example, the habit of hearing a lunchtime alarm at school may be sufficient to induce reflex gastrointestinal activity after a period of regular conditioning that relates the sound of the alarm to eating.

Clinical application:
Alzheimer disease (AD) may begin before the age of 50 with symptoms so slight and ambiguous that early diagnosis is difficult. One of its first symptoms is memory loss, especially for recent events. A person with AD may ask the same questions repeatedly, show a reduced attention span, and become disoriented and lost in previously familiar places. Family members often feel helpless and confused as they watch their loved one's personality gradually deteriorate beyond recognition. The AD patient may become moody, confused, paranoid, combative, or hallucinatory—he or she may ask irrational questions such as, why is the room full of snakes? The patient may eventually lose even the ability to read, write, talk, walk, and eat. Death ensues from pneumonia or other complications of confinement and immobility. Diagnosis of AD is confirmed on autopsy. There is atrophy of some of the gyri (folds) of the

cerebral cortex and the hippocampus, an important center of memory. Nerve cells exhibit neurofibrillary tangles—dense masses of broken and twisted cytoskeleton. In the intercellular spaces, there are senile plaques consisting of aggregations of cells, altered nerve fibers, and a core of "amyloid protein" the breakdown product of a glycoprotein of plasma membranes.

Language and Speech

It is important to note that the left hemisphere is usually dominant with respect to language, even in left-handed people. Therefore, this hemisphere is called **"speech-dominant"** or the **"categorical"** hemisphere. It takes important decisions and issues orders for actions by the body. **In most people, the left hemisphere has a more control over language, math, and logic. While the right hemisphere is geared towards musical, artistic and other creative endeavors** but with much less role in making decisions or issuing of orders and called the **"nonspeech-dominant"** or the **"representational"** hemisphere. Non-language-dominant hemisphere is involved in "body language"—the nonverbal emotional (affective) components of language. These areas allow the rhythm or tone of our voice and our gestures to express our emotions when we speak, and permit us to comprehend the emotional content of what we hear. For example, a soft, melodious response to your question conveys quite a different meaning than a sharp reply.

The development of the faculty of speech depends first on the ability to hear spoken words. A young baby starts first to learn the meaning of the heard words then tries to imitate them by vocalization (uttering simple sounds) then by verbalization (uttering words). So, speech is learned basically through hearing. If a person is born deaf, he cannot develop the faculty of speech and is destined to be dump. Perception of spoken words is the function of the primary auditory sensory area in the temporal lobe at the floor of the lateral sulcus. Signals are then conveyed to the adjacent auditory sensory association area. This area understands the meaning of the heard words. It feeds the message of the heard words to the Wernicke's area which correlates them with other related items stored in memory in the process of thinking.

Written words are perceived by the primary visual sensory area in the occipital lobe. The signals are then conveyed to the visual sensory association area which understands the meaning of words. The message is then fed to the Wernicke's area which correlates them with other related items stored in memory in the process of thinking.

Wernicke's area is found in the posterior part of the superior temporal gyrus. It receives input signals from the sensory association areas. It is the memory store tor language. It decides what words are suitable and in what sequence to express a certain idea. Wernicke's area is very well developed in the categorical but not in the representational hemisphere. It is connected with **Broca's area** (word formation center) in the premotor cortex via the "arcuate fasciculus.

Broca's area is in the prefrontal association cortex. It stores the motor programs for different words. When it is activated, it stimulates the motor cortex at certain pattern to produce words by coordinated contractions of the respiratory, laryngeal, pharyngeal, lingual and labial muscles. A fiber tract, the **arcuate fasciculus**, connects Wernicke's area with Broca's area to coordinate aspects of understanding and executing speech and language skills.

Area for hand skills within the premotor cortex stores the motor programs for writing of words or drawing of figures by the muscles of the hand. It receives input signals from Wernicke's area via the arcuate fasciculus.

Clinical evidence indicates that Wernicke's area is essential for the comprehension, recognition, and construction of words and language, whereas Broca's area is essential for the mechanical production of speech. Patients with a defect in Broca's area show evidence of comprehending a spoken or written word but they are not able to say the word. In contrast, patients with damage in Wernicke's area can produce speech, but the words they put together have little meaning.

The mechanism of speech: Speech passes by four steps to occur:

1. Formation of thoughts and ideas that will be expressed in speech: This is the function of the visual, auditory, and other sensory areas.

2. Choice of suitable sentences and phrases to express the ideas: This is the function of Wernicke's area and sends output signals to Broca's area.

3. Word formation: This is the function of Broca's area which receives input signals from Wernicke's area and sends programmed impulses to the primary motor cortex to move the muscles of speech in a specific sequence to produce different words.

4. Verbalization: It is the coordinated contraction of muscles of speech in a certain sequence to produce spoken words. This is the function of the motor cortex, the motor nerves and the muscles of speech. Ideas may be expressed in writing. In this case, Wernicke's area feeds the signals to area for hand skills to write the desired words.

Both hemispheres intercommunicate with each other via fiber pathways in the corpus callosum and the anterior commissure. This communication prevents interference between the functions of the two sides of the brain. The Wernicke's area in non-dominant hemisphere is important for understanding and interpreting music, nonverbal visual experiences, spatial relationships between the person and the surroundings, communicating the emotions involved with language and some other types of intelligence.
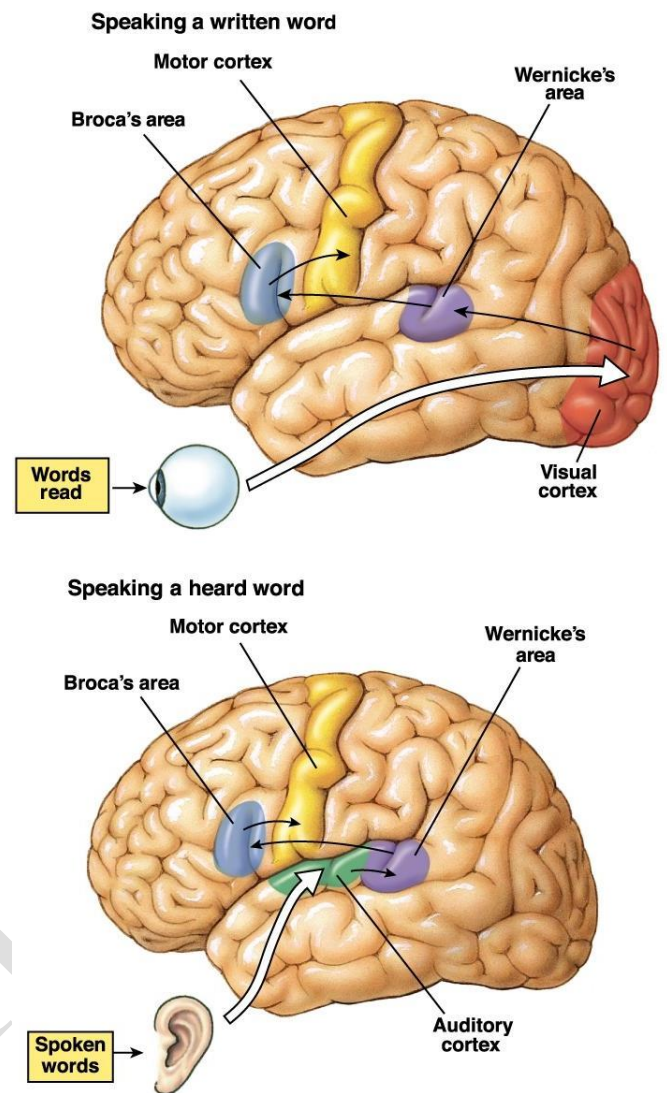
Brain waves

Electrical recording from the outer surface of the head demonstrates continuous electrical activity in the brain that transfer to the surface of the scalp. EEG waves consist of alternating excitatory and inhibitory synaptic potentials in the pyramidal cells of the cerebral cortex. These electrical activities are determined mainly by the activity of RAS and other brain structures. These waves are called brain waves and the record is called an electroencephalogram (EEG). The character of the waves is highly dependent on the degree of activity of the cerebral cortex, and the waves change markedly between the state of wakefulness and sleep and coma. The waves can be classified as:

1. alpha waves (α): They occur at frequency between 8-13/sec and their voltage usually is about 50 microvolts and are found in EEGs of almost all normal adult persons when they are awake in a quiet resting state of cerebration with closed eyes and occur most intensely in the occipital region but also be recorded at times from the parietal and frontal regions of the scalp. It is assumed that the alpha waves result from spontaneous activity of the thalamocortical system and possibly including the RAS pathways. The frequency of alpha rhythm is decreased by:

- Low blood glucose,
- Low body temperature,
- Low level of adrenal glucocorticoid hormones,
- High arterial partial pressure of CO_2.

It is increased by the reverse conditions. When the eyes are opened or when conscious mental activity is initiated, the alpha rhythm is replaced by fast, irregular low voltage activity with no dominant frequency (beta rhythm). This phenomenon is called alpha block.

2. Beta waves (β): They occur at frequency of more than 14-25 cycles/sec and rarely 50 cycles/sec. These are most frequently recorded from the parietal and frontal regions of the scalp. Most beta waves appear during activation of the CNS when the awake person's attention is directed to some specific type of mental activity i.e. during alert wakefulness or open the eyes in bright light.

3. Theta waves (τ): They have frequency of between 4-7 cycles/sec. These occur mainly in the parietal and temporal regions in children, but they also occur during emotional stress in some adults, particularly during disappointment and frustration. These same waves also occur in many brain disorders.

4. Delta waves (δ): They are very large waves include all the waves below 3.5 cycles/sec. These occur in infancy, in deep sleep (slow wave sleep), and in serious organic brain disease. These waves can occur strictly in cortex independent of activities in lower regions of the brain.

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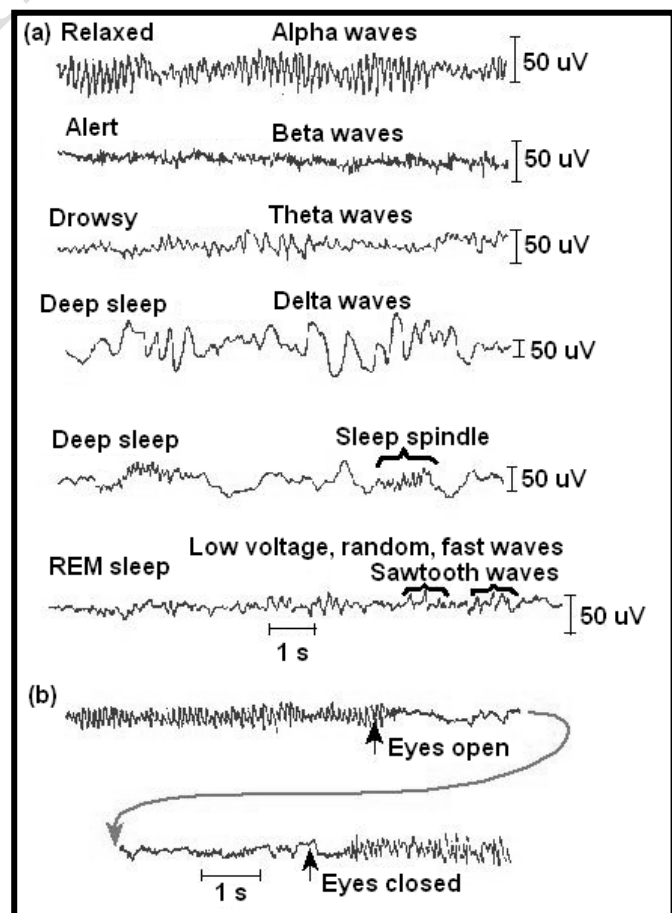
Sleep

It is defined as a state of unconsciousness from which a person can be aroused by appropriate sensory or other stimuli. Waking and sleeping periods follow each other in a circadian rhythm (i.e. 24 hr rhythm) which is synchronized with the daily light-dark cycle. This synchronization is the function of the suprachiasmatic nucleus of the hypothalamus which receives collateral from the visual pathway. Physical and psychological factors affect the onset and duration of sleep. E.g. cold and fear prevent the onset of sleep, whilst fatigue and boredom facilitate its onset. During each night a person goes through stages of two different types of sleep that alternate with each other. These are called:

1. **Slow wave sleep:** In which the brain waves are very slow. This type of sleep forms about 75% of sleep time during each night which is restful type of sleep that the person experience during the first hour of sleep and after having been kept awake for many hours. Slow wave sleep is generally divided into four stages (1, 2, 3, and 4). During stage 1 and 2, the person is in light sleep; stages 3 and 4 are stages of deep sleep. Stage 4 is the phase of typical delta rhythm. Since the frequency of EEG waves during stage 3 and 4 is low, this phase is known as slow wave sleep. In this type of sleep the voltage of the EEG waves become very low of **delta wave** but this is broken by **sleep spindles** (which are short spindle-shaped bursts of alpha waves that occur periodically). In stages 2, 3, and 4 of slow wave sleep, the frequency of the EEG waves becomes progressively slower and end with delta type waves. Episodes of sleepwalking are more common in children than in adults and occur predominantly in males. They may last several minutes. Sleepwalkers walk with their eyes open and avoid obstacles, but when awakened they cannot recall the episodes.

2. **Rapid eye movement sleep (REM, desynchronized sleep or paradoxical sleep):** In which the eyes undergo rapid movements despite the fact the person is still asleep. This type of sleep occurs in form of periodical episodes and occupy about 25% of the sleep time of the young adult (80% in premature infants, 50% in full-term neonates), and recur about every 90 minutes and lasts 5-30 min. The first such period is occurring about 90 min after the person falls asleep. It is not so restful and it is usually associated with remembered dreaming. In REM sleep, the EEG suddenly changes back to the characteristics of the early stages of wakefulness (**beta waves**) indicating a high level of activity in the brain during this period of sleep. When the person is extremely tired, the duration of each bout of REM sleep is very short and it may even be absent, On the other hand, as the person becomes more rested through the night, the duration of the REM bouts greatly increases.

It has been postulated that stimulation of norepinephrine-secreting nerve fibers of the locus ceruleus can activate large acetylcholine-secreting neurons in the RAS might in turn activate many portions of the brain which cause the excess activity of these regions that associated with this type of sleep. However, these signals are not channeled appropriately in the brain to cause normal conscious awareness that is characteristic of wakefulness.

Function and importance of sleep: The need for sleep is evident. However, it is not known how sleep provides a daily rejuvenation and revitalization of body functions and renewal of wellbeing. Slow-wave sleep appears to be the restorative stage. It assists in regulation of body repair. During sleep there is:

- A decrease in peripheral vascular tone, hear rate and consequently blood pressure,
- A decrease in vegetative functions of the body,
- A decrease in respiratory rate, and
- A decrease in basal metabolic rate and glucose consumption,
- Temperature regulation is absent, and the core body temperature moves toward the ambient temperature.
- The pupil is markedly constricted

Slow-wave sleep	Rapid eye movement sleep (REM, or paradoxical sleep)
[1] It forms about 75% of sleep time	It forms about 25% of the sleep time
[2] It is restful type of sleep	It is not so restful
[3] EEG waves become very low of delta wave but this is broken by sleep spindles (which are a short spindle—shaped bursts of alpha waves that occur periodically).	EEG waves are of the early stages of wakefulness (beta waves)
[4] Dreams actually occur but are not remembered.	It is associated with remembered dreaming;
[5] Sleepwalking (somnambulism), bed-wetting (nocturnal enuresis), and night terrors occur during slow-wave sleep. Gastrointestinal motility increases	It is usually association with teeth-grinding (bruxism) and penile erection, sleep paralysis indicating strong inhibition of the spinal projections from the reticular formation of the brain stem. Gastrointestinal motility decreases.
[7] The person is more easier to be aroused by sensory stimuli	The person is more difficult to be aroused by sensory stimuli and yet persons usually awaken spontaneously in the morning during an episode of REM sleep and not from slow wave sleep.

- Persons who are deprived of sleep become irritable, fatigued, disoriented and unable to concentrate. Personality disorders such a paranoid thoughts, auditory and visual illusions or hallucinations may be encountered in persons who are deprived of sleep. Deprivation of REM sleep may lead to anxiety disorders. Relatively prolonged REM deprivation does not seem to have adverse psychological effects. However, rats deprived of all sleep for long periods lose weight in spite of increased caloric intake and progressive malfunction of the mind and also causes abnormal behavioral activities of the NS and eventual death. Therefore, sleep in some way not clear yet restores both normal sensitivities of and normal balance among the different parts of the CNS.
- During infancy and childhood, the reduction in sleep time from 16 hours to 10 hours occurs almost entirely by a reduction of the amount of time spent in REM sleep.
- In adulthood, the sleeping time is about 7 hours; the reduction in sleep time is caused by a reduction in the time spent in the sleep stages of slow-wave sleep.
- Elderly individual spends less than 6 hours of each day sleeping. Phase 4 of slow-wave sleep declines gradually, and may disappear in the elderly causing their sleep to be light and interrupted. a person about 60 years of age spends most of the sleeping time in stage 1 and 2 slow wave sleep. This may force such individuals to take afternoon naps to compensate for lost sleep. .
- Alcohol and some sleep medications (barbiturates and others) suppress REM sleep but not slow-wave sleep. On the other hand, certain tranquilizers, such as diazepam (Valium) reduce slow-wave sleep much more than REM sleep.

Mechanism of sleep: There are three theories to explain how sleep is induced. All of them are valid and operating for induction of sleep and controlling the waking/sleeping rhythm.

1. The metabolic theory: During wakefulness, brain cells produce sleep-inducing substances, among which is a **sleep-inducing factor** (**factor-S,** a glucopeptide) which accumulates in the CSF. When it reaches a certain level it induces slow wave sleep. The concentration of factor-S in the brain declines steadily during sleep leading finally to termination of sleep and start of wakefulness. **Serotonin** is considered as a "sleep hormone" because it stimulates the production of these sleep-inducing substances.

2. The passive theory: The **ascending reticular activating system** (ARAS) sends facilitatory signals to the cerebral cortex to increase its excitability and maintain the wakeful, alert state. According to the passive theory, sleep is induced when the facilitatory signals from the ARAS to the cortex are withdrawn. This occurs when the activity of the ARAS is depressed either by <u>fatigue</u> (after a long period of wakefulness) or by <u>lack of sensory input signals</u> or <u>corticofugal signals</u>. This theory explains how sleep is rapidly induced by physical and mental relaxation in a comfortable bed in a quiet, dark room at comfortable temperature. Under these conditions, all sensory signals are reduced to minimal and the ARAS activity is markedly reduced. Mental relaxation eliminates any excitatory corticofugal signals and helps the onset of sleep.

3. The active theory (sleep centers): According to this theory there are specific centers which induce slow wave sleep, others which induce REM sleep. There is awaking/sleeping oscillator which regulates the activity of these sleep centers. Sleep is induced by induction of slow wave sleep, REM sleep follows automatically.

    (a) Slow wave sleep center: The **raphe magnus nuclei** of the upper medulla and lower pons are considered as a <u>slow wave sleeping center</u>. Their stimulation induces slow wave sleep. Their damage leads to prolonged insomnia. Inhibitory fibers from the raphe nuclei project to the ARAS and the cerebral cortex. These fibers are serotonergic so drugs that block the synthesis of serotonin produce prolonged insomnia.

    (b) REM sleep center: The **nucleus ceruleus** of the pons is considered as a <u>REM sleep center</u>. Its stimulation converts slow wave sleep to REM sleep. It stimulates the cerebral cortex and inhibits the raphe nuclei. It inhibits the facilitatory reticular formation leading to marked decrease in the skeletal muscle tone. A lesion in the nucleus ceruleus abolishes REM sleep, but slow wave sleep can still occur.

    (c) waking/sleeping oscillator center: The **suprachiasmatic nucleus** of the anterior hypothalamus is responsible for synchronizing the waking/sleeping rhythm with the 24-hr light/dark cycle. It is considered as the waking/sleeping oscillator center. The suprachiasmatic nucleus acts by stimulating the raphe nuclei which in turn induce sleep. Damage of this nucleus leads to intense wakefulness. This eventually leads to severe exhaustion which could be fatal.

The cycle between sleep and wakefulness: It is the most obvious and important diurnal rhythm. The possible mechanism for causing the rhythmicity of the sleep-wakefulness cycle is the following:

- When the sleep centers are not activated, the RAS begins spontaneous activity. This in turn excites both the cerebral cortex and the peripheral nervous system. Then, positive feedback signals come from both these areas back to the RAS to activate it still further.
- After the brain remains activated for many hours, the neurons within the RAS will fatigue and the sleep-promoting centers become activated, Consequently, the positive, feedback cycle between the RAS and the cortex and also between the RAS and the peripheral nervous system will fad and inhibitory effects of sleep centers as well as inhibition by possible sleep-producing chemical transmitter substances will take over, leading to rapid transition from the wakefulness state to the sleep state.
- Then during sleep, the excitatory neurons of the RAS gradually become more and more excitable because of the prolonged rest while the inhibitory neurons of the sleep centers become less excitable, thus leading to a new cycle of wakefulness.

Neurotransmitters associated with the ascending reticular activating system, and therefore the awake state, include **acetylcholine**, **norepinephrine**, and **dopamine**. The role of acetylcholine in the alert awake state is mimicked by nicotine, a drug that binds nicotinic cholinergic receptors; likewise, the role of the catecholamines is mimicked by drugs such as amphetamines and cocaine. In another area involved in awaking the brain, the hypothalamus, neurotransmitters include **histamine** and **orexin**. The role of histamine in maintaining the awake state is evident when an individual takes an antihistamine, which makes the person drowsy. Orexin is a recently discovered peptide whose awakening actions are being explored by pharmaceutical companies in the development of drugs to keep people awake. Other areas of the brain are involved in inducing sleep. Slow-wave sleep is induced by the forebrain. Recent research suggests that **adenosine** is a critical neurotransmitter for the induction of Slow-wave sleep. One of the current theories on the stimulatory effects of caffeine suggests that caffeine blocks adenosine receptors, thereby inhibiting sleep.

Cerebrospinal fluid (CSF) system

It has a volume of about **150 ml** and found in the ventricles of the brain, in the cisterns around the brain, and in the subarachnoid space around both the brain and the spinal cord. All these chambers are connected with one another and the pressure of the fluid is regulated at a constant level. CSF can be sampled with a lumbar puncture.

The CNS has three extracellular fluid compartments

1. Blood plasma contained inside the vascular system (approximately 70 mL).

2. Interstitial fluid located outside the vascular system in contact with neural cells and glia (approximately 250 mL).

3. CSF located within the ventricular system and subarachnoid space (approximately 150 mL).

The major function of the CSF is to:

[1] Forms a **protective water jacket** which cushions the brain within its solid vault. This is due to fact that the brain actually floats in the fluid. Therefore, a blow to the head moves the entire brain simultaneously with the skull, causing no one portion of the brain to be momentarily contorted by the blow.

[2] During periods of intense activity, neurons and glia tend to swell due to accumulation of metabolites and other osmotically active materials. **CSF allows water to shift from CSF to cells** without causing any gross change in CNS volume.

[3] CSF provides the CNS with a **stable extracellular environment** from large swings in plasma chemical composition. Because it is renewed constantly, it also prevents buildup of neuronal waste products, transmitters, and ions.

CSF formation:

- CSF is formed at a rate of about 500 ml / day.
- One thirds of this fluid originates as a **ultrafiltration of blood plasma** through choroidal capillaries in the four ventricles, mainly in the two lateral ventricles. Two third or more is **secreted** by choroid plexus and ependymal cells which actively transport sodium, chloride and bicarbonate ions into the ventricles and water follows the resulting osmotic gradient.

CSF circulation: The ventricular system is a series of interconnected chambers inside the CNS that are filled with CSF. CSF exits the ventricular system via holes in the fourth ventricle (the foramina of Luschka and Magendie) into the subarachnoid space and flows over the surface of the brain and spinal cord.

CSF drainage: CSF eventually drains back into the venous system at specialized areas of arachnoid membrane called **arachnoid granulations**. CSF is drained into arachnoid villi from where it enters subdural sinuses. The reabsorption shows passive diffusion caused by hydrostatic pressure difference. To maintain a stable CSF volume, the rate of production of CSF by the choroid plexus must be the same as the rate of CSF absorption at arachnoid granulations. The circulation of CSF replaces the CSF volume approximately four times per day.

CSF pressure: CSF pressure when measured when one is lying in a horizontal position from lumbar spinal segments (between L3 and L4), ranges from **70** to **150** mm of CSF. CSF pressure at above 115 mm CSF, filtration and absorption will be equal. The CSF pressure normally is regulated almost entirely by absorption of the fluid through arachnoidal villi to superior sagittal sinus. The reason for this is that the normal rate of CSF formation is constant. On the other hand, the villi function like valves that allow the fluid and its contents to flow readily into the blood of the venous sinuses while not allowing blood to flow backward in the opposite direction. Normally, this valve action of the villi allows CSF to begin to flow into the blood when its pressure is about 1.5 mm Hg greater than pressure of the blood in the venous sinuses. Then as the CSF pressure rises still higher, the valves open widely, so that under normal conditions, the pressure almost never rises more than a few mm of Hg higher than pressure in the venous sinuses. On the other hand, diseases that involved the villi can cause high CSF pressure. As the CSF fluid absorption is stopped, the fluid accumulates, giving rise to external hydrocephalus (communicating hydrocephalus). Blockade in ventricular system or foramen of Luschka and Magendie leads to accumulation of CSF proximal to block and results in internal hydrocephalus (noncommunicating hydrocephalus).

CSF composition: CSF is an isotonic fluid. CSF is similar to brain interstitial fluid. This is because the free communication between the brain interstitial fluid and CSF. The surfaces of the ventricles are lined with thin epithelial cells called ependyma and the outer surface of the brain is covered by a thin membrane called the pia mater. Both of which (ependyma and pia mater) are extremely permeable so that almost all substances that enter the CSF can also diffuse readily into the interstitial fluid of the brain through these membranes, and vice versa. Therefore, the resulting characteristics of the brain interstitial fluid and consequently the CSF become the following relative to plasma:
- Osmotic pressure approximately is equal to that of plasma.
- Has very little protein,
- Na, Cl, and Mg ion concentrations are greater than in plasma,
- Whereas K, Ca ions, HCO_3^- and glucose (30% less) concentrations are lower.

The low concentration of protein and HCO_3^- in CSF make it to have a low buffering capacity, which allows the **central chemoreceptors** to sense changes in blood carbon dioxide levels through small changes in CSF pH.

Movement of solutes from arterial plasma into the brain is restricted by the **blood-brain barrier** and the **blood-CSF barrier.** There are areas of the brain lacks the presence of such barriers such as some areas of the **hypothalamus**, **pituitary gland,** and **pineal body.** The ease of diffusion in these areas is important because they have sensory receptors that respond to different changes in the body fluids and their responses provide the signals for feedback regulation of each of the factors.

Blood-brain barrier (BBB): The interstitial fluid surrounding neurons is protected from changes in the plasma composition by a blood-brain barrier. However, there is free exchange of water and solutes between the interstitial fluid of the brain and the CSF across the ependymal
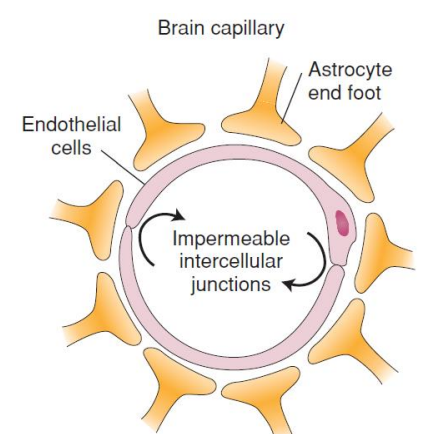
cells, which line the ventricular system. Therefore, it follows that the composition of CSF must be carefully regulated, which is achieved by actively secreting CSF, via the choroid plexus epithelia. Cerebral capillaries at birth lack blood brain barrier. There is a free movement of substances between blood and brain tissue and that is why, when severe jaundice occurs in newborn (hemolytic disease of newborn), the bile pigments cross the brain capillaries and damage the basal ganglia. This leads to extrapyramidal disorder and the condition is known as **kernicterus**. In adults, the blood brain barrier is fully developed and hence only lipid soluble molecules and respiratory gases can pass through brain capillaries. There are two important factors which facilitate development of blood brain barrier. They are:

[1] Presence of **tight junctions** between the endothelial cells of brain capillaries.

[2] The end feet of **astrocytes** ending on the brain capillaries also contribute to the barrier.

Breakdown of the blood-CSF barrier occurs in bacterial meningitis. Bacterial invasion of the choroid plexus epithelial cells allows the bacteria to gain access to the CSF, a medium that facilitates bacterial replication due to its paucity of host immune cells.

General Properties of the BBB:

1. Large molecules do not pass through the BBB easily such as plasma proteins, cholesterol. In general, the threshold molecular weight for allowing free diffusion is below 400–600 daltons.
2. Non lipid soluble molecules do not penetrate into the brain. However, BBB is highly permeable to CO_2, O_2, and most lipid soluble molecules which rapidly cross through into the brain. Glucose is an important exception and is a crucial substrate for neuronal tissue. Glucose enters the brain by facilitated diffusion via carriers present in capillary endothelial cell membranes.
3. Molecules that have a high electrical charge to them are slowed.

The functions of the BBB are:

[1] It maintains a constant environment for neurons in the CNS and protects the brain from endogenous or exogenous toxins.

[2] It prevents the escape of neurotransmitters from their functional sites in the CNS into the general circulation.
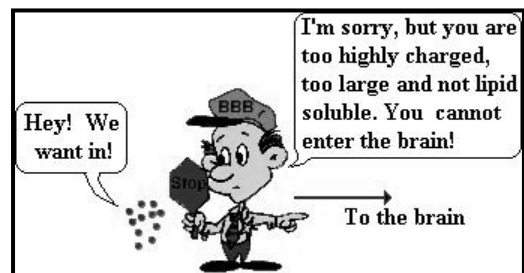

The BBB can be broken down by:

1. Hypertension (high blood pressure): Sudden severe increase in blood pressure opens the BBB.
2. Development: the BBB is not fully formed at birth.
3. Hyperosmolarity: A high concentration of a substance in the blood can open the BBB. Intravenous injection of hypertonic fluids (which is used clinically to extract cerebral edema fluid).
4. Microwaves: exposure to microwaves can open the BBB.
5. Radiation: exposure to radiation can open the BBB.
6. Infection: exposure to infectious agents can open the BBB.
7. Trauma, Ischemia, Inflammation, Pressure: injury to the brain can open the BBB.

Injury (e.g. inflammatory or neoplastic disease) to the BBB is reversible and takes about **2-3 weeks to be repaired.**

Brain areas outside the blood–brain barrier: 'Windows of the brain' are characterized by higher capillary densities and by the presence of fenestrated capillaries. They help form a functional interface between the CNS and the endocrine system, sensing hormonal changes. They are essentially midline structures located adjacent to the ventricular spaces
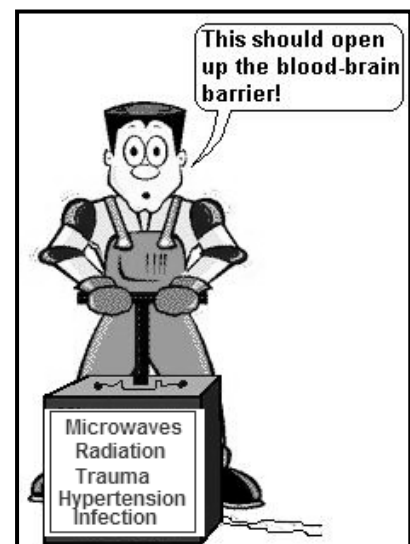
and arising from the ependymal lining of the ventricular system. The circumventricular organs, which abut on the third and fourth ventricles, can be classified as either:

Blood-CSF barrier: The choroid plexuses epithelial layer is continuous with the ependymal cell layer that lines the ventricles, but unlike the ependymal layer, the choroid plexuses epithelial layer has **tight junctions** in between the cells on the side facing the ventricle (apical surface). These tight junctions prevent the majority of substances from crossing the cell layer into the CSF; thus the choroid plexuses act as a **blood-CSF barrier**.

Cerebral blood flow (CBF): Cerebral blood flow (CBF) is the blood supply to the brain in a given period of time. In an adult, CBF is typically **750 ml per minute**. Although the brain constitutes only 2% of an adult's body weight, it receives **15%** of the blood and consumes **20% of the body's oxygen** and **glucose**. The major energy source for the brain is glucose. However, in prolonged hypoglycemia greater than 48 hours (starvation) the major energy source for the brain is ketone bodies. This equates to an average perfusion of 50 to 54 ml of blood per 100 grams of brain tissue per minute. CBF is about 80 ml/100 g/ min in gray matter and about 20 ml/100 g/min in white matter. If CBF is deceased to less than 10 ml/ 100 g/ min, irreversible tissue damage can occur at normal body temperatures. As in the coronary circulation, CBF is autoregulated, meaning that it remains constant between a blood pressure of 50-150 mm Hg. Within the physiological range, autoregulation protects the brain against hypoxic damage with a reduction in cerebral perfusion pressure, and against hyperaemia, capillary damage and cerebral edema with increased perfusion pressure. When the mean pressure is greater than 150 mm Hg, the BBB may be disrupted. The curve is shifted to a higher mean blood pressure in patients with chronic hypertension. Autoregulation is lost with arterial hypotension or hypertension outside the specified limits, raised intracranial pressure, hyperviscosity and raised arterial PCO_2. Regional metabolic activity, arterial O_2 and CO_2 concentrations help in determining regional CBF. Unlike the coronary circulation, cerebral resistance vessels are more sensitive to PCO_2 than PO_2. Therefore, even slight increase in PCO_2 can cause a large increase in CBF. The response to arterial carbon dioxide tension is mediated by the hydrogen ion concentration in the extracellular fluid of the vascular smooth muscle.

Causes of increased cerebral blood flow

- Hypoxia
- Hypercapnia
- Hyperthermia
- Rapid eye movement sleep

Causes of reduced cerebral blood flow

- Hypocapnia
- Hyperoxia
- Hypothermia

Many drugs have effects on CBF; for example, barbiturates constrict cerebral blood vessels, while volatile anesthetic agents dilate them. Constriction of the cerebral vasculature can help decrease intracranial pressure, and dilation can increase intracranial pressure.

Intracranial pressure (ICP): It is the pressure inside the cranium. Within certain limit, if one of the three brain compartments (i.e., CSF, blood vessels, and brain tissue) increases in volume, it is compensated by successfully by a decrease in volume of one or both of the other two compartments without an associated change in intracranial pressure.