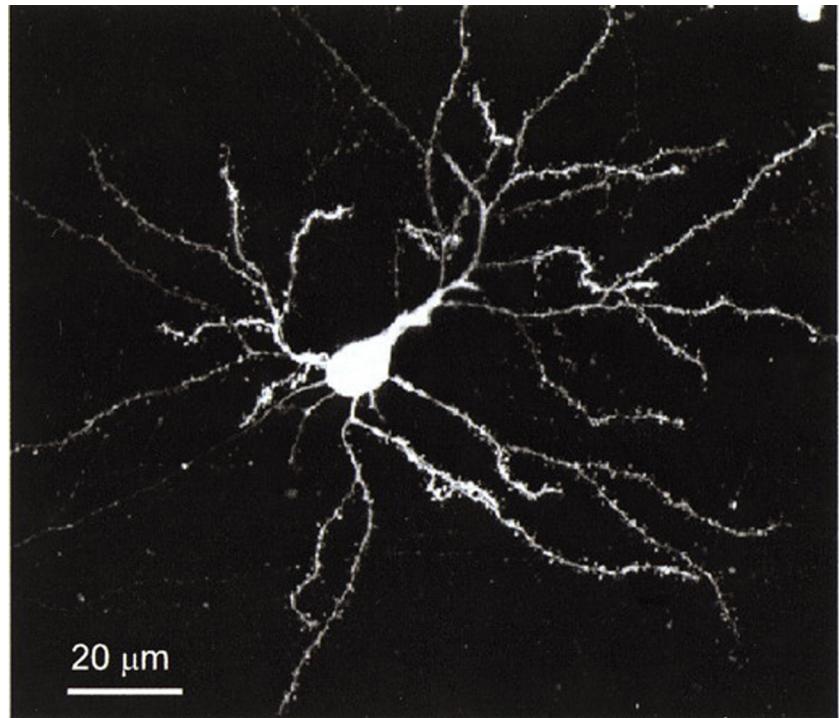


# How memories are encoded?



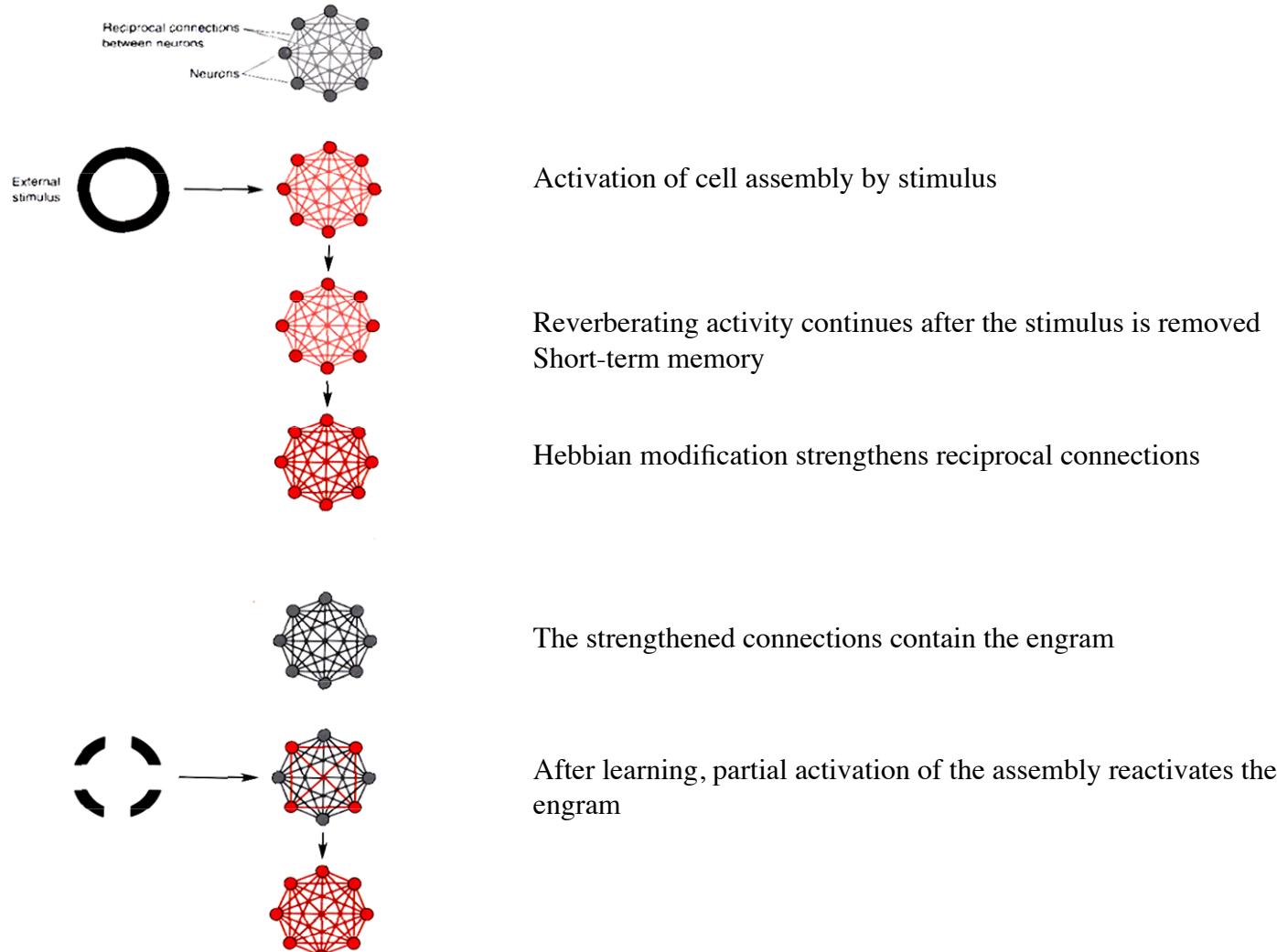
How could experience be written into  
neuronal memory?

Synaptic function  
Intrinsic electrical properties  
Morphology

## Synaptic hypothesis of learning

Storage capacity: consider the neocortex  $\sim 2^{11}$  cells,  $2 \times 10^{15}$  synapses,  $\sim 10^{16}$  bytes  
10,000Gbytes

## Hebbian Learning



## Hebb's postulate

*“When an axon of cell A is near enough to excite cell B and repeatedly or 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, is increased.”*

*From the “Organization of Behavior” by D. O. Hebb (1949)*

Cells that fire together are wired together

(1949)

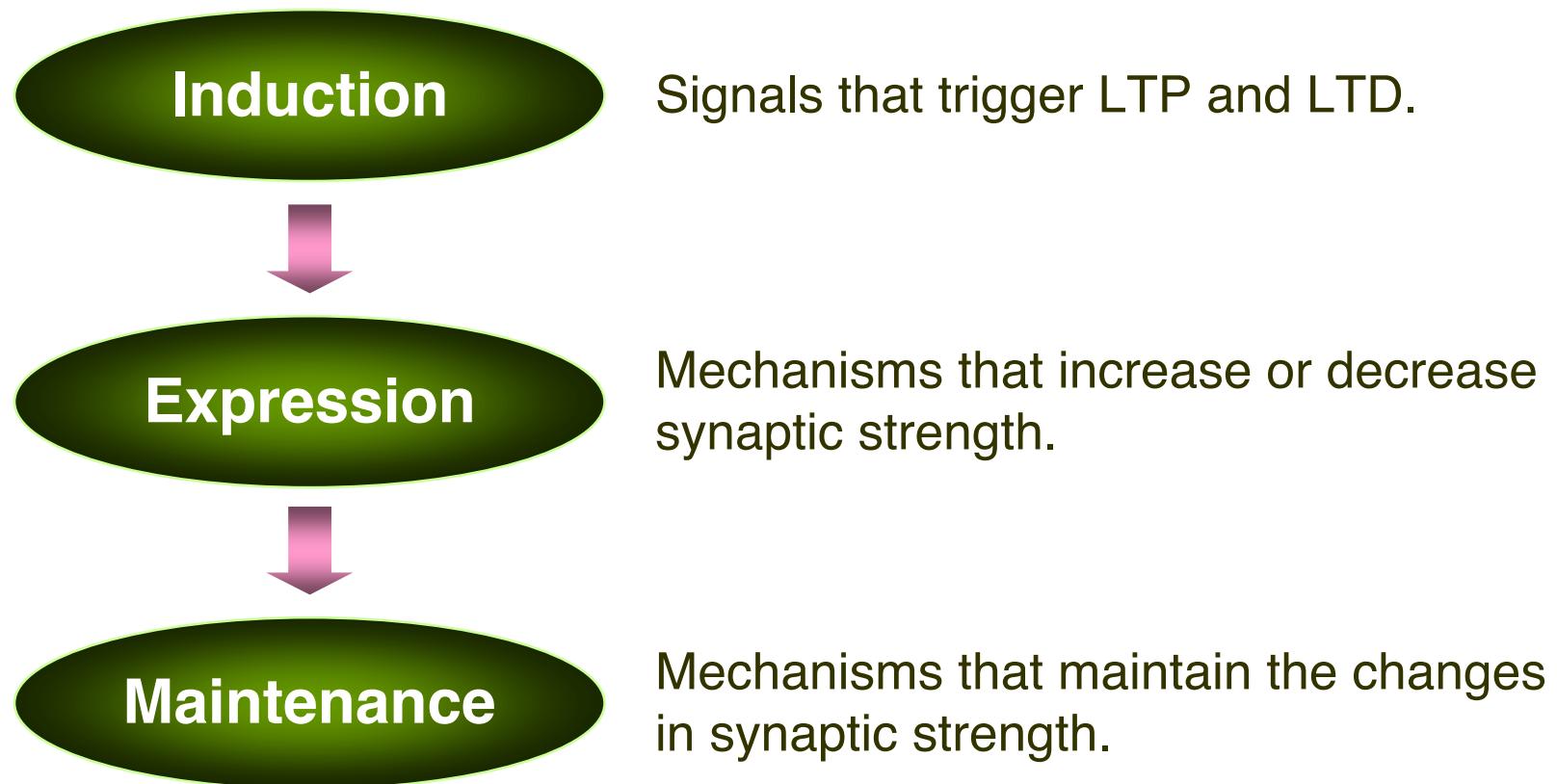
## *Stent's postulate*

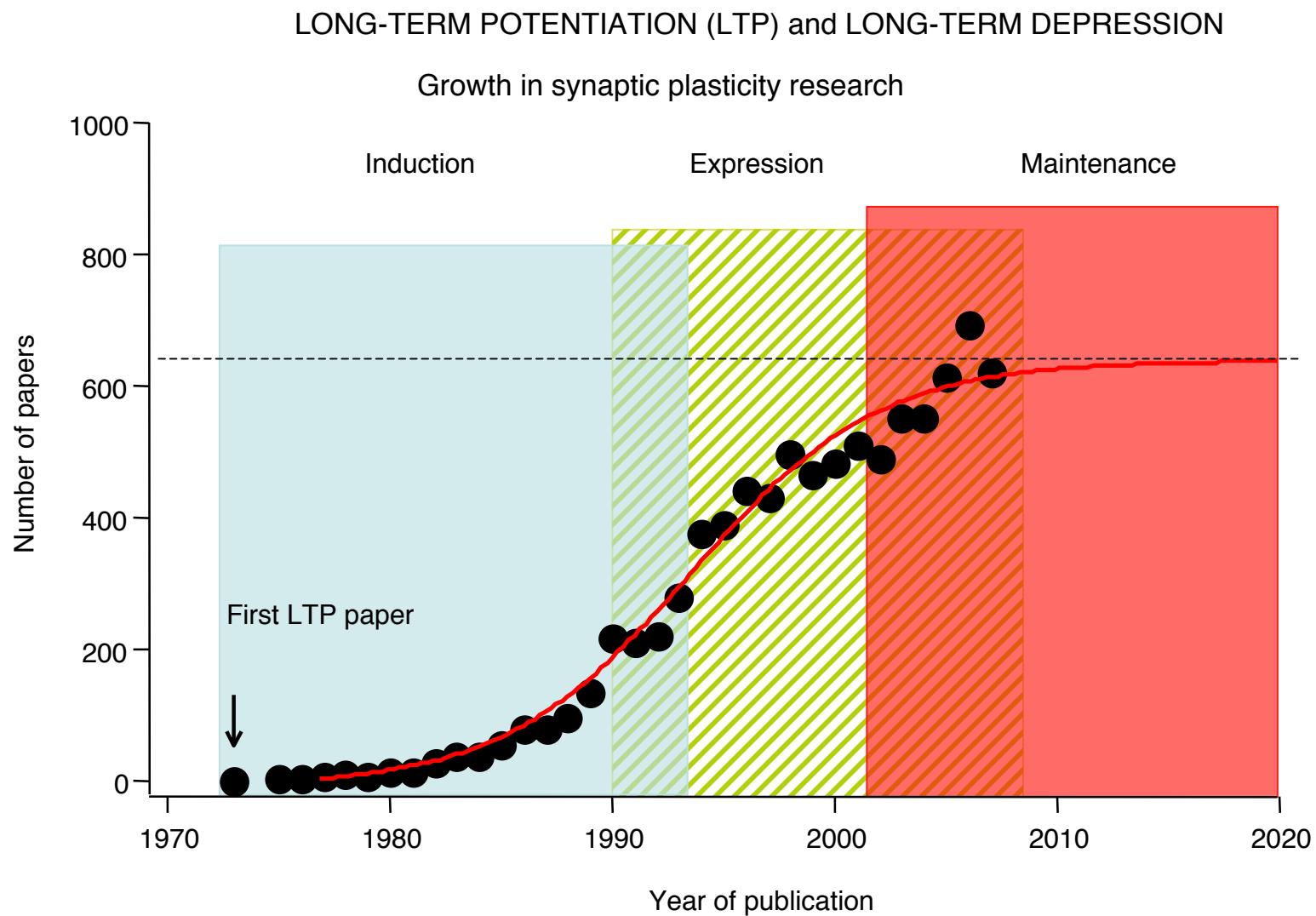
*“When an axon of cell A repeatedly and persistently fails to excite the postsynaptic cell B while cell B is firing under the influence of other presynaptic axons, metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is decreased.”*

Cells that fire out of sinc lose their link

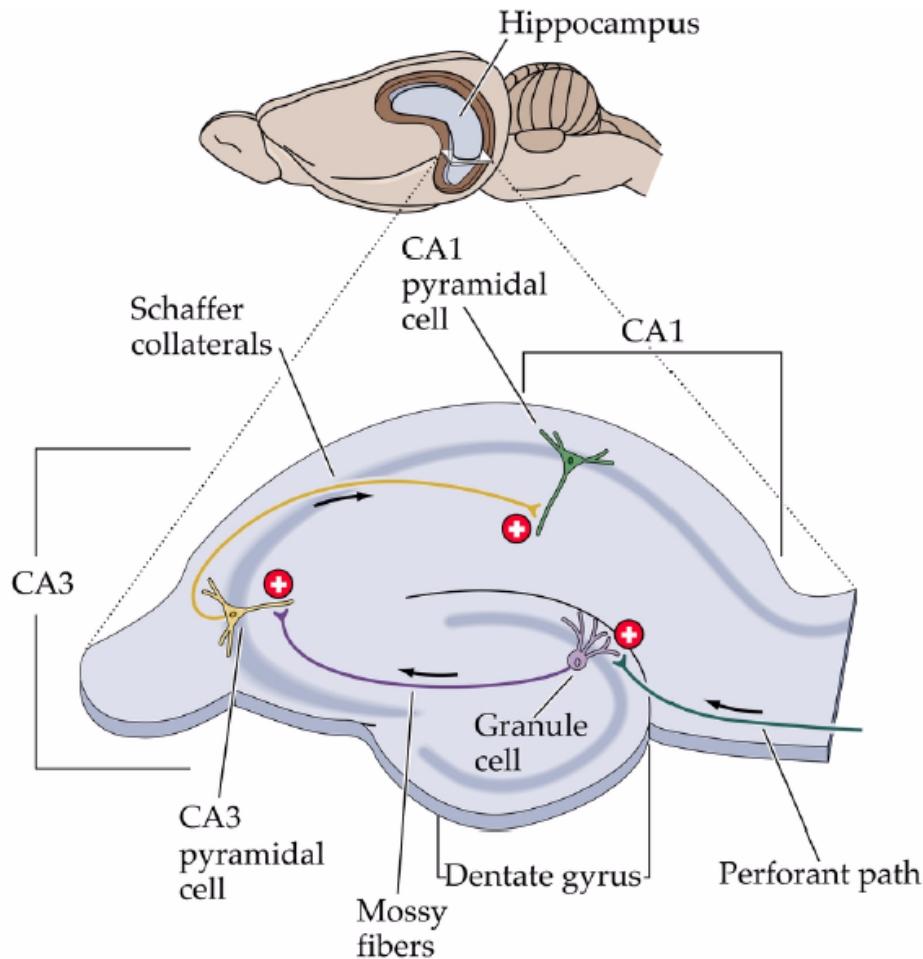
(1973)

## Different aspects of LTP and LTD



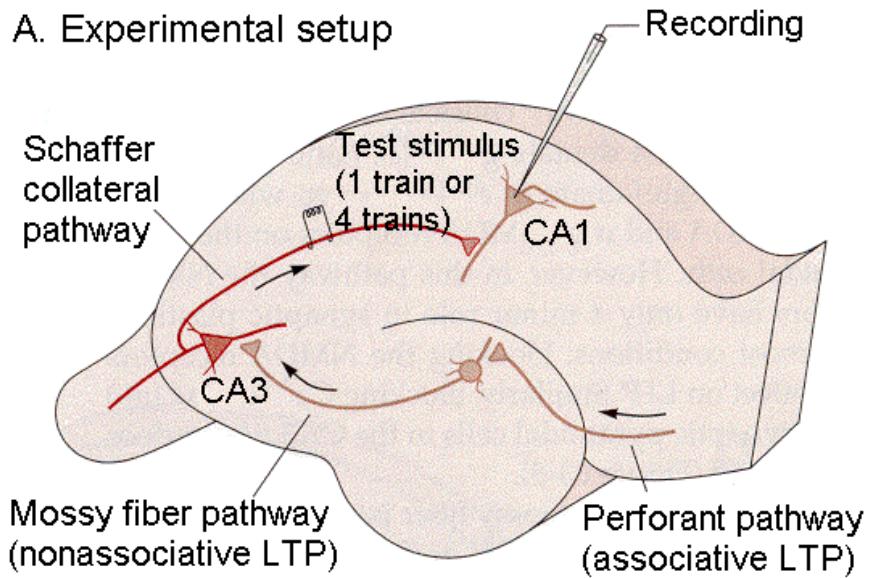


# The hippocampus and hippocampal slice

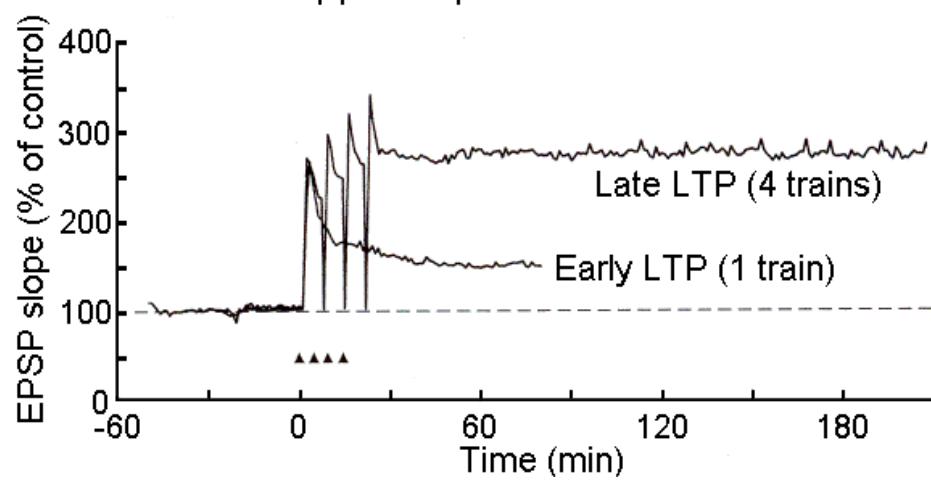


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### A. Experimental setup



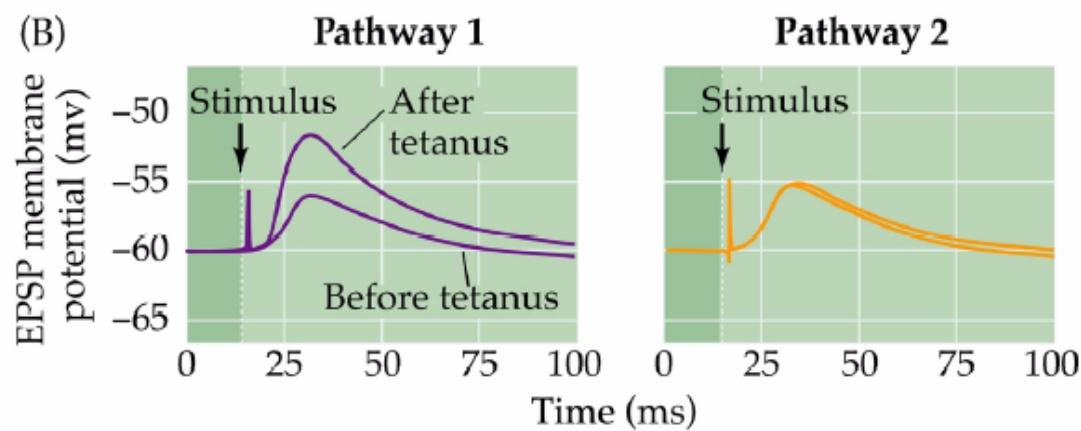
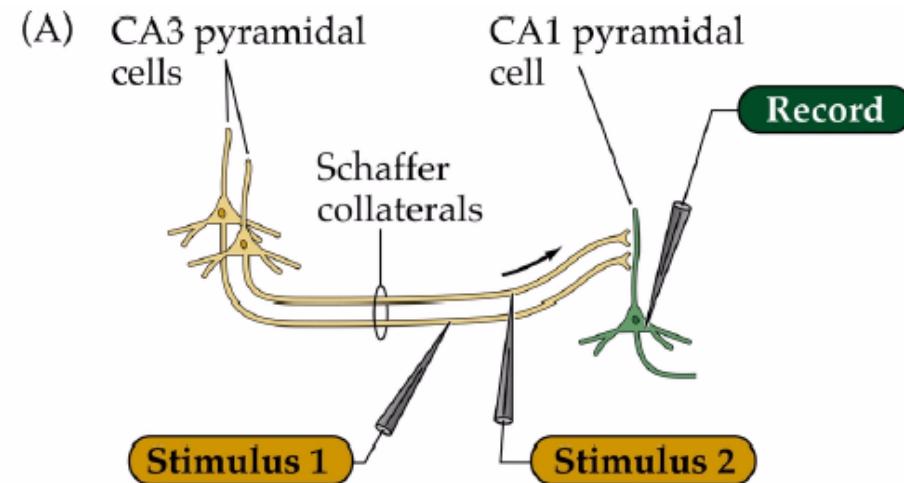
### B. LTP in the hippocampus CA1 area



Long-term potentiation (LTP): lasting, non-decremental increase in the synaptic response magnitude.

In this case it was induced with tetanic stimulation (high frequency)

## LTP is input-specific (mostly confined to activated synapses)



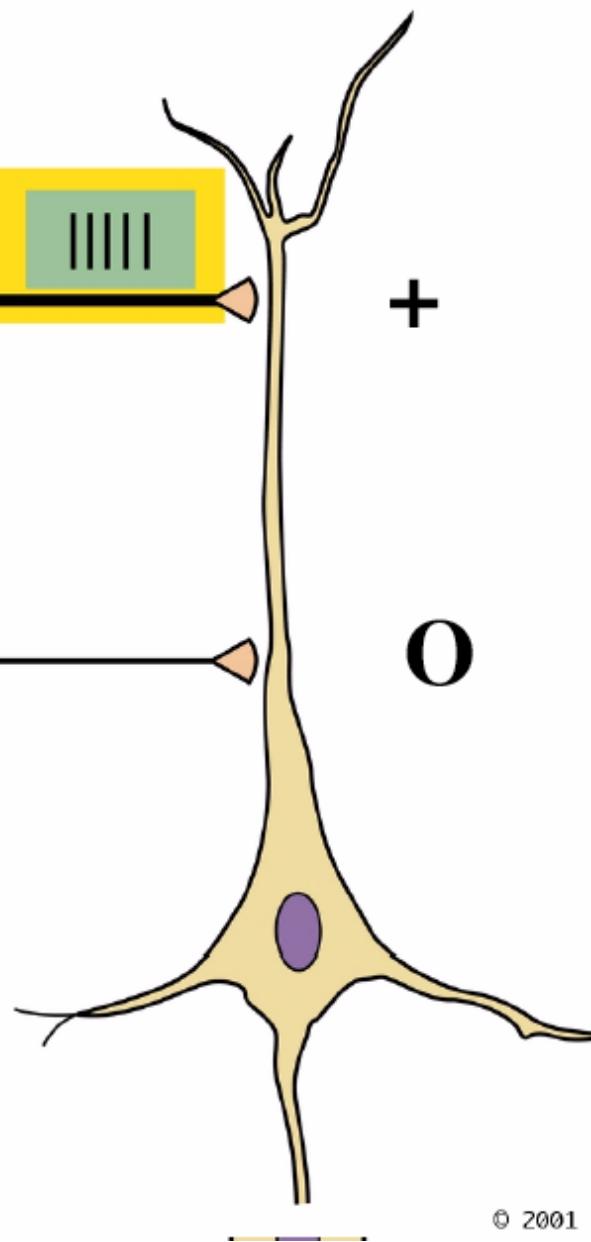
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(A) Specificity

Pathway 1:  
Active

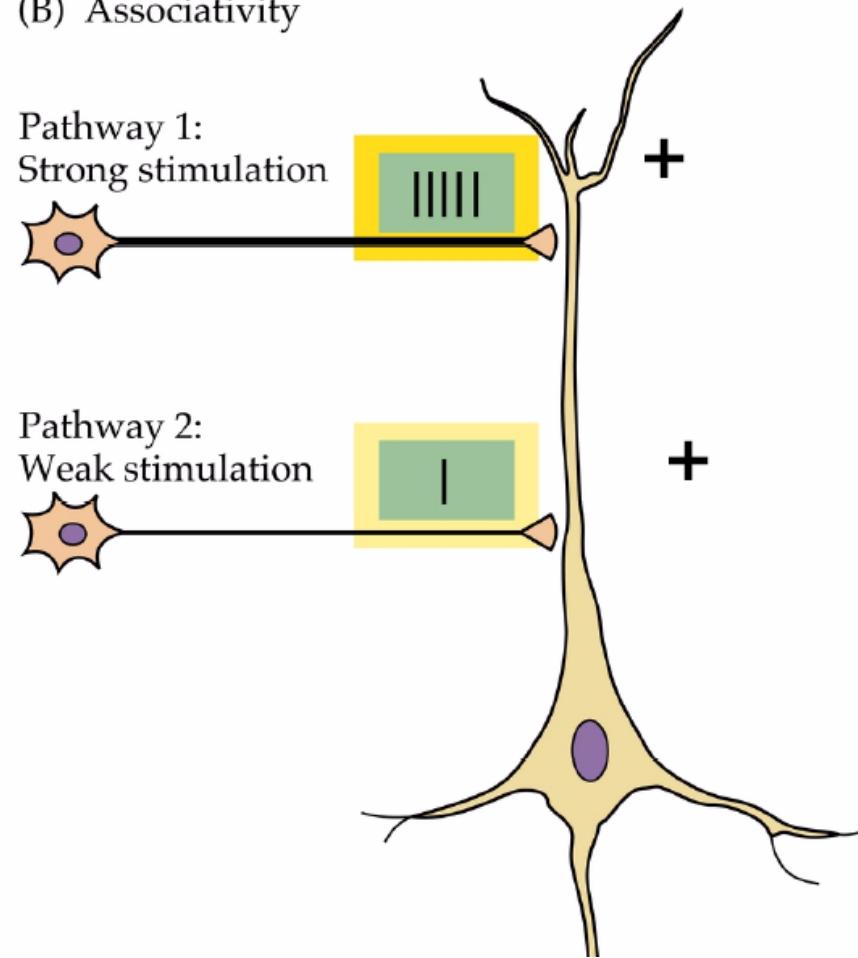


Pathway 2:  
Inactive

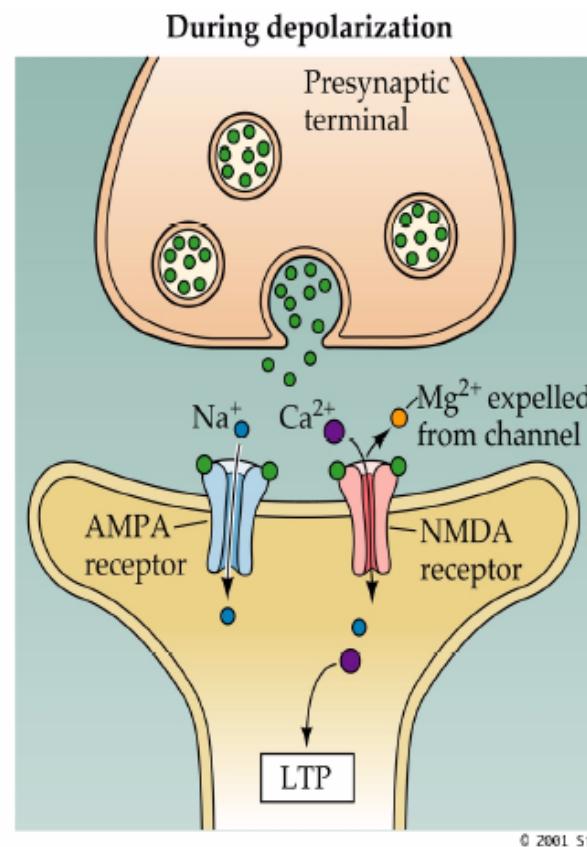
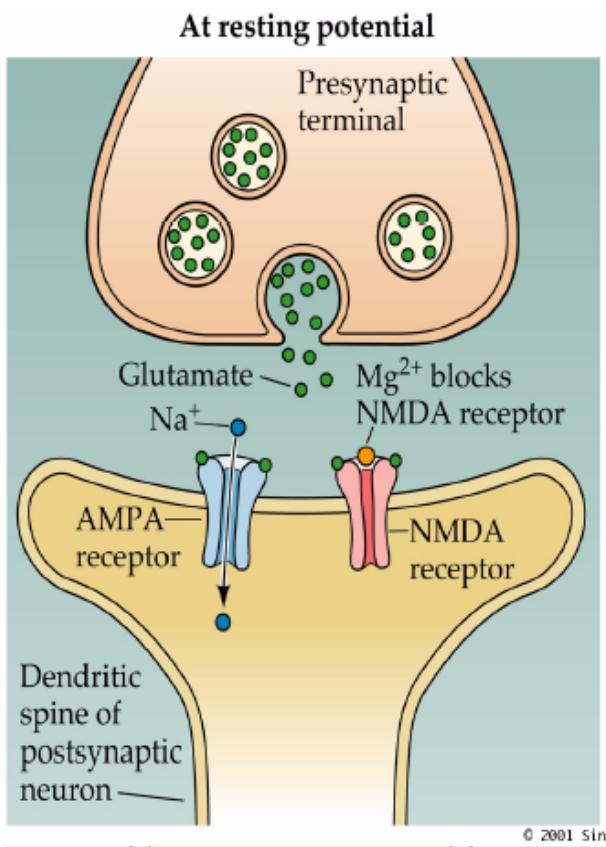


## LTP is associative

(B) Associativity

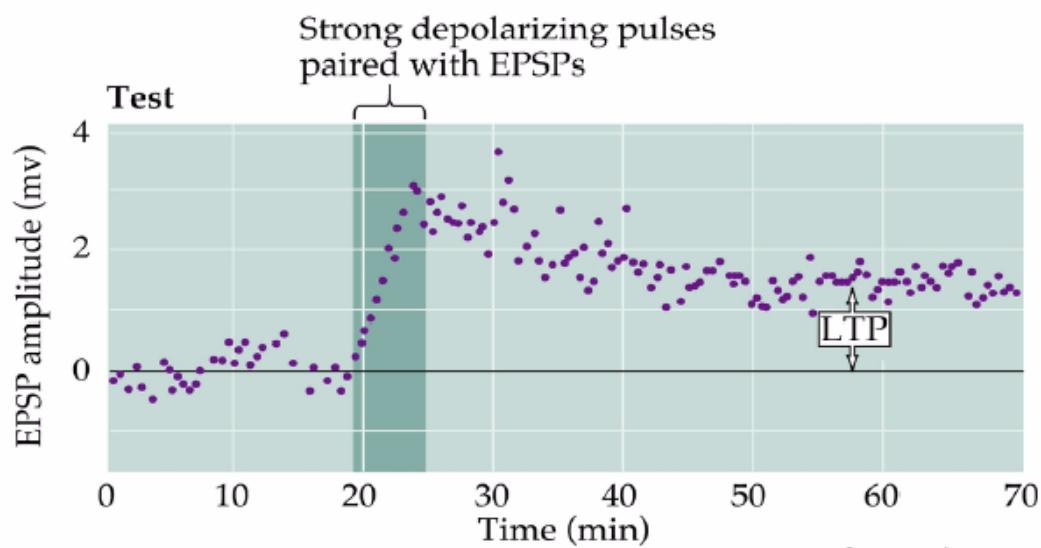
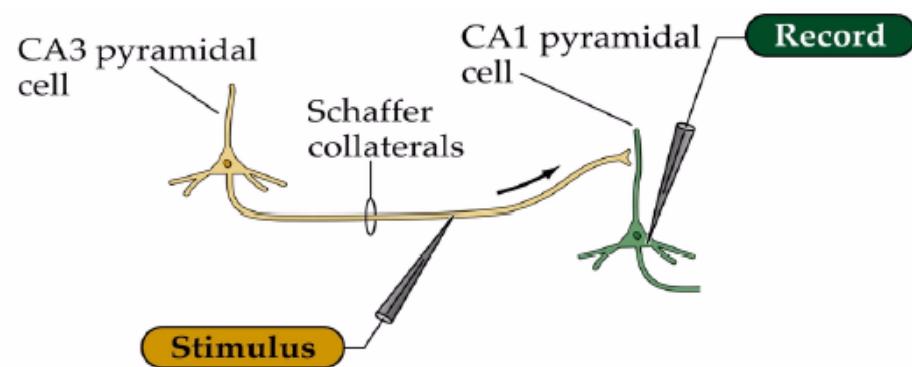


# NMDA receptor confers associativity



NMDA receptor is the “coincidence detector”

# Pairing-induced LTP



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LTP may be induced by:

synaptic tetani

pairing low frequency stimulation with  
postsynaptic depolarization

LTP induction is blocked by:

postsynaptic hyperpolarization

NMDA-R antagonists

pairing with depolarization to  $E_{Ca}$

LTP may be induced by:

photolysis of caged Ca

postsynaptic injection of constitutively active  
Ca-calmodulin-dependent protein kinase II

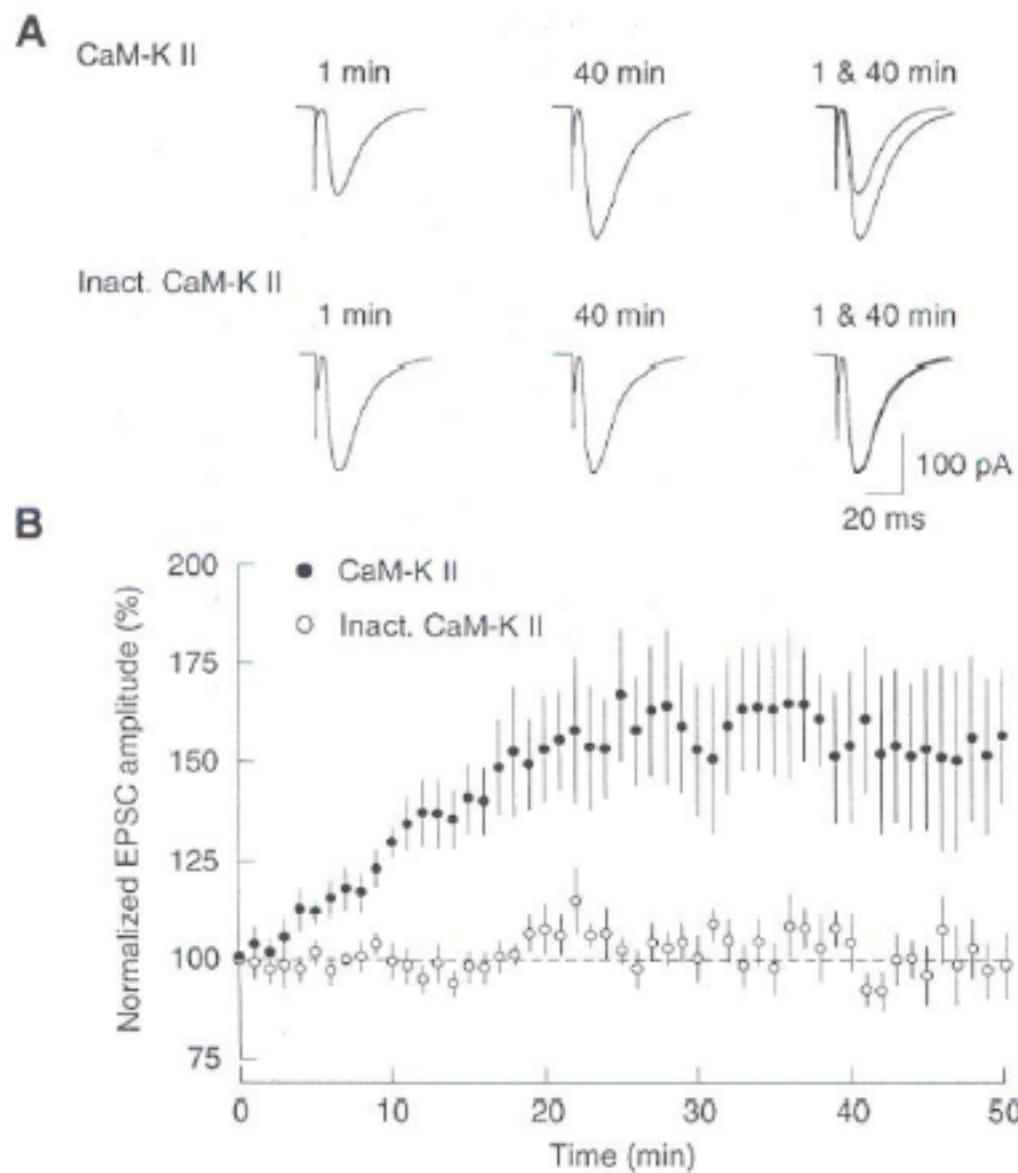
LTP induction is blocked by:

strong Ca chelators (BAPTA)

inhibitors of CaMK II

mutant mice which lack CaMKII activity

## Postsynaptic Active CaMKII causes an LTP-like effect



# Expression

Mechanisms that increase or decrease synaptic strength.

## How to make a synapse stronger?

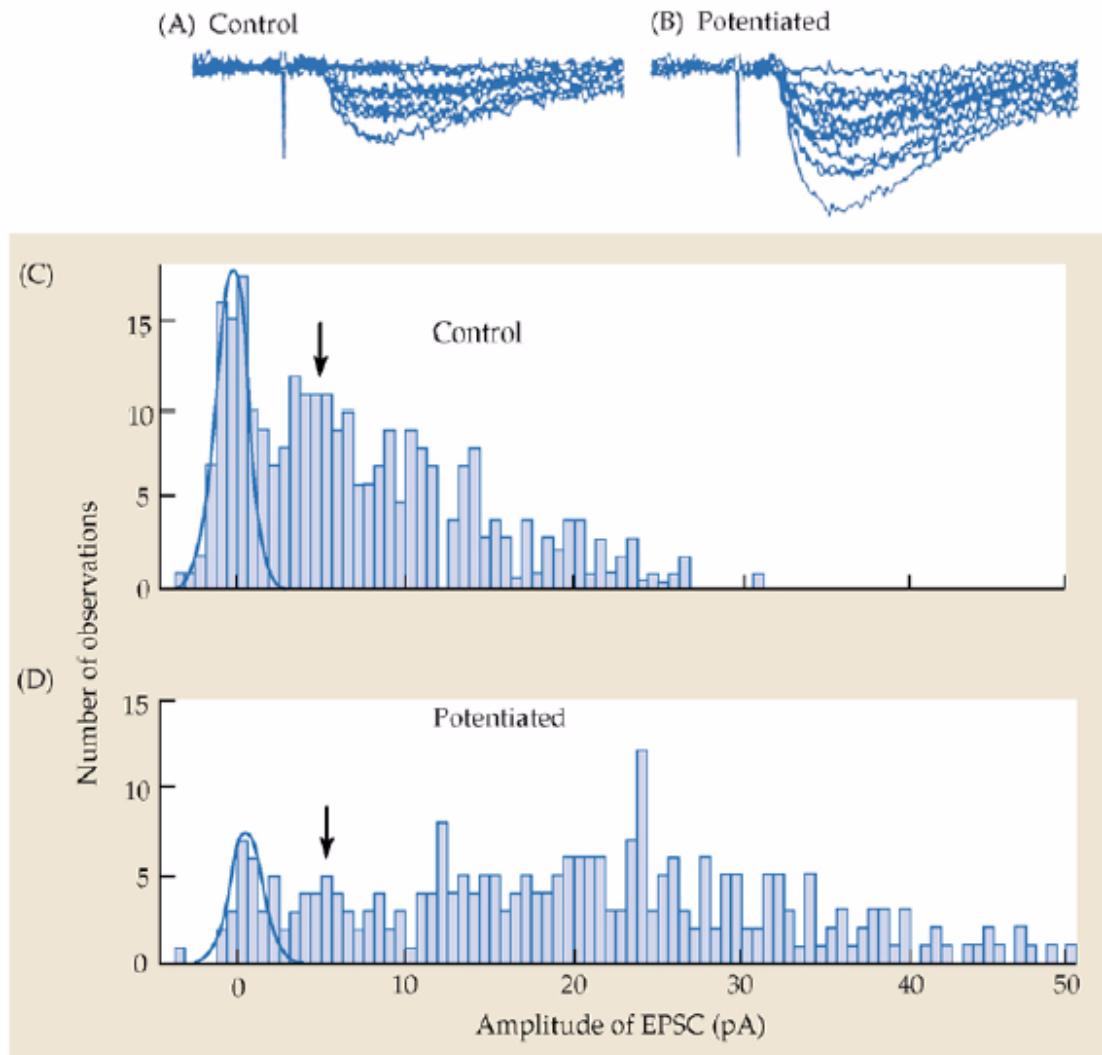
### Presynaptic:

- Increase probability of release
- Increase amount of transmitter-vesicle

### Postsynaptic:

- More receptors
- Increased unitary conductance
- Increased agonist affinity
- Altered kinetics
- Increased conduction from synapse to recording site

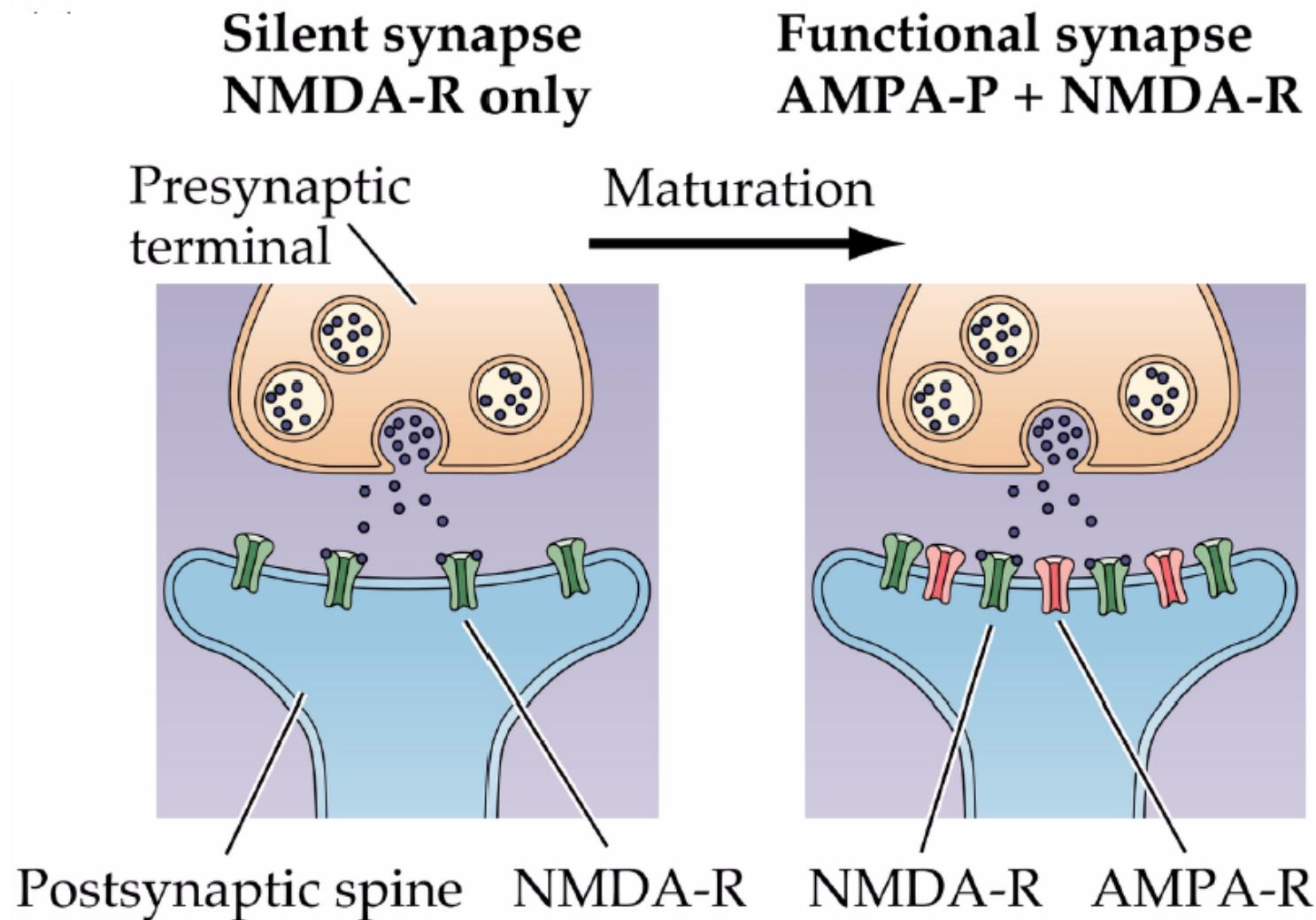
# Lower synaptic failure rate after LTP



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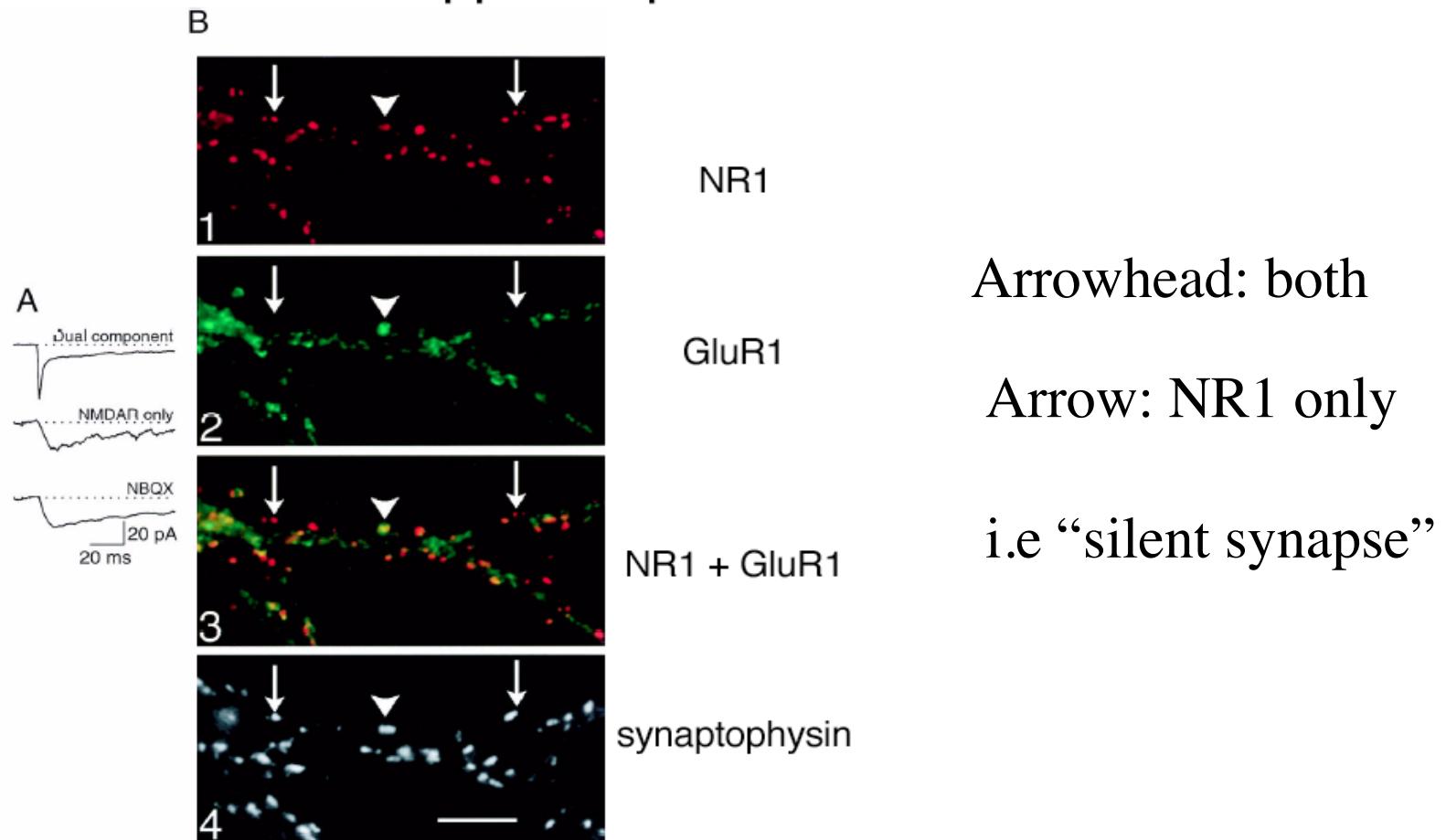
Recordings made with “minimal stimulation”

# The “silent synapse” model



# Evidence for silent synapses: Immunocytochemistry in cultures cells

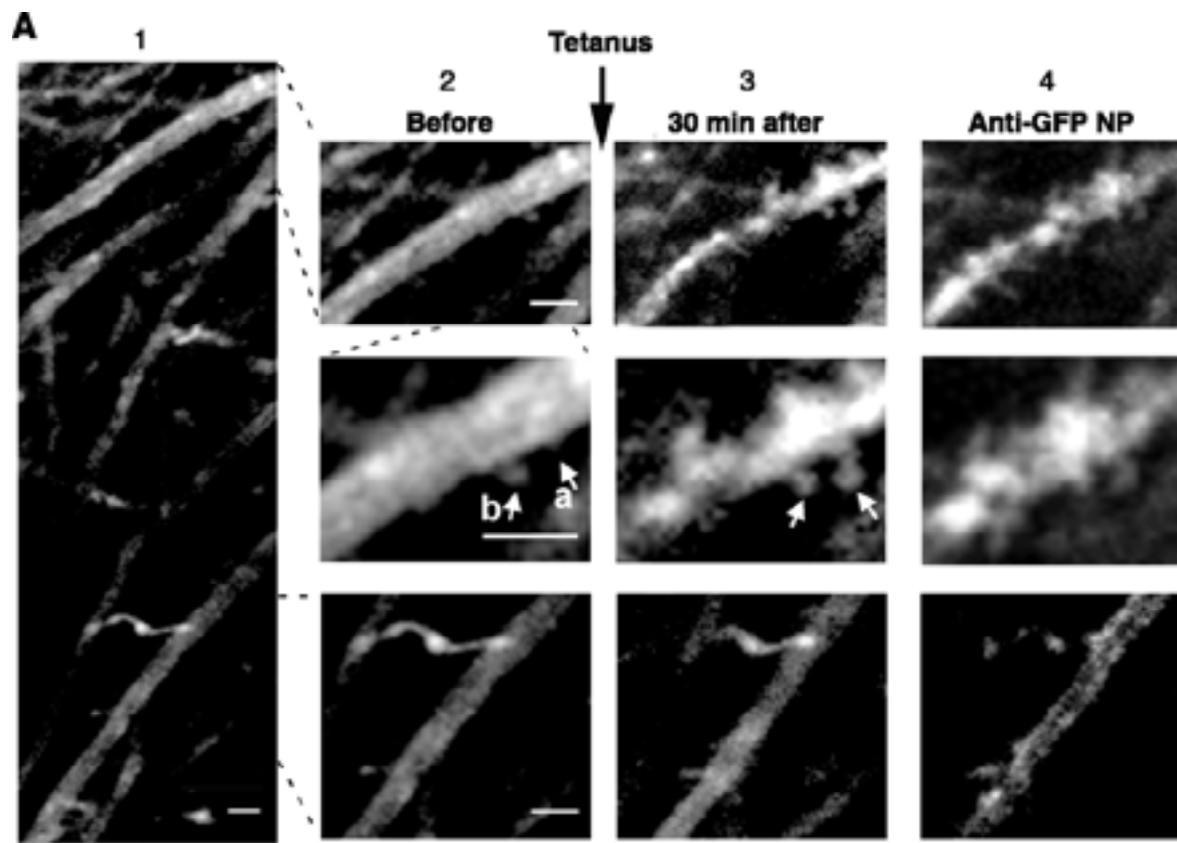
## NMDA-only mEPSCs and NR1-only puncta In cultured hippocampal neurons



# Evidence for silent synapses: live TPM imaging

Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation.

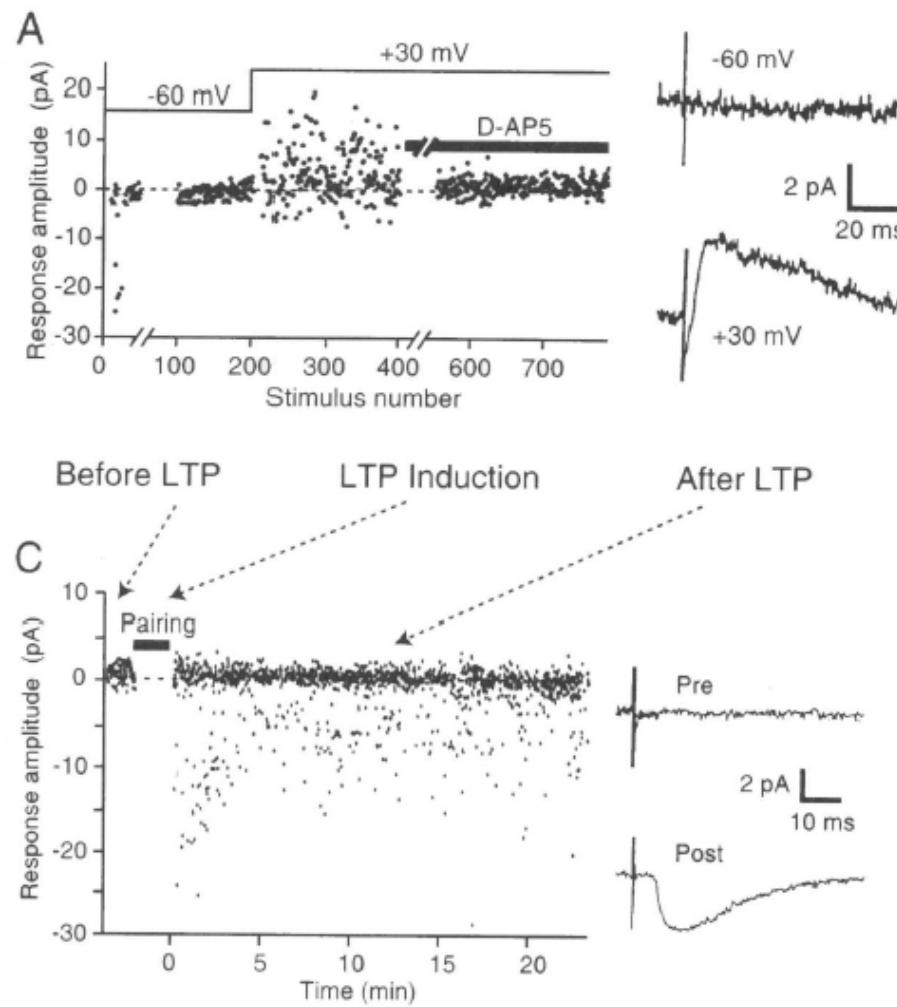
By Shi et al. (1999) Science 284: 1811-1816.



Cultured slices -viral infection with GluR1-GFP gene

Look at the arrows

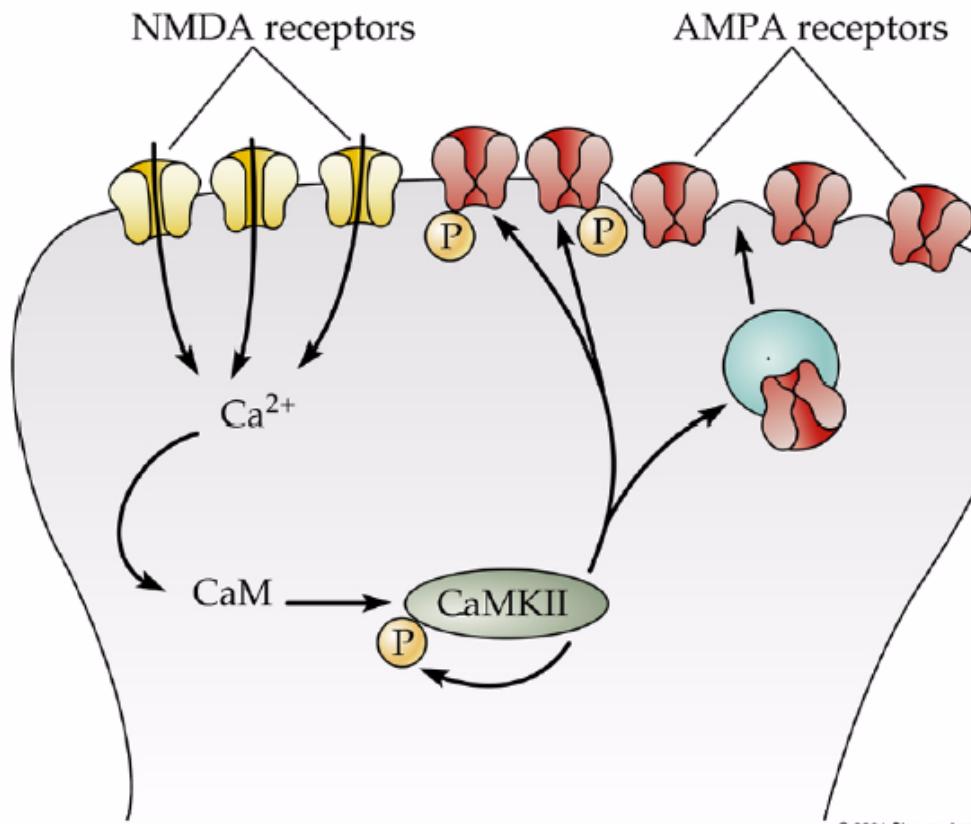
## Electrophysiological evidence for silent synapses: the “free lunch”: experiment -->



Synapse that contain Only NMDAR's: no response at negative potential.

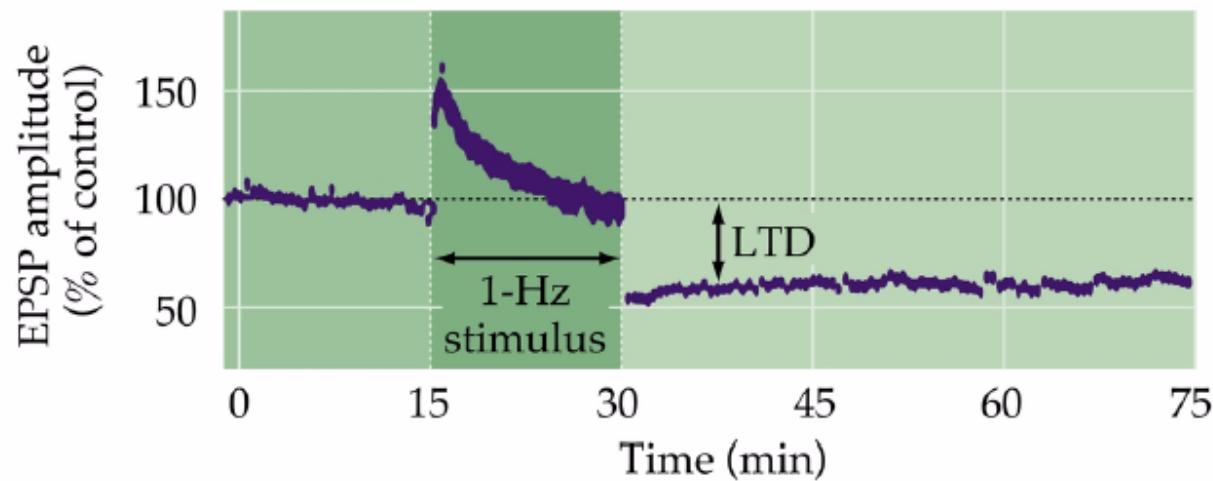
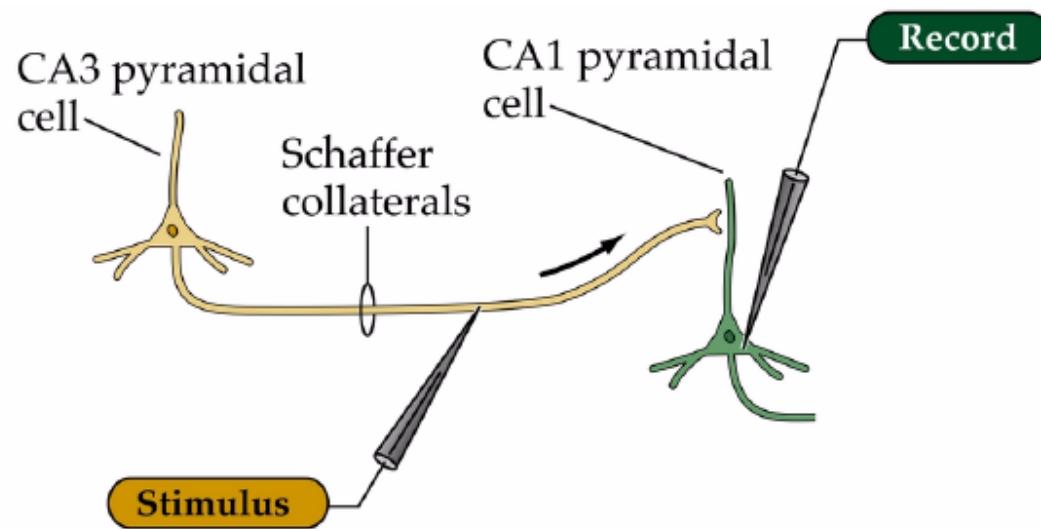
After pairing:  
response at negative potential.

# The Malinow/Nicoll/Malenka model of LTP expression



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# Hippocampal LTD



# Hippocampal LTD

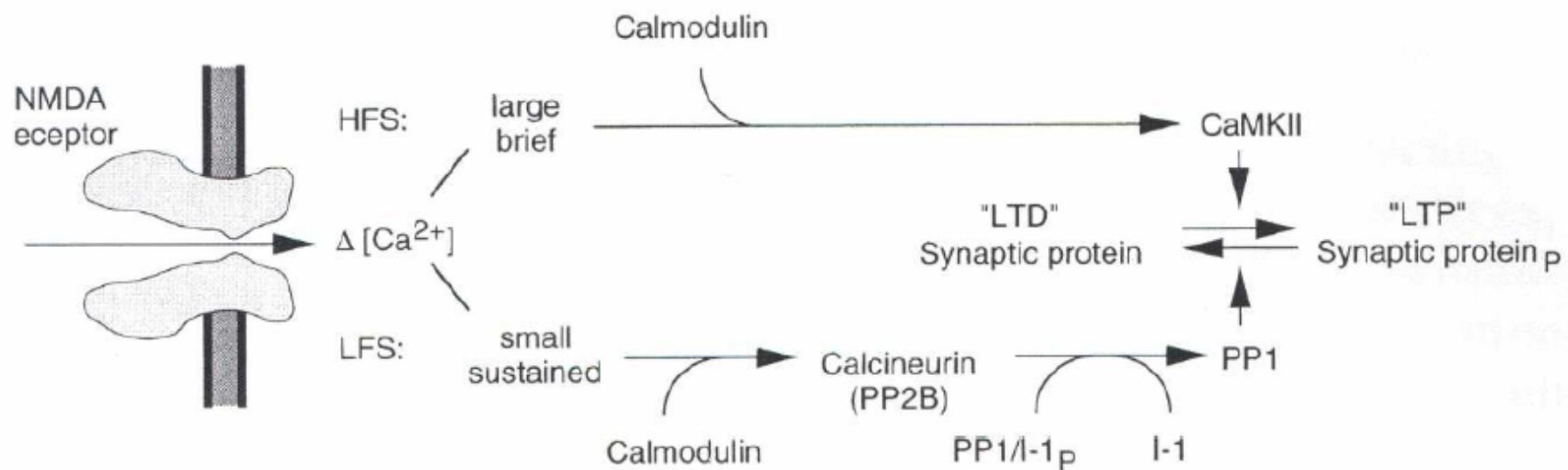
May be produced by:

prolonged low-frequency stimulation  
bath-applied glutamate  
pairing with depolarization to -40 mV

Is blocked by:

NMDA-R antagonists  
postsynaptic Ca chelators  
postsynaptic calcineurin/PP-1 inhibitors  
mutants which lack calcineurin activity

# How can Ca influx through NMDA-Rs trigger both LTP and LTD?



**There are several other forms of LTP and LTD that do not require activation of postsynaptic NMDA-Rs:**

LTP at the hippocampal mossy fiber-CA3 and cerebellar parallel fiber-Purkinje cell synapses utilizes a cascade involving presynaptic Ca flux via voltage-gate channels/activation of Ca-sensitive adenylyl cyclase type I/PKA activation/phosphorylation of RIM1 ser-413/increased transmitter release

LTD at the cerebellar parallel fiber-Purkinje cell synapse involves activation of postsynaptic mGluR1/diacylglycerol production and Ca transients/PKC activation/phosphorylation of GluR2 ser-880/PICK1 binding to GluR2/clathrin-mediated endocytosis of postsynaptic AMPA-Rs.

The million dollar question:

## Are LTP/D involved in memory?

-Blocking LTP/D blocks the formation of memories  
APV-Morris maze- mutants

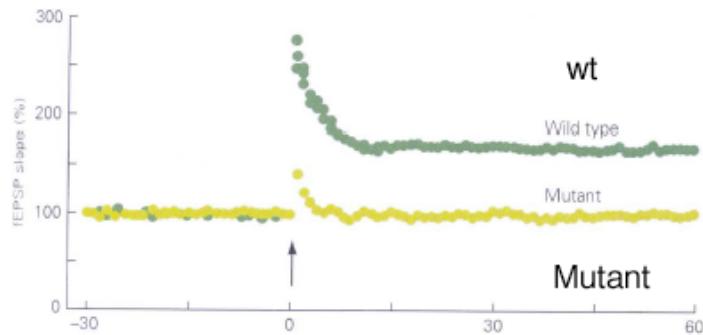
-Saturation of LTP erases memories  
Limited by the proportion of synapses altered. Difficult to do in a large distributed network

The formation of memories increases the responses

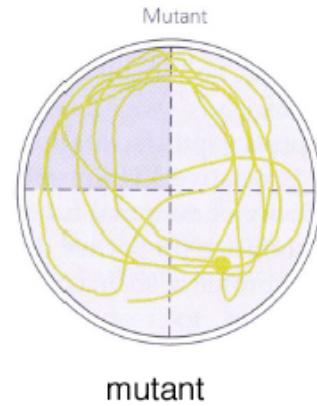
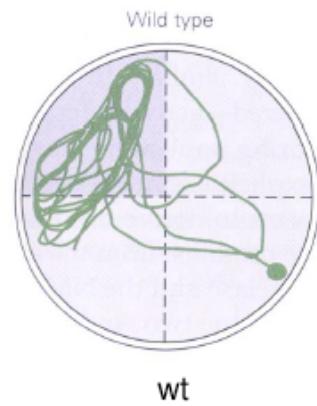
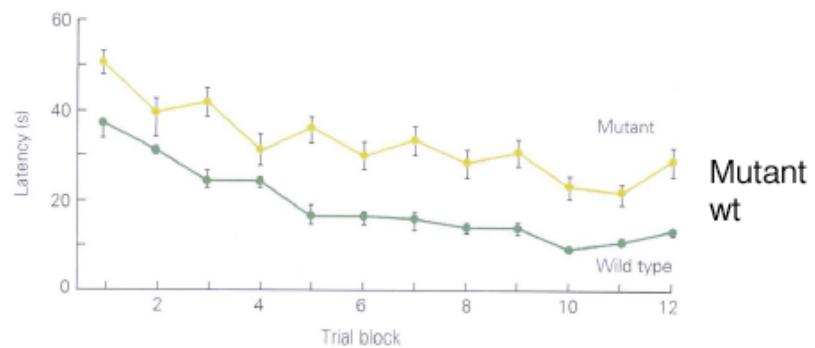
Firs trial was dissapointing. It was just the heat  
Memories saturate LTP

# LTP and watermaze learning deficits in CA1-restricted NR1 null mouse (will lack LTP and LTD)

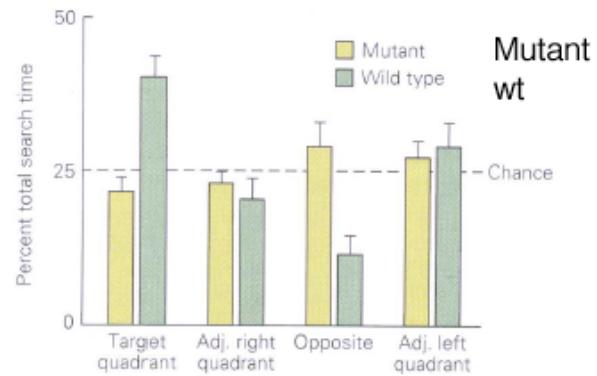
A LTP defect in the Schaffer collateral pathway



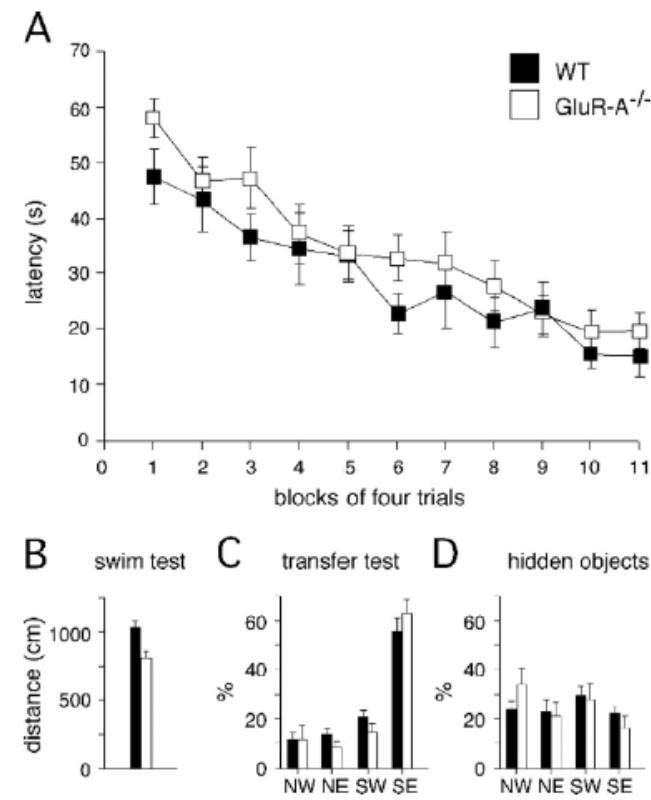
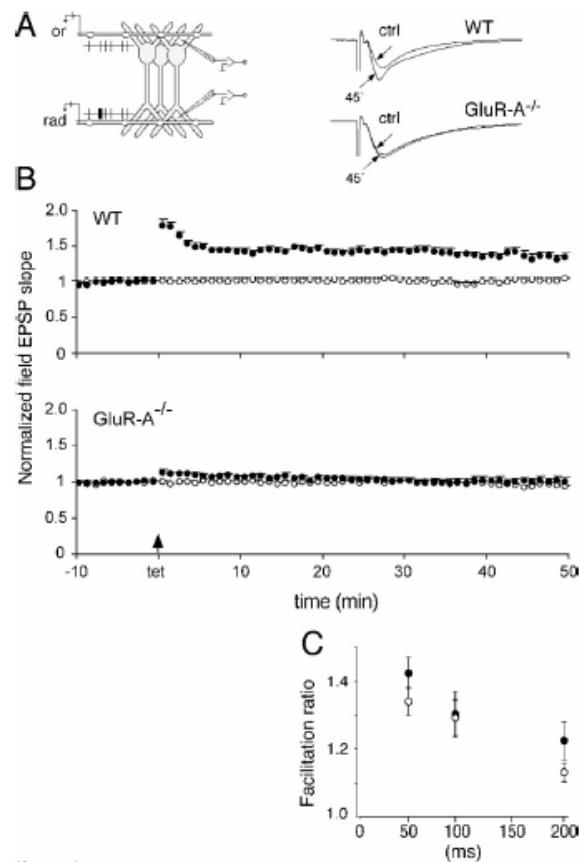
2 Escape latencies



b Search time



# Impaired CA1 LTP but normal watermaze learning in GluR1 (GluRA) null mice



Caveat: later work showed that pairing-induced LTP was intact in the GluR1 null mouse. Moral of story: do a big walk in parameter space.

## **What will take to really test the hypothesis that LTP/LTD underlies certain forms of learning?**

First, it will take a model system where there is a circuit level understanding of how making synapses weaker or stronger constitutes real behavioral memory.

Second it will take very specific and subtle molecular manipulations of LTP/LTD. Deletion of receptors or kinases/phosphatases has too many side-effects. Perhaps phosphorylation-site mutant knock-ins of the relevant kinase substrates will be the way to go.

## **Main points to take away from this lecture:**

- 1) Synaptic plasticity is only one possible way to store information in the brain.
- 2) Hippocampal LTP is compelling as a model for memory not only because it is long-lasting, but also because it is input-specific and associative.
- 3) The biophysical properties of the NMDA-R (voltage-dependent Mg block and Ca permeability) confer associative LTP induction.
- 4) Hippocampal LTP requires a Ca/CaMKII cascade.
- 5) Hippocampal LTP is largely expressed postsynaptically, by insertion of functional AMPA-Rs.
- 6) Hippocampal LTD can reverse LTP.
- 7) Hippocampal LTD involves an NMDA-R/Ca/phosphatase cascade.
- 8) While the hypothesis that LTP/LTD underlie memory is attractive, it remains unproven.

A nice (very thorough) recent review:

Lynch MA. Long-term potentiation and memory.  
Physiol Rev. 2004 84(1):87-136.