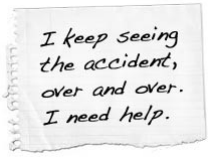
LEARNING TO FEAR,

and to extinguish fear.

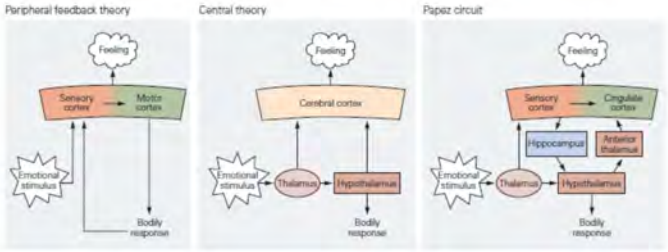
Ray Luo
RIKEN BSI, UCLA

Fear is critical for survival in the real world.

But too much fear can destroy someone's life.



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



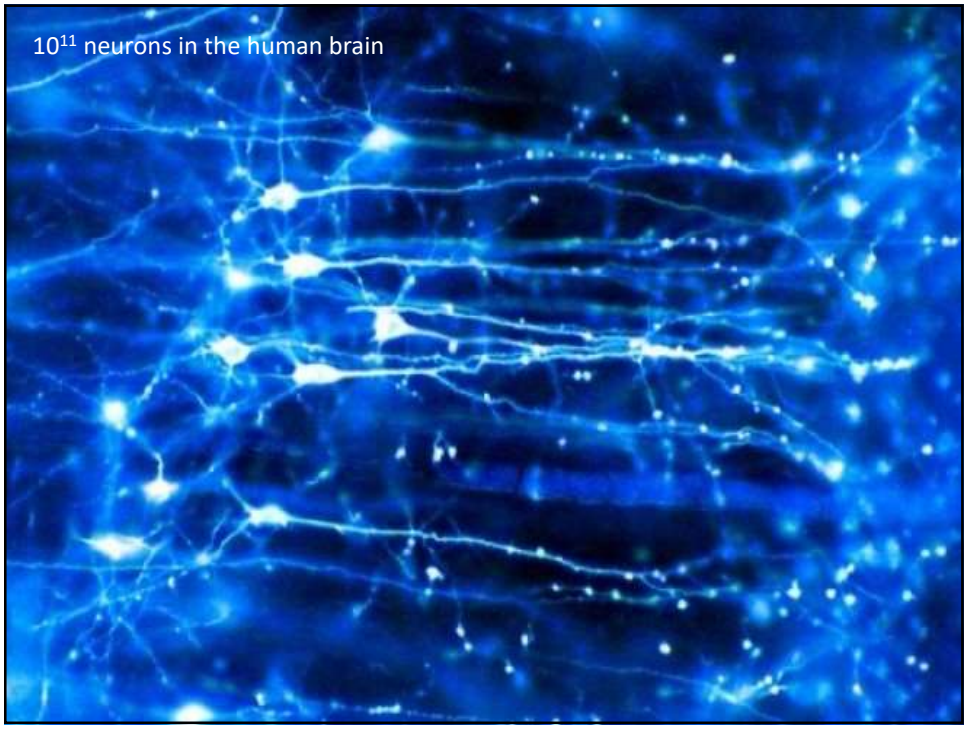
LeDoux, 1996

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

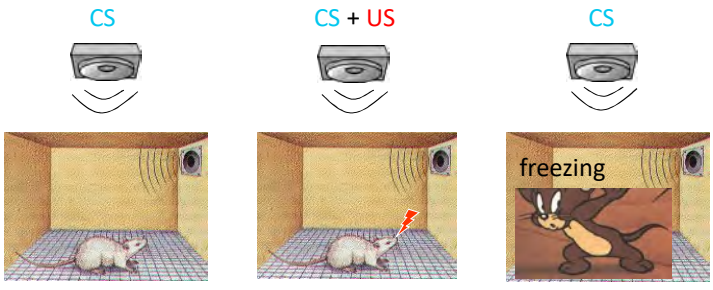
- Bizarre sexual behavior.
- Oral fixation.
- Lack fear.
- Amygdala is lesioned.

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

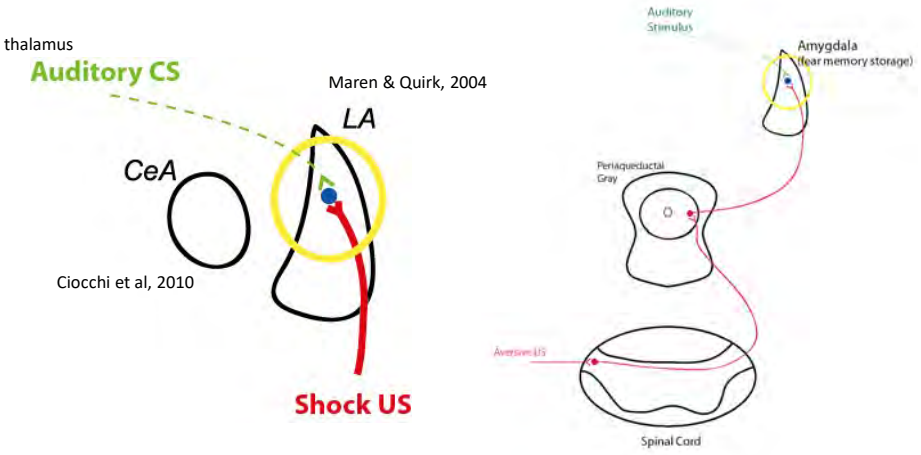
10^{10} people on Earth



Pavlovian classical conditioning can serve as a model for fear learning.

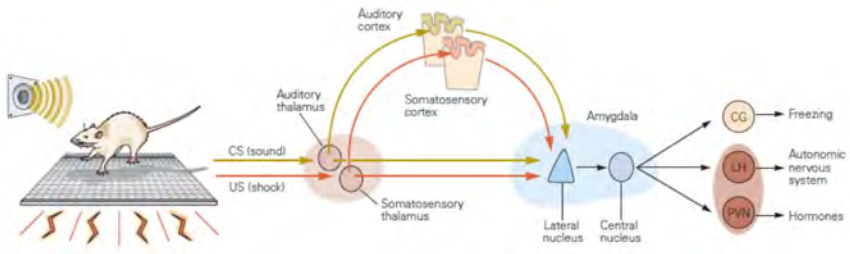


Microcircuitry in the amygdala mediates fear conditioning.



Johansen et al, 2010

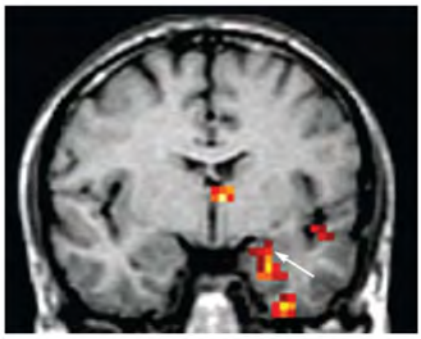
Microcircuitry in the amygdala mediates fear conditioning.



Medina et al, 2012

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

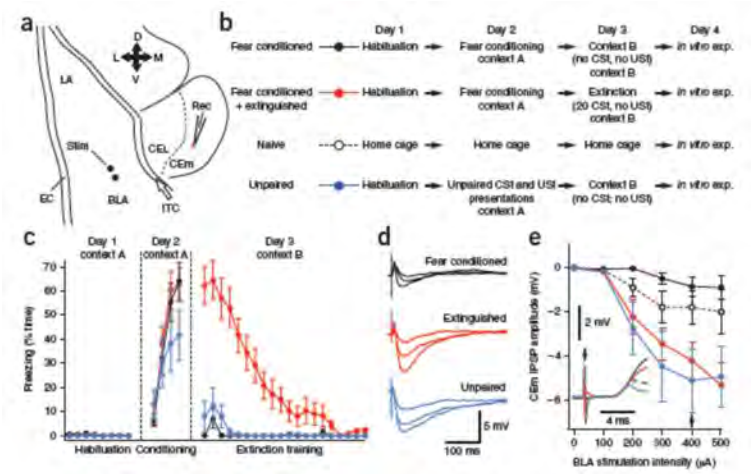


LaBar et al., 1998.

Fear extinction is presentation of CS repeatedly without shock US.

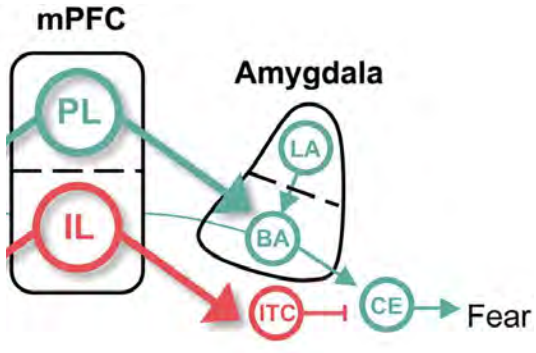
- How do we get rid of bad memories?
- Extinction is a new form of memory.
- Renewal: return of fear in new context.
- Reinstatement: return of fear with single shock.
- Spontaneous recovery: return of fear with passage of time.

Inhibition of central medial amygdala following extinction training.



Amano et al., 2010

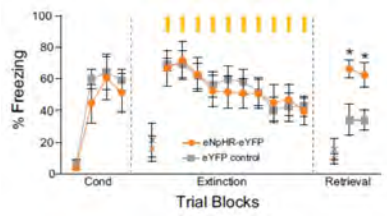
Microcircuitry in the prefrontal cortext mediates fear extinction learning.

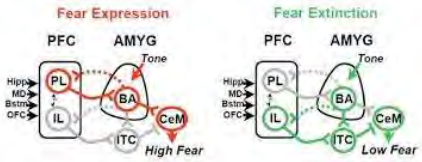


Quirk et al, 2009

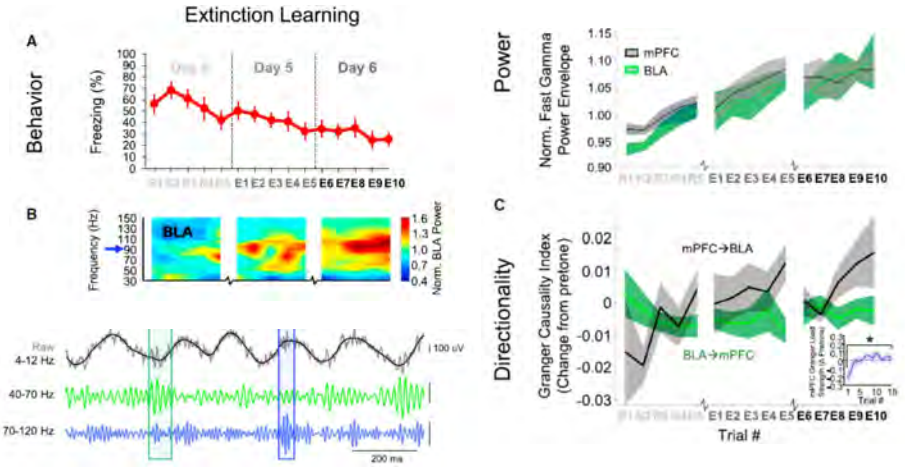
Effects on extinction can be during acquisition or during retention.

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





Fear extinction circuitry may require coordination of different sites.



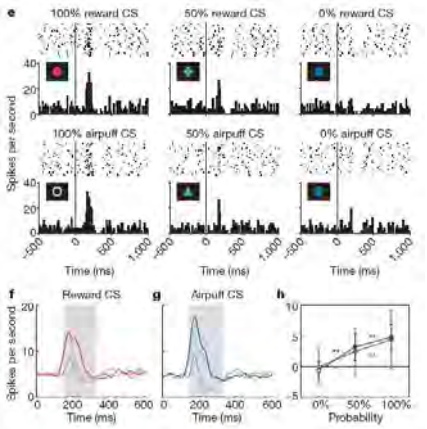
Stujenske et al., 2014

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

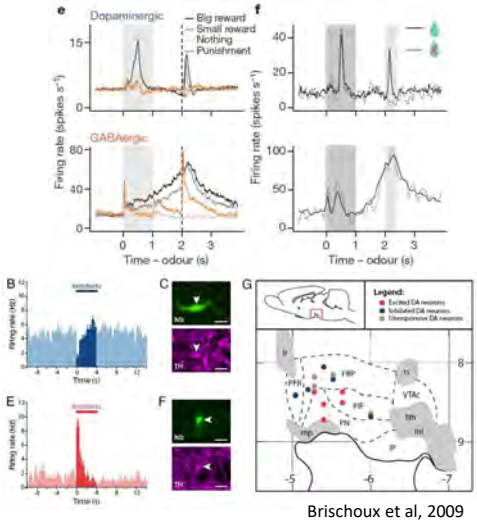
- Noradrenergic system enhances fear memory (Soeter et al, 2011).
- Aversive events affect dopamine transmission (Badrinarayan et al, 2012).
- Serotonin depletion leads to attenuated fear response (Hindi et al, 2012).

- Is dopamine system involved in fear and extinction learning?

Midbrain dopamine neurons may also respond to aversive signals.

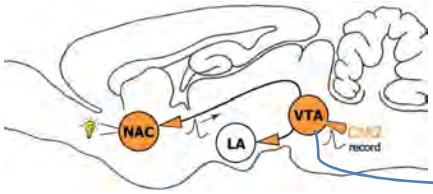


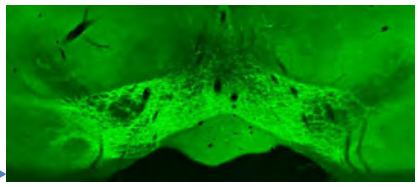
Matsumoto & Hikosaka 2009

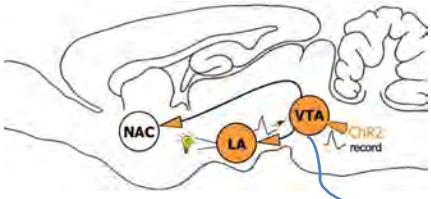


Brischoux et al, 2009

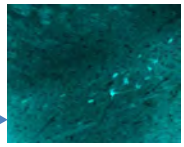
Optogenetic identification of VTA to LA and VTA to NAc dopamine projections.

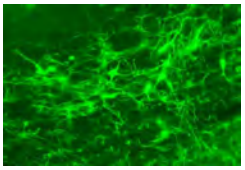






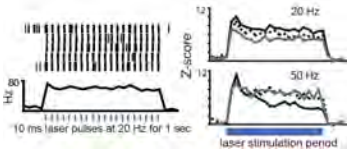
Fluorogold



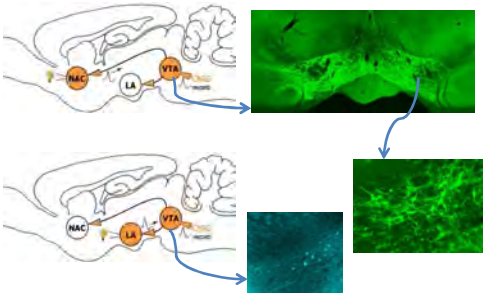


Halorhodopsin

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

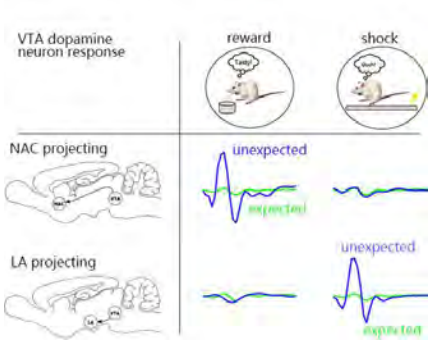


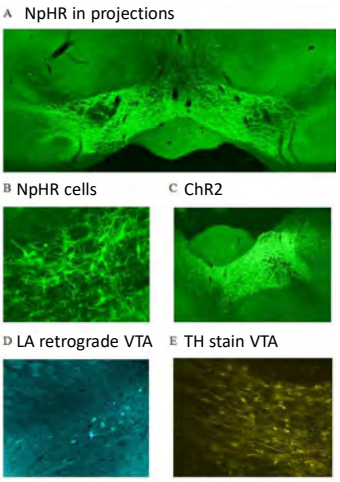
Johansen et al., 2010



- 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.

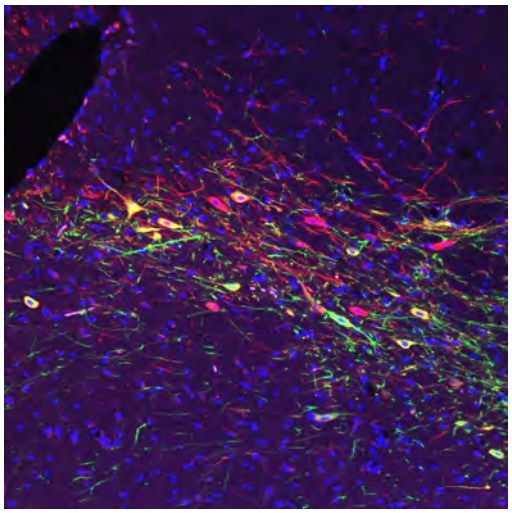
Hypothesis: VTA to LA projections code for aversive prediction error.

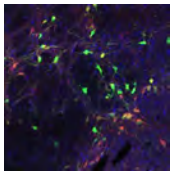




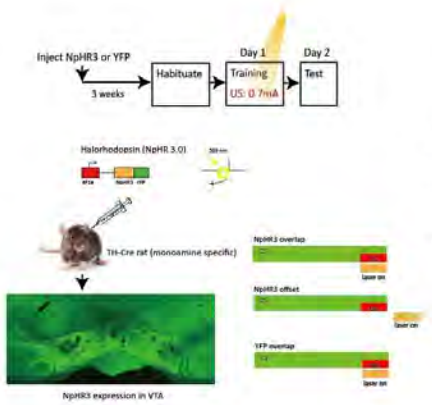
Approach: Optogenetic manipulation of VTA dopamine cells.

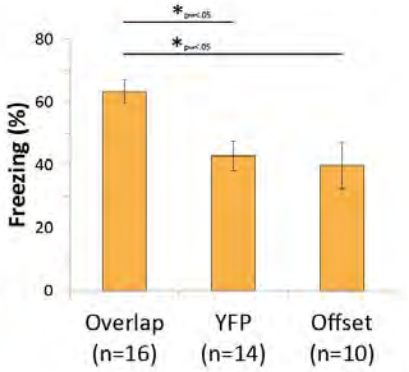
- TH (red) labeling dopaminergic cells in TH-cre animals.
- GFP (green) labeling NpHR (right) and Arch (below) infected cells.
- DAPI (blue) nucleus.





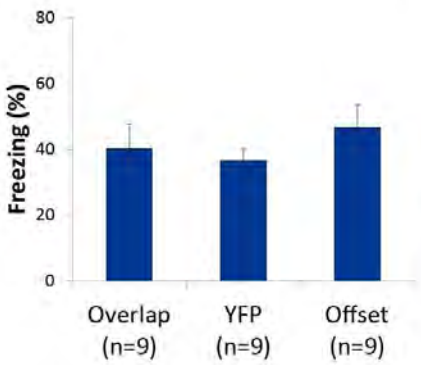
Optogenetic inhibition of VTA dopamine cells during shock US presentation increases fear learning.

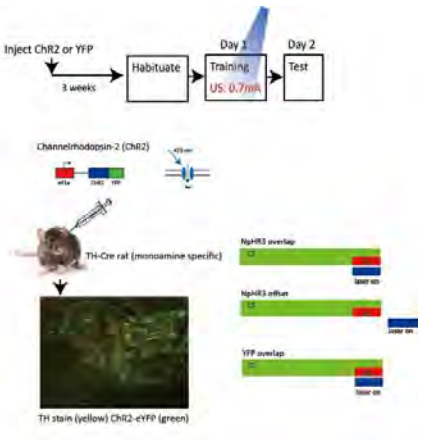




In collaboration with Luca Aquili

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





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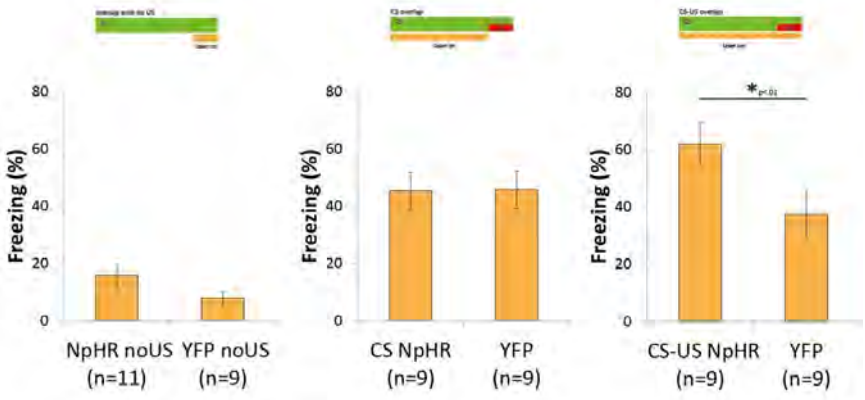
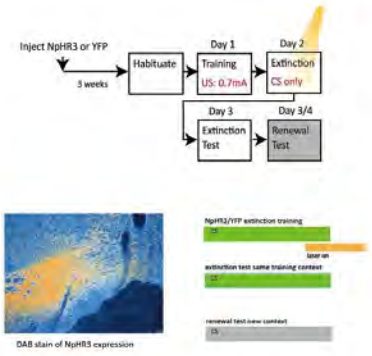
Neither optogenetic inhibition during CS nor following CS alone affects fear learning.

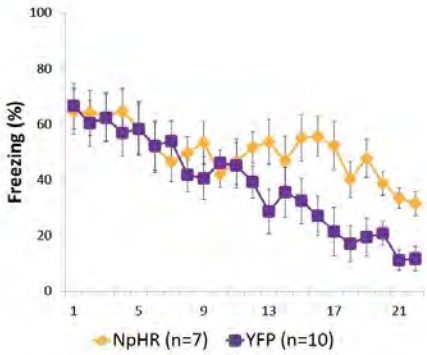


In collaboration with Luca Aquili

Does VTA dopamine neurons affect extinction learning?

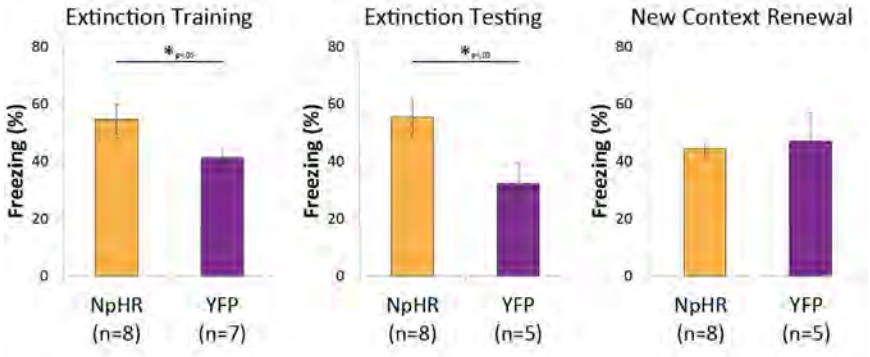
Optogenetic inhibition of VTA dopamine cells during period of expected US presentation.





riken bsi rayluo.bol.ucla.edu/projects

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



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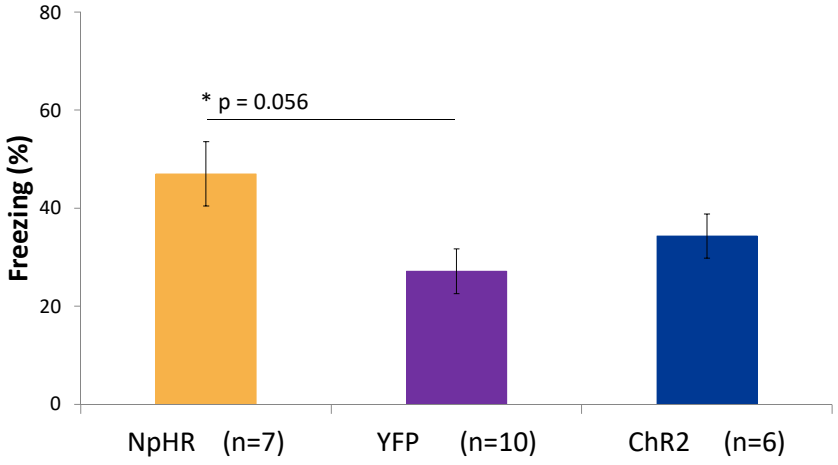
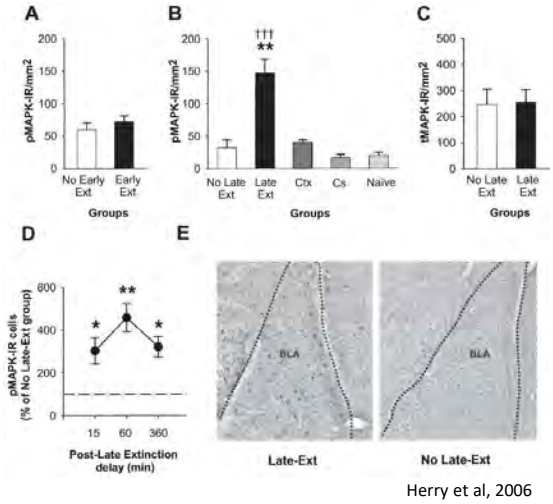
Optogenetic activation of VTA dopamine cells during expected US does not affect extinction.

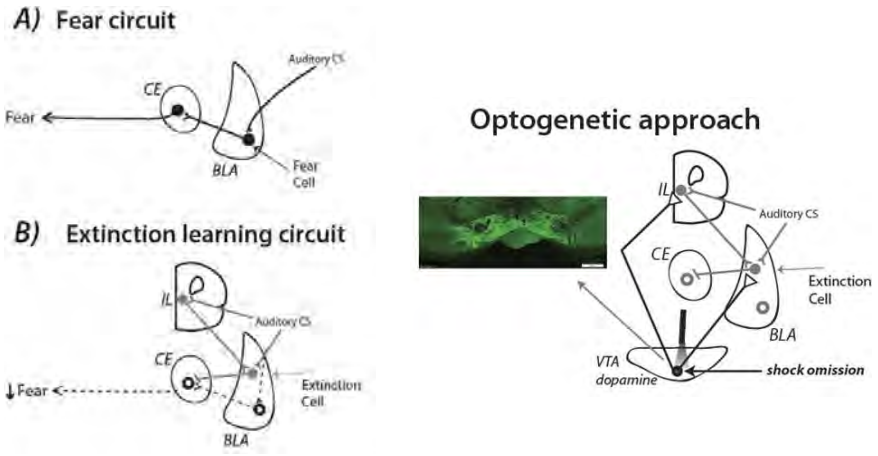


Extinction of fear is associated and requires BLA MAPK phosphorylation.



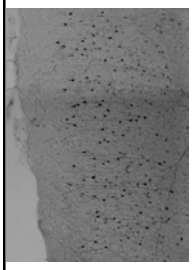
Herry et al, 2006

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

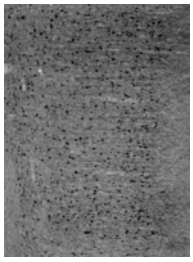


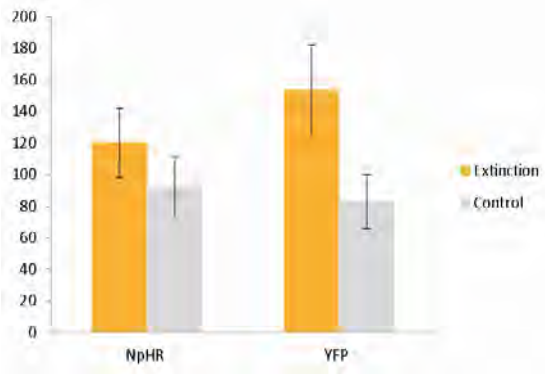
Inhibition of VTA dopamine during omissions in extinction reduces MAPK phosphorylation in mPFC (IL).

Extinction
NpHR:
53.9 cells/mm2



Extinction
YFP:
220.8 cells/mm2

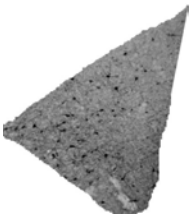


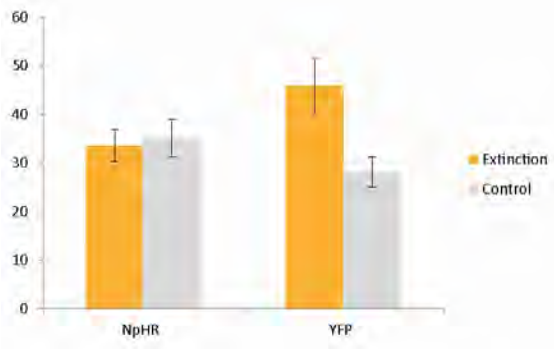


Inhibition of VTA dopamine during omissions in extinction reduces MAPK phosphorylation in BLA (LA).

Extinction
NpHR:
14.0 cells/mm2

Extinction
YFP:
56.2 cells/mm2





What are VTA and LA cells doing during fear learning?

learning actual expected

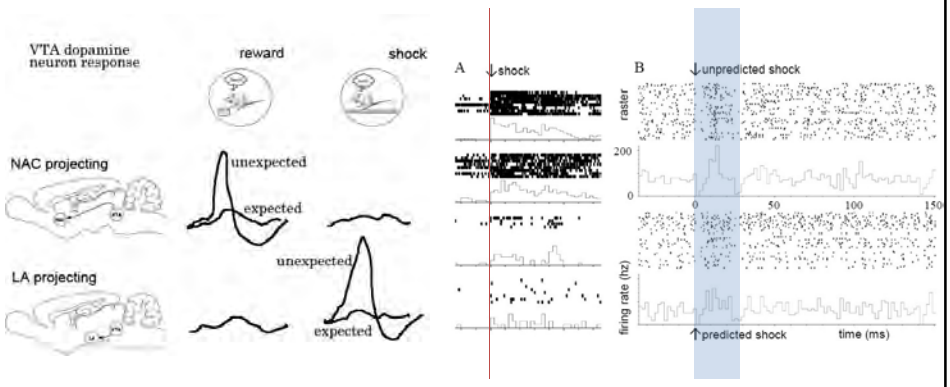
$$\Delta V \propto (\lambda - \Sigma V)$$

US CS

Rescorla & Wagner, 1972

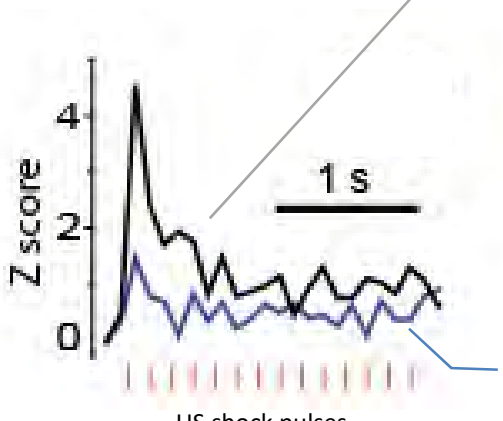
Prediction error coding can explain learning in classical conditioning.
Model explains phenomena such as blocking and learning asymptote.

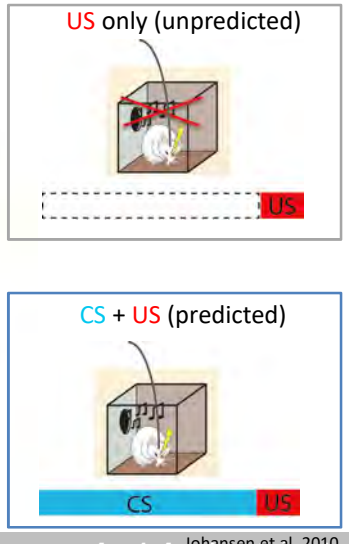
Do VTA to LA projections code for aversive prediction error?



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

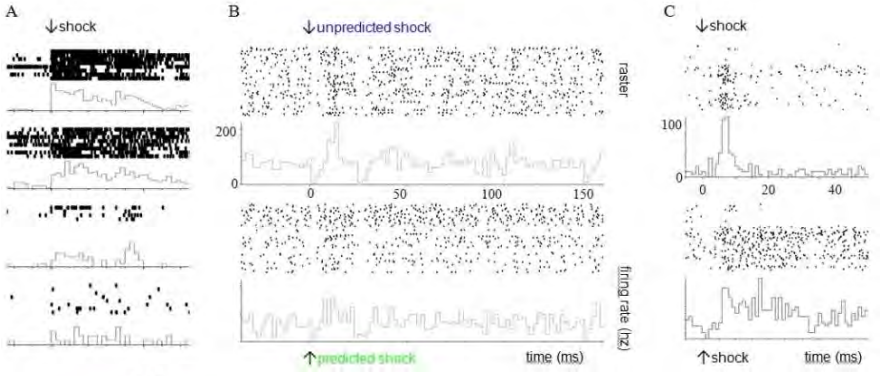
$$\Delta V \propto (\lambda - \Sigma V)$$





Johansen et al, 2010

VTA neurons respond to aversive outcomes and outcome contingencies.

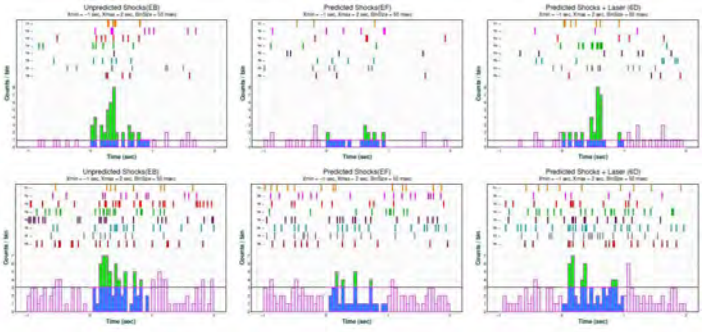


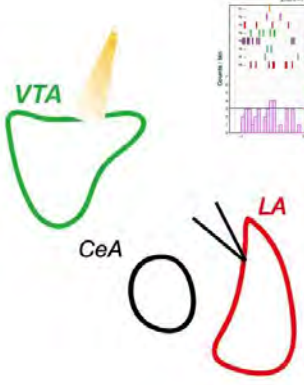
learning = a difference between actual and expected:

$$\Delta V = \delta = (\lambda - \Sigma V)$$

prediction error US CS

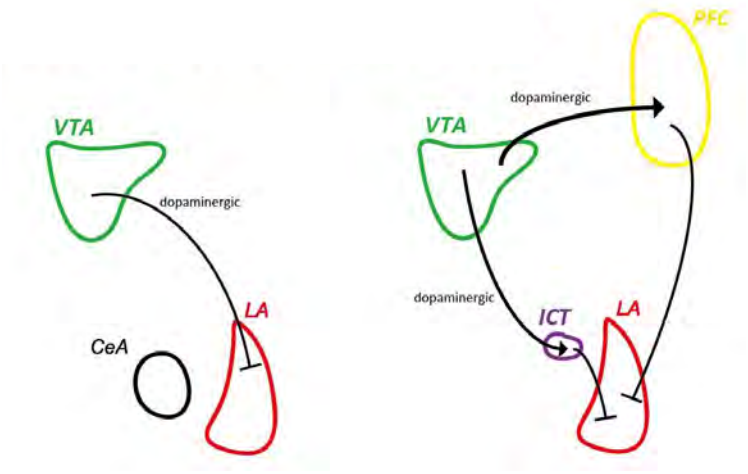
LA pyramidal cells respond to unpredicted shocks and to prediction errors in trained animals.



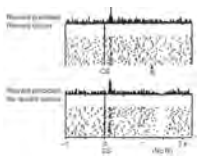


Preliminary: 209 cells, 72 shock reponsive, 24 prediction error.

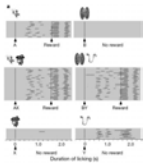
Circuit model of fear and extinction learning: modulation by VTA dopamine neurons.



Midbrain dopamine neurons encode rewarding as well as aversive signals.



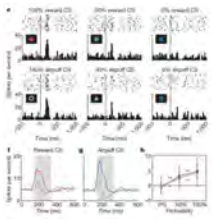
Schultz et al, 1997



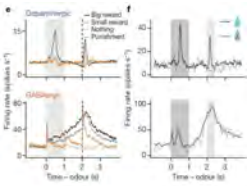
Waelti et al, 2001

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?

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

Questions?