

# Can traumatic memories be erased?

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BBRF Webinar • April 14, 2020

# Disclosures

- Salaried 9-month faculty member at Texas A&M University
- Research funded by NIH (R01MH117852, RO1MH065961)
- Honorarium from Elsevier as Editor-in-Chief of *Behavioural Brain Research*
- No corporate relationships or interests
- I am a basic scientist, not a clinician



# Fear..Terror..Trauma

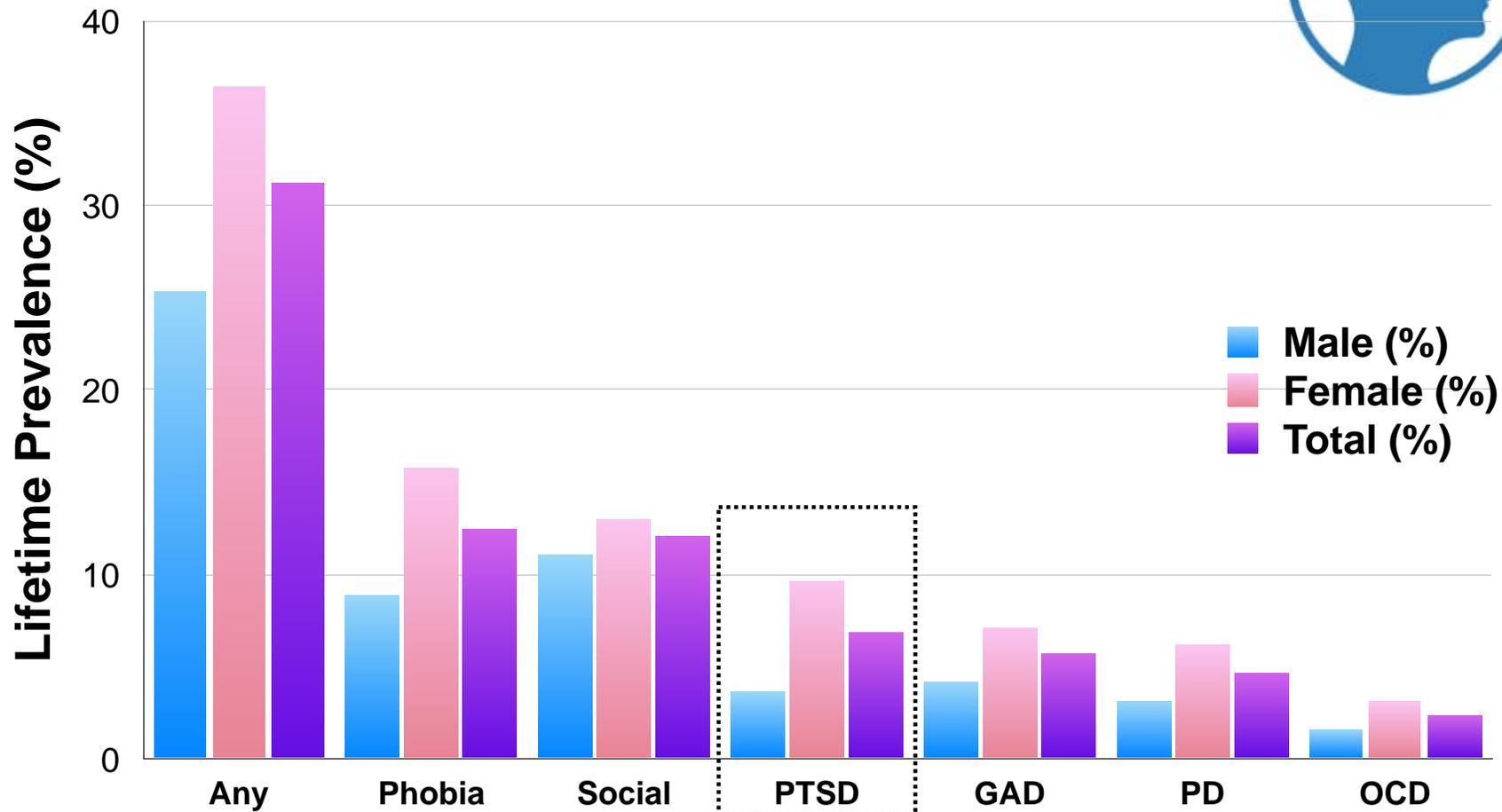
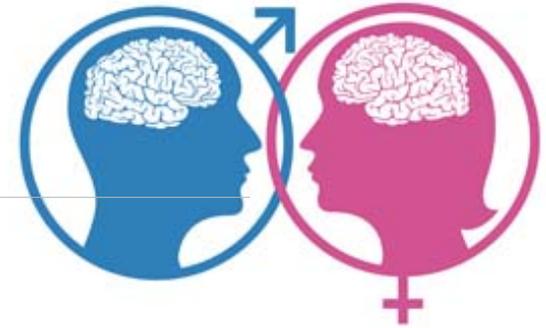


# Learning to fear

- Forming fear memories is adaptive
  - Survival depends on detecting and avoiding both new and past threats
- ...but traumatic memories can lead to psychopathology
  - post-traumatic stress disorder (PTSD)
- Anxiety disorders are most prevalent mental health disorder in world



# Prevalence of anxiety disorders



*From National Comorbidity Survey-Replication, 2001-2003.*

# Post-traumatic stress disorder (PTSD)

- PTSD is anchored to a traumatic event (i.e., a memory)
- Direct or perceived threat to life:
  - Natural disaster
  - Combat trauma or terrorist attack
  - Domestic or sexual abuse
  - Death of a loved one
  - Motor vehicle accident
  - Physical or sexual assault
  - Emergency medical crisis





# PTSD can co-occur with many disorders



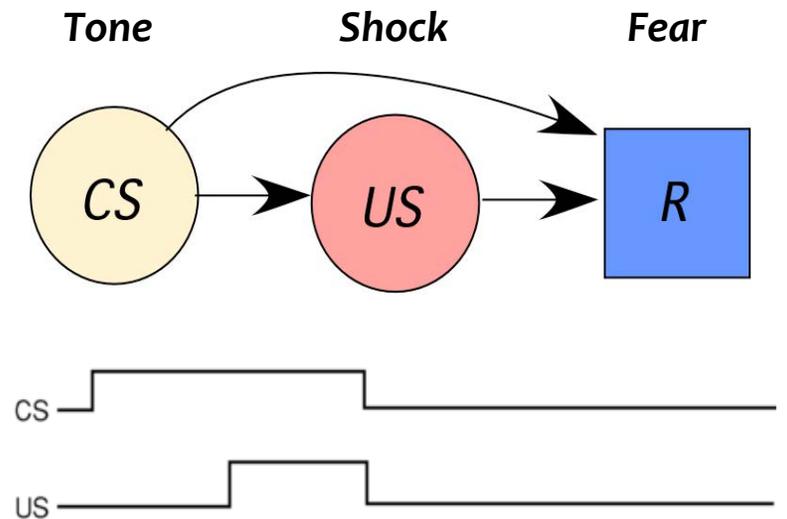
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**Bioscience**

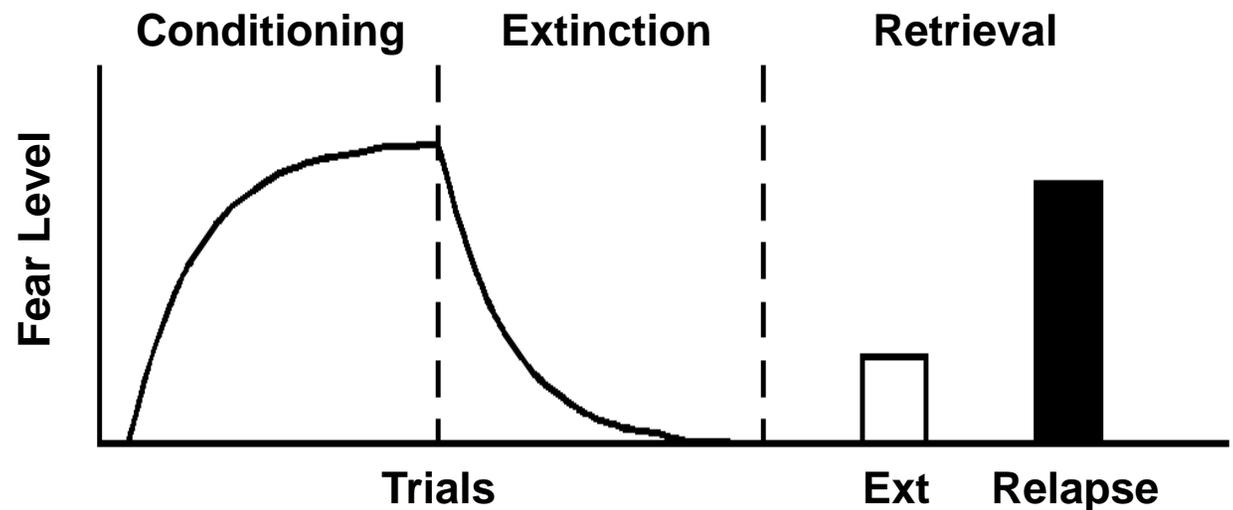
# Learning to fear: Pavlovian fear conditioning

- Fundamental form of associative learning modeling aspects of PTSD
- High level of experimental and parametric control
- Characterized in both animals and humans



# PTSD, fear conditioning, and extinction

- **Fear conditioning** (*learning*)
  - Trauma-associated stimuli evoke learned fear (*fear memory*)
- **Extinction** (*new learning*)
  - Experiencing trauma-associated cues in a safe setting reduces fear (*extinction memory*)
- **Relapse**
  - Time, stress, or context change cause fear to return



# How do you treat PTSD?

- Cognitive-behavioral therapies (CBT) generally more effective than medications
- *Prolonged exposure (PE) therapy* is an effective form of CBT
  - Repeatedly confront fears in a safe setting (*extinction procedure*)
  - Often accompanied with relaxation techniques
  - Goal is to reduce fear and other PTSD symptoms



# Extinction memories are *labile*

- Extinction *suppresses* fear memories, but....
- Fear *relapses* under a variety of conditions
- Extinction *does not erase* the fear memory...



# Extinction is not *erasure!*

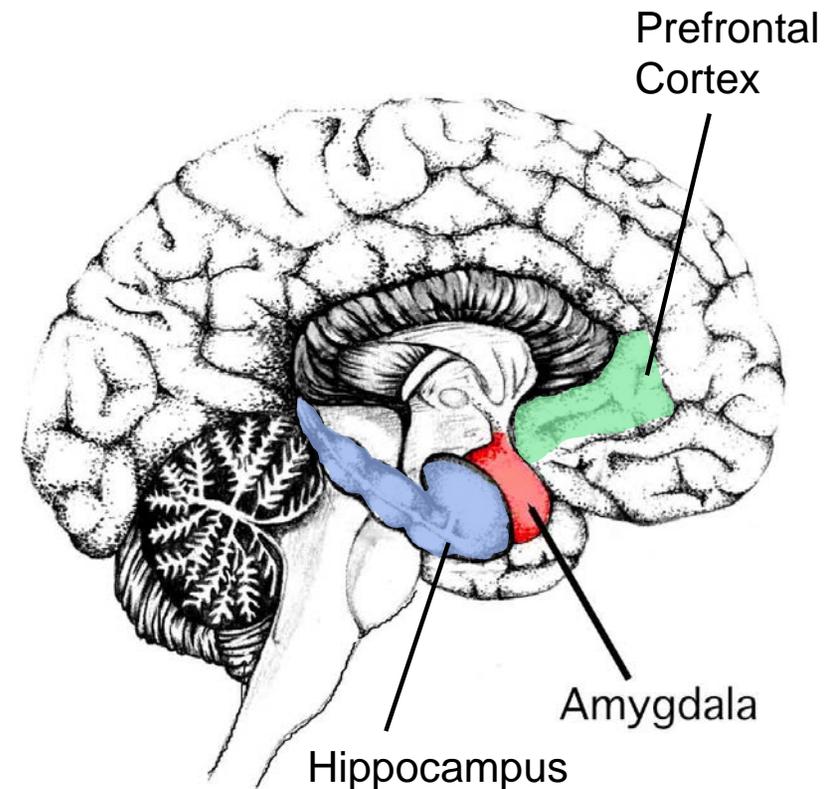
- Extinction fosters new *inhibitory* learning
- Konorski (1967): “in the course of extinction the inhibitory connections are being formed *side by side* with the totally preserved excitatory connections”



Konorski (1967). *Integrative Activity of the Brain.*

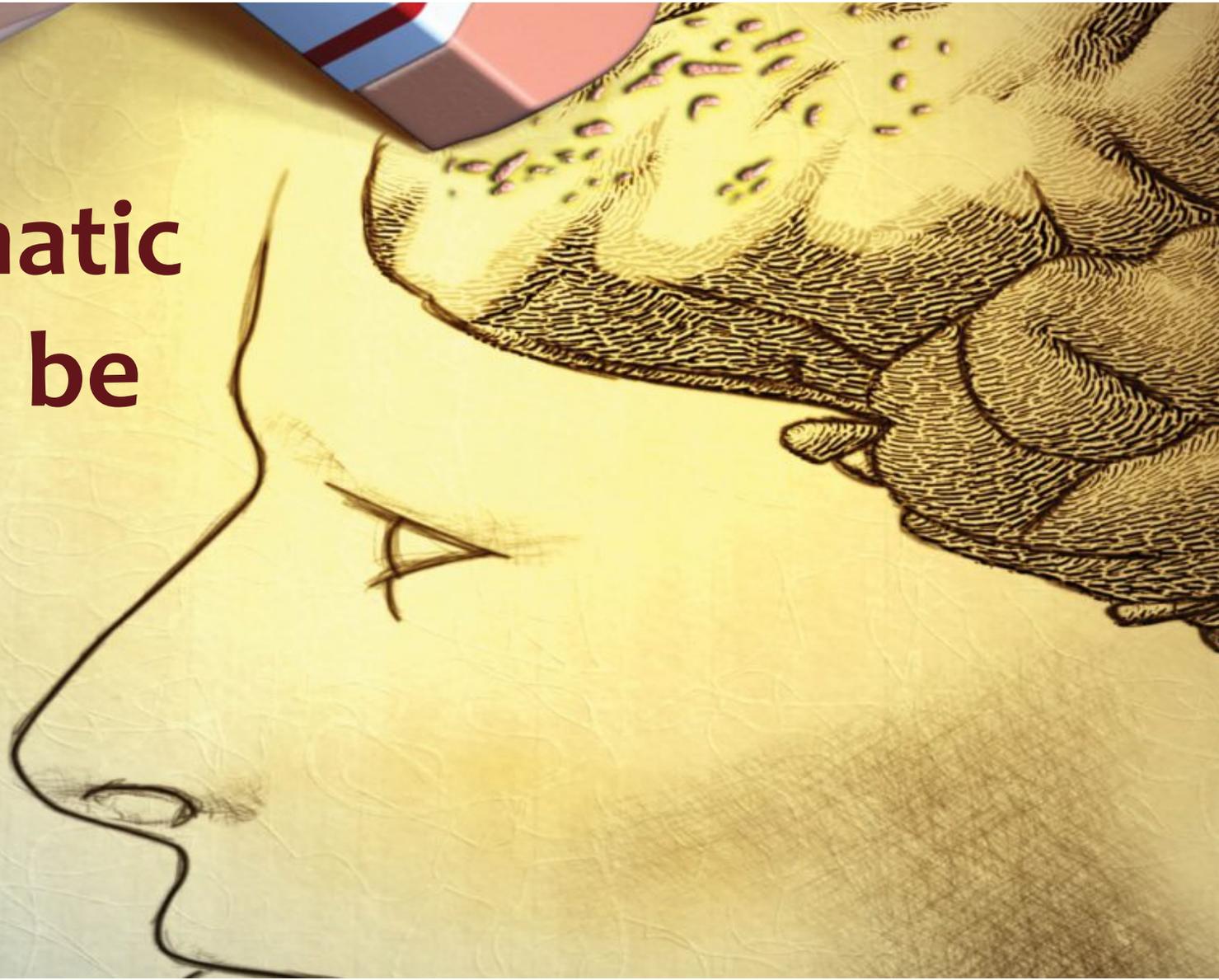
# Brain circuits for fear, extinction, and relapse

- Fear conditioning
  - Trauma memories formed in amygdala
- Extinction
  - Prefrontal cortex inhibits fear memories in the amygdala
- Context (who, what, where, when)
  - Hippocampus places memories in context and drives relapse



*Maren, Phan, Liberzon. (2013). Nature Rev Neurosci.*

**Can traumatic  
memories be  
erased?**



# Memory erasure as science fiction?

- Men in Black (1997)
  - “Neuralyzer” used to wipe memories of alien encounters



# Memory erasure as science fiction?

- Eternal Sunshine of the Spotless Mind (2004)
  - Couple in a soured relationship has memories of each other erased



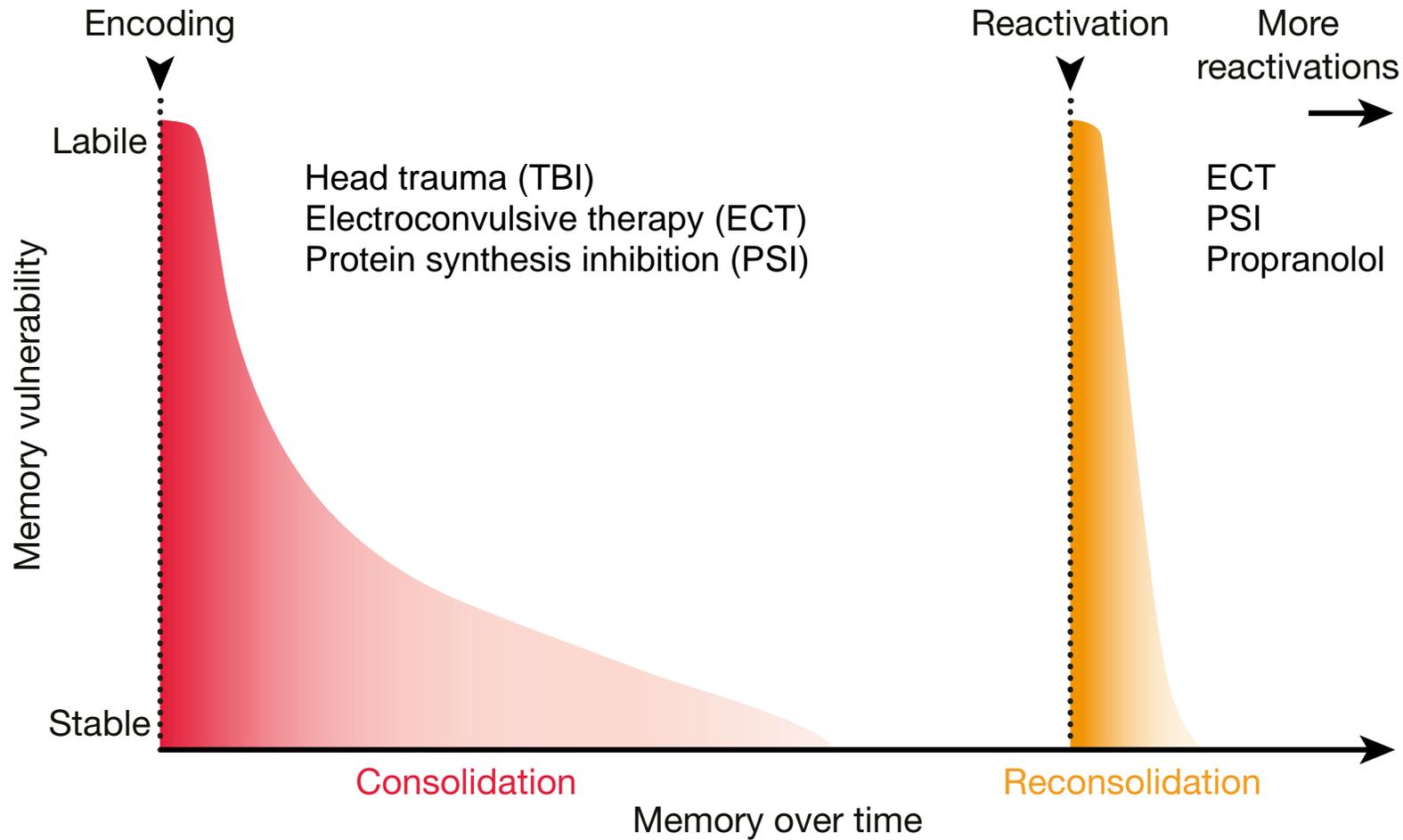
## Memory editing from science fiction to clinical practice

Elizabeth A. Phelps<sup>1,2\*</sup> & Stefan G. Hofmann<sup>3</sup>



Science fiction notions of altering problematic memories are starting to become reality as techniques emerge through which unique memories can be edited. Here we review memory-editing research with a focus on improving the treatment of psychopathology. Studies highlight two windows of memory vulnerability: initial storage, or consolidation; and re-storage after retrieval, or reconsolidation. Techniques have been identified that can modify memories at each stage, but translating these methods from animal models to humans has been challenging and implementation into clinical therapies has produced inconsistent benefits. The science of memory editing is more complicated and nuanced than fiction, but its rapid development holds promise for future applications.

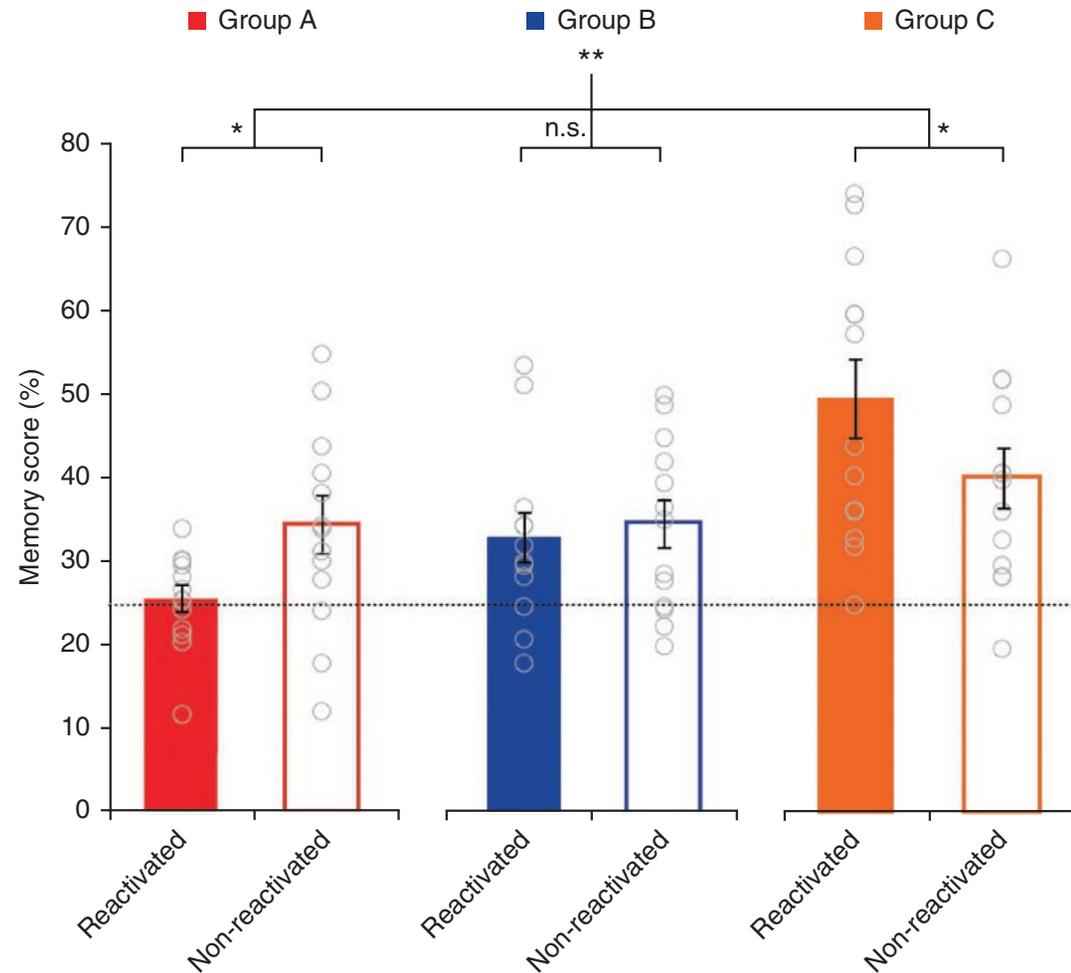
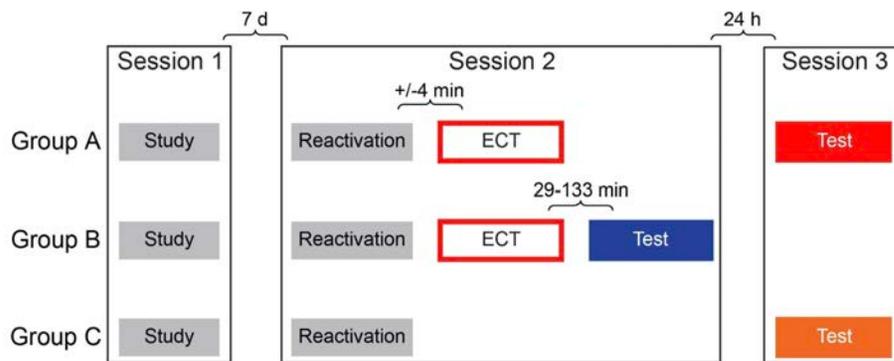
# Windows to edit (erase?) memory



Phelps and Hofman (2019)

# Disrupting reconsolidation in humans

- Patients underwent ECT for monopolar depression
- ECT delivered after reactivation of an emotional story learned 1 week earlier



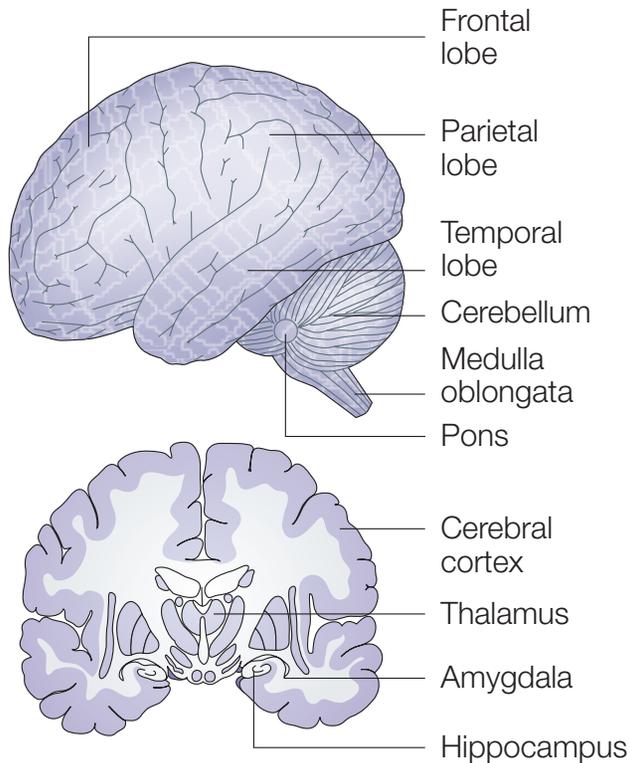
# Selectively targeting memories in brain



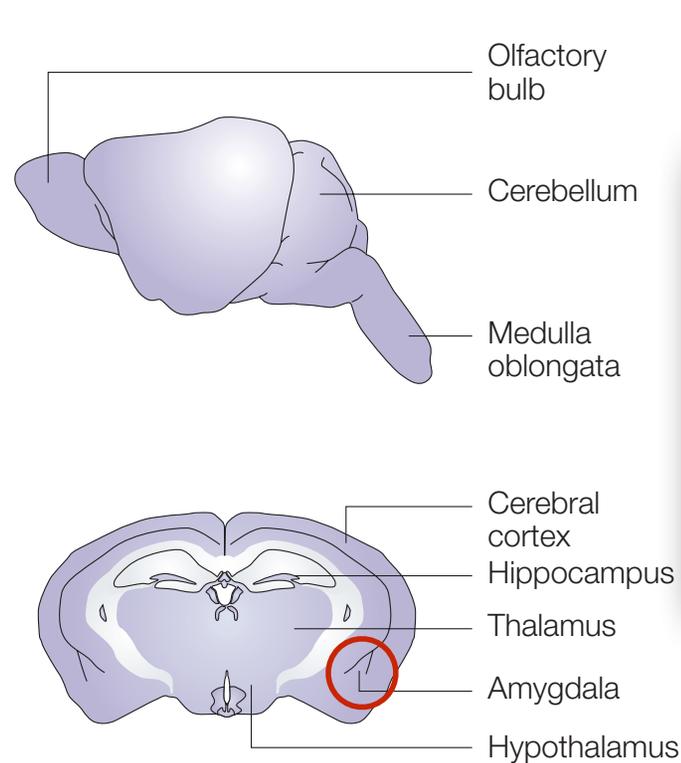
# Erasing a memory trace

- Josselyn & Frankland target fear memories in mouse amygdala

Human brain



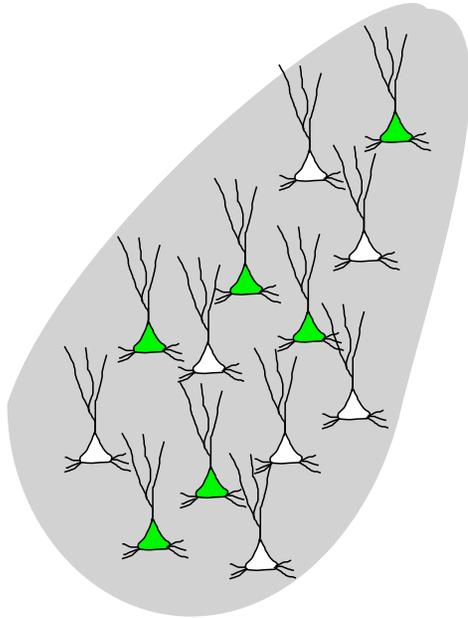
Mouse brain



Han et al. (2009). *Science*

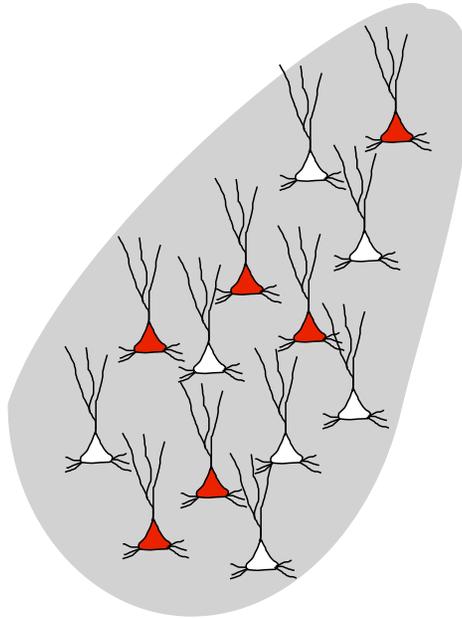
# Erasing a memory trace

Capture memory neurons during learning



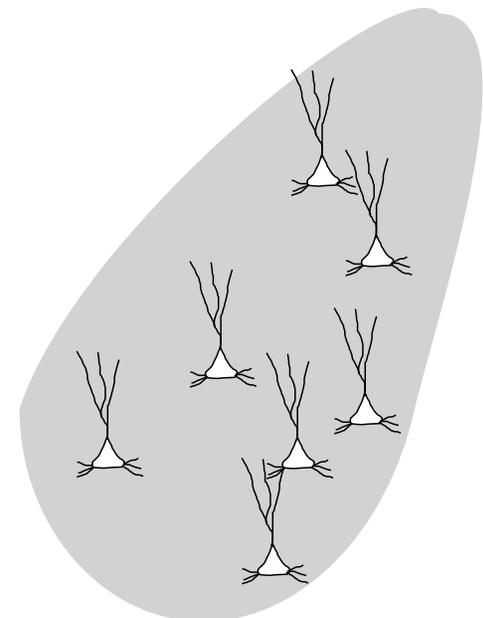
▲ Memory neuron

After learning, inject toxin to kill memory neurons



▲ Targeted with toxin

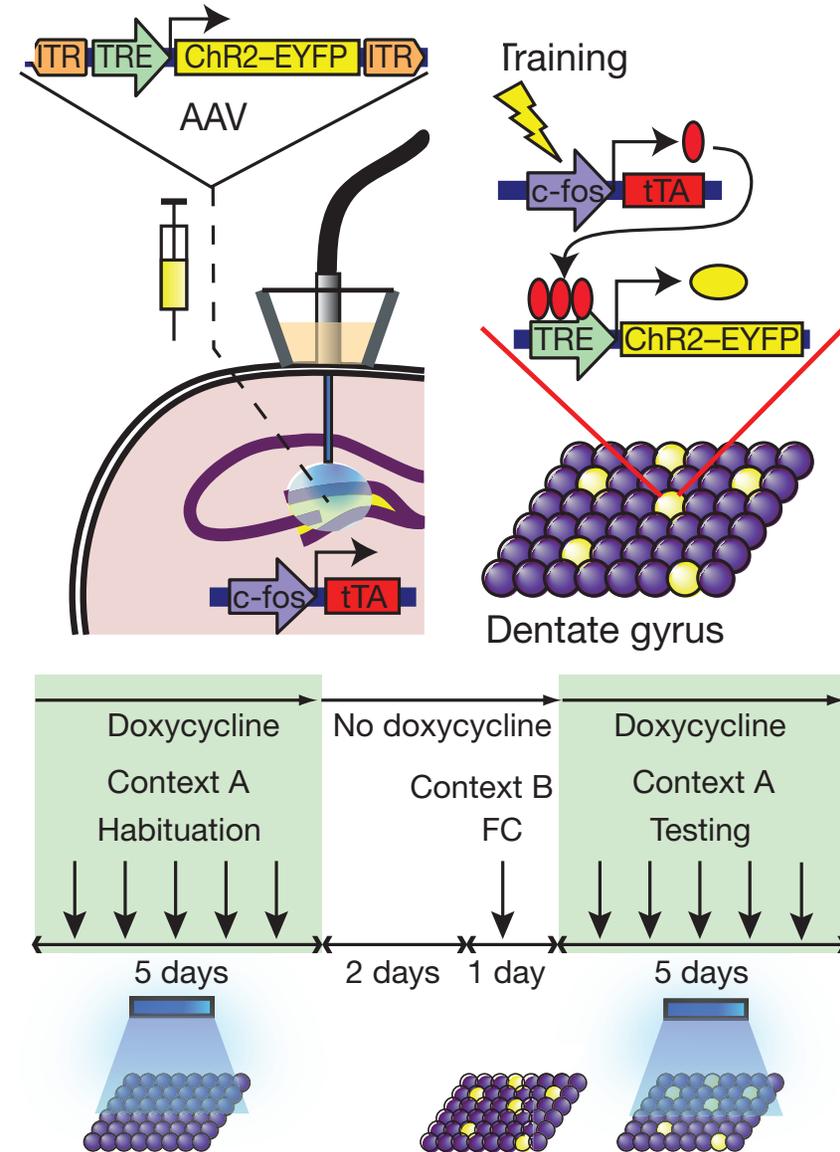
Fear memory erased



Memory neurons deleted

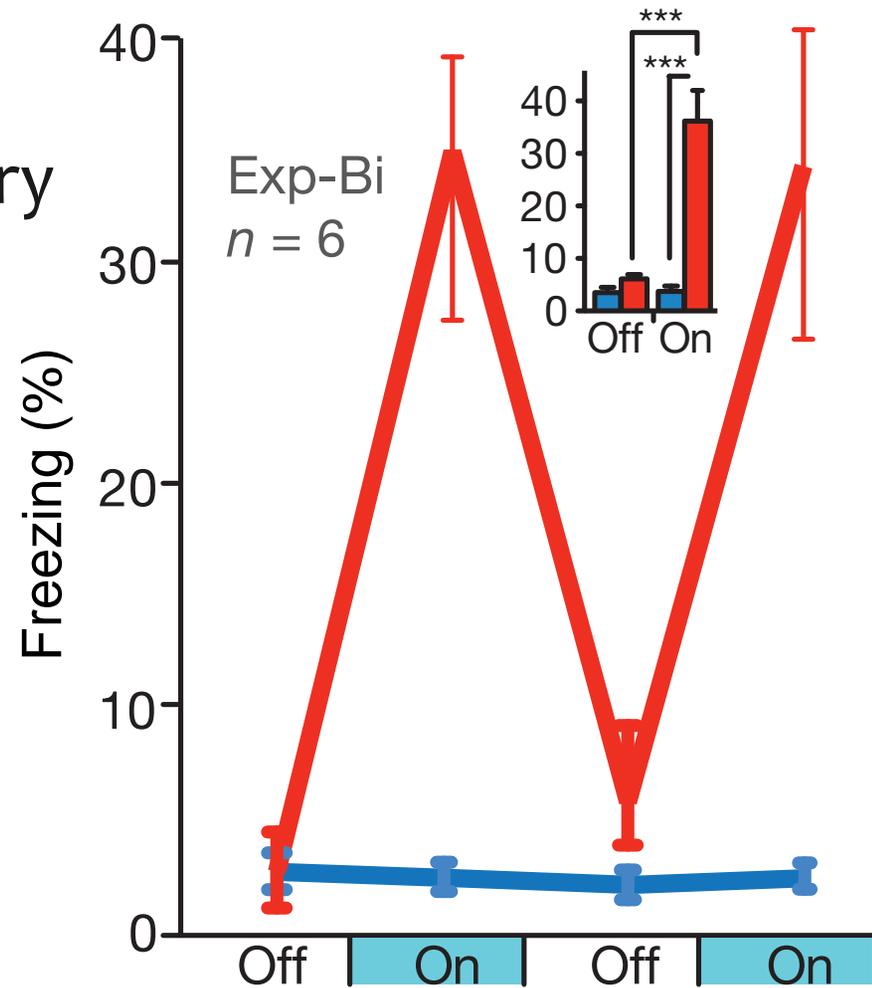
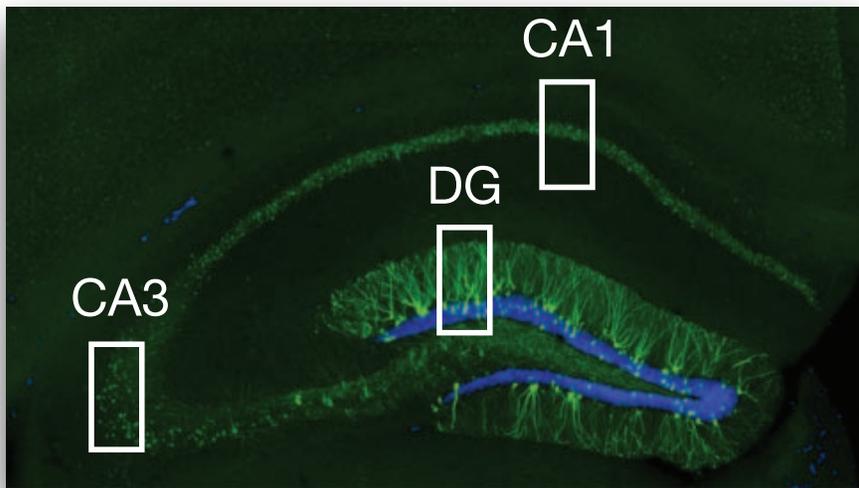
# Reactivating memories

- Tonegawa lab captures memory neurons during fear conditioning



# Reactivating memories

- Liu and Tonegawa capture memory neurons during fear conditioning
- Optical reactivation of neurons produces fear



Liu, Ramirez...Tonegawa (2012). Nature

# Capturing engrams

- Activity-dependent tagging typically performed during *learning*
- Includes both sensory representations of context and shock and associations between the two
- ***Can memories be captured during retrieval?***



# Capturing memories during retrieval

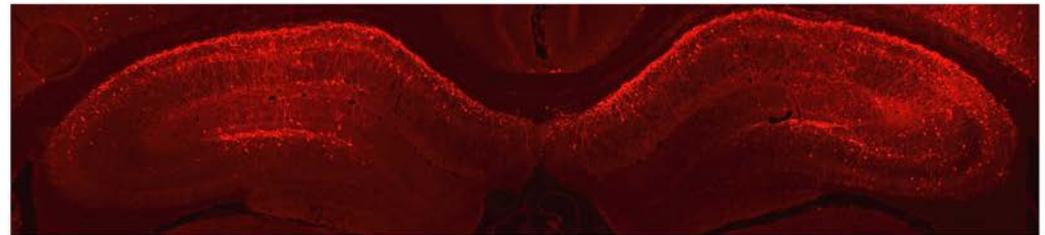
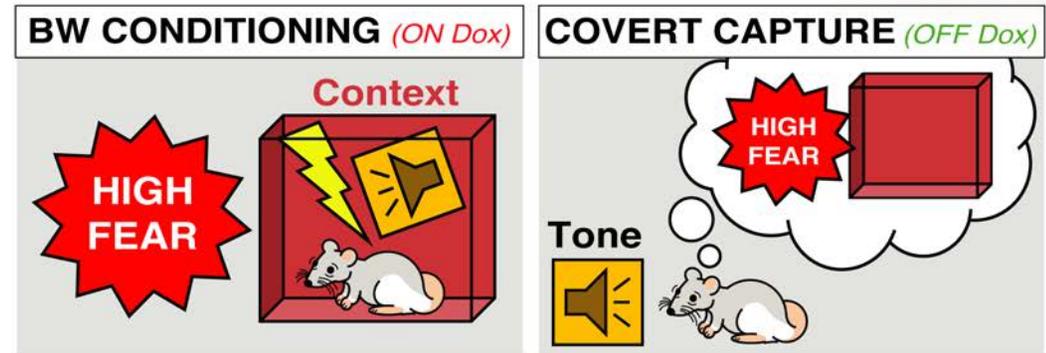
- Normal memory recollection driven by retrieval cues
- Clinical therapies use retrieval cues (“imaginal exposure”) to reactivate remote traumatic memories
- *Can fear memories be retrieved and captured with “imaginal” cues?*



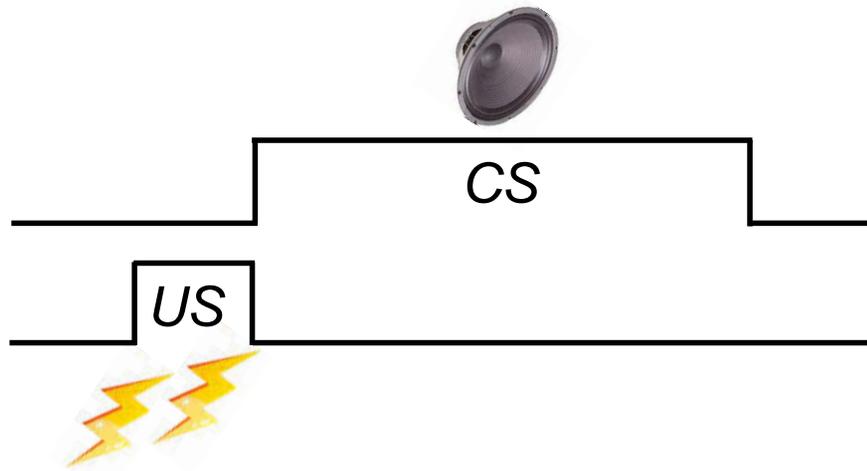
# “Covert capture” of a fear memory



- Capture hippocampal neurons activated by “imaginal” fear memory retrieval
- Re-activate neurons with a systemic drug (CNO)
- Does activating captured neurons cause fear?

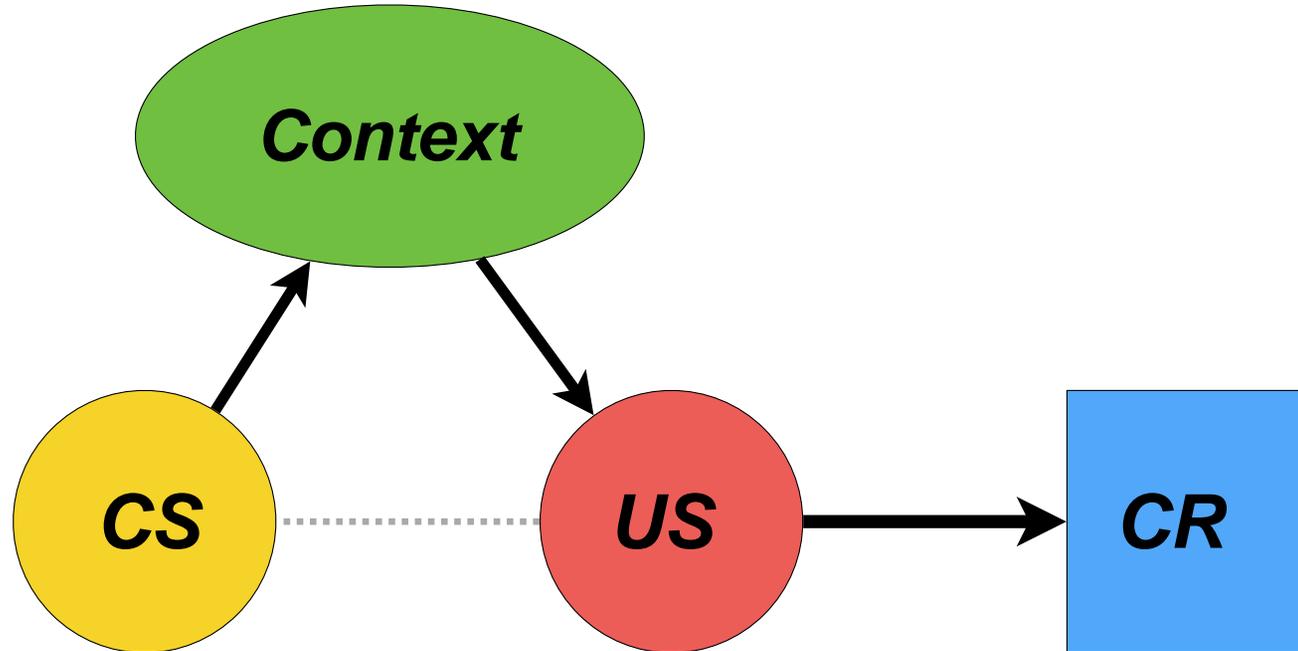


# Backward fear conditioning

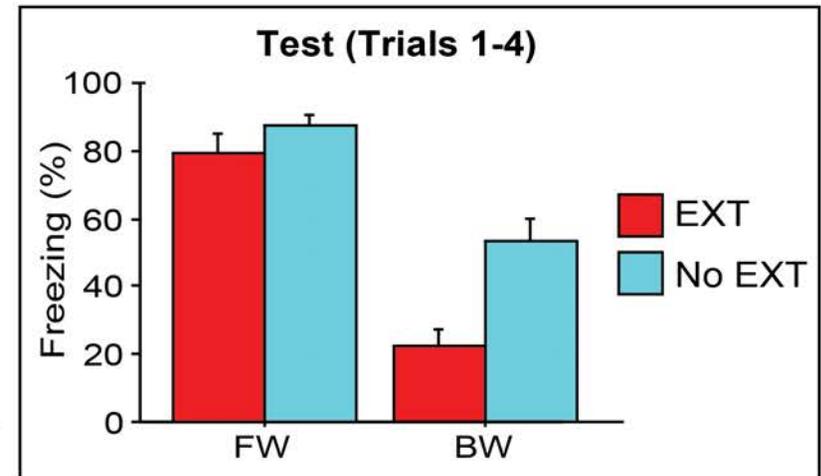
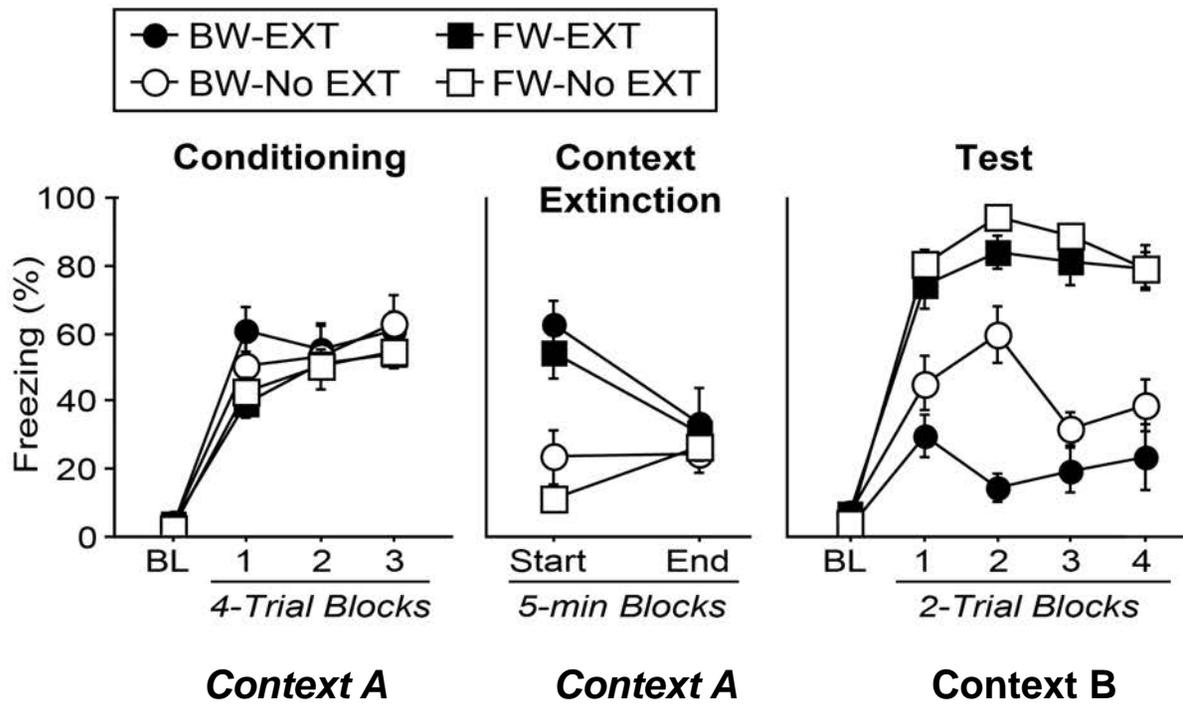


**Fear to CS without  
CS->US association**

# Backward fear conditioning: mediation by context

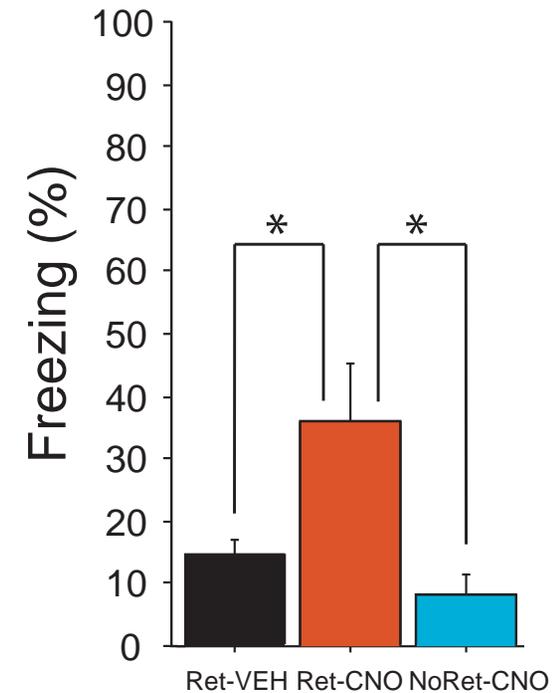
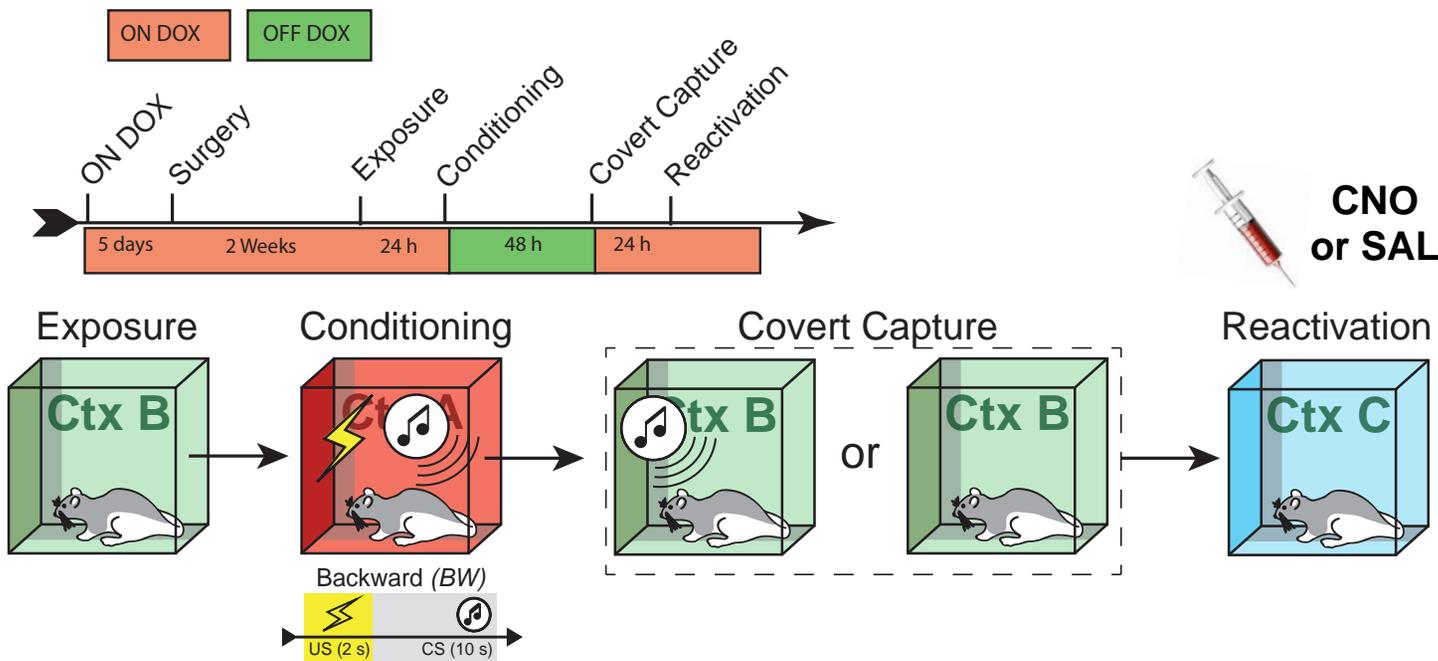


# Context extinction reduces freezing to a backward CS



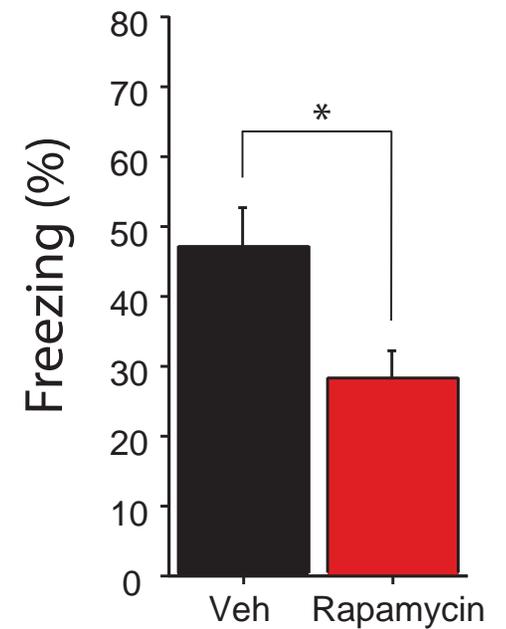
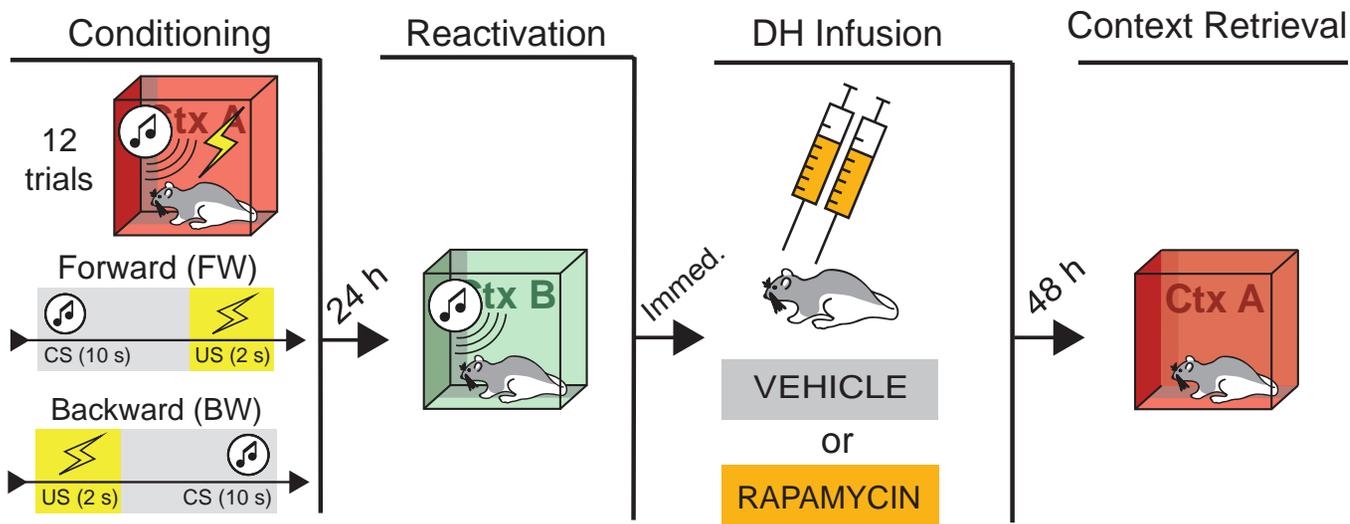
Goode, Ressler and Maren, unpub.

# Capture and reactivation of a fear memory



Ressler and Maren, unpub.

# Rapamycin impairs reconsolidation



*Ressler, Goode and Maren, unpub.*

# Cautions, caveats, and questions

- Manipulations that cause amnesia often induce retrieval failure, not true erasure
  - “Forgotten, but not gone”
  - Prior work has not demonstrated that memory loss is complete or permanent (savings?)
- Memory is highly associative, can a memory truly be “selectively” erased?
- Is memory erasure ethical?
  - What are we (as individuals or as a culture) without memories of the past, good or bad?



# Conclusions

- Exposure therapy does not erase traumatic memories (relapse)
- Retrieved/reactivated memories are susceptible to disruption
- Modern tools allow selective targeting and manipulation of *engrams* (neural representations of memory)
- Translation to clinic must proceed with cautions and caveats in mind



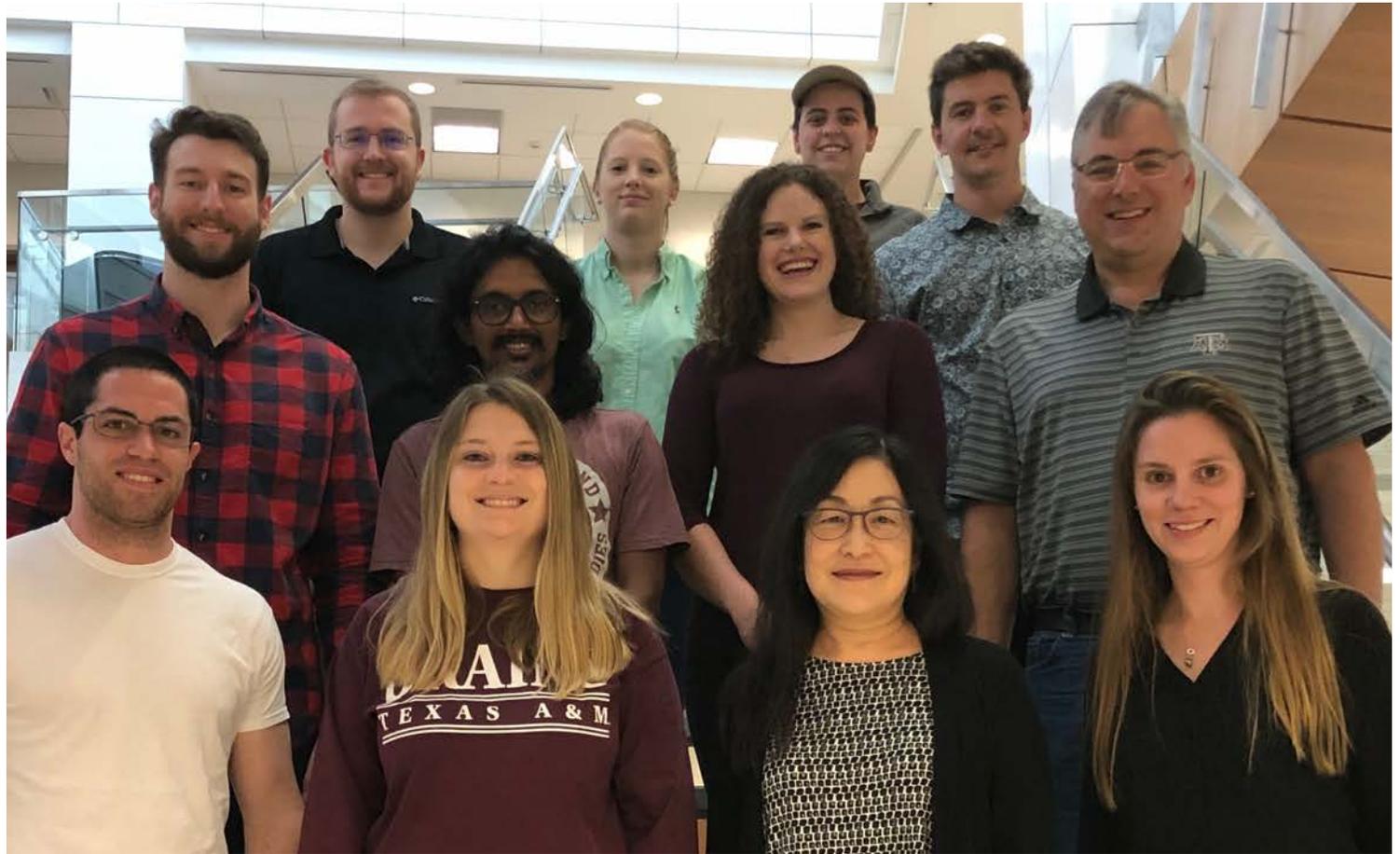
# Thanks!

## **Current:**

Annalise Binette  
Laila Dayani  
Michael Totty  
Olivia Miles  
Jianfeng Liu  
Cecily Oleksiak  
Karthik Ramanathan  
Reed Ressler

## **Past:**

Jingji Jin  
Tom Giustino  
Travis Goode  
Paul Fitzgerald  
Martin Payne  
Angie Wang



Collaborators: Susumu Tonegawa and Dheeraj Roy (MIT)

