Computational cognitive neuroscience: 4. Synaptic Plasticity

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"We are what we can remember"

- We have several types of memory (short-term, long-term, explicit, implicit, working, etc.). All are based on changes in synaptic weights.

- It is widely accepted that long-term memories of all kinds are stored in the brain in the patterns of synaptic weights in the relevant brain areas (i.e. cortex, hippocampus, cerebellum, etc.).

- Do all different brain areas possess the same ability of plastic synaptic changes throughout the whole life?

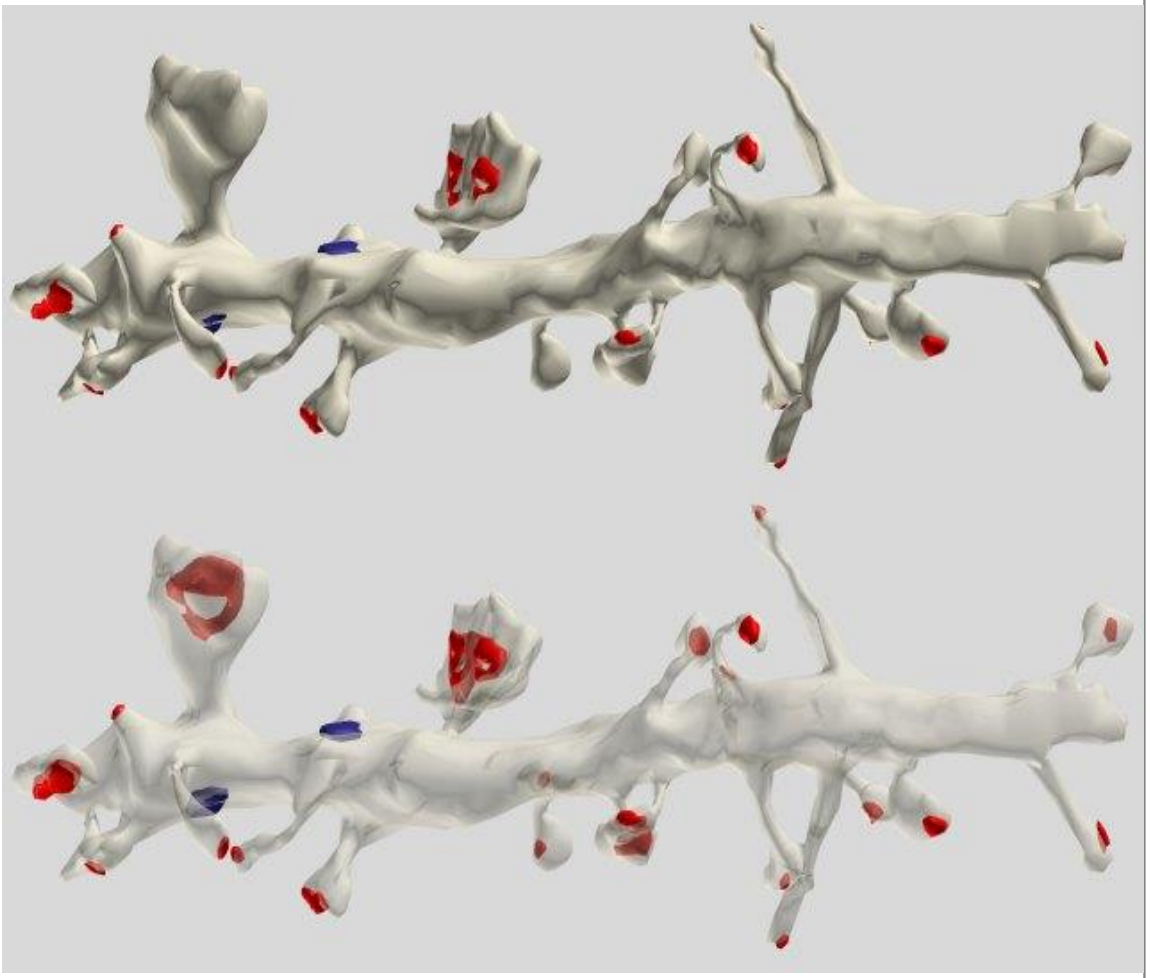
- It turns out that the so-called primary sensory areas exhibit synaptic plasticity only during the so-called critical periods of time after birth whereas associative areas of the cortex are plastic all the time.

Learning and the brain plasticity

- **Synaptic plasticity** underlies the brain plasticity, which is a lifelong ability of the brain to reorganize neural circuits based on new experience.
- Organism's ability to store, retain, and subsequently recall information is called a **memory**.
- The process of acquisition of memories is called ***learning***.
- We distinguish short-term and long-term memory, which are based on short-term and long-term synaptic plasticity, respectively:
  - Long-term potentiation of synaptic strengths (**LTP**)
  - Long-term depression of synaptic strengths (**LTD**)

Spines

- Postsynaptic spines are numerous small protrusions on dendrites.
- 90% of excitatory synapses in the cortex are on spines, the rest of excitatory and all inhibitory synapses are on dendritic shafts and soma.
- Red area(s) on spines are PSD – postsynaptic density, where the postsynaptic receptors and their supporting molecules are.



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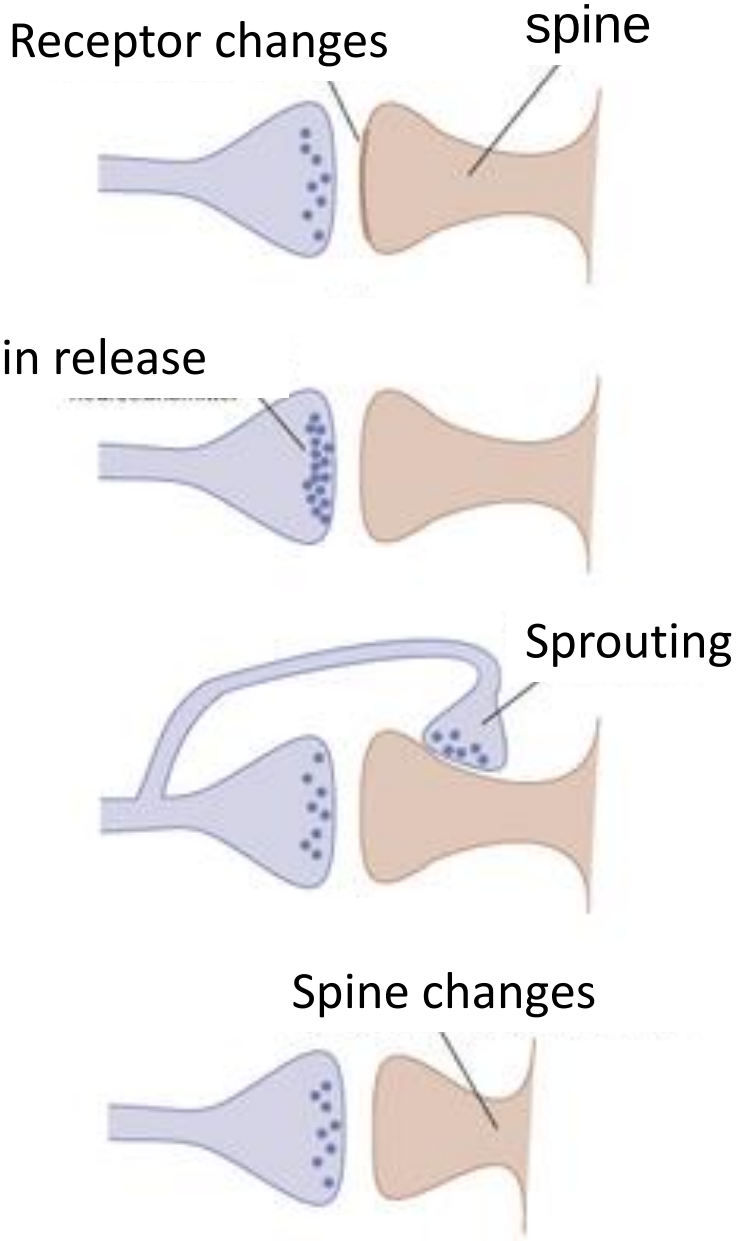
http://synapses.clm.utexas.edu/anatomy/compare/compare.stm

Synaptic plasticity: mechanisms

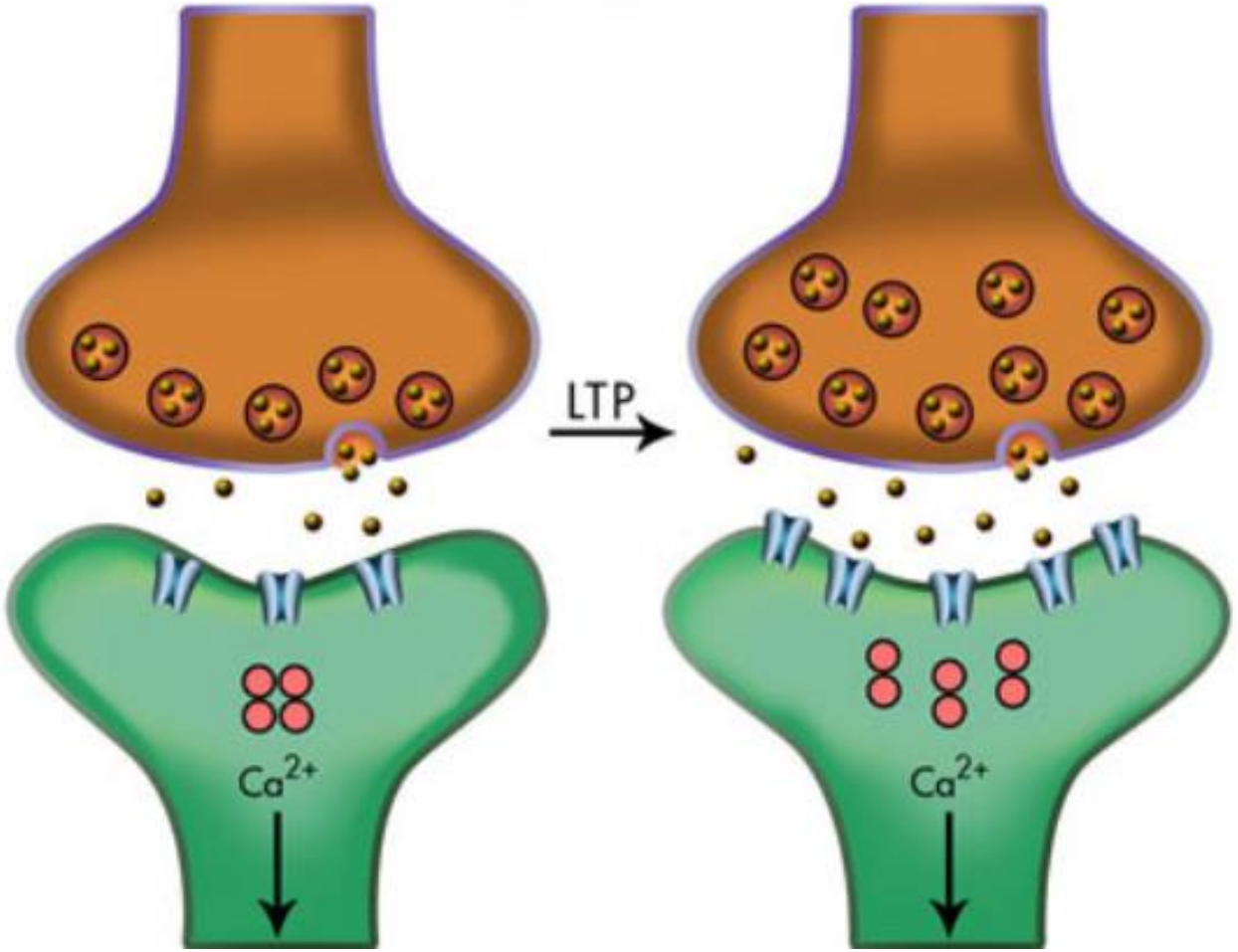
- Synaptic plasticity is the ability of the synapse to change the strength (efficacy) – applies to excitatory synapses

- Mechanisms:
  - Change in the number or properties of postsynaptic receptors
  - Changes in the number of released vesicles with neurotransmitter
  - Sprouting: synapses grow new sprouts, changes in the number of synapses
  - Changes in the shape of spines (affects their electric properties)



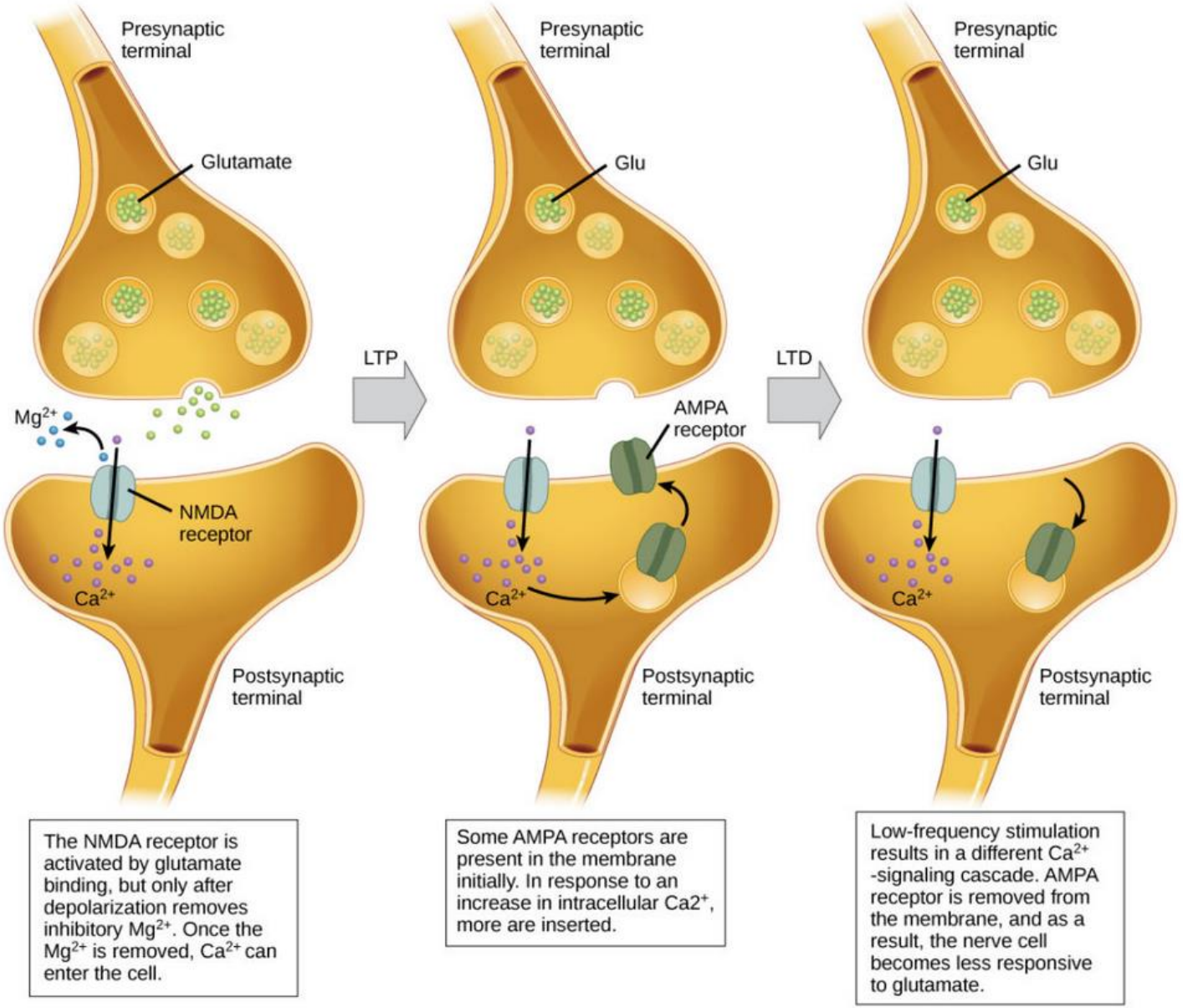
LTP: change in neurotransmitter release

- https://www.neuroskills.com/brain-injury/neuroplasticity/mechanisms-of-plasticity/



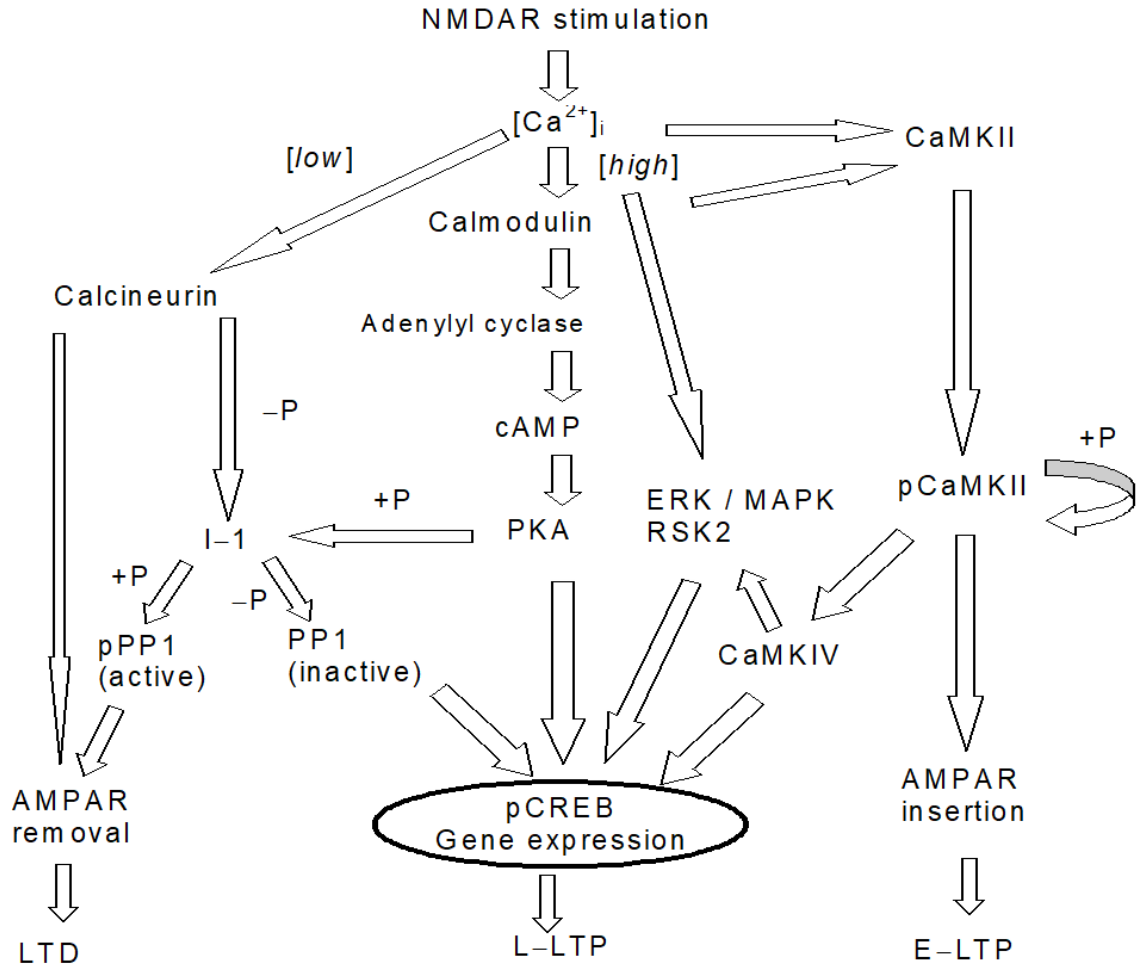
LTP and LTD: change in receptor number

- https://courses.lumenlearning.com/wm-biology2/chapter/synaptic-plasticity/



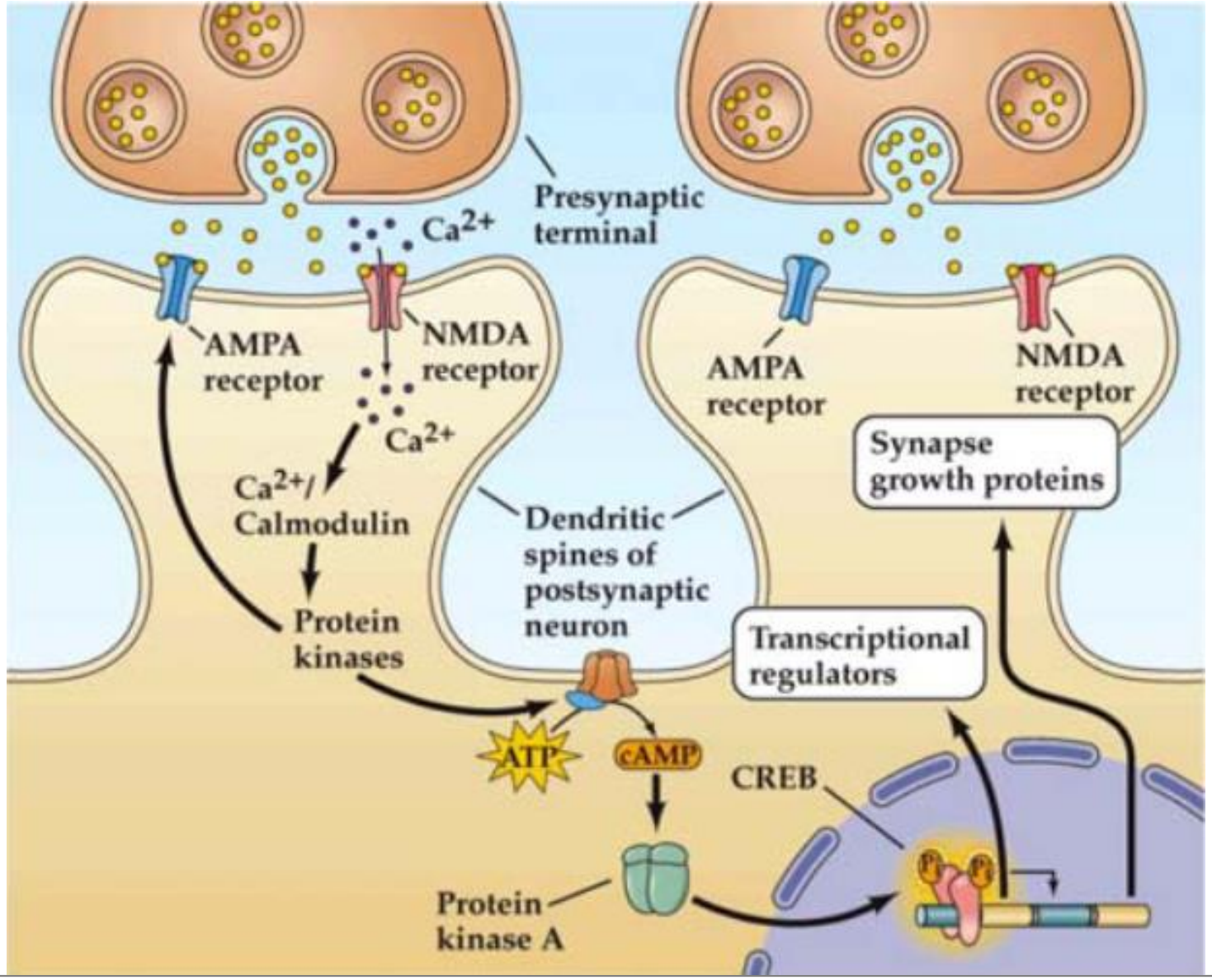
LTP and LTD: biochemical pathways

- Abbreviations: P = phosphorus, E-LTP = early LTP (1-3 hours), L-LTP = late LTP (> 24 hours), CaMK = Ca/Calmodulin dependent protein kinase, cAMP = cyclic adenosine monophosphate, PKA = cAMP-dependent protein kinase A, ERK/MAPK = extracellular signal-regulated protein kinase/ mitogen-activated protein kinase, RSK2 = ribosomal S6 kinase 2, CREB = cAMP-responsive transcription factor, PP1 = protein phosphatase 1, I-1 = inihibitor 1, +P = phosphorylation, -P = dephosphorylation.



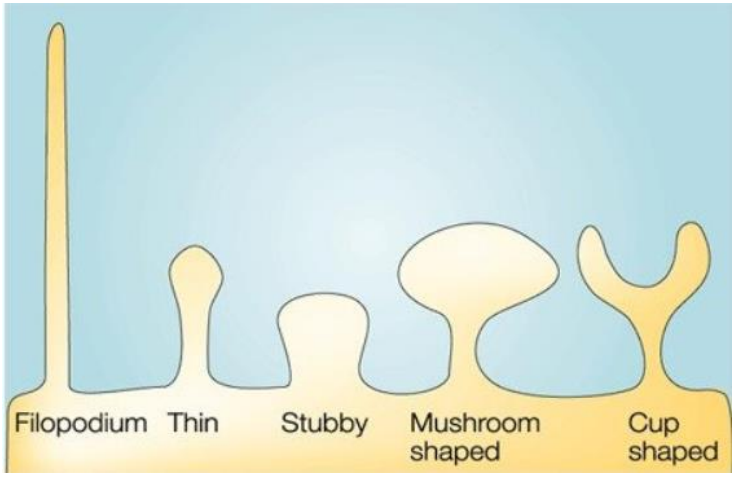
LTP: growth of new synapses

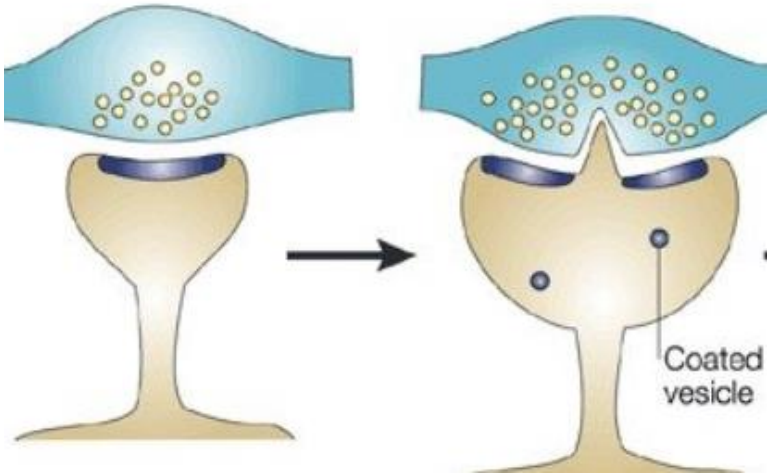
- Old synapse
- New synapse



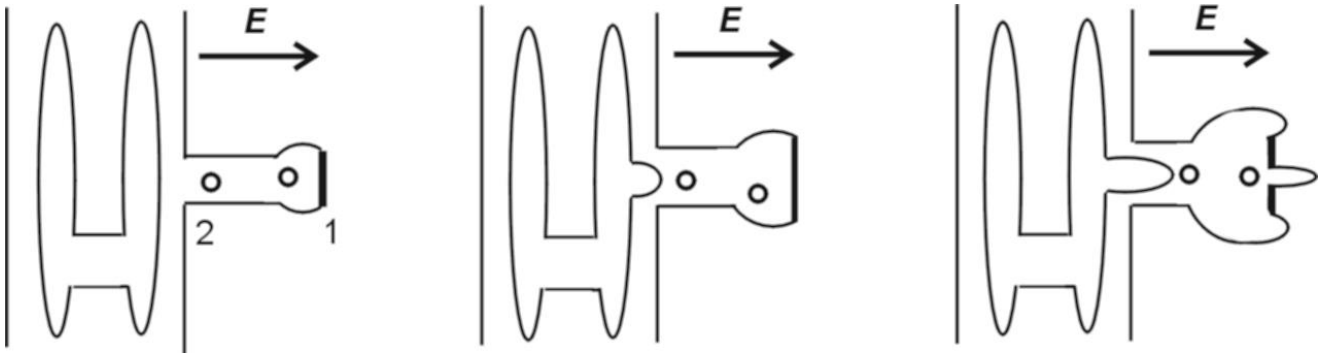
LTP: change of spine size and shape

- Spine shapes and change of spine size and shape during LTP (Hering and Sheng, 2001, https://www.nature.com/articles/35104061



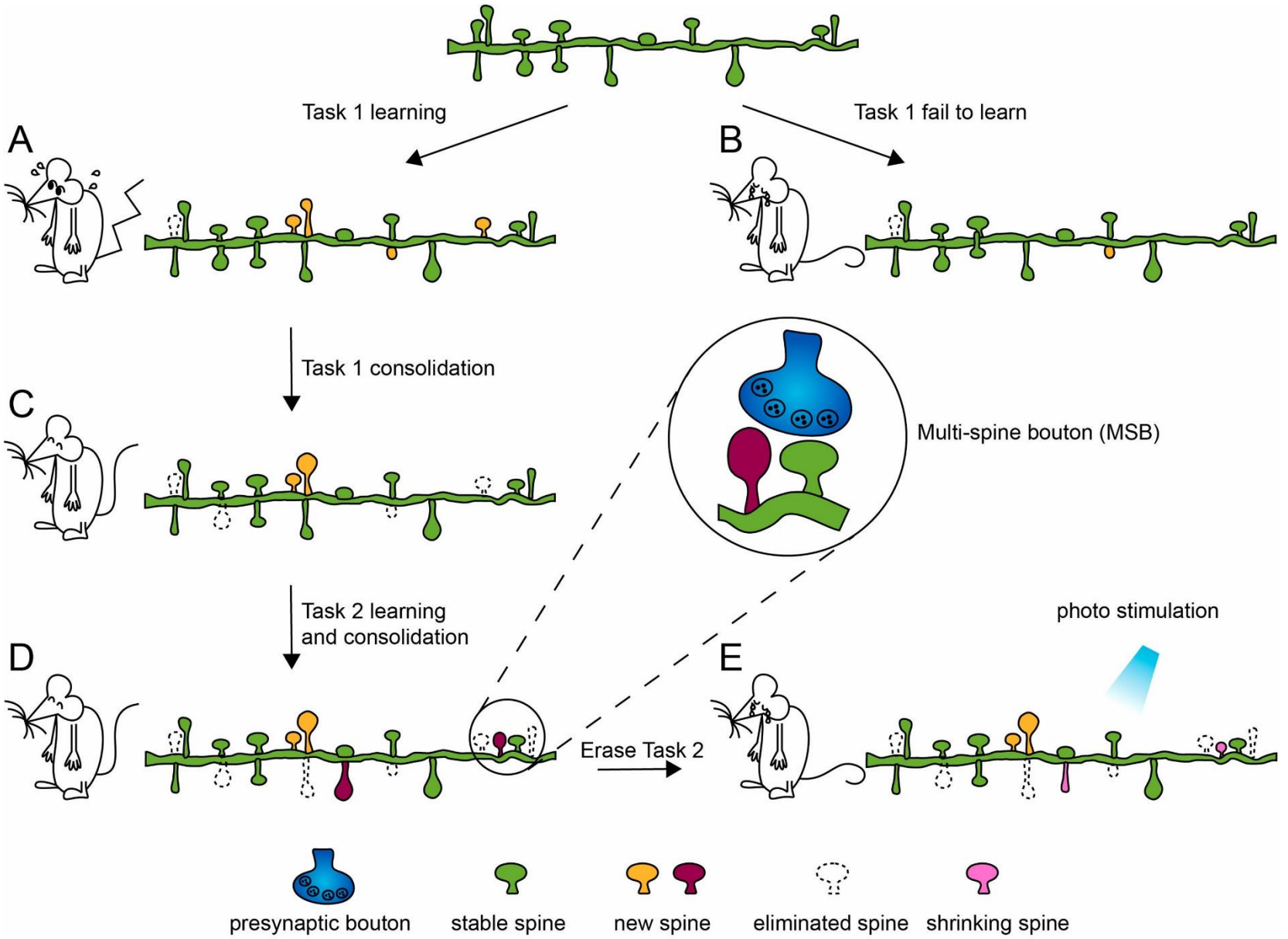


- Benuskova L (2000) The intra-spine electric force can drive vesicles for fusion: a theoretical model for long-term potentiation. Neuroscience Letters 280(1): 17-20.



LTP and LTD: change in shape and spine number

- Ma and Zuo, 2022, https://doi.org/10.1016/j.semcdb.2021.05.015

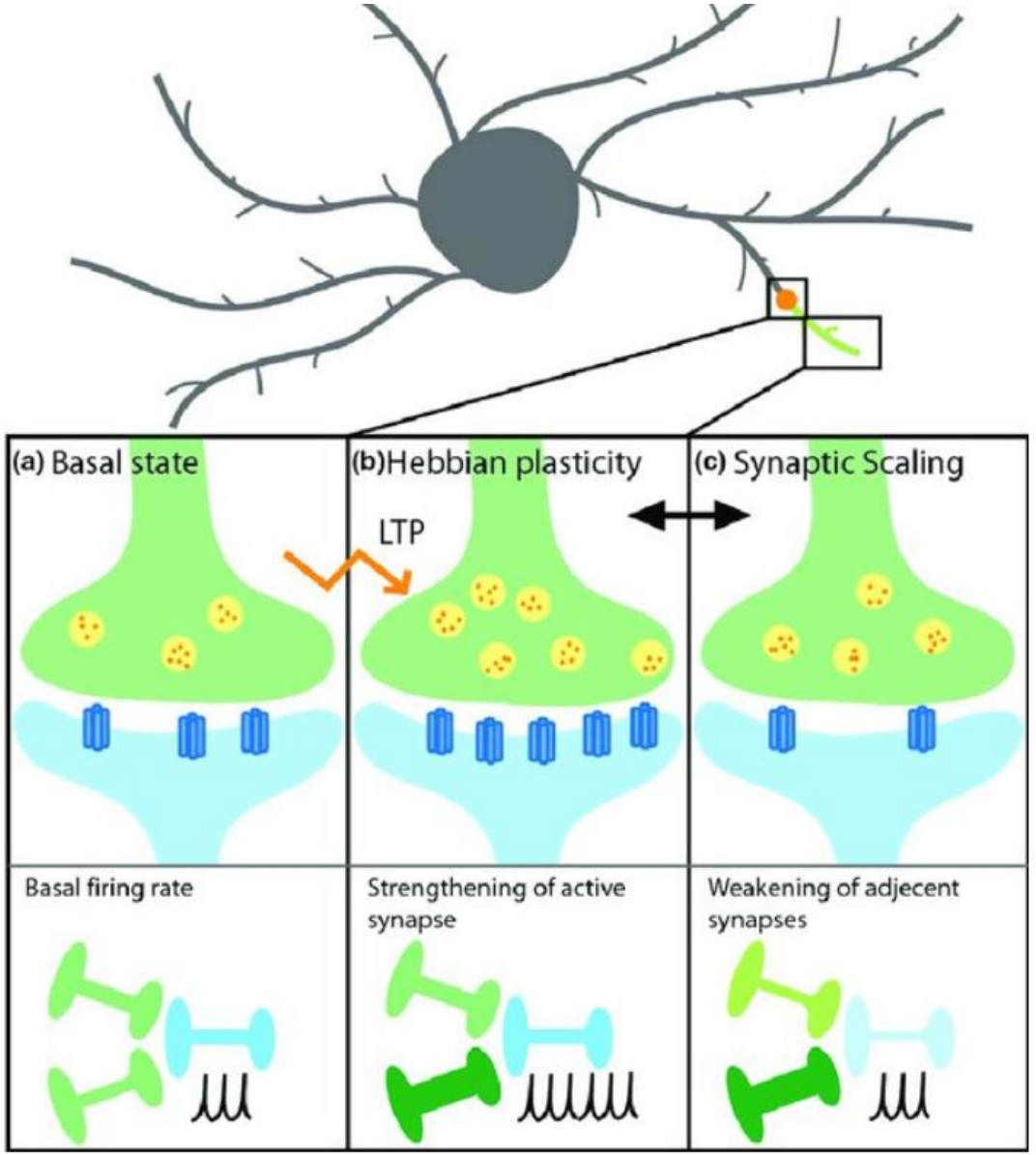


Hebb rule and synaptic scaling

- Schaefer et al., 2017, https://doi.org/10.1111/jnc.14107

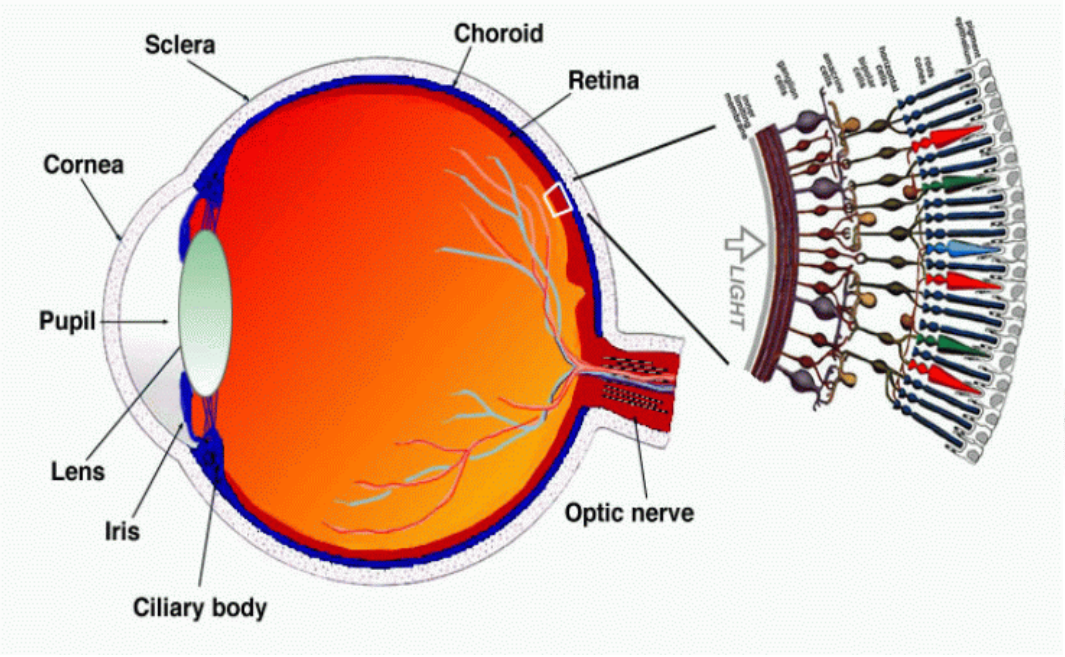
- **Hebb rule**: *When an axon of cell A is near enough to excite a cell B and* ***repeatedly or persistently*** *takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."* (1949)

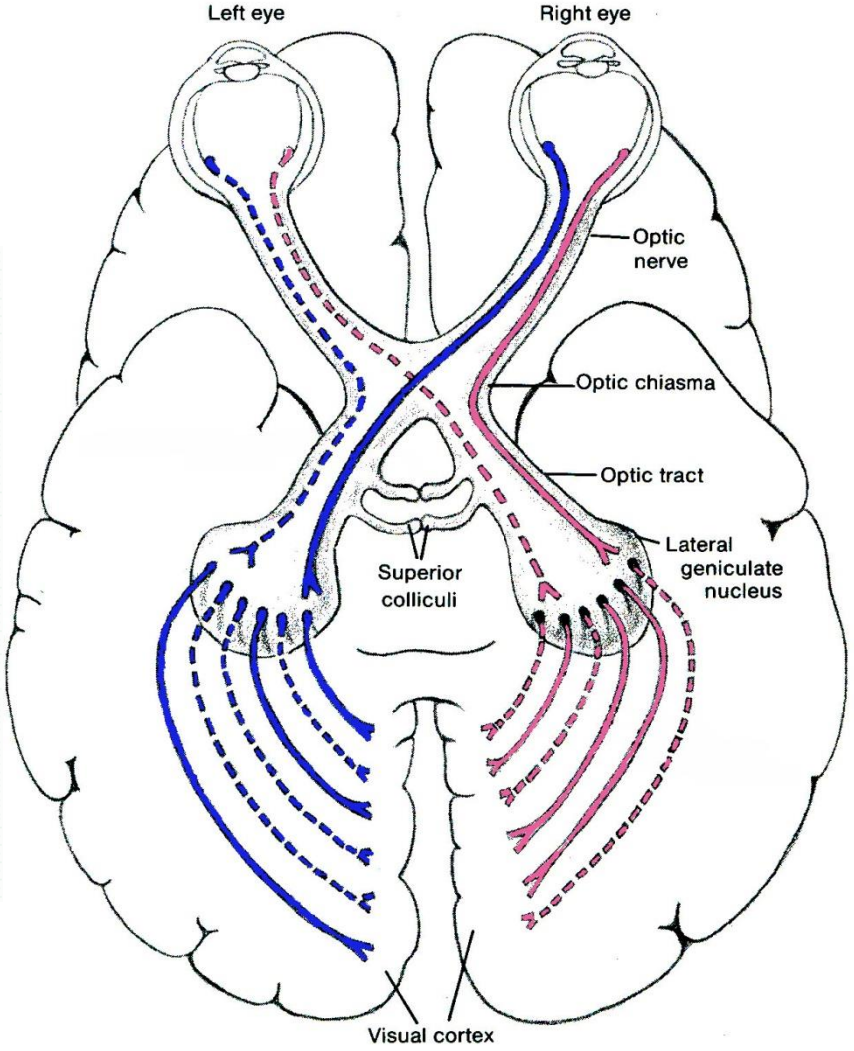
- **Synaptic scaling or heterosynaptic plasticity** acts through weakening synapses adjacent to the potentiated synapse to restore homeostasis and optimal global firing rate.



Plasticity in the developing visual system

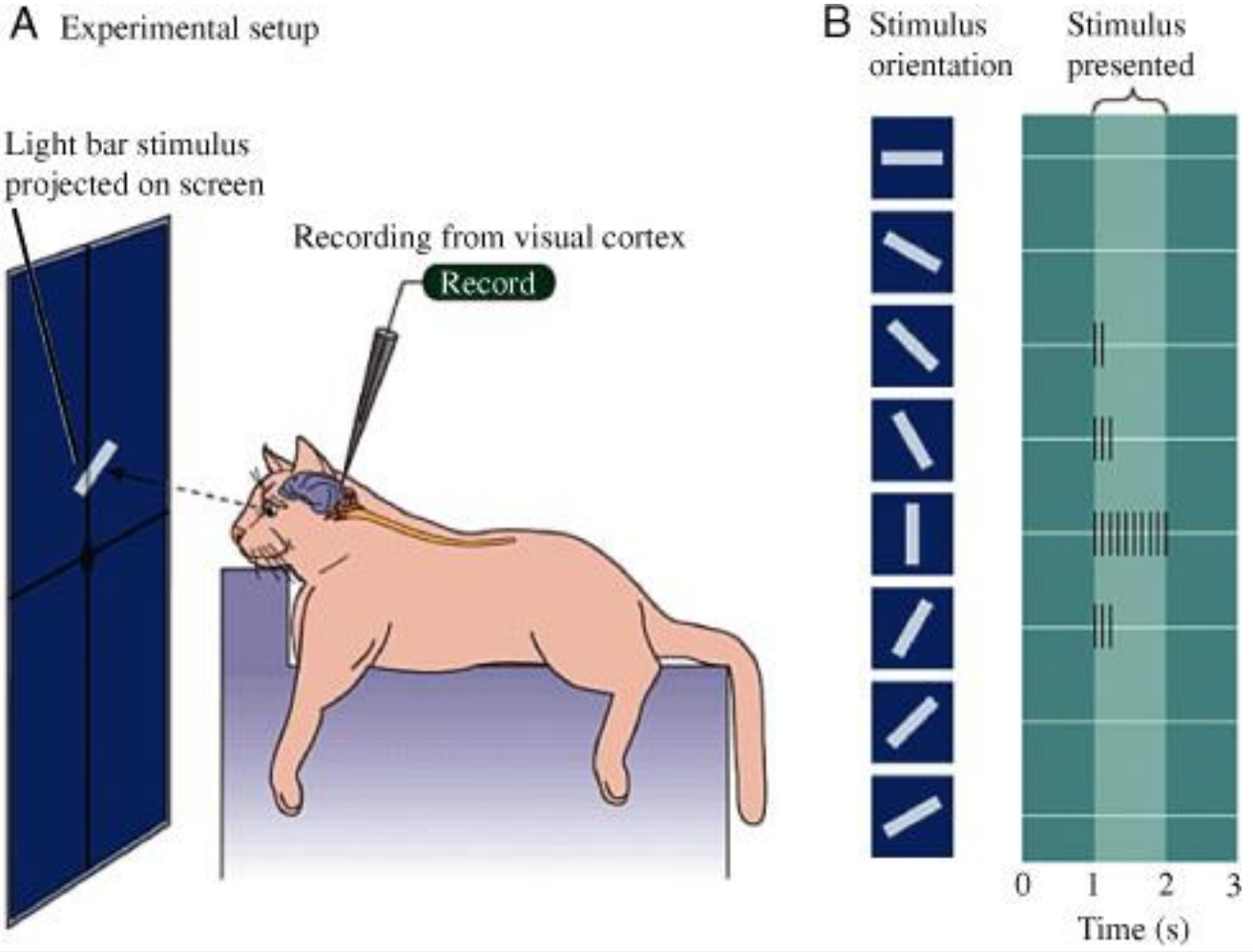
- Visual signals travel from neurons in the eye retina through the optic nerve to the LGN (lateral geniculate nucleus) in the thalamus and from there to the primary visual cortex V1.





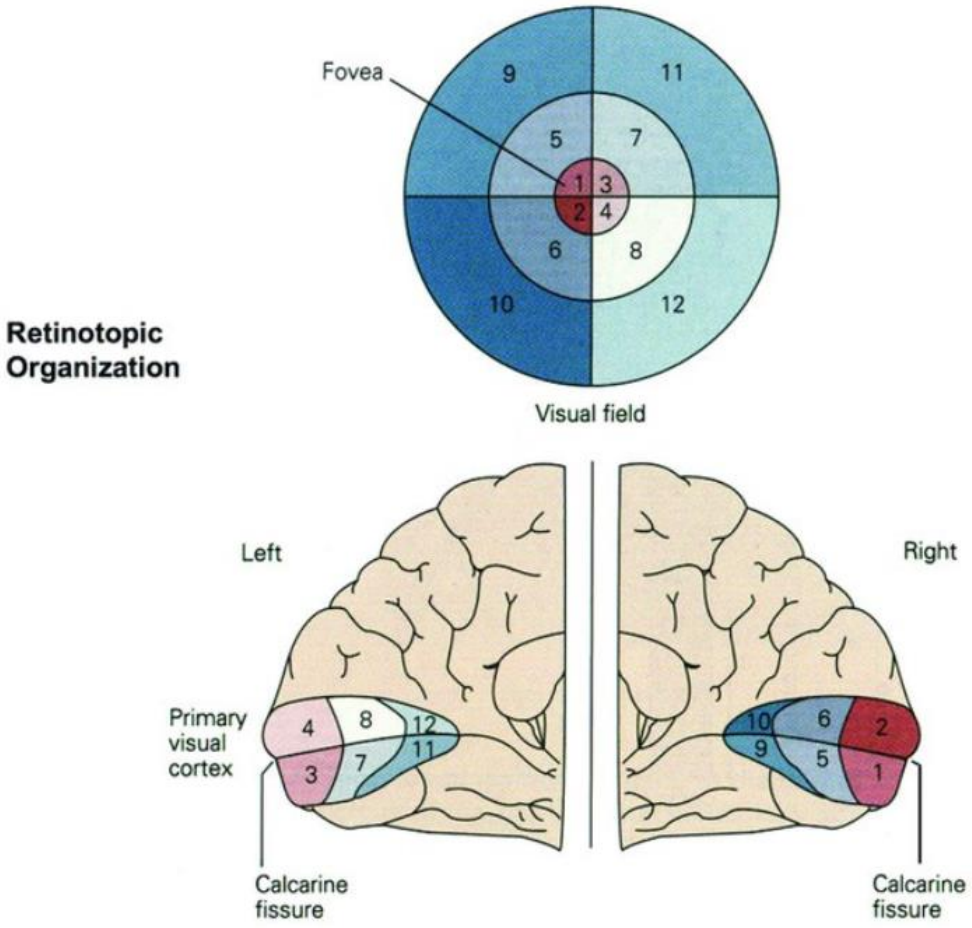
Receptive fields of V1 cells are oriented bars

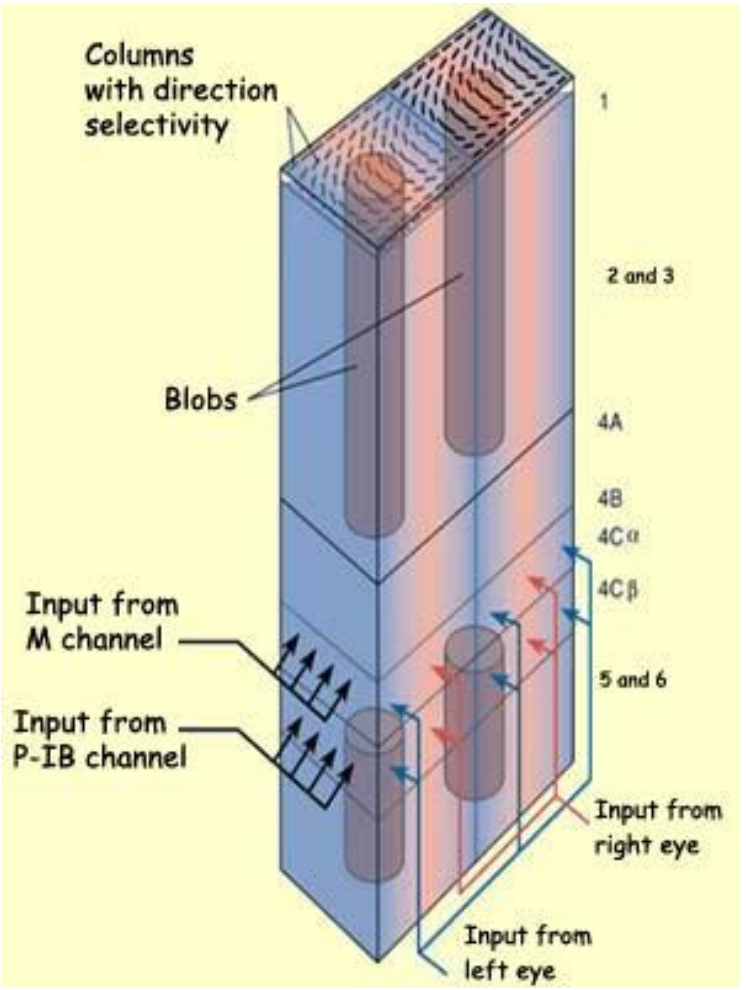
- Recording neural activity in V1 neurons in response to stimuli of different shapes revealed that neurons respond to the light bars of different orientations (Nobel Prize to Hubel and Wiesel, 1981), thus V1 "receptive fields" have the shape of light bars of different angles.



Orientation selective cells V1

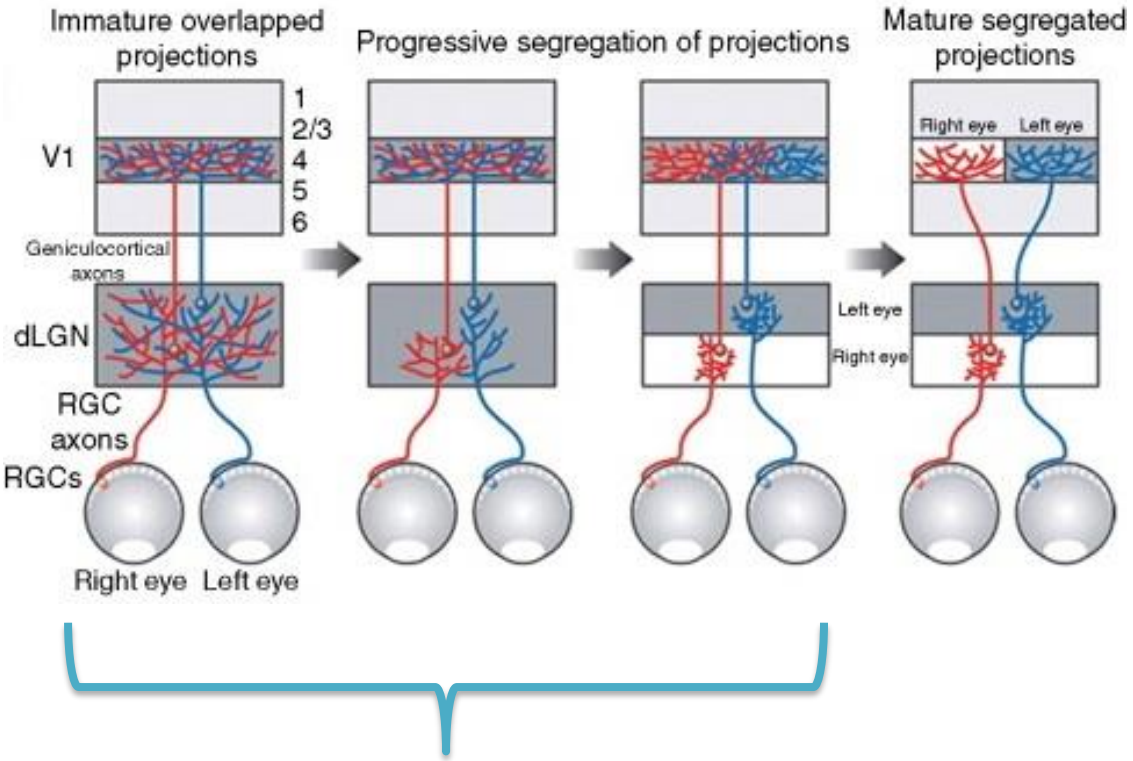
- All neurons within a single cortical column respond to the bars of the same angle. Columns covering all angles form a hyper-column. "Blobs" are cells sensitive to colour. Each point in the visual field is processed by a single hypercolumn (Paulun et al., Front. Comput. Neurosci., 2018)

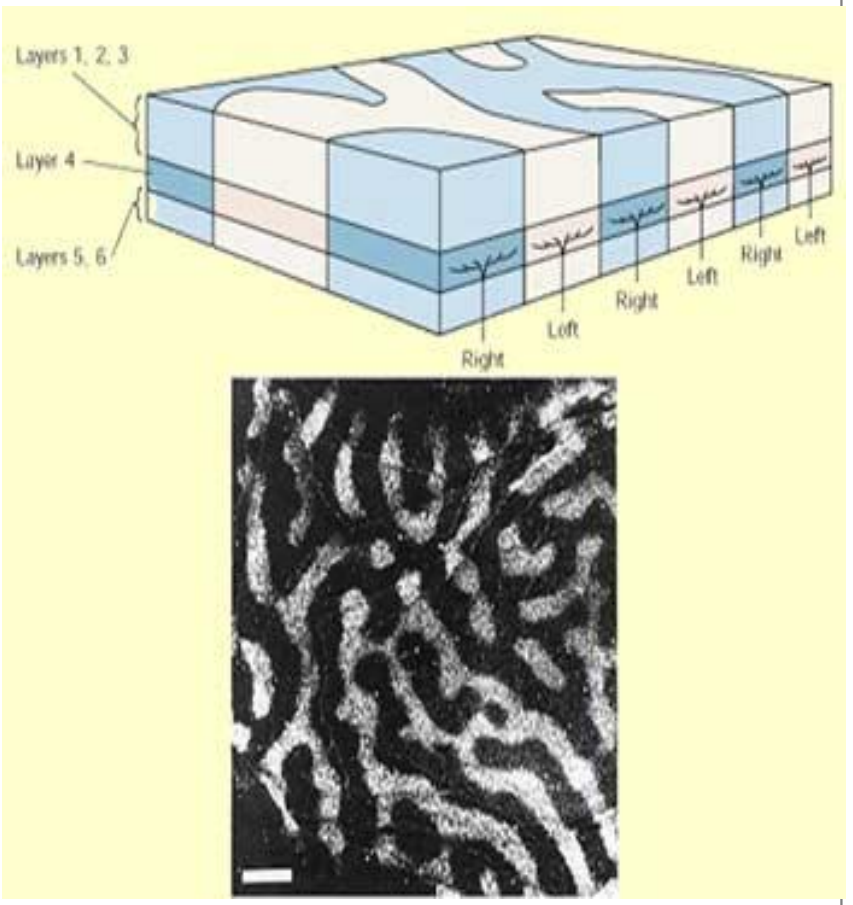




Ocular dominance in V1

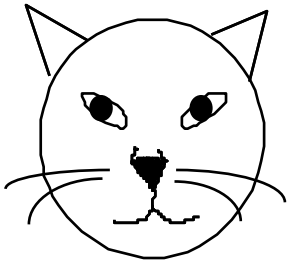
- Ocular dominance stripes: cells respond either to the left or right eye or both, depending on the stage of development (Luo and O'Leary, 2005)



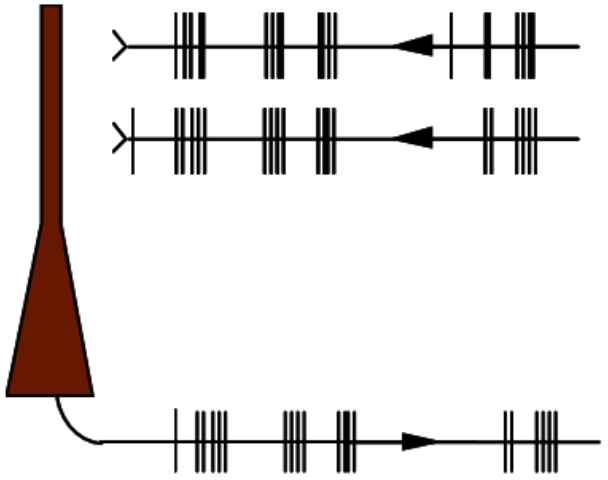


- Plastic synaptic connectivity during critical period of development of V1.

Normal Rearing



- Normal development of OD in NR (normal rearing) is Hebbian.
- Synapses of the right and left eyes drive the cortical cell in sync and they both strengthen.
- Initial connectivity and other factors cause the spectrum of OD.

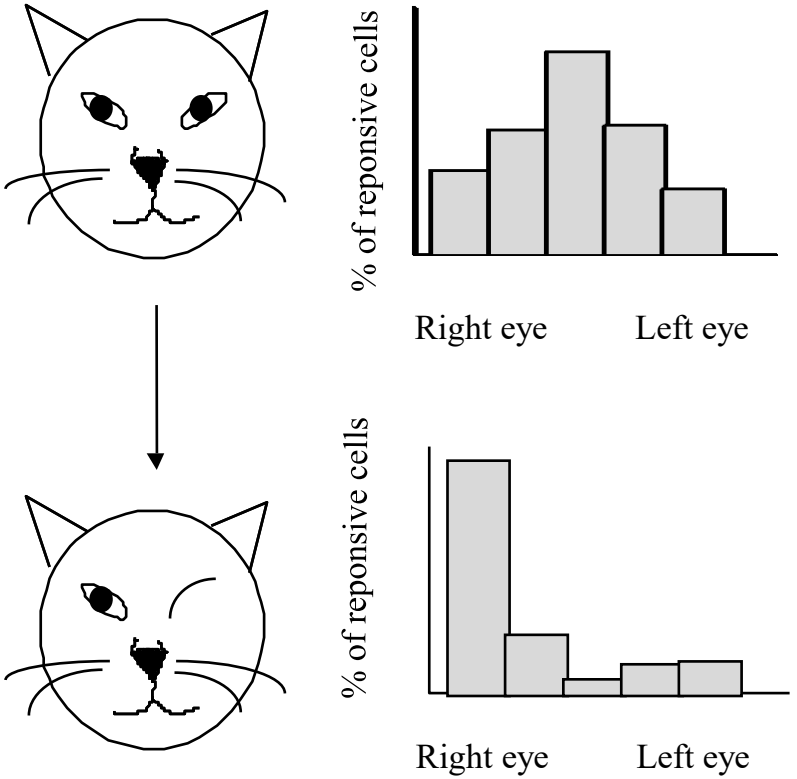


Right eye (open, relays patterned activity)

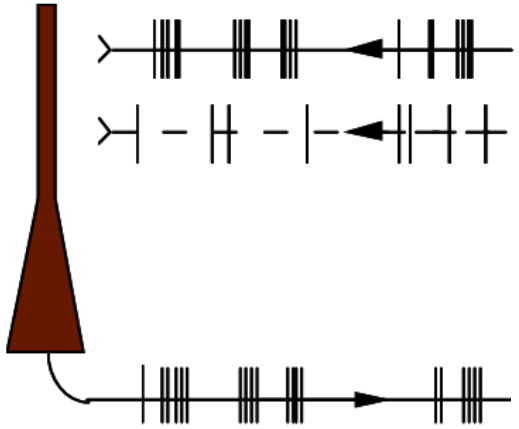
Left eye (open, relays the same patterns)

Output in sync with both eyes spikes

Monocular Deprivation



- The shift in OD in MD is Hebbian.
- Synapses of the right (open) eye that drive the cortical cell strengthen.
- Synapses from the left eye (the closed one) weaken.

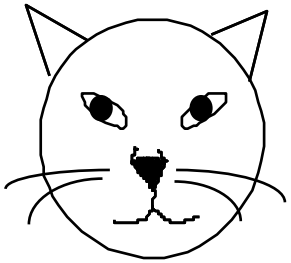


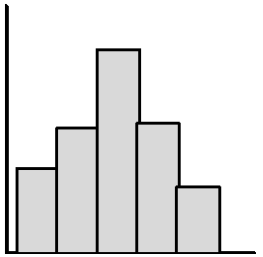
Right eye (open, relays patterned activity)

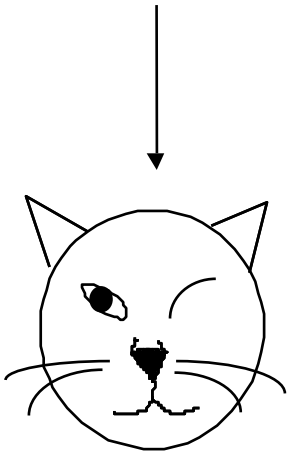
Left eye (closed, relays only noise)

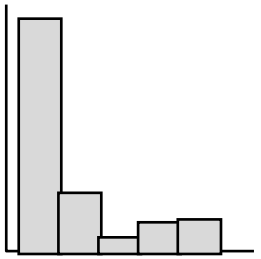
Output in sync with the right eye spikes

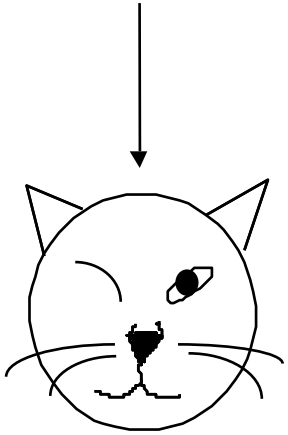
Reverse suture: not Hebbian

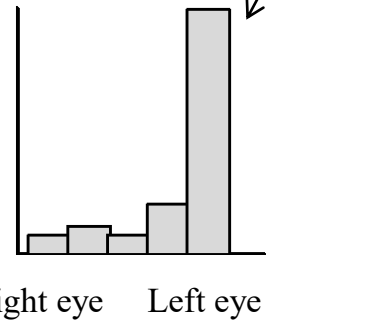






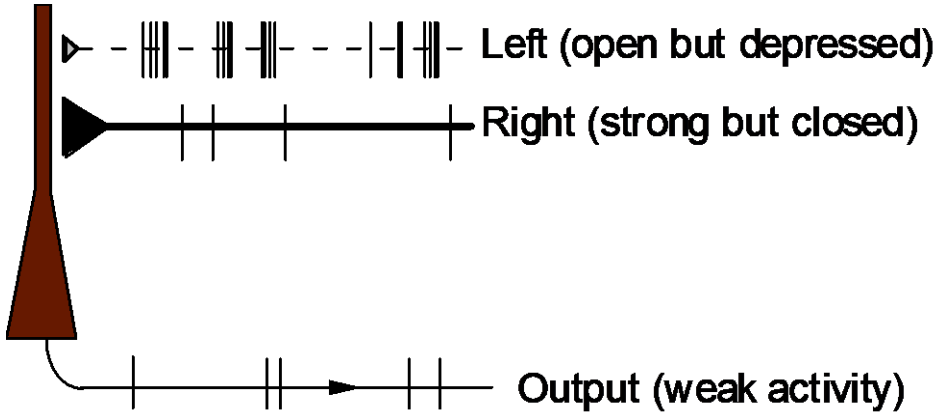




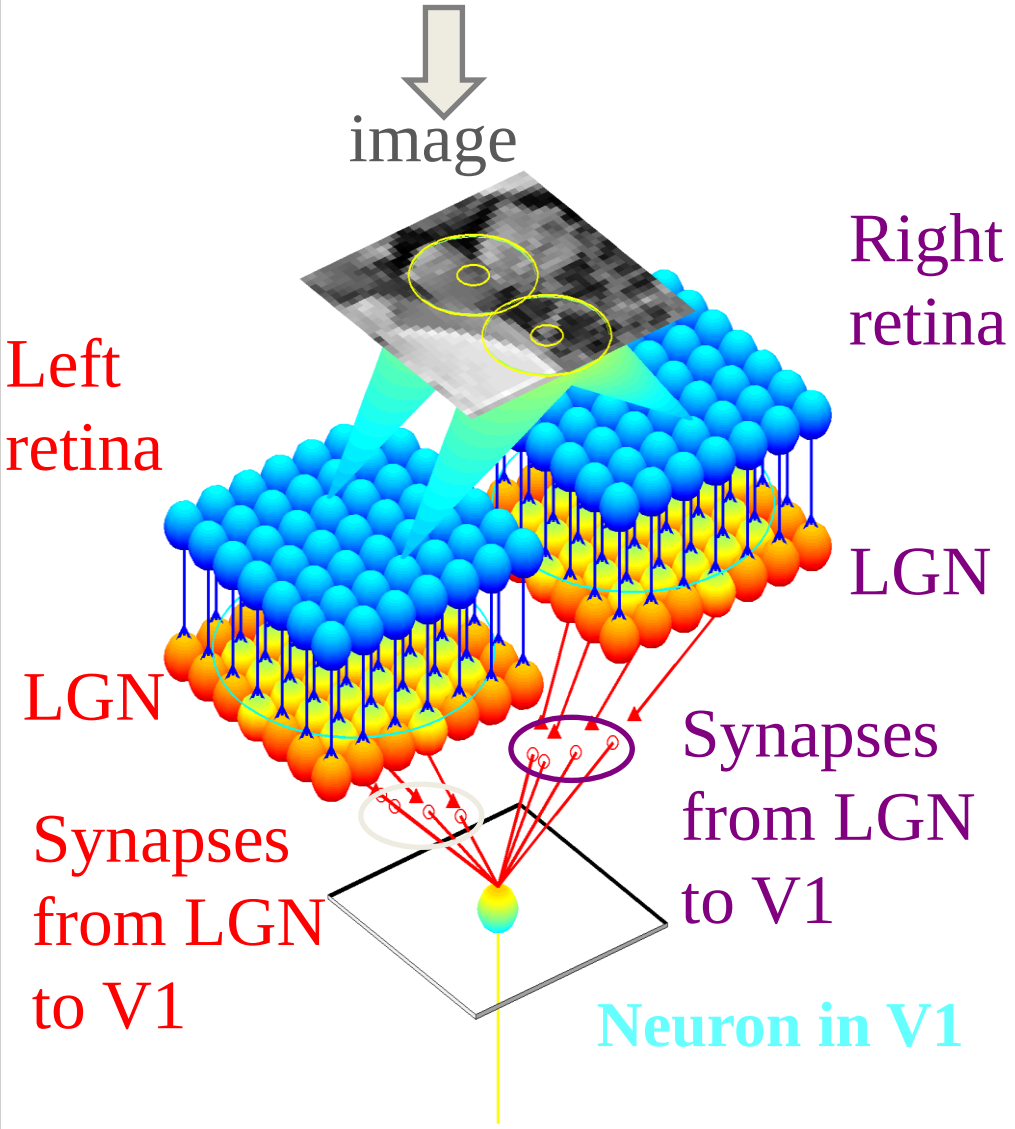


- The Hebbian learning cannot explain reverse suture experimental results, when formerly closed eye becomes dominant.

- Not really, b/c it would predict that closed eye synapse will go to zero and cannot recover.



Computational model

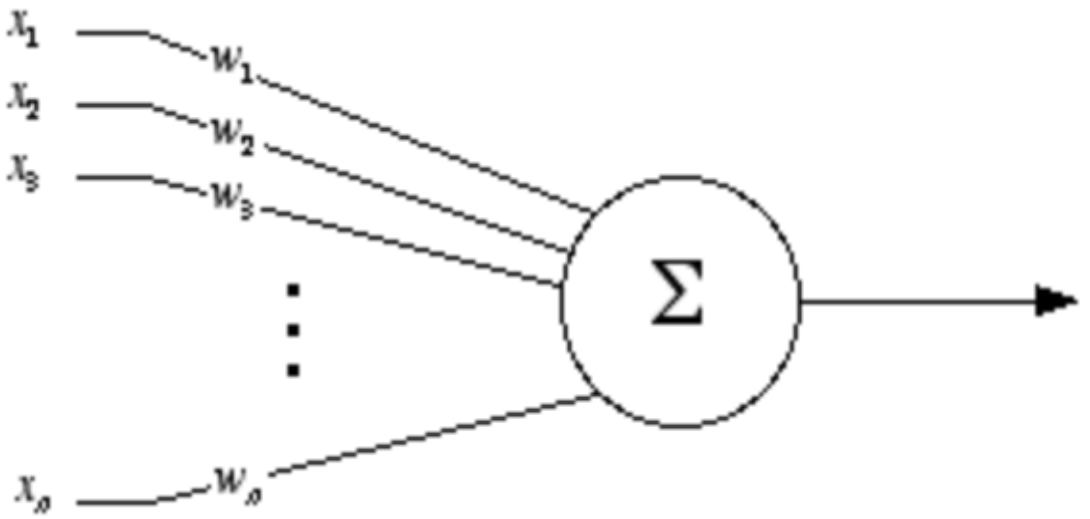


- The neural network model of the development of ocular dominance and orientation selectivity in V1
  - set up the circuitry reflecting the anatomy of the modelled visual system
  - choose model of a neuron in V1
  - implement the synaptic plasticity rule for synapses between LGN and V1 cortical neuron
  - define the activity patterns coming from LGN
  - simulate the model

Receptive Field Plasticity (Harel Shouval)

Rate model of a V1 neuron

Inputs x'_j = levels of shade in the given image pixel



- Input is comprised of a "patterned" input (from some input pattern) plus random noise, i.e. $x_j = x'_j$ + *random noise*. (i.e. small random number)

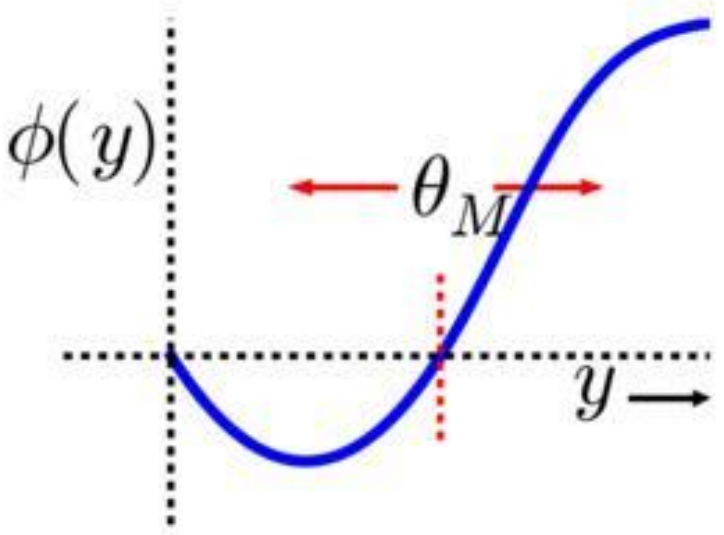
- If the eye is closed, then the input is just a random noise: x_j = *random noise*.

Bienenstock, Cooper & Munro (BCM) theory (1982)

$$\frac{dw_j}{dt} = \eta\, x_j\, \phi(y, \theta_M)$$

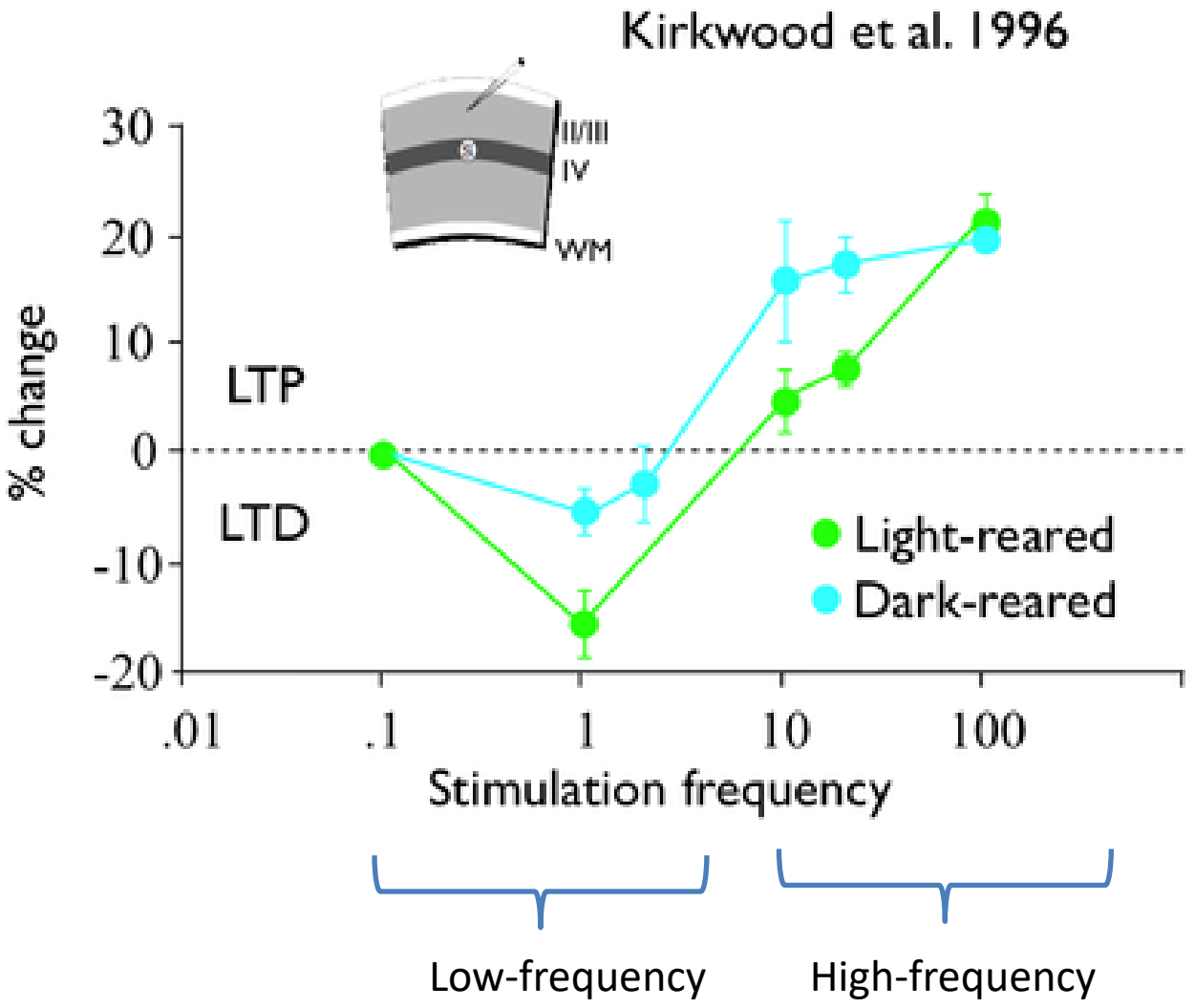
- Dependent variables: synaptic weights w_j; synaptic inputs x_j; y the output frequency and modification threshold θ_M
- η the learning speed, is the parameter.
- ϕ is the modification function and has a shape of parabola:

$$\phi(y, \theta_M) = y(y - \theta_M)$$



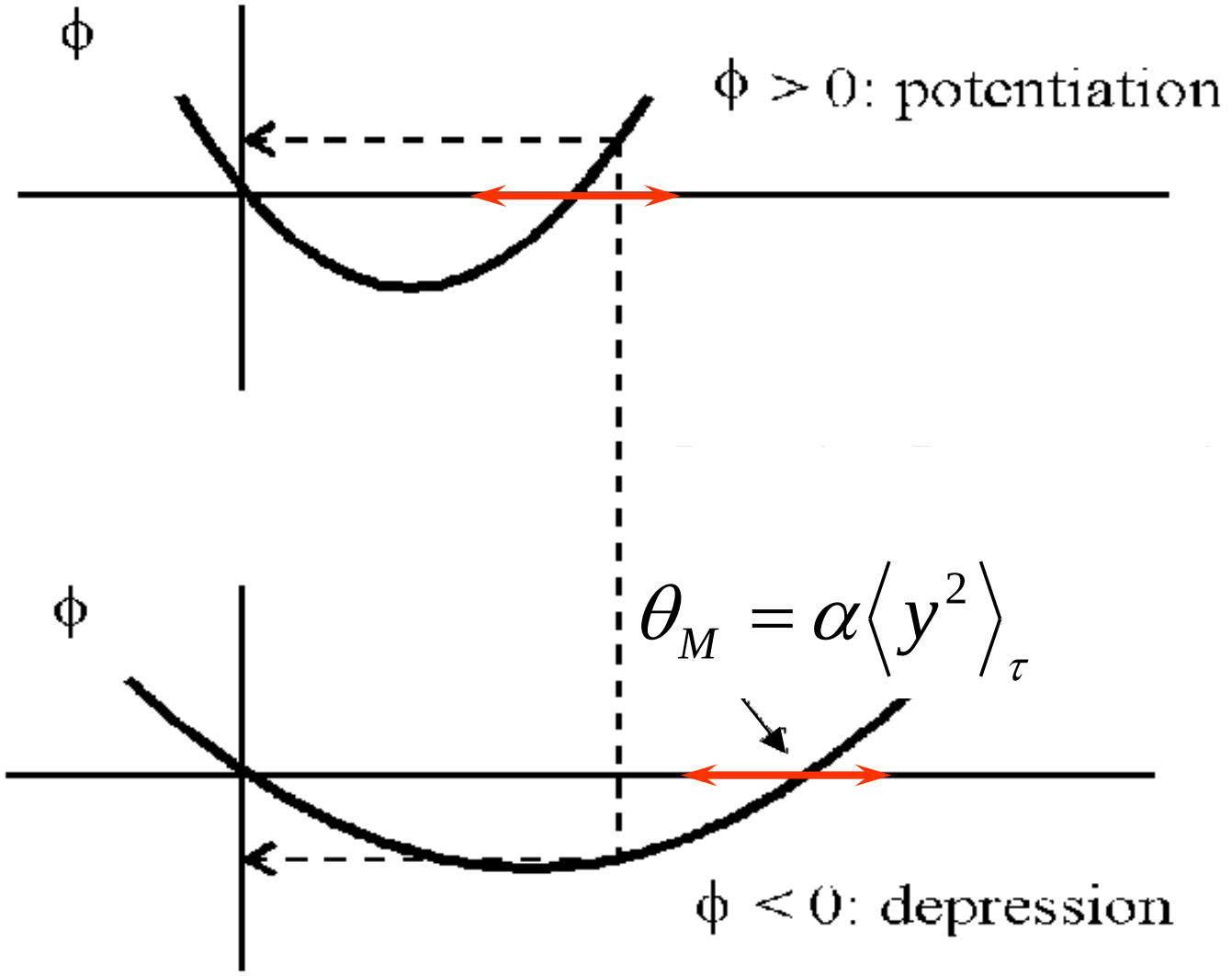
Experimental evidence for θ_M

- It is easier to obtain synaptic potentiation in the cortex of dark-reared animals and it is harder to induce synaptic depression in these cortices (cyan curve).
- The opposite is true for light-reared (NR) visual neurons in V1 (green curve).



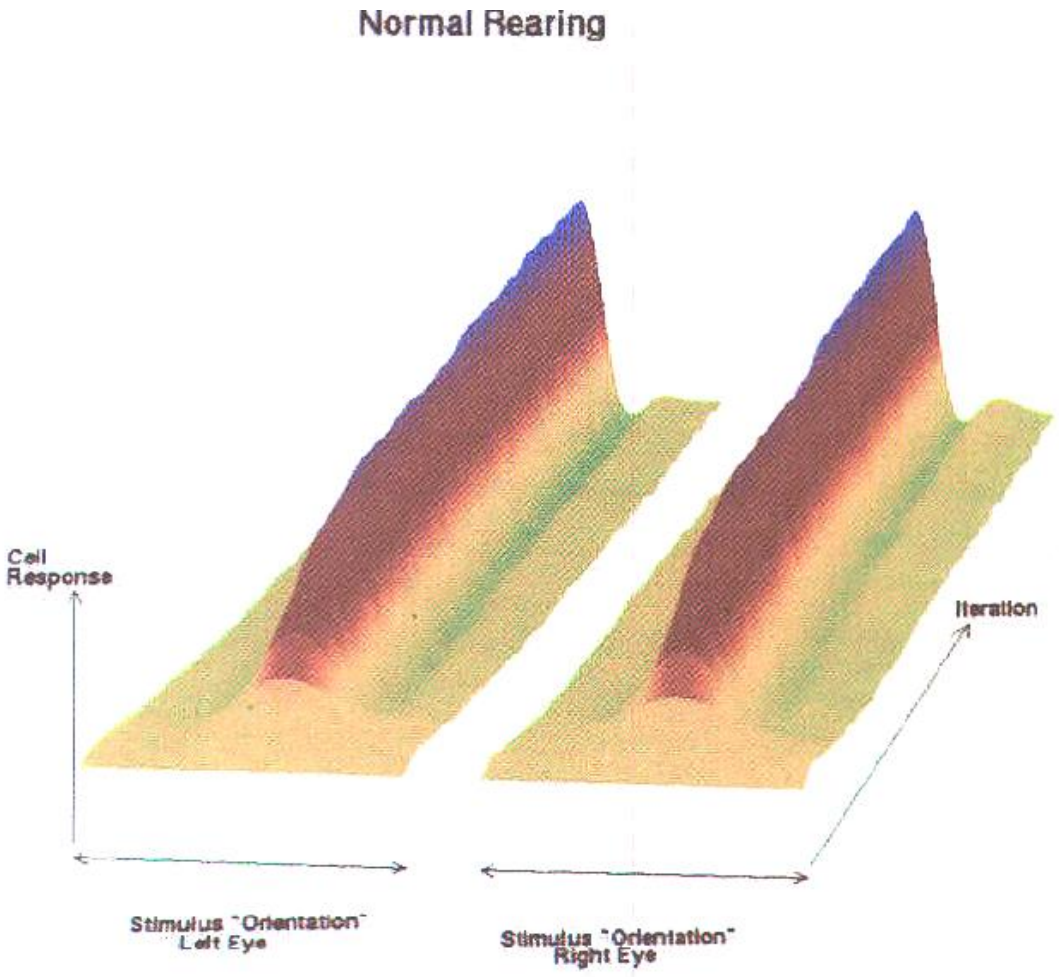
The BCM threshold: metaplasticity

- In 1996, Abraham and Bear coined the term **metaplasticity**, i.e. the outcome of synaptic plasticity depends on the previous activity of a neuron (TINS, 1996)



Results of the BCM model: NR

- During NR both eyes receive the same patterned input.
- The cortical cell develops the same OD for both eyes.
- In this example both eyes are equally dominant (the cell response is proportional to the weights of the inputs synapses).



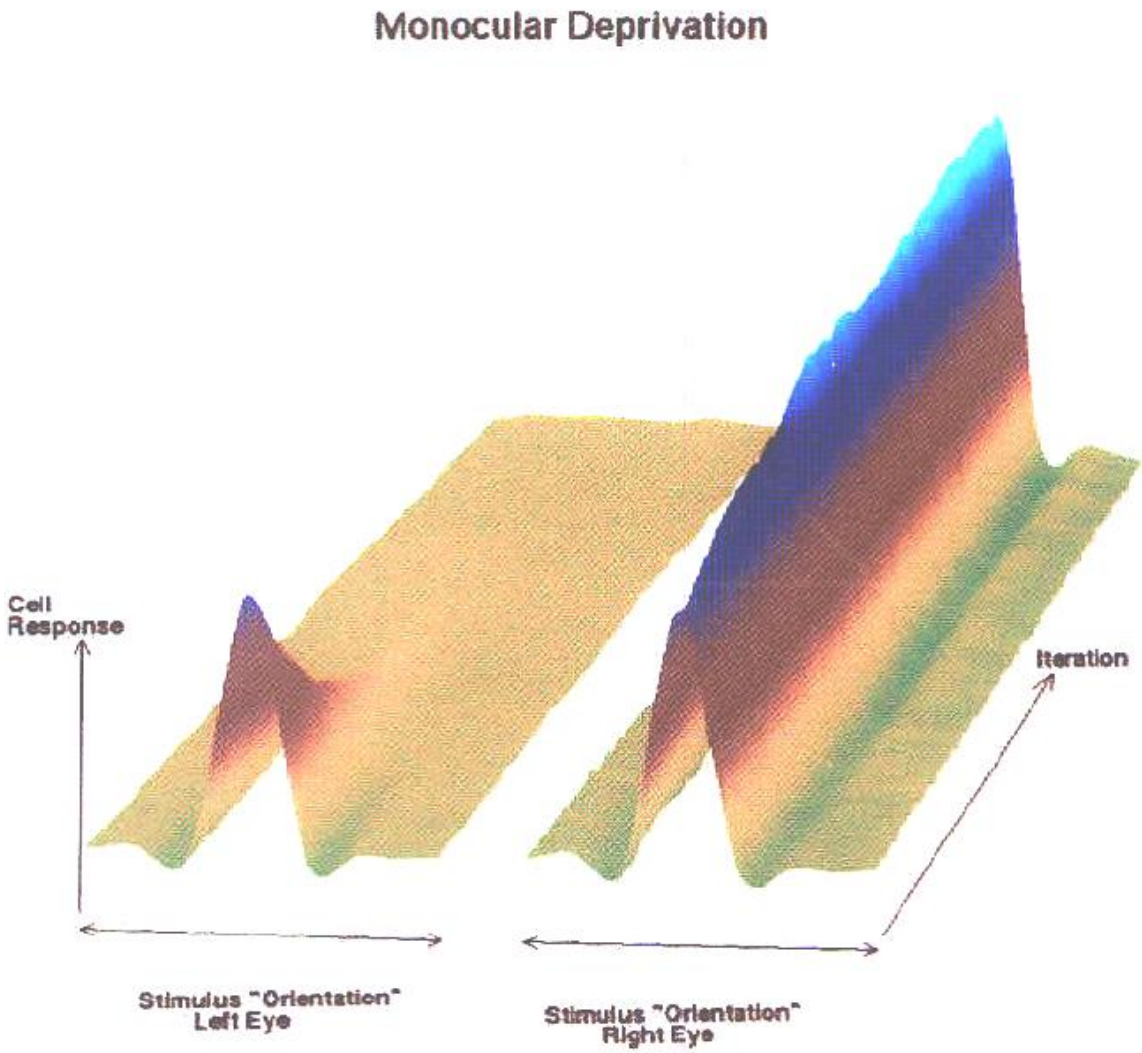
Picture taken from Clothiaux, Bear, Cooper (1991) Journal of Neurophysiology, vol. 66, No. 5, pp. 1785-1804.

Results of the BCM model: MD after NR

- During MD after NR, first both eyes develop binocular OD and then **only** the open eye receives patterned input, while the closed eye relays only random uncorrelated noise through its synapses.

- Synapses belonging to the closed (left) eye weaken and so does the responsiveness of the cortical cell to stimulation of the closed eye.

- The synapses belonging to the open eye become stronger.

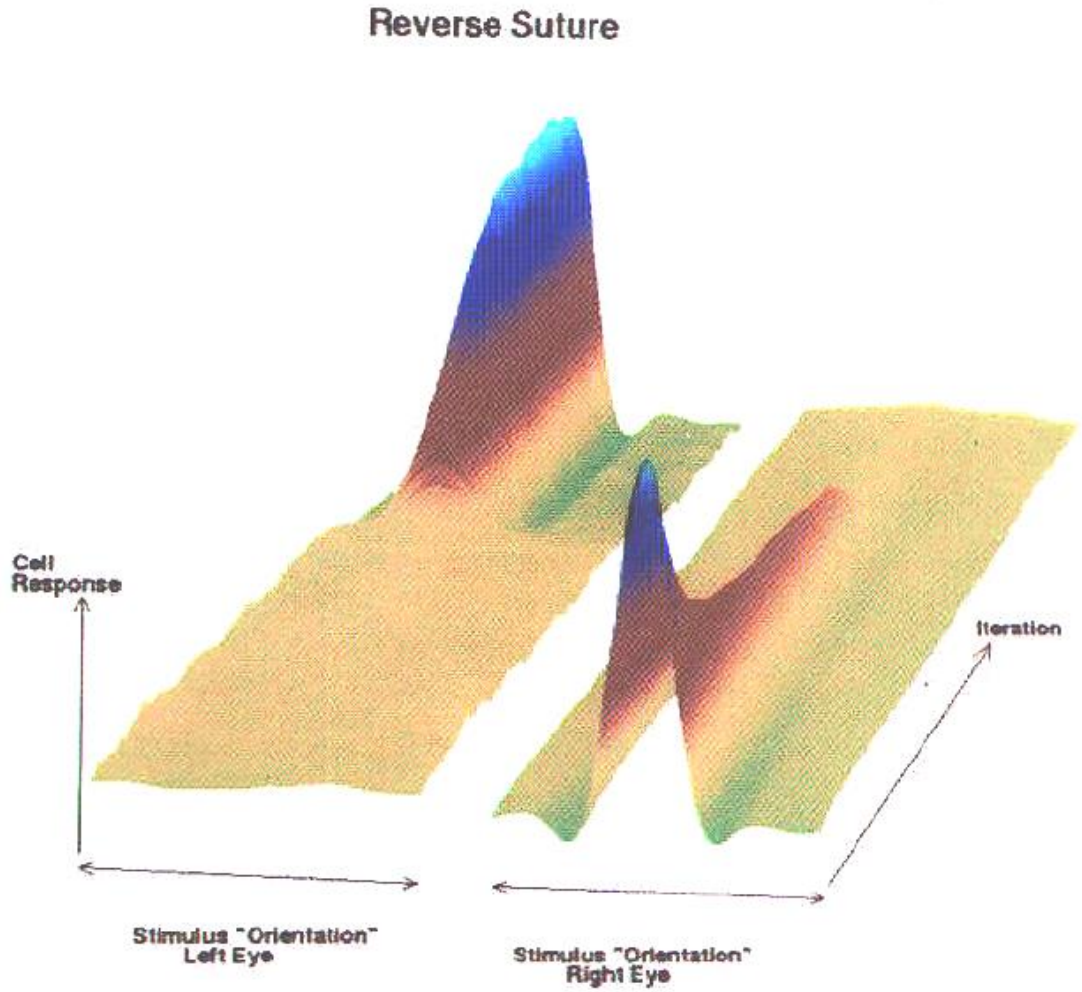


Picture taken from Clothiaux, Bear, Cooper (1991) Journal of Neurophysiology, vol. 66, No. 5, pp. 1785-1804.

Results of the BCM model: RS after MD

- During RS after MD, first the newly closed (right) eye looses dominance because its synapses relay only noise.

- The newly opened (left) eye synapses began to strengthen only after the synapses of the formerly open eye have had weakened first.

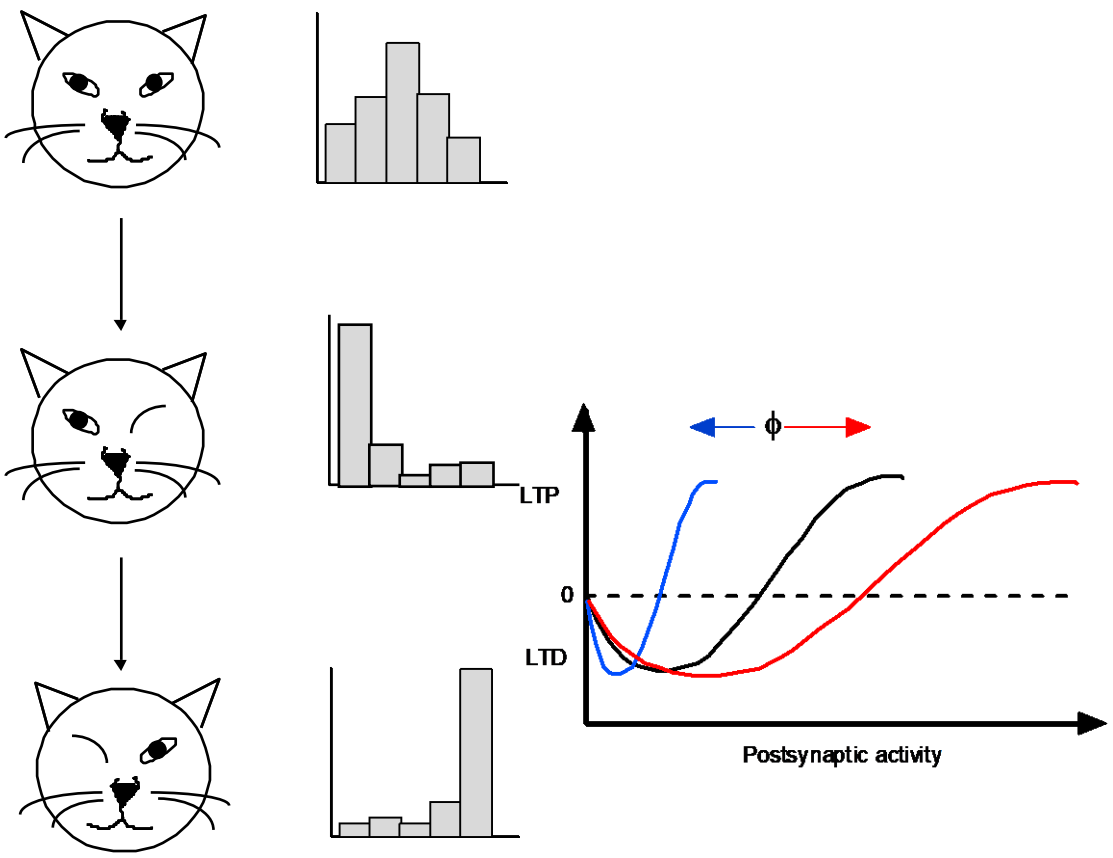


Picture taken from Clothiaux, Bear, Cooper (1991) Journal of Neurophysiology, vol. 66, No. 5, pp. 1785-1804.

Success in RS simulation due to dynamic θ_M

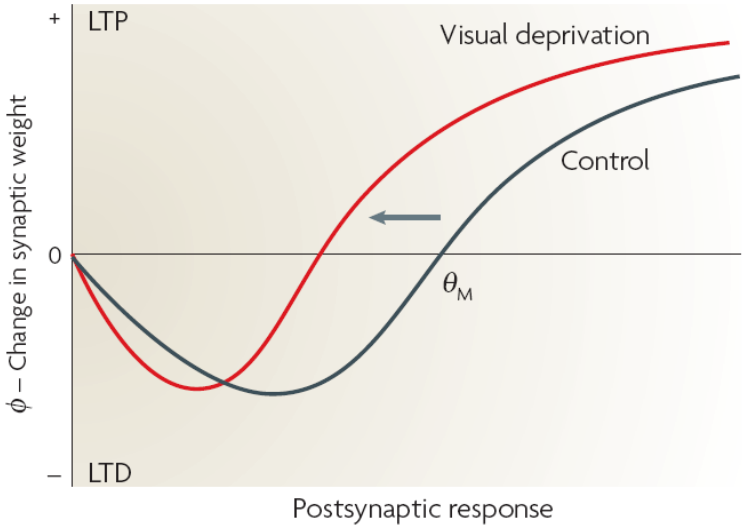
- After closing the right eye and opening the left eye, modification threshold θ_M slides to the left, because the overall activity level drops due to the fact that newly closed eye relays only noise and synapses of previously open eye are still weak.

- The shift in θ_M to the left allows the weak left eye synapses to strengthen and as they get stronger, θ_M gradually slides to the right.

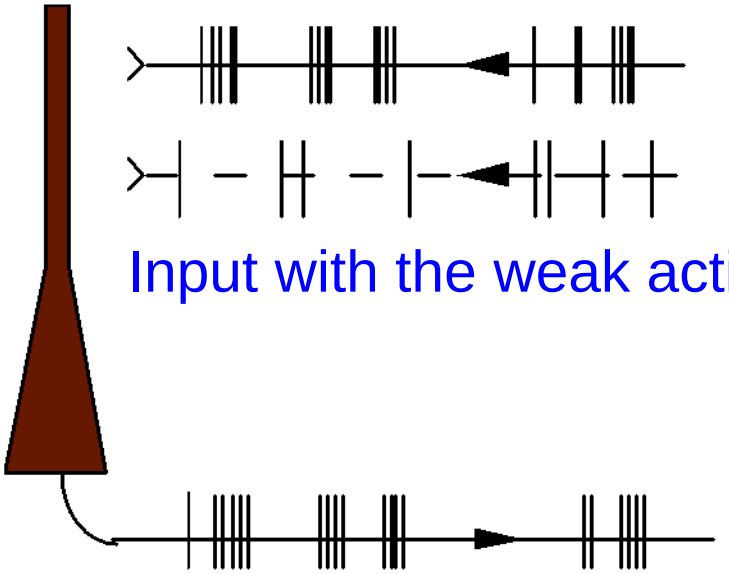


Homeostatic (balancing) properties of θ_M

- θ_M varies as a function of *prior* time-averaged postsynaptic activity.
- θ_M varies for **all** excitatory synapses on the postsynaptic cell.
- θ_M value determines that some synapses will strengthen, and some will weaken, leading to an overall balance of all inputs.



Input with strong activity will potentiate



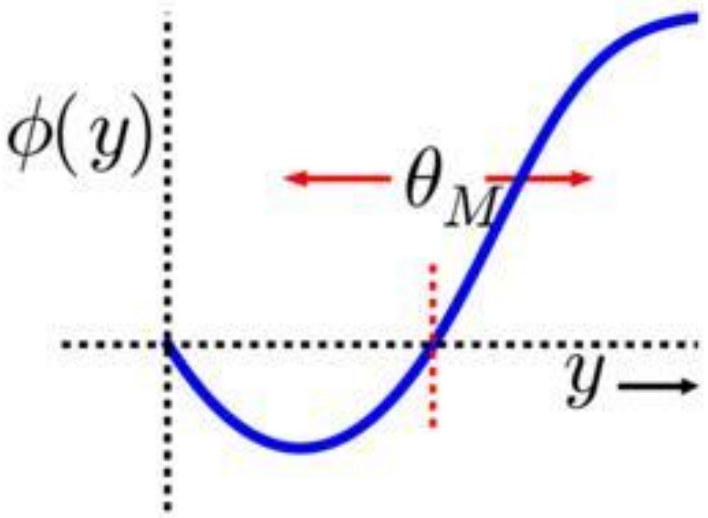
Input with the weak activity will depress

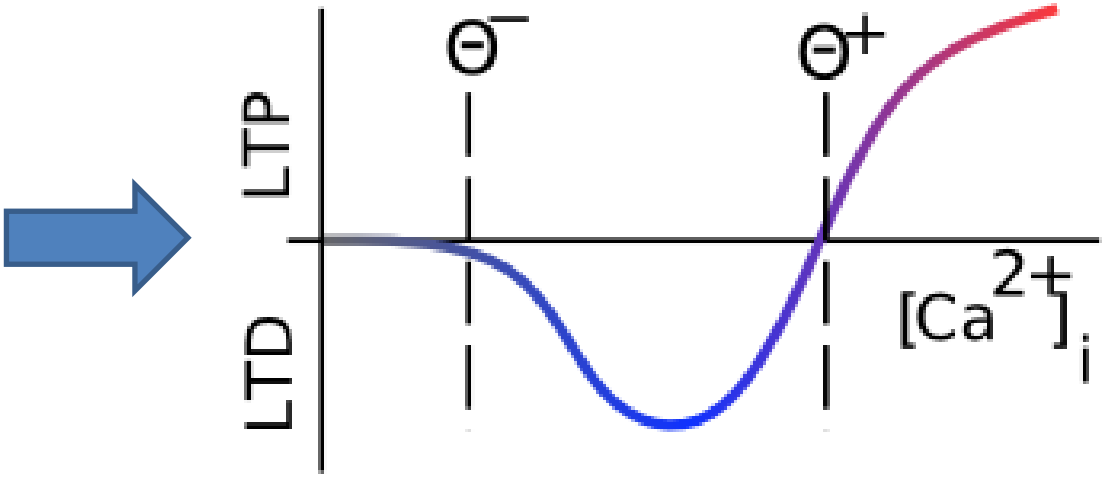
XCAL model of O'Reilly

- XCAL = eXtended Contrastive Attractor Learning model

- It is an **unsupervised learning** model inspired by the BCM dynamic threshold for LTP, but includes also a threshold for depression LTD.

- So XCAL works with two thresholds: θ^- and θ^+ and Ca^{2+} concentration.



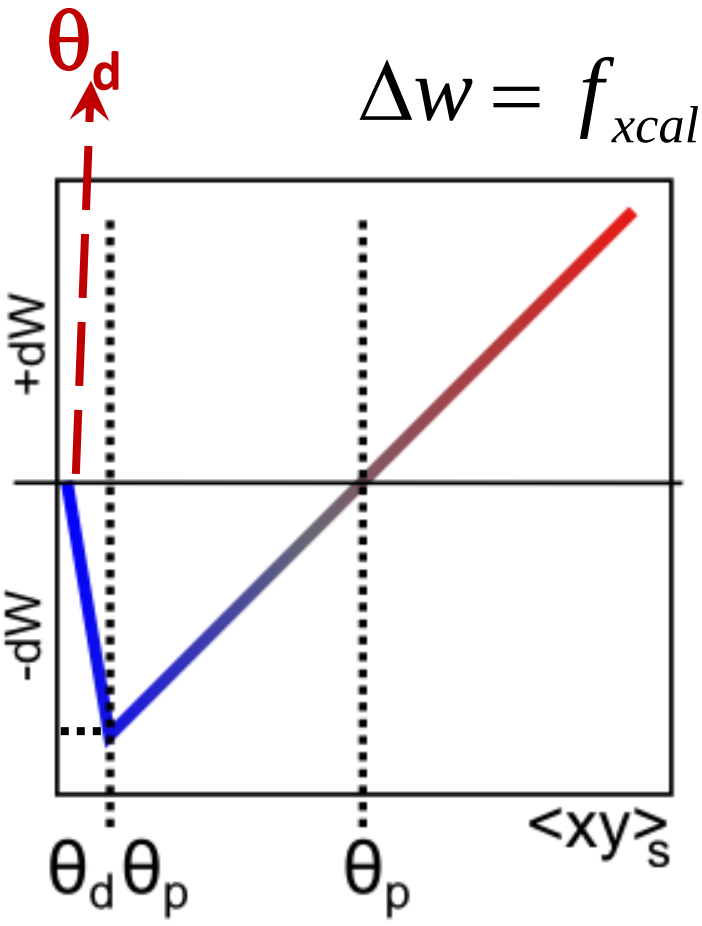


The function f_{xcal}

- Let x be the activity of the sending neuron and y be the activity of the receiving neuron. Then the change in synaptic weight $\Delta w = f_{xcal}$.

- The f_{xcal} is the piecewise linear function function of the **short-term (~100 ms) average** activity of the sending neuron (x) times the output receiving neuron (y), i.e. $\mathbf{\langle xy \rangle_s}$

- Where LTD threshold $\theta_d = 0.1$ is a constant, and $\theta_p = \langle y \rangle_l$ is the dynamic LTP threshold equal to the **long-term (~ 10 s) average** of the postsynaptic activity y.



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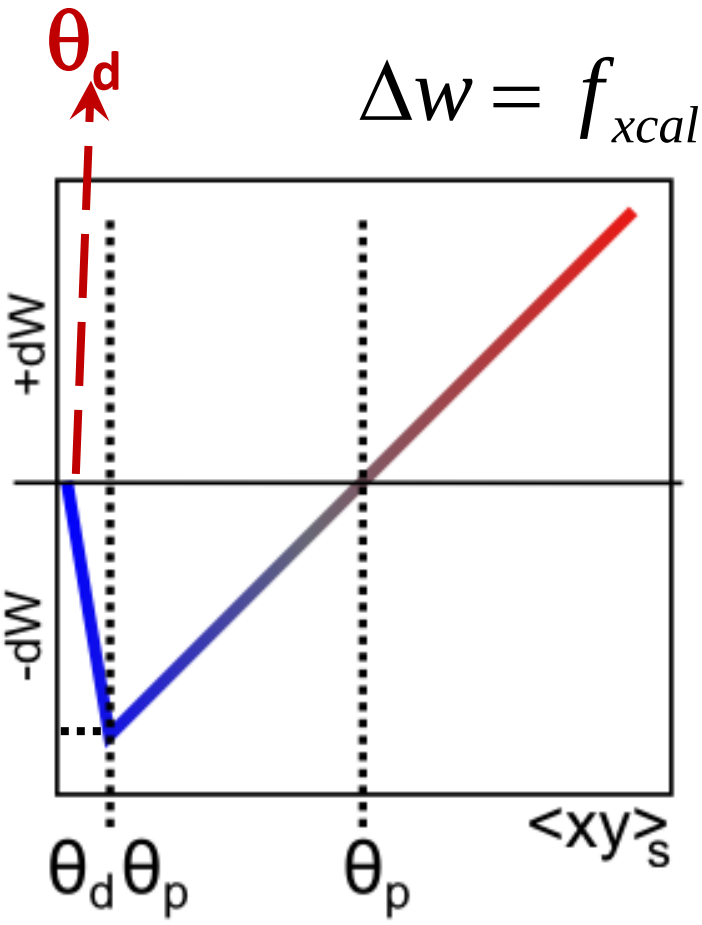


- The f_{xcal} is the piecewise linear function mathematically expressed by the formula

$$f_{xcal} = \begin{cases} xy - \theta_p & \text{if } xy > \theta_p\theta_d \\ -xy(1-\theta_d)/\theta_d & \text{if } xy \le \theta_p\theta_d \end{cases}$$

- We calculate the average $\langle xy \rangle_S$ over the time interval S ~ 100 ms consisting of iterations 1, 2, …, S as:

$$\langle xy \rangle_S = \frac{xy_1 + xy_2 + \ldots + xy_S}{S}$$

$$\Delta w = f_{xcal}$$

- Let x be the activity of the sending neuron and y be the activity of the receiving neuron. Then the change in synaptic weight is:

$$\Delta w = f_{xcal}\left(\langle xy\rangle_s, x\langle y\rangle_l\right) = f_{xcal}\left(xy, xy_l\right)$$

- Here xy is understood to be the short-term average synaptic activity (on a time scale of a few hundred milliseconds – the time scale of Calcium accumulation that drives synaptic plasticity, and y_l is the long-term average activity of the postsynaptic neuron on the scale of tens of seconds.

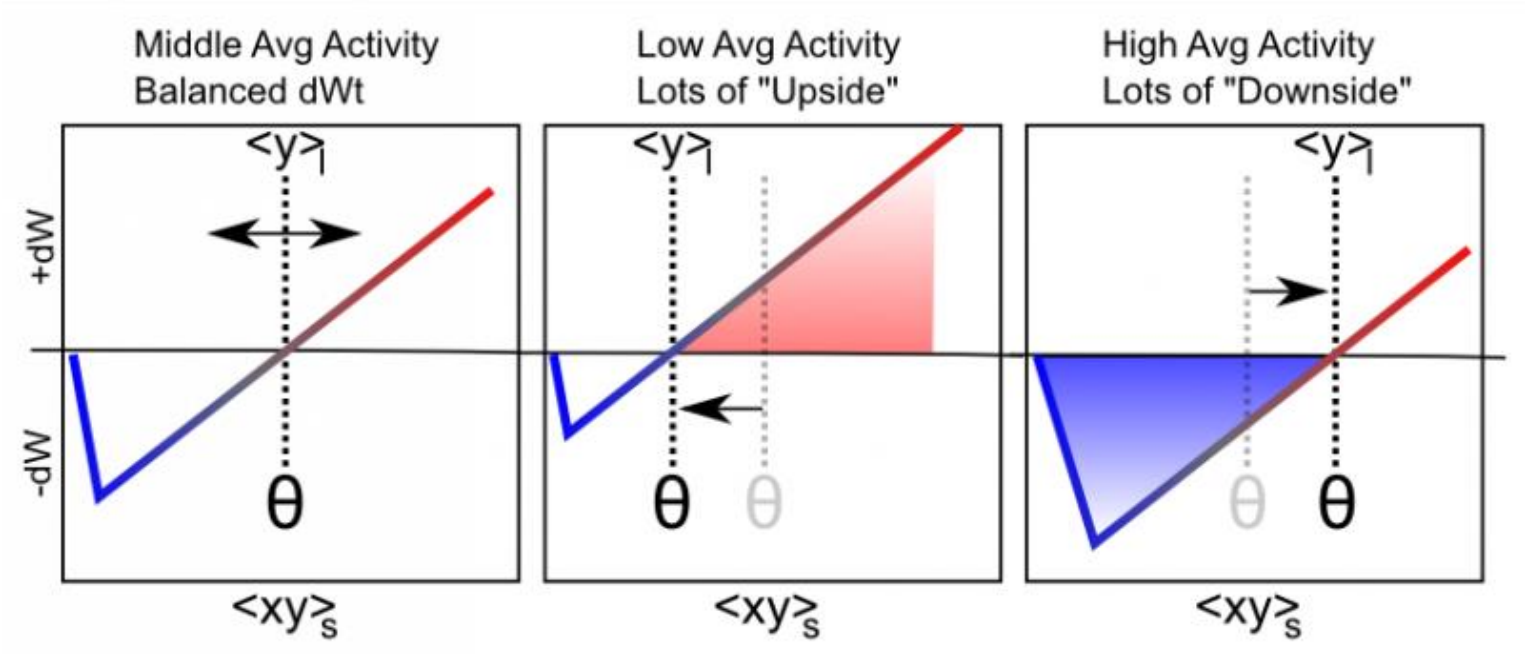
- y_l is calculated like this ($\tau_l = 1$s, min a max are minimal and maximal w, resp.):

$$\text{if } y > 0.2 \text{ then } y_l = y_l + \frac{1}{\tau_l}\left(\max - y_l\right)$$

$$\text{else } y_l = y_l + \frac{1}{\tau_l}\left(\min - y_l\right)$$

Homeostasis resulting from the function f_{xcal}

- Figure shows how the dynamic threshold $\theta = \theta_p$ drives homeostatis/balance:



- Neurons that have low average activity $\theta = \langle y \rangle_l$ are much more likely to increase their weights because the threshold θ is low (the graph in the middle), while those that have high long-term average activity are much more likely to decrease their weights because the threshold θ is high (the graph on the right).

Unsupervised learning leads to self-organisation of weights

- Critical elements of the self-organizing learning dynamics in the network of excitatory and inhibitory neurons:
  - **Inhibitory competition** – only the most strongly driven neurons get over the inhibitory inputs and can get active. These are the ones whose current synaptic weights best fit ("detect") the current input pattern.
  - **Rich get richer, i.e.** positive feedback loop – only those neurons that get active are capable of learning (b/c when $y = 0$, then $xy = 0$, and the $f_{xcal} = 0$). Thus, the neurons that already detect the current input are the ones that get to further strengthen their ability to detect these inputs.
  - **Homeostasis**. Raising the dynamic threshold θ for highly active neurons, causes their weights to decrease for all but their most preferred input patterns, and thus restoring homeostasis.

Error-Driven Learning

- Self-organizing or unsupervised learning is commonly used for finding meaningful groupings inherent in the data and exploratory purposes.

- In supervised learning, our goal is to match the input with output using available data.

- To learn these more challenging types of problems, we need error-driven learning. Intuitively, error-driven learning is much more powerful because it drives **learning based on differences between the actual and desired output *y*** not just the dynamics of input and output signals.

- **Differences (or errors) between expectation and real outcome tell us much more precisely what we need to do to learn to solve a problem.**

Medium-time scale dynamic threshold

- The same floating threshold behaviour from the BCM-like self-organizing aspect of XCAL learning can be adapted to perform error-driven learning, in the form of **differences between a real outcome vs. an expectation**.

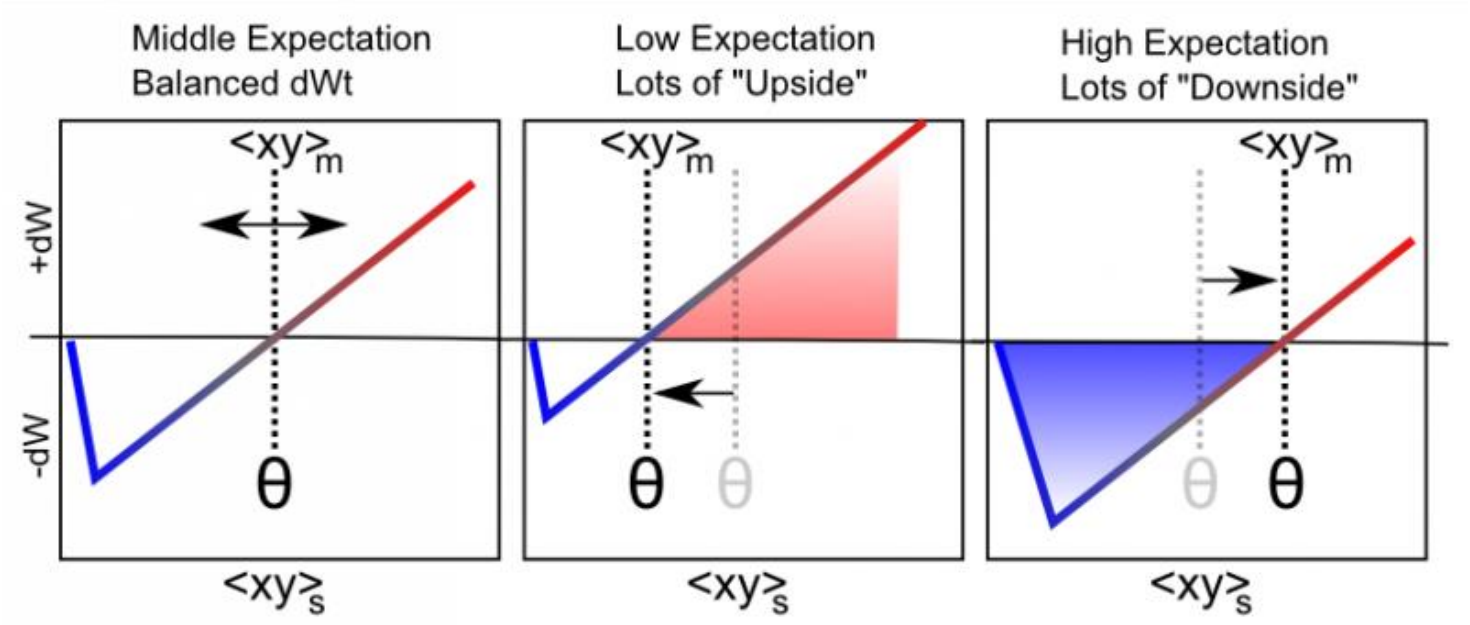
- Specifically, we speed up the time scale for computing the floating threshold and also have it to reflect synaptic activity, not just the receiver activity, i.e.:

$$\Delta w = f_{xcal}\left(\langle xy\rangle_s, x\langle y\rangle_m\right) = f_{xcal}\left(x_s y_s, x_m y_m\right)$$

- where **$\langle y\rangle_m$ is the new medium-time scale average** synaptic activity, which we think of as reflecting an **emerging expectation** about the current situation, which develops over roughly one second of neural activity. The most recent, **short-term neural activity $\langle xy\rangle_s$ reflects the actual outcome**.

Medium-time scale dynamic threshold

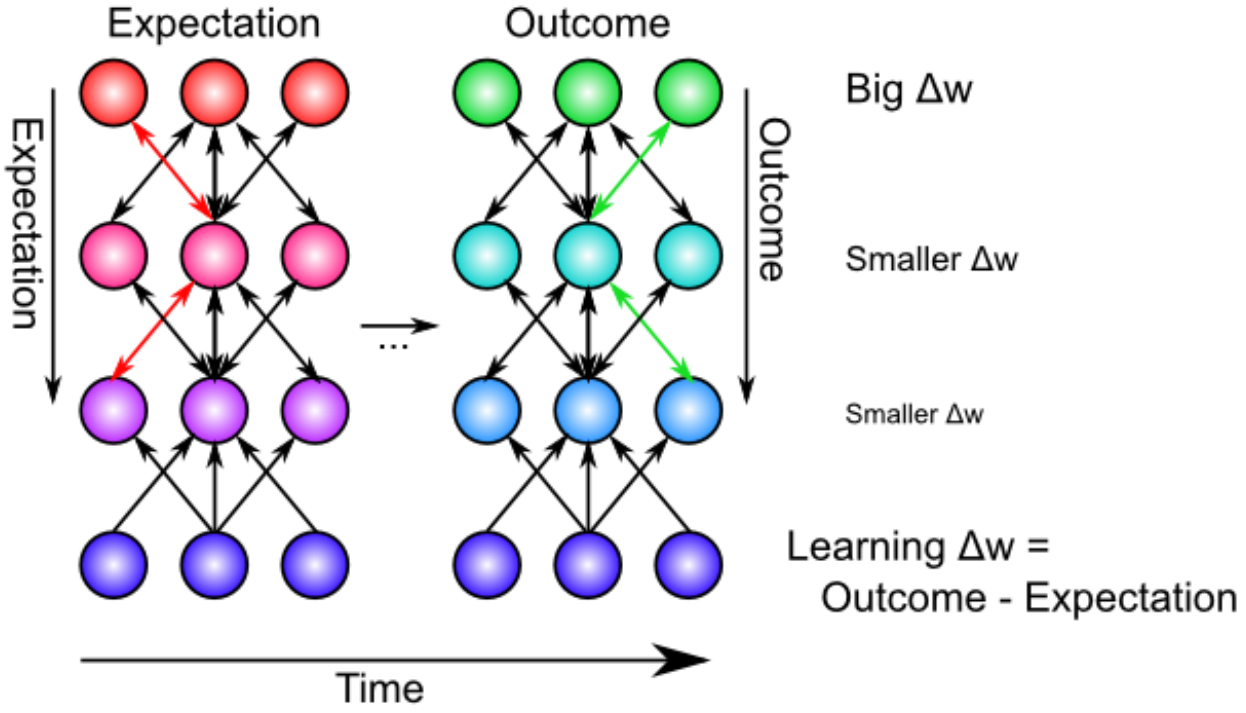
- The figure shows how the dynamic threshold as a function of medium-term average synaptic activity produces error-driven learning:



- If the short-term average outcome $\langle xy \rangle_s$ produces greater activation of neurons than did **expectation $\theta = \langle xy \rangle_m$** , the weights go up (middle graph), while when $\langle xy \rangle_s$ is smaller than expectation, the weights go down (the right-most graph). The latter corresponds to low vs. high expectation.

Error-driven learning in a neural network

- The key idea behind the error-backpropagation learning is that error signals arising in an output layer *propagate backward* down to earlier (hidden) layers, so that the network can eventually produce the correct expectations on the output layer.

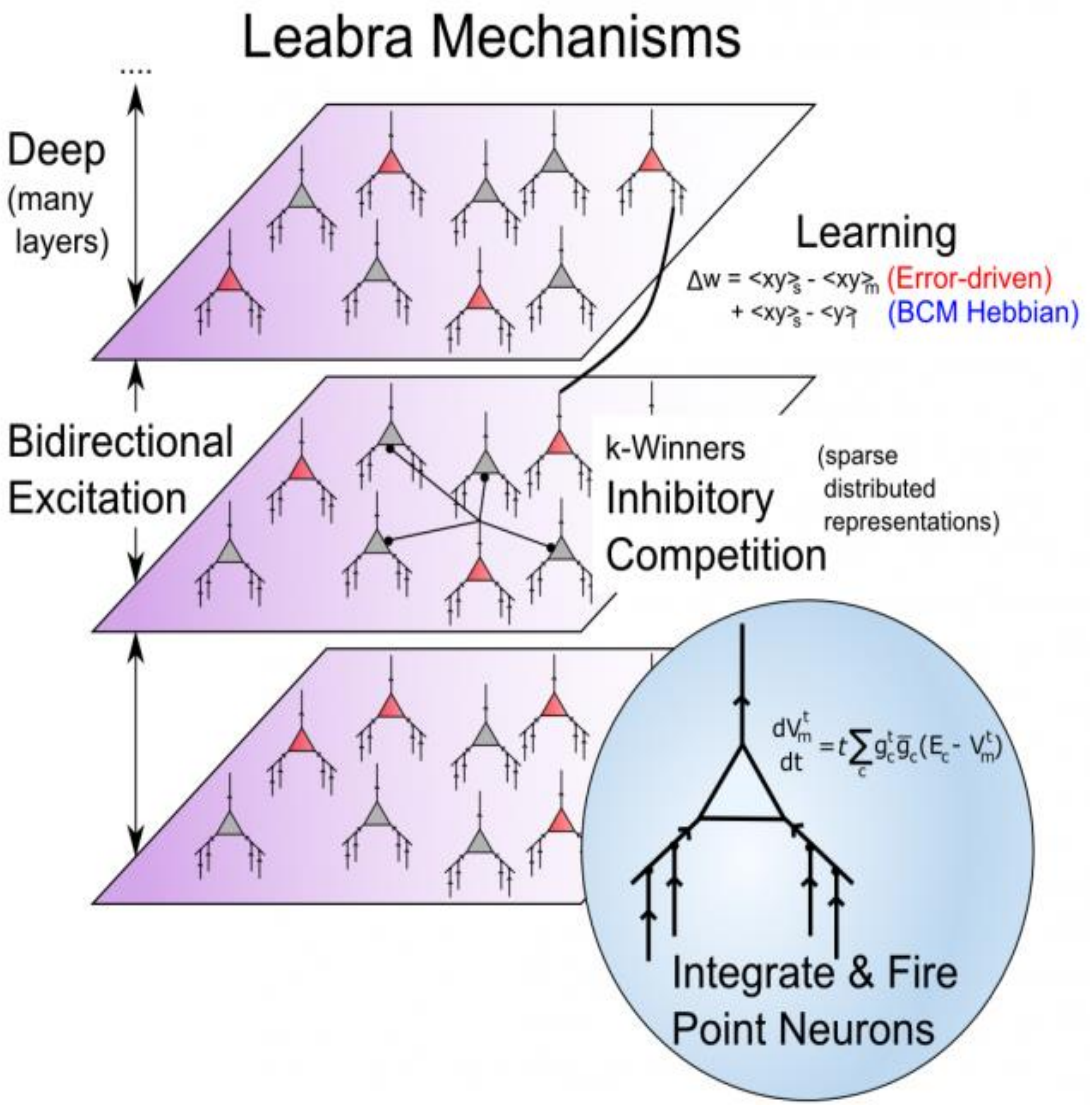


- Expectation and outcome are calculated in a forward manner whereas Δw is calculated in the backward manner, and these two phases alternate until the expectation = outcome and learning is stopped.

The LEABRA framework

- LEABRA stands for *Learning in an Error-driven and Associative, Biologically Realistic Algorithm* – the name is intended to evoke the "Libra" balance scale, where in this case the balance is reflected in the **combination of error-driven and self-organizing learning** ("associative" is another name for Hebbian-like learning).

- The FFFB inhibitory functions producing **k-Winners-Take-All** dynamics are also implemented in the LEABRA framework.

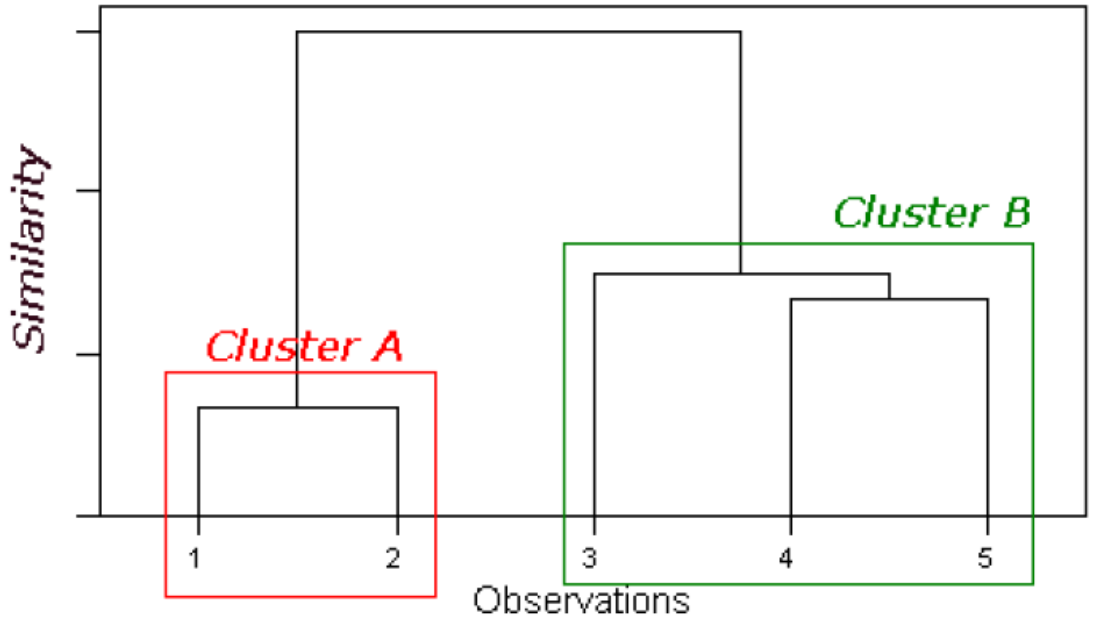


Combination of Self-Organizing and Error-Driven Learning in the LEABRA framework

- A weighted average of the two θ's is computed, using a "lambda" parameter $0 < \lambda < 1$ to weight the long-term receiver neuron average (self-organizing) relative to the medium-term expectation:

$$\Delta w = f_{xcal}\left(x_s y_s, x_m\left(\lambda y_l + (1-\lambda) y_m\right)\right)$$

- Such a network can deal with tasks involving forming categories or clusters of similar inputs.



Summary

- Learning in a neural network amounts to the modification of synaptic weights, in response to the local activity patterns of the sending and receiving neurons. These synaptic weights are what determine what an individual neuron detects, and thus are the critical parameters for determining neuron and network behaviour.

- In other words, everything you know is encoded in the patterns of your synaptic weights, and these have been shaped by every experience you've had - as long as those experiences got your neurons sufficiently active.

- Critical periods for plasticity were documented in the visual and auditory primary cortices, albeit of different duration and sharpness of termination. Most cortical and brain areas are plastic during the whole life, i.e. somatosensory, motor, frontal and associative areas, etc.