



Biological Psychology

M5X00908 Brain, Behaviour, and Cognition (BBC)

Lecture 5: Learning, Memory, and Amnesia

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Amnesic Effects of Bilateral Medial Temporal Lobectomy



- **H.M. – Epileptic who had his temporal lobes (including hippocampus, amygdala, & adjacent cortex) removed in 1953.**
- **Removal of one medial temporal lobe had been successful in other patients, so medial portions of both temporal lobes were removed.**
- **His seizures were dramatically reduced but so was his long-term memory.**
- **Mild retrograde amnesia and severe anterograde amnesia**



Amnesic Effects of Bilateral Medial Temporal Lobectomy



Retrograde

- **Backward-acting**
- **Unable to remember the past**

Anterograde

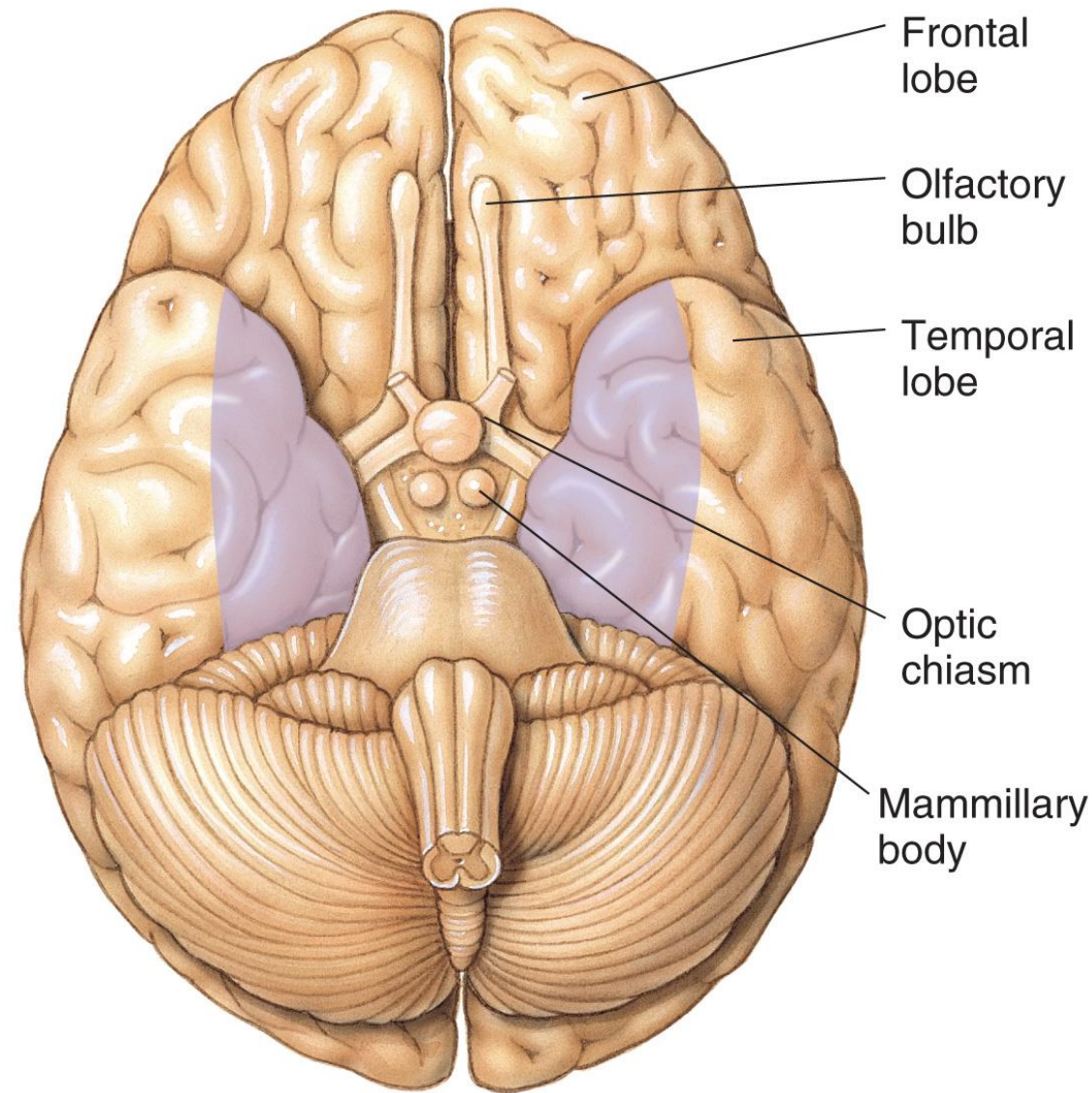
- **Forward-acting**
- **Unable to form new memories**

Amnesic Effects of Bilateral Medial Temporal Lobectomy



While H.M. is unable to form most types of new long-term memories, his short-term memory is intact

Figure shows the Medial temporal lobectomy. The portions of the medial temporal lobes that were removed from H.M.'s brain shown in a view of the inferior surface of the brain.



Formal Assessment of H.M.'s Anterograde Amnesia: Discovery of Unconscious Memories



- **To characterise his memory deficit, researchers measured his performance on various tasks (7 in total)**
- **Some tasks (e.g., Digit span & Block-tapping memory-span) showed extent of his LTM deficits.**
- **The remaining tests (mirror-drawing, rotary pursuit, incomplete-picture, and Pavlovian conditioning), suggested his brain was capable of storing long term memories but had no conscious awareness of them**

Formal Assessment of H.M.'s Anterograde Amnesia: Discovery of Unconscious Memories



- **Digit span** – H.M. could repeat digits, provided the time between learning and recall was within the duration of STM
- **Digit span +1** - he had to verbally repeat 5 digits read to him at 1 second intervals, once repeated correctly the same 5 digits were given again but with 1 new digit added on the end, and so on.
 - After ~25 trials non-brain damage participants can repeat about 15 digits but HM could not even repeat back the 8 digit sequence.
- **Block-tapping memory-span test** – this test demonstrated that H.M.s' amnesia was global – not limited to one sensory modality.
 - Nine blocks were spread out on a board in front of him and he was asked to watch the neuropsychologist touch a sequence of them and then to repeat back the same sequence of touches.
 - He could do this for 5 blocks (which is within normal range) but he could not do it for 6 even if the same sequence was done 12 times.

Formal Assessment of H.M.'s Anterograde Amnesia: Discovery of Unconscious Memories



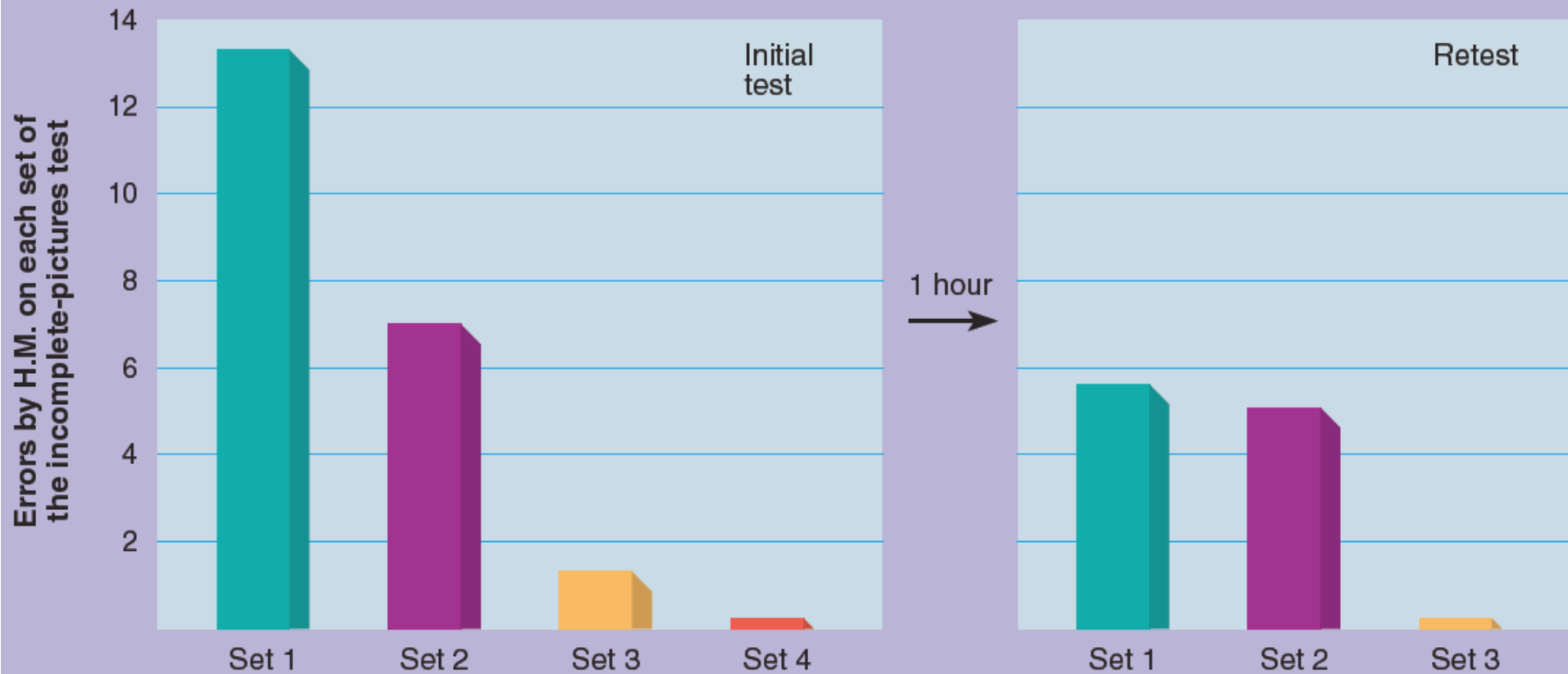
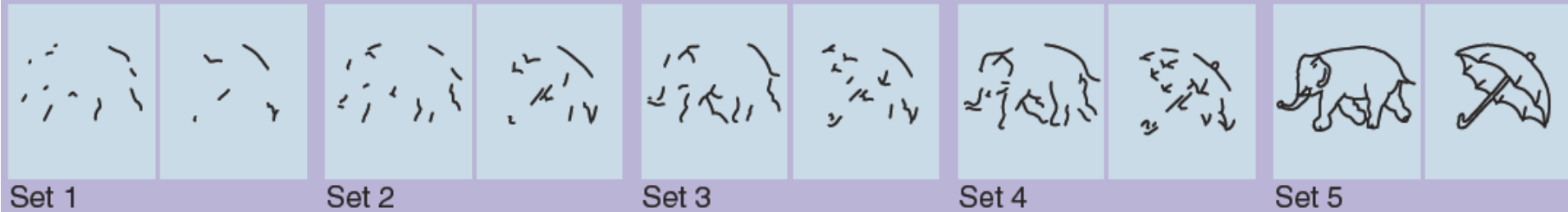
- **Mirror-drawing test:** Indication his anterograde amnesia did not involve all long-term memories.
 - Draw line in boundaries of a star shape by watching hand in the mirror.
 - Would often go outside boundaries but as time went on performance improved: indicated retention of the task but to him he had never done the task before.
- **Rotary pursuit test:** keep tip of stylus in contact with target rotating on a turntable: his performance improved over 9 daily sessions despite him claiming he had never seen the test.

Formal Assessment of H.M.'s Anterograde Amnesia: Discovery of Unconscious Memories



- Improvements also seen in non-sensorimotor tasks e.g., **incomplete-pictures task**: 5 sets of fragmented drawings, with each set containing drawings of the same 20 objects but the sets differ in degree of sketchiness going from very sketchy to almost complete.
- Asked to identify the 20 objects from set 1 and any that were not recognized were presented in their version 2 and so on.
- Performance significantly improved after only an hour but he had no recollection of having ever performed the task.
- Finally, HM also learned an eye-blinking Pavlovian condition task where a tone would sound just before a puff of air goes in the eye – the trials were repeated until the tone on its own elicited the eye blink – 2 years later he retained this response to the tone but again had not recollection of the training.

Incomplete-picture task





Three Major Scientific Contributions of H.M.'s case

- Medial temporal lobes are involved in memory
- STM, remote memory, and LTM are distinctly separate – H.M. is unable to move memories from STM to LTM, a problem with memory consolidation
- Memory may exist but not be recalled – as when H.M. exhibits a skill he does not know he has learned (explicit vs. implicit)

Explicit vs. Implicit Memories



Explicit

- **Conscious memories**

Implicit

- **Unconscious memories, as when H.M. shows the benefits of prior experience**

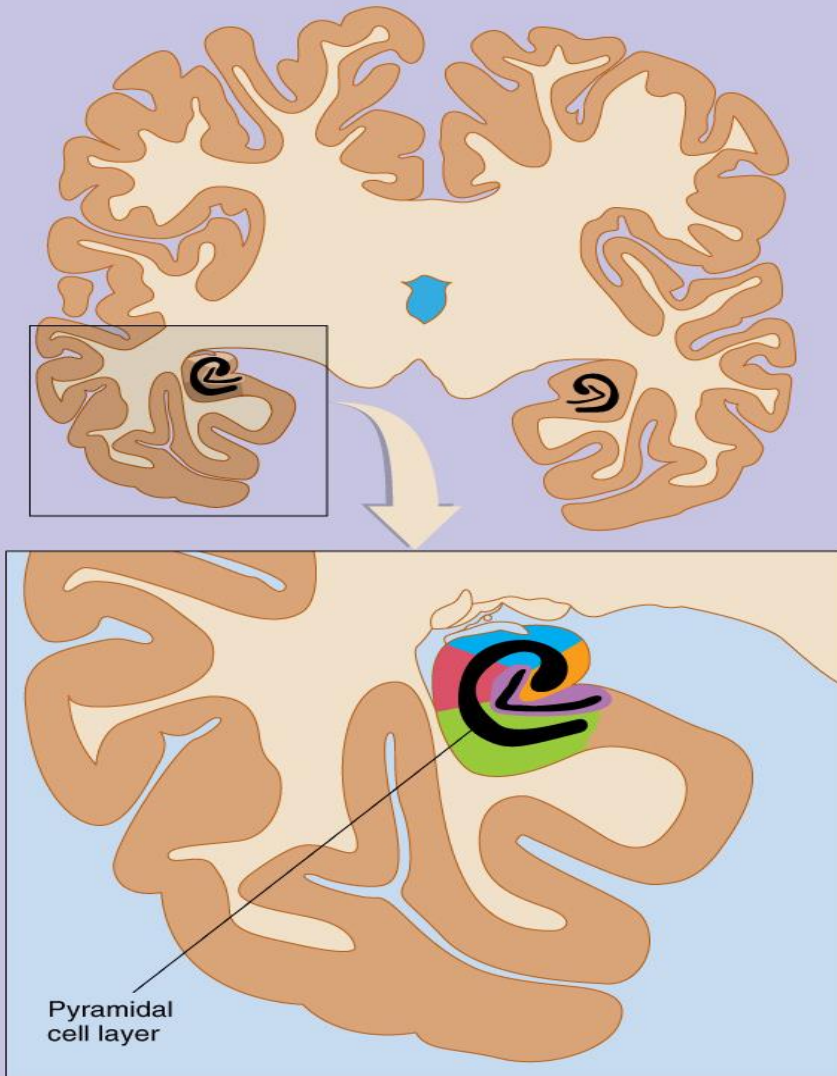
Medial Temporal Lobe Amnesia



- **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 that one has experienced) does not**
- **Medial temporal lobe amnesiacs may have trouble imagining future events**



Effects of Cerebral Ischemia on the Hippocampus and Memory



- R.B. suffered damage to just one part of the hippocampus (CA1 pyramidal cell layer) and developed amnesia
- R.B.'s case suggests that hippocampal damage alone can produce amnesia
- H.M.'s damage and amnesia were more severe than R.B.'s

Amnesia of Korsakoff's Syndrome

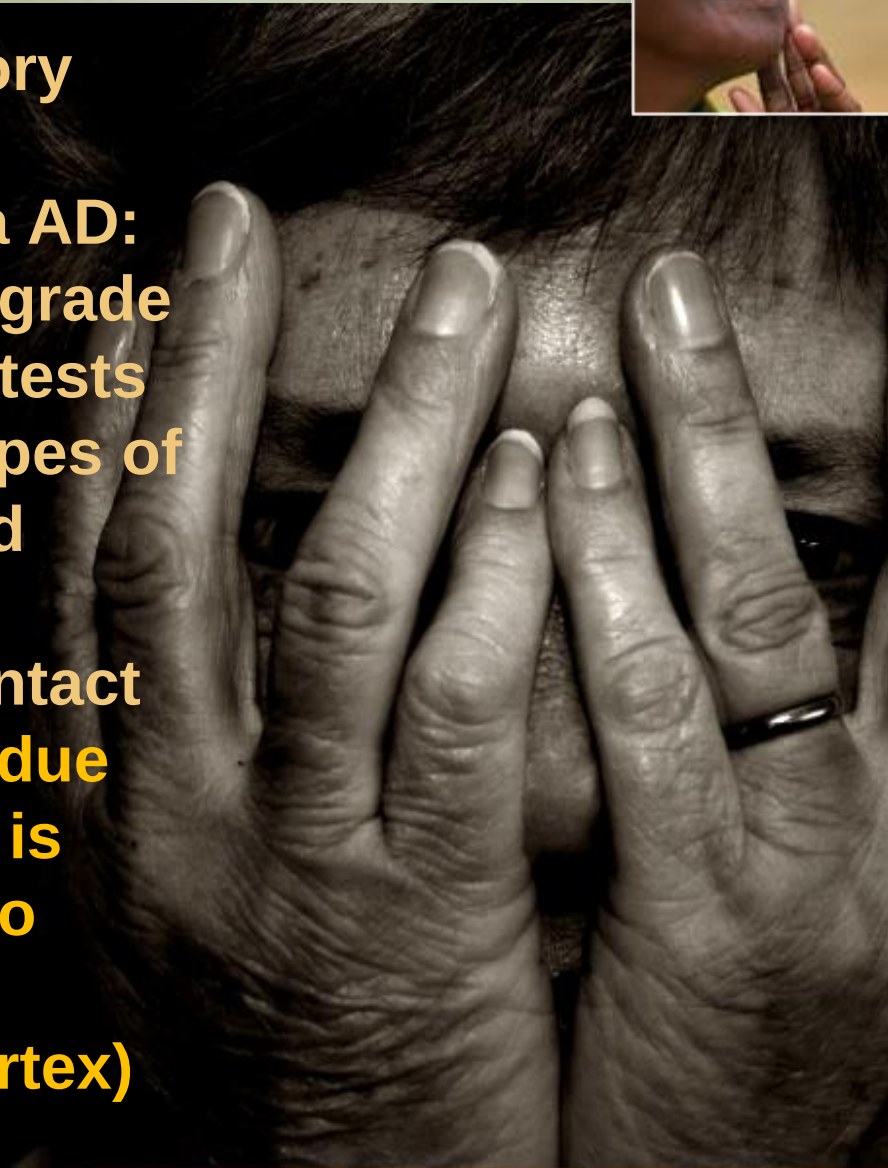
Most commonly seen in severe alcoholics (or others with a thiamine deficiency)

- Characterized by amnesia, confusion, personality changes, and physical problems
- Damage in the medial diencephalon: medial thalamus + medial hypothalamus
- Amnesia comparable to medial temporal lobe amnesia in the early stages
- Differs in later stages (it becomes progressive, complicating its study)



Amnesia of Alzheimer's Disease (AD)

- Begins with slight loss of memory and progresses to dementia
- General deficits in pre-dementia AD:
 - Major anterograde and retrograde amnesia in explicit memory tests
 - Deficits in STM and some types of implicit memory – verbal and perceptual
- Implicit sensorimotor memory intact
- Decreased acetylcholine levels due to basal forebrain degeneration is thought to be involved – but also other brain areas (e.g., Medial temporal lobe and prefrontal cortex)



Amnesia after Concussion: Evidence for Consolidation



- **Posttraumatic amnesia:** concussions may cause retrograde amnesia for the period before the blow and some anterograde amnesia after.
- The same is seen with comas, with the severity of the amnesia correlated with the duration of the coma.
- Period of anterograde amnesia suggests a temporary failure of memory consolidation



Gradients of Retrograde Amnesia and Memory Consolidation



- **Concussions disrupt consolidation (storage) of recent memories**
- **Theory to account for consolidation process:**
Hebb's theory- memories are stored in the short term by neural activity circulating in closed circuits
- **Interference with this activity prevents memory consolidation by changing the structure of the synapses involved.**
- **Examples:**
 - **Blows to the head (i.e., a concussion)**

Gradients of Retrograde Amnesia and Memory Consolidation



- Research using electroconvulsive shocks (ECS) (current administered to brain through electrodes) has shown that disrupting activity erases the memories that have not been converted to structural synaptic changes.
- ECS studies also provide evidence of the time taken for memory consolidation to occur, but different studies have suggested seconds, to a few minutes, to a few hours.
- Also, some studies found that retrograde amnesia produced by an electric shock can disrupt memories up to 3 years:
 - Thus, long gradients of retrograde amnesia are inconsistent with consolidation theory, which suggests memories are consolidated within a few minutes.

The Hippocampus and Consolidation



- H.M's retrograde amnesia suggests hippocampus & related structures play role in memory consolidation because removal of temporal lobes disrupted formation of new memories after the surgery.
- Perhaps the hippocampus stores memories temporarily (**standard consolidation theory**)
 - Consistent with the temporally graded retrograde amnesia seen in experimental animals with temporal lobe lesions
- Or, perhaps the hippocampus stores memories permanently, but they become "stronger" over time (**Multiple-trace theory: Nadel & Moscovitch, 1997**).

Reconsolidation



- Also, notion exists that reconsolidation can happen: each time a memory is retrieved from LTM, it is temporarily held in STM, where it can once again become susceptible to posttraumatic amnesia unless it is reconsolidated.
- Research has infused a protein-synthesis inhibitor called anisomycin in to the amygdalae of rats shortly after they had been required to recall a fear conditioning trial.
- The rats ended up having retrograde amnesia for the fear conditioning because anisomycin was present in their amygdalae.

Neuroanatomy of Object-Recognition Memory



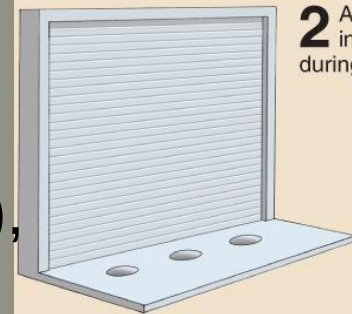
- **Studying patients is one way to discover aspects of memory, but they lack control & deliberate lesion to human brain would not be feasible.**
- **So, animal models of human brain damage that produces amnesia have been developed.**
- **Early animal models were deemed a failure because lesions of medial 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

- 1970s: animal model of H.Ms case developed – monkeys with bilateral medial temporal lobectomies showed LTM deficits in explicit memory through the **delayed nonmatching-to-sample test**.....
- Monkey is presented with an object & under it is food, after a delay (where screen is lowered), monkey is presented with 2 objects – one the same as before & new object – the monkey needs to remember old object to know that it needs to look under new object to find the food.
- Like H.M., performance was normal when memory needed to be held for only a few seconds (within the duration of STM)



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.

Delayed Nonmatching-to-Sample Test for Rats



- Lesions to monkey hippocampus achieved through aspiration (suction method).
- However, due to size & location of monkey hippocampus other areas of cortex receive damaged.
- With rats, the set-up of the brain results in little damage to other brain areas when aspiration is done.
 - Also, their hippocampus is so small that it can be lesioned either electrically or with a neurotoxic injection (less residual damage).
 - See Figure 11.12 in Pinel for diagram of difference between locations of rat & monkey hippocampus.

Delayed Nonmatching-to-Sample Test for Rats



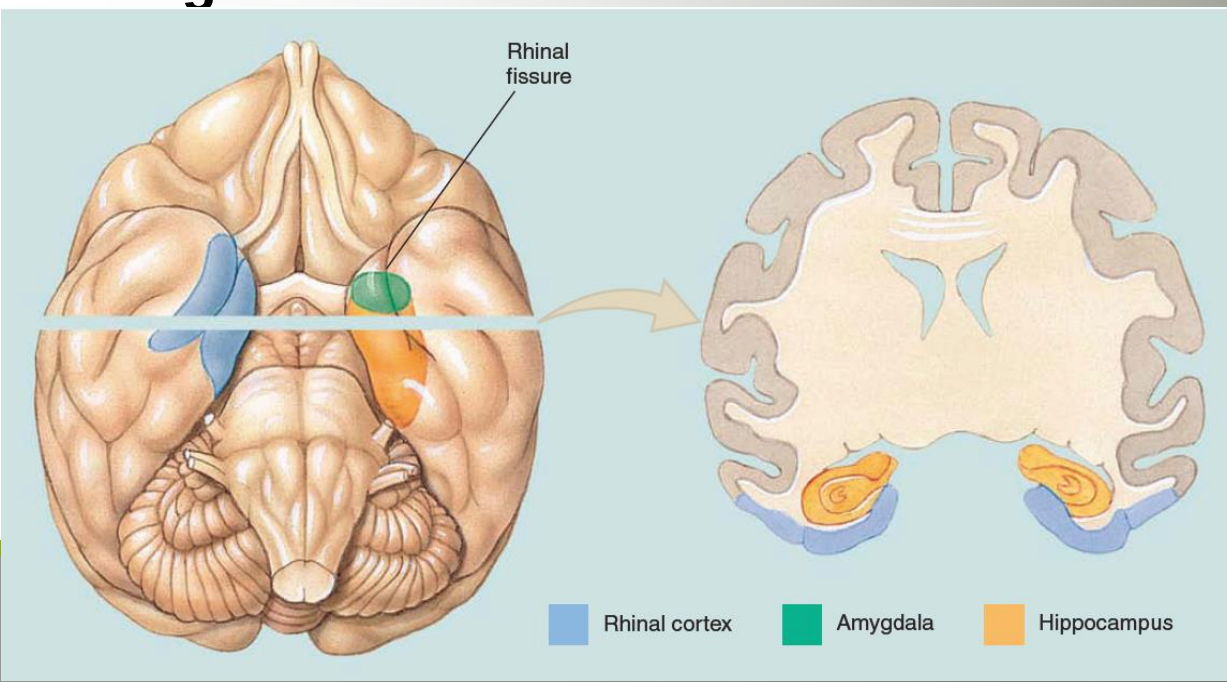
- Version of the nonmatching to sample task used with rats involves putting them in to a Mumby box.
 - Example of this in Figure 11.13 in Pinel.
- Performance on the task in rats resembles that seen in monkeys – good ability when the brain is intact, poor performance after medial temporal lobe lesion.



Neuroanatomical Basis of the Object-Recognition Deficits Resulting from Medial Tempal Lobectomy



- By 1990s research challenged whether hippocampal damage is the key factor in medial temporal amnesia.
- Bilateral removal of the rhinal cortex consistently results in object-recognition deficits
- Bilateral removal of the hippocampus produces no or moderate effects on object recognition
- Bilateral removal of the amygdala has no effect on object recognition



The figure here shows the 3 major structures of the medial temporal lobe

A Paradox



- **Complete removal of the hippocampus results in a moderate deficit in object recognition, but small lesions of the hippocampus (from ischemia) lead to a severe deficit**
- **How can this be?**



A Hypothesis



- **Ischemia-induced hyperactivity of CA1 pyramidal cells damages neurons outside hippocampus (through excessive release of excitatory amino acids), which explains ischemia-induced object recognition deficits.**
- **Bilateral hippocampectomy (removing hippocampus on both sides) prevents this ischemia-induced deficit**
- **Supported by functional brain-imaging studies where rats have had induced ischemia by tying their carotid artery to restrict blood flow to the brain**

Hippocampus and Memory for Spatial Location



- Rhinal cortex plays an important role in **object recognition**
- Hippocampus plays a key role in memory for **spatial location**
 - Hippocampectomy of rats produces deficits on Morris water maze and radial arm maze
- Many hippocampal cells are **place cells**, responding when a subject is in a particular place and to other cues
 - **Grid cells** also found in hippocampus and entorhinal cortex



Comparative Studies of the Hippocampus

- Similar findings seen in Food-caching birds: need to remember location of food stores hidden around their territory.
- These birds have larger hippocampus than non-food caching birds.
- However, primate studies are inconsistent:
- Perhaps discrepancies due to different testing paradigms (navigating the actual environment vs. sitting still and locating on a computer screen).

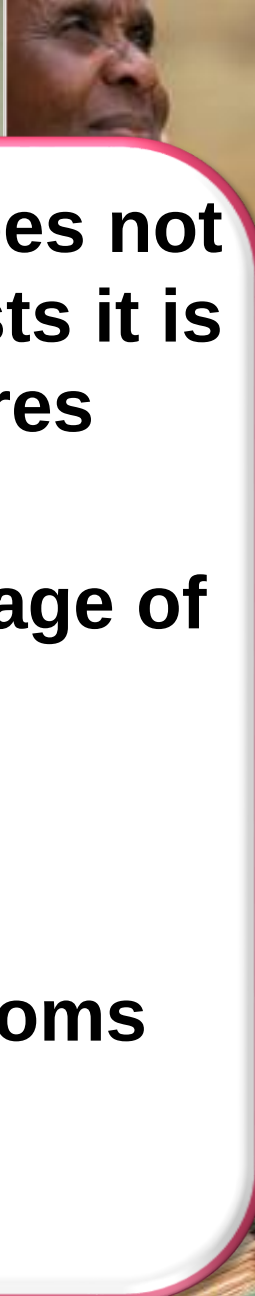




Theories of Hippocampal Function

- **Cognitive map theory:** hippocampus constructs & stores allocentric maps of the world:
 - These are 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, it can depend on other behaviors
 2. Hippocampal damage sometimes impairs behavior without a spatial component
 3. The hippocampus is large and complex and its component substructures need to be evaluated in more detail

Where Are Memories Stored?



- The fact that destruction of one brain area does not lead to complete loss of all memories suggests it is stored diffusely throughout the brain structures that were involved in its formation.
- Some structures have particular 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**

- Plays a special role in memory for the emotional significance of an experience.
 - Evidence from rats with amygdala lesions don't show typical fear response.
 - But may not store memory – instead strengthens emotional memories stored in other structures

Where Are Memories Stored?



- **Prefrontal cortex:** Temporal order of events & working memory
 - Tasks involving a series of responses
 - Different part of prefrontal cortex mediate different WM
 - Evidence from functional brain imaging studies & patients with lesions.
- **Cerebellum:** Stores memories of sensorimotor skills:
 - Evidence from Pavlovian condition of eye blink response in rabbits.
 - Tone & puff of air to the eye are conditioned then tone on its own causes the rabbit to close its eye
 - Recording activity in the cerebellum & lesioning the area suggest the effects of sensorimotor conditioning is stored in the form of changes in the way the cerebellum responds to the tone
- **Striatum:** Habit formation - consistent relationship between stimuli and response

Why would the brain develop separate stores



• Protection

- If all memory was held in one brain structure then damage to that area would result in a complete loss of all types of memory.
- To prevent devastating effects of damage to one particular area.
 - Some memory items will be damaged but others preserved.
- 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.

Synaptic Mechanisms of Learning and Memory



- So far focus has been on brain structures & what they are involved in.
- However, what happens when one of these structures is damaged.
- We need to focus on the neuroplasticity & molecular events that underlie learning & memory
- Hebb (1949): Changes in synaptic efficiency are the basis of LTM.
- Research has found that there is facilitation of synaptic transmission following electrical stimulation to presynaptic neurons
- This has been termed long-term potentiation (LTP).
 - Synapses are made stronger by repeated stimulation

Long-Term Potentiation (LTP)



- LTP is consistent with the synaptic changes hypothesized by Hebb.
- LTP has 2 main properties:
 1. It can last for many weeks, even months
 2. It only occurs if presynaptic firing is followed by postsynaptic firing
- Hebb's postulate for learning
 - Co-occurrence of firings in pre- and postsynaptic neurons necessary for learning and memory



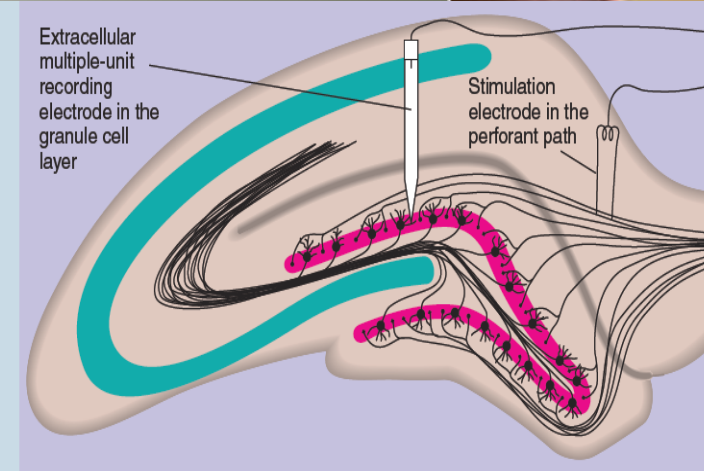


- **Evidence:**
- **LTP can be elicited by electrical stimulation of presynaptic neuron; mimics normal neural activity**
- **LTP effects are greatest in brain areas involved in learning and memory**
- **Learning can produce LTP-like changes**
- **Drugs that impact learning often have parallel effects on LTP.**
- **Induction of LTP blocks learning of Morris water maze**
- **LTP occurs at specific synapses shown to participate in learning and memory.**

LTP as a Neural Mechanism of Learning and Memory

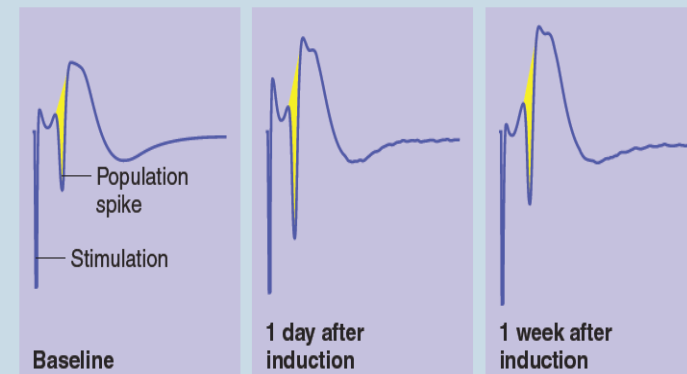


- Single low-intensity pulse of current given through stimulation electrode to perforant path (major input to dentate gyrus).
- Response recorded through extracellular multiple unit electrode in granule cell layer of the hippocampal dentate gyrus.
- Purpose of initial stimulation to determine initial baseline response.
- Then, high intensity & high frequency stimulation lasting 10secs given to perforant path to induce LTP.
- Then granule cells response to single pulses of low intensity current is measured again after various delays.
- Charts show transmission at granule cells synapses was still potentiated 1 week after the high frequency stimulation.



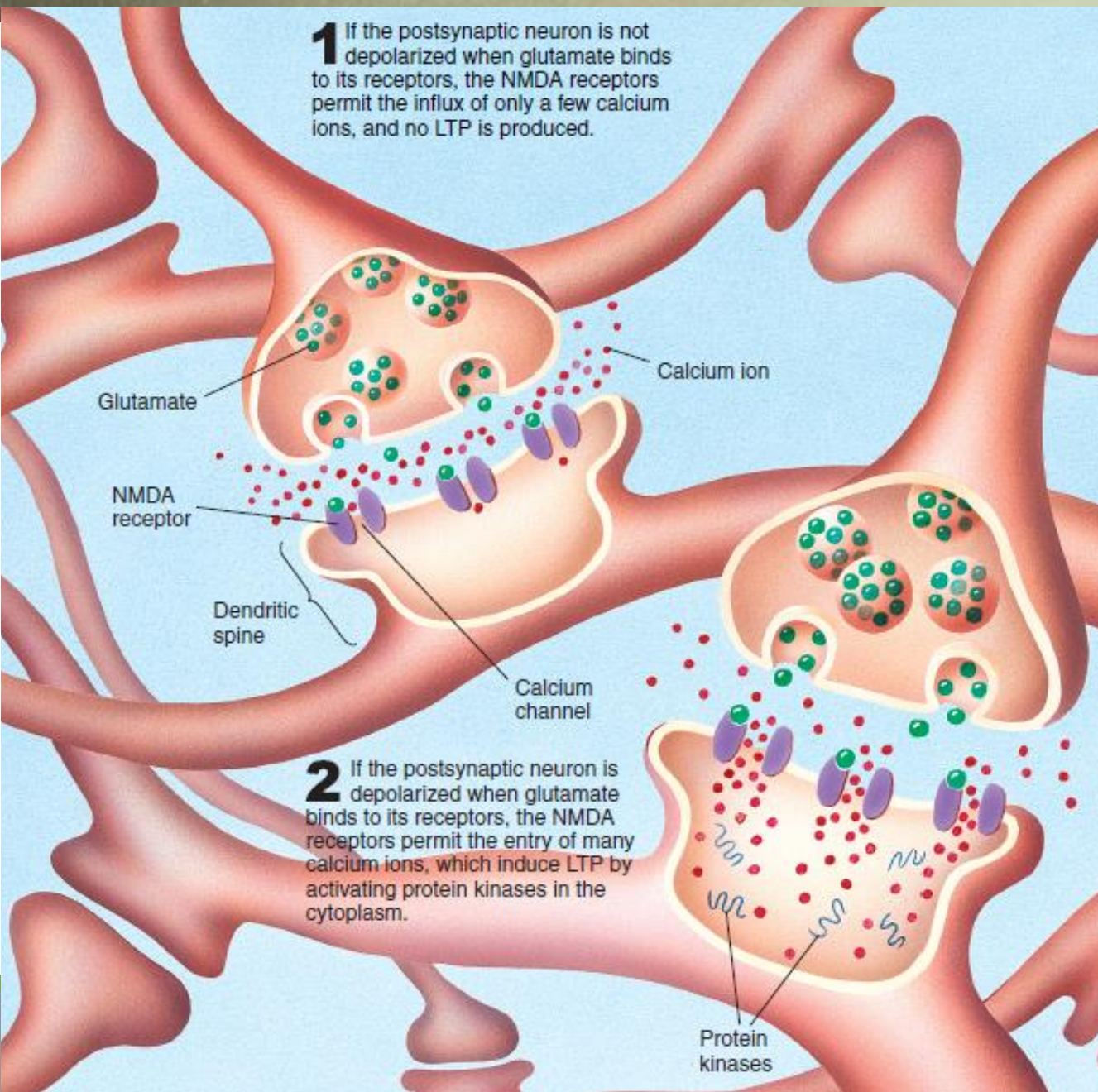
A single pulse of stimulation was administered to the perforant path, and the baseline response was recorded by an extracellular electrode in the granule cell layer. Then, several trains of intense high-frequency stimulation were applied to the perforant path to induce the LTP.

A single pulse of stimulation was administered 1 day later and again 1 week later to assess the magnitude of and duration of the potentiation. The usual measure of LTP is the increased amplitude of the *population spike*, in this case, the spike created by the firing of a greater number of granule cells.



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



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

Induction of LTP: Learning



- Ca^{2+} influx only occurs if there is the co-occurrence that is needed for LTP, leading to the binding of glutamate at an NMDA receptor that is already depolarized
- There is evidence that calcium produces its effects by activating **protein kinases**, which is a class of enzymes that influence chemical reactions in a cell and this 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 & post synaptic neurons, which indicates complex mechanisms.
- Examinations into neural mechanisms of LTP has contributed to other discoveries in neuroscience
- Once known that only synapses that were depolarized before high frequency stimulation were involved in LTP, a mechanism for keeping the events at one set of synapses on a postsynaptic neuron from affecting other synapses on the same neuron became apparent
 - This was due to the dendritic spines – the calcium ions that enter the dendritic spines do not pass out of it easily so their effects are only felt where they are.

Maintenance and Expression of LTP:

Storage and Recall



- Also maintenance of LTP involves structural changes which depend on protein synthesis
 - A number of structural changes have been described such as the increase in the size of the neuron
 - This knowledge has changed how we think about the way neurons store experiences.
- Following this, a search was on for a mechanism that changes the neurons structure based on the neurons activity.
- This led to the discovery of transcription factors – intracellular proteins that bind to DNA & influence the operation of a particular gene.

Maintenance and Expression of LTP:

Storage and Recall



- Because induction on LTP begins in postsynaptic neurons and maintenance and expression involves presynaptic changes, there must be some signal that passes from postsynaptic neuron back to the presynaptic neuron.
- At synapses where NMDA receptors are predominant this is a soluble gas neurotransmitter nitric oxide, which is synthesized in postsynaptic neurons in response to calcium influx & then diffuses back to presynaptic neurons.
- Finally it is now apparent that astrocytes play a role in synaptic transmission and effect LTP, which means more work other than just looking at neurons is needed.

Variability of LTP



- **Most LTP research has focused on NMDA-receptor-mediated LTP in the hippocampus, but LTP is mediated by different mechanisms elsewhere**
- **LTD (long-term depression) also exists, which occurs in response to prolonged low frequency stimulation of the presynaptic neurons.**
- **Much of LTP and neural basis of memory is still a mystery, despite many research discoveries**

Infantile Amnesia



- **Explicit and implicit memory can be demonstrated in normally functioning, intact subjects.**
 - **Skin conductance responses (implicit memory) elicited by pictures of preschool classmates, whether they were explicitly recognized or not.**
 - **Modern incomplete-pictures test: Previously seen pictures were recognized sooner (implicit memory) than new pictures, whether the old pictures were explicitly recognized or not**



Nootropics: Do They Work?



- **Nootropics or Smart drugs: substances thought to improve memory**
- **Limited research has shown that no purported nootropic has memory-enhancing effects in normal people**
- **Most research done on animals or with humans with memory difficulty.**
- **Also research on humans usually has low numbers, is not well controlled and makes little effort to differentiate between different types of memory.**

Next Week....



- **The Research Methods of Biopsychology**
- **Essential Reading....**

Pinel, J. P. J. *Biopsychology*. Chapter 5.