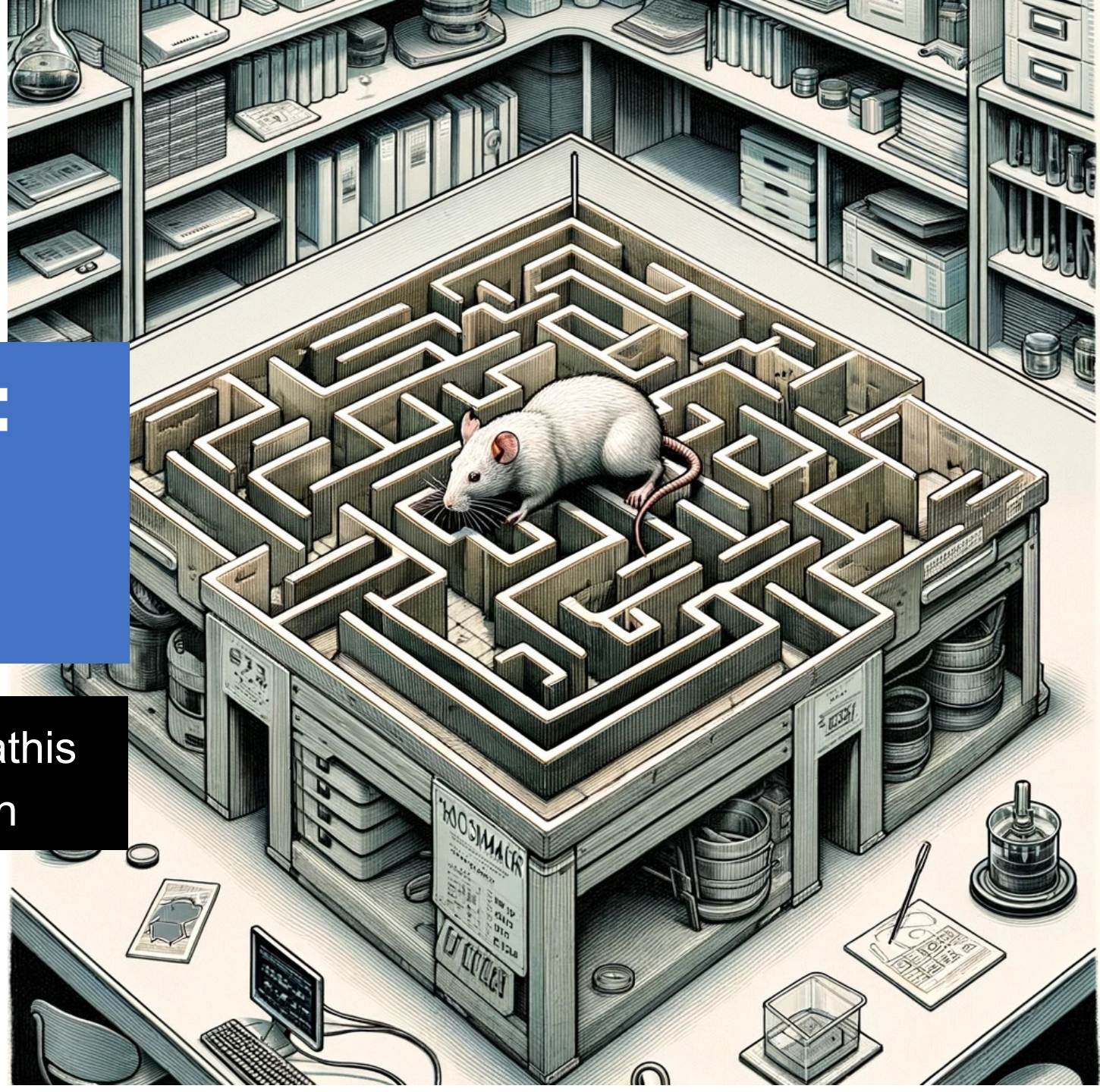


NX-311 Neuroscience: Memory & cognitive maps of space

Guest lecture: Alexander Mathis
alexander.mathis@epfl.ch

Credit:
References are provided per slide;
Many slides courtesy of M.W. Mathis

Lecture 10, Nov 24th 2025



Memory covers many phenomena

Looking up a phone number and then calling it

Recalling your first date

Knowing the capitol of Austria

Knowing how to carve on ice

Remembering the last item

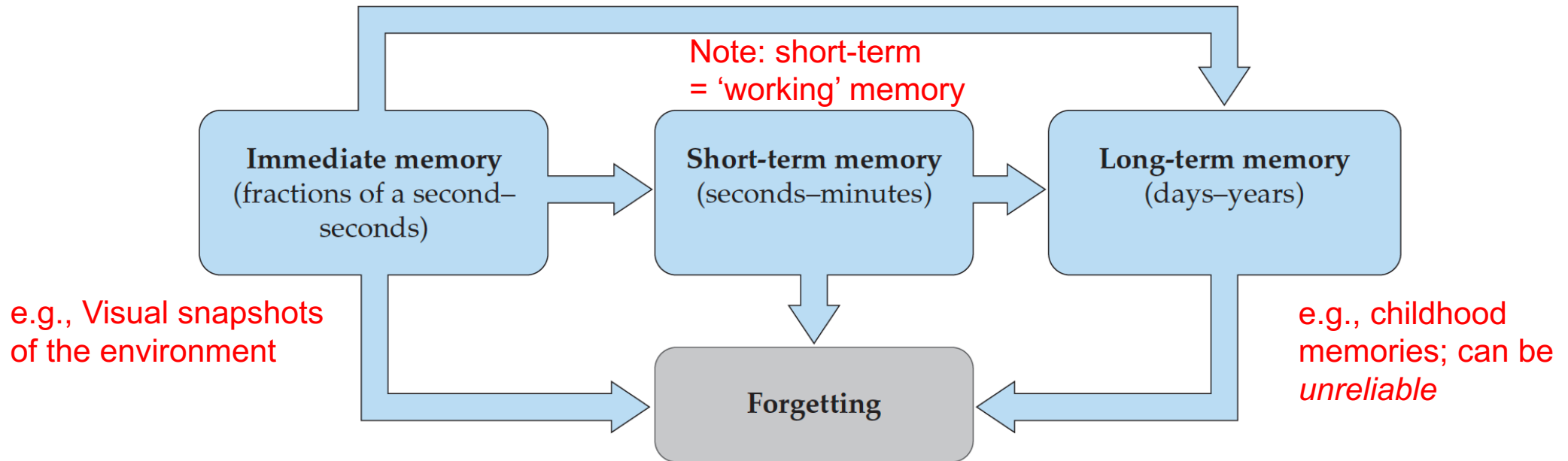
Knowing how to drink as a newborn

Food aversion after food poisoning

Memory

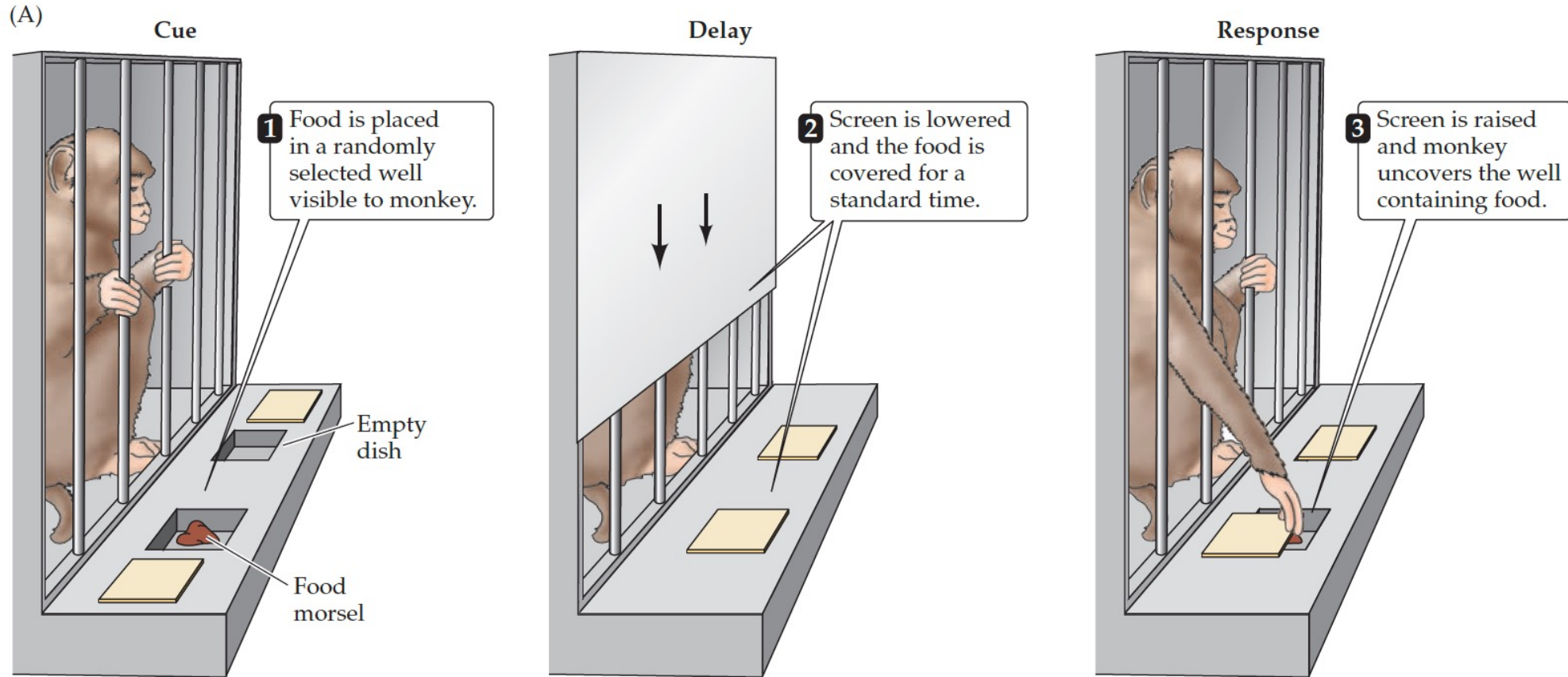
- Critically important capacity of all brains
- A way to store information from past experience and to retrieve it
- Can be either conscious or subconscious
- Brings past experiences, situations (a multisensory percept) back into consciousness
- In animals changes in behavior provide evidence of memory

Taxonomy: Memory is often classified by its **duration**



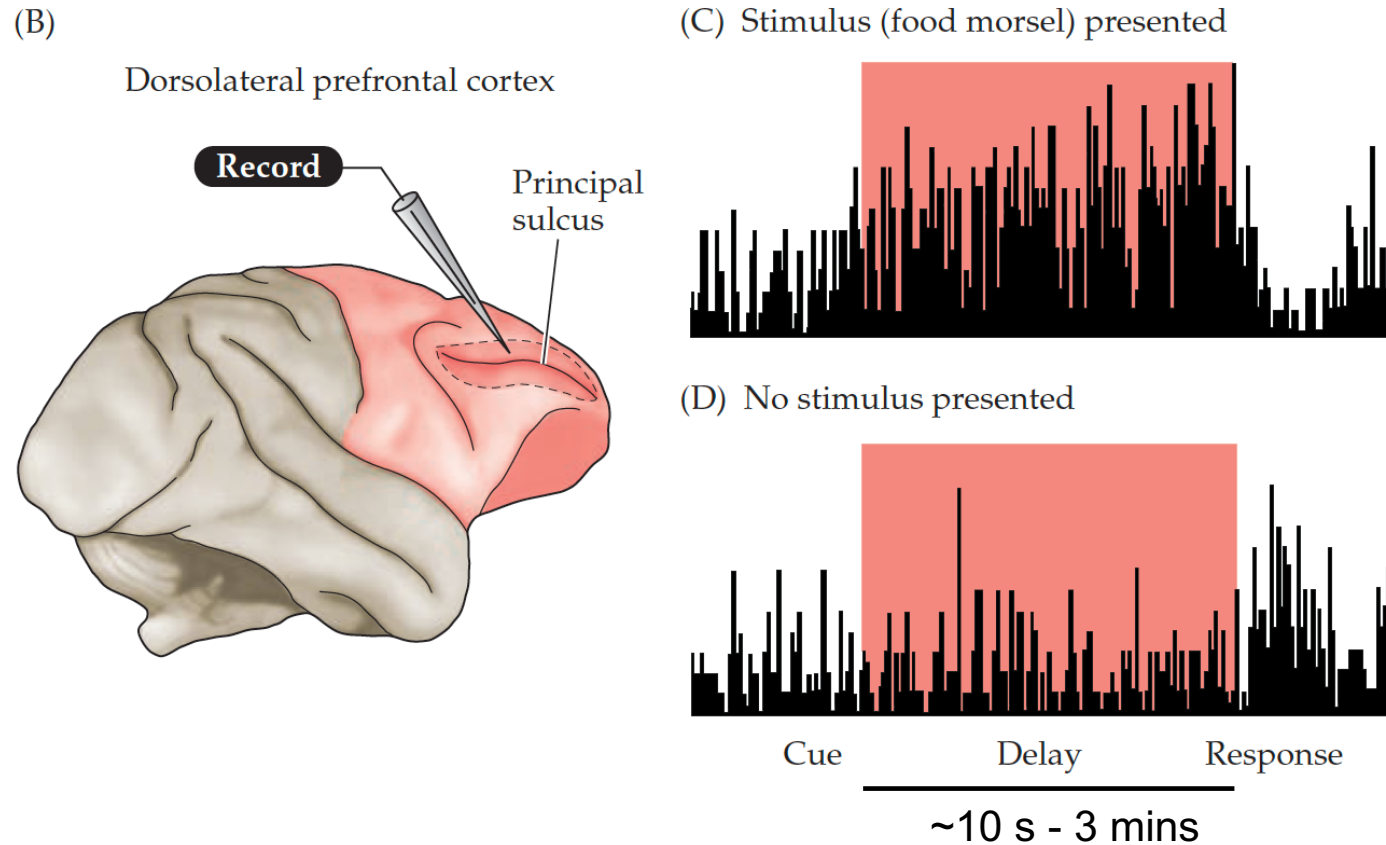
Short-term memory
(or 'working memory')

The "delayed response task" can be a test of **working memory**



- During a **delay period** (10 s - 3 mins), the monkey needs to 'keep in mind' where food is hidden
- Thus 'working memory' is a short-term memory important for organizing **future purposeful behavior**

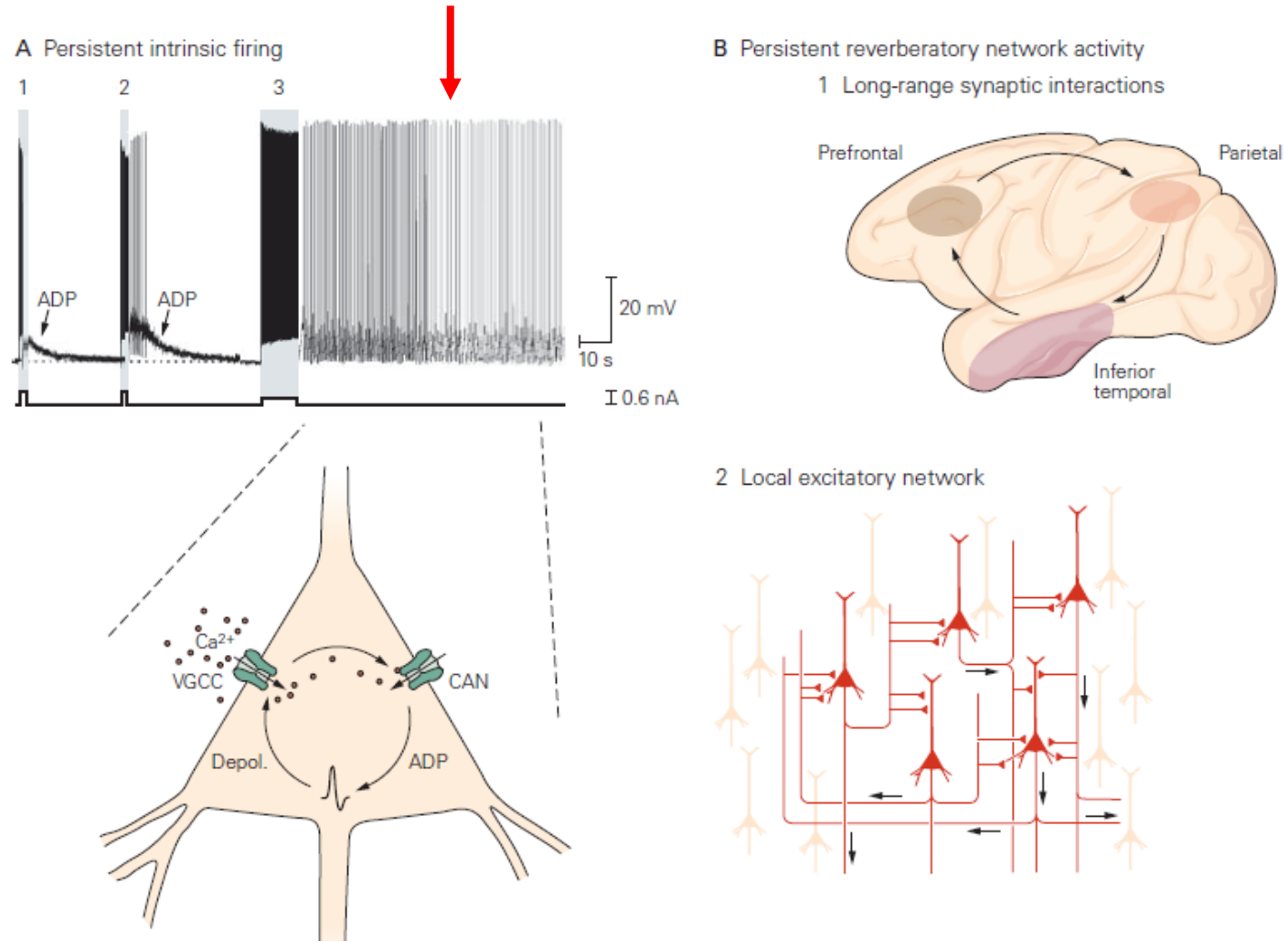
Neural activity in prefrontal cortex during the delayed response task



Note:

- Prefrontal cortex is part of Frontal association Cortex
- This neuron (and many others) are **active during the delay**
- This is NOT 'motor' activity: when the monkey responds activity goes down
- If NO food was hidden there would be no response (only when there is a **purpose** or goal)

Slice recordings of prefrontal neurons show **persistent firing**



Persistent action potential firing may arise due to

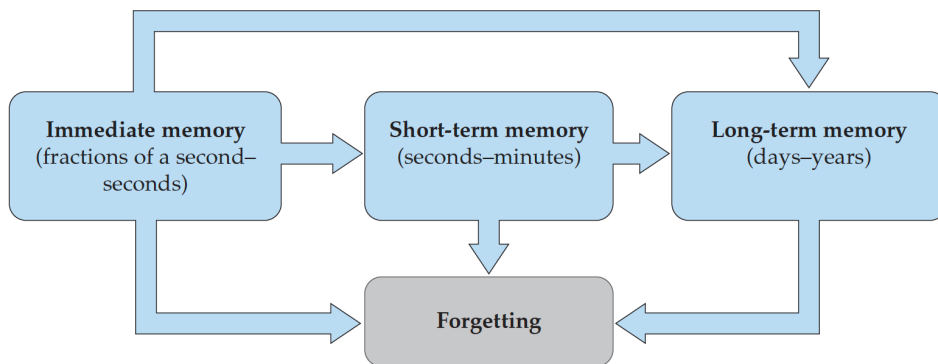
(1) the intrinsic electrical properties of prefrontal cortex neurons

(ADP – after depolarization; CAN = Ca²⁺-activated nonselective cation channels)

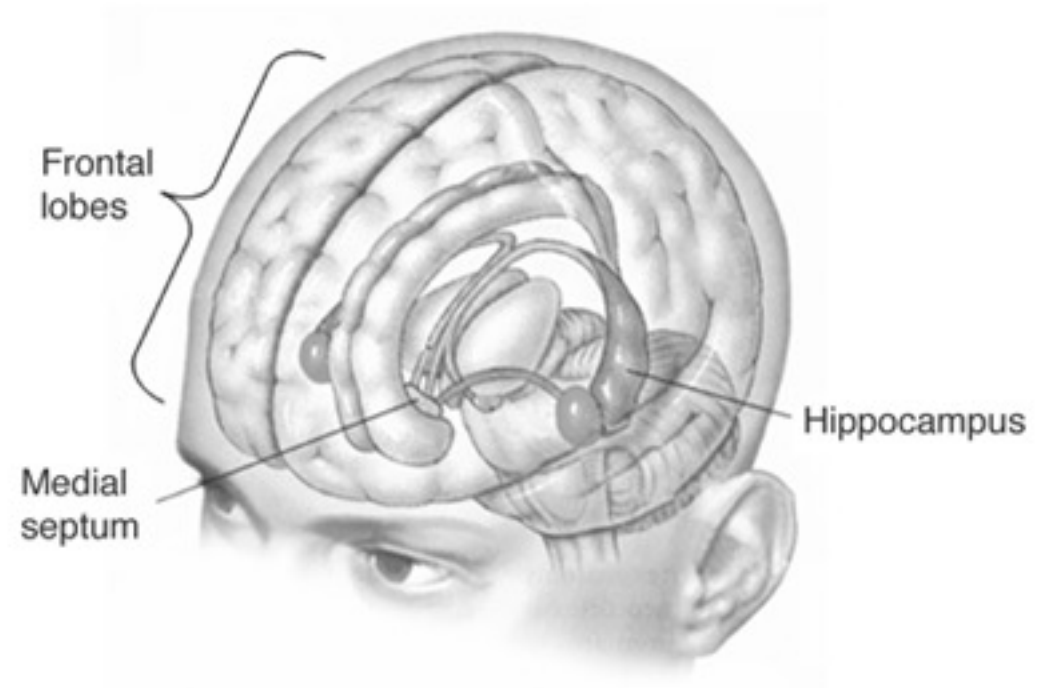
(2) **and/or** excitatory neural networks (long-range / local) leading to "reverberatory" activity

Long-term memory

Is there a functional taxonomy?



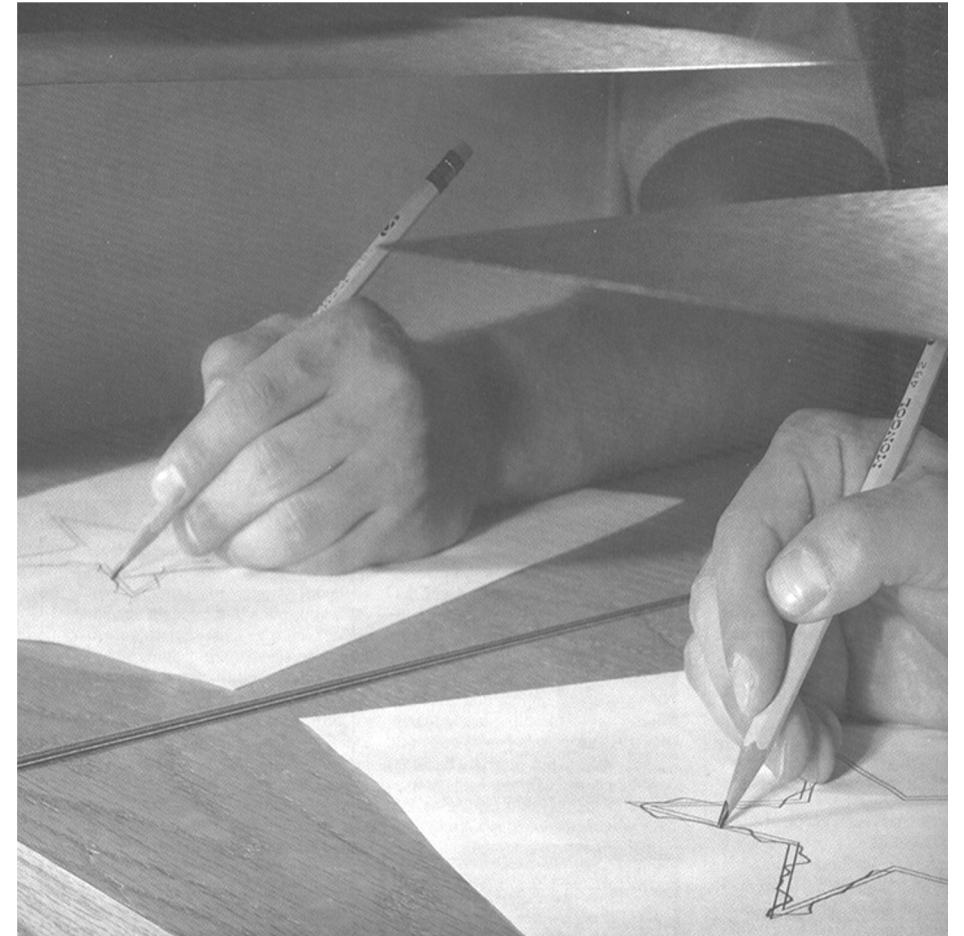
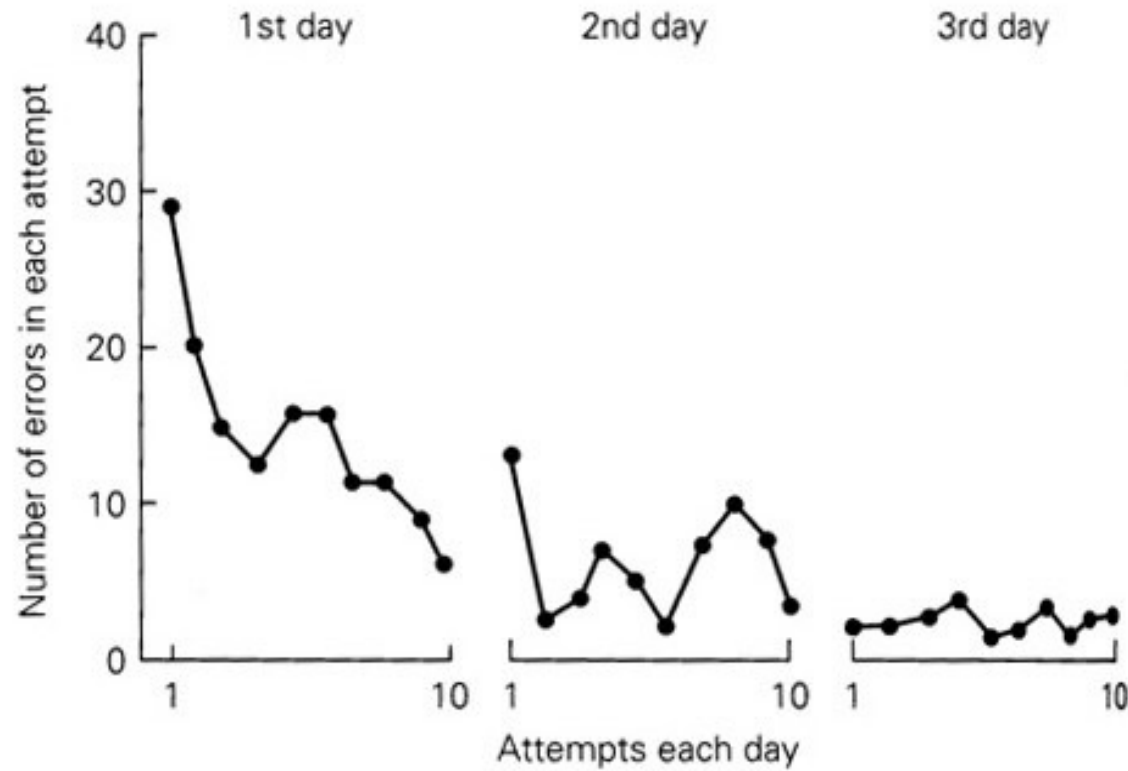
Patient H.M.





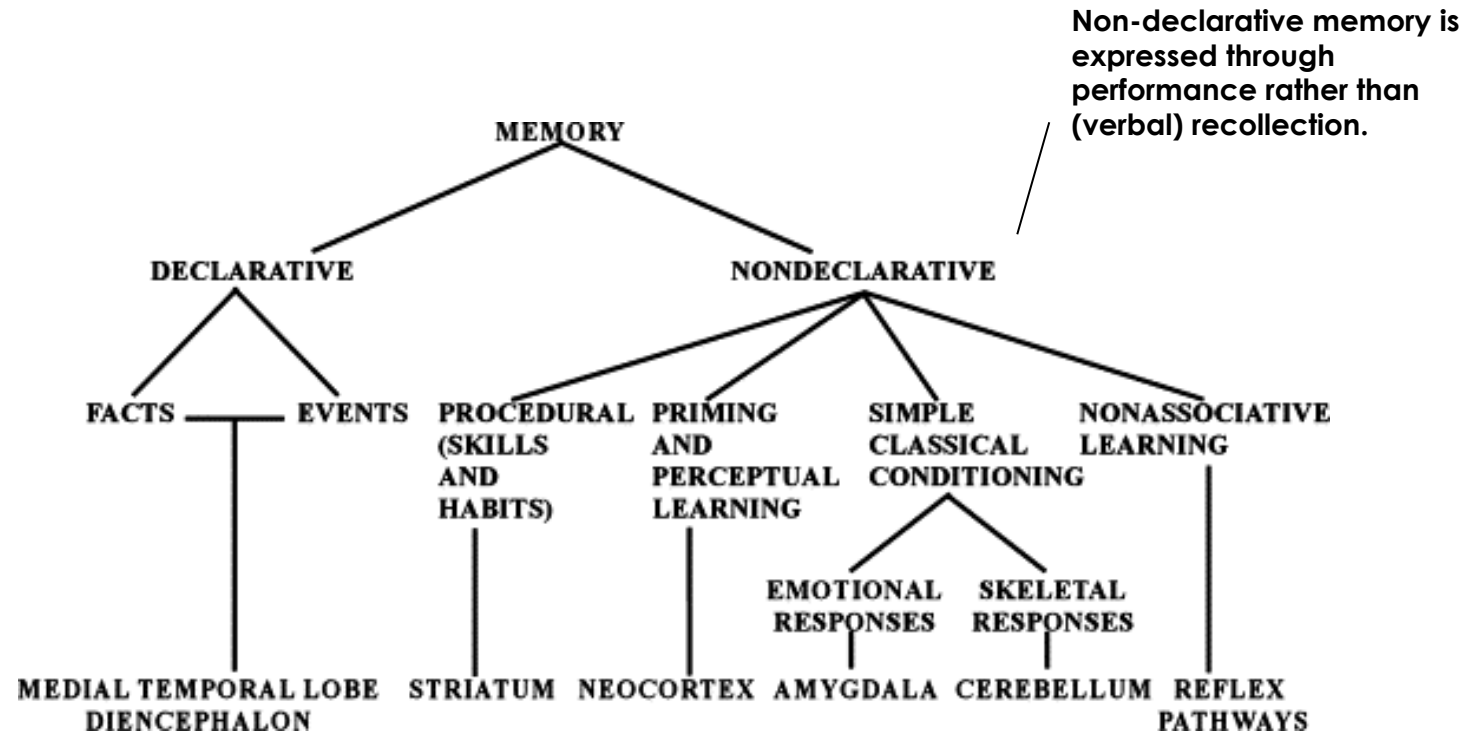
Milner 1962: mirror drawing could be learned over a period of days by the severely amnesic patient H.M. in the absence of any conscious memory of having practiced the task before

Milner (1962) Physiologie de l'hippocampe.

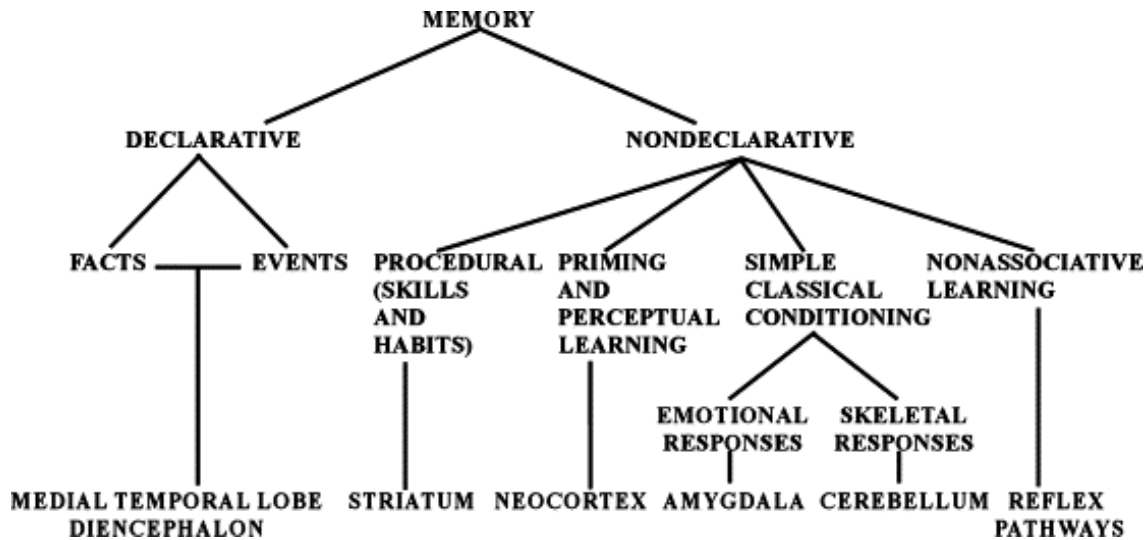


Kandel et al. Principles of Neural Science 2000 (62-2)

Memory systems of the brain

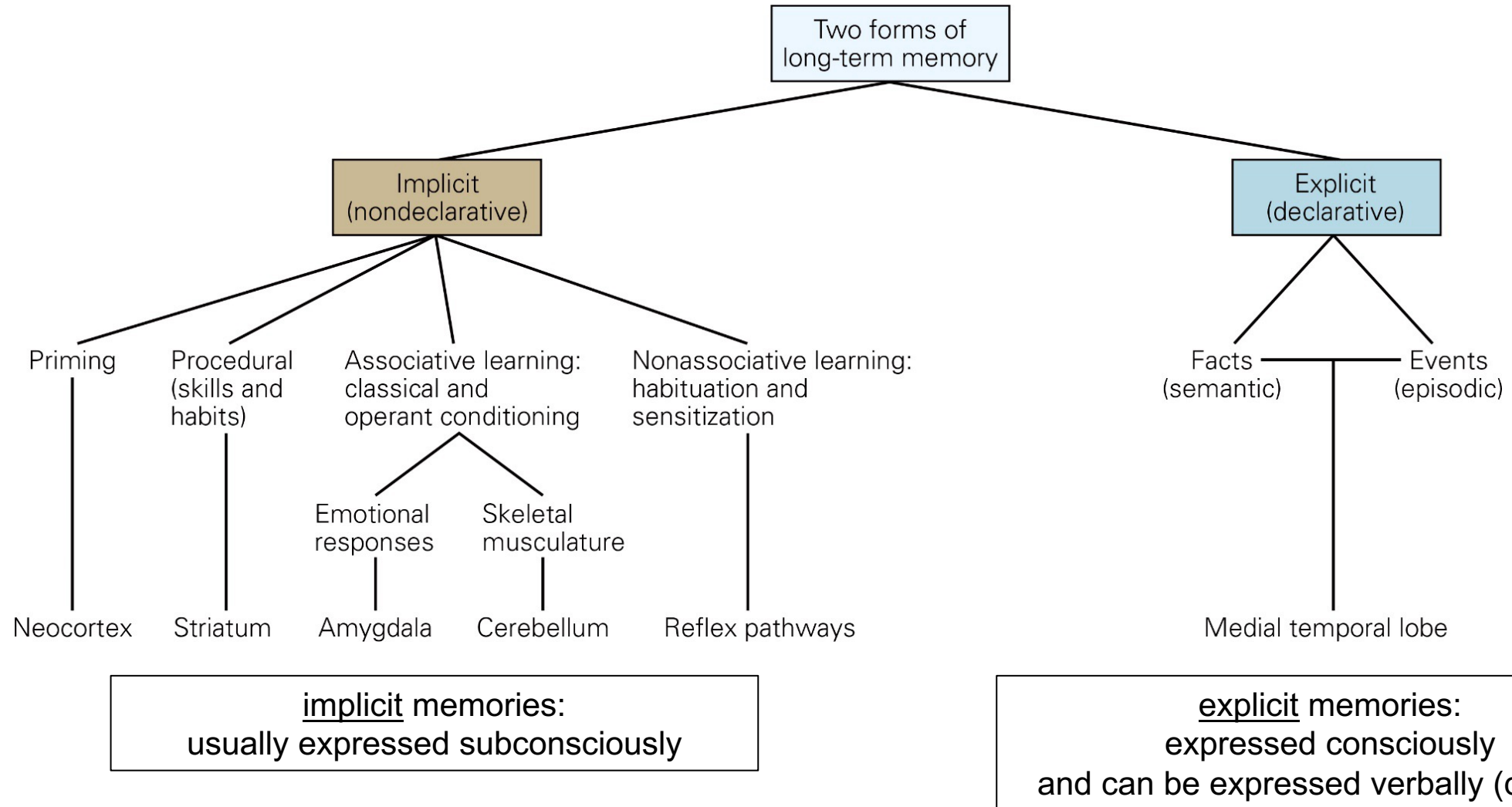


Back to our examples



- Working memory: Looking up a phone number and then calling it
- Declarative/events: Recalling your first date
- Declarative/facts: Knowing the capitol of Austria
- Skills: Knowing how to carve on ice
- Working memory: Remembering the last item
- Reflex/phylogenetic memory that is refined with experience: Knowing how to drink as a newborn
- Classical conditioning: Food aversion after food poisoning

Long-term memory is classified according to memory content and access to consciousness: **explicit** versus **implicit**

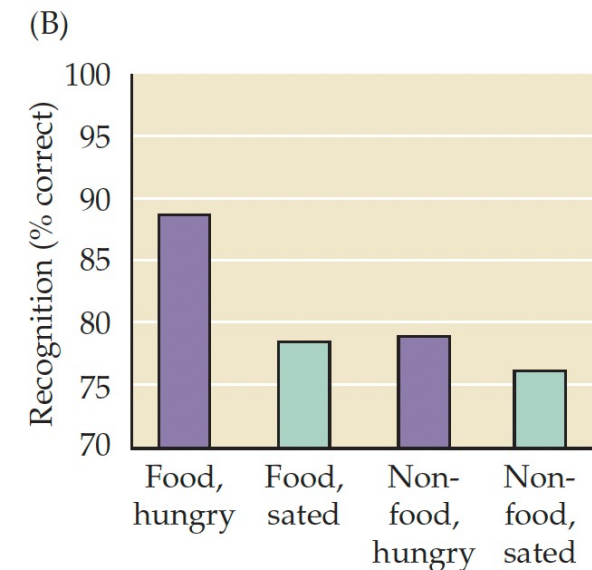
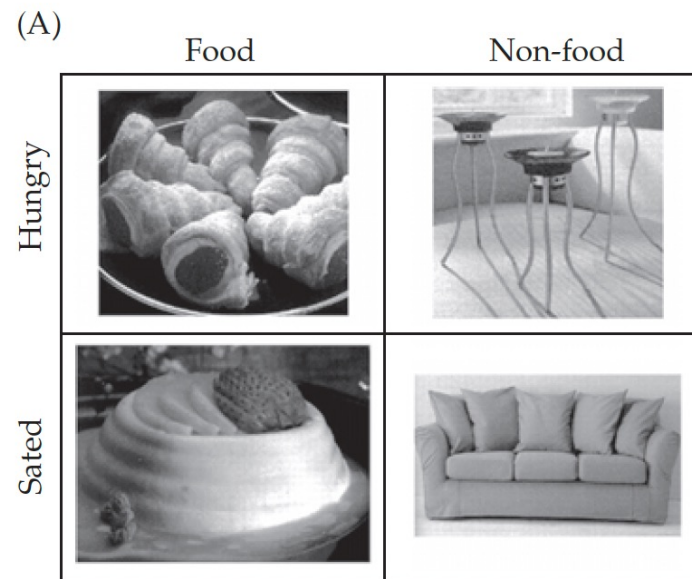


Memory performance
depends on motivation

Food pictures are better recognized when hungry

FIGURE 30.6 Motivated memory.

(A) Subjects studied a set of pictures of food and non-food (i.e., furniture) items and were later tested for their ability to discriminate the pictures they had seen from a new set of pictures. In one condition, subjects were made hungry by withholding food for several hours. (B) Memory for food items was significantly enhanced when subjects were hungry, but there was no significant effect of hunger on memory for non-food pictures. Results like these emphasize the importance of motivation and interest for memory performance. (From Morris and Dolan, 2001.)



Memory performance
depends on expertise &
context

Remember as many items as possible

elephant

bicycle

mountain

keyboard

symphony

notebook

telescope

butterfly

chocolate

umbrella

library

volcano

guitar

horizon

whisper

lantern

compass

meadow

crystal

thunder

Remember as many items as possible

xQ7mK2

pLw9Zt

fN4hRj

bYu8Gv

sD3nMx

kWr6Tp

cJ5qFz

vH2aBn

gT9xLm

jR4wKp

mF3dQv

wK8hTj

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tL6zBm

yS2vGk

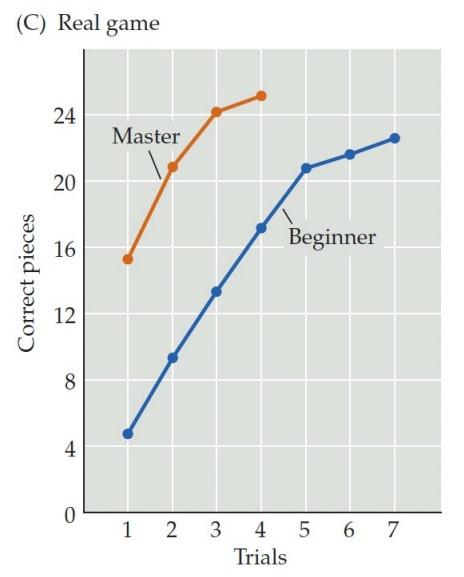
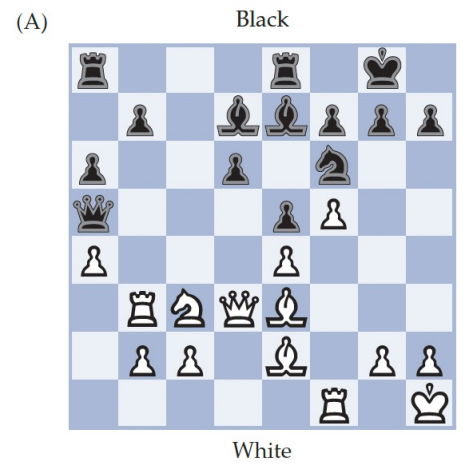
hD9cFp

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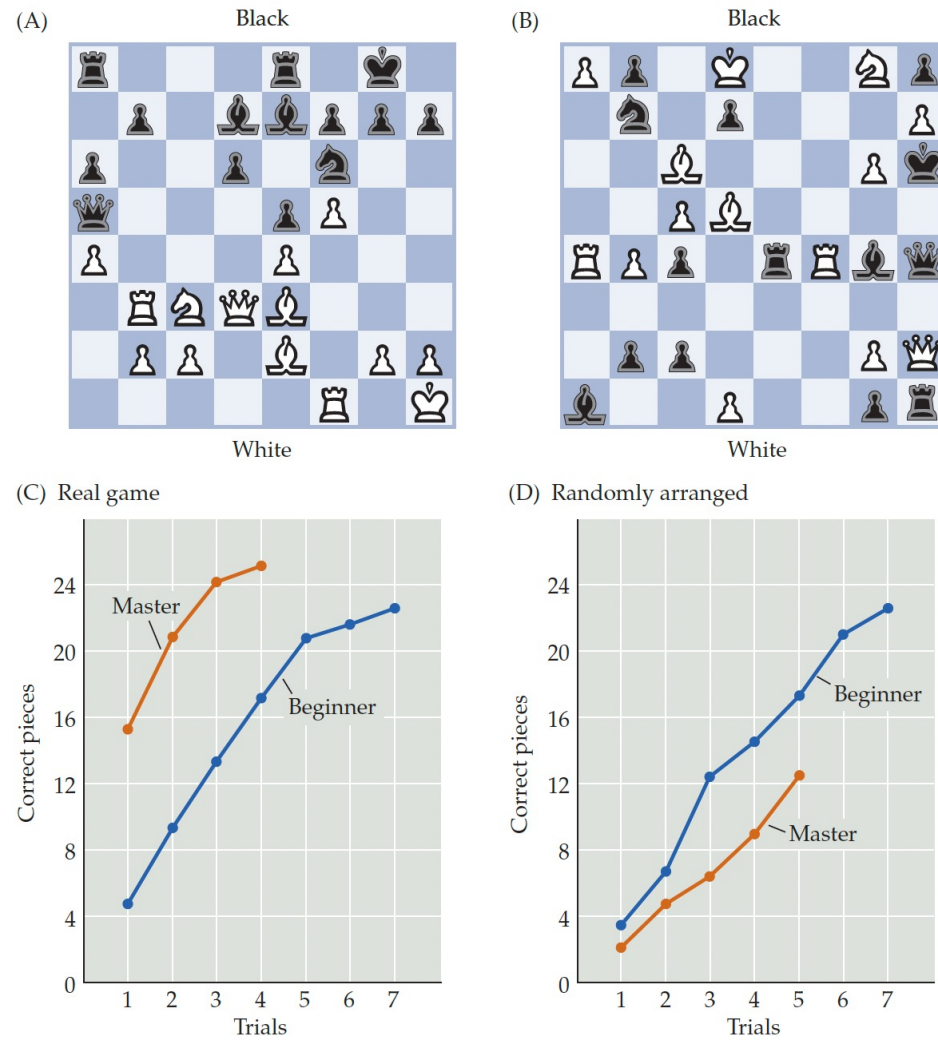
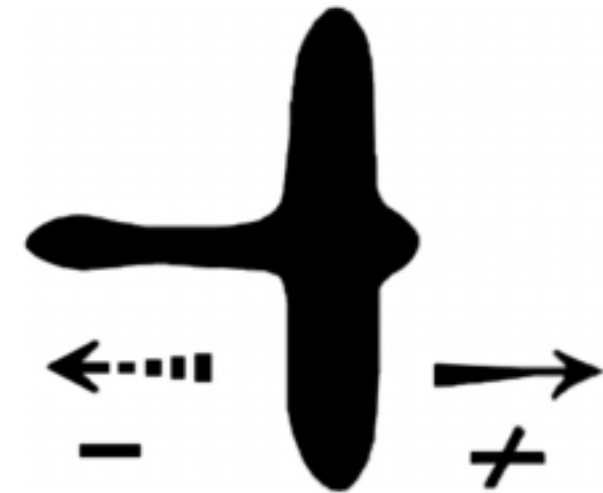
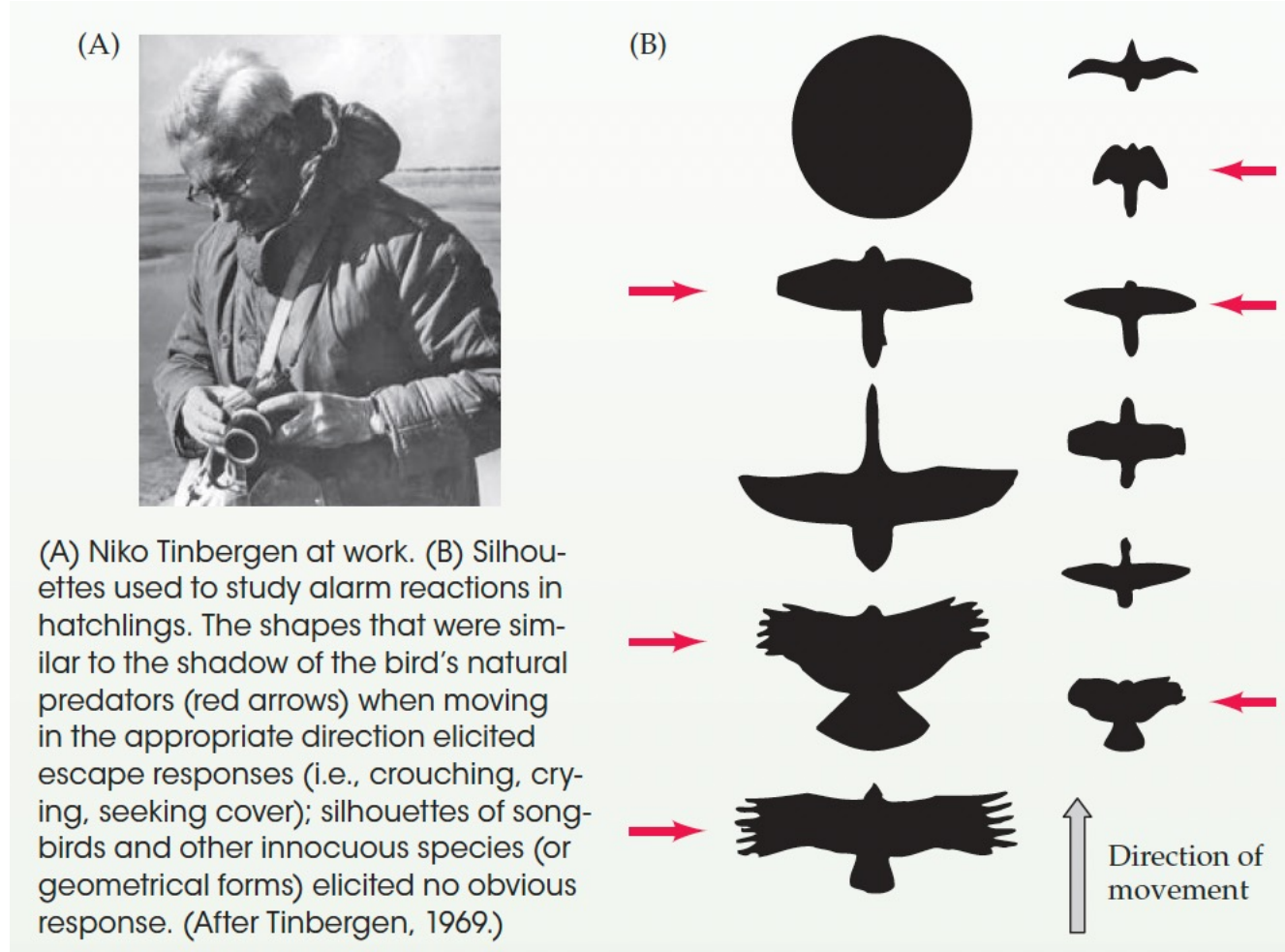


FIGURE 30.5 Retention of briefly presented information depends on past experience, context, and perceived importance. (A) Board position after white's 21st move in game 10 of the 1985 World Chess Championship between A. Karpov (white) and G. Kasparov (black). (B) A random arrangement of the same 28 pieces. (C,D) After briefly viewing the board from the real game, master players reconstruct the positions of the pieces with much greater efficiency than beginning players. With a randomly arranged board, however, beginners perform as well as or better than accomplished players. (After Chase and Simon, 1973.)

Even longer-term...

Phylogenetic
memory

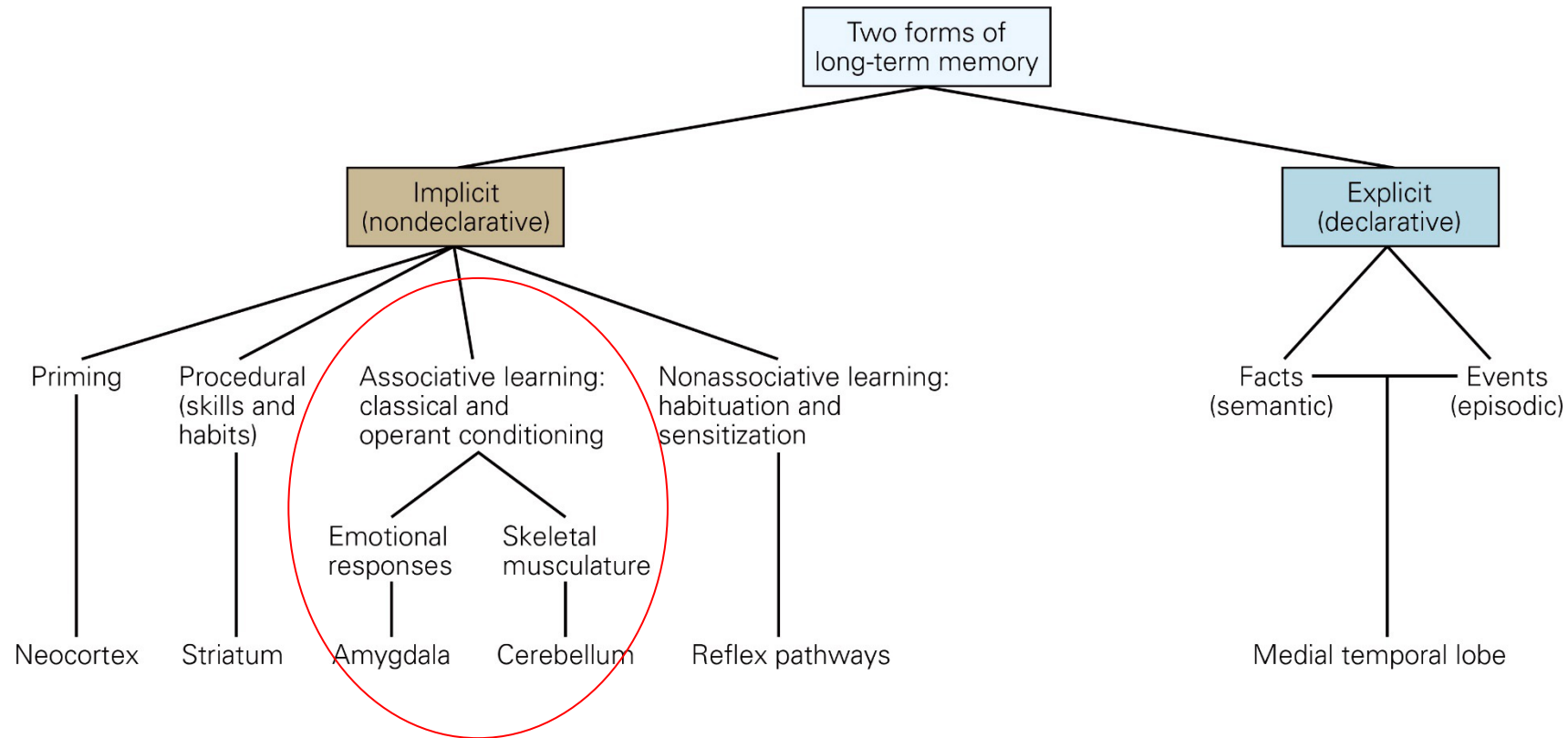
Innate memory



Hawk/goose effect, Wikipedia

Classical and operant conditioning

Classical conditioning: an implicit (non-declarative) long-term memory



implicit memories:
usually expressed subconsciously

explicit memories:
expressed consciously
and can be expressed verbally (declare)

Definitions

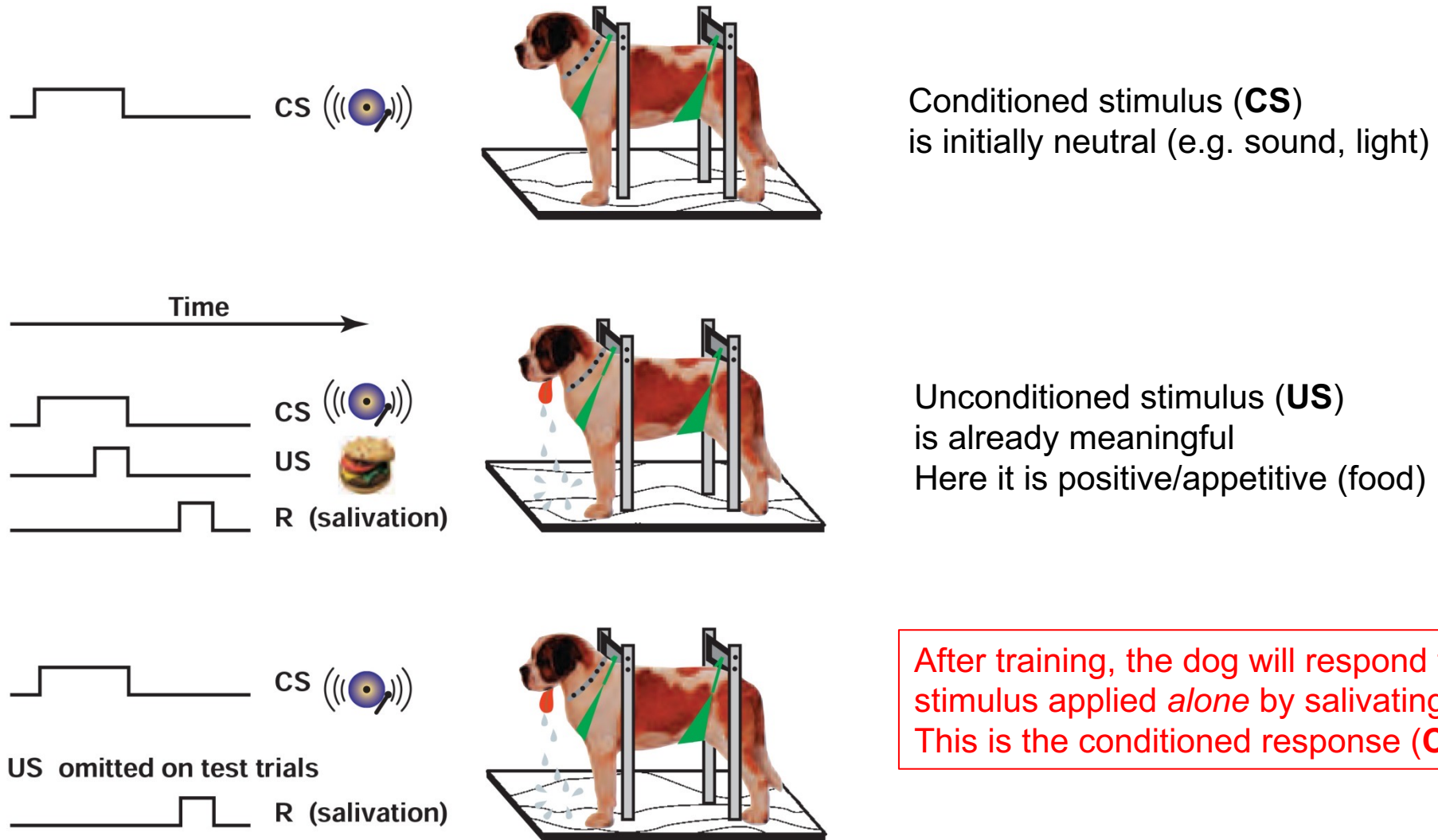
Classical (Pavlovian) conditioning:

- Drive animals to produce a **novel response** to a previously neutral stimulus
- A **previously "neutral" stimulus** (the **conditioned stimulus CS**)
 - gains control over e.g. a defensive / or appetitive reaction
 - when temporally paired with a strong **reinforcing (unconditioned) stimulus (US)**
 - such as **pain ('aversive')** or **food ('appetitive')**

Operant conditioning (instrumental learning):

- The outcome of the experiment depends on the behavior of the animal
- A "reinforcer" is **only** given upon a specific behavior of the animal
e.g., a (hungry) rat learns to press one of two possible buttons to receive a food reward

The classical "Pavlov's dog" conditioning experiment



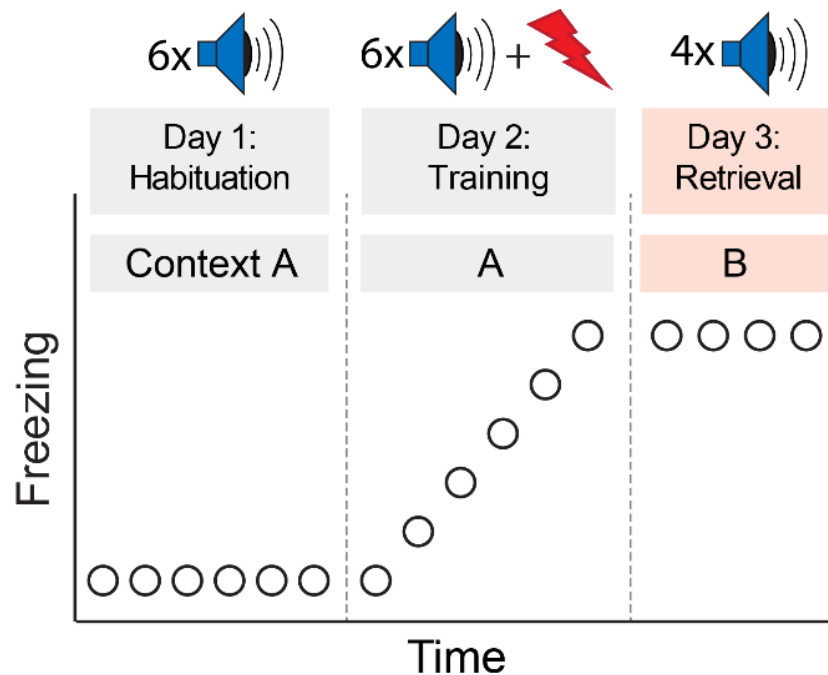
In this **appetitive** conditioning an *implicit, or non-declarative* memory is formed

Aversive conditioning / "fear learning"



CS: An innocuous sensory stimulus
(tone of 7 kHz, 80 dB, 0.1 s, 30x)

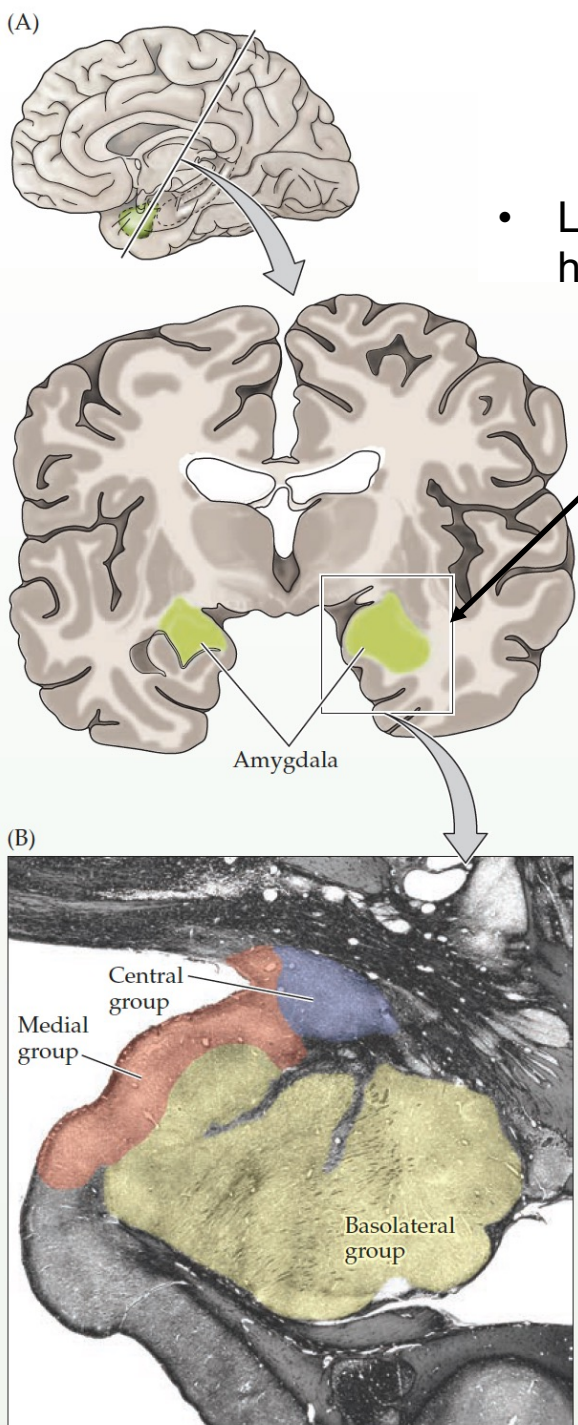
US: A mild electric footshock
Activates nociceptors on the feet and probably
other low-threshold mechanoreceptors



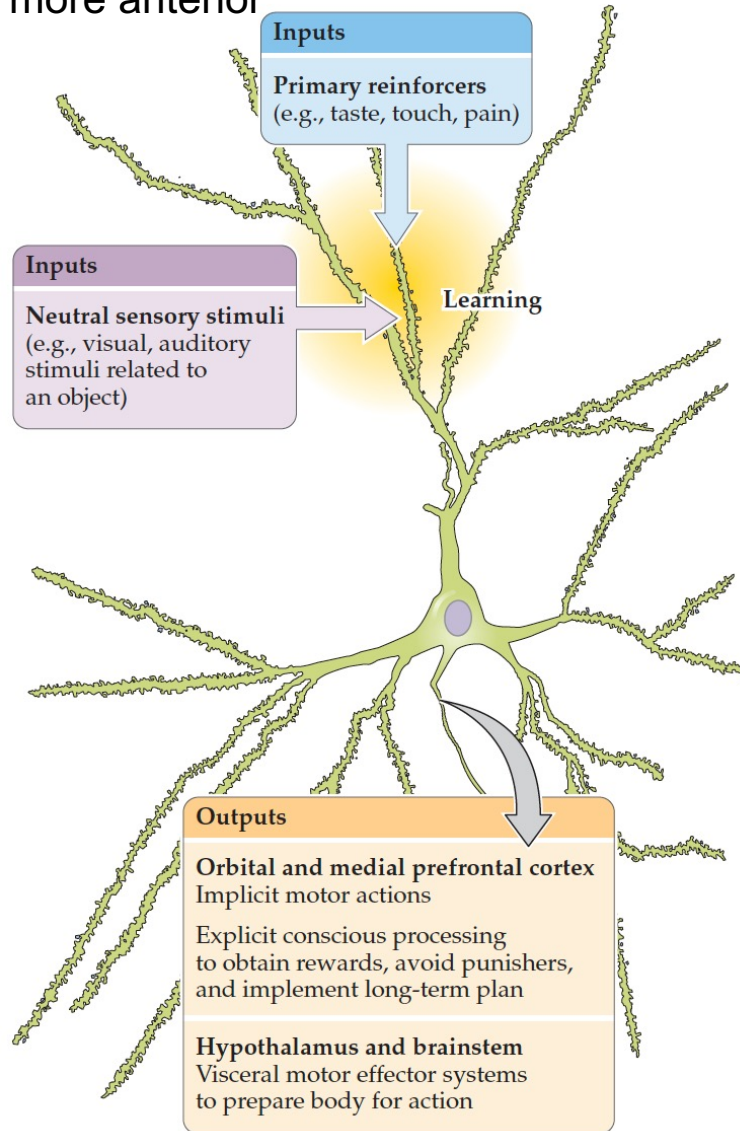
CR: freezing (behavioral immobility)
An evolutionary useful response in
the presence of a not clearly present threat

In this **aversive** conditioning again
an *implicit, or non-declarative* memory is formed

The amygdala is implicated in fear learning

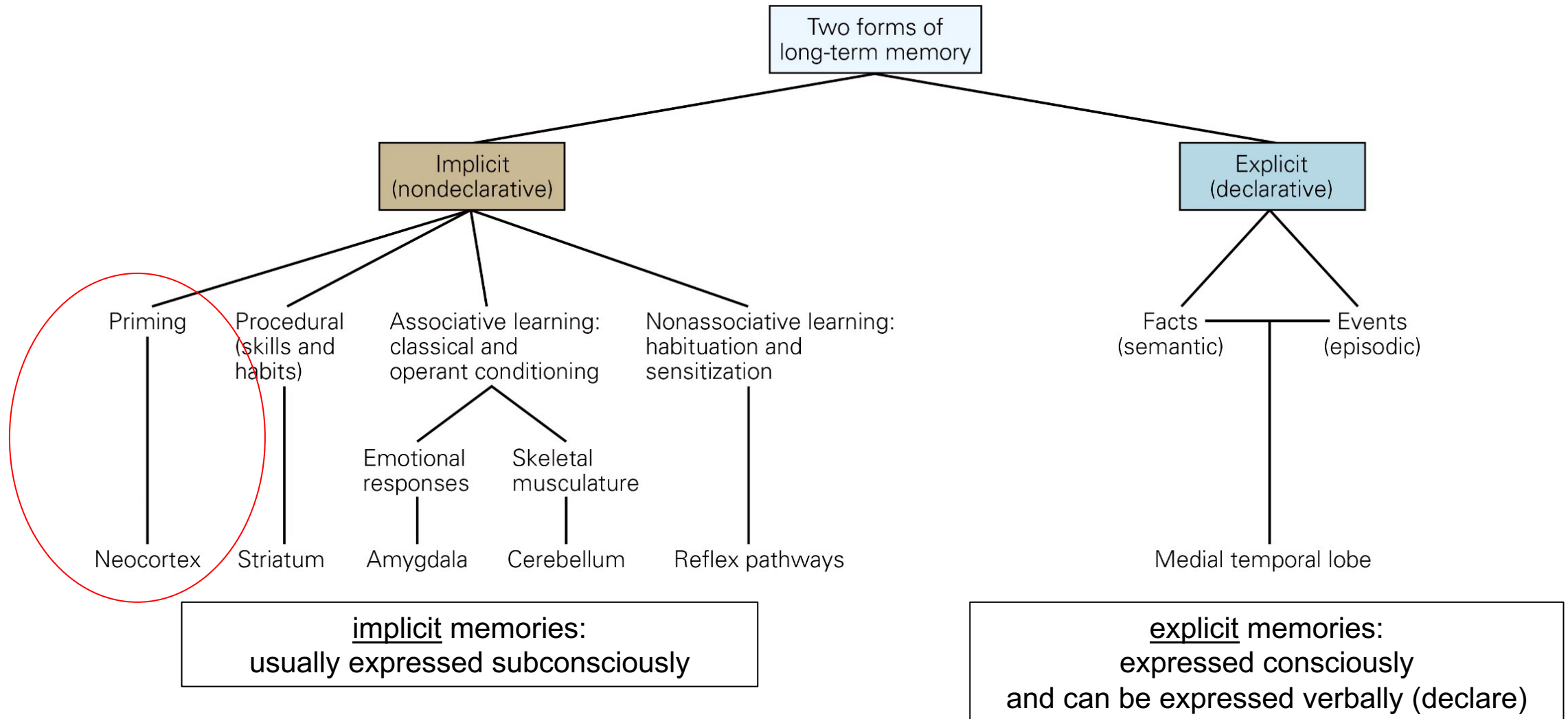


- Located deep inside the **temporal lobe**, (like the hippocampus but more anterior)



Priming

Long-term memory is classified according to memory content and access to consciousness: **explicit** versus **implicit**



Priming: change in processing due to previous encounter

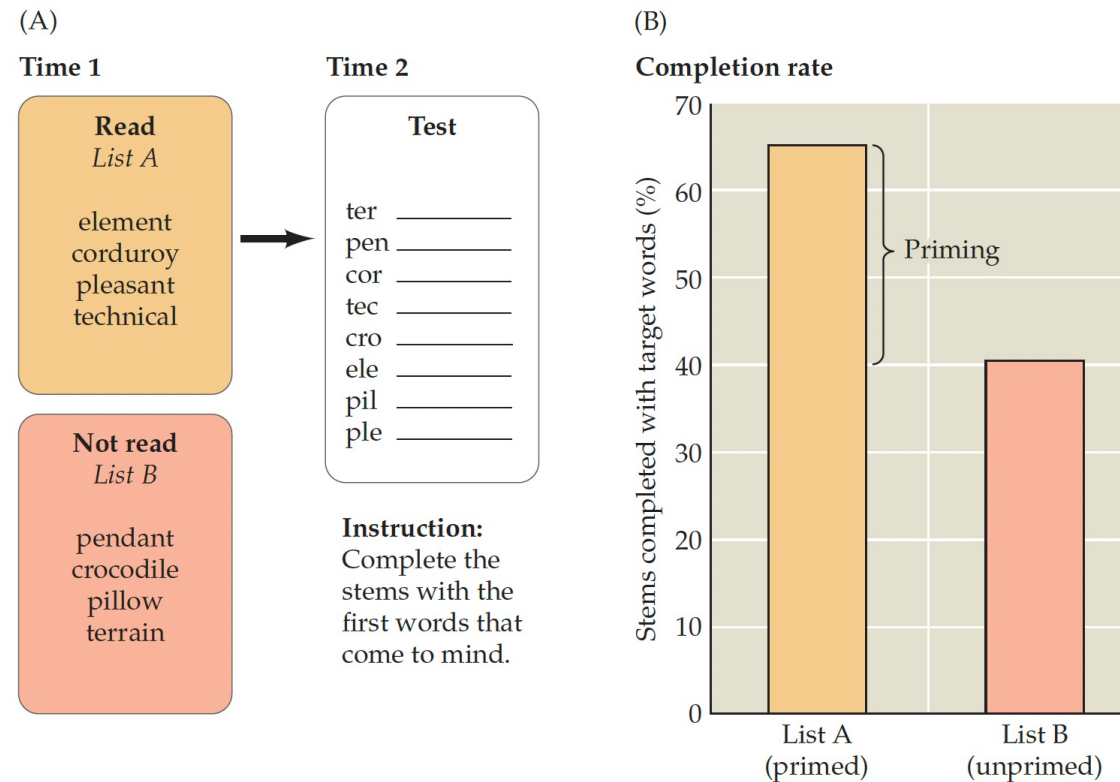
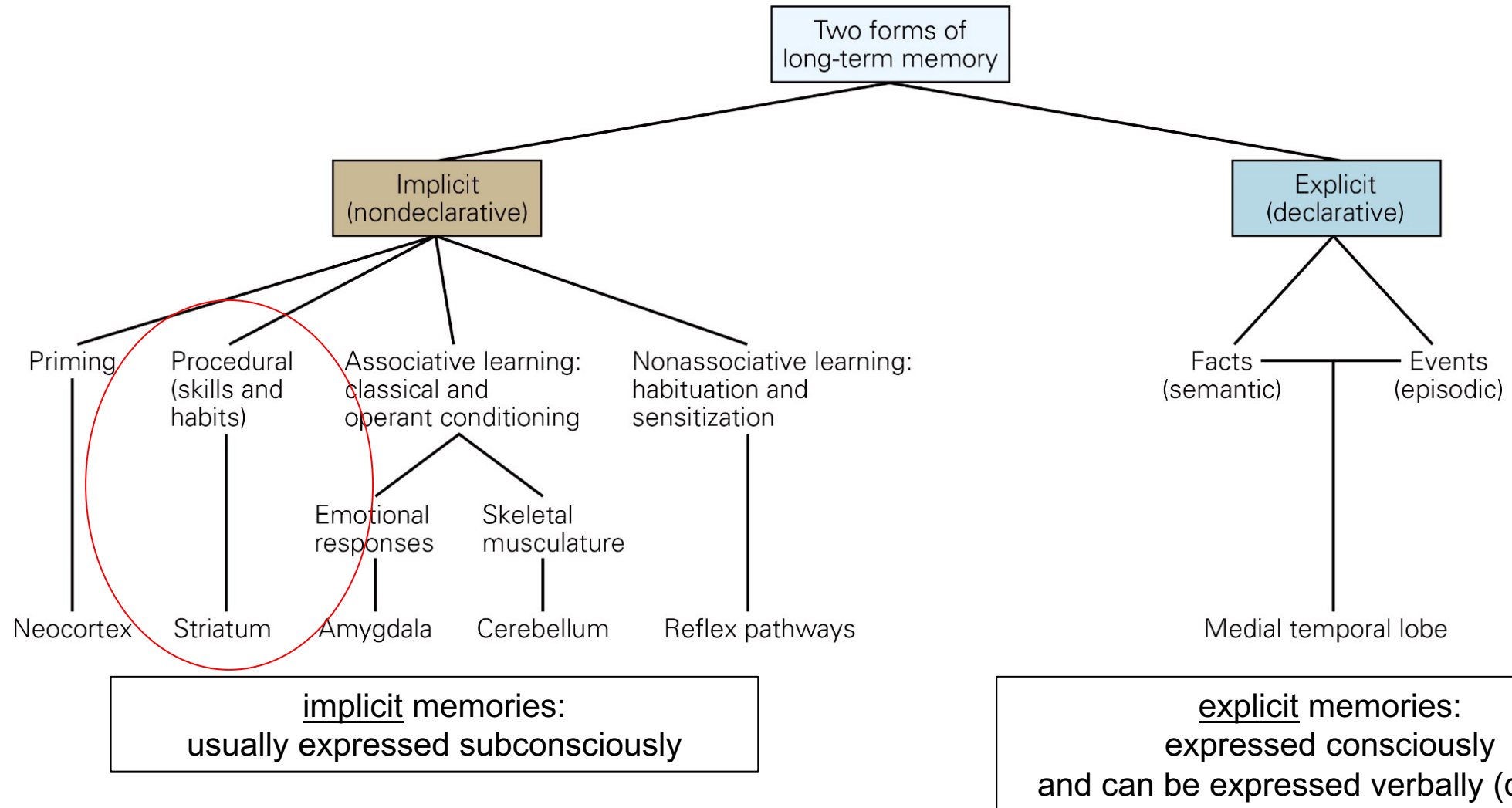


FIGURE 30.3 Priming. (A) In a commonly used test, the subject is presented at time 1 with a list of words to study (list A) and is later tested using a word-stem completion task (time 2). The stems could also be completed from list B, which comprises words the subject did not see during the initial session. (B) Subjects typically complete the stems with about 25% more studied than unstudied words; this percentage represents the effect of priming.

Procedural learning

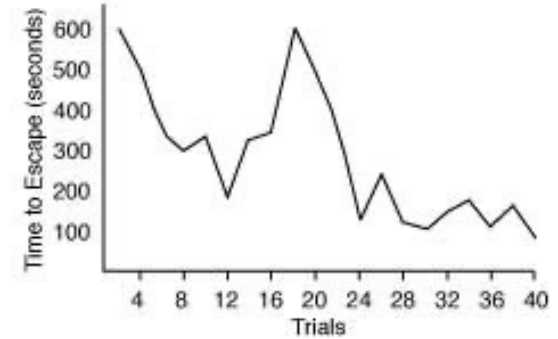
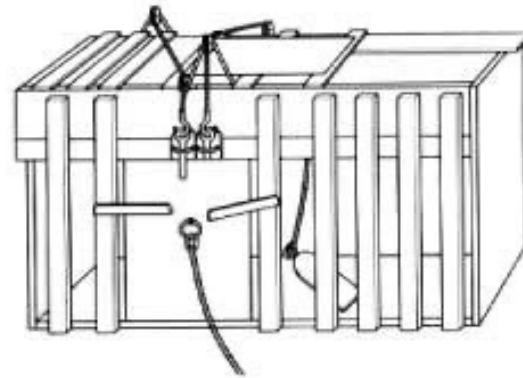
Long-term memory is classified according to memory content and access to consciousness: **explicit** versus **implicit**



Thorndike's escaping experiment

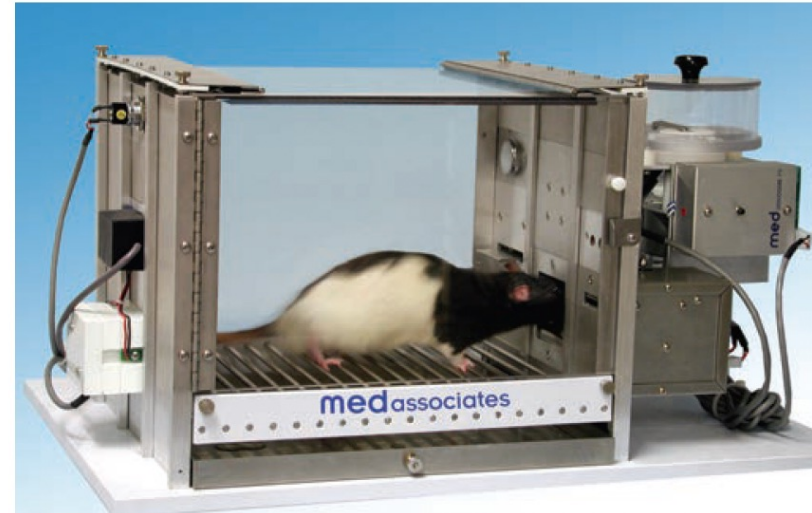


Edward Thorndike



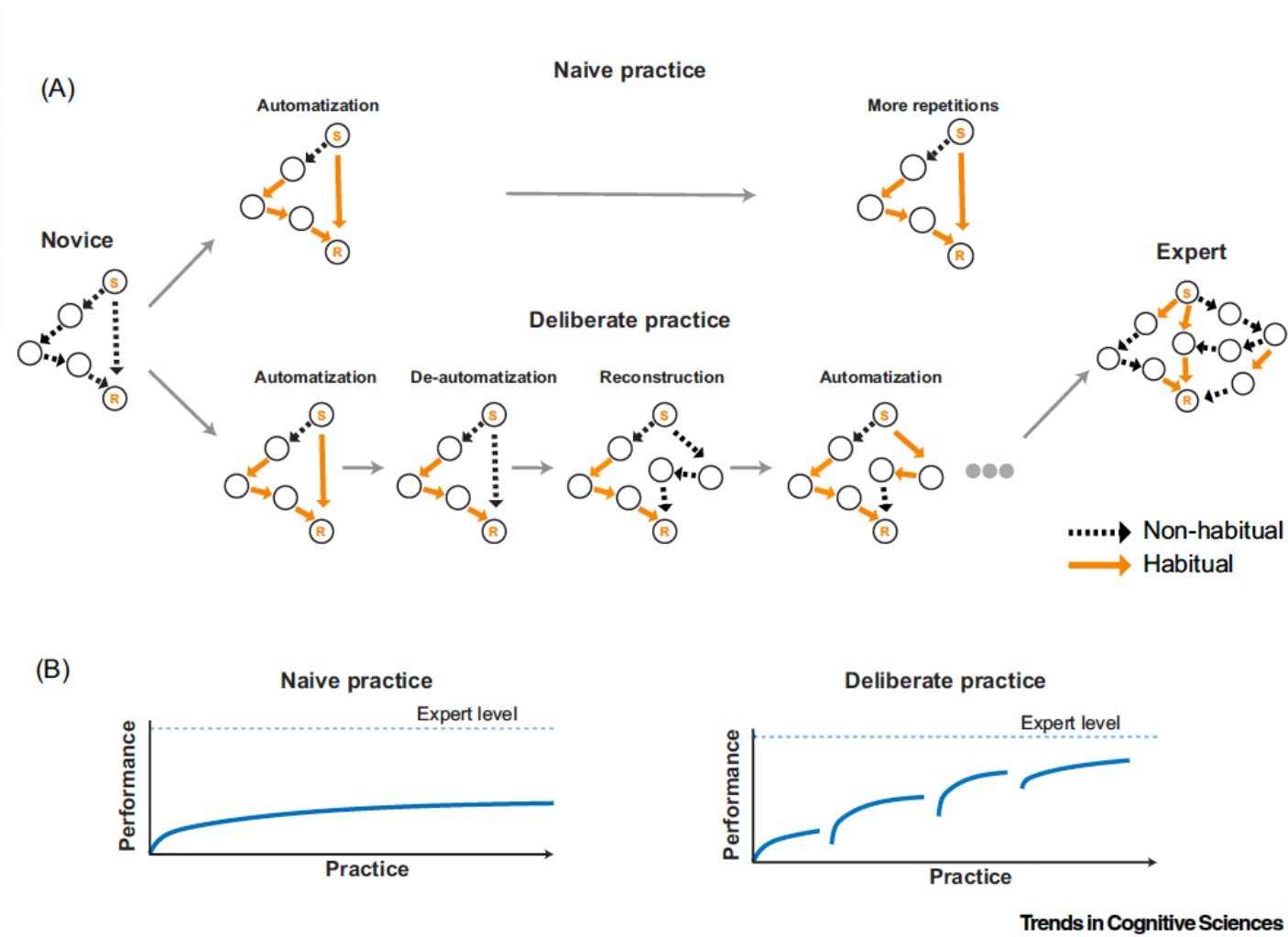
Adapted from Domjan, 1993 (modified from Thorndike, 1898 [left] and Imada & Imada, 1983 [right])

Skinner box

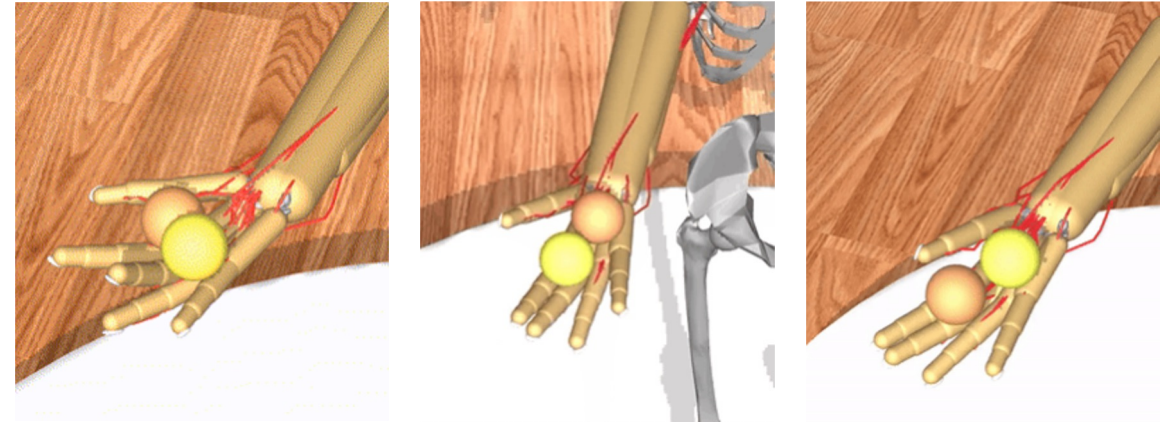
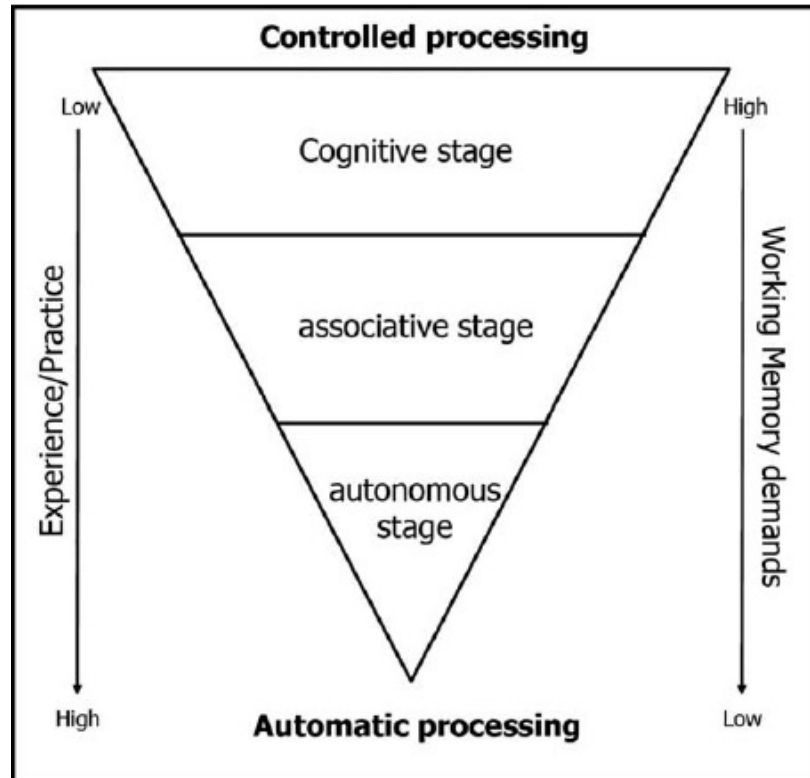


Purves, Figure 30.7

Skill learning



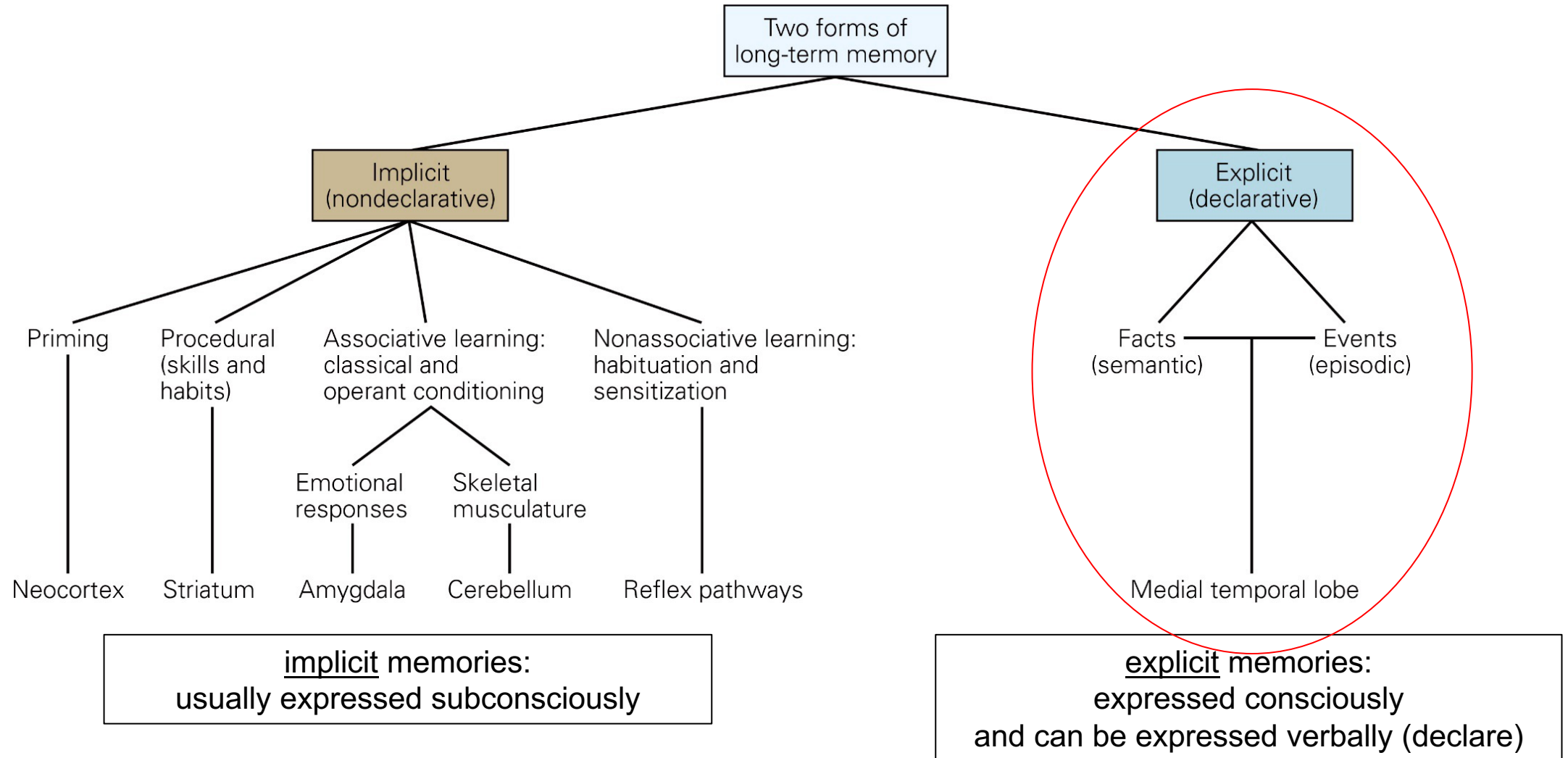
Fitts Posner's 1967 model of skill learning



Chiappa, A. S., Tano*, P., Patel*, N., Ingster, A., Pouget, A., & Mathis, A. Neuron 2024*

Explicit memory

Long-term memory is classified according to memory content and access to consciousness: **explicit** versus **implicit**



Explicit memories involve multiple distinct operations

(1) Memory encoding

- New information is attended to and linked to existing information
- Thorough encoding makes a memory more durable (e.g., multiple sensory modalities)
- *Emotional context* is also very important

(2) Memory storage

- Neuronal plasticity mechanisms allow a memory to be retained over time (in specific brain sites like the hippocampus)

(3) Memory consolidation

- Process that makes temporarily stored information more stable (across association cortices)

(4) Memory retrieval

- Recall (e.g. a sensory cue / a request "*what did you eat today*") brings back to mind various kinds of information and binds them into a coherent memory
- E.g. a central concept (e.g. "*pasta*") is associated with (vision, smell, the *context* of your meal)
- Retrieval is similar to perception: it is a 'constructive process'

(5) Memory forgetting

Why is it important to forget?

The case of patient H.M.



Henry Molaison (patient H.M.)

- Henry Molaison ('H.M.') suffered from untreatable temporal lobe epilepsy
- To treat the epilepsy, doctors performed bi-lateral surgical removal of the hippocampus, amygdala, and part of temporal association cortex (at age 27 in 1953)

After surgery:

- Strong memory deficits (**amnesia**)
- He *could* remember events for ~5 mins (thus, working memory was *intact*)
- But he *could not* recognize the psychologist who treated him an hour earlier ("*who are you?*")

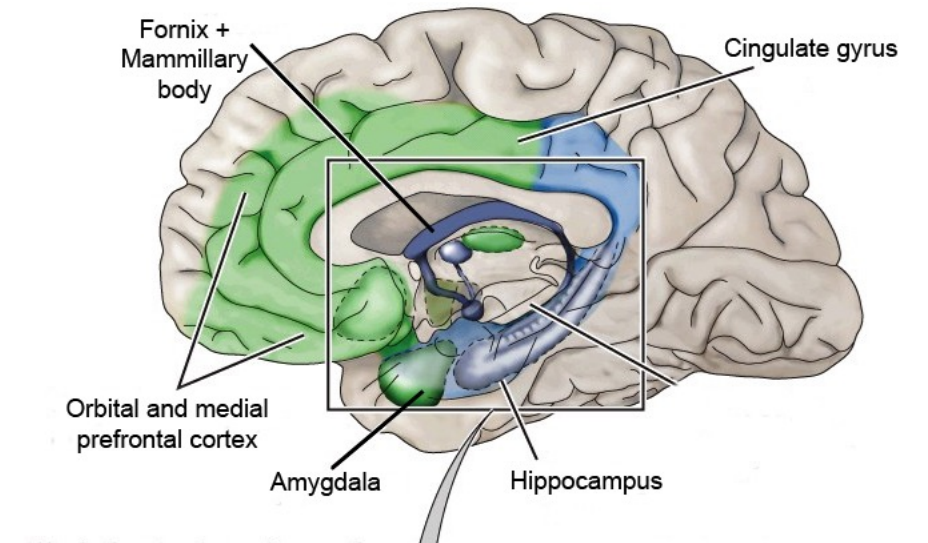
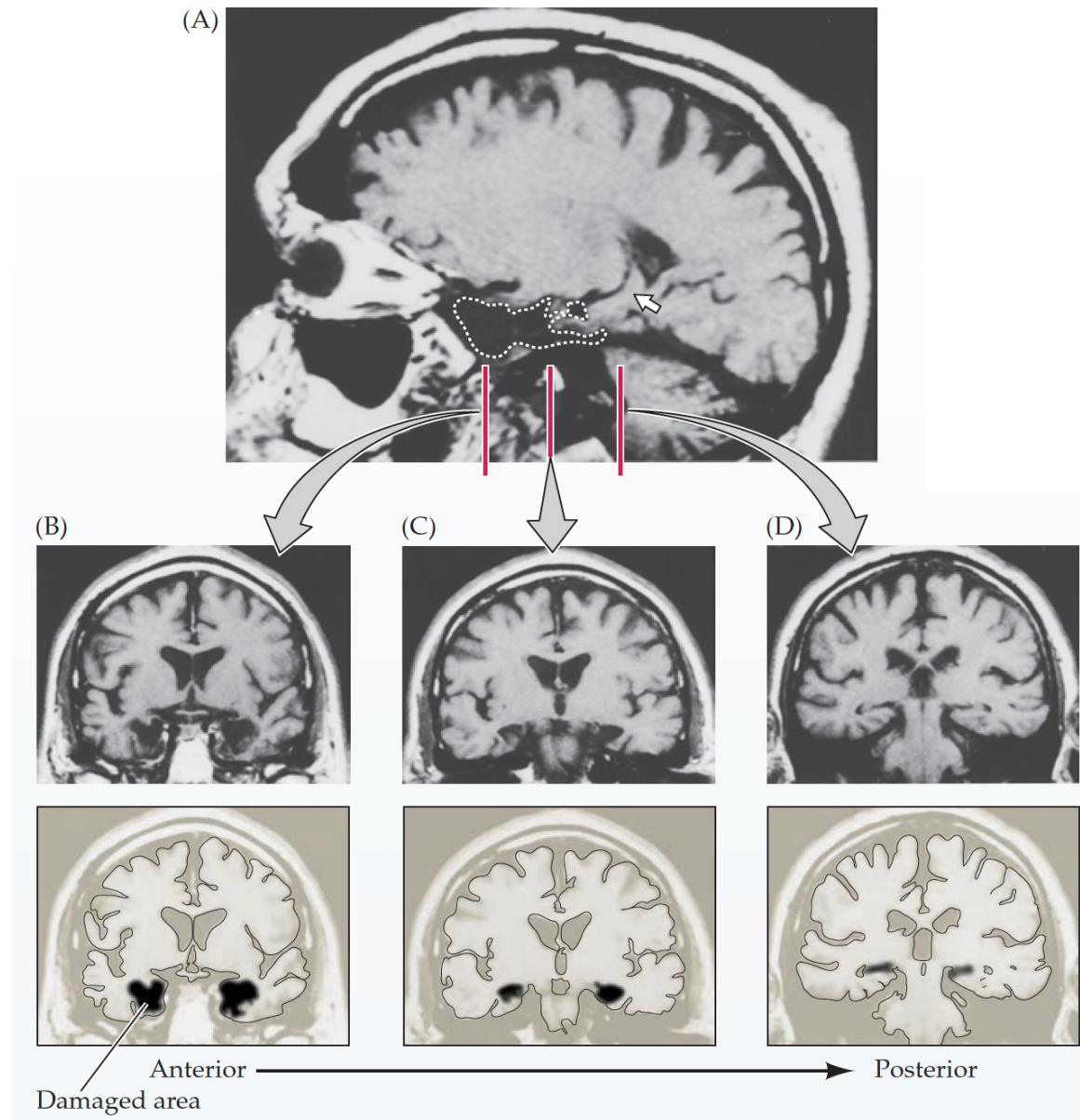
Thus, a strong deficit in explicit (here: episodic) memory and also in explicit semantic ("facts") memories

Notably:

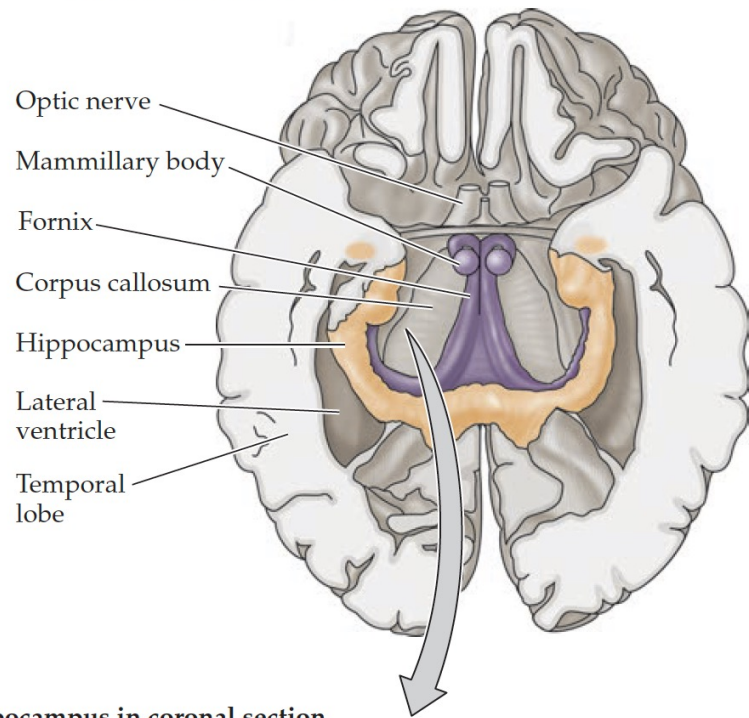
- His IQ was not affected
- Other forms of new memories / learning were unaffected (e.g. working memory; procedural memory)
- He could recall events that were quite long ago (>5 years)

Conclusion: **Hippocampus and temporal lobe are centrally important for forming new long-term, explicit memories.**

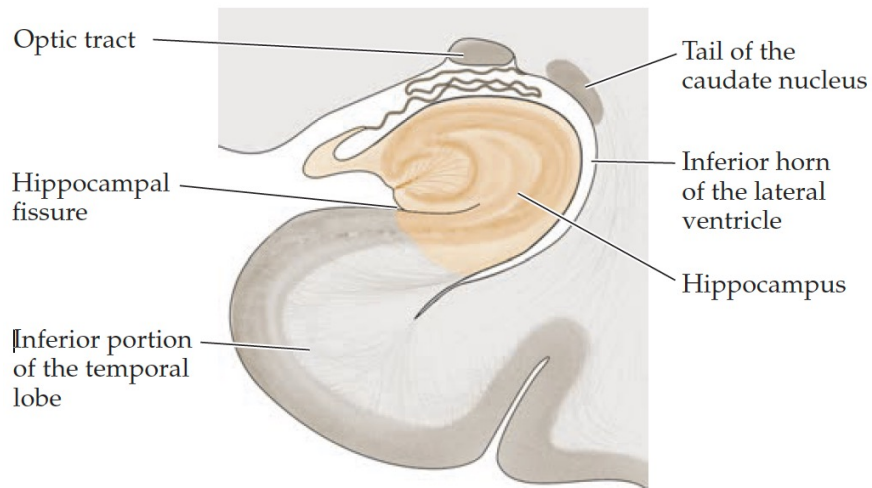
Magnetic resonance imaging (MRI) of the lesions in patient HM



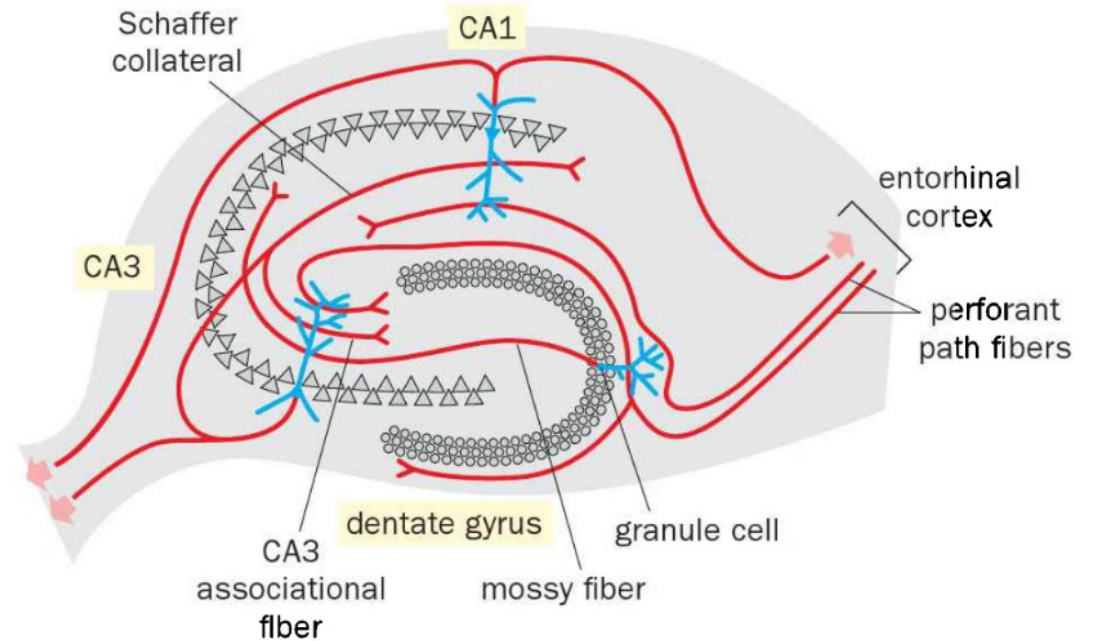
(B) Ventral view of hippocampus and related structures with part of temporal lobes removed



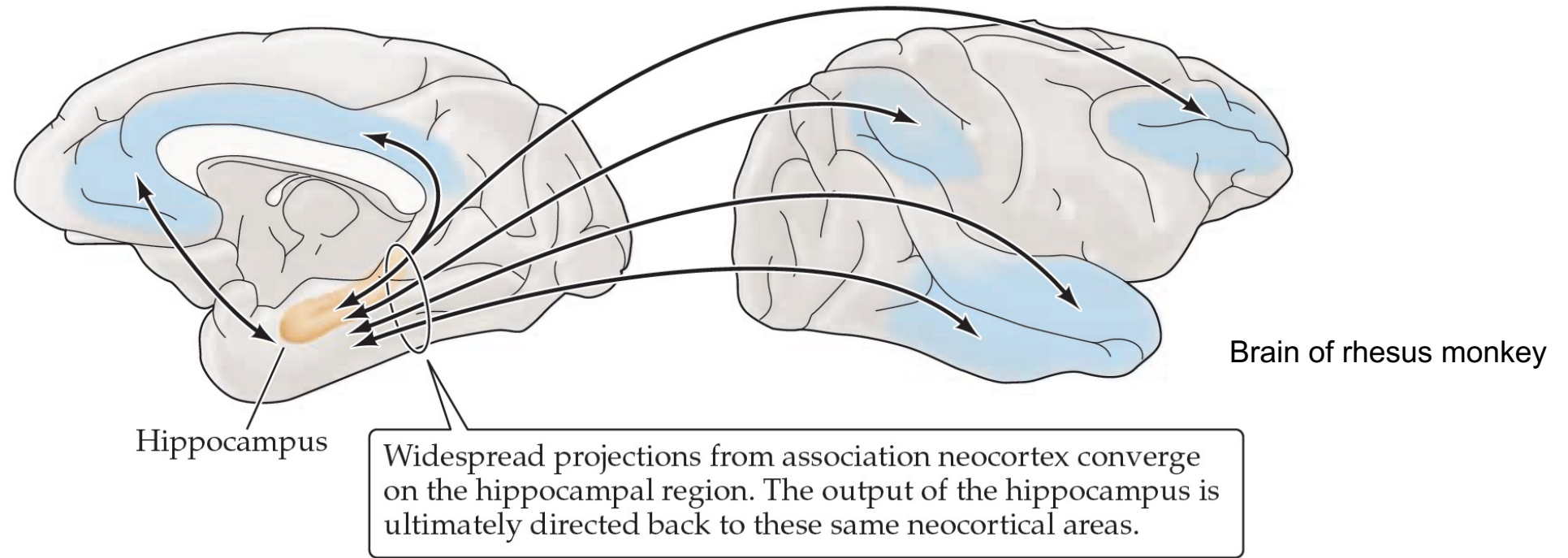
(C) Hippocampus in coronal section



Location of the hippocampus in the human brain



Communication between hippocampus and cortex in memory formation



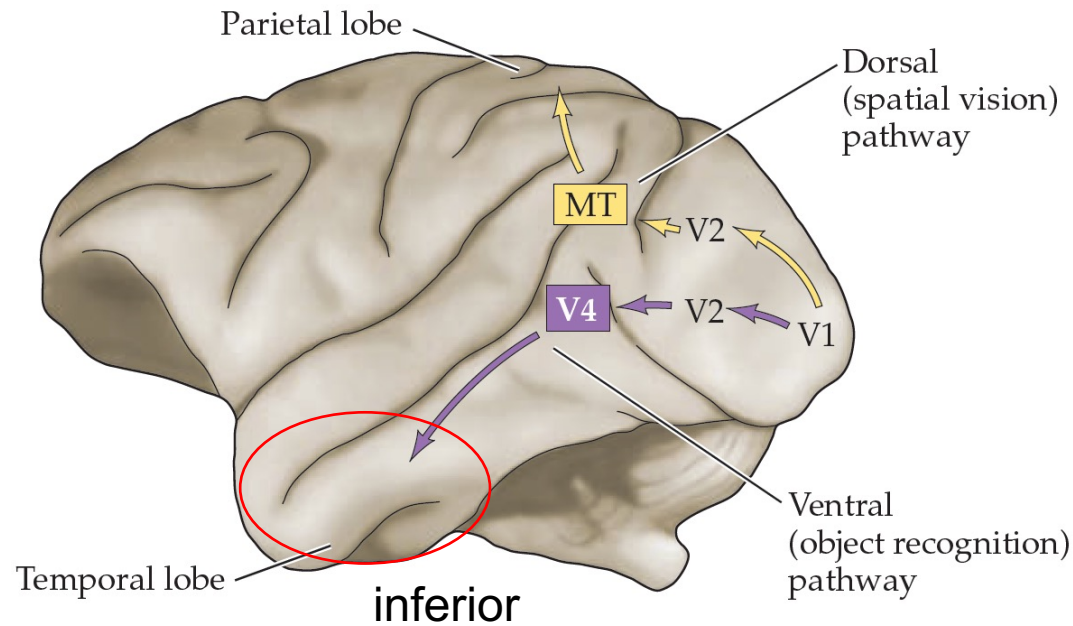
Current model of memory formation:

- Temporal association cortex / hippocampus first stores a "slimmed-down" memory (e.g. central concept of a memory)
- The central concept (e.g. 'pasta') can then be linked with other sensory associations *via* connections to all four associative cortices
- **Formation** of long-term memory **depends on the hippocampus**
- After many years, long-term explicit memories become independent of the hippocampus (the memory is then stored in several **cortical areas** in a distributed fashion = 'engram')

'Concept' cells in temporal lobe / hippocampus
recorded in conscious human patients

... provide a clue into the mechanisms of
declarative memory

Reminder from vision: The 'ventral stream' of visual processing goes toward the **inferior temporal lobe**



Dorsal stream
Analyzes motion, depth

Ventral stream
Represents shape, color, **identifies** objects and e.g. faces

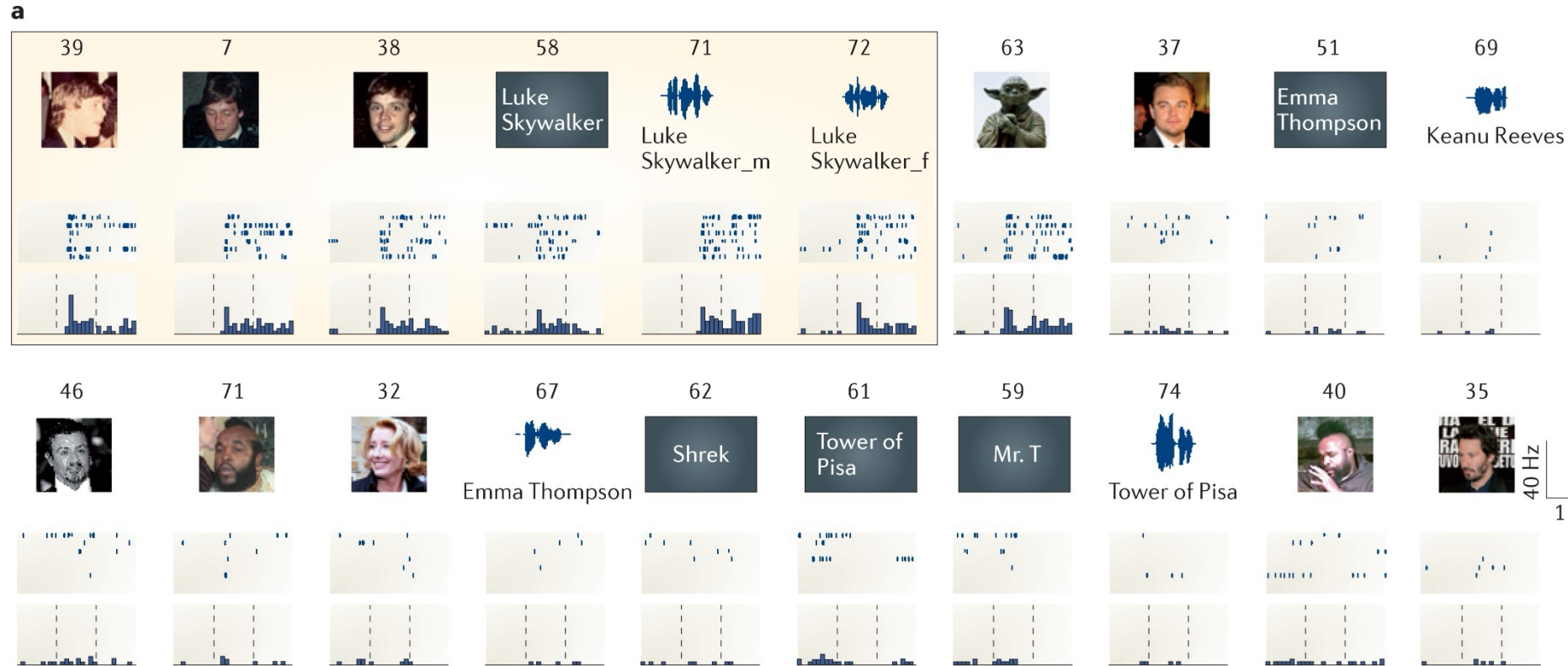
A related brain disorder:

Damage to (right) inferior temporal lobe can cause

Prosopagnosia (**agnosia** of faces; face = *prosopon* in Greek)

An inability to recognize familiar faces

Recordings in the medial temporal area and hippocampus reveals 'concept' neurons

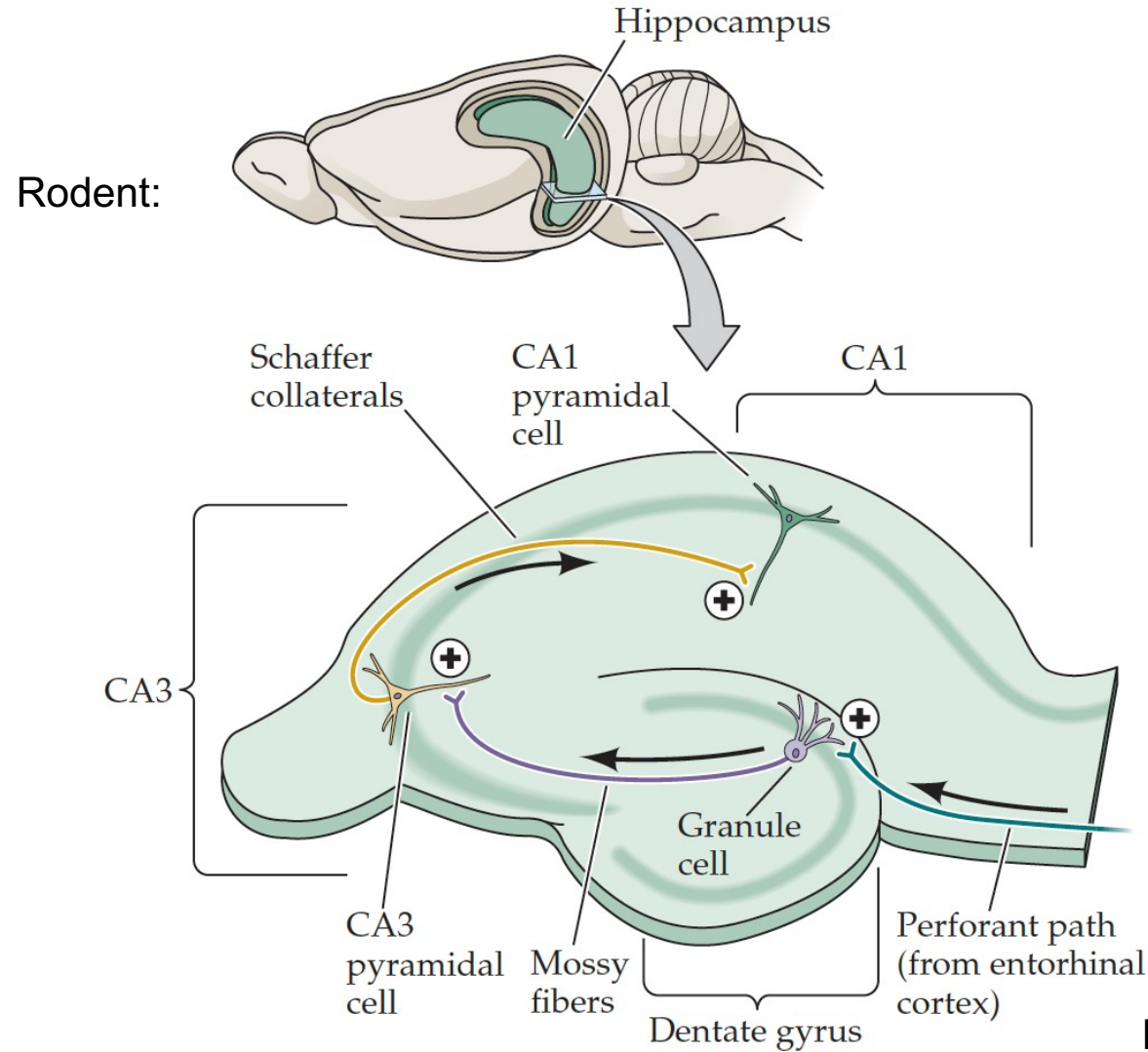
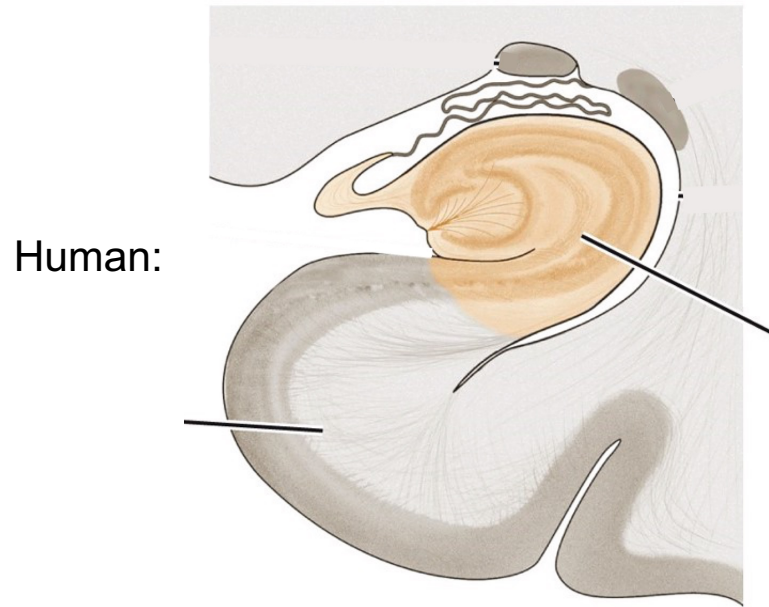


- Example of a single neuron which responded specifically to *images*, the *written and spoken name*, of "Luke Skywalker"
- This neuron encodes a "**concept**" rather than sensory details

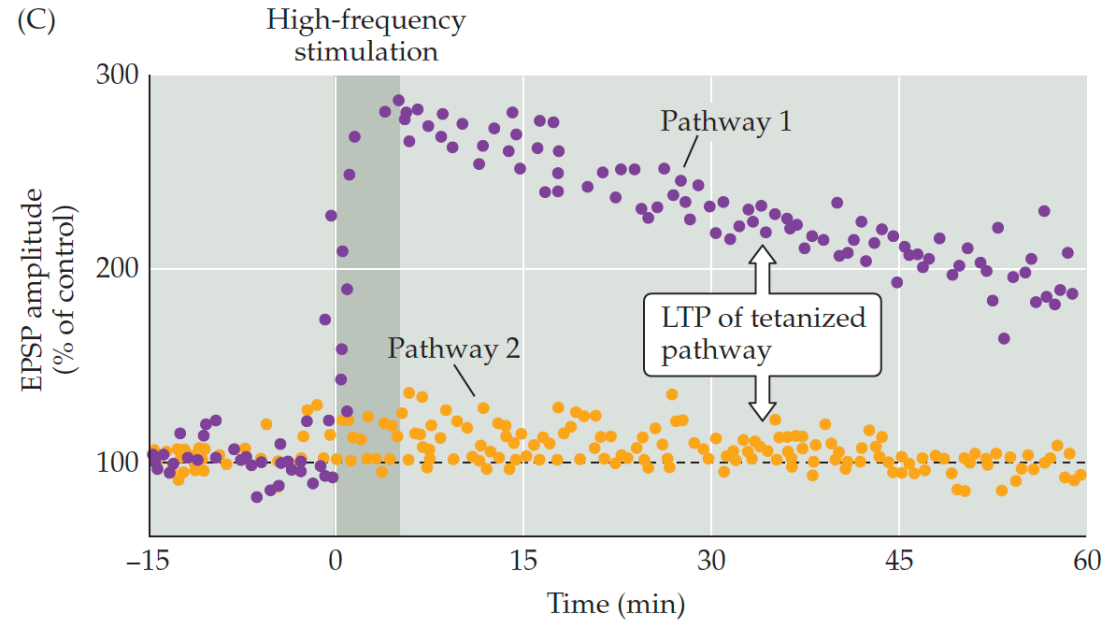
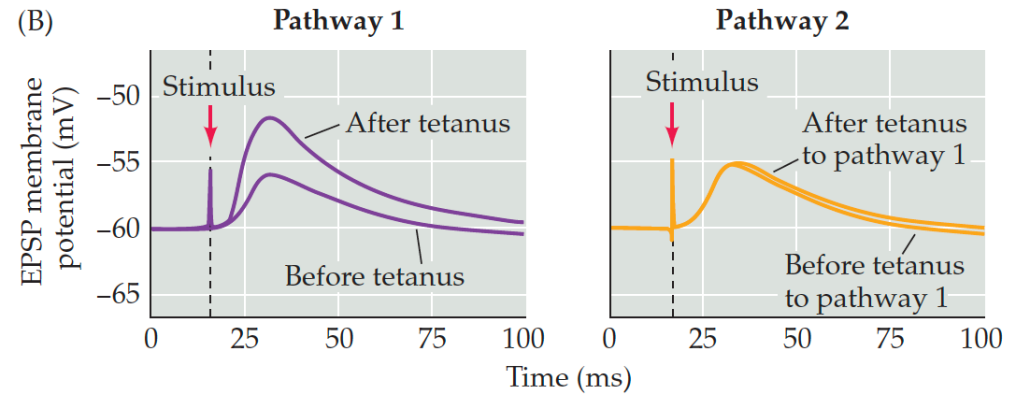
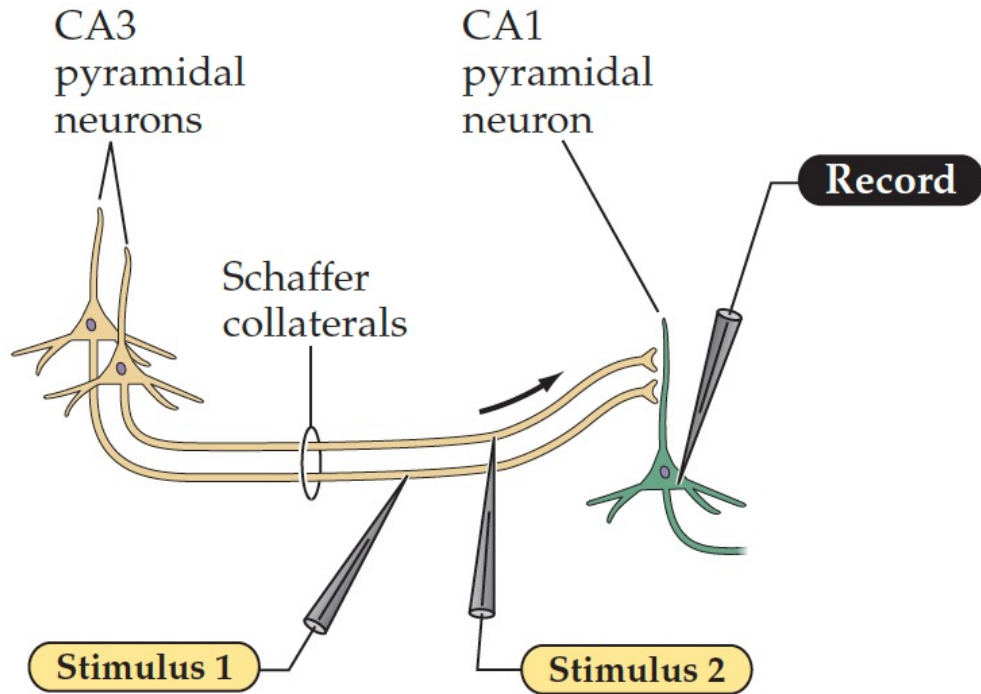
The hippocampus:

a model for *in-vitro* studies of synaptic plasticity

The hippocampal circuit in a rodent as a model preparation (brain slice preparation)

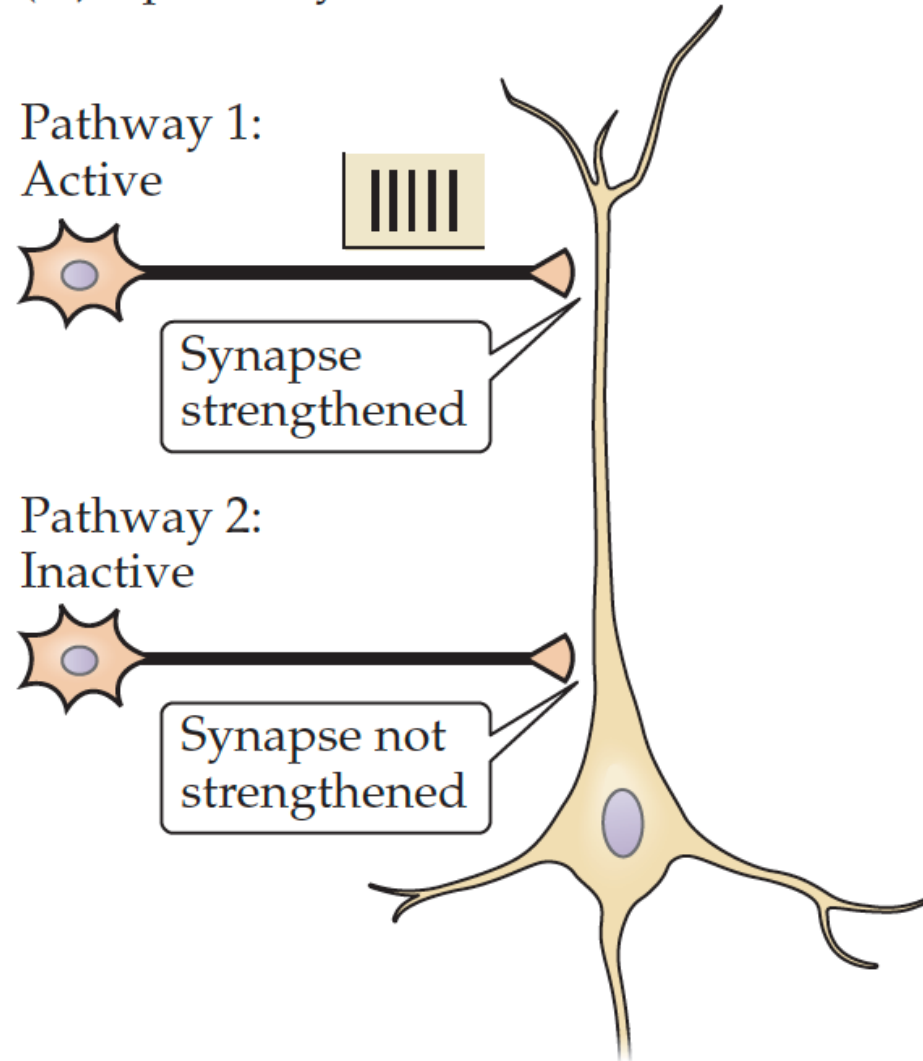


Tetanic (high-frequency) stimulation of CA3 → CA1 synapses drives Long-Term Potentiation (LTP) of EPSPs

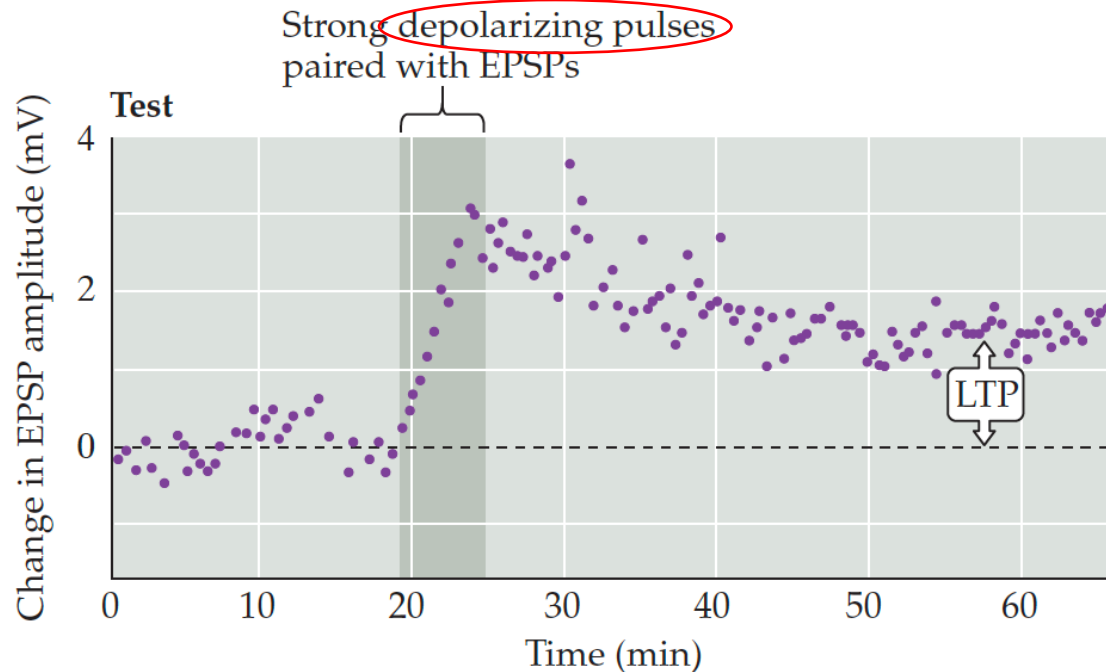
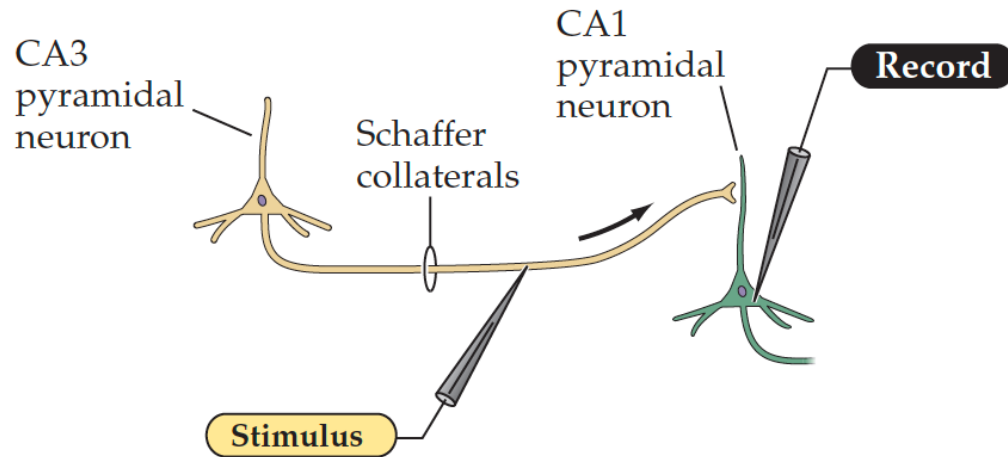


LTP is specific to the activated synapses (because presynaptic glutamate release is required)

(A) Specificity



Pairing presynaptic stimulation and postsynaptic activity (depolarization through a recording pipette) also causes LTP

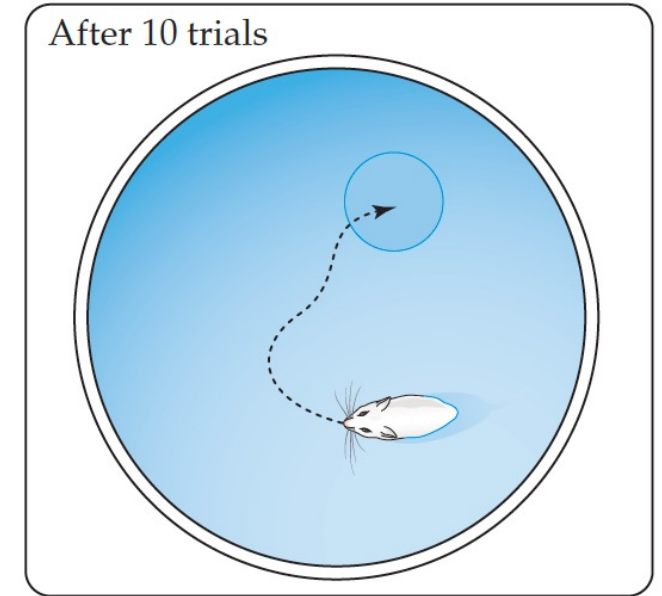
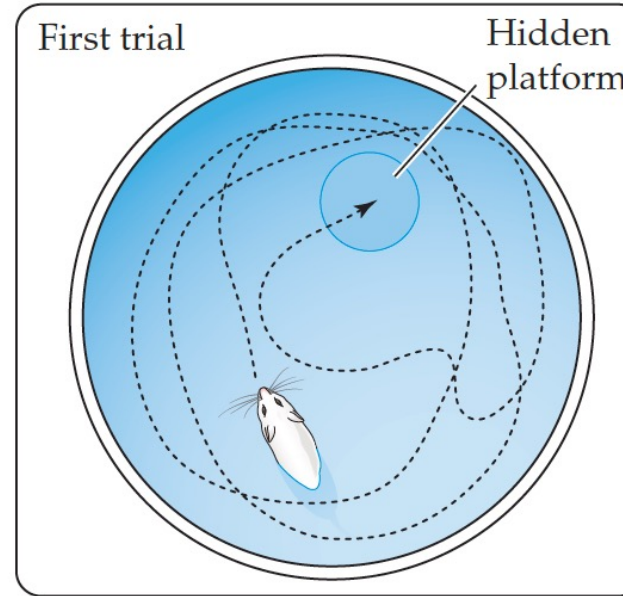
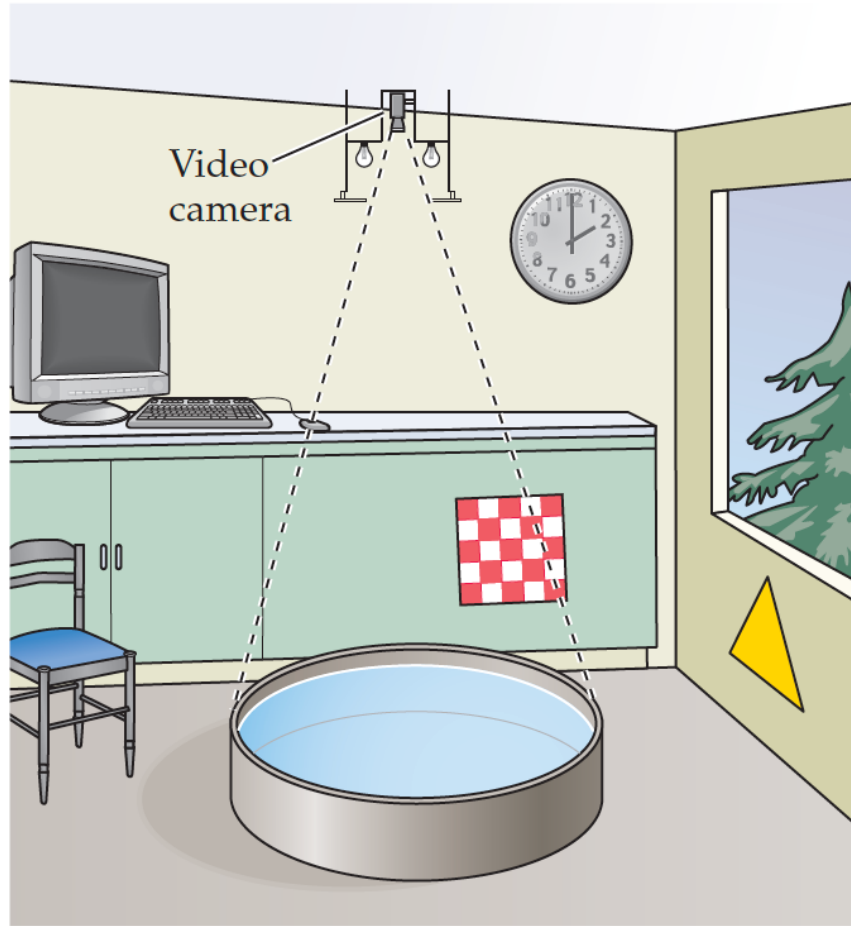


- LTP in response to coincident pre- and post-synaptic neural activity
- **Hebb's principle:** coordinated pre- and post-synaptic activity strengthens a synapse
- Molecular mechanism: NMDA-receptor-based

- Long-term potentiation (LTP) of synaptic transmission is a 'candidate' mechanism for learning & memory
- This idea can be tested in mouse models, e.g. by genetic knock-out of NMDA receptors

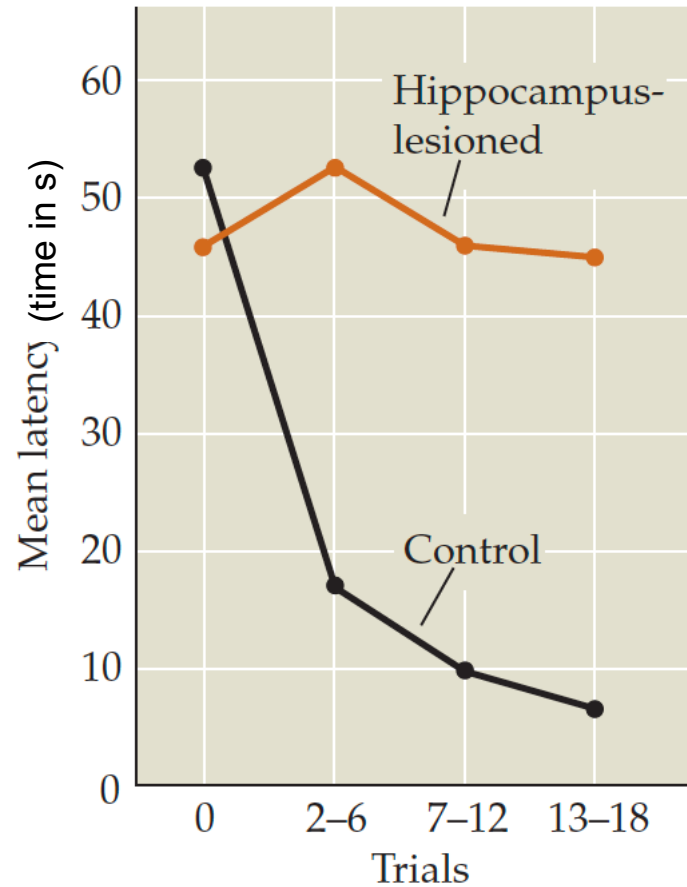
First let's introduce the physiological role of the hippocampus in **rodents**

The Morris water maze: a spatial memory test for rodents

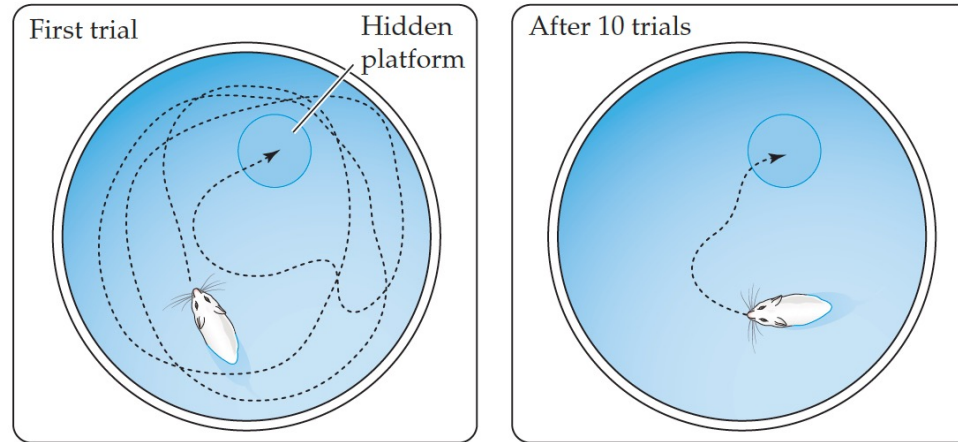


- Milky water with a non-visible platform that is surrounded by landmarks
- A rat learns to find the platform using "spatial memory" based on these visual landmarks (presumably based on hippocampal "place cells")

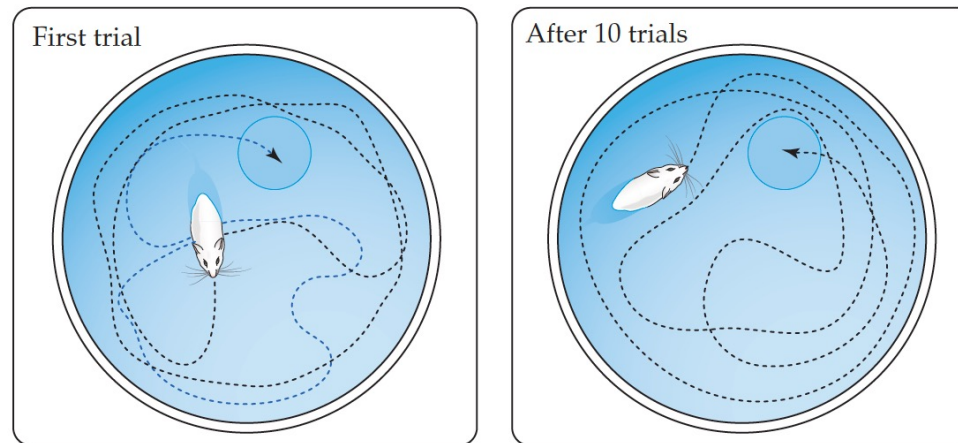
Lesioning (destroying) the hippocampus in rats leads to the absence of spatial learning in the Morris water maze



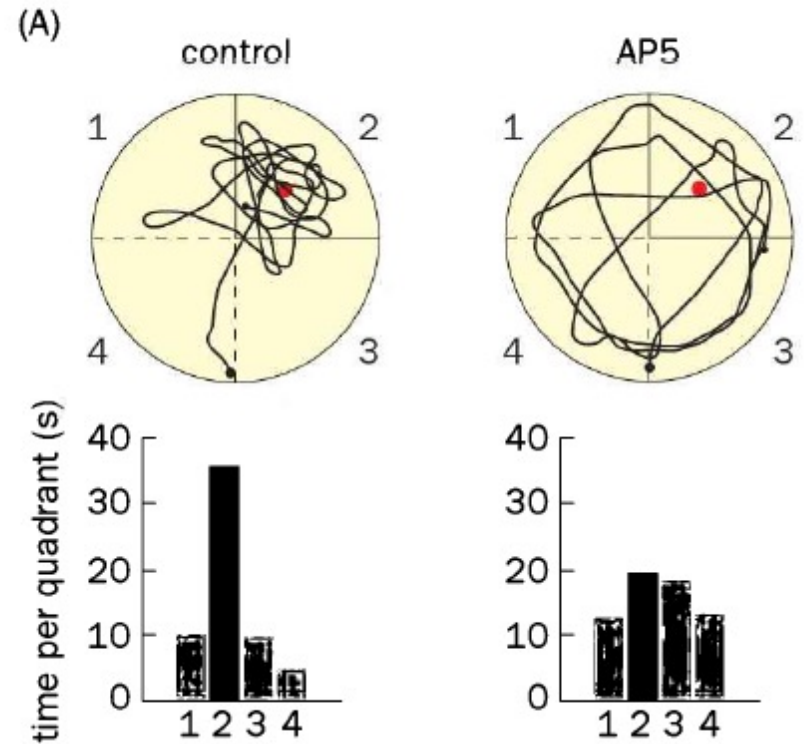
(C) Control rat



(D) Rat with hippocampal lesions



Hippocampal NMDA receptors are required for spatial memory in rodents



Injection of the NMDA antagonist, D-AP5, into the rat hippocampus

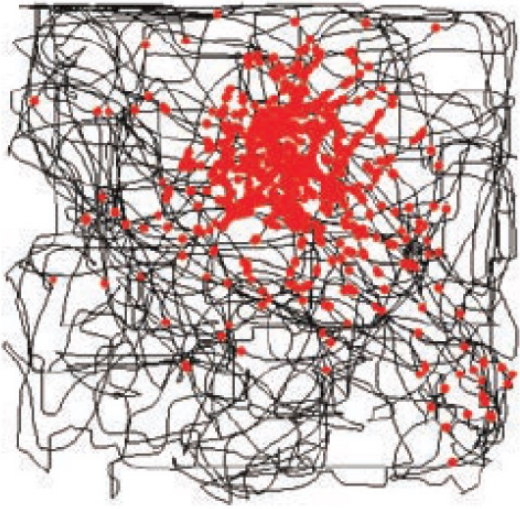
Note:

- After the learning sessions, the platform was removed from quadrant 2
- Control rats focus their search on quadrant 2, D-AP5 injection blocks the spatial memory

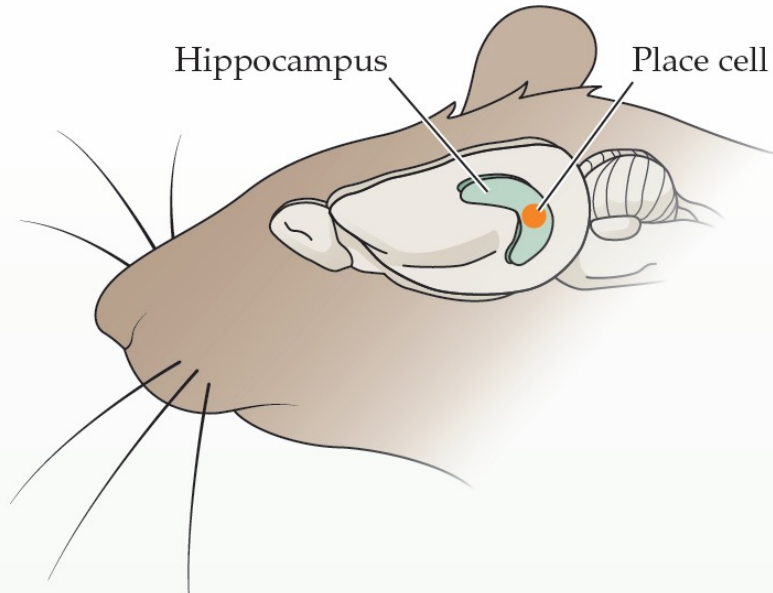
Cognitive maps (of space)

Hippocampal CA3 and CA1 neurons fire APs when the animal is in specific locations of space ('place cells')

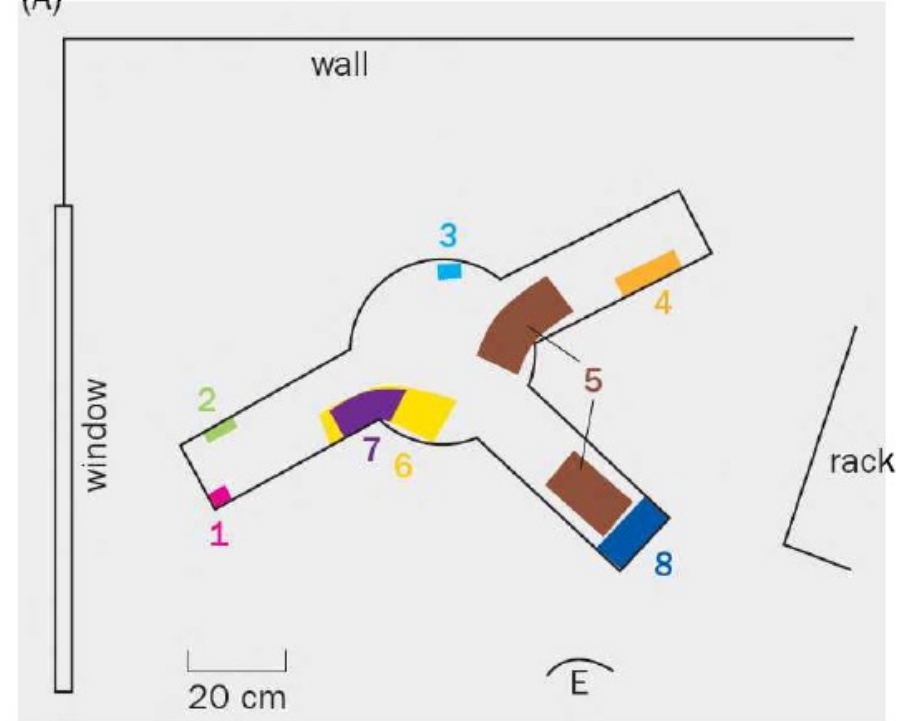
(A)



Red = locations where the cell fired
Black = walking trajectory of the animal



(A)



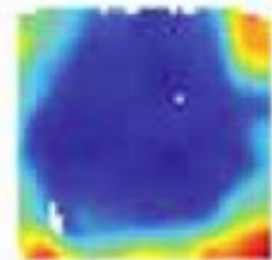
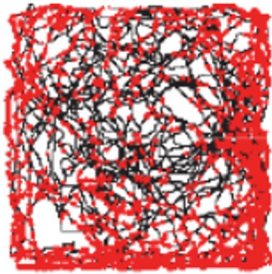
Location-specificity of 8 place cells recorded in the hippocampus of a freely moving rat

The basic elements of the cognitive map

Medial entorhinal cortex

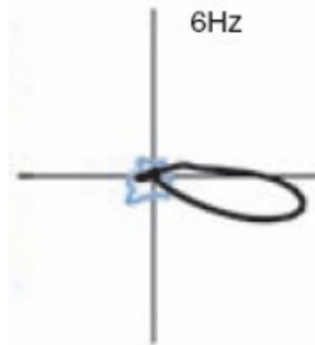
Hippocampus

Border cells



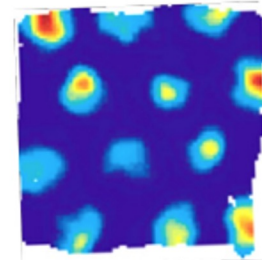
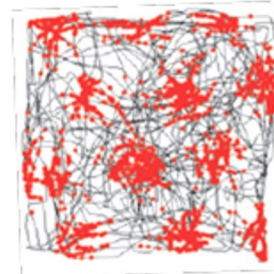
Moser, O'Keefe, Knierim 2008

Head-direction cells

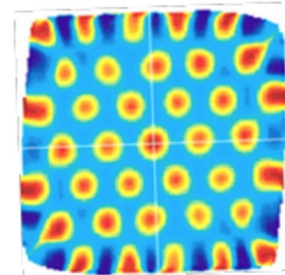


Ranck, Taube 1980s

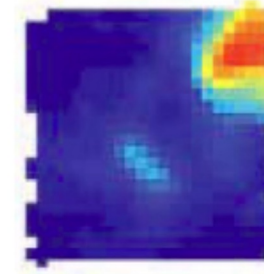
Grid cells



Mosers 2005

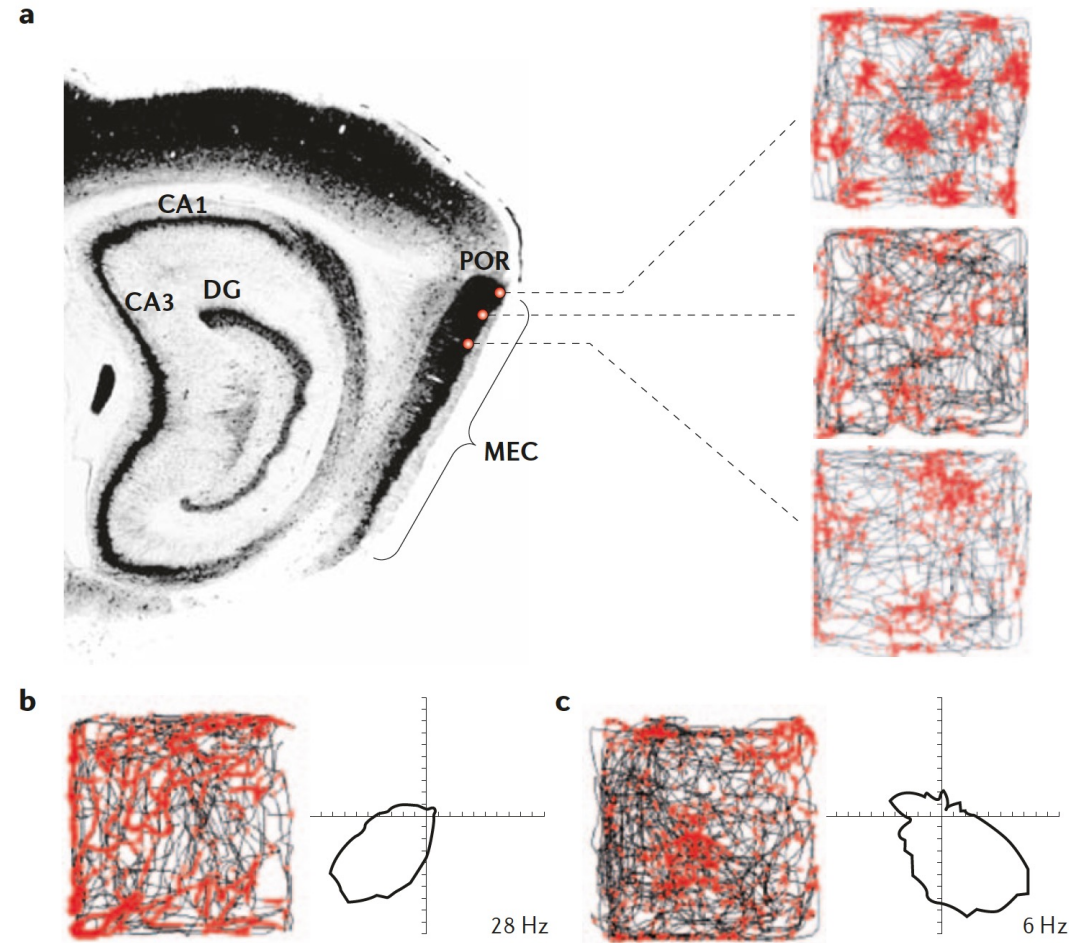


Place cells



O'Keefe 1971

Grid cells exist at multiple scales and some are direction selective

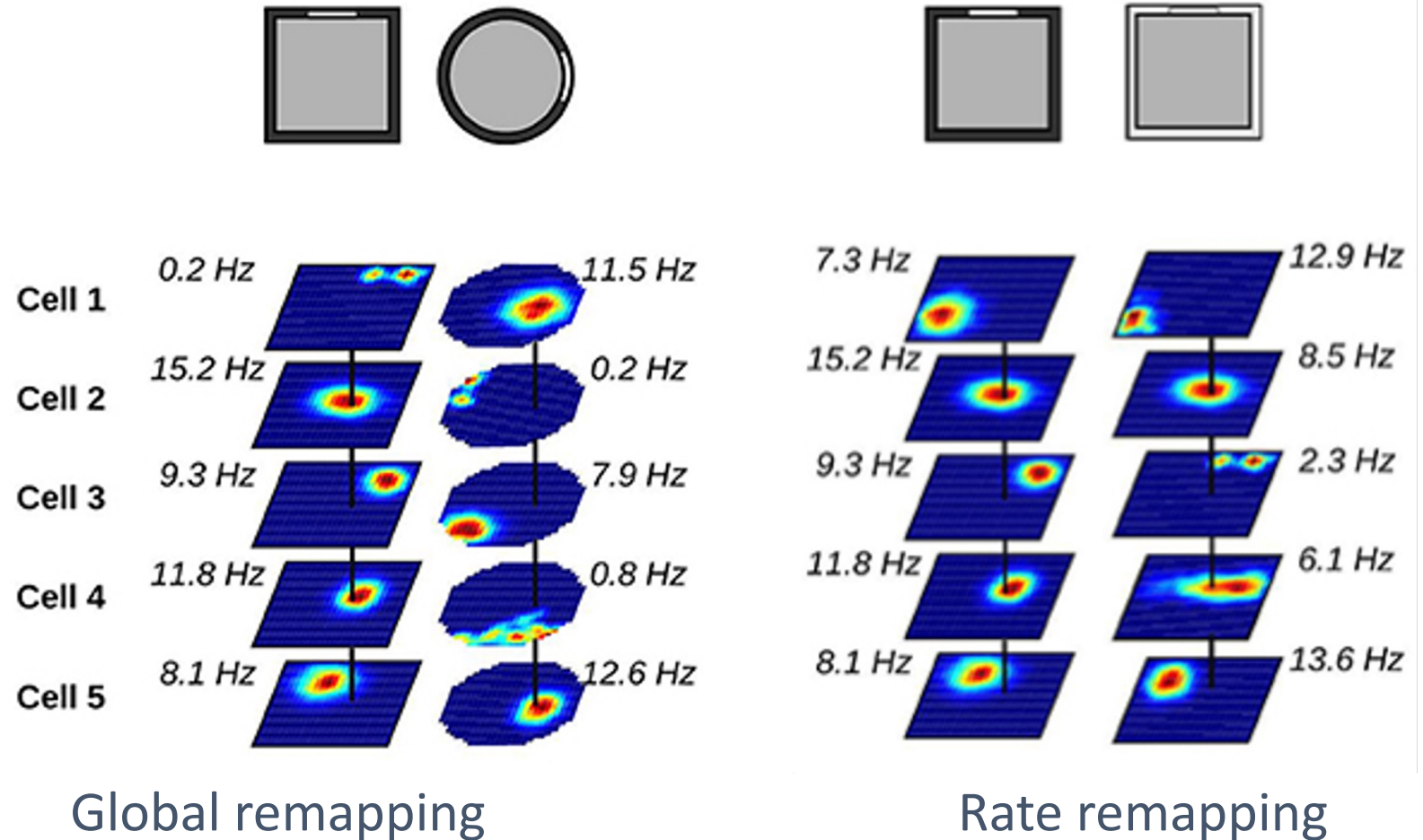


Place cells remap in novel contexts

Place cell locations remap when context changes drastically (*global remapping*)

Smaller context changes are encoded as changes in firing rate (*rate remapping*)

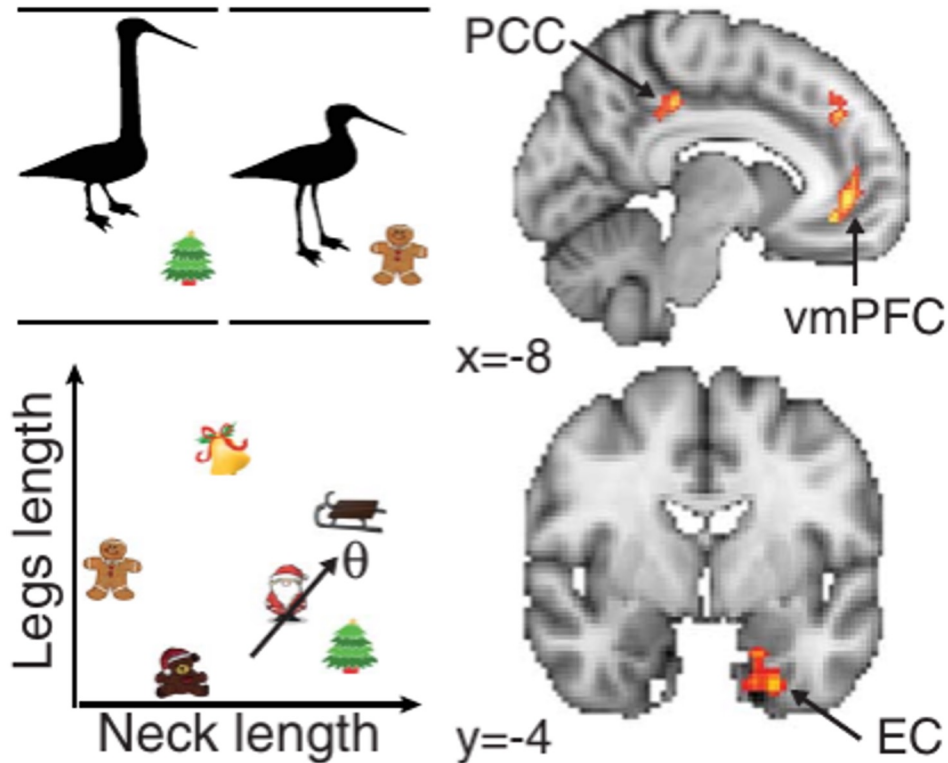
Allows place cells to **encode multiple spaces and adapt to new environments**



Place cells in the hippocampus

- Place cells form when the animal is in a new environment and remain stable thereafter
- Place cells are influenced by landmarks, but are also stably active in the dark
- Place cells receive input from "grid cells" in the entorhinal cortex (EC)
- Thus, locations are encoded in a different way in the EC and then in the hippocampus

Encoding of abstract spaces



Participants in an fMRI scanner learned **association between objects and birds** (with variable neck and leg length) -> a novel abstract 2D space

During trajectories through that space **grid-like activity** in entorhinal cortex can be observed

This shows that the cells underlying **physical space also encode abstract space**

Diseases of memory

Alzheimer's disease

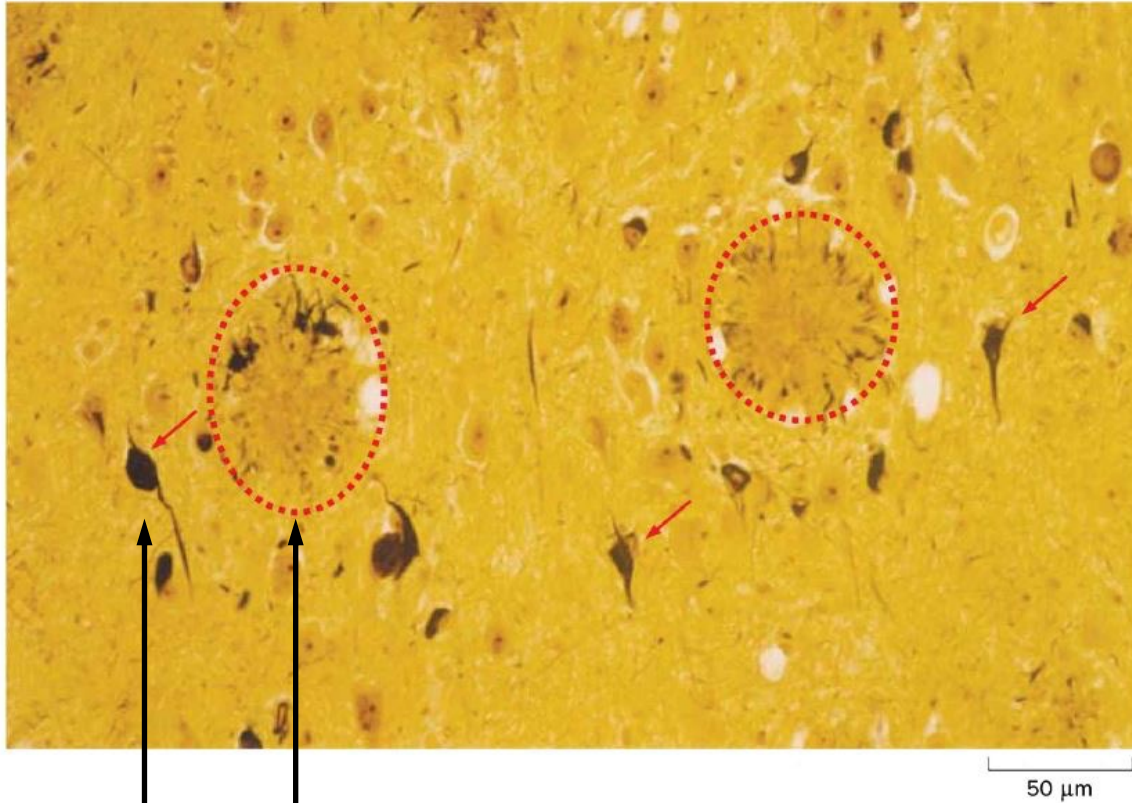
- A **neurodegenerative disorder** described in 1907 by Alois Alzheimer (who also noted the histological changes)
- Age of onset >60 years for "late onset", most forms are "sporadic"
- Incidence, **5-10%** at 65 years and higher thereafter
- Familial forms: earlier (40 - 60 years old), inherited autosomally-dominant

Clinical signs:

- impairment of recent memories and attention
 - failure of language skills
 - failure of visual and spatial orientation
 - alterations of personality
 - gradually patients lose their ability to cope with daily life
-
- Morphological signs (in post-mortem brains)...

Morphological signs of Alzheimer's disease (AD):

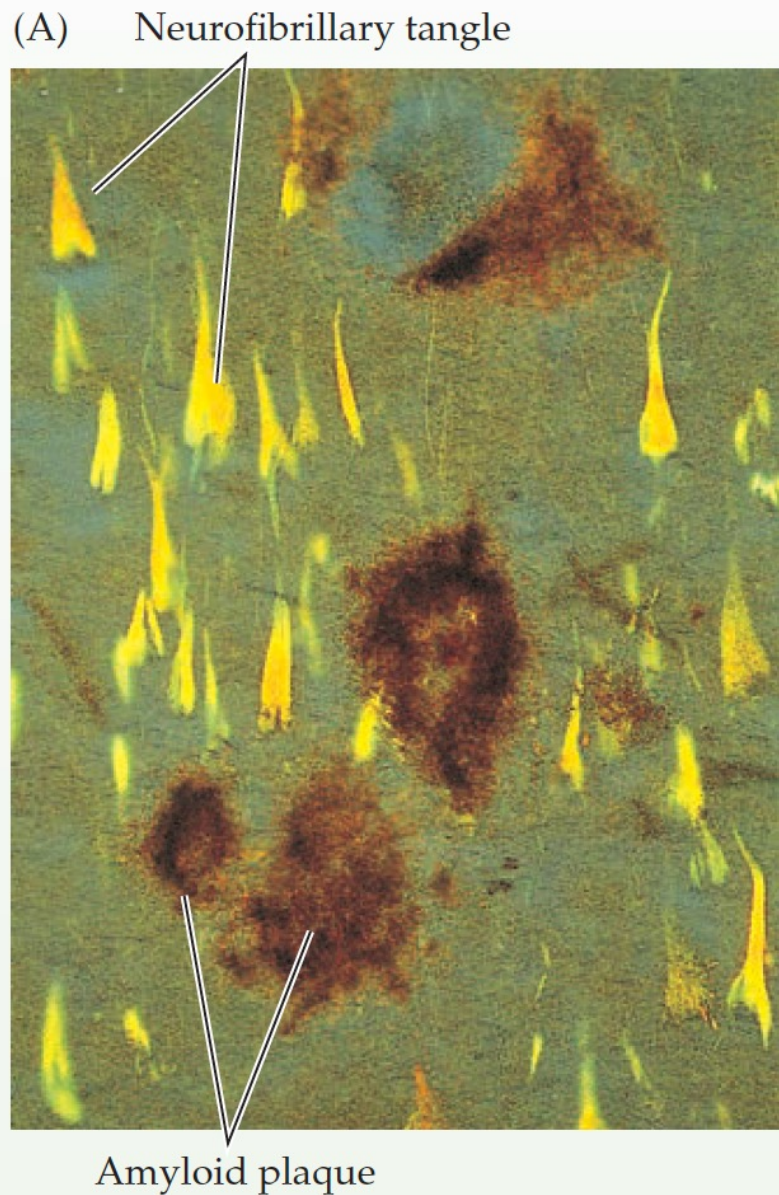
(A)



Neurofibrillary tangles (abnormal cytoskeletal filaments inside neurons)

Amyloid plaques (extracellular deposits, ~50 μm wide) contain "**Aβ**" peptides

Histological alterations occur in the neocortex, hippocampus, temporal lobe and some brainstem nuclei



Summary: Learning & Memory: Important concepts and keywords

- Memory: definitions in terms of time-scale and kinds (implicit, explicit, procedural, declarative)
- Role in and relationship between Prefrontal Cortex and short-term memory
- Explicit, episodic memories: role of hippocampus and temporal lobe
- What patient H.M. tells us about the locus and kinds of memory
- 'Concept cells' in temporal lobe and hippocampus in humans
- Long-term plasticity at excitatory synapses studied in hippocampus (which synapse; which fundamental mechanism)
- Role of the hippocampus for spatial navigation & spatial memory as studied in rodents
- Classical conditioning as a form of 'implicit' long-term memory
- Alzheimer's Disease and its putative underlying mechanisms