Lecture 19 (Dec 5th):
Learning and Memory: Neural Mechanisms

*Lecture Outline*

1) Hebbian Mechanisms explain Classical Conditioning
   (and Learning in General)

2) *Neural* Underpinnings of Hebbian Mechanisms
   Long-Term Potentiation, LTP and Long-Term Depression, LTD

3) Examples of Hebbian Mechanisms in *Visual Cortex*
   (via an “LTP-like” mechanism)

4) Relationship between LTP and Learning/Memory Behavior

5) Non-Hebbian Neural Mechanisms
   e.g., Habituation (Aplysia) You can SKIP Sensitization

I will try to point out places where things are NOT well understood (e.g., LTD and Habituation)
Learning = Memory
and, whenever we learn something, the BRAIN must be changing!

Donald Hebb: *Learning* must be a *change* at the *synapse*

Hebbian Mechanism:

Increase in *synaptic strength* (i.e., connectivity) between a PRE- and POST- synaptic neuron when the two neurons are active simultaneously.

Or…. “Neurons that fire together get wired together”!

Increase in synaptic strength = the **effect** of the Neurotransmitter on the postsynaptic neuron becomes *larger*
Let’s revisit Classical Conditioning

We can think of this in terms of NEURONS in these brain areas!

i.e., “Neurons that fire together get wired together”!

This is an example for Implicit memory, but this kind of phenomenon happens for Explicit memories too!
Demonstrating Hebbian Mechanisms in Neurons
in vitro (i.e., in a dish)

Hippocampus Slices (in vitro)
1) Measure “baseline” response of POST-synaptic neurons to single pulse onto axons of the PRE-synaptic neurons.

2) Tetanus: Administer 1 - 10 sec of intense, high frequency (~100 Hz) stimulation of PRE-synaptic axons

**NOTE:** This produces a lot of simultaneous activity in the PRE- and POST- synaptic neurons!

3) The POST-synaptic response to a single pulse is now much larger than “baseline”, i.e., Synapse is STRONGER! This is LTP!

In a few slides, LTP = the effect of the Neurotransmitter on the postsynaptic neuron becomes larger
LTP: “Neurons that fire together, get wired together” (Hebbian)

Now….. Long Term Depression (LTD) (still Hebbian!)

“Neurons that don’t fire together, become less wired together”: Anti-correlated (not simultaneous) activity between a PRE-synaptic and POST-synaptic neuron will weaken the synapse between the two.

NOTE: Throughout the brain, postsynaptic neurons receive from multiple presynaptic neurons
Examples of Hebbian Mechanisms in the Visual System:

1) Monocular Deprivation: Kittens reared with monocular lid suture -> deprived eye

All of visual cortex is devoted to the experienced eye!!

2) Monocular Deprivation: Kittens reared with monocular lid suture -> deprived eye

….. while GABA agonist poured onto visual cortex (NOTE: GABA = inhibitory)

All of visual cortex is devoted to the deprived eye!!
How exactly does the synapse get stronger in LTP?
I cannot find an explanation for LTD … and we will be disappointed again when we get to Habituation

**Neurotransmitter = Glutamate (Amino Acid)…becomes more effective**

**Receptors for Glutamate:**

1) **AMPA** receptor: When Glutamate binds to it, AMPA receptor lets in Na\(^+\), which depolarizes neuron

2) **NMDA** receptor: When Glutamate binds to it, and if neuron is depolarized (from AMPA), NMDA receptor lets in Ca\(^{2+}\)

Ca\(^{2+}\) is KEY. Produces a protein inside the neuron that makes more AMPA receptors on dendrites (therefore Glutamate from a presynaptic neuron is more effective) …… this is LTP!

- Cannot produce LTP if use an *antagonist* drug that blocks NMDA.
  What kind of evidence is this for the role of NMDA?

- Once LTP is produced, NMDA receptors are no longer needed (and NMDA antagonists do not affect)…. because LTP is really about creating more AMPA receptors!

You don’t need to know the LTP events in super detail
**LTP and Learning/Memory Behavior**

**Assumption:** LTP is a process underlying learning because both LTP and learning (like Pavlov dog), follow Hebbian principles

**Known:**
- Functional NMDA receptors are necessary for the production of LTP (*last slide*)

**Prediction:**
- Drugs that block NMDA receptors should block *learning*  
  YES (shown in fish and rats)  
- Also, data from genetically modified mice:  
  - Abnormal NMDA receptors -> impaired learning  
  - Extra NMDA receptors -> better than normal learning
Neural Mechanisms of *Non-Hebbian* (Non-Associative) Learning
(also a change in synaptic strength, but not Hebbian!)

e.g., HABITUATION: a decreased response to repeated exposure
(e.g., a jackhammer in the background)

### Aplysia

If touch siphon, withdraws the gill

**HABITUATION:**
The withdrawal response becomes *less intense over time*
Neural Mechanisms of Habituation

Why use Aplysia to investigate the neural mechanism?

Have relatively few and large (1 mm) neurons, which are easily identified.

First, what is NOT responsible for Habituation (in blue)

Then, what IS responsible for Habituation (in red)

NOTE: This is obviously NOT Hebbian!

How do we reconcile this with LTP??!!??!!? No one knows!!

Do not confuse Habituation with LTD! LTD happens in the context of LTP!