Overview of Lecture: Nervous systems. see the schedule for reading and watching assignments

THE FOLLOWING PREVIEW HAS BEEN APPROVED FOR ALL AUDIENCES

Bullet Points:
• nervous systems: similar parts, different interactions
• organization in vertebrates
• developing connections
• info processing - reflexes
• neurons - resting potentials
• integration of information
• “decisions” – action potentials
• synapses & mechanisms
• neurotransmitters
• addiction
• depression
• impulsivity
• learning GxE
Learning Goals:

1. Be able to describe the patellar reflex and explain how it creates a negative feedback system that can maintain a postural position without ongoing conscious control.

2. Be able to describe and explain how neurons integrate spatial and/or temporal graded potentials in the dendrites and “make a decision” at the axon hillock.

3. Be able to describe the nature of the action potential that travels down the axon and how it encodes information transmitted to the pre-synaptic terminal.

4. Be able to use an example to describe and explain the roles of neurotransmitters, postsynaptic receptors and presynaptic reuptake pumps in normal synaptic signal transmission. How can a SSRI increase the effective level of serotonin in a synapse. How can prolonged manipulation of a transmitter or transmitter-mimicking drug lead to addiction and withdrawal symptoms when the transmitter/drug is reduced?

5. Be able to describe and explain (briefly and at a very general level) the role of dopamine synaptic signaling in mood (pleasure), addiction, impulsivity (including gambling and not eating marshmallows) and receptivity to positive feedback in education.
The human nervous system is a vastly complex network of functionally interconnected cells whose detailed structure is at present beyond reach. All our actions, calculations, feelings, memories, dreams—consciousness itself—emerge from its workings. To understand this colossal, enigmatic structure, experimentally amenable model animals with tractable nervous systems many orders of magnitude smaller are studied. A popular choice has been the worm *Caenorhabditis elegans*, a nematode 1 mm long with a nervous system containing fewer than 400 neurons. …

Although it is a mistake to consider small invertebrates as primitive, their systems may be closer to the ancestral condition than those of their larger cousins. Insights into that ancestral condition can help us understand function today. Garrison et al. (1) and Beets et al. (2), add to a growing body of evidence that
Animal nervous systems are remarkably similar at the cellular level - how neurons work – but differ at higher levels of organization, ex: the structure and function of their brains. [recall: Sponge Bob has no neurons or brain]

Typically, neurons:
1. Gather information from sensors or other neurons at the dendritic tree.
2. Integrate information from various sources as small postsynaptic voltage changes at the axon hillock and “decide” whether to send it along.
3. Transmit the information along the axon as voltage action potentials of varying frequency.
4. Neurotransmitters communicate the signal across the chemical synapse and activate effector or back to 1.
Neuronal Roadmap

As the neural system develops, a distinctive network of interneuron connections is created. **Neural circuit formation requires an intricate orchestration of...** cell migration, axon guidance, dendritic growth, synaptic target selection, and synaptogenesis.

Colón-Ramos et al. (p. 103) find that, in the nematode worm *C. elegans*, the supporting glial cells provide the requisite road map for making these [initial] connections. ... consistent with observations made in vertebrates and highlights the importance of glial cells in specifying precise neural connectivity.

Glial cells are important in neural development of functional connections

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**Glial Promote Local Synaptogenesis**

Through UNC-6 (Netrin) Signaling in *C. elegans*


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*but then these initial connections are “sculpted” by experience; early on, many are lost; things get simplified; then “sculpting” continues as learning*

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A cultured sensory neuron extending a growth cone with long thin filopodia, photo by Ken Balazovich
Muscle length & velocity are monitored by muscle-spindle stretch receptors. Activation of these receptors initiates the postural reflex: motor neurons of synergists are activated (+) to shorten antagonists are inhibited (−).

Note: these reflexes have evolved (are “designed”) to process incoming info very quickly and initiate adaptive responses very quickly – without time consuming conscious deliberation and dithering. But – we can consciously control them and move our legs or suppress a blink.

Different reflexes mature or fade at diff times and can be used to track neural development.

http://en.wikipedia.org/wiki/Reflex

Adult human reflexes
Baby reflexes not seen in adults
All cells have a **resting potential** (ionic gradients) across the plasma membrane, but **neurons have voltage-sensitive permeability** (**voltage-gated ion channels**).

Membrane potentials are determined by:

Water-soluble ions cannot dissolve in the phospholipid plasma membrane; they must either be pumped by membrane proteins or diffuse through ion channels, which are aqueous pores made of specific transmembrane protein molecules. These molecular channels are selective for specific ions.
Within neurons, **graded potentials** integrate information – inputs at dendrites and **action potentials** transmit decisions – outputs along axons.

At an *excitatory synapse*: an excitatory postsynaptic potential (EPSP) (depolarization) results when ligand-gated sodium channels are opened (ex by glutamate).

At an *inhibitory synapse*: an inhibitory postsynaptic potential (IPSP) (hyperpolarization) results when ligand-gated chloride channels are opened (ex by glycine or GABA).

The postsynaptic cell's membrane potential is the result of **temporal & spatial summation** of the EPSPs and IPSPs at the many excitatory and inhibitory synapses on the cell.
An action potential (AP; 2-5) is a self-propagating unidirectional wave of opening & closing of voltage-gated Na\(^+\) and then K\(^+\) ion channels.

In myelinated axons, APs manifest saltatory \{skippy\} conduction; allows small diameter axons to be fast; Myelin is lost in multiple sclerosis (MS) & “cross-talk” scrambles messages.

Depolarization sends electrical field loops ahead and behind.

The unidirectionality results from hyperpolarization behind (5) but resting (1) in front.

Consider ‘crazy-bone’ initiation of AP in middle of axon – direction?

APs: long-distance transmission of information w/o degradation (or processing); information encoded by which axons are active & the frequency of APs in axon.
Most graded signals originate at chemical **synapses** on the dendritic tree.

Pre-synaptic reuptake transporter proteins remove neurotransmitter from cleft, turn the signal off.

SSRIs like Prozac are **Selective Serotonin Reuptake Inhibitors**: serotonin signal ‘lasts longer.’ Extasy (MDMA) is a serotonin reuptake inhibitor; Cocaine and ritalin are dopamine reuptake inhibitors.

The signal from a pre- to a postsynaptic neuron is a chemical **neurotransmitter** stored in presynaptic vesicles. Depolarization of the axon terminal causes the release of neurotransmitter into the synaptic cleft.
This Is How Your Brain Becomes Addicted to Caffeine

Structurally, caffeine closely resembles adenosine (which is a byproduct of cellular respiration).

**Caffeine** can fit neatly into our brain cells’ receptors for adenosine, effectively blocking them off. [an adenosine “receptor antagonist”]

Normally, adenosine locks into these receptors and produces a feeling of tiredness.

This explains why regular coffee drinkers build up a tolerance over time - because you have more adenosine receptors, it takes more caffeine to block a significant proportion of them and achieve the desired effect.

This also explains why suddenly giving up caffeine can trigger withdrawal effects.

[similar for drugs that increase dopamine levels – reduced # dopamine receptors]

The good news is that, compared to many drug addictions, the effects are relatively short-term. You only need to get through about 7-12 days of symptoms without drinking any caffeine. During that period, your brain will naturally decrease the number of adenosine receptors on each cell,
Each time you move a skeletal muscle it is because **acetylcholine (Ach)** has been released from a neuron to activate muscle.

Alzheimer's Disease is associated with a 90% loss in the brain's production of Ach in the basal forebrain and hippocampus.

**Nicotine** mimics **Ach** at neuromuscular junction, autonomic & CNS.
Cocaine, opiates, nicotine and alcohol produce rewarding effects by promoting the release or inhibiting the presynaptic reuptake of dopamine.

{Addiction is associated with reduced density of dopamine receptors}

Parkinson’s Disease (PD) is accompanied by a selective destruction of dopamine neurons in the substantia nigra of the midbrain. PD is treated with L-dopa, a precursor of dopamine in the brain.

Schizophrenia is treated with drugs which block the binding of dopamine to its postsynaptic receptor sites.
GLU (glutamate) is the main excitatory neurotransmitter in the brain. Its actions are mediated at two types of receptor (NMDA and AMPA) involved in memory formation.

GABA (gamma-aminobutyric acid) is the main inhibitory neurotransmitter in the brain.

- Adenosine induces drowsiness & sleep [blocked by caffeine]
- Endorphins/Enkephalins are endogenous opiates found throughout the brain. Involved in pain reduction and pleasure (they enhance the effects of dopamine).
- NO increases vasodilation and blood flow [breakdown inhibited by Viagra]
A popular theory is that a breakdown in signaling by the brain neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is critically involved in the symptoms of clinical depression, but the nature of this defect has proved elusive.

The study by Svenningsson et al. (Science 311, 77 2006) identifies an interaction between a brain protein called p11 and a serotonin receptor (5-HT1B subtype) that has been previously associated with mood regulation.

... the authors show that a deficit of p11 is linked to depression.

Antidepressants and electroconvulsive therapy (ECT) all caused an increase in the amount of p11 in the brains of mice. So, it’s pretty convincing that p11 is associated with the main therapeutic action of antidepressant drugs.

The brain messenger dopamine is traditionally known as the 'pleasure molecule', linked with our desire for food and sex, as well as drug and gambling addictions.

Using brain imaging, Pessiglione et al. (2006) scanned healthy human volunteers as they gambled for money after taking dopamine altering drugs ...

(treated w/ haloperidol, which blocks dopamine receptors)

... confirming the critical role of dopamine in integrating reward information

Dopaminergic Network Differences in Human Impulsivity

https://www.scientificamerican.com/article/dopamine-impulsive-addiction/

Dopamine Determines Impulsive Behavior: Brain scans illuminate the internal connection among the neurotransmitter, impulsiveness & addiction.

Katherine Harmon on July 29, 2010.

A study by Buckholtz et al. showed that people who were more impulsive have less active dopamine receptors in their midbrain but their brains release large quantities of the neurotransmitter when stimulated.
In the late nineteen-sixties, Carolyn Weisz, a four-year-old with long brown hair, was invited into a “game room” at the Bing Nursery School, on the campus of Stanford University. …

A researcher then made Carolyn an offer: she could either eat one marshmallow right away or, if she was willing to wait a few minutes, she could have two marshmallows when he returned. … Then he left the room.

[decades later, the children who couldn’t resist the 1st treat]

Don’t!
The secret of self-control.
Jonah Lehrer MAY 18, 2009

Children who are able to pass the marshmallow test enjoy greater success in adulthood. 

See: http://www.youtube.com/watch?v=M0yhHKWUa0g

Dopaminergic Network Differences in Human Impulsivity
Some children, particularly those with a more fearful temperament, are more sensitive than others to the influence of parents, teachers, and environment. Kegel et al. (2011) attempt to link this with a particular genetic polymorphism. Preschool children played a literacy-geared computer game that delivered instruction and assignments to all participants, but differed in whether it delivered feedback about the children's choices. A feature that distinguished the groups of children was whether they carried the long variant of the dopamine D4 receptor gene, which is associated with lower dopamine reception efficiency. [quality]

For education, just as for shoes, a good fit to the individual produces the best result. *genotype x environment interaction* !!!

Methylphenidate [*ritalin*] for ADHD: Mechanism of Action
Flavio Guzman, MD September 19, 2017

The prefrontal cortex regulates attention, behavior and emotion. Deficits in prefrontal cortex functioning have been linked to ADHD symptoms:

- poor impulse control, weak sustained attention and heightened distractibility.

Norepinephrine (NE) and dopamine (DA) [*catecholamines*] are key neurotransmitters.

**Methylphenidate [*ritalin*]** inhibits the reuptake of dopamine and norepinephrine. This increases dopaminergic and noradrenergic activity in the prefrontal cortex and may explain its efficacy in ADHD. [*adderrall/amphetamine increases DA release*]

There is an inverted-U dose-response for catecholamines and prefrontal abilities.

In 2015, a meta-analysis of high quality clinical trials found that **therapeutic doses of amphetamine [*adderall*] and methylphenidate [*ritalin*]** result in [brief] modest improvements in cognition, including working memory, episodic memory, and inhibitory control, **in healthy adults without ADHD**.

... using the drugs as study aids ... does not actually improve GPA.

Adverse effects include anxiety/nervousness, nausea, and insomnia.
The COMT gene [catechol-O-methyltransferase] carries the assembly code for an enzyme that clears dopamine from the prefrontal cortex, where we plan, make decisions, anticipate the future … There are two variants of the gene. One variant [Met158] builds enzymes that slowly remove dopamine. The other variant [Val158] builds enzymes that rapidly clear dopamine. We all carry the genes for one or the other, Stress floods the prefrontal cortex with dopamine – one COMT variant clears it slowly, the other rapidly.

Warriors versus worriers: the role of COMT gene variants.
… individuals with Val158 [fast] alleles may have better performance when stressed, while individuals with Met158 alleles may have better performance when not stressed.

BUT note: large samples, small effect sizes
-probably some truth to this, but explains only a little