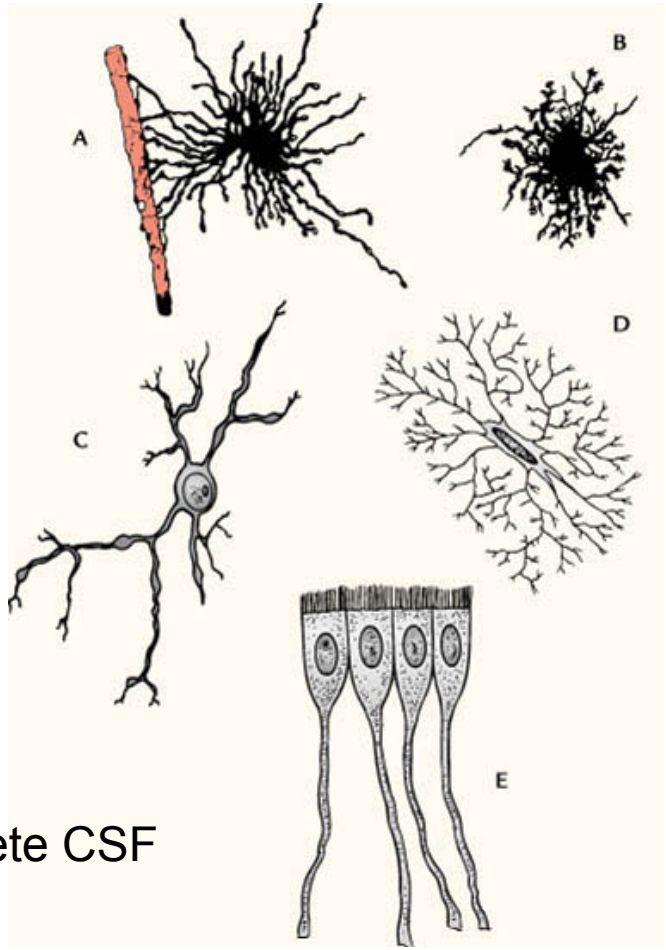
Neurons, Part 2

- Glial cells
- Short-term synaptic plasticity
- Long-term synaptic plasticity
- Cellular homeostasis

Types of glia in the CNS

Astrocytes: most common; metabolic support, including recycling of neurotransmitters and K^+ buffering; blood-brain barrier

Oligodendrocyles: myelinate axons in the CNS

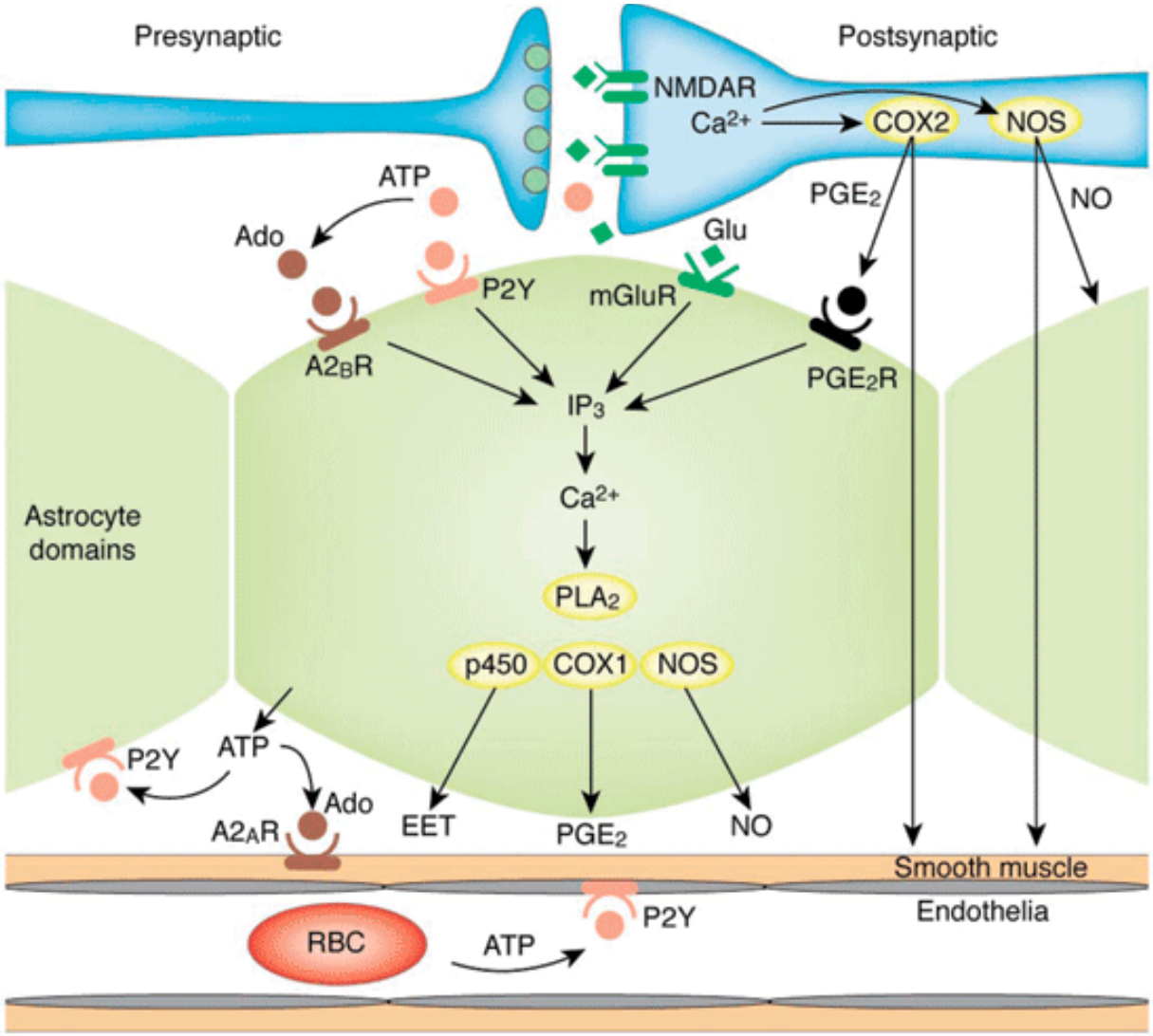


Microglia: patrol the CNS for immune purposes

Ependymal cells: secrete CSF

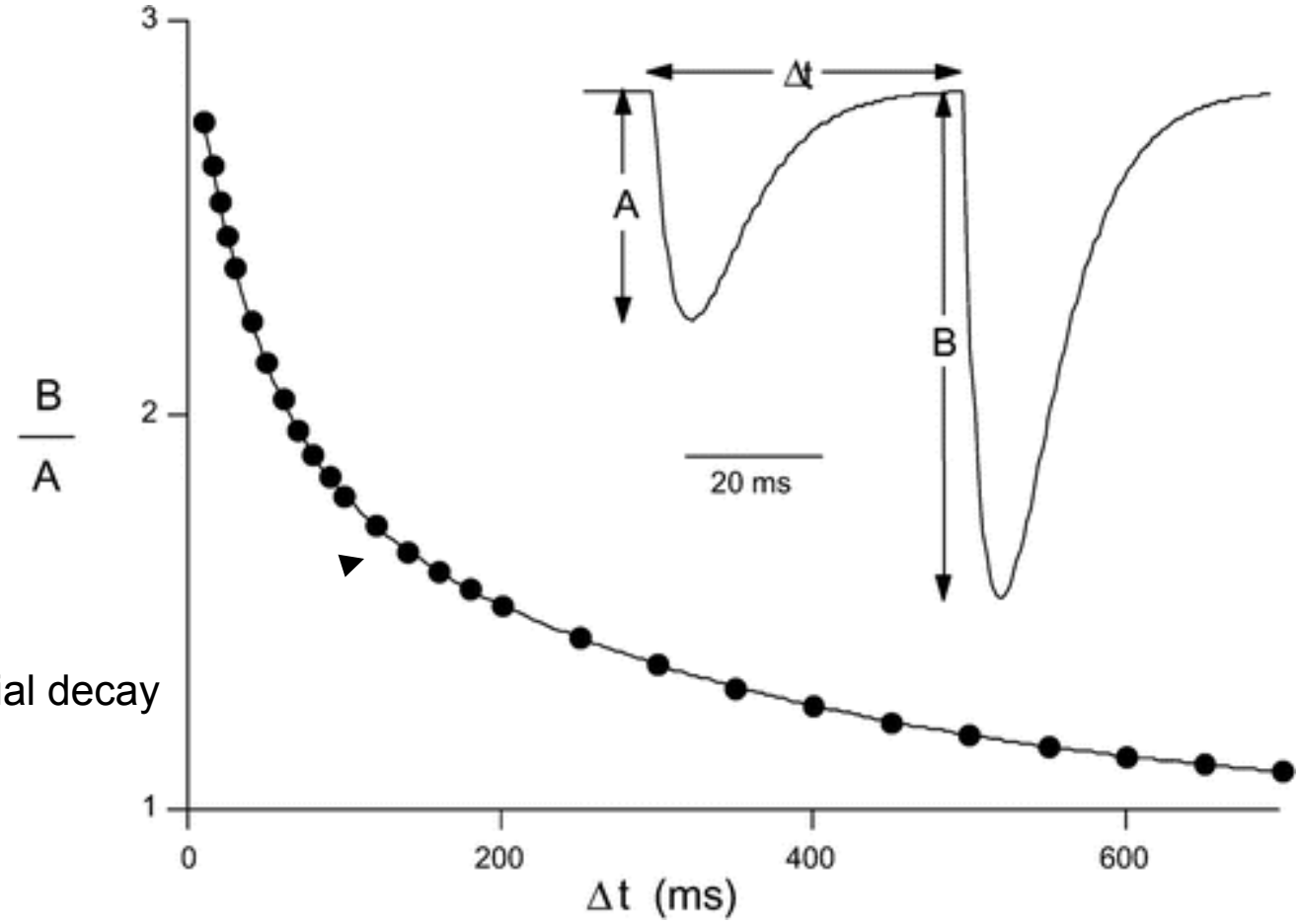
Berne and Levy

Astrocytes in neurovascular coupling



Iadecola & Nedergaard (2008) *Nature Neurosci* 10: 1369 - 1376

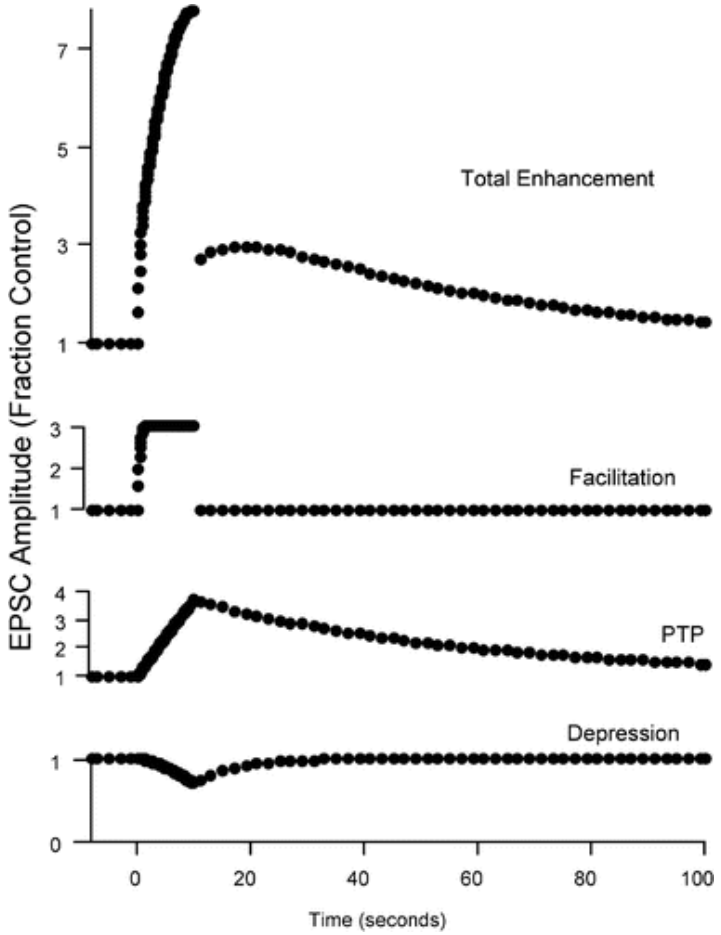
Short-term facilitation of EPSCs



Biexponential decay

Zucker and Regehr (2002) *Ann Rev Physiol* 64: 355-405

Multiple time scales



Zucker and Regehr (2002) *Ann Rev Physiol* 64: 355-405

Multiple time scales of short-term enhancement

Component	Time constant
F1 facilitation	20-100 ms
F2 facilitation	150-400 ms
Augmentation	~ 7 s
Post-tetanic potentiation	1-5 min

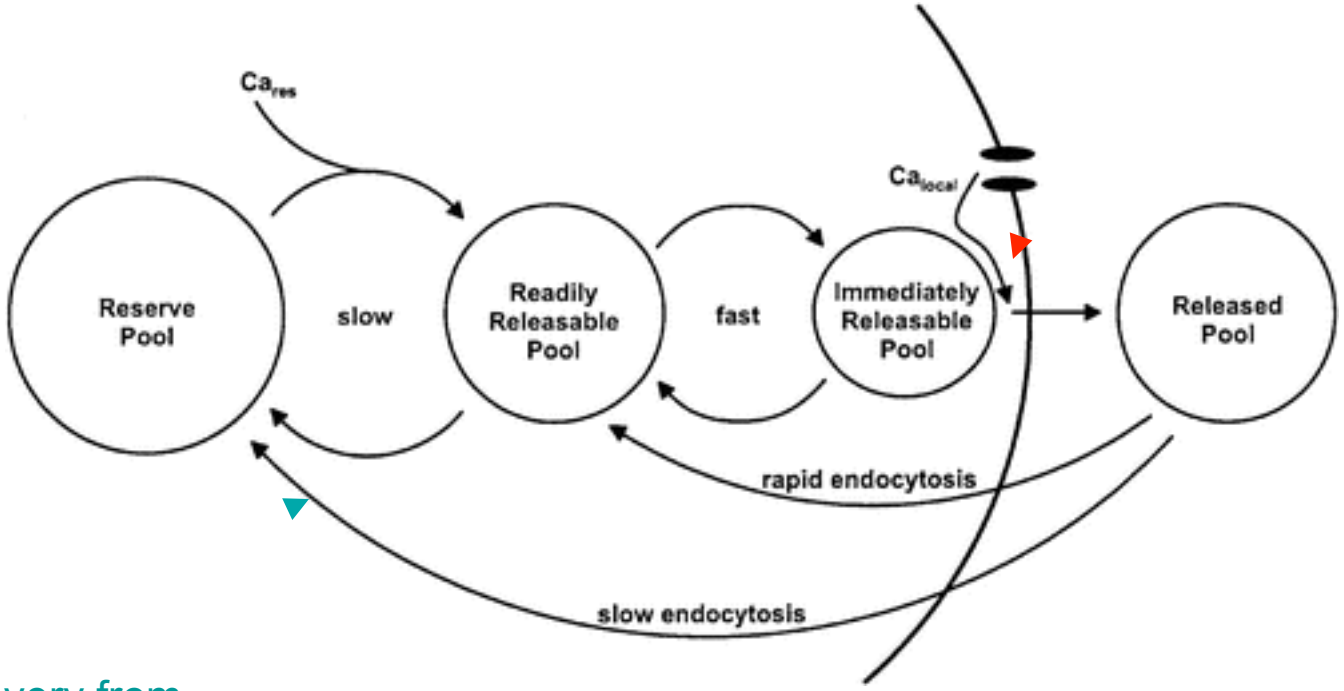
Fisher et al. (1997) *Trends Neurosci* 20:170-177

Short-term enhancement is linked to presynaptic Ca^{2+}

- Elevating presynaptic Ca^{2+} enhances synaptic transmission
- Buffering presynaptic Ca^{2+} reduces synaptic enhancement
- Reducing Ca^{2+} influx reduces synaptic enhancement

Experimental results suggest multiple "pools" of vesicles

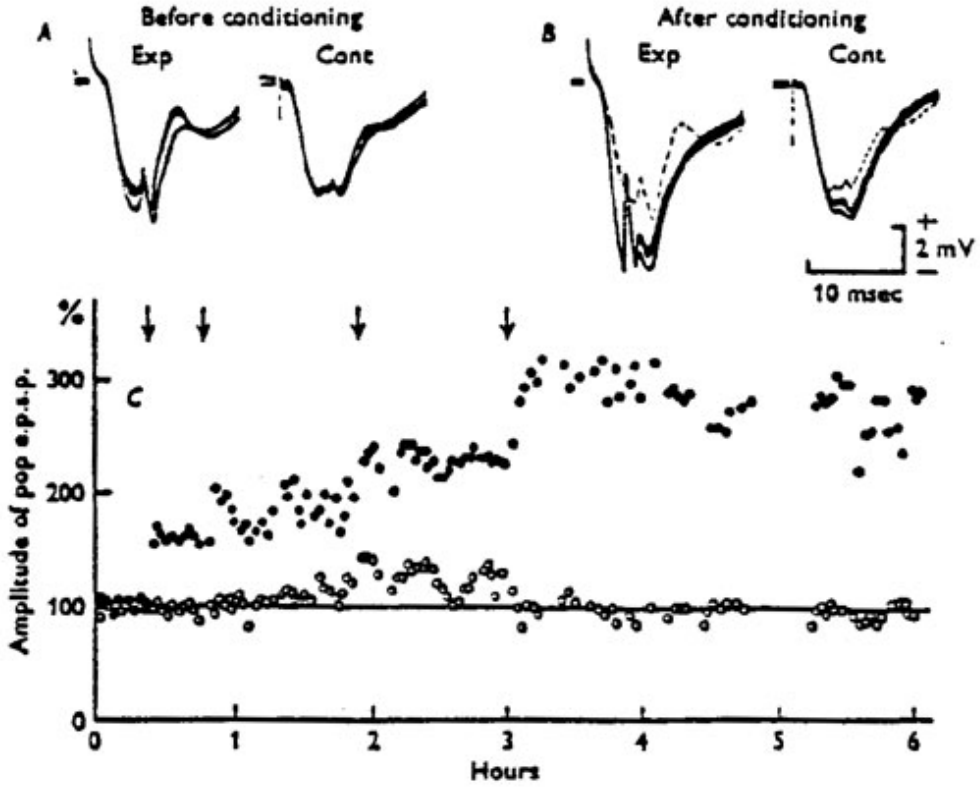
F1, F2: residual Ca^{2+} near release site



Aug, PTP, recovery from depression: residual Ca^{2+} throughout the terminal

Zucker and Regehr (2002) *Ann Rev Physiol* 64: 355-405

Long-term potentiation in the hippocampus



An experiment in which all three standard parameters of the evoked response were potentiated. Three superimposed responses obtained in the synaptic layer for both the experimental and control pathways are shown in *A* (before conditioning) and in *B* (2·5 hr after the fourth conditioning train). *C*, graph showing the amplitude of the population e.p.s.p. for the experimental pathway (filled circles) and the ipsilateral control pathway (open circles) as a function of time. Each point was obtained from the computed average of thirty responses by measuring the amplitude of the negative wave 1 msec after its onset. The values are plotted as percentages of the mean pre-conditioning value. Conditioning trains (15/sec for 10 sec) were given through a medially placed conditioning electrode at the times indicated by the arrows.

Bliss & Lomo (1973)
J Physiol 232: 331-356

Milestones in research on synaptic plasticity

1. Discovery of LTP (Bliss and Lomo, 1973).

2. LTP is input specific (Andersen et al. 1977; Lynch et al. 1977).

3. LTP is cooperative (McNaughton et al. 1978; Levy and Steward, 1979; Lee 1983).

4. LTP is associative (McNaughton et al. 1978; Levy and Steward, 1979; Barrionuevo et al. 1983).

5. LTP requires postsynaptic depolarization (Kelso et al. 1986; Gustafsson et al. 1987).

6. LTP requires NMDA receptor activation (Collingridge et al. 1983).

7. LTP requires postsynaptic Ca^{2+} elevation (Lynch et al. 1983).

8. LTP has multiple phases: induction, early, and late (see Roberson et al. 1996).

9. Early LTP requires protein kinases (Lisman, 1994; Malenka et al. 1989; Malinow et al. 1989).

10. Late LTP requires gene expression and protein synthesis (see Roberson et al. 1996).

11. Activated synapses are tagged for protein-synthesis dependent LTP (Frey and Morris, 1997).

12. Discovery of LTD (Levy and Steward, 1983; Stanton and Sejnowski, 1989).

13. LTD requires NMDA receptors and Ca^{2+} (Dudek and Bear, 1992; Mulkey and Malenka, 1992).

14. Discovery of STDP (Markram et al. 1997; Bell et al. 1997; Bi and Poo, 1998).

Input specificity

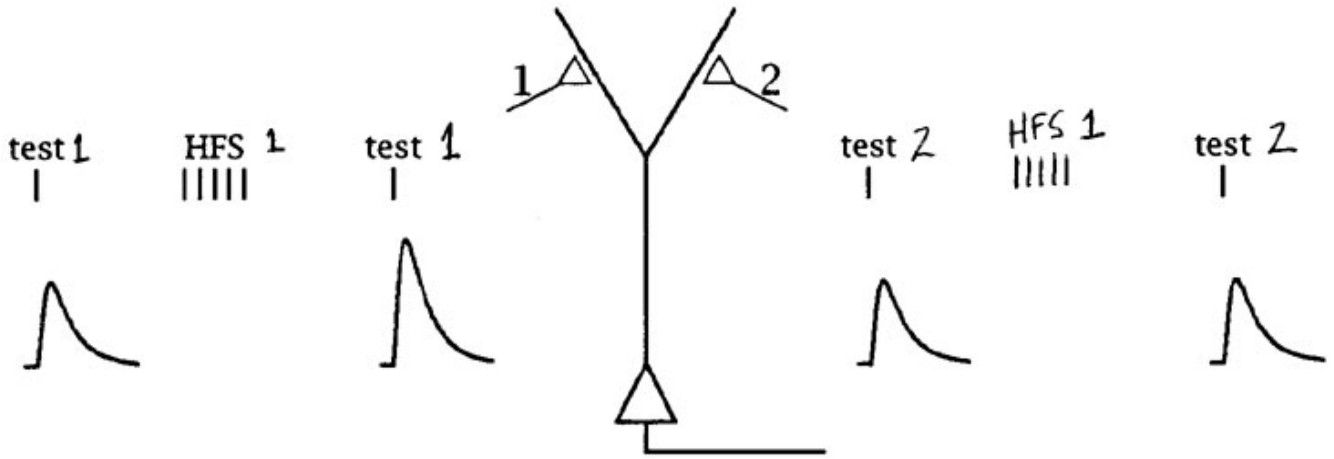


Figure 15.4 Input specificity for LTP. Both synapses 1 and 2 are tested before and after HFS, but only synapse 1 receives HFS and only synapse 1 displays LTP.

from Johnston & Wu (pg. 449)

NMDA receptors are required for LTP in most cases

Pre-tetanus | Post-tetanus in APV | Post-tetanus

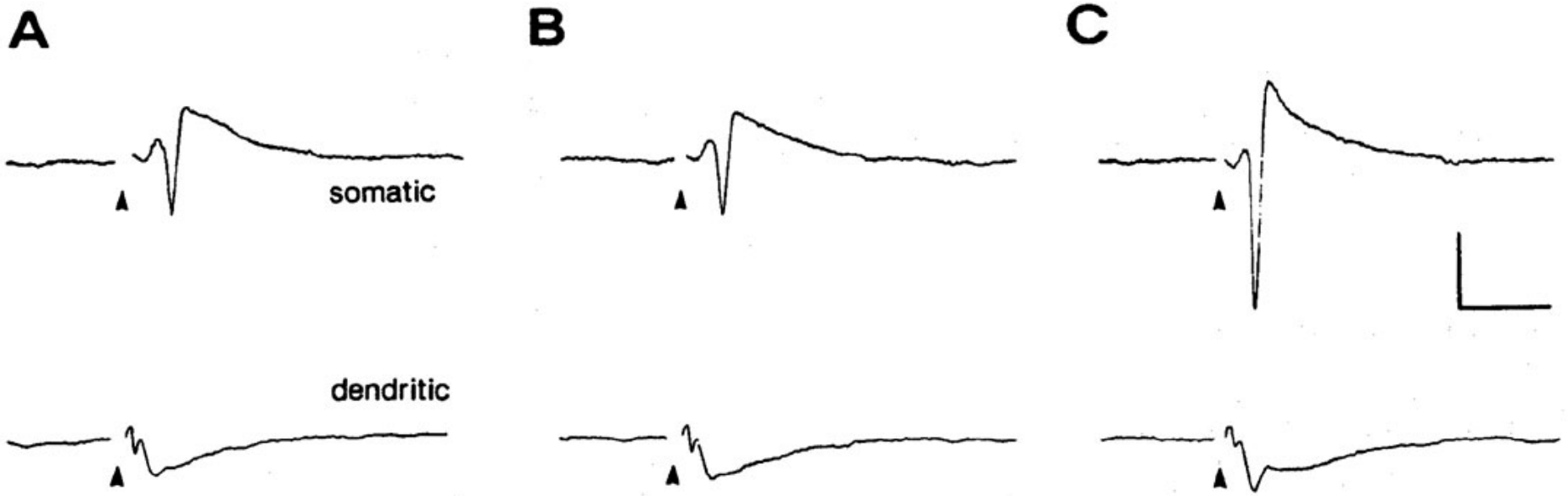
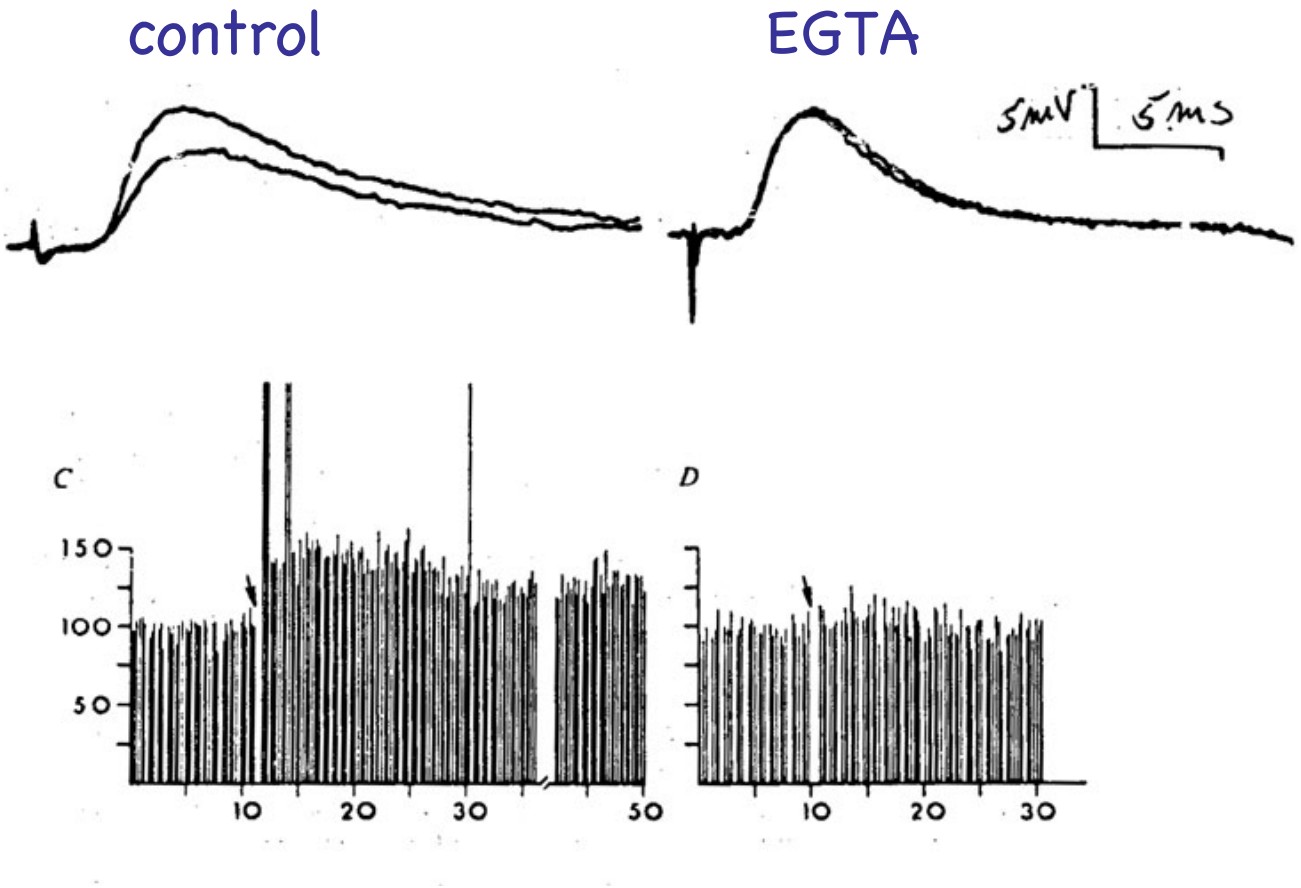


Fig. 3. *APV blocks the induction of LTP. Recordings were obtained simultaneously from the cell body (somatic) and apical dendritic regions of CA1 in response to low frequency stimulation (0.033 Hz) of the Schaffer collateral–commissural pathway. (The dendritic responses illustrated were obtained using a lower stimulus intensity.)* **(A)** *Responses in the presence of 50 μM D-APV.* **(B)** *Responses 15 min following a tetanus (100 Hz, 1 s) still in the presence of APV.* **(C)** *Responses 15 min following a second, identical tetanus given after APV had washed out. Scale bars are 4 mV and 10 ms.* (Kindly provided by E. J. Coan.)

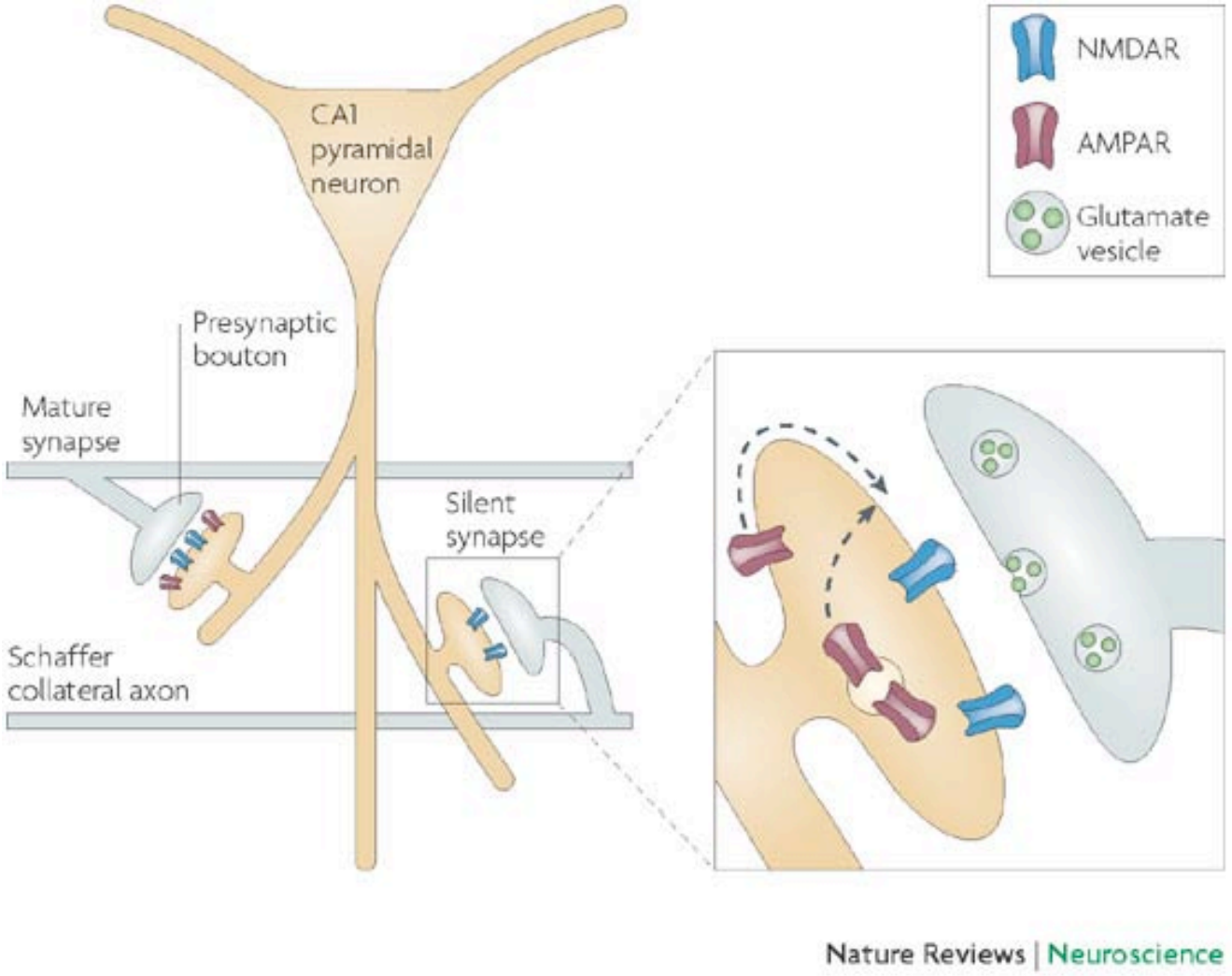
from Collingridge & Bliss 1987

Elevation of intracellular Ca^{2+} is required for induction of LTP



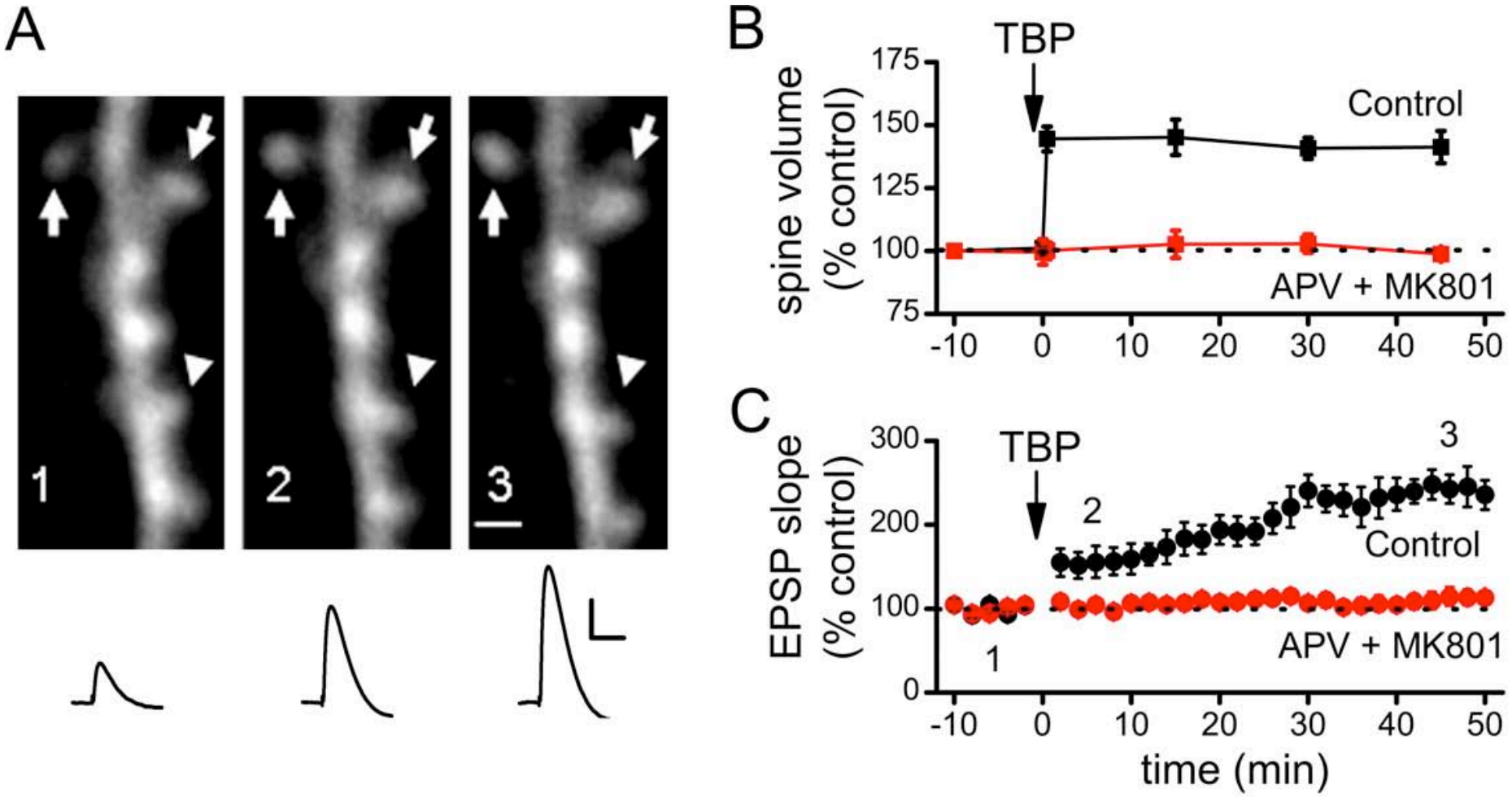
Lynch et al. 1983

AMPA receptor insertion is critical for expression of early LTP



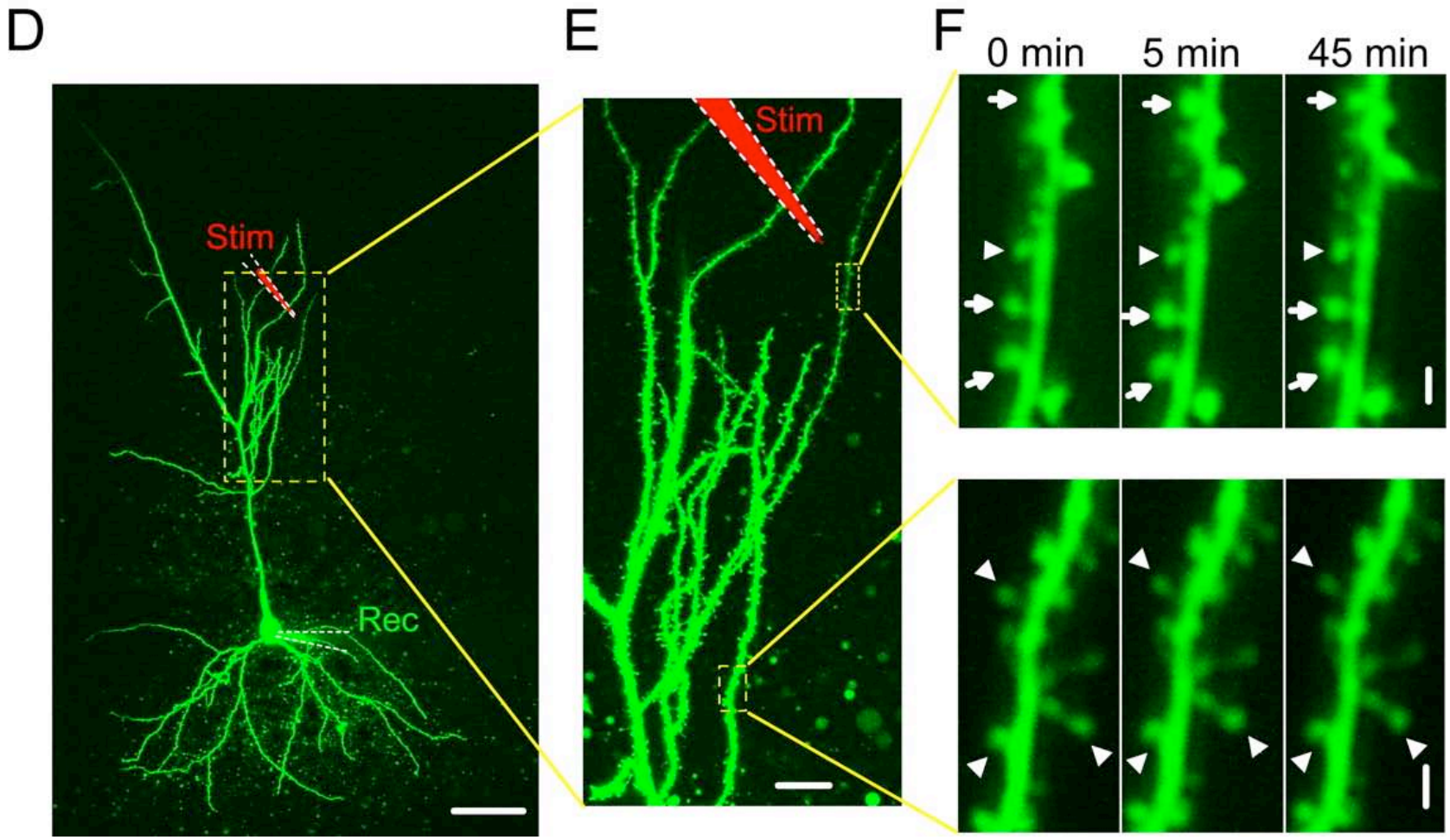
Kerchner and Nicoll (2008) *Nature Rev Neurosci* 9: 813-825

LTP involves rapid changes in spine volume



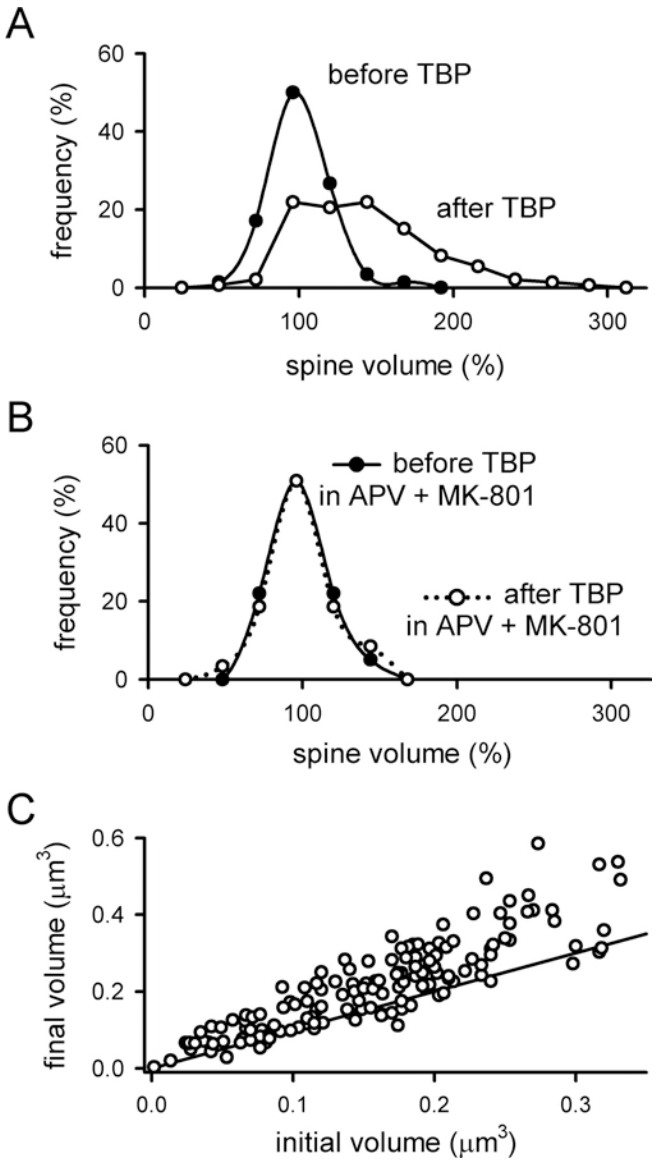
Yang et al. (2008) *J Neurosci* 28: 5740-5751

More images of spines



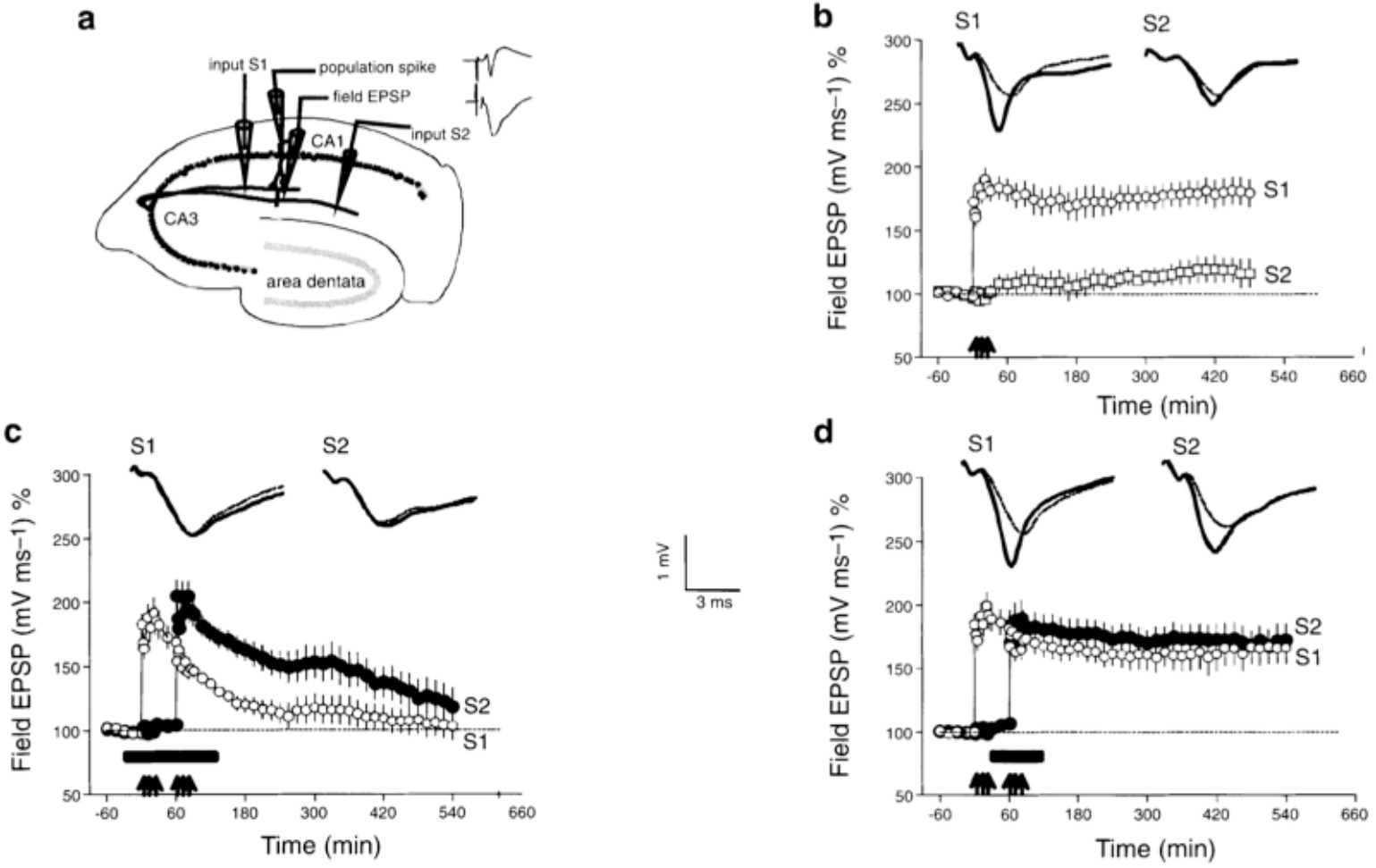
Yang et al. (2008) *J Neurosci* 28: 5740-5751

Quantitative analysis of spine volume



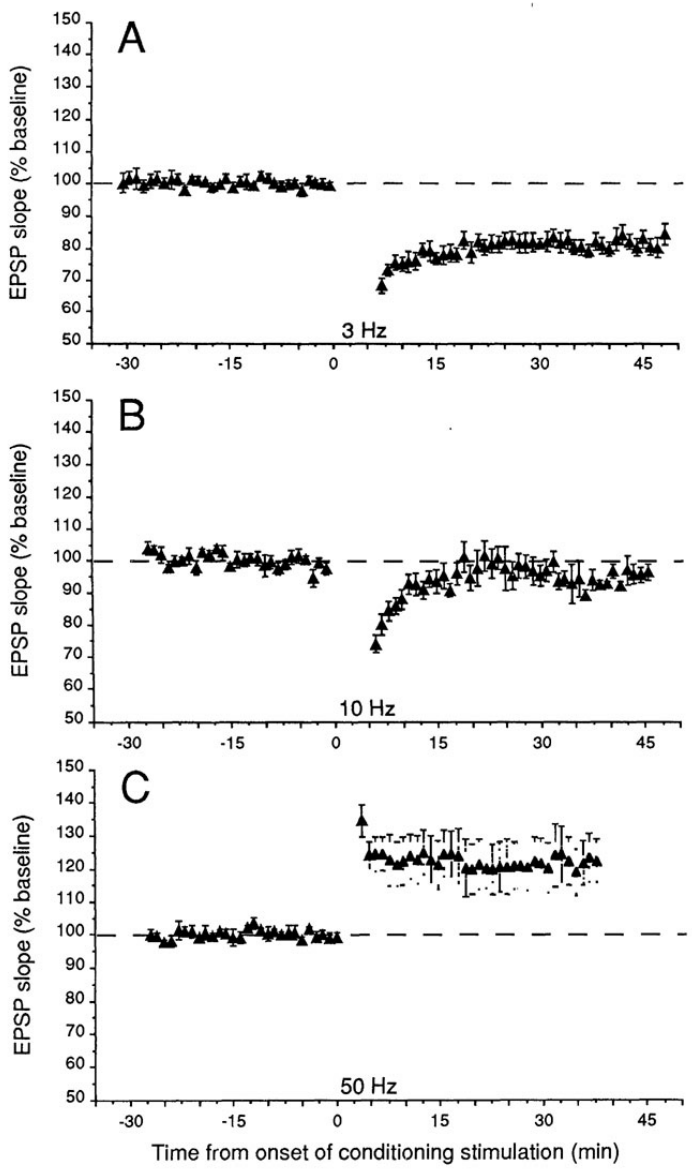
Yang et al. (2008) *J Neurosci* 28: 5740-5751

LTP maintenance requires protein synthesis and synaptic "tagging"



Frey and Morris (1997) *Nature* 385: 533-536

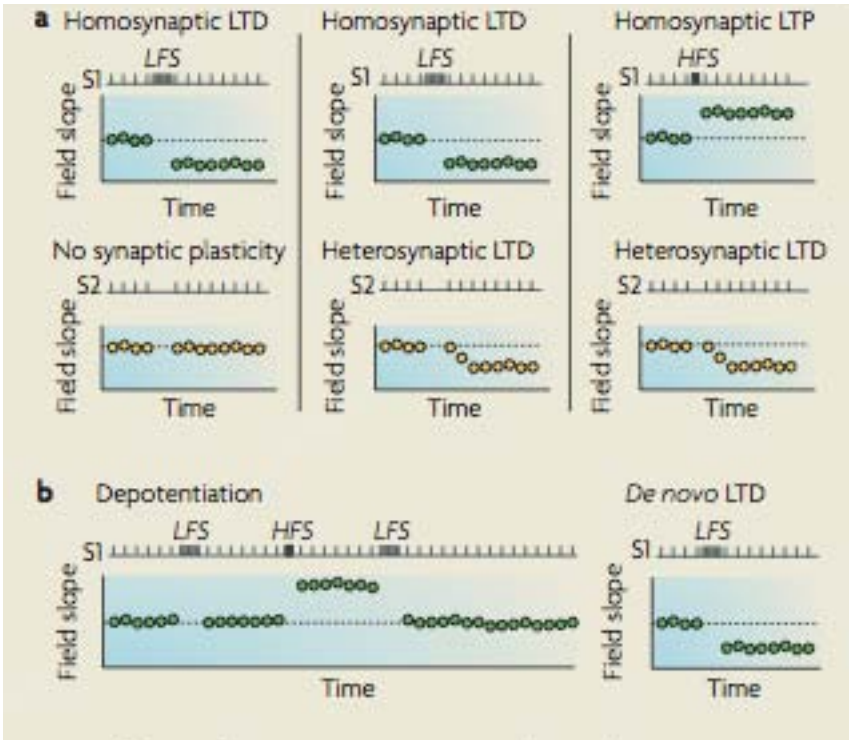
LTP is complemented by LTD

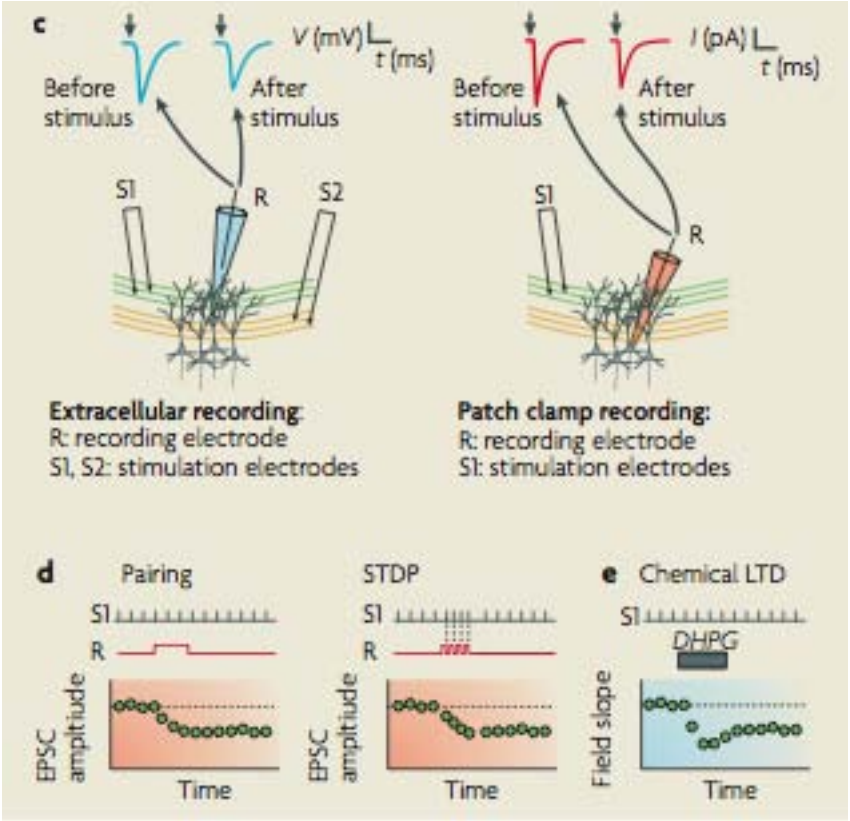


Also Ca^{2+}-dependent!

Dudek and Bear, 1992

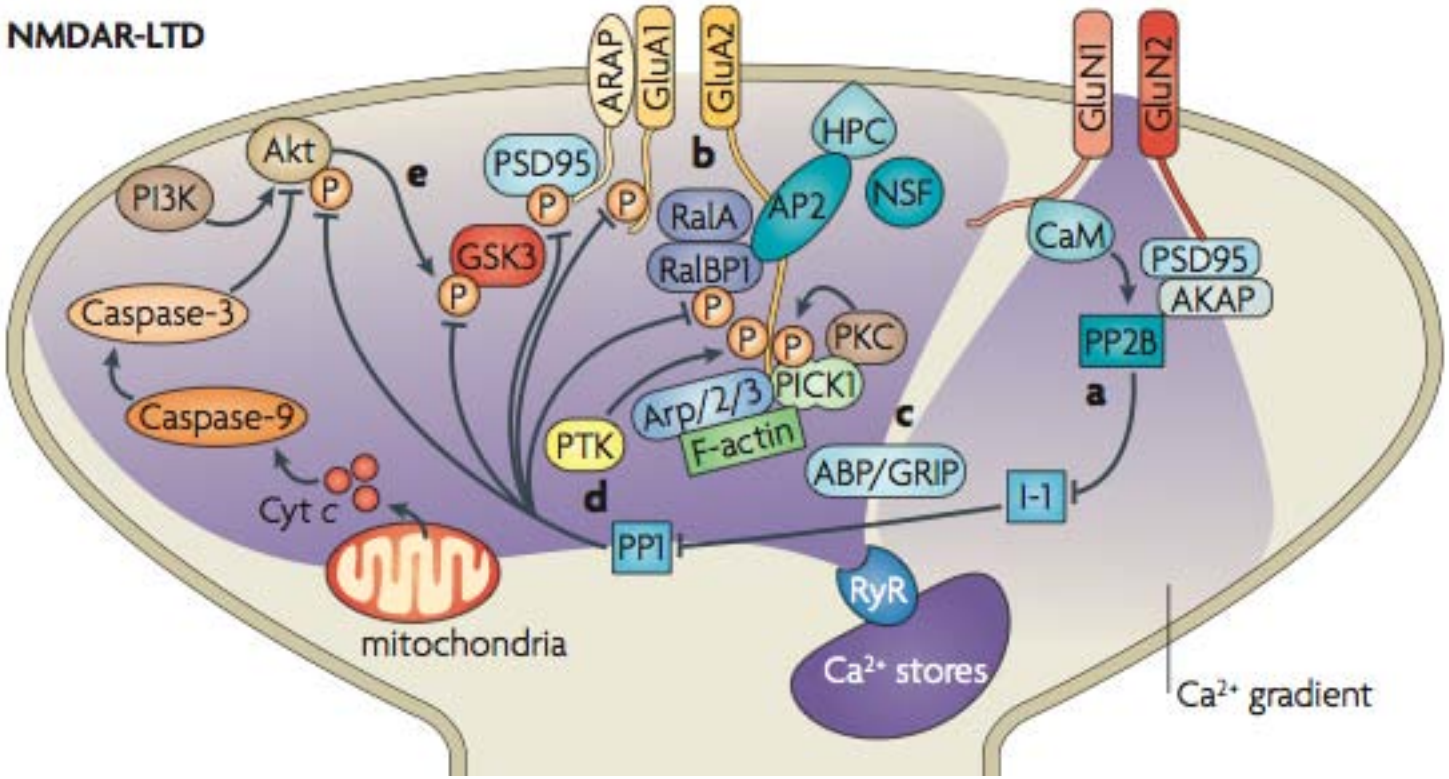
LTD has many forms





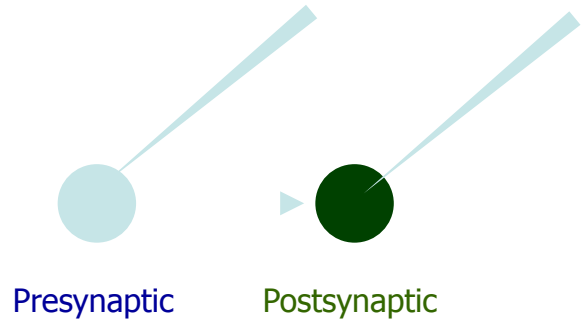
Collingridge et al. (2010) *Nature Rev Neurosci* 11: 459-473

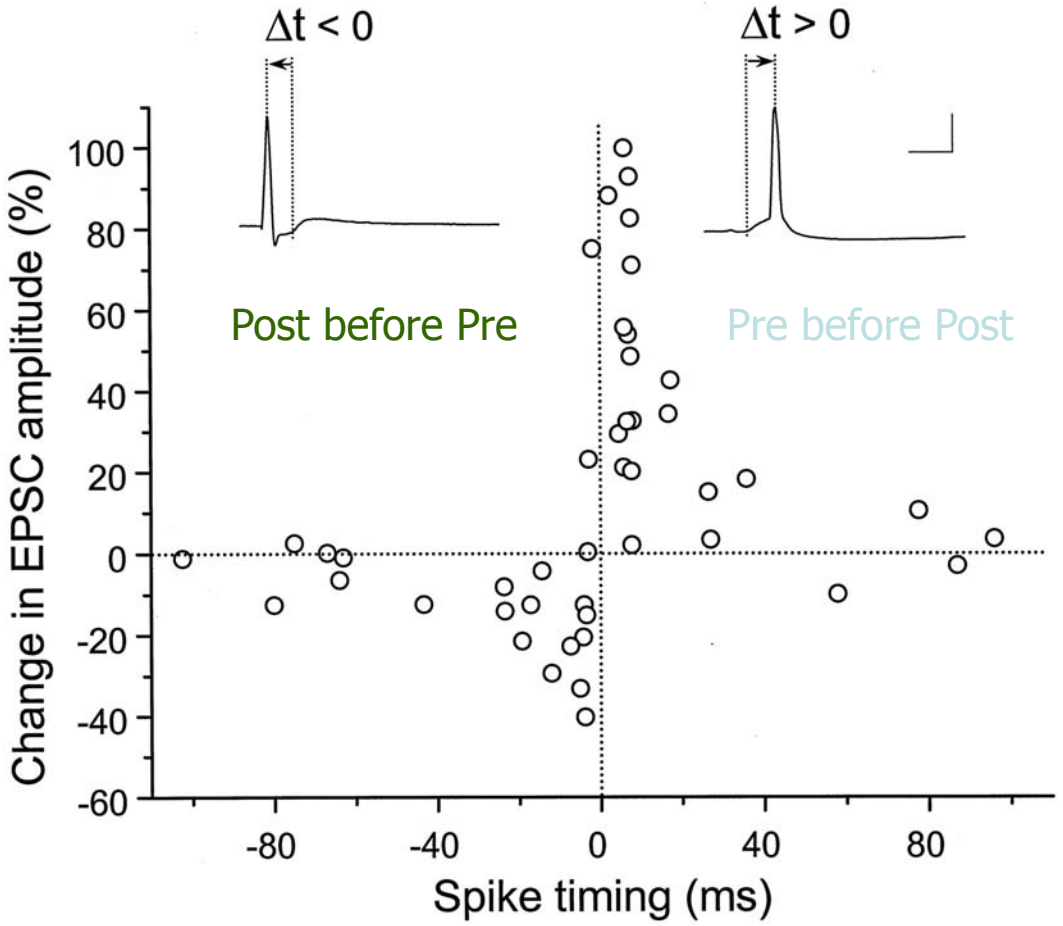
NMDA-dependent LTD



Collingridge et al. (2010) *Nature Rev Neurosci* 11: 459-473

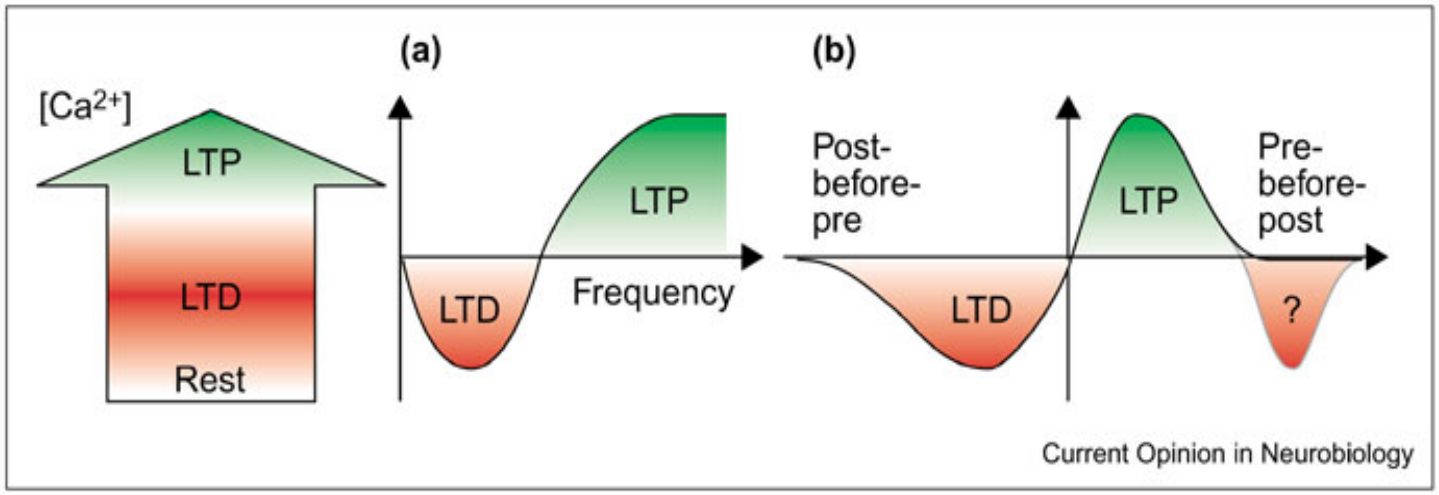
Spike-timing-dependent plasticity





Bi and Poo (1998) *J Neurosci* 18:10464-10472

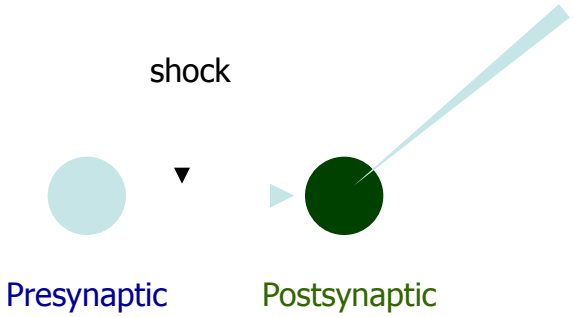
The Ca^{2+}-level hypothesis

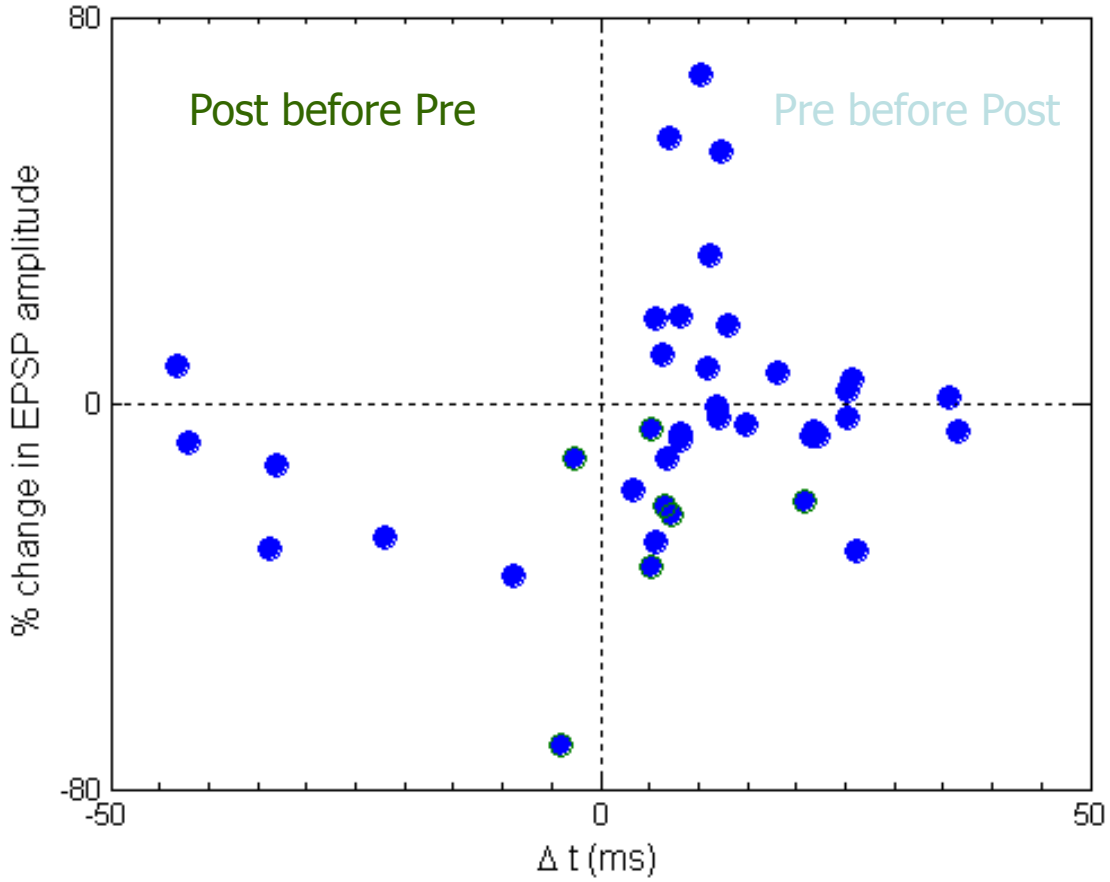


Sjöström and Nelson 2002

1. Can potentially explain both "traditional" LTP/LTD and STDP
2. A "sliding threshold" rule can provide network stability (http://www.scholarpedia.org/article/BCM_rule)

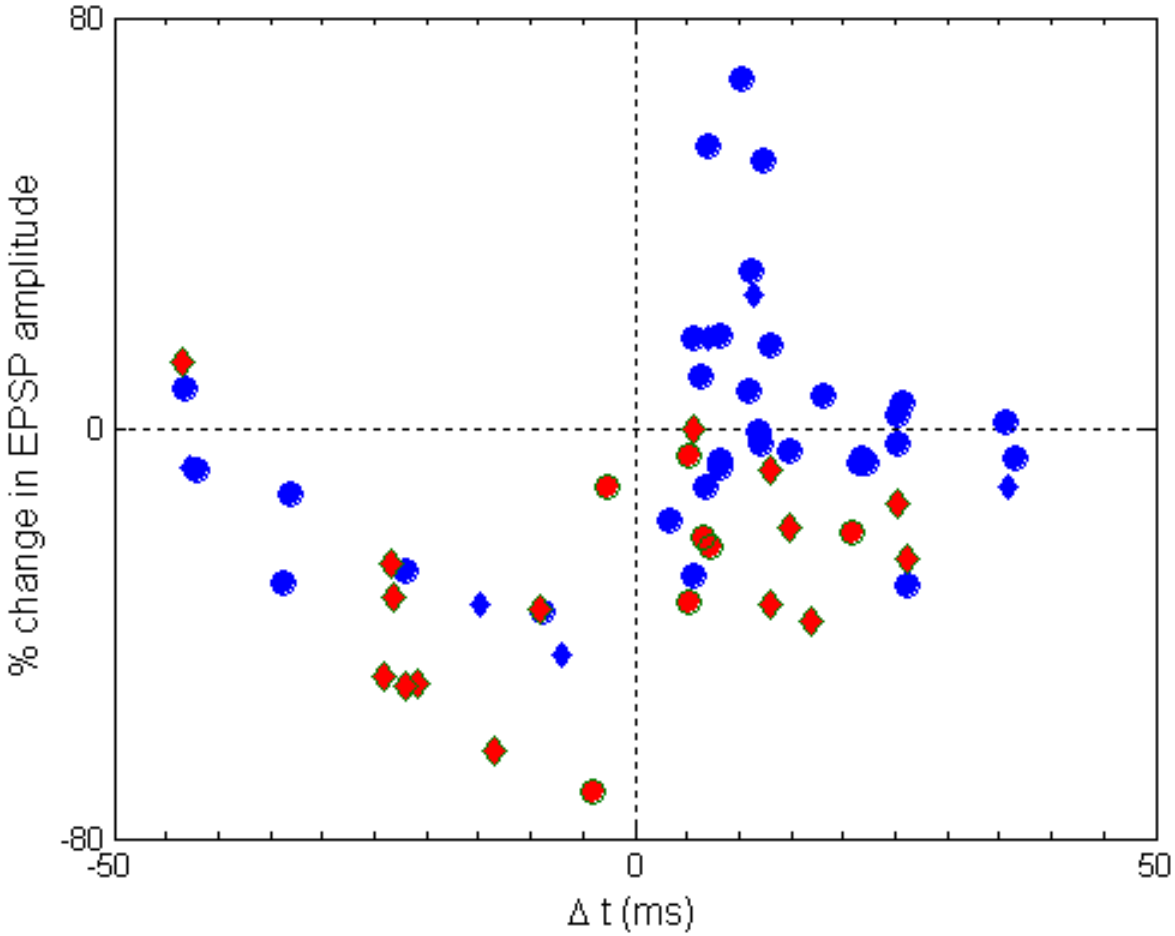
STDP in the entorhinal cortex





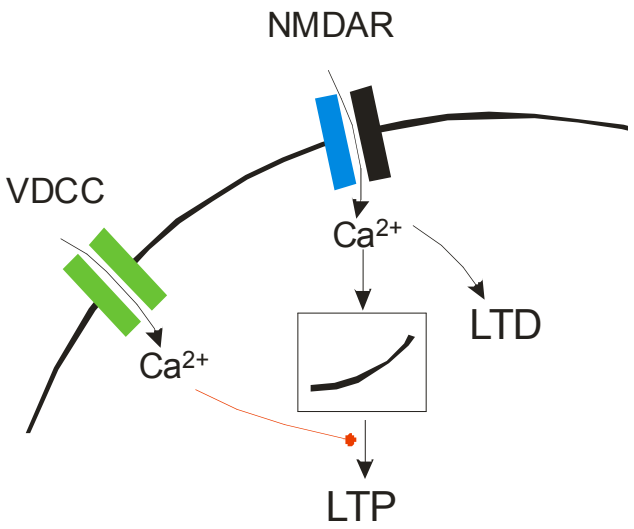
Zhou et al. (2005) *PNAS* 102: 19121-19125

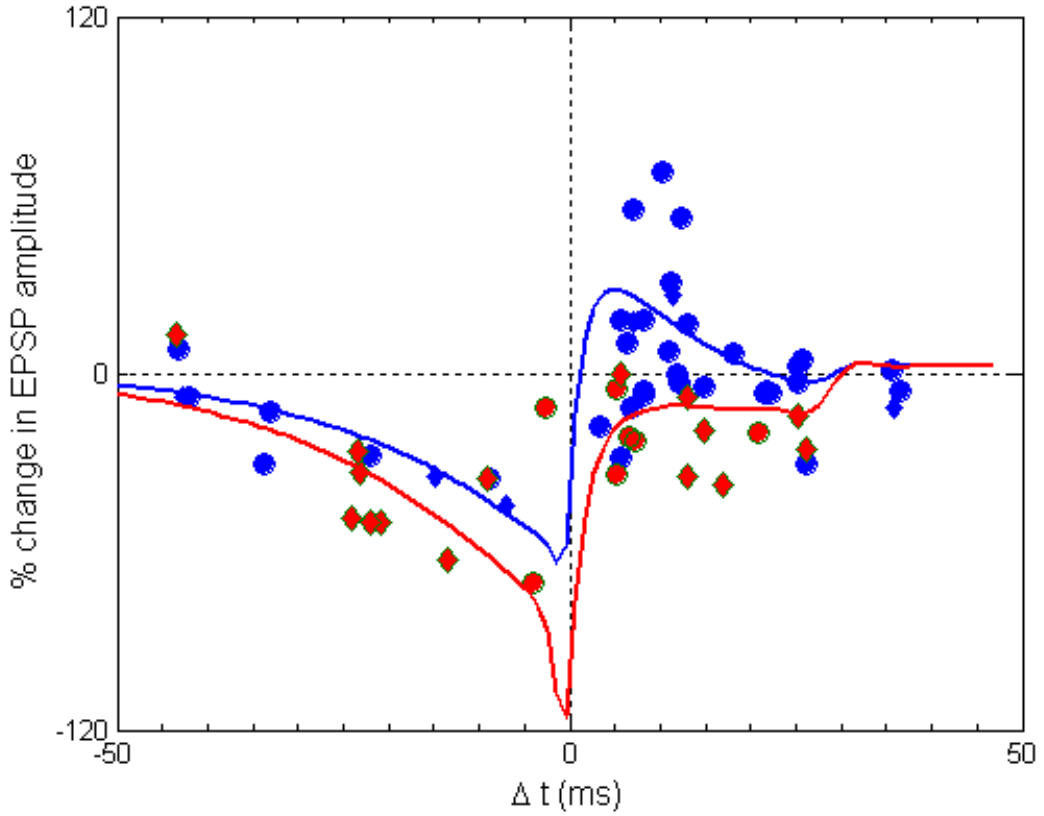
Broader spikes (and larger Ca^{2+} transients) lead to enhanced LTD



Zhou et al. (2005) *PNAS* 102: 19121-19125

A Ca^{2+}-feedback model can account for our data



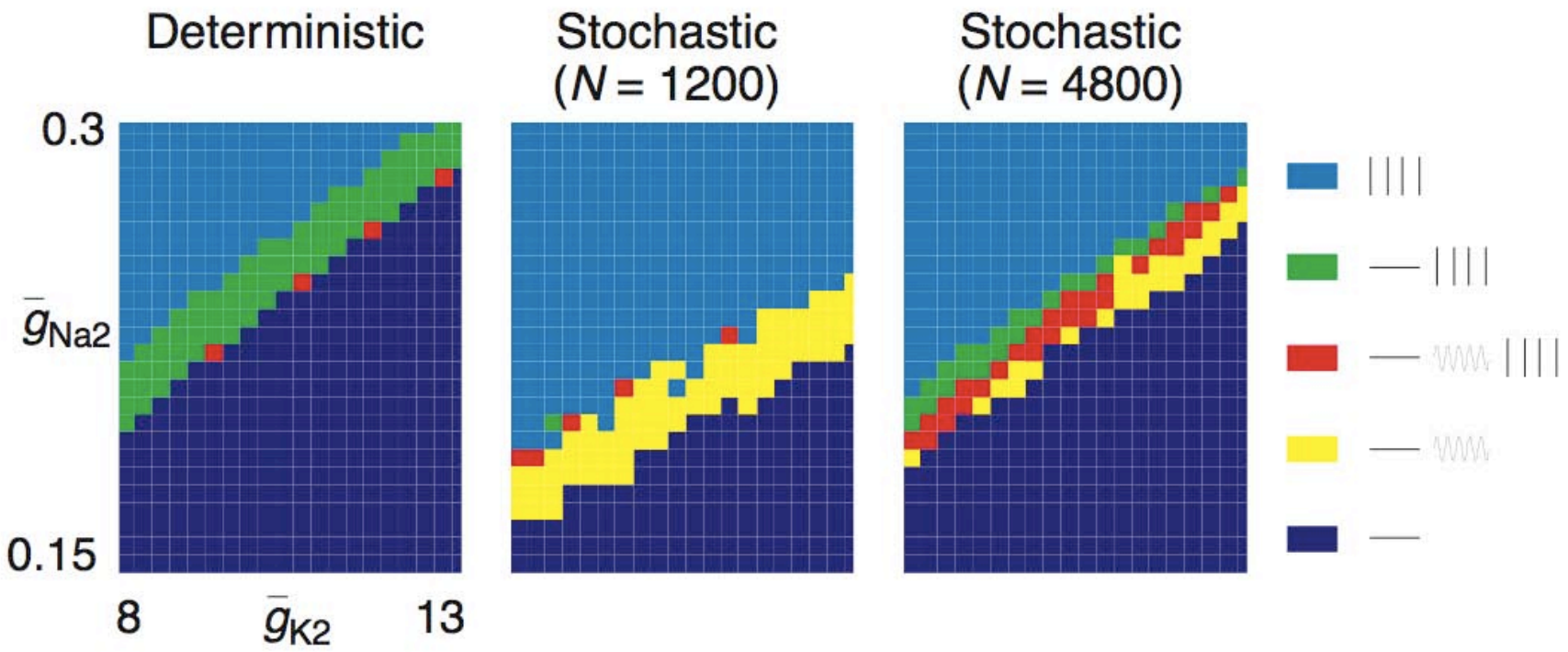


Zhou et al. (2005) *PNAS* 102: 19121-19125

Other important issues in long-term synaptic plasticity

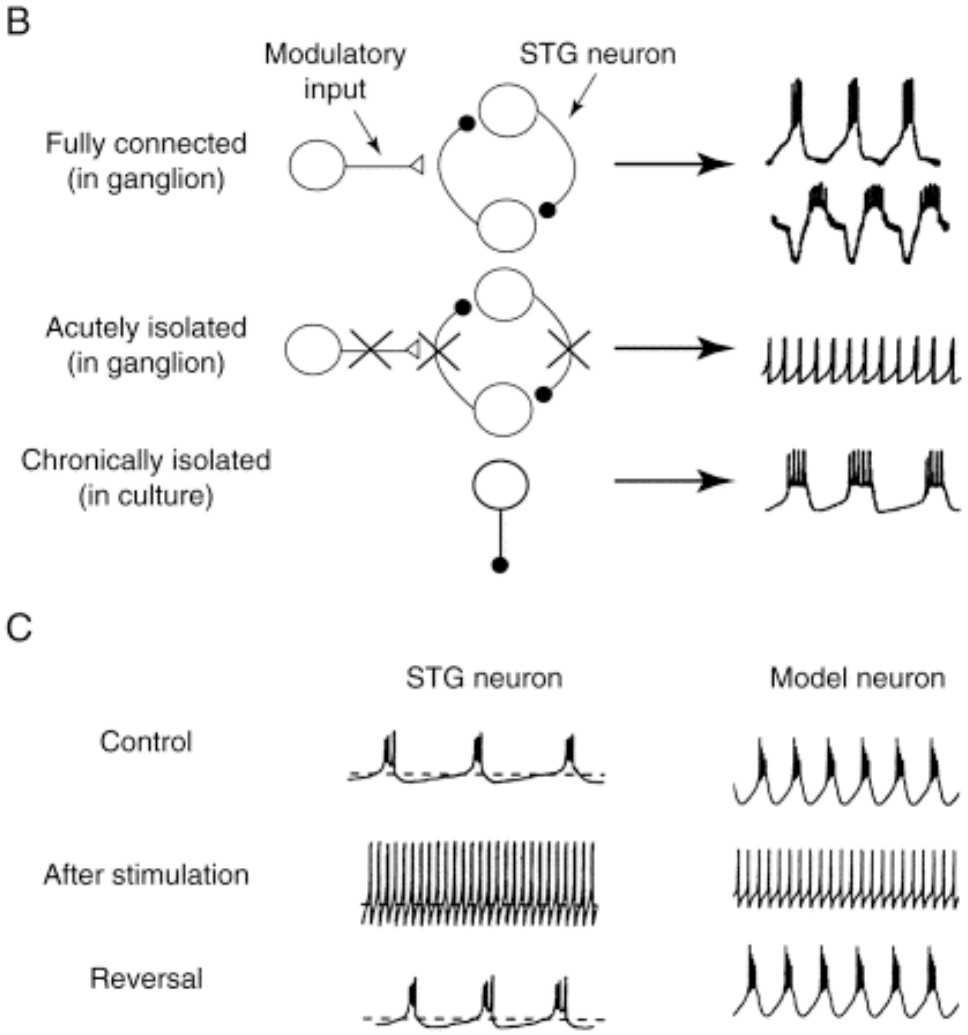
1. Is LTP/LTD/STDP really responsible for learning?
2. There appear to be many different forms of LTP in different cell types, at different synapses, and with different stimulus protocols
3. Where does the protein synthesis occur?
4. What about inhibition?
5. What about changes in excitability?

Models can be picky about their parameters



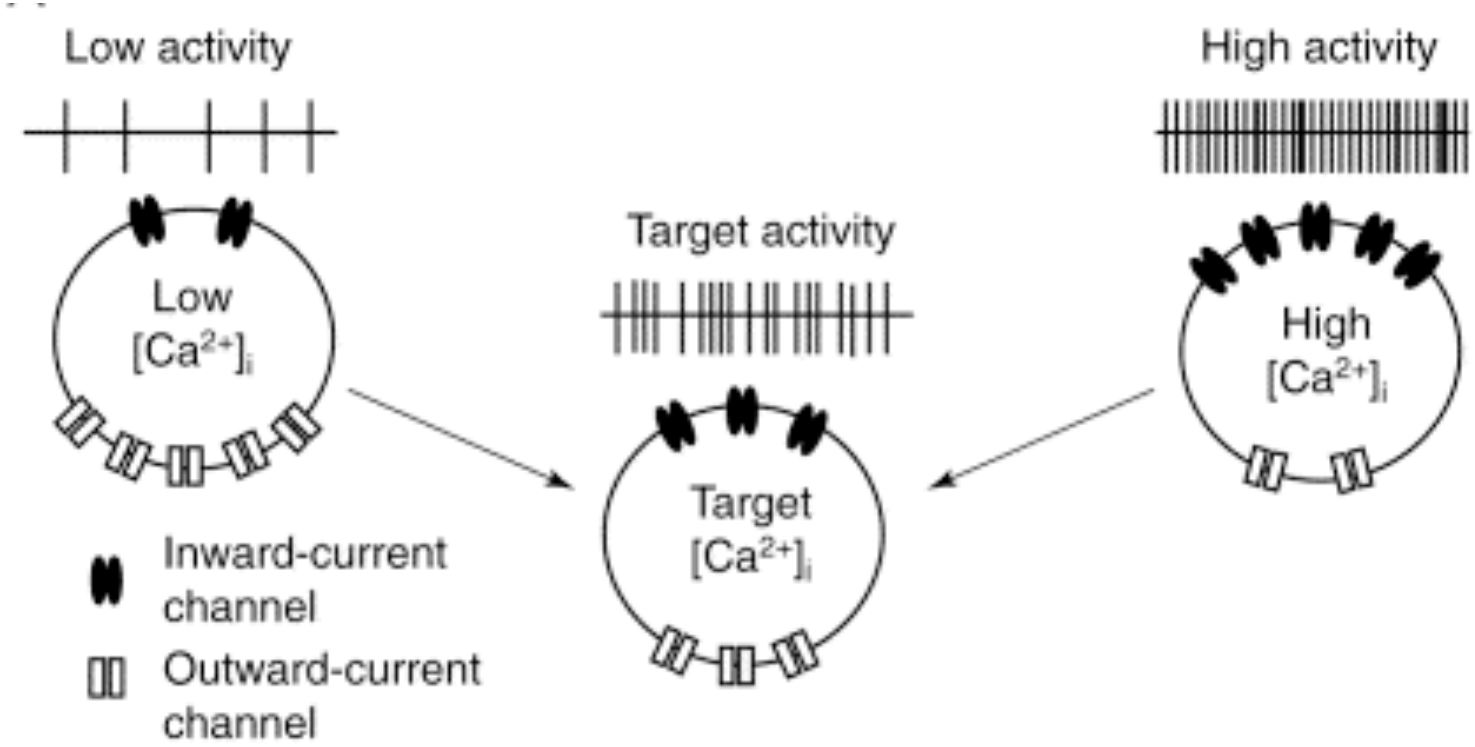
White et al. (2000) *Trends Neurosci* 23: 131-137

Cultured neurons "tune" their properties



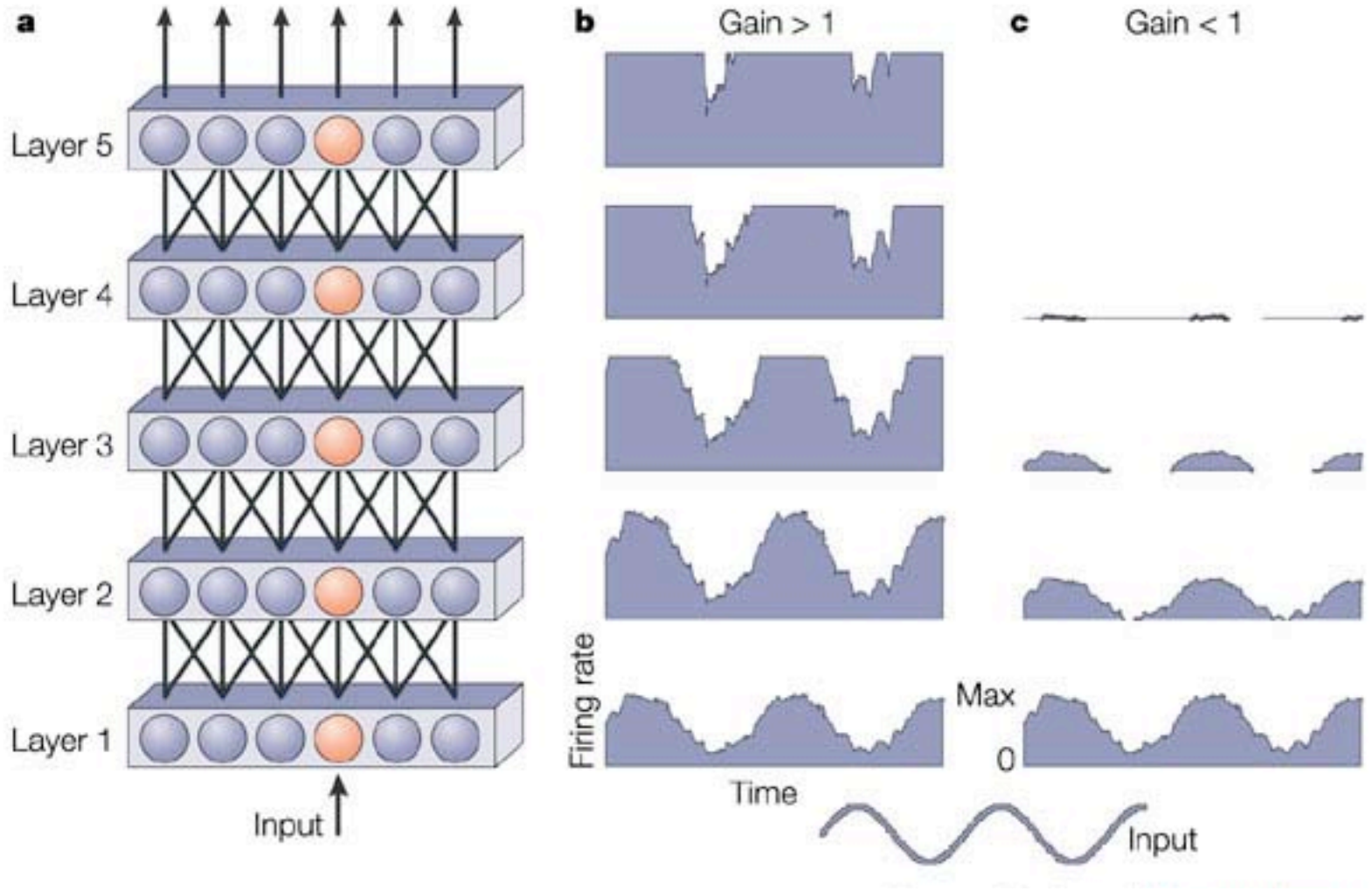
Turrigiano (1999) *Trends Neurosci* 22: 221-227

Calcium -- all things to all neurons?



Turrigiano (1999) *Trends Neurosci* 22: 221-227

The need for synaptic tuning

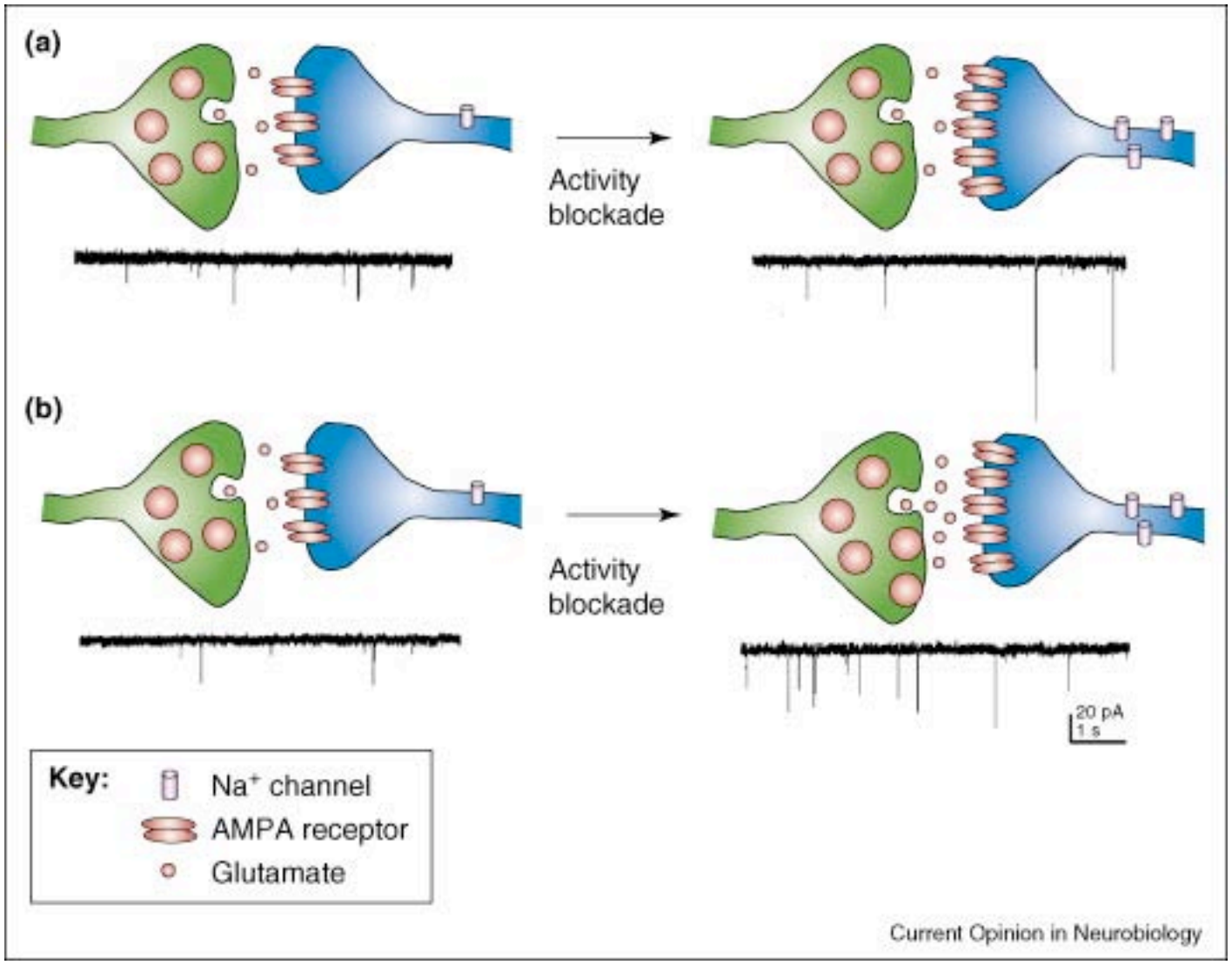


Turrigiano (2004) *Nature Rev Neurosci* 5: 97-107

Synaptic scaling

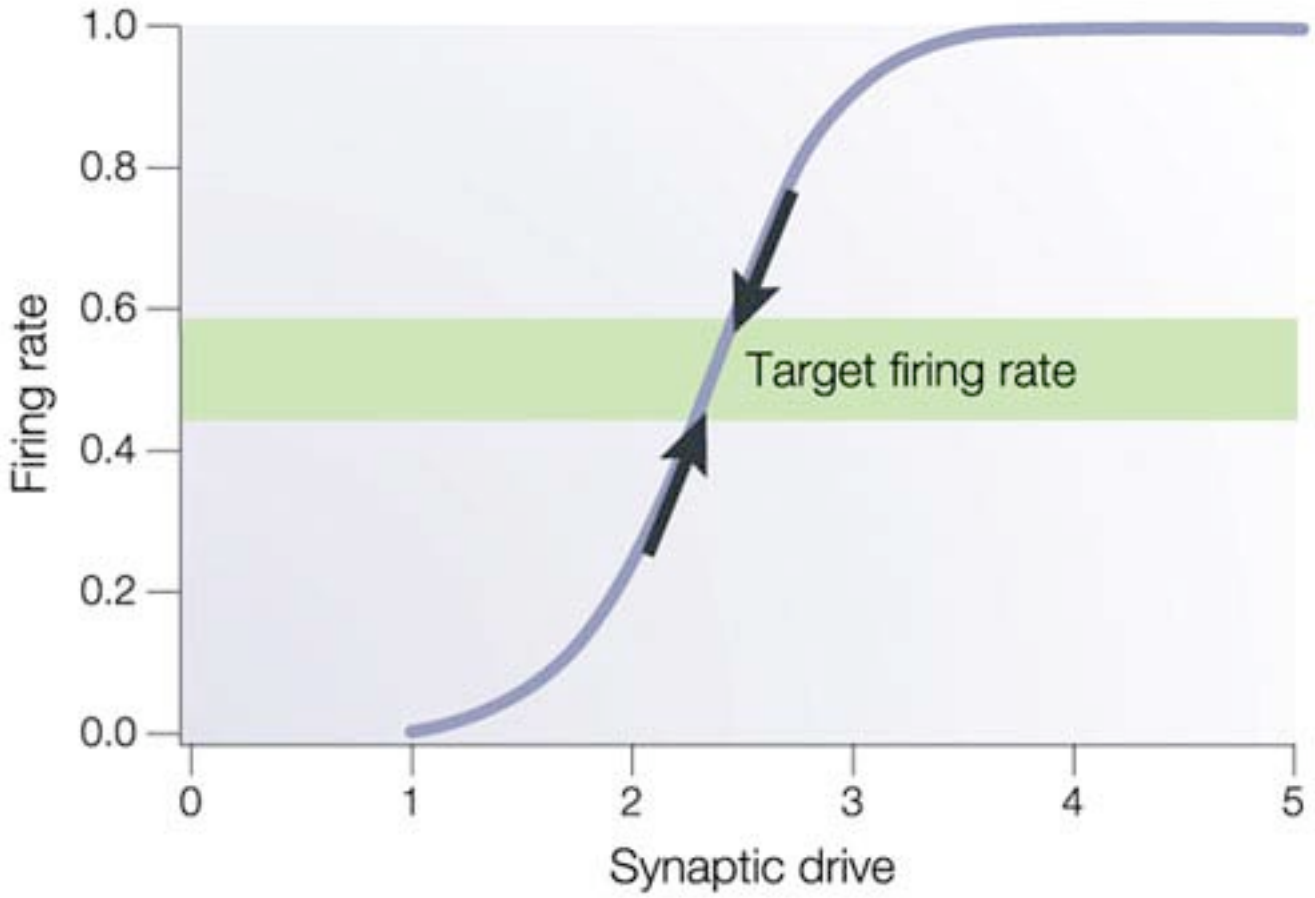
< 2.5 weeks in culture

> 2.5 weeks in culture



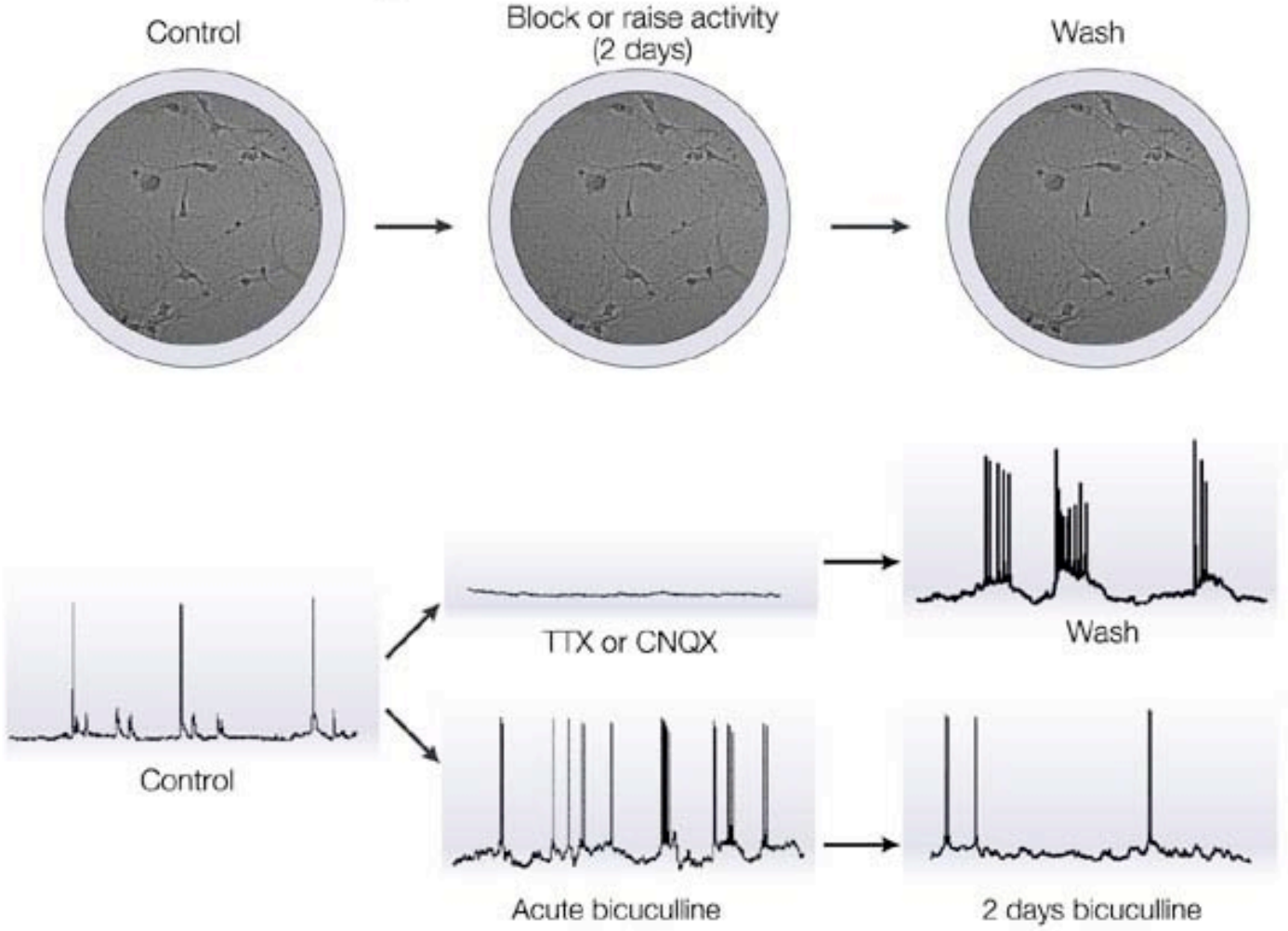
Turrigiano (2007) *Curr Opin Neurobiol* 22: 221-227

Finding the right rate



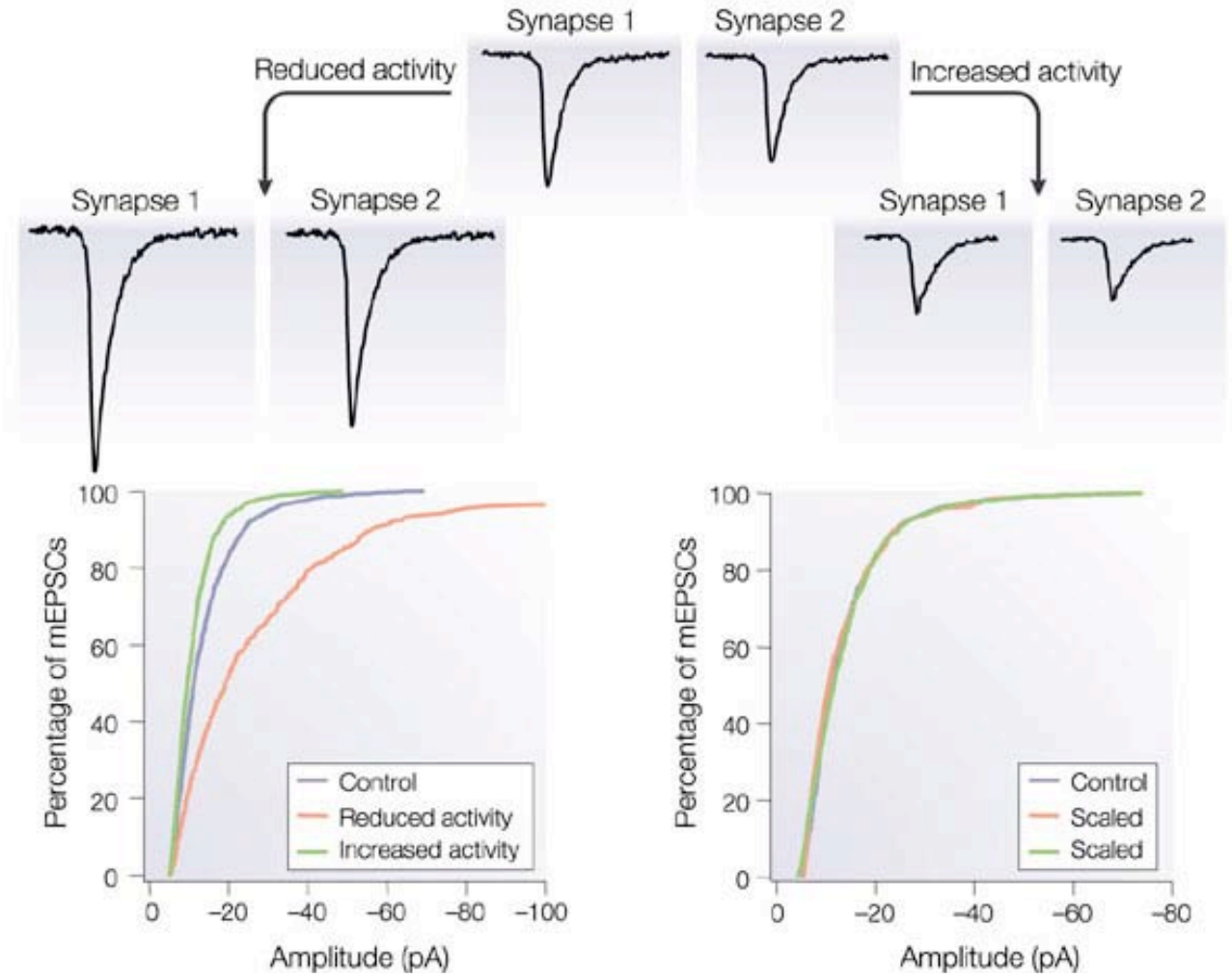
Turrigiano (2004) *Nature Rev Neurosci* 5: 97-107

Firing-rate homeostasis in synaptically coupled networks



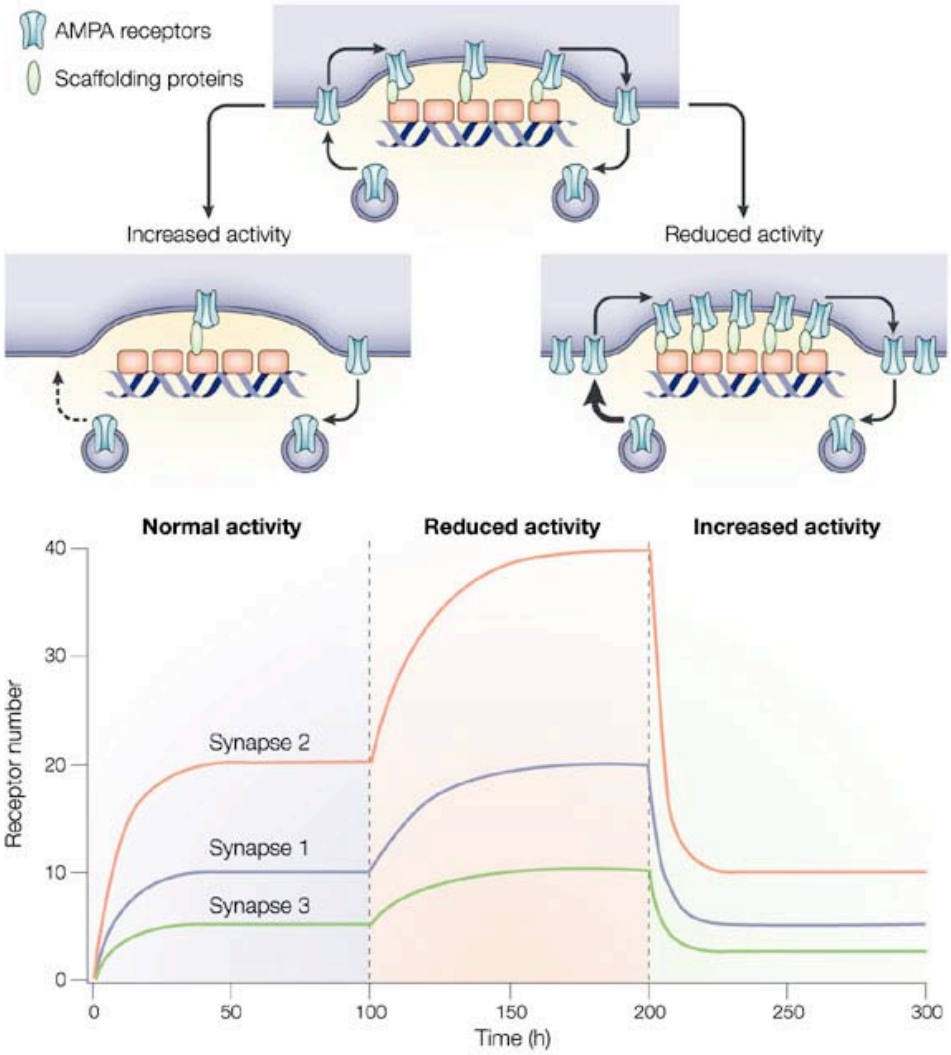
Turrigiano (2004) *Nature Rev Neurosci* 5: 97-107

Relative synaptic weights are maintained with synaptic scaling



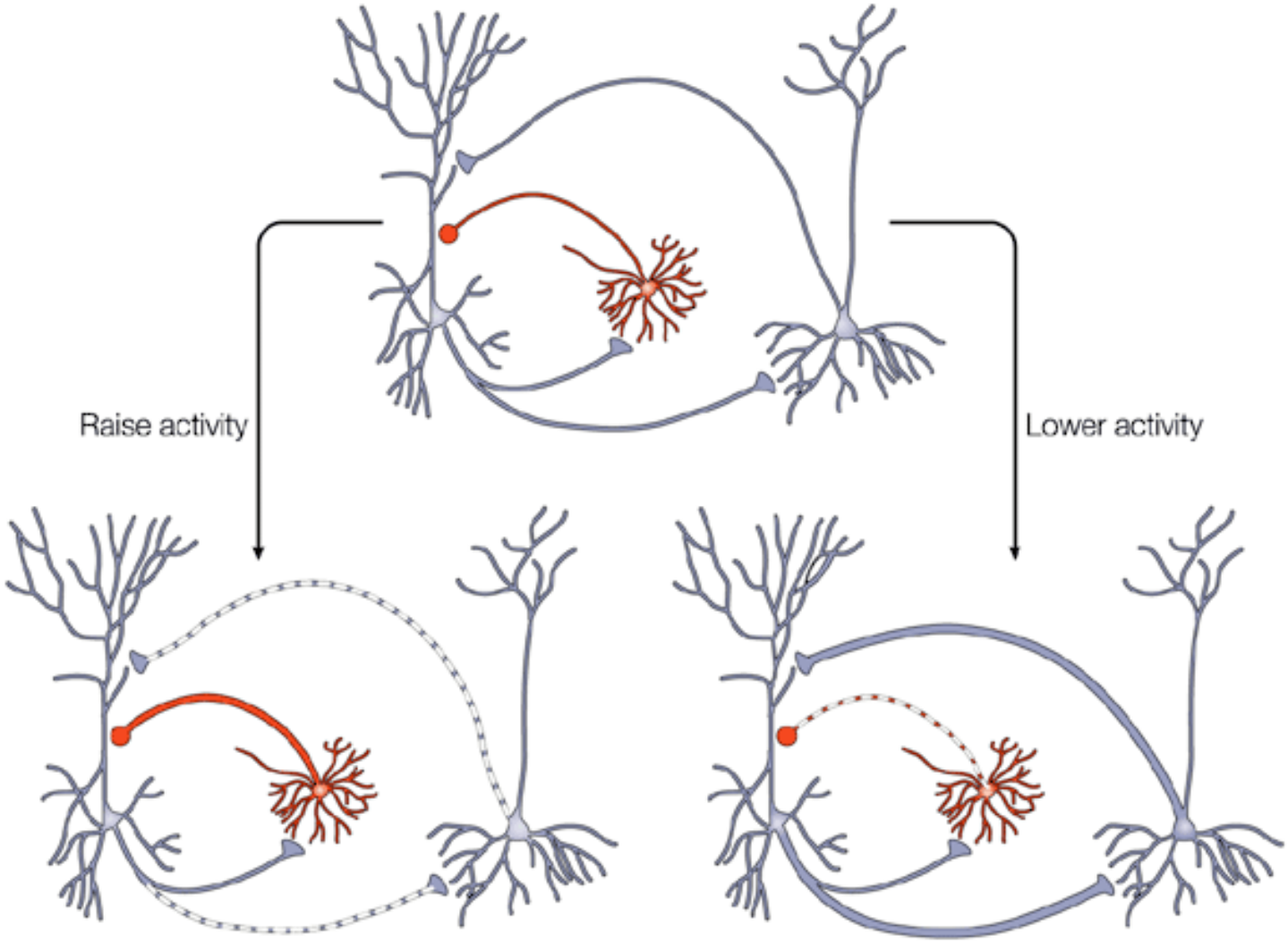
Turrigiano (2004) *Nature Rev Neurosci* 5: 97-107

AMPA insertion and deletion rates are modulable



Turrigiano (2004) *Nature Rev Neurosci* 5: 97-107

Anatomical connections are modulable



Turrigiano (2004) *Nature Rev Neurosci* 5: 97-107