Intro. To Neuroscience

Chapter 1- Cells of the NS

- Oligodendrocytes- create myelin in the CNS
- Microglia- immune cells of the CNS
- Neurons
- Astrocytes-acts as a buffer and maintains neurons
- Ependymal cells- lines the ventricles and circulates the CSF
    - Choroid plexus creates the CSF from blood
- Neurons
    - Dendrites branch
        - Covered with dendritic spines
        - Contain NT receptors
            - Postsynapse
        - Presynaptic region of neuron is the region before the synapse
        - Turn chemical into electrical
    - Synaptic cleft
        - Area between neurons
        - NT diffuse through this region
        - Can be chemical or electrical synapses
    - Info goes chemical-electrical-chemical ect
    - Pass info to the cell body, then to the hillock, then to the axon
- Cell body
    - Contains all the organelles
    - Has to have general functions
    - Has specialty functions
    - Structure is different
        - MT, microfilaments, neurofilaments for structure

        - Arranged in particular ways for shaping
- Axon hillock
    - Cone shaped
    - Beginning of the axon
    - Neurofilaments and microtubules are packed more tightly into the axon
    - Feeds into the initial segment of the axon
    - Acts as a computer to decide whether or not the signal is enough to generate the AP (integration)
- Axon
    - AP propagation
    - All three structural parts present
    - Move from cell body to terminals
    - Can be covered in myelin
    - Variety of sizes and shapes
    - Microfilaments usually associated with the plasma membrane
    - Microfilaments most dense at nodes of ranvier
        - Gaps in the myelin
- Myelin
    - covering of the axons
- need to be able to transport from cell body to axon without having the signal go away
    - anterograde-towards synapse
        - often used to move things like NT's from the cell body to axon
    - retrograde-from synapse to cell body
- Neuron can sense the outside environment
    - Nerve growth factors
    - Chemical way to tell nerve that connection is still strong
    - Brought up to the cell body
- Axon terminal

- Has a concentration of synaptic vesicles containing NT's
- Can have multiple NT per vesicle
- Calcium buffering plays a role in NT release
- The vesicles fuse with the presynaptic membrane and releases the NT's
- Diffusion of chemicals takes time
    - Slower than electrical but large benefits in terms of modulation
- NT's bind to ligand gated receptors on the post synaptic membrane
    - Many times it takes multiple NT's to bind to open the channel

- Glial cells
    - Most common is the astrocyte
    - 10x more glial cells than neurons
- Astrocyte
    - Diversity of functions
        - Support
        - Buffers the ions
        - Make up the BBB
        - Produce metabolites such as pyruvate and lactate + glucose
        - Antioxidant protection provided to neurons
            - Gsh and sod
        - Protect neurons from oxidative stress
- Gliotransmitters
    - Released directly from astrocyte and affect neurons
    - Similar to NT's
    - Don't produce an AP, but under certain circumstances they can release them
- Endothelial cells
    - Make up the capillaries in the brain
    - Tight junctions between them

    - Components of the blood cant easily move out
    - This protects the brain
    - Astrocytes help form an additional layer
- Oligodendrocytes
    - CNS myelin
        - Schwann cells in the PNS
    - Myelin speeds up transmission
    - Difference in myelin in CNS vs PNS
        - Oligodendrocyte in CNS myelinates multiple axons
        - Schwann cell only myelinates one internode
    - Larger impact to losing an oligodendrocyte
- Perinodal astrocytes
    - Astrocytes found near the nodes of ranvier
    - Help buffer ion concentration
    - Make contact with the neurons
    - High concentration of ion channels
- Microglial cells
    - Immune cells of the CNS
    - Monocyte precursors that come from blood cells
    - Rest if no issues
    - Signals (ATP) tell microglia to move to site of infection/dead cells
    - Cause inflammatory response
    - Act as macrophages when fully activated
- Ependymal cells
    - Fluid filled spaces of the brain filled with CSF
    - Lines the ventricles of the brain
    - Specialized choroid plexus cells filter the CSF from the blood

Chapter 2- signaling

- Negative membrane potential of -60-70 mv
    - Inside negative relative to outside
    - The membrane acts as a capacitor to separate the charges
- Membrane potential changes in response to signals
    - Can depolarize or hyper-polarize
- Synaptic potential
    - Arises from NT released at synapse by the presynaptic cell
- AP
    - Large all or none response that conveys info and can lead to the generation of more AP's down the line
- Depolarize a neuron with no channels
    - The current is passive, no leakage
- Add channels (leak currents)
    - The voltage leaks out, and when shut off, returns back in
- Transporters
    - Require some form of energy to bring an ion or molecule against its gradient
    - Slower than channels
- Channels
    - Allow ions to diffuse down a gradient
    - Cause selective permeability to certain ions
    - Diffusion
- Ions flow to try and reestablish equilibrium
- Nernst equation shows equilibrium of one ion
    - Ex= (58/z)log(x2/x1)
    - X2= outside the cell concentration
    - X1= inside of cell concentration

- Na permeability increased during the rising phase of the AP, and falls during the repolarization phase
- Goldman's equation gives the membrane potential with multiple ions
    - Vm= 58 log (ion concentrations)
    - Negative ions= inside/outside
    - Positive ions= outside/inside
- Hotchkins and kats
    - Discovered the role of Na and K in the AP
- The permeability of the cell to Na goes up a bit during the AP
    - If you lower the surrounding Na, you get a lower AP peak
- AP peak is always the same height, as long as the ion levels are held constant

Chapter 3-voltage dependence

- Permeabilities are voltage sensitive
    - Inject voltage, can create an AP
- When the cell was clamped at 0 and depolarized, two currents were seen
    - An early inward current (shorter)
    - A later outward current
- The early inward current (Na)
    - Increases in magnitude until about 0 mv, then reverses to an outward current at +55mv
- Late current (K)
    - Continually increased and did not reverse
- Graph: the inward current is shown below the x axis, and the outward is above the x axis
- Early current depends on Na
    - Remove Na from outside the cell, get no inward current
    - Still get the outward current
    - Same if Na channels blocked by TTX

- Late outward current
    - Block the K channels with TEA, don't get the outward current
    - Still get the inward current
- Conductance=the reciprocal of RESISTANCE
    - Tells us if something can move across a membrane, while current tells us if it IS moving across
- Measure current
    - I=g(Vm-Ex)
    - Current=conductance X driving force
    - Inverse relationship if current stays constant
- Na conductance
    - Quick spike but quickly goes back to baseline
    - Due to their quick inactivation
- K conductance
    - Doesn't inactivate, plateaus
- Conductances are voltage dependent
- AP model
    - Resting potential, no conductance in the voltage gated channels
    - Depolarization opens channels, creating conductance, and ions flow according to their driving force
    - Then the Na channels inactivate (ball and chain mechanism)
    - Slow K to close, undershoot=hyperpolarization
- Refractory periods
    - Absolute
        - Due to Na inactivation, unable to fire another AP
    - Relative
        - Due to hyperpolarization
        - Also due to some Na channels going from inactivated to closed position

        - Only fire a suprathreshold stimulus
- AP's are generated in passive flow
    - Will decrease in amplitude the further it travels
    - Must be above threshold (-55) by the time it reaches the next group of voltage gated channels (nodes of ranvier or axon hillock)
    - Can determine this by the length constant
- Active flow
    - The flow of ions through channels
    - Reestablishes this depolarization
    - NO ATP REQUIRED
- The larger amplitude is a safety factor to make sure that the voltage is above threshold
- Speed of the AP
    - Larger axon is faster
    - Myelination is faster
        - Less leaking and an increase in capacitance (charges are separated)
        - Large energy cost, so must be used in beneficial places

Chapter 4- channels

- Voltage clamp-full cell
- Patch clamp-individual channels
- Individual currents are microscopic
    - 1-2 pa
    - Similar characteristics to the whole cell when summed together
    - Still have reversal at the Eq potential
    - Individual channels have random, stochastic, behavior
    - Only a probability up to .8 that an Na channel will open
    - Similar probability that it will inactivate
    - K only goes to .6

- Ca activated K channel
    - Calcium binds to open the channel and let K out
- 2nd messenger channels
- Toxins
    - Alpha toxin
        - Longer AP because more Na comes into the cell
    - Beta toxin
        - Lowers the membrane potential when channels open up
- Transporters
    - Active transporters use ATP directly
    - Secondary active transporters use energy, but not directly ATP
        - Use the concentration gradient of one molecule to move another molecule against its gradient
- Na/K pump
    - Depends on ATP
    - Critical role in reestablishing ion concentrations
    - Removes 1 net + charge
        - 3 Na in
        - 2 K out
    - Doesn't have a large effect on membrane voltage
        - Except in smaller neurons
- Small neurons
    - Exhibit a train
        - Have a prolonged hyperpolarization after AP
- Inhibit the Na/K pump with ouabain
    - Used to treat CHF
    - Na decreased outside the cell
        - More Ca comes into the cell, more forceful contractions

- Time constant= membrane resistance X capacitance
    - T=RmCm
    - How fast a neuron reacts to depolarization
- Length constant-how far it travels
    - Length constant = Squ root (dRm/4Ri)
- The amount of Na ions flowing into the cell is higher during the repolarization phase
    - **The current is at its peak during this time**
    - This is due to a lower conductance yet a much higher driving force

MS

- MS diagnosis
    - More than one lesion on the brain or spinal cord
    - More than one relapse separated by more than 1 month
- 4 types
    - Relapsing/remitting
        - Temporary periods of disability followed by full or partial recovery
        - Pt returns to baseline
    - Progressive relapsing
        - Significant recovery immediately following a relapse but gradual worsening of symptoms
        - Baseline gets worse
    - Primary progressive
        - Gradual progression of disease from onset with no relapses or remittances
    - Secondary progressive
        - Steady progression with relapses and minor remittances
- Causes
    - Unknown
    - Ideas are

        - Autoimmune response
        - Virus/bacteria trigger
        - Genetic linkage
        - BBB damage
- Results in
    - Inflammatory response
    - Demyelination
    - Axonal loss and oligodendrocyte death
- Autoimmune
    - APC leads to naive t cells to turn into TH1 and TH2
    - TH1 cells go through BBB and kill myelin
    - Killer T cells (CD8)
        - Can release molecules toxic to neurons
            - NOO, INF, TNF
    - B cells
        - Can release antibodies that lead to demyelination
- Loss of myelin leads to AP failure
    - Only a few Na channels in the bare region
    - Get these new 1.6 and 1.2 channels
    - They aren't the greatest and have their faults
    - 1.6
        - Lets in Na constantly
        - Get an AP
        - But more Ca comes in, triggers death of neuron later
        - Short term benefit only
- Inflammation
    - Can lead to energy failure

    - The Na/K pump no longer works
    - Get cell death
- EAE model
    - Experimental autoimmune encephalomyelitis
    - The model that fits MS, but kills very fast
- Drugs
    - Daclizumab
        - Il2 receptor antibody
        - Decreases the amount of new lesions in the body
    - Copaxone
        - Random polymer of 4AA's from MBP (myelin binding protein)
        - Shift T cells from pro-inflammatory TH1 to a regulatory TH2 state
        - Suppresses inflammation
    - Tysabri
        - Antibody against alpha 4 integrin
        - Prevents migration of lymphocytes into the brain
        - Blocks their adhesion molecule
        - PML can develop
            - Progressive multifocal leukoencephalopathy
            - Demyelination disease that is more rapid and fatal than MS
        - Activates the JC virus sometimes because the immune system in the brain is depressed

Chapter 5- Synapse

- Two types of synapses
    - Electrical
    - Chemical
- Post synaptic neuron
    - Can fire with a short delay after the presynaptic neuron

- Not just ions
    - ATP, second messengers can flow

- Chemical neurotransmission
    - AP propagates to the terminals
    - Voltage gated Ca channels
    - Clathrin coated vesicles with neurotransmitters
    - Exocytosis
    - Whole process is Ca dependent

- Loewi
    - Stimulated vagus nerve-slows the heart rate
    - Known as ACH
    - 2nd heart slowed down due to the presence of chemicals-get chemical stimulation in absence of electrical

- Types of signaling
    - Endocrine
    - Paracrine
    - Ect

- Neurotransmitters
    - Present in presynaptic cell
    - Release Ca dependent
    - Post synaptic cell has specific receptors

- Types
    - Small molecule NT's
        - Produced in the terminals themselves
        - Enzymes used to produce the NT's are produced in cell body
            - Moved to terminal via slow axonal transport
        - Stored in clear core vesicles
        - Released with low level Ca stimulation

- Peptide transmitters
    - Found in the dense core of vesicles
    - Tend to look black on electron micrograph
    - Enzymes and NT precursors are in the same vesicle
        - Synthesized in the vesicles
    - Fast transport to the terminals from the cell body
    - Released with prolonged Ca activation

- NT's released at the axon terminal
    - Binds to the receptors
    - Removed from the synapse
        - Either diffusion away
        - Reuptaken by presynaptic neuron

- Glutamate
    - Taken up by astrocytes and converted to glutamine and transported back to neurons
    - Toxic at high levels
        - Excitotoxicity
        - Can lead to oxidative stress

- Ca importance
    - Rise in presynaptic Ca level
        - Necessary and sufficient for NT release
    - Na/K flux moves signal from the hillock to terminal
    - Ca then takes over info propagation

- Neuromuscular junction experiments
    - Stimulate motor axon using the AP produced
    - End plate potential (EPP)
        - Depolarization above
        - Hyperpolarization below

- Get mini end plate potentials (MEPP)
    - Even without stimulation
    - Potential change from one vesicle of NT
        - quanta
    - Bathe muscle cell in low Ca
        - Normal EPP's are reduced to subthreshold EPP's
        - Not calcium dependent
- Large endplate potentials
    - Many vesicles released
    - Calcium dependent

- Voltage clamp method
    - Study NT release
        - TEA for K blockers
        - TTX for Na blockers
        - Cadmium-inhibits Ca channels
        - Kelator-blocks effects of Ca
    - Presynaptic Ca current coming into the cell
        - Below the 0 mark causes an increase in membrane potential
        - When there is no depolarization, there is a graded potential
    - Inject Ca directly into the presynaptic cell
        - Get depolarization that results in postsynaptic cell due to the propagation
    - Presynaptic cell has large Ca levels and appears darker
- Frequency of AP ensures the release of specific vesicles
    - Why not use electrical synapses?
- Chemical neurotransmission
    - Modulation is powerful to NS
    - Low frequency stimulation leads to small molecule NT release

    - High frequency stimulation leads to both types released
        - Neuron has more than 1 type of NT-release differentially
- Binding to the presynaptic proteins
    - Synapsin crosslinks vesicles to actin cytoskeleton to keep them in place close to membrane
    - Cam kinase II will remove synapsis from actin
        - Ca dependent
    - The vesicles move to the wall, dock then priming for release
    - SNARES
        - Snare 25, synaptobrevin (in vesicle), syntaxin
        - Bind to help vesicle dock
    - Needs Ca to fuse
- NT release
    - Need to act on the post synaptic activator
    - Patch clamp
        - Each channel opens briefly-need a lot to open
        - Microscopic currents
    - Post synaptic potential created by an EPC (End plate current)
    - Current through channels produces the positive depolarization
- Voltage clamp
    - Inward current through ACH-r is positive (but below x axis since inward)
    - At 0 mv, no current
    - Then above zero reverses to outward current
        - 0 mv is the reversal potential
        - Where the current not the ions reverse direction
    - 0 mv not exactly halfway due to ion flow and driving force
    - Remove Na or K, shift the reversal potential
    - 10 Na to 1 K flow

        - Due to the driving force for Na being 10X larger
- Muscle
    - End plate current almost always generates an AP
    - Both inhibitory and excitatory in neurons
- EPSP
    - Always depolarizing
    - E rev above threshold
- IPSP
    - Can be depolarizing or hyperpolarizing
    - Always have an E rev lower than threshold
- If only one ion flows through, the reversal potential is equal to the eq potential of the ion
- Dendrites act as summators of EPSP's and IPSP's
- Can use the length constant to calculate how far the potential propagates through the dendrites/cell body (even if just a graded potential)
- Spatial summation
    - Summation in space
    - The potentials arise from different sites at the same time and sum depending on where they are located on the dendrite
- Temporal summation
    - Sum in time
    - The same synapse firing close in time
- Disinhibition
    - Off response
    - Get an AP when releasing the cell from hyperpolarization
    - Hyperpolarization moves the Na channels from inactivated to closed
    - The depolarization via the Na leak currents to get back to resting potential is enough to fire an AP
    - Lowers the threshold level

Chapter 6- Neurotransmitters

- Ionotropic receptors
    - 3-4 membrane helicies
    - Need 4-5 subunits for a structure
- Metabotropic
    - 7 membrane domains
    - No ion channel
    - C termini bind intracellular g proteins
    - 2nd messengers
    - Longer lasting effect than ionotropic but take longer to activate
- GABA
    - Major inhibitor of the brain
    - Glutamate (excitatory) is a precursor to GABA
    - GAD converts glutamate to GABA
    - Gabatransaminase converts GABA to glutamate
- GABA receptor
    - Ionotropic
    - 2 sites for GABA to bind
    - Many regulatory sites which end up being drug sites
    - The current decays over time due to a stepped nature of response
- Dopamine
    - Catecholamine
    - Excitatory
    - L-DOPA precursor
        - BBB permeable while Dopamine is not
    - Found in the Striatum of the brain
        - Substantia nigra and Ventral tegmentum area

- Glutamate
    - Excitatory
    - Glutaminase- glutamine to glutamate in the neurons
    - Transported into vesicles by V-Glut transporter
    - Removed by EAAT's or glutamate transporters
        - Excitatory AA transporters
    - Glutamate receptors
        - NMDA
        - AMPA
        - mGluR
- NMDA receptor
    - Blocked by Mg ion at resting potential
    - Needs depolarization to unblock
    - Allows Ca to flow in
- AMPA
    - Allows Na to come in to depolarize
    - Works with NMDA to bring in Ca
- PCP
    - Models schizophrenia
    - NMDA abnormalities thought to be a cause
- Ip3 releases Ca- see Ca waves through connected astrocytes
- Excitatory Glutamate transporters
    - Coupled to Na/K pump for energy
    - Need secondary active transport
    - Use the Na gradient to bring glutamate into the cell
    - Reverse transport leads to excitotoxicity
- XCT

    - Uses glutamate flowing out of the cell to bring cys into the cell
    - Excitotoxicity leads to cys being pumped out of cell
        - Works in reverse
    - Cys is the rate limiting producer of SOD
        - SOD converts free radicals of Oxygen into H2O2
        - Then glutathione converts H2O2 into H2O
- PSD95 blocks NO
    - Some level of NO needed to help prevent excitotoxicity
- Excitotoxicity is linked to diseases such as ALS due to the SOD mutation

Chapter 8- Plasticity

- Synaptic plasticity
    - Synapses not fixed-constantly changed
    - LTP-long term potentiation
    - LTD-long term depression
- Facilitation
    - Presynaptic AP's close in time can increase the EPSP in the postsynaptic cell
    - Short term change
- Buildup of calcium in the presynaptic terminal
    - This causes a greater NT release
    - 10ms in between AP's causes a greater NT release
    - After 50 ms almost no effect
- Augmentation
    - Adjust the Ca level in the presynaptic cell
    - Decrease-moderate stimulus trains
    - Don't run out of vesicles
    - Boosting of the postsynaptic response over several seconds
    - Potentiation on a longer time scale

- All short term plasticity is Ca related

- Habituation of the sea slug
  - Leads to a decrease in response
  - Can get a return of the response if paired with something new like a shock
  - Short term learning can be prolonged for days

- Steps
  - Serine binds to sensory neuron
  - cAMP made by Adenyly cyclase
  - cAMP binds to PKA and liberates catalytic subunits
  - PKA phosphorylates many substrates and decreases opening of K channels after an AP
  - Let more Ca into the cell
  - More glutamate is released

- Structural changes are long term changes

- LTP-get a 300% increase in EPSP amplitude
  - LTP can last for a year or longer in some places

- Synapses change shape and can store memory

- LTP properties
  - State dependent
    - Depend on PSM voltage
    - Single presynaptic stimulus won't change
    - Needs to be paired with a strong post synaptic potential
    - Create more EPSP
  - Specificity
    - LTP is restricted to active synapses
    - An active signal is strengthened because it selectively strengthens important ones
  - Associativity

        - Potentially a way to link different senses
- Ca that flows in can lead to more AMPA receptors being placed in the membrane
    - Thanks to Calmodulin kinase II
- Development
    - Silent synapses only have NMDA receptors
    - Framework for synapse pruning
    - The ones that stay get AMPA receptors
    - Others removed
- Can inhibit protein synthesis-lose the EPSP in the postsynaptic cell
- LTP depends on protein production
- LTD (long term depression)
    - Helps encode long term info
    - Increase the difference between strengthened and non-strengthened synapses
    - LTD results from low stimulation level to presynaptic cell
    - LTD is not a zero stimulus
        - It is just a low basal level of vesicular release that may lead to LTD
        - Decrease in the EPSP amplitude
- Low frequency stimulation
    - Increase in Ca in the post synaptic cell
    - Activates phosphatases rather than kinases
    - Phosphatases dephosphorylate substrates and internalize AMPA receptors
    - Get a reduced glutamate response
- Mechanism
    - Pre before post = LTP
    - Post before pre= LTD because the receptor is already blocked
- Overall 4 types of potentiation
    - Facilitation

        - Increased presynaptic Ca
    - Depression
        - Decreased vesicle strength
    - Augmentation
        - Increased Ca binding for vesicular release (Munc-13?)
    - Potentiation
        - Gene regulation

From Test2

- Blocked Ca dependent phosphatases in a hippocampal cell?
    - Less AMPA receptors would be internalized because the job of these phosphatases is to internalize AMPA receptors for LTD
- Fatt and Katz identified the phenomena of quantal release of NT's
- Aplysia sensitization
    - Adenylyl cyclase production of cAMP
    - cAMP directly activates PKA
- Depression increases the ration of NMDA to AMPA receptors
    - Decreases AMPA because of Ca dependent phosphatases
    - The NMDA number doesn't change
- When the E rev is equal to Eq potential of the ion, the resting membrane potential is the same
    - Need to depolarize or hyperpolarize to see ion flow
    - Ion flows back towards E rev (depends on which way you depolarize/ hyperpolarize
- Pathological is disease
    - Chemical vs electrical pathological
        - Dysfunctional gap junctions
        - Excitotoxicity
- Skeletal muscle voltage at the neuromuscular junction= End plate Potential

    - At the post synaptic neuron= post synaptic potential
- Current at the NMJ=End plate current
    - At the postsynaptic cell= postsynaptic current
- Chemical synapse evolution
    - More modifiable
    - Different time scales and amplification of the signal are two benefits
- Botulism and tetanus toxins
    - Inhibit vesicular release
    - SNAP25, syntaxin, synaptobrevin all inhibited
- ALS mouse-had SOD-1 common mutation
- Many neurodegenerative diseases have protein aggregation issues
- Dlg-4 knockout cant learn well-essential for simple forms of associative learning
- Dlg2- paralog deficit in both mice and humans
- SOD1 kills directly and indirectly
    - See figure 2 of the paper
- TDP-43 and FUS
    - RNA processing proteins that may lead to ALS toxicity

ALS

- ALS and FTLD are on a spectrum together
    - There is no real distinction between the diseases
- Proteomosomes
    - Degrade proteins (not organelles) tagged with ubiquitin
- Autophagosomes
    - Degrade organelles and abnormal proteins
    - Fuse with lysosomes to degrade things
- TDP-43 and FUS
    - Both involved in RNA processing

    - Most well known RNA processing proteins that lead to ALS
- SOD1
    - Also a common ALS mutation
    - Misfolding of the protein
    - Leads to sticky ends and toxicity in the cell

Central Pattern generators

- Rhythmic movements such as swimming, walking, and breathing re generated by circuits in the NS called CPGs
- CPG's studied in many animals
- EMG wires stuck into the shell of a crab to record the electrodes as in vivo
- Triphasic motor pattern
    - LP, PY, PD (Pyloric rhythm)
    - Rhythm changes attributed according to behavioral state
- Somatogastric NS
    - Study in vitro-put the NS flat in a dish and do separate recordings
    - Intracellularly with microelectrodes
        - Cell body of the neurons
    - Extracellularly with wires around nerve
        - Recording of AP times
- No feedback when in vitro
- Feedback is essential because it produces a fixed pattern
- The connectivity of the rhythm can be understood through diagrams
- Inhibition is necessary for pattern generation
- Connectome-wiring diagram for all sorts of animals
    - Need to see the dynamics to create the connectome
    - Trying to understand the other way
    - Need the strength and time course and properties of synapses
- Crustacean

- 2 commissure ganglia (COG)
- 1 esophageal ganglia (EOG)
- Send projections down the nerves
- Left intact-see complex patterns
- PD-oscillations
- Slower gastric mill level
- Happening simultaneously with fast rhythm
- Gastric mill-moves teeth inside stomach
- Pyloric rhythm moves filter on the back end of stomach (ongoing)

- Pyloric neurons
  - Rhythm generators
    - Bursting pacemaker neurons
      - Depolarize without inputs
    - Oscillations can arise from circuit interactions
  - Oscillation
    - Reciprocal inhibition can result in rhythmic alternations between functional antagonists
    - Half-center oscillators
    - 2 or more cells that don't burst
    - Connect with reciprocal inhibition
- Add H conductance-hyperpolarization
  - Activated inward current (depolarize) after inhibition
- H current helps the cell escape from inhibition and allows it to cross the threshold
- Emergent oscillation
  - Doesn't depend on bursting neurons but arises from synaptic connections
- Timing determined by the circuit
  - Period
  - Latency

    - Divide time by period to get the d phase
- Variability of pyloric period
    - Vary in period time among organisms
- Invariance of phase relationships
    - Invariant
    - Relative timing
- Compensation
    - Slow down or speed up
- Multiple processes that determine when each part fires
    - Interaction between multiple cell processes that allow a CPG to be phase constant

SWIMMY

- First spike is larger than the rest because the cells cant recover fully from the hyperpolarization period
- IPSP's caused by an interneuron
- Can swim because of alternations between bursts
- Hyperpolarize one neuron
    - -10ma will do it
    - See the effect on the circuit
    - The one that is directly affected will be silenced
- Facilitation can be seen by a second AP firing when sub-threshold
- Depression- second one doesn't fire even when above threshold
- Generator
    - Doesn't follow any other cell
    - Begins the circuit
    - Not affected by the hyperpolarization from any other cell
- Follower
    - Changes firing pattern when other cells are hyperpolarized

Aging

- Changes in the body and brain occur
    - Reduction in things like temp regulation and hearing and other senses
    - Collegen less elastic
    - Immune system decrease
    - Neuronal conduction velocity decrease
- Behavioral changes
    - Reduced short term memory
    - Forgetfulness
    - Confusion
    - Errors in judgment
    - Reduced learning rate
    - Decrease in:
        - Brain size
        - Gray matter
        - Dendrite diameter
        - Synaptic vesicle number
    - Increase in:
        - Ventricular volume
        - Astroglia size
        - Myelin thickness
        - Plaques
- Alzheimer's
    - Most common brain degenerative disorder
    - Begins with mild memory deficits/neuronal death
    - Accompanied by
        - Slow movements

        - Bad coordination
        - Confusion
    - Associated with temporal, frontal, and parietal cortices
    - Diagnosis
        - Suspected, probable, definite (only after death or with a brain biopsy)
    - Classifications
        - Sporadic
            - No clear cut genetic basis
            - May have a genetic predisposition
        - Familial
            - Inherited disease associated with families
- Causes
    - NT
        - Deterioration of:
            - ACH, norepi, serotonin, somatostatin
        - Ach hypothesis
            - Specific deterioration of the cholinergic system
            - Connects the midbrain nuclei to the cerebral cortex
    - B-Amyloid/abnormal protein
        - Amyloid precursor protein (APP)
        - Abnormal proteolytic processing
            - Secretase cuts APP-usually creates soluble non-sticky products
            - Abnormal cleaving leads to sticky ends and plaques
    - Tau protein hypothesis
        - Abnormal processing
        - MT associated protein (MAP)
        - Tau found throughout neuron

        - Tau hyperphosphorylated
        - Tau is often associated with PHF
        - Distributed differently in degenerating neurons
    - Presenilins
        - Mutations in ps-1 and ps-2
        - Chromosome 21?
        - FAD-genetic cause
        - Facilitate formation of AB plaques
    - ApoE4
        - Facilitates cholesterol's entry into the cell
        - Apoe4 correlated-dominates familial
        - ApoE3 dominates general population
        - Sporadic AD-specific predisposition ApoE4
    - Genetic factors
        - Most just increased risk factors, not a guarantee
- AB and APP exist on chromosome 21
    - Individuals with down's syndrome have a higher rate of AD
- Risk factors
    - Females
    - Family history of neurodegenerative diseases
    - Less education

Memory

- Declarative (explicit)
    - Site is the hippocampus
    - Responsible for facts/events
- Non-declarative (procedural/implicit)
    - Know sequences of events

    - Don’t think about
    - Skills and habits
- There is a time aspect to memory
    - No exact science
    - Long term usually starts after 30 seconds
    - Hippocampus can lose memories because it can only hold so much
    - New info can cause the old info to be lost
- Finite # of things can be stored in memory
    - 7±2
    - Can increase via practice
    - Other way to increase is chunking
- Interference tasks can remove previously learned things
- Kim peek (rain man)
    - Has an incredible memory
    - Elaborate encoding that creates good retention
- Lose aspect of the brain- study its effects
- HM
    - Lost hippocampus
    - Lost his ability to convert STM to LTM
    - Did not lose his ability to do procedural tasks
        - Could still learn skills
        - Didn’t remember learning it
- May be PKM-zeta that works as glue to fix connections between neurons that were active before

Parkinson’s

- Optogenetics
    - Shine light (using fiber optic cable)
    - Wavelength of light activates specific proteins

    - Change membrane potential of cells through light
- Ed boyden (ted talk)
    - 1 billion people with brain disorders
    - Pharmacology treatments alleviate symptoms but cannot cure
    - Neurons get installed solar panels
        - Respond to light after fiberoptic cables are put in
        - Rhodopsin-charged particles enter when opened by light
        - Can get this protein in these cells
    - Light sensitive receptor
        - Deliver to some cells and not to others
    - Brain signals that drive learning
- PTSD
    - Over time the animal fears the tone
    - By activating certain brain parts, get over fear
- Can make a mouse see with light activation of bipolar cells
- Parkinsons symptoms
    - Motor symptoms
        - Tremors
        - Stiffness and rigidity
        - Declarative memory problems
- Substantia nigra
    - Dopamine-some oxidation production in the cell
- Motor cortex in general
    - In Parkinson's lot more inhibition to brain stem and spinal cord
    - May have an effect during earlier years that predisposed you to PD
- Mutations predispose to PD
    - Lrrk2, pink1, park genes, alpha-synuclein

- Alpha-synuclein
    - Normally has a role in NT release and recycling of endosomes
- Lrrk2
    - Similar role
    - Degrades vesicles
    - Phosphorylates for endocytosis
- Lewy body aggregations
    - Kill the cells off
    - Intracellular-don't allow for normal movement
- Tabacco and coffee actually protect against PD?
- Rural areas see an increased incidence rate
- Pesticides
    - Chemicals in the environment lead to PD
    - Interactions between the genes and environment
- Dedifferentiate somatic cells to stem cells (IPS)
- Cells that don't have the alpha-synuclein mutation weren't as susceptible to mutations from pesticides
- Music therapy
    - Listening to music while doing tasks
    - Helps the PD sufferers complete tasks
- Deep brain stimulation
    - Electrode that triggers the neurons to fire not randomly
- L-Dopa
    - Drug that can help symptoms at first
    - Eventually sensitized and need more and more
    - Eventually get to a point where it is no longer useful to treat symptoms