

# Lecture 21. Learning 6- What is a Memory

*Professor Christiane Linster*

## Pre-lecture preparation

- (1) Watch pre-lecture video on optogenetic techniques
- (2) Read Box 24.4 on pages 858 – 859
- (3) Review Figure 24.25 page 855
- (4) Review Hippocampal circuitry
- (5) Review fear conditioning

## Learning Objectives

To understand current ideas of memory formation

- (1) Be able to understand how memories can be accessed and measured in humans and other animals.
- (2) To understand the concept of false memories
- (3) To understand how memories can be manipulated in life and experimentally
- (4) To understand the basic concepts of neuronal manipulations with genetic tools
- (5) To follow an experiment in which memories are created in a mouse brain by optogenetic stimulation of neurons Be able to design experiments to test current models of memory consolidation
- (6) To summarize concepts of plasticity learned in the series of lectures

## Lecture Outline

- (1) Memories can be fragile and easily manipulated. It can often be difficult to distinguish “real” memories from false memories
- (2) In animal experiments it has been shown that memories are changed every time they are recalled and can be associated with a novel concept or behavioral outcome
- (3) Recent experiments using optogenetic techniques have shown that artificial activation of neurons in a specific context and learning situation can lead to a “false” or “experimenter created” memory.

## Study Questions

## Lecture 21: What is a memory?

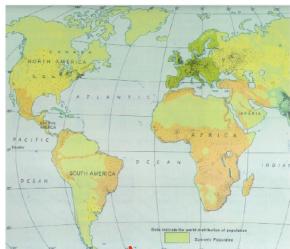
Christiane Linster  
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W247 Mudd Hall  
Office hours Wed. 1:30-2:30 or by appointment

**Declarative memory**  
(Medial temporal lobe; diencephalon)

Facts

Events



1 place



people

Procedural memory:  
skills and habits  
(Striatum)

implicit

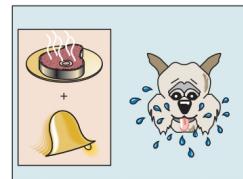


**Nondeclarative memory**

Classical conditioning

Skeletal musculature  
(Cerebellum)

Emotional responses  
(Amygdala)



## Lectures 16-21: Learning and memory

- Lecture 16** NMDA receptor allows to “associate” two events at the level of a synapse
- Lecture 17** Learning at the synaptic level: LTP and LTD
- Lecture 18** Learning at the network level: how are LTP and LTD involved in changing networks ?
- Lecture 19** Learning while behaving: sequences of events and STDP
- Lecture 20** Remembering: Consolidation of what has been learned
- Lecture 21** **What is a memory?**

## Lecture 21: What is a memory?

- (1) To understand the concept of false memories
- (2) To understand how memories can be manipulated in life and experimentally
- (3) To understand the basic concepts of neuronal manipulations with genetic tools
- (4) To follow an experiment in which memories are created in a mouse brain by optogenetic stimulation of neurons
- (5) Be able to design experiments to test current models of memory consolidation
- (6) To summarize concepts of plasticity learned in the series of lectures

## **“Creating memories”**

Concepts you have learned that will be integrated in this lecture:

Na<sup>+</sup> and action potentials

Gene expression and activation

Classical conditioning

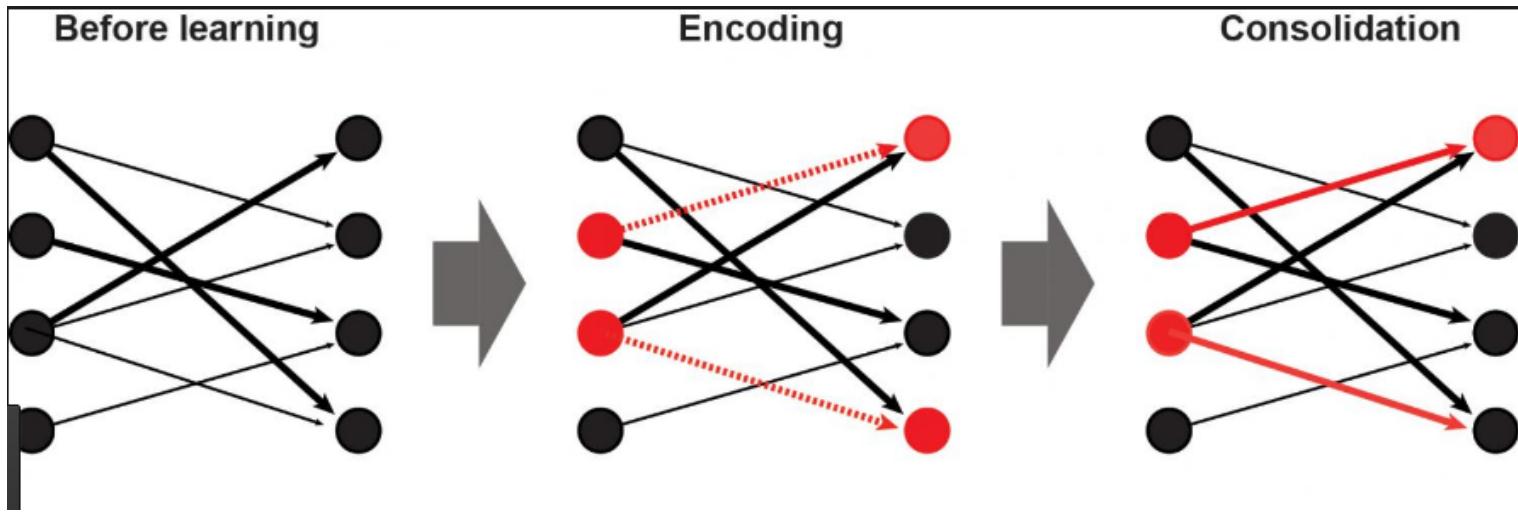
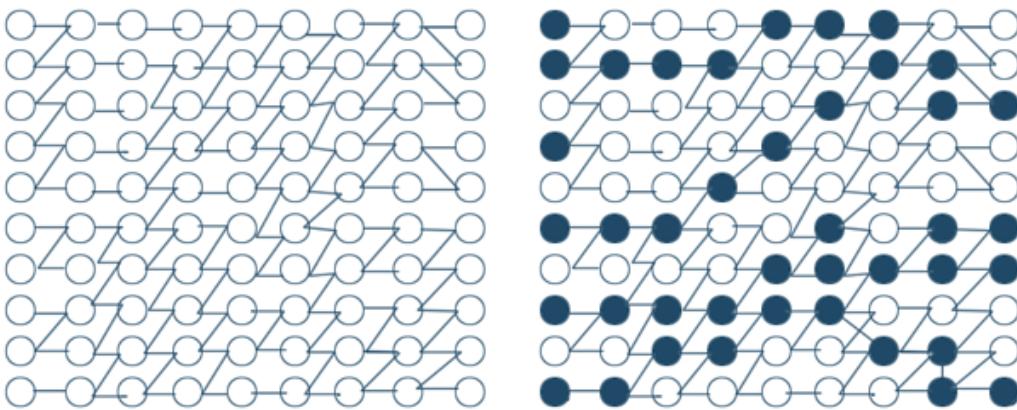
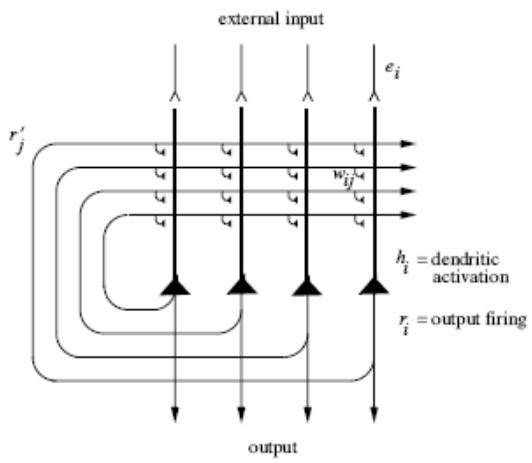
Distributed memories

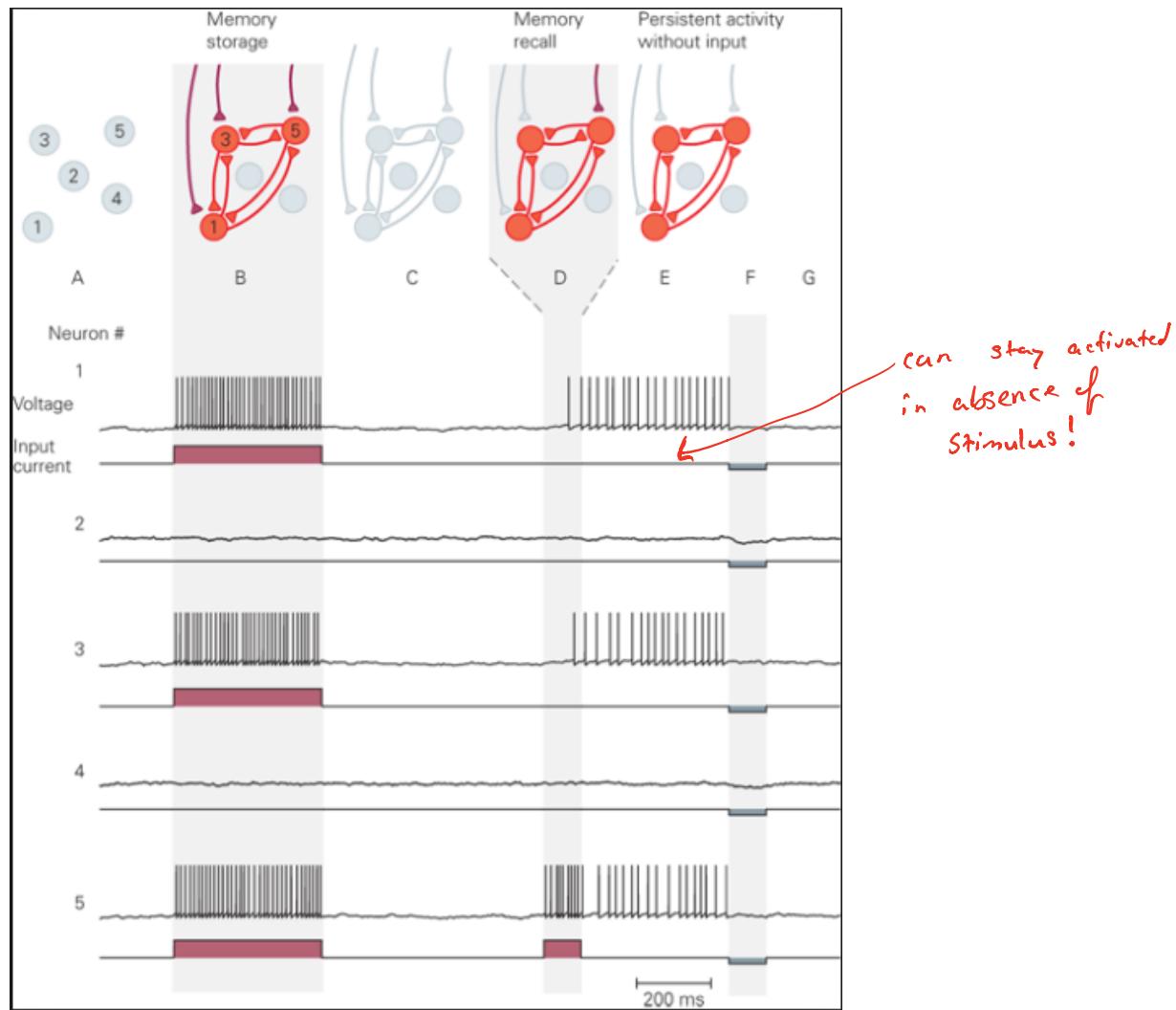
## What is a memory?

Network

## Neural substrates of such memories?

- Cerebellum
- Hippocampus
- Synapses





## Evidence that a given neural ensemble represents a “memory”?

Need {  
or  
① Destroy Memory  
② Create artificial Memory

## **“Creating memories”**

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**Na<sup>+</sup> and action potentials**

Distributed memories

Gene expression and activation

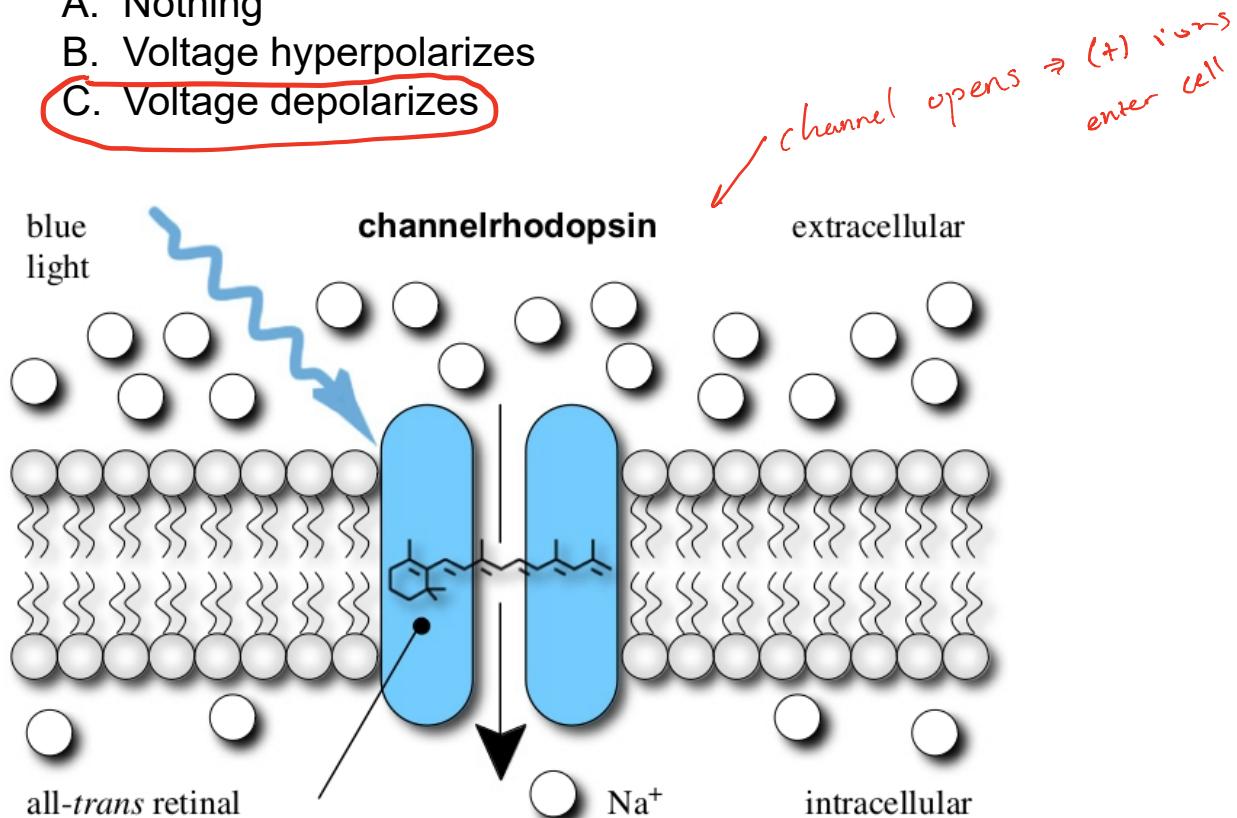
Classical conditioning

Distributed memories

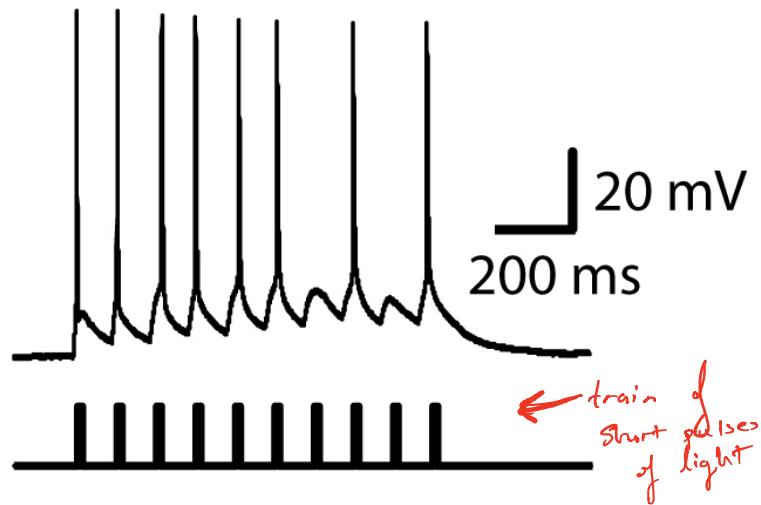
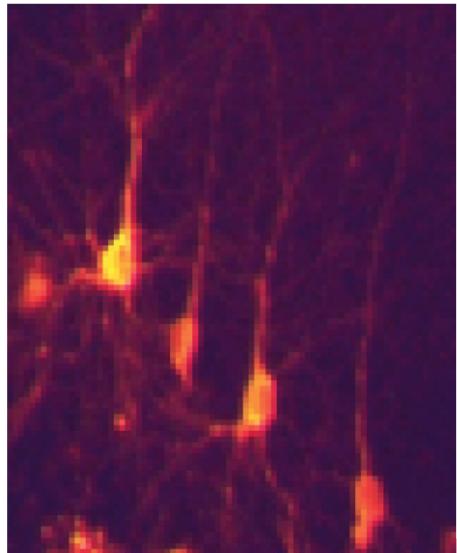
## Clicker question

What happens at the inside of the cell when  $\text{Na}^+$  enters the cell?

- A. Nothing
- B. Voltage hyperpolarizes
- C. Voltage depolarizes



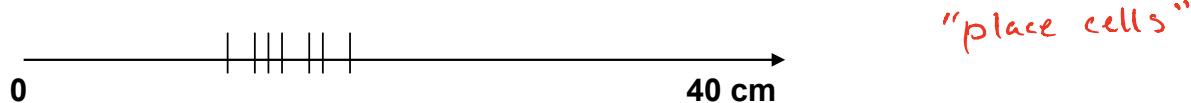
## Light activation of neuronal firing



Action potentials in neurons, which express the light-gated ion channel *channelrhodopsin*, evoked by illumination with blue light.

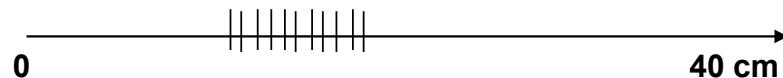
## Clicker question

You engineer a mouse in which pyramidal cells in a mouse have a light activated Cl<sup>-</sup> channel inserted. You are recording the following spike train in a cell when the mouse runs on a track

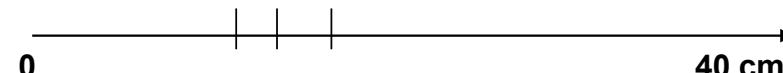


What is the most likely change you would observe if you shine the light on the hippocampus?

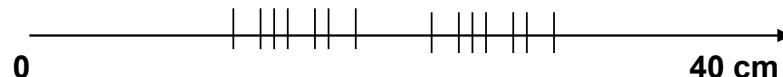
A



B



C

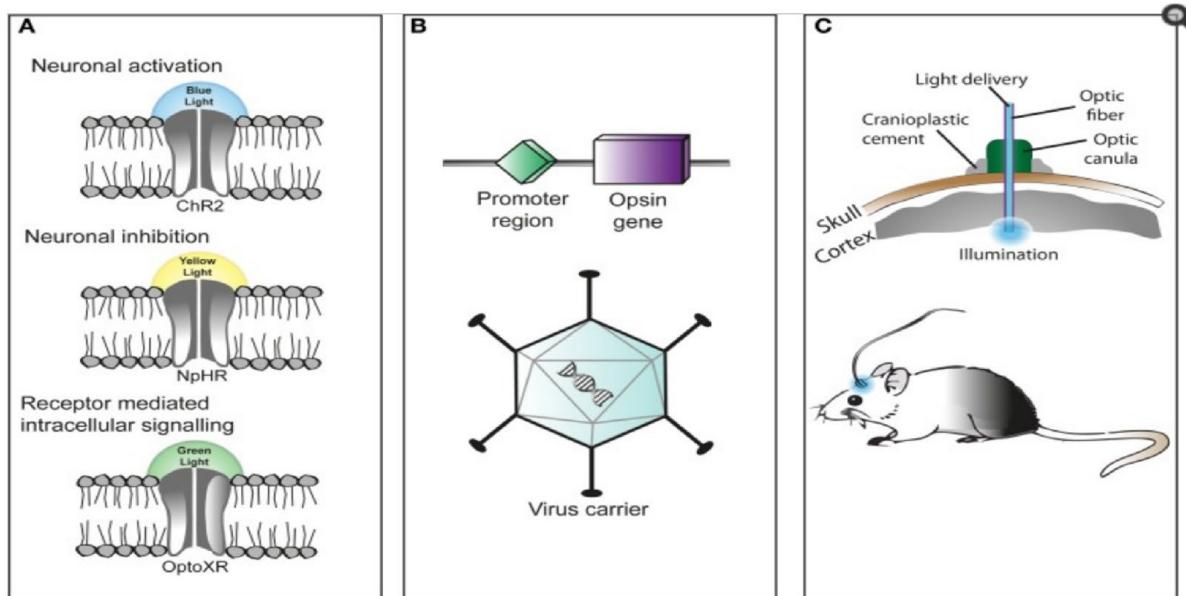


activating light activated Cl<sup>-</sup> channel, cell hyperpolarizes which can prevent it from firing.

## Advantages of optical stimulation of neurons:

- High temporal control
- High control of which neurons are stimulated
- Pathway specific stimulation

Figure 1



<https://www.youtube.com/watch?v=7Mmsah0v9Qc>

↑  
Watch This

This video is showing how optogenetic activation of the extended amygdala hypothalamic circuit rapidly evokes voracious feeding of high-fat foods.

## **“Creating memories”**

Concepts you have learned that will be integrated in this lecture:

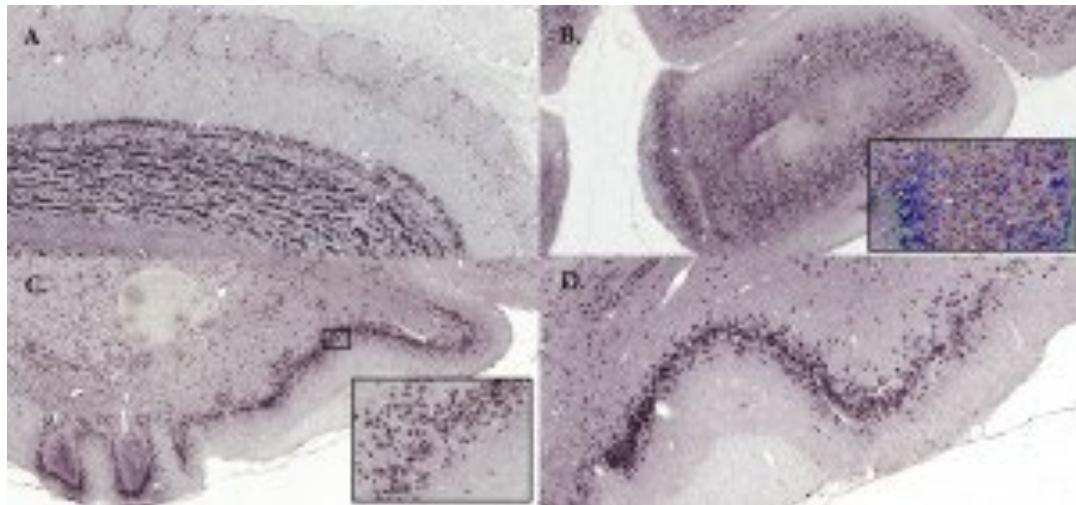
Na<sup>+</sup> and action potentials

**Gene expression and activation**

Classical conditioning

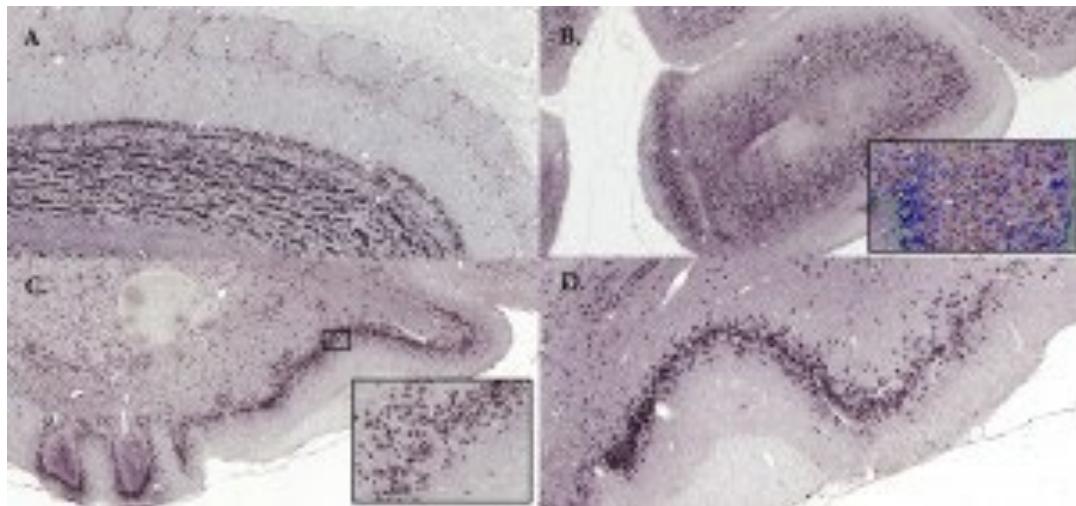
Distributed memories

**Immediate Early Genes (IEGs) can be used to label neurons activated by a stimulus, context or situation.**



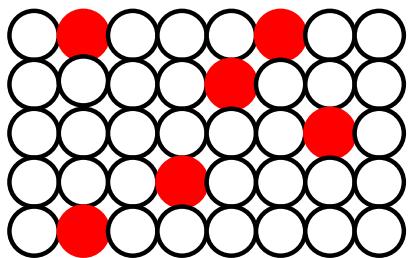
**Immediate early genes (IEGs)** are genes which are activated transiently and rapidly in response to a wide variety of cellular stimuli. They represent a standing response mechanism that is activated at the transcription level in the first round of response to stimuli, before any new proteins are synthesized.

Immediate Early Genes (IEGs) can be used to label neurons activated by a stimulus, context or situation.

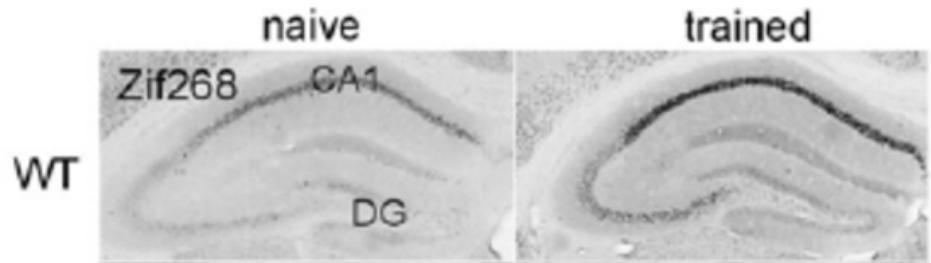


Scientists can target a specific subset of cells involved in memory formation by **linking ChR2 expression to a c-Fos promoter**—a gene commonly used to label neurons involved in memory formation. Light can then be used to “reactivate” neurons that were active in a specific context.

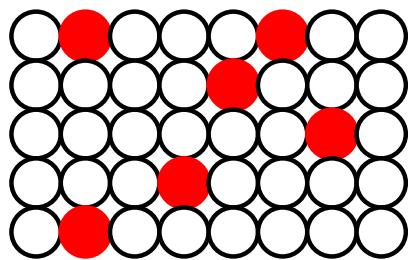
## Linking ChR2 expression to a Fos promoter



Neuron fires -> activation of IEG

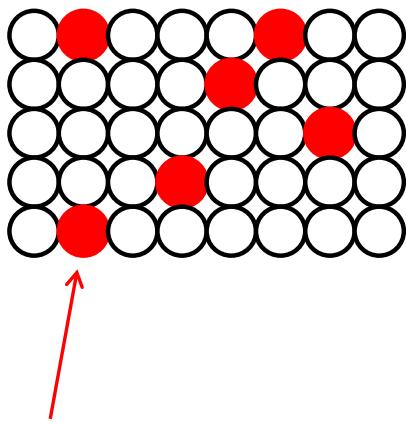
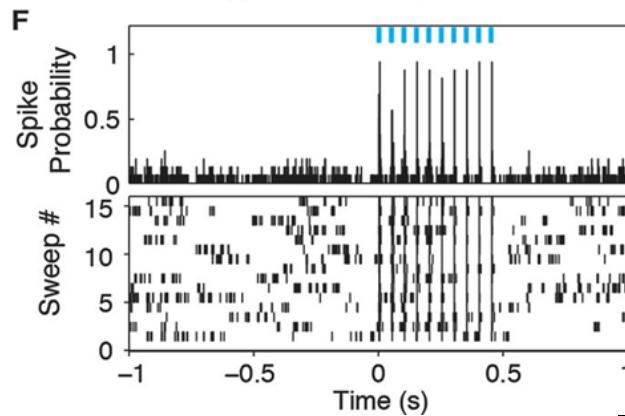


## Linking ChR2 expression to a Fos promoter

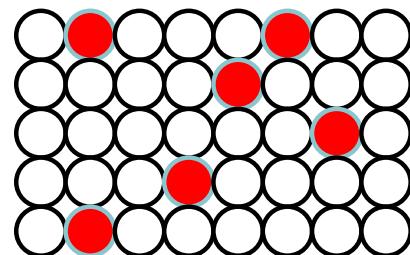
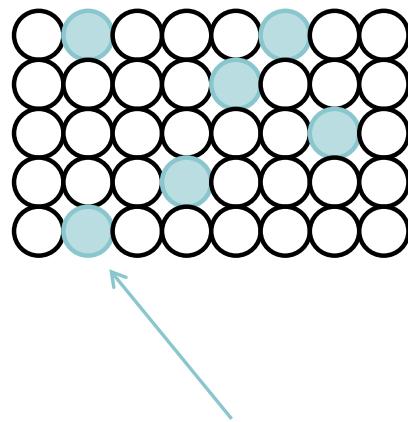


Neuron fires -> activation of IEG -> expression of ChR2

## Linking ChR2 expression to a Fos promoter

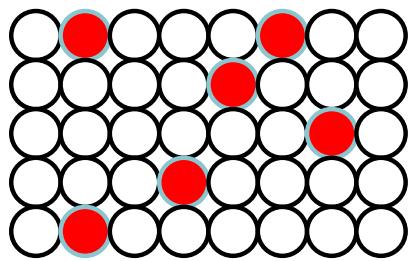
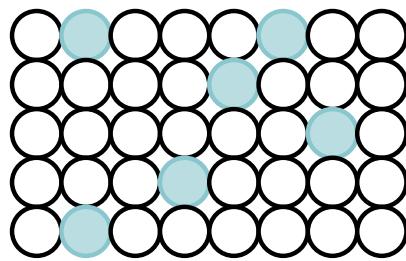
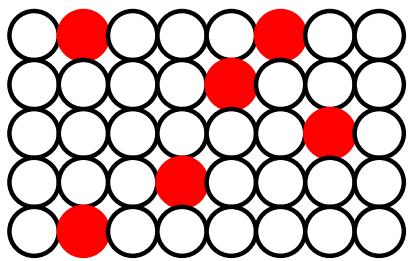


Neuron fires -> activation of IEG -> expression of ChR2



Blue light -> neurons fire

## Linking ChR2 expression to a Fos promoter



Neuron fires -> activation of IEG -> expression of ChR2

Blue light -> neurons fire

The experiment: can a memory for a behavioral context be evoked by artificial stimulation of neurons outside that context?

**Creating a false memory in the hippocampus.** Ramirez et al. 2013. *Science* 341(6144): 387-391

[Science](#). 2013 Jul 26;341(6144):387-91. doi: 10.1126/science.1239073.

## Creating a false memory in the hippocampus.

[Ramirez S](#), [Liu X](#), [Lin PA](#), [Suh J](#), [Pignatelli M](#), [Redondo RL](#), [Ryan TJ](#), [Tonegawa S](#).

### Neuroscientists plant false memories in the brain

MIT study also pinpoints where the brain stores memory traces, both false and authentic.

Anne Trafton, MIT News Office

**the guardian**

False memory planted in mouse's brain

MIT Scientists Create False Memories in Mice, Creep Out All Other Species  
Don't worry, it'll be a while before people can implant a false memory in your brain.

**Science News**

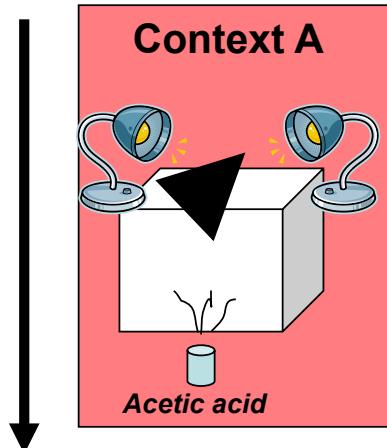
... from universities, journals, and other research organizations

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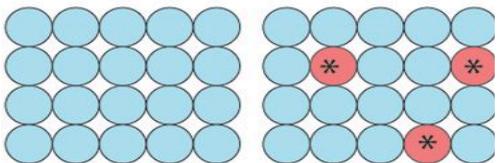
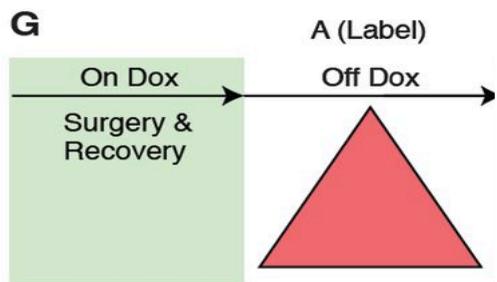
**Stimulating Brain Cells Can Make False Memories**

## **Context?**

(1) Express ChR2 in neurons responding in context A

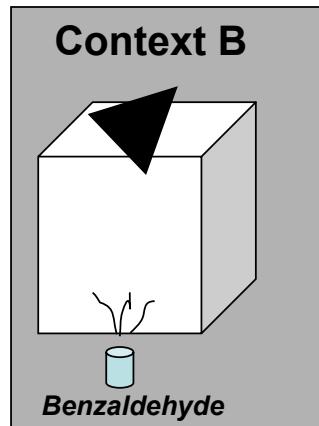


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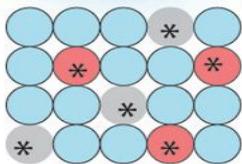
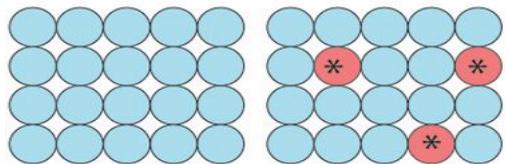
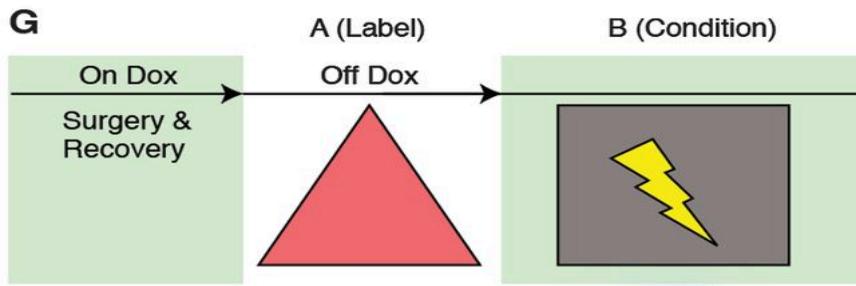


(1) Express ChR2 in neurons  
responding in context A

(2) Light activation of  
Context A neurons  
+ foot shock  
In context B



G

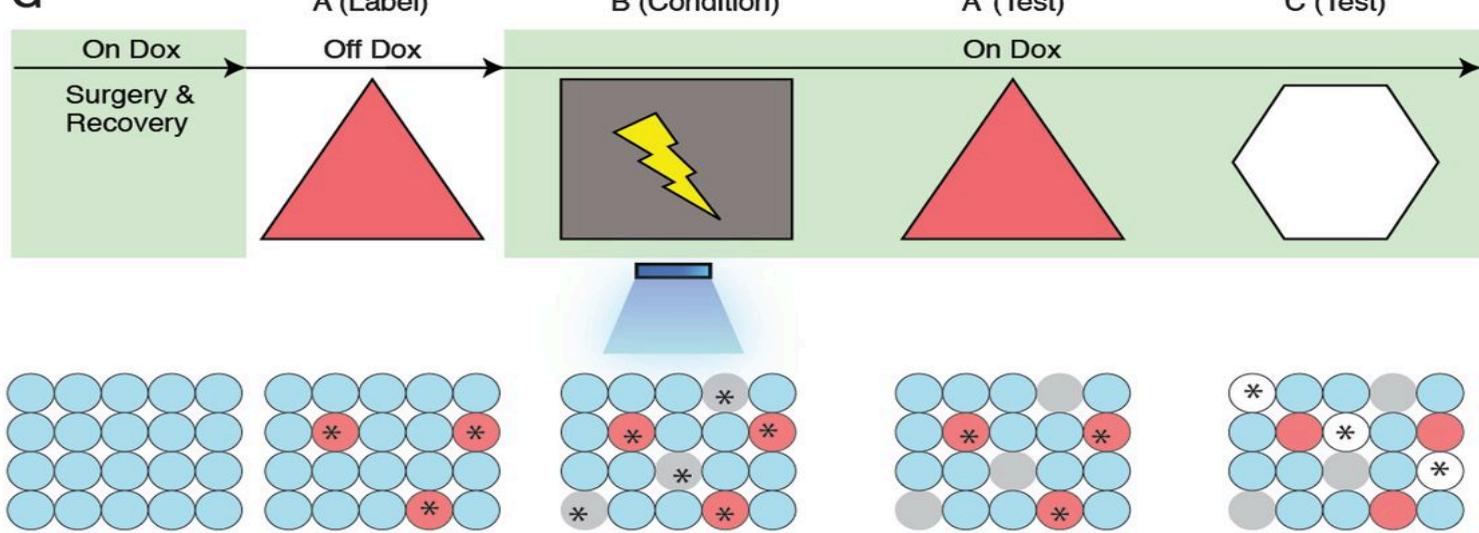


(1) Express ChR2 in neurons  
responding in context A

(2) Light activation of  
Context A neurons  
+ foot shock  
In context B

(3) Freezing response recorded

G



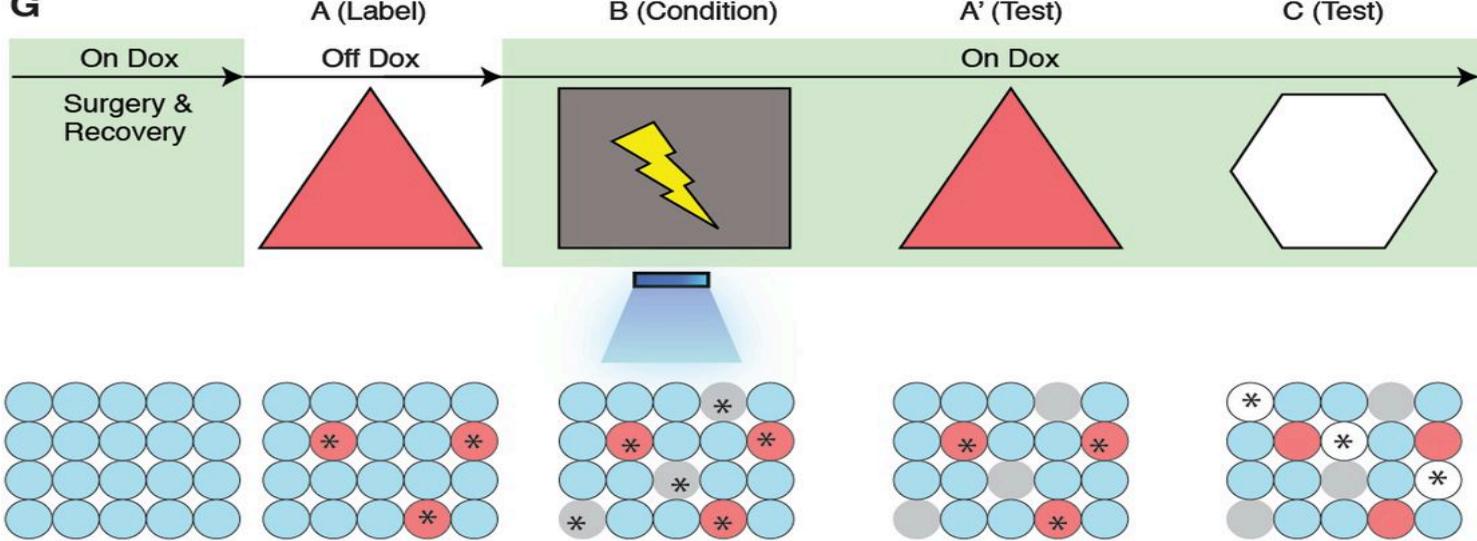
(1) Express ChR2 in neurons responding in context A

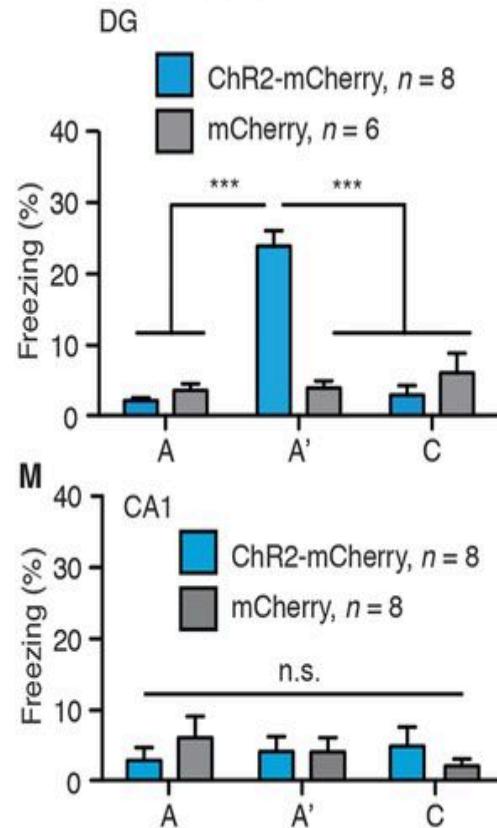
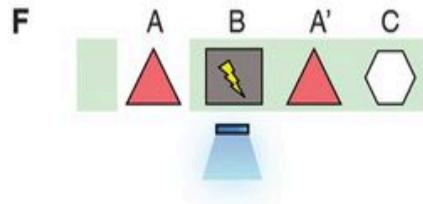
*A associated with foot shock because of light activation during foot shock*

(2) Light activation of Context A neurons + foot shock In context B

(3) Freezing response recorded

G





Express ChR2 in neurons  
responding in context A

Light activation of  
Context A neurons  
+ foot shock  
In context B

Freezing response recorded in A and  
C

**What did we learn?**

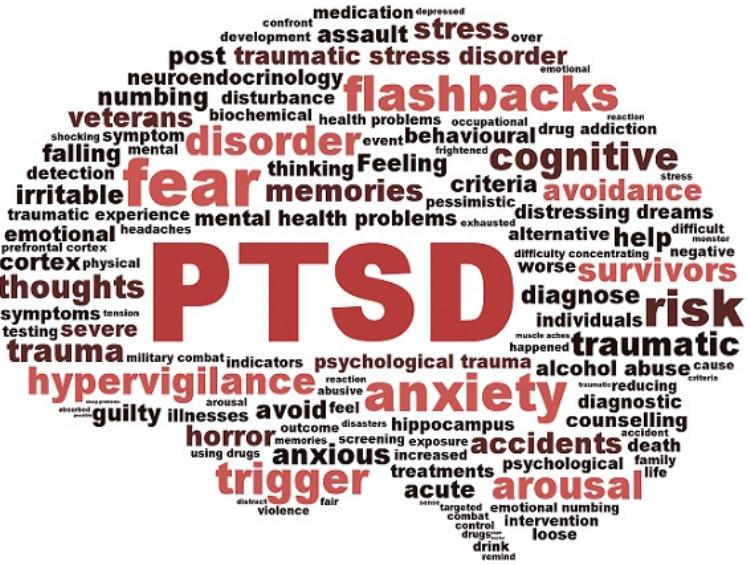
## Extra credit opportunity: experimental design

***This is NOT a required assignment, but is worth one day's worth of participation extra credit (in addition to your attendance in class today).***

- 1. Go to blackboard and open the “In-class activity 3/13” folder***
- 2. Download the worksheet***
- 3. By 7 PM today, submit your worksheet to the Turnitin assignment. Make sure everything is in your own words.***
- 4. You may work alone or with ONE partner. If you work with a partner, you may submit identical worksheets, but you must both submit to receive extra credit. Make sure to include your partner’s name on the worksheet. Both team members must have been present during lecture for credit.***

# It's 2038: Can we design an optogenetic treatment for PTSD?

*What if in twenty years we had a safe and reversible way to express channelrhodopsin in human brain?*

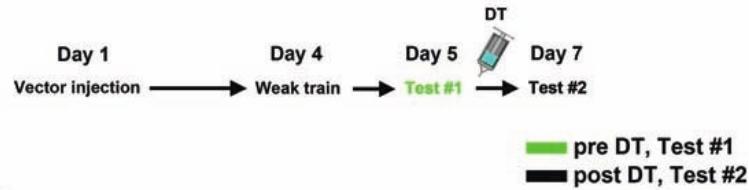


## **It's 2038: Can we design an optogenetic treatment for PTSD?**

***Questions to fill in on the worksheet:***

- What kinds of memories will you target?**
- What experimental subjects will you recruit? Who are your control subjects?**
- How will you locate the cells or synapses that “contain” the memory you’re targeting?**
- How will you manipulate activity in the cells or synapses?**
- How will you test whether the treatment worked?**
- What is one WEAKNESSES for your approach— what potential problems do you foresee and how might you address them?**

## Fear memories have reportedly already been altered or deleted in mice



## Selective Erasure of a Fear Memory

Jin-Hee Han,<sup>1,2,3</sup> Steven A. Kushner,<sup>1,4</sup> Adelaide P. Yiu,<sup>1,2</sup> Hwa-Lin (Liz) Hsiang,<sup>1,2</sup> Thorsten Buch,<sup>5</sup> Ari Waisman,<sup>6</sup> Bruno Bontempi,<sup>7</sup> Rachael L. Neve,<sup>8</sup> Paul W. Frankland,<sup>1,2,3</sup> Sheena A. Josselyn<sup>1,2,3\*</sup>

By targeting and killing specific neurons in amygdala, mice stop associating a tone with a mild shock

→ interpretation, they forgot

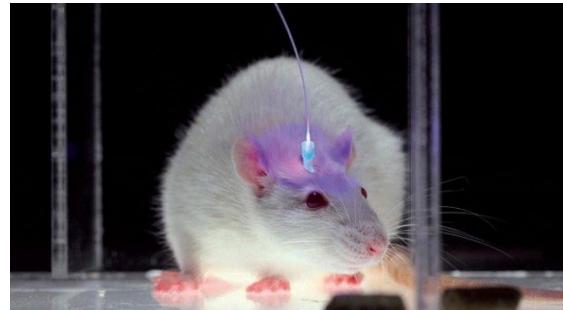


Science, 2009

## If we could alter human memories ... should we?

**Do you think:**

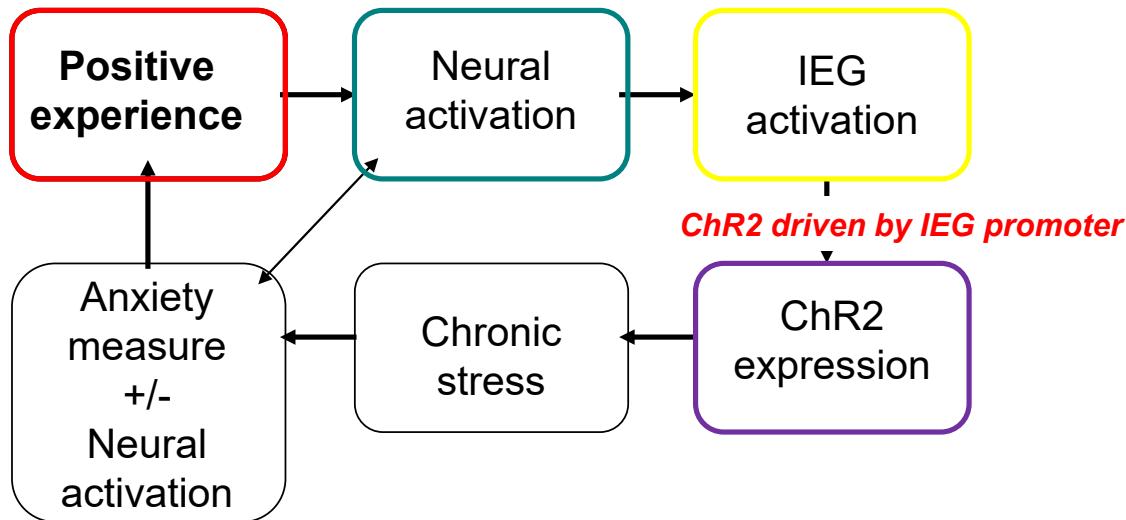
- Who (if anyone) should be eligible to ask for memory alteration?
- Should only certain kinds of memory be altered?
- Who should make decisions about the treatment?



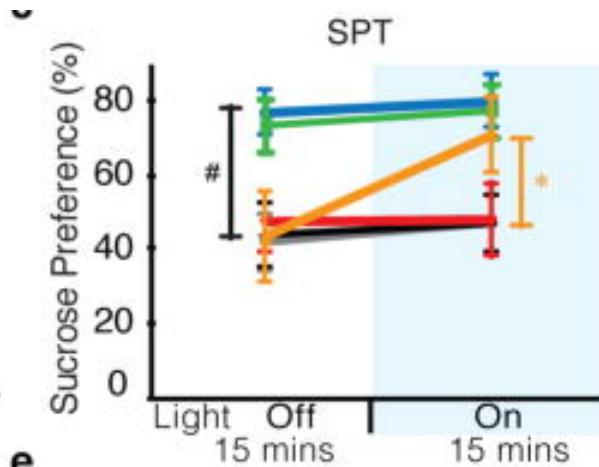
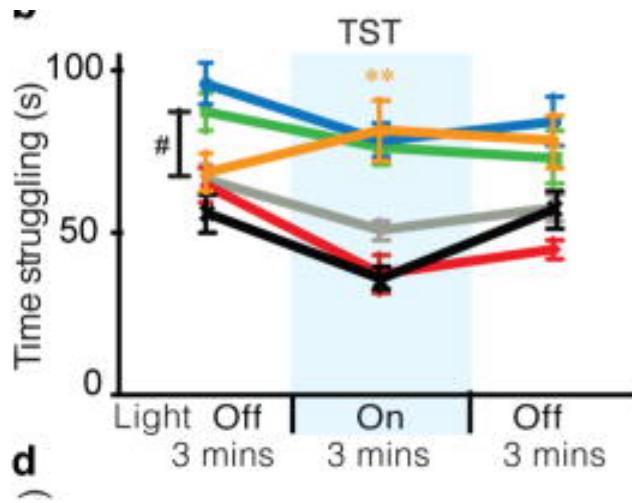
# Activating positive memory engrams suppresses depression-like behavior

Steve Ramirez,<sup>1</sup> Xu Liu,<sup>1,2,3</sup> Christopher J. MacDonald,<sup>1</sup> Anthony Moffa,<sup>1</sup> Joanne Zhou,<sup>1</sup> Roger L. Redondo,<sup>1,2</sup> and Susumu Tonegawa<sup>1,2,\*</sup>

- (1) Mice are exposed to a positive, rewarding situation (exposure to females)
- (2) Mice undergo chronic stress
- (3) Anxiety behaviors are measured with and without re-activation of neurons associated with positive experience.



- Did not undergo stress
- Stress + ChR2 in response to pleasant experience**
- Stress but ChR2 not expressed (light control)
- Stress+neutral experience
- Stress+negative experience



“Depressed” animals spend less time struggling when restraint  
 “Depressed” animals have a decreased preference for sucrose

**“Reactivation” of neurons activated by a pleasant experience can reduce the effects of subsequent stress**

**Presence of maternal odor can reduce effects of subsequent stress**

**How do these results relate to the experiments you proposed?**

**What are the possible ethical implications?**



## Lectures 16-21: Take home messages

- (1) NMDA receptors act as “AND” gates. Presynaptic activity in the form of transmitter release and postsynaptic activity in the form of depolarization and Mg<sup>+</sup> release have to be true to open channel and let Ca<sup>+</sup> in.
- (2) Long term potentiation (LTP) and depression (LTD) depend on pre and postsynaptic activity, Ca entry into the postsynaptic cell and the degree of NMDA receptor activation.
- (3) Experimental evidence links LTP/LTD to neural and behavioral changes in response to learning
- (4) In spike timing dependent plasticity (STDP), the direction of change in synaptic strength depends on the timing of pre and postsynaptic events. STDP constitutes a self normalizing leaning rule, works well with noisy spike trains and has been proposed as a learning rule for sequences of events. An example of such sequences are hippocampal place fields.
- (5) Human memories are thought to be distributed in neural assemblies formed by “hebbian” learning.
- (6) Temporal lobe (hippocampus) is crucial for the formation of new memories and the transfer of memories from short term to long term storage (consolidation)
- (7) A model of memory consolidation proposes that time scales of plasticity in hippocampus and neocortex determine memory transfer and the replay during sleep is essential for consolidation.



