Chapter 5. Memory

Circuitry in brain: partly genetic and mostly environmental
How it works?
The process of evolving a unique brain
The essence of the individual depends on experience and memory

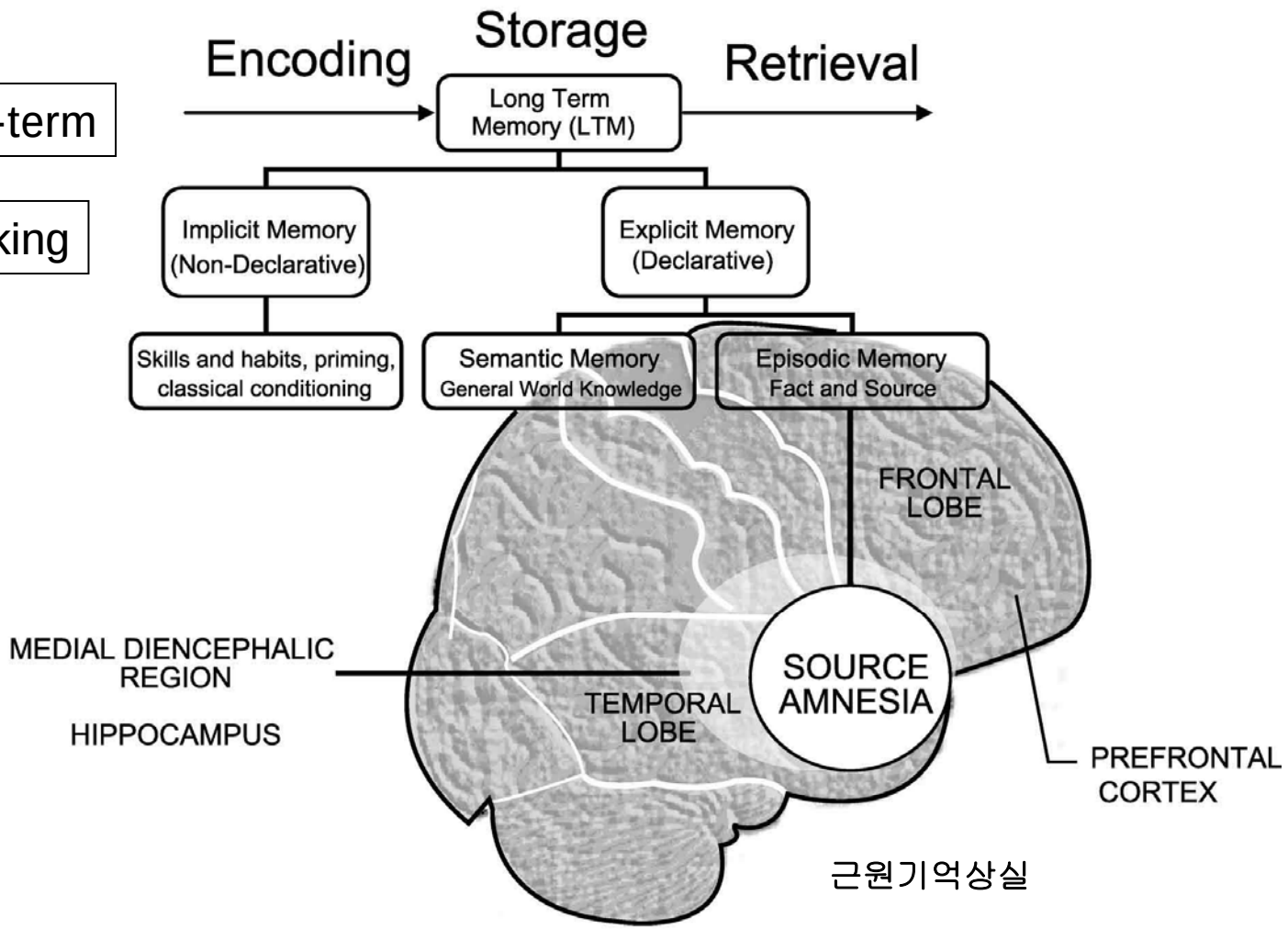
Memory

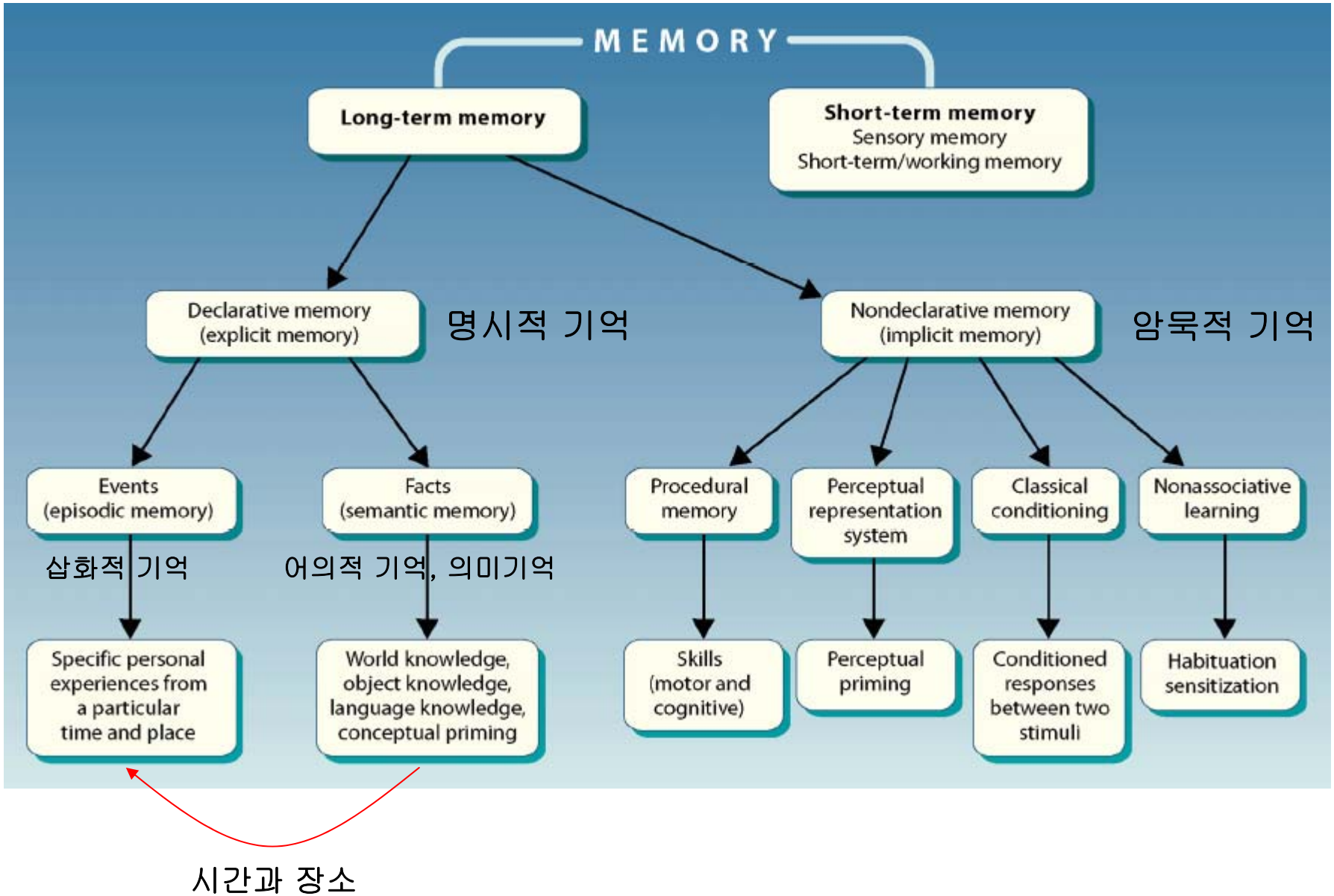
Sensory: just a second observation
Short-term: cf. working memory
Long-term: implicit & explicit (semantic & episodic)

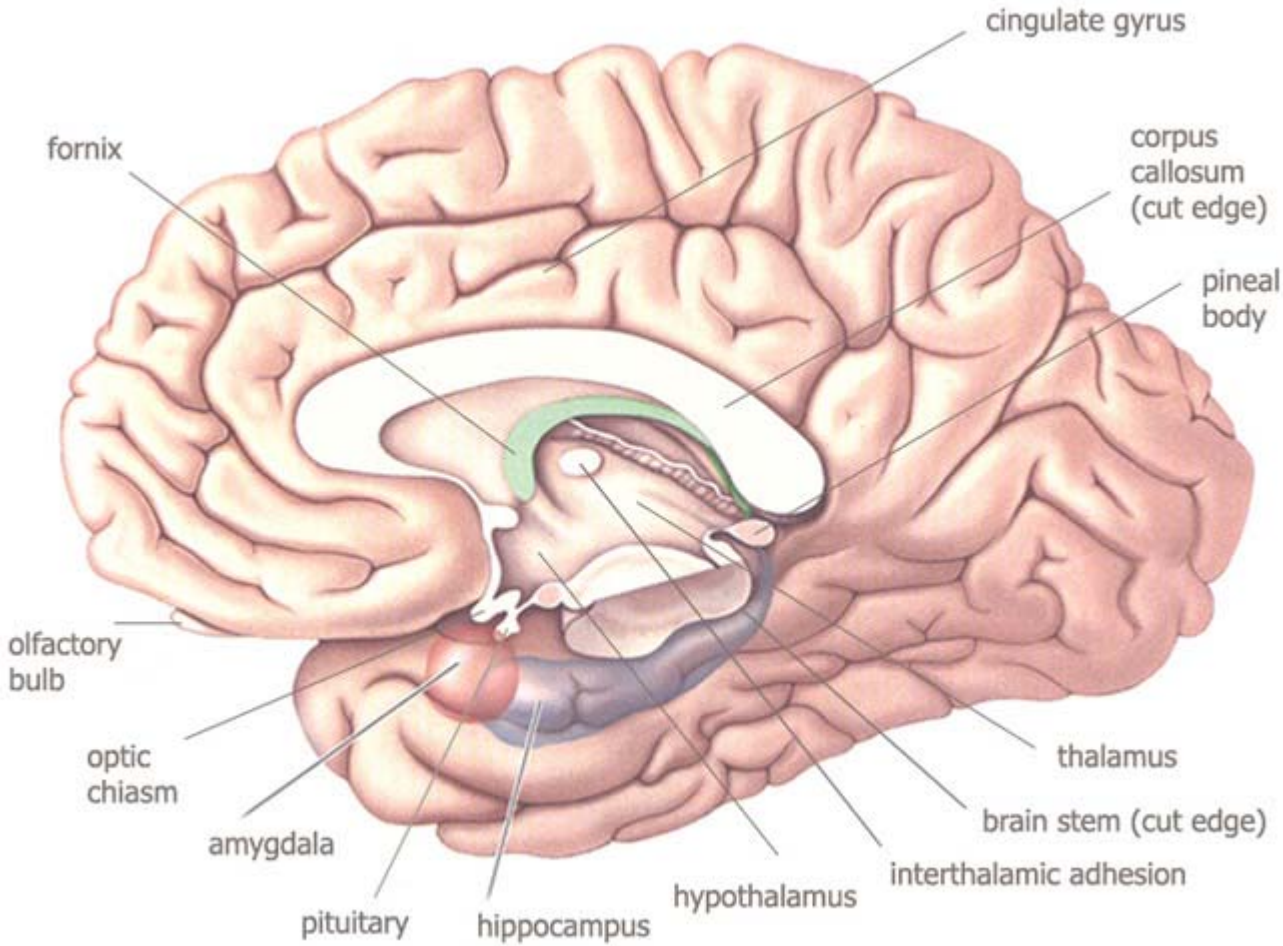
Sensory

Short-term

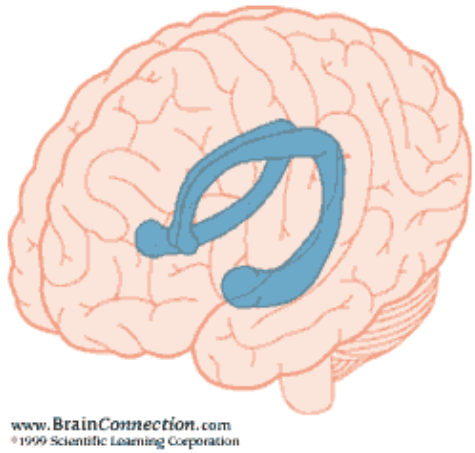
working



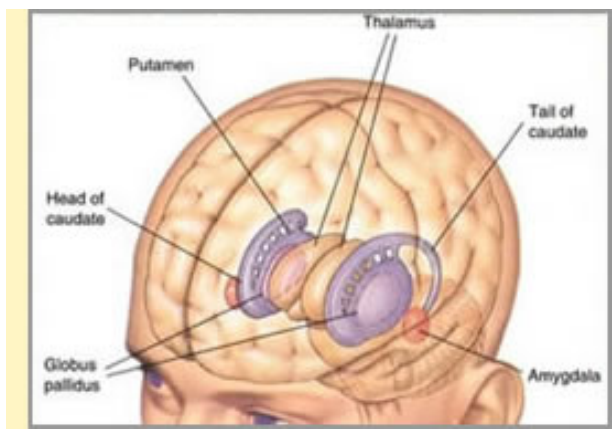

MEMORY
Long-term memory
Short-term memory
Sensory memory
Short-term/working memory
Declarative memory
(explicit memory)
명시적 기억
Nondeclarative memory
(implicit memory)
암묵적 기억
Events
(episodic memory)
Facts
(semantic memory)
Procedural
memory
Perceptual
representation
system
Classical
conditioning
Nonassociative
learning
삽화적 기억
어의적 기억, 의미기억
Specific personal
experiences from
a particular
time and place
World knowledge,
object knowledge,
language knowledge,
conceptual priming
Skills
(motor and
cognitive)
Perceptual
priming
Conditioned
responses
between two
stimuli
Habituation
sensitization
시간과 장소



hippocampus



thalamus



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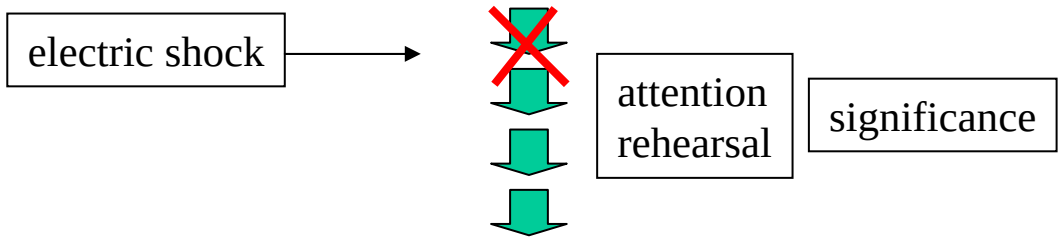
Short-term memory: transient, highly unstable, vulnerable process



Long-term memory: more permanent and dormant

Implicit and explicit memory

- Implicit memory:
  past experiences influence perceptions, thoughts & actions without awareness that any info from past is accessed

Procedural (절차기억)

- Explicit memory:
  conscious access to info from the past
  ("I remember that..")
  -> involves conscious recollection
  -> term often used synonymously with episodic memory

Semantic (의미기억)
Episodic (일회기억)

H.M.

Brain surgery to control epilepsy: medial temporal lobe
Trapped in the present: remember events before operation (up to two years beforehand)
Amnesic: short-term memory is working but not lead to long-term memory

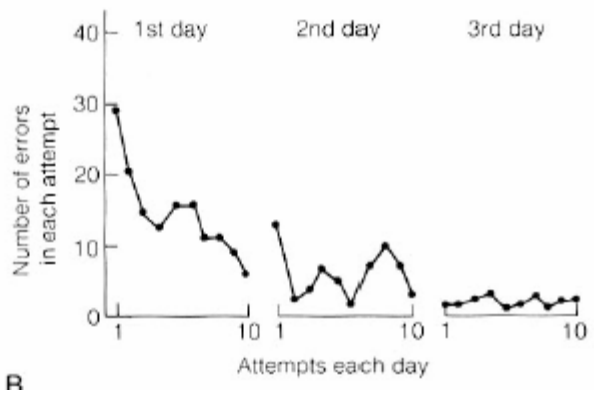
Implicit memory is working: mirror tracing task
Does not conscious of remembering the event of learning

HM: Amnesic

- Mirror tracing task, Milner, 1965

HM: Amnesic

- improvement in H.M. for mirror tracing task
- no conscious recollection of previous training episodes



Memory: processing & consolidation

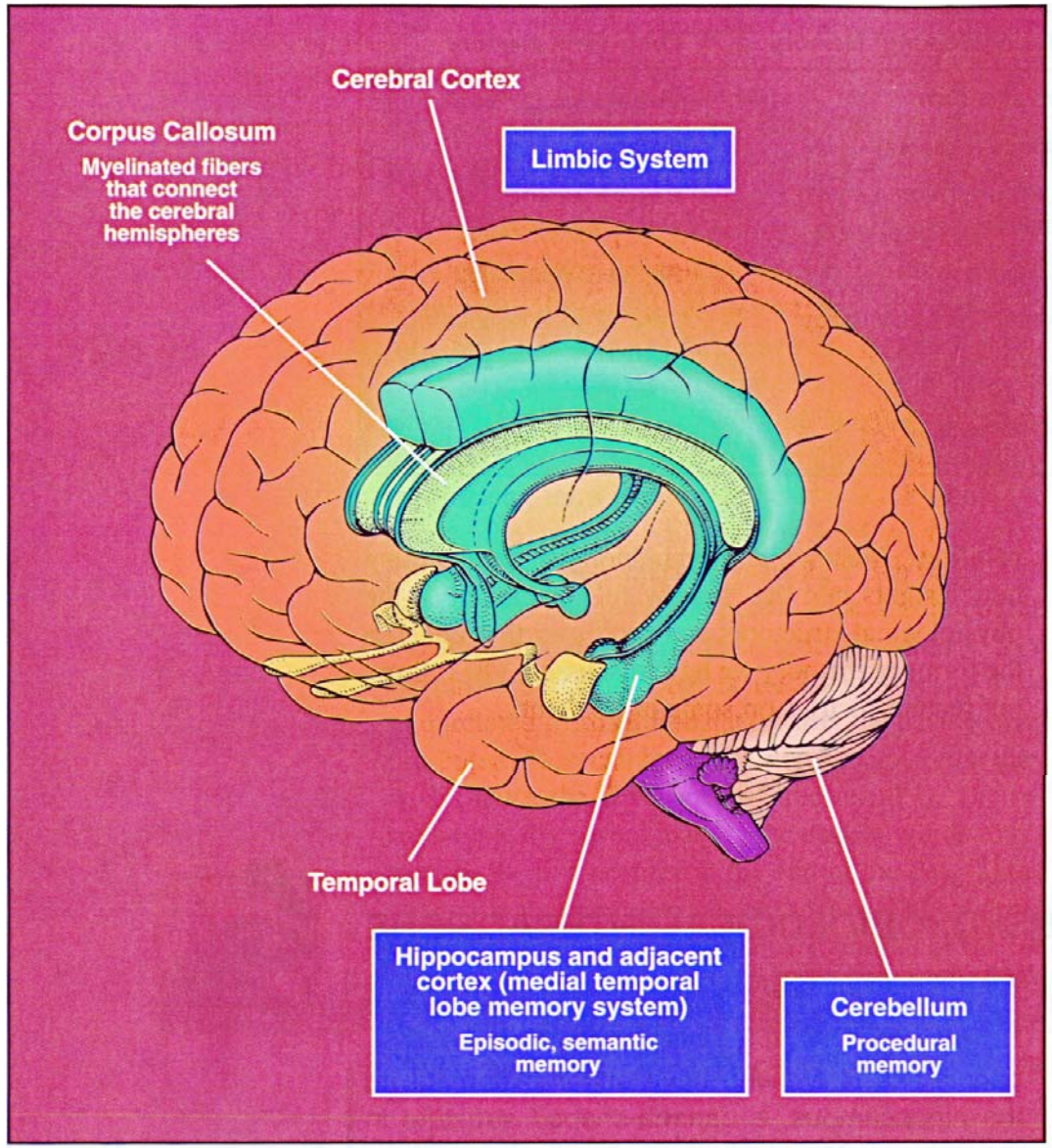
Medial temporal lobe (hippocampus)

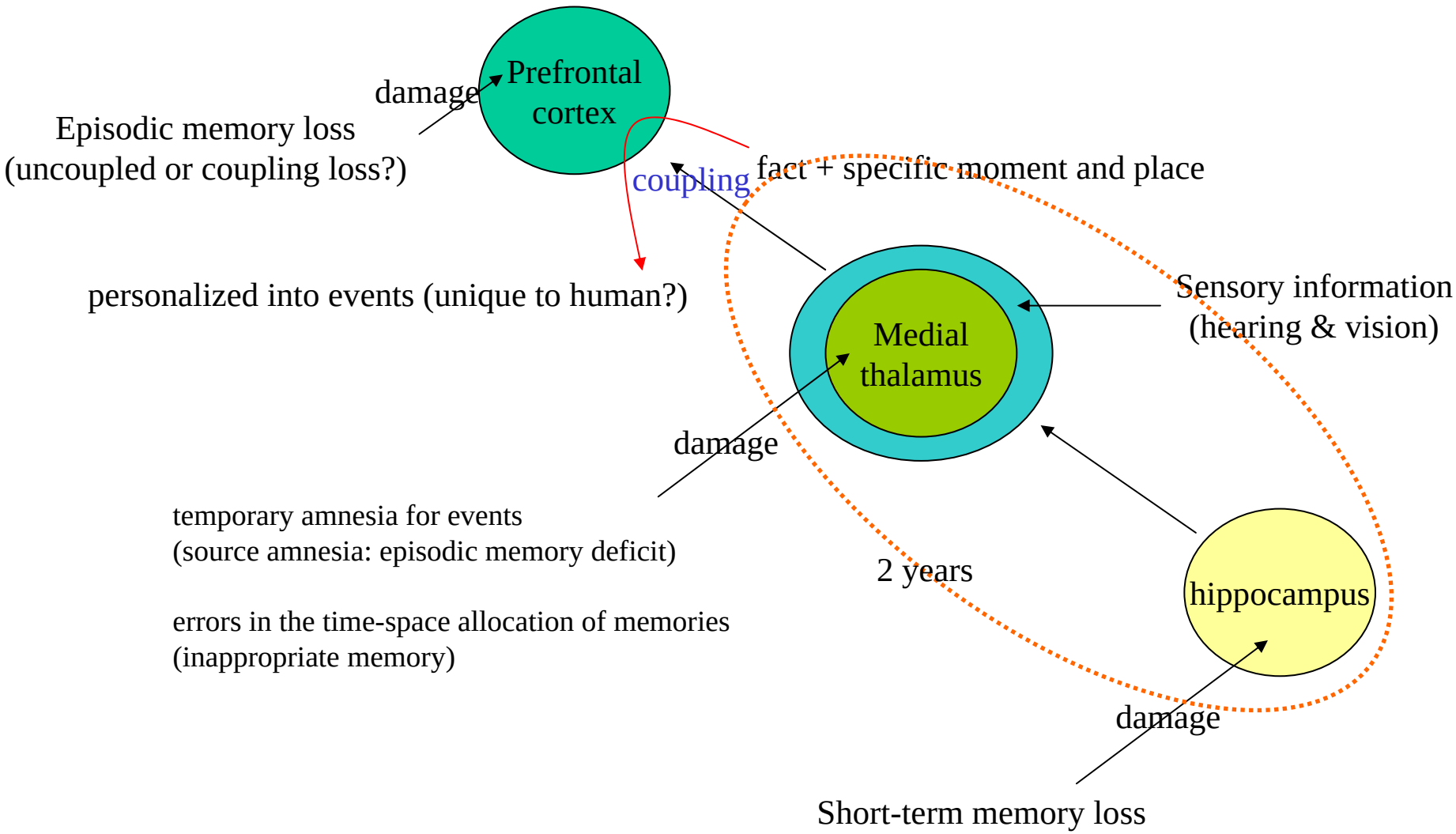
↓

Medial thalamus

↓

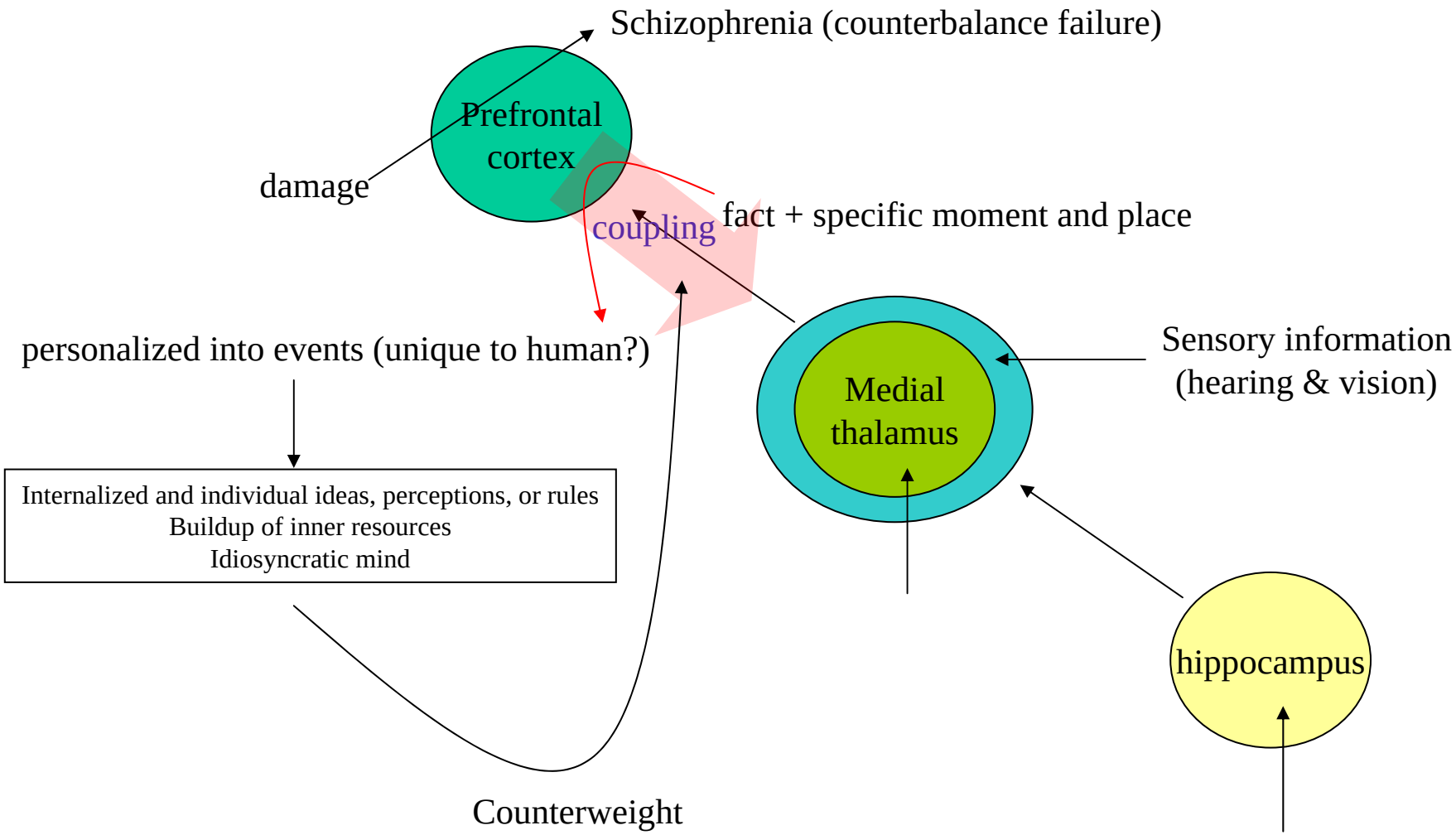
Cortex





Events: unique & personal
Facts: generic & free of time and space frames of reference

Schizophrenia: counterbalance failure?



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Amnesia

Anterograde amnesia (선행성 건망증, 전향기억상실):
everything that happened since his surgery

Retrograde amnesia (역행성 건망증, 역행기억상실): damage in large brain area
loss of memory for everything that happened before being taken into the hospital,
and even before the onset of the illness

Amnesia

- Types:
  - Retrograde: cannot remember old memories
  - Anterograde: cannot form new episodic memories
- Retrograde amnesia is more rare
- Sources
  - Blow to head, Concussion
  - Korsakoff syndrome (severe vit. B1 deficiency)
  - Alzheimer's
  - Damage to hippocampus, thalamic structures
  - ECT (electroconvulsive shock therapy)
  - Midazolam: artifically induced amnesia

Anterograde Amnesia

- Inability to acquire new information (think of "memento")
- Does not affect short-term memory
- Does not affect general knowledge from the past
- But, it is difficult to learn new facts
- Affects memory regardless of modality (visual, auditory, tactile, etc). Spares skilled performance
- Hyper-specific memory for those skills that are learned after onset – learning is expressed only in context in which it was encoded

Retrograde amnesia

- Temporal extent can vary:
  - ECT: months or weeks
  - Korsakoff's, Alzheimer's: years
- Temporal gradient:
  - early memories are better remembered than memories before trauma
  - New memories continue to undergo neurological change: memory consolidation
- Retrograde amnesia often becomes less severe over time
  - Most remote memories are likely to return first
- Does not affect overlearned information (e.g. skills)

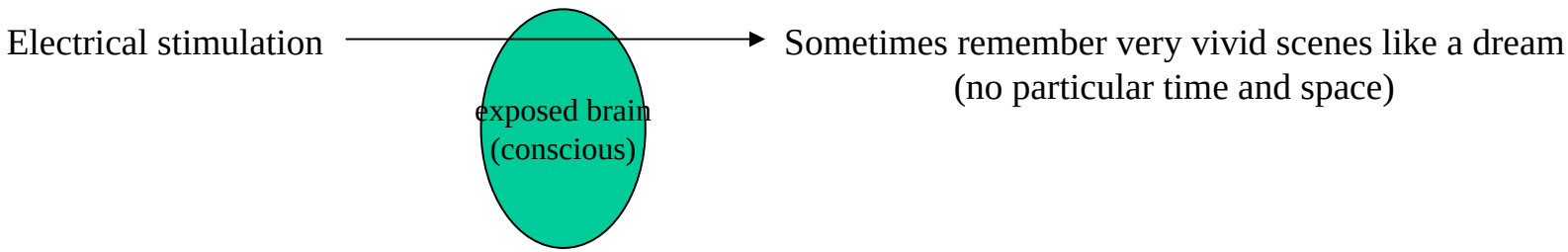
How memory is stored in brain?

Karl Lashley

Removal of rat cortex area: the more the worse
The entire cortex plays an important role in the storage of memory

Penfield experiment (1881-1976)

No fixed area for a particular memory
Stimulation of different places led to same memory and the vice versa
Probably activated the same circuit



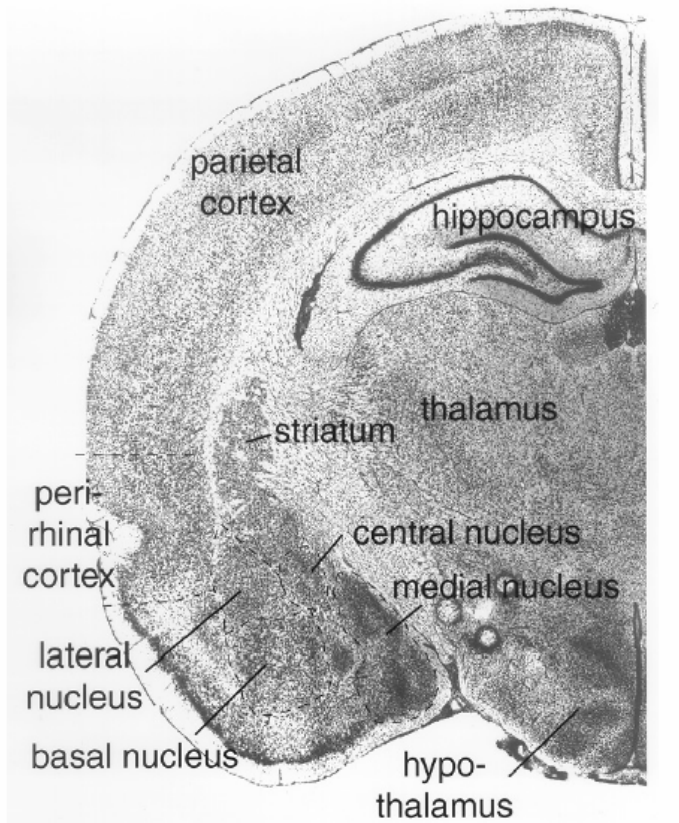
Stephen Rose

The memory would be distributed by different levels of circuitry
No single cell or exclusively committed group of cells

Memory function is distributed

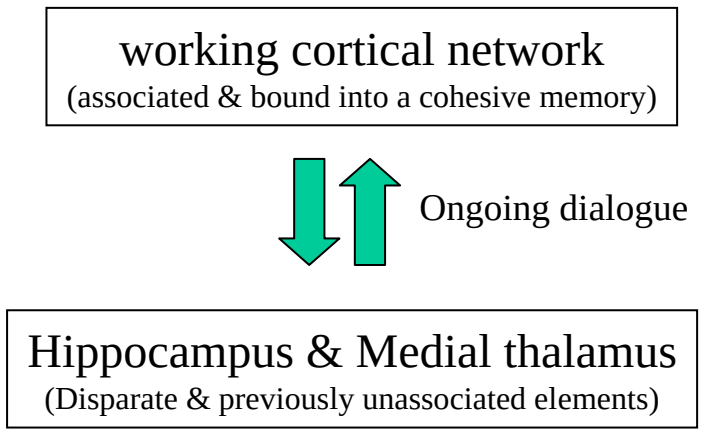
Molecules and Genes for Memory

- Memory function is distributed
- Memories are stored in the connections between neurons: synapse
- Synaptic physiology: rules for plasticity, special channels, molecules and genes.

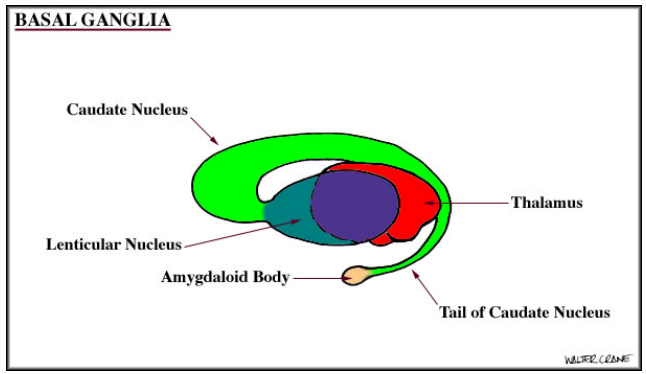


Consolidation of memory in the cortex: association

Highly transient and dissociable phase of short-term memory
Short-term memory lasts at most for half an hour

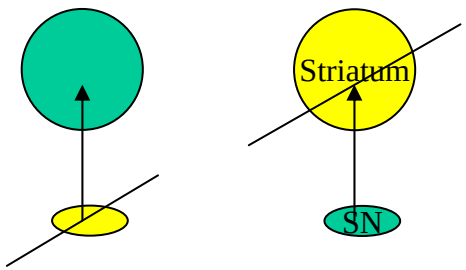


Implicit memory (암묵적 기억)



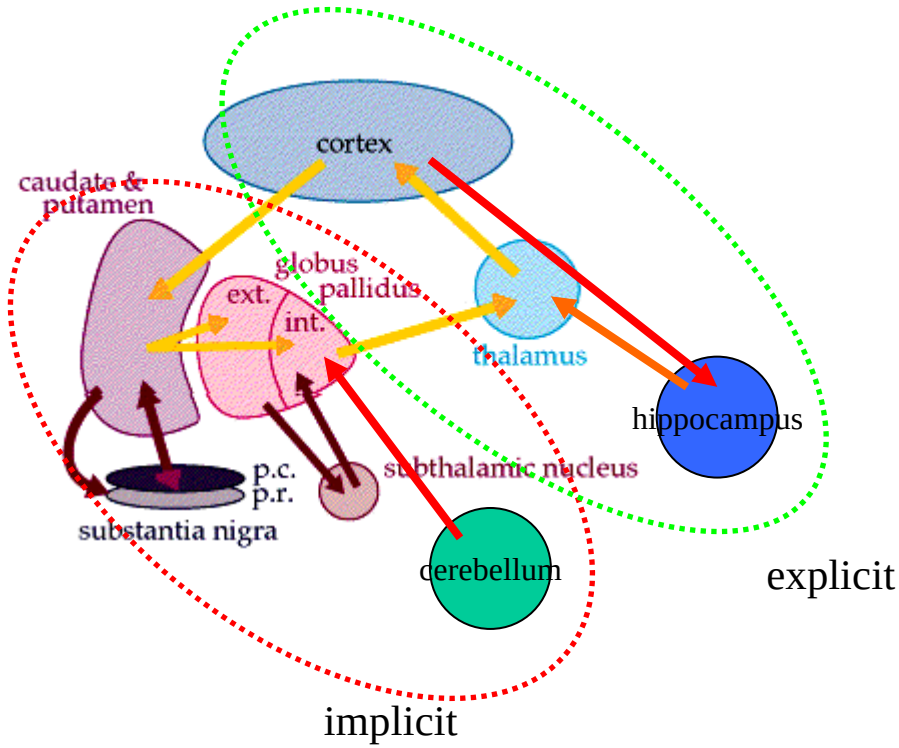
- Habit & Skill
- Basal ganglia: a sequence of movement
- Cerebellum: conditioning involving movement
- No direct reciprocal connection to cortex
- Without attention & conscious effect: probably an autonomous circuit

Parkinson's Huntington's



No dialogue
One side reaction

No problem in explicit memory
But implicit memory is impaired



Memories are stored in the connections between neurons: synapse

Ramon Y Cajal (1894)

“Mental exercise facilitates a greater development of … the nervous collaterals in the part of the brain in use. In this way, preexisting connections between groups of cells could be reinforced by multiplication of the terminal branches”

Lord Sherrington (1897)

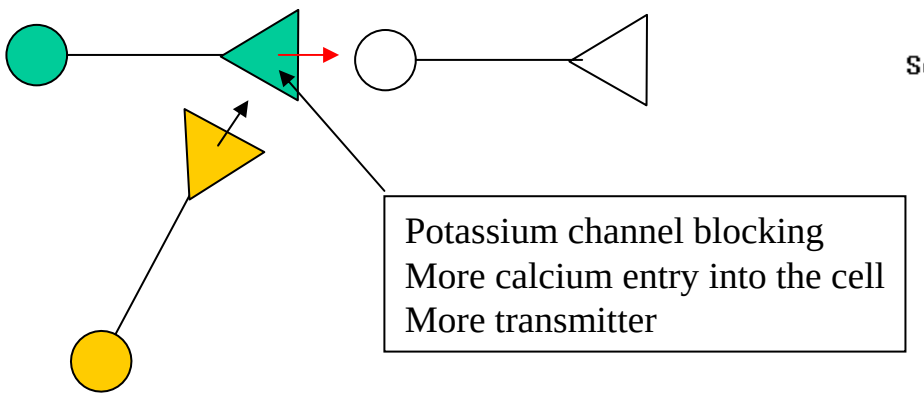
“…each synapsis offers an opportunity for a change in the character of nervous impulses, that the impulse as it passes over from the terminal arborescence of an axon into the dendrite of another cell, starts in that dendrite an impulse having characters different than its own”

1940s Donald Hebb (1949)

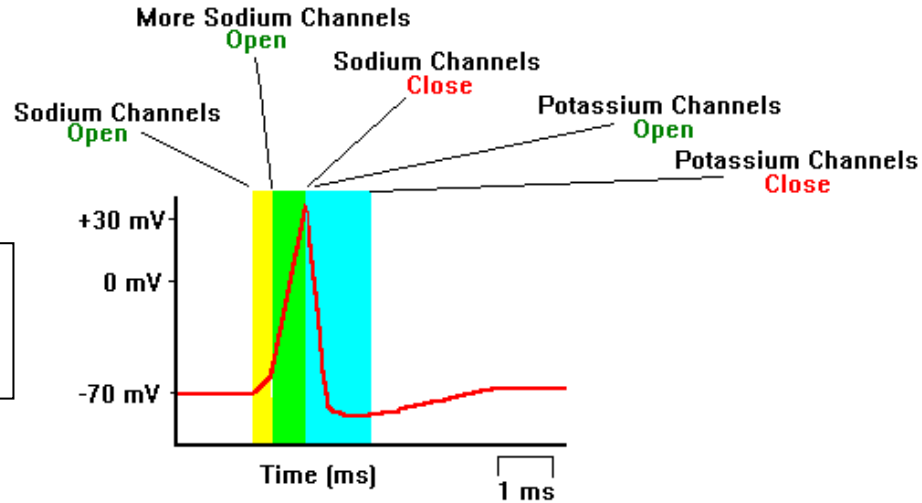
“When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased”

Presynaptic & postsynaptic strengthening

Aplasia

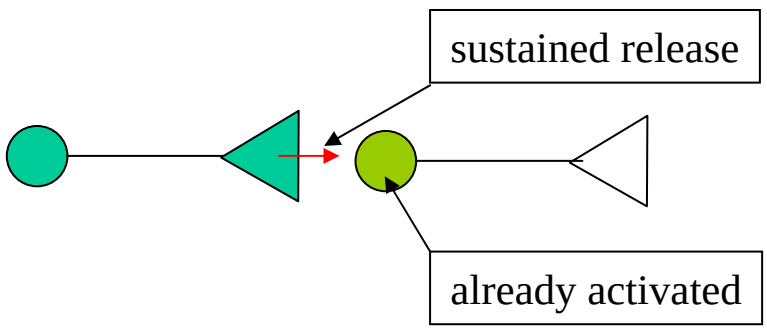


Potassium channel blocking
More calcium entry into the cell
More transmitter



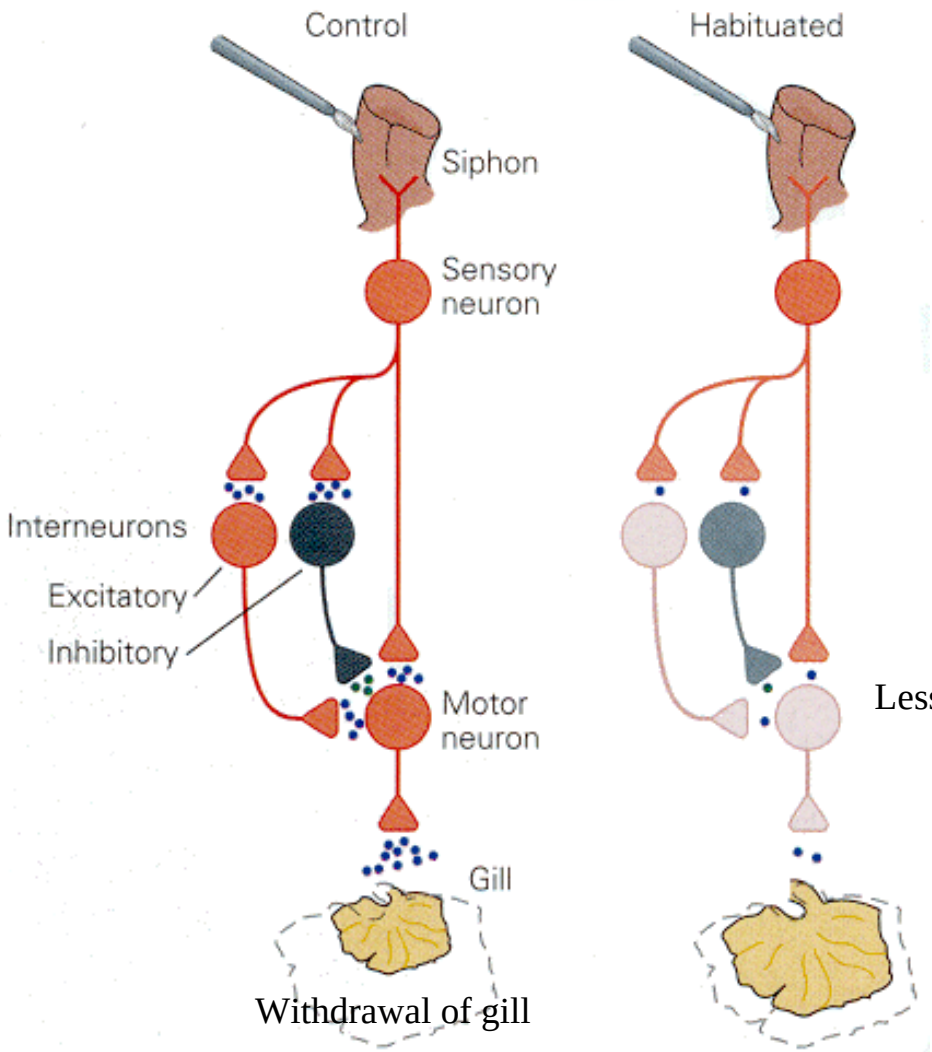
Human

long-term potentiation (LTP): strengthening of hardworking synapses
coincident & sustained stimulus
NMDA receptor (glutamate receptor)



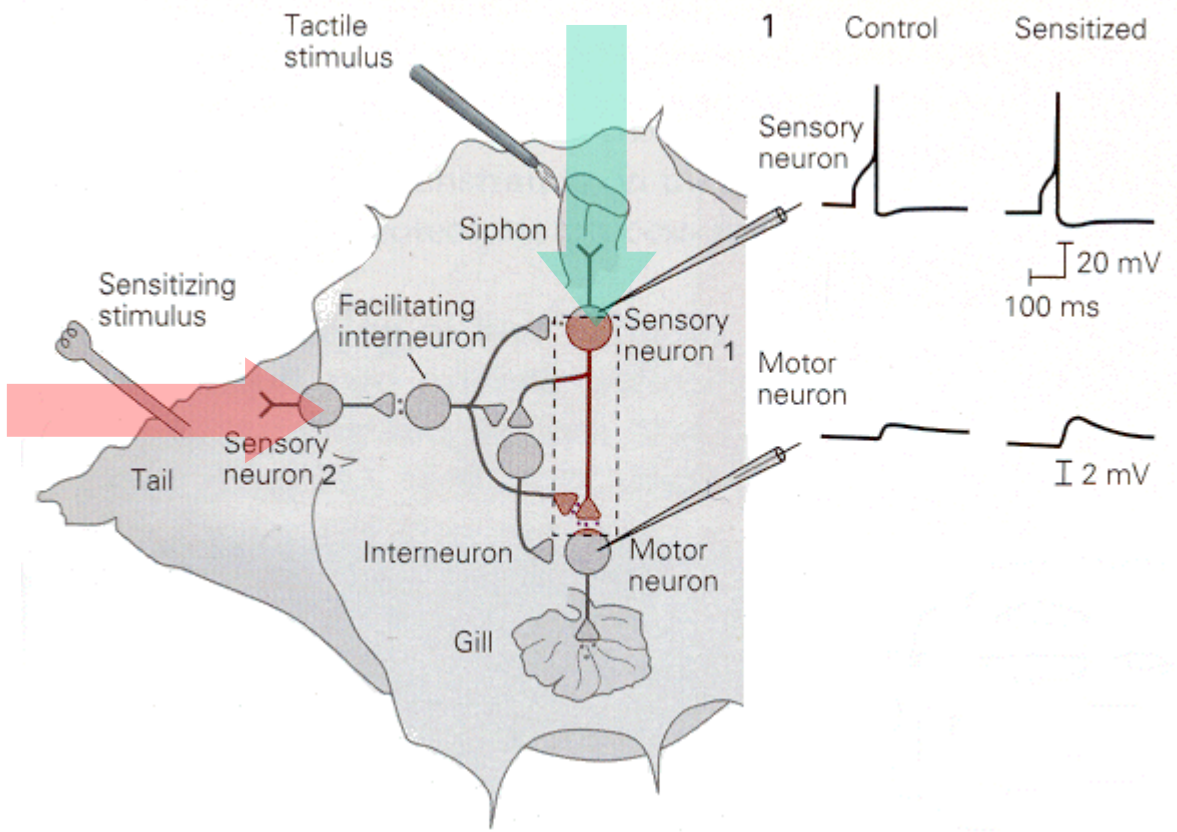
Strengthened synapse
Response to modest stimulus
LTP

Habituation. Simplified neural circuits involved in the habituation process in *Aplysia*. There are about 24 sensory neurons in the siphon; these are glutaminergic. They synapse on 6 motor neurons that innervate the gill and various interneurons as shown. The control condition is shown on the left, the habituated condition on the right. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)



Less dopamine (why?)

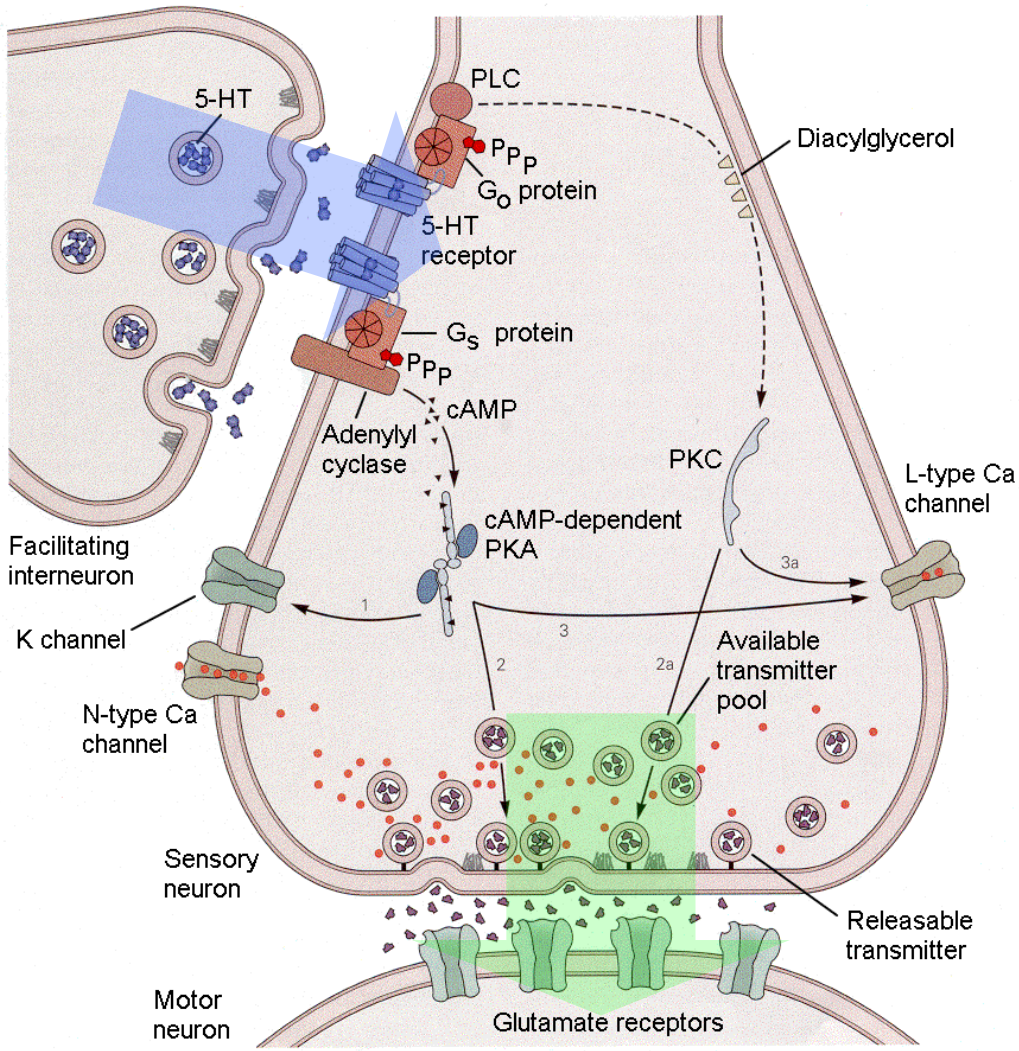
Sensitization. It is produced by applying a noxious stimulus to the tail of the Aplysia's tail, activated sensory neuron 2. This, in turn activates a facilitating interneuron that enhances transmission in the pathway from the siphon to the motor neuron. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)



http://www.unmc.edu/Physiology/Mann/mann19.html

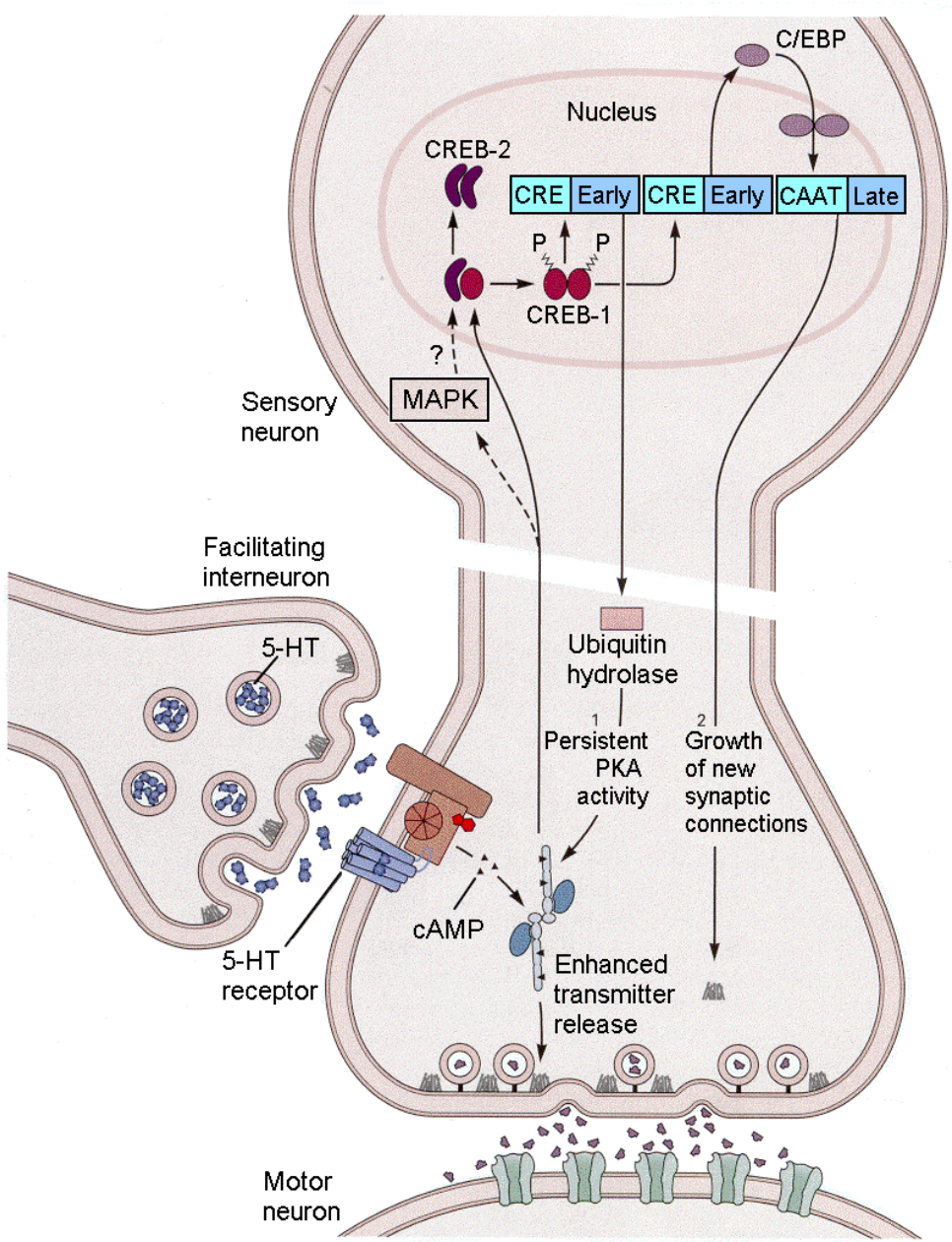
The molecular mechanism of sensitization. The synaptic and chemical events underlying presynaptic facilitation involved in producing sensitization. See text for details. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)

5-HT
cAMP
PKA activation
Phosphorylation of K channel
Closing K channel
Increased Ca transport
Increased neurotransmitter release



With only short-term tail stimulation, the sensitization will fairly quickly disappear when tail stimulation ceases. However, the sensitization can be made relatively permanent by repeated tail stimulation. This long-term sensitization (and also long-term habituation) occurs because there are structural changes that occur in the presynaptic terminals (sensory neuron 1, for example). With sensitization, there is an up to 2-fold increase in the number of synaptic terminals in both sensory and motorneurons. Alternatively, with habituation, there is a one-third reduction in the number of synaptic terminals. Both of these changes require altered protein synthesis by mechanisms shown in Fig. 19-7.

Fig. 19-7 - Long-term storage of implicit memory for sensitization involves changes shown in Fig. 19-6 plus changes in protein synthesis that result in formation of new synaptic connections. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)



Long-term memory
Permanent changes inside the targeting cell

Hebb rule:

The hypothesis proposed by Donald Hebb that the cellular basis of learning involves strengthening of a synapse that is repeatedly active when the postsynaptic neuron fires.

“Neurons that fire together get wired together.”

What permanent changes?

Genes, proteins, cellular responses
(receptor gene, receptor, increased transport)
Connections (synaptic contacts)
The more experiences, the more connections
Two important proteins: cell adhesion molecules (CAM), growth-associated protein (GAP-43)
CAM: sugar incorporation is important

GAP-43: high expression during exon growth & activated during LTP

Memory improvement: by making more associations in any kinds

Increase of Dendritic Spines in animals housing in a Complex Environment

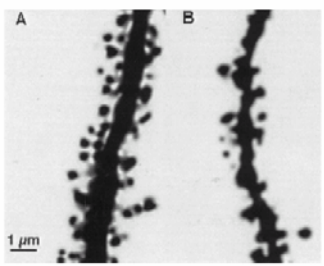
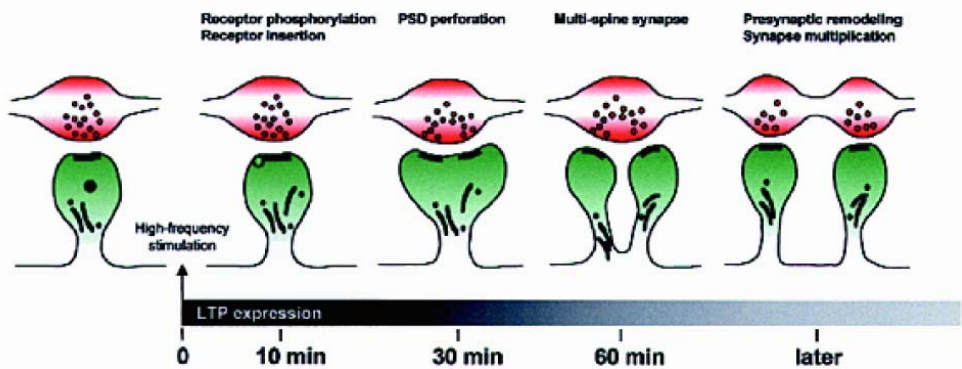


Figure 2. Examples of basal dendritic segments from CA1 pyramidal cells in a rat trained in the complex environment (*A*) and in an isolated rat (*B*). The spine densities for these two segments were 2.71 and 1.75 spines per micrometer, respectively. Spine densities in isolated rats were usually < 2.0 spines per micrometer and never exceeded 2.4 spines per micrometer. Reprinted with permission from [56]: © (1994) National Academy of Sciences, USA.

Moser et al. PNAS 1994

Strengthening of Synapse at different time-scales



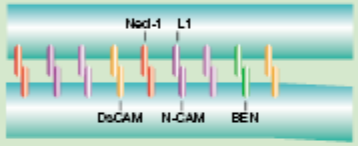
Cell Adhesion Molecules in the CNS

Toshiaki Sakisaka and Yoshimi Takai

Journal of Cell Science
jcs.biologists.org

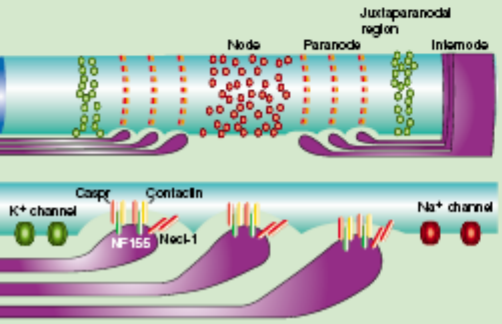
Axon-axon contacts

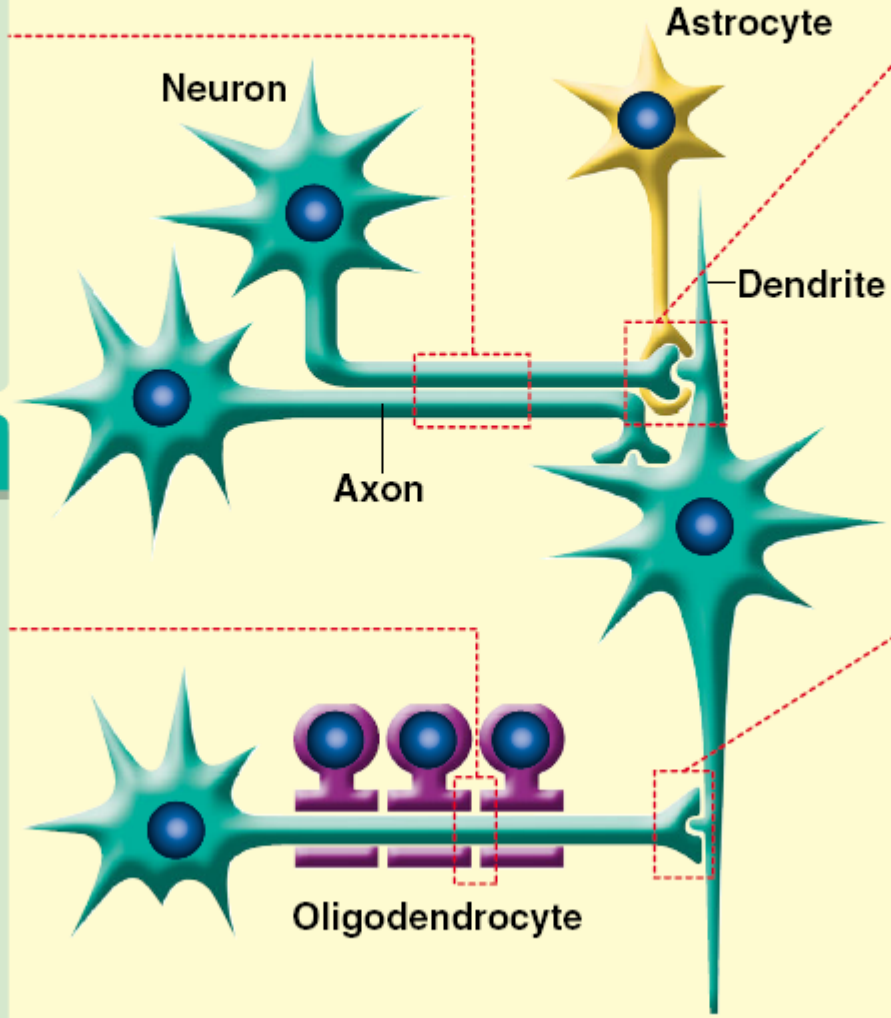
L1
N-CAM
BEN/DM-GRASP
DsCAM
Necl-1



Paranodal junctions

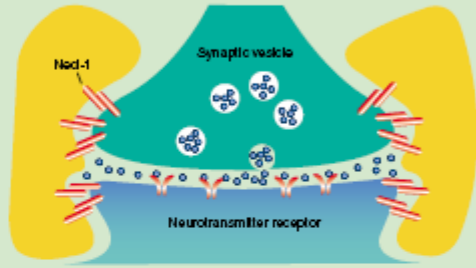
Contactin
Caspr
NF155
Necl-1





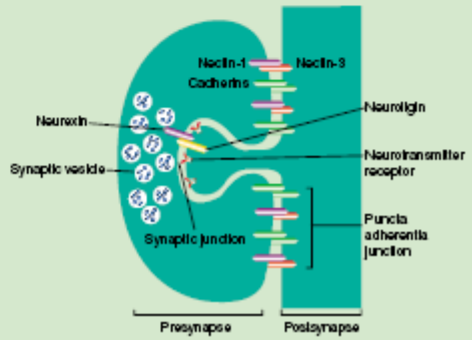
Axon-astrocyte contacts

Necl-1



Synapses

Cadherins	N-CAM
Nectin-1/-3	Neuroligin
Neurexin	SYG-1/SYG-2
Protocadherins	Sidekick
Eph/ephrin	L1



Learning

Long-term potentiation:

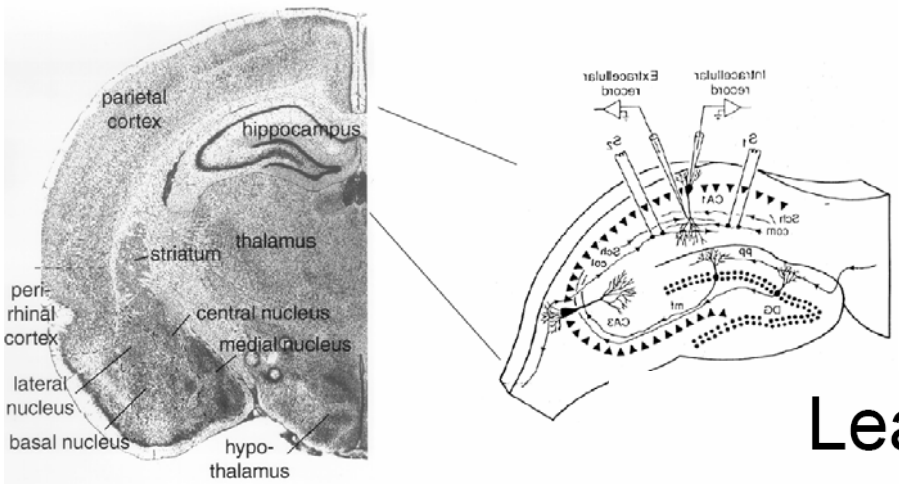
Discovered by Lomo (1966)

A long-term increase in the excitability of a neuron to a particular synaptic input caused by repeated high-frequency activity of that input.

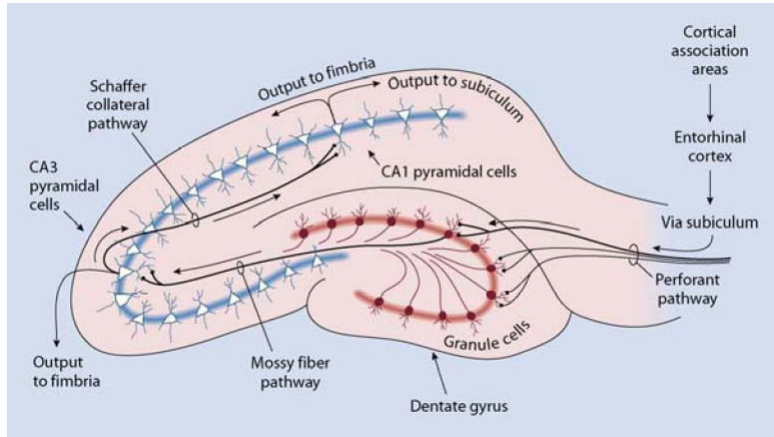
Mechanisms of Synaptic Plasticity

Induction of Long-Term Potentiation: For Associative Conditioning

Learning in a Dish: Hippocampal Slice



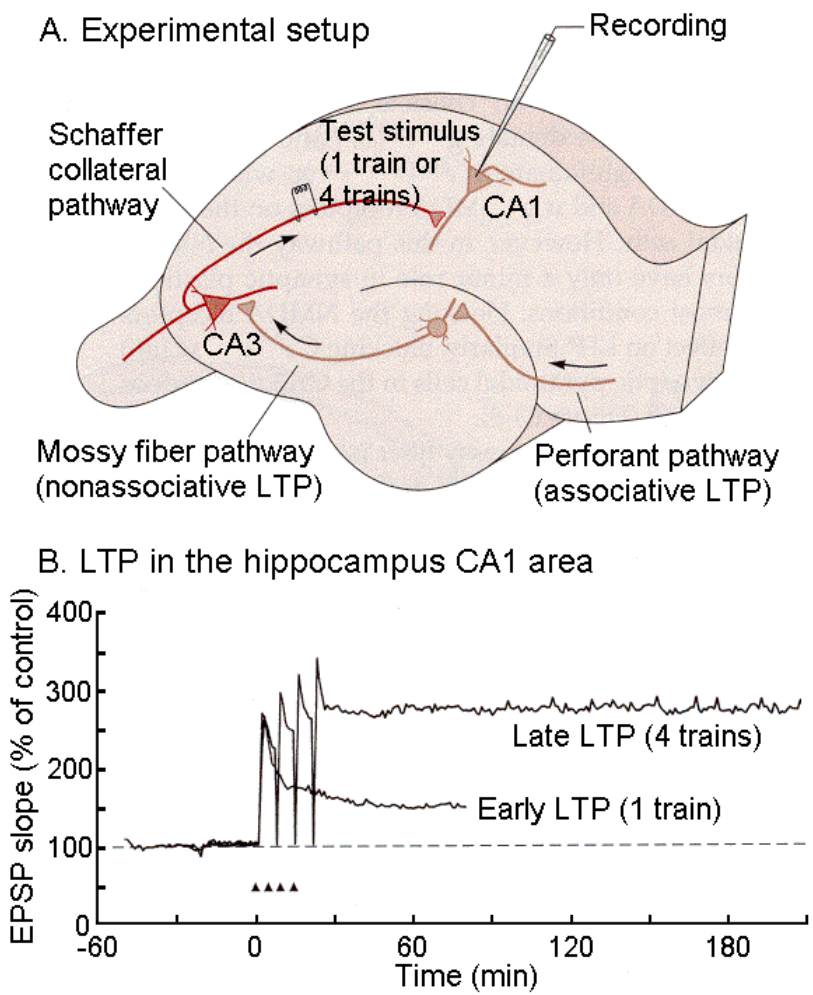
Bliss and Lomo (1973)



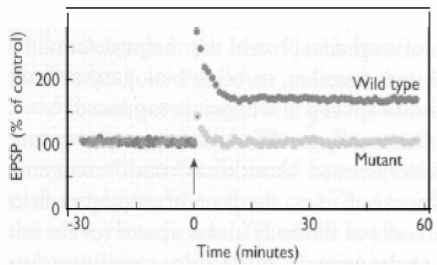
Learning in a Dish: Some conclusions from LTP experiments

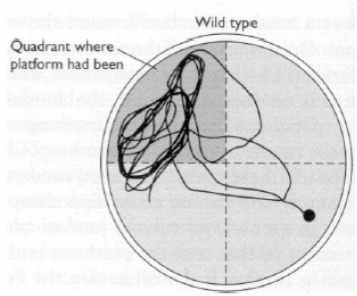
- LTP is synapse specific.
- LTP requires activation of the output cell (post-synaptic). Synapses strength increases only if pre and post-synaptic neurons are active at the same time. Weak synapses can only be potentiated in associations.
- NMDA channel is crucial for induction of LTP but it is not needed for maintenance of LTP. Therefore the maintenance of LTP must occur by changes in other receptors.
- One cannot by-pass the NMDA channel by depolarizing the cell. Ca influx must occur at close proximity to the synapse.

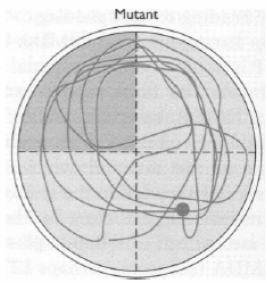
Fig. 19-8 - A. Experimental setup for demon-strating LTP in the hippocampus. The Schaffer collateral pathway is stimulated to cause a response in pyramidal cells of CA1. B. Comparison of EPSP (excitatory postsynaptic potential) size in early and late LTP with the early phase evoked by a single train and the late phase by 4 trains of pulses. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)

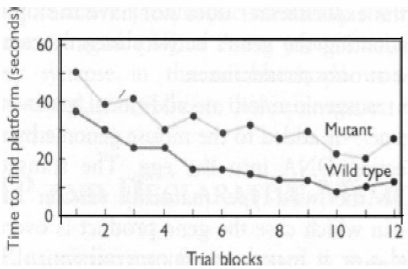


NMDAR-KO Mouse









No NMDAR → No LTP in Hippocampus → No Spatial Learning

NMDA Receptors

Found in hippocampus CA 1 field

Normally, Mg++ blocks Ca++ channel so when glutamate binds to receptor, Ca++ cannot enter to depolarize cell.

After LTP, Mg++ ions are displaced so when glutamate binds to receptor, Ca++ enters cell to depolarize.

Fig. 19-9 - During normal low-frequency trans-mission, glutamate interacts with NMDA and non-NMDA (AMPA) and metabotropic receptors.

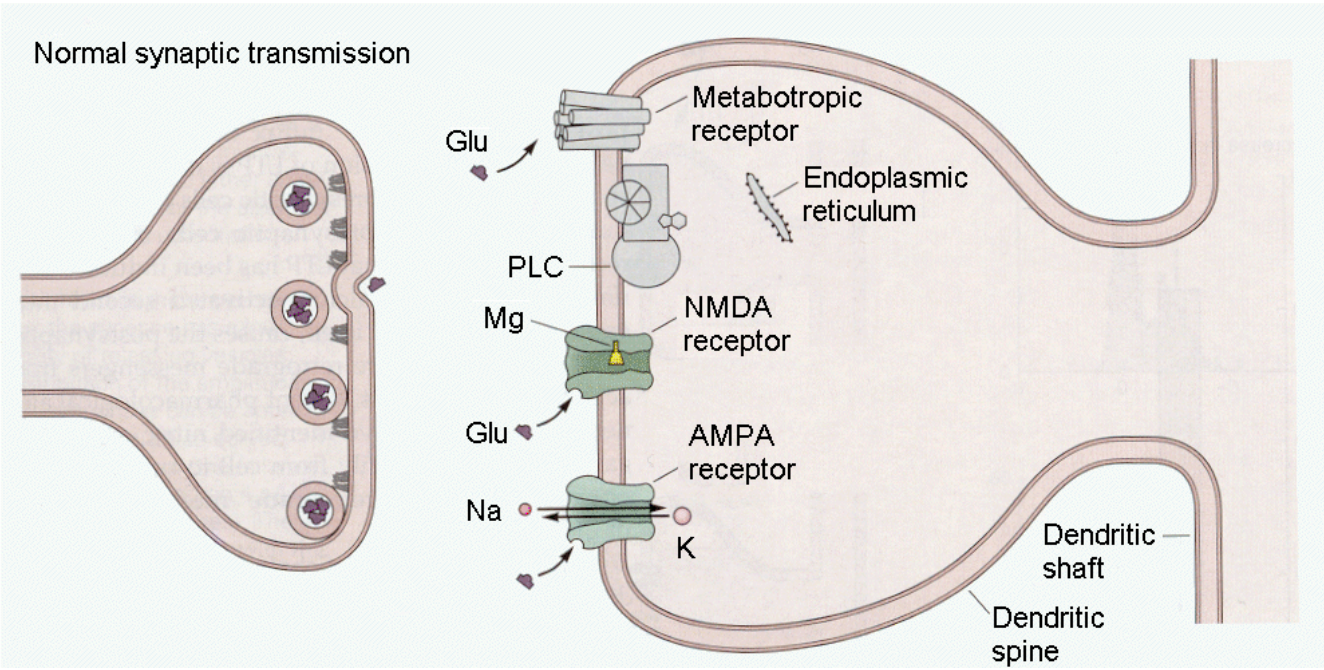
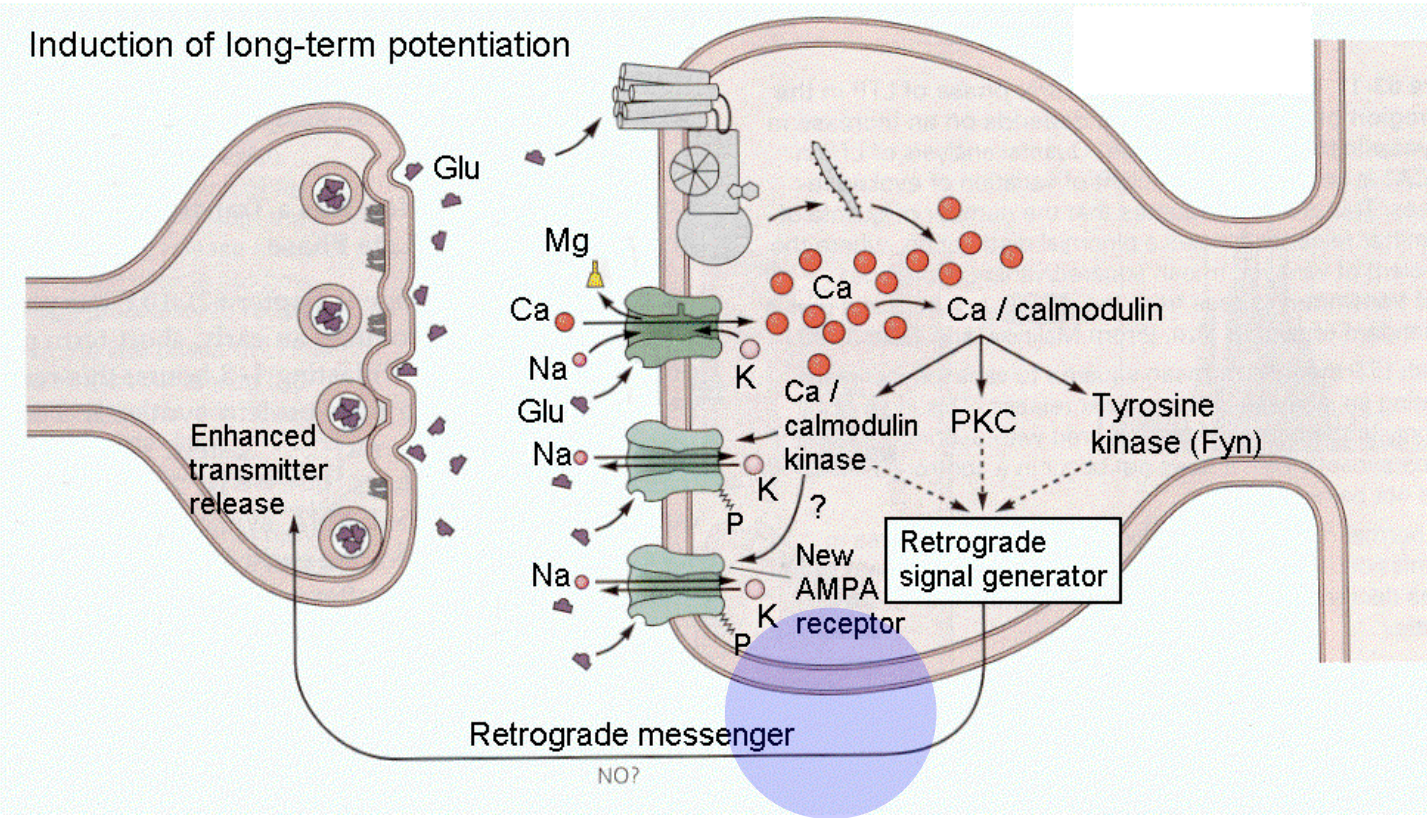


Fig. 19-10 - With high-frequency stimulation other events occur as described in the text. (Kandel, ER, JH Schwartz and TM Jessell (2000) *Principles of Neural Science*. New York: McGraw-Hill.)

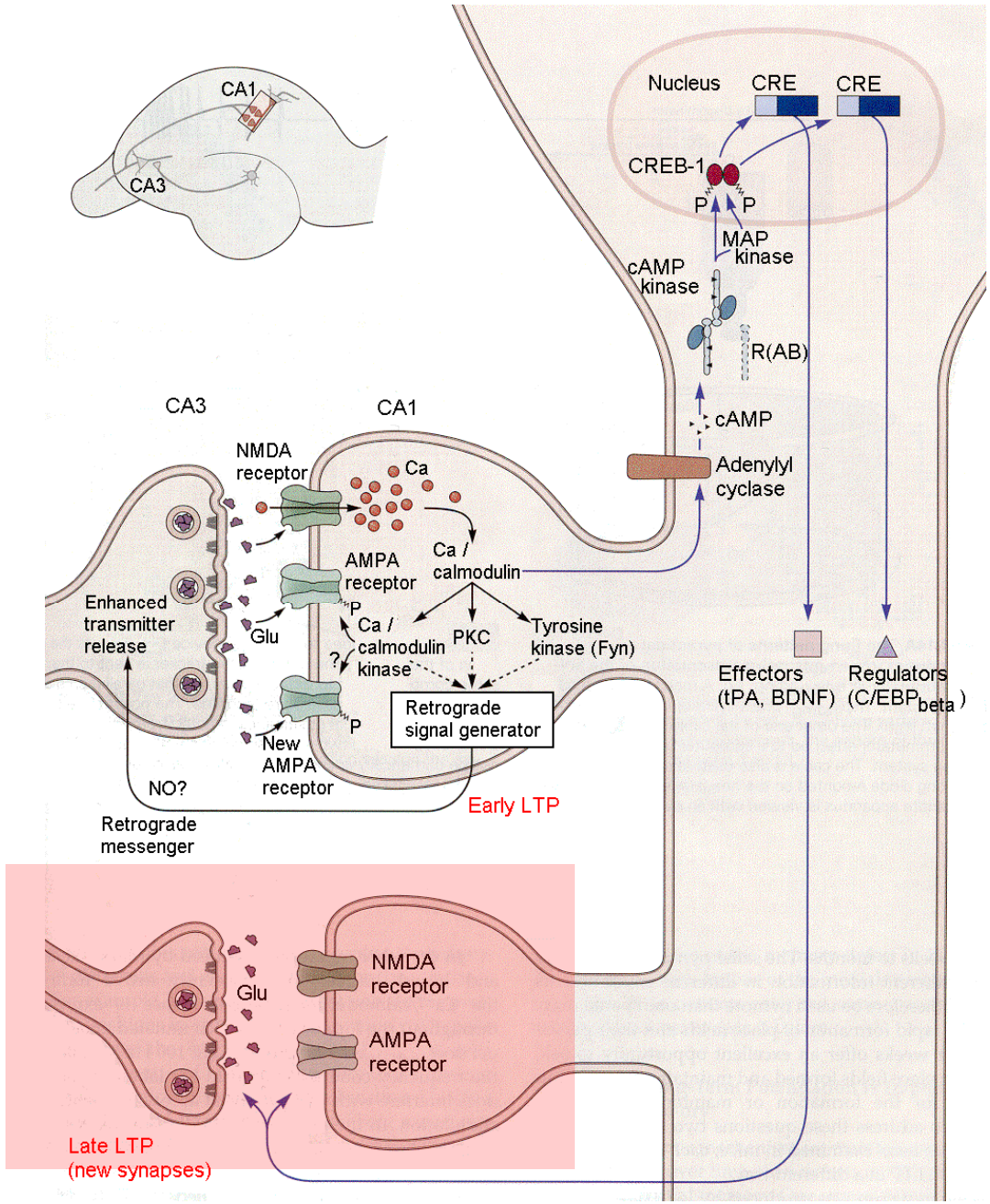


LTP results in the insertion of new AMPA (non NMDA) receptors into the dendrite.

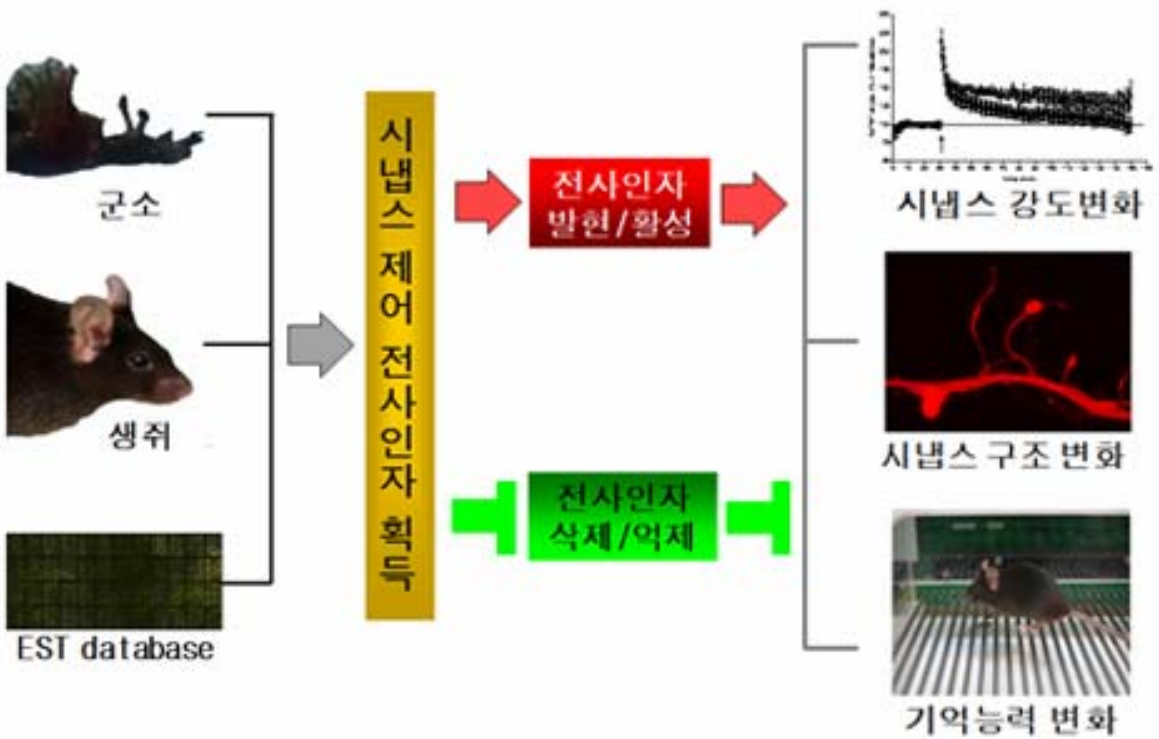
AMPA receptors are ionotropic glutamate receptors.

More glutamate receptors means stronger potentials in an active synapse.

Fig. 19-11 - For LTP to last (Late LTP) the events of Fig. 19-10 must also lead to changes in protein synthesis and to formation of new synaptic connections.



- 1900's : Synapses as a site of learning is proposed.
- 1970's : Long-term synaptic plasticity is shown.
- 1980-2003 : Key molecular and genetic factors in synaptic plasticity are discovered. Link to learning behavior is demonstrated.
- Future : Bridging the gap between molecular neuroscience with systems/cognitive neuroscience.
- Therapeutic applications.



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