Learning and Memory

- Learning deals with how experience changes the brain
- Memory refers to how these changes are stored and later reactivated

The Case of H.M.

- H.M. suffered from severe, intractable epilepsy
- He apparently had epileptic foci in both medial temporal lobes
- Unilateral medial temporal lobectomy (removal of a portion of the lobe) had proven successful in patients with one epileptic focus
- Bilateral medial temporal lobectomy was prescribed for H.M.; this included removal of the hippocampus and amygdala

The Case of H.M. – Results of the Surgery:

- H.M.’s convulsions were reduced in severity and frequency
- His measurable I.Q. increased from about 104 to 118
- He remained an emotionally stable individual
- H.M. suffered from devastating amnesia

Forms of Amnesia:

- Anterograde:
  - Amnesia for events that occur after some disturbance to the brain, such as head injury or certain degenerative brain diseases.

- Retrograde:
  - Amnesia for events that preceded some disturbance to the brain, such as a head injury or electroconvulsive shock.

H.M.’s Memory Deficits

- H.M. has minor retrograde amnesia for the events of the 2 years preceding the surgery
- He has normal memory for events in the remote past and normal short-term memory
- However, he has severe anterograde amnesia – he cannot form long-term memories for most events that occurred after his surgery
– Spared Learning Abilities

– Short-term memory:
  • Immediate memory for events, most of which are not consolidated into long-term memory.

– Long-term memories:
  • Relatively stable memory of events that occurred in the more distant past, as opposed to short-term memory.

H.M.’s task was to draw a line within the boundaries of a star-shaped target by watching his hand in a mirror.
H.M. was asked to trace the star 10 times on each of 3 consecutive days.
His performance improved over time, despite his having no conscious recollection of having performed the task before.

H.M.’s memory for the items on the test was indicated by his ability to recognize the more fragmented versions of them when he was re-tested.

Pavlovian conditioning
• Tones and a puff of air to the eye were presented to H.M.; he blinked in response
• Two years later, he retained this conditioned pairing almost perfectly, though he had no conscious awareness of his previous training

Impact of H.M.’s Case
• Showed that the medial temporal lobes are important for forming and organizing memory
• Challenged the view that mnemonic (memory-related) functions are diffusely distributed throughout the brain
• Renewed efforts to relate specific brain structures to specific mnemonic processes
• Supported the theory that there are different modes of storage for short-term and long-term memories
• Provided the first evidence that implicit (without conscious awareness) memory could survive in the absence of explicit (conscious) memory

Divisions of Long-term Memory

Medial Temporal Lobe Amnesia
• The ability to form implicit long-term memories, coupled with difficulty forming explicit long-term memories, is often seen in cases of medial temporal lobe amnesia.
• Research on these amnesics has suggested that some kinds of explicit long-term memories are more likely to be disrupted.
• Problems with *episodic memory* (memories for the events of one’s own life) are more common than problems with *semantic memory* (memories for general facts or information)

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Patients who have experienced cerebral ischemia (disruption of blood flow) often suffer from medial temporal lobe amnesia

• Patient R.B. suffered ischemic damage to his brain during heart surgery.
• He had pattern of amnesia similar to H.M.’s, though his was not as severe.
• Obvious brain damage was restricted to the CA1 region of the hippocampus (supported the idea that the hippocampus was particularly important for some forms of memory)

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**Korsakoff’s Amnesia**

• Korsakoff’s syndrome:
  • Brain damage resulting from malnutrition associated with chronic alcoholism.
    – Severe anterograde amnesia
    – Severe retrograde amnesia
      » Most severe for recent memories
      » Also affects memories of events from years before (remote events)
    – Amnesia believed to be associated (in part) with damage to the mediodorsal nuclei of the thalamus

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**Activity Is Reduced In The Frontal Lobes Of Patients With Korsakoff’s Syndrome**

• PET scans from a normal patient (larger image) and a patient suffering from Korsakoff’s syndrome (the inset)
• Red and yellow represent areas of high metabolic activity

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**Korsakoff’s Syndrome**

  – Confabulation:
  • The reporting of memories of events that did not take place without the intention to deceive; seen in people with Korsakoff’s syndrome.

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**Alzheimer’s Disease**

• A major cause of amnesia; first symptom is often a mild loss of memory
• In addition to both *anterograde* and *retrograde* amnesia, patients often display deficits in short-term memory and some forms of *implicit* memory (those involving verbal or perceptual material, but not those involving sensorimotor learning)

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**Posttraumatic Amnesia**

• Blows to the head can lead to a disturbance of consciousness (concussion), a complete loss of consciousness (coma), and amnesia
• Patients with posttraumatic amnesia generally have both anterograde and retrograde amnesia
• The retrograde amnesia seen after concussion or coma is typically worse for most recent memories
  – this led to the suggestion that older memories are stored in a more permanent form through
Animal Models Of Amnesia (Similar to H.M.’s)

Delayed Nonmatching-to-Sample Task
- Work with animal models of amnesia (delayed nonmatching-to-sample task = DNMS) suggests that the hippocampus is important for some, but not all, forms of memory
- The DNMS task requires the ability to form long-term memories.

The Hippocampus and Memory for Spatial Location
- The hippocampus plays a particularly important role in spatial memory
- Two tasks are widely used to test spatial memory in rodents
  - Morris Water Maze
  - Radial Arm Maze

Morris Water Maze
- Requires rats to learn the location of an invisible stationary platform and find it when swimming in opaque (milky) water
  - Rats with hippocampal lesions have great difficulty
  - Control rats easily learn the task

Hippocampal Place Cells
- Animals need to know where they are at all times, so they can hunt, explore new territories and find their way home
- Additional evidence for the importance of the hippocampus in spatial memory comes from the existence of place cells
- Each hippocampal place cell is activated when an animal is in a certain region in its environment
- A place cell that fires when an animal is in one position will stop firing when the animal moves to a different place

Place Cell Firing Patterns
- In animals and humans, spatial memories are first formed in the hippocampus
- Humans also use the hippocampus to acquire and store so-called declarative
memories, involving all the events with which a person is involved during waking hours.

- Most scientists believe that the hippocampus is essential for processing and consolidating new memories

### How Are Memories Formed?

- Memories can be formed by strengthening the connections between existing neurons to improve the effectiveness of their communication.
- Long-Term Potentiation (LTP) is an enduring increase in synaptic strength (efficacy) resulting from prior activity (experience) at the synapse.
- LTP is an important model for studying the type of mechanisms that may underlie memory.

### Long-Term Potentiation (LTP)

- LTP is the kind of change postulated by Donald Hebb to underlie memory:
  - It can persist for a long time (weeks in vivo).
  - It occurs only when the both the presynaptic and postsynaptic neurons are simultaneously active = “cells that fire together wire together”
  - Hebbian Theory:
    - In general, synapses are strengthened when the pre- and postsynaptic neurons are simultaneously active and weakened when their activity is not synchronized.
    - Hebb first suggested the importance of correlated activity in strengthening synapses (1940s)

### Evidence That LTP Is Related To The Neural Basis Of Learning And Memory

- LTP can be produced by patterns of electrical stimulation that mimic normal brain activity.
- LTP is most prominent in brain structures that are implicated in learning and memory.
- Behavioral conditioning can produce LTP-like changes in the hippocampus.
- Many drugs that influence learning and memory have parallel effects on LTP.
- Mutant mice that display little hippocampal LTP have difficulty learning the Morris water maze.

### LTP Is Often Studied In The Rodent Hippocampal Slice Preparation
Many Forms of LTP Depend on Changes at Glutamate Synapses

- The brain has several types of receptors for glutamate
- AMPA receptors and NMDA receptors are both ionotrophic receptors (they open an ion channel in the postsynaptic cell)
- AMPA receptors open sodium channels – if many AMPA receptors are activated, the postsynaptic membrane becomes significantly depolarized
- The NMDA receptor channel opens (and sodium and calcium pass through) only when the membrane is already significantly depolarized
- This requirement for co-occurrence of activity provides further support for Hebb’s postulate and the putative role of LTP in learning

Coincidence Detection by the NMDA Receptor

Understanding the molecular basis of LTP may help us understand the biochemistry of learning

Understanding the molecular basis of LTP may help us understand the biochemistry of learning

- Mice lacking AMPA receptors also have defects in both LTP and memory
- LTP experiments have helped to identify many of the putative memory enhancing drugs currently being studied as possible components of memory systems

What about other types of drugs that might improve memory?

- Many “memory boasting” supplements increase blood flow to the brain
  - Ex. Ginko biloba – dilates blood vessels, and may have other effects on the brain as well
  - Sometimes produces small improvements when given to Alzheimer’s patients or other people with memory problems
  - Results currently more equivocal for younger, normal brains