Cognitive Neuroscience
Memory

Memory is information that a person has about the internal and external environments. Memory is central to the study of cognitive neuroscience, but is not a single entity, and may be defined in many ways. Learning is the ability to acquire memory through experience.

Information is stored in the brain as memory on a long-term basis.

Long-term memory

From many types of evidence, it is believed that long-term memory (LTM) is acquired through experience (learning) and is stored in the neocortex.

Long-term memory (LTM) is stored in a substrate of cortical neurons and their connections in cortical (memory) networks.

LTM includes content (what the information is about) and processes (the operations of retaining, manipulating, and utilizing acquired information).
It is believed that:
1. All cognitive functions use the LTM cortical substrate.
2. However, the functions differ in the portion and type of LTM used at any given time.
3. No cognitive function, including LTM, has a fully dedicated cortical area or network.
4. So, LTM is distributed across multiple areas and networks.

LTM can be divided into 3 types:
1. **factual** (semantic): memory of what we believe to be true, although cognitive neuroscience is generally not concerned with how we determine whether a belief is true. Memories about the world that are expressed verbally, but cannot be localized in autobiographical time.
2. **episodic** (personal, autobiographical, event): memory of specific details about one’s history, including people, places, time, events, and circumstances.
3. **skill** (procedural, know-how): memory of how to do things. Behavioral memory resulting from learning a skill or operation. Includes several kinds of abilities, all of which are unconscious and expressed through performance. It is slow & accumulates through repetition over many trials.
Classification of human memory by timescale

Timescale roughly corresponds to the time that the memory is held before it is lost. It is lost due to decay or interference. The different timescales are approximate and do not necessarily imply different mechanisms.

1. Short-Term Memory (STM): lasts on a time scale of seconds to minutes -- e.g. number sequences. It includes:
   - **iconic memory**: lasts on a time scale of a few seconds -- related to continued activity in sensory system. Sometimes referred to as storage in a "sensory buffer".
   - **sensory memory**: memory that is specific to a single sensory modality, and quickly fades after stimulus presentation.
   - **working memory**: sensory memory that is explicitly retained to perform a goal-directed behavior.

2. Intermediate-Term Memory: lasts on a time scale of hours to days -- e.g. environmental positional relations

3. Long-Term Memory (LTM): lasts on a time scale of weeks to years -- relatively permanent
Memory and learning

Memory is closely related to learning, and may be considered in terms of the way that information in memory is learned. In biological systems, memory entails learning (the acquisition of information), and learning implies retention (memory) of such information.

Karl Lashley searched for the location in the brain where memory is stored (the “engram”) after learning, but he failed. Although the engram, as a stored representation of experience in the brain, is sure to exist, it is now generally agreed to consist of multiple features distributed across different brain locations.

Animal learning

1. Associative learning

Learning of relations among different stimulus types and behaviors.

a. Classical conditioning: association of initially neutral stimulus with a physiological response. Also called Pavlovian conditioning from Ivan

b. Operant conditioning: association of behavior and its consequences (how to "operate" something). Animal has to perform some task to achieve a goal. Each response is followed by a reinforcement or punishment.

2. Nonassociative learning

Involves experience with only a single stimulus type.

a. Habituation: decrement in magnitude of a response to repeated stimulation

b. Sensitization: progressive amplification of a response to repeated stimulation (e.g. repeated scratching of skin becomes painful)

c. Imprinting: formation of fixed behaviors during critical period, usually in early life.
Stages of processing

A memory must be acquired, stored, and accessible to be successful. Some have proposed that memory processing takes places in stages:
a. **Encoding**: the stage of processing incoming information to create memory representations in LTM.
   i. **Acquisition**: transfer of stimuli to the sensory buffer, and then to STM.
   ii. **Consolidation**: stabilization of STM to form LTM.
b. **Storage**: maintenance of “permanent” memory representations in LTM.
c. **Retrieval**: the accessing of information from LTM to create a cognitive representation or execute a behavior.

Traditional stages are non-physiological. In neurophysiological terms, memory results from cortical network formation by Hebbian principles:
a) **encoding** occurs by the perceptual processing of incoming sensory information
b) **consolidation** occurs by the modification of synaptic connections in cortical memory networks, forming new memory networks or altering old ones
c) **storage** is the maintenance of existing memory networks
d) **retrieval** occurs by the activation of existing memory networks
Formation of LTM

1. Long-Term Memory (LTM) is information stored in memory networks distributed throughout the cerebral cortex.

2. Percepts are interpretations of the world in the context of prior memory.

3. The formation of percepts involves activation of cortical memory networks.

4. Perception leads to new LTM formation by either:
   (a) expanding and modifying pre-existing memory networks if those networks are sufficient to explain the sensory information; or
   (b) creating new memory networks if pre-existing memory networks are insufficient to explain the sensory information.

5. *Consolidation* is the stabilization and strengthening of LTM by the modification of synaptic connections between neurons in cortical memory networks.
Memory consolidation

1. Consolidation is strengthened by several different influences, including:
   a) attention
   b) repetition (rehearsal & practice)
   c) emotion (affect)
   d) motivation (goals)

2. Consolidation is controlled by the medial temporal lobe (hippocampal) system, with emotional evaluation provided by the amygdala.

1. Consolidation is based on Hebbian association principles in an autonomous, self-organizing manner, i.e. as a result of concurrent activity without outside control:
   a) At the cellular level, memory formation occurs by synaptic modification that associates the activities of different cells. Glutamate is the major neurotransmitter at cortical excitatory synapses: the NMDA glutamate receptor is activated by synaptic activity in a Hebbian manner (i.e., as a result of pre- and post-synaptic activity). The NMDA glutamate receptor is thought to be the basis for long-term potentiation (LTP) in the cortex.
b) At the network level, this synaptic modification leads to the functional association of memory networks within and across modalities.

- consolidation involves memory network stabilization and strengthening
- consolidation associates memory networks at different hierarchical levels within unimodal memory networks, between unimodal memory networks of different modalities, and between unimodal memory networks and symbolic memory networks of transmodal association cortex

**Amnesia**

Amnesia is a memory deficit due to brain damage, disease, or psychological trauma. The loss of memory for events that occur after a lesion is called *anterograde amnesia*. Loss of memory for events from before the lesion is called *retrograde amnesia*. Retrograde amnesia may exhibit a *temporal gradient*, measuring the severity of loss over the previous life span.
The medial temporal lobe memory system

The medial temporal lobe (MTL) system includes:
(1) the hippocampus
(2) surrounding entorhinal cortex, perirhinal cortex, parahippocampal cortex
(3) anterior thalamic nuclei and mammillary bodies

Evidence that the MTL is required for normal acquisition of declarative memory comes from 3 sources:
   1) studies of human patients with brain lesions & memory deficits
   2) lesion studies in animals
   3) neuroimaging studies in healthy humans
1) Evidence from amnesia

Bilateral removal of the MTL in patients produces profound amnesia. This procedure was performed by Dr. William Scoville on a small number of subjects in the 1950s. Once the effect of the procedure was recognized, it was stopped. One such patient was Henry Molaison (patient H. M.). His memory impairment and brain were repeatedly studied over a span of decades. He was unable to recall experiences that occurred after the surgery, but he could learn new skills. 

Evidence for involvement of the hippocampus proper in anterograde amnesia also comes from patients with transient global amnesia (TGA) – transient loss of blood flow in hippocampus causes anterograde amnesia and time-limited retrograde amnesia (for a short period before the onset).

Based on human amnesia studies, it is now believed that:
A. the MTL is necessary for the brain to acquire new long-term memories of events and facts, but not long-term skill memories or short-term sensory memories
B. there are at least two different types of memory:

1. Declarative (explicit) memory
   Cognitive memory, involving recognition of sensory patterns, attachment of emotional value, that is accessible to conscious recall. It is relatively fast & may occur with only 1 presentation. It includes:
   a) Episodic memory (for events)
   b) Semantic memory (for facts)

   Declarative memory depends on the MTL.

2. Nondeclarative (implicit) memory
   Memory that is not accessible to conscious recall. It includes:
   a) Procedural memory
   b) Perceptual memory
   example: perceptual priming

   Nondeclarative memory does not depend on the MTL.
2) Evidence from animals with medial temporal lobe lesions

a. Studies in monkeys show that:

   i. damage to the hippocampus directly or to its input & output connections with neocortex produce severe memory impairments.
   ii. damage restricted to the surrounding neocortical areas produces significant memory deficits.
   iii. damage to the amygdala does not produce memory deficits when the neocortex surrounding the hippocampus is spared. Although not crucial for episodic memory, the amygdala is important for emotional memory.
   iv. the MTL is not essential for short-term perceptual or working memory.

b. Studies in rodents show that:

   i. the hippocampus is involved in the storage & retrieval of *contextual memory*. 
3) Evidence from human neuroimaging studies

Functional brain imaging studies are done with healthy human volunteers with intact memory. They seek to answer the question of whether the hippocampus is active in the encoding of new LTM, the retrieval of stored LTM, or both.

fMRI studies typically use the subsequent-memory paradigm in which participants are presented with items to be subsequently remembered. These studies have investigated both the encoding and the retrieval of LTM.
fMRI studies show that:

1) the human hippocampus is active when new information is encoded.

2) the hippocampus is also involved in the retrieval of episodic LTM, but not memories based just on familiarity.

3) the perirhinal cortex (PRC) alone is sufficient to recognize that an item is familiar, but the hippocampus is necessary to remember a full episode of experience.

4) relational information for items in LTM reappears by reactivation of the original cortical areas that provided input to the hippocampus during the original encoding.

5) frontal cortex is involved in encoding and retrieval of LTM.

6) successful memory retrieval involves retrosplenial cortex (RSC) and lateral posterior cingulate cortex (PCC).

7) involvement of these medial cortical areas in memory encoding requires self-referential items.

8) in conscious rest, when thought is about self-related past & future scenarios, these areas are functionally interconnected with a distributed network of cortical association areas called the default mode network.
Short-term memory

*Evidence for a two-stage model of human memory*

Hermann *Ebbinghaus* (1885) began the modern history of human memory studies when he tested his ability to recall lists of nonsense syllables.
Graphs of retention in such studies (top) suggest that memory consists of two stages: short-term and long-term.
The Atkinson-Shiffrin model of human memory was based on the view that sensory information first passes into a short-term memory store (first stage) and then into a long-term memory store (second stage).

The model implies that the rapid decline in retention in the first 3 days represents loss from the short-term memory store (with limited capacity & rapid decay), and that the much slower decline thereafter represents loss from the long-term store (with unlimited capacity & little or no decay).

It also implies that, for information to be retained permanently, it has to be transferred from short-term to long-term storage.

Two empirical effects are well known in free recall studies:

**primacy effect**: first words in a list are better recalled than subsequent words

**recency effect**: last words in a list are better recalled than preceding words
Evidence exists that presentation of *distractors* between word presentation and recall interferes with the recency effect, but not the primacy effect.

The two-stage model of memory is consistent with this result: the first words in the list pass quickly into long-term storage and are thus not as vulnerable to interference as later words.

The model is also consistent with evidence from the *anterograde amnesia* suffered by patients, like H.M., from bilateral hippocampal damage: they could recall recent events but could not form new long-term memories.

This result would be predicted if the ability to transfer items from STM to LTM were lost. It was interpreted as meaning that recent recall depends on STM in neocortex, and thus is not susceptible to bilateral hippocampal damage, but long-term recall requires the hippocampi to convert STM to LTM (also in neocortex).

Some reports have said that anterograde amnesia patients have lost the primacy effect while retaining the recency effect.

This result is also consistent with the 2-stage model if the ability to transfer items from STM to LTM were lost. That is, the first items in the list would not be transferred to LTM, and their recall would not be better than latter items. The recency effect would be retained because the last items in the list would still be “new” in STM.
Fuster presents evidence against two-stage models of memory:

1. *Warrington* reported cases of amnesic patients who had lost the recency effect while retaining the primacy effect.

2. When plotted on log-log axes, the retention graphs do not suggest two stages. Rather, they indicate that the rate at which information is lost (i.e., the forgetting rate) slows down over time.

3. Evidence from electrical currents applied to the head in humans and animals suggested that the extent of the loss of recent memories that was produced was a simple function of time after learning. That is, these results did not indicate two stages of memory.
Fuster concludes that:

1. Consolidation operates on information as soon as it is perceived, and it does so continuously over time.

2. The cognitive networks of the cortex are the only neural substrate for memory storage. Consolidation appears to occur by modification of (strengthening of some, weakening of other) synapses in cortical networks.

3. Short-term memory does not require a separate stage of storage, a separate storage site or system in the brain to maintain it.
Perceptual memory

The content of memory is almost always *heterogeneous*, i.e. it consists of many different kinds, e.g. sensory, spatial, motor, semantic, emotional, conceptual.

This fact suggests that perceptual memory is represented by a *heterarchical* network, i.e. one that spans widely dispersed memory networks.

Fuster: “Any perceptual memory is an associative conglomerate of sensory and semantic features at many levels of the cognitive hierarchy of perceptual knowledge.”

Perceptual memory is also *hierarchical* – it grows into unimodal and polymodal associative cortex from an innate (phyletic) sensory memory in primary sensory cortices.
From Mesulam, 1998:

1) The figure on the left illustrates how a vast associative network develops in transmodal areas, associating unimodal networks in different patterns of association. The highest levels of integration correspond to conceptual memory.

2) The figure on the right illustrates a hypothesized transmodal network node that associates concurrent activity in different transmodal networks.
The *solidity* of long-term memory refers to its resistance to loss from injury.

Factors influencing memory solidity:
1) hierarchical rank: higher rank is usually associated with greater redundancy of content & with greater access to more association pathways; greater hierarchical rank $\rightarrow$ greater resistance to injury
2) strength of connections: memories with associations that are more specific (e.g. dates, names) are less solid (more vulnerable to loss) than memories with associations based on general concepts. The latter are related to more memories and thus more reinforced by repeated activation.

Memory is also subject to *hemispheric specialization*. Each hemisphere can acquire memories and motor skills apart from the other. Nonetheless, some memory networks extend across both hemispheres through associative fibers in the corpus callosum.
Executive memory

The history of research on the frontal lobe has emphasized its role in action rather than memory, except as a store of short-term or working memory.

However, the study of patients with frontal lobe injury provides ample evidence for the frontal cortex as a store of long-term executive memory.

Just as in the non-frontal cortices the perceptual hierarchies are based on low-level sensory areas, the executive hierarchy in the frontal lobe is based on low-level motor areas.

Deficits caused by frontal lobe lesions:
1) inability to recount serial actions (retrospective memory)
2) planning deficit: inability to formulate new plans of behavior (prospective memory)

The planning deficit may be seen as a disorder in the memory of executive sequences (i.e. action memory networks or schemas of action).

Networks in the lateral prefrontal cortex in particular are responsible for storing memory of schemas, plans, and programs of action.
Evidence about executive memory comes from Fuster’s microelectrode studies in monkeys: prefrontal neurons integrate sensory information over time for the execution of behavioral acts that depend on that information.

In a delayed paired-associate task:

a. the animal is required to associate tones with colors after an intervening delay.
b. the animal is rewarded for choosing the color that matches the tone.
c. the animal responds according to previously learned tone/color associations.

Successful selection of the correct matching color depends on both working memory (holding the sample information) and long-term memory networks (storing the paired-stimulus associations).
Fuster et al (2000) recorded prefrontal neurons that had joint preferences for paired sensory items, e.g. low-pitch/green or high-pitch/red:
   a. prefrontal neurons fired preferentially to both pitch and color.
   b. the recorded neurons represented samples from prefrontal networks that stored the learned tone/color associations.

Executive memory consolidation is thought to operate in the same way as for perceptual memory:
   1) Concrete, stereotypical, and automatic movements are consolidated in motor cortex.
   2) More general and abstract components of action are consolidated in prefrontal cortex. These include the rules and contingencies of a task.
   3) With practice, the common elements of many action sequences generate overarching prefrontal networks that abstract the commonalities of those elements into action schemas.
Future memory:
1. Evidence that the lateral prefrontal cortex is essential for the representation of plans suggests that this area “can form within itself networks that represent future action”. Thus, prefrontal cortex may be said to store “memory for the future”.
2. Once such networks are formed, goal-directed behavior requires that certain ones be selectively activated in choosing one course of action over another. This selective activation may be considered as retrieval of future memory.
3. Since the ability to store multiple future actions has great survival value, it is probably related to the high degree of phylogenetic expansion of prefrontal cortex in humans. This ability may also play an important role in creative thought and general intelligence.

Executive memory solidity:
Local frontal lesions at lower hierarchical levels are more harmful to low-ranking memory than they are at higher levels to high-ranking memory. This is because of the higher degree of interconnectivity of network nodes at higher levels due to divergence and convergence of connections in ascending the hierarchy.

Executive-perceptual memory:
Memory of past sequences of behavior in autobiographical context, i.e. with respect to specific time and space references, involves networks that incorporate both executive and perceptual items.
These networks probably depend on the heavy interconnectivity of prefrontal and posterior cortical areas.

Executive symbolic memory:
1. The action schema is a symbolic representation that is equivalent to the perceptual symbolic representations of the posterior cortex.
2. The high-level action schema of the frontal lobe (in orbitofrontal cortex) may be the form in which social regulations are instantiated in the brain.
Retrieval of memory

Memory retrieval entails activation of networks that were previously created by consolidation.

Remember, in consolidation, long-term memory is formed by synaptic modification between columnar assemblies according to Hebbian principles as a result of their concurrent activity in perception. Thus, consolidation preserves the patterns of association of perceptual activity in the connectional structure of memory networks.

Retrieval involves reactivation of the concurrent activity in the same patterns that produced the memory networks. In the “convergence zone” hypothesis of Damasio, re-activation of a high-level memory network also re-activates the lower-level memory networks from which it was formed.
Factors that alter memory retrieval:

1) some amnesias result from lowered solidity due to aging or disease, e.g. degradation of memory content due to decline in memory network solidity (synaptic strength).

2) other amnesias result from a failure of the retrieval mechanism, e.g. as occurs after physical insult.

After blunt force trauma, memory for events before and after the trauma is often impaired. Over time, retrieval ability improves, with the period of amnesia both before and after trauma shrinking. Eventually, the bulk of the amnesia disappears, but some period of time remains irretrievable due to lack of consolidation.

3) psychogenic block: dynamic defenses against anxiety may make emotion-laden memories irretrievable by normal recall.

4) over-retrieval: obsessive-compulsive disorder leads to uncontrollable retrieval of perceptual memory, motor memory, or both.
Not all memory contents are equally retrievable.

Factors affecting degree of access to memory content:
  a) degree of consolidation at different hierarchical levels (e.g. general facts recalled better than specific facts)
  b) practice
  c) rehearsal
  d) attention
  e) emotion
  f) type of retrieval (e.g. memories retrieved more easily by recognition than recall)

Patients with bilateral hippocampal damage (e.g. H.M.) show memory retrieval problems:
  a) It was originally believed that H.M.’s impairment was primarily anterograde, i.e. for information following surgery (reflecting an inability to consolidate new long-term memories).
  b) However, subsequent testing revealed that he also had extensive retrograde amnesia (reflecting an inability to retrieve existing memories). His retrograde amnesia covered most events 3-4 days prior to surgery.
PET studies have also implicated the hippocampal system in memory retrieval.

Thus, current thinking is that the hippocampal system is necessary for:
1) consolidation of new memories
2) retrieval of existing memories for a short time in the past (perhaps those memories not completely consolidated)

Memory retrieval can be initiated by:
1. sensory input
2. inputs from other activated memory networks
3. inputs from the internal milieu:
   a. influences from visceral systems
   b. influences from limbic system

We next consider each of these three types of initiation in more detail.
1) Memory retrieval by sensory input

a) Microelectrode studies in inferior temporal cortex of monkeys trained on **paired associates** show that neurons there respond similarly to either of two associated visual stimuli. This suggests that representations of both visual stimuli have been incorporated into an IT memory network, and that it can be activated (and the memory retrieved) by either stimulus.

b) Microelectrode studies in somatosensory cortex of monkeys show that neurons there respond similarly to the touch of an object and to a visual stimulus that has been behaviorally associated with it.

c) Organization of memory by category facilitates the retrieval of memory items. This may be due to the associative structure of memory networks across hierarchical levels.
   i. Activation of memory networks at one hierarchical level by sensory input may activate associated memory contents at other levels, thus facilitating retrieval.
   ii. Even just cueing of an item’s category may facilitate its retrieval through priming of cross-level associations.
2) Memory retrieval by other memory networks

One memory network may be activated as part of a sequence of associative retrievals. The activated network may subsequently retrieve a second network through associative connections. In principle, any memory retrieval operation externally or internally initiated may act as the source of further retrievals.

3) Memory retrieval by the internal milieu

a. visceral systems

Subcortical brain structures integrate visceral functions (temperature control; fluid control and thirst; eating, digestion, and hunger; reproduction; sleep; stress control; fear).

The amygdala-hypothalamus-septum system controls the visceral systems.
Through the thalamus, it sends signals to the orbitofrontal cortex, which may then activate memory networks. For example, the feeling of hunger (arising in a visceral system) may activate memories related to food (in the cortex).

b. limbic system

Processes initiated by external stimuli are thought to feed into the amygdala at the same time as, or before, they reach cortex.

The confluence of internal and external signals in the cortex may underlie such phenomena as *state-dependent learning* and *fear conditioning*, where internal limbic signals (about the state of the organism) affect the learning process.

Cortical networks that associate visceral and emotional inputs with perceptual items from the external senses may be considered to represent *emotional memory*.
Emotional “coloring” of memory can sometimes distort retrieval. In false memory, the recollection of long-term memory may be inaccurate or incorrect due to its emotional content.

The terms explicit and implicit memory have traditionally referred to semantic and motor types of memory.

Fuster, however, considers them to relate to different degrees of consolidation and memory strength: any memory may be explicit when it is newly consolidated, but may gradually become more and more implicit as it consolidates as a result of continued usage and/or practice. Explicit memory requires conscious effort for its retrieval, whereas implicit memory does not.

Therefore, Fuster proposes that the distinction between explicit and implicit memory be defined in neural terms by differences in: (1) consolidation, (2) strength of connection, (3) state of activation.

Different states of activation may be seen in the phenomenon of priming. Priming is the facilitation of memory retrieval of an item as a result of previous exposure to a stimulus that is related to that item:

a) Priming may be understood as the partial pre-activation of cortical memory networks that are associated with the priming stimulus.
b) Experimentally, the facilitating effect of priming may be seen by the enhanced probability, speed, or accuracy of the retrieval.
c) The first stimulus need not be recognized for priming to occur, nor must it even reach conscious awareness.

Summary on memory retrieval:
1) the cerebral cortex may be considered as a vast web that associates all kinds of long-term memories, i.e. that contains networks for all kinds of memory.
2) activation of networks in this web brings about retrieval of the associated memories
3) the retrieval of memory from this web can be very selective, i.e. retrieval may activate very specific, localized networks.
4) the retrieval of memory may spread from one network to another in a sequence of recollections (a “train of thought”).