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Prediction and modulation of fear.

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Jlab
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FOR THE NEURAL CIRCUITRY OF MEMORY

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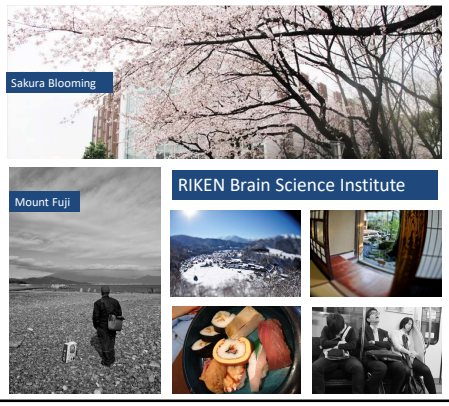

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Ability to predict aversive threats must be learned reliably and quickly.

Aversive events can affect everyday life.

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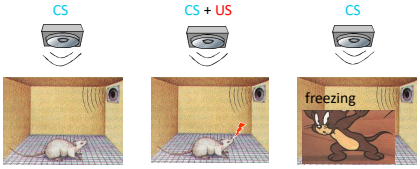
Pavlovian fear conditioning can serve as a model for aversive prediction.



habituation training testing

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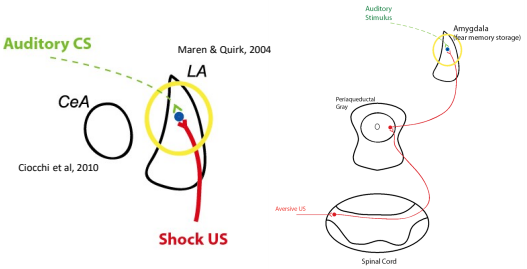
Microcircuitry in the amygdala mediates fear conditioning.



Johansen et al, 2010

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Prediction and modulation of fear circuits are important for adaption in complex world.

- Prediction is using sensory cues to guide adaptive behavioral responses.
- Predictability is influenced by strength of stimuli, amount of learning, and interference of sensory cues.

- Modulation is changing the effectiveness of a predictive cue based on context.
- Modulation is dependent on situation, generalizability of the learned response, attention, and salience.

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Prediction error coding can explain learning in classical conditioning.

learning actual expected

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

US CS

Rescorla & Wagner, 1972

Model explains phenomena such as blocking and learning asymptote.

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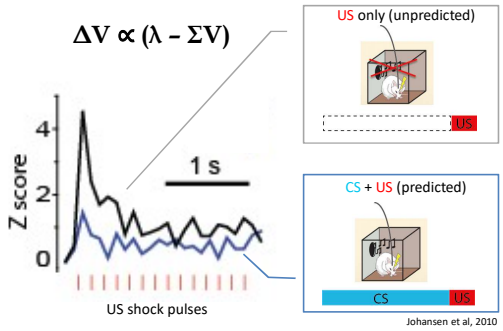
Prediction error coding can explain differential responses to predicted vs. unpredicted US.

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



Johansen et al, 2010

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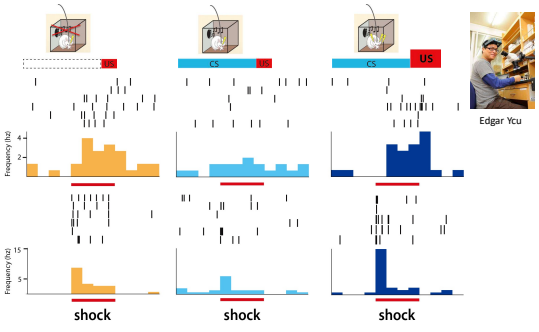
LA pyramidal cells respond to unpredicted shocks and to stronger shocks in trained animals.



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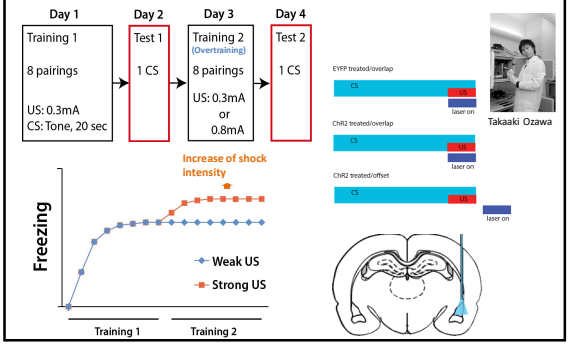
Hypothesis: LA pyramidal neurons set levels for fear learning.



Takaaki Ozawa

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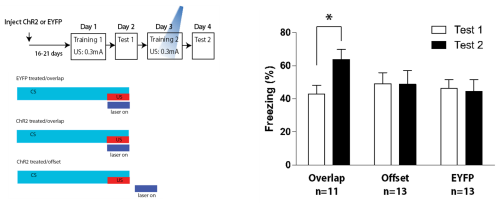
Activation of LA pyramidal cells during US period increases learning asymptote.



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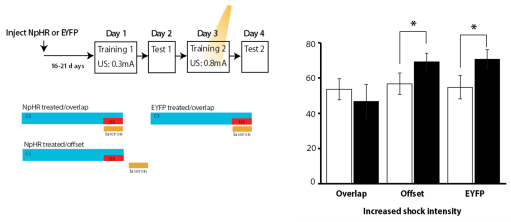
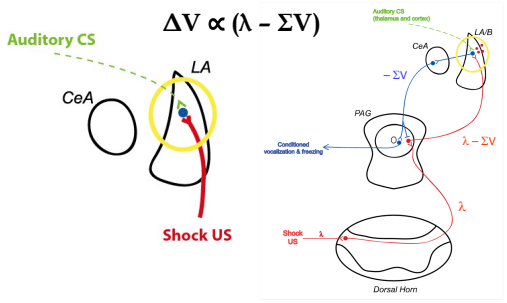
Inhibition of LA pyramidal cells during US period blocks increases in learning asymptote.



Question: What circuit is computing sum of associative inputs (CS)?

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

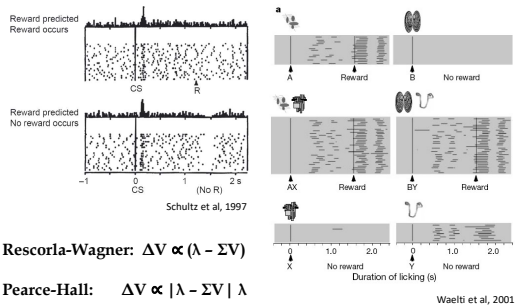


Question: How is fear learning modulated by different transmitter systems based on context?

- 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 learning?

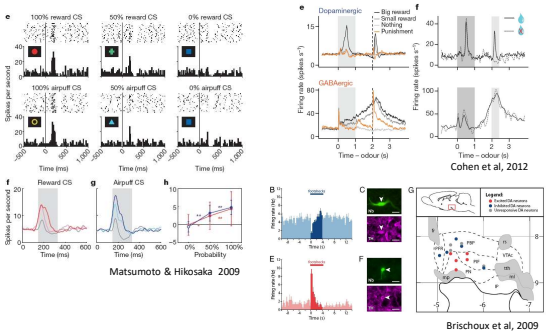
Midbrain dopamine neurons code for reward and reward prediction error.



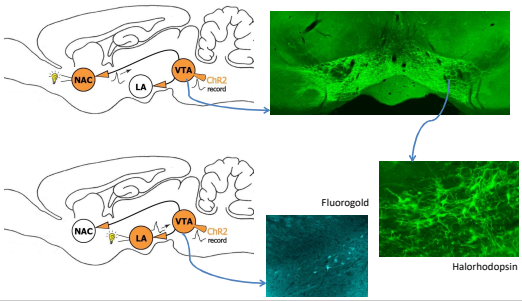
Rescorla-Wagner: $\Delta V \propto (\lambda - \Sigma V)$

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

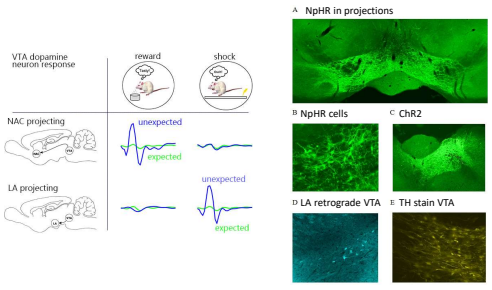
Midbrain dopamine neurons may also respond to aversive signals.



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



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



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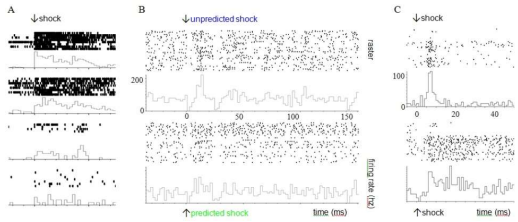
VTA neurons respond to aversive outcomes and outcome contingencies.



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

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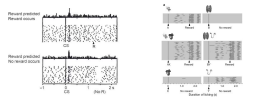
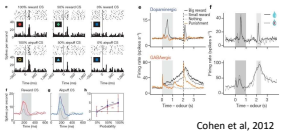
Midbrain dopamine neurons encode rewarding as well as aversive signals.



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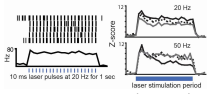
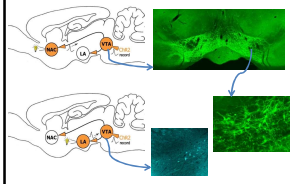
Use optogenetics to identify dopamine cells, trace their projections, manipulate activity.



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.

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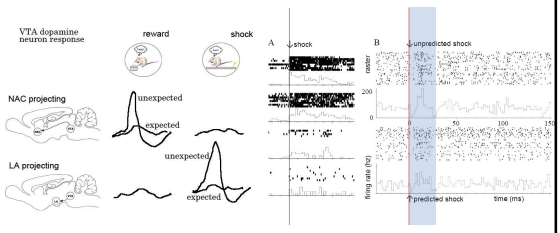
Do VTA to LA projections code for aversive prediction error?



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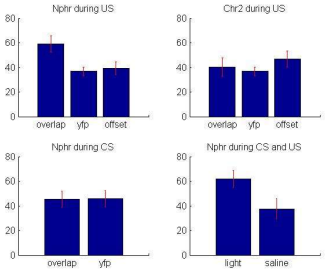
Inhibition of dopamine neurons during US period enhances fear learning.



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