COGS 107B - Section A06
~ Week 8 ~

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Midterm questions?

Info on the board will be added to presentation slides

Final - either in class Thursday of Week 10 or during finals week (Tuesday, 4/19 @ 11:30am)
Learning and Memory I

Principles: Fire together, wire together
Memory

- There are four different kinds of memory we will focus on in this class:
- 1. Simple Associative Memory
  - I: Pavlovian fear conditioning - tone + foot shock
- 2. Procedural/Implicit Memory
  - II: Reach-to-grasp experiment, sound perception experiment, basal ganglia vs. cerebellum experiment
- 3. Episodic/Declarative/Explicit Memory
  - II: Hippocampal place cells depend on context
- 4. Working Memory
  - II: Prefrontal cortex + parietal cortex
Three Important Glutamate Receptors

1. Non-NMDA Receptors (excitatory ionotropic)
2. NMDA Receptors (excitatory ionotropic)
3. Metabotropic glutamate receptor (mGluR)

When an AP is fired and causes NT release - the Non-NMDA receptors on the postsynaptic cell are the first ones activated
   ○ Usually the EPSP resulting from one AP is not enough to trigger an AP in the postsynaptic neuron

Experiment: caused a neuron to fire 5 APs in quick succession - led to the postsynaptic neuron to fire an AP
   ○ Both the pre- and post- cells are CO-ACTIVE
   ○ When the post- cell is depolarized enough by non-NMDA receptors, a magnesium molecule on the NMDA molecule is removed and the NMDA receptors can now actively depolarize the cell

Now, only cause the presynaptic neuron to fire 1 AP - the resulting EPSP has grown dramatically → Activation of both Non-NMDA and NMDA Receptors
Synaptic Efficacy

- Synaptic Efficacy (or synaptic strength) is defined as the amount of depolarization in neuron B after the firing of one action potential in neuron A - how big of a depolarization does neuron A cause in neuron B?
- This is referred to as Long-Term Potentiation (+) or Long-Term Depotentiation (-)
- Changes in synaptic efficacy as Hebbian Learning - “Neurons that fire together, wire together”
visualization of potentiating, depressing, and unchanged synapses following stimulation of hippocampal CA3 inputs into CA1 region of hippocampus

Becker et al., Neuron, 2008
synaptic potentiation (as in figure) and synaptic depression are changes in the amount of depolarization in a post-synaptic neuron when an input neuron (presynaptic) releases neurotransmitter following an action potential – such alterations in depolarization amount are termed changes in ‘synaptic efficacy’

changes in synaptic efficacy can reflect either changes in depolarization caused by increases or decreases in the amount of neurotransmitter released by an action potential (presynaptic change) and/or increases or decreases in the amount of response of the postsynaptic neuron to the same amount of glutamate released by the presynaptic neuron

post-synaptic changes usually reflect changes in the shape of the synapse, changes in the number of ionotropic receptors, changes in the kinetics of ionotropic receptors, and/or development or retraction of contacts (synapses) between neurons

changes in synaptic efficacy often depend on the timing and/or amount of co-activity between two neurons (as in ‘fire together, wire together’)

for any two connected neurons, the co-activity rules for synaptic change may differ greatly

co-activity leading to changes in synaptic efficacy may depend on the presence or absence of a third party such as a neuromodulator or a peptide
Synaptic Efficacy

- There are many ways to change synaptic efficacy:
  - 1. Presynaptic Change vs. a Postsynaptic Change
    - **Presynaptic:** increase the amount of neurotransmitter released during each action potential → leads to a higher probability of activating non-NMDA receptors (not every receptor is active all the time!)
    - **Postsynaptic:** changes in the shape of the synapse and the number of ionotropic receptors → the more receptors are on the membrane, the higher the chance of depolarization
  - 2. Changes in **Kinetics** of Non-NMDA Receptors
  - 3. **Co-activity**
    - **Co-activity Rules** - co-activity refers to whether two neurons are firing at the same time or not // the order matters much of the time
    - Co-activity leading to changes in synaptic efficacy may depend on the presence or absence of a third party peptide or neuromodulator (acetylcholine?)
Dendritic Spine Morphology Matters

- Immature dendritic spines have long, skinny shapes that increase the internal resistance of the spine → slower conductance of action potentials
- Mature dendritic spines have shorter, fatter shapes that decrease the internal resistance
- It is more difficult for EPSPs to travel down immature dendritic spines than mature dendritic spines
- A huge amount of input comes into the spines of the dendrites rather than the actual cell body
Dendritic Spine Morphology Matters

- **Fragile X Mutation** produces intellectually disabled individuals (mutation to X chromosome)
- Fragile X is a mutation of the *fmr* gene on the X chromosome, which encodes a protein that operates on other genes
- Fmr usually inhibits the production of mGluR (metabotropic glutamate receptors) → activation of these receptors causes production of new/immature spines
- The mutation to the *fmr* genes leads to an increased activation of mGluR → more production of immature spines
Spike timing dependent plasticity: changes in synaptic 'efficacy' between two neurons (one presynaptic, the other postsynaptic) related to the relative timing of their action potentials.

- Post-synaptic neuron fires before pre-synaptic neuron ($\Delta t < 0$)
- Pre-synaptic neuron fires before post-synaptic neuron ($\Delta t > 0$)

Intracellular electrode for recording of synaptic potentials and action potentials or for stimulation of an action potential.

Synaptic potential in post-synaptic neuron resulting from a single presynaptic spike.

Synaptic depression (or depotentiation)

Synaptic potentiation

Time of firing of post-synaptic neuron minus time of firing of pre-synaptic neuron.

Bi and Poo, ARN, 2001
Key Ideas - Spike Timing Dependent Plasticity

- Changes in synaptic efficacy between two neurons related to the relative timing of their action potentials
- Synapses are plastic - they can be potentiated or depotentiated
- **Synaptic Learning Rule:** coactivity and order matters
- If you have two neurons, A and B, and manipulate their firing rates in relation to each other, you will either increase or decrease the synaptic strength between the two:
  - Potentiation - stimulate neuron A, then stimulate neuron B within 80 ms → this increases the synaptic strength between the two as they ‘fire and wire together’ and information in the form of NT is sent from neuron A to neuron B
  - Depotentiation - stimulate neuron B, then stimulate neuron A within 80ms → this decreases the synaptic strength between the two because they are firing out of order and no information is being sent between the two
Co-activity rules for synaptic efficacy change depend on neuromodulatory systems.

- **no ACh, no NE (as in NREM sleep)**
- **ACh + NE (as in waking)**

**Spike-timing (post minus pre)**

- **NE, no ACh (??)**
- **ACh, no NE (e.g., REM sleep)**
Key Ideas - Neuromodulators and Synaptic Efficacy

- Neuromodulators have an important and powerful impact on synaptic efficacy:
- 1. No ACh, No NE (similar to NREM sleep) $\rightarrow$ normal synaptic efficacy rules, both order and coactivity matter
- 2. ACh and NE (similar to waking) $\rightarrow$ normal synaptic efficacy rules, both order and coactivity matter
- 3. No ACh, NE present (??) $\rightarrow$ anything within an 80ms time period gets *potentiated*, only coactivity matters
- 4. ACh present, No NE (REM sleep) $\rightarrow$ anything within an 80ms time period gets *depotentiated*, only coactivity matters
learning 101: Pavlovian fear conditioning – association of an initially neutral tone (CS) with a foot-shock results in ‘freezing’ responses when the tone alone is played

Auditory cortex / auditory thalamus (neurons excited by sound stimulus - CS) vs. somatosensory cortex / somatosensory thalamus (neurons excited by shock stimulus - US)

Hippocampus (place information) and IT (visual item information) before pairing

Lateral amygdala after pairing

Central amygdala

Freezing response, increased heart rate, etc.
Key Ideas – Pavlovian Fear Conditioning

- Illustrated spike timing dependent plasticity in the context of Pavlovian learning.
  
- In this experiment, a rat hears a tone that is paired with a foot shock. This activates a huge amount of depolarization from the auditory cortex/somatosensory cortex into the lateral amygdala, which is associated with the action of learning.

- The lateral amygdala then sends a large depolarization into the central amygdala, which mediates the fear response (increased heart rate, freezing behavior, etc.).

- Then, the rat just hears the tone without the shock present.

- The learned association in the brain is so strong, that just the tone alone (auditory cortex activation) is enough to completely depolarize this system and elicit the fear response.

- This means that not only were non-NMDA receptors activated during the tone + shock, but also NMDA receptors → this led to more active receptors and a greater depolarization with a small signal.
re-remembering: memories are ‘labile’ — their recall makes them vulnerable to erasure or consolidation

curing PTSD by taking advantage of the ‘labile’ nature of some memories:

**Day 1:** Humans develop eye-blink responses to tones (the conditioned stimuli - CS) paired with shocks (the unconditioned stimuli – US).

**Day 2:** Two groups are exposed to the CS after having been given placebo (top graphs) or propranolol (middle graphs), a compound that blocks the action of norepinephrine (NE). A third group is given propranolol, but not exposed to the CS.

**Day 3:** An set of ‘extinction’ trials (presentation of CS in absence of US) is given and eye-blink responses are recorded. Blocking the action of NE on day 2 is shown to have the effect of ‘erasing’ the CS-US association.

**Day 4:** Usually, as in the placebo condition, the US given alone reverses the extinction of the CS-US association that was achieved on day 3. Blocking the action of NE on day negates this.
Key Ideas – Memories are Labile

- In this experiment, humans receive a shock to the eyelid that is paired with a tone → researchers looking at the impact of the neuromodulatory system (NE) on memory and associations.
- There are three experimental groups that undergo four days of experimental testing.
- Day 1: all groups are presented with a tone and a shock to their eyelid – they develop an eye-blink/cringe response when the tone is played.
- Day 2: Group A returns and only hears the tone, they leave.
- Group B is given a drug called propranolol (blocks NE in the brain) and they hear the tone // Group C is only given propranolol without hearing a tone.
- Day 3: All three groups are exposed again to the tone. Group A and C demonstrate a cringing response – the paired association of the shock + tone is still present and active. Group B does not demonstrate a cringing response.
- Blocking NE while pulling up the fear association memory depotentiated (greater proportion of ACh in the brain) – demonstrates that memories are labile/manipulable.
Key Terms

- Fire together wire together
- Simple associative memory
- Synaptic Efficacy
- Long Term Potentiation
- Long Term Depotentiation
- Hebb/Hebbian Learning
- Glutamate receptors
- Non-NMDA receptor
- NMDA receptor
- Metabotropic Glu receptor (mGluR)
- Coactivity Rules
- Dendritic spine morphology matters
- Immature vs. Mature spine
- Fragile X Syndrome
- Fmr gene
- Spike timing dependent plasticity
- How can synaptic efficacy change (post/pre synaptic)
- Synaptic plasticity learning rule
- ACh/NE impact on synaptic (de)potentiation
- Labile
- Propranolol (NE impact on memory recall and fear conditioning)
- ACh leads to a bias towards depotentiation
- Pavlovian fear conditioning
- Central amygdala
- Lateral amygdala
Learning and Memory II

Principle: Implicit vs. Explicit Memory
Implicit/procedural learning I: rat reach-to-grasp as a model of motor skill learning - ‘more is better’ and ACh helps

Rats learn, across days, to efficiently reach and grasp a small sugar pellet.

Over those days, the muscle patterns used in grasping adapt.

Over those days, the area of primary motor cortex taken up by neurons associated with the reaching limb grows.

If ACh inputs to the primary motor cortex are removed, neither the learning nor the changes in motor cortex occur.

Kargo and Nitz, JNS, 2003
Mod. from Conner et al., Neuron, 2003
Summary - Rat Reach-to-Grasp (Implicit Memory)

- Rat is in an environment with a Plexiglas wall that has a small hole in it - the rat can poke his nose through the hole to get a sugar pellet.
- Experimenter eventually moves pellet back further away from the hole, so the only way the rat can grab it is to learn how to move its arm in a certain way to effectively sweep the pellet towards its mouth.
  - Fragile X mice never learn how to do this.
- This is a classic motor skill learning test.
- Recorded the primary motor cortex and 10-12 muscles of the rat forearm.
- Over 10-12 days, the rat goes from 20% effective rat of getting the pellet to 70% (Chiba) or 90% (Nitz).
- Spiking activity in the primary motor cortex was refined and changed across two weeks.
- The rat learned three things: (1) posture adjustment, (2) how to reach, (3) refinement of motor control.
- Found that at the end of training, a bigger amount of motor cortex was devoted to the rat forelimb - the training had increased the representation of the necessary muscles in the brain.
- Chiba found that if you lesion cholinergic (ACh) neurons in the basal forebrain that project into the cortex, you lose the ability to refine movement and change neural connections in the primary motor cortex.
implicit/procedural learning II: perceptual skill learning - ‘more is better’ – ACh helps

Rats trained to make a nosepoke if they detect a 4 kHz tone show improvements in detection over days of training.

Over the same time period the topographic representation of pitch in primary auditory cortex changes such that more neurons respond to 4 kHz tones.

Polley et al., JNS, 2006

In separate experiments, pairing of a 9 kHz tone with stimulation of ACh neurons in the basal forebrain changes the topographic representation in primary auditory cortex such that more neurons respond to 9 kHz tones.

Kilgard et al., Science, 1998
Summary - Perceptual Skill Learning (Tone) (Implicit Memory)

- In this task, rats are trained to press a lever if they detect a 4 kHz tone and get a food reward
  - If they press the lever when it is not a 4 kHz tone, the light go out for a short period of time
- Researchers looked at the primary auditory cortex of the rat, where there is a tonotopic map of low to high frequencies
  - Found a remarkably large expansion of the number of neurons that prefer 4 kHz tones after this training
- Second experiment: researchers played a 9 kHz tone at the same time as they stimulated the basal forebrain of the rat, which released ACh
  - Found that this stimulate potentiates the inputs from the medial geniculate nucleus to the auditory cortex, leading to a hugely expanded area of neurons responding to a 9 kHz tone based solely on neuromodulatory pairing without actually training the rat
in training (below), the rat is taught to move to the goal to obtain reward

subsequently, on test trials (above), the maze is turned upside-down and the rat demonstrates whether he has learned to ‘make a left’ at the ‘T’ (a response strategy) or to ‘move to that place in the room’ (a place strategy)

if the rat is asked this question early in training (within the first couple of days), one tends to see a ‘place’ strategy and ACh is high in the hippocampus

if the rat is asked this question late in training, one tends to see a ‘response’ strategy and ACh is high in the basal ganglia

early in training, when one would normally expect a ‘place’ strategy, inactivation of the hippocampus (the home of ‘place cells’) results in the emergence of a response strategy

late in training, when one would normally expect a ‘response’ strategy, inactivation of the basal ganglia (proposed to select responses via the direct pathway) results in the emergence of a place strategy

thus, the animal has learned two separate strategies which compete for expression
Key Ideas – Basal Ganglia vs. Hippocampus

- ACh-based competition between the Basal Ganglia and Hippocampus
- A rat is trained on a T-maze: starts at the base of the T and learns over many trials that there is a cheerio on the left side of the T
- Researchers then turn the T 180 degrees in the allocentric environment (and don’t put a cheerio in the maze): which way will the rat go?
- Two hypotheses:
  - 1. Place Strategy
    - The hippocampus is home to place cells – in this strategy, the hippocampus dictates that the rat should go to the left-hand side of the allocentric space, because that is the same PLACE as the cheerio used to be
  - 2. Response Strategy
    - The basal ganglia helps integrate motor movements – the rat will follow the same sequential pathway he followed before (straight + left turn) which will lead him to the right-hand side of the new orientation
Basal Ganglia vs. Hippocampus continued

- So which strategy did the rat learn? Both.
- If you train the rat for 1-2 days then switch the maze, the rat will follow the place strategy.
- If you train the rat for 3-4 days then switch the maze, the rat will follow the response strategy.
- If you lesion the hippocampus then test the rat on day 1 or 2, he will follow the response strategy.
- If you lesion the basal ganglia then test the rat on day 3 or 4, he will follow the place strategy.
- ACh is dictating this change – ACh is higher in the hippocampus during days 1-2, and higher in the basal ganglia during days 3-4.
- Importance of neuromodulatory systems on learning and behavior.
Episodic memory (memory for events and their ordering - a form of explicit memory):

Hippocampal cell activity in a 'place' often depends on the places previously or subsequently visited (this is termed retrospective and prospective place coding).

For one block of trials, the animal must travel to the west end when placed at either the N or S start point.

For the next block, the animal must travel to the east end when placed at either the N or S start point.

Some hippocampal neurons fire in a certain place, but only if they reached that place from the N as opposed to the S side - their activity depends on the character of the full episode and is termed 'retrospective'.

Some hippocampal neurons fire spikes (green dots) when the animal is in a certain part of the maze (here the S arm) - this is seen irrespective of the direction taken after reaching the middle.

Other hippocampal neurons are 'prospective' - they fire in a certain place depending on where the animal will go from that place - they too have activity dependent on the full episode.

Adapted from Ferbinteanu and Shapiro, Neuron, 2003.
For awhile, human researchers and rat researchers disagreed on the function of the hippocampus: is it used for spatial navigation (rats) or episodic memory (HM)?

This study demonstrated that the spatial navigation cells (place cells) in the hippocampus use episodic memory to greatly increase their navigation abilities.

A rat was placed in a + - maze and was able to start from either the North or South ends, and would run around. Researchers recorded hippocampal place cells during this task and found three important new cells:

1. Retrospective Place Encoding Cells – firing was dependent on how the rat got to a specific place field // trajectory-dependent cell that depends on past context
2. Prospective Place Encoding Cells – firing dependent on where the rat was going from a specific place field // trajectory-dependent cell that depends on future context
3. Irrespective Place Encoding Cells – the regular place cells we have learned about previously // fired when the rat was in a specific place field, regardless of the past or future context
working memory: holding items in memory (7±2) is achieved through interaction of the prefrontal and parietal cortex

an example: prefrontal ‘top-down’ influences on parietal cortex during an oculomotor delayed response task – inactivation of prefrontal cortex via cooling depresses ‘working memory’ responses of parietal cortex neurons and increases errors

parietal neuron has delay-period activity specific to the N and NW targets

delay-period activity for the same neuron is depressed when prefrontal cortex is inactivated

cue + delay

delay + action
Key Ideas – Working Memory

- Working memory as an active process from perception $\rightarrow$ action
- In working memory, there are two main groups of neurons that fire at different points during stimulus presentation and response
  1. Cue-delay cells (discovered by Joaquin Fuster) fire during stimulus presentation and during the first part of the delay period
  2. Delay-response cells begin firing during the delay period and peak during the stimulus response task
- These cells were observed in the brains of primates completing a working memory task (remember where the square was on the screen and then move your eyes to the place when directed) in both the Prefrontal Cortex and the Posterior Parietal Cortex
- When researchers cooled the PFC (impairs function) they saw a loss of the working memory process in the Posterior Parietal Cortex as well
- Demonstrated that the PFC orchestrates and is the core source of working memory in other parts of the brain, and is organizing this perception $\rightarrow$ action process
Key Terms

- Implicit vs. explicit memory
- Episodic/Declarative memory
- Working memory
- Reach-to-grasp rat task
- Impact of ACh on implicit procedural learning in rats
- Tonotopic map
- Basal ganglia vs. Hippocampus
- T-maze
- + - maze
- Place-specific activity fields
- Place strategy vs. response strategy
- Retrospective place encoding cell
- Prospective place encoding cell
- Irrespective place encoding cell
- Joaquin Fuster
- Cue delay neurons
- Delay action neurons
- Prefrontal cortex, Posterior parietal cortex and working memory
Have a great weekend!