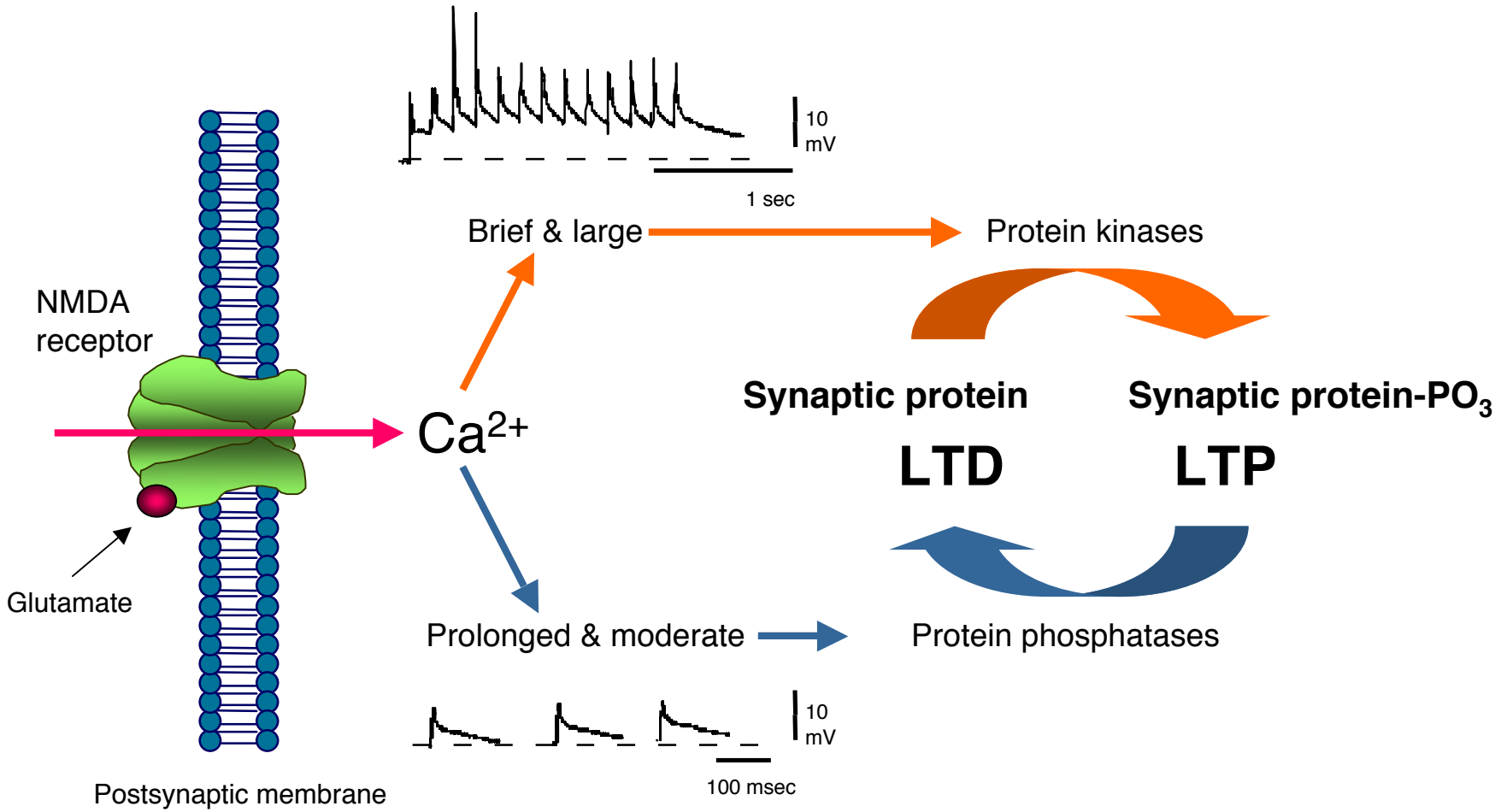
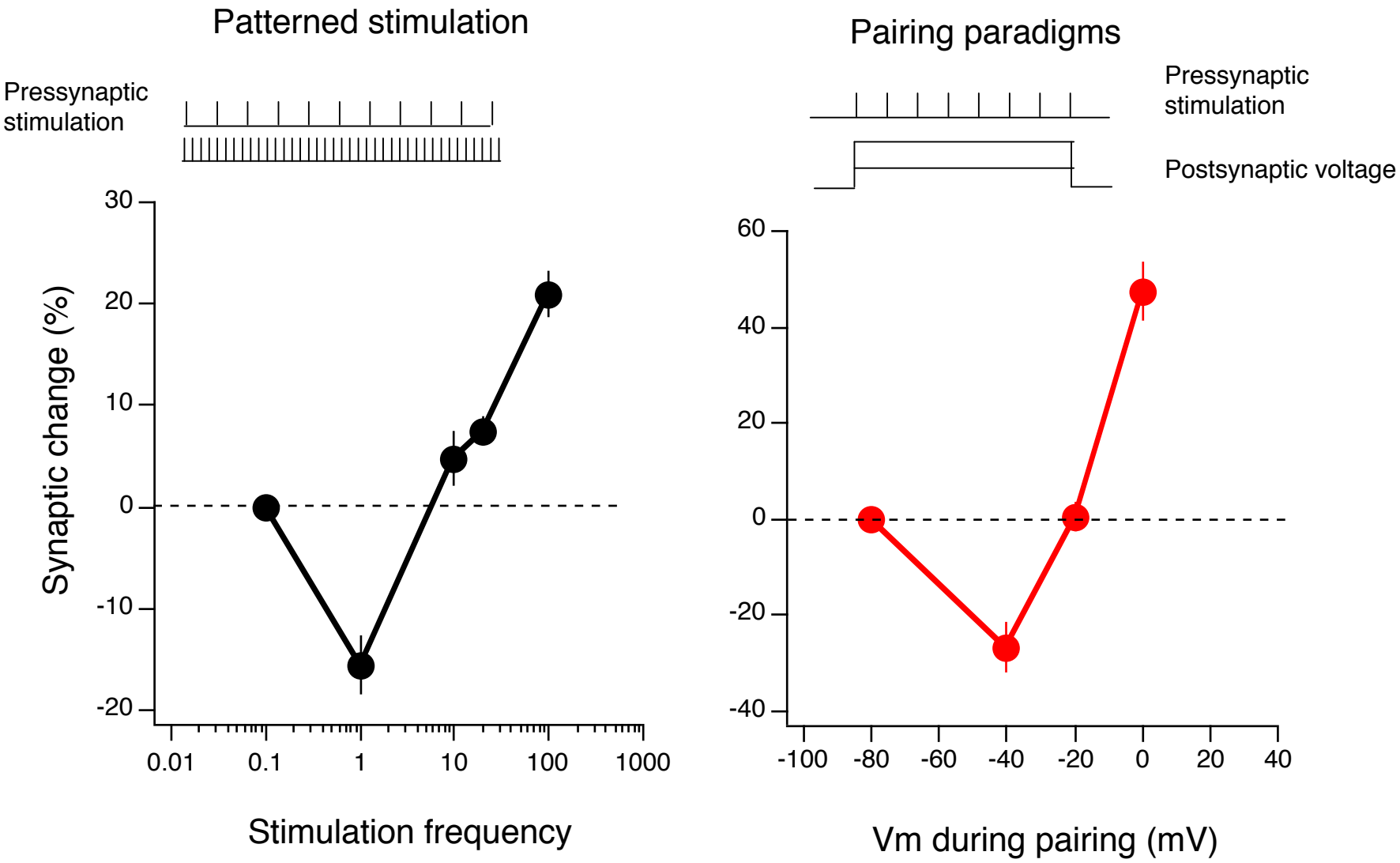
Spike timing dependent plasticity: how plasticity might really happens

Homeostatic regulation of synaptic plasticity: why and how regulate LTP and LTD

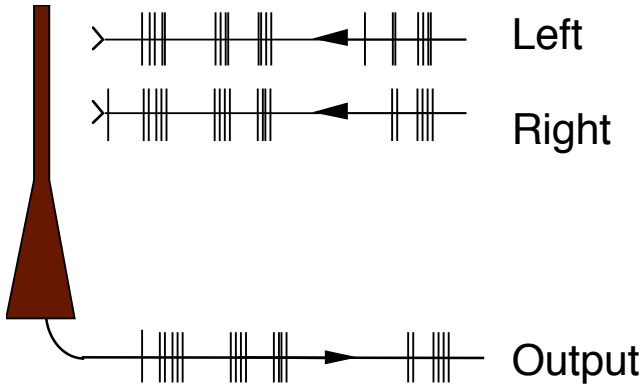
Current model of LTP and LTD



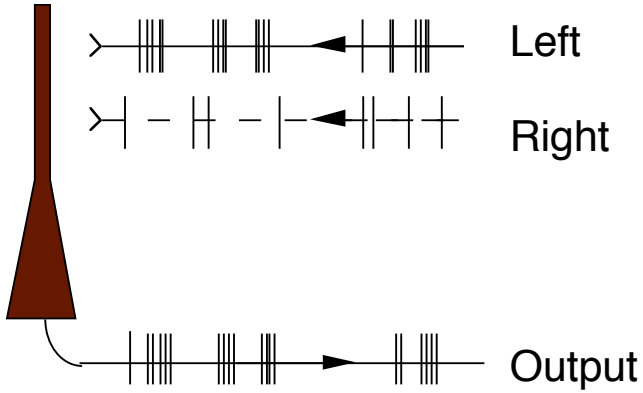
NMDAR activation determines the polarity and magnitude of plasticity
Selective induction of LTP or LTD by targeting NMDAR activation



Theory: plasticity linked to the correlation of activity
Remember HEBB.

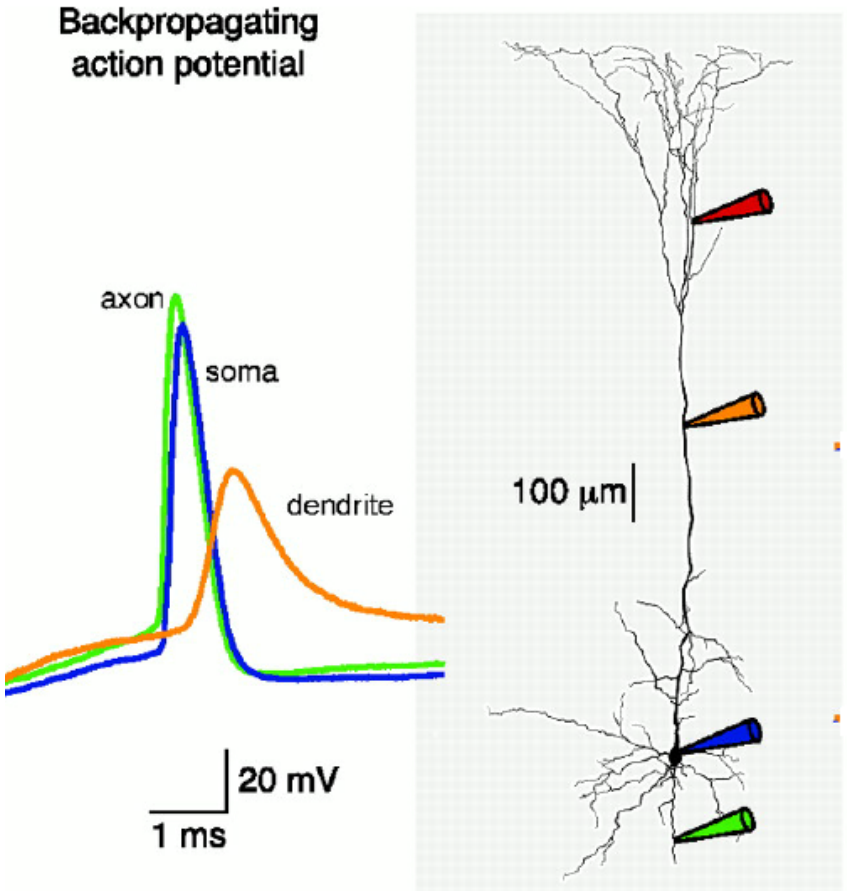


Neurons that fire together wire together.



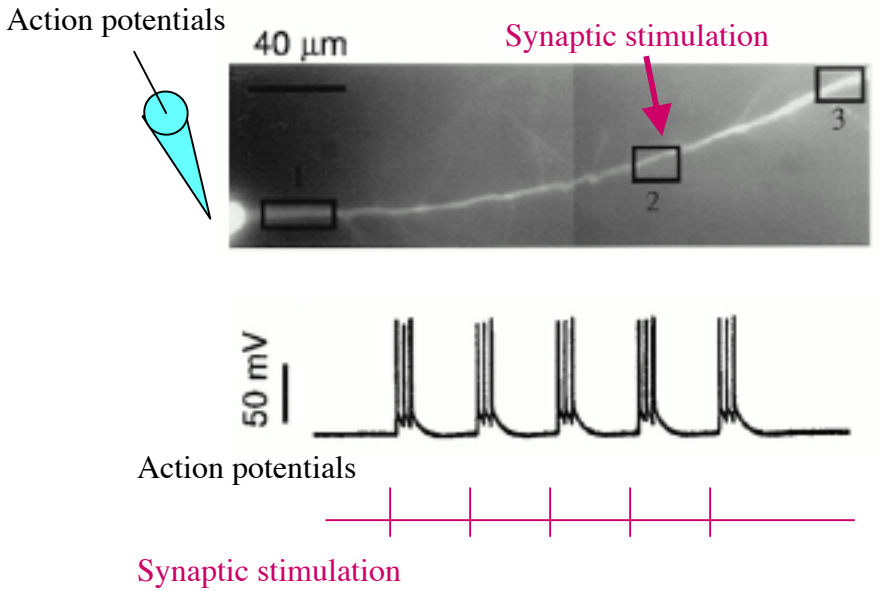
Neurons that fire out of sync lose their link.

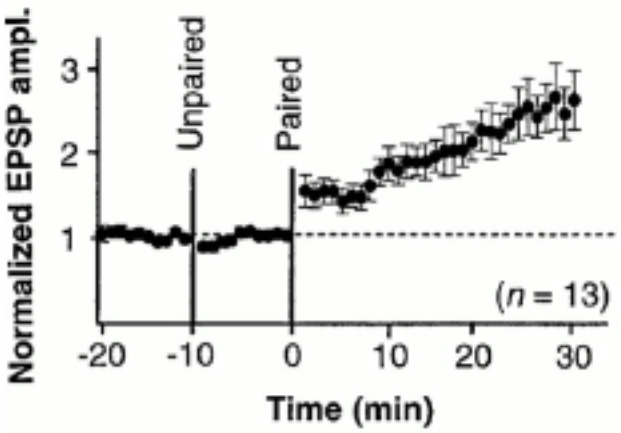
Action potentials back-propagate into the dendrites



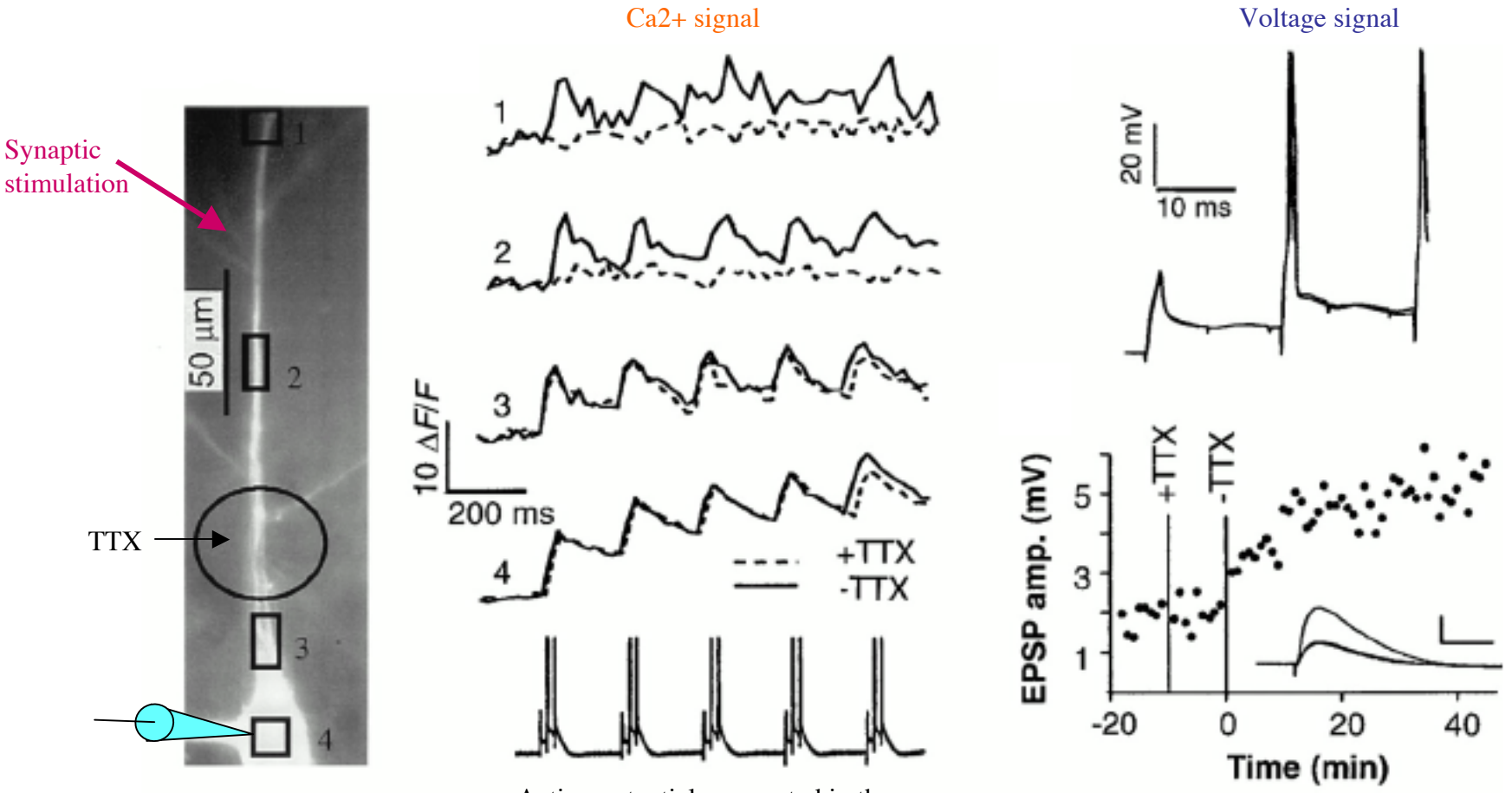
Stuart & Sakmann

Induction of LTP by pairing action potentials with synaptic activation



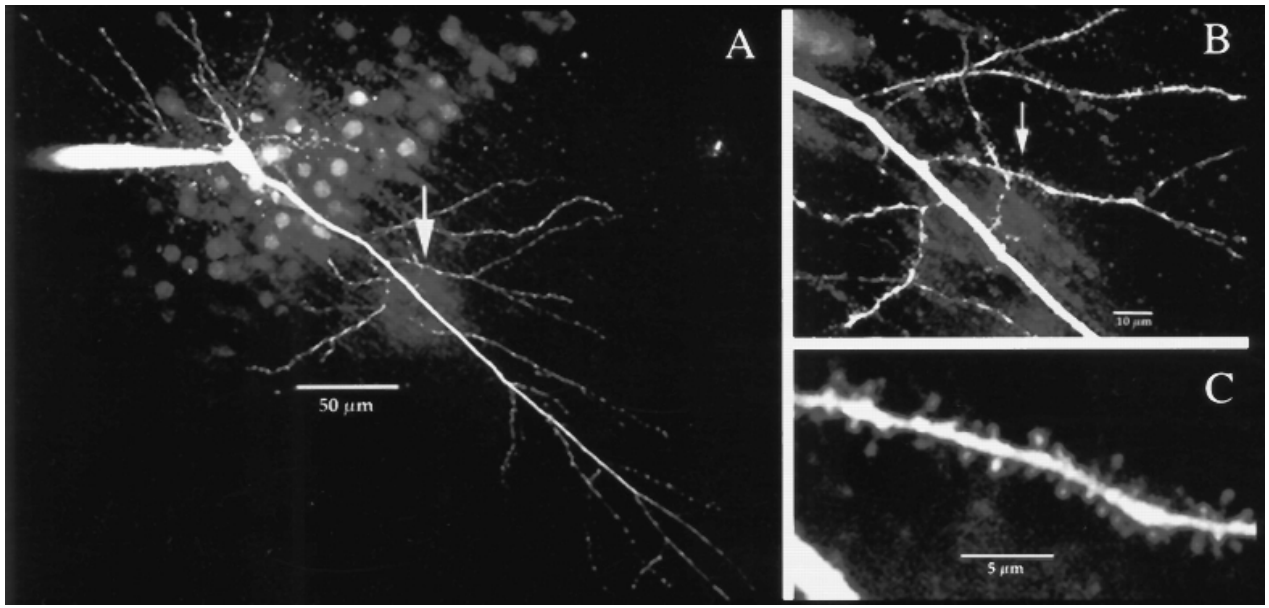


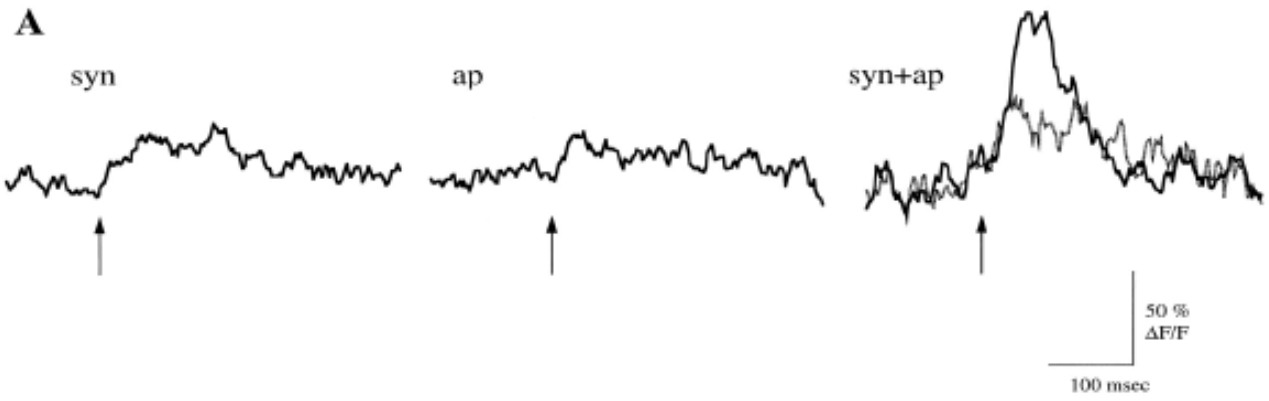
Back-propagation of action potential is essential for the induction of LTP



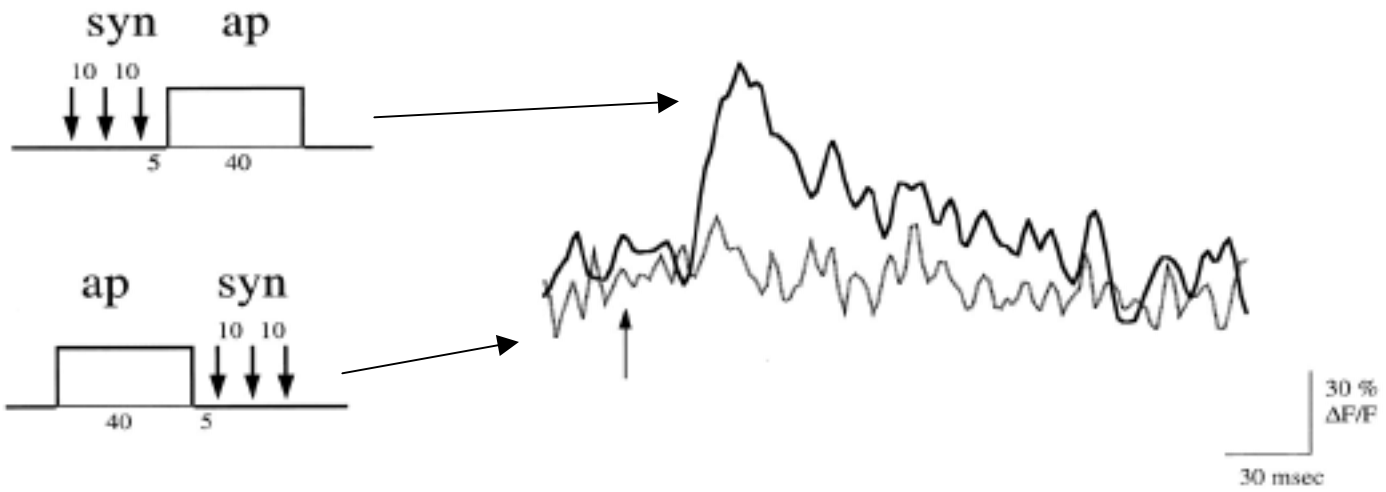
Action potentials generated in the soma

Two-Photon Ca-imaging reveals supralinear interactions between AP and synaptic activation

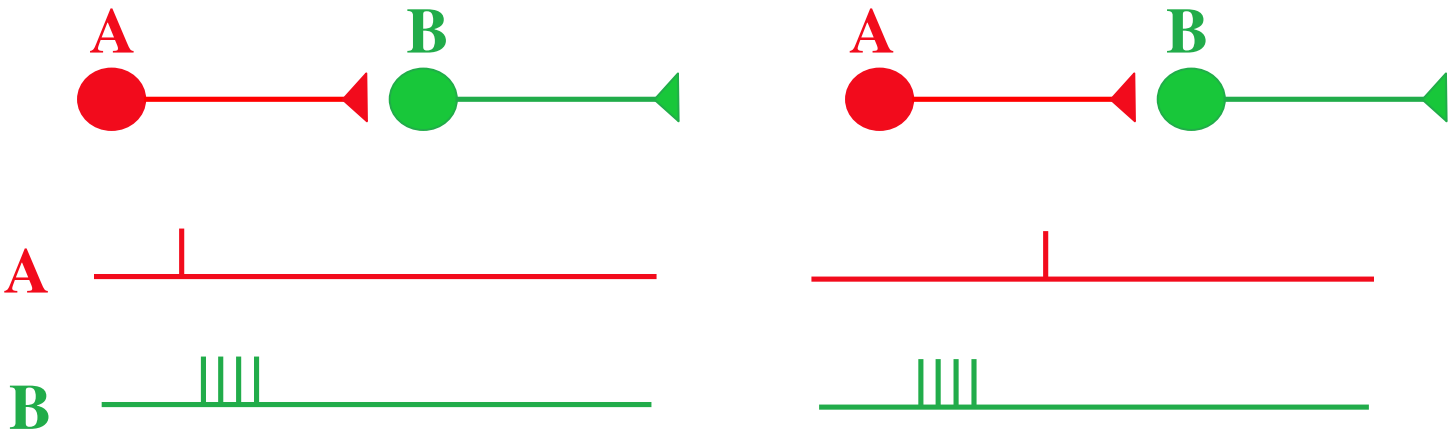




Supra-linear interactions requires A precise timing

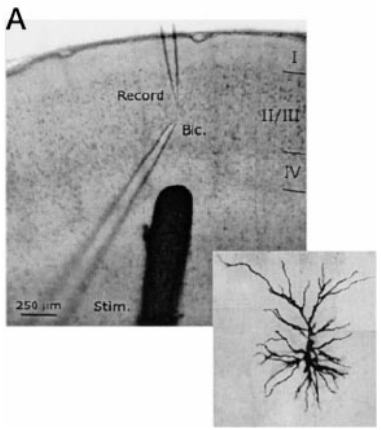


Basic Rules and Mechanisms of Synaptic Plasticity
Spike Timing-Dependent plasticity: STDP



Hebb's postulate:
If A then B, then potentiate
Long-term potentiation
LTP

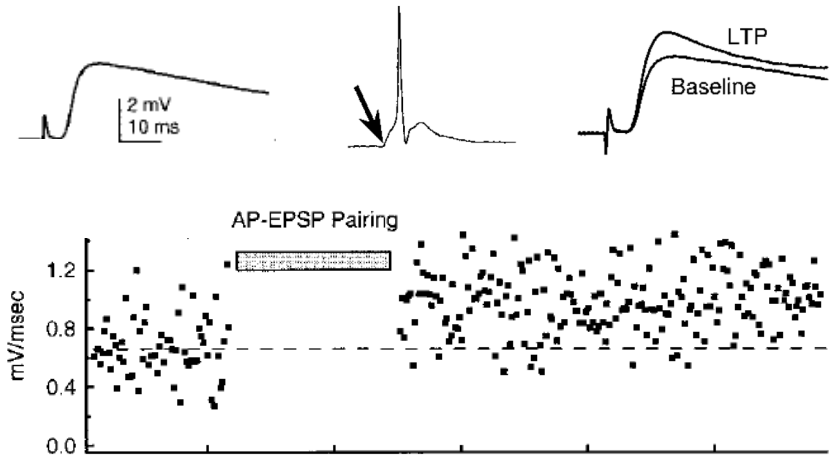
Stent's postulate:
If B then A, then depress
Long-term depression
LTD

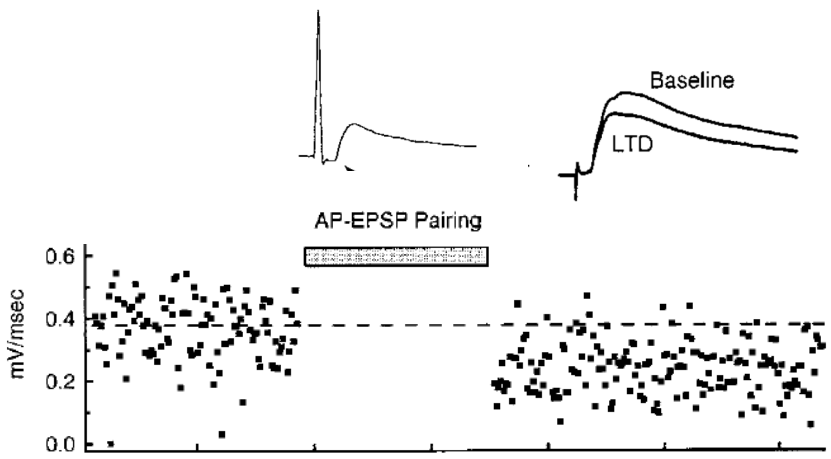


Example of Hebbian and anti-Hebbian plasticity in cortex

Pre then post-> Long term potentiation (LTP)

Post then pre-> Long term depression (LTD)



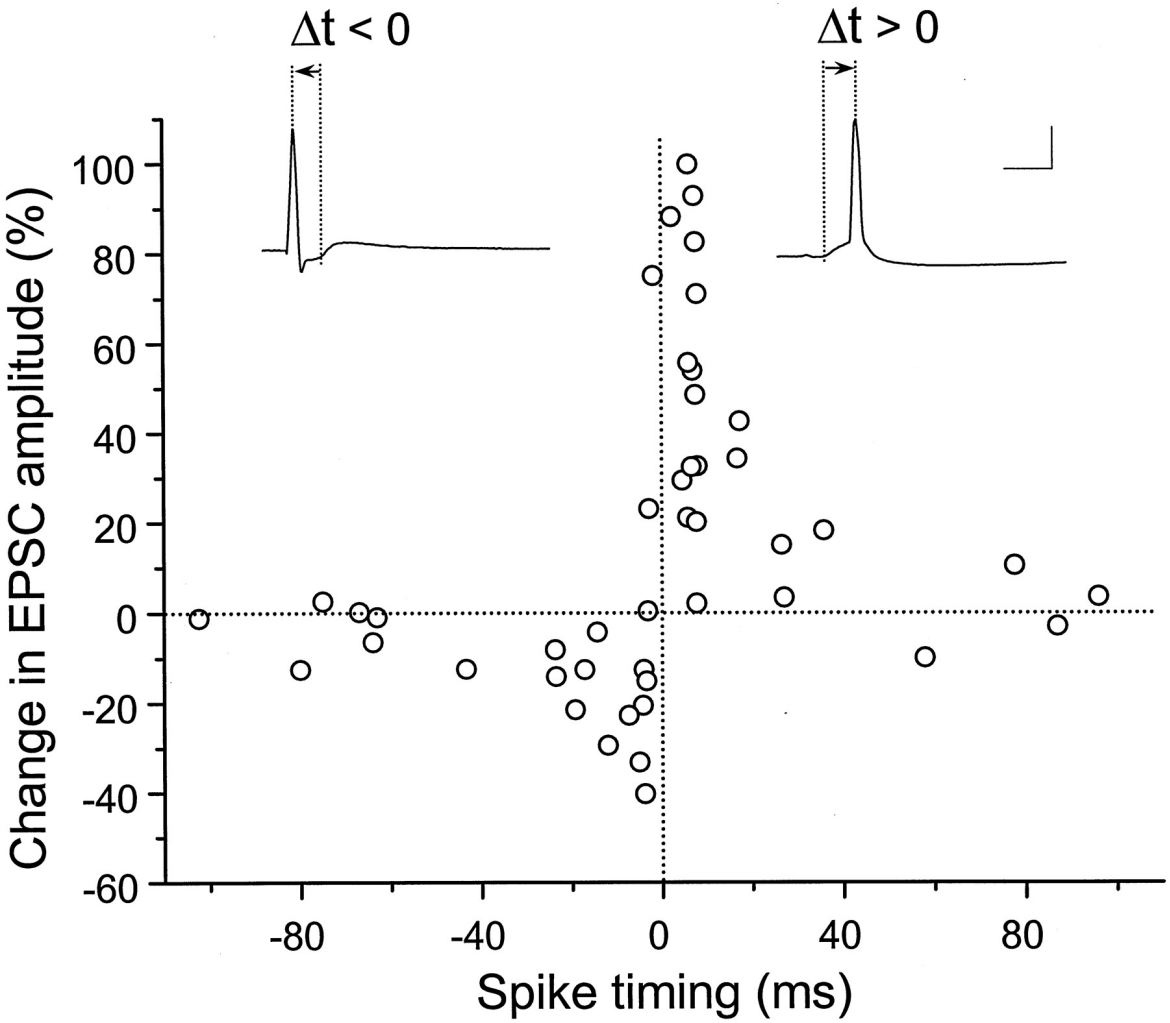


Time (10 min)

Daniel E. Feldman*
Neuron, Vol. 27, 45–56,

Spike timing dependent plasticity (STDP)

Timing codes for **polarity** and magnitude of plasticity



Bi and Poo JNS 18: 10464

Hallmarks of Spike timing dependent plasticity (STDP)

-Timing codes for **polarity** and magnitude of plasticity

-Strictly based on temporal correlations, not on the levels of activity.
-Rules that "encode" causality:

pre then post->LTP

post then pre-> LTD

-Synaptic changes could be computed from "spike trains"
-Fullfils the "letter" of the Hebbian and anti-Hebbiean rules

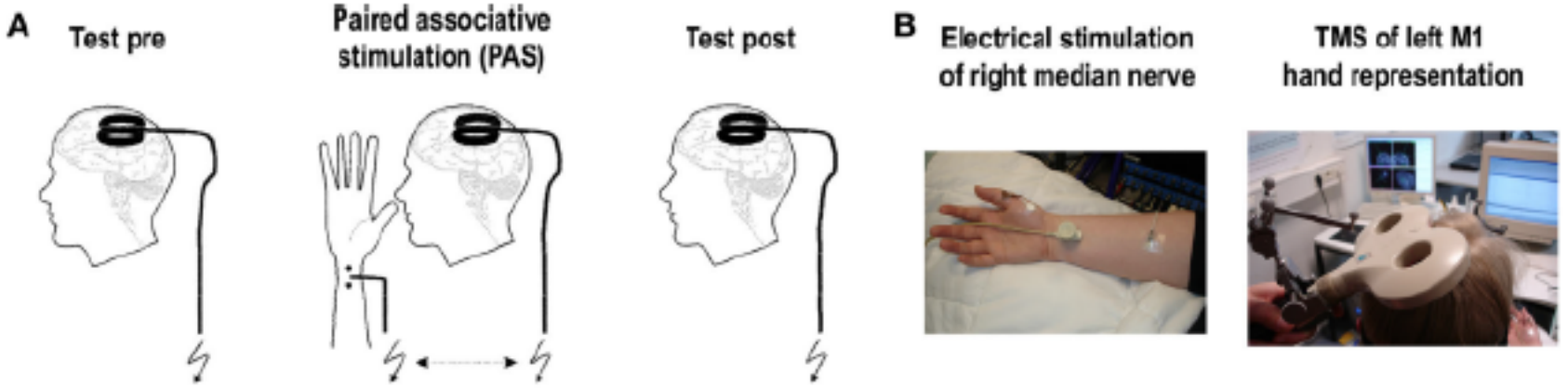
How Timing codes for the **polarity** of plasticity?

pre then post->LTP: easy, the AP "boosts" the activation of the NMDAR by reducing the Mg block

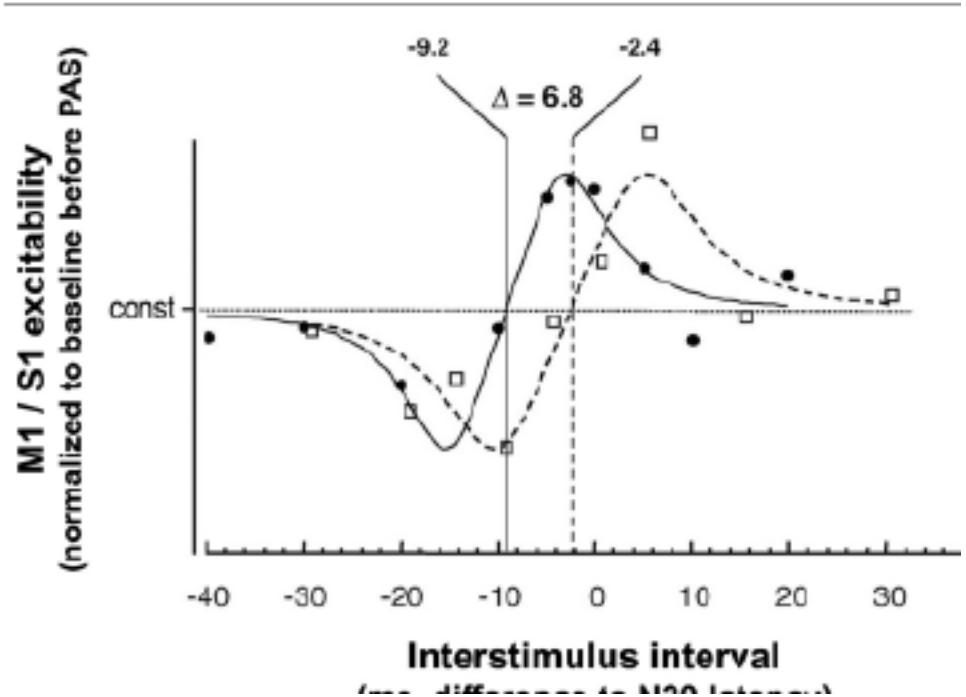
post then pre-> LTD: several hypothesis

1) Ca entry during the AP. Ca is not fully removed by the time synapses are activated and help to bring [Ca]i to the LTD threshold
2) Ca entry during the AP desensitizes the NMDAR so it does no reach the threshold for LTP. (contradicts 1)
3) Ca entry during the AP favours the production of endocannabinoids, which in turn reduces presynaptic release (LTD and LTP do not reverse each other)

STDP in humans II



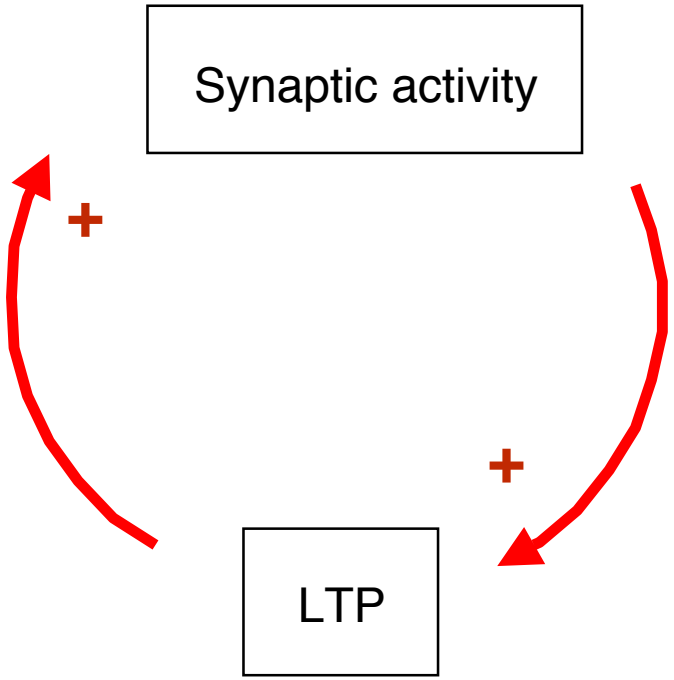
-Transcranial magnetic stim (TMS) on motor cortex evokes a motor response in the hand (MEP).
-Pairing the TMS with electrical stim. of the nerve induces plasticity of the MEPS. In a timing dependent manner

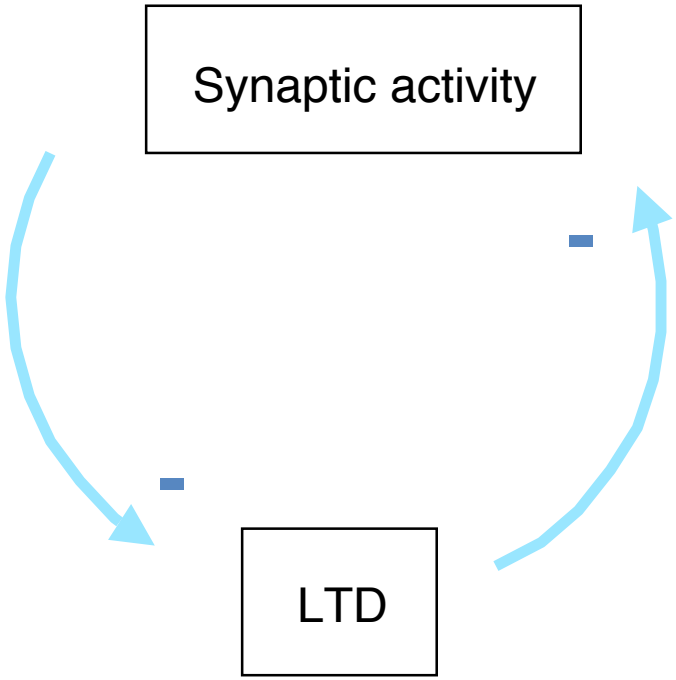


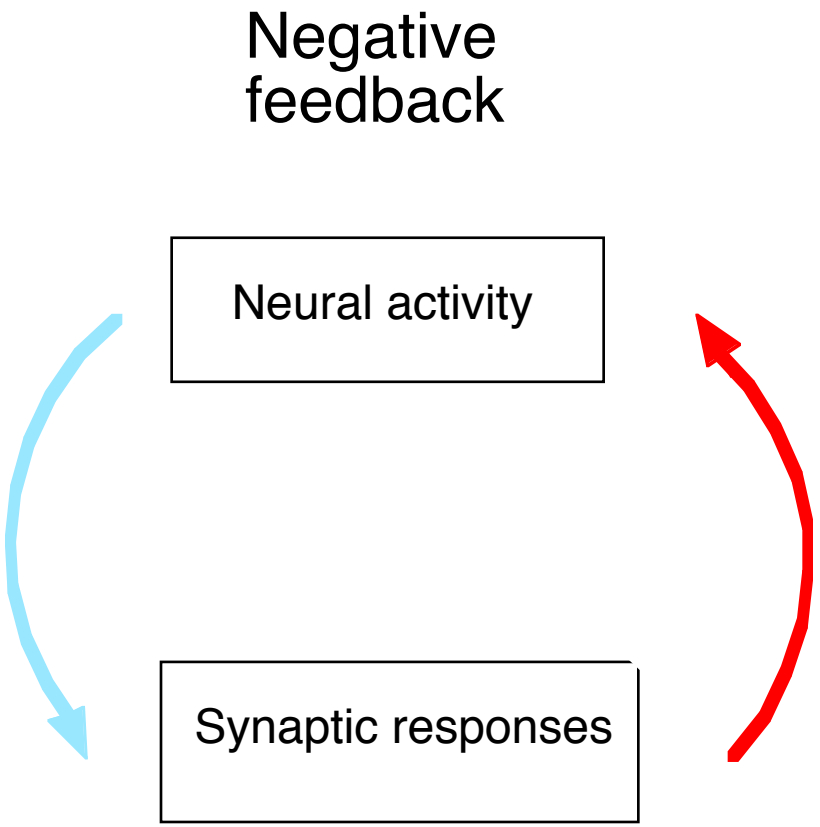
Metaplasticity: regulation of synaptic plasticity

Need for the regulation of synaptic plasticity

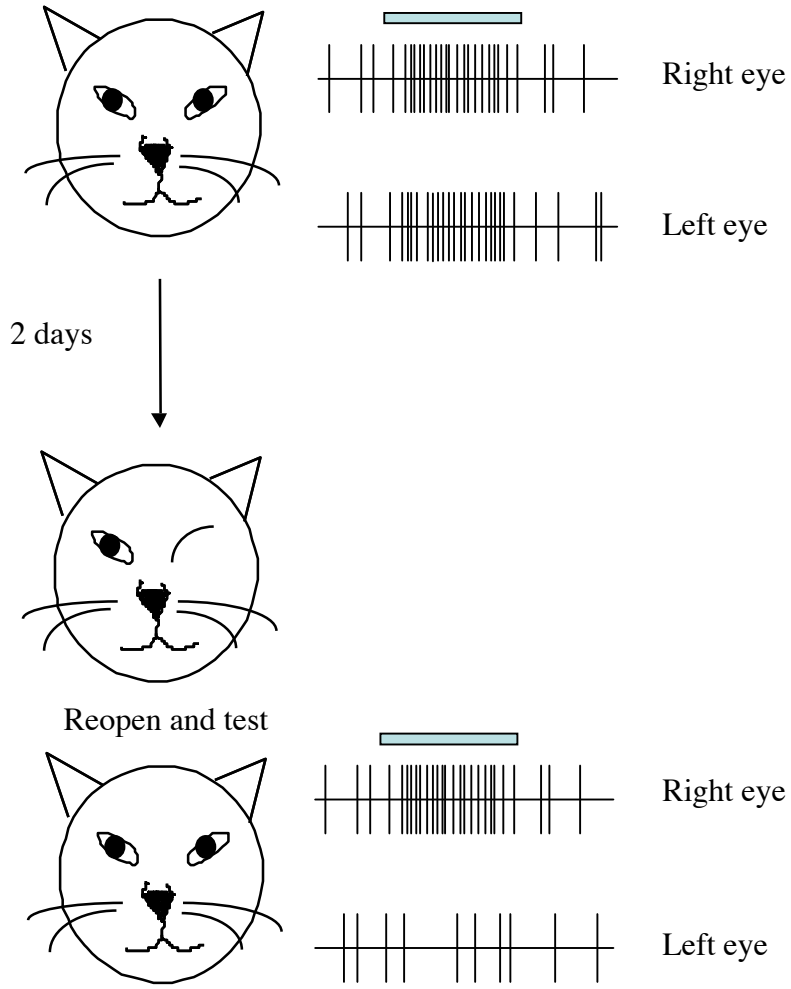
Networks built with LTP and LTD only tend to be bi-stable
Neural activity and LTP/LTD can enter in a vicious circle






Negative
feedback
Neural activity
Synaptic responses

Experimental results in visual cortex require additional explanation

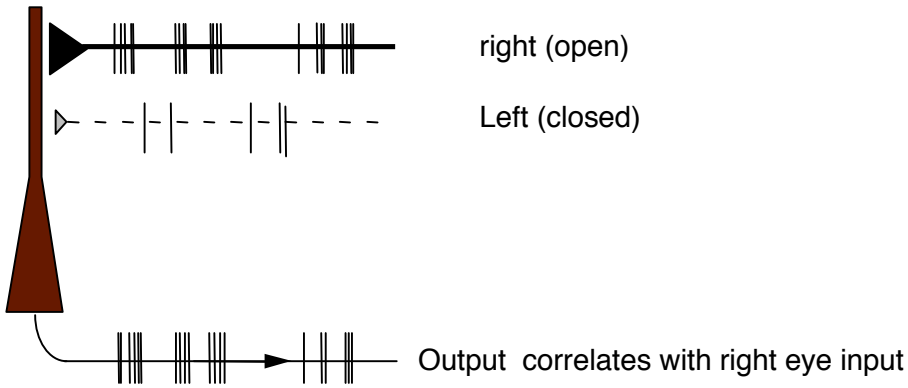


Classical experiments of monocular deprivation

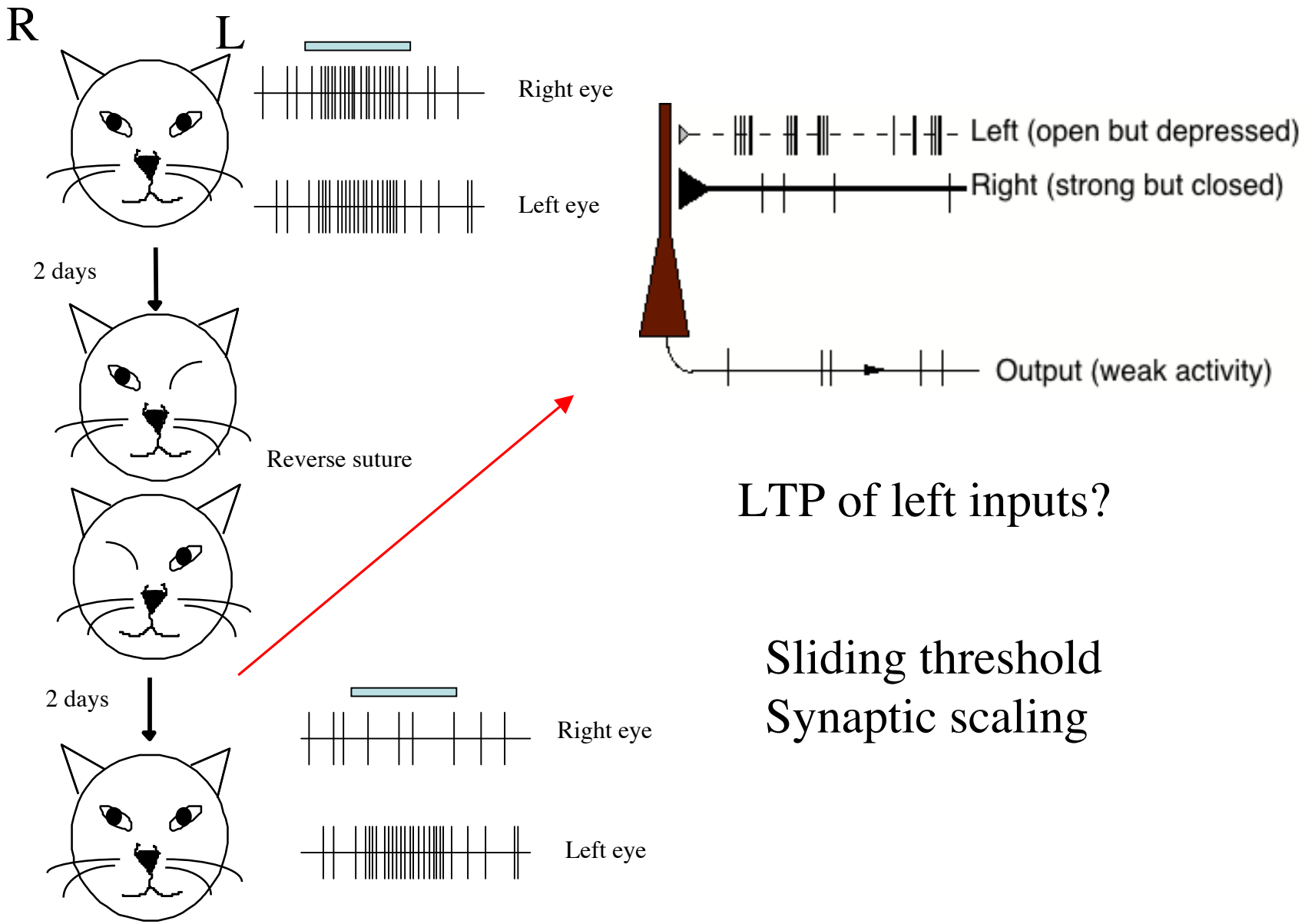
Cells in the visual cortex tend to be binocular and respond to stimulation in both eyes, with different preferences, though.

Closing one eye for a brief period causes a shift in the responses towards the non-deprived eye.

These shifts in ocular dominance can be easely interpreted as resulting from LTP/D like mechanisms



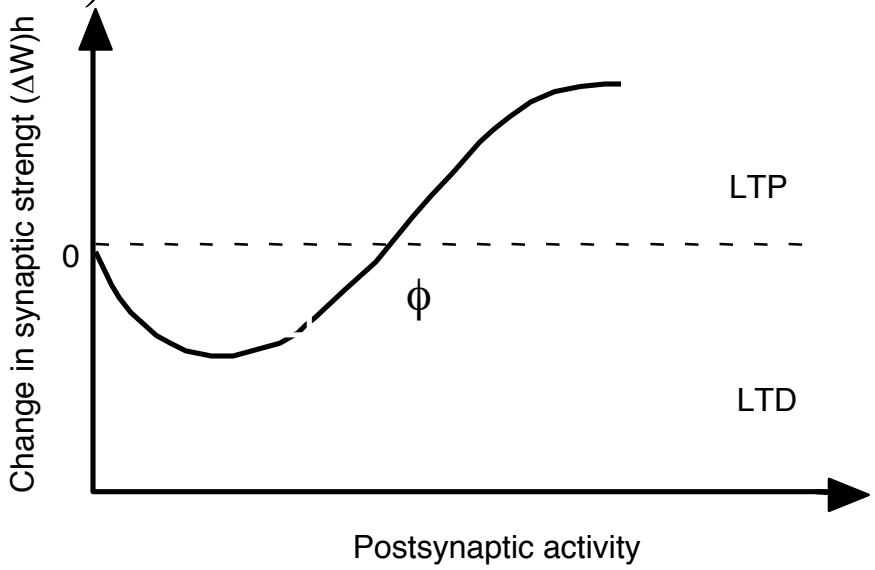
Reverse suture experiments



LTP of left inputs?

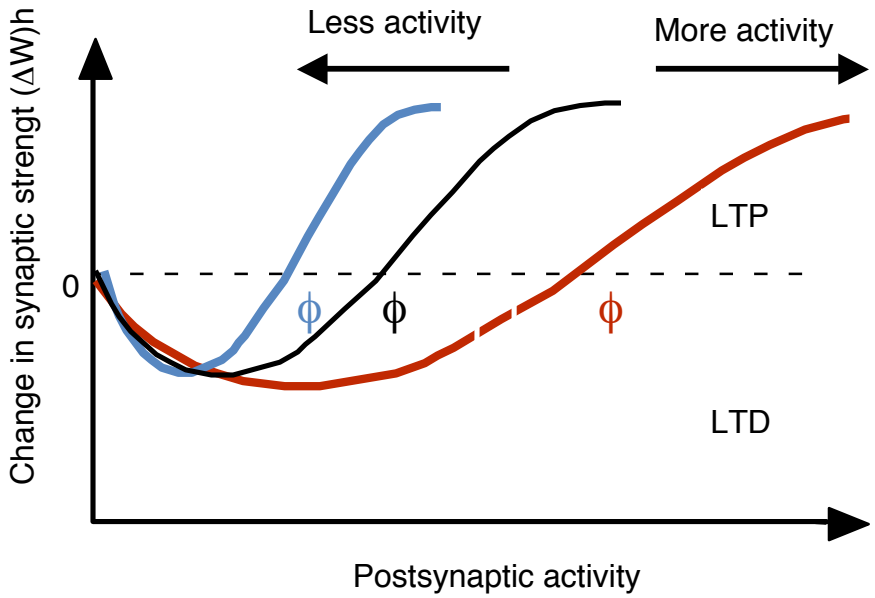
Sliding threshold
Synaptic scaling

Sliding threshold: the BCM model (Bienenstock, Cooper, Munroe)



1: $\Delta W=F(Pre*[Post-\Phi])$

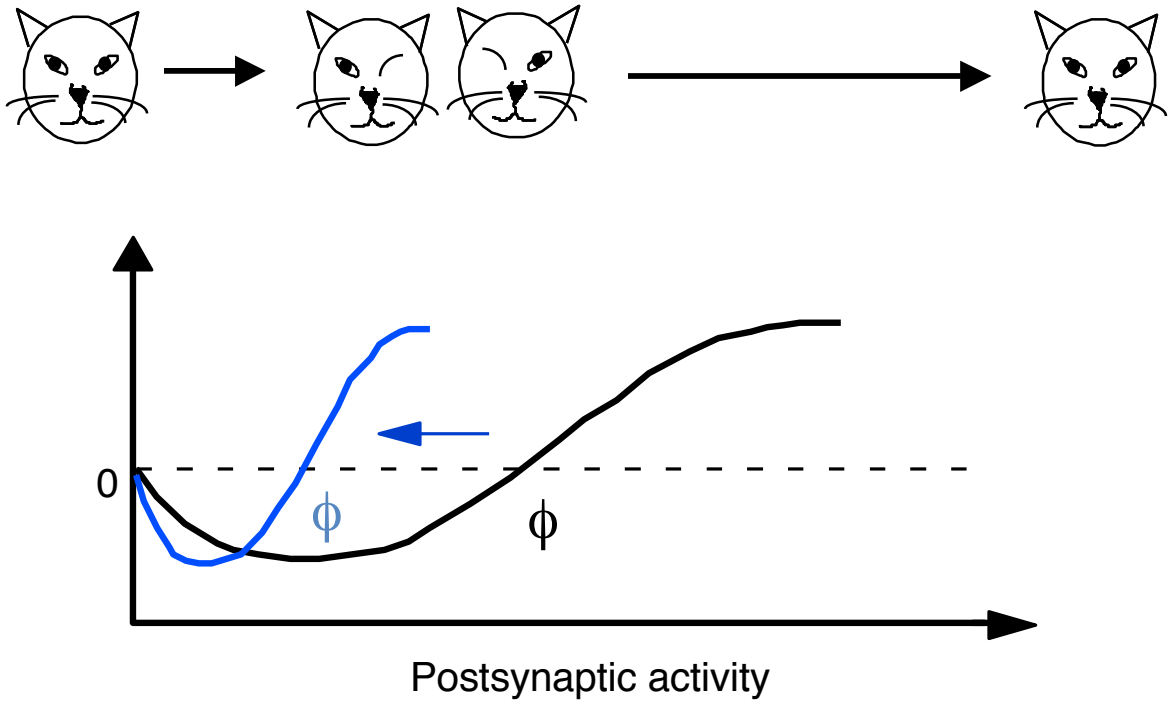
W=synaptic weight
Pre = presynaptic activity
Post= postsynaptic activity
Φ = modification threshold



2: Φ is not fixed, it depends on history

Φ= depends on previous activity:

The threshold for LTP decreases when postsynaptic activity is low



Φ slides to a lower level and then LTP of left inputs happens

Evidence: It is easier to obtain LTP in the cortex of dark-reared animals and it is harder to induced LTD in these cortices

Synaptic scaling

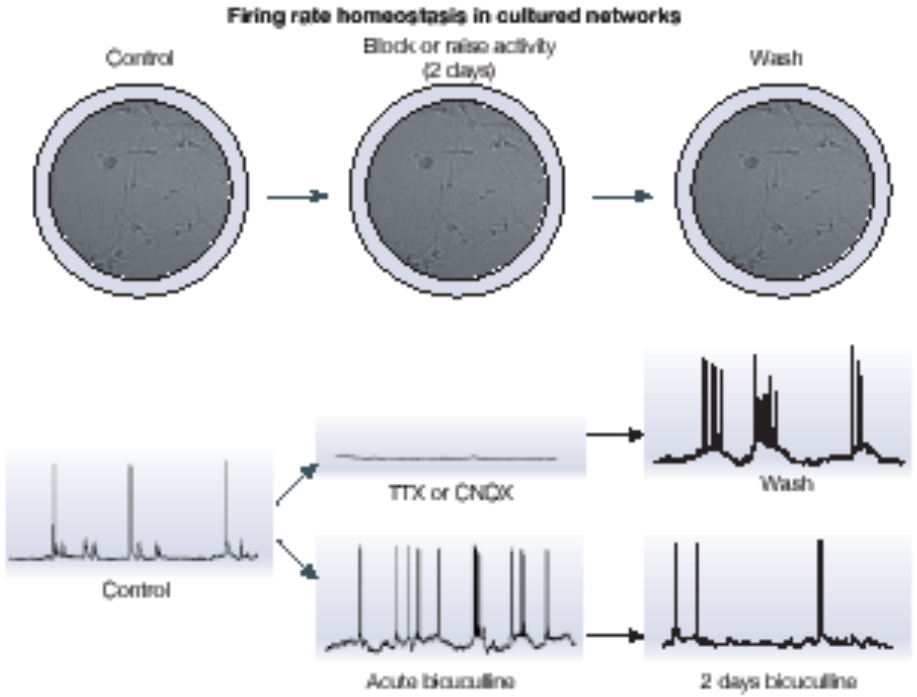


Figure 3 | **Evidence for firing rate homeostasis in cultured networks.** Cultured cortical networks are composed of interconnected excitatory pyramidal and inhibitory interneurons, and develop spontaneous activity after a few days *in vitro* (control). This activity can be pharmacologically manipulated for long periods. Blockade for two days of spiking activity with tetrodotoxin (TTX), or of excitatory glutamatergic synapses with CNQX, generates a rebound phenomenon whereby the excitability of the network is increased when the drugs are removed (wash). A more direct test of the idea of firing rate homeostasis is to raise activity acutely with bicuculline (acute bicuculline), and then to follow activity over time. After two days in bicuculline, activity has returned almost to control levels (2 days bicuculline). These experiments, and others like them, indicate that homeostatic mechanisms adjust the cellular and synaptic properties of cortical networks to compensate for changes in synaptic drive.

Low firing rates
Increase synaptic drive

High firing rates
Reduce synaptic drive

By scaling up or down all synapses, the cell keeps constant the level of excitation while it preserve the relative strength of the synapses.
It maintains activity without disturbing "memories"

Previously in TTX Previously in Biccuculine

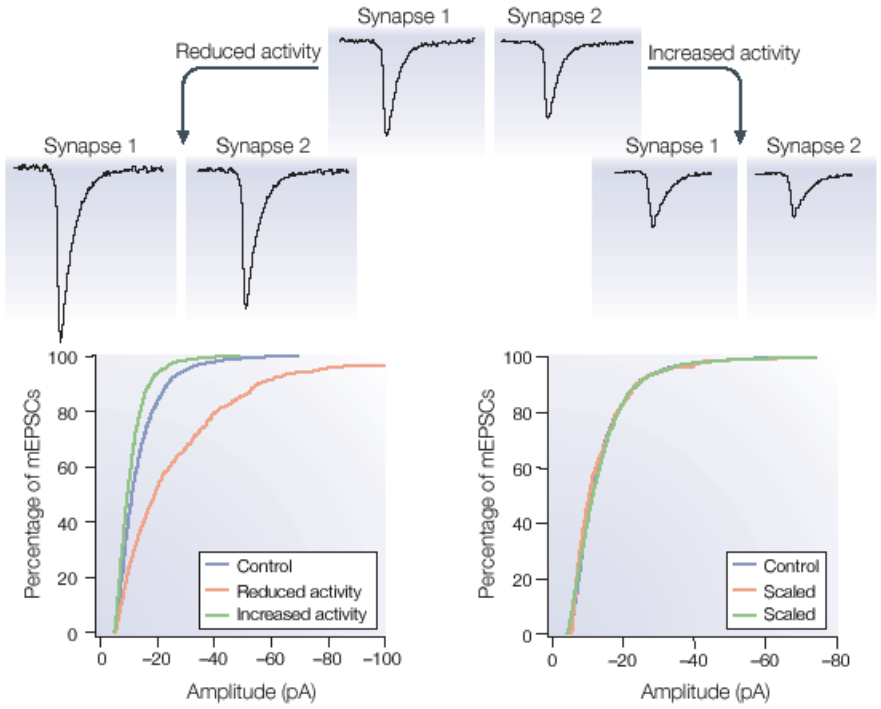


Figure 4 | **Synaptic scaling induces a multiplicative change in the distribution of synaptic weights.** Increased activity reduces the amplitudes of miniature excitatory postsynaptic currents (mEPSCs) onto cortical pyramidal neurons, whereas decreased activity has the opposite effect, indicating that quantal amplitude is regulated in a homeostatic manner by prolonged changes in activity. Plotting mEPSC amplitudes as a cumulative histrogram (lower panels) shows that the entire distribution of amplitudes is increased (reduced activity) or decreased (increased activity). If these distributions are scaled up or down by multiplying each value in the experimental distribution by the same factor, they overlay the control distribution almost perfectly, indicating that all excitatory synapses onto pyramidal neurons are scaled up or down multiplicatively by prolonged changes in activity. Lower panels modified, with permission, from REF. 77 © (1999) Elsevier Science.

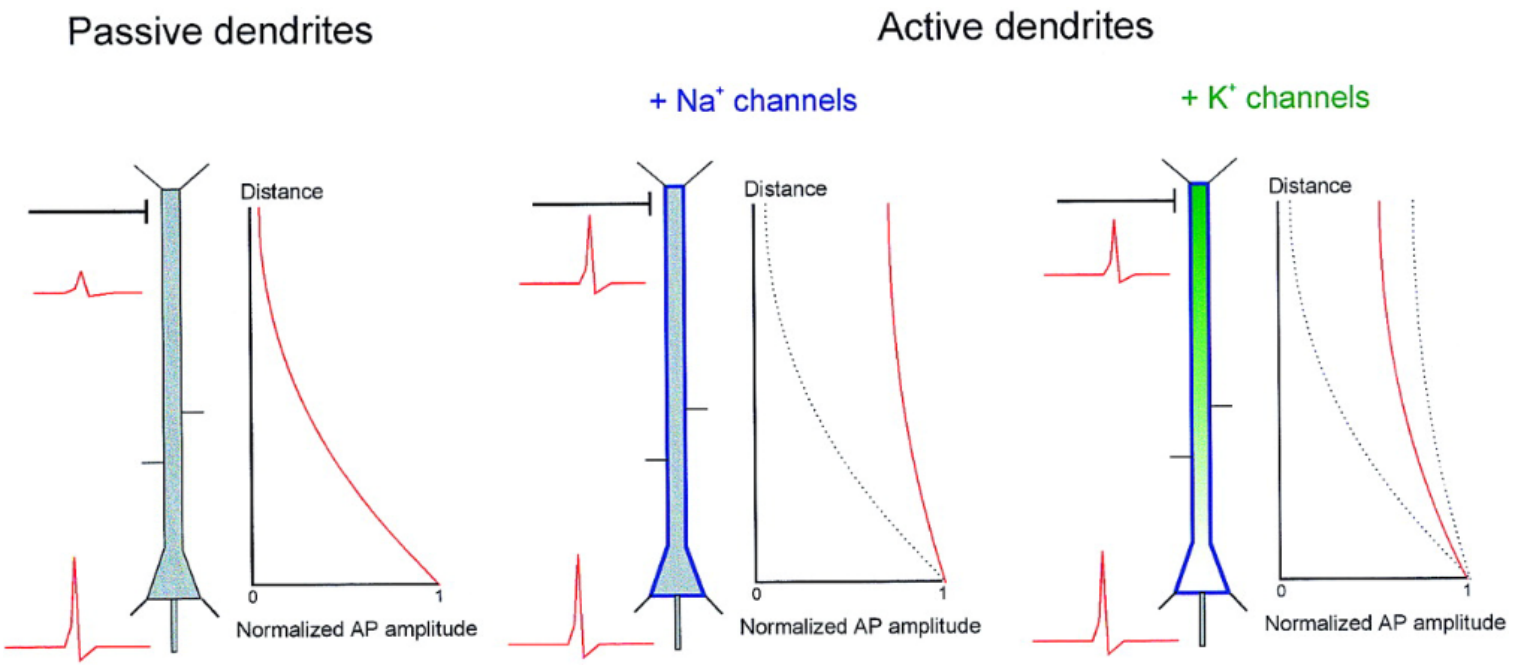
Note that S2/S1remain constant

Not shown: Scaling does not depend on NMDAR's

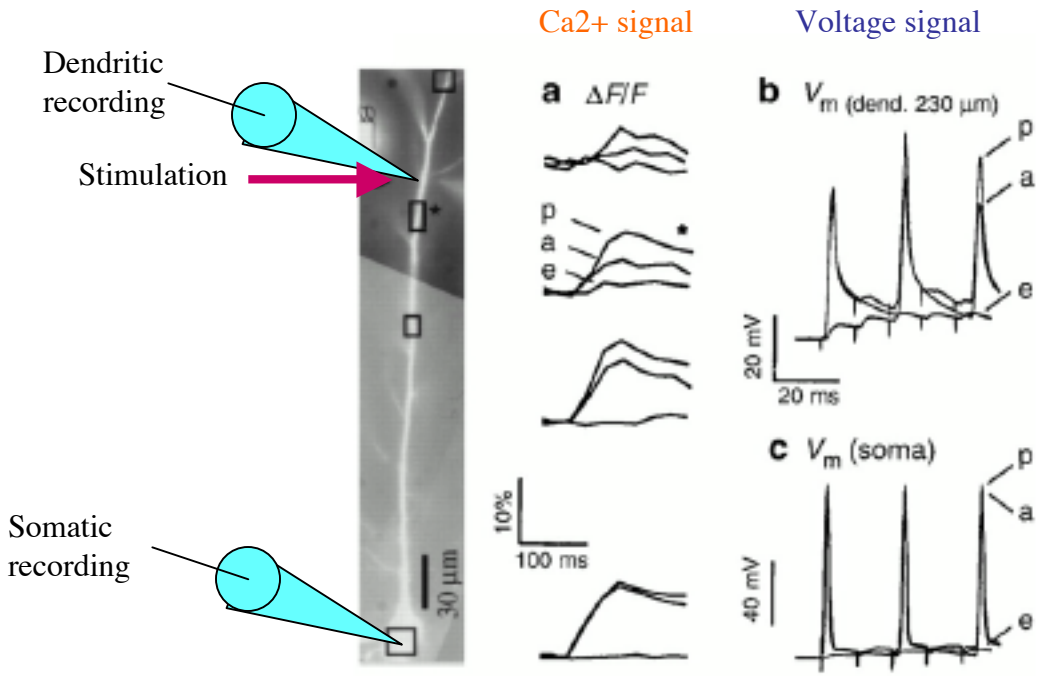
Evidence: spontaneous minis are larger in deprived cortex

Sliding threshold	Synaptic scaling
Global: affects all synapses	Global: affects all synapses
Dark rearing reduces threshold for LTP in visual cortex	Dark rearing increases the size of the unitary responses in visual cortex
Does not affect stored memories	Does not affect stored memories

Differences between active and passive dendrites



Back-propagating action potential "helps" Ca entry During synaptic activation



Magee & Johnston