Synaptic Plasticity

synaptic connectivity constantly changes in response to activity and other factors

During development: provides the basic "wiring" of the brain's circuits

Throughout rest of life: basis of "learning"

Synaptic Plasticity

"*plasticity*" - may last from milliseconds to years

short-term plasticity - change in the amount of NT released by the presynaptic neuron in response to an AP ("functional")

facilitation, *augmentation*, and *potentiation* all forms of enhanced NT release

related to altered Ca++ levels in the axon terminal

depression is a decrease in NT release

related to a decrease in the available NT vesicles

Synaptic Plasticity

long-term plasticity (~30 min to lifetime)

Long-term potentiation (LTP) / Long-term depression (LTD)

initially caused by *post-translational modifications* of existing proteins

e.g., *upregulating* glutamate receptors

later sustained by changes in *gene expression* creating new proteins

physical changes, including growth of new synapses etc ("structural")

Learning and memory

Learning: the process of acquiring new information

Memory: the process by which we store and retrieve / recall information

3 main types: sensory / short-term / long-term

3 main processes:

Encoding / Consolidation: information from the environment is *transduced* into neural "codes" within the brain (sensation)

Storage: retaining the information over time

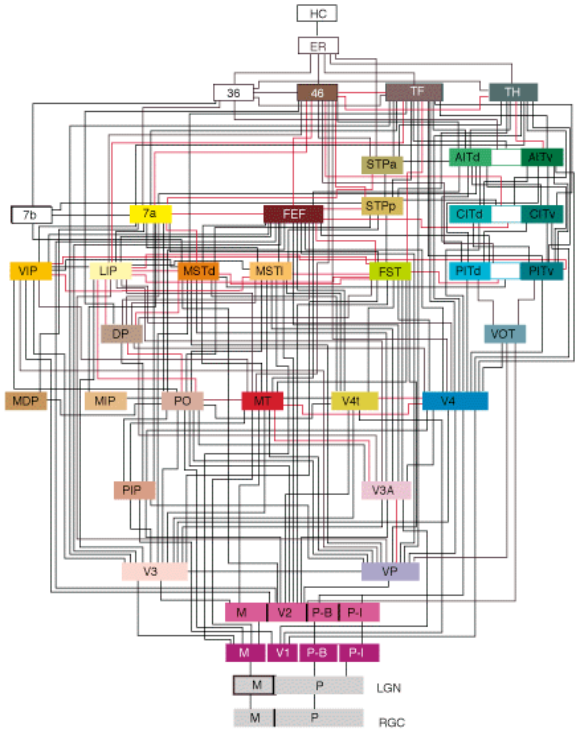
Retrieval: pulling the information out of storage

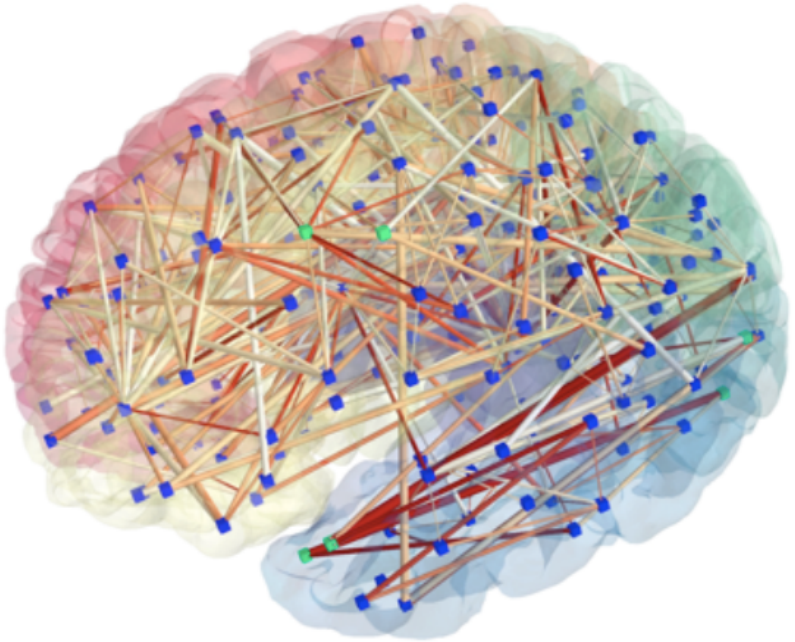
ENCODING / CONSOLIDATION

nervous system is a big mass of “interconnected” biological tissue

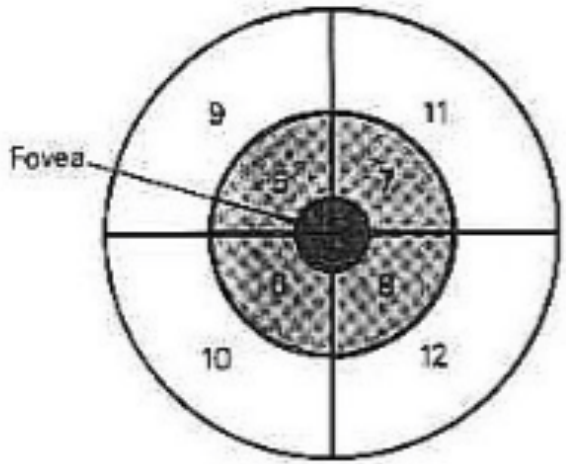
parallel and serial networks within massively parallel networks

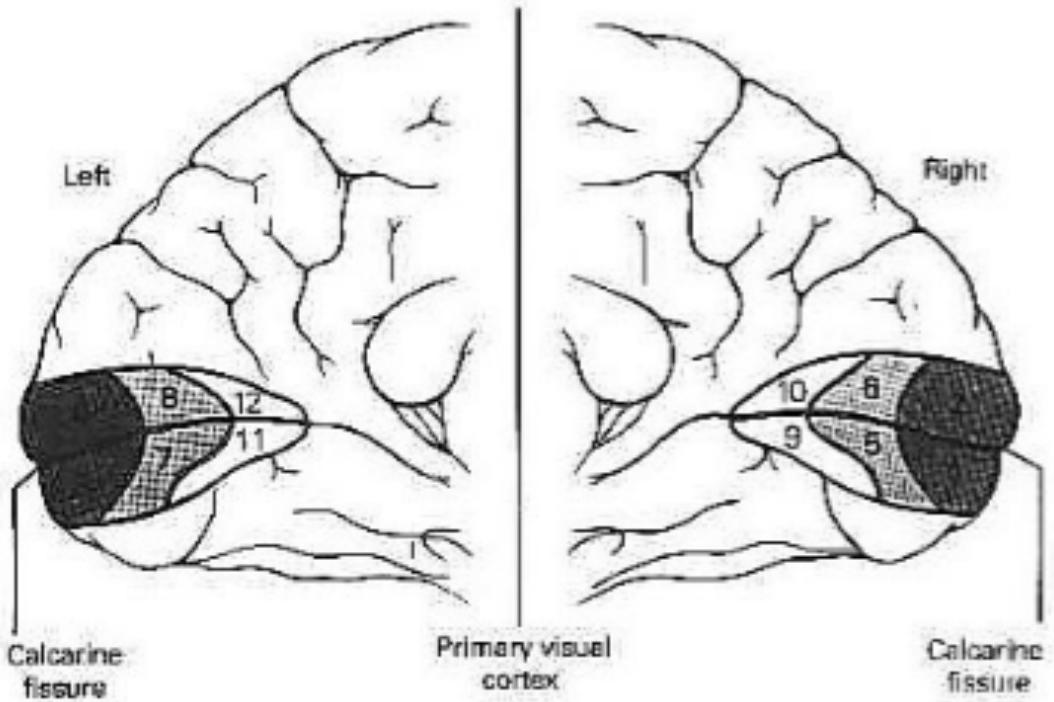
sensations cause changes in spatiotemporal activity patterns of the cortex – we experience this as our “perception” of reality

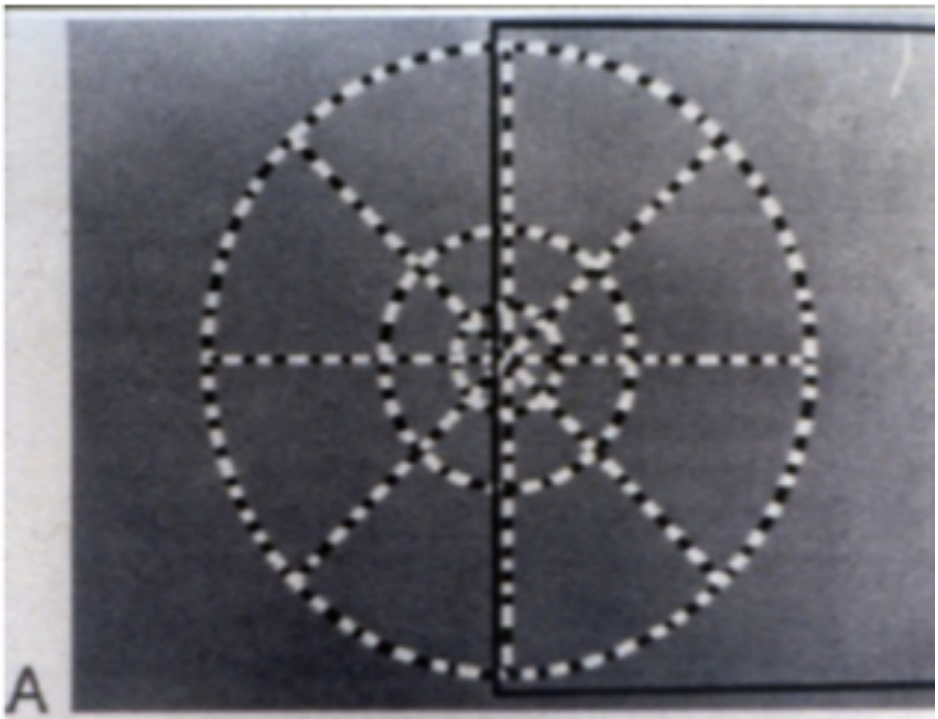




ENCODING / CONSOLIDATION







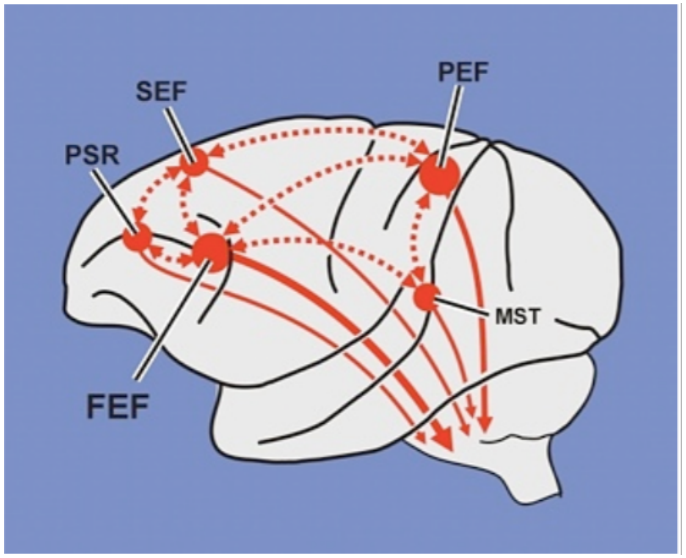
ENCODING / CONSOLIDATION

areas that are active at the same time tend to become more strongly connected (and vice versa)

Donald Hebb - "*fire together / wire together*"

via functional and structural changes

activity in 1 area is more likely to induce activity in connected areas



ENCODING / STORAGE

Consolidation - transduction into neural code (spatiotemporal patterns of cortical activity)

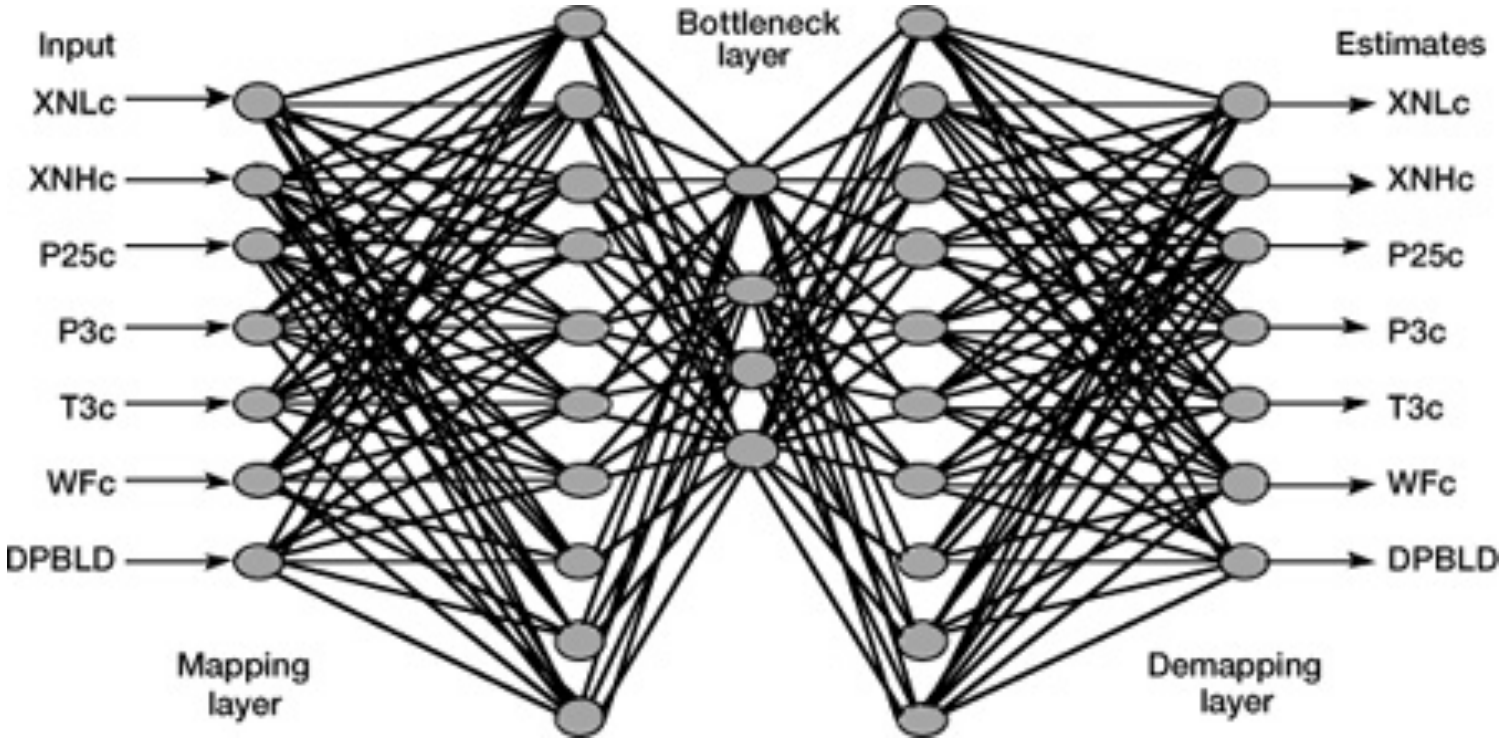
Storage - long-term synaptic changes in cortical connections

the biological basis of *learning* depends upon the ability of neurons to modify their synaptic connections within neural circuits based on experience

Storage

Involves the retention of “information” through networks of associations

- Connections between cortical areas
- Auto-associative neural networks

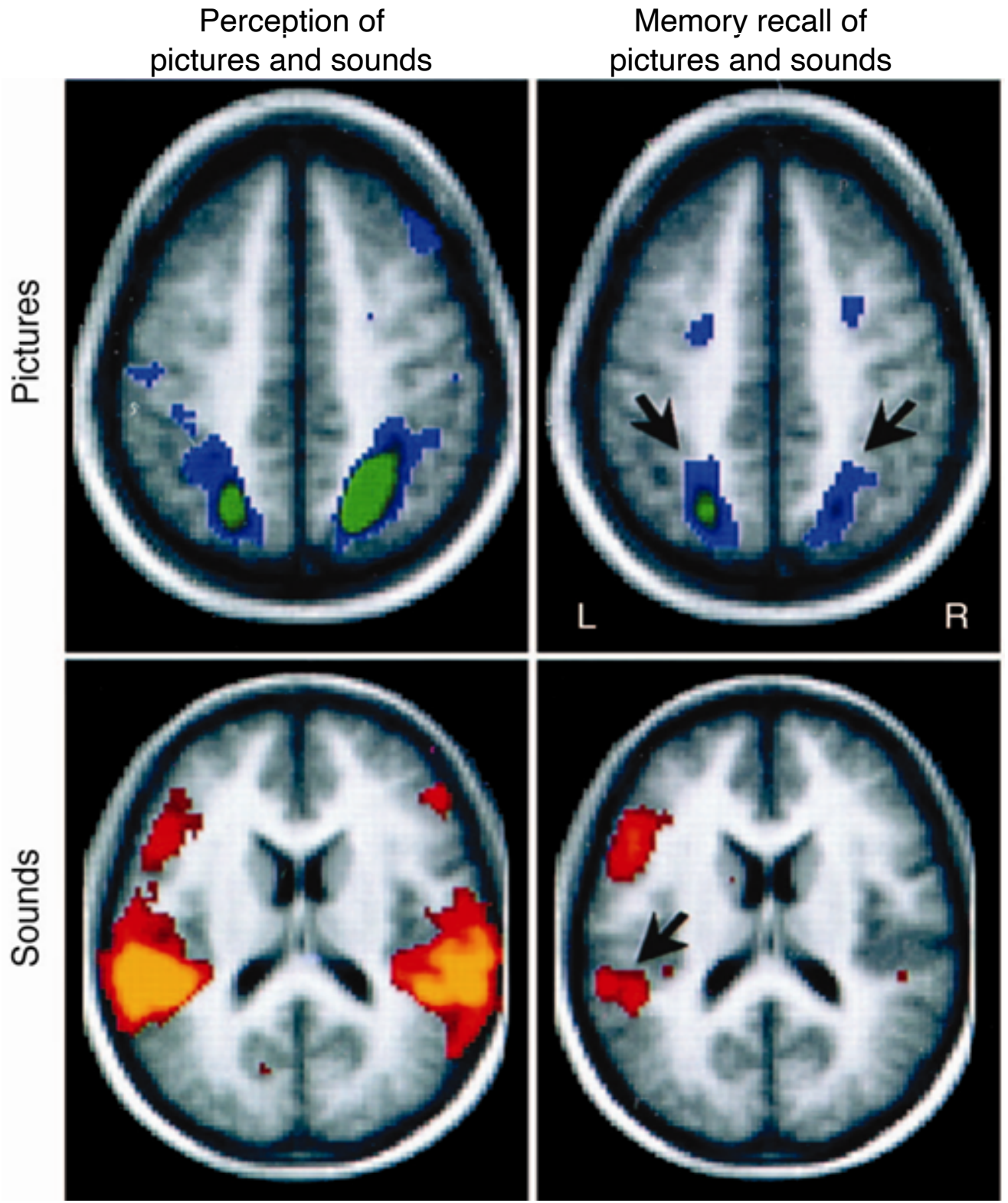


Retrieval

Gaining access to and being able to use information stored in memory.

Reactivating cortical patterns

- Retrieval (memory) happens when we re-experience similar spatiotemporal patterns in cortical activity
  - Retrieval cue: any stimulus that is used to activate retrieval
    - Multiple cues work best
    - State (internal) and context (external) are important cues


Perception of
pictures and sounds
Memory recall of
pictures and sounds
Pictures
Sounds
L
R

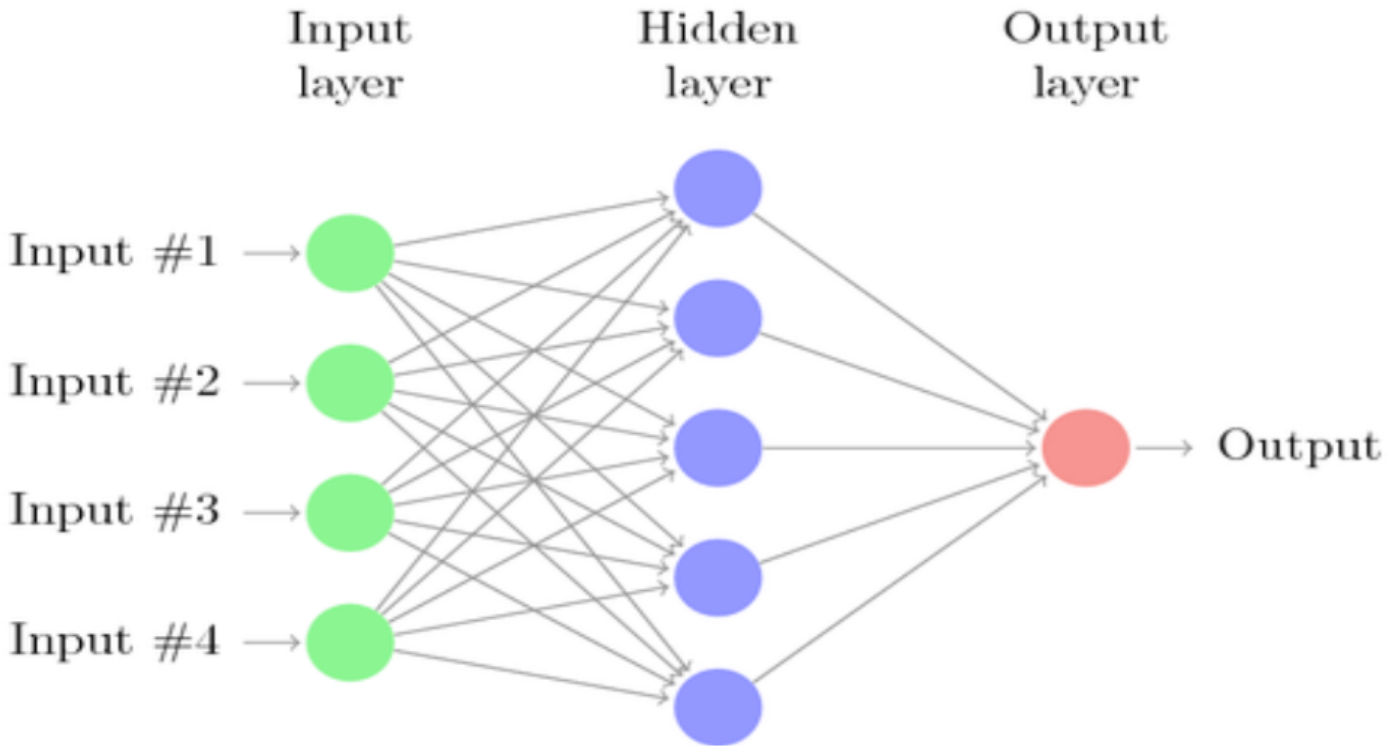
Retrieval

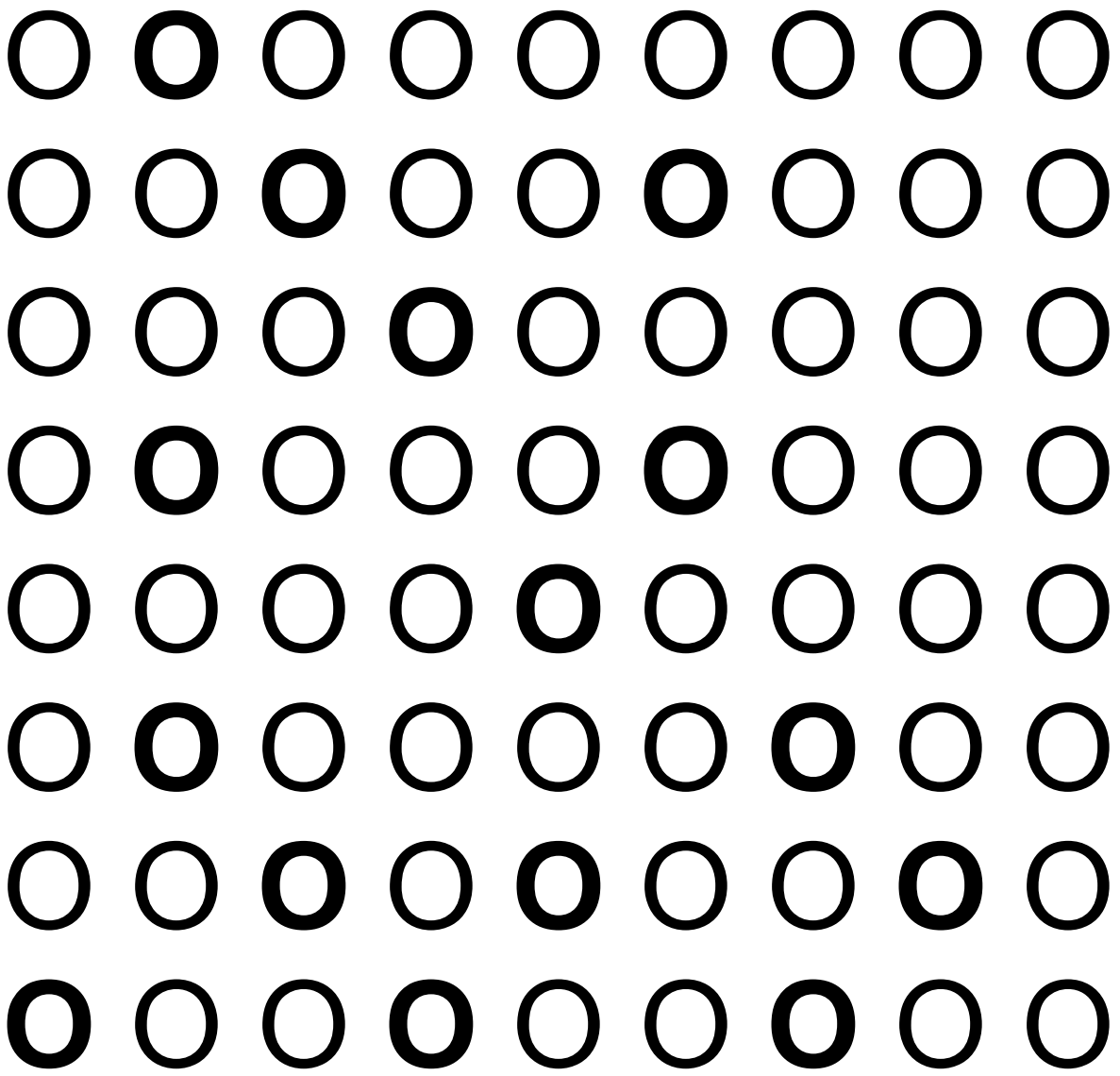
a neural network can process large amounts of information with only a small group of viable neurons

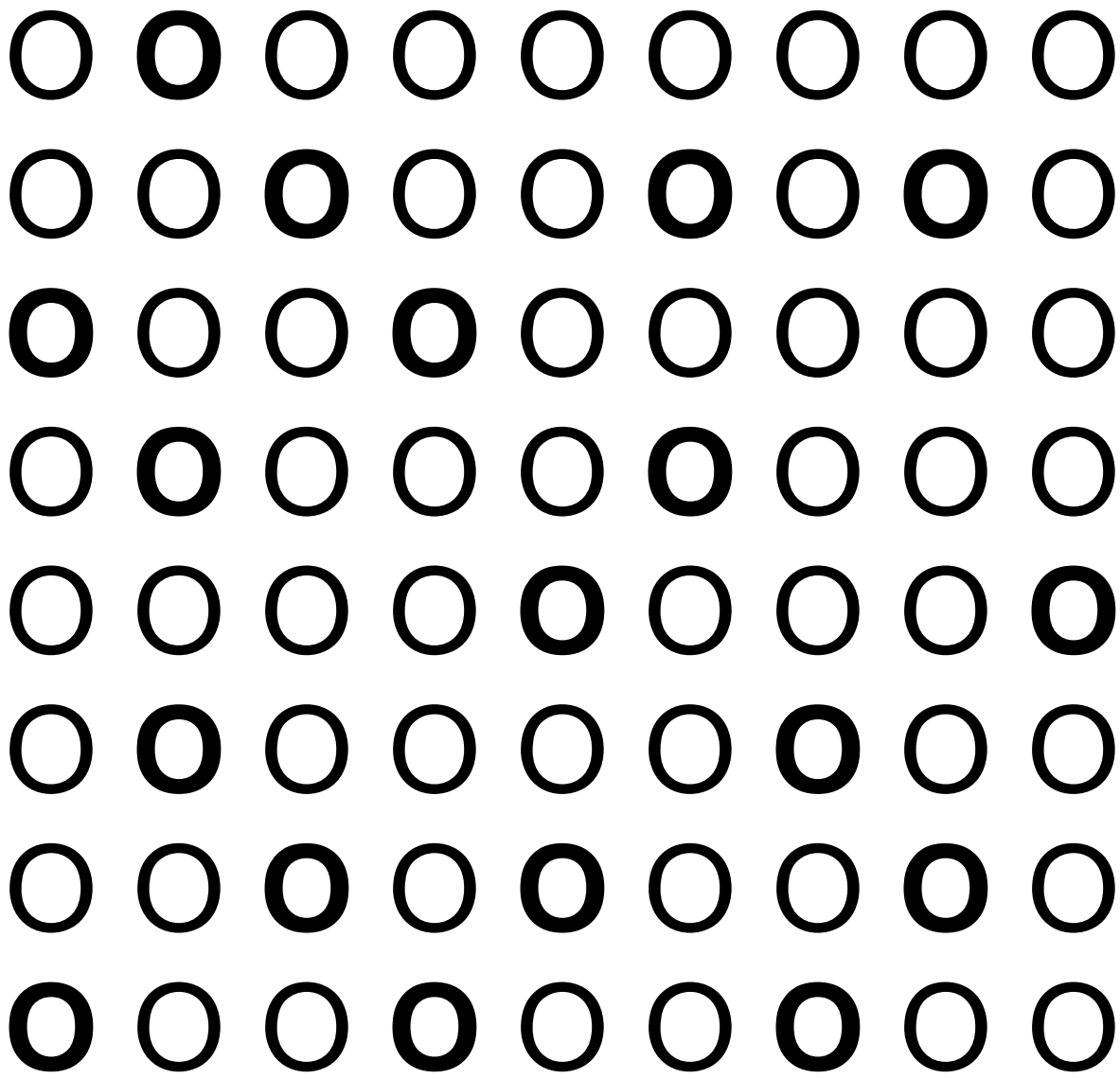
will yield output based on partial input

Many stimuli will induce memory of a person

One stimuli will elicit many memories







- Déjà vu – activating a similar “spatiotemporal” “fuzzy” memory (?)

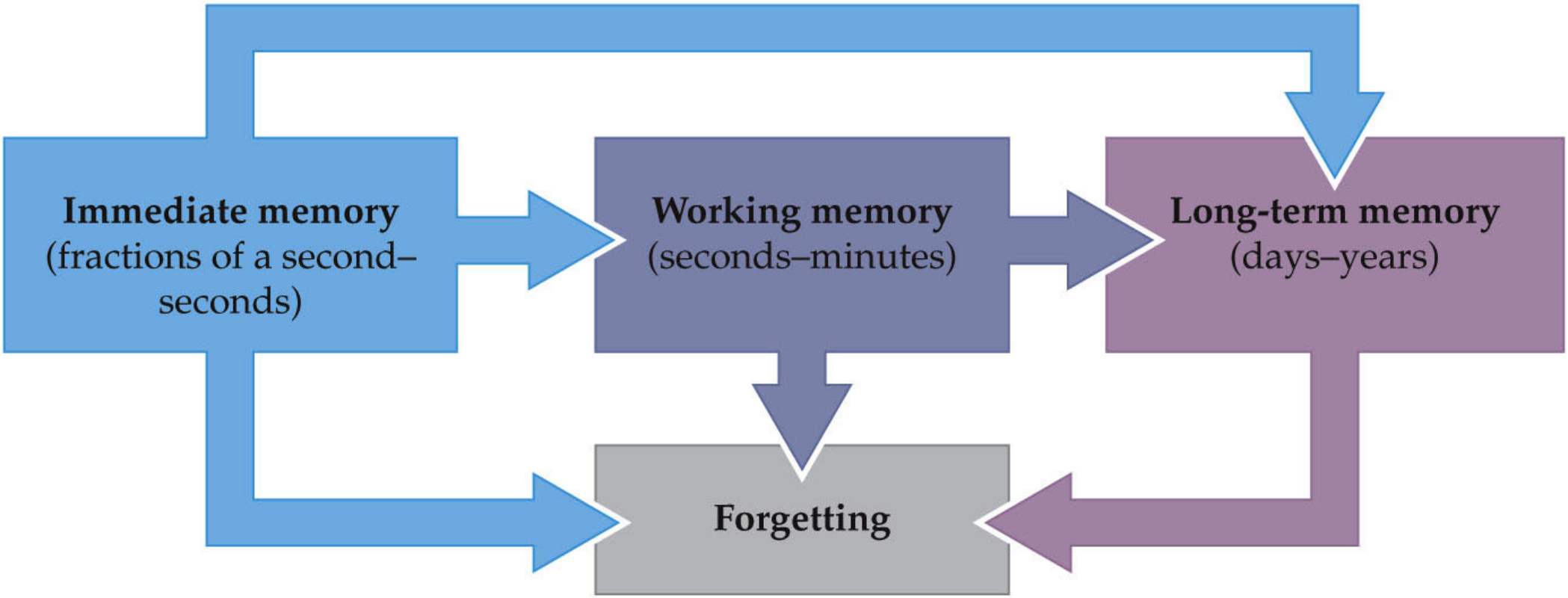
3 main types of memory:

Sensory (immediate) - artifact of sensory processing

Short-term / working memory - functional changes (reverberating circuits, more / less NT)

Long-term - physical changes (more / less terminals and dendrites)

a behavioral continuum, but with distinct physiological processes

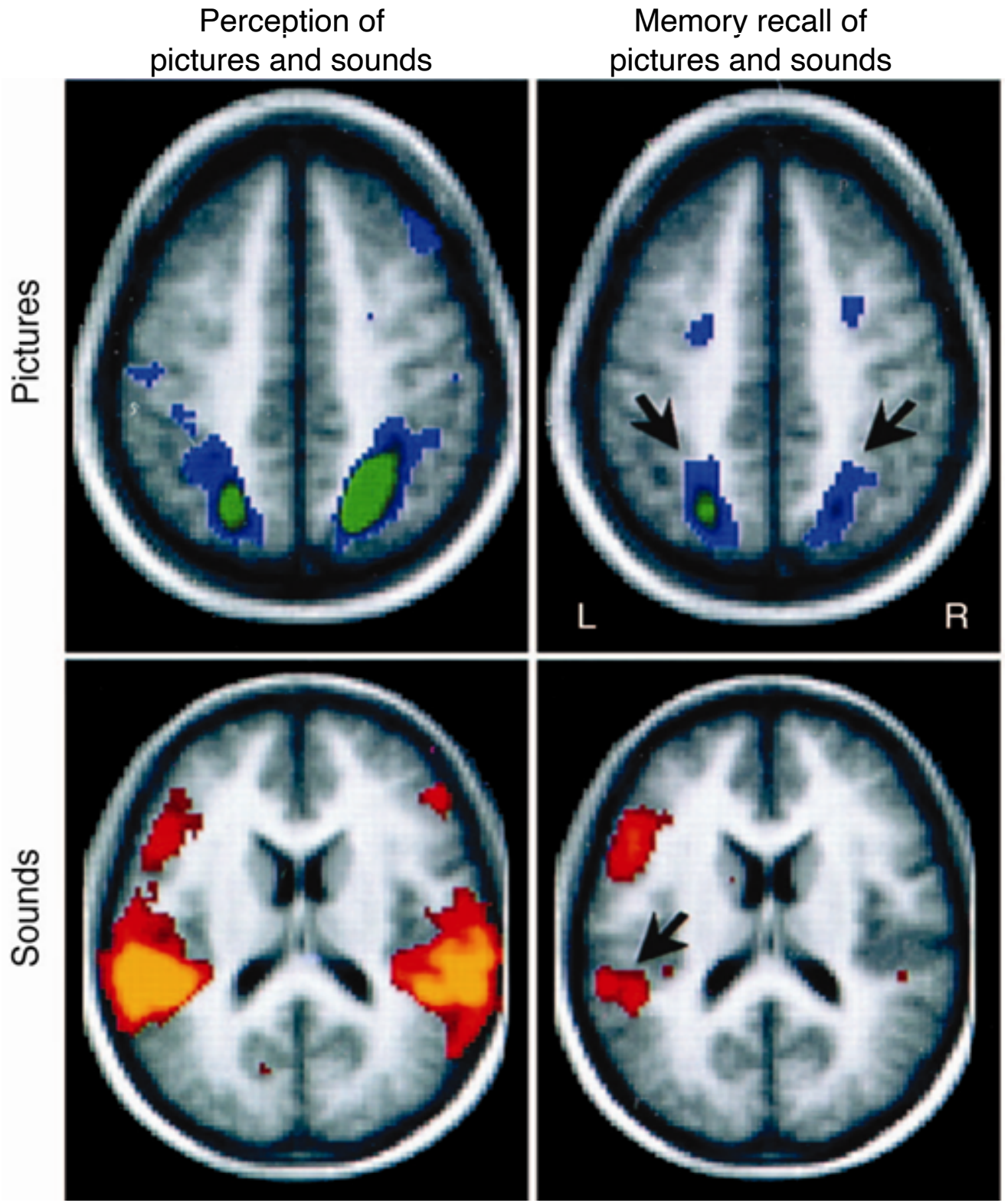

Immediate memory
(fractions of a second–
seconds)
Working memory
(seconds–minutes)
Long-term memory
(days–years)
Forgetting

Sensory (immediate) Memory

Holds incoming sensory information for very brief periods of time (seconds or less)

Artifact of sensory processing and the elicited patterns of cortical activity

- “iconic” = visual sensory register
- “echoic” = auditory sensory register
- etc


Perception of
pictures and sounds
Memory recall of
pictures and sounds
Pictures
Sounds
L
R

Characteristics of STM

Duration = information only remains in STM for a short period of time (seconds to minutes)

Capacity = amount of information that can be held in STM is limited.

Depends on the type of stimulus and the number of meaningful units, called *chunks*

~5-7 chunks of info

Working Memory

Small amounts of information held in memory for short periods of time

until distracted

Visual encoding = an image is formed in the mind

Activity in visual cortex

Phonological encoding = auditory; based on sound

Activity in auditory cortex

etc

higher order cognition - math etc

we can be consciously aware of the information, actively "keeping" it in STM ("working memory")

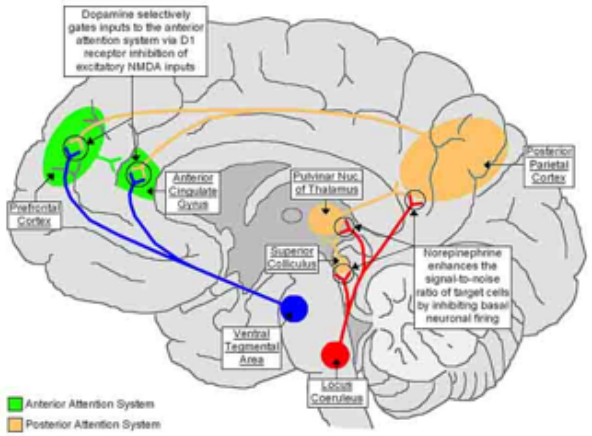
reverberating circuits in PFC

“Working memory” components:

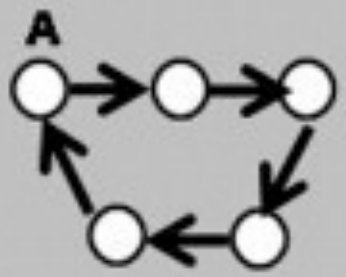
“Central executive”: Prefrontal cortex is directly connected to sensory areas, controlling these processes and directing activity within the brain

Visual-spatial memory: “visuo-spatial sketchpad” involves forming mental images.

Auditory memory: “phonological loop” involves repeating information to yourself



Short-Term/Working Memory



5 neurons

1 synapse per neuron

1 SINGLE CIRCUIT from neuron A, back to neuron A, involving all the neurons and all the synapses

3 neurons

2 synapses per neuron

4 POSSIBLE CIRCUITS leading from neuron A back to neuron A through different synaptic pathways involving all the neurons

Long-Term memory

Vast “library” of stored information and memories (patterns of cortical activity)

Unlimited capacity and duration

distinct cellular processes from STM

Long-Term memory

Exposure and Rehearsal

Simple exposure to information, even many times, does not guarantee that it will get stored in LTM.

Maintenance rehearsal = “rote” memorization; also not the best method.

Elaborative rehearsal = focuses on meaning of the information

Levels of Processing:

Information that is *processed* more deeply will be remembered more easily later on

Types of Long-Term Memory

Declarative memory: relational knowledge

“explicit” - conscious, intentional memory retrieval

Divided into episodic and semantic memory.

Episodic = where and when info was learned.

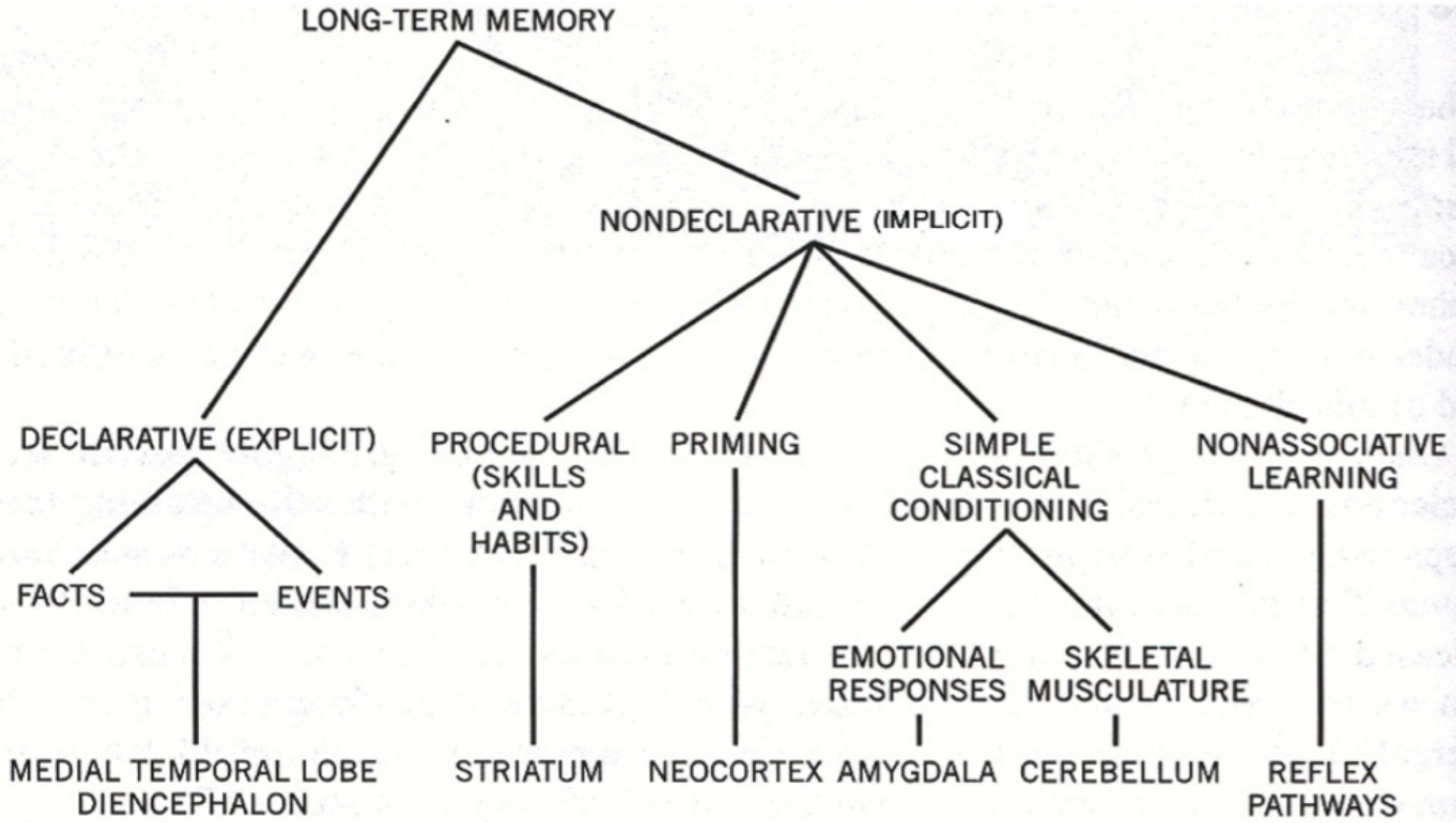
Semantic = general knowledge

1 trial learning

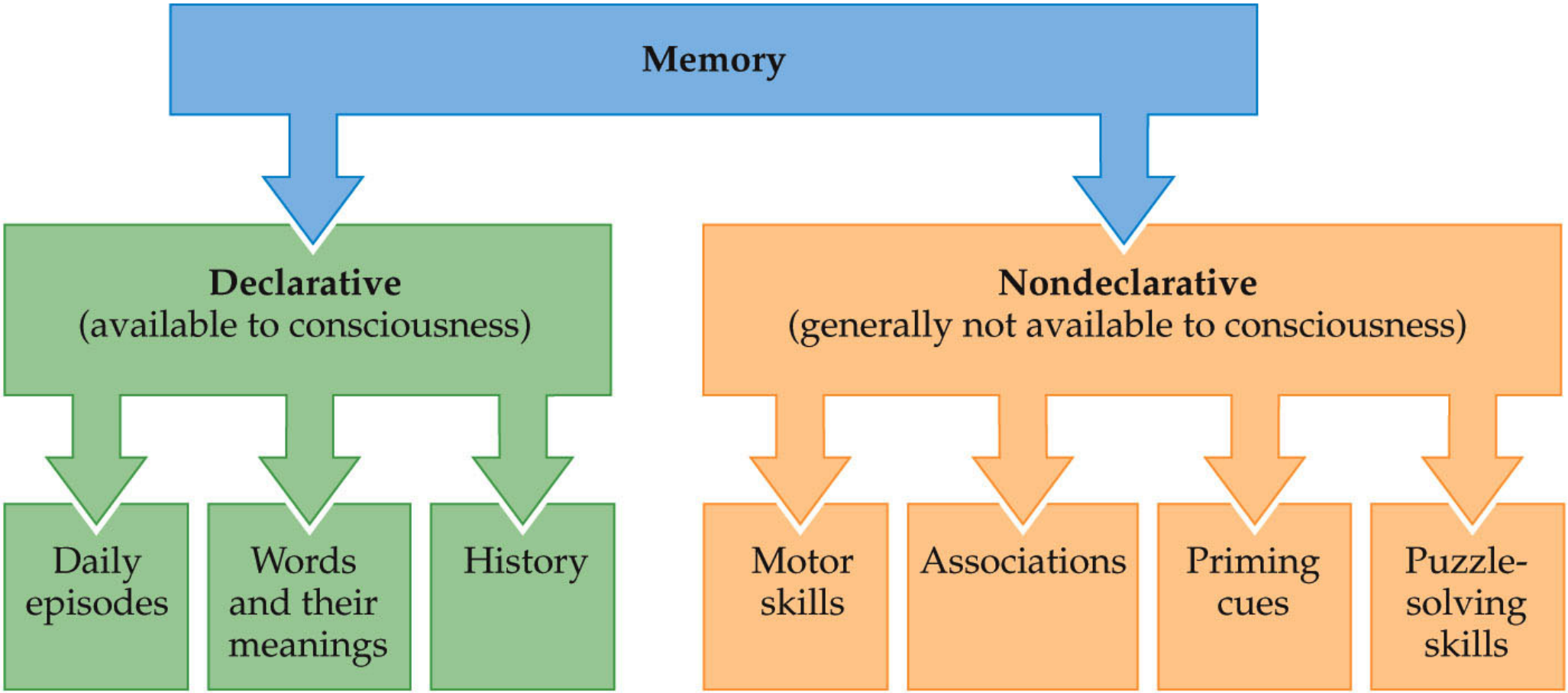
Procedural memory: skills and actions

“implicit” – memory can infl uence behavior without conscious awareness

- generally requires several trials to acquire


LONG-TERM MEMORY
NONDECLARATIVE (IMPLICIT)
DECLARATIVE (EXPLICIT)
PROCEDURAL (SKILLS AND HABITS)
PRIMING
SIMPLE CLASSICAL CONDITIONING
NONASSOCIATIVE LEARNING
FACTS
EVENTS
EMOTIONAL RESPONSES
SKELETAL MUSCULATURE
MEDIAL TEMPORAL LOBE DIENCEPHALON
STRIATUM
NEOCORTEX
AMYGDALA
CEREBELLUM
REFLEX PATHWAYS

NEOCORTEX


Memory
Declarative
(available to consciousness)
Nondeclarative
(generally not available to consciousness)
Daily episodes
Words and their meanings
History
Motor skills
Associations
Priming cues
Puzzle-solving skills

Forgetting

As interesting to researchers as how we remember.

Possible mechanisms:

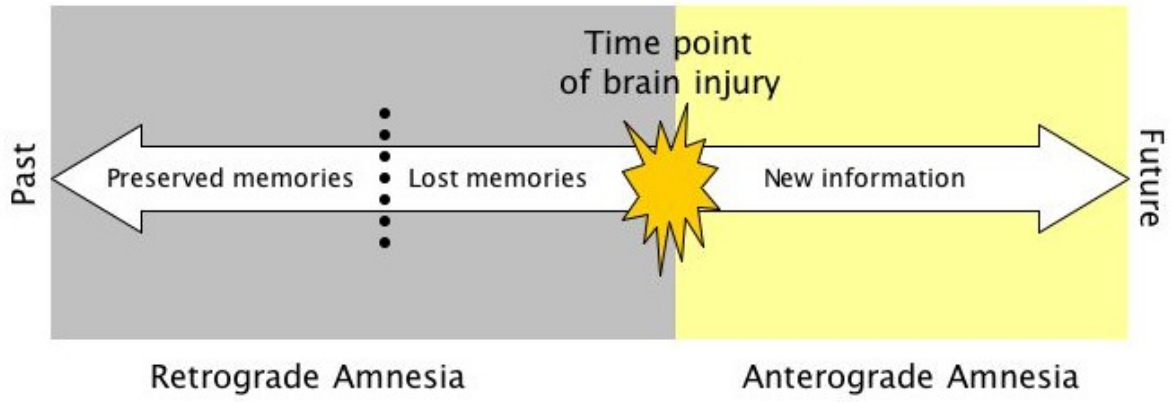
- Encoding failure
- Decay theory
- Interference
- Motivated forgetting
  - “Active” forgetting

Amnesia

Retrograde amnesia: memory loss for events prior to onset.

Anterograde amnesia: memory loss for events after onset.

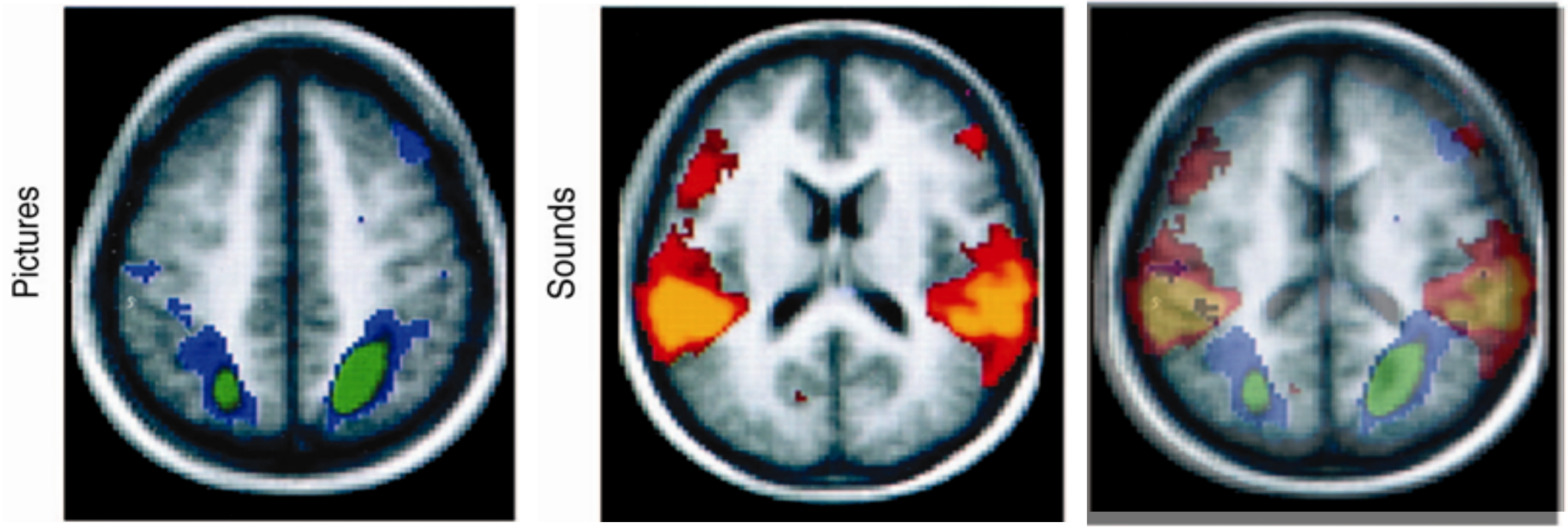
Infantile amnesia: loss of childhood memories before the age of 2 or 3 years.



The Hippocampus and Learning / Memory

Neurons that fire together wire together (Hebb)

Multiple reactivation of spatiotemporal cortical patterns cause neuroplastic (functional / structural) changes to reinforce these patterns



The Hippocampus and Learning / Memory

Different types of info are encoded by different brain regions / processes:

"procedural" info by direct, multiple reactivations of sensory cortical patterns

along w/ basal ganglia & cerebellum

"declarative" / relational / contextual (1 trial) info by the sensory cortical patterns + hippocampus

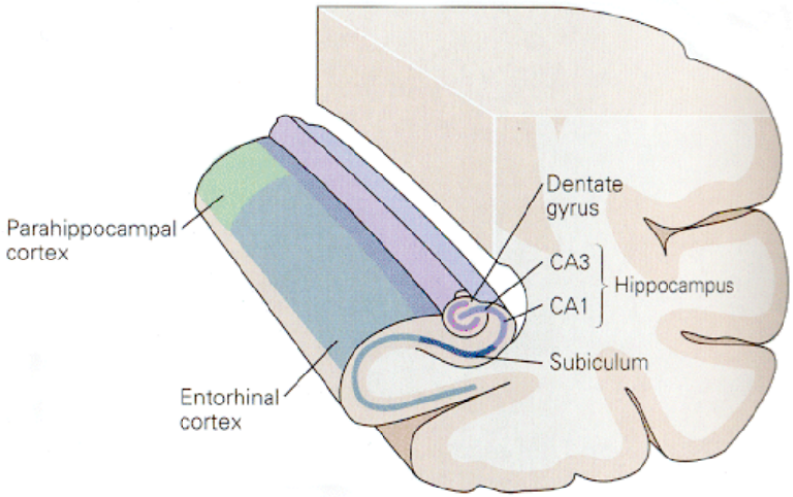
"emotional" info from a declarative memory by the amygdala

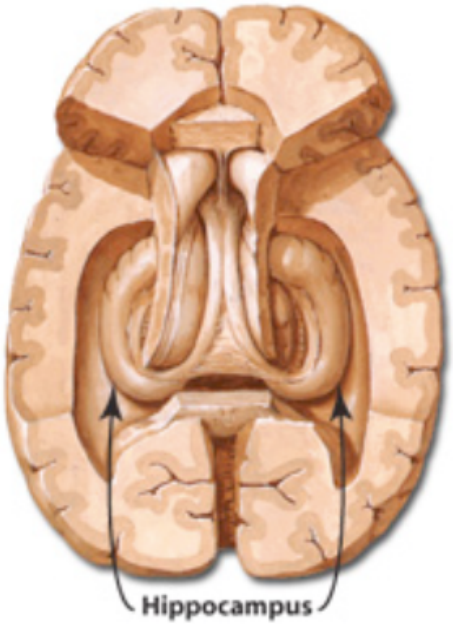
The Hippocampus and Learning / Memory

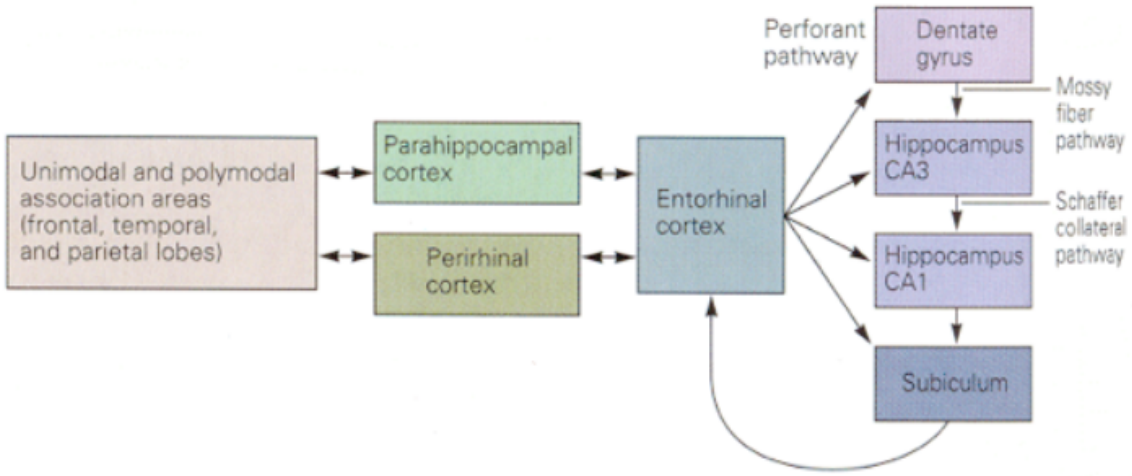
- the *hippocampal formation* can be thought of as the "highest level of association cortex"
  - receives convergent inputs from all sensory areas

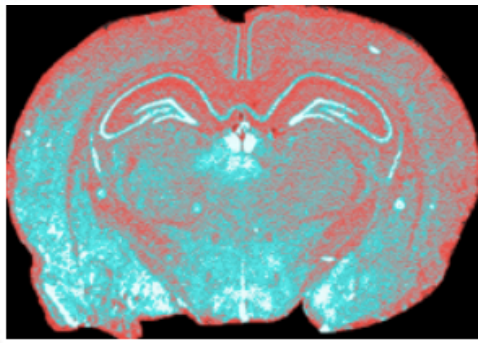
humans - S-shaped curved structure in the medial temporal lobe

rodents - follows the curve of the the lateral ventricle (more dorsal)





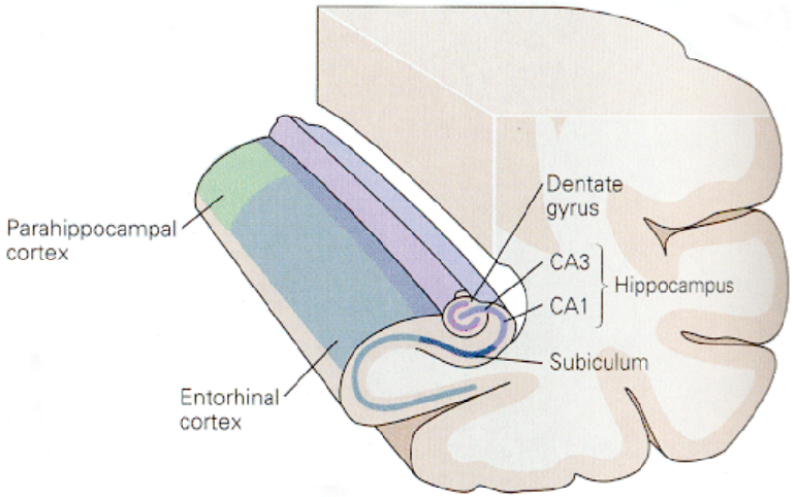


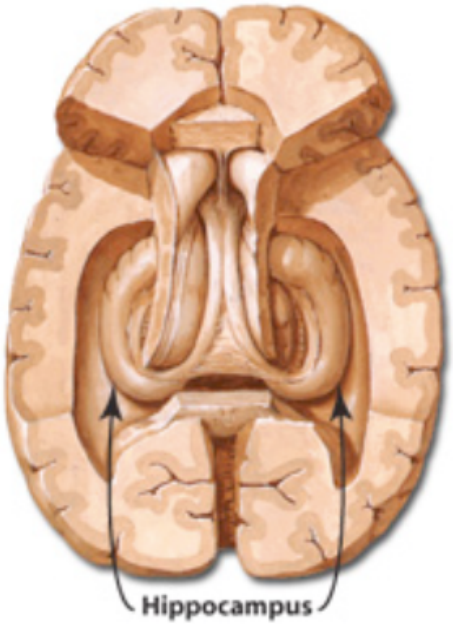


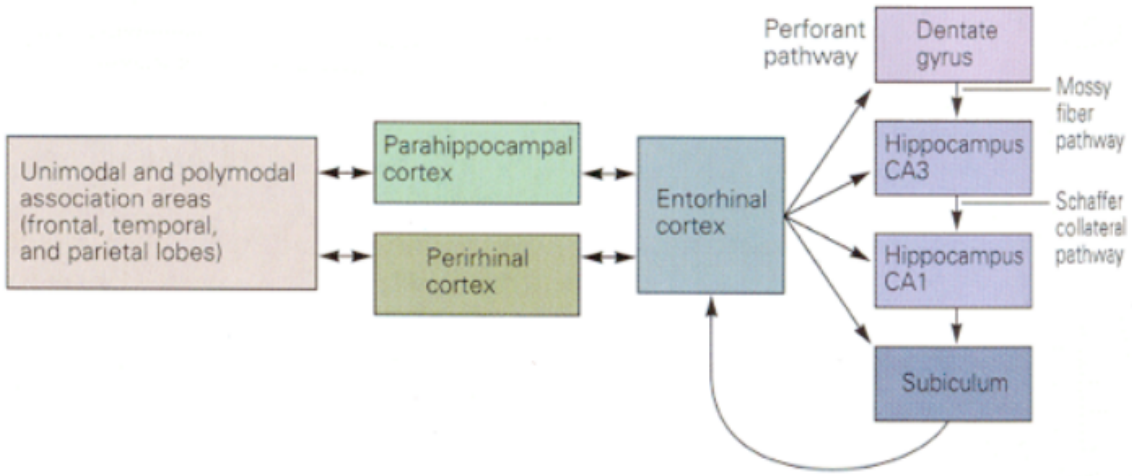
The Hippocampus and Learning / Memory

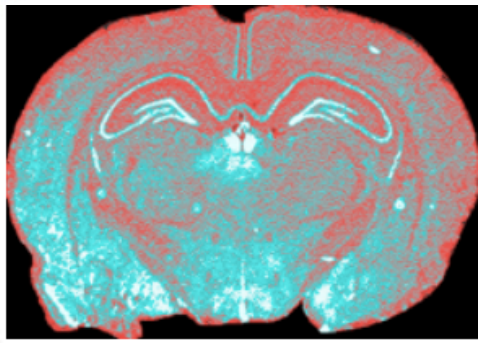
areas include:

- parahippocampal, perirhinal & entorhinal cortex
- dentate gyrus
- Ammon's horn (areas CA1-CA4)
- subiculum / presubiculum / parasubiculum
- output pathways form the fimbria-fornix

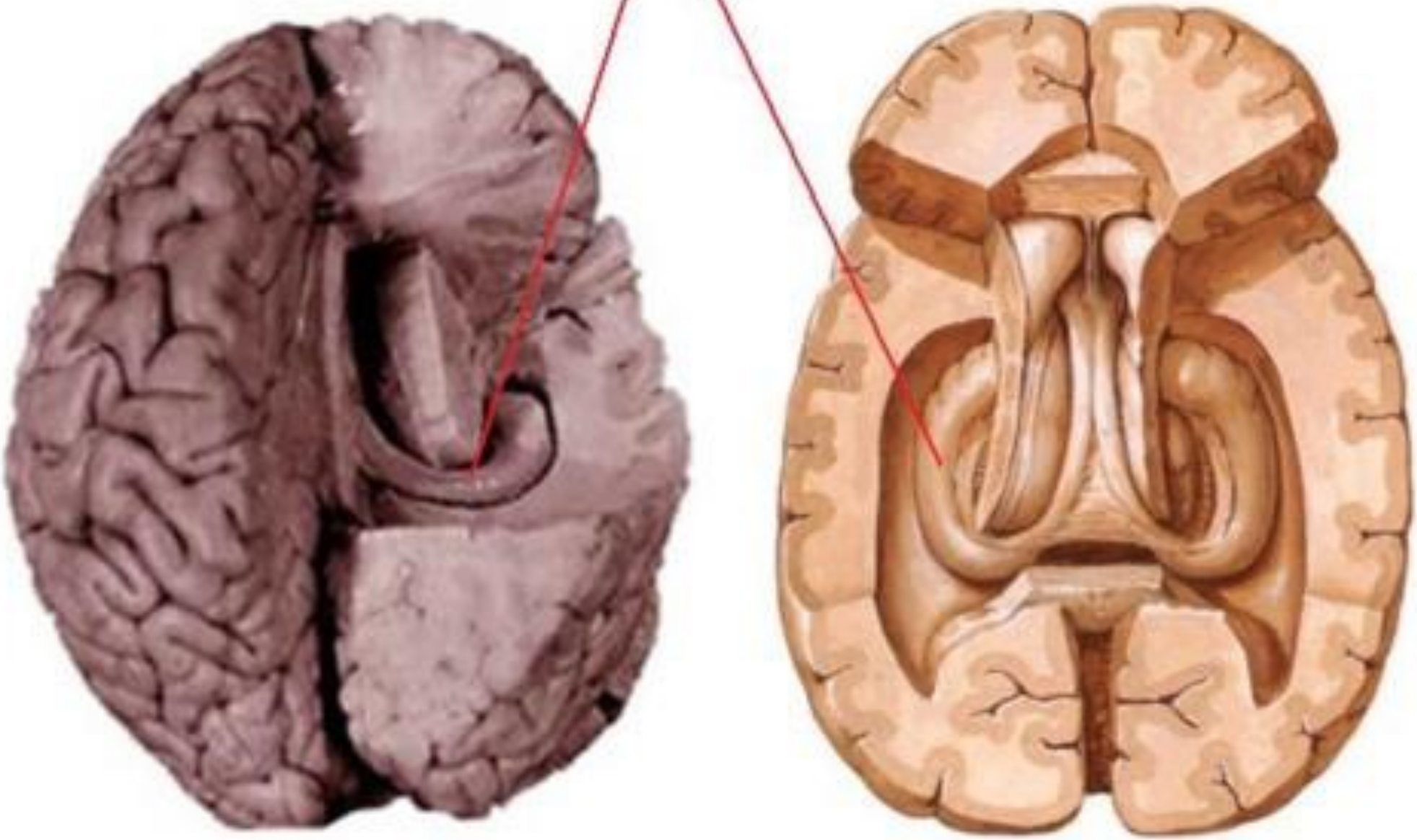


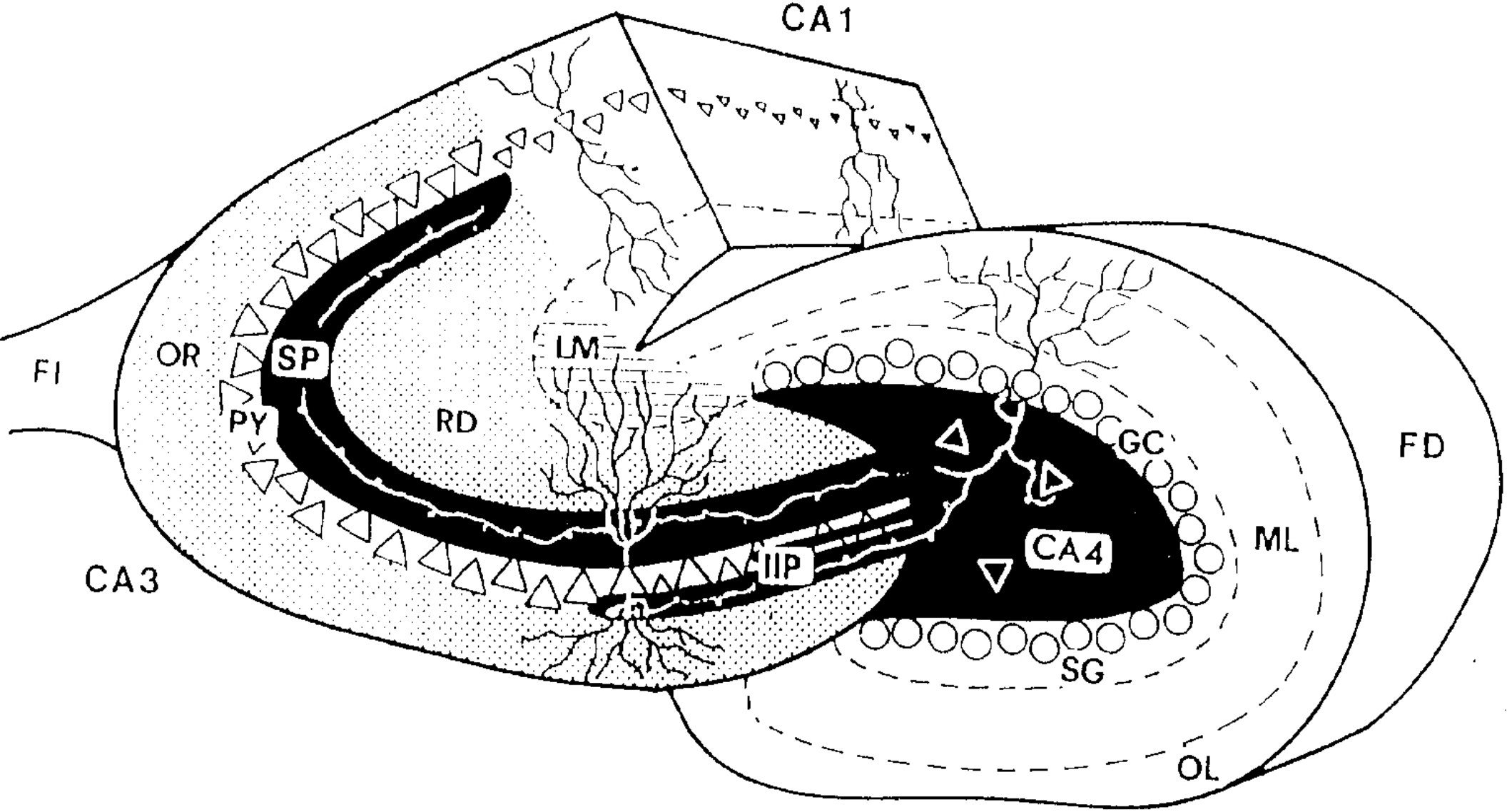


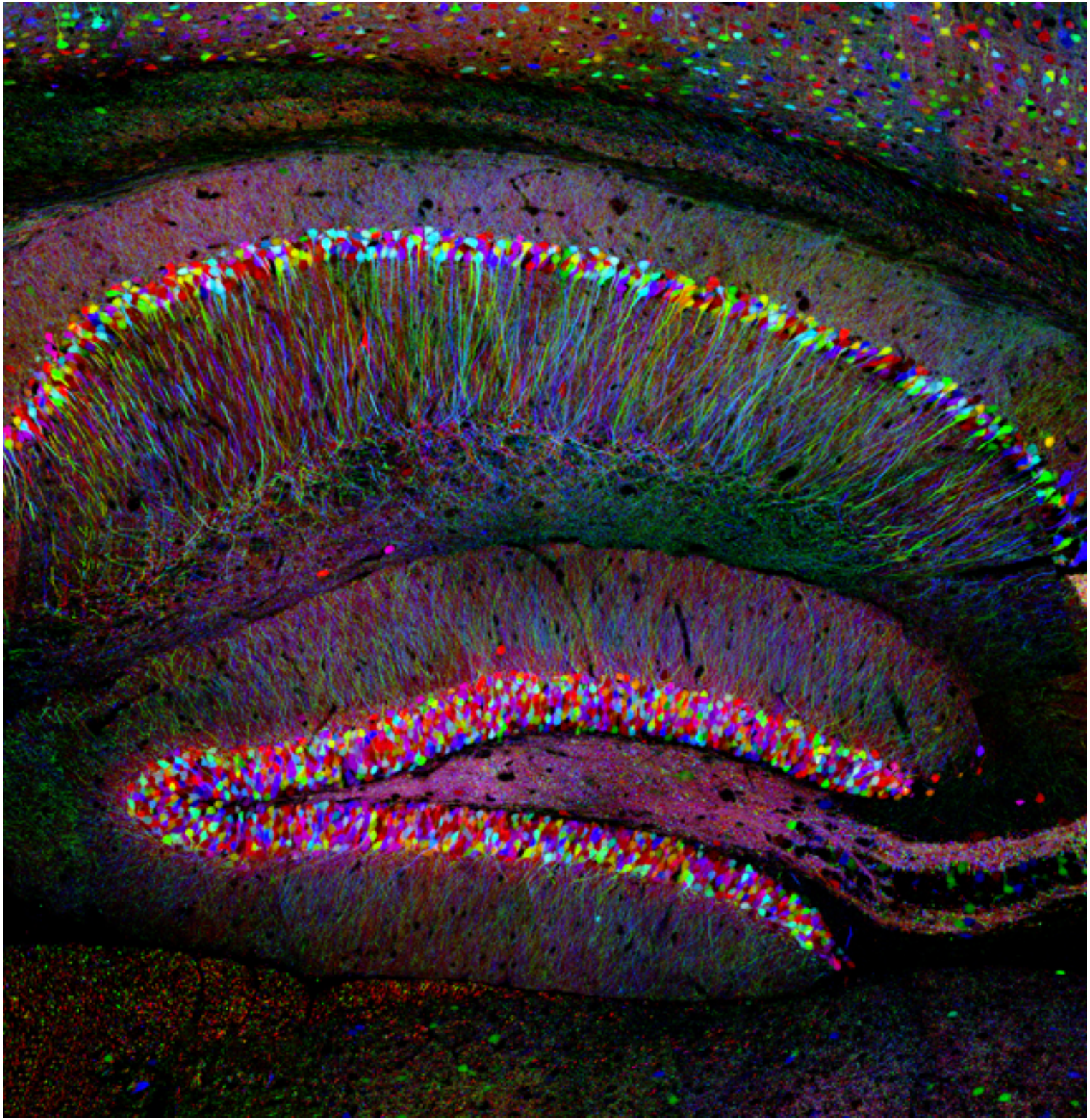




Hippocampus

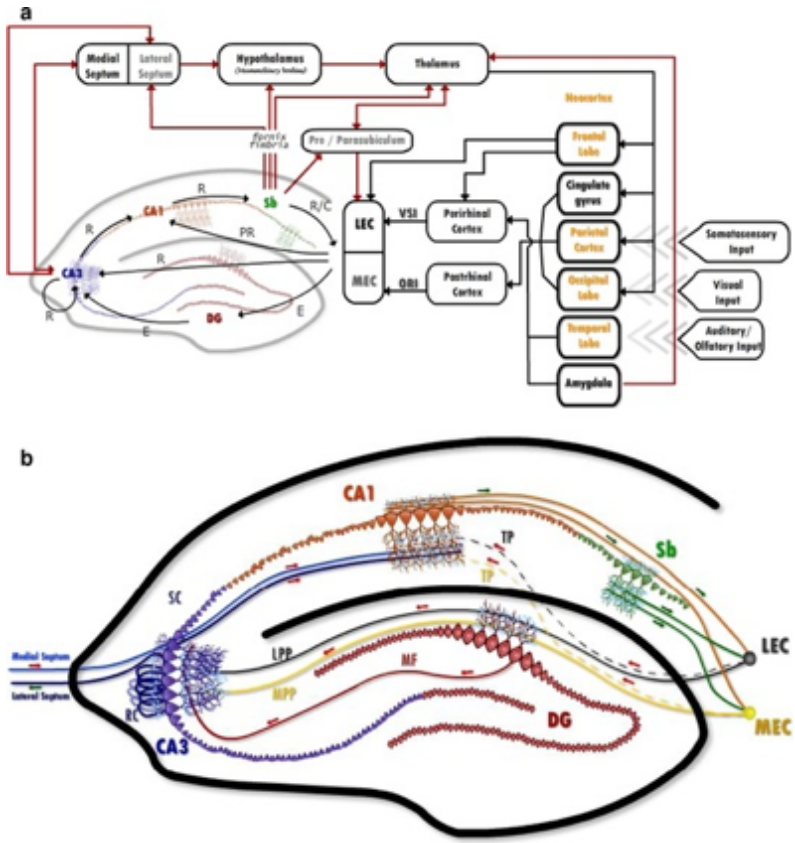


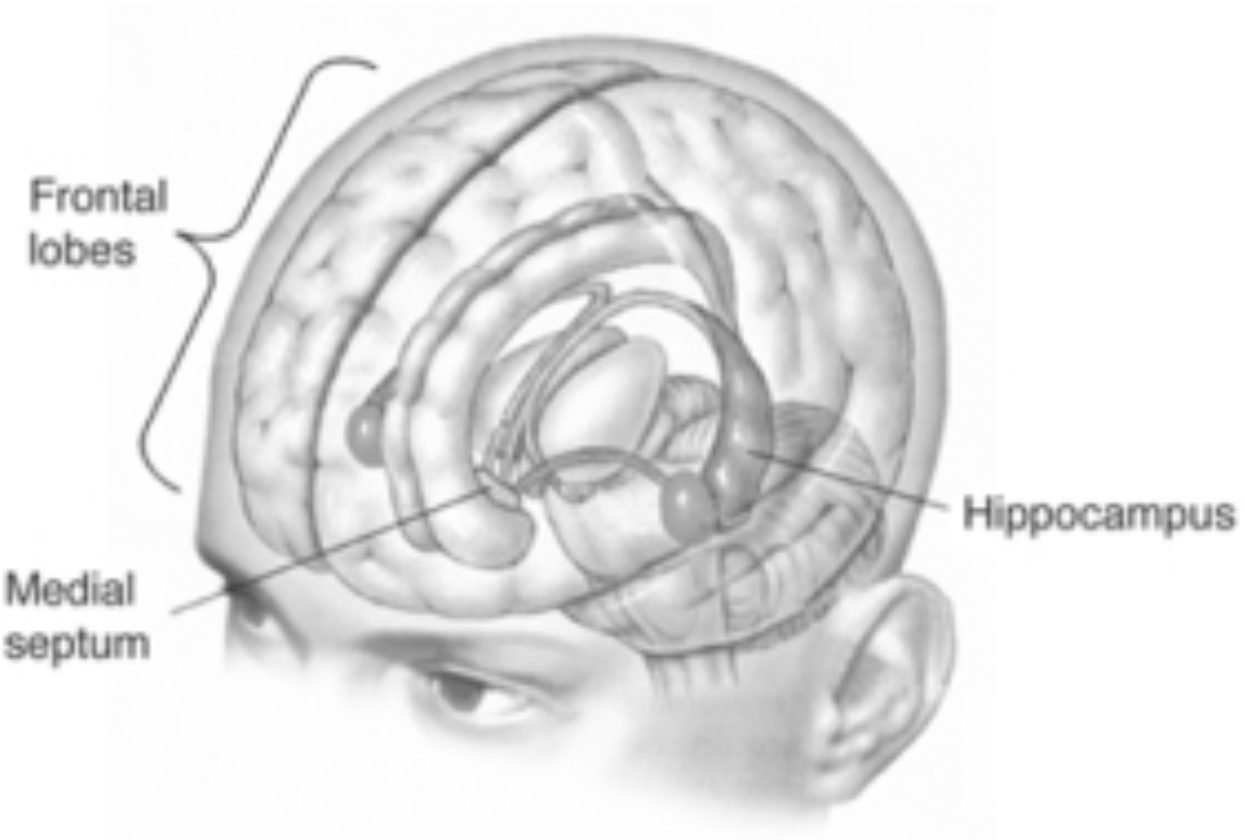

CA1
FI
OR
SP
PY
RD
LM
GC
FD
ML
CA4
IIP
CA3
SG
OL



The Hippocampus and Learning / Memory

inputs from the neocortex alter its circuitry to set up an "index" of cortical locations (long-term synaptic change) for the *combined perceptual patterns* that may make up a given memory





The Hippocampus and Learning / Memory

role of hippocampus is to initially "tie together" specific stimuli ("relationships" / context)

JUST LIKE procedural memories, *consolidation* of perceptual associations into long-term memories in the cortex requires multiple activations

repeated or continual activation of a particular hippocampal index gradually strengthens the associations of cortical areas making up a memory

probably takes place during sleep - rapid, looped replay

eventually, the cortex can generate the appropriate spatiotemporal patterns and generate a memory without the hippocampus

The Hippocampus and Learning / Memory

bilateral hippocampal damage disrupts learning, memory formation and retrieval of recent "declarative" memories:

severe / global *anterograde amnesia*

temporally graded *retrograde amnesia*

Spared:

remote memories

immediate memory

perceptual / motor / cognitive functions ("procedural" memories)

may not remember learning the task, but when prodded to continue, they can perform at normal levels

The Hippocampus and Learning / Memory

Lateralized:

left - verbal material such as story content

right - spatial tasks (localization of objects), facial recognition

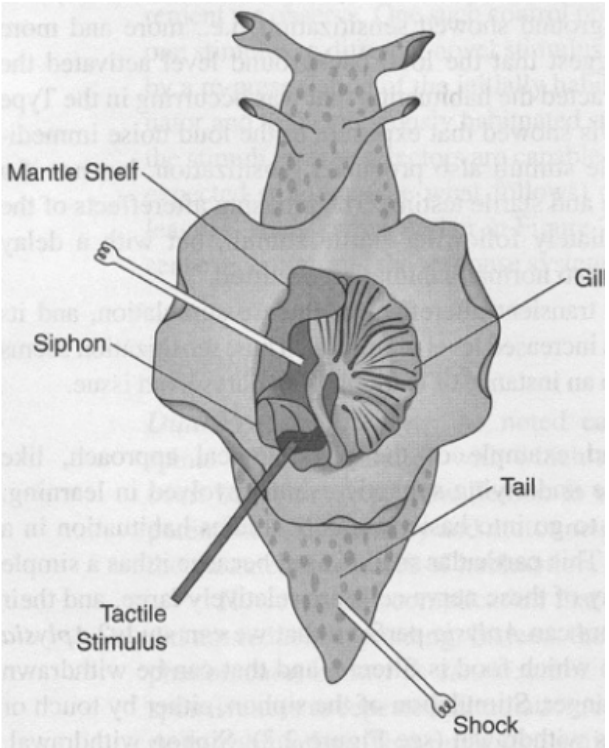
trouble remembering verbal material if the learning process is *image*-mediated

memories older than about three years are not affected by hippocampectomy

the hippocampus is not necessary for retrieval or storage of older memories

SNAIL MODEL OF HABITUATION

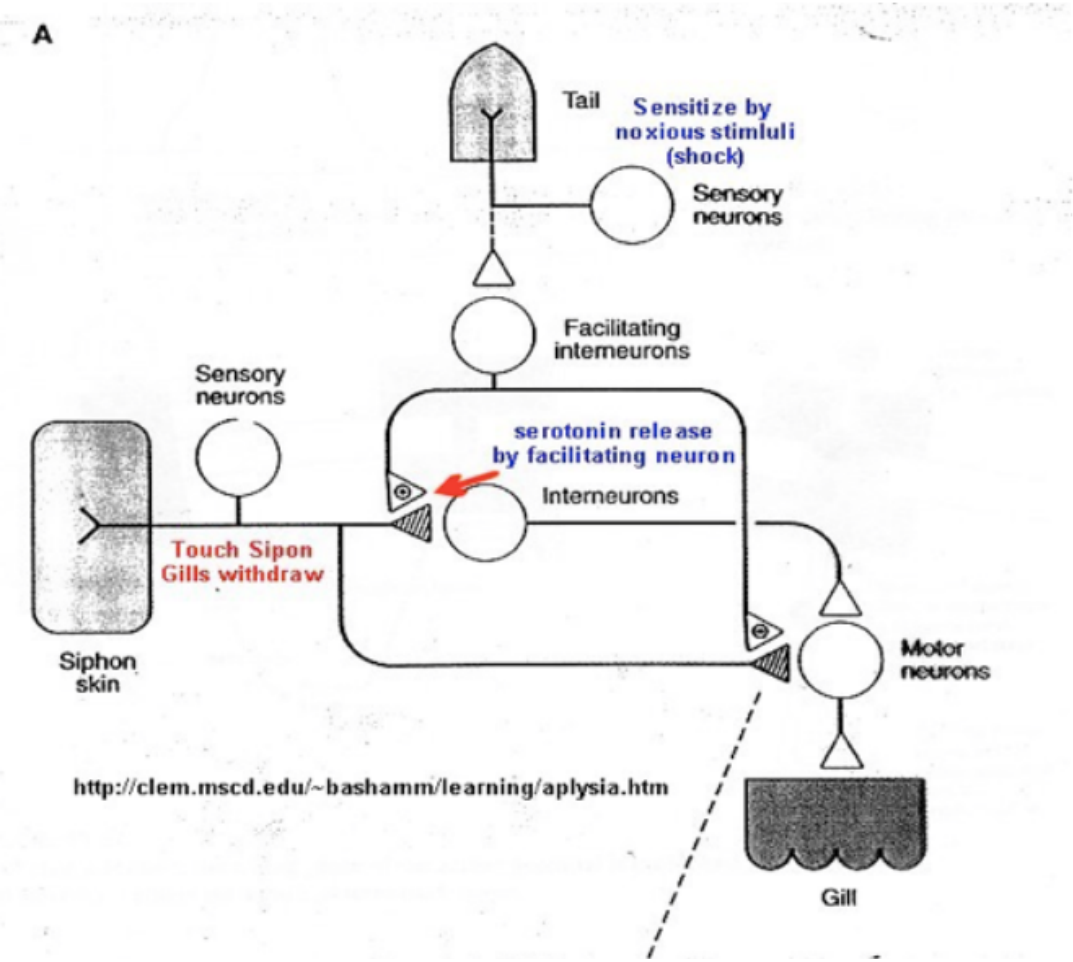
- Eric Kandel's research with *Aplysia* shows that learning is a physiological process
  - gill withdrawal reflex ("reflex arc")
  - siphon is an organ that takes in sea water
    - lightly brushing siphon causes gills to withdraw

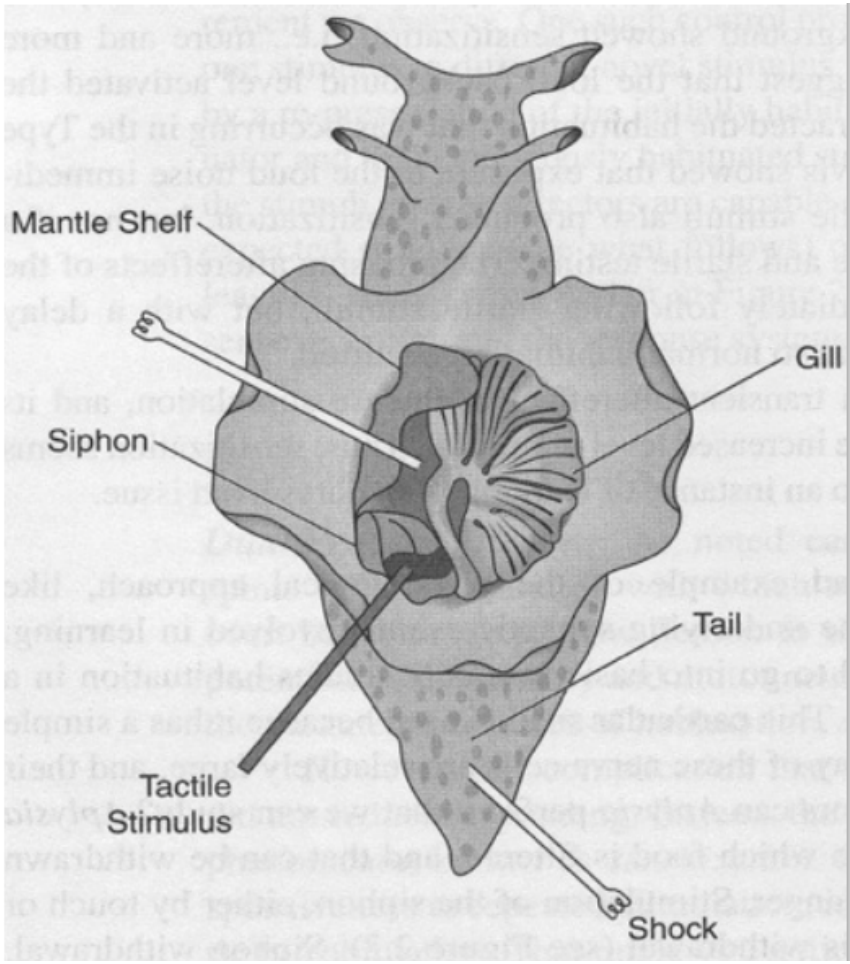


SNAIL MODEL OF HABITUATION

40 BIG sensory neurons in siphon > 6 motor neurons in gill muscles (excitatory / glu)

plus some excitatory / inhibitory *interneurons*





SNAIL MODEL OF HABITUATION

- continued stimulation causes this withdrawal reflex to *habituate* (response stops)

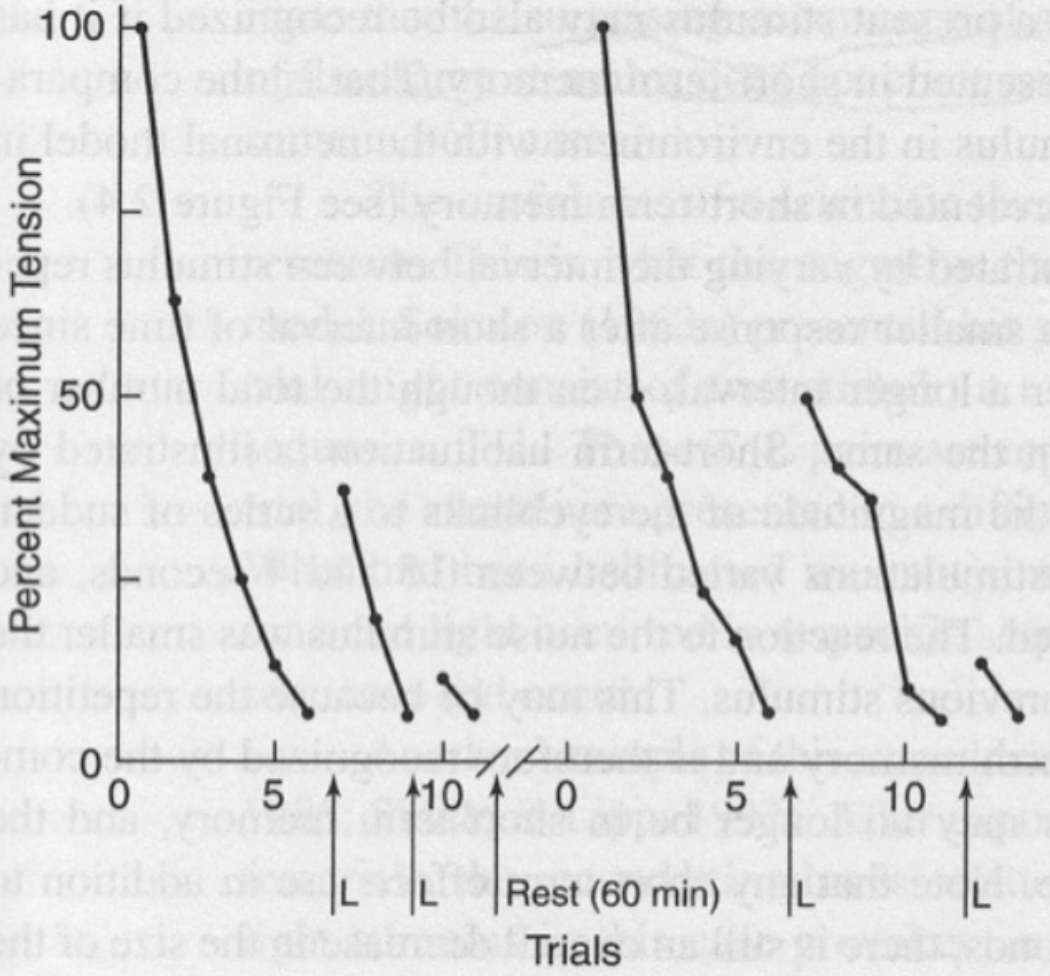


FIGURE 2.3 Habituation of Siphon Withdrawal of *Aplysia* to a Tactile Stimulus. The response measured is the tension of the siphon withdrawal to tactile stimulation. Dishabituation to the tactile stimulus occurs following presentation of a light stimulus.

Source: Lukowiak & Jacklet, 1972.

SNAIL MODEL OF HABITUATION

- stimulation still produces APs in sensory neurons
- synaptic structures responsible for vesicle release

are inactivated

  - mobilization of transmitter vesicles is decreased
  - voltage dependent Ca++ channels become

  inactivated with repeated stimuli

- each sensory neuron AP releases fewer NT vesicles

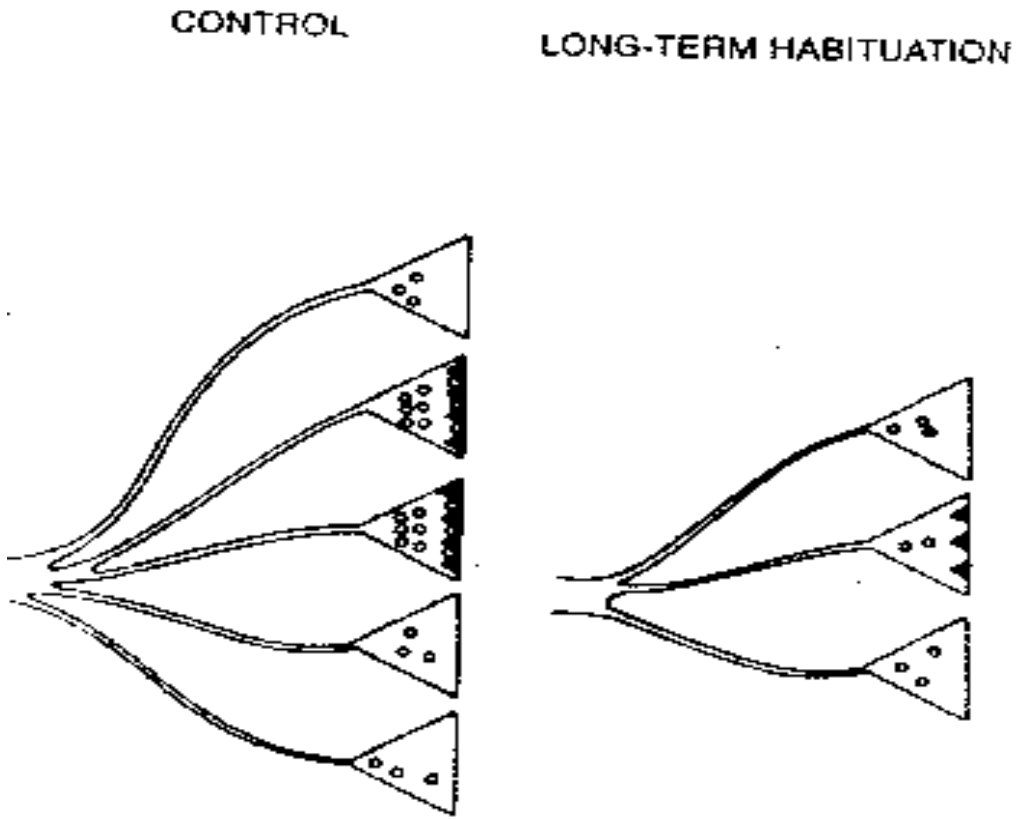
SNAIL MODEL OF HABITUATION

- produces smaller EPSP in motor neurons & interneurons (functional change)
  - less likelihood of generating APs (and therefore gill withdrawal)
  - decrease in response is learning
  - transient functional change in neural circuit = *short term memory*

SNAIL MODEL OF HABITUATION

doing this repeatedly results in a structural change of the axon terminals

some terminals totally retract



SNAIL MODEL OF HABITUATION

change in protein synthesis mediated by genes that maintain axon terminal structures

loss of input causes postsynaptic dendritic arbor to shrink

- reduced numbers of synaptic connections
- *long-term memory*

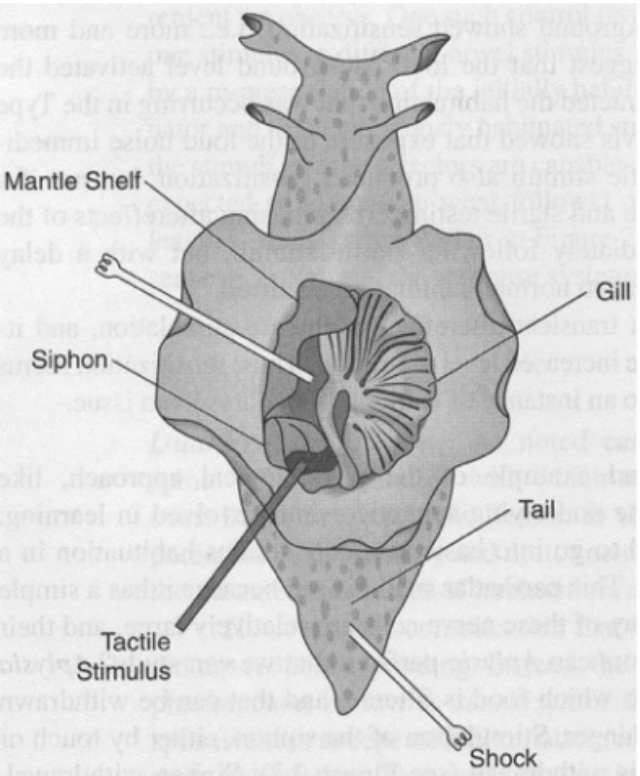
- after several weeks of no stimulus, terminals start to grow back and system returns to baseline
  - *forgetting*

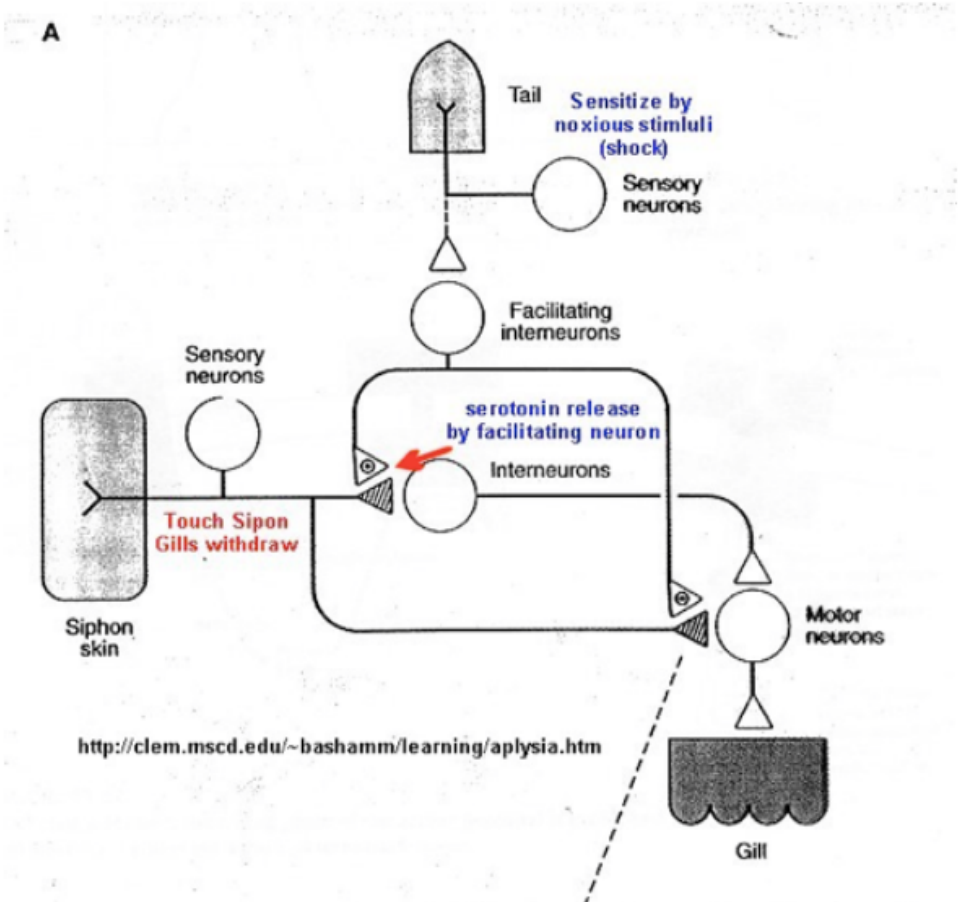
SNAIL MODEL OF SENSITIZATION

sensitization - an *increase* in reflex magnitude

shock tail > brush siphon > stronger gill withdrawal

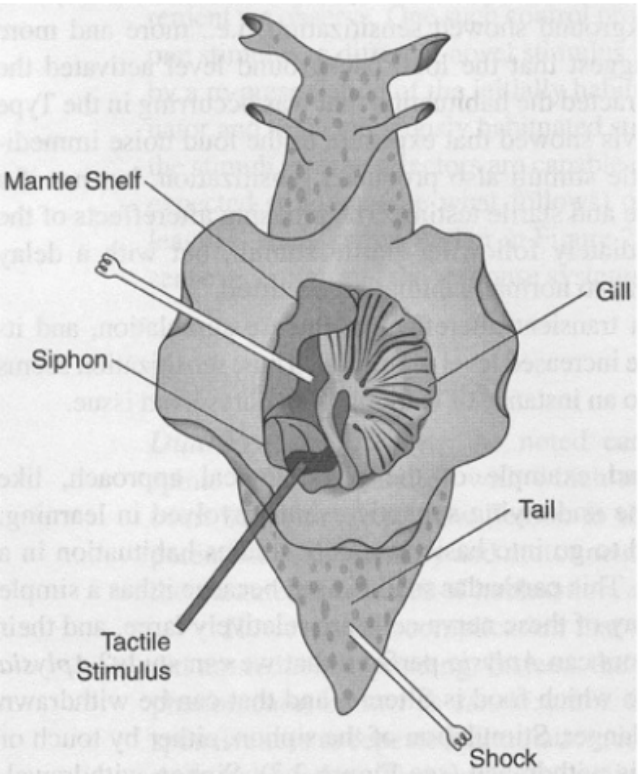
involves same set of neurons with addition of *modulatory interneurons* from tail (more complex)

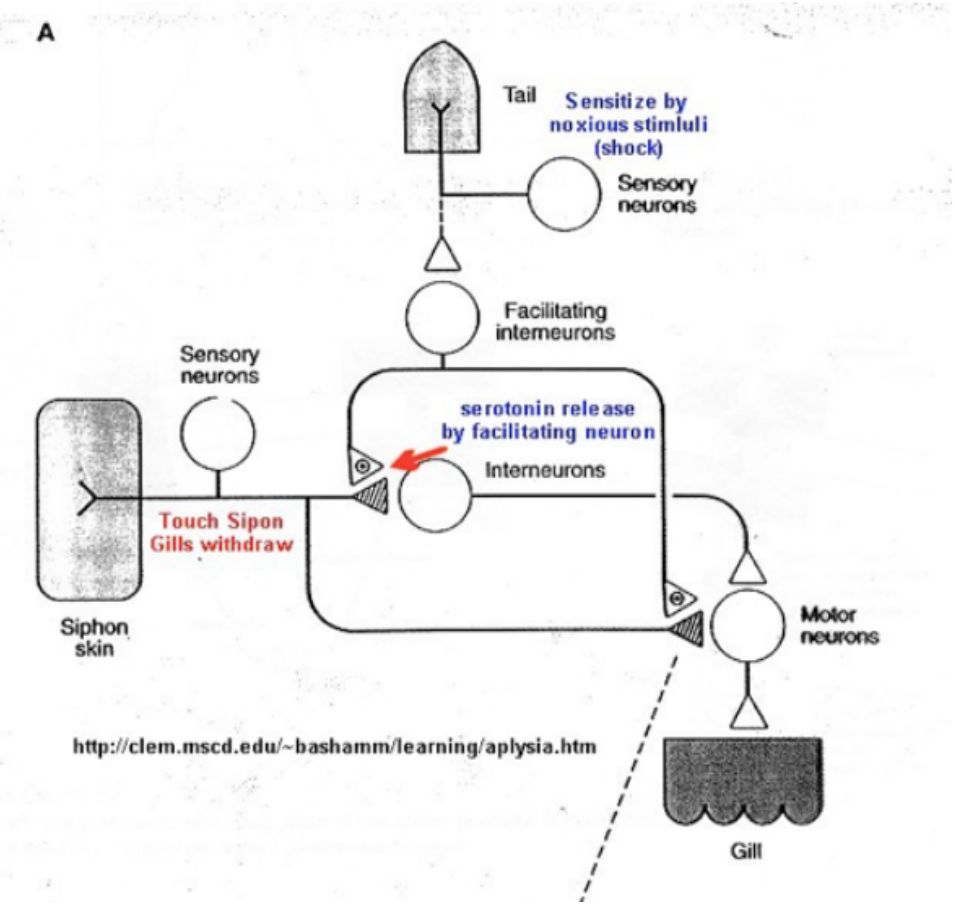




SNAIL MODEL OF SENSITIZATION

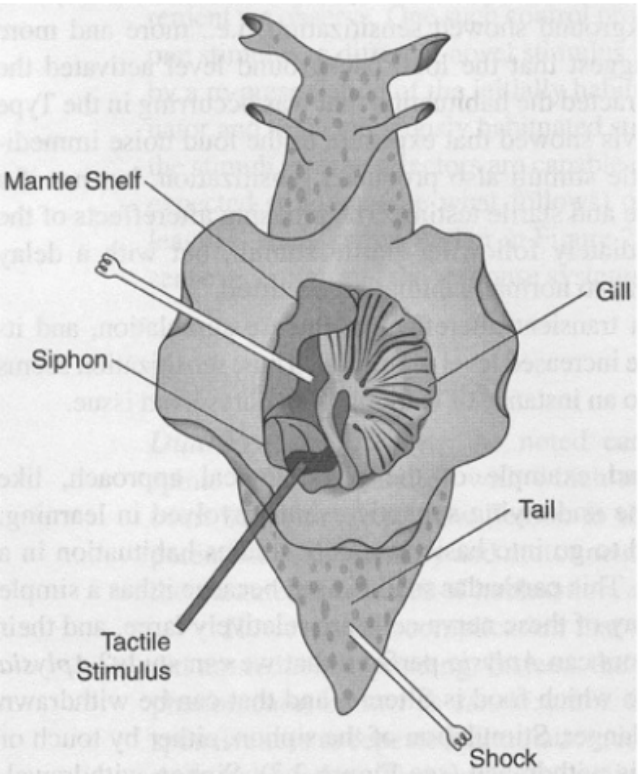
sensitization results in release of more excitatory transmitter from sensory neurons onto the motor neurons (opposite of habituation)

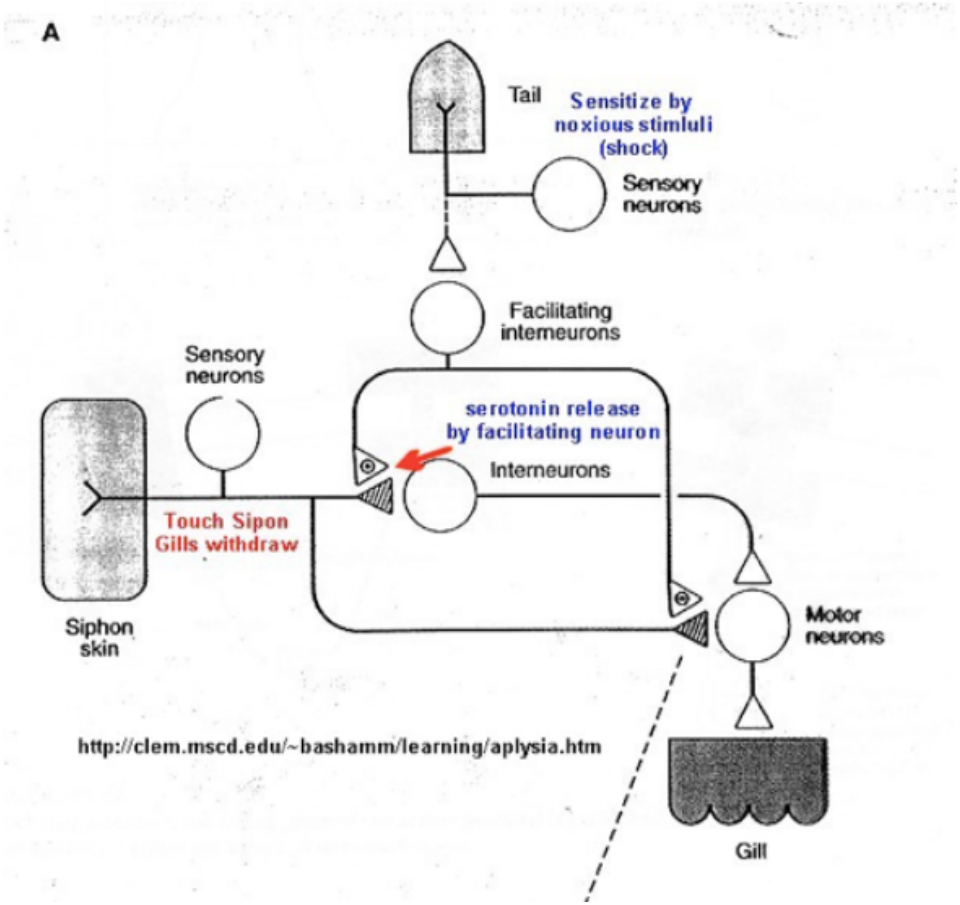




SNAIL MODEL OF SENSITIZATION

Serotonin (aka 5-HT) from *facilitating interneurons* binds to receptors on siphon sensory neuron axon terminals and creates changes inside the neuron that increase release of NT vesicles





SNAIL MODEL OF SENSITIZATION

at first: transient functional change (STM)

- repeated initiates a cascade of intracellular enzymatic events
  - CREB activates genes to synthesize proteins
    - neurotrophic factors (BDNF, NGF, etc)

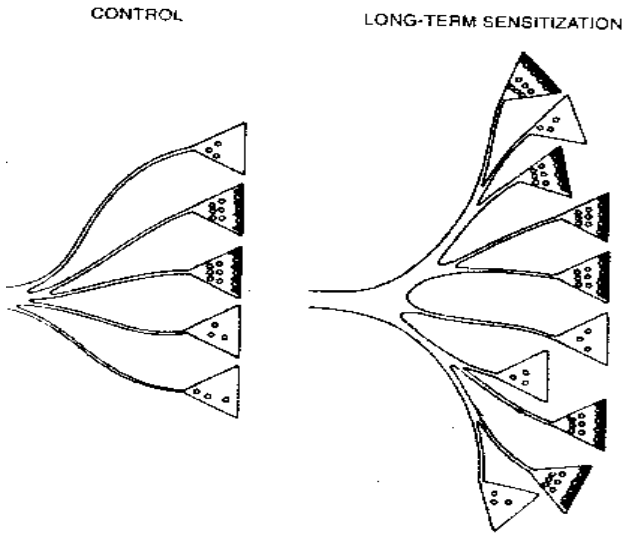
SNAIL MODEL OF SENSITIZATION

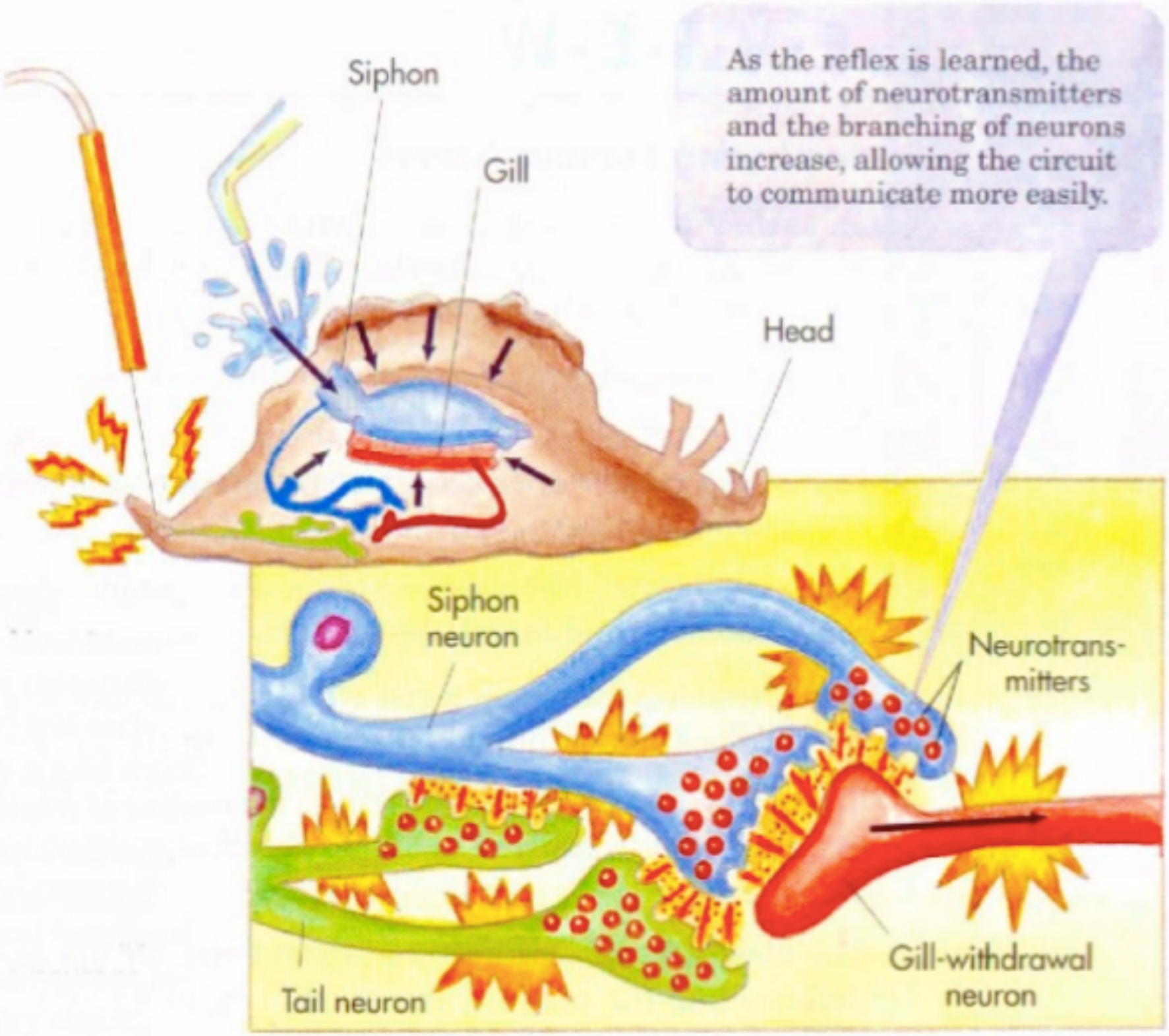
more NT and/or receptors

- structural changes - more axon terminal branches, neural connections, etc. (LTM)

LONG-TERM MEMORY REQUIRES MAKING NEW PROTEINS

(prevented by drugs that inhibit protein synthesis)

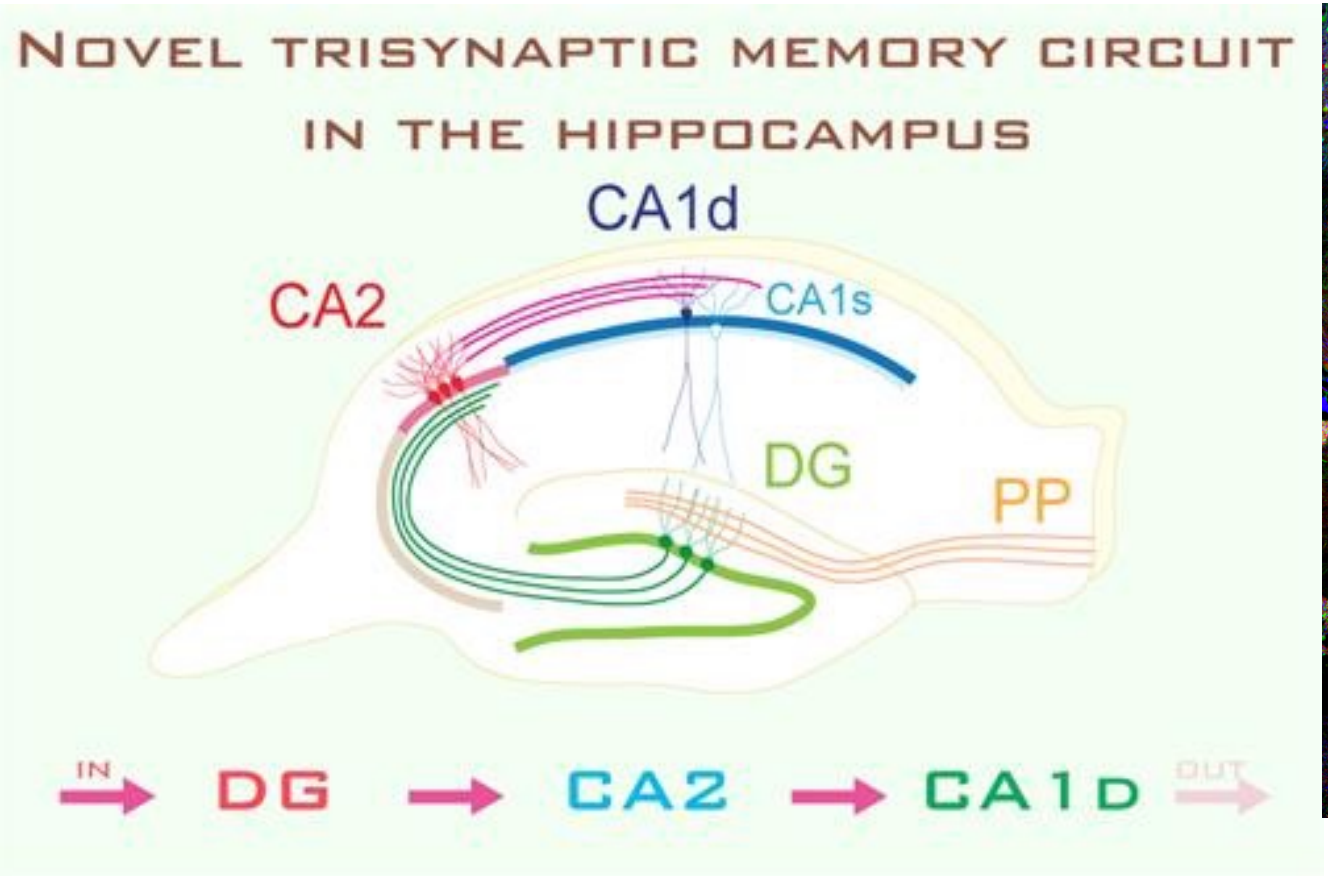


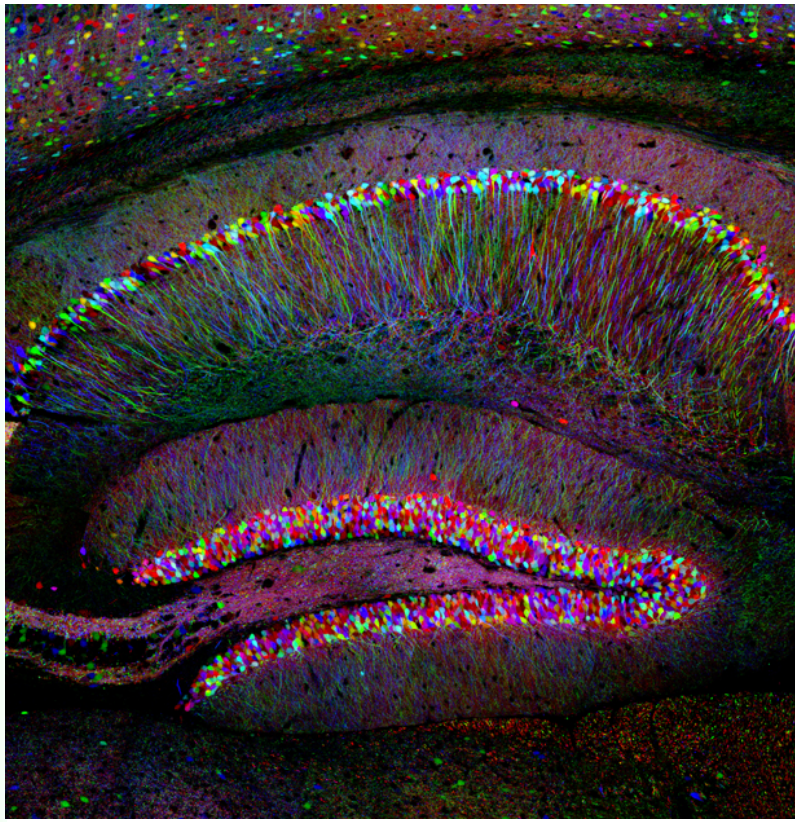

As the reflex is learned, the amount of neurotransmitters and the branching of neurons increase, allowing the circuit to communicate more easily.
Siphon
Gill
Head
Siphon neuron
Neurotrans-mitters
Tail neuron
Gill-withdrawal neuron

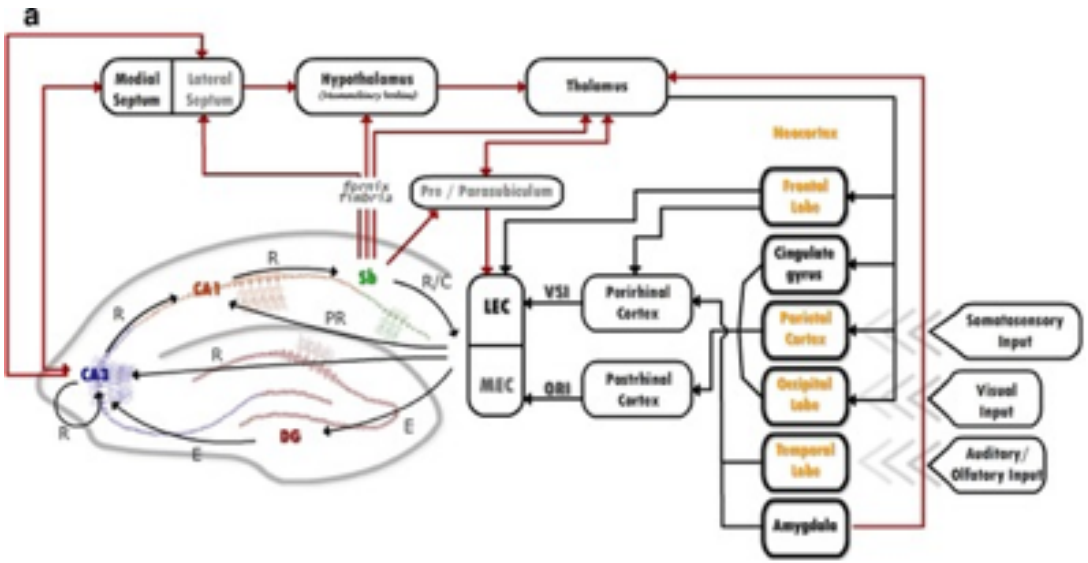
BACK TO MAMMALS AND THE HIPPOCAMPUS

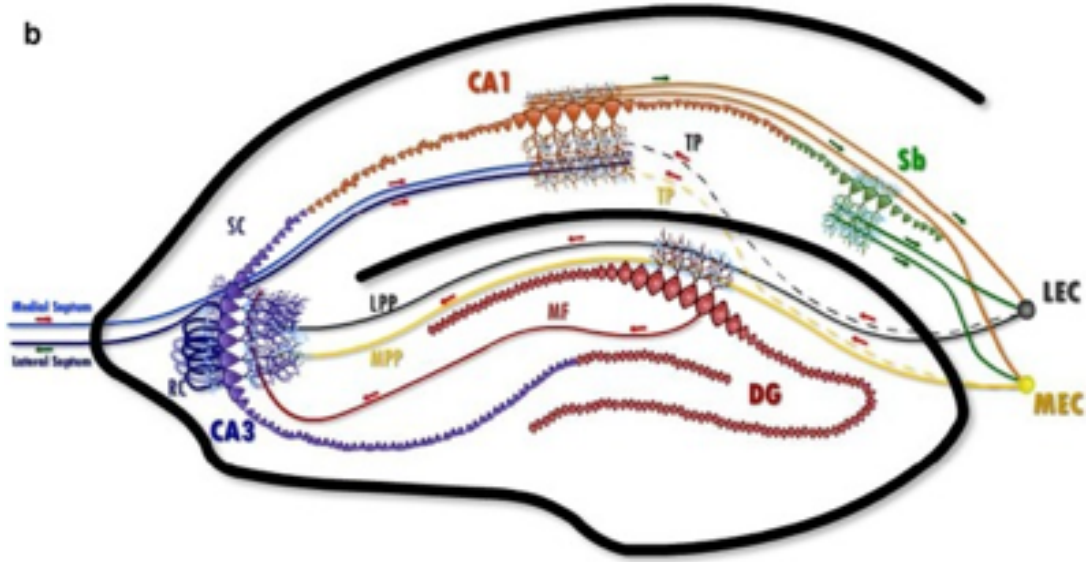
The Hippocampus, NMDA Receptors, and Learning

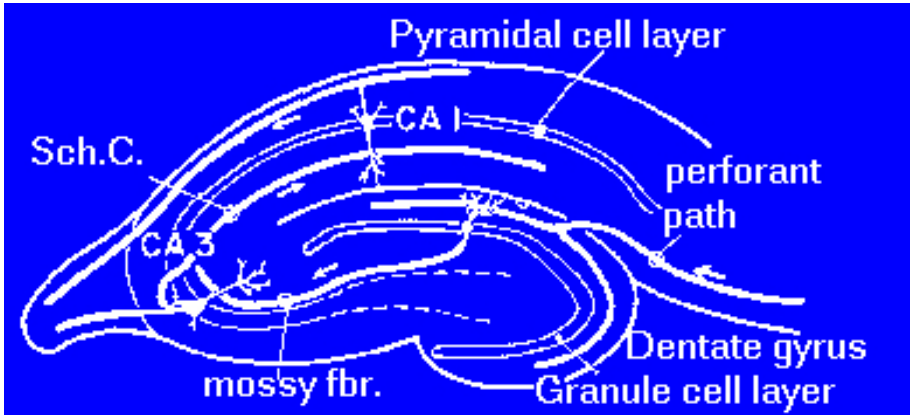
- ***tri-synaptic pathway:***
  - essentially a one-way avenue through the hippocampus
    - widespread cortical inputs and outputs
  - hippocampal circuits set up an "index" of activity patterns that initially "assists" in the cross-cortical association process





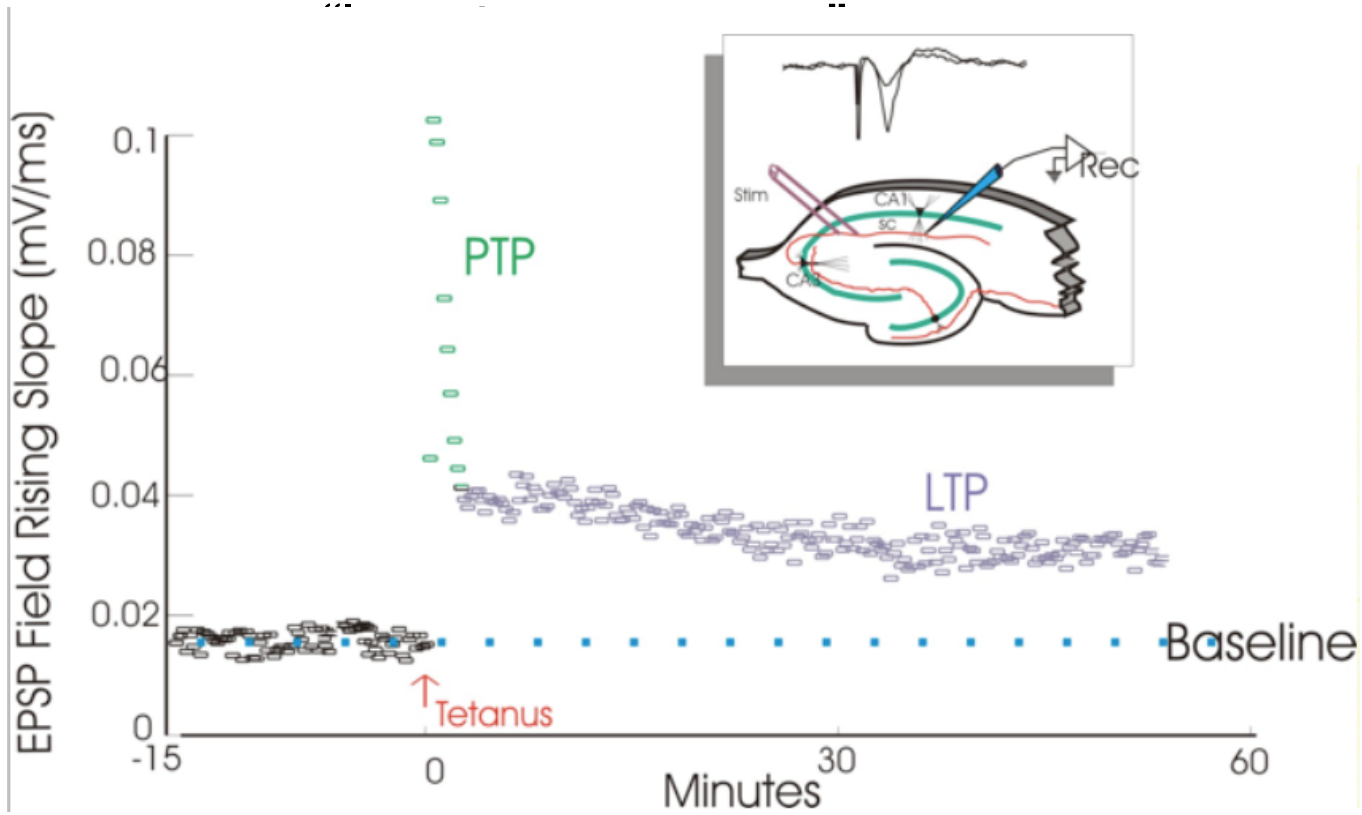

a
Medial Septum
Lateral Septum
Hypothalamus
Thalamus
Neocortex
fornix fimbria
Pro / Parasubiculum
Frontal Lobe
Cingulate gyrus
Parietal Cortex
Occipital Lobe
Temporal Lobe
Amygdala
Somatosensory Input
Visual Input
Auditory/ Olfatory Input
Perirhinal Cortex
Postrhinal Cortex
LEC
MEC
VSI
ORI
CA1
CA3
DG
Sb
R
R/C
PR
E

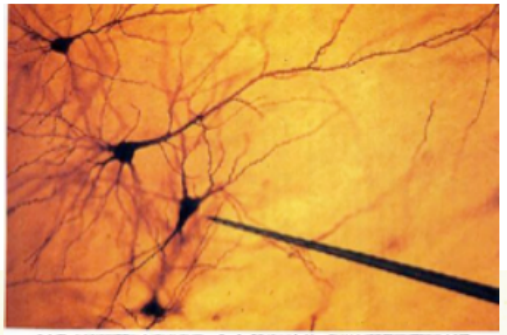

b
CA1
Sb
TP
SC
LPP
MF
MPP
LEC
MEC
DG
CA3
RC

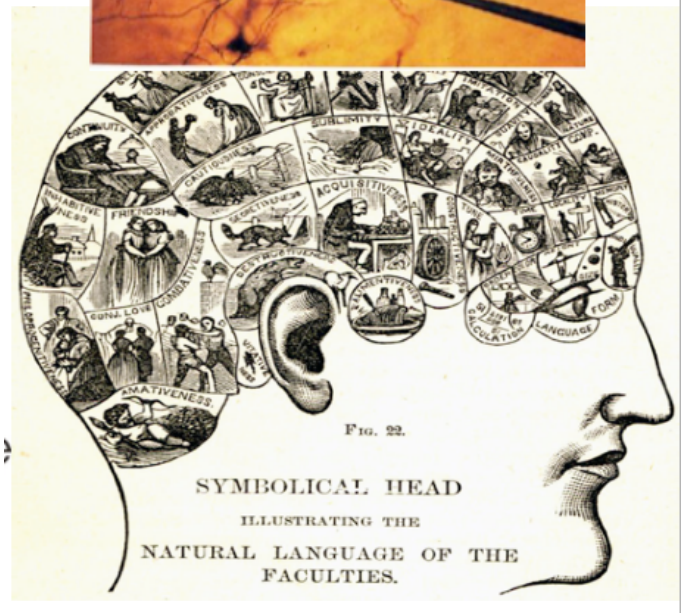

Pyramidal cell layer
CA I
Sch.C.
perforant path
CA 3
Dentate gyrus
mossy fbr.
Granule cell layer

The Hippocampus, NMDA Receptors, and Learning

- placing the hippocampus in a Petri dish and electrically stimulating axons in the pathway will produce EPSPs in the CA1 pyramidal neurons (output cells)
  - a high frequency (*tetanic*) burst of stimulation produces a long-lasting increase in EPSPs to subsequent, "normal" stimuli
  - so, efficacy of synapse is enhanced ("potentiated") by a single "experience"







LTP and LTD

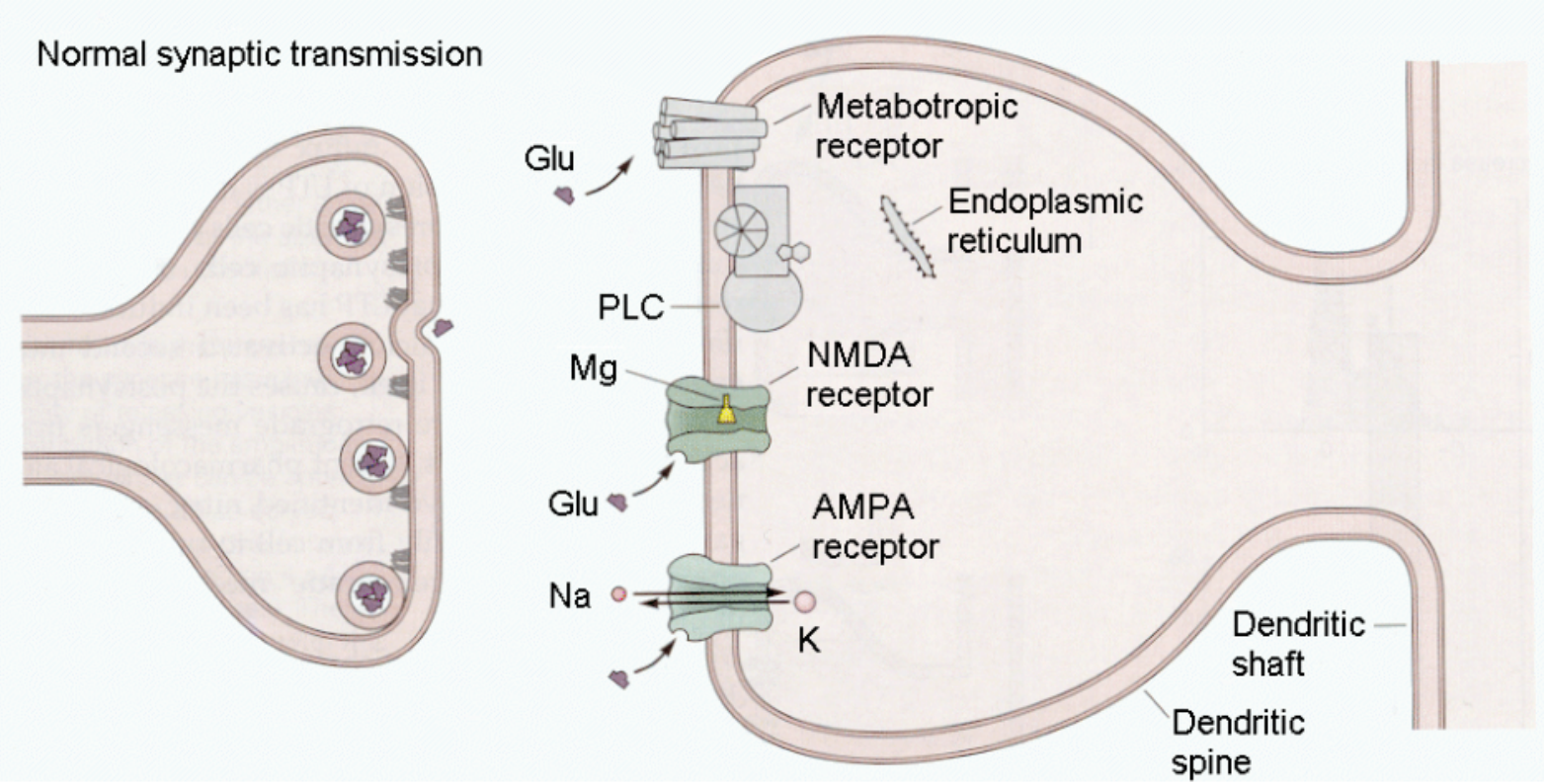
LTP IN GENERAL:

occurs between neurons that use the “excitatory” amino acid glutamate (glu)

several types of postsynaptic glu receptors:

N-methyl-d-aspartate (NMDA) receptor-channels

non-NMDA



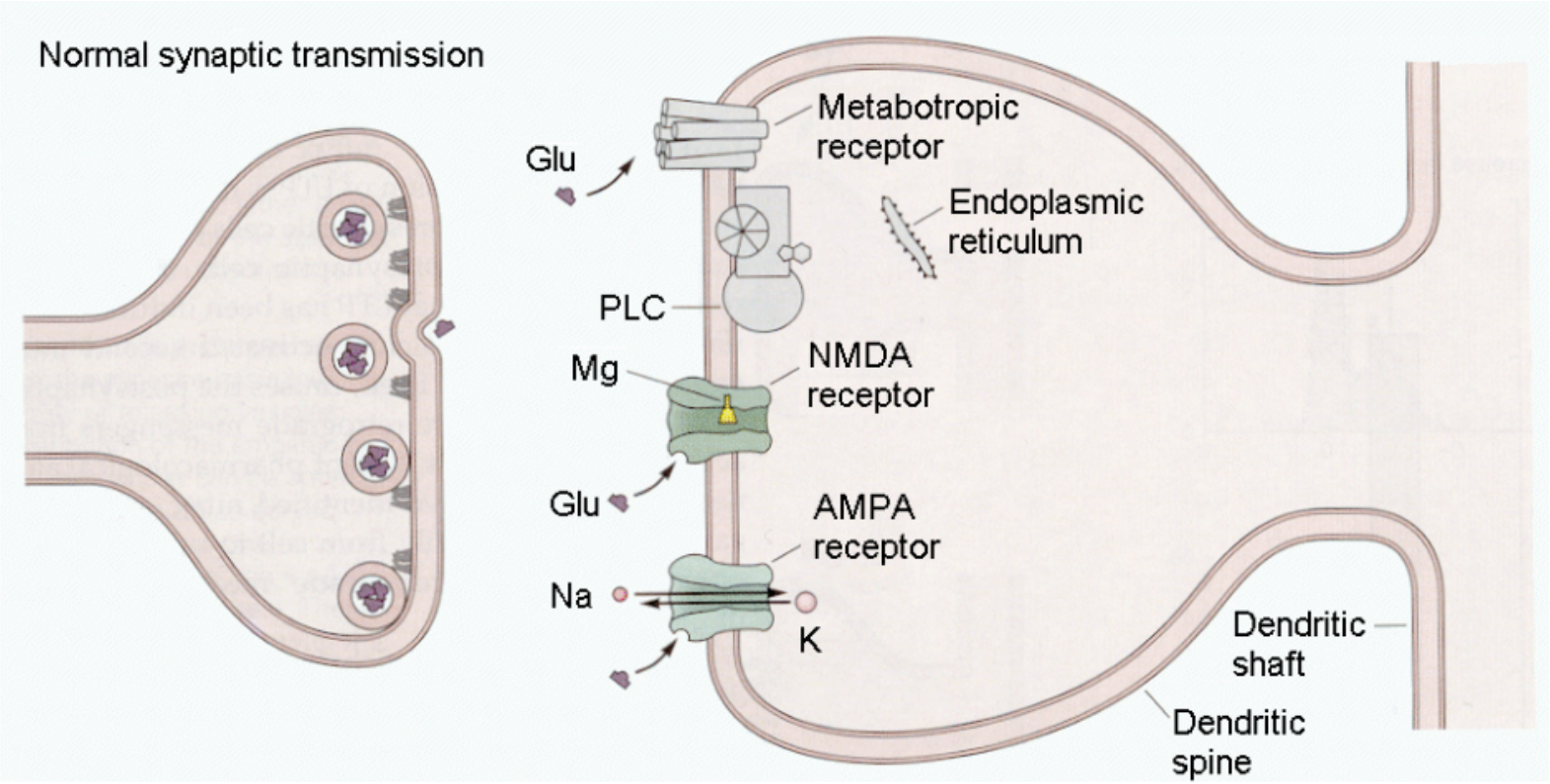
LTP and LTD

The NMDA-type receptors open ion channels **BUT** they are usually blocked by Mg^{++}, so they don't participate in EPSPs

NMDA receptors are "doubly-gated" ion channels ("associative")

A strong enough EPSP causes the Mg^{++} to pop out, allowing Ca++ (among other ions) into the dendrite

requires both NT and voltage (EPSP)



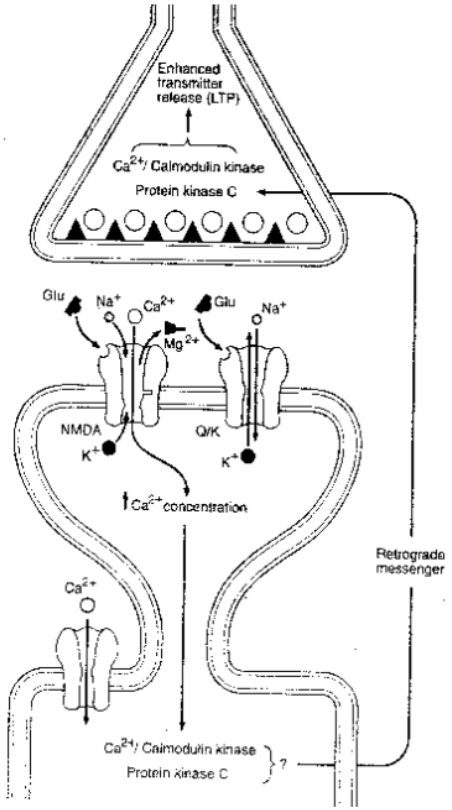
LONG-TERM POTENTIATION (LTP)

Molecular mechanisms most likely involve NMDA subtype of glutamate receptor

"doubly-gated" - transmitter AND depolarization (*associative*)

Ca++ entry ultimately activates CREB, causing changes in the nucleus leading to protein synthesis (long-term)

- To avoid "saturation", the opposing mechanism also exists (LTD)



LTP and LTD

Mammalian models of the biological basis of L/M

- *long term depression* (yin)
- *long term potentiation* (yang)

- Both follow the "Hebbian" rule - "neurons that fire together wire together":
  - increases in synaptic efficacy ("potentiation") occur when the firing (AP) of a presynaptic neuron repeatedly participates in the successful firing of the postsynaptic neuron ("in-phase")
  - the absence of a correlation between pre- and post- firing ("out-of-phase") results in decreased synaptic efficacy ("depression")
    - keeps system from "saturating"

LTP and LTD

physical shape of dendrite changes (morphological plasticity – protein synthesis)

dendritic spines may help to compartmentalize ion influx

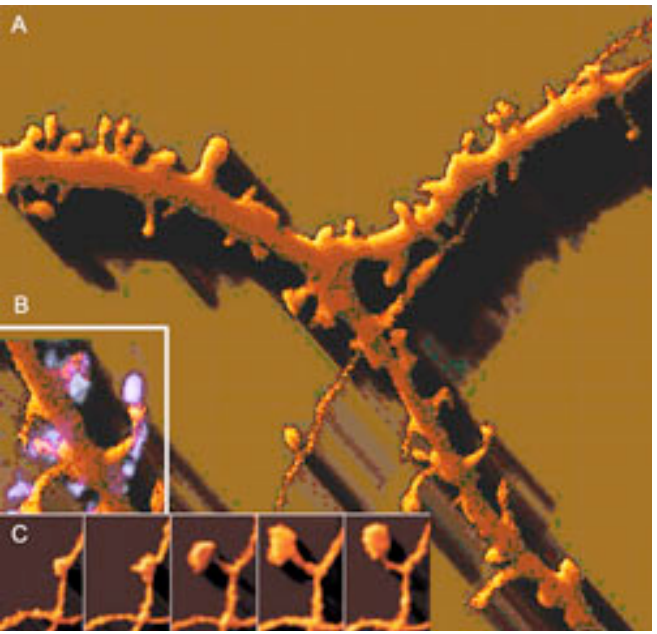
protecting the postsynaptic neuron from the buildup of toxic levels of Ca^{++} through NMDA channels

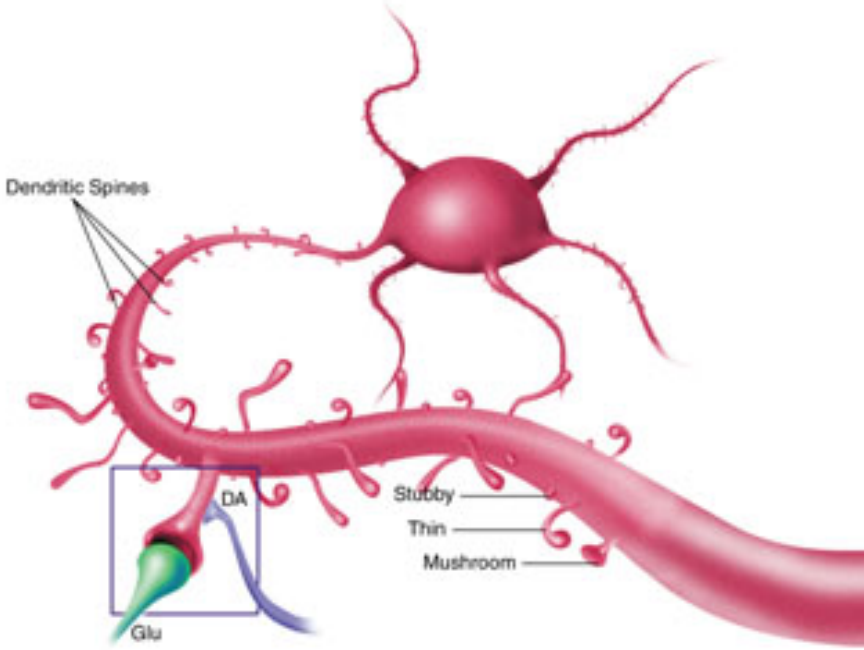
isolating synapses

increased numbers of receptors on dendrite

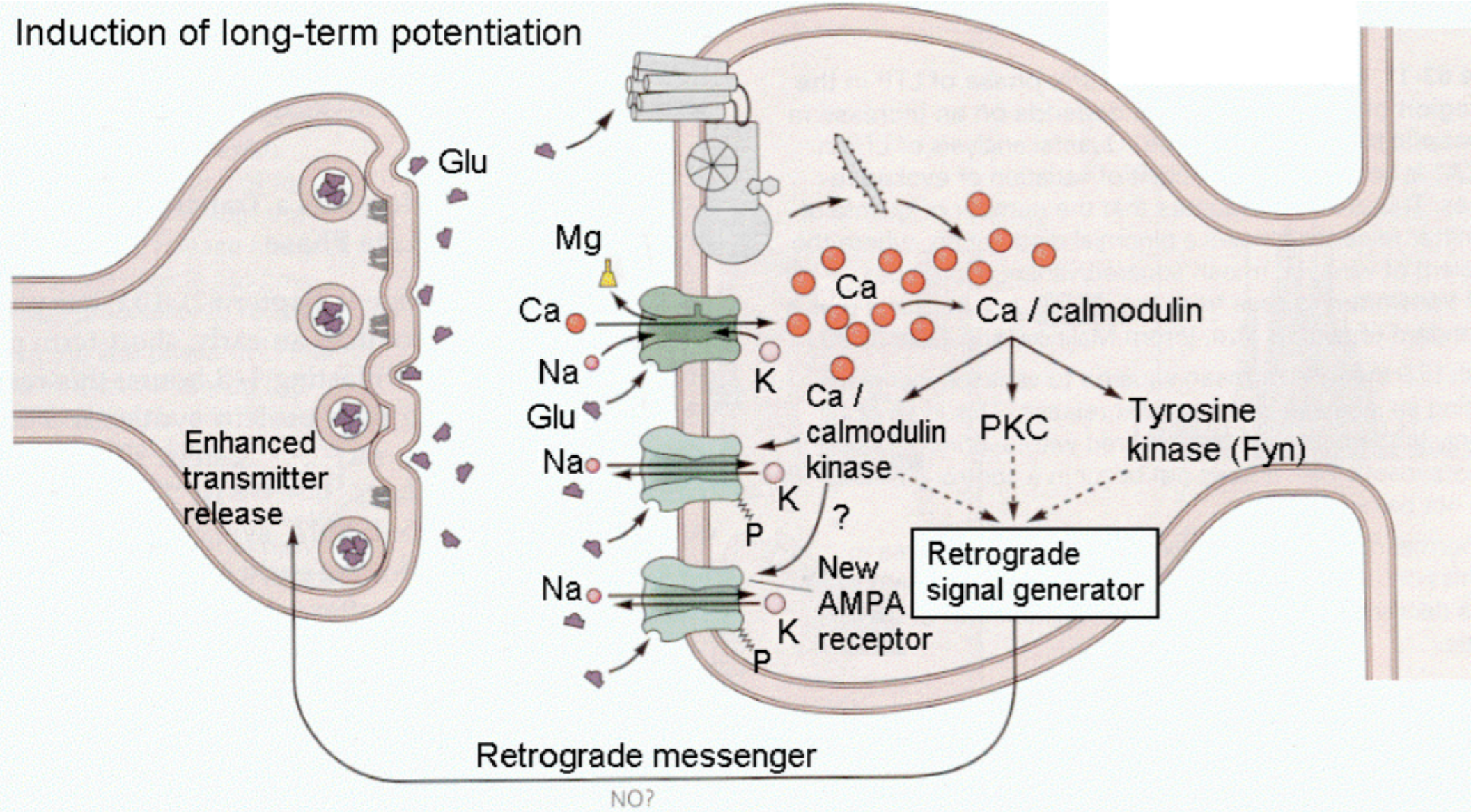
postsynaptic cell relays some info back across the synapse with *retrograde messengers,* letting *only* the presynaptic neurons *that had just fired* know that their firing resulted in an AP in the postsynaptic neuron

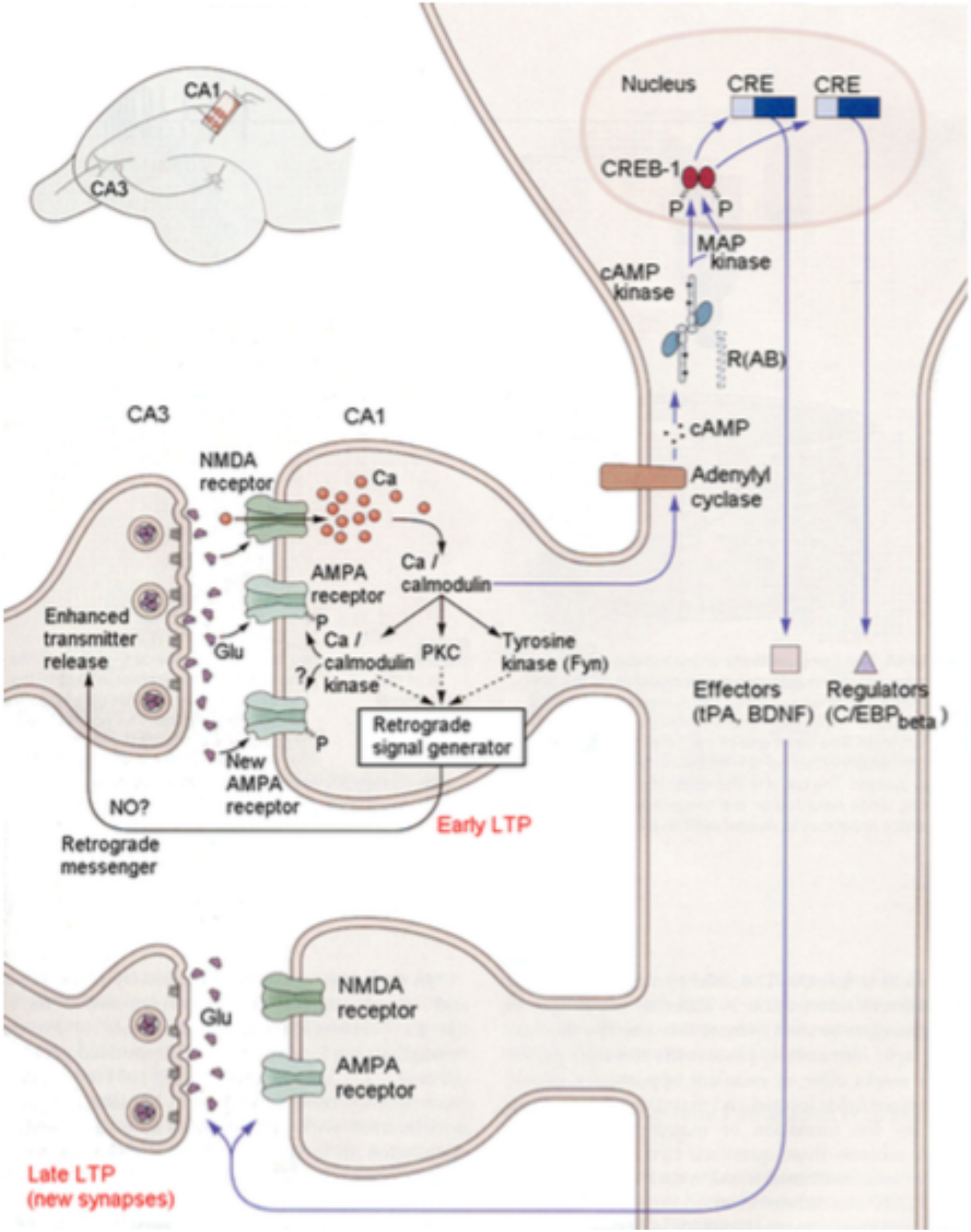
increases NT release, etc





LTP and LTD


Induction of long-term potentiation
Glu
Mg
Ca
Na
Glu
Na
Na
K
K
K
P
P
Ca
Ca / calmodulin
Ca / calmodulin kinase
PKC
Tyrosine kinase (Fyn)
?
New AMPA receptor
Retrograde signal generator
Enhanced transmitter release
Retrograde messenger
NO?


CA1
CA3
Nucleus
CRE
CRE
CREB-1
P
P
MAP kinase
cAMP kinase
R(AB)
cAMP
Adenylyl cyclase
CA3
CA1
NMDA receptor
Ca
Ca / calmodulin
AMPA receptor
P
Enhanced transmitter release
Glu
Ca / calmodulin kinase
?
PKC
Tyrosine kinase (Fyn)
Retrograde signal generator
P
New AMPA receptor
NO?
Retrograde messenger
Early LTP
Effectors (tPA, BDNF)
Regulators (C/EBP beta)
Glu
NMDA receptor
AMPA receptor
Late LTP
(new synapses)

LTP and LTD

Why is LTP a good model of LTM?

easy to induce in the hippocampus, a part of the brain associated with memory

LTP develops rapidly, even after 1 trial

LTP is long-lasting

specific - only synapses activated during stimulation are potentiated

other synapses (even on the same neuron) are not

associative - neurons that fire together wire together

when a presynaptic neuron fires (AP) AND the postsynaptic neuron also fires, the synaptic “strength” between those 2 neurons grows

LTP and LTD

LTP is NOT memory (artificial lab phenonenon)

studied at the synapse, but occurs over networks (infinite capacity for different patterns)

neuroplasticity between large cortical networks = learning / memory

Maybe LTP and "real learning" use similar biochemical mechanisms

magnitude of LTP elicited from an animal's hippocampus is correlated with that animal's learning ability

enriched environment produces morphological changes in synapses and neuronal reactivity

long-term changes in synaptic strength observed after conditioned learning – across species

blocking the NMDA receptor, which inhibits LTP, also makes learning difficult

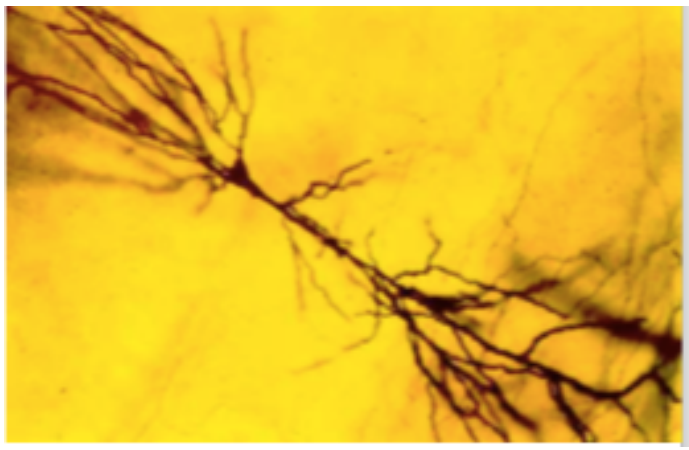
"knocking out" the various proteins building blocks of this mechanisms prevents new learning

The Hippocampus, NMDA Receptors, and Learning

Hippocampal CA1 *pyramidal neurons* (output cells) have been strongly associated with learning and memory and demonstrate high degrees of neuroplasticity

The high density of NMDA receptors in CA1 neurons may, to a large degree, explain both the function of the hippocampus in learning and memory and its ultrasensitivity to *excitotoxic* damage caused by oxygen deprivation, etc

extremely “plastic” nature also makes them particularly sensitive to the effects of over-excitation



Consolidation / Encoding

Any type of memory aid is a *mnemonic device.*

Involves reorganizing information into meaningful units and using cues to help in retrieval.

Examples: chunking, acronyms, dual coding (method of loci).

Schemas

Mental framework, or organized pattern of thoughts that are developed through experience.

Involved in the formation of expert knowledge.

Create a *perceptual set*, which involves the organization and interpretation of information in a certain way.

Easier to learn new info

Hippocampal Function Summary

Cortical neurons involved in the perceptual areas of a "memory" become more sensitive to the activity of others

if one neuron (or column of neurons) fires, the rest of the circuit does as well

Gene activation > protein synthesis makes it easier for neurons to "pass along" their excitability

new receptors, new ion channels, more neurotransmitter, etc

Remembering also involves protein synthesis

recreating a memory alters the connections based on current state of brain