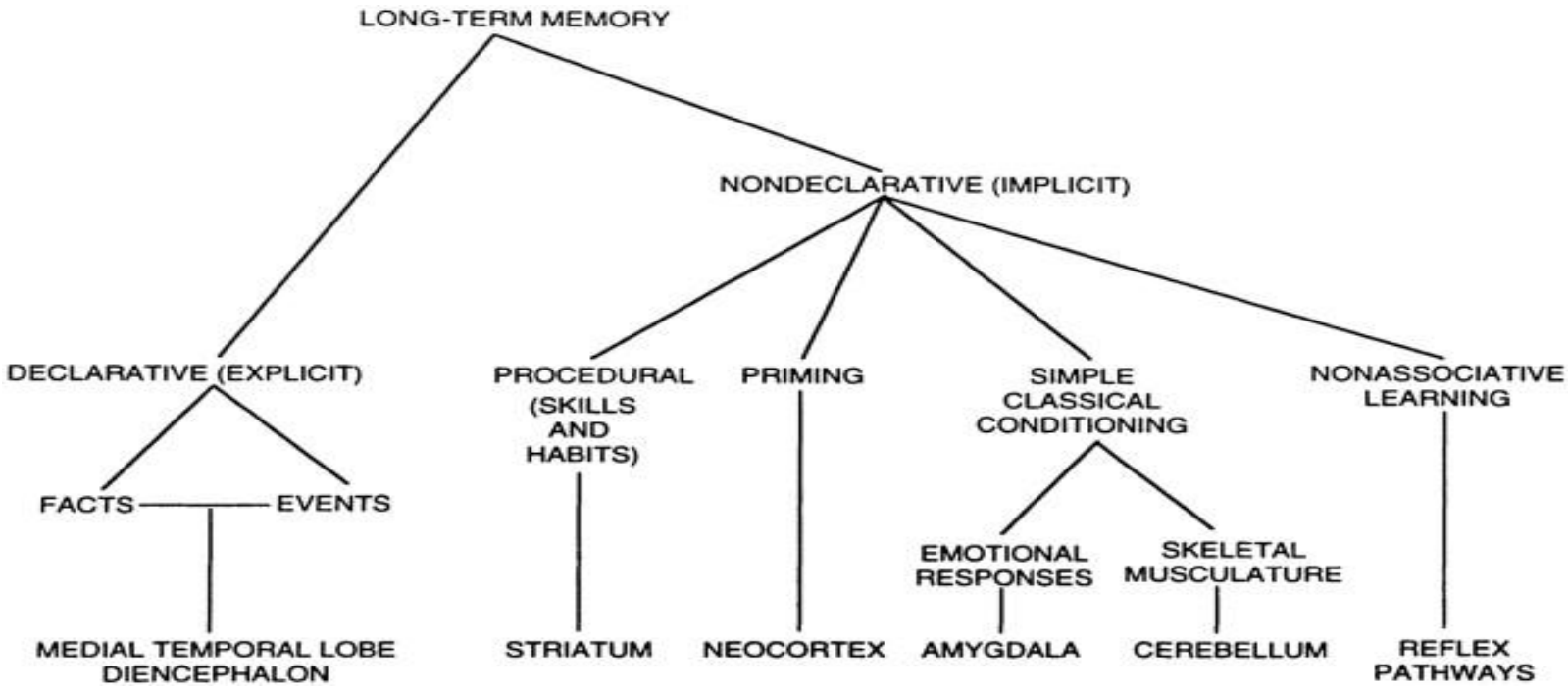
Taxonomy of mammalian memory systems



Milner et al., *Neuron*

HM - Henry Gustav Molaison

H. M.’s lesion

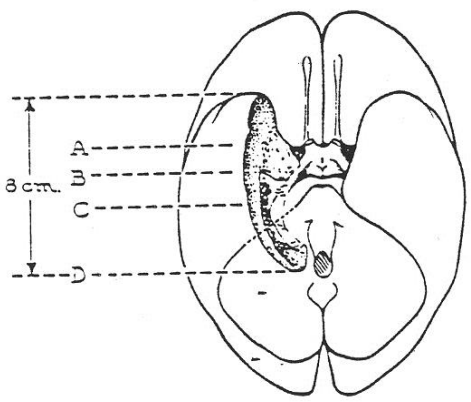
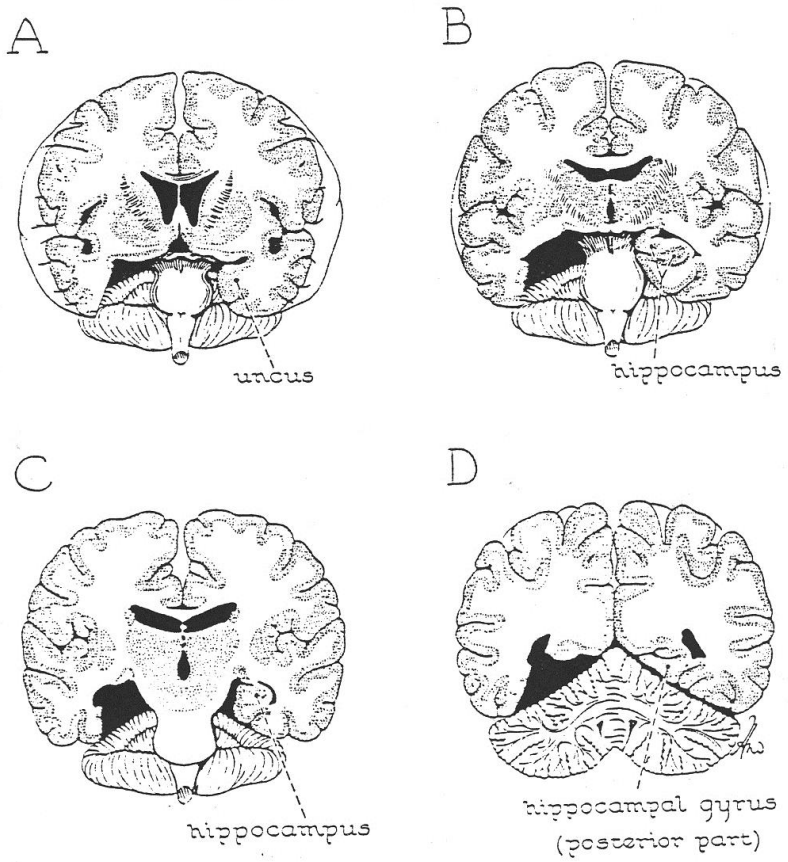
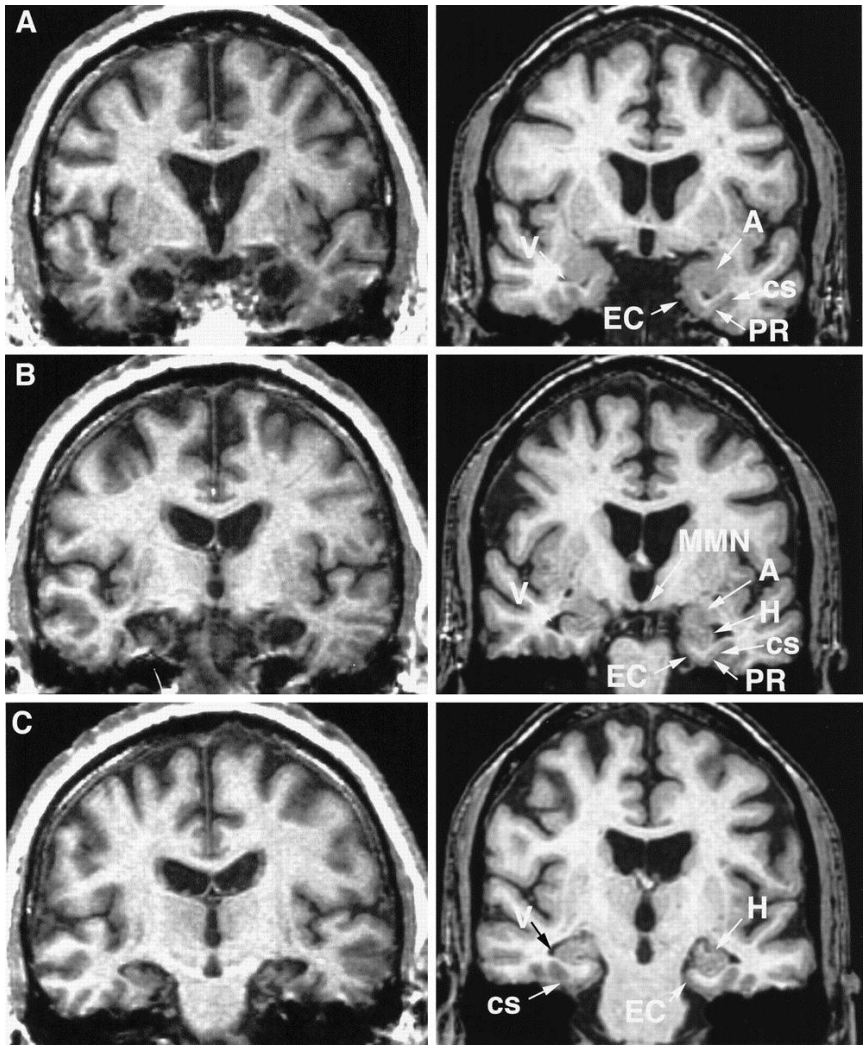


FIG. 2.—Diagrammatic cross-sections of human brain illustrating extent of attempted bilateral medial temporal lobe resection in the radical operation. (For diagrammatic purposes the resection has been shown on one side only.)

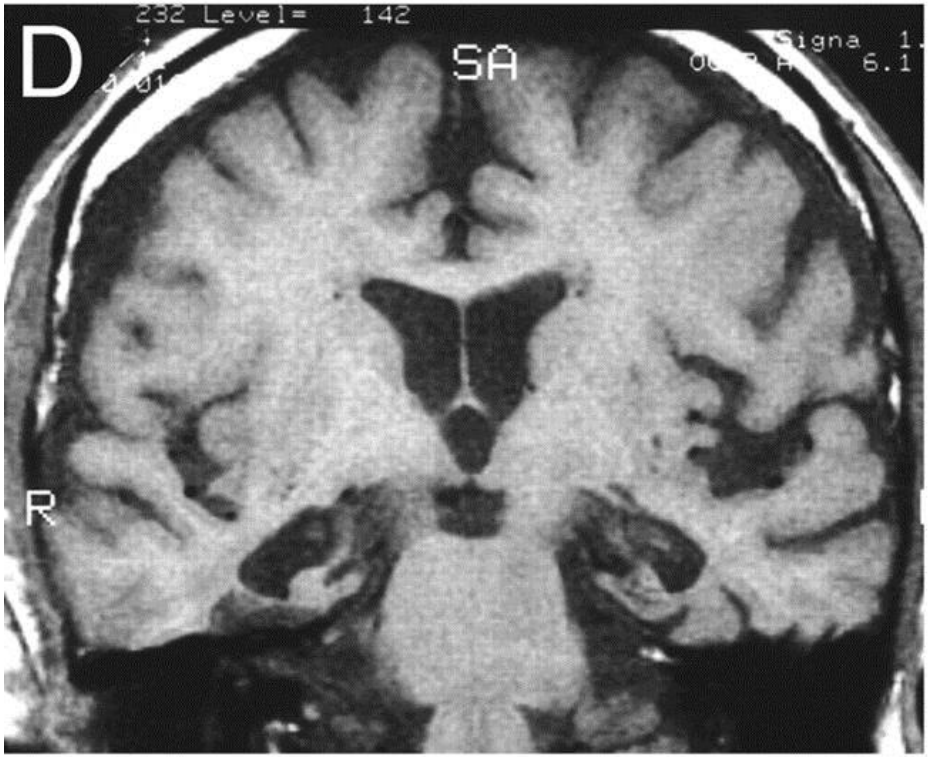


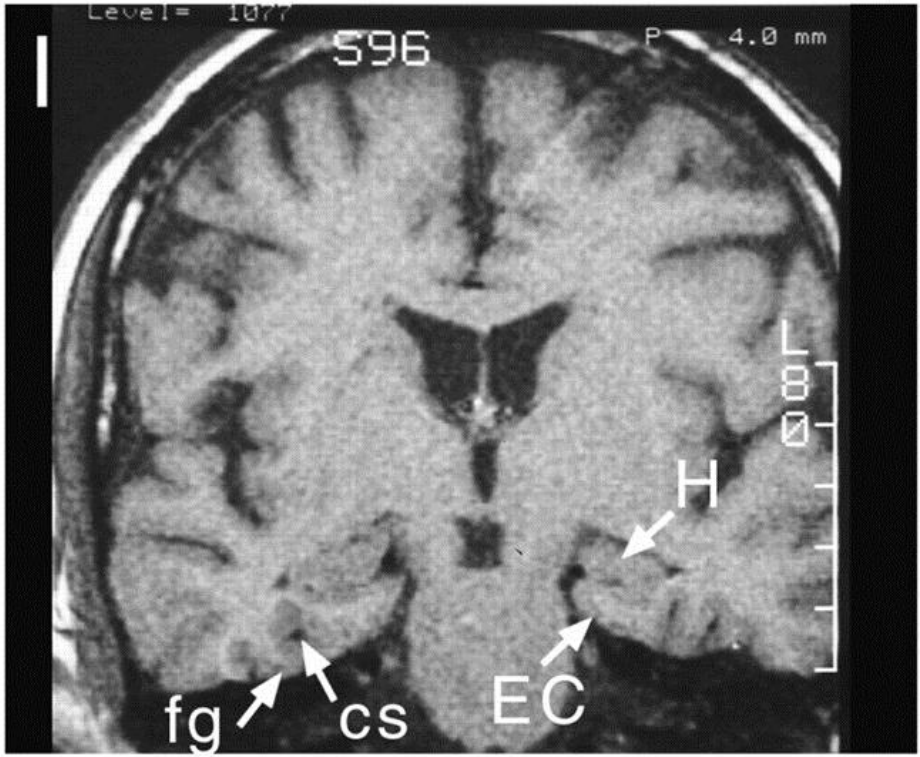


Scoville and Milner J. Neurol Neurosurg Psych, 1957

Corkin et al., J. Neurosci., 1997

Patient E. P. replicates the impairment seen in H. M.

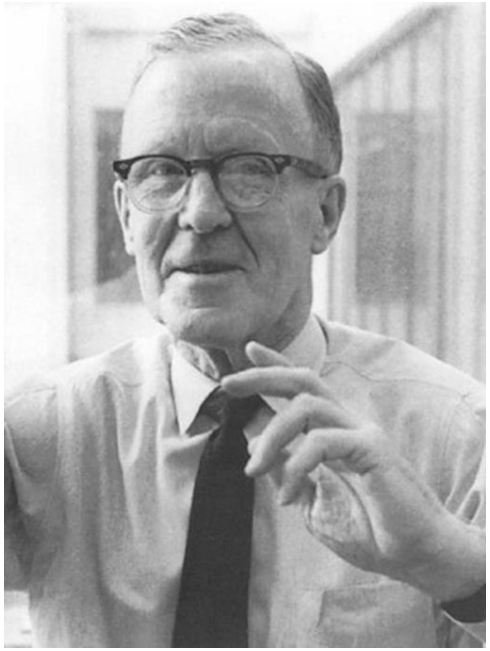




Stefanacci et al., J. Neurosci. 2000

D. O. Hebb
The Organization of Behavior, 1949

"When the axon of cell A …….. excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased".

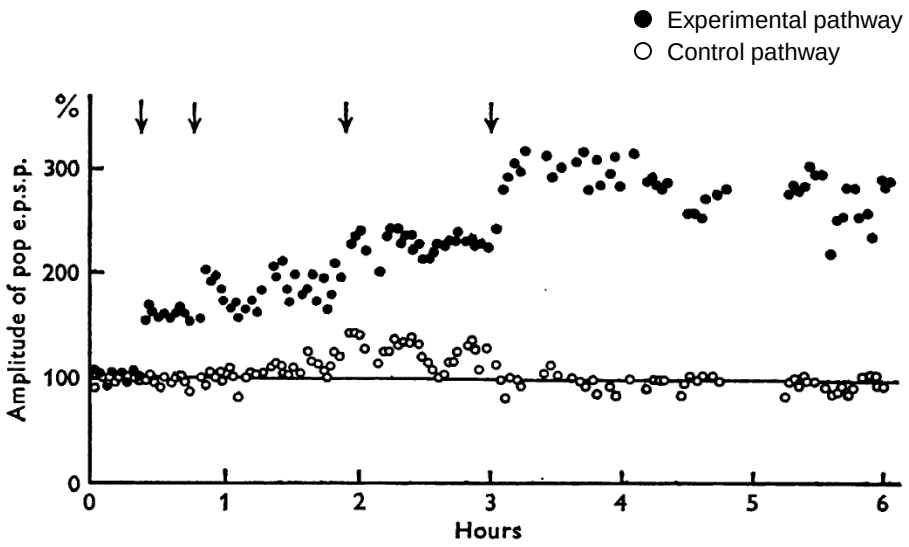


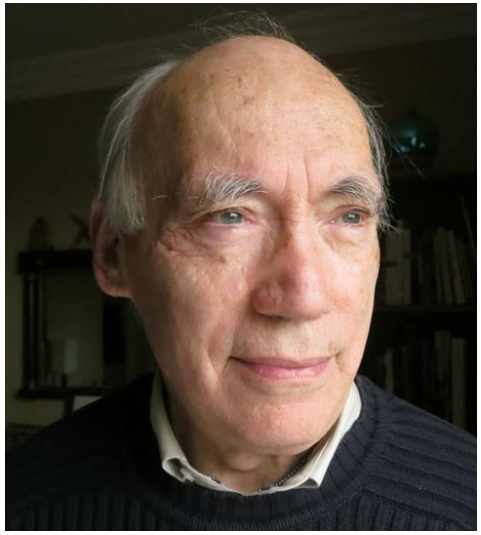
J. Physiol. (1973), **232**, *pp.* 331–356
With 12 text-figures
Printed in Great Britain

LONG-LASTING POTENTIATION OF SYNAPTIC TRANSMISSION IN THE DENTATE AREA OF THE ANAESTHETIZED RABBIT FOLLOWING STIMULATION OF THE PERFORANT PATH

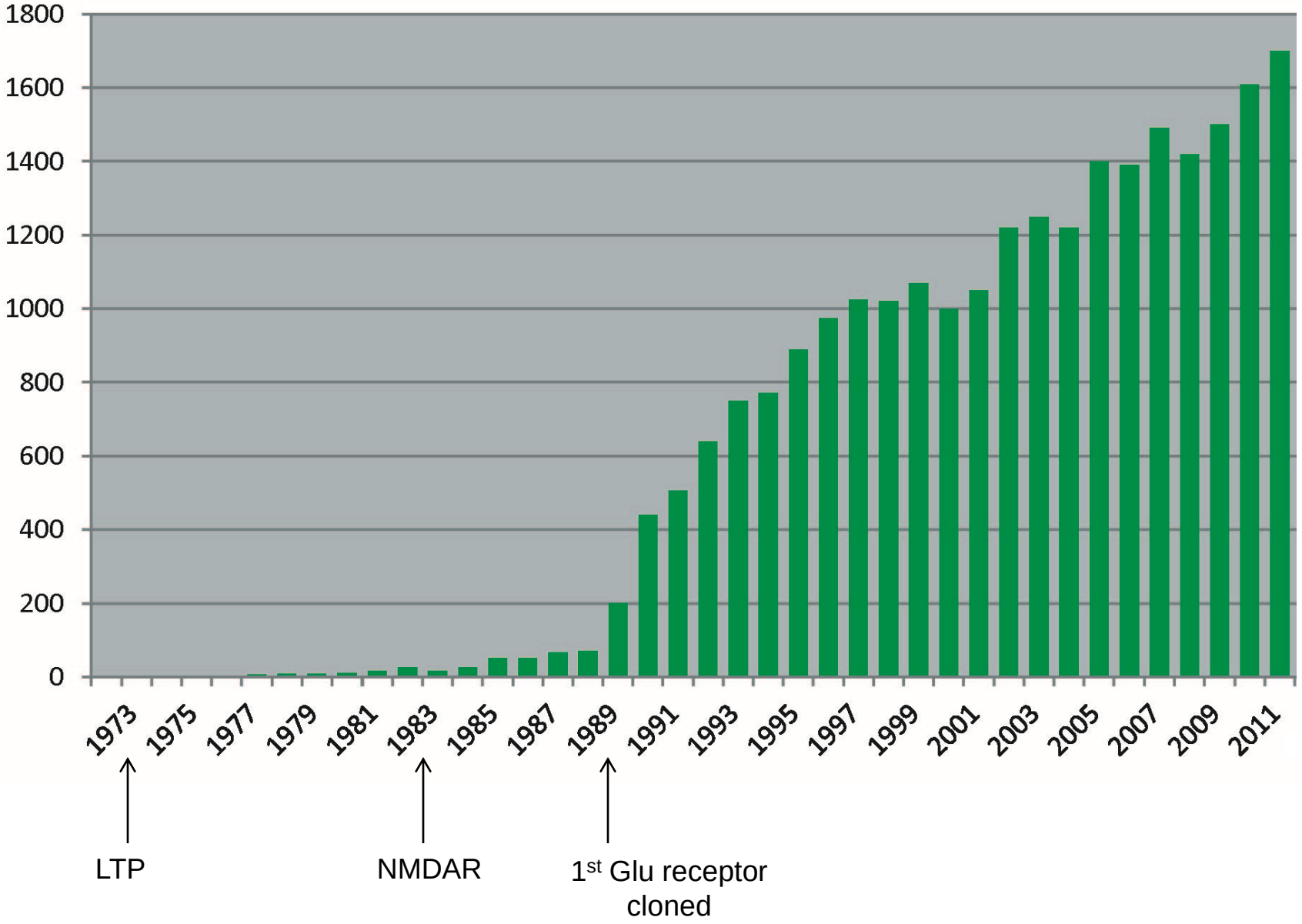
BY T. V. P. BLISS AND T. LØMO

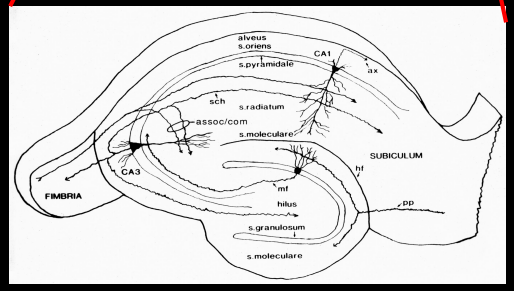
From the National Institute for Medical Research, Mill Hill, London NW7 1AA and the Institute of Neurophysiology, University of Oslo, Norway





Search “long term potentiation”: ~27,000 papers and still going strong

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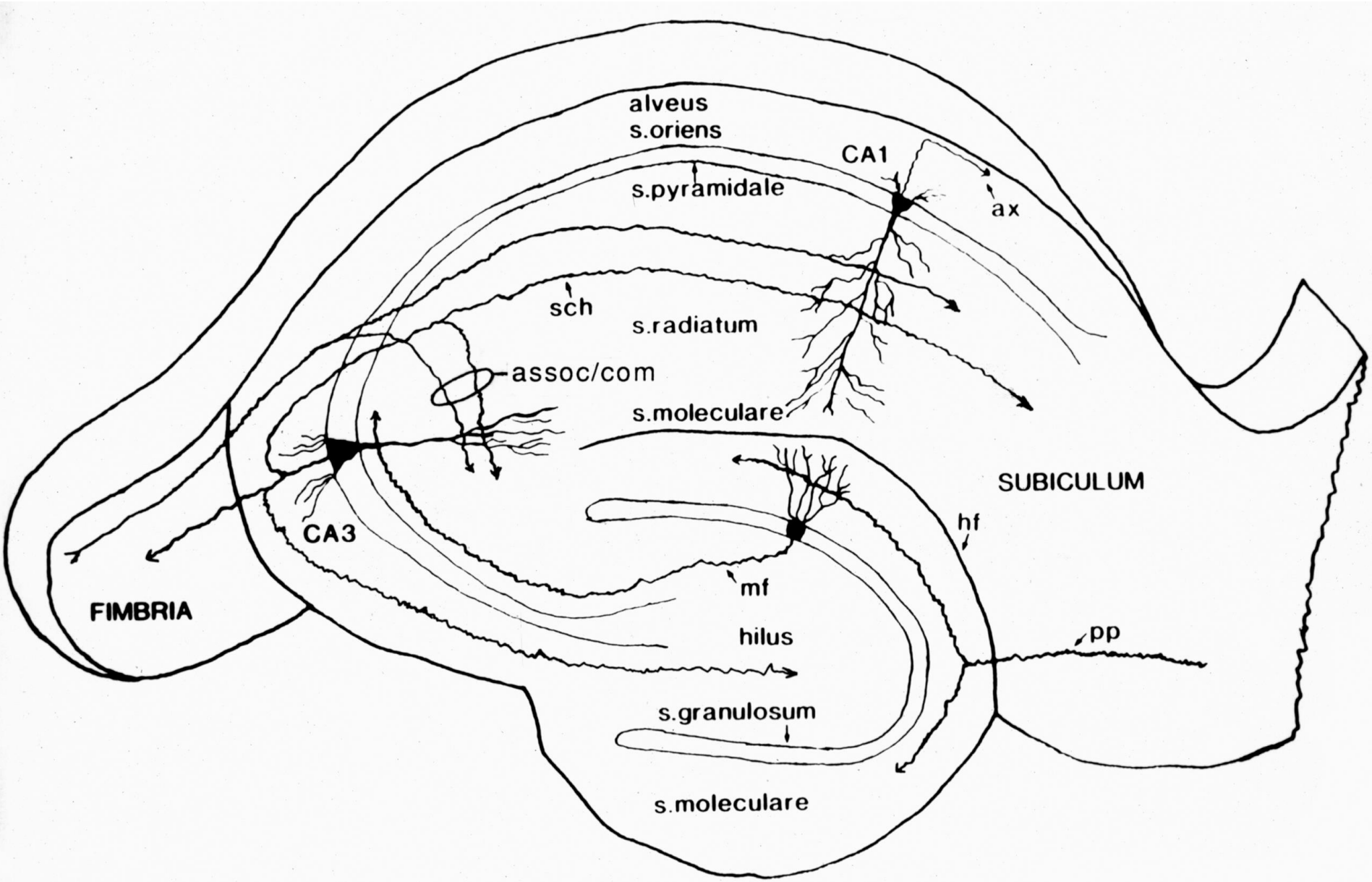
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mf
FIMBRIA
hilus
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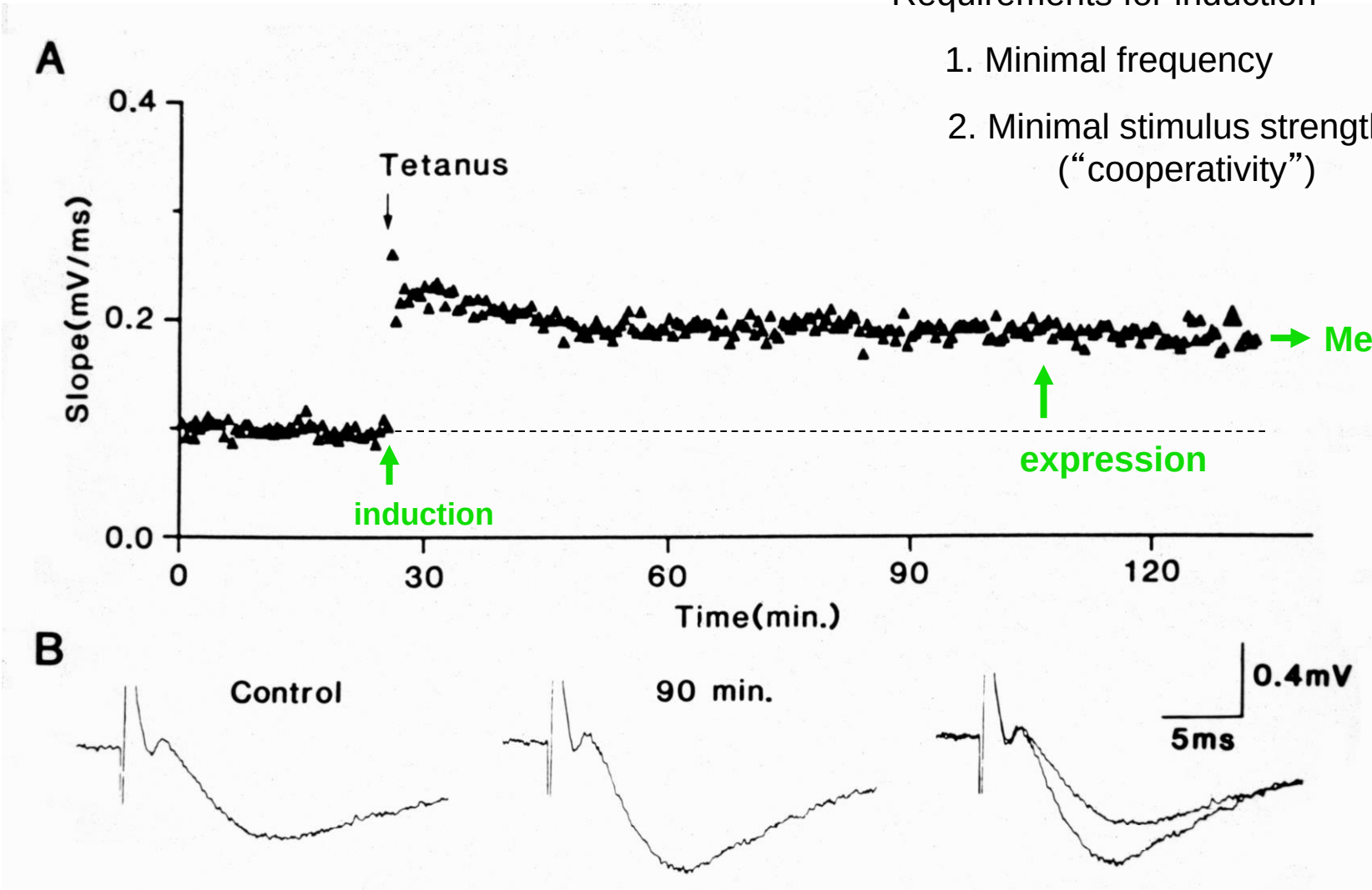
Hippocampal Long-Term Potentiation (LTP)

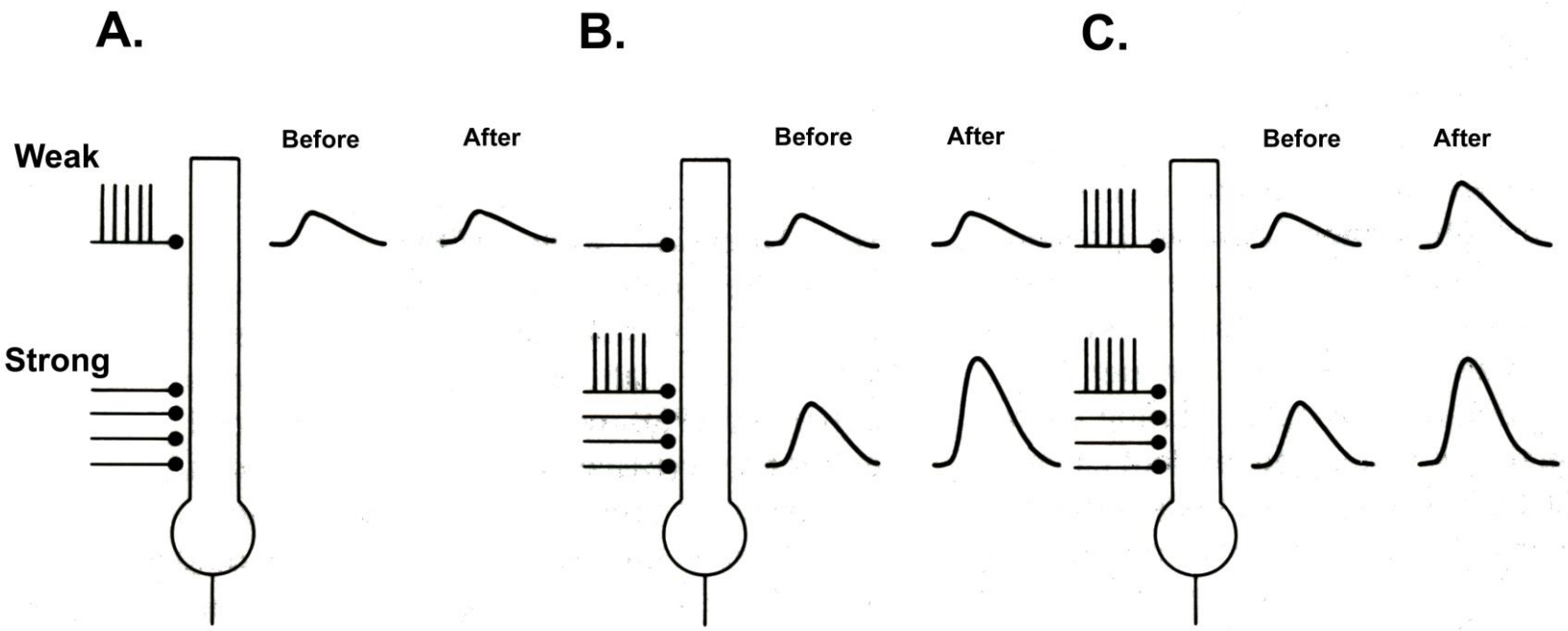
Requirements for induction

1. Minimal frequency
2. Minimal stimulus strength ("cooperativity")



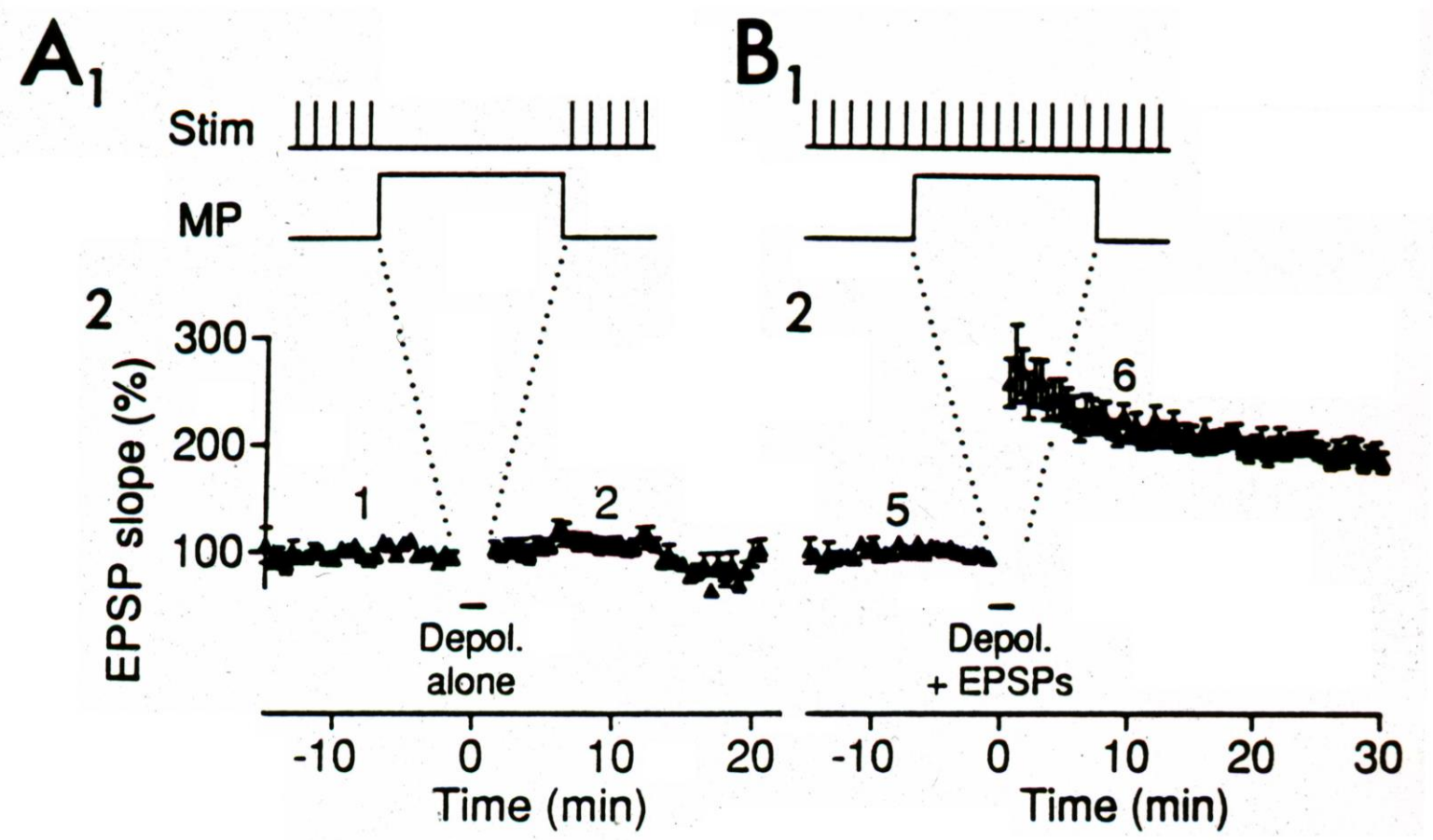
Induction mechanisms of LTP/LTD

Associative nature of LTP
“associativity”



1. Pathway (synapse?) specificity
2. Near simultaneous activation
3. Proximity of pathways, not important
4. Thus, signal from strong to weak is extremely fast and widespread

LTP requires synaptic activation and depolarization

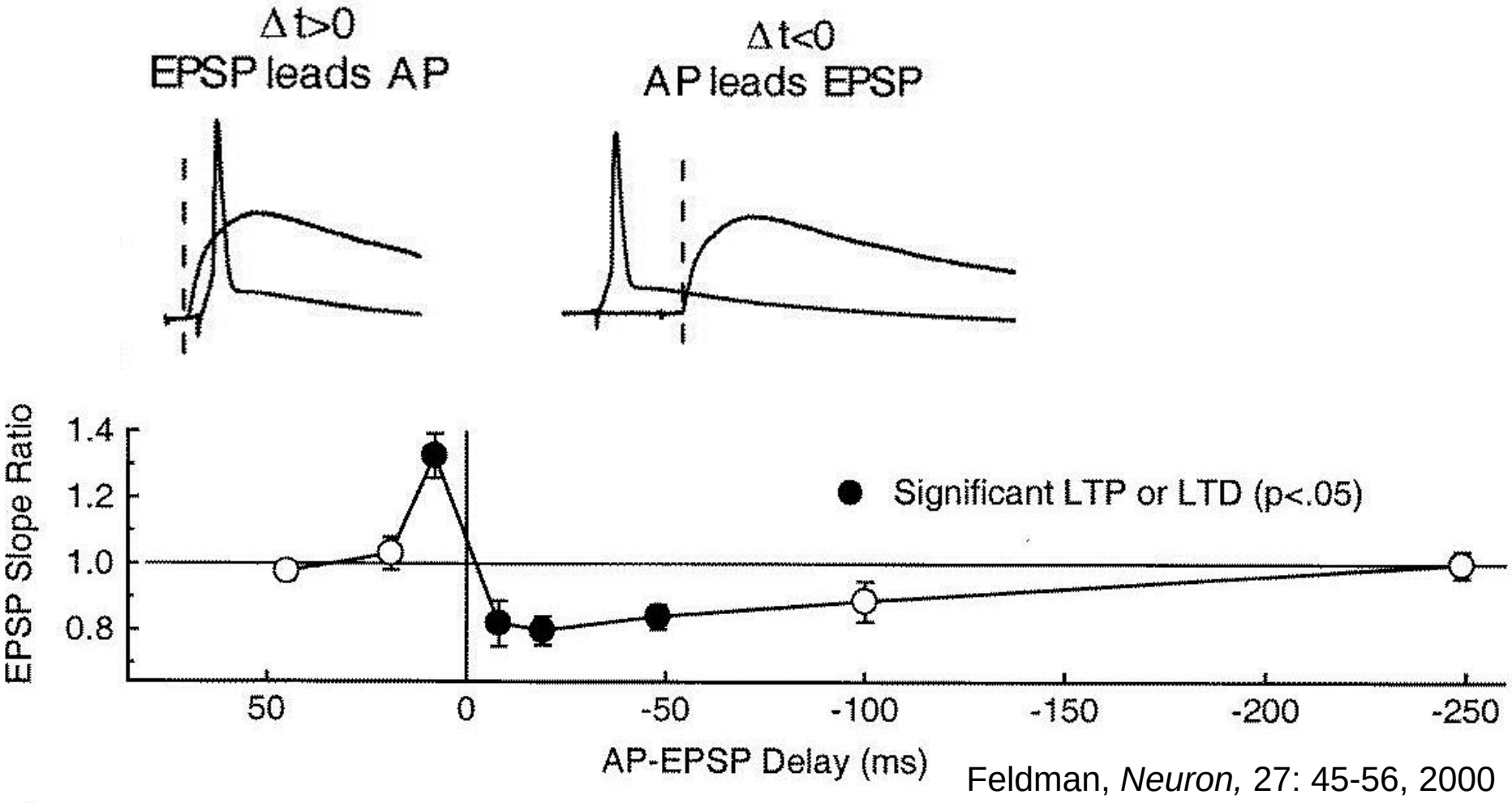


Don't need a tetanus

Only two requirements

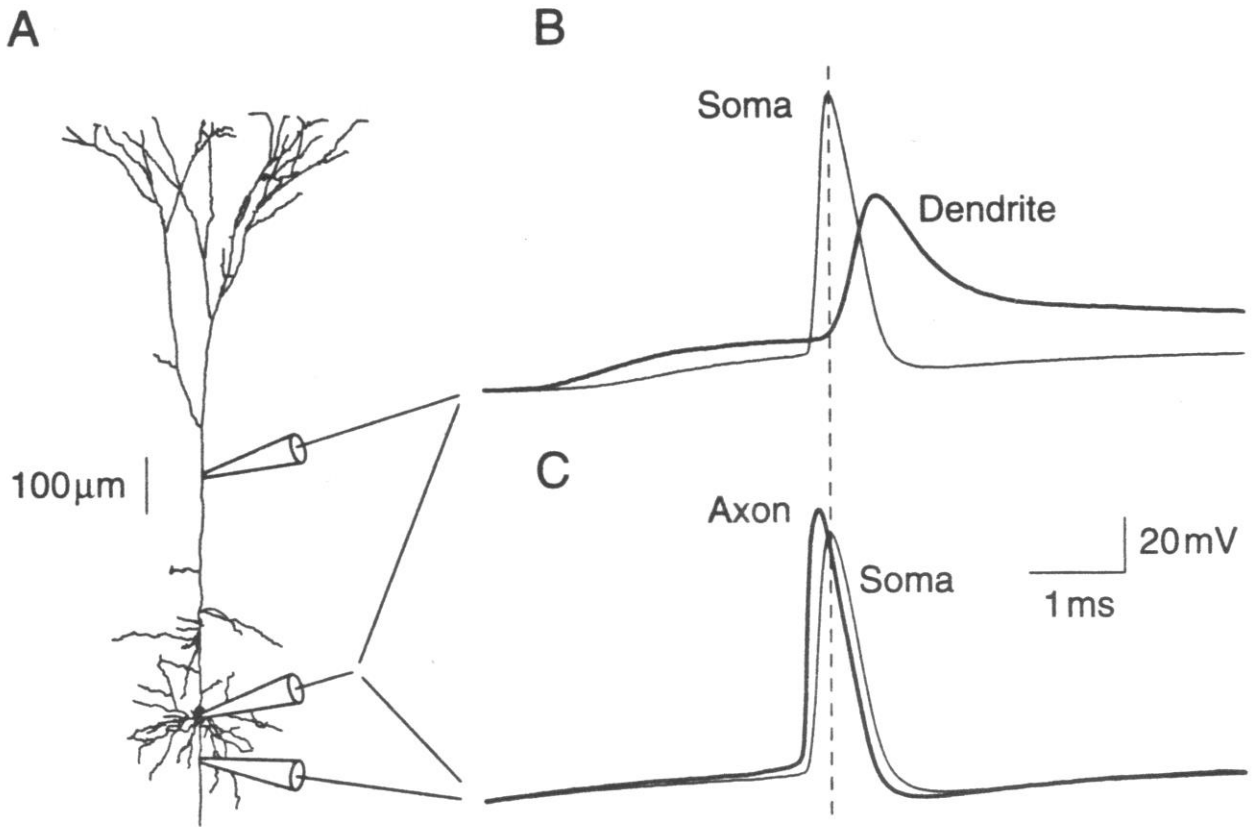
1. Synaptic activation
2. Depolarization

Spike timing-dependent plasticity



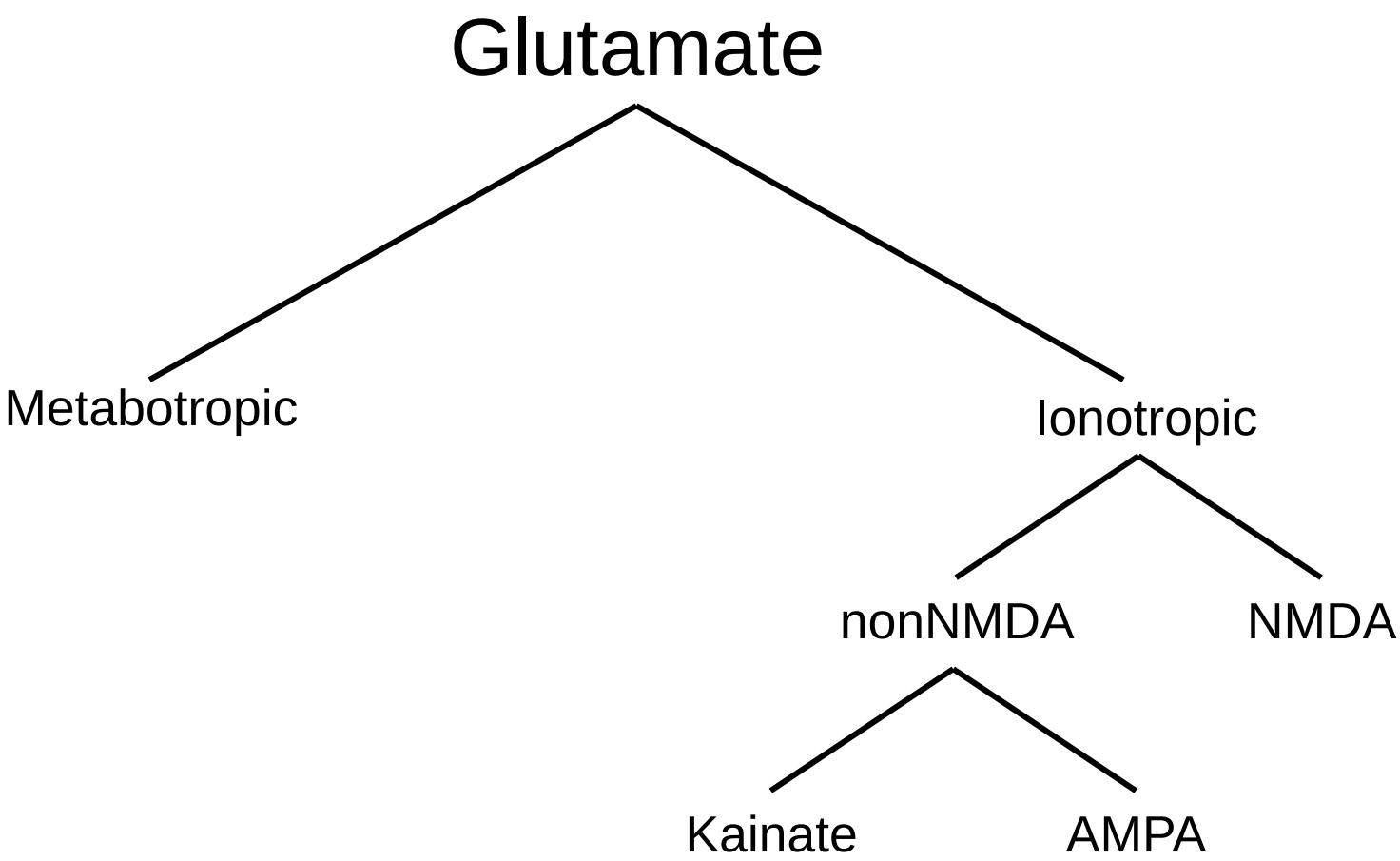
Feldman, *Neuron,* 27: 45-56, 2000

Action potential backpropagation

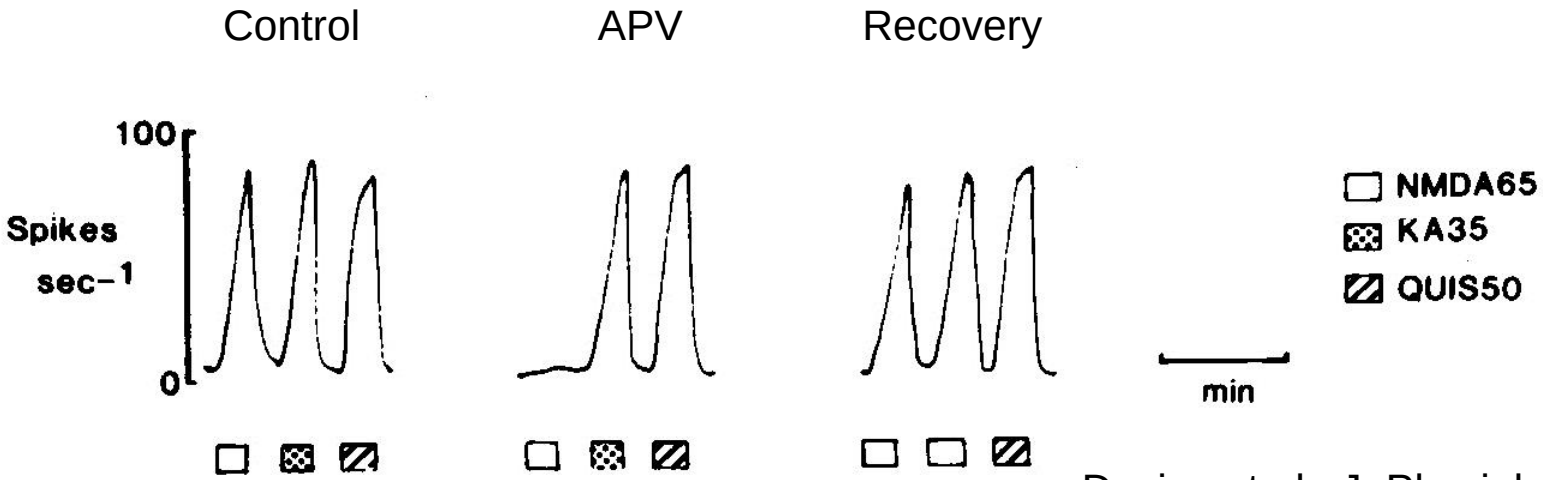


Stuart et al., *TINS,* 20: 125-131, 1997

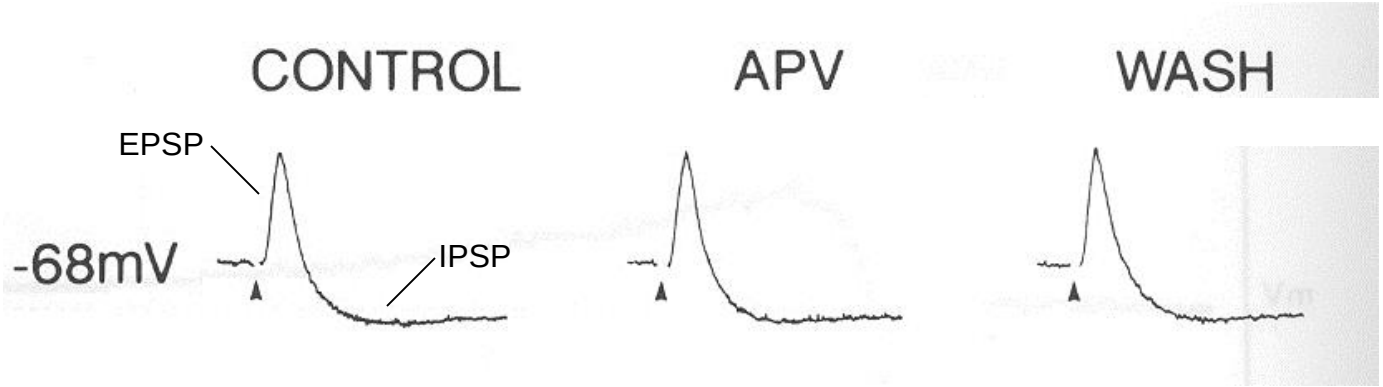
Glutamate Receptor Subtypes



Neurons respond to applied NMDA, but synaptic response are not effected by an NMDAR antagonist

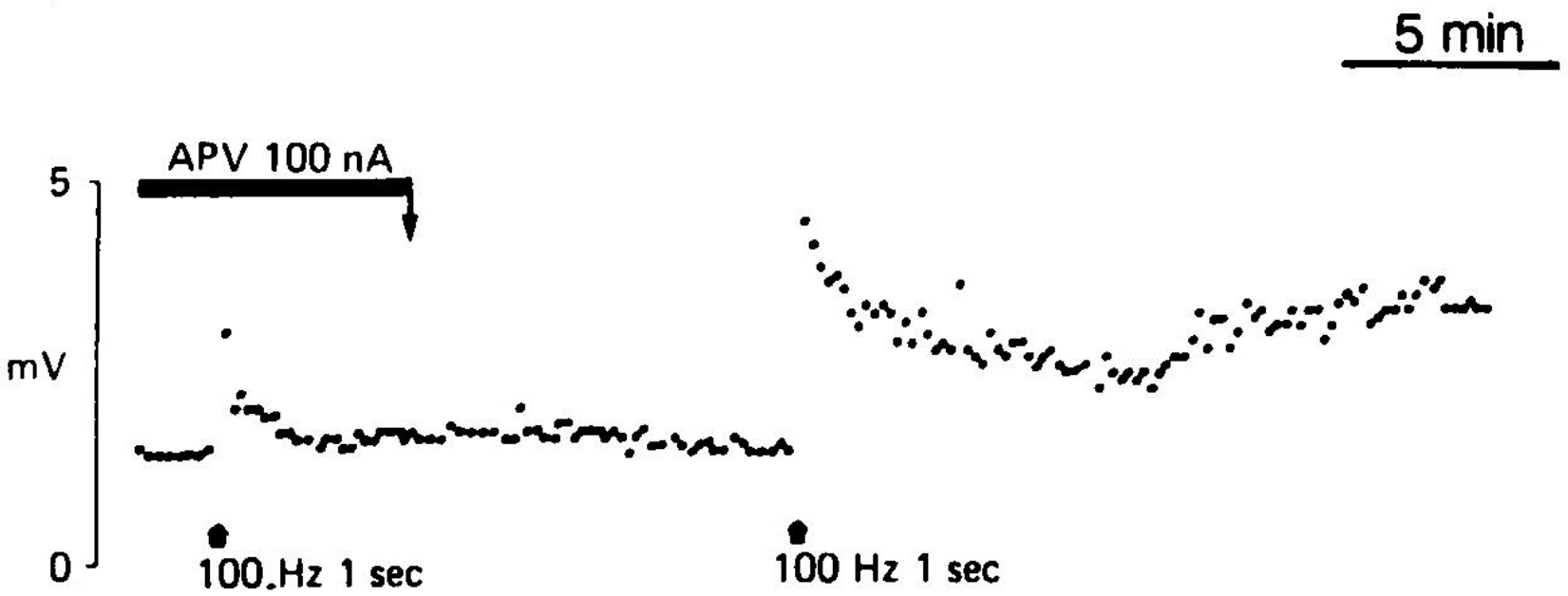


Davies et al., J. Physiol. 1983



Collingridge et al., J. Physiol. 1984

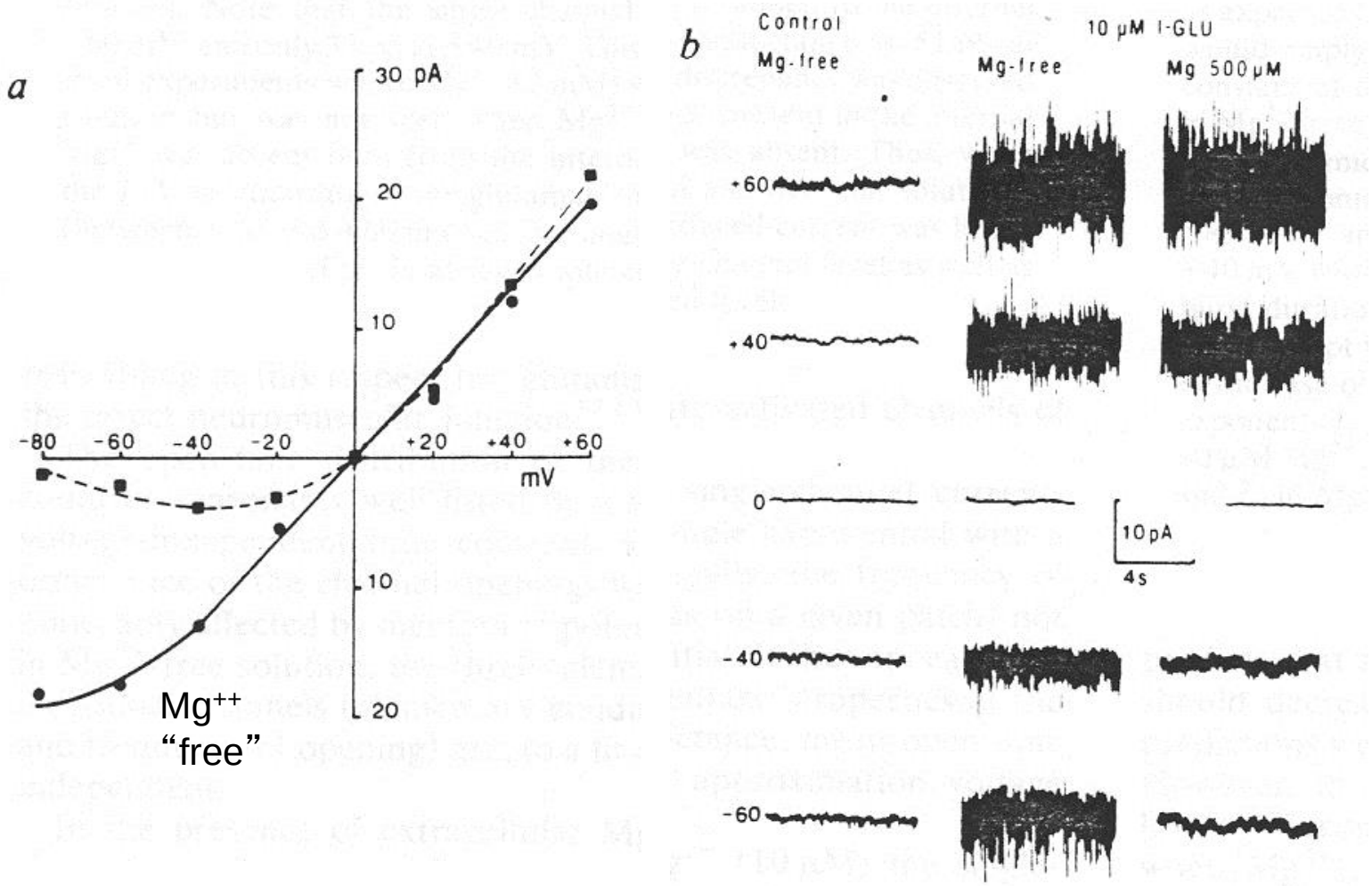
LTP is blocked by NMDA receptor antagonists, but the EPSP is unaffected



"the present study has shown that the NMDA receptor plays no role in the mediation of synaptic transmission, but may be involved in the generation of l.t.p."

Collingridge et al., *J. Physiol.* 334: 33-46, 1983

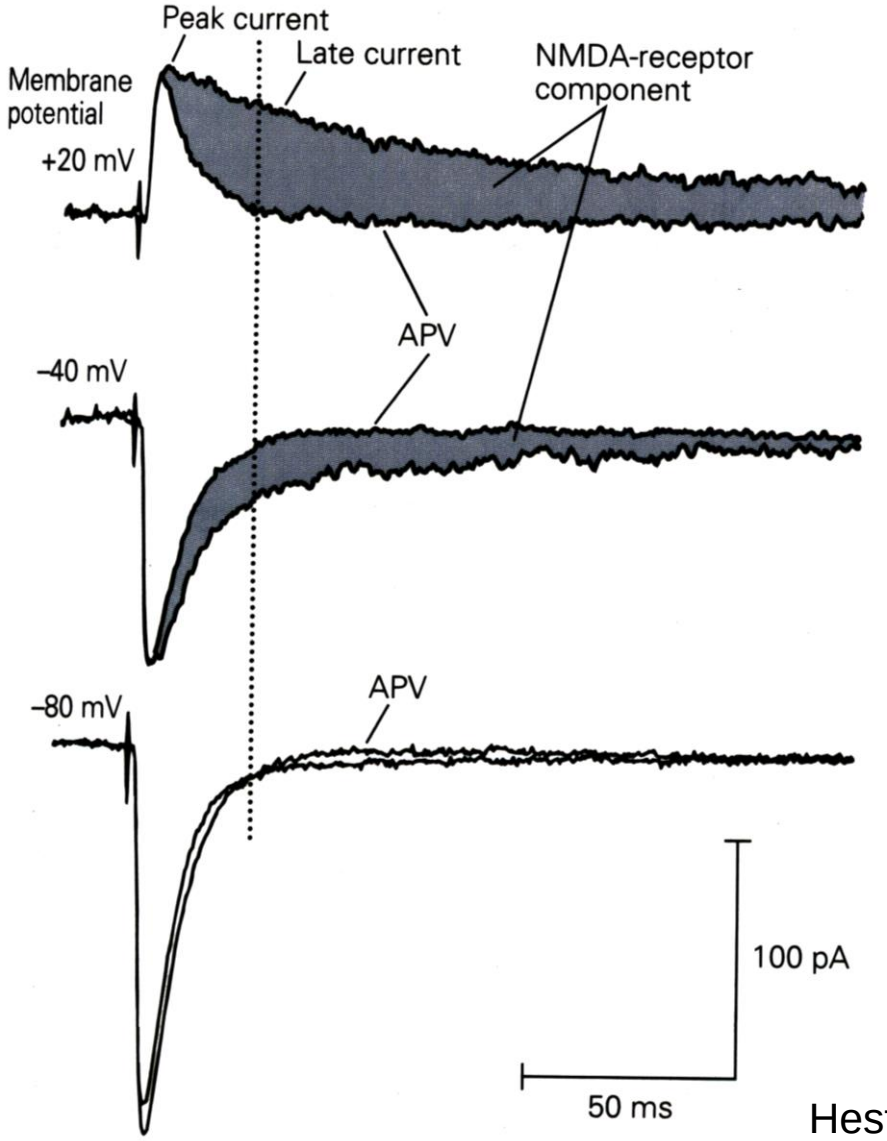
NMDA currents are voltage dependent



Extracellular Mg^{++} accounts for the voltage dependence

Nowak et al., *Nature* 307:462-465, 1984

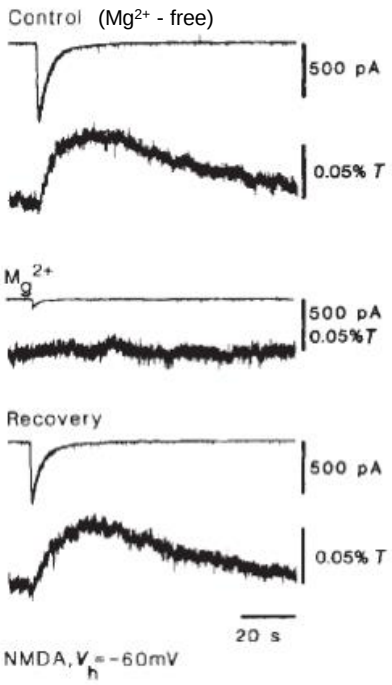
Synaptic AMPA and NMDA receptors

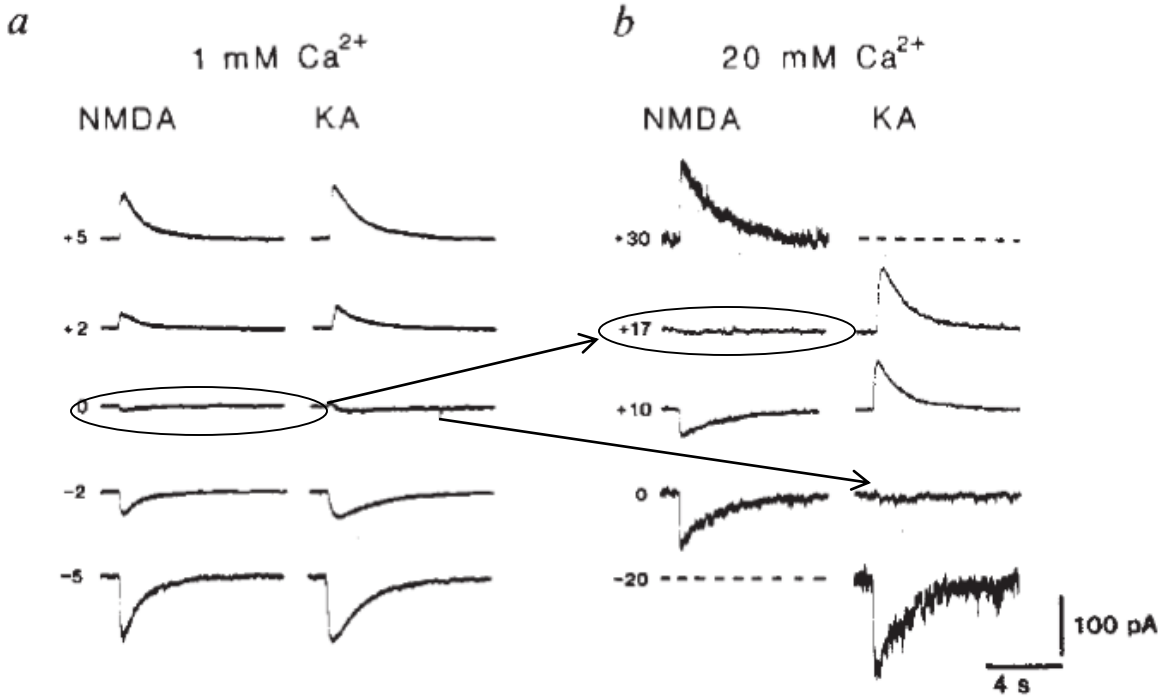


Hestrin et al., *J. Physiol.*, 1990

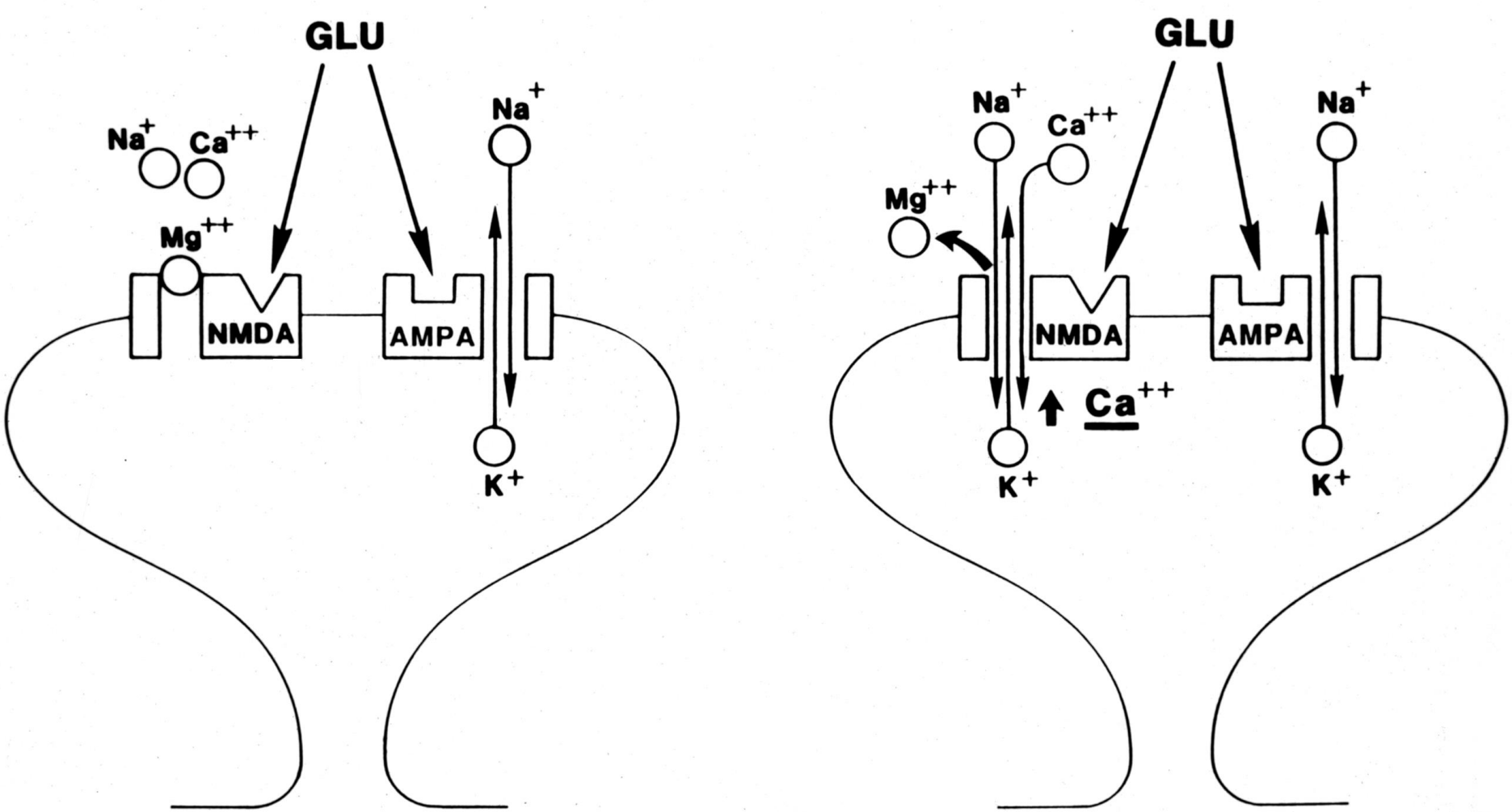
NMDARs, but not AMPARs, are permeable to calcium

Ca^{+2} imaging

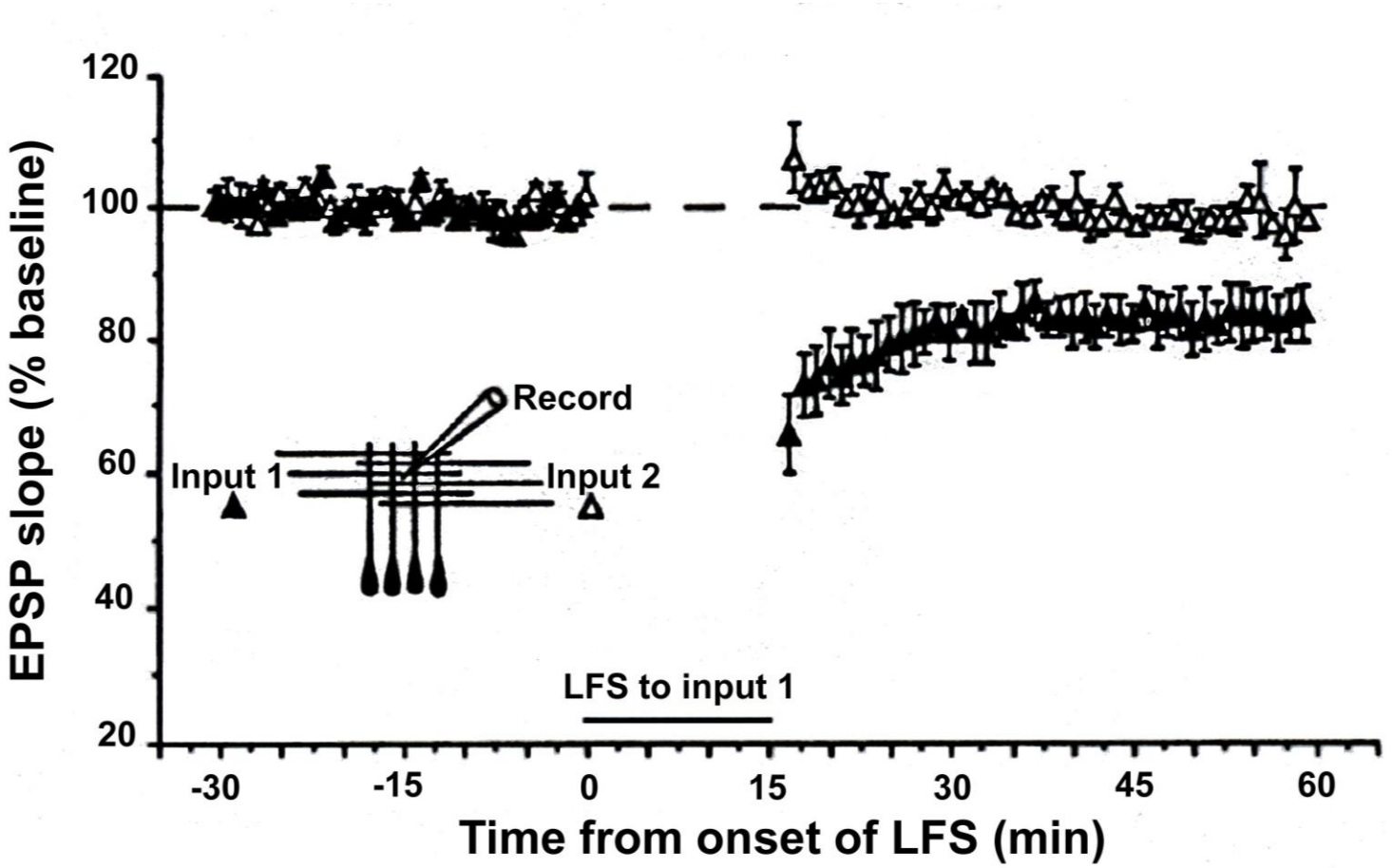




MacDermott, et. al., Nature 321: 519, 1986


Normal synaptic transmission
GLU
Na+
Ca++
Mg++
Na+
NMDA
AMPA
K+
During depolarization
GLU
Na+
Ca++
Mg++
Na+
NMDA
AMPA
Ca++
K+
K+

LTD induced by low frequency stimulation



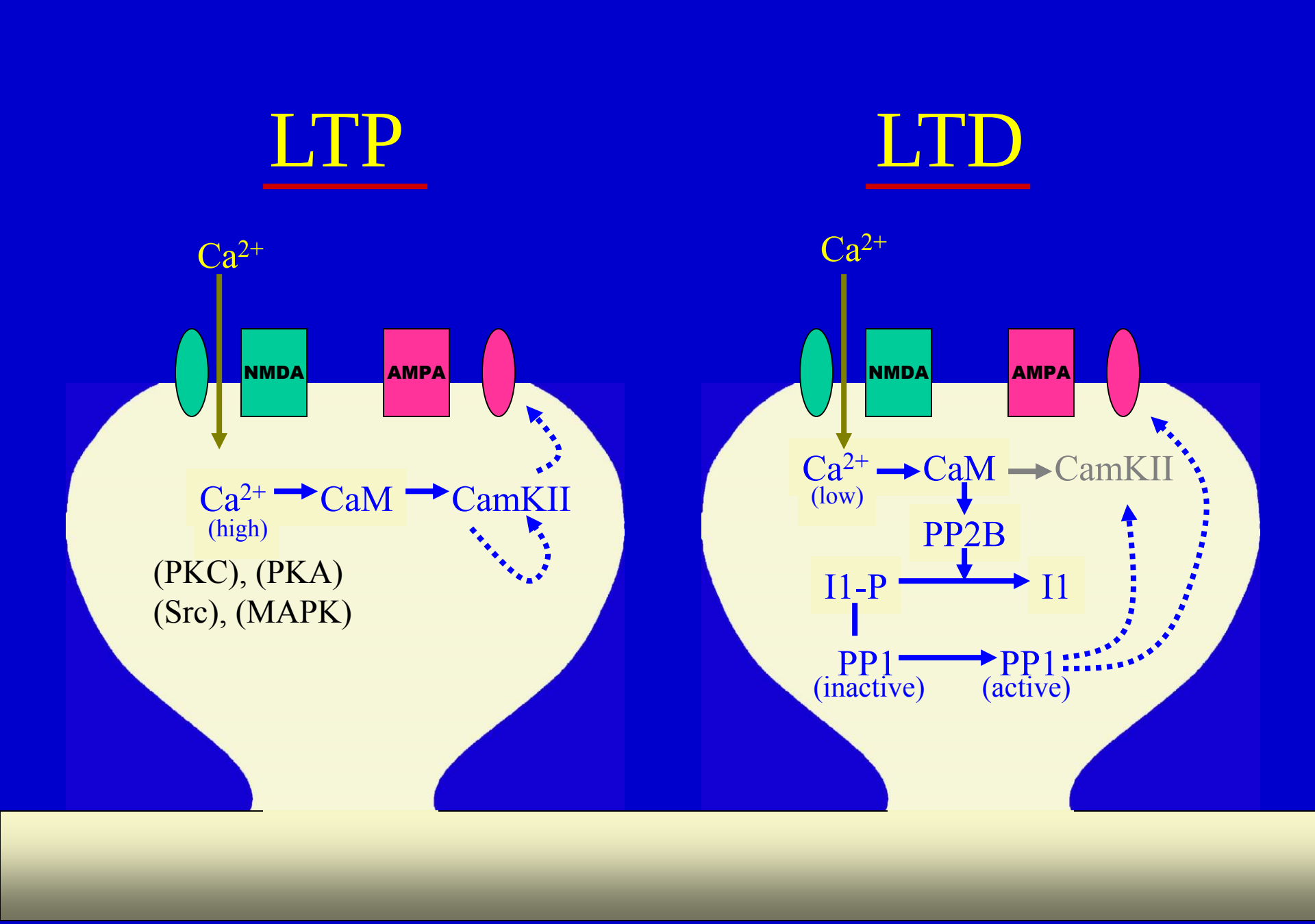
Dudek and Bear, *PNAS,* 89: 4363-7, 1992

LTP

- Induced by high-frequency stimulation
- Input specific
- Saturable
- Reversible
- Requires rise in postsynaptic calcium
- Requires activation of NMDA receptors

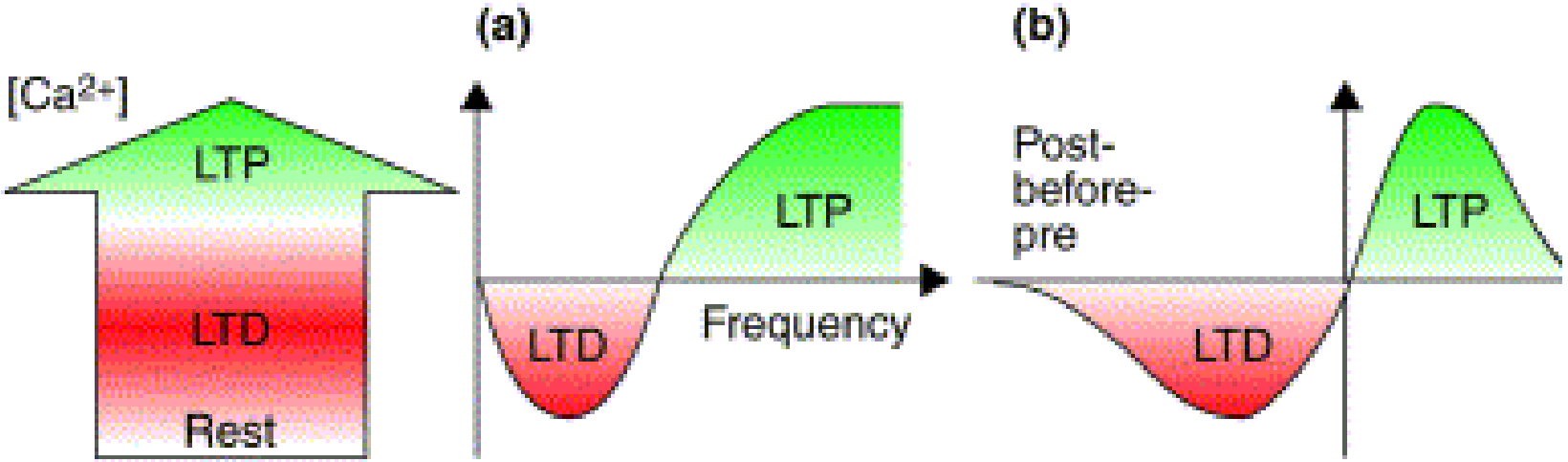
LTD

- Induced by low-frequency stimulation
- Input specific
- Saturable
- Reversible
- Requires rise in postsynaptic calcium
- Requires activation of NMDA receptors



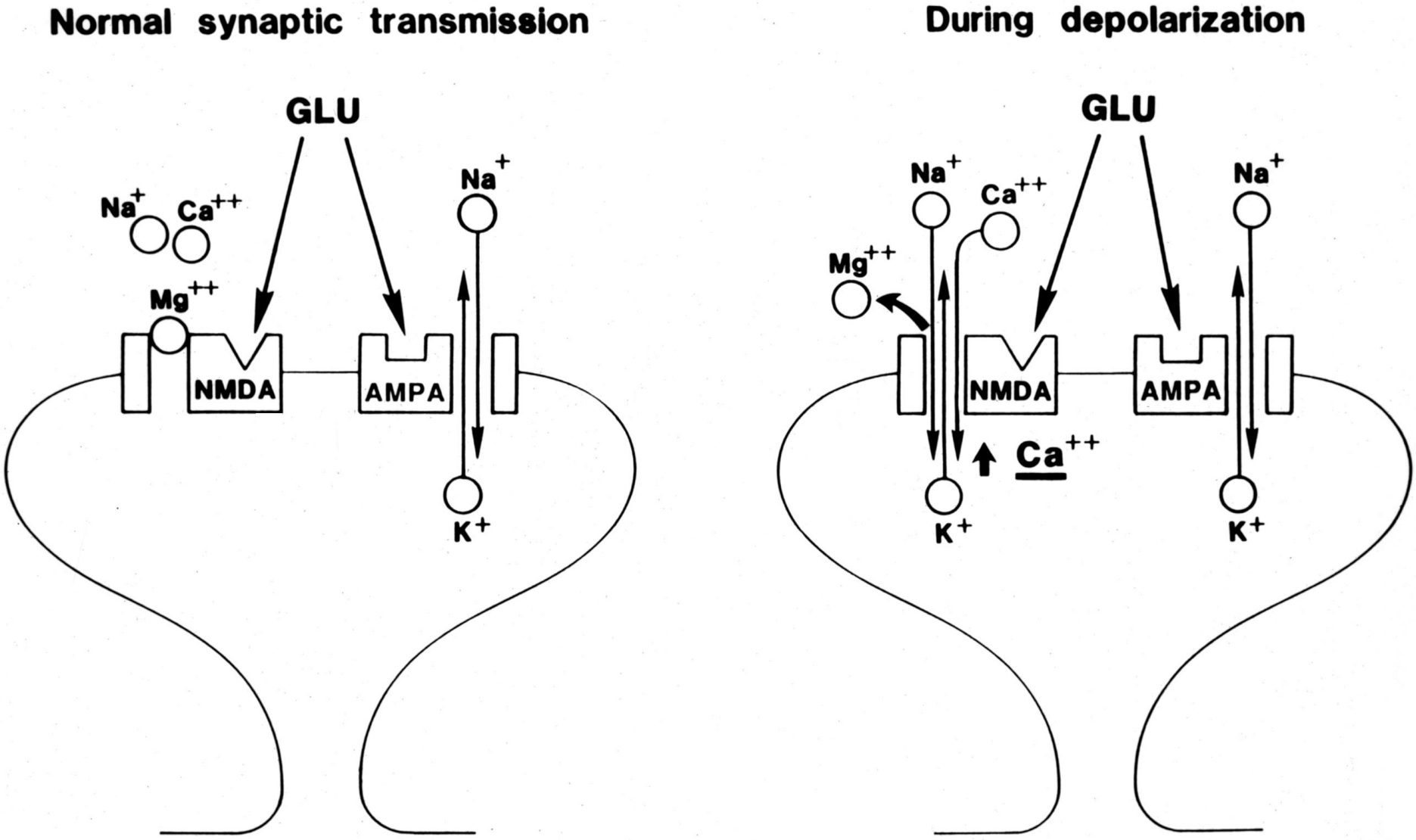
Malenka, *Cell*, 1994

The level of Ca^{++} determines the polarity of synaptic plasticity



Sjostrom and Nelson, *Curr. Opin. Neurobiol.* 2002

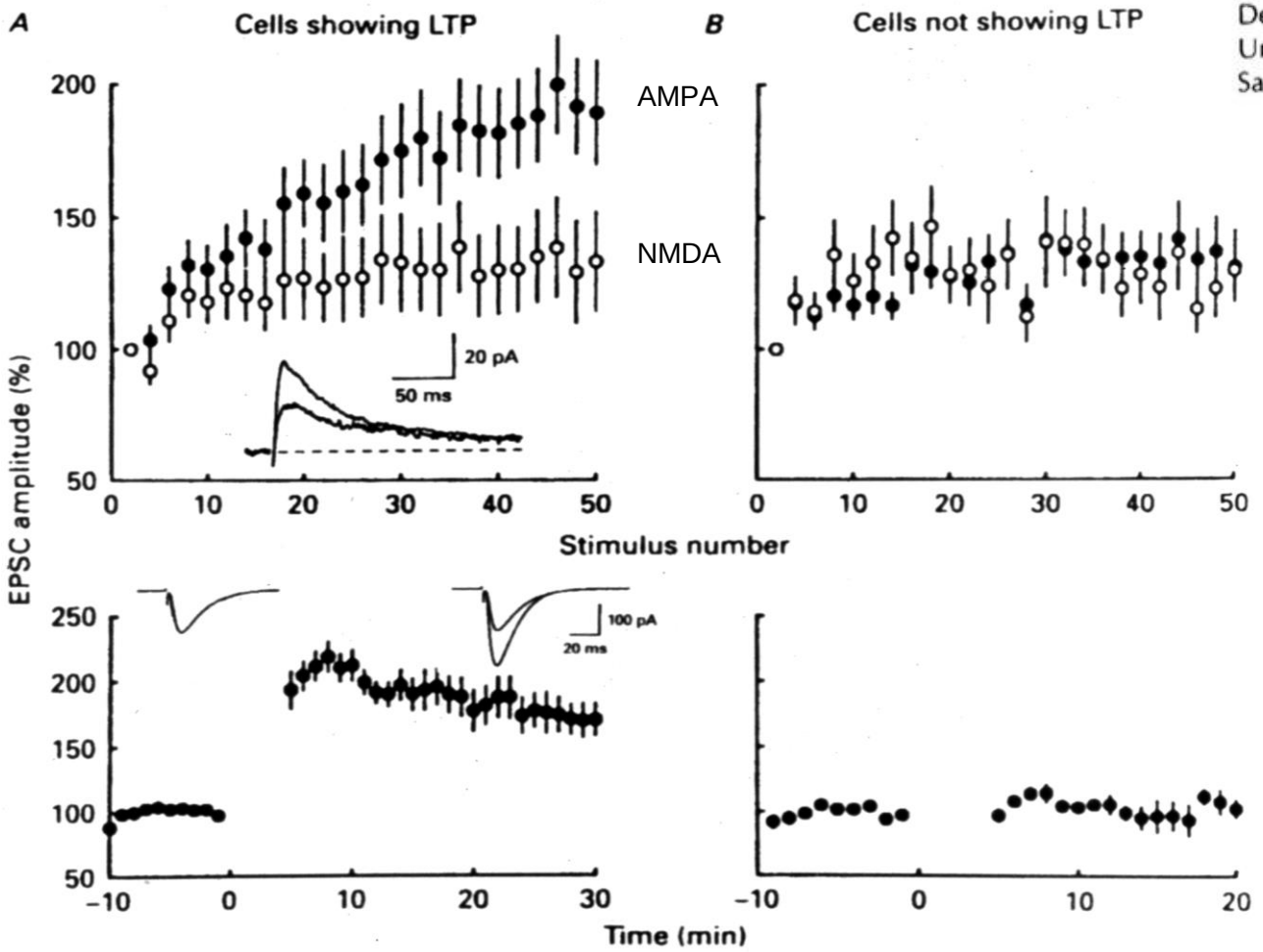
Expression mechanisms of LTP/LTD


Normal synaptic transmission
GLU
Na+
Ca++
Mg++
Na+
NMDA
AMPA
K+
During depolarization
GLU
Na+
Ca++
Mg++
Na+
NMDA
AMPA
Ca++
K+
K+

Neuron, Vol. 1, 911-917, December, 1988, Copyright © 1988 by Cell Press

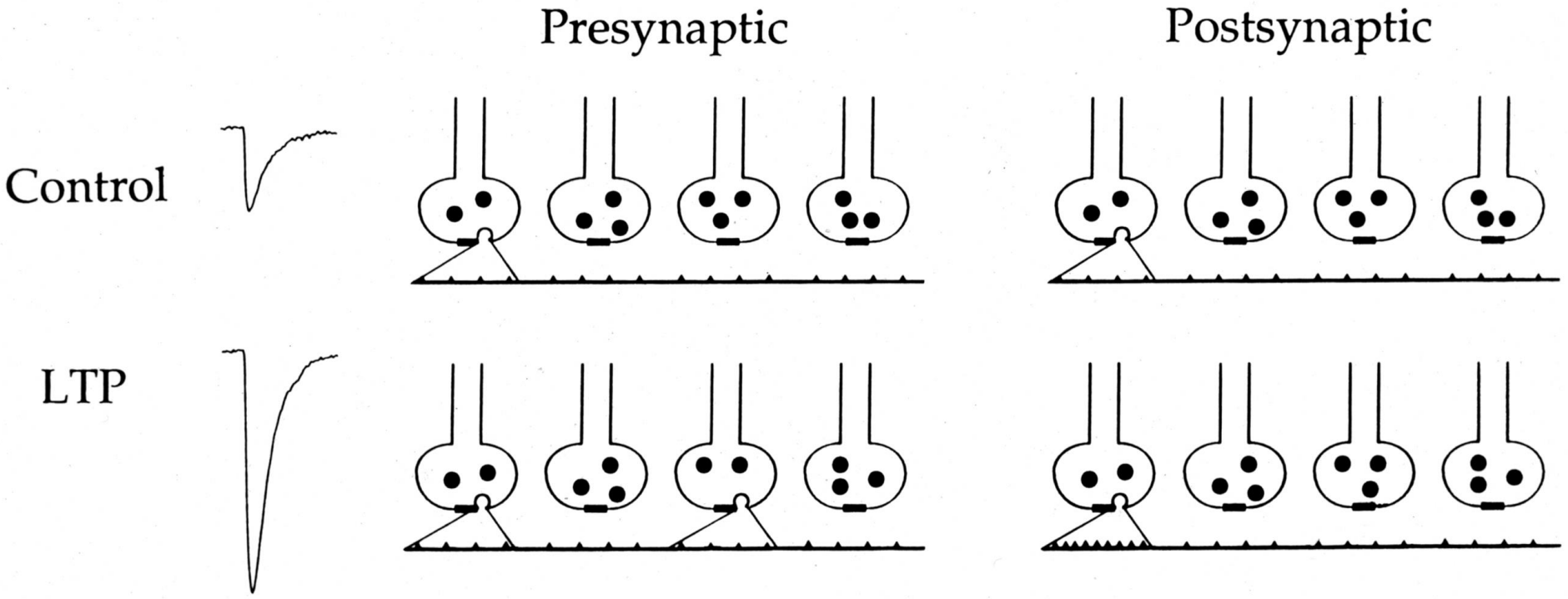
A Persistent Postsynaptic Modification Mediates Long-Term Potentiation in the Hippocampus

Julie A. Kauer, Robert C. Malenka, and Roger A. Nicoll
Departments of Pharmacology and Physiology
University of California
San Francisco, California 94143



Perkel and Nicoll, *J. Physiol.*471:481 (1993)

“Quantal analysis” and LTP



Presynaptic mechanism for long-term potentiation in the hippocampus

John M. Bekkers & Charles F. Stevens

The Salk Institute, Howard Hughes Medical Institute,
10010 North Torrey Pines Road, La Jolla, California 92307, USA

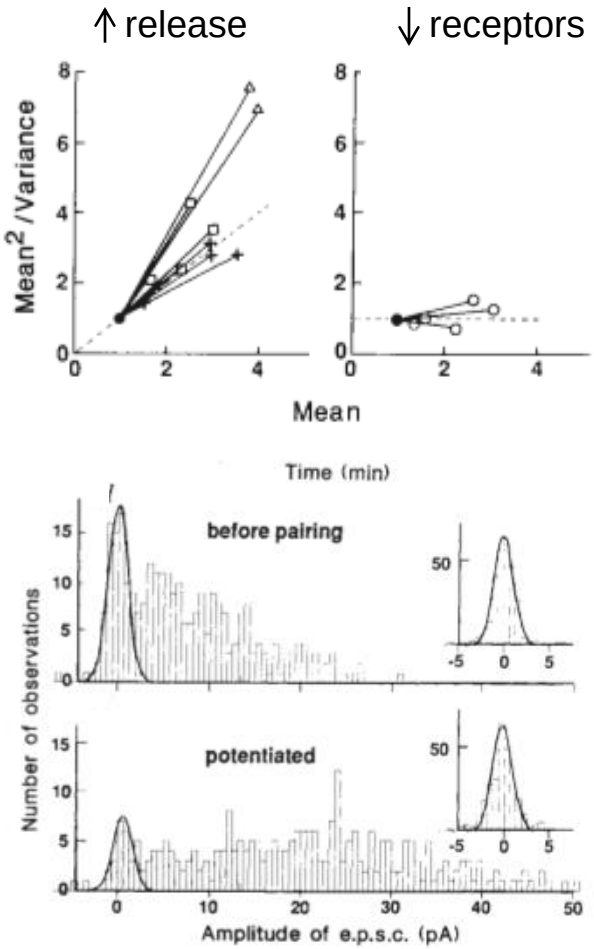
NATURE · VOL 346 · 12 JULY 1990

LETTERS TO NATURE

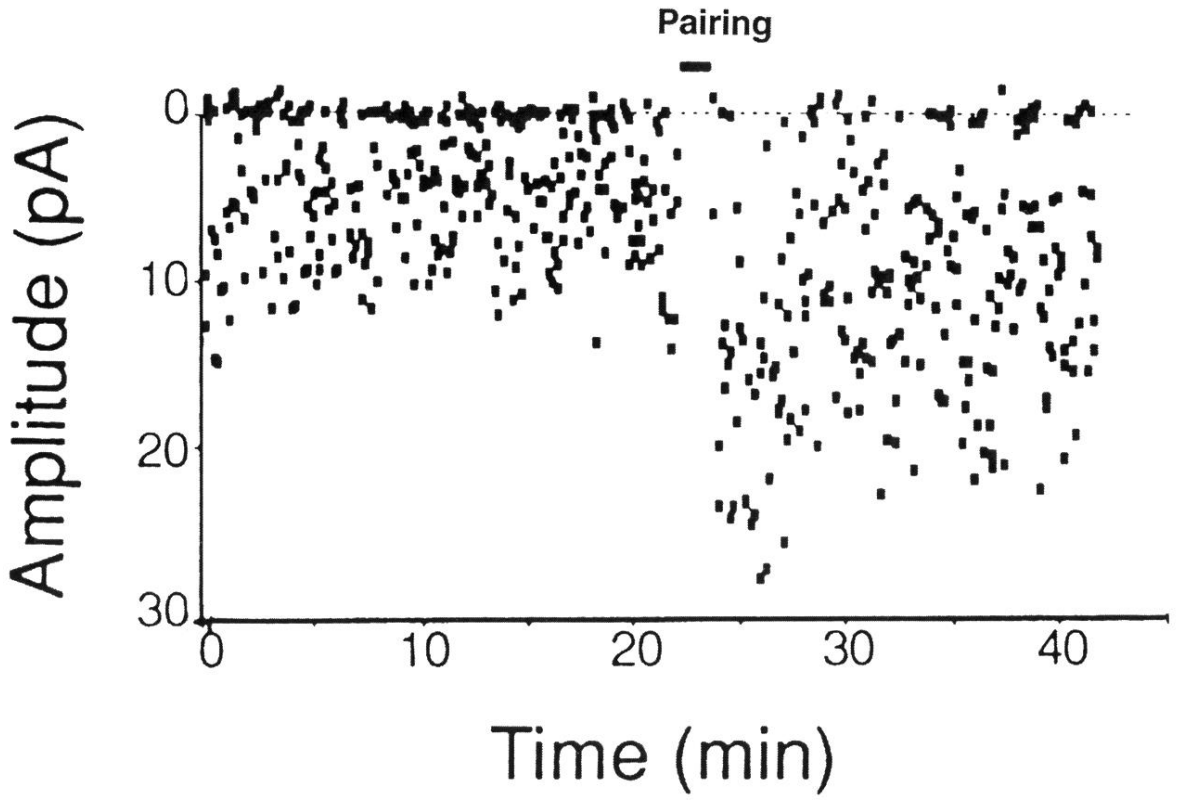
Presynaptic enhancement shown by whole-cell recordings of long-term potentiation in hippocampal slices

Roberto Malinow* & Richard W. Tsien

Department of Molecular and Cellular Physiology, Beckman Center,
Stanford University Medical Center, Stanford, Claifornia, 94305, USA



Synaptic failure rate decreases during LTP



Kullmann and Nicoll *Nature* 1992

Can molecules explain long-term potentiation?

Joshua R. Sanes and Jeff W. Lichtman

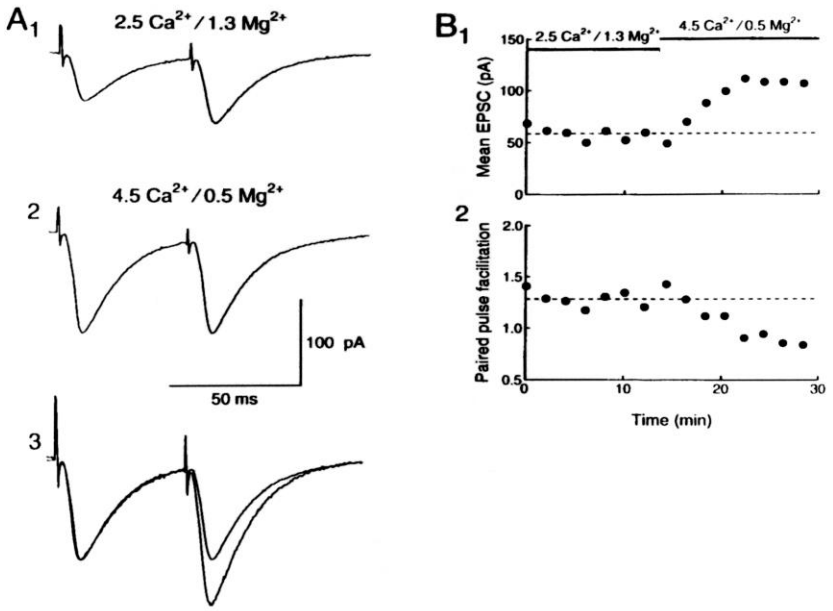
Although over 100 molecules have been implicated in long-term potentiation and depression, no consensus on their underlying molecular mechanisms has emerged. Here we discuss the difficulties of providing molecular explanations for cellular neurobiological phenomena.

nature *neuroscience* • volume 2 no 7 • july 1999

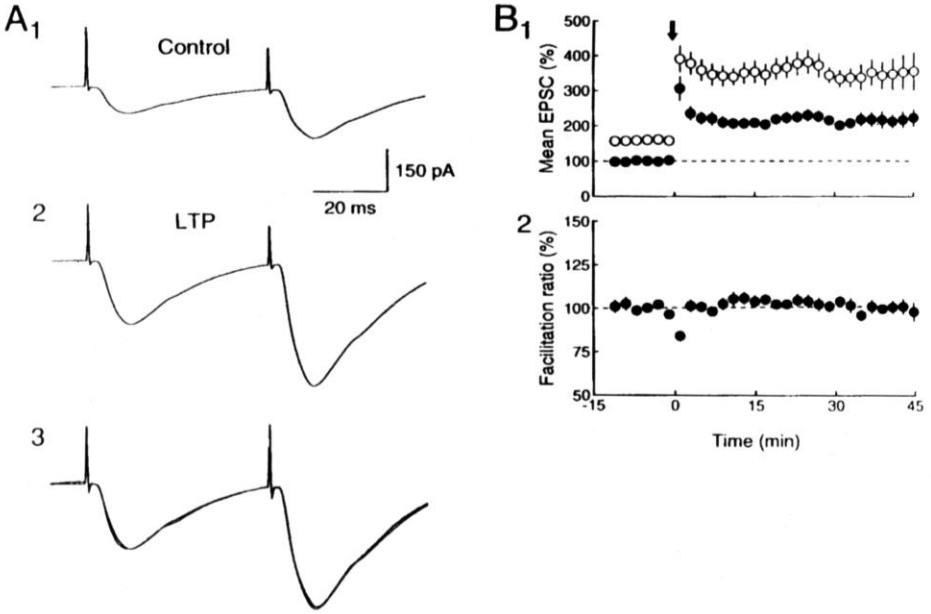
"Does LTP exist? ….when humans go looking for something they often find it – even when it is not there…seeing a…Mickey Mouse in a peculiar arrangement of clouds"

Increasing P_r Decreases Paired Pulse Facilitation (PPF): LTP Does Not

Increasing Ca/Mg ratio

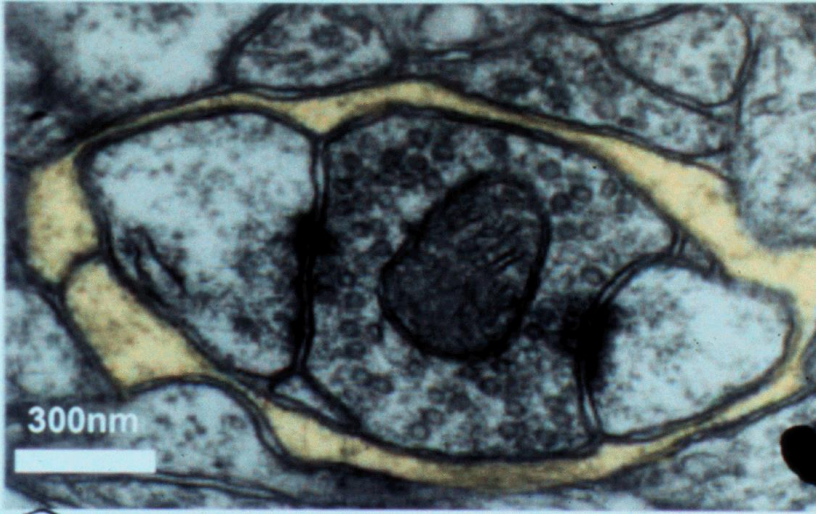


LTP

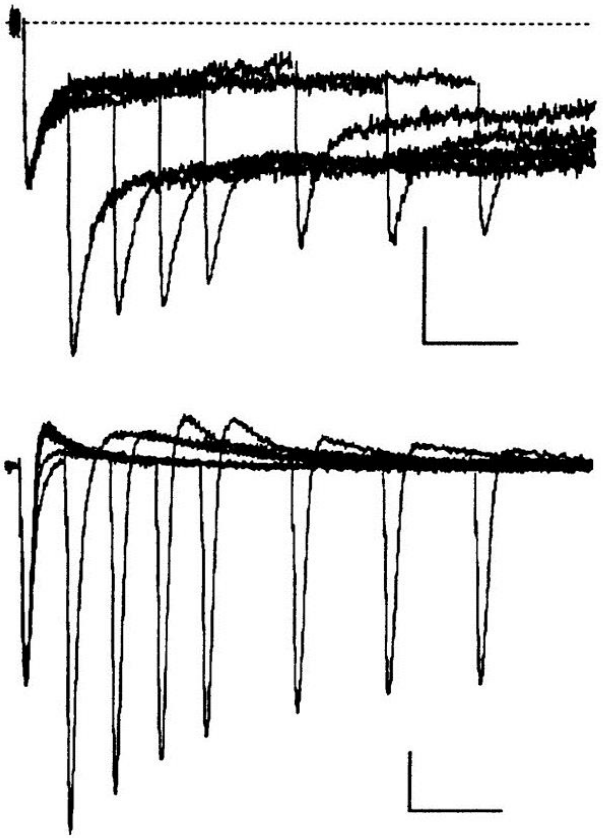


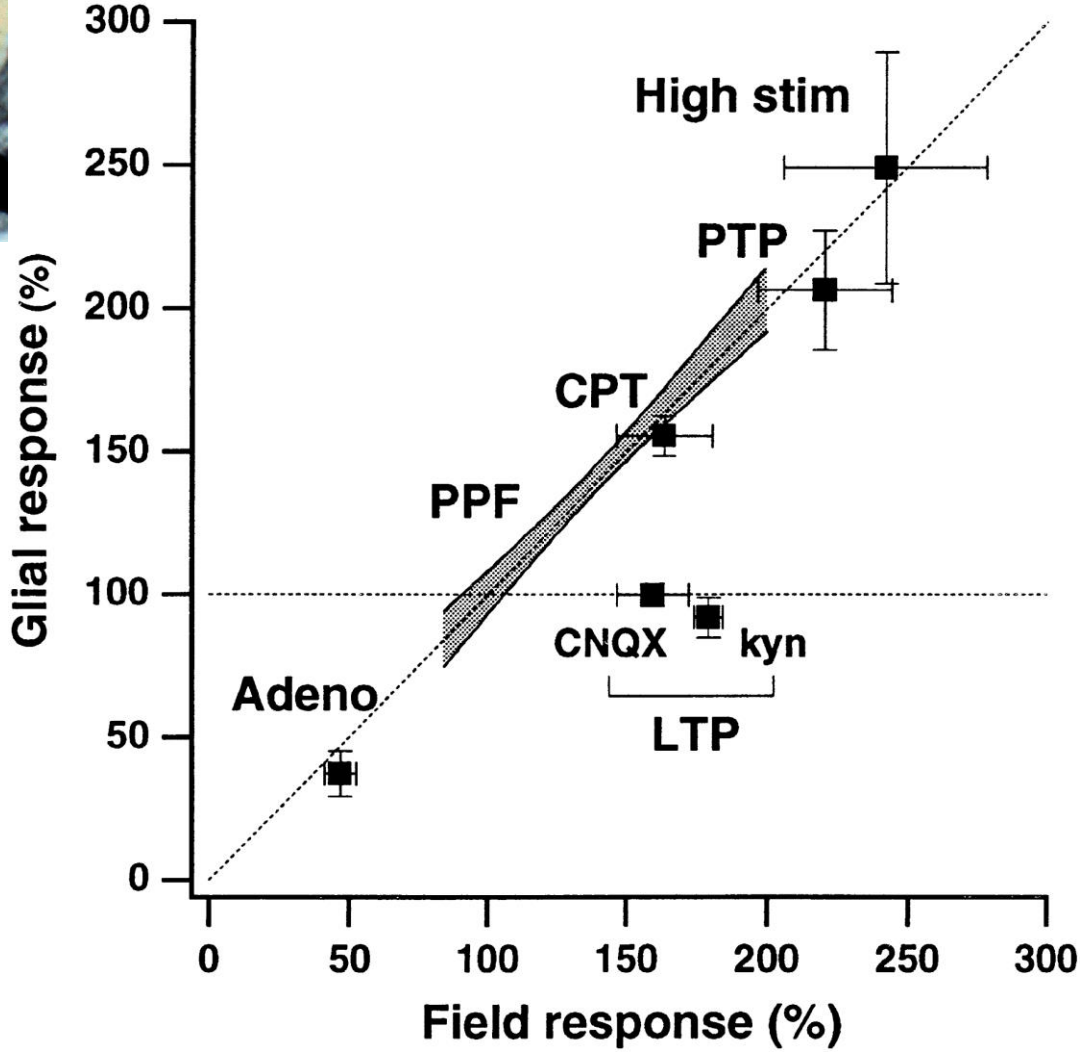
Manabe et al., *J. Neurophysiol.* 70: 1451-1459 (1993)

Monitoring synaptically released glutamate with glial glutamate transporter currents



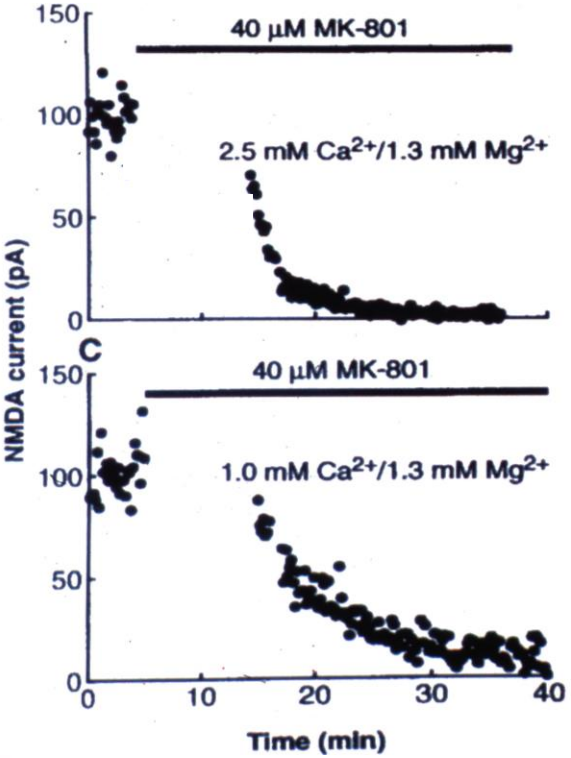
Spacek, 1985

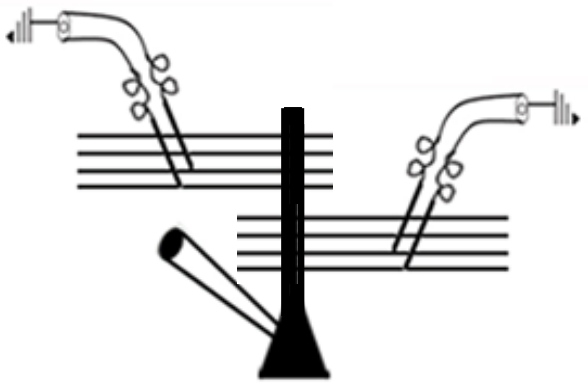


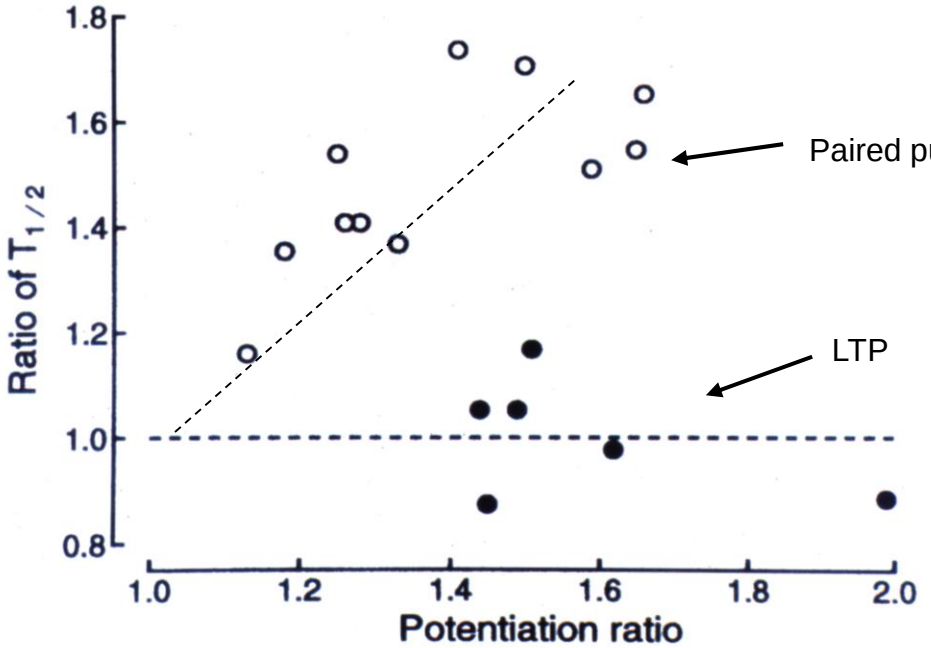


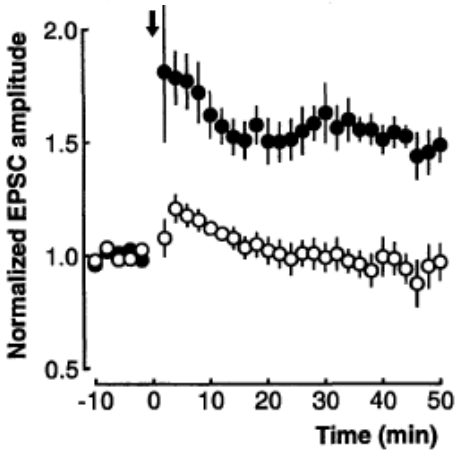
Luscher, et al., *Neuron, 1998*

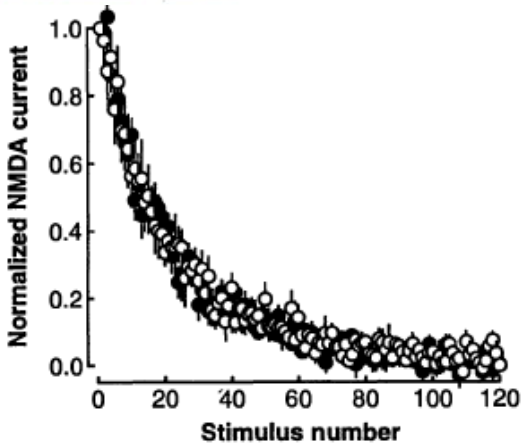
MK-801 Fails to Detect an Increase in Glutamate Release During LTP





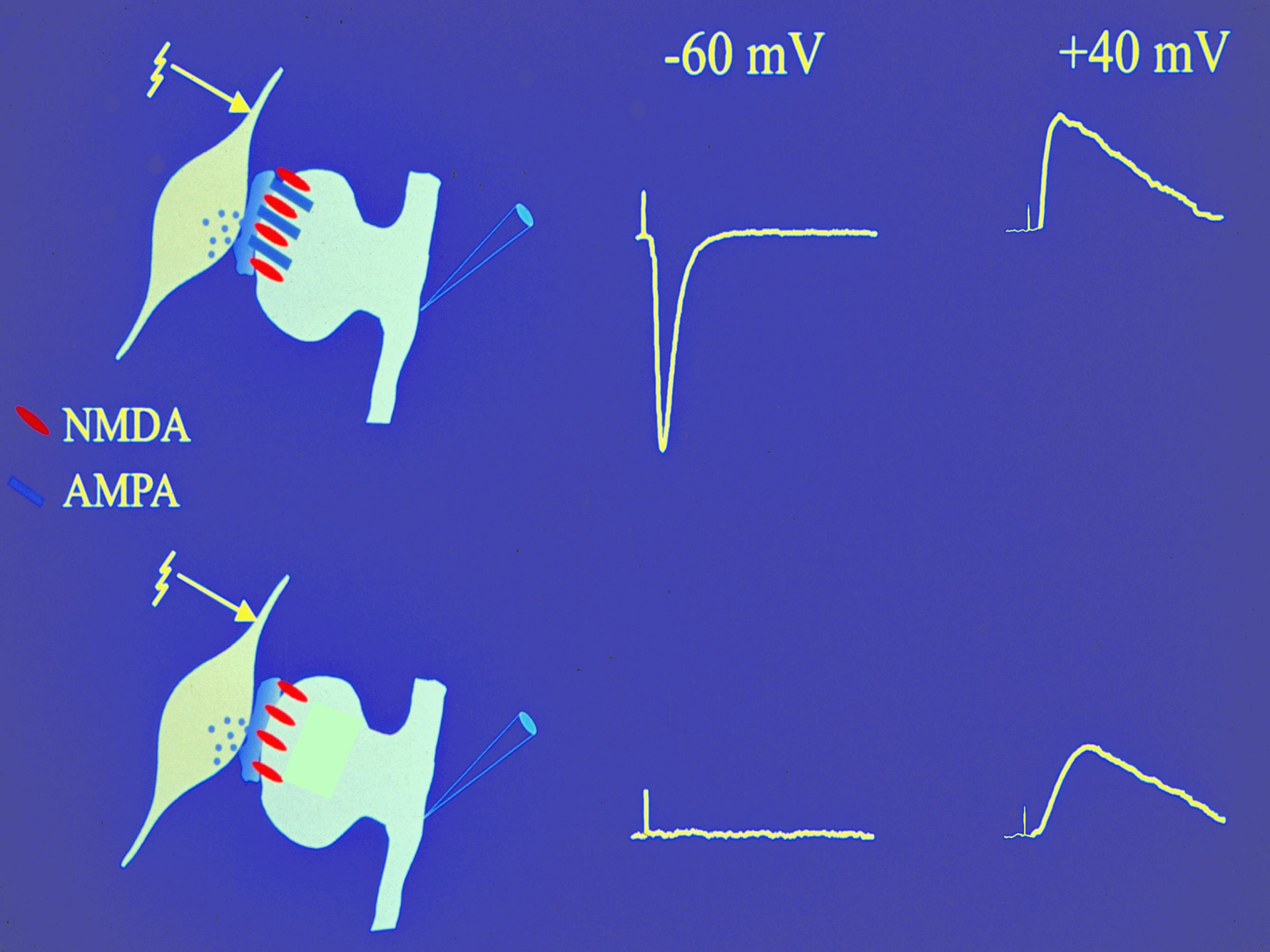




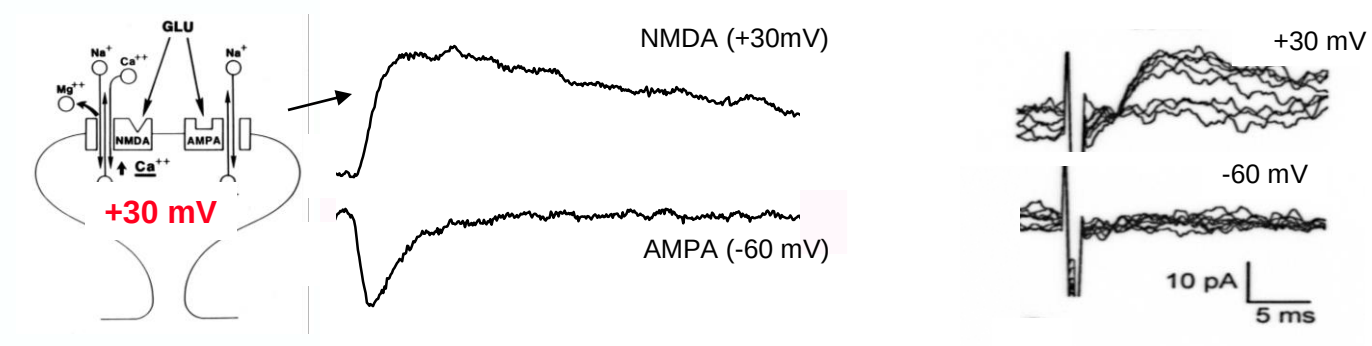


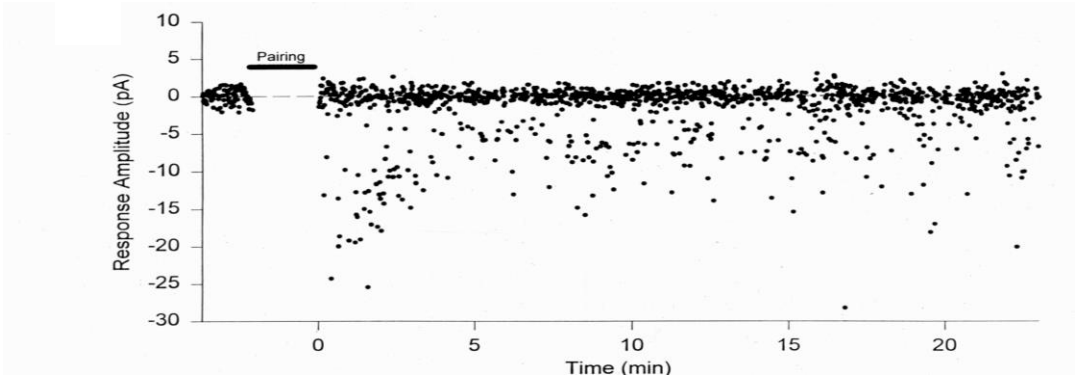
"How can the present results be reconciled with studies using quantal analysis? The decrease in failures is usually interpreted as an increase in P_r. Alternatively, the decrease in failures could reflect the appearance of patches of functional AMPA receptors on the postsynaptic cell".

Manabe and Nicoll Science 1994

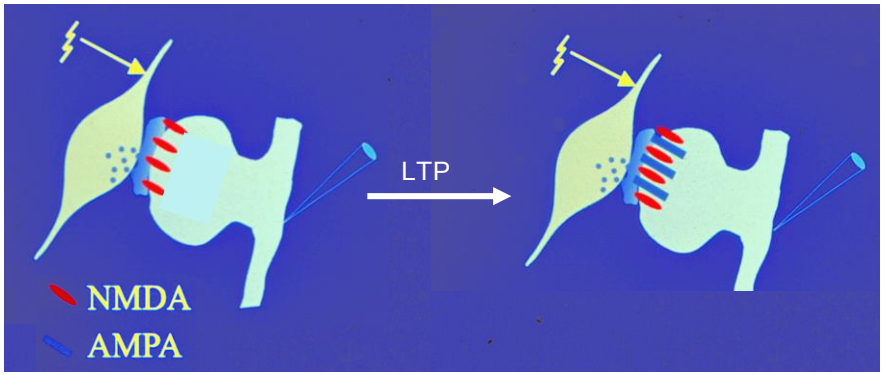

-60 mV
+40 mV
NMDA
AMPA

Silent Synapses





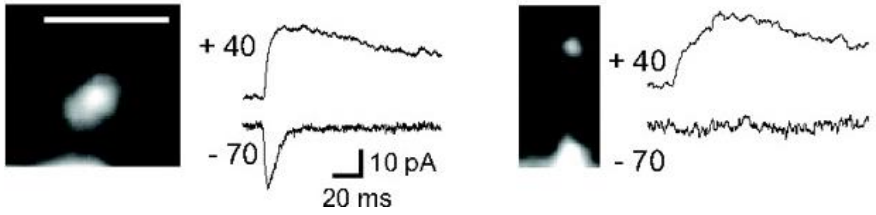
AMPAfication can occur in the absence of any change in the NMDA response



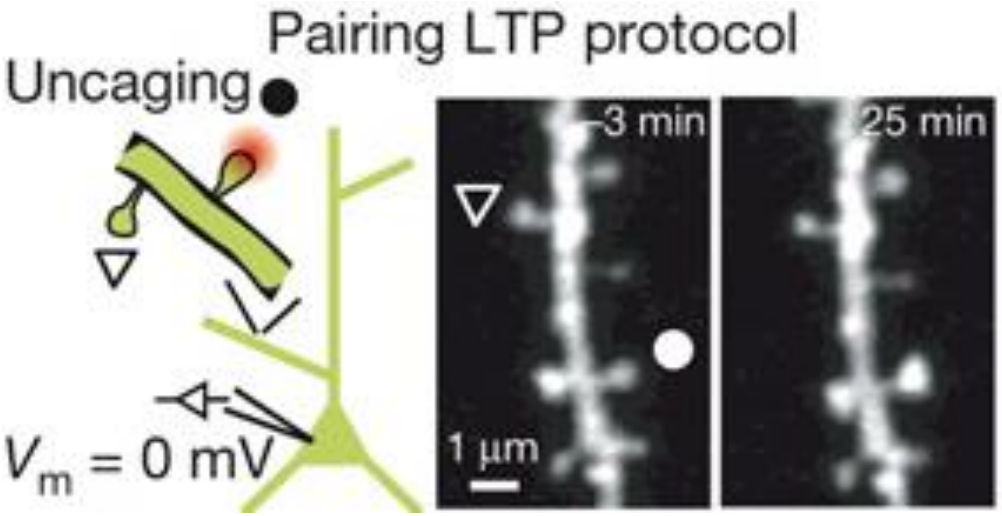
Isaac *et al., Neuron,* 15:427 (1995)

also: Liao et al., *Nature* (1995)

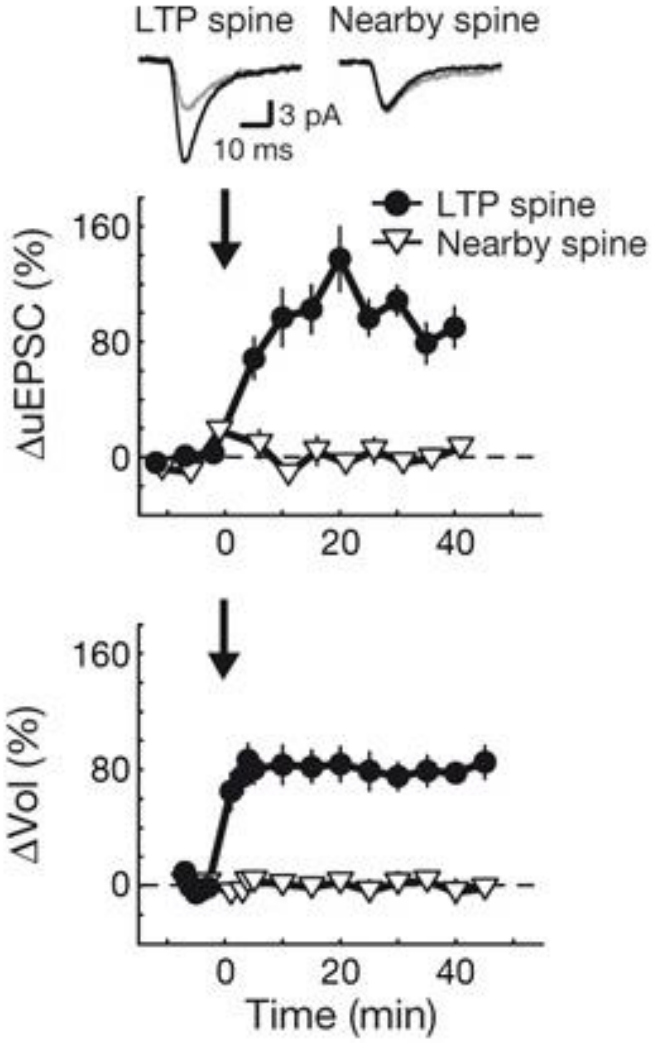
Synapse specific LTP of glutamate uncaging responses on single spines



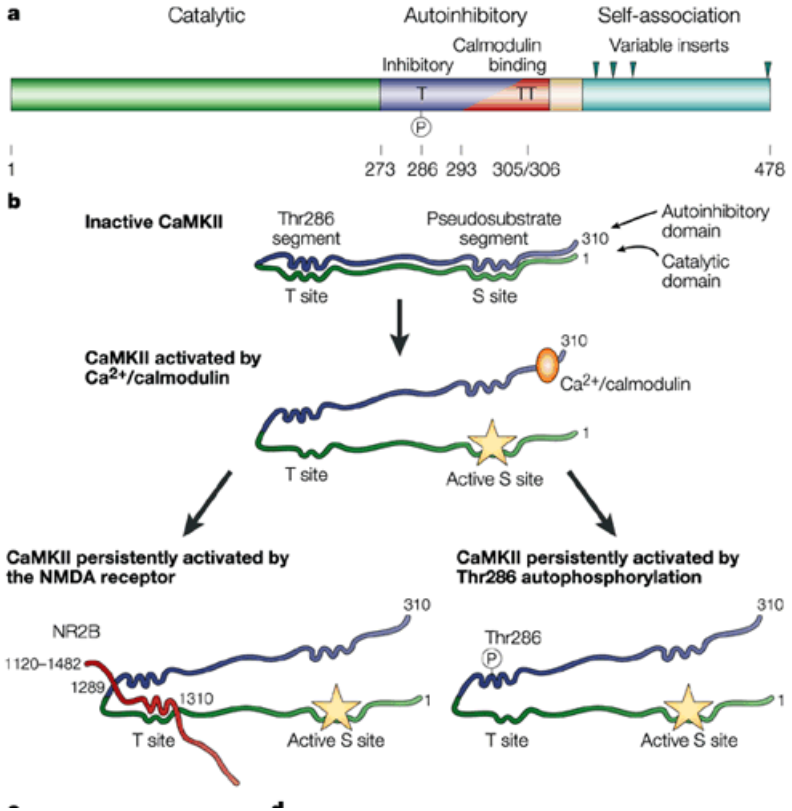
Beique et al., PNAS 103:19535-19540 (2006)



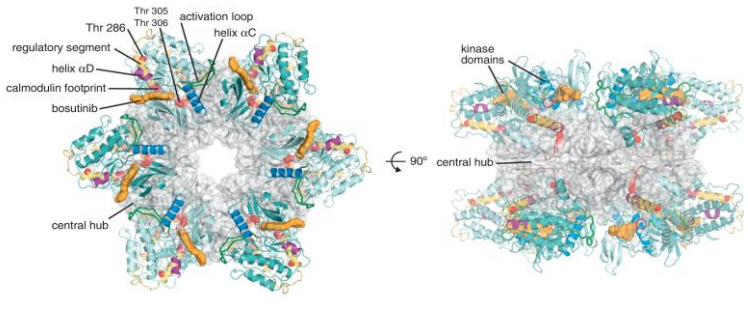
Harvey and Svoboda Nature 450:1195-2000 (2007)



Structure and regulation of CaMKII

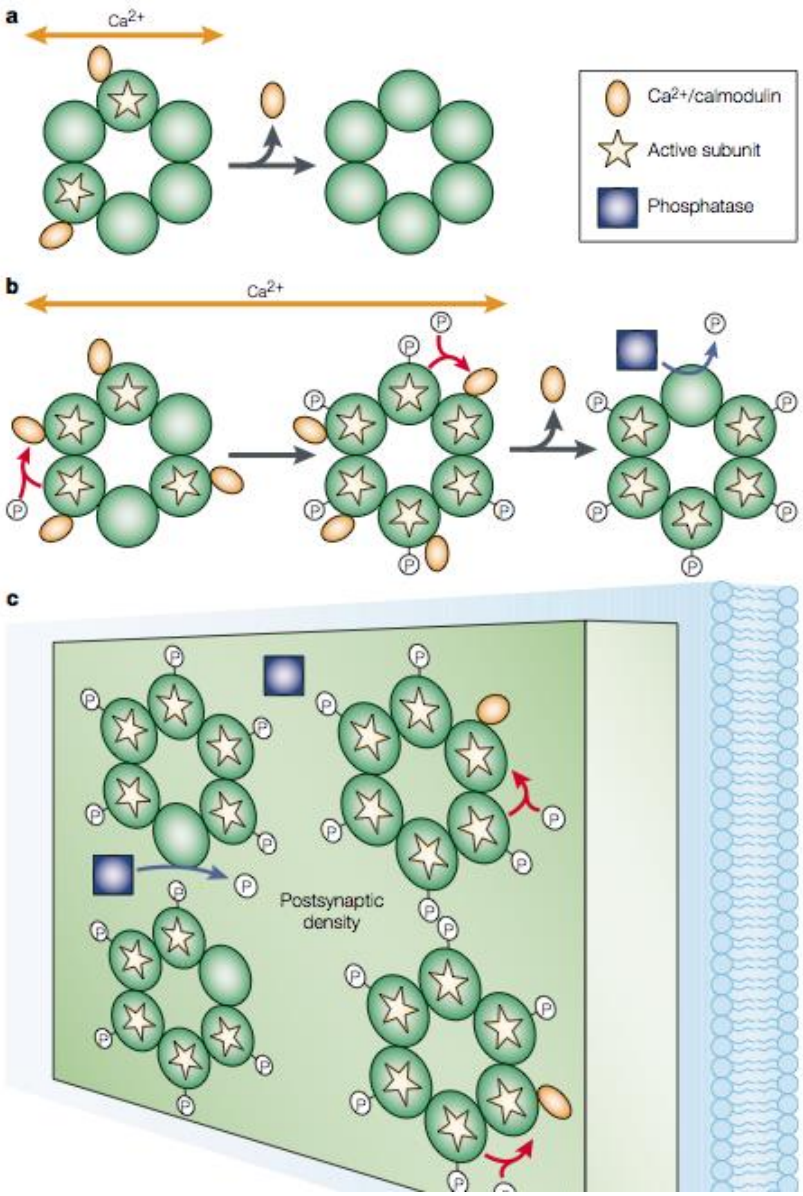


Lisman et al., Nat. Rev. Neurosci., 2002



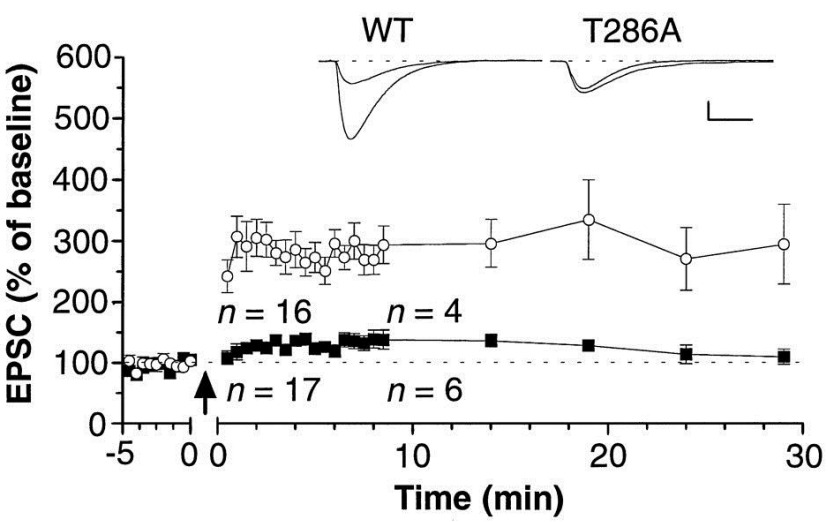
Stratton, et al. Curr. Op. Structural Bio., 2013

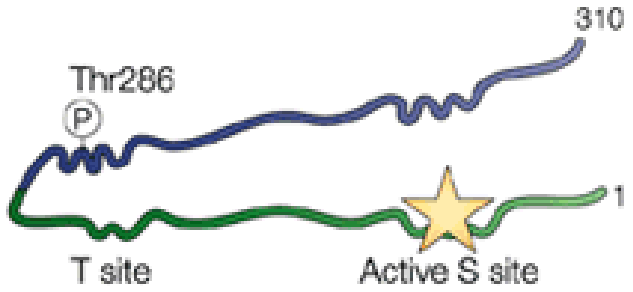
Different forms of CaMKII activation

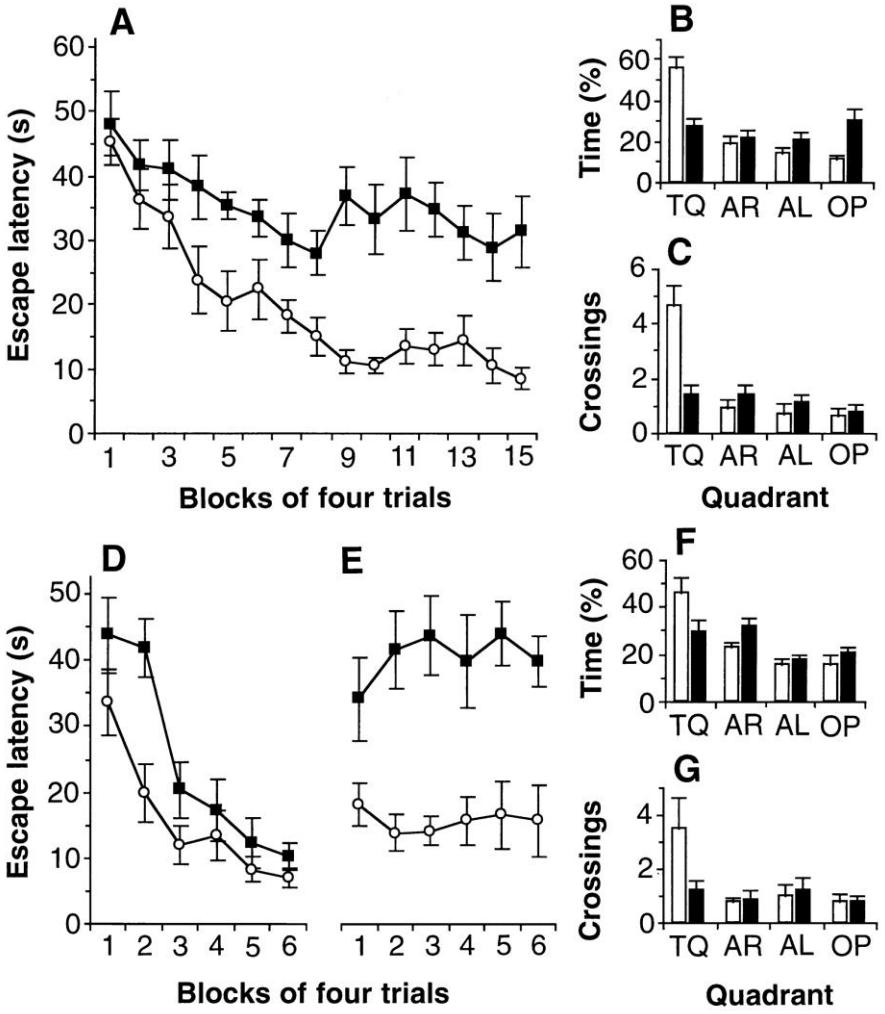


Lisman et al., Nat. Rev. Neurosci. 2002

Autophosphorylation at Thr^{286} of the α Calcium-Calmodulin Kinase II in LTP and Learning

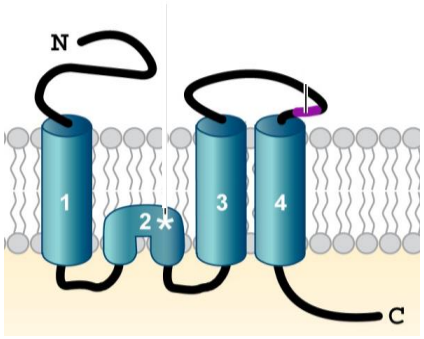




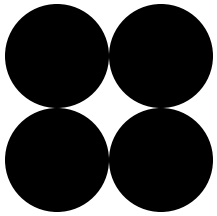


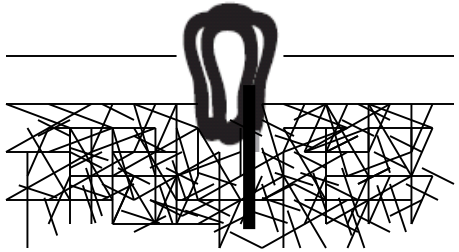
K P Giese et al. Science 1998;279:870-873

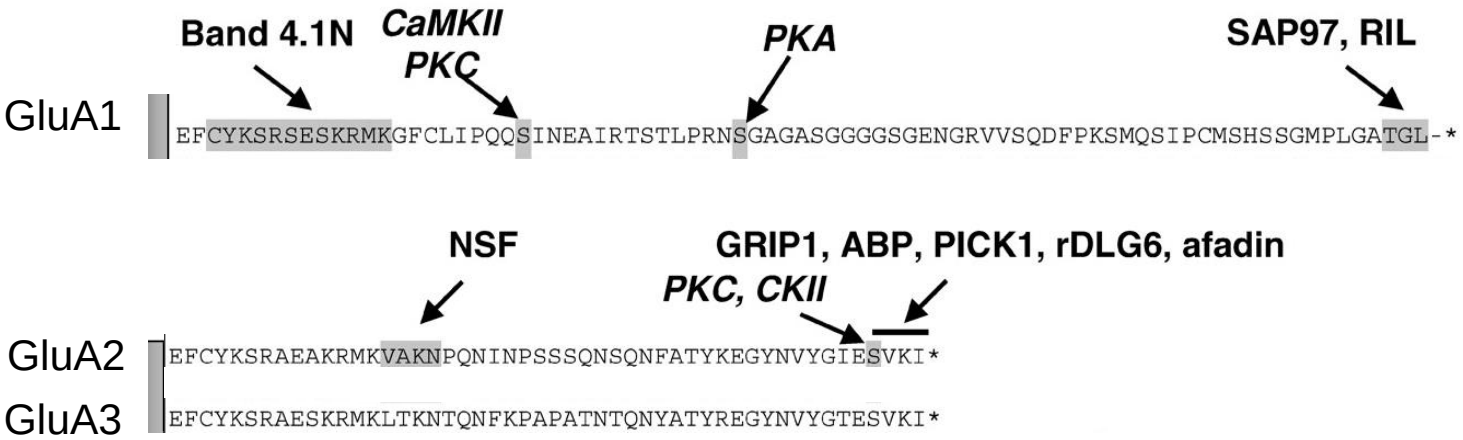
The C-tails are sites for protein-protein interactions and phosphorylation



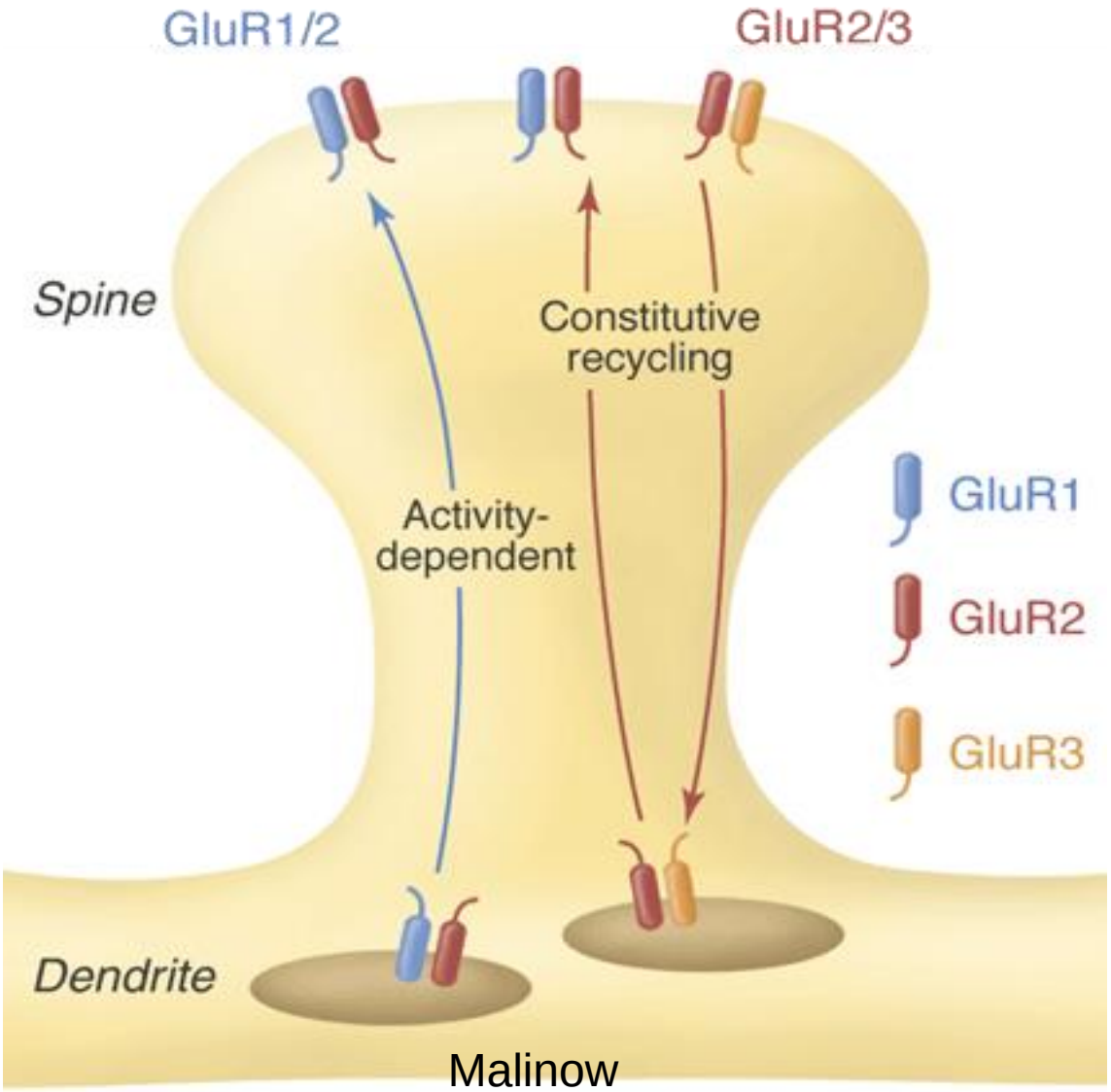
GluA1 - GluA3





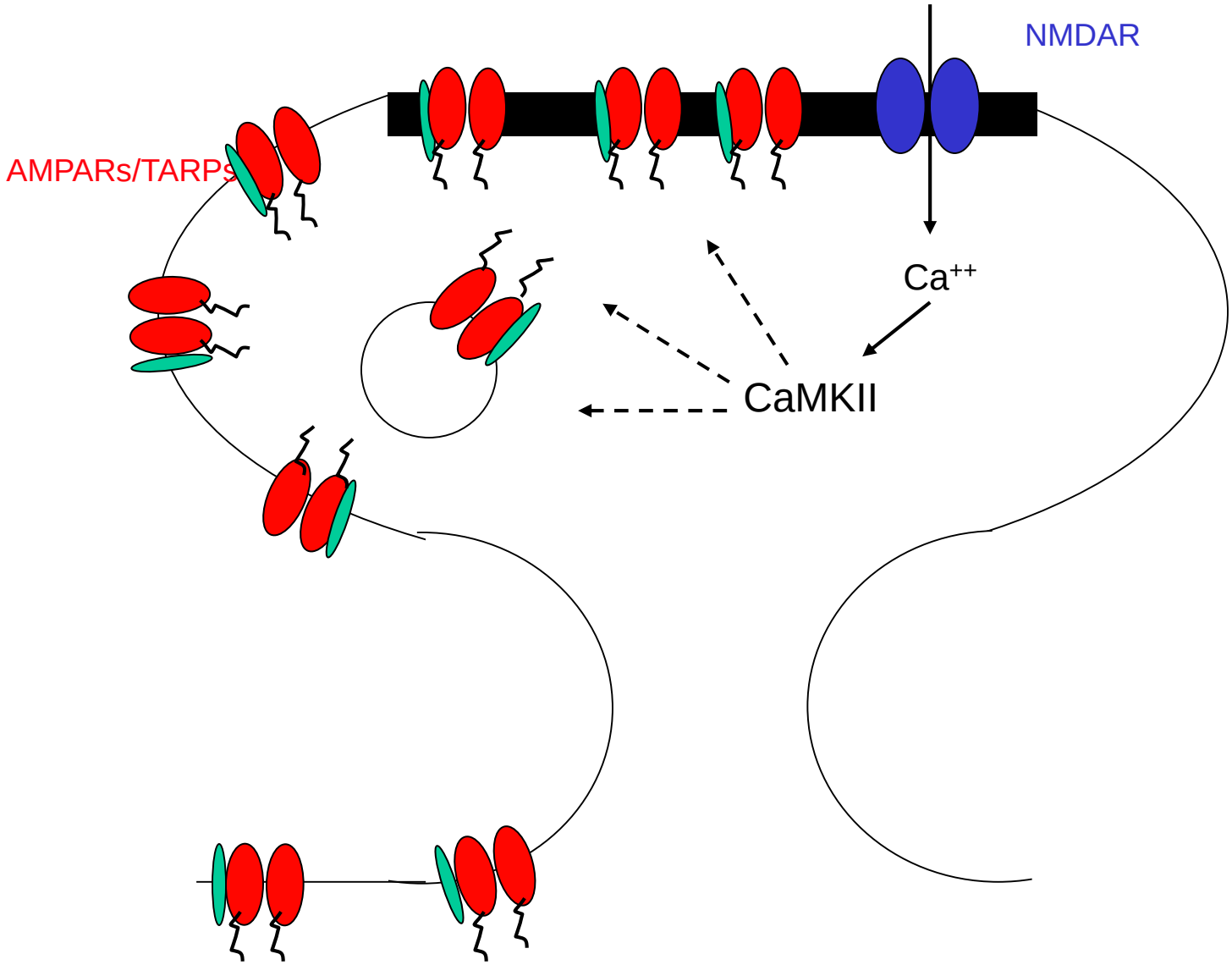


Role of subunits and their C-tails in AMPA receptor trafficking

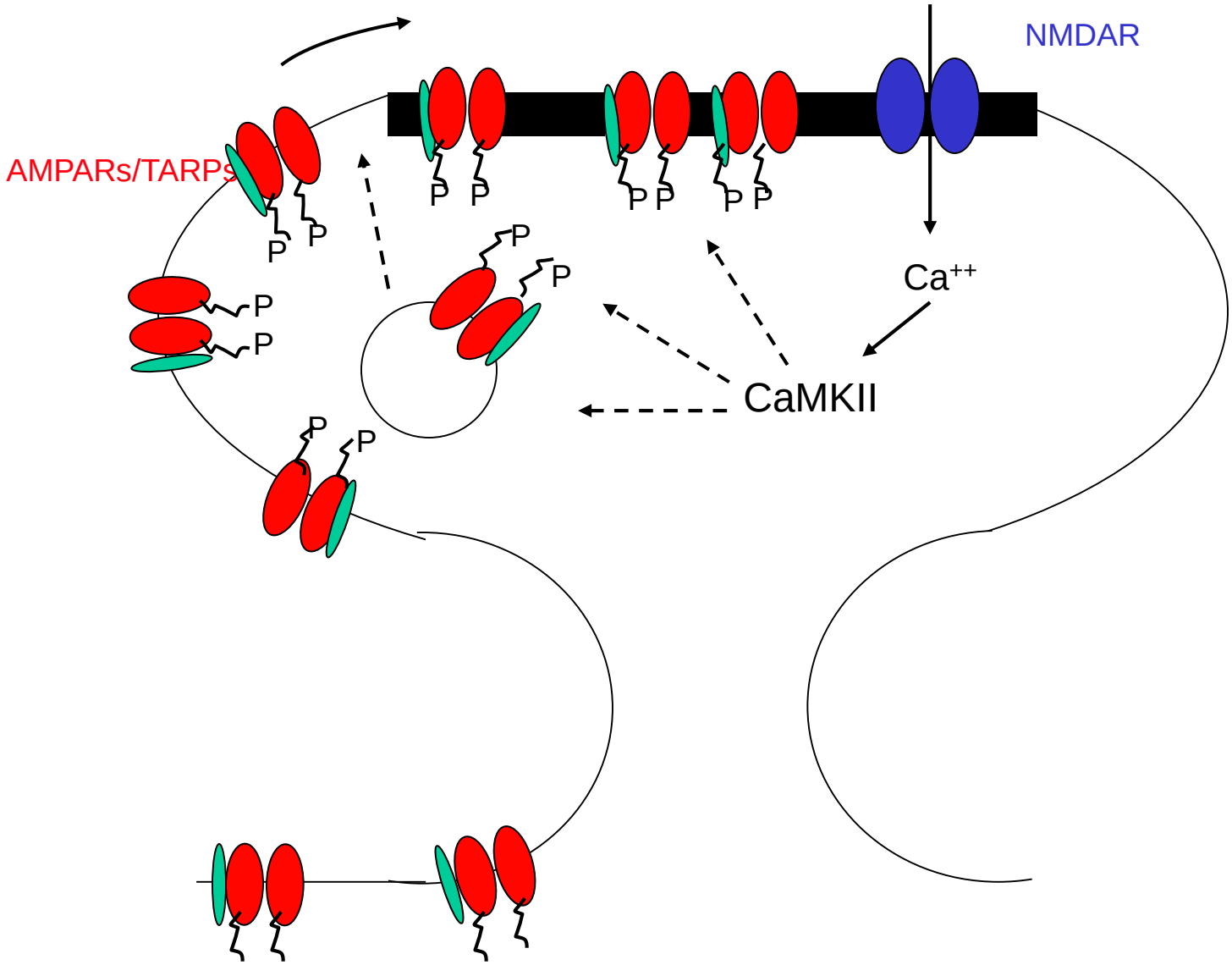


Malinow

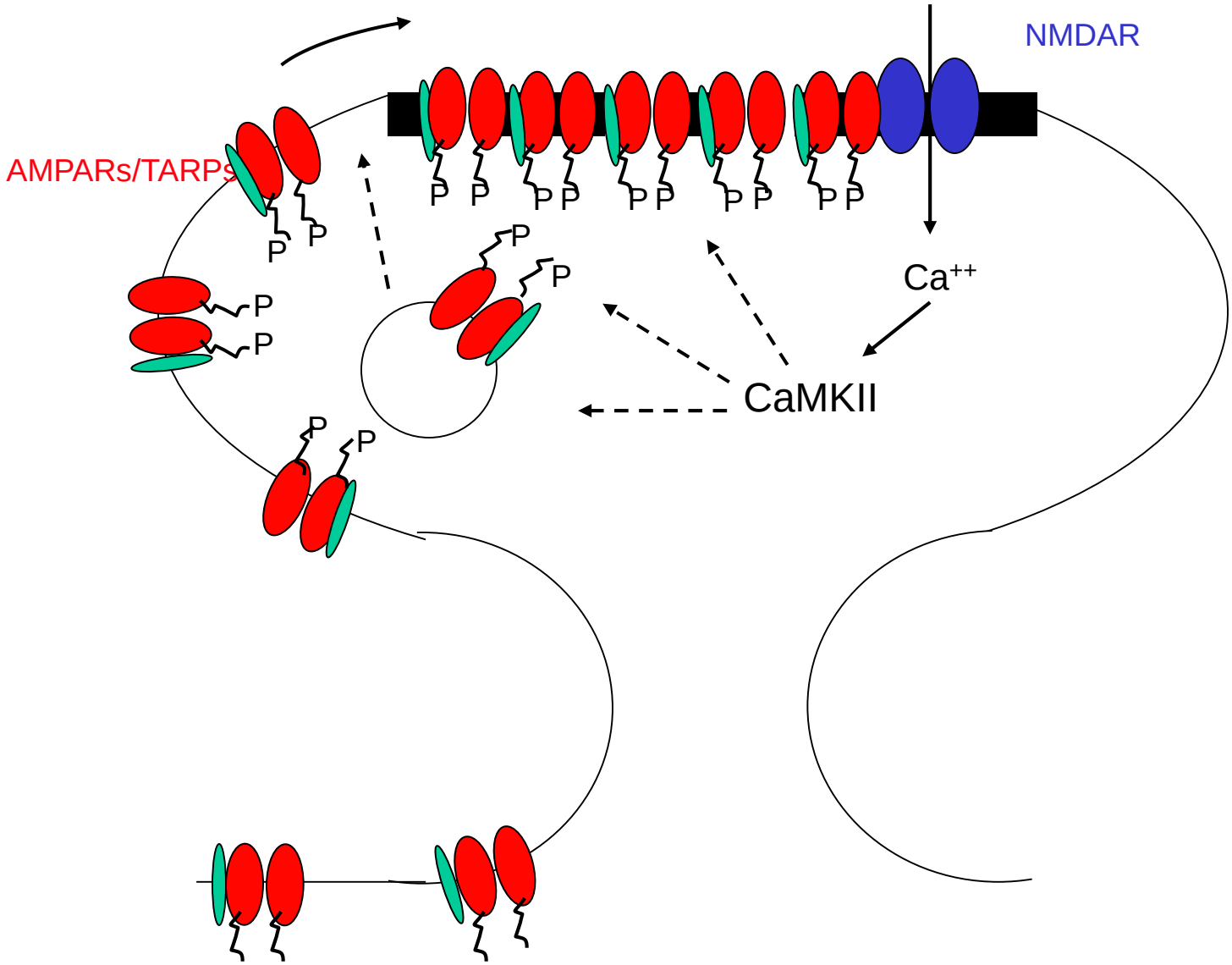
Receptor Centric Model



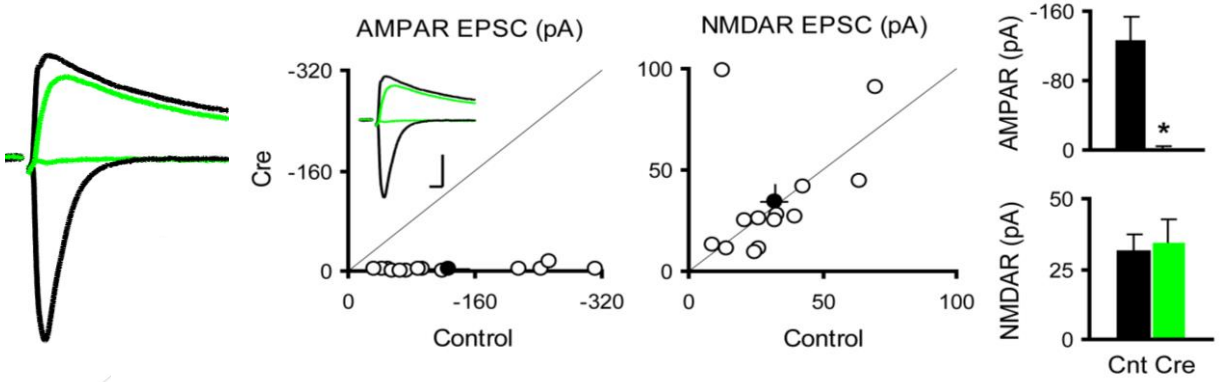
Receptor Centric Model



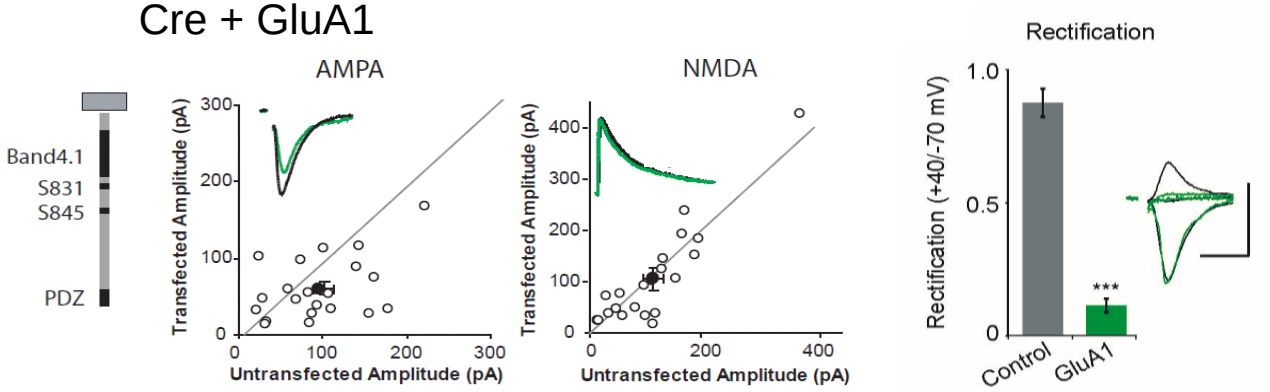
Receptor Centric Model



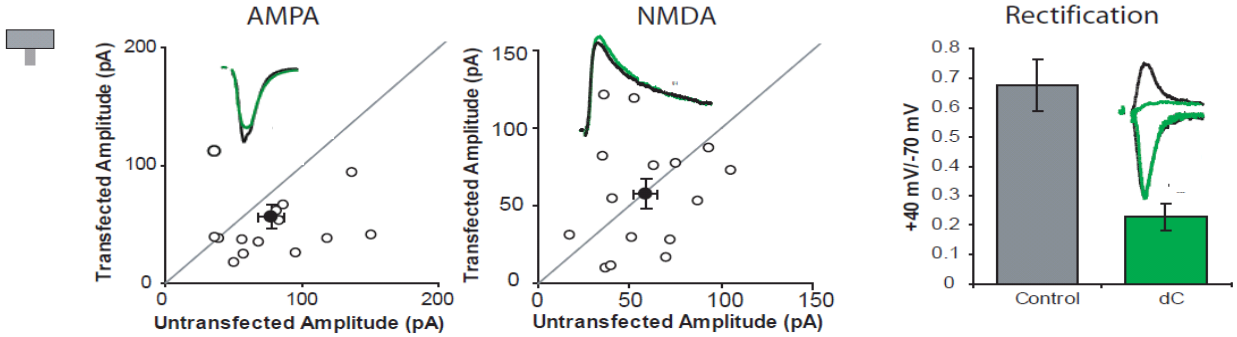
Single Cell deletion and replacement of AMPAR subunits



Cre + GluA1



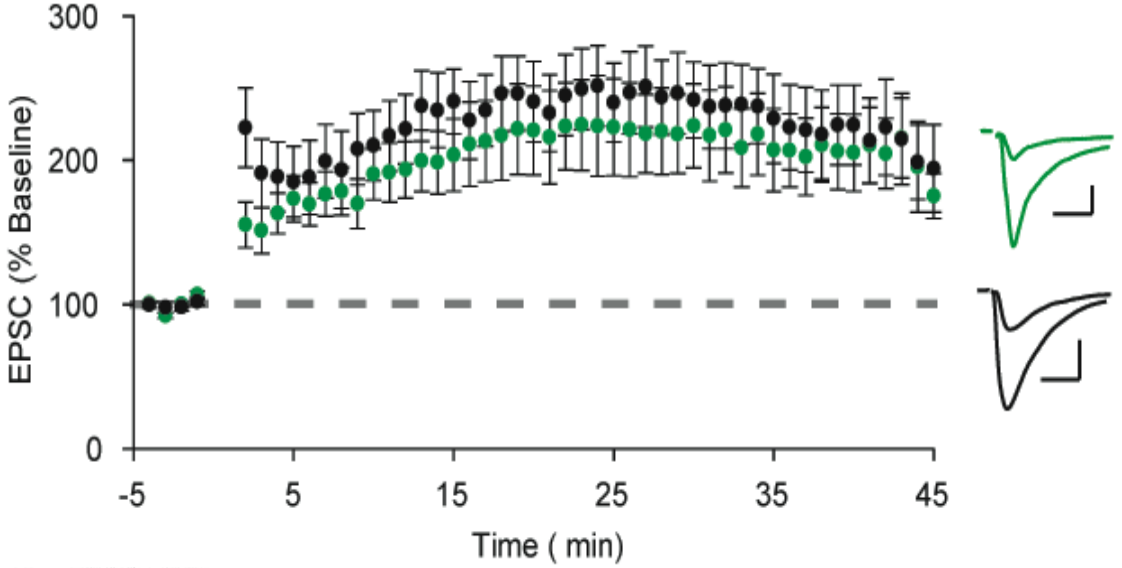
Cre + GluA1ΔC



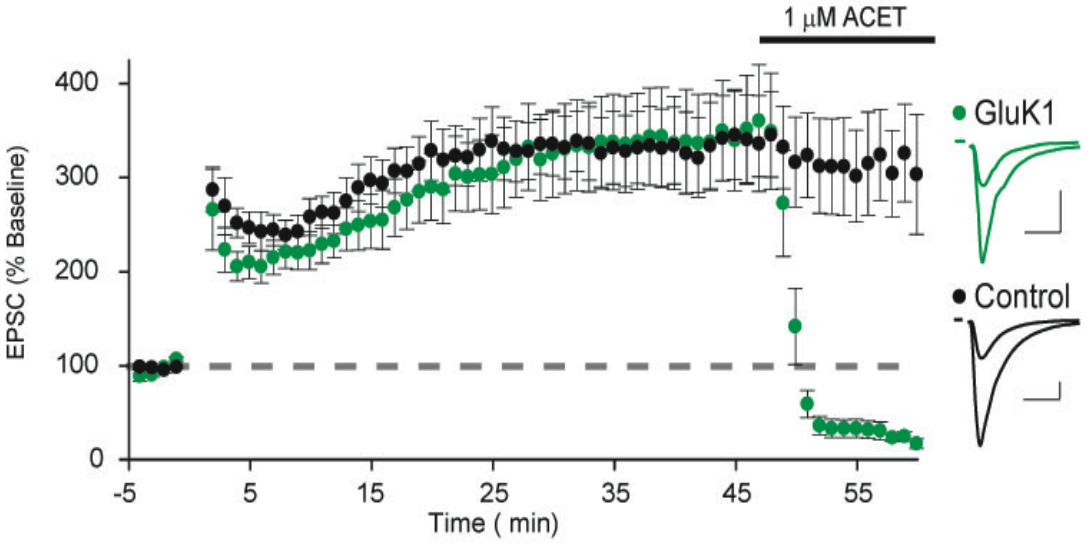
The C-tail of GluA1 is not required for synaptic targeting

Single Cell deletion and replacement of AMPAR subunits

GluA1ΔC

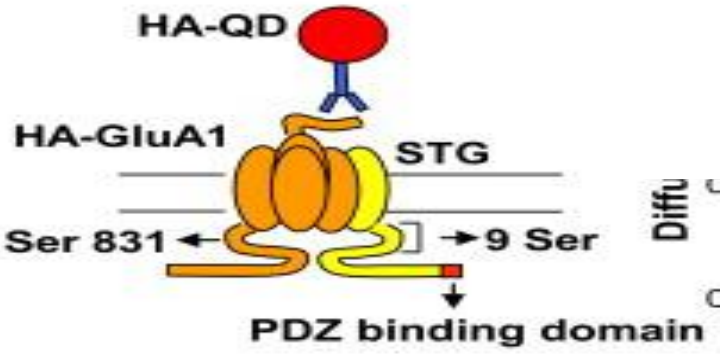


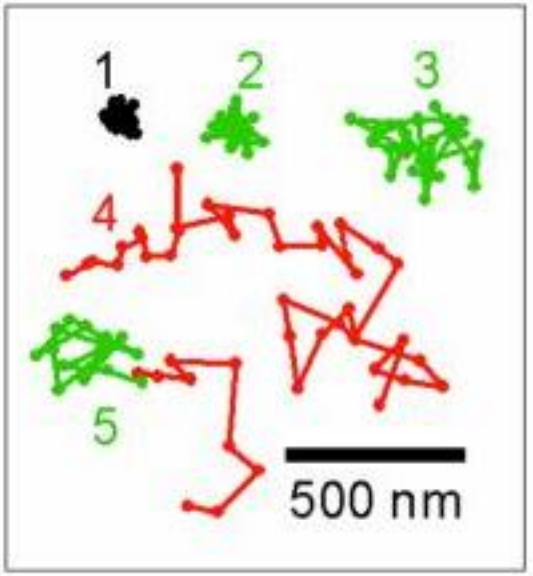
Kainate receptor



Single particle tracking of AMPARs

Cy5 labeled Anti-GluA2 antibodies





Tardin et al. EMBO J. (2003)

PSD Centric Model (Capture)