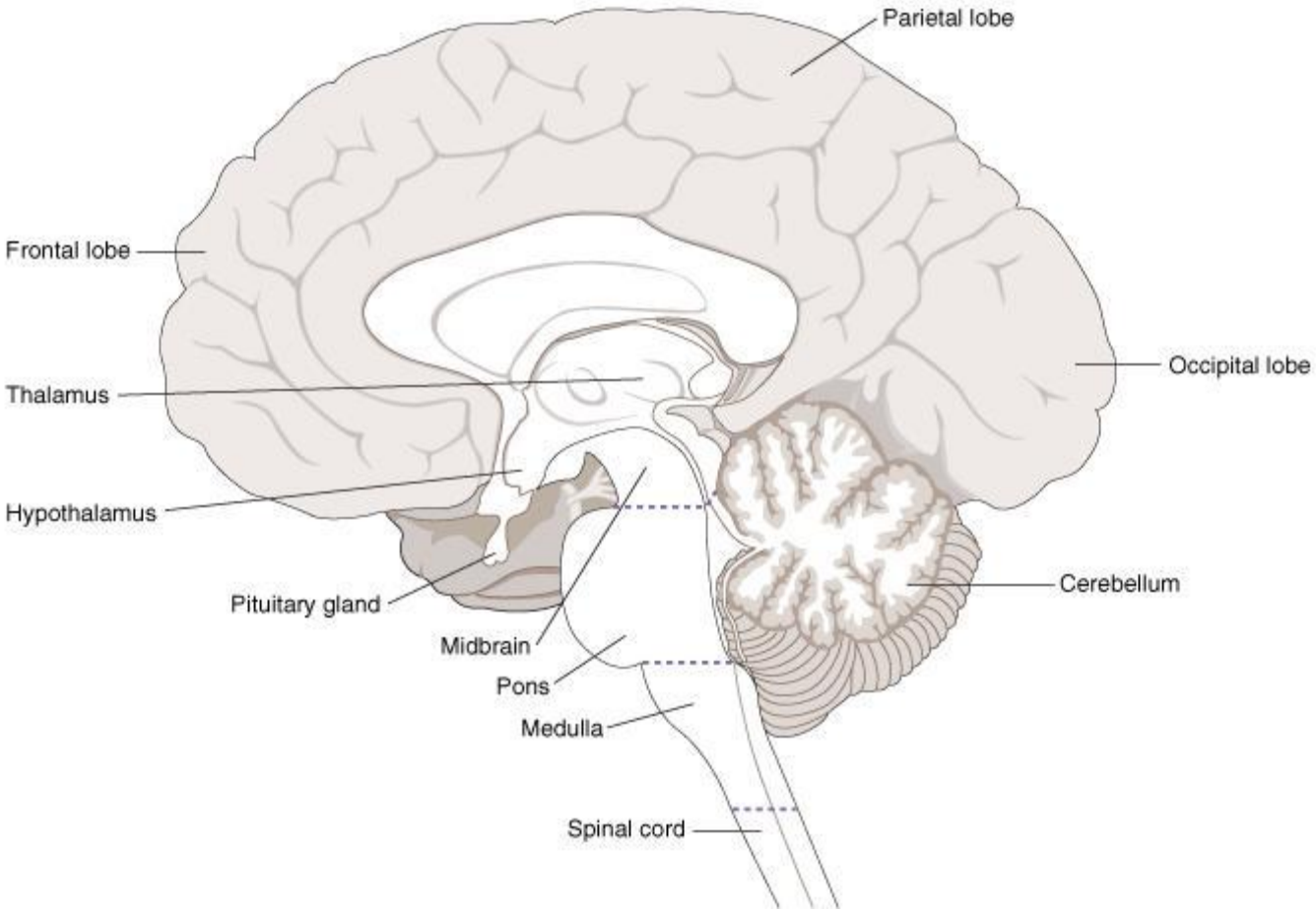
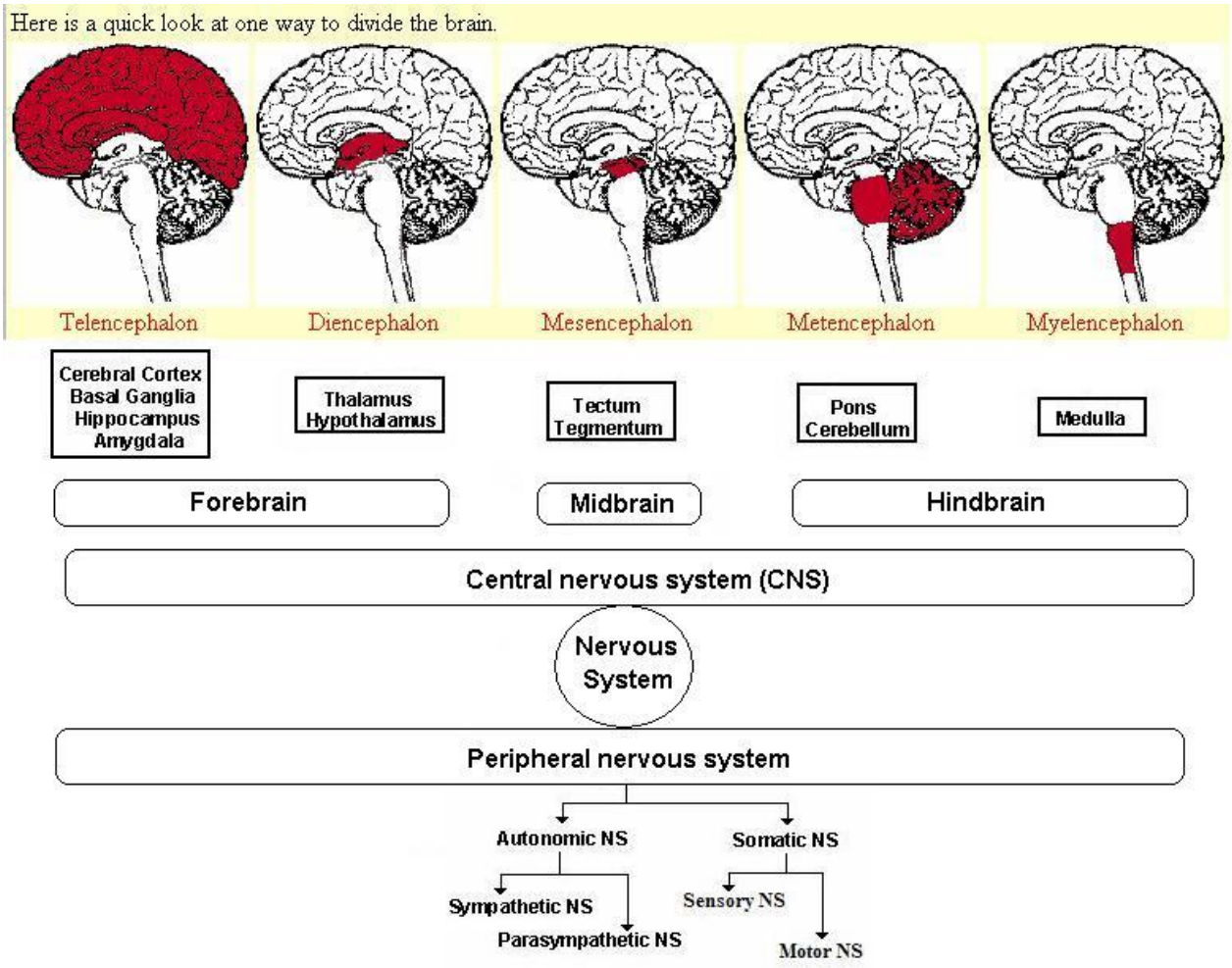
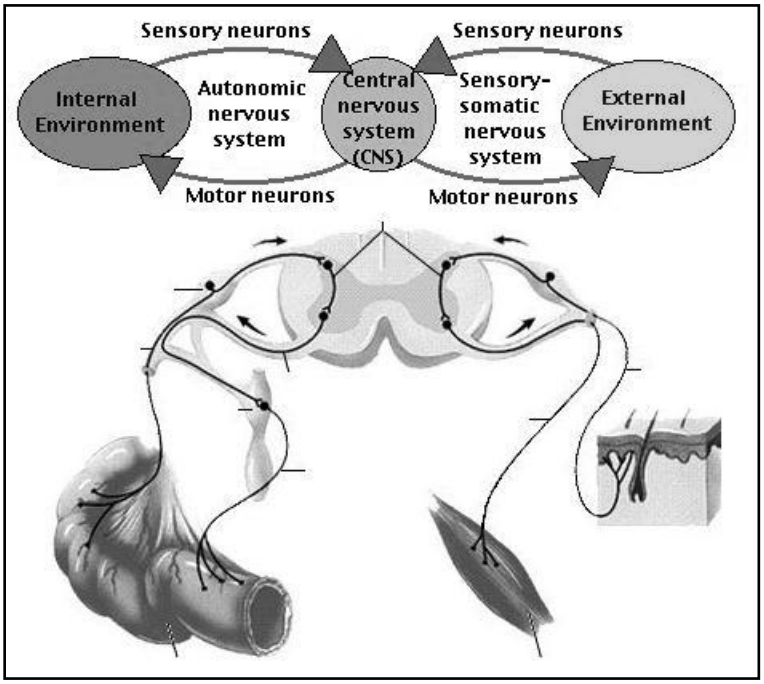
# The central nervous system






## 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).

More than 99% of all sensory information is discarded by the brain as unimportant. A small fraction of the selected important sensory information is processed in the CNS and then either appropriate motor response occurs (through sensory-somatic or autonomic nervous systems) or to be stored by a process called memory.

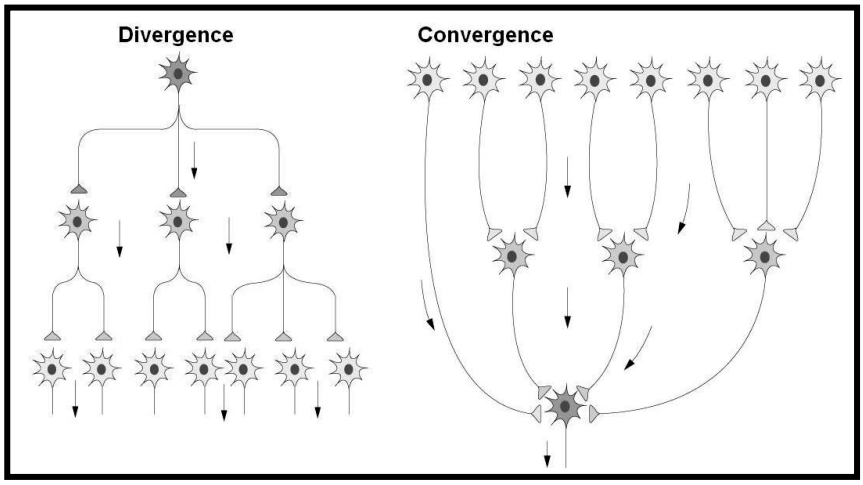
**The functional levels of CNS**: The intercommunication between the external environment and the CNS is mediated by the *sensory-somatic peripheral nervous system*, while the intercommunication between the internal environment and the CNS is mediated by *autonomic peripheral nervous system*. The CNS 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, mesencephalon, 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.

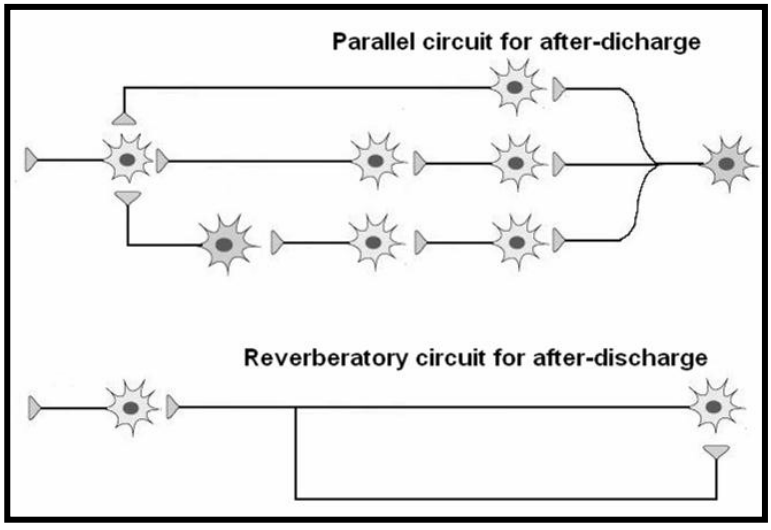
**The neuronal pools:** Neuronal pool (or nuclei or centers) is a collection of intercommunicated neurons. Each pool has its own special characteristics of organization which cause it to process signals in its own special way. The examples of such pools are basal ganglia, specific nuclei in the thalamus, 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 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.



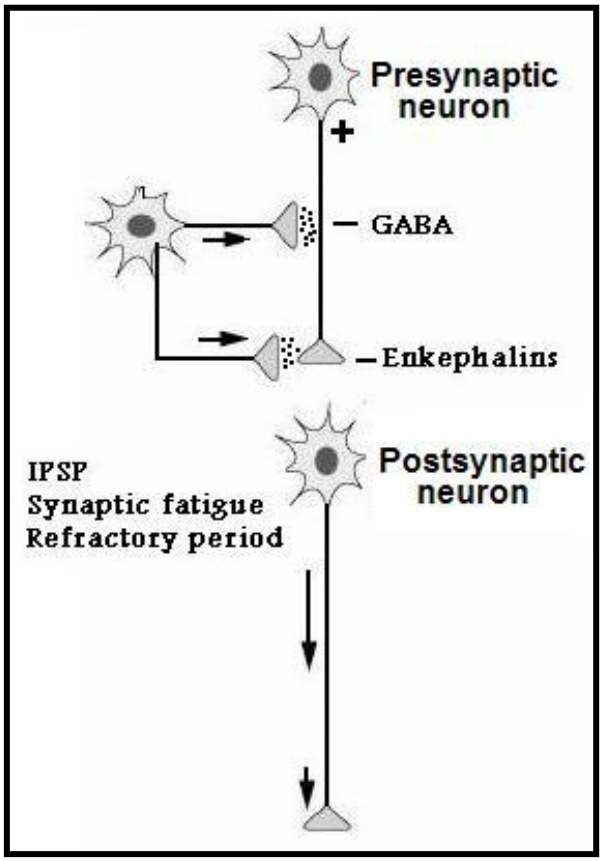
**[c]-** Reverberatory circuit for after-discharge: When excitatory signal stimulate a neuron in a neuronal pool, the excited neuron in the pool feeds back to re-excite itself. Examples of reverberatory system are those which occur during respiration in which the inspiratory neuronal pool in the medulla become excited for about 2 sec 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 occur 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 enkephalins) 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.

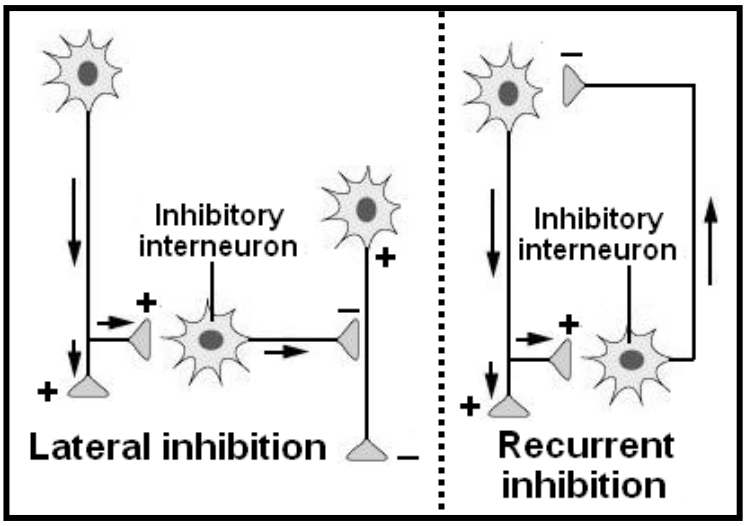
**(2) Postsynaptic inhibitory mechanism:** This type of inhibition can be due to the generation of IPSP at the postsynaptic membrane or the occurrence of the synaptic fatigue in which the signal becomes progressively weaker with the more prolonged period of excitation. Other form of synaptic inhibition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

# Sensory functions of the CNS
# Sensory receptors and their basic mechanisms of action

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. Each type of receptors has its own histological structure. The skin, for example, contains various types of sensory endings. These include naked nerve endings, expanded tips on sensory nerve terminals (which include Merkel's disks and Ruffini endings), and encapsulated endings (which include Pacinian corpuscles and Krause's end-bulb). Although cutaneous sensory receptors are not stimulus-specific according to their histological appearance, they are physiologically specific.

- Merkel cells and Ruffini endings respond to steady pressure and stretch
- Pacinian corpuscles and Meissner's corpuscles give the sense of vibration
- There are separate warm and cold receptors
- Hair receptors associated with skin hairs allow you to feel the displacement of hairs
- Several types of pain receptors respond to mechanical trauma or very high or low temperatures

| Type of Mechanoreceptor | Location | Adaptation | Sensation Encoded |
|---|---|---|---|
| Pacinian corpuscle | Subcutaneous; intramuscular | Very rapidly | Vibration, tapping |
| Meissner's corpuscle | Nonhairy skin | Rapidly | Point discrimination, tapping, flutter |
| Hair follicles | Hairy skin | Rapidly | Velocity, direction of movement |
| Ruffini's corpuscle | Hairy skin | Slowly | Stretch, joint rotation |
| Merkel's receptors | Nonhairy skin | Slowly | Vertical indentation of skin |
| Tactile discs | Hairy skin | Slowly | Vertical indentation of skin |

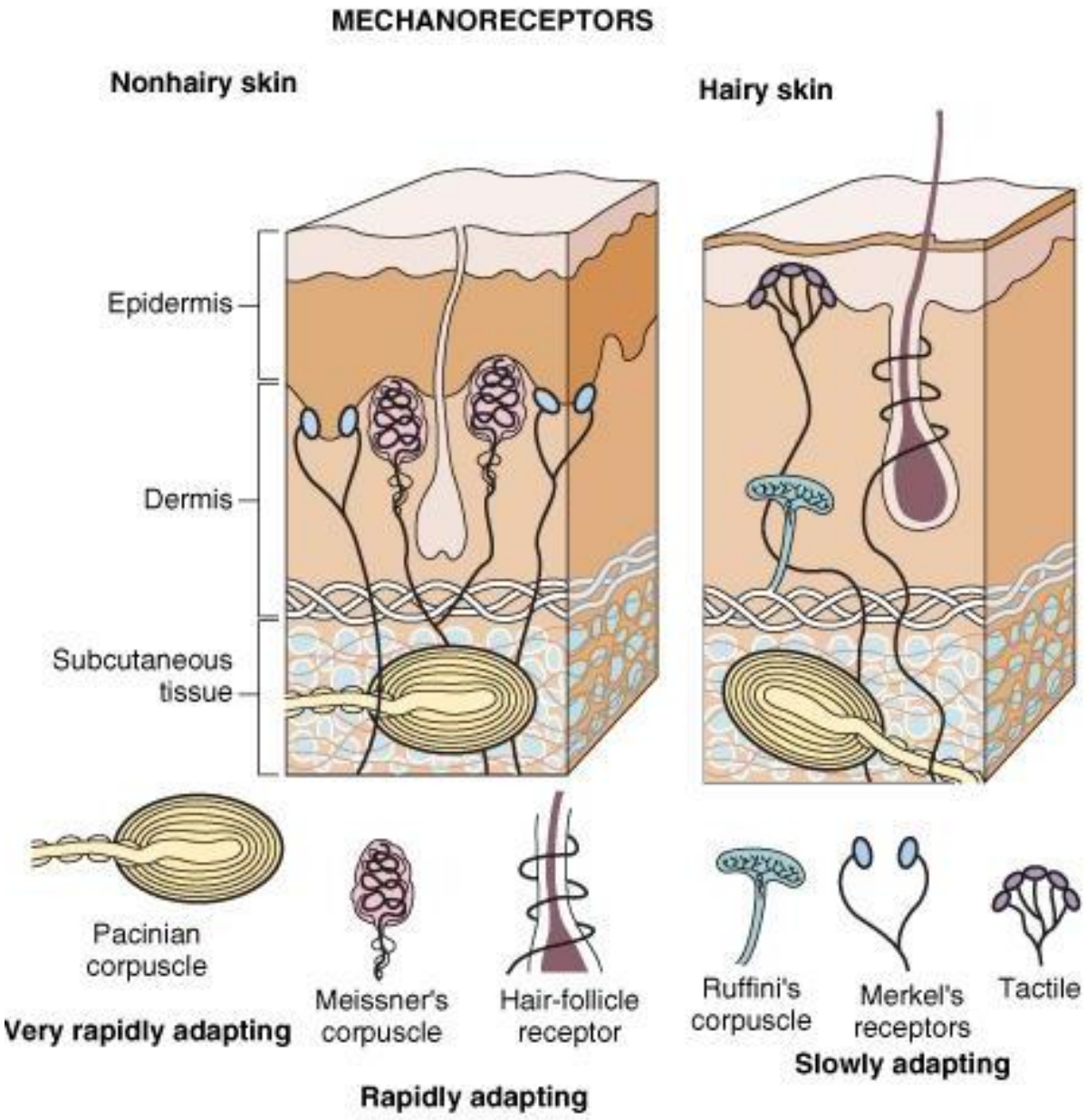



**Figure 3-8 Types of mechanoreceptors found in nonhairy skin and hairy skin.**

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 tactile sensations (touch, pressure, vibration, tickles, itch), hearing, equilibrium, and the position sense. An example of such receptors is the Pacinian corpuscle (which detect vibration), Ruffini`s corpuscle (which detect pressure), Merkel`s (which detect the site), Meissner`s corpuscles (which detect the rate of stimulus application and present in non-hairy skin), joint receptors, stretch receptors in muscle, hair cells in auditory and vestibular systems.

**[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 be 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:** Which are the sensations that arise from the skin and subcutaneous tissues (joint capsules and ligaments) and include:

- Tactile sensations (touch, pressure, tickling, itch, the position (or proprioceptive), Vibratory, and stereognosis sensations,
- Pain sensation (from skin and from viscera),
- Thermal sensations.

**(b)- Special senses:** Which 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, the pH, and other body fluids chemistry and pressure.

## 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 for which a sensory receptor is most sensitive is called the adequate stimulus.

***2— The specificity of the nerve fiber attached to the receptor:*** Each nerve fibers is specialized to transmit only one modality of sensation. 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.

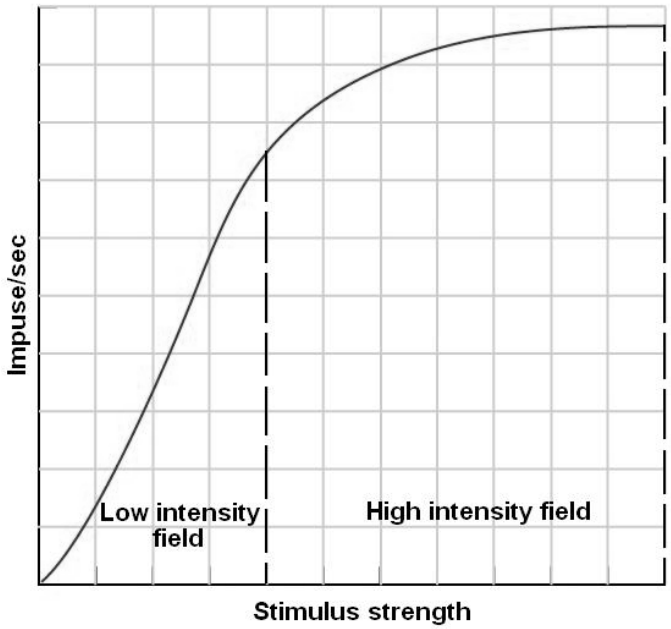
***3— The ability to generate a receptor potential (generator potential):*** The mechanism used by the receptor to produce the receptor potential varies depending on the type of receptor. The stimulus that excites the receptor:

**[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 change in the membrane potential of the receptor is called **receptor 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. In addition, 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).

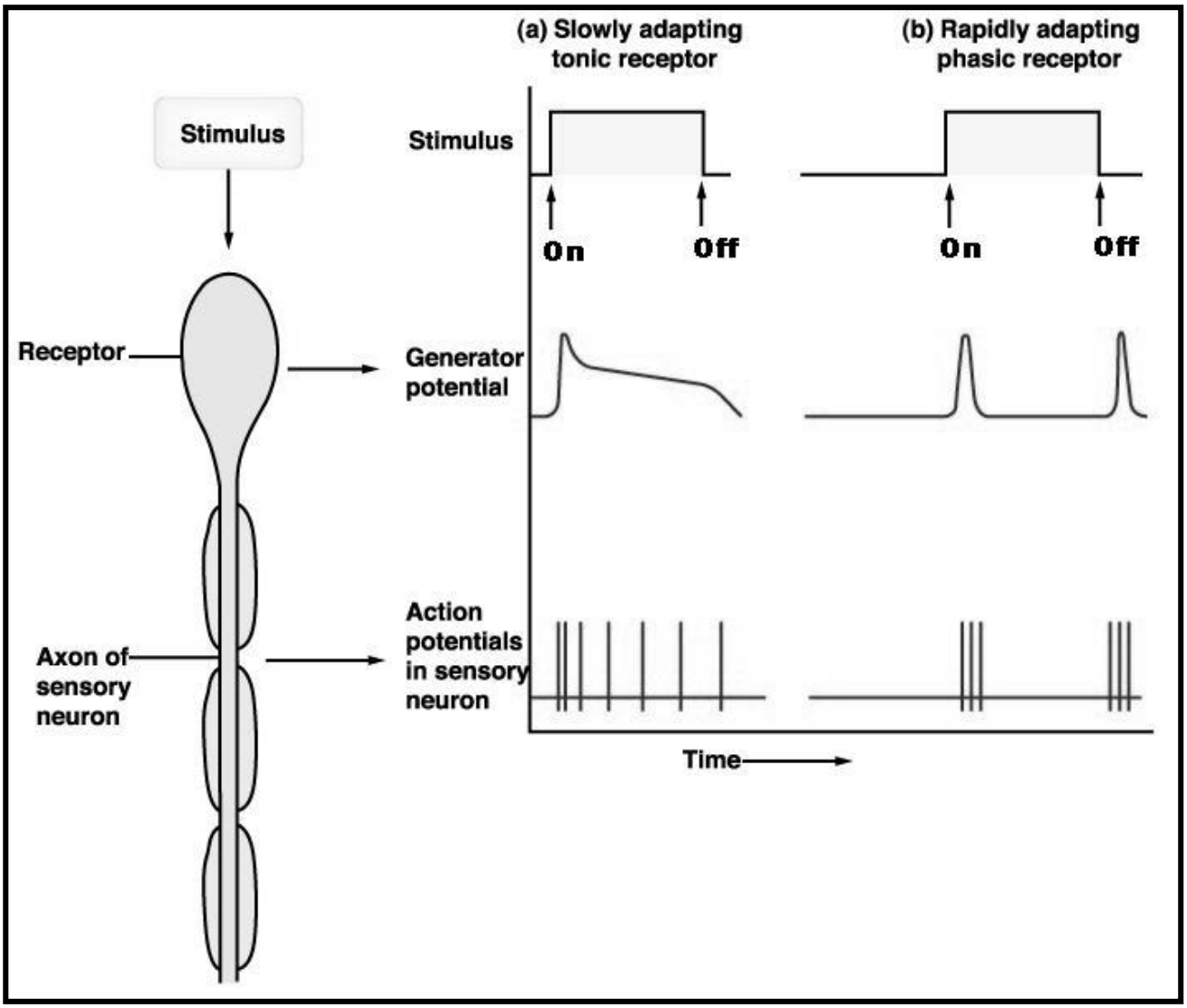



The brain can recognize the intensity of the stimulus that is transmitted to it by:
**[A]** Variation in the frequency of the action potential generated by the activity in a given receptor (called ***temporal summation****)* and
**[B]** By variation in the number of receptor activated (called ***spatial*** *summation*).

***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, 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:

**1—Tonic receptors:** Which 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 apprised 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, the baroreceptors of the arterial tree, the chemoreceptors of the carotid and aortic bodies, and some of the tactile receptors.

**2—Phasic receptors:** Which 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.




**Physiological classification of nerve fibers:** The fibers are divided into the following general types:

**1. Type *A* fibers**: They are the typical myelinated fibers of spinal nerves that conduct impulses at high velocities. They subdivided into:

- Alpha (α) fibers with conduction velocity between 60-120 m/sec. They include fibers that originated from the muscle spindles and Golgi tendon organs and fibers that innervate somatic motor effector tissues.
- Beta (β) fibers with conduction velocity between 30—90 m/sec. They include fibers that originated from touch and pressure receptors and from muscle spindles.
- Gamma (γ) fibers with conduction velocity between 6—60 m/sec. They include motor fibers to the muscle spindles.
- Delta (δ) fibers with conduction velocity between 6-30 m/sec. They include fibers that carry pain, temperature, crude touch, pressure and pricking sensations.

**2. Type B fiber:** They are myelinated fibers that conduct impulses at lower velocity than type A nerve fibers. They include fibers of the preganglionic autonomic nervous system.

**3. Type *C* fibers:** They are very small unmyelinated nerve fibers that conduct impulses at low velocities. They include fibers which carry pain, itch, temperature, crude touch sensations, and fibers of the postganglionic sympathetic nervous system.

The relative susceptibility of type A, B, and C nerve fibers to conduction block produced by various agents is as follow:

| Susceptibility to | Most susceptible | Intermediate susceptible | Least susceptible |
|---|---|---|---|
| **Pressure** | A | B | C |
| **Local anesthetics** | C | B | A |
| **Hypoxia** | B | A | C |

**The somatic sensations:** These are of 3 main types:

- **Tactile sensations (touch, pressure, tickling, itch, position (proprioceptive) and vibratory sensations).**
- **Pain sensation.**
- **Thermal sensations.**

**[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, vibration, and cutaneous tension: 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. All low-threshold mechanoreceptors are innervated by relatively large myelinated axons (type Aβ), ensuring the rapid central transmission of tactile information. They are frequently classified as separate sensations but they are all detect by the same types 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.

***To investigate the touch sensory system: Two-point discrimination:*** A method frequently used to test tactile capabilities is to determine a person's two-point discriminatory ability. In this test, two needles are pressed against the skin, and the subject determines whether two points of stimulus are felt or one point. On the tips of the fingers a person can distinguish two separate points even when the needles are as close together as 1 to 2 mm. However, on the person's back, the needles must usually be as far apart as 30 to 70 mm before one can detect two separate points. The reason for this is that there are many specialized tactile receptors in the tips of the fingers in comparison with a small number in the skin of the back.

**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.

**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 type A 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). It can be divided into two subtypes 1. Static position, which means conscious recognition of the orientation of the different parts of the body with respect to each other and 2. Kinesthesia, which means conscious recognition of movements and the rates of movement of the

different parts of the body.

**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.

**[2] Pain sensation**: An unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain is a protective mechanism for the body, 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.

You may not like it, but we need pain. Pain acts as a warning system that protects you. Pain says, "Warning, Warning....stop what you doing and do something else". For example, if you have your hand on a hot stove, pain tells you to stop touching the stove and remove your hand. In this way, pain protects your body from injury (or further injury if you have already hurt yourself). Pain also helps healing...because an injury hurts, you rest.

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 pain | Chronic pain |
|---|---|
| **[1]** Occurs within about 0.1 sec after a pain stimulus is applied. | Occurs after a sec or more and then increases slowly over a period of many sec and sometimes even minutes. |
| **[2]** It is felt in the skin. | It is felt both in the skin and in almost any internal tissue |
| **[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 opiods. |
| **[5]** The 2ed order neuron is terminated in the thalamus. | The 2ed order neuron is terminated in the reticular formation (reticular activating system) but gives collaterals to the thalamus. |
| **[6]** 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. |
| **[7]** It can be highly localized | It is very grossly localized |

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.

Pain can be originated from the skin (superficial pain) or from deeper structures such as from the muscles, ligaments or viscera (deep pain). Unlike superficial pain, deep pain is poorly localized, nauseating, and frequently associated with sweating and changes in blood pressure.

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

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

**2- Thermosensitive pain receptors:** Which are sensitive to extreme of heat or cold.

**3- Chemosensitive pain receptors:** Which are sensitive to various chemical substances such as bradykinin, serotonin (or 5HT from platelets), histamine (from mast Cells), potassium ions ( from damaged Cells), acids, prostaglandins (from arachidonic acid released from damaged cells), acetylcholine, and proteolytic enzymes. Some of these substances are actually cause direct damage to the pain nerve endings especially proteolytic enzymes, while other such as bradykinin potassium ions, serotonin, histamine, bradykinin, prostaglandins, leukotrienes and substance P released at sites of injury sensitise nociceptorsand and cause direct extreme stimulation of pain nerve fibers without necessarily damaging them. Nociceptors may then respond to non-painful stimuli leading to tenderness described as hyperalgaesia. 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 and without them, the nociceptors are less likely to become sensitised and therefore less pain impulses will be transmitted. They reduce pain by blocking peripheral sensitization.

Pain receptors are of tonic type. Under some conditions, the threshold for excitation of the pain fibers becomes progressively lower and lower as the pain stimulus continues, thus allowing these receptors to become progressively more activated with time.

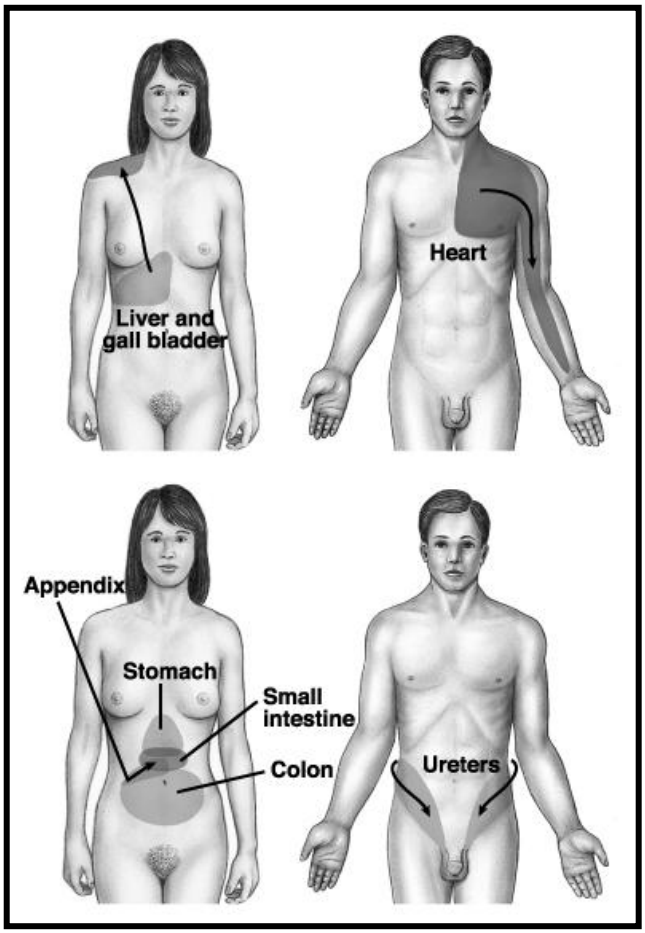
Ischemia can cause pain due to [l] accumulation of large amounts of lactic acids in the tissues and [2] due to the production of other chemical agents from the tissues as a result of the cell damage.

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**

That is the pain felt in a part of the body considerably remote from the tissues causing the pain. 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 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 ischaemia 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.

Primary visceral afferent pain fibers from the pelvic, abdominal, and thoracic viscera enter the spinal cord and synapse on second-order neurons in the dorsal horn of the spinal cord. However, other neurons synapse upon neurons in the intermediate gray region of the spinal cord near the central canal. These neurons, in turn, 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 arcuate fibers that form the contralateral medial lemniscus and eventually synapse on thalamus from which a fourth-order neuron projects to cerebral cortex. This dorsal column visceral sensory projection now appears to be the principal pathway by which painful sensations arising in the viscera are detected and discriminated. The discovery of this visceral sensory component in the dorsal-column medial lemniscal system has helped to explain why surgical transection of the axons that run in the medial part of the dorsal columns (a procedure termed midline myelotomy) generates significant relief from the debilitating pain that can result from visceral cancers in the abdomen and pelvis. These new discoveries have renewed interest in midline myelotomy as a palliative neurosurgical intervention for cancer patients whose pain is otherwise unmanageable. This is achieved by interrupting the second order axons of this pathway within just a single spinal segment. In so doing, this procedure offers some hope to patients who struggle to maintain a reasonable quality of life in extraordinarily difficult circumstances.

## 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 nonpainful stimulus may perceived 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. Certain patient populations are at risk of inadequate pain control and require special attention. These include: Paediatric patients, Geriatric patients, Patients with difficulty in communicating (due to critical illness, cognitive impairment or language barriers).

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.**

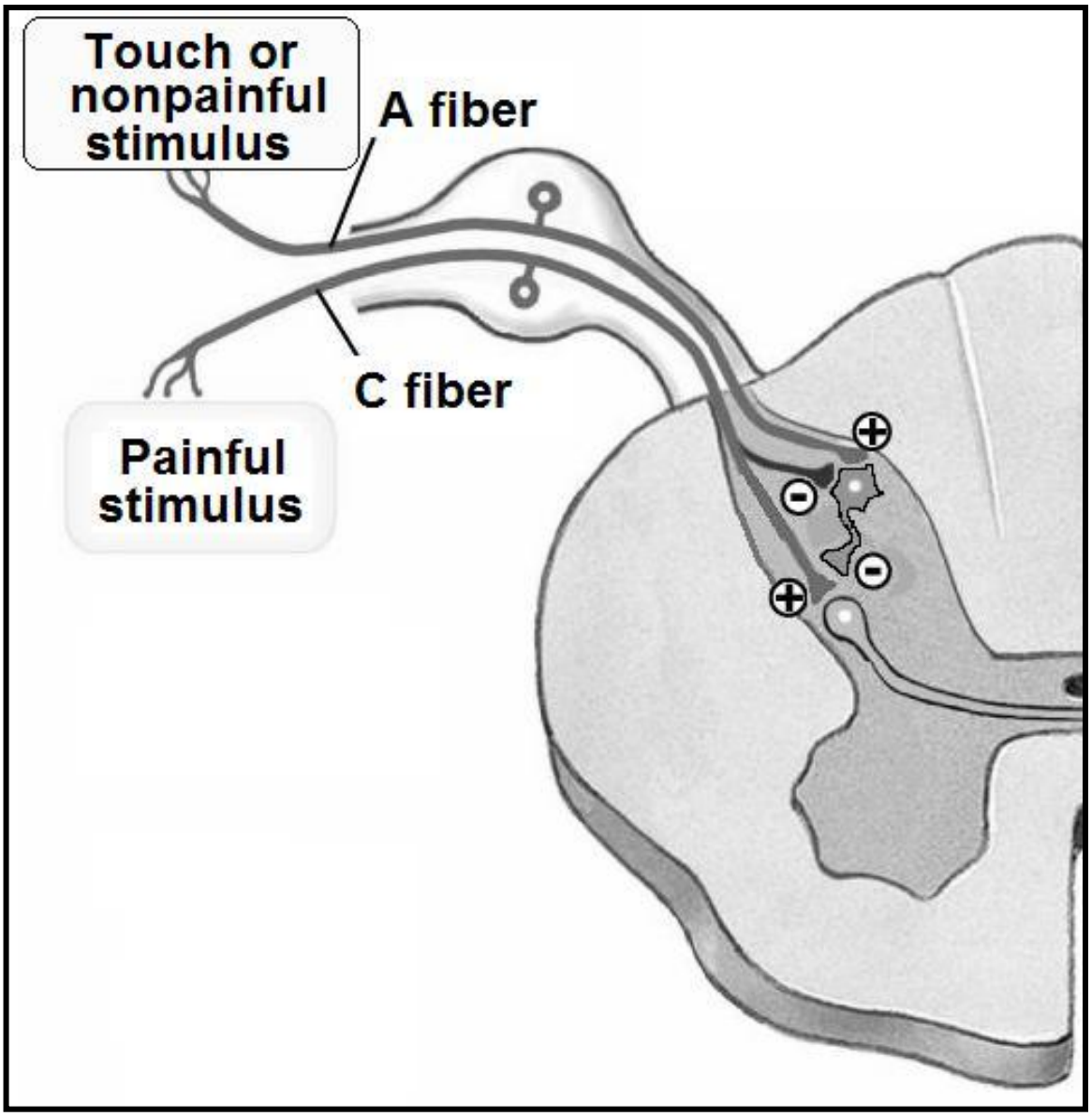
**[C] Pain inhibitory complex** located in the dorsal horns of the spinal cord.

**[D]** plus other **accessory components** (such as periventricular nuclei around the third ventricle and medial forebrain bundle in the hypothalamus).

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 and ventral columns and terminate in the neurons of the pain inhibitory complex of the spinal cord secrete **serotonin** at their endings which stimulate these neurons 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 morphine 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 (cells in SG stimulated, decrease pain signal). Stimulation from small fibres (C fibers) opens gate (cells in SG 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.




**[3] 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 and the signals are conducted through A and C nerve fibers.

**[2]** The warmth receptors which respond maximally to temperature slightly above body temperature and the signals are conducted through C nerve fibers.

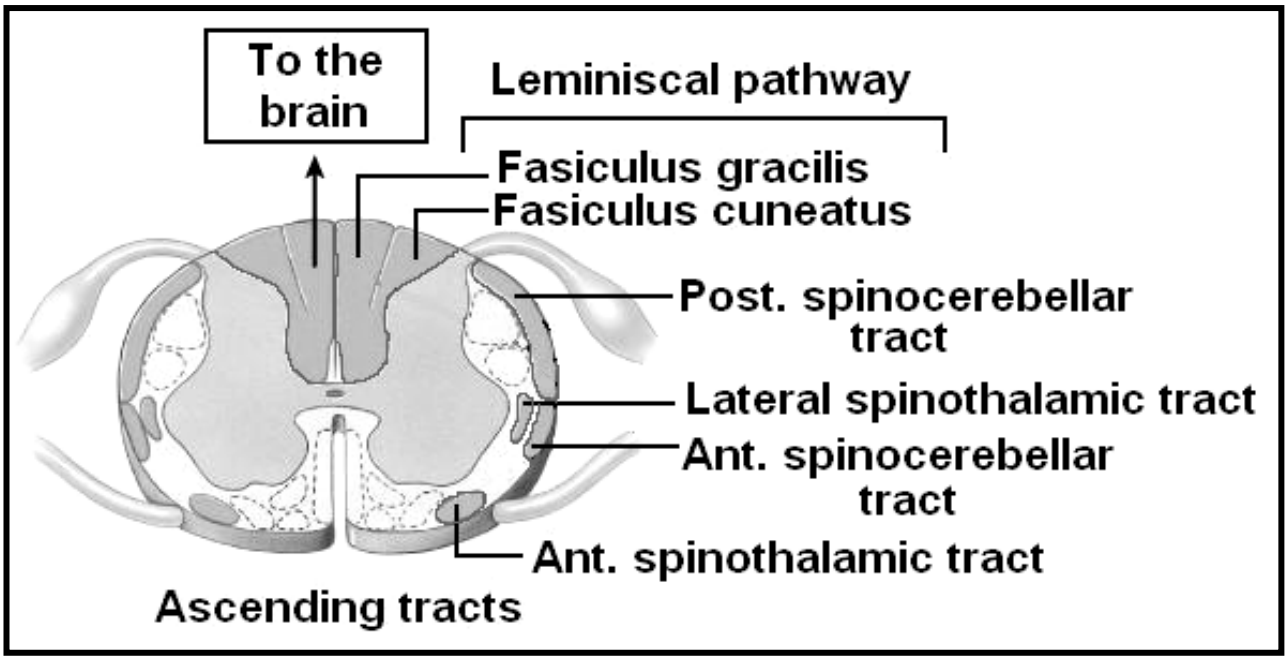
In most areas of the body there are three to ten times as many cold receptors as warmth receptors. The person determines the different gradations of thermal sensations by the relative degrees of stimulation of the different types of receptors. Because the number of cold or warmth receptors in any one 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.

**Signs of lesions of peripheral sensory pathways:** With complete lesion of peripheral sensory nerves all forms of sensation are lost in the area supplied by the affected nerve but without following the dermatomal pattern due to the fact that neighboring nerves overlap into the territory of the affected nerve. If the afferent fibers of a reflex arc affected, the reflex concerned is lost. With lesions of the posterior root of the spinal cord all forms of sensation are lost but the distribution of the loss follows a dermatomal pattern, and loss of reflexes subserved by the involved root.

## The course of the somatic sensations through the spinal cord (The somatosensory system)

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 one of two sensory pathways:




**1— the dorsal column pathway (leminiscal system)**: In which:

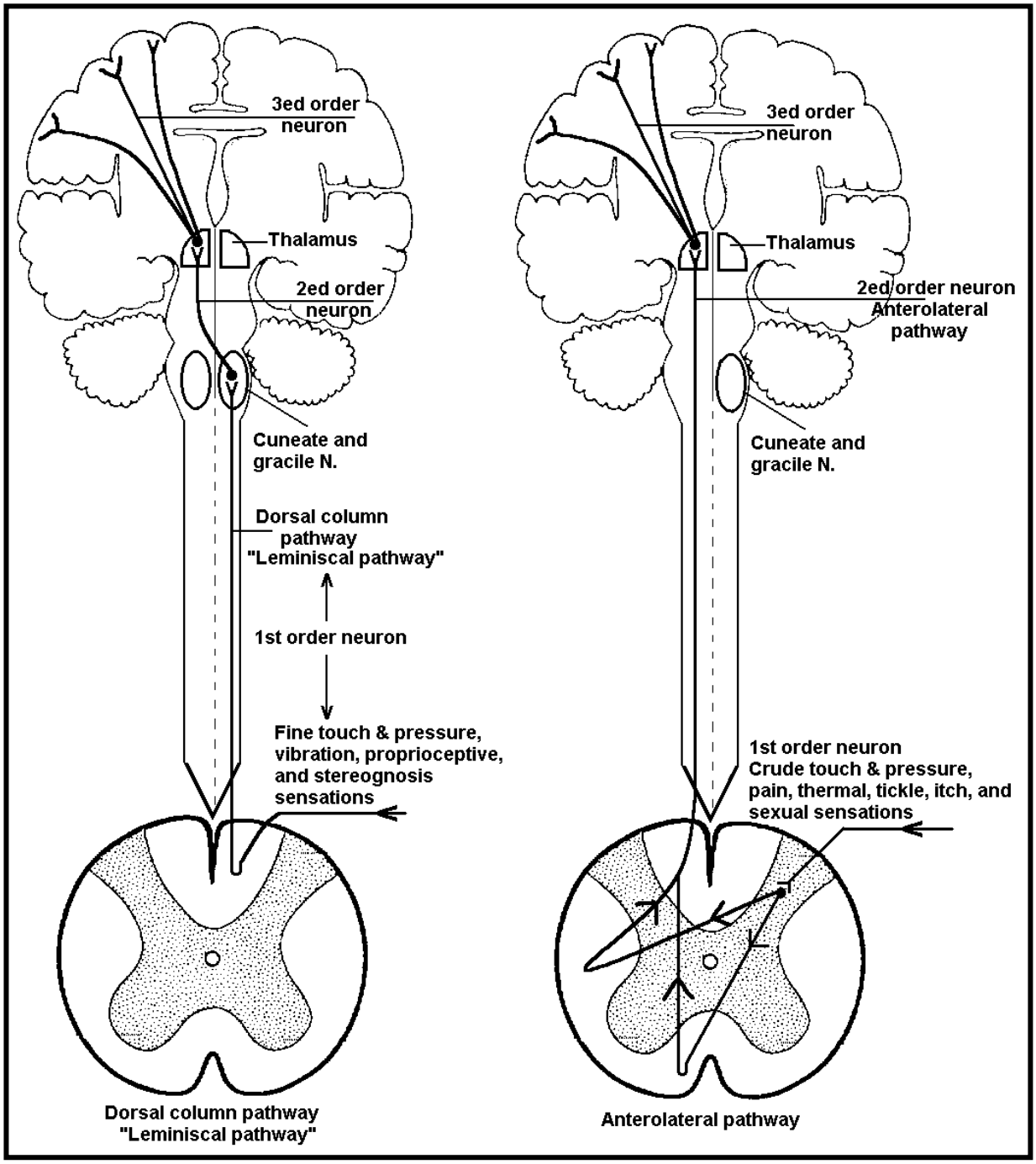
[A] First order neurons (dorsal root sensory fibers) enter the dorsal column of the spinal cord and then pass up on the same side of its entrance in the spinal cord to the medulla, where they synapse in the cuneate and gracile nuclei.

[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, proprioception*.**

Collaterals from the fibers that enter the dorsal columns pass to the substantia gelatinosa of dorsal horn of the spinal cord. These collaterals may modify the input signals from other cutaneous sensory systems including the pain system. Therefore, the dorsal horn represents a **gate** in which impulses in the sensory nerve fibers are modified. This gate is also affected by impulses in descending tracts from the brain.




**2— the anterolateral pathways (spinothalamic pathway):** In which:

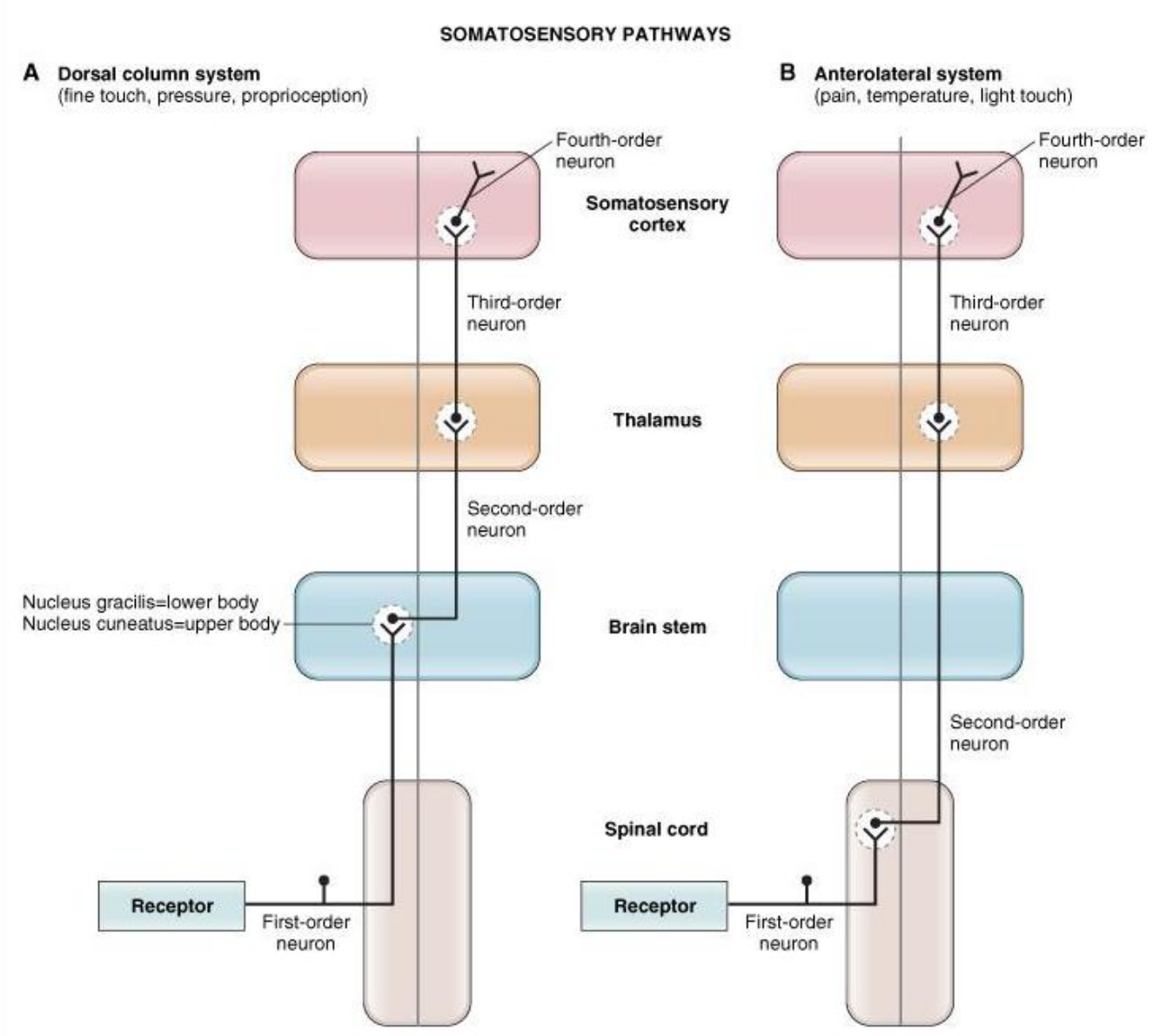
[A] First order neurons (dorsal root sensory fibers) enter the dorsal horns of the spinal cord and synapse with the second order neurons.

[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, pass to the reticular formation of the medulla, pons, and mesencephalon through a spinoreticular pathway and through spinotectal tract. From these areas, higher order neurons are transmitted from reticular formation to the cortex.

[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*.**

*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.*



**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.*

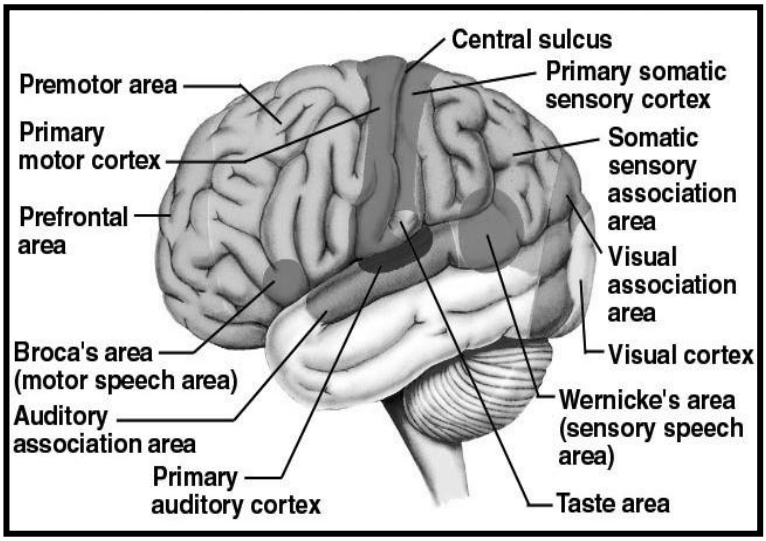
**[3]** In the brain stem, the spinothalamic tract and medial lemniscus run close together. Therefore, lesion of the **upper brain stem** usually *affects all forms of sensation on the contralateral side of the body*.

**[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.*

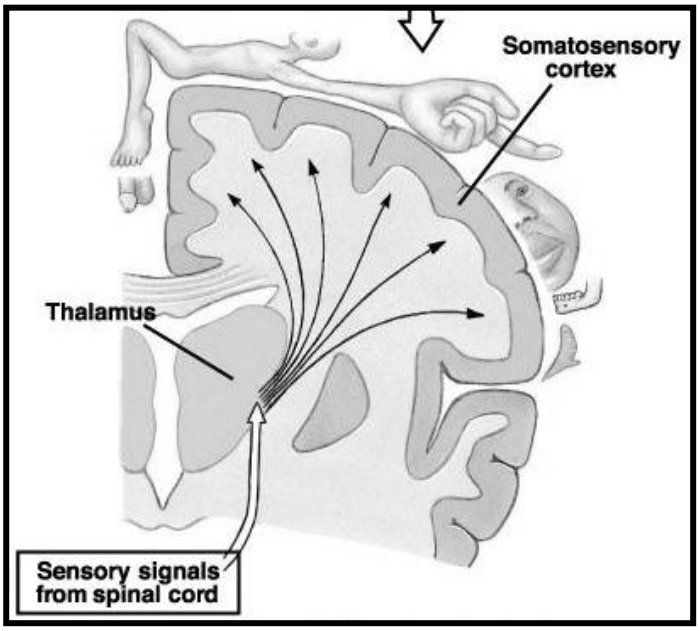
**Higher interpretation of sensory signals:** This is achieved by the cerebral cortex in the following areas: **[1] Primary sensory areas.**
**[2] Sensory association areas.**
**[3] Wernicke's area.**




**[1] Primary sensory areas:** Which 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 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. Wide spread excision of primary somatic sensory area does not abolish and present the following signs:

- ❖ The person is unable to localize 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:** Which 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. In these areas, interpretation of the sensory signals is achieved by giving the brain the simplest meaning and characteristic of the sensory signal. Destruction of the sensory association area greatly reduces the capability of the brain to analyze and interpretate different characteristics of sensory experiences.

*Damage to these parts of the brain is associated with specific deficits known as* ***agnosias*** *and* ***apraxias****.*

*Agnosia is a failure to recognize an object even though there is no specific sensory deficit. It reflects an inability of the brain to integrate the information in a normal way.*

*Apraxia is the loss of the ability to perform specific purposeful movements even though there is no paralysis or loss of sensation. An affected person may be unable to perform a complex motor task on command (e.g. waving someone goodbye) but may be perfectly capable of carrying out the same act spontaneously. Other apraxias may result in failure to use an everyday object appropriately or to construct or draw a simple object (**constructional apraxia).** A deficit in the control of fine movements of one hand can be caused by damage to the premotor area of the frontal lobe on the opposite side. This is known as **kinetic apraxia.***

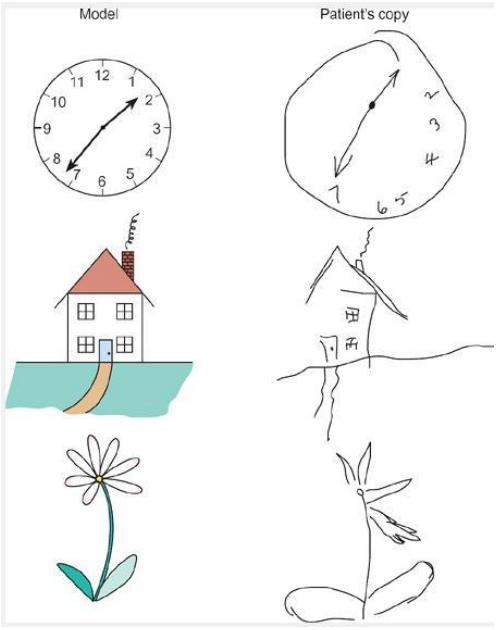
*Damage to auditory sensory association area leads to inability to understand the spoken word (auditory receptive aphasia, or word deafness).*

*Damage to visual sensory association area leads to inability to understand the written word (visual receptive aphasia, or word blindness). Another example is visual object agnosia in which the visual pathways appear to be essentially normal but recognition of objects does not occur. If an affected person is allowed to explore the object with another sense, by touch for example, they can often name it. Nevertheless, they may not be able to appreciate its qualities as a physical object. Thus, they may see a chair but not avoid it as they cross a room.*

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.

**When the somatic association area is removed, the person especially:**

- Loses the ability to recognize complex objects and complex forms by the process of feeling them **(astereognosis**). Stereognosis is the ability to determine what an object is just by using the modality of touch. Usually, the patient is asked to close their eyes and recognize, by just feeling, a familiar object (coin, a key, a safety pin, a paper clip) placed into the hand.
- Disturbance of the spatial aspects of sensation. This may causes disturbance of the body image and of spatial orientation. For instance the patient may be unable to recognize part of his own body on the side opposite to the lesion or may feel that it is distorted. He may ignore one side of his own body. Patient has no sock on one foot because of sensory neglect. The right side lesions lead to neglect of the left side of the body. Affected individuals ignore the left side of their own bodies, leaving them unwashed and uncared for. They ignore the food on the left side of their plates and will only copy the right side of a simple drawing. Many are blind in the left visual field although they are themselves unaware of the fact.



- **[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 the 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 plays the greatest role in interpretation of the complicated meanings of different sensory experiences. It is important to note that the left hemisphere is usually dominant with respect to language, even in left-handed people. 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

Following severe damage to this area in the dominant side of the brain:

A person might hear perfectly well and even recognize different words but still might be unable to arrange these words into a coherent thought. Likewise, the person may be able to read words from the printed page but be unable to recognize the thought that is conveyed. Therefore, this type of aphasia is called Wernicke's aphasia or sensory aphasia. This is an example: "I called my mother on the television and did not understand the door. It was too breakfast, but they came from far to near. My mother is not too old for me to be young." In Wernicke's aphasia, speech is fluent but "empty", and the substitutions of one word for another ("telephone" → "television") are common. In addition, the patient is unable to perform mathematical operations, and unable to think through logical problems. In addition, the formation of thoughts and choice of words in order to communicate is the function of the Wernicke's area. Therefore, Wernicke's area in the dominant hemisphere is the sensory area for language interpretation. When Wernicke's area in the dominant hemisphere is destroyed, the person normally loses almost all intellectual functions associated with language or verbal symbolism, such as ability to read or to write.

To investigate the integrity of Wernicke's area you can the following test:

*Examiner: What kind of work did you do before you came into the hospital?*

*Patient: Never, now mista oyge I wanna tell you this happened when happened when he rent. His – his kell come down here and is - he got ren something. It happened. In thesse ropiers were with him for hi - is friend - like was. And it just happened so I don't know; he did not bring around anything. And he did not pay it. And he roden all o these arranjen from the pedis on fromiss pescid.*

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.

**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 perform functions different from those in other layer. For examples:

1- Layers I and II receive a diffuse nonspecific input from the reticular activating system that can facilitate the whole brain at once.
2- The neurons in layer III send axons to other closely related portions of the cerebral cortex.
3- The incoming sensory signals excite mainly neuronal layer IV first, then the signals spread toward the surface of the cortex and also toward the deeper layers.
4- The neurons in layer V and VI send axons to more distant parts of the NS.

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

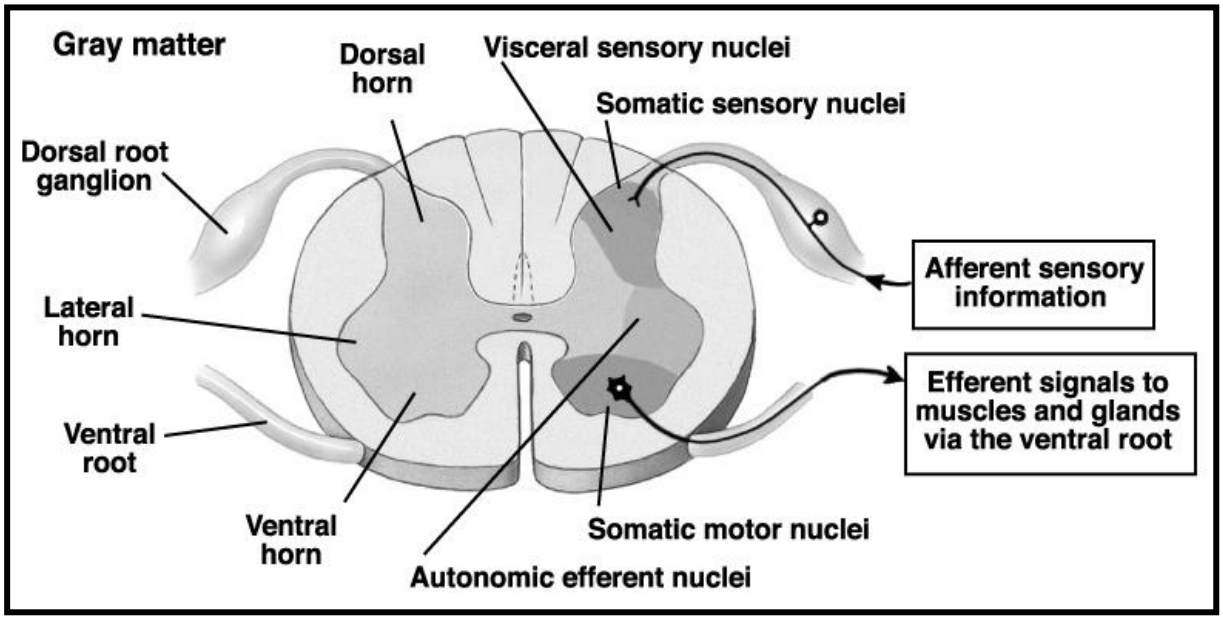
beginning of analysis of the meanings of the sensory signals.

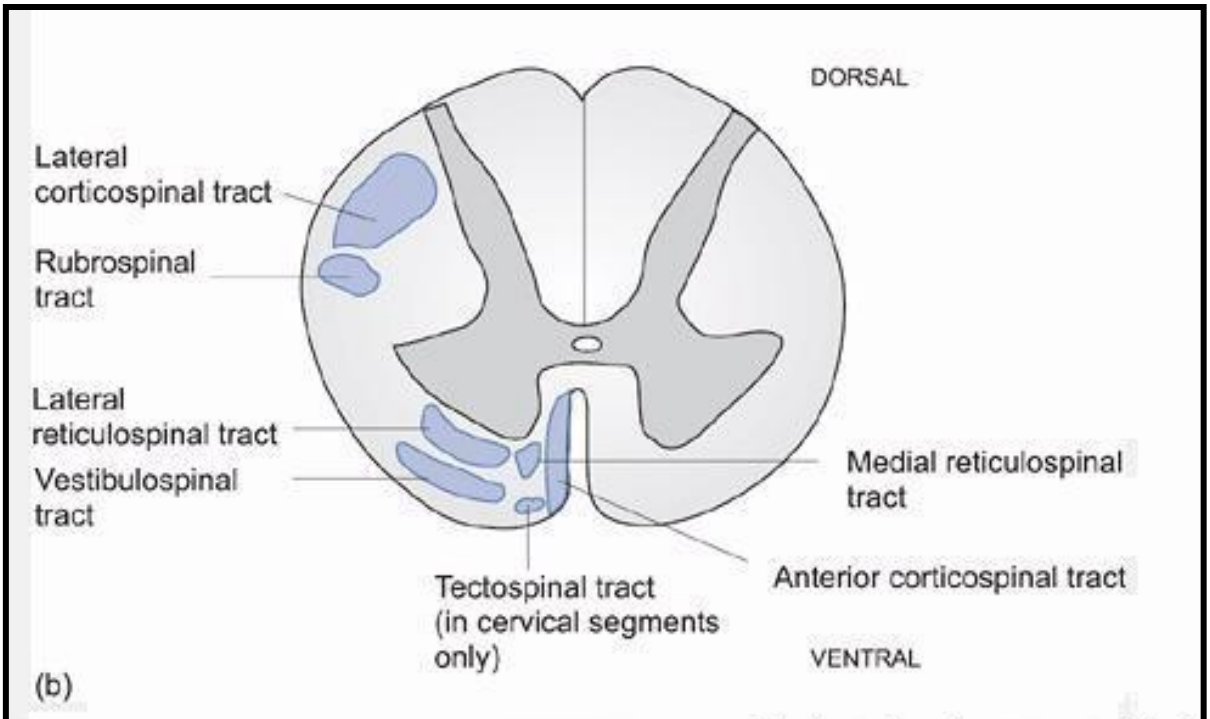
**The corpus callosum plays an essential role in integrating the activity of the two cerebral hemispheres:**

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.

Severance of the corpus callosum, which interconnects the two hemispheres, has shown that the two hemispheres have very specific capabilities in addition to their role in sensation and motor activity. Speech and language abilities are mainly located in the left hemisphere, together with logical reasoning. The right hemisphere is better at solving spatial problems (aware of the environment), was capable of logical choice and non-verbal tasks such as emotional response.

# Motor functions of the CNS




The position of the major motor pyramidal and extrapyramidal descending pathways within the spinal cord

**Descending pathways involved in motor control**

- **The reticulospinal tracts** are largely uncrossed and terminate on interneurons within the spinal cord which influence mainly the muscles of the trunk and proximal parts of the limbs. They seem to be important in the maintenance of certain postures and in startle reactions. The medial (pontine) reticulospinal tract enhances the extensor tone, whereas the lateral (medullary) reticulospinal tract inhibits extensors.
- The fibers of **the vestibulospinal tract** mostly make synaptic contact with interneurons in the ipsilateral spinal cord. These interneurons control the activity of extensor muscles and are important in the maintenance of an erect posture, making adjustments in response to signals from the vestibular apparatus. A direct uncrossed descending pathways known as the lateral vestibulospinal tracts, which can excite extensor and inhibit flexor motor neurons (excites antigravity muscles) especially related to movements of the head. The medial vestibulospinal tracts makes connections with cervical and upper thoracic spinal motor neurons which are involved in reflex adjustments of the head in the space to mentain posture via stimulation of spinal cord neurons that innervate neck musculature.
- The red nucleus receives afferent information from the cortex, cerebellum, and basal ganglia. Fibers of **the rubrospinal tract** terminate in the contralateral gray matter of the spinal cord, and synapse with interneurons controlling both flexor and extensor muscles. The rubrospinal tract is involved in large movements of proximal musculature of the limbs. It inhibits activity of extensors, and increases activity of flexors. Voluntary movements are impaired following lesions to this tract.
- **The tectospinal tract** projects to contralateral cervical regions of the cord and makes synaptic contact with interneurons controlling head and eye movements. The tectospinal tract has an important function in mediating contralateral movements of the head in response to auditory, visual and somatic stimuli. For instance, a flash of light to your LEFT causes you to turn your head to the LEFT.
- **The corticospinal tract:** The lateral corticospinal tracts (direct tract) of the cord are concerned with distal limb muscles and hence with skilled movements especially of the hands and fingers. The ventral (anterior) corticospinal (corticoreticulospinal tracts, indirect tract) are concerned with axial and proximal limb (girdle) muscle contraction.

## The motor functions of the CNS can be divided into:

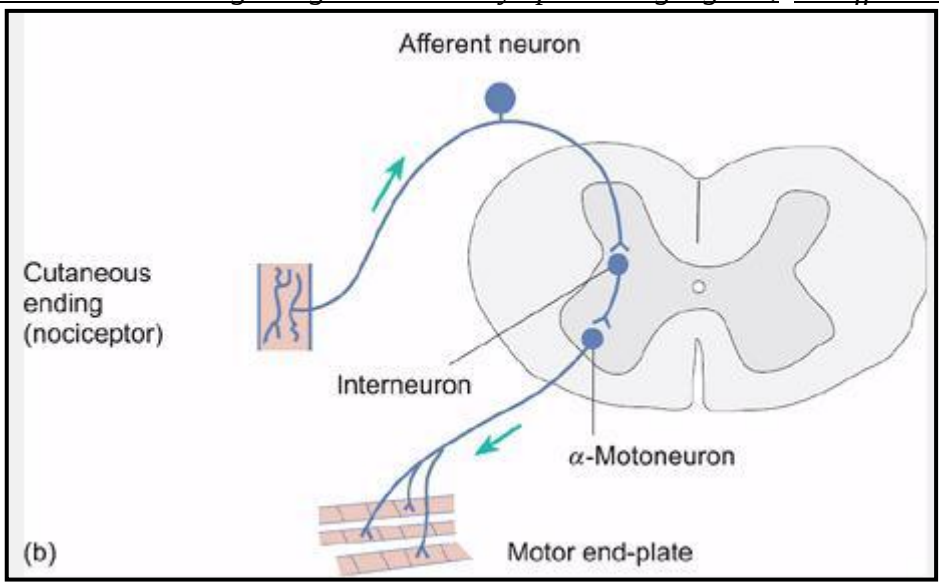
- **Movement,** There are three classes of movements:

  **[a] 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.

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

  **[c] Rhythmic motor patterns** (mixed pattern) which combine voluntary & reflexive acts such as chewing, walking, running. It is initiated and terminated voluntarly, but once initiated it become repeatitive and reflexive.
- **Posture and balance,**
- **Communication.**

The basic unit of reflexes is the **reflex arc**. The arc consists of a *sense organ (receptor), an afferent neuron, one or more synapses in a central integrating station or sympathetic ganglion, an efferent neuron, and an effector.* 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.

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

**A- The 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* lower motor neurons 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 two types:

1. **The alpha motor neurons**: Which give off large nerve fibers (type A alpha nerve fiber) that innervate the large skeletal 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.

**C-** 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.

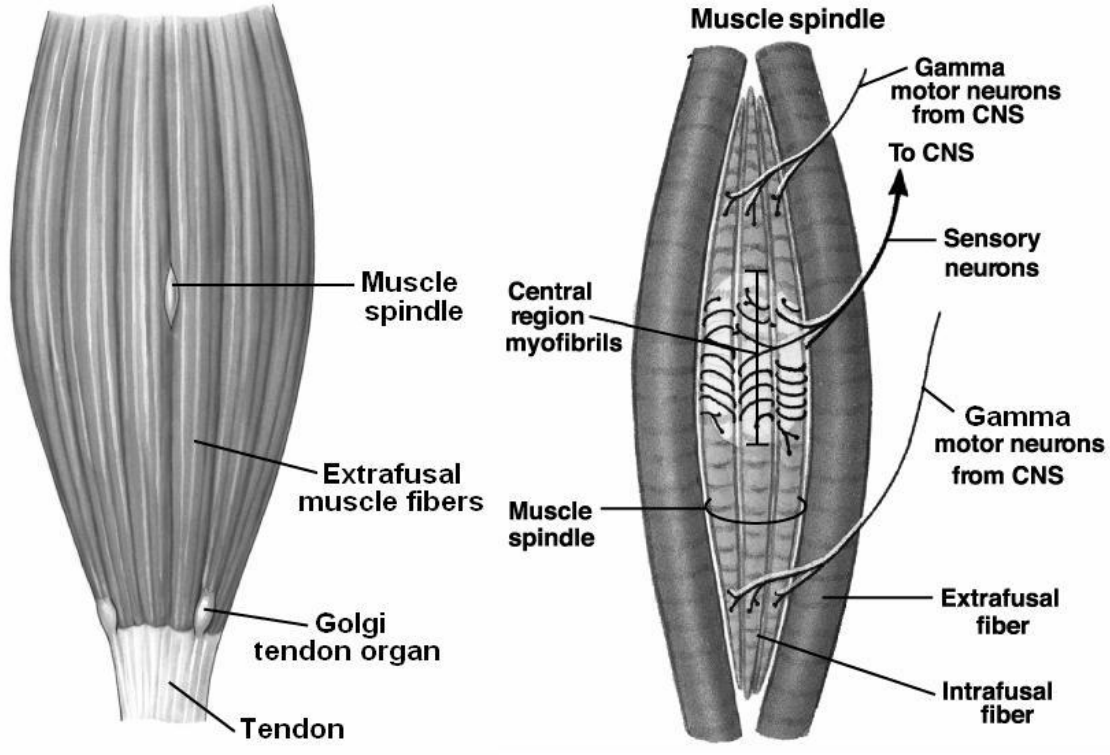
Some of the anterior motor neurons immediately after the motor axons leave the soma give collateral branches to innervate adjacent interneurons called **Renshaw cells** which are located in the ventral horn of the spinal cord. These cells in turn are inhibitory cells that transmit inhibitory signals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

- The recurrent inhibition is important to allow only the initial impulses arriving at a motor neuron 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 and these are:

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

**2— Golgi tendon organs:** Which 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.



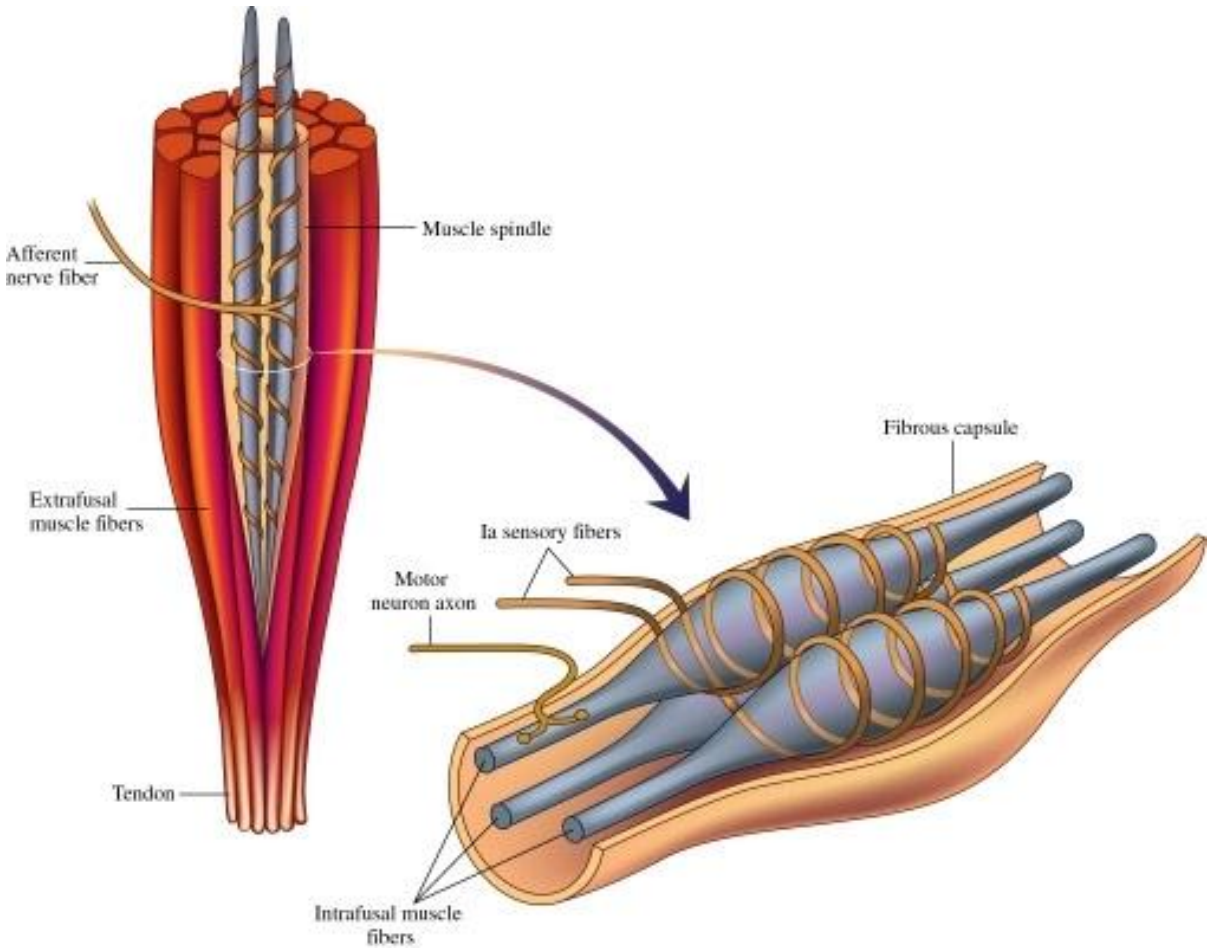

**Muscle spindle:** Each muscle spindle consists of 3—10 specialized muscle fibers enclosed in a connective tissue capsule. These fibers are called *intrafusal muscle fibers* to distinguish them from the *extrafusal muscle fibers* which are the regular contractile units of the muscle. The intrafusal 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 stretch the midportions 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 will stretch the midportions of the spindle and therefore excite the receptor and increases the rate of firing while shortening the midportion 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 midportion of the muscle spindles emit sensory nerve impulses continuously. 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. This can be achieved to a large degree:

**[A] <u>Directly</u> by continuous tonic discharge of descending tracts and these are:**

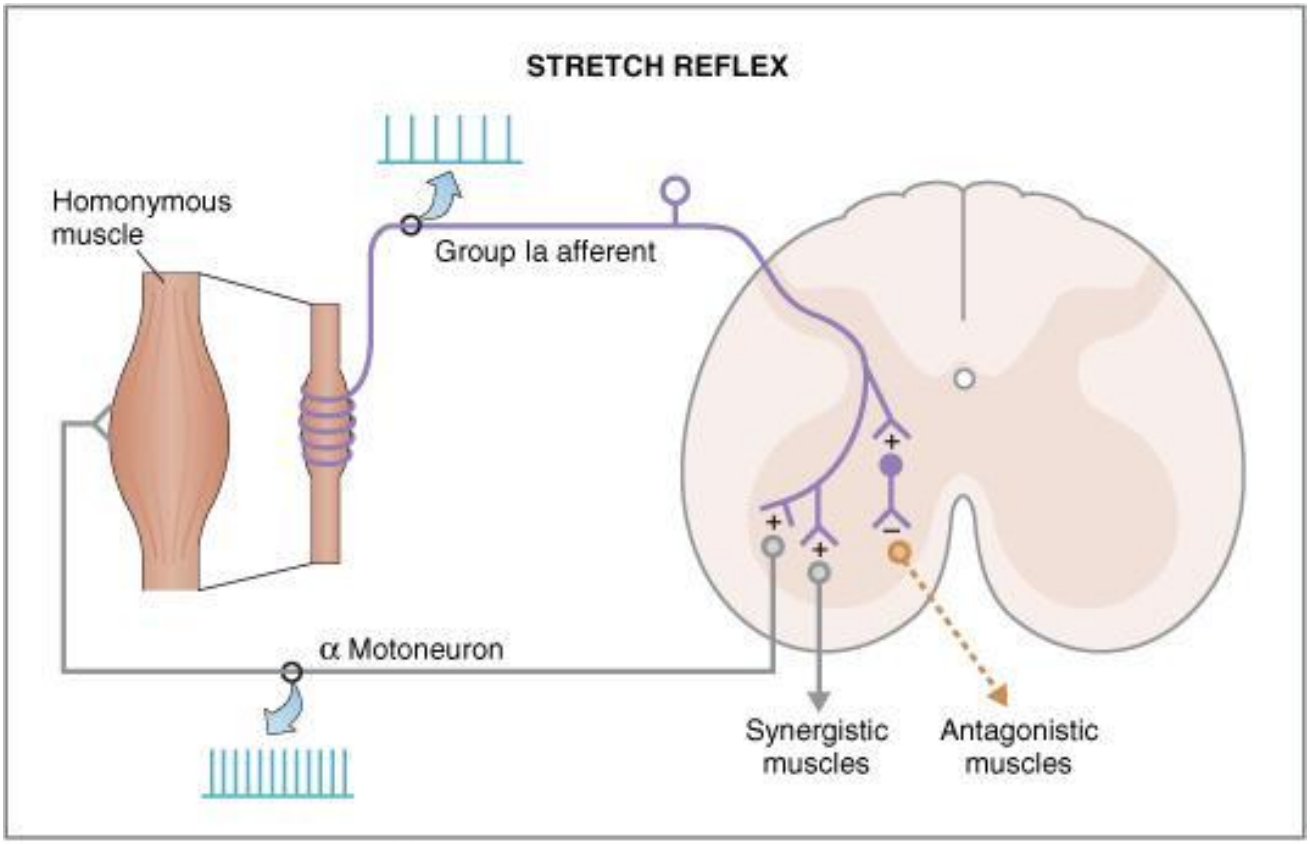
- **Pontine reticulospinal tract (excitatory).**
- **Medullary reticulospinal tract (inhibitory).**
- **Vestibulospinal tract (excitatory).**
- **Corticospinal tract (excitatory).**
- **Rubrospinal tract (inhibitory).**

**[B] <u>Indirectly</u> by number of areas in the brain such as:**

- **Cerebellum (excitatory or inhibitory).**
- **Basal ganglia (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.

**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**.




**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, the midportion 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).

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

**[B] Other functions of the stretch reflex are:**

- **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.
- **Damping or smoothing function** of the stretch reflex: 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.
- **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.

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 bisynaptic 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.

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 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.

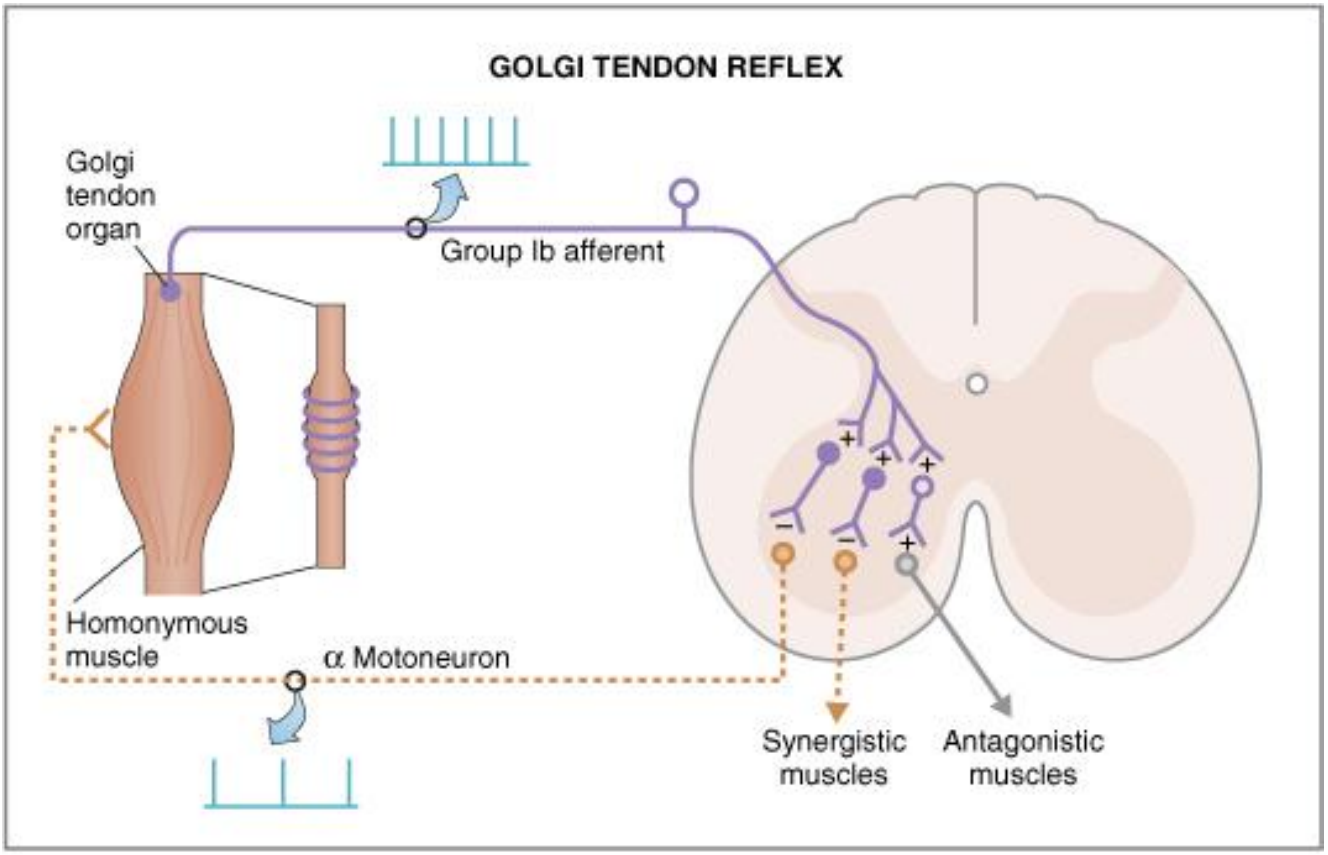
**The Golgi tendon reflex:** It is a reflex mediated by Golgi tendon organs. When the Golgi tendon organs of a muscle are stimulated by increased muscle tension due to active muscle contraction (or to much less extent passively by stretching the muscle), signals are transmitted into the spinal cord and excite inhibitory interneurons that in turn inhibit the anterior alpha motor neurons innervated the same

muscle from which signals were originated. This 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 negative feedback mechanism 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.

***Clinical applications**: When the muscle is **hypertonic**, **passive** and **sustained** muscle stretch will lead to an effect:*

***【1】 Clasp—knife effect (reflex):** In this effect, moderate muscle stretch will lead to muscle contraction by excitation of the muscle spindles. However, sustained passive stretch of a higher magnitude will lead to development of a higher muscular tension resulting in excitation of Golgi tendon organ and, therefore, reflex inhibition of the muscle involved (inverse stretch reflex). The resulting*

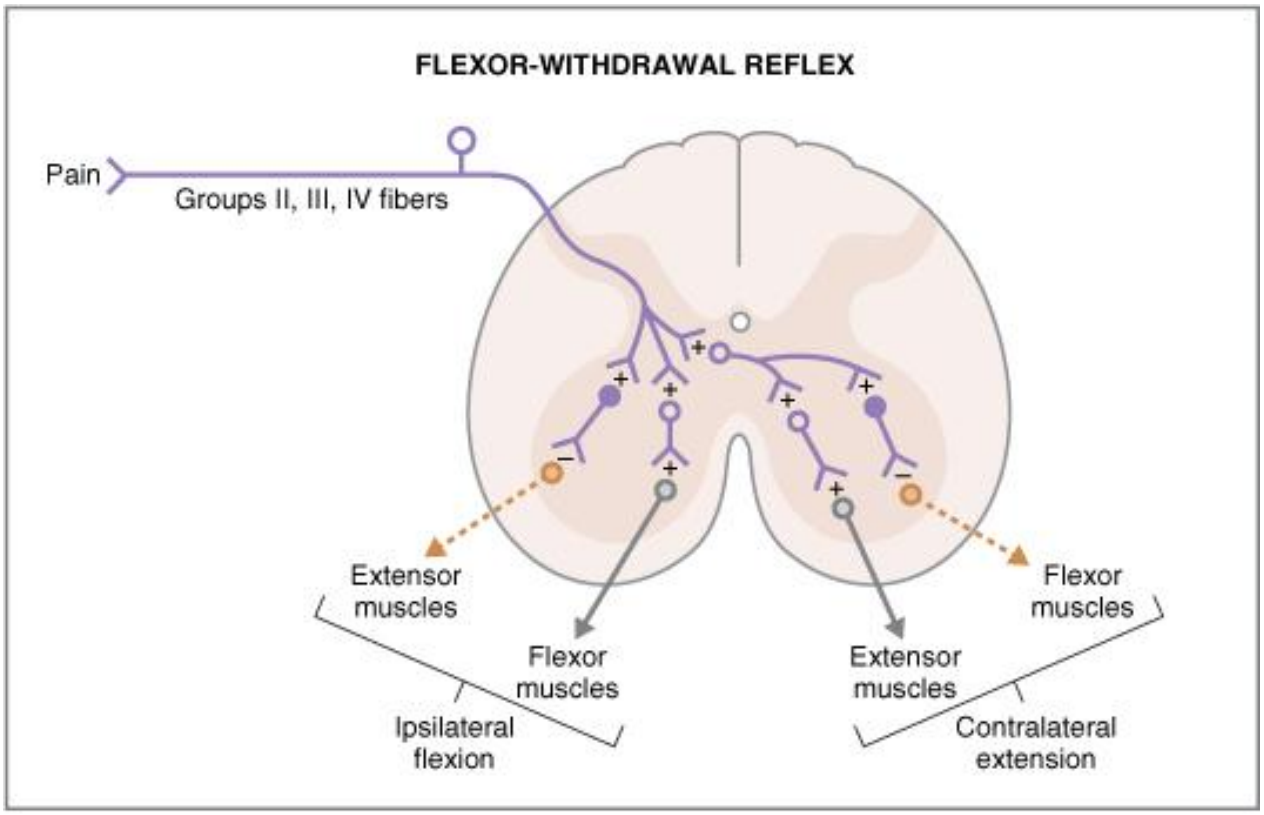
*pattern is as follow: moderate stretch ➔ muscle contraction, strong stretch ➔ muscle relaxation. Therefore, a sustained passive muscle stretch in a hypertonic muscle shows a sequence of resistance followed by given. This reflex can be seen in disease of the corticospinal tracts (hypertonicity or spasticity)*

***[2] Clonus**: It is due to increased gamma efferent discharge. This is a sign in which there is a regular, rhythmic contraction of a hypertonic muscle subjected to sudden sustained passive stretch. Ankle clonus is a typical example. This is initiated by brisk, sustained dorsiflexion of the foot, and the response is rhythmic planter flexion at the ankle. The stretch reflex-inverse stretch reflex sequence may contribute to this response.*

**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.
4- Circuits to cause crossing of the signals to the other side of the cord with reciprocal innervation (inhibition 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.**
**3. The cerebellum.**

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 tract) and the activities of the cerebellum, all influence directly or indirectly:

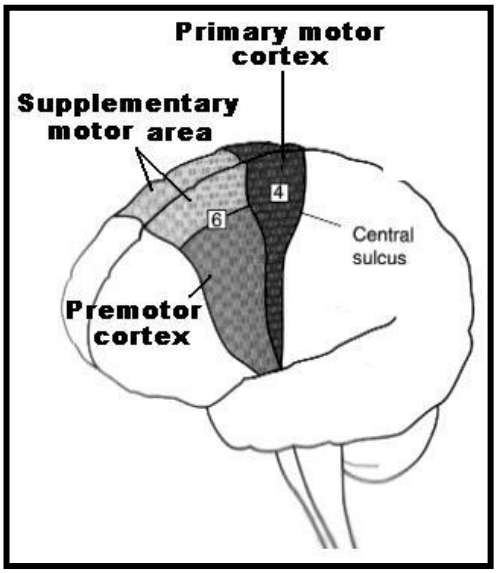
**[1].** The cells of the anterior horn of spinal cord or motor cranial nuclei from which the lower motor neuron runs to motor unit**.** Therefore, the lower motor neuron is the final common path for all efferent impulses directed at the muscle. The inputs converging on the motor neurons bring about 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.

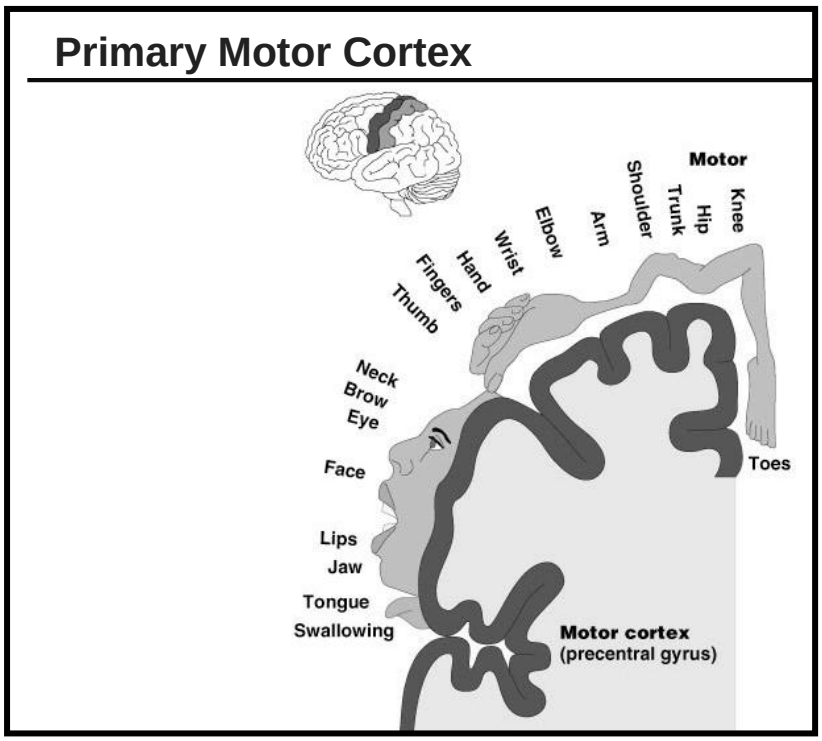



The motor cortex divided into three separate divisions:

**[1] The primary motor cortex (Brodmann's area 4):** 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. 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. More than one half of the entire primary motor cortex is concerned with controlling the hands and the muscles of speech which are highly developed in human being.

This area is responsible for conscious voluntary control of precise, skilled movements of either individual muscles or small groups of muscles.

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.




**[2] The supplementary motor cortex (Brodmann's area 8 and 9):** This is located on medial surface of the frontal lobe slightly anterior to the primary motor cortex. It is responsible for global mental planning of complex motor sequences and sends these instructions to the premotor Area. When movement sequences are rehearsed mentally, but not performed physically, then neurons in the supplementary motor area are active and the premotor cortex is quiescent. It is important in movements that require both hands eg tying one's shoe laces.

Damage to this area leads to the following:
Patient cannot tie shoe laces.
Impaired selection of a particular movement sequence like impairs one's ability to reach around barriers.

**[3] The premotor cortex (Brodmann's area 6):** 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 global mental planning received from the supplementary motor area. When movement due to occur, then the premotor cortex, under instructions from the supplementary motor area transmits instructions to the specific primary motor areas which in turn activate specific motor units for the intended movement. There is a reason to believe that hundreds of learned different patterns of movements are stored in the premotor cortex, which in combination can produce thousands to millions movements which could allow almost any type of motor activity. To achieve these results, the premotor area sends its signals into the primary motor cortex to excite multiple groups of muscle either directly or indirectly (or through basal ganglia ➔ thalamus ➔ primary and premotor motor cortex).

## Damage to this 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.

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 uncoordinated utterances or an occasional simple words such as "no" or "yes". Patients with lesion of Broca's area (in the dominant hemisphere) frequently suffer from paralysis of the opposite side (right) of the body. An example of Broca`s aphasia:
"Ah ... Monday ... ah Dad and Paul [patient's name] ... and Dad ... hospital. Two ... ah doctors ..., and ah ... thirty minutes ... and yes ... ah ... hospital. And, er Wednesday ... nine o'clock. And er Thursday, ten o'clock ... doctors. Two doctors ... and ah ... teeth. Yeah, ..., fine.

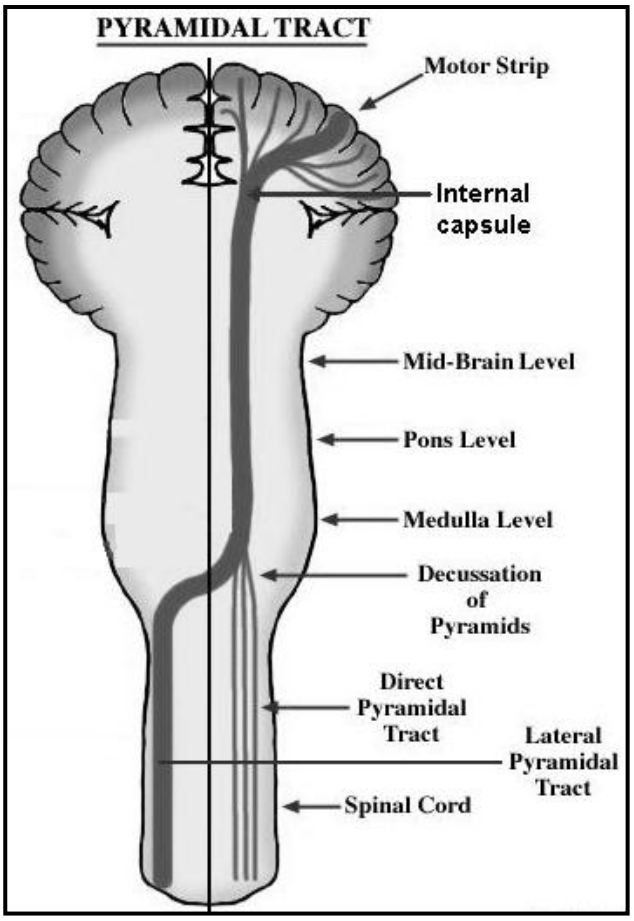
2. **The voluntary eye movement area** for controlling eye and eyelid movements such as blinking. Damage to this area prevents a person from voluntarily moving the eyes toward different objects. Instead, the eyes tend to lock on specific objects, an effect controlled by signals from the occipital region. 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 *40% from the primary motor cortex*, few of them from ***giant pyramidal cells***, also called ***Betz cells***, *40% from premotor cortex*, and 20% from the somatic sensory areas at the parietal lobe.




The centrifugal nerve fibers that pass 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 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%) then crosses to the opposite side and descends in **the lateral corticospinal tracts (direct tract)** of the cord. Finally terminating on excitatory (for the agonist muscles) or inhibitory (for antagonist muscles) interneurons, which in turn synapse with anterior motor neurons. These fibers are concerned with 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%) do not cross to the opposite side in medulla but pass ipsilaterally down the cord

through the reticular formation in the **ventral (anterior) corticoreticulospinal tracts (indirect tract)**, but these fibers terminate bilaterally mainly at the level of synapse with 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.**

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**.

The cerebral cortex itself and subcortical structures (basal ganglia, brain stem reticular formation, 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.

In addition to providing fibers that run in the corticospinal and corticobulbar tracts, the somatic sensory area and related portions project to the premotor area. Lesions of the somatic sensory area cause defect in motor performance that are characterized by inability to execute learned sequences of movements such as eating with a knife and fork.

Almost all of the cranial nerves receive **bilateral** innervation from the fibers of the pyramidal tract. This means that both the left and right members of a pair of cranial nerves are innervated by the motor strip areas of both the left and right hemispheres. This is a safety mechanism. If there is a unilateral lesion on the pyramidal tract, both sides of body areas connected to cranial nerves will continue to receive motor messages from the cortex. The message for movement may not be quite as strong as it was previously but paralysis will not occur. The two exceptions to this pattern are the portion of CN XII **(hypoglossal Nerve**) that provides innervation for tongue protrusion and the part of CN VII (facial Nerve) that innervates the muscles of the lower face. These only receive **contralateral** innervation from the pyramidal tract. This means that they get information only from fibers on the opposite side of the brain.

Therefore, a unilateral upper motor neuron lesion could cause a unilateral facial droop or problems with tongue protrusion on the opposite side of the body. For example, a lesion on the left pyramidal tract fibers may cause the right side of the lower face to droop and lead to difficulty in protruding the right side of the tongue. The other cranial nerves involved in speech and swallowing would continue to function almost normally as both members of each pair of nuclei still receives messages from the motor strip. Because most cranial nerves receive bilateral innervation, lesions of the upper motor neurons of the pyramidal tract must be bilateral in order to cause a serious speech problem.

On the other hand, unilateral lesions of the lower motor neurons may cause paralysis. Lesions to the axons of the cranial nerves are called **peripheral lesions**. This occurs because the lower motor neurons are the final common pathway for neural messages traveling to the muscles of the body. At the level of the lower motor neurons, there is no alternative route which will allow messages from the brain to reach the periphery. Muscles on the same side of the body as the lesion will be affected. Lesions on the cranial nerve nuclei located in the brain stem are called **bulbar lesions**. The paralysis that they produce is called **bulbar palsy**. When bilateral lesions of the upper motor neurons of the pyramidal tract occur, they produce a paralysis resembling that which occurs in bulbar palsy. For this reason, the condition is known as **pseudo-bulbar palsy**.

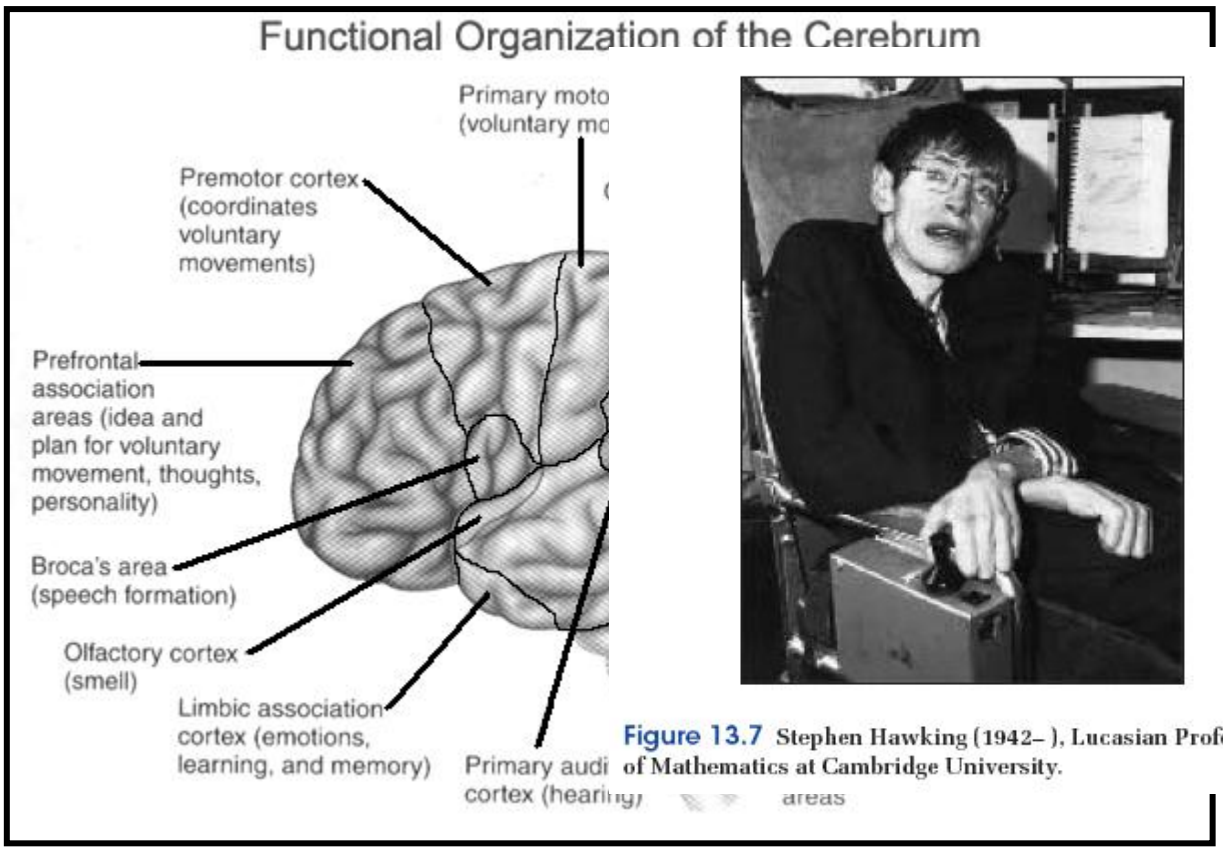


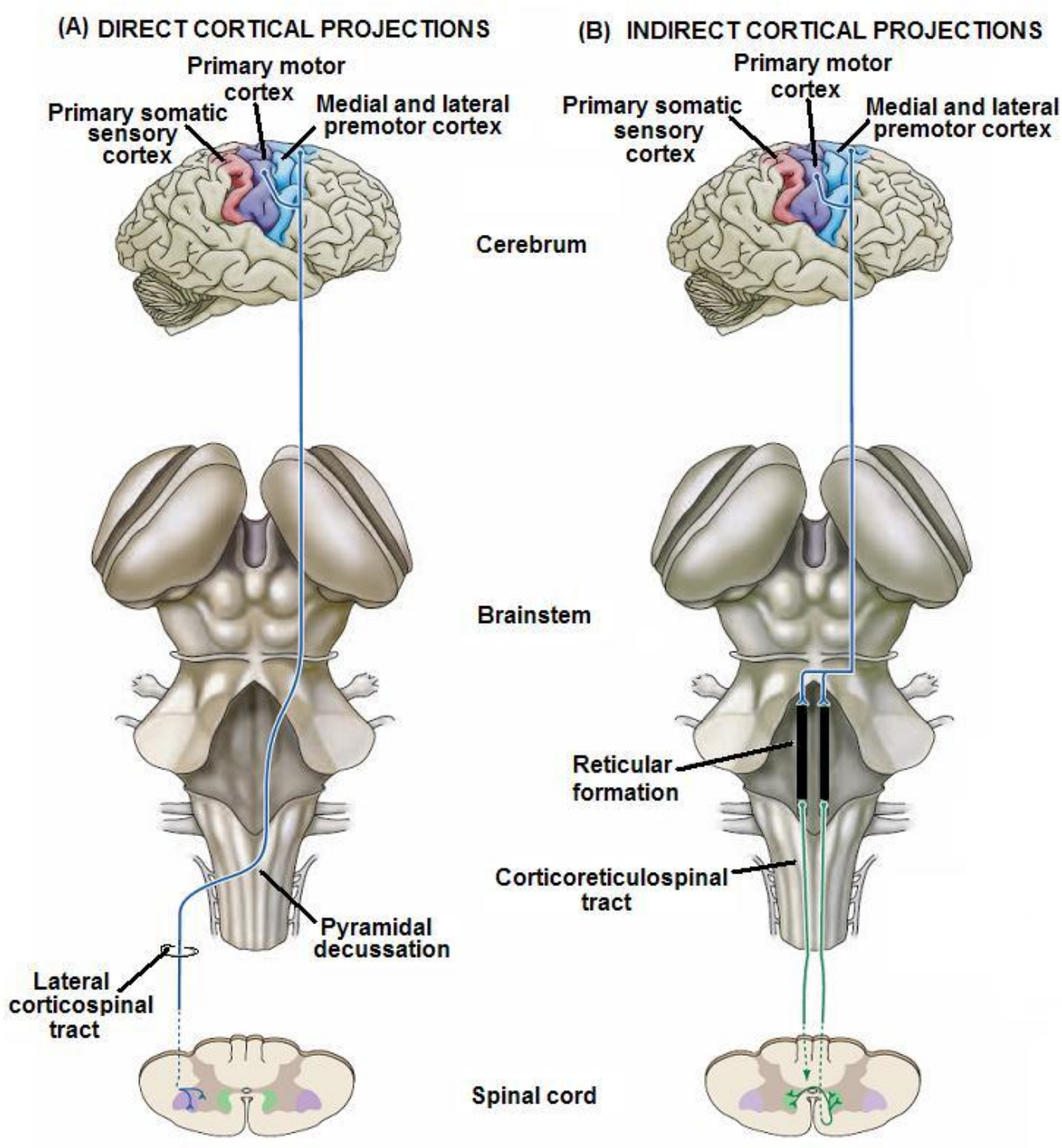

**Figure 13.7** Stephen Hawking (1942– ), Lucasian Professor of Mathematics at Cambridge University.

***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. Signs of polio include muscle pain, weakness, and loss of some reflexes, followed by paralysis, muscular atrophy, and sometimes respiratory arrest. The virus spreads by fecal contamination of water. Historically, polio afflicted mainly children, who sometimes contracted the virus in the summer by swimming in contaminated pools. The polio vaccine has nearly eliminated new cases.*

*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.*

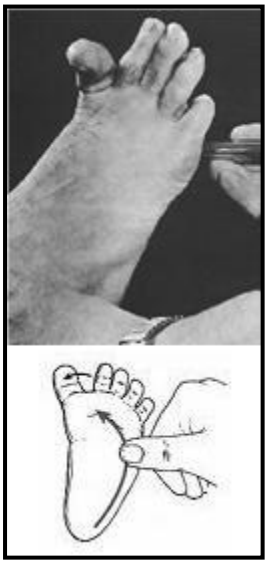

(A) DIRECT CORTICAL PROJECTIONS
Primary motor cortex
Primary somatic sensory cortex
Medial and lateral premotor cortex
Pyramidal decussation
Lateral corticospinal tract
(B) INDIRECT CORTICAL PROJECTIONS
Primary motor cortex
Primary somatic sensory cortex
Medial and lateral premotor cortex
Cerebrum
Brainstem
Reticular formation
Corticoreticulospinal tract
Spinal cord

**The extrapyramidal system:** 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 direct pyramidal system. This system is concerned mainly with:

- ***Postural control and stability,***
- ***Inhibits unwanted muscular activity,***
- ***Maintains muscle tone,***
- ***It has projections that carry autonomic motor impulses to voluntary muscles in the body, including the muscles for speech, facial expression, and swallowing. During speech, muscles are receiving input from both the pyramidal and extrapyramidal systems. it is involved in gross motor movement rather than fine. It is responsible for facial expression such as sadness, irony and happiness.***

**Extrapyramidal system includes:**

- **Basal ganglia**,
- **Reticular formation**,
- **Vestibular nuclei**,
- **Red nuclei**,
- **Substantia nigra**,
- **Tectum**,
- **Subthalamic nucleus**,
- **Cerebellum**



When a firm tactile stimulus is applied to the lateral sole of the foot, two reflex arcs are stimulated at the same time one through the pyramidal system and the other through the extrapyramidal system. In normal condition, the reflex arc of the pyramidal system suppresses that of the extrapyramidal system and therefore downward bending of the toes is elicited in response to sensory stimuli from the bottom of the feet. However, when the damage occurs to the pyramidal system without involving the extrapyramidal system, the same tactile stimulus to the sole will produce extension of the great toe and fanning outward of other toes. This type of response is called the **Babinski sign**, which used clinically to detect damage specifically in the pyramidal portion of the motor control systems. The cause of this sign is due to the stimulation of the withdrawal protective type of reflex of the extrapyramidal system unopposed by the damaged pyramidal system.

The main spinal **extrapyramidal tracts** include the subcorticospinal pathways which are:

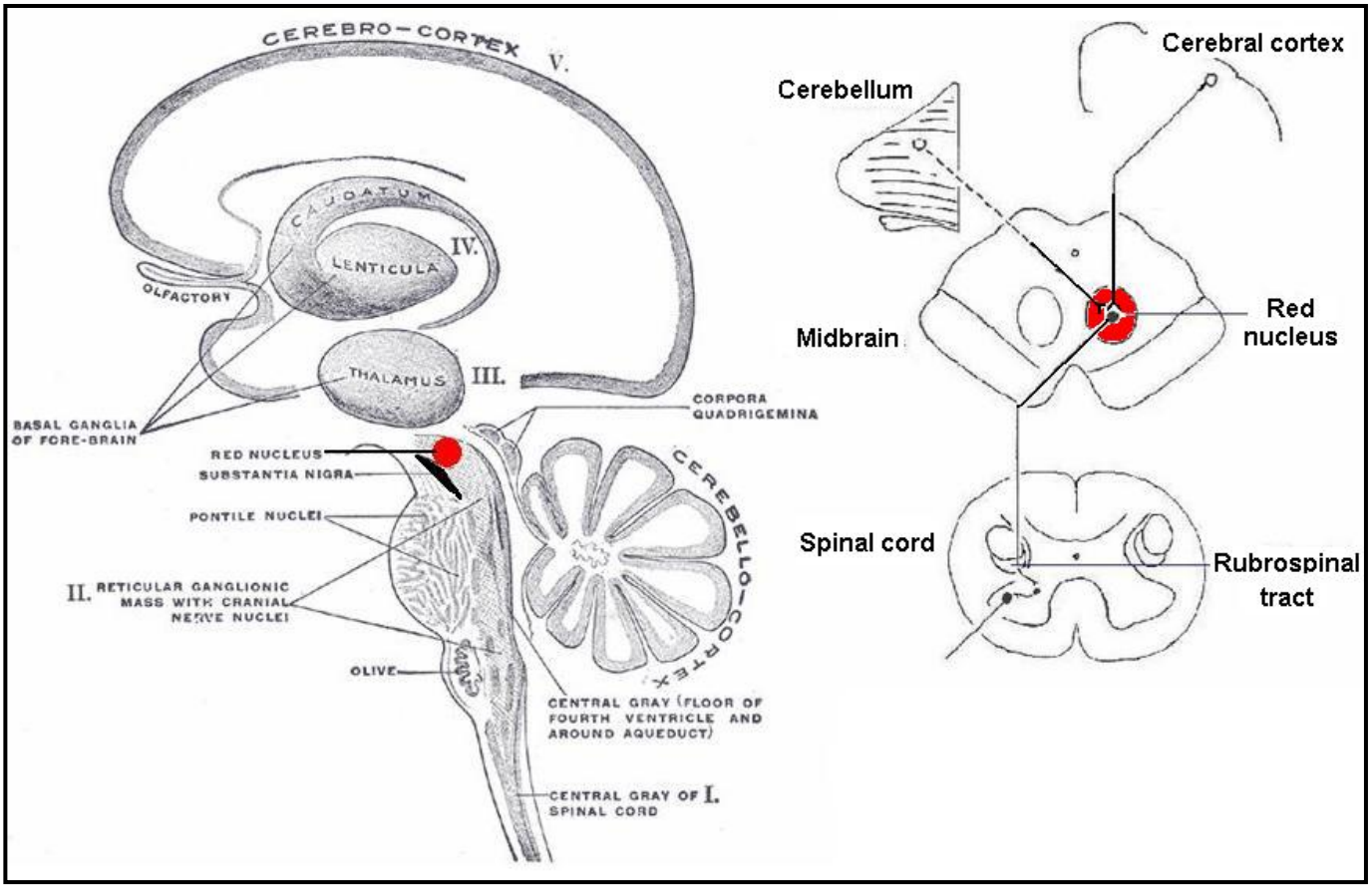
- **Tectospinal tract** (from the superior colliculus of the tectum and is involved in the control of neck muscles),
- **Vestibulospinal tract** (from vestibular nuclei),
- **Reticulospinal tracts** (from pontine and medullary reticular formation),
- **Rubrospinal tract** (from the red nucleus).

## 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. It receives fibres from the deep cerebellar nuclei and cerebral cortex 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. 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. The rubrospinal tract is involved in large movements of proximal musculature of the limbs. It inhibits activity of extensors, and increases activity of flexors.

When the pyramidal fibers are destroyed alone, discrete movements can still occur, except that the movements of the fingers and hands are considerably impaired. Lesion or inactivation of the red nucleus, or of the rubrospinal tract leads to deficits in the use of the contralateral distal limb that closely resemble those observed after lesions of the motor cortex or of the corticospinal tract.




From the upper end of the spinal cord and throughout the entire extent of the brain stem (medulla, pons, mesencephalon) there is an area of diffuse neurons collectively known as the **reticular formation**. It is made up of small neurons arranged in complex intertwining nets. The Reticular Formation represents a rostral extension of the interneuronal 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 hypothalamus, 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.

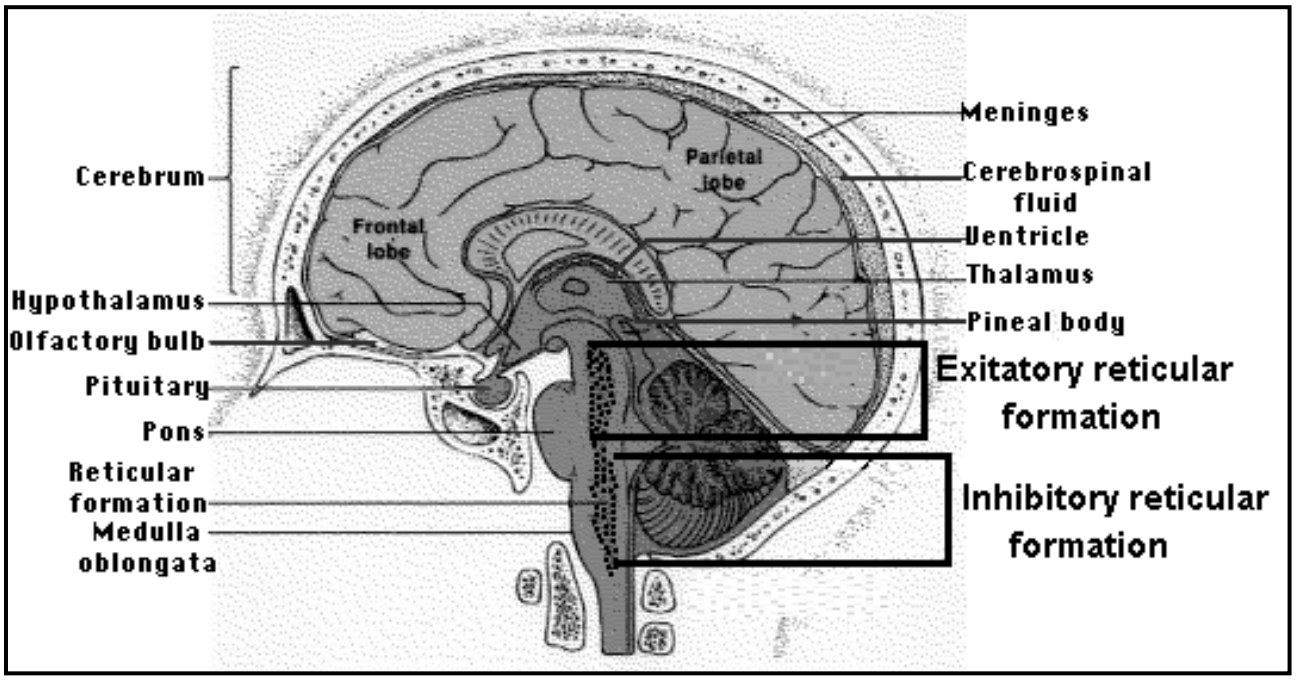
**How is the Reticular Formation organized?**

Can be arranged in 3 longitudinal medial -to- lateral zones on either side of the midline.

- **Raphe nuclei**, the neurons in these nuclei secrete **serotonin;** its rostal projections are active in sleep program while the caudal projections modulate pain perception, motor responses, autonomic functions, and arousal.
- **Medial (Magnocellular) zone nuclei** (lateral to Raphe nuclei) and includes gigantocellular reticular nucleus, paramedian pontine reticular formation (PPRF), precerebellar reticular nuclei, and locus ceruleus. The nerve fibers from this area secrete **norepinephrine**). These projection neurons modulate motor responses and postur, pain sensation, autonomic functions, and arousal.
- **Lateral (Parvocellular) zone nuclei** located lateral to Medial Zone nuclei and include parvocellular reticular nucleus, parabrachial area, and lateral reticular nucleus. These interneurons help coordinate autonomic reflexes and simple behavior mediated by the cranial nerves.

**Functions of the Reticular Formation:** The ascending and descending 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
- The control of consciousness




**1. The regulation of posture:** The reticulospinal tracts are two long descending pathways associated with the control of movements and posture. 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. 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.

**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 by monoaminergic (NE, 5-HT) projections that originate from neurons in the periaqueductal gray region and serotoninergic raphe magnus nucleus, and from noradrenergic cell groups in the pons, including the locus ceruleus. In the spinal cord, these projections inhibit nociceptive neurons through direct and indirect connections in the superficial layers of the dorsal horn.

**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).

**5. The control of consciousness:** Ascending monoaminergic (NE, 5-HT) projections from the rostral reticular formation to the cerebral cortex and thalamus increase wakefulness and vigilance as well as the responsiveness to sensory stimuli, a state known as arousal.

With respect to 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. The inhibitory area comprises the caudal portion of the medulla. Stimulation in the facilitatory area results in contraction of physiologic extensors (through pontine reticulospinal tract) whereas stimulation in the inhibitory area tends to inhibit the physiological extensors (through medullary reticulospinal tract). The neurons in the facilitatory area are tonically active, and their activity is controlled by descending influences from the motor cortex, basal ganglia, and cerebellum. The neurons in the inhibitory reticular formation generally are not tonically active but must be activated by descending commands from higher centers.

**Reticular activating system (RAS)**

The mesencephalic and upper pontine portions of the reticular formation (extensor facilitatory) seem to 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 and also descending projections to the spinal cord as excitatory reticulospinal tracts. These pathways control the overall degree of activity of the cortex, other subcortical nuclei and the segmental spinal activities. Ascending projections from the rostral reticular formation to the cerebral cortex and thalamus increase wakefulness and vigilance as well as the responsiveness to sensory stimuli, a state known as **arousa**l. These pathways form an ascending reticular activating system (RAS). The ***gigantocellular nucleus*** of the reticular formation is a principal activator portion of the RAS. The neurons of this nucleus release acetylcholine at their terminals, which acts as excitatory transmitter.

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*** from almost any part of the body which enter the reticular formation either directly or through collaterals from other tracts (spinoreticular tracts, spinothalamic tracts, and spinotectal tracts). 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

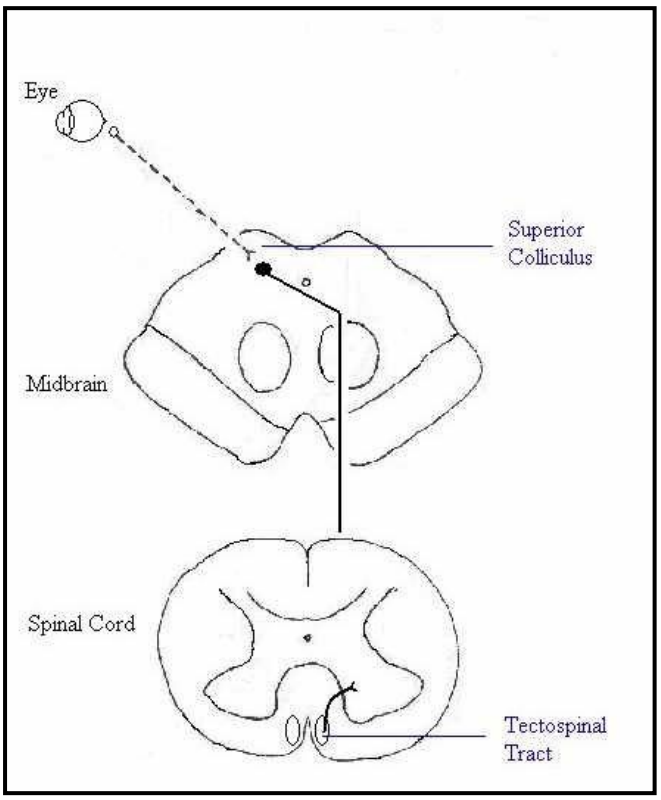
reticular formation via direct fiber pathways. This may explain the importance of moving around when one wishes to remain awake.

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 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 axons cross to contralateral side of body just below periaqueductal gray matter and project to medial interneurons in upper cervical segments. The tectospinal tract has an important function in mediating contralateral movements of the head in response to auditory, visual and somatic stimuli. For instance, a flash of light to your LEFT causes you to turn your head to the LEFT. This reflex would involve a projection from the retinae to the RIGHT superior colliculus (retinocollicular), and then the long CROSSED tectospinal axons to the LEFT side of the cervical spinal cord. This is a protective reflex. **Superior colliculi** are visual reflex center (in humans, the superior colliculus (SC) is involved in the generation of saccadic eye movements and eye-head coordination. **Inferior colliculi** responsible for auditory (Startle) reflex. A reflex 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 and tracts of passage, 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, and psychostimulant drugs (such as cocaine) directly target this area. 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.

**Subthalamic nucleus**

Subthalamic nucleus is a small lens-shaped nucleus in the brain where it is a part of the basal ganglia system. As suggested by its name, the subthalamic nucleus is located ventral to the thalamus. It is also dorsal to the substantia nigra and medial to the internal capsule.

**Ceruleospinal System**

Ceruleospinal system originates in locus ceruleus in upper pons and from some neurons in pontomedullary reticular formation (transmitter: norepinephrine) descends in ventrolateral part of lateral column with widespread synaptic connections onto interneurons and motoneurons (predominantly inhibitory)

## Vestibular System

The vestibular system controls balance. It is synaptically linked to the extrapyramidal system. So that persons with extrapyramidal disorders frequently also have problems with balance and may experience frequent falls. The main sensory organ is semicircular canals of the vestibular apparatus. 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 send axons (via the inferior cerebellar peduncle) to the flocculonodular lobe of the cerebellum to maintain equilibrium. The major tracts and functions of the vestibular system include:

**1. Mentain the body and the head posture:**

- A direct uncrossed descending pathways known as the lateral vestibulospinal tracts, which can excite extensor and inhibit flexor motor neurons (excites antigravity muscles) especially related to movements of the head.

Lesions involving the vestibular nerve, nuclei, and descending pathways will result in problems such as stumbling or falling TOWARDS THE SIDE OF THE LESION. For example, if you have a patient with a lesion that has destroyed the LEFT vestibular nerve, then the LEFT vestibular nuclei and the LEFT lateral vestibulospinal tract are "tuned" down. Meanwhile, the normal RIGHT nerve is fine and firing away and thus the RIGHT lateral vestibulospinal tract is also in good shape. The two lateral vestibulospinal tracts usually counteract each other functionally, but now the RIGHT side takes over. The end result? STUMBLING AND FALLING TO THE WEAK SIDE, IN THIS CASE TO THE LEFT. Again, here Romberg sign is positive while the eyes are closed.

- Bilateral descending pathways known as the medial vestibulospinal tracts. This pathway makes connections with cervical and upper thoracic spinal motor neurons which are involved in reflex adjustments of the head in the space to mentain posture via stimulation of spinal cord neurons that innervate neck musculature.
- Tracts leading to and from the cerebellum (reflex of equilibrium), which gives cerebellum the information it needs to adjust any motor skills it happens to be controlling at the time. Normally the cerebellum and higher centers contribute inhibitory projections to the lateral vestibular nucleus that tends to counterbalance its excitatory influence on the antigravity muscles.

**2. Mentain the retinal image while the head is moving:**

- Tracts leading to and from 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 vestibuloocular 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 vestibulocortical 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

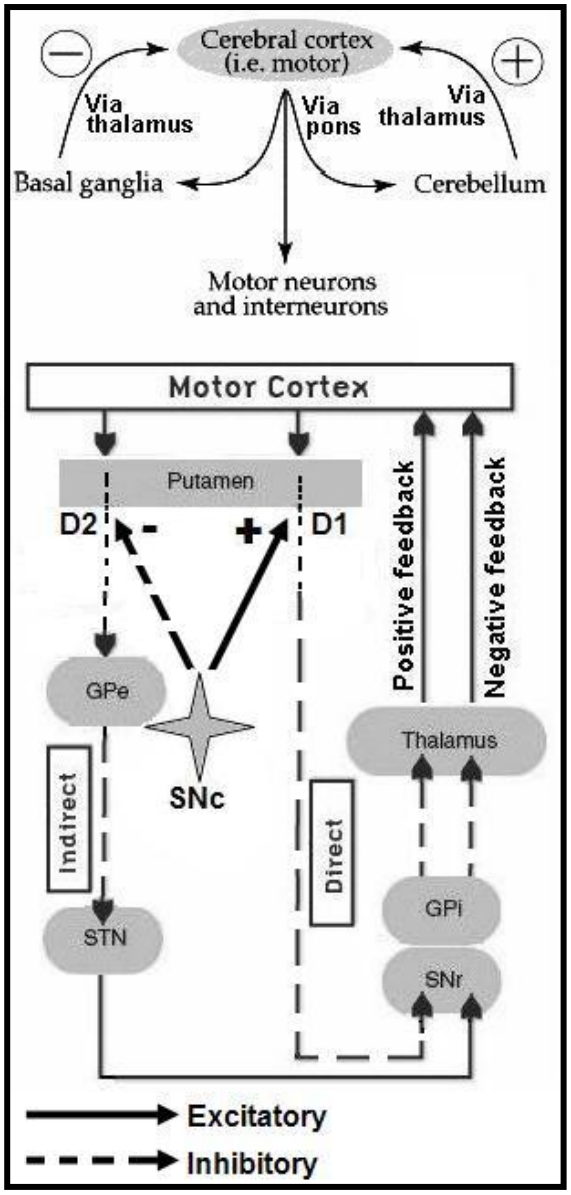
The Basal ganglia are a group of functionally related nuclei located bilaterally in the inferior cerebrum, diencephalon and midbrain. Complex neural connections link the basal ganglia with the cerebral cortex and the thalamus. Because the basal ganglia do not make any direct sensory or motor connections with the spinal cord, their contribution to the control of movement is made indirectly through the sensory and motor cortex. Motor cortex sends information to basal ganglia and cerebellum, and both structures send information right back to cortex via the 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, and a disturbance in either system will show up as movement disorders.

*The basal ganglia participate in the control of smooth movement of the body, establishing posture, suppressing unwanted movements, besides some of the involuntary muscle contractions that originate in the brain stem or spinal cord.*

Physiologically, the basal ganglia composed of the following nuclei:

1. Caudate nucleus. ] striatum
2. Putamen nucleus. ] (neostriatum, striate body)
3. Globus pallidus.
4. Subthalamic nuclei (body of Luys).
5. Substantia nigra.




The metabolism of the basal ganglia is unique in a number of ways. These structures have high oxygen consumption. The copper content of the substantia nigra and the nearby locus ceruleus is particularly high.

- **The caudate** and **putamen** receive most of the input from cerebral cortex; in this sense they are the doorway into the basal ganglia.
- **Globus pallidus interna (GPi)** and **substantia nigra pars reticulata (SNr**) are the outflow of almost all inhibitory signals from the basal ganglia back to thalamus. The two output nuclei of the basal ganglia, GPi and SNr, *tonically* inhibit their target nuclei in the thalamus.
- The **inhibitory outflow signals** from globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr) to the thalamus are modulated by two parallel pathways that project from the striatum. These two pathways are:

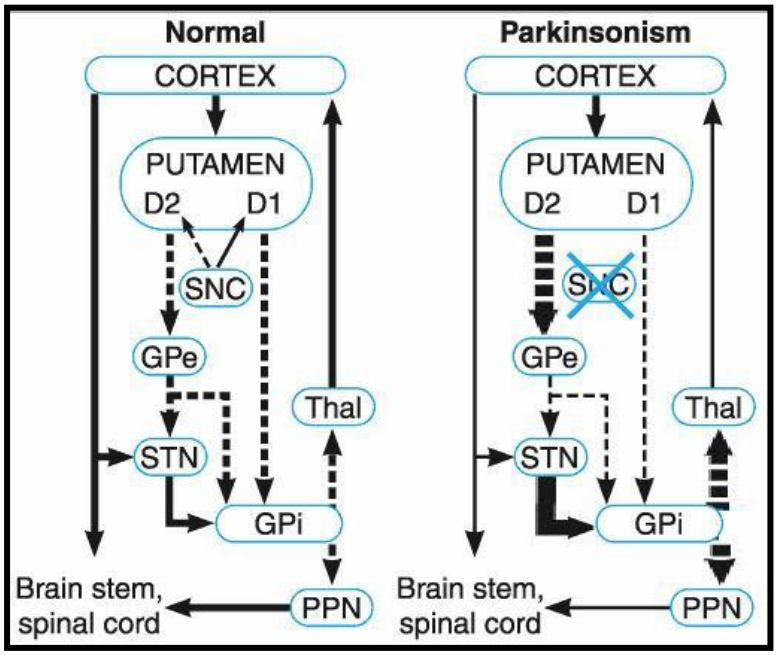
**[1] Direct pathway** has **positive feedback**, decreases inhibition on the thalamus, i.e, an increased stimulation from the cortex will decreases the inhibition on the thalamus, and consequently an increase stimulation of the cortex, and vice versa. It is consisting of the loop – Cortex $^{+}$ ➔ striatum $^{-}$ ➔ GPi $^{-}$ ➔ thalamus $^{+}$➔ cortex .

**[2] Indirect pathway** has **negative feedback**, increases inhibition on the thalamus, i.e, an increased stimulation from the cortex will increases the inhibition on the thalamus, and consequently a decrease stimulation of the cortex, and vice versa. It is consisting of the loop - Cortex $^{+}$ ➔striatum $^{-}$ ➔ GPe $^{-}$ ➔ STN $^{+}$ ➔ GPi ➔ thalamus $^{+}$➔ cortex.

**Direct pathway:** Disinhibits motor thalamus, and thus activates thalamo-cortical neurons. Consequently, activates motor cortex and facilitates movement.

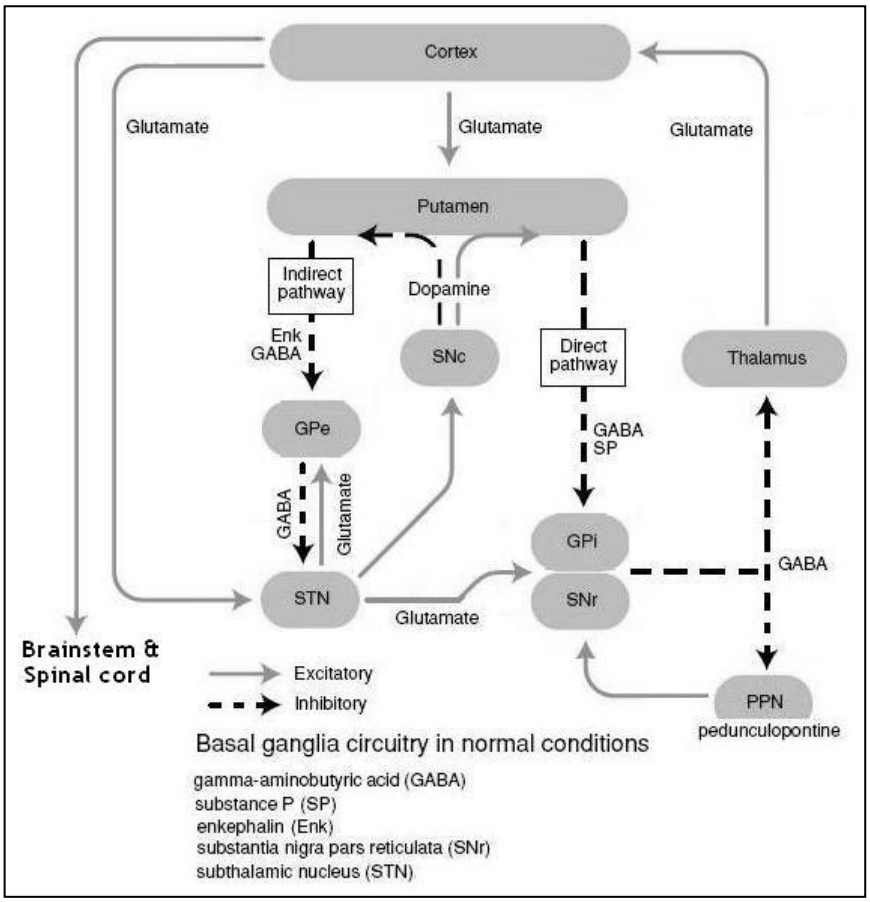
**Indirect pathway:** Inhibits motor thalamus, and thus inhibits thalamo-cortical neurons. Consequently, inhibits motor cortex and inhibits movement

The two striatal output pathways are affected differently by the dopaminergic projection from the **substantia nigra pars compacta (SNc)** because they have different dopamine receptors (D1 and D2). 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. This correlates well with the presumed function of dopamine, which behaves like a reinforcing signal. These pathways may provide a mechanism whereby patterns that the child perceives as rewarding or beneficial are ultimately strengthened within the basal ganglia. Disorders of this system may lead to incorrect patterns or excessive positive or negative feedback.




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).

Although there are many different neurotransmitters used within the basal ganglia (principally ACh, glutamate, GABA, and dopamine), the overall effect on thalamus, whether positive or negative feedback, is **inhibitory**. All circuits completing a closed feedback loop with the cortex. In fact, the basal ganglia receive virtually all their input signals from the cortex itself and in turn return almost all their output signals back to the cortex. The neurotransmitter GABA (always) and dopamine (in most parts of the brain) function as inhibitory agents. Therefore, GABA and dopamine neurons in the feedback loops from the cortex through the basal ganglia and then back to the cortex make virtually all these loops inhibitory feedback loops. This effect results inhibitory signals transmitted from the basal ganglia to cerebral cortex. Therefore, widespread destruction of the basal ganglia causes muscle rigidity throughout the body.



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 gangli 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, 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 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 excuted 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 supress 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 for the sensory input to it and the information already stored in memory. Consequently, most of our motor actions occur as a consequence of cognition or thinking process (thought) generated in the brain. 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 how rapidly the movement is to be performed** (the change of time) and **how large the movement will be** (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 timing 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 neurotransmitter GABA (always) and dopamine (in most parts of the brain) function as inhibitory agents. Therefore, GABA and dopamine neurons in 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 causes muscle rigidity throughout the body.

**Disorders of Function**

Clinically, disease or degeneration of the basal ganglia, cerebral cortex and sometimes the thalamus gives rise to **disturbances of muscle tone (rigidity)** and various disorders of movement known as **dyskinesias (difficult movement)**. Voluntary control and regulation of movement only is disordered; there is no paralysis, paresis or inabil ity to plan or execute motor acts. The cerebral cortex and corticospinal tract play an important role in neural mechanisms of all dyskinesias. All forms of abnormal involuntary movement are abolished by general anesthesia, ablation of the motor cortex, or interruption of the corticospinal tract, and they are eased during sleep. They tend to be exaggerated when a patient becomes self-conscious, anxious, or excited. There are two main classes of dyskinesias;

**1) Hyperkinetic Dyskinesias** characterized by increased motor activity and are associated with abnormally low levels of basal ganglia output. Hyperkinetic Dyskinesias Disorders include **chorea** (Huntington's, Sydenham's), **athetosis**, **hemiballismus**, **dystonia** and **tics**. They are all characterized by excessive motor activity in the form of abnormal, involuntary, purposeless movements, difficulty continuing and stopping ongoing movement, abnormalities of muscle tone (hypertonia - muscle rigidity), and tremor.

**2) Hypokinetic Dyskinesias** characterized by decreased movement. Hypoknetic disorders have been attributed to excessive inhibition of the thalamus by the basal ganglia. Lesions of the globus pallidus result in inability to maintain postural support. The head bends forward so that the chin touches the chest, and the body bends at the waist. Because the globus pallidus is the major outflow tract of the basal ganglia, it is possible that the motor deficit occur because the cortex is deprived of information it needs to automatically control the trunk muscles. An example of hypokinetic dyskinesias is **Parkinson's disease**, in which there is overactivity of the inhibitory pathways from the striatum to the globus pallidus. The symptoms include lead-pipe rigidity, tremor, and reduced voluntary movement due to significant impairment in the initiation of movement (akinesia) and a lack, or reduction in the amplitude and velocity of movement (bradykinesia).

**Hemiballismus** is wild, violent flinging movements of the extremity, appears on the side opposite the lesion.

**Chorea** is rapid, irregular, aimless, involuntary movements of the muscles of the limbs, face, and trunk that seems to move randomly from one part of the body to another.

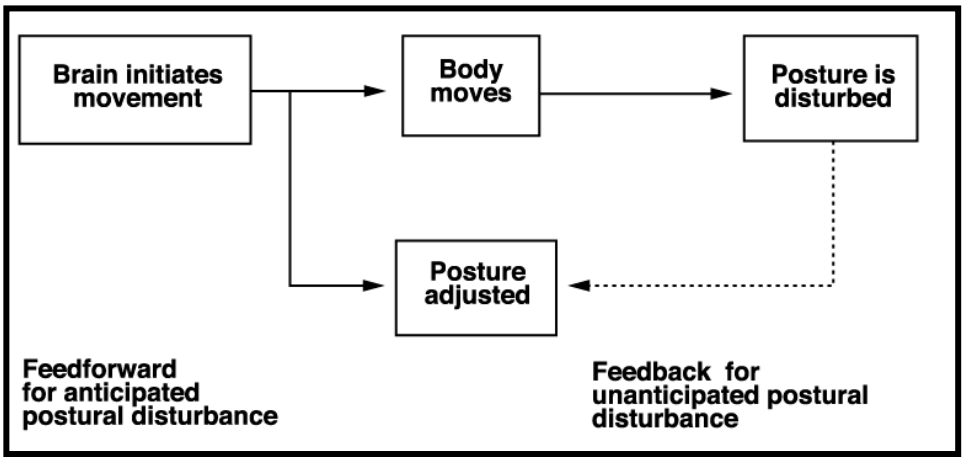
**Athetosis** is a continuous, slow, irregular, writhing and twisting motions of the limbs, fingers, and hands.

**Dystonia** is a twisting, tonic-type movement of the head and trunk.

## Summary of Actions of Descending Motor Pathways:

- **Corticospinaltract:** Control of voluntary movement on the contralateralside of the body, especially fine control of the digits.
- **Corticobulbarpathway:** Control of brainstem motor nuclei, relays for control of voluntary movement, selection of output from other descendingpathways.
- **Rubrospinaltract:** Voluntary movement (similar to corticospinal), integration of voluntary movement with cerebellarcontrol.
- **Tectospinaltract:** originates in the superior colliculus, regulates contralateral movements of the head.
- **Lateral Vestibulospinaltract:** postural adjustments.
- **Medial Vestibulospinaltract:** adjustments of head position.
- **Reticulospinaltracts:** voluntary movement, head orienting movements, initiation of locomotion, postural adjustments, control of respiration, startle reflex, escape behaviours, motor inhibition, thermoregulation, and control of various autonomic systems (eg, vasomotor tone, micturition, sexual function)

**Control of equilibrium (or posture)**: To control posture, there should be a background contractions 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 and also, to provide 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. This is achieved through signals to the spinal cord to control posture and balance by interplay between excitation and inhibition of the antigravity muscles to control equilibrium.




**[A] The excitatory signals are:**

**[1]-** Excitatory signals from pontine reticular formation through **pontine reticulospinal tract** (excites mainly the extensors and to less extent the flexors).

**[2]-** Excitatory signals to extensors and inhibitory signals to flexors from vestibular nuclei through **lateral vestibulospinal tract**. While **medial vestibulospinal tract** makes connections with cervical and upper thoracic spinal motor neurons that play a role in maintaining the normal position of the head in space via innervation of spinal cord neurons that innervate neck musculature.When functioning normally, the vestibular system carries out its functional duties with relatively little intrusion into consciousness. These duties include

- Detection and conscious **perception** of the position and movement of the head.
- Reflex control of **eye movements** during motion of the head, providing for stabilization of the retinal image and target fixation.
- Reflex contractions of **trunk and limb muscles** to compensate for movement and maintain balance and equilibrium.

**[3]-** Signals to control the contralateral muscles of the neck from superior colliculus through **tectospinal tract**. The superior colliculus has input from the retina, visual cortex, inferior colliculus, and somatosensory nerves. It helps move the head in response to new stimuli or maintain position relative to the body.

**[B] The inhibitory signals are:**

**[2]-** By inhibitory signals from medullary reticular formation through **medullary reticulospinal tract** (inhibits mainly the extensors and to less extent the flexors).

**[3]-** By inhibitory signals to extensors and excitatory signals to flexors from the red nucleus through **rubrospinal tract**.

In the normal state there is a balance between the facilitatory and inhibitory descending influences, ensuring an appropriate activation of antigravity muscles and regulation of postural tone. This is achieved by:

**[1]-** By inhibitory signals that originate mainly from **basal ganglia**. Therefore, sectioning of these inhibitory pathways will cause a considerable degree of rigidity of all the antigravity muscles in the body as it occur by transection of the brain stem at the superior border of the pons, a spasm occurs almost exclusively in the antigravity muscles (extensor spasm). This pattern of spasticity is called decerebrate

rigidity. This rigidity is due to a diffuse facilitation of stretch reflexes resulting from increased general excitability of the motor neuron pool and increase in rate of discharge in the gamma efferent neurons. This is due to the interruption of inhibitory signals of the descending tracts from basal ganglia that normally keep the intrinsic activity of reticular and vestibulospinal tracts pathways in check. The effect is further enhanced by removal of the cerebellum, which keeps in check the activity of the vestibulospinal pathway.

**[2]-** By cerebellum which controls the activity of excitatory and the inhibitory signals in order to get proper contraction and relaxation of agonist and antagonist axial and girdle muscles.

**[3]-** By signals from **the joint proprioceptors** especially of the neck to the vestibular nuclei and the reticular formation. These informations apprise the NS about the orientation of the head with respect to the body for the maintenance of equilibrium. For instance, when the head is leaned in one direction by bending the neck, impulses from the neck proprioceptors keep the vestibular apparatuses from giving the person a sense of malequilibrium. They do this by transmitting signals that exactly oppose the signals transmitted from the vestibular apparatuses. However, when the entire body leans in one direction, the impulses from the vestibular apparatuses are not opposed by the neck proprioceptors therefore, the person in this instance does perceive a change in equilibrium status.

**[4]-** By **pressure signals** from the footpads to apprise the CNS whether weight is distributed equally between the two feet or whether weight is more forward or backward on the feet. The same thing can apply for the pressure receptors over various parts of the body. An example of it is the movement against winds in which the air pressure against the front of the body signals that a force is opposing the body in a direction different from that caused by gravitational pull, as a result, the person leans forward to oppose this.

**[5]-** By **visual signals** to control the posture. Even slight linear or rotational movement of the body instantaneously shifts the visual images on the retina, and this information is relayed to the equilibrium centers. Many persons with complete destruction of the vestibular apparatus have almost normal equilibrium as long as their eyes are open and as long as they perform all motions slowly. But, when moving rapidly or when the eyes are closed, equilibrium is immediately lost.

The flocculonodular lobes of the cerebellum seem to be especially concerned with equilibrium functions of the semicircular canals. Destruction of either semicircular canals or flocculonodular lobes causes loss of equilibrium during rapid change in direction of motion but does not seriously disturb equilibrium under static conditions. Uvula of the cerebellum plays an important role in static equilibrium.

**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, 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.

**Signs of lesion of the upper motor neuron (pyramidal and extrapyramidal systems)**: Damage to the motor cortex or the pyramidal tracts due to interruption of blood supply to it is called ***stroke***. The term **"upper motor neuron"** is preferable to "pyramidal tract" because the signs traditionally described under the "pyramidal tract" are not those of a pure pyramidal tract lesion but rather one involving both the pyramidal tract and subcorticospinal pathways (extrapyramidal tracts). A single upper motor neuron with its cell body in the cerebral cortex and its axon making direct synaptic contact with a lower motor neuron is uncommon except for the muscles involved in moving the fingers.

**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):**

**[1]** 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 cerebellum

The little brain, also termed the motor autopilot, helps regulate movements and posture, influences muscle tone, eye movements and balance.

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.* Cerebellum has wide interconnections with various parts of the NS and with the peripheral sensory receptors.

The cerebellum receives information from:

[1] **Spinal cord** through the dorsal spinocerebellar tracts which apprises the cerebellum of the momentary status of dynamic and static muscle length and muscle tension, positions and rates of movement of the parts of the body, and forces acting on the surfaces of the body. And the ventral spinocerebellar tract which apprises the cerebellum that the motor signals have indeed arrived at the cord and it also apprises the cerebellum of the intensity of the signals.

[2**] Eyes and ears** through tectocerebellar tract from colliculi.

[3] **Cerebral cortex** through corticopontocerebellar tract. Afferent fibres from the temporal, parietal, occipital and frontal lobes of the cerebral cotrex pass through the internal capsule and crus cerebri and synapse in the pontine nuclei. From here, the fibres enter the cerebellum through the middle cerebellar peduncle and terminate in the contralateral cerebellar hemisphere. the largest source of mossy fibers which transmitte information about muscle movements planned by cortex.

[4] **Olivary nucleus** through olivocerebellar. Afferent fibres from the temporal, parietal, occipital and frontal lobes of the cerebral cotrex pass through the internal capsule and synapse in both the ipsilateral and contralateral inferior olivary nuclei. From here, the fibres enter the cerebellum through the inferior cerebellar peduncle and terminate in the contralateral cerebellar hemisphere. This tract is the sole source of climbing fibers.

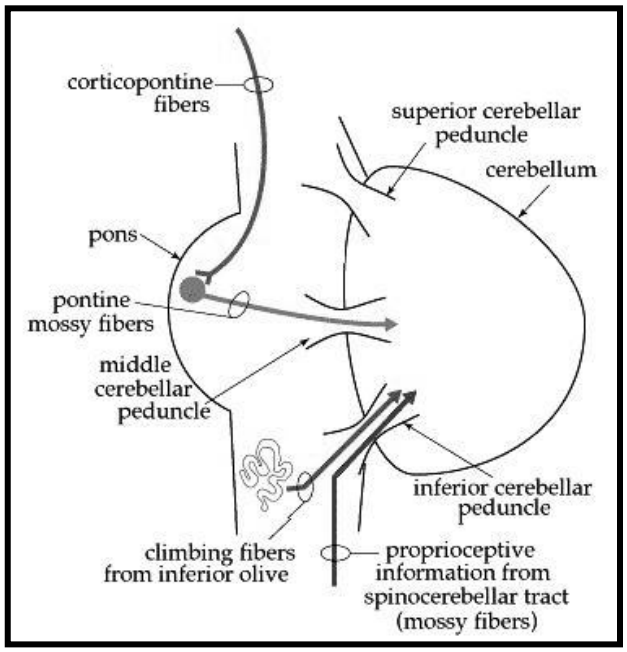
[5] **Cuneate nucleus** through cuneocerebellar tract which transmitte the same information as dorsal spinocerebellar tract but from neck and upper limbs.

[6] **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). Both are excitatory which send collaterals to the deep nuclei and pass to the cortex.

**The cerebellum has two important structures:**

**[1]. External cerebellar cortex** separated by white matter from the deep cerebellar nuclei. The cerebellar cortex contains only 5 types of neurons; Purkinje, granule, basket, stellete, and Golgi cells. The axons of the **Purkinje cells** are inhibitory (the neurotransmitter is gamma amino butyric acid, GABA) and are the only output from the cerebellar cortex pass to the deep nuclei. The granule cells (excitatory cell) receive input from the mossy fibers and send their bifurcated axons (called parallel fibers) to synapse with other cells at the cerebellar cortex. The stellate and basket cells are inhibitory interneurons, which synapse with Purkinje cells. Golgi cells are inhibitory interneurons, which receive input from parallel fibers and from mossy fibers and from Purkinje cells and send their inhibitory axons synapse with granule cells.




**[2]. 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. The output of the deep cerebellar nuclei to the brain stem and thalamus is always excitatory. Therefore, almost all the cerebellar circuit seems to be concerned solely with modulating or timing the rate of excitatory output of the deep cerebellar nuclei to the brain stem and thalamus.

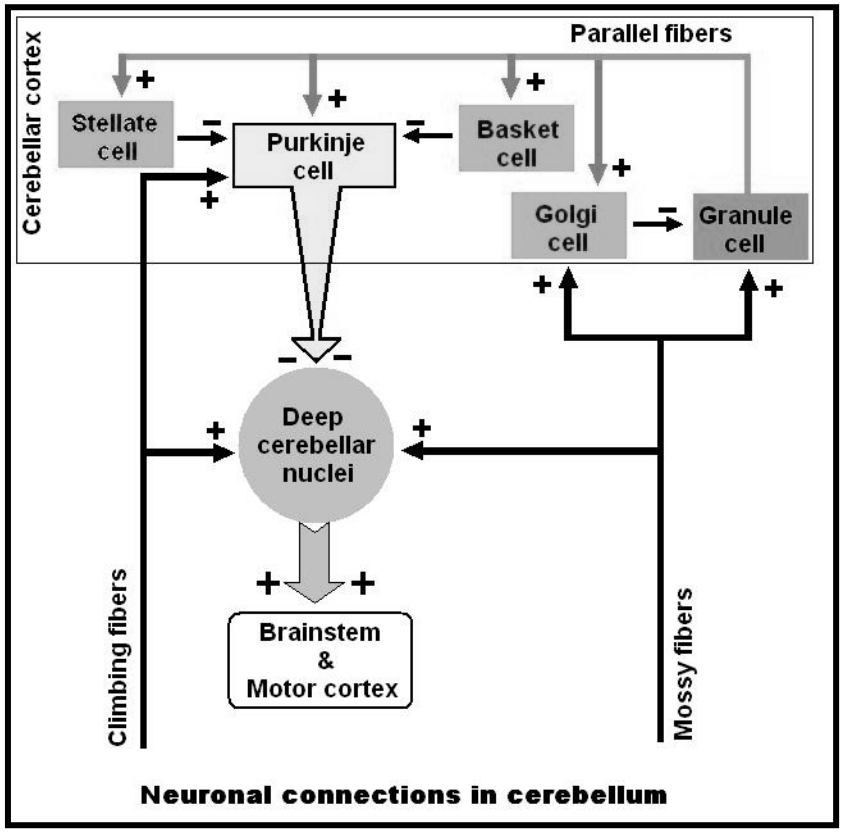
**The special features of the cerebellar neuronal circuit are:**

**[1]** There are no reverberatory pathways in the cerebellar neuronal circuits, so that the input—output signals are very rapid and never persist for long periods of time.

**[2]** Another special feature is that many of the cells of the cerebellum are constantly active, and the deep nuclear cells continually send output signals to the other areas of the motor system. A decrease of the nuclear cell-firing rate can provide an inhibitory output signal from the cerebellum, while an increase in firing rate can provide an excitatory output signal.

**[3]** All cerebellar cortical cells are inhibitory except the granule cells which are excitatory.

**[4]** The climbing fiber inputs exert a strong excitatory effect on single Purkinje cell whereas mossy fiber inputs exert a weak excitatory effect on many Purkinje cells via the granule cells in addition to excitation of other cells (basket and stellate cells which are inhibitory to Purkinje cells, and Golgi cells which inhibit the transmission from mossy fibers to



granule cells).

# The main functions of cerebellum

**1 - 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 *dysdiadochokinesia.* In which jumbled movements occur instead of the normal coordinate movements. In addition, speech is affected, a condition called *dysarthria.*

**2— Monitors, compare, 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 *dysmetria or past pointing*), 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 *intention tremor*.

**3—** The cerebellum functions with the spinal cord and brain stem to **control postural and equilibrium movements.** 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 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.

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 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 *rebound* 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, ***hypotonia*** 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.

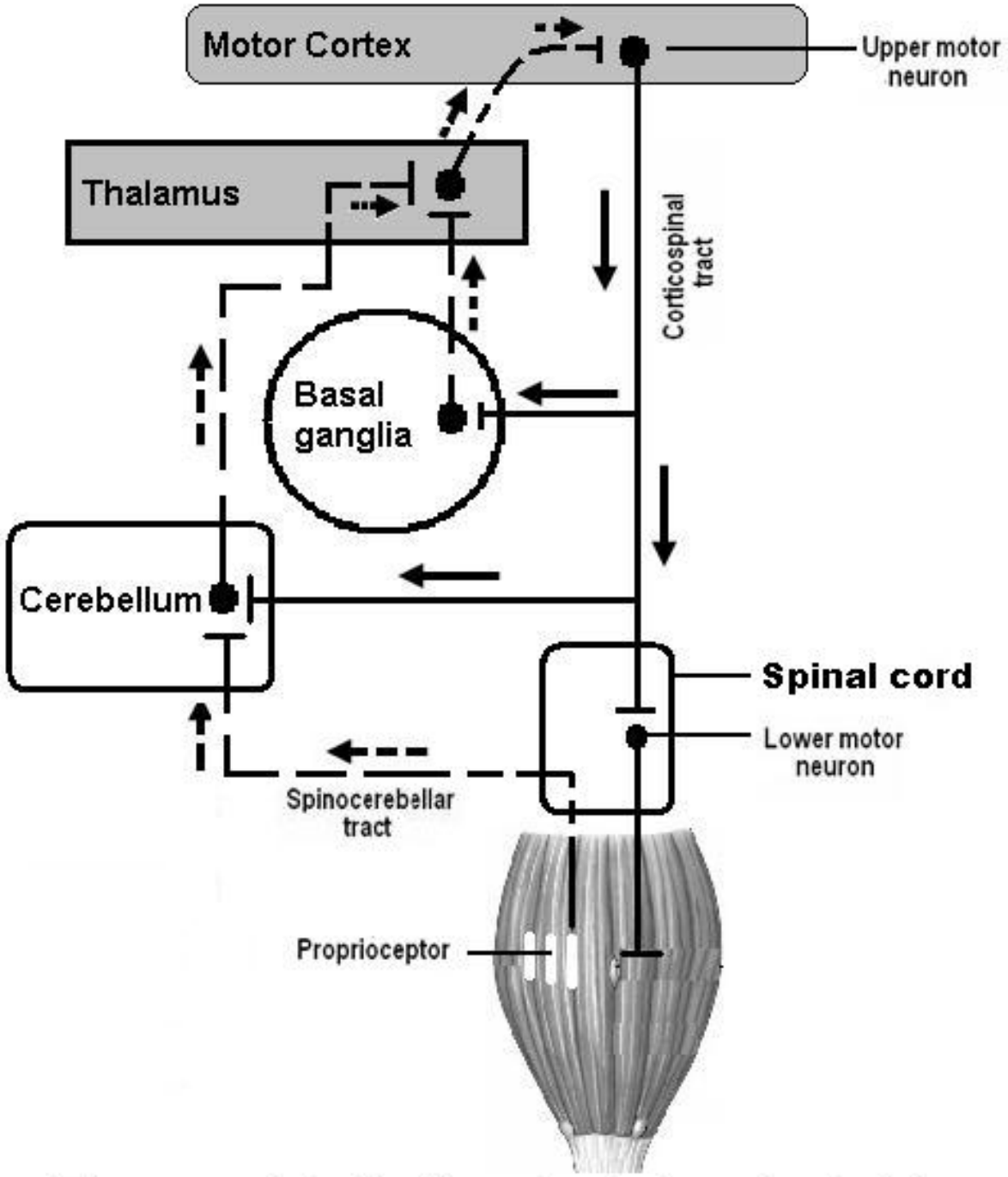
**5— Cerebellum also plays a role in predicting other events** besides movements of the body. For instance, the rates of progression of both auditory and visual phenomena can be predicted. An example, a person can predict from the changing visual scene how rapidly he is approaching an object.

**6— 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.

**The sensory and motor engrams**:

**1. The sensory engrams of the motor movements:** In which the sequential pattern of movement of learned slow and complex motor activities are stored in the somatic sensory areas. Then the person can use this sensory engram as a guide for the motor system of the brain to follow in reproducing the same pattern of movement. An examples of sensory engrams are 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,The motor activity dictated by the sensory engram is checked by feedback signals from peripheral sensory receptors to sensory cortex to correct any error if the peripheral sensory signals do not match with the sensory engram.

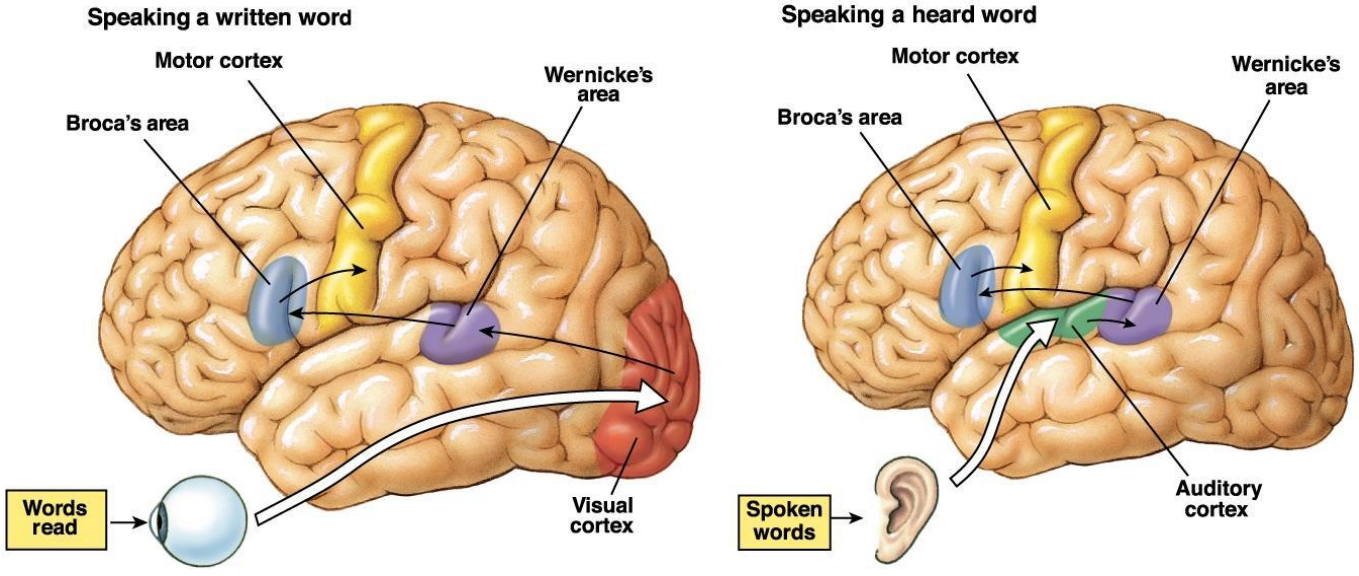
**2. The motor engrams of the motor movements:** In which the sequential pattern of movement of learned rapid, and complex motor activities is stored in the motor cortex as well as in the sensory cortex. Many motor activities are performed so rapidly that there is insufficient time for sensory feedback signals to control these activities. For instance, the movements of the fingers during typing occur much too rapidly for somatic sensory signals to be transmitted to the somatic sensory cortex or even to directly to motor cortex and for these then to control each discrete movement. The motor activities dictated by the motor engram can occur entirely without sensory feedback control. However, the sensory system still determines whether or not the act has been performed correctly. This is achieved after the act has been performed and helps in correction the act in the next time it is performed. It is believed that the control of these rapid coordinate muscular movements involves primary motor and premotor cortex, basal ganglia, and cerebellum.




The neuronal circuit of the main structures involved in the control of motor activitv

**Language and Speech Are Coordinated in Specific Areas of Association Cortex:**

The ability to communicate by language, verbally and in writing, is one of the most difficult cognitive functions to study because only humans are capable of these skills. Thus, our knowledge of language processing in the brain has been inferred from clinical data by studying patients with aphasias (disturbances in producing or understanding the meaning of words) following brain injury, surgery, or other damage to the cerebral cortex. Two areas appear to play an important role in language and speech: **Wernicke's area**, in the upper temporal lobe, and **Broca's area**, in the frontal lobe. Both of these areas are located in association cortex, adjacent to cortical areas that are essential in language communication. Wernicke's area is in the parietal-temporal-occipital association cortex, a major association area for processing sensory information from the somatic sensory, visual, and auditory cortices. Broca's area is in the prefrontal association cortex, adjacent to the portion of the motor cortex that regulates movement of the muscles of the mouth, tongue, and throat (i.e., the structures used in the mechanical production of speech). 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. 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. Language is a highly lateralized function of the brain residing in the left hemisphere. This dominance is observed in left-handed as well as right-handed individuals. Moreover, it is language that is lateralized, not the reception or production of speech. Thus native signers (individuals who use sign language) that have been deaf since birth still show left-hemisphere language function. The corresponding areas in the right or non-language-dominant hemisphere are involved in "body language"—the nonverbal emotional (affective) components of language. These areas allow the lilt 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 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 which 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 memory

Memory is one of the activities of the human mind. **It is the capacity of the brain to store, retain, and subsequently recall information**. There are multiple types of classifications for memory based on duration, nature and retrieval of perceived items. Physiologically, *memories are caused by the formation of a memory trace (engram) which are changes (include new or facilitated pathways) 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*. 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 three distinct types of memory:

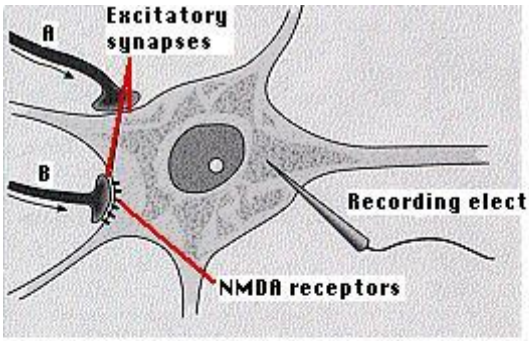
1— Sensory memory.
2— Primary memory or short-term memory.
3— Secondary memory or long-term memory.

**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 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 (synaptic potentiation).

**2— Primary memory or short-term memory (STM) or working memory:** As sensory inputs flood into our cerebral cortex, they are processed, and some 5% of this information is selected for transfer to STM. It is the memory of facts, words, numbers, letters, or other information for a few sec to a few minutes at a time. For instance, memorizing 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.

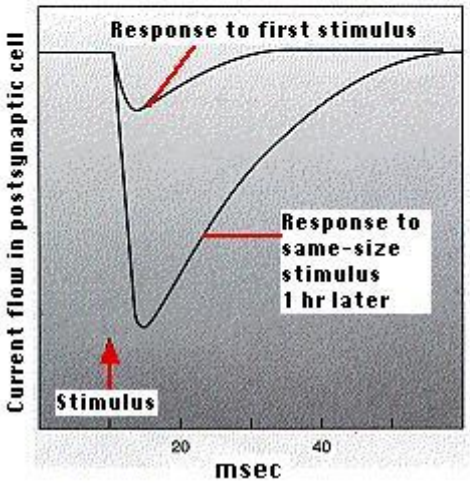
The possible mechanism for primary memory is ***reverberating circuit* theory**. It is possible that the

sensory signals reaching the cerebral cortex can set up reverberating after—discharge circuits in the local area of the cortex itself or perhaps evens back and forth between the cortex and other subcortical areas. Then, as the reverberating circuit fatigue, or as new signals interfere with the reverberations, the primary memory fades away. Other possible explanation of short-term memory is ***long-term potentiation***. Long-term potentiation (LTP) refers to an extended period of time (minutes to hours in vitro and hours to days and months in vivo ) in which the connection between two nerve cells is strengthened or potentiated that results from repeated positive feedback loops. Glutamate-induced increase in intracellular $Ca^{++}$ is a key player in LTP.




Rapid, repeated intense stimulation of presynaptic neurons evokes action potentials in the postsynaptic neuron but over time these synapses become **increasingly sensitive** so that a constant level of presynaptic stimulation becomes converted into a **larger** postsynaptic output (graph on right). This phenomenon, which can last for weeks, is called **long-term potentiation** (**LTP**).

**3— Secondary memory (long—term memory "LTM", fixed memory, and permanent memory):** It is the storage in the brain of information that can be recalled at some later time, hours to years later. <u>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.</u> The long-term memory is subdivided into the **intermediate long-term memory**, which lasts for days or weeks and can be disrupted, and the **long lasting long-term memory**, which lasts for years. The long lasting long-term memory is the storage in the brain of highly overlearned information as one's own name and address. This memory is difficult to disrupt, and it is seldomly affected in retrograde amnesia. This type of memory results from some actual alterations of the synapses either physical or chemical. 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. Some of the theories behind this type of memory are:




***1. Anatomical or physical changes in the synapses***: Fixation of memories in the brain results from anatomical changes in the synapses themselves, 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.

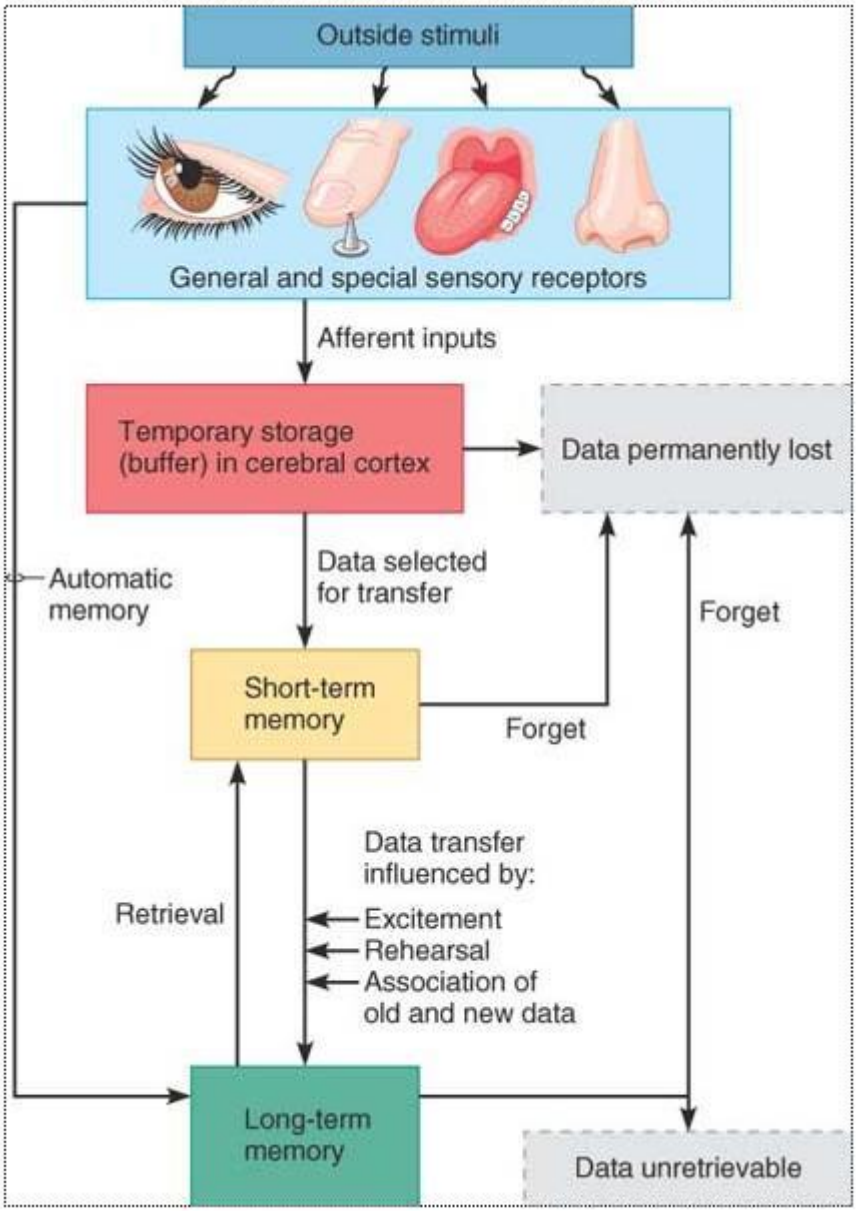
2***. Chemical changes in the presynaptic terminal or the postsynaptic membrane*** causing the memory paths to become facilitated for days or weeks thereafter. Memory resides in a number of brain locations, but a neural mechanism for memory, called Long Term Potentiation (LTP), has been demonstrated in the hippocampus of the limbic system.

**<u>Stages in the formation and retrieval of memory:</u>** The main stages in the formation and retrieval of memory from an information processing perspective are:

***A. Encoding***: 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. This temporary storage (or memory), or working memory, depends on a different network of brain structures than long term memories do. **Encoding process** is a procedure for transforming something a person sees hears, thinks, or feels (as if the information in the computer RAM) into a memory (as if the computer hard disk). It is some thing like the

"Paste" function in computer`s term. Scientists have determined there are different methods in how we lay down our memories.

**B. Storage** or **consolidation** of memory (creation of a permanent record of the encoded information): For the primary memory to be converted into a secondary memory it must become consolidated, i.e. the synapses must become permanently facilitated. The process of memory consolidation apparently involves fitting new facts into the various categories of knowledge already stored in the cerebral cortex. This process requires 5-10 minutes for minimal consolidation and an hour or more for maximal consolidation. During the process of consolidation, the new memories are not stored randomly in the brain but instead are first codified into different classes of information and then stored in direct association with other memories of the same type (in computer`s term as if storing different files according to their types). The transfer of information from STM to LTM (i.e consolidation) is affected by many factors, including:




**1. Emotional state.** We learn best when we are alert, motivated, surprised, and aroused. For example, when we witness shocking events, transferal is almost immediate. Norepinephrine, a neurotransmitter involved in memory processing of emotionally charged events, is released when we are excited or "stressed out," which helps to explain this phenomenon.

**2. Rehearsal.** Rehearsal or repetition of the material enhances memory. Rehearsal of the same information again and again accelerates and potentiates the degree of transfer of primary into secondary memory, and therefore also accelerates and potentiates the process of consolidation.

**3. Association.** Tying "new" information to "old" information already stored in LTM appears to be important in remembering facts.

**4. Automatic memory.** Not all impressions that become part of LTM are consciously formed. A student concentrating on a lecturer's speech may record an automatic memory of the pattern of the lecturer's tie.

. 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.

***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** in association with areas of the **temporal lobes** 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 results in only slight memory loss.

**Hippocampi** and some **thalamic nuclei** 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.

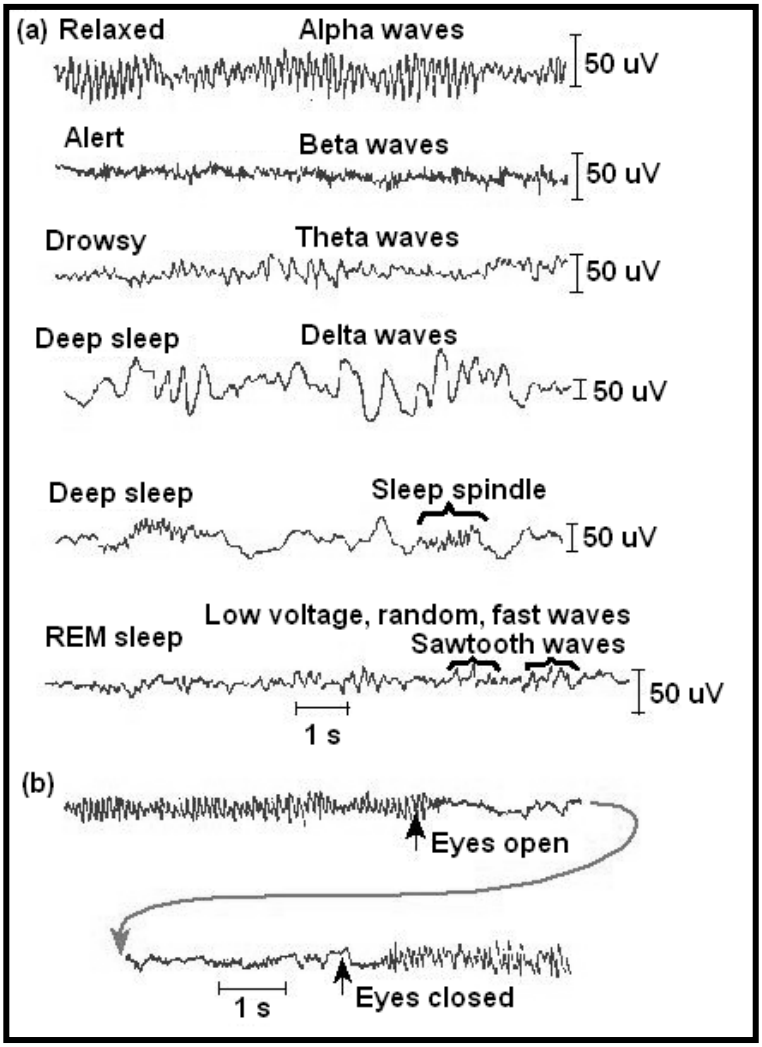
People with hippocampal lesions usually do not have difficulty in learning physical skills that do not involve verbalization or symbolic types of intelligence.

***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.*

# 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. 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, a low body temperature, a low level of adrenal glucocorticoid hormones, and a 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 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.

# Sleep

It is defined as a state of unconsciousness from which a person can be aroused by appropriate sensory or other stimuli. 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). 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. During this sleep there is a decrease in peripheral vascular tone, in blood pressure, in vegetative functions of the body, in respiratory rate, and in basal metabolic rate. In addition, dreams actually occur very often and nightmares also occur during this type of sleep but are not remembered. In addition, sleepwalking (somnambulism), bed-wetting (nocturnal enuresis), and night terrors occur during slow-wave sleep. 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. 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. The drugs like benzodiazepines (e.g., valium) and increasing age decrease the duration of REM sleep and stage 4 of slow-wave sleep. REM sleep decrease with age, and wake periods occur in increasing number. This is why elderly people believe that they do not sleep sufficiently.

**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 well being. The function of sleep is believed to occur during the slow-wave and REM sleep. Slow-wave sleep appears to be the restorative stage. It assists in regulation of body repair. During sleep, reduction in body temperature, metabolic rate, glucose consumption, and release of catabolic hormones take place. Sleep is believed to play a role in allowing the brain to analyze short-term memory stores and review the day's events by eliminating nonessential information or emotional problems and retaining necessary data in long-term memory. 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. Deprivation of REM sleep may lead to anxiety disorders. These manifestations are transient, and the person reverts to normal once the regular sleep-wake cycle is restored.

| Slow-wave sleep | Rapid eye movement sleep (RES) |
|---|---|
| **[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; the heart rate and respiration usually become irregular which is characteristic of dream state. |
| **[5]** Sleepwalking (somnambulism), bed-wetting (nocturnal enuresis), and night terrors occur during slow-wave sleep. | It is usually association with teeth-grinding (bruxism) and penile erection |
| **[6]** No muscle movements and the muscle tone is depressed | A few irregular muscle movements occur which include rapid movements of the eyes, the muscle tone is very depressed (except those muscles which control breathing, eye movement, and ear ossicles) indicating strong inhibition of the spinal projections from the reticular formation of the brain stem |
| **[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. |

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. Temperature regulation is absent, and the core body temperature moves toward the ambient temperature.

During infancy, approximately 16 hours of every day are spent asleep. This figure drops to 10 hours during childhood and to 7 hours during adulthood. Elderly individual spends less than 6 hours of each day sleeping. During infancy and childhood, therefore, 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 reduction in sleep time is caused by a reduction in the time spent in the sleep stages of slow-wave sleep. Phase 4 sleep declines gradually, and may disappear in the elderly causing their sleep to be light and interrupted. This may force such individuals to take afternoon naps to compensate for lost sleep.

**The active theory of sleep**: According to the active theory of sleep, sleep most likely is caused by an active inhibitory process, inhibiting other parts of the brain. This inhibition is achieved by stimulation of *sleep- promoting centers such as:*

*[1] The raphe nuclei* in the lower half of the pons and in the medulla. Many of fibers from these raphe neurons secrete **serotonin**. This center is believed to be responsible for slow-wave sleep.

*[2*] Some areas in *the nucleus of tractus salitorius* which is the sensory region in the medulla and pons for visceral sensory signals entering the brain via the vagi and glossopharyngeal nerves. These regions use **norepinephrine** as a neurotransmitter and probably responsible for REM sleep.

*[3]* Other areas in the *lower brain stem* and diencephalon such as region in *the hypothalamus* and some areas in *the thalamus*.

*[4]* Some of the *sleep factors* produced by the brain may induce a sleep such as muramyl peptide, nonapetide and another sleep factor.

*Lesions in these areas may lead to high state of wakefulness due to the released of the RAS from inhibition*.

**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. Next, positive feedback signals come from both these areas back to the RAS to activate it still further. However, after the brain remains activated for many hours, even the neurons within the RAS will fatigue to some extent 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 periphery 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.

Prolonged wakefulness or complete deprivation from either REM or slow-wave sleep is often associated with weight loss 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.

On the somatic functions of the body, there is a cycle of moderately enhanced and depressed nervous excitability that follows the cycle of wakefulness and sleep. During wakefulness, there is enhanced sympathetic activity and numbers of impulses to the skeletal muscles to increase muscle tone. Conversely, during sleep, sympathetic activity decreases, while parasympathetic activity occasionally increases. Therefore, arterial blood pressure falls, pulse rate decreases, skin vessels dilate, activity of GIT sometimes increases, relaxation of muscles, fall of basal metabolic rate by 10—30%.

**Disorders of sleep:** Disorders of sleep are divided into two major categories and these are:

**[1] Narcolepsy**: This is inappropriate attack of sleep. Individuals with this disorder suddenly fall asleep without regard for the time of day, location, or the activity in which they are engaged. Narcolepsy can have any of the following four characteristics: **Sleep attacks** which are brief, and can occur at any time without any warning. **Cataplexy** is a complete loss of muscle tone that frequently occurs following emotional excitement while the subject is awake. **Sleep paralysis** occurs when a person in bed and is ready to fall asleep and during it the subject can be aroused by external stimuli such as touch or sound. **Auditory** and **visual hallucination** which occur during sleep paralysis as the subject is falling asleep (hypnagogic hallucination) and it may occurs while the subject is waking up (hypnopompic hallucination).

**[2] Insomnia**: Inability to obtain the amount and quality of sleep required to maintain normal function. There are four major causes of insomnia [a] disturbances in the circadian rhythm [b] emotional disturbances [c] anticipation of not being able to sleep, and [d] restless leg syndrome (which is a condition in which patients have the urge to keep their leg in motion before falling asleep.

Drugs like barbiturates were used frequently for the treatment of insomnia by increasing the sleeping time but they reduce the duration of stage 3 and 4 of slow-wave sleep and REM sleeping time. Therefore, treatment with barbiturates reduces the quality of sleep. Benzodiazepines (like valium) decrease the sleep onset time and increase the duration of sleep but reduce the duration of REM sleep and stage 4 of slow-wave sleep.

Mechanism and function of dreams (by P Maquet): Man has been fascinated by his dreams for ages. The discovery of rapid eye movement (REM) sleep revived the interest in dream research. The objective study of dream content allowed the characterization of the main features of human dreams: its perceptual content, its pervasive emotional background, its oddity. The particular pattern of cerebral activity observed during REM by functional neuroimaging seems to match these features. Firstly, the perceptual aspects of dreams would be related to the activation of posterior (occipital and temporal) cortices. Accordingly, patients with occipito-temporal lesions may report a cessation of visual dreams imagery. Secondly, emotional features in dreams would be related to the activation of amygdalar complexes, orbito-frontal cortex and anterior cingulate cortex. Thirdly, the activation of mesio-temporal areas would account for the memory content commonly found in dreams. Fourthly, the relative hypoactivation of the prefrontal cortex would explain the alteration in logical reasoning, working memory, episodic memory and executive functions that manifest themselves in dream reports from REM sleep awakenings. Despite these recent results, the precise neural correlates of dreaming remain elusive. Likewise, the functions of dreams are unknown, although usually related to the functions of sleep itself.

# The Limbic System

It is the entire basal system of the brain that mainly controls the person's emotional behavior and drive (instinctual behavior). The **hypothalamus** is the central elements of the system surrounded by other **subcortical structures** of the limbic system (the septum, paraolfactory area, epithalamus, anterior nuclei of the thalamus, and portions of the basal ganglia, hippocampus, and amygdala). Surrounding limbic areas is the **limbic cortex**, which includes uncus, parahippocampal gyrus, cingulate gyrus, subcallosal gyrus, and orbitofrontal cortex. The reticular formation and allied regions of the brain stem are very important for mediating the behavioral functions elicited by the limbic system. A very important two—ways route of communication between the limbic system and the brain stem reticular formation is via medial forebrain bundle and other short pathways.

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. 3- into the infundibulum to control most of the secretary functions of pituitary gland.

# The functions of the hypothalamus:

***A— The vegetative control functions***:

**1— Cardiovascular regulation**: Hypothalamus controls the heart and blood pressure through its effect on cardiovascular control centers in the reticular substance of the medulla and pons. This includes the decrease or increases the heart rate and the blood pressure.

**2— Regulation of body temperature**: Certain areas in the hypothalamus sensitize the change in the body temperature and also control the mechanisms for adjusting the body temperature back to normal level.

**3— Regulation of body water**: Hypothalamus regulates body water by two ways:

**[A]— By creating the sensation of thirst** through thirst center. This is achieved by:

*(1). Increase in the plasma osmolarity:* 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 thirst center neurons return to normal. Therefore, the neurons of this center act as osmoreceptors, which are stimulated by an increased osmotic pressure of the body fluids to initiate thirst and drinking.

*(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) 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.

**[B]- By controlling the excretion of water in the urine**. When the body fluids become too concentrated, i.e. the osmotic pressure of the plasma is increased, the hypothalamus, through the osmoreceptor cells, stimulates the secretion of 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.

**4— Regulation of 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.

**5— GIT and feeding regulation**: Many GIT activities and reflexes such as licking the lips and swallowing are integrated in the hypothalamus through mammillary bodies. Feeding regulation is achieved by two hypothalamic centers and these are **hunger** (or feeding) **center** and **satiety center**. The former evokes eating behavior (promotes appetite) which appears to be chronically active, while the latter opposes the desire for food (anorexia) which functions by inhibiting the feeding center.

In addition, *amygdala* and the *cortical areas of the limbic system* in association with hypothalamus are also involved in the neuronal regulation of appetite. Some areas of amygdala and cortical areas of the limbic system increase feeding, while others inhibit feeding. In addition, amygdala and the cortical areas of the limbic system determine the type and quality of food that is eaten. Activation of feeding behavior requires signals from both the peripheral and central gustatory systems. Some of these signals have been well characterized. For example, a decrease in blood glucose concentration of an animal activates glucose-sensitive hypothalamic neurons, and activation of these neurons increases the drive for food. Bilateral destruction of amygdala causes psychic blindness in the choice of foods that the subject eats regarding its type and quality. The cortical regions of the limbic system seem especially to play a role in the animal's drive to search for food when it is hungry.

**6— Regulation of circadian rhythm (biological clock):** Your body has more than 100 circadian

rhythms. Each unique 24-hour cycle influences an aspect of your body's function, including body temperature, hormone levels, heart rate, blood pressure, etc, even pain threshold. The suprachiasmatic nuclei of the hypothalamus and preoptic nuclei are the dominant pacemakers for many circadian rhythms in the body to 24-hour light-dark cycle such as secretion of ACTH and melatonin, as well as sleep-wake cycles, and the body temperature rhythm. Circadian periodicities are changes in biological variables that occur daily. It appears that the suprachiasmatic nuclei (the biological clock) takes the information on day length from the retina, interprets it, and passes it on to the pineal gland (a pea-like structure found on the epithalamus), which then secretes the hormone melatonin in response. Secretion of melatonin peaks at night and ebbs during the day. 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. Melatonin secretion decreases with age. Destruction of the biological clock disrupts many biological rhythms, such as oscillations in body temperature, other vegetative functions and the sleep-wake cycle.

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. A number of other disorders, for example sleep disorder is associated with irregular or pathological functioning of circadian rhythms.

***B— Endocrine control functions:*** Stimulation of certain areas of the hypothalamus causes the anterior pituitary gland to secrete its hormones. As the blood courses through the hypothalamus before reaching the anterior pituitary, releasing hormones and inhibitory hormones are secreted into the blood by various hypothalamic nuclei. They are then transported in the blood to the anterior pituitary where they act on the glandular cells to control the release of the anterior pituitary hormones.

***C- Emotional and instinctual behavioral control functions:***

*1. Reward centers*: They are also called pleasant or satisfaction centers. Stimulation these centers cause pleasure, satisfaction, and tranquility. These centers are located mainly in the hypothalamus. Less potent centers are found in the amygdala, the hippocampus and other areas of the brain.

*2. Punishment centers*: They are also called unpleasant or aversion centers. Stimulation of these centers cause terror, pain, fear, defense, escape reactions, rage, and all the other elements of punishment. The most potent areas for punishment have been found in the central gray area surrounding the aqueduct of Sylvius in the mesencephalon and extending upward into the hypothalamus and thalamus. Less potent punishment areas are found in the amygdala and the hippocampus. In rage (which is an emotional pattern due to strong stimulation of the punishment centers of the brain) the animal takes the position of attack with a defense posture, extends its claws, lift its tall, hiss, spit, growl, develop piloerection, wide-open eyes, and dilated pupils.

Stimulation of the punishment centers can frequently inhibit the reward centers completely indicating that the punishment centers take precedence over the reward centers. Almost everything that we do is related in some way to reward and punishment. If we are doing something that is rewarding, we continue to do it, if it is punishing, we cease to do it. Reward and punishment are important in learning and memory. If the sensory experience causes neither reward nor punishment, the cortical response becomes progressively more and weaker with repeated stimulation until it fads away. The repeated of such stimuli causing the person to become habituated to them and thereafter ignores it. Thereafter, the person is hardly at all to remember of such stimuli. However, if the stimulus causes reward or punishment rather than indifference, the cortical response becomes progressively more and more intense with repeated stimulation instead of fading away. This response is said to be reinforced. Thereafter, the person builds up strong memory traces for sensations that are either rewarding or punishing.

*3. Sexual behavior*: The behavior components that accompany the sexual act, the urge to copulate and the coordinated sequence of events that lead to copulation are regulated to a large degree in the limbic system and hypothalamus. 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.

*4. Learning processes:* Learning is a change of behavior caused by neural mechanisms affected by experience. Memory refers to neural storage mechanisms for experiences. The hippocampus is involved in learning and memory.

[A] Non-associative learning means that the learning is unassociated to the stimuli. Habituation refers to a gradual diminution of a response by repetition of a stimulus; because experience show that the stimulus is unimportant. Sensitization is the opposite of habituation. Firstly, a strong threatening stimulus triggers a certain response, but repetitions of the stimulus increase the size of the response in order to avoid the threat. This evaluation is called the reward and punishment hypothesis. The neural processes are probably related to the function of the hippocampus.

[B] Associative learning is the process of learning by associations between stimuli. The free radical nitric oxide (NO) modulates learning. Conditioning refers to a neural process of associative learning, where there is a temporal association (optimum 0.5 s) between a neutral stimulus (eg, a sound before food) and an unconditioned stimulus (food) that elicits a response (gastro-intestinal secretion). Repetition of the sound-food manoeuvre develops into a conditioned reflex, where the sound alone elicits salivary secretion. In operant conditioning the response is associated with reinforcement, which changes the probability of the response. Positive and negative reinforcement increases the probability of the response, whereas punishment reduces its probability. Learning is highly improved by happiness. Light stress is an advantage in learning something new. However, substantial stress is not helpfull in the recall process, and stress can completely block the memory.

***D— Control of excitement and alertness*** in association with other structures of the limbic system: Stimulation of certain regions of the hypothalamus greatly excites the RAS and therefore causes wakefulness, alertness and excitement. In addition, the sympathetic NS becomes excited in general, causing increasing the arterial B.P, pupillary dilatation and enhancing other activities associated with sympathetic activity. On the other hand, stimulation of some areas in the limbic system, hypothalamus, or in the thalamic portions of the RAS often inhibits the mesencephalic portion of the RAS, causing somnolence, and sometimes actual sleep.

**The functions of amygdala**: Amygdala has extensive connections with various parts of the brain. play its important role on the mediation and control of major affective activities like friendship, love and affection, on the expression of mood and, mainly, on fear, rage and aggression The amygdala, being the center for identification of danger, is fundamental for self preservation.

1. The amygdala is believed to help in choosing the pattern of the person's behavioral response so that it is appropriate for each occasion.
2. Stimulation of amygdala causes almost all the same effects as those elicited by stimulation of hypothalamus plus still other effect.
3. Bilateral lesions in the amygdala cause hyperphagia with indiscriminate ingestion of all kinds of food (omniphagia), loss of fear, decrease aggressiveness, tameness, and excessive sex drive, psychic blindness, has extreme curiosity about every thing, forgets very rapidly, has a tendency to place everything in its mouth.

**The functions of hippocampus**: Hippocampus becomes habituated to indifferent signals, but learns from signals that cause either reward (pleasure) or punishment. Hippocampus is the "brain librarian" (helps the cortex to store new signals into the long lasting long-term memory). Bilateral removal of the hippocampi in epileptic patients permanently disrupts the ability to learn anything new (anterograde amnesia). Other lesions of the hippocampi reduce previously learned memory material (retrograde amnesia. Long-term alterations imply a rise in the number of synapses. Cholinergic synapses in the midbrain septum are essential to our memory, and these neurons are dependent upon the nervous growth factor. Repeated activation of a sensory pathway increases the reaction of pyramidal cells. Such a reaction may last for

weeks in the hippocampus and be involved in storage and retrieval of new information in the long-term memory. Our memory (cortex and hippocampus) works as a filter. Perhaps only 1 per mille of all received signals contain useful or emotional information and are catched in the memory. Unfortunately, we are unreliable witnesses, because we invent emotional "information" concerning a factual experience. The easiest facts to remember are those that make sense. All facts, concepts and acquired skills are stored in a ready-to-use fashion. Feelings play a large role in memory, and strong impressions that are charged with emotion etch themselves into our memory. The hippocampus has extensive connections with most portions of the cerebral cortex as well as with the basic structures of the limbic system. The hippocampus is particularly vulnerable to several disease processes, including **ischemia**, which is any obstruction of blood flow or oxygen deprivation, **Alzheimer's disease**, and **epilepsy**.

1. Stimulation of different areas in the hippocampus can cause almost any one of different behavioral patterns, such as rage, passivity, excess sex drive, etc.
2. Very weak electrical stimuli can cause local epileptic seizures and hallucinations that persist for many seconds after the stimulation is over.
3. Bilateral removal of hippocampus for treatment of epilepsy in some patients causes anterograde amnesia and some times retrograde amnesia.

**Thalamus:** Lesion or stimulation of the medial dorsal and anterior nuclei of the thalamus is associated with changes in emotional reactivity. However, the importance of these nuclei on the regulation of emotional behavior is not due to the thalamus itself, but to the connections of these nuclei with other limbic system structures.

## Functions of specific chemical transmitter system for behavior control:

**1- The epinephrine—serotonin system**: Large numbers of norepinephrine— secreting neurons are located in the reticular formation especially in the locus ceruleus which sends fibers upward to most parts of the limbic system, thalamus, and cerebral cortex. Also, many serotonins—producing neurons are located in the midline raphe nuclei of the lower pons end medulla and also project fibers to many areas of the limbic system and to some areas of the brain.

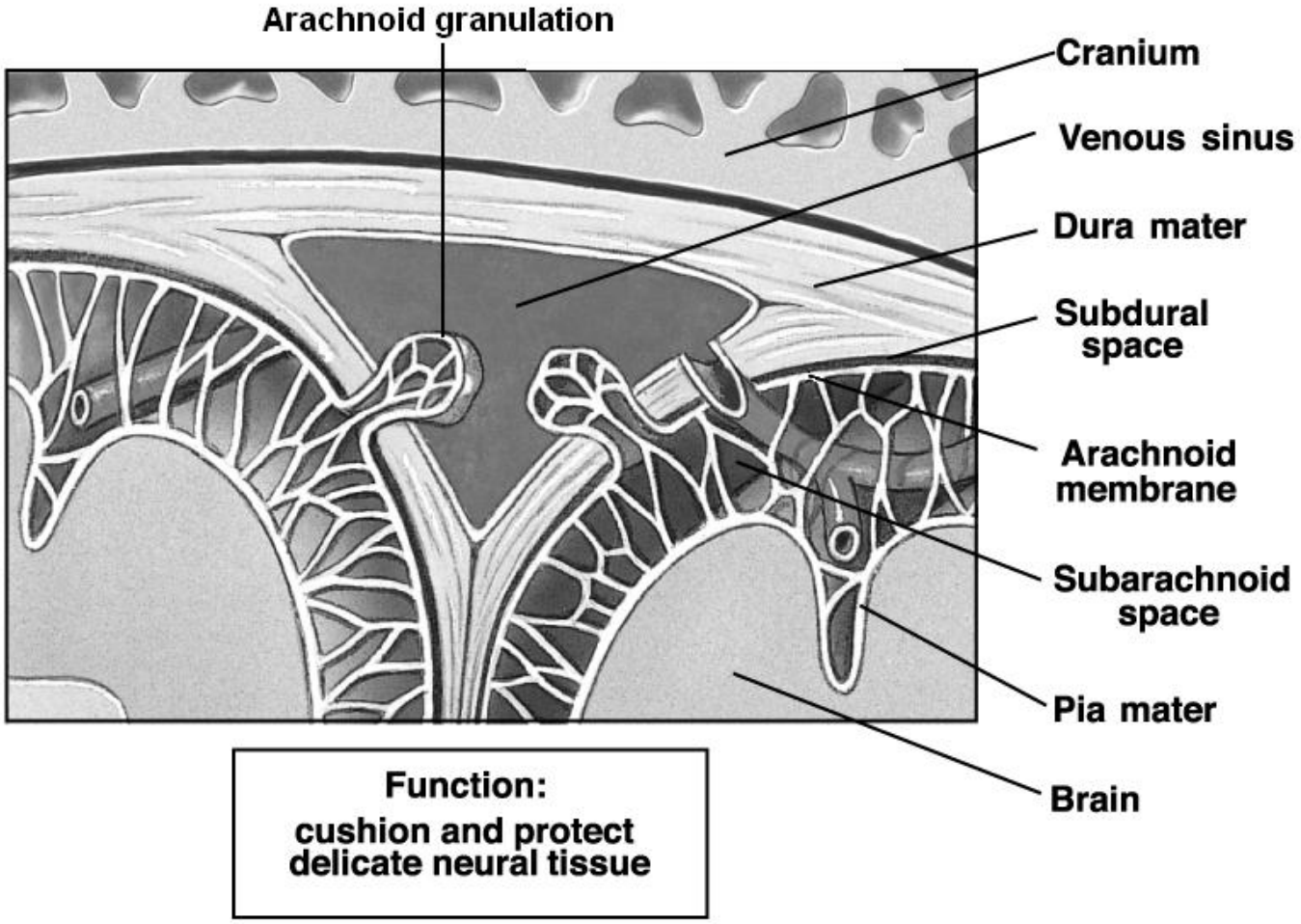
Mental depression psychosis might be caused by diminished formation of either norepinephrine or serotonin or both. This suggestion is supported by finding that the drugs that block the secretion of norepinephrine or serotonin cause depression and the drugs that increase norepinephrine and serotonin at the nerve endings can treat about 70% of patients with depression. In addition, some patients with mental depression alternate between depression and mania (manic-depressive psychosis) can be treated with drugs that block the formation or action of norepinephrine and serotonin during the manic condition.

**2—The dopamine system**: The dopaminergic neurons are located in the substantia nigra and ventral tegmentum. The dopaminergic neurons located in substantia nigra project inhibitory effects on the basal ganglia. The dopaminergic neurons of tegmentum project fibers to the limbic system via mesolimbic dopaminergic system. Schizophrenia might be caused by excess secretion of dopamine in the brain. This suggestion is supported by finding that drugs that cause excess release of dopamine in the brain may cause schizophrenic symptoms and the drugs that decrease the secretion of dopamine by the dopaminergic nerve endings or decrease the effect of dopamine on subsequent neurons can treat patients with schizophrenia.

**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.

# 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 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]** Alteration of volume can compensate for fluctuations in amount of blood within skull and thus keep total volume of cranial content constant.

**[3]** Low K ion concentration allows neurons to generate very high electrical potentials.

CSF is formed at a rate of about 500 ml / day. Two thirds or more of this fluid originates as a secretion from choroid plexuses in the four ventricles, mainly in the two lateral ventricles. Additional amounts of fluid are secreted by all the ependymal surfaces of the ventricles, the arachnoidal membranes, and from the brain itself through the perivascular spaces that surround the blood vessels entering the brain. The CSF in the ventricles flows through the foramens of Magendie and Luschka to the subarachnoid space, which is absorbed through the arachnoid villi into veins.

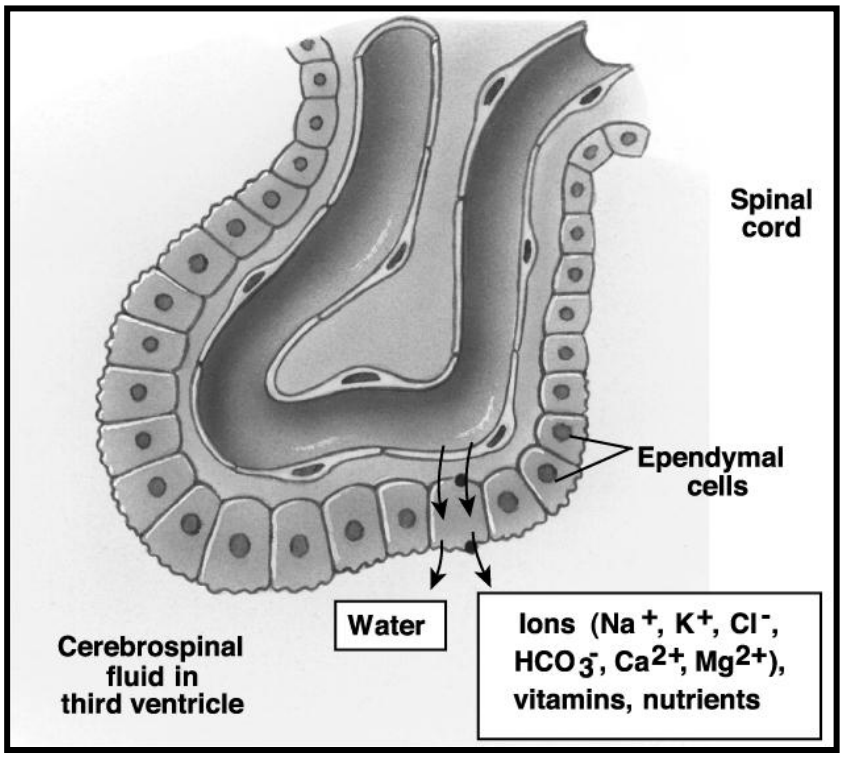
The composition of CSF is essentially the same as that of extracellular fluid of the brain. There appears to be free communication between the brain interstitial fluid and CSF. The surfaces of the ventricles are lined with thin epithelial cells called ependyma and the outer surface of the brain is covered 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.

Brain interstitial fluid is in effect an ultrafiltration of plasma with its composition modified by transport processes in the endothelial cells of the cerebral capillaries and the choroid epithelium. Therefore, the resulting characteristics of the brain interstitial fluid and consequently the CSF become the following:

- Osmotic pressure approximately 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 normal pressure in the CSF system when one is lying in a horizontal position average **130 mm of water** pressure (with a range between 65-195 mm of water), i.e., about 10 mm Hg pressure (by dividing mm of water pressure by 13.6, which is the specific gravity of mercury).




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, in diseases that involved the villi, can cause high CSF pressure.

If an obstruction occurs in the ventricular system or foramina, the result is called *noncommunicating hydrocephalus*; if the obstruction is at the arachnoid villi, it is called *communicating hydrocephalus.*

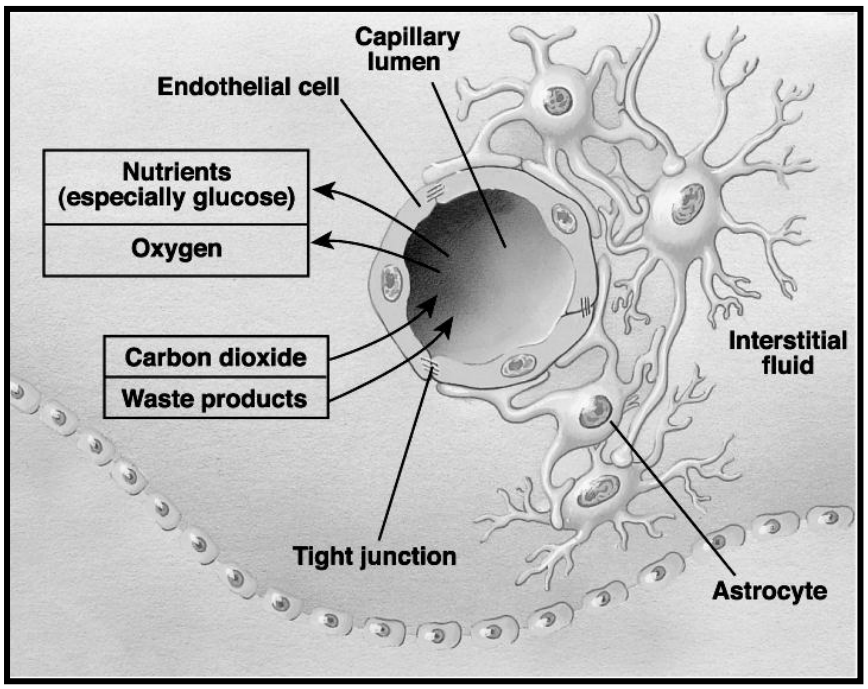
**Blood-brain barrier (BBB):** There are barriers between the blood and the CSF (called **blood-CSF barrier** due to the epithelial cells of the choroid plexus) and between the blood and interstitial fluid of the brain (called **blood-brain barrier** due to the endothelium of the cerebral capillaries in conjunction with astrocytic processes). However, both barriers are similar.

In general, blood-brain and -CSF barriers are highly permeable to water, $CO_2$, $O_2$, and most lipid soluble substances such as alcohol and most anesthetics, slightly permeable to the electrolytes, and almost totally impermeable to plasma proteins, cholesterol (because both of them have large molecular size), and most non-lipid soluble large organic molecules.

The cause of the low permeability of these barriers is due to the tight junctions between the endothelial cells of the capillaries and epithelial cells of the villi.

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. The BBB can be disrupted temporarily by inflammation, irradiation, tumors, sudden severe increases in blood pressure or by intravenous injection of hypertonic fluids (which is used clinically to extract cerebral edema fluid).

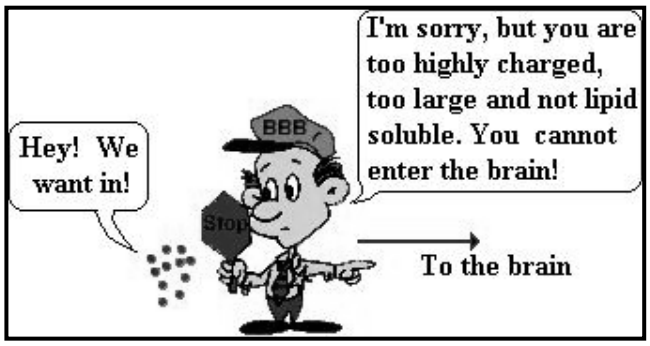



### The functions of the BBB are:

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

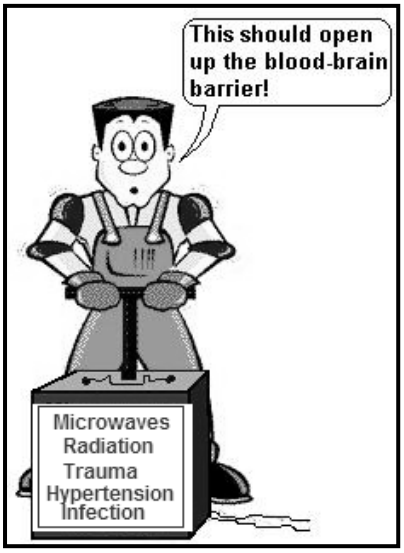
[2] It prevents the escape of neurotransmitters from their functional sites in the CNS into the general circulation.

[3] Drugs penetrate the BBB to varying degrees. For example, nonionized (lipid-soluble) drugs cross more readily than ionized (water-soluble) drugs.




### General Properties of the BBB:

1. Large molecules do not pass through the BBB easily.
2. Low lipid (fat) soluble molecules do not penetrate into the brain. However, lipid soluble molecules, such as barbituate drugs, rapidly cross through into the brain.
3. Molecules that have a high electrical charge to them are slowed.




### The BBB can be broken down by:

1. Hypertension (high blood pressure): high blood pressure opens the BBB
2. Development: the BBB is not fully formed at birth.
3. Hyperosmolitity: a high concentration of a substance in the blood can open the BBB.
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.

**Cerebral blood flow (CBF):** 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 mean blood pressure of 50-150 mm Hg. 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. 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 $PO_2$. So even slight increase in $PCO_2$ will cause a large increase in CBF.

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.

**In summary:** The main functions of different structures of the Brain:

**Medulla (also called medulla oblongata):**

1 - continuous with spinal cord
2 - contains ascending & descending tracts that communicate between the spinal cord & various parts of the brain
3 - contains vital centers:

- cardioinhibitory center, which regulates heart rate
- respiratory center, which regulates the basic rhythm of breathing
- vasomoter center, which regulates the diameter of blood vessels
- Others such as many autonomic reflexes, cough, gag, vomit, digestion.

4 - origin of five cranial nerves (VIII or vestibulocochlear, IX or glossopharyngeal, X or vagus, XI or accessory, & XII or hypoglossal)

**Pons:**

1 - Bridge connecting spinal cord w/ brain & parts of brain w/ each other
2 - Origin of four cranial nerves (V or trigeminal, VI or abducens, VII or facial, & VIII or vestibulocochlear)
3 - contains pneumotaxic center (a respiratory center)

**Midbrain:**

1 - Corpora quadrigemina - visual reflexes & relay center for auditory information.
Two pairs of rounded knobs on the upper surface of the midbrain mark the location of four nuclei, which are called collectively the "corpora quadrigemina." These masses contain the centers for certain visual reflexes, such as those responsible for moving the eyes to view something as the head is turned. They also contain the hearing reflex centers that operate when it is necessary to move the head so that sounds can be heard better.
2 - Cerebral peduncles - ascending & descending fiber tracts
3 - Origin of two cranial nerves (III or oculomotor & IV or trochlear)
Thalamus -
4 - Relay station for nearly all sensory impulses (except olfaction)
5- substantia nigra - helps control motor function

**Hypothalamus:**

1 - Control of Autonomic Nervous System
2 - Reception of sensory impulses from viscera
3 - Intermediary between nervous system & endocrine system
4 - Control of body temperature
5 - Regulation of food intake
6 - Thirst center
7 - Part of limbic system (emotions such as rage and aggression)
8- Sex drives
9 - Part of reticular formation

**Thalamus:**

Major sensory relay center.

**Pineal gland:**

Helps set sleep/wake cycles, makes melatonin.

**Reticular formation:**

1 - portions located in the spinal cord, medulla, pons, midbrain, & hypothalamus

2 - needed for arousal from sleep & to maintain consciousness

**Cerebellum:**

"great comparator", 2nd largest portion of brain, coordinates motor function.

**Cerebrum:** largest portion of brain, conscious thoughts, awareness, higher functions.

a. grey matter cortex - neuronal cell bodies making connections, 1/2 cm thick outer portion.
b. white matter - neuronal axons, deeper portion of cerebrum.

Cerebral Hemispheres (R and L differences).

a. right hemisphere - art, music, imagination, left side sense & motor.
b. left hemisphere - language, logic, math, right side sense & motor.

Corpus Callosum - thick white band of axons connecting R & L hemispheres.

Cerebral Lobes (five major lobes).

a. frontal - judgement, personality, motivation, voluntary motor, Broca's area on L side.
b. parietal - sensory areas, some speech understanding.
c. temporal - auditory areas, learning, memory.
d. occipital - visual areas.
e. insular -not visible from surface.

**Basal ganglia:**

masses of gray matter in each cerebral hemisphere
important in control of voluntary muscle movements

**Limbic System:**

1 - consists of a group of nuclei + fiber tracts
2 - located in part in cerebral cortex, thalamus, & hypothalamus
3 - Functions:
aggression
fear
feeding
sex (regulation of sexual drive & sexual behavior)