



From Science Magazine, 2005

Synaptic plasticity

Computational approaches to
memory and plasticity 2016

Rishikesh Narayanan

Indian Institute of Science
Bangalore

What is plasticity?

Plasticity is the ability of a system to change or deform and thereby adapt to the environment.

In the neuronal context, the ability of a neuron or synapse to change its properties in response to incoming stimulus is referred to as plasticity

Broad types of neuronal plasticity

Synaptic plasticity: Changes pertaining to synapses

Intrinsic plasticity: Changes in properties intrinsic to neurons

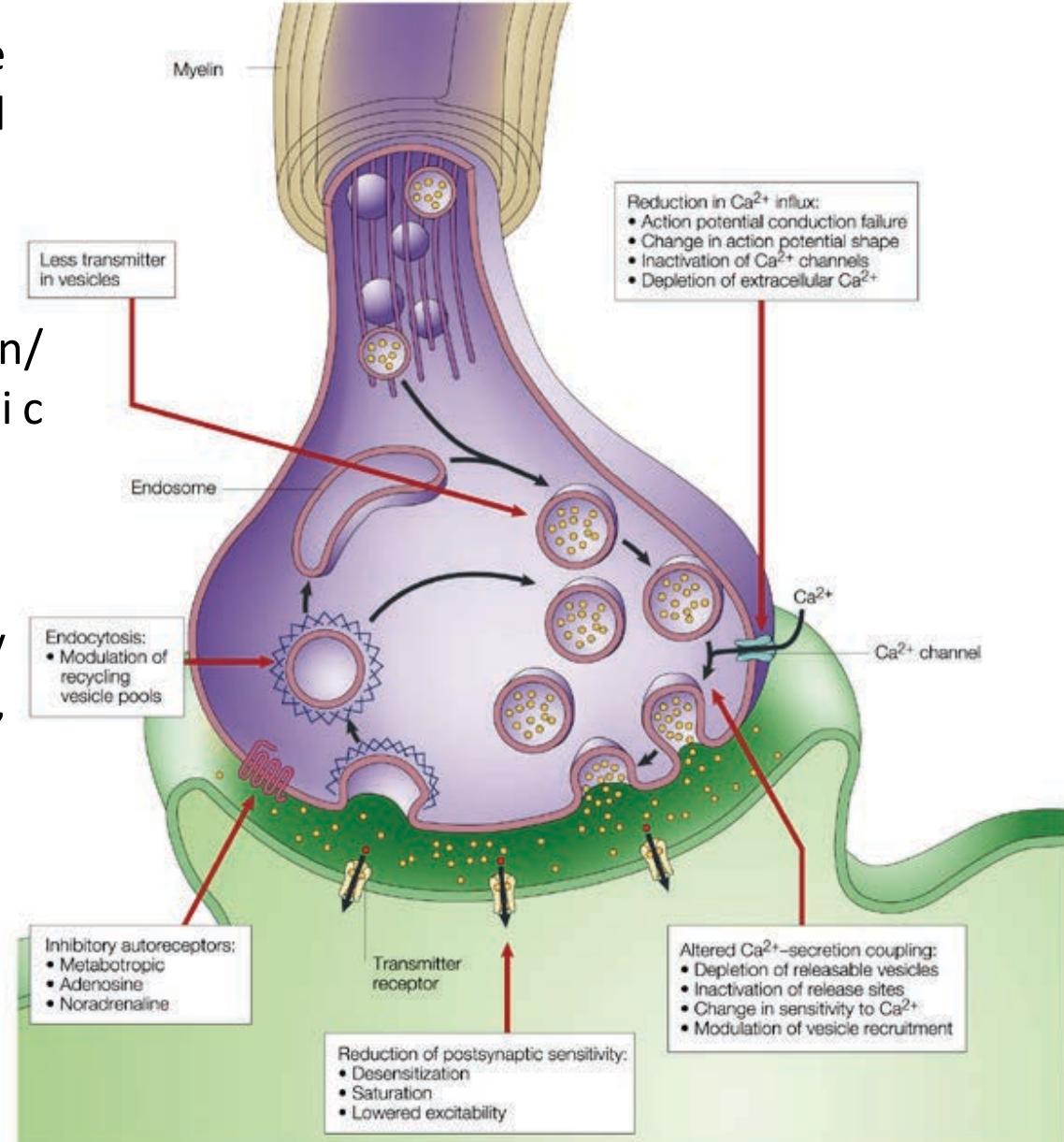
Structural plasticity: Changes in dendritic and/or spine structure

Short-term synaptic plasticity

Use-dependent plasticity on the tens of milliseconds to several minutes time scale.

e.g., Paired pulse potentiation/depression, post-tetanic potentiation, augmentation

Most such short-term plasticity mechanisms are presynaptic, rather than postsynaptic



Lectures by Misha Tsodyks on
July 11th

Zucker and Regehr, Ann. Rev. Physiol., 2002
Abbott and Regehr, Nature, 2004

Gersdorff and Borst, NRN, 2002

Nature Reviews | Neuroscience

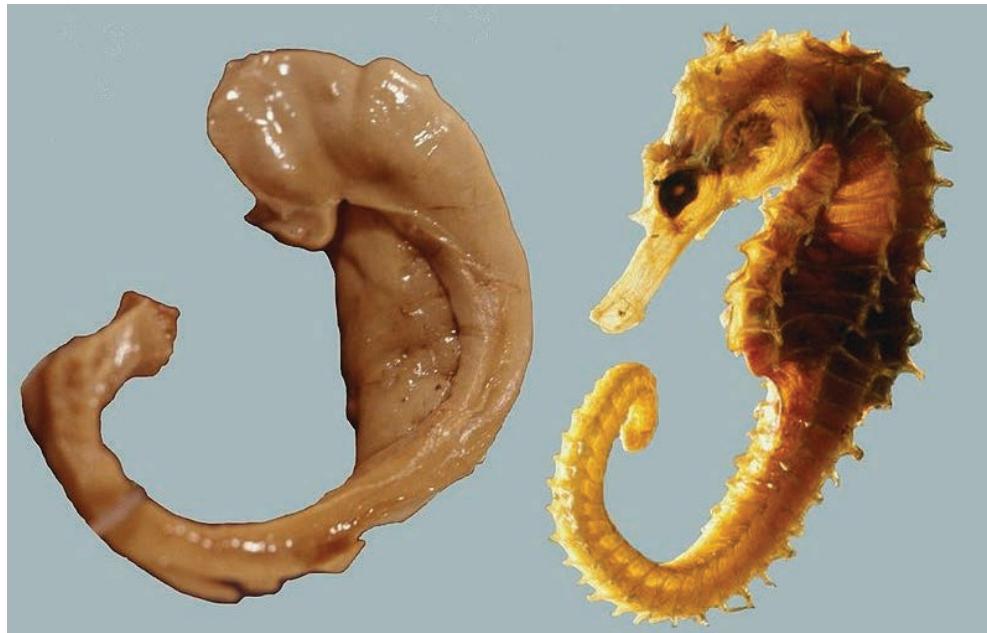
Choosing the right system is important in studying a phenomenon!

The hippocampus

Named so by Julius Caesar Aranzi (1587). Latin: *hippocampus*, from Greek: ἵππος, "horse" and Greek: κάμπος, "sea monster")

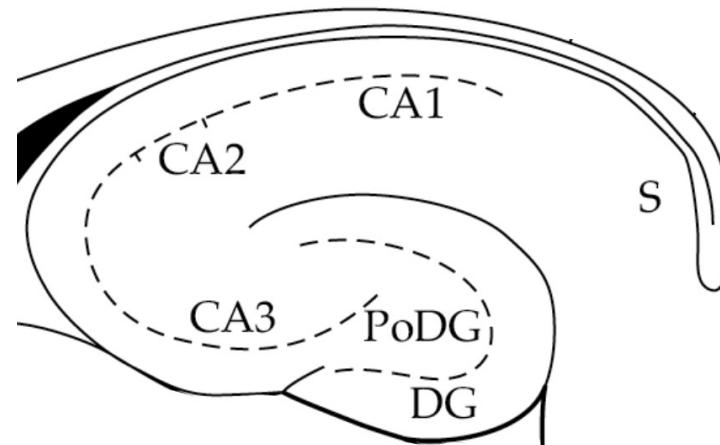
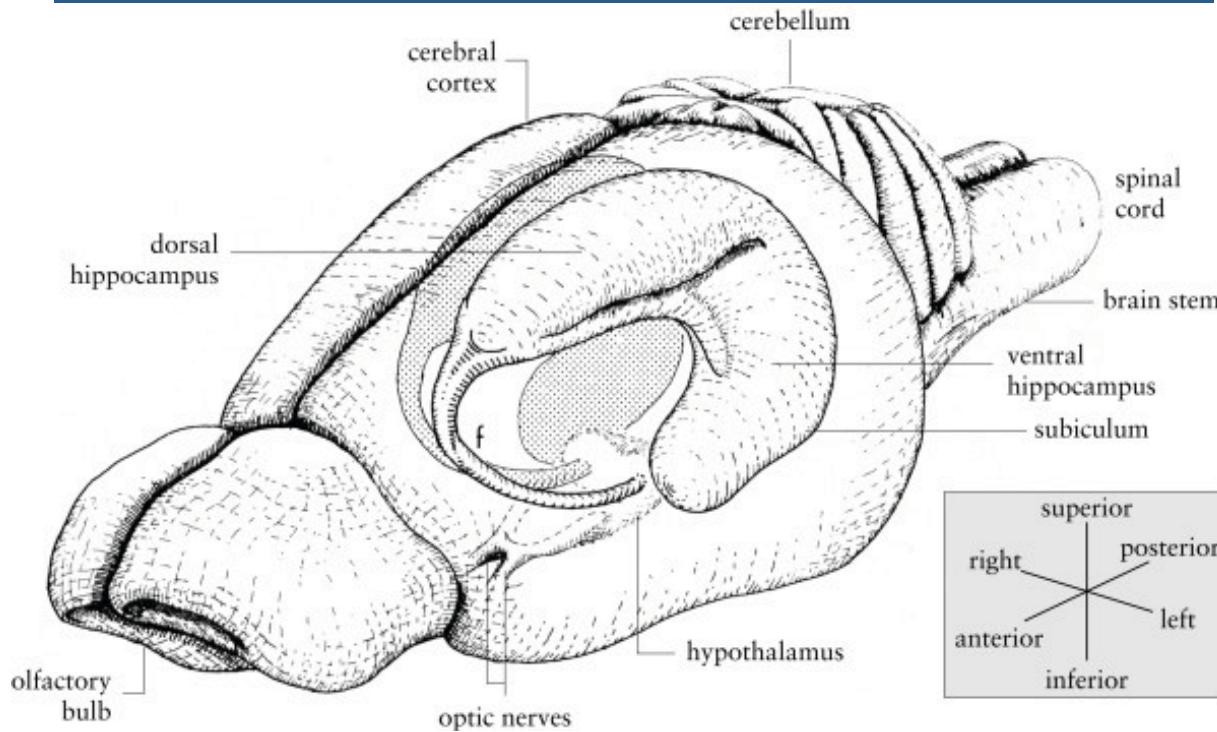
Also named by de Garengeot, as "cornu Ammonis", meaning horn of (the ancient Egyptian god) Amun

Histological divisions of hippocampus are still called CA1, CA2 and CA3



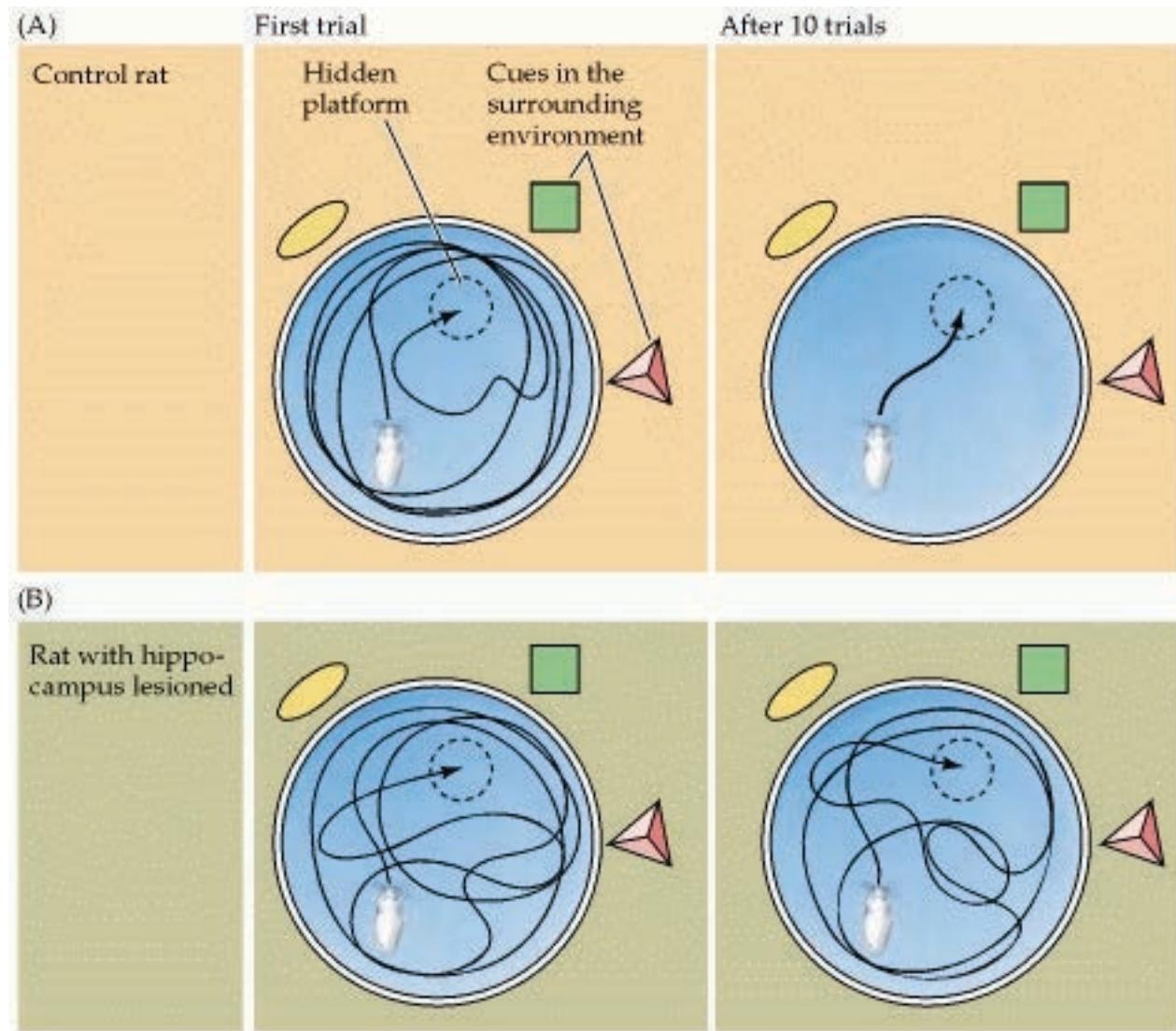
[Wikipedia](#)

The mammalian hippocampus is a good system for studying long-term synaptic plasticity



Why?

Hippocampus is involved in learning and memory



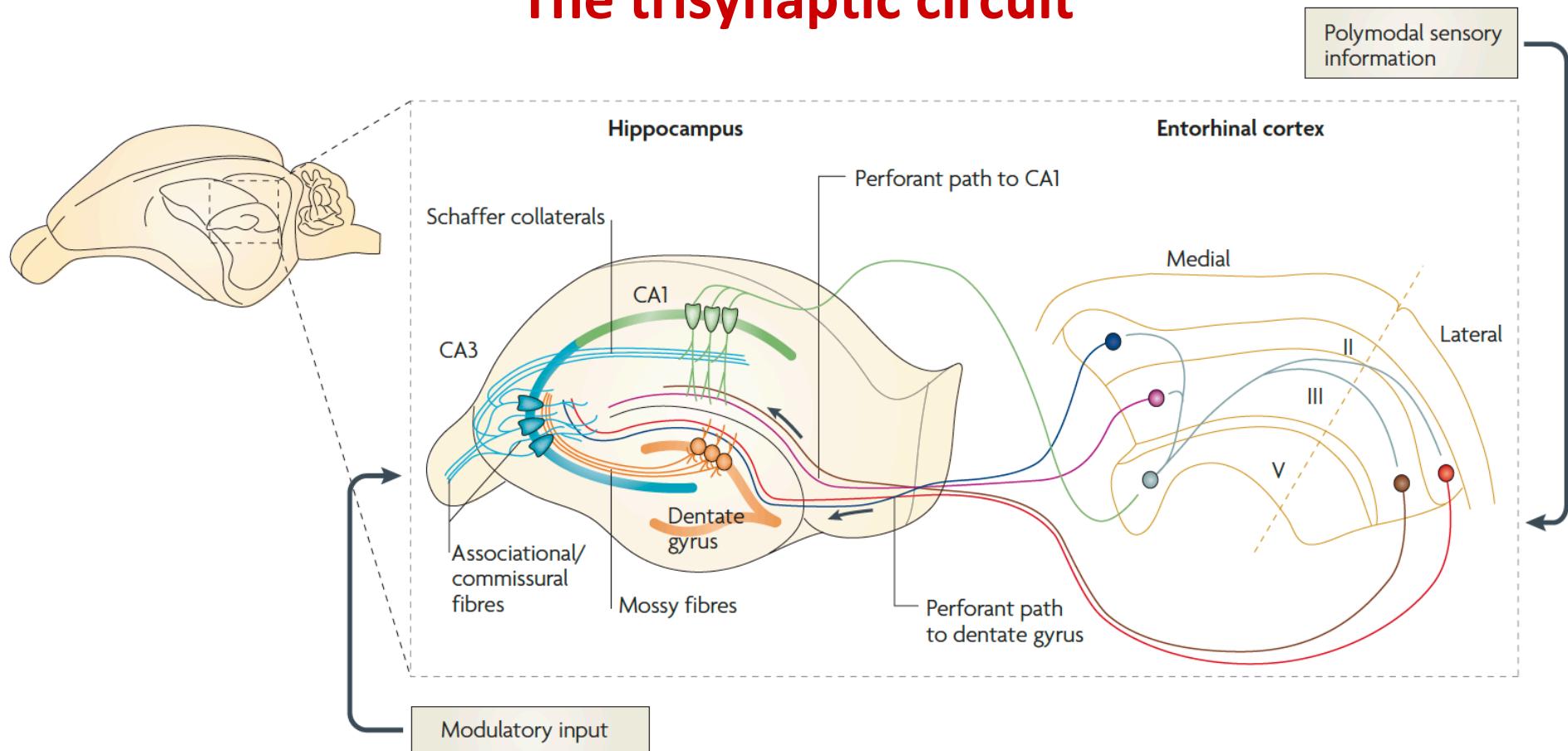
HM, Henry Molaison
(1926–2008)

Hippocampal lesions impair the animal's ability to learn spatial tasks

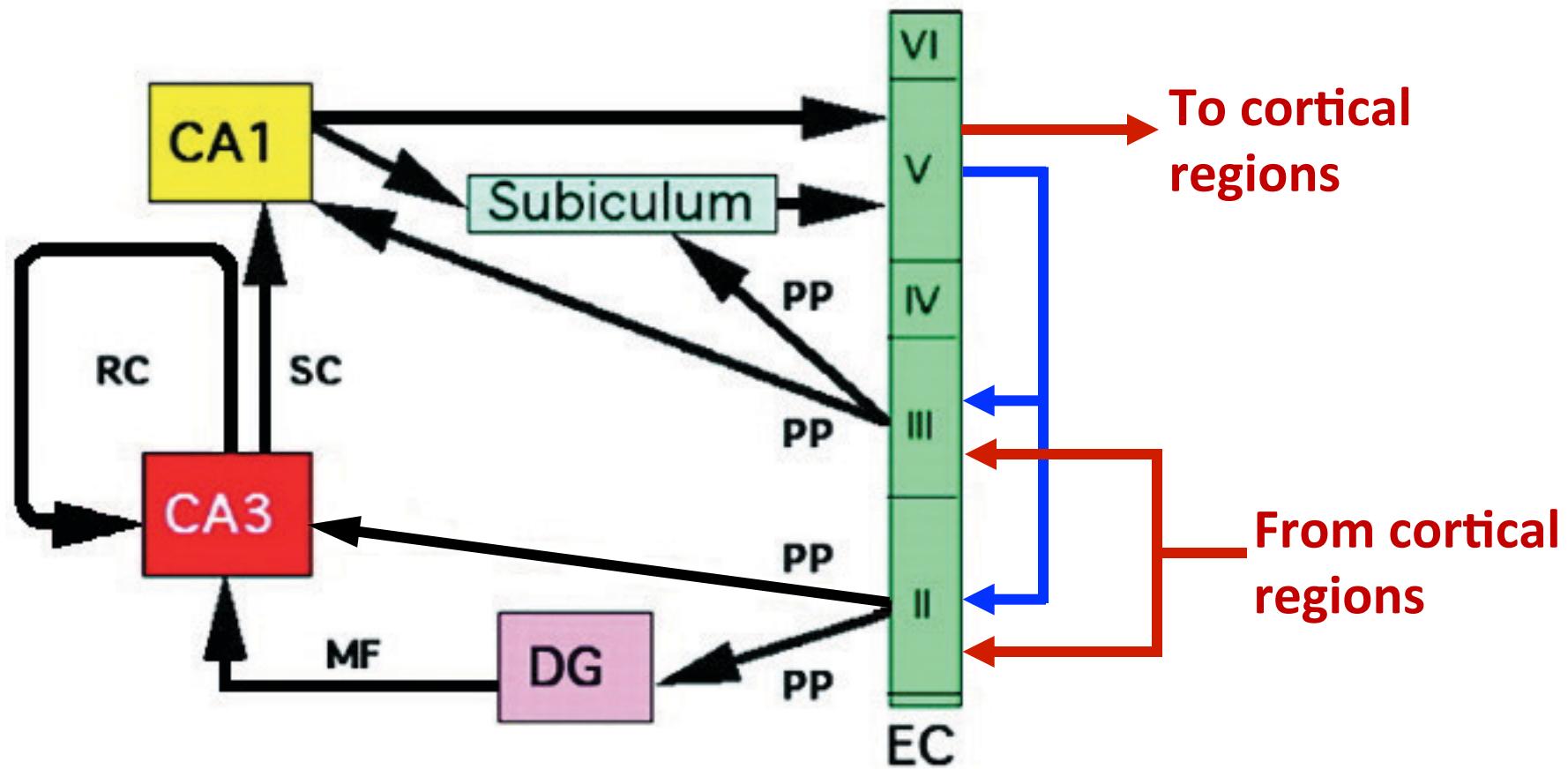
Purves, Neuroscience Book

The circuitry is neatly organized making recordings and interpretations easier

The trisynaptic circuit

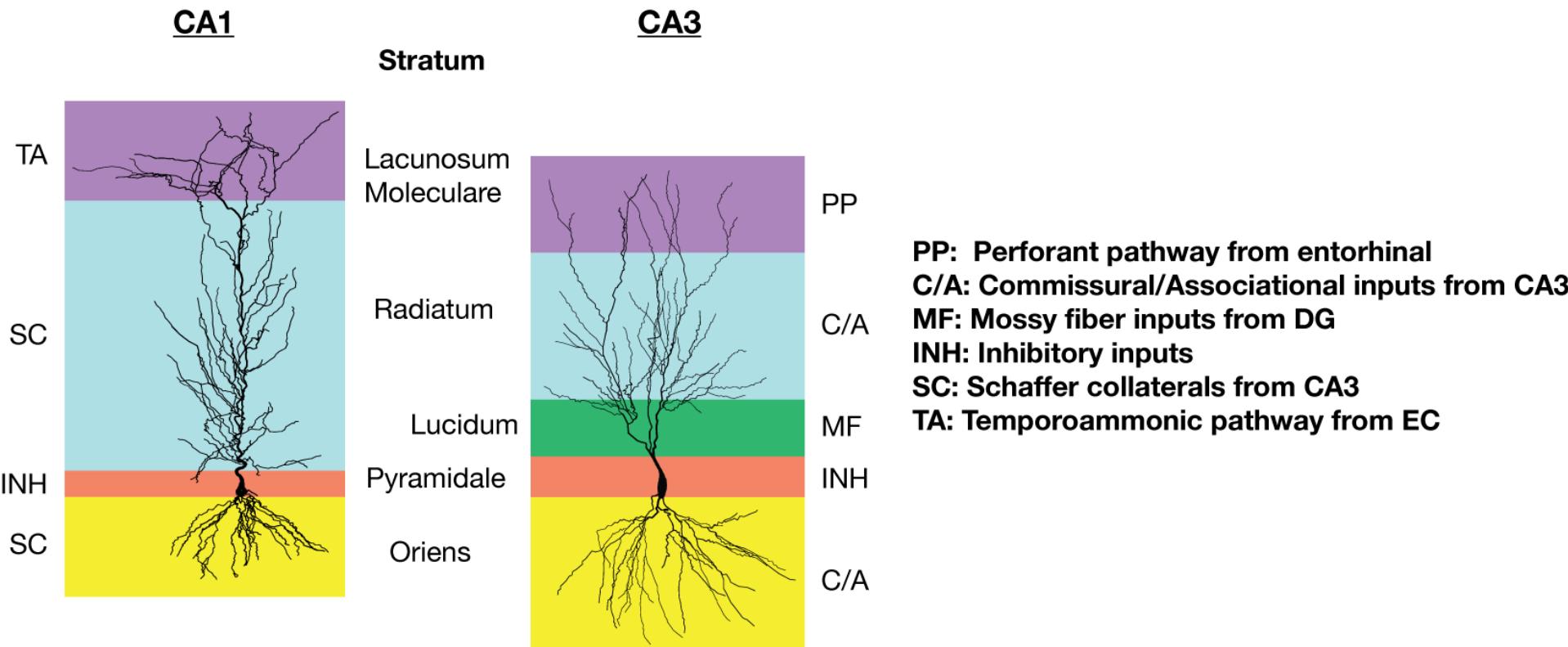


The trisynaptic circuit

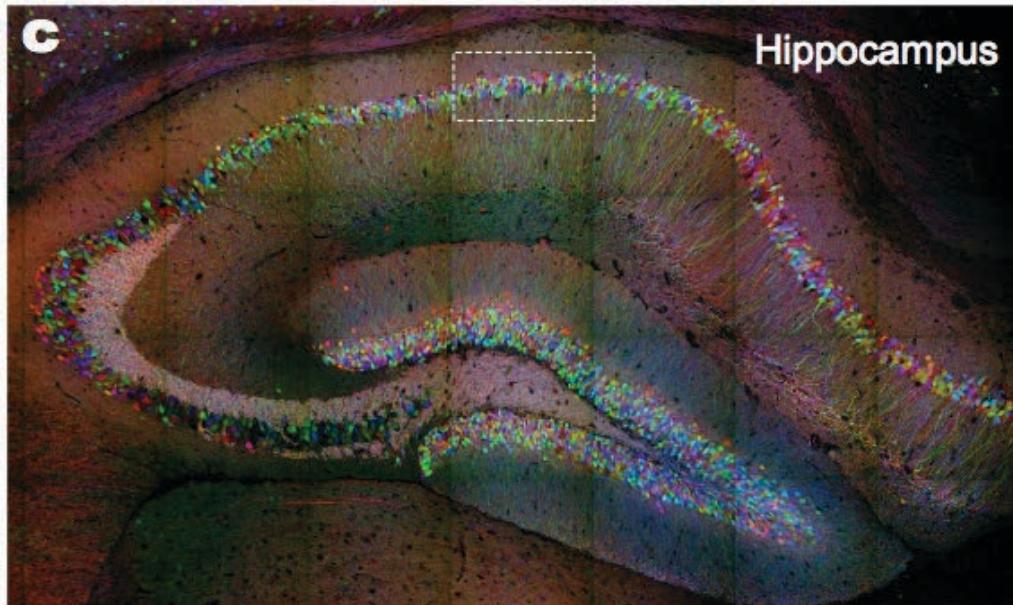


Inputs are nicely organized into different strata

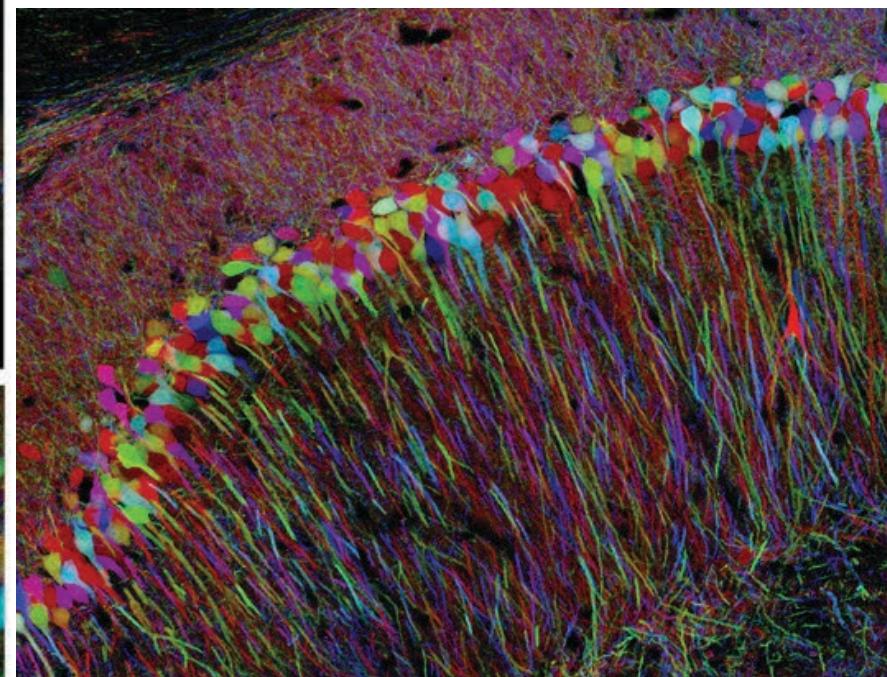
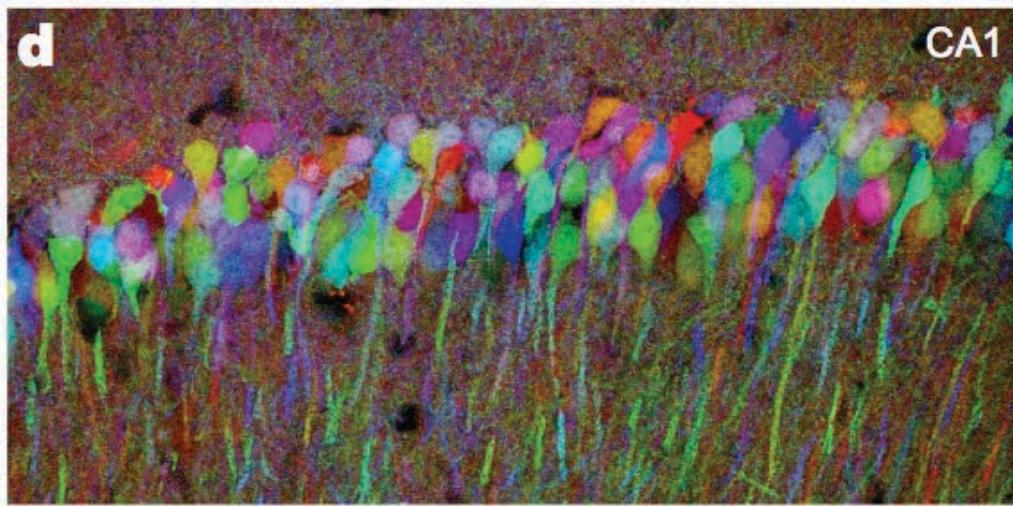
Synaptic inputs into these neurons is strafigied, so studying particular synapses becomes easier



Field recordings become easier because cells are all organized in a regular fashion



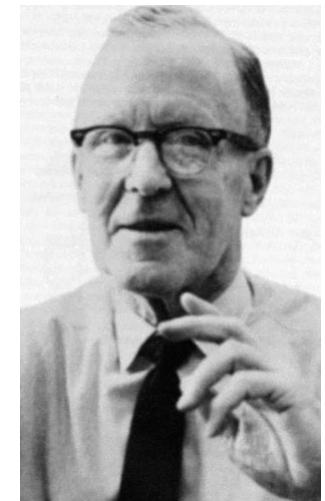
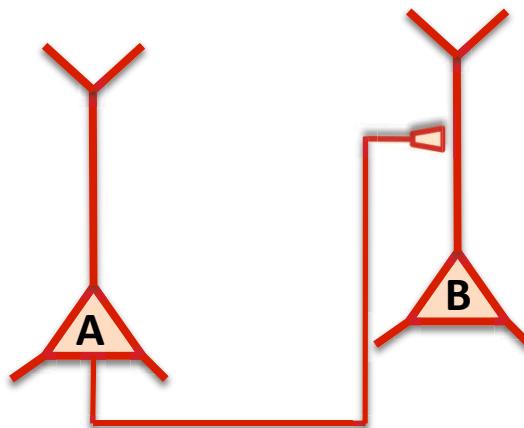
Distance measurements are also easier here with dendritic recordings!!



Brainbow mouse: each neuron has a different color!

Donald Hebb's postulate

“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 process or metabolic change takes place in one or both cells, such that A’s efficiency, as one of the cells firing B, increases.”



- Repeated simultaneous activation of two cells *strengthens the synapses that link them*

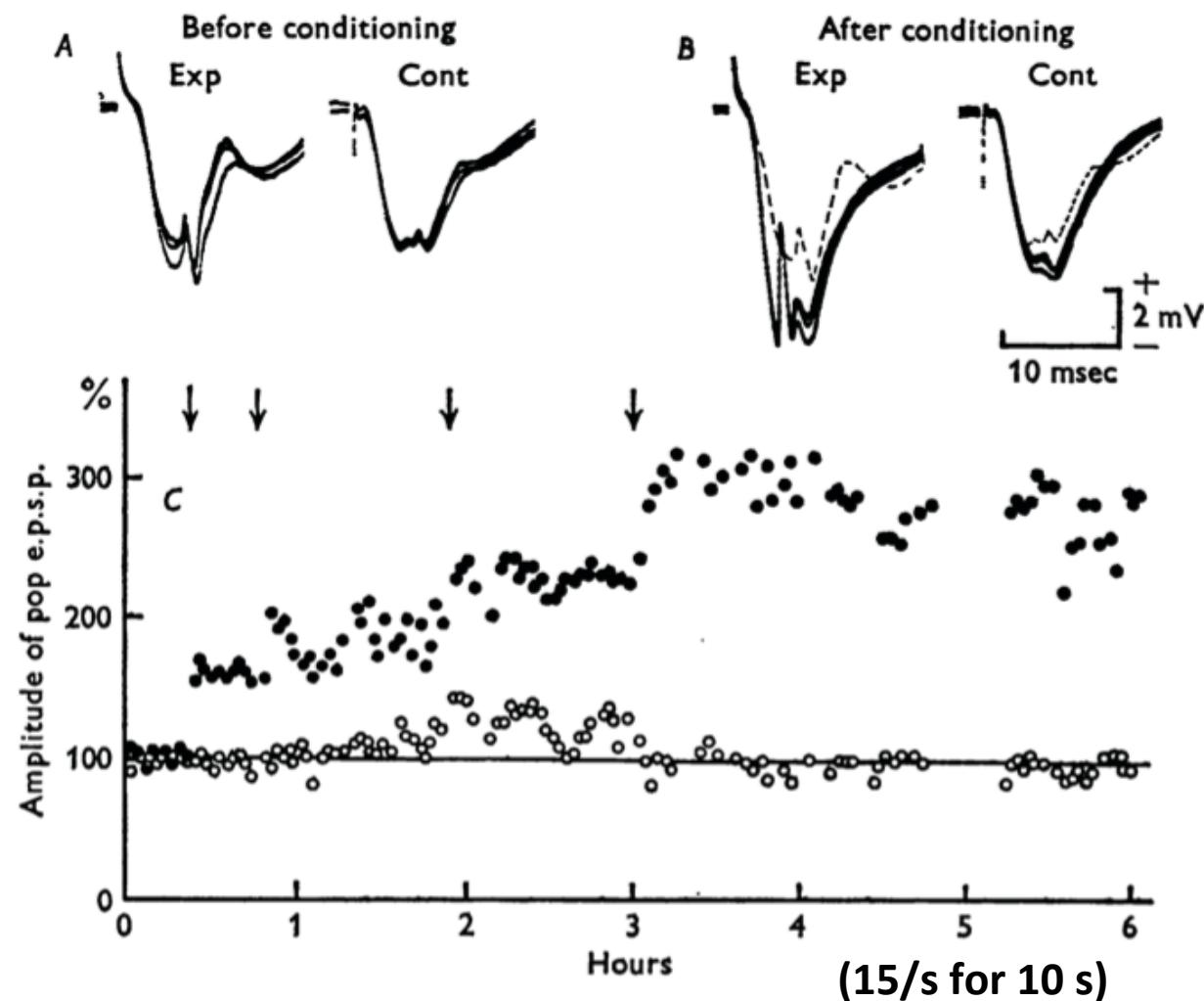
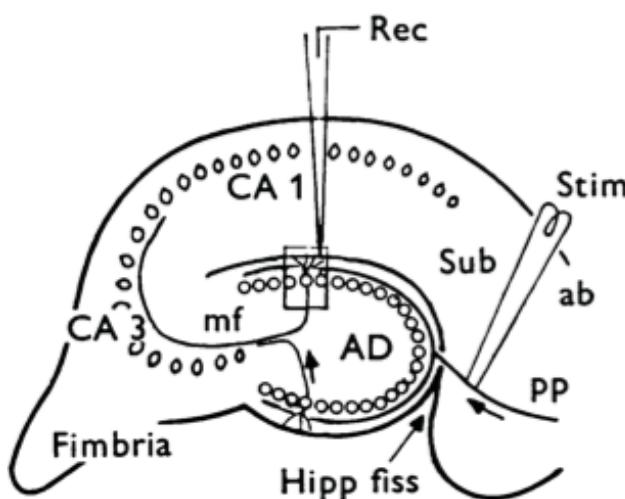
Proposed in 1949

- “*Cells that fire together wire together*”

Long-term potentiation (LTP)

Bliss and Lomo, 1973

~30 years after Hebb's postulate

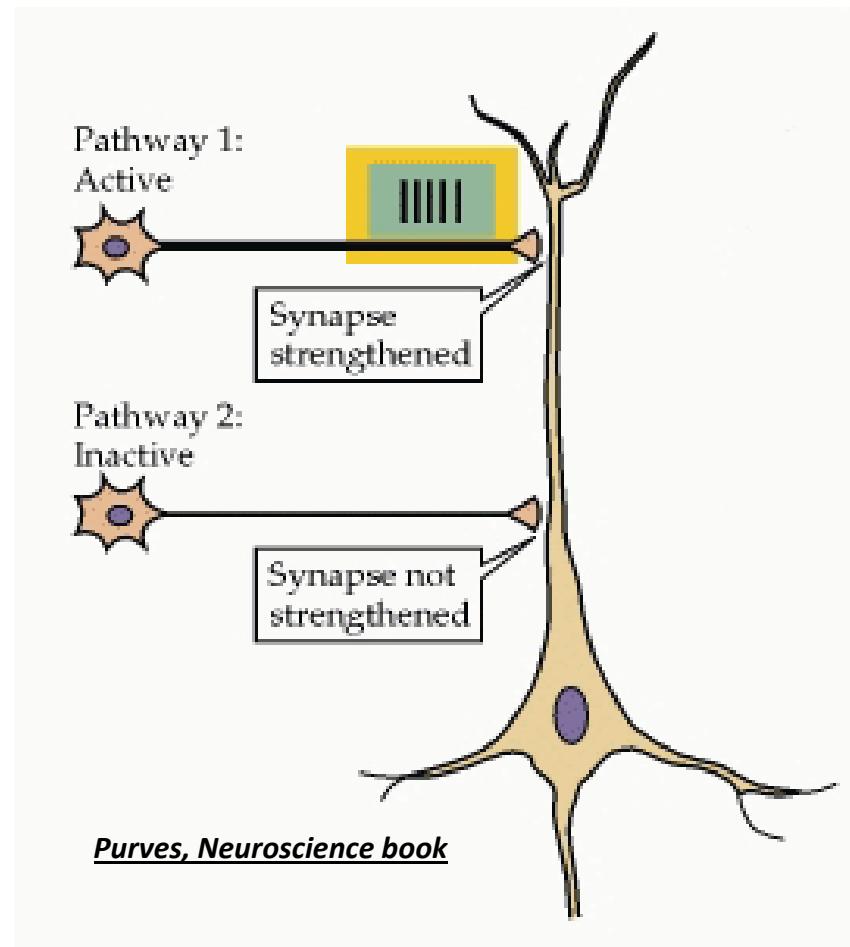


What causes LTP Induction?

So, what happens at induction, and what drives these properties?

Early (1980's) hypothesis:

- It is local postsynaptic depolarization! Potentiation occurs if and only if the synapse is active at a time when the region of the dendrite at which it terminates is sufficiently depolarized
- input specificity and associativity can all be explained under this framework



How to test this hypothesis experimentally?

Tetanus is not required, just depolarization during test pulses is sufficient for PTP/LTP!

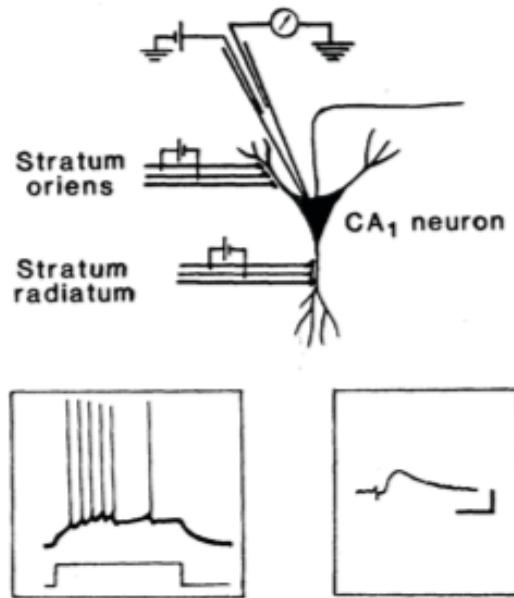
Sufficiency of depolarization + non-tetanic synaptic stimulation for inducing LTP

UC: unpaired conditioning trains

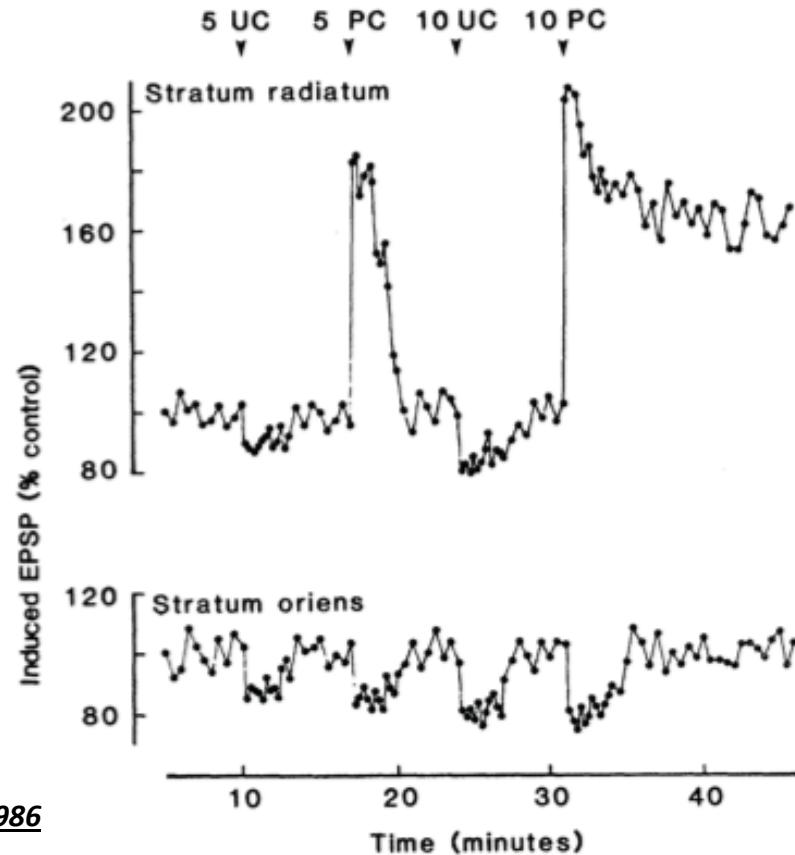
PC: paired conditioning trains

0.2 Hz stimulation!

Conditioning pulse is depolarization occurring before the synaptic stimulation



Sastry et al., Science, 1986

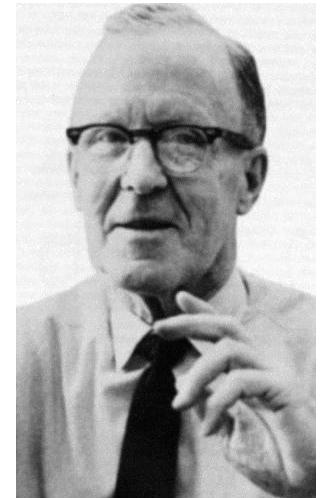


Evidence for the necessity of depolarization for LTP was provided by (Malinow and Miller, Nature, 1986), where they injected hyperpolarizing current during tetanus, and got NO LTP!

Hebb's postulate

LTP is a coincidence detector of presynaptic activity and postsynaptic depolarization!

“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 process or metabolic change takes place in one or both cells, such that A’s efficiency, as one of the cells firing B, increases.”

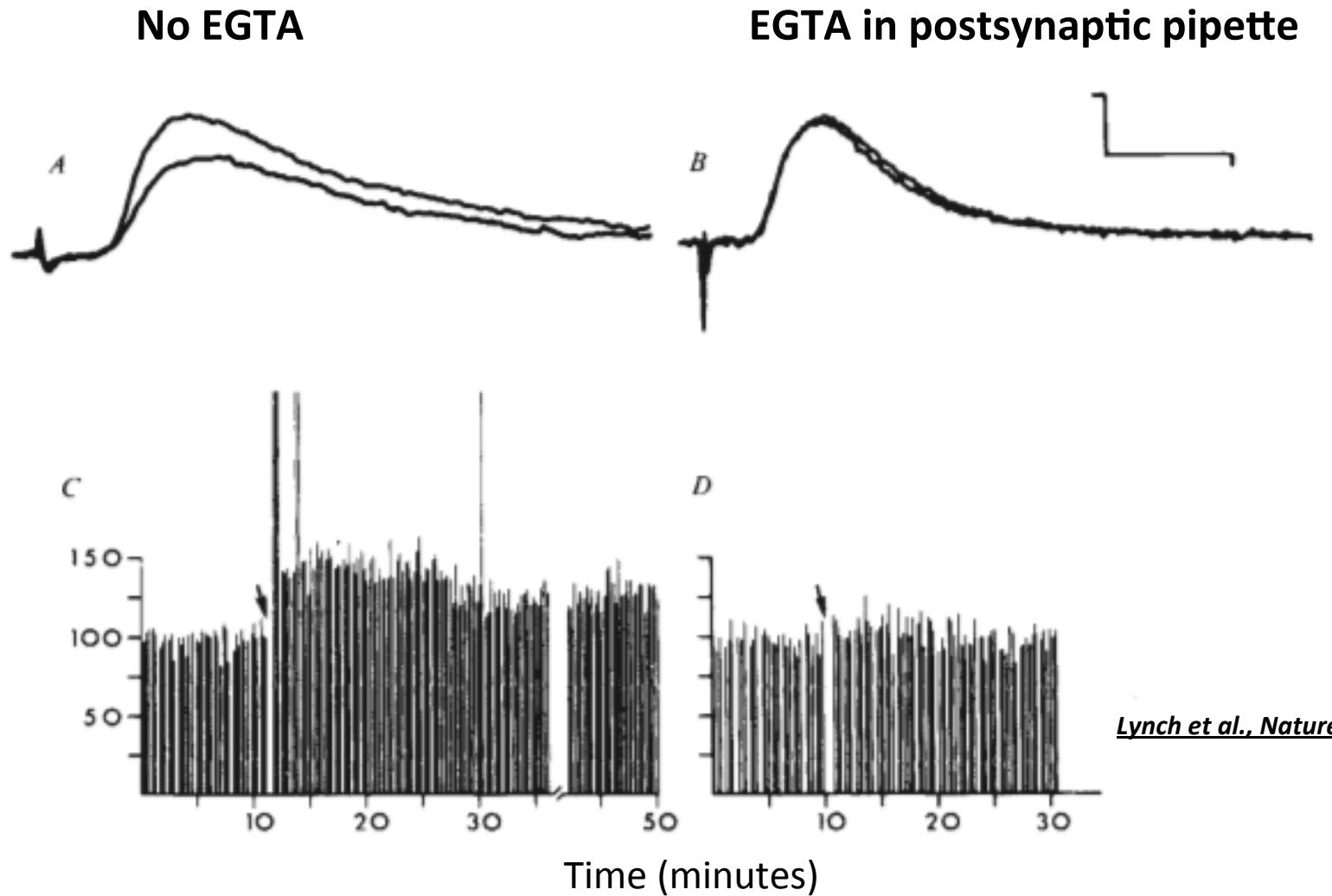


With depolarization, you just increase the probability that A fires B!

Donald Hebb

Requirement 1: Detecting coincidence of pre- and post-synaptic activity

Calcium: The all important ion!!

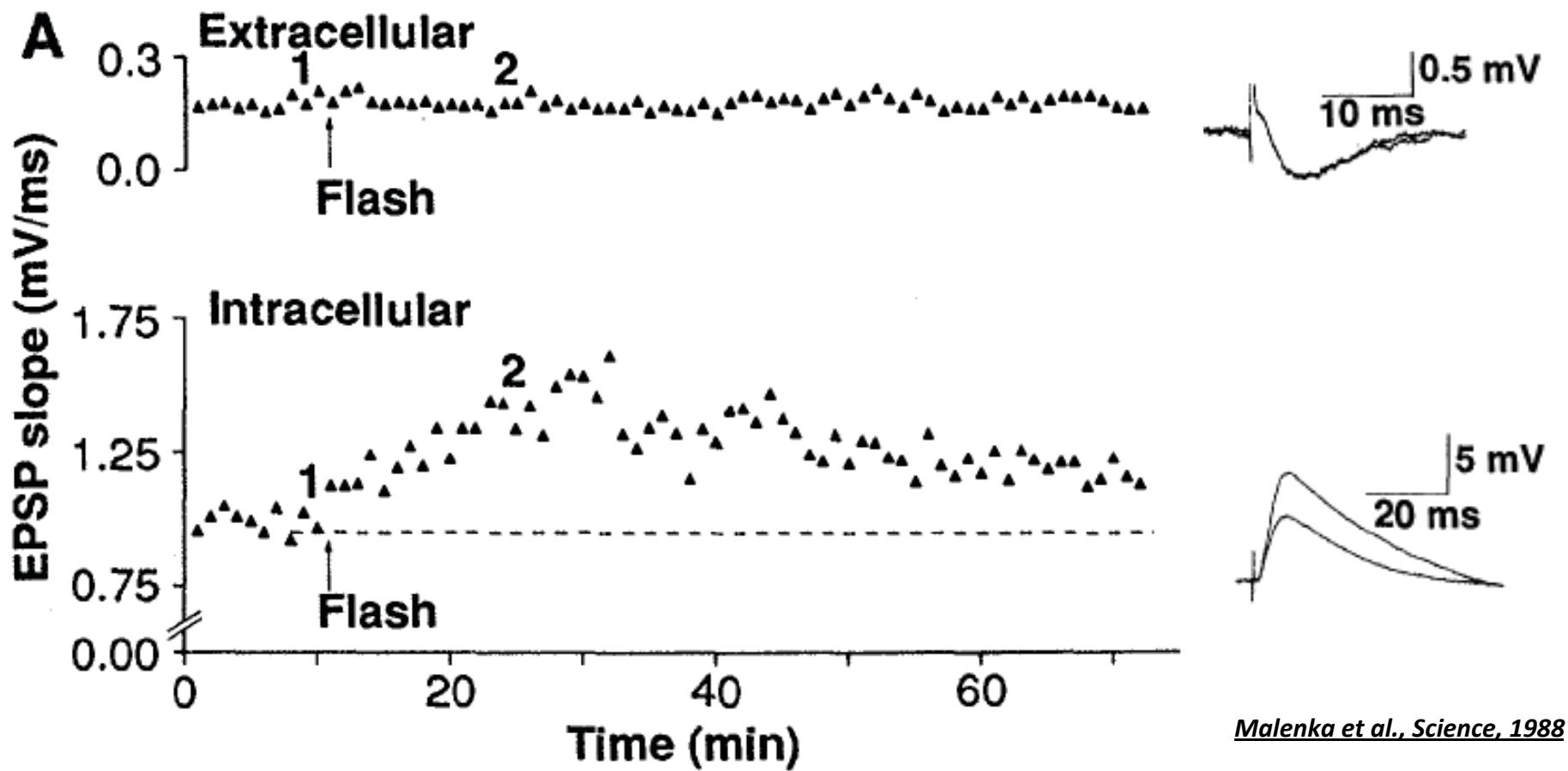


Lynch et al., Nature, 1983

Postsynaptic calcium elevation is necessary for LTP induction!

Postsynaptic calcium elevation is sufficient to induce LTP

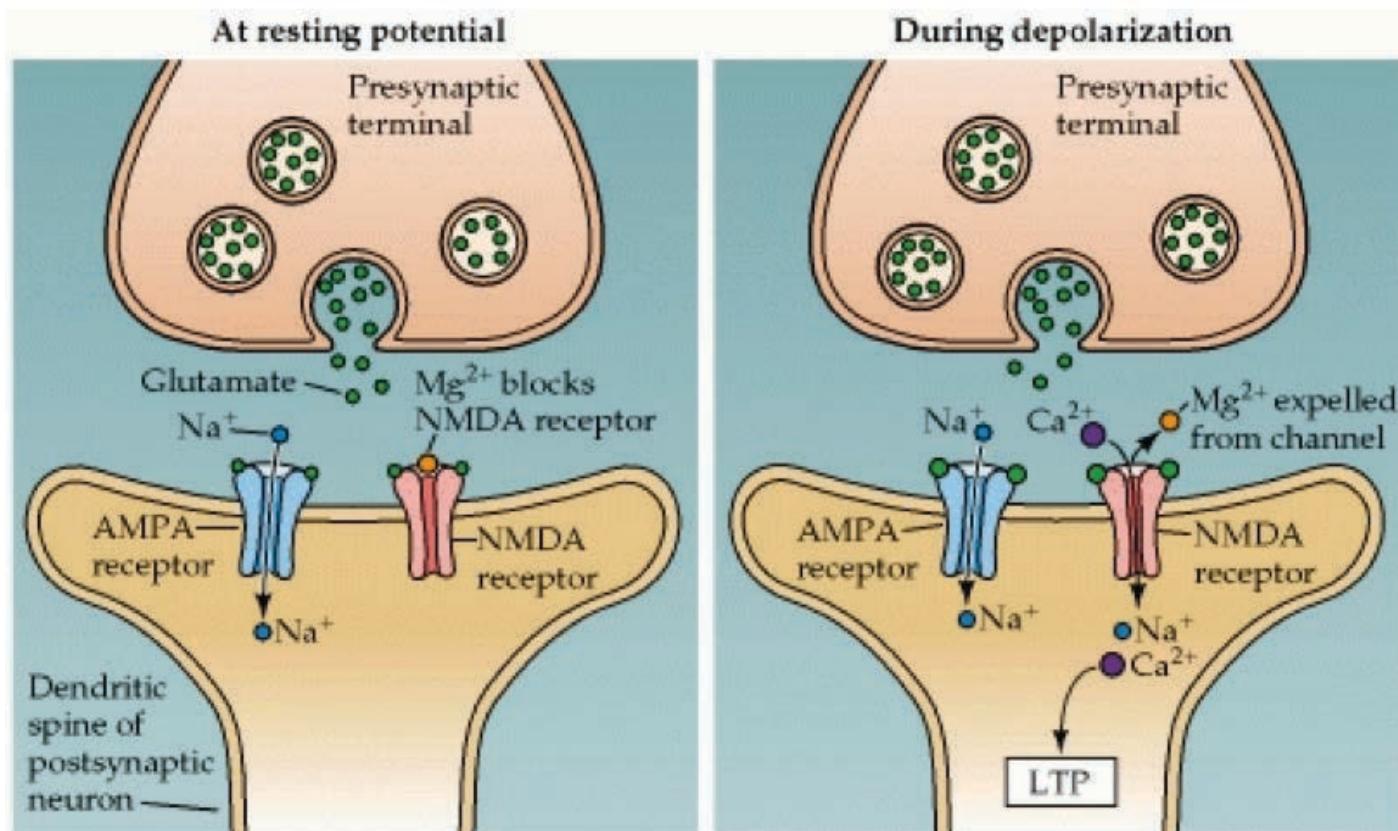
Nitr5 is present postsynaptically, and releases free calcium on UV Photolysis



Requirement 2: Elevation in postsynaptic calcium

Wish list!

A coincidence detector of pre- and post-synaptic activity that would let calcium in when it detects coincidence!

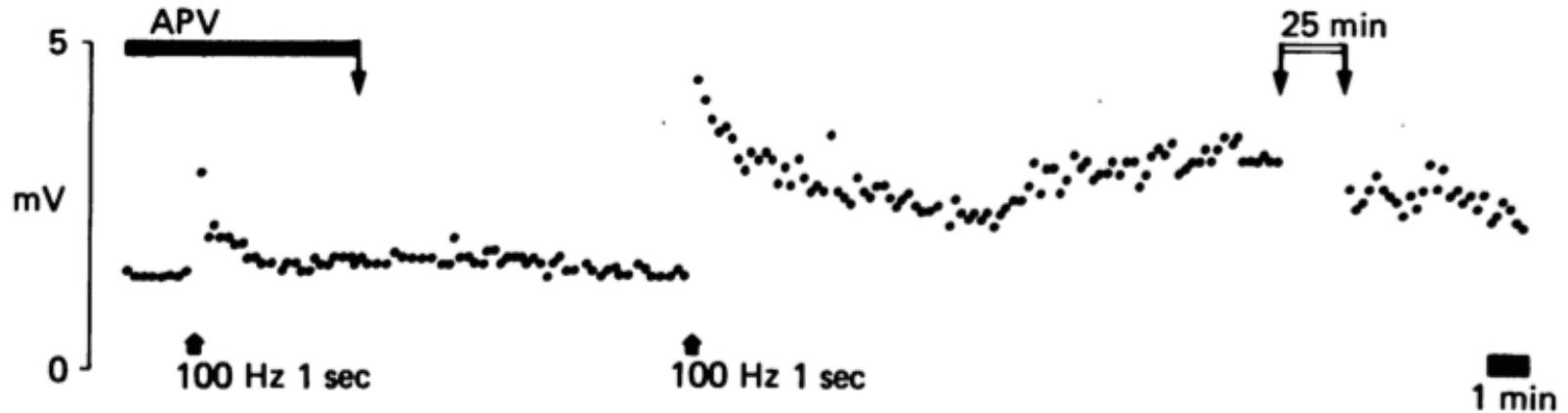


Purves, Neuroscience Book

"NMDAR is Hebb Molecule"

How do you test the link between NMDAR and LTP?

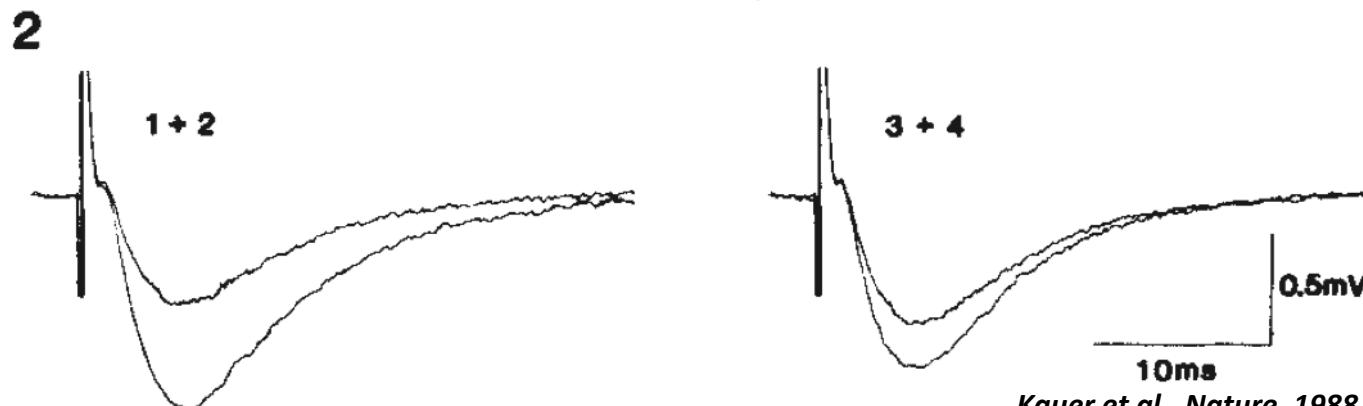
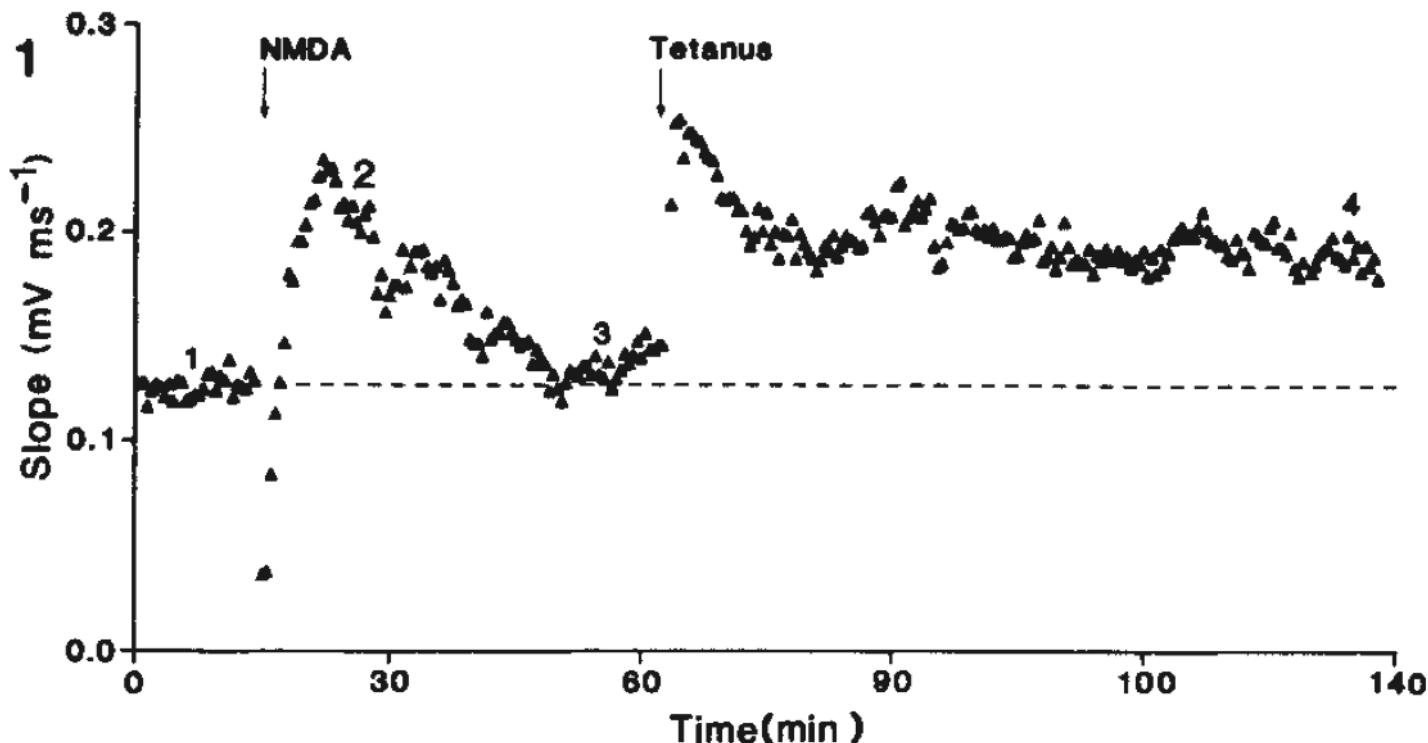
Necessity: Pharmacological agents



Collingridge et al., J. Physiology, 1983

How do you test the link between NMDAR and LTP?

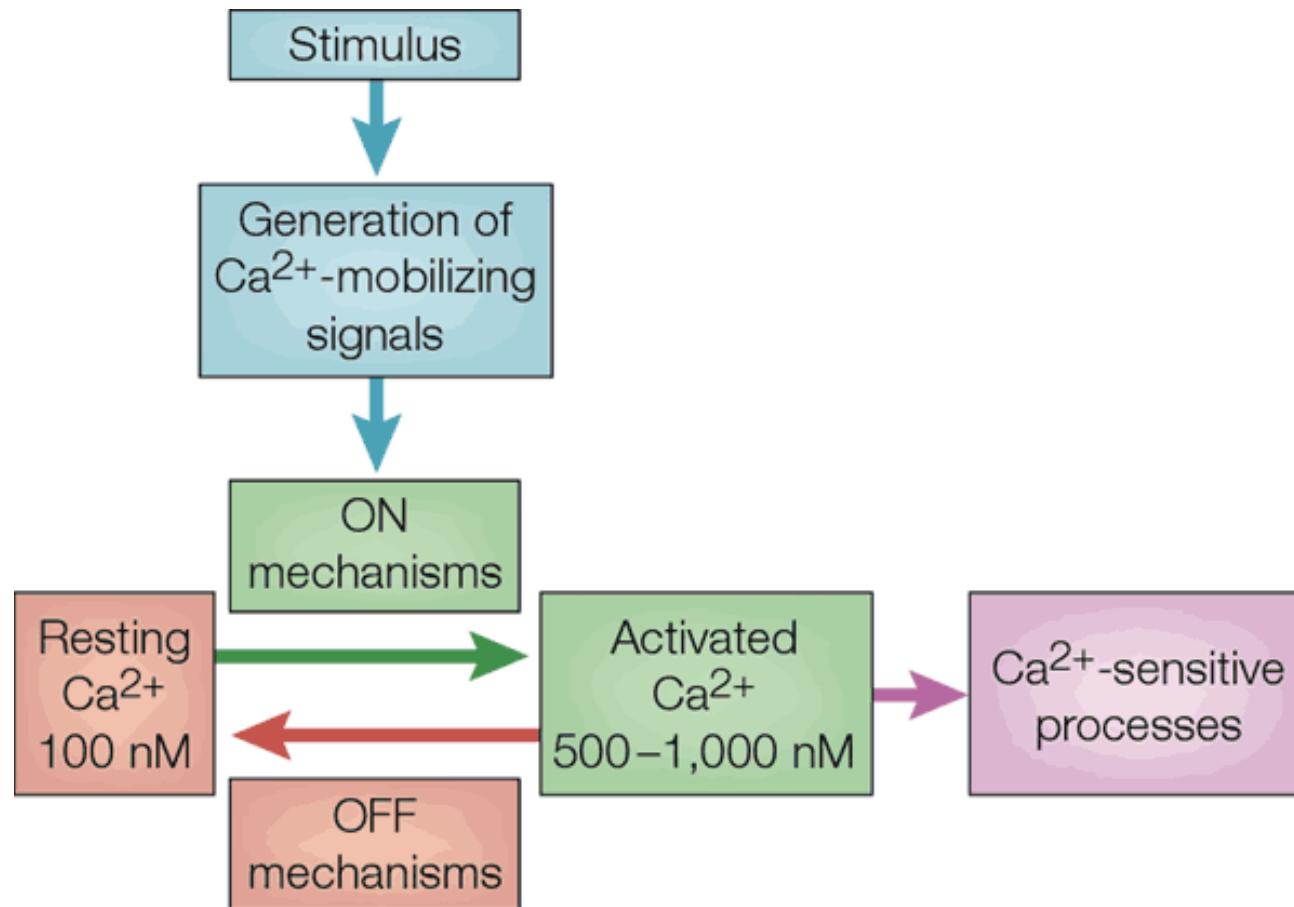
Sufficiency?



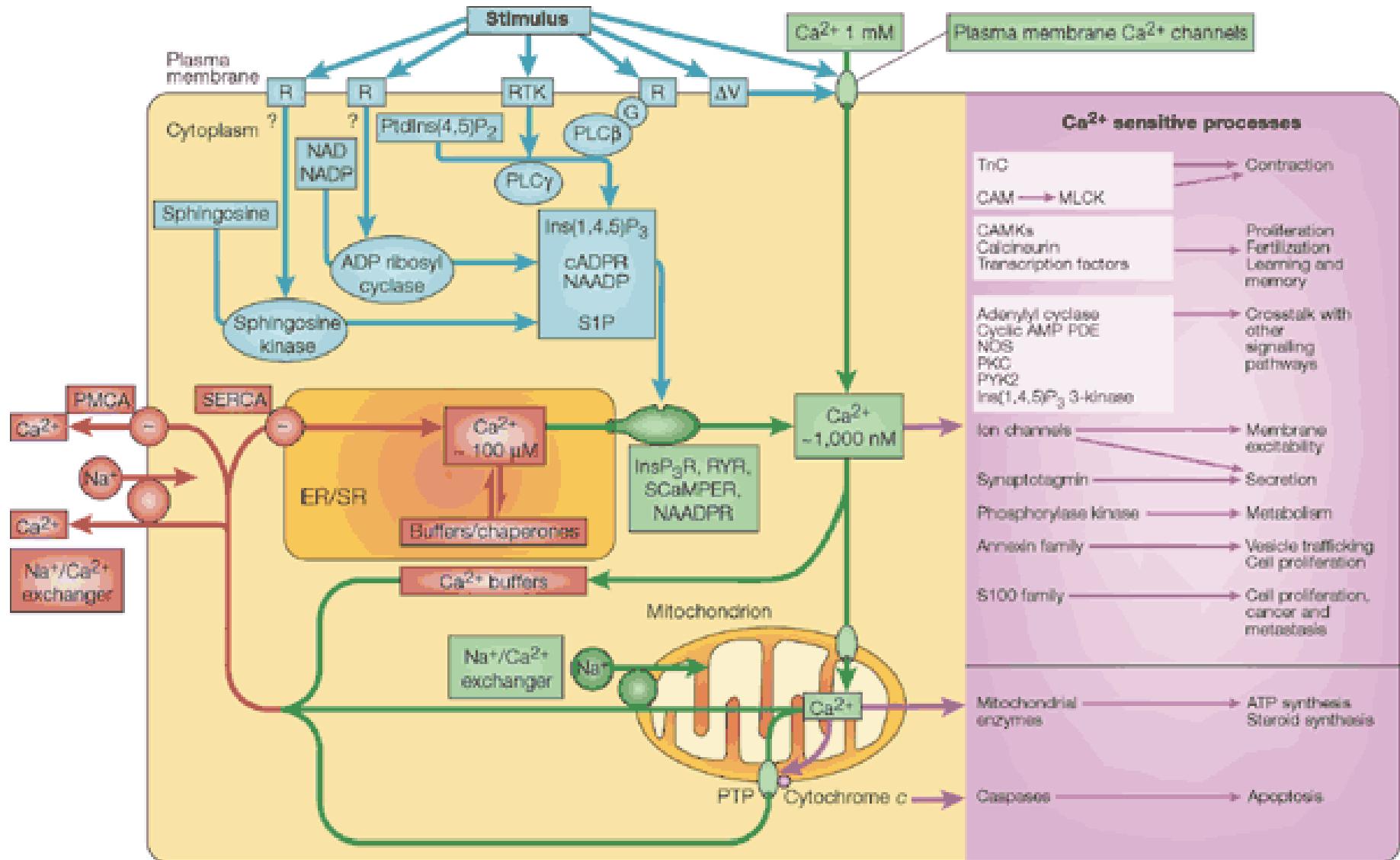
Kauer et al., Nature, 1988

Are NMDA receptors the only possible calcium source for induction of LTP?

Calcium is a very tightly regulated intracellular messenger

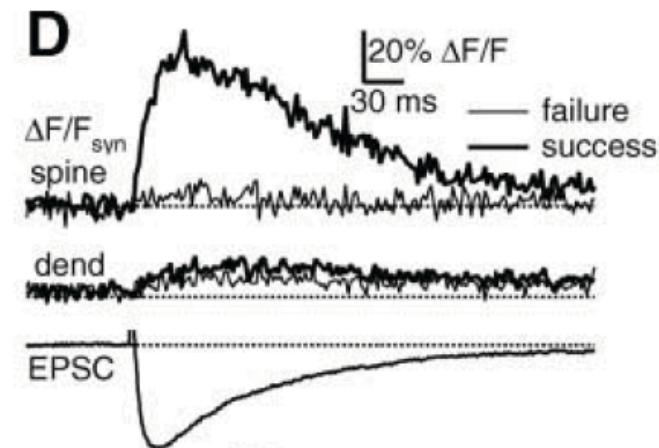


The multiple ON and OFF mechanisms



Synaptically evoked calcium signals are localized

Spine Ca^{2+} signal



Sabattini et al., Neuron, 2002

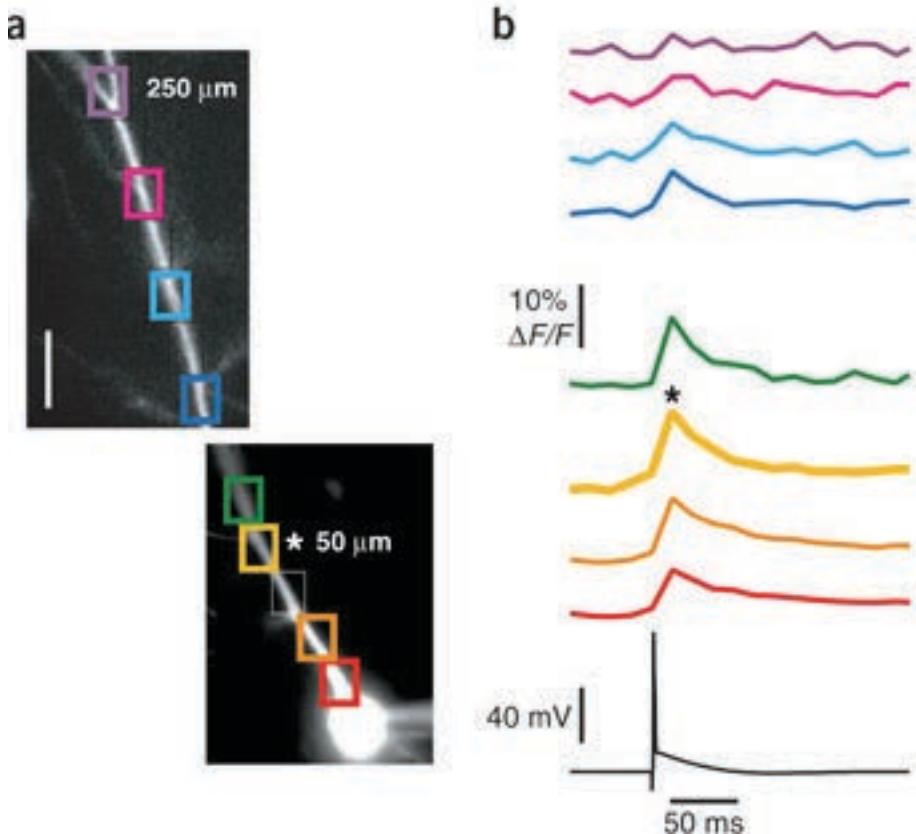
Ca^{2+} (un)certainty principles.

Introducing a Ca^{2+} indicator distorts the amplitude, time course and spread of $[\text{Ca}^{2+}]$ signals because they compete to bind calcium and their diffusion is different

For more info, see (Sabatini et al., Current Opinion Neurobiology, 2001),
(Yasuda et al., Science STKE, 2004) and (Higley and Sabatini, CSHL Persp. Biol., 2012)

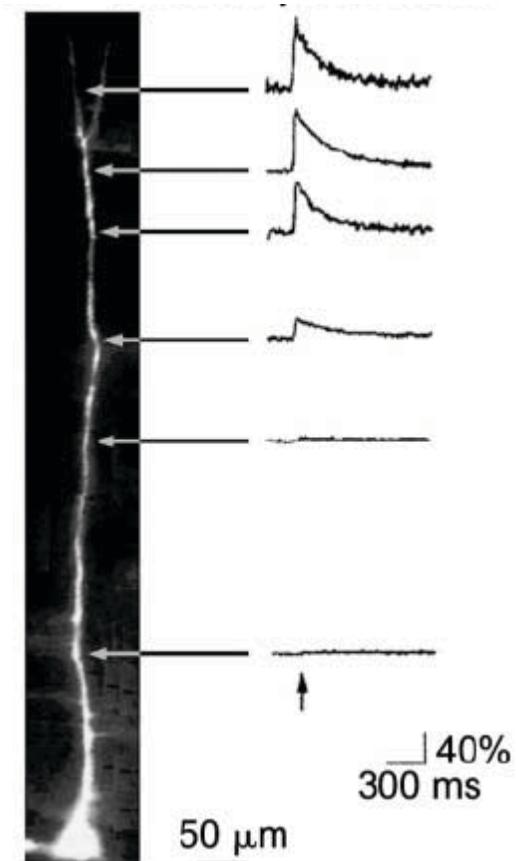
Spike-evoked calcium transients spread: VGCCs

Backpropagating action potential



Frick et al., Nat. Neurosci., 2004

Dendritic spikes

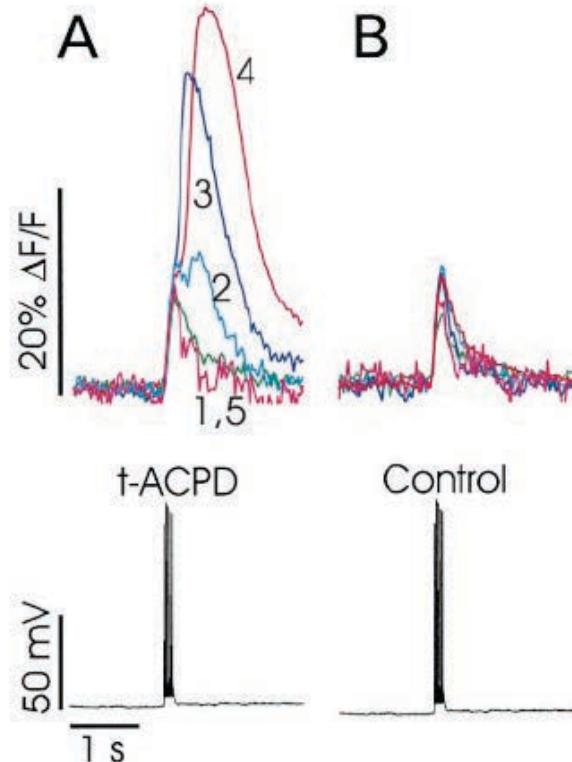
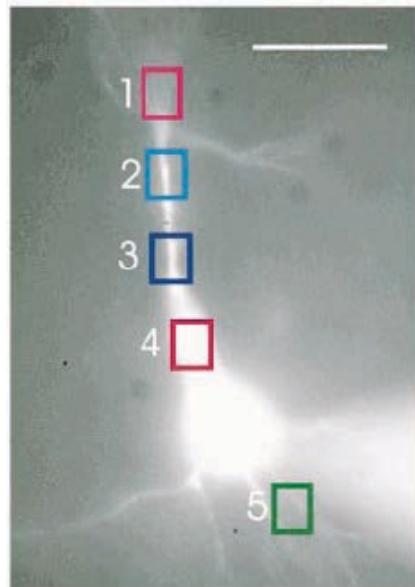


Schiller et al., J Phys., 1997

Calcium influx is largely due to voltage gated calcium channels (VGCC) on the dendritic membrane opened with depolarization induced by action potentials (see Miyakawa et al., Neuron, 1992)

Intracellular waves can be initiated with calcium release from the endoplasmic reticulum

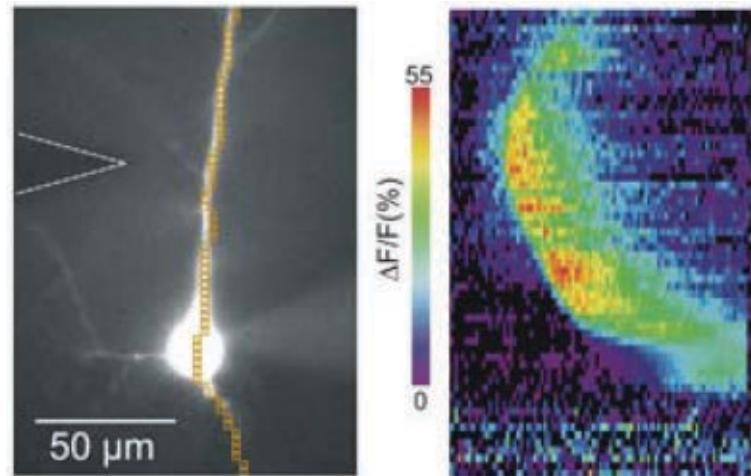
bAP in the presence of mGluR agonists



Nakamura et al., Neuron, 1999

Synaptic stimulation

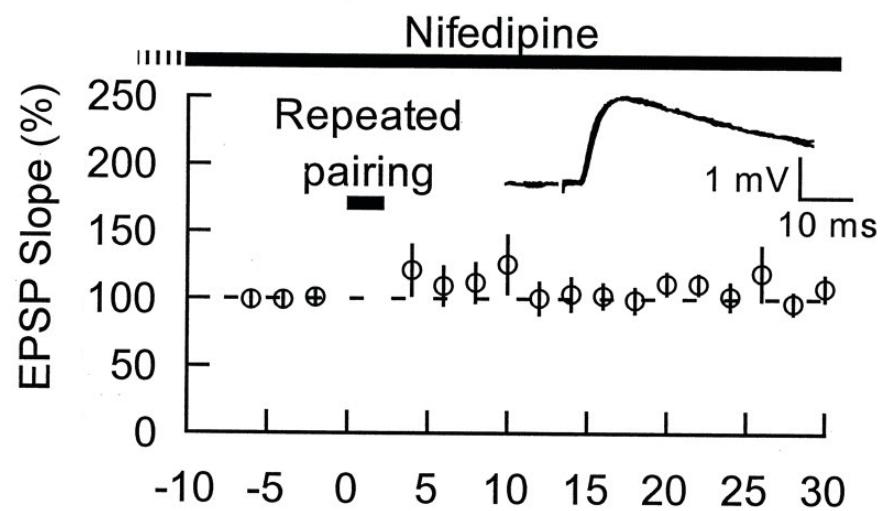
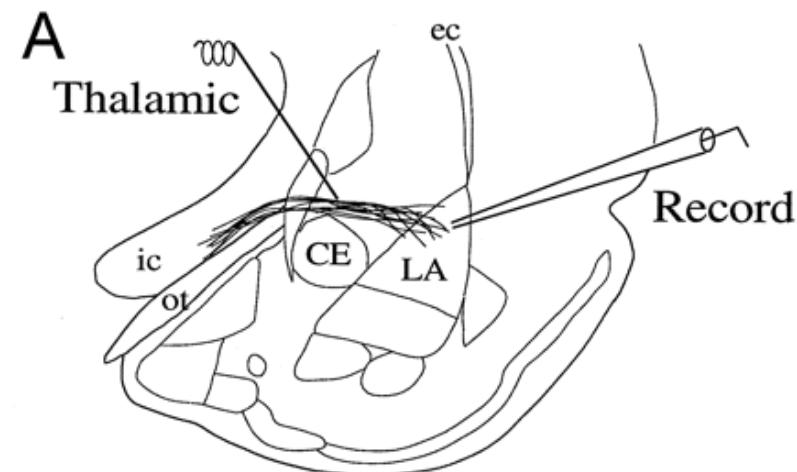
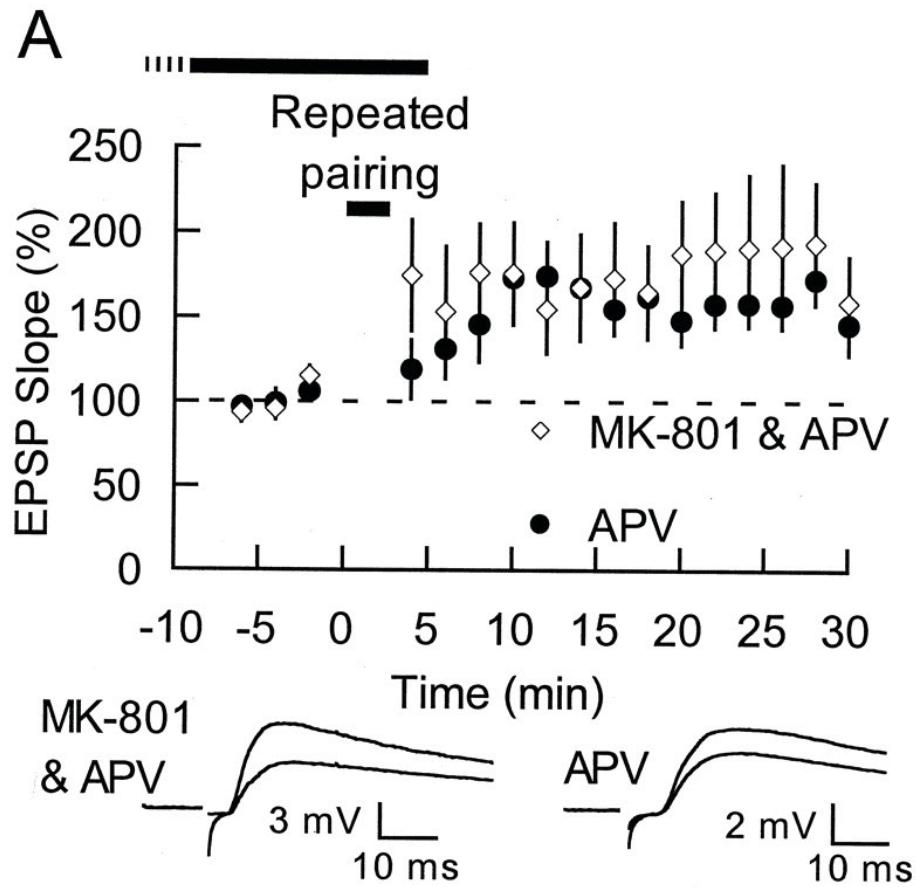
Stimuli at 100 Hz for 0.5 s



Watanabe et al., J. Phys. 2006

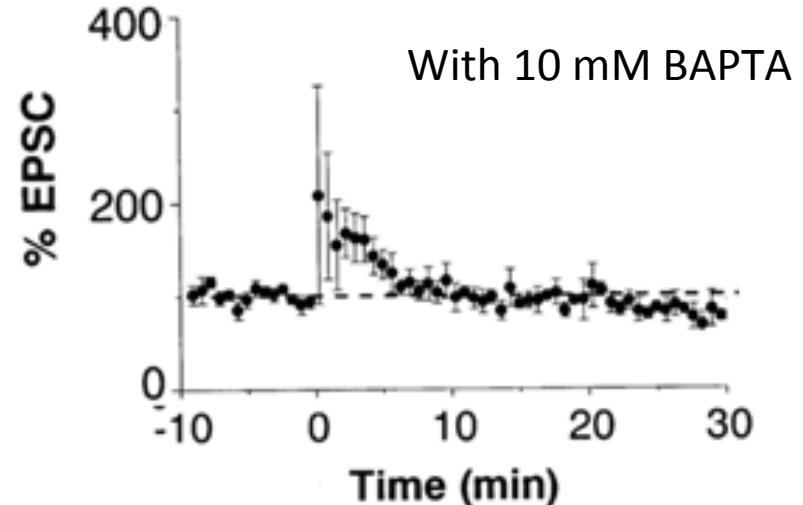
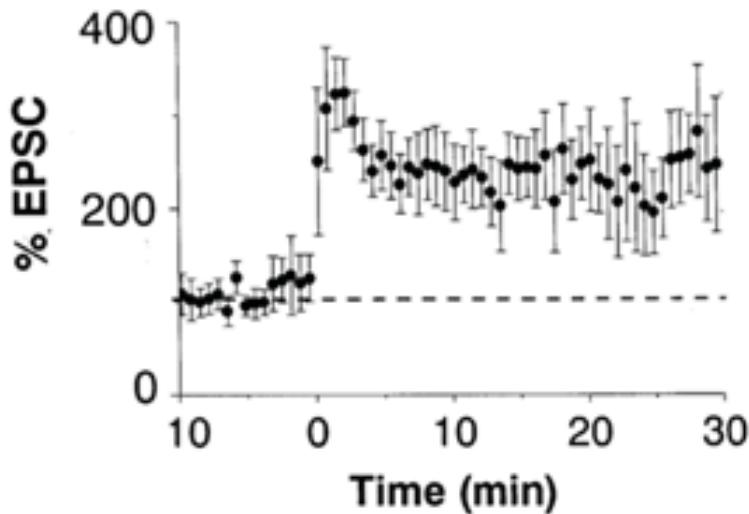
Release of calcium from stores are typically mediated by InsP_3 and Ryanodine receptors located on the endoplasmic reticulum

Example for VGCC-dependent LTP



Example for CPAMPAR-dependent LTP

EPSC plasticity in Amydalar interneurons

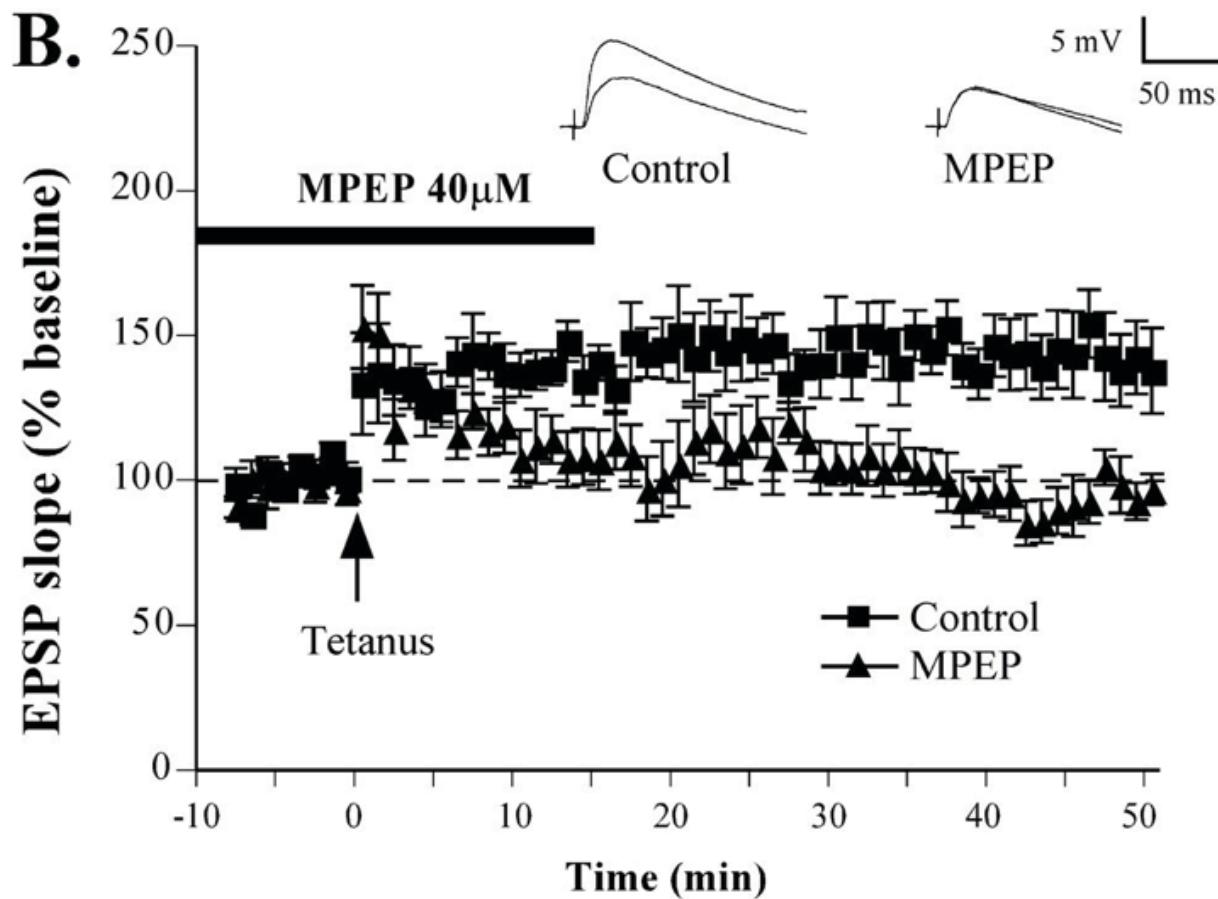


Done by voltage clamping @ -70 mV, so no VGCC's are activated!

These synapses do not have NMDA receptors

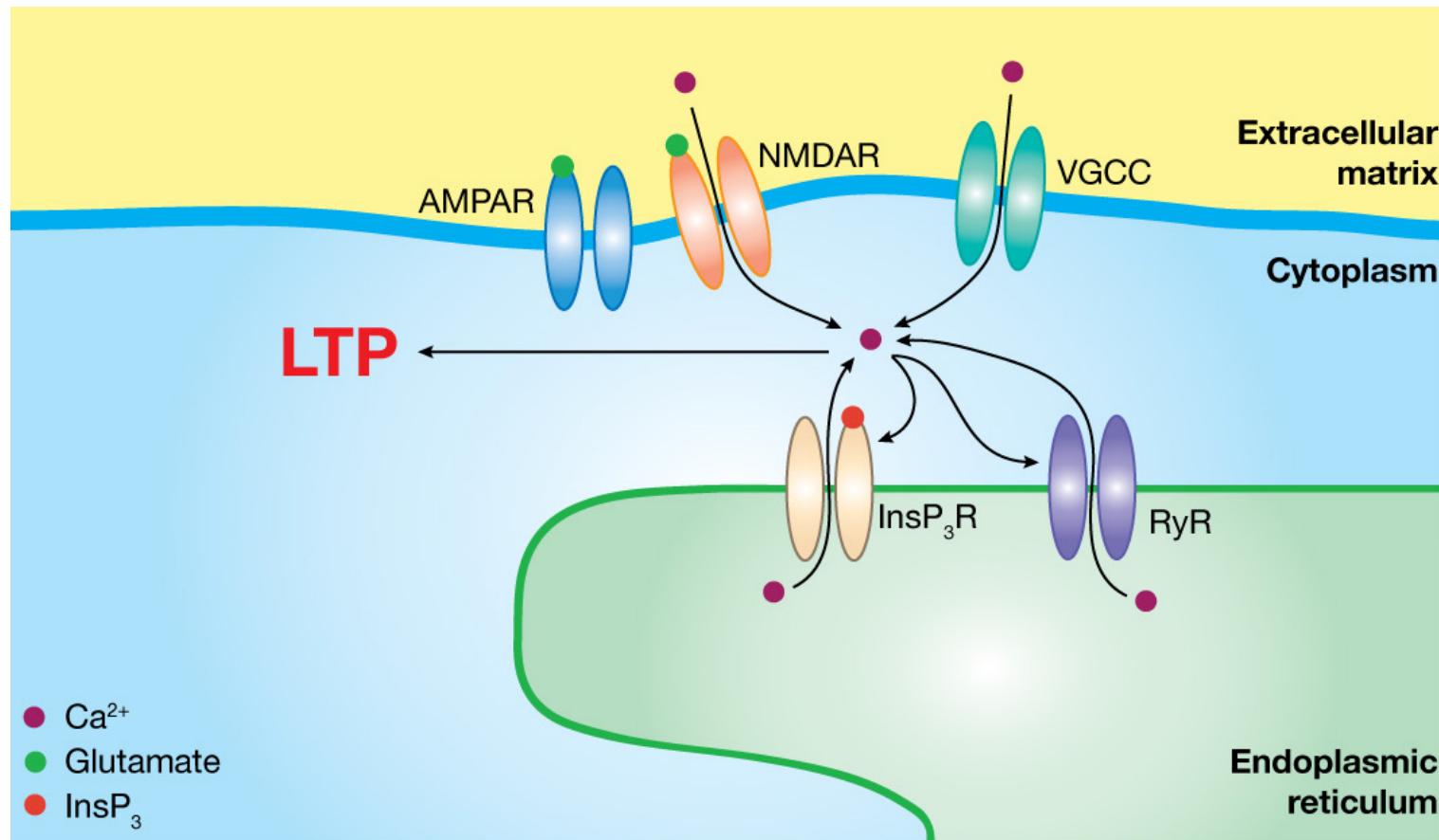
Example for mGluR-dependent LTP

Group I mGluR's could lead to release of calcium from ER through InsP₃Rs



NMDARs are not the only calcium source for inducing LTP

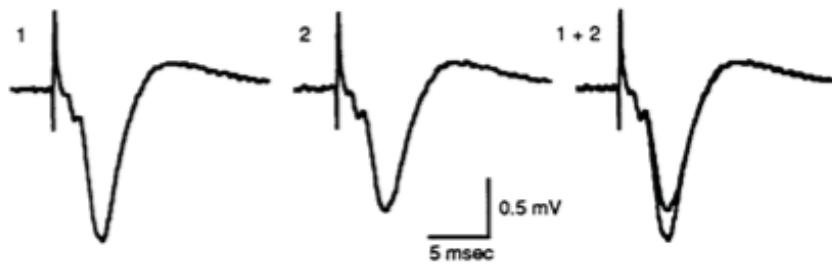
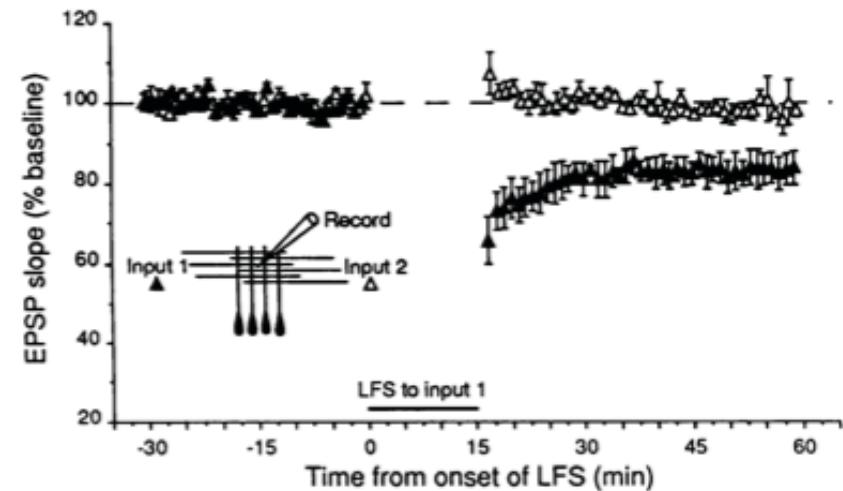
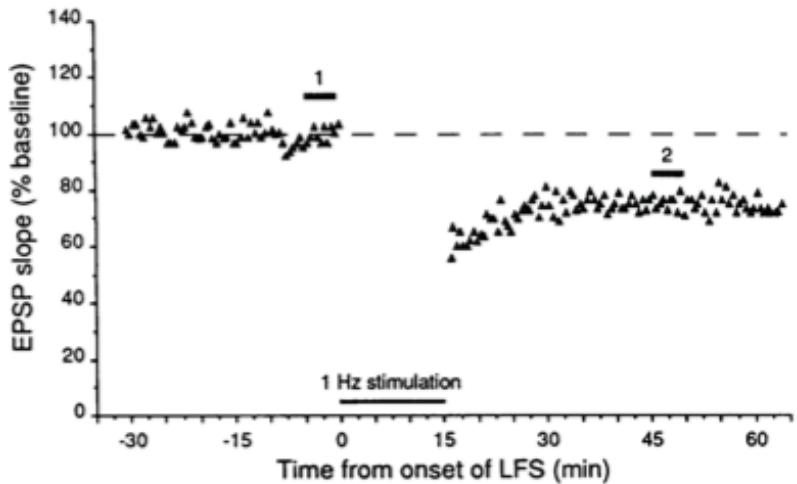
Calcium enters through one or more sources, and leads to the induction of LTP



Bidirectionality

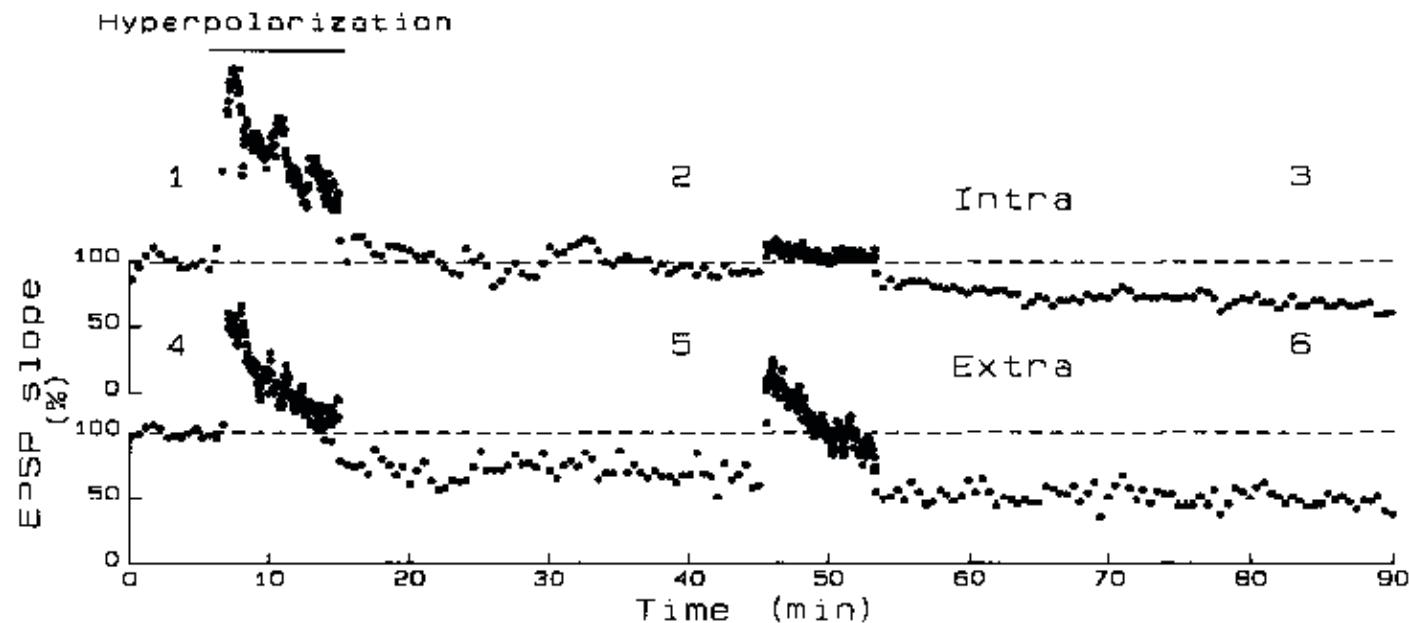
Question: Shouldn't plasticity be bidirectional for stability??

Long-term depression



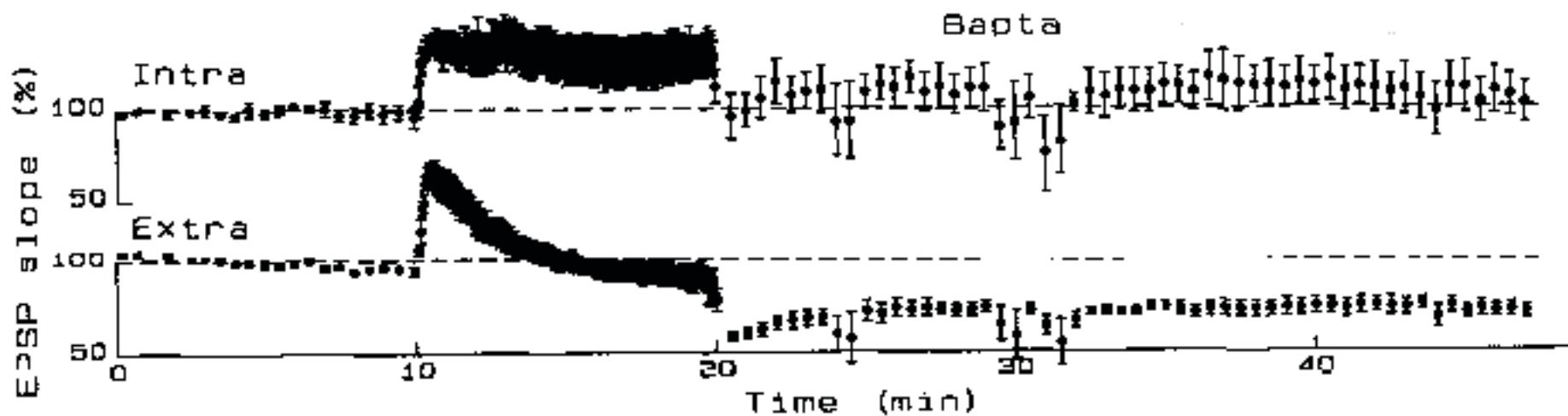
Long-term depression also exhibits input specificity

LTD is depolarization-dependent, too!!!



Mulkey and Malenka, Neuron, 1992

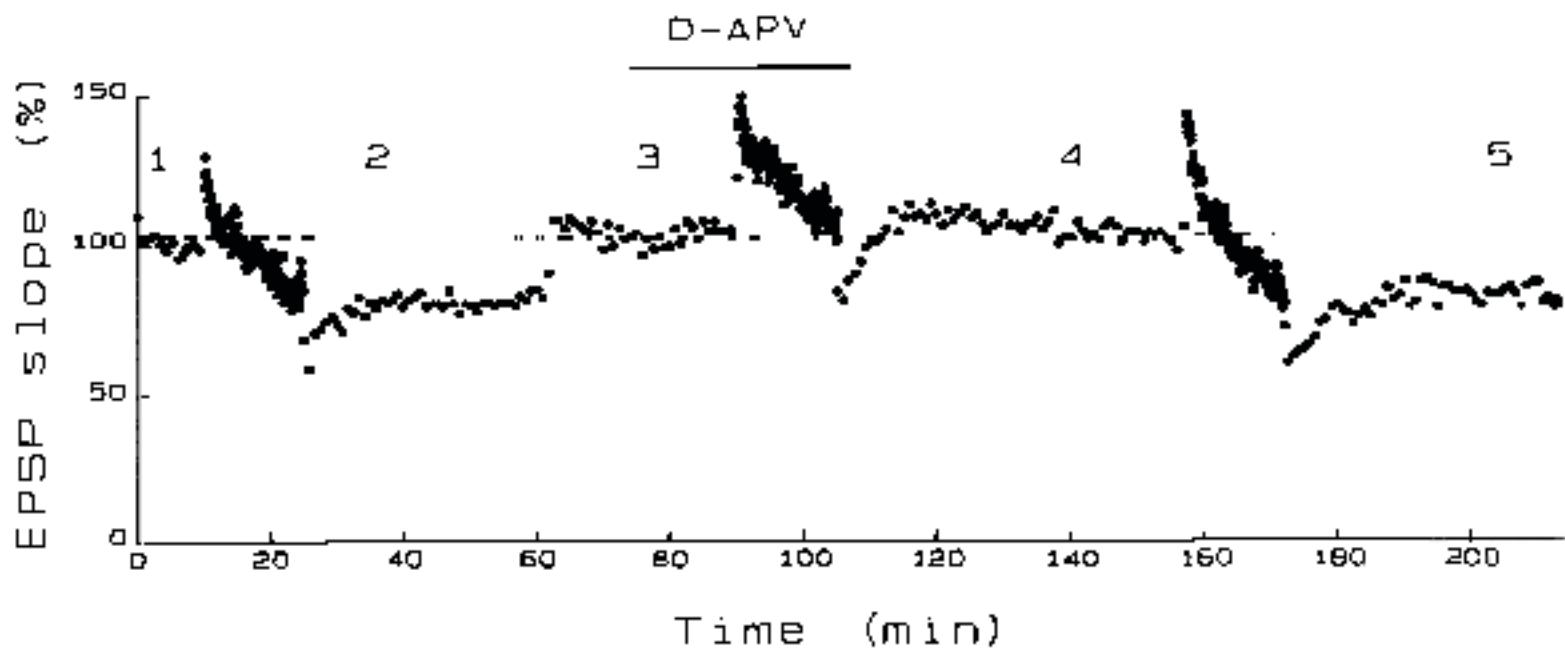
Surprise! Surprise!! LTD is $[Ca^{2+}]_i$ dependent, too!!!



Mulkey and Malenka, Neuron, 1992

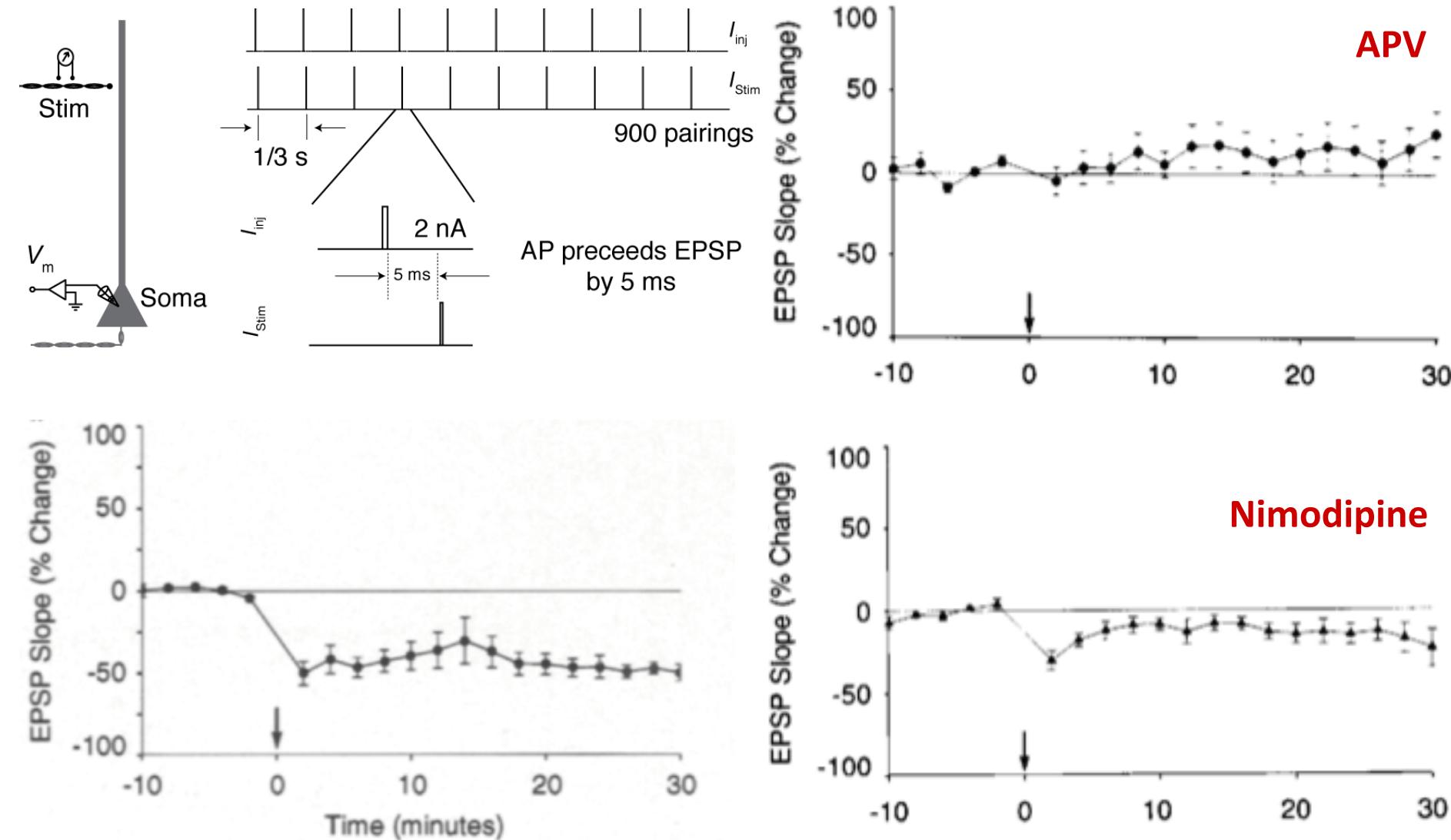
Calcium can come from NMDARs

Or from several other sources, depending on the form of LTD

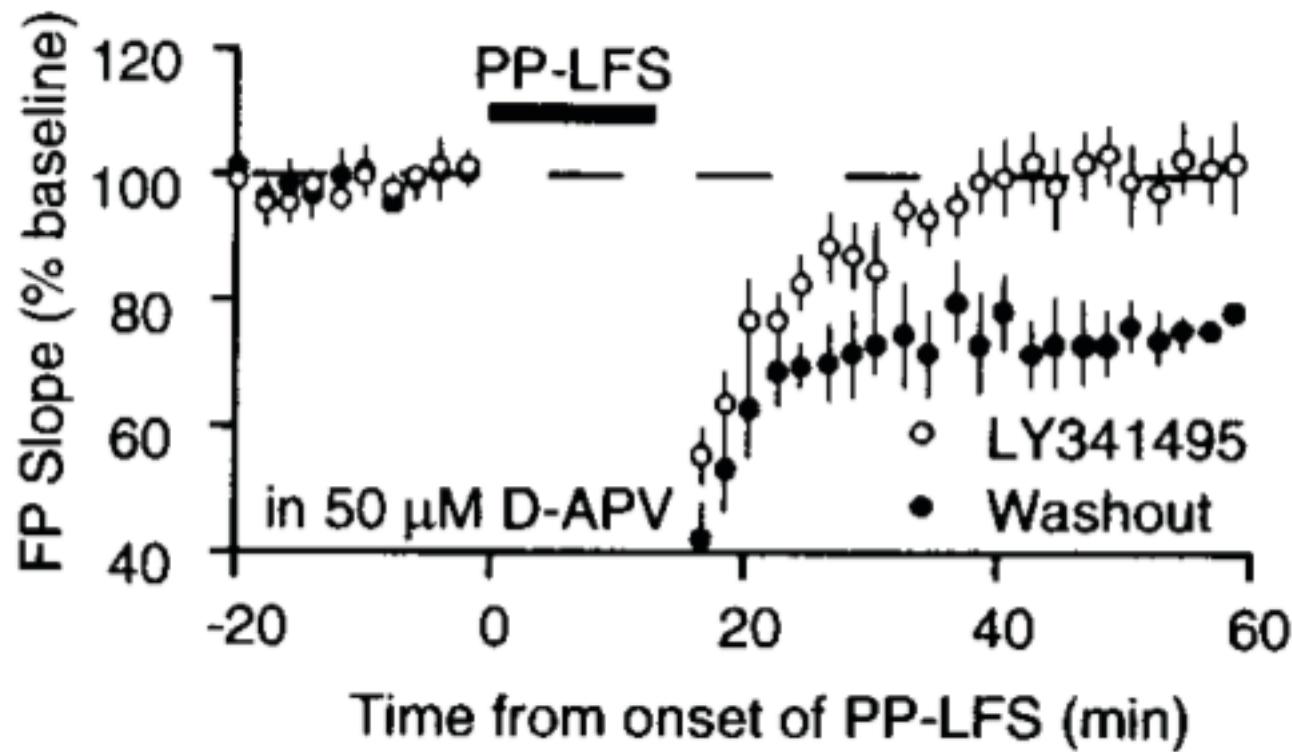


Mulkey and Malenka, Neuron, 1992

Or, from both NMDARs and VGCCs



Or, metabotropic glutamate receptor-dependent influx of calcium through InsP₃Rs

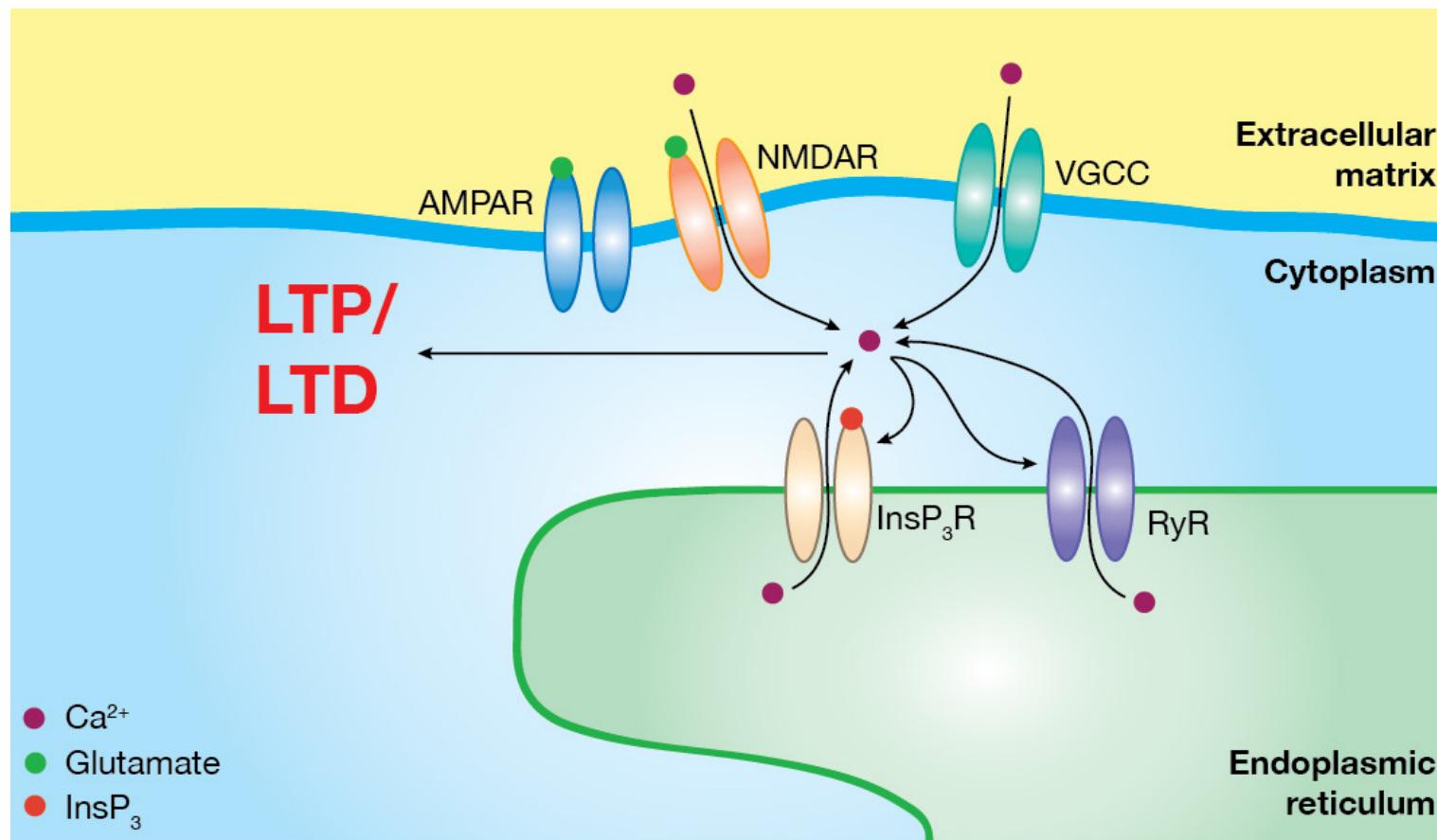


LY341495: mGluR antagonist

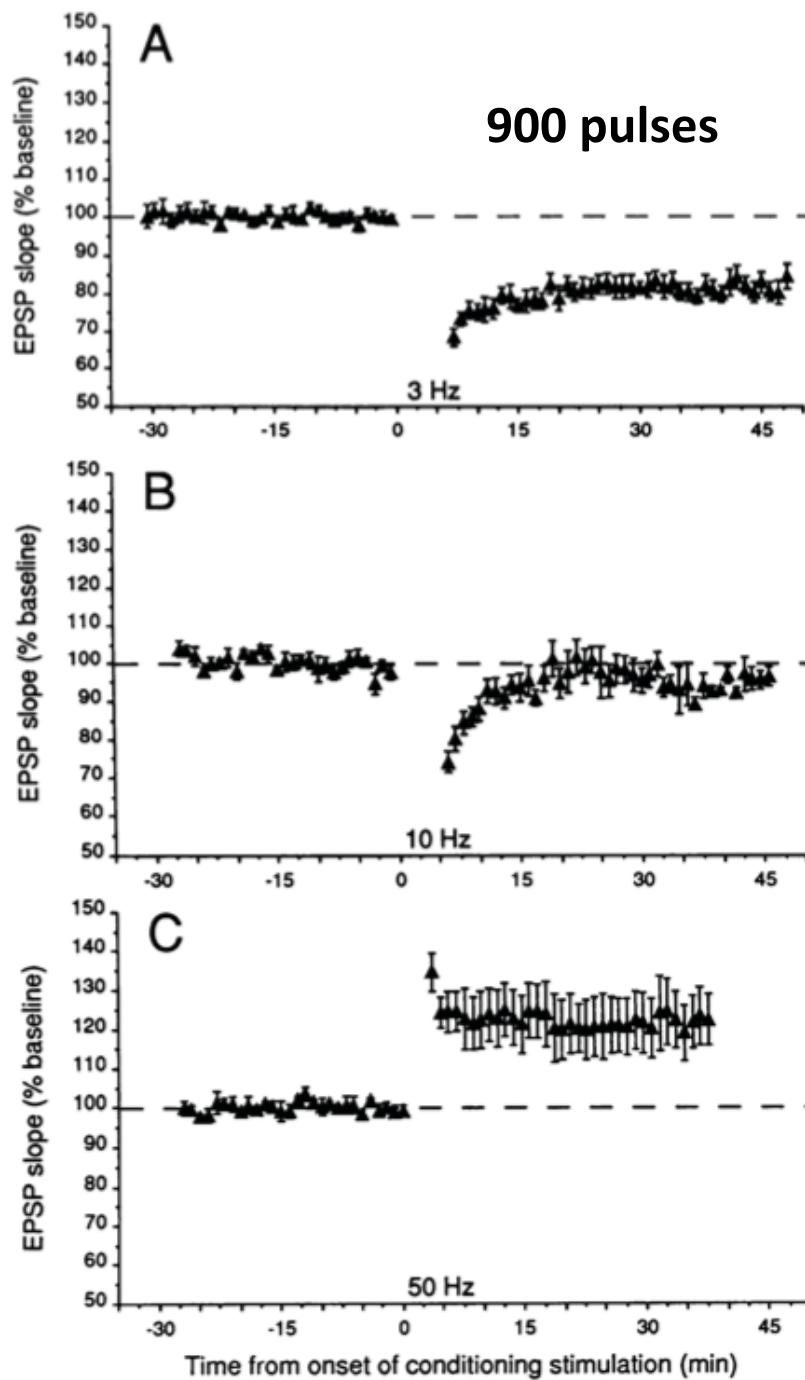
Washout: After washing out LY

LTP is dependent on depolarization, elevation of postsynaptic calcium through NMDAR's/VGCC's/ER receptors!!

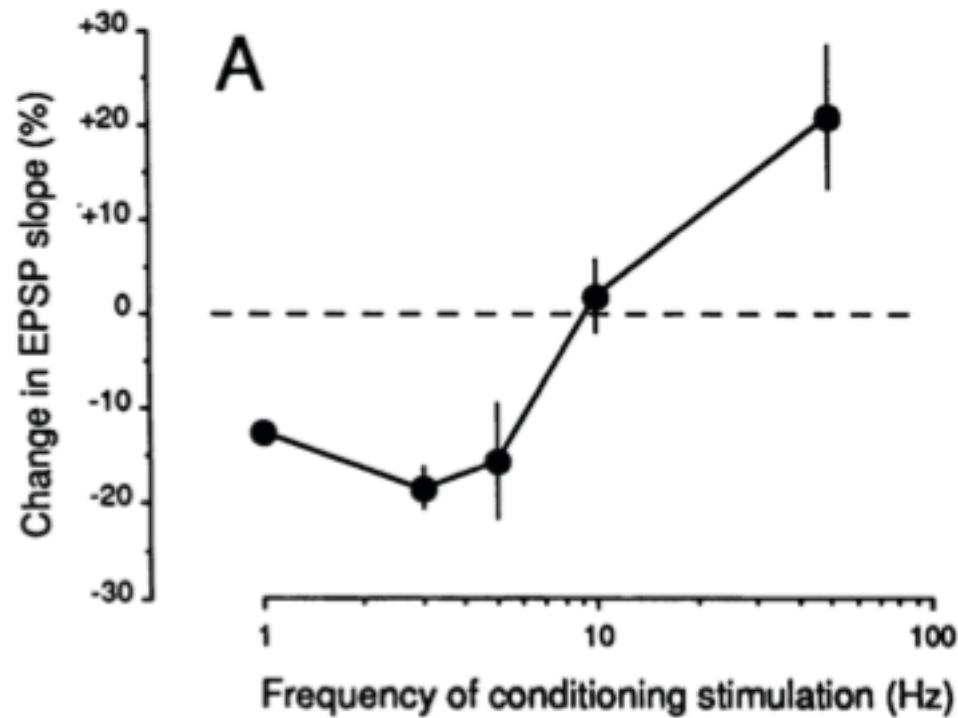
So is LTD!!!

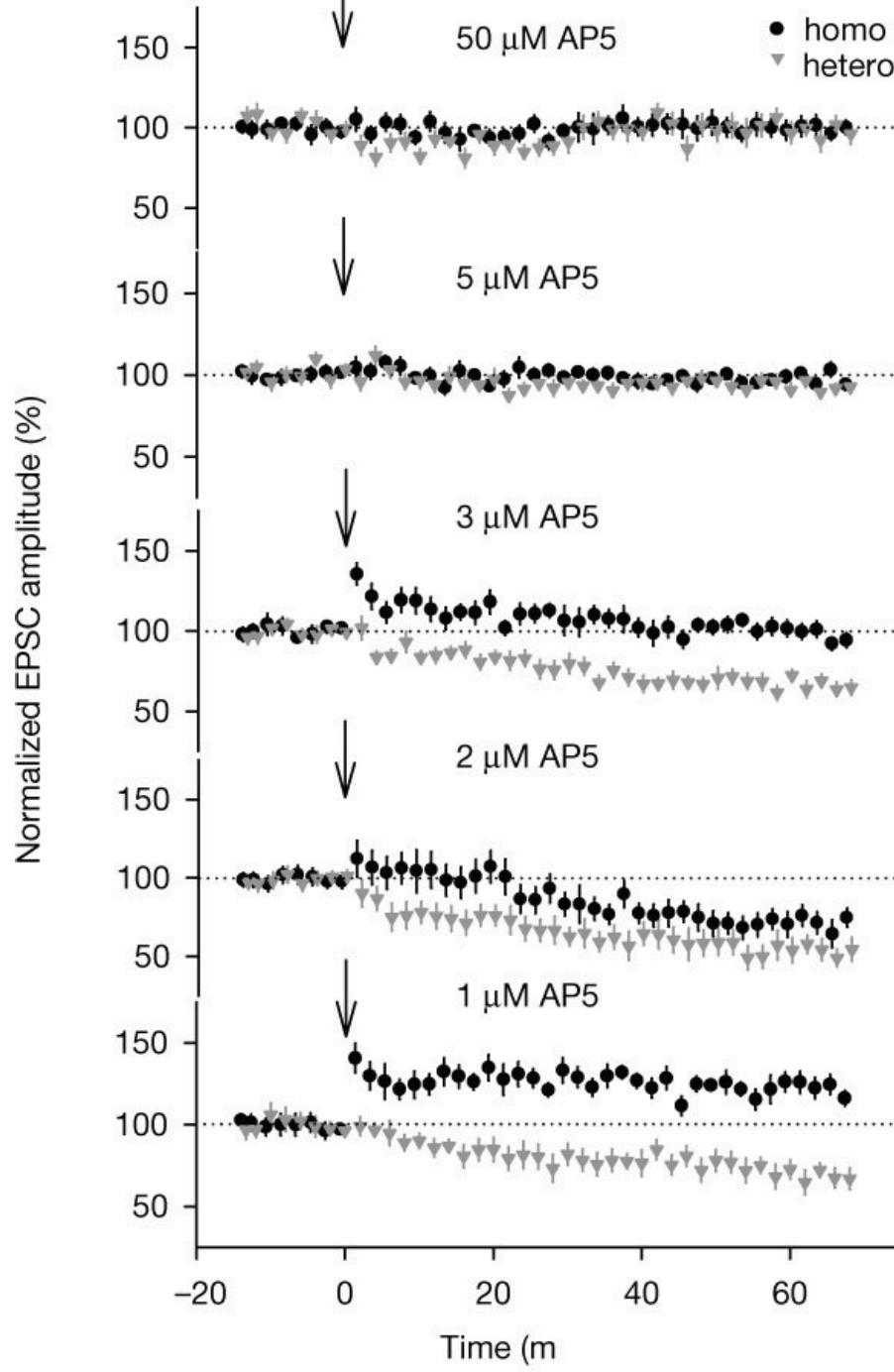


So, what property of the induction stimulus determines whether it is LTP/LTD?

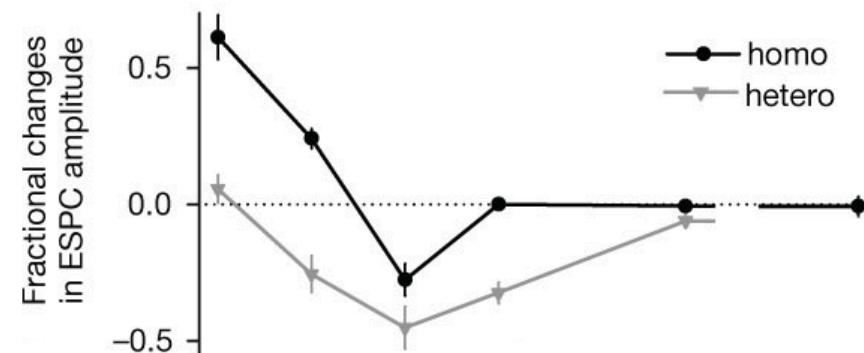


Frequency of stimulus?

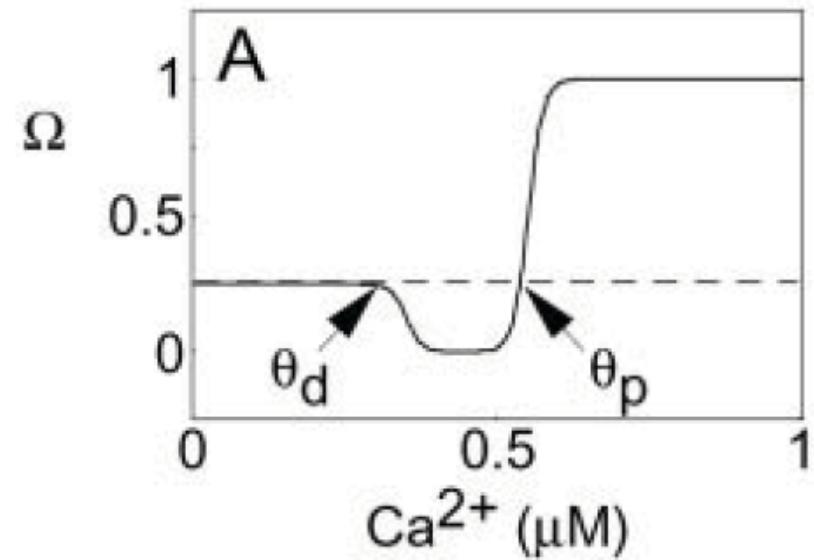
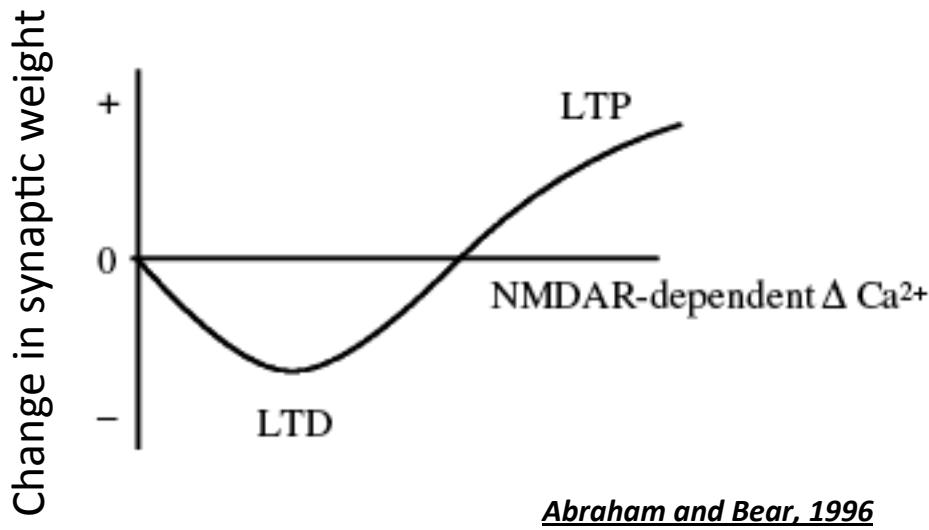


a

Amount of calcium?



Amount of calcium entering?



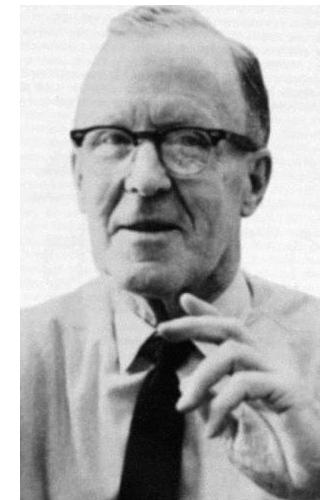
General consensus?: Low-levels of longer lasting calcium leads to LTD, while high-levels of short-lasting calcium leads to LTP

Both amplitude and kinetics of calcium matter, apart from a 1000 other things!

Spike timing dependent plasticity

What did Hebb really say?

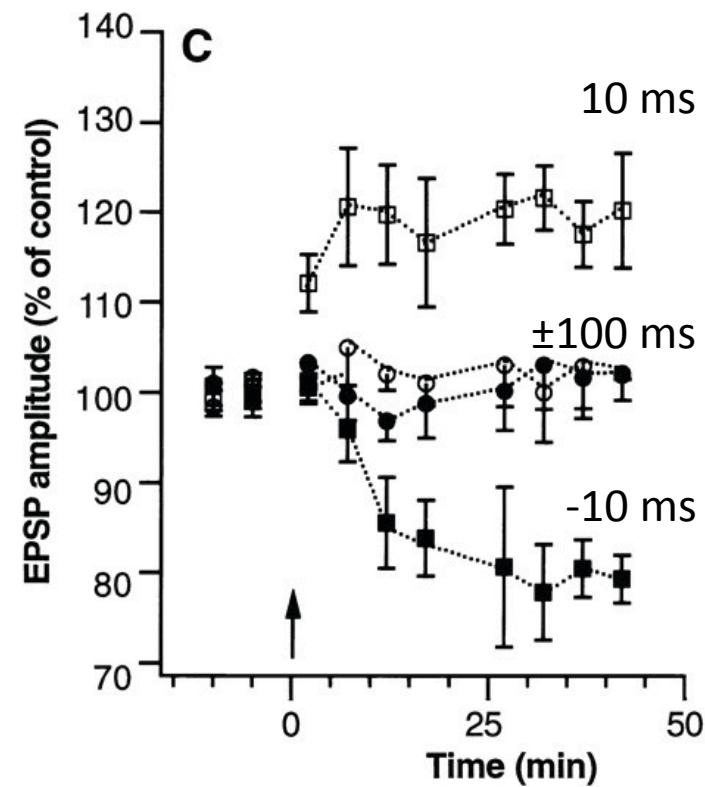
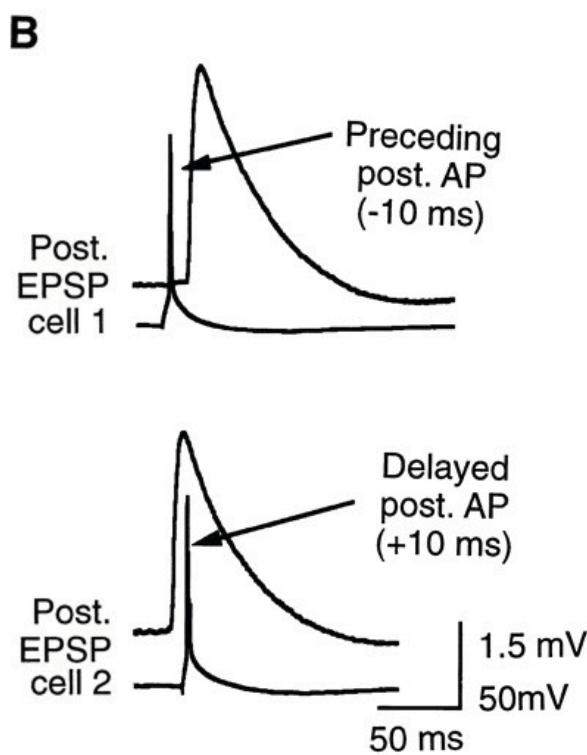
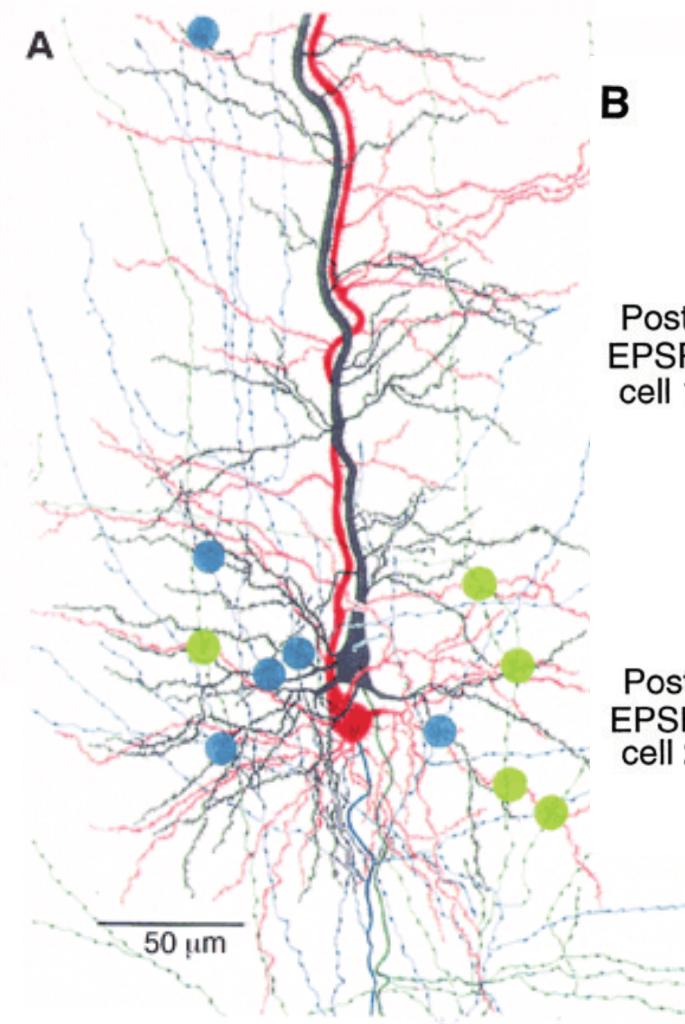
“When an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells, such that A’s efficiency, as one of the cells firing B, increases.”



Donald Hebb

There is a mention about temporal relationship between the action potentials of cell A and cell B

STDP: Spike timing dependent plasticity



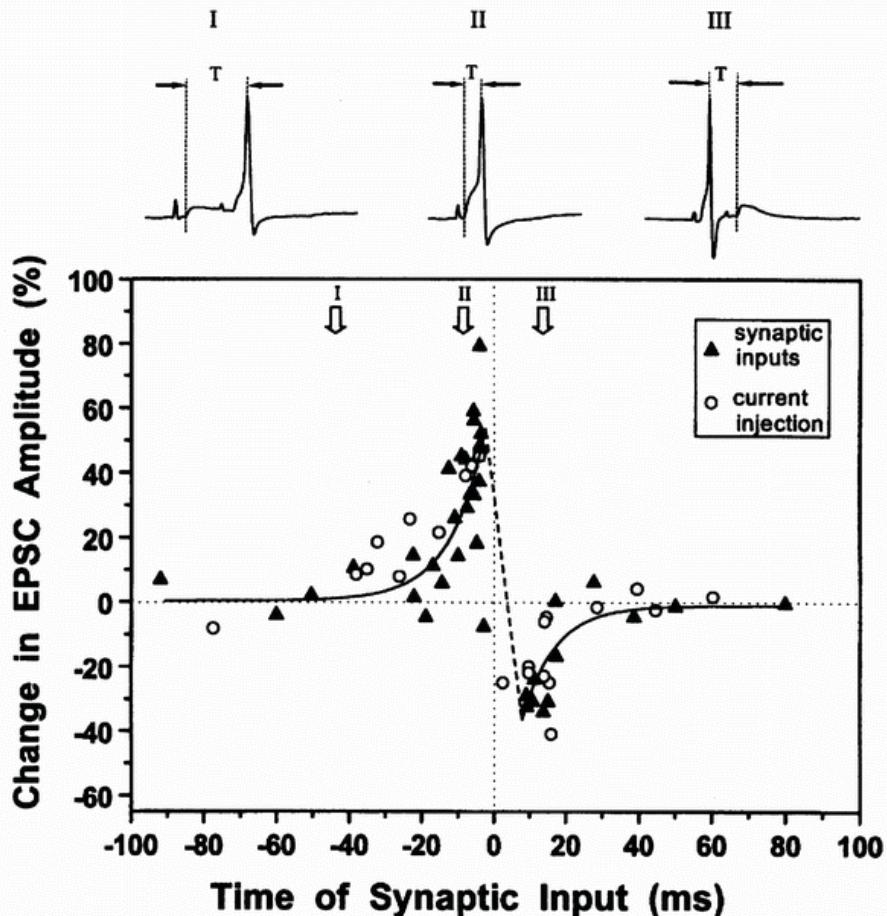
10-Hz train of 5 APs repeated 10 to 15 times every 4 s

Markram et al., Science, 1997

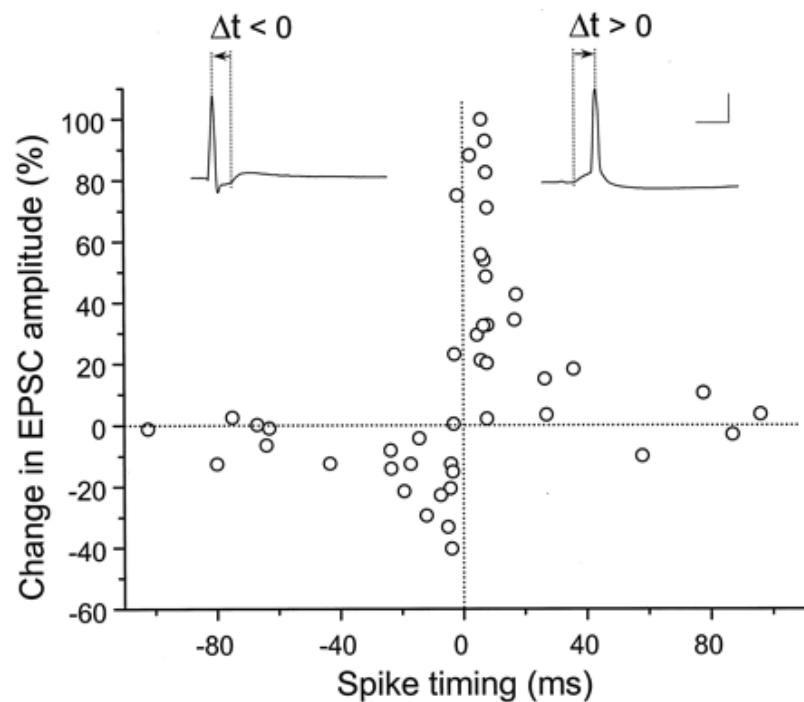
Two bidirectionally connected cells in Layer V neocortex made to fire APs with a 10 ms

STDP

Xenopus tectal neurons



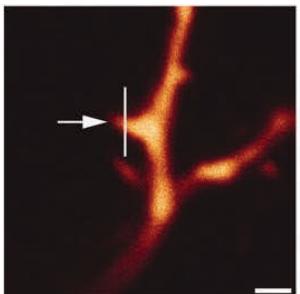
Rat Hippocampal culture neurons



Bi and Poo, JNS, 1998

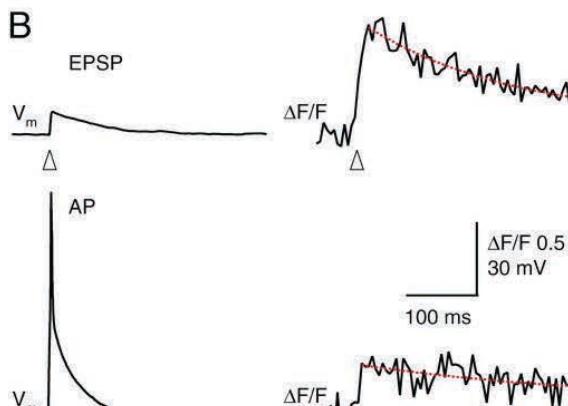
Zhang et al., Nature, 1998

A



Calcium detection of positive and negative timing

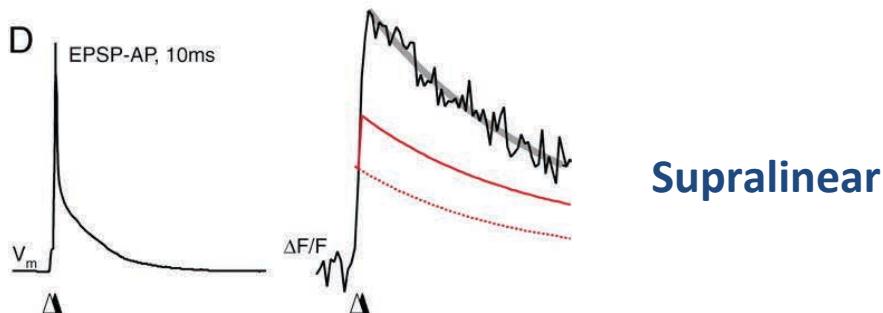
B



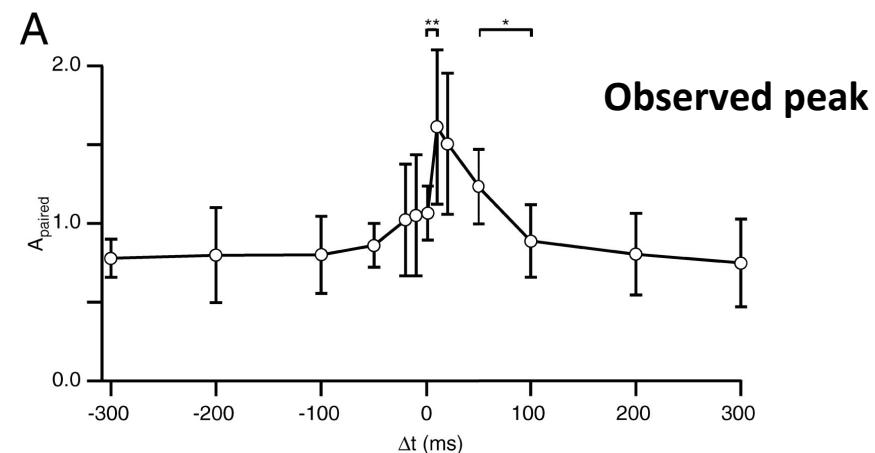
C



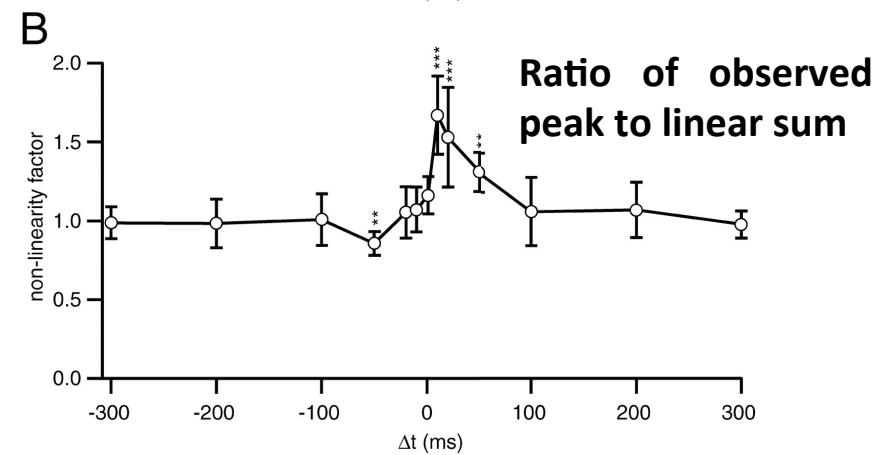
D

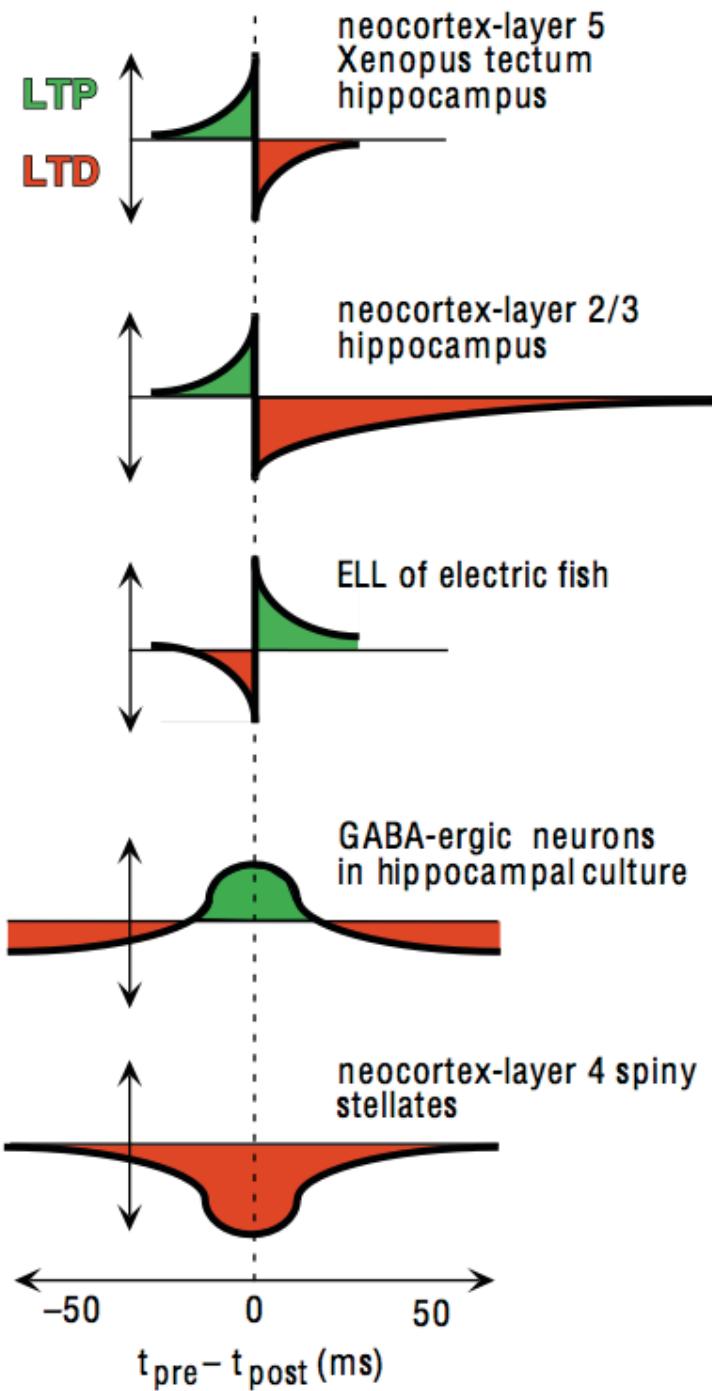


A



B





Different synapses have different plasticity profiles!

Expression mechanisms

Question: What comes after Calcium??

What is phosphorylation and what is dephosphorylation?

Phosphorylation is the process of adding a phosphate group to a protein.
Dephosphorylation is the process of its removal.

It is a common regulatory mechanism, and can lead to conformational changes in the underlying protein.

What are kinases?

Kinases form a family of enzymes that transfer phosphate groups from high-energy donor molecules, such as ATP, to specific substrates. i.e. Phosphorylation!

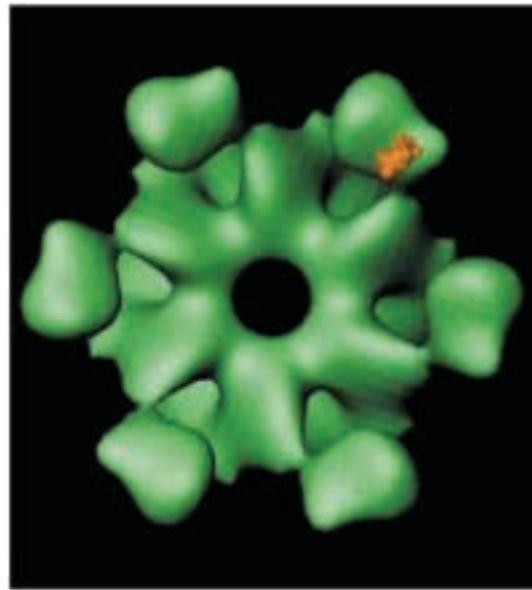
What are phosphatases?

Phosphatases are a family of enzymes that are involved in the removal of phosphate groups from their substrates. i.e. Dephosphorylation!

Proteins can have multiple sites for phosphorylation, each of which can be specific to a given kinase/phosphatase.

CaMKII: An important kinase for LTP!

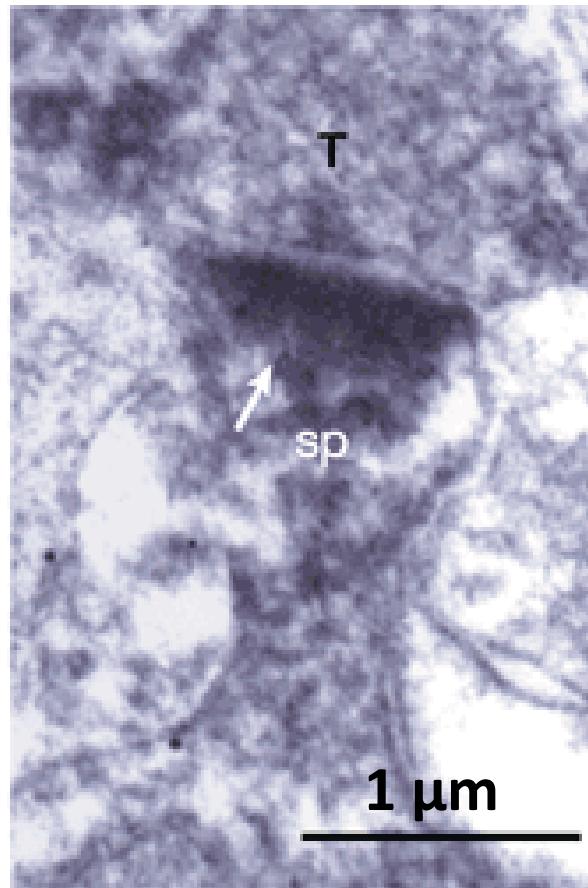
Calcium/calmodulin-dependent protein kinase II



Lisman et al. Nature Reviews Neuroscience, 2002

Three-dimensional structure of CaMKII, showing one of the hexameric rings formed by six subunits, forming a gear-like structure

CaMKII in the postsynaptic density is ideally positioned to detect local Ca^{2+} entry



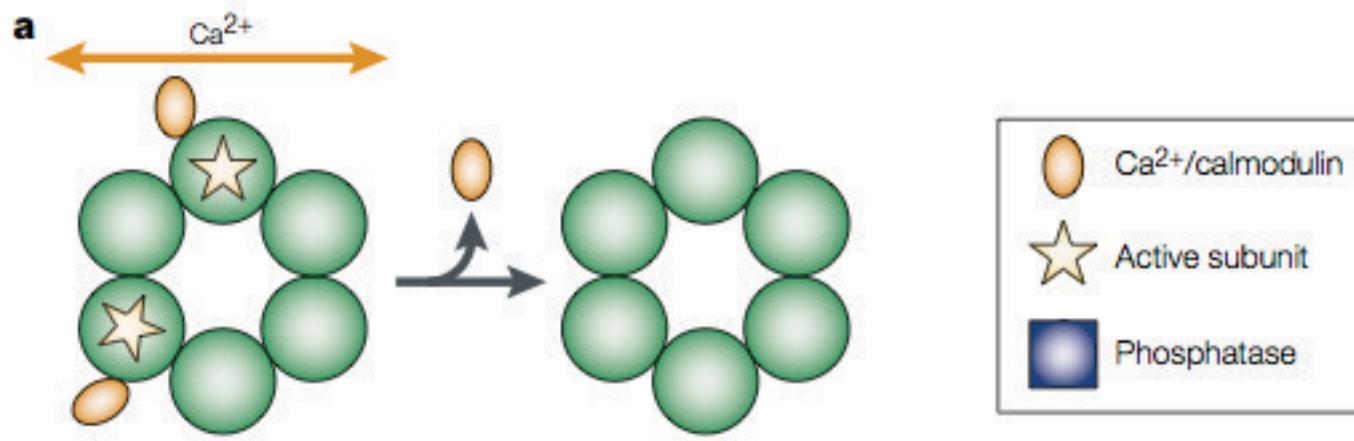
sp: Spine

T: presynaptic terminal

Lisman et al. Nature Reviews Neuroscience, 2002

What happens when calcium enters the cell during tetanus?

1. Calcium binds to calmodulin and Ca^{2+} /Calmodulin binds to CaMKII subunits to activate them

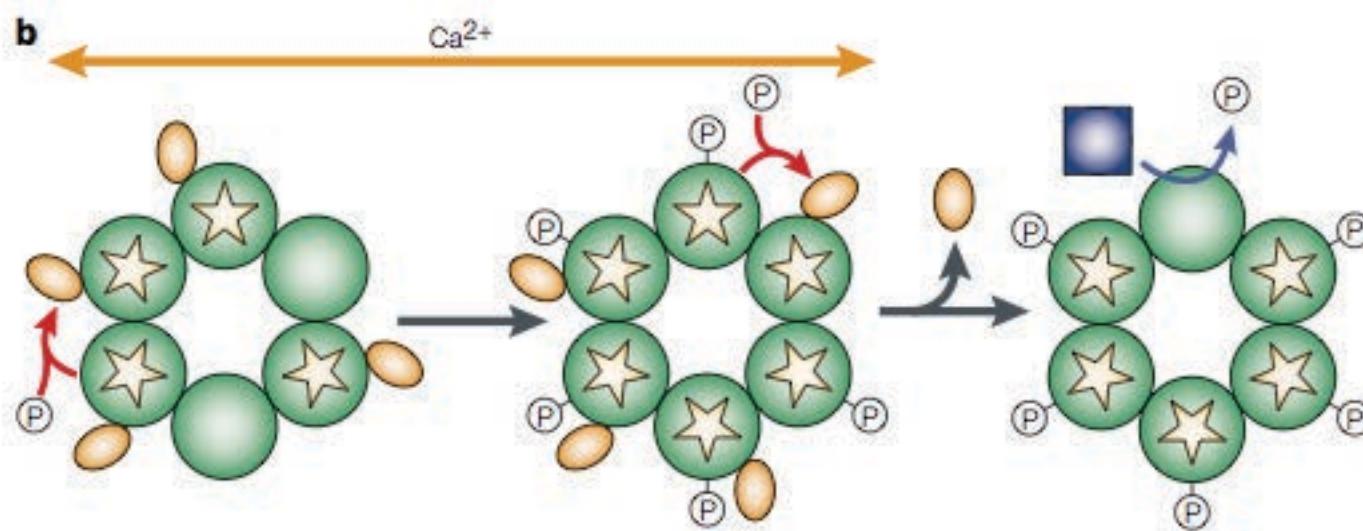


Lisman et al. Nature Reviews Neuroscience, 2002

If the duration/magnitude of calcium influx is low, nothing happens after this, and it gets inactive within 0.1– 0.2 s after calcium levels drop

Initiation and propagation of autophosphorylation

2. When two molecules of $\text{Ca}^{2+}/\text{Calmodulin}$ bind to different subunits of the same structure, conformational changes occur, making one phosphorylate the other!

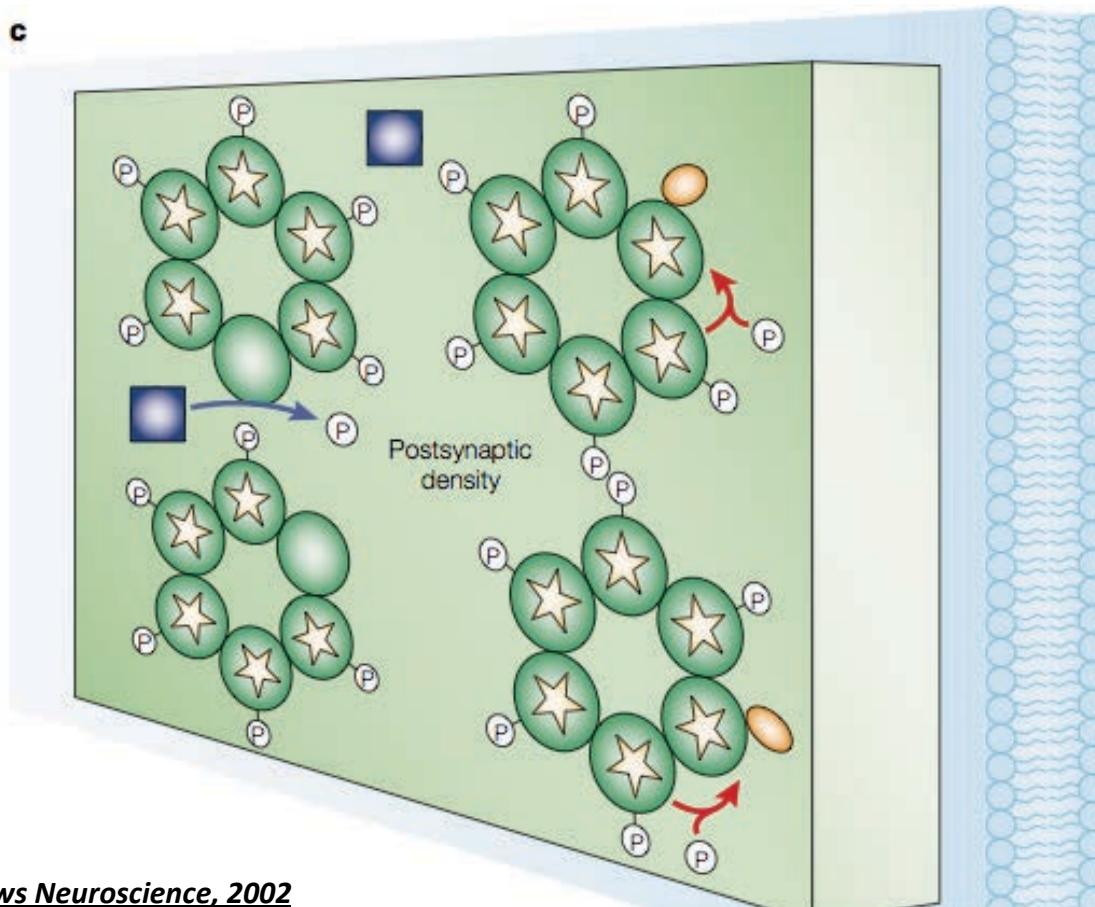


Lisman et al. Nature Reviews Neuroscience, 2002

3. Phosphorylation propagates along the ring, and propagation requires lesser calcium because only one $\text{Ca}^{2+}/\text{Calmodulin}$ is required.

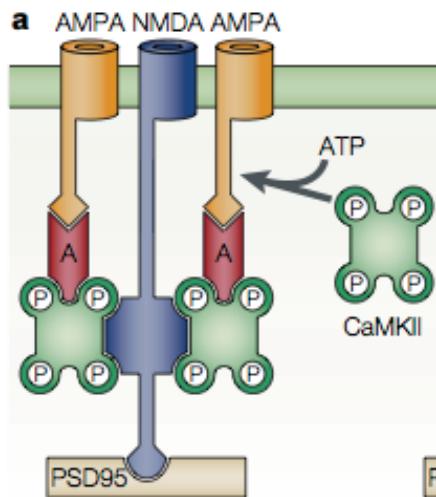
Persistence of phosphorylation

4. Once phosphorylated, it persists EVEN after Ca^{2+} levels are down, as long as dephosphorylation rates are lower than phosphorylation rates!



CaMKII then acts on AMPAR in two ways

1

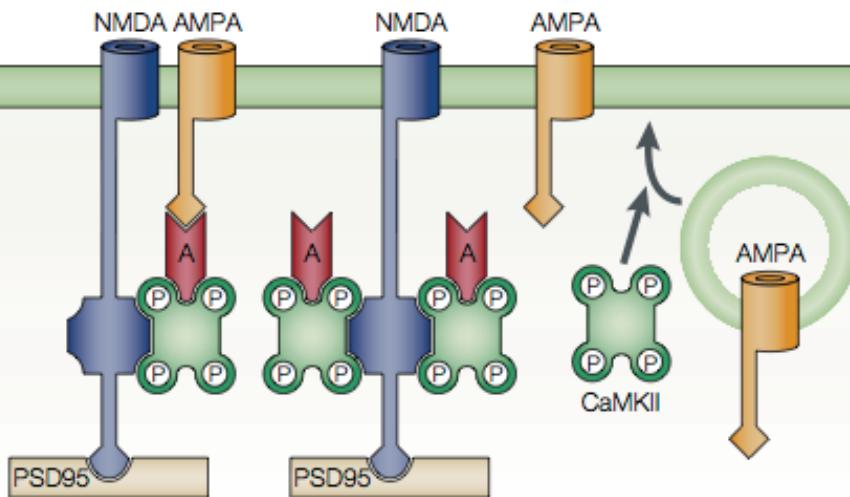


Phosphorylation of existing AMPA channels

The diagram illustrates the NMDA receptor signaling pathway. It features a blue NMDA receptor subunit (PSD95) anchored to a green PSD (post-synaptic density) protein complex. A red AMPA receptor subunit is shown nearby. A green CaMKII dimer is also part of the complex. Two arrows point from the NMDA receptor to the CaMKII dimer, indicating its activation by NMDA receptor signaling. A curved arrow points from the CaMKII dimer back to the NMDA receptor, representing a feedback loop.

Binding to NMDA channel and structural organization of additional AMPA anchoring sites

2



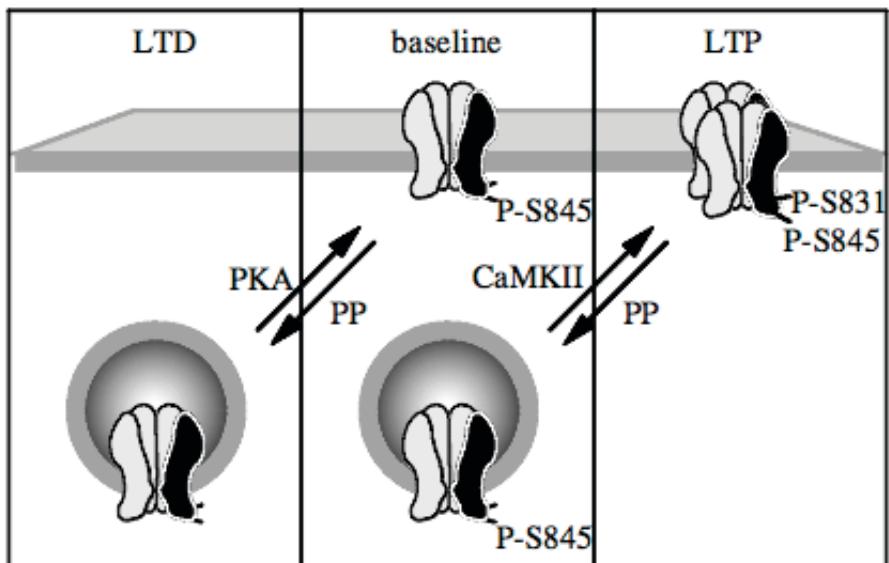
Stimulation of vesicle-mediated delivery of AMPA channels to fill existing anchoring sites (or new sites)

Lisman et al. *Nature Reviews Neuroscience*, 2002

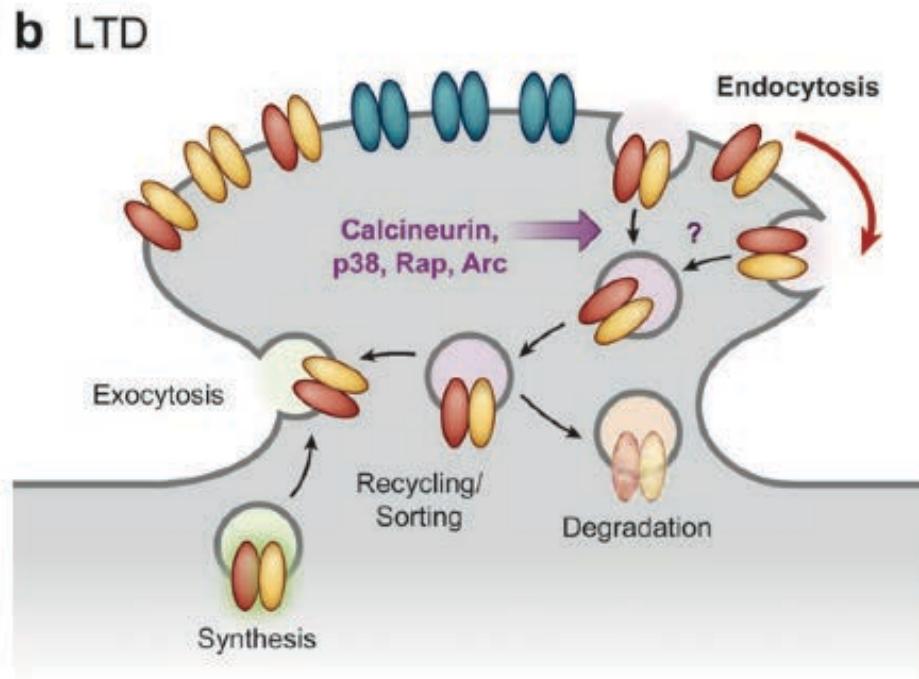
Also see Lisman et al., Nat. Rev. Neurosci., 2012

Insertion of AMPARs and increase in their conductance have been directly visualized/demonstrated!

LTD involves internalization of receptors or reduction of AMPAR conductance



Bear, PTRSL, 2003



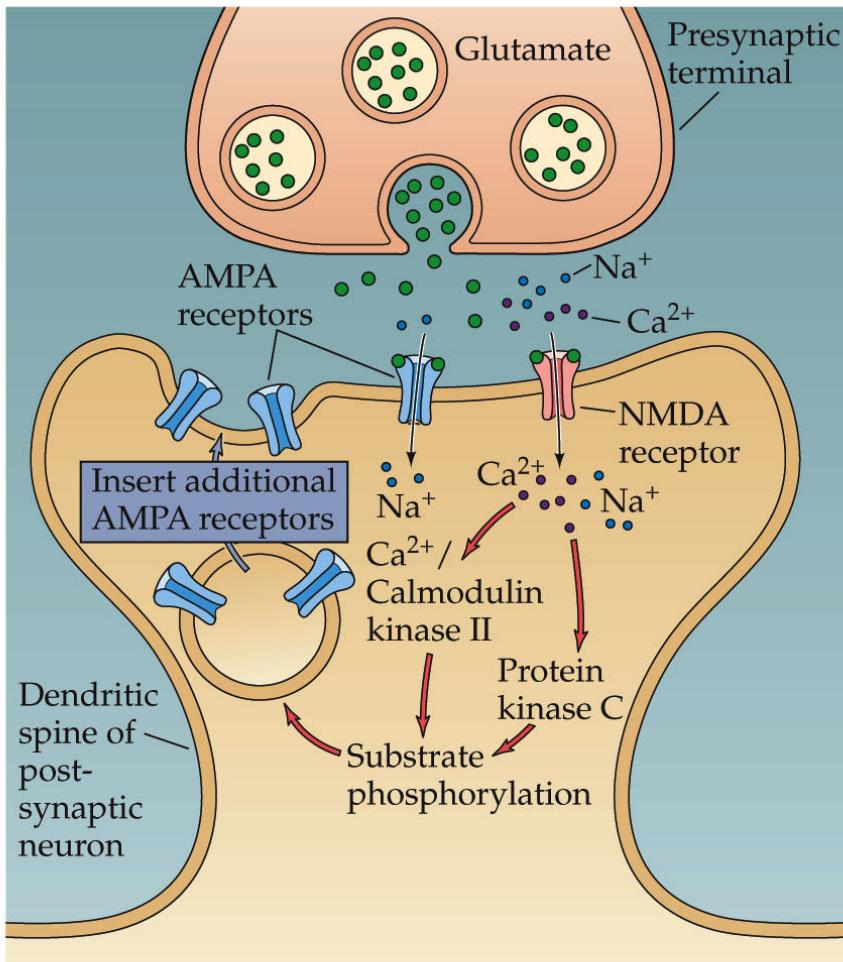
○ NMDA receptor ○ GluR1 subunit ○ GluR2 subunit

Dephosphorylation is through protein phosphatases

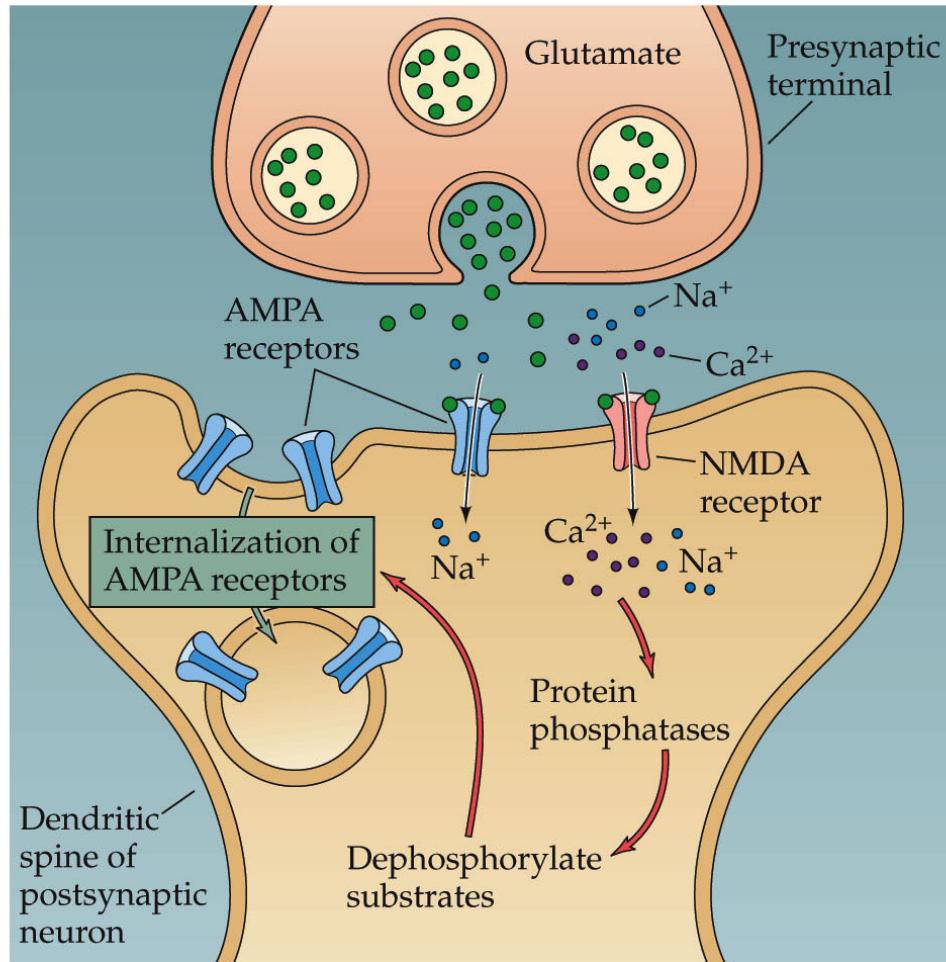
Different synapses, different rules!

Hippocampus

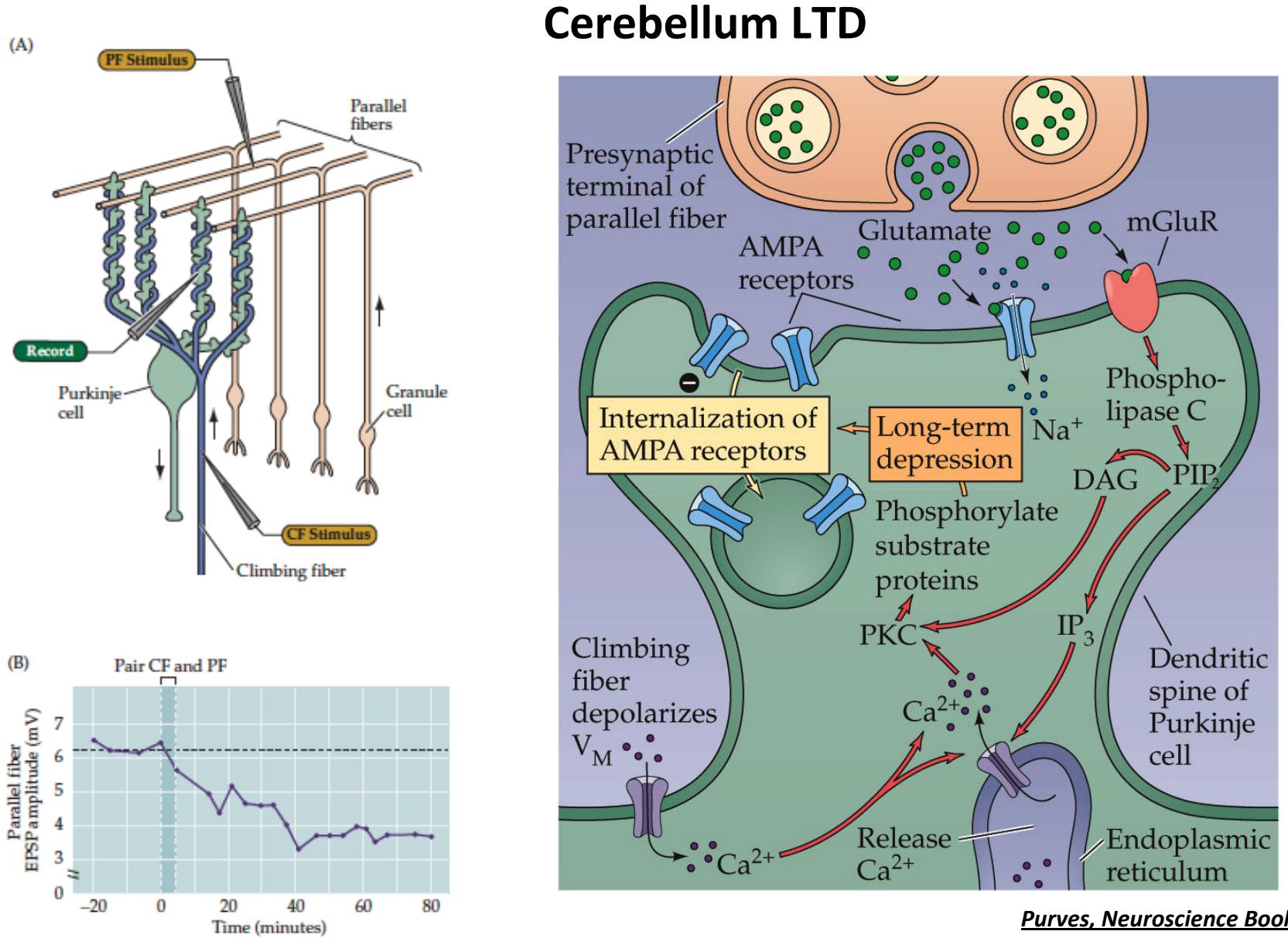
LTP



LTD

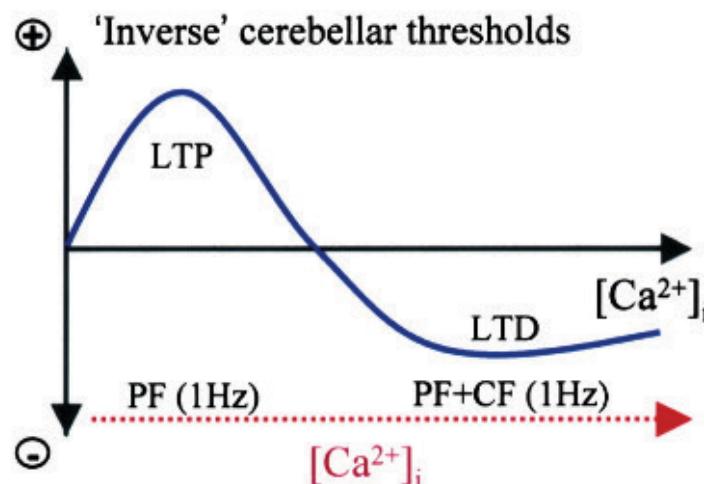
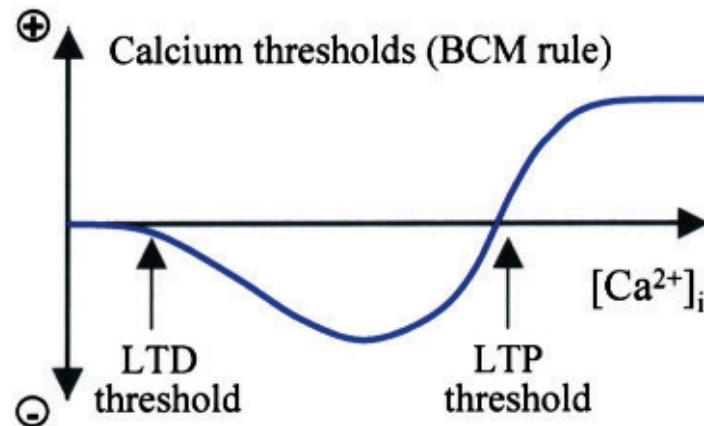


Different synapses, different rules!

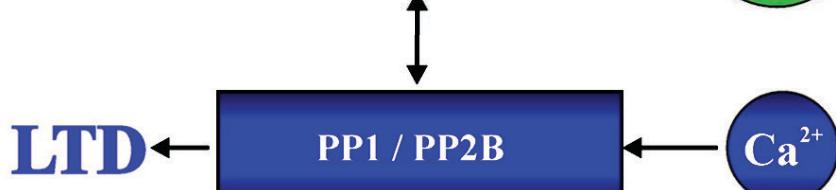
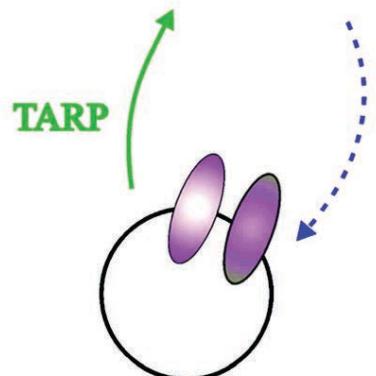
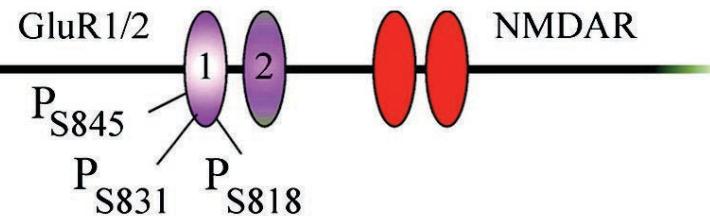


Different synapses, different rules!

Induction in hippocampal vs. cerebellar synapses

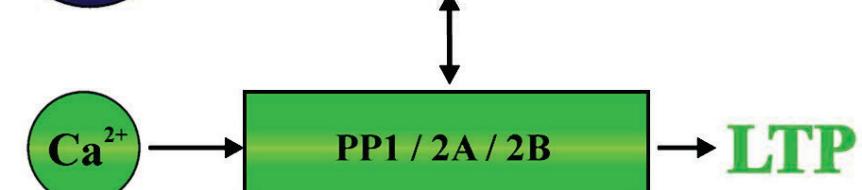
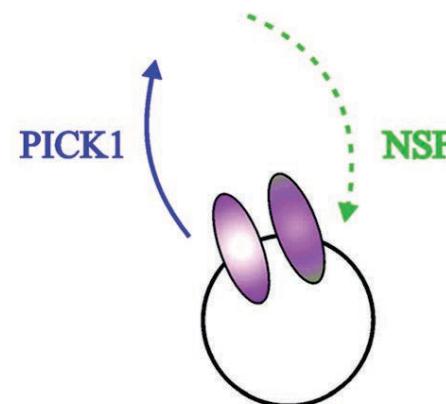
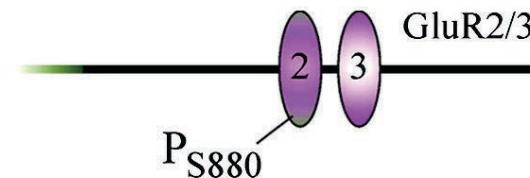


Different synapses, different rules!



Hippocampus

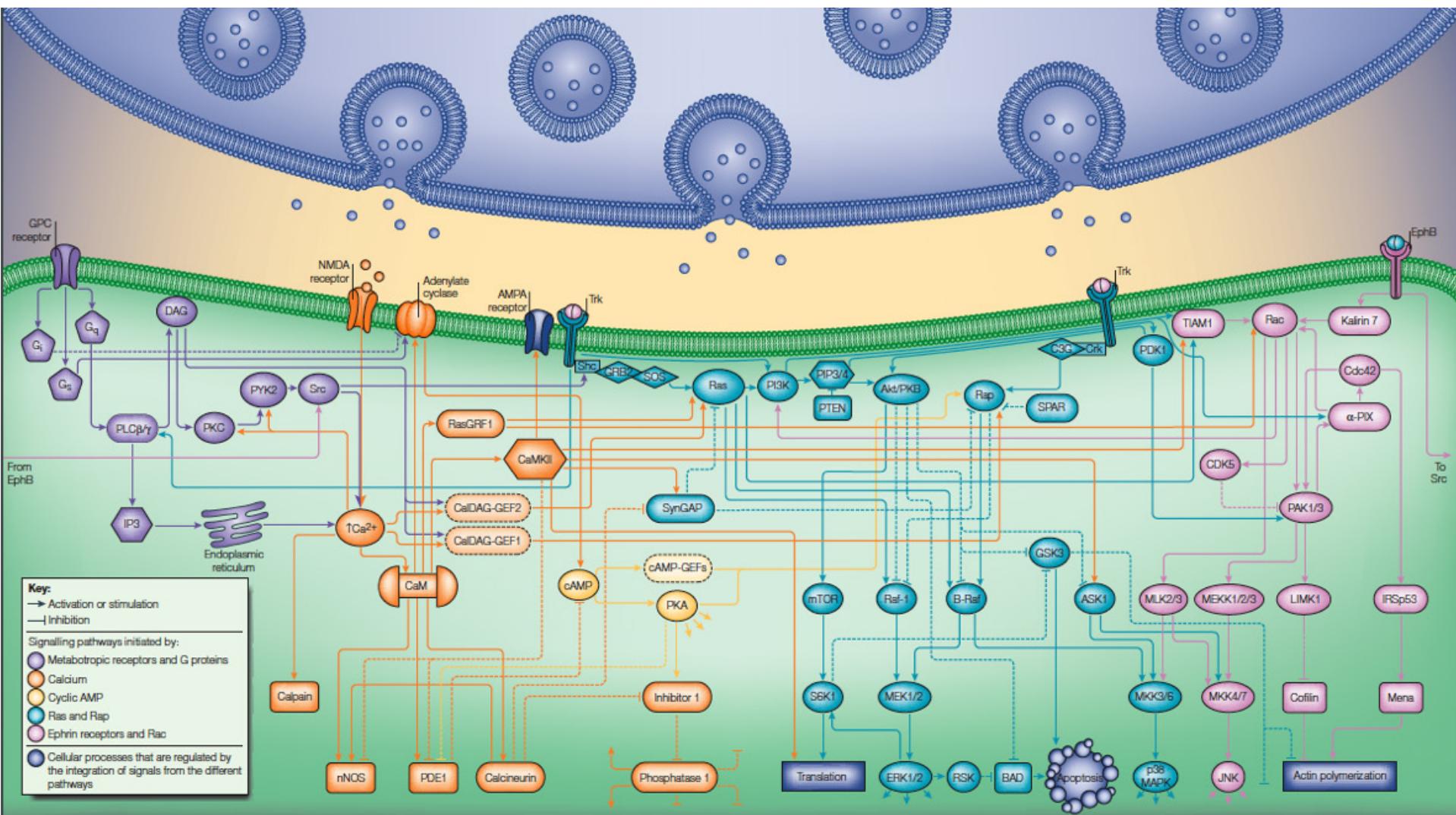
Pyramidal cell



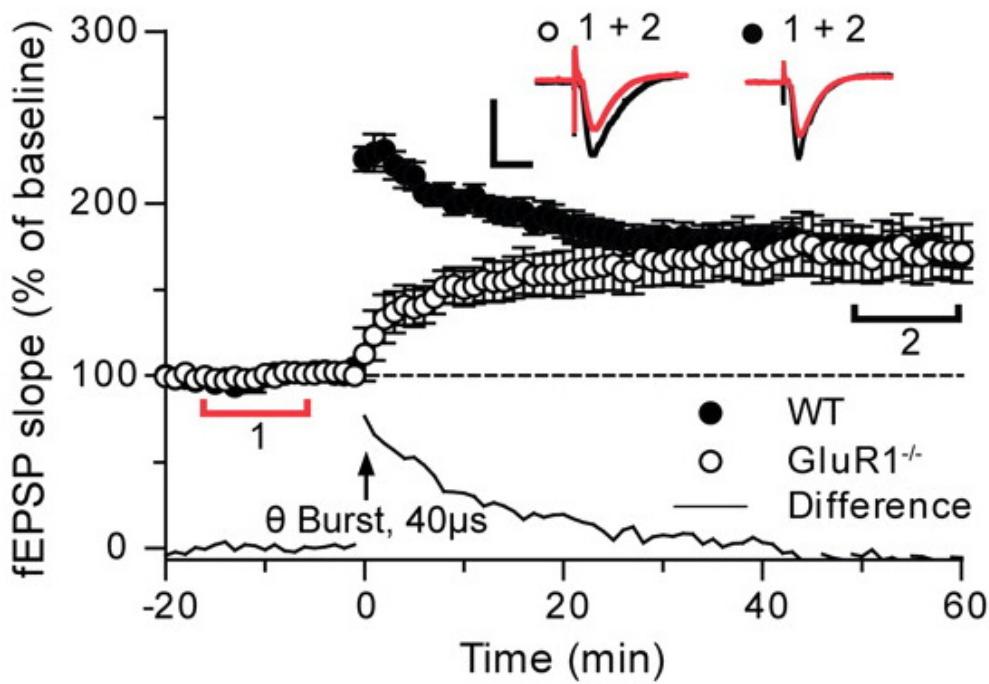
Cerebellum

Purkinje cell

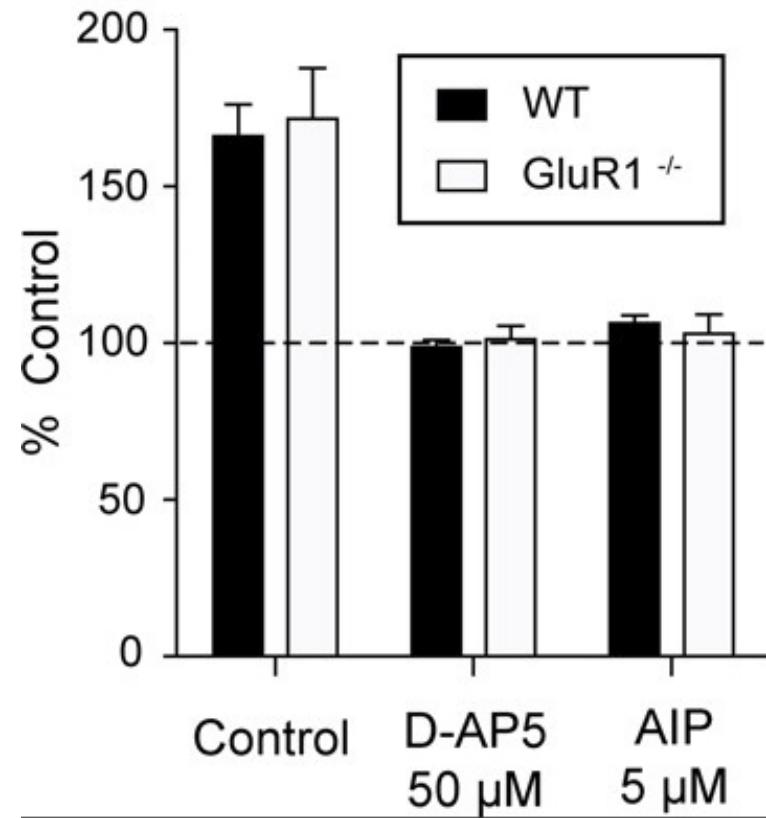
Postsynaptic pathways: some of them!



Knocking out GluR1 still produces LTP!!!



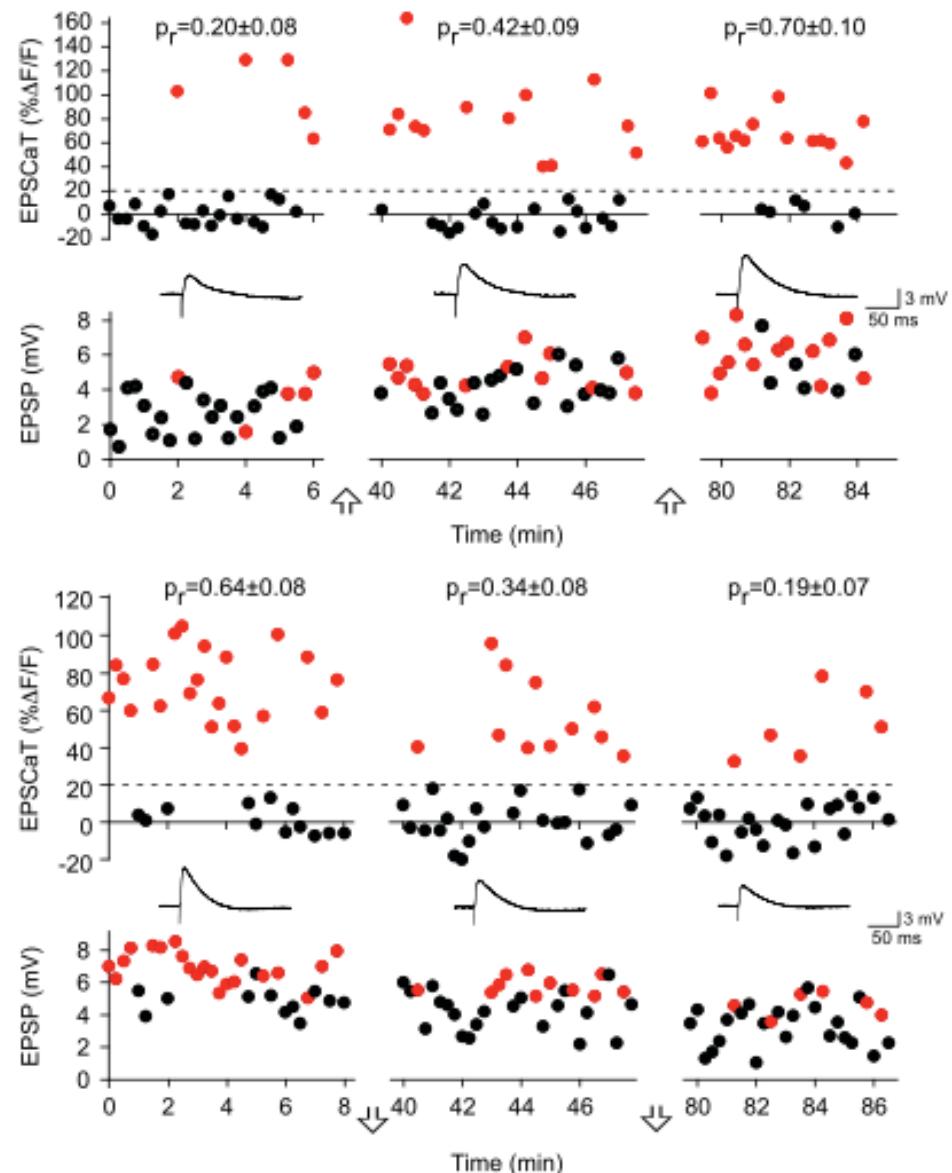
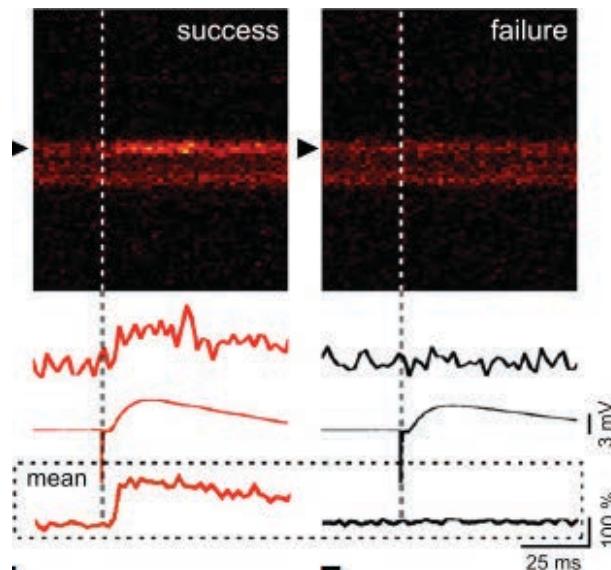
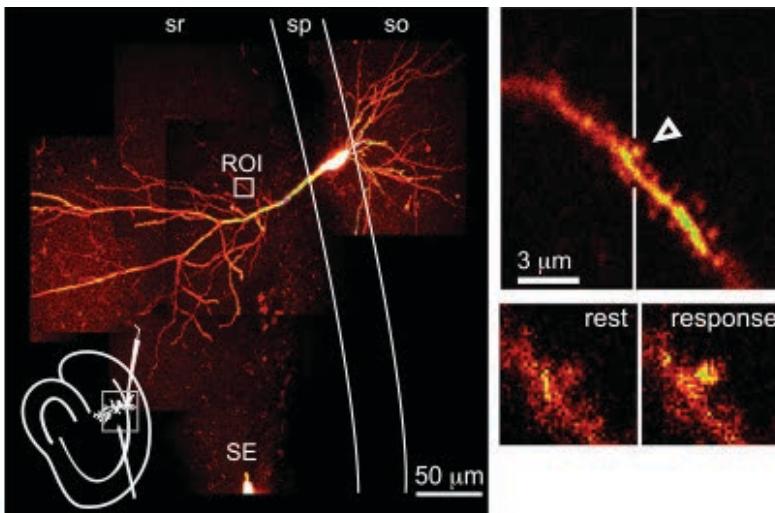
Phillips et al., JNS, 2008



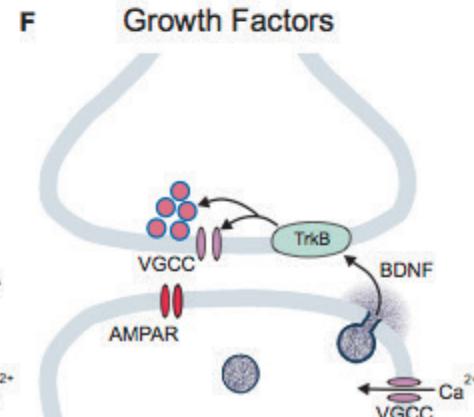
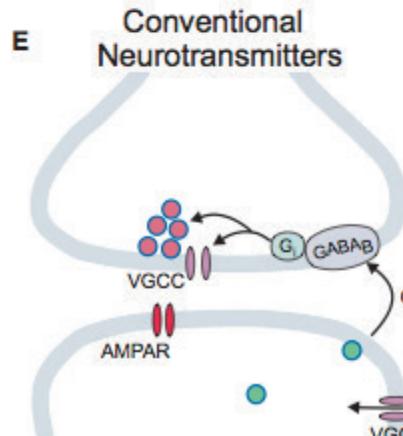
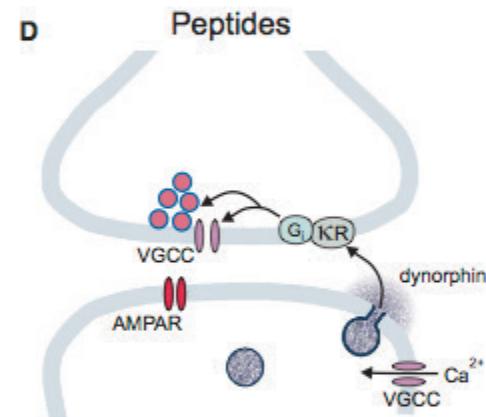
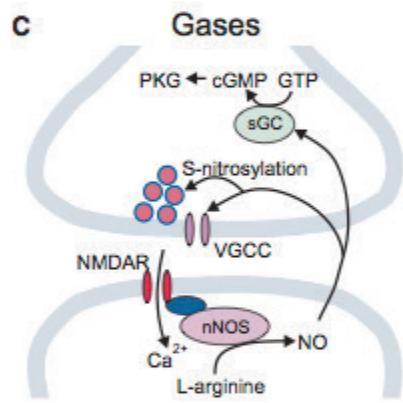
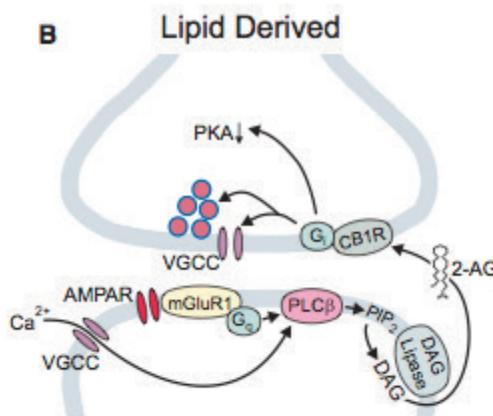
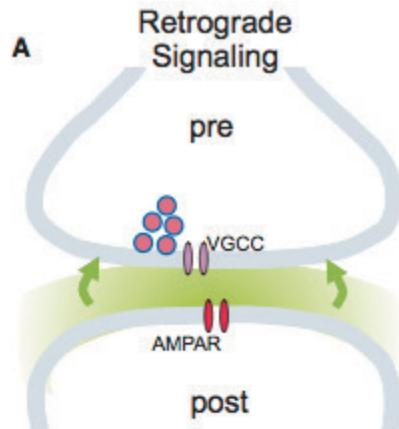
Autocamtide-2-inhibitory peptide (AIP) is a highly specific inhibitory peptide of CaMKII

Optical quantal analysis: LTP & LTD!

No significant changes in amplitude of calcium response, only in probability!



Retrograde signaling mechanisms



All these pathways have been implicated in synaptic plasticity, one way or the other!

You still require postsynaptic calcium elevation for most of these

See Regehr et al., Neuron, 2009, for a review.

The field is still growing...!

