Synaptic Plasticity : Spike-timing dependent plasticity (STDP)

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slides : http://www.biomedicale.univ-paris5.fr/~mgraupe/stdp/

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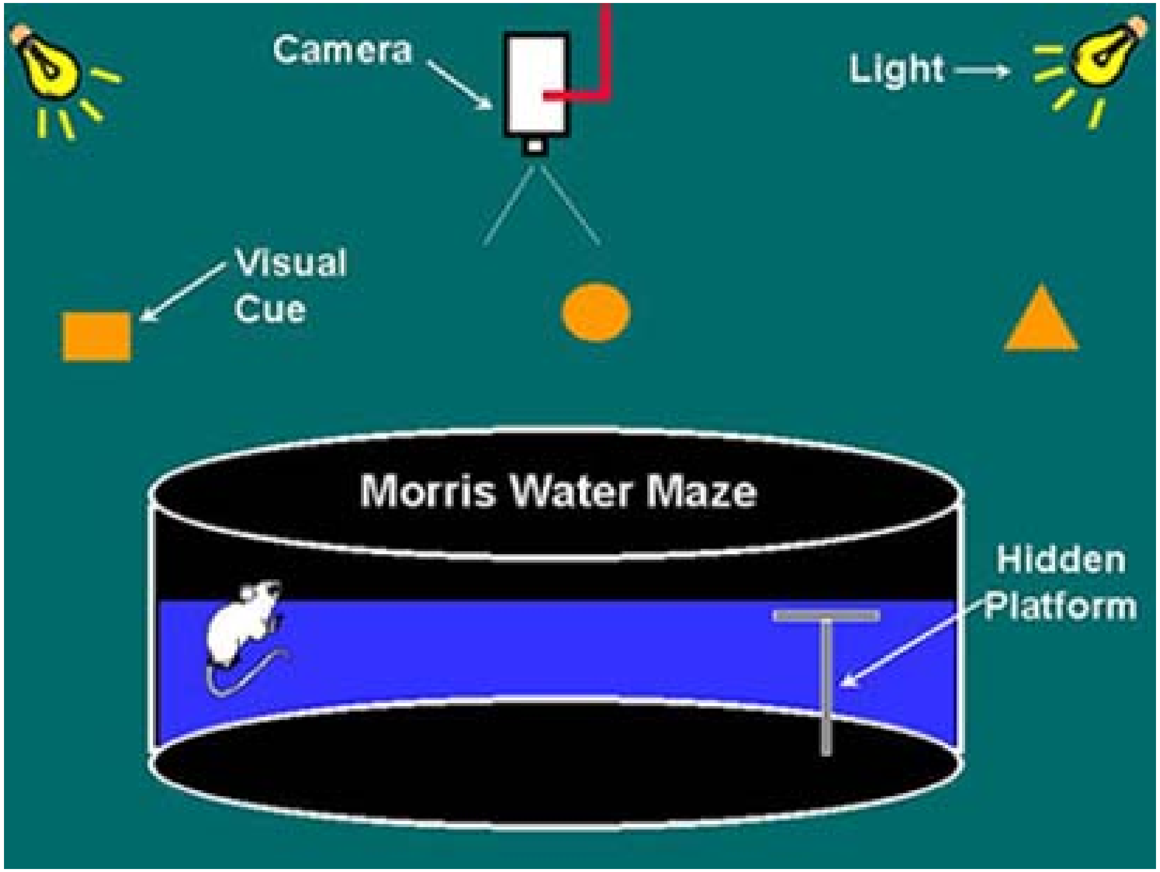
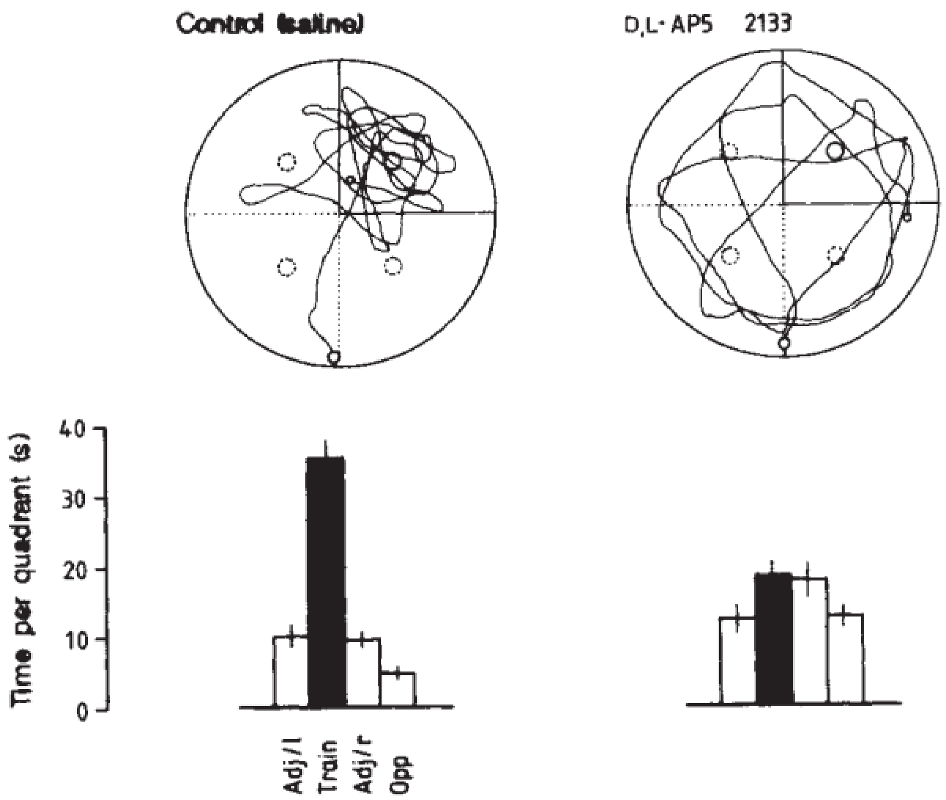
Why are we interested in synaptic plasticity ?



[Morris *et al.*, 1986]

Relation between LTP and learning/memory



- NMDA receptor required to learn platform location [Morris *et al.*, 1986]
- NMDA receptor required to form spatial memories (place fields)

[McHugh *et al.* 1996]

Outline : STDP ... spike-timing dependent plasiticity

1. STDP : introduction and history
2. Phenomenology of STDP
3. Induction mechanisms
4. Biophysical models of STDP
5. STDP *in vivo*

Outline

1. STDP : introduction and history
2. Phenomenology of STDP
3. Induction mechanisms
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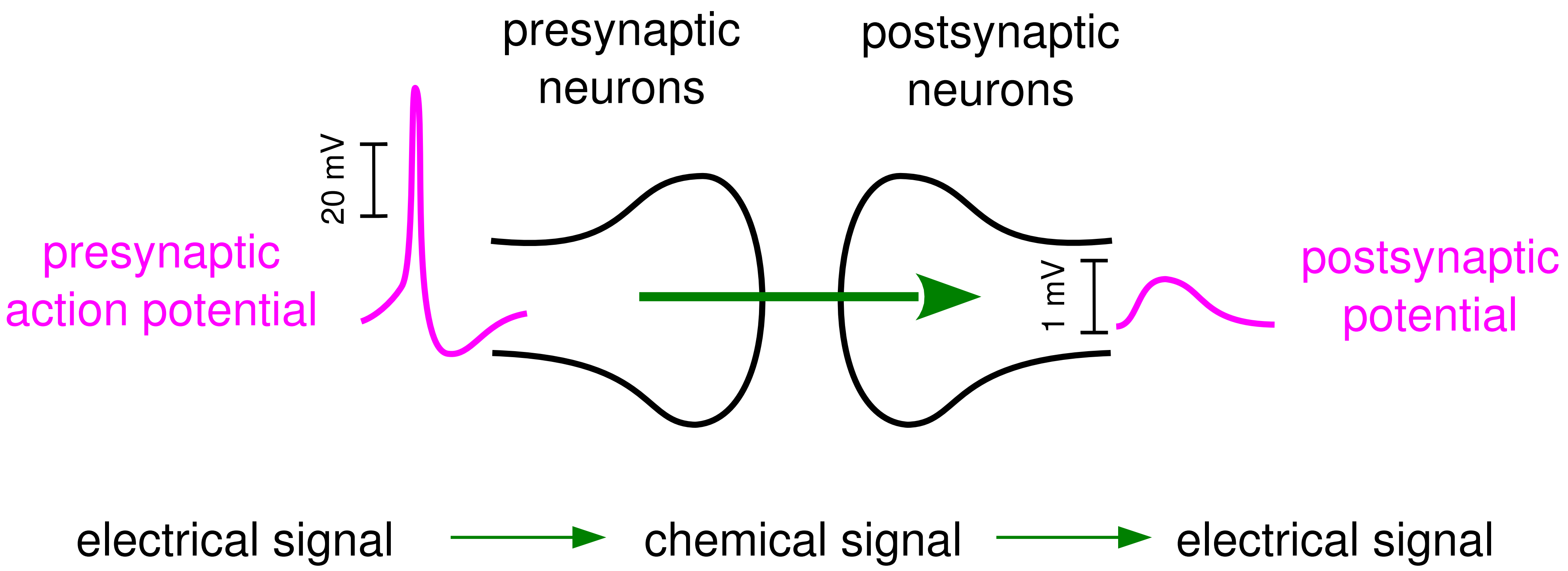
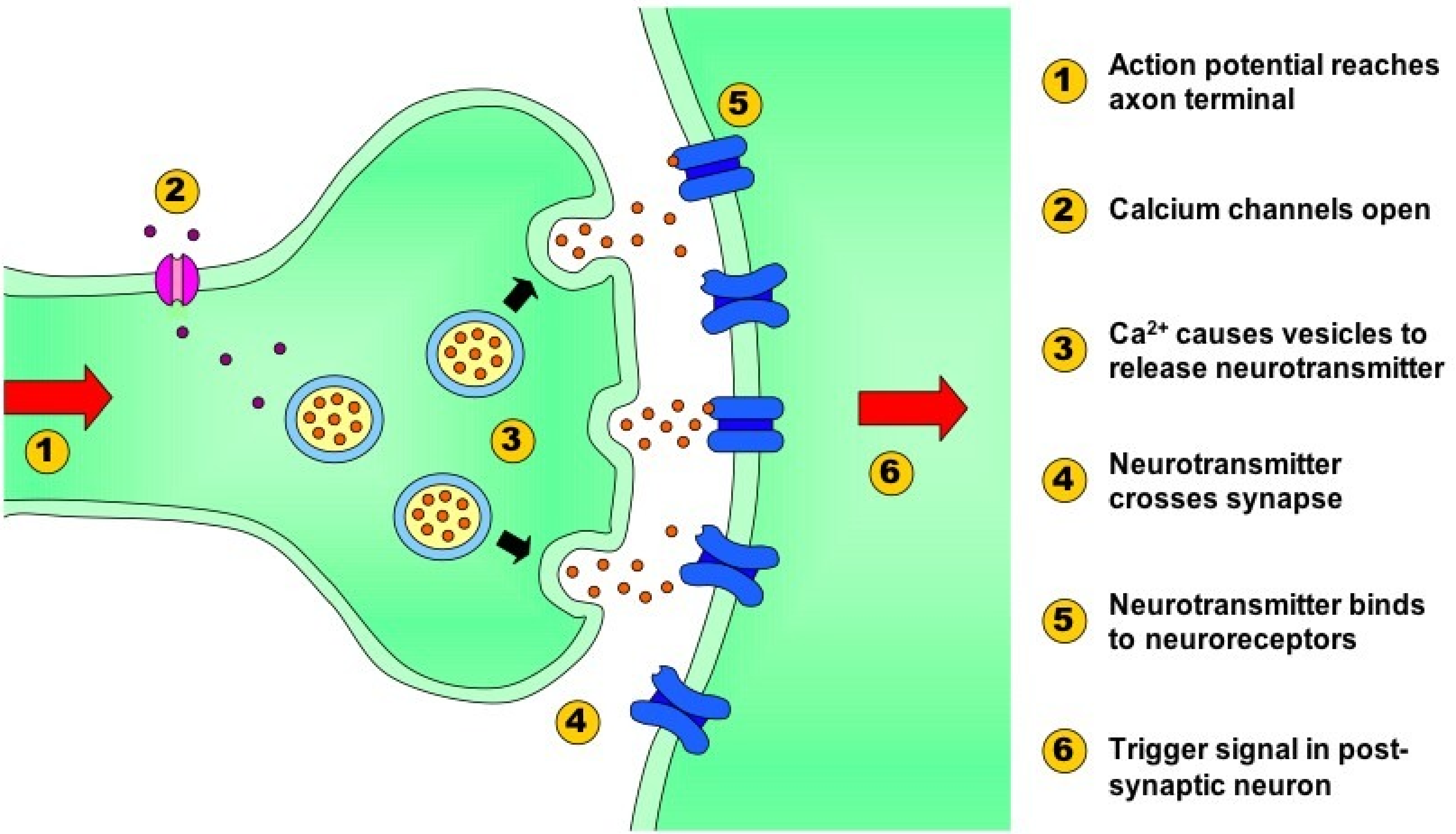
Chemical synapse : transmits electrical signals



- directional transmission
- conversion of signals allows for flexibility/plasticity

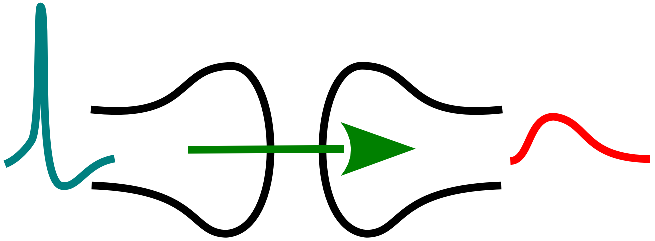
Chemical synapse : underlying biological machinery



http://outreach.mcb.harvard.edu/animations/synaptic.swf

Chemical synapse : excitatory or inhibitory

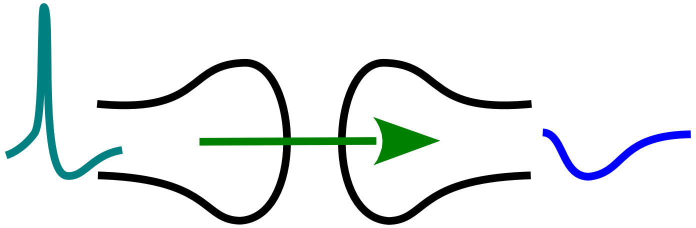
Excitatory synapse



depolarization:
excitatory postsynaptic potential (EPSP)

neurotransmitter	receptor
glutamate	AMPA, NMDA
acetylcholine	nAChR, mACHR
catecholamines	G-protein-coupled receptors
serotonin	5-HT_3, ...
histamine	G-protein-coupled receptors

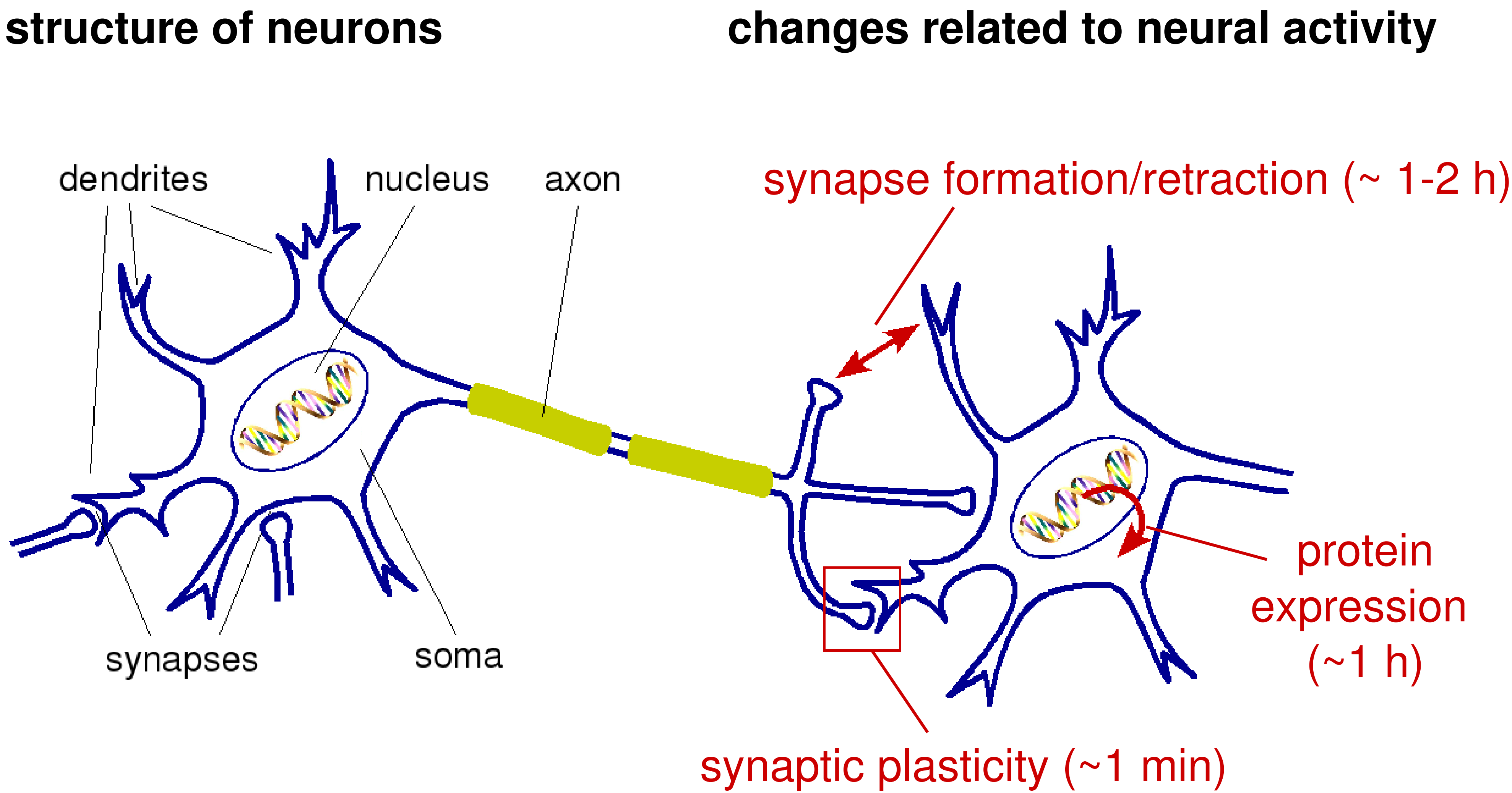
Inhibitory synapse



hyperpolarization:
Inhibitory postsynaptic potential (IPSP)

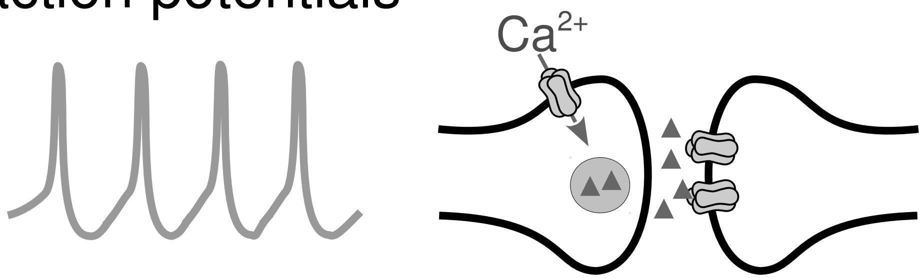
neurotransmitter	receptor
GABA	$GABA_A$, $GABA_B$
glycine	GlyR

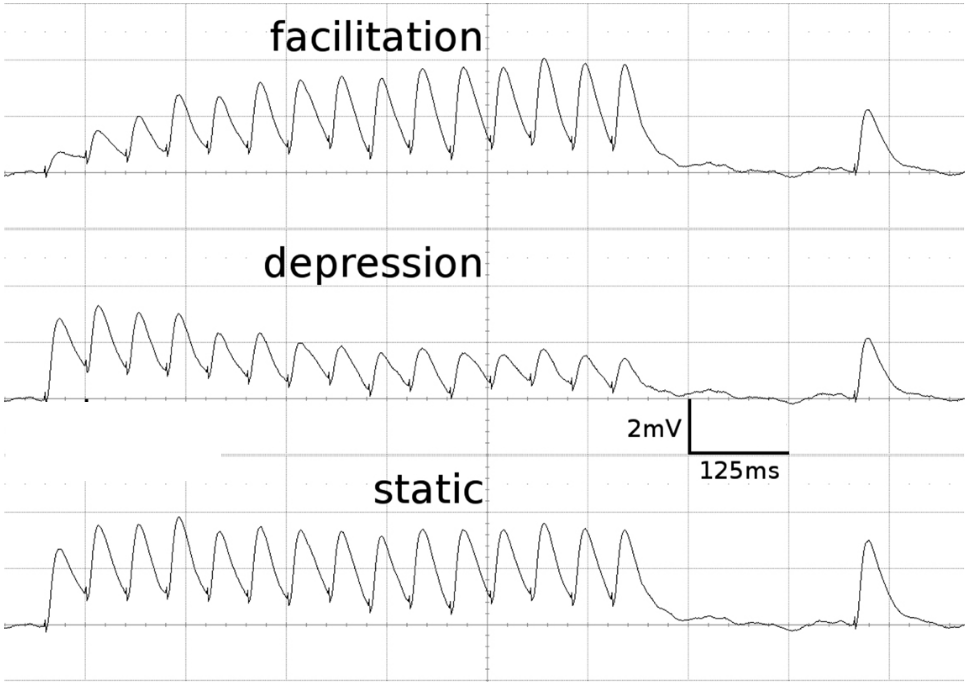
Different forms of plasticity



Short-term synaptic plasticity

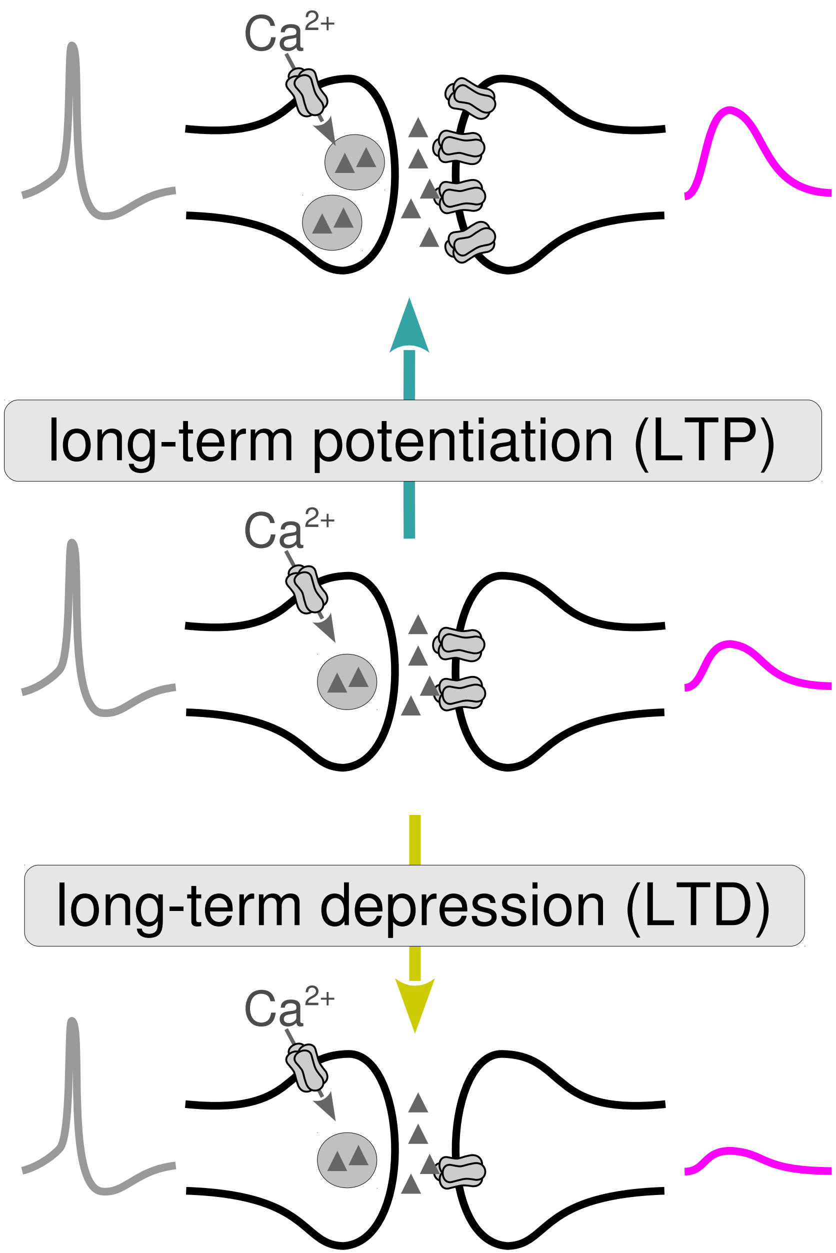
train of presynaptic action potentials





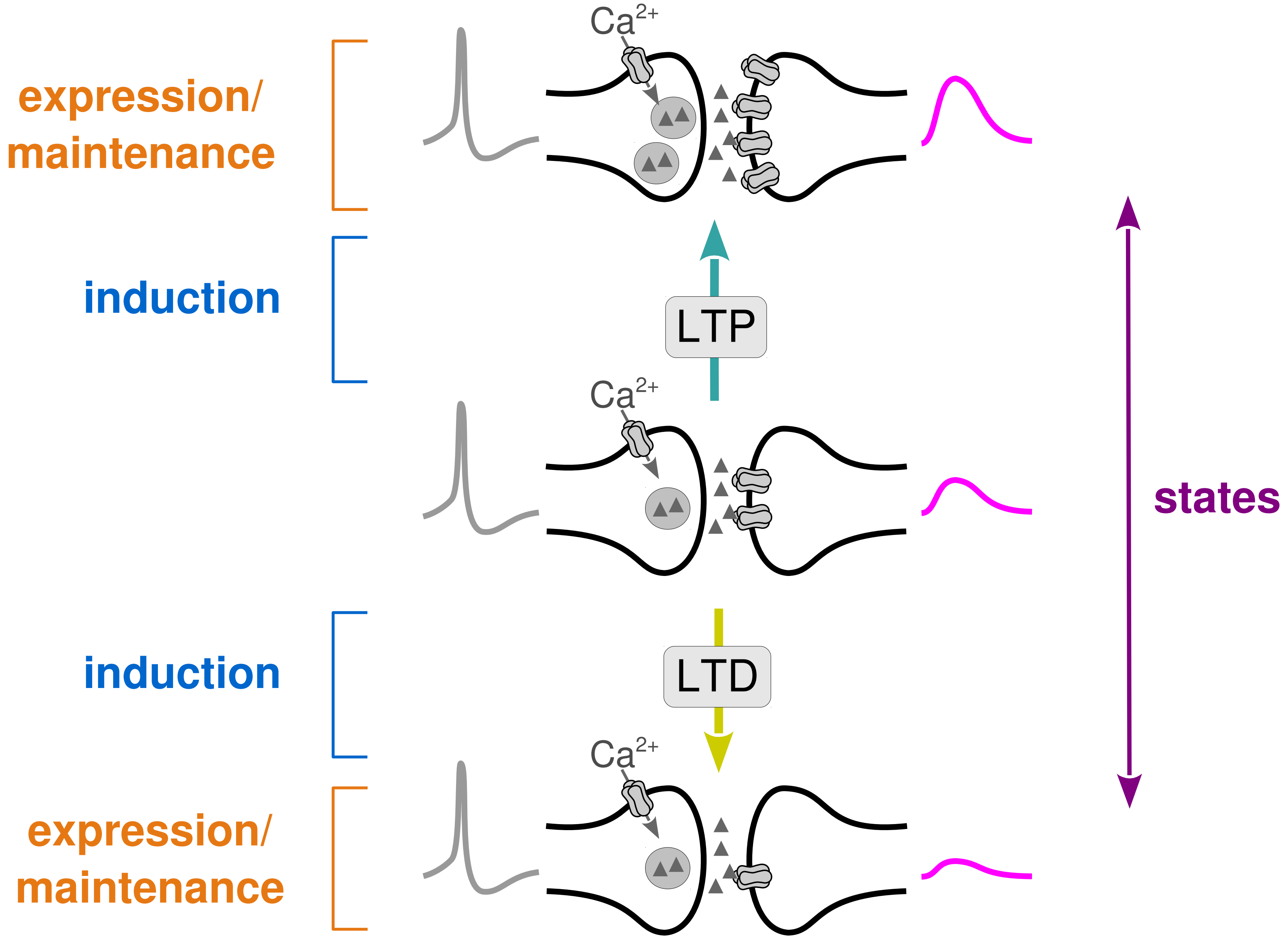
- transient change in transmission efficacy
- time scale of changes ~1 sec

Long-term synaptic plasticity

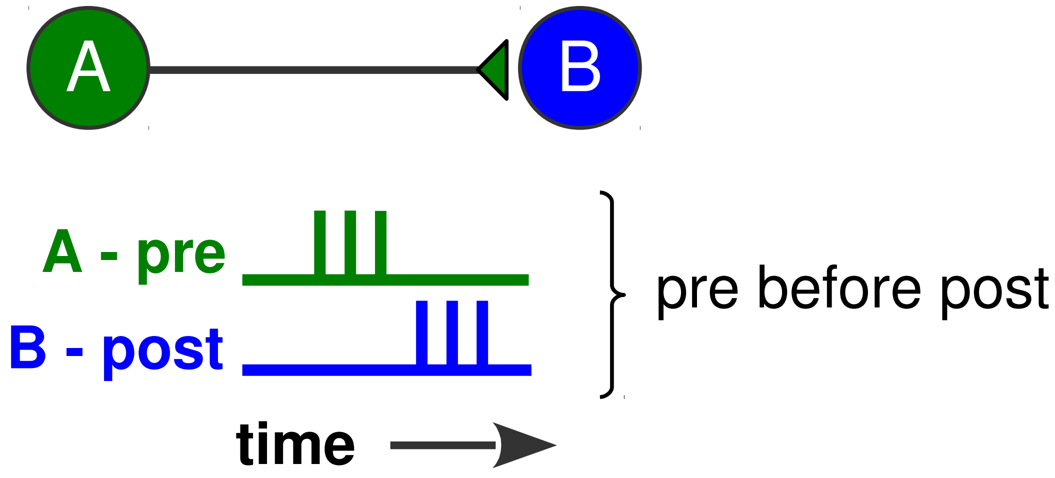


- long-lasting change (>60 min) in transmission efficacy
- time scale of induction ~ 1 min

Synaptic plasticity: induction, maintenance & states



LTP induction: early conceptual work

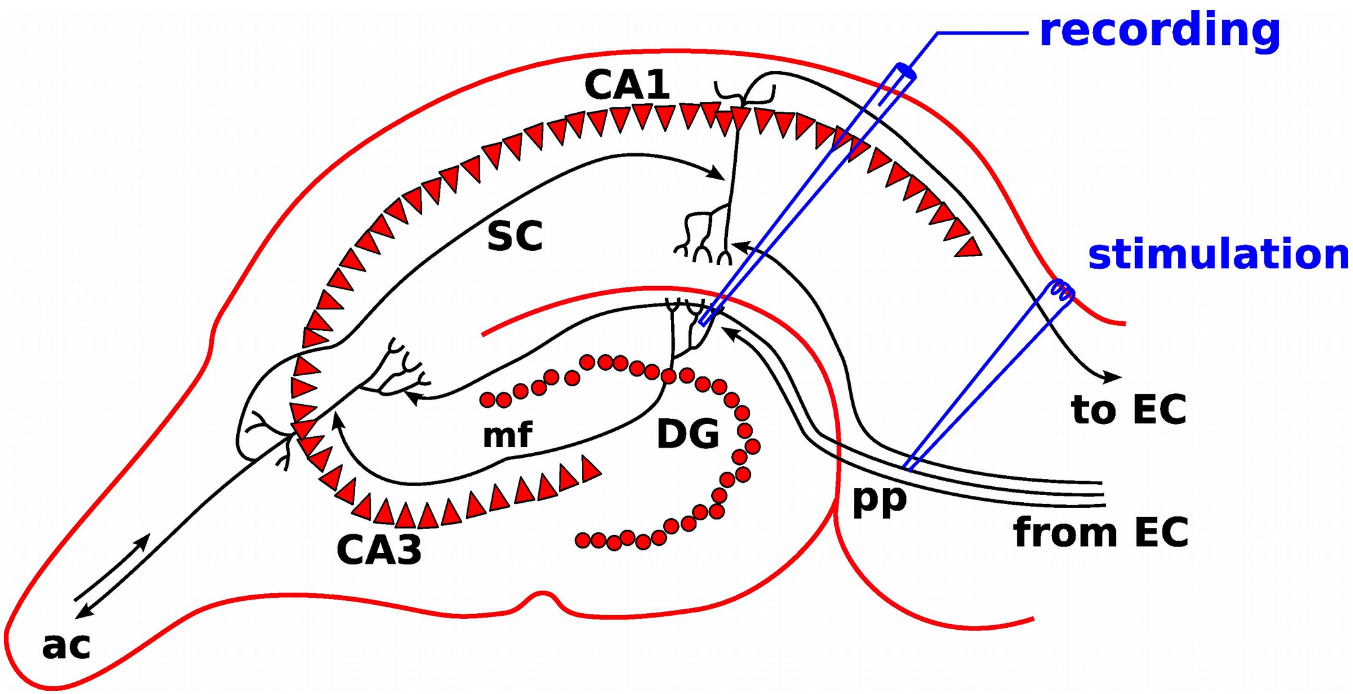


"When an axon of cell A is near enough to excite a cell B and *repeatedly* and *persistently* takes part in firing it, some growth or metabolic changes take place in one or both cells such that A's efficiency, as one of the cells firing B, is *increased.*"

[Hebb 1949;
see also Konorski 1948]

Induction: first experimental work in hippocampus

hippocampus

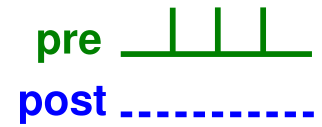


EC	...	enthorhinal cortex
DG	...	dentate gyrus
CA3/1	...	cornu ammonis 3/1

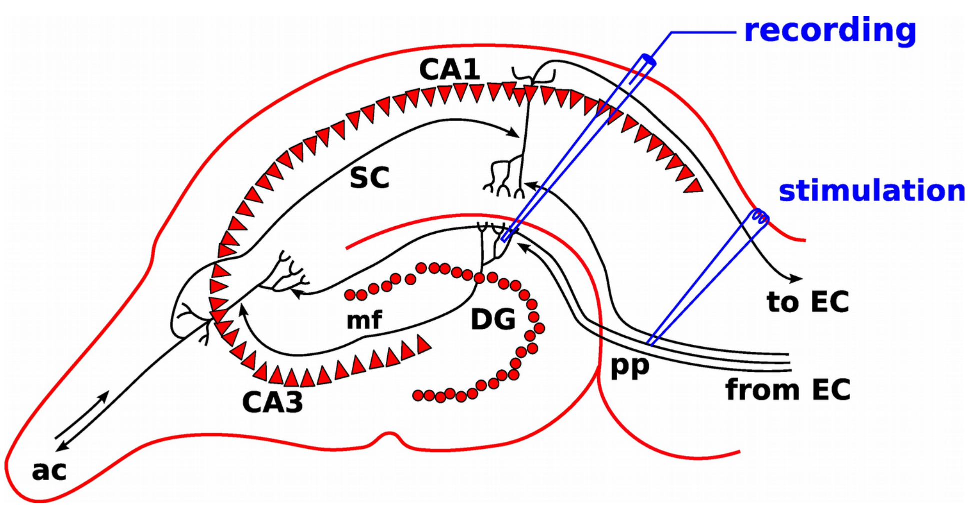
pp	...	perforant path
mf	...	mossy fibres
ac	...	associational commissural path
sc	...	Schaffer collateral

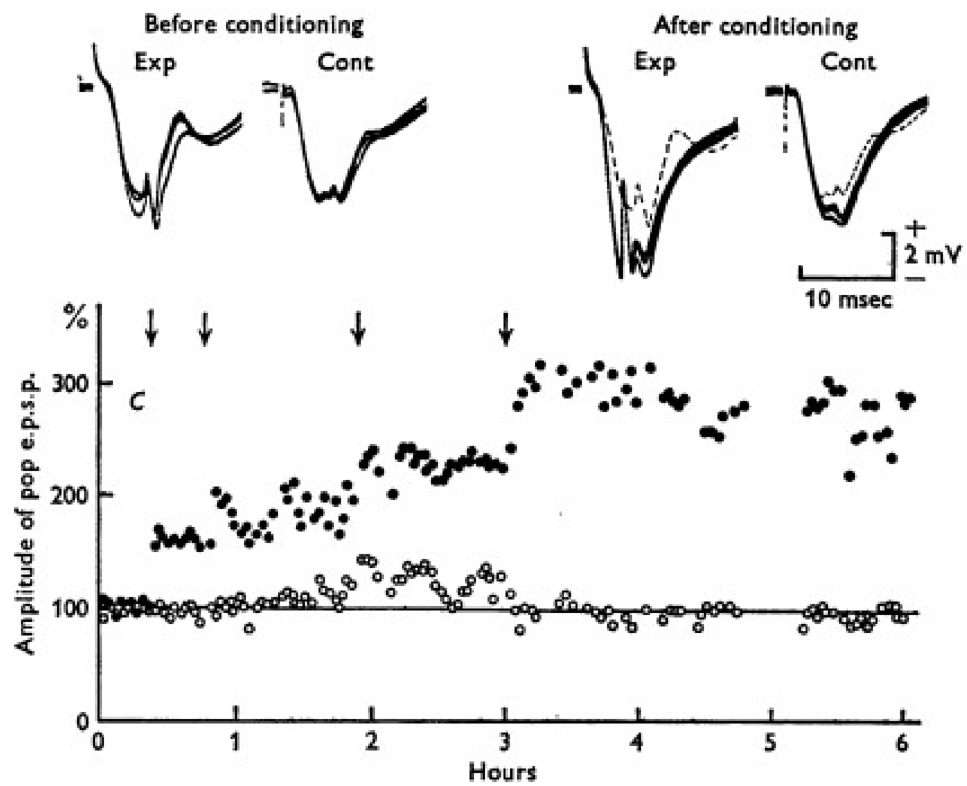
Induction: LTP through high frequency stimulation

hippocampus (in vivo)



10-20 Hz for 10-15 sec
or 100 Hz for 3-4 sec

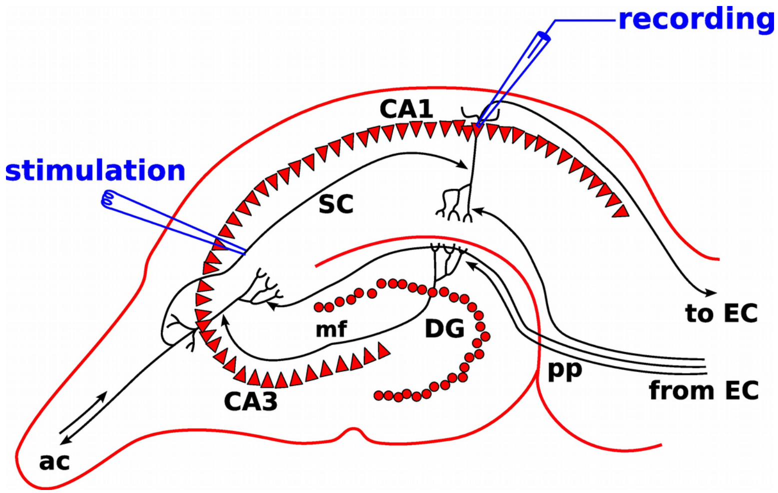


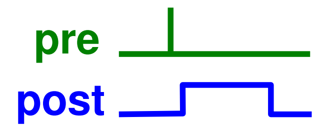


[Bliss and Lømo 1973]

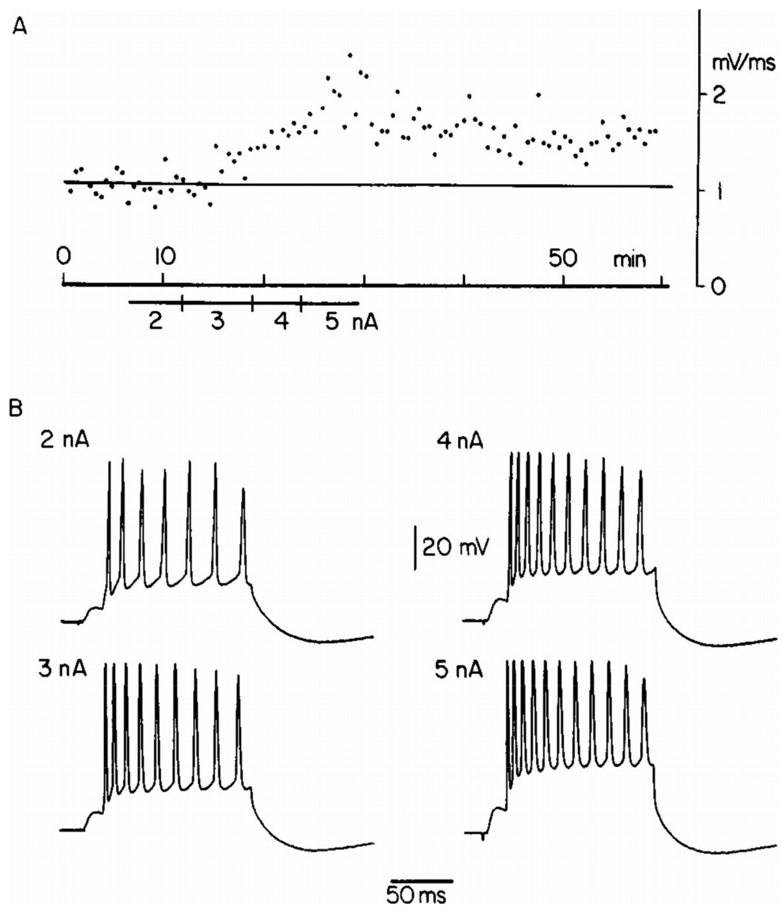
LTP from pre-stimulation paired with post-burst

hippocampus (slices)





20-30 pairings @ 0.1 Hz

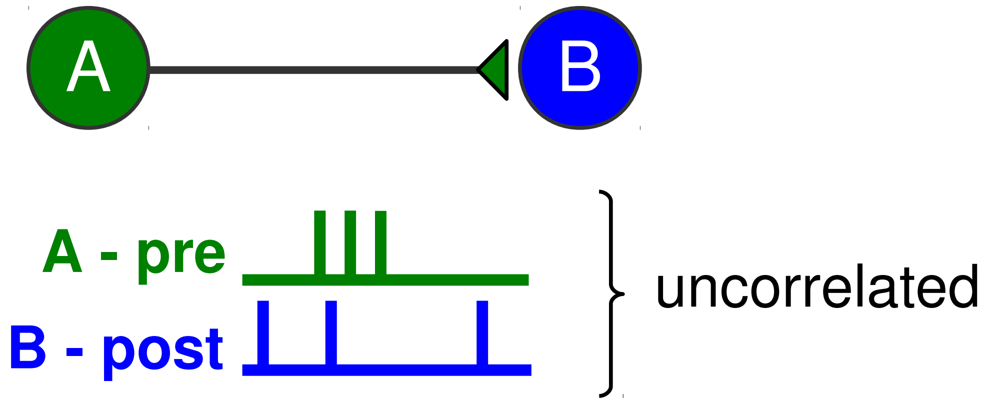


hippocampus & cortex

[Baranyi & Feher, Nature 1981
Barrionuevo & Brown, PNAS 1983;
Kelso et al. PNAS 1986;
Sastry et al. Science 1986
Gustafsson et al. 1987;
Fregnac et al. Nature 1988]

[Gustafsson et al. 1987]

LTD induction: postulate of Stent

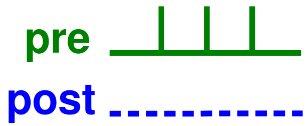


"When the presynaptic axon of cell A *repeatedly* and *persistently* fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is *decreased*."

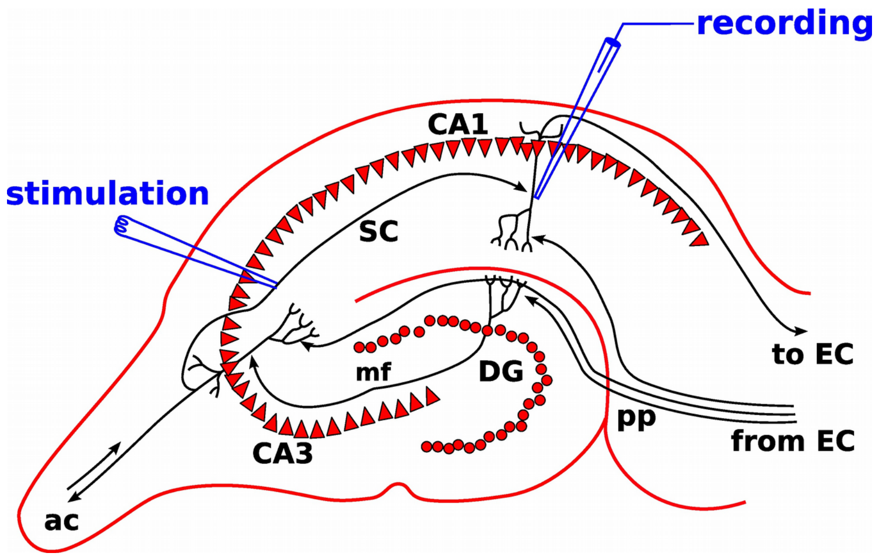
[G. Stent 1973;
see also Sejnowski 1977, von der Malsburg 1973, Bienenstock et al. 1982]

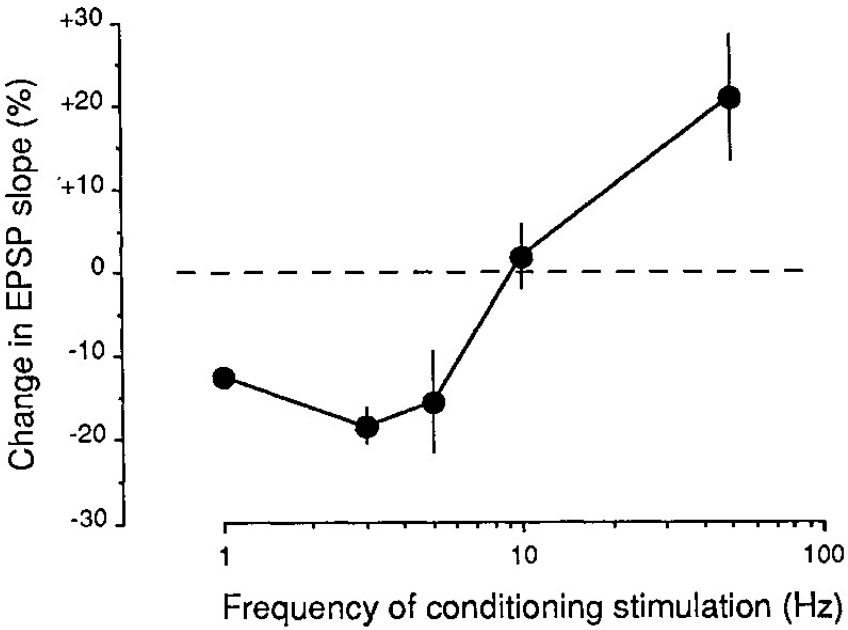
Plasticity induction: LTD obtained at low frequencies

hippocampus (slices)



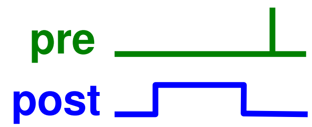
900 pulses at 1-50 Hz





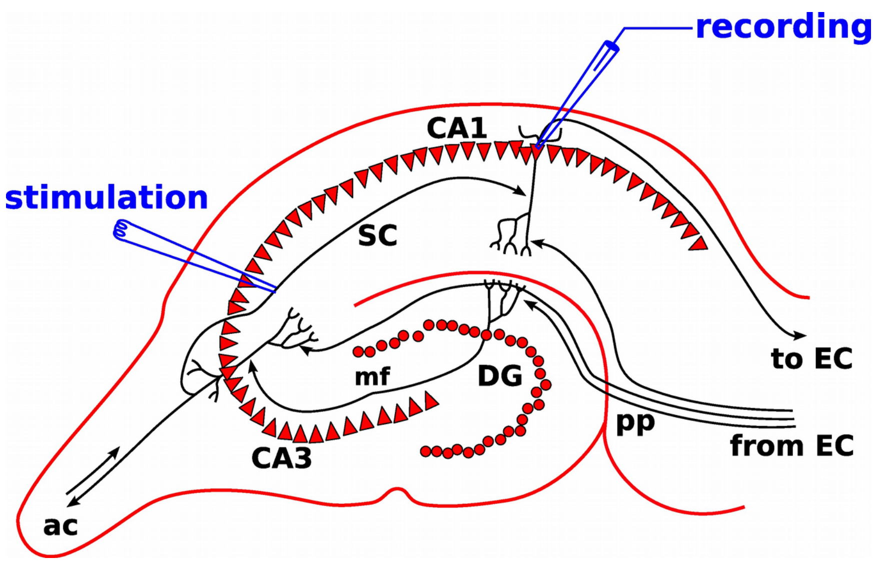
[Dudek and Bear 1992;
Dunwiddie and Lynch 1978]

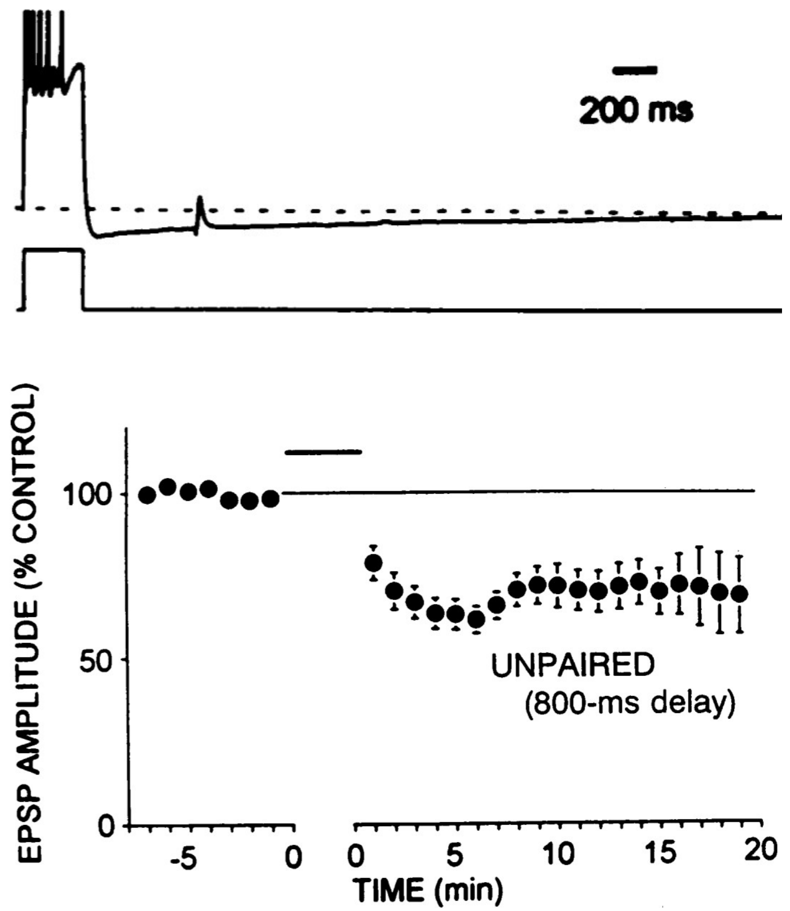
LTD from post-burst followed by pre-stimulation



50-100 pairings @ 0.1 Hz

hippocampus
(slice cultures)

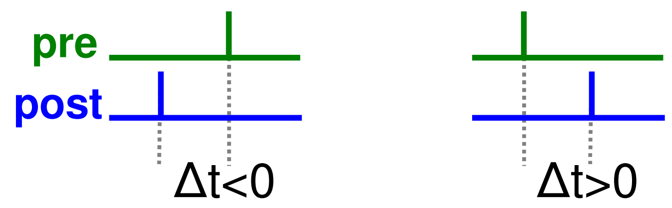




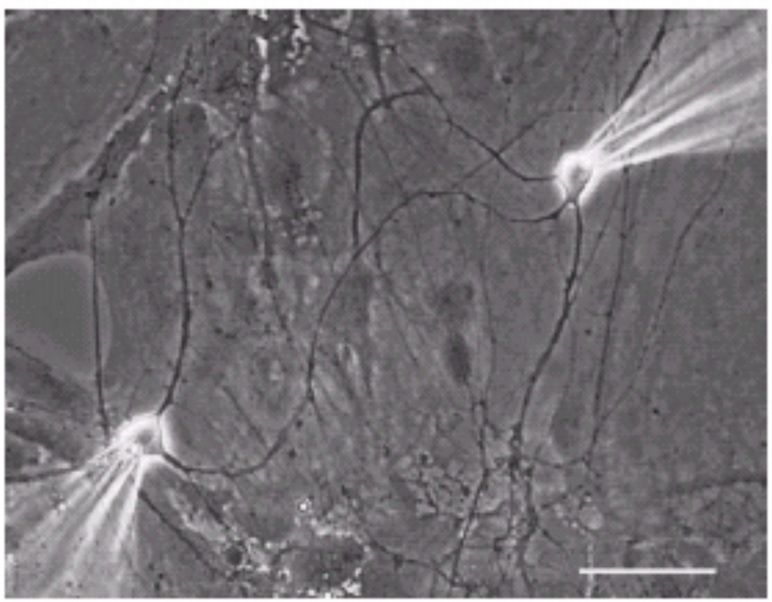
[Debanne et al. *PNAS* 1994]

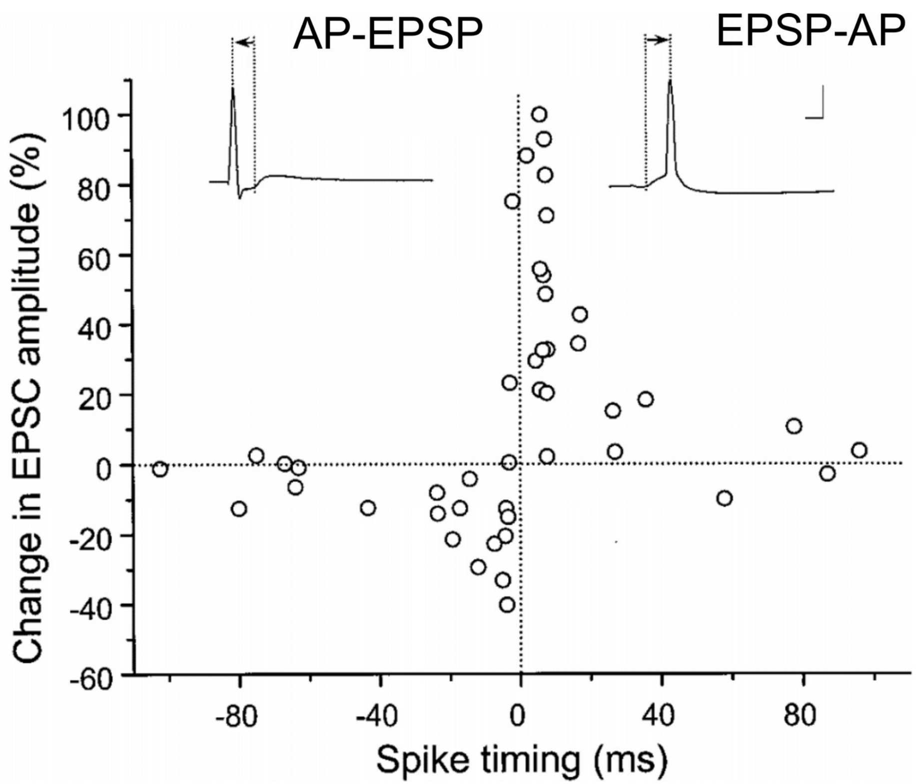
STDP : plasticity from single spike-pairs

60 pairings @ 1 Hz



hippocampal cultures

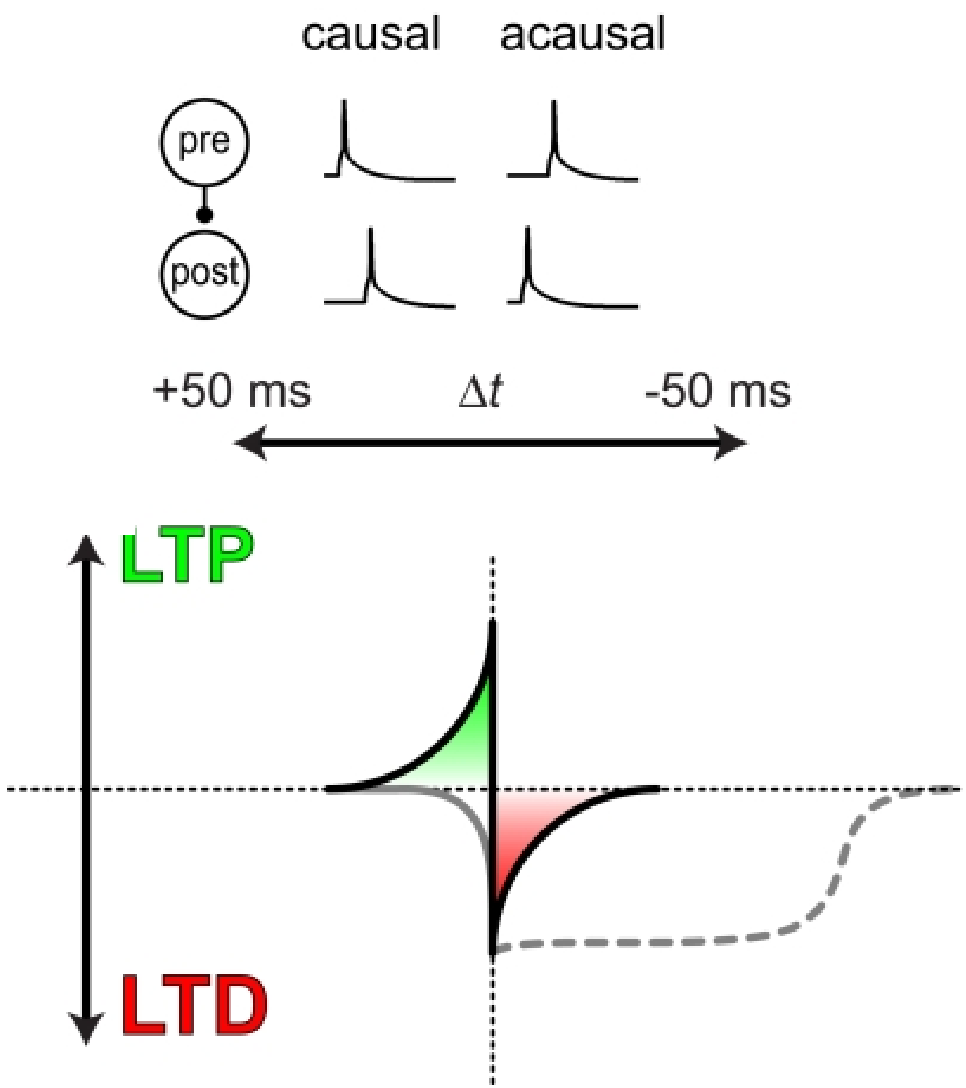




[Bi & Poo, J Neurosci 1998]

[Magee & Johnston 1997; Zhang et al. 1998; Markram et al. 1997; Sjöström et al. 2001; Feldman 200]

STDP



[Markram et al. *Front Synaptic Neurosci* 2011]

- causal activity → LTP

  acausal activity → LTD

  [Markram et al. 1997; Bi & Poo 1998; Zhang et al. 1998]

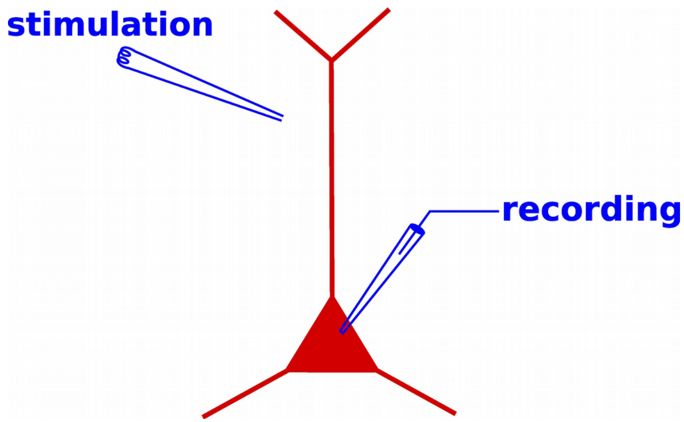
- at some synapses, LTD window is extended [Feldman 2000; Sjöström et al. 2001]
- postsynaptic bursting relaxes timing requirement

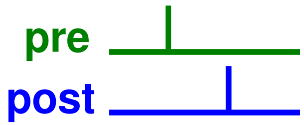
  [Debanne et al. 1994; Sjöström et al. 2003]

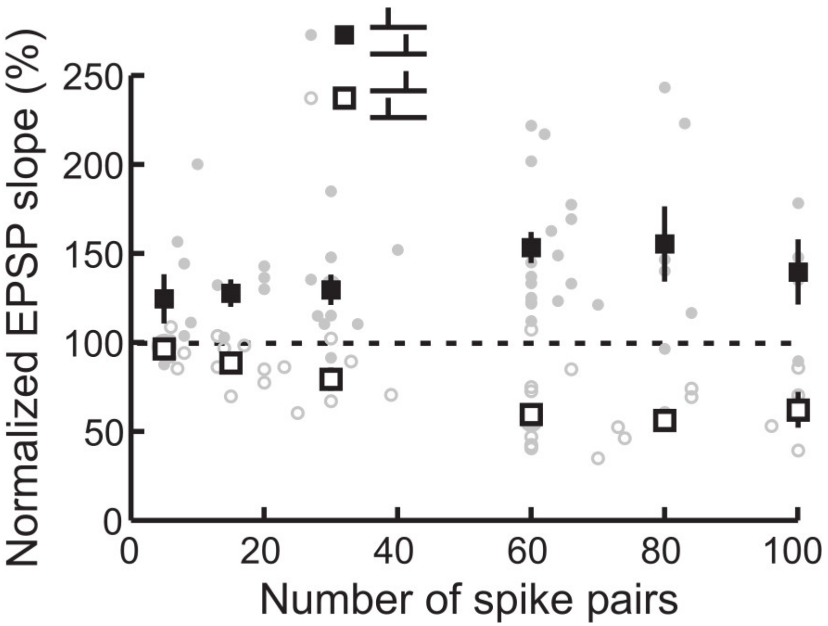
Outline

Number of pairing

visual cortex slices



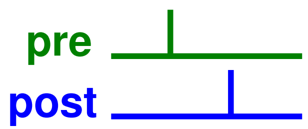




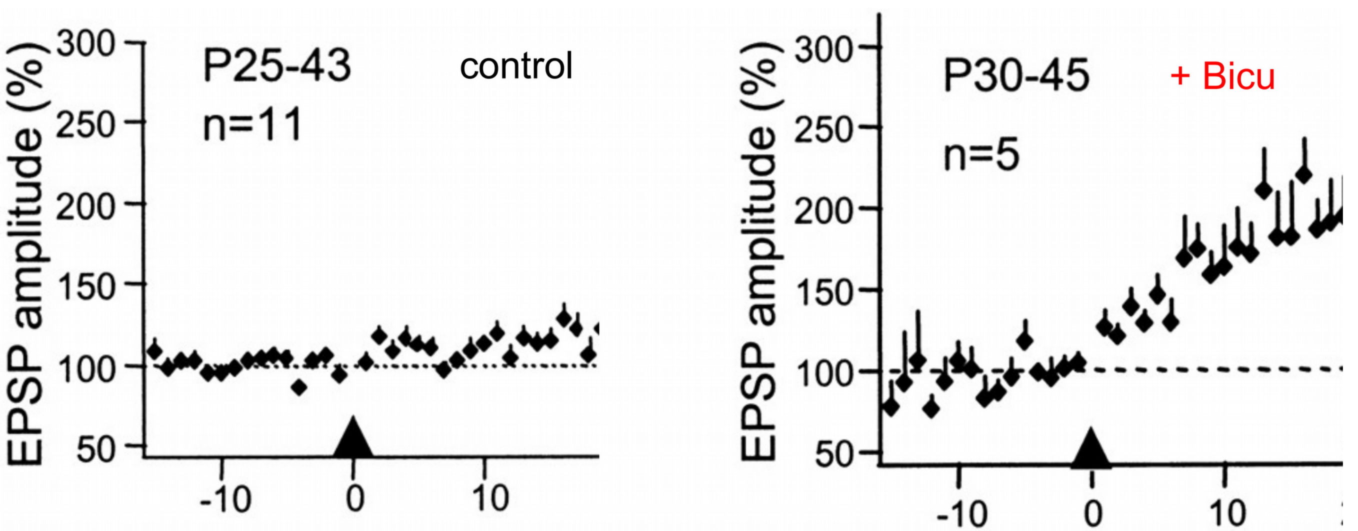
[Froemke et al. 2006]

Role of synaptic inhibition

hippocampal slices



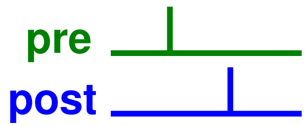
Δt = +10 ms, 30 pairings @ 0.2 Hz



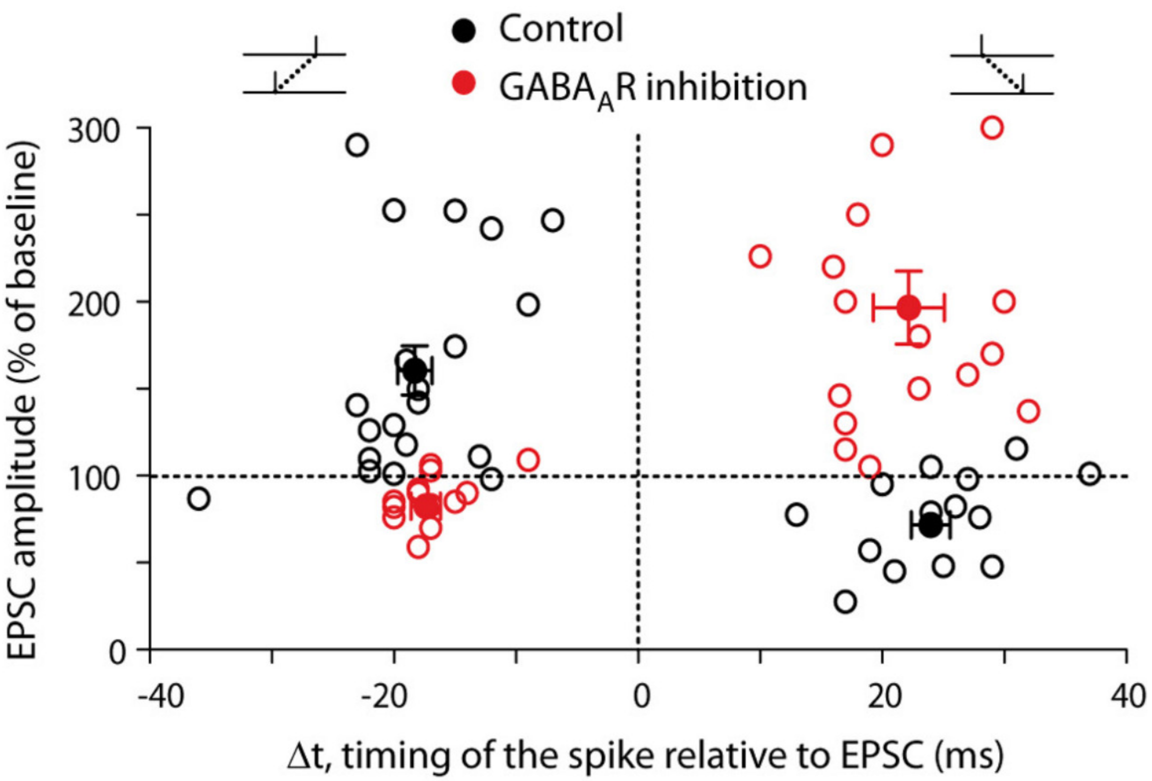
[Mederith et al. *J Neuroci* 2003]

Role of synaptic inhibition

cortico-striatal synapse onto medium spiny neurons (MSN, slices)



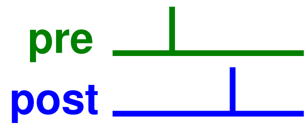
100-150 pairings @ 1 Hz



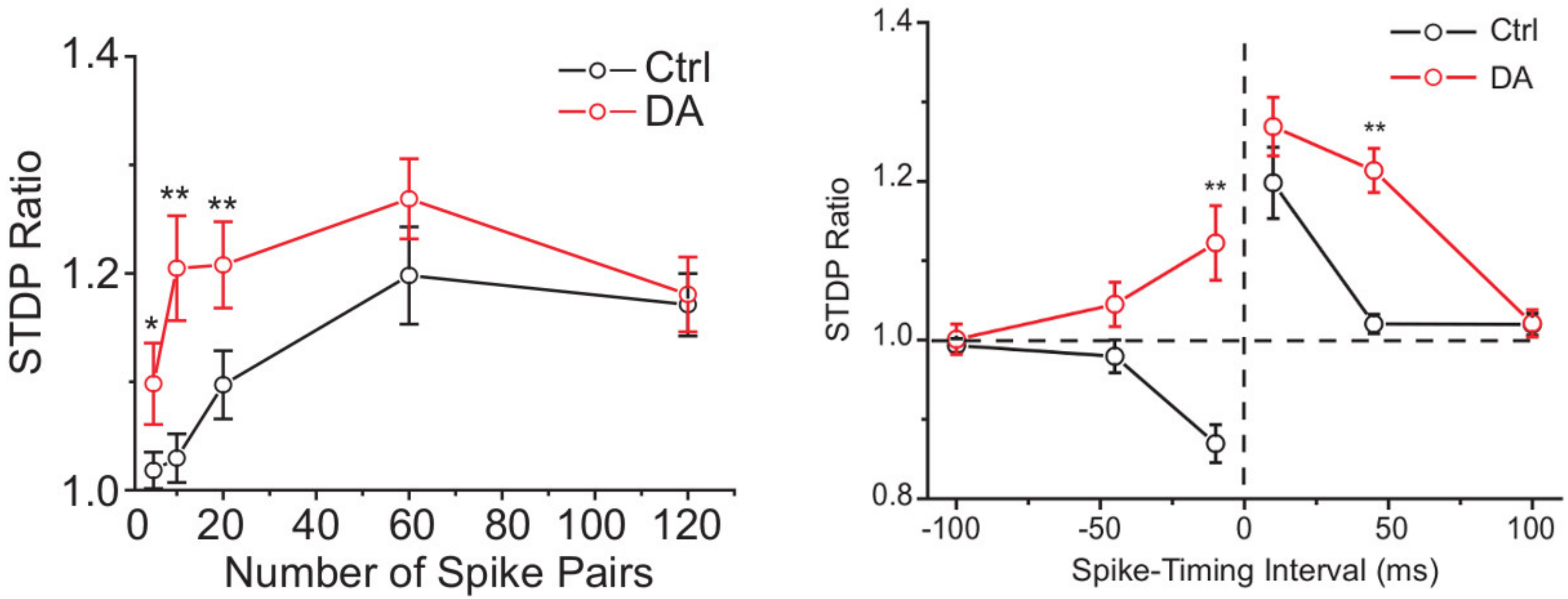
[Paille et al. *J Neurosci* 2013]

Role of neuromodulation - Dopamine

hippocampal cultures



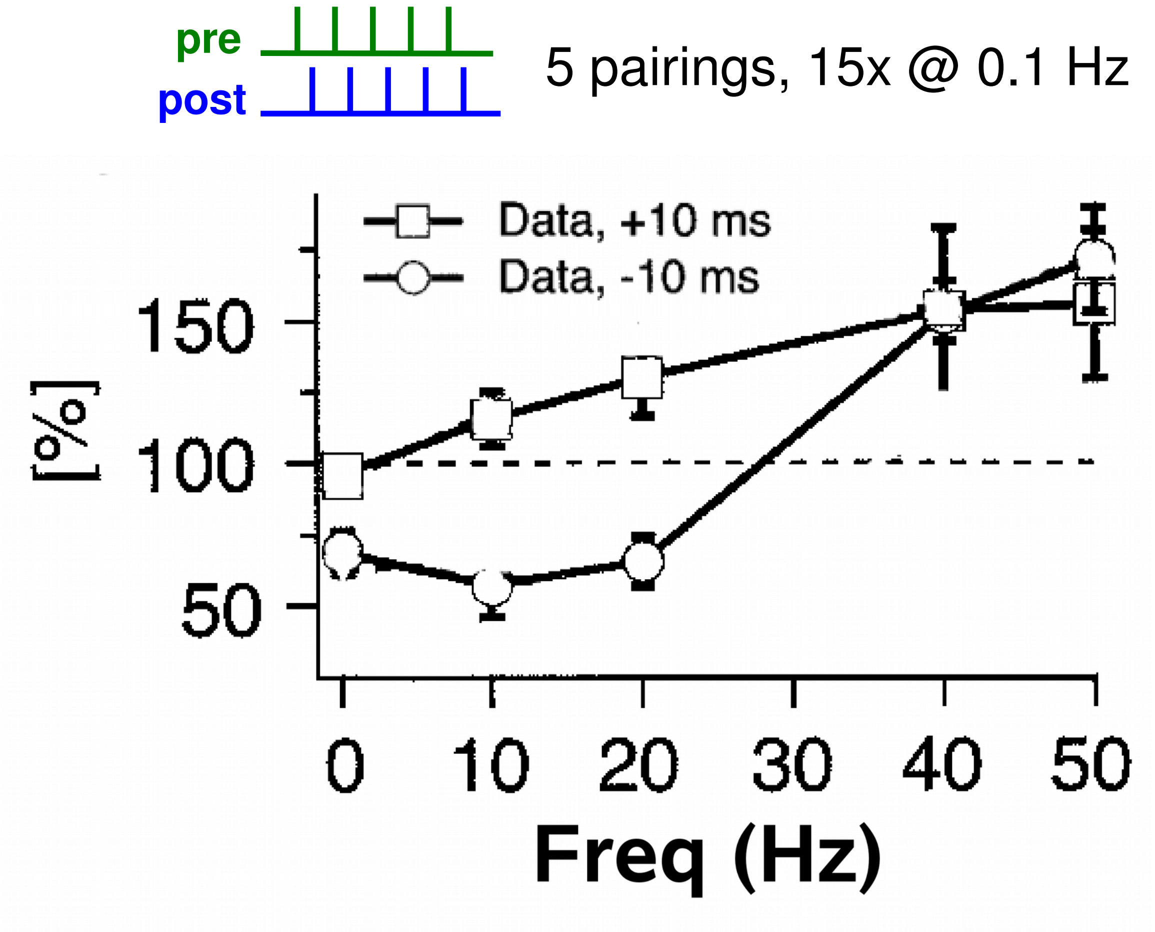
60 pairings @ 1 Hz



[Zhang et al. *PNAS* 2009]

STDP depends on frequency of spike-pairs

cortical slices



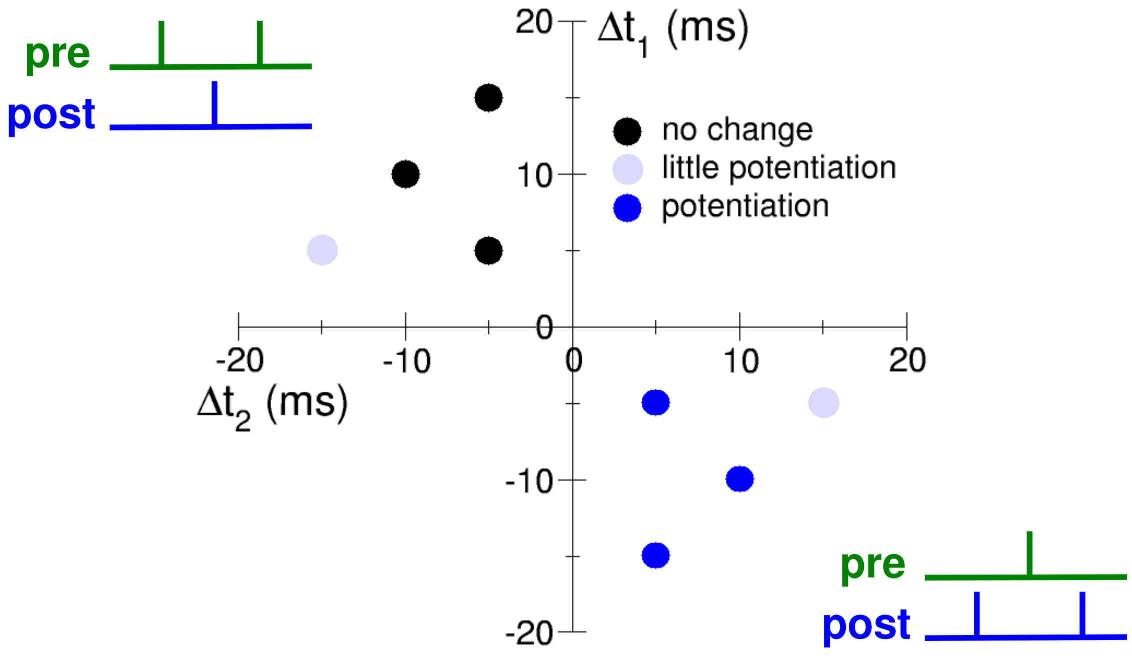
5 pairings, 15x @ 0.1 Hz

[Sjöström et al. *Neuron* 2001]

Non-linearity in STDP induction protocols

hippocampal cultures

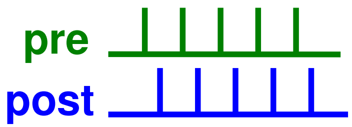
60 pairings @ 1 Hz



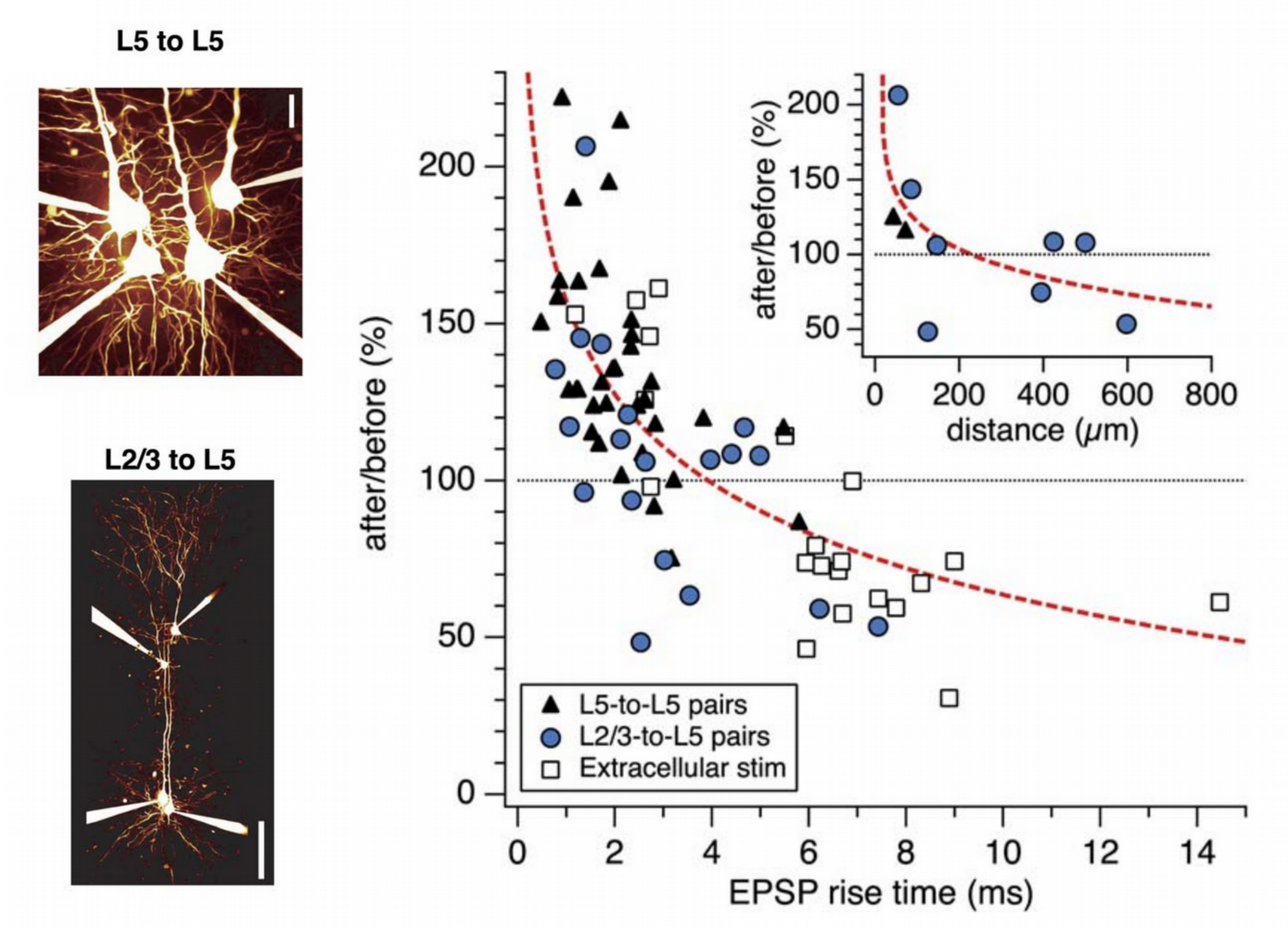
[Wang et al. *Nat Neurosci* 2005]

STDP depends on synaptic location

cortical slices

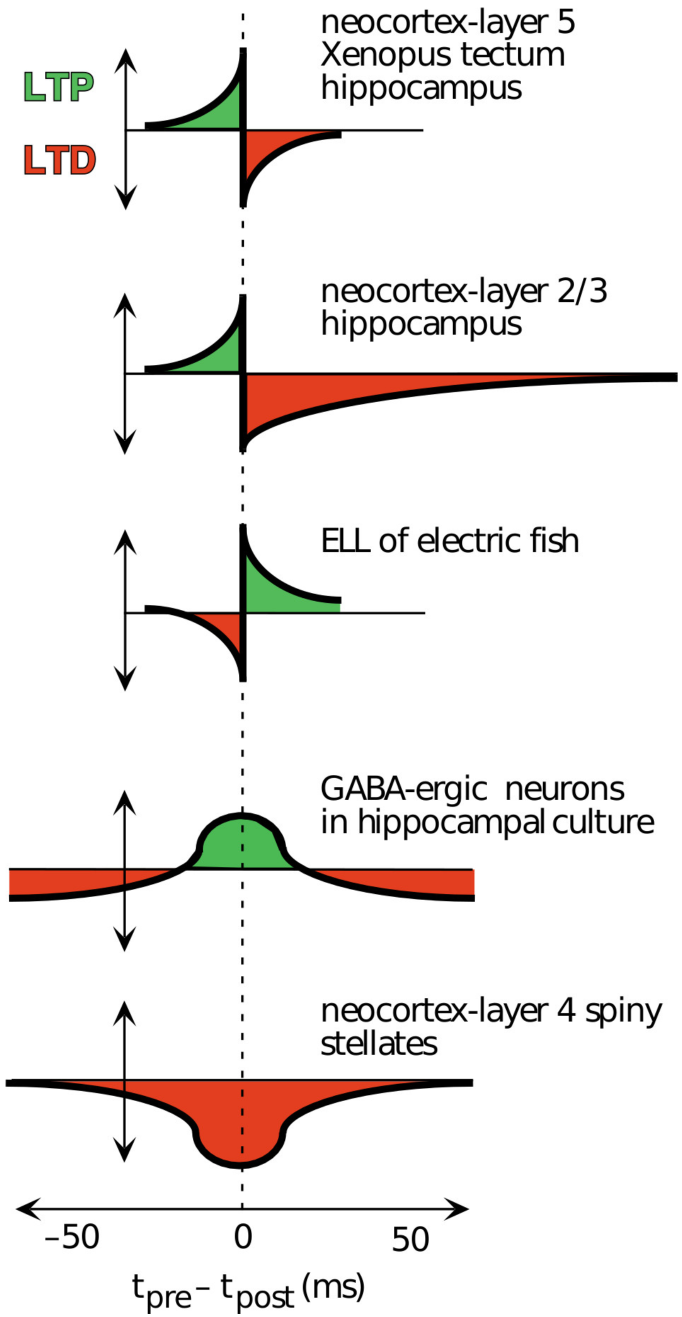


Δt=10 ms, 5 pairings, 15x @ 0.1 Hz



[Sjöström & Hausser, Neuron 2006]

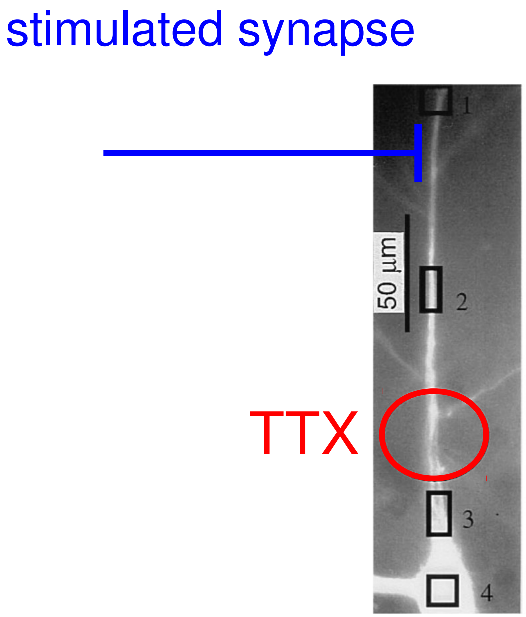
STDP windows depends on brain structure

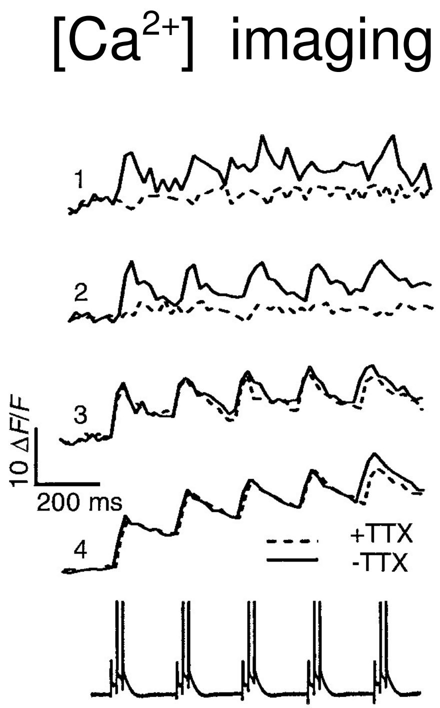


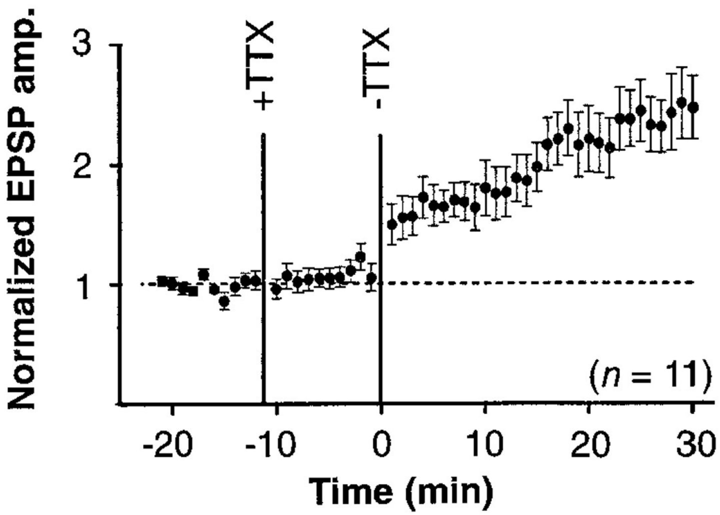
[Abbott & Nelson *Nat Neurosci* 2000]

Outline

Backpropagating action potential required for STDP

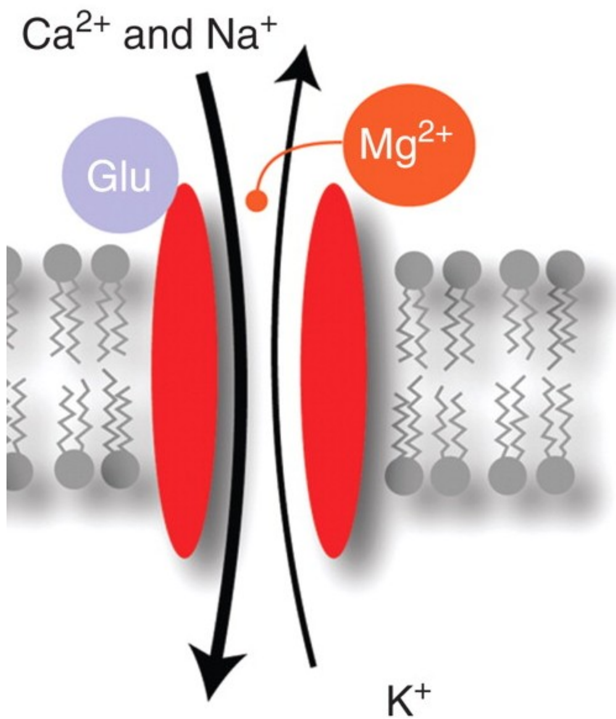




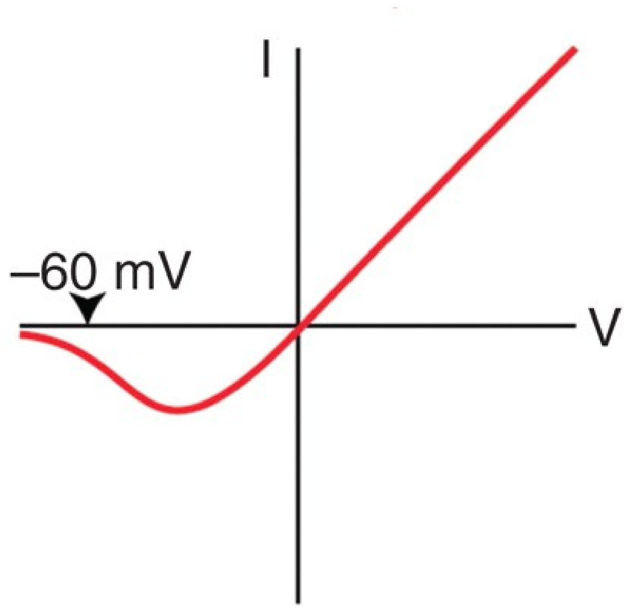


[Magee & Johnston *Science* 1997]

Postsynaptic NMDA receptor



current-voltage relationship



- coincidence detector :

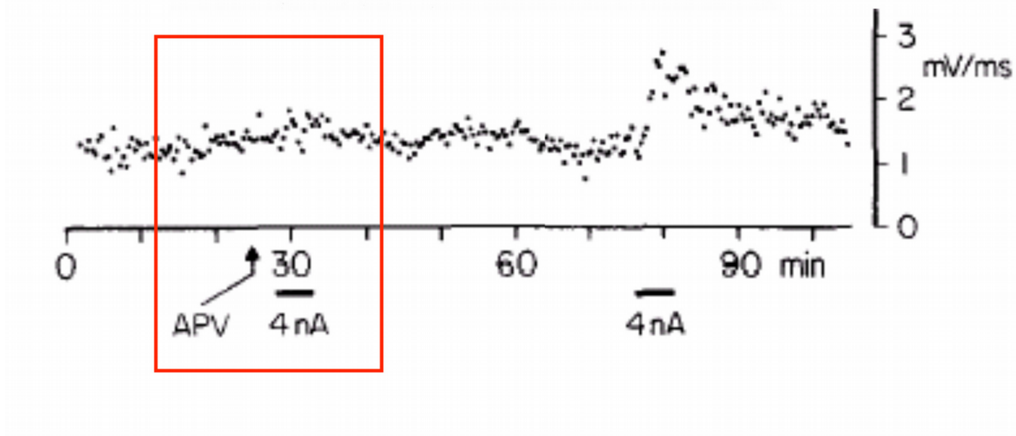
  presynaptic action potential → glutamate (Glu)

  postsynaptic depolarization → Mg^{2+} block is expelled

- calcium permeable

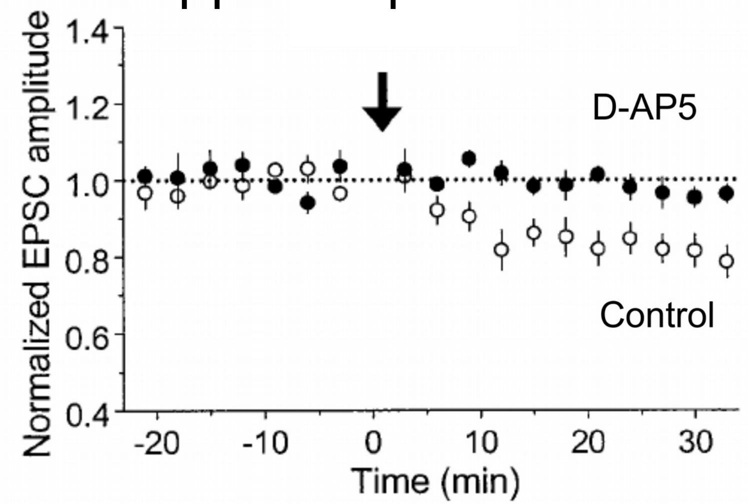
STDP requires NMDA receptor activation

hippocampal slices



[Gustafsson et al. *J Neurosci* 1987]

hippocampal cultures



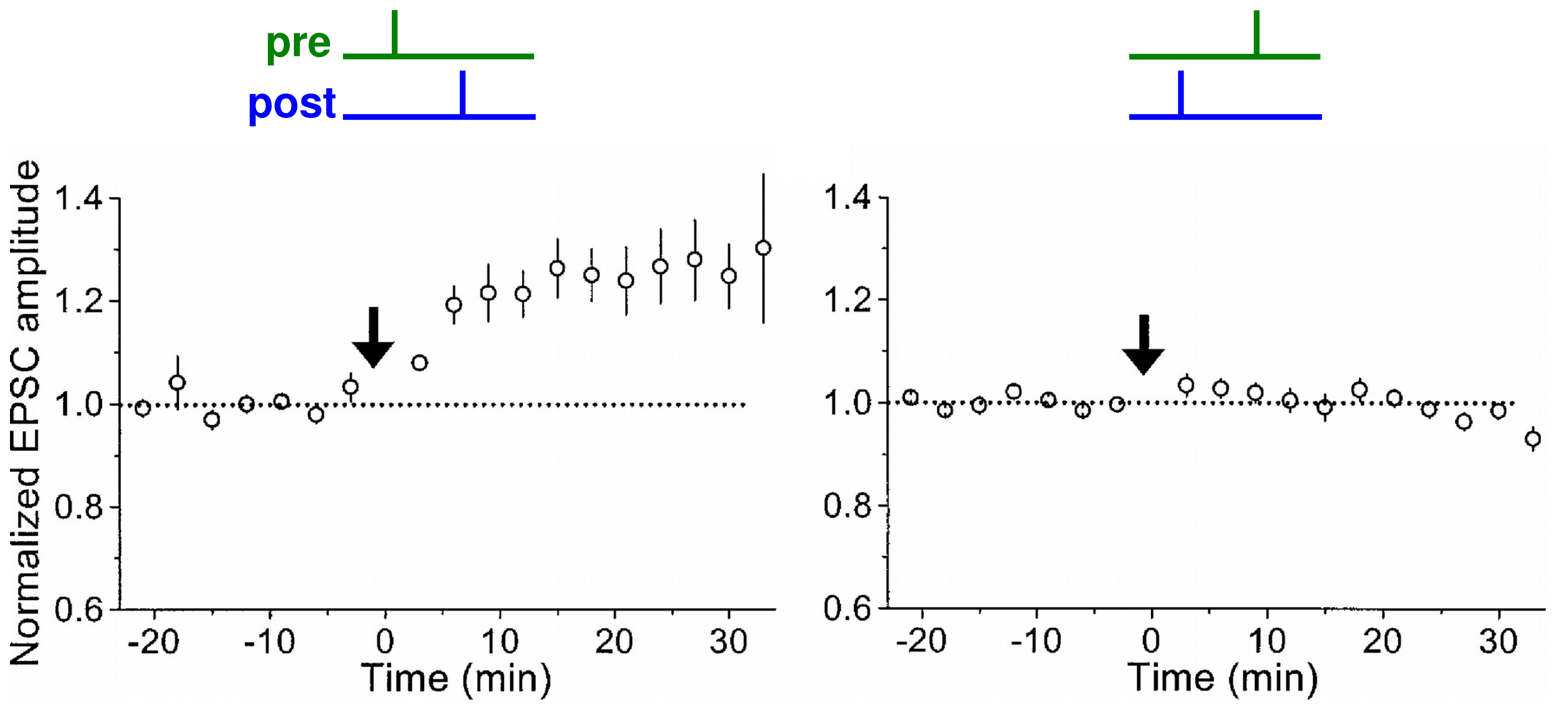
[Bi & Poo *J Neurosci* 1998]

NMDAR antagonist blocks STDP induction

- CA3-CA1 pyramidal cell synapse
- CA3-CA3 pyramidal cell synapse
- Layer V – layer V synapse
- Layer II/III
- Layer IV stellate cell synapse
- Dorsal cochlear neurons (brainstem)
- Retino-tectal synapse

Voltage-dependent Ca channels required for LTD

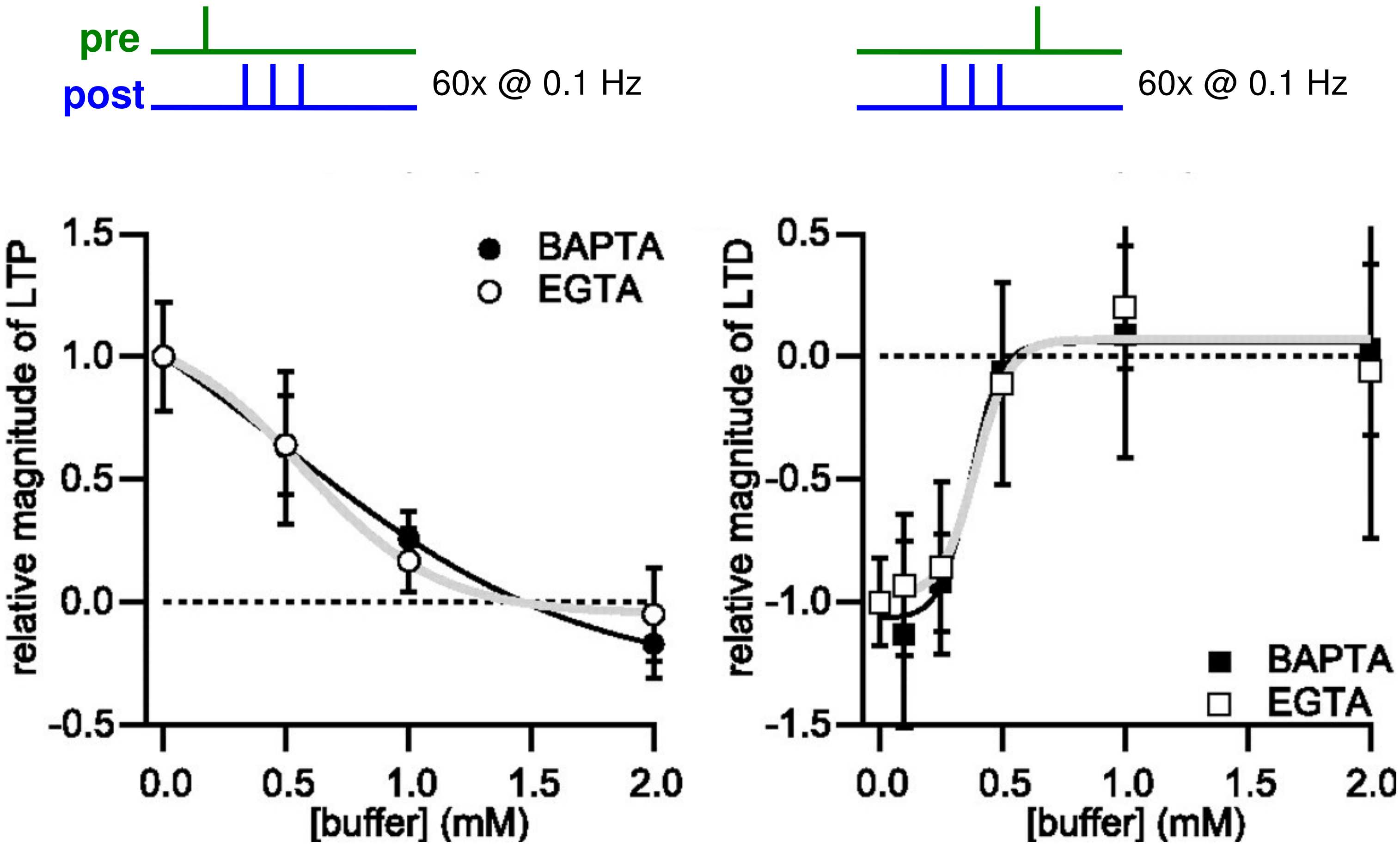
hippocampal cultures
+ nimodipine (L-type channel blocker)



[Bi & Poo *J Neurosci* 1998]

Postsynaptic calcium *required* for plasticity

cortical slices

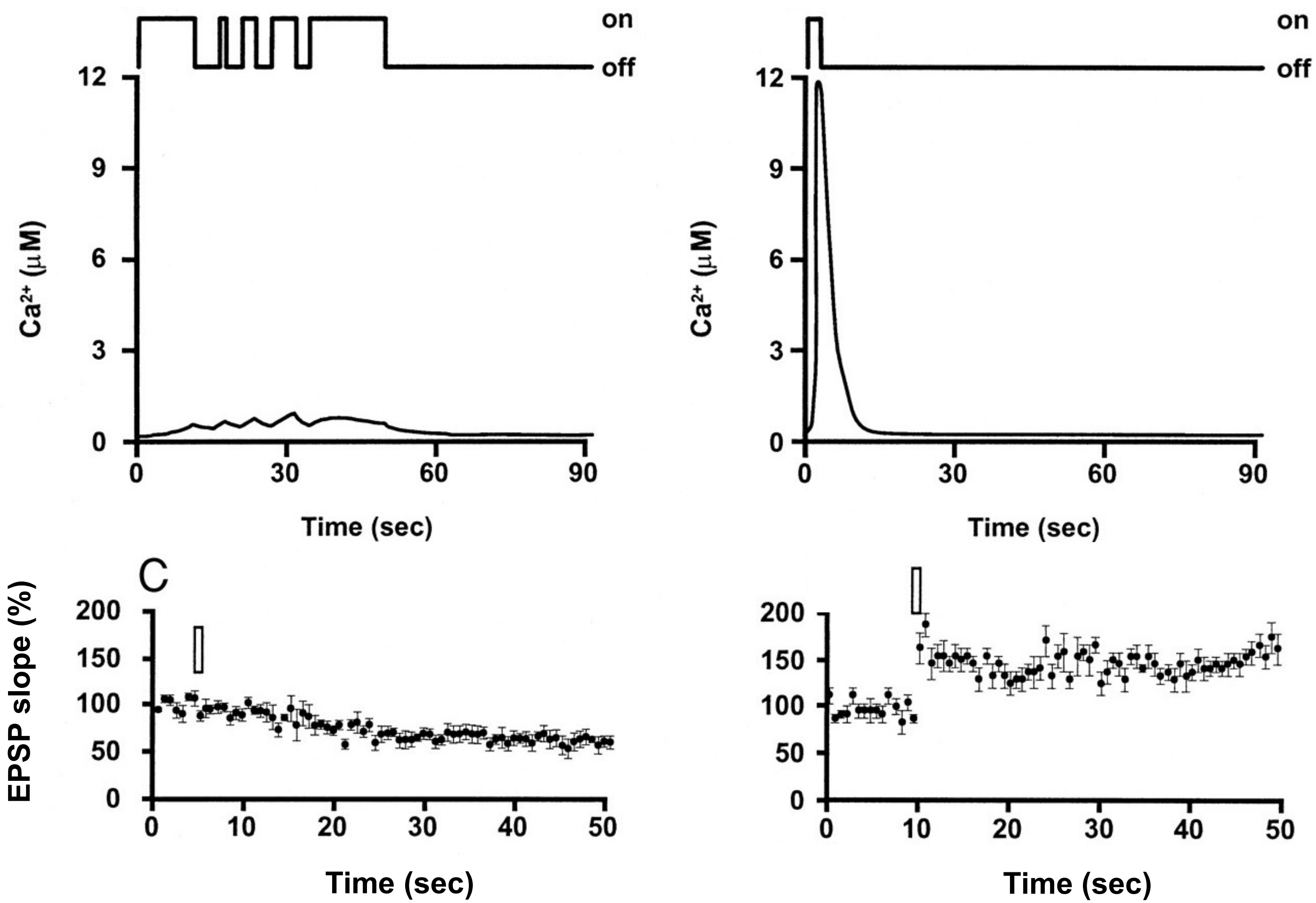


[Nevian & Sakmann *et al.*, 2006]

- LTP/LTD equally sensitive to fast and slow [Ca^{2+}] buffers

Postsynaptic calcium *sufficient* for plasticity

hippocampal slices

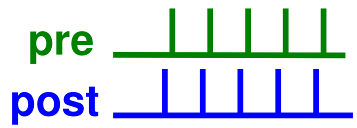


[Malenka *et al.* 1988; Yang *et al.*, 1999]

- LTP induced by brief, large amplitude [Ca^{2+}] increases
- prolonged, modest rise in [Ca^{2+}] elicits LTD

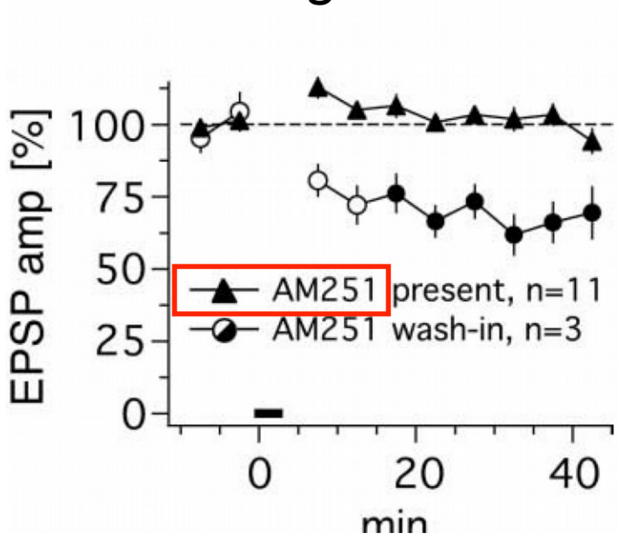
Cortical LTD: presynaptic Cannabinoid receptors required

cortical slices

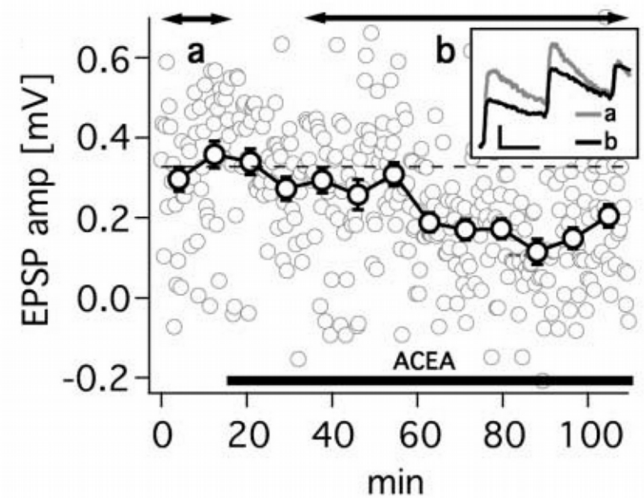


Δt = -10 or -25 ms, 20 Hz, 5 pairings, 15x @ 0.1 Hz

CB1R antagonist = no tLTD



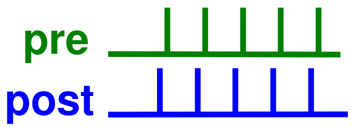
CB1R agonist= cLTD



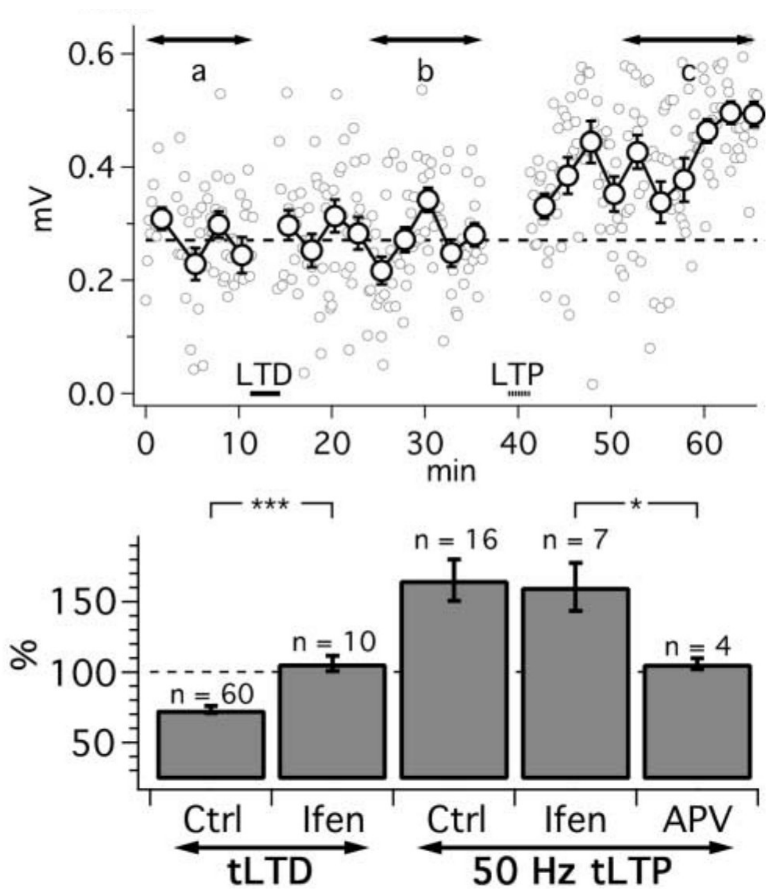
[Sjöström et al. *Neuron* 2003]

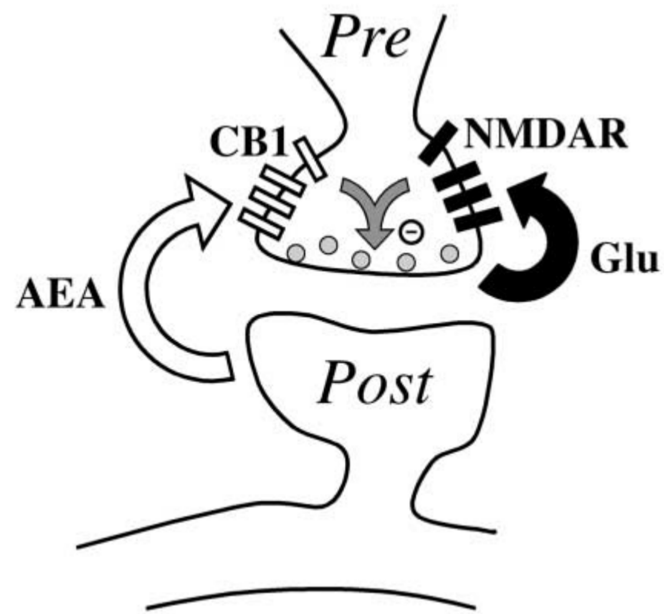
Cortical LTD involves presynaptic NMDA receptors

cortical slices + ifenprodil (NR2B subunit antagonist)



Δt = -10 or -25 ms, 20 Hz, 5 pairings, 15x @ 0.1 Hz





[Sjöström et al. *Neuron* 2003]

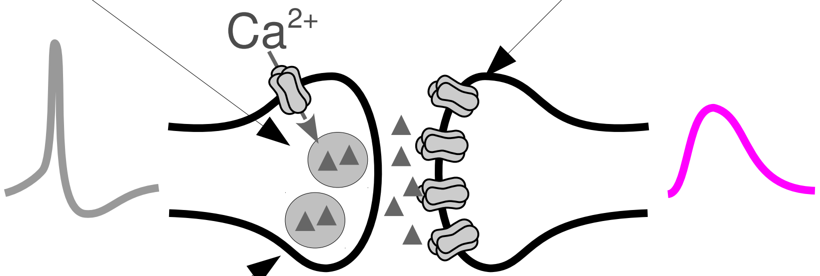
Expression of long-term changes

presynaptic

postsynaptic

neurotransmitter vesicle number

number of AMPA receptors

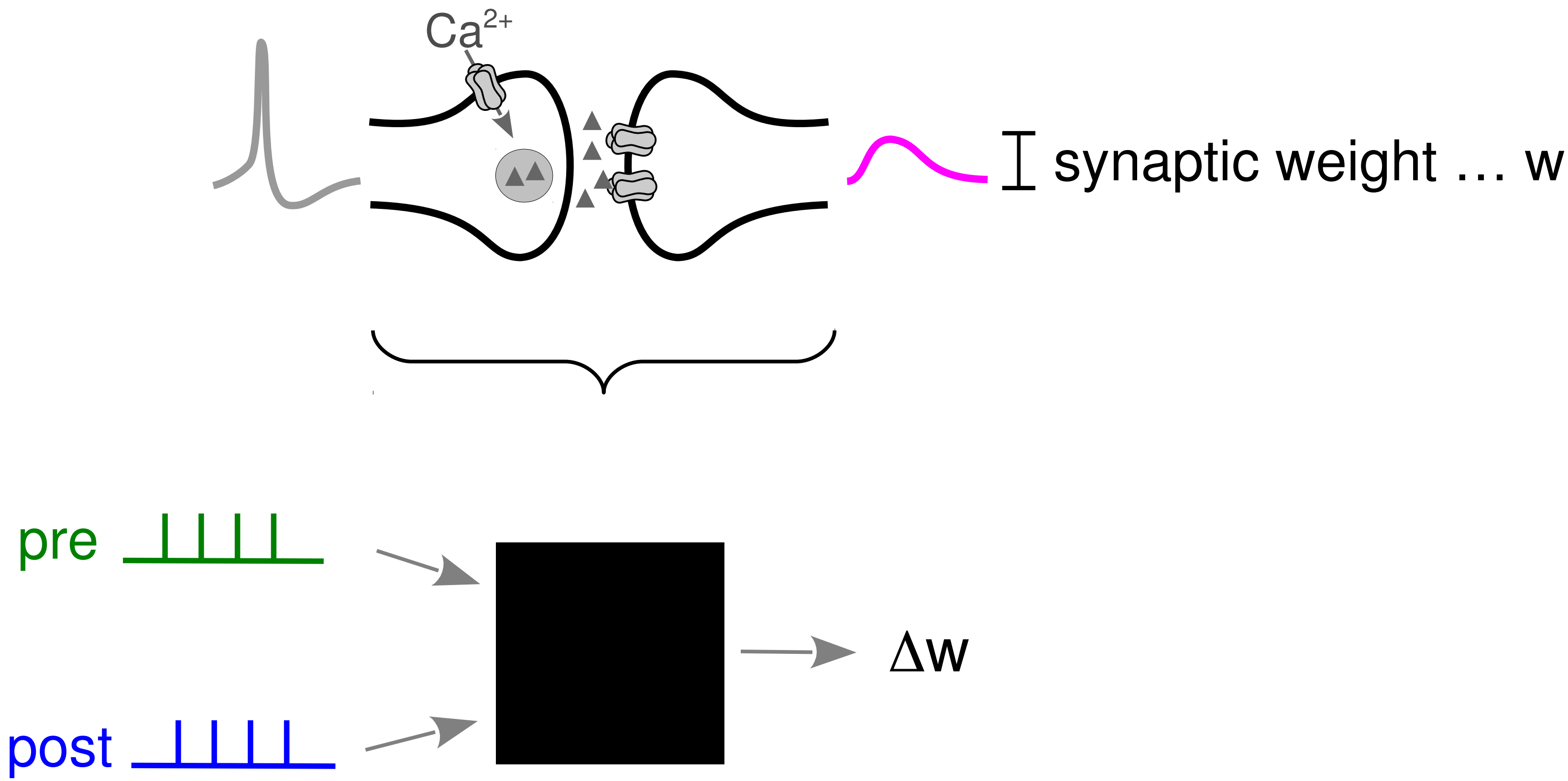


probability of vesicle release

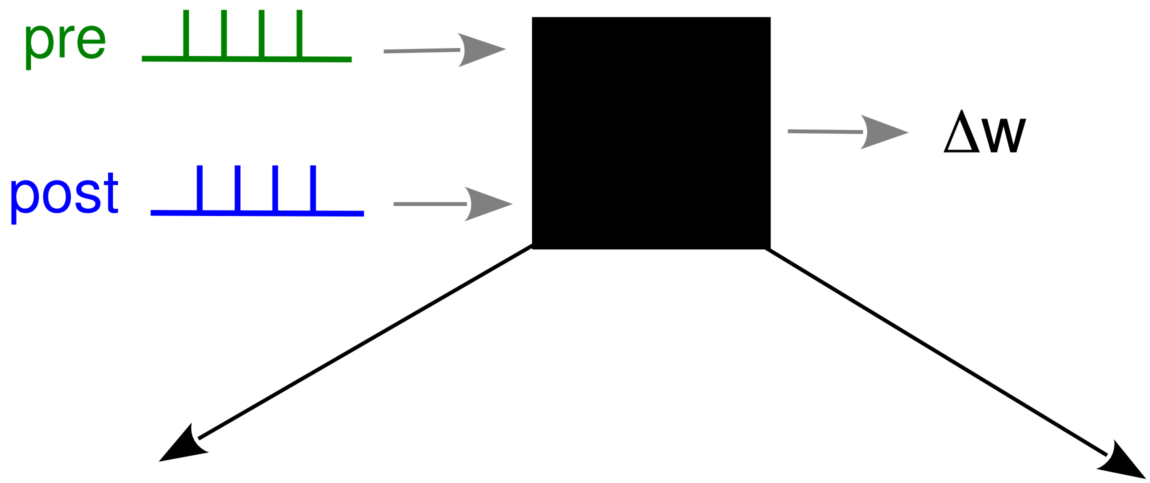
conductance of AMPA receptors

Outline

Modeling : translation from spikes to plasticity results



Modeling approaches : phenomenological vs. biophysical



phenomenological models of LTP/LTD

- use pre- and postsynaptic spike times or rate to calculate change in synaptic strength
- conversion can involve arbitrarily complex mathematical models

biophysical models of LTP/LTD

- resolve *parts* of the underlying biological machinery involved in the induction of plasticity
- degree of biological detail varies largely

Modeling studies : phenomenological vs. biophysical

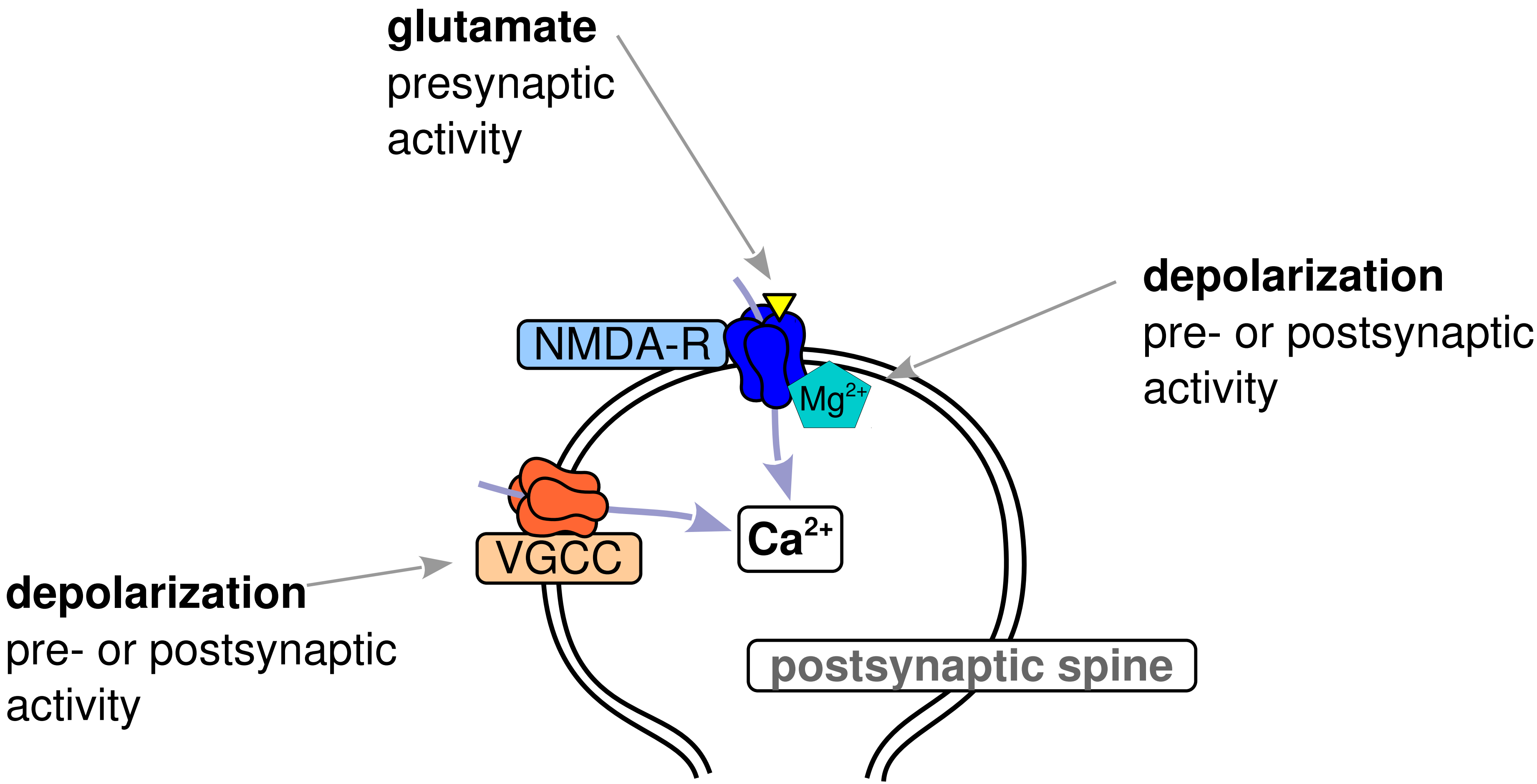
phenomenological models of LTP/LTD

- rate-based plasticity models
  [Hebb, 1949; Bienenstock *et al.*, 1982; Oja, 1982]
- spike-timing based models
  [Gerstner *et al.*, 1996; van Rossum *et al.* 2000; Song, 2000; Pfister & Gerstner, 2006]

biophysical models of LTP/LTD

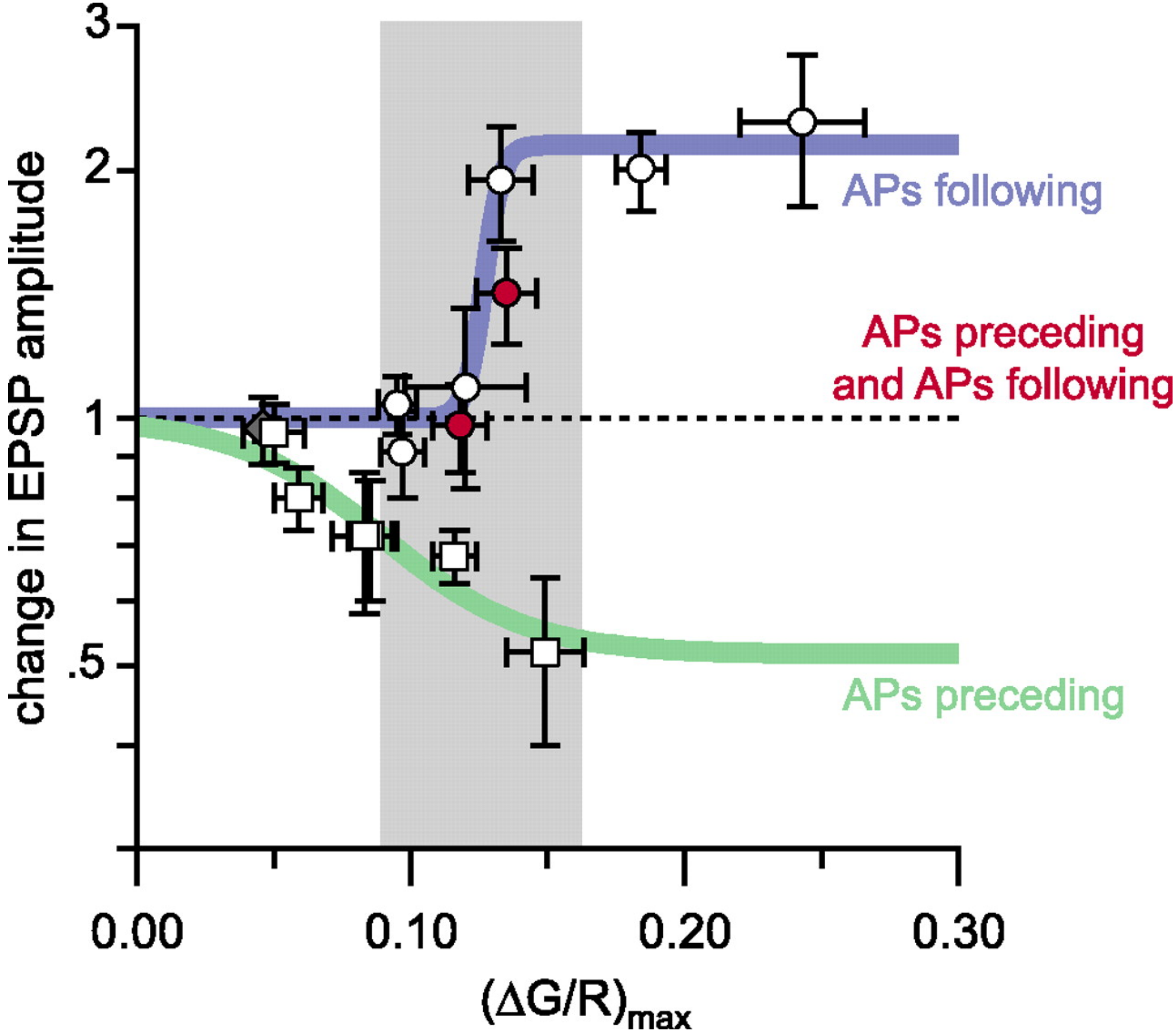
- Ca^{2+} – dynamics based models
  [Karmarkar *et al.*, 2002; Shouval *et al.*, 2002; Rubin *et al.*, 2005; Graupner & Brunel 2012]
- CaMKII kinase-phosphatase system
  [Crick 1984; Lisman, 1985; Okamoto & Ichikawa, 2000; Zhabotinsky, 2000; Graupner & Brunel, 2007; Urakubo *et al.*, 2008]
- extensive protein networks
  [Bhalla & Iyengar, 1999; Hayer & Bhalla, 2005]
- local clustering of receptors
  [Shouval, 2005]

Ca^{2+} - based models



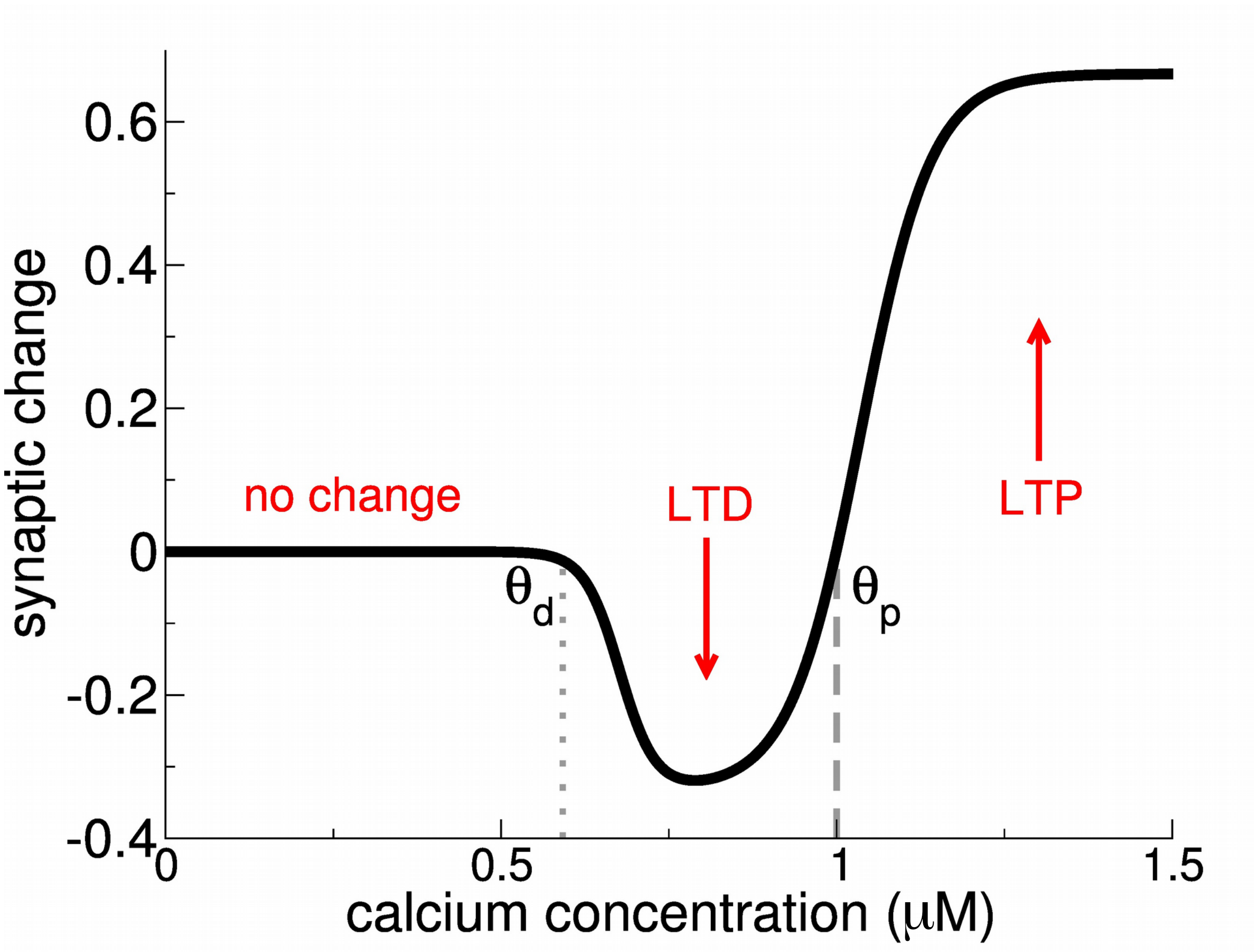
[Collingridge *et al.*, 1983; Markram *et al.*, 1997; Bi & Poo, 1998; Nevian & Sakmann 2006]

Peak Ca^{2+} amplitude does not predict LTP or LTD



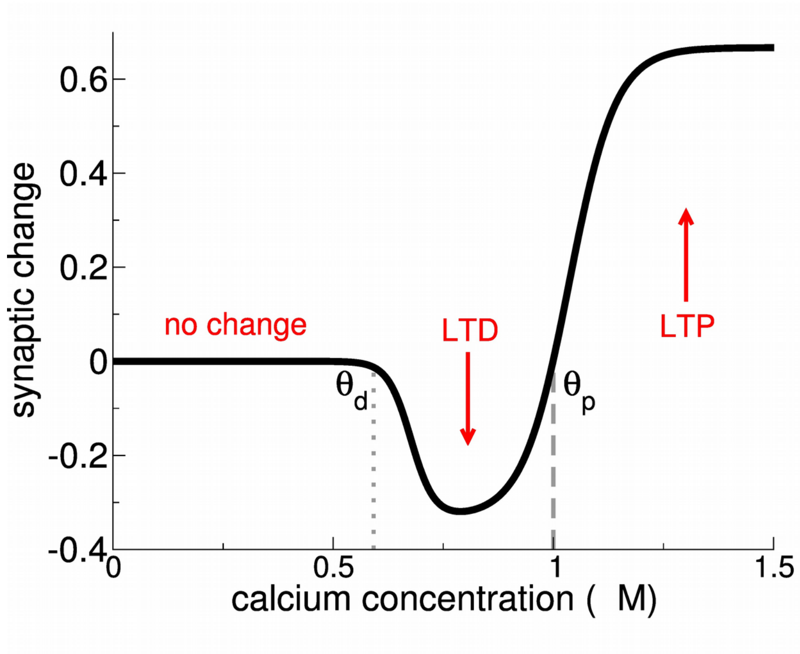
[Nevian & Sakmann *et al.*, 2006]

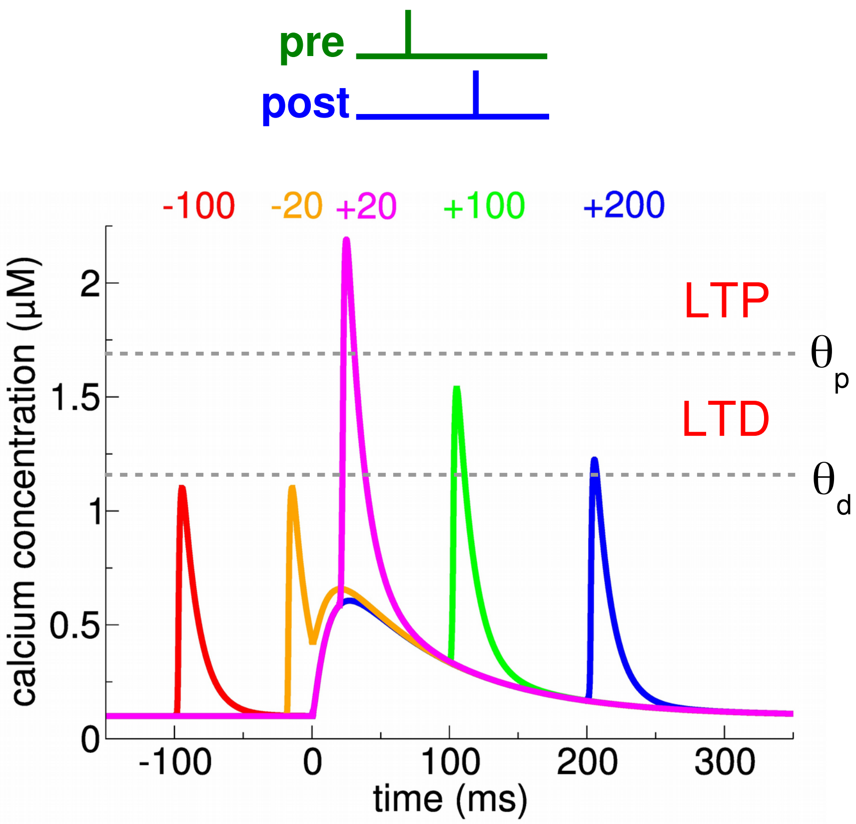
Calcium control hypothesis



[Shouval *et al.*, 2002]

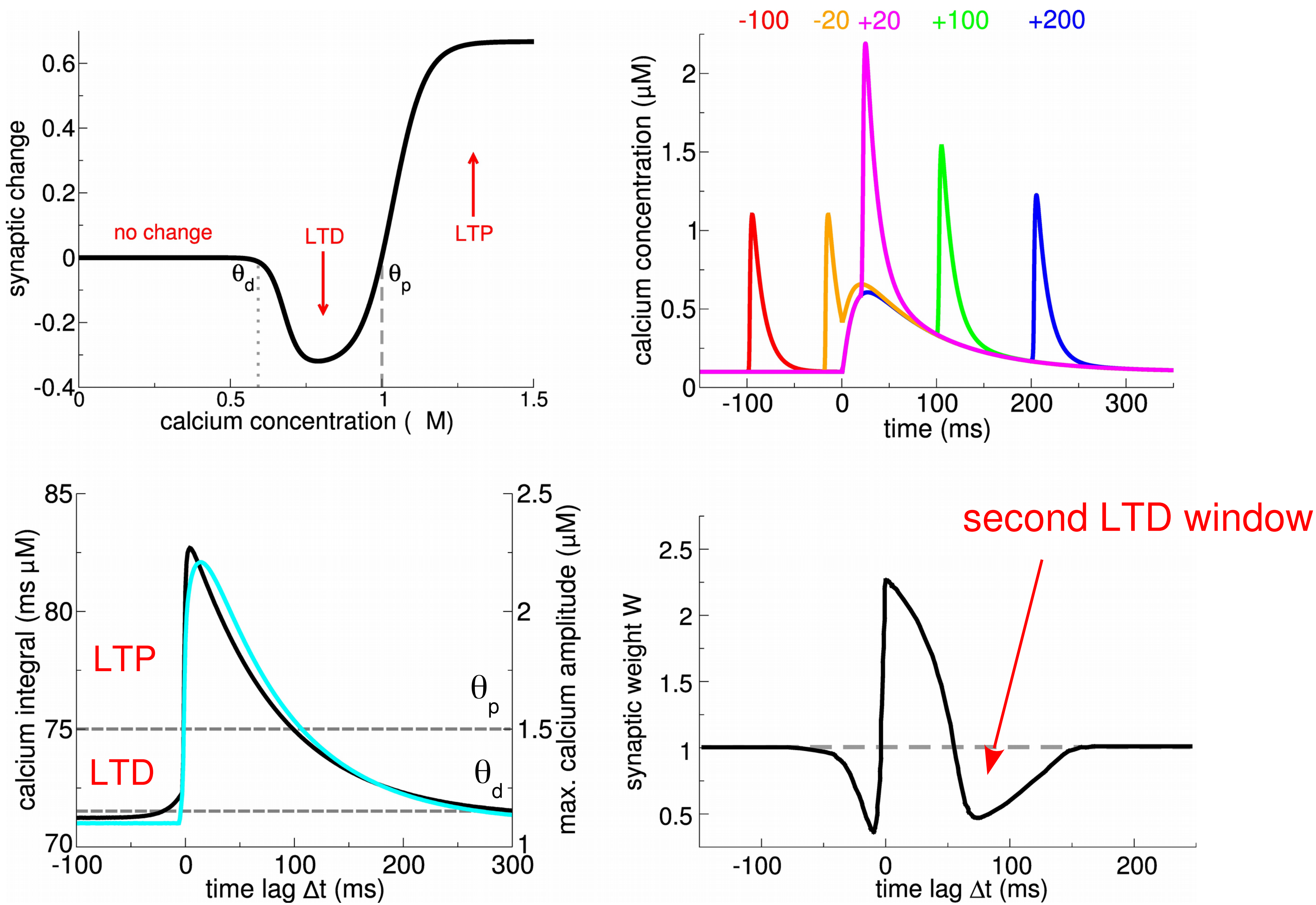
Calcium control hypothesis





[Shouval *et al.*, 2002]

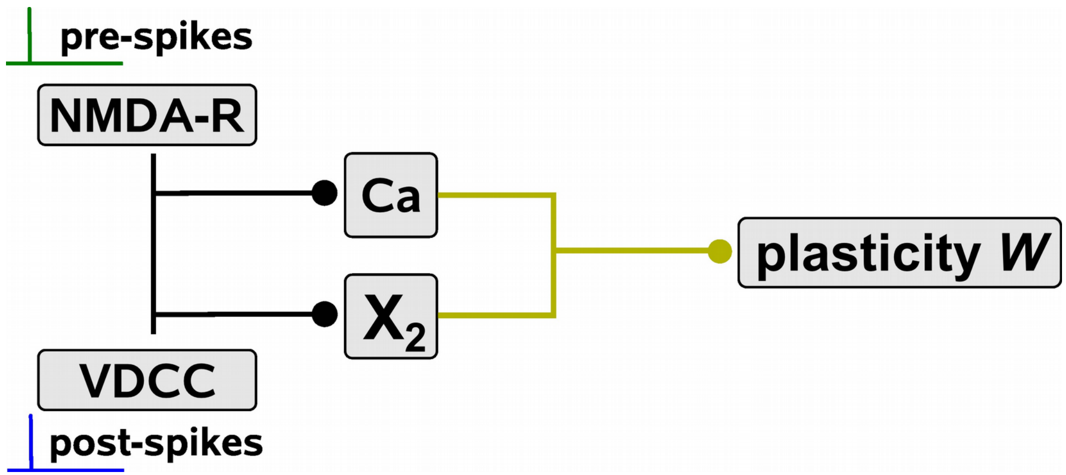
Calcium control hypothesis



[Shouval *et al.*, 2002]

More complex read-out mechanisms of Ca^{2+} signal

- two distinct but converging dynamical variables [Karmarkar *et al.*, 2002; Badoual *et al.*, 2006]



More complex read-out mechanisms of $[Ca^{2+}]$ signal

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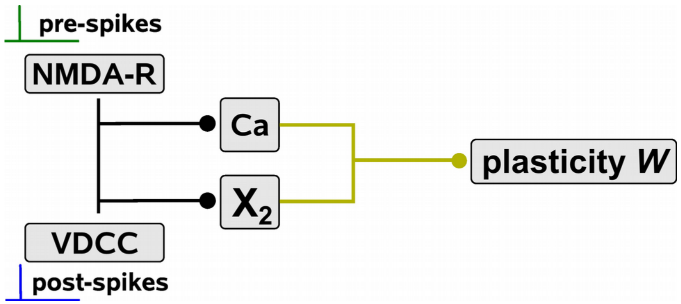
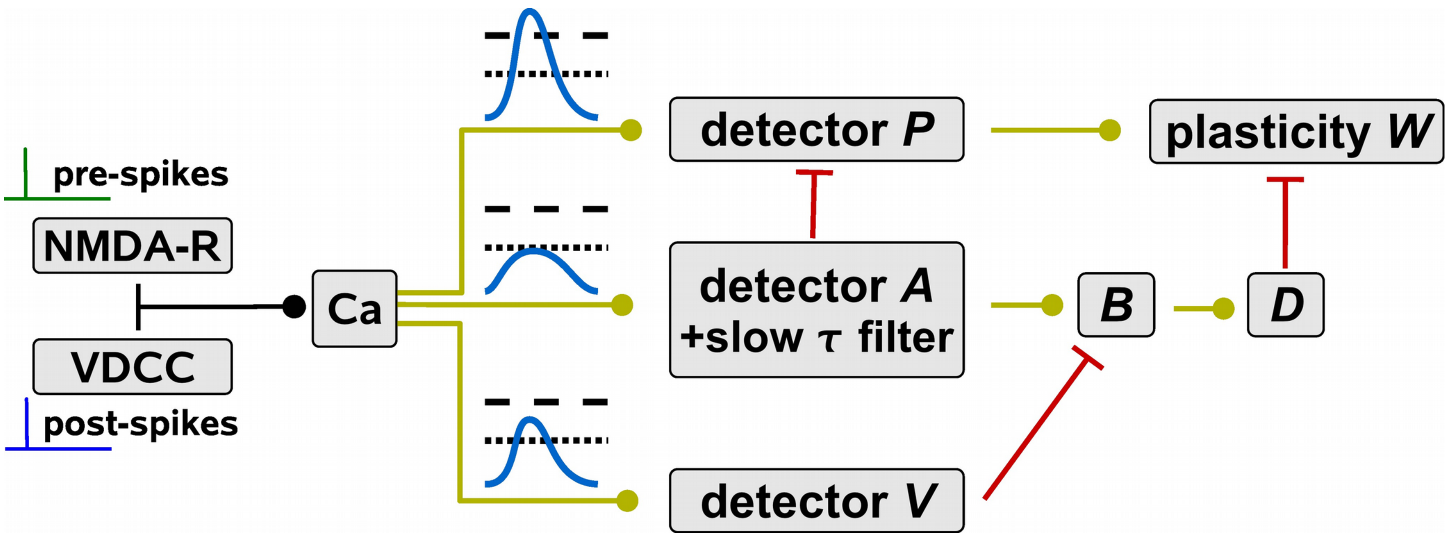


- phenomenological read-out of $[Ca^{2+}]$ [Rubin *et al.*, 2005]



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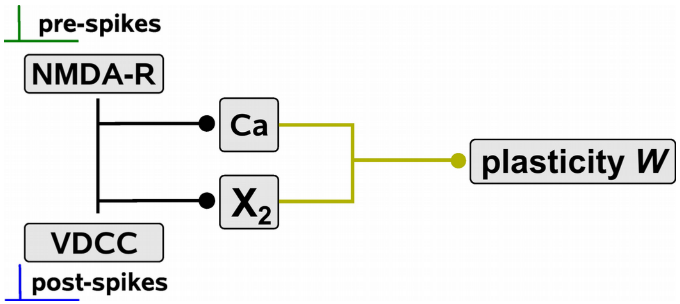

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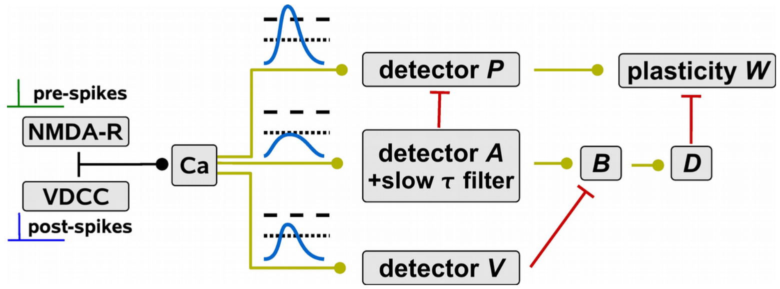
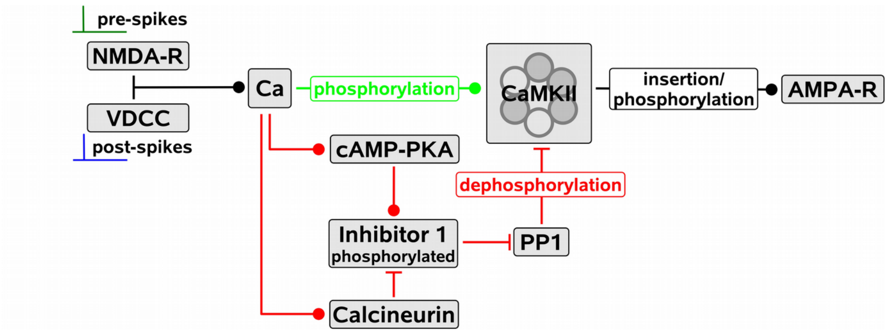
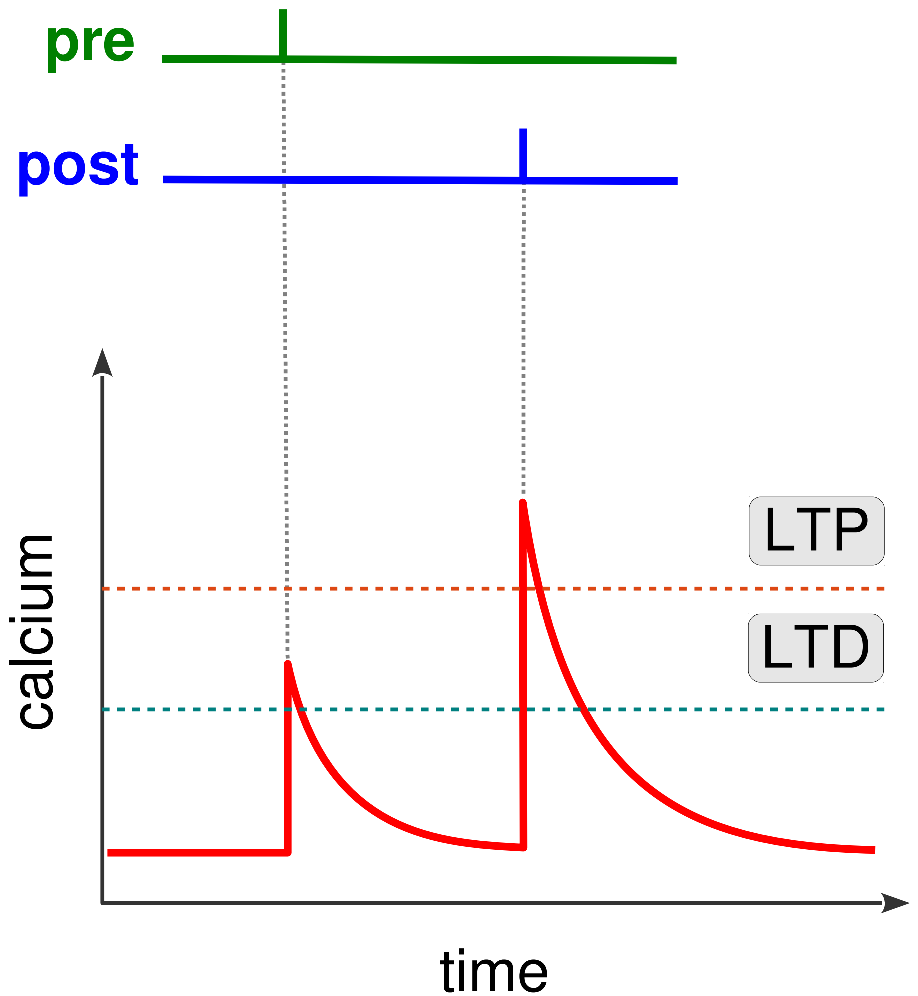


- protein signaling cascade activated by [Ca^{2+}] [Graupner & Brunel, 2007; Urakubo *et al.*, 2008]

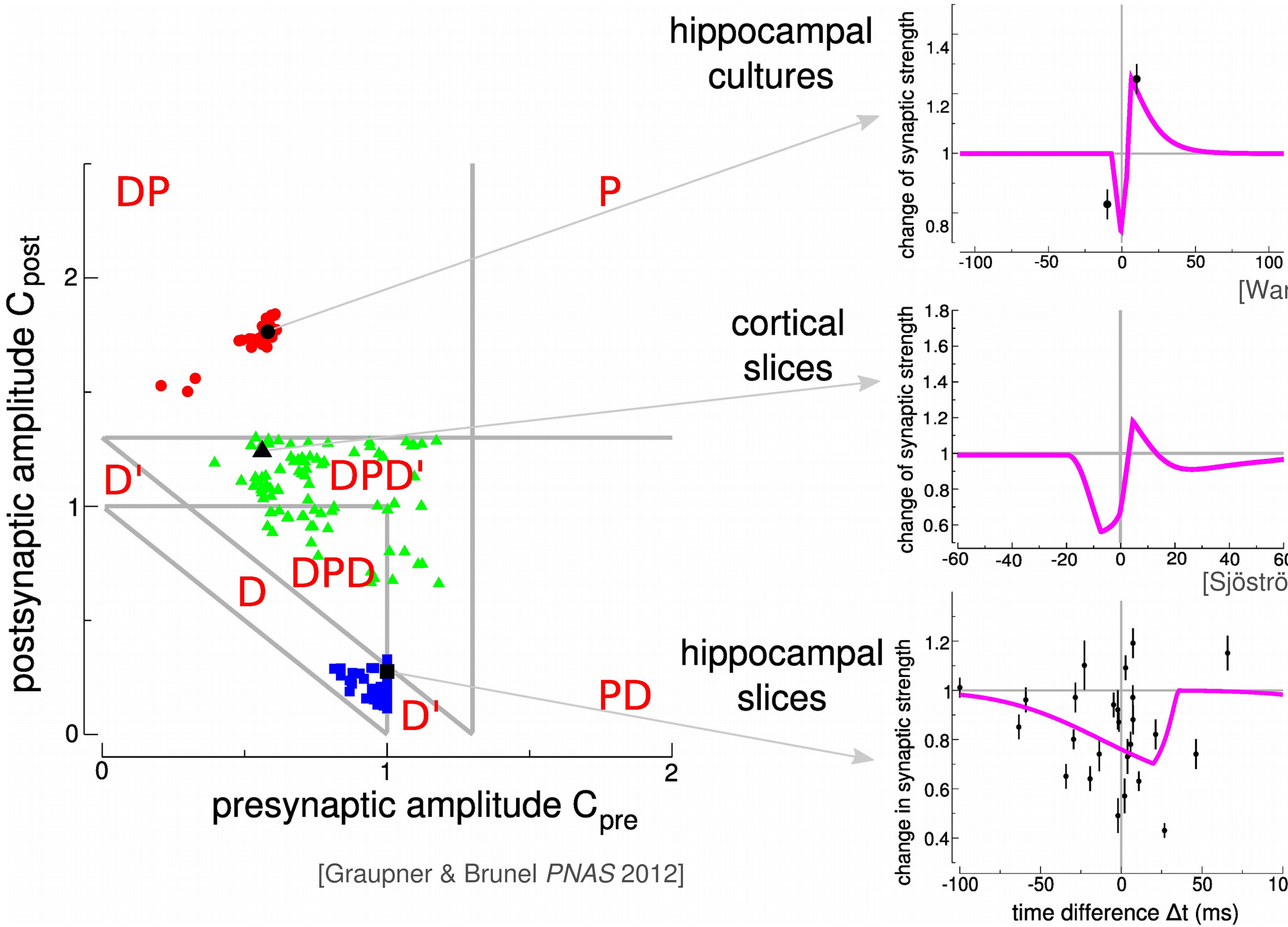


Varying Ca-amplitude → diversity of STDP curves



[Graupner & Brunel *PNAS* 2012]

Experimental diversity explained by different Ca-dynamics



[Graupner & Brunel *PNAS* 2012]

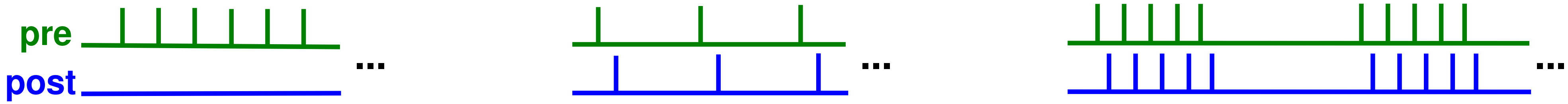
[Wang *et al.*, 2005]

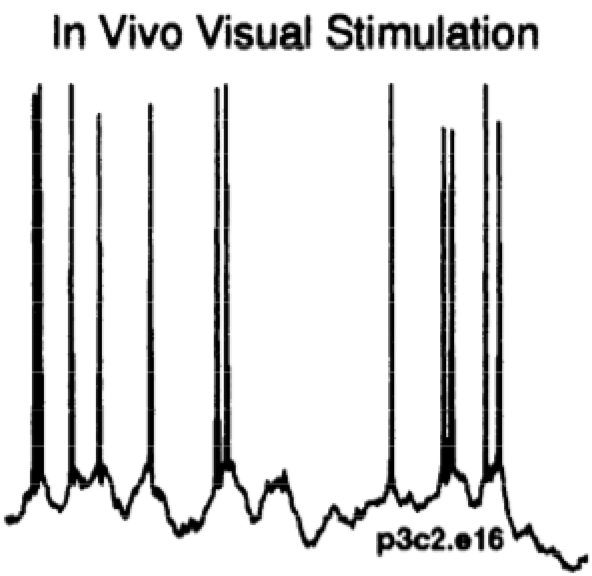
[Sjöström *et al.*, 2006]

[Wittenberg & Wang, 2006]

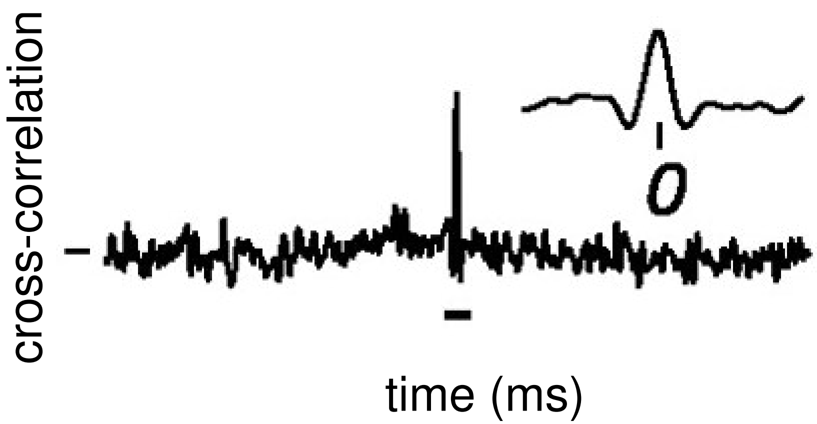
Outline

Realistic firing is highly irregular



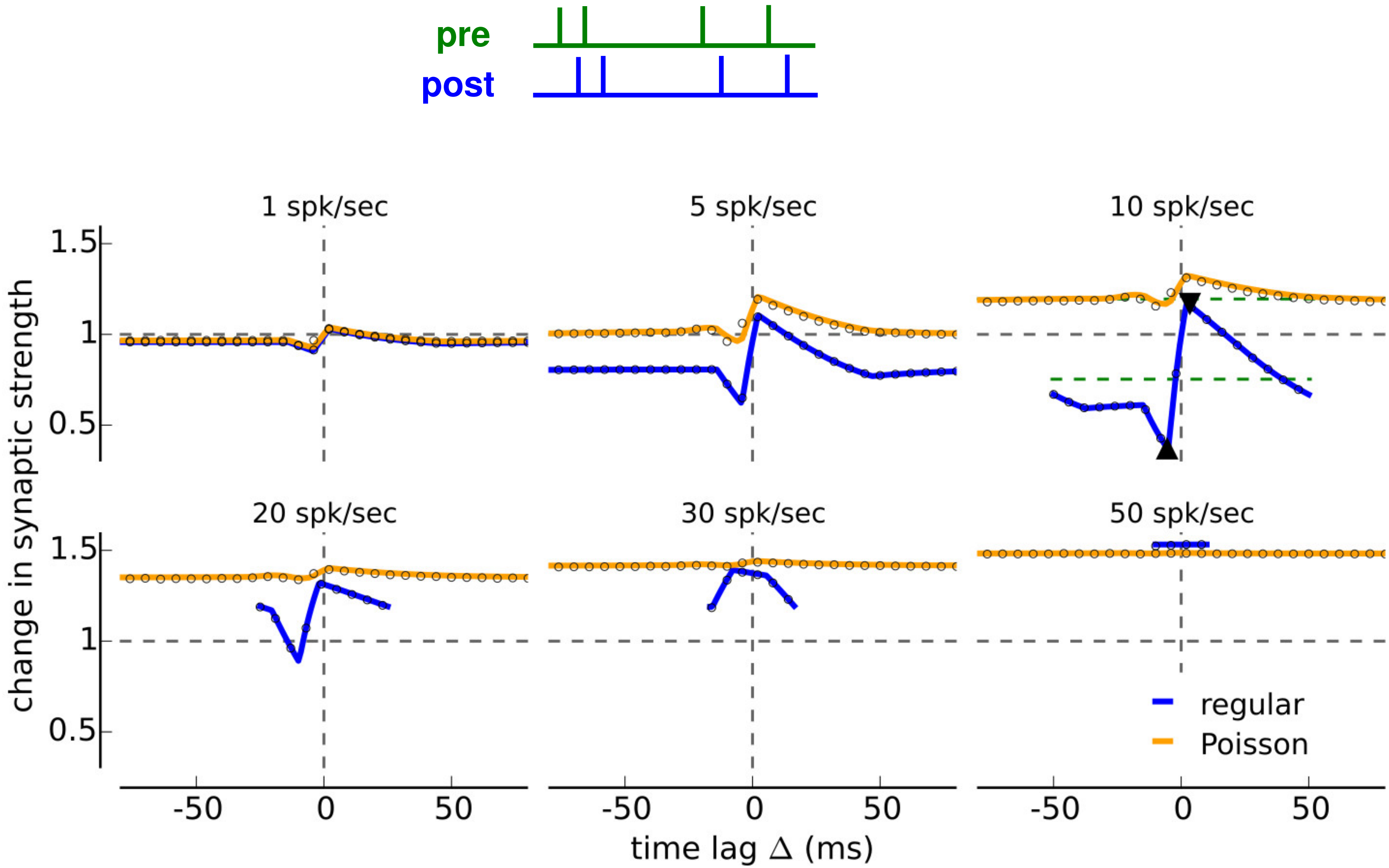


[Holt *et al.*, 1996]



[Kohn and Smith, 2005]

Irregular spike-pairs flatten STDP curve

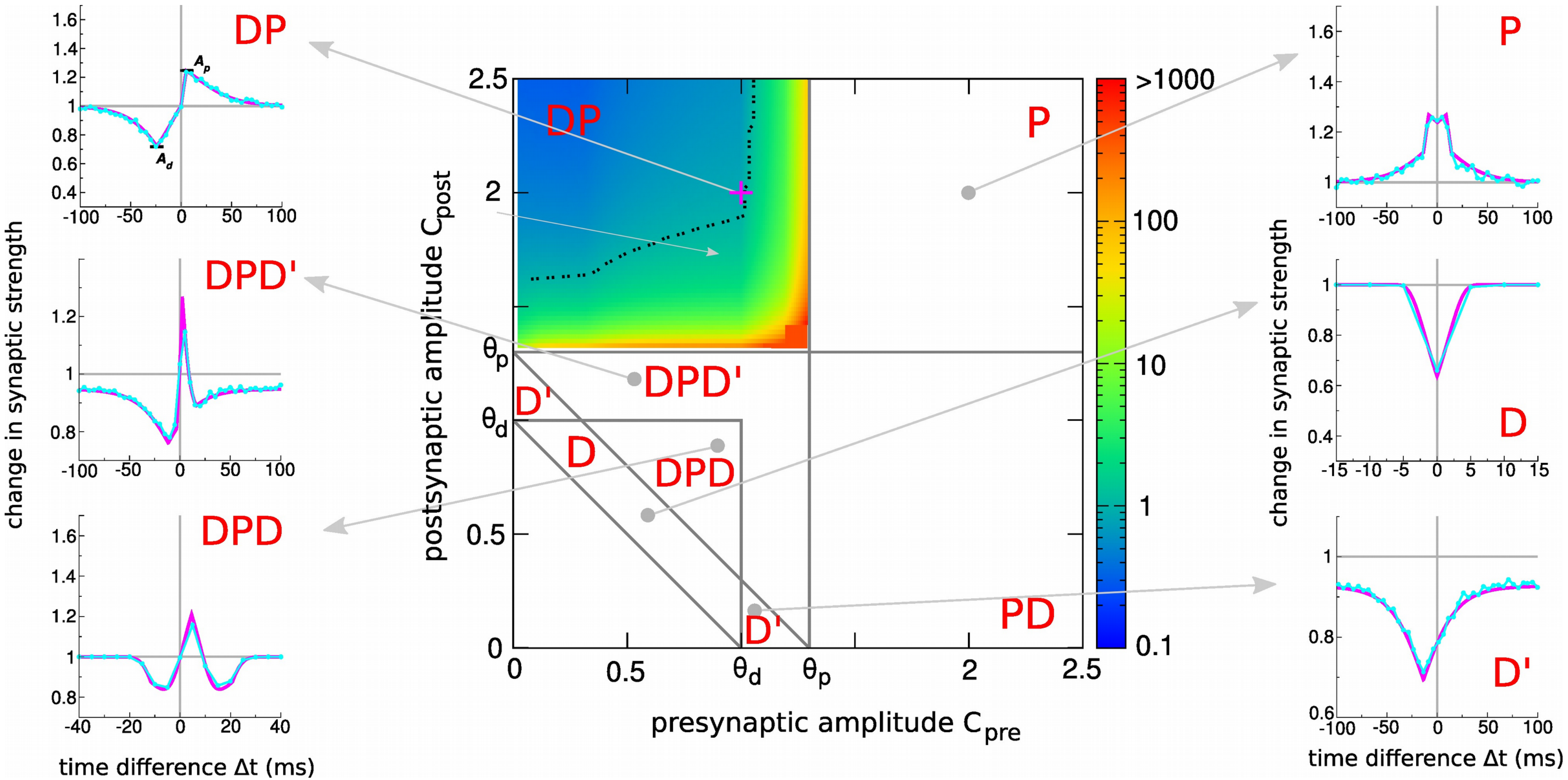


[Graupner et al. *unpublished*]

Conclusions

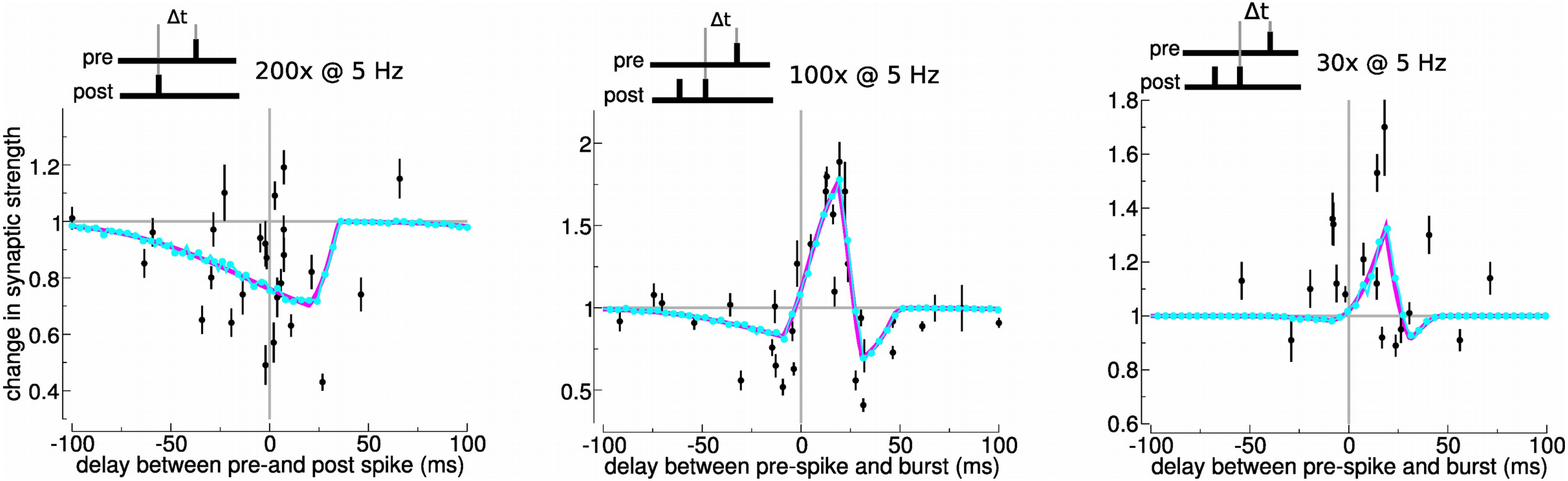
- STDP : temporally asymmetric form of synaptic plasticity induced by tight temporal correlations between the spikes of pre- and postsynaptic neurons
- induction: coincident pre- and postsynaptic activity lead to calcium influx through NMDA receptors, triggering intracellular signaling cascades
- biophysical model resolve various aspects of the synaptic machinery involved in plasticity induction, most commonly the postsynaptic calcium dynamics
- the role of STDP for learning in the living animal remains elusive

Diversity of STDP curves : spike-pair stimulation



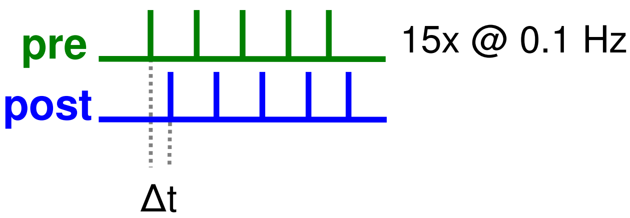
[Graupner & Brunel, 2012]

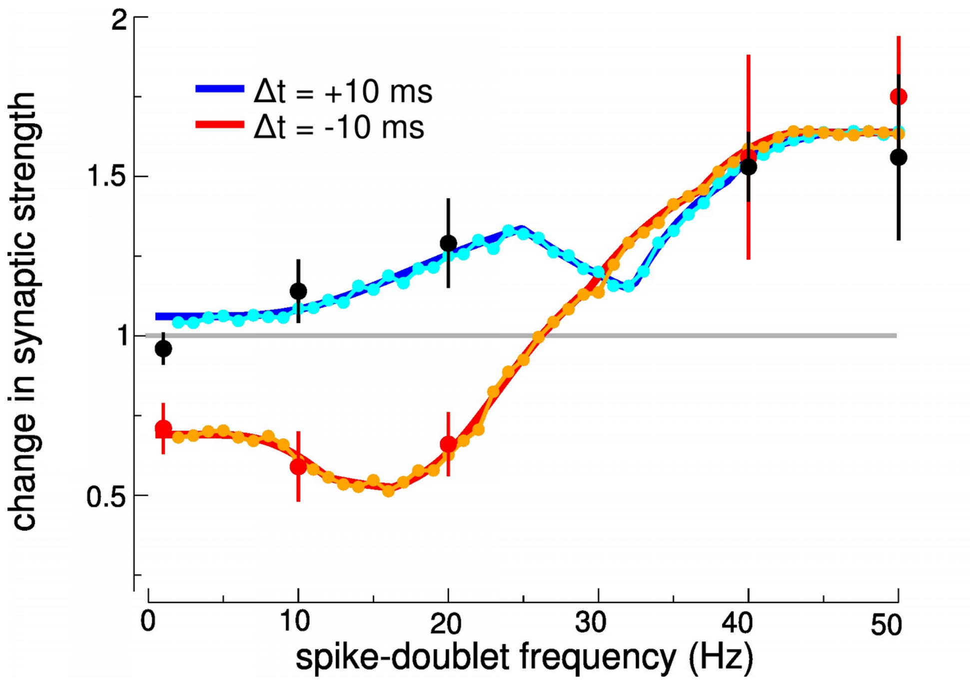
Malleability of hippocampal STDP explained by Ca^{2+}

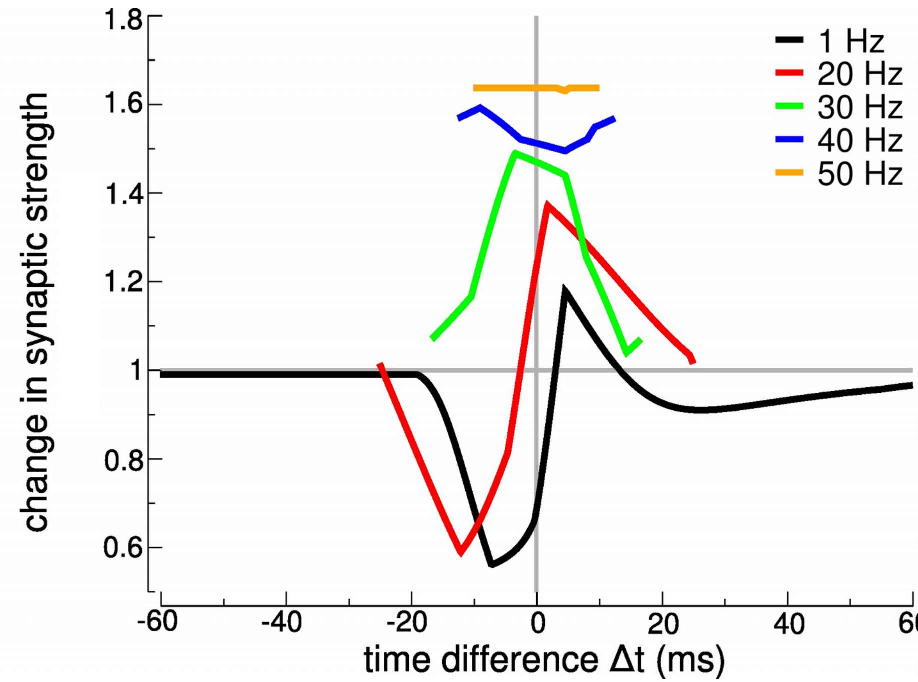


[Wittenberg & Wang, 2006]

Firing rate dependence in cortical slices

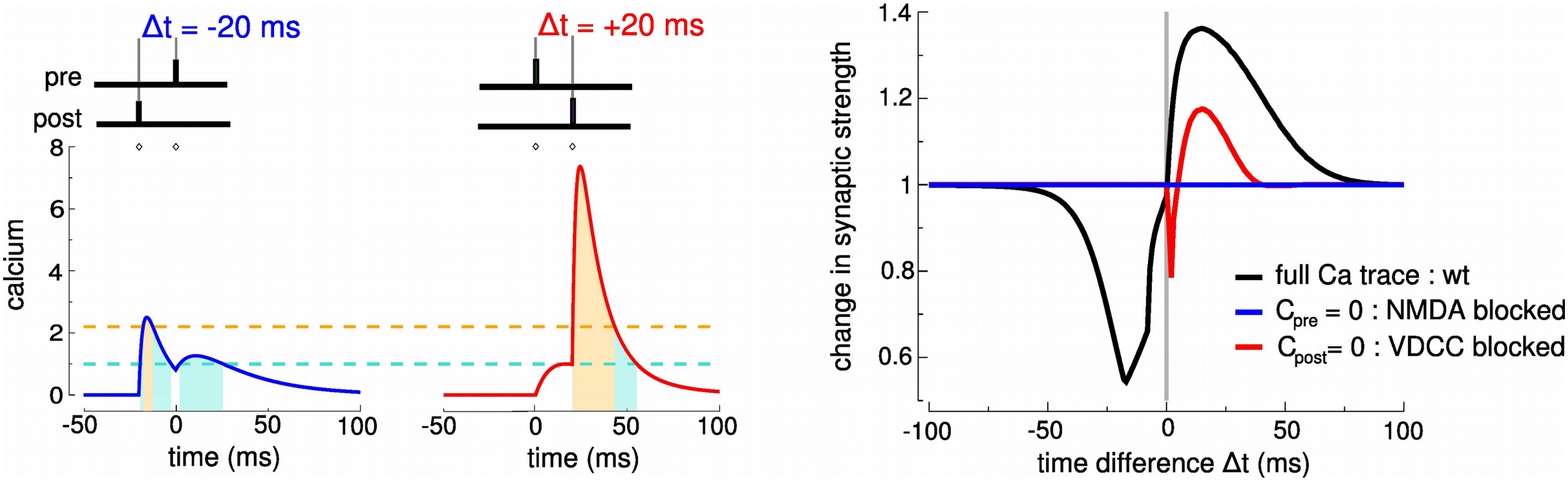






[Sjöström *et al.*, 2001]

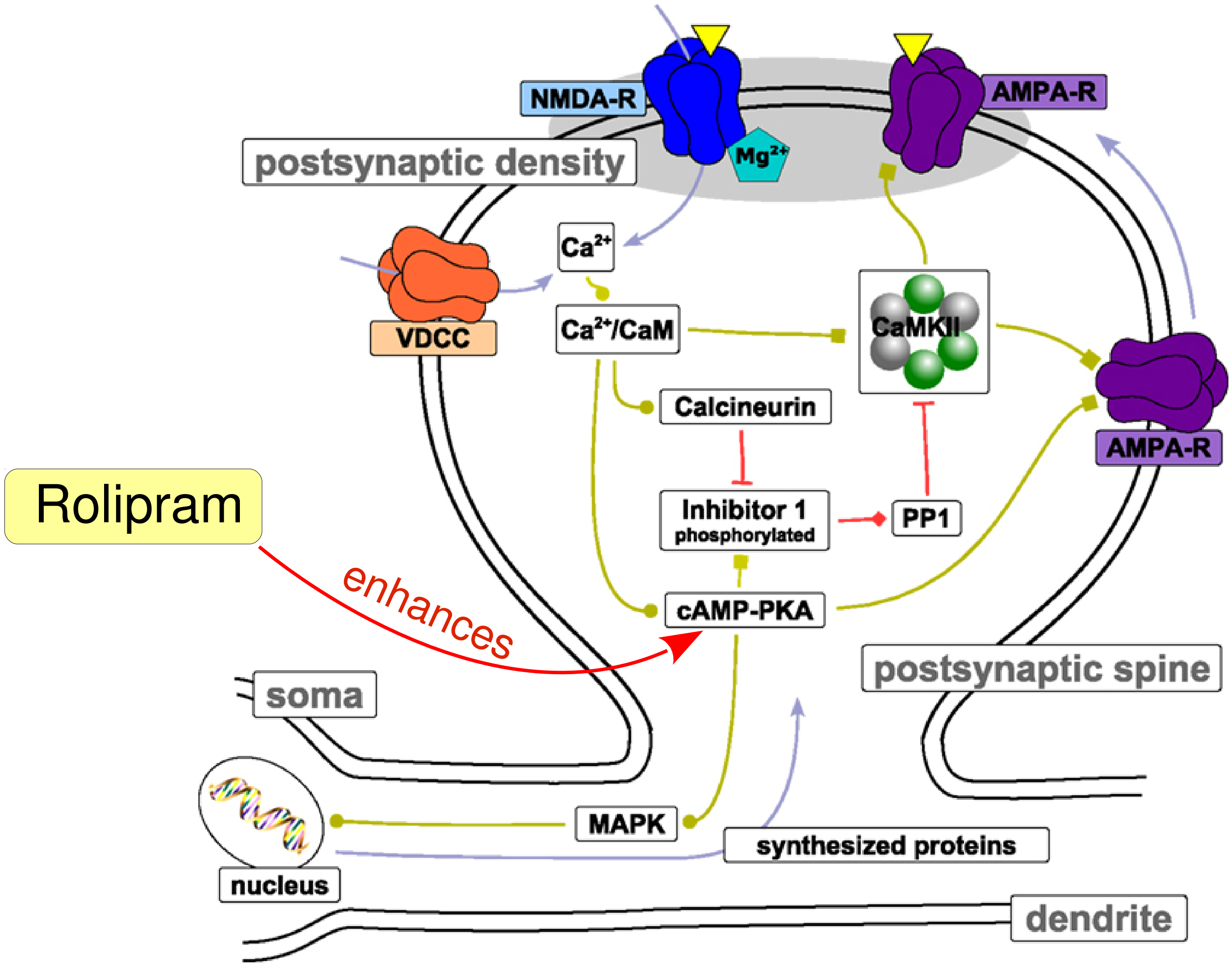
Pharmacological manipulations explained by Ca^{2+}



[Bi & Poo, 1998; Nevian & Sakmann, 2006]

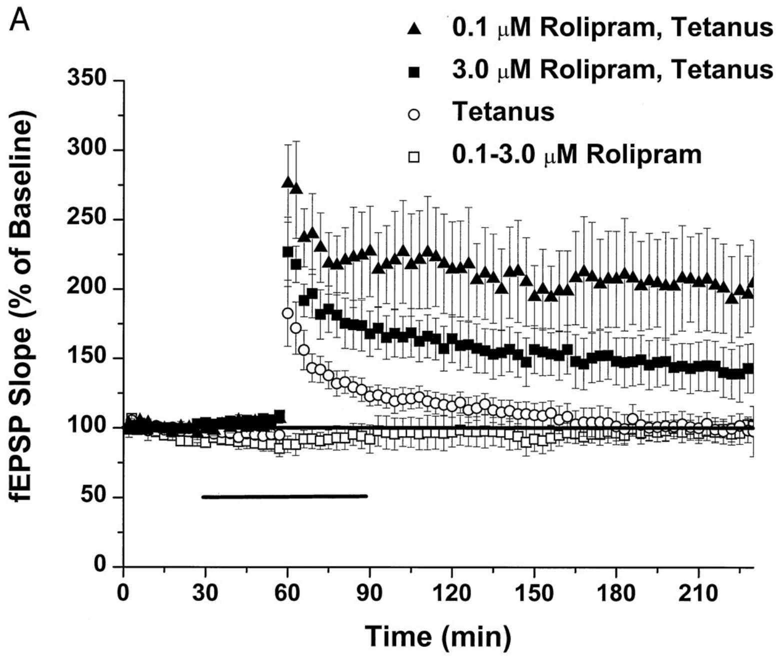
- nonlinear, finite rise time calcium transients necessary to reproduced pharmacological block experiments

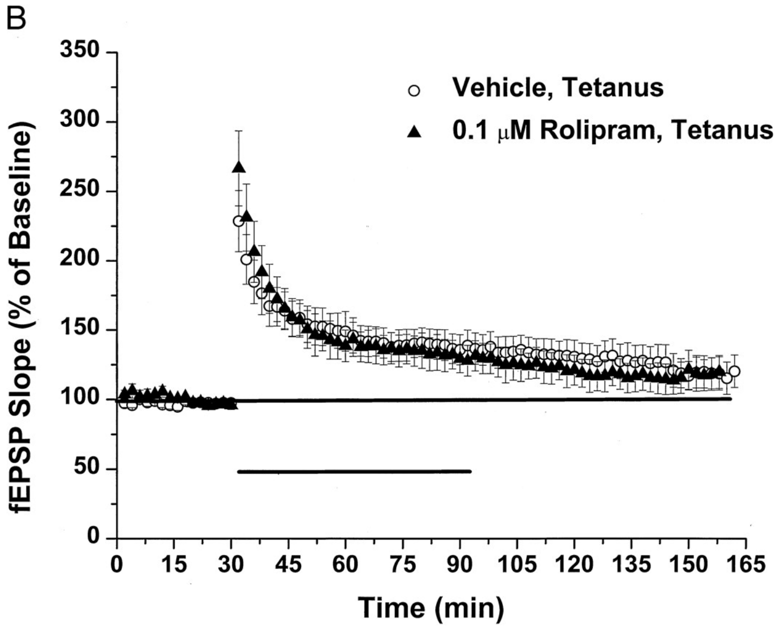
Study the effect of nootropic drugs (memory enhancer)



Rolipram … selective phosphodiesterase-4 inhibitor

Study the effect of nootropic drugs



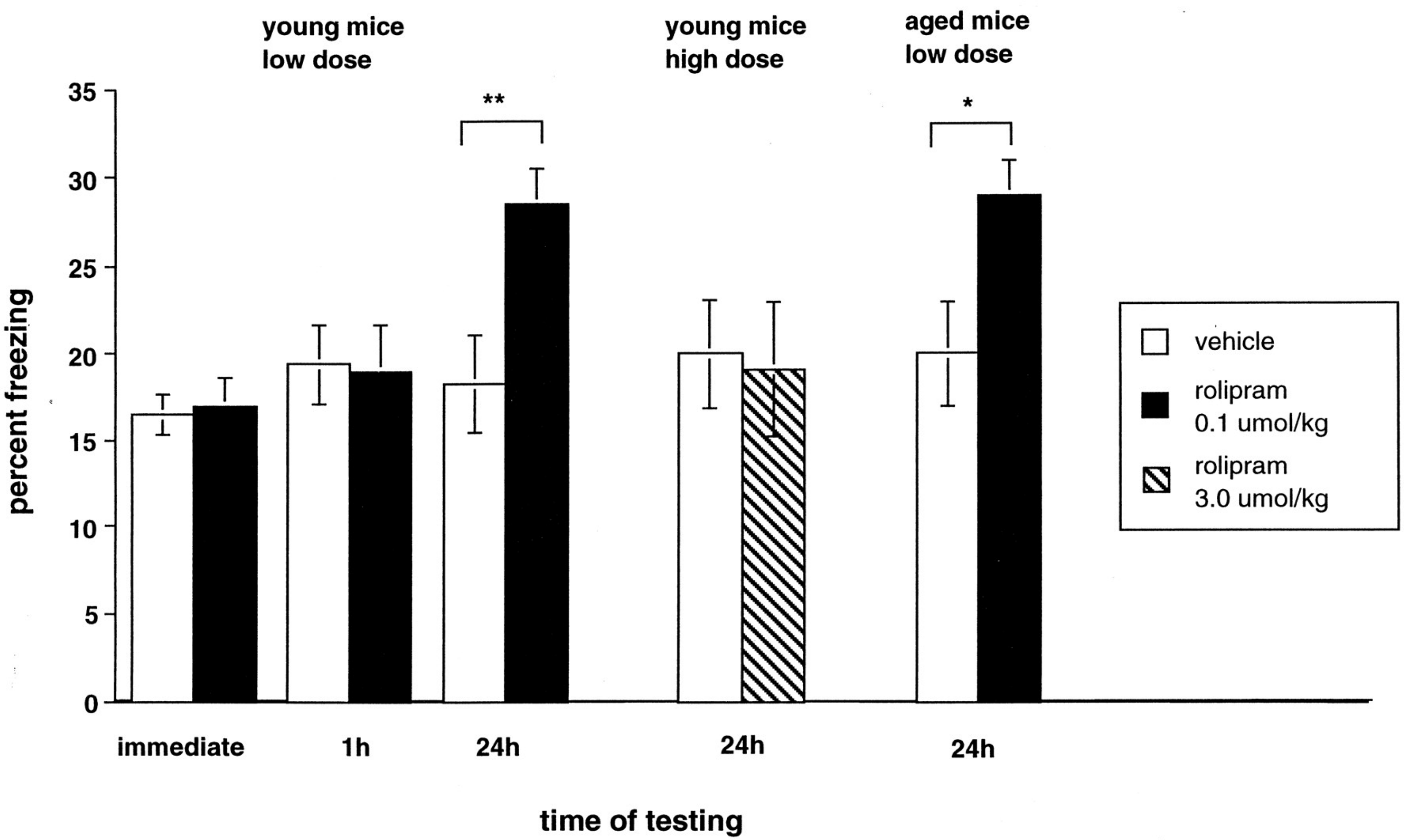


- boosting of cAMP *during* stimulation increases LTP

[Barath *et al.*, 1998]

Study the outcome of nootropic drugs

- Rolipram enhances memory



[Barath *et al.*, 1998]