principle: ‘fire together – wire together’

"The general idea is an old one, that any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated', so that activity in one facilitates activity in the other." (Hebb 1949)

"When one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs (or enlarges them if they already exist) in contact with the soma of the second cell." (Hebb 1949)
changes in synaptic efficacy can reflect either changes in depolarization caused by increases or decreases in the amount of neurotransmitter released by an action potential (presynaptic change) and/or increases or decreases in the amount of response of the postsynaptic neuron to the same amount of glutamate released by the presynaptic neuron.

post-synaptic changes usually reflect changes in the shape of the synapse, changes in the number of ionotropic receptors, changes in the kinetics of ionotropic receptors, and/or development or retraction of contacts (synapses) between neurons.

changes in synaptic efficacy often depend on the timing and/or amount of co-activity between two neurons (as in ‘fire together, wire together’)

for any two connected neurons, the co-activity rules for synaptic change may differ greatly.

co-activity leading to changes in synaptic efficacy may depend on the presence or absence of a third party such as a neuromodulator or a peptide.
visualization of potentiating, depressing, and unchanged synapses following stimulation of hippocampal CA3 inputs into CA1 region of hippocampus

Becker et al., Neuron, 2008
Dendritic spine morphology (shape) matters

Immature spines have long, skinny shape that increases the internal resistance of the spine

Mature spines are shorter and wider = decreased internal resistance

More difficult for EPSPs to travel to cell body along immature spines than mature spines

Fragile-x mutation: mutation of \textit{fmr} gene on X chromosome found in 35\% of intellectually disabled individuals (e.g. Down syndrome)

Dendritic spines of cortical neurons in fragile-X mice (mental retardation) are longer / immature

\textit{Fmr} gene responsible for shutting off production of \textit{mGluR} receptors

Activation of \textit{mGluR} receptors causes production of new (immature) dendritic spines

Dolan et al., Neuron, 2007
spike timing dependent plasticity: changes in synaptic ‘efficacy’ between two neurons (one presynaptic, the other postsynaptic) related to the relative timing of their action potentials

- post-synaptic neuron fires before pre-synaptic neuron: $\Delta t < 0$
- pre-synaptic neuron fires before post-synaptic neuron: $\Delta t > 0$

intracellular electrode for recording of synaptic potentials and action potentials or for stimulation of an action potential

synaptic potential in post-synaptic neuron resulting from a single presynaptic spike

synaptic depression (or depotentiation)

synaptic potentiation

Bi and Poo, ARN, 2001

time of firing of post-synaptic neuron minus time of firing of pre-synaptic neuron
co-activity rules for synaptic efficacy change depend on neuromodulatory systems

- **no ACh, no NE (as in NREM sleep)**
- **ACh + NE (as in waking)**
- **NE, no ACh (??)**
- **ACh, no NE (e.g., REM sleep)**
Sequential neuromodulation of Hebbian plasticity offers mechanism for effective reward-based navigation (Brzosko et al., 2017)

ACh biases STDP toward depression

DA retroactively converts Ach-facilitated t-LTD into t-LTP

Rodent’s position is coded by place cells and it’s movement is determined by action neurons. Action cells receive information from place cells as well as form other action cells.

During exploration Ach facilitates synaptic depression. When reward, signaled via DA, promptly follows exploration, synaptic depression is converted into potentiation.

When cholinergic depression is included in the model:

Learning of a displaced reward location is facilitated.
Firing rate homeostasis

Lower firing

Raise firing

Synaptic scaling

Presynaptic terminal

Postsynaptic terminal

Potentiation

Scaling

Target activity

High activity

Target activity
learning 101: Pavlovian fear conditioning – association of an initially neutral tone (CS) with a foot-shock results in ‘freezing’ responses when the tone alone is played.

conditioned stimulus (CS)

conditioned + unconditioned stimulus (US)

conditioned stimulus

curiosity

‘shock and awe’ (freezing)

conditioned freezing

auditory cortex / auditory thalamus (neurons excited by sound stimulus - CS)

somatosensory cortex / somatosensory thalamus (neurons excited by shock stimulus - US)

lateral amygdala

central amygdala

hippocampus (place information)

IT (visual item information)

freezing response, increased heart rate, etc.

before pairing

after pairing
curing PTSD by taking advantage of the ‘labile’ nature of some memories:

Day 1: Humans develop eye-blink responses to tones (the conditioned stimuli - CS) paired with shocks (the unconditioned stimuli – US).

Day 2: Two groups are exposed to the CS after having been given placebo (top graphs) or propranolol (middle graphs), a compound that blocks the action of norepinephrine (NE). A third group is given propranolol, but not exposed to the CS.

Day 3: An set of ‘extinction’ trials (presentation of CS in absence of US) is given and eye-blink responses are recorded. Blocking the action of NE on day 2 is shown to have the effect of ‘erasing’ the CS-US association.

Day 4: Usually, as in the placebo condition, the US given alone reverses the extinction of the CS-US association that was achieved on day 3. Blocking the action of NE on day negates this.