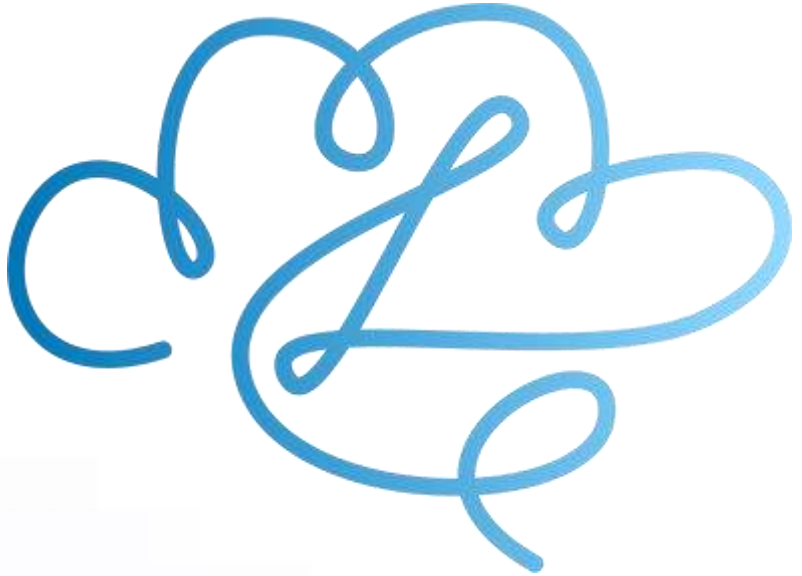
How Does a Fearful Experience Alter Our Past Memories



Denise J. Cai, PhD
Associate Professor
Department of Neuroscience
Mount Sinai

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CAI LAB

@denisejcai
@MiniscopeTeam

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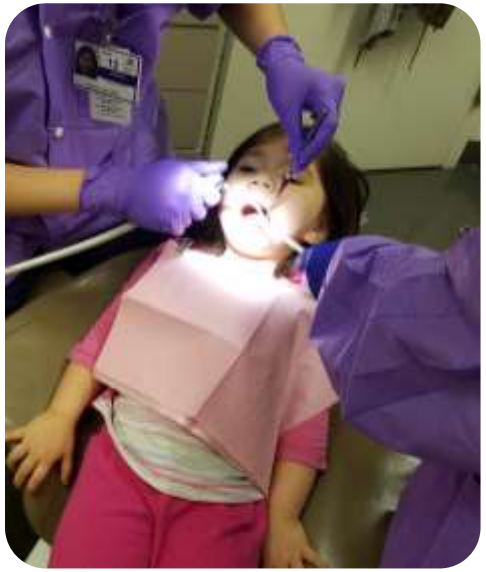
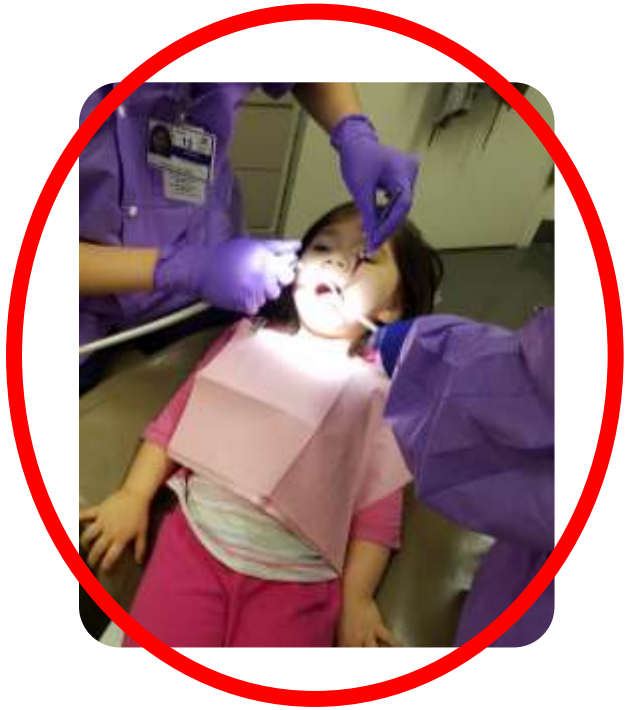
Icahn School of Medicine at Mount Sinai

Memories define our human experience



How are aversive memories stored in the brain?



Why study how trauma memories are stored?

The majority of the population will experience a traumatic event at one point in their lives:

- Military trauma
- Sexual assault
- Child abuse
- Vehicular accidents
- Natural disasters
- Covid-19
- The list goes on ….

Consequences on psychiatric function are widespread:

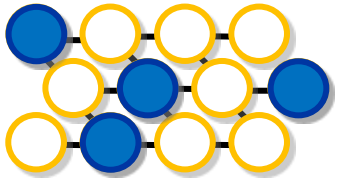
- Post-traumatic stress disorder (PTSD)
- Anxiety and depression
- Substance dependence

Why is mental health research important to me?

How are memories stored in the brain?

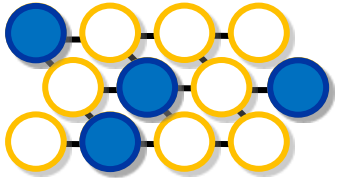
Memory Encoding

Neuronal Ensemble



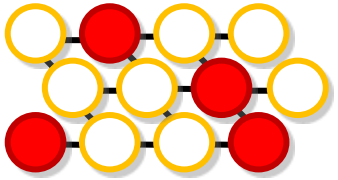
Memory Recall

Neuronal Ensemble



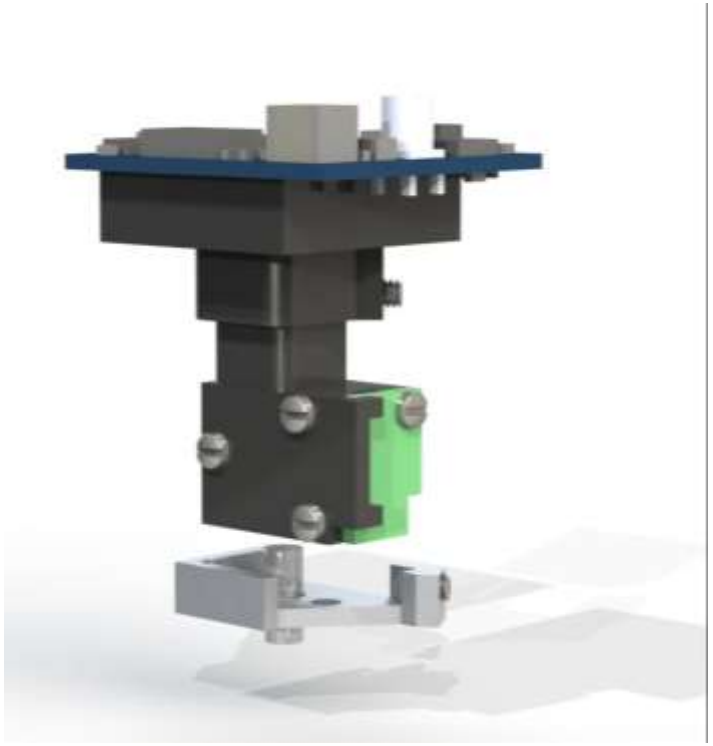
Recall Different Memory

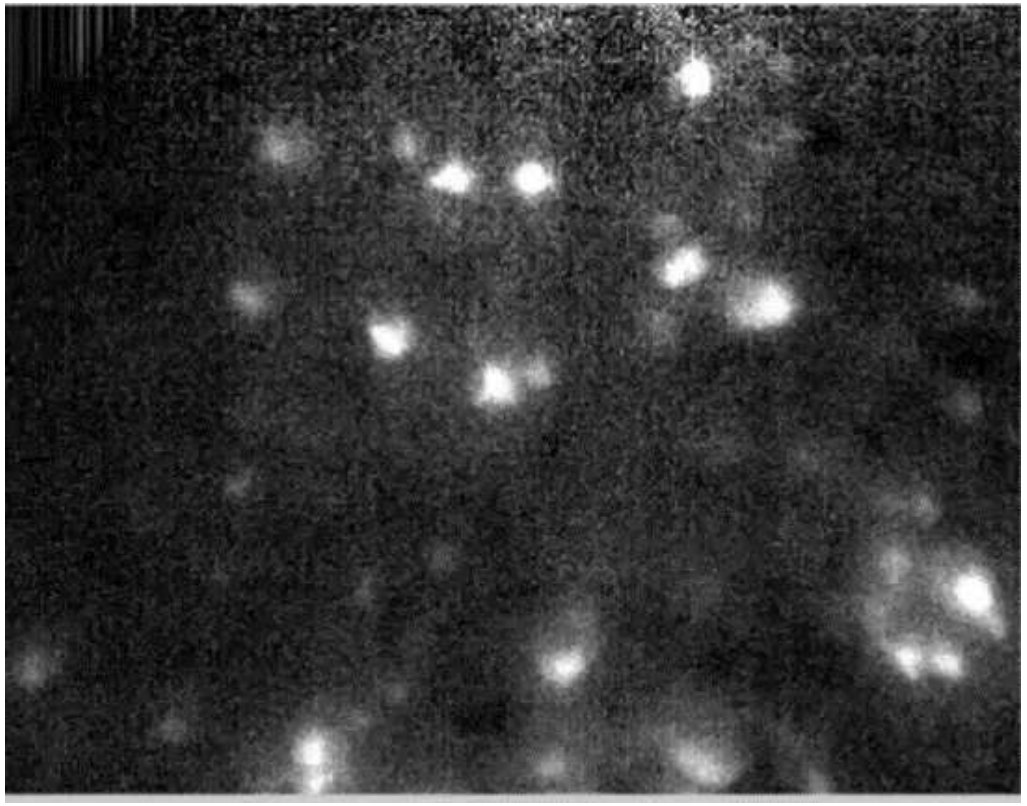
Neuronal Ensemble



Memory Cell

Peering into the awake and active brain…



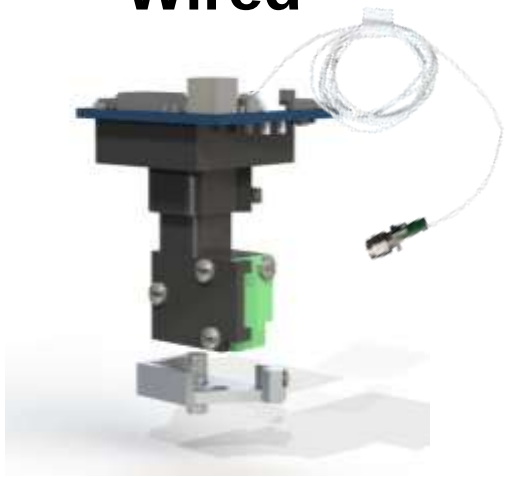


Open-Source Miniscopes (UCLA)

Cai, Aharoni, Shuman, Shobe et al., *Nature*, 2016

Sharing open-source neurotechnology globally

Wired



Cai, Aharoni, Shuman, Shobe et al., *Nature*, 2016

Wire-free

Shuman, Aharoni, Cai et al., *Nature Neuroscience,* 2020

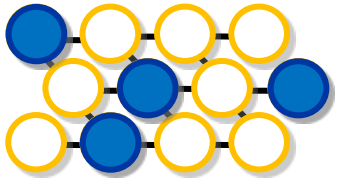
- Wiki: www.miniscope.org
- 4,300+ registered Wiki users
- 2,400+ Miniscopes built
- 550+ labs building scopes
- 1 Miniscope system ~$2,000
- Discussion board/Google group
- Hands-on workshops (1,000+ participants)

Alcino Silva, Peyman Golshani, **Daniel Aharoni**, Tristan Shuman

Memories are encoded in neuronal ensembles

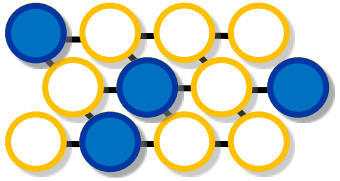
Memory Encoding

Neuronal Ensemble



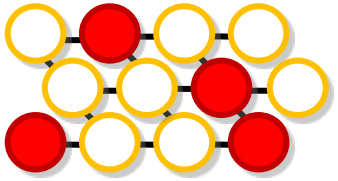
Memory Recall

Neuronal Ensemble



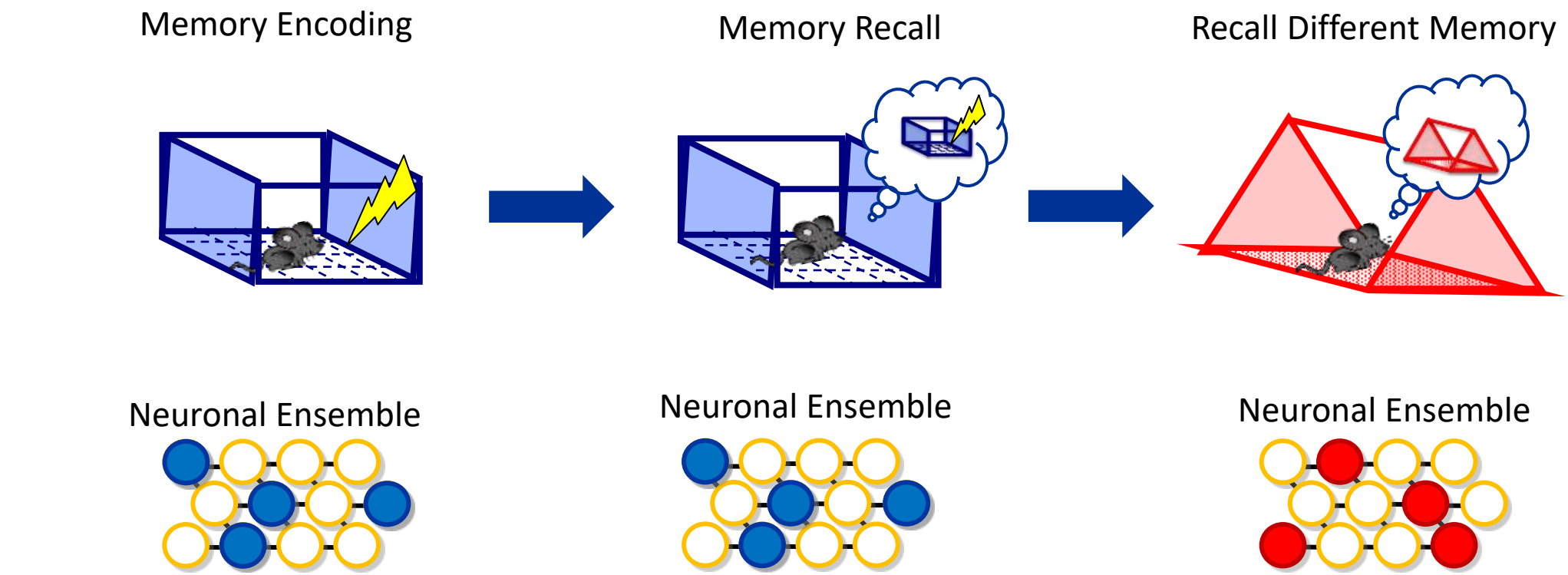
Recall Different Memory

Neuronal Ensemble



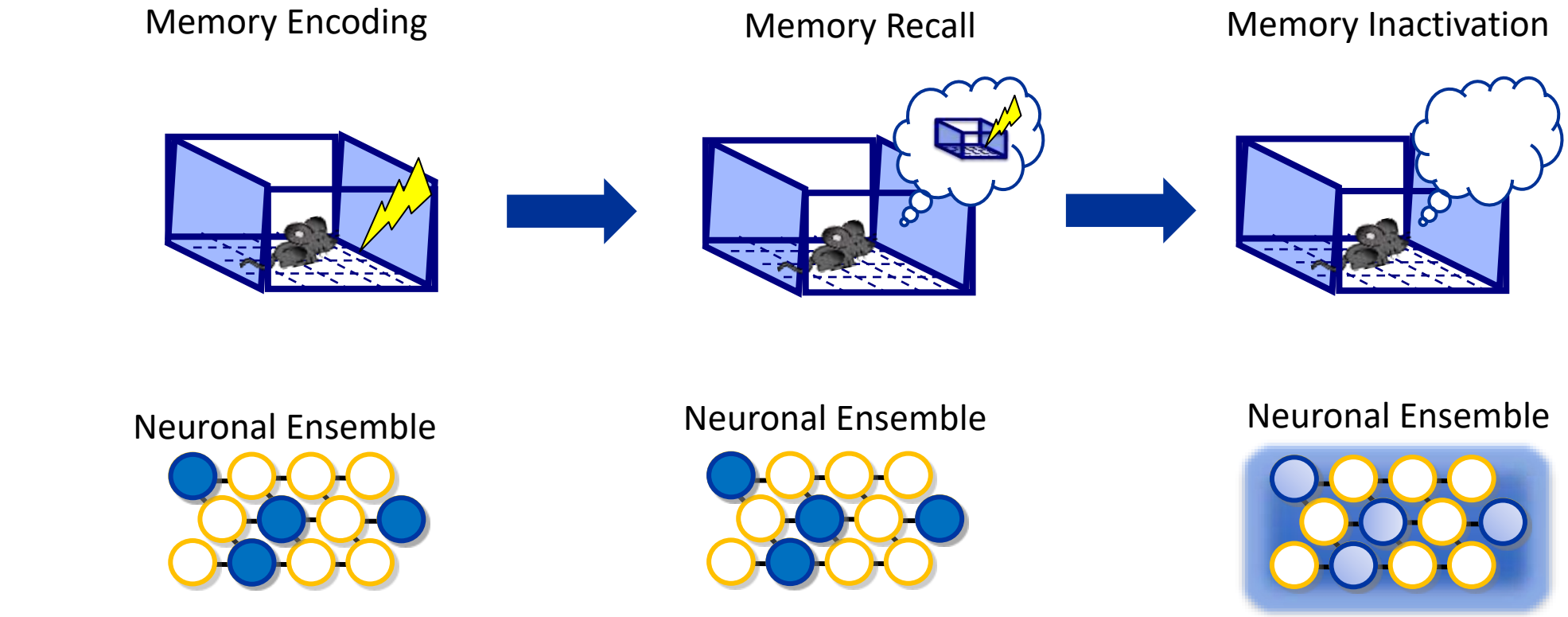
Memory Cell

How to “see” memories in the brain?



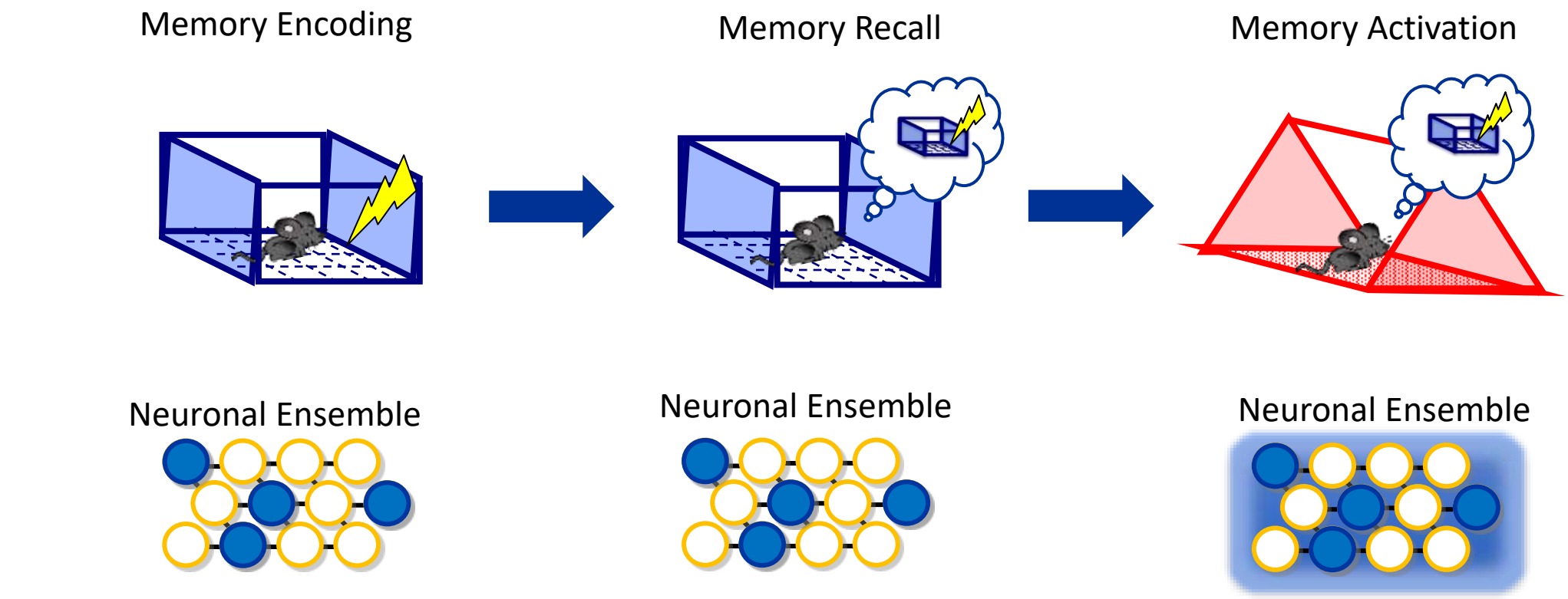
Guzowski et al., *Nat Neuro* 1999; Reijmers et al., *Science* 2007; Deng et al., *eLife* 2013, Cai et al., *Nature* 2016

Erase aversive memories?



Han et al., *Science* 2007; Zhou et al., *Nat Neuro* 2009; Denny et al., *Neuron* 2014

Artificially activate memories?



Liu et al., *Nature* 2012; Yiu et al., *Neuron* 2014; Ramirez et al., *Nature* 2015; Roy et al., *Nature* 2016; Vetere et al., *Nature Neuro* 2019

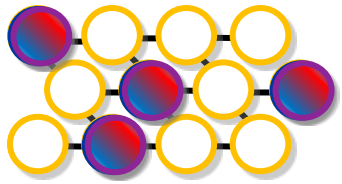
How are related memories linked in the brain?

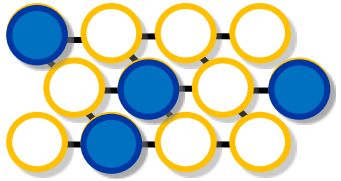
How are aversive memories linked with other memories?

Sugary raspberry gimlets

time

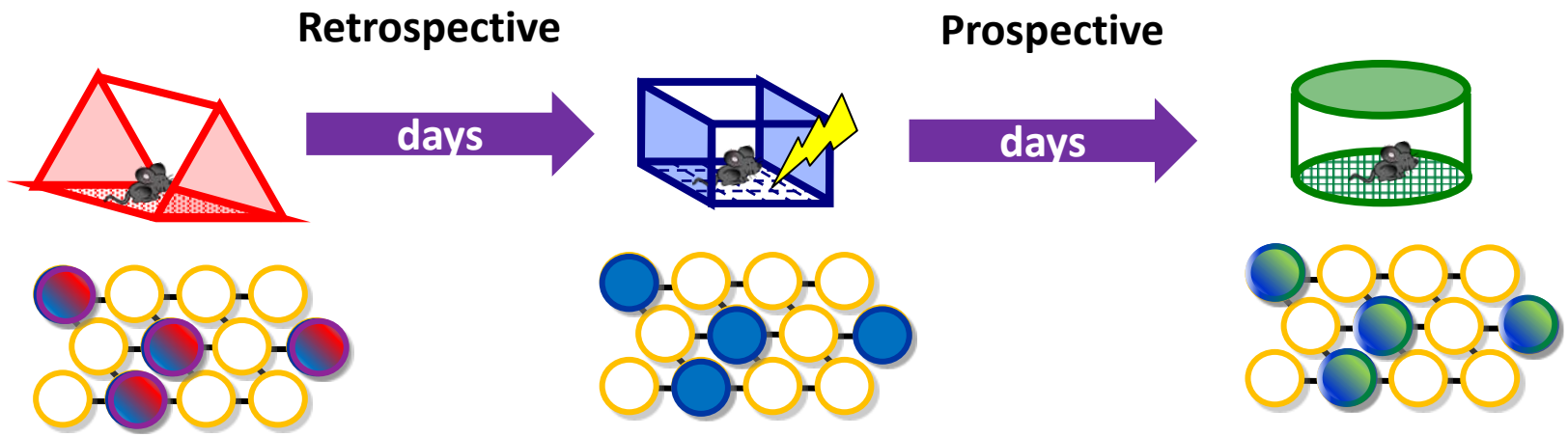
Filling cavities at dentist



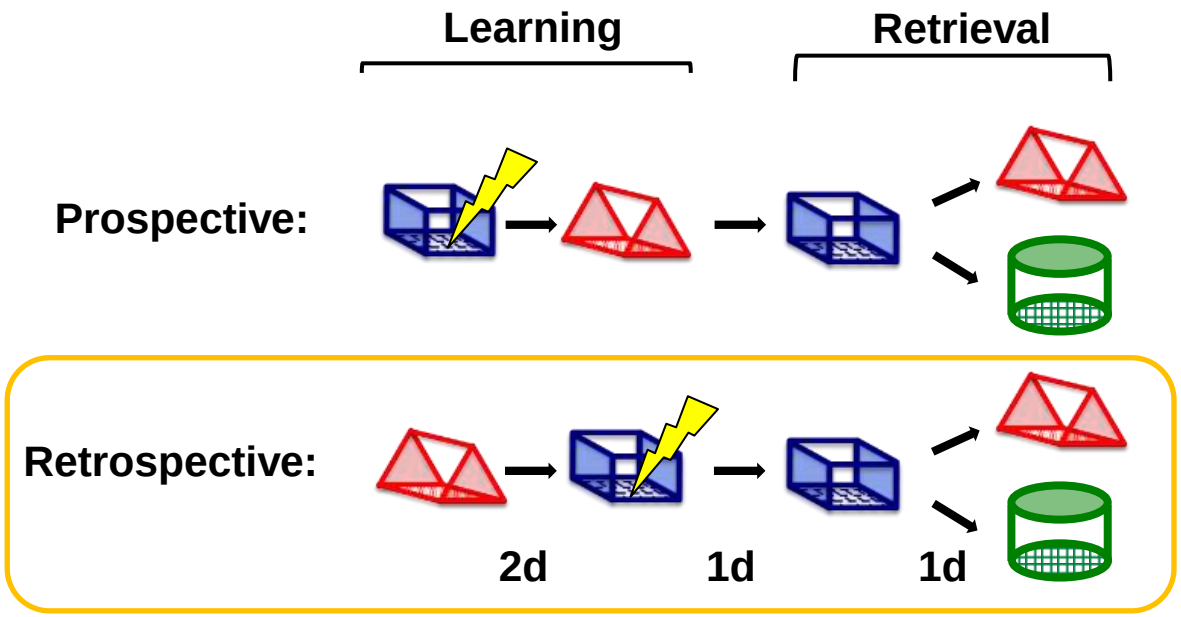


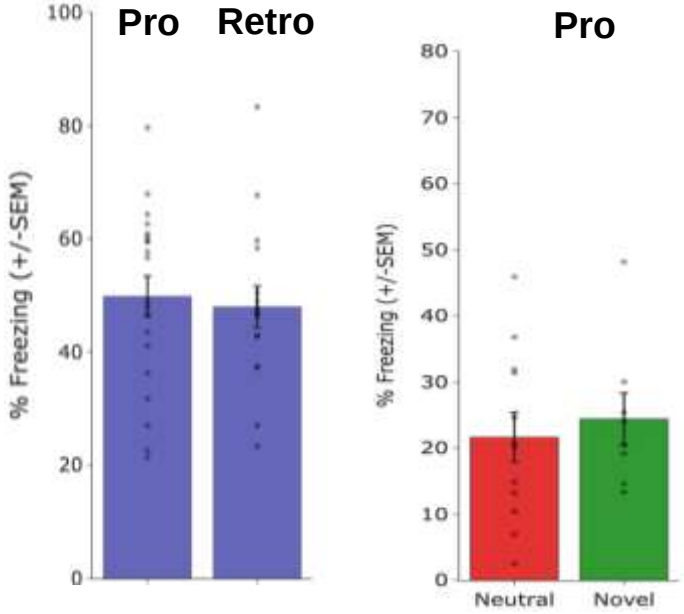
Linking the present to the past
to predict future outcomes

How are aversive memories linked with other memories?



Aversive event is linked to prior neutral memory





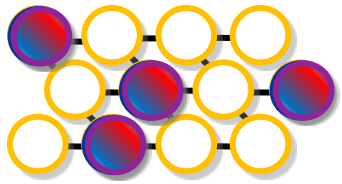
Yosif (Joe) Zaki, Denisse Morales-Rodriguez, Taylor Francisco

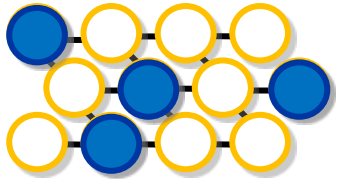
Why link memories retrospectively?

Sugary raspberry gimlets

time

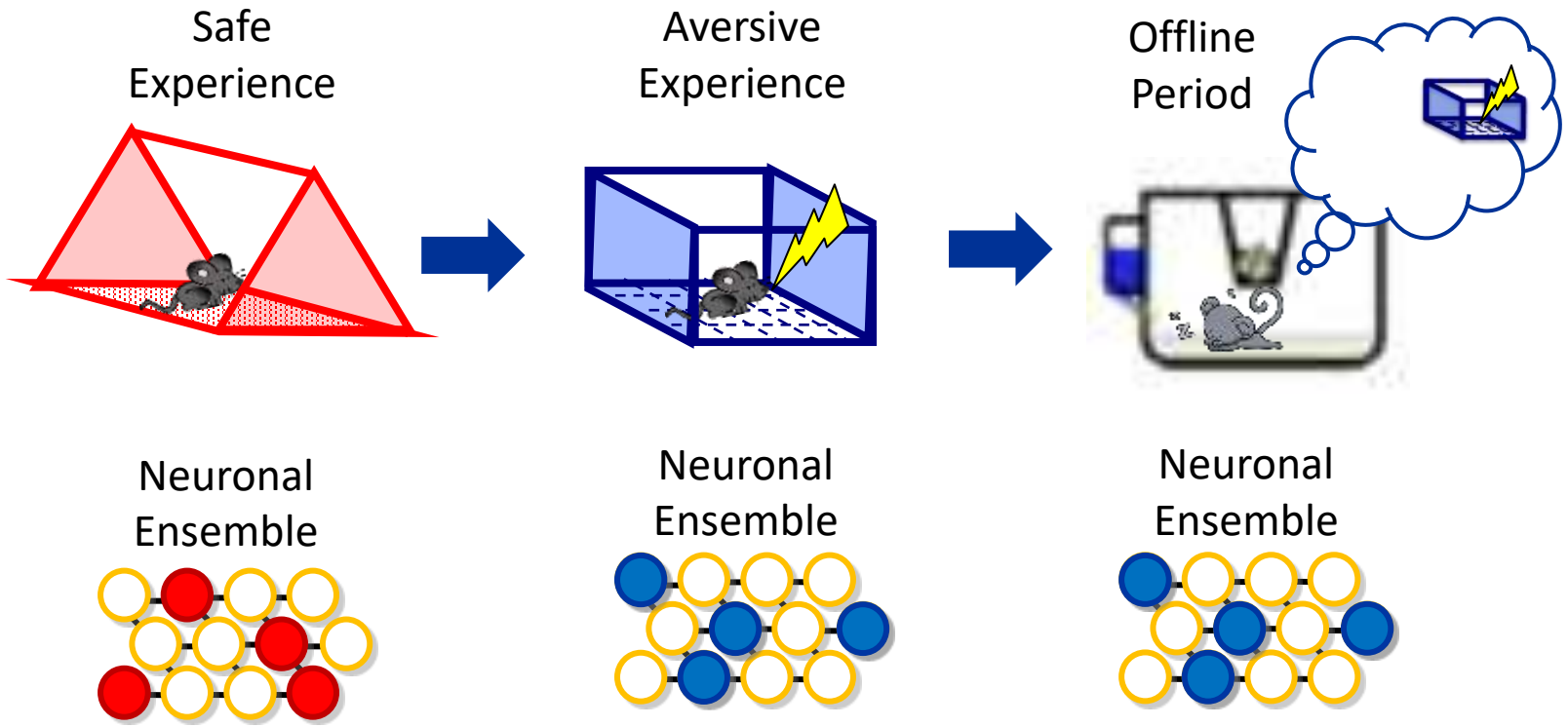
Filling cavities at dentist





Linking the present to the past
to predict future outcomes

How are aversive events linked with prior memories?



Ji & Wilson, *Nature Neuro*, 2006, Cai et al., *PNAS*, 2009, Cai et al., *Beh Neuro*, 2009, Jezek et al., *Plos Bio*, 2010

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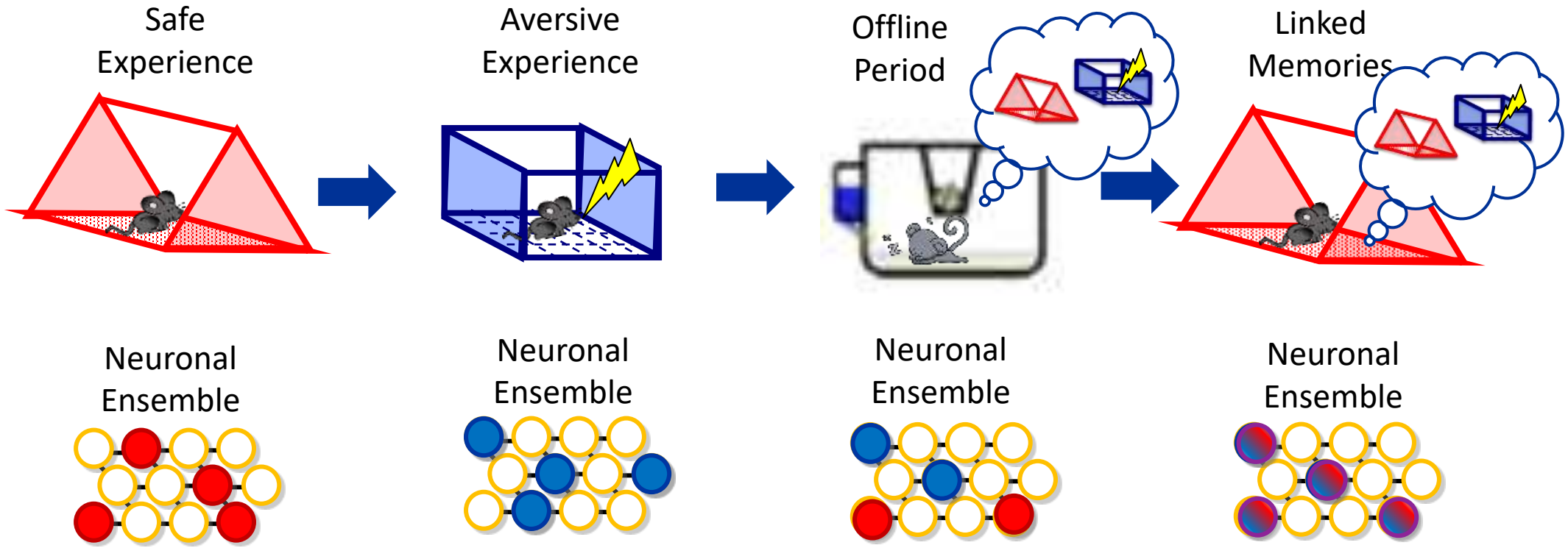
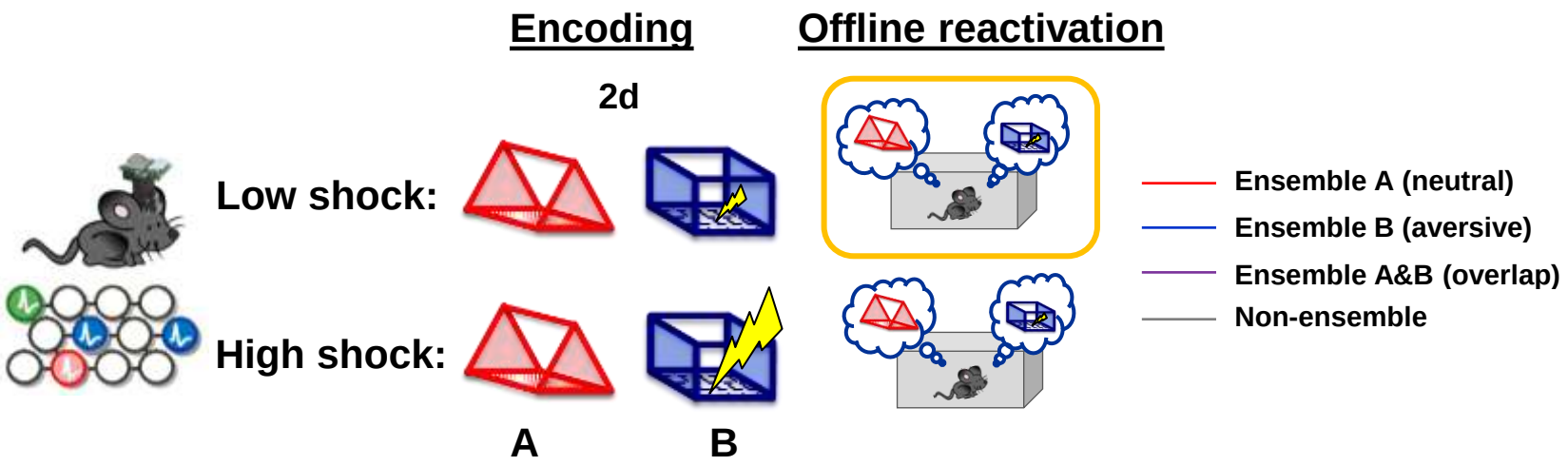


Ji & Wilson, *Nature Neuro*, 2006, Cai et al., *PNAS*, 2009, Cai et al., *Beh Neuro*, 2009, Jezek et al., *Plos Bio*, 2010

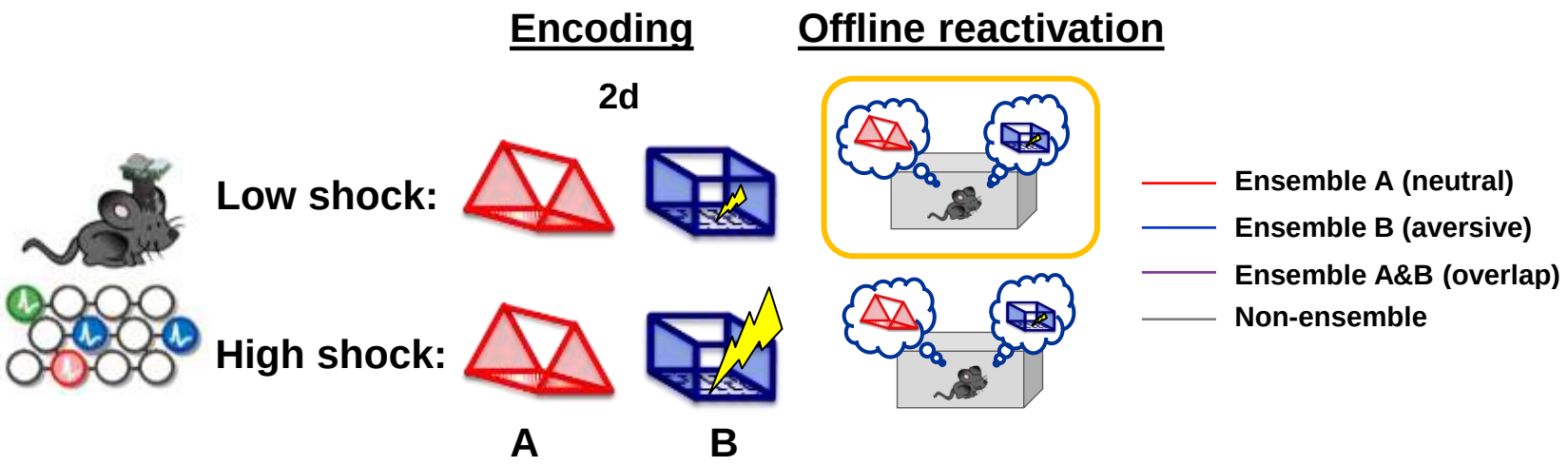
Does negative valence increase ensemble reactivation of past memories?

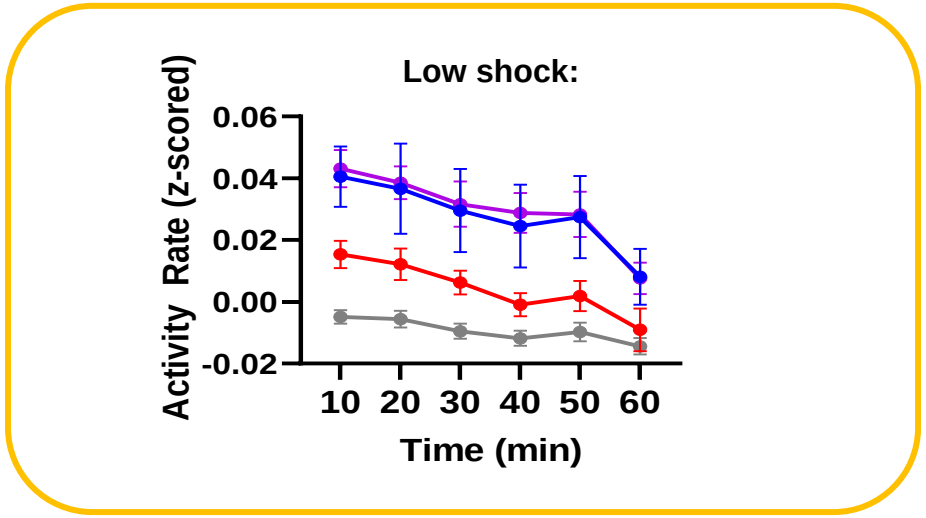


Low shock:

Yosif (Joe) Zaki

Does negative valence increase ensemble reactivation of past memories?





Yosif (Joe) Zaki

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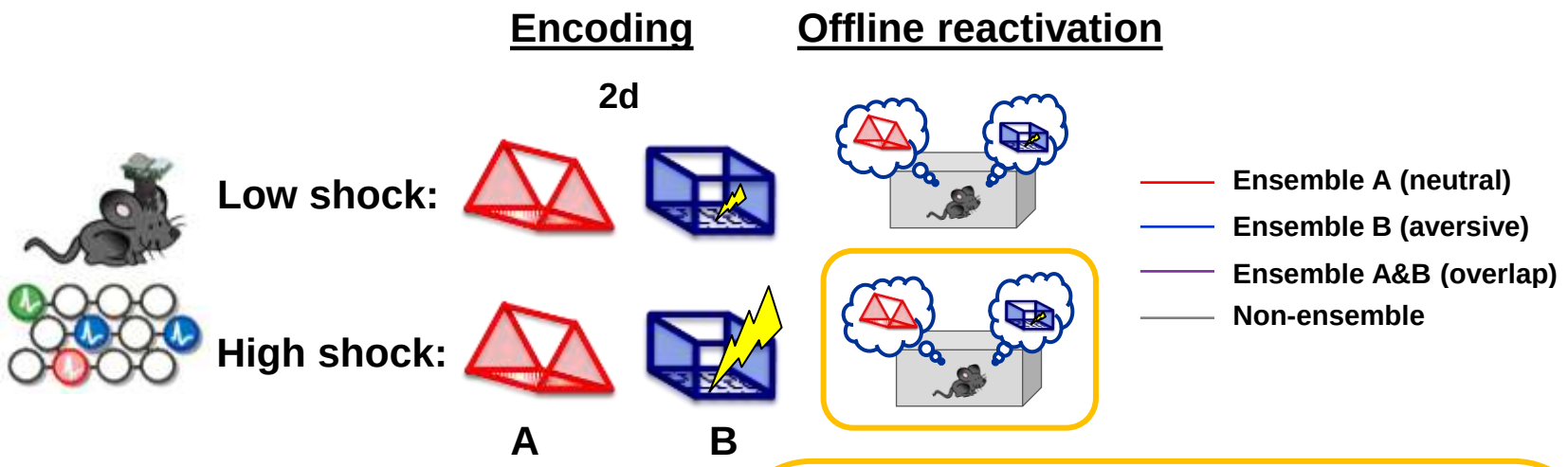
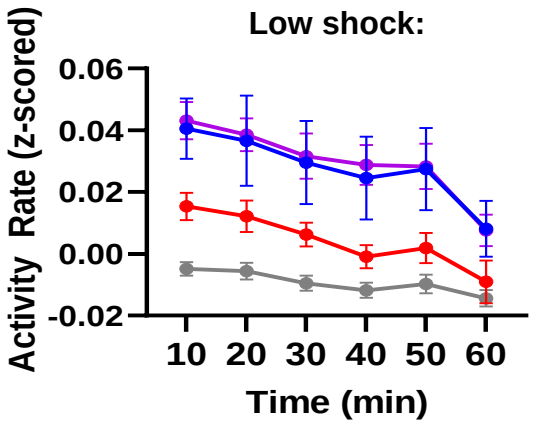
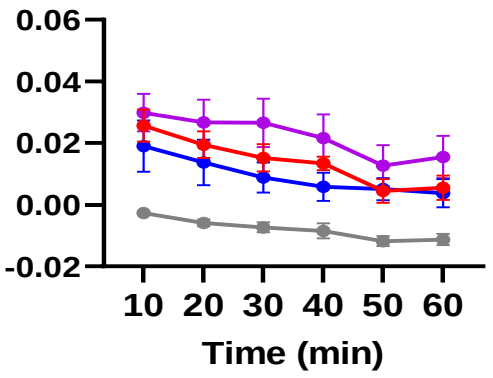
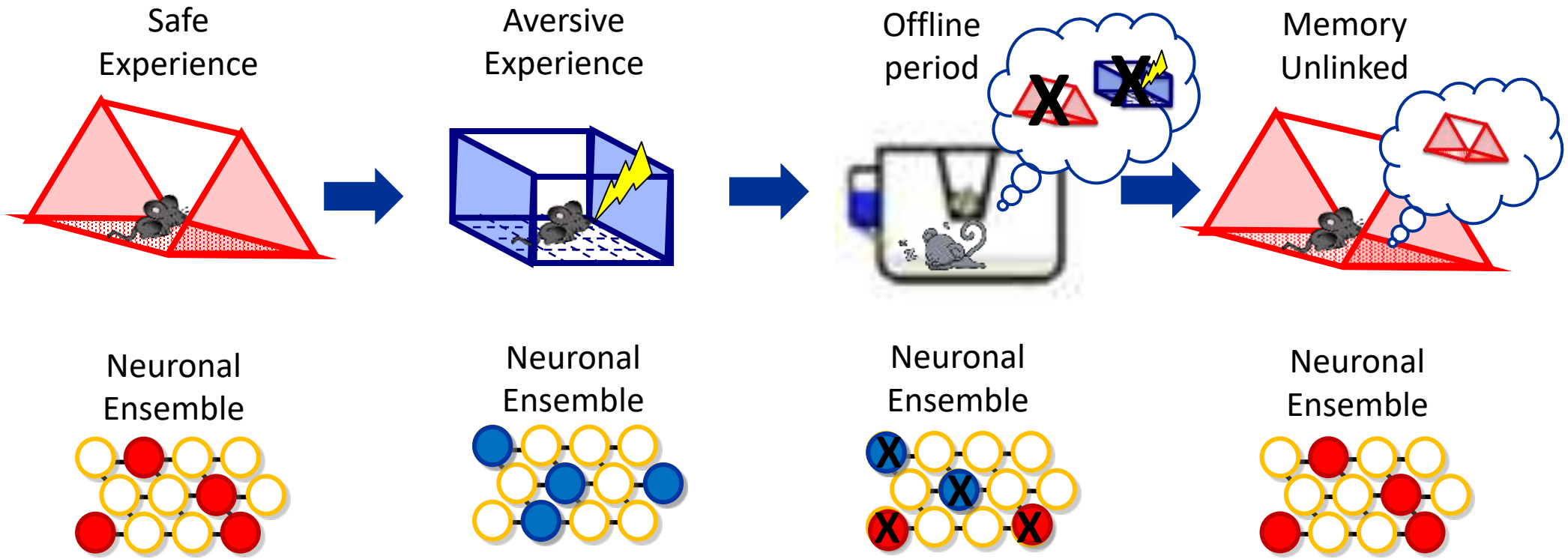






Yosif (Joe) Zaki

Decreasing offline reactivation unlink memories?



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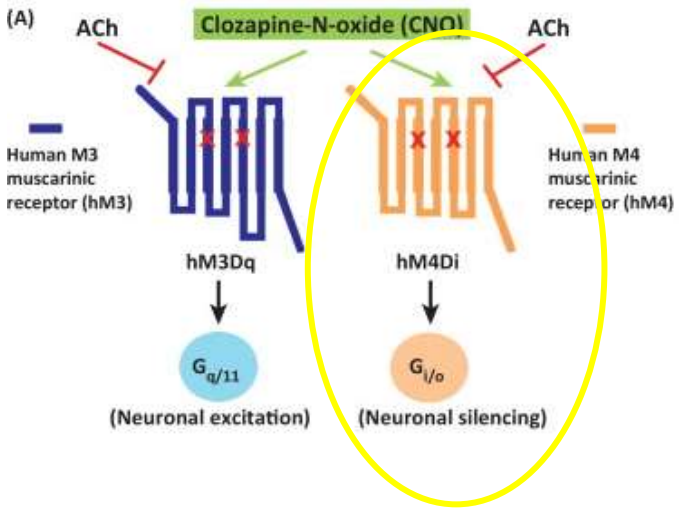
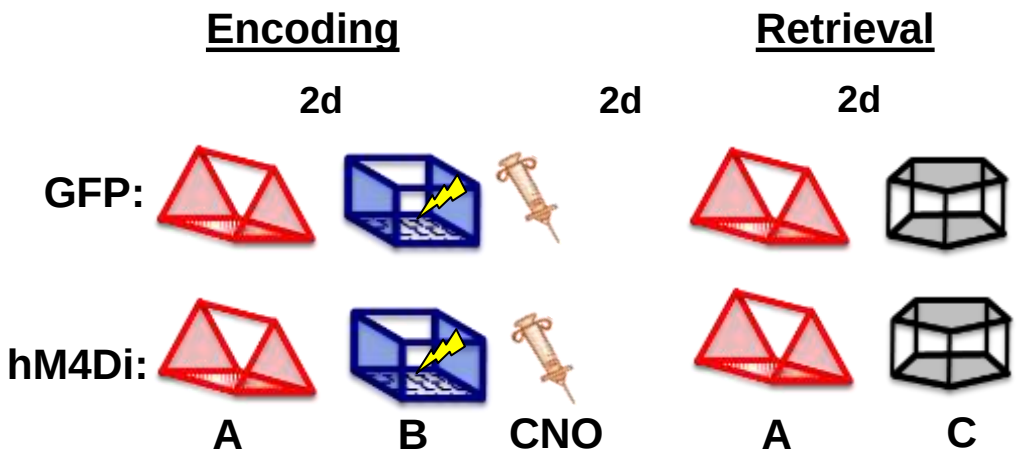
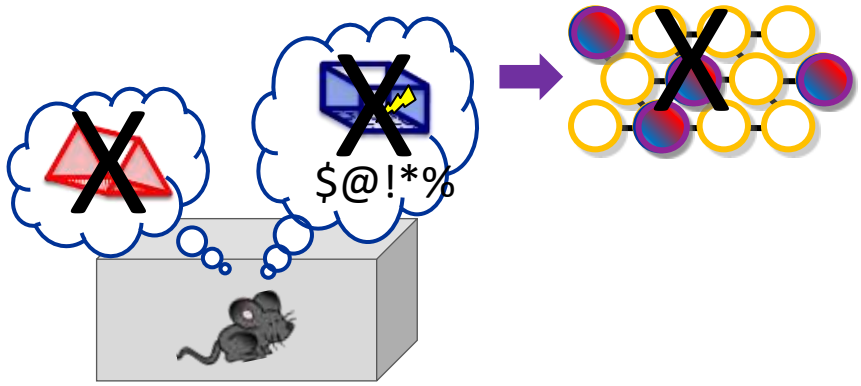
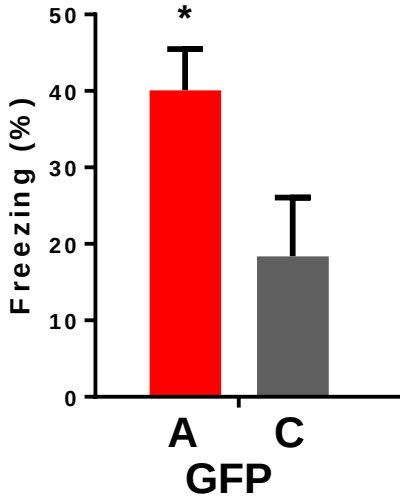


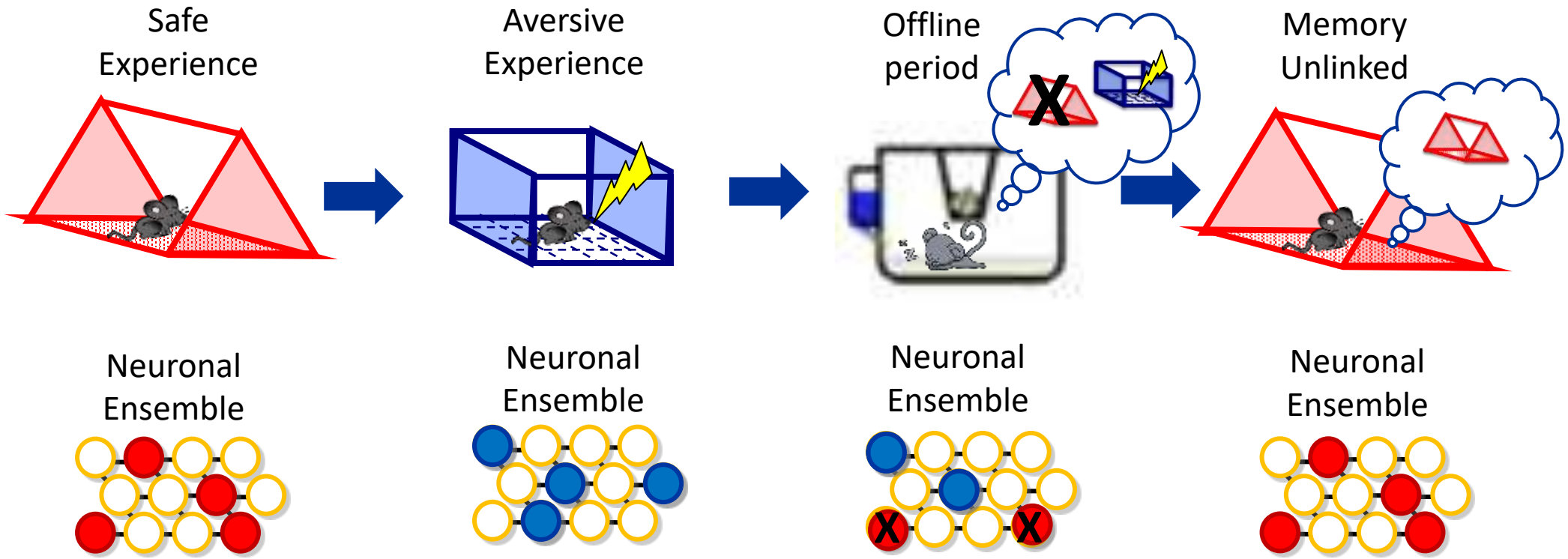






Zachary Pennington

Decreasing offline reactivation unlink memories?



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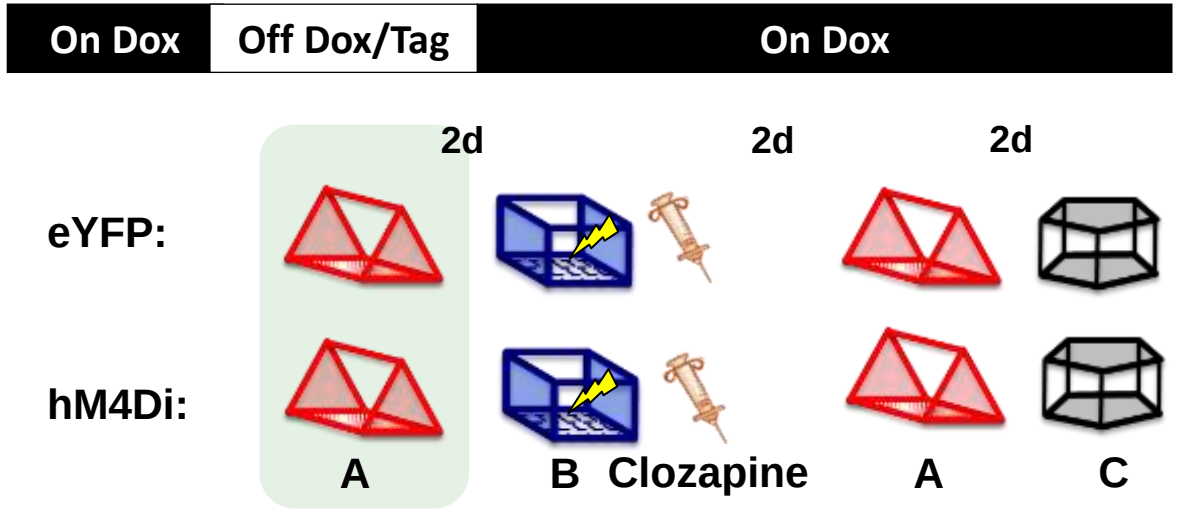
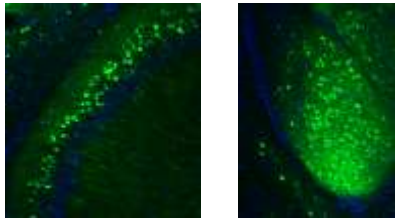


Hippocampus & Amygdala



<u>TetTag-DREADD Virus</u>

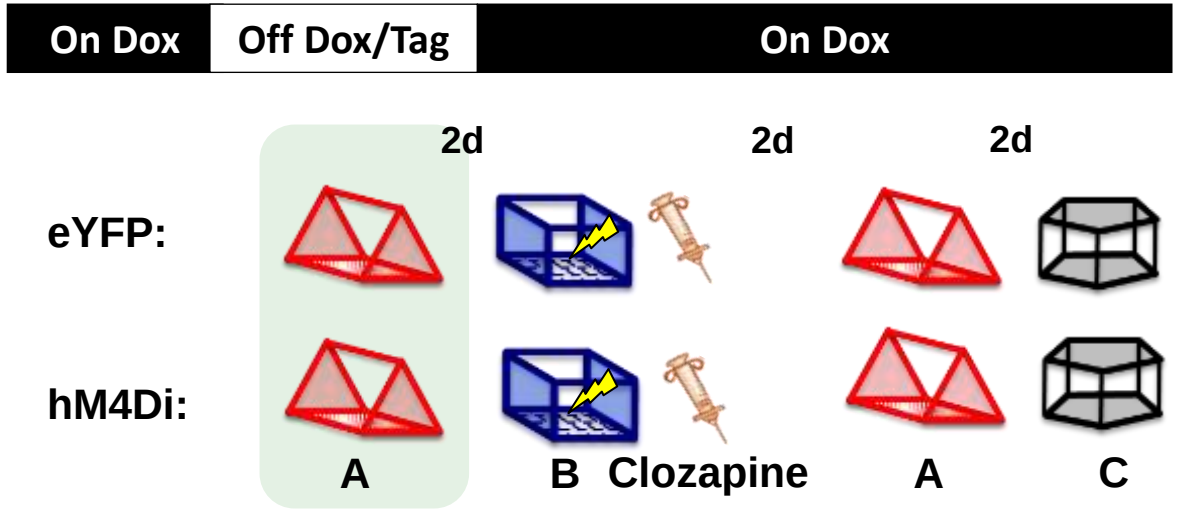
eYFP: cFos-tTA + TRE-eYFP

hM4Di: cFos-tTA + TRE-hM4Di-eYFP

(Virus courtesy of Steve Ramirez)

Yosif (Joe) Zaki

Decreasing offline reactivation unlink memories?



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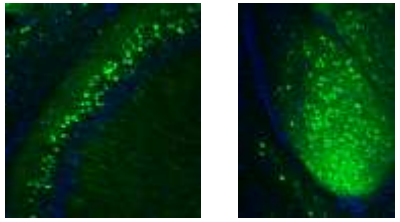

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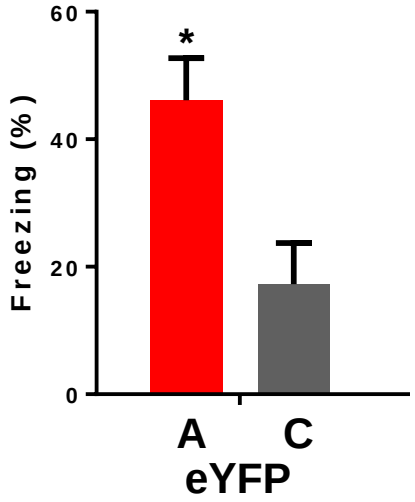
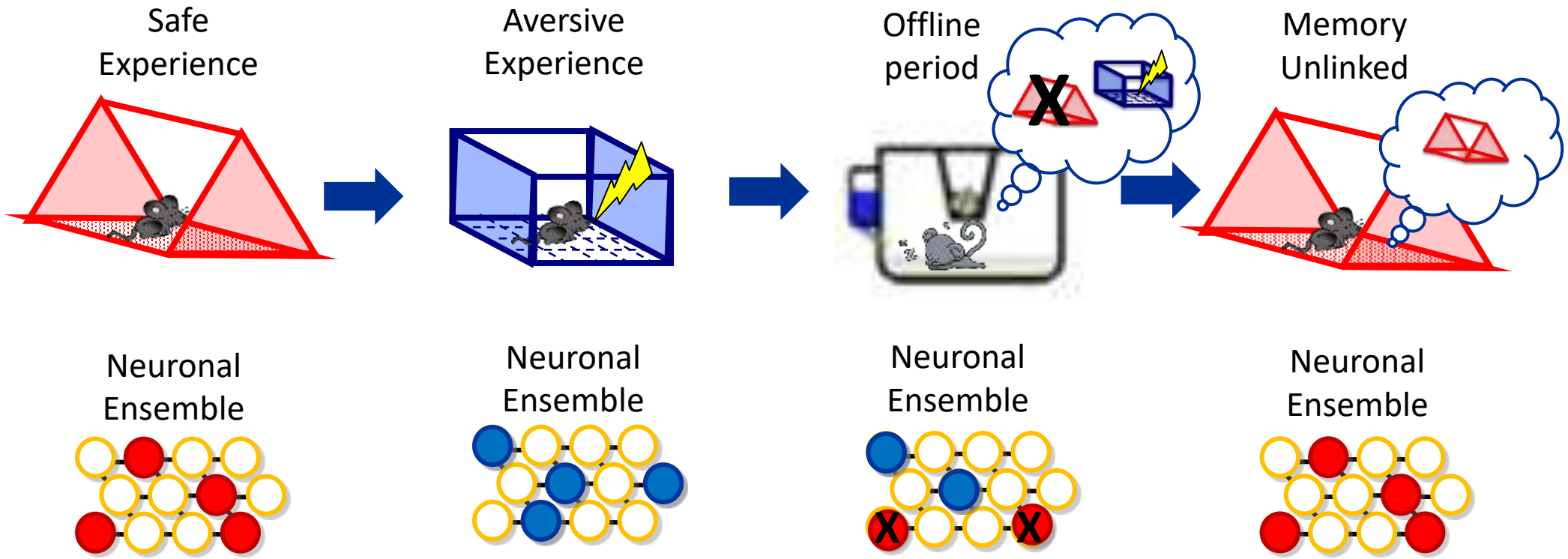


Yosif (Joe) Zaki

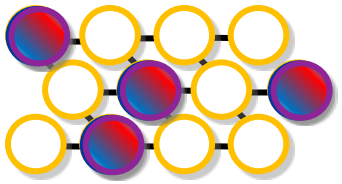
Decreasing offline reactivation unlink memories?



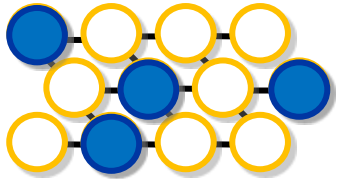
Linking to the past to predict the future

Sugary raspberry gimlets

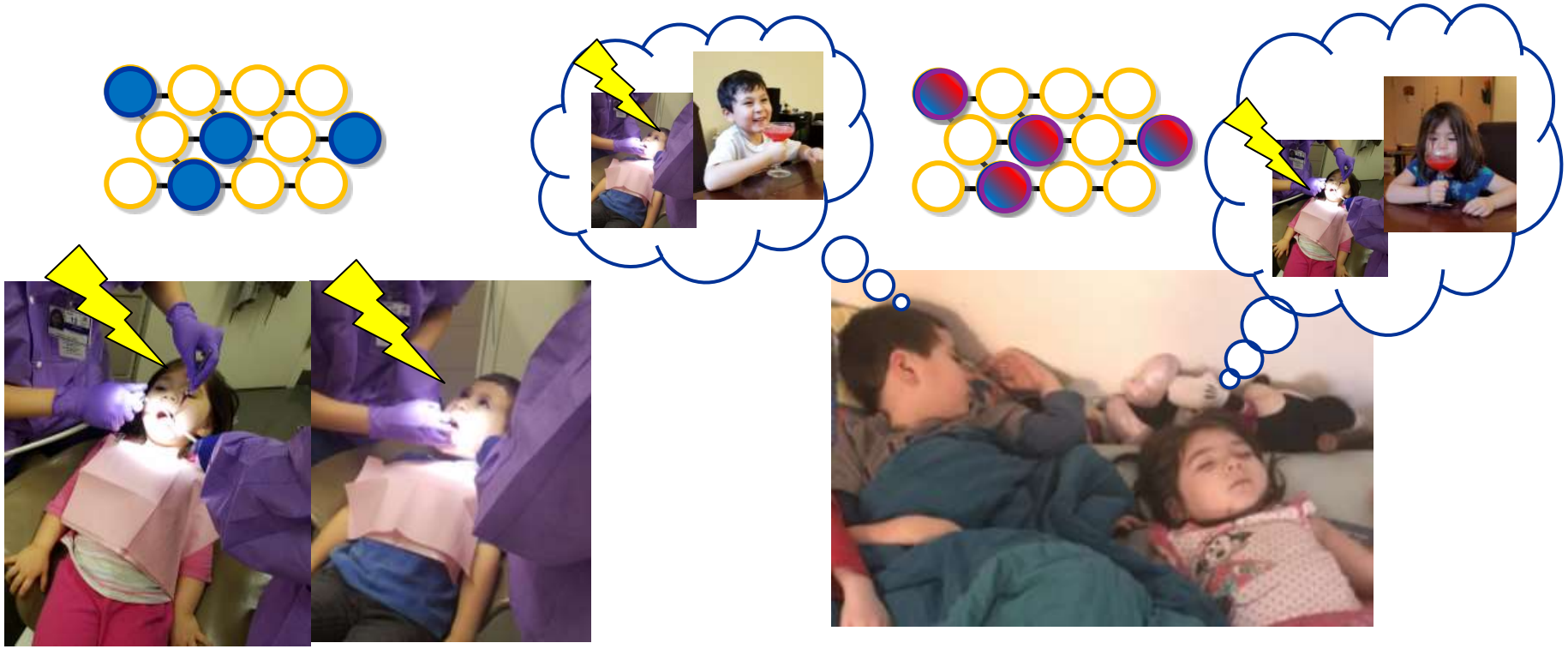
time



Filling cavities at dentist

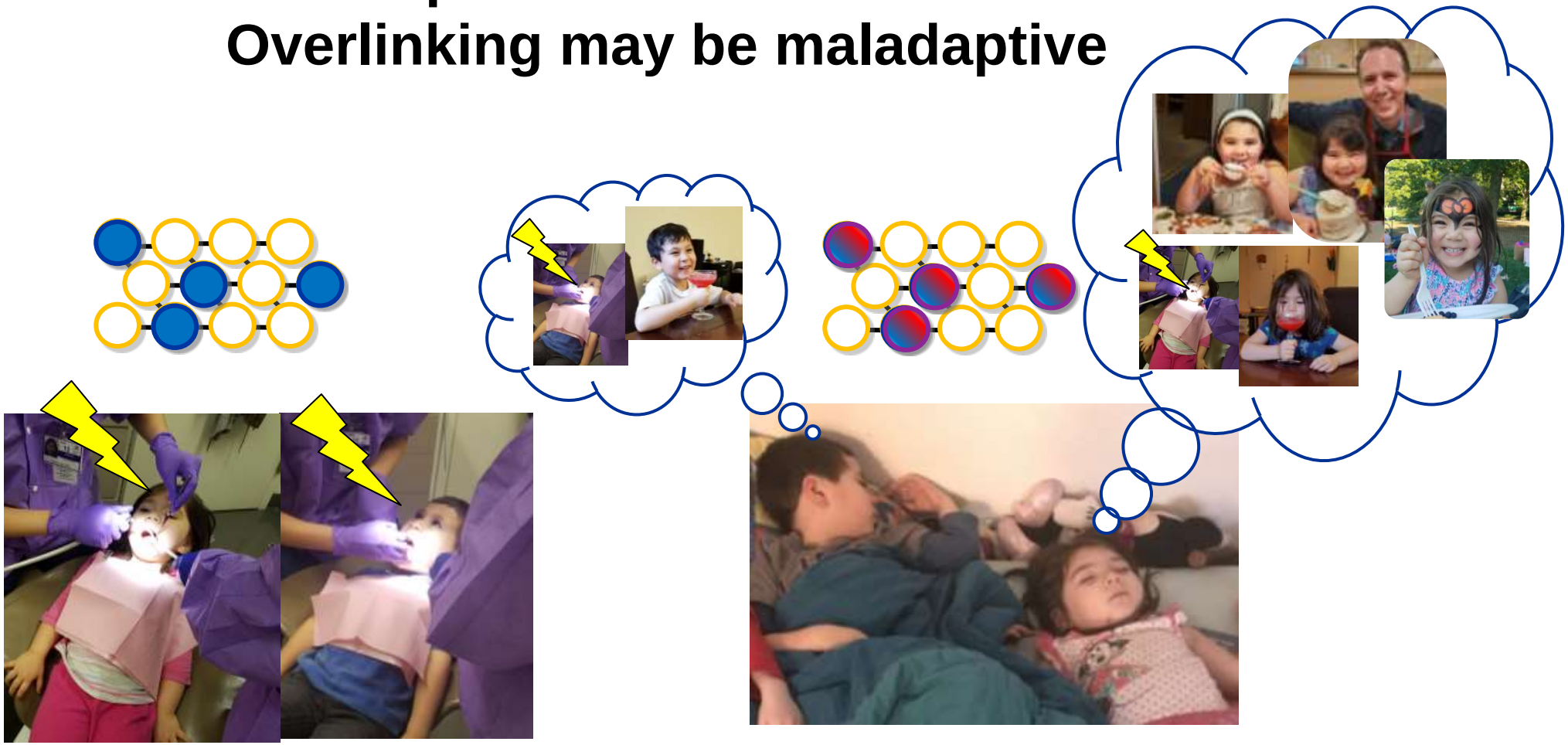


Aversive experiences are linked to past memories through reactivation during offline periods

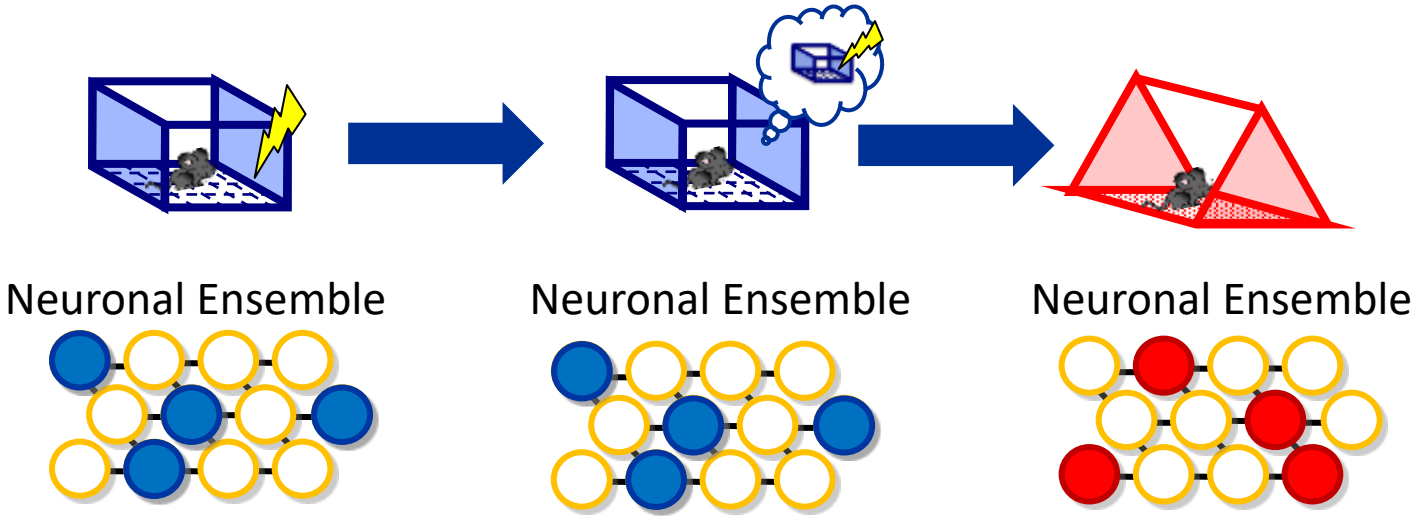


Linking to the past to predict the future.

Implications for PTSD:
Overlinking may be maladaptive



Take-home message



1) Memories are stored in neuronal ensembles in the brain.

2) Memories can be “erased” or “activated” by manipulating neuronal ensembles.

3) Aversive experiences are linked with past memories during offline periods.

TEAM WORK

makes the dream work

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Maojuan Zhuang
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Paul Kenny
Alex Smith
Paul Slesinger
Dan Kircher
Mark Baxter
Bill Janssen
Scott Russo
Steve Ramirez
Alcino Silva
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Sima Rabinowitz
Kafui Dzirasa

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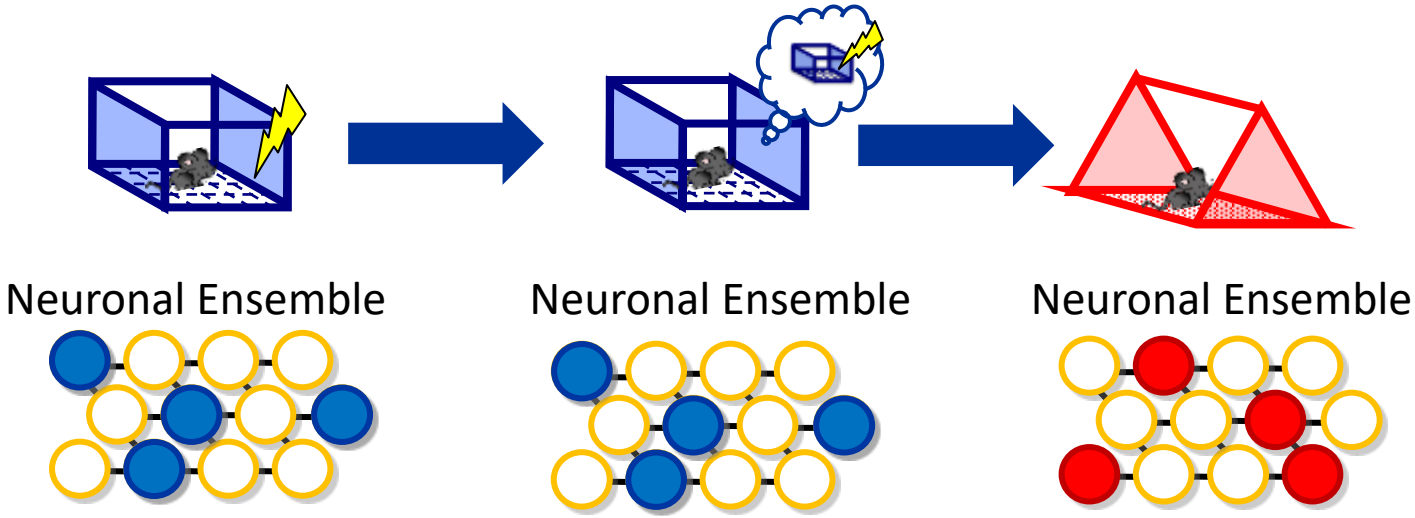
Take-home message

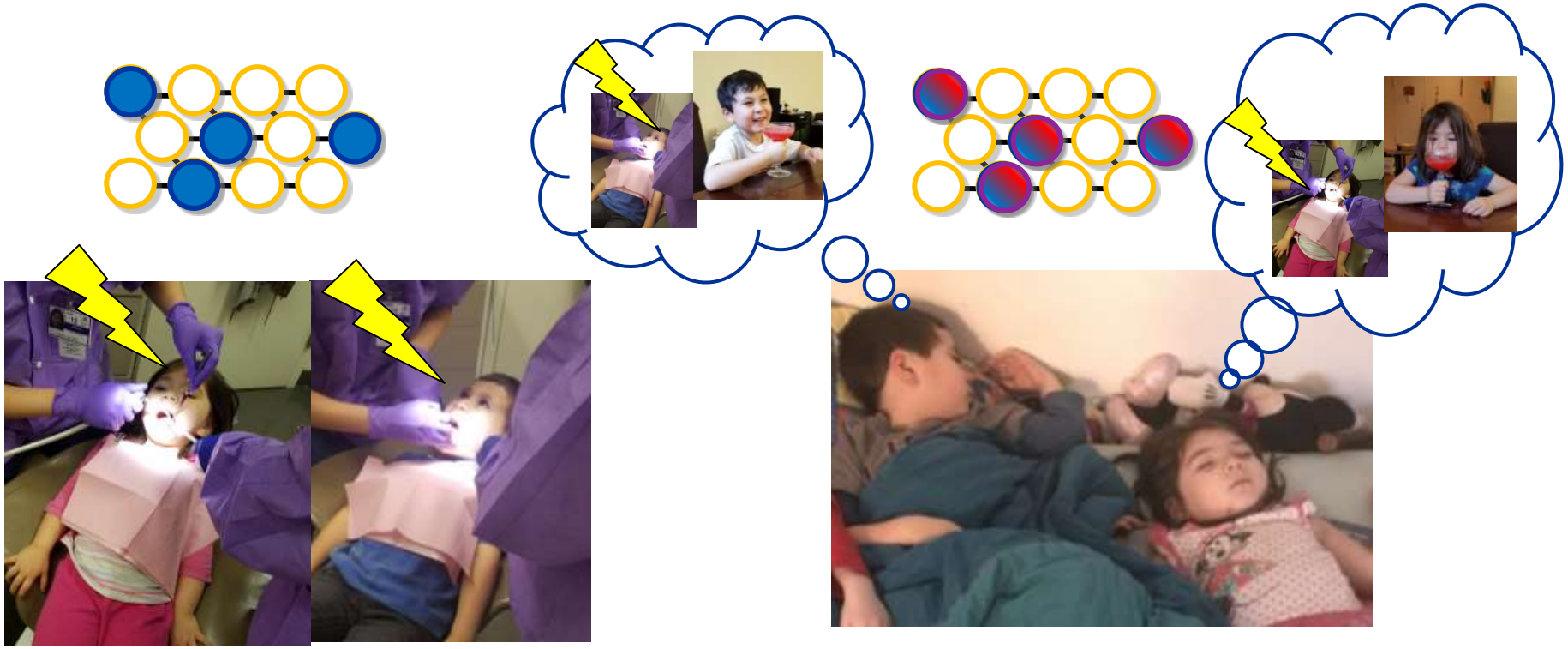


1) Memories are stored in neuronal ensembles in the brain.

2) Memories can be “erased” or “activated” by manipulating neuronal ensembles.

3) Aversive experiences are linked with past memories during offline periods.

Aversive experiences are linked to past memories through reactivation during offline periods



Linking to the past to predict the future.