

# Neurophysiology of Learning and Memory

The basis of learning and memory are synapses. There are 2 types of those - Electrical and chemical synapses. Electrical synapse function via gap junction, therefore are fast, but lacking plasticity.

We have approximately an order of  $10^{14}$  synapses (syn- together and haptein - hug, press) -- Ch. S. Sherrington.

A typical neuron forms thousands of synapses. Synaptic delay approx. 1 ms.

Santiago Ramón y Cajal Hebb's Law - When an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place. Cells that fire together wire together birds of feather flock together.

## Synaptic plasticity

### Immediate processes of short synaptic plasticity

Phosphorylation increases intracellular calcium levels (second messenger) by entering the NMDA receptor cell, or by releasing intracellular reserves.

### Long-term synaptic plasticity

Insertion of receptors into the synaptic cleft synthesis of new proteins increases in the number of synaptic knobs sprouting of collateral fibers (sprouting) increases the outflow from presynaptic terminals through a retrograde signal.

Study via EPSP (Excitatory Postsynaptic Potential), fEPSP (field Excitatory Postsynaptic Potential).

In lower invertebrates - *Aplysia californica*.

## Long-term potentiation

LTP described by Tim Bliss and Terje Lomo in the hippocampus of an anesthetized rabbit as a long-term increase in EPSP after tetanus stimulation. High-frequency stimulation is essential.

Perforant pathway associative LTP, mossy fiber pathway, CA3, CA1.

In one training, there is an early phase (partial increase and gradual fading): AMPA activation, depolarization, NMDA unblocking, Ca-calmodulin kinase II, PKC, MAPK, parallel activation of adenylyl cyclase, cAMP, activation of PKA. With more training, late LTP induction: MAPK (ERK) shows persistent activity.

Protein kinase Mzeta can maintain a memory trace in a matter of days is atypical in that it has a self-phosphorylating function and by activating it keeps itself active. Controversial topic, some people refuse to believe that the memory trace is caused by one molecule. Experiment with a ZIP inhibitor (thus erasing the memory trace), but ZIP is probably not quite specific to Mzet. Science 2006, 313(5790):1141-4.

## Long-term depression

LTD is the opposite of long-term potentiation, it consists in low-frequency stimulation.

Metabotropic glutamate receptors or cannabinoid receptors (also coupled with G-protein) play a role. There are a number of types of LTD, but it is not clear whether some are only given by experimental setting, or are some general.

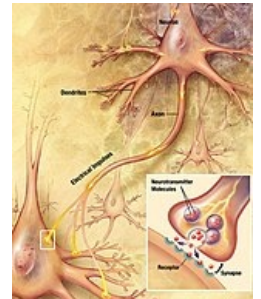
## LTP-to-memory relationship

LTP or LTD --- does not equal memory, but is the result of the same mechanisms that the organism uses to create a memory trace.

- Experience -> Change in synaptic efficacy (natural plasticity) -> Memory.
- Tetanization -> Change in synaptic transmission efficiency (LTP) -> Increase in EPSP (non-physiological tetanus...).

**Animals with NMDA receptor blockade do not learn where the islet is in the maze.**

Distributed coding memory.



Chemical vs. Electrical Synapses

# Pathophysiology of memory

Amnesia was only declarative in H. M. based on this, a distinction was made between declarative and non-declarative anterograde.

The prefrontal cortex (PFC) as a structure key to working memory in animals except primates, the prefrontal region is rather smaller and its homology with PCF in primate is a subject of debate.

Dopaminergic Phineas Gage (1948) are important for the functioning of working memory.

Hippocampus controls the spatial memory, declarative memory in humans (CA1, CA2, CA3), perforating pathway, entorhinal cortex (Glu), medial septum (ACh, GABA). place cells O'Keefe and Dostrovsky 1971 – spatially specific activity.

Basal ganglia, amygdala - Non-declarative memory.

## Methods of study

Study can take place in vitro, in vivo electrophysiology, recording from moving animals.

### Multiple single unit recording

- **Hippocampal place cells**
- **Tetragens** (Szymusiak & Nitz, Curr Prot Neurosci 6.16, 2002)
- **Clustering** - Sorting the multi-unit record into individual neurons
- **Firing rate maps** (Muller & Kubie, 1987) – Neuronal activity follows the rotation of orientation signs
- **Remapping** - Rate and global (Colgin et al., Trends Neurosci, 2008)
- **Time series**
- **Neuronal ensembles**

Ferbinteanu and Shapiro, Neuron, 2003 - Firing neurons not only according to where the animal is, but also according to where it came from.

- **Overdispersion** (Fenton et al., J Neurosci, 2010) - Local neurons are not local, but rather map the experience of an animal. They are not equally active in different environments, the activity may change as the environment changes.
- **Entorhinal grid cells** (Hafting et al., Nature, 2005) - Hexagonal network of cells, the scale changes depending on where the neuron is located (dorsal have a very small scale, ventral coarser). – triangulation hexagonal network of the surrounding environment. They are active in any environment.

### Intervention techniques

- **Permanent lesions** - Aspiration, surgical, thermocoagulation, excitotoxic, selective neurotoxins.
- **Temporary inactivations** (functional lesions) - Implanted cannulas for intracranial injections, tetrodotoxin, other ion channel blockers, CNQX AMPA antagonist, inhibitory neurotransmission agonists (muscicoline), local application of agonists and specific receptor antagonists.
- **Genetic manipulations** - Knock-out, knock-down, knock-in; Cre recombinase; cell type-specific promoters; inducible Tet-O system.

### IEG imaging

Neural activity triggers the expression of immediate-early genes --- IEGs in neurons. For her, there is no need for protein synthesis. Genes e.g.: Arc (effector early gene).

- Messenger RNA -
  - In situ hybridisation: radioactive/FISH
  - qPCR
  - Northern blot is less used method, more often PCR
- Protein
  - Immunohistochemistry
  - Western blot

Guzowski et al., 1999, Nat Neurosci

### Optogenetics

Cationic canapé, chloride pump, light-sensitive chimeric GPCR, combination of different wavelengths, viral vectors, combination with other transgenes (Cre recombinase, tetracycline transactivator (tTa)) Zhang et al., 2010, Nature Prot

Creating false memories: Ramirez et al., Science 2013.

## Clarity samples

Degreased tissues fixed in the polymer, degreasing will allow light to pass through, trigger optogenetic structures, in situ hybridization, experiments can be repeatedly carried out.

## Links

### External links

- [Protein kinase C zeta type - Wikipedia](#)
- [Henry Molaison - Wikipedia](#)
- [Phineas Gage - Wikipedia](#)
- [Tetrode \(biology\) - Wikipedia](#)