



The Brain, Biology and Cognition (BBC)

Learning, Memory, and Amnesia

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Synaptic Mechanisms of Learning and Memory

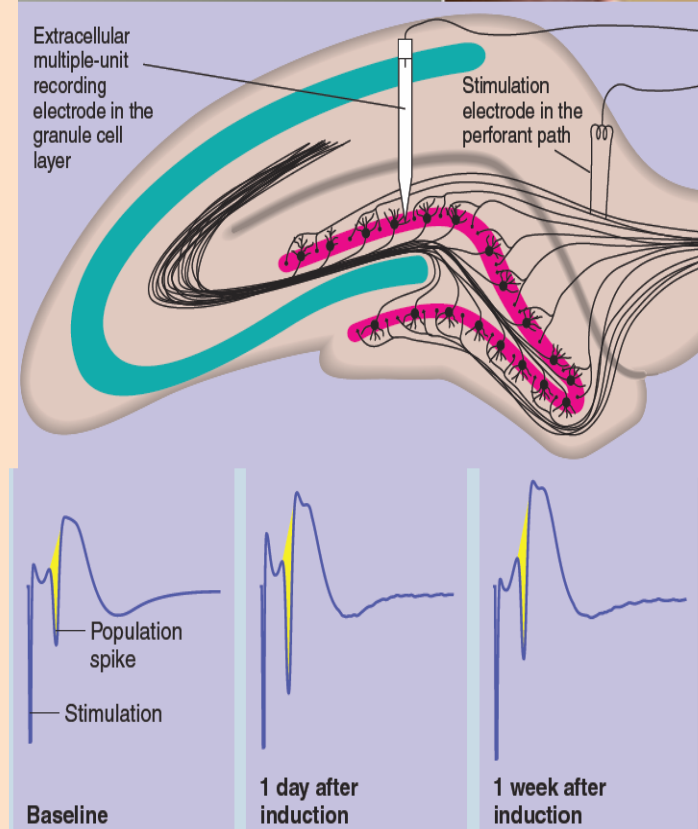


- Hebb (1949): Changes in synaptic efficiency are basis of LTM.
- Facilitation of synaptic transmission following electrical stimulation to presynaptic neurons
- **Long-term potentiation (LTP).**
 - Synapses made stronger by repeated stimulation
- Two main properties of LTP:
 1. It can last for many weeks, even months
 2. Only occurs if presynaptic firing followed by postsynaptic firing

LTP as a Neural Mechanism of Learning and Memory

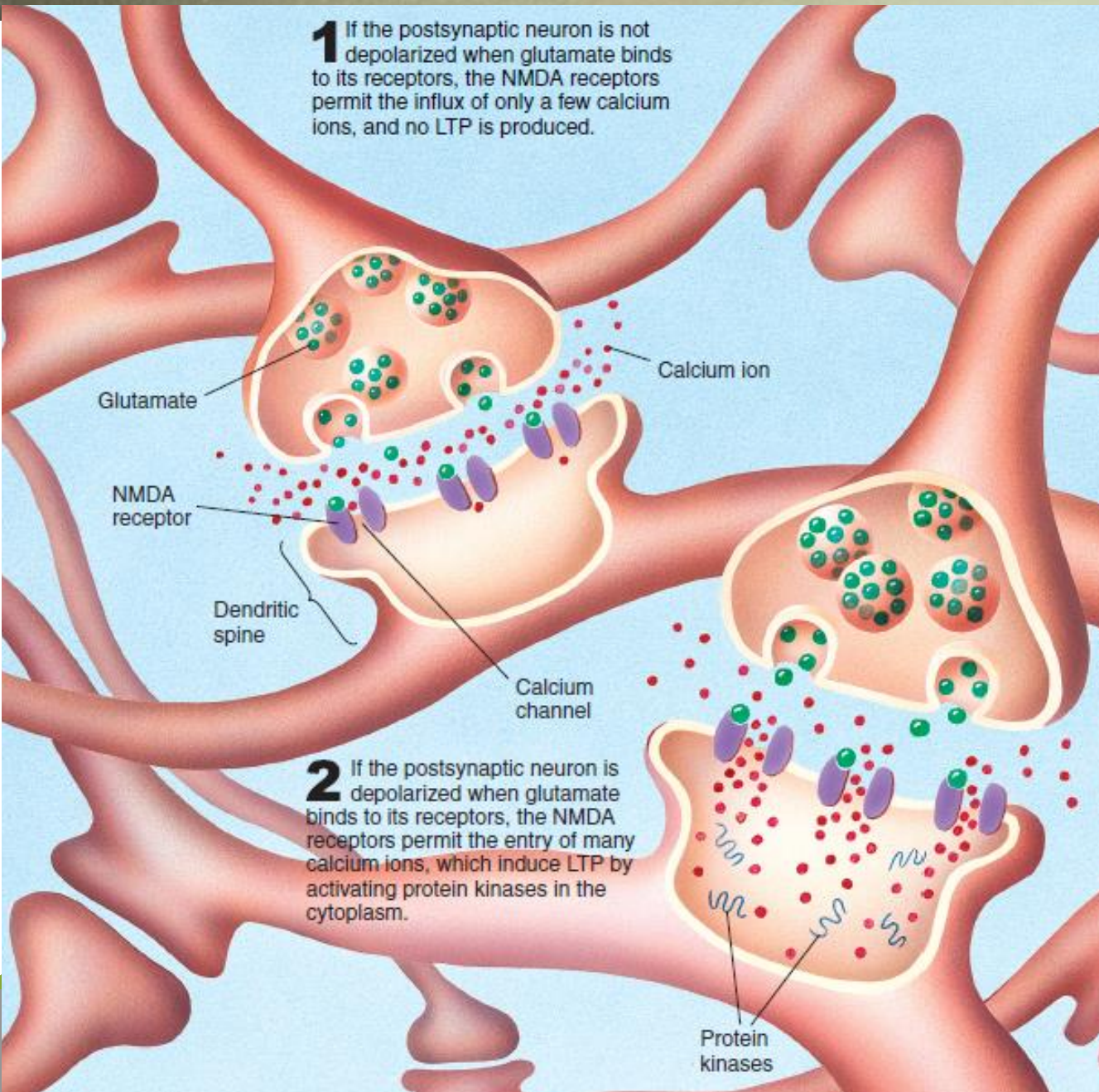


- **Inducing LTP:**
- Single low-intensity electrode pulse of current to perforant path (major input to dentate gyrus).
- Response recorded in granule cell layer of hippocampal dentate gyrus.
- Initial stimulation determines baseline
- Then, high intensity/frequency stimulation
- Granule cells response to single pulses of low intensity current measured after various delays.
- Transmission at granule cells synapses still potentiated 1 week after high frequency stimulation



LTP in granule cell layer of rat hippocampal dentate gyrus. (Traces courtesy of Michael Corcoran, Department of Psychology, University of Saskatchewan.)

LTP as a Neural Mechanism of Learning and Memory



1 If the postsynaptic neuron is not depolarized when glutamate binds to its receptors, the NMDA receptors permit the influx of only a few calcium ions, and no LTP is produced.

2 If the postsynaptic neuron is depolarized when glutamate binds to its receptors, the NMDA receptors permit the entry of many calcium ions, which induce LTP by activating protein kinases in the cytoplasm.

LTP can be viewed as a three-part process:

- 1. High frequency stimulation inducing LTP (learning)**
- 2. Maintenance (memory)**
- 3. Expression (recall)**

Induction of LTP: Learning



- NMDA glutamate receptor prominent at synapses where LTP most commonly studied.
- NMDA receptors do not respond unless glutamate binds to it **and** neuron is partially depolarized
- Calcium (Ca^{2+}) channels do not open fully unless both conditions are met
- Influx of calcium ions triggers action potentials and cascade of events in postsynaptic neuron that induces LTP.

Induction of LTP: Learning



- Evidence that calcium produces effects by activating **protein kinases**
 - Class of enzymes that influence chemical reactions in a cell and induces changes causing LTP
- Protein kinase inhibitors block the induction of LTP.

Maintenance and Expression of LTP:

Storage and Recall



- **Maintenance and expression of LTP involve changes in pre and post synaptic neurons.**
- **Structural changes depend on protein synthesis**
 - **E.g., increase size of neuron**
- **Transcription factors – intracellular proteins that bind to DNA and influence operation of particular genes.**
- **Induction on LTP begins in postsynaptic neurons and maintenance/expression involves presynaptic changes**
 - **Suggests signal passes from postsynaptic back to presynaptic - E.g., soluble gas neurotransmitter nitric oxide**

Memory and the brain



Evidence from imaging research with healthy controls supports idea that:

- 1. We have separate STM and LTM, and**
- 2. Both composed of further sub-components**

E.g., Henson et al. (2000): fMRI suggests

- Phonological store: Left interior parietal area**
- Articulatory process: Left prefrontal lobe area**

Zimmer (2008): brain areas involved in

- Visual processing: Occipital and temporal lobes**
- Spatial processing: parietal cortex**

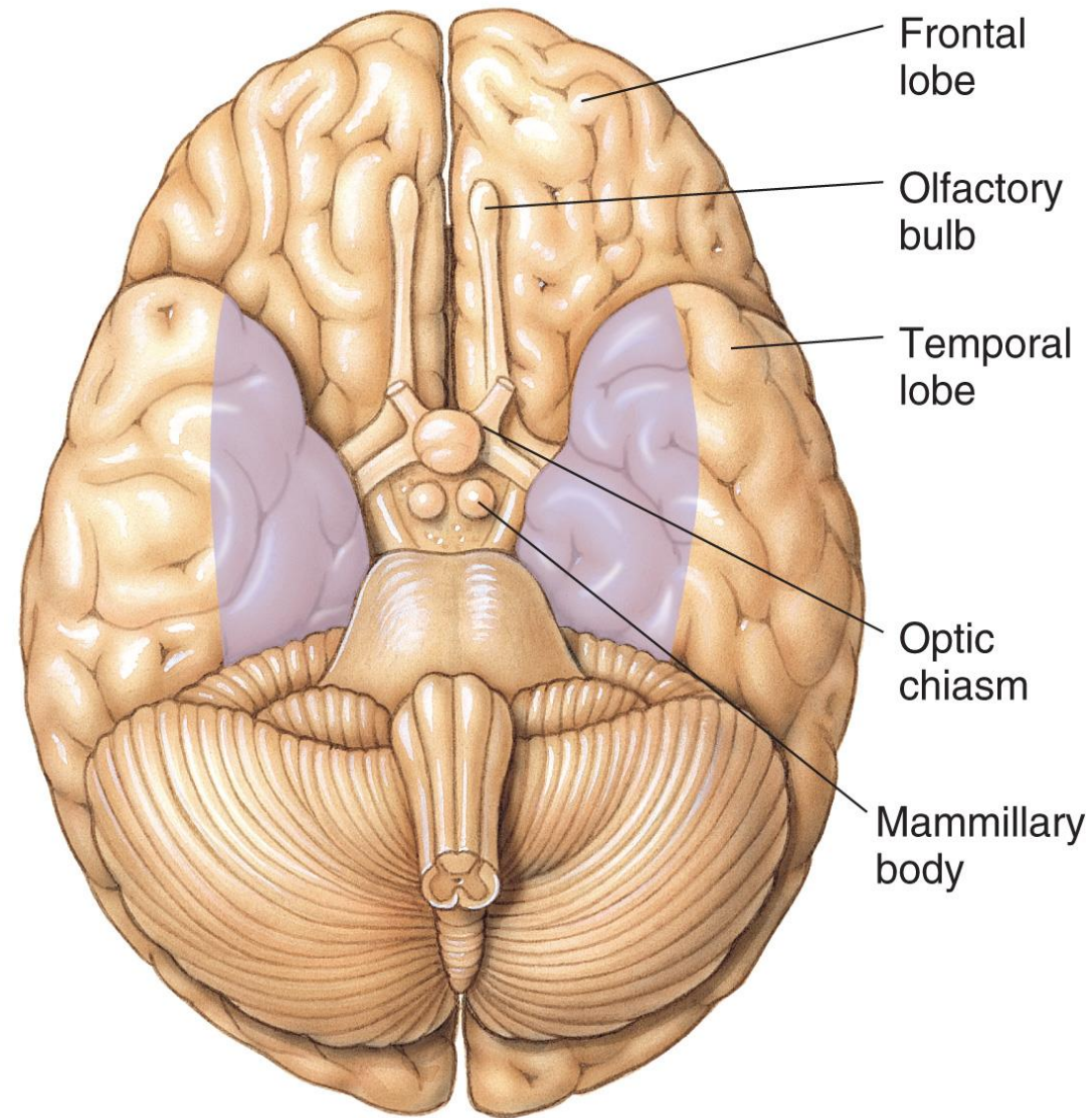
Neurological Research



However, most research conducted on patients with brain damage – especially amnesia:

- **Anterograde:** Inability to remember info after damage
- **Retrograde:** Inability to remember info prior to damage
- **Case of Clive Wearing: Life without memory**

Patient H.M.



Epileptic who had medial temporal lobes removed (including hippocampus and amygdala) to reduce experience of seizures

Following surgery, STM and memory for info prior to surgery was relatively intact.

However, he was unable to form most types of new long-term memories

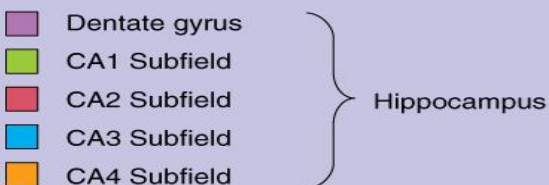
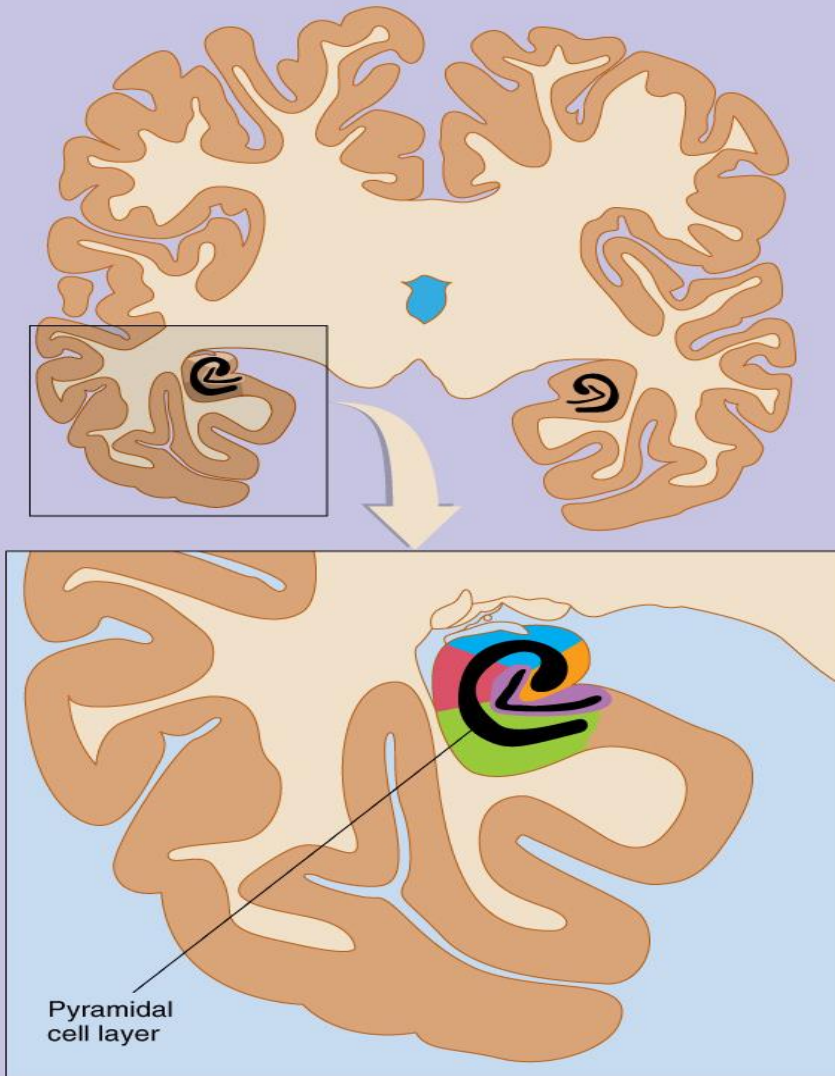
Medial Temporal Lobe Amnesia



- **Not all patients with this form of amnesia are unable to form new explicit long-term memories**
- **Semantic memory (general information) may function normally while episodic memory (events one has experienced) does not**
- **Medial temporal lobe amnesiacs may have trouble imagining future events**



Effects of Cerebral Ischemia on Hippocampus and Memory



- R.B. suffered damage to just one part of hippocampus (CA1 pyramidal cell layer) and developed amnesia
- Suggests hippocampal damage alone can produce amnesia
- But as we will see later, this conclusion has been challenged.

Episodic vs. Semantic memory: Evidence from brain-damaged patients



Spiers et al. (2001): 147 cases of amnesia with damage to hippocampus or fornix.

- Episodic memory impaired in all cases
- Fewer issues with semantic memory

Vargha-Khadem et al. (1997): Two patients with bilateral hippocampal damage

- Poor episodic but normal range semantic memory.
- Considered as stronger evidence as damage occurred at age before semantic memory developed.

Episodic vs. Semantic memory: Evidence from brain-damaged patients



Episodic memory depends on hippocampus

Semantic memory depends on entorhinal, perirhinal, and parahippocampal cortices.

- **Damage to hippocampus and cortices leads to episodic & semantic deficits (Vargha-Khadem et al., 1997)**
- **Damage only to hippocampus leads to greater deficits in episodic memory (Bindschaedler et al., 2011).**

Episodic vs. Semantic memory: Evidence from Retrograde Amnesia



Greater retrograde amnesia for episodic memory compared to semantic memory (Bayley et al., 2006)

Theory to explain retrograde amnesia:

- **Consolidation**: Long-lasting physiological “fixing” of episodic memories in the hippocampus.
 - Hippocampus plays role in consolidation as removal of temporal lobes disrupts formation of new memories.
 - Recently formed memories still being consolidated are vulnerable to interference and thus forgetting.

The Hippocampus and Consolidation



- Perhaps hippocampus stores memories temporarily
standard consolidation theory
 - Over time memories stored elsewhere, which protects them from hippocampal damage.
- Or perhaps hippocampus stores memories permanently, but they become “stronger” over time
(Multiple-trace theory: Nadel & Moscovitch, 1997).

Reconsolidation



- **Each time a memory is retrieved from LTM, it is temporarily held in STM, where it can again be susceptible to posttraumatic amnesia**
 - **Unless it is reconsolidated.**
- **Evidence:**
 - **Infuse protein-synthesis inhibitor into amygdalae of rats after being required to recall fear conditioning trial.**
 - **Rats developed retrograde amnesia for fear conditioning.**

Episodic vs. Semantic memory: Evidence from brain-damaged patients



- **Semantic Dementia: Severe issues with semantic but relatively intact episodic memory.**
- **Damage to anterior temporal lobes resulting in loss of info about meaning of words and concepts**

Double-dissociation:

- **Amnesic patients: poor episodic but intact semantic.**
- **Semantic dementia: poor semantic but intact episodic**

Evidence for separate LTM systems: Procedural Memory



Procedural Memory (skill learning):

- **Often intact in amnesiacs**
- **Evidence from serial-reaction time tasks**
 - **Respond as quickly as possible to target stimulus:**
- **Evidence from motor skill task:**
 - **Driving ability (steering, speed control, safety errors, driving with distraction) of two amnesiacs comparable to healthy controls (Anderson et al., 2007).**

Evaluation: Declarative vs. Procedural



Cannot assume one task is only performed with use of either declarative or non-declarative memory.

Specifics of task could involve either system depending on:

- **Conditions of task (single vs. dual)**
- **Characteristics of participant (stressed vs. not-stressed)**

Possibly an interaction between systems?

Skill learning involves hippocampus (Albouy et al., 2013).

Implicit vs. Explicit distinction?



Based on conscious access to stored info.

- Systems involving conscious access rely on hippocampus while systems not involving conscious access do not.
- However, inconsistent findings led to alternative theories

Henke (2010): rejects consciousness as criteria for distinguishing between memory systems.

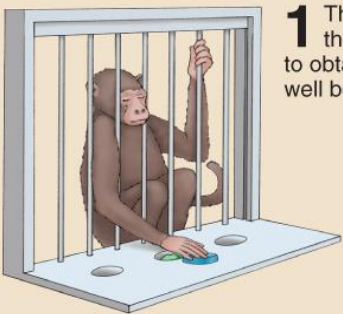
- Instead: systems should be identified on type of *processing*:
- Rapid encoding of flexible associations (episodic: hippocampus)
- Slow encoding of rigid associations (procedural/semantic: basal ganglia)
- Rapid encoding of single items (recognition familiarity: parahippocampal gyrus)

Neuroanatomy of Object-Recognition Memory



- **Human research lacks control and deliberate lesions to a human brain would not be ethical.**
- **So, animal models have been developed.**
- **Early models failed because lesions of medial temporal lobe structures did not lead to anterograde amnesia in rats or monkeys.**
- **Also, many studies only involved implicit memory tests and only suggested hippocampus was key.**

Neuroanatomy of Object-Recognition Memory



1 The monkey moves the sample object to obtain food from the well beneath it.



2 A screen is lowered in front of the monkey during the delay period.



3 The monkey is confronted with the sample object and an unfamiliar object.



4 The monkey must remember the sample object and then select the unfamiliar object to obtain the food beneath it.

- 1970s: animal model of H.Ms case developed
- Monkeys with bilateral medial temporal lobectomies showed LTM deficits in explicit memory through
 - **Delayed nonmatching-to-sample test.....**
- Like H.M., performance was normal when memory only needed to be held for a few seconds, but lesions hindered performance.

Delayed Nonmatching-to-Sample Test for Rats



- Lesions to monkey hippocampus achieved through aspiration (suction method).
- However, due to size and location of monkey hippocampus, other areas of cortex receive damage.
- Set-up of rat brain = little damage to other areas.
 - Also, hippocampus is so small, it can be lesioned electrically or with neurotoxic injection (less residual damage).



- See Figure in Pinel.

Delayed Nonmatching-to-Sample Test for Rats



- Version of nonmatching to sample task used with rats involves Mumby box.
 - Example in Pinel.
- Performance resembles that seen in monkeys
 - Good ability when brain intact, poor performance after medial temporal lobe lesion.



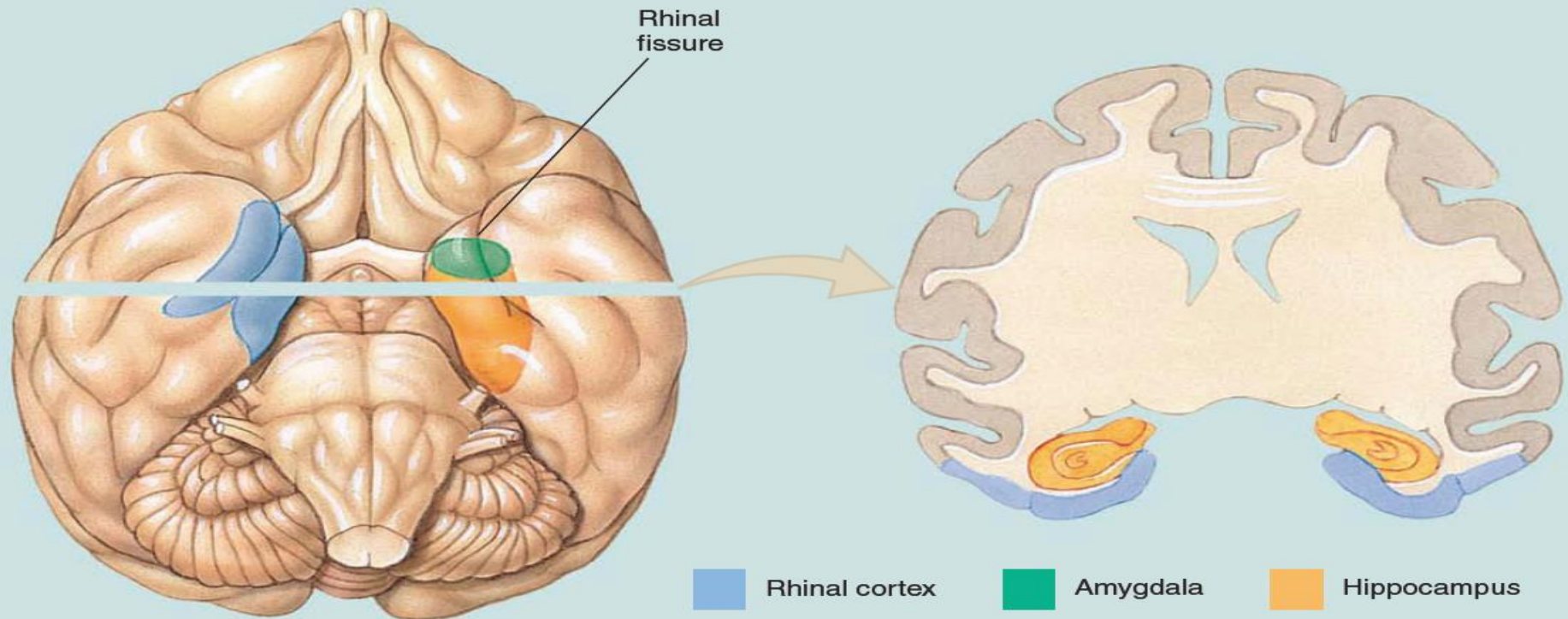


**Complete the worksheet on
the delayed nonmatching-to-
sample tests used with
monkeys and rats**

Neuroanatomical Basis of Object-Recognition Deficits Resulting from Medial Temporal Lobectomy



- 1990s research challenged if hippocampal damage in medial temporal amnesia.
- Bilateral removal of rhinal cortex = object-recognition deficits
- Bilateral removal of hippocampus = no effects on object recognition
- Bilateral removal of amygdala = no effect on object recognition



A Paradox



- **Complete removal of hippocampus = moderate deficit in object recognition**
- **But small lesions of hippocampus lead to severe deficit**
- **How can this be?**



A Hypothesis



- **Ischemia-induced hyperactivity of CA1 pyramidal cells damages neurons outside hippocampus (excessive release of excitatory amino acids).**
- **Explains ischemia-induced object recognition deficits**
- **Whereas bilateral hippocampectomy prevents ischemia-induced deficit**
- **Supported by fMRI where rats have induced ischemia by tying carotid artery to restrict blood flow to brain**

Hippocampus and Memory for Spatial Location



- Rhinal cortex plays role in **object recognition**
- Hippocampus plays role in **spatial location memory**
- Many hippocampal cells are **place cells**, responding when in a particular place and to other cues
 - **Grid cells** also found in hippocampus and entorhinal cortex



Comparative Studies of the Hippocampus

- Similar findings in Food-caching birds:
- Need to remember location of food stores hidden in their territory.
- Have larger hippocampus than non-food caching birds.
- Primate studies inconsistent:
- Perhaps discrepancies due to different testing paradigms (navigating actual env vs. sitting still/locating on computer screen).





Theories of Hippocampal Function

- **Cognitive map theory:** hippocampus constructs and stores allocentric maps of the world:
 - Representations of space based on relations among external objects/landmarks.
- Challenges to this theory:
 1. Firing of place cells sometimes depends on more than spatial location
 2. Hippocampal damage sometimes impairs behavior without spatial component
 3. Hippocampus is large/complex and component substructures require further evaluation

Where Are Memories Stored?



- **Destruction of one brain area does not lead to complete loss of all memories.**
- **Suggests memories are stored diffusely throughout brain structures involved in their formation.**
- **Some have roles in storage of memories**
 - **Hippocampus – spatial location**
 - **Perirhinal cortex – object recognition**
 - **Mediodorsal nucleus – Korsakoff's symptoms**
 - **Basal forebrain – Alzheimer's symptoms**

Where Are Memories Stored?



- **Inferotemporal Cortex**

- Involved in visual perception of objects
- Stores memories of visual patterns
 - Evidence from recording of neurons in monkeys

- **Amygdala**

- Memory for emotional significance of experience.
 - Rats with amygdala lesions do not show fear response.
 - But may not store memory, just strengthens emotional memories stored in other structures

Where Are Memories Stored?



- **Prefrontal cortex:** Temporal order of events and working memory
 - Tasks involving series of responses
 - Different part of prefrontal cortex mediate different WM
- **Cerebellum:** Stores memories of sensorimotor skills:
 - Pavlovian condition of eye blink response in rabbits.
- **Striatum:** Habit formation - consistent relationship between stimuli and response

Why would the brain develop separate stores



• Protection

- If all memory held in one structure, damage would result in complete loss of all memory.
- To prevent devastating effects of damage to one area.
- Link to other brain facets, such as amygdala being important for emotion.
 - Memories are stored in brain structures that were involved in their formation and processing.