KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

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Module:

Biological Foundations of Mental Health

Week 4:

Biological basis of learning, memory and cognition

Topic 3:

The effects of activity, experience and deprivation on the nervous system

Part 1 of 5

Topic list

This week, we will be looking at the following topics:

- Topic 1: Learning, memory and synaptic plasticity
- Topic 2: From the dynamic synapse to synaptopathies
- ***Topic 3: The effects of activity, experience and deprivation on the nervous system***

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Lecture outline

1. **Hebbian synaptic plasticity:** theory and experimental proof
2. **Segregating inputs through Hebbian plasticity:** how does activity shape the visual system?
3. **Integrating inputs through Hebbian plasticity:** how does experience and deprivation shape the visual system?
4. **Critical periods:** how does inhibition serve as a permissive factor for Hebbian plasticity?
5. **Re-opening the critical period:** therapeutic approaches to recovering function in the deprived nervous system.

Part 1

Part 1

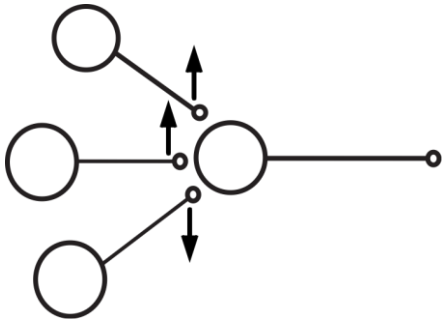
Hebbian synaptic plasticity: theory and experimental proof

Hebbian synaptic plasticity

Donald Hebb

The Organization of Behavior

Hebbian synaptic plasticity: '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 the efficiency of A, as one of the cells firing B, is increased'.



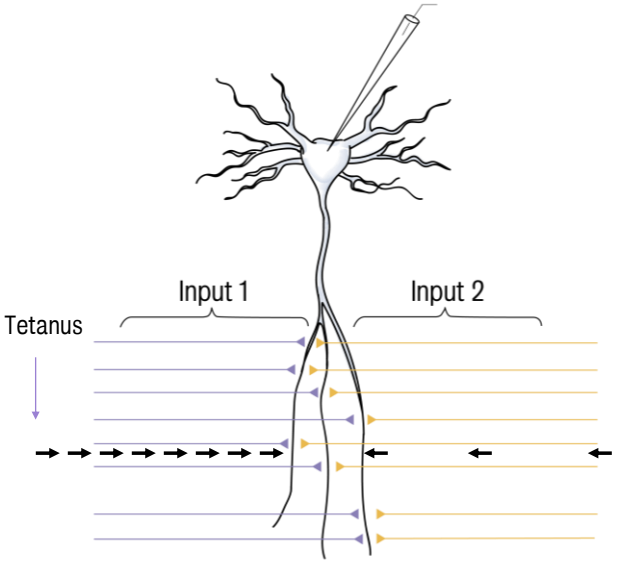
Synapses can be strengthened or weakened based on if pre- and post-synaptic cells are correlated or not in activity.

'Fire together, wire together'

Synaptic plasticity allows experience to shape connections that already exist by increasing or decreasing their efficacy.

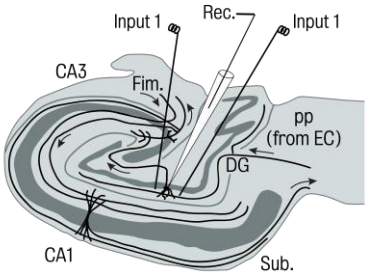
Input specificity

Input specificity is a prediction of the Hebbian theory, stating that synaptic plasticity can occur at one synapse without affecting its neighbour.



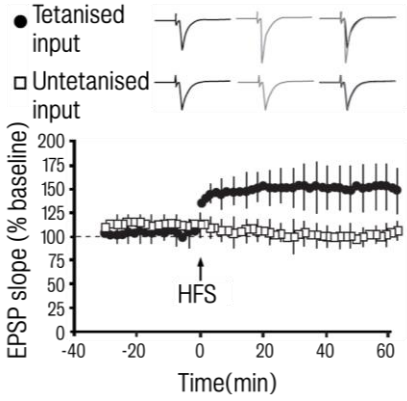
Long-term potentiation (LTP) in the human hippocampus

LTP is the most commonly studied form of Hebbian plasticity and relies upon electrophysiological stimulation and recording techniques.



Slice of human hippocampus

Strength of synaptic response to electrical pulses



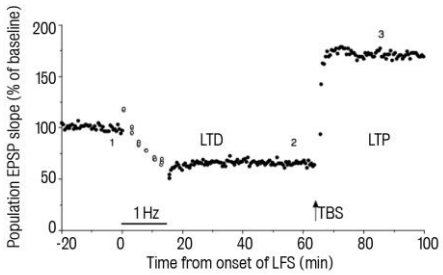
Input-specific, long-lasting Hebbian synaptic plasticity

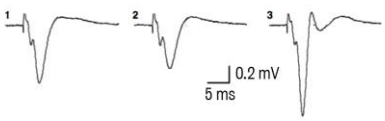
Beck et al., 2000

Long-term potentiation and long-term depression

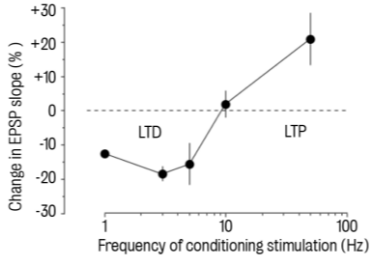
Synapses are bidirectionally modifiable: both LTD and LTP can be observed longitudinally at the same synapses.

Long-term depression (LTD) and long-term potentiation (LTP) at the same synapse





Determining the frequency of the modification threshold for LTD/LTP



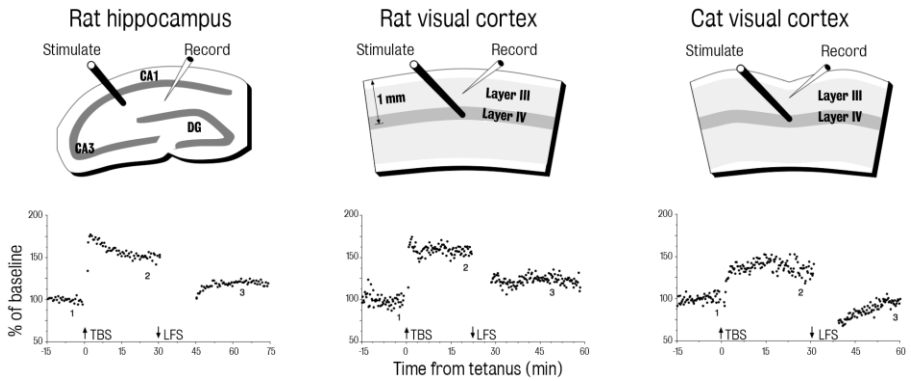
Low frequency stimuli induce LTD, while higher frequencies induce LTP.

The **modification threshold** is the frequency at which no change in synaptic strength will occur; in this case 10 hz.

Dudek & Bear, 1992; 1993

Bidirectional synaptic plasticity

Principles of bidirectional synaptic plasticity generalise from rodent hippocampus to neocortex and to other species of animal.



All show similar degrees of LTP and LTD when assessed with electrophysiology.

Kirkwood et al., 1993

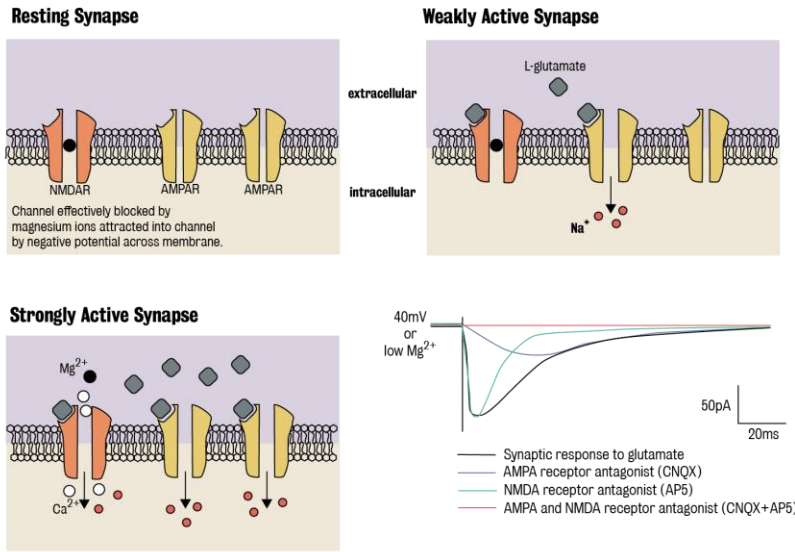
The NMDA receptor as a coincidence detector

AMPA receptors:

- an ion channel opened by glutamate which allows the flow of positively charged ions into a neuron
- carries the major synaptic current
- responsible for excitatory fast synaptic transmission
- LTP and LTD expressed through changes in AMPA conductance.

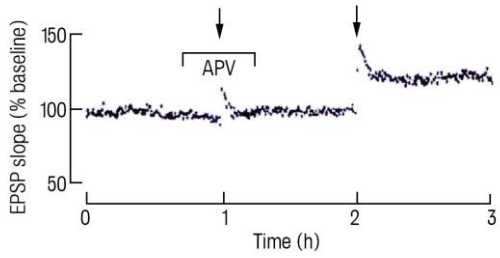
NMDA receptors:

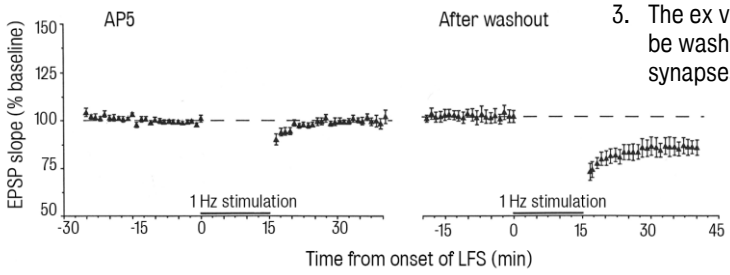
- an ion channel allowing flow of positively charged ions into neurons
- glutamate-binding and voltage-dependent; channel open only when glutamate is bound and post-synaptic neuron is depolarised
- ideal coincidence detector to fulfill the Hebbian criterion of simulataneous pre- and post-synaptic activity
- calcium conductance through the NMDAR is the critical factor for plasticity to occur



Cooke & Bliss, 2006

Evidence from AP5 (APV)





The NMDA receptor antagonist AP5 (or APV) blocks the induction of both LTP and LTD.

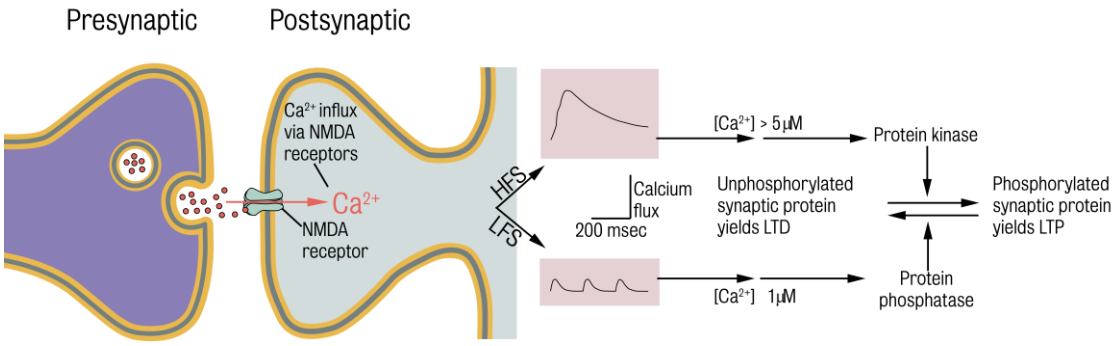
This demonstrates the following:

1. The NMDA receptor is the biological solution to Hebb's theory.
2. LTP can still be induced after washout.
3. The ex vivo slice is advantageous as it allows drugs to both be washed on and off at appropriate times, showing that synapses are not irreparably altered by drug delivery.

Collingridge et al., 1983; Dudek and Bear, 1992, 1993

How can inverse effects on synapses share mechanism?

The concentration of post-synaptic calcium differs between LTP and LTD due to the different dynamics of post-synaptic activation produced by high and low-frequency stimulation.



Different calcium-sensing enzymes are activated by high and low concentrations of calcium ions: kinases such as AMPA receptors change their properties and some phosphatases have the reverse effect.

Summary

- Hebbian plasticity is an activity-dependent strengthening of synapses between co-active neurons or weakening of synapses between neurons with uncorrelated activity.
- Hebbian plasticity is modelled experimentally *in vitro* and *in vivo* through electrical stimulation to produce long-term potentiation (**LTP**) or long-term depression (**LTD**), which respectively strengthens or weakens synapses. The frequency of stimulation is a major determinant of the direction of change – high for LTP and low for LTD. LTP and LTD occur at most synapses in the nervous system.
- Hebbian plasticity is **input-specific**, as it occurs only at synapses that have undergone activity and does not occur at neighbouring inactive synapses on the same neuron. It is also **long-lasting**.
- The NMDA subclass of glutamate receptor is often a key mechanism in the induction of LTP as it is an ion channel that conveys calcium ions only when two coincident events occur – glutamate binding and post-synaptic depolarisation – thus it serves as **a detector** of the defining events in Hebbian LTP – correlated pre- and post-synaptic activity. It is also a key mechanism for many forms of Hebbian LTD!
- Hebbian plasticity is not accurately described by the statement 'Fire together, wire together'. Hebbian plasticity **can only change existing synapses**. It does not involve the formation of new synapses!

References

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End of part 1