Chapter 1

This chapter presents elements of neurobiology that form the necessary preparation for a student of computational neuroscience. The chapter is organized as follows. Section 1 describes the biology of a single neuron, and the basic neuronal signaling mechanisms, electrical and chemical. Section 2 describes the overall organization of human nervous system.

1.1 Neuron: Structure and Function

In this section, we give a brief outline of the structure and function of a neuron. At the outset, we must note that a neuron is not a specific cell, but a general term given to a large class of cells that share certain properties. This family of cells vary greatly in their morphology and the mechanisms and molecules they use to signal to each other. Therefore, it is impossible to describe the structure and function of neurons in all their rich variety in a short chapter. The present chapter gives a description of the structure and function of a typical neuron. The following chapter describes how the processes described verbally in the present chapter may be described mathematically.

1.1.1 Structure of a neuron:

- A neuron is primarily a cell. Therefore, like any other cell it has a cell body wrapped inside a cell membrane. It has a nucleus that contains the chromosomes which constitute the genetic information. It has other standard cellular components, the organelles like mitochondria, golgi bodies, nissil bodies, endoplasmic reticulum and so on. But what distinguishes a neuron from most other cells is the rich and elaborate wiring that seems to emerge from the cell body, also called *soma* (fig. 1.1.1.1). Neurons vary greatly in terms of the number of these wiry structures that stick out of the cell body. While a neuron like the bipolar cell, found in the retina of the eye, has only two wires sticking out of the soma, there are neurons like the purkinje cell in the cerebellum, which have about one or two lakh wires per cell. In fact, even at a first glance, this wiring seems to be something odd about a neuron. One would not be totally off track if one surmised that it is these wires that make neuron a special cell, and, by extension, the brain a special organ. Hence broadly, depending on the Dendrite, we can classify the Neuron as (fig. 1.1.1.2).

- 1)Unipolar cell: 1 wire sticking out of the soma.
- 2)Bipolar cell: 2 wires sticking out of the soma.
- 3)Multipolar cell: Many wires sticking out of the soma.
- 4)Pseudounipolar Neuron

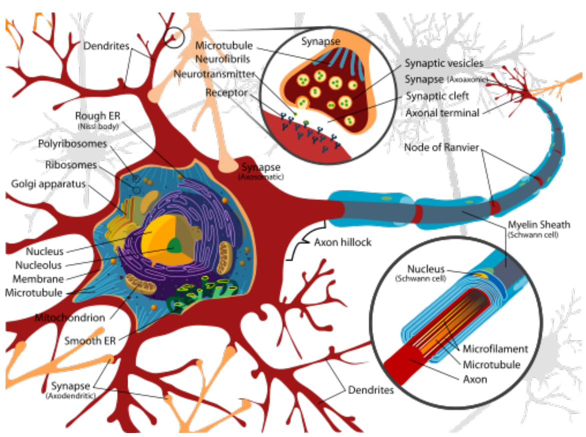


Figure 1.1.1.1: Internal structure of a neuron

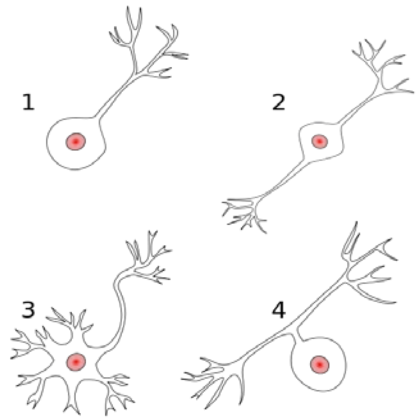


Figure 1.1.1.2: Classification of Neuron based on Dendrites

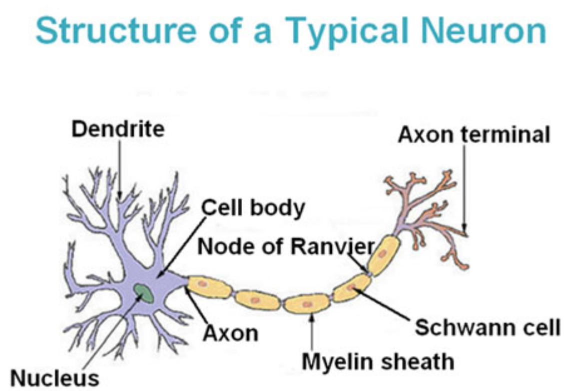


Figure 1.1.1.3: Structure of a neuron

On a closer look, one can distinguish two distinct portions in the wiring system: one portion has shorter, more densely distributed wiring, known as the dendrites; the other portion, consisting typically of a single long wire, known as an axon, branches out into smaller axon terminals at the far end. Neurons use these dendrites and axons to receive and transmit signals to each other. Signals *from* other neurons are received by the dendrites, while signals *to* other neurons are transmitted by axon and its terminals. Thus a neuron can be regarded as an input-output system with dendrites as the inputs and the axon terminals as its outputs. Signals from one neuron to another are transmitted across a small gap – between the axon terminal of one neuron and the dendrite of another neuron – known as the synapse (fig. 1.1.1.3).

1.1.2 Electrophysiology of a neuron:

The basis of electrical signaling in a neuron is the fact that there is voltage difference between the interior of the neuron relative to the space surrounding the neuron, the extracellular space. This voltage, known as the membrane potential, is a constant (of about -70 mV) in resting conditions. However, when a neuron is stimulated, by one of several factors, the membrane voltage can show both positive and negative deviations. These voltage variations carry signals across the body of a neuron, and also contribute to signals that are transmitted from one neuron to another across the synapse.

Electrophysiology is a branch of physiology that deals with electrical phenomena related to biological systems. This field of science, in turn, has its roots in electrochemistry, a branch of chemistry that deals with the relationship between ions and electricity, a common example of which is a battery. A basic principle of electrochemistry states that when two compartments containing of an ion X, in different concentrations, are separated by a membrane that is selectively permeable to that ion, then, at equilibrium, voltage difference is generated between the two compartments. This voltage difference, known as the Nernst potential, depends on the ratio of equilibrium ion concentrations in the two compartments. Mathematical aspects of the Nernst potential are described in the next chapter.

1.1.3 Ions and ion channels:

Membrane potential in a neuron, or to that matter in any cell that has a membrane potential, is generated due to a difference in concentrations between the interior of the cell and the extracellular space. There is not one but several ions that contribute to the membrane potential, the key players being: Na+, K+, Cl- and Ca2+. The membrane potential is some sense, a combined effect, of the Nernst potentials of these individual ionic species. But to generate a Nernst potential we mentioned above that we require a semi-permeable membrane (fig. 1.1.3.1).. That is to generate a Nernst potential for Na+, we need the membrane to be semi- or selectively permeable to Na+, and so on. What about the membrane produces this semi-permeability or selective permeability?

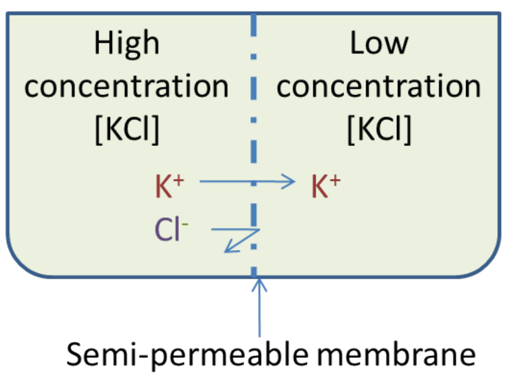


Figure 1.1.3.1: Neural Signaling with a semipermeable membrane

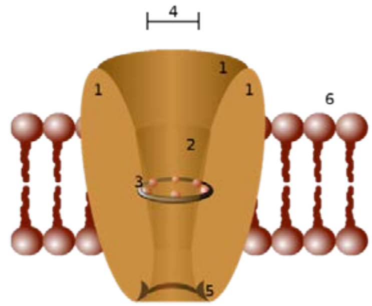
Neural membrane is impregnated with tiny pores, known as ion channels, that allow passage of ions. These channels, which are constituted by membrane spanning proteins, are usually selective to specific types of ions. Thus a sodium channel shows high selectivity to Na+ ions, though it allows passage of minute quantities of other ions. Similar is the case with channels of other ions – potassium channels, chloride channels, calcium channels etc.

Different ions are distributed differently across the neural membrane. For example, in resting conditions, sodium concentration is higher outside the cell, than inside. Therefore the Nernst potential of sodium is positive inside. Thus when only sodium ions are present, the membrane potential is equal to the Nernst potential of sodium, i.e., positive inside. On the contrary, potassium ion concentration is higher within the cell than without, making the corresponding Nernst potential negative inside. Thus when only potassium ions are present, Nernst potential is negative inside.

$$V_1 - V_2 = \frac{RT}{Z_x F} \ln \frac{[X]_2}{[X]_1}$$

V1-V2 - Nernst potential for ion 'X'
$[X]_{1,2}$ – concentrations of 'X'
Z_x – Valence of 'X'
R – Ideal gas constant
T – Absolute temperature
F – Faradays' constant
RT/F = 26 mV at T=25^{o}C (Z_x = +1)

The ability of a channel (fig. 1.1.3.2).to allow ions is not fixed for all time. Channels can be in OPEN or CLOSED states. A channel in OPEN state has naturally greater permeability than in CLOSED state. OPEN channels also offer greater electrical conductance to the ions to which they are permeable.



- **1** - channel domains(typically four per channel),
- **2** - outer vestibule,
- **3** - selectivity filter,
- **4** - diameter of selectivity filter,
- **5** - phosphorylation site, **6** - cell membrane.

Figure 1.1.3.2: Structure of a Channel

The conductance of a channel determines the contribution of the Nernst potential of the corresponding ionic species, to the membrane potential. Earlier we stated that, when only potassium ions are present, the membrane potential is negative, and when only sodium ions are present, the membrane potential is positive. Now we consider a small variation of that scenario. Consider a situation when both sodium and potassium ions are present (with the usual intra- and extra-cellular distributions) but only potassium channels are open (which is effectively the same as not having sodium ions). Again we have a negative membrane potential. Similarly if only sodium channels are open, we have a positive membrane potential. Thus we can think of sodium and potassium channels are knobs for turning the membrane potential up and down. To keep the membrane voltage negative, as it is in the resting conditions, keep the potassium channels open, with sodium channels closed. To take the membrane potentials to positive levels, open the sodium channels and shut down the potassium channels. These intuitive considerations will be made more rigorous mathematically, in the following chapter.

1.1.4 Ion channels and Gating:

We mentioned above that ion channels can be switched between OPEN and CLOSED states by various factors. This switching of the state of ion channels is known as *gating*.

There are 4 factors that drive channel gating: a) ligand-gating, b) voltage-gating, 3) phosphorylation c) stretch.

Ligand gating: In ligand-gating (fig. 1.1.4.1) a molecule binds to the ion channel and changes its confirmation (shape), thereby changing its open/close state.

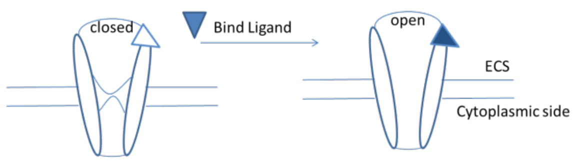


Figure 1.1.4.1: Ligand Gating

Voltage-gating: In this form of gating (fig. 1.1.7), it is the membrane voltage that controls channel gating. The fact that these channels are gated by voltage implies that their conductance is a function of membrane voltage. Therefore, the voltage-current characteristics of a voltage-gated or voltage-sensitive channel, are nonlinear. These channels do not obey the Ohm's law. These nonlinear conductances are crucial in generating neural signals in the form of sharp voltage spikes known as *action potentials*.

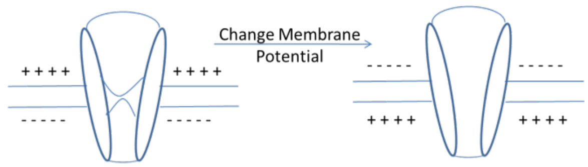


Figure 1.1.4.2: Voltage Gating

Phosphorylation-gating: In this form of gating (fig. 1.1.4.3), the channel goes to an open state form closed state when a phosphate group is attached to the channel, a process known as phosphorylation. The energy required for opening the channel comes from the phosphate group.

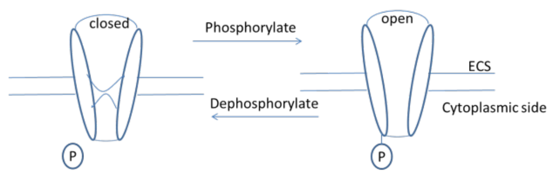


Figure 1.1.4.3: Phosphorylation Gating

Stretch-gating: Stretch of the cell membrane can also open channels. This mechanism converts a stretch event into an electrical event, since the opened channels permit current. Such channels (fig. 1.1.4.4) are found, for example, in nerve endings that transduce touch in skin.

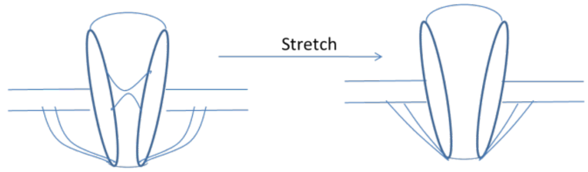


Figure 1.1.4.4:Stretch Gating

Each neuron receives signals via its dendrites, from other neurons; the dendritic signals flow towards the soma and combined at a part of the soma called the axon hillock; signals that arise from the axon hillock then propagate along the axon; at the end of the axon collaterals the axonal signals are transmitted to other neurons via the synapse. The cycle continues…

Thus, signaling in a neuron may be divided into four stages (fig. 1.1.5.1):

1.1.5 Stages of Neural Signaling:

1) Signaling over the dendritic tree
2) Summation at the axon hillock
3) Signal propagation along the axon and its collaterals
4) Signal transmission across the synapse

Neural signals are electrical and chemical:

So far we have been talking about neural "signals" rather vaguely without specifying the nature of these signals. Neural signals are electrical or chemical depending on the site of the signals. Among the 4 signaling components mentioned above, the first three are electrical, while the last one, signal transmission across the synapse, is a chemical step.

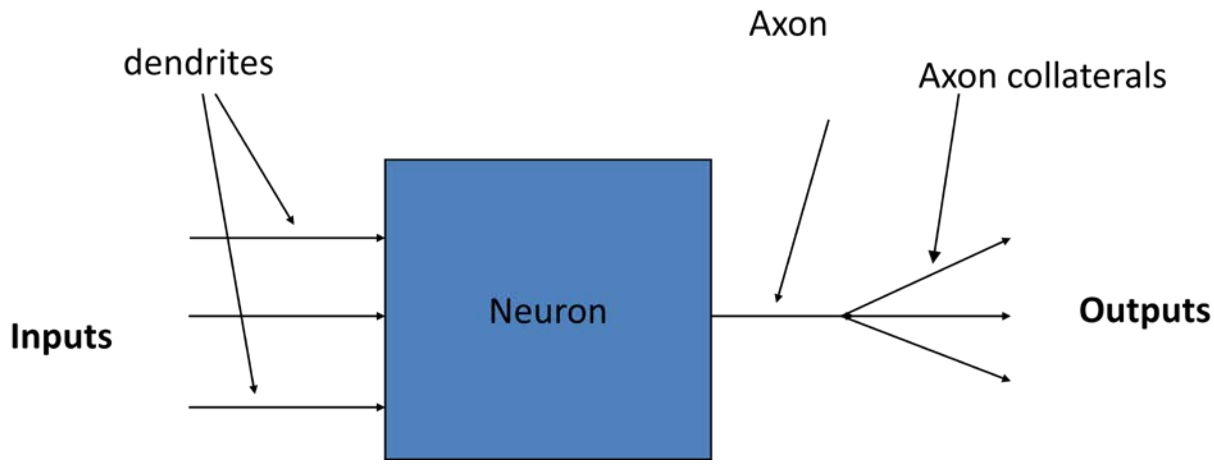


Figure 1.1.5.1: A neuron as an input/output system. Inputs from other neurons are received by the dendritic tree. Signals generated by a neuron are transmitted/broadcast to other neurons by the axon collaterals.

1.1.5.1 Dendritic signals:

The signals that are received at a dendritic branch from the axon terminal of another neuron, via a synapse, is in the form of a local voltage change. This voltage change can be either positive or negative, depending on the nature of the synapse. This voltage deviation propagates, like a wave, towards the cell body. Propagation along a dendrite is lossy (fig. 1.1.5.1.1). Therefore, the wave as it propagates loses amplitude and widens in time. Different waves, positive and negative, originating at different times, at different locations on the dendritic tree, flow towards the soma and get summated there.

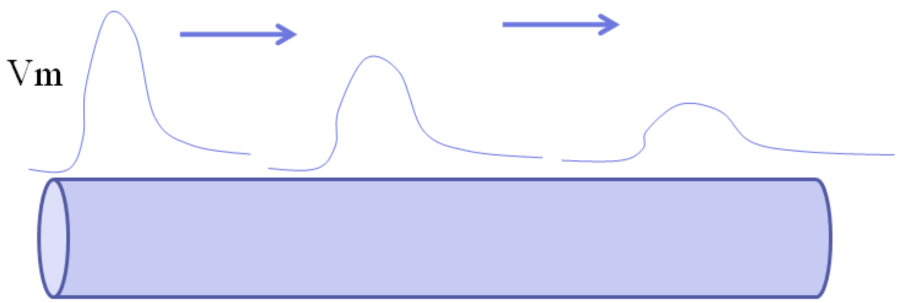


Figure 1.1.5.1.1: Dendritic propagation.

1.1.5.2 Summation at the soma and Action Potential:

The voltage waves arriving from the dendritic arbor, get summated at the soma (fig. 1.1.5.2.1), or more specifically the axon hillock, a knobby part of the soma at the root of the axon. The axon hillock has a high concentration of voltage-sensitive sodium and potassium channels, which is the reason behind a special response property of a neuron known as the "all-or-none" response. To illustrate this "all-or-none" response consider a thought-experiment in which you inject a pulse of current into a neuron. A small current pulse produces a small transient, upward deviation in the neuron voltage (fig. 1.1.5.2.2). As the current pulse amplitude is increased, amplitude of the voltage deviation also grows proportionally until the response reaches a threshold voltage level. Beyond this threshold, the neuron's voltage continues to increase rapidly up to a high value and sharply drops to the original resting potential (fig. 1.1.5.2.3). This transient, rapid rise and fall of neuron voltage is known as Action Potential (AP). It has 3 phases:

- Rising Phase
- Falling Phase

- After Hyperpolarisation

Refractory period of the AP is a short period of time after an action potential has occurred, the cell membrane cannot fire another action potential. This can be *Absolute refractory period:* voltage-gated Na+ channels won't open again or *Relative refractory period*: cell is hyperpolarized

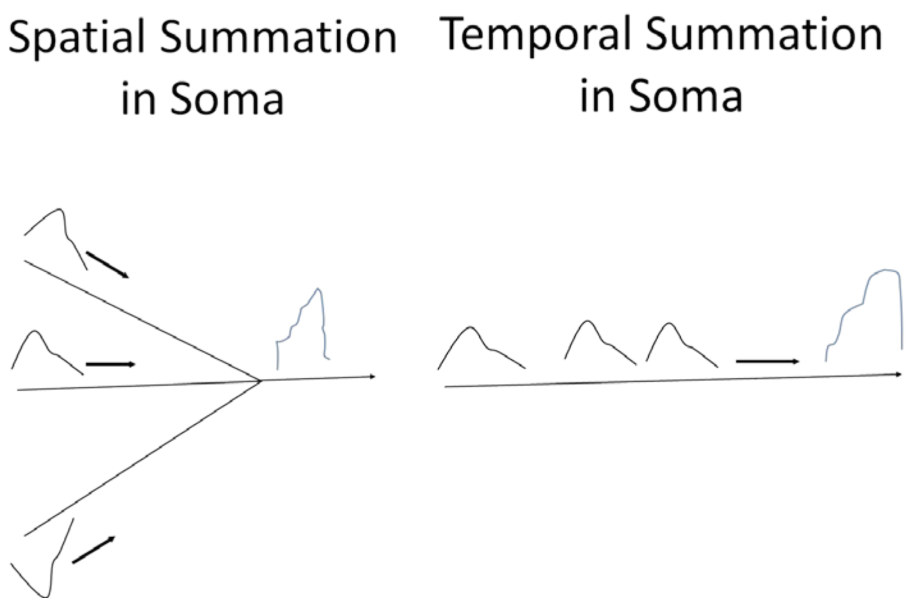


Figure 1.1.5.2.1: Summation at Soma

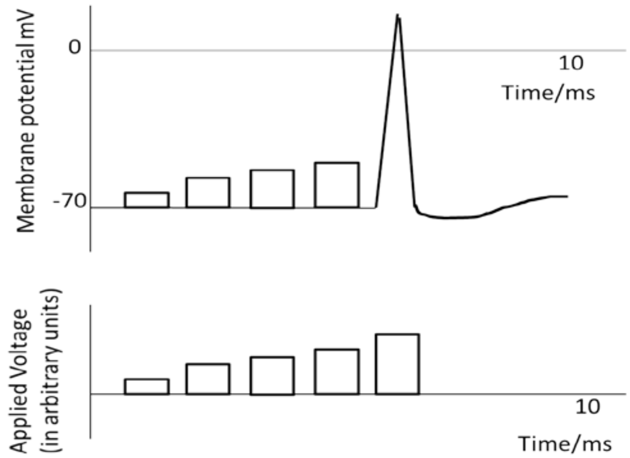


Figure 1.1.5.2.2: All or none Law

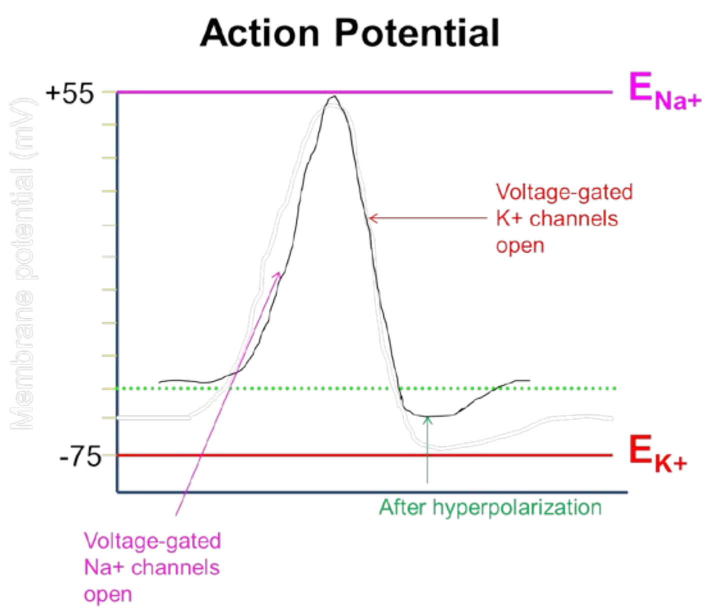


Figure 1.1.5.2.3: Phases in an Action Potential

When voltage waves of different amplitudes and signs flow towards the soma, they add up to change the local voltage of the soma. If that change is positive and exceeds a threshold value, an AP is produced at the axon hillock. If the net voltage change does not exceed the threshold value, no AP is produced (fig. 1.1.5.2.4). The state in which a neuron produces an AP is known as an *excited state*, as opposed to the usual resting state of the neuron when the voltage is a low, constant value.

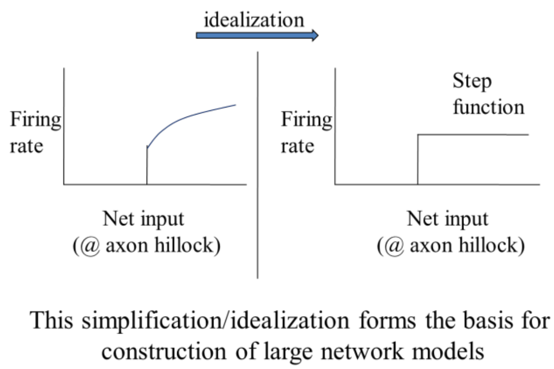


Figure 1.1.5.2.4: Neuron as a Thresholding Device

1.1.5.3 **Axonal propagation**:

The AP produced at the axon hillock propagates along the axon and reaches the axon collaterals. An important difference lies in the manner in which an AP propagates along the axon, and a voltage wave propagates along the dendrites. A voltage wave loses its amplitude and also spreads in time as it propagates down the dendritic tree towards the soma. But an AP propagates intact, without losing amplitude or spreading in time, as it propagates along an axon (fig. 1.1.5.3.1).

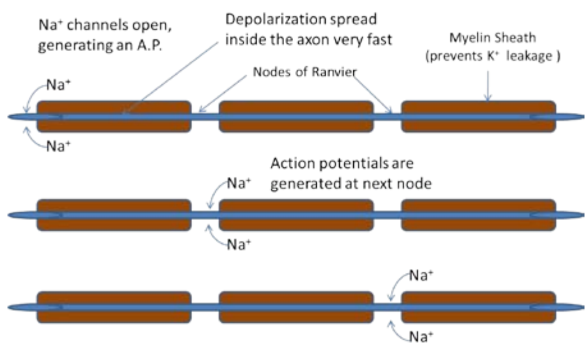


Figure 1.1.5.3.1: Axonal Propagation

This is possible because of presence of special molecular machinery on the axon and also in the axon hillock. This machinery is responsible for charging up the signal as it propagates along the cable (fig. 1.1.5.3.2).

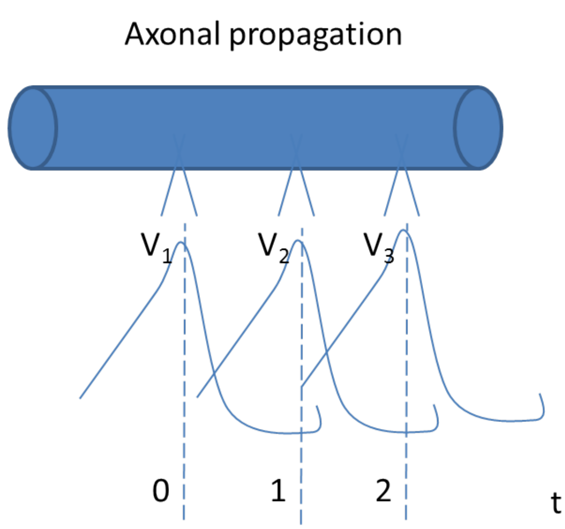


Figure 1.1.5.3.2: Axonal Propagation

1.1.5.4 Synapse

The synapse forms the functional connection between two neurons. It is a convenient window through which one neuron signals to another. The synapse is what makes the brain a *network* of neurons and not a mass of cells. Most importantly, it is the site of most learning and memory in the brain. It is now believed that whenever the brain learns something, the result of learning is somehow encoded in the properties of synapses. Recognition of the importance of the synapse in understanding brain function has led to a whole movement known as "Connectionism."

The synapse is a special structure where all the neurochemical machinery for neuron to neuron signaling is concentrated. Its design ensures that a signal released by a neuron has maximal effect on a target neuron with minimum attenuation. Based on the nature of signal used, synapses are classified as i) electrical synapses and ii) chemical synapses.

1.1.5.4.1 Electrical synapses

Electrical synapses are direct cell-to-cell contacts. They are mediated by gap junctions, which form corridors that directly connect cytosols of two neurons (fig. 1.1.18). These corridors can permit passage of ions and small molecules. Thus two neurons coupled by gap junctions can electrically signal to each other by exchange of ions.

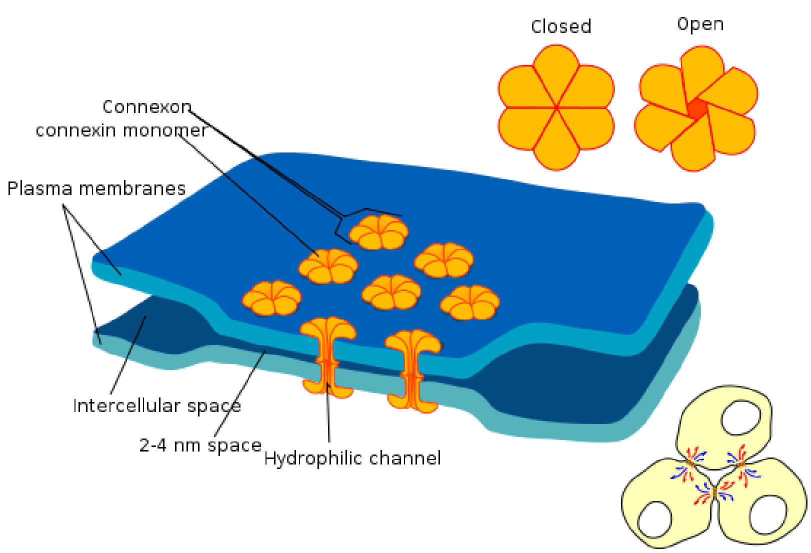


Figure 1.1.5.4.1: Electrical Synapse

Electrical synapses are typically bidirectional i.e., signal propagates in both directions(from neuron A to neuron B and back). This is because the electrical synapses may be simply regarded as a passive conductance that links the membrane voltages of two neurons. (There are, however, rectifying gap junctions in which conductance is greater in one direction than the other, analogous to a diode in electronic circuits. These may still be considered bidirectional with some asymmetry.)

1.1.5.4.2 Chemical synapses

In a chemical synapse, signaling is mediated by a chemical messenger that transduces electrical changes in one neuron and translates it into appropriate electrical changes in a target neuron. Fig. 1.1.5.4.2 shows the microstructure of a synapse.

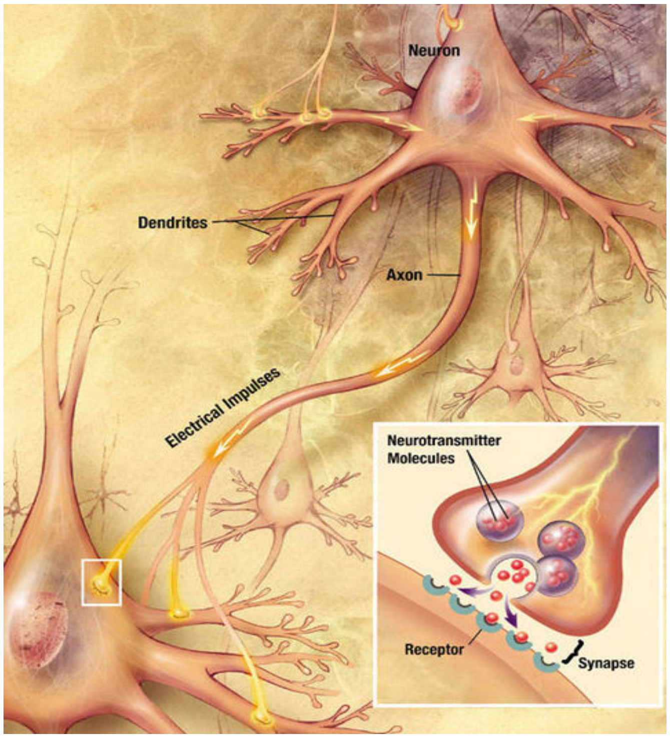


Figure 1.1.5.4.2: Chemical Synapse

Some terminology is in line. Transmission across a chemical synapse is unidirectional proceeding from the *presynaptic* neuron to the *postsynaptic* neuron. Synapse is simply a site where the axon terminal of the presynaptic neuron, known as the presynaptic terminal, and an appropriate part of the postsynaptic neuron, known as the postsynaptic terminal, are held in close proximity. The pre- and post- synaptic terminals have no physical contact and are separated by a gap known as the *synaptic cleft.* The cleft is rather narrow with a gap of only about 20 nm. Such close apposition of the pre- and post-synaptic terminals in a synapse makes possible a reliable transmission with minimal loss

1.1.6 Neurotransmission:

As mentioned above signaling processes up to the time when an AP arrives at an axon terminal are electrical, while the signal transmission across the synapse involves exchange of chemicals. When an AP arrives at an axon terminal, a special substance, known as the neurotransmitter, is released from the terminal, by exocytosis. This release is probabilistic and every AP need not produce a PSP. The neurotransmitter diffuses through a 20 nm gap contained in the synapse, known as the synaptic cleft, and reaches the dendrite of another neuron.

Action of neurotransmitter on the dendrite produces a voltage change in the dendrite known as the Post Synaptic Potential. This is simply the positive or negative deviation from the membrane potential of the dendrite, as described above. A positive voltage is more likely to propagate to soma and increase its local voltage, contributing its subsequent excitation. Therefore, a positive change is known as the Excitatory Post Synaptic Potential (EPSP). On the other hand, a negative change, when it propagates to the soma, tends to prevent the neuron from excitation. In other words, it tends to inhibit the neuron. Therefore, such voltage change is known as the Inhibitory Post Synaptic Potential (IPSP). A synapse at which a EPSP is produced is called an excitatory synapse while the synapse at which an IPSP is produced is an inhibitory synapse. Now let us take a closer look at the process of neurotransmission. What makes one transmission event produce an EPSP as opposed to an IPSP? There are three molecular players in the process of neurotransmission: neurotransmitter, receptor and an ion channel. When the transmitter molecules released from the presynaptic terminal diffuse towards the postsynaptic terminal and bind with a receptor, which is associated with an ion channel. The binding event between the neurotransmitter and the receptor opens the associated ion channel. If the channel that is opened is a Na+ channel, the local, postsynaptic membrane potential increases, which is the EPSP (fig. 1.1.6.1). On the other hand, when the ion channel that is opened is a K+ or a Cl- channel, it results in a negative deviation in the postsynaptic membrane voltage, which is an IPSP (fig. 1.1.6.2).

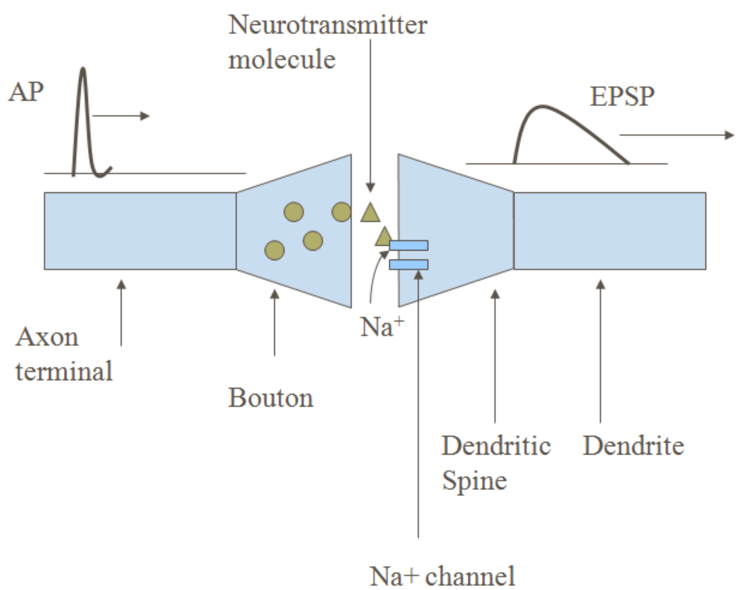


Figure 1.1.6.1: Excitatorry Post Synaptic Potential (EPSP)

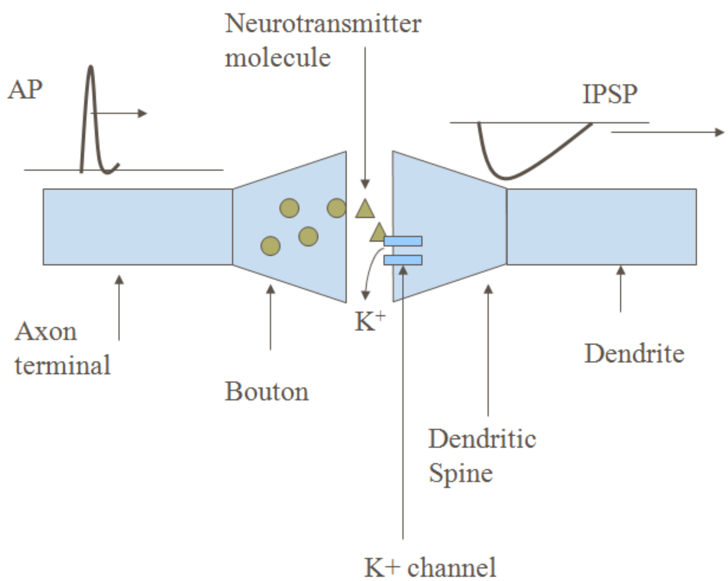


Figure 1.1.6.2: Inhibitory Post Synaptic Potential (IPSP)

Let us consider a few basic facts about neurotransmitter, receptor and ion channels.

1.1.6.1 Neurotransmitter:

In terms of their action, neurotransmitters may be broadly classified into excitatory and inhibitory neurotransmitters. A neurotransmitter that produces an EPSP is known as an excitatory neurotransmitter, an important example of which is glutamate. Similarly a neurotransmitter that produces an IPSP is an inhibitory neurotransmitter, a key example of which is Gamma Aminobutyric Acid (GABA). Glutamate and GABA are two important neurotransmitters in the brain. Over half of all brain synapses release glutamate, and about 30-40% of all brain synapses release GABA. Increased glutamate transmission tends to increase the overall excitation in the brain, while GABA transmission has the opposite effect. The push-pull effect due to glutamate and GABA keep the brain in a state of balance between over-excitation and total inhibition.

Neurotransmitters vary in terms of their speed of action, scope of action, spatial extent of their action etc. However, in terms of chemistry, the classes of neurotransmitters: i) amino acids, ii) biogenic amines, iii) others and iv) neuropeptides.

The below three categories of neurotransmitter are grouped under the general class of *fast-acting neurotransmitters*, since their post-synaptic effects show up at the time scales of milliseconds.

i) Amino Acids: There are 4 main candidates in this category: glutamate, aspartate, □ amino-butyric acid (GABA) and glycine. These are fast acting, capable of producing post-synaptic currents within a few milliseconds. Glutamate and aspartate are prominent excitatory transmitters, while GABA and glycine are inhibitory. Most rapid neurotransmission in vertebrate nervous systems is mediated by this class of neurotransmitters.

ii) Biogenic Amines: There are 5 substances in this category: acetylcholine (Ach), norepinephrine, dopamine, serotonin and histamine. Their activity is much slower than the amino acid neurotransmitters, lasting over a duration of hundreds of milliseconds. However, as it is almost always the case in biology, there are exceptions. The speed of transmission depends on the type of receptor. For example, Acetylcholine acts fast when the transmission in mediate by a nicotinic receptor and slow acting in case of a muscaranic receptor.

iii) Others: adenosine, nitric oxide etc.

In addition to the above 3 classes, there is another broad class of neurotransmitters known as neuropeptides. These are basically peptides, short chains of amino acids, which can have action on the postsynaptic side. The neuropeptides are said to be slow-acting since their postsynaptic action occurs over time scales of seconds.

iv) Neuropeptides β-endorphin is an important example of a neuropeptide which interacts with opioid receptors in the brain. These are short chains of amino acids, acting over a time scale of minutes or more. This class of neurotransmitters is sometimes present along with ("colocalized") with other fast-acting neutransmitters. Release of this type of neurotransmitter occurs at a greater firing rate of the presynaptic stimulus, compared to what it takes to release fast acting neurotransmitters.

A question that often arises regarding neurotransmitters is: does a synapse release a single neurotransmitter or multiple neurotransmitters? A general principle of neurotransmission, called Dale's principle, states that a neuron releases only a single transmitter. This is not true since a single neuron can release multiple transmitters from its synapses, a phenomenon known as *cotransmission*. Thus a modified form of Dale's principle, due to Sir John Eccles, states that "at all the axonal branches of a neuron, there was liberation of the same transmitter substance or substances." Thus the same set of neurotransmitters are released by a neuron throughout its lifetime at its synapses.

1.1.6.2 Receptors

Receptors are grouped as 1) ionotropic or 2) metabotrophic receptors, based on the manner in which they interact with the associated ion channel.

1) In ionotropic receptors, the receptor or the binding site is located on another part of the protein complex that forms the ion channel.
2) In metabotrophic receptors, the biding of neurotransmitter and receptor activates a series of intra-cellular events, one of which is the channel opening.

A given neurotransmitter can have several receptors.

Examples:

1) Glutamate receptors: 3 ionotropic and 1 metabotropic.
    a. Ionotropic receptors: N-methyl D-aspartate (NMDA) receptor, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor, kainate receptor.
    b. Metabotropic receptor: mGluR receptor.
2) GABA receptors: are of two classes.
    a. GABAa receptors are ionotropic
    b. GABAb receptors are metabotropic

1.1.7 Structural Classification of Synapses:

Above we described a synapse structurally as a meeting point between axon terminal of the presynaptic neuron and an "appropriate part" of the post-synaptic neuron. Synapses are actually classified on the basis of what this "appropriate part" of the post-synaptic neuron is.

1) Axodendritic synapses: These synapses occur between axon terminals of one neuron and a dendrite of another. Further, this contact can occur at the shaft of the dendrite, or at a dendritic spine. It has been observed that synapses on dendritic spines are usually excitatory. When a signal is transmitted across an axodendritic synapse it undergoes

certain attenuation as it propagates down the dendritic tree towards the soma of the post-synaptic neuron. This propagation also involves a certain delay.

2) Axosomatic synapses: In these synapses, the axon terminal of one neuron makes contact with the soma of another. Typically these synapses happen to be inhibitory. By virtue of their proximity to the soma, signals across axosomatic synapses are more effective than signals from axodendritic synapses.

3) Axoaxonic synapses: Existence of axoaxonic synapses seems counterintuitive since a synapse is supposed to be junction between the output end of a neuron (its axon terminal) and the input end (dendrite or soma) of another neuron. However such synapses do exist. Signal across an axoaxonic synapse typically modulates transmission across one of the above two types of neurons.

1.1.8 Synaptic Transmission:

To summarize, a synapse simply converts an electrical event on the pre- side (arrival of AP) into an electrical event on the post- side (EPSP or IPSP). This conversion is done by an intermediate chemical step mediated by the trinity of Neurotransmitter-Receptor-Ion Channel. Fig. 1.1.8.1 shows the major structural components of a chemical synapse.

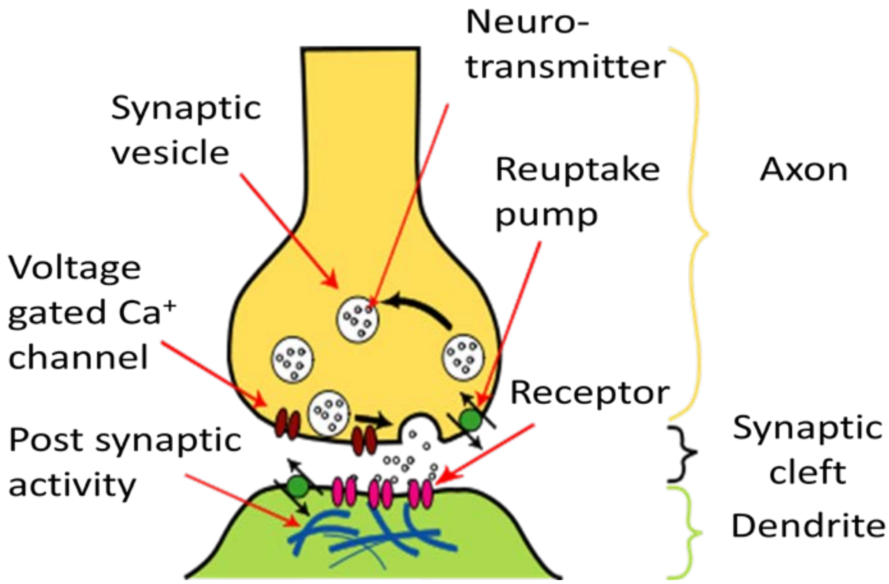


Figure 1.1.8.1: Major structural components of a synapse

How does this transformation of an AP on the pre- side to a PSP on the post- side take place? Complex molecular machinery is used for this purpose. Let us a take a closer look at the series of events involved in this conversion.

Step 1: AP generated at the axon hillock arrives at the axon terminal or the pre-synaptic terminal.

Step 2: AP arrival increases local membrane potential in the pre-synaptic terminal.

Step 3: Voltage-sensitive Ca++ channels open. Ca++ rushes into the pre-synaptic terminal.

Step 4: Increased Ca++ concentration in the pre-synaptic terminal causes vesicles containing neurotransmitter to fuse with pre-synaptic membrane and release neurotransmitter into the synaptic cleft. Such spewing out of material by cells is known as exocytosis.

Step 5: Neurotransmitter diffuses through the synaptic cleft and binds to receptor molecules on the post-synaptic membrane

Step 6: The binding event signals to associated ion channels to open/close

Step 7: Current influx/efflux through the open channels produces a (E/I)PSP across the post-synaptic membrane.

There are certain secondary, "clean up" events that accompany the above events.

Step 4b: (Vesicle recycling): When vesicles fuse with the pre-synaptic membrane, the membrane of the vesicle fuses with plasma membrane increasing the surface area of the pre-synaptic membrane. If this process goes on indefinitely, there will not be any membrane left for synthesis of new vesicles. However, the vesicular membrane patch that fused with the pre-synaptic membrane is recycled, taken back into the pre-synaptic terminal for synthesizing new vesicles. This process is thought to occur via several intricate mechanisms.

Step 5b: Transmitter molecules that are released into the synaptic cleft do not linger there for ever. They are removed from that region by several mechanisms. This removal is necessary to terminate the transmission process. Otherwise prolonged exposure of post-synaptic receptors to transmitter molecules makes the receptors insensitive to subsequent signals coming from the pre-synaptic side. Removal of transmitter from the cleft is done by 3 mechanisms: 1) diffusion, 2) enzymatic degradation (breaking down of transmitter by specific enzymes) and 3) re-uptake (transmitter molecules are actively taken back into pre-synaptic terminals and packaged into newly synthesized vesicles).

1.1.9 Synaptic Strength:

Since the PSP produced as a result of a single AP on the presynaptic side has variable magnitude, we can introduce the notion of synaptic strength. There is no single, textbook definition of synaptic strength. Biologically speaking there are several factors, both pre- and post-synaptic, that determine the synaptic strength. A reasonable definition of synaptic strength could be:

Synaptic strength = average PSP produced in response to an AP on the presynaptic side.

Synaptic strength figures as an important quantity in any discussion of information processing in the brain, since this strength varies as an effect of learning and memory. Results of learning and memory seem to be coded in the form of synaptic strength. This labile quality of synapses is known as synaptic plasticity.

1.2 Organization of the Nervous System: An Overview

The nervous system can be broadly classified into two major categories – the Central Nervous System (CNS) and Peripheral Nervous System (PNS) (Fig. 1.2.1).

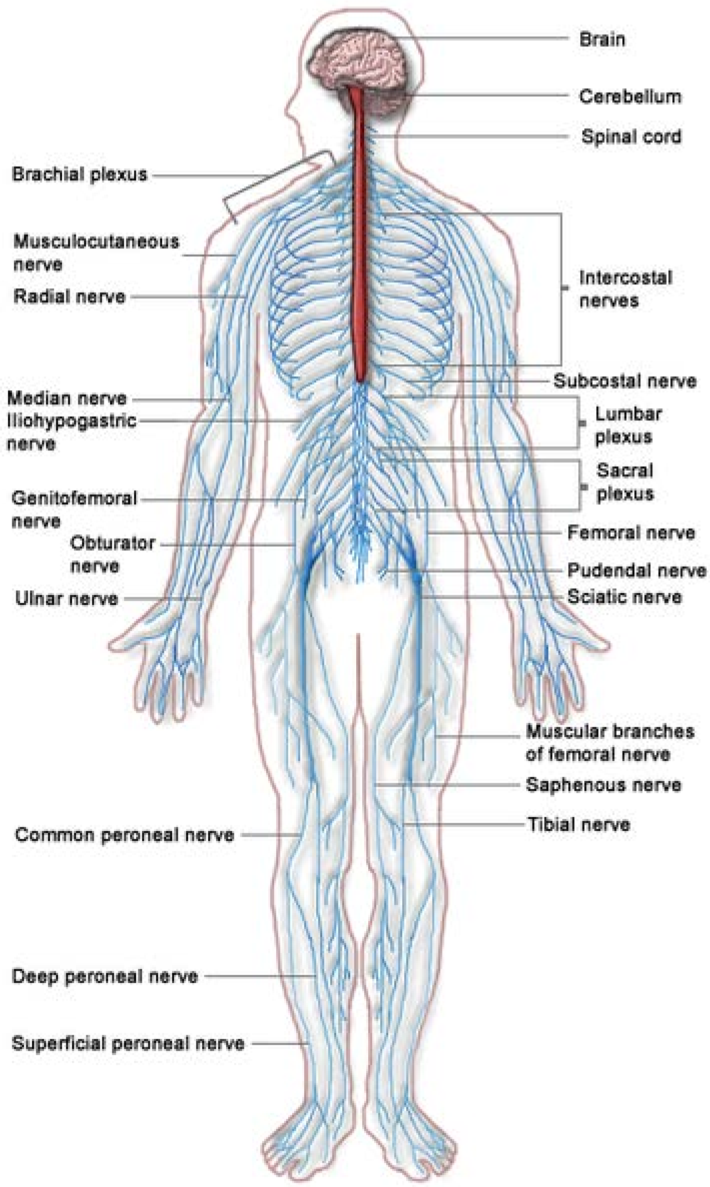


Figure 1.2.1: Human Nervous System

1.2.1 Central Nervous System

The central nervous system consists of the brain and spinal cord.

- **Brain**

  The brain consists of the cerebrum, cerebellum and brain stem (containing the midbrain, pons and medulla oblongata).

- **Spinal Cord**

  The **spinal cord** is a long, thin, tubular bundle of nervous tissue and support cells that extends from the brain (the medulla oblongata specifically). The brain and spinal cord together make up the central nervous system (CNS).

1.2.2 Peripheral Nervous System

The peripheral nervous system is divided into two parts – the somatic nervous system and the autonomic nervous system.

- **Somatic Nervous System**

  The somatic nervous system performs two major functions – sensory and motor. The sensory nerves innervate skin, muscles and joints, and provide information about muscle and limb position, etc. It is majorly composed of 12 cranial nerves and 33 spinal nerves.

- **Autonomic Nervous System**

  The autonomic nervous system can be classified into two major parts – the sympathetic and parasympathetic nervous systems. The sympathetic system participates in the body's reaction to stress, and helps in reacting to an emergency ("fight or flight") situation. The parasympathetic system conserves body resources and maintains homeostasis. About 75% of all parasympathetic nerve fibres are in the vagus nerve.

Example – Sympathetic nerves control the sudden increase in heart rate during a stressful situation, whereas the parasympathetic nerves participate in lowering the heart rate during rest.

A third part of the autonomic nervous system, called the enteric system, specifically controls the smooth muscles in the intestine.

1.2.3 Nerves

A nerve is an enclosed, cable-like bundle of axons (the long, slender projections of neurons) in the peripheral nervous system. A nerve provides a common pathway for the electrochemical nerve impulses that are transmitted along each of the axons.

There are three major types of nerves –

- Afferent nerves conduct signals from sensory neurons to the central nervous system, for example from the mechanoreceptors in skin.
- Efferent nerves conduct signals from the central nervous system along motor neurons to their target muscles and glands.
- Mixed nerves contain both afferent and efferent axons, and thus conduct both incoming sensory information and outgoing muscle commands in the same bundle.

Nerve fibres may also be classified into various categories based on the speed at which they conduct electrical impulses.

- Type A – Large, myelinated fibres (~120 m/s conduction velocity)
- Type C – Small, unmyelinated fibres (~0.5 m/s)

Myelin sheath – A sheath which may cover nerve fibres; it helps in faster conduction of electrical impulses.

1.2.4 Central Nervous System – Details

1.2.4.1 Cerebrum

The cerebrum consists of two hemispheres, joined by a large bundle of axons called the corpus callosum. The hemispheres are also connected by a smaller bundle of fibres called the anterior commisure.

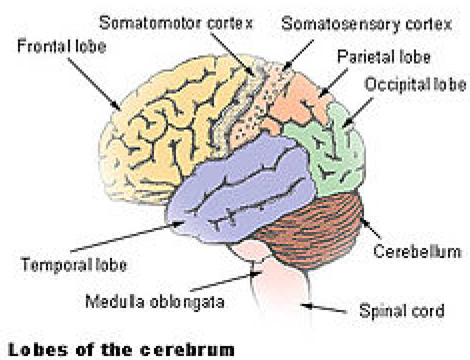


Figure 1.2.4.1.1: Lobes of the cerebrum.

The cerebrum can be broadly classified into four lobes –

- Frontal lobe - The **frontal lobe** is in the front of each cerebral hemisphere (Fig. 1.2.4.1.1 - 1.2.4.1.2). It is separated from the parietal lobe by a vertical gap called central sulcus, and from the temporal lobe by a deep fold called the lateral (Sylvian) sulcus. Primary motor cortex, which controls voluntary movements of the body is located in the precentral gyrus, forming the posterior border of the frontal lobe. Prefrontal cortex - The **prefrontal cortex** (P.F.C.) is the anterior part of the frontal lobes of the brain, lying in front of the motor and premotor areas.

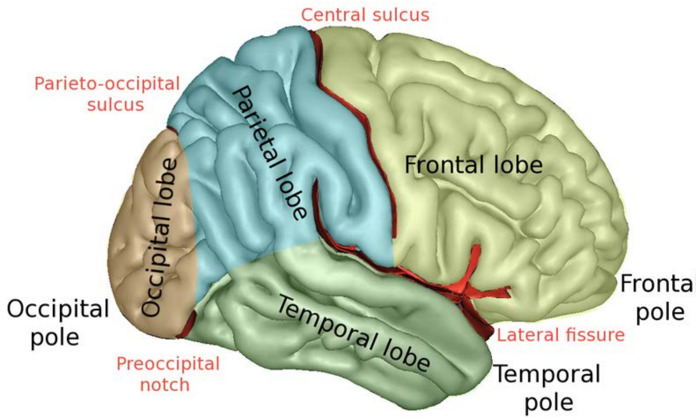


Figure 1.2.4.1.2: Lobes of the cerebrum.

- o This brain region has been implicated in planning complex cognitive behavior, personality expression, decision making and moderating social behavior – a whole range of activities that are summarily described as executive function.

- Parietal Lobe - The **parietal lobe** is above the occipital lobe and behind the frontal lobe. It consists of the somatosensory cortex located at the anterior extreme, in the postcentral gyrus (Fig. 1.2.4.1.3). The somatosensory cortex processes touch information coming from mechanoreceptors located in the skin, muscles and joints.

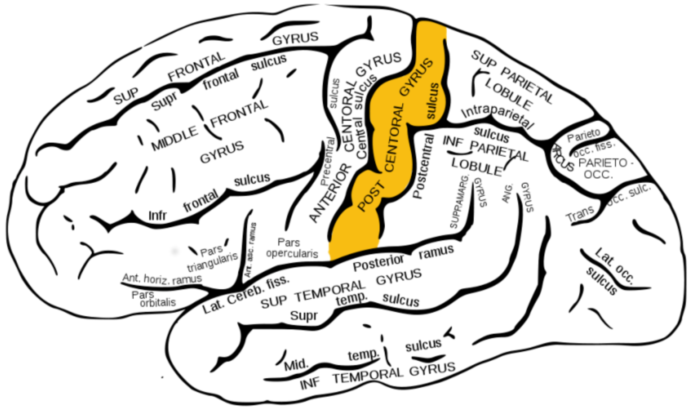


Figure 1.2.4.1.3: Post central Gyrus

Inferior parietal lobe consists of areas that process higher aspects of vision like spatial sense.

By virtue of its strategic location amidst three primary sensory cortices – somatosensory cortex, visual cortex and auditory cortex, - inferior parietal lobe as sensory association areas which integrate information from the three sensory modalities and extract abstract concepts.

- Temporal Lobe – The **temporal lobe** is located beneath the Sylvian fissure, a shared border between the temporal and frontal lobes.

  Primary auditory cortex, involved in auditory processing, is located in the superior part of temporal lobe, bordering on the sylvian fissure.

  The temporal lobe contains a deep structure called hippocampus, whose functions include spatial navigation, declarative memory, and memory consolidation.

Wernicke's area, which spans the region between temporal and parietal lobes, plays a key role, in language understanding, while Broca's area, which is in the frontal lobe, is responsible for language production (Fig. 1.2.4.1.4).

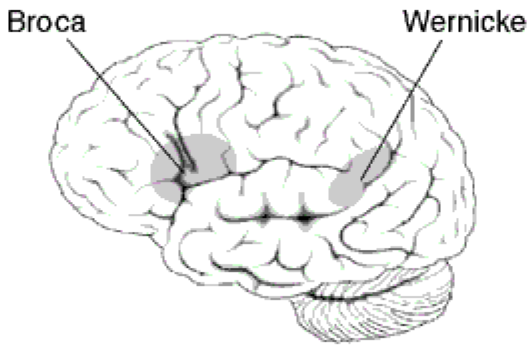


Figure 1.2.4.1.4: Lobes of the cerebrum.

The inferior part of temporal lobe has cortical areas that are responsible for recognizing complex visual objects, like for example, faces.

- Occipital Lobe – The **occipital lobe** has primary and higher areas of the visual cortex.
    - The primary visual cortex is commonly called V1 (visual one). It is partly located in the medial side of occipital lobe and partly in the posterior pole of the occipital lobel. V1 is often also called striate cortex because it can be identified by a large stripe of myelin, the Stria of Gennari. Visually driven regions outside V1 are called extrastriate cortex. There are many extrastriate regions, and these are specialized for different visual tasks, such as visuospatial processing, color discrimination and motion perception (Fig. 1.2.4.1.5).

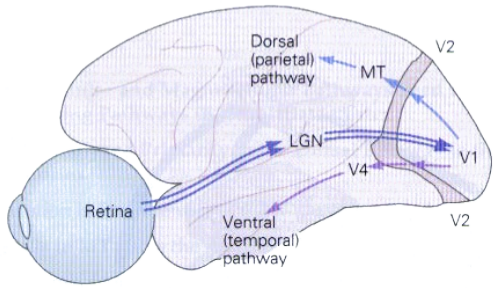


Figure 1.2.4.1.5: The Striate cortex

- Secondary and higher visual cortical areas extend from the occipital lobe and are spread over the neighboring parietal lobe.

Deep Brain Structures:

- Hypothalamus - The **hypothalamus** is an important structure controlling our autonomous function. It links the nervous system to the endocrine system via the pituitary gland. The hypothalamus controls body temperature, hunger, thirst, fatigue, sleep, and circadian cycles (Fig. 1.2.4.1.6).

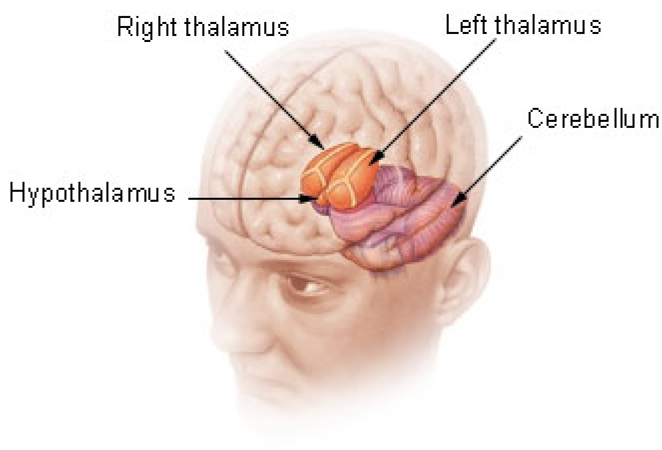


Figure 1.2.4.1.6: Thalamus and Hypothalamus

- Thalamus – The **thalamus** is located between the cerebral cortex and midbrain. It is an important hub through which most sensory information reaches the sensory cortex. It is involved in regulation of consciousness, sleep, and alertness (Fig. 1.2.4.1.6).
- Reticular Activating System - The **reticular activating system (RAS)** is an area of the brain responsible for regulating arousal and sleep-wake transitions.
- Limbic System - The **limbic system** is a set of brain structures involved in processing emotions, and is closely related to autonomous function. This system includes the hippocampus, amygdala, anterior thalamic nuclei, septum, limbic cortex and fornix (Fig. 1.2.4.1.7).

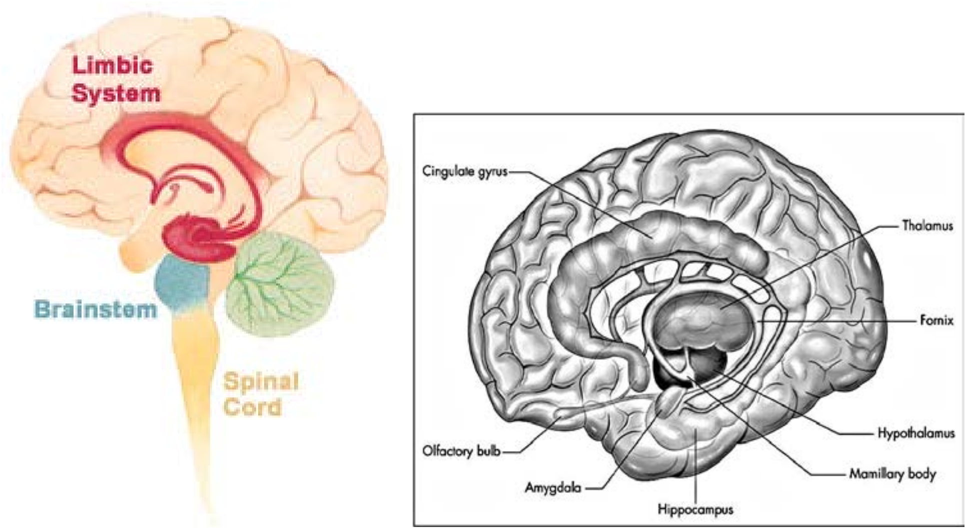


Figure 1.2.4.1.7: Limbic system

- Amygdala – This almond-shaped structure is located bilaterally in the medial temporal lobes of the brain. A part of the limbic system, this structure is involved in fear conditioning (Fig. 1.2.4.1.8).
- Basal Ganglia - The **basal ganglia** (or **basal nuclei**) are a deep brain circuit consisting of 6 or 7 nuclei. This circuit receives inputs from the cortex and projects back to the cortex. It has key functions like reward processing, action selection, working memory etc (Fig. 1.2.4.1.8)

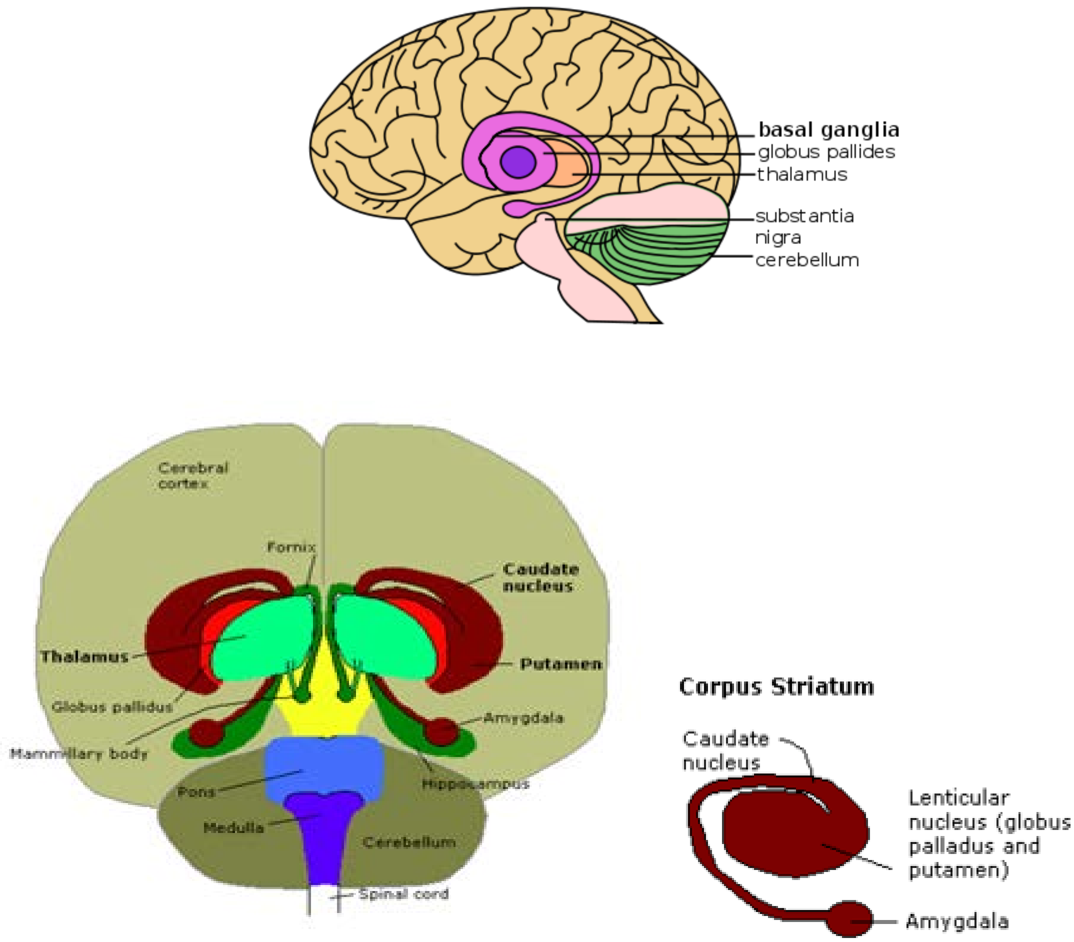


Figure 1.2.4.1.8: Diencephalon and Rhombencephalon

Damage to the basal ganglia can be associated to neurological and neuropsychiatric disorders like, for example, Parkinson’s disease

The following section will discuss the brain stem and cerebellum (Fig. 1.2.4.1.8)–

- Brain Stem – The brain stem is a sort of a bridge area between the cerebrum and the spinal cord. It comprises of three regions: midbrain, medulla oblongata and pons. It consists of a lot of important control centers and anatomical features. Centers for controlling cardiac and respiratory function; for regulating sleep and arousal; for controlling eating and drinking are located here.

- Medulla – This structure is a direct rostral (“towards nose”) extension of the spinal cord. Its primary functions include: regulation of blood pressure and respiration.
- Pons - The **pons** is a a part of the brain stem, located below the midbrain and above medulla oblongata. It consists of wiring that carries: 1) motor signals from the cerebrum down to the cerebellum and medulla, and 2) sensory signals from the body into the thalamus.
- Cerebellum - The **cerebellum** (Latin for *little brain*) is a distinct structure located posteriorly under the hemispheres. It is generally thought of as a motor control unit, though its role in cognitive and affective function is well-established. It is involved in control of fine movement, equilibrium, posture, and motor learning.
- Spinal Cord - The **spinal cord** is a long, tail-like bundle of nerve fibers that extends from the brain (the medulla oblongata specifically) along the spine. It has three key functions:
    - Carrying motor signals from the brain to the muscle
    - Carrying sensory information in the reverse direction
    - Coordinating reflexes