# Week 09 Lecture 41

Synapse:
A synapse is a specialized junction between two neurons where signals (in the form of neurotransmitters) are transmitted from one neuron (the presynaptic neuron) to another (the postsynaptic neuron).

Synaptic Transmission:
1. Action Potential Arrival: The process starts when an action potential (an electrical signal) travels down the axon of the presynaptic neuron to its axon terminals.

2. Calcium Ion Influx: The action potential reaching the axon terminal causes voltage-gated calcium ion (Ca2+) channels to open. This allows Ca2+ to flow into the neuron.

3. Neurotransmitter Release: The influx of Ca2+ triggers the release of neurotransmitter molecules. These neurotransmitters are stored in vesicles (small sac-like structures) within the axon terminal. Upon calcium entry, these vesicles fuse with the presynaptic membrane and release their contents into the synaptic cleft (the space between the presynaptic and postsynaptic neuron) via exocytosis.



4. Neurotransmitter Binding: The released neurotransmitters diffuse across the synaptic cleft and bind to specific receptors on the postsynaptic neuron's membrane. These receptors can be either ionotropic (directly affecting ion channels) or metabotropic (acting through intracellular signalling mechanisms).

5. Postsynaptic Potential Generation: When neurotransmitters bind to ionotropic receptors, they cause an immediate change in the postsynaptic neuron's membrane potential. This change can either be excitatory (increasing the likelihood of an action potential in the postsynaptic neuron) or inhibitory (decreasing that likelihood).

6. Signal Termination: For the signal to be brief and precise, the neurotransmitter's effect needs to be terminated quickly. This can occur through:
- Reuptake: Neurotransmitters are taken back into the presynaptic neuron for reuse.
- Degradation: Enzymes present in the synaptic cleft break down certain neurotransmitters.

Ionotropic Receptors:
- Ionotropic receptors are ligand-gated ion channels that open or close in response to the binding of a neurotransmitter or other ligand.
- Direct and rapid activation – When a ligand binds, the channel immediately opens or closes.
- Effects are typically fast and short-lived.

- Structure: They have a channel pore that allows ions such as Na+, K+, Ca2+, or Cl- to flow through the membrane.
- Examples: NMDA, AMPA receptors for glutamate; GABA-A receptors for GABA; nicotinic acetylcholine receptors.

Metabotropic Receptors:
- Metabotropic receptors, also known as G-protein coupled receptors (GPCRs), are receptors that do not have a channel that opens or closes. Instead, they activate internal signaling pathways through G-proteins.
- Indirect activation – ligand binding initiates a cascade of intracellular events.
- Effects are slower in onset but longer-lasting compared to ionotropic receptors.
- Examples: GABA-B receptors for GABA; muscarinic acetylcholine receptors; many receptors for neuropeptides and hormones.

G-Protein Coupled Receptors (GPCRs):
- GPCRs are a large family of cell membrane receptors that detect molecules outside the cell and activate cellular responses.
- Upon ligand binding, GPCRs activate an intracellular G-protein. This G-protein then activates an intracellular messenger to relay the signal.



# Week 09 Lecture 42

Modification of Synaptic Strength on the Pre-synaptic Side:
- Vesicle Increase: An increase in the number of synaptic vesicles being released will increase neurotransmitter release, enhancing synaptic strength.
- Calcium Concentration: Calcium is essential for neurotransmitter release. An increase in intracellular calcium concentration can potentiate neurotransmitter release.
- Proteins: Changes in proteins like synaptotagmin (involved in vesicle release) can modify neurotransmitter release. Also, modifications in vesicle recycling and docking machinery affect release efficacy.
- Neurotransmitter Reuptake: Reducing reuptake (by inhibiting transporters) can increase the amount of neurotransmitter in the synaptic cleft, prolonging its action.

Modification of Synaptic Strength on the Post-synaptic Side:
- Surface Area: An increase in the post-synaptic surface area (e.g., by dendritic spine growth) provides more space for neurotransmitter receptors, enhancing synaptic strength.
- Receptor Density: Increasing the number of neurotransmitter receptors on the post-synaptic membrane can amplify the response to a neurotransmitter.
- Receptor Sensitivity: Post-translational modifications (like phosphorylation) can increase receptor sensitivity, modifying synaptic strength.

NMDA and AMPA:

1. NMDA Receptors: A type of ionotropic glutamate receptor that is permeable to calcium, potassium, and sodium. It requires both glutamate binding and post-synaptic depolarization (due to magnesium block) to activate.
2. AMPA Receptors: Another type of ionotropic glutamate receptor, primarily permeable to sodium. Activation leads to rapid depolarization.
3. Synaptic Plasticity: The sequential activation of AMPA and NMDA receptors plays a critical role in long-term potentiation (LTP) and synaptic plasticity.
4. Calcium's Role: Calcium influx through NMDA receptors can activate intracellular pathways leading to enhanced synaptic strength.

IPSC, EPSC, EPSP, IPSP:
1. IPSC (Inhibitory Post-synaptic Current): A current resulting from the opening of ion channels by inhibitory neurotransmitters, usually leading to an influx of chloride or an efflux of potassium, hyperpolarizing the neuron.
2. EPSC (Excitatory Post-synaptic Current): A current resulting from the opening of ion channels by excitatory neurotransmitters, typically causing an influx of sodium or calcium, depolarizing the neuron.
3. EPSP (Excitatory Post-synaptic Potential): A depolarization of the post-synaptic membrane caused by excitatory neurotransmitters, making it more likely for the neuron to fire an action potential.
4. IPSP (Inhibitory Post-synaptic Potential): A hyperpolarization of the post-synaptic membrane caused by inhibitory neurotransmitters, making it less likely for the neuron to fire an action potential.



# Week 09 Lecture 43

Structural Plasticity and the Brain:
1. Structural plasticity refers to the brain's ability to change its physical structure in response to learning, experience, or environmental changes.
2. Involves processes like synaptogenesis (formation of new synapses), dendritic branching, and axonal sprouting.

Expansion of Maps in the Brain
1. Brain Maps: Specific regions of the brain are dedicated to processing information from specific parts of the body or from specific types of sensory input.
2. Example – Somatosensory Cortex and Digits Representation:
   - The somatosensory cortex has a mapped representation of different body parts.
   - Typing two fingers together would result in two regions which represent inputs to the two figures becoming merged as a single region in the brain.
   - With increased use or sensory input to a specific digit (like the fingers of a musician), the cortical area representing that digit may expand.
   - Conversely, lack of use or sensory deprivation may shrink the represented area.

Critical Period
1. A time window during development when the brain is particularly sensitive to certain stimuli, and experiences during this time can have long-lasting effects on brain function and structure.
2. Missing certain stimuli during the critical period can lead to deficits, while the introduction of specific stimuli can lead to enhanced capabilities.

Tonotopy and Critical Period
1. Tonotopy: Represents the spatial arrangement of where sounds of different frequencies are processed in the brain.
2. If an individual is exposed to a specific frequency during the critical period, the area of the auditory cortex that responds to that frequency can expand. This could make an individual more sensitive to that particular frequency.

Changes in Visual System – Monocular Deprivation
1. Monocular Deprivation: Closing one eye during a critical period of visual development.
2. The synaptic connections related to the closed eye weaken while those related to the open eye strengthen.
3. In the visual cortex, the representation of the closed eye shrinks, and that of the open eye expands.
4. This can lead to amblyopia (lazy eye) if not corrected in time.



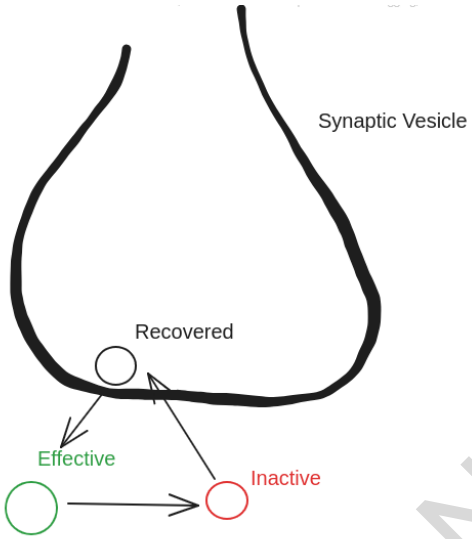
Classification of Plasticity
1. Based on Time Scales:
   - Short Term: Last on the order of seconds or minutes
   - Long Term: Lasts on the order of months or lifetime
2. Based on Increase or Decrease:
   - Potentiation/Facilitation: Connection strength increases. The recorded post-synaptic current magnitude is greater than in the previous case.
   -Depression: Connection strength decreases. The recorded post-synaptic current magnitude is lesser than in the previous case

# Week 09 Lecture 44

The three state short-term depression model can be read in this paper
https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002117#s2
*Methods* section, *Dynamic synapses* subsection

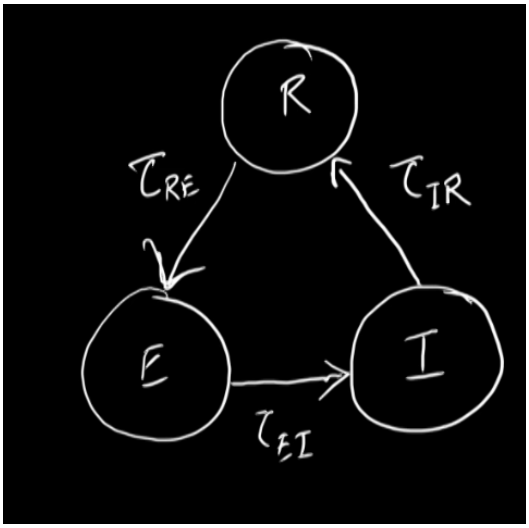
Depressing Synapse Model:

- Assume a fixed resource supply of neurotransmitters split into three states:
  - Recovered (R)
  - Effective (E)
  - Inactive (I)
- Initial conditions:R = 1, E = 0,  I = 0
- Let r, e, i be a fraction of neurotransmitters in each state
- since three states capture all the neurotransmitter pool, the sum of fractions representing each state should be 1.
- $r + e + i = 1$






- Recovered pool in the neurotransmitters are released and go to the “Effective stage”. But all effective neurons don’t make it to post-synaptic neurons, some get converted into an “inactive” state. From the inactive state, chemicals called “Transporter” take inactive neurotransmitters back to the synaptic vesicle.

- 


The above shows the time constants for conversion of one state to other state.

- The differential equations governing each fraction(taken from paper)
-

$$\frac{dx_r}{dt} = -\mathcal{M}\frac{x_r}{\tau_{re}} + \frac{x_i}{\tau_{ir}}$$

$$\frac{dx_e}{dt} = +\mathcal{M}\frac{x_r}{\tau_{re}} - \frac{x_e}{\tau_{ei}}$$

$$\frac{dx_i}{dt} = \frac{x_e}{\tau_{ei}} - \frac{x_i}{\tau_{ir}}.$$



(M is 1, if there is a spike, M is zero otherwise)

- E is the fraction considered responsible for post-synaptic current. Over a few seconds, E decreases hence causing the post-synaptic current to decrease. Later when E converts to I and finally to R, the current reaches the initial value. Hence, this 3 state model is used to model Short Term Depression.

# Week 09 Lecture 45

In the previous lecture, we saw how to model Short Term Depression. This lecture will discuss how to model Short Term Facilitation using two ideas -

1. Calcium Buffer on Pre-synaptic neuron
2. De-sensitization on Post-synaptic neuron

Calcium Buffer on Pre-synaptic neuron:
Let n(t) be the recovered pool, and the effective and inactive pool be considered together as 1 - n(t)

$$\frac{dn}{dt} = \frac{1-n}{\tau_r} - \Sigma_j \delta(t - t_j)\, p(t)\, n(t)$$

Here p(t) is the probability of release which is proxy for calcium buffer,
(the delta function is used to represent spike timings, takes 1 when there is a spike, 0 when there is no spike)
$\tau_r$ is a time constant

$$\frac{dp(t)}{dt} = \frac{p_0 - p(t)}{\tau_f} - \Sigma_j \delta(t - t_j)\, a_p (1 - p)$$

Here $a_p$ is an adjustable parameter
$a_p\, p(t)\, n\,(t)$ represents conductance of post-synaptic neuron
$\tau_f$ is a time constant

De-sensitization on post-synaptic neuron side:
Let D(t) represent the non-desensitized pool of receptors(active receptors)

$$\frac{d\,D(t)}{dt} = \frac{1-D(t)}{\tau_D} - \Sigma_j \delta(t - t_j)\, a_D\, p(t)\, n(t)\, D(t)$$

$a_D$ is an adjustable parameter
$\tau_D$ is a time constant