Forget It!

Blue Mice Group
COGS 11
Prof. Boyle
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Reconsolidation and Consolidation

- **Reconsolidation**
  - Process of recalling previous consolidated memories and “updating” them

- **Consolidation**
  - Process of converting short-term new memories into long term memories
  - New memories fragile, must undergo consolidation to persist

- **Active vs Inactive states**
  - Active = modifiable; can be enhanced
  - Inactive = stabilized memories
Is Reconsolidation Really Happening?

- Combined study with Nader, Schafe, and LeDoux’s lab at NYU’s Center for Neural Science
  - Protein-synthesis inhibitor put to the test
  - Began by conditioning animals with “fear memory”
    - Tone followed by shocking rat’s feet
  - Injected inhibitor into animals, then exposed to the tone 1 day later
    - 40% of animals froze vs control group where 80% froze
  - Retrieval → destabilization of consolidated memories
    - Reconsolidation process endures the memories
Testing in Humans without Drugs

- **Scenario 1:**
  - Trained task #1 on Day 1
  - Trained task #2 on Day 2
  - Subjects retested on Day 3, and showed improvement with both tasks

- **Scenario 2:**
  - Trained task #1 on Day 1
  - Retested task #1 followed by training of task #2 on Day 2
  - Subjects retested on Day 3, and showed a decrease in performance with task #1 but unaffected performance with task #2

- **Task #2 interfered with the reconsolidation of task #1**
Norepinephrine’s Role (or not)

- **Thomas Study**
  - Knockout animals (unable to produce NE)
  - Contextual memory $\rightarrow$ apparatus environment
    - Hippocampus and amygdala
  - Cued memory $\rightarrow$ shock tone
    - Amygdala
  - NE critical for retrieval of contextual memories
  - NE not critical for consolidation of contextual memories or retrieval of cued memories
Norepinephrine's Role (or not)

- Mcgaugh and Roozendaal study
  - Corticosterone (glucocorticoids)
    - Impairs retrieval
  - Corticosterone + Propranolol (blocks Beta-adrenergic receptors)
    - Retrieval continues as normal
  - NE may enhance memory retrieval except with high levels of glucocorticoids it impairs

- Conflicts
  - “Conditions are phasic”, unable to know long term
  - Extrapolating from mice, limited memories and conditions to study on mice
Memory Extinction

- Extinction occurs after animal learned association of tone with a shock
  - When repetitively presenting the tone without the shock, new memory will replace the original fear memory
  - However, protein-synthesis inhibitors impair formation of these new memories
- Shock free exposure (SFR)
  - 3 mins SFR → injection → interrupted reconsolidation effect (less freezing)
  - 30 mins SFR → injection → interrupted extinction effect (more freezing)
New Possibilities for PTSD Treatment

- Calmodulin Dependent Protein Kinase II (CaMKII)
  - “the key molecule underlying learning in memory”

- Tsien and colleagues at the Medical College of Georgia manipulated aCaMKII protein expression in mice
  - Overexpression of aCaMKII -> mice unable to remember objects and fear-inducing stimuli
  - Memory deficit reversible by suppressing aCaMKII overexpression
New Possibilities for PTSD Treatment

- These findings offer “a molecular paradigm by which we can actually erase a specific memory”
  - New treatment possibilities for PTSD
    - Erasure of specific memories using chemical manipulations
    - Downstream substrates of CaMKII overexpression as possible drug targets
Manipulating Memory
RECALL,

- Reconsolidation is an adaptive process.
- Memories can indeed be retrieved, manipulated, deleted and enhanced via biomolecular methods or talk therapy.
The things we fear are not necessarily available to our conscious minds and the fear response we express is not necessarily controlled by triggers we are aware of. “ ~Ledoux

Originally, researchers thought that memories involving sounds require the auditory cortex, but by performing brain lesions, LeDoux and his team showed that the auditory cortex was not necessary in creating fear memories, but the auditory thalamus was.

They tested their hypotheses that it is the thalamic rather than cortical input to the amygdala that processed sounds with fear by lesioning the auditory thalamus.
Manipulating Memory

For simple sounds, either pathway could provide the amygdala with auditory information.
“The results showed for the first time that the brain could create emotional memories without awareness.” - Ledoux

Why is this profound?
In the late 1990s the Presidents Council of Bioethics said that it would be unethical to alter memories.....
Manipulating Memory

Most Cognitive Neuroscientists however think that it is perfectly acceptable to do so in order to alleviate debilitating fear.
Exercise Can Erase Memories

Running in animals has been shown to have a variety of effects on the brain, including ENHANCED memory function and NEUROGENESIS in the hippocampus. A correlation between running and these positive effects has also been observed in humans.
Exercise Can Erase Memories

- Recall, (no pun intended!) that NEUROGENESIS is the process by which new neurons are formed in the brain.
- Neurogenesis is abundant during prenatal brain development and early infancy, but then it decreases sharply.
Exercise Can Erase Memories

Dentate Gyrus - Part of Hippocampus

- We’ve learned that a healthy hippocampus is essential in the ability to form new memories, particularly for declarative memory function. This has most notoriously been illustrated with patient H.M.
- The dentate gyrus is thought to be one place in the adult human brain where adult neurogenesis can occur.
Something to consider: the dentate gyrus not only is one of the few regions where neurogenesis occurs, but it receives no direct inputs from other cortical structures.

- Part of the hippocampal formation.
- Contains granule cells, which project to the pyramidal cells and interneurons of the CA3 subfield of the hippocampus.
- The granule cells are the principal excitatory neurons of the dentate gyrus.
- The major input to the dentate gyrus [Perforant pathway] is from the entorhinal cortex, and the dentate gyrus receives no direct inputs from other cortical structures.
- The dentate gyrus is also one of the few regions of the brain where neurogenesis takes place. Neurogenesis is thought to play a role in the formation of new memories.
Exercise Can Erase Memories

The research in this article built upon the known increase in neurogenesis in running in mice to answer a very interesting question....
Is NEUROGENESIS necessarily a GOOD thing for MEMORY?
Exercise Can Erase Memories

Fuhgeddaboudit!
Exercise Can Erase Memories

Is there indeed an inverse relationship between the two?

Ability to create/retrieve long-term memories

Hippocampal Neurogenesis
Exercise Can Erase Memories

Here’s what they did:

Mice were taught to fear a particular environment.

Only SEDENTARY mice remembered their fear.

EXERCISERS FORGOT their fears.
Running imposes so many physiological changes, so the researchers even increased neurogenesis pharmacologically in the mice to separate this from other factors..

The mice still forgot!
The researchers also showed the correlated relationship by pharmacologically inhibiting neurogenesis in exercising mice and infant mice.

Guess what happened?
Exercise Can Erase Memories

They remembered BETTER!
The researchers provided more evidence linking neurogenesis to memory: Guinea pigs have reduced neurogenesis in infancy compared with mice and tended to remember a fearful experience for a much longer time than did infant mice.
Exercise Can Erase Memories

Everyone can do it -
Even a dumb jock!

Come on everybody-
Punk Rock!

(Actual cheer from St. Francis Prep HS, NYC  :-)

[Image of three football players in locker room]
If you know what’s good for you, you better keep in mind:

- The topic of adult human neurogenesis remains very controversial.
- It’s a long way from mouse to man.
- These memories were FEAR BASED. Would other types of declarative memories be affected in the same fashion?
- Hyperthymesia.
Reactivating Forgotten Memories

- Memory engram cells
  - Specific neurons that are active during formation of a memory
  - Discovered at RIKEN-MIT Center for Neural Circuit Genetics by Susumu Tonegawa and colleagues
  - If engram cell synapses are not strengthened through protein synthesis, the memories associated with them are lost
    - those memories can be reactivated by stimulating their associated engram cell

- Tonegawa and his colleagues theorize that there is an engram cell ensemble pathway for each memory
  - Pathway encompasses multiple brain areas
  - Engram cell ensembles in each area are connected for specific memories
New Possibilities for Alzheimer’s Treatment

● “Brain researchers have been divided for decades on whether amnesia is caused by an impairment in the storage of a memory, or in it’s recall.”

● Tonegawa’s findings suggest that past memories lost in retrograde amnesia may simply be inaccessible for recall and not completely erased
  ○ Reactivation of specific “lost” memories by manipulating engram cell ensemble pathways
    ■ Further research may offer new treatment possibilities for Alzheimer’s and other forms of amnesia
New Possibilities for Alzheimer’s Treatment

Lost Memories Reactivated in Mice