

Synaptic Plasticity — Lecture 6

LTP/D Expression

Neuronal Physiology and Plasticity

Aug 2018 Semester

In the previous classes ...

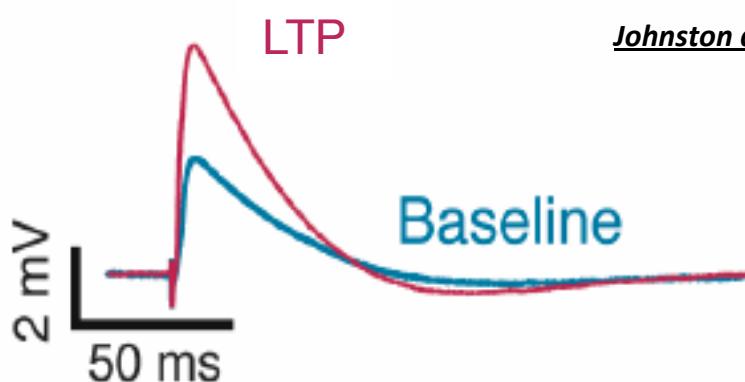
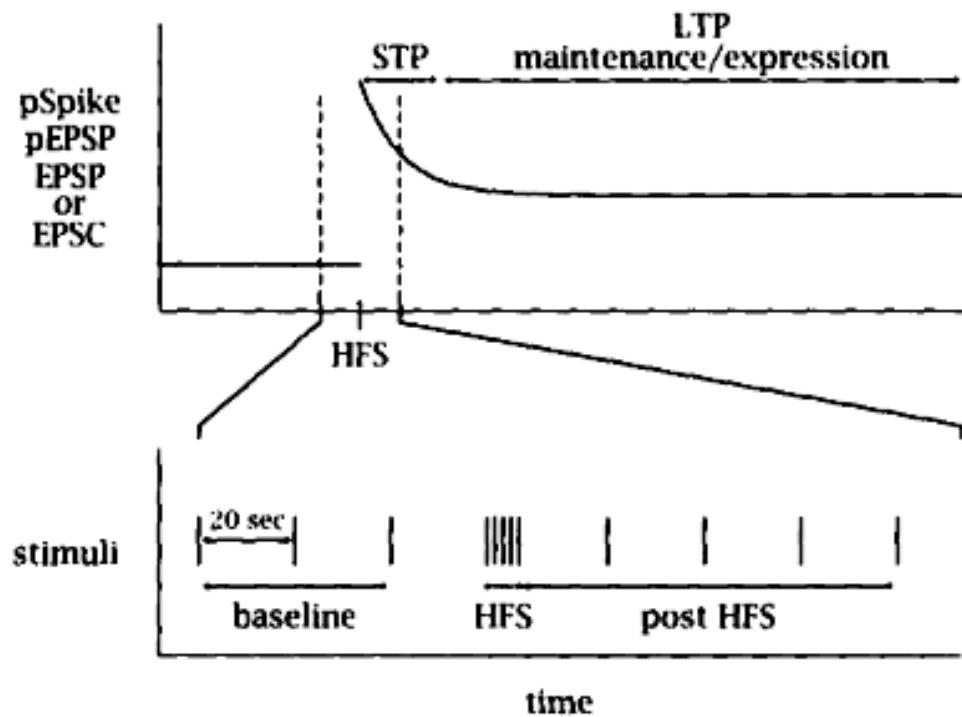
Basic LTP properties: persistence, specificity, cooperativity, associativity

LTP induction: HFS, depolarization and calcium entry consequent to NMDAR/VGCC/mGluR activation, various LTP protocols

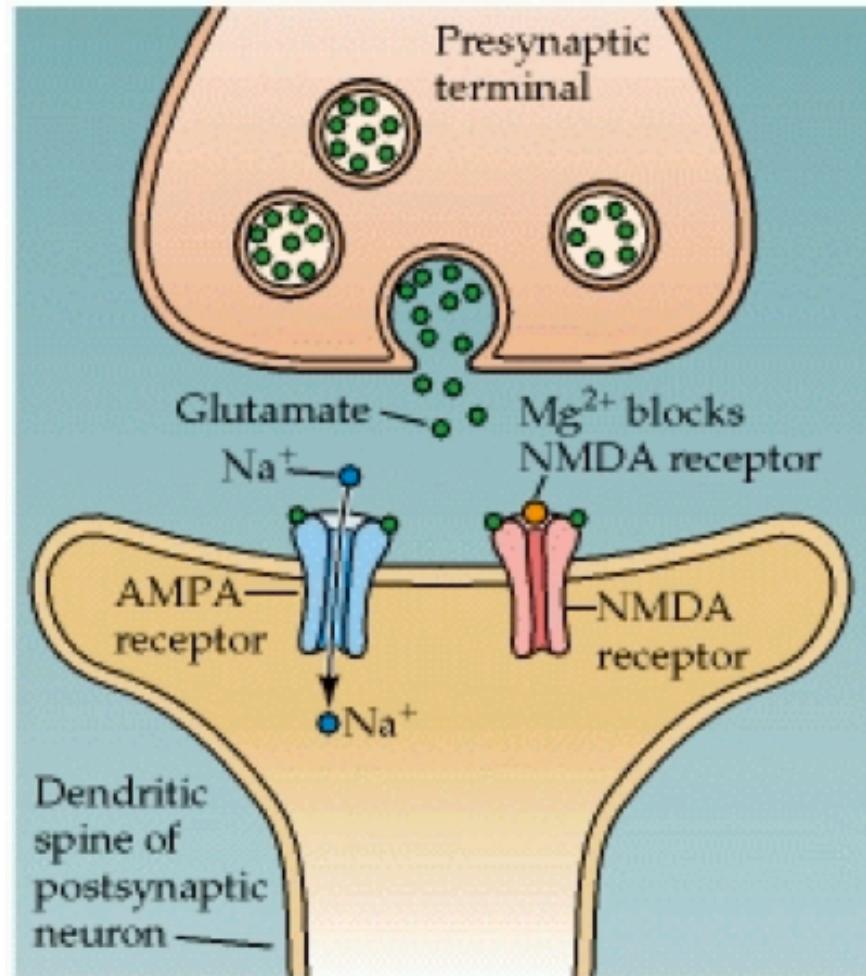
LTD induction: LFS, depolarization and calcium entry consequent to NMDAR/VGCC/mGluR activation, various LTD protocols

STDP: distance dependence and synapse dependence

But, then, what really changes to alter synaptic weight?



Narayanan and Johnston, Neuron, 2007



Purves, Neuroscience Book

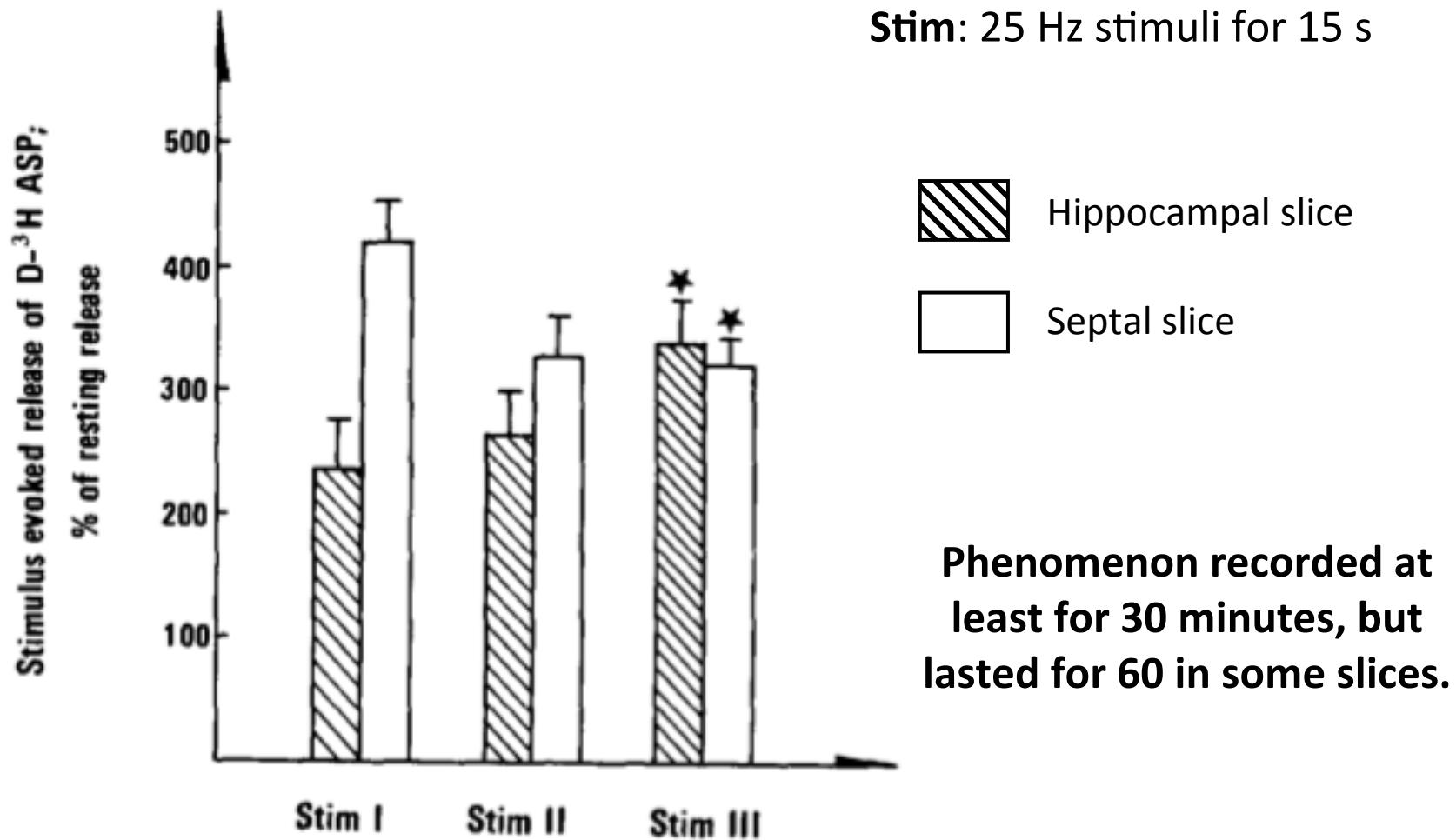
And, how do you test each of these possibilities?

Pre or Post?

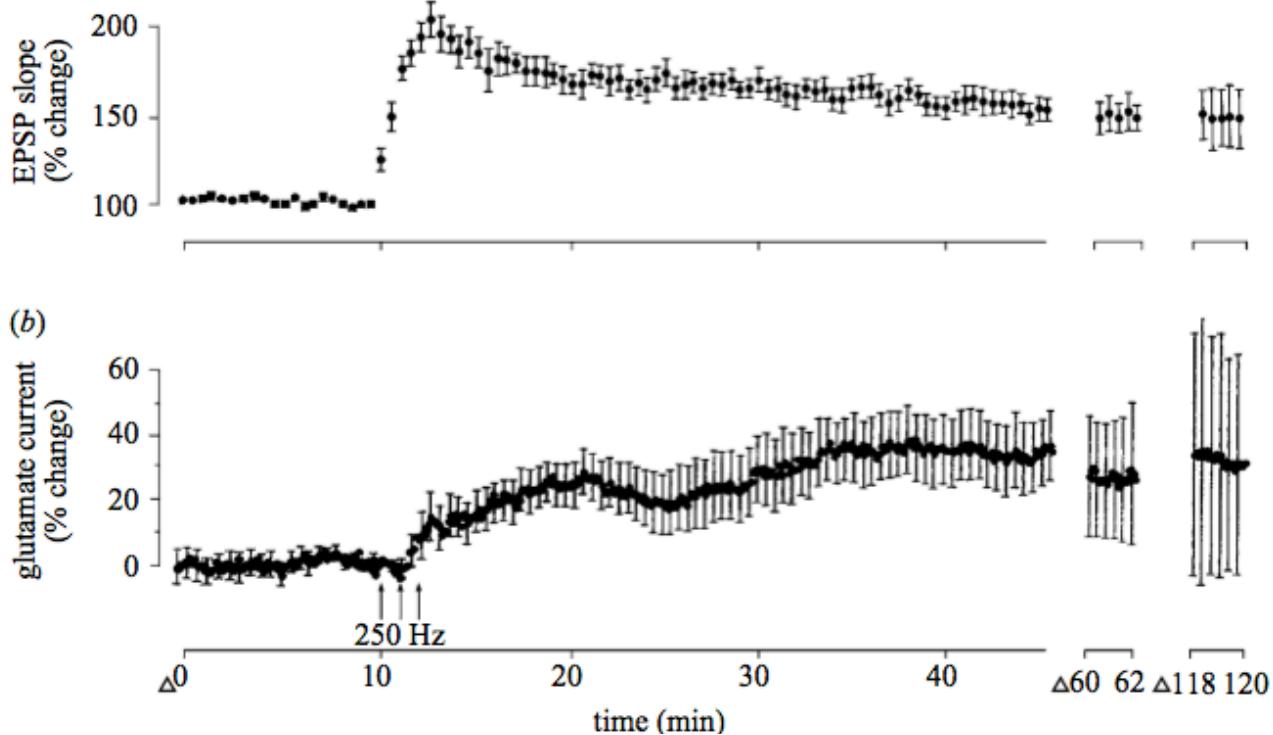
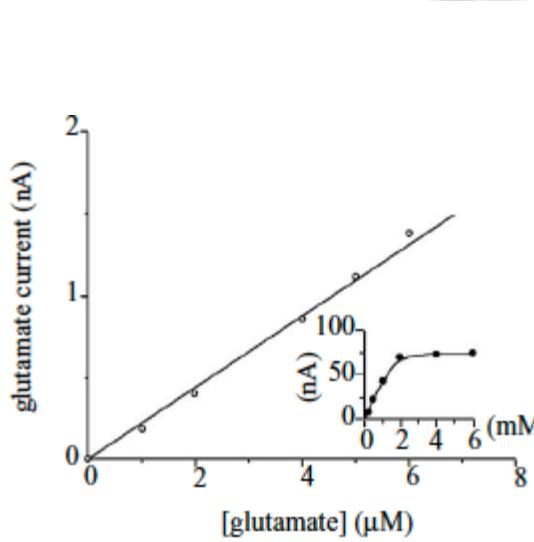
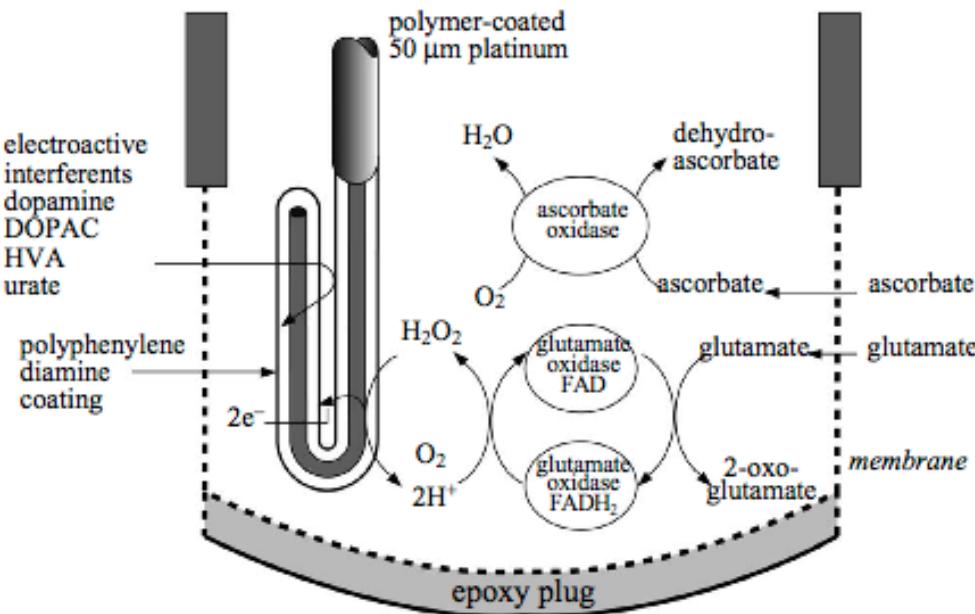
The question that has haunted LTP/D the most!

Group 1: Of course, it is Pre!

Measuring transmitter release using radio-labeled aspartate

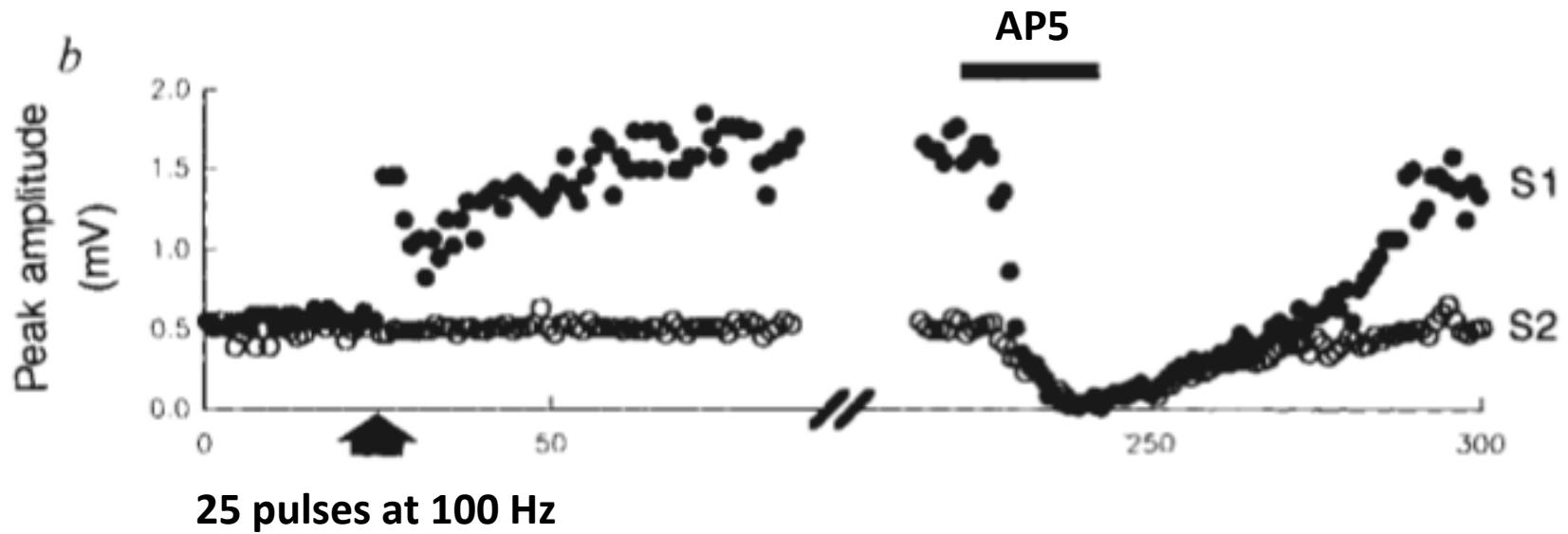


Advanced glutamate electrode



Changes in NMDA receptor currents ALSO!

Experiments performed in the presence of CNQX and picrotoxin



S1: LTP pathway; S2: Control pathway

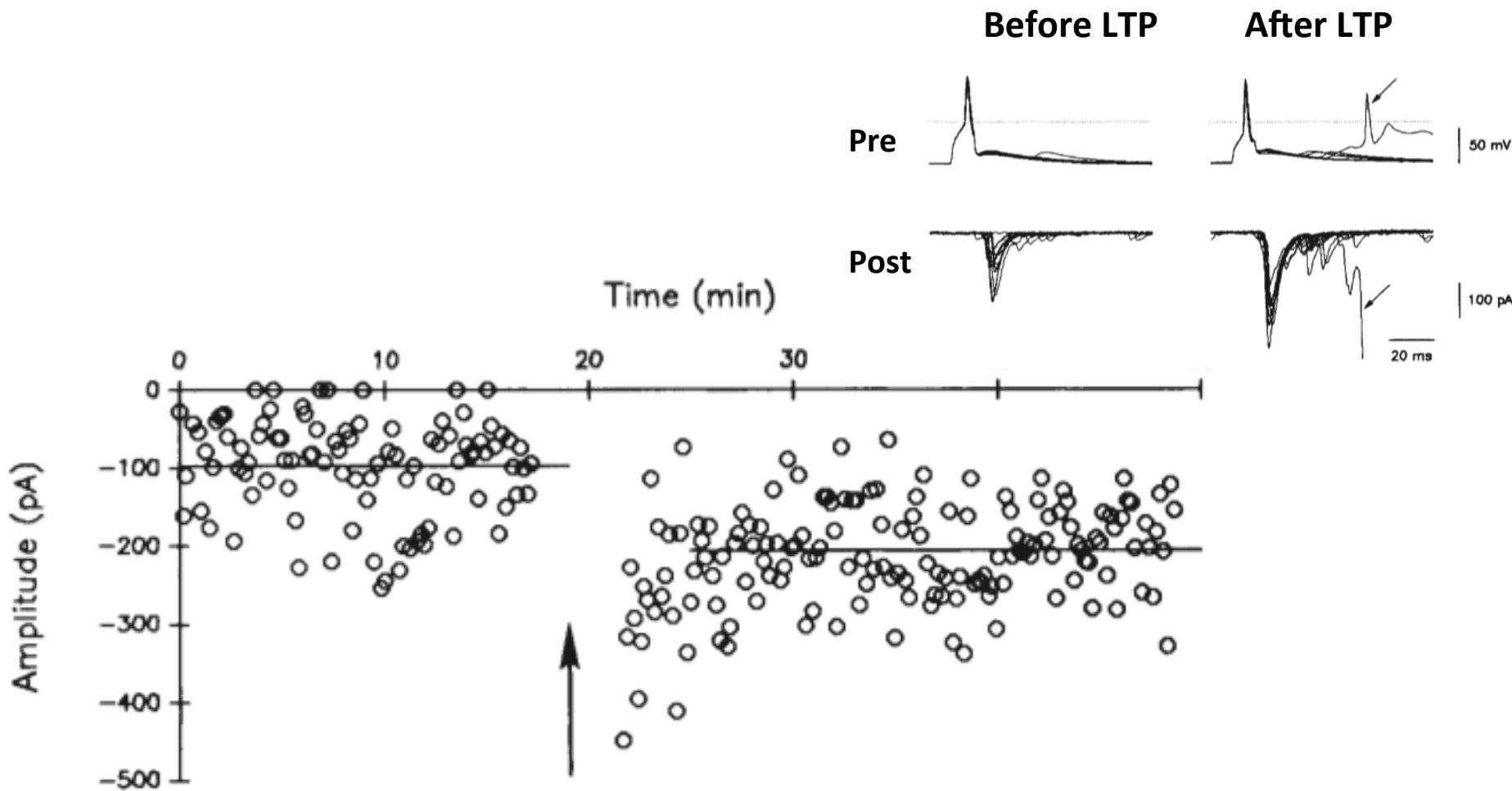
AP5 abolishes all transmission confirming the role of NMDAR

Quantal analysis

Quantal analysis is almost impossible in central neurons. Why?

- They have dendrites, cable filtering and now, ion channels and their plasticity
- One way to circumvent is to do paired recordings and induce LTP in the pair, but finding pairs in CA1 is difficult! And there could be multiple contacts in a pair, and there are channels.
- With the noise and the attenuation through cable filtering, most of the miniature events die (See Magee and Cook, Nat. Neurosci., 2000)!

In cultures, finding pairs is easier...!



We still have the problem of multiple connections or formation or removal of old pairs

So, you run quantal analysis with pairs in cultures

If you assume a simple binomial distribution:

$$r = \left(\frac{C_v^B}{C_v^A} \right)^2 = \frac{(1-p)^B}{(1-p)^A} \frac{N^A p^A}{N^B p^B}$$

Mean, $\mu = Npq$

Variance, $\sigma^2 = Np(1-p)q^2$

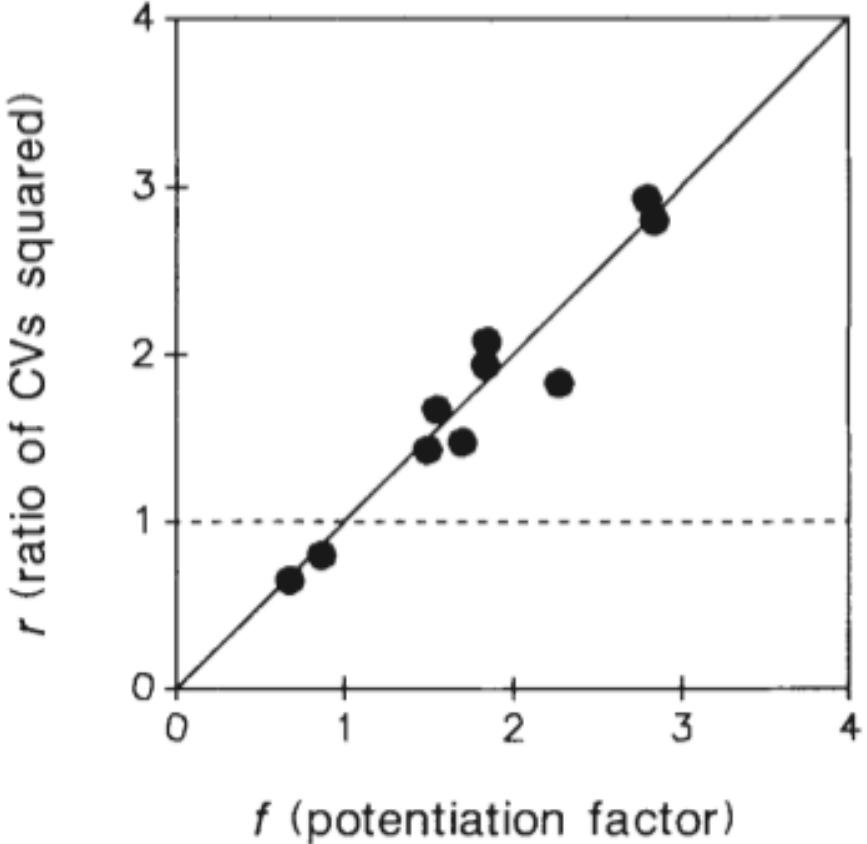
$$C_v^2 = \frac{\sigma^2}{\mu^2} = \frac{1-p}{Np}$$

which is independent of q! So, C_v is a good presynaptic-only measure!

N: number of release sites

p: probability of release

q: mean quantal size (mEPSC size)



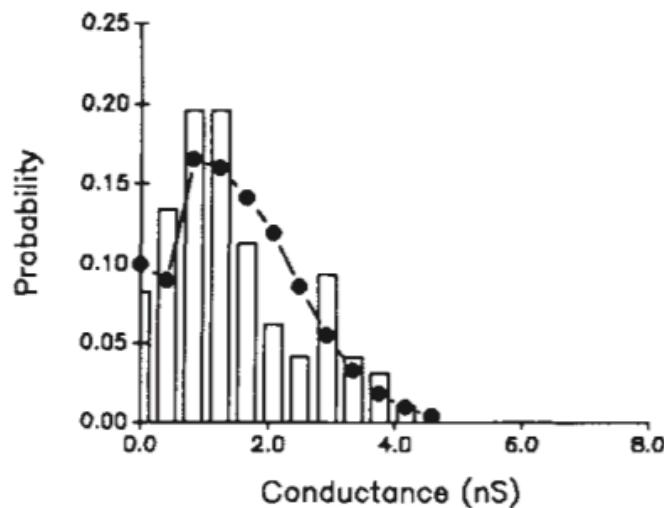
So, it is N or p, but not postsynaptic!
How to test for N vs. p?

Also see (Malinow and Tsien, Nature, 1990)

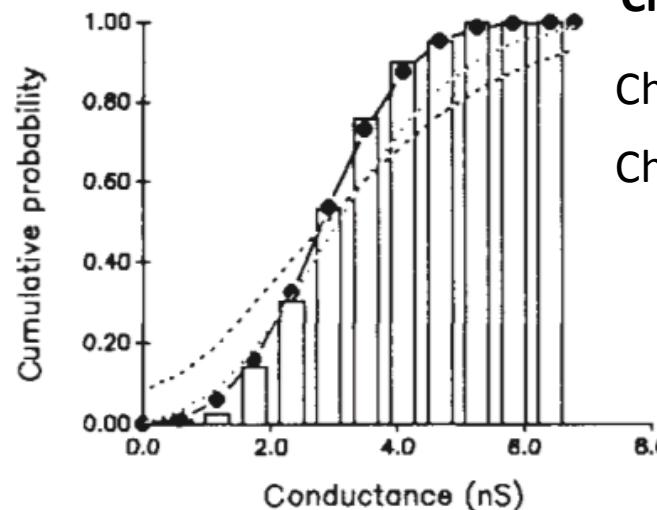
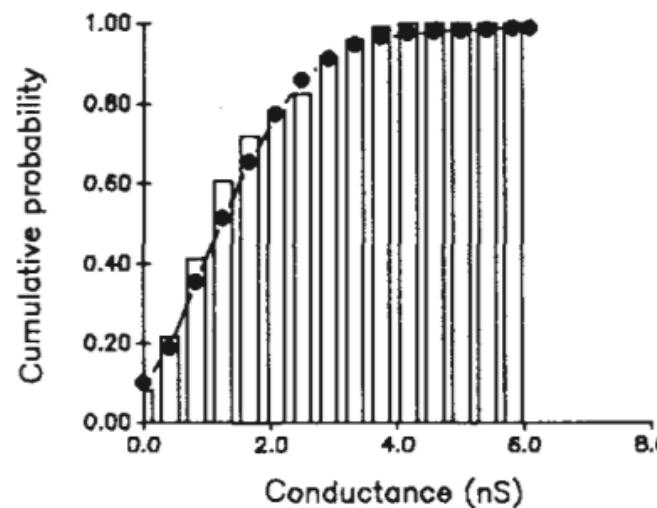
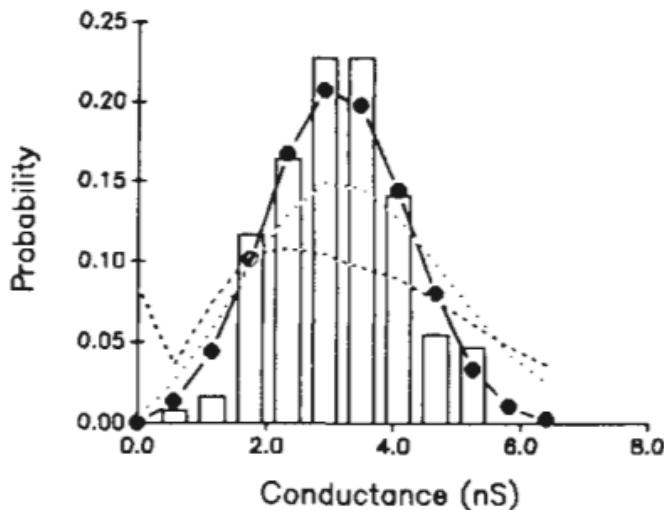
Bekkers and Stevens, Nature, 1990

Statistical analysis says it is p!

Before LTP

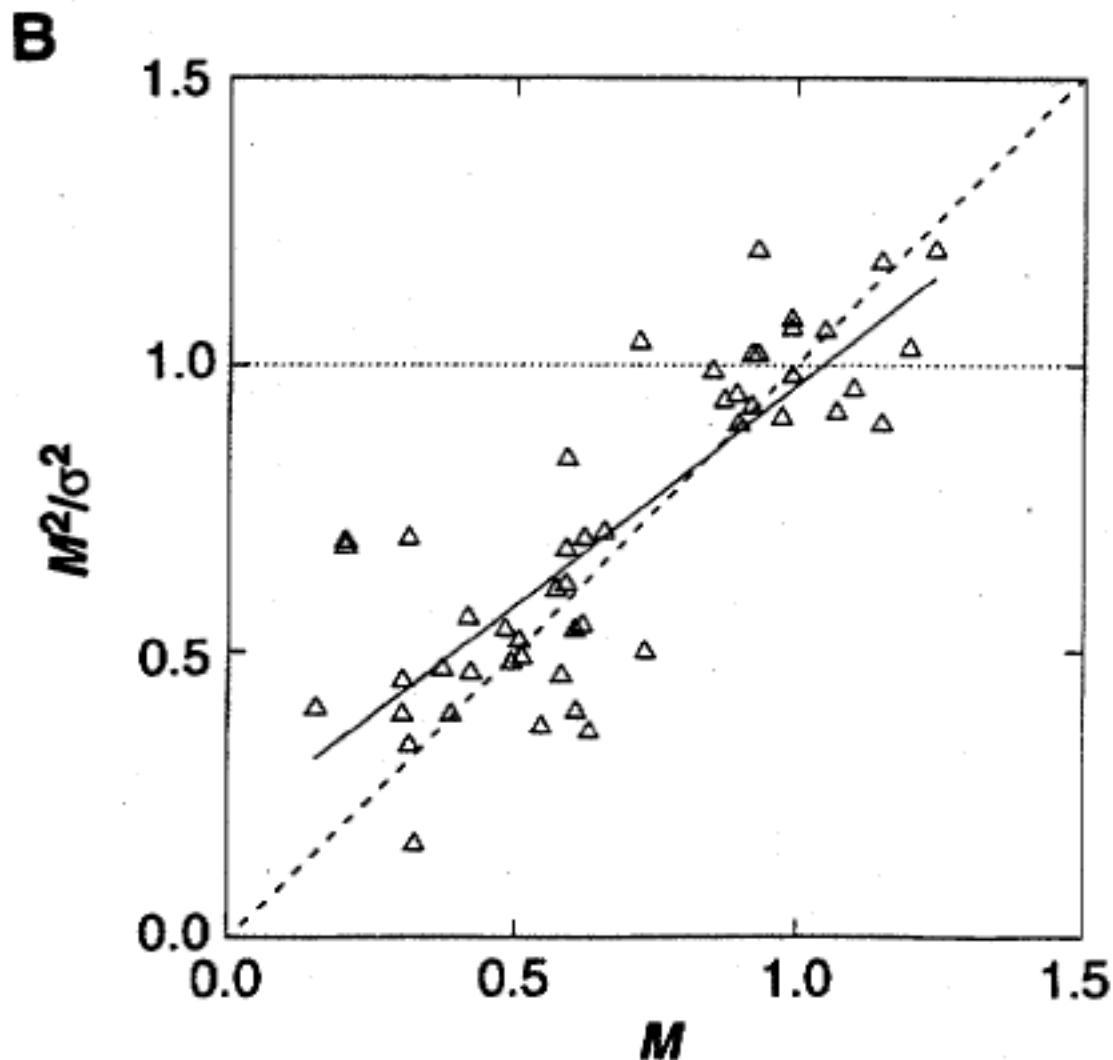


After LTP

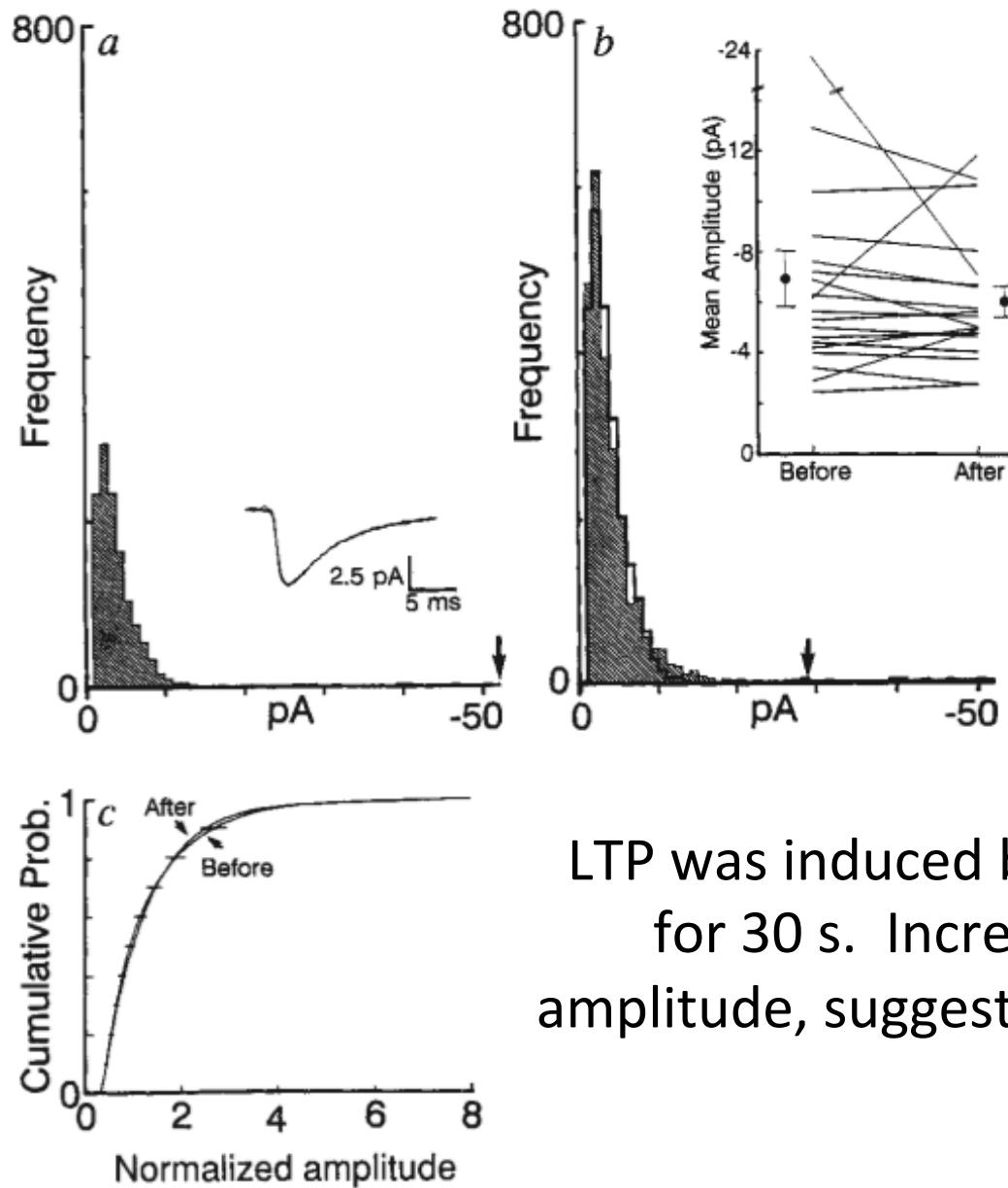


Change in p only
Change in N only
Change in q only

Such evidence exists with LTD as well!



Increase in frequency of miniature events

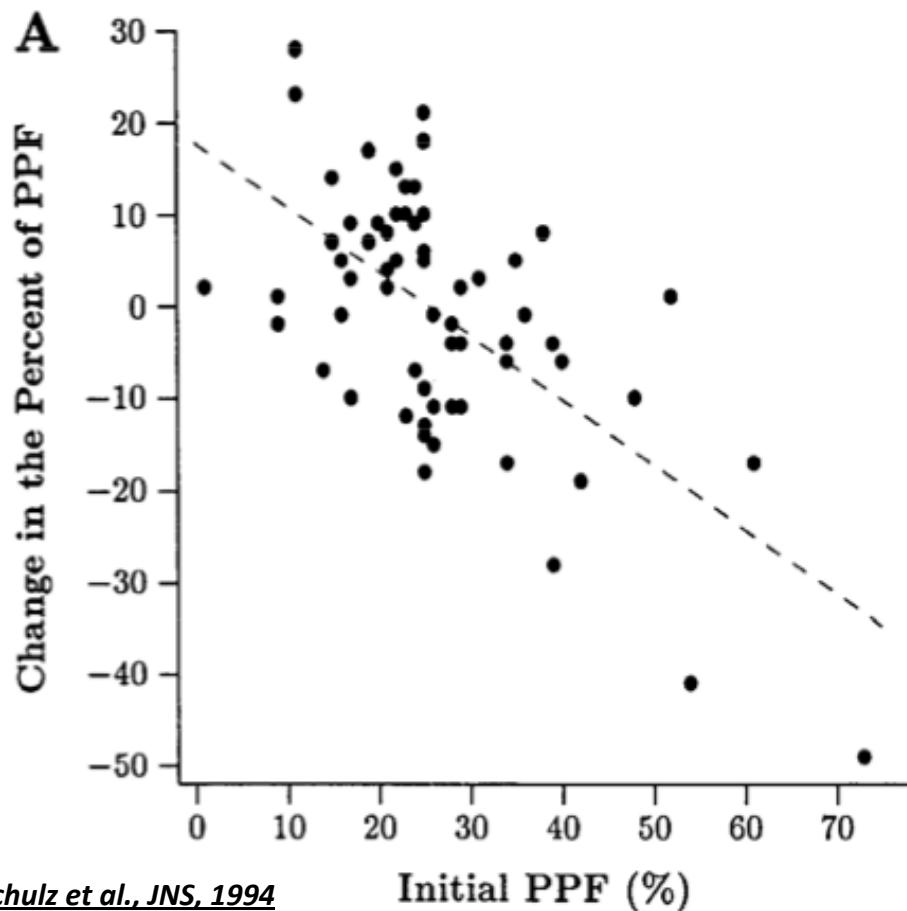


Culture neuron WCVC,
but Cesium in pipette.
But...

Done in the presence of TTX

LTP was induced by treatment with glutamate for 30 s. Increase in frequency, but not amplitude, suggesting presynaptic changes only!

Paired pulse facilitation



Interpretation: Both n (number of release sites), and p (probability of release) should have changed for this to occur!

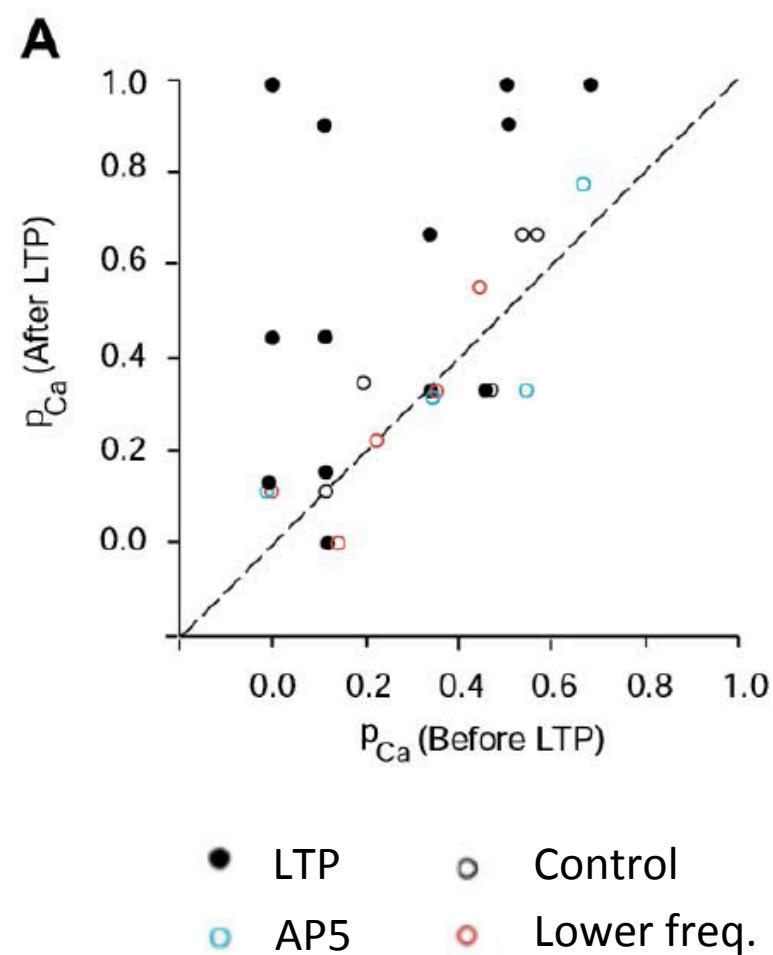
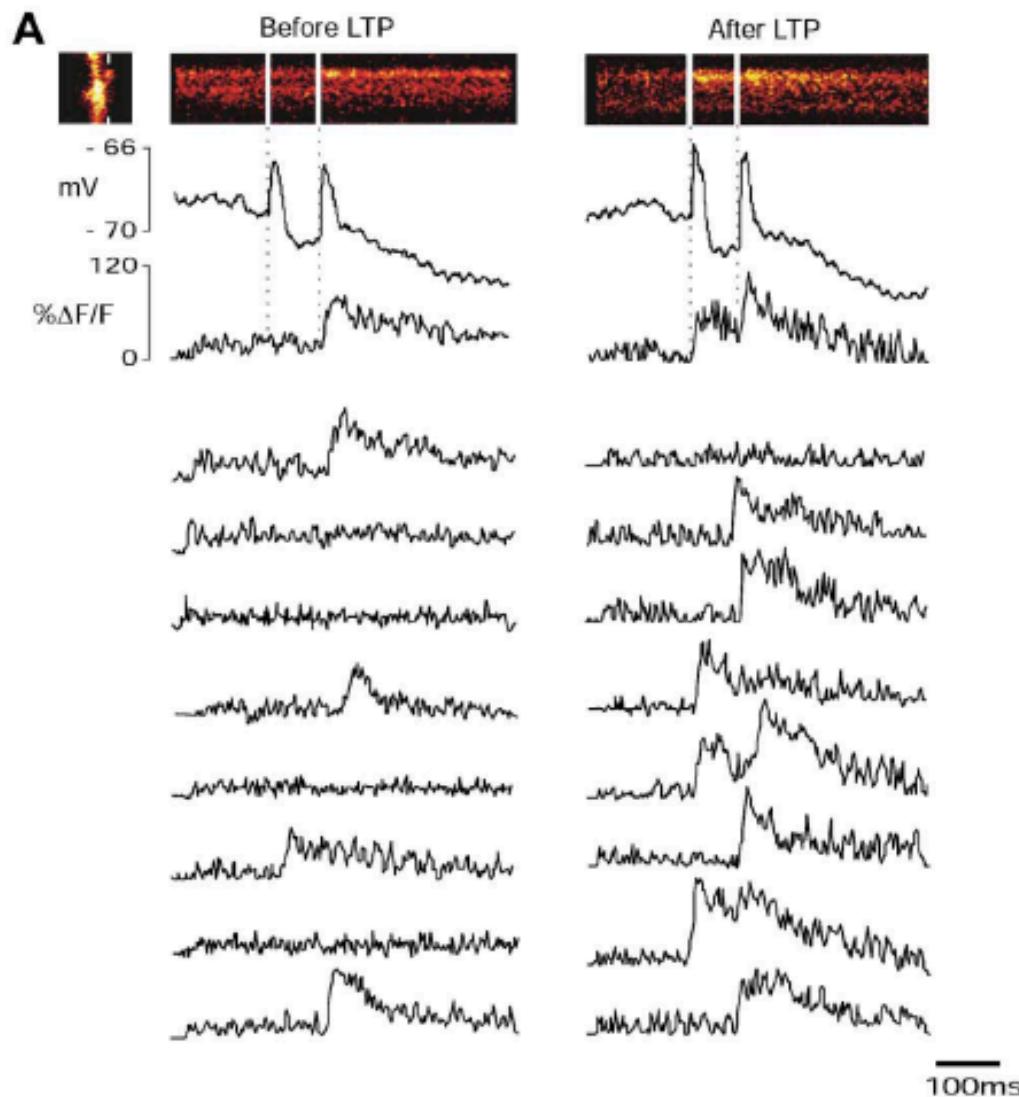
Only p changes: All decrease, and no increase!

Only n changes: No change in PPF!

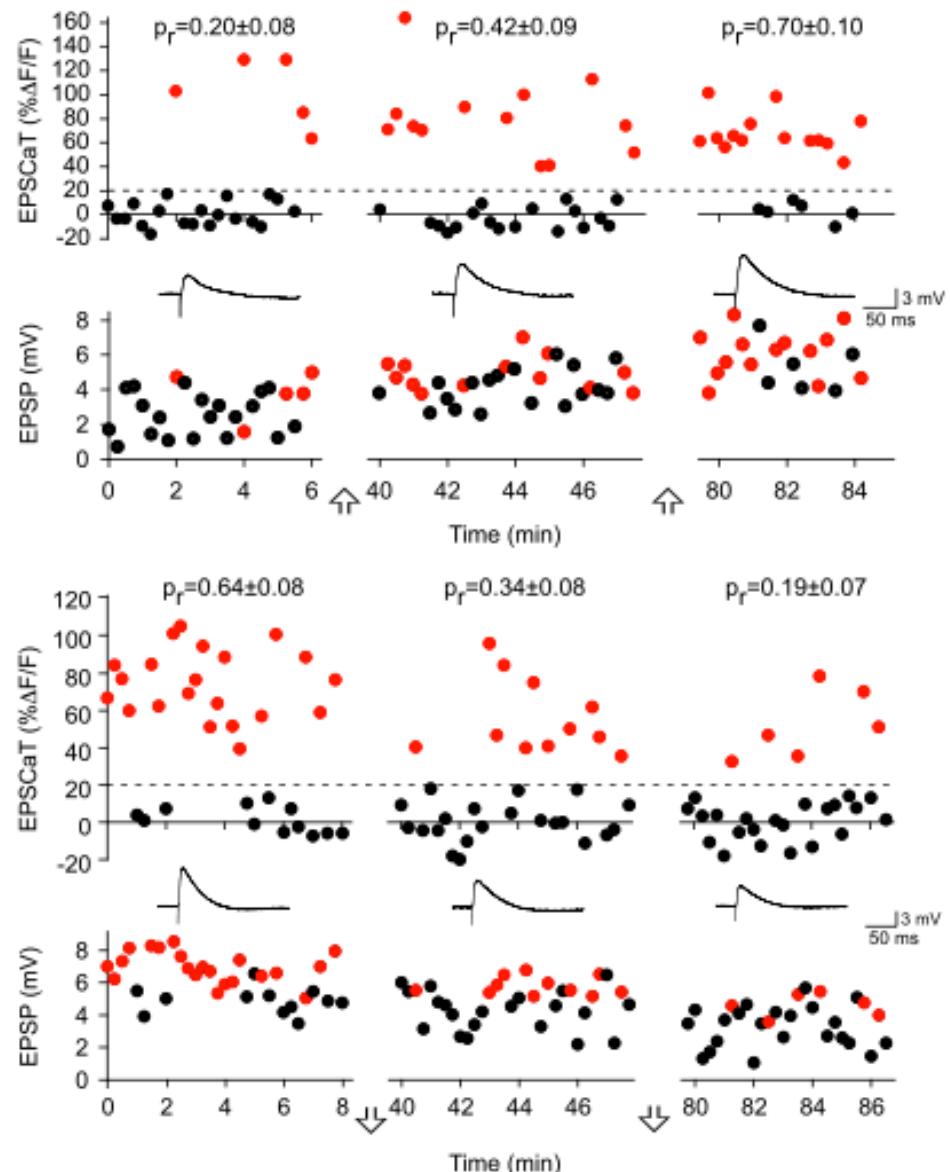
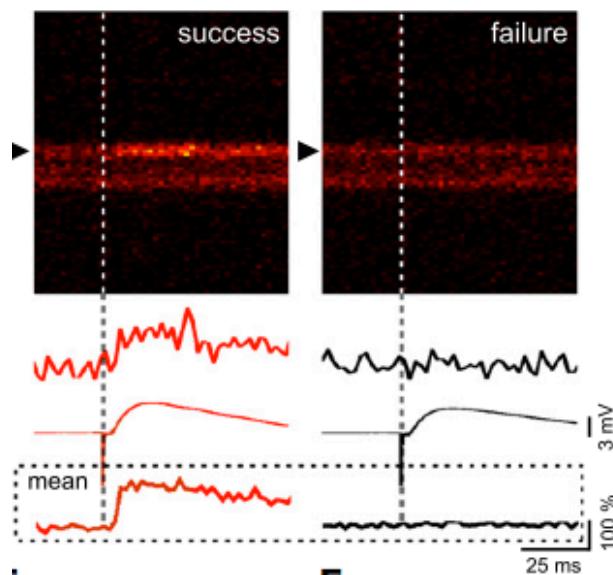
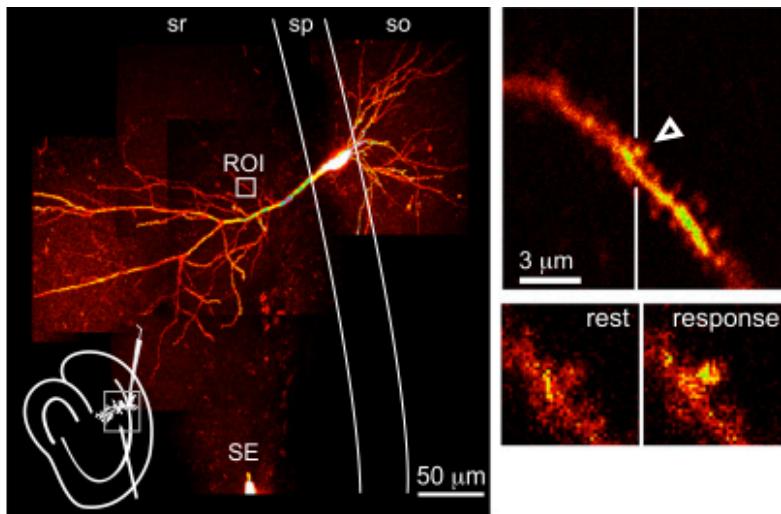
No change in n or p : No change in PPF!

Previous studies: average PPF remained constant, so it is not presynaptic!

Optical quantal analysis



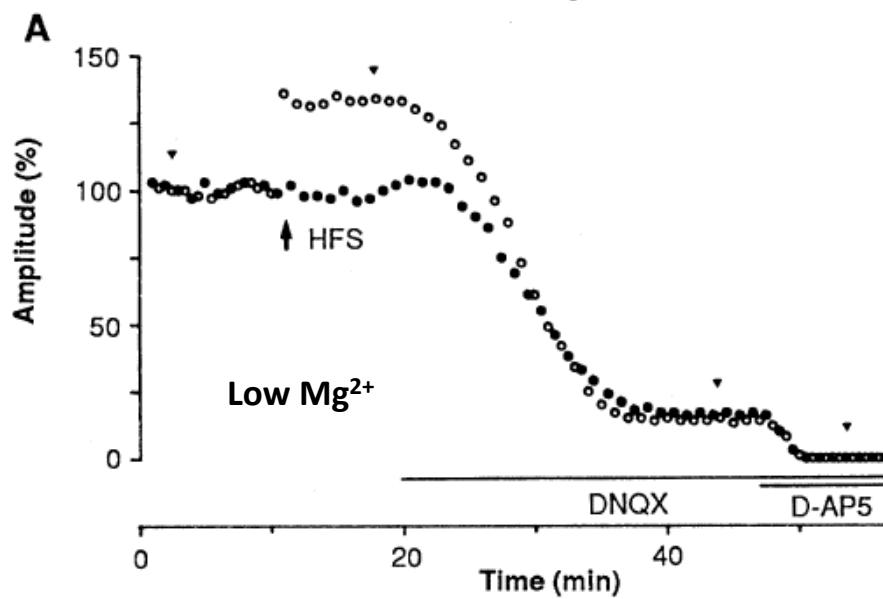
Optical quantal analysis: LTP & LTD!



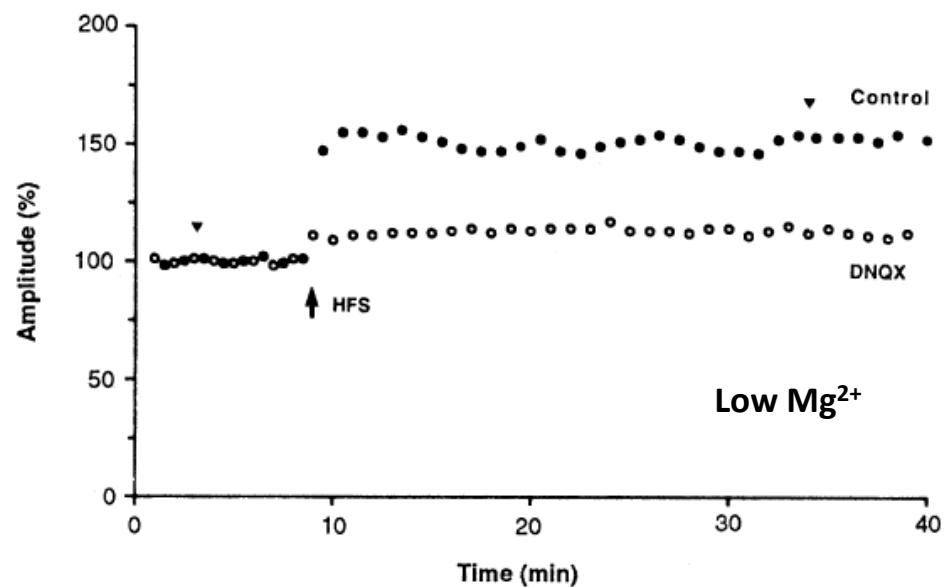
Group 2: Of course, it is Post!

Differential changes in NMDA and non-NMDA currents

Post-LTP, the non-AMPA component is not changed



No LTP is induced with AMPA receptors blocked



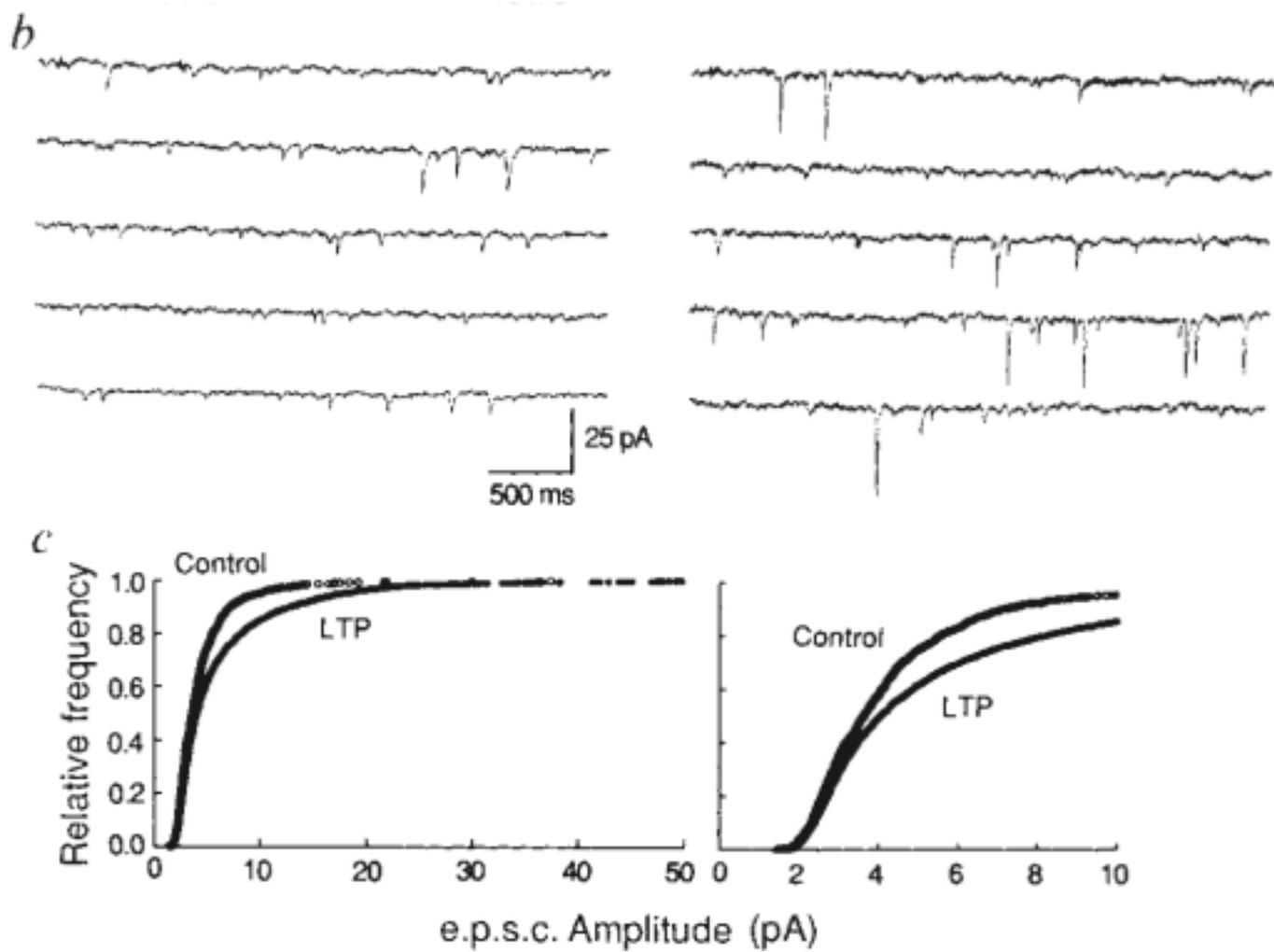
They were able to induce LTP with AMPA receptors blocked only during induction

Also see Muller and Lynch, PNAS, 1988

Muller et al., Science, 1988

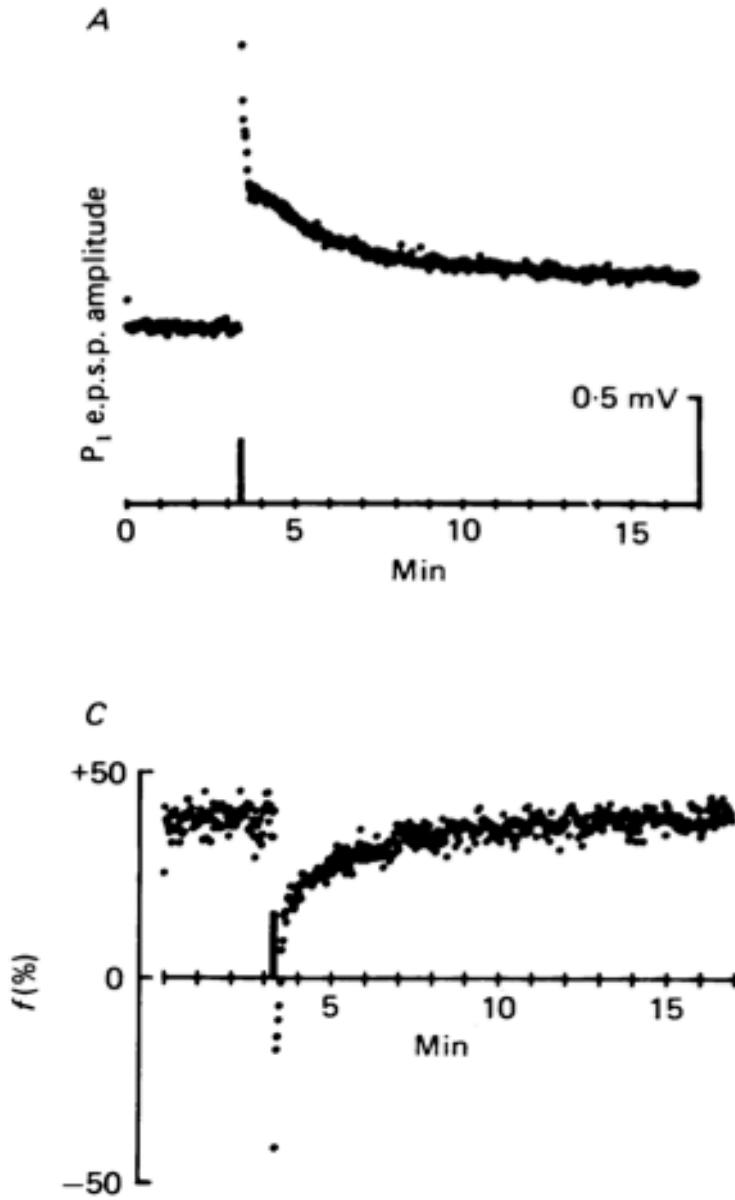
Changes in spontaneous & miniature current amplitudes

Spontaneous vs.
miniature EPSC



sEPSC frequency did not change during the period

No changes in PPF with LTP

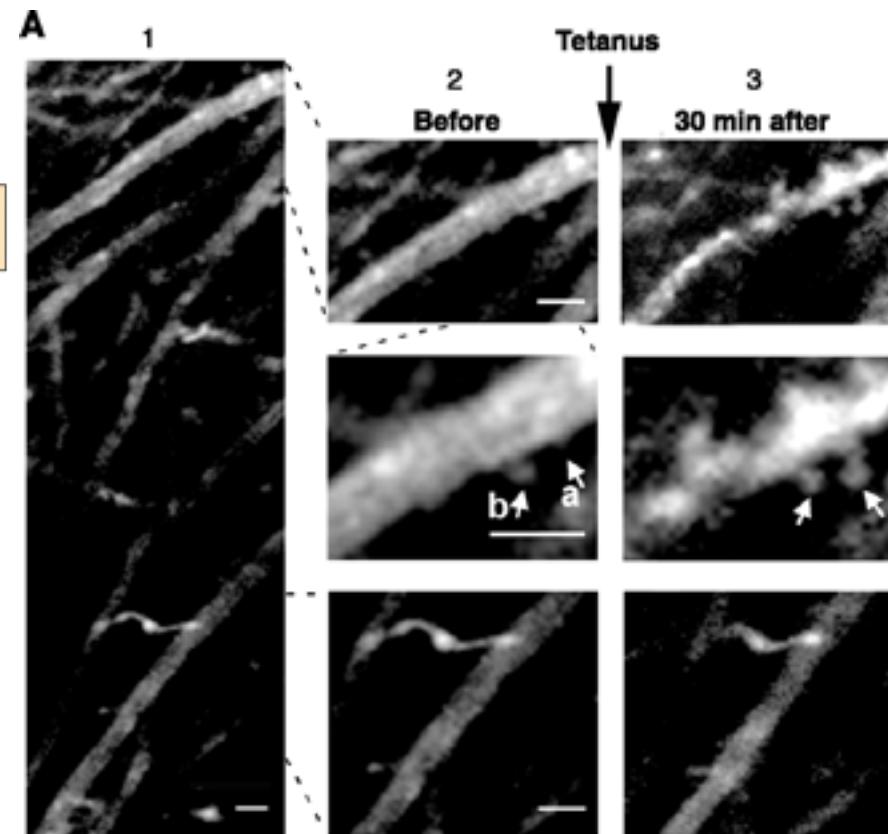
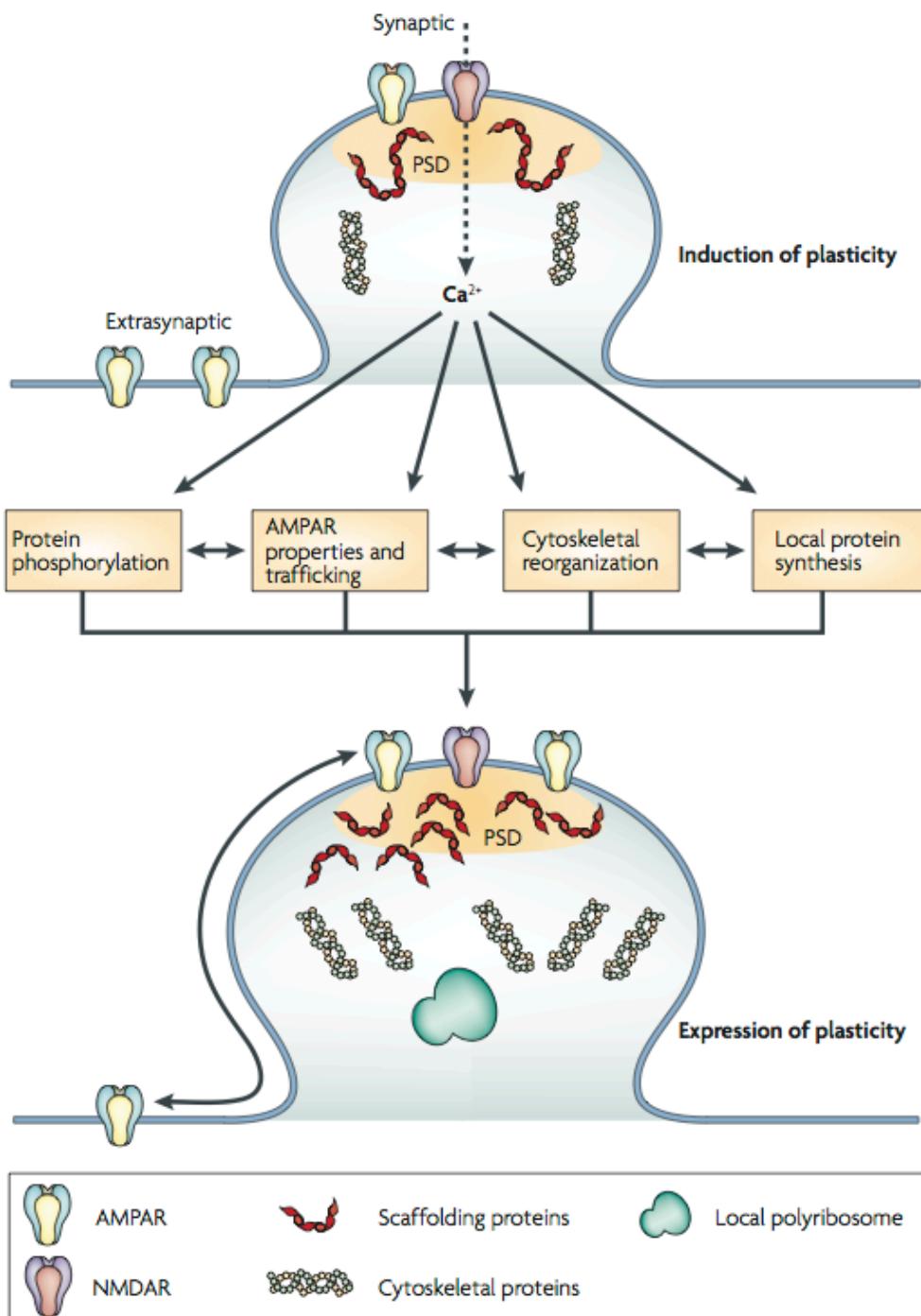


Paired pulse responses measured throughout; IPI: 25 ms.

There are a number of studies showing this, and a number of others that show the absence of changes in quantal content and in transmitter concentration as well.

Direct demonstration of receptor trafficking

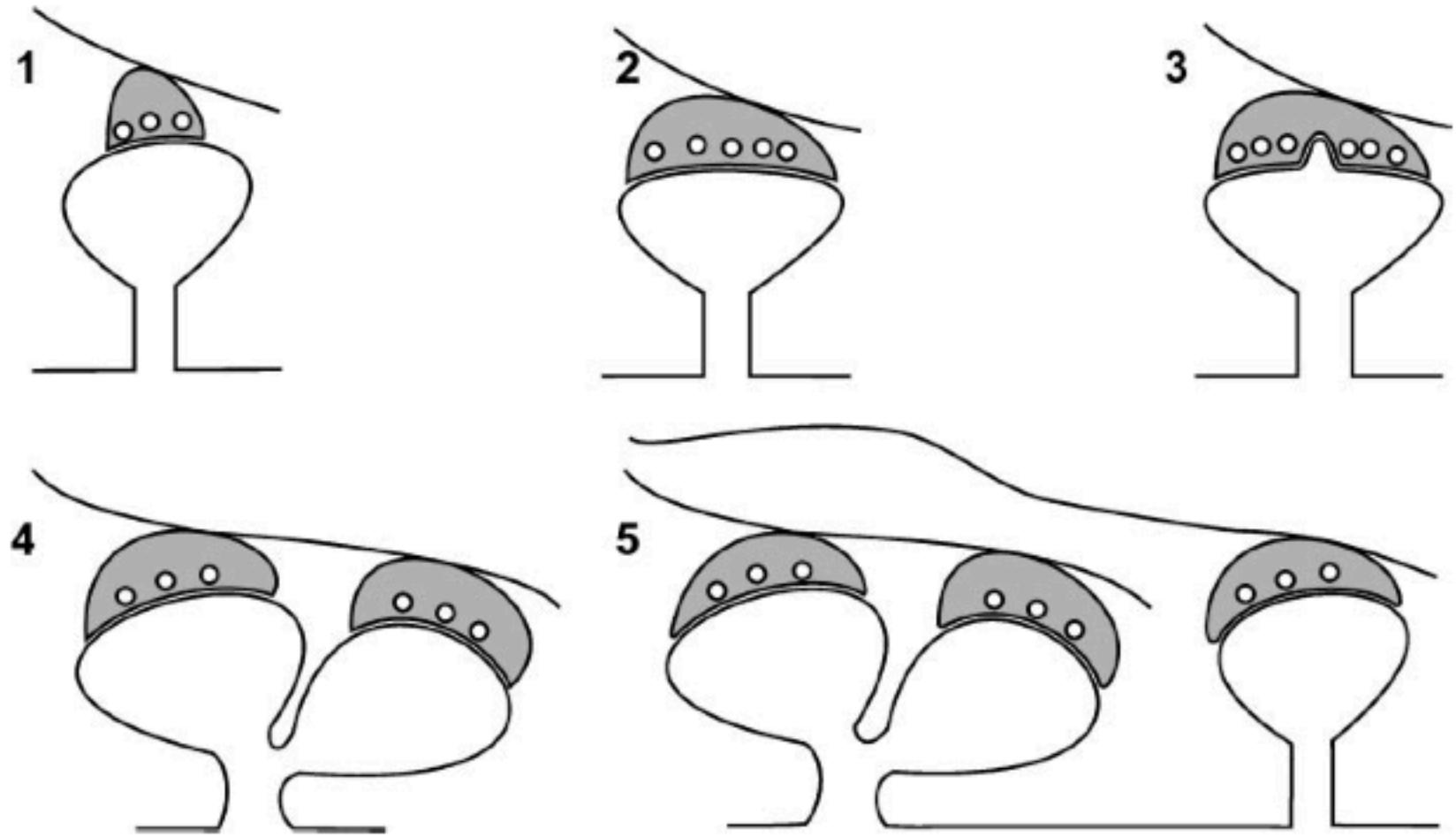
Surface expression of GluR1-GFP assessed with fluorescent immunostaining



Shi et al., Science, 1999

Derkach et al., Nature Reviews Neuroscience, 2007

Changes in spine shapes, and formation of new spines



But, there are accompanying presynaptic changes as well!

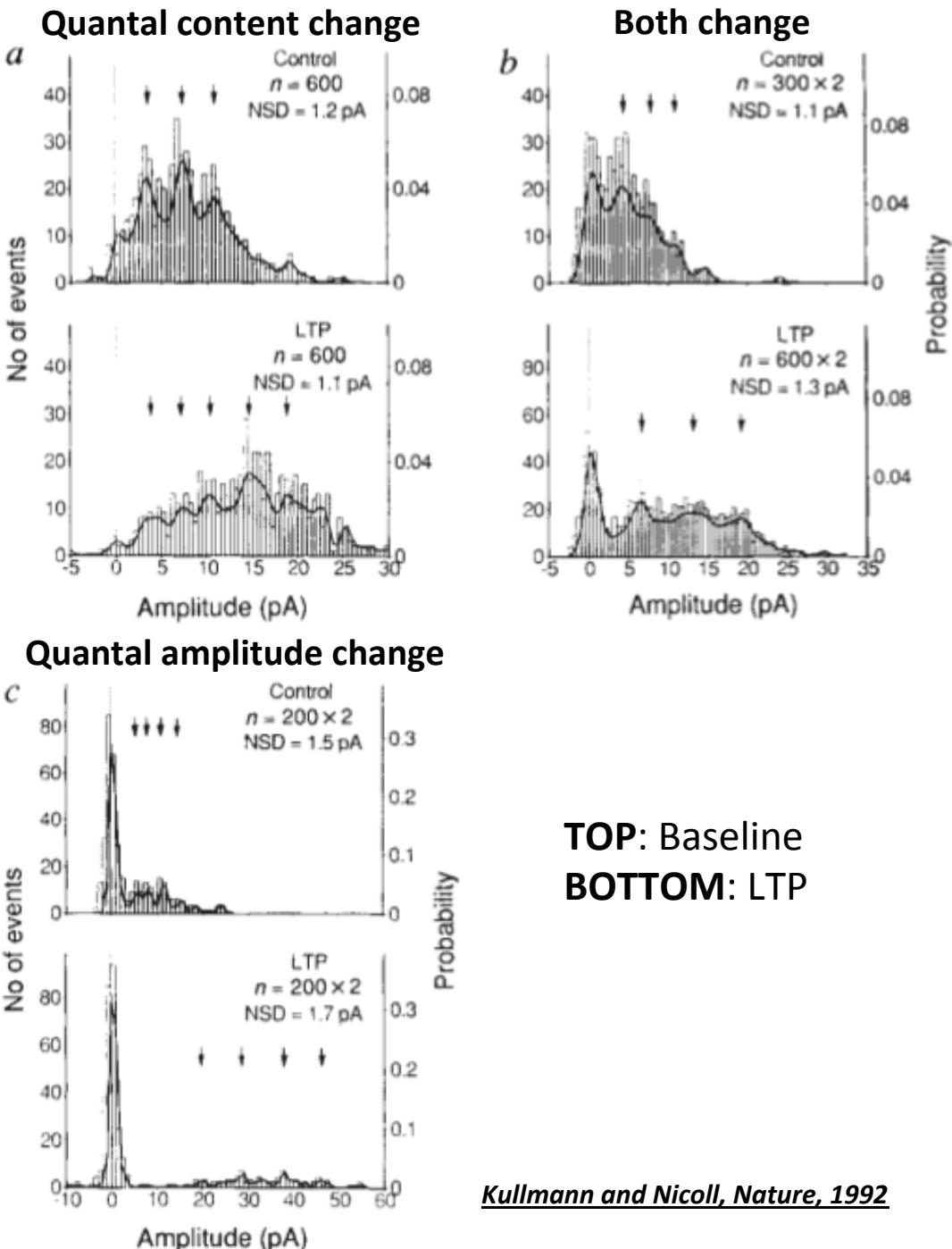
Group 3: Relax, guys, it is both!!

It can be any and all!

So many parameters play a role, including the initial values of quantal parameters!

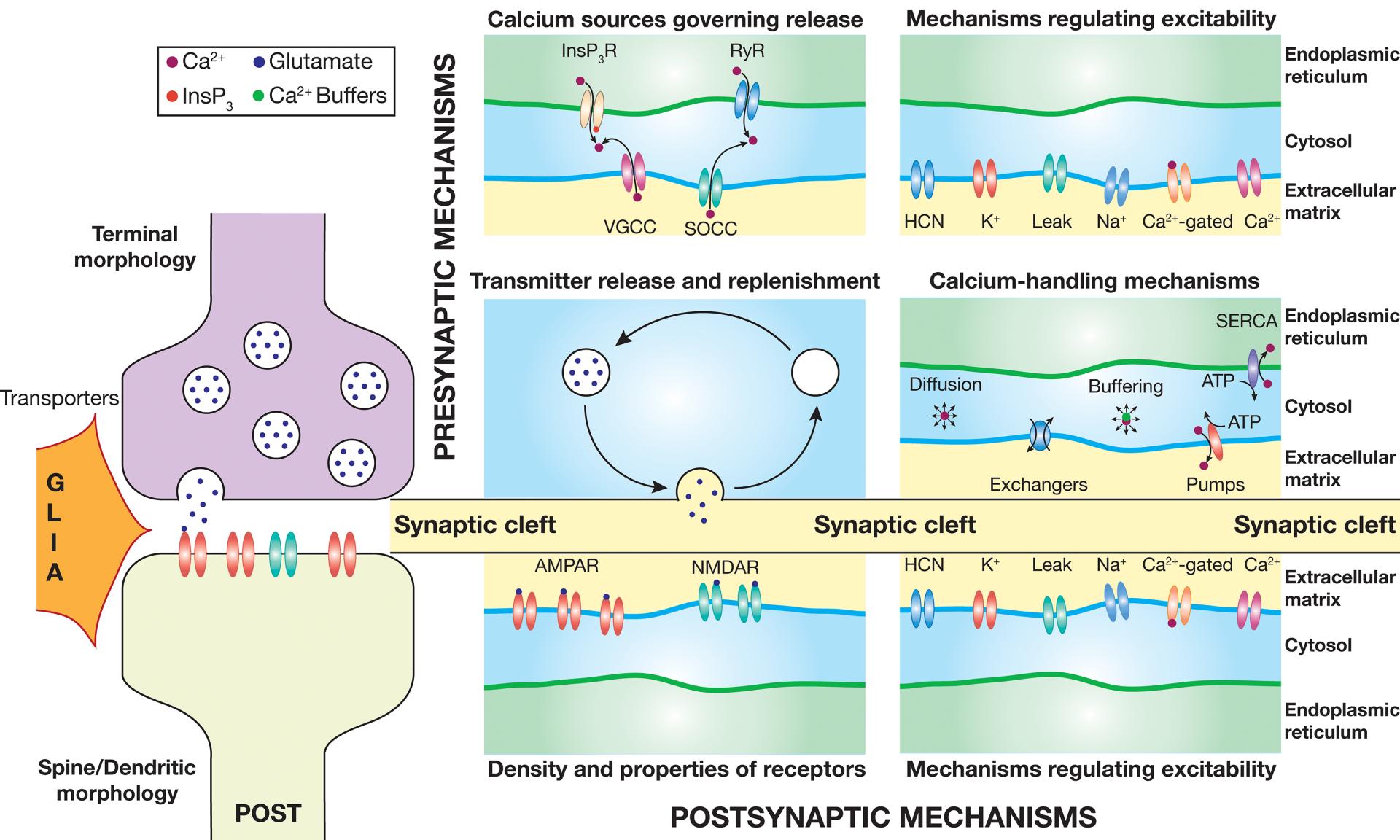
See Larkman et al., Nature, 1992; Liao et al., Neuron, 1992.

Read Lisman, Neuron, 2010, for a nice and short review!



Kullmann and Nicoll, Nature, 1992

Several mechanisms governing expression of synaptic plasticity (both long- and short-term)



What did we learn today??

LTP expression: Pre vs. Post!

The use of (optical or otherwise) quantal analysis in teasing apart pre vs. post in expression of LTP/D! **Remember**: Non-optical quantal analysis is almost impossible in central neurons and their synapses!

C_V and PPF are good measures for assessing presynaptic changes.

AMPAR trafficking and spine shape change postsynaptically!

Expression can be either pre, post, or both — depends on particular synapses, brain region, protocol used, state of the network, neuron and synapse, etc!