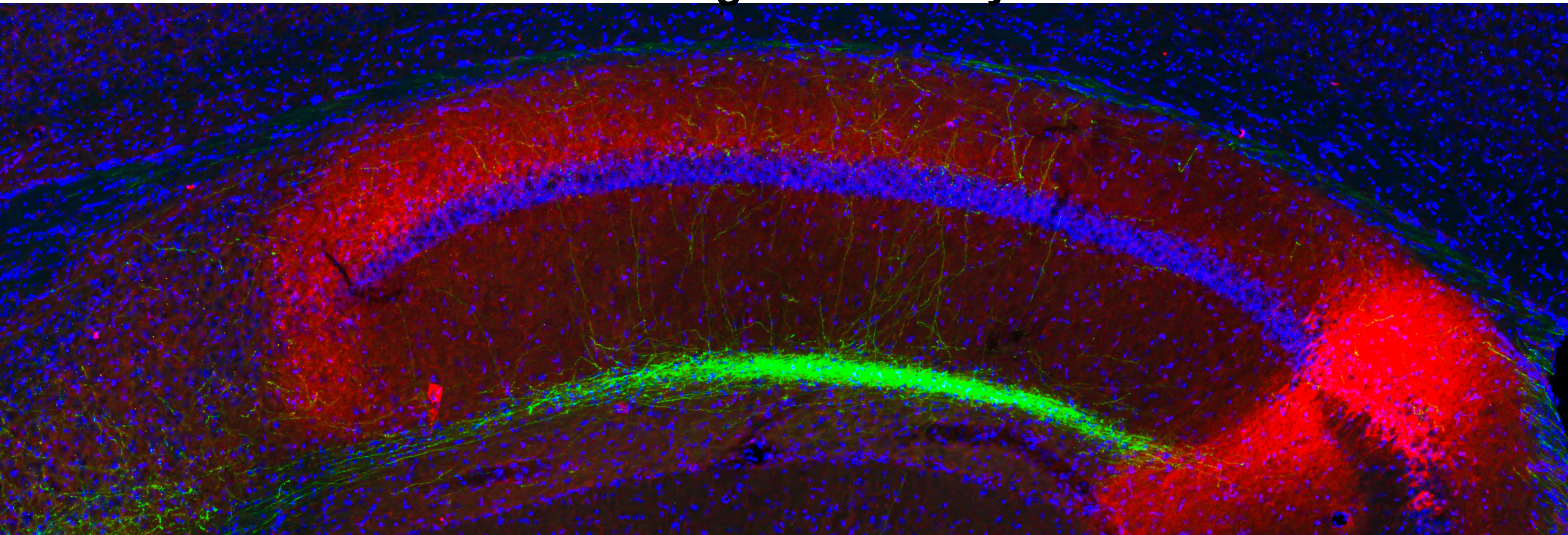
Applied Neuroscience

Columbia Science Honors Program Fall 2016

Learning and Memory



Learning and Memory

Learning and Memory

Objective: Current Understanding of Learning and Memory

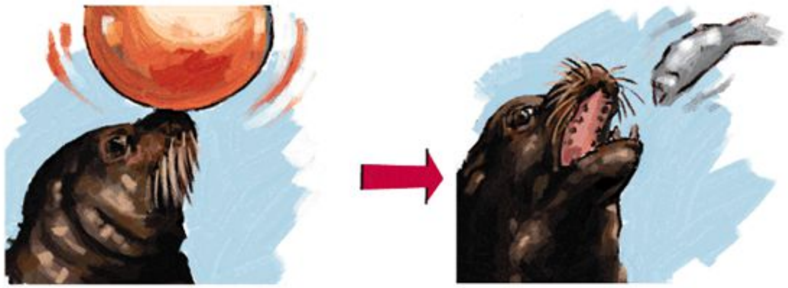
Agenda:

1. Learning
   - Associative vs. Non-Associative Learning
   - Drosophila Case Study
2. Introduction to Memory
   - Structure and Function of Memory
   - Types of Memory
3. Memory Disorders
   - HM Case Study
   - Place Cells in Rats
   - Alzheimer’s Disease
   - Jill Price Case Study
4. Computational Models of Memory
   - Man vs. Machine
   - Introduction to Neural Networks

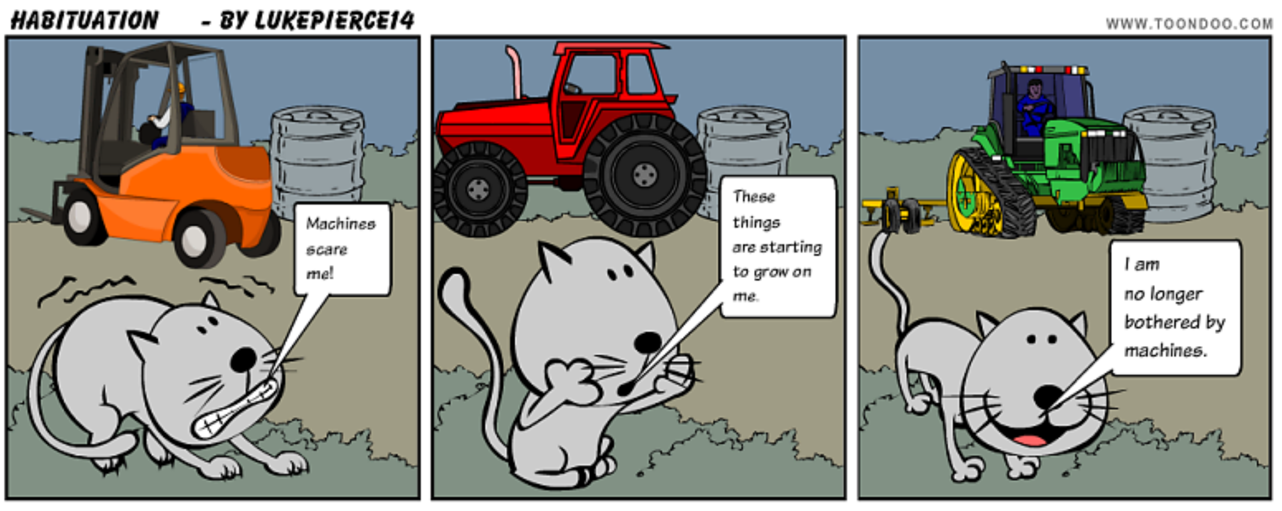
Animal learning paradigms

Associative vs. non-associative learning

- Associative learning: animals learn association between two stimuli or a behavior and a stimulus
  - Classical conditioning
  - Operant conditioning
- Non-associative learning: animals change response to stimuli without association with a positive or negative reinforcement
  - Habituation
  - Sensitization



Seal learns to expect a snack for its showy antics



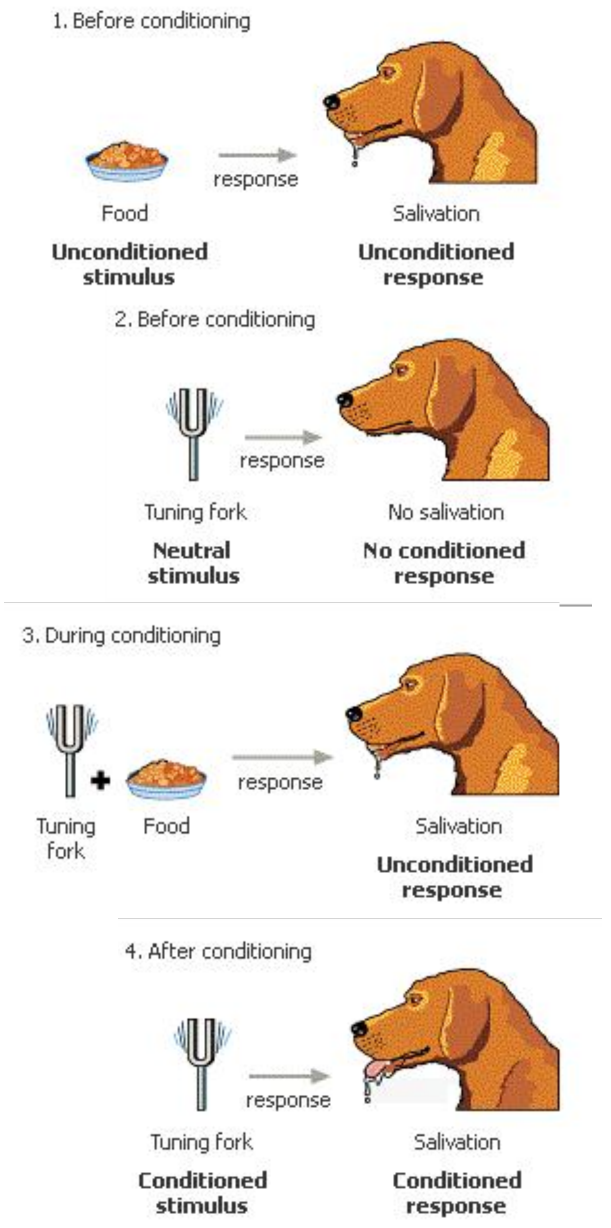
Associative learning

Conditioned stimulus (CS) vs. unconditioned stimulus (UCS)

- CS: previously neutral stimulus, after being associated with an unconditioned stimulus, triggers a conditioned response (i.e. dogs salivating when they see owner, who serves them food)
- UCS: unconditionally, naturally and automatically triggers a response (i.e. smelling one of your favorite foods)

Classical conditioning: Pavlovian conditioning

- Pavlov repeatedly presented a dog with food after the ringing of a bell
- When bell sounded without presentation of food, dog would still respond to bell as if it were food
- Amount of saliva produced by bell ringing increased as dogs were more frequently exposed to coupling of food presentation and bell ringing
- **Conditioning the dog to salivate at the sound of the bell was caused as a result between the connection between the CS and UCS**

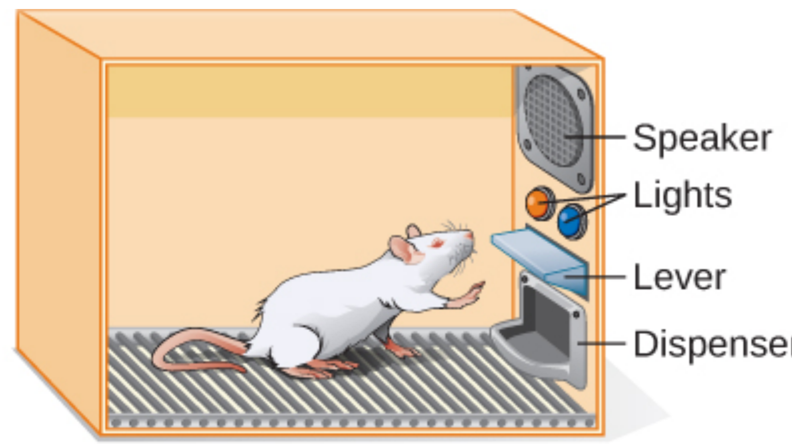


Associative learning

<u>Operant conditioning</u>:
Same as classical conditioning, except associating CS with UCS becomes associated with a reward

Skinner box

- Rat is placed inside the Skinner box
- If the rat pressed a lever inside the box, the box would release a food pellet
- With each instance of lever pressing, the operant is reinforced by reward with food
- Rat learns that pressing lever results in food, so increasingly presses it



Non-associative learning

Habituation:
Ability to discontinue response to highly repetitive stimuli

Results in recovery of the original response

Can be either short-term or long-term, depending on the presentation and interval between stimuli

Stimulus-specific

- If you change the stimulus, you see recovery of the response

Sensitization:
Increase in responsiveness as result of repeated application of a stimulus or aversive stimulus

Results in a response stronger than the original one

Usually temporary

- Can last for up to a week but not generally a long-term effect
- With a stronger stimulus, the effects are larger

Not highly stimulus-specific

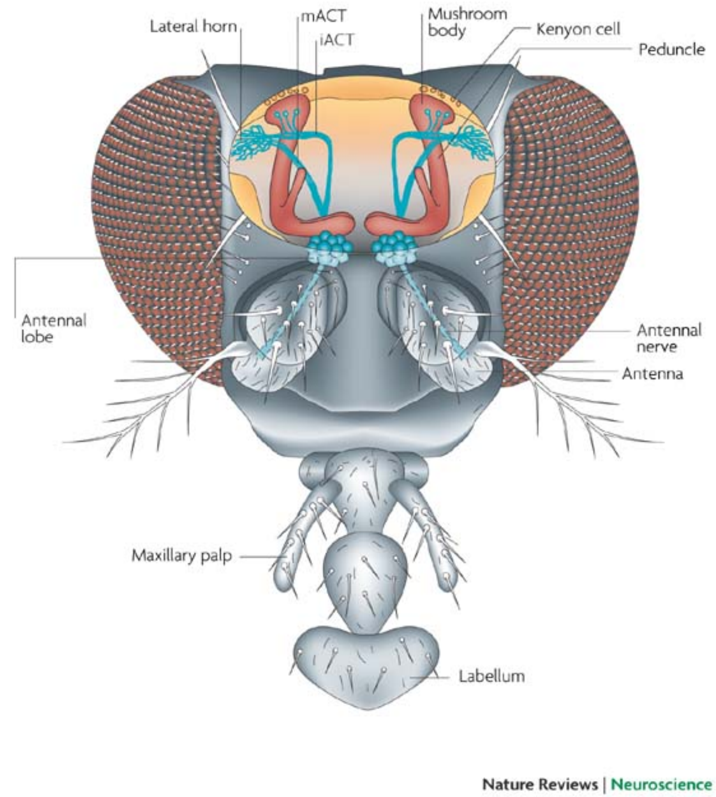
- If an animal is aroused, it is usually aroused to a variety of cues

Drosophila case study

Most commonly studied form of learning and memory in Drosophila is olfactory classical conditioning.

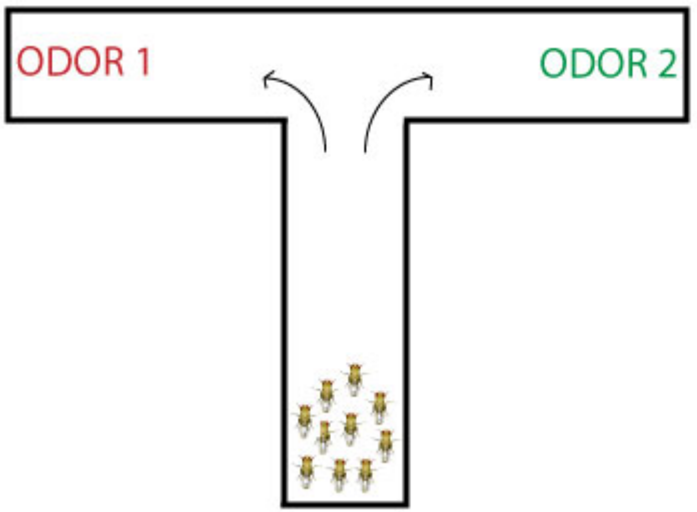
Why study this in flies?

- Flies are particularly good at learning odors (at least in the lab)
- Olfactory system in insects is homologous in structure and function to vertebrates
- Olfactory classical conditioning (i.e. reward learning in which organism learns the association between an odor and a reinforcer like mild electric shock or food) is learned quickly



Experimental task and design

Olfactory classical conditioning requires flies to associate an odor (CS) with a negative (electric shock) or positive (sucrose reward) stimulus (UCS).



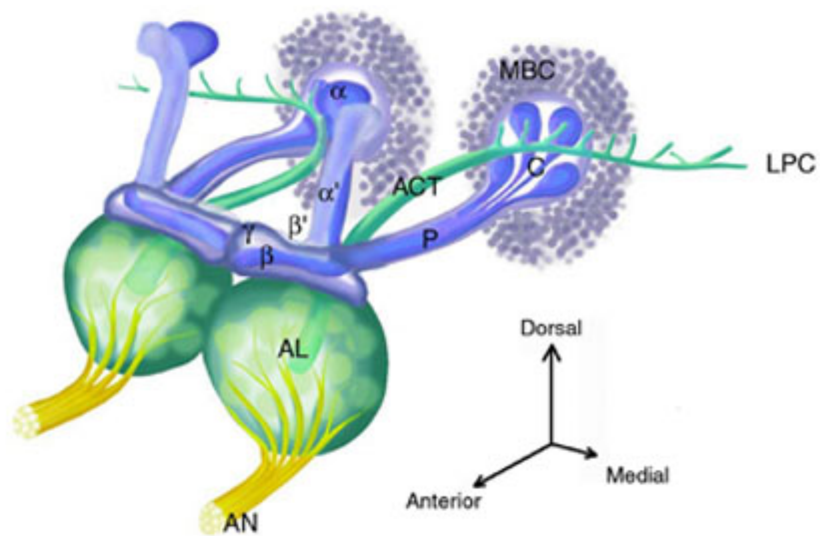
How is this done?

- Traditionally, this is done using groups of flies submitted to two different odors CS+ and CS-, with only one of them (CS+) presented at the same time as the UCS
- Memory of this conditioning is tested in a T-maze where trained flies must choose between the two odors
- By increasing the time between acquisition and testing, it is possible to test short, middle and longer-lasting forms of memory

Results

<u>What happens?</u>

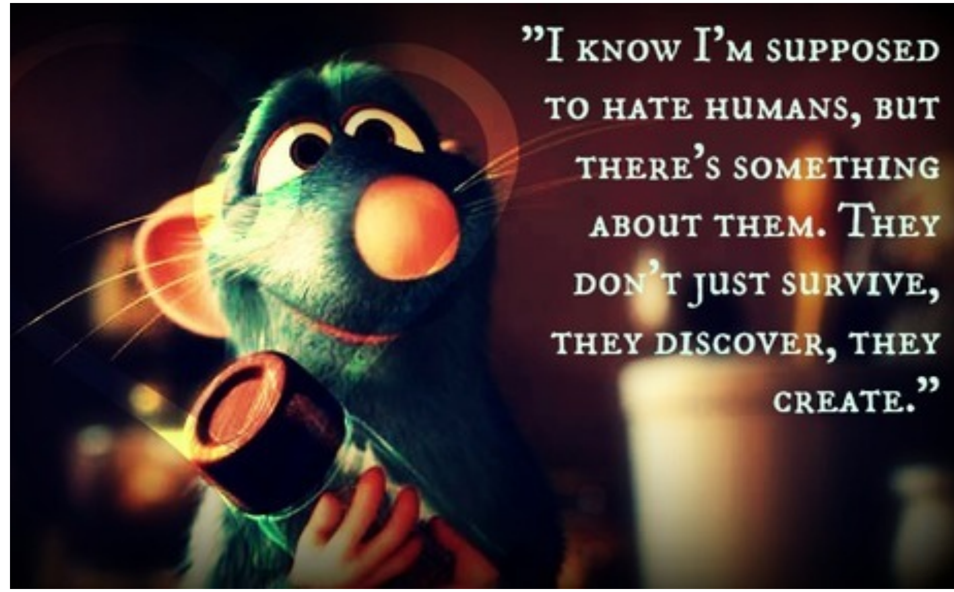
- The association between the odorant and the US changes the behavioral value associated with the odor
- The plasticity associated with this value change takes place in a region of the CNS where the olfactory information and US information intersect
- Most studies have shown that the mushroom body (MB) is required for normal olfactory learning



Introduction to Memory

What is memory?

Memory: changes in the activity or connectivity of neural systems that are triggered by stimuli or brain states and ***persist over a duration longer than triggering events***



Why do we need memory?

Memory serves an **adaptive role:**

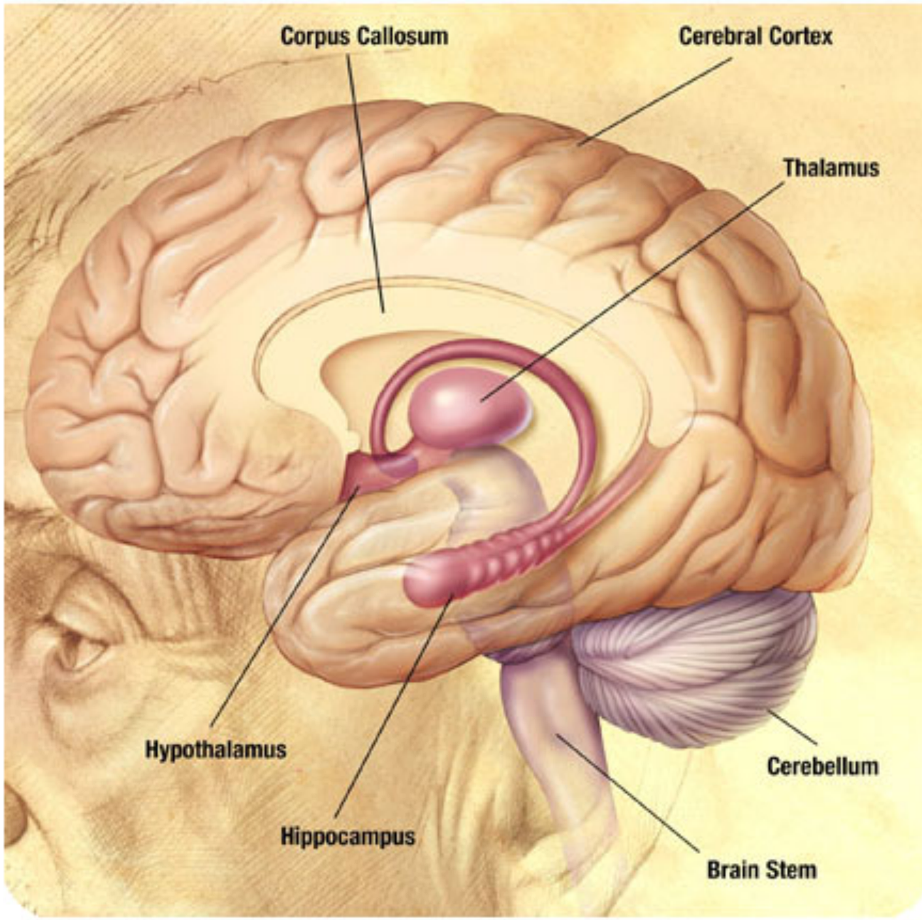
1. We learn from our experiences
2. We generalize faster
3. We can make predictions

Learning, Inference, and Prediction

Memory research uses:

1. Neuroscience
2. Computer Science
3. **Information Theory:** studies the quantification, storage, and communication of information

Introduction to Memory



Limbic System: controls emotions and instinctive behavior (includes hippocampus and parts of cortex)

Thalamus: receives sensory and limbic input and sends to cerebral cortex

Hypothalamus: maintains homeostasis and controls internal clock of body

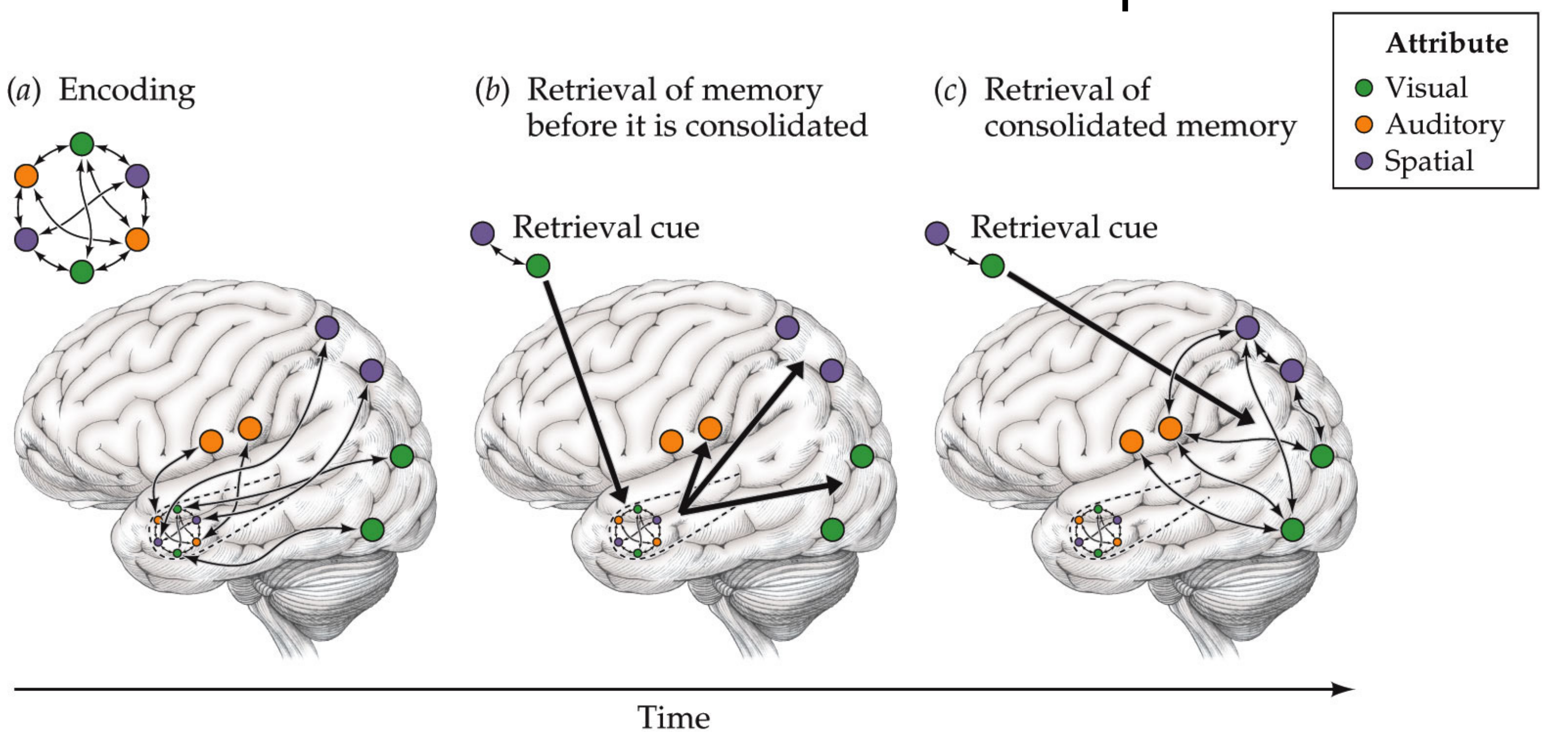
Hippocampus: where short-term memories are converted to long-term memories

Introduction to Memory

Where is memory?

Multiple Brain Regions are involved in encoding memory as shown below by fMRI studies

fMRI: uses MRI technology that measures brain activity by detecting changes in associated with blood flow. Cerebral blood flow and neuronal activation are coupled.



Seven Sins of Memory

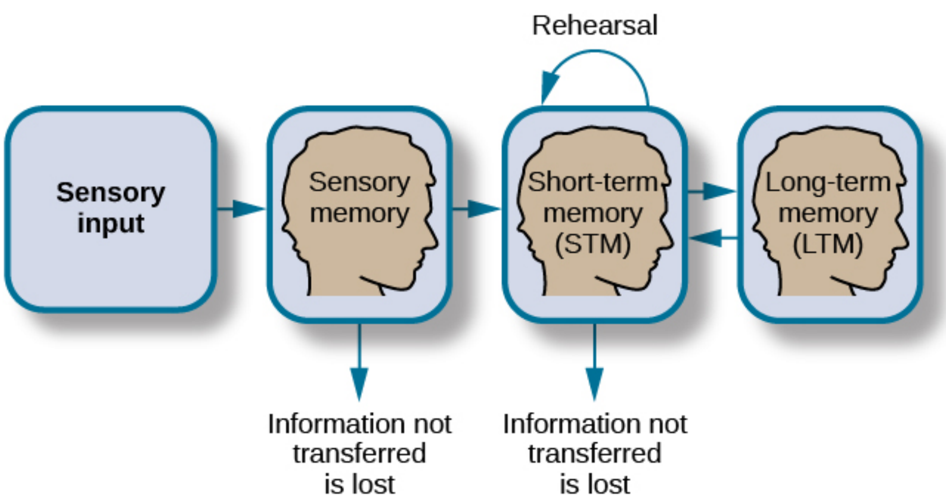
Sin	Description	Example
Transience	Decreasing accessibility of memory over time	Simple forgetting of long-past events
Absent-Mindedness	Lapses of attention that result in forgetting	Forgetting location of car keys
Blocking	Information is present but temporarily accessible	Tip-of-the-tongue
Misattribution	Memories are attributed to an incorrect source	Confusing a dream for a memory
Suggestibility	Implanted memories about things that never occurred	Leading questions produce false memories
Bias	Current knowledge and beliefs distort our memories of the past	Recalling past attitudes in line with current attitudes
Persistence	Unwanted recollections that we can never forget	Traumatic war memories

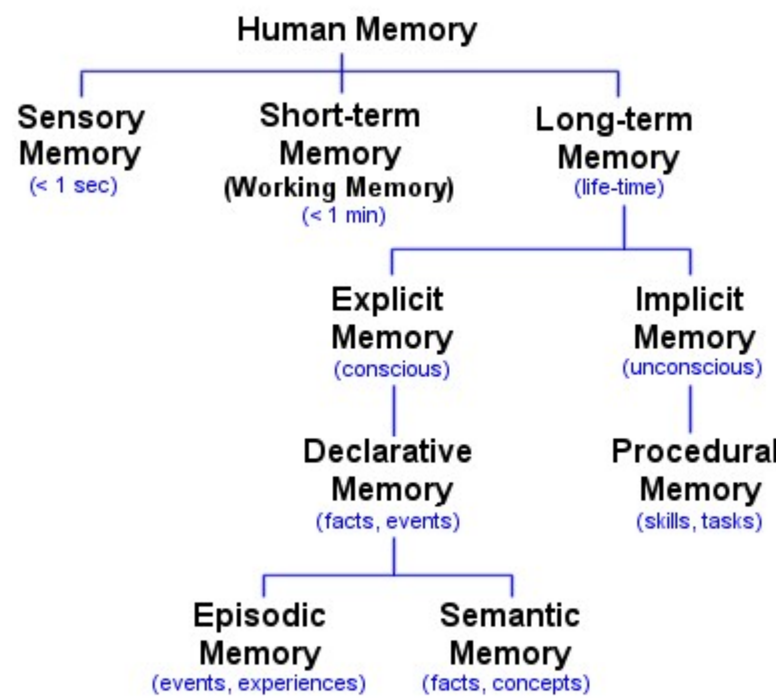
Credit to Professor Daniel Schacter, Chair of Psychology at Harvard University

Types of memory

- Models of memory include a sequence of three stages: **sensory, short-term and long-term memory**
- Different types of memory have their own mechanism of action
- This sequential model is called modal, multi-store or the Atkinson-Shiffrin model (developed in 1968)

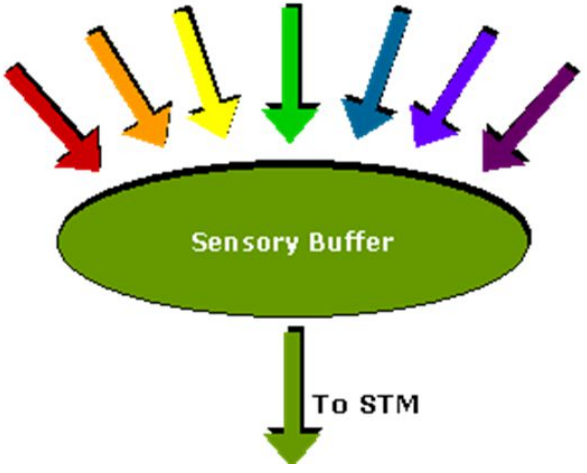
- A second model (levels-of-processing model) shows memory as a function of mental processing, in a hierarchical way





Sensory memory

- Shortest-term element of memory
- It is the ability to retain impressions of sensory information after the original stimuli has ended (**buffer**)
- Stimuli detected by senses can be:
  - Ignored: disappear almost instantaneously
  - Perceived: enters our sensory memory
- Decays very quickly – usually 200-500 milliseconds after perceiving an item
- Other names for sensory memory, based on the type of sensory stimulation:
  - Iconic memory: visual
  - Echoic memory: auditory
  - Haptic memory: touch
- Information is passed from sensory to short-term memory via **attention**



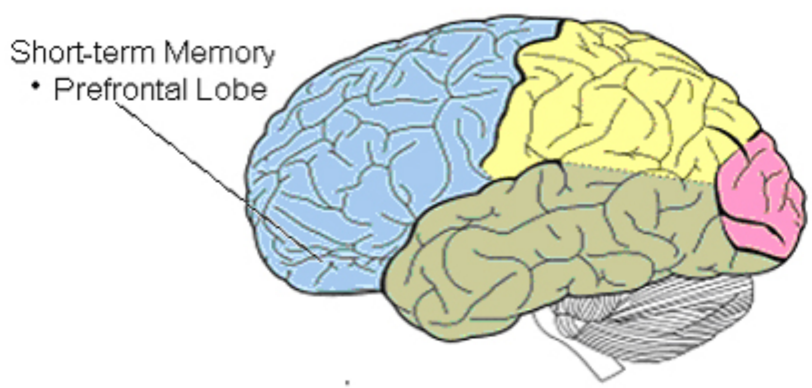
Short-term (working) memory

- Important for temporary recall of information
- Gives you the ability to remember and process information at the same time
- It holds a small amount of information (seven items or less)
- For a short amount of time (10-15 seconds, sometimes up to a minute)

What are some examples of short-term memory?

Short-term (working) memory

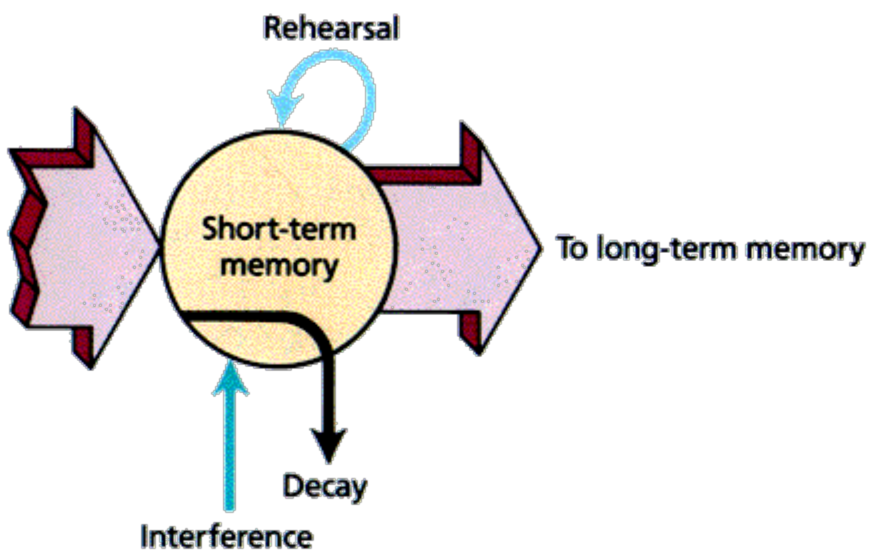
- Information will quickly disappear unless a conscious effort is made to retain it
- **Working memory** is often interchanged with short-term memory
- Central executive part of **prefrontal cortex** is important for short-term memory
  - It serves as a temporary store for information and also calls up information from other parts of the brain
  - This area has two neural loops: one for visual data and other for language



Short-term (working) memory

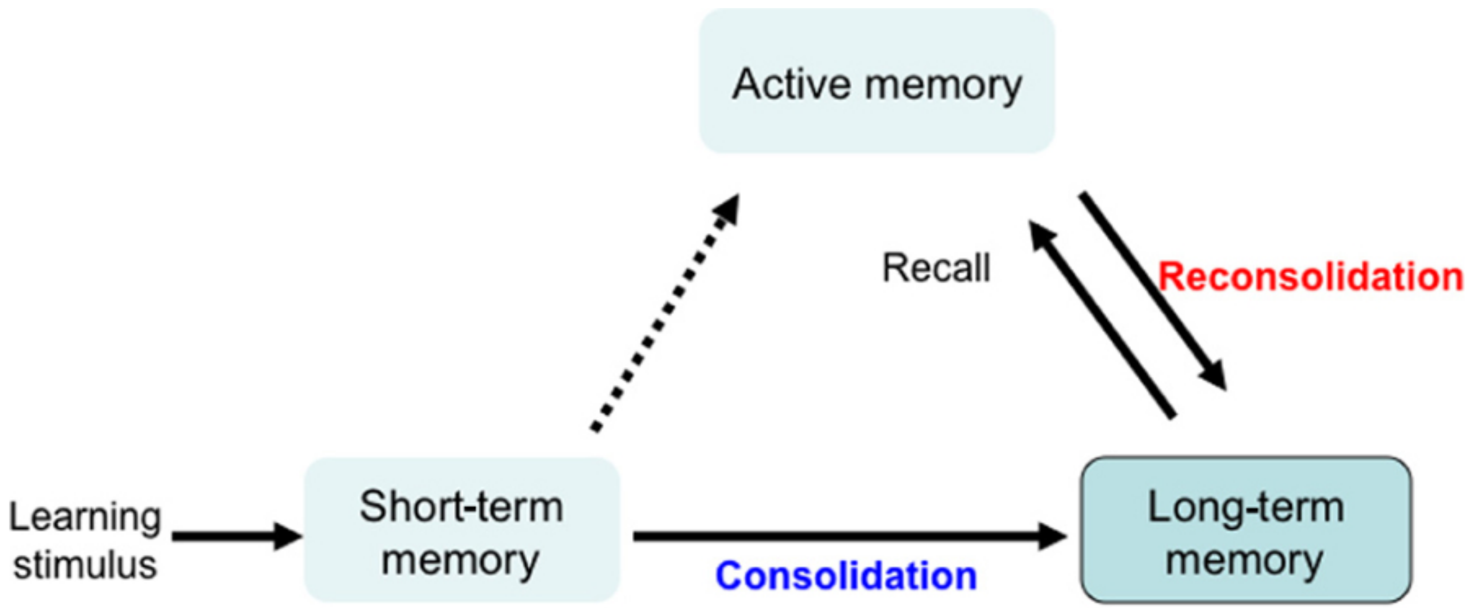
Time scale of short-term memory

- Assumed that short-term memory spontaneously decays over time
- Can be extended by repetition or **rehearsal**, so information re-enters short term memory store
  - i.e. through reading items out loud or by mental stimulation
- When several elements are held in short-term memory simultaneously, they compete with each other for recall
- Newer content pushes out older content (**displacement**)



Long-term memory

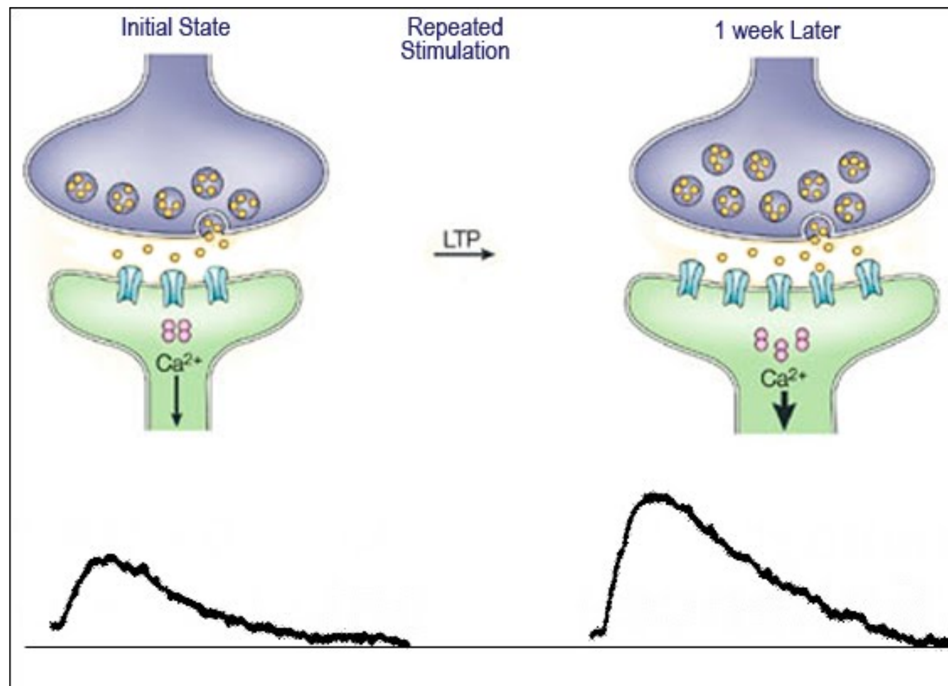
- Intended for storage of information over long periods of time
- Long-term memory decays very little over time
- Debate as to whether we actually forget at all or just becomes increasingly difficult to access certain items from memory
- Short term memories become long term memories through **consolidation**. This is done through:
  - **Rehearsal**
  - **Meaningful association**



Long-term memory

How does this happen in the brain?

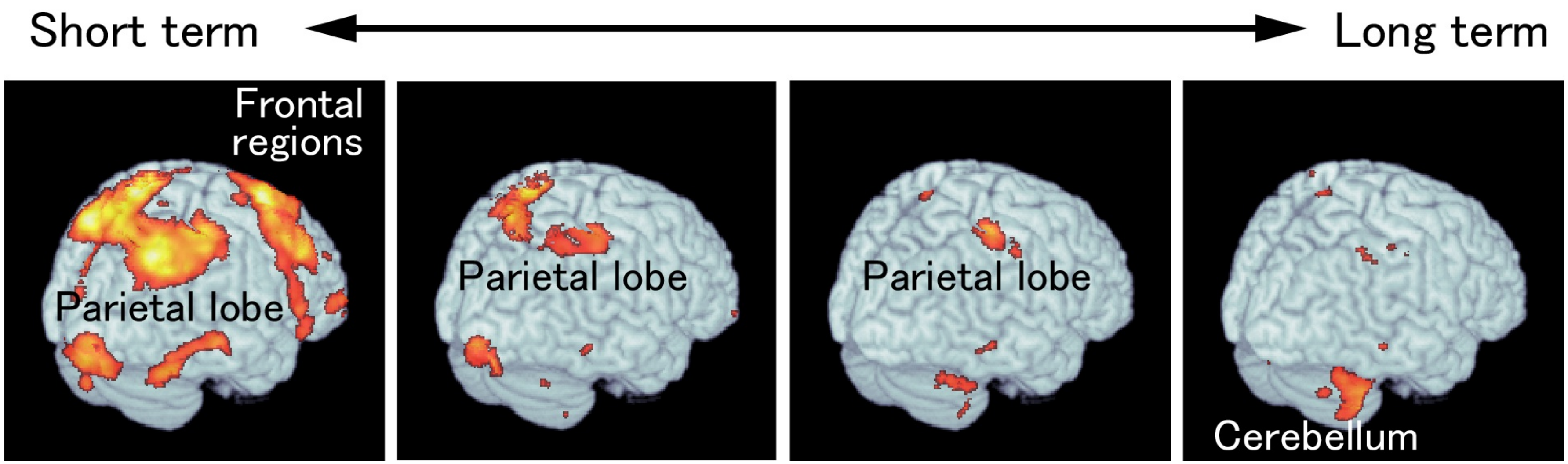
- Long-term memory involves a process of physical changes in the structure of neurons in the brain – this is called **long-term potentiation**.
- Whenever something is learned, circuits of neurons in the brain are created, altered and strengthened
  - Neurons communicate with each other through junctions called synapses
  - Through creation of new proteins and transfer of neurotransmitters across synapses, the communicative strength of certain circuits in the brain are reinforced
  - With repeated use, the efficiency of these synapse connections increases



Long-term memory

<u>Where does this happen in the brain?</u>

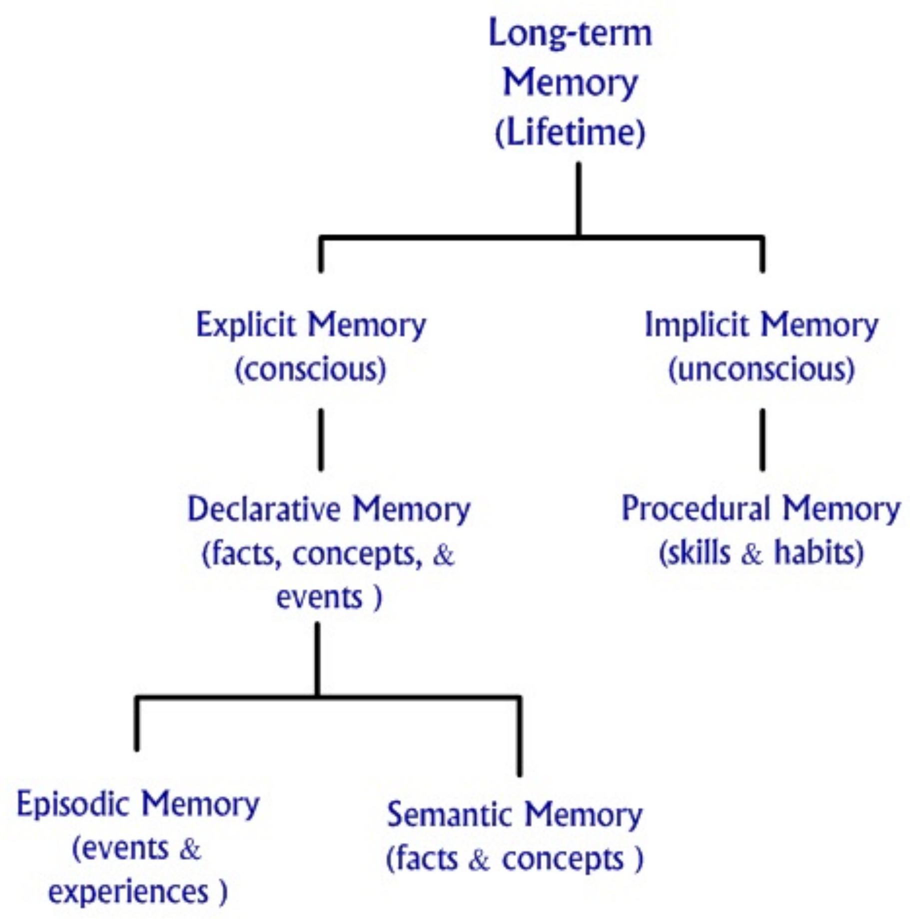
- Short term memory: more transient changes in **frontal**, **prefrontal** and **parietal lobes** of the brain
- Long term memory: more stable and permanent changes in **hippocampus** and other brain areas (like **cerebellum** and **amygdala**)



Long-term memory

<u>Different types of long-term memory:</u>

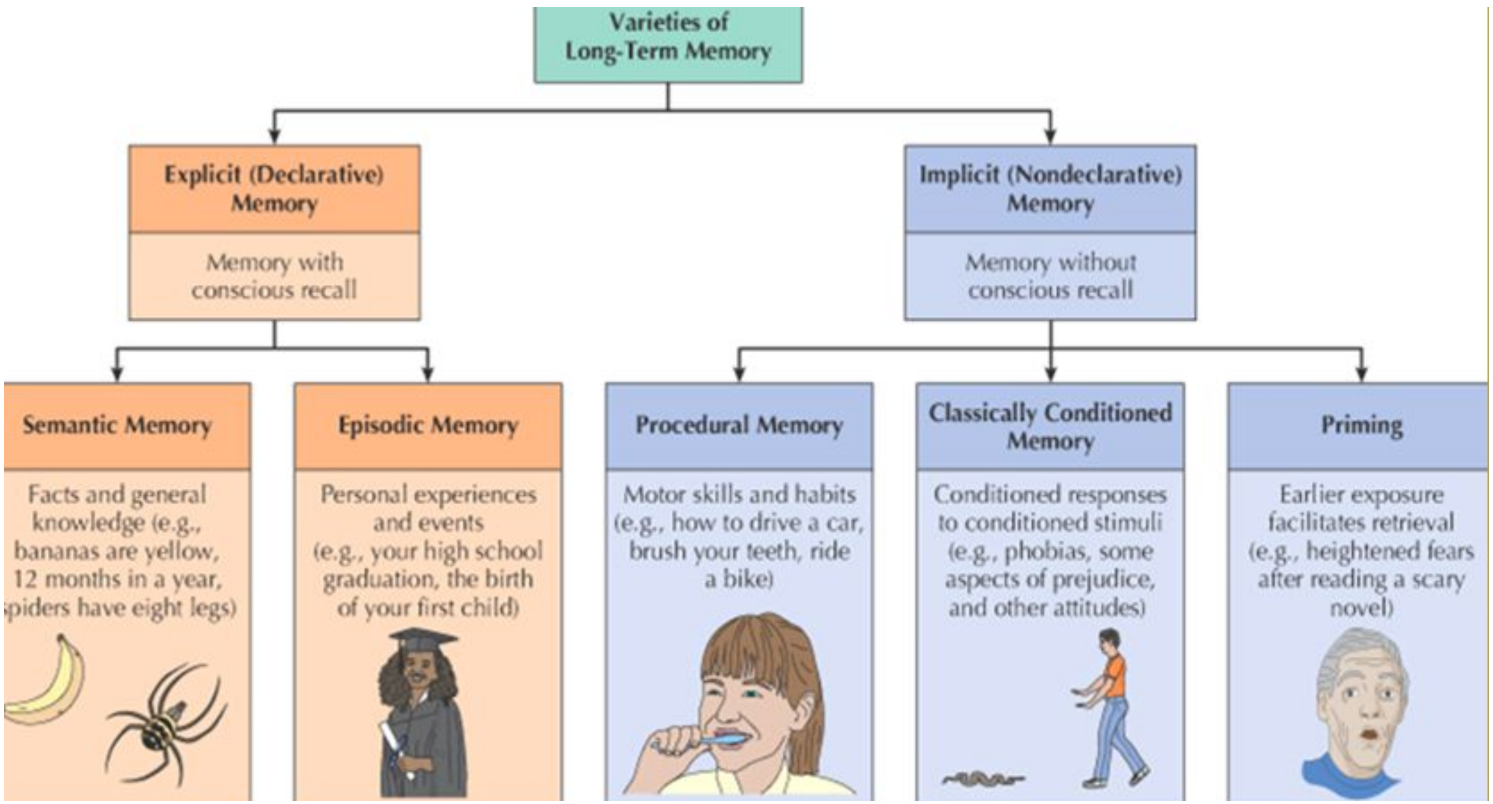
- <u>Explicit</u> (declarative) and <u>implicit</u> (procedural)
  - Declarative can be broken down into episodic and semantic memory
- Alternate classification: <u>retrospective</u> and <u>prospective</u>



Explicit and implicit long-term memory

<u>Different types of long-term memory:</u>

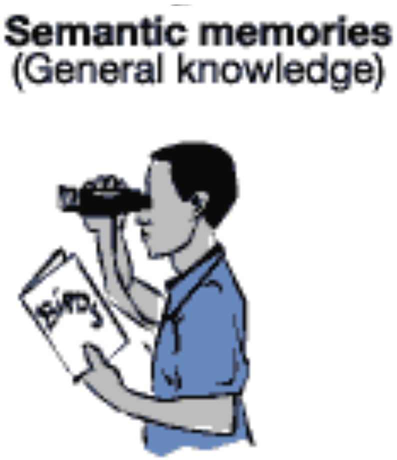
- Explicit (declarative) vs implicit (procedural)
- <u>Declarative</u>: memory of facts and events
  - Memories that can consciously recalled
- <u>Procedural</u>: memory of skills and how to do things



Declarative long-term memory

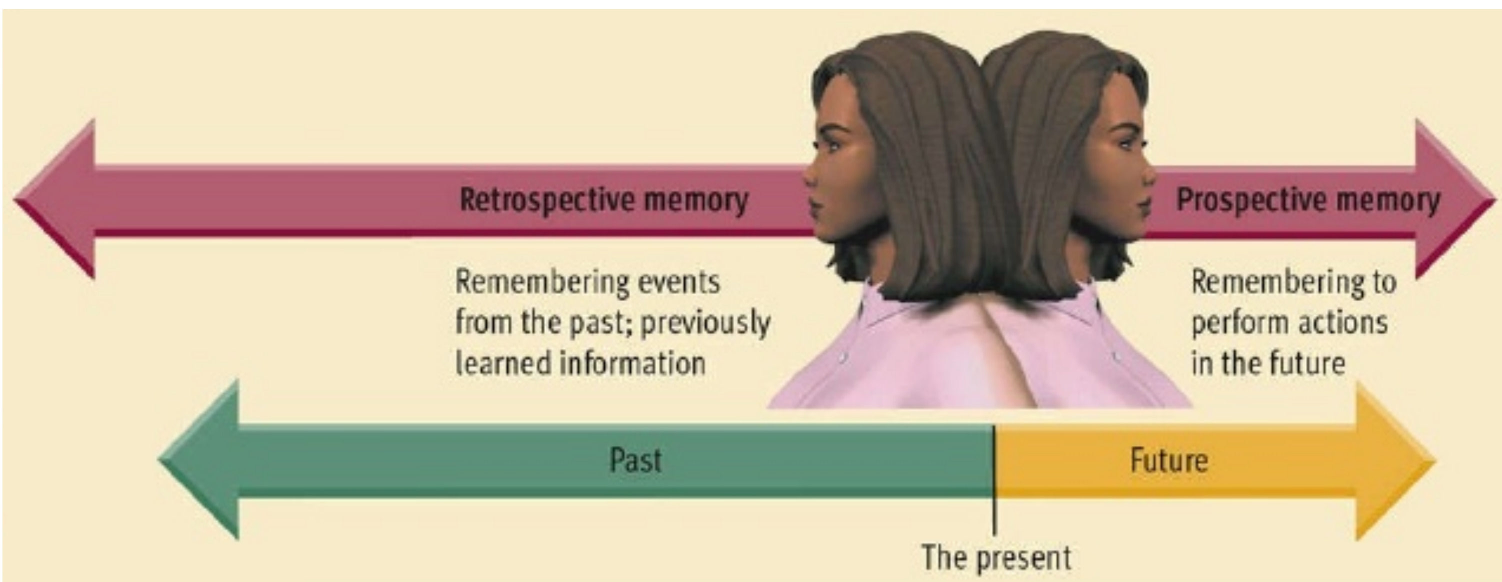
<u>Subdivisions of declarative memory:</u>

- <u>Episodic</u>: memory of experiences and specific events in time
  - Memory of autobiographical events and usually emotional charge/ context is part of the memory
- <u>Semantic</u>: structured record of facts, meanings, concepts and knowledge about the external world
  - Independent of personal experience and spatiotemporal context



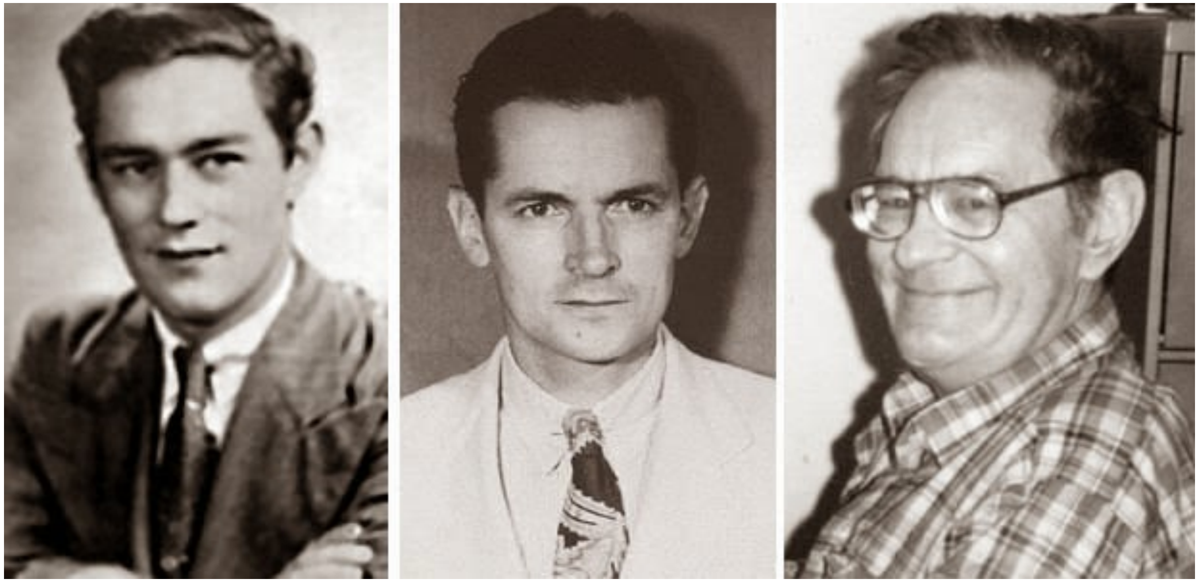
Retrospective and prospective memory

- Alternate classification is based on temporal direction of memories
- Retrospective memory: content to be remembered is in the past
  - Contains: semantic, episodic, autobiographical memory and declarative memory
- Prospective memory: content to be remembered in the future ("remembering to be remembered")
  - Either event-based or time-based
  - Often triggered by a cue (i.e. going to the doctor at *4 pm*)



Case Study on Memory: Henry Molaison (HM)

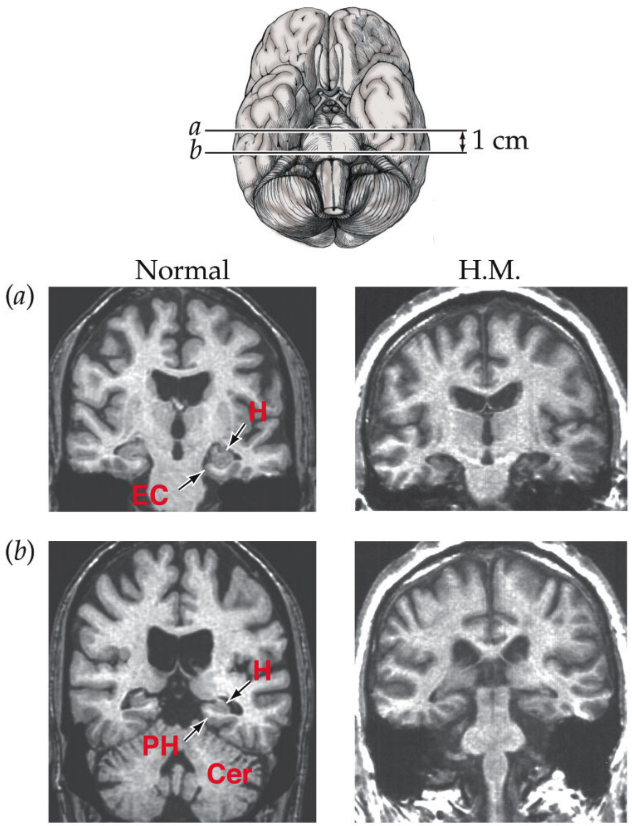
Henry Molaison and Brenda Milner

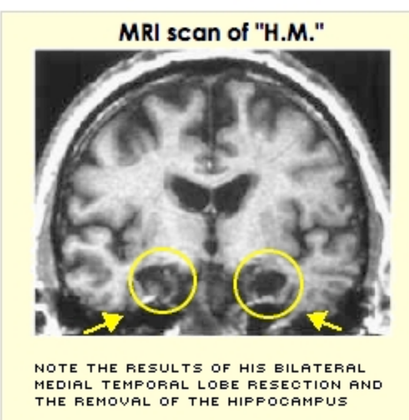


Understanding the Human Brain: A Lifetime of Dedicated Pursuit

Thank You, Professor Brenda Milner

Case Study on Memory: Henry Molaison





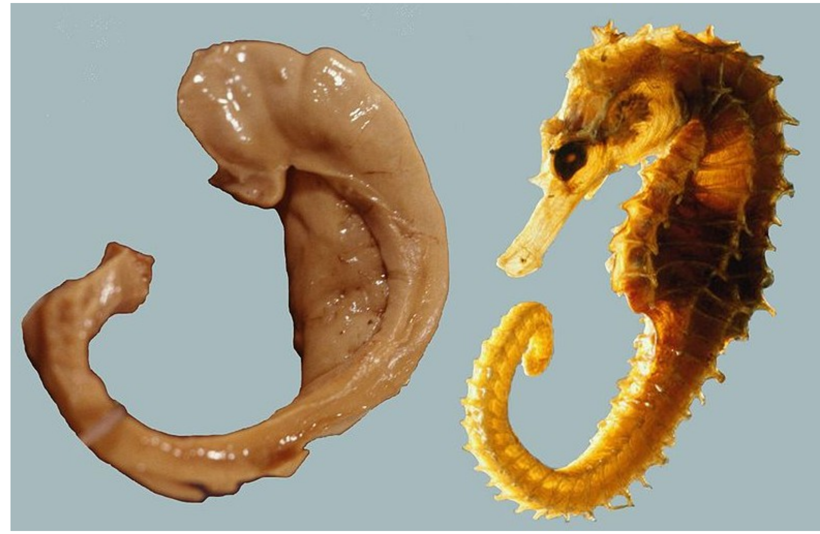
Anterograde Amnesia: Problems of learning new facts

- Specific to episodic memories
- Procedural memories intact
- Implicit memory performance intact
- Verbal learning disrupted

Damage to the hippocampus or to regions that supply its inputs and receive its outputs causes anterograde amnesia *as evidenced by Henry Molaison Case Study*

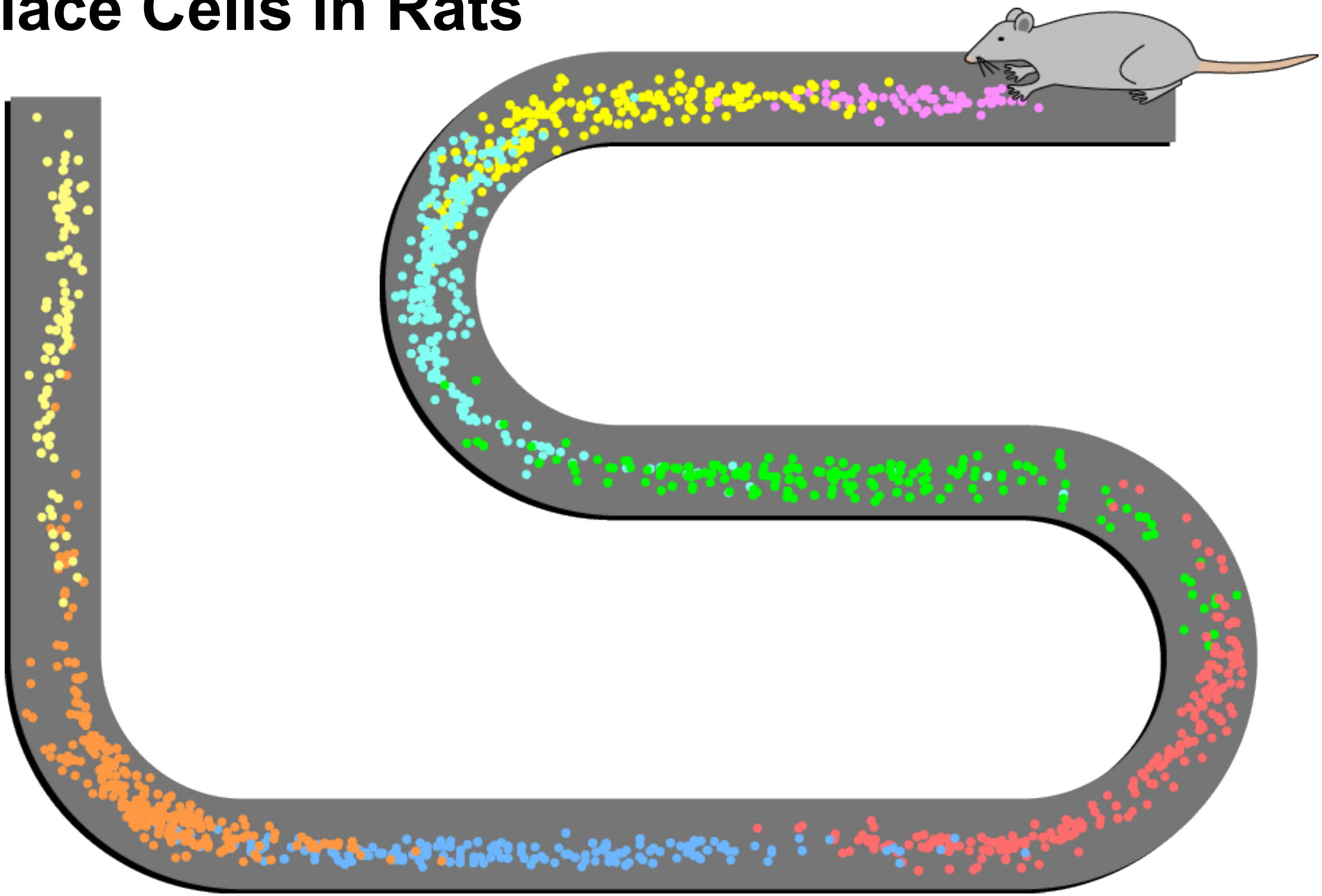
Role of the Hippocampus

1. **Formation of new episodic memories**
   Anterograde amnesia (HM)
2. **Cognitive Map**
   Place Cells in Rats
   Spatial Attention Cells in Monkeys
3. **Configurable Association Theory**
   Rats with hippocampus lesions are impaired on tasks requiring them to recognize cue configurations



Hippocampus means "seahorse"

Place Cells in Rats



Place Cell: A type of pyramidal neuron within the hippocampus that becomes active when an animal enters a particular place in its environment (***place field***)

Case Study on Memory: Alzheimer's Disease

Alzheimer's Disease (AD)

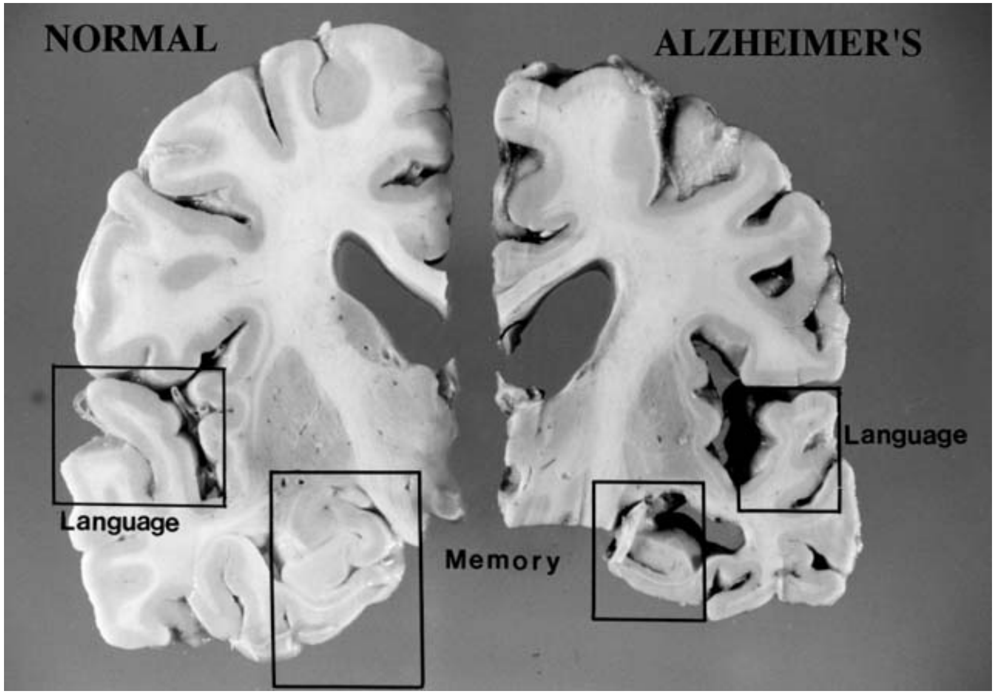
- Cortical and Progressive Dementia

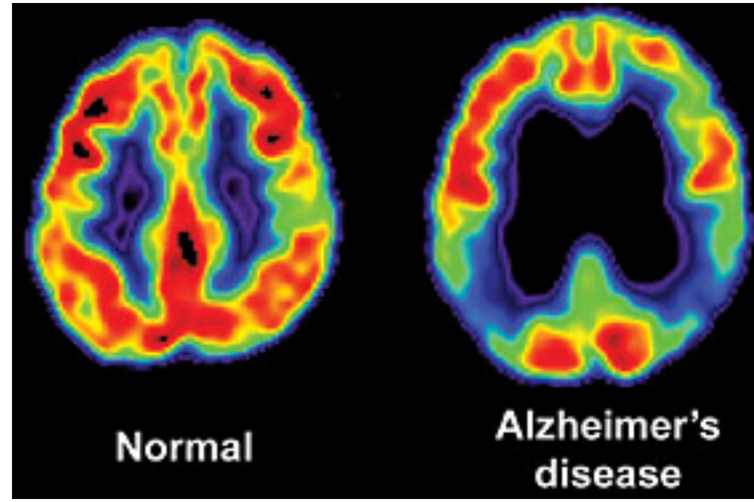
  Pre-Clinical AD
  - Signs of AD are first seen in entorhinal cortex and then proceed to the hippocampus
  - Affected regions begin to shrink as nerve cells die
  - Changes can begin 10 to 20 years before symptoms appear
  - **Memory Loss** is the **first** sign of AD

  Mild to Moderate AD
  - AD spreads through the brain and the cerebral cortex begins to shrink as more and more neurons die

  Severe AD
  - Extreme shrinkage, patients are completely dependent on others for care.
  - Death from pneumonia and other infections

Alzheimer's Disease (AD)



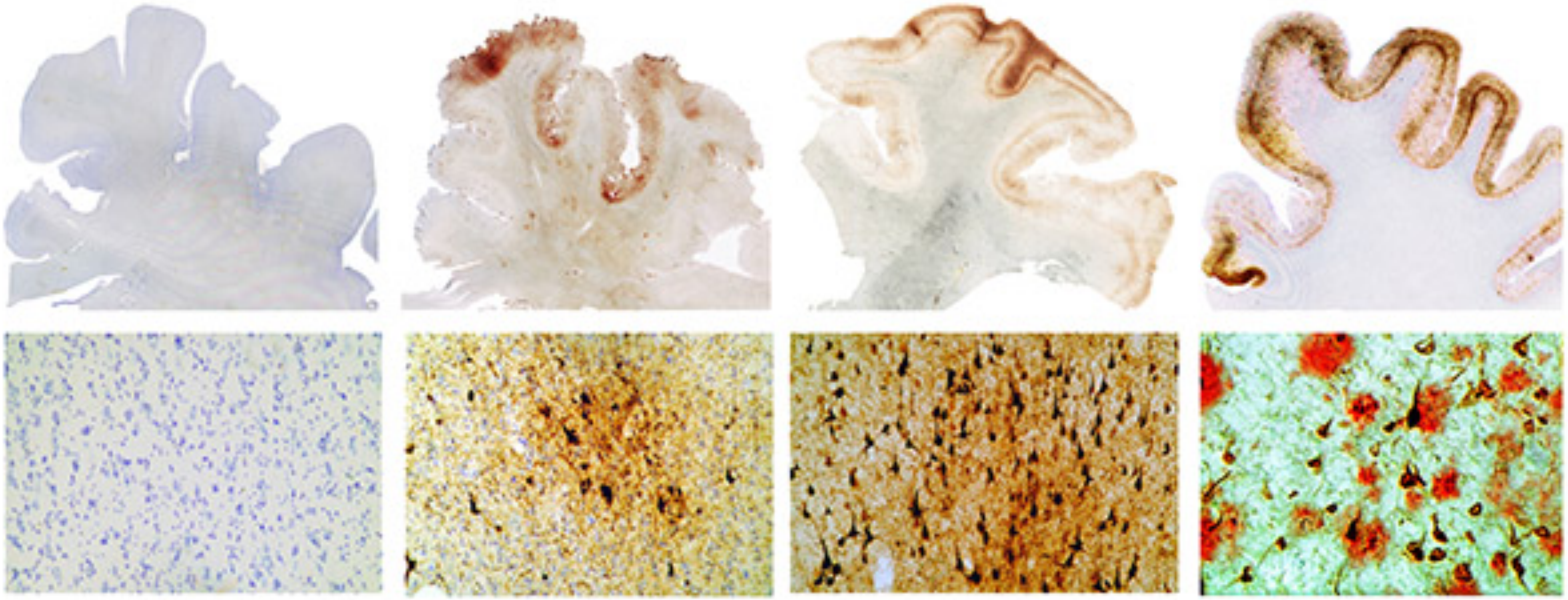


1. Extreme Shrinkage of Cerebral Cortex
2. Extreme Shrinkage of Hippocampus
3. Severely enlarged ventricles

Positron Emission Tomography (PET):
Uses a small amounts of radiotracers (analog of glucose, *fludeoxyglucose*) to evaluate organ and tissue function

Intense labeling of organs that use glucose extensively

Alzheimer's Disease (AD)

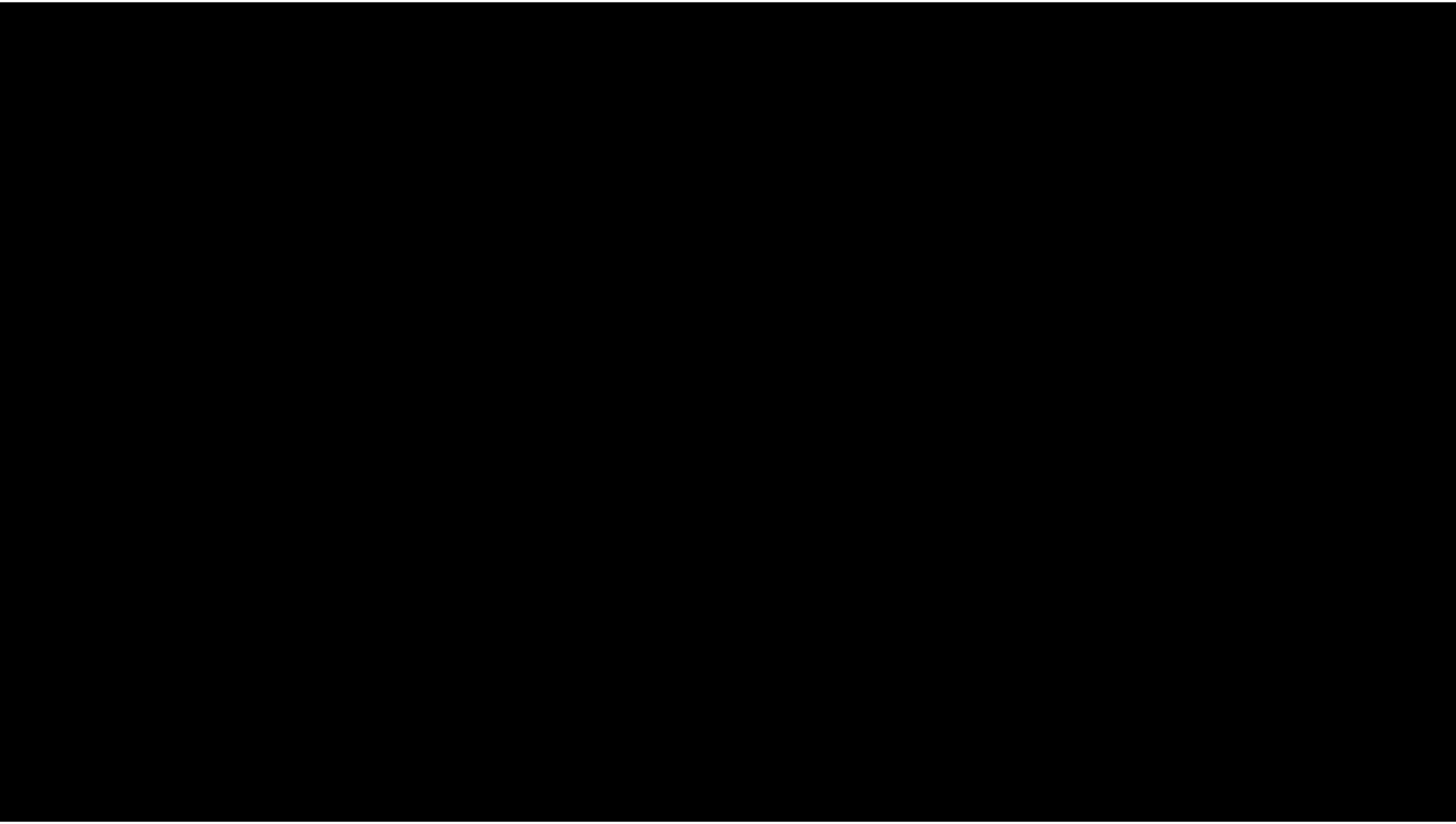


Neurofibrillary Tangles (NFT): aggregates of hyper-phosphorylated tau protein (changes in cytoskeleton)

B-Amyloid Plaques: Peptides of 36-43 amino acids that aggregate as plaques (incorrectly folded proteins)

Case Study on Memory: Jill Price

Case Study on Memory: Jill Price



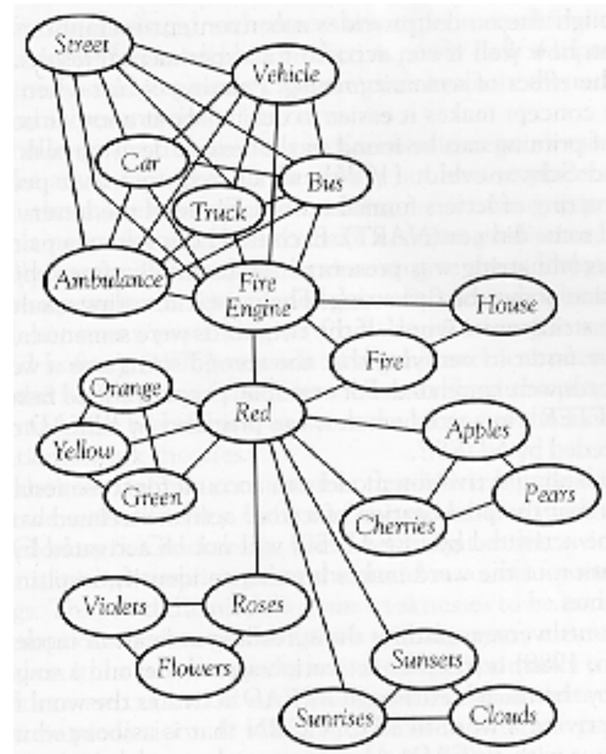
Jill Price

Hyperthymesia

- Condition of possessing an extremely detailed autobiographical memory
- Studied by three UCI neurobiologists: Elizabeth Parker, Larry Cahill and James McGaugh
- Attributed it to two defining characteristics:
  - Spending an excessive amount of time thinking about one's past
  - Displaying an extraordinary ability to recall specific events from one's past
- Causes:

  Psychological: information coded is semantic, so semantic clues are used in retrieval
    - Once memory is retrieved, it is episodic and follows a spreading activation model

  Biological: temporal lobe and caudate nucleus were both enlarged – can be attributed to atypical neural development



Brain Regions for Memory

Case studies have taught us what brain regions are involved in encoding memories:

Memory	**Brain Regions Involved**
Recalling pictures	Right prefrontal cortex and parahippocampal cortex of both hemispheres
Recalling words	Left prefrontal cortex and left parahippocampal cortex are activated
Consolidation of Memory	Hippocampus
Storage of Long-Term Memory	Cerebral Cortex (near where memory was first processed and held in short-term memory)

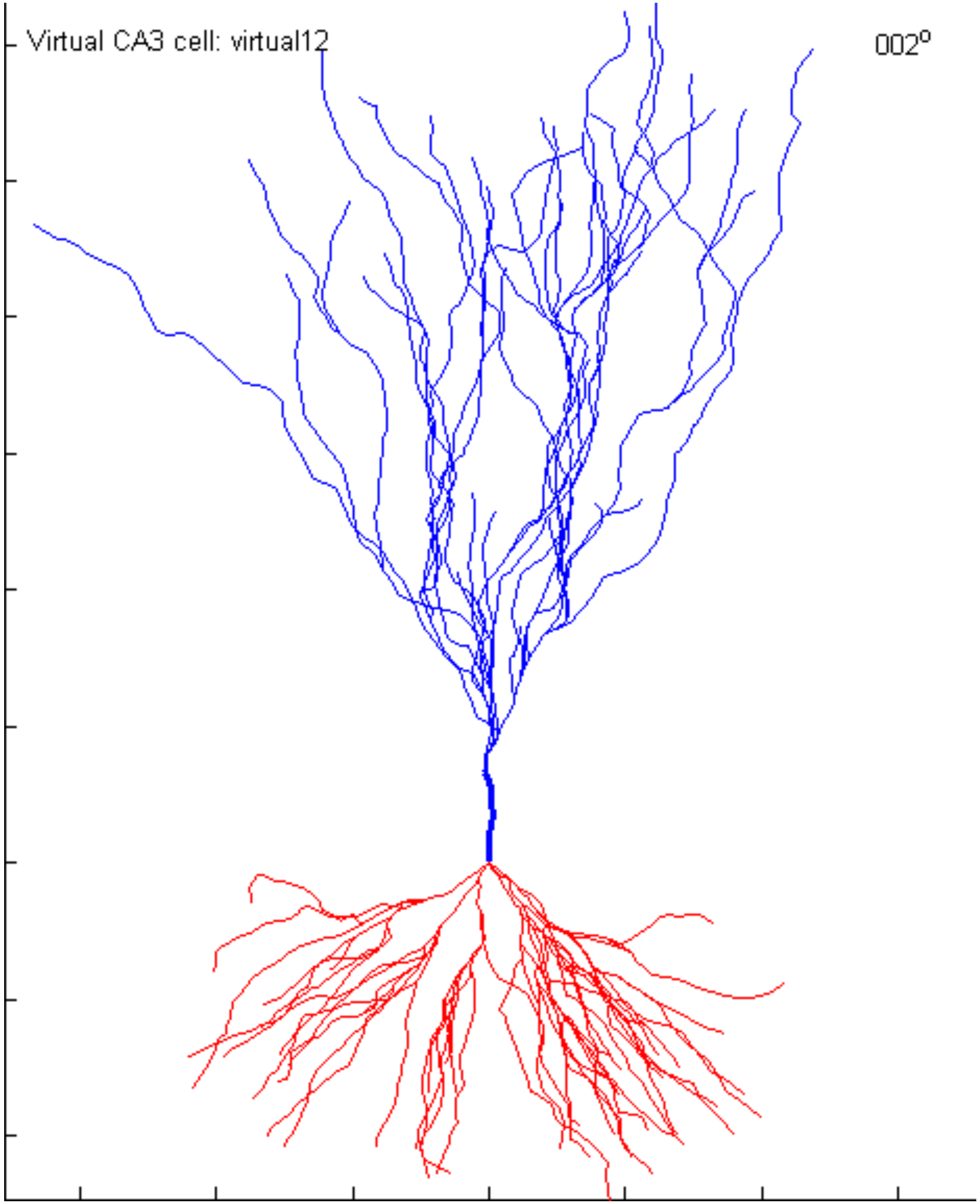
Summary:

1. Pre-Frontal Cortex
2. Hippocampus
3. Cerebral Cortex
4. Amygdala (Memory Modulation and part of **Temporal Lobe**)

Memories are made of this

"He was still too young to know that the heart's memory eliminates the bad and magnifies the good, and that thanks to this artifice we manage to endure the burden of the past."
Gabriel Garcia Marquez

Pyramidal Neurons: found in the cerebral cortex, the hippocampus, and the amygdala
Pyramidal neurons are the primary excitation units of the mammalian pre-frontal cortex and the cortico-spinal tract.



What creates a memory in the brain?

Many biophysical variables are involved, including:

- *Neural voltage*
- *Synaptic activation, strength, and connectivity*
    - *How does a chemical synapse work?*
- *Pre-synaptic vesicles*
    - *What variable in regards to action potentials controls the amount of neurotransmitter release on the pre-synaptic neuron?*
- *Phosphorylation levels*
    - *What does a phosphate group look like?*
- *mRNA concentrations*
- *Transcriptional regulation*
- *Neuro-modulatary signals*
    - *What part of the brain is involved in modulation of memory?*
- *Glia*

Man v. Machine

How can we compare the forms of memory in humans and computers?

Structures of Memory:

- **Random Access Memory (RAM) and the Hippocampus**
- **The Hard Drive and the Cerebral Cortex**
- **Central Processing Unit (CPU) Cache and Neuronal Network Attractors**

Features of Memory:

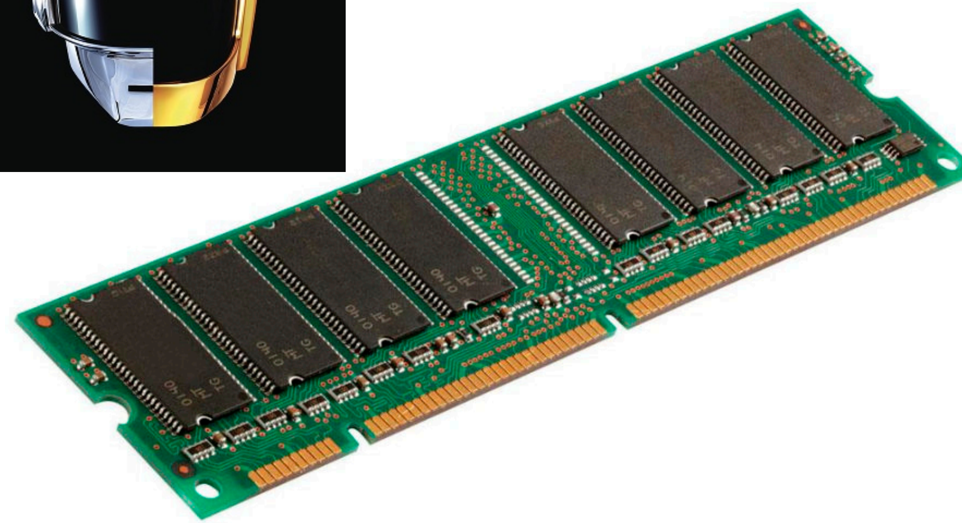
- **Protected Memory and Explicit Memory**
- **Memory Swapping and Writing**

Random Access Memory (RAM) and the Hippocampus

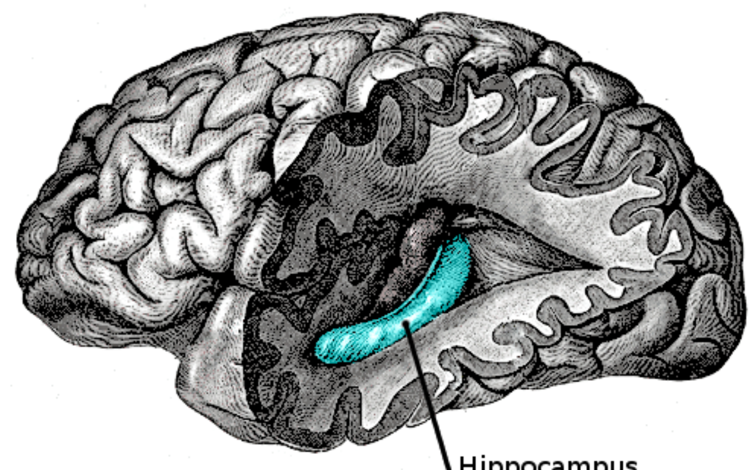
Random Access Memory: place in a computing device where the OS, application programs and data current in use are kept so they can be reached by the device's processor

Data remains in the RAM as long as the computer is running*. *If you turn off a computer, the RAM is gone.

RAM provides a quick access to a memory in any location.



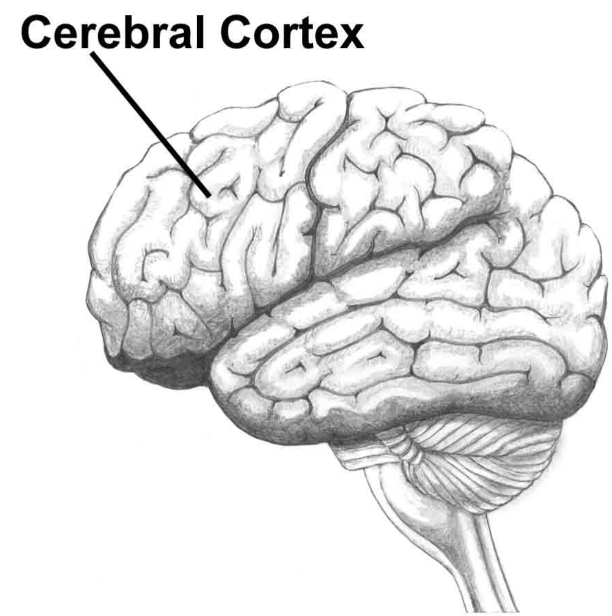
Humans have a form of RAM: **Short-Term Memory** (used to recall immediate actions). Both share **structural homogeneity.**



The Hard Drive and the Cerebral Cortex

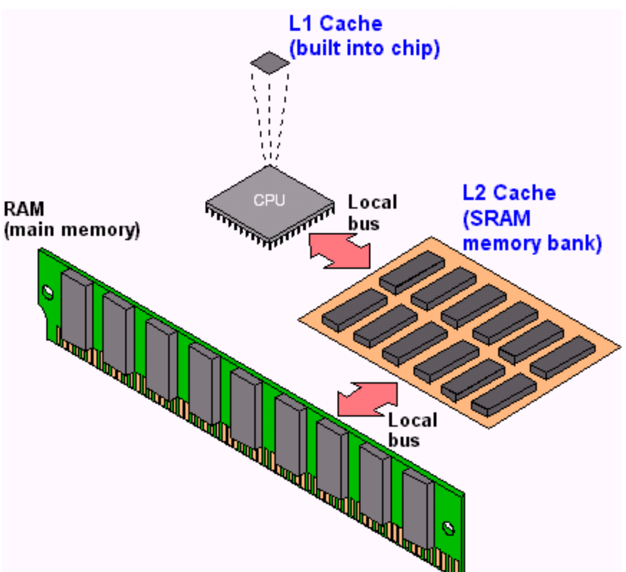
In addition to RAM, a complimentary form of storage for long-term memory in computers is **the Hard Drive (HD).** A hard drive has lower bandwidth (100 Mbytes/s) but can store much more (500 Gbytes). **This is where all of your data and programs are located.**

Bandwidth:
[1](Computer) Range of frequencies used for transmitting a signal
[2](Human) Energy or mental capacity required to deal with a situation



Cerebral cortex is the presumed site of human long-term memory. Recollecting old memories varies in timescale for both the cortex and HD (read/write speed depends on where memory is stored).

Central Processing Unit (CPU) Cache and Neuronal Network Attractors

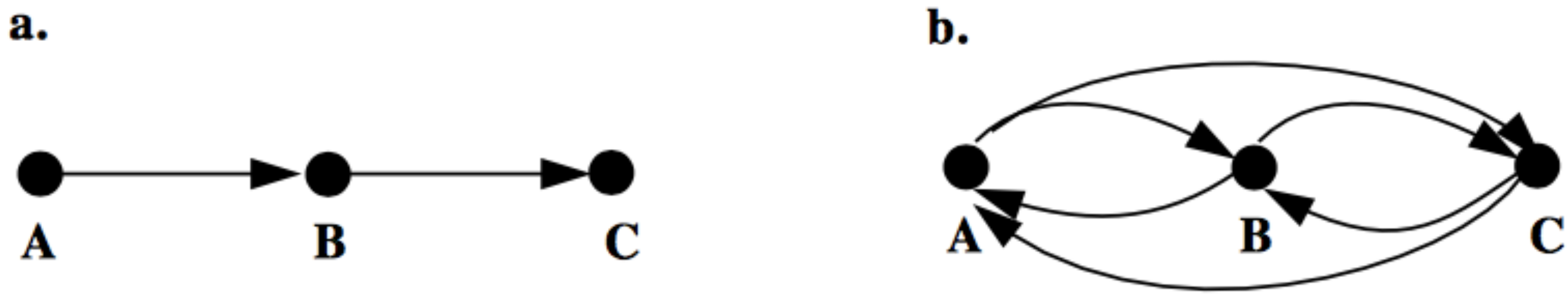


CPU Cache: a smaller, faster memory which stores copies of data from frequently used main memory locations

How Caching Works (Transfer of RAM)
CPU caches are small pools of memory that store information the CPU is most likely to need next. **L1 Cache** is built into microprocessor chip itself and performs **cache hits.** **A cache miss,** however, means the CPU must find data elsewhere. The **L2 Cache** is used for this (It is slower but larger than L1 Cache).

A CPU Cache is the main difference between a computer and a human. Our brains do not have multiple levels of storage working at distinct speeds. Memory storage is distributed all over cortex (a giant cache).

Introduction to Neural Networks



A. Feed-forward network: Information flows directly from one layer of neurons to the next without feedback

In the brain, the existence of such network connectivity is rare (an example of it is between the retina and the LGN)

B. Recurrent network: Information is connected with feedback

In the brain, these networks are ubiquitous.

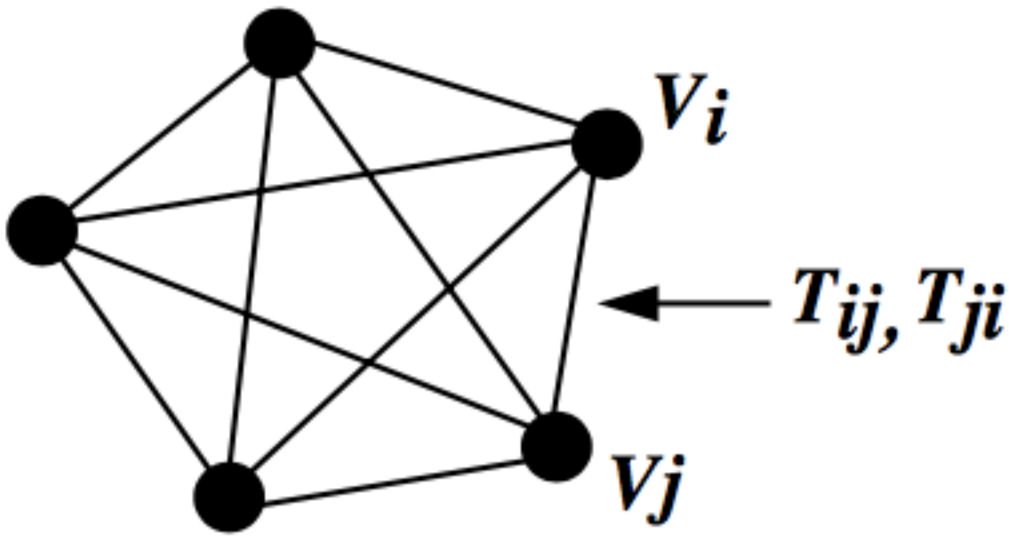
Role of Feedback in Neural Networks

What difference does feedback make in a neural network?
Feedback is a way to create a memory from memory-less components. More specifically, we create a persistent state through non-persistent parts with **feedback.**

"Reverberating Activity Loops" *were proposed by Rafael Lorente de No and Donald Hebb. The idea is that excitation among units in a circuit* ***enables*** *excitation to persist* ***beyond the duration of exciting stimulus.***

Short-term memory *uses changes in activity*
Long-term memory *uses changes in synaptic connections (**Long-term potentiation (LTP)** is used for memory acquisition)*

Modeling Memory: Attractor Neural Networks



V_i*: *denotes activity state of* neuron i *in the network

***T_{ij}*: *denotes strength of the connection from* neuron j *to* neuron i**

Attractor Neural Network: recurrent neural network with symmetric connections that act in two ways

$$V_i \rightarrow 1 \quad \textit{if} \quad \sum_{j \neq i} T_{ij} V_j > 0$$

$$V_i \rightarrow -1 \quad \textit{if} \quad \sum_{j \neq i} T_{ij} V_j < 0$$

Each neuron has two states, **+1 and -1**, and changes its state, V_i, according to rule on left

Features of Memory: Protected Memory and Explicit Memory

Explicit Memory: Memory used consciously
Implicit Memory: Memory not necessarily used consciously
(Example: We know how to walk but we don't have to think to walk)
This separation of between explicit and implicit memory is done at neuronal level and happens in computers.

Memory Protection: way to control memory access rights on a computer that is built-into an OS
When you write a program that needs some memory for its behavior, the OS allocates some space into it. Why? To prevent the program from accessing any other memory and rewriting it

Distinguishing our memories is a way to protect them.

Features of Memory: Memory Swapping and Writing

What is memory swapping?

When a program asks for memory then what is available in the RAM, the OS uses the hard drive (HD) to allocate space needed. This is known as **memory swapping.**

Since hard drives are slower than RAM, this leads to a great loss in performance.

This is why MATLAB programs can slow down. Your program cannot tell if its data is being stored on the hard drive or the RAM. In other words, memory swapping is not transparent.

Do humans do memory swapping?

No, the human brain was well-designed to work within its memory limits. However, we compensate for our memory by taking notes *(we swap data to a piece of paper using a pen).*

Memory Storage System

Based on what we see in computers and humans, we can define features we desire in a **memory storage system:**

1. States that can persist over time
2. Adequate storage capacity (can hold a great number of states)
3. Different inputs to be remembered should trigger ***persistence*** of different memory states
4. Memory states are robust to noise
   What are examples of noise in the brain?
   Signals can fail and neurons can spike stochastically.
5. Memories are retrievable given appropriate cues

Which feature would differ between short-term memory and long-term memory?

Next Time

Introduction to Machine Learning and Neural Networks

Javascript Tutorial

Paul Sajda Lab Tour: