Meds 371, Systems Neuroscience

University of Connecticut Health Center

Memory and Learning

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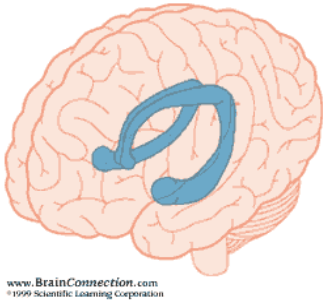
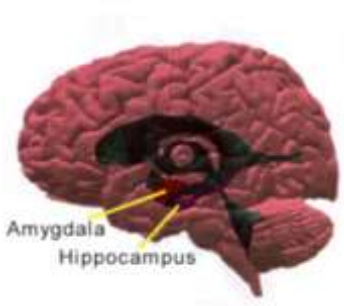
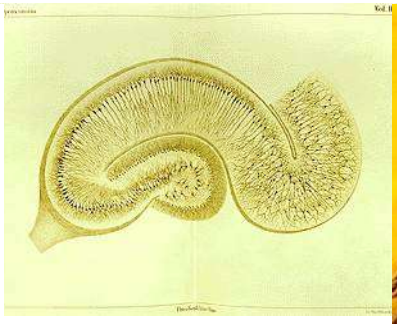
Department of Neuroscience

Sources:
Purves Textbook: Chapter 31, Memory
Review article: Lisman and Grace (2005) *Neuron*





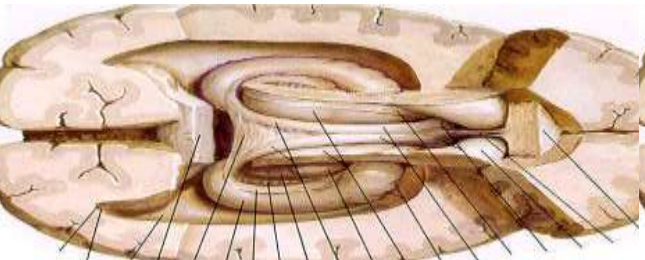


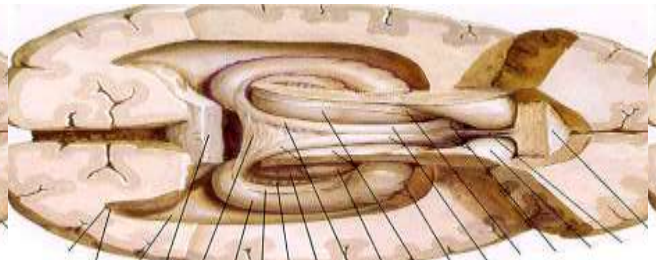
Why study learning + memory?

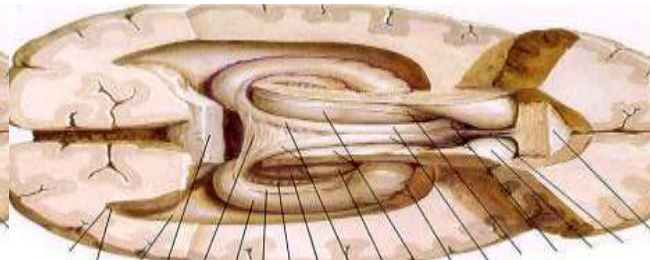
Understanding Memory Formation and Storage

1. **Is essential for understanding the brain function.**

2. **May improve preventive and therapeutic strategies for treatment of memory disorders in clinical practice.**







Memory disorders in clinical practice

The Korsakoff syndrome
is the result of nutritional depletion, i.e. thiamine deficiency, alcohol abuse.

Herpes encephalitis
There is characteristically a fairly abrupt onset of acute fever, headache and nausea. Neck rigidity, vomiting, and motor and sensory deficits may take several days to emerge

Epilepsy (transient epileptic amnesia)
This refers to the minority of transient global amnesia cases in whom epilepsy appears to be the underlying cause.

Alzheimer's Disease
Neurodegenerative, 5-10% population above 65, 45 % population above 85. Intracelular – neurofibrilary tangles, Extracellular – amyloid plaques, loss of neurons. Limbic system.

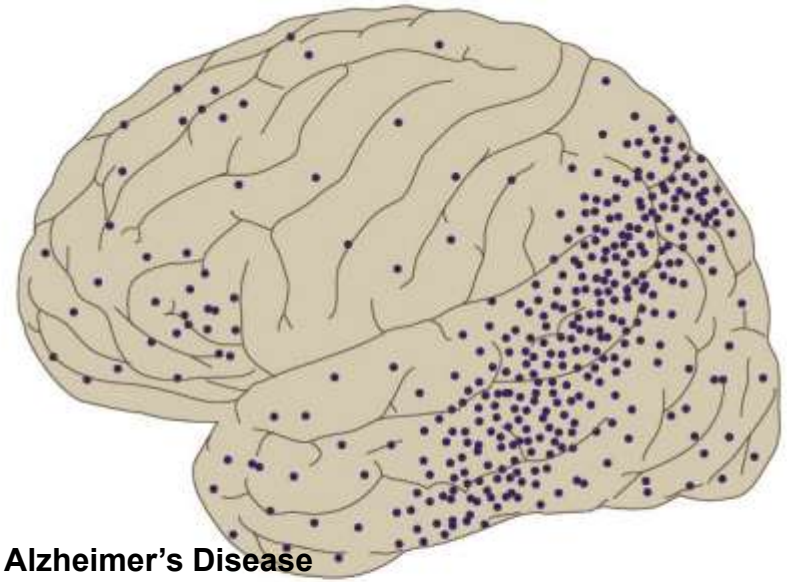
Severe hypoxia
Severe hypoxia can give rise to an amnesic syndrome following carbon monoxide poisoning, cardiac and respiratory arrests, or suicide attempts by hanging or poisoning with the exhaust pipe from a car.

Vascular disorders (cerebrovascular insult - stroke)(intracranial hemorrhage)
Vascular disorders can particularly affect **memory**, as opposed to general cognitive functioning, in (i) thalamic and medial temporal infarction, and (ii) sub arachnoid haemorrhage.

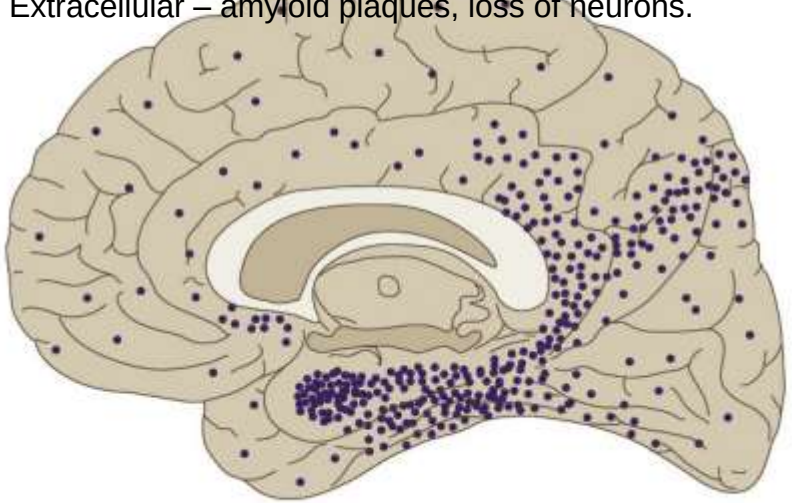
Head injury (Commotion, Contusion)
(Head injury can give rise to either transient or persisting amnesia.

Box 31D Alzheimer's Disease

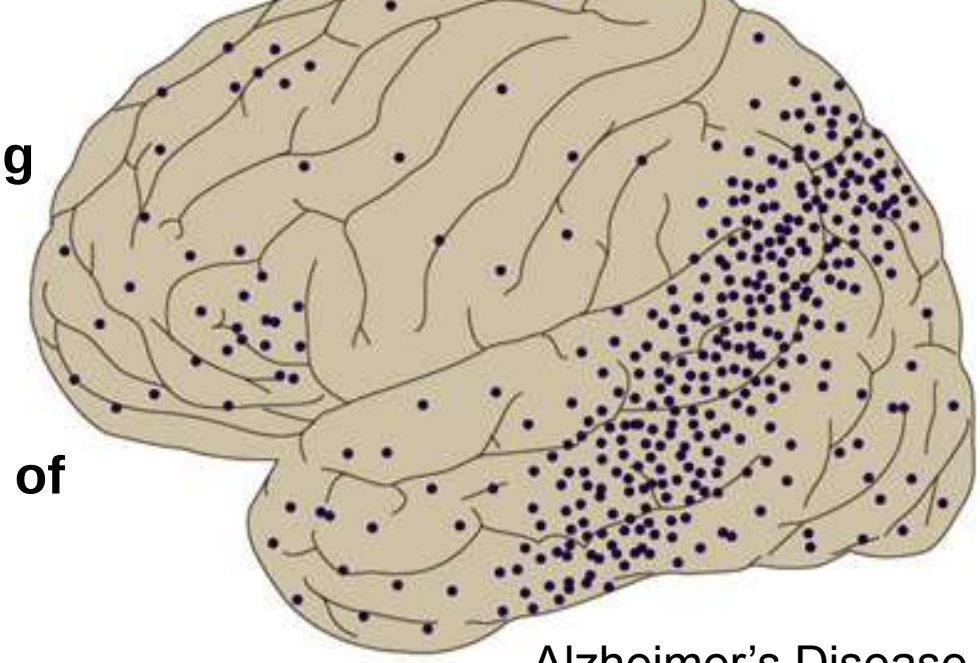
(B)



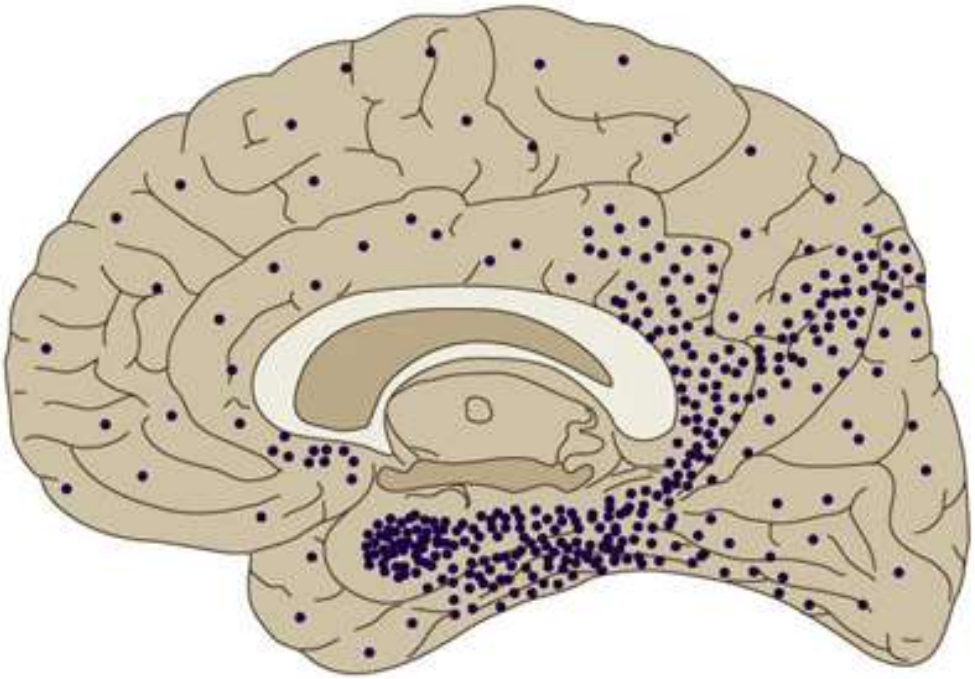
Alzheimer's Disease
Neurodegenerative, 5-10% population above 65, 45 % population above 85. Intracelular – neurofibrilary tangles, Extracellular – amyloid plaques, loss of neurons.



- ❑ **Cognitive impairment (thinking and judgment).**
- ❑ **Emotional behavior.**
- ❑ **Personality changes and loss of social skills.**
- ❑ **Poor Memory (getting lost on familiar routes).**
- ❑ **Poor perception.**
- ❑ **Language impairment.**
- ❑ **Flat mood. Losing interest in things previously enjoyed.**



Alzheimer's Disease

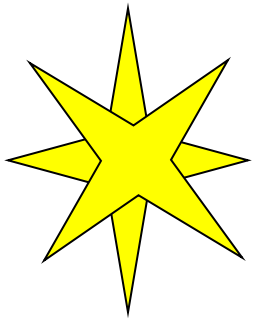


Memory

is a behavioral change caused by an experience.

Learning

is a process of acquiring memory.



Temporal categories of memory

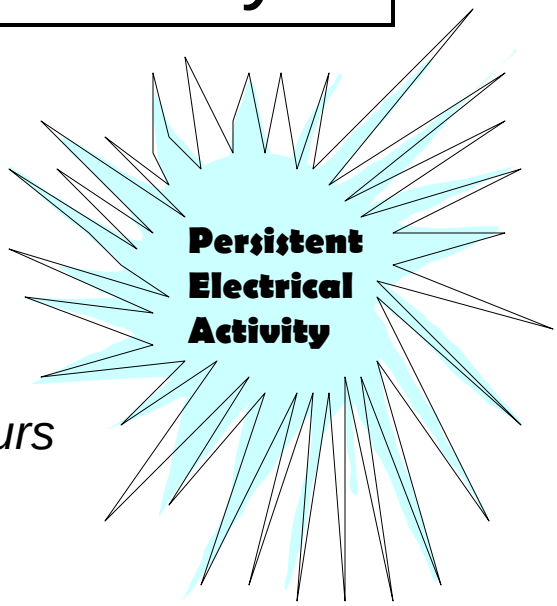
Qualitative categories of memory

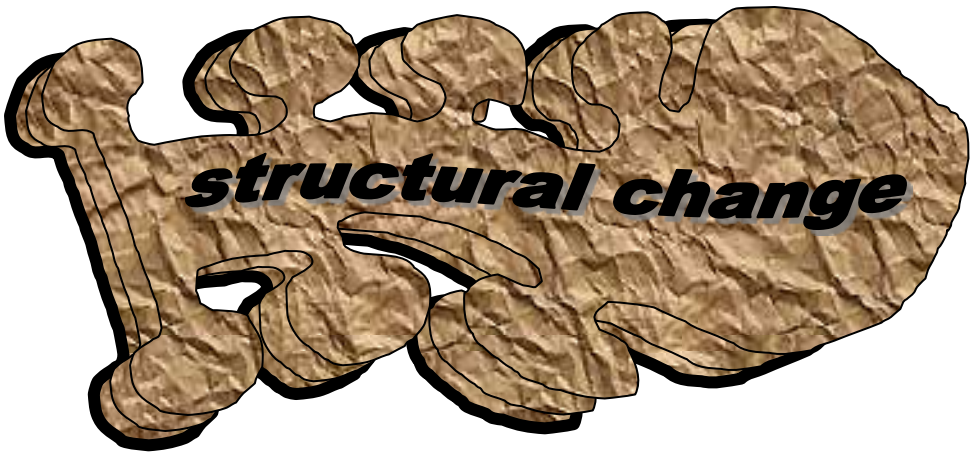
Temporal Categories of Memory

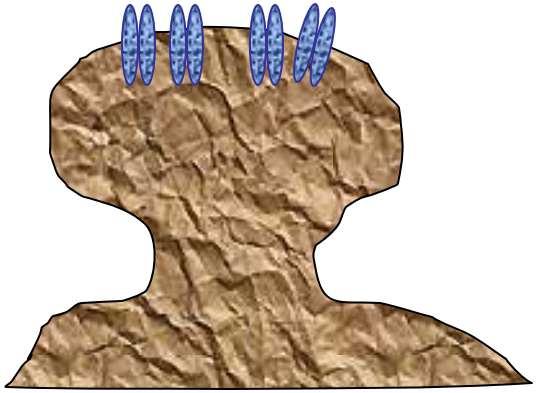
sequence

- Immediate — *fraction of a second*
- Short-term (working memory) — *several seconds*
- **Long-term** — ***days - years***

minutes - hours







ultrastructural change

declarative

Explicit

- Highly Flexible
- Involves association of multiple bits and pieces of information

Factual knowledge of people, places, and things

Semantic

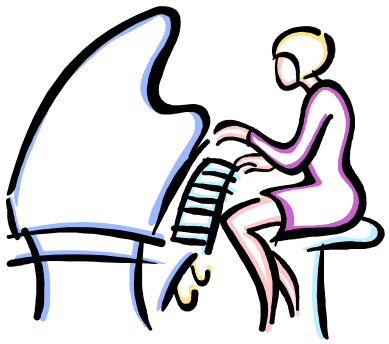
Episodic

non-declarative

Implicit

procedural

- Rigid
- Tightly connected to the original stimulus conditions under which learning occurred



Examples of Explicit (Declarative) Memory

Name

Phone number

Address

Sequence of events

Distribution

of objects

Examples of Implicit Memory

Non-declarative

Ball juggling; Bicycle riding, Musical instrument (violin); Tennis (serve, forehand, backhand, volley). Puzzle solving. Poker game.

Memory loss (based on the clinical case)

Patient **H**.**M**.

H.M. grew up outside of Hartford, Connecticut, and was by all accounts an amiable young man with above average intelligence. He liked to go ice skating and to listen to mystery shows on the radio.

On his sixteenth birthday, Henry had his first grand mal seizure. After that point, the paralyzing seizures arrived with increasing frequency, until by the summer of 1953, he was experiencing as many as **eleven** episodes per week. He was unable to hold a steady job, and his prospects for independent living seemed dim. There were not many effective treatments available for epilepsy in 1953, so it was with a mixture of hope and trepidation that Henry's family turned to Dr. William Scoville and his **experimental** surgery.

Henry G. Molaison

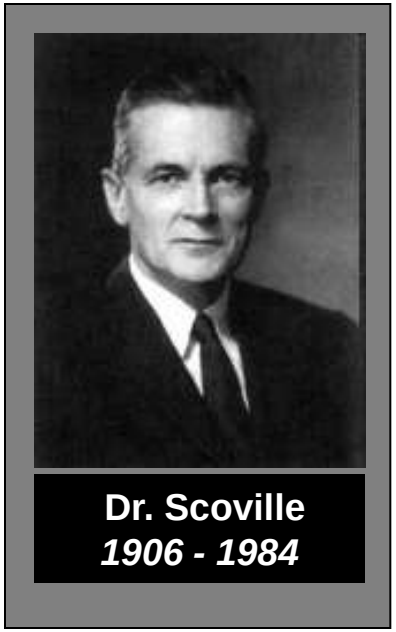
Patient **H.M.**

"He is known in the medical and scientific literatures as "the amnesic patient, H.M." He was born in Manchester, CT and graduated from East Hartford High School. In 1953, he underwent an experimental brain operation at the Hartford Hospital to relieve his seizure disorder. Immediately after the operation, Mr. Molaison showed a profound amnesia, which became the topic of intense scientific study for more than five decades. From age 27 on, he was unable to establish new memories for events in his everyday life and to acquire general information about the world in which he lived. His memory impairment was "pure" and not accompanied by intellectual or personality disorders. For this reason, and because the **operation has not been repeated**, he is the most widely studied and famous case in the neuroscience literature of the 20th and 21st centuries. Mr. Molaison's contributions to knowledge about memory have been groundbreaking, and researchers worldwide are in his debt. Burial will be private. Henry G. Molaison, 82, of Windsor Locks, CT died on Tuesday.

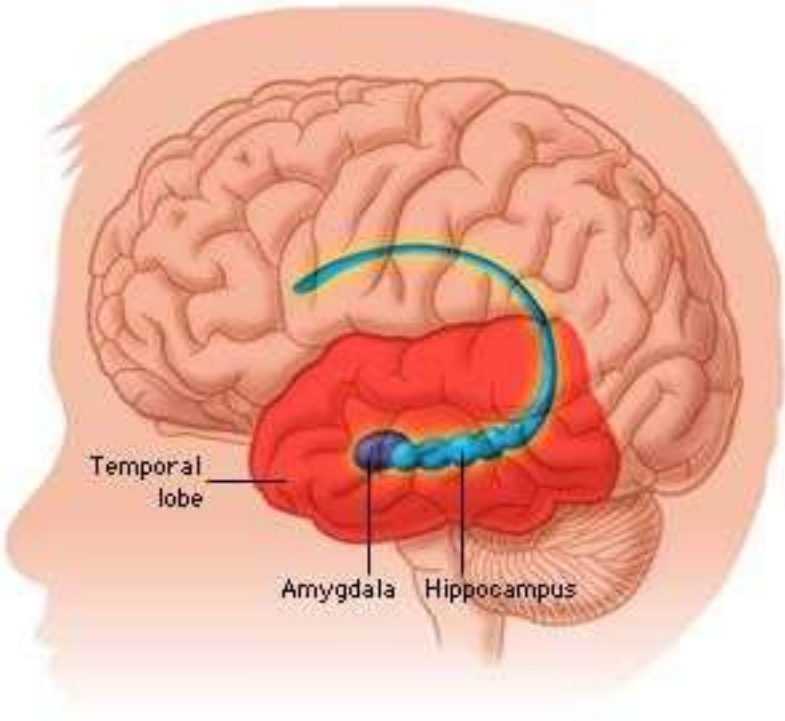

East Hartford

BRADLEY INTERNATIONAL
Gateway to New England

Patient H.M.



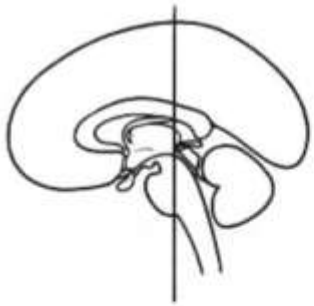
Dr. Scoville
1906 - 1984



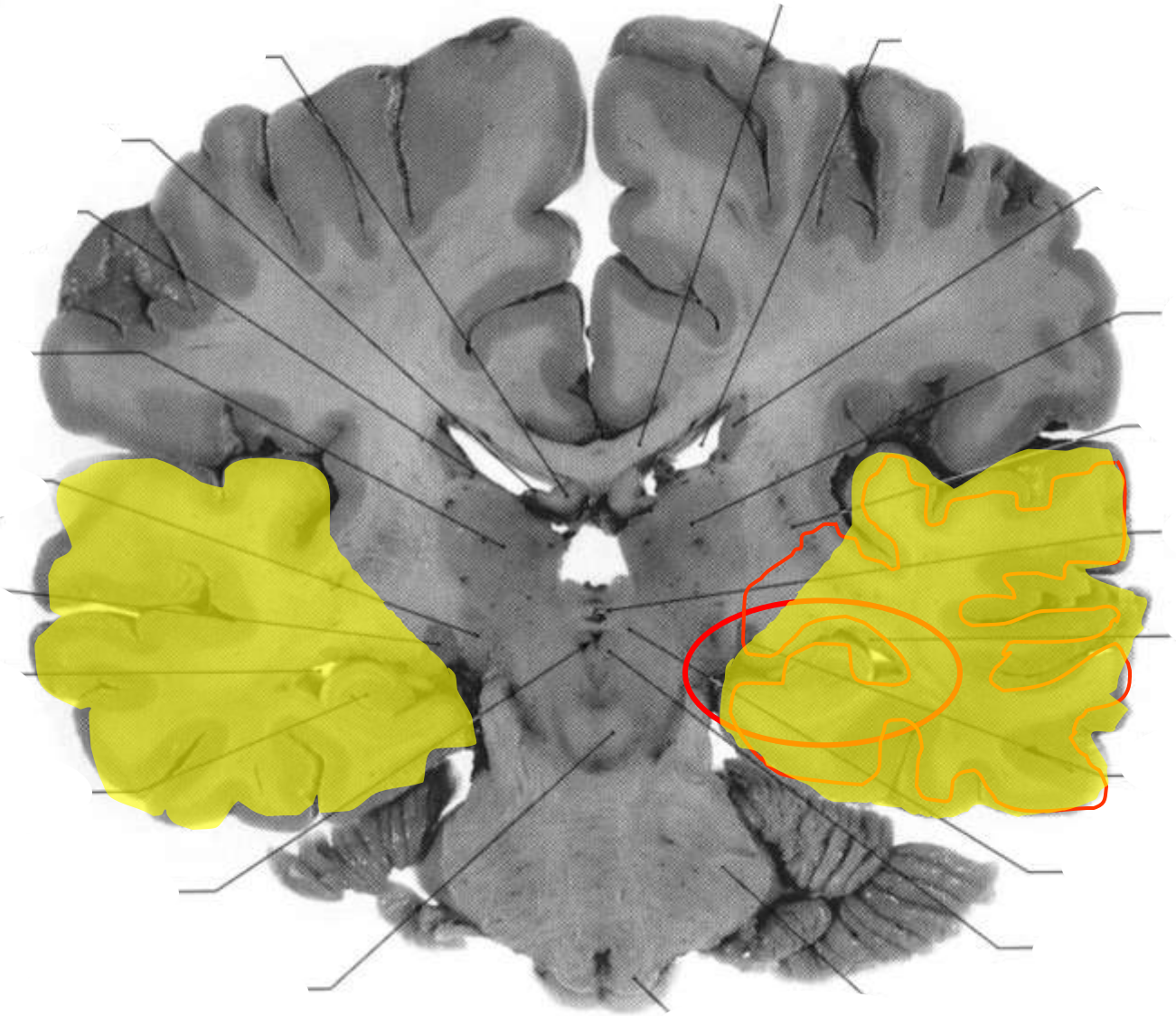
REMOVED BILATERALY

1. **Temporal cortex**
2. **Perirhinal cortex**
3. **Entorhinal cortex**
4. **Amygdala**

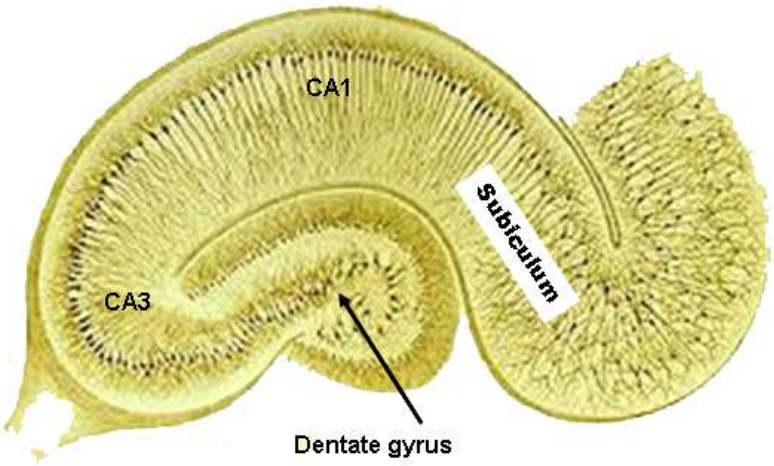
Dr. Scoville removed a large chunk of Henry's right and left temporal lobes, which was a crucial decision because the brain is symmetrical and thus most important structures are duplicated. Altogether, Henry lost about a fist-sized portion of his brain, which encompassed (on both sides) the hippocampus, the amygdala, and the entorhinal and perirhinal cortices.

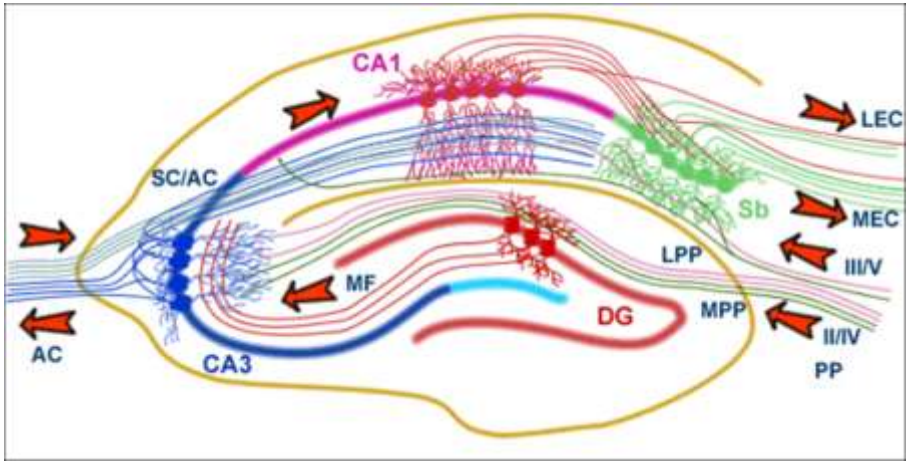


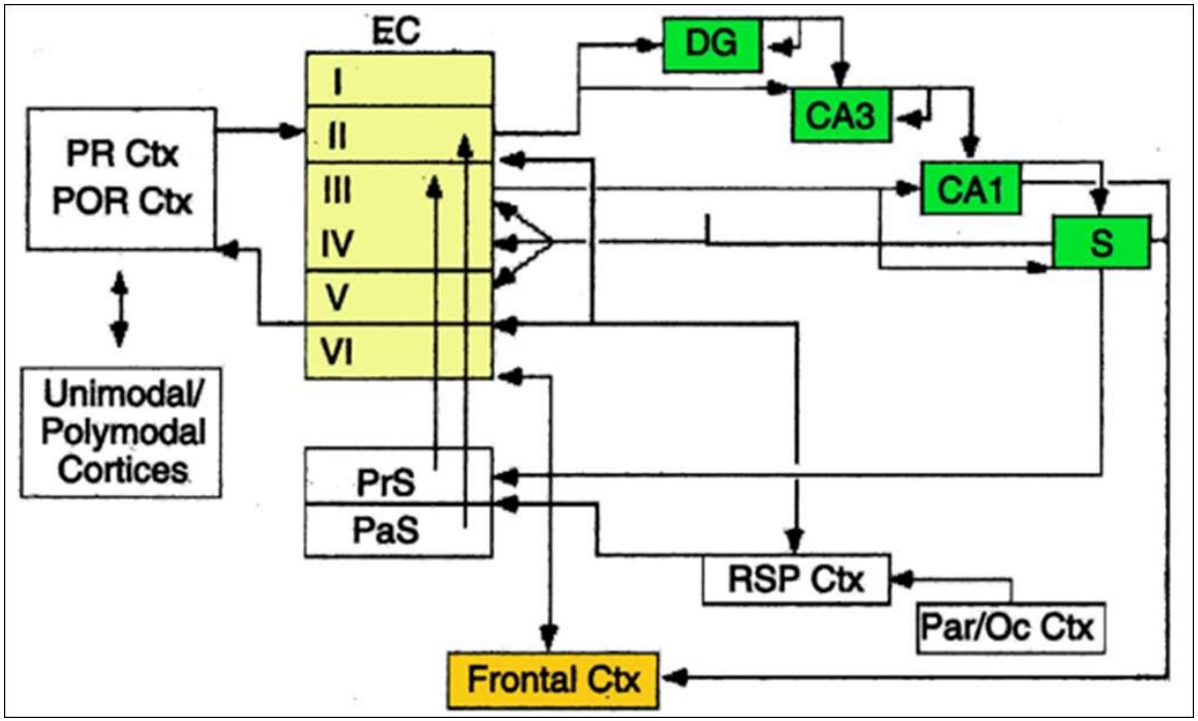
HIPPOCAMPUS - in the temporal lobe



lateral entorhinal cortex (LEC)







Cortical Inputs to Hippo

EC – entorhinal ctx.

PR – perirhinal ctx.

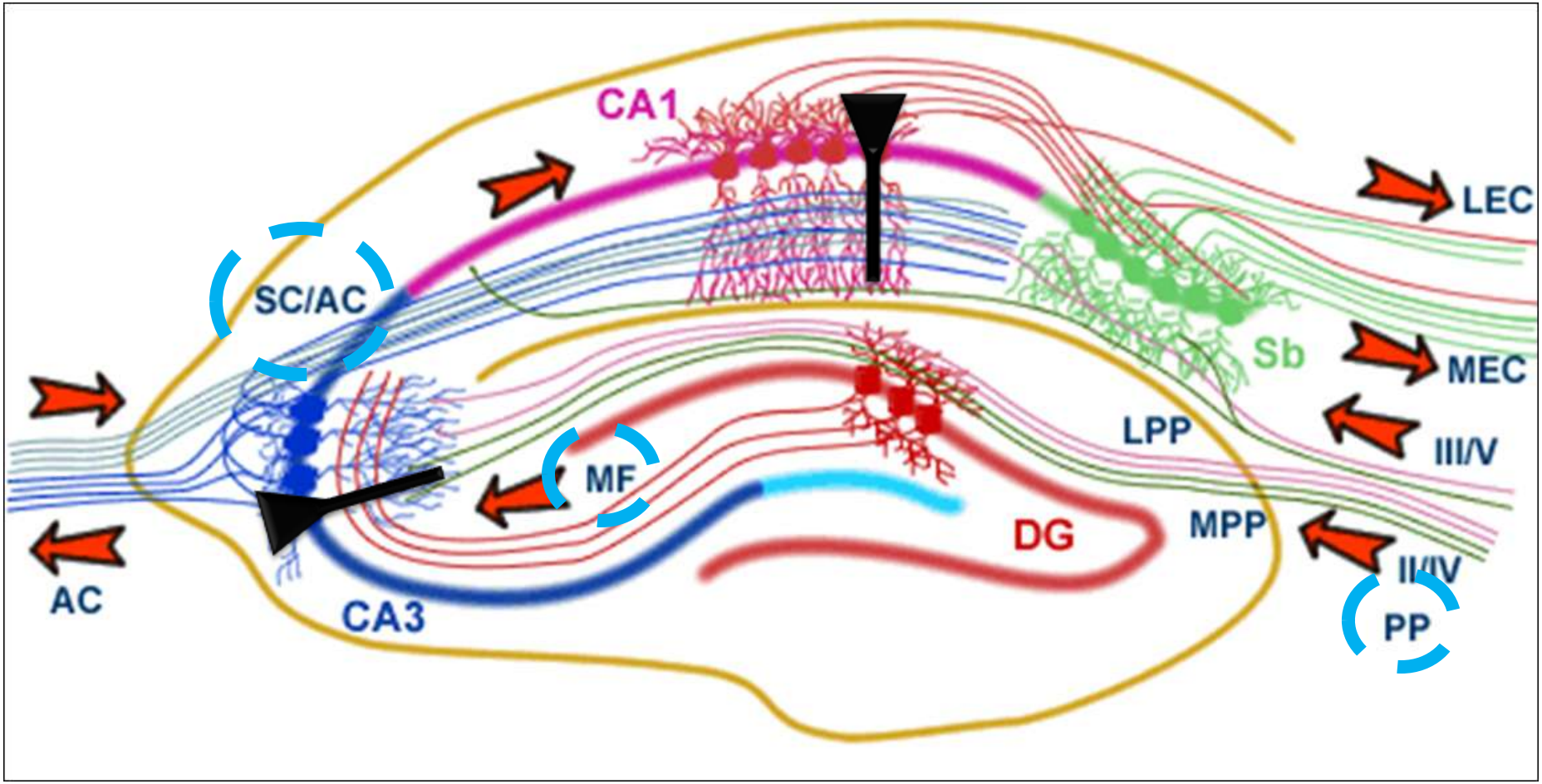
POR – postrhinal ctx.

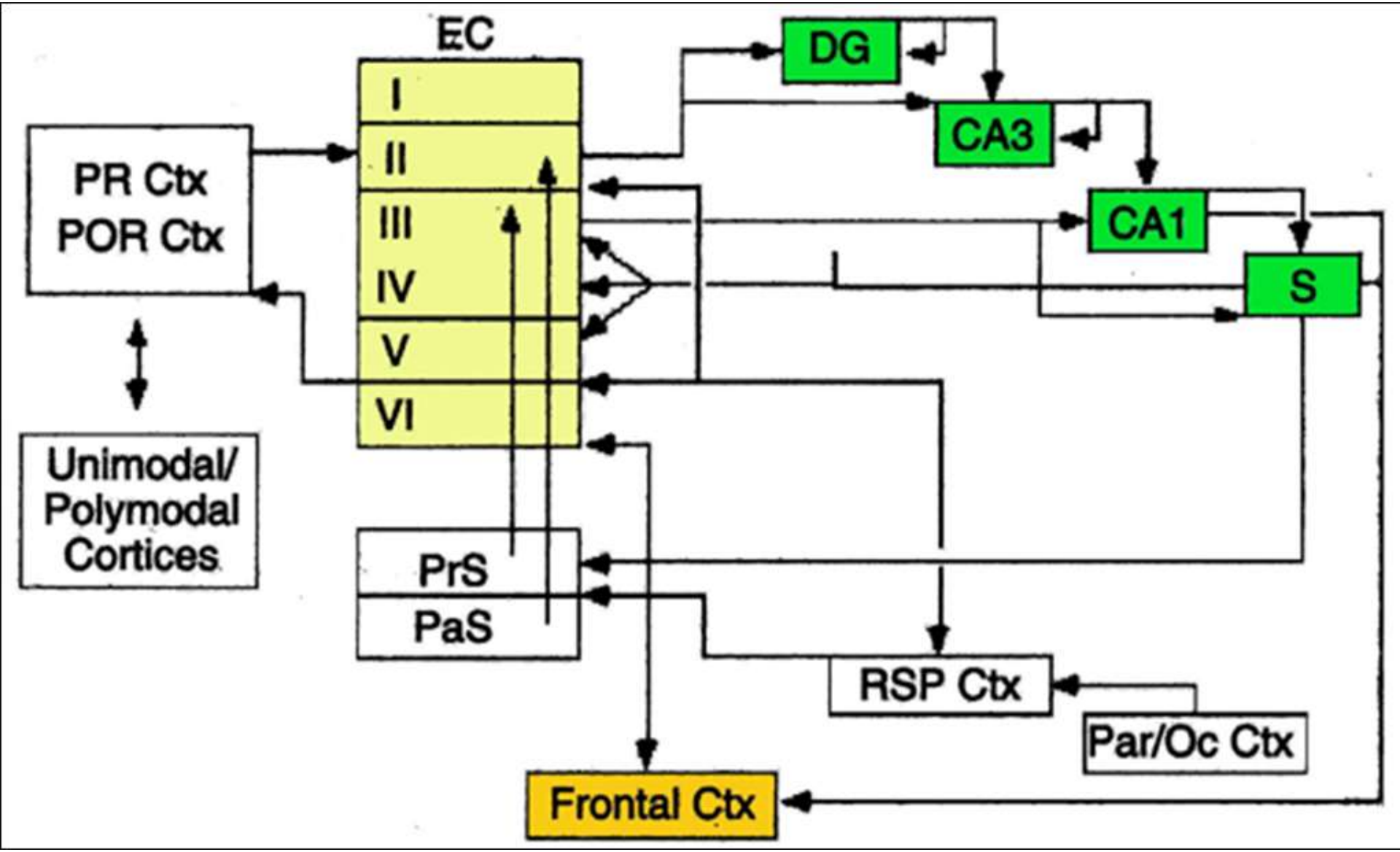
(parahipocampal gyrus in human)

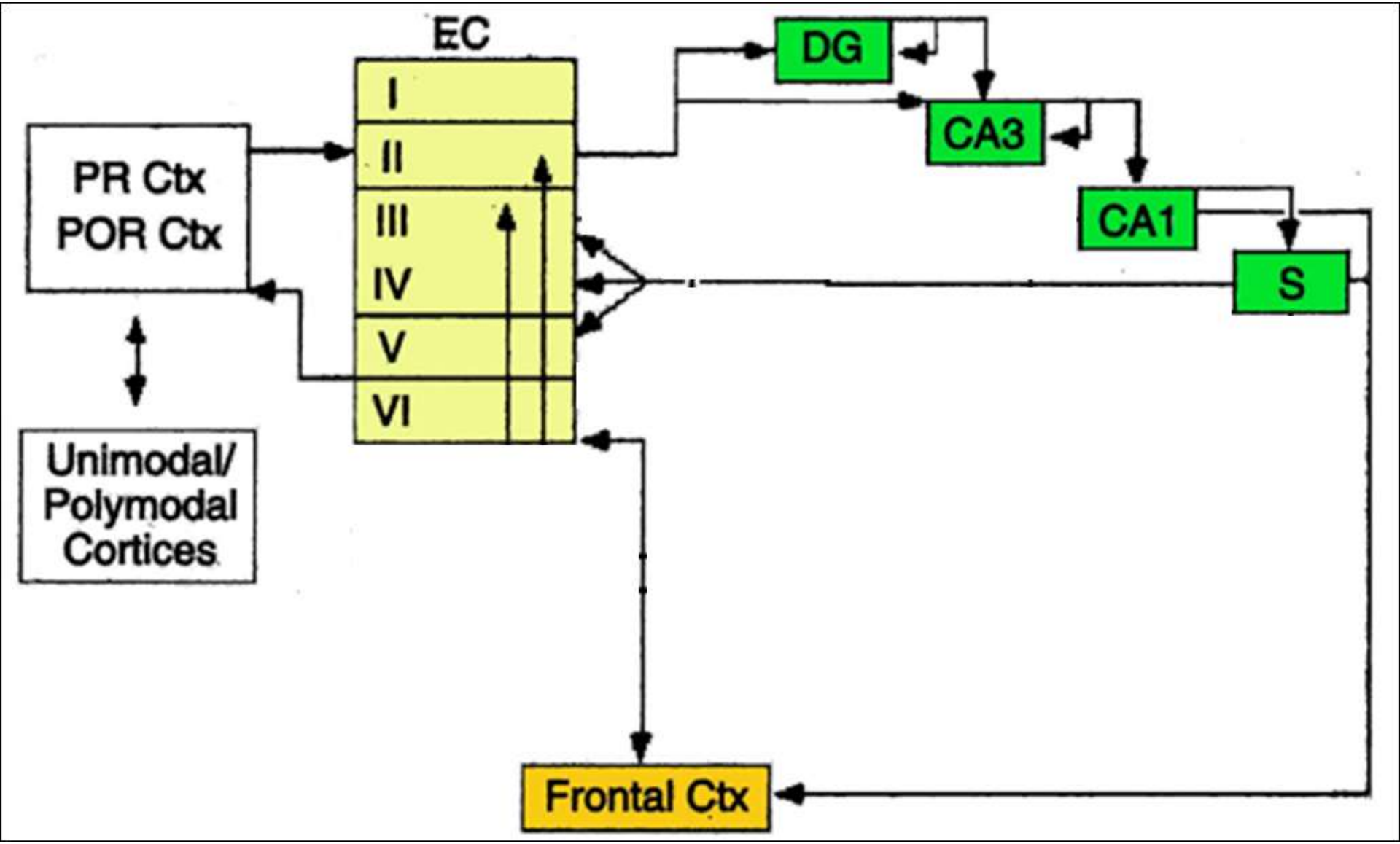
RSP – retrosplenial ctx.

Par/Oc – pariet. Occip.

Prefrontal Cortex


CA1
LEC
SC/AC
Sb
MEC
LPP
III/V
MF
DG
MPP
II/IV
AC
CA3
PP


EC
I
II
III
IV
V
VI
PR Ctx
POR Ctx
Unimodal/
Polymodal
Cortices
PrS
PaS
DG
CA3
CA1
S
RSP Ctx
Par/Oc Ctx
Frontal Ctx


EC
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II
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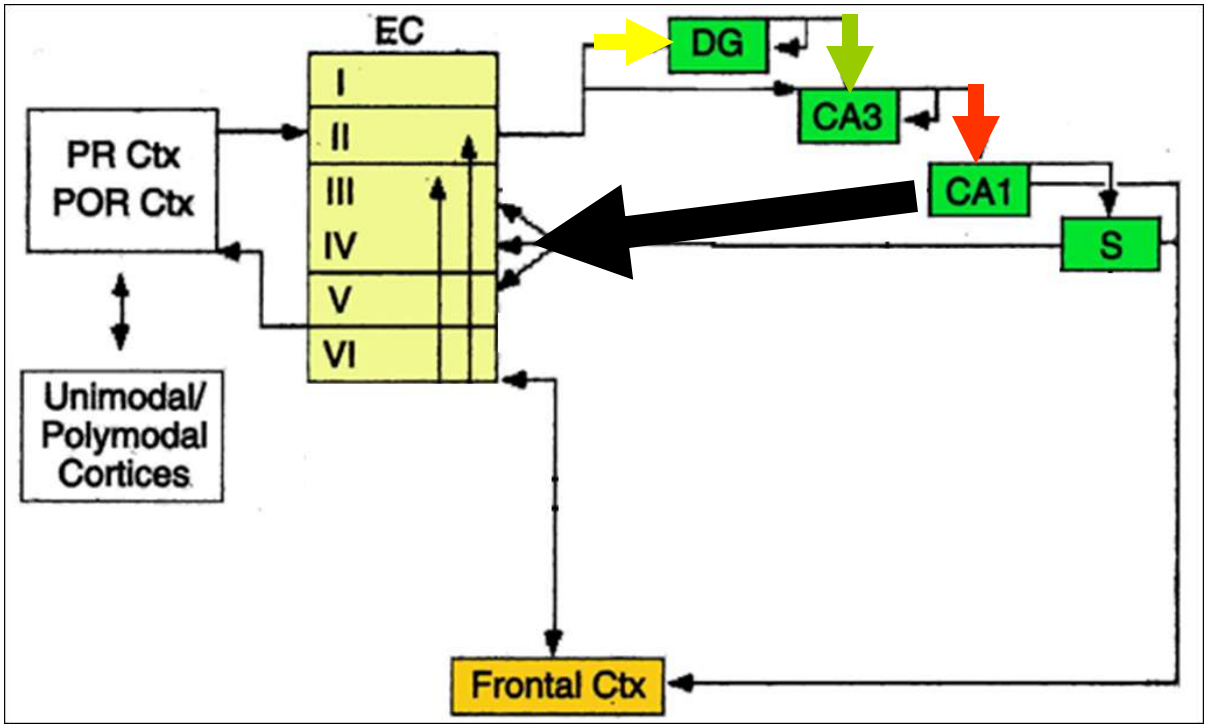
V
VI
PR Ctx
POR Ctx
Unimodal/
Polymodal
Cortices
DG
CA3
CA1
S
Frontal Ctx

Unidirection progression of Excitatory Synaptic Inputs

Trisynaptic Circuit



Perforant Path

Mossy Fiber

Schaffer Collat

In the trisynaptic pathway, information flows from layer II of the entorhinal cortex to the dentate gyrus through the perforant path. Mossy fiber axons from dentate gyrus granule cells synapse on neurons in CA3, which project to CA1 pyramidal cells through the Schaffer collaterals. Finally, CA1 neurons relay information back to layer V of the entorhinal cortex.

Patient H.M. (four points)

❑ Hen
long-t

1. Explicit memories stored long time ago

❑ Als
time.
numb
normally on these kinds of tasks. Thus, his **working memory** (or scratch-pad memory) seemed unaffected by the loss of his hippocampus.

2. Working Memory

❑Henr
though
skill le
the hippocampus.

3. Implicit Memory

❑ **Th**
perm

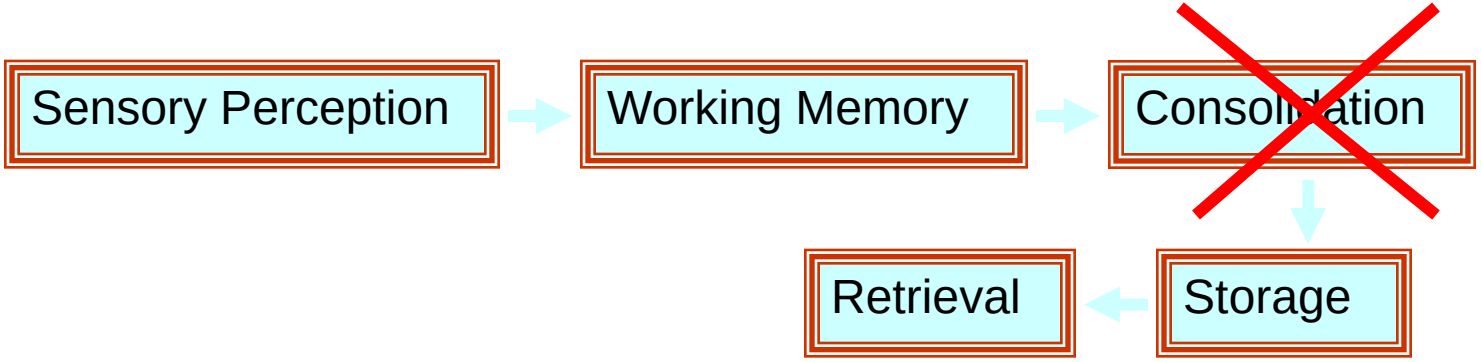
4. Explicit memories cannot be stored

Patient H.M. (conclusions)

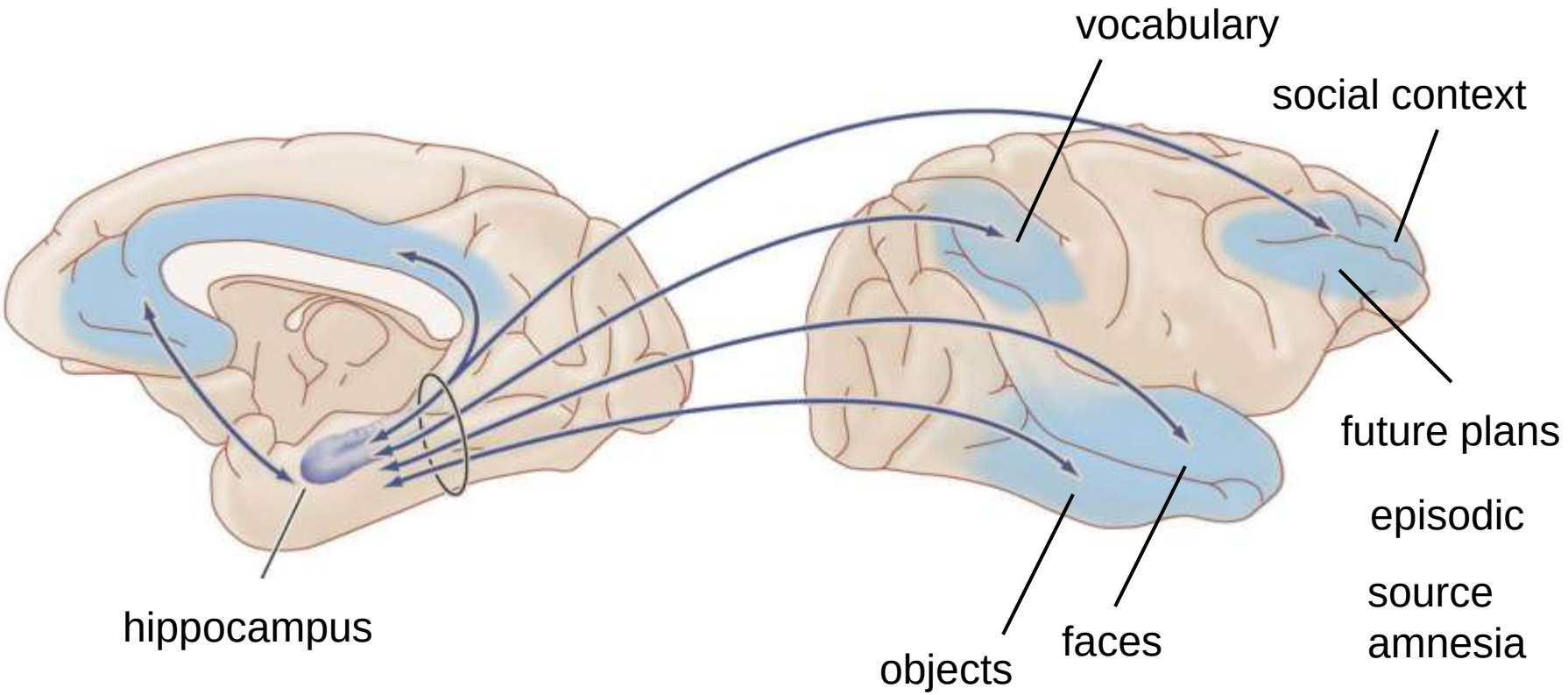
Based on the patterns of Henry's memory loss, researchers formed the following hypotheses about memory formation:

1) Short-term memories are biologically different from long-term memories because they do not require the hippocampus for formation.

2) Long-term memories are stored throughout the brain, but the hippocampus is necessary for the information to reach long-term storage. Once the memory is permanently stored, however, the hippocampus is no longer required. Said another way: the hippocampus is important for long-term memory formation, but not for memory maintenance or retrieval.

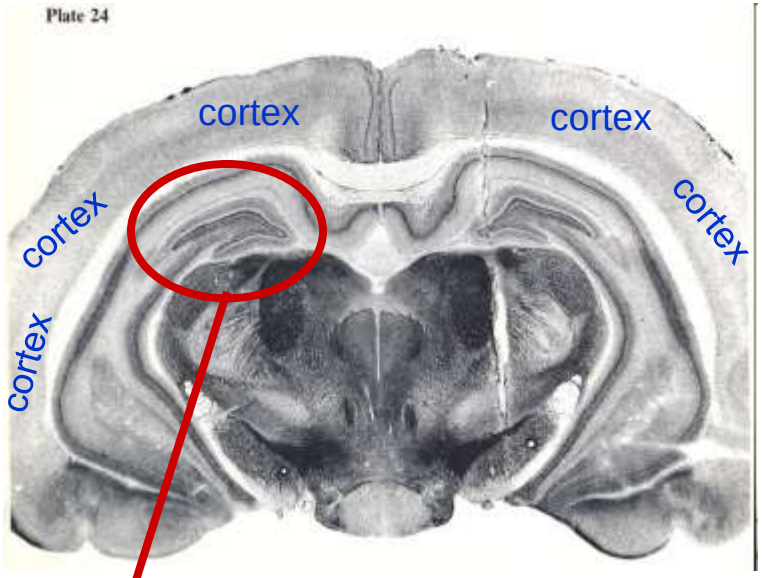


Anatomical Bases of The Explicit Long-Term Memory

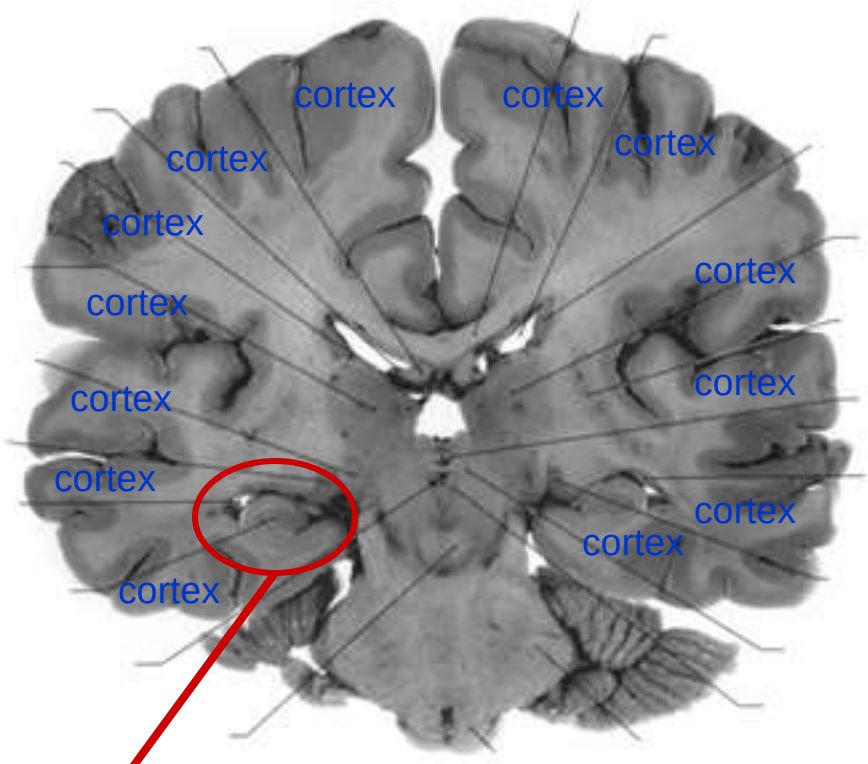


Explicit Memory - Factual knowledge of people, places, and things.

HIPPOCAMPUS – VS. HIPPOCAMPUS

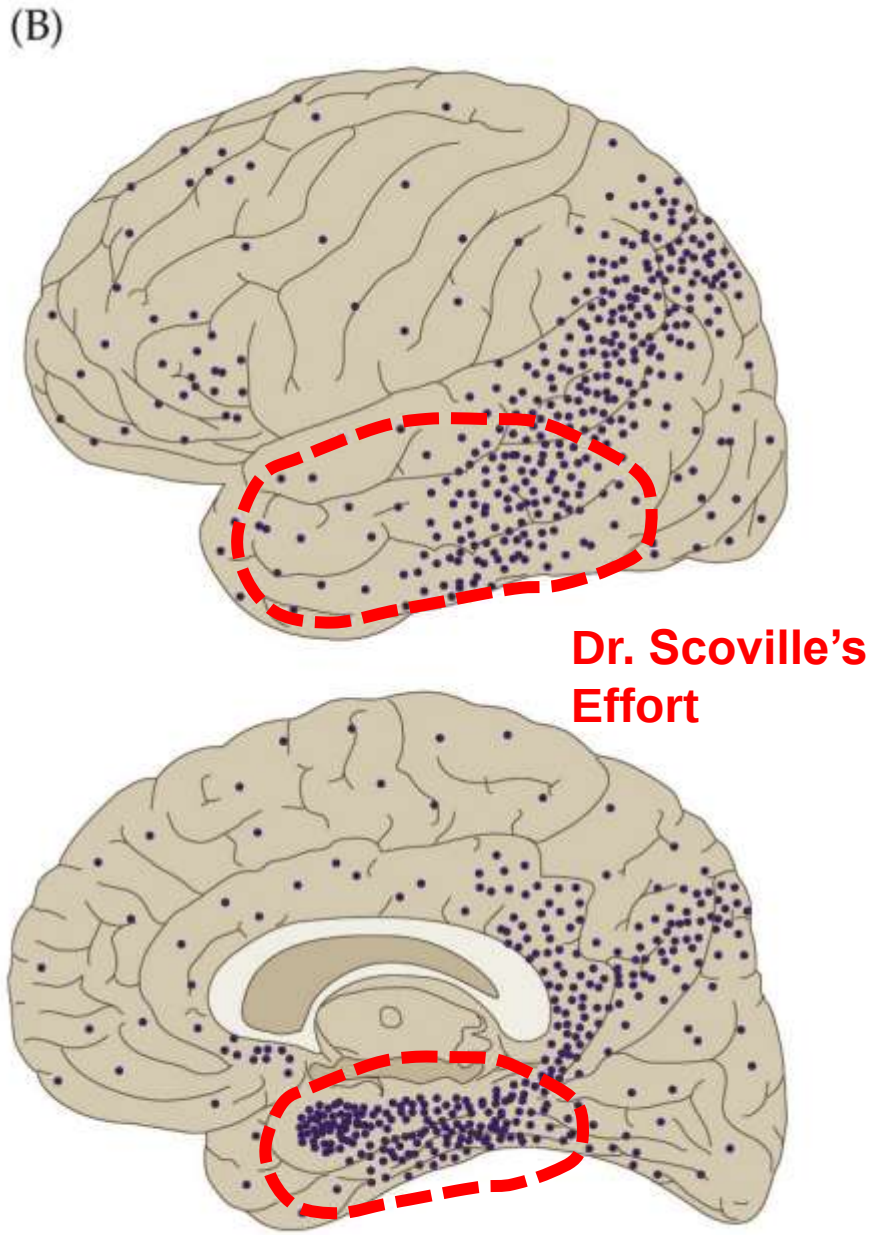


hippocampus **RAT**



hippocampus **HUMAN**

Box 31D Alzheimer's Disease – Patient HM

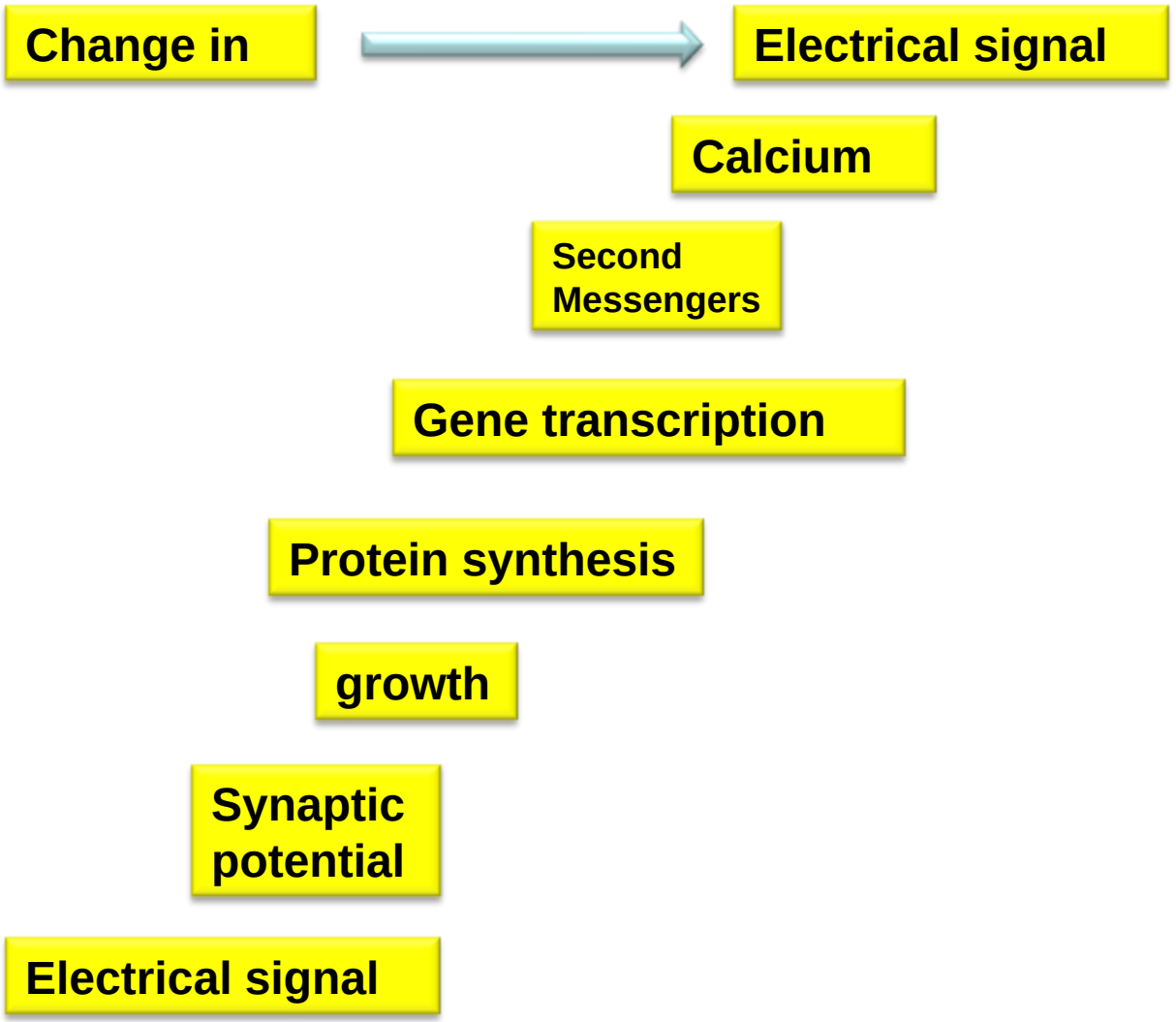


This concludes the material presented in the textbook.

In the reminder of the session we will learn about:

- 1. Cellular bases of learning.
- 2. Dopamine role in learning and memory.

Cellular / Molecular Bases of Learning

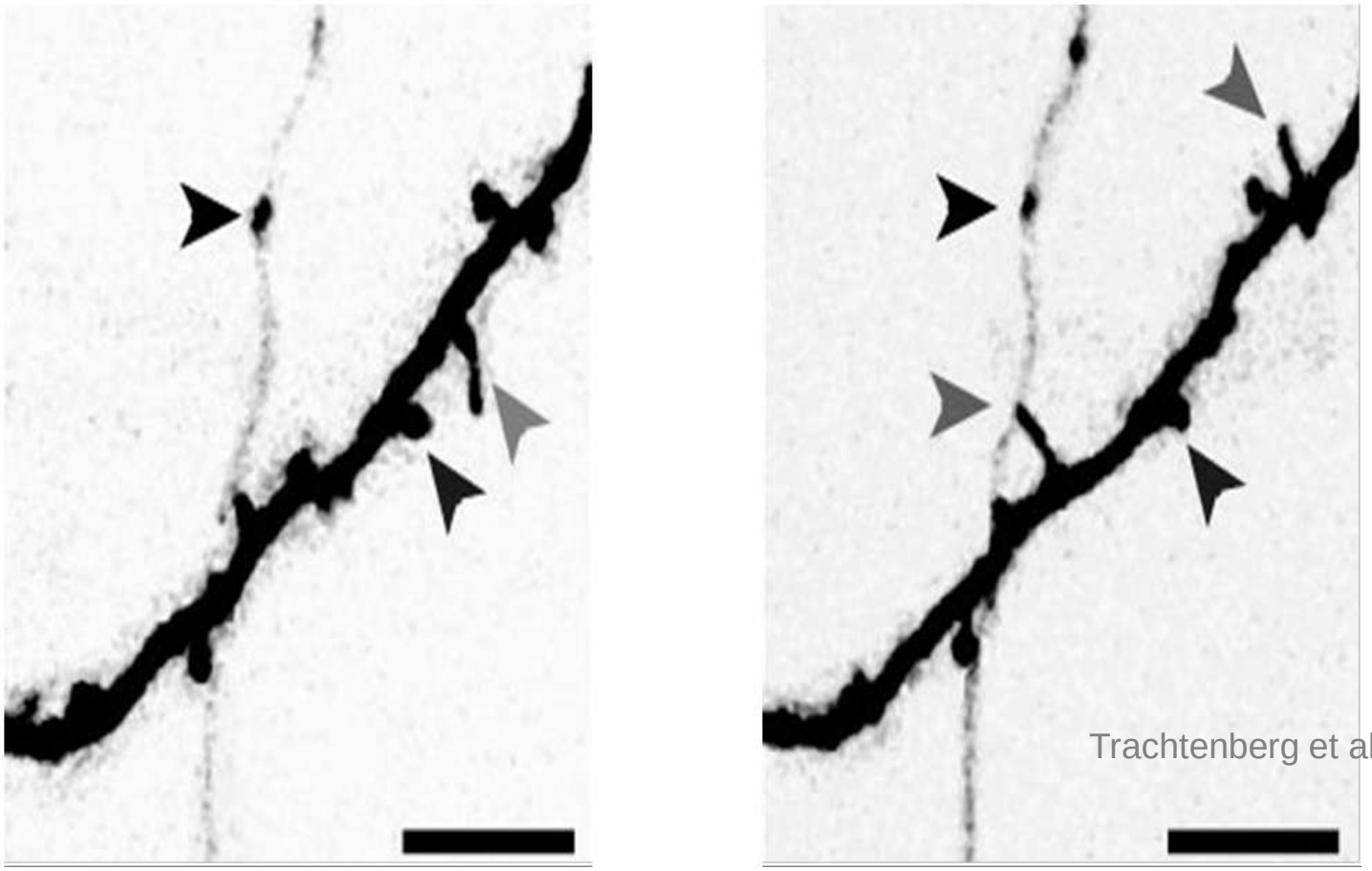


Cellular and Molecular Bases of Learning

I. Changing the wiring between neurons (formation of new synapses).

II. Changing the strength of existing synapses (transient or long-lasting modification of neurotransmission)

Changing the wiring between neurons

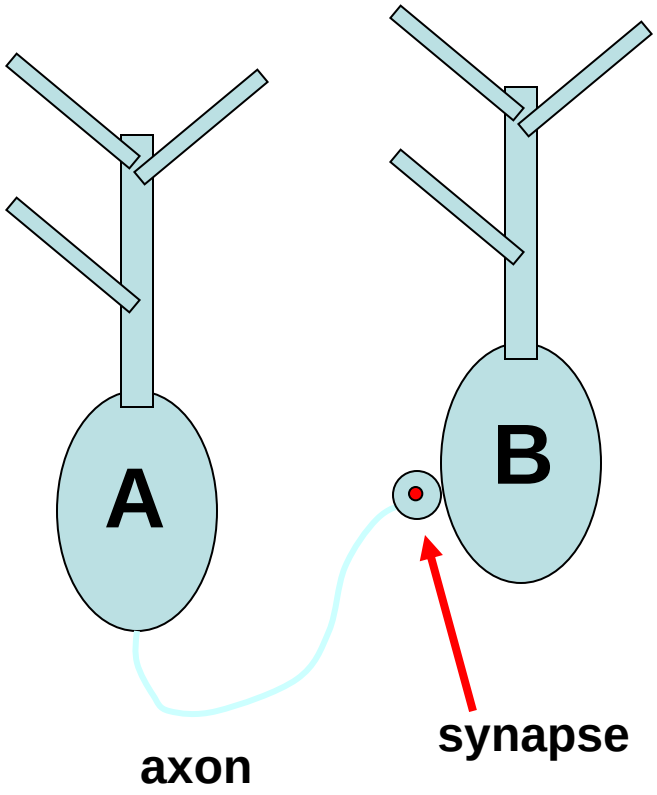


Trachtenberg et al., (2002)

Current thinking about long-term memory in neocortex is focused on changes in the strengths of connections between neurons. But ongoing structural plasticity in the adult brain, including synapse formation/elimination and remodeling of axons and dendrites, suggests that memory could also depend on learning-induced changes in the cortical 'wiring diagram'. Given that the cortex is sparsely connected, wiring plasticity could provide a substantial boost in storage capacity, although at a cost of more elaborate biological machinery and slower learning.

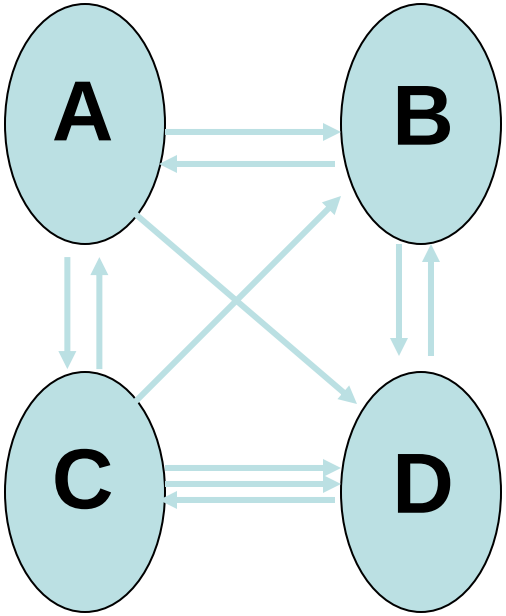
Hebb's Postulate

When an axon of cell **A**
is near enough to excite cell **B,**
or repeatedly or consistently
takes part in firing it,
some growth process or metabolic
change take place
in one or both cells
such that **A**'s efficiency
is increased.



Hebb's Postulate

What Fires together, Wires together.



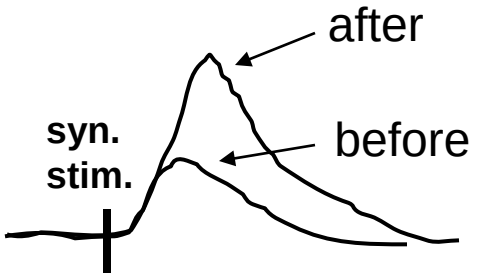
Abundance of synapses

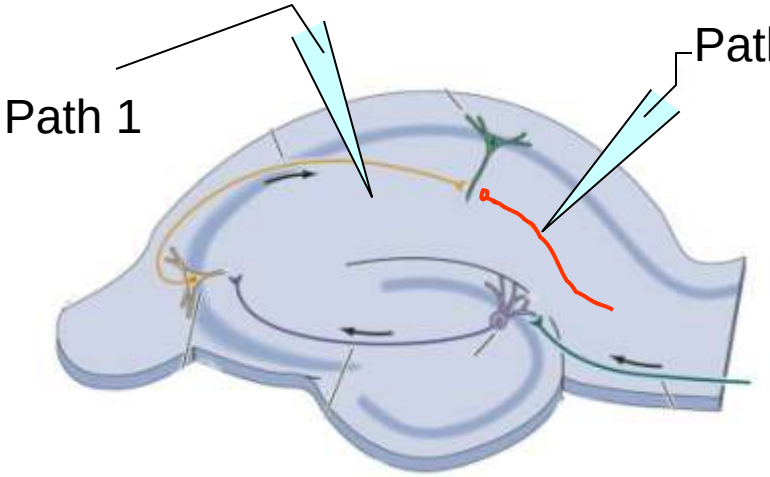
Example: Pruning of synaptic contacts in brain development

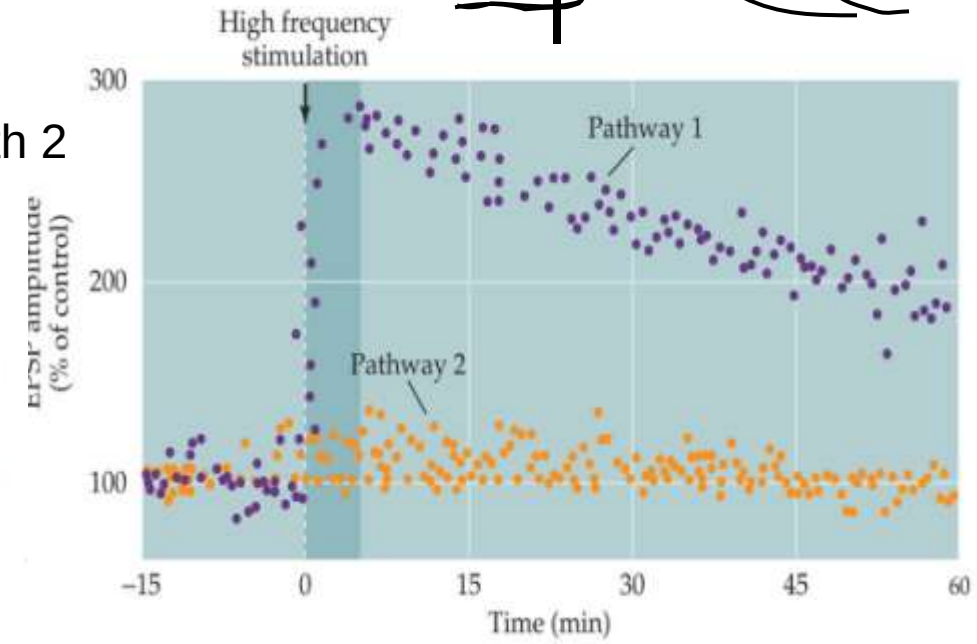
Changing

the strength of the synapse

Long-term Synaptic Potentiation



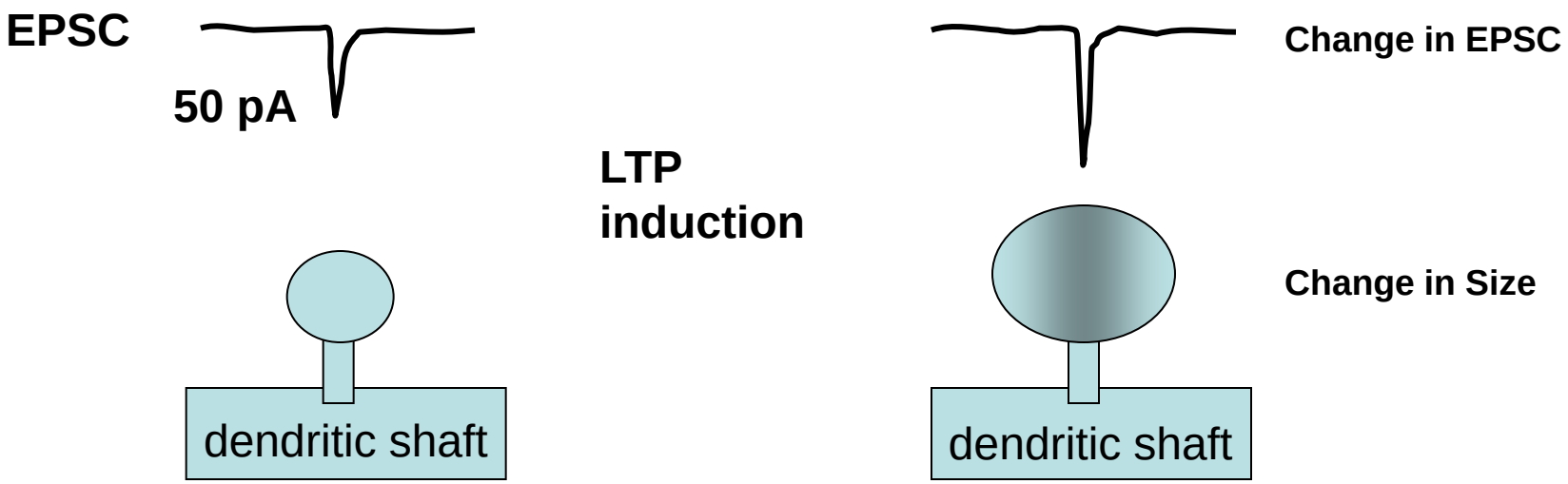




traditional mechanism for adult plasticity

Spontaneous and Evoked Synaptic Currents

It has been reported that the size of **mEPSCs** recorded at the soma after glutamate activation of single spines is positively correlated with the number of dendritic spines, or simply the size of the spine head, that is, large spines produce large synaptic responses.



Excitatory Post-Synaptic Current (EPSC)

Changing

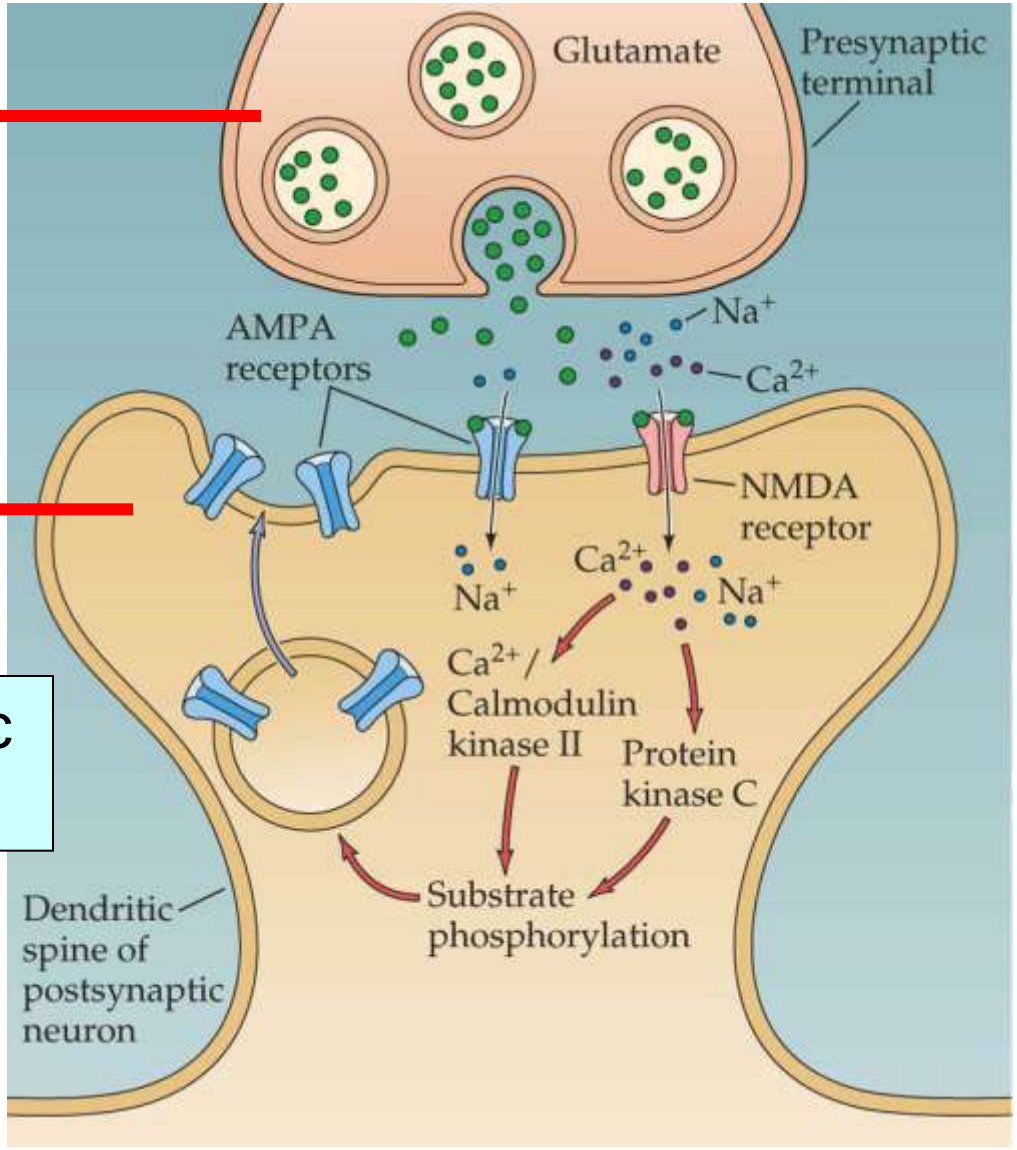
the strength of the synapse

traditional mechanism for adult plasticity

PRESYNAPTIC

POSTSYNAPTIC

homosynaptic mechanism



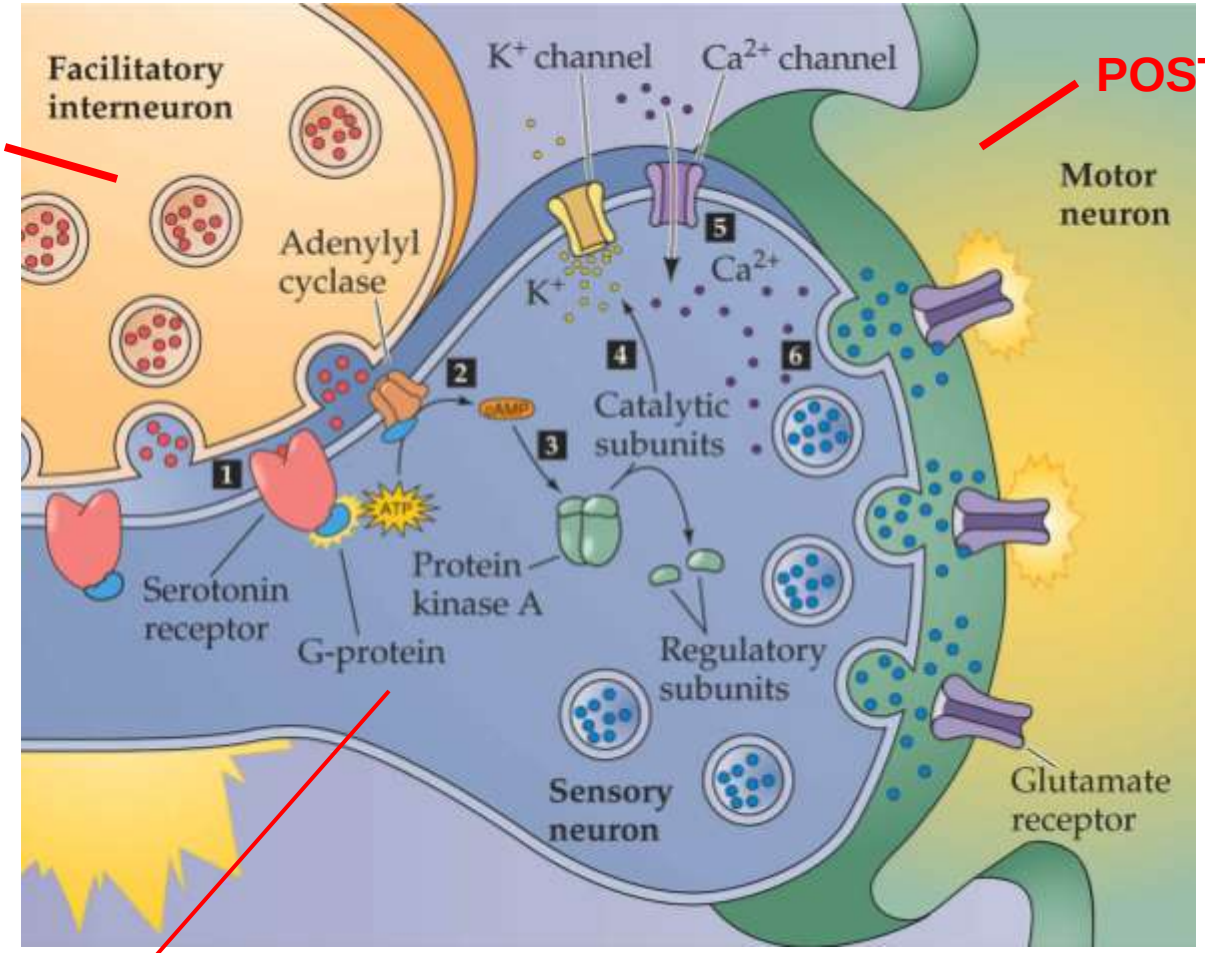
Changing

the strength of the synapse

traditional mechanism for adult plasticity

MODULATORY NEURON

Third Neuron
Hetero-synaptic Neuron



POSTSYNAPTIC

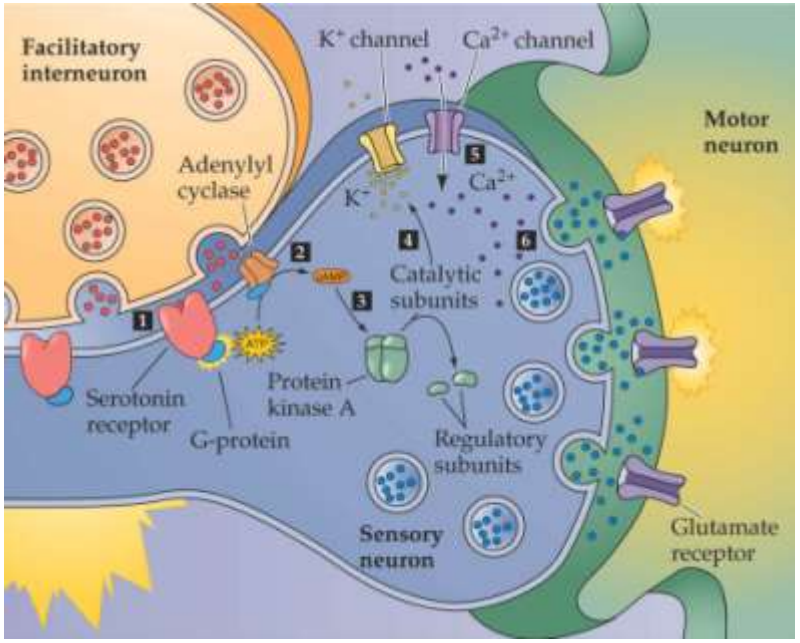
PRESYNAPTIC

heterosynaptic mechanism

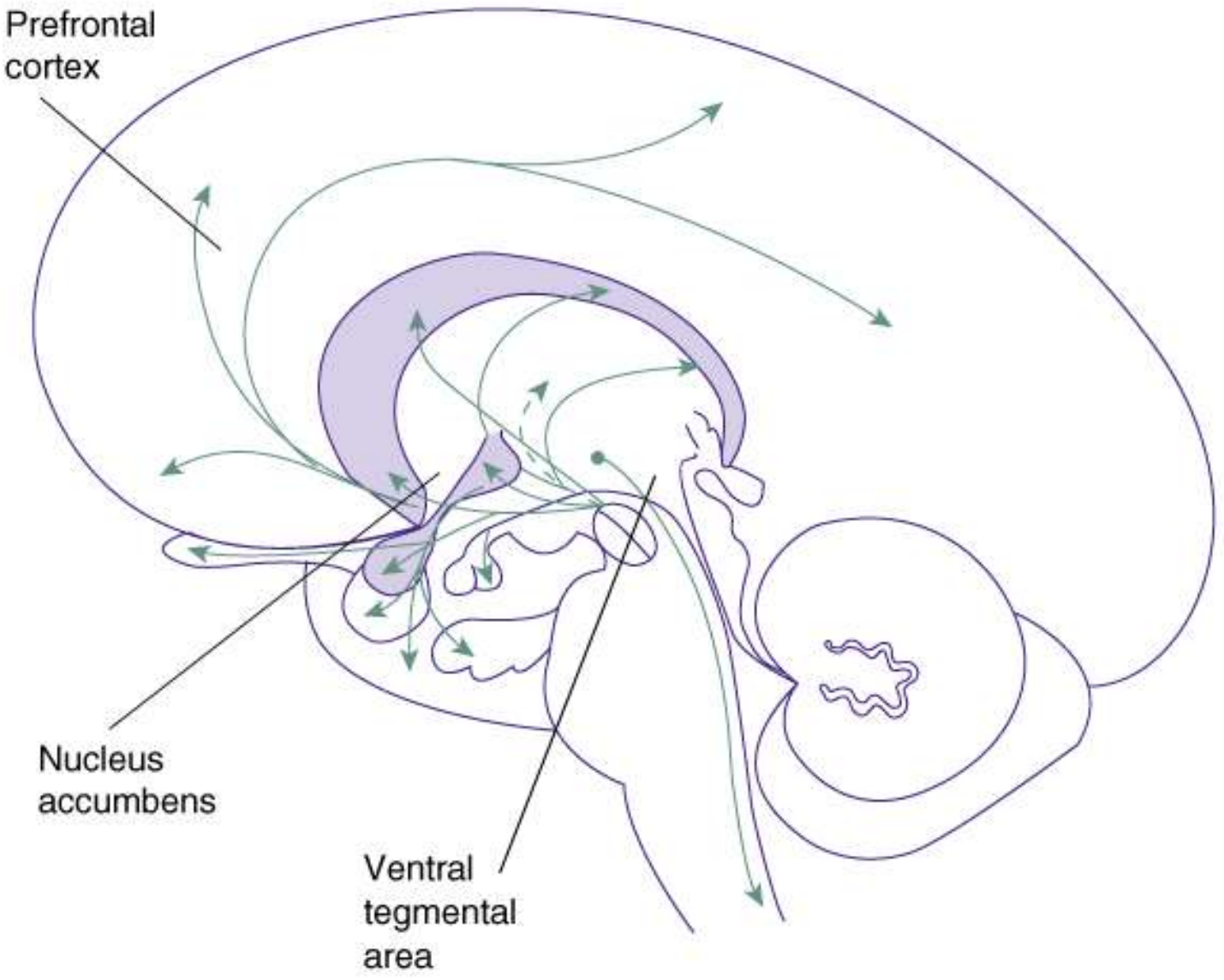
Heterosynaptic potentiation

Neuromodulators such as **serotonin** and **dopamine** might be integral parts of memory formation circuits

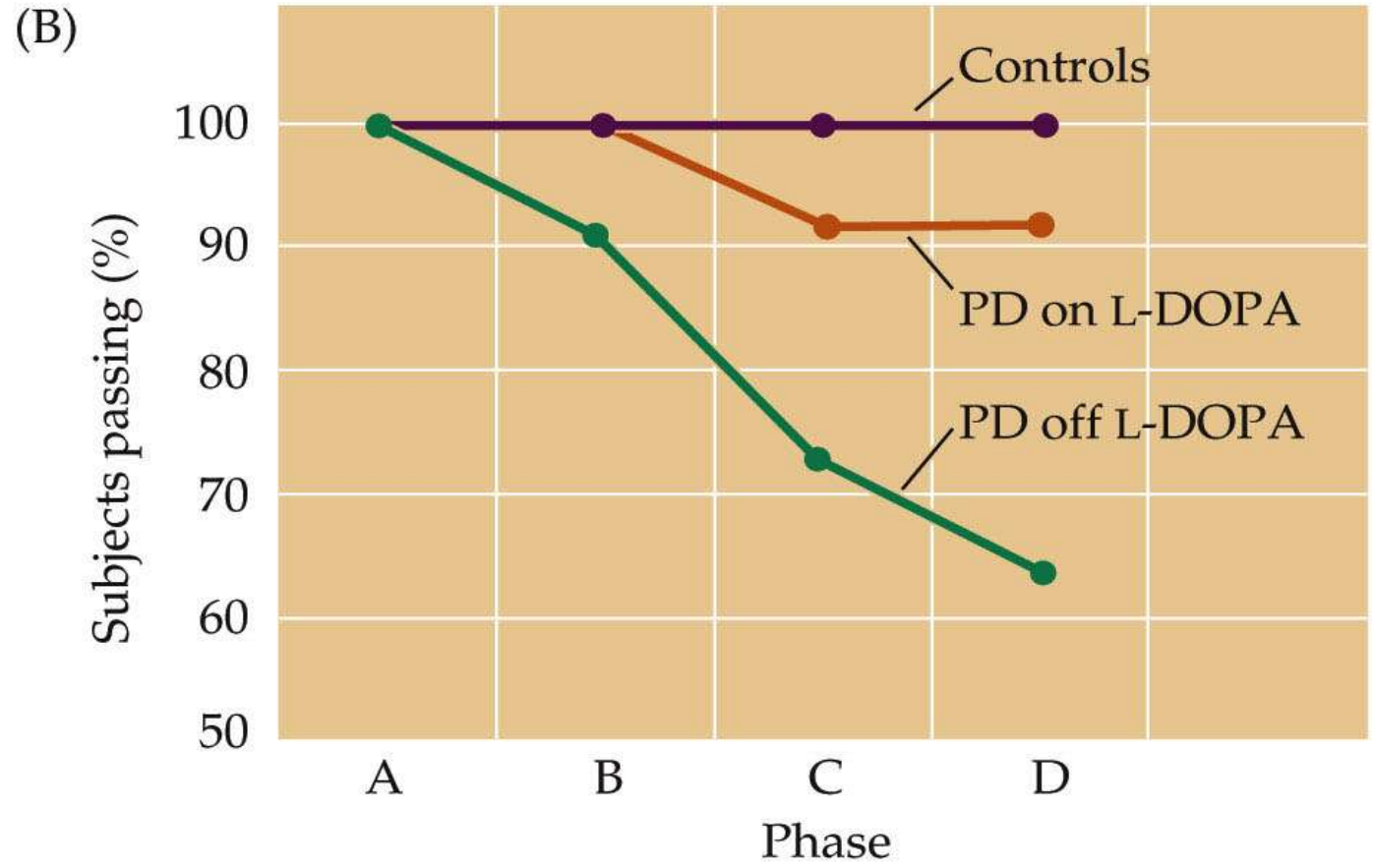
Example 1.



Dopaminergic Neurons Live in VTA and Project to PFC.



Example 2.



***NEUROSCIENCE, Fourth Edition,* Figure 31.13**

Example 3.

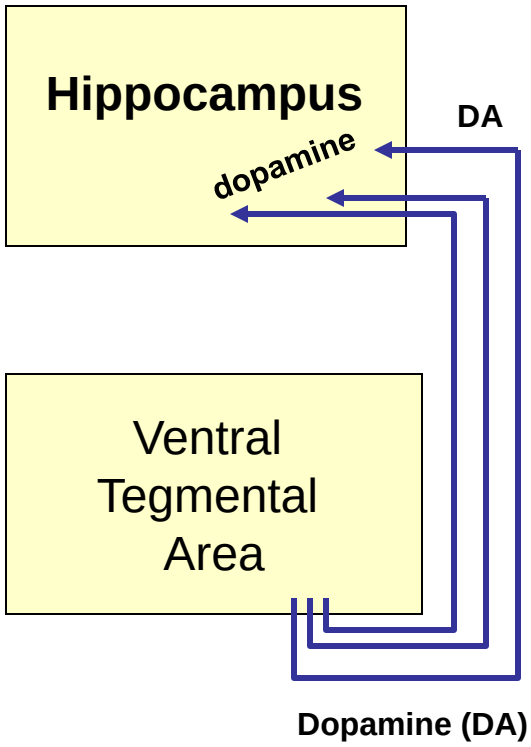
The Role of Dopamine in Learning and Memory

based on the Review article by

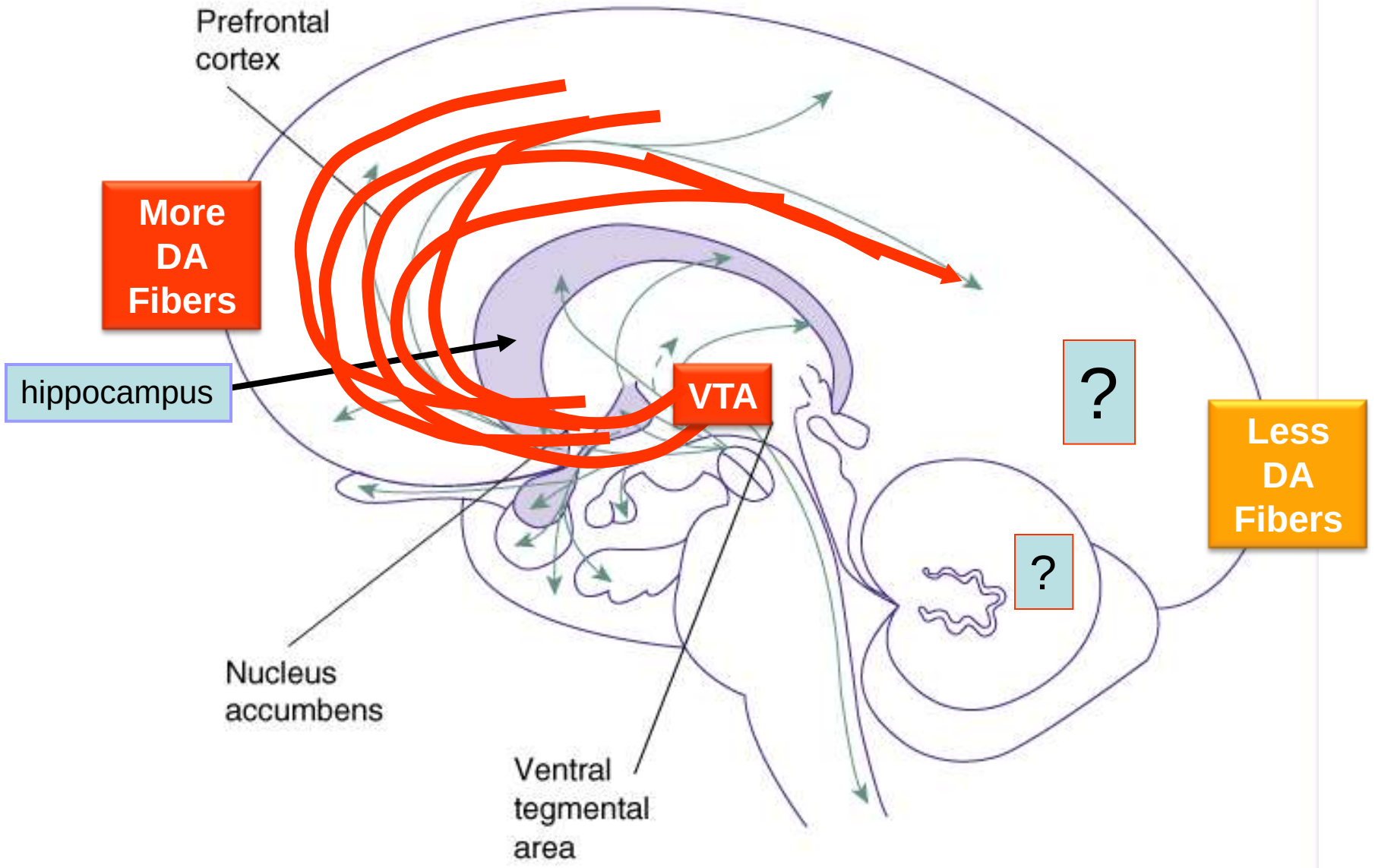
John Lisman and Anthony Grace (2005) *Neuron*

There has been considerable investigation of the modulation produced by noradrenaline and acetylcholine, but the role of dopamine (DA) has been less extensively studied, because of the early view that the hippocampus did not receive a significant dopaminergic innervation.

It is now clear that the hippocampus does receive such innervation from Ventral Tegmental Area (VTA).



Dopaminergic Neurons in VTA Project to PFC and hippocampus.



The computation of novelty is the comparison of incoming information with stored memories. If incoming information is different from stored memories, then it is considered a novelty.

The hippocampus is a temporal lobe structure that is vital for the encoding and recall of episodic memory.

Hippocampus

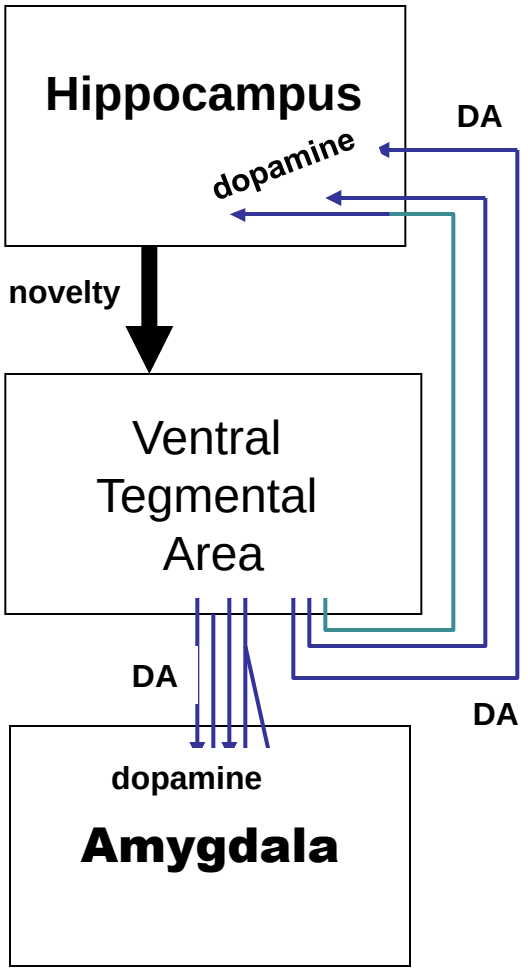
Several lines of experimental evidence indicate that the computation of novelty is taking place in the hippocampus. **(1)** Single-unit recordings and **(2)** imaging studies using PET and fMRI as well as **(3)** c-Fos expression all indicate that presentation of a novel stimulus produces a robust increase in hippocampal activity

(4) interfering with hippocampal function inhibits the orienting of rats to novel stimulus configurations.

(5) humans with hippocampal lesions are less responsive to novel stimuli.

LATENCY ARGUMENT

Measurements of hippocampal evoked responses in CA1 indicate that a form of novelty (expected versus unexpected conditioned stimuli) can be detected in less than 100 ms. The rapidity of this detection suggests that the hippocampus could be part of the circuit that initiates the short-latency novelty-dependent firing of the VTA and is not simply responding to it.

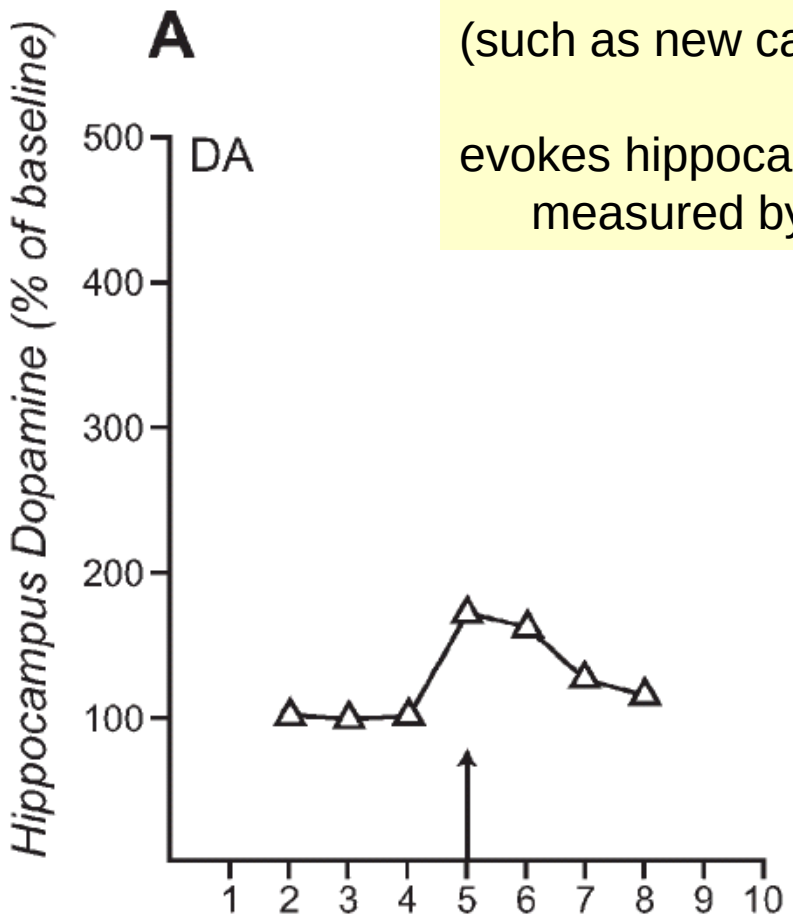


The hippocampus and VTA form a functional loop designed to detect novelty and to use this novelty signal to control the entry of behaviorally significant information into the hippocampal store of long-term memory.

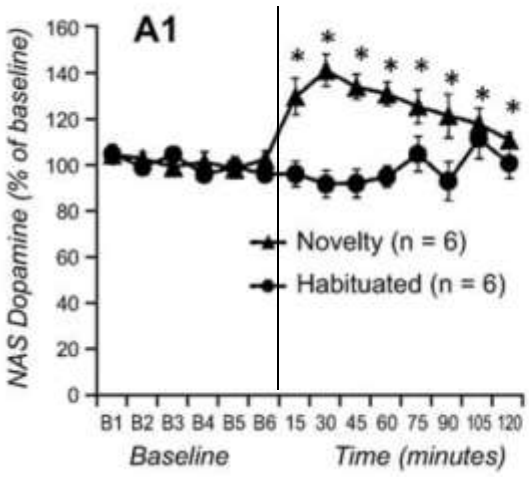
Exposure of the rat to a novel environment

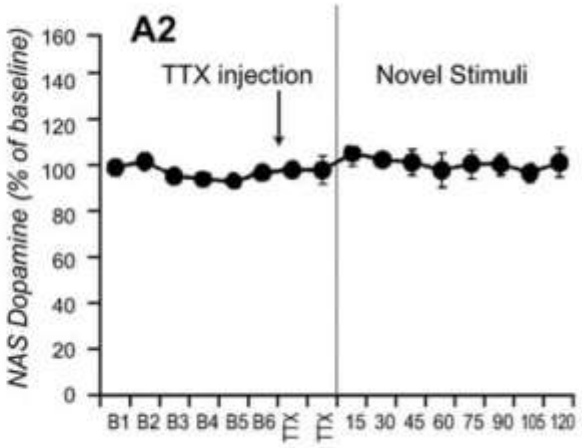
(such as new cage)

evokes hippocampal DA release as measured by microdialysis and HPLC.



Ihalainen et al., 1999.



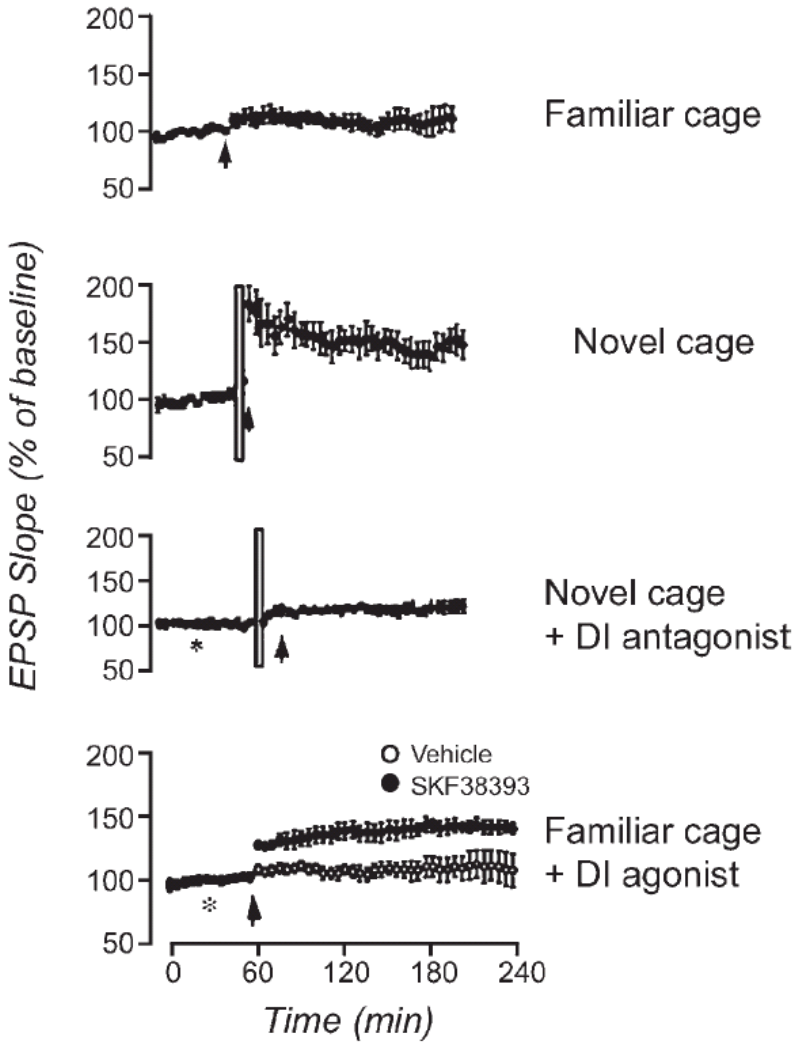


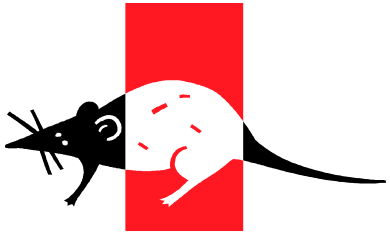
Legault and Wise, 2001

(**A1**) Putting a rat in a novel cage, but not a familiar cage evokes DA release in the **accumbens**. (**A2**) The novelty-dependent release of DA is blocked by TTX injection into the subiculum (**hippocampus**).

Scientists were able to generate a behaviorally significant novelty event by allowing rats to enter a part of their cage from which they were previously restricted. This event led to substantial activation of the VTA, as evidenced by the DA released in a VTA target, the nucleus accumbens.

To test whether this release was dependent on the hippocampus, TTX was injected into the ventral subiculum, an output structure of the hippocampus that receives direct excitatory input from CA1. TTX caused a nearly complete block of the novelty-induced DA release





Li et al., 2003.

(Top) A weak tetanus to the Schaffer collateral input to CA1 pyramidal cells fails to evoke LTP when the animal is placed in a familiar cage.

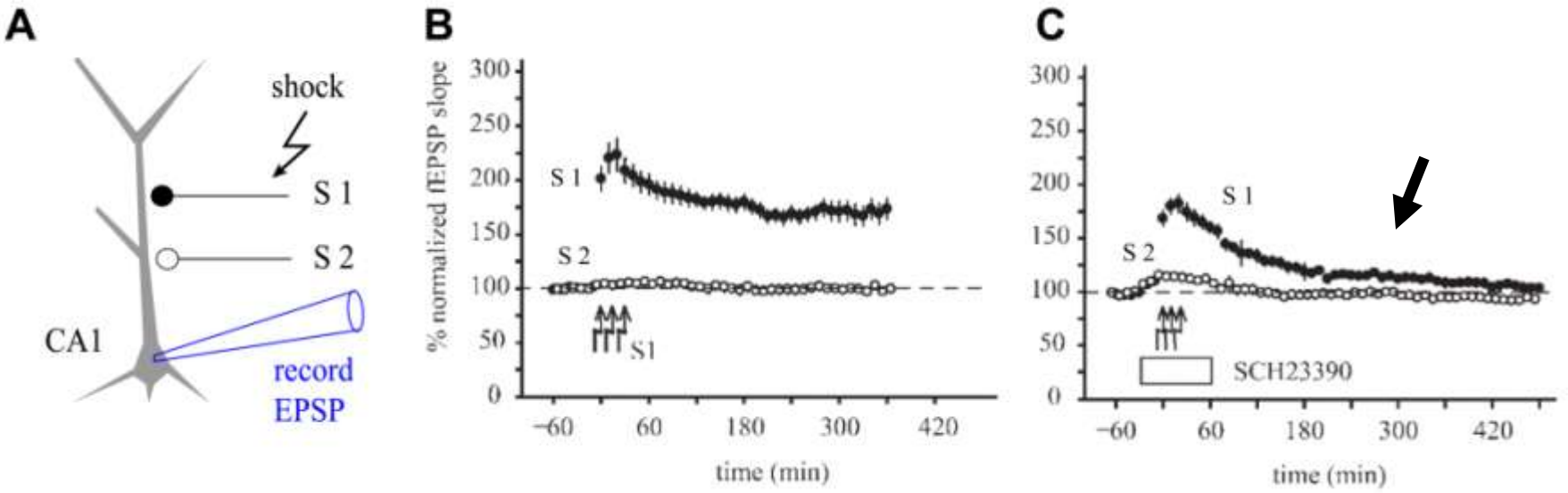
(Second down). After the animal is placed is a novel cage, the same stimulus evokes LTP.

(Third down) This LTP can be blocked by a systemic D1 antagonist.

(Bottom) Conversely, systemic application of a D1 agonist allows the stimulus to evoke LTP even in the familiar cage.

Li, S., Cullen, W.K., Anwyl, R., and Rowan, M.J. (2003). Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. Nat. Neurosci. *6*, 526–531.

Dopamine release in the hippocampus is important for maintenance of the long-term synaptic plasticity (late phase of LTP).



(A) Experimental design – brain slice – whole-cell patch clamp recording – extracellular stimulation electrodes S1 and S2. (B) LTP (closed circles) in the CA1 region of a slice preparation is induced by three tetani (100 Hz); no LTP occurred in the control pathway (open circles). (C) The same stimulation given in the presence of the selective D1 dopamine receptor antagonist SCH23390 produced only early LTP. Note that late phase of LTP is missing (arrow).

Morris et al., 2003.

SUMMARY Dopamine Role in LTP Formation

The MAIN finding of *Li et al., 2003* is that:

novelty-mediated dopamine release into the hippocampus facilitates the formation of LTP

in the striatum radiatum of CA1 pyramidal neurons
(CA3-to-CA1 pathway, also known as Schaeffer collaterals).