Memory Systems III
How Stored: LTD and Consolidation

Reading:
BCP Chapter 25
Learning is the acquisition of new knowledge or skills. Memory is the retention of learned information.

Many different kinds of information are learned and remembered (e.g., facts, events, skills). Evidence suggests that no single brain structure or cellular mechanism accounts for all learning. Moreover, the way in which information of a particular type is stored may change over time.

Where stored
- Types of Memory
- Cortical structures

How stored
- Engram
- Long-term potentiation
- Long-term depression
- Consolidation
Neural network models suggest that memory is stored in groups of neurons via a unique pattern or ratio of activity across the assembly.

Physical change of memory ► modification of synaptic weight (some up, others down)

The strengthening of synaptic connections (as measured by an increase in EPSP amplitude) is called long-term potentiation.

LTP is induced when NMDA receptors are activated by glutamate and the post-synaptic cell is strongly depolarized at the same time. In this case, calcium enters the cell and activates kinases that temporarily phosphorylate existing AMPA receptors and cause insertion of new AMPA receptors.
The weakening of synaptic connections (as measured by a decrease in EPSP size) is called long-term depression (LTD).

LTD can be induced using stimuli that evoke a modest postsynaptic response, for example a tetanic stimulation at low frequencies (1-5 Hz). The effect is site-specific: homo-synaptic LTD.
Induction of LTD

Evidence suggests that LTD (like LTP) is induced by a rise in postsynaptic calcium. But how can the same signal, $\text{Ca}^{+2}$ entry through the NMDA receptor, trigger both LTD and LTP?

The key difference lies in the level of NMDA receptor activation (bidirectional regulation):
- low level $\Rightarrow$ LTD
- high level $\Rightarrow$ LTP

Instead of activating kinases, modest levels of calcium activate protein phosphatases that dephosphorylate AMPA receptors and cause receptor internalization.

![Bidirectional regulation diagram]
Glutamate Receptor Trafficking

Stable synaptic transmission: AMPA receptors are replaced (every 15 mins) maintaining the same number.

LTD and LTP disrupt equilibrium via bidirectional regulation of AMPA receptor (maximum current flow via phosphorylation and) location (off/on membrane)

“Egg carton” model of AMPA receptor trafficking, where a protein called post-synaptic density PSD-95 comprises the slot protein:
- LTP increases the number of slots (where new AMPA receptors initially containing the GluR1 subunit are inserted)
- LTD reduces the number of slots (destroys PSD-95 and AMPA receptors)
LTP and LTD have been studied extensively in the hippocampus. Is NMDA receptor-dependent plasticity observed elsewhere? Recent research indicates that the same mechanism is indeed observed throughout cortex. For example, bidirectional synaptic plasticity is found in area IT (inferotemporal cortex), an area that stores visual information including familiar faces.
LTP, LTD and Memory

LTP and LTD have been studied extensively; what evidence links them to memory?

Monitoring state of synaptic transmission during learning
• in inhibitory avoidance experiments, rats learn to associate a place (the dark side of a box) with an aversive experience (a foot shock). This type of learning is not subtle, and LTP is readily observable in the hippocampus (right).
• exposure to a novel environment without a foot shock causes LTD instead.

Blocking NMDA receptors with antagonists
• no learning in inhibitory avoidance expts
• in water maze experiments, NMDA receptor blockers prevent learning of location of the escape platform

Genetic knockouts/knockins
• knockout CaMKII (no learning)
• knockout/in number of NMDA receptors (reduced/enhanced learning)
Synaptic Homeostasis

If unchecked, then synaptic plasticity could lead to unstable neuronal responses; that is, a little LTP leads to further potentiation, whereas a little LTD leads to further weakening until stimulus selectivity (and memory) is lost.

Homeostatic mechanisms (over hours to days) are needed to provide stability and keep synaptic weights within useful dynamic range:

- Metaplasticity
- Synaptic scaling

Metaplasticity: the synaptic modification threshold between LTD and LTP changes depending on synaptic history and cellular activity. When activity rises (falls):

- the modification threshold slides up (down)
- increasing (decreasing) the ratio of NR2A/NR2B subunits in NMDA receptors (NR2A admit less calcium; NR2B admit more calcium)
Synaptic Homeostasis 2

Homeostatic mechanisms (over hours to days) are needed to provide stability and keep synaptic weights within useful dynamic range:

- Metaplasticity
- Synaptic scaling

Synaptic scaling: adjustment of absolute synaptic effectiveness that preserves the relative distribution of synaptic weights

Mechanism
- calcium entry via voltage-gated Ca\(^{2+}\) channels
- bidirectional activation of CaMKIV (high/low levels of calcium increase/decrease activity)
- removal/insertion of both AMPA and NMDA receptors
At glutamatergic ionotropic synapses, plasticity is induced by changing the number of phosphate groups attached to AMPA receptors and regulating the number of AMPA receptors at the synapse.

Phosphorylation, however, is not a viable long-term consolidation mechanism because:
- phosphorylation is not permanent
- protein molecules are routinely replaced

Evidence suggests that short-term and long-term phases of memory depend on different molecular mechanisms:
- short-term (early-LTP): kinases
- long-term (late-LTP): protein synthesis
Phosphorylation of synaptic proteins, and memory, could be maintained if the kinases, the enzymes that attach phosphate groups to proteins, were made to stay “on” all the time.

Normally, kinases are tightly regulated and are “on” only in the presence of a second messenger (e.g., calcium).

Recent evidence suggests that some kinases can become independent of their second messengers:
- CaMKII
- PKMζ

Molecular Switch Hypothesis: kinases that can auto-phosphorylate could stay “on” all the time. CaMKII is such a kinase, where a large enough calcium influx promotes (for a time) faster phosphorylation than de-phosphorylation.
Recent evidence has implicated a new kinase in the maintenance of early phase LTP: protein kinase M zeta.

Strong synaptic activation, and the corresponding rise in calcium concentration, triggers a burst of synaptic protein synthesis (recall that dendritic spines contain free ribosomes), and the generation of PKMζ from mRNA in the spine.

PKMζ phosphorylates proteins involved in regulating AMPA receptor number. In addition, it is involved in the regulation of proteins involved in mRNA translation; thus, it promotes (for a time) its own synthesis.

A small protein called ZIP temporarily inhibits the function of PKMζ, and can erase memories.
Kinases have the ability to preserve memories for a time (short-term: on the order of hours), but ultimately the self-generating mechanisms fail.

Evidence suggests that new proteins are needed to convert temporary storage into permanent storage (late-LTP). That is, after LTP induction, dendritic spines must signal the soma to produce new proteins, and these must travel back to the spine to effect a permanent change.

The message to transcribe new proteins is dependent on the concentration of cyclic AMP (cAMP), which increases in response to calcium influx. cAMP activates protein kinase A, which travels to the soma where it phosphorylates CREB-1, a gene transcription activator (CREB: cyclic AMP response element binding protein).
How do the newly formed consolidation proteins travel back to the exact spines that triggered their synthesis?

Evidence suggests that there is a synaptic tagging mechanism (lasting ~2 hours), believed to involve phosphorylation of synaptic proteins by various kinases including CaMKII and PKMζ.
How do the newly formed consolidation proteins ensure that potentiation is long-term?

Evidence suggests that blocking protein synthesis fails to disrupt memories that have already been consolidated. This suggests that continual protein synthesis is not required … rather, it suggests that the lasting imprint of new protein synthesis is the construction or demolition of synapses.

Recent advances in microscopy and cell labeling have made it possible to observe that putting a rat in a complex environment filled with items to explore increases the number of synapses per neuron by 25% in occipital cortex.