

# Mathematische Modelle und neuronale Korrelate der Angstverarbeitung nach traumatischen Ereignissen

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<http://github.com/philiphoman/vie2018/>

# PTSD as a learning disorder: a clinical vignette



Credit: <http://www.x-rayscreener.co.uk>

- USA combat veteran with PTSD
- Injured by explosion while on street patrol in Iraq
- Acquired fear reaction to a trash pile used to hide an improvised explosive device
- Trash piles along the street now trigger fear reaction

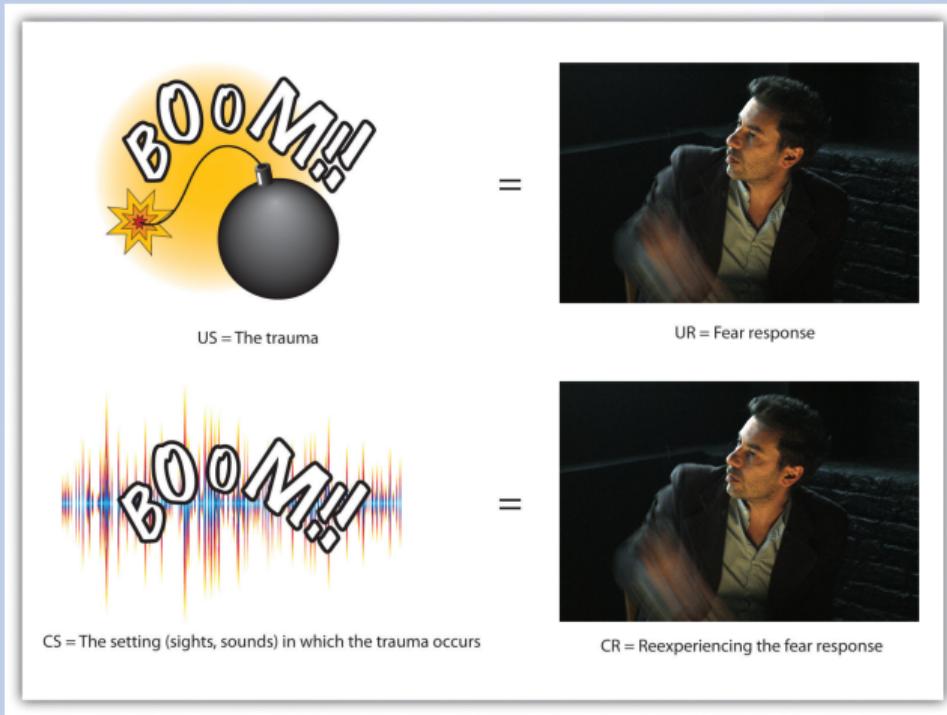
Lissek and Van Meurs 2015



# PTSD as a learning disorder

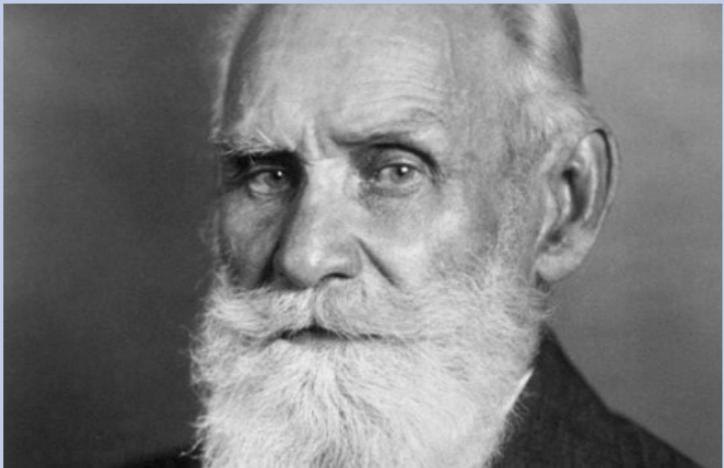
- Explicit conditioning episode
- Conditioned fear response
- Primary symptoms:
  1. Re-experiencing
  2. Avoidance
  3. Hypervigilance
- Of trauma-exposed individuals, 10-30% develop PTSD
- Why?

# Pavlovian fear conditioning

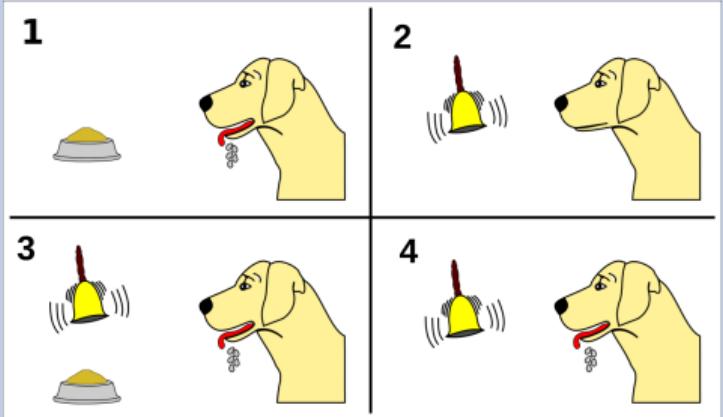


Credit: <http://open.lib.umn.edu>

# Learning by association



Ivan Pavlov (1849 - 1936)



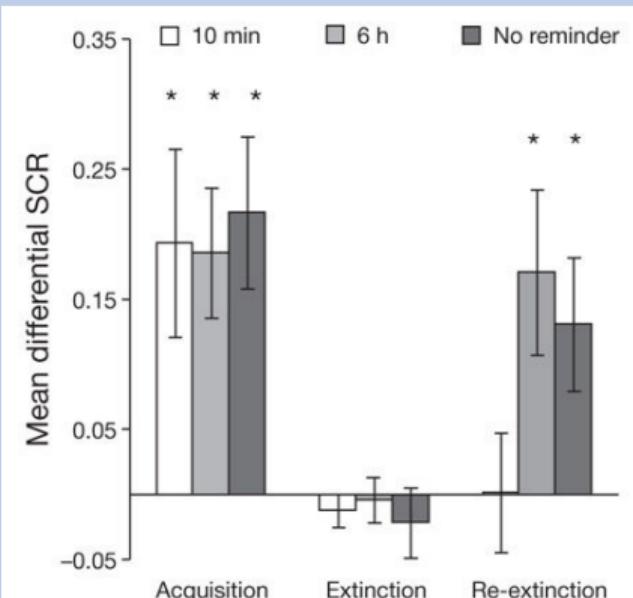
Credit: <https://www.psychestudy.com>

# Forgetting the memory of fear



**Daniela Schiller**

Dept. of Psychology, New York University



Schiller et al. 2010, Nature



# Posttraumatic stress disorder (PTSD)

- PTSD is unique: we have a highly relevant disease mechanism
- The disease mechanism:
  1. Helps understand the pathophysiology
  2. Suggests a suitable treatment
- Computational modeling to describe the mechanism



# Warum mathematische Modelle?

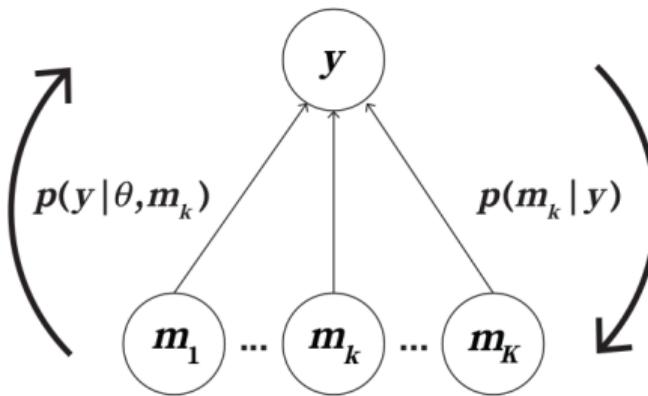
Messbares Angstverhalten ( $y$ ) = Mathematisches Modell ( $m$ ) + Noise ( $e$ )

# Warum mathematische Modelle?

## Differentialdiagnose durch Modellselektion

**Symptom**  
(Verhalten oder  
Physiologie)

**Hypothetischer  
Mechanismus**



$$p(m_k | y) = \frac{p(y | m_k) p(m_k)}{\sum_k p(y | m_k) p(m_k)}$$

Stephan et al. 2017



# Grundannahme

Mit den Modellen sind wir näher an den  
krankheitsrelevanten Mechanismen



# Grundannahme

Finden mit den Modellen die entscheidenden Parameter für:

1. Differentialdiagnostik
2. Individuelle Therapie



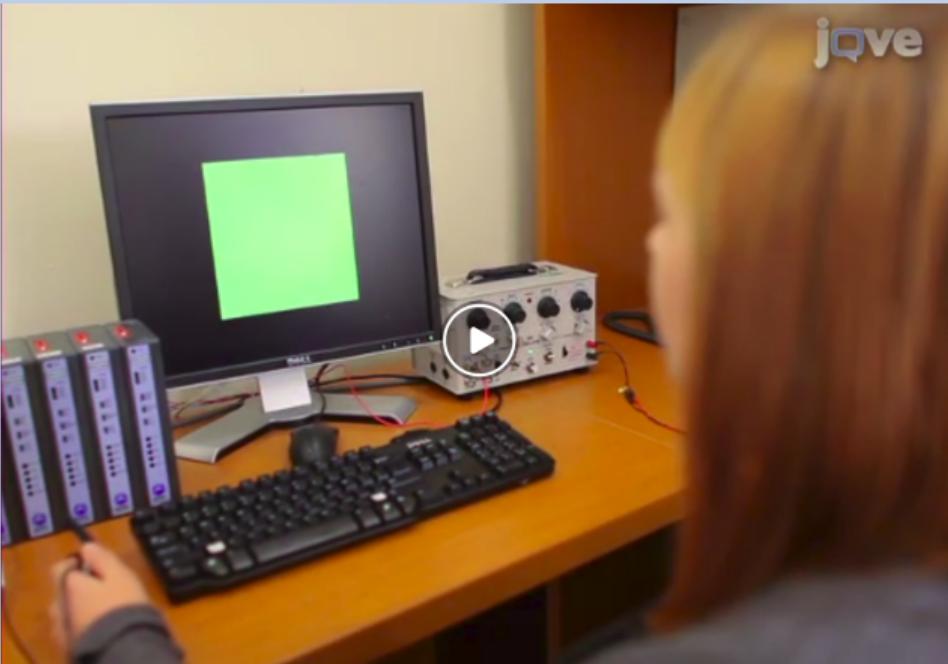
# PTSD is unique in that we seem to have a mechanism

## Fear conditioning:

- Helps understand the pathophysiology
- Suggests a treatment (exposure therapy)

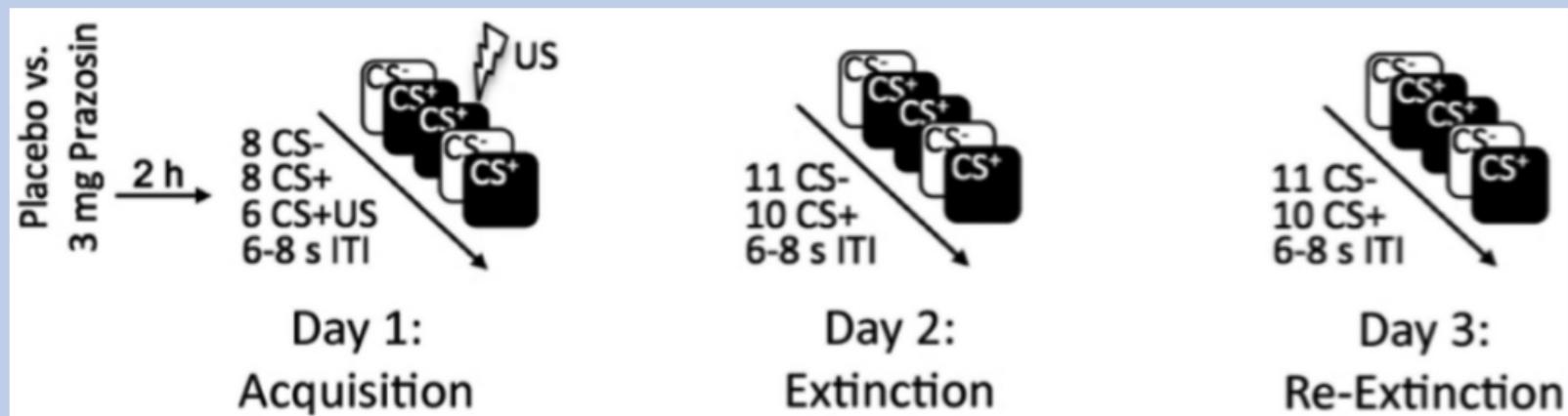


# A mechanism we can study in the lab



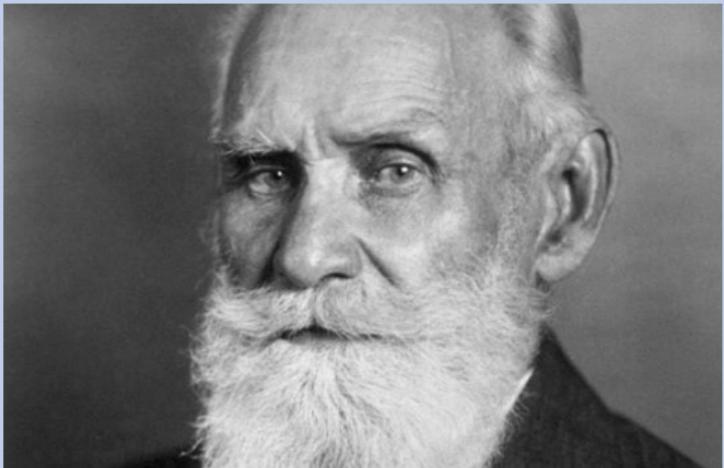
Schiller et al. 2013, J Vis Exp

# A mechanism we can study in the lab

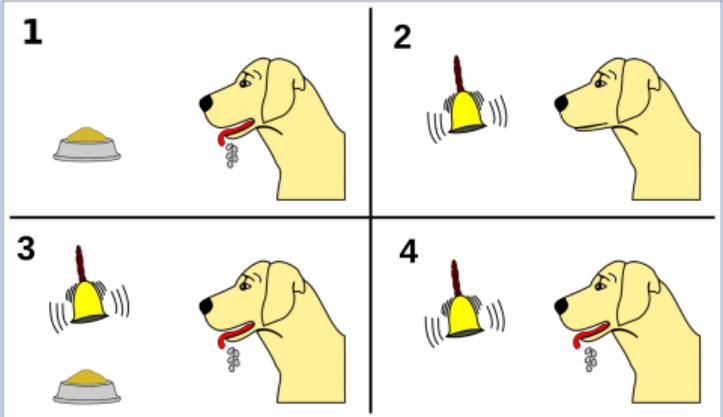


Homan et al. 2017, Learn Mem

# Learning by association

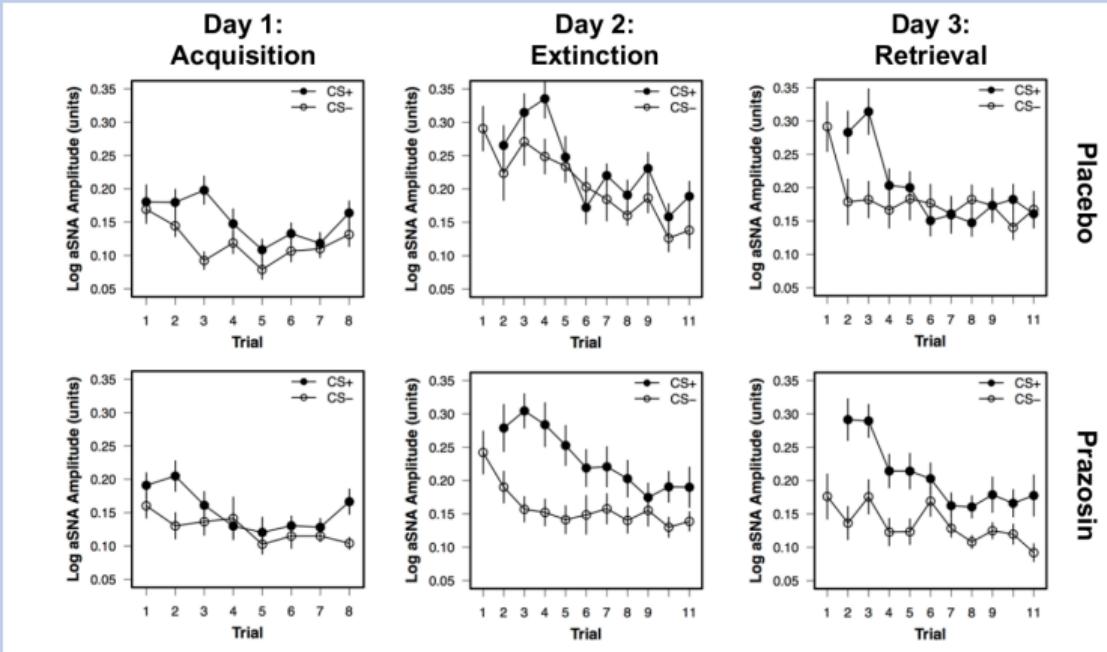


Ivan Pavlov (1849 - 1936)



Credit: <https://www.psychestudy.com>

# A mechanism that can be modulated with a drug (Prazosin)



Homan et al. 2017, Learn Mem

# But: PTSD is more than this mechanism

## Associative (Pavlovian):

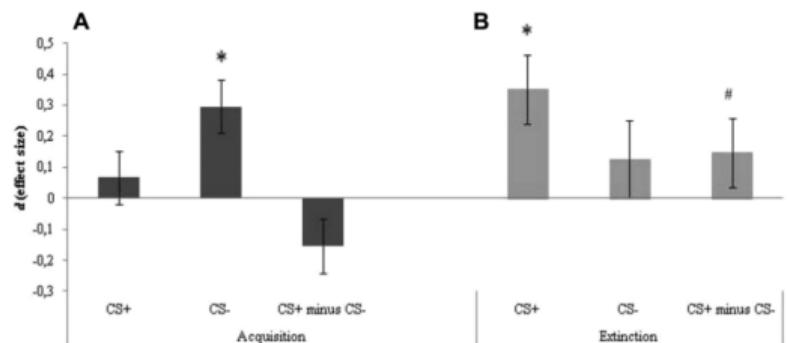
- Resistance to fear extinction
- Increased fear excitation
- Reduced fear inhibition
- Over-generalization

## Non-associative:

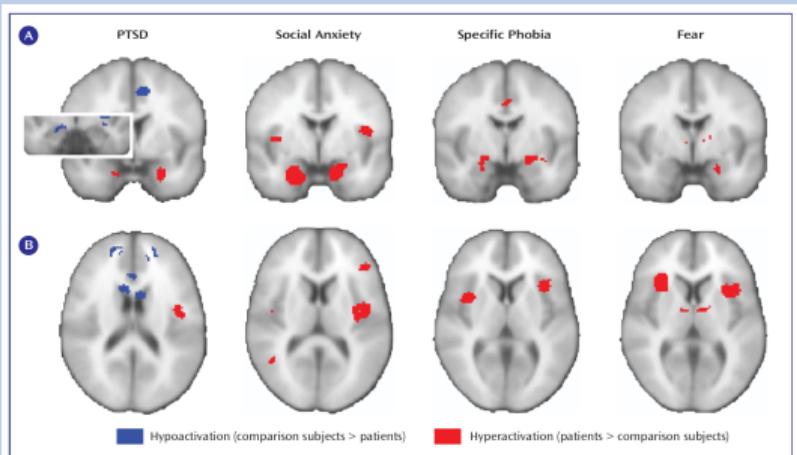
- Failure to habituate to fear relevant stimuli
- Sensitization (hyper-arousal)

# Fear conditioning and extinction in PTSD

*Review: Updated Meta-Analysis of Fear Conditioning in Anxiety Disorders*

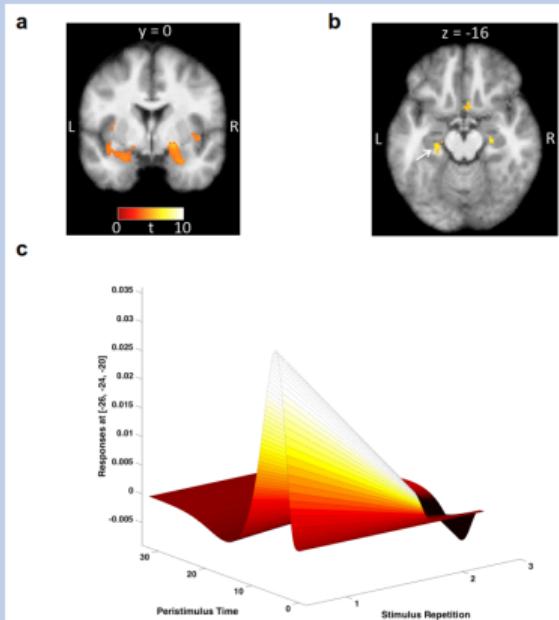


Duits et al. 2015, *Depress Anxiety*



Ektin and Wager 2007, *Am J Psychiatry*

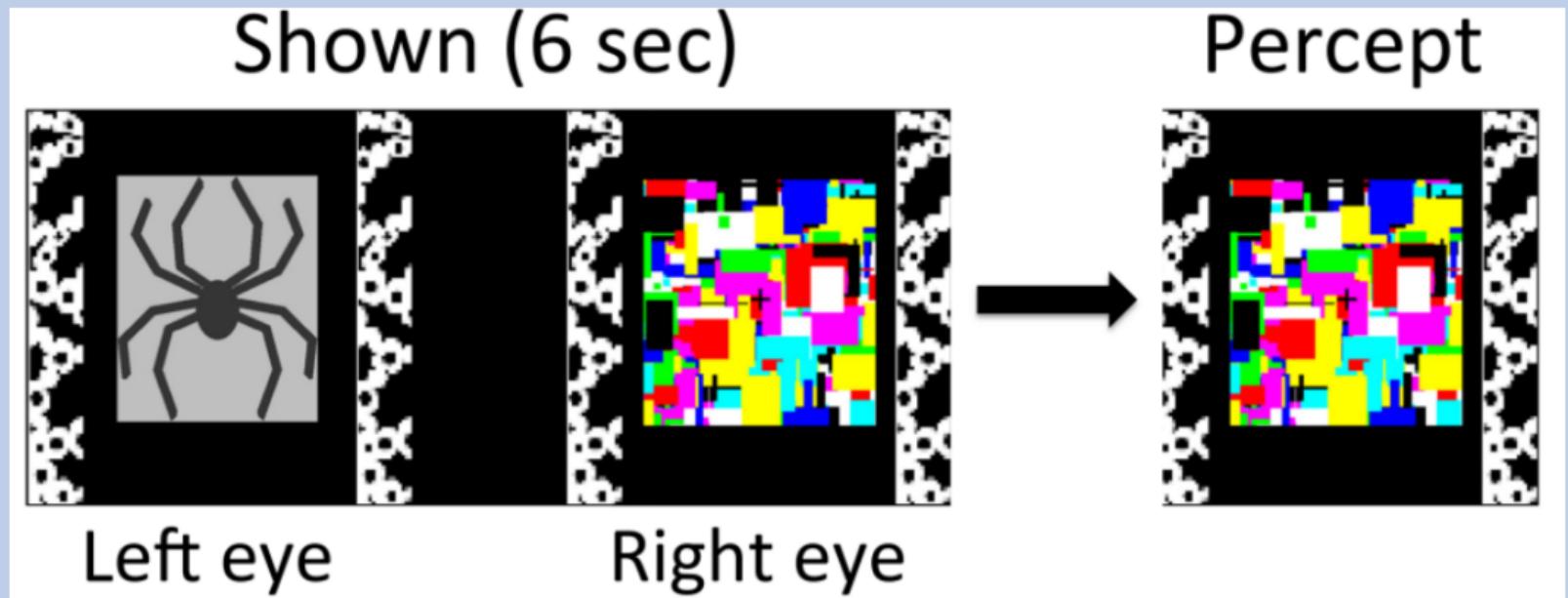
# A central role for the amygdala



- Activates in response to aversive stimuli
- Is the neural correlate of the conditioned response
- Activates even without conscious awareness of the stimulus

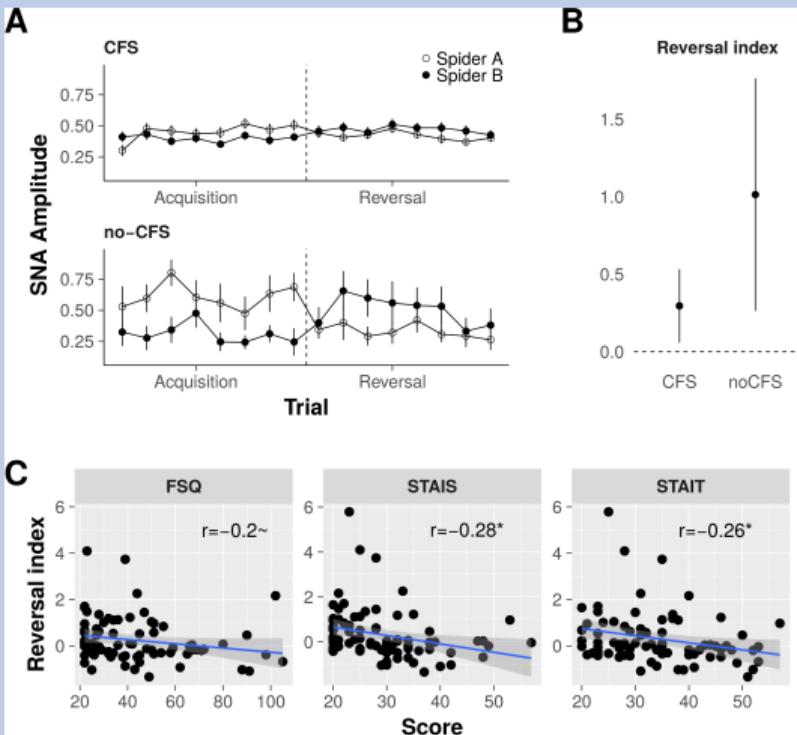
Homan et al. 2017, Neurobiol Learn Mem

# Fear conditioning without conscious awareness



Homan et al., submitted

# Fear conditioning without conscious awareness

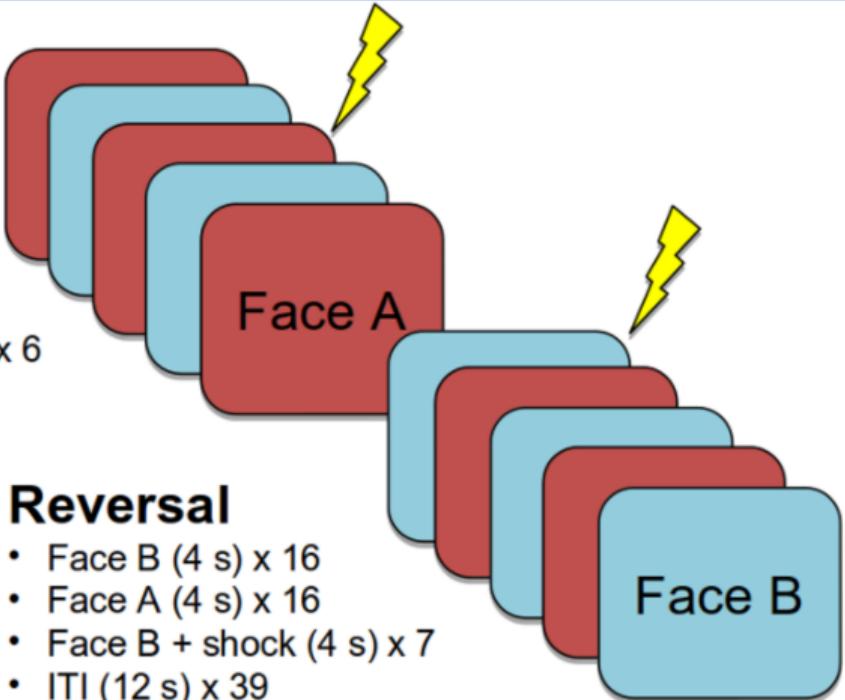


Homan et al., submitted

# Beyond fear conditioning: reversal learning

## Acquisition

- Face A (4 s) x 12
- Face B (4 s) x 12
- Face A + shock (4 s) x 6
- ITI (12 s) x 30



## Reversal

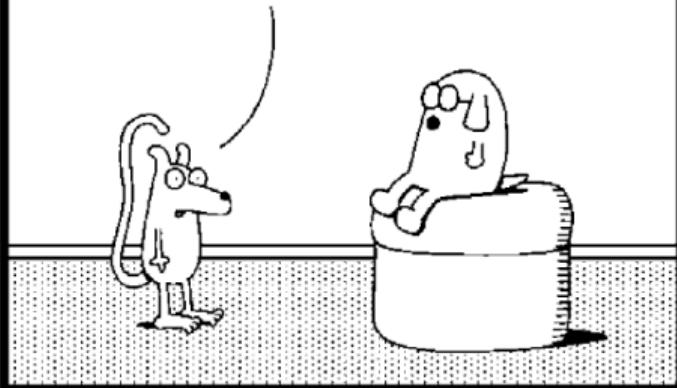
- Face B (4 s) x 16
- Face A (4 s) x 16
- Face B + shock (4 s) x 7
- ITI (12 s) x 39

Homan et al., in revision



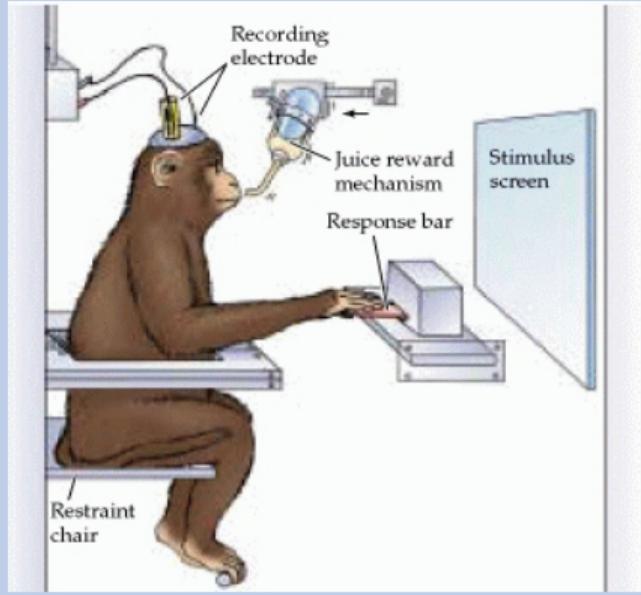
# Learning from being wrong

I'M ALWAYS WRONG  
ABOUT EVERYTHING.  
WHAT CAN I DO TO  
FIX THAT?



DILBERT: © Scott Adams/Dist. by United Feature Syndicate, Inc

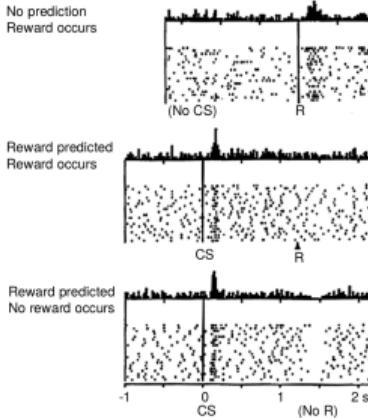
# Dopamine and prediction error



## A Neural Substrate of Prediction and Reward

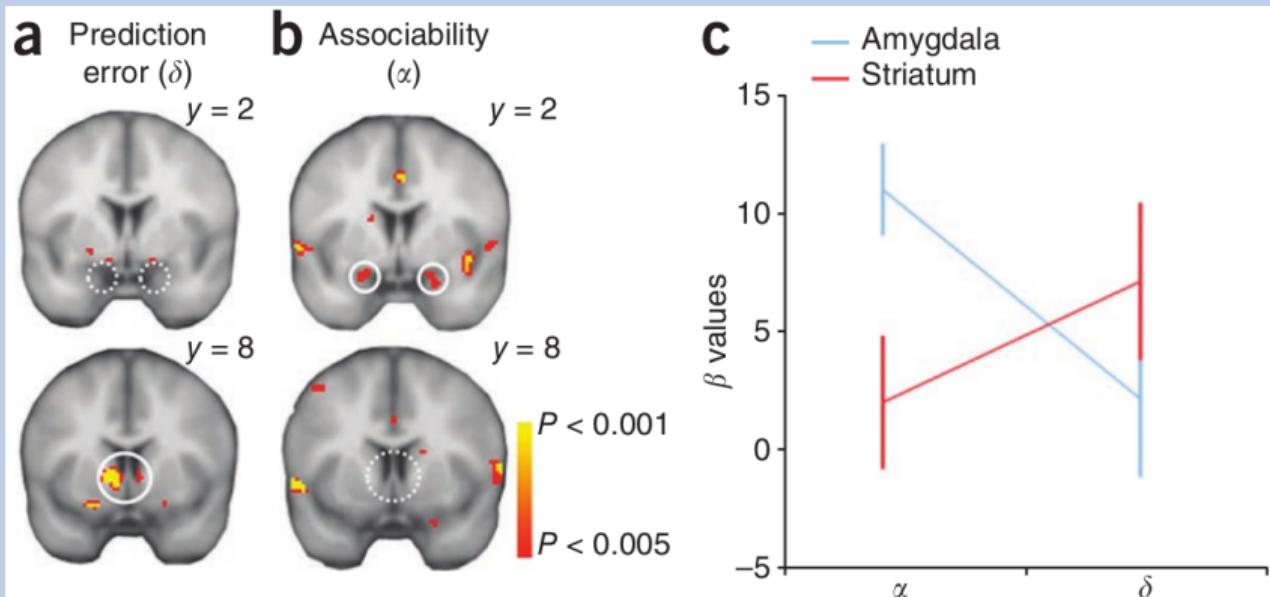
Wolfram Schultz, Peter Dayan, P. Read Montague\*

Do dopamine neurons report an error  
in the prediction of reward?



Schultz, Dayan, Montague 1997, Science

# A computational approach to fear reversal learning

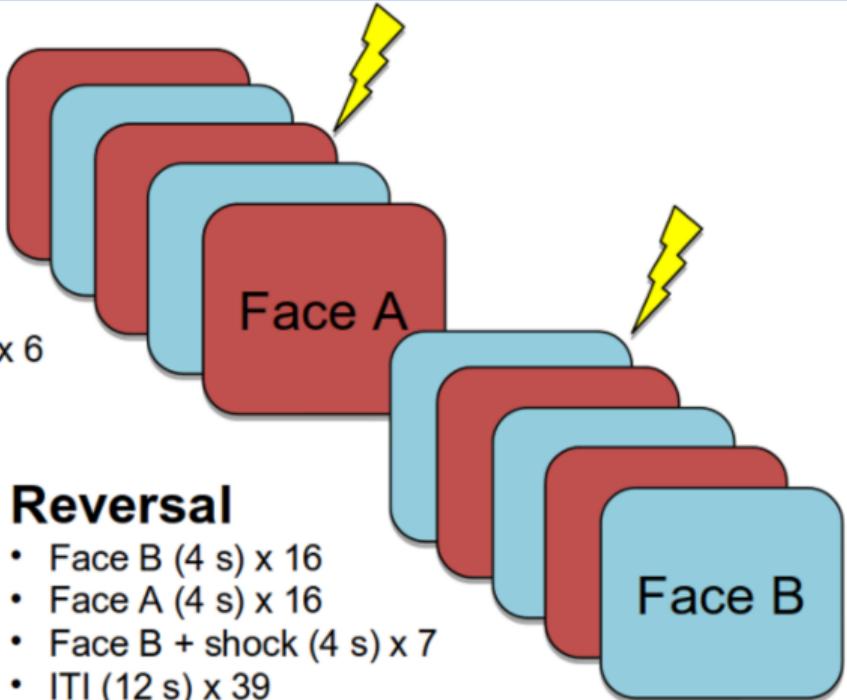


Li et al. 2011, Nat Neurosci

# Fear learning in combat veterans

## Acquisition

- Face A (4 s) x 12
- Face B (4 s) x 12
- Face A + shock (4 s) x 6
- ITI (12 s) x 30

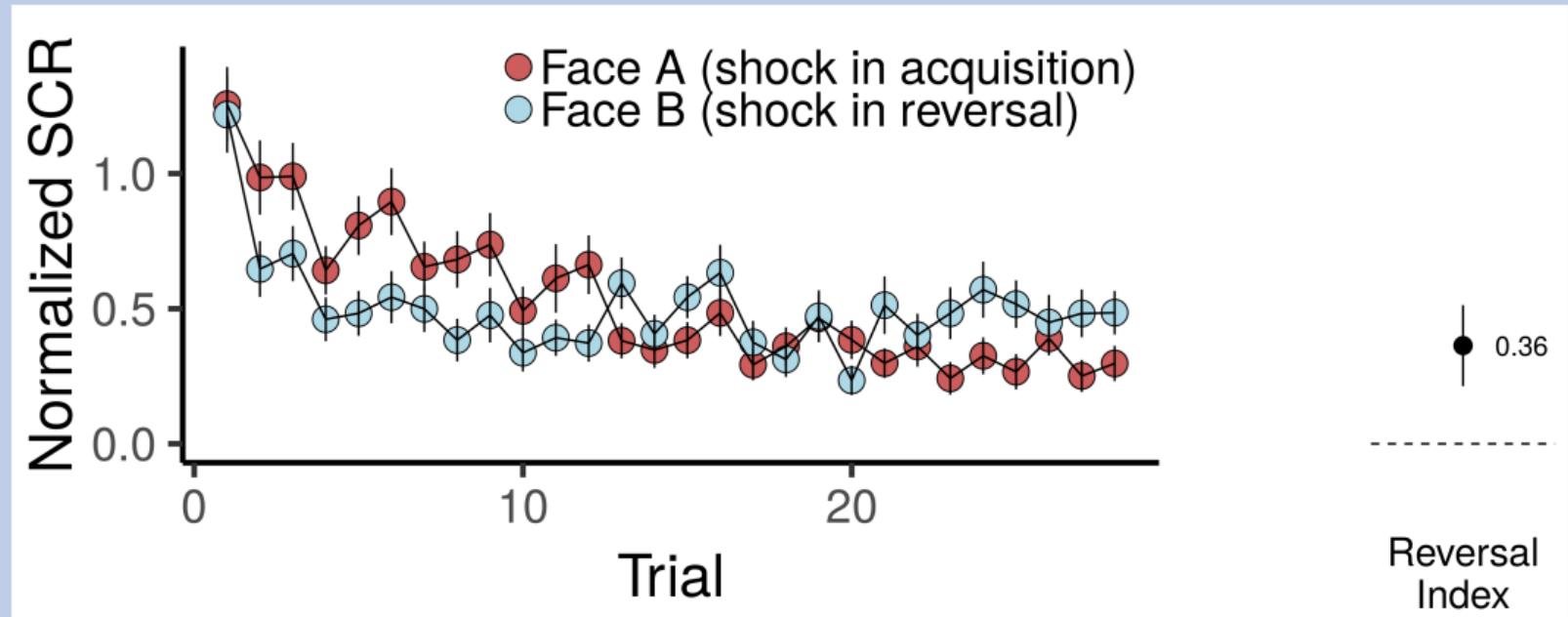


## Reversal

- Face B (4 s) x 16
- Face A (4 s) x 16
- Face B + shock (4 s) x 7
- ITI (12 s) x 39

Homan et al., in revision

# Fear learning in combat veterans

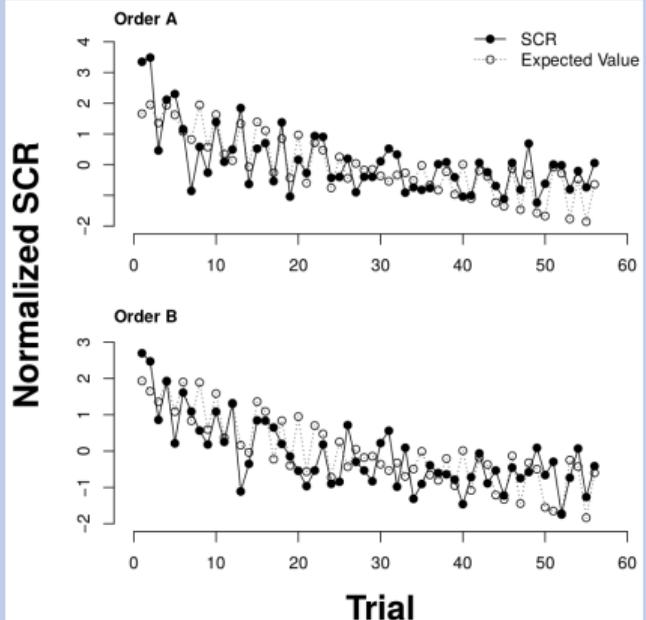


Homan et al., in revision

# Modeling fear learning behavior: learning from surprise

$$V_{n+1}(x_n) = V_n(x_n) + \alpha \delta_n$$

$$\delta_n = r_n - V_n(x_n)$$

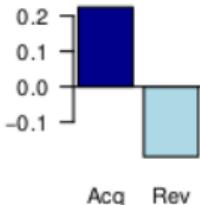
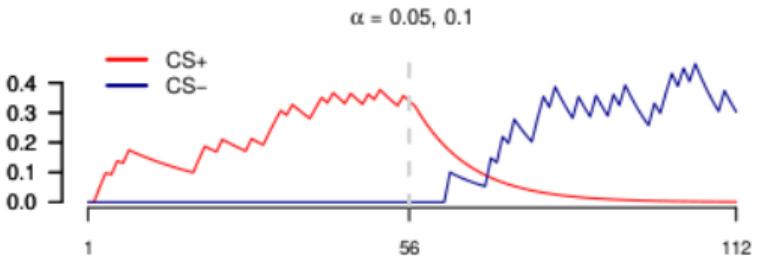


Homan et al., in revision

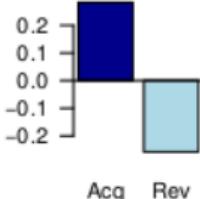
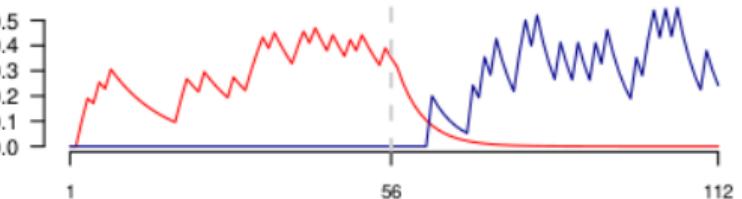
# The learning rate determines the volatility of the behavior

$$R-W \text{ model: } v_{t+1} = v_t + \alpha(\lambda - v_t)$$

Expected Value



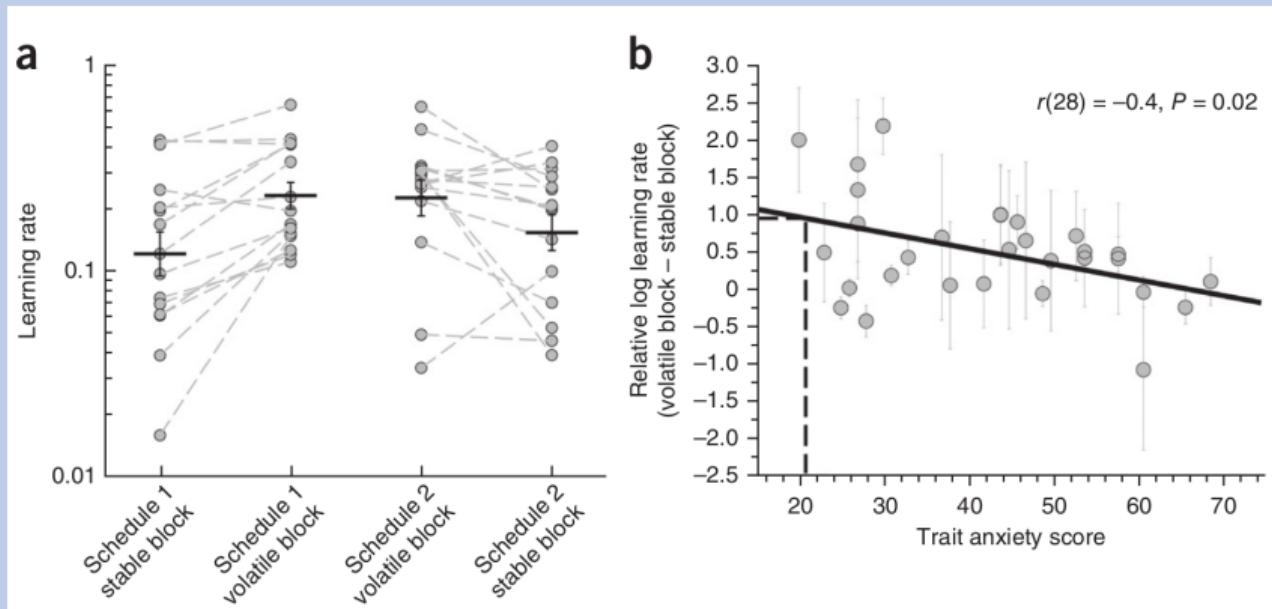
$$\alpha = 0.1, 0.2$$



Trial

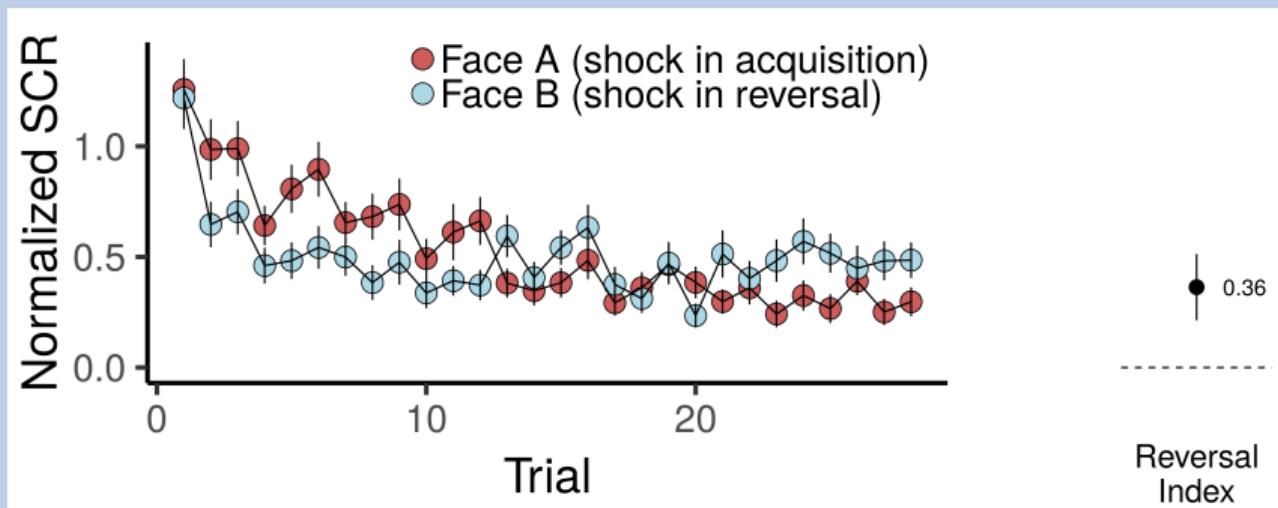
Homan et al., in revision

# Anxiety and volatility



Browning et al., 2015, Nat Neurosci

# Describing observed data

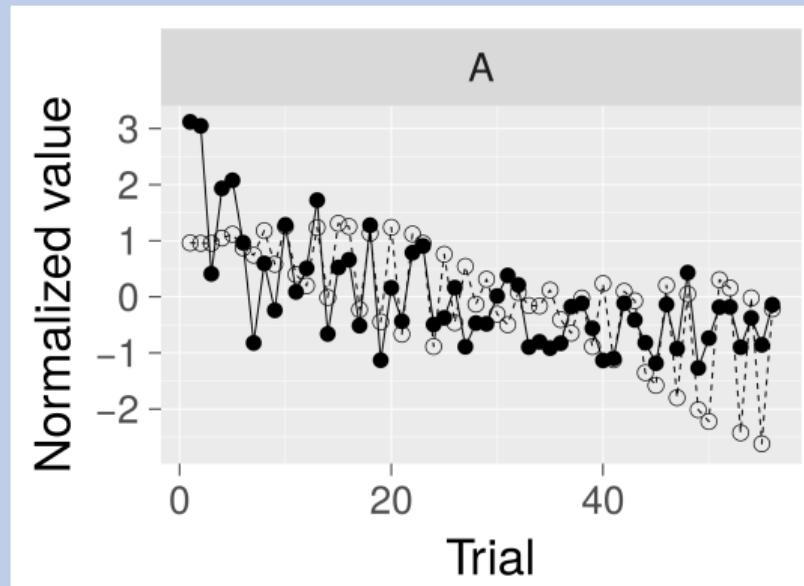


Homan et al., in revision

# Modeling fear learning behavior: considering surprise and attention

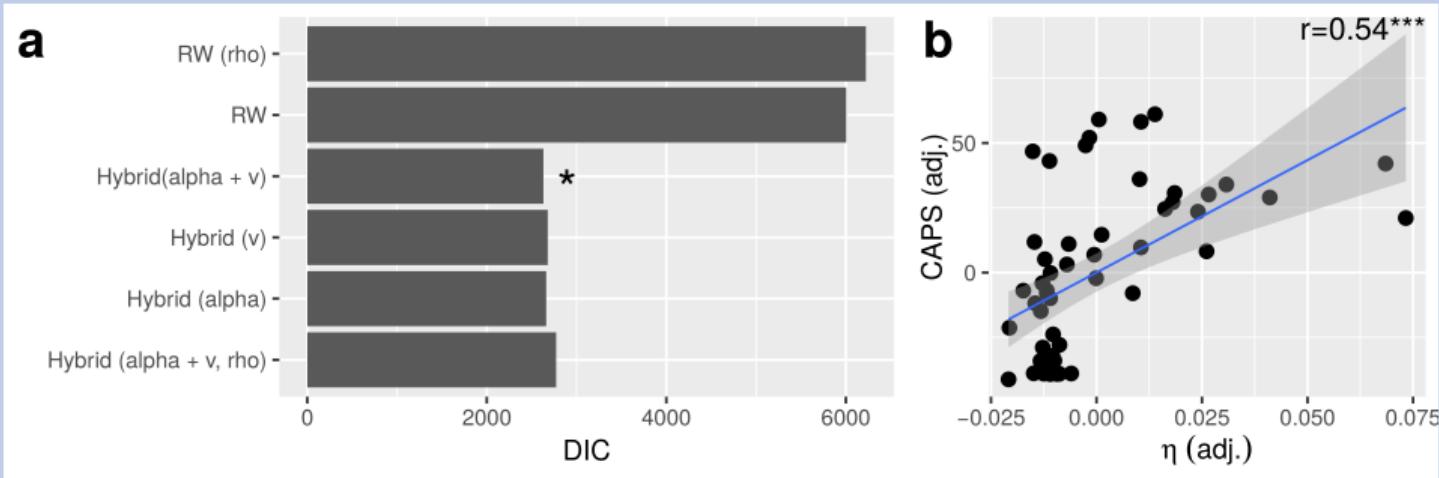
$$V_{n+1}(x_n) = V_n(x_n) + \kappa \alpha_n(x_n) \delta_n$$

$$\alpha_{n+1}(x_n) = \eta |\delta_n| + (1 - \eta) \alpha_n(x_n)$$



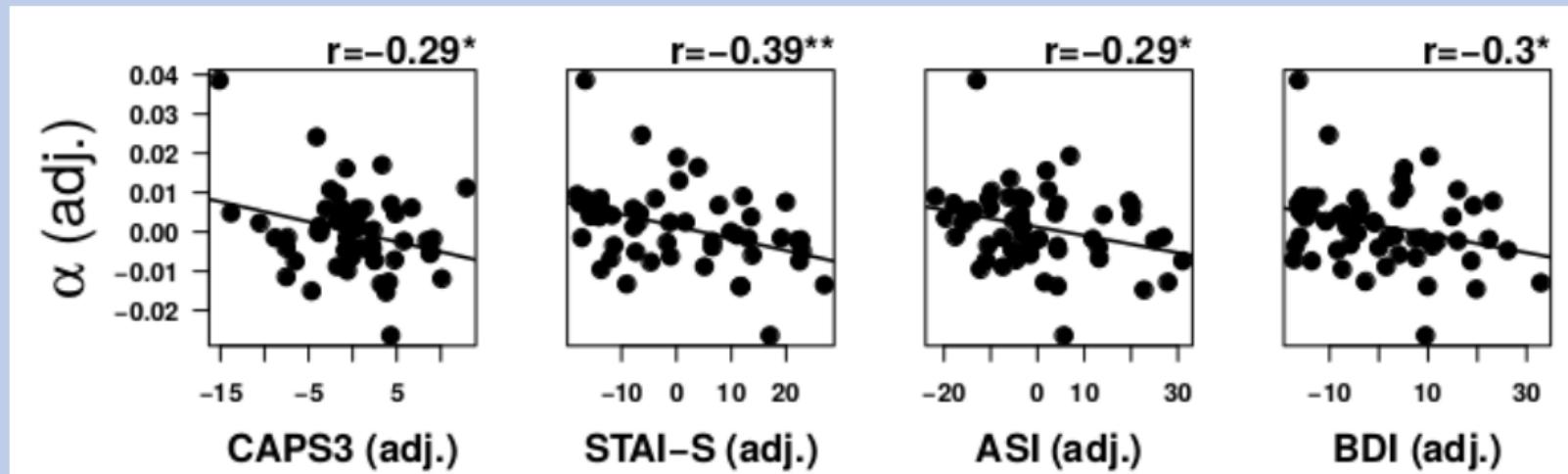
Homan et al., in revision

# Model predictions correlate with PTSD symptoms



Homan et al., in revision

# Model predictions correlate with PTSD symptoms

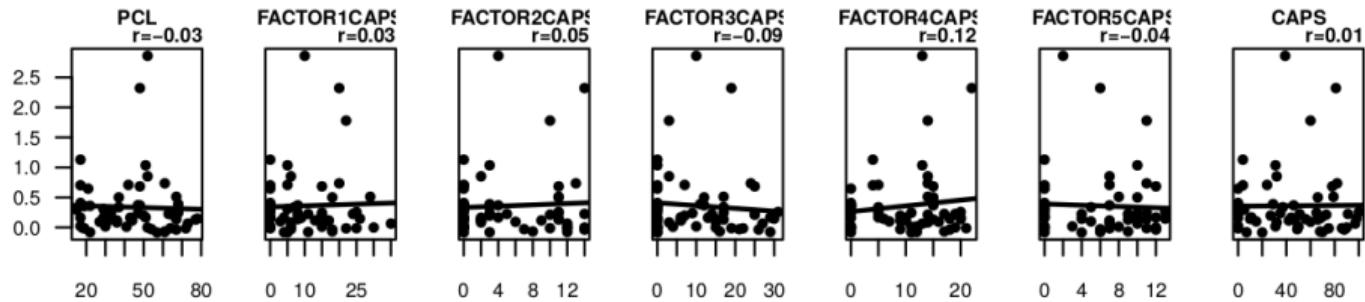


Homan et al., in prep.

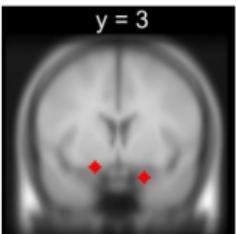
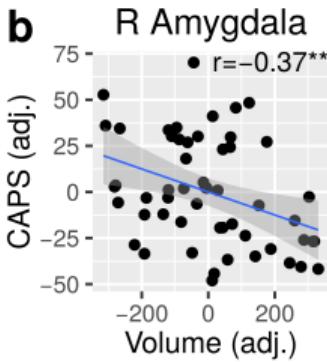
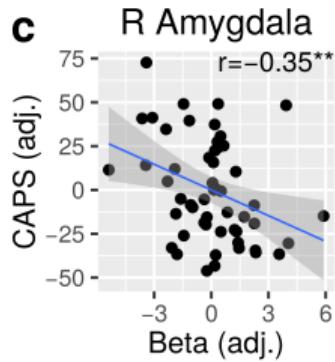
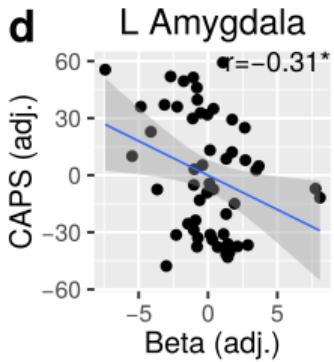
# ... whereas the observed behavior does not!

## Reversal Learning

VCC|PTSD



# Amygdala computations contribute to PTSD symptoms

**a****b****c****d**

Homan et al., in revision



# Summary

- Computational modeling detects differences in learning rate
- Both amygdala structure and computations contribute to PTSD
- Amygdala activity encodes expected aversive value (shocks)



# Conclusion

## Clinical implications:

1. Lower learning rates predicted higher numbing/depression symptoms
2. Suggests that depression should be treated before extinction therapy



# Acknowledgments

## Mount Sinai School of Medicine

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