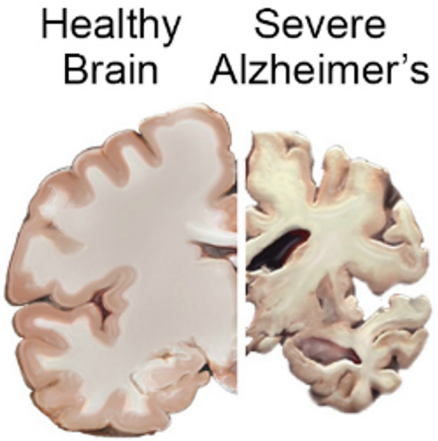
BraiNY Journal Club

Optogenetic stimulation of dentate gyrus engrams restores memory in Alzheimer's disease mice

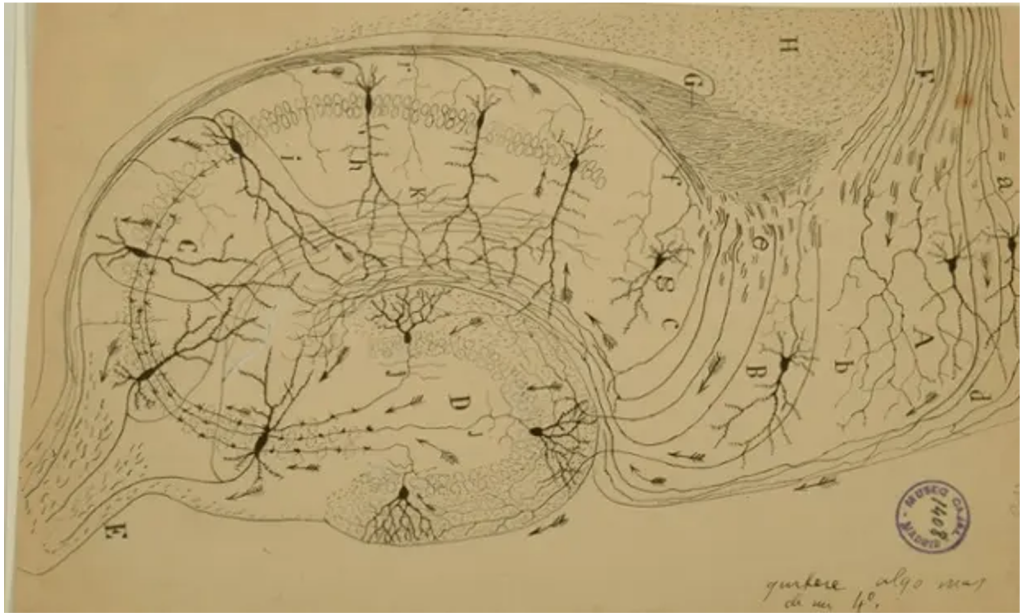
Intro to Alzheimer's Disease (AD)



- AD is the most common neurodegenerative disorder – over 6 million Americans may have dementia caused by AD.

- AD is initially a disorder of memory, but as the disease progresses more serious symptoms are present including mood and behavioral changes, confusion, severe memory loss, and cognition difficulty
- Amyloid beta (Aβ) and tau aggregation are the pathological hallmarks of the disease.
- AB pathology often starts in the hippocampus, a key brain region for memory.

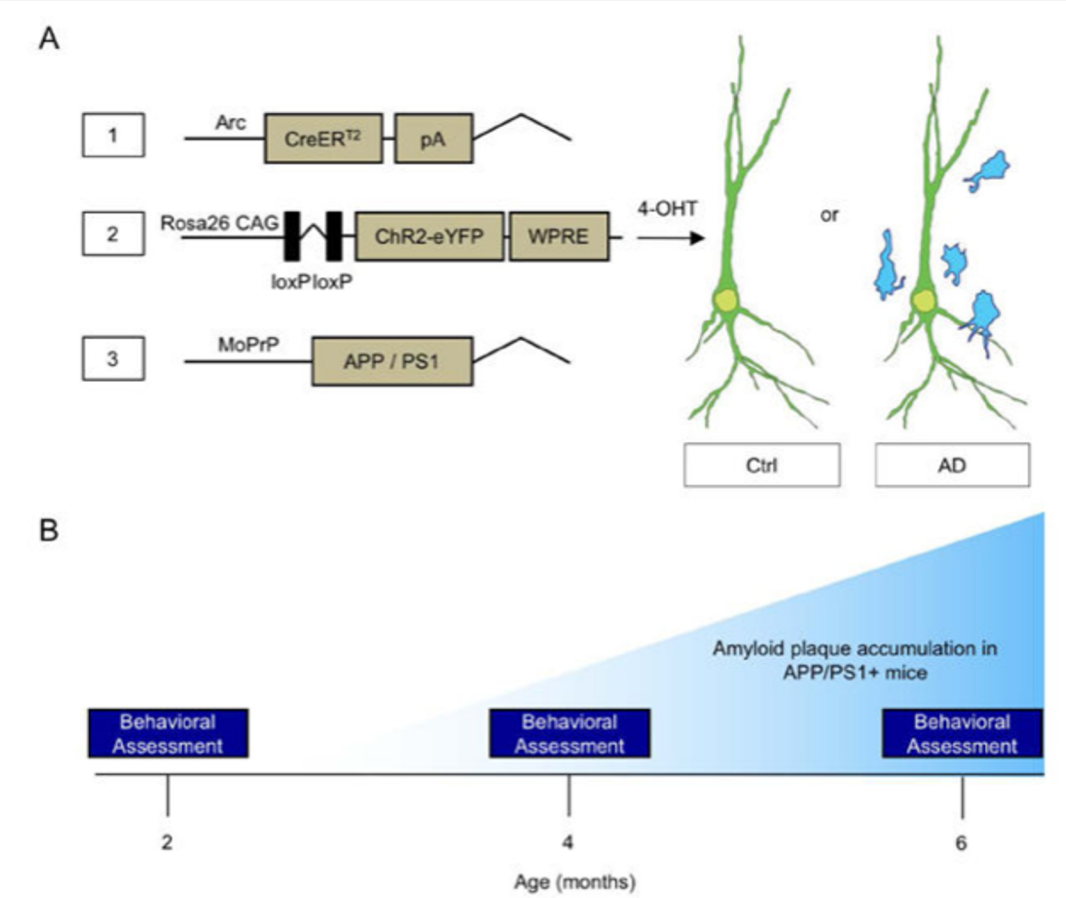
The hippocampus is important for memory formation and is affected by AD



Drawing by Ramon y Cajal of the hippocampus

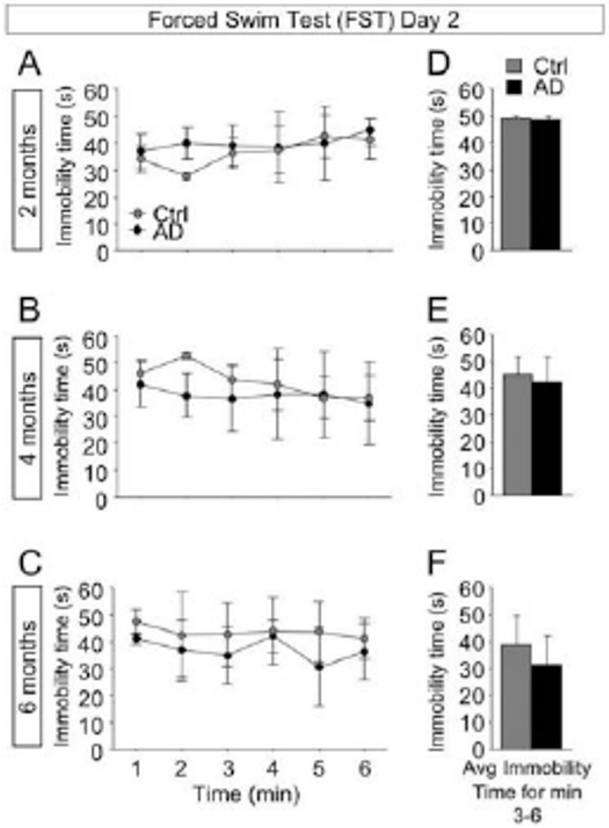
- The hippocampus is critically important for learning and memory
- Without the hippocampus, no new long term memories can be formed
- In Alzheimer’s disease, Aβ and tau aggregation often begins in the hippocampus

Figure 1: Experimental Design



- This paper uses a genetically modified mouse where mutations that cause early onset AD in humans (presenilin and amyloid precursor protein) are introduced into a mouse brain.
- Aβ aggregates appear at ~4 months of age.
- Behavioral testing at 2, 4, and 6 months of age.

Figure 2: AD mice are not more anxious or depressed than normal mice



- AD mice perform the same as control mice in tests that measure depression & anxiety
- Neither AD nor Ctrl mice get more depressed/anxious as they age
- Four different behavioral tests were used here
  - Forced Swim (depression)
  - Open Field (anxiety)
  - Elevated Plus Maze (anxiety)
  - Novelty Suppressed Feeding (anxiety)

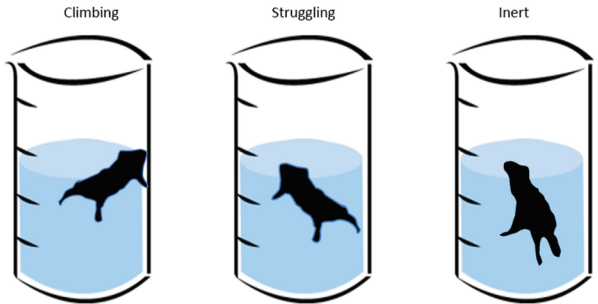
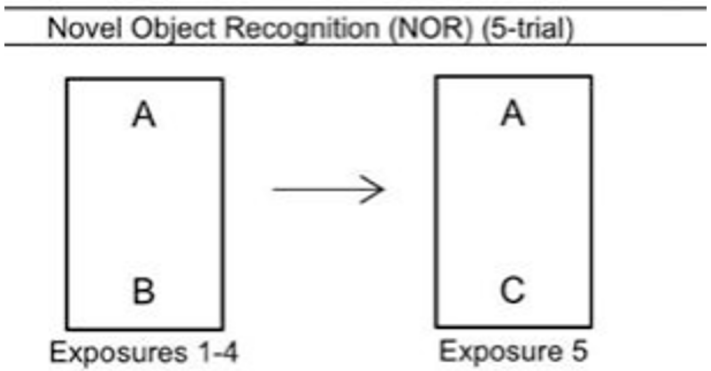
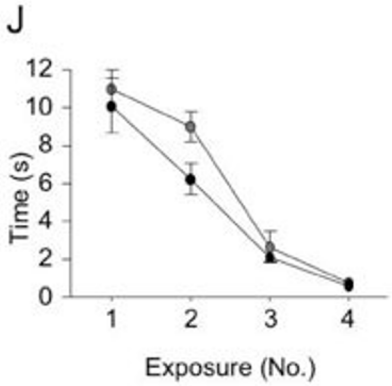
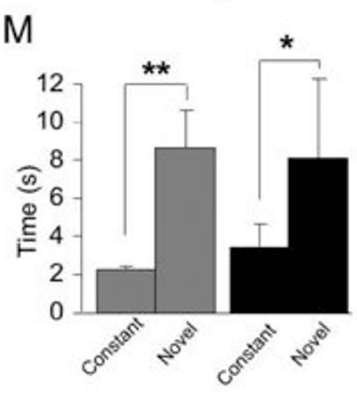


Figure 3: AD mice perform as well at Ctrl mice in novelty detection tests

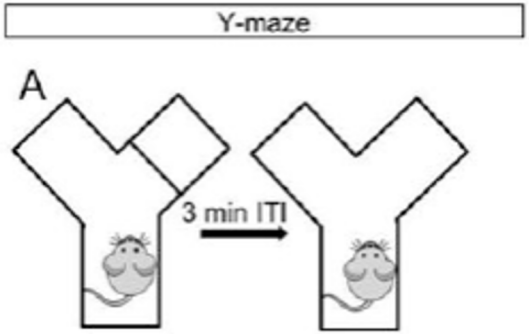






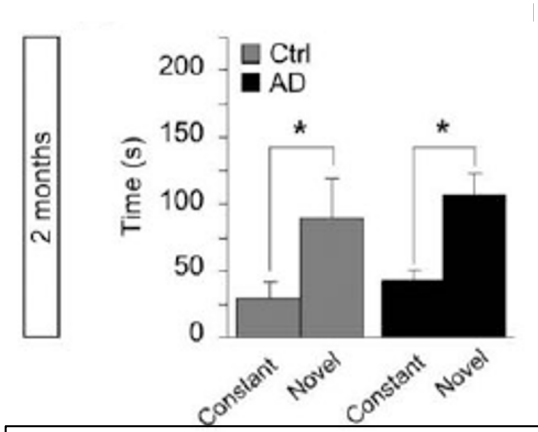
- Mice prefer novel objects to familiar objects. This tests the ability of mice to recognize and remember new objects.
- AD mice perform as well as controls in detecting a novel object
- There is no change in performance as the mice age

Figure 4: AD mice are worse at a spatial memory test. All mice get worse as they age.

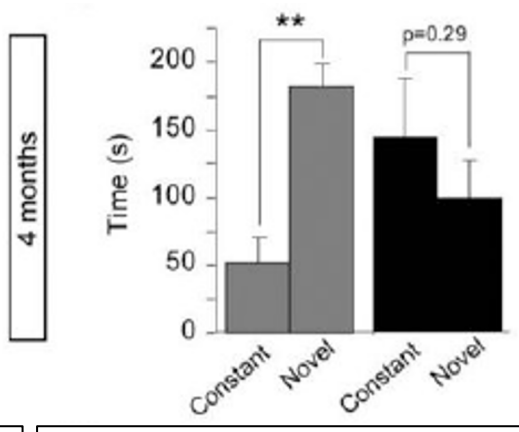


In the Y maze test, one arm is open for the mouse to explore, and one arm is closed off until the test

Spatial memory requires the hippocampus. By 4 months of age, plaque formation has begun in the hippocampus



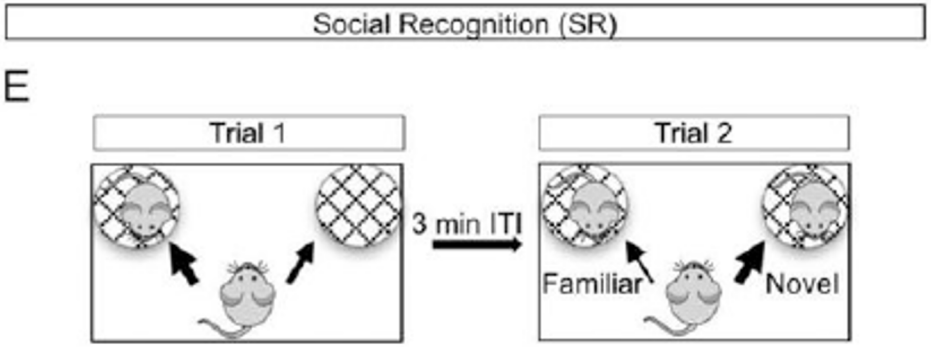
At 2 months, all mice recognize the novel arm of the maze



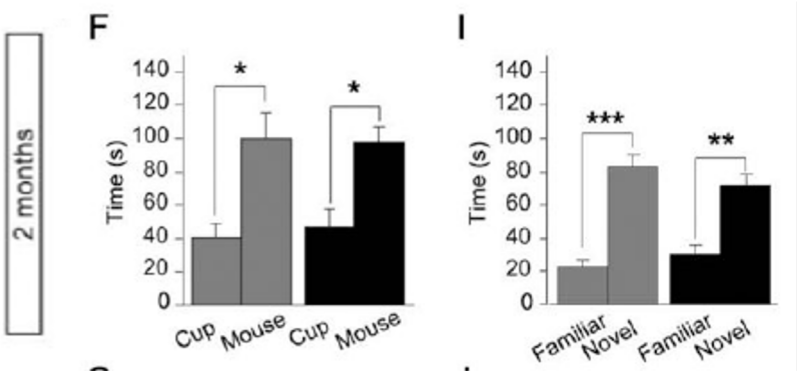
By 4 months, AD mice no longer remember which arm is novel

By 6 months, all mice do poorly recognizing the novel arm

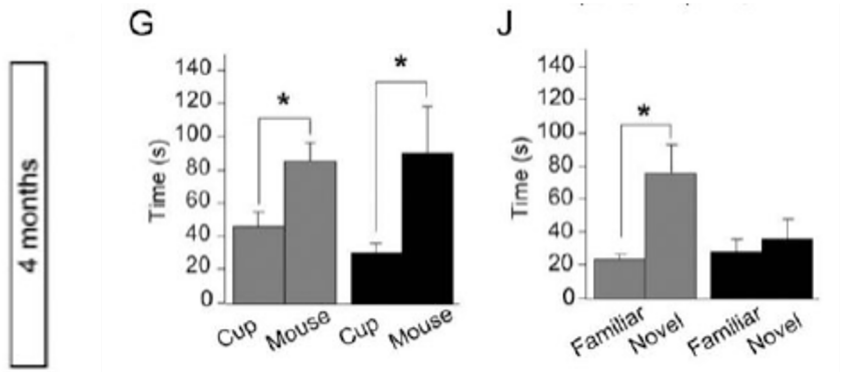
Figure 4: AD mice are worse at social memory test.



- All mice spend more time exploring a mouse than an empty cup (F,G,H).
- At 6 months, all mice spend equal time with the novel and familiar mice.



At 2 months, all mice spend more time with a novel mouse



At 4 months, AD mice no longer spend more time with the novel mouse

Figure 5: Contextual fear memory is impaired in AD mice

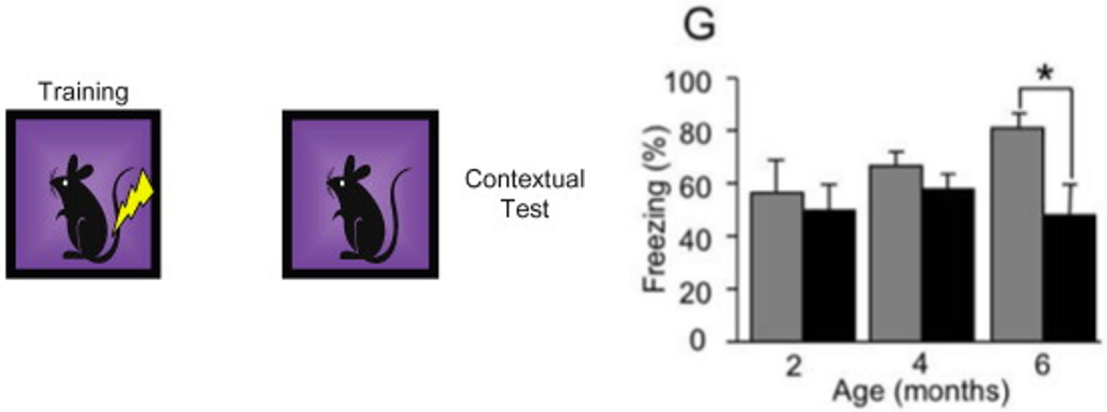
Novel environment (light, odor, sound) + Foot shock =

Conditioned Response (freezing)

conditioned stimulus

unconditioned stimulus

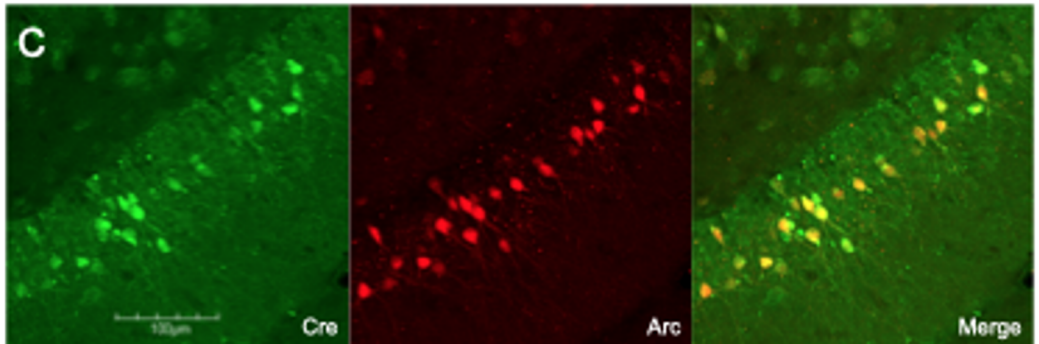
Fear associated with novel environment



- Mice undergo contextual fear conditioning tests using either 1 or 3 foot shocks.
- Ctrl mice remember the fear conditioning context and freeze when put into the box. AD mice freeze significantly less at 6 months.

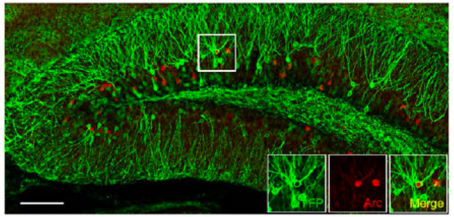
Permanently labeling a memory in a mouse brain

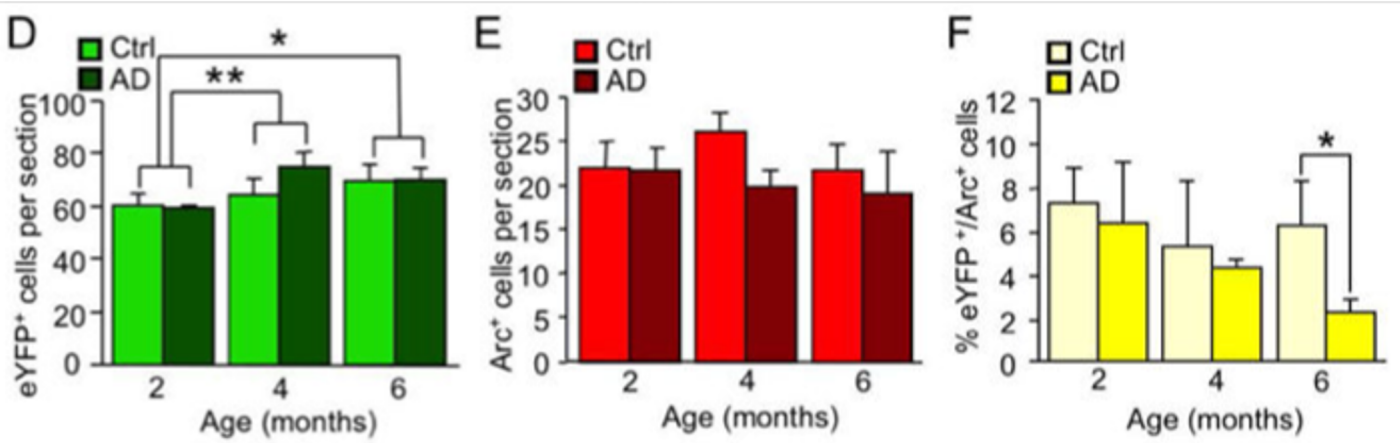
- Immediate early genes like Arc are turned on for a short time after a neuron is active.
- In the hippocampus, neurons that are active during formation of a memory will express Arc (and can be labeled with an antibody)



- The Arc-CreER mouse is designed so that when a drug (4-OHT) is given to the mouse, all neurons that are active for ~4 hours are permanently labeled (with yellow fluorescent protein (YFP)).
- The Arc-CreER mouse can tell you which neurons are involved in a particular memory.

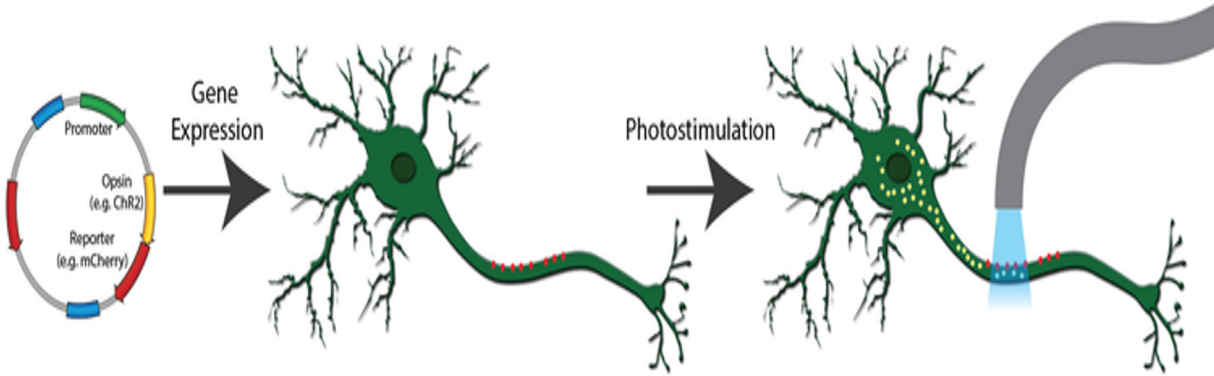
Figure 5: Labeling the fear memory





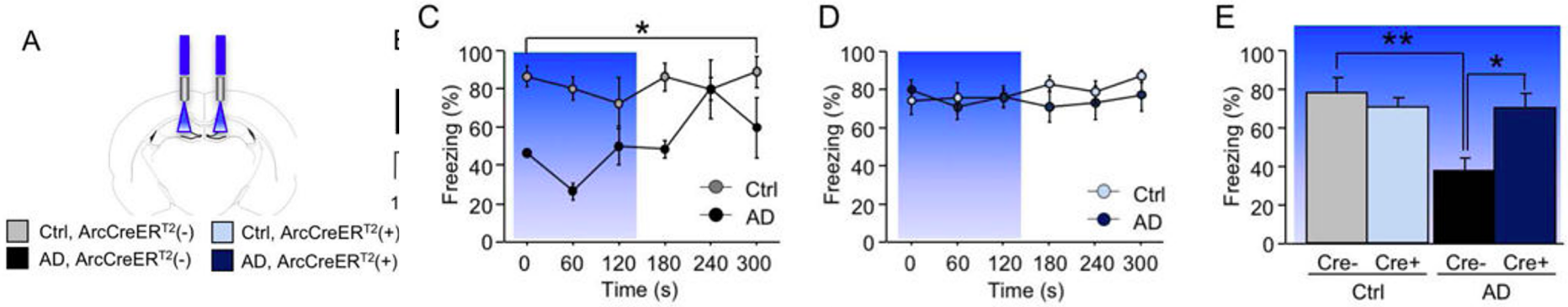
- At the time of the fear conditioning, mice are given 4-OHT to label any active neurons with YFP (green) (Memory Encoding).
- After being put back in the fear context at 6 months, the brains are then stained for active cells with an Arc antibody (red) (Memory Recall).
- Cells that were active both at the time of learning and during the memory of the fear context will be co-labeled red and green
- 6 months of age, but not 2 or 4 months of age, AD mice had significantly less co-labeled DG cells than did Ctrl mice, suggesting that the originally-encoded memory trace was not being recalled properly and that the behavioral deficit was paralleled by impaired DG memory traces

Optogenetics: a molecular genetics method to control the firing of neurons



- Channelrhodopsin is an ion channel found in microbes that opens in response to light. When it's put into a neuron, you can use LED light to cause a neuron to fire. This technique is called optogenetics.
- Optogenetics can be used to understand which neurons are important for a behavior. By turning on certain neurons in the brain with optogenetics, you can show that those neurons control a specific behavior like eating or aggression.

Figure 6: Turning on neurons with optogenetics improves memory in AD mice



- In these mice, neurons that are active during memory encoding (following delivery of 4-OHT) will express channelrhodopsin and can then be turned on by an LED light.
- Reactivating neurons that were labeled during the fear memory encoding helps the AD mice remember. When the light is on (blue boxes), AD mice freeze the same as the control mice
- This improvement is not long-lasting. The mice only do better when the light is on.