Neuroscience M101A Notes

Lecture Notes

9/27 - Week 0

- Cells can interact within itself and between others.
    - Intra - How signals propagate within
    - Inter - How signals propagate to another cell
- Brain and spinal cord are CNS, and nerves are PNS.
- Number of neurons may not change, but how those connections interact (the plasticity) will change.
- Soma is the cell body and the nucleus is contained within.
- Dendrites and soma are the receiving area. Vast majority of input are onto the dendrites. Once it gets to the soma, information integration happens and if it passes the threshold at the axon hillock, then a signal will get propagated along that one main axon (which could have branches).
    - Primary axons can have branches.
- Axon hillock has heaviest density of sodium channels, doesn't have any myelin.
- Axons are long distance communication. Dendrites are receiving information and take place on short scales (distance between dendrite and the soma).
- Synaptic potential decays over distance.
- Neurons can differ in terms of the number/size/location of dendrites and the length of the axon and the shape of the soma.
- Feedback circuit are where cells are presynaptic and postsynaptic to a target.
- Axo-dendritic synapse is where signal goes from axon to dendrite.
    - More modulatory to control axon potential
- Axo-somatic synapse is where signal goes from axon to soma.
    - For fast communication
- Axo-axonic synapse is where signal goes from axon to axon.
    - Controls excitability of the target
- Neuron relaying information to multiple neurons that are in different places will use divergence to send its signals to each of them.
    - Redundant information
    - Example of axon branching
    - Want to make a complex motion and send the "plan" to all the places that need the info
- Convergence is when the signals will get integrated in some higher level place
    - All the receptors from different areas like the wrist and finger and all that info may be converging onto a single neuron in the spinal cord for example. The upstream neuron will have all the info.
    - Integrating signals to get big picture view to go to the nervous system.

- Voltage is always measured with respect to 2 points.
    - It's a measurement of a potential to do work based on position and charge.
    - It's the difference in potential between the 2 points.
        - V = E_inside - E_outside
    - We don't really care about the absolute voltage, but rather the relative potential of 2 points.
- There must be a voltage across a membrane. Every cell that is alive has a voltage across it, which drives processes.
- To measure the membrane potential, one pole is the ground (will be the reference) and the other pole goes inside the cell and the pipette itself has some solution that is a conducting medium.
    - Always inside - outside.
- Typical resting membrane potential is -60.
- Resting potential is the subset of the membrane potential, which is the voltage across membrane at any time.
- Every cell has a resting potential, most cells are between -40 and -70.
- Fact that there is a voltage difference means there is some sort of charge separation.
- At the macro level, charge is equal, but at particular local areas in the cell, there will be charge separation. At the membrane level, we violate the macro level because some ion has permeated the membrane leaving behind the ion that it was paired with.
    - Macro vs microscopic electro neutrality.

9/28 - Week 0

- (V) Voltage - Difference in potential between 2 points.
    - Units are volts
    - Biological relevance is that it is basically equal to the membrane potential.
- (I) Current - Rate of movement of electric charge
    - Units are amperes
    - Biological relevance is the movement of ions
- (R) Resistance - Hindrance of current (movement of electric charge)
    - Units are ohms
    - Biological relevance is the difficulty associated with ions in moving through channels or the selective permeability of the membrane. Resistance across cell membrane is pretty high.
- (G) Conductance - The extent to which current (movement of electric charge) can flow
    - Units are siemens (mho)
    - Biological relevance is ease of ions to move through channels (the easiness for ions to move)
- (C) Capacitance - Parallel plates that store charge.
    - Units are farads

    - Biological relevance is basically the cell membrane because it's kind of like a plate that separates charge. When you have that capacitance, it allows voltage to build up.
- Channels are like resistors and conductors depending on if they are open/closed and other characteristics.
- Important Equations
    - Ohm's Law V = IR
    - R = rho * Length / Area
    - G = 1 / R
    - C = epsilon * A / d
    - Q = CV
- Resistors in series will have their resistances summed, while resistors in parallel will have the reciprocals summed. Basically the opposite for conductance
    - Series
        - Rtotal = R1 + R2
        - 1 / Gtotal = (1 / G1) + (1 / G2)
    - Parallel
        - 1 / Rtotal = (1 / R1) + (1 / R2)
        - Gtotal = G1 + G2
- Specific conductance (g_m) refers to conductance per unit area. (Siemens / cm^2)
- Cell size and conductance and resistance
    - A bigger cell -> bigger surface area -> more channels -> less "ion traffic" -> more ions can move through -> conductance goes up -> resistance goes down
        - Also makes sense because with more channels, then you have more circuits in parallel, which means conductance will increase.
    - A smaller cell -> smaller surface area -> less channels -> more "ion traffic" -> less ions can move through -> conductance goes down -> resistance goes up
- Cell size and capacitance and charge
    - Q = CV and C = epsilon * A / d
    - A bigger cell -> area will increase -> capacitance goes up bc it's proportional with area -> Q increases in order to keep the same voltage

10/2 - Week 1

- Ion channels are how charge gets in and out of the cell.
- Current flow creates voltages transiently or temporarily, which perturbs the resting potential and creates some sort of communication from one cell to another.
- The origin of the resting potential is how that charge separation and voltage gets created.
- Everywhere in the cell, you have isopotential meaning that if there is no action potential happening or anything, then you have that same resting potential everywhere in the cell.
    - Then, how do we get that axon hillock region to be a different potential. How do we get it to be less negative and actually cause an action potential?

- Channels/pores on the membrane could be voltage gated, ligand gated, etc
- Each of the channels on the membrane are conductors (inverse of resistance) which allow charged particles to flow.
    - Good conductors are ionic solutions, metals, cytoplasm (which is just a salt solution) etc
        - Current can flow easily through the cytoplasm
- High conductance state is where you have a lot of channels that are open, allowing the charge to move. This is also a state of low resistance.
    - Let's say you have X channels in the membrane and they're all in parallel.
    - Parallel conductors will sum. The more channels that are open, the higher the conductance state.
- The key is the number of channels that are open (not necessarily the total number of channels)
- The channels are not static, they're in flux, they're opening and closing based on the conditions in the cell.
    - If you have 500 channels in the membrane, doesn't mean they're all open, they are selective and in flux.
- Ohm's Law says that if you apply current across a resistor, you will get a voltage.
    - V = IR
    - Current is normally the independent variable, voltage is the thing you measure, and so you can solve for the resistance.
- Ohm's Law also says that if you apply voltage across a conductor, you will get a current.
    - I = Vg
    - Voltage is normally the independent variable, current is the thing you measure, and so you can solve for the conductance (and resistance by extension).
- There is a linear relationship between all these values.
- Conductance is the slope in a V vs I graph where V is x-axis and I is y-axis.
    - So, if the line is linear, then the slope is the same, and thus there isn't really anything changing in the cell.
    - When the slope decreases, that means that conductance decreased, and that means that resistance got higher, and that means that channels probably closed. This is for a fixed voltage situation.
- Ohm's Law experiment is you applying a current, and looking at the voltage or vice versa. That would change the axes on your graph, either an IV and VI graph.
- When V is the x axis, it is the independent and thus we are clamping a voltage and looking at the resulting current.
- To repeat, conductance is our proxy for open ion channels
- There is also a time dependence for ion channels. Let's say we do a VI experiment and we control the voltage, and record the current.
    - So basically, in your VI graph, you can have a line that represents the conductance and that particular time step.

    - If the slopes are different at different time periods, then you know that the number of open channels is varying since the different slopes means that the conductance is changing over time.
- However, there are also times where Ohm's Law is not followed and the conductance changes as the voltage changes which results in a non-linear curve on the VI graph. This is referred to as membrane rectification.
    - This happens because the resistance/conductance of a membrane is static and thus the number of channels can increase, the number of open channels can as well, and so because of that the current and voltage can change.
- Inactivation is the characteristic that channels can open rapidly and close down just as quickly.
    - Channels will open and close based on voltage and time (for some channels)
- A capacitor is composed of a conductor and insulator between the plates.
    - They basically store and separate charge.
    - There is a relationship between voltage across a capacitor, and charge flowing as a result. There will be some steady state and the charges will align.
        - Also, if charges are flowing (there is a current), then a voltage will be generated.
    - Q = VC
- Cannot have a voltage without a charge separation on that capacitor
- Cell membrane can be modeled by a capacitor. It is a capacitor at first approximation and basically when it is at rest, but it is a leaky capacitor in that you can take some point charge and at some time t_1, it will be on the inside of the cell, and at t_2, it will be on the outside of the cell.
    - This is because of the fact we have channels and that those point charges can move.
- For an infinitely small piece of the membrane, we can model it as a RC circuit
    - Battery - Concentration gradient
        - Sodium battery, potassium battery, etc
    - Resistance - The channels
    - TODO
- Charged particles or ions can't really get past the cell membrane without those pores or channels. Thermodynamics don't allow for it. Molecules are hydrated, tough to pass the hydrophobic area, etc.
- Different channels have different properties
    - Diameter (Small, big, etc)
    - Selectivity (Only sodium, only potassium)
- Pumps are different from channels since it is energy dependent, and it often works against gradients to maintain them.
    - The concentration gradient in cells don't change.
    - Voltages do however, since it doesn't take a whole lot of charge to move to cause change in voltage.

    - Pumps are also too slow since it is energy dependent and there's a whole process. Instead, we have the channels are make use of the law of diffusion which allows charges to move instantaneously, assuming the correct concentration gradient.
- Ion channels are highly regulated proteins.
- Gated vs non-gated channels
    - Non-gated channels are always open, and they're the ones responsible for the resting potential of the cell since they are the ones that kind of determine the equilibrium state of the cell.
    - Gated are either in the closed or open states, always in the binary state. These channels open based on some stimuli which causes it to physically change configuration.
- Going from closed to open state for a channel causes an increase in conductance (and by effect current change and voltage change which then leads to action potential).
- Voltage gating and ligand gating are the two types of gated channel
    - Voltage gating: If there is a specific voltage, the channel will open.
        - Potassium and sodium gated channels are examples
    - Ligand gating: Needs an actual ligand to bind
        - Neurotransmitter channels are examples. Glutamate for example will bind to the channel, which opens the channel. The channel has a unique ligand binding.
        - Can also have receptors on the inside of the cell. One example is one of those calcium receptors, which when those molecules bind on the inside of the cell, then the channel will open.
- The change in the number of open channels -> Increased conductance -> Increased current -> Increased voltage -> The signal that allows to get to the threshold and to the creation of the action potential.
    - We said "increased" above, but really just mean the deltas. Decrease in open channels will create the opposite effects.
    - Voltage changes are the signals for communication. The voltage change is the key.
- Patch Clamp Technique
    - Whole cell recording
        - Gives you an average of what's going on in the cell
        - Tells you membrane potential
    - Inside-out recording
        - Just get a little piece of membrane and look at that one particular ion channel and look at those properties.
- The macroscopic and microscopic curves are pretty similar to each other.
- Origin of the membrane potential
    - For neurons, we see that there is a gradient between the inside and outside of the cell for a lot of substances.
    - Potassium gradient is from in to out

    - Sodium gradient is from out to in
    - There are proteins inside of the cell, not in the extracellular space. These fixed anion proteins are what balance the high potassium content of the cell.
- High conductance and high permeability mean the same thing pretty much.
    - Conductance is a function of permeability and the concentration gradients.
    - TODO
- Permeability at rest is referring to the flow through the non-gated channels. This establishes the resting potential.
- K/Na permeability ratio is very high
    - Lots of potassium channels open at rest, but not a lot of sodium channels open at rest.
- Generation of the resting potential is determined by the equilibrium potential and the relative permeabilities of the permeable ions in the system.
    - If not permeable, then doesn't directly contribute to the resting potential.
- What is an equilibrium potential for an ion?
    - Concentration force and electric force on an ion.
        - Concentration force is the force an ion experiences if there is a difference in concentration between two areas. The ion will feel a force to go over to the side with less.
        - Electric force is the force an ion experiences if there is a difference in electric charge (and thus a voltage) between two areas. The ion will feel a force to go over to the side which makes the overall charge more neutral. The positive ions will feel a force to go to the negative side.
    - These forces are vectors since they have magnitude and direction.
    - When the two forces are equal and opposite, then there is no net flow of charge which means that there won't be any voltage change, and thus you'll be at rest.

10/4 - Week 1

- If you had a voltmeter and put one of the electrodes into the cell, everywhere within a neuron (in the soma, in the axon, in a dendrite), given that the cell is not undergoing an action potential or anything, you'll get the same voltage reading (-40 to -70). This is the property of being isopotential.
    - But let's say one pole is in the soma and one is in the dendrite, the reading would be 0 because there is no difference in electric potential within the neuron.
- Electrochemical gradient is made up of concentration force (force caused by the difference in the concentrations of the ions) and electrical force (voltage generated by the passive diffusion of an ion due to that concentration gradient previously mentioned).
    - TODO Double check
    - If zero permeability, then you may have a concentration force, but no electric force. Therefore, there is no voltage.
- Macroscopic electroneutrality is maintained even when you have different concentrations (???)

- When one ion diffuses, then electric vector forms. From electrical POV, that ion wants to come back to the negative side. But the chemical vector is a lot bigger. And thus more ions will move in that original direction. What will happen over time is that the chemical gradient will decrease and the charge separation increases and thus greater electric gradient in the opposite direction. And then at some point, the electric vector will be equal but opposite to the chemical vector. This is the point at which the rate of movement of the ion moving in and out are equal and opposite.
    - One key is at the end is that the chemical gradient has not changed at all. There is absolutely no concentration change.
    - The equilibrium potential of the ion in question is the voltage at the end of this process. That voltage should not be changing anymore because there is no gain/loss of charge.
- So aka the equilibrium potential for an ion is the voltage necessary to counter tendency of ion to diffuse down its chemical gradient.
    - When at equilibrium for a charged particle, the voltage across membrane is constant, which is basically when the cell is at resting potential. Electric force is equal and opposite to concentration force.
    - E_ion is your resting potential (V_R).
    - Voltage being constant means that the net current for that ion at equilibrium is 0.
- Driving force is V_R - E_ion.
- Ionic current is conductance * driving force
- Nernst equation describes the electrochemical gradient for one ion.
    - Allows you to predict which direction ion would flow if you allow it to flow. And you can predict the voltage that would be caused as a result of that ion flow.
- E_ion is a function of temperature, the charge of the ion, and the concentrations of the ions on both sides.
    - E_ion = RT / ZF 2.3 log [ion_out] / [ion_in]
- In a glial cell and we have 1 ion permeability, then V_R = E_ion. This expects that the Nernst relationship is obeyed.
- If the concentration of the outside concentration of the ion increases, the E_ion will increase linearly in a log graph.
- An experiment would be to increase the outside concentration of the ion, then check the graph and if the voltage increases linearly and it follows the Nernst equation, then you have only one ion permeability, but if it doesn't, then you probably have multi-ion permeability.
    - If you were to plot outside concentration of 1 ion vs the resting potential, then if it's a linear line, then it is one ion permeable. If there is a deviation, then you know something else is permeable.
- On normal cells, the concentration of sodium is high on the outside and low on the inside. This means we'll have a chemical force pointing inside. The electrical force is out to in because the inside of the cell is really negative. Both are in the same direction and the electrochemical gradient is large and in the same direction. However, the permeability is pretty small. The inward sodium movement is trying to depolarize the cell.

- If the E_ion of a particular ion is not equal to the voltage across the membrane, then the driving force is not equal to 0, and thus the current is not 0.
    - E_Na is +50, and thus voltage will almost never get to that. Sodium is trying to come in in order to get that potential up to E_Na.
- Ions flow down their electrochemical gradients in the direction that brings the membrane potential to their individual equilibrium potentials.
    - You will be closest to the E_ion that is most permeable in the system, and in most cases K is the more permeable ion than sodium.
- Goldman equation determines the membrane potential for cases where you have multi-ion permeability.
    - The concentrations of the ion * permeabilities for each ion is what the membrane potential depend on.
    - Cations are outside over inside while anions are inside over outside.
    - The equation boils down to the Nernst relationship if you're only looking at one ion.
- You can also approximate the resting potential through the fractional conducation relation, which is a weight average of all the conductances multiplied by the E_ions.
- Since E_Na > V_R in most situations, sodium is constantly trying to leak in, but if the potential ever gets to above -40, then the cell wouldn't survive. The way the cell takes care of this is that is has sodium pumps that helps us keep the right concentrations.
- Ions like sodium and potassium are almost never at equilibrium. For sodium, since they have such small permeability, then it doesn't matter.
- Cells communicate using electrical or chemical signaling.

10/5 - Week 1

- Pumps help maintain gradient which is important because we want to keep a really negative voltage within the cell.

10/9 - Week 2

- Graded potential (synaptic potential) is a voltage generated across the membrane due to another cell.
    - Its amplitude can fluctuate depending on the amount of NT released as well as the number of synapses involved.
    - In contrast, the action potential is all or nothing.
- Receptor potentials are the same as synaptic potentials, it's just that they're generated by receptors.
- There is no one synapse that can generate 20 mV of change in membrane potential.
    - 20 mV is normally the charge required to get to threshold.
    - Thus we need temporal and spatial summation
- Synaptic integration is how synaptic potentials are combined together and used to communicate with other cells.

- Spatially segregated are when the synapses are at different locations on the postsynaptic cells.
- When the NT binds to the receptors on the postsynaptic cell, then there will be a small amount (1-3 mV) of depolarization.
- If you have 2 synapses that are spatially segregated, then you have to stimulate both at the same time (before the 1st one decays back to 0) to reach the threshold.
- When you summate individual synaptic potentials, it combines to form the compound synaptic potential.
    - Compound potential is graded because it is depend on magnitude of individual synaptic potentials.
- IPSPs allow the cell to have a brake against firing and create hyperpolarization.
- Each synapse is a current injector as a consequence.
- Size of the synaptic potential depends on how much NT gets released and how much current comes in/out as a result of the opening channels, and then that affects the resulting voltage change.
- Let's say you had a bunch of channels and they are all open at rest and they affect the value of the membrane potential. Cell is modeled as a capacitor. The capacitance of the membrane is a constant and so is the resistance/conductance. The channels responsible for voltages are not changing at rest. This is passive property.
    - However, if we have other channels that are closed at rest, but can open later, then we increase the conductance and decrease the resistance. This is an active property of the membrane.
- The main passive properties of the membrane are R_m, C_m, and R_a which is the longitudinal resistance. At rest, these values don't change. Tau is also one of these properties since it is = R_m * C_m
- After NT attach to receptor, then receptor opens, current flows, and the voltage changes. This is an active property.
- If there is an inward flow of current into the membrane, then the cell is depolarizing (an EPSP), since we assume that we're talking about flow of positive ions into the cell or flow of negative ions out of the cell.
- Any patch of membrane can be an RC circuit. The channels will together have some resistance, the battery is the gradients and the flow of ions, and then in parallel you have the capacitor.
    - When the receptors open up, then ions are able to flow, a current gets created, and then that current separates and some of it goes to the resistor and some goes to the capacitor.
    - Based on this assumption that the membrane is an RC circuit, let's look at how we can determine the shape of the voltage curve.
- So, after we get the current injection, what happens after from a physics POV?
    - If the circuit only had a resistor, then the shape of the current and the voltage would be the same because V = IR
    - However, we have a capacitor involved. Once we inject the current then the voltage curve will look like an exponential rise and then exponential decay.

- The first thing that happens when you inject current is that the current will start to charge the capacitor (some of current goes toward the resistor), but the capacitor will contain like charges and the charging will slow down. Then, when the injected current stops, then the capacitor will release the charge.
- The time constant Tau is the time it takes to change voltage to 63% of the delta V (difference between initial and steady state).
    - It allows us to look at how the shape of the voltage decay of an EPSP will look.
        - Didn't say anything about the rise because the resistance is changing and thus the Tau is decreasing causing a short circuit.
- Long Tau promotes temporal and spatial summation since it takes longer for the voltage to increase and decay back down, so you have a longer time for additional synapses to integrate and actually cause the action potential.
    - Tau is normally 2-20 ms
    - Short Tau means a fast decay and thus less time for additional synaptic potentials to combine with each other.
- When you introduce capacitance (as opposed to just resistance) then you elongate the time.
- Let's say you have 2 postsynaptic neurons that are receiving input from the same neuron. The 2 have different properties and probably different Taus. Thus, you could have different behaviour since one cell might create an action potential because the signals are able to sum during to the long Tau and subsequent long time it takes for the voltage to decay.
- Neuron with a longer tau will probably generate more action potentials given that the number of synaptic potentials are the same.
- Dendrites don't support action potentials. No voltage gated channels on those dendrites. Cannot generate action potentials on the dendrites, you only have ligand gated channels that attach to NTs.
- Big question is how does synaptic potential at a dendrite affect the action potential that gets created at the axon hillock?
    - Current is generated at the dendrite will flow toward the soma and axon hillock and you gotta trust that the current doesn't decay on the way. If you have a sufficient enough current, then the voltage created will likely cause the membrane potential to reach the threshold and fire.
- Graded/synaptic potentials decay with distance. This is called decremental conduction.
- At first, everywhere in the cell and everywhere in the cells are all isopotential because the cell is at rest.
    - Then let's say you have a synapse on of the dendrites, NT is released, they attach to receptors, they open, then inward current flows, and that region at the synapse will get more positive. That region is positive relative to everywhere else, and thus those charges will want to move to the other areas (which are less negative). There is a longitudinal voltage gradient that gets created. Positive ions want to go from positive to negative. Current/charges will flow.
    - The charges will go down the gradient and the charges will leak out a little.

    - Everywhere after that subsynaptic membrane, you have passive membrane properties.
    - At any spot in the cell, the current will be less than the current generated at the synapse itself since we are losing charge/current as it is moving from the synapse to the soma/axon hillock.
        - The charges are going down and out. The current will split. The ratio of the current split will depend on the resistances of the axial resistance and R_m.
- To review, the max current is at the synapse.
- At each patch of the membrane, the resistance is constant. You can look at the change in voltage at each patch by looking at V = IR where I is changing as it goes out of the dendrite and down the dendrite.
- I think there is a difference between the current across the membrane and the current going down the dendrite?
- Lambda is the distance where the voltage has decayed to 37% of the peak source voltage.
    - Large lambda = little decay in voltage, takes a longer distance for the voltage to dissipate.
    - Small lambda = large decay in voltage
- Lambda increases with diameter of the dendrite.
    - This is because the cross sectional area increases exponentially, and then R_a goes down.
- Lambda is proportional to sqrt(R_m) / R_a
- Neurons with larger lambdas will be more efficient in relaying potentials from the dendrites to the axon hillock.
    - Voltage decays a lot less and thus more current should get to the axon hillock and it's more likely that we get an action potential.
- So once the current reaches the axon hillock and we get a change in voltage, then we have to see if the threshold is met, then the action potential will occur.
- As the current is moving down, then you have other voltage gated channels that start to open as well causing an exponential depolarization that pushes the neuron more towards the threshold.
    - This is the portion where the membrane voltage is behaving nonlinearly. This is when you see the contribution of active membrane properties.

10/11 - Week 2

- The frequency of the action potentials tells us something about the signal.
    - This is different from the conduction velocity.
- Action potential is an all-or-none event.
- Rising phase for the action potential is where the membrane potential increases rapidly. Voltage goes from -70 to go to almost +40. Membrane's capacitor is now discharging.

- The overshoot phase is where the voltage goes positive and that is where the peak voltage occurs. For a small moment of time, the voltage inside with respect to outside is positive.
- The falling phase is where there is repolarization, basically bringing the voltage back to normal. However, we don't just go back to rest, we actually undershoot and goes more negative than the resting potential.
    - The undershoot is called the after hyperpolarizing potential (AHP).
- The different shapes of action potentials in different cells is the result of the different sizes of the cells.
- If the voltage go way up above the threshold, nothing sums or anything. To encoding of the magnitude of the stimulus, the frequency of the resulting action potentials would change. More spikes for a voltage change that goes way above the threshold.
    - Changes in frequency when you're above threshold, rather than summation.
- Know the relationship between changes in conductances (outside stimuluses), then know the resulting current, and the resulting voltage change.
    - Delta g -> current flow -> Delta voltage
- When some ions get permeable, the value for g changes and thus that value * the driving force will show you the quantitative measure of the current that results.
- Phases of AP
    - Rising phase of AP -> Increase gNa
    - Repolarization -> gNa inactivation and increase in gK
    - AHP -> Vm approaches Ek
- At threshold, some of the sodium channels open, thus increasing the conductance, and then as the voltage goes up, some start to close really quickly (sodium inactivation). And at some point, they all close which stops inward current, and starts the repolarization phase. At this same time, during the peak (a bit after the start of the AP), potassium channels (which are also voltage dependent) start to open and you can imagine that the driving force is huge at that time (Vm of +50 and Ek of -90), and the potassium ions start to go out. There is thus a large potassium outward current, thus bringing the Vm back down. Since you have both sodium inactivation and such a large outward current for potassium, you undershoot the voltage at resting potential and go way towards Ek.
- Peak of the action potential is just shy of ENa
    - Cannot go above ENa there's less and less driving force as Vm goes up to ENa. There's also no other ion that has an E_ion higher than ENa and thus no other forces causing Vm to increase.
- Hodgkin cycle says that as you open some channels, Na flows in, and there's a little depolarization, which causes more sodium channels to open, and that causes sodium to flow in, and the cycle keeps going.
    - As Vm climbs, more channels start to open
    - This is positive feedback.
- Voltage, current, and conductance are both independent and dependent variables at different stages.

    - Current comes in -> Creates voltage -> Open up more channels -> Creates more current -> Cycle
- Repolarization is caused by opening of potassium channels and the inactivation of the sodium channels.
    - Those potassium channels are voltage dependent. They activate when the cell is depolarized. This is the stimulus for those channels to open. Since the driving force is huge, then there is going to be a huge outward flow of K.
        - One thing is note is what's happening to the leakage channels of K. Those also are having outward K current. But these leakage channels are pretty weak in comparison to the voltage gated ones.
        - Another interesting thing is that these potassium channels show no inactivation, unlike the voltage gated sodium channels.
    - Sodium inactivation: These channels are time and voltage dependent, and so as they start closing, there is a reduction of gNa and then a reduction of inward Na current.
- The repolarization does not stop at rest, and the reason it goes further is because the potassium conductance stays on for pretty long and the conductance is higher than the conductance at rest, and thus more current will flow out until Vm gets close to Ek.
- If those voltage gated K channels aren't time dependent, they will only start closing when the voltage is at a low enough value.
    - This concept is de-activation, not inactivation. This is because the cause of the closing is from the voltage dependence rather than any sort of time dependence.
    - TODO inactivation vs deactivation
- Refractory period reflects the minimum amount of time there must be between the starts of two consecutive action potentials.
    - How such after an AP is initiated can another AP occur?
- A cell is refractory to a stimulus if there is no AP even if you're hitting threshold using a threshold stimulus. Means you're still in the refractory period.
- Absolute refractory period says that in a period after an AP, even if you get a suprathreshold stimulus, you will never get an AP and the cell remains refractory.
- Then, let's give larger intensity stimulus after the absolute refractory period
- Relative refractory period says that there is a period after the AFP where an increased intensity of stimulus will give you an AP (the normal threshold stimulus isn't enough).
    - So, basically during this period, you can get an AP if you really want, but you need a larger stimulus.
- During AFP, even if you have the required stimulus, you just can't get enough channels to open since they are all refractory. During RFP, the channels are starting to recover from reactivation, and thus it is possible to open some of them up and get an AP but you need a big stimulus.
- If you know AFP, then you can determine what your maximum firing rate is.
- Voltage clamp experiment is where you artificially clamp it (put the Vm to +60 or -40 or whatever) in order to record the subsequent current flow.
    - So when you get to threshold, you stop that voltage from shooting up.

    - E_ion is fixed for a given experiment anyway.
    - You can measure current and then measure conductance as a function of time and voltage.
- Independent variable is always voltage, and the dependent one is the current.
- You need to break the Hodgkin cycle in order to measure everything, can't do it during the AP.
- Voltage clamp eliminates ionic current?
- TODO voltage clamp experiment stuff

10/16 - Week 3

- Hodgkin cycle is the cycle of voltage affecting current and then affecting voltage which affects current, etc. Therefore, we can't accurately measure any of the values. To break the cycle, we developed the voltage clamp so that we can measure current.
    - Clamp the voltage to a certain level and then look at the measure of current over time. Then you calculate the conductance.
- Two components (early inward current of sodium, late outward current of potassium) to the current that results from a voltage clamp experiment that sets the voltage at a depolarized membrane potential.
- As you start to clamp higher and higher voltages, the resulting early inward current gets smaller in terms of the peak. This is because when you increase the voltage, the conductance gets larger as you get a larger number of channels open. However, the current gets smaller because at the point is starts getting smaller, the conductance is constant at that point and you're at g_max and the relationship between V and I is linear. Then, the current will start to decrease as you start to clamp higher and higher voltages because the driving force is getting smaller (Vm is getting closer to ENa).
- Channel blockers will alter the configuration of the sodium and potassium channels.
    - TTX blocks sodium channels.
- For the voltage clamp experiments, you can also make sure you're just measuring the current of one ion by using channel blockers on the other ions.
- During the clamp, dV/dt = 0 and thus all the membrane current is ionic and the experiment gets rid of capacitive current (???)
- A sodium channel is only a single protein (no polypeptide subunits).
- Channelopathies are modifications to channels.
- Synaptic potentials that we get at dendrites will decay as it goes to the soma/axon hillock. However, the action potentials will not decay at all and will propagate faithfully, and will regenerate.
- That action potential is a coded message has to propagate faithfully over any distance and it can't decrement and can't fail.
- Graded potentials not good for long distance communication because the signal decays.
- When an AP gets generated, the peak voltage that you get at the source will stay the same at all the points along the axon as it travels. The AP will propagate both ways if the

input is in the middle of the axon. However, the lowest threshold is at the axon hillock and so there's not really any space for the signal to travel backward.
- You won't have any backpropagation of an AP from hillock into soma and then into dendrites because those dendrites don't have voltage gated channels.
- AP propagation is like igniting a fuse.
- AP faithful propagation
    - Leftmost region gets depolarized, lots of positive ions, passive current flow to the right, depolarize that next region to threshold, causes an AP in that region, lots of positive ions in that region, and then cycle at every region on the axon.
- AP's don't propagate backwards because of the absolute refractory period.
- AP propagation in myelinated axons
    - Internode is the place where the myelin is wrapped around. The node (of Ranvier) is between the wrapped myelin. The myelin affects the speed at which the AP propagates.
    - At the internode region, there are no voltage gated sodium channels and thus you can't get AP regeneration in that region, and they can only happen at the nodes.
    - The one caveat is that you have to make sure that the current doesn't passively decay between the end of one node and the start of another.
- Passive current flow critical for AP propagation for both myelinated and unmyelinated neurons.
- Conduction velocity is the speed that the AP travels from one point to another down the axon, and can vary between 0.1 and 100 m/sec in CNS.
- The factors that affect conduction velocity are:
    - Decrease membrane capacitance -> Increase CV (membrane's distance is constant, but the myelin increases the distance and that decreases the capacitance)
    - Increase diameter of axons -> Increase CV (Increase diameter will decrease the axial resistance which increases the conduction speed)
    - Increase temperature -> Increase CV (Since ions move faster)

10/18 - Week 3

- Action potential propagation in MS patients
    - MS patients have lost some of the myelin and thus the current gets lost (leaks out during the sections that should have myelin) and it takes longer to initiate the AP or there is not enough current and voltage change to reach threshold.
    - Myelin is a good insulator which helps keep the passive current going as it travels down the axon.
- Chemical vs electrical synapses
    - Chemical is where you have NT release from one neuron to another.
    - Electrical is through gap junctions and is always excitatory and is very rapid.

        - Presynaptic neuron has a physical connection to the postsynaptic neuron. There is no gap in between. Electrical signal goes from one cell to another and immediately depolarizes the next neuron.
        - The downside is that you have to opportunity to make a modification to that stimulus.
- Vast majority of transmission is through chemical synapses.
    - In invertebrates, you have a lot of electrical transmission.
- Subsynaptic membrane is the region on the postsynaptic neuron that contains the NT receptors.
- Steps of chemical synaptic transmission
    - AP invades the terminal and depolarization of the terminal. There are lots of voltage gated calcium channels in the terminal. Depolarization is the stimulus to open up those channels.
    - Depolarization increases conductance of calcium, and thus you get more calcium in the terminal.
    - Calcium stimulates the exocytosis of a vesicle that contains NTs. Each of the vesicles contain about the same number of molecules.
        - More depolarization, more calcium comes in, more NT gets released
    - NT diffuses across the gap to the receptors.
    - Binding stimulates ionic conductance change on the subsynaptic membrane.
    - Active current flow into the postsynaptic neuron and that neuron gets a voltage change.
    - Removal of NT from the cleft. The NT doesn't stay bound to the receptor forever.
- Let's look closer at the synaptic potentials
    - NT released from the terminal and then binds to the postsynaptic cell and the conductance change occurs.
    - The magnitude of the change in conductance at the synapse is proportional to the amount of NT binding.
- Hodgkin Huxley sodium channels are voltage dependent. The greater voltage you have, the more the conductance increases. However, these receptors on the postsynaptic neuron are ligand dependent. Their conductance change is a function of the amount of NT. Voltage does not make a difference.
- If we want to calculate the current generated at a synapse,
    - I = delta g * [Vm - Esyn]
    - Delta V = I * Rinp
- When you have an NT that attaches to a receptor and opens up a synapse channel that is permeable to Na, the depolarization is very small and thus we need spatial and temporal summation to occur so we get to threshold.
- When you have an NT that attaches to a ligand gated channel, it opens an ionophore that opens rapidly that allows both sodium and potassium to go through. The net current is the sum of the K current and the Na current.
    - For this situation, you could reach a situation where the net current is 0 because the inward sodium current is equal to the outward potassium current.

    - E_syn is the voltage where the net synaptic current is 0 (situation above).
        - E_mem = E_syn
- Specific NT binding determines which synaptic channels open.
- Relationship between E_syn and membrane potential determines the direction of current.
- If the amount of NT is constant and thus the conductance is constant as well, the driving force is what determines the magnitude of the synaptic current.
- For contraction of single muscle fibers, you have an end plate potential that has a 20-30 mV change and you will always get an AP.
    - At central synapses, the change is only 1-3 mV
- Is synaptic transmission quantized or is there an arbitrary number of NT that gets released?
- There is sometimes spontaneous release (mini end plate potential) of the NTs but the amount is so small that it doesn't really matter.
- Next experiment is to stimulate the axon and then record the evoked response. The hypothesis is that the amplitude of response should be multiples of the mEPP. Want to be able to prove that transmission is quantized.
- If things are quantized, then every stimulation produces a probability for 0,1,2,etc multiples of mEPP.
    - They found that smallest evoked response is 1 mEPP.
- Conclusion is that neurotransmission is quantized.
- Changes in external calcium concentration will increase the driving force and thus will increase the probability of release of NT filled packets from the terminal.
    - No change in mEPP
    - Number of evoked failures decreases, increased probability of higher amplitude evoked responses and increased probability of more NT release.
        - Histogram extended to the right
    - Frequency of occurrence of spontaneous mEPPs increase.
    - Doesn't affect the size of the quanta
    - Doesn't directly affect anything on the postsynaptic neuron.
- If you reduce the number of postsynaptic receptors, the unit response amplitude decreases, probability of release is the same.
    - Histogram shifts to the left
    - Also the magnitude of the mEPP decreases, because you have less receptors.
- NT release is quantized.

10/23 - Week 4

- Motor systems refers to the biology that creates behavior, the neural connections that hook our brain with the muscles that let us move.
- The systems in the top are the motor cortex (which is in the brain) and the brainstem which is near the bottom.

    - Motor cortex responsible for planning and initiating and directing voluntary movements. Basal ganglia talks to motor cortex for proper initiation of movement.
    - Brainstem is more for basic movements. Cerebellum talks to brainstem for sensory motor coordination of ongoing movement.
- Lower motor neurons are in the brain stem
    - Low means low with respect to the muscle
- Reflexes keep you from falling, they are mediated by simple neural circuits in the spinal cord.
    - Some of the reflexes can be completely handled in the spinal cord or brain stem without needing that signal to go up to the motor cortex.
- Rhythmic - Needs more complex parts of nervous system, particularly a central pattern generator that can regulate a circuit.
- Voluntary movement requires the higher level components, like the cortex, basal ganglia, and cerebellum.
- Movements often classified into involuntary and voluntary and some can be in the middle.
- Reflex uses neurons in spinal cord while the voluntary movement require neurons in the cortex.
- Motivated by - sensory feedforward.
    - Watching the ball fall if you're trying to catch it
- Guided by - sensory feedback
    - Movement of the arm after the ball hits the hand
    - Muscle movement as a result of some external stimulus.
- In tracer injections, anterograde is where dye travels from soma down the axons while retrograde is where the dye travels from nerve terminals back towards the soma.
- IEG's are genes whose mRNA is rapidly transcribed right after that neuron starts to fire action potentials.
- Functional MRI is not sensitive enough? Scale is too large with in vivo.
- Muscle is the effector, the thing that affects change.
    - Our focus is the skeletal muscle.
- The skeletal muscles are composed of extrafusal and intrafusal muscle fibers.
    - The extrafusal fibers generate the mechanical forces required for movement.
- The muscles are connected to the bones, and when the muscles contract, they move the bones.
- Inside the extrafusal fibers, there are fibers connected muscle spindles, and inside the spindles, there are another set of fibers called intrafusal fibers. When they contract, they signal about the contractile state of the extrafusal fibers because they have sensory endings that can find info about the state of the extrafusal fibers, instead of actually moving the bones. Extrafusal fibers do the work of moving the skeleton.
- The extrafusal fibers are innervated by alpha motor neurons which are in the ventral horn of the spinal cord. To find those neurons, use a retrograde die that can move up to the soma.

- Intrafusal fibers innervated by gamma motor neurons and they are right next to the alpha motor neurons for the same muscle.
- Synergist muscles produce similar motor action when contracted
    - Soleus and gastrocnemius
    - When they contract they do the same thing
- Antagonist ones produce the opposite moto action.
    - Flexor and extensor, bicep and tricep
    - When they contract, they do the opposite thing
- Contralateral muscles are the muscles of opposite limbs.
- The lower motor neurons that innervate the muscles that are lower in the body are also lower on the brain stem. This type of organization is being somatotopically organized. Same with lateral and medial directions for muscles that are more distal and more proximal.
- Projection neuron is one where the cell body and the terminal are in separate brain areas.
    - Local circuit neurons are where the two are located within the spinal cord. The cell body and the axon are both in the spinal cord.
    - Interneuron cell body and terminal and within the same general brain area.
- Projection neuron needs the interneurons there in order to get communication through in the chord.
- Motor unit is the firing of a single alpha motor neuron and the subsequent contraction of the fibers that the neuron is connected to.
    - The motor unit represents the smallest force that you can get.
- Specifically a motor unit refers to the complex that includes the AMN and all the fibers that it innervates.
- Motor neuron releases Ach at the neuromuscular junction which causes an end plate potential and causes an action potential.
- If you want to increase the muscle force, stimulate the motor unit more frequently, recruit more motor units (stimulate more fibers), and change the type of motor units that you stimulate.
- Stimulation of different motor neurons can cause different reactions from the muscle fibers in terms of how many action potentials are created.
- Motor units can be fast fatigable, fast fatigue resistant, or slow fatigable.
- Slow fatigable MUs and fast-fatigable ones are different in the threshold, the force created, the soma size, and the energy source.
    - Slow is based on oxidative energy source, while fast has a glycolytic source.
- Slow fatigable MUs are easy to bring to threshold.
    - Exercises like standing use these motor neurons.
- For effortful exercises, need to use fast fatigable and there requires a lot more stimulation.
    - Those motor units are in a lot more contact with more muscle fibers.

Monti Paper Notes

- Overall goal is to analyze disorders of consciousness by using different types of techniques and analysis. The results were that of the patients tested who were in a minimally conscious state had brain activations that reflect some awareness and cognition, which can result in a reclassification of the state of consciousness in some patients.
- Goal of these tests is to be able to determine if the patient has capacity for response to stimulation, and to then see if there is a way to have reproducible communication with the patient.
    - If we have this reproducible and consistent communication, then that is the upper boundary of a minimally conscious state.
- The functional MRI is the main tool that they use to measure the metrics and features associated with a minimally conscious state.
- When the patients were in the scanner, they performed imagery tasks where they responded to yes/no questions by thinking of imagery that corresponded with the different answers.
- The 5 patients that were able to modulate their brain activity showed activation in the supplementary motor area. The responses generated were voluntary and reliable and repeatable blood-oxygenation level dependent responses. When they were admitted to the hospital, they were admitted in the vegetative state. The tests show that there is some form of awareness with these patients,
- For the oher 49 patients there was no significant fMRI changes during the tasks.
- One of the main conclusions is that there is potential for fMRI to bridge the dissociation that can occur between behaviour observable in a clinical test and the actual level of cognitive function.

10/25 - Week 4

- Movement is broken down into reflexes, rhythmic, and voluntary
- Different types of control
    - Hierarchical - UMNs tell LMNs what to do
    - Parallel - Motor systems acting redundantly, seen with the synergist muscles.
- To figure out the neurons responsible for a particular movement, you can use anatomical methods (stains, dyes, tracers), in vitro and in vivo electrophysiology, in fMRI vs the other kind of MRI, and in immediate early gene expression.
- In the category of LMNs, you have alpha MNs, gamma MNs, and local circuit interneurons.
- Alpha MNs - innervate the extrafusal fibers
- Gamma MNs - innervate the intrafusal fibers
- Nerves carrying info from the outside to the CNS are called afferent.
    - Normally the sensory neurons
- Nerves carrying signals out from the CNS are called efferent.
    - Normally the motor neurons

- Interneurons have their cell body and their nerve terminal in the same location.
- Sensory neurons called the 1a afferents have their cell bodies in the dorsal root ganglia.
- The sensory endings on the end of muscle spindles have mechano-sensitive receptors.
- Myotatic reflex
    - You have certain reflexes where as a result of your muscles lengthening as a result of some external force, then you automatically create some counteracting force.
    - You have a neuron that looks for a certain stretch and that neuron fires a lot when the stretch happens.
    - The 1a afferent neuron will sense the stretch (through mechanosensitive channels) and will signal to the alpha motor neuron that shortens the muscle to actually cause the counteracting force.
- Tendons are what connect muscles to bones.
- Basically a sensory neuron will sense some external force, it signals to the motor neuron, and that MN fires and the extensor/flexor muscle fibers it is connected to contract.
    - There can be interneurons in between that switch the signal from excitatory signals to inhibitory signals. This is useful for keeping the sign the same for the extensor and then swapping the sign for the flexor. (Or the other way around)
- The myotatic reflex is basically where an AP occurs in a sensory neuron that then excites an alpha motor neuron which then excite the extrafusal fibers.
- Flexor reflexes are reflexes where you have similar external stimuli, and on the same side, the flexor gets excited and the extensor gets inhibited. However, on the opposite site of the body, the opposite happens. The interneuron helps this happen as it is able to switch the sign.
    - They specifically mediate the withdrawal of a limb from a painful stimulus. A common example if placing your foot on a tack.
- Gamma MNs interact with intrafusal fibers and cause them to contract, but the function of those are different from that of the extrafusal ones. The gamma MNs adjust the tension in the spindle. Increased activity in those gamma MNs increases the tension of the muscle fibers.
    - The tension of the spindle needs to be adjustable because if the intrafusal fiber is slack, it’s not going to detect the next stretch.
    - When the extrafusal fibers contract, the intrafusal need to contract. Same with relaxing. The two need to be in concert with each other.
- 1a afferent tells us about the lengthening of the muscle, 1b afferent neurons are connected to a sensory system associated with muscles in the Golgi tendon organ. The 1b neurons detect contraction of the muscle.
- When the muscle contracts, that's what lengthens the Golgi and that causes mechanosensitive receptors to signal.
- Spindle signals about muscle length while the tendon organ signals about muscle contraction.

- Spindles are in parallel with the extrafusals while the tendon organs are in series with the extrafusals.
- Central pattern generators are the circuits that give rise to rhythmic motor activity.
    - Capable of producing rhythmic patterns of activity in absence of actual sensory input.
- To find out the basis of more complex functions, we have to use model systems of other animals.
- Rhythmic activity in neurons depend on the permeabilites of ions and the channels on the neurons.
- Need the calcium activated potassium channel, NMDA receptor (glutamate receptor), and the AMPA type glutamate receptor.
    - When you apply glutamate, you open the AMPA receptor which lets in sodium. Glutamate binds to the NMDA receptor, but at hyperpolarized potential, magnesium ions sit in the channel and don't let any ions flow through. As positive ions come in and the neuron becomes depolarized, that's when more ions start to flow through the NMDA receptors as the magnesium ions move out because of the positive charges repelling with the sodium ions.
    - Then for the falling phase (after the AP), calcium also comes through the NMDA receptor channels. It binds to the calcium activated potassium channel and then potassium goes out and the neuron becomes hyperpolarized.
- The above shows the oscillatory characteristic of the neuron.
- Reciprocal inhibition is a way to turn tonic/constant excitation into rhythmic activity.
    - Local circuit inhibitory interneurons are the reason.
    - Let's say one interneuron starts firing. It has an axon collateral/branch that goes to an inhibitory interneuron and then that interneuron sends inhibitory signal to the interneuron on the top. The middle interneuron has a collateral to goes to itself and starts inhibiting itself which means it stops inhibiting the top interneuron, and then it starts firing. When it does so, it excites a 2nd middle inhibitory interneuron which tells the bottom neuron to stop firing. Then, the 2nd interneuron starts inhibiting itself, which causes the bottom neuron to start firing, and then then whole cycle starts up again.

10/30 - Week 5

- An ionotropic receptor is one that allows ions to pass through it.
    - The other type of receptor would be metabotropic which activate 2nd messengers in the cell which affect other channels which eventually affect ion flow. This means the effect is slower in the end.
    - Ionotropic receptor will work on a faster timescale than the metabotropic one.
- Central pattern generators can also get affected by descending inputs.
- Ascending information of the spinal cord is sent up to higher brain regions. A copy of what's going on is sent up.

- 1A afferents help for rhythmic behavior since we get more info, but they are not absolutely required.
- Brain has 3 major motor cortical areas
    - Primary motor (M1)
    - Premotor (PMA)
    - Supplementary motor cortex (SMA)
- Corticospinal tract have cell bodies in the cortex and extend down to the spinal cord
    - Provides a direct output from primary motor cortex.
    - Lateral corticospinal tract
    - Ventral corticospinal tract control posture
- Corticobulbar tract have cell bodies in the cortex and extend to the face.
- Spike triggered averaging can reveal which cortical motor neurons control movement.
- Directional tuning is when a neuron fires more frequently based on a particular direction.
- If the arm is controlled by two neurons and one prefers movement in the 0 direction and then other prefers in the 90 direction. So if they fire both equally, the arm will move in the 45 direction.
- Mirror neurons fire prior to sensory input.

Clinical Correlation

- Neurological exam
    - Goal is to tell where the lesion is before the imaging.
    - Want to localize and figure out where the problem is
- Neurological exam tests all the different parts of the brain
    - Mental Status
        - Determines level of alertness and cooperation
        - Figure out the attention the patient is giving, the orientation they are in, are they fluent when they're talking, are they able to remember things, and some tests on higher functioning.
        - How are they reacting to you, how is their mood.
    - Cranial Nerves
        - Helps us localize what's going on in the brain stem.
        - Test the 12 different cranial nerves separately
        - CN1: Testing of the smell
        - CN2: Testing of vision and testing the optic nerve
        - CN3: Pupil reactivity and eye movement
        - CN4: Eye movements
        - CN5: Muscles of mastication
        - CN6: Also eye movements
        - CN7: Facial nerve (smile not equal) and taste in different areas of the tongue
        - CN8: Hearing
        - CN9: Taste and uvula

        - CN10: How we talk or phonation.
        - CN11: Head turn and shoulder shrug
        - CN12: Tongue protrusion
    - Motor System
        - Assess the tone and the muscle bulk and strength and abnormal movements.
        - Also check agonist and antagonist muscle pairs and grade according to the scale.
        - Do the pronator drift experiment and the orbiting test.
    - Reflexes
        - Do different tests on body parts and that will tell you which reflex pathways are good and which aren't.
        - Patellar reflex
    - Sensory System
        - Light touch, pain/temperature, and vibration
    - Coordination
    - Station and Gait
        - Basically can they walk across a room
- Exam starts broad and then hones in on specific things
- All the tests help to map out the patterns of weakness that helps us localize.

11/1 - Week 5

- The amount of territory on the cortex devoted to a particular part of the body reflects the importance and the function.
- Spike triggered averaging is the act of figuring out the activity of single neurons at a time.
    - From this you can figure out the direction that a neuron responds to the most. You can construct a tuning curve for each neuron.
    - For each of the 8 directions, you can create a vector where the angle is the neuron's preferred direction and the length is the peak firing for that direction.
        - So each of the vectors will be pointing in the same direction, they just have different lengths.
- The map in the primary motor cortex can change with experience.
    - If you lose function for a particular area (some motor neurons get damaged causing no functionality) and then remap, you can see that the territory gets taken over by neurons controlling other areas.
        - It could be that the removal uncovered pre existing connections that we can now see. However, it could also be that the removal causes an anatomical rewiring of the connections.
- Synaptic plasticity refers to changes in the strength of synapses between neurons.
- Anatomical plasticity refers to changes in the structure of neural connections.
- Behavioural plasticity refers to changes in behavior due to external circumstances.
    - Comes about based on the synaptic and anatomical changes.

- More cortical area given to the trained sequence.
- Different motor areas activated during actual movement vs imagined movement.
    - More territory needed to do the complex movement.
- There is some redundancy in the motor system as shown by the other tracts.
    - Tectospinal, reticulospinal, vestibulospinal tracts
- Reticular formation is part of one of the indirect pathways.
- Basal ganglia isn't just one place.
- Motor cortex gives you command for movement and basal ganglia helps you actually plan out the movement and suppress the movements that we don't want.
- Components of the basal ganglia
    - Caudate and putamen are referred to as the striatum. Those neurons are inhibitory and connected to group of neurons called Globus pallidus and Substantia nigra pars reticulata. Those are inhibitory as well as they connect to the thalamus (not considered part of the basal ganglia).
- Striatal medium spiny neurons receive excitatory input through corticostriatal pathway.
    - Local circuit neurons synapse onto the soma in a negative way.
- Globus pallidus neurons, however, are spontaneously active and thus they are always inhibiting the thalamus.
    - When the medium spiny neurons aren't silent, then opposite??

11/8 - Week 6

- Cerebellum modulates gross movement.
- Inputs to the cerebellum are cortical, vestibular, and modulatory.
- Specifically, the cerebellum is the lateral surface of the cerebral hemisphere. It's right behind the brain stem. It sits at the back base of the brain and is right next to midbrain and brainstem.
- 3 components of the cerebellum
    - Spinocerebellum: Receives inputs from spinal cord.
    - Cerebrocerebellum: On either side of the Spinocerebellum. Gets input from the cortex.
    - Vestibulocerebellum: Receives input from the vestibular system (ear?).
- Peduncles are cables bringing in fibers into the cerebellum. Allows for inputs and outputs into the cerebellum.
- Cerebellum receives somatosensory, visual, auditory, vestibular (balance), proprioceptive (movement in space) info and combines all of this info.
- Cerebral cortex provides the most inputs to the cerebellum.
    - Most goes to the cerebrocerebellum.
- Vestibular inputs go through the inferior peduncle and go to the Vestibulocerebellum.
- Spinal inputs also go through the inferior peduncle.
- Basically, different inputs from different places going through different components in the cerebellum.

- Mossy fibers relay info from the cortex and they synapse on granular cells (which are in the granular cell layer) which synapse onto Purkinje cells (cell bodies in the respective layer and the dendrites go into the molecular layer).
- Inferior olive outputs go through inferior peduncle and they go to cerebellar cortex and serves to modulate input?
- Climbing fibers are different from mossy ones because they come from the inferior olive and synapse directly with Purkinje cells, they don't mess with the granular cells. They are "climbing" on Purkinje cells, the fibers wrap around the Purkinje cell dendrites and thus they get a lot of info.
- Purkinje cells have a large surface area with their dendrites and thus they get a lot of stimulus.
- 2 classes of excitatory inputs (climbing fibers, mossy fibers)
    - Mossy bring in sensory information from the cortex.
    - Climbing bring in info from inferior olive.
    - Both also send axon collaterals to the deep nuclei. They send info to LMNs and UMNs. The Purkinje cells output onto the deep cerebellar nuclei.
- Only output from the cerebellum come from the deep cerebellar nuclei.
- 1 climbing fiber per Purkinje cell because it wraps around. However, there are a lot of parallel fibers that can also help excite the cells.
    - If you stimulate a parallel fiber, then you just get a single spike.
    - If you stimulate a climbing fiber, then you get complex spike because there are so many places of contact and synapses.
- Two ways to modulate movement. Change the deep nuclei or the synapses from climbing fibers onto Purkinje cells.

11/9 - Week 6

- Fast fatigable motor units will have motor neurons that are connected to a lot of muscle fibers.
- As your work increases, the motor units that get recruited will go from slow to fast fatigue-resistant to fast fatigable.
- Rhythmic activity
    - Glutamate binds to the AMPA receptor. This causes the receptor to open the channel and lets positive ions (sodium and calcium) in. As the cell depolarizes there is repulsion between the positive ions inside and the magnesium ions that are sitting in the NMDA receptor. Those ions are blocking the channel at rest. Once the positive charge builds up, the magnesium gets knocked out and the channel starts to open up, which lets in more calcium and sodium. Once the calcium is in the cell, it binds intracellularly and this opens up the channel for potassium to flow out which repolarizes the cell. After a while, AMPA receptor stops responding to glutamate, which is called desensitization. Also, as K+ leaves the cell, the positive charges start to exert less repulsion, causing the magnesium ions to come back to the NMDA receptor.

    - This cycle repeats over and over which causes the rhythmic behavior.
- Function of different tracts in the body (Prefix tells you where the signal is coming from)
    - Rubrospinal: Proximal muscles of arms
    - Reticulospinal: Posture
    - Vestibulospinal: Balance and posture (from your ears)
    - Tectospinal: Head position and eye - Head movement in response to visual stimuli.
    - Corticospinal: From cortex to the spinal cord
    - Corticobulbar: From cortex to the brainstem
- Basal ganglia modifies upper motor neuron behavior.
- Indirect pathway modulates the direct pathway to some extent. Opposes the direct pathway.

11/13 - Week 7

- Dopamine is the transmitter that is lost during Parkinson's disease.
    - It helps us move. If you lose dopamine in either pathway, result is always to not excite the motor cortex and less movement.
    - Adding dopamine to the direct pathway encourages movement.
    - Specifically, Parkinson's causes loss of dopaminergic cells.
- Whether dopamine binds to D1 or D2 receptors, the result is movement, regardless of pathway.
- Basal ganglia is also involved in organizing thought and emotions, not just movement and action.
- Cerebellum informs us about error between expected and actual movement and gets us to pay attention to key stimuli.
    - If movement goes as planned, cerebellum firing output decreases. Vice versa otherwise.
- Cerebellar cortex outputs go to the deep cerebellar nuclei and that output goes through the superior cerebellar peduncle and that goes to the superior colliculus as well as to the thalamus which goes to the motor cortex.
- Cerebellum helps us pay attention to external sensory feedback.
- Purkinje cells make only one synapse each to the parallel fibers, while there are a lot of synapses between the climbing fibers and the Purkinje cells.
- Motor learning is trial and error learning, which is different from declarative learning which is you just receiving information from others.
    - Nobody can tell you motor learning, but rather it is procedurally learned.
        - Ex) Riding a bike or hitting a baseball
    - The circuits for motor learning often involve simple reflex pathways linking sensory input to motor output.
    - The reflex on the bike is you trying to stabilize yourself, and learning is not getting off balance in the first place.

- Classic conditioning is a type of procedurally learned behavior. Involves a reflex where unconditioned stimulus automatically produces an unconditioned response.
    - Doesn't have to be trained or conditioned by the experimenter since it is a reflex.
- The experiment looks to associate a new conditioned stimulus with the US stimulus. The CS will now trigger without the US.
    - The common example is associating food with a bell sound, then the dog salivates when the bell rings, if you train the dog to pair those two things together. The dog learns to associate the bell with the food. Learned to associate something on top of a reflex pathway.
- Synaptic plasticity refers to the ability of the presynaptic neuron to cause an AP in the postsynaptic neuron.
- The plasticity at the Purkinje cell and parallel fiber synapse contributes to motor learning.
    - This can only have when both are co-active, causes a long term depression at the synapse.

11/15 - Week 7

- Retinal ganglion cells connect the eyes and the brain.
- Photoreceptor cells responsible for detecting light.
- 5 major sensory systems were visual, auditory, tactile, olfactory, and gustatory.
- Photo transduction is transfer from light energy to neural energy.
- Cone photoreceptors are on when there is daylight. They focus on the fine details in images.
- Among sensory receptors, only rods and cones hyperpolarize in response to stimulus.
- All sensory pathways require stimulus and a receptor for detecting that stimulus.
    - The stimulus can be light, pressure, sound, etc.
- Receptors can be:
    - Chemoreceptors: Presence of chemicals
    - Mechanoreceptors: Various forms of mechanical energy
    - Thermoreceptors: Temperature
    - Nociceptors: Painful stimuli
    - Photoreceptors: Light
- Receptors are the special nerve endings of neurons and each responds to its own stimulus.
- Olfactory receptors are in lots of places and involved in variety of functions.
- Taste receptors also are similar, they detect nutrients in food, regulate immune response, etc
- All sensory receptors adapt (except some pain receptors) and it's the ability of the receptor to silence itself in the presence of stimulus that is there for a long period of time. The advantage is that once it's aware of the past stimulus, then the receptor can be used to detect new stimuli.
- Adaptation can be fast or slow and that can affect how much the neuron fires after a particular stimulus has been there for a while.

- Synesthesia is the phenomenon where one sensory input causes the involuntary experience of another?
    - Associations of sounds with colors
    - Certain sounds causing sensations in the body
    - Certain tastes experienced when hearing words.
- There are also lots of metaphors for synesthesia
    - Loud colors, bitter cold, etc
- You can think of sound as a mechanical wave and needs a medium in which to travel. It needs to push air/water particles.
    - Won't hear anything in a vacuum.
- The sound wave created has a certain frequency (pitch) and intensity (loudness).
- You can objectively measure the intensity (energy / time * area) but the loudness is subjective.
- The ear consists of the outer, middle, and inner ear
- The auditory canal acts as a closed tube resonator and enhances sounds.
    - Designed to increase our sensitivity to speech and music.
- Ossicles act as levers increasing the sound pressure.
- Organ of Corti is where the receptors for hearing are located. This structure is covered by the tectorial membrane.
- Scala media is filled with endolymph fluid. Perilymph is fluid in the scala vestibuli and scala tympani.
- Endolymph electrical potential is much more positive than perilymph.
    - Called endocochlear potential.
- In the basilar membrane, the cochlea narrows from base to apex.
- High frequency sounds lead to vibration of basilar membrane closer to the base. Low frequency closer to the apex.
- Basilar membrane is tonotopically organized. Certain parts vibrate in response to certain wavelengths.
- Hair cells are what do the transduction of sound energy, and they contain stereocilia.
- In the presence of sound, there is a traveling wave in the cochlea, and the membrane moves, causing stereocilia to bend in one direction, which causes the potassium channels to open, allowing potassium to enter the hair cells (goes from endolymph to perilymph), causing depolarization, and calcium channels to open.
- Outer hair cells play a role in amplification of sound
    - They can expand or contract, pushing against the tectorial membrane, and push the basilar membrane downward and also closer to tectorial membrane.
    - Sound intensity is a result of the firing rates of the neurons.
- Phase locking refers to the idea that the fiber will respond to a particular point in the sound wave.
- Once hair cells are activated they release NT onto spiral ganglion cells.
- Patients with Broca's aphasia: know "what they want to say, but cannot get it out;
- Patients with Wernicke's aphasia: could speak, but their speech is often incoherent and made no sense have reduced understanding of spoken and written language.

- Primary auditory cortex is tonotopically organized.
- 2 hemispheres of the brain act differently to sounds.
- When presented tones, left ear is faster, and vice versa with clicks.
- If sound reaches left ear first, it has more time to travel and will reach further than info coming from the right. MSO responds when excitatory signals from both nuclei arrive at the same time.
- LSO also encodes sound location through interaural intensity differences.
- They both localize sound but LSO is employed when there's low frequency sounds
- Conductive hearing loss prevents sound from activating hair cells in the cochlea.
    - Ear wax, ear infection, something in your ear
    - Can be corrected medically or surgically.
- Sensorineural hearing loss is damage to the cochlea or to the nerve pathways from inner ear to the brain or to the hair cells.
    - Often can't be repaired.
- Cochlear implants are electrodes that stimulate spiral ganglion cells. If we can stimulate them at certain locations in the basilar membrane, then we can restore some hearing.
- Syndronic loss is where you have problems in additions to hearing loss.
- Mutation of DFNB1 affects supporting cells in the inner ear and is responsible for deafness in patients.
- Mammals can't regenerate hair cells.

11/15 - Week 7

- The corpuscles are able to tell you the change in stimulus. After the receptors have adapted to a particular stimulus, then there is no potential that gets created, unless there is a change (such as removal of the stimulus).
    - A stripped corpuscle wouldn't generate an AP when there is a removal of the external stimulus, while the intact one will generate one because it detects a change.
- Speech is around 2 - 5 kHz.
- Outer hair cells allows amplification of sounds below a frequency of 2 kHz.
- Any lesions in the cochlear nuclei would cause complete deafness, while if you have a lesion in the superior olive then you'd only affect one side, since that is the part where the auditory nerve splits.
- LSO helps us determine the location for higher frequency sounds.
- No rhythmic behavior because no modulation of the interneurons.
- In the MSO, one of the neurons is the middle will be the one that fires when it receives a signal from the left side and the right side. Depending on which neuron, that will tell us which side is stronger.
    - The neurons are coincidence detectors

11/20 - Week 8

- Check Wei-Hao's notes

11/27 - Week 9

- Somatosensory system covers the entire body. They aren't localized in a small organ, like photoreceptors in the eye or hair cells in the cochlea.
- Somatosensory system handles touch, pain, temperature, and body position (proprioception) in space - position of limbs.
- Based on the stimuli, there are different types of receptors.
    - Mechanoreceptors - Physical distortion
    - Nociceptors - Damaging stimuli
    - Thermoreceptors - Temperature changes
    - Proprioceptors - Monitor body position
    - Chemoreceptors - Certain chemicals
- Somatosensory afferents send info from the skin to central circuits.
    - The receptors have to stimulated, and then the signal is sent to the dorsal root and then different pathway to the brain.
    - Touch, pain, and other senses have different pathways to the brain so that the signals don't mix.
- Information from the face is sent through the trigeminal ganglia.
- The neurons in the dorsal root and pseudounipolar because axon is sent to both the periphery as well as to the spinal cord.
- Mechanoreceptors are encapsulated, while nociceptors and thermoreceptors have free nerve endings.
- Different types of mechanoreceptors in the skin
    - Pacinian corpuscle (15%): Very sensitive receptors, very large receptive fields though so you don't use them for very precise stimuli, very low threshold and thus little stimuli needed to activate it.
    - Meissner's corpuscle (40%): Very close to the skin, sensitive to low frequency vibration such as moving an object across your hand.
    - Merkel's disks: Also close to surface of the skin, smallest receptive field, responsible for fine discrimination of the stimuli, tactile discrimination.
    - Hair follicle receptors: Provide info about distortion or pressure applied to the hair on the skin.
    - Ruffini's corpuscle: Respond to sustained pressure, located in the dermis, not concerned with fine discrimination.
- If we move fingers across Braille letters, then we look at the activity for each of the receptors. Merkel mechanoreceptors are the ones that precisely fire in accordance with the symbols.
- The receptors have different adaptation rates.
    - Meissner and Pacinian are fast adapting.
    - Merkel and Ruffini's are slow adapting.
- ABeta are afferents that provide info about touch.
- ADelta are afferents that provide info about pain and temperature.

- Spinal segments can be separated into cervical, thoracic, lumbar, and sacral.
    - Different patches of skin communicate with different areas on the spinal cord.
- Signal from the receptors will go into the dorsal root and then travel up the dorsal columns to the medulla, and then make connections with the gracile and cunea nucleus, and then they travel contralaterally and go up to the brain?
    - This is called the dorsal column-medial lemniscal pathway.
- Trigeminal nerves are the ones that allow for signal transfer from receptors on the face to the brain.
- 3b section on the brain gets most of the stimulus from the thalamus. The section handles mechano changes.
- 3a deals with proprioception.
- Relative size of the somatosensory cortex devoted to each body part is correlated with the density of sensory input
- There is a difference between pain and nociception
    - Pain is the feeling
    - Nociception is the actual sensory process that provides the signals that trigger the pain.
- After skin gets damaged, that area gets more sensitive to other external stimulus.
- Gate theory of pain modulation refers to when descending systems can modulate the transmission of the ascending pain signals.

11/29 - Week 9

- Retina is neuronal tissue and contains cells that are sensitive to light, and they transfer the light energy to neural energy, and the ganglion cells go to the thalamus which is then sent to V1 visual cortex, and then to special cortical regions in the brain.
- The cornea has the purpose of refracting the incoming light to focus it on a very particular location, fovea, on the retina.
    - Has a very large refractive power, which is a function of the focal length.
- Optic nerve consists of the axons of the ganglion cells which serve as the in between of thalamus and retinal cells.
- Glaucoma is the disease of retinal ganglion cells and their axons.
    - It's caused by high levels of intraocular pressure caused by possible problems with the drainage of aqueous humor.
- With age, the elasticity of the lens is reduced (getting round or flat depending on where you want to focus) and that's why older people need reading glasses.
- Hyperopia is caused when the picture is formed after the light reaches retina, and to fix that, you use a convex lens.
- Myopia is caused when the picture is formed before the light reaches retina, and to fix that, you use a concave lens.
- Visual field/acuity is the amount of space viewed by the retina when the eye is fixated ahead.
    - When ahead, then 150 degrees (90 on temporal, 60 on nasal)

- 20/20 vision means you can see line 8 from 20 feet away.
- Photoreceptors (rods, cones) -> bipolar cells -> ganglion cells
    - This structure isn't that logical since the light reaches the photoreceptors which are at the very back of the eye, and then the signal has to come to the front.
- Reflecting tapetum layer has the purpose of taking light that wasn't absorbed by the photoreceptors, and it reflects that light onto the retina.
- Rods and cones both have outer segment (phototransduction takes place here), inner segment, and synaptic terminal.
- Rod photoreceptors are more sensitive and thus they are for dim light situations. Cones are responsible for daylight and color vision and high resolution.
    - Certain luminance at which rods and cones will work. Basically depends on the outside light intensity.
- Skinny tall cells are the rods, and the fat ones are the cones.
- Photoreceptors are renewed in that the tips/disks are removed and more disks are built by cells.
- Macula is part of the central retina, and within the macula, we have the fovea. The light gets focused onto the fovea. Rod and cone photoreceptors are not distributed evenly, we have many more rods than cones, but most cone photoreceptors are in the fovea and the macula.
- In the central retina, there is 1:1 between cone and ganglion cell.
- In the peripheral retina, there could be a lot of cone cells going to one ganglion cell. Basically there is a lot of convergence of signal.
- There is a foveal pit and at the bottom you have the cone cells.
    - If something happens to this area, there is a loss of central vision.
- There is a blind spot somewhere because there are no photoreceptors in that area.
- Photoreceptors are depolarized in the dark and when light is received they hyperpolarize, which is the opposite to what cells normally do.
- Basically, everything takes place in the outer segment of the rod/cone cells. In the dark, there is a high concentration of cGMP and those bind to ligand gated ion channels, allowing sodium and potassium to enter the cell. When the photoreceptors are stimulated by light, there is hydrolysis of cGMP causing its concentration to go down, and thus not letting as much potassium and sodium through and thus hyperpolarization.
    - The cause of the cGMP concentration going down is that light hits rhodopsin, which causes a conformational change, and then transducin is activated, and then the alpha subunit will dissociate, change GTP to GDP and then will bind to PDE, and then cGMP to GMP. Then, channels are closed because not enough cGMP.
- By absorption of one photon of light, there needs to be signal amplification.
    - One light activated rhodopsin can activate 800 transducin molecules.
    - 1 active molecule of PDE can hydrolyze many cGMP.
- If we hyperpolarize, we need to repolarize in some way. When level of calcium goes down, guan cyclase is activated and that can produce more cGMP.

- We have 3 different cones that each respond to light with different wavelengths which gives us the ability to perceive different colors.
- When you enter a dark room, your pupils enlarge, there is rhodopsin regeneration, and your rod photoreceptors will be of use.
- When you have a lot of light, less calcium
- When center cone gets hyperpolarized, the on center bipolar cell will be depolarized, and off center will be hyperpolarized, and those signals are relayed to the ganglion cells.

11/30 - Week 9

- For tasting sweet stimuli, you have T1R2 and T1R3 G protein coupled receptors.
- For tasting unami stimuli, you have T1R1 and T1R3 G protein coupled receptors.
- You can also taste salty and sour through cation channels.
- So basically for identifying different types of tastes, you have different types of receptors or ion channels.
- All the taste receptor cells have the same process of getting stimulated and releasing NTs onto the next cell.
- Taste receptors can potentially respond to different tastes, although to different levels. The neurons are tuned to respond greatest to a single taste stimulus.
    - However, in olfactory receptor cells, it expresses one protein and each cell responds to different odors with different preferences.
- Olfactory system is the only one that doesn't go through the thalamus, it hits the pyriform cortex directly.
- Taste system does indeed go from taste buds to the thalamus and then to the insular cortex.
- Taste cells are not considered neurons, but rather specialized epithelial cells.
- Both smell and taste receptors have short lifetimes and regenerate often.

12/4 - Week 10

- Bipolar cell's receptive field is the area or patch on the retina for which that cell responds to.
    - The receptors in the field make direct connections with bipolar cells and some with horizontal cells (and then with bipolar).
        - Horizontal cells are connected to the surround photoreceptors.
        - Bipolar cells are directly connected to the center photoreceptors.
- The center cone cells make connections with the on-center and the off-center bipolar cell.
    - On-center: Metabotropic receptors, opposite of photoreceptor, mGluR6
    - Off-center: Ionotropic receptors, same as photoreceptor, AMPA kainate
- Both of the above cells will communicate with their respective ganglion cells.
- Response from the center is slightly stronger than surround
    - Even if you have inhibition from the surround, the center won't be affected as much. Response from center is more significant.

- Horizontal cells connect the surround cells to the bipolar cells.
    - Horizontal cells inhibit the center?
    - When horizontal cells are depolarized, they will try to hyperpolarize the center photoreceptors and vice versa.
- More contrast in illumination will cause off-center bipolar cells to fire more.
    - Dark spot in the center and illumination of surround will cause the greatest response from the off-center bipolar cell.
    - Light spot in the center will cause the greatest response from the on-center bipolar cell.
        - In that case, if you make the surround area darker, then there will be a depolarization and the horizontal cells will have a slight effect on increasing the response of the on-center cell.
- For different backgrounds, the rate of firing will change differently as luminance of the test spots increase.
- 3 types of retinal ganglion cells
    - Magnocellular
        - Respond to large moving targets.
    - Parvocellular
        - Allows you to focus and get high resolution images. Useful for shape perception.
        - Red on green off cells
    - Koniocellular
        - Blue on yellow off cells
- Red on green off means that the cell will fire when red light is in center and gets inhibited when green light is the surround.
    - When red is just in the center, we'll get lots of activation. When red everywhere, then you get inhibition from the surround onto the center (even though we have green off in the surround, red light will also stimulate those photoreceptors since there is a good bit of overlap between the two wavelength distributions.) Basically the cells won't be stimulated to the max but there will be some excitation and thus some inhibition on the center.
- Bipolar cells make connections with ganglion in the inner plexiform layer.
- There are lots of functional groups of ganglion cells depending on how they connect with the on/off bipolar cells.
- Each type of GC tiles the retinal surface, and thus completely covers every visual image.
- This means that every point in the retinal surface is reported upon at least once by each of the diverse types of RGC.
- Amacrine cells play a role in ganglion cell activity. Need different types of ACs to regulate different types of RGCs.
- Axons from the nasal retina will decussate so info from right side of visual field will cross.
- RGCs will transmit info to the LGN and then to the primary visual cortex.

- ipRGCs are similar to rods and cones in that they are photosensitive, they can be activated by light, and then send info to the thalamus and other places to signal about lighting conditions. ipRGCs have melanopsin.
- Pretectum sends info to the eyes telling them to constrict.
- Cutting left optic tract will cause loss of vision from right field.
- Cutting the optic chiasm will cause loss of nasal retina cells which means loss of temporal visual info.
- Structure of LGN and the layers allows info to be coming from both eyes and from all types of RGCs.
- Visual map is preserved from the retina up to the visual cortex.
- The visual signals from each eye remain segregated in the LGN
- Orientation specific RGCs are responsible for shape detection. Direction specific ones will be responsible for motion detection.

12/6 - Week 10

- 3 main pathways in visual perception
    - Magnocellular, blob, and parvo-interblob pathways. Each originate from different type of RGC.
    - P-type ganglion cells are the majority and thus that pathway would be favored.
- There is some mixup from each pathway to other pathways, so they are not pure.
- Hard to find blue cone cells in the fovea,
- Each pathway provides different info about the visual image.
    - Blob pathway shows info about color
    - Parvo for static perception
    - Magno for movement.
- There is a piece of the cortex which is the part necessary to analyze points in visual field.
- There are many of these cortical modules to analyze the whole visual field. There are 2 sets of orientation specific columns.
- There are two streams, ventral and dorsal, that show how info gets relayed from V1.
    - Dorsal goes to parietal lobe. Helps with landmark discrimination problem because it gives you the spatial awareness.
    - Ventral goes to temporal lobe. Helps with object discrimination problem.
- Different layers of the visual cortex are really preprocessing for the other areas the info gets sent to. Starts with V1 and then gets more and more complex in terms of the info flow.
- V4 is also shape perception associated with color
- Perception is the internal representation of the outside world
    - Color perception is through the activity of the different cone cells.
- Color constancy is the ability to see the object's color the same regardless of the luminance of the outside environment. Wavelength reflected from the object inside may be different from the wavelength reflected when the object is inside. But in both cases, we perceive green, the actual color.

    - Basically, the reasoning is chromatic adaptation, where as the environment changes, the wavelength reflected changes, and then the cones adapt to the presence of the longer wavelength. We see a partial red, but more of the expected green.
- Size of the object perceived depends on the size of the image presented on the retina and location of the object wrt our eye.
- The perception of depth is dependent on relative size (comparing different objects sizes), interposition (putting one object over another), linear perspective (parallel lines?), light and shade (something looks convex or concave depending on the shade and assumption of where the light is coming from), and aerial perspective (Far away objects seem blue-ish).
- Macula degeneration
    - Dry form: Deposits or debris from tissue in macula
    - Wet form: New blood vessels grow underneath retina.
- Glaucoma: Caused by high intraocular pressure.

Clinical Correlation 2

- Patient had seizures and memory problems. Started on anti-seizure medication.
    - Normal brain scan, CT head, and brain waves had abnormalities.
    - After medication. began having memory problems, forgetting names of friends.
    - Mom was convinced it was the medication
- Look at the past history in terms of medical (seizures prior), surgical, social (substance use), and family.
- Then go to physical exam where you take the vital signs like temp, bp, heart rate.
- Then go to general exam where you look at the physical characteristics like mood, cardiac behavior (regular heart rate), abdomen (soft, non-tender), skin, no acute distress, etc.
- Then go to neurological exam - Asking different questions, speech, knowledge, comprehension, spelling, recalling things. Then you start testing the cranial nerves. .
    - Couldn't do the recall, 8 quarters question, soft and slow speaking
- Main assessment is 19 year old women with 2 months of seizure, worsening memory problems, looks anxious, calculations off
    - The outside hospital that treated here said there was normal imaging and an abnormal EEG.
- Differential diagnosis is the process of differentiating between two or more conditions that share similar signs or symptoms.
- What's causing this?
    - Drugs
    - Structural issues in the brain
    - Genetic seizure disorders
    - Inflections, inflammations, metabolic conditions, psychiatric

- Then, more symptoms come up. Heart rate elevated, more anxious, pure fear, saying weird things, started hallucinating, having delusions, spiked fever, etc.
    - Typically, normal seizures don't cause the above.
- MRI results
    - Left frontal lobe has flair intensity when MRI is done.
    - Bilateral hippocampal hyperintensity.
    - Temporal lobes also look swollen, possible inflammation
- Had inflammatory markers in the spinal fluid. Something is inflamed in the CNS
- Anti NMDA Receptor Antibody Positive -> Anti-NMDA Receptor Encephalitis
    - Next step is to check for cancer
- Treated with rounds of immunosuppression.
    - Calm the immune system down and tumor restriction if that is what is creating the antibodies.
- NMDA receptor is an ion channel and has functions in synaptic plasticity. Ligand gated. Balance is important with this receptor activity.
- Encephalitis is the inflammation of the brain.
- With this disease, autoantibodies cause a reduction in NMDA receptors.
- The clinical symptoms for this disease were anxiety, memory issues, seizures, etc
- Have high index of suspicion.
    - Check CSF, EEG, and MRI

12/7 - Week 10

- Taste is labeled line, and everything else is population coding
    - Individual taste receptor cells exhibit only one type of receptor, which is specific. But when you look at the entirety of the tongue, we're looking at the population of the papilla, and thus you're looking at a bunch of different receptors.
- Pain symptoms
    - Where they decussate so that you know how that affects what sensations you lose.
- Retinol is the molecule that is doing the conformational change and it is located in rhodopsin.
- 2 signal amplification steps during hyperpolarization of the photoreceptors, when light is shone.
    - Rhodopsin -> transducin -> PDE
    - PDE decreases the concentration of cGMP.
- Photoadaptation - There is an inhibition of the hyperpolarization that you normally get when light is shone.
    - Overall goal is to decrease the amount of hyperpolarization.
    - A low calcium level is a cause of something that interacts with rhodopsin kinase and guanylate cyclase in order to achieve that main goal.
- The reason the off center and on center bipolar cells have different responses to the photoreceptor cells is that they have different receptors on their surfaces.

- Hearing is the special case since the process to get to depolarization uses potassium. It is doing the of calcium normally.
    - The material from the endolymph is already extremely positive.
- Mechanoreceptors are inside of hearing system (where the hair cells have the cilia that bend and that's how they depolarize) and the pain system.
- Hair cells cannot regenerate like cells in taste and smell, which get replaced often.
- All the sensory systems use cranial nerves.
    - Hearing - Vestibulo cranial nerve
    - Vision - Optic nerve
    - Smell - Some nerve
    - Taste - 3 of them
    - Pain - Some nerve
- We don't see inhibitory networks in taste system.
- Inhibitory networks in the pain/somatosensory system through the pain gateway thing. There are inhibitory signals to the pain fibers when you rub a stubbed toe. Inhibition in vision in the case of center/surround. Inhibition in hearing in the case of MSO (idk the olive that does sound intensity differences to localize the sound). Inhibition in smell through mitral and tufted cells, which act like horizontal cells in that they modulate info.
- Olfaction and vision both use g-protein cascades. Olfaction uses cAMP while vision uses cGMP.
- Tastes can be separated into tastes that use channels vs those that use g protein coupled receptors.
- Photoreceptor cells release glutamate onto the bipolar cells (not GABA). They aren't inhibitory, but rather they are just hella hyperpolarized.
- There are a lot more outer hair cells than inner ones and they do a lot of the work associated with sound amplification.

12/12 - Review Session

- All sensory receptors adapt.
- Outer hair cells amplify sound intensity. They are cochlear amplifiers, they don't mess with the frequency. The cells move the basilar membrane which helps in the inner hair cells depolarize since the stereocilia in the inner hair cells are moving around. The outer hair cells act at very low intensities, when we can't determine the sound intensity. Basically, outer hair cells important only when sound intensity is very low.
- Stria vascularis is the component that pumps potassium into the scale media and thus the endolymph.
- Tip links are the components that physically open the receptors that they are attached to.
- Phase locked neurons are the ones that fire at certain time periods.
    - Used to determine the sound frequency. If you look at a certain neuron that is phase locked with a sound of a particular frequency, you can look at that neuron's behaviour and figure out frequency then.

- Ability to discern higher frequencies is decreased because we don't have phase locking to inform us.

Textbook Notes

Chapter 2 - Electric Signals of Nerve Cells

- Receptor potentials are due to the activation of sensory neurons by external stimuli.
    - Amplitudes will be graded by the magnitude of the sensory stimulus.
- Synaptic potentials refer to information transmission from one neuron to another.
- Axons are honestly not great electrical conductors, and so to compensate, we have action potentials.
- Amplitude of the action potential is independent of the magnitude of the current used to evoke it.
    - Intensity of stimulus is thus in the frequency of the action potentials, not the amplitude.

Chapter 9 - The Somatosensory System

- Somatic sensation begins with the nerve fibers who have cell bodies in the ganglia along the spinal cord (dorsal root ganglia for example) and who have projections to the periphery which are in charge of detecting that external stimulus. The signal will travel from the periphery through the cell body, and then up to the CNS.
    - Those neurons in the ganglia are called pseudounipolar because they have peripheral and central components that are continuous.
- Some of these fibers will have specialized receptor cells that tune the fiber to detect certain stimulations, but some will have free nerve endings, important for detecting pain.
    - Ones with encapsulated endings are more sensitive.
- The different types of fibers differ in their axon diameter size, size of the receptive field which is the area of skin over which stimulation results in a change in the rate of APs.
- Receptive fields for certain fibers are smaller when you are located in an area with a large number of those fibers.
- Afferents can be fast adapting, which is useful when conveying info about changes in ongoing stimulation. They can also be slow adapting, which is better for info about the spatial attributes of the stimulus.
- Nociceptors are another kind of afferent, and they have free nerve endings and they are sensitive to forces that elicit pain.
- These afferents can cause multiple responses to a particular stimulus and thus there are parallel pathways, each different in terms of conduction velocity, receptive field size, and types of stimulus.
- The 4 main types of afferents are Merkel, Meissner, Pacinian, and Ruffini.

    - Ruffini and Pacinian are both afferents will large receptive fields. Merkel and Meissner have smaller ones.
    - Merkel and Ruffini are both slow adapting, which Meissner and Pacinian are fast adapting.
    - Merkel cells are good with signaling the static aspect of a touch stimulus on the fingertips. Really good with spatial resolution.
    - Meissner cells are good with detecting vibration.
    - Pacinian are good with detecting large scale vibrations such as holding something in your hand.
    - Ruffini are sensitive to stretching of limbs
- Dorsal columns of the spinal cord are where the axons from the periphery project to. The columns are topographically organized such that lower limbs are more medial and in the gracile tract, upper limbs more lateral in the cuneate tract. Both tracts end in their respective nucleus.
    - Those neurons inside the nuclei then send their axons to the thalamus (specifically the VPL). Those axons are called internal arcuate fibers. They form a tract called a medial lemniscus, and then somehow at the end, the fibers representing the upper body are in medial portion of the tract, and the fibers representing the lower body are in the lateral portion.
- The neurons in the VPL send their axons to the primary and secondary somatosensory cortices.
- Neurons in the trigeminal ganglion will send info through the trigeminal nerve about sensory info from the face.
- (Pg. 205)

Chapter 10 - Pain

- Nociception is the perception of injurious stimuli.
- The nerve endings that initiate the sensation of pain are called nociceptors. They have cell bodies in the dorsal root ganglia and send axons into the periphery and into the spinal cord / brainstem.
- Axons associated with nociceptors are unmyelinated and thus conduction velocity is slow.
    - All pain falls into A-delta group which contain myelinated axons and are fast, or into the C fiber group which have unmyelinated axons and are slow.
    - All conduction of pain information is relatively slow though, compared to everything else.
- The axons that are responsive to mechanical and thermal stimuli don't discharge at a different rate when there is painful stimuli delivered.
- First pain is sharp pain and the longer lasting pain sensation is called the second pain.
    - A delta fibers responsible for first pain, and C fibers for second.
- Type 1 A delta fibers respond to intense mechanical and chemical stimulation and not as much to heat (high threshold), and vice versa for Type 2 A delta fibers.

- The C fibers are more polymodal in that they respond generally equally to all types of stimuli.
    - However, each type of C fiber nociceptor can have its preferences.
- The main group of pain receptors are transient receptor potential channels.
    - TRPV1 is the receptor that detects substances similar to capsaicin.
- The projections from the cells in the dorsal root ganglia will go to the periphery and to the spinal cord. The ones that go to the spinal cord will branch into ascending and descending collaterals, which form the dorsolateral tract of Lissauer.

Chapter 11 - The Eye

- Photoreceptors have the main job of turning light energy that reaches them into electrical signals that can be understood and analyzed by different parts of the brain.
- Retina is the innermost layer in the eye and it contains the photoreceptors.
- Light rays first pass through the cornea, the outermost layer, and then go through aqueous humor and then through the vitreous humor, 80% of the volume of the eye, and then to the retina.
- Cataracts are opacities in the lens that create dark spots in people's visions.
    - Causes a cloudiness of the lens. Cornea and lens are supposed to be clear. The opacity will interfere with the light going through the lens and reaching the retina.
- Cornea and the lens have the job of refracting light so that images are formed on the retina.
    - Lens can adjust its shape and roundness through the ciliary muscles. These dynamic changes are called accomodation.
- Macula is circular region in the center of the retina. Supports high visual acuity especially at the fovea.
- Classes of neurons in the retina: Photoreceptors (rods, cones), bipolar cells, ganglion cells, horizontal cells, amacrine cells
- The axons of the ganglion cells form the optic nerve which carries the retinal info to the rest of the CNS.
- Photoreceptors have a light sensitive photopigment which is what allows them to transduce the light energy they receive.
- The photoreceptors are in the outermost layer because the pigment epithelium have processes that surround the tips of the outer segments of the photoreceptors.
    - That pigment epithelium helps to replace the disks in the outer segments of the rods and the cones, by pinching odd clumps at the tip of the photoreceptors.
- The photoreceptors don't fire action potentials but rather they have graded potentials when no light is being shone onto them.
- The tl;dr with the hyperpolarization when light is shone is that light will cause cGMP concentration to go down which closes channels which reduces the influx of positive sodium and calcium ions, which means the efflux of potassium will be greater and thus the cell's membrane potential will get more negative or hyperpolarized.
- Cones are better for specificity while rods are better for sensitivity.

    - As illumination increases, cones become more and more dominant.
    - Rods can produce a reliable response for 1 photon of light while cones need 100 or so.
- Scotopic -> Mesopic -> Photopic vision is the vision described from rods to cones being used.
- Rods have a lot more convergence as there are many rods for every rod bipolar and a number of rod bipolars for every amacrine. However, there is a 1:1:1 ration for cones to bipolar cones to ganglion cells.
    - Convergence makes the rods a better detector of light because small responses to single photons can be aggregated into one big signal, but it also reduces the resolution because you don't exactly know what location a response came from.
- The fovea has a large density of cone cells.
- We can perceive color because our photoreceptors respond differently to different wavelengths of light.
    - Cones each have different photopigments which allows them to be differently sensitive to light of different wavelengths.
- Color vision issues generally come from failure to make one of the cone pigments. This could depend on the genes that code for these pigments and if there was a mutation in that gene for the individual. For example, there could be an alteration in the M or L cone pigment as a result of chromosomal crossing.
- There are two classes of ganglion cells, on-center and off-center. Same with bipolar cells.
    - Main difference between the two is that bipolar cells have graded potentials, and ganglion cells have APs.
- The ganglion cells have to be able to accomodate for the changes in the luminosity of the environment as the eye is looking at different objects.
- The firing rate of an RGC is dependent not only on the light intensity of the objects in the visual field, but also on the luminance conditions in the environment.

Chapter 12 Central Visual Pathways

- Axons from ganglion cells project through the optic nerve and go to the optic chiasm. Some of the fibers cross and some don’t in a process called decussation. Axons on each side form the optic tract, which thus contains fibers from both eyes. This allows info from the two retinas to be processed by the same cortical site. After the chiasm, the next target is the LGN of the thalamus, and then the signal goes to the cerebral cortex, like a lot of other pathways in the thalamus.
    - The map of the hemifield established in the LGN to maintained in the projections to the cortex.
- After the chiasm, some axons can project to the pretectum instead of the LGN, and this is the part of the brain that handles the pupillary light reflex. In order for that reflex to occur there are connections with the Edinger-Westphal nucleus and they terminate in the

ciliary ganglion whose neurons innervate the ciliary muscles in the iris which decreases the diameter of the pupil.

- There are lots of types of ganglion cells and they differ in their pattern of projection to central visual targets.
- These ganglion cells have their own light sensitive photopigment called melanopsin and they can modulate response without signal from rods or cones.
- Due to the way images are inverted, objects in the temporal part of the visual field are seen by the nasal part of the retina. Same with superior and inferior.
- The left visual field can be seen by the nasal retina of the left eye and the temporal retina of the right eye.
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- Filter properties of neurons are dependent on orientation preference and direction of stimulus motion.
- Visual cortex has spiny and aspinous neurons. The pyramidal spiny neurons are the source of axonal projections that leave the cortex. The smooth ones are responsible for cortical inhibition.
- Cortex divided into 6 layers.
    - Inputs from the LGN terminate in the 4C and 4A layers. You can have neurons in 4C that project to 4B and to 2/3. Some neurons in 2/3 will project and terminate in 5.
- The axons that terminate in 4C contain the main information from the LGN.
- Inside the cortex, there are columns of neurons that have similar receptive field properties, responding to the same types of stimulation.
    - The adjacent columns have significant overlap. The overlap can be in the location of the receptive field they respond to or also the orientation.
- Most of the neurons in this cortex are binocular, in that they're responding to stimulation of both left and right eye. The axons from the LGN will initially terminate in eye specific ocular dominance columns in layer 4, but then the signals converge.
- The LGN, like the V1, also has layers. The first 2 are magno layers and the last 4 are parvo layers. They get input from different types of RGCs. Depending on what type of layer you're in, the neuron will project to different parts of the 4C layer in V1.

Chapter 13 - The Auditory System

- Sound is the pressure waves generated by vibrating air molecules.
    - Those sound waves have characteristics like waveform, phase, amplitude (loudness), and frequency (pitch).
- Humans can hear in the range of 20 Hz to 20kHz.
- The primary auditory cortex, which is also organized tonotopically, supports basic auditory functions, such as frequency discrimination and sound localization.
- Auditory system transforms the sounds into patterns of neural activity, and then integrated with the signals from the other senses.

- In the middle and outer ears, the waves are collected and are amplified in order to be transmitted to the cochlea. In the inner ear, the characteristics are transduced by the hair cells and encoded through electrical activity of the nerve fibers.
- As this decomposition occurs, we notice tonotopy in that sound frequency is handled at different areas in the cochlea.
- Focus of the external ear (pinna, concha, auditory meatus) is to gather sound energy and focus it on the eardrum/tympanic membrane, specifically we amplify sounds in the 2-5 Hz range. It also has the function of filtering different sound frequencies to determine the elevation of the sound source.
- Job of the middle ear is to match low impedance airborne sounds to higher impedance fluid of the inner ear. Pressure is boosted at the tympanic membrane in order to make sure the sound doesn't reflect as it moves toward the fluid. Pressure increase created by directing the sound onto smaller oval window and ossicles create mechanical advantage as well.
- Inner ear is where the transduction happens, specifically the cochlea. It has the job of amplifying sound, converting into neural signals, and decomposes wave forms into their simpler components.
- Different parts of the basilar membrane will respond (specifically the hair cells are the ones that respond) most intensely to a particular frequency.
    - Points for high frequency are at the base of the membrane, low frequency is closer to the apex.
    - The distance that the wave will travel along the unrolled cochlea/membrane will depend on its frequency.
    - The hair cells are the ones that are sensitive to the frequency.
- The traveling wave that gets created by the sound and passes through the cochlea is what displaces the hair cells that are in between the basilar membrane (on the bottom) and the tectorial membrane (on the top). Movement of the tectorial membrane bends the stereocilia on the hair cells and leads to voltage changes.
- When a hair bundle is deflected toward the tallest stereocilium, then K+ channels open and the cell depolarizes, causing calcium to come in, and the release of NTs.
    - If it bends in the opposite direction, then hyperpolarization occurs.
- Inner hair cells work to detect and transmit sound while outer hair cells specifically contribute to amplification.
- When you're inside of the cochlea it's coiled up into 3 different compartments, scala vestibuli, scala tympani, and scala media. First two are filled with perilymph and last one is filled with endolymph that is more positive.
    - The apical end of the hair cells is exposed to the endolymph and the basal end is exposed to the perilymph.
- Phase locking occurs when you have a particular wave as input and the responses to that wave are locked on the particular phase that the wave was at when the first response was made.
- Those hair cells then synapse with spiral ganglion cells and they move through an auditory nerve to branch to 3 divisions in the cochlear nucleus (anteroventral,

posteroventral, dorsal). The targets of the neurons in those cochlear nuclei include the superior olivary complex, then the nuclei of the lateral lemniscus, then inferior colliculus, and then MGN of thalamus and then finally the auditory cortex.

- For frequencies below 3 kHz, we are able to perform sound localization by using interaural time differences. The medial superior olive is the component that computes these differences. It has cells with bipolar dendrites and they get inputs from the left and right anteroventral cochlear nucleus, and the MSO works by detecting whether the excitatory signals arrive from both sides at the same time. This relies on the fact that phase locking works at low frequencies.
- For frequencies higher than 2 kHz, one side of the head gets most of the sound and the other gets a “shadow” form with less intensity. This difference is intensity tells us about the location of the sound. The lateral superior olive is the component that figures this out. LSO will get excitatory info from one side and inhibitory from the other.
- MSO computes the location of a sound by interaural time differences. LSO does so through interaural intensity differences. MSO does it for lower frequencies and LSO does it for higher frequencies.

Chapter 15 - The Chemical Senses

Olfactory System

- Olfactory system processes info about the identify and concentration of airborne stimuli called odorants.
- The odorants first interact with the olfactory receptor neurons in the olfactory epithelial sheet. Those neurons have olfactory cilia that come down into the mucus area. The odor molecules bind to the receptor proteins on the cilia and the signal goes from the cilia through the neuron and the axons project up to the olfactory nerve and then to the neurons in the olfactory bulb. The nerve passes through the cribriform plate. The signals then travel through axons from neurons in the bulb through the olfactory tract straight to the pyriform cortex, bypassing the thalamus.
- Greater smelling ability from other animals can be explained by the number of olfactory receptor neurons and the odorant receptor proteins.
- Anosmias are defects where someone can't smell a particular odor because of the inactivation of a type of receptor gene.
- Mucus is produced by Bowman’s glands in the olfactory epithelium, and it helps trap and remove harmful agents.
- The mucus layer and the surrounding helper cells is called the nasal mucosa.
- The olfactory neurons, and specifically the cilia are subjected to dangerous outside stimuli and thus there is a cycle of generation and degeneration. This is controlled by a population of neural stem cells in the olfactory epithelium.
    - They are the only neurons with long axons that are regenerated.
- Odorants that are exposed to the cilia create a stronger electrical response than those exposed to the cell body since the cilia have a larger cellular surface for the odorants to bind to.

- The receptors that are on the cilia on the olfactory neurons are G-protein coupled ones.
- There are 950 different odorant receptor genes, thus indicating a large number of types of receptor proteins.
- Most of the olfactory neurons express only one type of odorant receptor gene.
- When an odorant binds to a receptor on the cilia, this causes the alpha subunit in the G_olf protein to dissociate, and that activates ACIII protein which causes an increase in cAMP (the output of that protein) which opens channels that allow sodium and potassium to flow in which depolarizes the neuron. Once the calcium levels are high enough, there is an exchanger that extrudes calcium and transports sodium in order to repolarize the membrane.
    - Both of the proteins are in the knob and the cilia which is where the transduction of the stimuli takes place.
- Individual ORNs are sensitive to subsets of stimuli, it just depends on the expression of the different receptor genes in each of the neurons.
- Glomeruli are spheres inside of the olfactory bulb and they are the target of the axons of the ORNs. Each glomerulus receives input from olfactory neurons expressing particular receptor protein. Within the glomeruli, you'll find the dendrites of mitral cells that are the projection neurons of the bulb. The axons of the ORNs synapse with the dendrites of the mitral cells and there is a large degree of convergence (lots of axons of ORNs for every mitral cell). The mitral cell axons in each of the bulbs (each of them contains a bunch of glomeruli) forms a bundle called the lateral olfactory tract that projects to the accessory olfactory nuclei, and I assume that info goes to the pyriform cortex.
- Tufted cells and periglomerular cells also help to sharpen the sensitivity of the glomeruli.
- Granule cells synapse with the basal dendrites of the mitral cells and they establish local inhibitory circuits with the mitral cells.
- Individual glomeruli respond specifically to distinct odorants.

Gustatory System

- Food molecules interact with the receptor proteins on taste cells located on taste buds. Those cells synapse with the primary axons from 3 cranial nerves and they project to the gustatory nucleus. Axons from gustatory part of the solitary nucleus project to the ventral posterior medial nucleus which is in the thalamus. The signal then goes up to the insular and frontal taste cortices.
- Taste buds are distributed along the surfaces of taste papillae.
- Taste cells also have the degeneration and regeneration property because they are directly exposed to external stimulus.
- Important note that these taste receptor cells are not neurons.
- 3 types of papillae:
    - Fungiform - Highest density at the tip of the tongue, mushroom structure
    - Circumvallate
    - Foliate.
- Lowest concentration of stimuli required to detect taste by single papillae - threshold concentration
- Taste system categorizes into salt, sour, sweet, bitter, and umami.

- Different regions of the tongue have different thresholds for various tastes.
- Sour and bitter tastes are least sensitive at the tip, while sweet and umami and salty are most sensitive.
- Tasting salt involves amiloride sensitive channels and sour involves H+ sensitive channels.
- Sweet involves T1R2 and T1R3 G-protein coupled receptors.
- Bitter and Umami both involve the same downstream process of PCLB2 -> IP3 -> TRPM5 but bitter has a T2R receptor, while umami has a T1R1 and T1R3.
- One taste receptor cell can have multiple taste receptor proteins/channels on it, allowing it to identify different types of tastes.

Chapter 16 - Lower Motor Neuron Circuits and Motor Control

- Lower motor neurons directly innervate skeletal muscles.
    - The neurons are controlled by local circuits in the spinal cord and brainstem, and the upper motor neurons are what influence the local circuits.
- Lower motor neurons are the final pathway for a variety of sources (upper motor neurons, sensory neurons, etc) to the skeletal muscles.
- Lower motor neurons send their axons out of the brainstem and to the skeletal muscles in the head and the body.
    - The local circuit neurons are what provide the synaptic input to the LMNs.
- Upper motor neurons are in the brainstem or cerebral cortex and they have axons that synapse with the local circuit neurons.
- The cerebellum has efferent pathways to the upper motor neurons.
- Basal ganglia prime the upper motor neurons for initiation of movements.
- Gamma motor neurons regulate sensory input by setting the intrafusal muscle fibers to appropriate lengths, and alpha motor neurons innervate the extrafusal muscle fibers which are the fibers that actually create the forces needed for movement.
- Most muscle fibers are only innervated by a single motor neuron.
- Small α motor neurons innervate relatively few muscle fibers and form motor units that generate small forces.
- Types of motor units
    - Slow motor units - Important for activities that require sustained muscular contraction. Often the neurons have lower thresholds for activation.
    - Fast fatigable motor units - Larger alpha motor neurons and they are responsible for running and jumping.
    - Fast fatigue resistant motor units - Intermediate size neurons. Generate twice the force as small unit, but also more resistant to fatigue.
- The large motor units have more muscle fibers that get innervated per motor neuron.
- If you increase/decrease the number of active motor units, you can control the amount of force produced by a muscle.
- Reflexes often entail a sensory response to a muscle stretch. That response sends a signal to the motor neuron that innervates the muscle that has been stretched.

    - That sensory signal originates in the muscle spindles.
- The muscle spindles comprise of 8-10 intrafusal fibers.
- The fibers have 1a afferent neuron axons wrapped around them and they have mechanosensitive receptors that are able to detect the stretches in the fibers and fire action potentials afterward.
- Reciprocal innervation is when you have interneurons that form inhibitory connections with the alpha motor neurons in the spinal cord.
- Stretch of muscle -> stimulate 1a afferents -> innervate muscle spindles -> signal travels to alpha motor neuron -> response back
- Gamma motor neurons are the ones that control the excitability of the muscle spindles which affects how much the afferents can affect them. They synapse on the end of the spindles and can make them contract.
    - In other words, they regulate the gain of the stretch reflex by adjusting the level of tension in the intrafusal muscle fibers.
        - High gain means that a change in the tension of the IF fibers will cause a large change in number of alpha motor neurons affected and the amount of contraction for the EF fibers.
    - They basically make sure that as the length of the muscle changes as a result of the contractions/lengthenings of the extrafusal fibers, the tension in the muscle spindles also changes so that there is no decrease in 1a afferent firings.
        - Specifically, we can talk about the case where the muscle contracts and elongates. When it elongates, then the fibers stretch and you get a lot of firing from the 1a afferents. However, when it contracts, then you would think there would be no firing, but the muscle spindles detect the deviations from the desired length, and the gamma motor neurons fire and cause the contraction of the IF fibers.
- Each Golgi tendon organ is innervated by a single 1b sensory axon. These organs are in series with the extrafusal fibers.
- Golgi tendon organs are sensitive to increases in muscle tension that arises from muscle contraction but they are not very sensitive to passive stretch.
    - When there is some sort of passive muscle stretch, the 1a afferents are the ones that fire frequently, the 1b afferents are a lot less (since the fibers can stretch more than the tendon can).
    - However, when a muscle is contracted, the difference is that the EF fibers are contracting, thus causing slack in the IF fibers and thus 1a afferents don't fire as much. However, the rate of firing from the 1b afferents increases and is in contact with an inhibitory local circuit that innervates the same muscle and decreases the muscle tension after the initial contraction.
- Golgi tendon system sends inhibitory signals to its AMNs and it is a negative feedback system that regulates muscle tension.
- Muscle spindle system monitors muscle length while the Golgi tendon system monitors muscle force.

- Flexion reflex associated with painful stimulus and also involves withdrawal of the limb and opposite reaction on the contralateral limb.
- Local circuit neurons have central pattern generators that are capable of controlling the timing and coordination of complex movement. The local circuits don't just deal with the reflexes.
    - Specifically, these cpgs are circuits.
- Each limb seems to have central pattern generators that are responsible for the limb's movement during locomotion.
- We can show that the movement is not dependent on sensory input or input from higher level brain areas. The cfg itself is responsible for the alternating of the flexion and extension of the limb.

Chapter 17 - Upper Motor Neuron Control of the Brainstem

- UMNs in the cerebral cortex are involved in planning and initiation of complex movements.
    - Their axons go down either the corticospinal tract (goes from cortex to spinal cord) or the corticobulbar tract (goes from cortex to brainstem).
- Facial movements that can be performed unilaterally are governed by the contralateral motor cortex.
- Lateral corticospinal tract forms pathway from cortex to lateral portions of the ventral horn and they mostly synapse onto local circuit neurons, but some go directly to alpha motor neurons.
- Scientists found the organization of the motor cortex by looking at the location of muscle contractions and the site of electrical stimulation on the cortex.
- There are also local circuits in the cortex and the spinal cord and that helps neurons communicate in order to do complex movements.
- For certain types and directions of movement, certain neurons had unique firing rates before the actual motion.
    - Neurons show less activity if the direction of the movement of the hand differs from the neuron's preferred direction.
- Spike triggered averaging allows us to look at the influence of a single neuron on a population of lower motor neurons.
- Mirror motor neurons are those that fire APs when the object observes another person doing an action that would activate those neurons if the subject was doing it themselves.
- UMNs in the cortex can send signals to muscles by sending them directly to interneurons in the spinal cord, or can send info to the brainstem that then project to the spinal cord.
    - Direction projections provide the speed and the agility in movements.
- Reticular - feedforward and vestibular - feedback? TODO

Chapter 18 - Modulation of Movement by Basal Ganglia

- Basal ganglia and cerebellum don't influence the lower motor neurons, these two structures regulate the UMNs in the cortex.

- As a whole, basal ganglia refers to a set of important nuclei within the cerebral hemispheres. In general, these help modulate the movements of the body by communicating with the UMNs.
- The main structures in the basal ganglia are the caudate and putamen (collectively the striatum), the globus pallidus, the substantia nigra, and the subthalamic nucleus.
- The striatum is basically the input zone for the basal ganglia since the neurons here are how inputs get into the basal ganglia. The neurons in particular are medium spiny neurons. Those neurons then send info to the globus pallidus and the substantia nigra pars reticulata, which act as the outputs of the basal ganglia. The neurons in the globus pallidus go to the thalamus which goes to the cortex. The neurons in the substantia nigra pars reticulata go to the superior colliculus (center that commands head and eye movements). Those neurons are inhibitory to the superior colliculus.
    - The thalamus serves as kind of a relay point between the globus pallidus and the UMNs.
    - On average, more than 100 medium spiny neurons for one neuron in the globus pallidus, so there's lots of convergence.
- The cerebral cortex is the biggest source of the inputs to those medium spiny neurons in the striatum. This is the corticostriatal pathway.
- Medium spiny neurons rate of firing increases before movement, and they also increase at the termination of a movement sequence.
- In normal cases, after the signal travels through the pathways, the thalamic neurons will get disinhibited and can trigger activation of the UMNs in the cortex.
- Direct pathway in the basal ganglia basically goes from the motor/cerebral cortex to medium spiny neurons in the striatum, to globus pallidus, to thalamus, to frontal cortex.
- In the indirect pathway, there are some medium spiny neurons in the striatum (so same input from cortex to striatum) that project to the external segment of the globus pallidus, which tend communicates with the subthalamic nucleus (which also gets a positive influence from the cortex), which positively interacts with the globus pallidus internal segment.
    - Also in the indirect, you have dopaminergic inputs from the substantia nigra pars compacta to the striatum, and those inputs are inhibitory (contrast that with the normal inputs from the cortex which are excitatory).
- The indirect pathway antagonizes the activity of the direct pathway.
    - Indirect pathway normally increases the inhibitory influences of the basal ganglia, while the direct pathway does the opposite.
    - From a high level, they are in charge of making sure there are no unwanted movements.
- The big difference between direct and indirect is for a set of excitatory signals coming in from the cortex, direct pathway will end up disinhibiting the thalamus (more output activity to cortex) and the indirect one will inhibit the thalamus (more inhibitory output).
    - Direct: Cortex -> Striatum -> GPi -> thalamus
    - Indirect: Cortex -> Striatum -> GPe -> subthalamic nucleus -> GPi -> thalamus

- All the neurons in the striatum and the globus pallidus (internal and external segments) act inhibitory.
- Neurons in the striatum either have a D1 or D2 receptor. D1 receptors are excitatory and D2 ones are inhibitory. So if dopamine binds to a neuron with a D2 receptor, the neuron activity in the striatum is going to go down (therefore not as much inhibition of GPe -> disinhibition for subthalamic nucleus -> activity in GPi -> inhibition in thalamus).
- Release of dopamine in the striatum increases the responsiveness of the direct pathway to corticostriatal input (a D1 effect) while decreasing the responsiveness of the indirect pathway (a D2 effect).
    - Parkinson's disease causes the loss of nigrostriatal dopaminergic neurons, so there are going to be less of those effects and so there is going to be more inhibitory output from the basal ganglia.
- Huntington's disease is where there is degeneration of the spiny neurons that communicate with the globus pallidus external. The result is that there is less inhibition of GPe, which means less activity in the subthalamic nucleus which means less activity in the GPi, and less inhibition (more activity) of the thalamus and thus the UMNs are more likely to fire, in cases where the basal ganglia should've stopped it.

Chapter 19 - Modulation of Movement by Cerebellum

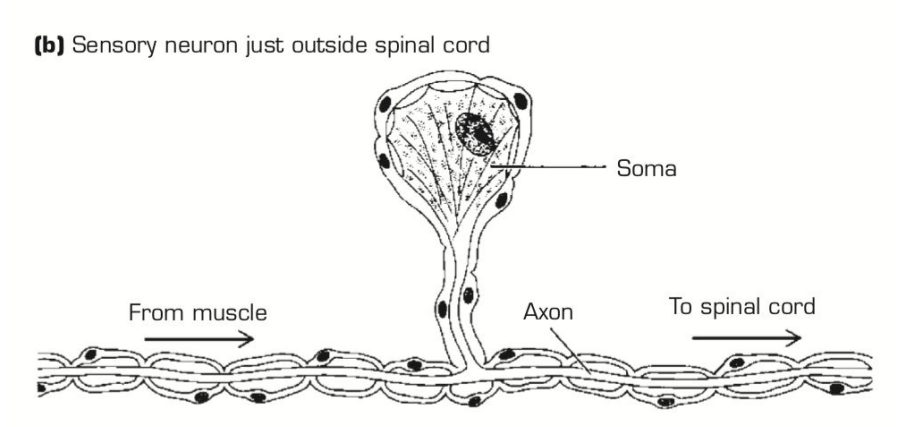
- Cerebellum also works by modulating the activity of UMNs, and the high level focus is to detect the difference between an intended movement and the actual movement.
- Cerebellum divided into 3 parts.
    - Spinocerebellum - Receives input from the spinal cord. As you go to the sides, you get more input from the distal muscles. The vermis is the most medial strip and that is concerned with the proximal muscles.
    - Cerebrocerebellum - Largest area and receives input from the cerebral cortex. Concerned with the regulation of highly skilled movements. Inputs go through the middle cerebellar peduncle.
    - Vestibulocerebellum - Receives input from the vestibular nuclei in the brainstem and deals with regulation of movements that maintain posture and equilibrium.
- Main ways that cerebellum communicate with other parts of the brain is through cerebellar peduncles.
    - Superior cerebellar peduncle is where the efferent neurons are (located in the deep cerebellar nuclei) and where axons project to motor nuclei of the thalamus and to some UMNs.
    - Middle cerebellar peduncle is afferent pathway to the cerebellum.
    - Inferior cerebellar peduncle contains both pathways, mainly to and from the vestibular nuclei.
- Cerebellum gets input from pontine nuclei and inferior olive nuclei.
- The destination of a lot of afferent pathways are Purkinje cells.
- Axons from the pontine nuclei are called mossy fibers and they synapse onto granule cells, and they synapse with the Purkinje cells.

- Mossy fiber -> granule cells -> parallel fiber -> Purkinje cell -> Deep cerebellar nuclear cell
- Climbing fiber -> wrap around Purkinje cell -> Deep cerebellar nuclear cell
- Climbing fibers come from the inferior olive neurons, coming through inferior peduncle.

Cellular Physiology of Nerve + Muscle Notes

Chapter 1 - Origin of Electrical Membrane Potential

- The patellar reflex is known as the knee jerk reflex.
- When the tendon is tapped, sensory neurons sense the stretch of the muscle and send signals to the spinal cord, which is received by the motor neurons, which send a signal back down telling the quad muscle to contract.
- Sensory stimulus -> signal transmitted -> sensory pathway carries info into nervous system (afferent pathway) -> motor output (efferent pathway)
- Cell body is the soma.
- Dendrites are the ones that receive signal from other neurons.
- Axon transmits signals over long distances.
- Structure of motor neuron and sensory neuron is a little different.
- Sensory neurons don't really have dendrites, they get the signal at the peripheral end of their axon.



- The electrical signals that neurons send arise from the changes in electrical voltage difference across the cell membrane (membrane potential).
- Intracellular microelectrodes are placed inside the nerve fiber to measure the difference between the intra and extracellular space.
- Membrane potential always inside with respect to the outside.
    - If membrane potential is negative, then the inside is more negative than the outside.

- Action potential is the jump is the signal that gets created from the jump in membrane potential.
- Synapse is where the signals from one neuron are transmitted to another.
- Chemical synapses are where the action potential causes the cell to release a chemical substance like a neurotransmitter to the other cell.
    - Those chemicals then diffuse across and change the membrane potential for the target cell.

Chapter 2 - Composition of Intracellular and Extracellular Fluids

- Water molecules make up 99% of all molecules in the body.
    - 55% of water is in cells, and the rest is outside.
- ECF is plasma, lymphatic fluid, and interstitial fluid.
- Compositions of ICF and ECF

Table 2-1 Simplified compositions of intracellular and extracellular fluids for a typical mammalian cell.

	Internal concentration (m*M*)	**External concentration (m*M*)**	**Can it cross plasma membrane?**
K^+	125	5	Y
Na^+	12	120	N*
Cl^-	5	125	Y
A^-	108	0	N
H_2O	55,000	55,000	Y

- Inside of the cell is almost always more negative than the outside. The resting membrane potential is about 60 - 100 millivolts.
- Small and nonpolar molecules can generally cross the plasma membrane.
- In the membrane, about ⅓ of the material is lipid and the rest is protein.
- A lot of genes code for membrane proteins.
- Freeze fracture electron microscopy allows you to visualize the protein molecules in the membrane.
    - Tissue is frozen in liquid nitrogen, sliver is shaved with knife, outside side is E face (external) and inside is P face (protoplasmic). Some proteins stay on one side and some on the other. The other proteins will look like bumps in the surface.

Chapter 4 - Membrane Potential: Ionic Equilibrium

- For charged particles, whether they will pass through the membrane will depend on both the concentration gradients as well as the electrical potential across the membrane.
    - Basically both diffusional and electrical forces are affecting that movement.

- Diffusion potential is the potential difference across a membrane generated by the difference in the concentrations of the ions. Can only be generated if the membrane is permeable to that ion.
    - When the concentrations are the same, that's when no diffusion potential is created and so there's no force that is pushing the ions in either direction.
- Voltage can also be called the electromotive force, which represents how the voltage is the driving force for the movement of charges.
- Electric potentials are recorded when you have one ion that crosses to the other side, leaving behind the counter ion.
- Equilibrium for an ion dependent on concentrational and electrical forces.
- Nernst equation allows you to calculate the equilibrium potential for an ion, depending on its charge and its concentrations inside and outside of the cell.
    - Nernst equation only applies to 1 ion at a time.
- Macroscopic electroneutrality says that the concentration of cations and anions in a compartment must be the same.
- Donnan equilibrium shows the conditions that must be met in order for two ions to be able to cross the cell membrane at the same time at equilibrium. Basically it means that their equilibrium potentials must be the same, and thus the concentrations are basically the only thing that you can control.

$$[K^+]_o[Cl^-]_o = [K^+]_i[Cl^-]_i$$

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- Real animal cells are not at equilibrium most of the time and must expend metabolic energy to maintain certain concentrations of ions through pumps.
    - The resting potential is thus called a steady state potential because energy is being used to keep the concentration gradients at certain values, and purposefully not at equilibrium for the given ions.
- Sodium pumps will remove sodium out of the cell against both the concentrational and electrical gradients.

Chapter 5 - Membrane Potential: Ionic Steady State

- The factors that determine the membrane resting potential are the ion concentrations at the beginning and the relative ion permeabilities.
- The permeability is determined by the ionic properties of the pores/channels.
- The Goldman equation is the extension of the Nernst one, but it just takes into account the concentrations and permeabilities of all the ions involved.
- The influx of sodium into the cell means that there is a movement of charge which means that there is a current. When the currents caused by inflow of sodium and outflow of potassium, then there is net current of zero, and voltage will be constant.
- The driving force, or the difference between the current membrane potential and the equilibrium potential of the ion, determines the magnitude of the current that flows.

- Membrane conductance is an index of the ability of that ion to carry current across the membrane.
    - The higher the conductance, the greater the current for a given driving force.

$$i_K = g_K(E_m - E_K)$$

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    - Single channel current will depend on the single channel conductance and the driving force.
- Membrane conductance to an ion is heavily correlated with the membrane permeability to that ion.
    - The current itself is dependent on concentration and permeability.

Chapter 6 - Generation of Nerve Action Potential

- The ionic permeability to certain ions can vary. This will eventually change the overall membrane potential (because of the Goldman equation).
- An increase in sodium permeability for example will cause E_m to increase greatly and become closer to E_Na as opposed to being closer to E_K.
    - In order to increase the permeability, more channels have to be open to letting sodium through.
    - As the membrane becomes more depolarized, the number of open channels increases, which creates an exponential effect.
- On the other hand, there is still outward potassium current that could stop the exponential growth. However, the depolarization has to be large enough to produce a net inward membrane current. Basically, it has to reach the threshold potential.
- Factors that influence the value of the threshold are the density of sodium channels, and the strength of the connection between depolarization and opening of those channels.
- Sodium channel inactivation is what causes the eventual repolarization of the membrane.
- (Page 69)