Learning and Memory

Underlying biology of a memory

- “a memory” here includes learning facts, remembering events, learning new skills
- Subtle changes among synapses distributed across several brain areas
- Learning-induced neuroplasticity

The importance of the bilateral hippocampi

- Lesion study
- Anterograde amnesia
- Dissociation from procedural memory

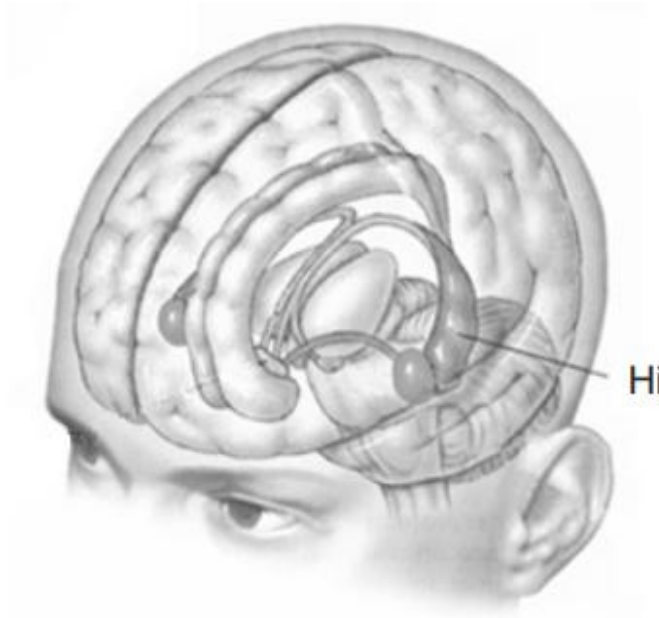


Figure 13.2 The location of the hippocampus in the medial temporal lobe (top). A dissected hippocampus and fornix (bottom left) looks like a seahorse (bottom right).

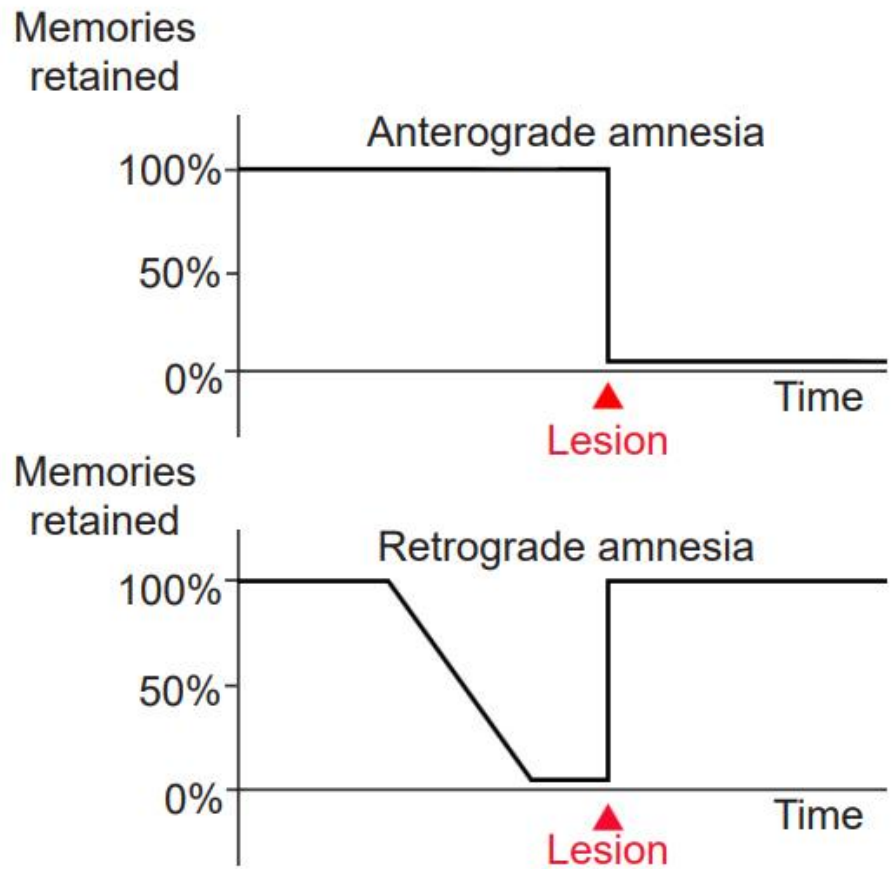


Figure 13.4 In anterograde amnesia, a person is unable to create new memories following a lesion (top). In temporally-graded retrograde amnesia, older memories are better retained while recent memories are more likely lost.

Types of memory

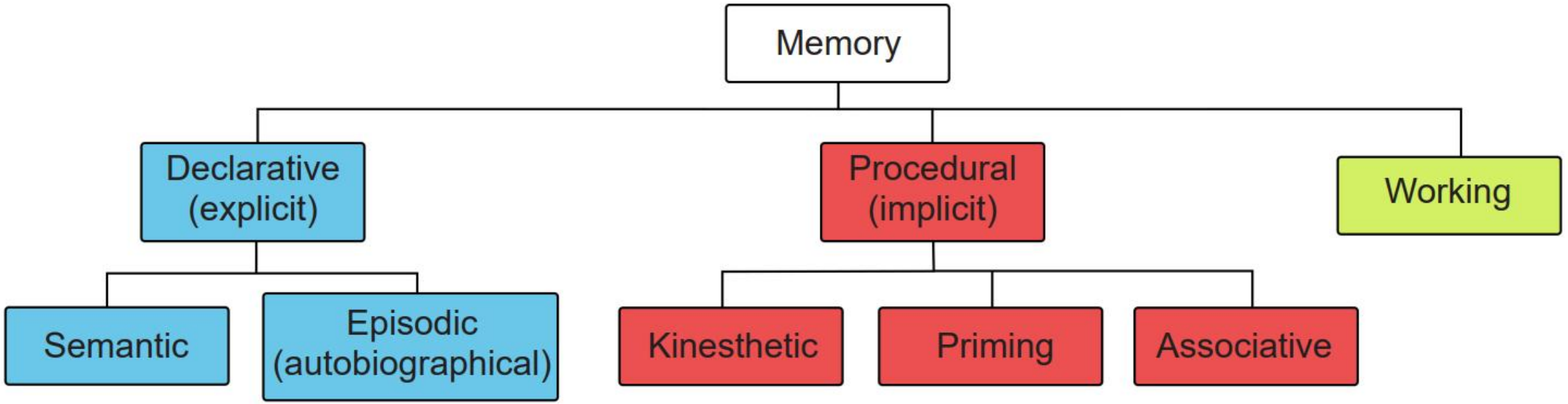


Figure 13.3 Summary diagram of some of the major subtypes of memory.

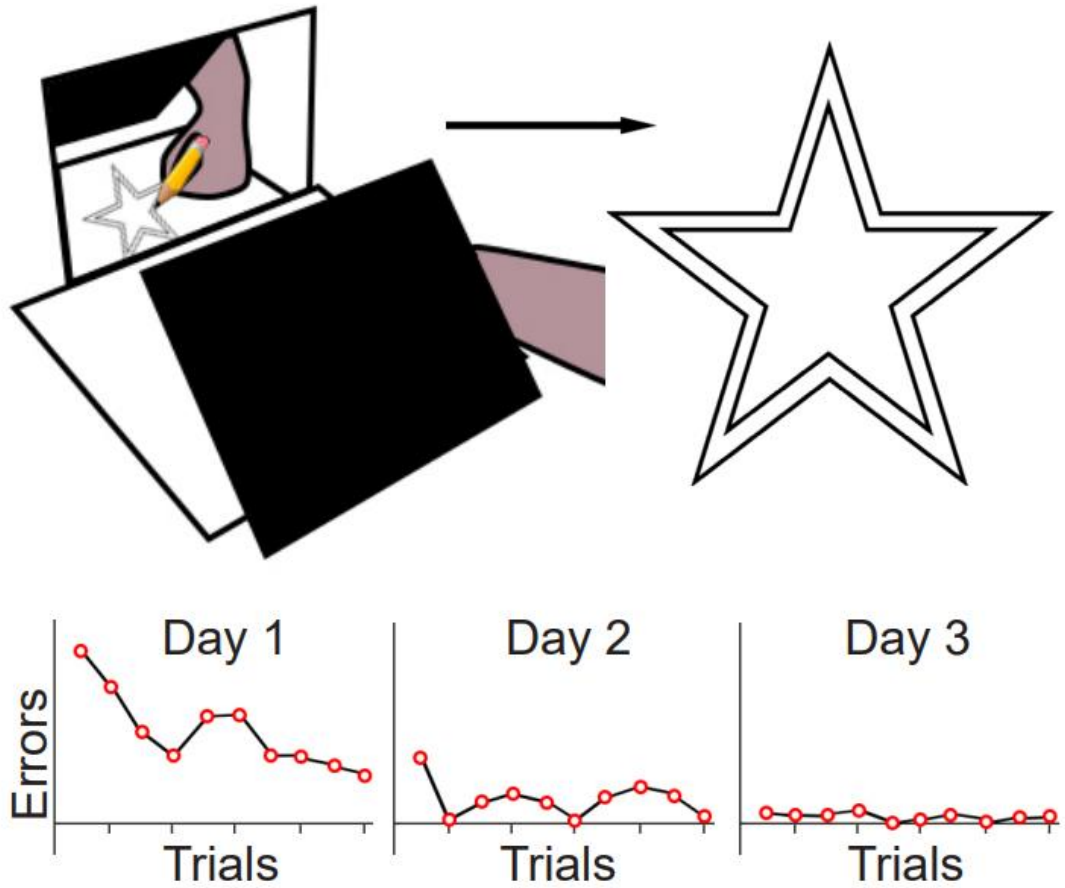
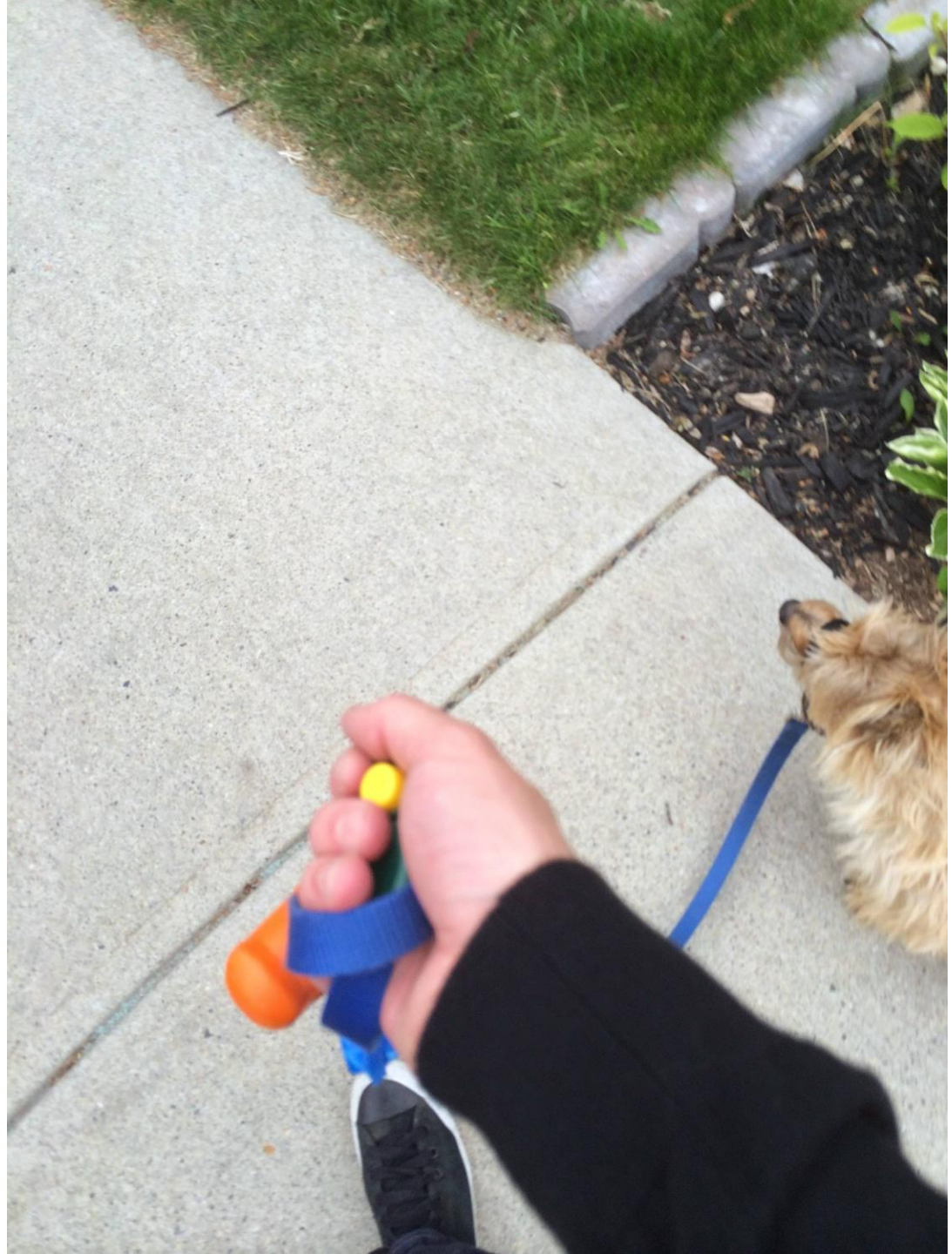


Figure 13.5 Patient HM performed poorly on the mirror tracing task (top), but improved at the task over time despite having no memory of performing the task (bottom).



Trial 1:	Prompt	4 8 2 6
Expected response		6 2 8 4
Trial 2:	Prompt	2 8 7 9 1
Expected response		1 9 7 8 2
Trial 3:	Prompt	8 4 1 1 8 6
Expected response		6 8 1 1 4 8

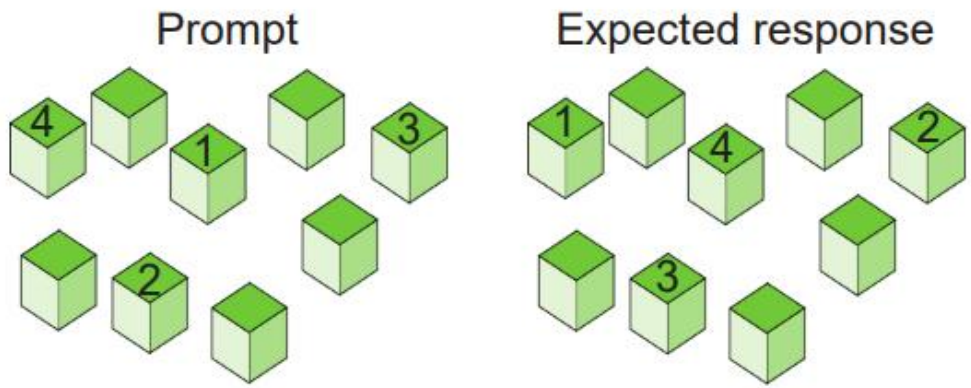
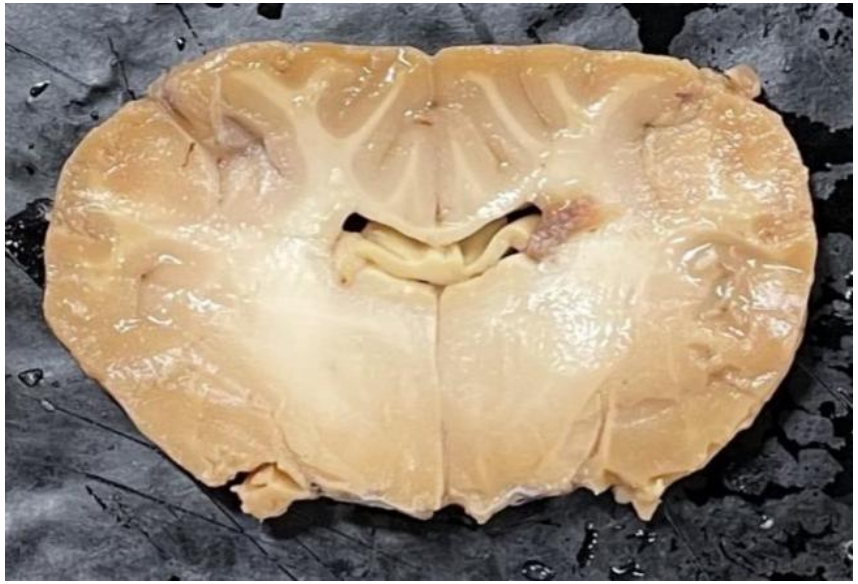
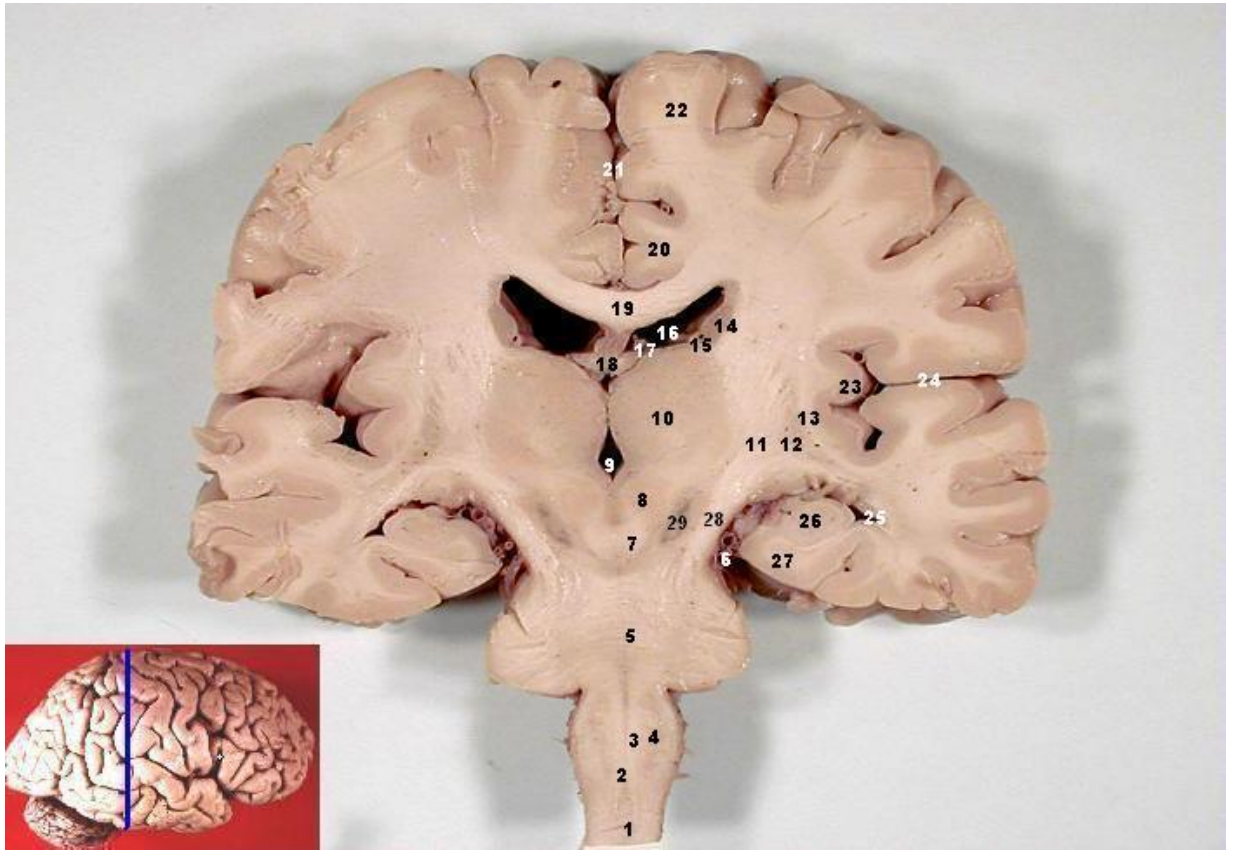


Figure 13.7 The digit span test (top) and the Corsi block tapping test (bottom) are measures of working memory.

Neural structures involved in learning and memory

The hippocampus





By Patho via CC-BY 2.5

The hippocampus

- Part of the **limbic system** (evolutionarily ancient brain network important for memory and emotion)

Hippocampal circuitry

- Trisynaptic circuit
- Recall: Cortex is organized in layers
- Outputs of layers 2 and 3 in **entorhinal cortex** send signals to the granule cells of the hippocampus's **dentate gyrus** via the **perforant pathway**
- Neurons of dentate gyrus send signals to the **CA3** region via the **mossy fibres**
- Neurons of CA3 send signals to **CA1** via **Schaffer collaterals**

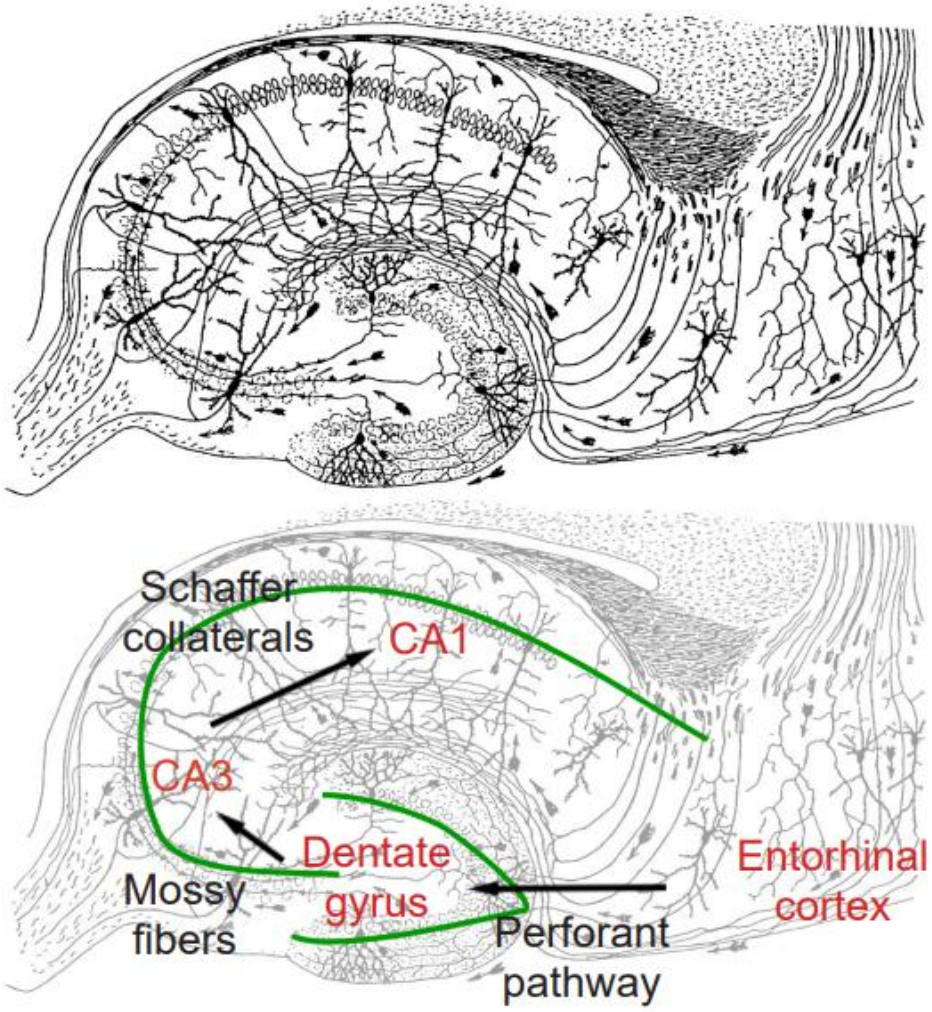


Figure 13.8 The circuitry of the hippocampus as illustrated by Ramon y Cajal (top) and as a schematic diagram (bottom). Structures are labeled in red and communication pathways are in black.

Cornu ammonis (CA)

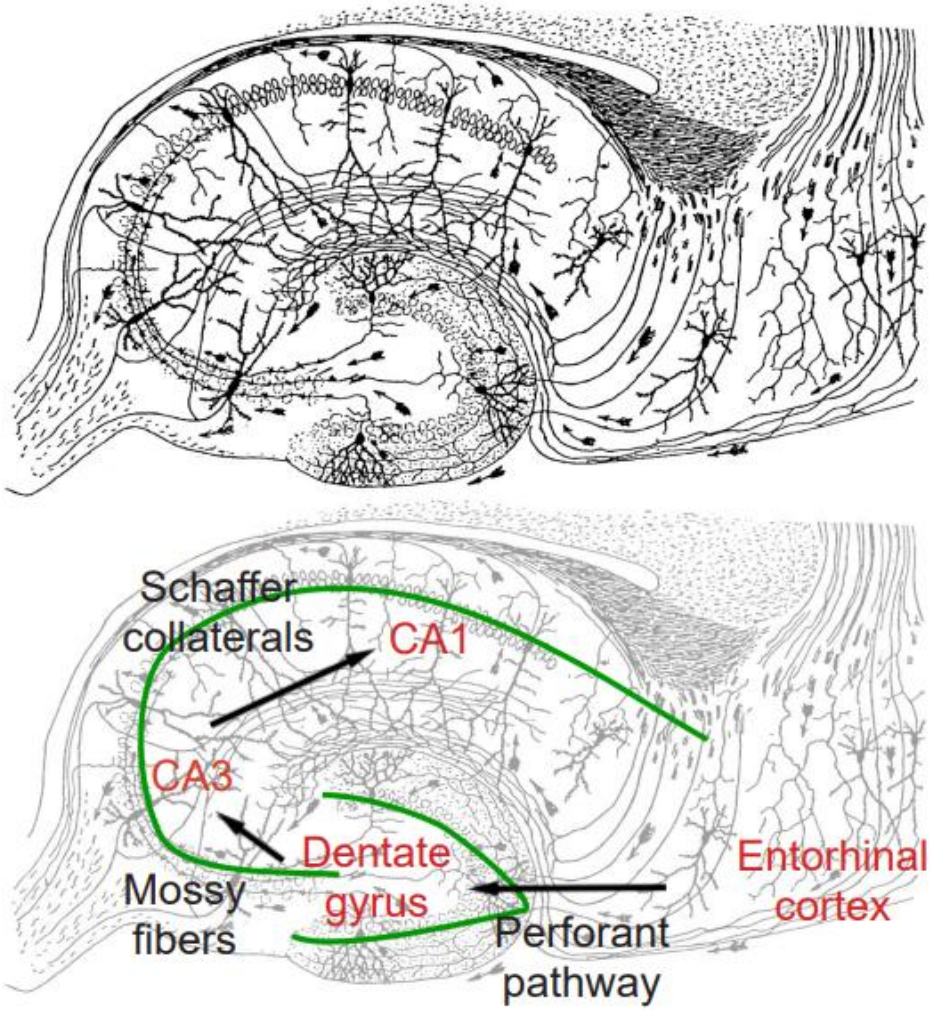
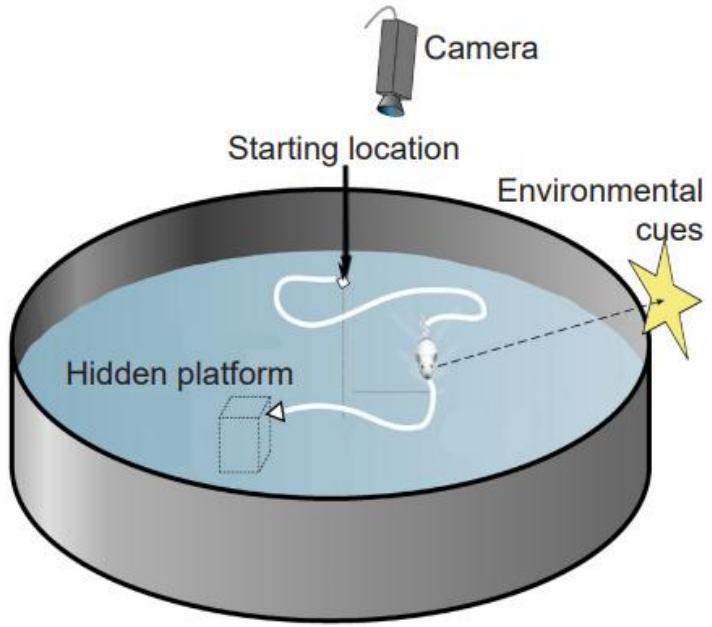


Figure 13.8 The circuitry of the hippocampus as illustrated by Ramon y Cajal (top) and as a schematic diagram (bottom). Structures are labeled in red and communication pathways are in black.

Spatial memory

- Allow us to navigate through space
- Impaired with hippocampal damage



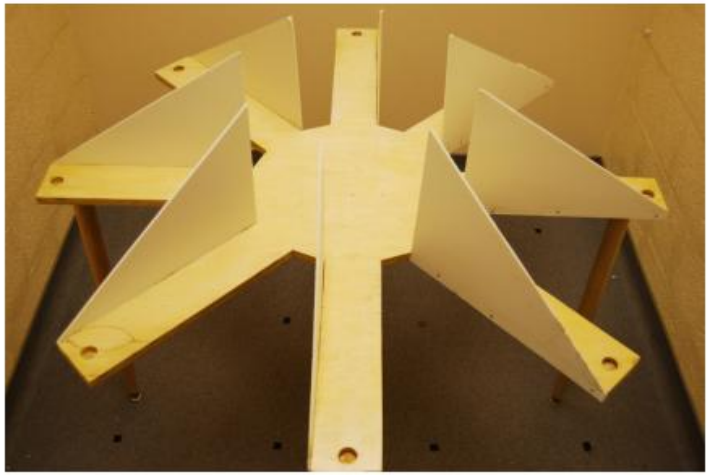


Figure 13.9 The Morris water maze (top) and the radial arm maze (bottom) are behavioral tests to assess spatial memory.

Neural structures involved in memory

- Hippocampus
  - HM – forming new memories
  - Spatial memories
- Amygdala
- Inferotemporal cortex
- Prefrontal cortex
- Striatum
- Cerebellum

Amygdala (ah-MIG-dah-lah)

- From Greek word for almond due to its shape
- In the medial temporal lobe at the anterior end of the hippocampus
- Consists of several subnuclei
  - Basolateral amygdala: fear memories and reward processing
  - Central nucleus of the amygdala: physiological response in emotions and perception of emotion

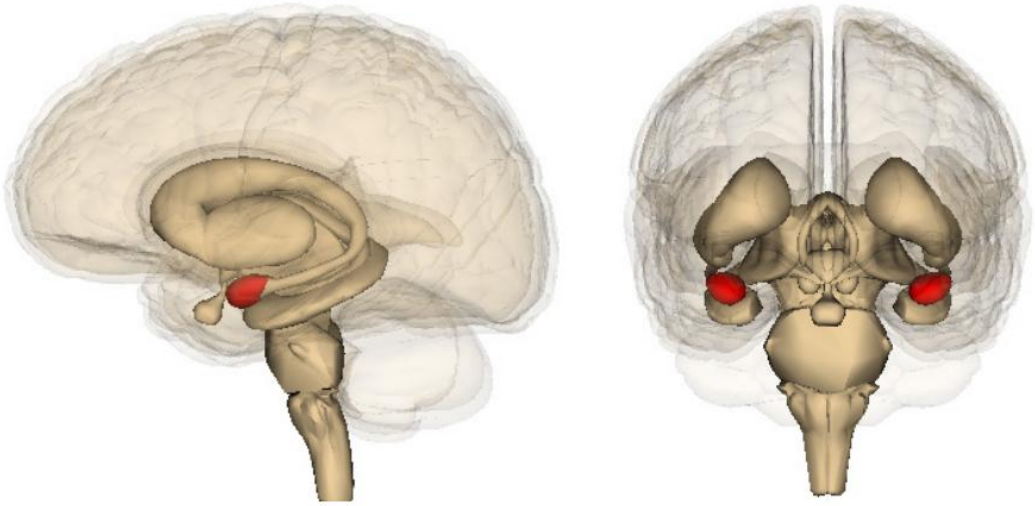


Figure 13.10 The amygdala are temporal lobe structures that contribute to the salience of emotional stimuli.

Amygdala: formation and storage of emotional memories

- Both positive and negative valence
- Foot-shock paradigm (non-human model of PTSD)
- Amygdala lesions prevent the rodent from freezing (block fear conditioning)
- Hippocampal lesions do not

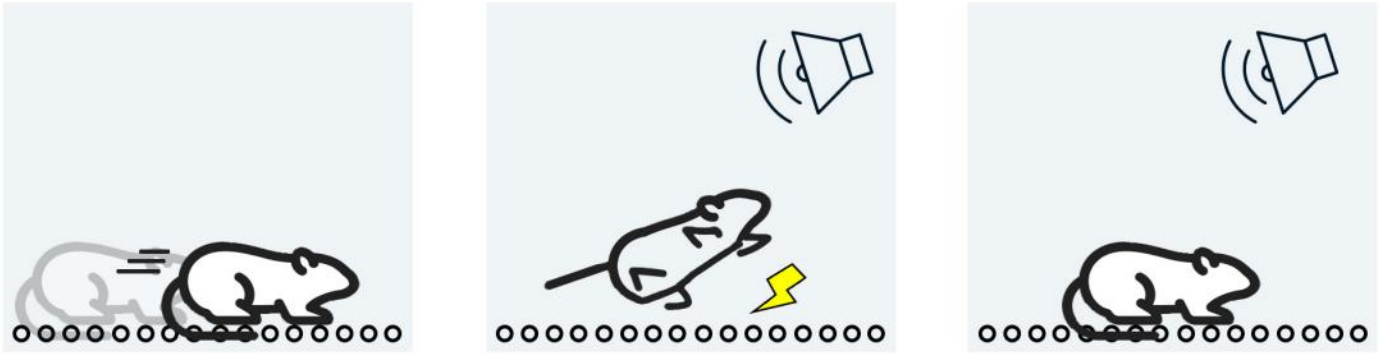


Figure 13.11 In the fear conditioning paradigm, a rodent is put into a room with medal rods as the floor (left). Then, a sound tone is repeatedly paired with a foot shock (middle). When the sound is played again, the rodent may exhibit freezing behavior (right).

Inferotemporal cortex

- Part of the ventral visual stream (Chap 7)
- Stores some components of visual memory
- E.g., when we recognize a person or an object
- Experiment to test visual memory:
  - Present a series of abstract shapes
  - Ask participants to respond to repeated shapes
  - After viewing 10,000 images for a few seconds each, participants able to identify a previously seen image successfully 83% of the time

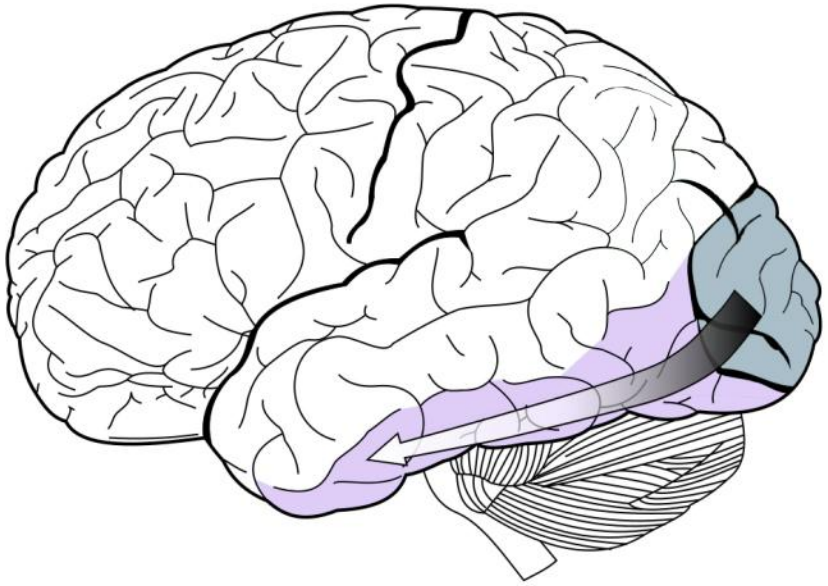


Figure 13.12 The inferotemporal cortex is one of the signaling pathways important for visual memories.

Parts of the inferotemporal cortex

- Fusiform cortex
- Fusiform face area
- Parahippocampal place area

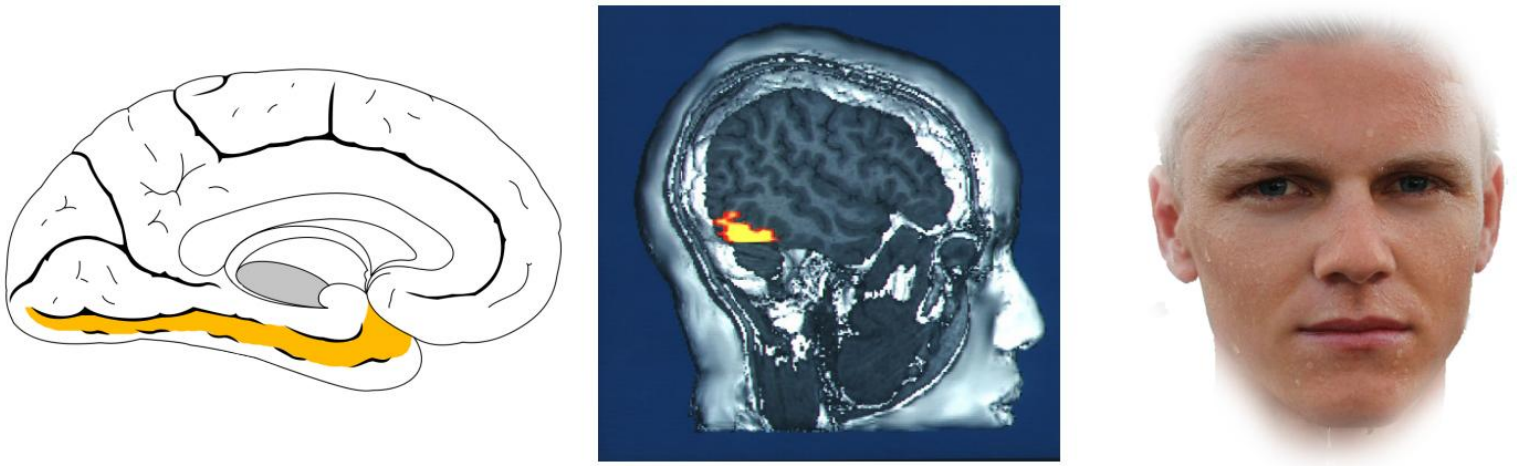


Figure 13.13 The inferotemporal cortex (left, sagittal view) is part of the ventral stream of visual perception, and is likely one site of visual information storage. Within the IT is the fusiform gyrus (middle), which is specifically activated strongly in imaging studies when a person is shown with a facial stimulus (right).

Prefrontal cortex

- Short term and working memory
- Strokes, frontotemporal dementia
- Strong projections to hippocampus

Striatum

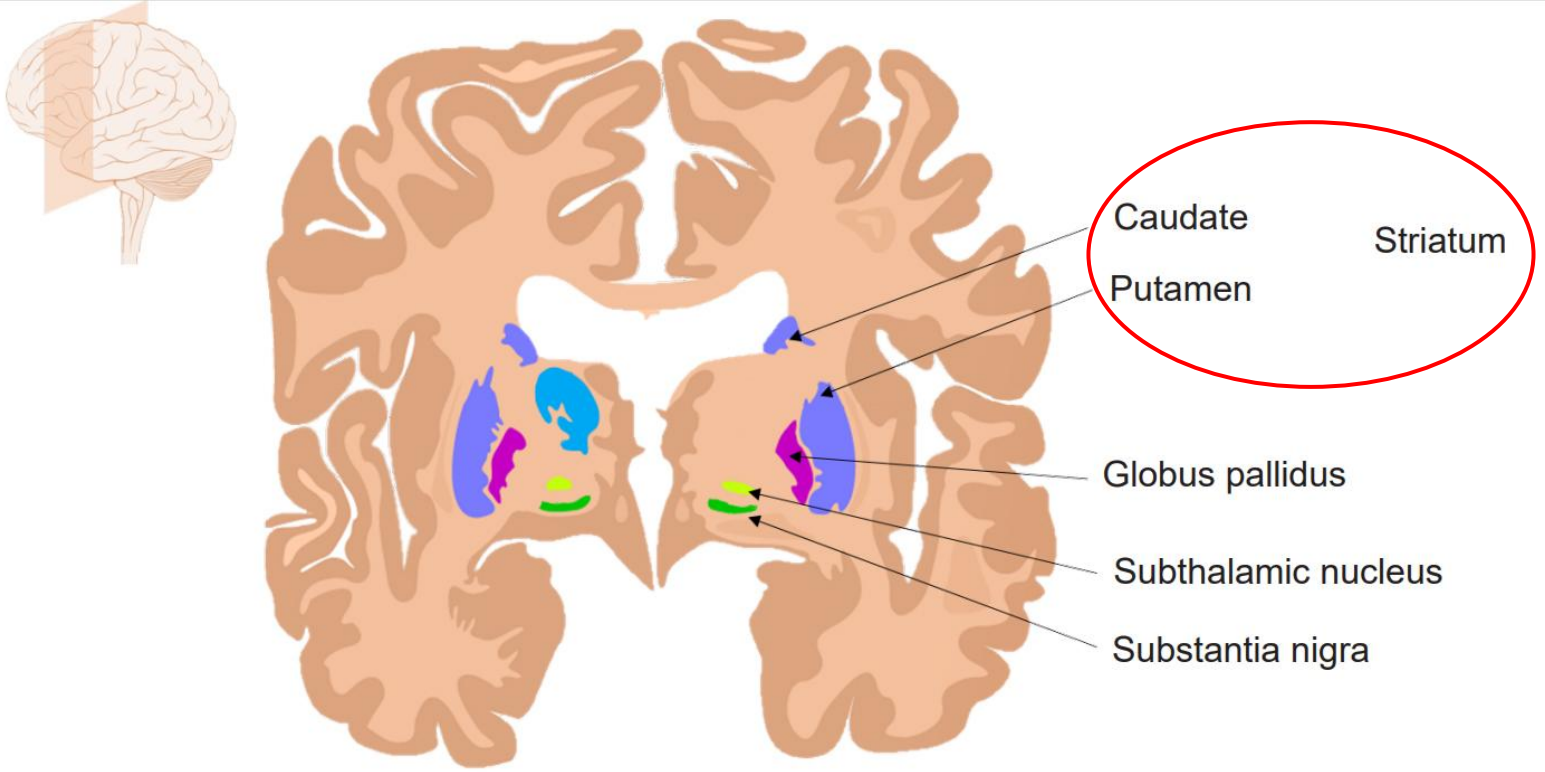


Figure 13.14 Several subcortical brain areas make up the basal ganglia.

- Procedural memory
- Habitual responding (pros and cons?)
- Obsessive compulsive disorder
- Rodent test: Self grooming
- Substance use disorder (think about habitual motor actions)
- Role of reward circuitry in learning

Cerebellum

- Motor functions (Chapter 10)
- Procedural memory, particularly performance of motor abilities
- Learning new motor skills likely requires changes in the circuit strength of cerebellar neurons
  - What do “changes in the circuit strength” look like?

Hypermnesia

- Rare
- Patient Solomon Shereshevsky, studied by A.R. Luria
  - Russian newspaper reporter
  - Recall nearly any memory with perfect precision, even after several years
  - E.g., Whole pages from books on any subject in any language
  - Co-morbid executive dysfunction, multimodal synesthesia, possible Autism
  - “The connection between the worlds he created in his mind and the world he lived in was so visceral that Shereshevsky could elevate his heart rate by simply imagining he was running after a train. He could raise the temperature of one hand and lower the other by picturing one hand on a stove and the other resting on a block of ice.” (https://lithub.com/the-man-who-remembered-everything-and-thought-it-was-normal/)

The importance of forgetting

- https://www.columbiapsychiatry.org/news/why-forgetting-good-your-memory

Cellular mechanisms of learning

- The weight of the brain increases dramatically over the first 10 years of life, but levels out after that (https://humanorigins.si.edu/human-characteristics/brains)
- Yet we still learn and remember a lot!
- How?

Synaptic plasticity

- New pieces of information are held in the connections between cells, not just in the cells themselves

What do I mean by “pieces of information are held”?

- Information is represented at different levels depending on modality, technology, and context

How much information can the brain store?

- 150 trillion synapses per adult human brain
- Different combinations of activity at these synapses possible

Stages of a memory

1. Encoding
2. Consolidation
3. Storage
4. Retrieval

Encoding

- Putting the memory into storage
- We cannot possibly encode (store) all the sensory inputs we receive
- Stimuli relevant to survival (e.g., predator cues) are more likely to be encoded
- Stimuli we attend to are more likely to be encoded

Consolidation

- Enables the memory becoming more permanent
- Nova Scotian Donald Hebb
- Textbook correction: he was not a clinical neuropsychologist (which is usually what “neuropsychologist” means
- “neurons that fire together wire together”
- When cells fire together repeatedly, the synapse is strengthened for future communication, making the next signal more robust
- When cells do not fire together, their connection is weakened
- Hebbian learning, Hebbian synapse
- This was just Hebb’s theory; evidence came later
- The specific circuit of neurons that represent the piece of information stored is called the **memory trace** or **engram**

Consolidation via reverberating circuits

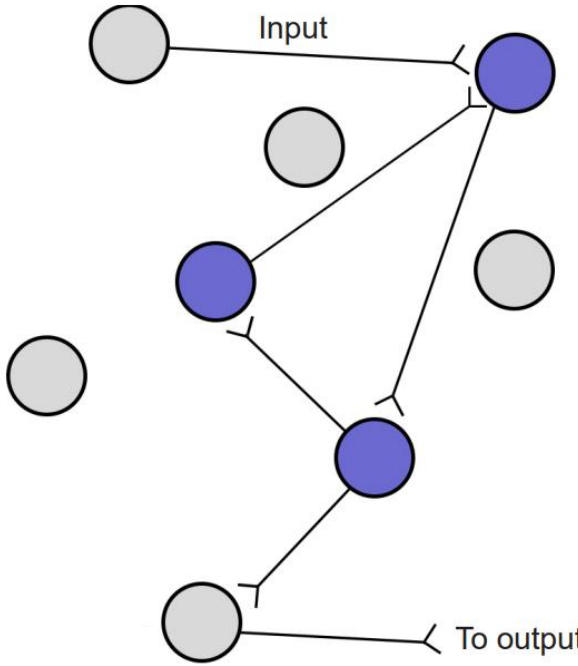


Figure 13.15 A reverberating circuit (purple) is a series of neurons that are activated repeatedly with the activity of a positive feedback circuit.

Impact of consolidation

- Possible that consolidation “moves” memory trace from subcortical structures like the hippocampus to the neocortex
- Neocortex
  - Thought to be evolutionarily younger than other
  - Mostly made up of the bumps and folds visible from lateral, anterior, posterior, and dorsal view of the brain
- Evidence: HM
- Suggests process takes around two years

When does consolidation take place?

- Primarily during sleep
- REM sleep for procedural memory
- Non-REM sleep for declarative memory
- Using EEG to deprive specific sleep stages
- Role of dreaming unknown

Retrieval

- Bringing back the specific engram
- Occurs for both declarative and procedural memories
- Free recall versus cued recall

Reconsolidation

- Happens during retrieval
- Retrieving the engram involves replaying the activity of the relevant circuit
- Sometimes parts of the engram get emphasized, lost, or changed
- Possible explanation for false memories
- Impact on eyewitness testimony
- Link to PTSD

Special populations of neurons

- Place cells - hippocampus
- Grid cells - entorhinal cortex
- Concept cells (aka Jennifer Aniston neurons) – temporal lobe cortex

Place cells

- Special population of pyramidal cells in the hippocampus
- Neurons increase their firing activity (ie action potentials) when the animal is in a particular location in an environment
- Contribute to location and navigational memory
- Help create a spatial map of the animal's surroundings
- Not topographically organized – adjacent areas of the environment do not necessarily activate adjacent hippocampal place cells

Grid cells

- Entorhinal cortex (input to hippocampus via perforant pathway)
- Increase firing activity when the animal is at an intersection of a “grid” in a wide-open, previously explored environment.
- Overlap of multiple grids gives the animal an idea of its surroundings

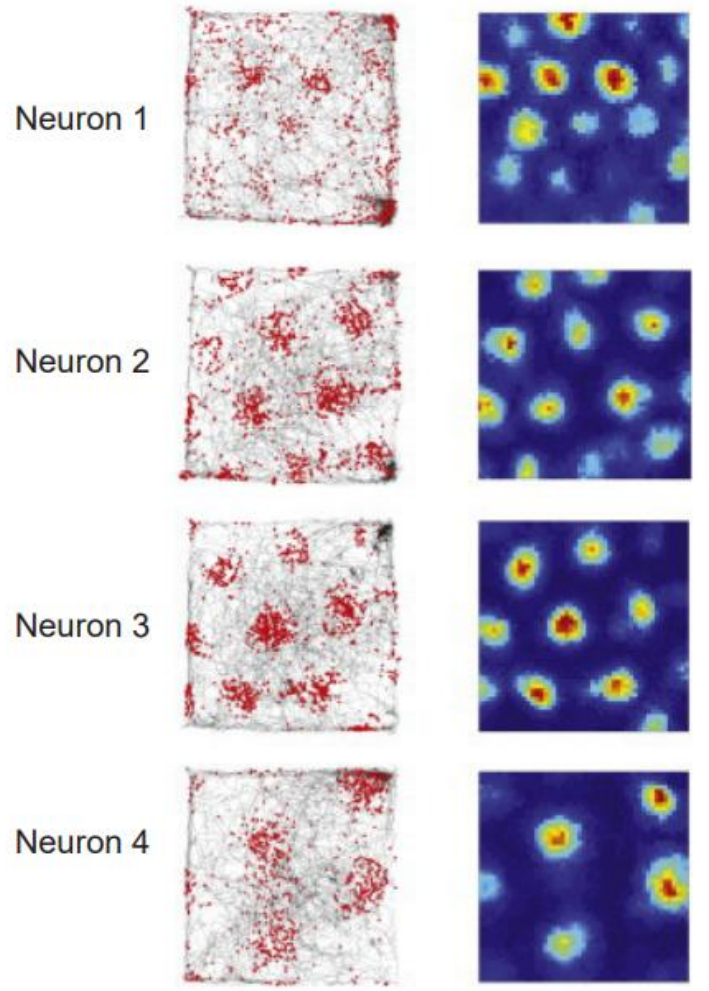


Figure 13.16 A rat is tracked (left, gray) as they move through an open field. Individual grid neurons spike when the rat passes through particular areas of the open field (left, red). Heat map (right) showing high neuronal activity in warm colors (red and yellow) with low activity in cool colors (blue).

Grid cells and place cells

- https://www.researchgate.net/figure/Grid-and-place-cells-work-together-to-determine-the-animals-position-Schematics-of_fig1_364312896

Concept cells

- Cortical neurons in the temporal lobe that increase firing activity exclusively in response to stimuli associated with highly-specific concepts
- Not necessarily the same modality or physical properties

Figure 13.17 Concept cells change their firing pattern in response to the presentation of highly specific stimuli, such as the character Luke Skywalker (portrayed by actor Mark Hamill; images 1, 3, and 5). Visually similar but conceptually different stimuli (male brunette actors appearing in film), like pictures of Leonardo diCaprio (image 2) or Keanu Reeves (image 4), fail to induce changes in firing. However, visually distinct but conceptually-related stimuli, like the picture of Yoda (a related character from the same series of films; image 6) may also drive the concept cells to fire.

Molecular mechanisms of learning

- Substrates of learning can be found at the level of synapses
- **Synaptic plasticity**
- Increase in synaptic strength: Long-term potentiation (LTP)
- Decrease in synaptic strength: Long-term depression (LTD)
- Both LTP and LTD can occur at both excitatory and inhibitory synapses

Long-term potentiation

- Bliss and Lomo wanted to test Hebb's theory about cells that fire together wiring together
- Stimulating electrode among the axons of the perforant pathway
- Recording electrode in the dentate gyrus
- Single stimulation pulse caused neurons to depolarized, as measured via the recording electrode
- This observation is called a field excitatory post-synaptic potential (fEPSP).
- Field = "big" area. More than one neuron is depolarizing/having an EPSP
- Next, they zapped the axons at 100 Hz for 3 seconds

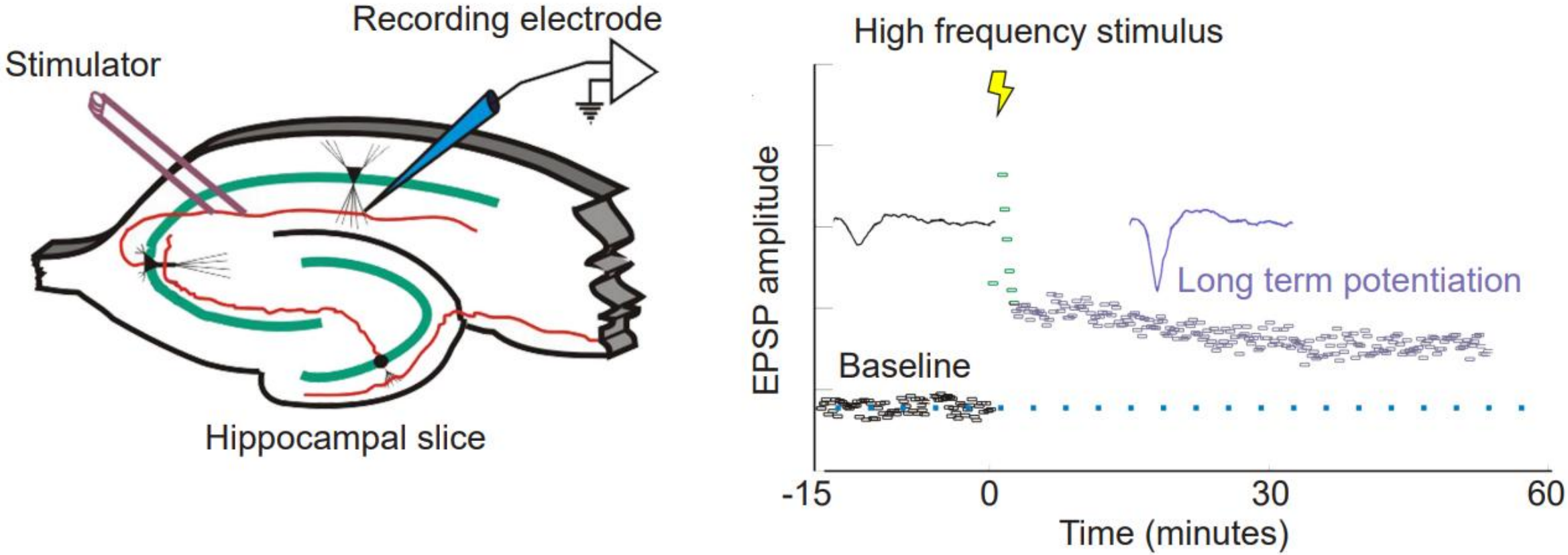


Figure 13.18 Schematic of the recording configuration of Bliss and Lomo's experiments (left) demonstrating that high frequency activation of the Schaffer collaterals while recording the field EPSP in the CA1 region leads to long term potentiation (right).

Bliss and Lomo’s Findings

- High frequency stimulation leads to an enhancement of fEPSP in response to a single stimulus (single zap)
- Measurable one year later

Cellular and molecular mechanisms of LTP

- AMPA and NMDA ionotropic glutamate receptors
- Recall from Chap 5: When glutamate binds to AMPA, Na+ channels open, causing cell to depolarize

NMDA receptors

- Ionotropic
- Pore blocked by Mg^{2+} (larger than pore, electrochemical gradient attracts Mg^{2+} towards receptor)
  - Because of this, NMDA receptors are not activated unless glutamate binds AND the cell is depolarized
  - Coincidence detector
- Permeable to Ca^{2+}
- Increases in intracellular postsynaptic Ca^{2+} lead to LTP

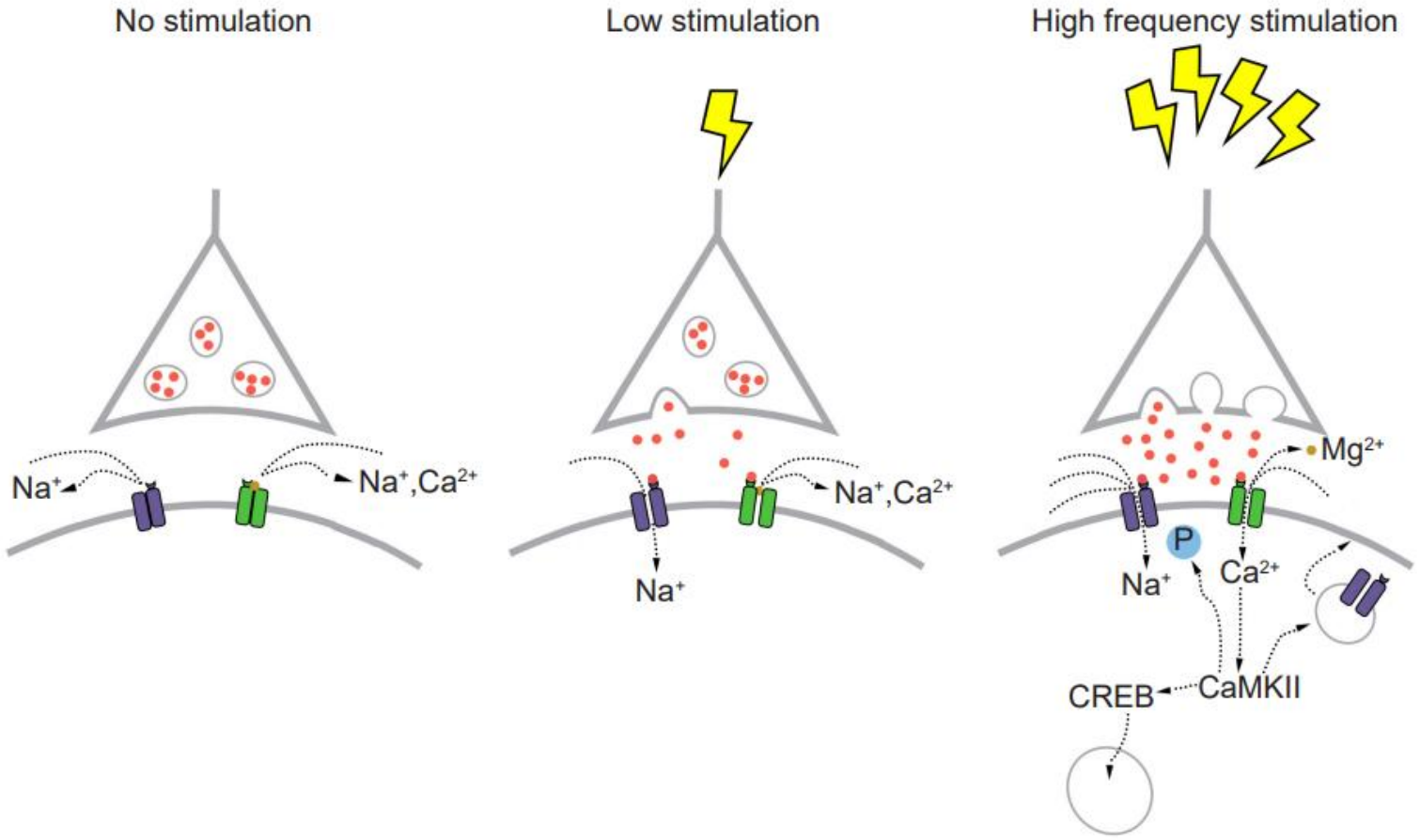


Figure 13.19 Molecular mechanisms explaining postsynaptic LTP. At no stimulation, glutamate (pink) does not strongly activate the AMPA receptors (purple; left). A single presynaptic depolarization causes some glutamate to be released, which activates AMPA receptors, causing postsynaptic depolarization (middle). At high frequency stimulation, significant glutamate release activates AMPA receptors, strongly depolarizing the postsynaptic cell, which causes the Mg^{2+} ion to leave from the NMDA receptor (green). Ca^{2+} enters through the NMDA receptor, and can trigger long term changes in the molecular components of the neuron (right).

- Increases in intracellular postsynaptic Ca^{2+} lead to LTP by activating
- CaMKII – enzyme (calcium/calmodulin-dependent protein kinase II)
  - Kinase – phosphorylates proteins
    - Phosphorylates AMPA receptors which makes them better at passing currents
    - Increases tracking of AMPA receptors to membrane
    - Interacts with transcription factor cAMP response element-binding protein (CREB)
      - Moves into the nucleus and instructions it to synthesize more mRNA for the AMPA receptor

Long-term depression

- Gill withdrawal reflex decreases after repeated innocuous brush strokes
- **Habituation**: suppression of a normal reflex behaviour
- (but we also use this word more broadly)

Figure 13.20 *Aplysia californica* was the model organism first used to demonstrate the neuronal level changes that underlie the habituation behavior.

LTD experiment

- Induce action potential firing in the somatosensory neurons receive information from the skin of the siphon
- Measure EPSP in the motor neurons that control the muscles of the gill
- After habituation: motor EPSPs smaller

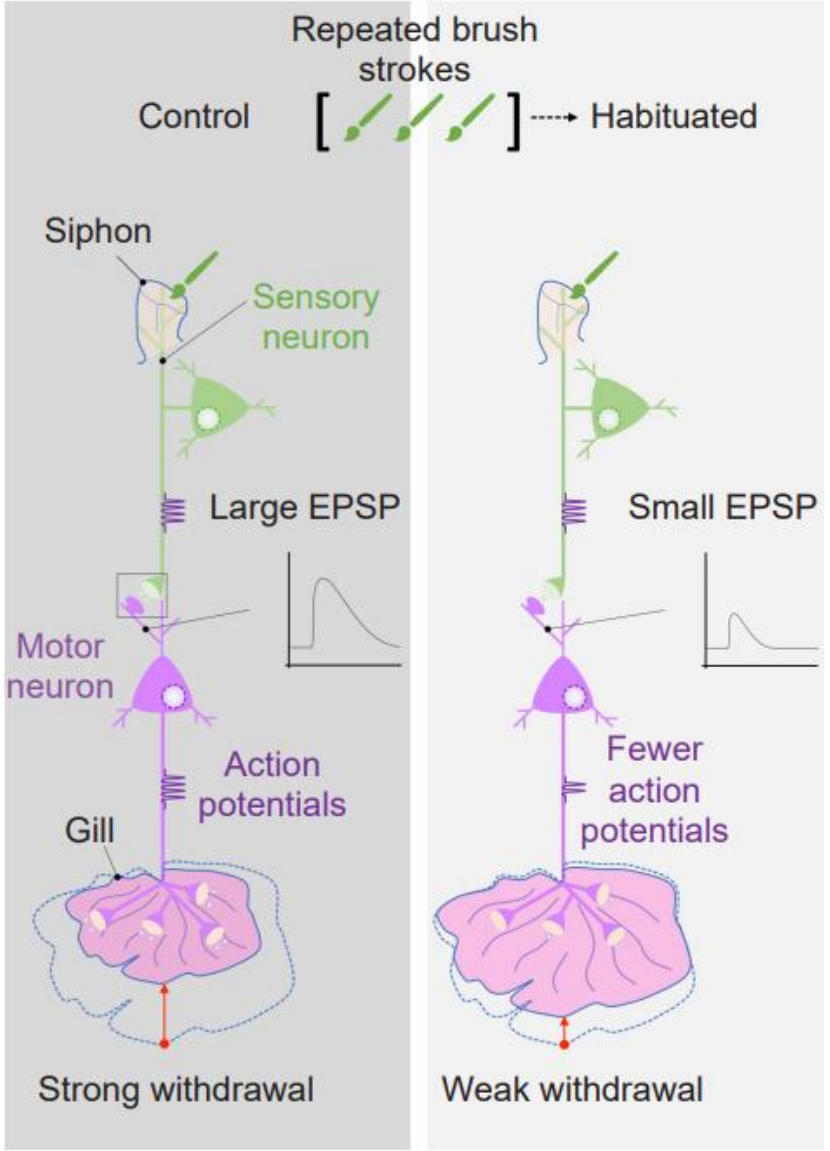


Figure 13.21 Habituation of the gill withdrawal reflex was modeled by Kandel using Aplysia. Repeated brush strokes to the siphon caused cellular level changes that led to decreased gill withdrawal.

Sensitization

- Pair siphon brush stroke with painful electric shock
- Larger motor reaction and larger motor EPSP observed
- Mechanism
  - Interneurons that synapse onto the motor neurons
  - Activated by noxious stimuli to release serotonin
  - Which activates cAMP in the terminals of the motor neurons
  - cAMP increases the probability of neurotransmitter release and strengthens the gill withdrawal reflex

Compare and contrast sensitization and LTP

- Both related to synaptic plasticity
- Both result in easier depolarization of the post-synaptic cells
- sensitization results in cAMP increases (which increases presynaptic NT release);
  - What caused the increase in cAMP?
    - Noxious stimuli activates interneurons -> releases more serotonin -> results in more cAMP in the motor neurons
  - What is the molecular mechanism of LTP?
    - Glutamate binds to AMPA -> cells depolarize
    - NMDA receptors are blocked by Mg2+ at the resting potential. Once cell is depolarized, Mg2+ is less attracted and pore is no longer blocked.
    - Ca2+ can pass through
    - Increases in intracellular postsynaptic Ca^{2+} lead to LTP by activating
      - CaMKII – enzyme (calcium/calmodulin-dependent protein kinase II)
        - Kinase – phosphorylates proteins
        - Phosphorylates AMPA receptors which makes them better at passing currents
        - Increases tracking of AMPA receptors to membrane
        - Interacts with transcription factor cAMP response element-binding protein (CREB)
          - Moves into the nucleus and instructions it to synthesize more mRNA for the AMPA receptor

Endocannabinoid-mediated LTD

- Postsynaptic depolarization activates PLC and diacylglycerol (DAG) lipase to create endocannabinoids
  - Retrograde neurotransmitters: produced at dendrites and send signals to axons
- Metabotropic receptors (mainly CB1) inhibits cAMP signaling, which decreases neurotransmitter release probability.

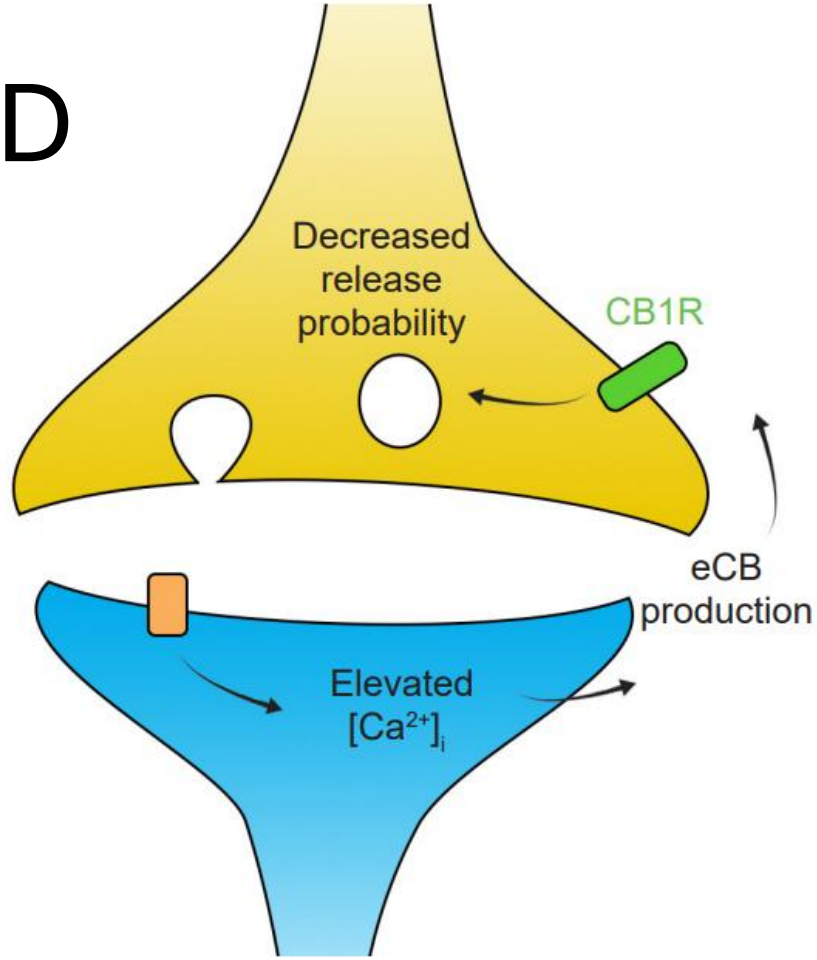


Figure 13.22 Endocannabinoid-mediated LTD is a result of a retrograde signal that decreases release probability.