Hebbian Learning

MEDS 470 / NRSC 500B

David Hartley’s Neural Vibrations (1705-1757)

David Hartley attempted to explain the mechanisms of central control.

He formulated the theory of neural vibrations according to Sir Isaac Newton’s laws of motion. He proposed that stimuli produced neural vibrations that travelled afferently to the brain or efferently to peripheral areas. Furthermore, Hartley suggested that the frequency of vibrations could summate to encode/transmit different types of information.

Alexander Bain's Contribution (1872)

Harper, K. (2019). Alexander Bain's Mind and Body (1872): An underappreciated contribution to early neuropsychology. *Journal of the History of the Behavioral Sciences, 55*(2), 139–160. https://doi.org/10.1002/jhbs.21963

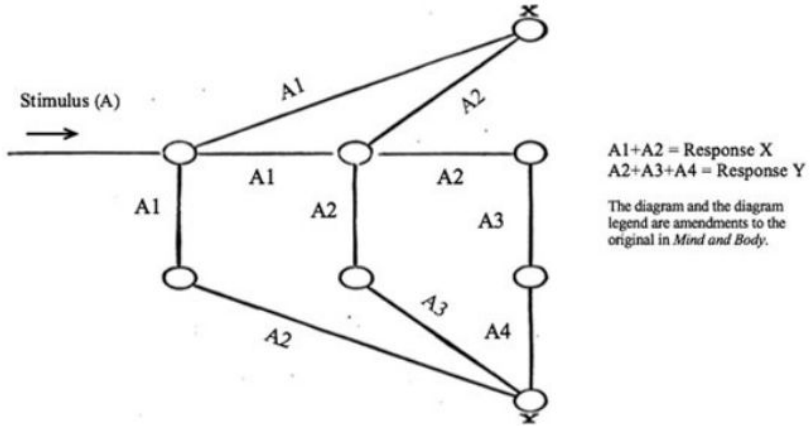


FIGURE 4 Bain (1872, p. 115, amended)

Bain proposed a mechanism of neural communication similar to that of Donald Hebb.

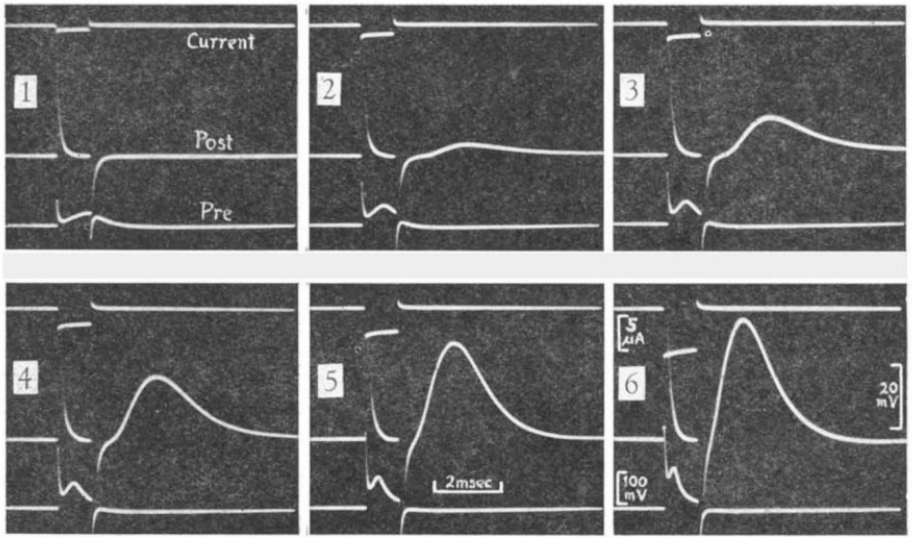
He postulated that neurons formed groupings and that such groupings had plastic-like qualities.

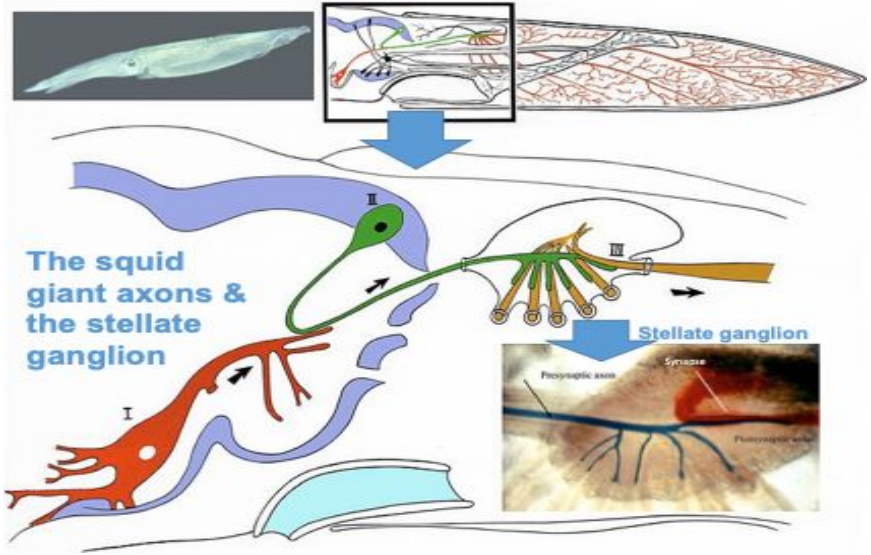
For example, he suggested that connections between neurons were malleable and influenced by their unique levels of stimulation.

Bain also proposed that chemical processes were involved in neurotransmission far before the knowledge of the NT.

Bernard Katz

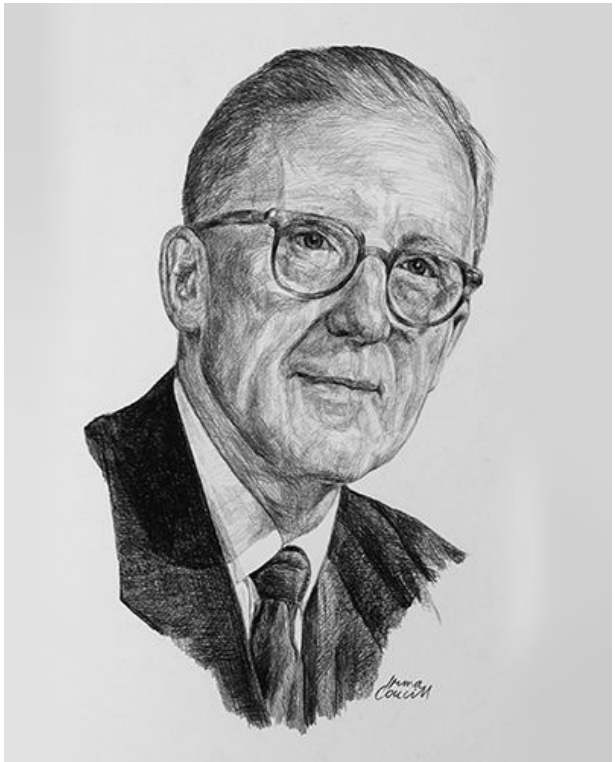
Katz, B., & Miledi, R. (1967). A study of synaptic transmission in the absence of nerve impulses. *The Journal of Physiology*, *192*(2), 407–436. https://doi.org/10.1113/jphysiol.1967.sp008307





Katz revealed the first evidence of synaptic plasticity with his experiments on giant squid axons. He observed characteristics of the synapse, including input-output regulation concerning firing frequency and the role of ions in generation membrane potential.

Donald Hebb - Organization of Behaviour (1949)



Proposed mechanisms behind neural communication in terms of synaptic plasticity

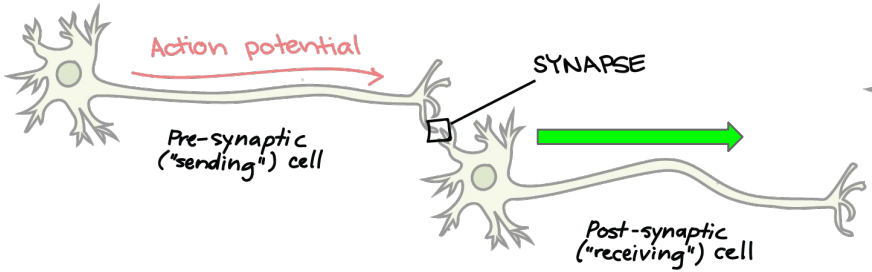
Father of Hebbian Learning

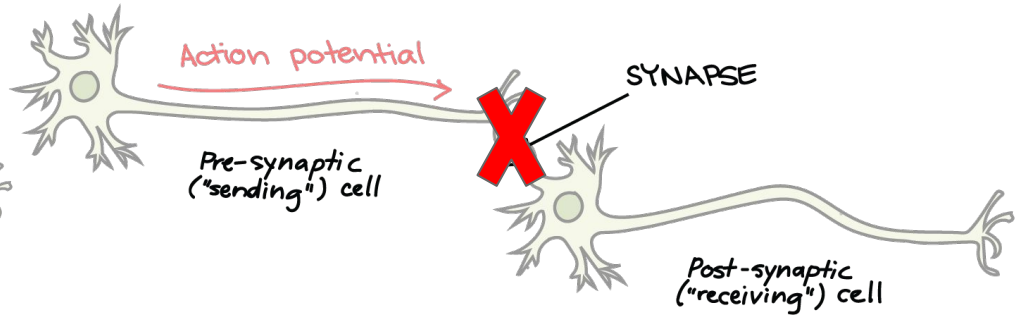
Donald Hebb suggested that memories are encoded in terms of synaptic strength.

“Neurons that fire together wire together.”

Connections (synapses) between proximal neurons can be strengthened or weakened (plastic properties)

Hebbian Learning Continued



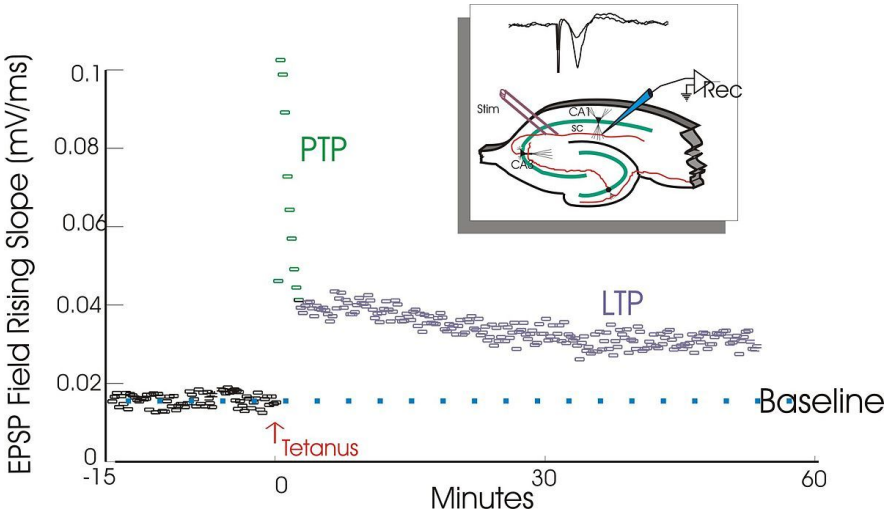


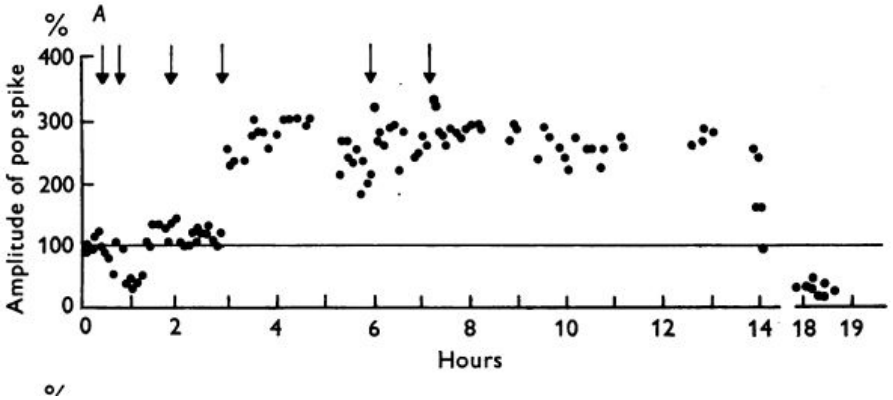
When neuron A is in close proximity to neuron B and repeatedly takes part in activating a postsynaptic response, the strength between the two neurons increases.

When neuron A is in close proximity to neuron B and repeatedly fails to propagate an action potential, the strength between the two neurons decreases.

LTP - Bliss and Lomo (1973)

Bliss, T. V. P., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, *232*(2), 331–356. https://doi.org/10.1113/jphysiol.1973.sp010273

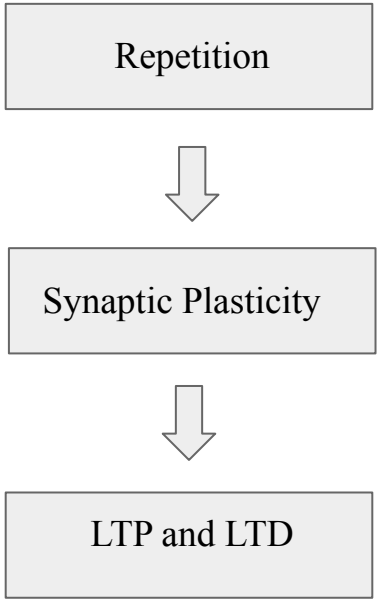




In the 1973 study, Bliss and Lomo stimulated the perforant pathway to the dendritic area of the hippocampus in rabbits. They found that after undergoing high-frequency stimulation (tetanus), the rabbits saw potentiation to the amplitude of EPSP, the granular cell depolarization and the amplitude and latency of the spike signalling discharge. These findings lead them to hypothesize about mechanisms increasing the efficiency of conditioned synapses.

QUIZ QUESTIONS - ANSWERED

What do we mean by Hebbian Learning?



Repetition

Ericsson, K. A., Krampe, R. T., & Tesch-Römer, C. (1993). The Role of Deliberate Practice in the Acquisition of Expert Performance. Psychological Review, 100(3), 363–406. https://doi.org/10.1037/0033-295X.100.3.363

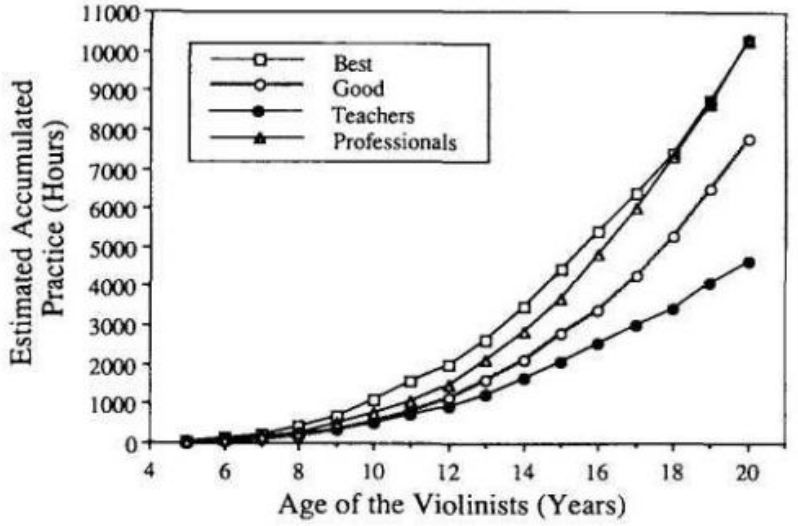


Figure 9. Accumulated amount of practice alone (on the basis of estimates of weekly practice) as a function of age for the middle-aged violinists (△), the best violinists (□), the good violinists (○), and the music teachers (●).

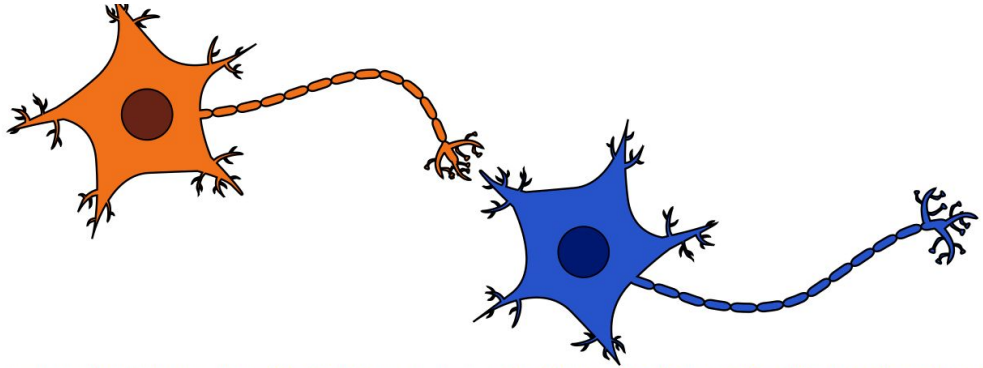
Ericsson studied four population groups through retrospective reports on practice habits.

He hypothesized that nature rather than nurture might play a role in developing expertise.

He found that the main distinguishing factor between world-class musicians and the other participants was the number of hours practiced.

Basis of the 10,000-hour rule -> Deliberate practice

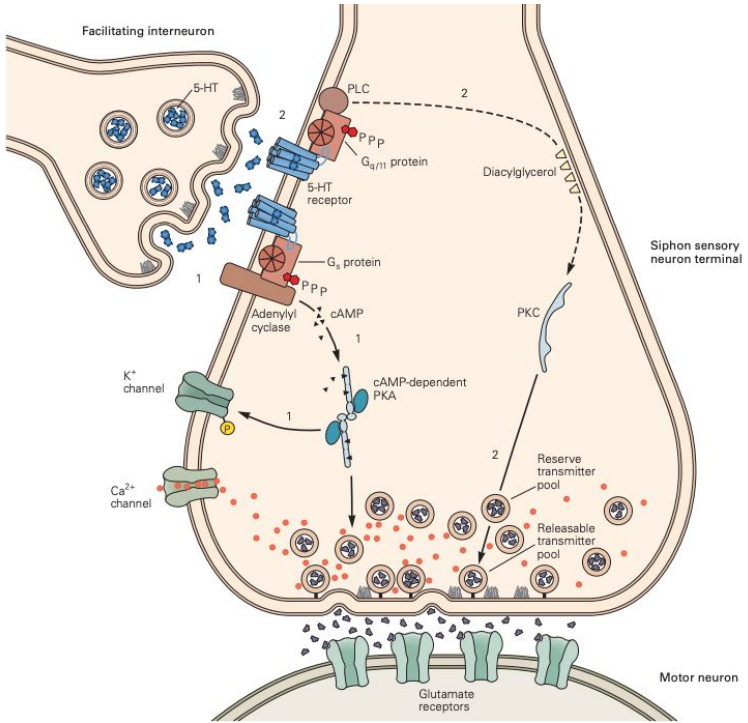
Synaptic Plasticity



Proposed mechanisms responsible for changes in synaptic strength between neurons:

1) Changes in presynaptic neurotransmitter release
2) Synaptic growth and pruning
3) Modulation of postsynaptic receptors

Neurotransmitter Modulation

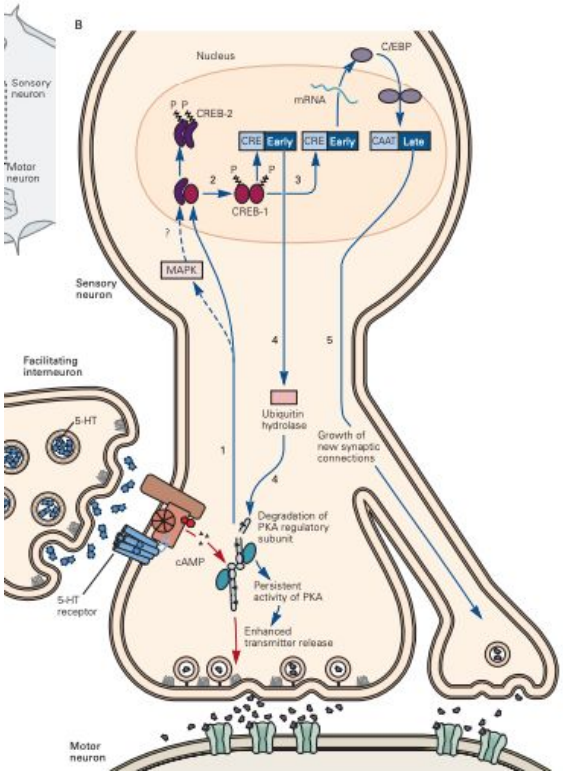


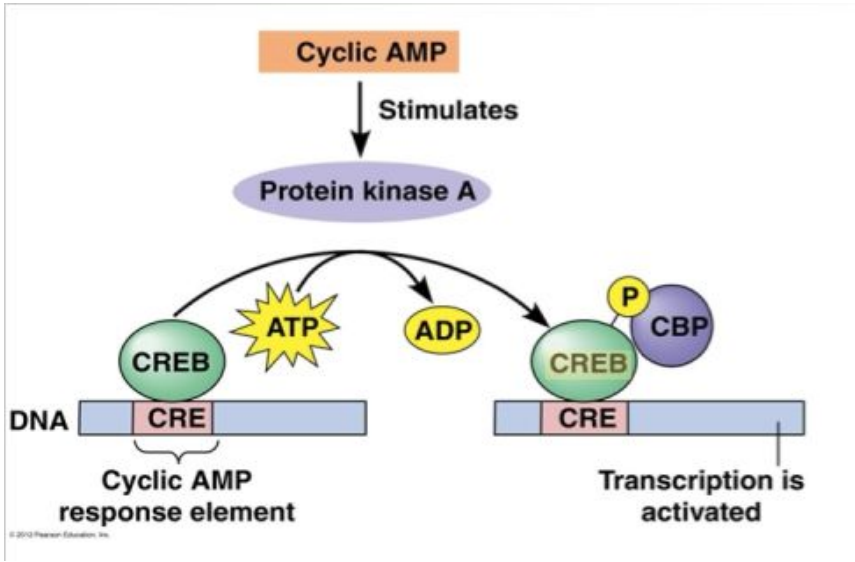
Facilitating Interneuron: Serotonin (5-HT) release increases NT release via a G-coupled feedback mechanism.

G_s cAMP activation -> PKA (regulatory subunit binding activates catalytic subunit) -> phosphorylates presynaptic K+ channels decreasing their activity. Resulting prolonged AP -> increased Ca2+ influx and effect.

$G_{g/11}$ increases phospholipase activity -> produces diacylglyceral -> PKC. Phosphorylation events result in increased vesicle motility = increases exocytosis of glutamate.

Synaptic Growth - Gill Withdrawal Reflex



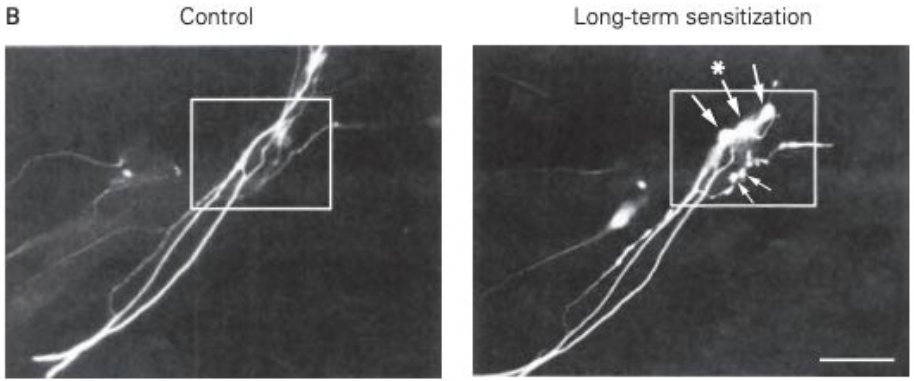


Growth of synaptic connections via changes in gene expression. Mediated by the cAMP -> PKA -> MAPK pathway.

Seen in *Aplysia* forming new long-term memory (gill withdrawal sensitization).

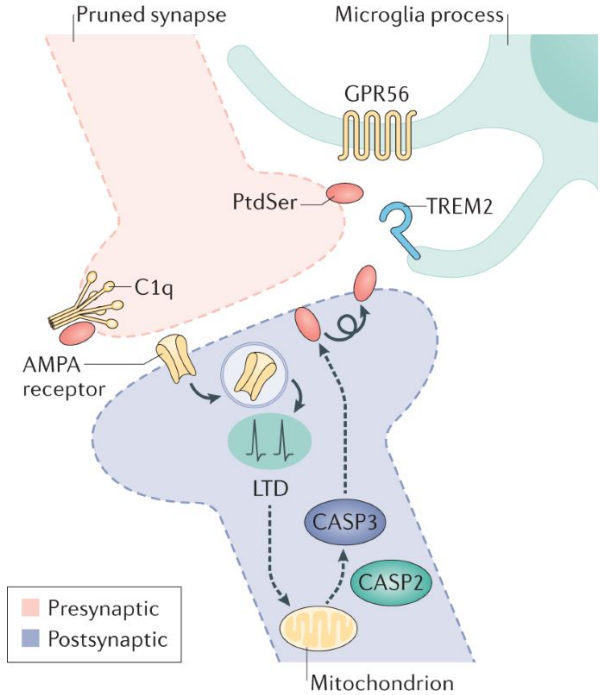
Growth / Pruning

Györffy, B. A., Kun, J., Török, G., Bulyáki, É., Borhegyi, Z., Gulyássy, P., Kis, V., Szocsics, P., Micsonai, A., Matkó, J., Drahos, L., Juhász, G., Kékesi, K. A., & Kardos, J. (2018). Local apoptotic-like mechanisms underlie complement-mediated synaptic pruning. *Proceedings of the National Academy of Sciences - PNAS*, 115(24), 6303–6308. https://doi.org/10.1073/pnas.1722613115



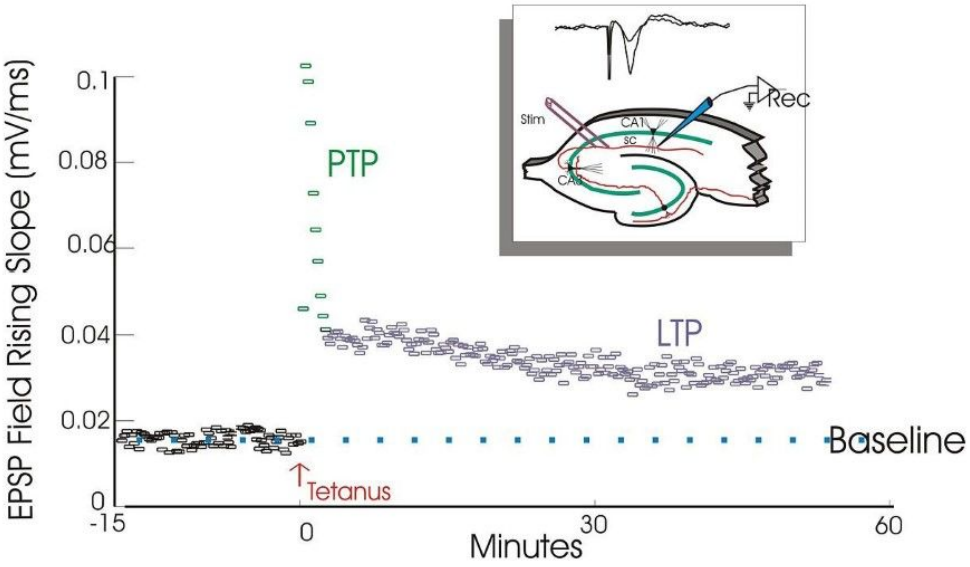
Synapses must be selectively marked by serotonin to facilitate the productive use of proteins.

Dormant synapses can be recruited via serotonin signalling to initiate transcription (cytoplasmic polyadenylation element binding CPEB is thought to play a mediating role by activating or repressing translation when binding to 3' untranslated region (UTR))



Microglia are thought to play a role in degrading unused connections. Györffy and colleagues (2018) identified a protein tag C1q that is thought to tag the presynaptic axons for degradation. This tagging process mirrors apoptotic-like processes seen in the immune response to pathogens.

LTP and LTD



Changes at the synaptic level due to repetition can lead to long-term potentiation or long-term depression.

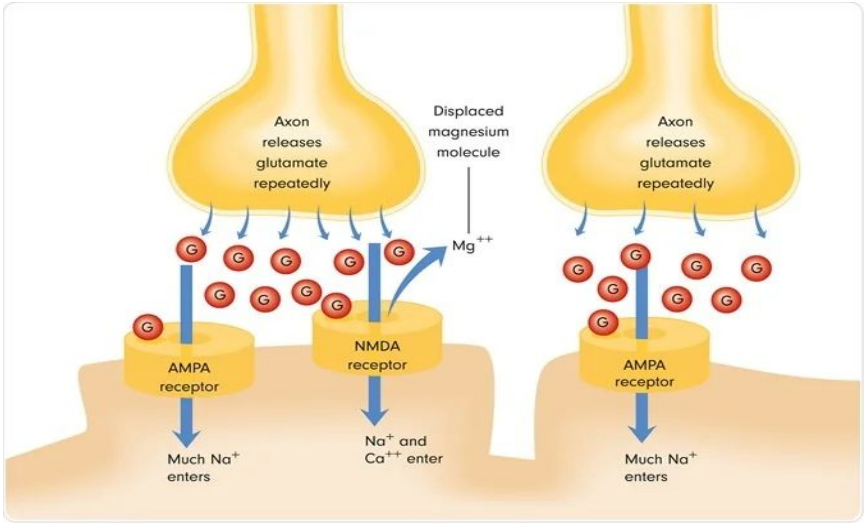
LTP increases the effect of EPSP for the same firing frequency, decreases the latency period associated with discharge, and increases postsynaptic response.

LTP and LTD are spike time-dependent:

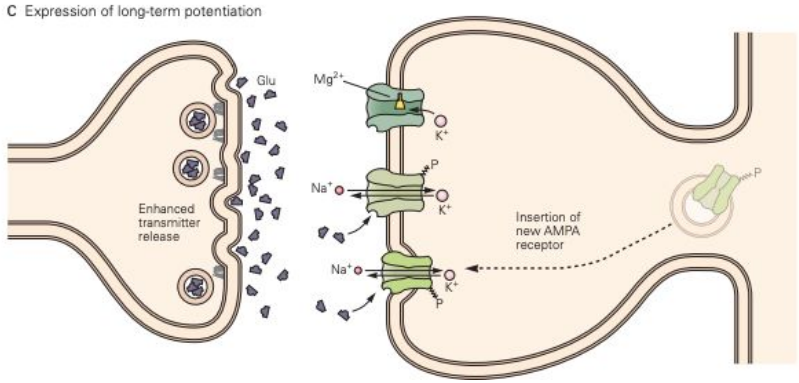
The closer in time the pre and postsynaptic neurons fire, the higher the potentiation response.

If the postsynaptic neuron does not fire in response to the presynaptic neuron (fires out of order), LTD weakens the synaptic connection.

STDP and Receptor Regulation

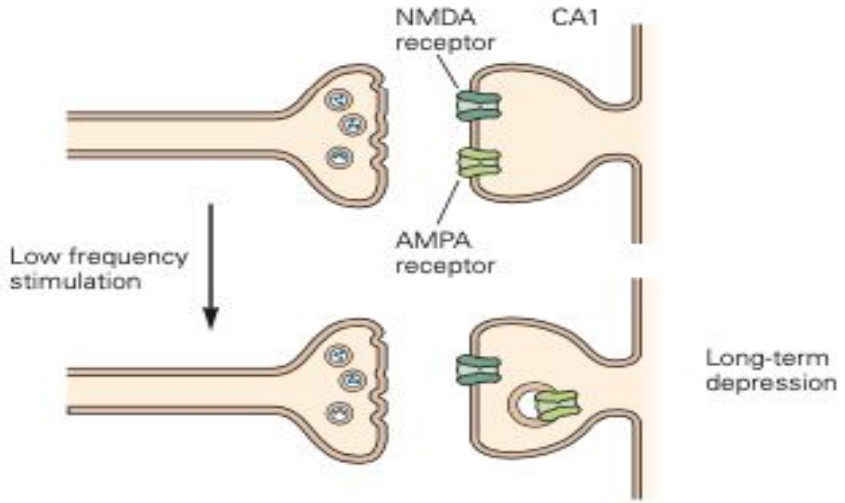


Timing of depolarization dictates the magnitude of the excitatory response. Depolarization of the postsynaptic neuron generates enough force to expel Mg+ from NMDA receptors. If this occurs following the presynaptic depolarization, glutamate can readily bind NMDA receptors and increase Ca+ influx in the postsynaptic neuron. If the postsynaptic neuron precedes the presynaptic depolarization, no glutamate will be available to bind, and little downstream AP propagation will occur.



Postsynaptic calcium influx is required to activate the second messenger PKC (via calcium/calmodulin-dependent kinase CaMII), which enhances the current through AMPA receptors and initiates retrograde signalling. The retrograde messenger (NO?) is responsible for inserting new receptors into the postsynaptic membrane.

LTD - Receptor Reuptake



Low-frequency stimulus / unsynchronized neuron firing results in decreased summative effects of graded potentials at the postsynaptic neuron. This results in a decreased chance of depolarization (less ability to relieve Mg2+).

Lower Ca2+ concentrations activate calcium-dependant phosphatase calcineurin rather than CaMKII. Downstream events activate phosphatases inhibiting the actions of GluA1. GluA2 activity is increased via PKC phosphorylation. (GluA1 and GluA2 are both subunits of AMPA receptors) The effect of their respective phosphorylation and dephosphorylation results in endocytosis of the AMPA receptors.

Bonus Information

The Journal of Neuroscience, August 15, 1999, 19(16):6795–6805

Mechanism of Cannabinoid Effects on Long-Term Potentiation and Depression in Hippocampal CA1 Neurons

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Cannabinoids, the active constituents of marijuana, are known to impair learning and memory. Receptors for cannabinoids are highly expressed in the hippocampus, a brain region that is believed to play an important role in certain forms of learning and memory. To investigate the possible contribution of cannabinoid receptor-mediated deficits in hippocampal function to the learning and memory impairments produced by marijuana, we studied the effects of cannabinoid receptor activation on two models of learning and memory, long-term potentiation (LTP) and long-term depression (LTD), in hippocampal slices. Although LTP and LTD of CA1 field potentials were blocked by cannabinoid receptor activation in the presence of Mg^{2+}, they

col. Cannabinoid receptor activation also reduced EPSCs and enhanced paired-pulse facilitation, while having no effect on the amplitude of spontaneous miniature EPSCs. Finally, as with cannabinoid receptor activation, inhibition of LTP by adenosine receptor activation could be overcome by removal of Mg^{2+} or depolarization of the postsynaptic membrane during tetanus. Our results indicate that cannabinoid receptor activation does not directly inhibit the molecular mechanisms responsible for long-term synaptic plasticity but instead impairs LTP and LTD by reducing presynaptic neurotransmitter release to a level below that required to depolarize the postsynaptic membrane to relieve Mg^{2+} blockade of NMDA receptors.

Minser and Sullivan studied the effects of active marijuana constituents on the hippocampus of mice.

Whole-cell patch clamp and field potential recordings of hippocampal slices were analyzed.

Findings:

NMDA receptors functioned comparably to the control in cannabinoid-exposed conditions when Mg+ was manually washed out.

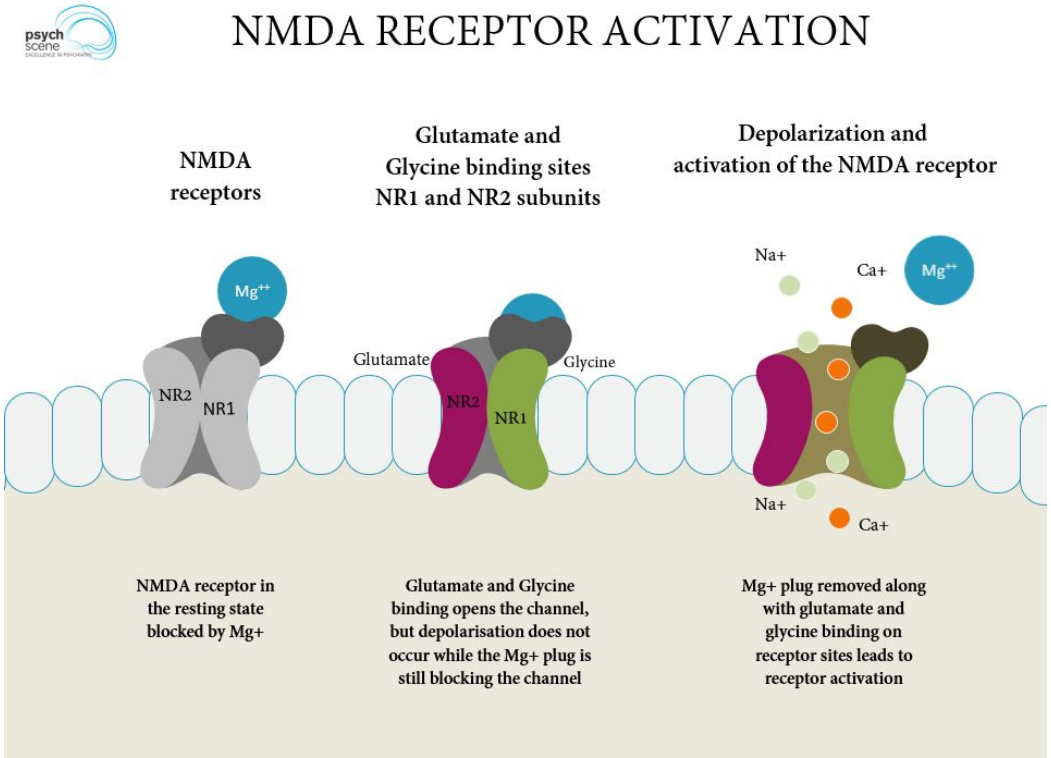
Tetanic stimuli also resulted in the near-normal function of NMDA receptors.

Implications:

The greatest mechanism impairing hippocampal LTP and LTD results from the reduced neurotransmitter release at the presynaptic neuron. (inability to effectively expel Mg+)

Mechanism

https://www.youtube.com/watch?v=8-m_J2CnYho



Δ9-tetrahydrocannabinol (Δ9-THC) binds CB1 receptors in the endocannabinoid system.

CB1 activation initiates G-coupled protein reactions, including the cyclic AMP/protein kinase A pathway which works to inhibit voltage-gated Ca2+ channels and increase the activation of K+ channels.

This effectively decreases NT release at the presynaptic bouton.

Due to decreased NT, NMDA receptors are not sufficiently activated to clear Mg+ from blocking the channel.

This mechanism impairs LTP and LTD.