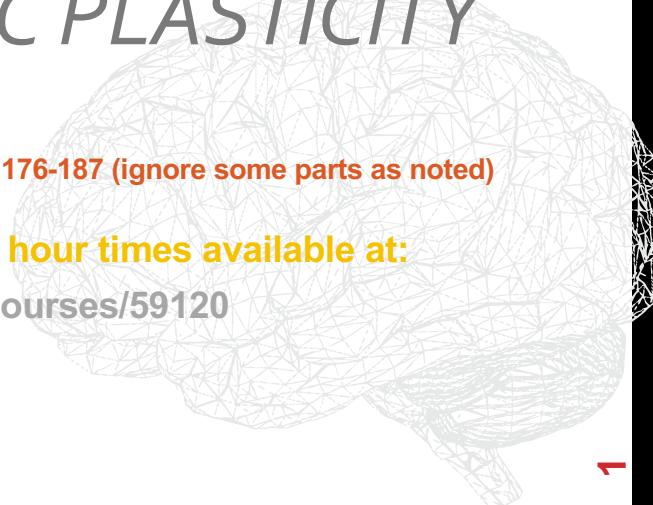


Neuro 80 Lecture 18

Nov 6, 2019



# **MCB/Neuro 80 - Neurobiology of Behavior**

## **Today's Topic:**

# ***MEMORY – SYNAPTIC PLASTICITY***

Lecture 18

Optional reading: Purves et al., Neuroscience 6th pages 176-187 (ignore some parts as noted)

Lecture notes, review questions, office hour times available at:

<https://canvas.harvard.edu/courses/59120>

# CLIMBING MT. POTENTIAL (IN PRACTICE)



# Synapses are dynamic – can be modulated

## What causes synaptic strength to change?

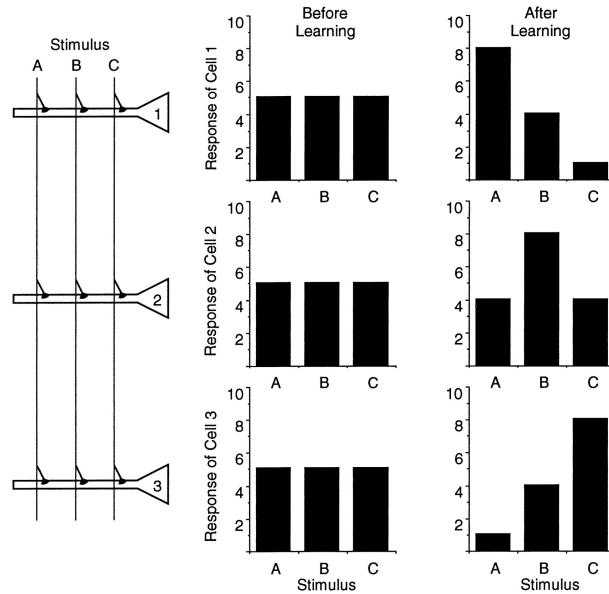
- Diseases (myasthenia gravis, startle disease...)
- Drugs (therapeutic, recreational...)
- Prior or ongoing activity (experience...learning?)

## What mechanisms lead to altered synaptic strength

- Rapid change in synaptic efficacy with no structural change
- Growth or shrinkage of synapse
- Addition or loss of synapses



# Synapses, learning and memory



# Long Term Potentiation and Hebb's postulate

Donald Hebb (1949)

---

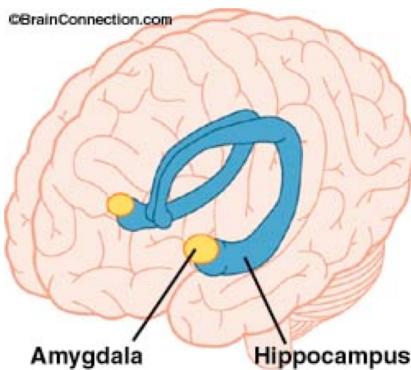
Let us assume that the persistence or repetition of a reverberatory activity (or "trace") tends to induce lasting cellular changes that add to its stability....

When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

## Why did LTP elicit so much excitement?

- LTP can last for weeks *in vivo*
- Occurs at many types of synapses
- Candidate for a cellular/molecular mechanism of learning & memory
  1. Persistent – long lasting changes
  2. Depends on strong or repeated stimuli
  3. Synapse-specific effects
  4. Associative properties (fire together, wire together)

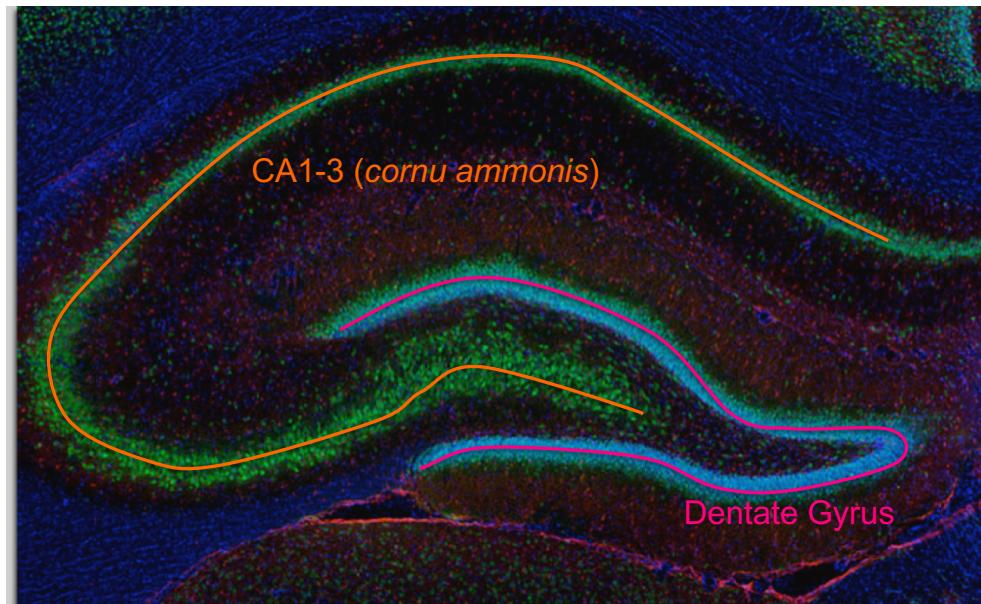
## Vertebrate model of LTP: Hippocampus



**Functions:** episodic memory consolidation, spatial navigation

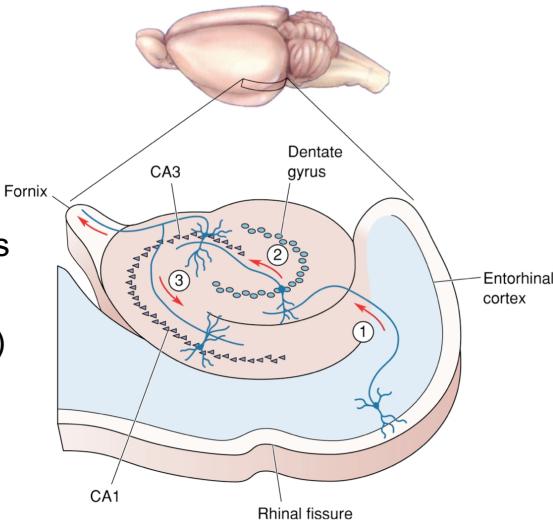
One of the most thoroughly studied areas of the mammalian brain due to highly structured synaptic pathway

Two cell layers form a horn-like pattern

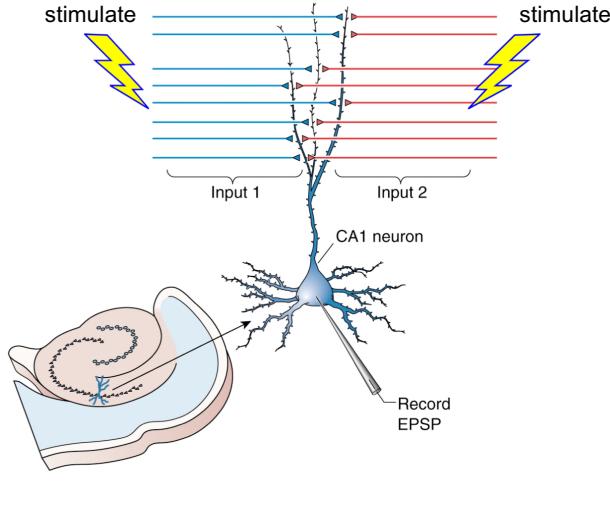


# Study of long-term plasticity: Hippocampus

- Hippocampus is critical region for memory
- Acute slices of the hippocampus contain intact synaptic connections that can be tested for plasticity
- Both Long Term Potentiation (LTP) and Long Term Depression (LTD) are prevalent in the hippocampus

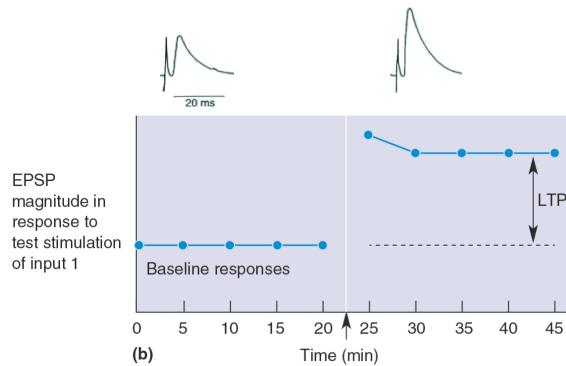


# Changing the strength of a synapse (LTP)



(a)

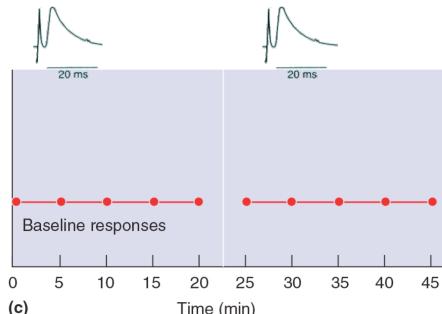
Copyright © 2010 Wolters Kluwer. All Rights Reserved



(b)

Copyright © 2010 Wolters Kluwer. All Rights Reserved

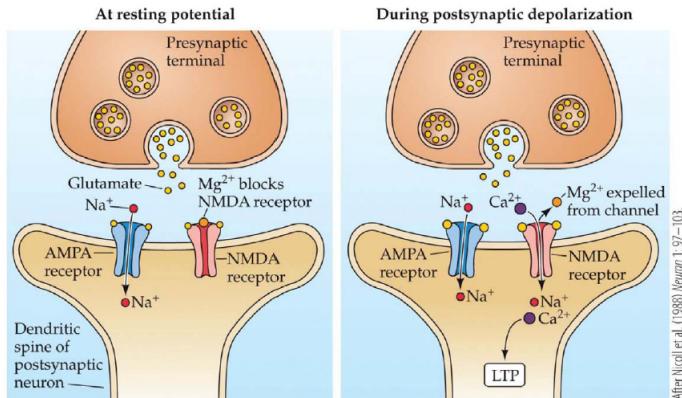
EPSP  
magnitude  
in response  
to test  
stimulation  
of input 2



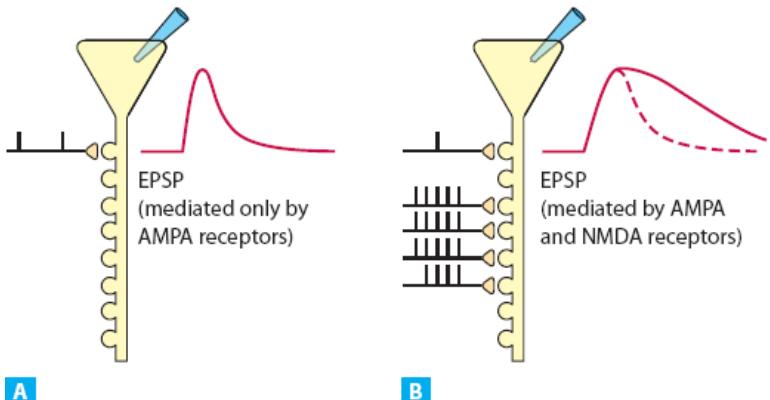
(c)

Copyright © 2010 Wolters Kluwer. All Rights Reserved

# AMPA and NMDA receptor-mediated EPSPs

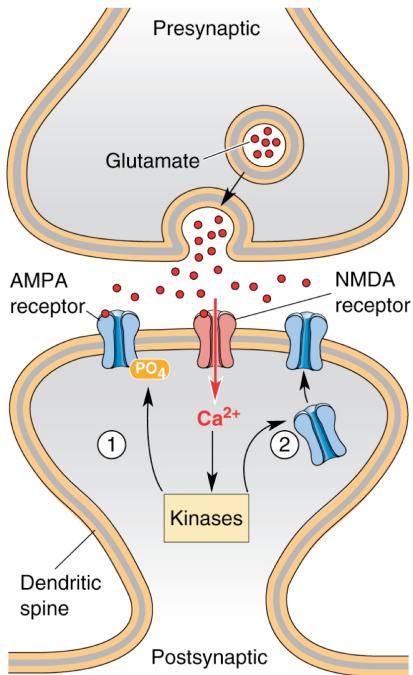


NEUROSCIENCE 6e, Figure 8.10  
© 2016 Oxford University Press



Source: Eric J. Nestler, Steven E. Hyman, David M. Holtzman, Robert C. Malenka: *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*, 3rd Edition:  
[www.neurology.mhmedical.com](http://www.neurology.mhmedical.com)  
Copyright © McGraw-Hill Education. All rights reserved.

# Mechanisms of synaptic strengthening



- Activation of NMDA receptors
- Calcium entry into “postsynapse”
- Enzymatic reactions (phosphorylation/dephosphorylation)
- Changes in postsynaptic receptors

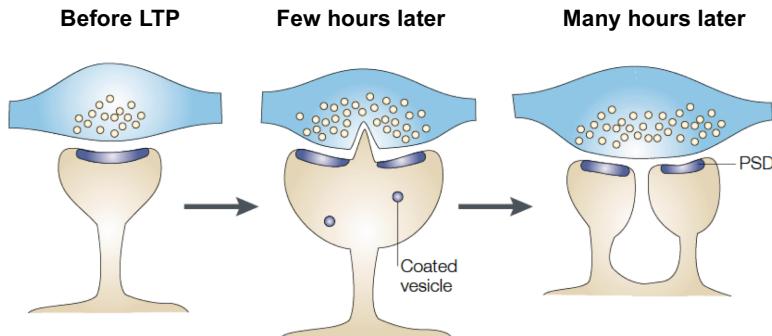
## Coincidence detection by NMDA receptors

Needs both presynaptic activity (glutamate release) and postsynaptic activity (depolarization)

# LTP can cause structural changes

## Spine Properties Affected:

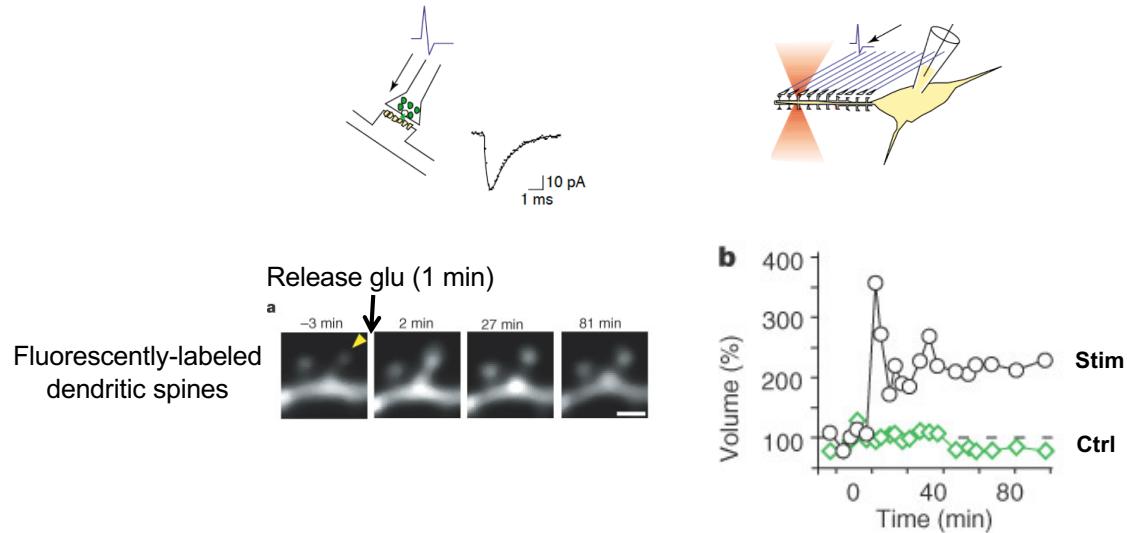
- Motility/Shape (actin dynamics)
- Stability of postsynaptic density (PSD) components
- Size (Volume, PSD, active zones)
- Number of Spines



Hering and Sheng, Nature Rev Neurosci 2001. 2: 880

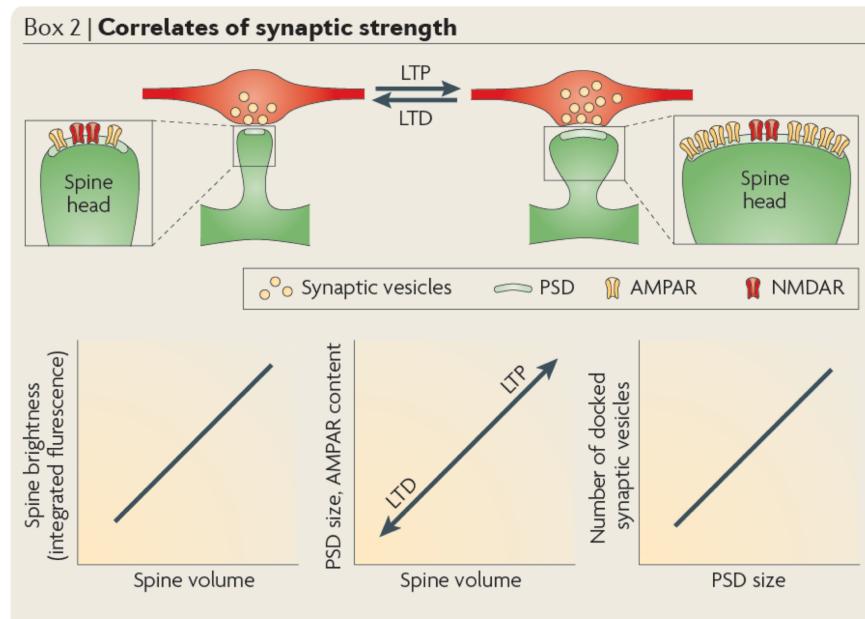
# Spine size increases after LTP

Releasing glutamate at single spine → LTP at a single spine

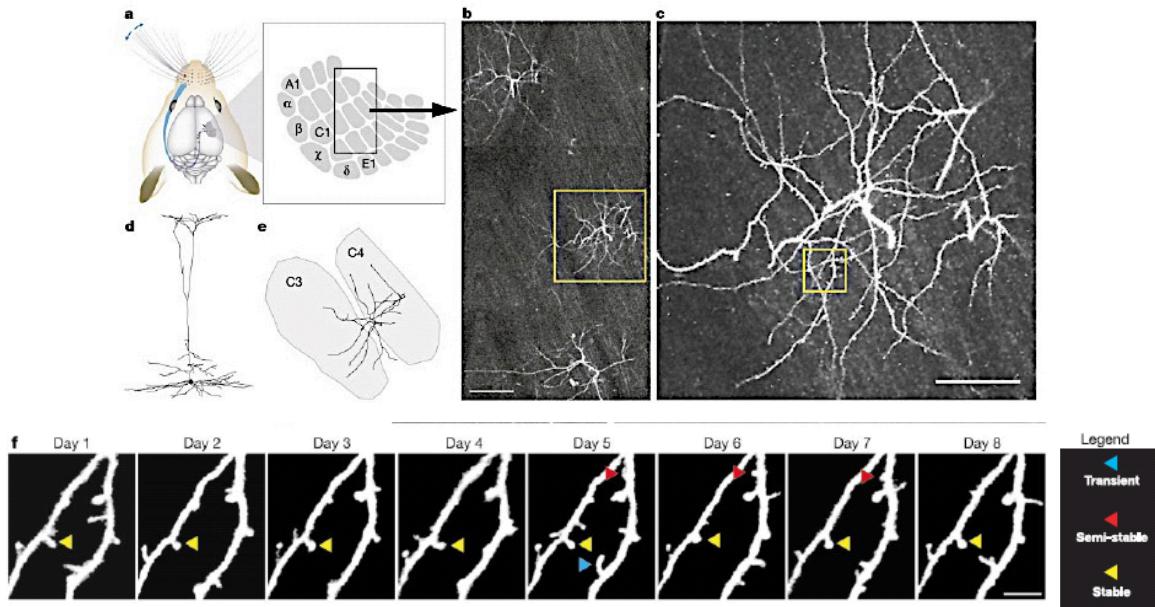


Matsuzaki et al. Nature 2004. 429: 761

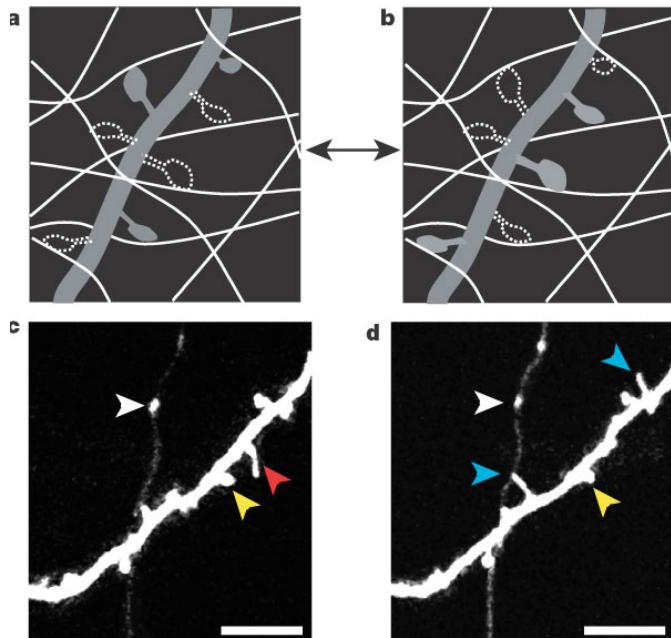
## Larger spines are stronger (larger EPSPs)



# Spines in intact brains can be dynamic

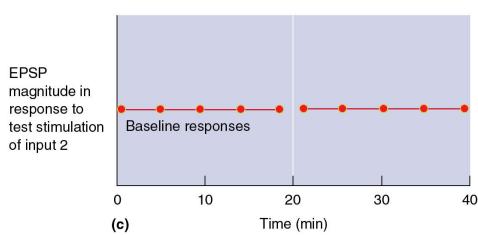
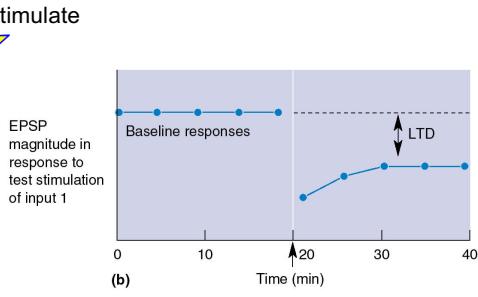
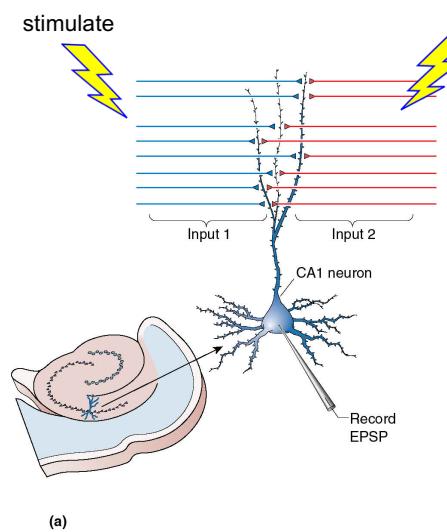


## Spine plasticity & wiring alterations

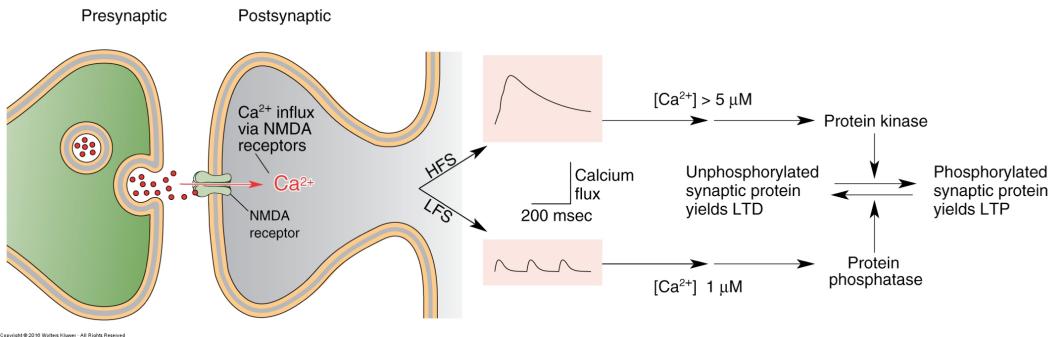


Chklovskii et al. Nature 2004. 431: 782.

# Weakening of synapses (LTD)

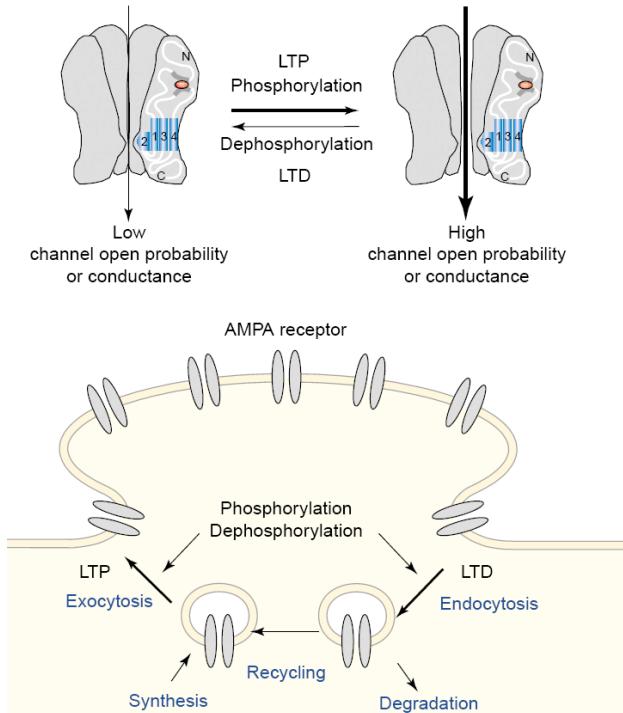


# Weakening of synapses (LTD)

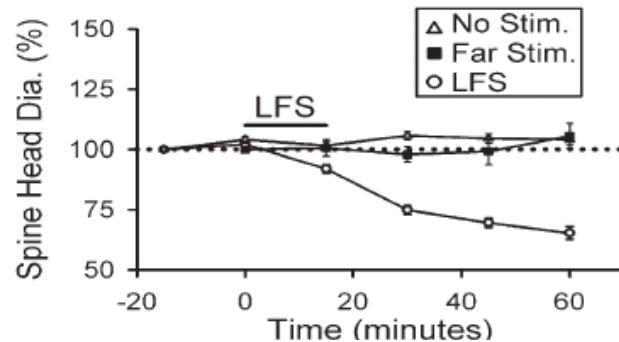
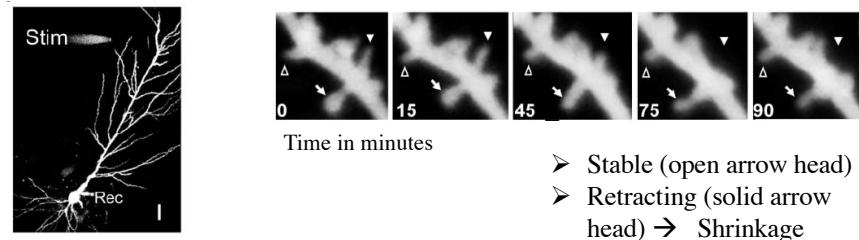


$Ca^{2+}$  can lead to either LTP or LTD, depending on timing and amount

# LTD & LTP have opposite effects on AMPA receptors



## Spines can shrink and retract during LTD



Neuron, Vol. 44, 749–757, December 2, 2004,

## LTD is a corollary of Hebb's postulate

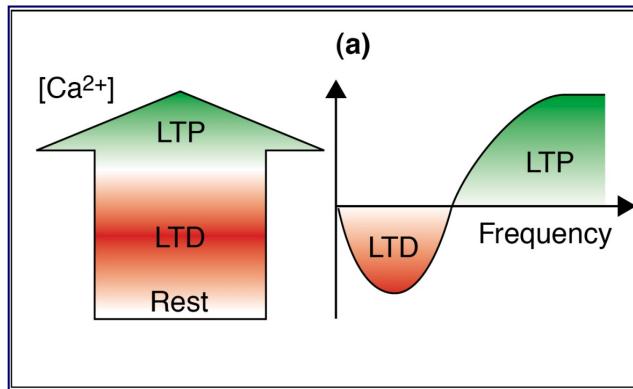
- When the presynaptic axon is active, and at the same time the postsynaptic neuron is *strongly activated* by other inputs, then the synapse formed by the presynaptic axon is strengthened

LTP: “Neurons that fire together wire together”

- When the presynaptic axon is active, and at the same time the postsynaptic neuron is *weakly activated* by other inputs, then the synapse formed by the presynaptic axon is weakened

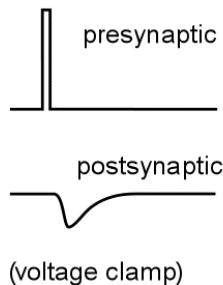
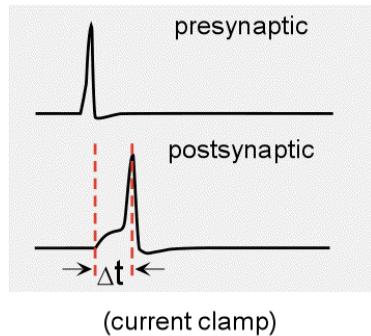
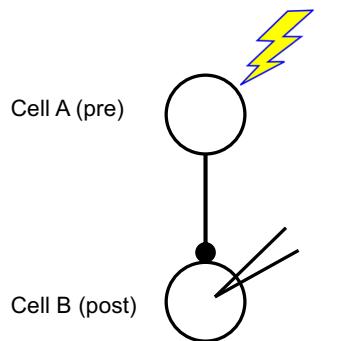
LTD: “Neurons that fire out of sync, unlink”

## How can increased calcium lead to both LTP and LTD?

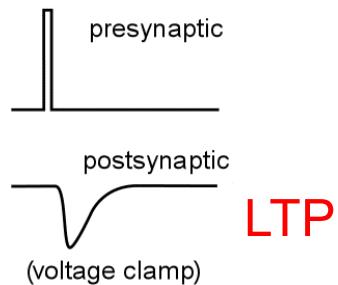
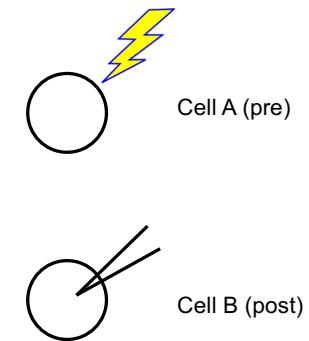


- A. Level of Ca<sup>2+</sup> at the spine determines LTD or LTP
- B. Low frequency synaptic firing (~ 1-10 Hz) produces LTD; high frequency synaptic firing (~50-100 Hz) produces LTP.

## More realistic situations: spike-time-dependent plasticity



- Repeat ~50 times
- Measure D EPSP



## Timing in LTP & LTD

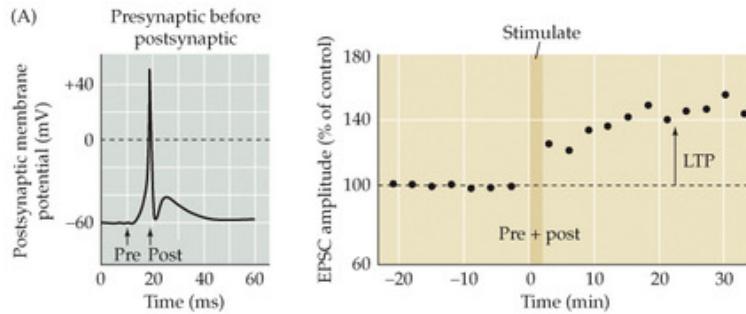
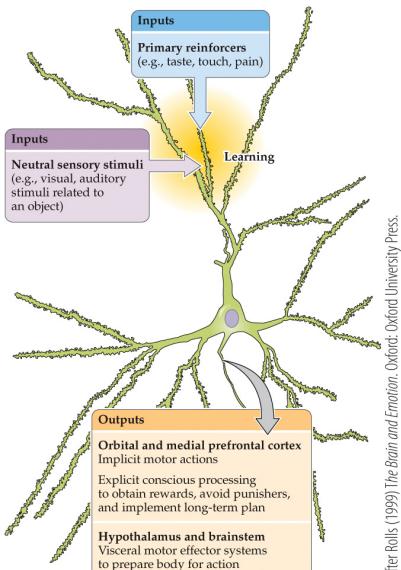
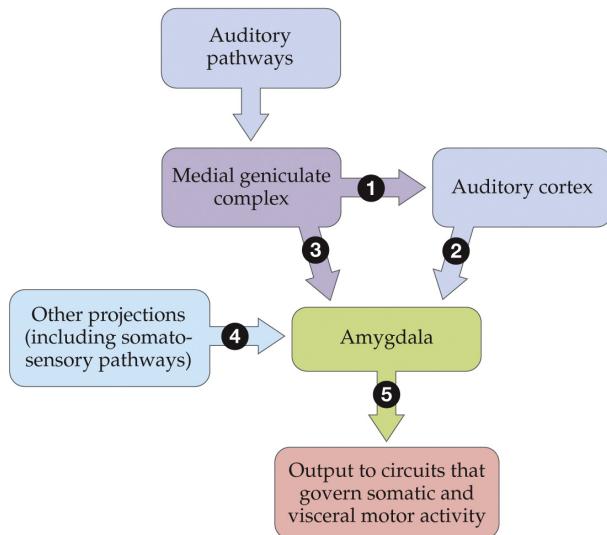


Fig 8.18 from Purves book

# Amygdala and fear conditioning



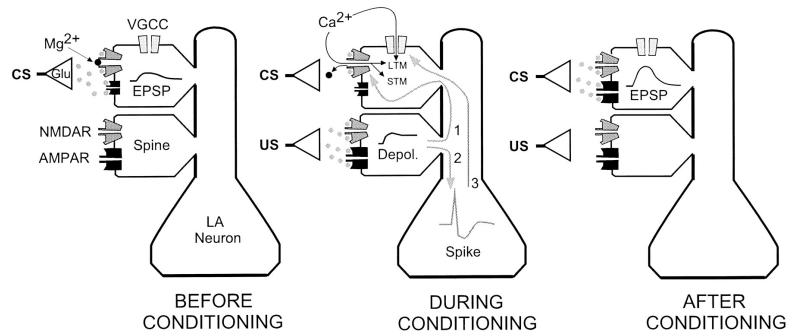
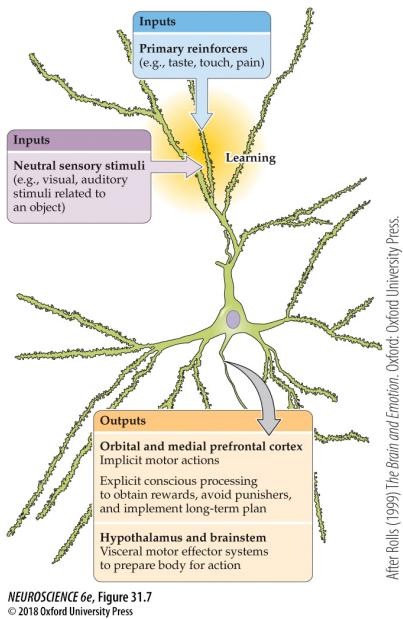
NEUROSCIENCE 6e, Figure 31.7  
© 2018 Oxford University Press



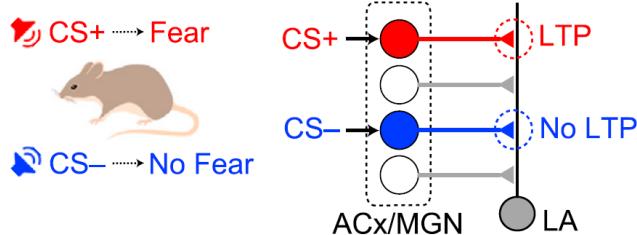
NEUROSCIENCE 6e, Figure 31.6  
© 2018 Oxford University Press

How do these changes can occur at a molecular & cellular level?

# Synaptic plasticity in amygdala – fear conditioning



Hugh T. Blair et al. *Learn. Mem.* 2001;8:229-242



Kim & Cho, 2017, *Neuron* 95, 1129–1146

# Summary

1. Long-term potentiation in hippocampus and relation to Hebb's postulate (synapse specificity)
2. Mechanisms of LTP – NMDA receptors, calcium influx, activation of CaMKII, more AMPA receptors on surface
3. Structural changes in synapse/spine.
4. Long-term depression – how it is induced, and mechanistic relation to LTP (NMDA receptors, calcium influx, but different signaling)

## Lecture 18 - Long Term Synaptic Plasticity

Pre-class notes for November 6, 2019

Reading: *Neuroscience ed. 5* by Purves et al., pages 176-186 (ignore Box 8B, page 182 and LTD in cerebellum on pages 185 and vicinity)

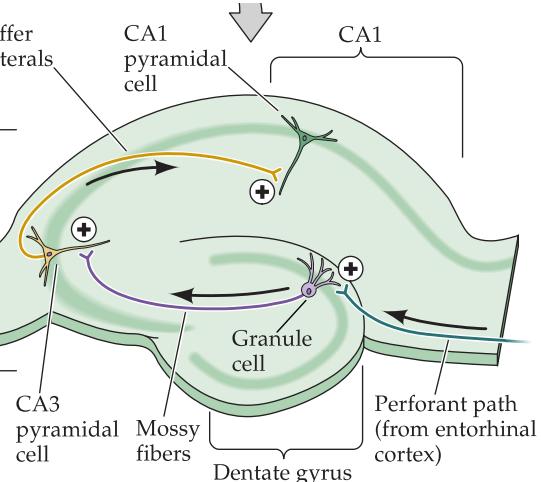
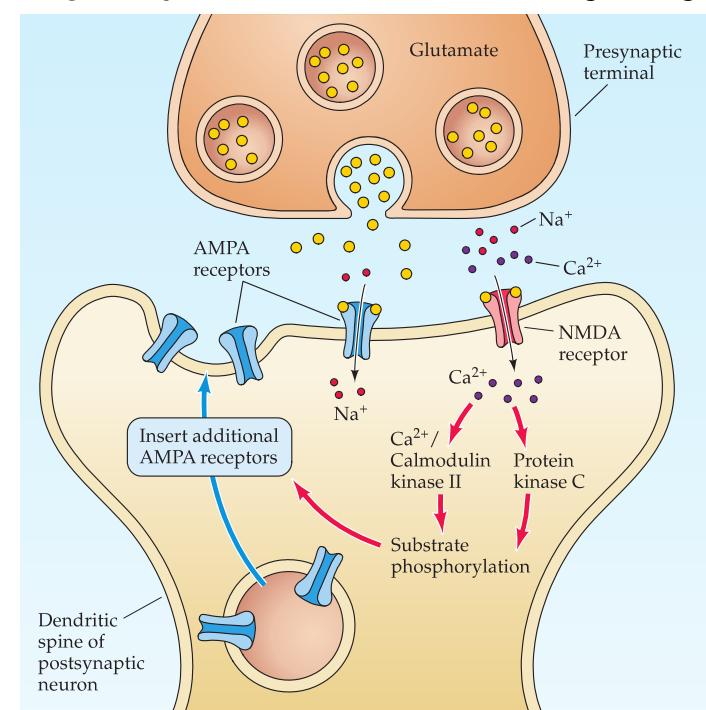
**Hebb's Postulate** - the idea that the timing of the pre and post synaptic firing of action potentials can alter the synaptic strength. Summarized as *Neurons that fire together, wire together* and *Neurons out of synch, loose their link*.

**Long term plasticity** - persistent changes in the strength of synaptic connectivity lasting hours, days, or longer.

**Hippocampus** - area of the mammalian brain, located in the temporal lobe, that is particularly important in memory formation and/or retrieval. Dissected slices of the hippocampus contain intact synaptic connections. Long term potentiation (see below) was first discovered in the hippocampus and it continues to be an important area for plasticity studies.

**NMDA receptor** - subtype of glutamate receptor that is typically permeable to  $K^+$ ,  $Na^+$  and  $Ca^{2+}$ . Extracellular  $Mg^{2+}$  blocks the pore of NMDA receptors at negative membrane potentials, so the channel acts as a *coincidence detector*: both glutamate (presynaptic release) and postsynaptic depolarization are required for current to flow through the channel.

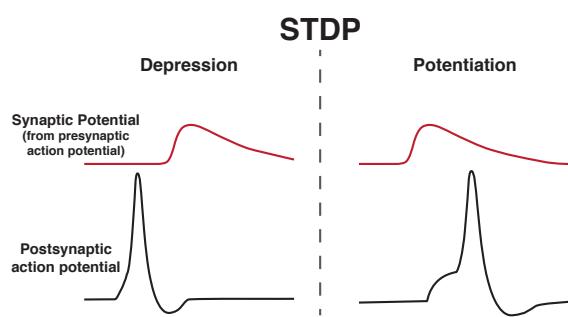
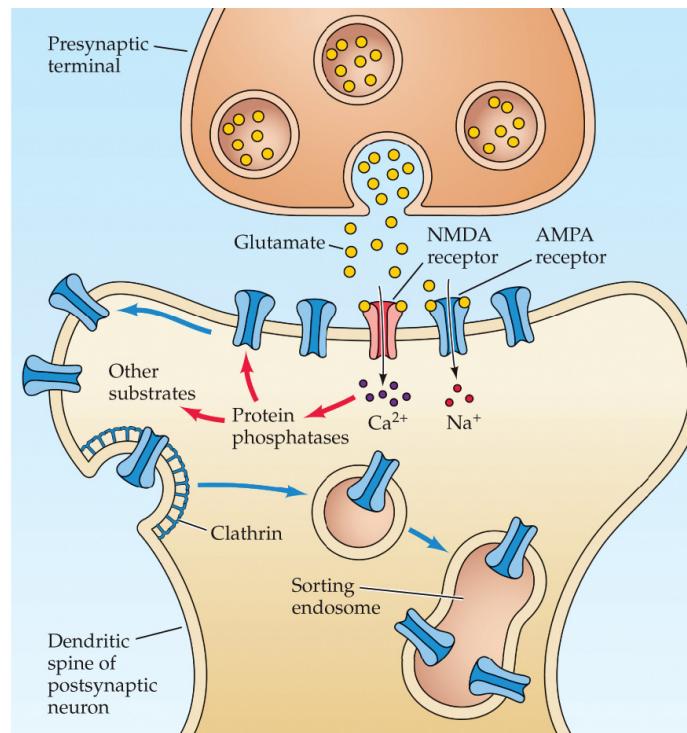
**Long term potentiation** - a sustained strengthening of synaptic connections caused by previous patterns of neuronal and synaptic activity. Initially discovered in the hippocampus and repeated at various synapses in the hippocampus. Usually a repeated, high intensity stimulation of the axons from CA3 cells, connecting to CA1 cells, leads to a strengthening (*potentiation*) of that synaptic connection. Frequent calcium entry through NMDA receptors causes a signaling cascade that eventually leads to insertion of additional AMPA receptors and even sprouting of additional synaptic connections (spines).



**Long term depression** - a sustained weakening of synaptic connections caused by previous patterns of neuronal and synaptic activity. Several different mechanisms have been found underlying LTD at different synapses. In the hippocampus, small, spaced activation and opening of NMDA channels leads to a signaling cascade which also eventually causes the internalization of AMPA receptors.

**Calcium signaling** - it may seem contradictory that both LTP and LTD can be triggered by calcium ions flowing into the cell through NMDA receptors, but it is important to consider how much calcium is entering the cell and for how long. A sustained, modest increase in calcium concentration activates protein phosphatases (PP2A and Calcineurin) and leads to a decrease in receptors and a smaller postsynaptic response, while a large, brief increase in the calcium concentration triggers kinases (CaMKII and Protein kinase C) which leads to more receptors and a stronger postsynaptic response (and also suppress or overrides any LTD responses).

### LTD at CA3 to CA1 synapse in the hippocampus



**Spike-timing-dependent plasticity (STDP)** - bidirectional changes in synaptic strength induced by varying the relative timing between the presynaptic and postsynaptic action potentials (spikes). Depression is induced when the EPSP arrives after the postsynaptic neuron spike. Potentiation is induced if the EPSP arrives before the postsynaptic spike.

**Learning Objectives:** (By the end of Lecture 12 you should be able answer the following)

1. Describe how LTP is initiated and recorded in the hippocampus.
2. Diagram the signaling cascade from glutamate release to insertion of AMPA receptors and eventual structural changes that leads to LTP in the hippocampus.
3. Explain how NMDA receptors act like coincidence detectors.
4. Discuss how the same signal,  $\text{Ca}^{2+}$  entry through NMDA receptors, can trigger both LTD and LTP.
5. Use a long-term plasticity mechanism (LTP, LTD, or STDP) to explain and illustrate Hebb's postulate.