

LEARNING TO FEAR,

and to extinguish fear.



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Fear is critical for survival in the real world.



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But too much fear can destroy someone's life: Post Traumatic Stress Disorder PTSD.

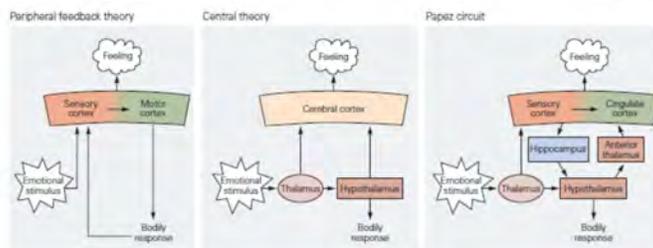
I keep seeing the accident, over and over. I need help.



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Early theories of emotion and fear implicate thalamic and cortical circuits.



LeDoux, 1996



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Klüver-Bucy syndrome: removal of temporal lobes of monkeys.

- Bizarre sexual behavior.
- Oral fixation.
- Lack fear.
- Amygdala is lesioned.



Figure 3: A monkey with Klüver-Bucy syndrome has lost his natural fear of snakes



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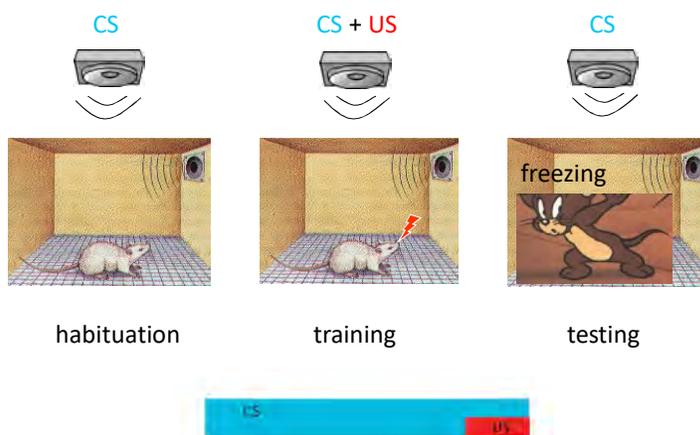
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10^{10} people on Earth

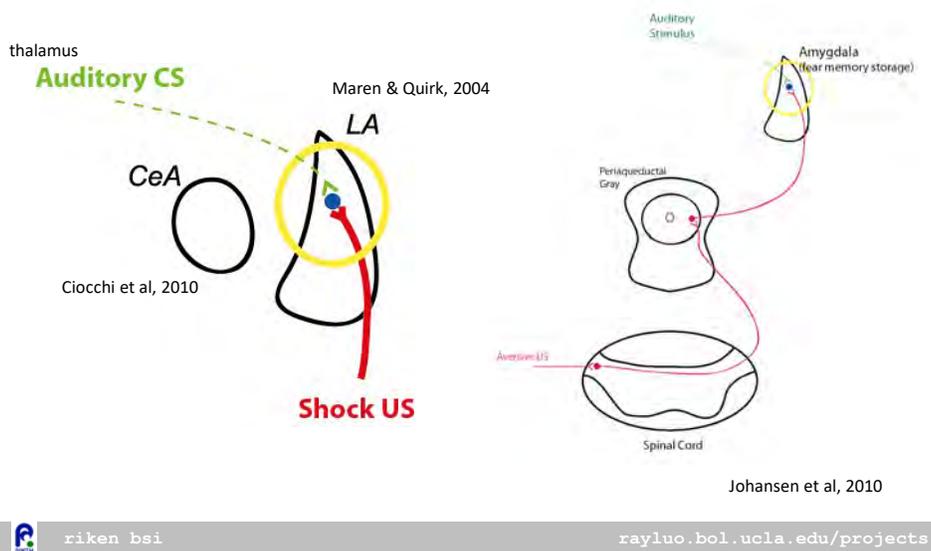




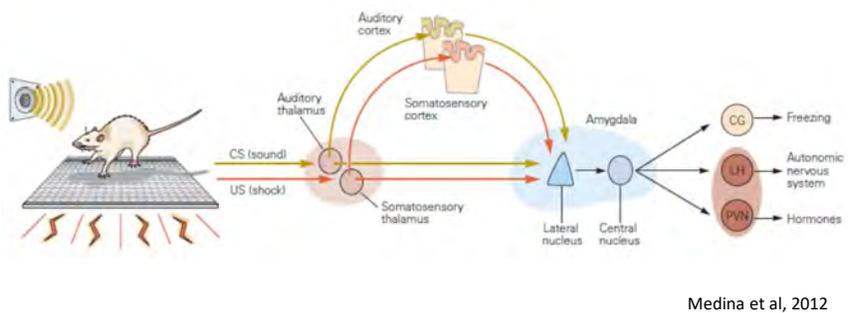
Pavlovian classical conditioning as a model for fear learning: CS tone, US shock, CR freezing.



Microcircuitry in the amygdala mediates fear conditioning.

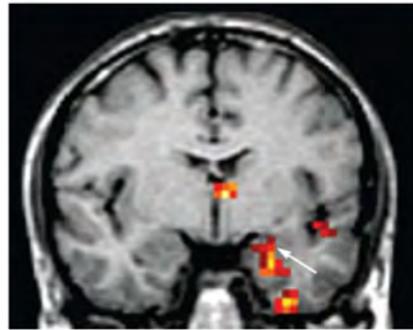


Microcircuitry in the amygdala mediates fear conditioning.



Human amygdala is involved in processing of fear and reward values.

- fMRI amygdala activation during CS-US pair.
- Conditioned by watching or warning of shock.
- Hippocampal lesion:
 - No explicit learning
 - But respond to CS
- Amygdala lesion:
 - No phys response
 - Recall conditioning



LaBar et al., 1998.



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Fear extinction is presentation of CS repeatedly without shock US.

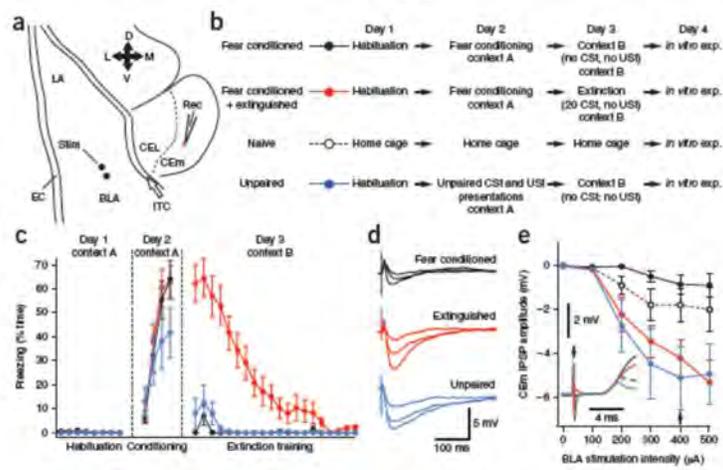
- How do we get rid of bad memories?
- Extinction is a new form of memory.
- Extinction is context dependent.
- Renewal: return of fear in new context.
- Reinstatement: return of fear with single shock.
- Spontaneous recovery: return of fear with passage of time.



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Inhibition of central medial amygdala following extinction training.



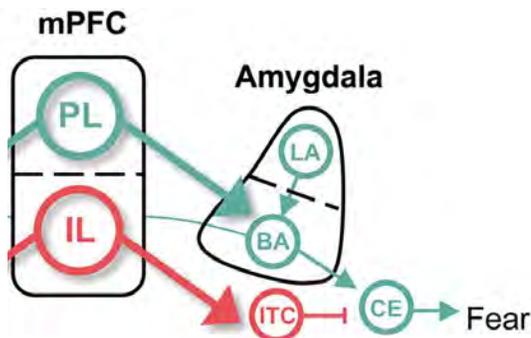
Amano et al., 2010



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Microcircuitry in the prefrontal cortex mediates fear extinction learning.



Quirk et al, 2009

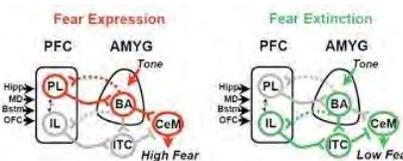
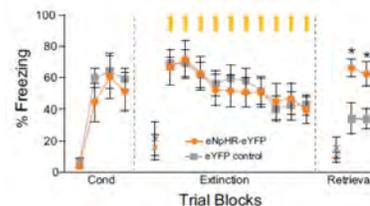


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Effects on extinction can be during acquisition or during retention.

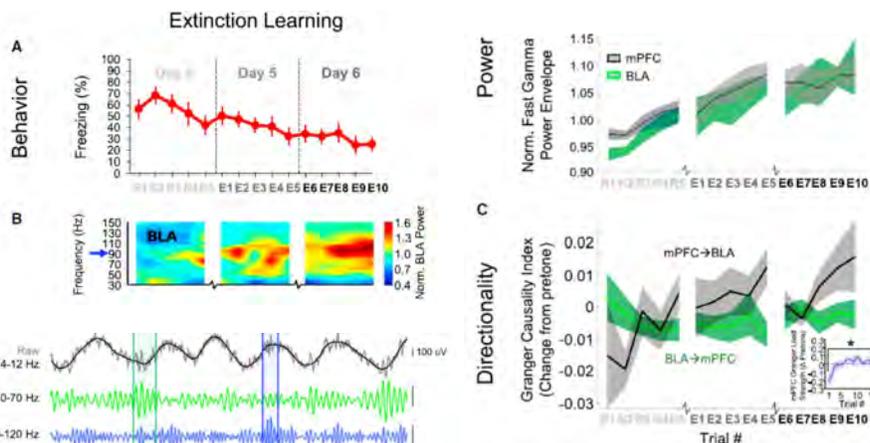
- Agonists of amygdala NMDARs facilitate extinction learning.
- BDNF activity required for long term extinction.
- Unlearning fear with immediate extinction or during reconsolidation.



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Fear extinction circuitry may require coordination of different sites.



Stujenske et al., 2014

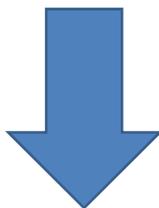


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Question: How is fear learning modulated by different transmitter systems based on context?

- Noradrenergic system enhances fear memory (Soeter et al, 2011).
- Aversive events affect dopamine transmission (Badrinarayan et al, 2012).
- Serotonin depletion leads to attenuated fear response (Hindi et al, 2012).



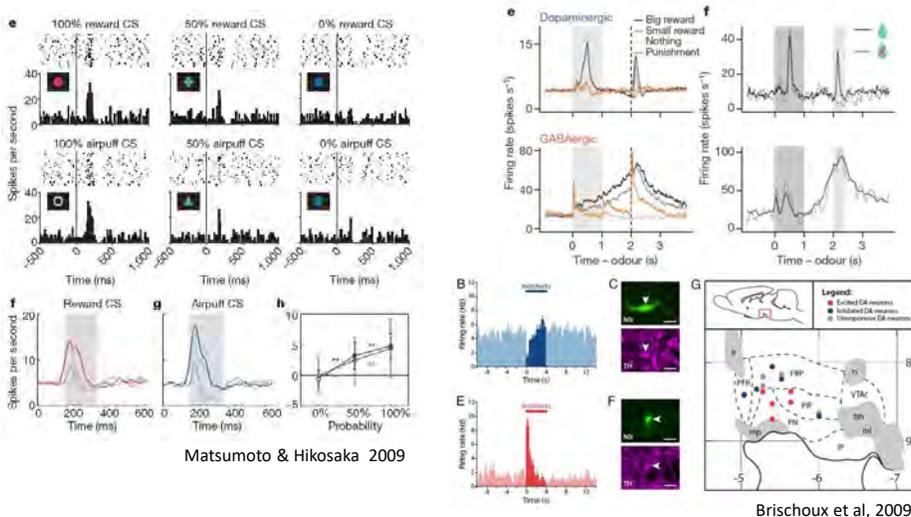
- Is dopamine system involved in fear and extinction learning?



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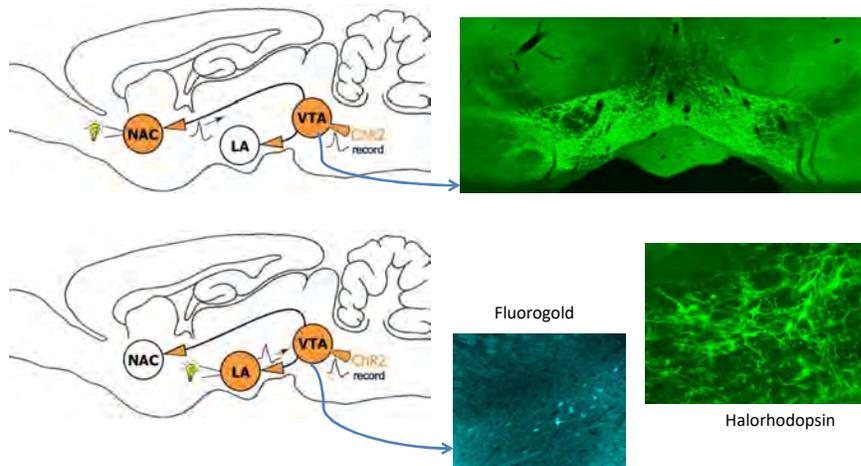
Midbrain dopamine neurons may also respond to aversive signals.



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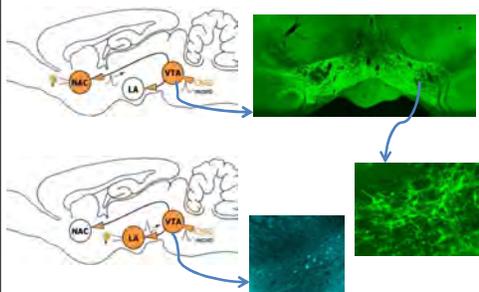
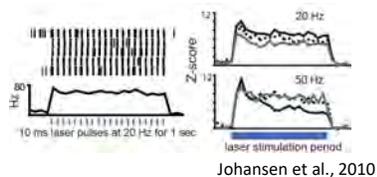
Optogenetic identification of VTA to LA and VTA to NAc dopamine projections.



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Use optogenetics to identify dopamine cells, trace their projections, manipulate activity.



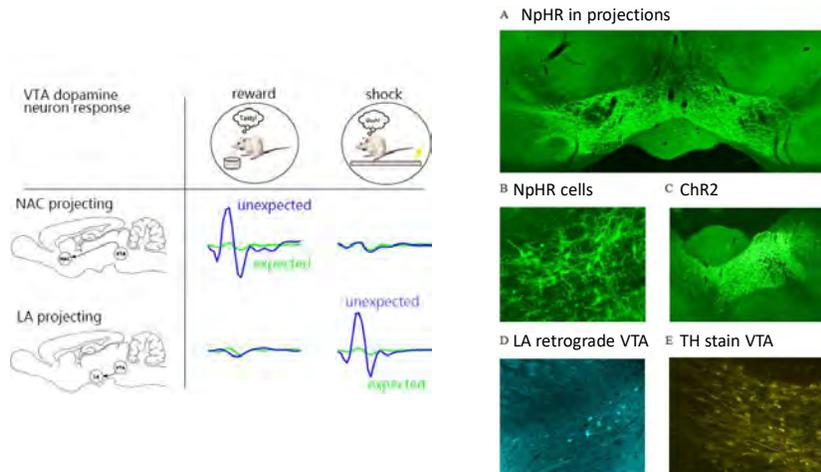
- TH-cre rats expressing a cre-dependent channelrhodopsin (ChR2) or halorhodopsin (NpHR) allows dopamine neurons – specific excitation *in vivo*.
- Virus containing ChR2 can reach terminals of transfected cells, allowing optical stimulation of their terminals at target structure to identify their projections.
- Inhibition of VTA dopamine cells during fear and reward learning using NpHR can reveal the role of dopamine neurons in appetitive and aversive learning.



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Hypothesis: VTA to LA projections code for aversive prediction error.

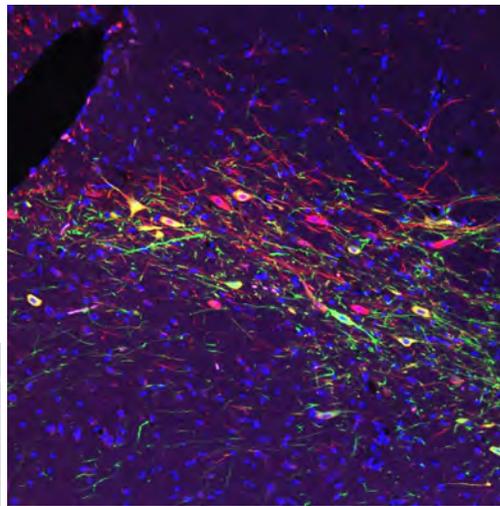
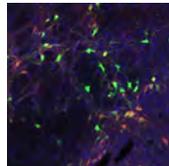


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Approach: Optogenetic manipulation of VTA dopamine cells.

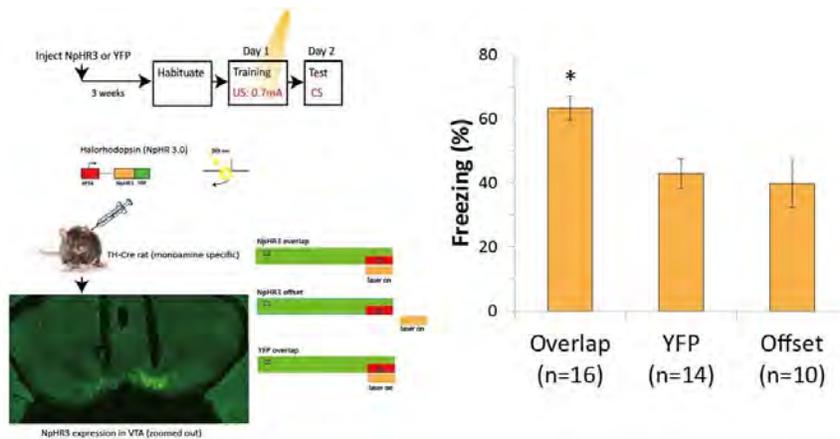
- TH (red) labeling dopaminergic cells in TH-cre animals.
- GFP (green) labeling NpHR (right) and Arch (below) infected cells.
- DAPI (blue) nucleus.



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Optogenetic inhibition of VTA dopamine cells during shock US presentation increases fear learning.



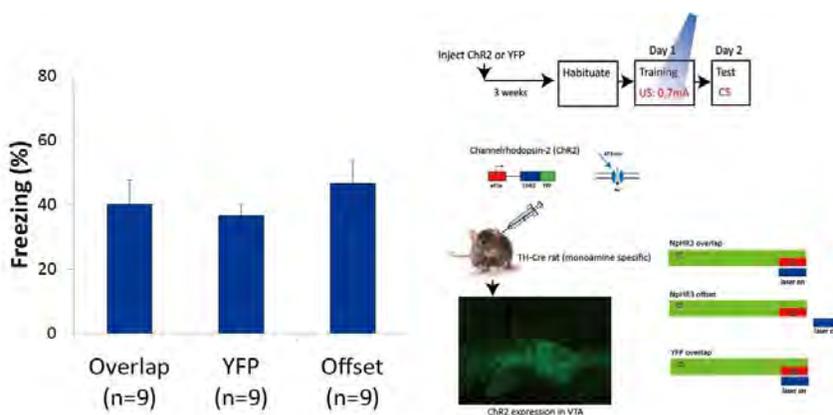
In collaboration with Luca Aquili



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Optogenetic excitation of VTA dopamine cells during shock US does not affect fear learning.



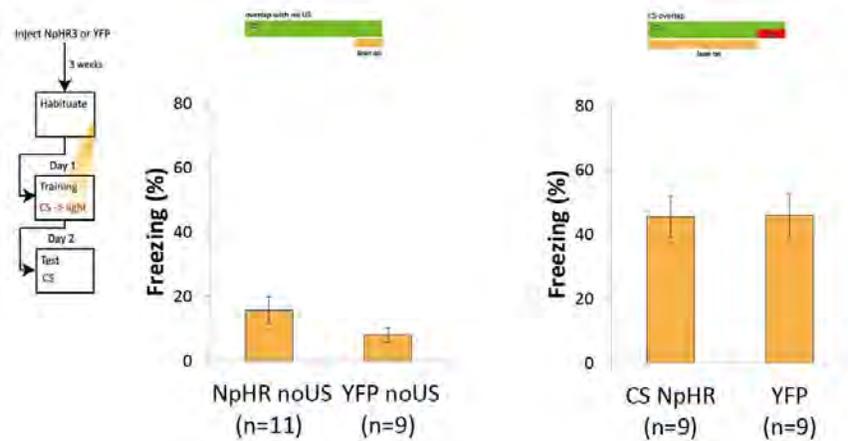
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Neither optogenetic inhibition during CS nor following CS alone affects fear learning.



In collaboration with Luca Aquili



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What are VTA and LA cells doing during fear learning?

learning actual expected

$$\Delta V \propto (\lambda - \Sigma V)$$

US

CS

Rescorla & Wagner, 1972

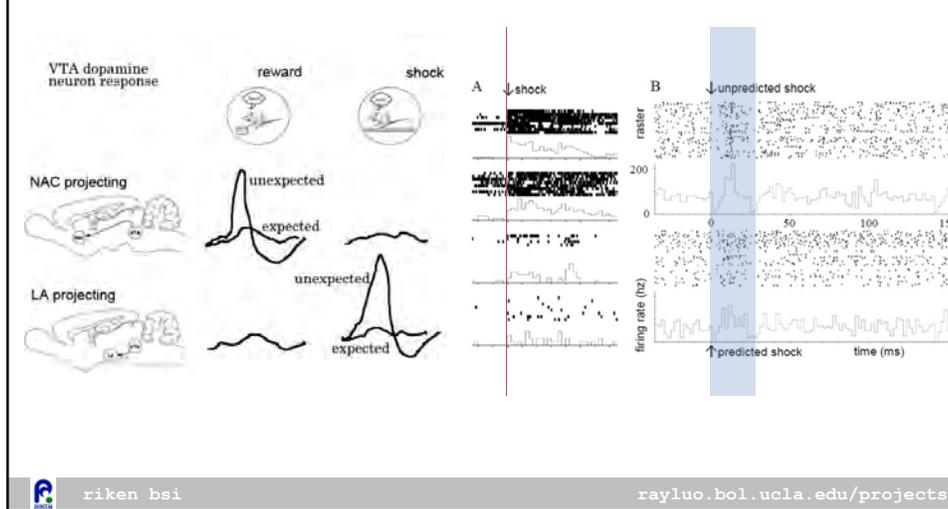
Prediction error coding can explain learning in classical conditioning.
Model explains phenomena such as blocking and learning asymptote.



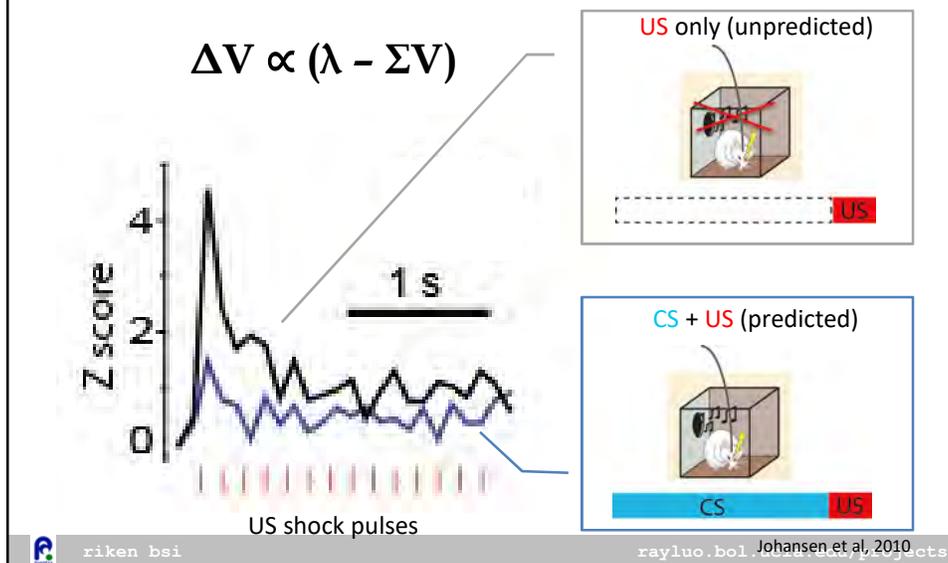
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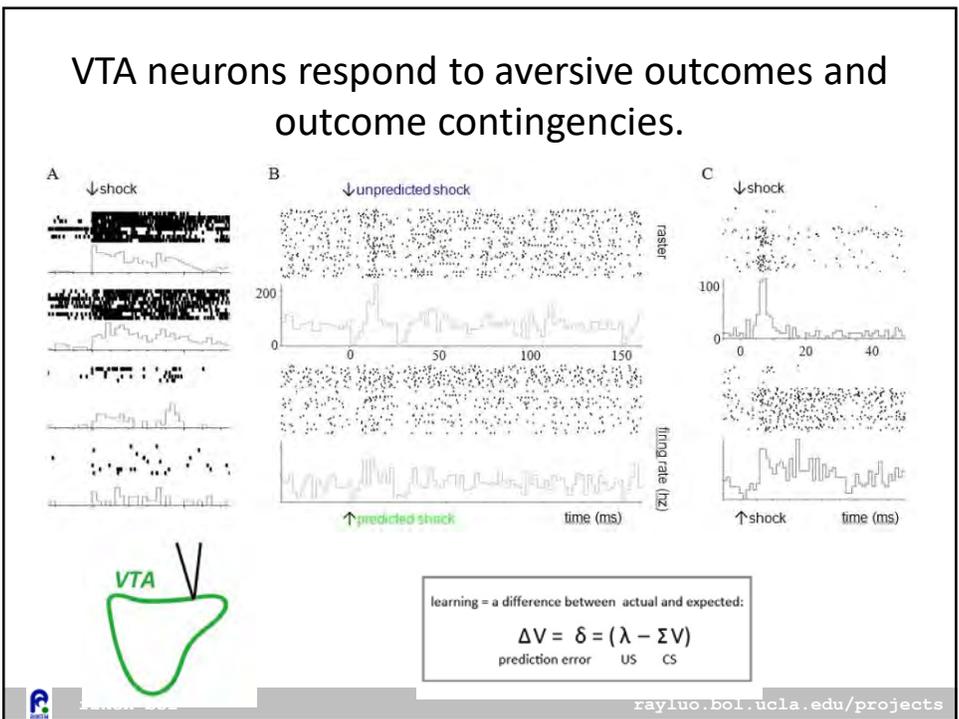
Do VTA to LA projections code for aversive prediction error?



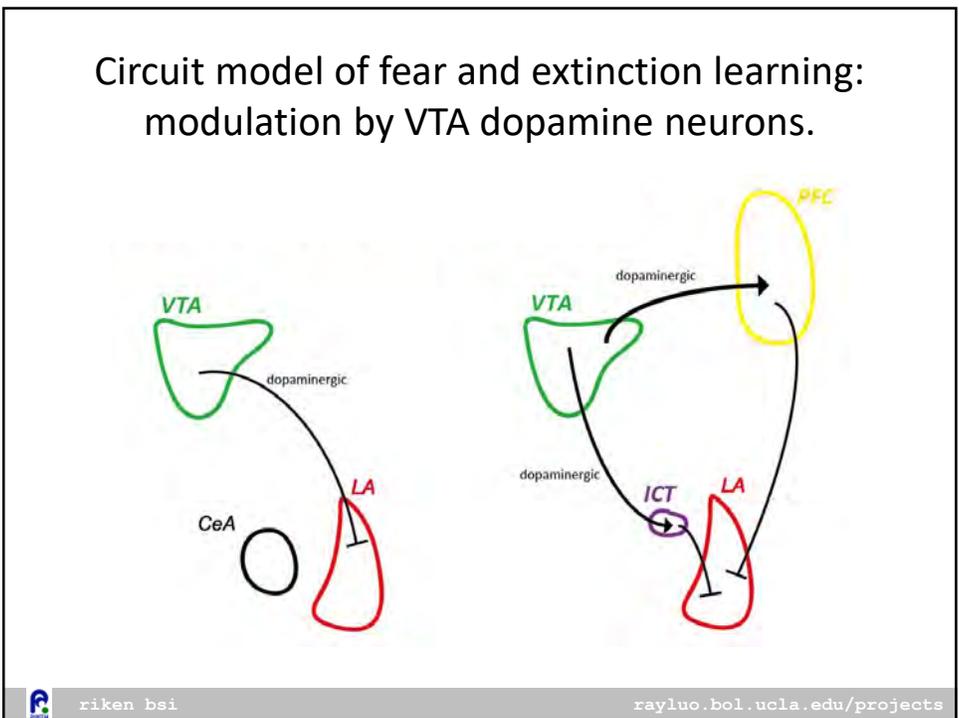
Prediction error coding can explain differential responses to predicted vs. unpredicted US.



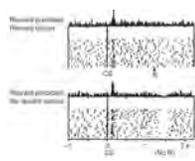
VTA neurons respond to aversive outcomes and outcome contingencies.



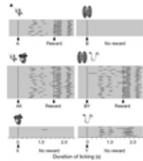
Circuit model of fear and extinction learning: modulation by VTA dopamine neurons.



Midbrain dopamine neurons encode rewarding as well as aversive signals.



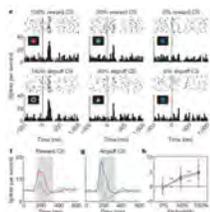
Schultz et al, 1997



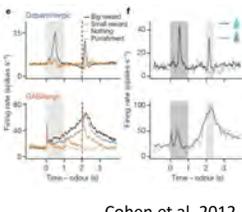
Waelti et al, 2001

Rescorla-Wagner: $\Delta V \propto (\lambda - \Sigma V)$

Pearce-Hall: $\Delta V \propto |\lambda - \Sigma V| \lambda$



Matsumoto & Hikosaka 2009



Cohen et al, 2012

- Ventral Tegmental Area (VTA) dopamine neurons fire in response to rewards and cues that predict reward.
- Firing rates are proportional to predictability of cue for reward, and is thus high early in learning, and decreases as prediction error is decreased when well learned.
- Recent results show putative VTA dopamine neurons responsive to aversive events.
- Question 1: where do these dopamine neurons project?
- Question 2: how do these dopamine cells affect learning?



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Review Questions.

- Post Traumatic Stress Disorder (PTSD) is a failure in which of the following processes?
 - A. inability to learn fear
 - B. inability to extinguish fear
 - C. inability to generalize fear to other contexts
 - D. inability to communicate fear to other humans
- A dog is trained by pairing a neutral light cue to delivery of food until he salivates to the presentation of light by itself. Which of the following is the conditioned stimulus (CS)?
 - A. food
 - B. salivation
 - C. tone cue
 - D. light cue
- We train an animal to freeze in response to a tone, then next day we present tones only to extinguish the fear. The day after that, we put the animal in a new room and present the same tones again. What happens?
 - A. the animal stops freezing to the tone because the new room is not threatening.
 - B. the animal stops freezing initially but then remembers the fear and begins to freeze.
 - C. the animal freezes to the tone more than at the end of the extinction day previously.
 - D. the animal freezes to the tone less than at the end of the extinction day previously.



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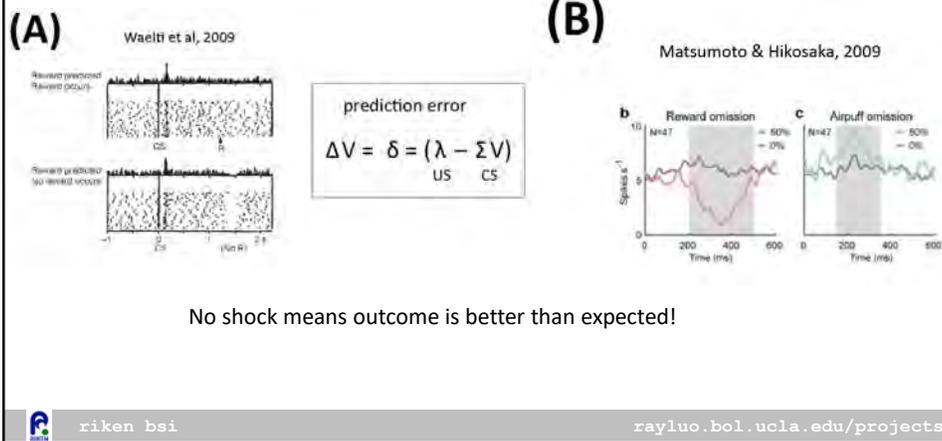
Does VTA dopamine neurons affect extinction learning?



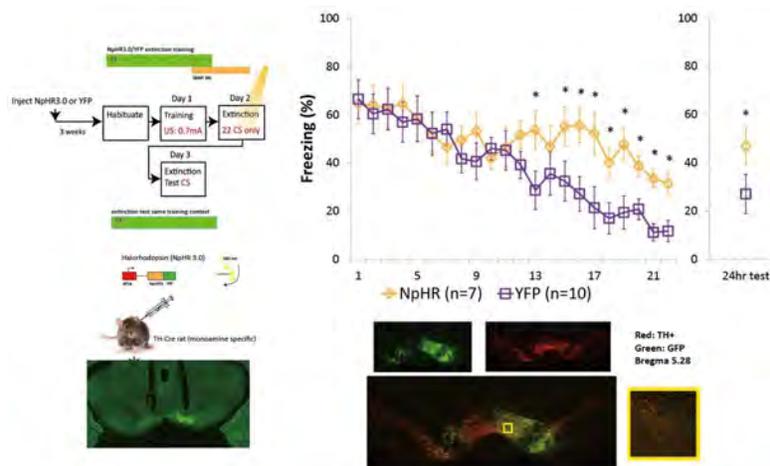
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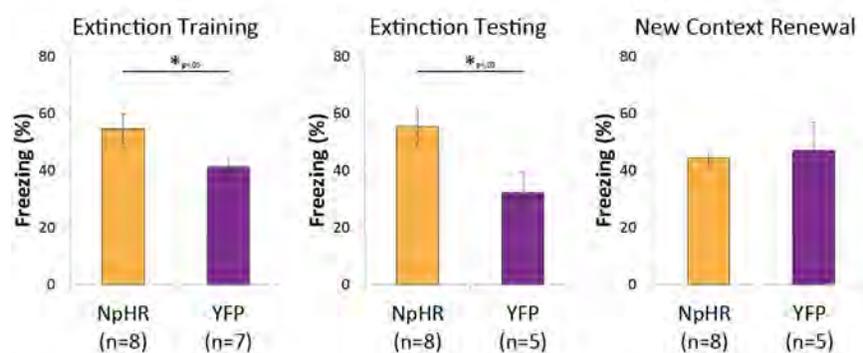
Reward prediction error coding dopamine cells may act during shock omission period.



Optogenetic inhibition of VTA dopamine cells during period of expected US presentation.



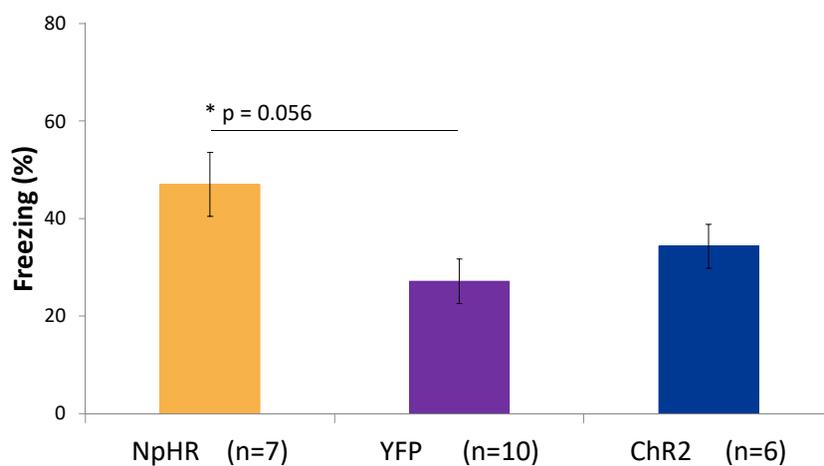
Extinction learning is reduced, but renewal of fear in a new context is unaffected.



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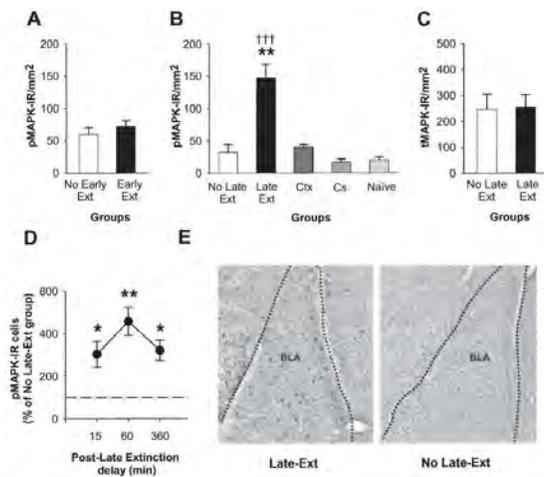
Optogenetic activation of VTA dopamine cells during expected US does not affect extinction.



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Extinction of fear is associated and requires BLA MAPK phosphorylation.



Herry et al, 2006

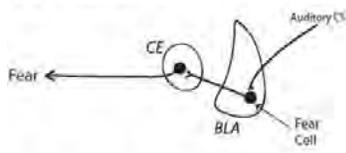


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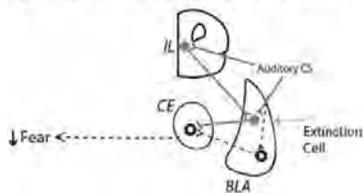
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Optogenetic inhibition of VTA dopamine neurons during omission period of fear extinction.

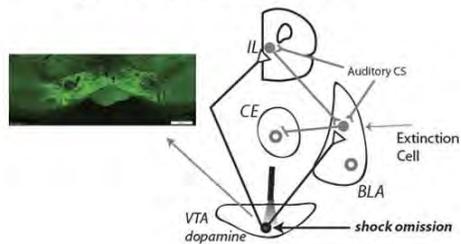
A) Fear circuit



B) Extinction learning circuit



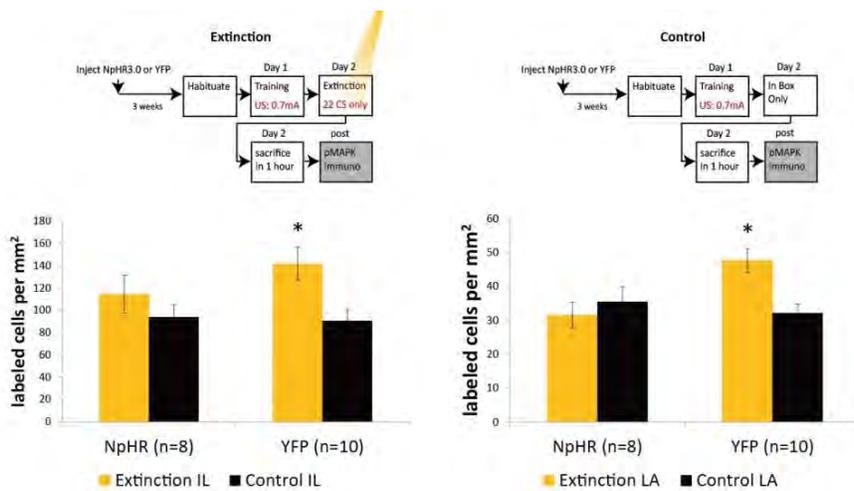
Optogenetic approach



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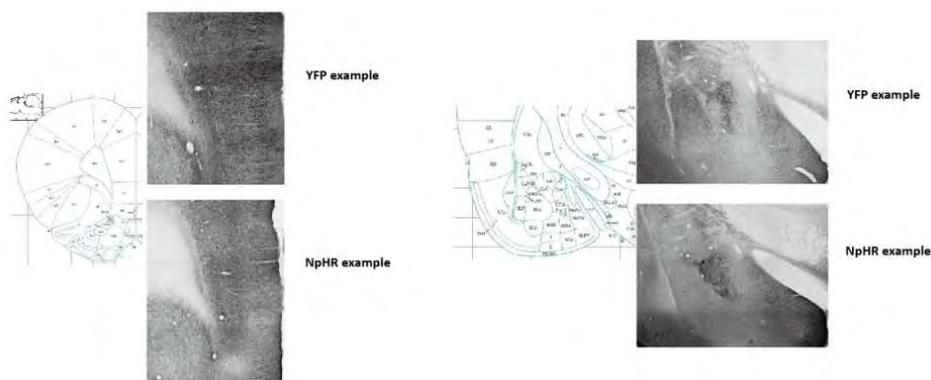
Inhibition of VTA dopamine during omissions in extinction reduces MAPK phosphorylation in BLA & IL.



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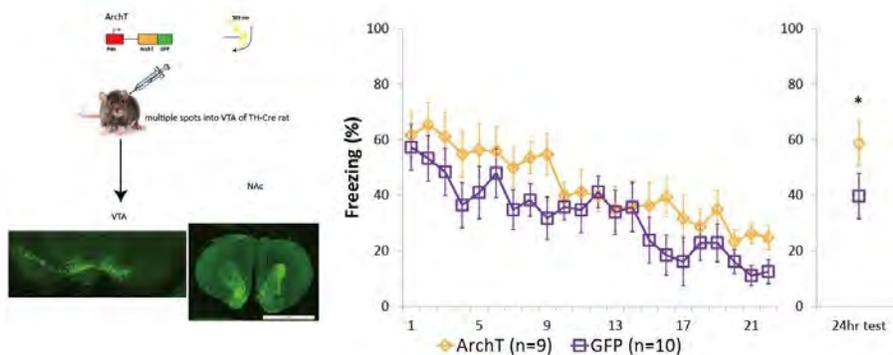
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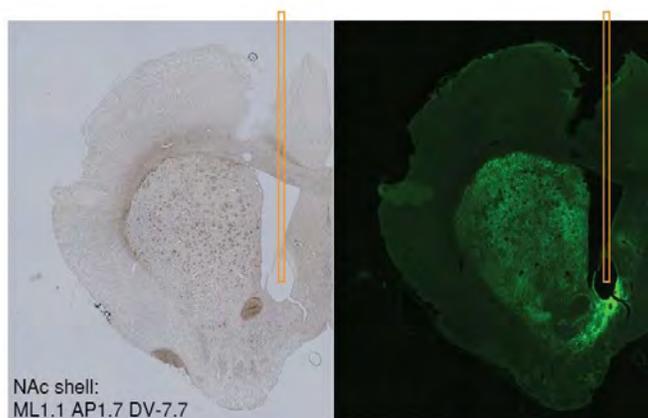
Inhibition of dopamine terminals in nucleus accumbens (NAc) during omitted shock period abolishes extinction learning.



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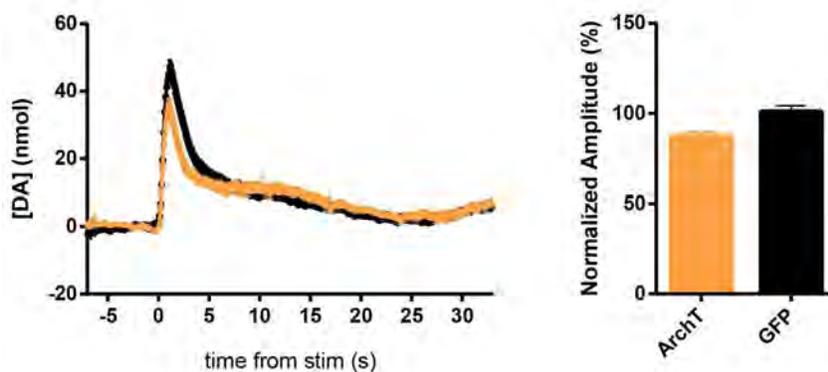
Recording dopamine release in nucleus accumbens (NAc) with fiber optic manipulation of terminals.



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Light inhibition of dopamine terminals in NAc reduces evoked amplitude.



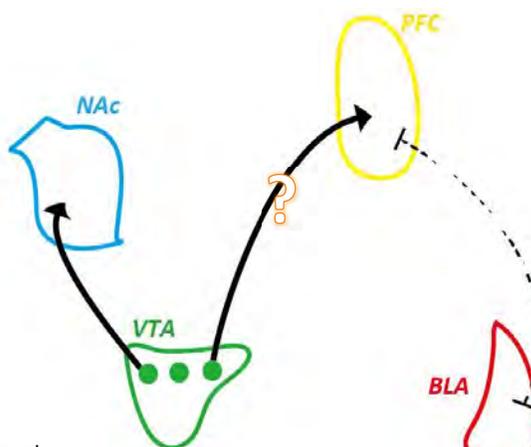
Upshot: light manipulation really reduces dopamine release during omission of shock.



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Extinction is modulated by differential dopamine projections to different areas.



Implication: PTSD treatment must be target to specific cell populations.



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RIKEN Brain Science Institute Josh Johansen laboratory (Neural Circuitry of Memory).



Ray Luo	Mami Kimura	Mai Iwasaki	Lindsay Preston	Akira Uematsu	Takaaki Ozawa	Joshua Johansen	Edgar Ycu	Baozhen Tan	Jenny Koivumaa	Jake Ormond	Touqueer Ahmed
Not shown:											
Ashwani Kumar	Hiroki Hamanaka	Yanqiu Tao	Anna Krejcirikova	Lifeng Yeh							


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Questions?

