

Introduction to Neurobiology

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1 About this course

Objective of the course is to learn how the nervous system produces behaviour, how we use our brains in our day to day lives, and how neuroscience can help explain the problems afflicting people today. There'll be focus on functional human neuroanatomy, and neuronal communication, to help understand how we perceive the world, do body movements, and interact with others.

2 Resources

- Coursera: Understanding the Brain: The Neurobiology of Everyday Life taught by professor of Neurobiology Peggy Mason, at the University of Chicago (<https://www.coursera.org/learn/neurobiology>)

3 Introduction

- **The Diving Bell and the Butterfly:** Jean-Dominique Bauby, locked-in syndrome.

4 The Nervous System

4.1 The Four Functions

The locked-in syndrome tells of the four basic functions of the brain/central nervous system.

1. **Voluntary Movement:** Every thing we do that is driven by the brain, both deliberate actions, such jumping, speaking, raising your hand, etc, and not so deliberate actions like wincing in reaction to stepping on a lego piece.
2. **Perception:** Perception is distinct from sensation; its what we consciously appreciate about sensation. Its what we're capable of being aware of such as vision, hearing, smell, taste, balance, position, lung pressure, etc.
3. **Homeostasis:** Used to keep body within its physiological limits. For example, making sure the body has enough oxygen, the right blood pressure, right body temperature. Also, homeostasis accounts for life cycle events like a mother giving birth, and the conditions needed for the child to be healthy. Altogether, a process of maintaining healthy internal conditions.
4. **Abstract functions:** Higher functions of the central nervous system like thinking, language, motivation, feeling emotion, etc. Also, plays a huge role in how we interact with other humans.

4.2 Central Anatomy

Mapping of the four functions to regions of the brain.

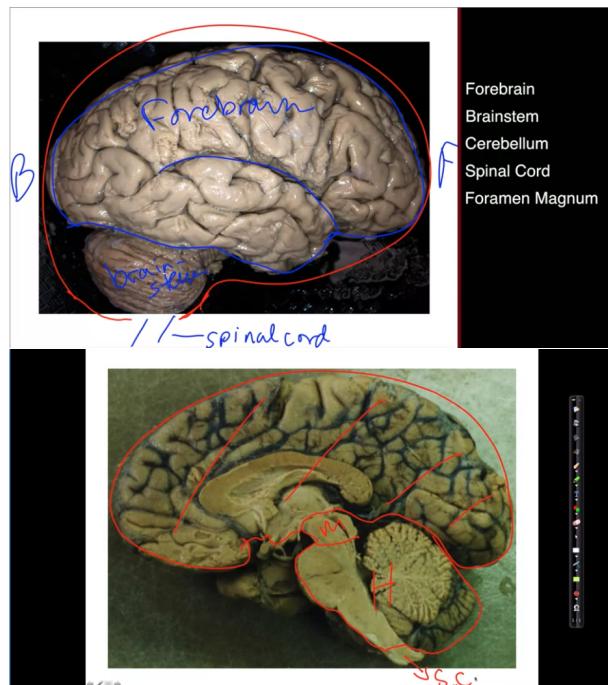
1. Motor neurons which exist in the brain stem, or the spinal cord are responsible for **voluntary movement**. There are less than 100,000 motor neurons, out of about 200 billion in the entire nervous system. Motor neurons in the brain system are responsible of movement of the mouth, face, hence speech, facial expressions, swallowing, etc. Motor

neurons in the spinal cord are responsible for bodily movements like movement of the arms, legs, etc.

2. **Perception** is entirely in the **Forebrain**; more specifically, it depends entirely on the **Cerebral Cortex**. Perception is one of the higher brain functions; if the information carried by neurons does not make it to the Cerebral Cortex, then there's no perception; there's no conscious appreciation/awareness of sensation.
3. **Homeostasis** depends on the **Forebrain, brain stem, and spinal cord**. The forebrain's contribution to homeostasis is hormonal. The brain stem has a varied contribution; it's responsible for the automatic changes we're not able to control, the autonomic (involuntary) functions of our nervous system. The spinal cord's contribution is similar to that of the brain stem.

The brain stem, and spinal cord serve as pathways for information, both incoming, and outgoing.

4. **Abstract functions** are entirely in the forebrain, and function independent of the brain stem, and spinal cord. The forebrain is the "seat of consciousness"; all perception, and abstract cognitive functions like memory, depend on the forebrain; more specifically, the cerebral cortex.



5 Neurons; the “stars” of the nervous system”

5.1 Parts of the Neuron

There are four parts to neurons.

1. Cell body, also known as the **Soma**. Place that keeps the cell going, makes all the materials needed for the entire neuron
2. **Dendrites**; they branch out of the cell body, creating a **tree like structure called the dendritic arbour/tree**. They're responsible for gathering information for the neuron. Information goes into the dendrites. Dendrites may be perceived as the ears of the neuron.
3. Information processed locally from dendrites, sent out through one **axon** which is more globally distributed compared to the dendrites. Axon can travel a metre; and ultimately carry information to a **synaptic terminal**.
4. **Synaptic terminals** are the point of information transfer between cells; information is carried to the terminal via axons. There's a small space between the synaptic terminal, and the receiving cell/dendrite; that space is where the event of information transfer occurs, which we know as a **synapse**.

5.2 Neuronal Uniqueness

A wide variety of ways the anatomy of neurons can make them different from each other. Neurons also differ in the sense of what the neurons are connected to, what neurons are talking to; the inputs and outputs. In addition to the **anatomy**, other differences include:

- **Excitability**: how talkative is the neuron. How much work is needed to get neuron to fire action potentials. How likely or unlikely is it to fire action potentials.
- **Neurotransmitters**: What chemical/substance does the neuron use to communicate. For instance, some neurons use serotonin. How does the neuron “speak”. Difference in communication speed. Affirmative vs negative.

5.3 Glial cells

Neuron don't exist on their own, they require the support of Glial Cells. There's a one-to-one mapping of neurons to glia. There's different types of Glial Cells:

1. **Astrocytes**: behave as sanitation workers of the brain. They collect the refuse of neurons, such as excess ions, and neurotransmitters. They also allow neurons to get to where they have to go during development. Synapses are enveloped in the processes of Astrocytes, which helps with maintaining them. Comprise about 20 percent of glial cells
2. **Oligodendrocytes (Central nervous sys.), and Schwann cells (Peripheral nervous sys.)**: Create myelin in their respective areas of the nervous system. Combined, these comprise about 75 percent of glial cells.
3. **Microglia**: comprise about 5 percent of glia. Immune cells from the blood lineage that have invaded into the central nervous system, and are idle as long as the human body is healthy. However they react to areas of damage, and sometimes even contribute to the damage. Implicated in several diseases like chronic pain, and neurodegenerative disorders like alzheimer's.

5.4 Myelin

Myelin is a **fatty wrap that goes around some axons**. The difference between a myelinated axon, and an unmyelinated axon/naked axon.

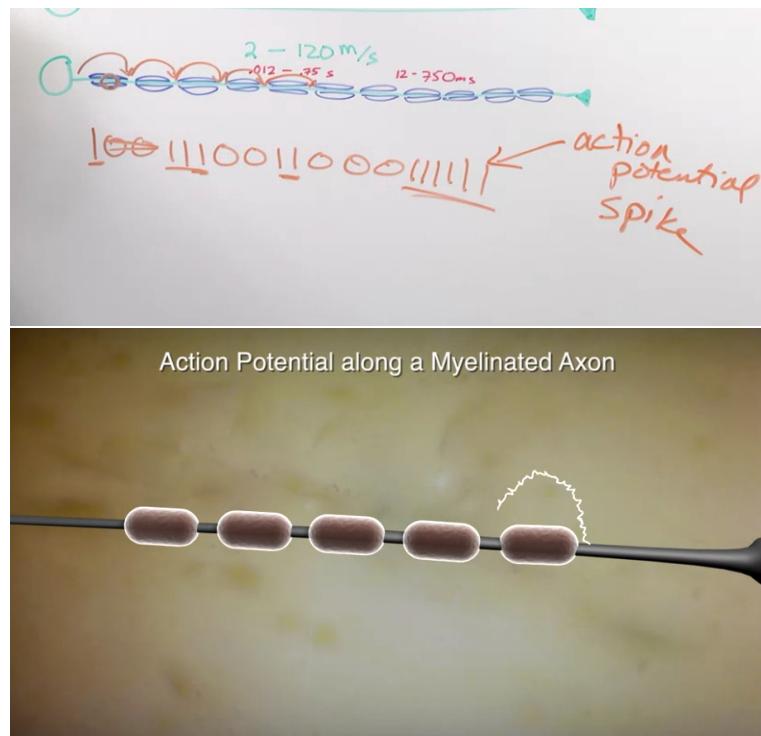
- **Unmyelinated** axons can only transfer information at a slow rate; about **0.2 - 1.0 m/s**
- **Myelinated** axons have myelin applied and carry information orders of magnitude faster than naked axons. the speed at which these axons carry information increases to **2 - 120 m/s**. A speed imperceptible to us humans.

Myelinated axons are significant especially in cases where we need information fast such as information about our balance, which we need the fastest. Neurons that support a posture against gravity, use myelinated axons.

The information that gets transferred through myelinated axons can be perceived as binary digits (**011001110111...**). What's important about this sequence of binary digits is less about whether it's a 1 or 0, but more of the

pattern of 1's that appear in the sequence. That is the neural code; the **1s represent action potentials or spikes**. The **timing** of the spikes is what carries information.

The spikes that traverse through the myelinated axon travel so fast because they jump between the gaps of the myelin wraps, thus not having to traverse through the wraps, and hence the entire physical distance of the axon; effectively shortening the distance, and time required for the action potential to travel.



However, consider if along the myelinated axon, there becomes less, and less myelin wraps. Our initial action potential, if starting as a string of bits say **001100111010110111101**, may come out on the other end due to the decrease in myelin wraps as a completely incoherent message inconsistent with the initial one, say: **000001001000100000100**. This is caused by what are known as **demyelinating diseases** which degrade the information transfer.

5.5 Demyelinating Diseases

Recall that Glial Cells that create Myelin are either in central nervous system, or Peripheral nervous system. Thus people who get demyelinating diseases either get it in the CNS, or PNS, but not both.

So the problem is either in the interaction between the **Oligodendrocytes** and the axon, in which case we get a **Central Demyelinating Disease**, which the most common by far is **Multiple Sclerosis**.

Or, there's a problem in the Schwann cells, and its interaction between with the axons. In which case, we get something like **Charcot-Marie-Tooth** which are a diverse group of hereditary demyelinating neuropathies.

Neural code is disrupted anywhere there is demyelination. Demyelination would mostly affect motor axons which travel information the fastest. **Symptoms someone gets from Multiple Sclerosis would depend on which axon group is affected.**

6 Central Nervous System vs. Peripheral Nervous System

Barrier between CNS, and PNS are made of three membranes; the meninges. There are **three meningeal layers that go from very weak, very tender (the pia) to very tough (the dura)**

6.1 Meninges

- Three meningeal layers
- **Pia** (very weak, most tender, and the inner most membrane; closer to the brain and spinal cord), **Arachnoid** (mid membrane, with spidery like structure). The **Dura** (outer most membrane, and the toughest)
- **Dura**, is the toughest sack, and what prevents concussions from happening all the time. It "floats" the brain in fluid and prevents it from banging about, and getting bruised.
- Neurons of these three membranes are entirely contained in the Central Nervous System
- The only neurons that leave the CNS are those that serve a motor function; these neurons **go out the meninges and into the periphery (PNS)**

- **Motor, and Autonomic neurons** that carry information from the CNS through the meninges, into the PNS
- **Sensory neurons** that carry information from the PNS, through the meninges to the CNS
- Neurons are either sensorial, or peripheral, based on where the cell body is, not where its axons, or dendrites are.
- Peripheral Neurons include **sensory, and autonomic** neurons, located in the autonomic ganglia
- These autonomic ganglia neurons, **share vulnerabilities with each other, but none with the neurons in the CNS**. A consequence of this is diseases like Congenital Insensitivity to Pain; where people who suffer a genetic mutation that prevent a group of sensory neurons from developing, like those that respond to injury (they don't feel pain).

6.2 Peripheral Diseases

Diseases that affect the nervous system, affect either CNS, or PNS. Meninges perform as a very effective barrier, that protects the CNS, from the diseases that the PNS is often more vulnerable to than CNS. As a result, two regions (PNS, and CNS), have different capacities for repair; PNS is better capable of repairing damage, as compared to the CNS.

Peripheral Nervous System is vulnerable to large molecules like **botulinum toxin**, viruses like **Polio, Herpes Zoster**.

- **Botulinum Toxin:** comes from spoiled food, primarily affects peripheral nervous system. Doesn't get past meninges.
- **Polio:** unlike the botulinum toxin, gets past the meninges. Gets through to the meninges, by **entering between the synapse between the motor neuron and the voluntary muscle**, travelling through the meninges by riding along the axon of a motor neuron. Once it gets through the meningeal layer, it **kills the motor neuron on that side**. As a result, there'll be an inability to control that muscle, or conduct voluntary movement to that neuron's corresponding motor actions.
- **Herpes Zoster:** produces what's commonly known as shingles. Blossoms, and makes copies of itself, inside cells in the sensory territory, causing a virus in that area, producing a rash on the skin.

6.3 Brain Tumors

To understand the origins of brain tumors, we must know the basics of cancer. Cancer tumors are cells that divide uncontrollably without limitations; they become immortal. Not only do they divide limitlessly, but also, the spread from one region of the body, to another, becoming bigger and bigger, and starting new tumors elsewhere. Hence, one source of brain tumors: **Metastasis**; tumors that start elsewhere like the lung, or colon, and spread to the brain.

Metastasis is a massive problem for brain. Brain tumors that expand uncontrollably, are constrained within the fixed, unexpanding, bony container that is the cranium. As a result, the limitless growth of tumors in the brain only increase pressure on the brain, which is problematic.

Besides metastasis, what are other sources of tumors in the brain? Neurons, fortunately do not divide; they are what's called **Post-mitotic** cells. Neurons don't divide, don't regenerate, have not any descendants; once they're born, they live, then die. Hence, this leaves the development of brain tumors to other to other cells in the brain; primarily, **Glial Cells**.

Glial Cells don't have the limitations of division that neurons do, thus can divide uncontrollably, creating **Glials, or Gliomas** (the tumors of glial cells); the most common brain tumor.

Meningiomas; another type of brain tumor. These are caused by uncontrolled division of meningeal cells.

Glandular cells (gland cells) are another major source of tumors in the brain. Namely, from the **Pineal Gland**, responsible for producing **melatonin** which helps us sleep, and also responsible for the daily rhythm of waking and sleeping. **Pituitary Adenomas** caused by uncontrolled division of the other glandular cells in our brain, the **Pituitary gland cells**. They're fairly common, and account for about 10-25 percent of inter-cranial tumors.

6.4 The Brain and the Spinal Cord

The two main components of the Central Nervous System: the Brain, and the Spinal Cord.

The **Foramen Magnum** is the point of connection between the spinal cord and the brain. Its an opening at the bottom of the skull, where the spinal cord, and brain connects.

7 Introduction to Neural Communication

The purpose of this section is to explore the ways in which neurons communicate with each other. At a high level, we know that neurons “talk” via electrical signals.

7.1 Electrical Language

In living organisms, **Ions**, molecules that have a charge, are what's used. Where the number of protons does not equal the number of electrons.

Three ions to consider: K^+ (**potassium ion**), the Na^+ (**sodium ion**), Cl^- (**chloride ion**).

Due the cell membrane being mostly fat, ions being most effective in water are unable to travel through the cell membrane, unless it's through the ion channel. The **ion channel** can be thought of as a door through the cell membrane that allows ions to travel in and out of the cell.

Chemical forces push ions out from the more concentrated inside of the cell, to the less concentrated exterior. **Electrical forces push ions in** from the ground, neutral charge of the outer cell, to the negatively charged inside cell.

Because ions are being pushed out of the inner cell due to chemical forces, and electrical forces pushing ions inside the cell due to negative charges in the cell, the membrane rests at the position of where the chemical forces, and electrical are even. Thus the cell sits at rest at about **-70mV to -60mV**. Hence, the neuron is likely to be resting at a negative potential, until something happens.

7.2 Basics of Electricity

Larger differences in potential energy creates greater currents. Larger resistance creates lower currents.

In the neuronal context, potential refers to what's the difference in potential from inside the cell, to outside the cell; this is called the **resting membrane potential**. A typical neuron's resting membrane potential is **-65mV**. $1mV = \frac{1}{1000}V$. The cell has a resistance. If none of the ion channels are open, the resistance is very high. But the more ion channels open, the lower the resistance. Current goes through the ion channels, and the resistance is between the inside, and outside of the cell.

7.3 Action Potential

Resting membrane potential is around $-65mV$, which is the potential around which the neuron oscillates. These oscillations of potential differences are usually in the range of $< 1mV$ to $-5mV$. Yet these small potential difference can travel along the neuron, but quickly die out. This isn't efficient for travelling long distances especially along long neurons. To compensate for these inefficiencies, neurons use **Action Potentials** which happen around **+20mV** and can have a potential difference as much as **100mV** from the resting potential. This can travel the distance of the longest neurons in our bodies.

Sodium ions are responsible for large positive changes in the membrane potential during an action potential. Sodium ions are also more concentrated outside the cell than inside, which causes the electrical forces to push it inwards into the cell's more negatively charged body.

The ability for a neuron to communicate over long distances, despite using action potentials is still limited by speed. Even when using action potentials, the speed a signal can travel from say the toe, to the brain is still slow... Unless an **insulator** called **myelin** is introduced.

8 Neurotransmitters

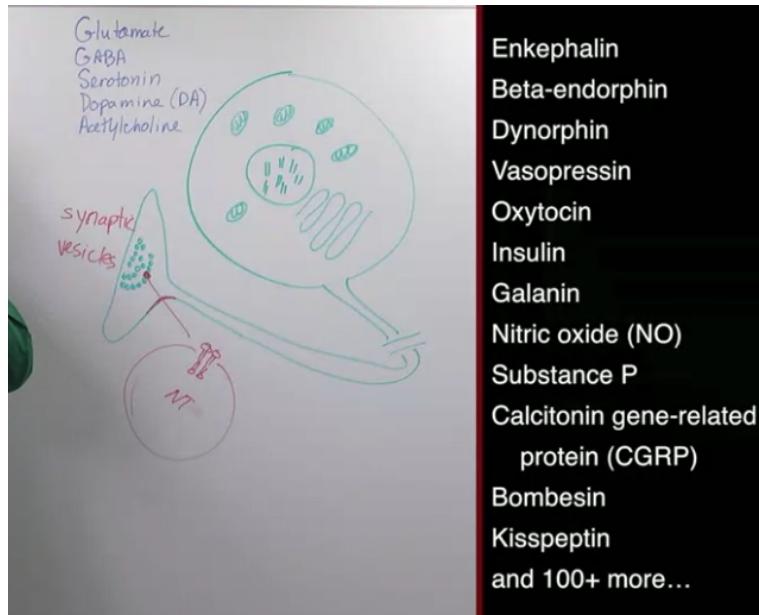
Neurotransmitters are a number of molecules that help neurons communicate from one neuron to another neuron. Although they serve other functions in the body, neurotransmitters are made, and packaged in the nervous system. They are released at synaptic terminals, enabling the communication between neurons.

8.1 Neurotransmitters synthesis

Synaptic vesicles are small entities with membranes like the cell, a **vesicular membrane**. Inside these vesicular membrane, are the neurotransmitters. A few examples of neurotransmitters include:

- Glutamate
- GABA
- Serotonin
- Dopamine

- Acetylcholine



Synthesis of neurotransmitters can be used as a therapeutic tool. For instance, in Parkinson's Disease, Dopamine isn't present, because the cells that make dopamine died. **Mass Effect**: which means taking the starting chemical, the **substrate**, and through a series of enzymatic processes, create a synthesise a neurotransmitter, and in the case of Parkinson's, Dopamine. Hence the substrate is used as the therapeutic; examples are Parcopa, Sinemet, etc.

8.2 Neurotransmitter Release

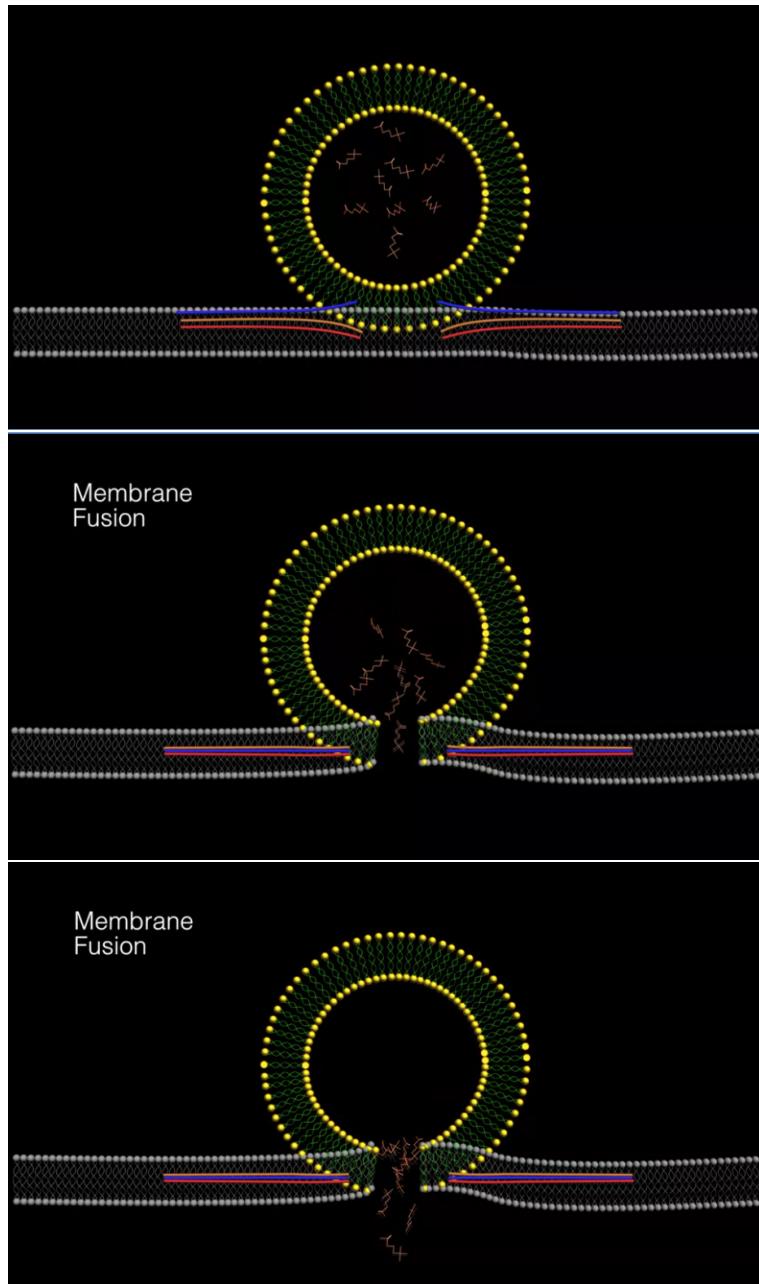
How the neurotransmitters packaged in the synaptic vesicles to create a synapse. However, the problem of fusion between two different membranes, a membrane, and a vesicular membrane, happening all the time, is posed; the challenge for the neurons will be to suppress this constitutive fusion. What we prefer is: have vesicles fuse to membrane only when action potential arrives.

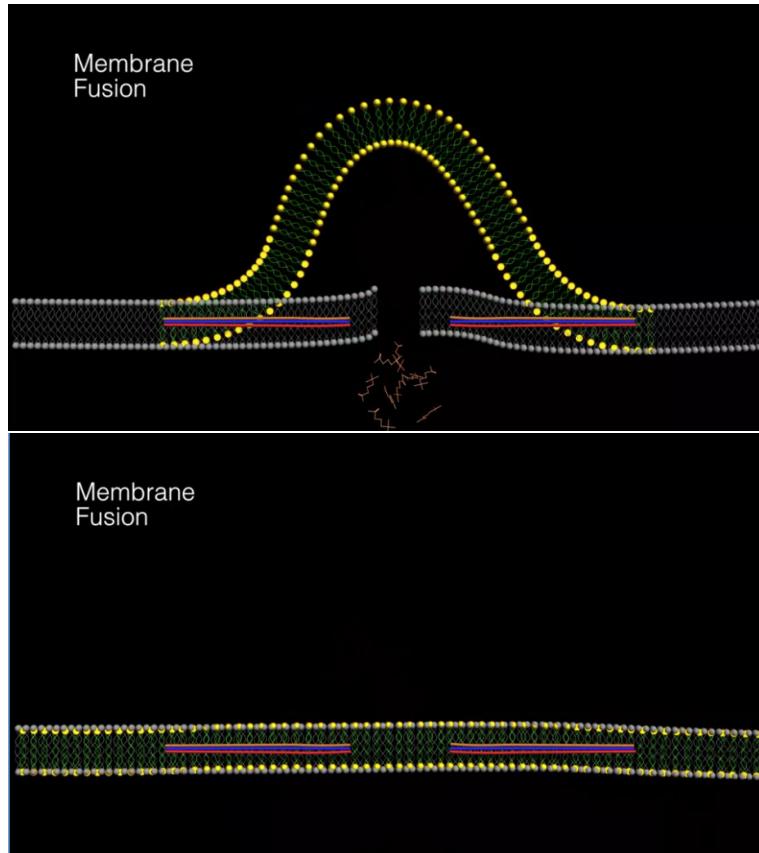
1. Suppress constitutive release
2. Link release in the synaptic terminal to action potential.

How does the neuron link release of neurotransmitters to the arrival of the action potential? Recall that the membrane potential is around $-65mV$.

When the action potential arrives, an ion channel is opened, where **Calcium ions (Ca^{2+})** are let in. Now the negative charge of the cell membrane spikes towards a positive charge from the concentration of calcium ions.

As a result, the vesicular membrane, and the cell membrane fuse, and during that fusion of the membranes, the synaptic vesicles release the neurotransmitters they had packaged within.





8.3 Clostridial Toxins

Botox (Botulinum Toxin); one of many clostridial toxins. What clostridial toxins are doing is essentially preventing neurotransmitter release by preventing synaptic vesicle fusion to the cell membrane. This prevention happens when the clostridial toxin cuts one of the snare pins in the snare complex, that allows fusion of the vesicular membrane with the cell membrane.

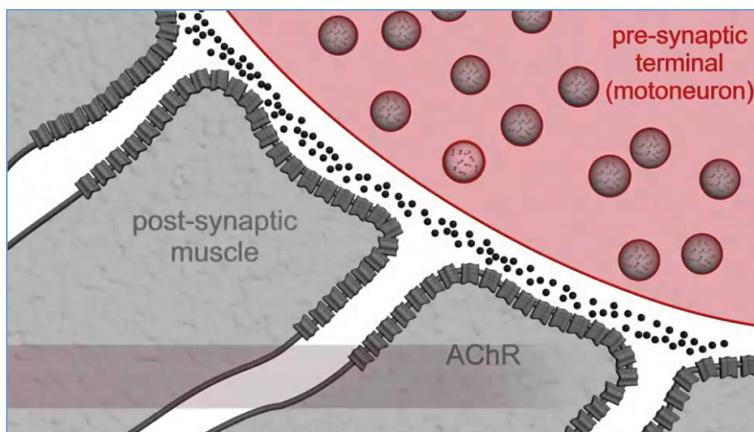
8.4 Signal Termination

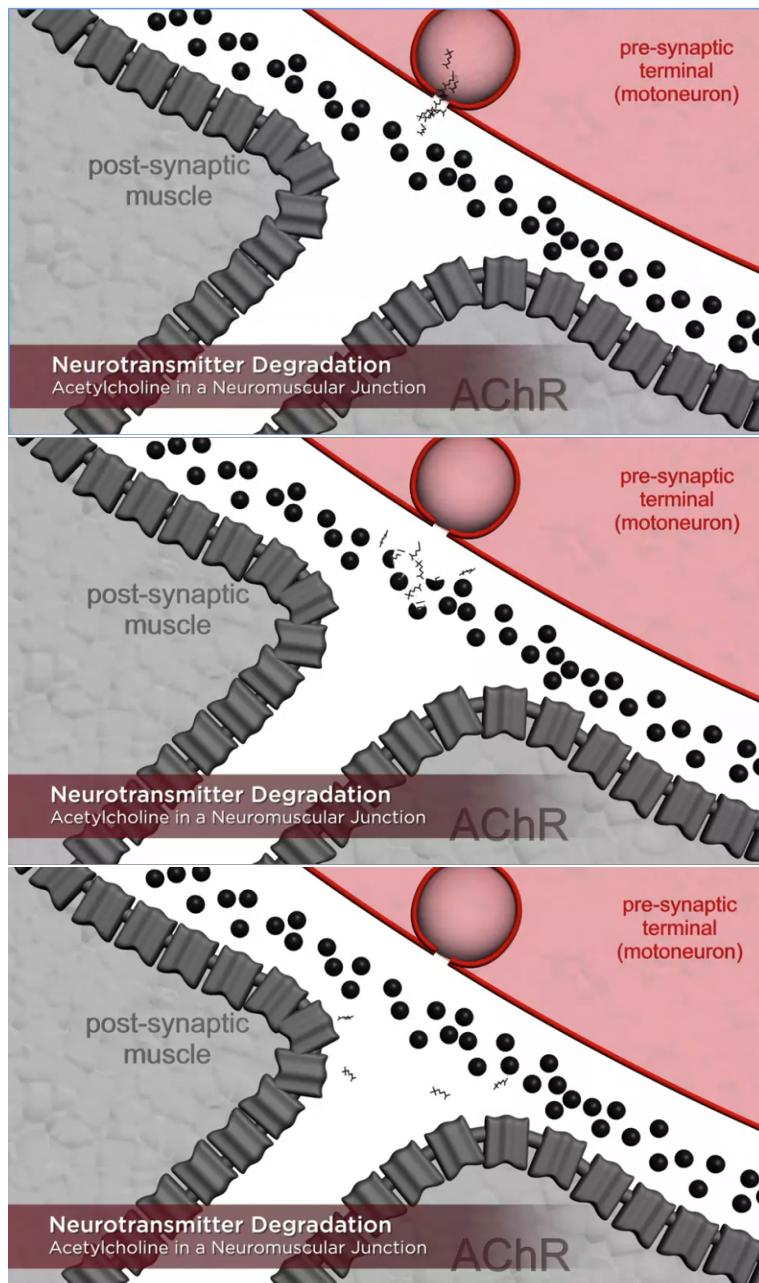
Some basics. The synaptic terminal where the release of neurotransmitters occurs, is called the **pre-synaptic**. Its duty is to get a message across to the second cell known as the **post-synaptic** cell. The whole event is known as a **synapse**. The pre, and post synaptic cells are separated by a small space known as the **synaptic cleft**.

Molecules of the neurotransmitters are going to make their way over to the post-synaptic. But the message being sent out during the synapse must

have an endpoint. Three different mechanisms to terminate the message of a neurotransmitter.

1. **Diffusion.** Neurotransmitters molecules naturally diffuse out. Post-synaptic only listens to a specific area of concentration of neurotransmitters. Thus if that area isn't concentrated, then the post-synaptic doesn't care.
2. **Re-uptake.** Transporters in the pre-synaptic, that take the neurotransmitters back up into the pre-synaptic, essentially recycling/reusing the neurotransmitters, re-packaging them up into synaptic vesicles for use later.
3. **Degredation.** Enzymes that sit out in the synaptic cleft that essentially eat up the neurotransmitters. For instance, when Acetylcholine is the neurotransmitter, the enzymes digest alot of it, only allowing a small amount to cross the synaptic cleft. Degredation is critical to terminating a motoneuron's message to a muscle. Blocking enzymes like **Acetylcholinesterase (AChE)** during degredation can be therapeutic like in the cases of **myasthenia gravis**, where muscle weakness is experienced, thus enabling the muscle to contract as needed. However, it can also be deadly, because the muscle, like the diaphragm can remain contracted since the enzyme to terminate the synapse, is being blocked, which in the case of the diaphragm means the host can't breathe.





8.5 Receptors

How does the post-synaptic cell “hear” the message sent via neurotransmitters? Post-synaptic cell receives messages via **multi-protein complexes called receptors**. **Receptors populate the post-synaptic membrane**. Neurotransmitters that haven’t been diffused across the synaptic cleft, or

degraded by enzymes, or repurposed by the pre-synaptic cell, will make it over to the receptors.

When a few neurotransmitters bind onto the receptors, the receptors make available to the ions from the neurotransmitters, pores which they can travel past the post-synaptic membrane. The direction in which the ions travel (in or out the cell), is contingent on the type of receptor it is. In general, there are **two basic classes of receptors: one that has an excitatory effect, and another that has a inhibitve effect.**

1. **Excitatory Receptor:** any receptor that takes the membrane potential (which is around $-65mV$) closer to the threshold for an action potential is considered excitatory. Eg: **Glutamate**
2. **Inhibitory Receptor:** any receptor that takes the membrane lower than $-65mV$ or lower than the resting membrane potential, is considered inhibitve. Eg: **GABA**

Neurotransmitters bind to their corresponding receptors. For instance, Glutamate neurotransmitters bind to Glutamate receptors (excitatory), and GABA neurotransmitters bind to GABA receptors (Inhibitory).

So what impacts do receptors have on diseases and therapeutics? For instance, losing receptors in a disease such as **myasthenia gravis**, where **Acetylcholine receptors are attacked, and destroyed by the antibodies the immune system makes**. Thus the muscles that ought to be stimulated as a result of signals from the motorneuron aren't received by receptors, and are either weakly stimulated, or not altogether. As a therapeutic, one way to supplement this is by introducing an Acetylcholinesterase inhibitor, to block the Acetylcholinesterase enzyme, effectively stoping or slowing down degradation, and allowing the ACh neurotransmitters to linger around longer to find the remaining ACh receptors that weren't killed off. An alternative therapeutic will be to use immuno-suppressants to dampen down the immune system from producing those antibodies that kill of the receptors.

8.6 Metabotropic Receptors

The type of receptor where neurotransmitters bind to it, resulting in an ion channel opening, are called, **Ionotropic receptors**

The class of receptors that don't result in a pore, or channel opening after neurotransmitters bind to it are called **Metabotropic receptors**. Metabotropic receptors don't lead to electircal changes. Instead, they're attached to **G-Protein**; Metabotropic receptors are also called **GPCRs (G-Protein Coupled Receptors)**. After neurotransmitters bind to metabotropic

receptors, the G-protein then go on to create enzymatic reactions. These reactions may vary from causing ion channels to open elsewhere, closing ion channels, etc. Compared to ionotropic receptors, metabotropic receptors are varied in terms of the effect they have; there are about 1000 types of metabotropic receptors, while there are less than 10 types of ionotropic receptors. Also, the time between binding of neurotransmitters to effect of metabotropic receptors, is much greater than that of ionotropic receptors.

9 Embodied Emotion

A study of how emotion is produced, and depend on the “feeling” of the body. Generally, emotions depend on body states. Part of the body states are voluntary, others are automatic. We focus on the automatic body states for now. Primarily, the **sympathetic, and para-sympathetic** nervous systems that give rise to these automatic body states.

9.1 Enteric Nervous System

The third part of the autonomic nervous system, is known as the Enteric Nervous system. Travels the length of the digestive tract; from the esophagus all the way to the anus. Along that length, **intrinsic neurons sit lining of the gastrointestinal tract; these neurons form the enteric nervous system. There are about 100 million.**

The enteric nervous system is responsible for pushing what we eat through our digestive system. It's the most automatic of the autonomic nervous system. In diseases like **Hirschspang's disease**, a **section of the GI tract is aganglionic**, it has no enteric neurons, thus what patients of this disease (typically children) experience is what they eat isn't pushed through the digestive tract. This can be solved surgically.

The enteric nervous system, although being able to handle the entire process individually, still communicates with the Central Nervous System. The information sent to the CNS from the enteric nervous system (which is about ten times greater than that coming from the CNS to the enteric), essentially holds the state of our GI tract; if we're full, gassy, hungry, bowel movements etc. And the information returned from the CNS, particularly the sympathetic, and para-sympathetic nervous system, is a way our mood may influence the state of our GI tract. For instance, if we're really excited, or nervous, there may be changes in bowel movements etc.