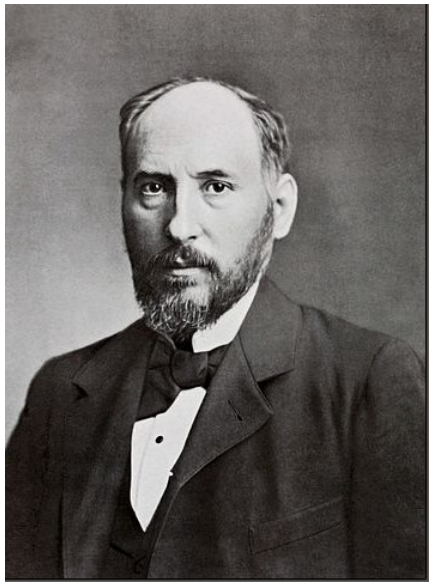
Synaptic Plasticity

- Synaptic Plasticity: a few historical aspects and biological aspects
- Hebbian learning and the Hopfield model
- Short Term Plasticity as substrate for working memory
- Metaplasticity and Reinforcement Learning

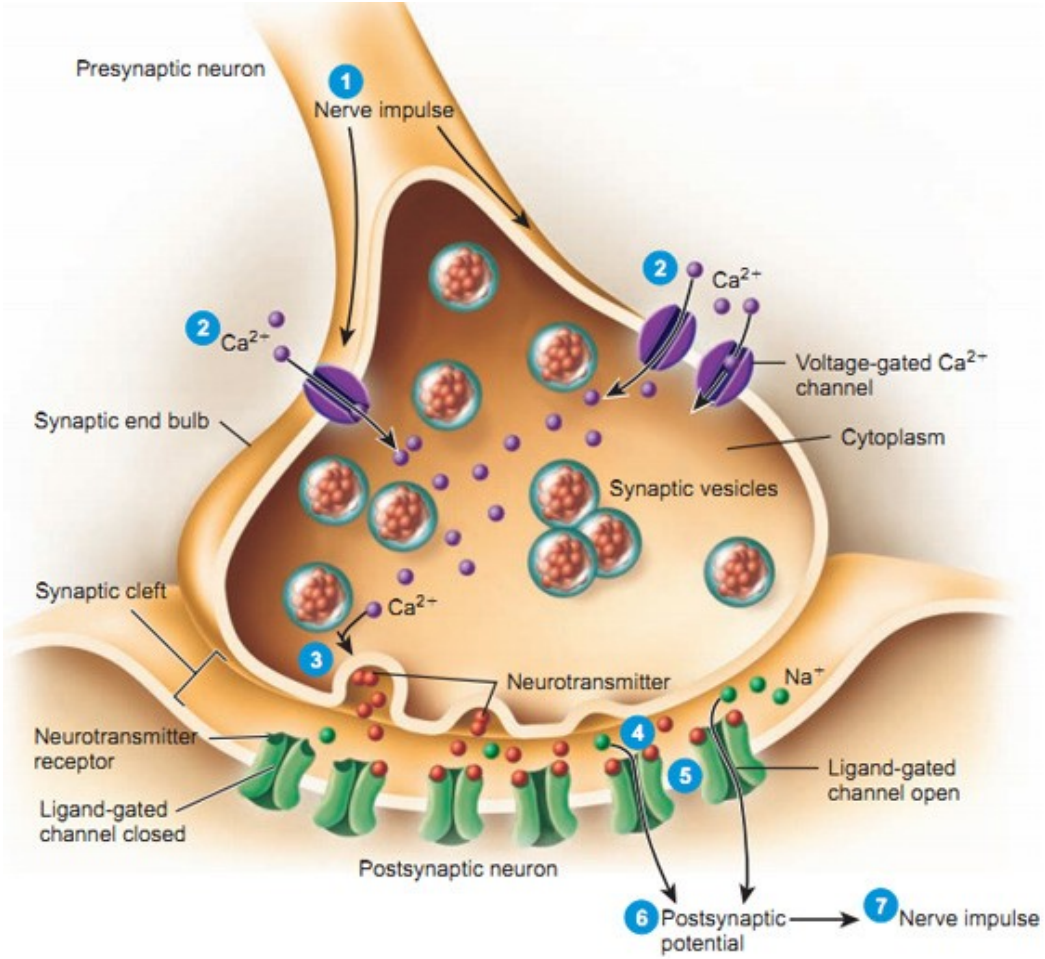
Synaptic Plasticity

- At the end of the 19th century it was recognized that the number of neurons did not increase significantly in adults
- However the nervous system was capable of generating short and long term modifications of behavior
- In 1894 Ramón y Cajal suggested that these effects could be generated by the strengthening of the connections between neurons



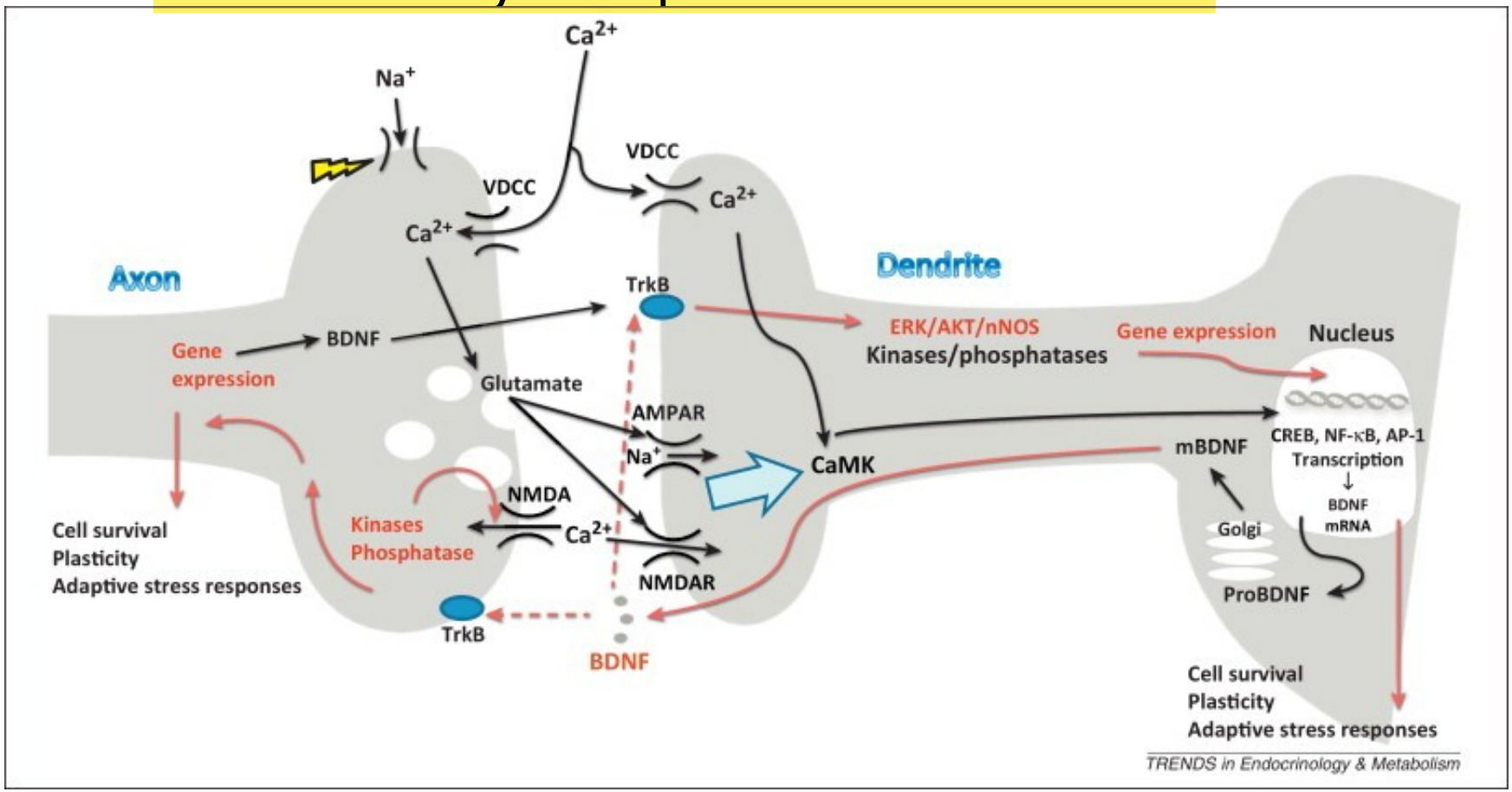
Synaptic Plasticity

- The synaptic structures



Synaptic Plasticity

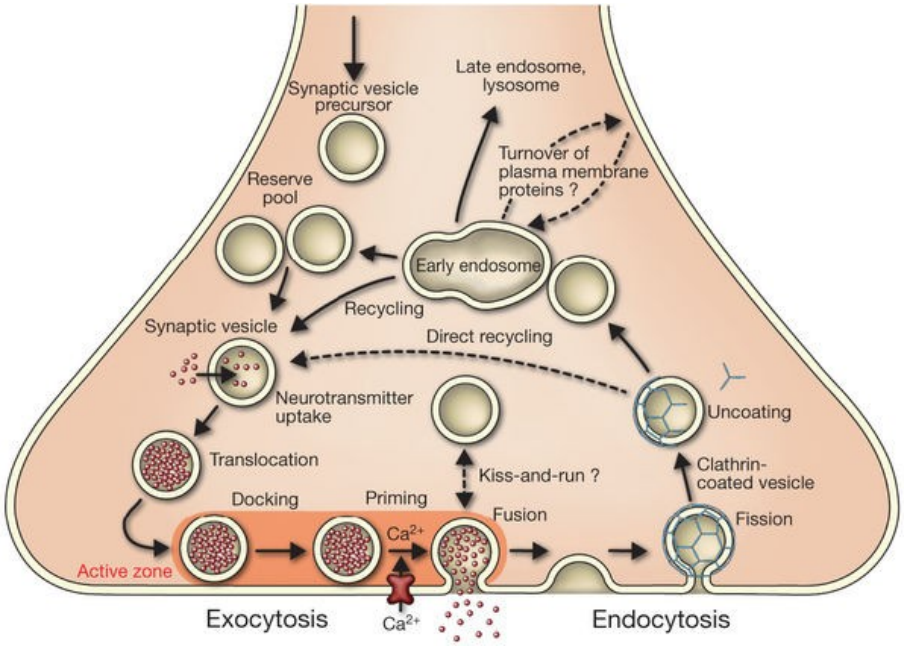
- This is a very complicated mechanism

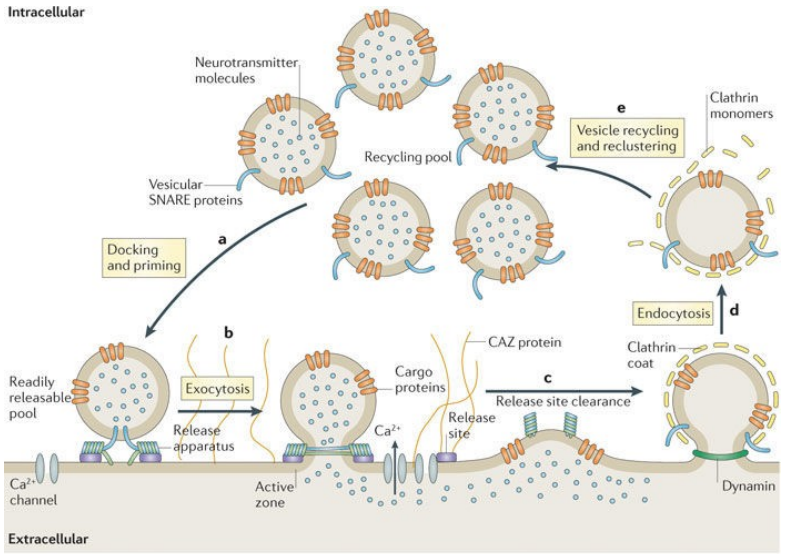


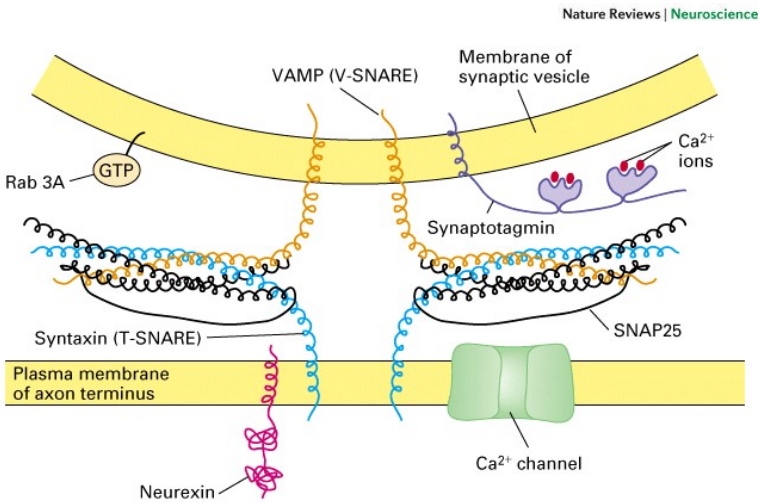
- Processes at almost every level

Synaptic Plasticity

- Presynaptic side

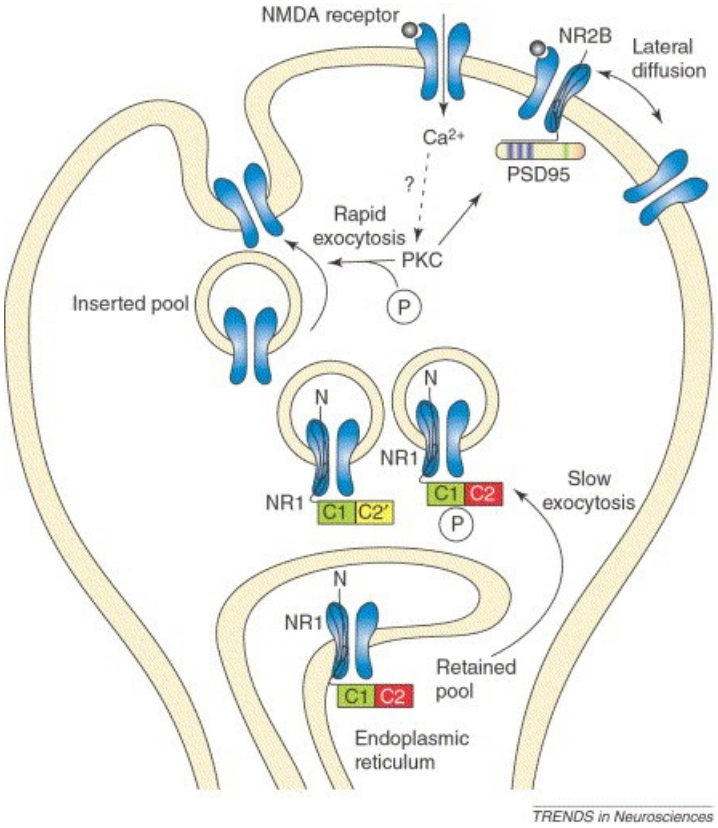


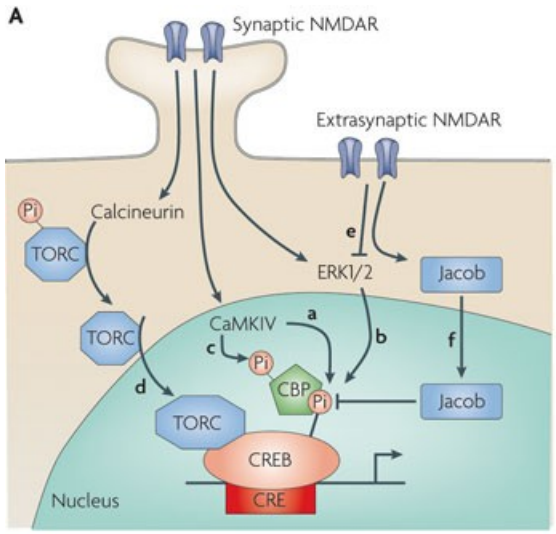


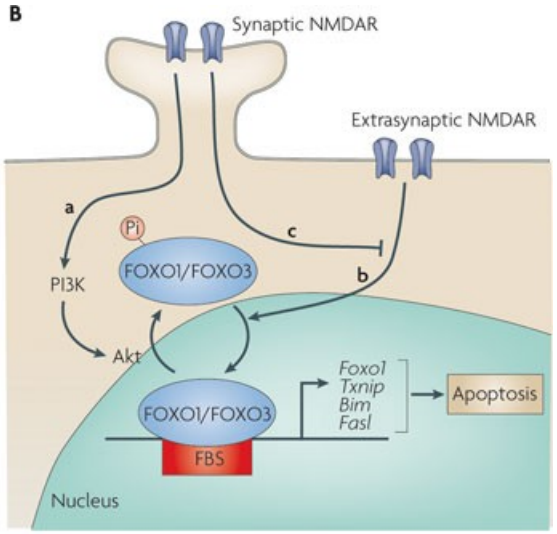


Synaptic Plasticity

- Postsynaptic side







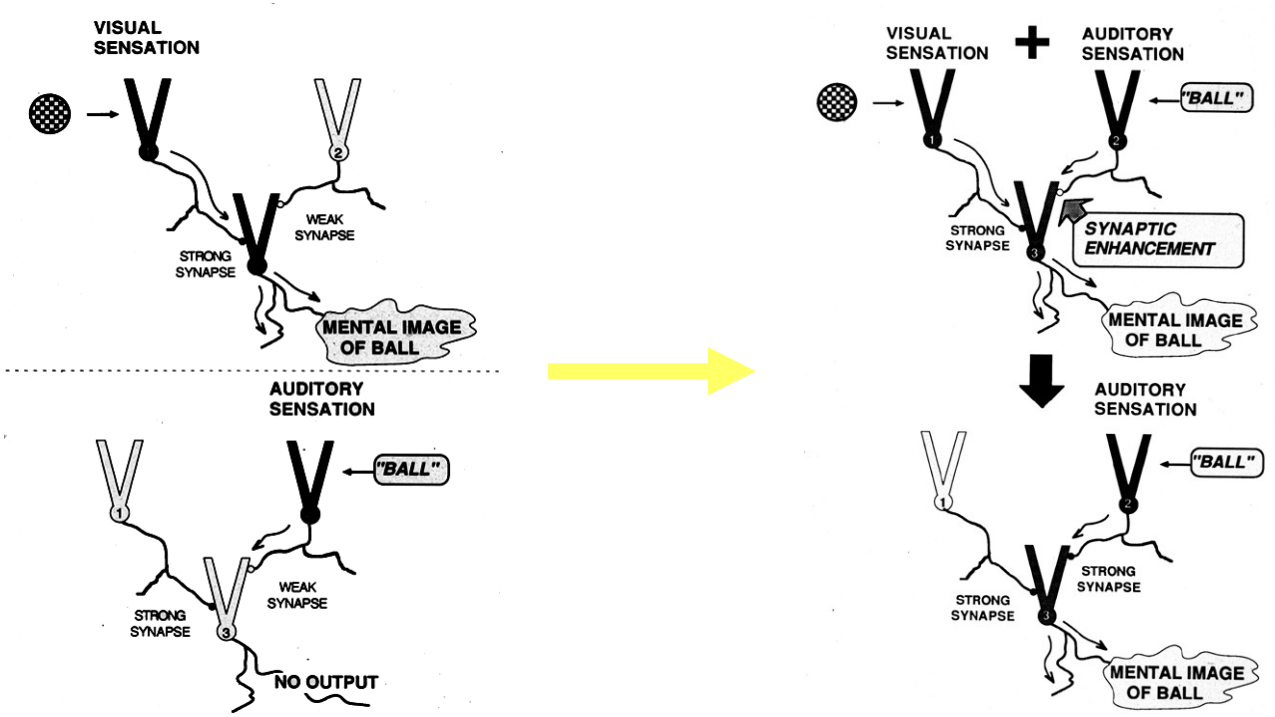
Nature Reviews | Neuroscience

Synaptic Plasticity

- The strengthening of the connections facilitated the communication between neurons

- In 1949 Donald Hebb proposed a mechanism where the synapses got strengthened or weakened according to the *correlation* between the pre- and post-synaptic activity

Synaptic Plasticity



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.

Synaptic Plasticity

- The biological evidence for this kind of mechanisms appears in 1966 in the experiments of Lømo in the hippocampus of anesthetized rabbits
- He observed that excitatory post-synaptic potentials (EPSPs) were reinforced for a long time if the afferents were stimulated with high frequency train of stimuli
- In 1973, Bliss, Lømo & Gardner-Medwin published two papers in which they reported that a "long-lasting potentiation" of hippocampal synapses could be induced by "tetanic" (i.e., high frequency) stimulation. These may be the most highly cited papers in neuroscience.

Synaptic Plasticity

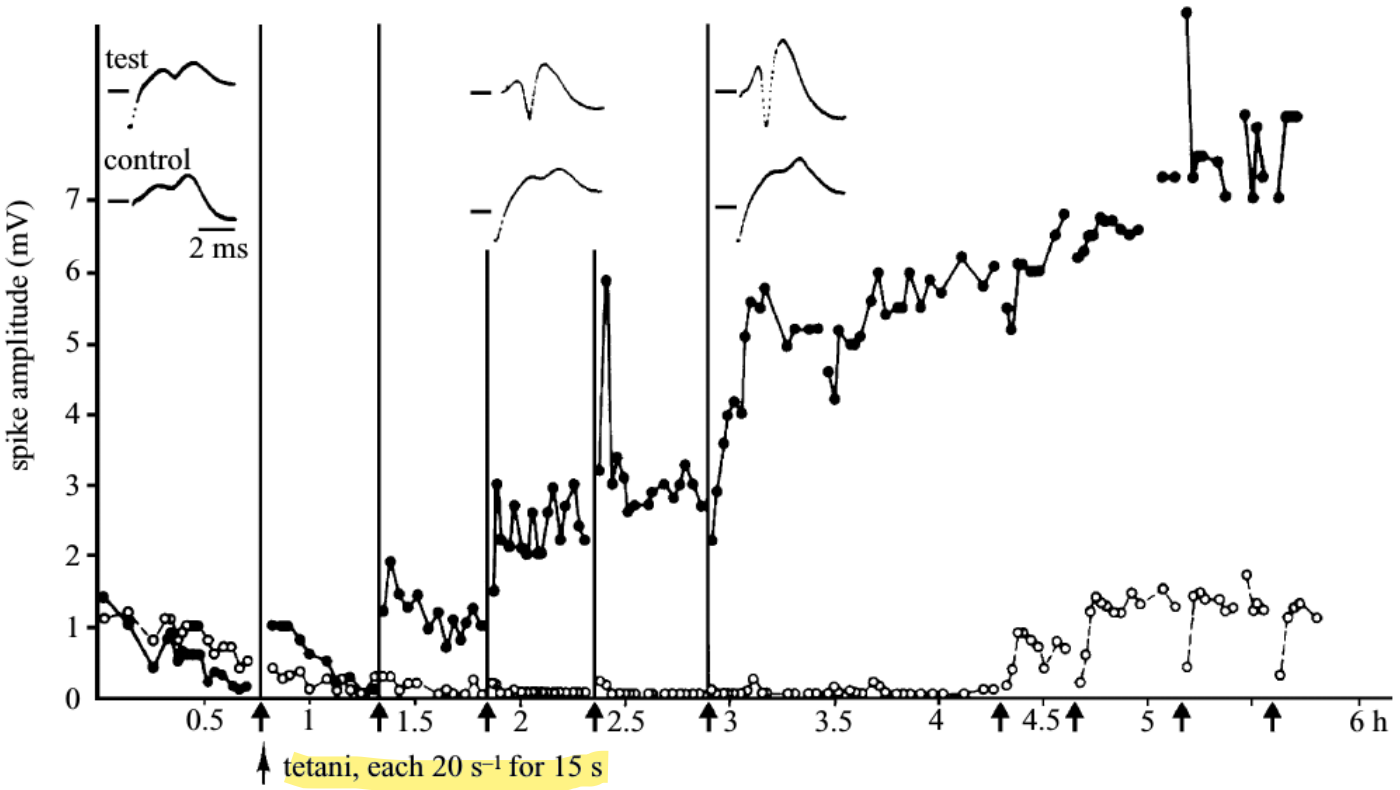


Figure 2. Long-lasting increases in efficiency of transmission at synapses on dentate granule cells induced by repetitive trains of stimuli to the perforant path in anaesthetized rabbits. Insets show responses in the granule cell body layer to single test stimuli to the perforant path at times corresponding to their positions along the abscissa. Trains of stimuli at 20 Hz for 15 s were applied (arrows), first on one side (five trains) then on the opposite side (four trains). The trains caused an increase in the amplitude (and a decrease in the latency) of the population without affecting the contralateral control side. Furthermore, the changes persisted for the duration of the acute experiment.

Lømo, The discovery of long-term potentiation (2003)

Synaptic Plasticity

- In their conclusion, the authors suggested several possible mechanisms for the enhanced EPSP, including increased transmitter release, an increase in post-synaptic sensitivity and a decrease in the stem resistance of dendritic spines.

- The debate about this continued for the next 25 years. Surprisingly, there was no mention of Hebb or his neurophysiological postulate for associative memory.

Synaptic Plasticity

- In 1973 Bliss and Gardner-Medwin observed the phenomenon in unanesthetized animals
- In 1975 the term long-term potentiation (LTP) was already used
- After that LTP was found in several other structures such as cerebral cortex, cerebellum and amygdala
- In fact it is suspected that LTP can be found at all excitatory synapses

Synaptic Plasticity

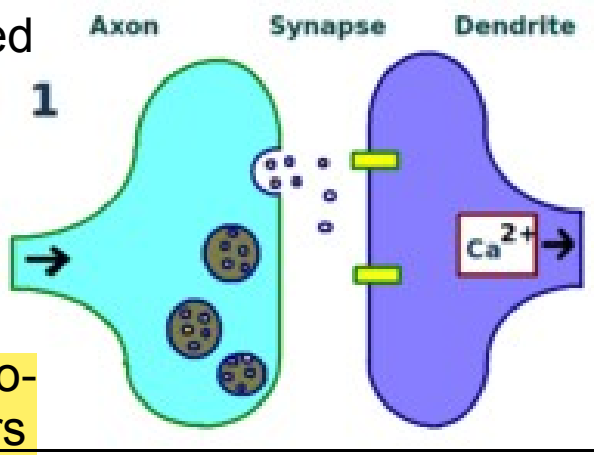
- Two main questions:
  - What is the biological substrate of LTP?
  - Does it really affect behavior?

- Biological substrate: this has proved to be a very difficult question
- Even in the hippocampus the mechanism is different between inmature and mature animals
- Sometimes LTP depends on NMDA receptors and sometimes on metabotropic Glutamate receptors

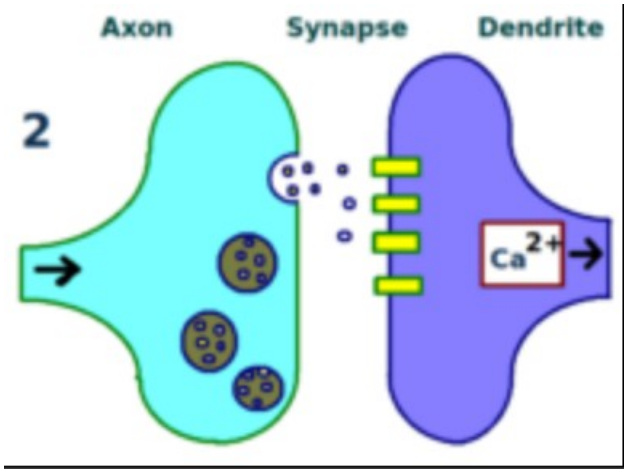
Synaptic Plasticity

- The generic mechanism should be like this

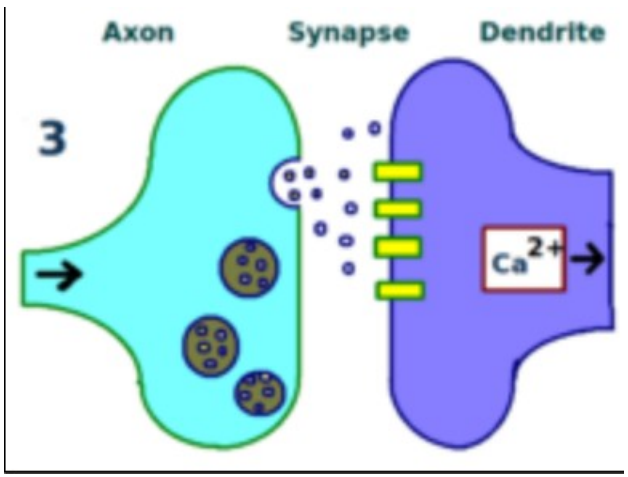
The synapses is stimulated

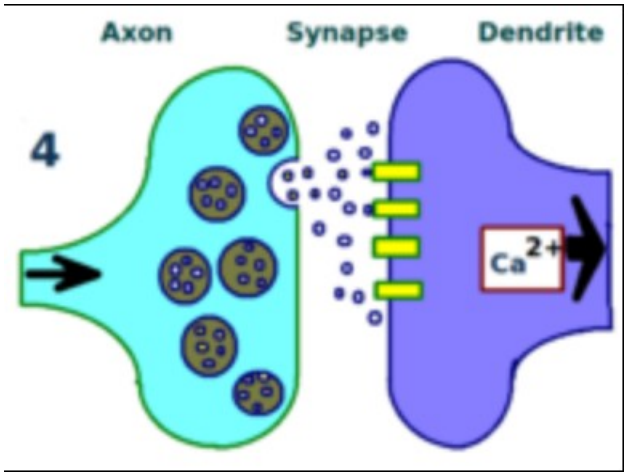


More neuro-transmitters



More receptors





Now there is a stronger link

Synaptic Plasticity

- The details of the signaling paths are still been studied
- Some of the require both pre- and post-synaptic depolarization (Hebbian) or only pre-synaptic (non-Hebbian)
- The NMDA receptor based potentiation is the most studied mechanism
- Main features:
  - Input specificity
  - Associativity
  - Cooperativity
  - Persistence (minutes to months)

Synaptic Plasticity

- LTP can be divided into
  - Early phase
  - Late phase
  - Maintenance or consolidation phase
  - Reconsolidation phase?

- Each of them involves different biochemical mechanisms that occur at different time scales

Synaptic Plasticity

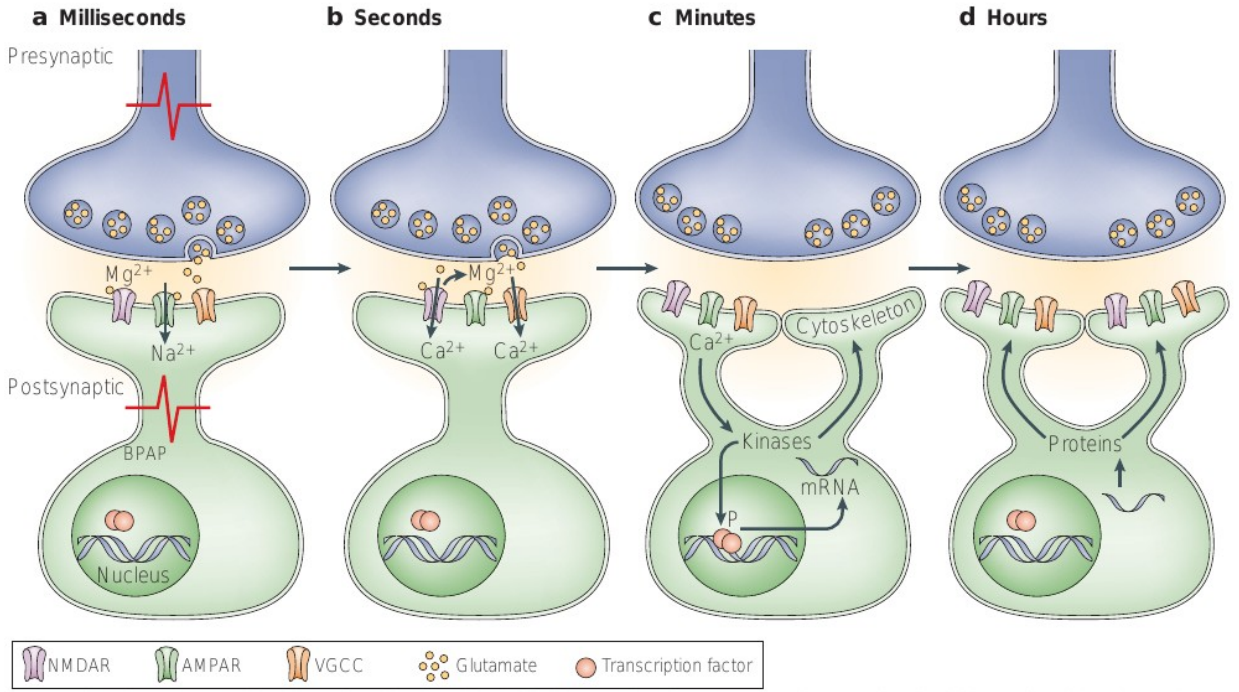
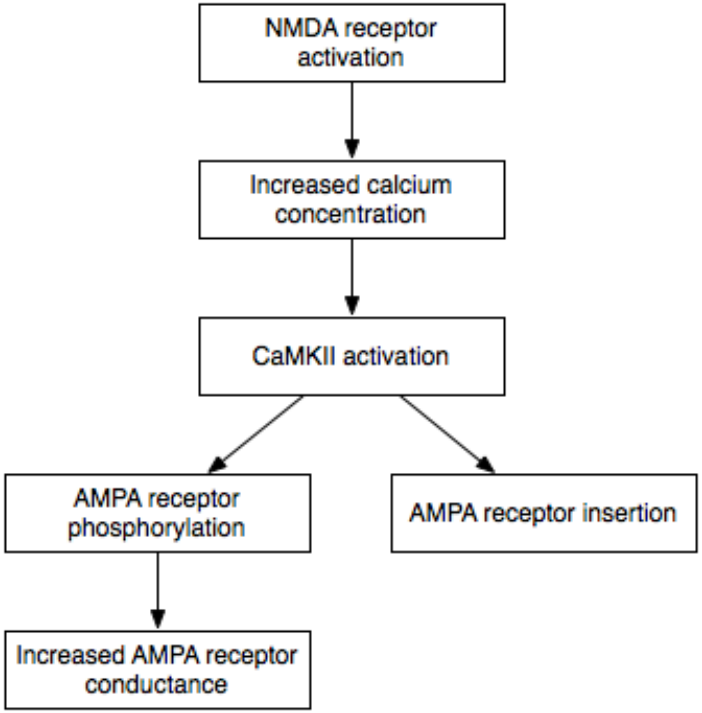


Figure 1 | **Molecular mechanisms involved in the initiation and maintenance of synaptic plasticity. a** | Activity-dependent release of glutamate from presynaptic neurons leads to the activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (AMPARs) and to the depolarization of the postsynaptic neuron. Depolarization occurs locally at the synapse and/or by back-propagating action potentials (BPAP)[23,26,31,32]. **b** | Depolarization of the postsynaptic neuron leads to removal of NMDA (*N*-methyl-D-aspartate) receptor (NMDAR) inhibition, by Mg^{2+}, and to Ca^{2+} influx through the receptor[27]. Depolarization also activates voltage-gated calcium channels, another source of synaptic calcium[28–30]. **c** | Calcium influx into the synapse activates kinases which, in turn, modulate the activity of their substrates[33,34]. These substrates contribute to local changes at the synapse, such as morphological alteration through cytoskeletal regulation[65,86], or induce the transcription of RNA in the nucleus by regulating transcription factors (TFs)[36]. **d** | Transcribed mRNA is translated into proteins that are captured by activated synapses and contribute to stabilization of synaptic changes[5]. VGCC, voltage-gated calcium channel.

- Lamprecht & LeDoux, 2004

Synaptic Plasticity

- The initial stage of NMDA receptor based LTP is based on phosphorylation of pre-existing AMPA receptors to increase their efficacy

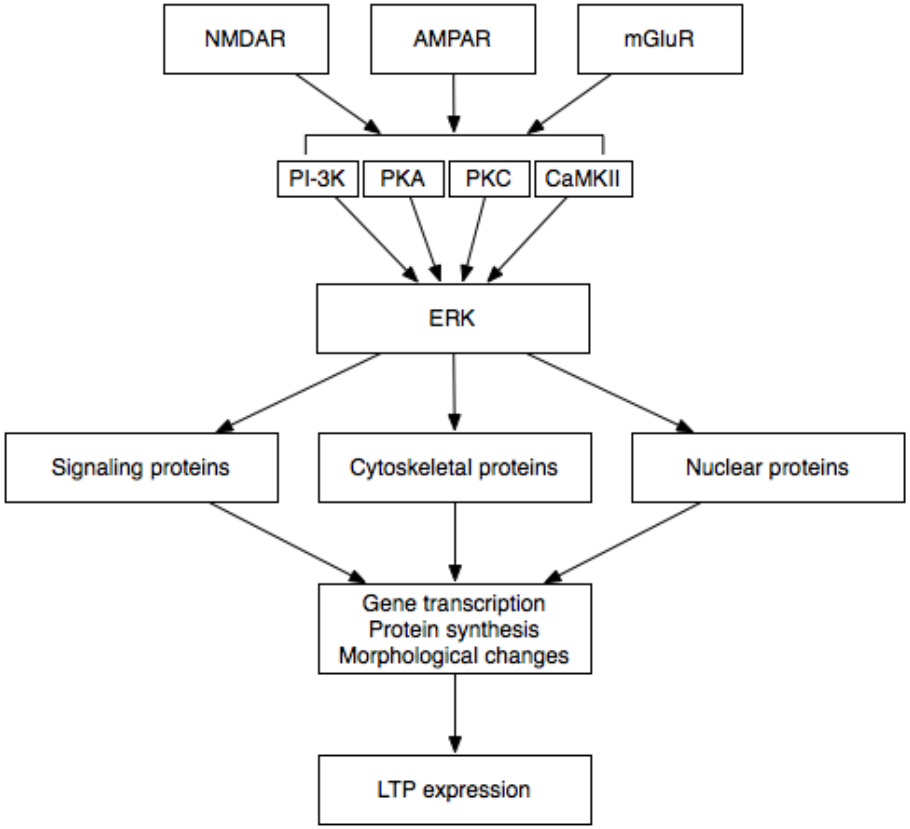


Synaptic Plasticity

- This mechanism does not require the synthesis of new proteins but it has a limited time span
- It is purely post-synaptic
- Some retrograde messenger is required to have a pre-synaptic effect
- These messengers have not been unequivocally identified (nitric oxide?)

Synaptic Plasticity

- The late phase requires synthesis of proteins



Synaptic Plasticity

- The maintenance phase requires (probably) structural changes in the dendritic structures (axonal buttons, dendritic spines) additionally to altered gene expression

- This is the stage that is less known. There are a lot of processes going on but it is not clear which is the dominant one

Synaptic Plasticity

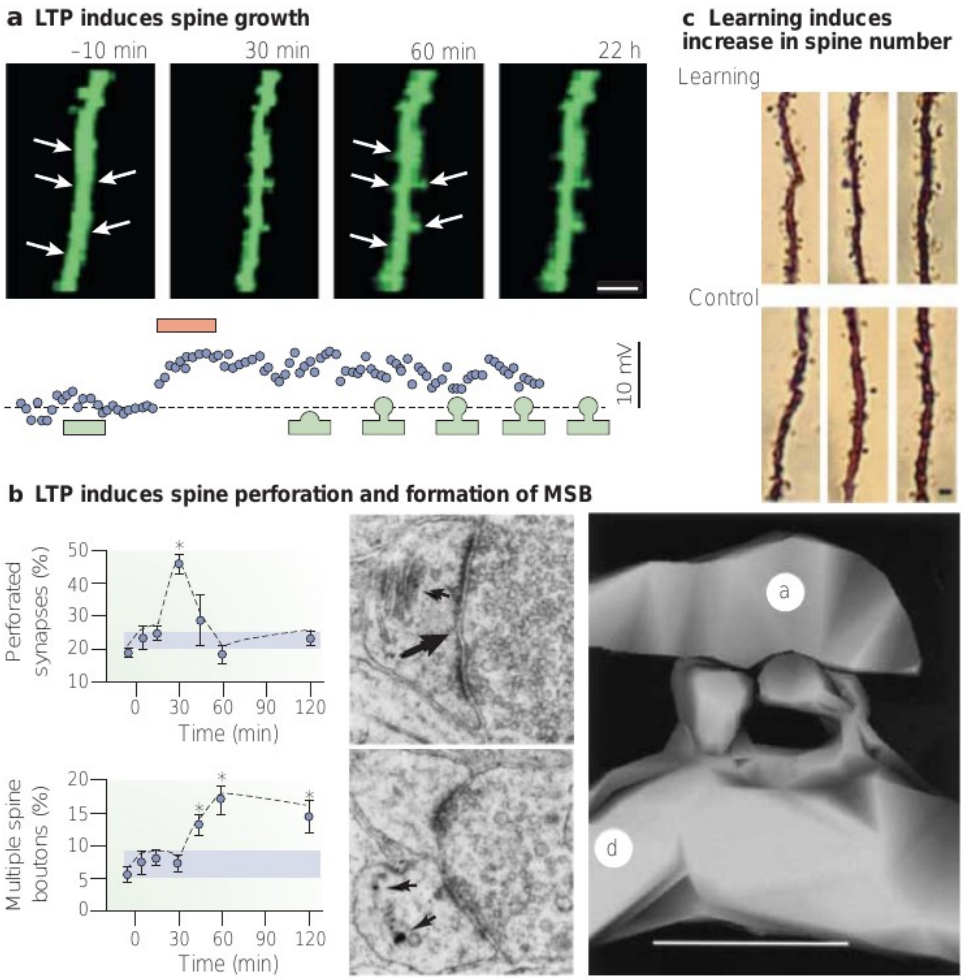


Figure 3 | **Methods used to monitor changes in dendritic spines following long-term potentiation (LTP) or learning. a** | Visualization of new spine growth (upper panel) after LTP (lower panel) of postsynaptic neurons using two-photon microscopy[65]. **b** | Detection of perforated spines and multiple spine boutons (MSB) after LTP using electron microscopy (left). A three-dimensional reconstruction of MSBs is also shown (right)[68]. a, axon; d, dendrite. Scale bar, 1μm. **c** | Detection of changes in spines 24 h after learning (trace eyeblink conditioning) using Golgi impregnation[71]. **a** modified, with permission, from *Nature* REF. 65 © (1999) Macmillan Magazines Ltd; **b** modified, with permission, from *Nature* REF. 68 © (1999) Macmillan Magazines Ltd; **c** modified, with permission, from REF. 71 © (2003) The Society for Neuroscience.

Lamprecht & LeDoux, 2004

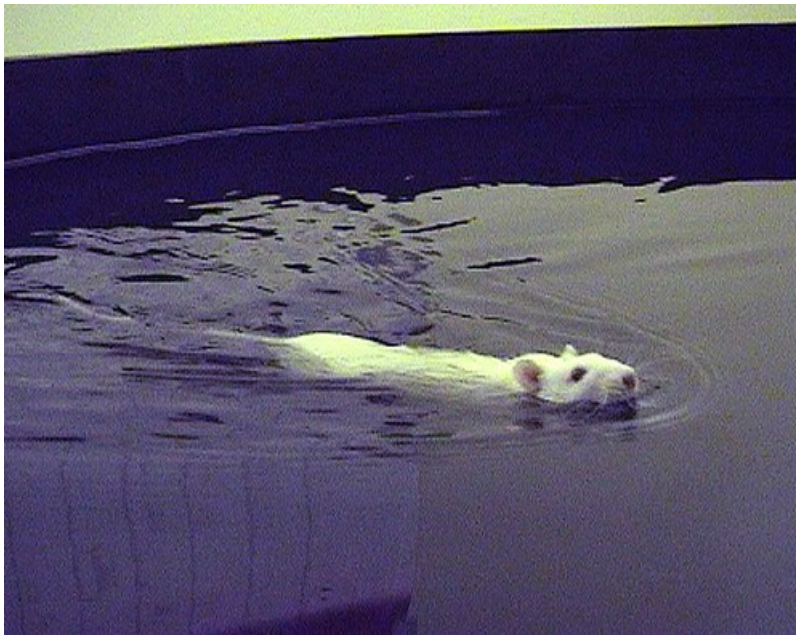
Synaptic Plasticity

- Anyway, what is the relation between all this and behavior?
- In 1986 Morris showed that LTP was necessary for the formation of memories *in-vivo*
- *Morris water-maze*

Synaptic Plasticity

- Animals where the NMDA receptors were blocked were unable to learn the position of the platforms where they could stand without swimming

- *In-vitro* analysis showed that LTP was indeed blocked



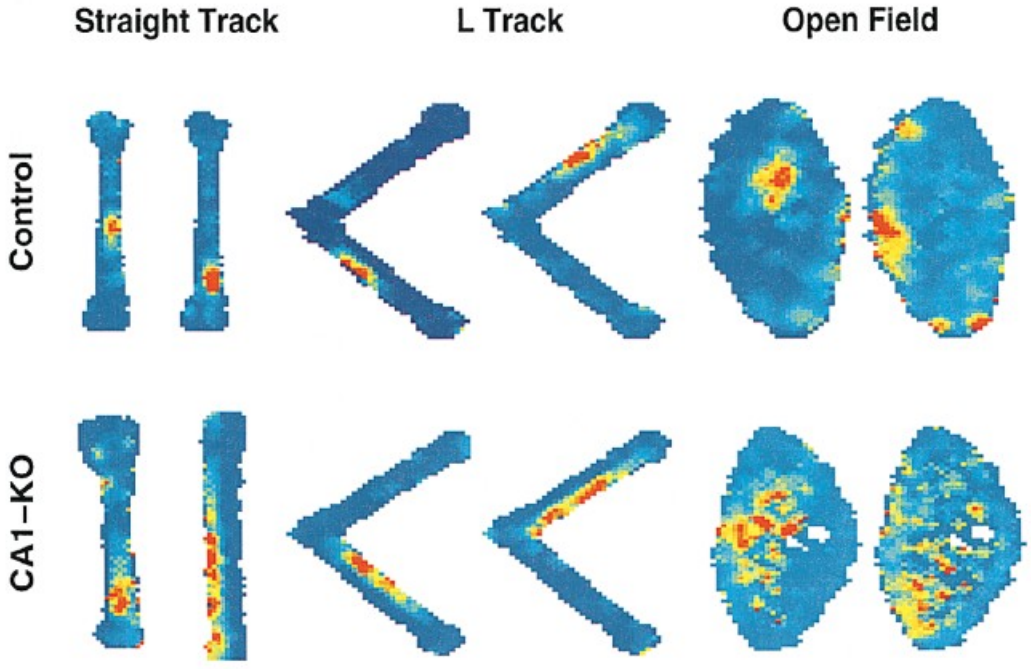
Synaptic Plasticity

- Experiments in 1996 (Tonegawa) showed that genetically altered mice with impaired NMDA receptors showed poor spatial navigation abilities and poorly selective hippocampal representation of space in CA1

Figure 1. NMDAR1 CA1-KO Mouse with Implanted Microdrive

Synaptic Plasticity

- Experiments in 1996 (Tonegawa) showed that genetically altered mice with impaired NMDA receptors showed poor spatial navigation abilities and poorly selective hippocampal representation of space in CA1



Synaptic Plasticity

- We can have also long term depression (LTD): the synapses can become *weaker* in certain circumstances
- First identified in the cerebellum when the Purkinje cells were stimulated with low frequency trains
- It was later discovered in the cortex and the hippocampus
- The biochemical pathways are less well understood than for LTP

Synaptic Plasticity

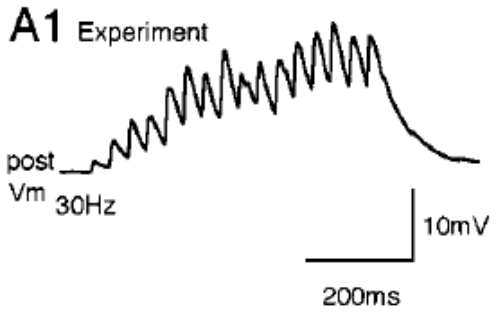
- LTD can be associative or non-associative
- Calcium ions are involved
- Phosphorylation of AMPA receptors
- Endocannabinoids...

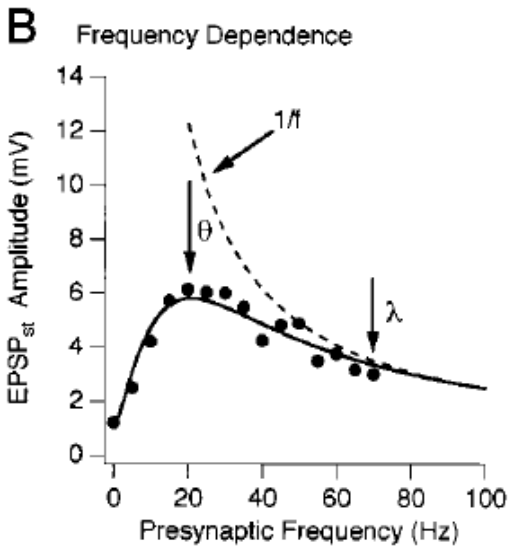
Synaptic Plasticity

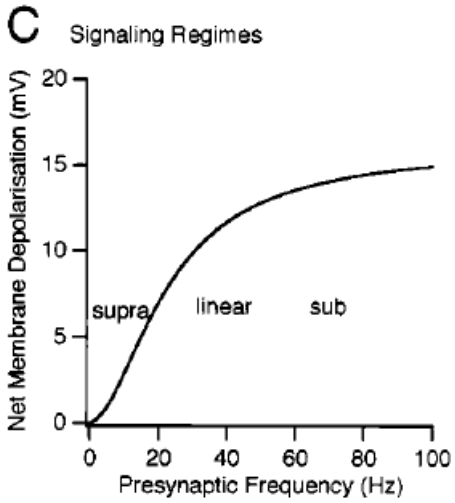
- There are also processes in shorter time scales:
  - Facilitation: tens of milliseconds
  - Augmentation: seconds
  - Potentiation: tens of seconds
- In fact more recent studies considerate a continuum of time scale (Fusi, et al. Cascade Models of Synaptically Store Memories, Neuron, 2005)

Synaptic Plasticity

- Short term plasticity (Markram et al. 1998)







Synaptic Plasticity

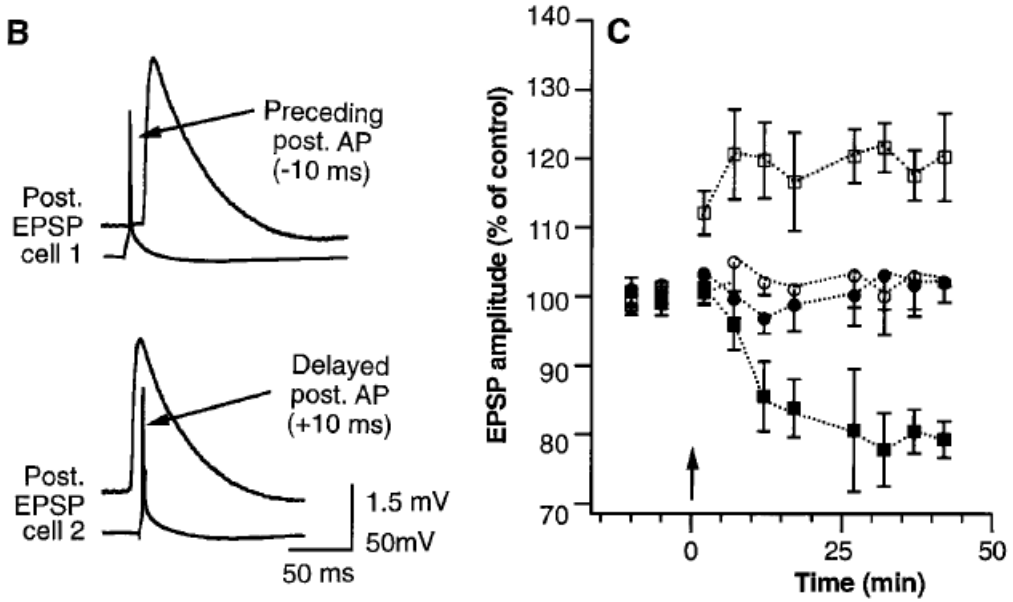
- Short term plasticity (STP) Markram et al. 1998
- The depression component (1/f) can be explained by the depletion of neurotransmitters in the synapses
- The facilitating part must involve some active process (involving calcium?)
- Possible substrate for working memory (lecture III)
- We will see the model of STP in the tutorial this afternoon

Synaptic Plasticity

- All these studies assume that the dominant factor that controls synaptic plasticity is the firing rate of the neurons
- Since the 70s it as suspected that the relative timing of the spikes could also have an effect
- This was demonstrated by Markram et al. (1997) and Bi and Poo (1998)

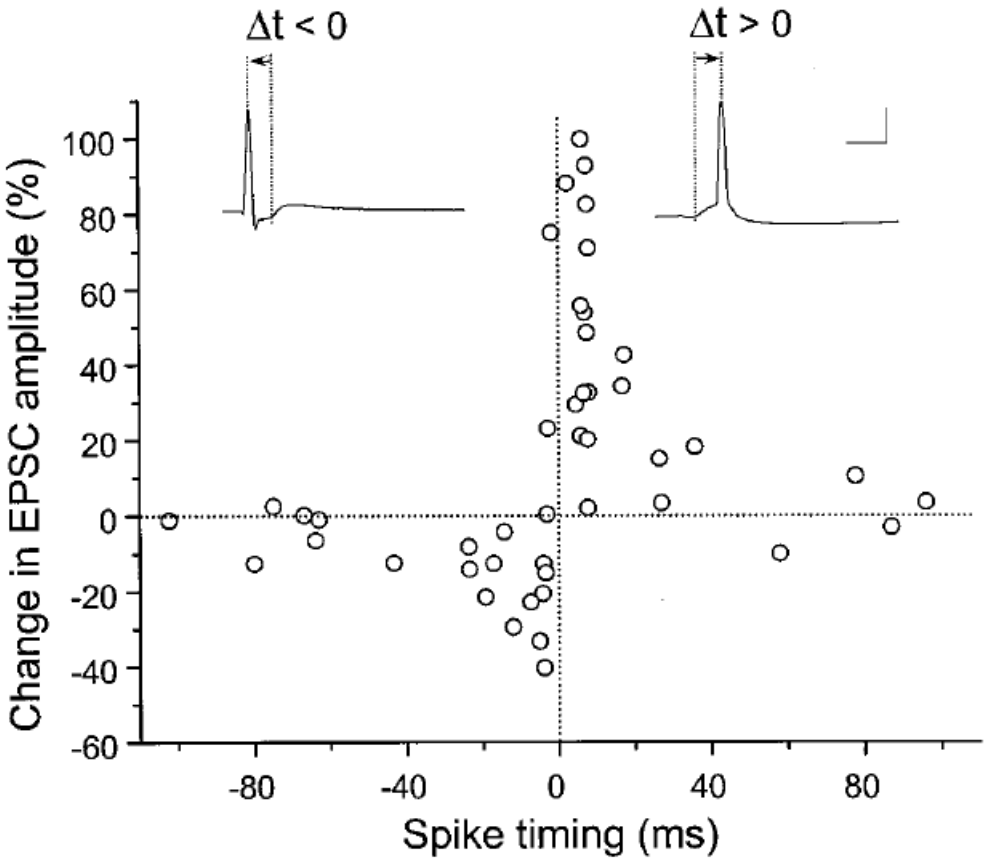
Synaptic Plasticity

- Markram et al., 1997 (neocortex)



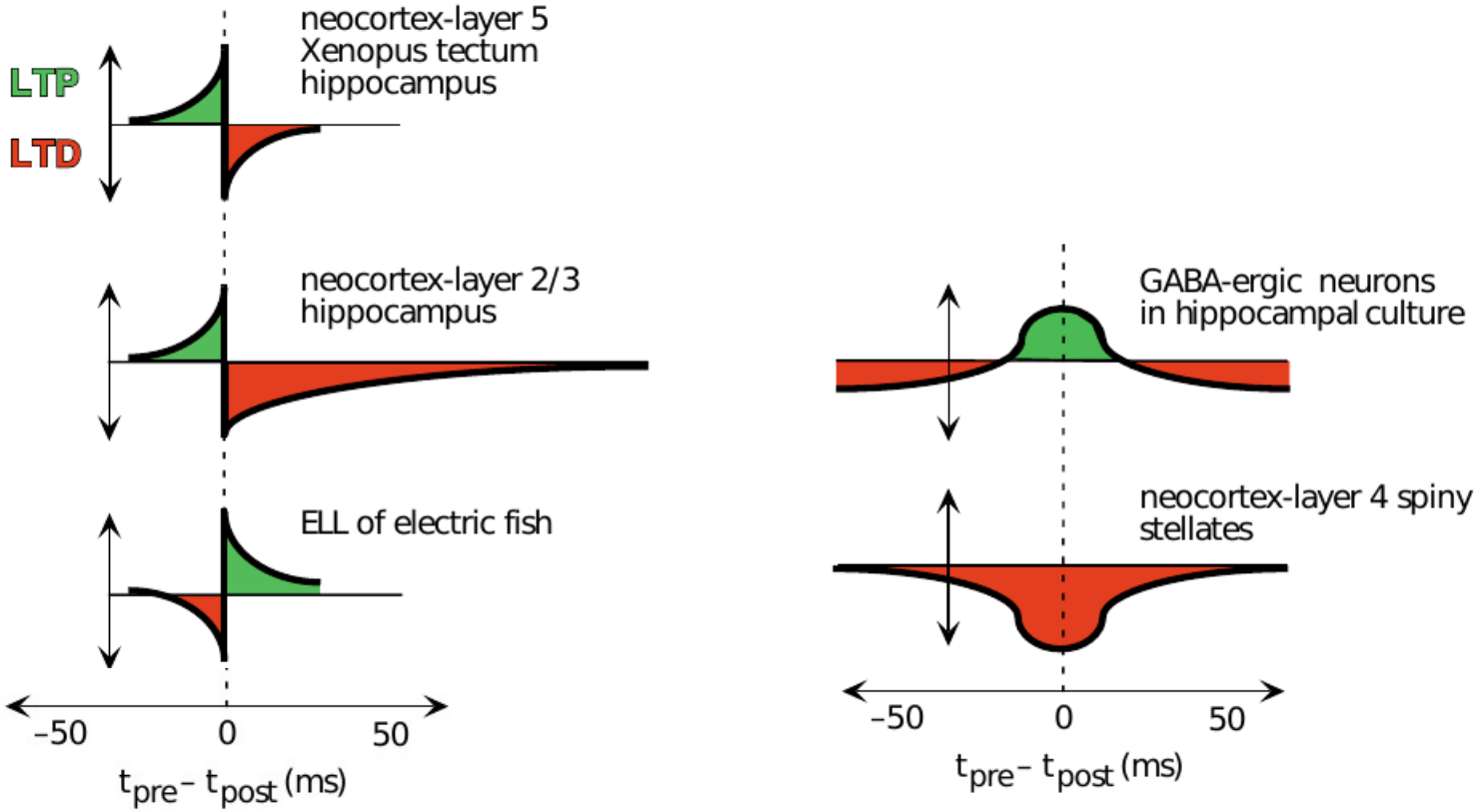
Synaptic Plasticity

- Bi & Poo, 1998 (hippocampus)



Synaptic Plasticity

- Additional studies have found Spike-Timing Dependent Plasticity (STDP) almost everywhere (Abbott & Nelson, 2000)



Synaptic Plasticity

- The understanding of the biochemical basis of STDP is a very challenging problem
- It seems to require a very fine tuned mechanism at the synaptic level
- Even if we build a model that predicts the behavior of pairs of spikes it tends to fail when we do an experiment with triplets (post-pre-post, pre-post-pre, etc.)

Synaptic Plasticity

- What is the functional role of STDP (improvement of reliability, control of temporal correlations, formation of maps and columns)?

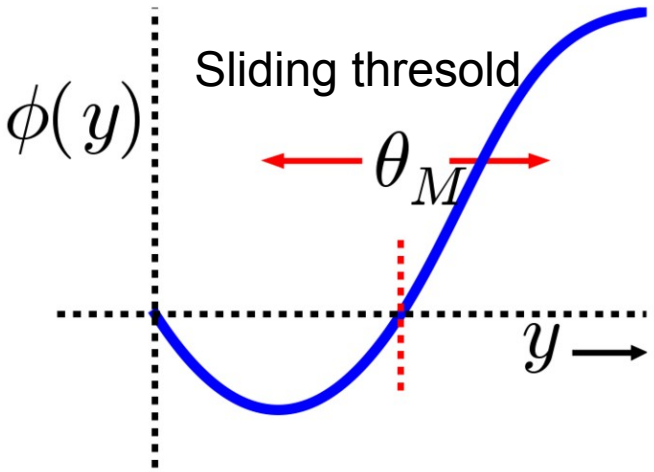
- Or it is some kind of epi-phenomenon, i.e., the only important feature is the dependence on the firing rates?

Synaptic Plasticity

- Unified framework for treating potentiation and depression:
  - Bienenstock, Cooper & Munro (1981)
  - BCM theory: It incorporates a sliding threshold that separates potentiation from depression
  - It was verified in hippocampus and cortex
  - It can be proved that under some conditions it can be derived from STDP (Izhikevich & Desai, 2003)

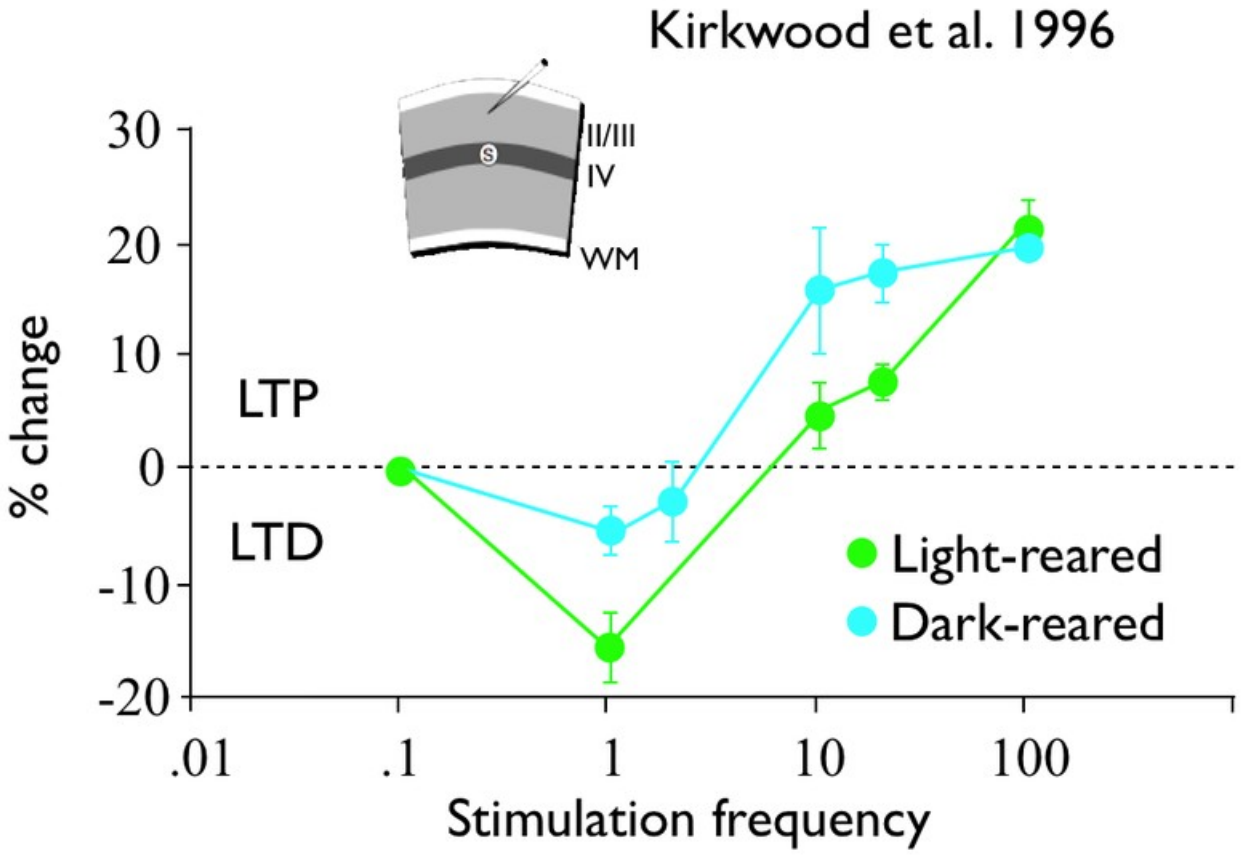
Synaptic Plasticity

- Unified framework for treating potentiation and depression
  - Input x_i
  - Synaptic efficacy w_i
  - Post-synaptic activity y
  - $dw_i/dt = \Phi(y)\, x_i - \varepsilon\, w_i$



Synaptic Plasticity

- Experimental validation



Synaptic Plasticity

- BCM rule has been generalized in multiple ways, see for instance Intrator & Cooper (1992) or Law & Cooper (1994)

- More recently triplet STDP rules have been shown to give generalized BCM rules, that take into account high order temporal correlations of the input (Gjorgjieva et al., 2001)

Learning and Plasticity

- Next lecture:
  - Hebbian rule and memory
  - Hopfield model and some generalizations
  - Experimental evidence