Chapter 14

Lecture 10

Learning and memory

- During the life span of an organism the brain of an organism is changing.
- Many experiences can contribute to changes in the brain, including:
  - Changes during development
  - Culture
  - Preferences (food/drinks, music, art, etc.)
  - Coping with neurological injury or disease
  - Coping with neurodegeneration (e.g. Alzheimer's disease)

These changes enable the organism to modify behavior, adapt to the environment, learn and remember.

- The underlying characteristic common to all those experiences is the ability to **learn**.

- **Neuroplasticity:** the nervous system's potential for physical or chemical change that enhances its adaptability to environmental change and its ability to compensate for injury

Lecture 10 outline

- Connecting learning and memory
  - Learning and Memory in the Laboratory
  - Two categories of memory
  - Personal memories
- Dissociating memory circuits
  - Explicit memory
  - Implicit memory
- Neural systems underlying memories
  - explicit memories
  - implicit memories
  - emotional memories
- Structural basis of brain plasticity
  - Synaptic change
  - Enriched experience
  - Sensory or motor training
  - Hormones, Trophic factor and drugs
  - Principles of brain plasticity
- Recovery from brain injury
  - Three legged cat
  - New circuit
  - Lost-neuron-replacement

Connecting Learning and Memory

- **Learning:** a change in an organism's behavior as a result of experience
- **Memory:** the ability to recall or recognize previous experience
    - **Memory Trace: a** mental representation of a previous experience
        - Presumed to correspond to some physical change in the brain

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

- Generally, we gather our information regarding learning and memory formation from behavioral changes and not by observing the brain directly.

- Problem: it is hard to make a laboratory animal (and sometime even people) to reveal what they remember.
- Solution: Thus, in the study of learning and memory we will use array of behavioral measures that are specifically designed to enable the subject to show their knowledge.

    - Different species "communicate" to as differently. Thus, the tests are specie-specific, for example:
- rats/mice- mazes or swimming pools.
- Monkeys- search hidden food, T.V. monitors,
- Humans- paper-and-pencil tests.

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

- **Pavlovian Conditioning**: learning procedure whereby a neutral stimulus (such as a tone) comes to elicit a response(such as salivation) because of its repeated pairing with some event (such as the delivery of food); also called classical conditioning or respondent conditioning.

Examples for pavlovian conditioning in research:

- **Eye-Blink Conditioning:** Commonly used experimental technique in which subjects learn to pair a formerly neutral stimulus to a defensive eye-blinking response

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

Examples for Pavlovian Conditioning in research:

1. Eye-Blink Conditioning: Commonly used experimental technique in which subjects learn to pair a formerly neutral stimulus to a defensive eye-blinking response.

In Eye-blink conditioning, a tone (or other neutral stimulus) is associated with painless puff of air to the participant's eye.

The tone is the conditioned stimulus (CS).
The air puff is the unconditioned stimulus (UCS).
Blinking in response to puff of air is unconditioned response (UCR)
Blinking in response to tone is conditioned response (CR)
The subject communicate to us that he learned that the tone predict a puff of air by blinking wher he hear a tone (CR).

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

Pavlovian Conditioning

- **Conditioned Stimulus (CS):** in Pavlovian conditioning, an originally neutral stimulus that, after association with an unconditioned stimulus (UCS), triggers a conditioned response
- **Unconditioned Stimulus (UCS):** a stimulus that unconditionally -- naturally and automatically -- triggers a response

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

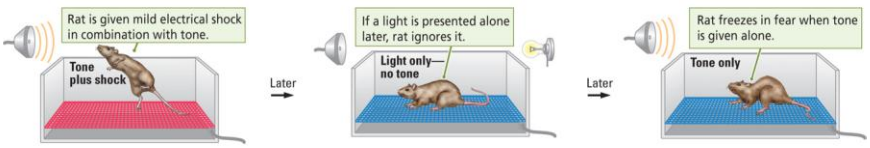
- **Unconditioned Response (UCR):** In classical conditioning, the unlearned, naturally occurring response to the unconditioned stimulus, such as salivation when food is in the mouth
- **Conditioned Response (CR):** In Pavlovian conditioning, the learned response to a formerly neutral conditioned stimulus (CS)

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

2. Fear Conditioning (example for pavlovian conditioning**):** learned association, a conditioned emotional response, between a neutral stimulus and a harmful event such as a shock

Tone: CS

Shock: UCS



Conclusion: The rat has learned an association between the tone and the shock, which produces a fear response. Circuits that include the amygdala take part in this learning process.

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

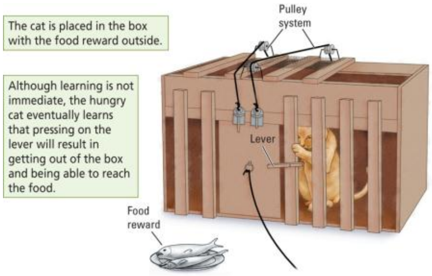
- The link between various motor responses and environmental events (i.e. eye-blink conditioning) is mediated by circuits in the cerebellum.
- Fear conditioning is mediated by the amygdala since the conditioned response to fear conditioning is emotional.

Connecting Learning and Memory
Studying Learning and Memory in the Laboratory

- **Instrumental Conditioning:** Learning procedure in which the consequences (such as obtaining a reward) of a particular behavior (such as pressing a bar) increase or decrease the probability of the behavior occurring again; also called operant conditioning

  - The variety of instrumental associations is huge. Thus, it is not surprising that this type of learning is not localized to specific circuits in the brain.

  - Thorndike's Puzzle Box: A hungry cat will eventually learn that pressing a lever will open the door so that it can reach food
    - Skinner's experiments with the pigeon are also considered an instrumental conditioning.



Connecting Learning and Memory
Two form of memory

- **Explicit memory:** Conscious, intentional recollection of previous experiences and information
  - Information about a specific event at a specific time & place
  - Example: Remembering details about a specific driving lesson

- **Implicit memory:** Unconscious, nonintentional recollection of previous experiences
  - Example: Improved driving ability, as a result of taking a specific driving lesson
    - Classical conditioning (Pavlov) and operant conditioning (Skinner) are examples of implicit memory formation

Implicit memories: Example of verbal learning

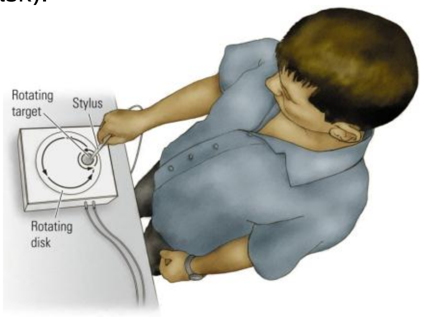
- Ask two groups of people to read one of two lists of words
  - List 1: spring, winter, car, boat
  - List 2: trip, tumble, run, sun
- Next, ask all participants to define a series of words, including the word *fall*
  - Participants who read list 1 typically define *fall* as the season between summer and winter
  - Participants who read list 2 typically define *fall* as the act of falling over
- Learning has clearly taken place, as the two groups respond differently based on past experience
  - Learning was not conscious, and participants were not aware that their responses would have been affected
    - Example of implicit memory formation

Implicit memories: Example of verbal learning

- It is easy to think about explicit memories – if you are recalling details of any specific experience then that is explicit memory
- Implicit memory are harder to conceptualize, as it is unconscious.

Implicit memories: Example of motor learning

- Pursuit-rotor task:
  - Small disc moves in a circular pattern on a moving turntable. Participant has to hold a pen in contact with the moving disc
    - Performance improves with practice, even in amnesiacs with deficits in explicit memory formation (i.e. the amnesiacs performance will improve even thogh they will not recall previous experience with the task).



Connecting Learning and Memory

- **Amnesia:** partial or total loss of memory
  - People with amnesia can perform normally on tests of implicit memory but not explicit memory
- **Learning Set:** an understanding of how a problem can be solved with a rule that can be applied in many different situations

Connecting Learning and Memory
Two form of memory

- **Declarative Memory:** Ability to recount what one knows, to detail the time, place, and circumstances of events; often lost in amnesia
- **Procedural Memory:** Ability to recall a movement sequence or how to perform some act or behavior

From a practical point of view, there is little difference between the implicit-explicit distinction and the procedural-declarative distinction

Connecting Learning and Memory

Encoding Memories

- Implicit information is processed in a "bottom-up" or data-driven manner
  - The implicit information is transferred from the sensory receptors to various subcortical and cortical brain regions.
  - Example: visual information regarding an object is going from the visual receptors (i.e. "bottom"), to the thalamus, the occipital cortex, and then through the ventral stream to the temporal lobe (i.e. "up") where it is recognized.

Connecting Learning and Memory

Encoding Memories

- Explicit information is processed in a "top-down" or conceptually-driven manner
  - The subject reorganizes the information before it is encoded.
  - Example: if you look for your keys, you will ignore other objects. Circuits in the temporal lobe (i.e. "top") form an image that influence the way incoming visual information (i.e. "down") is processed which will affect the information recall later.

Connecting Learning and Memory

Encoding Memories

- In implicit (unconscious) tasks, the person has a passive role; whereas in explicit (conscious) tasks, the person has an active role

- **Priming:** Using a stimulus to sensitize the nervous system to a later presentation of the same or a similar stimulus; often used to measure implicit memory

  Example for priming:

Example of priming

Example for implicit memory and priming:

- Give group of people to read the following list of words:
  - Sweet, chocolate, shoe, table, candy, horse, car, cake, coffee, wall, book, cookie, hat.
- After few minutes, read to the participants another list of words that include some of the words from the former list and some new words.
- Ask the participants to identify which of the words were also present in the first list and to indicate how certain they are in their answer.
  - One of the words on the second list was sugar. The majority of the participants indicate that sugar certainly appeared in the first list.
  - Indeed, in the first list we had many "sweet" words but sugar was not one of them..

Example of priming

Example for explicit memory and priming:

- Give group of people to watch a video clip of an accident in which a car collides with another car stopped in an intersection.
  - Ask one group to estimate how fast the car was moving when it **smashed** into the other car.
  - Ask the other group to estimate how fast the car was moving when it **bumped** into the other car.
- The results indicated that the instructions (smashed vs. bumped) biased the way the information was processed.
  - the speed estimation among participants that were instructed to estimated the speed of the car that smashed into the other car were higher from the speed estimated by particpants that estimated the speed of the car that bumped
  - Interestingly, both groups we certain that their speed estimation was accurate!!

Connecting Learning and Memory

Processing Memories

Overall we can categorize memories as explicit or implicit. However, the brain does not process all the implicit or all the explicit memories in the same way.

We can further categorize memories. For instance, by type of sensory information or by categorizing memories into:

- Short-term Memory (few minutes in duration)
  - Involves the frontal lobes
- Long-term Memory (indefinite duration)
  - Involves the temporal lobe
- But there is no single place in the nervous system that can be identified as the location of memory or learning

Connecting Learning and Memory

Storing Memories

- Information from each sensory modality (e.g., vision, audition) is processed and stored in different neural areas
  - Example: since the temporal lobe has specialized regions for processing shapes, colors, and other visual characteristic of an object, we can predict that those specialized regions also store memories related to a specific characteristic of an object.

  Indeed, Martin and colleagues (1995) have shown that :

  - Recall of colors activated a region in the ventral temporal lobe (just anterior to the region that process colors)
  - Recall of action words activated a region in the middle temporal gyrus (just anterior to the area that controls motion perception)

Connecting Learning and Memory
What Is Special about Personal Memories?

- **Episodic Memory:** Autobiographical memory for events linked to specific place and time contexts
  - The episodic memory also contain the presence and role we had in the specific event.
  - The episodic memory give us the concept of time as well as sense of personal role in constantly changing world.

- **Episodic Amnesia** (e.g. patient K. C.)
  - Inability to recall any personally experienced events
  - Associated with frontal lobe injuries or reduced blood flow to the frontal lobes
  - Frontal lobes may allow us to mentally travel through our past

Connecting Learning and Memory
What Is Special about Personal Memories?

K.C. was involved in a motorcycle accident which resulted in a serious traumatic brain injury.

- K.C cognitive ability and short term memory stayed intact
- K.C. know who he is, what schools he attended, when his birthday is etc.
- BUT K.C cannot recall any personally experienced events.
- He cannot recall any event, through out his life, that he personally attended.

  For example, K.C. recall going to school and the knowledge he obtained there but he cannot recall the school dance.

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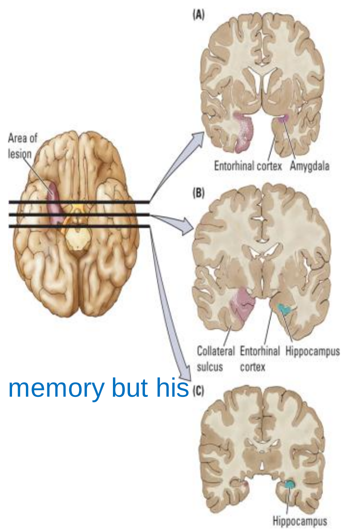
Dissociating Memory Circuits

Patient H.M. had severe epilepsy that could not be controlled by medications.

In 1953, William Scoville performed a bilateral medial-temporal lobe resection on H.M. for relief of epileptic seizures.

The areas removed from H.M.'s brain:

- Hippocampal formation
- Amygdala
- Adjacent cortices in medial temporal lobe



Following the surgery, H.M. had a intact implicit memory but his explicit memory was severely damaged

Dissociating Memory Circuits
Disconnecting Explicit Memory

- Following the surgery, H.M. suffered from a severe amnesia
  - He could not recall anything that had happened after the surgery in 1953 (**no explicit memory**)
- Despite this deficit, H.M. had an above average IQ, he performed well on perceptual tests, and he could still recall events from his childhood
- H.M.'s performance on implicit memory (such as the pursuit-rotor task) tests was left intact
- H.M. could recognize faces, including his own, probably because face recognition involve the parahippocampal gyrus which was partly intact on H.M.'s right side of the brain.

Dissociating Memory Circuits
Disconnecting Explicit Memory

The basal ganglia plays an important role in motor control

Many types of implicit memory involve motor learning (driving, riding bicycle, playing an instruments, etc.)

Thus, implicit memory is (probably) associated with the basal ganglia.

Dissociating Memory Circuits
Disconnecting Explicit Memory

Patient J.K. Developed Parkinson’s disease in his mid 70s and started to have memory problems at 78 years of age

- J.K. had impaired implicit memory with intact explicit memory
    - Probably caused by damage to basal ganglia
  - Impaired ability to perform tasks that he had done all his life
    - Example: could not figure out how to turn off the lights in his own bedroom
  - Could still recall explicit events

- Thus, the circuits responsible for explicit and implicit memories are separate.

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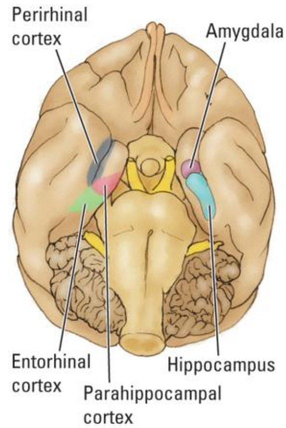
Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

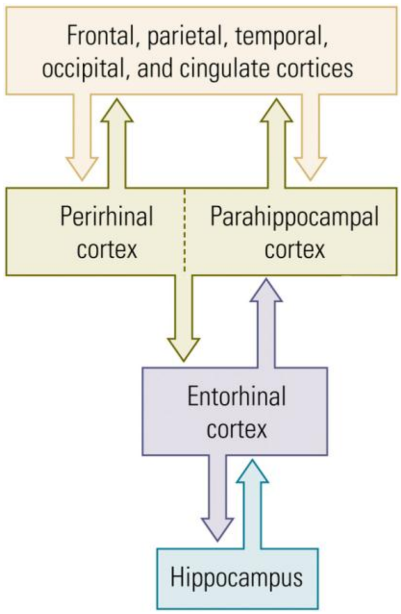
- Prime Structures for Explicit Memory
  - Medial temporal region
    - Hippocampus
    - Amygdala
    - Entorhinal cortex
    - Parahippocampal cortex
    - Perirhinal cortex
  - Frontal cortex



Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

- **Parahippocampal Cortex**
  - Cortex located along the dorsal medial surface of the temporal lobe
  - Receives connections from parietal cortex; believed to be involved in visuospatial processing
- **Perirhinal Cortex**
  - Cortex lying next to the rhinal fissure on the base of the brain
  - Receives connections from the visual regions of the ventral stream; believed to be involved in visual object memory
- **Entorhinal Cortex**
  - Both the parahippocampal and perirhinal cortices project to the entorhinal cortex. Thus, it is likely that the entorhinal cortex participate in a more integrative types of memory.
  - The entorhinal cortex show extensive cell death in Alzheimer's disease, a dementia characterized by severe deficits in explicit memory.

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories



- Perirhinal cortex implicated in visual memory of objects
  - What they look like
- Parahippocampal cortex implicated in visuospatial memory of objects
  - Where they are located
- Entorhinal cortex integrates both inputs
  - Puts the *what* and the *where* together

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

The Hippocampus is strongly associated with visuospatial memory

- **Visuospatial Memory**: Using visual information to identify an object's location in space
  - Monkeys with hippocampal lesions have difficulties with visuospatial learning (i.e. learning the location of objects)

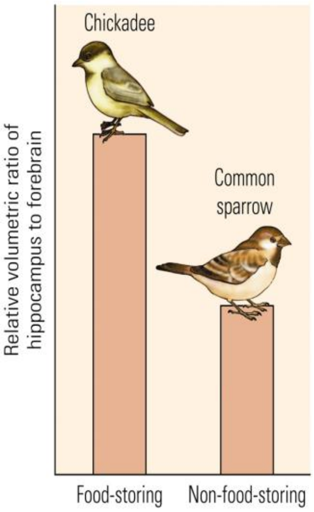
Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

The Hippocampus and Spatial Memory

Do animals with good spatial memory has bigger hippocampus?

- The hippocampal formation in food-storing birds and rodents is larger than the hippocampal formation in birds and rodents that do not store food.

- The posterior region of the hippocampus of Taxi drivers in London, UK is significantly larger than normal.



Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

Reciprocal Connections for Explicit Memory

- The temporal pathways of explicit memory are reciprocal: the neocortex projects to the entorhinal cortex, which projects back to the neocortex

- The benefits of reciprocal memory system:
  - Projections from the entorhinal cortex to the sensory cortical areas keep the sensory experience alive longer than the actual experience
  - The entorhinal cortex keeps the neocortex updated regarding what is being processed, which may help explain how this form of memory is conscious

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

- Indeed, the medial temporal regions play an important role in explicit memory.
- However, other structures are also important in explicit memory.

- Injuries to the frontal lobe does not cause people to be amnestic like HM or JK but they have difficulties with the temporal order of events.
  - Example: if we will show a series of photographs to patients. People like HM will not remember seeing the photograph whereas people with frontal injury will not be able to recall which photograph was shown first.

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

The Frontal Lobe and Short-Term Memory

- All sensory systems send information to the frontal lobes
- This information is not used for direct sensory analysis. Thus, is probably used for other purposes.
- It seems that frontal lobes are involved in many types of short-term memory.
- Example: during tasks in which monkeys must keep information in short-term memory over a delay, certain cells in the prefrontal cortex will fire throughout the delay
  - Animals that have not learned the task show no such cell activity

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

Tracing the Explicit Memory Circuit

- **Korsakoff's Syndrome:** permanent loss of the ability to learn new information (anterograde amnesia) and to retrieve old information (retrograde amnesia)
  - Korsakoff's Syndrome occur due to chronic alcoholism or malnutrition that produces a vitamin B_1 deficiency**.**
  - The B1 deficiency result in:
  - Cells death in the medial part of the diencepahlon (parts of the thalamus and hypothalamus)
  - Atrophy (loss of cells) in the frontal lobes (~80% of the patients)
  - Damage of brain stem structures

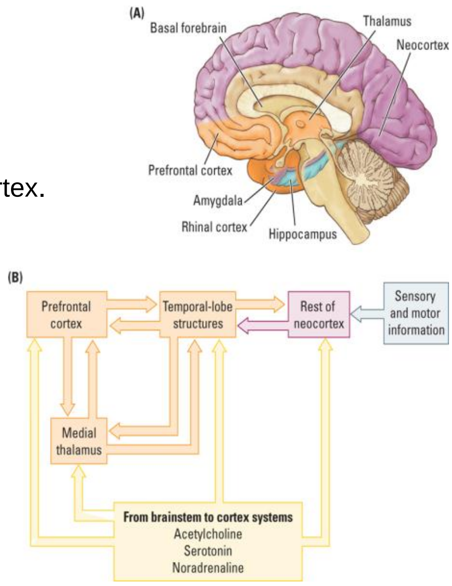
Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

Based on information gathered from patients with brain injury and animal models, Mishkin and colleagues (1982, 2000) proposed neural circuit for explicit memory that involves:

- Temporal Lobe Structures
- Frontal Lobe Structures
- Medial Thalamus
- Basal Forebrain-Activating Systems

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Explicit Memories

- ❑ The sensory regions in the neocortex send projections to the medial temporal regions.
- ❑ The medial temporal regions connect to the medial thalamus and prefrontal cortex.
- ❑ Basal forebrain structures are likely to play a role in maintaining appropriate levels of activity in the forebrain structures so they can process information
- ❑ The temporal lobe structures are hypothesized to be central to the formation of long term **explicit** memories.



Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Implicit Memories

Based on the notion that the basal ganglia is important for implicit memory, Mishkin and colleagues (1982, 1997) also proposed circuit for implicit memory that involve the:

- Basal Ganglia
- Ventral Thalamus
- Substantia Nigra
- Premotor Cortex

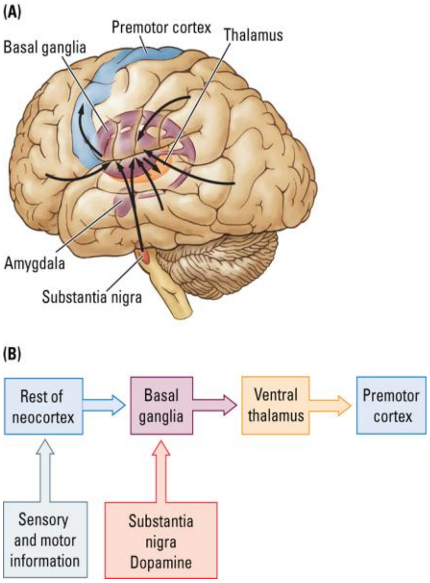
Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Implicit Memories

❑ The basal ganglia receive input from the entire neocortex.

❑ The basal ganglia send projections To the ventral thalamus and then to the premotor cortex.

❑ The basal ganglia also receive vast projections from dopamine-inducing cells in the substantia nigra.

- Dopamine is necessary for the function of neural circuits in the basal ganglia. Thus, it might be involved, indirectly, in the formation of implicit memory.



Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Implicit Memories

- Unconscious Nature of Implicit Memory
  - Mishkin believes that implicit memories are unconscious because the connections between the basal ganglia and cortex are unidirectional
    - Basal ganglia receives information from the cortex, but does not project back to the cortex
    - For memories to be conscious, there must be feedback to the cortex
      - Medial temporal lobe projects back to the cortex, so explicit memories are conscious

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Emotional Memories

- **Emotional Memory:** memory for the affective properties of stimuli or events
  - Could be implicit or explicit (example: you can react with fear to stimuli you identify but you can also fear something you do not seem to have specific memory)
  - Panic disorder: a pathology of emotional memory. People feel highly anxious but can not identify why.
  - Amygdala is critical for emotional memory
    - Damage to amygdala abolishes emotional memory but has little effect on implicit or explicit memory

Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Emotional Memories

- Proposed Circuit for Emotional Memory
  - Amygdala
  - Medial Temporal Cortex
  - Brainstem
  - Hypothalamus
  - Periaquaductal Gray Matter (PAG)
  - Basal Ganglia

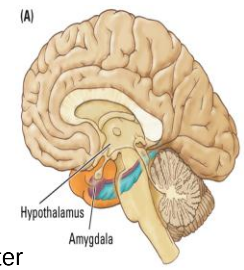
Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Emotional Memories

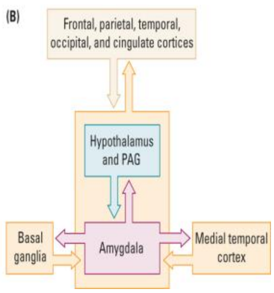
❑ The amygdala has strong connections with the medial temporal cortical structures and the cortex.

❑ The amygdala also send projections to areas that control:

- Autonomic response (e.g. heart rate, blood pressure): brain stem regions
- hormonal system: the hypothalamus
- perception of pain: periaqueductal gray matter

❑ The amygdala connect to the implicit-memory system by its connections with the basal ganglia.





Neural Systems Underlying Explicit and Implicit Memories
Neural Circuit for Emotional Memories

- Emotionally significant experiences (pleasant or unpleasant) tend to be vividly remembered Memory.
- McGaugh suggested that emotionally significant memories must activate hormonal and neural systems to imprint these memories.
- McGaugh further suggested that although many systems are likely to partake in those memories, the basolateral amygdala is essential.

Neural Systems of Explicit and Implicit Memories
summary

The neural basis of different types of learning and memory are associated with specific brain regions and brain circuits:

- Explicit memory is associated with the prefrontal cortex, the medial temporal lobe and regions related to them.
- Implicit memory is associated with the basal ganglia and the neocortex.
- Emotional memory is associated with the amygdala and related regions.

How the neurons in the different circuits change to store memories?

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Structural Basis of Brain Plasticity

- At the neural level, memory is associated with changes that take place at the synapse
  - The synapse is where one neuron influences another neuron
- Two Research Approaches
  1. Synaptic changes in the nervous system of “simple” organisms
     - Example: *Aplysia* *(fairly easy because we know* ***where*** *to look for the synaptic changes)*
  2. Synaptic changes in the mammalian brain (more complex because we need first to identify what are the synaptic changes that correlate with memory in mammals. Second, localize the synaptic changes to specific neural pathways. Third, analyze the nature of the synaptic changes in those pathways.)

Structural Basis of Brain Plasticity

- Now we will focus on the studies that identified synaptic changes correlated with various types of experience.
  - What is the general research strategy
  - What are the gross neural changes correlated with different types of experience.
    - Interestingly, the general synaptic organization of the brain is modified in a similar manner by the various types of experience.

Structural Basis of Brain Plasticity
Measuring Synaptic Change

Generally, experience may change the brain in one of two ways:

1. Modifying Existing Circuits
2. Creating novel circuits

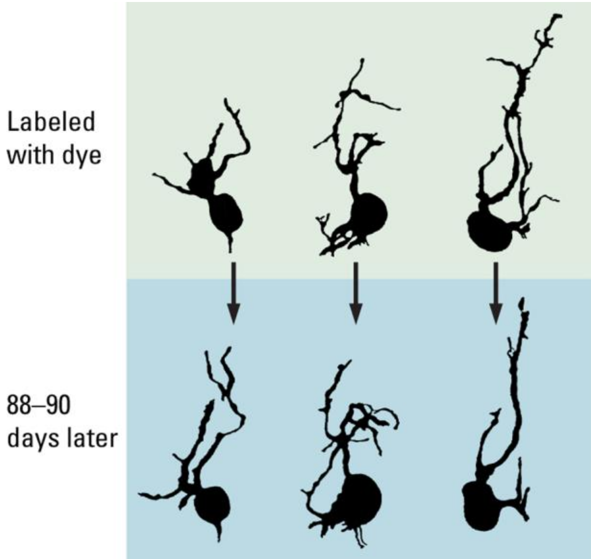
Structural Basis of Brain Plasticity
Measuring Synaptic Change

1. **Modifying Existing Circuits**

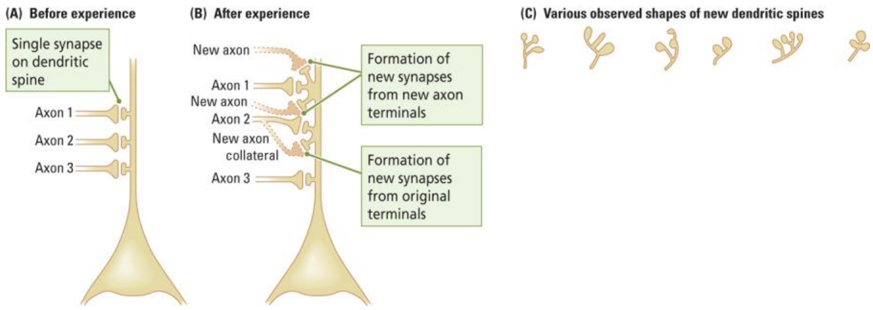
- Neurons change their structure in response to their changing experiences
- Changes in the number of dendrites can be used to infer synaptic changes
  - More dendrites = more connections
  - Dendritic changes=synaptic changes
- New synapses can form between neurons that are already connected or between neurons that were not previously connected

Structural Basis of Brain Plasticity
Measuring Synaptic Change

This figure depict changes in Dendrite over 3 months



Structural Basis of Brain Plasticity
Measuring Synaptic Change



<u>effects of experience:</u>

A. Before experience: each axon forms a synapse with a different dendritic spine.

B. Formation of multiple spine heads. Either the original axon divide and innervate two spine heads or new axon (or axon collaterals) innervate the new spine head.

C. Single dendritic spine can sprout multiple synapses.

Structural Basis of Brain Plasticity
Measuring Synaptic Change

- The growth of new synapses indicates modification of basic circuits that are already in the brain.
  - During development, brain circuits are being formed to allow processing of sensory information and production of movement (behavior).
  - It is likely that those brain circuits are the ones modified by experience to form memories.

Structural Basis of Brain Plasticity
Measuring Synaptic Change

2. **Creating Novel Circuits**

- Predominant view prior to the mid-1990s:
  - The mammalian brain does not make new neurons in adulthood

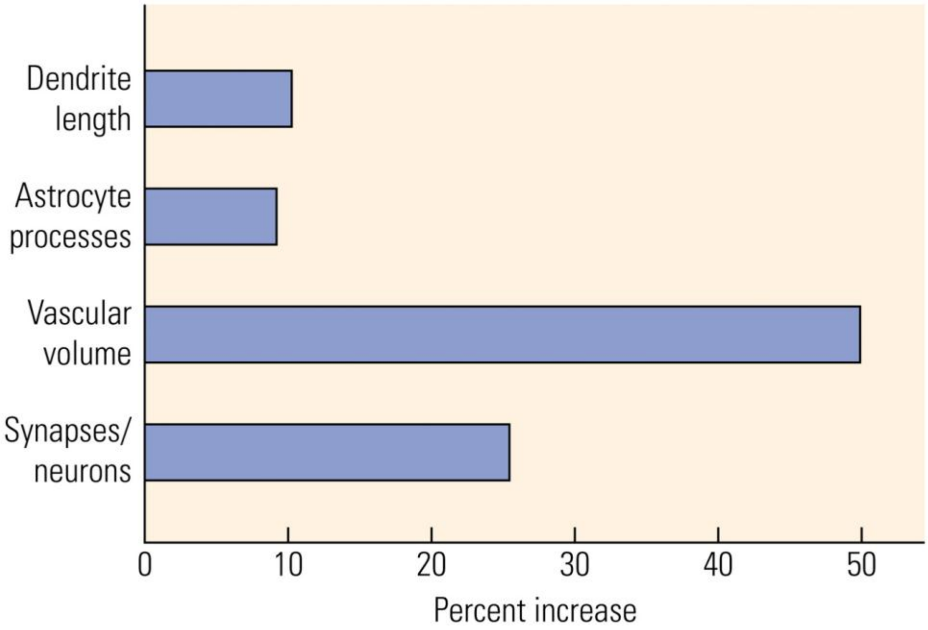
- There is now evidence that neurogenesis can occur in the adult brain, even in mammals
  - There are some indications for neurogenesis in the: olfactory bulb, hippocampal formation, and possibly the neocortex (frontal and temporal lobes)
  - The reason for neurogenesis is still unclear

- Adult neurogenesis may enhance brain plasticity which is especially important in learning and memory.

Structural Basis of Brain Plasticity
Enriched Experience and Plasticity

- Sensory or motor enrichment is a paradigm that induce brain stimulation
- Hebb took lab rats home and let them live in his kitchen. Back in the lab, those "kitchen" rats preformed better in various mazes compared to rats housed in standardized lab cage.s
- Hebb concluded that the environmental enrichment enhanced later learning
- Raising rats in enriched enclosures is associated with:
  - Increased brain weight (~10%)
  - More synapse per neuron
  - More dendrites
  - More astrocytes
  - More blood capillaries
  - More synapses per neuron
  - Increased mitochondrial volume
    - Marker of greater metabolic activity

Consequences of enrichment



Structural Basis of Brain Plasticity
Sensory or Motor Training and Plasticity

Indeed, the studies utilizing the enriched environment model have shown that complex environment can lead to neural changes in vast areas in the brain.

But, can specific experiences produce synaptic changes that are specific to a certain brain region?

- There are two ways to address this question:

1. Manipulating experience experimentally
2. Observing experience-dependent change in the human brain

Structural Basis of Brain Plasticity
Sensory or Motor Training and Plasticity

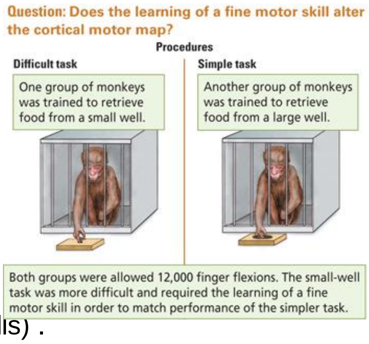
1. Manipulating experience experimentally

- Chang and Greenough (1982)
  - Placed patches over one eye of each rat so that the contralateral hemisphere was deprived of visual input
  - Trained rats on a maze
  - The visual cortex of the "trained hemisphere" (that received input from the eye without the patch) had more extensive dendrites

Structural Basis of Brain Plasticity
Sensory or Motor Training and Plasticity

1. **Manipulating experience experimentally**
Nudo and colleagues (1997): monkeys retrieve food from small or large food wells

- Small wells required skillful movements of one or two fingers, large wells allow use of an entire hand.
- More pronounced changes were observed in the motor cortex of monkeys involved in the more complex task (small wells) .



- **Conclusion:** the functional topography of the motor cortex is shaped not by mere repetition of a known motor skill but by learning new motor skills.

Structural Basis of Brain Plasticity
Sensory or Motor Training and Plasticity

1. Manipulating Experience Experimentally

- Ramachandran (1993)
  - Indirectly measured the cortical maps in individuals with limb amputations
  - When the face was stroked softly with a cotton swab, amputees reported sensations of being touched in the amputated hand
  - Possible explanation: since the amputated limb area in the motor cortex was not in use, the face area in the motor cortex expanded to occupy this unused area. However, the brain circuits sill respond to the activity in this cortex as representing input from the limb.
  - *May explain "phantom limb" pain*

Structural Basis of Brain Plasticity
Sensory or Motor Training and Plasticity

2. Experience-Dependent Changes in the Brain

- Scheibel and colleagues (1993): conducted many studies regarding the relationship between neuronal structure and education.
- In one study they found a relationship between the size of dendritic branching in Wernicke's area and the amount of education.
- In another study the have shown that among females dendritic branching in Wernicke's area is more extensive than in males.
  - This difference was already apparent at the age of 9!

Structural Basis of Brain Plasticity
Sensory or Motor Training and Plasticity

2. Experience-Dependent Changes in the Brain

- From the many experiments Scheibel and colleagues (1993) conducted, they came to two major conclusions
  - There is close relationship between the complexity of dendritic branching and the nature of the computational tasks performed by a brain area
    - Example: Neurons receiving input from fingers versus the chest wall
  - Life experience alters dendritic morphology
    - Example: Career word processors have greater differences between finger and trunk neurons than salespersons

Structural Basis of Brain Plasticity
Sensory or Motor Training and Plasticity

2. Experience-Dependent Changes in the Brain

Thus, we can conclude:

- specific experience can induce localized changes in synaptic organization.
- The synaptic organization probably form the structural basis of memory.

Structural Basis of Brain Plasticity
Plasticity, Hormones, Trophic Factors, & Drugs

Various compounds (such as psychoactive drugs, neurotrophic factors and hormones) can modify the brain.

Structural Basis of Brain Plasticity
Plasticity, Hormones, Trophic Factors, & Drugs

Hormones and Plasticity

Hormone levels can determine the structure of the brain and can elicit certain behaviors.

It was once believed that hormones can affect brain structure only during development.

Today we know that hormones can dramatically affect brain structure also In adulthood.

Structural Basis of Brain Plasticity
Plasticity, Hormones, Trophic Factors, & Drugs

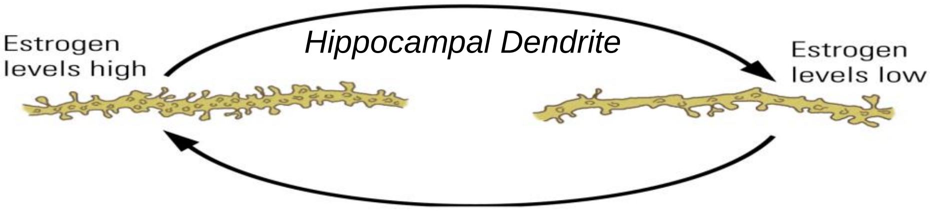
Hormones and Plasticity

- Sex-differences in the structure of cortical neurons depend on sex (gonadal) hormones.
- The gonadal hormones continue to affect the cell structure as well as behavior in adulthood.
- Women's performance in different cognitive tasks vary as their estrogen levels fluctuate across the menstrual cycle.
- Changes in estrogen also change the structure of neurons and astrocytes in the neocortex and the hippocampus.
- Theses changes are probably account to the observed behavioral fluctuation across the cycle.

Structural Basis of Brain Plasticity
Plasticity, Hormones, Trophic Factors, & Drugs

Hormones and Plasticity

- High levels of estrogen
  - More dendritic spines in the hippocampus
- Low levels of estrogen
  - More dendritic spines in neocortex but fewer dendritic spines in the hippocampus (might be related to memory decline in middle-aged females?)
- Low levels of testosterone
  - More dendritic spines in neocortex (related to decrease in spatial ability in aging males?)



Structural Basis of Brain Plasticity
Plasticity, Hormones, Trophic Factors, & Drugs

Hormones and Plasticity

- Glucocorticoids
  - Released from the adrenal cortex in times of stress
  - Assist in the metabolism of proteins and carbohydrates and the control of sugar levels in the blood and cells
  - Steady levels of glucocorticoids that are seen with prolonged stress may be neurotoxic
    - Stress can kill hippocampal cells
    - Can affect behavior. Especially behaviors related to spatial memory.

Structural Basis of Brain Plasticity
Plasticity, Hormones, Trophic Factors, & Drugs

Neurotrophic Factors and Plasticity

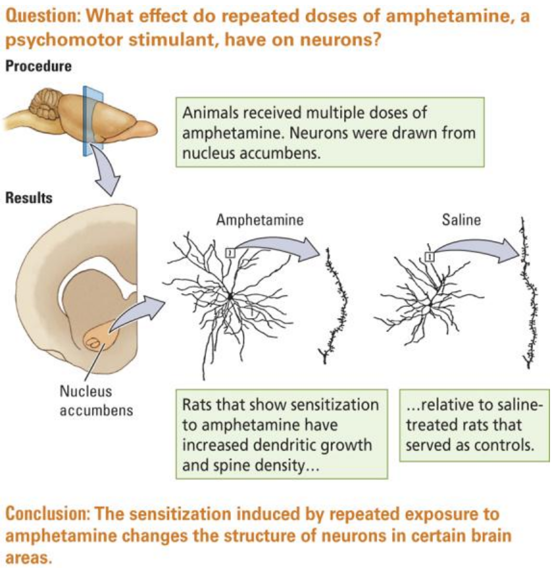
- **Neurotrophic factor:** chemical compounds that signal stem cells to develop into neurons or glia. It also involved with the reorganization of neural circuits.
- **Nerve Growth Factor:** Neurotrophic factor that stimulates neurons to grow dendrites and synapses and, in some cases, promotes the survival of neurons
- **Brain-Derived Neurotrophic Factor (BDNF)**
  - May enhance plastic changes, such as the growth of dendrites and synapses
  - Increased levels when animals learn to solve problems

Structural Basis of Brain Plasticity
Plasticity, Hormones, Trophic Factors, & Drugs

Psychoactive Drugs and Plasticity

Chronic abuse of psychoactive rugs may change the brain

- Drug-Induced Behavioral Sensitization: escalating behavioral response to the repeated administration of a psychomotor stimulant, such as amphetamine, cocaine, or nicotine; also called behavioral sensitization
  - Sensitization is associated with an increased number of receptors, synapses, and dendrites
  - These changes were localized to regions (e.g., prefrontal cortex, nucleus accumbens) that receive a large dopamine projection
  - Drug-Induced Behavioral Sensitization can be viewed as a memory for a specific drug



Structural Basis of Brain Plasticity

Some Guiding Principles of Brain Plasticity

1. Behavioral Change Reflects Change in the Brain

- Throughout life our brain change (development, memory, learning, drugs etc.).
- The changes in the brain affect our behavior.

Structural Basis of Brain Plasticity
Some Guiding Principles of Brain Plasticity

2. All Nervous Systems Are Plastic in the Same General Way.

Even the simplest animals (C. elegans, aplysia) demonstrate learning ability that correlates with neural plasticity.

Structural Basis of Brain Plasticity
Some Guiding Principles of Brain Plasticity

3. Plastic Changes Are Age Specific

At different ages, the brain respond differently to the same experience (especially during development).

Structural Basis of Brain Plasticity
Some Guiding Principles of Brain Plasticity

4. Prenatal Events Can Influence Brain Plasticity Throughout Life

For example: prenatal exposure to drugs may alter gene expression and long lasting effects on brain organization.

Structural Basis of Brain Plasticity
Some Guiding Principles of Brain Plasticity

5. Plastic Changes Are Brain-Region Dependent

Many experience-dependent modifications in the brain are region specific

Example: amphetamines increase spine density in the dorsolateral region of the prefrontal cortex whereas the spine density in the orbital regions are decreased

Structural Basis of Brain Plasticity
Some Guiding Principles of Brain Plasticity

6. Experience-Dependent Changes Interact

Throughout the life span the individual will experience numerous experiences which may influence each other.

Example: enriched environment induce profound organizational changes which can be blocked by prior exposure to psychoactive drugs

Structural Basis of Brain Plasticity
Some Guiding Principles of Brain Plasticity

7. Plastic Events Are Not Always A Good Thing

Plastic changes can also hinder behavior

Example: Drug induced damage to the prefrontal cortex may lead to poor judgment

Lecture 10 outline

- Connecting learning and memory
  - Learning and Memory in the Laboratory
  - Two categories of memory
  - Personal memories
- Dissociating memory circuits
  - Explicit memory
  - Implicit memory
- Neural systems underlying memories
  - explicit memories
  - implicit memories
  - emotional memories
- Structural basis of brain plasticity
  - Synaptic change
  - Enriched experience
  - Sensory or motor training
  - Hormones, Trophic factor and drugs
  - Principles of brain plasticity
- Recovery from brain injury
  - Three legged cat
  - New circuit
  - Lost-neuron-replacement

Recovery from Brain Injury

- **Traumatic brain injury (TBI):** damage to the brain that results from a blow to the head
- Donna suffered a **traumatic brain injury (TBI)**
  - Although she did show some recovery, her recovery was not complete: there were still things that she could not do
- **Three possible ways to recover from brain injury**
  1) Learn new ways to solve problems
  2) Reorganize the brain to do more with less
  3) Generate new neurons to produce new circuits

Recovery from Brain Injury
"Three-Legged Cat Solution"

- When a cat loses a leg, it is usually able to compensate, not by growing a new leg, but rather, by learning how to walk with only three legs
- The same ability to compensate is also present in humans
  - If someone loses a certain ability, such as being able to write with their right hand, they may be able to compensate by learning how to write with their left hand
  - It is likely that this compensation involve a change in the brain

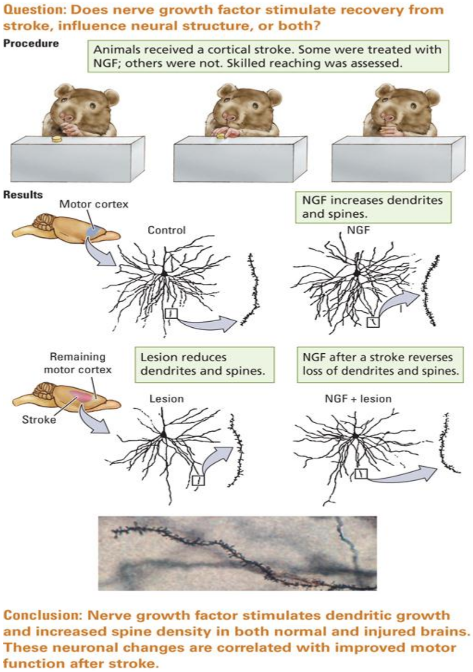
Recovery from Brain Injury
New-Circuit Solution

- In response to injury, the brain can form new connections and "do more with less"
- The amount of recovery is increased significantly if the person also engages in some form of intervention
  - Behavioral Therapy
    - Examples: Speech or physiotherapy which increase brain activity which promote neural change
  - Pharmacological Therapy
    - The patient will be given drugs that facilitate brain activity
    - Examples: Nerve growth factor, amphetamine

Giving NGF to an animal that had a damage to the motor cortex (due to stroke) will improve motor function.

The behavioral improvement is correlated with dramatic increase in dendritic branching and spine density in the motor cortex that was not damaged.

However, the motor skills will be improved but not recovered since some brain tissues are missing.



Recovery from Brain Injury
Lost-Neuron-Replacement Solution

A. Fetal Tissue Implantation

- To date there is only limited success in using fetal tissue implantation
- fetal tissue implantation is more suited for situations where only a small number of cells are needed
  - Example: Dopamine-producing cells in the Substantia Nigra for Parkinson's disease patients
  - The Parkinson's was not reversed but in some patients there was some functional gain.

Recovery from Brain Injury
Lost-Neuron-Replacement Solution

B. Replace Lost Cells

- The brain can make neurons in adulthood (“adult stem cells”), if these cells will migrate to the damaged area it can facilitate some form of recovery.
- Researchers have shown that infusing Neurotrophic factor (NGF) to the subventricular zone it would generate cells that migrate into the striatum and eventually differentiate into neurons and glia.
- Theoretically, trophic factors can be used to stimulate the subventricular zone to generate cells in the injured brain that will migrate to the injured area and restore some function
- It is possible that, in the future, trophic factors may be useful in the treatment of brain injury

Recovery from Brain Injury
Lost-Neuron-Replacement Solution

B. Replace Lost Cells

- Also, areas such as the hippocampus and the olfactory bulb were shown to produce new neuron in adults.
- Theoretically, it is possible that the formation of new neurons will be stimulated in intact regions of an injured brain and that the new neurons may facilitate the formation of new circuits which may restore (partial) function

A rat brain after cortical stroke

The same brain after treatment with growth factors

Infusion of epidermal growth factor into lateral ventrical induced neurogenesis in the subventricular zone.

The stem cells migrated to the injured area and filled it