

The Brain, Biology and Cognition (BBC)

Lecture 5: Learning, Memory, and Amnesia

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What is Memory?

Integral part of Cognitive processing

- Concerned with organisation of time
 - Keeps record of the past and future
- Possible to argue *central* to Psychology

Why are memories important?

- Essential for learning
- Holds information
- Affects the future
- Contributes to our identity
- Related to concepts of intelligence and ability

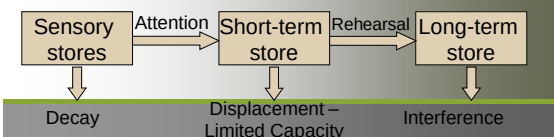


Architecture of Memory

Learning and Memory involve several stages:



Atkinson & Shiffrin (1968, 1971) Multi-Store Model
Three types of memory store were proposed



Issues with Multi-store Model



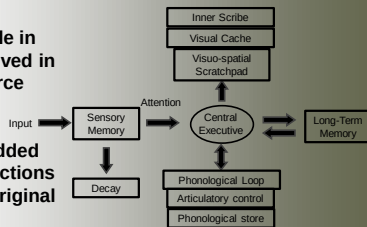
- Too simplistic: assumes STM & LTM are separate unitary structures: evidence now suggests they are not
- Suggests a one-way stream from STM to LTM
 - However: “Chunking” shows that LTM can assist STM with tasks
- Rehearsal does not guarantee transfer of info from STM to LTM: See Levels of Processing (Craik & Lockhart, 1972)
- STM can encode visual information: See Mental Rotation experiments (Shepard & Metzler, 1971)
- Suggests only information processed consciously can be transferred and stored in LTM: But implicit learning exists

Alternative: Working Memory Model

(Baddeley & Hitch, 1974; Baddeley, 1986, 2000)



- Multiple sub-systems within STM, seen as a set of processes rather than static unitary structure
- Acts on material we have just encountered & allows us to manipulate it.
- Plays an active role in learning & is involved in performing resource demanding tasks.
- Episodic Buffer added to account for functions not explained in original model



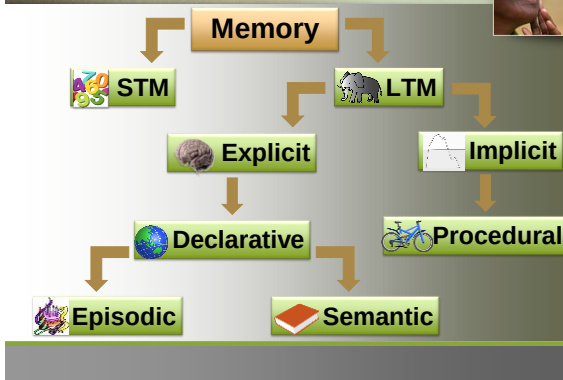
Long-Term Memory



Responsible for *all* info we retain/use

- A very large amount of information
 - Reflects complexity of the world and our behaviour within it
 - Not just to remember a sequence of numbers!
- Different *types* of information, e.g. Consider:
 - Year for Atkinson & Shiffrin publication?
 - Muscle movement to balance a bike
 - Memory for going to a concert or sports event
- LTM: made of separate memory systems due to fragmentation of different memory types:

Sub-divisions of LTM



Memory and the brain

Evidence from brain-imaging research with healthy controls to support the idea that:

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

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

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

Zimmer (2008): reviewed research on activity in brain areas involved in

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

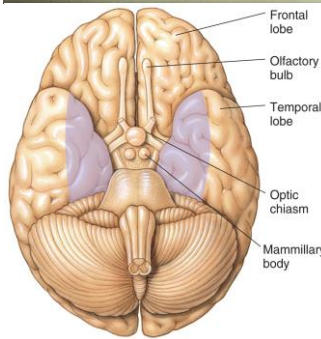
Destrebecqz et al. (2005): Explicit component of learning associated with prefrontal cortex and anterior cingulate activation, while striatum activation associated with implicit component.

Neurological Research

However, considerable research comes from patients with brain-damage – particularly those with amnesia:

- **Anterograde:** Inability to remember info after damage
- **Retrograde:** Inability to remember info prior to damage
- Patients have difficulty forming declarative memories but can readily form non-declarative memories.
- The case of Clive Wearing: Life without memory
- Patient KF – Shallice & Warrington (1970):
 - Damage to the temporal parietal lobe of the brain
 - Intact LTM but profound STM impairment – digit span of only 2
 - STM deficit limited to verbal material but not to meaningful sounds

Patient H.M.



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

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

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

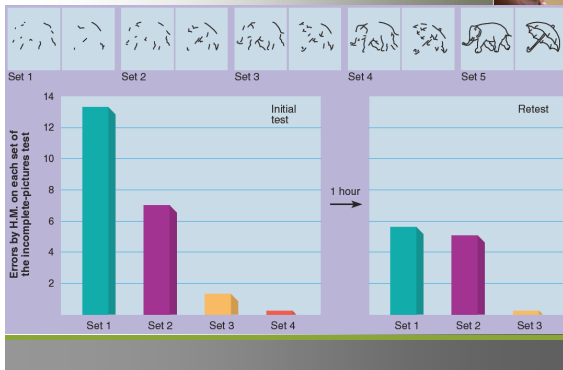


Formal Assessment of H.M.'s Anterograde Amnesia: Discovery of Unconscious Memories



- 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 he had no conscious awareness of them

Incomplete-picture task





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

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

Medial Temporal Lobe Amnesia



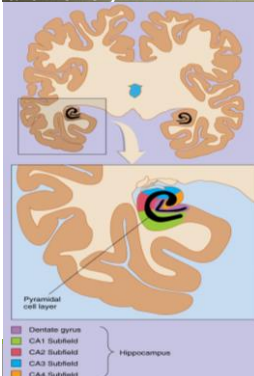
•Not all patients with this form of amnesia are unable to form new explicit long-term memories

•Semantic memory (general information) may function normally while episodic memory (events 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

•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
- Less problems with semantic memory

Vargha-Khadem et al. (1997): Two patients with bilateral hippocampal damage at age before semantic memory is developed.

- Both had poor episodic memory but semantic memory within normal range.
- Considered stronger evidence as semantic memory *intact*.

However:



Gardiner et al. (2008): one of the patients did have semantic memory problems:

- Rate of learning significantly slower than healthy controls.
- Re-studying suggested as explanation for original findings

Episodic memory depends on hippocampus

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

- Damage to hippocampus and cortices likely leads to both episodic & semantic deficits (Vargha-Khadem et al., 1997)
- Damage only to the 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): retrograde amnesia for episodic memories spans several years.
- Manns et al. (2003): retrograde amnesia for semantic memory is generally small.

Theory to explain retrograde amnesia:

- Consolidation: Long-lasting physiological consolidation of episodic memories in the hippocampus.
 - “Fixes” information in LTM.
 - Recently formed memories still being consolidated are vulnerable to interference and thus forgetting.

The Hippocampus and Consolidation



- The hippocampus and related structures play role in memory consolidation because removal of temporal lobes disrupted formation of new memories.
- Perhaps the hippocampus stores memories temporarily **standard consolidation theory**
 - Over time memories stored elsewhere, which protects them from hippocampal damage.
- Or, perhaps the 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 once again become susceptible to posttraumatic amnesia unless it is reconsolidated.
- Research has infused a protein-synthesis inhibitor in to the amygdalae of rats shortly after being required to recall a fear conditioning trial.
- The rats ended up having retrograde amnesia for the fear conditioning.

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



- Semantic Dementia: Severe issues with semantic memory but relatively intact episodic memory.
- Damage to anterior temporal lobes resulting in loss of info about meaning of words & concepts
- Adlam et al. (2009): patients able to perform comparably well to healthy controls when asked what, where, & when they had performed tasks in a previous 24 hour period.

Double-dissociation:

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

Evidence for separate LTM systems: Procedural Memory



Procedural Memory (also called skill learning):

- E.g., Sequence learning, Mirror tracing.
- Often intact in amnesiacs: e.g., H.M.
- Evidence from serial-reaction time tasks (P must respond as quickly as possible to a target stimulus):
 - In amnesiacs, performance is typically intact.
- Evidence from motor skill task: driving ability (Inc. steering, speed control, safety errors, driving with distraction) of two amnesiacs was comparable with those of healthy controls (Anderson et al., 2007).

Evaluation: Declarative vs. Procedural



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

E.g., weather prediction study: Ps use various cues to predict if it will be sunny/raining.

- Reber et al. (1996): amnesiacs did just as well as controls
 - Suggests the task involves procedural memory.
- Foeerle et al. (2006): Ps performed task either on its own or with a secondary task
 - Single task condition associated with medial temporal lobe activity (declarative memory), dual-task condition associated with activity in the striatum (non-declarative memory).
- Schwabe & Wolf (2012): Non-stressed Ps relied on declarative memory (hippocampus), stressed Ps relied on non-declarative memory (striatum)

What does this tell us?...



The specifics of the task can lead to the involvement of either the declarative or non-declarative memory system depending on:

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

Possibly an interaction between the systems?

Evidence suggests skill learning also involves the hippocampus (Albouy et al., 2013).

Functional connection between implicit & explicit memory (Robertson, 2012).

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, increase in inconsistent findings has led to alternative theories being developed.

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

- Instead: systems should be identified on the type of *processing* involved – she proposed 3 basic modes:
 1. Rapid encoding of flexible associations: involves episodic memory & involves the hippocampus.
 2. Slow encoding of rigid associations: involves procedural & semantic memory and involves the basal ganglia.
 3. Rapid encoding of single/unitised items: involves familiarity in recognition memory and depends on 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 were 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

- **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 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.

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 Temporal Lobectomy



- By 1990s research challenged whether hippocampal damage is 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

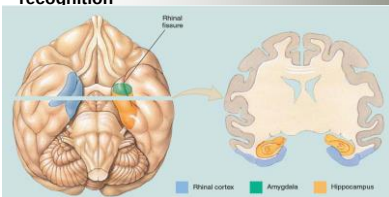


Figure shows the three major structures of the medial temporal lobe

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?



• Inference temporal 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 do not 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

• 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 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.
- 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



- What are the molecular events that underlie learning and memory?
- Hebb (1949): Changes in synaptic efficiency are the basis of LTM.
- There is facilitation of synaptic transmission following electrical stimulation to presynaptic neurons
- This is called **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



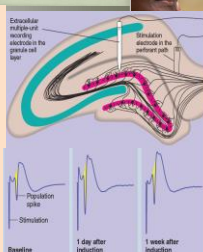
LTP as a Neural Mechanism of Learning and Memory



- 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.

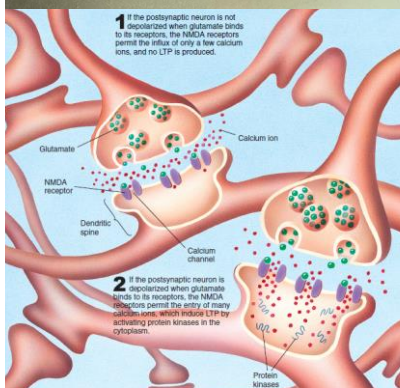
LTP as a Neural Mechanism of Learning and Memory

- **How is long term potentiation induced?**
- Single low-intensity pulse of current given through 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.
- Initial stimulation determines baseline response
- Then, high intensity/frequency stimulation for 10secs given to perforant path to induce LTP.
- Then granule cells response to single pulses of low intensity current is measured after various delays.
- Transmission at granule cells synapses was still potentiated 1 week after the 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



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 unless glutamate binds to it **and** the neuron is 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



- There is evidence that calcium produces its effects by activating **protein kinases**
 - A 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 & post synaptic neurons (a complex mechanism).
- It involves structural changes that depend on protein synthesis
 - E.g., increase in the size of the neuron
- A search then began 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



- Induction on LTP begins in postsynaptic neurons and maintenance and expression involves presynaptic changes, so there must be a 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 & diffuses back to presynaptic neurons
- Finally astrocytes play a role in synaptic transmission and effect LTP - so 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.
