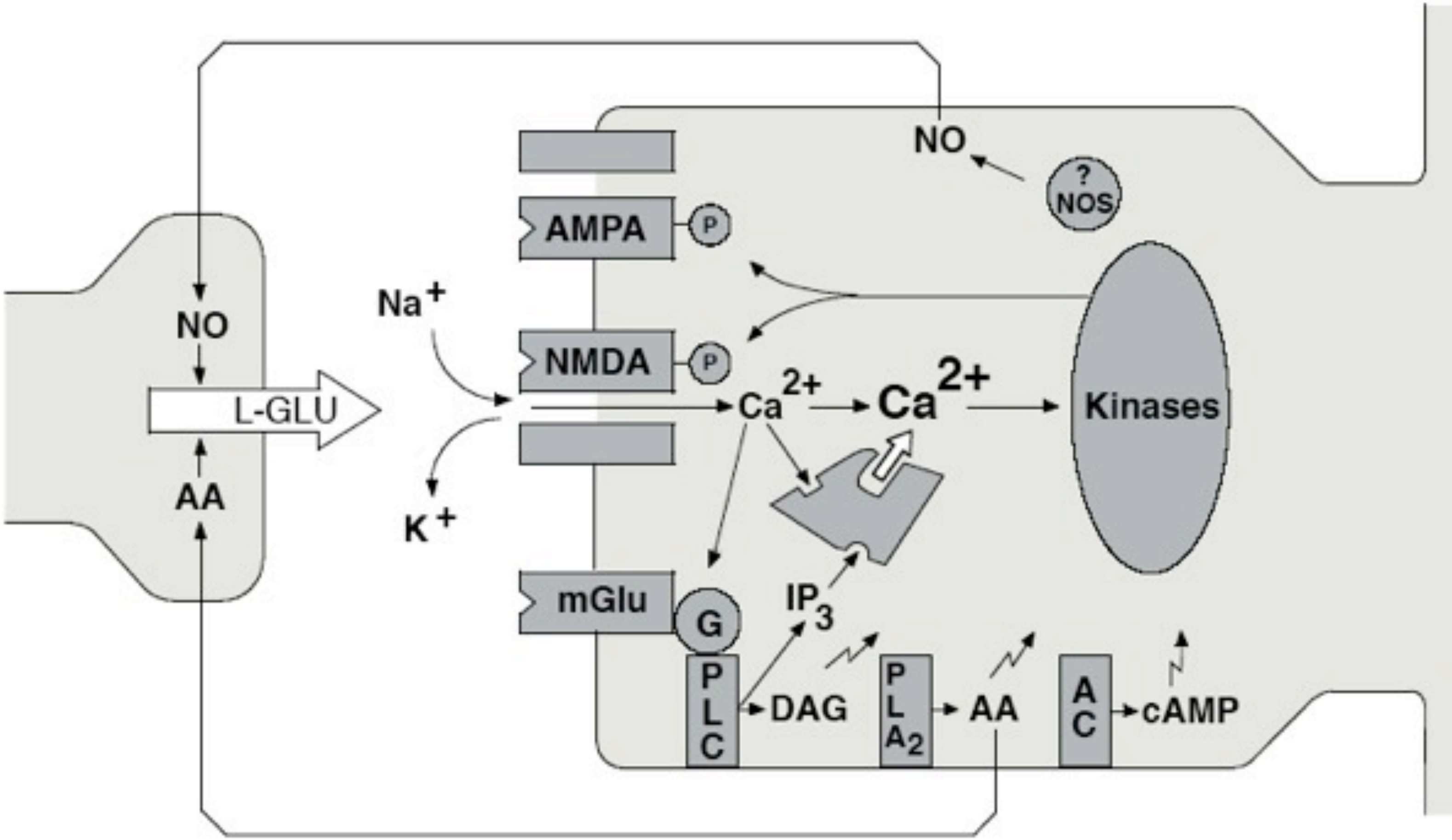
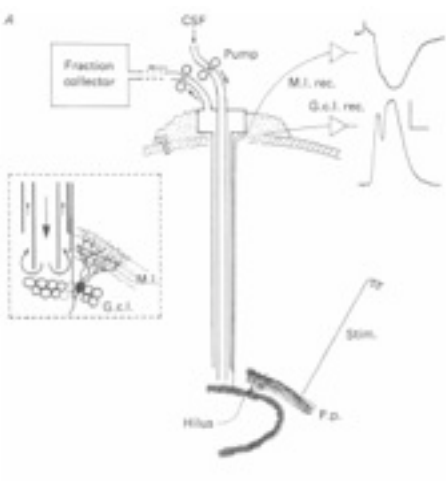
LTP: Presynaptic expression mechanisms

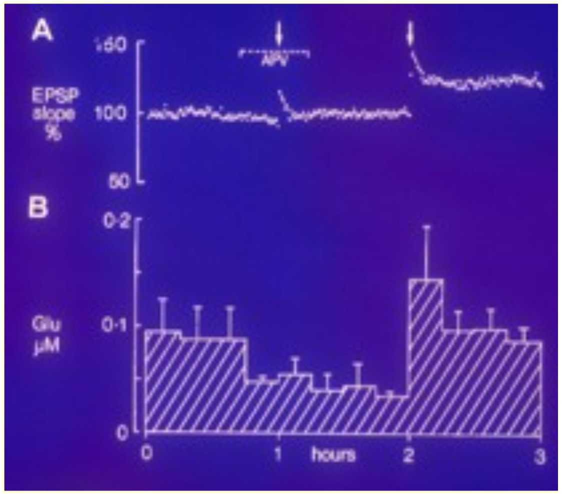
E-LTP expression cartoon



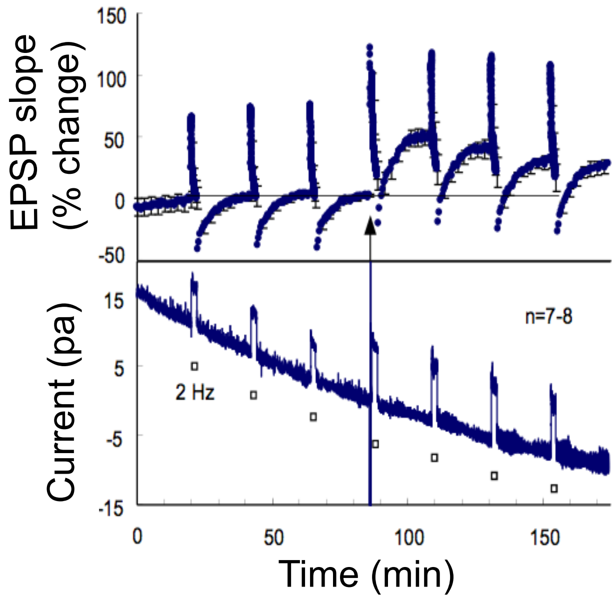
Evidence that LTP involves presynaptic changes

1. Sustained increase in glutamate efflux



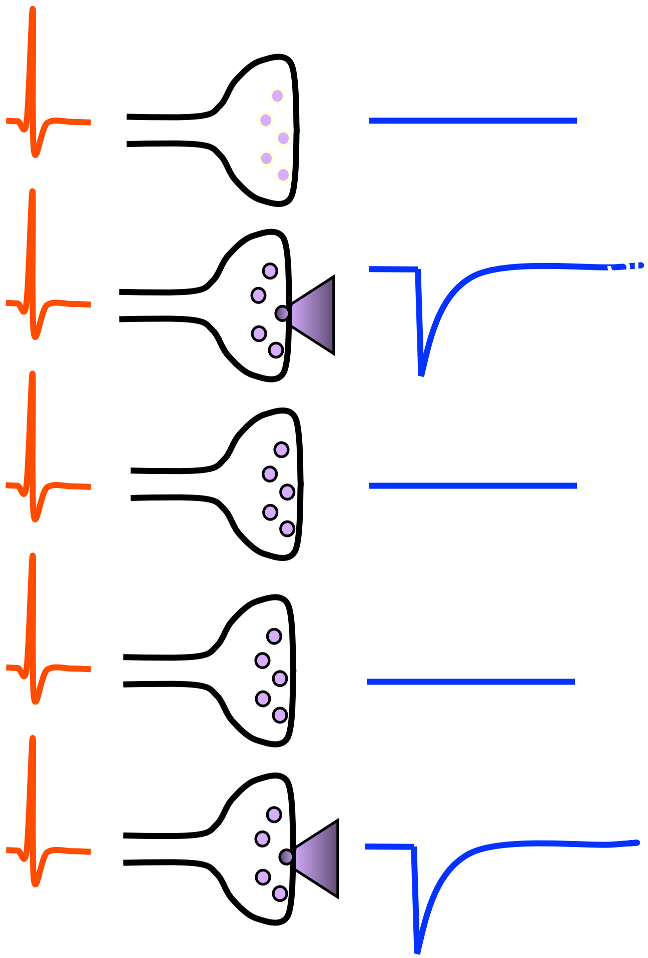


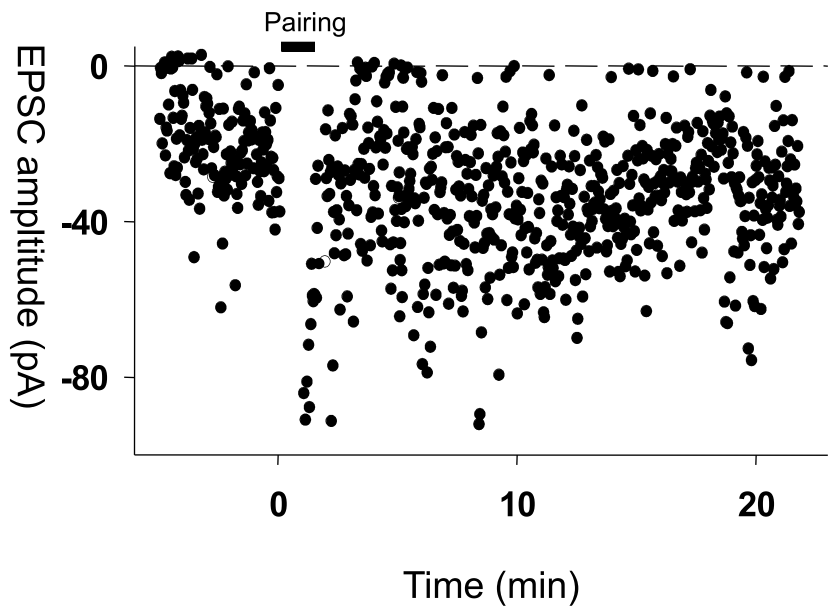
Bliss et al., 1986



Hirano, Bliss et al., unpub

Minimal stimulation analysis to determine failure rate

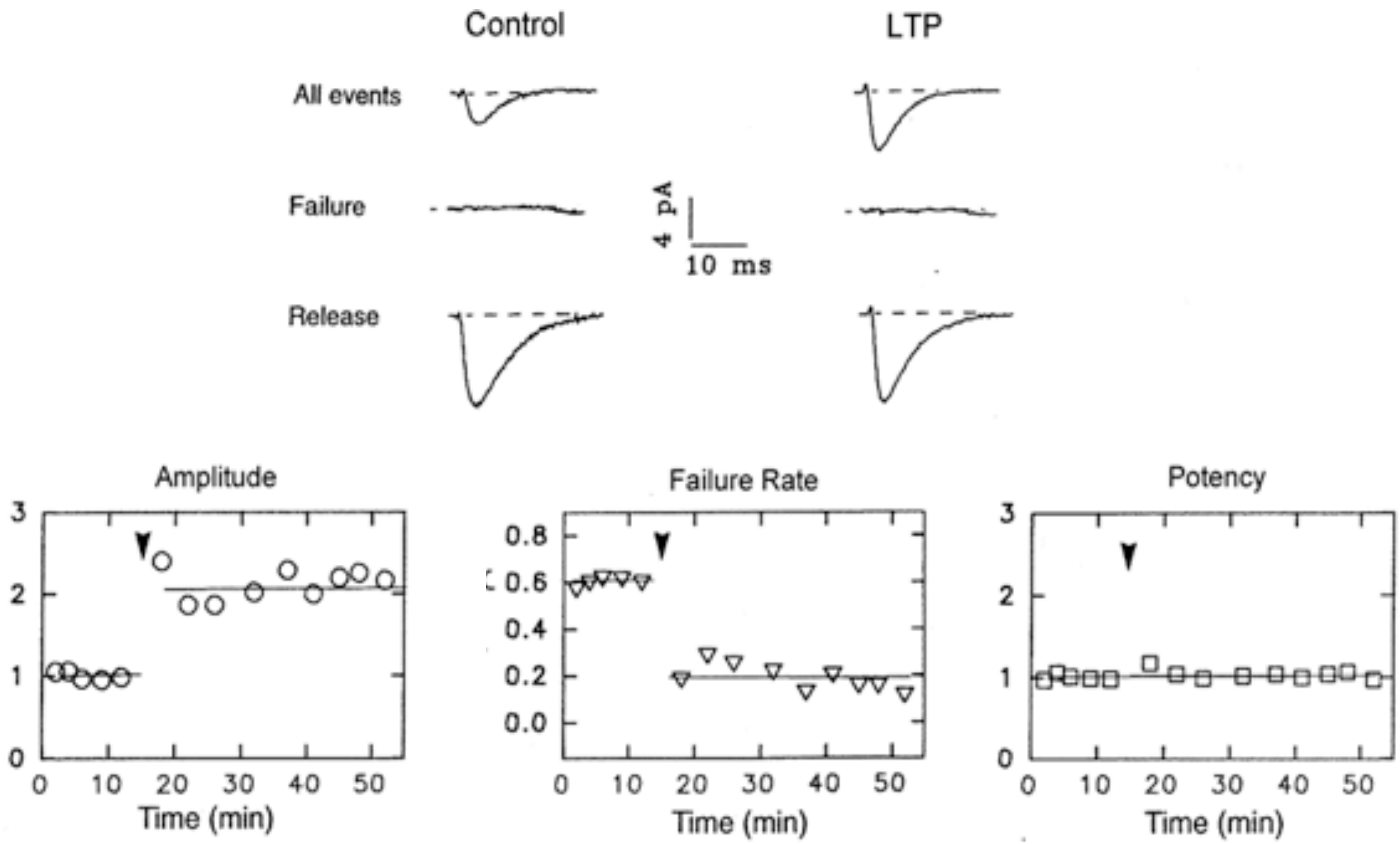




Benke et al., 1998

Evidence that LTP involves presynaptic changes

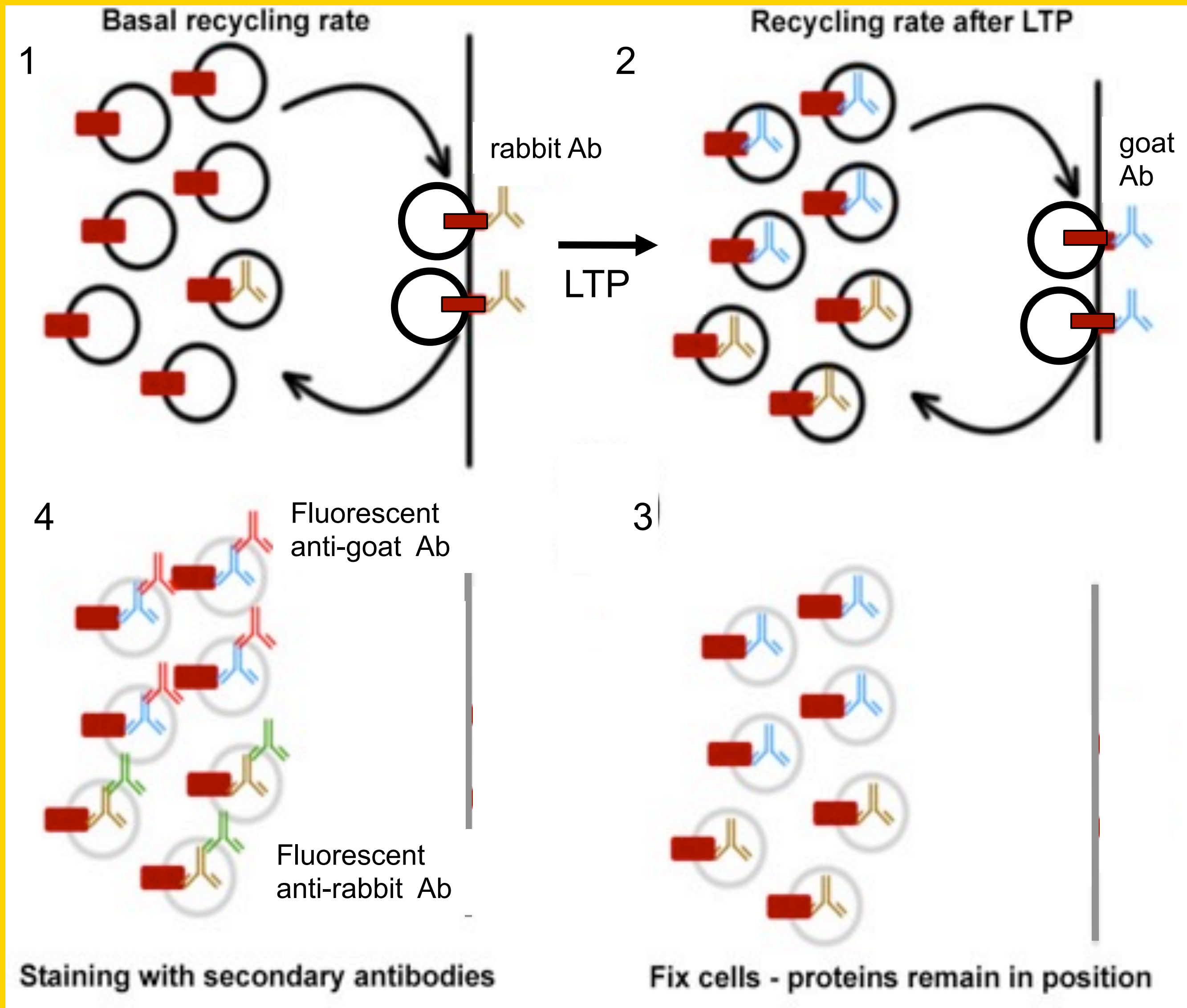
2. LTP can involve a change in failure rate



Stevens & Wang, 1994

Evidence that LTP involves presynaptic changes

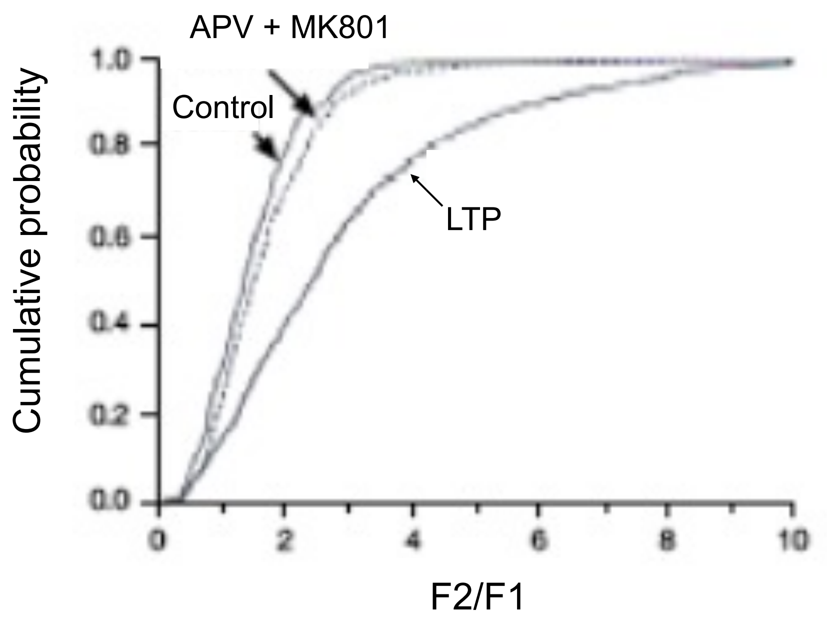
3. LTP involves an increase in vesicle recycling rate



Malgaroli et al., 1995

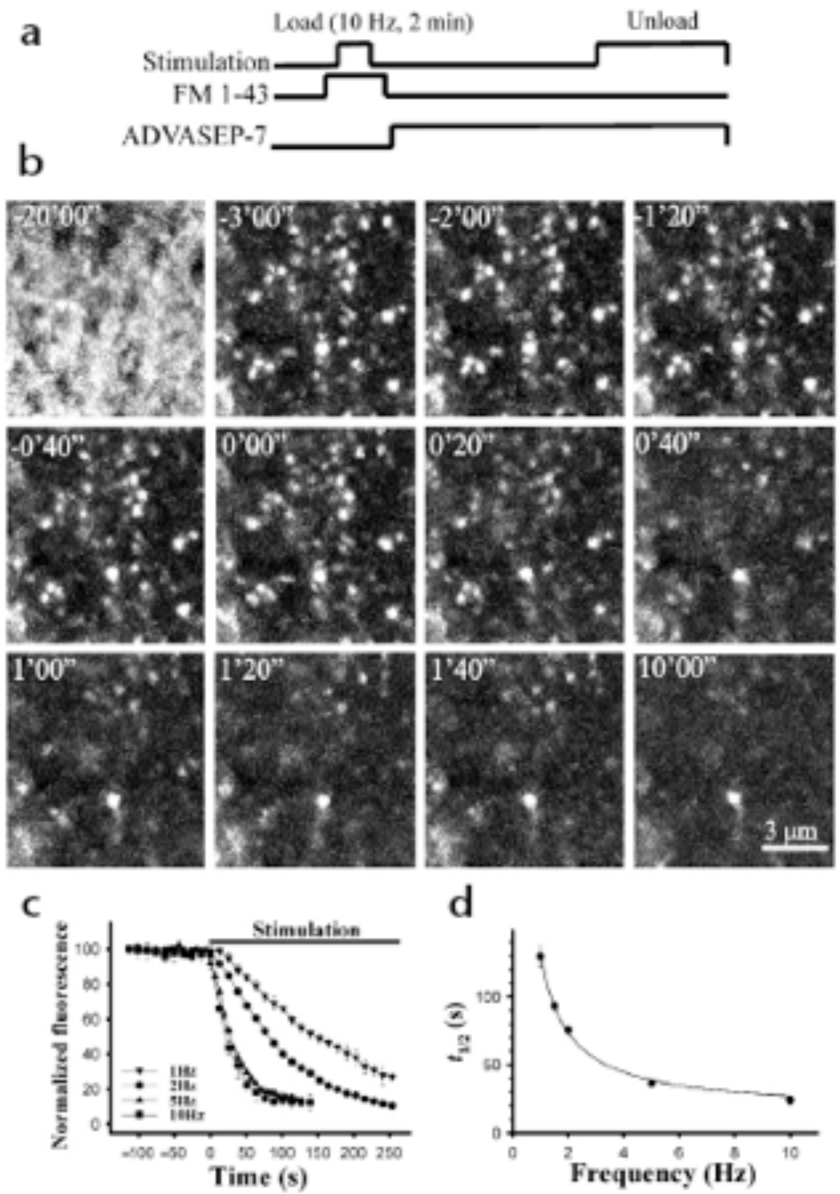
Evidence that LTP involves presynaptic changes

3. LTP involves an increase in vesicle recycling rate



Malgaroli et al., 1995

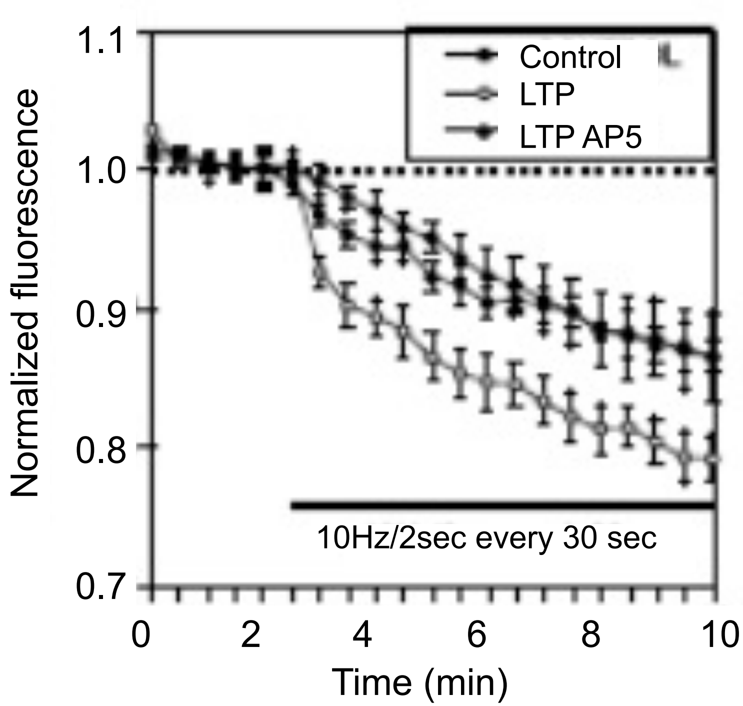
The fluorescent dye FM1-43 can be used to estimate the rate of vesicle fusion



Zakharenko et al., Nature Neurosci.(2001) 4:711-717

Evidence that LTP involves presynaptic changes

3. Increased activity-dependent 'destaining' of FM1-43-loaded terminals

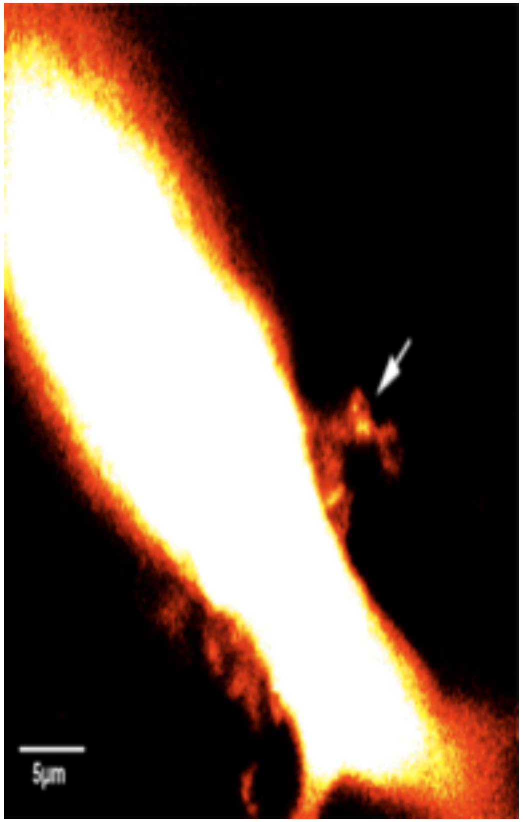


Stanton et al., 2005

Visualising transmission at single synapses using confocal microscopy

Calcium transients in a ‘thorny excrescence’

... and in a
simple spine



CA3 pyramidal cell proximal dendrite

Calcium transients in a ‘thorny excrescence’

... and in a
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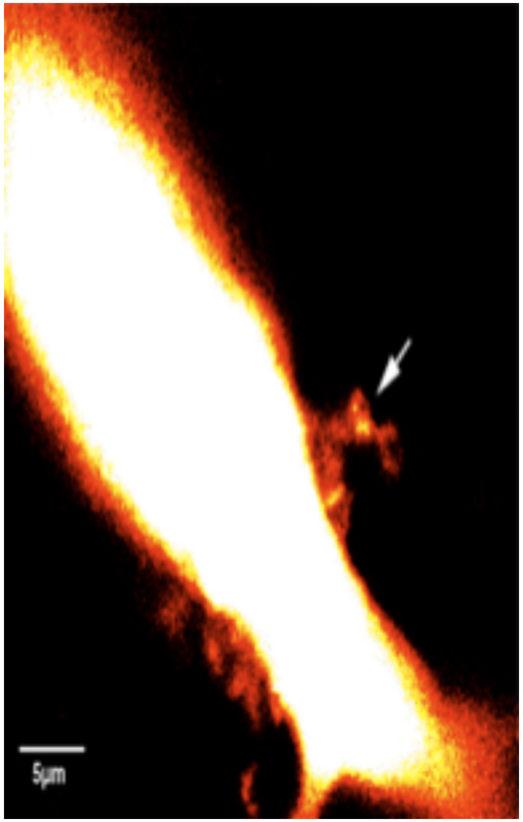
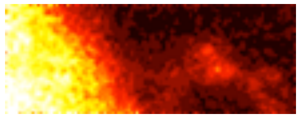
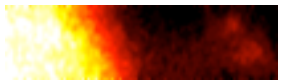
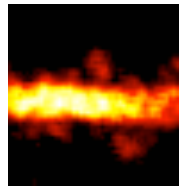


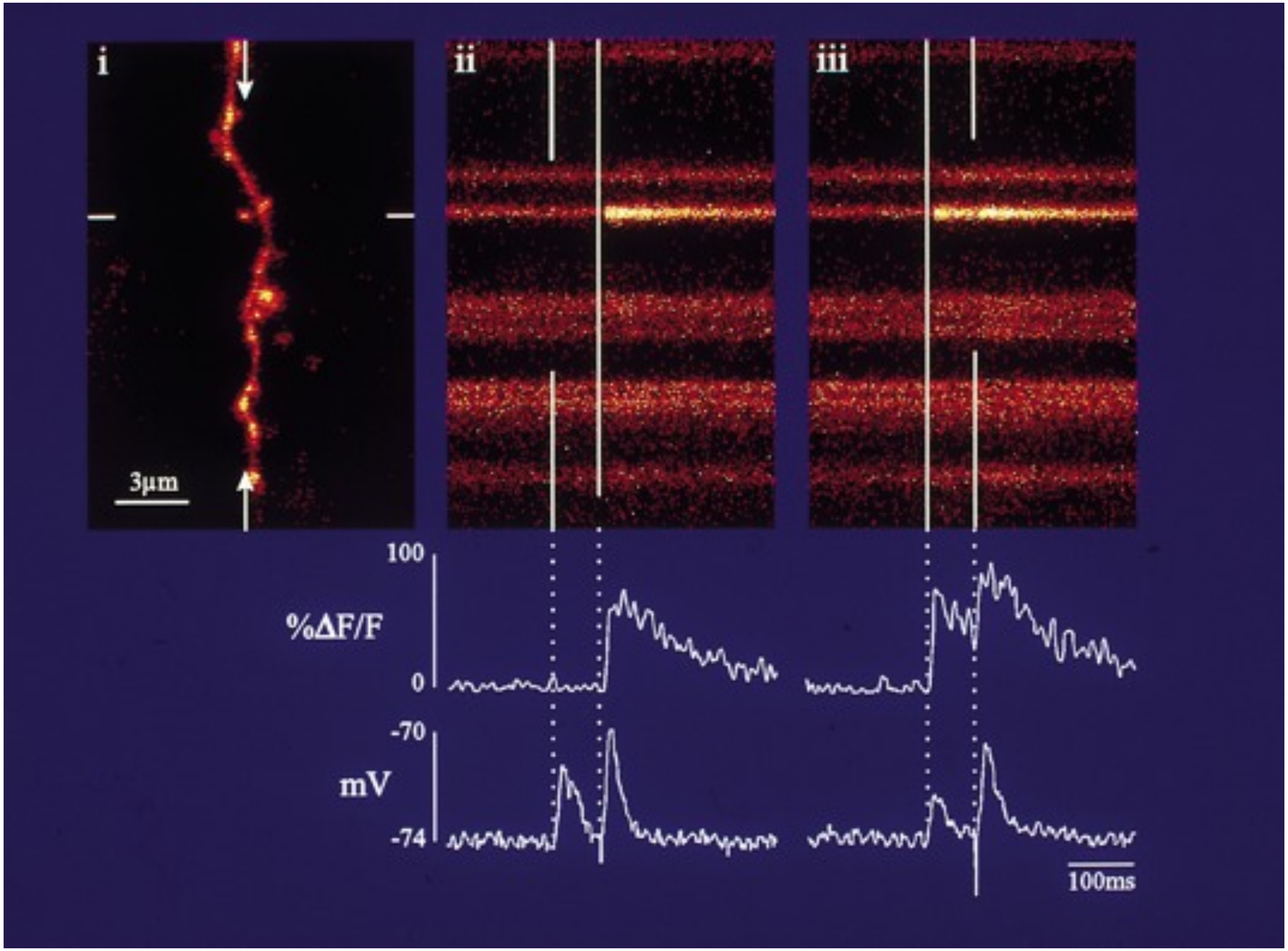






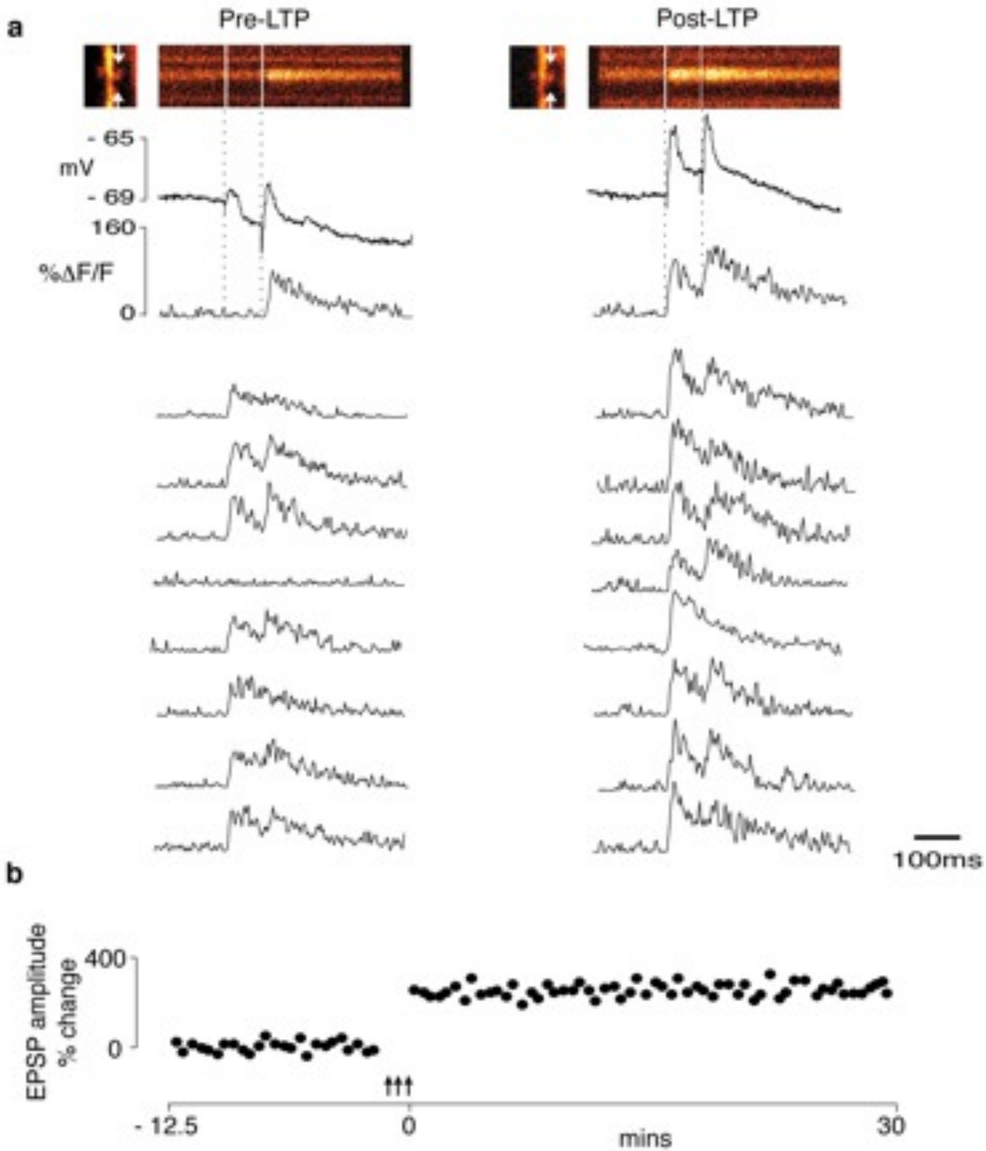
CA3 pyramidal cell proximal dendrite

The probability of release at a single synapse can be estimated by confocal microscopy in line scan mode

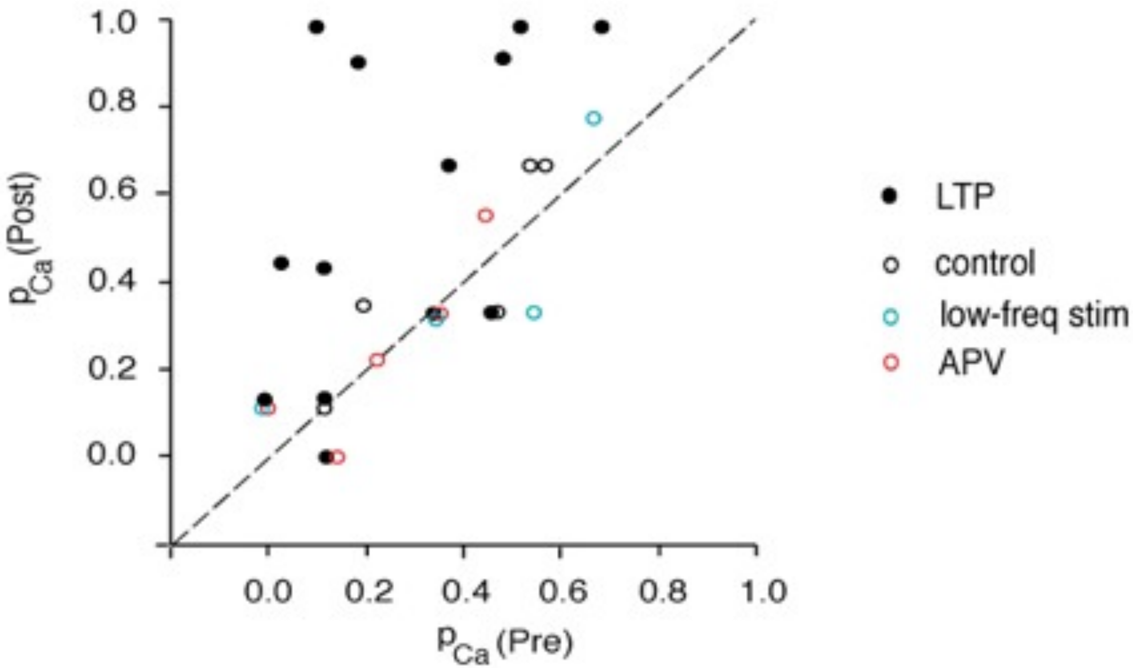


Emptage et al., 2003

Optical quantal analysis of LTP at a single synapse



Increase in p_{Ca} at single synapses 30 min after induction of LTP



Emptage et al., 2003

State-dependent LTP of hippocampal synapses

$$\text{Silent} \xrightarrow{\text{LTP1}} \text{unmasked (active)} \xrightarrow{\text{LTP2}} \text{potentiated}$$

p_1 $\qquad$ p_1 $\qquad$ $p_2 > p_1$

Ward et al., 2006

- Is LTP analog or digital?
- Bidirectional changes in P_{Ca}?

Don Dixon, Alan Fine

A digital brain: does it matter?

Number of hippocampal neurons 10^7

Number of synapses per neuron 10^4

Number of synapses 10^{11}

Number of possible memories $2^{10^{11}} = (2^{10})^{10^{10}} > 10^{10^{10}}$

A digital brain: does it matter?

Number of neurons in hippocampus 10^7

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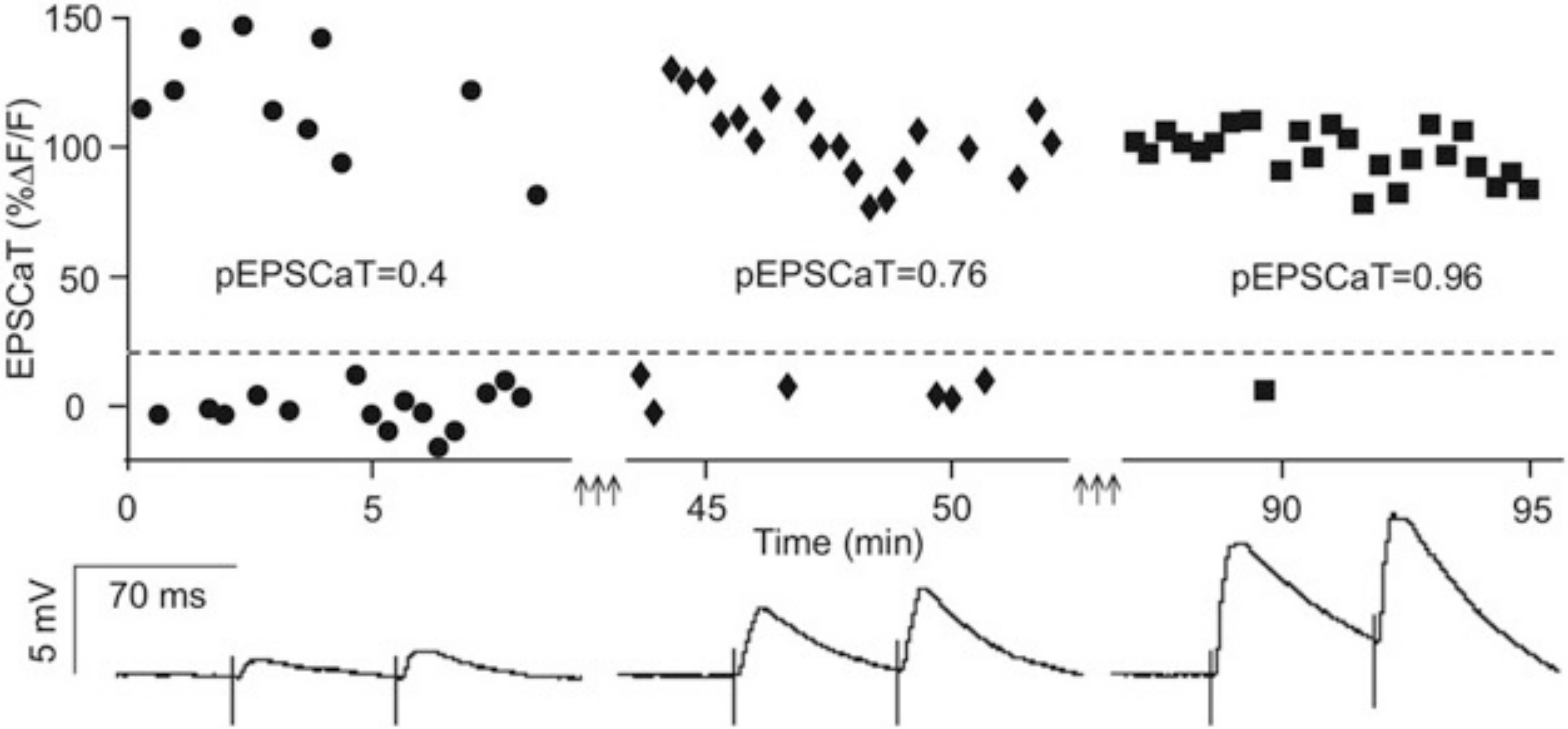
Number of synapses 10^{11}

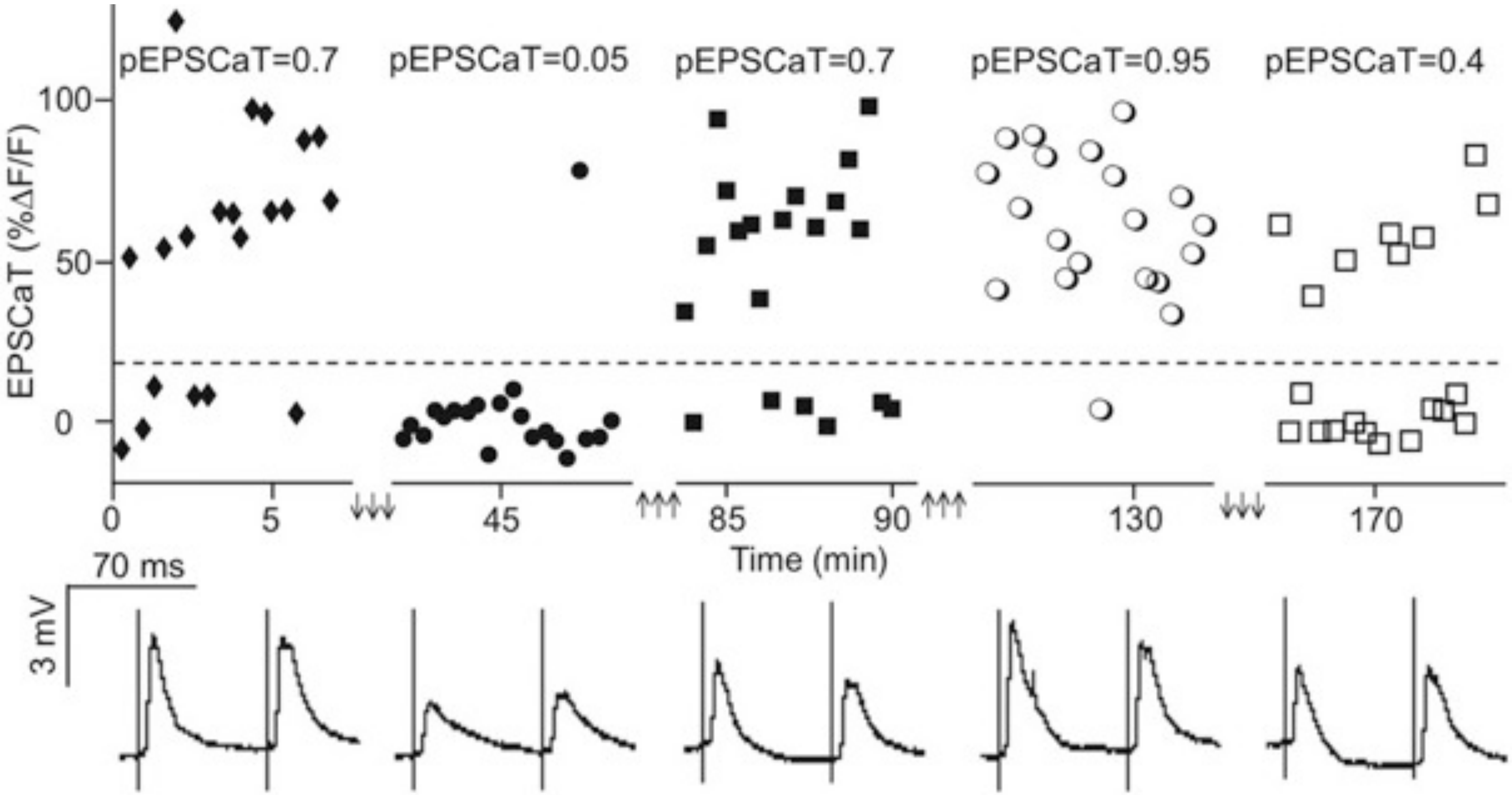
Number of possible memories $2^{10^{11}} = (2^{10})^{10^{10}} > 10^{10^{10}}$

Number of particles in the universe $10^{88} < 10^{100} = 10^{10^2}$

Incremental LTP at a single hippocampal synapse



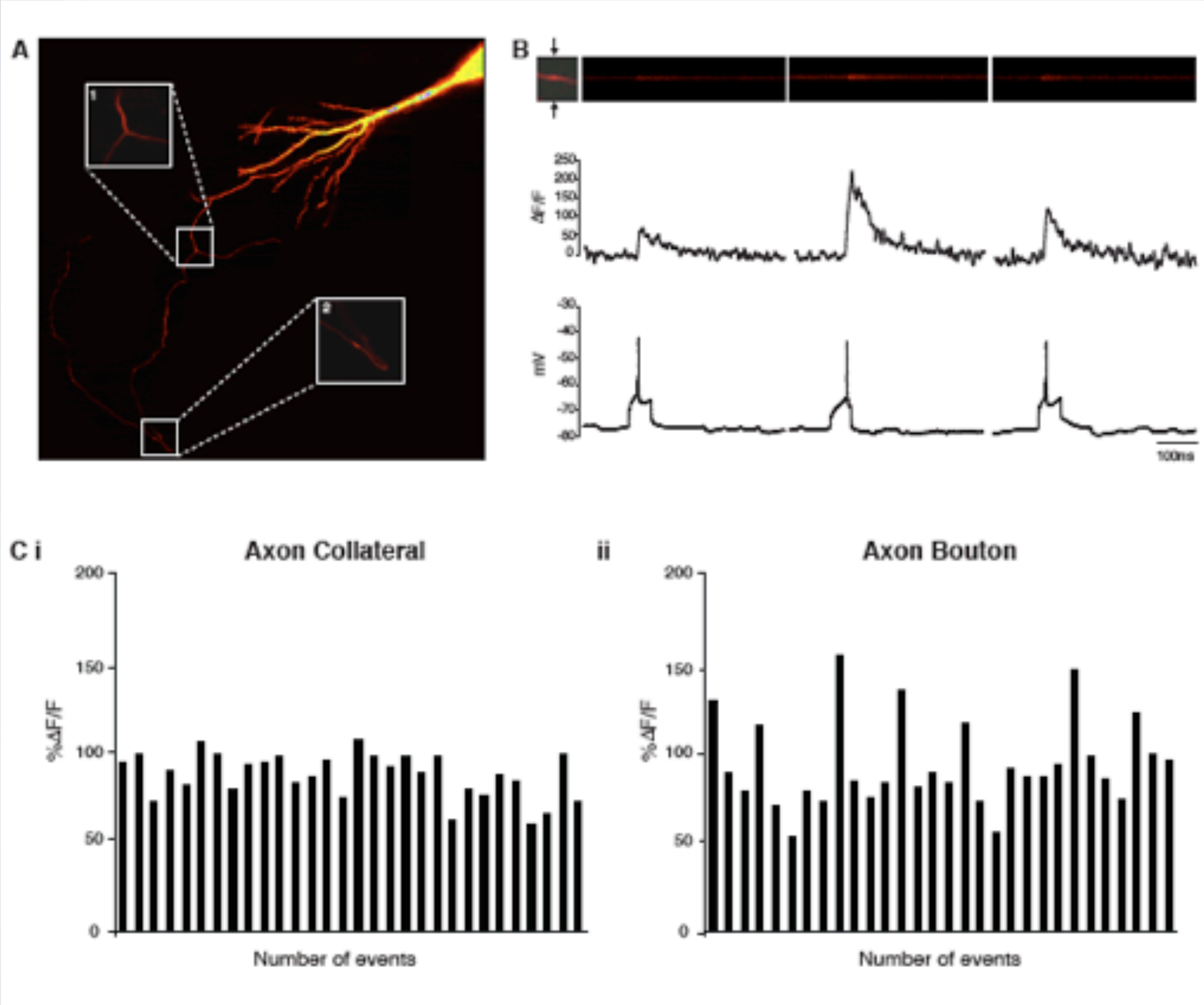
Bidirectional plasticity at a single hippocampal synapses



See Enoki et al., 2009

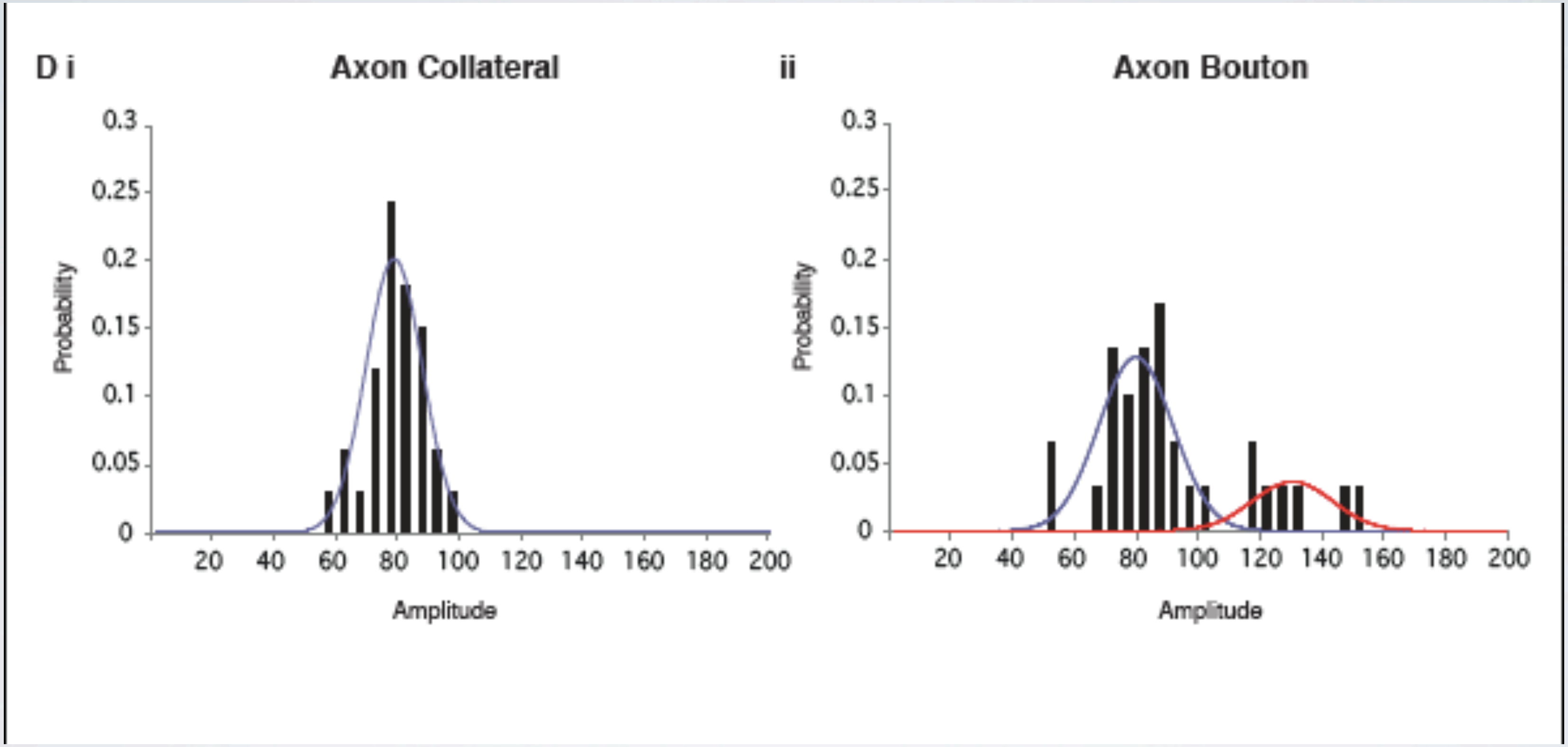
An alternative method of detecting transmitter release, and hence of estimating the probability of release p(r) ......

Calcium transients at presynaptic boutons

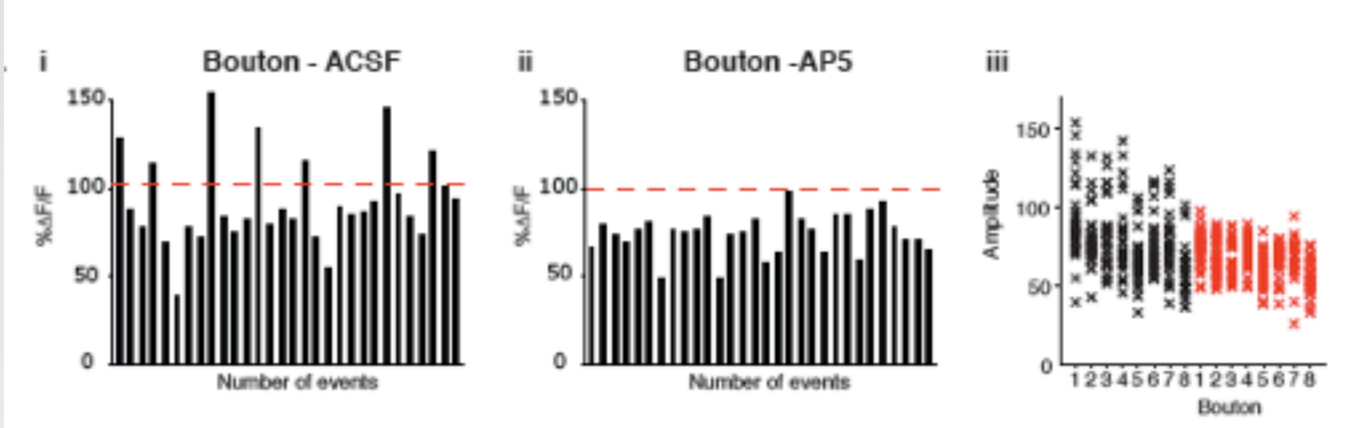


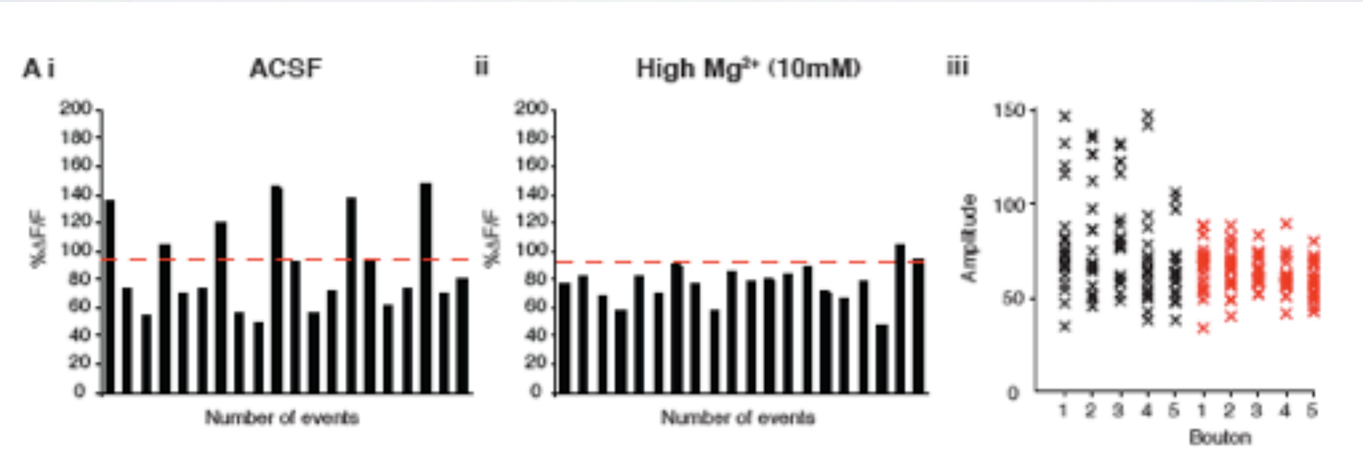
McGuiness et al., Neuron in press

Bimodal distribution of Ca transients in boutons but not in axons

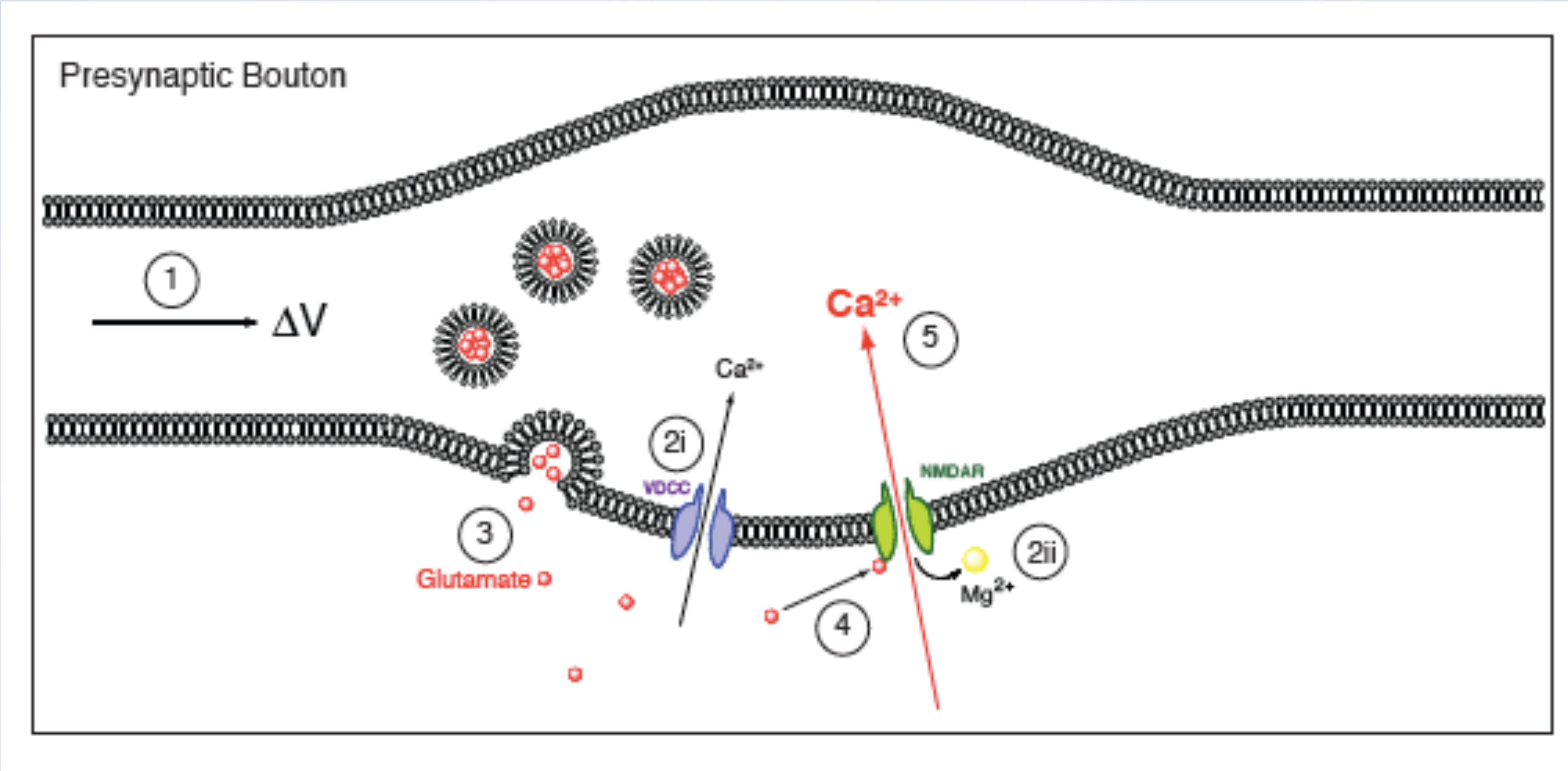


Large Ca^{2+} transients are blocked by AP5 and high Mg^{2+} ....

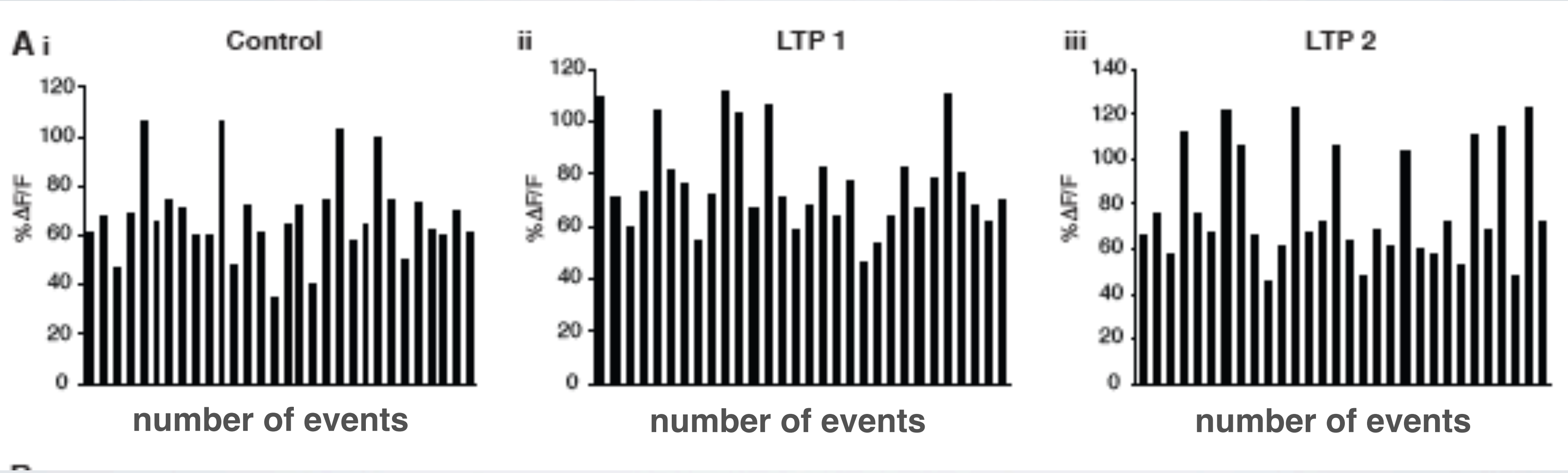


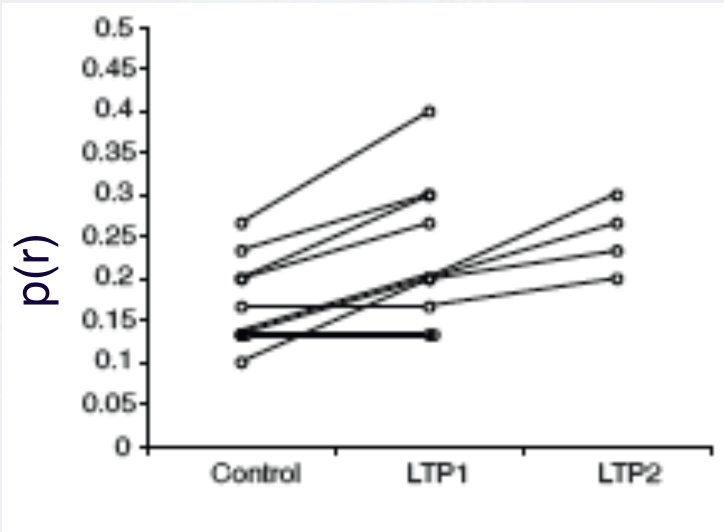


... indicating that they are NMDA receptor-mediated



After LTP-inducing stimulation, p(r) at the imaged bouton, as estimated by the proportion of large responses, is increased





If you were a postsynaptic sceptic what holes could you pick in these experiments?

How could you demonstrate a presynaptic component to LTP more convincingly?

Ahmed, M.S. and Siegelbaum, S.A. (2009) Recruitment of N-Type Ca^{2+} channels during LTP enhances low release efficacy of hippocampal CA1 perforant path synapses. Neuron 63:372-385

Benke, T., Lüthe, A., Isaac, J. T. R., and Collingridge, G. L. (1998). Modulation of AMPA receptor unitary conductance by synaptic activity. Nature *393*, 793-797.

Bliss, T. V. P., Douglas, R. M., Errington, M. L., and Lynch, M. A. (1986). Correlation between long-term potentiation and release of endogenous amino acids from dentate gyrus of anaesthetized rats. J Physiol *377*, 391-408.

Dolphin, A. C., Errington, M. L., and Bliss, T. V. (1982). Long-term potentiation of the perforant path in vivo is associated with increased glutamate release. Nature *297*, 496-498.

Emptage, N. J., Reid, C. A., Fine, A., and Bliss, T. V. P. (2003). Optical quantal analysis reveals a presynaptic component of LTP at hippocampal Schaffer-associational synapses. Neuron *38*, 797-804.

Enoki, R., Hu, Y. L., Hamilton, D., and Fine, A. (2009). Expression of long-term plasticity at individual synapses in hippocampus is graded, bidirectional, and mainly presynaptic: optical quantal analysis. Neuron *62*, 242-253.

Malgaroli, A., Ting, A. E., Wendland, B., Bergamascht, A., Villa, A., Tsien, R. W., and Scheller, R. H. (1995). Presynaptic component of long-term potentiation visualized at individual hippocampal synapses. Science *268*, 1624-1628.

Stanton, P. K., Winterer, J., Zhang, X. L., and Muller, W. (2005). Imaging LTP of presynaptic release of FM1-43 from the rapidly recycling vesicle pool of Schaffer collateral-CA1 synapses in rat hippocampal slices. EurJ Neurosci *22*, 2451-2461.

Stevens, C. F., and Wang, Y. (1994). Changes in reliability of synaptic function as a mechanism for plasticity. Nature *371*, 704-707.

Reviews:

Bliss, T.V.P. and Collingridge, G.L. (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31-39.

Bliss, T.V.P, Collingridge, G.L and Morris, R.G.M. Synaptic plasticity in the hippocampus (2007). In The Hippocampus Book, edited by Andersen, P., Morris, R.G.M., Amaral, D., Bliss, T.V.P., O'Keefe, J., Oxford University Press. Pp 343-474

Lisman, J.E. (2009). The pre/post LTP debate. Neuron 63:281-284.

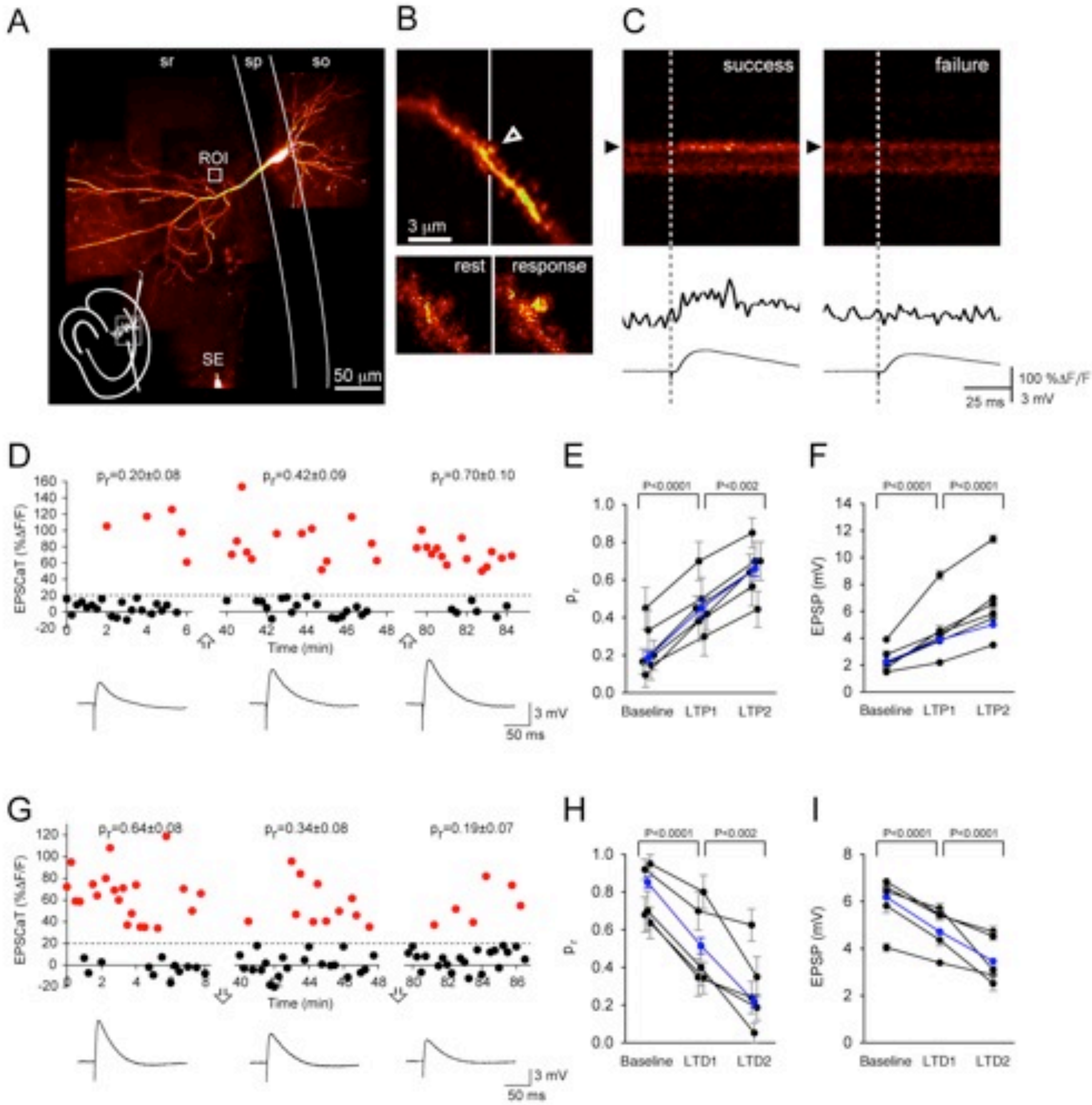
Is information storage (long-term plasticity) at individual synapses:

1) **digital (all-or-none) or analog (graded, incremental) ?**

[Petersen, Malenka, Nicoll & Hopfield (1998) PNAS USA 95:4732]

2) **unidirectional or bidirectional?**

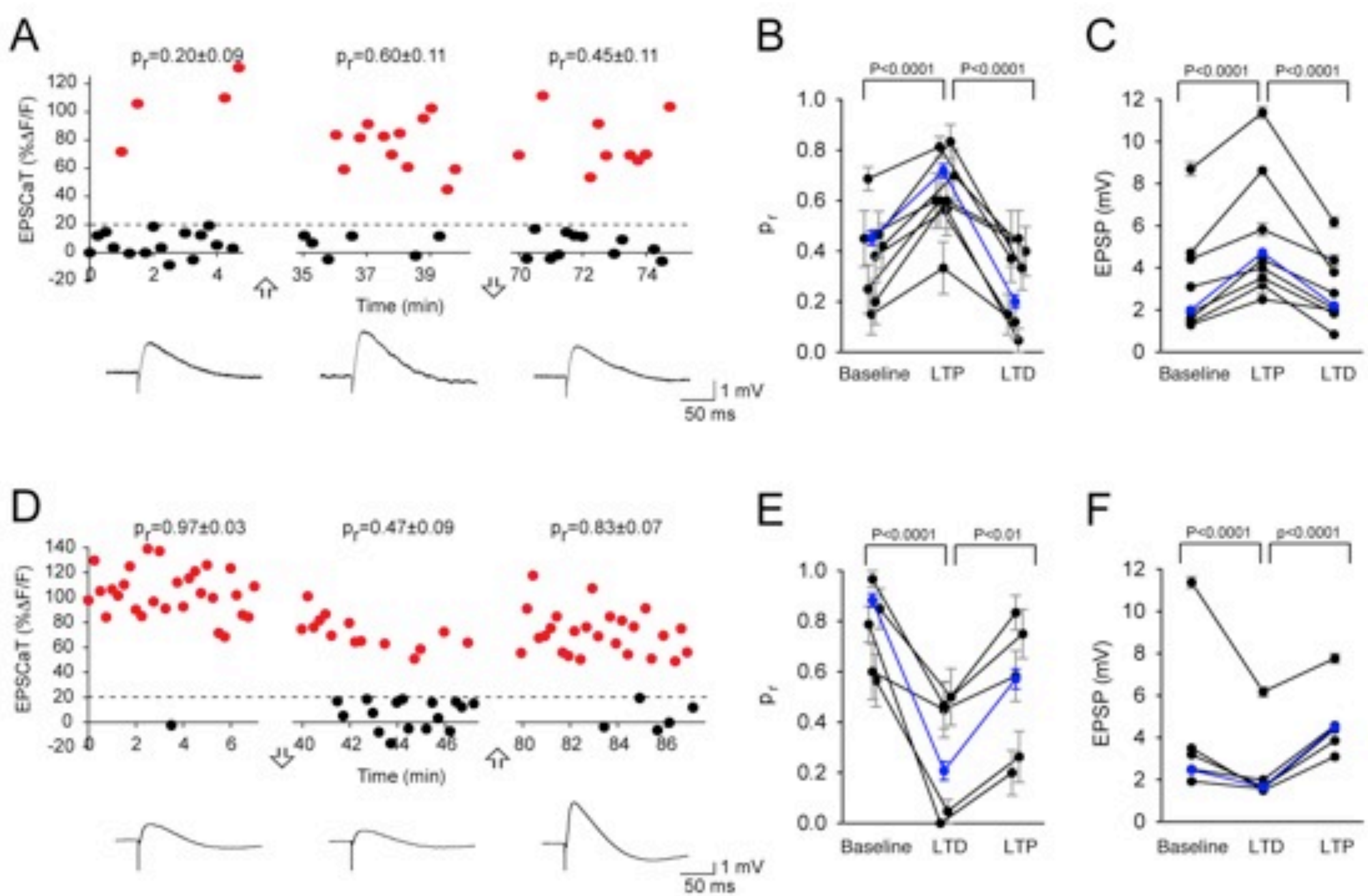
Imaging *incremental* LTP & LTD



Enoki et al. 2009 Neuron *62*: 242-253

Wed, 20 Oct 2010

Imaging *bidirectional* LTP & LTD



Enoki et al. 2009 Neuron *62*: 242-253

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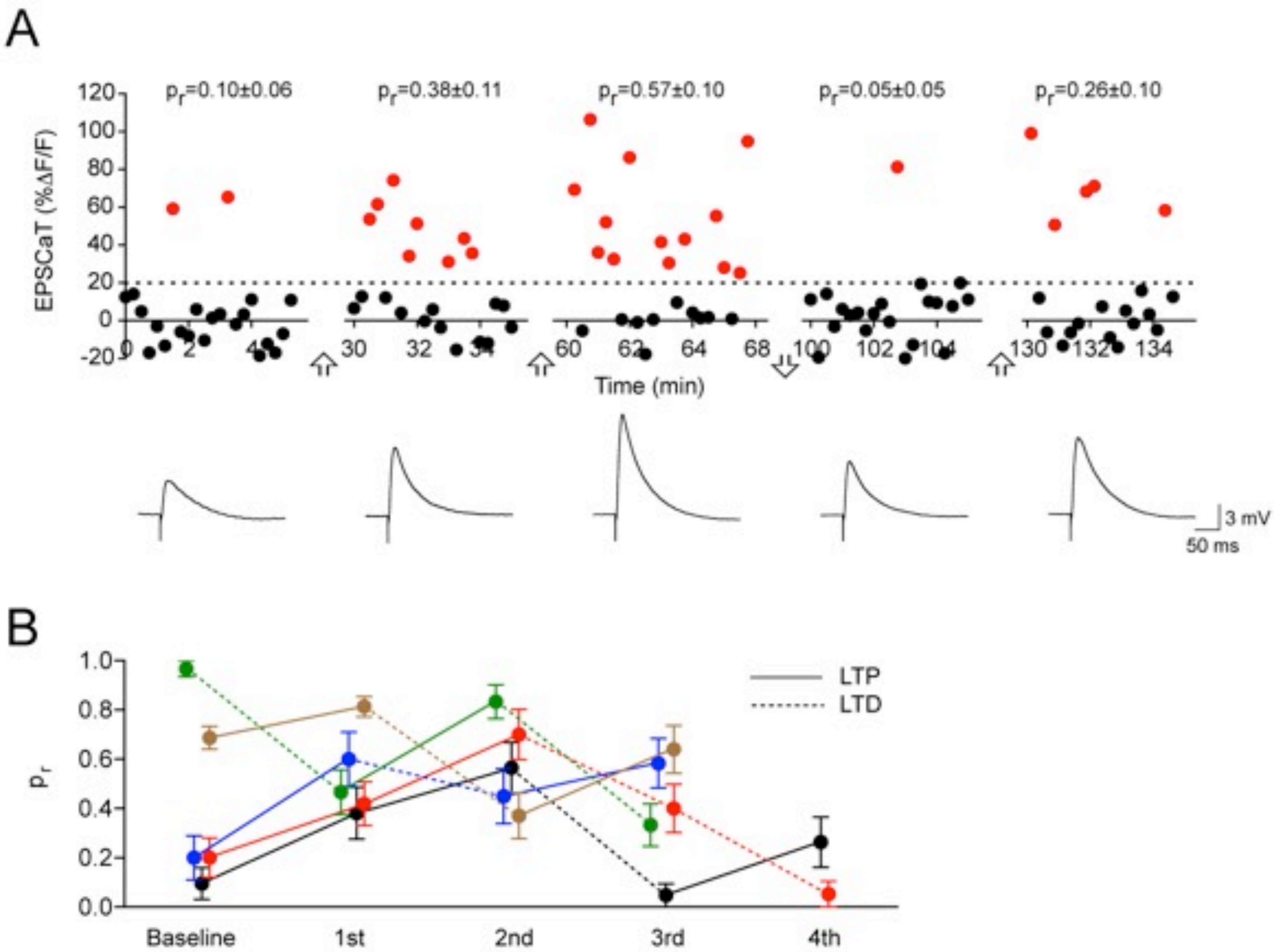
The strength of individual synapses can be modulated bidirectionally, in multiple increments, over a wide range



Enoki et al. 2009 Neuron *62*: 242-253

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How much do changes in

synaptic potency (q; mainly postsynaptic)

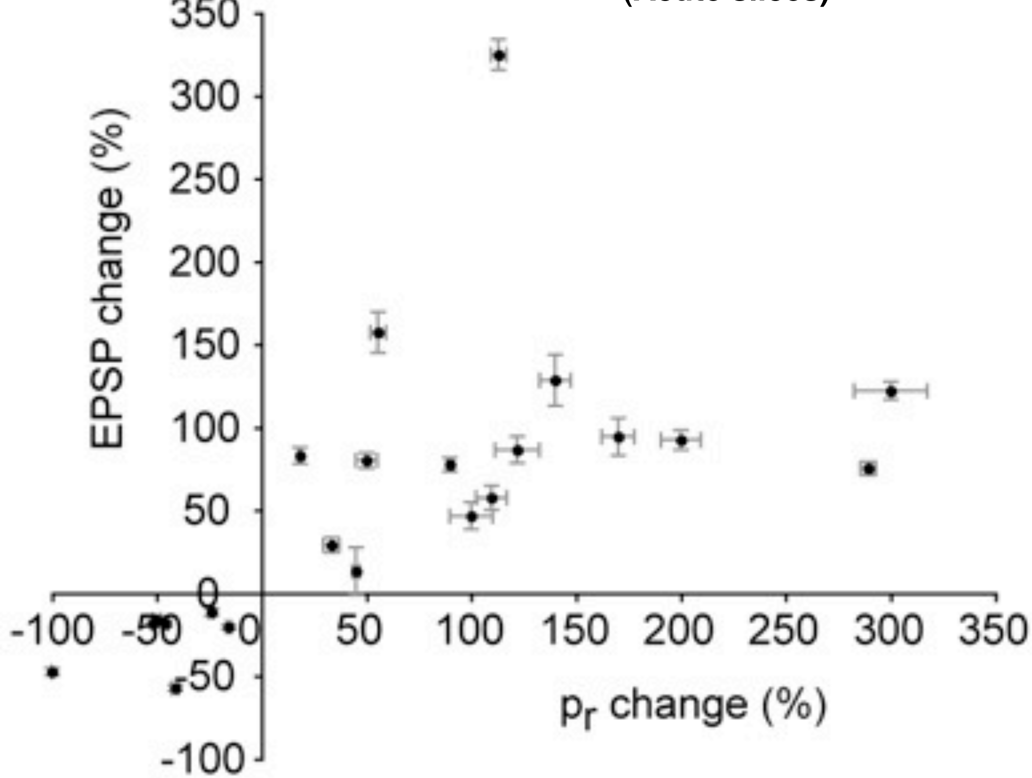
vs.

synaptic reliability (n,p; presynaptic)

contribute to the expression of LTP and LTD?

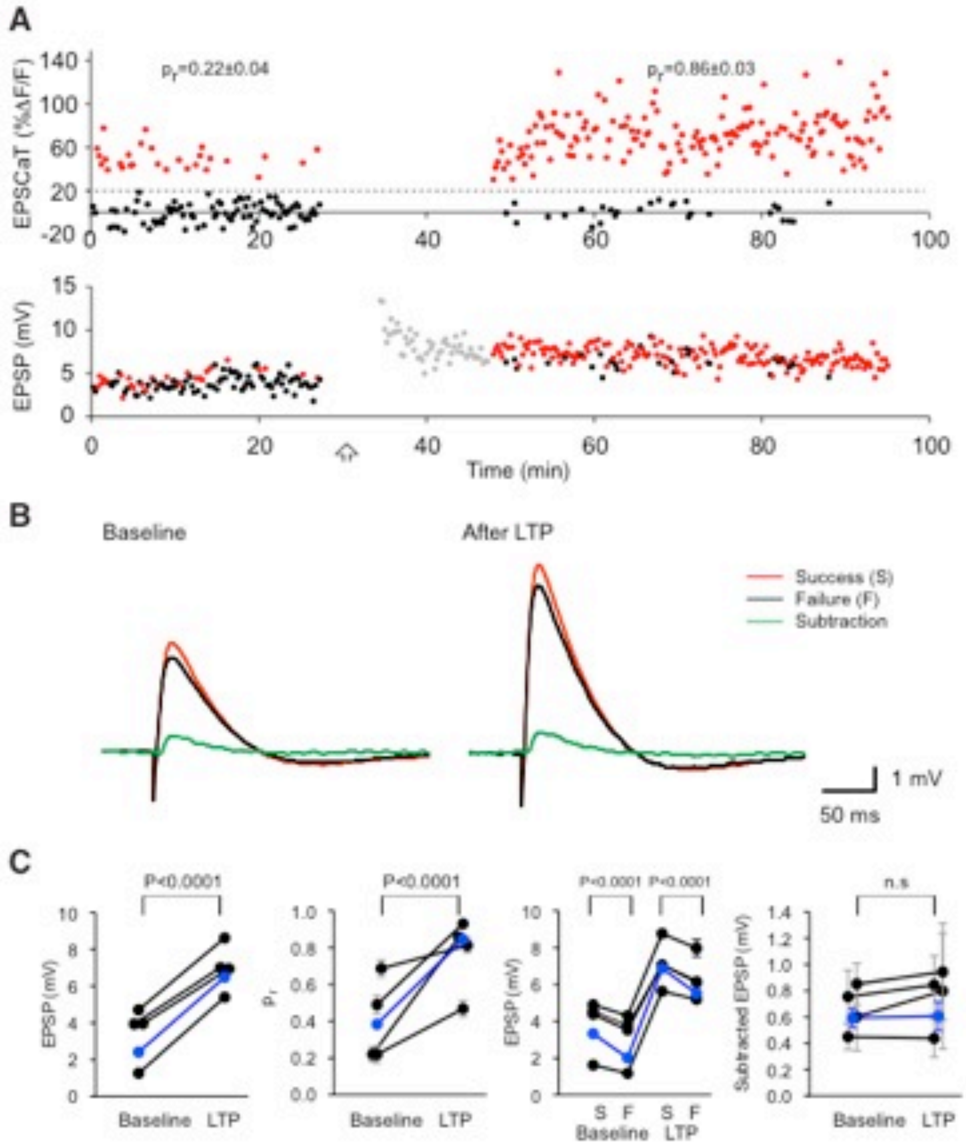
Long-term plasticity is expressed chiefly via changes in synaptic reliability (1)

$r^2 = 0.71$, $p<0.001$
(Acute slices)



Enoki et al. 2009 Neuron *62*: 242-253

Long-term plasticity is expressed chiefly via changes in synaptic reliability (2)



Enoki et al. 2009 Neuron *62*: 242-253

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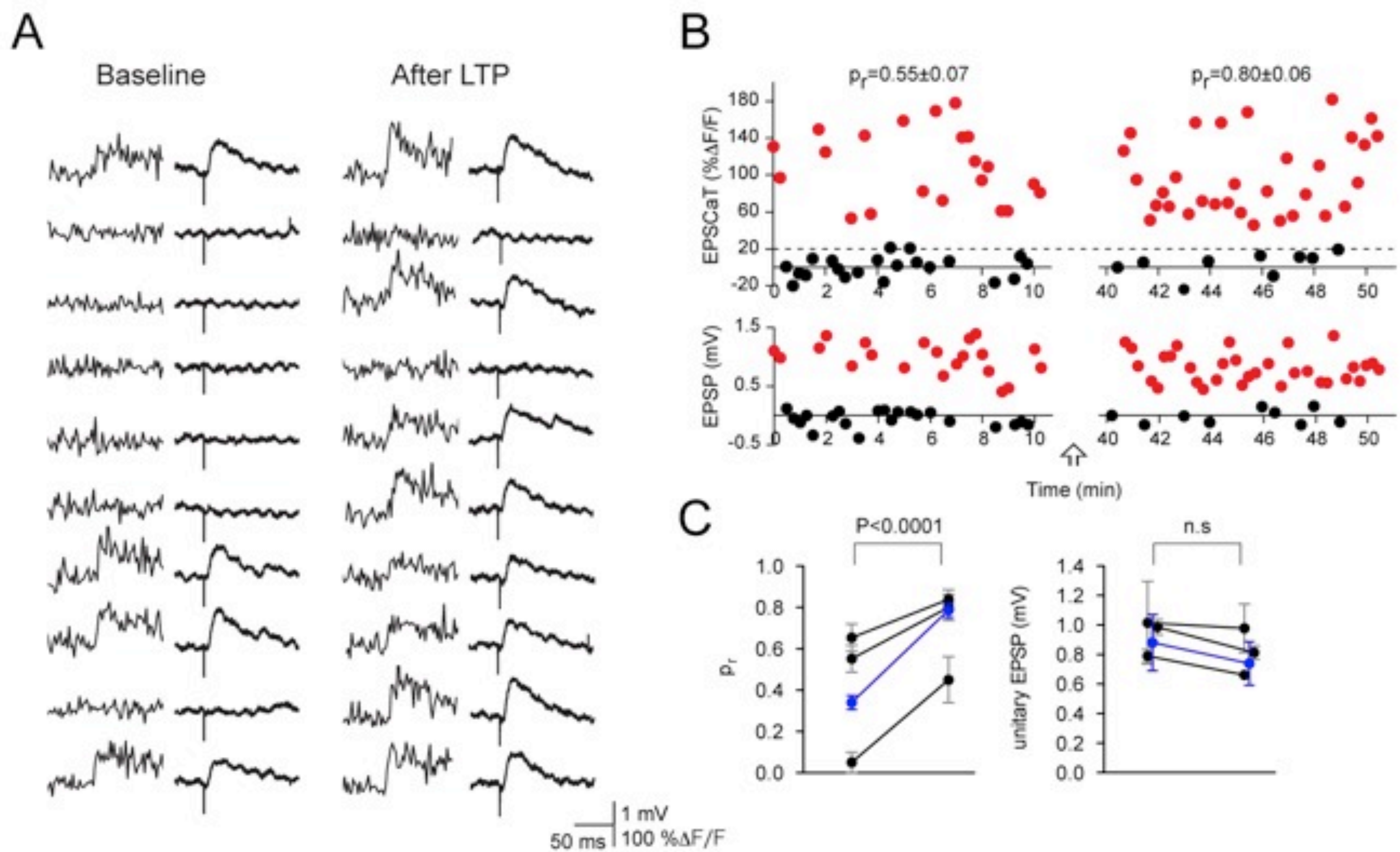
Long-term plasticity is expressed chiefly via changes in synaptic reliability (3)



Enoki et al. 2009 Neuron *62*: 242-253

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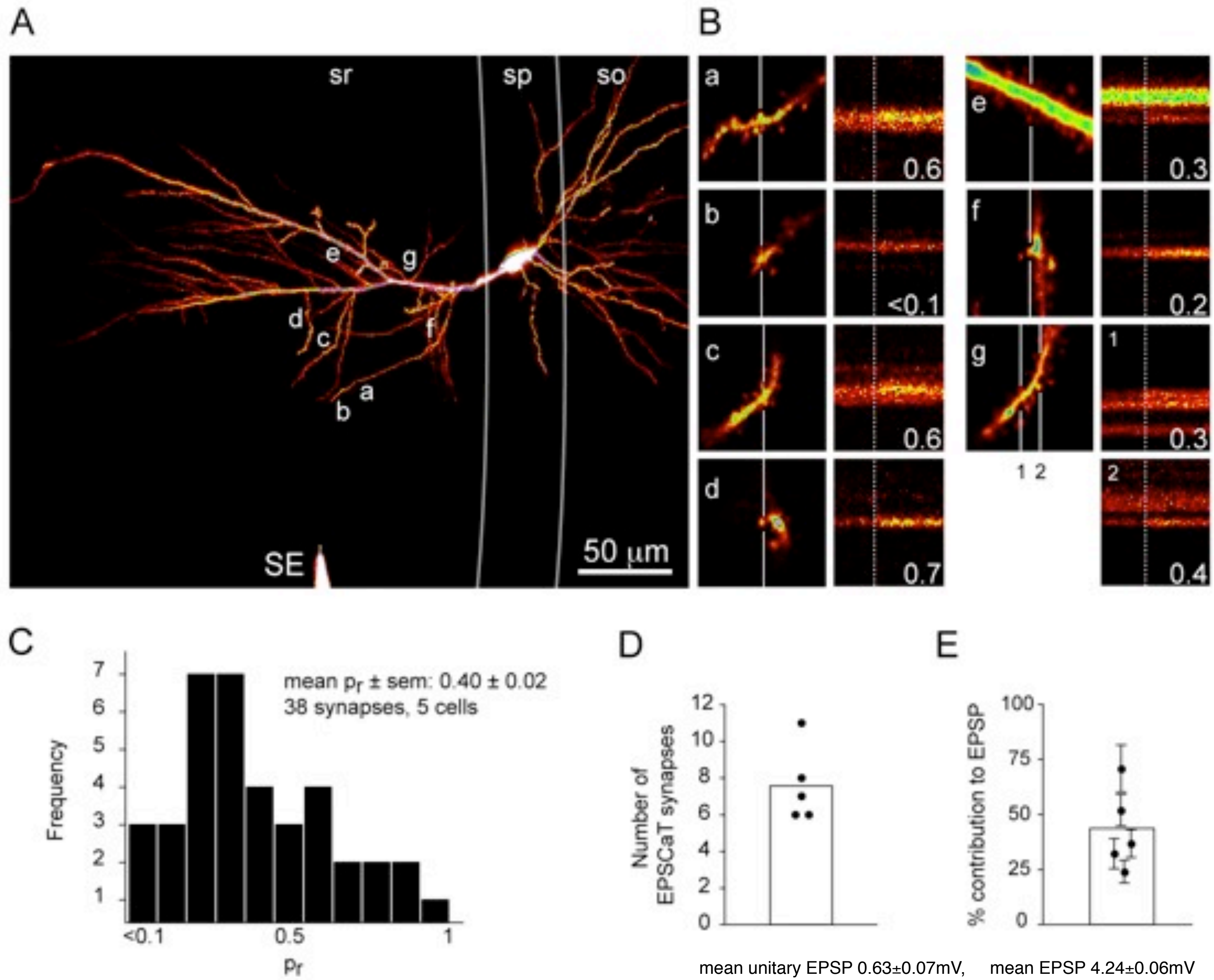
Long-term plasticity is expressed chiefly via changes in synaptic reliability (4)

EPSCaT-generating synapses are major contributors to the EPSP, not an unusual minority



mean unitary EPSP 0.63±0.07mV,   mean EPSP 4.24±0.06mV

Enoki et al. 2009 Neuron *62*: 242-253

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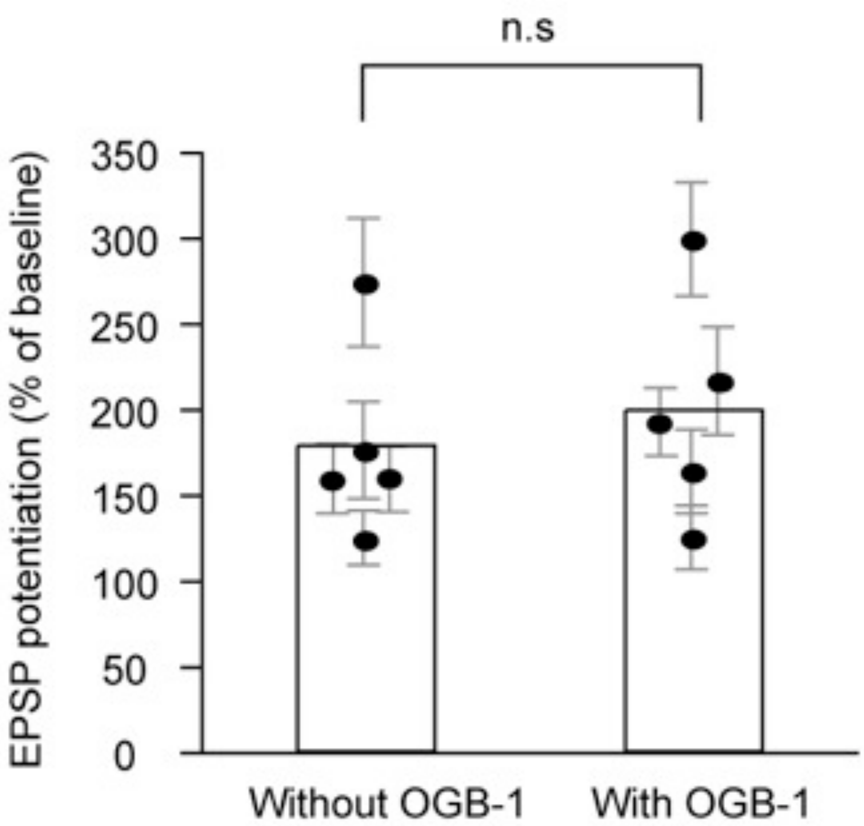
Absence of change in q is not an artifact of calcium buffering
(Postsynaptic loading with fluorescent calcium indicator does not affect LTP)



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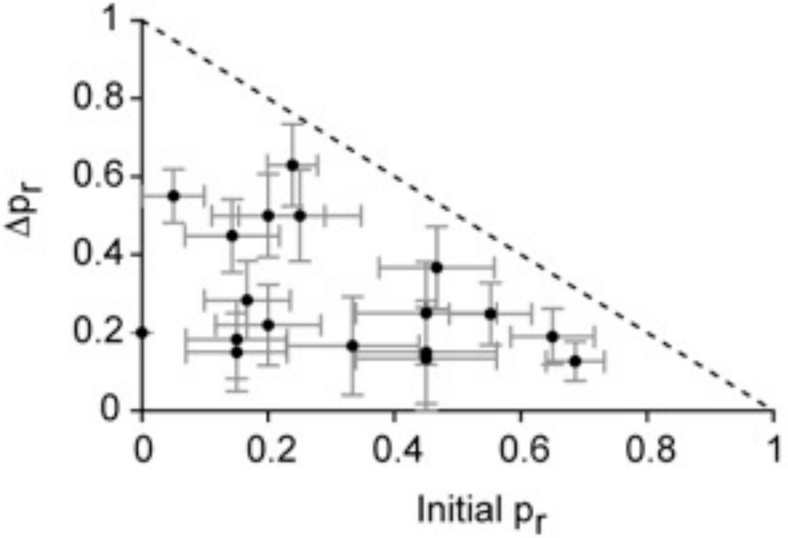
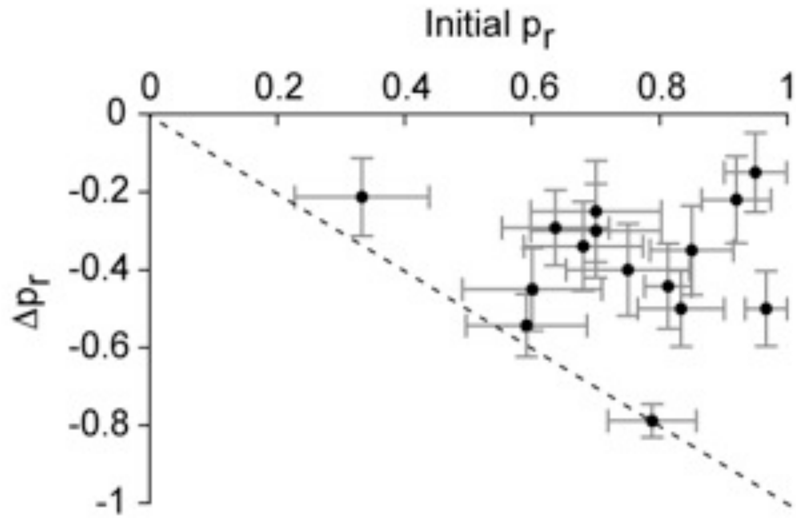
Magnitude of plasticity is not correlated with initial synaptic strength

(apart from constraint 0≤p≤1)

LTP



LTD



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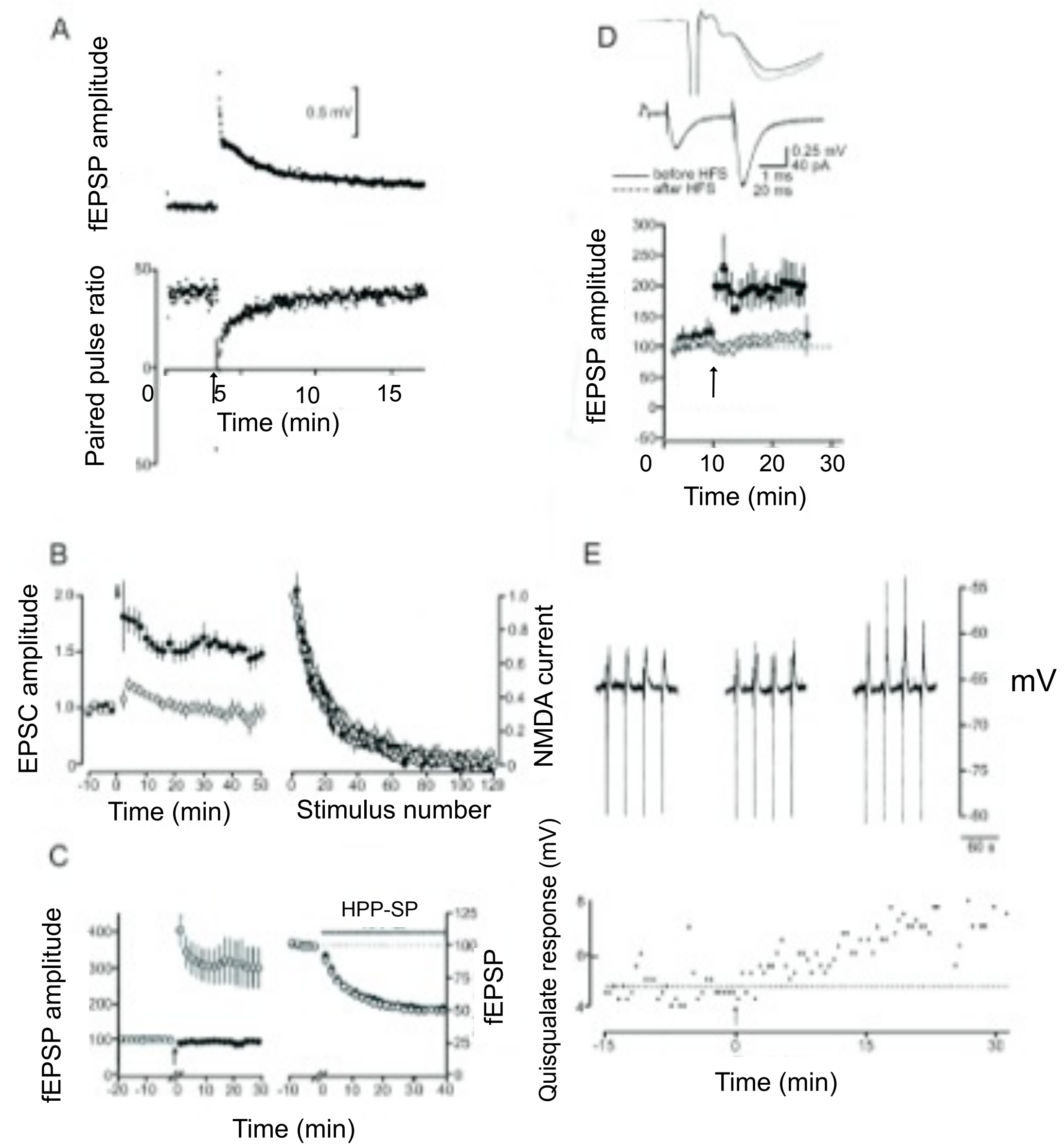
Evidence for postsynaptic changes



A McNaughton, 1982 B
Manabe & Nicoll, 1994 C
Mainen et al., 1998 D
Diamond et al., 1998 E
Davies et al., 1989