Synaptic Plasticity : Spike-timing dependent plasticity (STDP)

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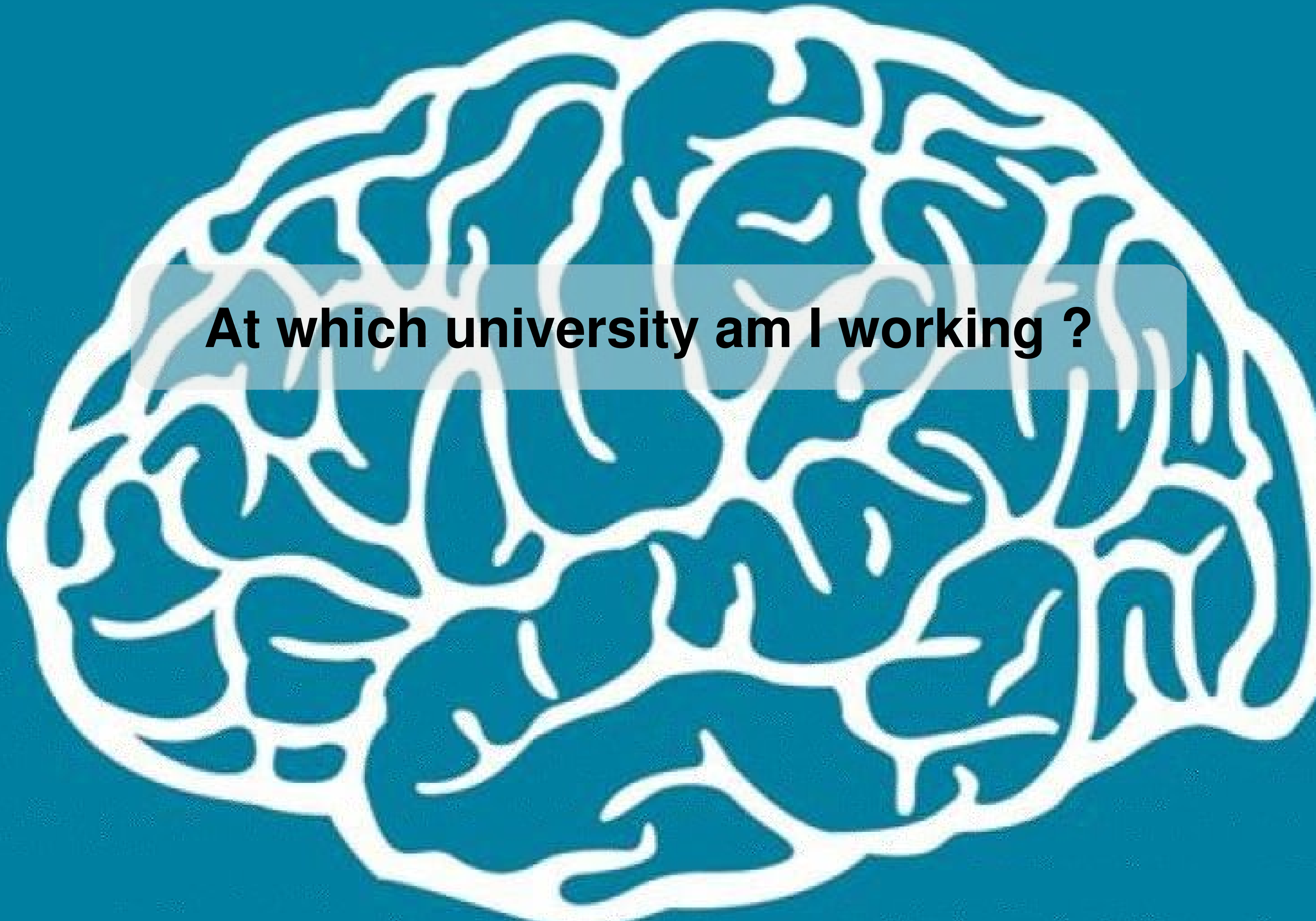
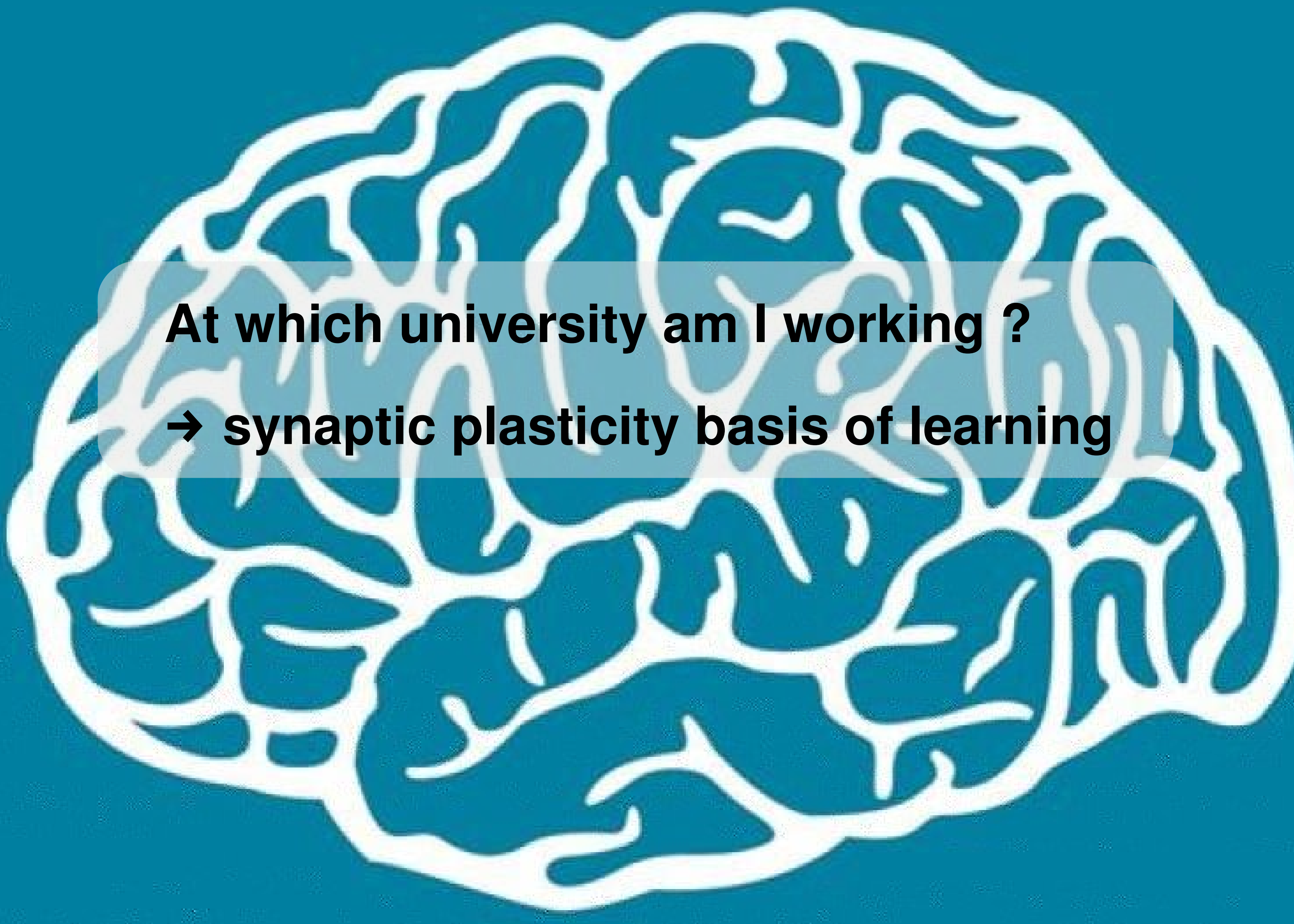
slides : http://www.biomedicale.univ-paris5.fr/~mgraupe/



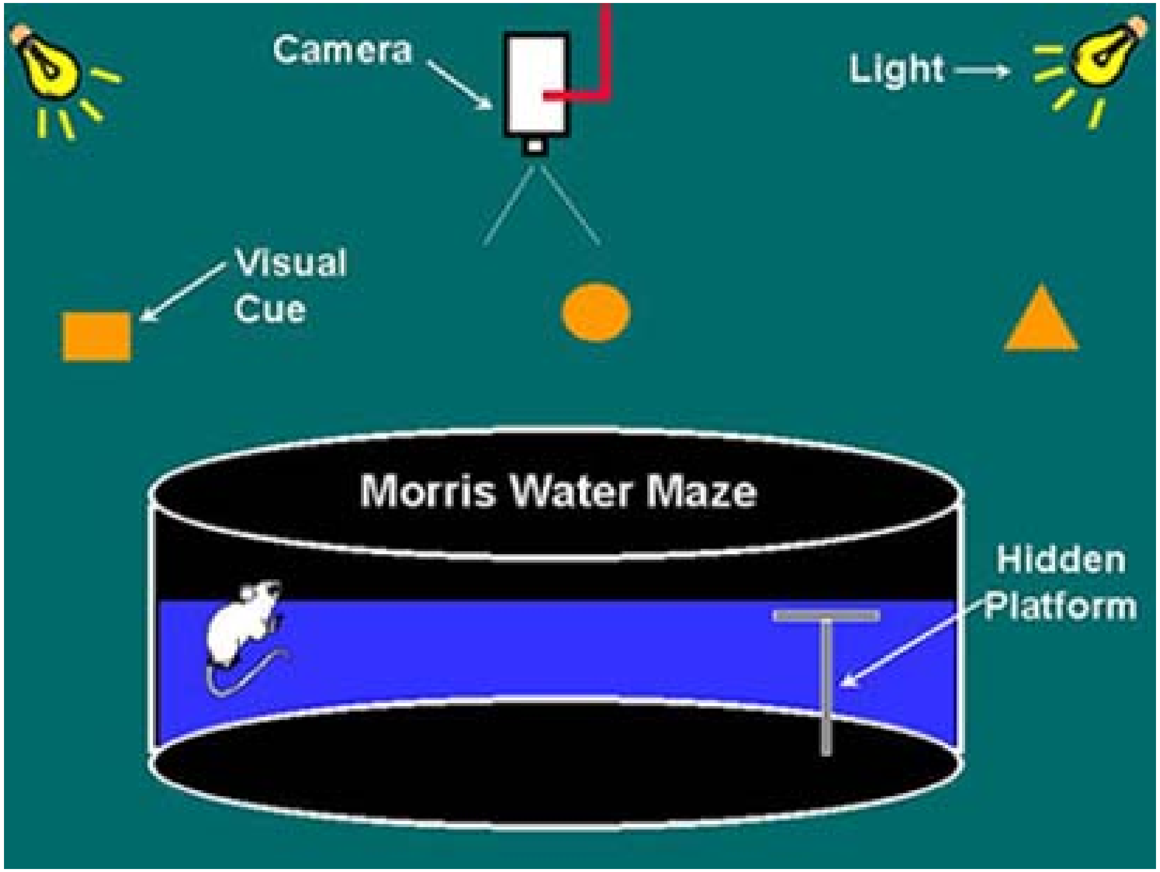
At which university am I working ?



At which university am I working ?

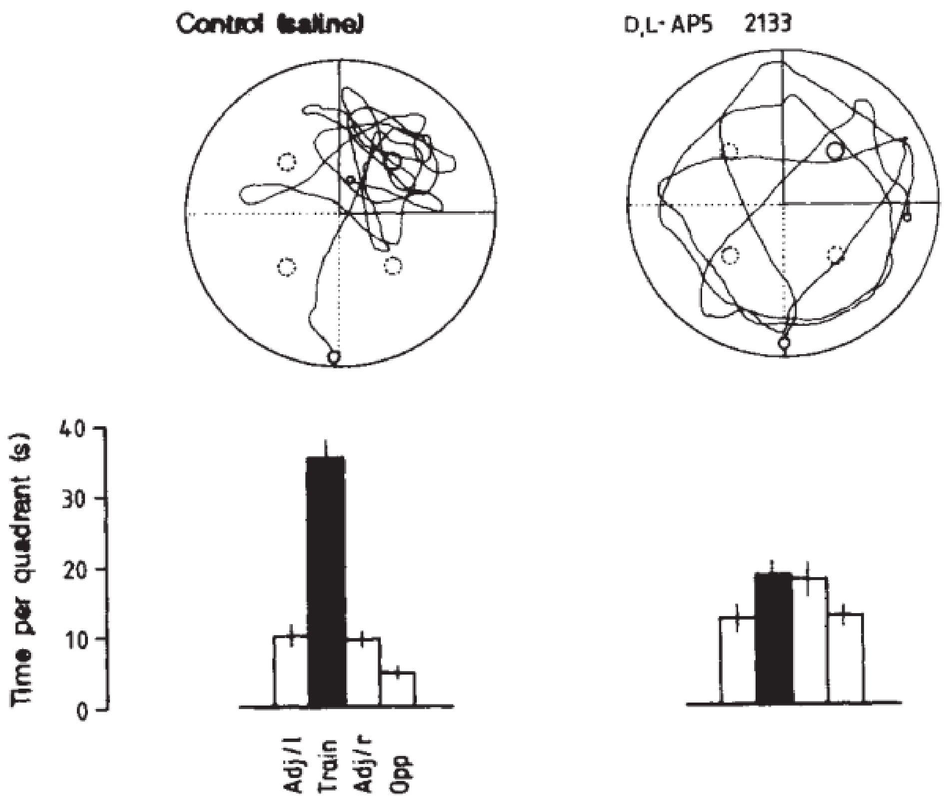
➔ synaptic plasticity basis of learning

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

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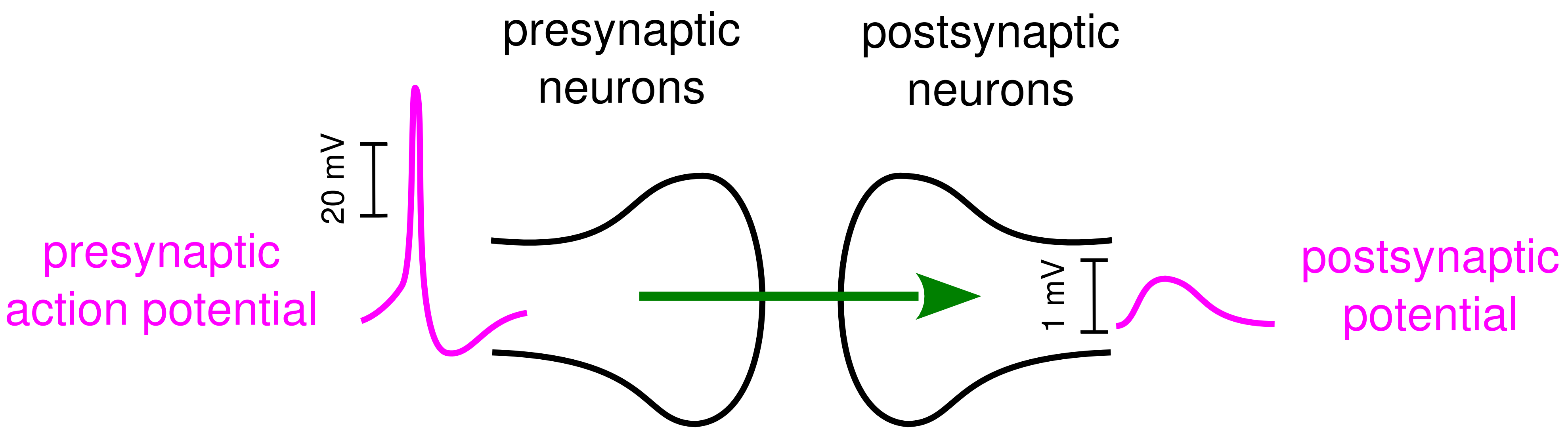
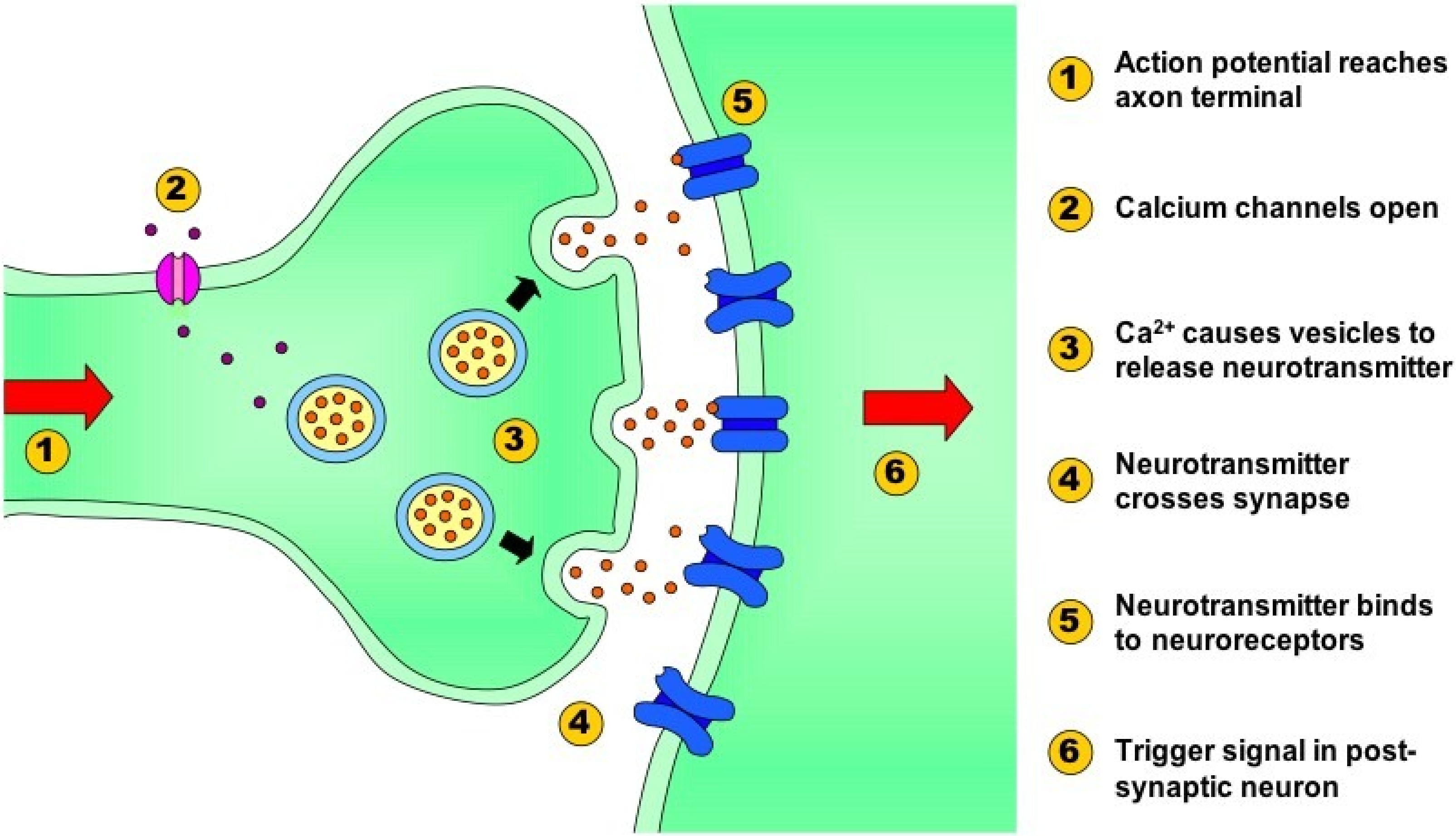
Chemical synapse : transmits electrical signals



electrical signal → chemical signal → electrical signal

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

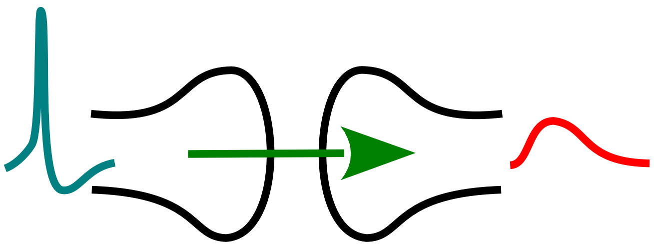
Chemical synapse : underlying biological machinery



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

Chemical synapse : excitatory or inhibitory

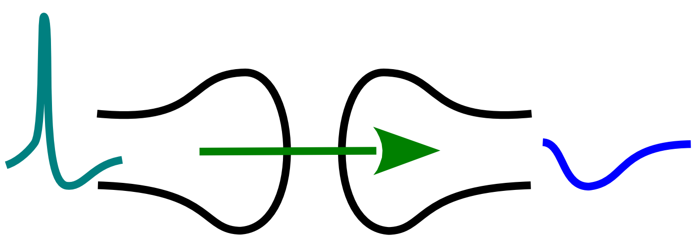
Excitatory synapse



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



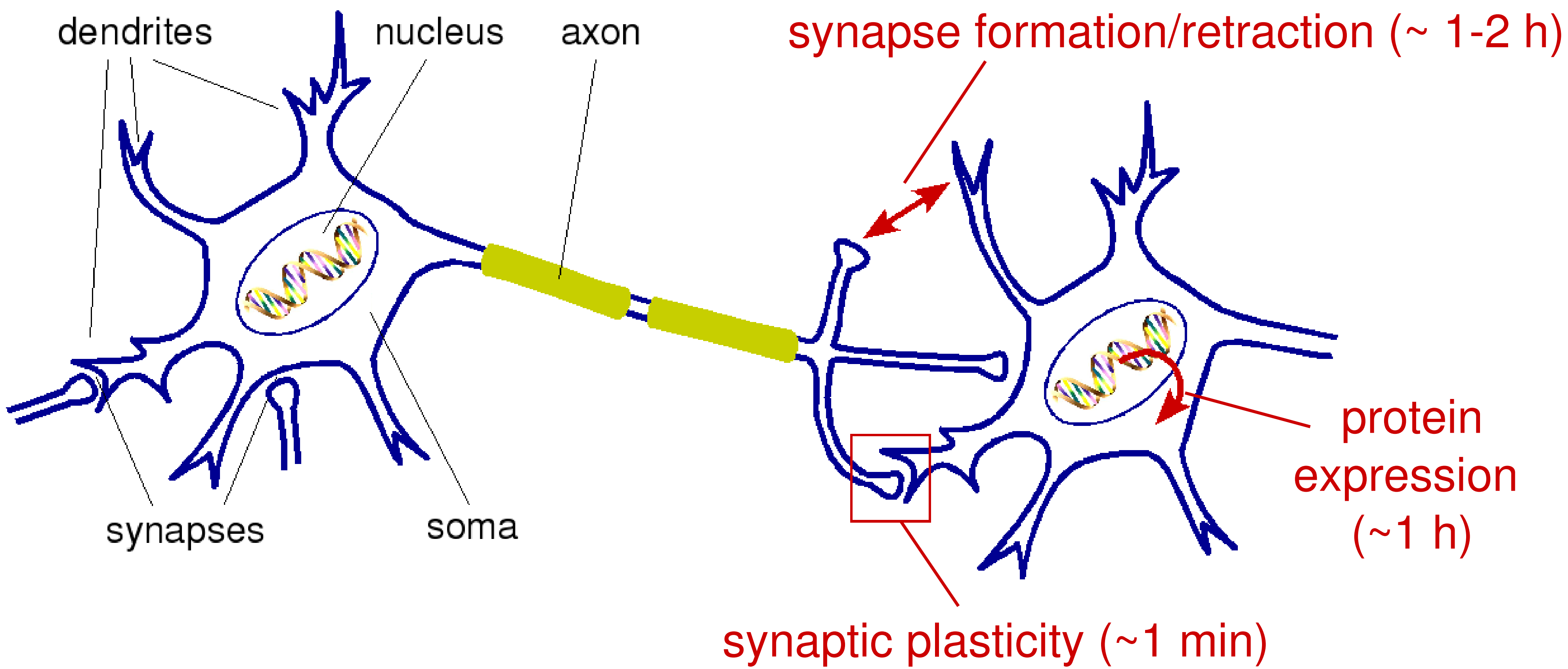
hyperpolarization:
Inhibitory postsynaptic potential (IPSP)

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

Different forms of plasticity

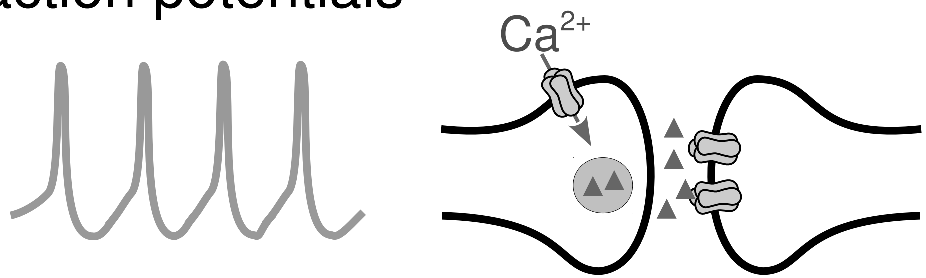
structure of neurons

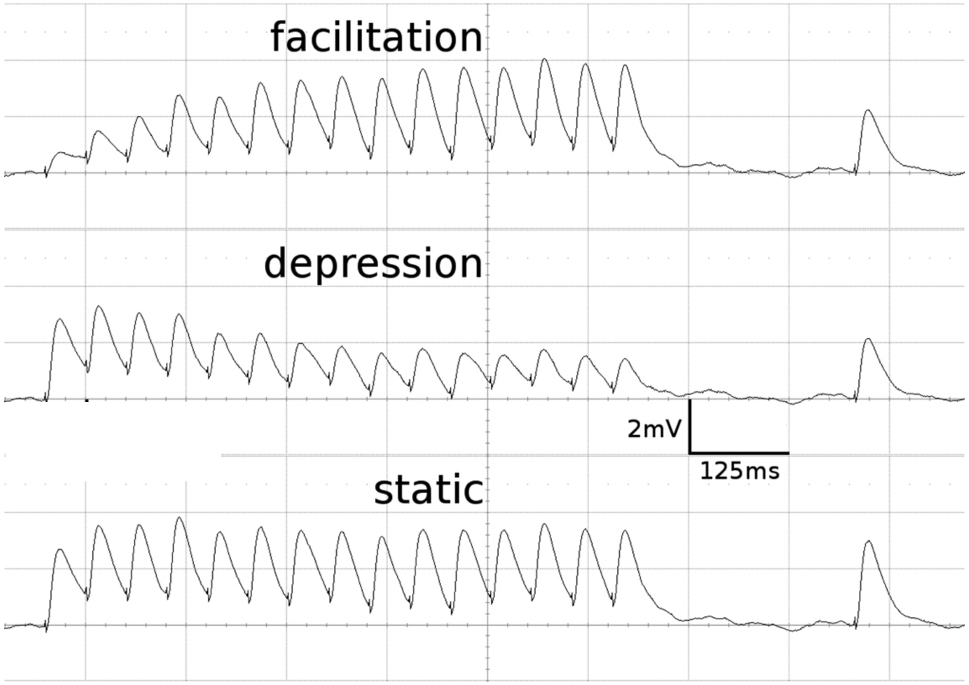
changes related to neural activity



Short-term synaptic plasticity

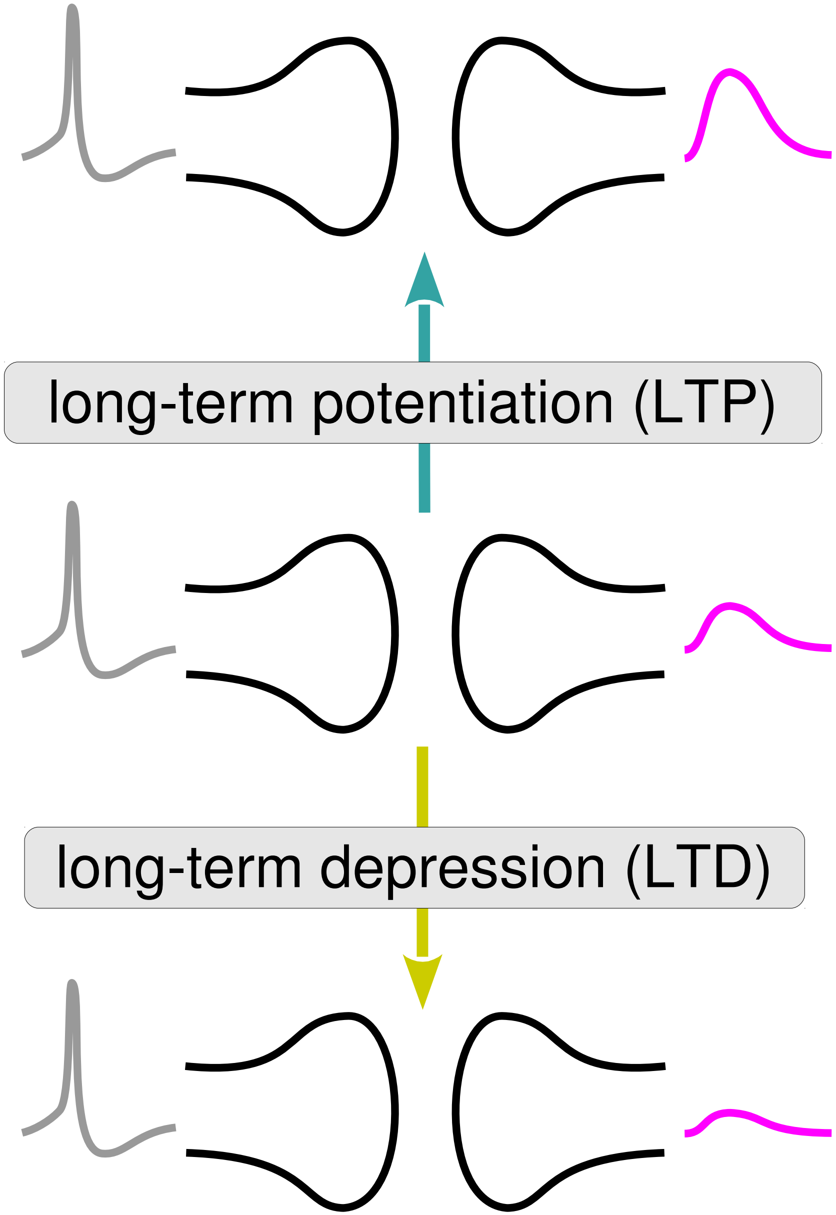
train of presynaptic
action potentials





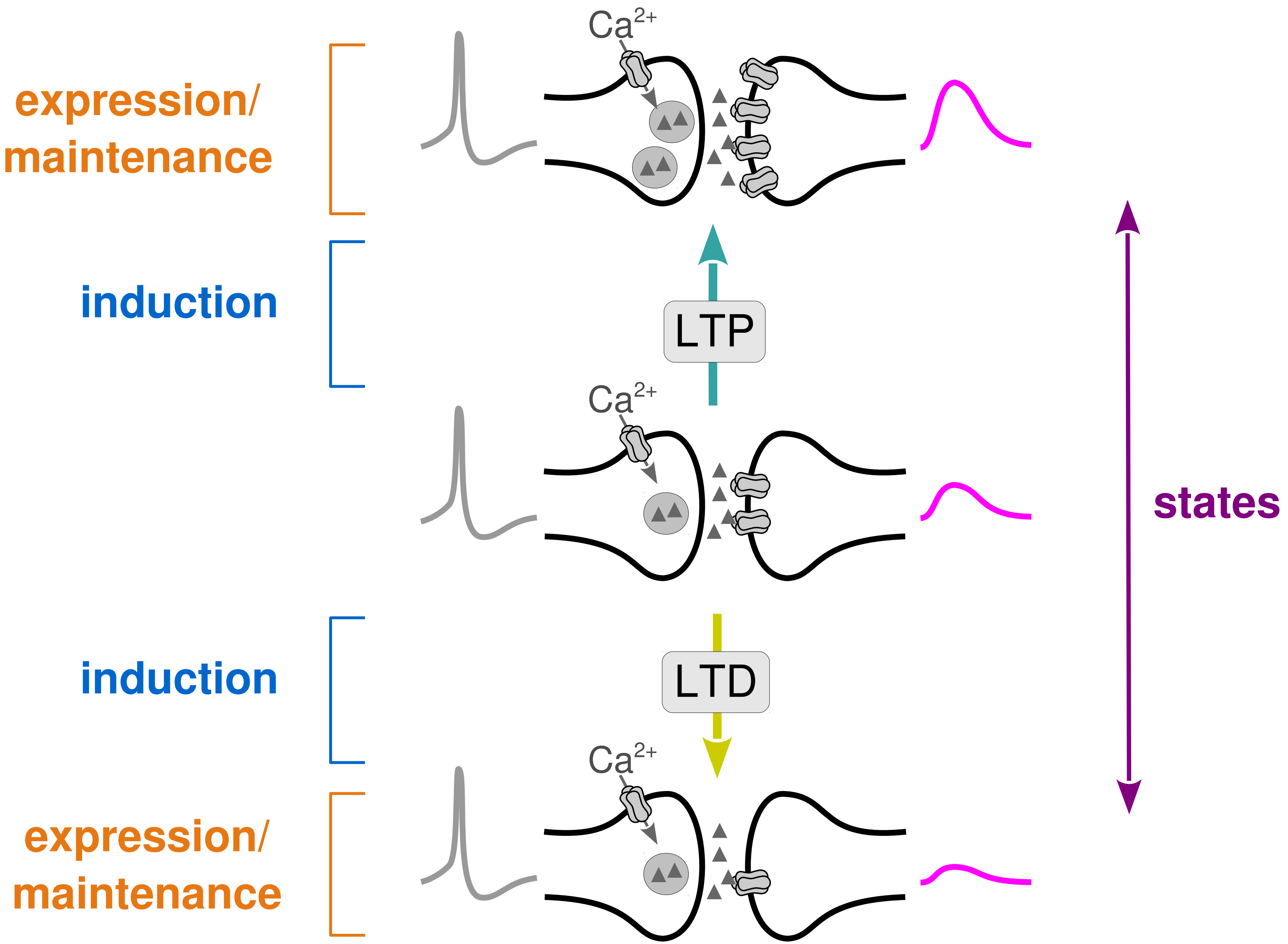
- transient change in transmission efficacy
- time scale of changes ~1 sec

Long-term synaptic plasticity

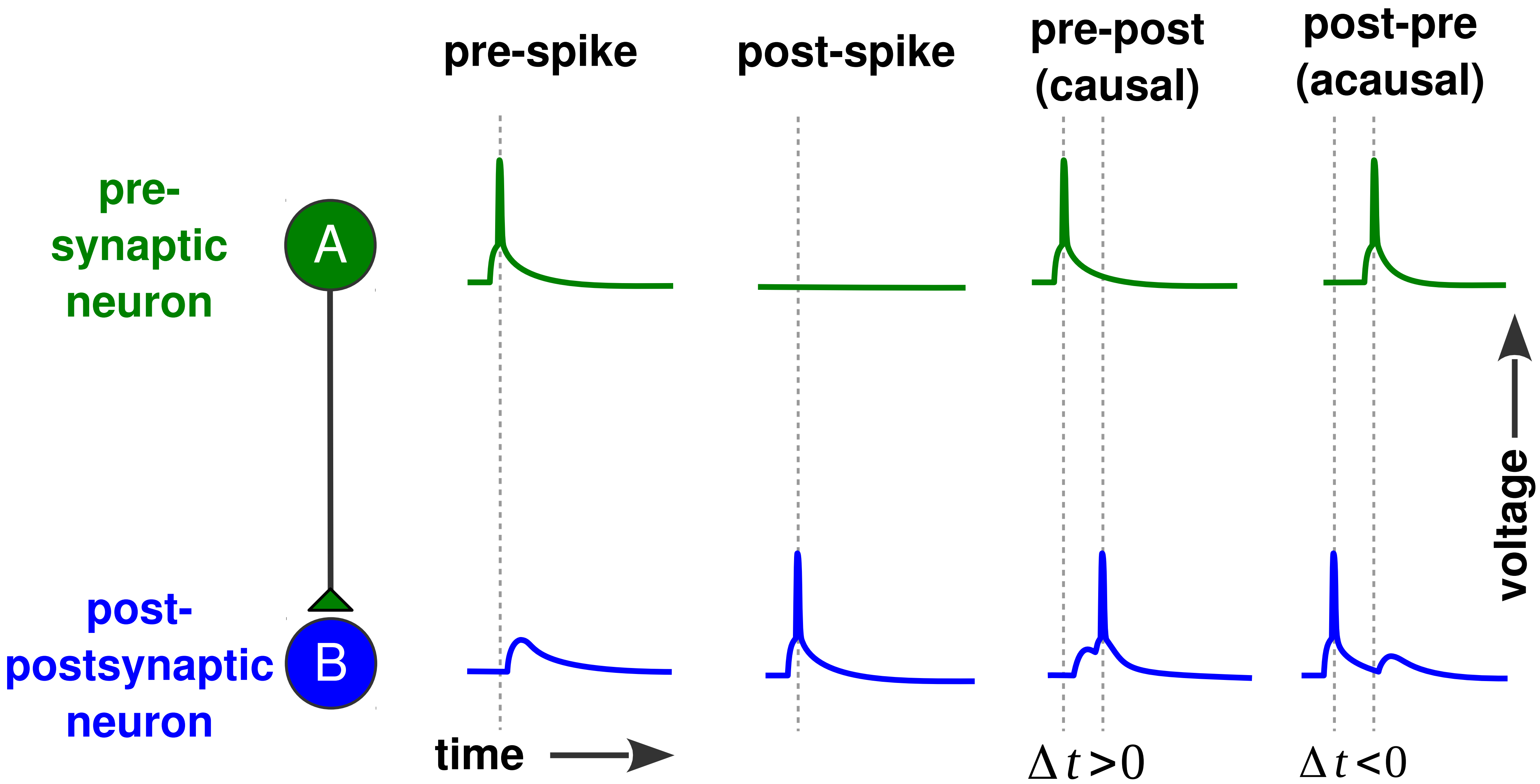


- long-lasting change (>60 min) in transmission efficacy
- time scale of induction ~ 1 min

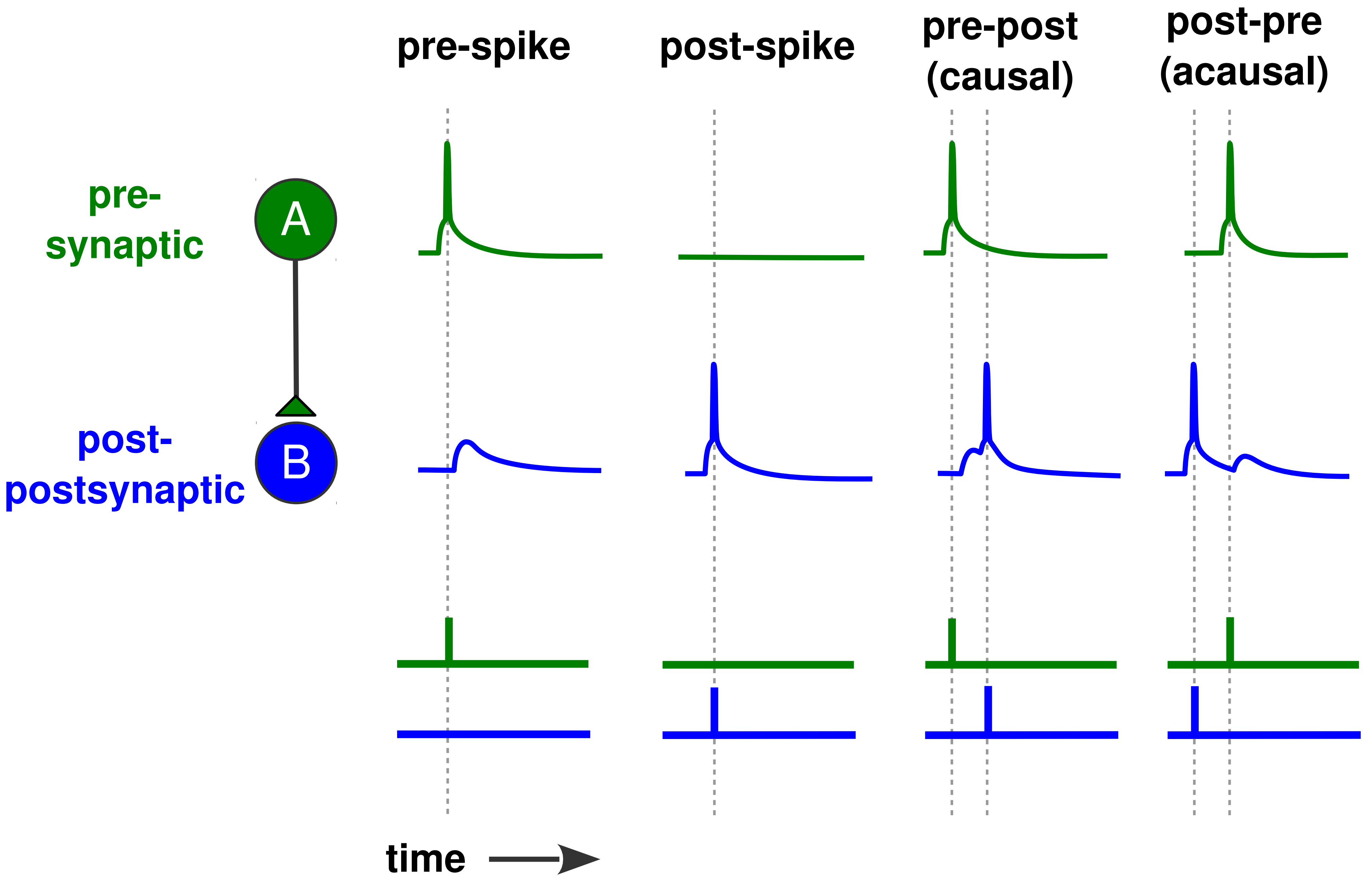
Synaptic plasticity: induction, maintenance & states



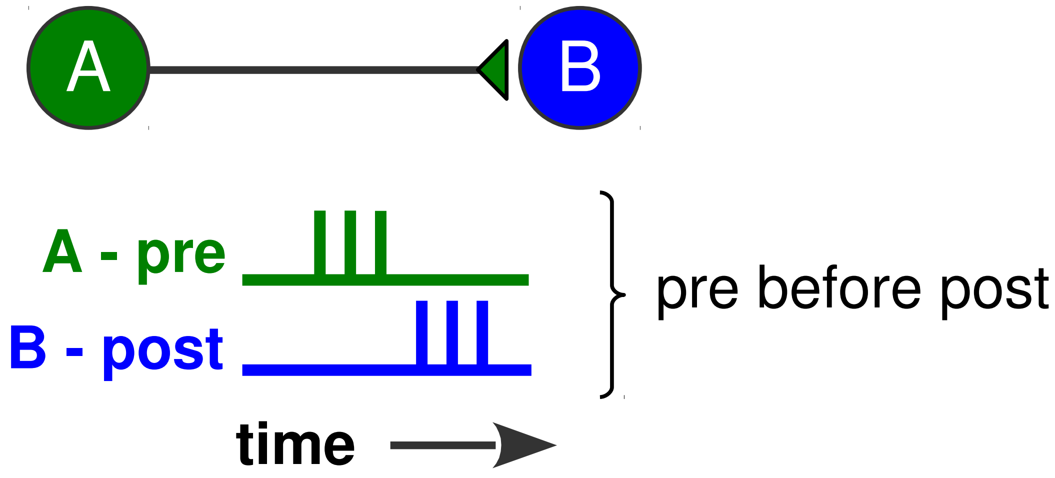
Spike timing : nomenclature



Spike timing : nomenclature



LTP induction: early conceptual work

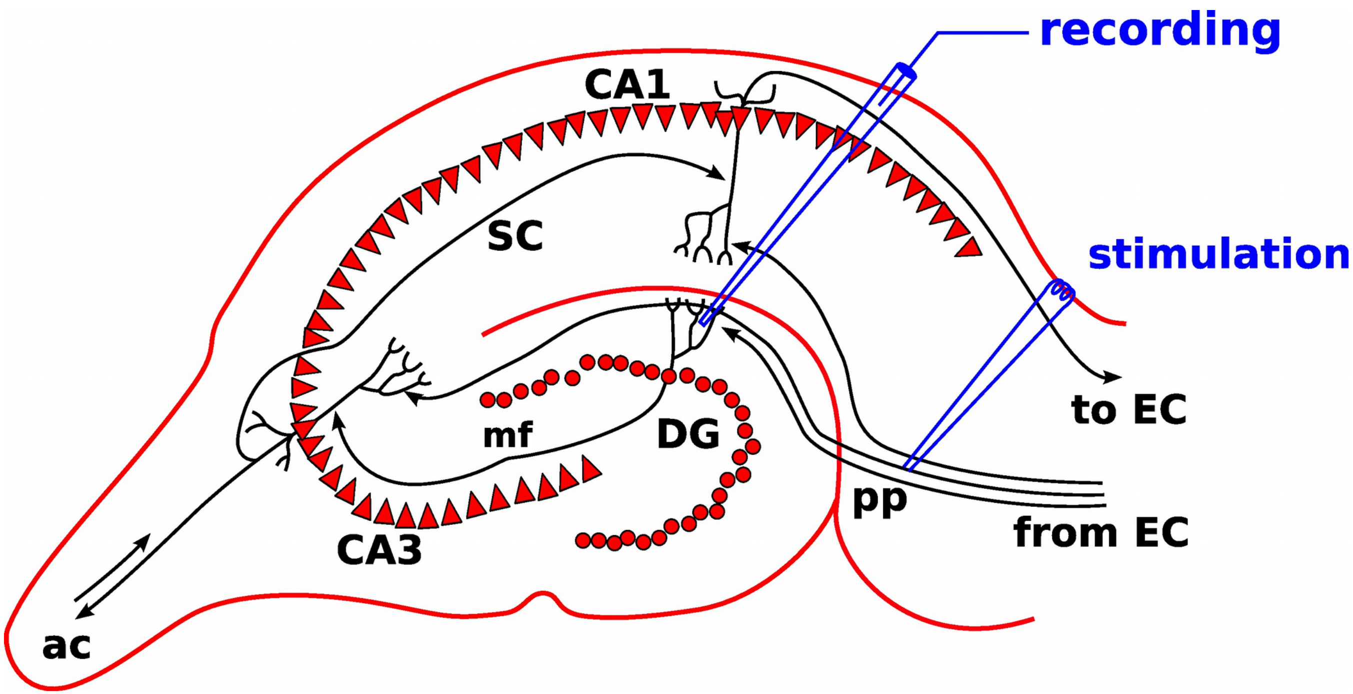


"When an axon of cell A is near enough to excite a cell B and *repeatedly* and *persistently* takes part in firing it, some growth or metabolic changes take place in one or both cells such that A's efficiency, as one of the cells firing B, is *increased.*"

[Hebb 1949;
see also Konorski 1948]

Induction: first experimental work in hippocampus

hippocampus

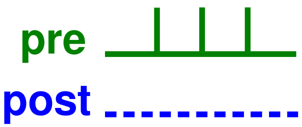


EC	...	enthorhinal cortex
DG	...	dentate gyrus
CA3/1	...	cornu ammonis 3/1

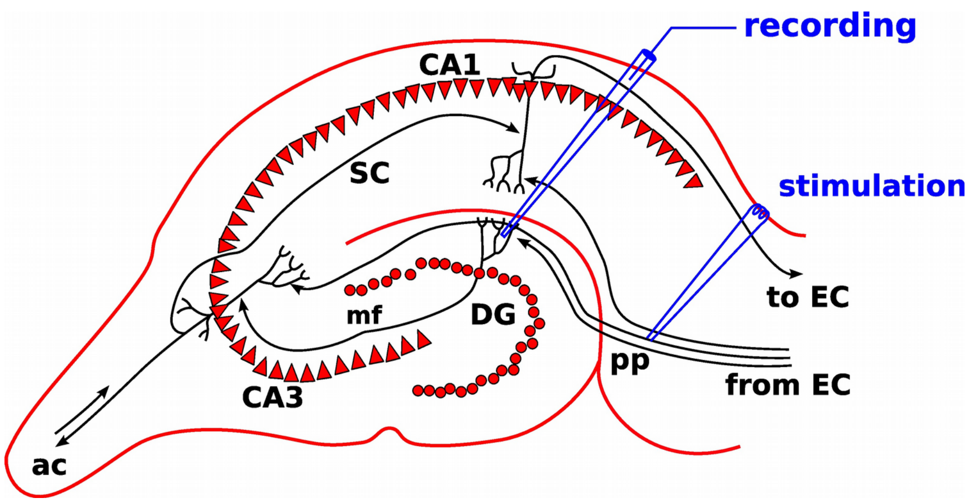
pp	...	perforant path
mf	...	mossy fibres
ac	...	associational commissural path
sc	...	Schaffer collateral

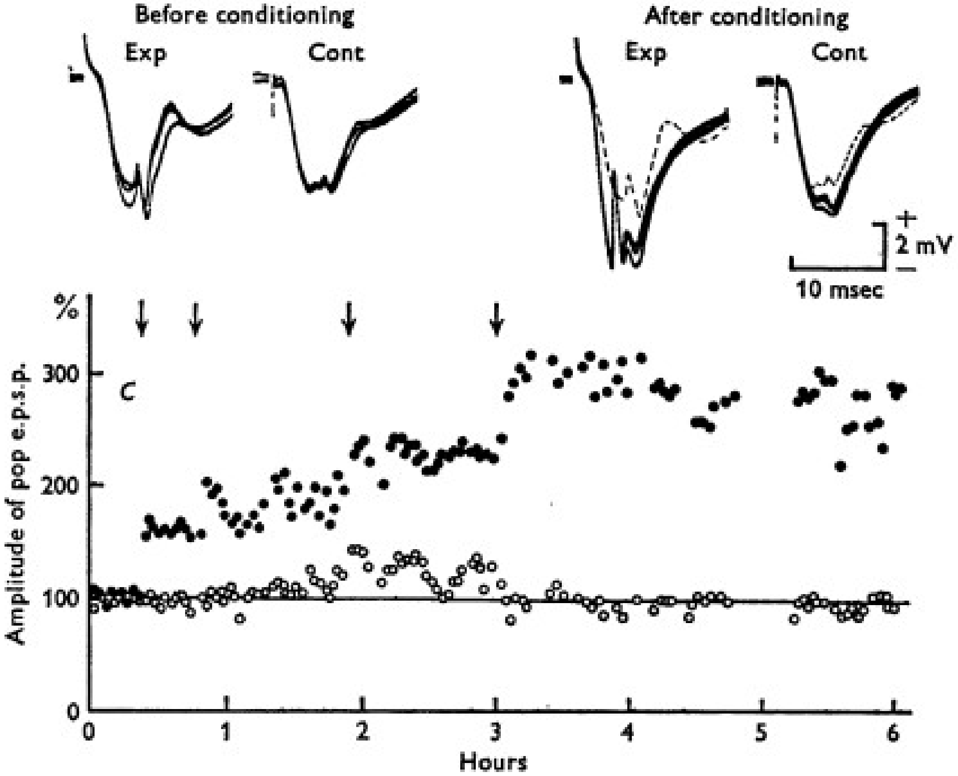
Induction: LTP through high frequency stimulation

hippocampus (*in vivo*)



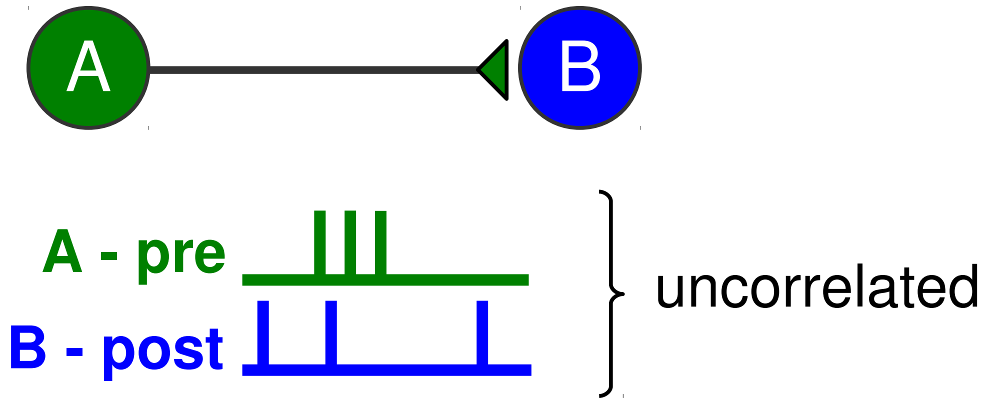
10-20 Hz for 10-15 sec
or 100 Hz for 3-4 sec





[Bliss and Lømo 1973]

LTD induction: postulate of Stent

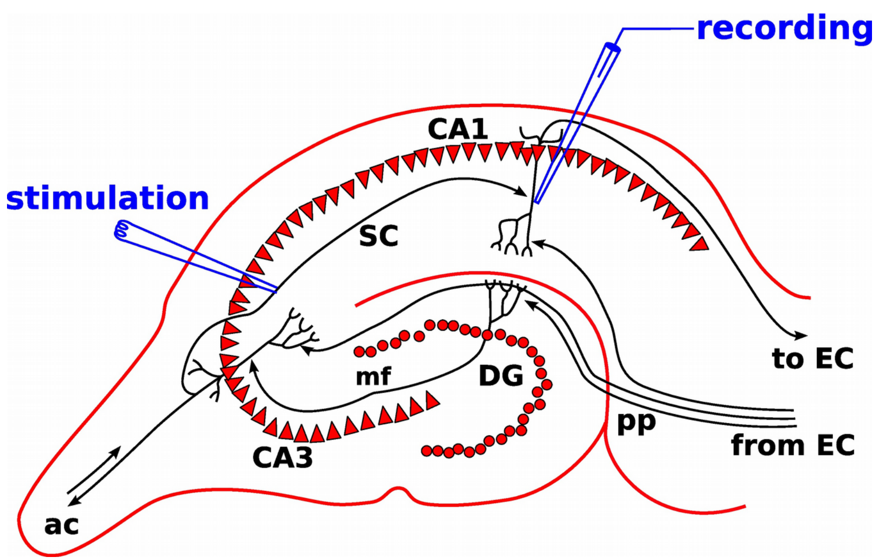


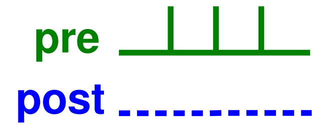
"When the presynaptic axon of cell A *repeatedly* and *persistently* fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is *decreased*."

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

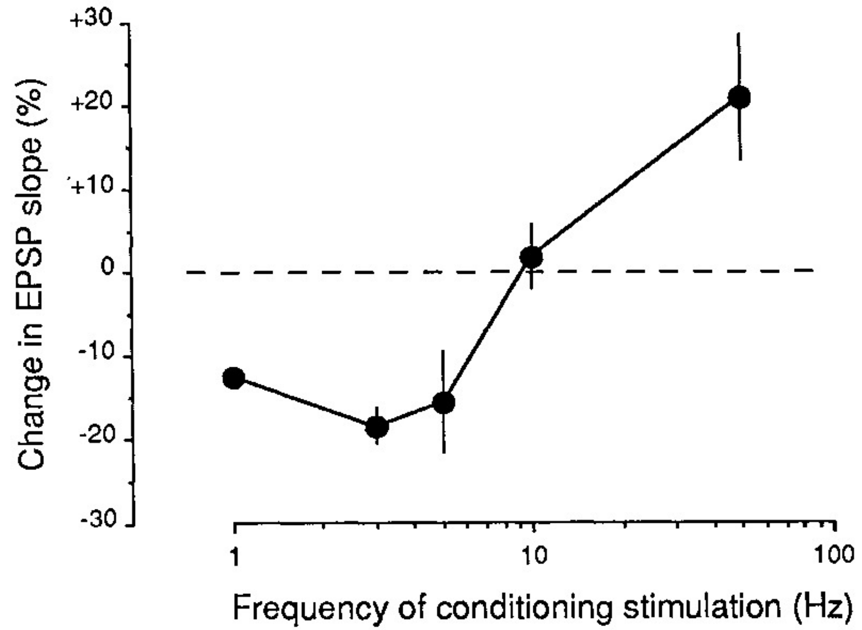
Plasticity induction: LTD obtained at low frequencies

hippocampus (slices)





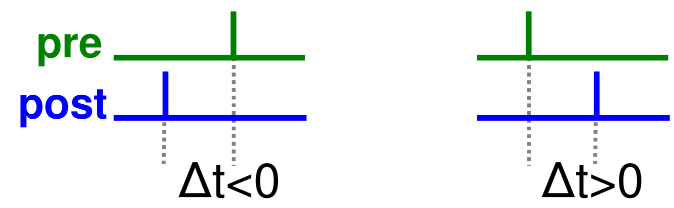
900 pulses at 1-50 Hz



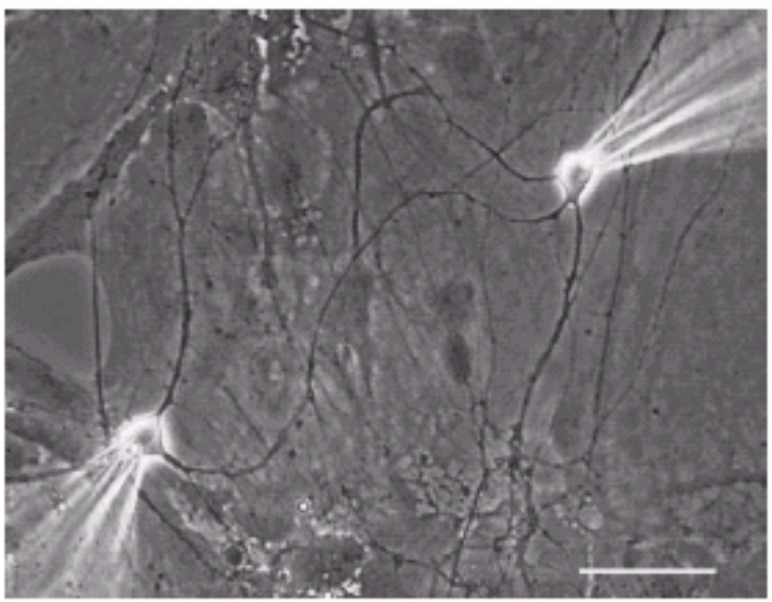
[Dudek and Bear 1992;
Dunwiddie and Lynch 1978]

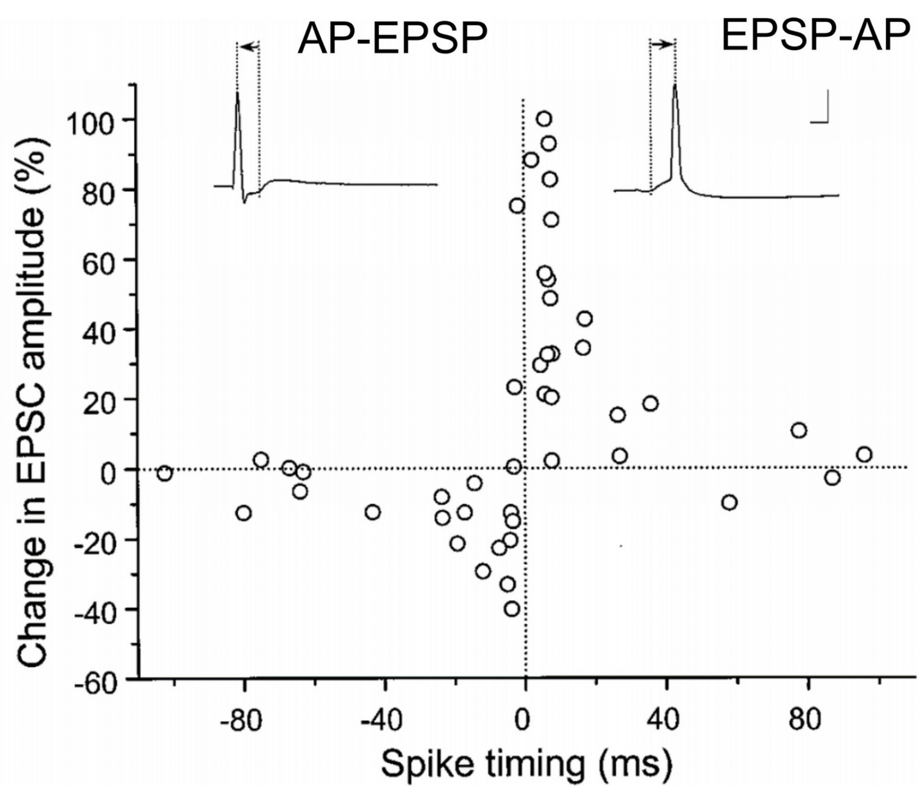
STDP : plasticity from single spike-pairs

60 pairings @ 1 Hz



hippocampal cultures



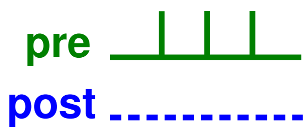


[Bi & Poo, J Neurosci 1998]

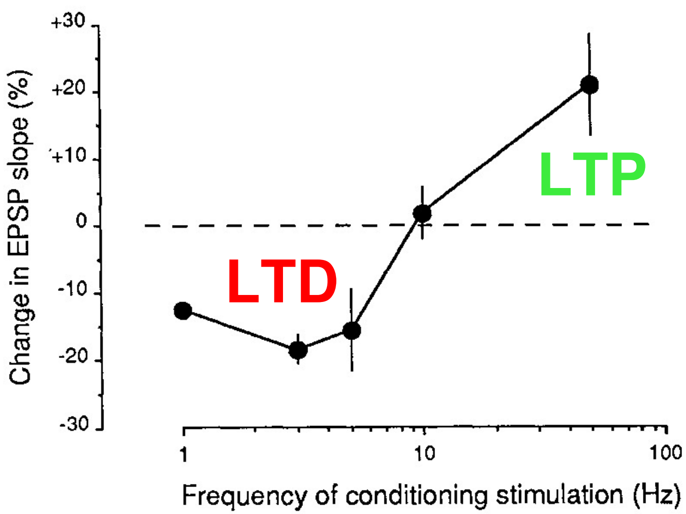
[Magee & Johnston 1997; Zhang et al. 1998; Markram et al. 1997; Sjöström et al. 2001; Feldman 200]

Frequency-dependent plasticity and STDP

frequency-dependent plasticity

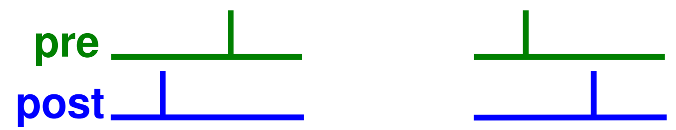


900 pulses at 1-100 Hz

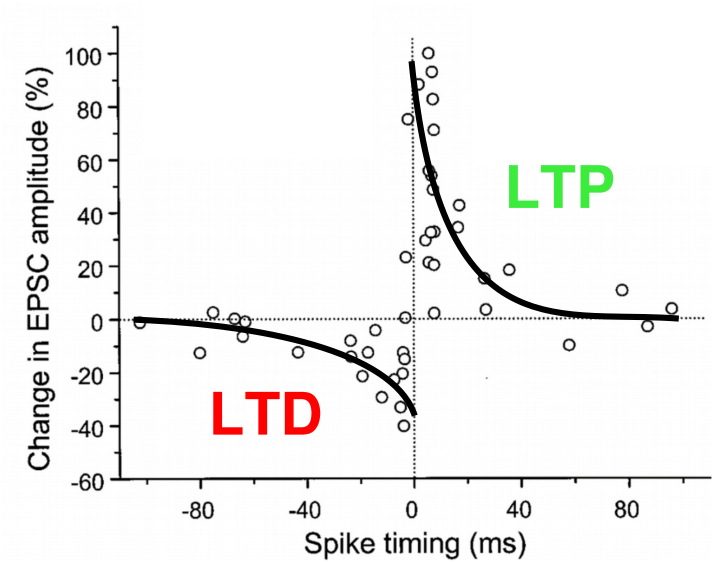


[Dudek and Bear 1992;
Dunwiddie and Lynch 1978]

spike timing-dependent plasticity



60 pairings @ 1 Hz



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

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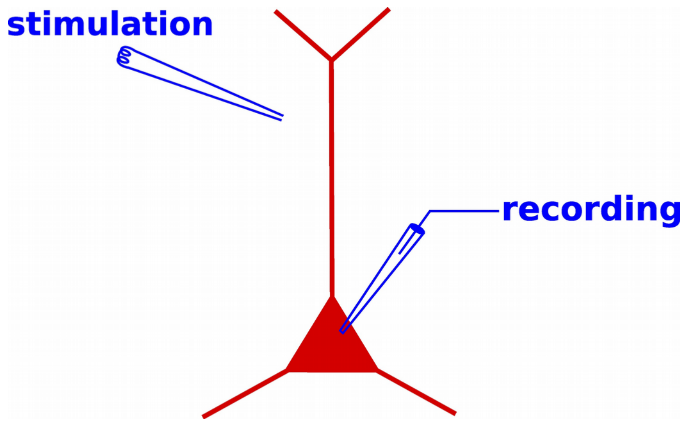
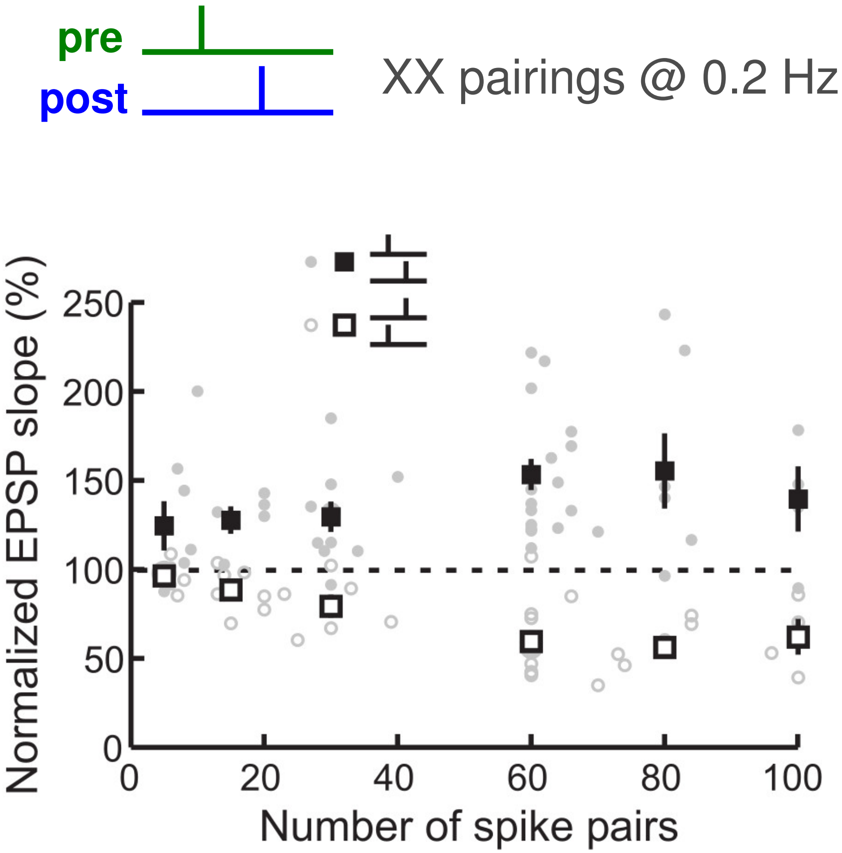
Number of pairing





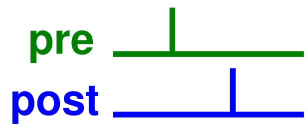
[Froemke et al. 2006]

- LTP induced with a few pairs
- LTD requires the presentation of ~20 stimulation pairs

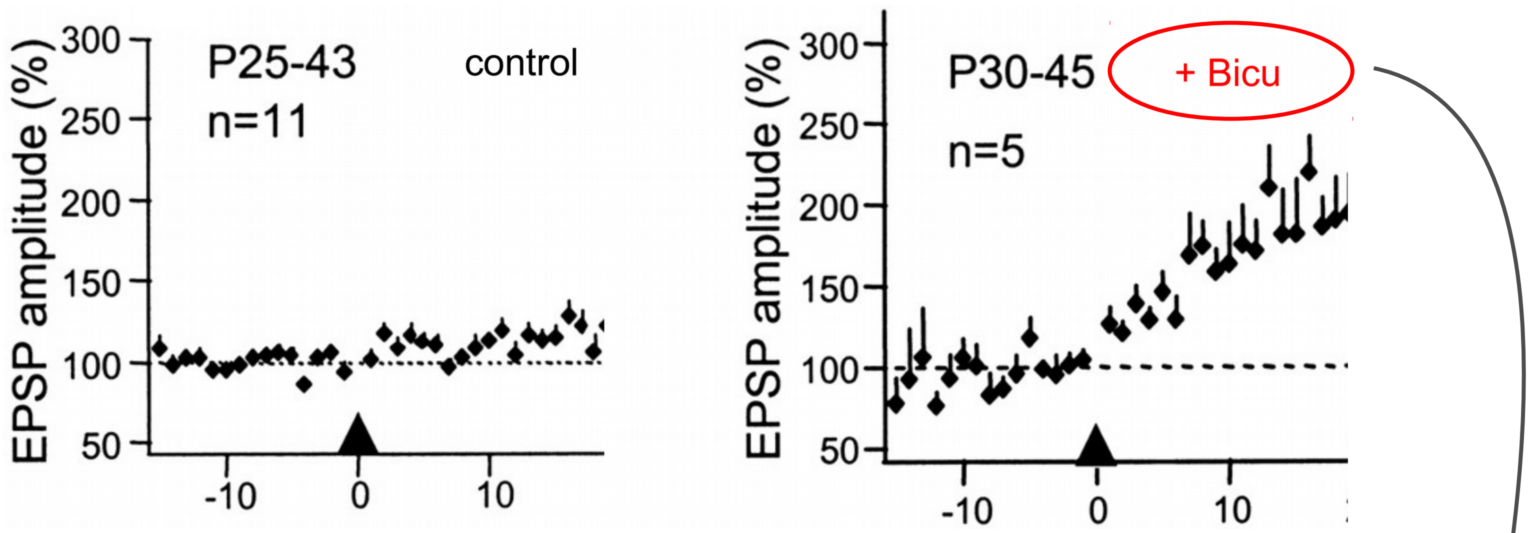
Role of synaptic inhibition

control
→ no plasticity

inhibition blocked
→ LTP



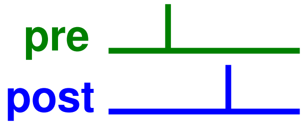
$\Delta t = +10$ ms



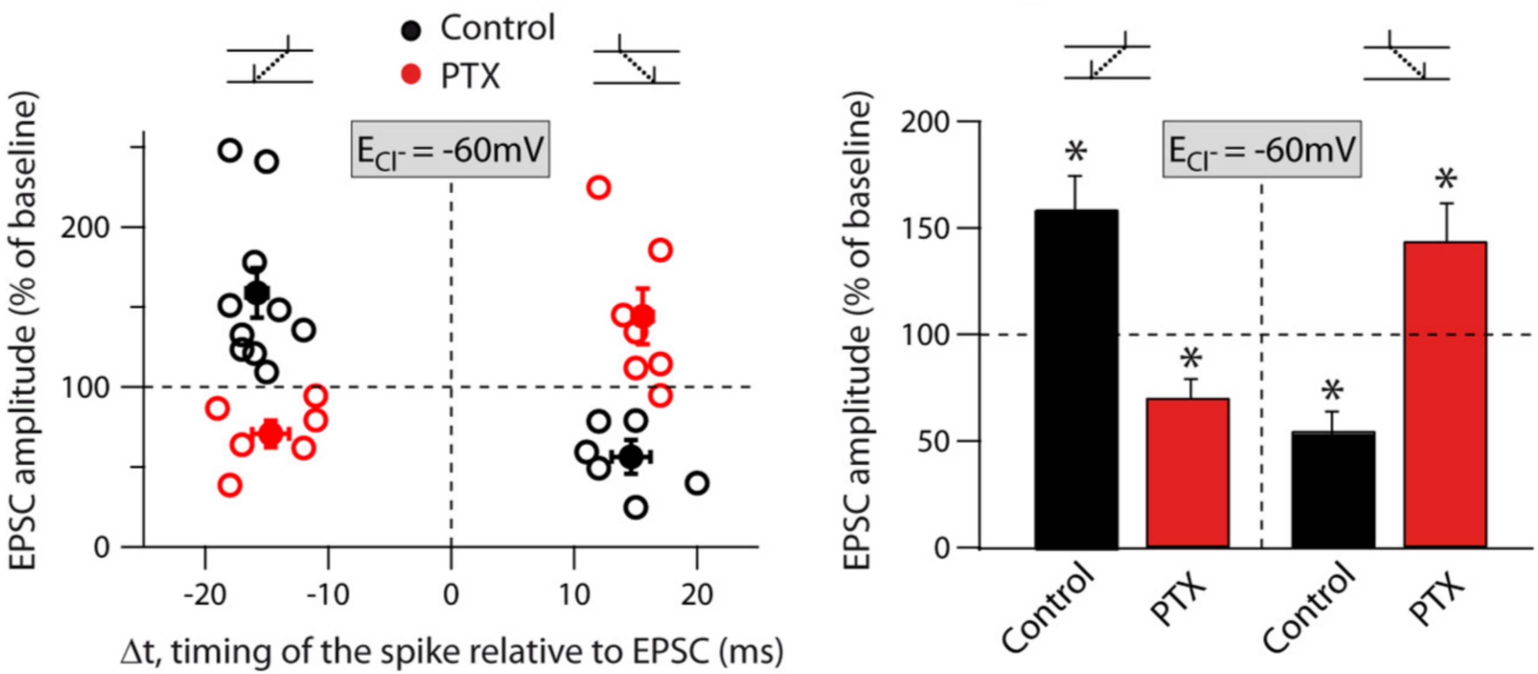
[Mederith et al. *J Neuroci* 2003]

Bicuculline is a competitive antagonist of $GABA_A$ receptors.

Role of synaptic inhibition



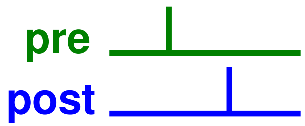
100-150 pairings @ 1 Hz



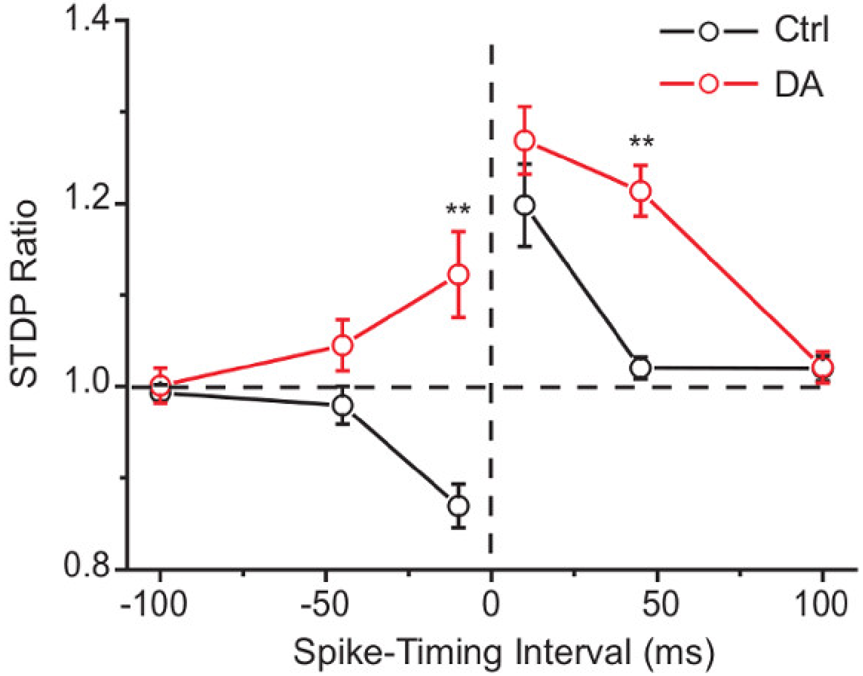
[Paille et al. *J Neurosci* 2013]

- inhibition inverts the STDP curve

Role of neuromodulation - Dopamine



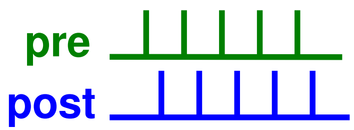
60 pairings @ 1 Hz



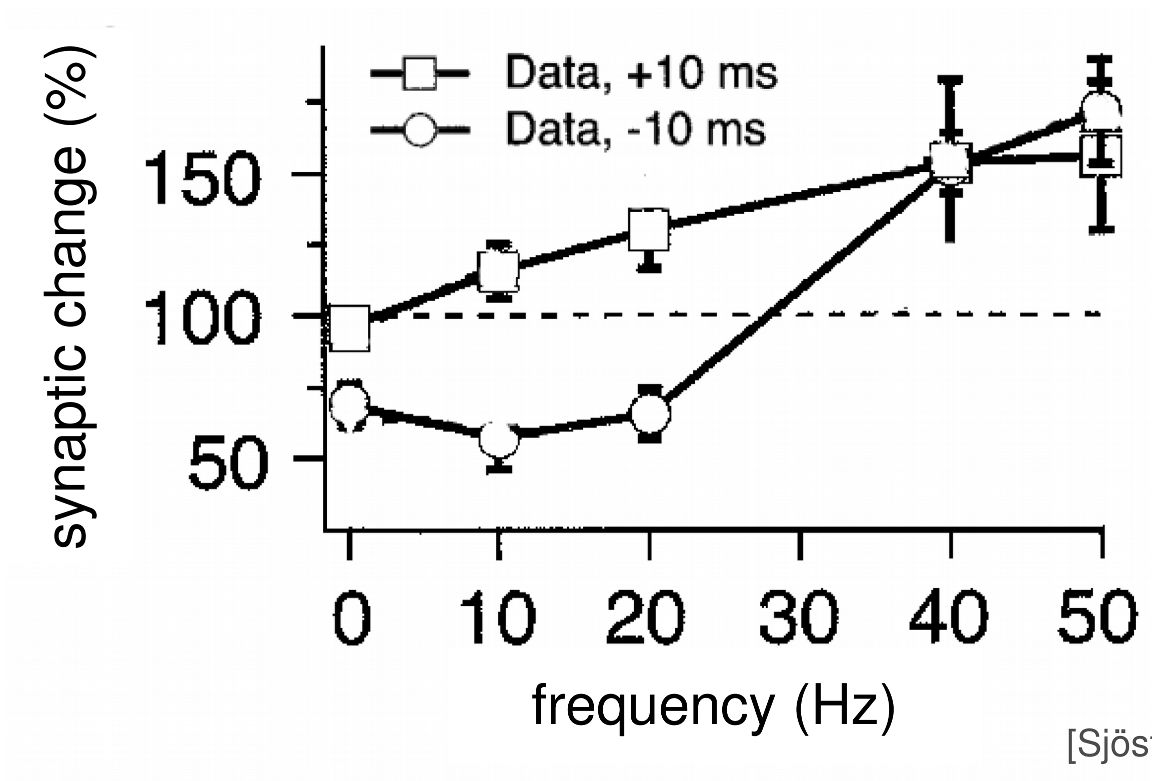
[Zhang et al. *PNAS* 2009]

- dopamine controls sign and magnitude of plasticity

STDP depends on frequency of spike-pairs



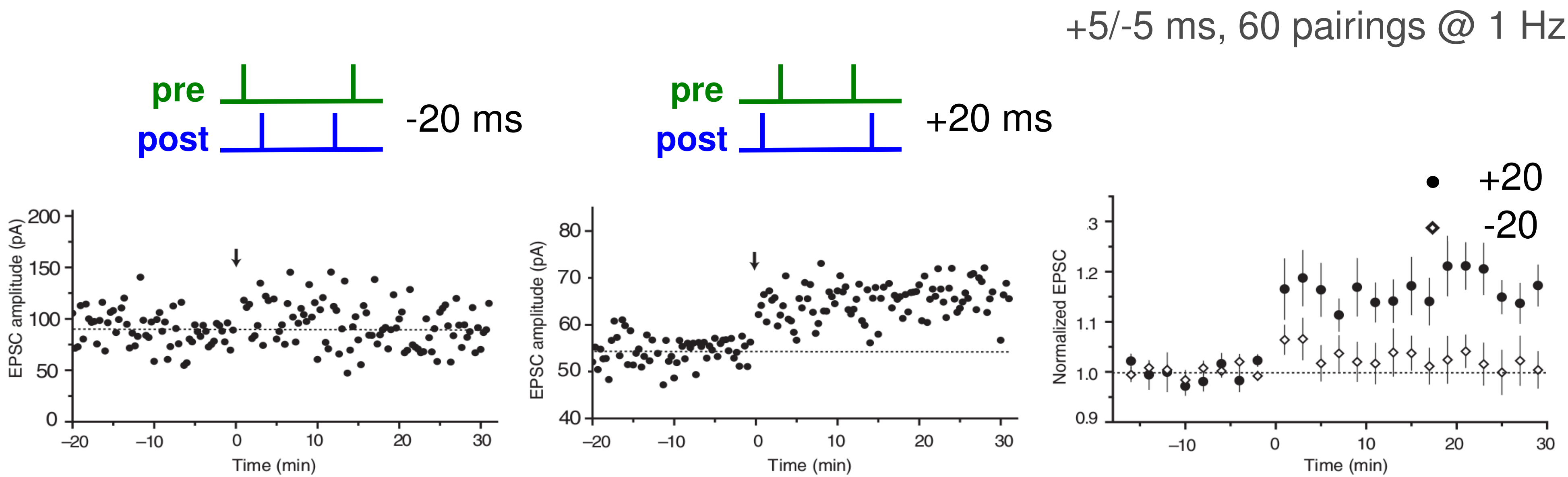
5 pairings, 15x @ 0.1 Hz



[Sjöström et al. *Neuron* 2001]

- post-pre pairings induce LTD at low and LTP at high frequencies

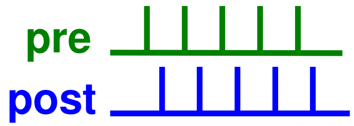
Non-linearity in STDP induction protocols



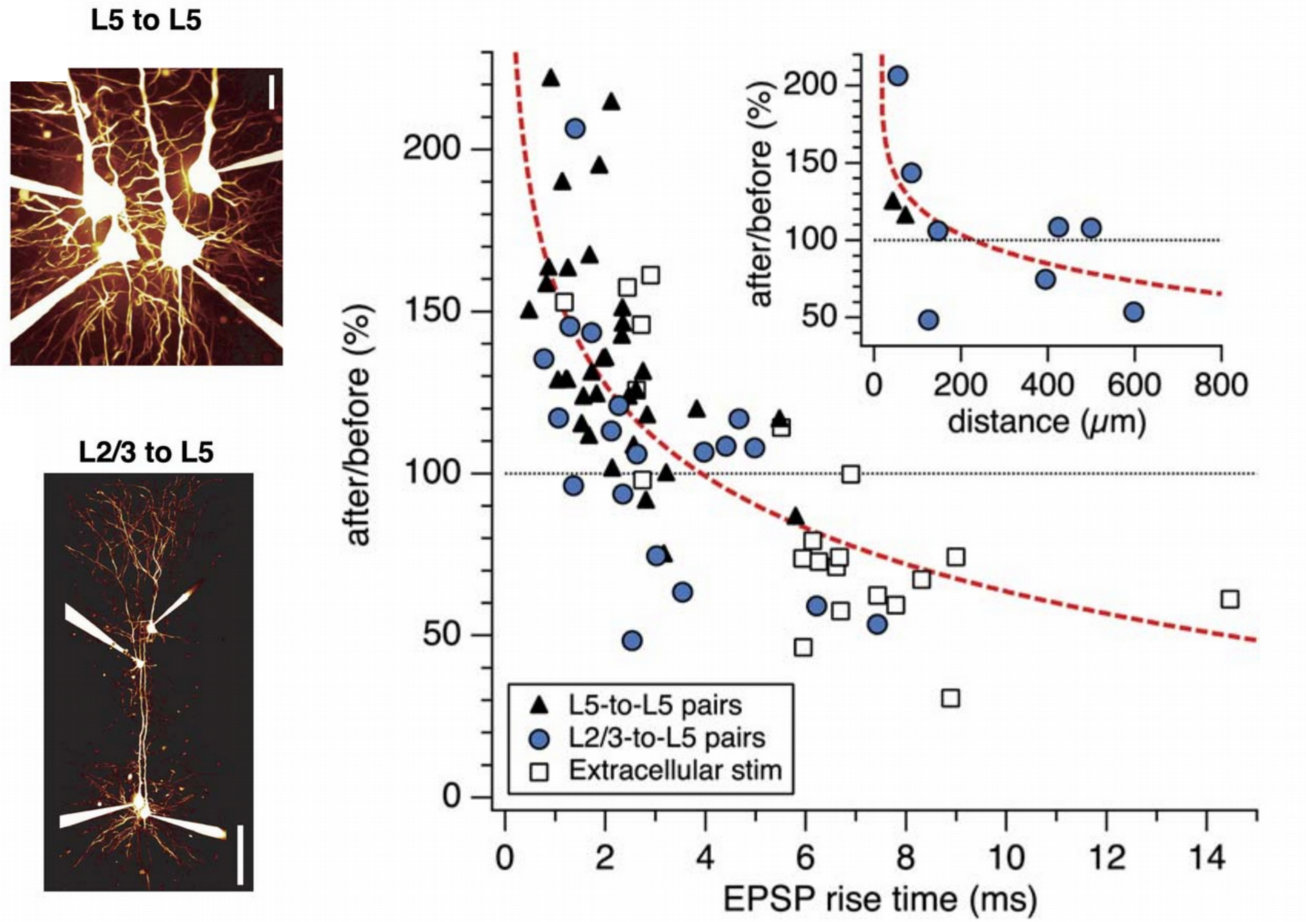
[Wang et al. *Nat Neurosci* 2005]

- Quadruplets : order of pre-post, post-pre pairs determines plasticity outcome

STDP depends on synaptic location



Δt=+10 ms, 5 pairings, 50 Hz, 15x @ 0.1 Hz

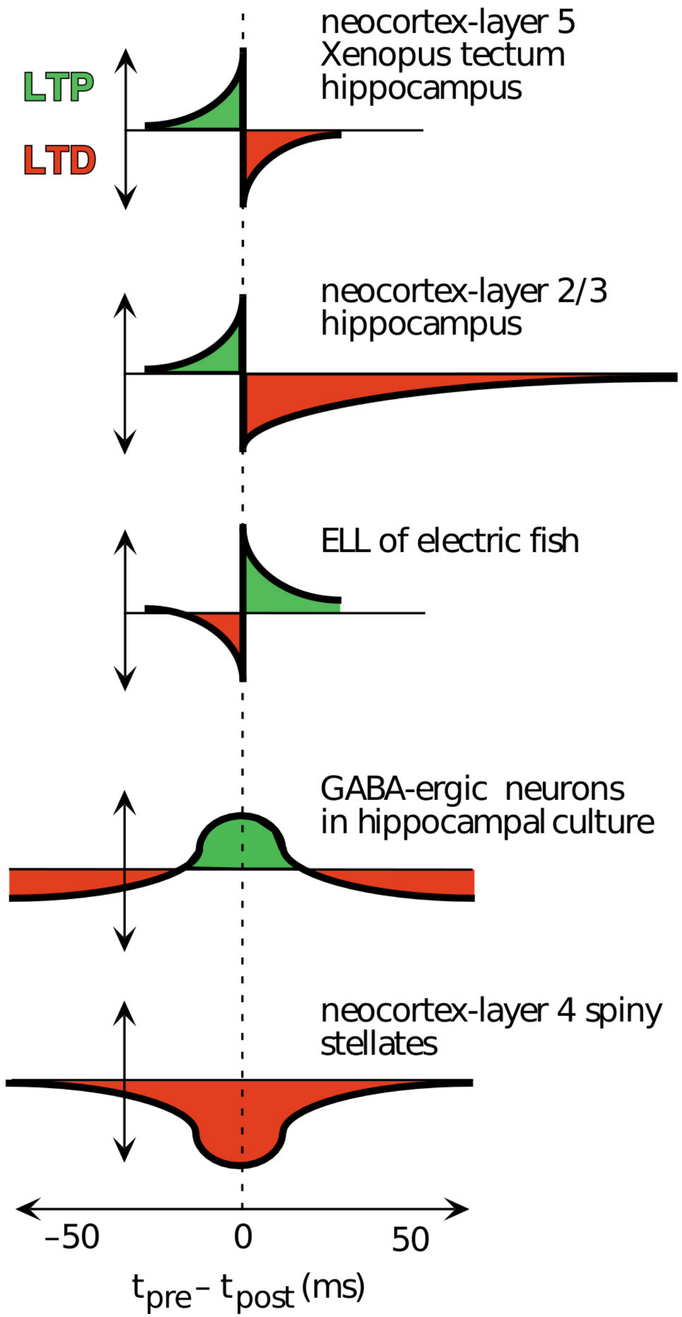


[Sjöström & Hausser, *Neuron* 2006]

[Froemke et al. *Nature,* 2005; Letzkus et al. *J Neurosci* 2006]

- Proximal synapse : LTP
- Distal synapse : LTD

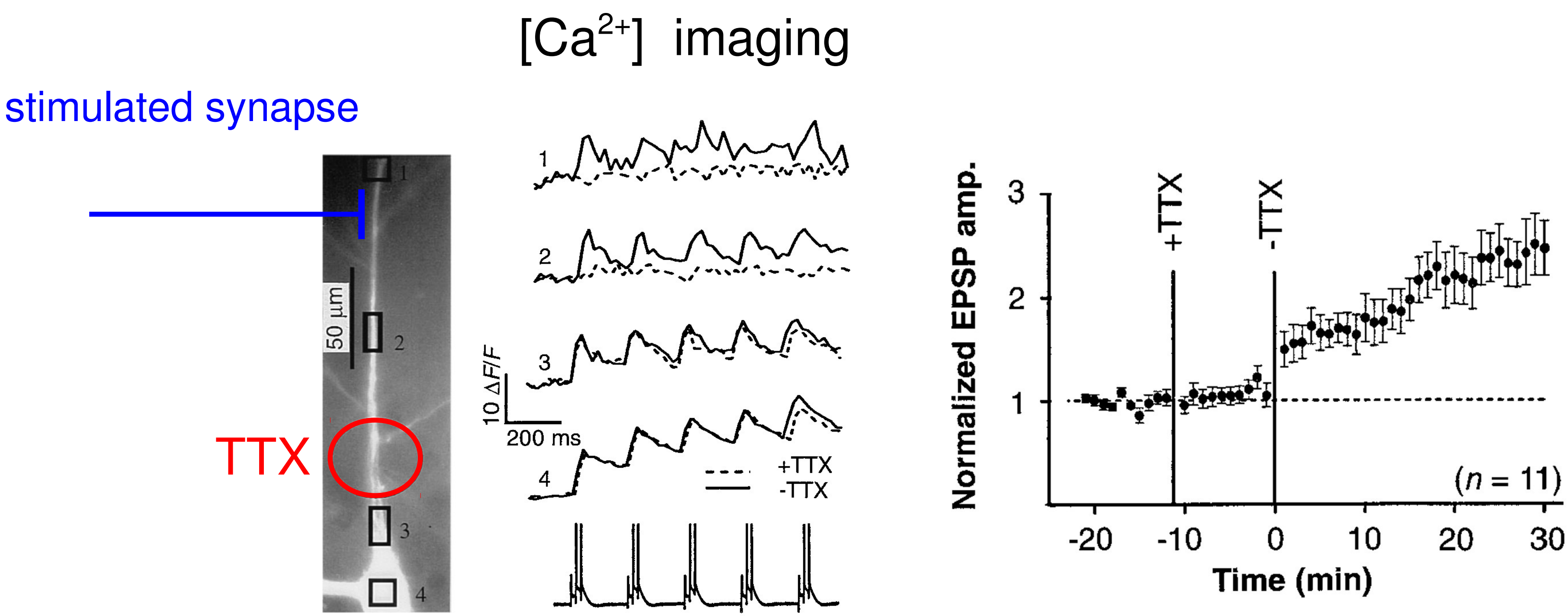
STDP windows depends on brain structure, synapse type



[Abbott & Nelson *Nat Neurosci* 2000]

Outline

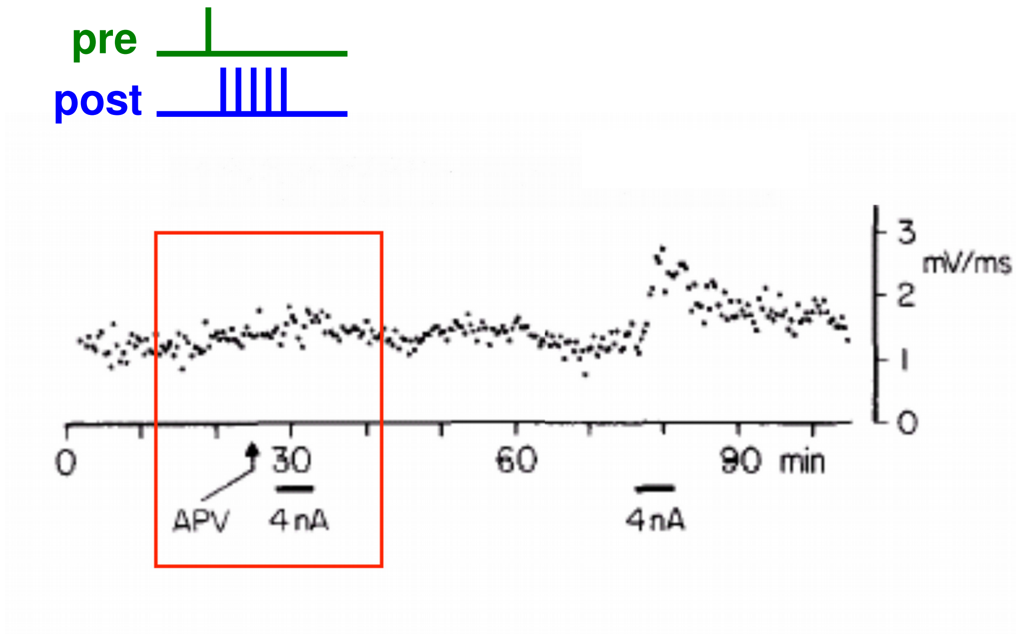
Backpropagating action potential required for STDP



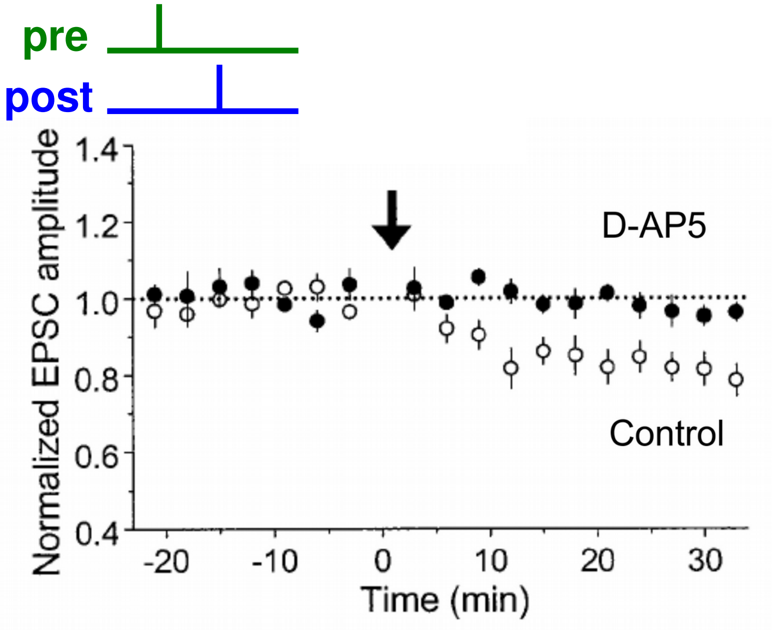
[Magee & Johnston *Science* 1997]

- Backpropagating action potential provides postsynaptic depolarization required for STDP

STDP requires NMDA receptor activation



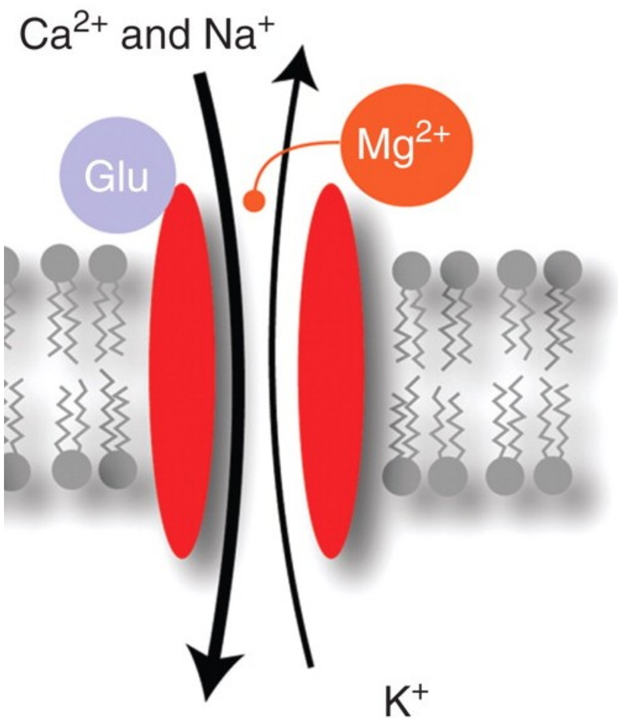
[Gustafsson et al. *J Neurosci* 1987]



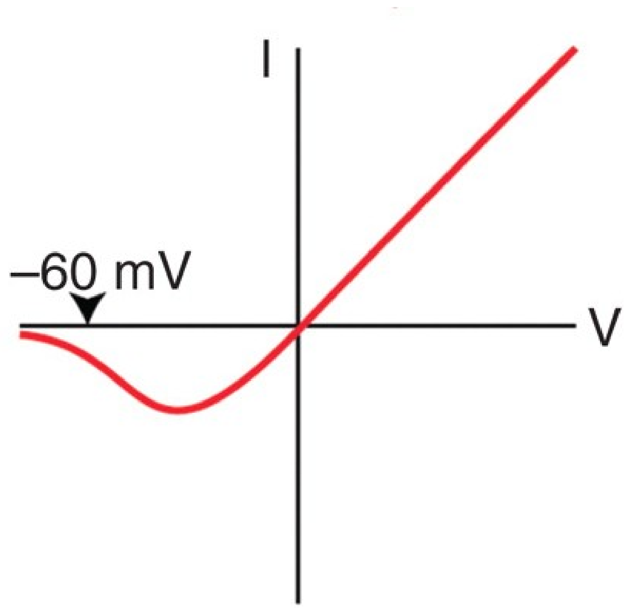
[Bi & Poo *J Neurosci* 1998]

- NMDAR antagonist blocks STDP induction
  (D-AP5 or APV is a selective NMDA receptor antagonist)

Postsynaptic NMDA receptor



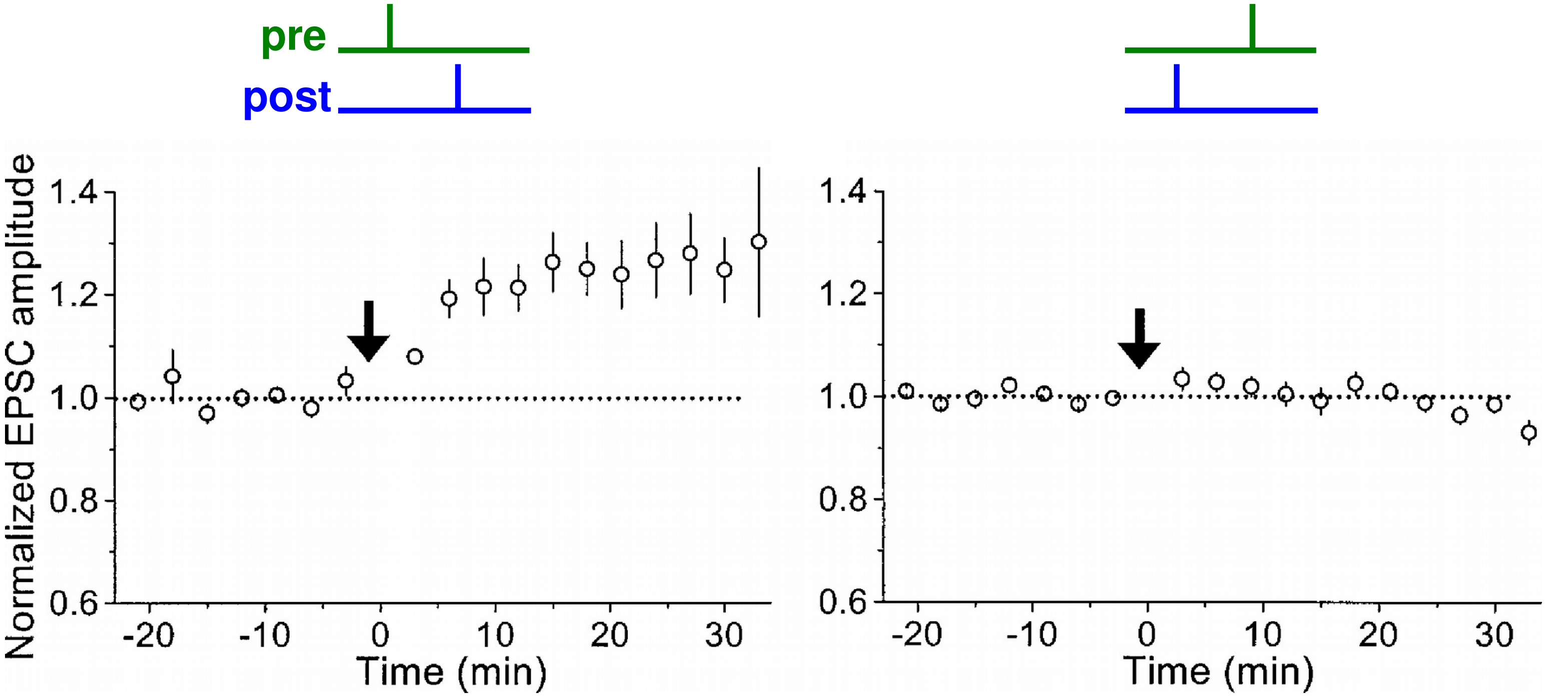
current-voltage relationship



- coincidence detector :
  presynaptic action potential → glutamate (Glu)
  postsynaptic depolarization → Mg^{2+} block is expelled
- calcium permeable

Voltage-dependent Ca channels required for LTD

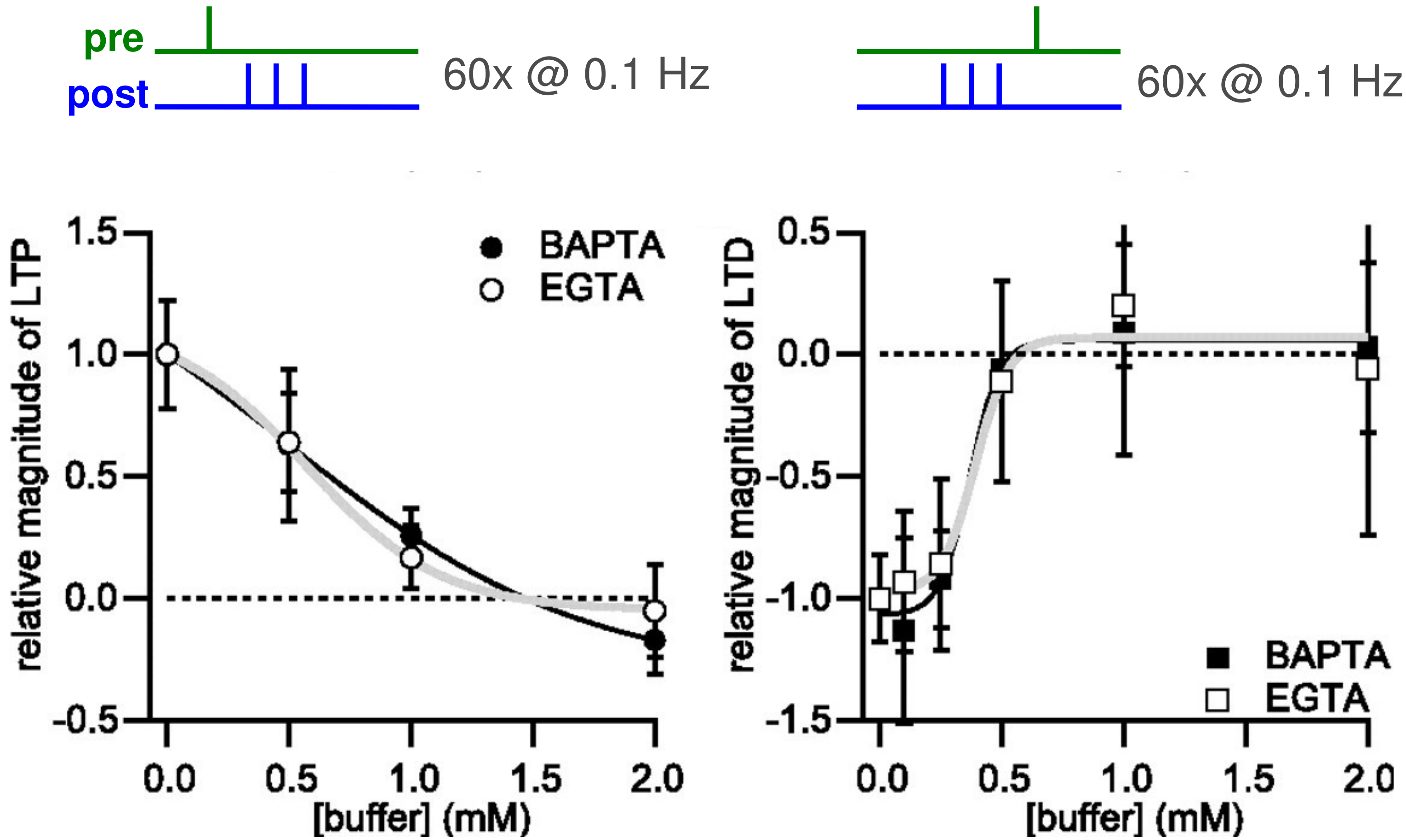
+ nimodipine (L-type calcium channel blocker)



[Bi & Poo *J Neurosci* 1998]

- LTD but not LTP involves the activation of L-type calcium channels

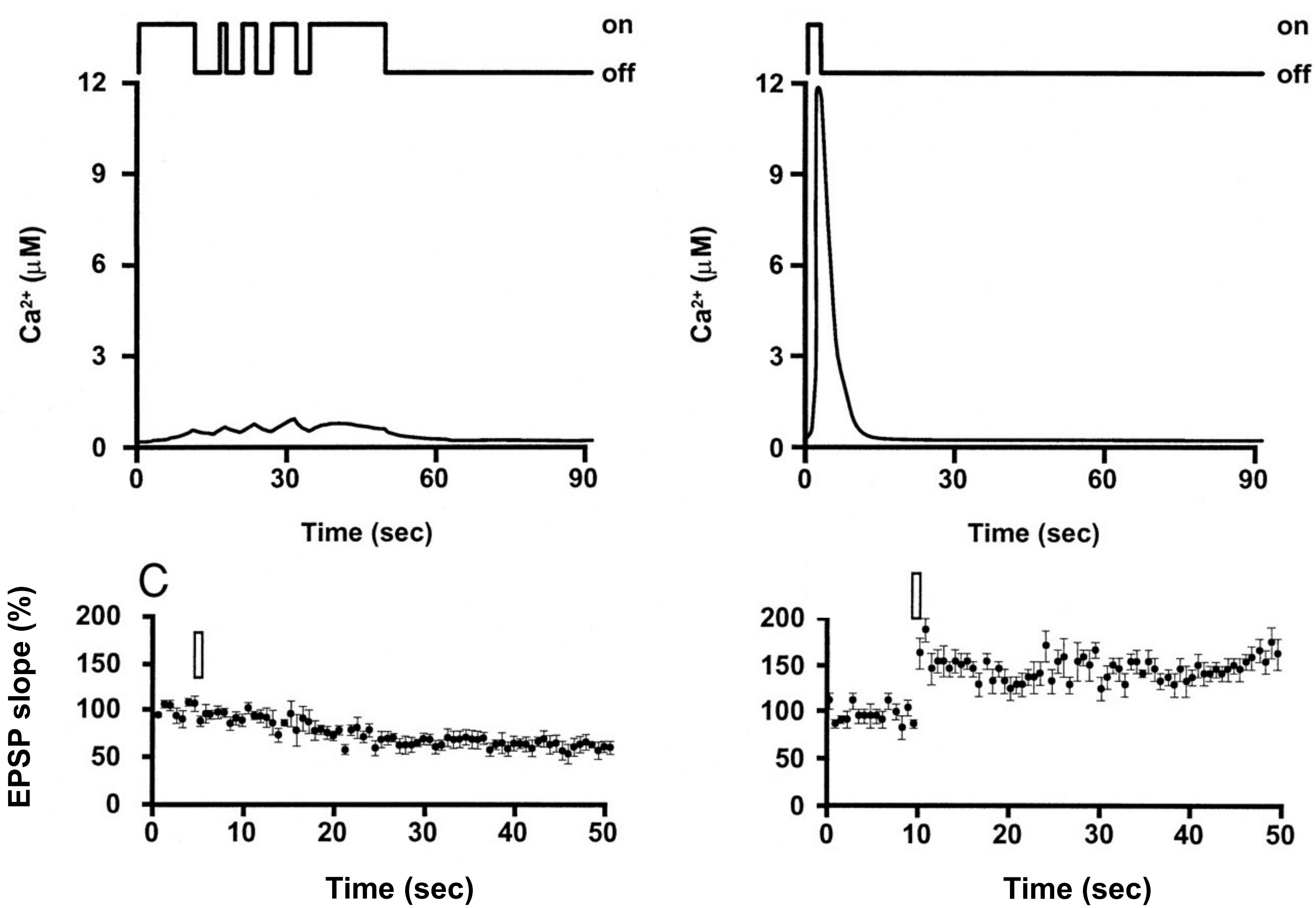
Postsynaptic calcium *required* for plasticity



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

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

Postsynaptic calcium *sufficient* for plasticity

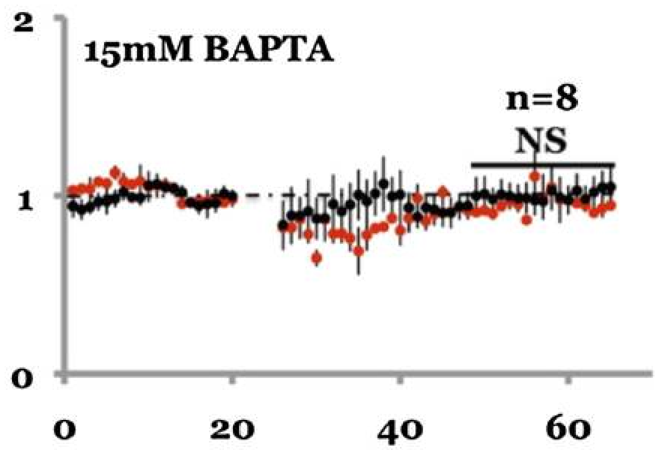


[Malenka *et al. Science* 1988; Yang *et al., J Neurophysiol* 1999]

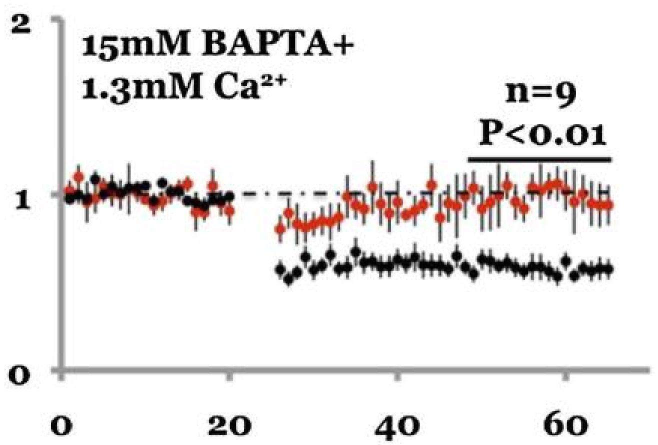
- LTP induced by brief, large amplitude [Ca^{2+}] increases
- prolonged, modest rise in [Ca^{2+}] elicits LTD

NMDA receptor activation but no calcium required for LTD

[Nabavi *et al.*, 2013, PNAS]



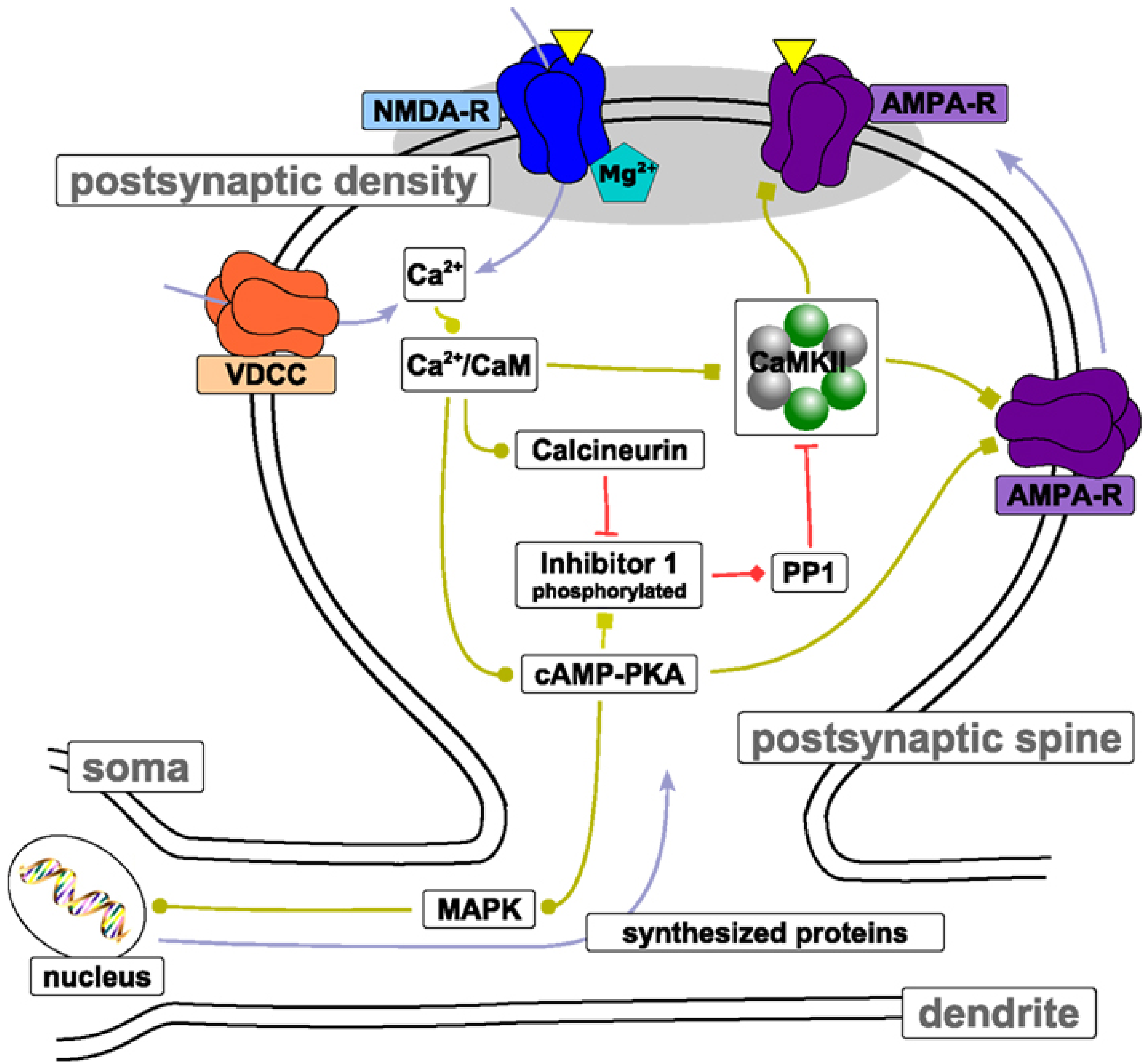
complete block of calcium



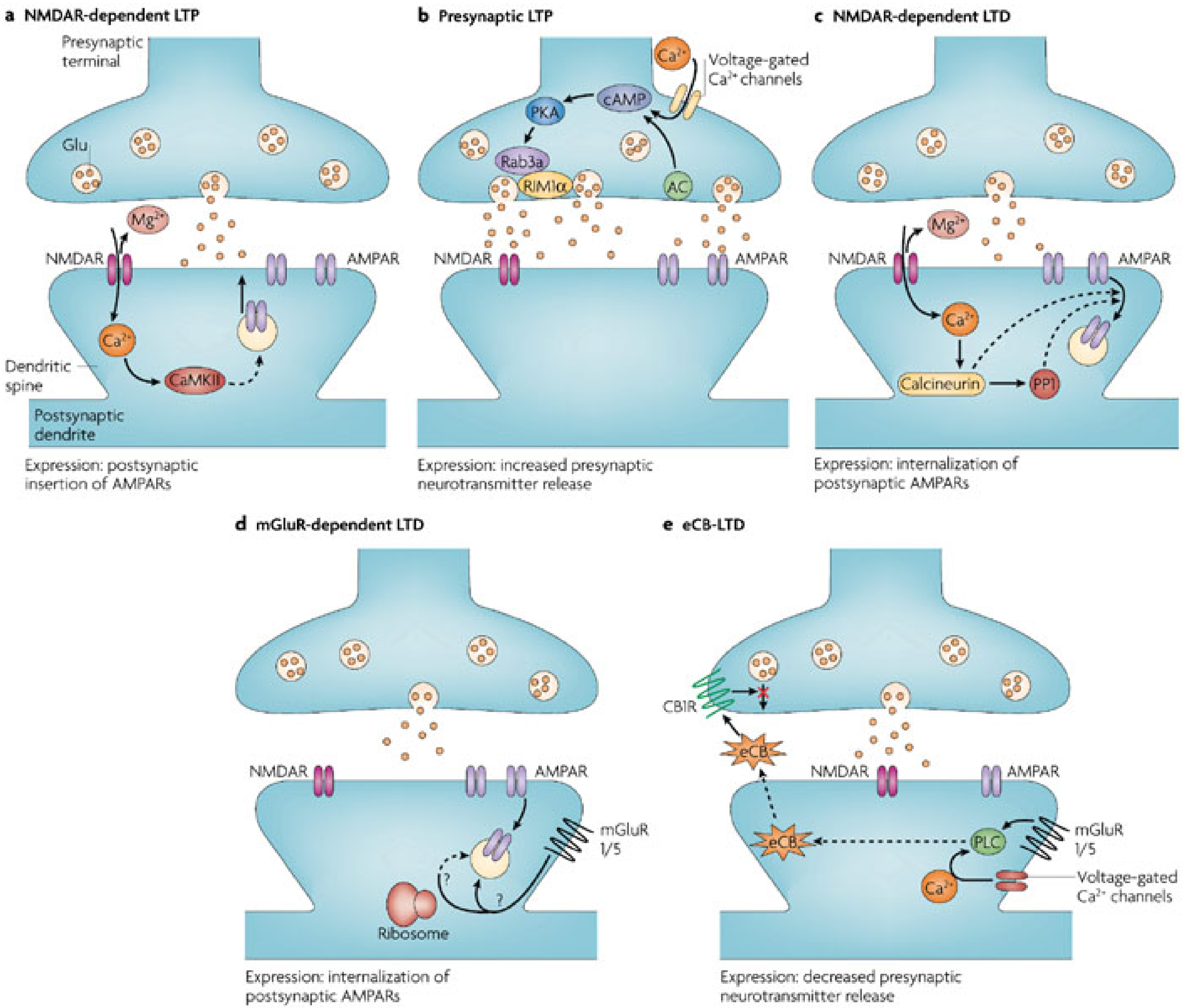
maintaining resting calcium levels

- ligand binding to NMDA receptors is sufficient for LTD
- basal levels of [Ca^{2+}] are permissively required

Signal pathways downstream of Calcium



Diversity of induction and expression pathways



[Kauer, Malenka. *Nat Rev Neurosci* 2010]

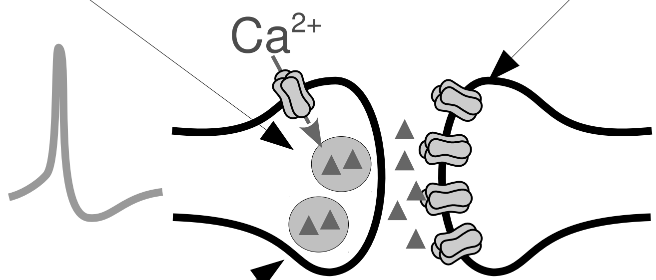
Expression of long-term changes

presynaptic

postsynaptic

neurotransmitter vesicle number

number of AMPA receptors

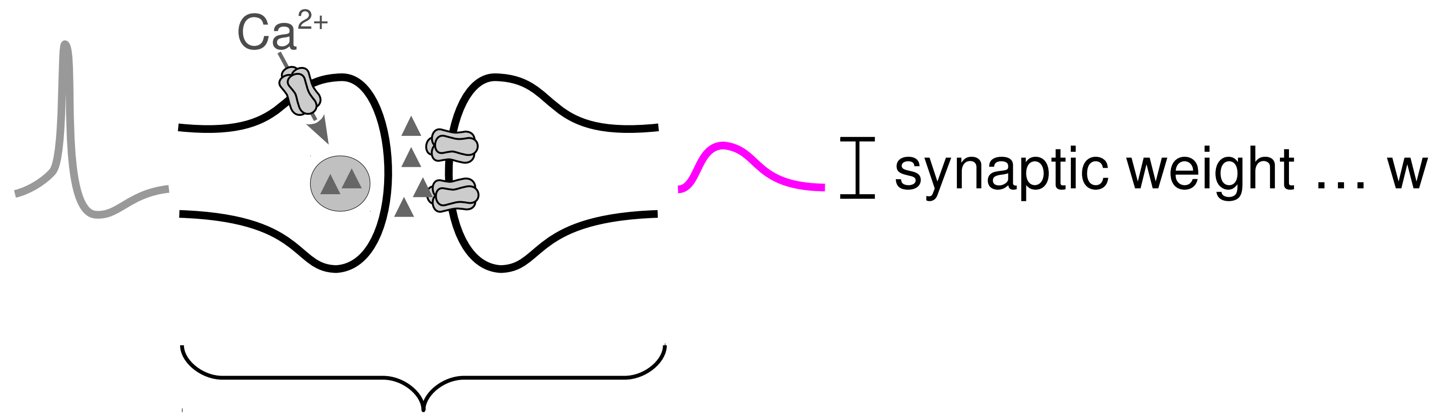


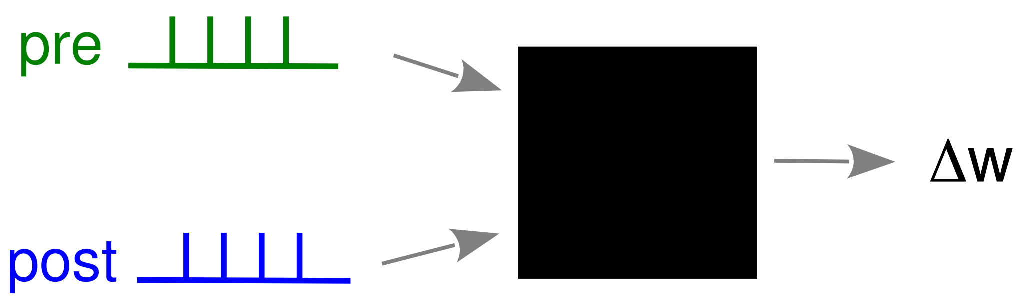
probability of vesicle release

conductance of AMPA receptors

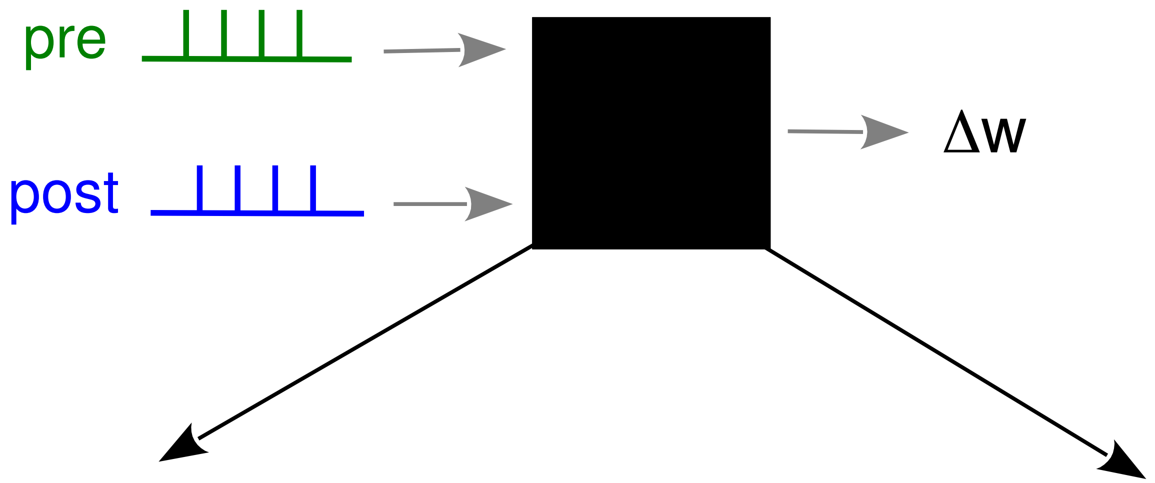
Outline

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]

Modeling studies : phenomenological vs. biophysical

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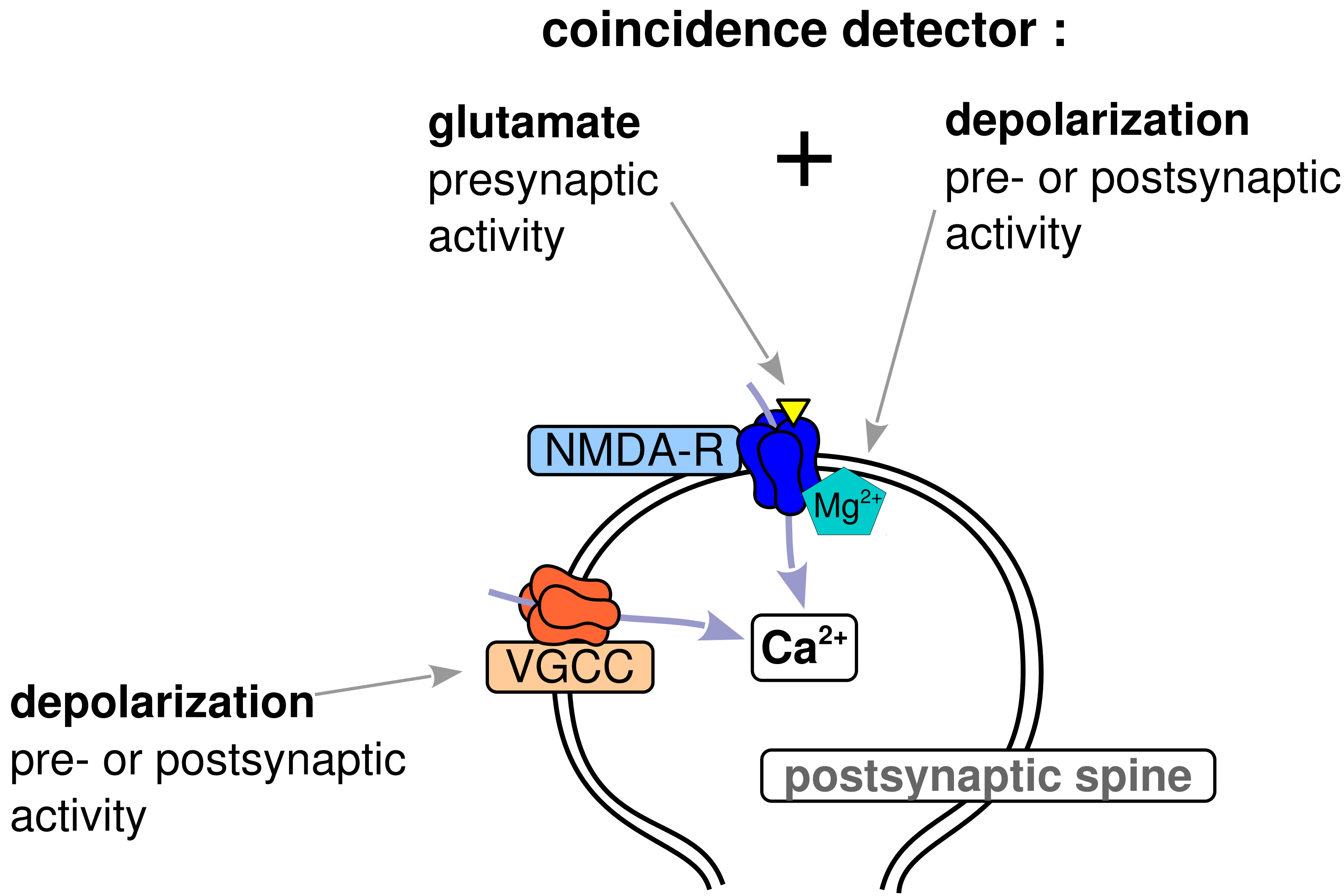
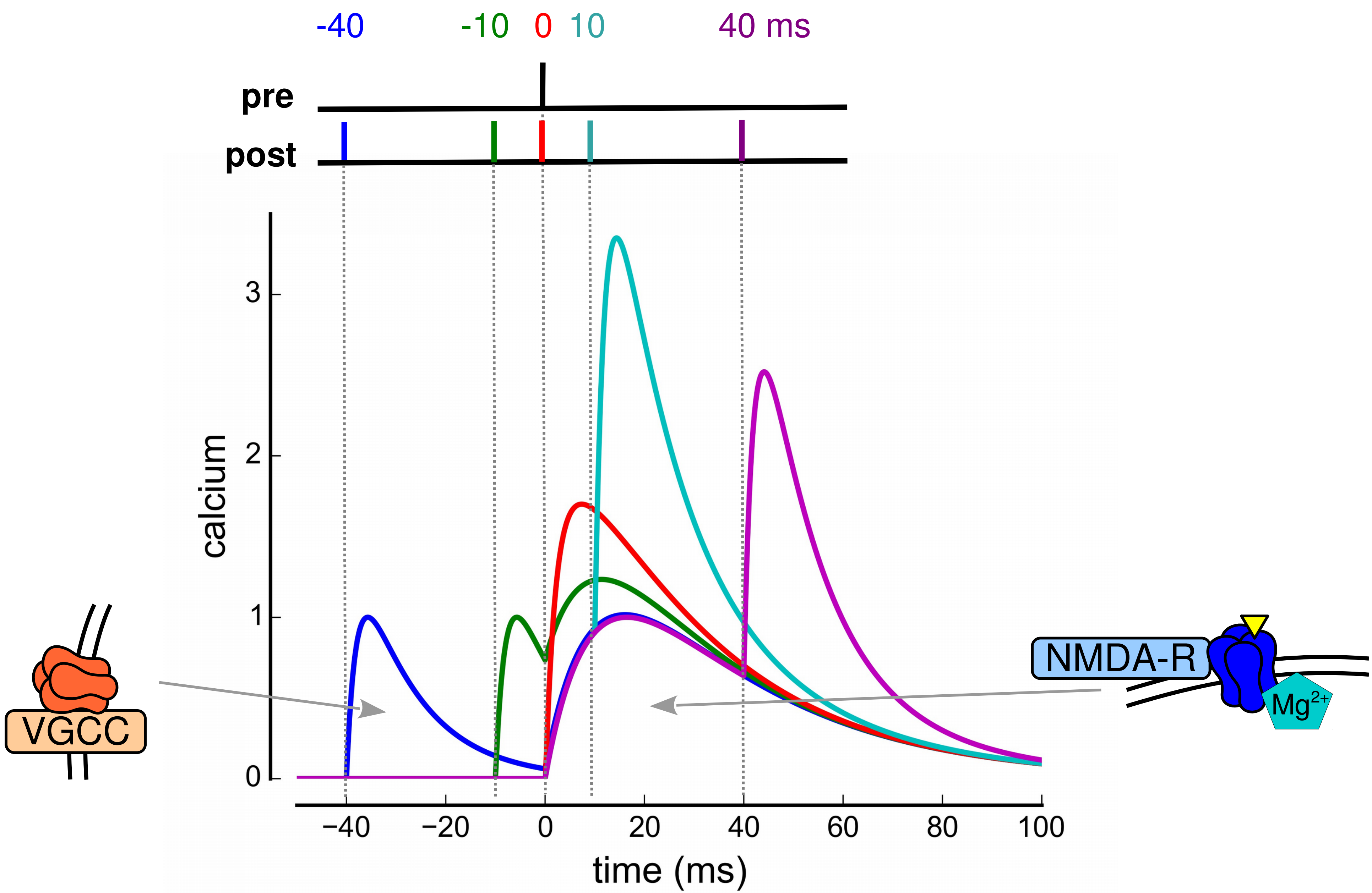
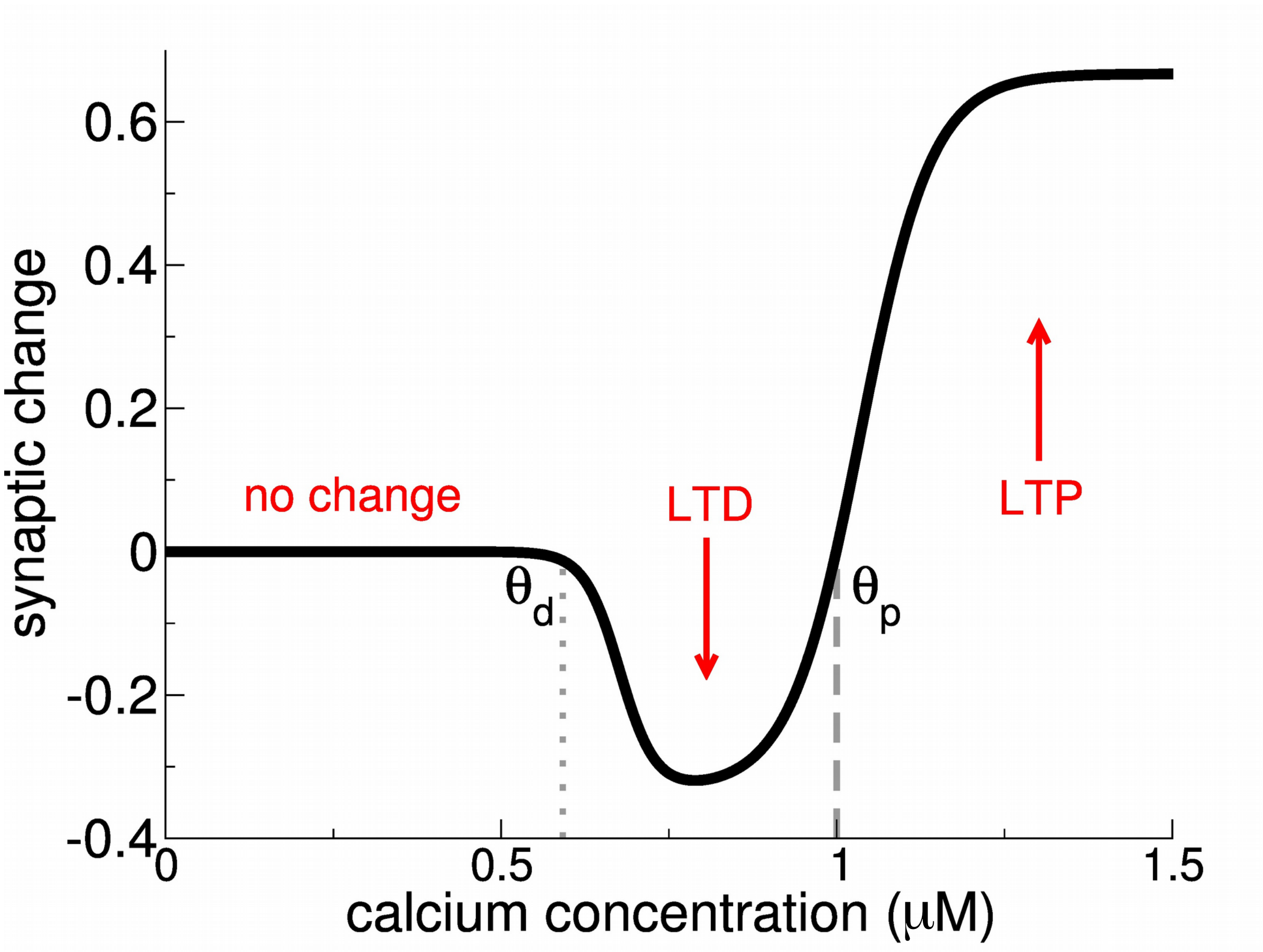
Calcium influx



Calcium transients from spike-pair stimulation

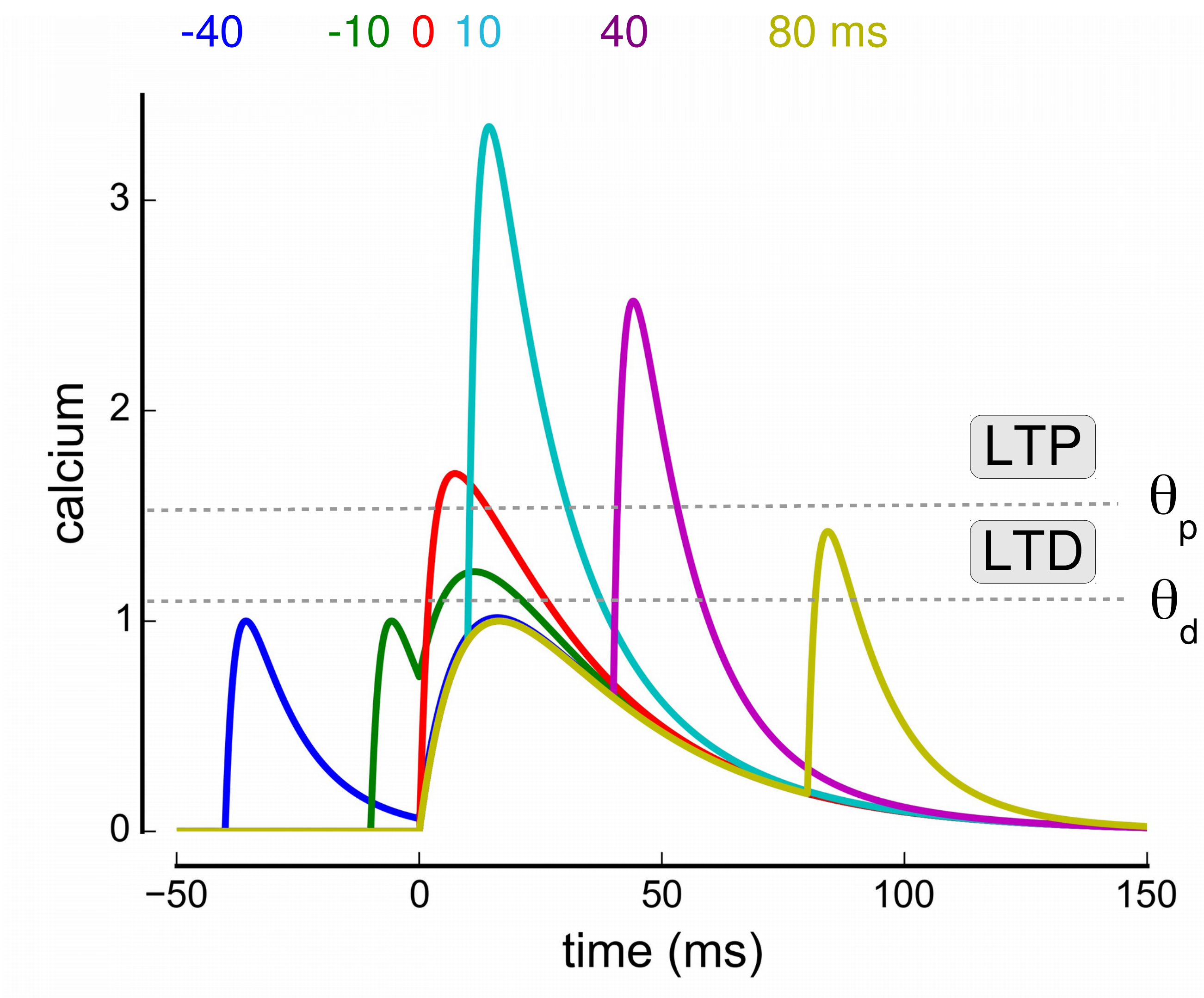


Calcium control hypothesis

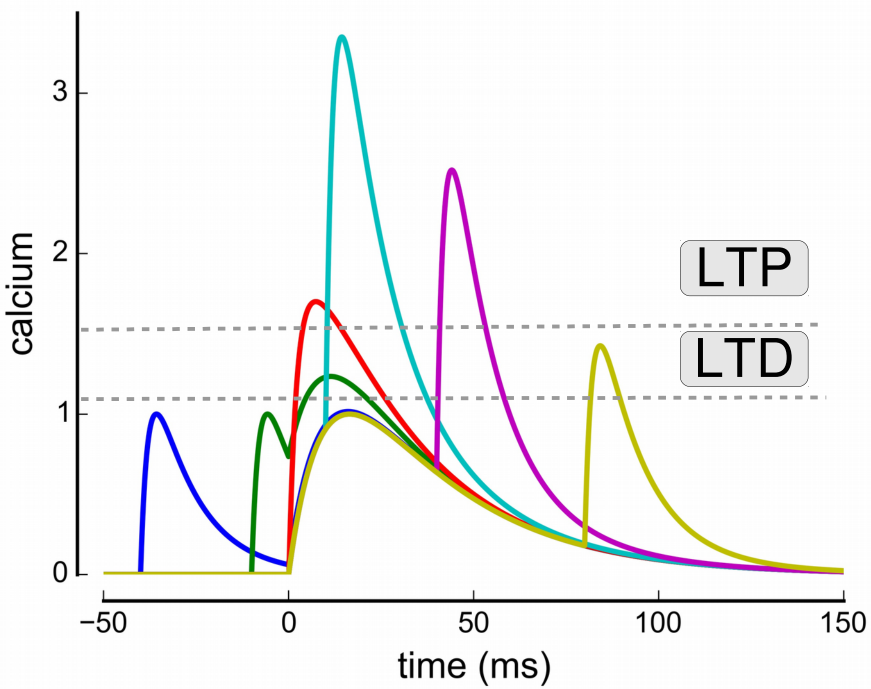


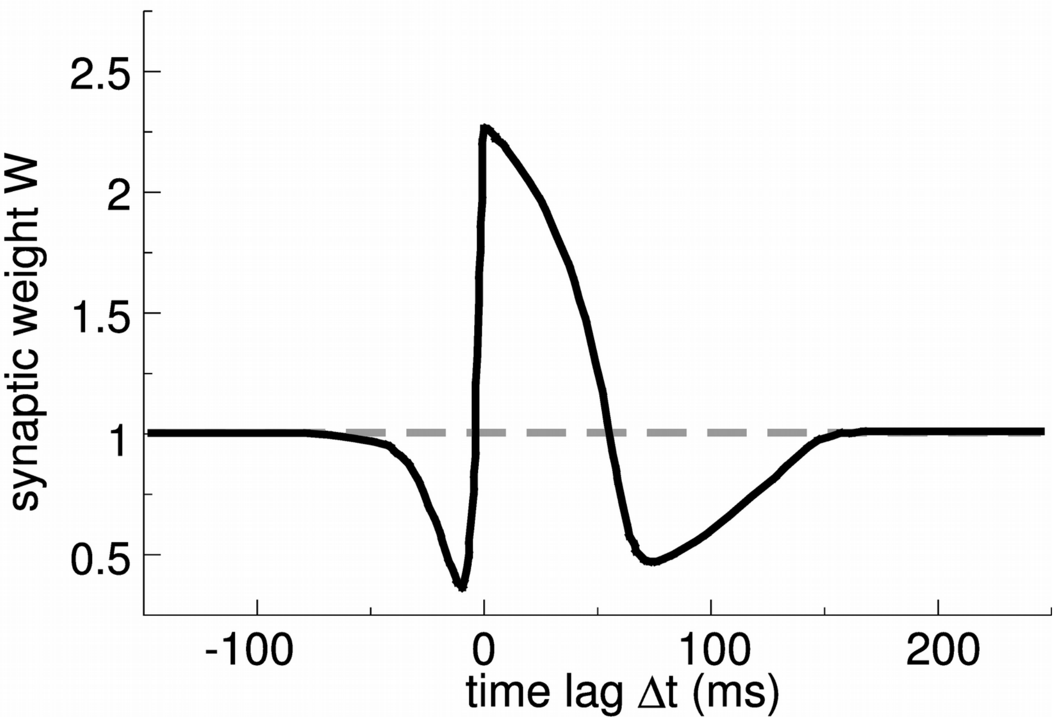
[Shouval *et al.*, *PNAS* 2002]

Calcium transients from spike-pair stimulation



STDP curve from calcium control hypothesis

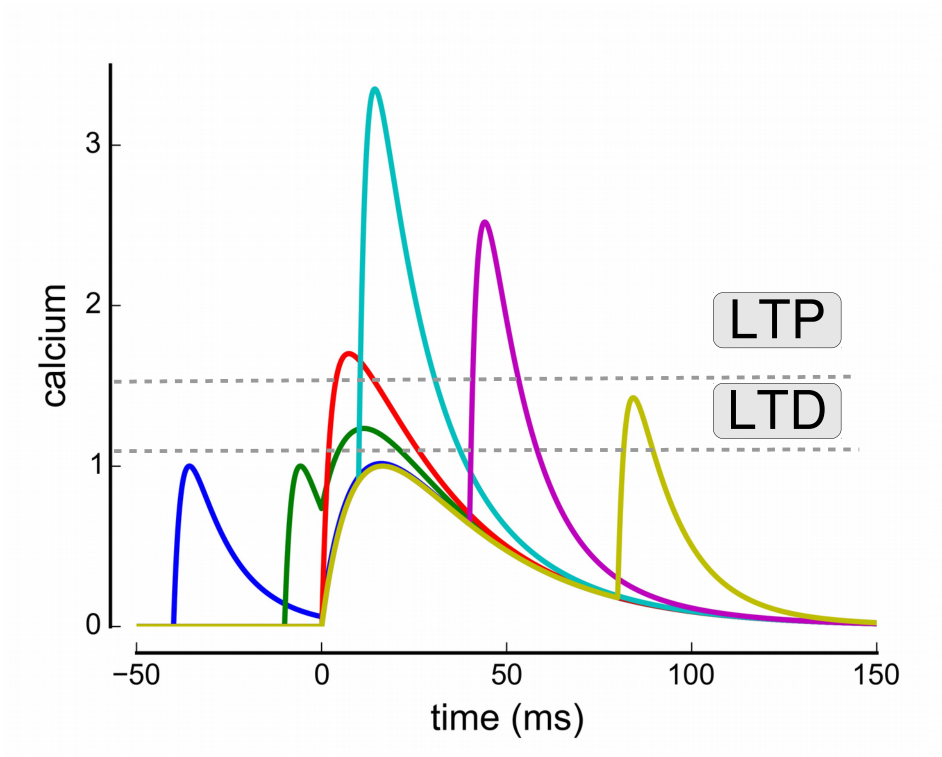


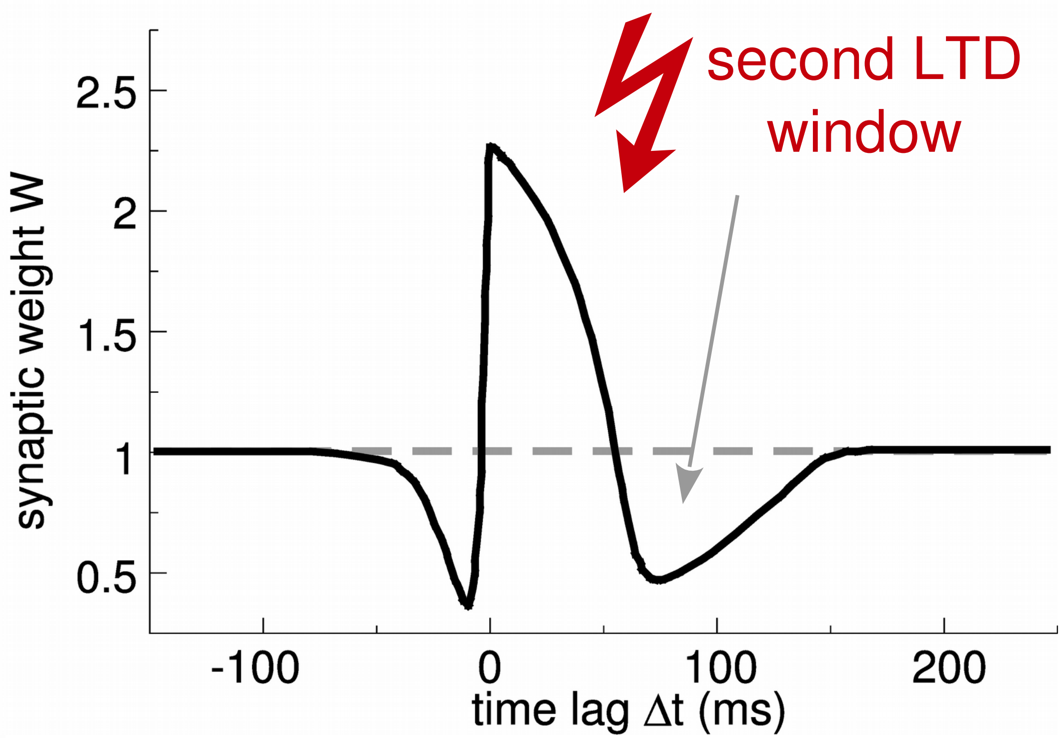


[Shouval *et al.*, *PNAS* 2002]

STDP curve from calcium control hypothesis

[Shouval *et al.*, 2002]

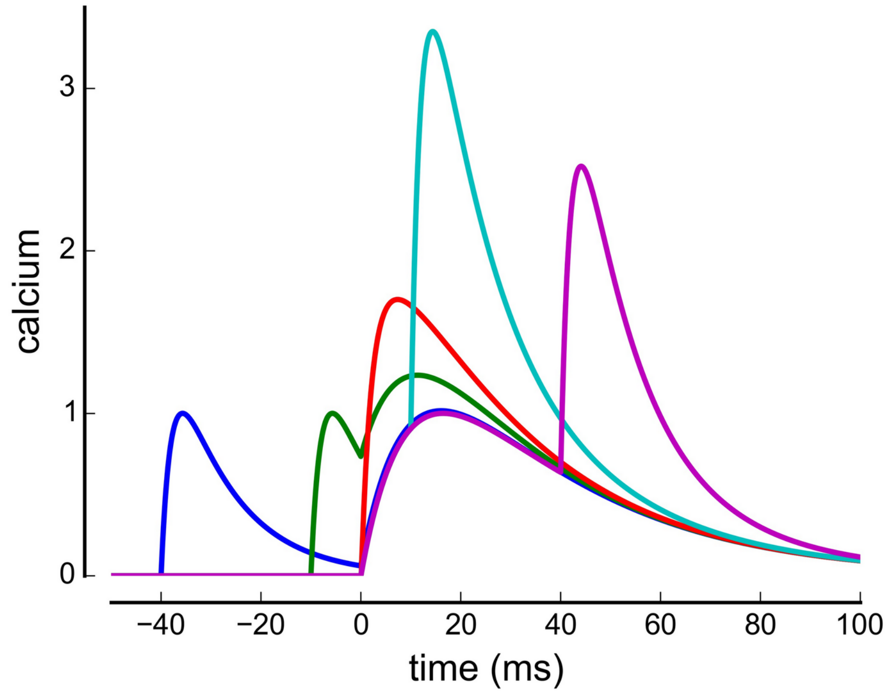




→ [Karmarkar *et al.*, 2002; Badoual *et al.*, 2006; Rubin *et al.*, 2005; Graupner & Brunel, 2007; Urakubo *et al.*, 2008]

Question : role of calicum in shaping STDP

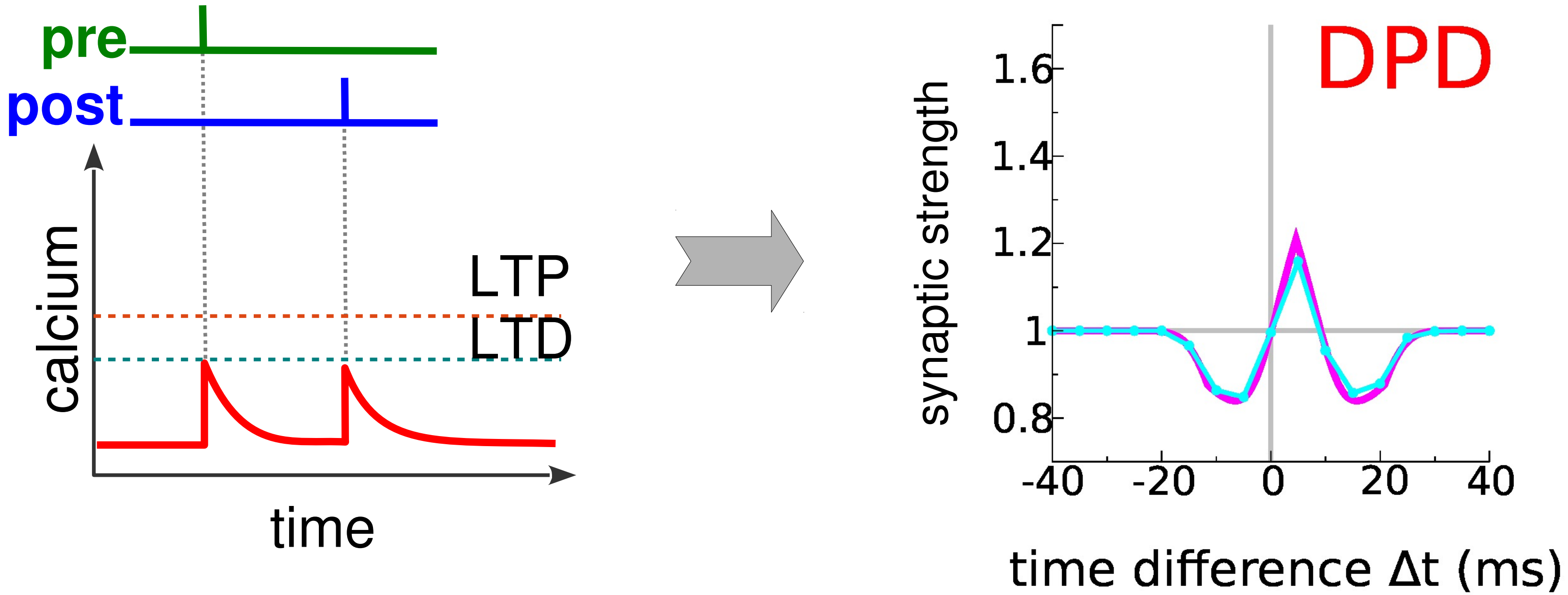
Can the dynamics of the postsynaptic calcium determine the outcome of synaptic plasticity ?



Calcium amplitudes determine shape of STDP curve

$C_{pre} < \theta_d$

$C_{post} < \theta_d$



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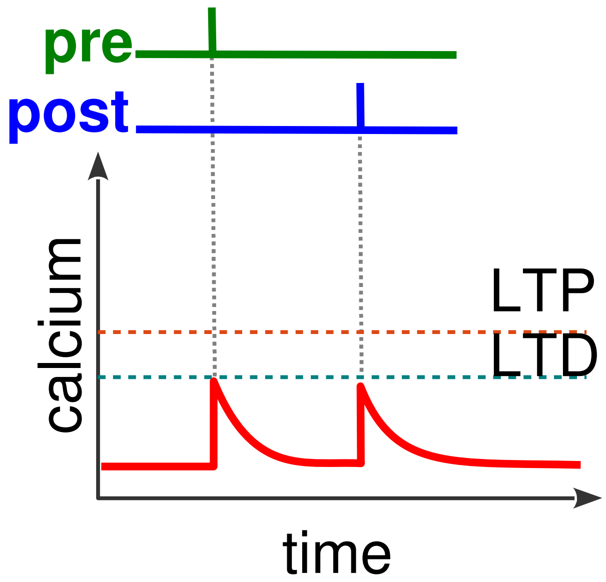
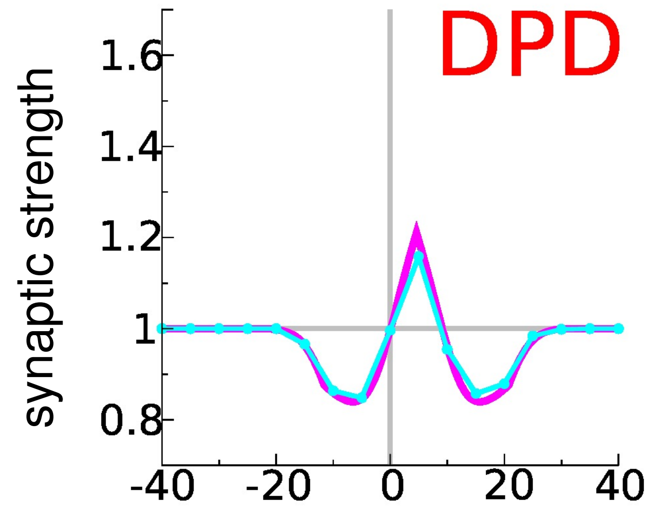
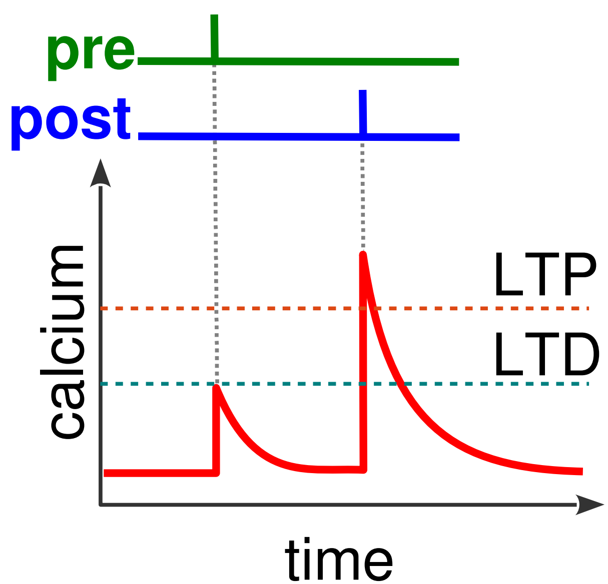
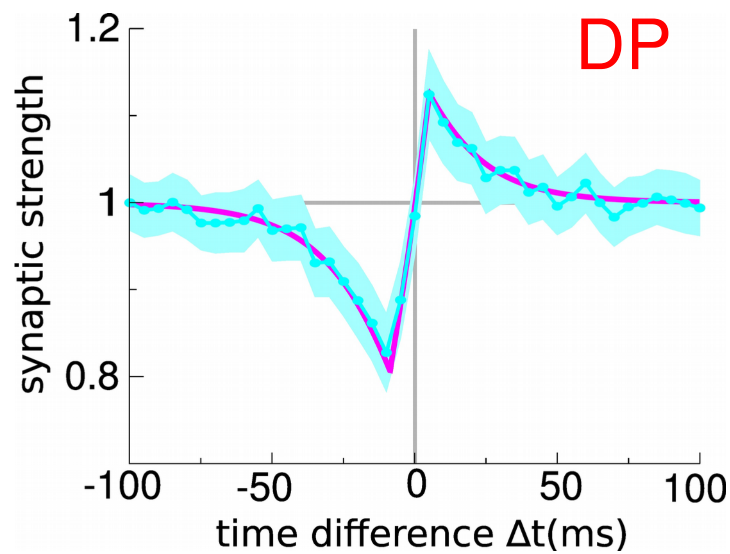




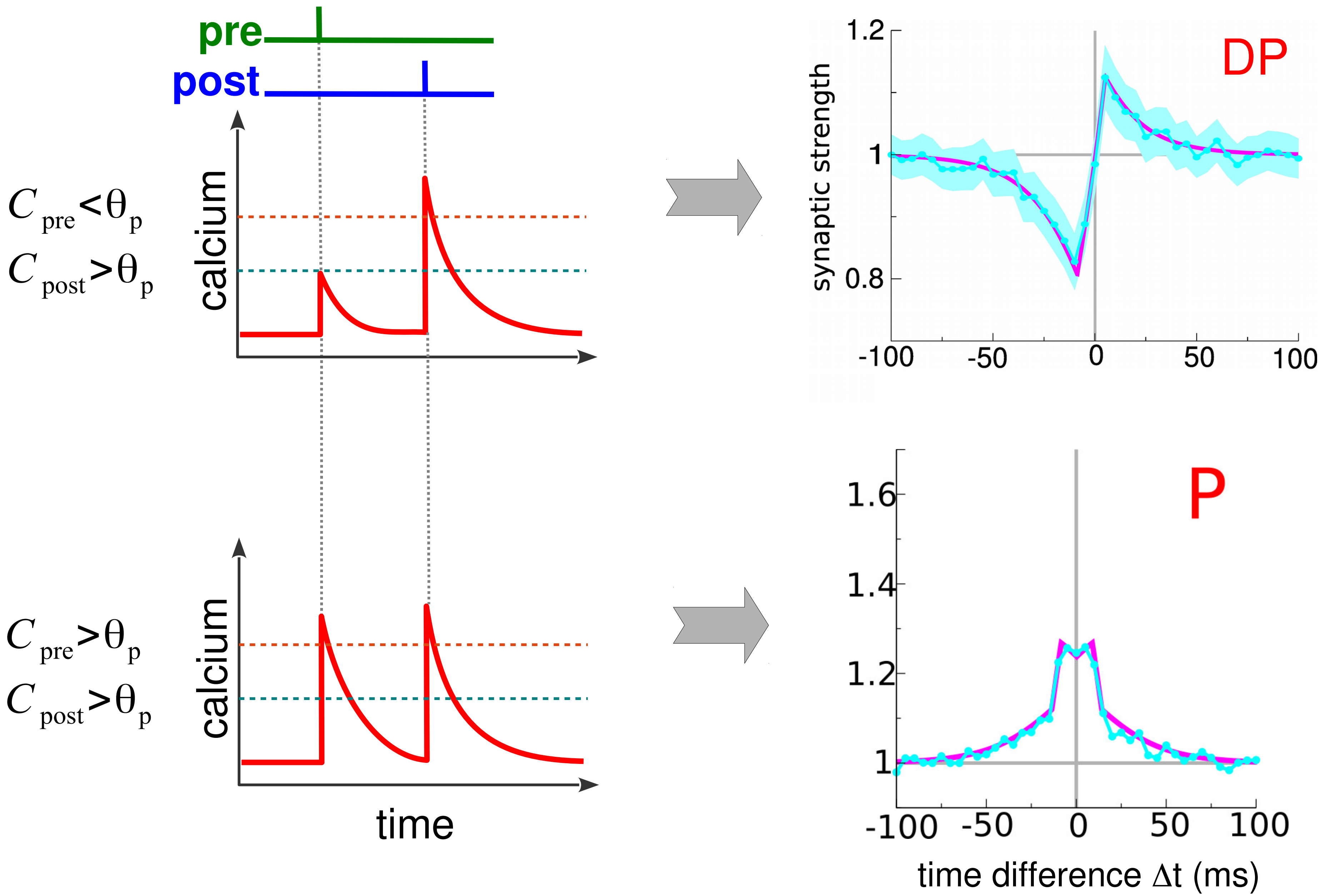
$C_{pre} < \theta_p$

$C_{post} > \theta_p$

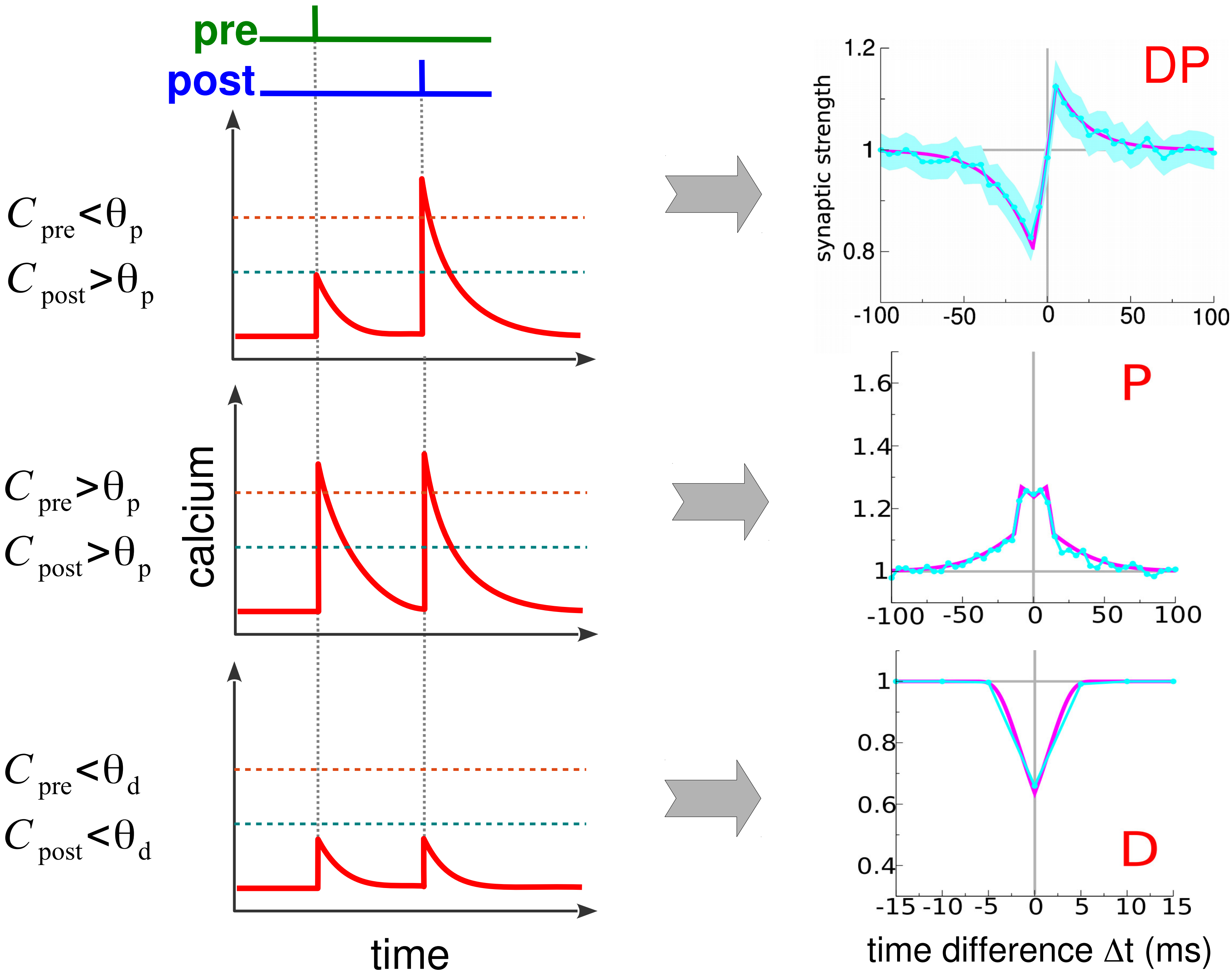




Calcium amplitudes determine shape of STDP curve

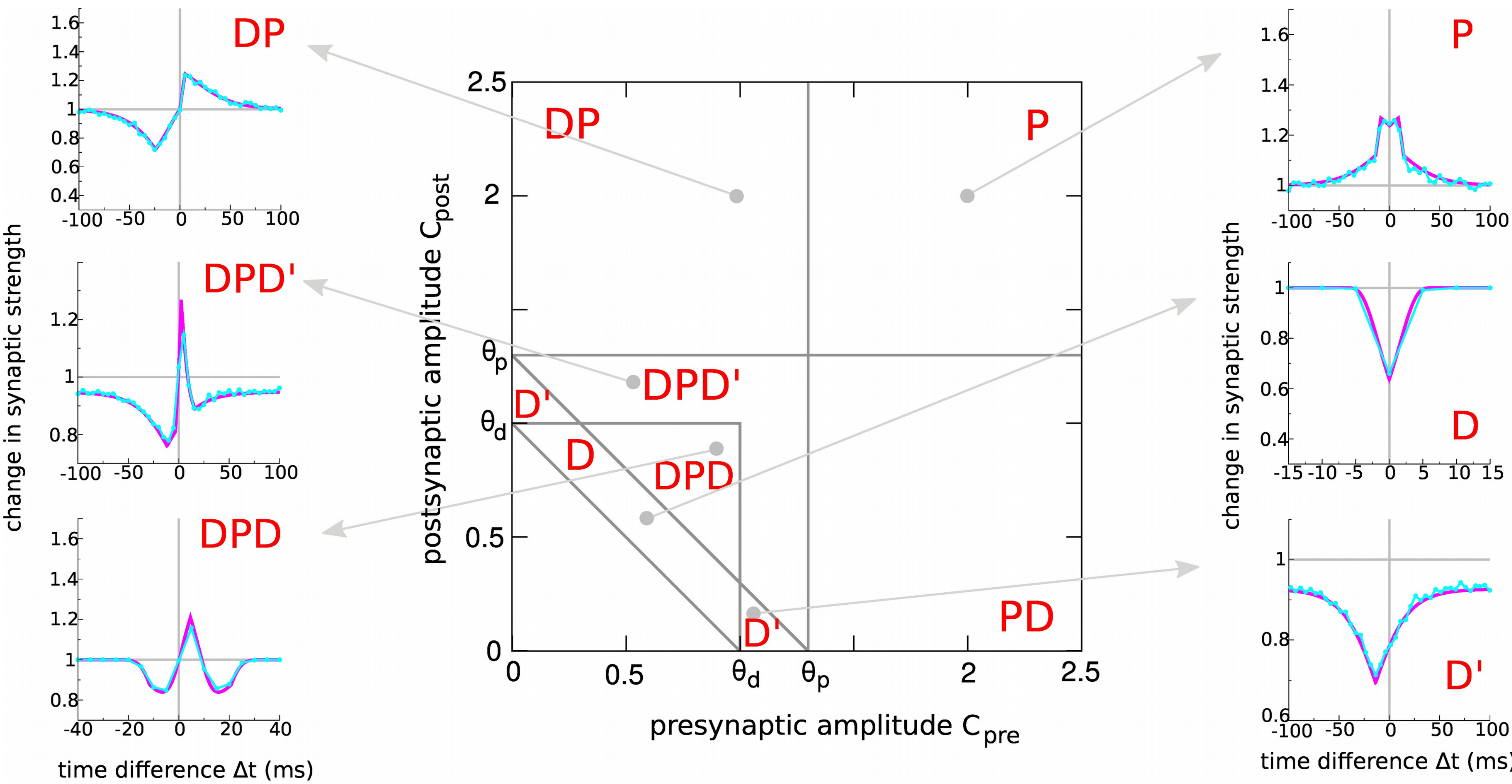


Calcium amplitudes determine shape of STDP curve



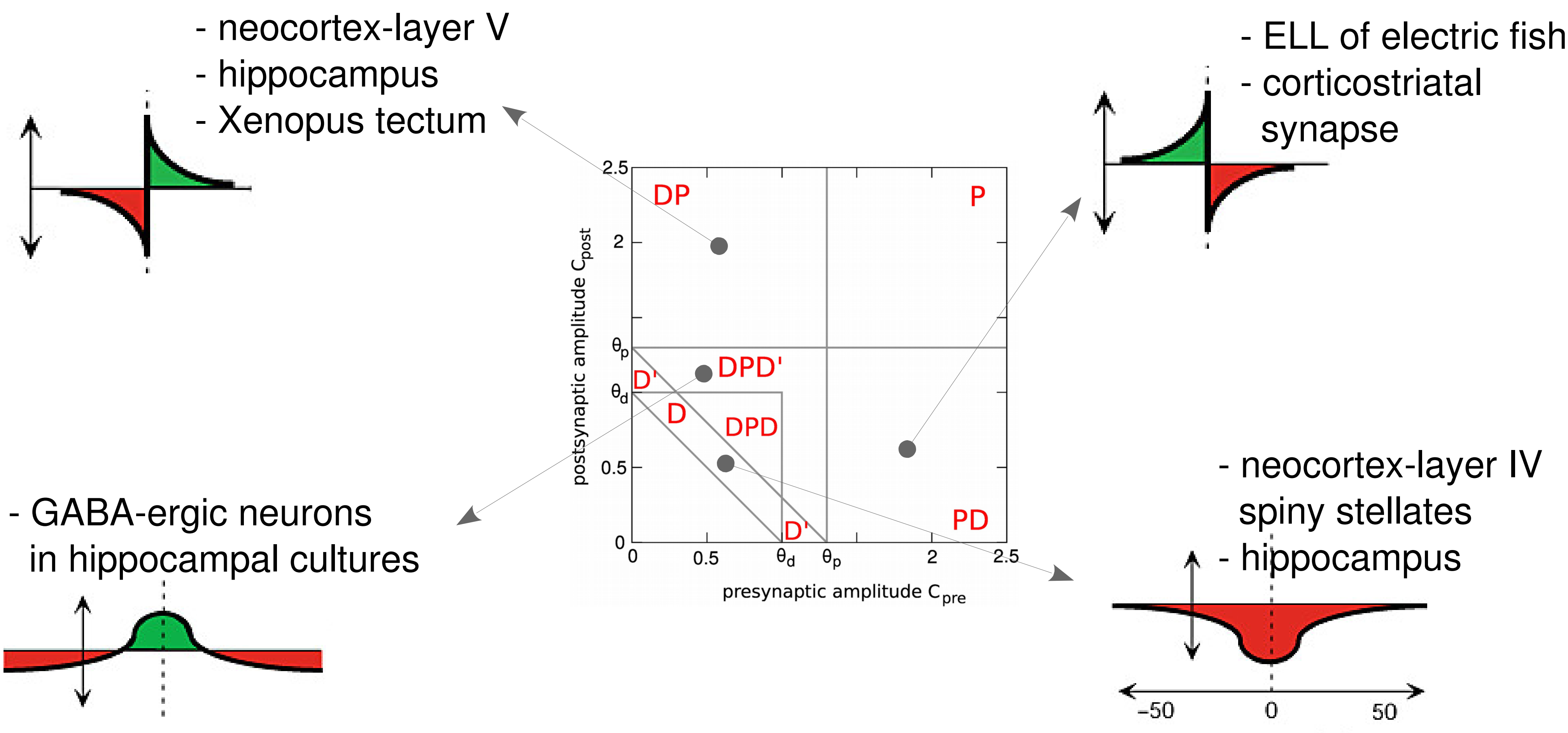
Diversity of STDP curves : spike-pair stimulation

D ... depression , P ... potentiation



[Graupner & Brunel, *PNAS* 2012]

Diversity of STDP curves : experimental results

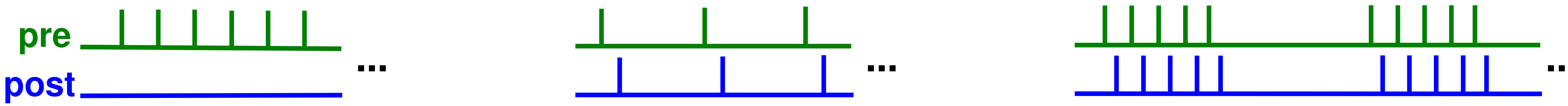


Outline

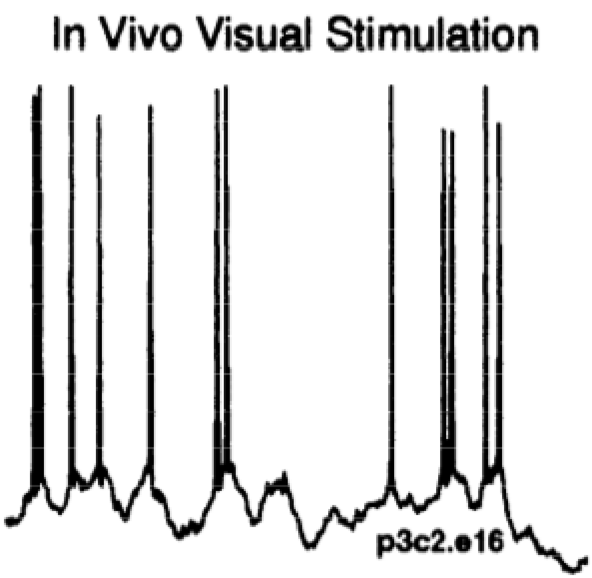
1. STDP : introduction and history
2. Phenomenology of STDP
3. Induction mechanisms
4. Biophysical models of STDP
5. STDP *in vivo* ?

Firing patterns : Realistic firing is highly irregular

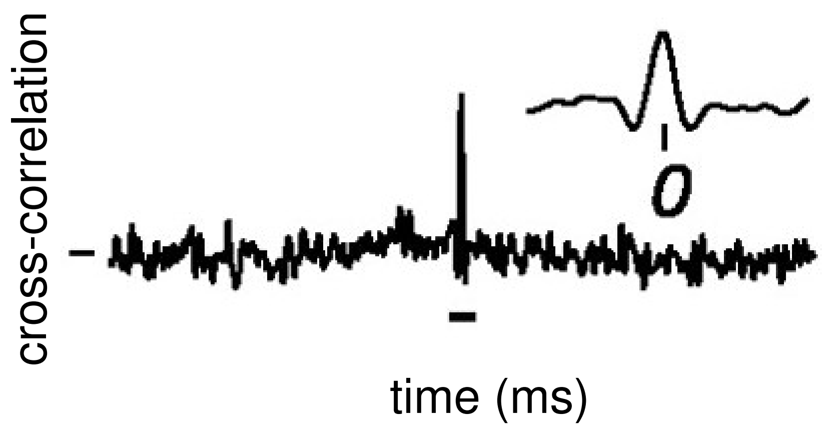
- stimulation protocols used to induce plasticity



- *in vivo* firing patterns



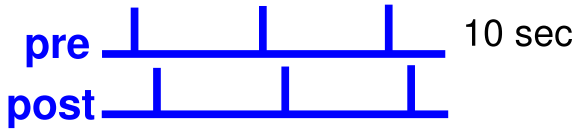
[Holt *et al.*, 1996]

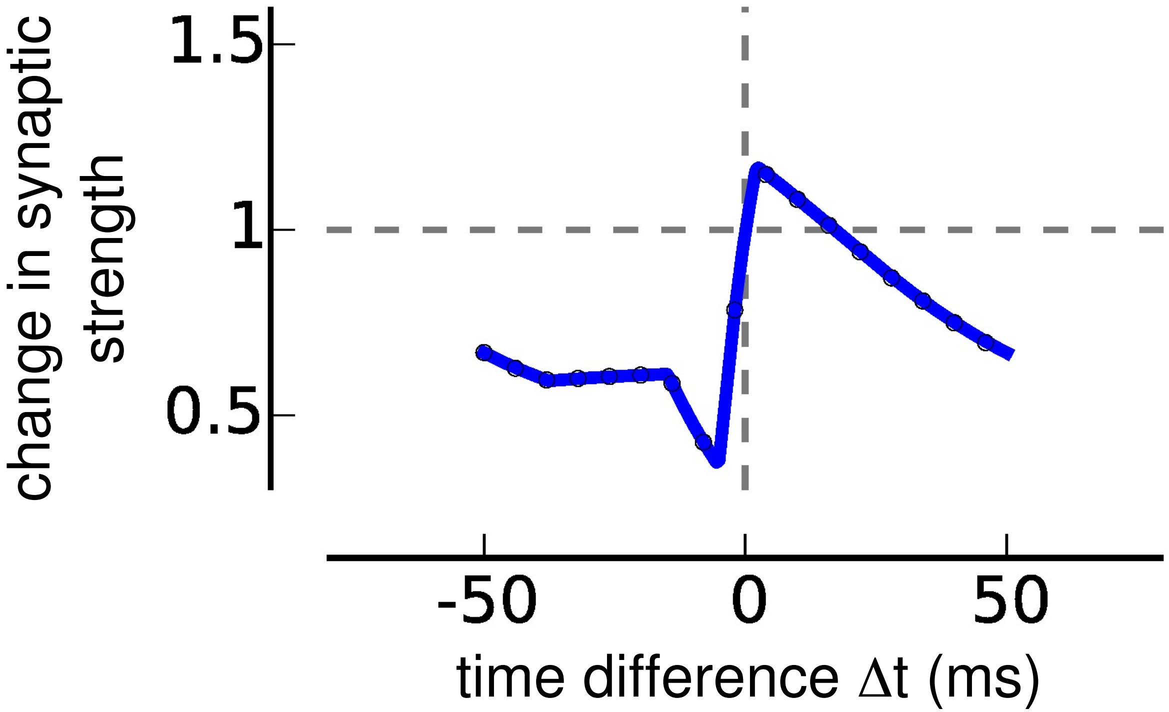


[Kohn and Smith, 2005]

Regular vs. irregular spike-pairs

regular spike-pairs

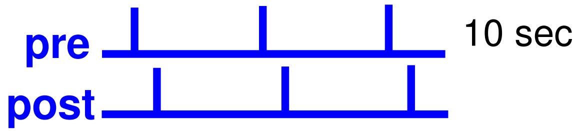




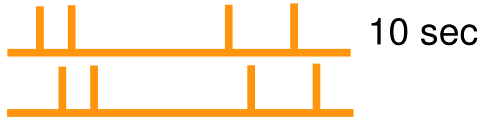
$$\nu_{pre} = \nu_{post} = 10 \text{ Hz}$$

Regular vs. irregular spike-pairs

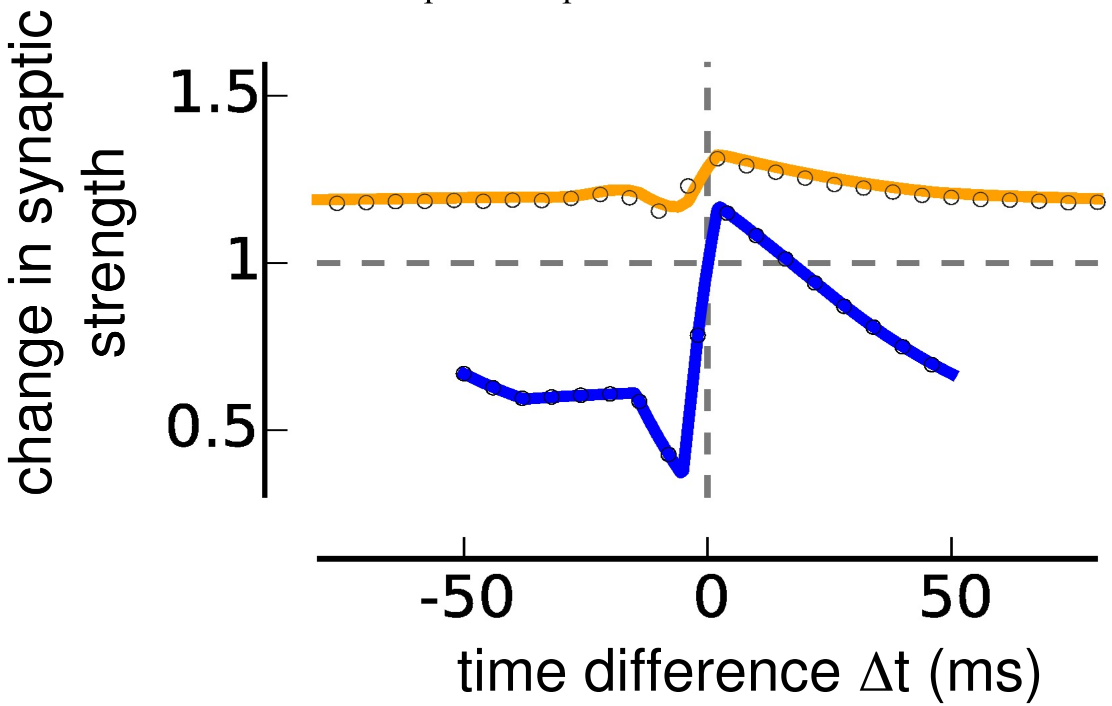
regular spike-pairs



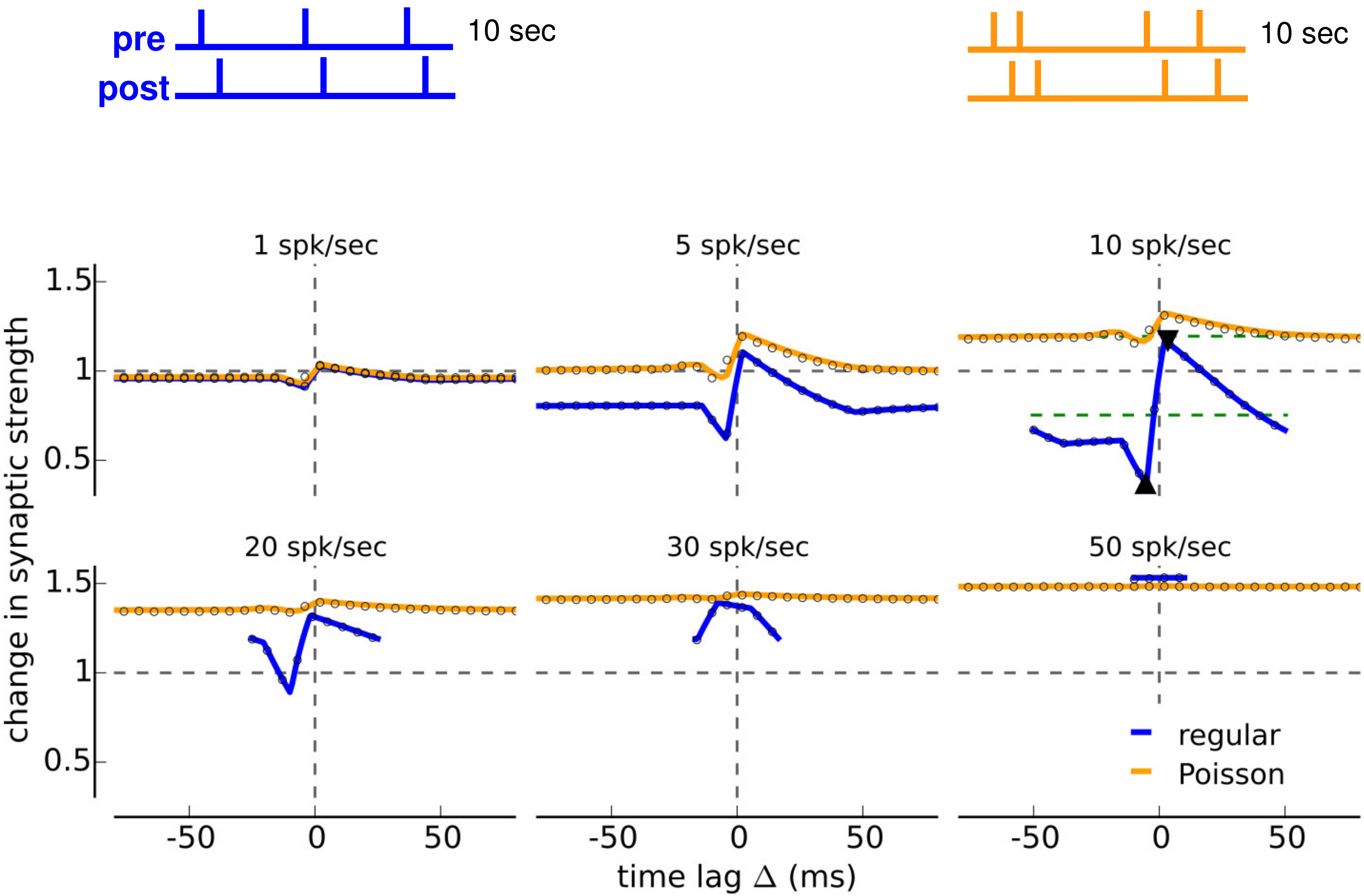
Poisson distributed spike-pairs



$\nu_{pre} = \nu_{post} = 10\,\mathrm{spk/sec}$



Irregular spike-pairs flatten STDP curve

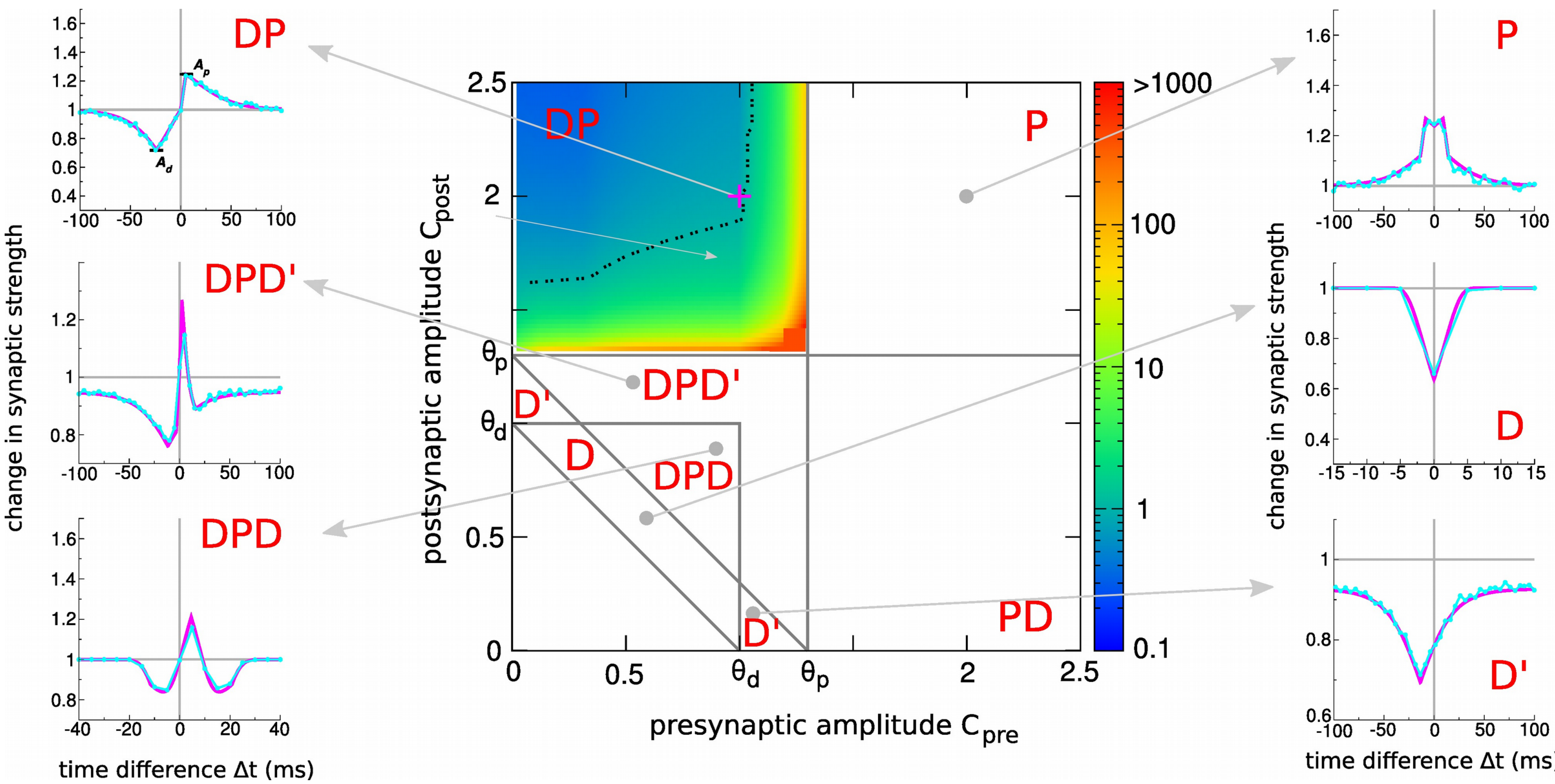


[Graupner, Wallisch & Ostojic. *J Neurosci* in press]

Conclusions

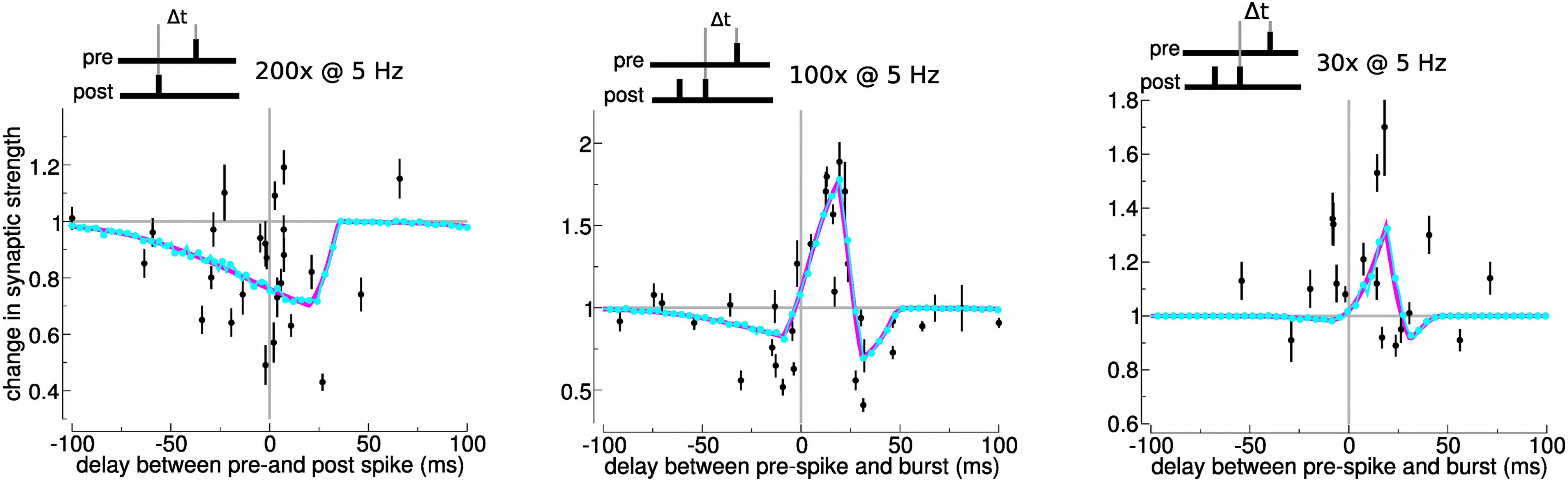
- STDP : temporally asymmetric form of synaptic plasticity induced by tight temporal correlations between the spikes of pre- and postsynaptic neurons
- induction: coincident pre- and postsynaptic activity lead to calcium influx through NMDA receptors, triggering intracellular signaling cascades
- biophysical 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



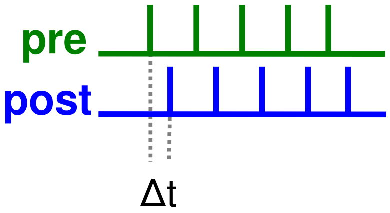
[Graupner & Brunel, 2012]

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

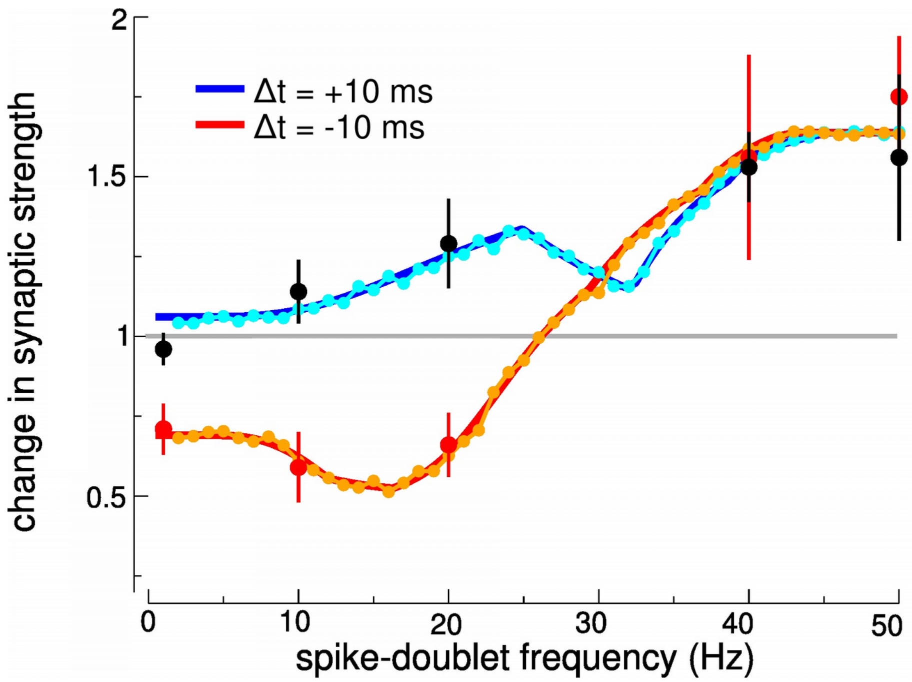


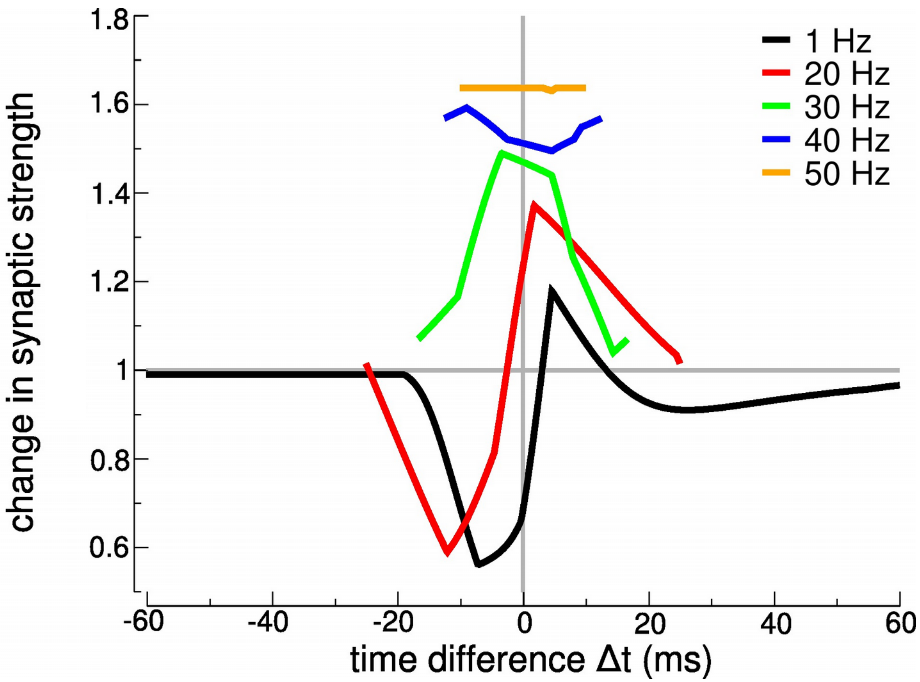
[Wittenberg & Wang, 2006]

Firing rate dependence in cortical slices



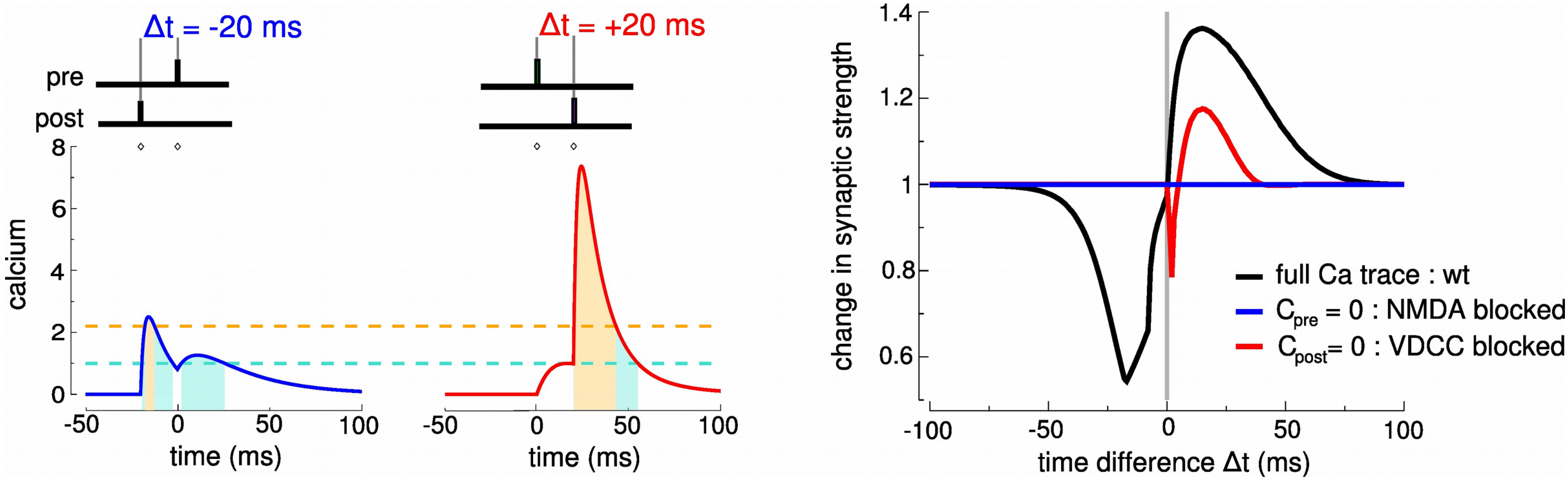
15x @ 0.1 Hz





[Sjöström *et al.*, 2001]

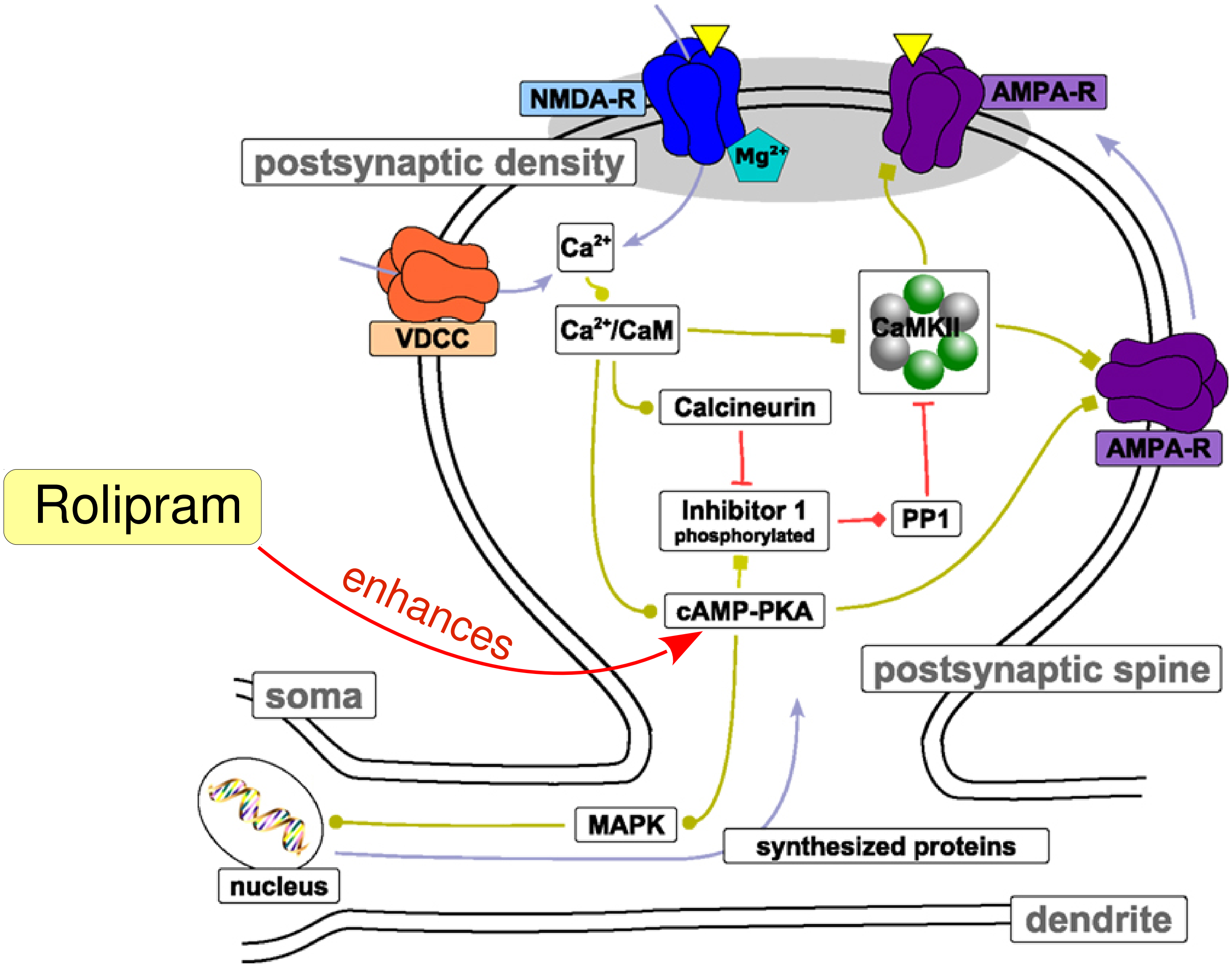
Pharmacological manipulations explained by Ca^{2+}



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

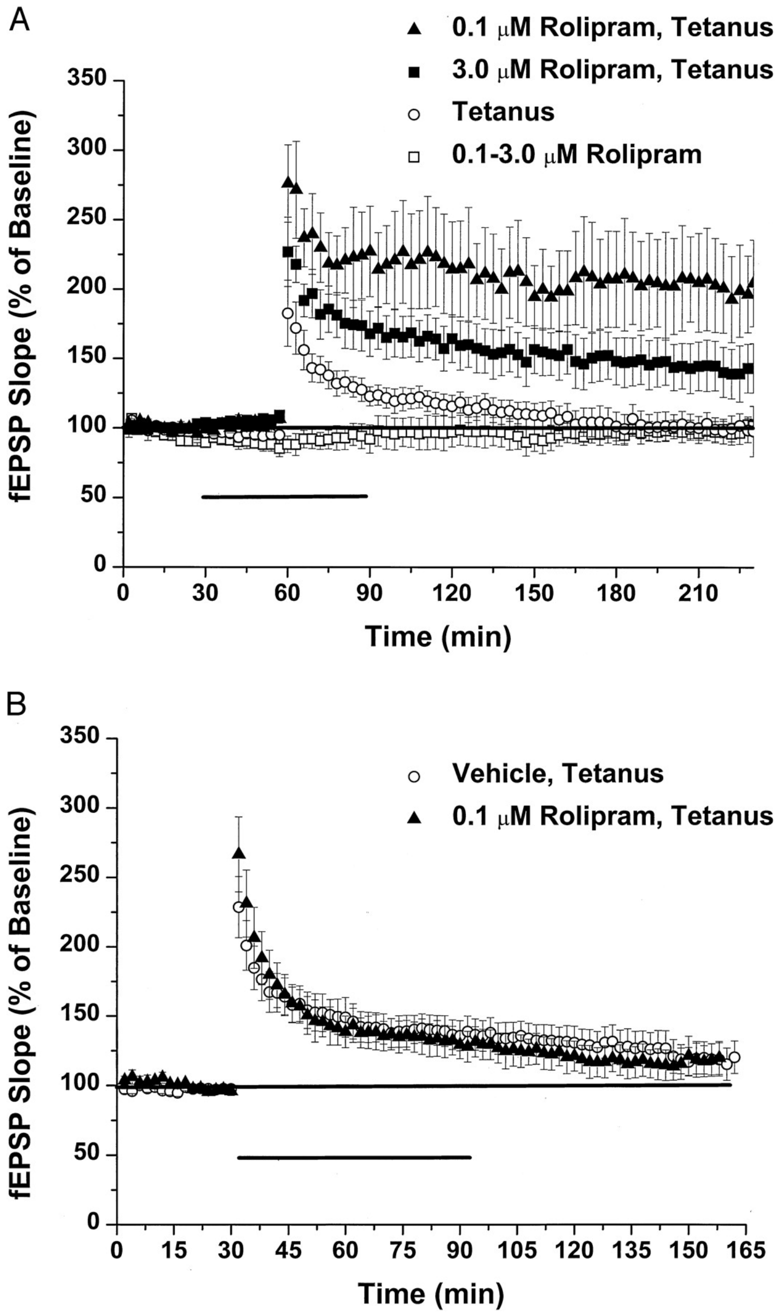
- nonlinear, finite rise time calcium transients necessary to reproduced pharmacological block experiments

Study the effect of nootropic drugs (memory enhancer)



Rolipram … selective phosphodiesterase-4 inhibitor

Study the effect of nootropic drugs

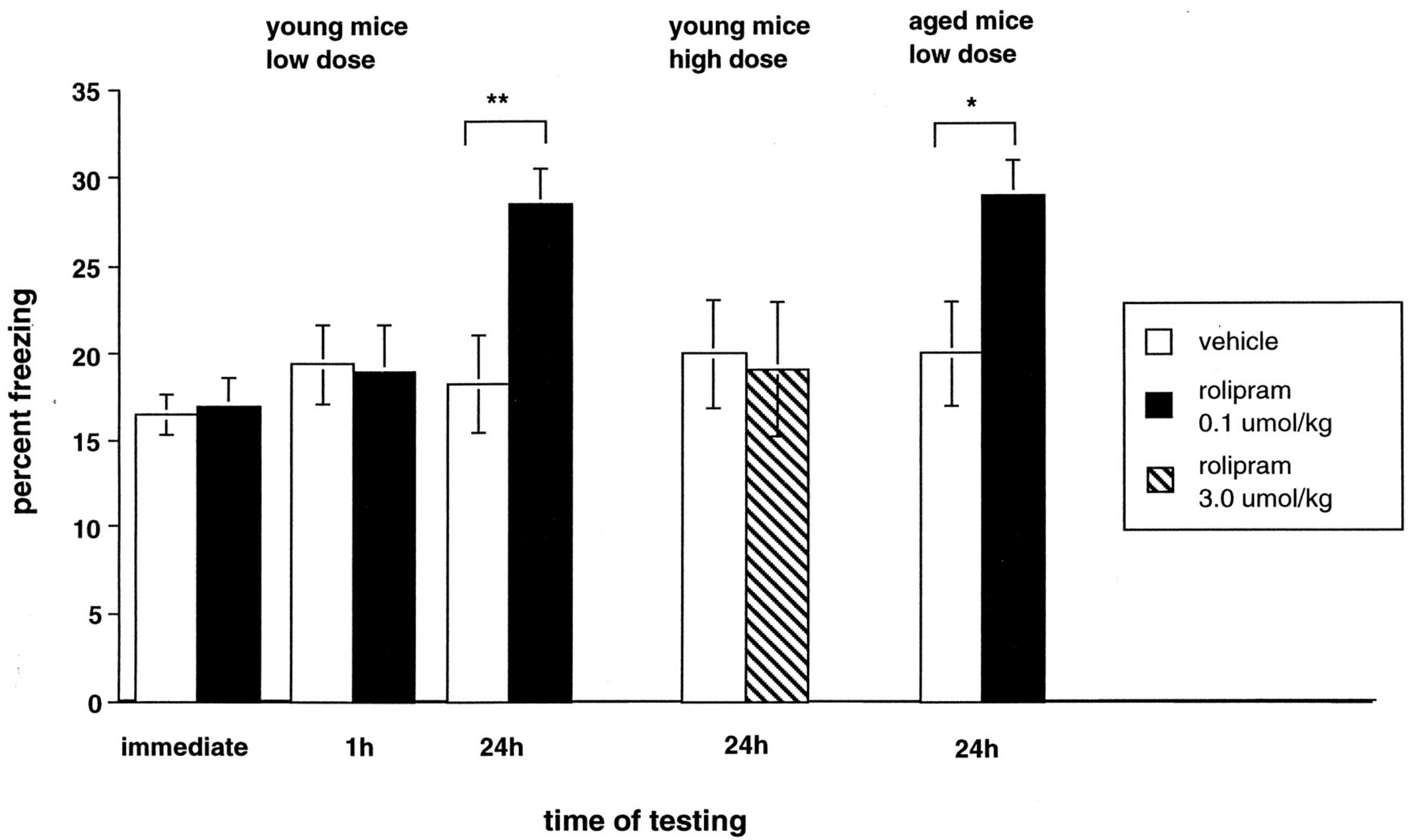


- boosting of cAMP *during* stimulation increases LTP

[Barath *et al.*, 1998]

Study the outcome of nootropic drugs

- Rolipram enhances memory



[Barath *et al.*, 1998]