

Neurocomputations of threat learning in combat veterans

Philipp Homan^{1,2,3}

¹The Donald and Barbara Zucker School of Medicine at Northwell/Hofstra, NY, USA

²The Feinstein Institute for Medical Research, Manhasset, NY, USA

³The Zucker Hillside Hospital, NY, USA

phoman1@northwell.edu

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



Conflicts of interest

Nothing to disclose



At a glance

- PTSD is unique: we have a highly relevant disease mechanism
- The disease mechanism:
 1. Explains the pathophysiology
 2. Suggests a suitable treatment
- We may learn even more with computational modeling

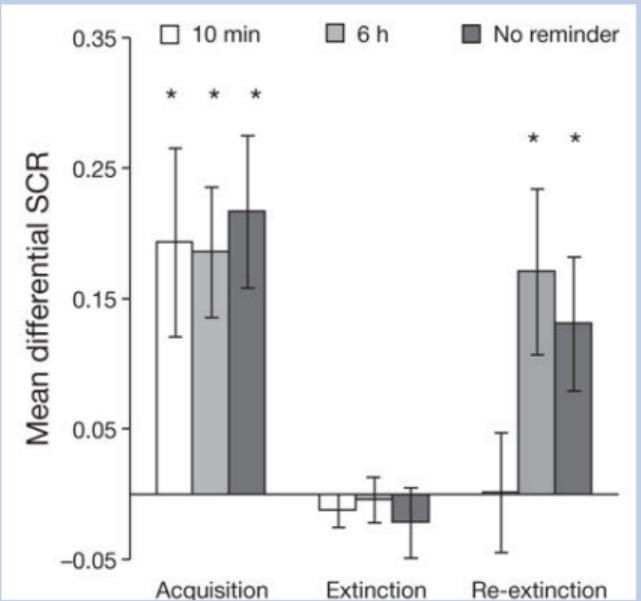


Introduction: Forgetting the memory of fear



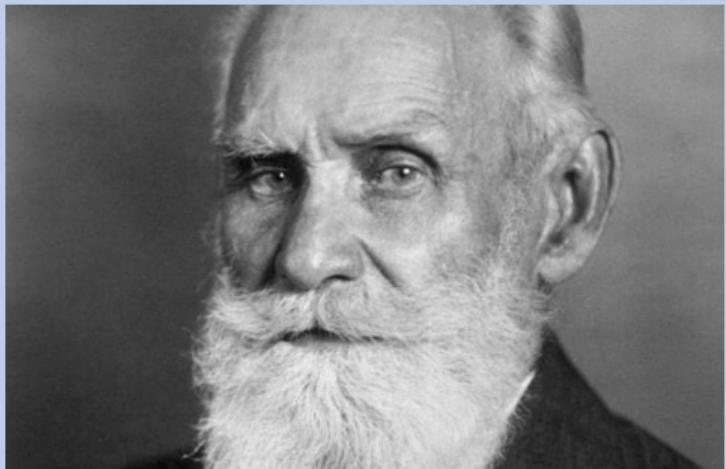
Daniela Schiller

Dept. of Psychology, New York University

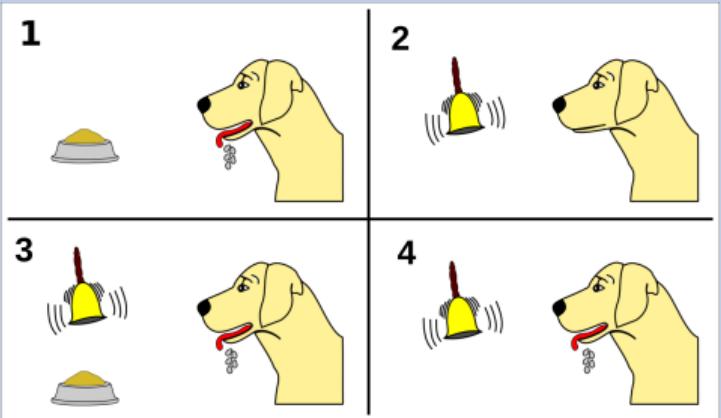


Schiller et al. 2010, Nature

Learning by association



Ivan Pavlov (1849 - 1936)



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

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

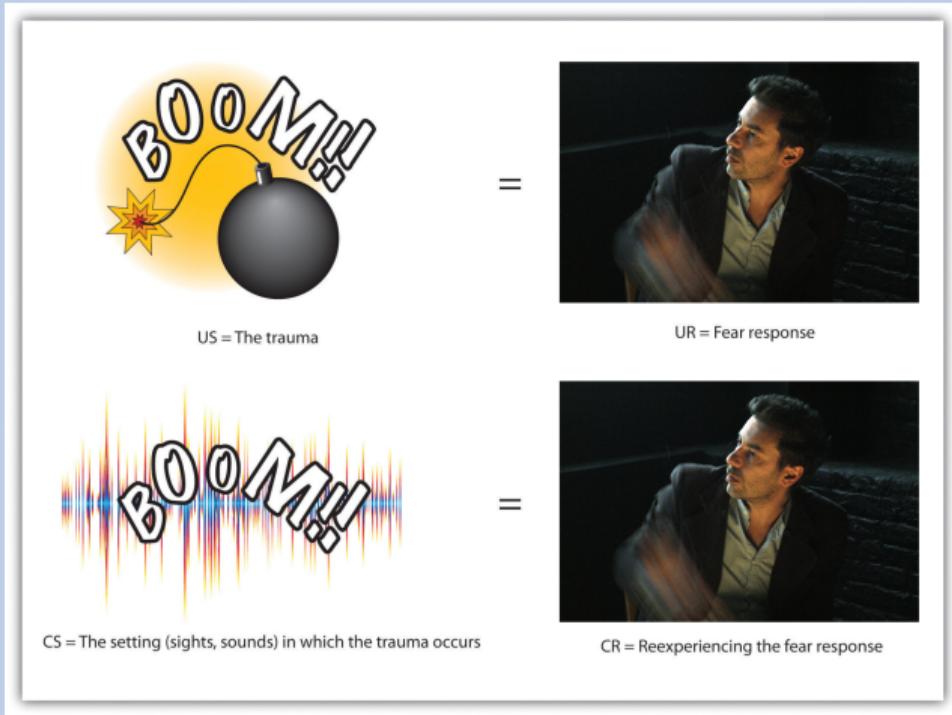


PTSD as a learning disorder

- 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>



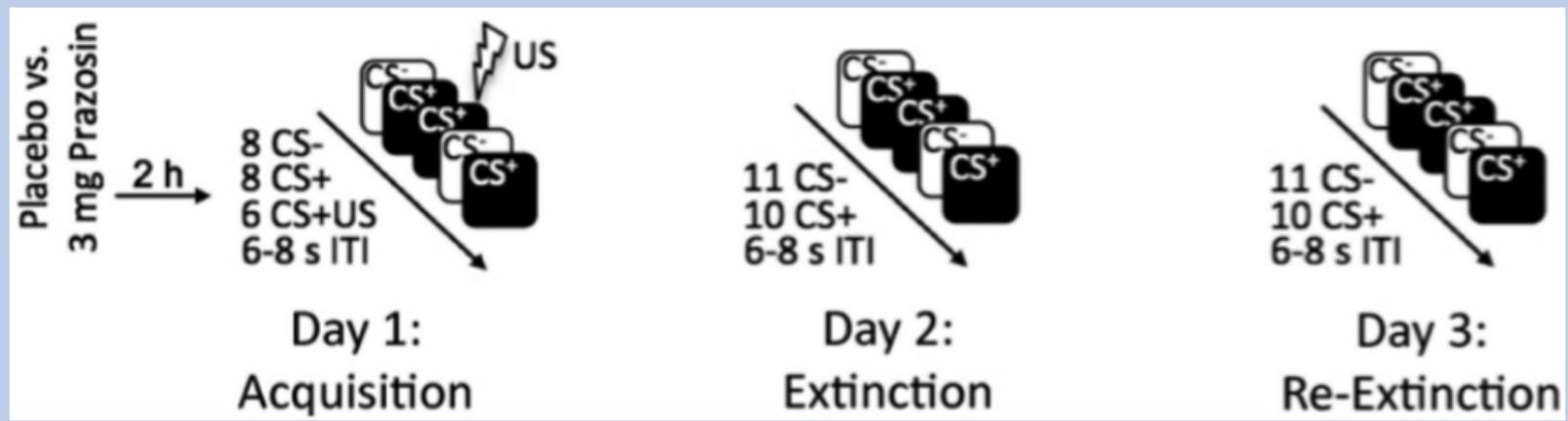
PTSD is unique in that we seem to have a mechanism

Fear conditioning:

- Explains the pathophysiology
- Suggests a treatment (exposure therapy)



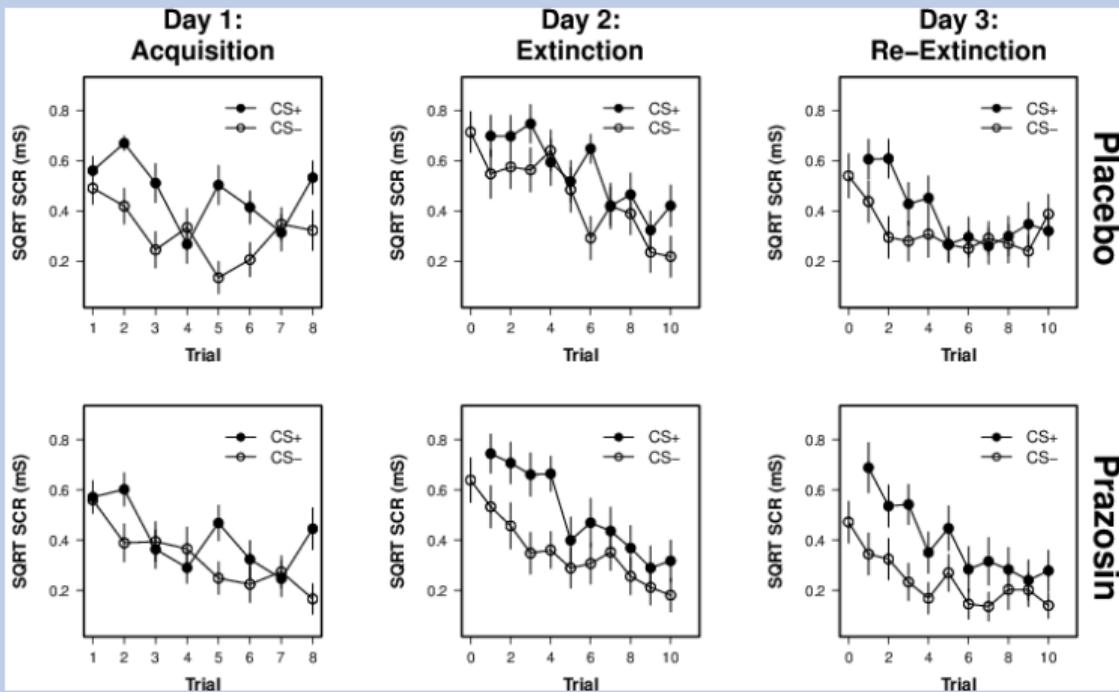
A mechanism we can study in the lab



Homan et al. 2017, Learn Mem



A mechanism we can study in the lab



Homan et al. 2017, Learn Mem

PTSD as a learning disorder



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Associative (Pavlovian):

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

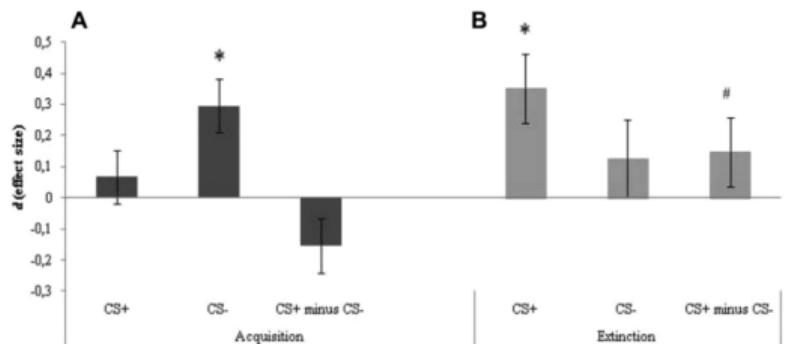
Non-associative:

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

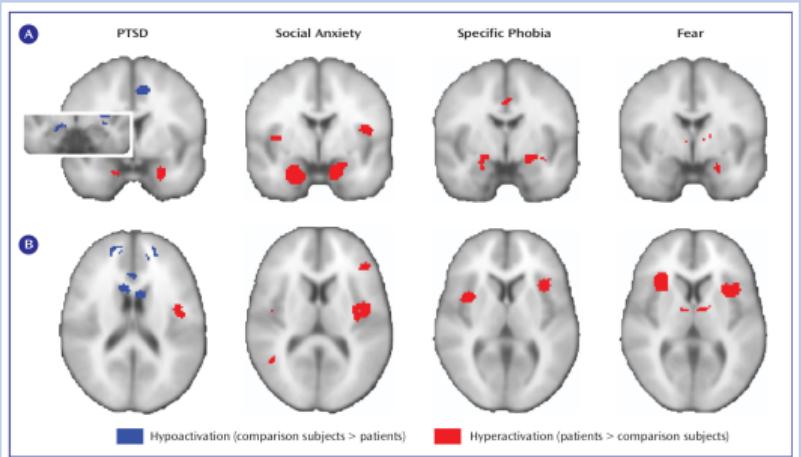


Fear conditioning and extinction in PTSD

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



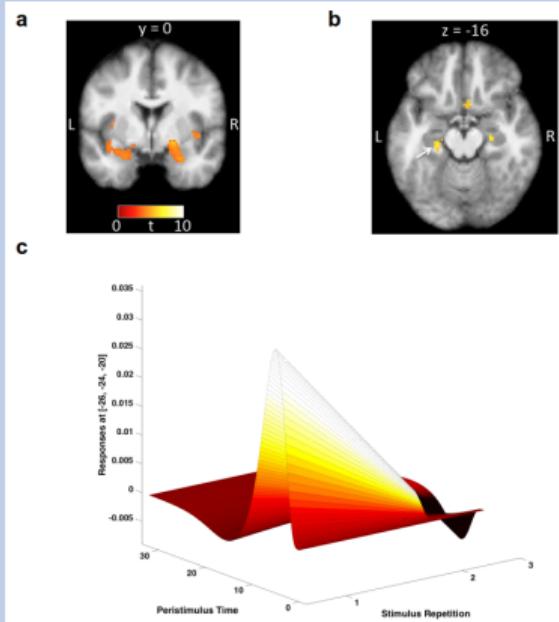
Duits et al. 2015, Depress Anxiety



Ektin and Wager 2007, Am J Psychiatry



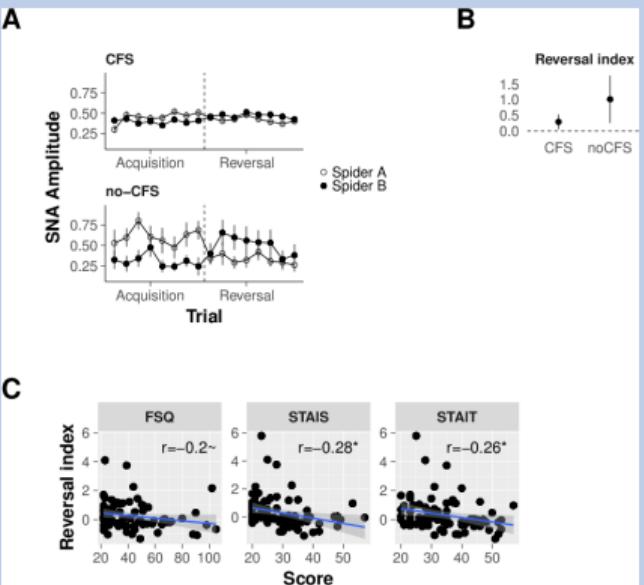
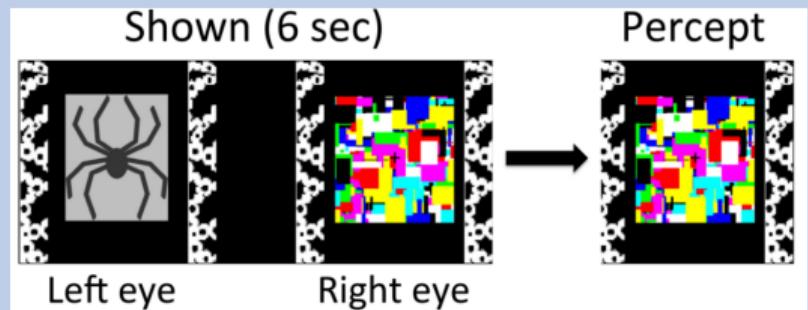
A central role for the amygdala



- 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

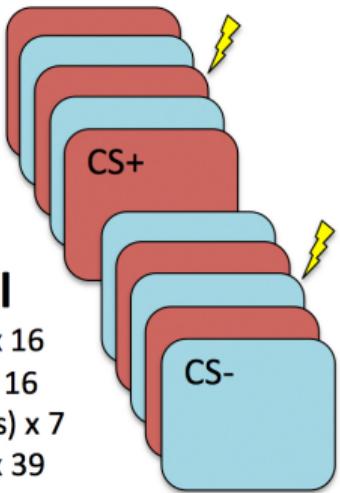


Homan et al., submitted

Beyond fear conditioning: reversal learning

Acquisition

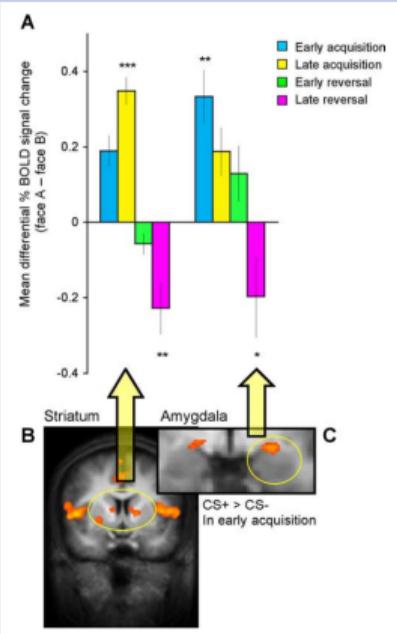
- CS+ (4 s) x 12
- CS- (4 s) x 12
- CS+US (4 s) x 6
- ITI (12 s) x 30



Reversal

- CS+ (4 s) x 16
- CS- (4 s) x 16
- CS+US (4 s) x 7
- ITI (12 s) x 39

Homan et al., in revision



Schiller et al. 2008, J Neurosci

Beyond behavioral analysis: computational modeling

Marr's levels of analysis

1

Why (goal)

2

What (algorithm)

3

How (implementation)

RDoC (units of analysis):

- Genes
- Molecules
- Cells
- Circuits
- Physiology
- Behavior

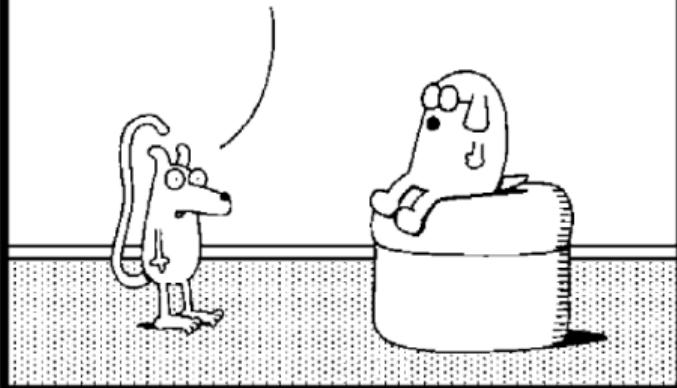
Van den Bos et al. 2017, Dev Cogn Neurosci

Learning from being wrong



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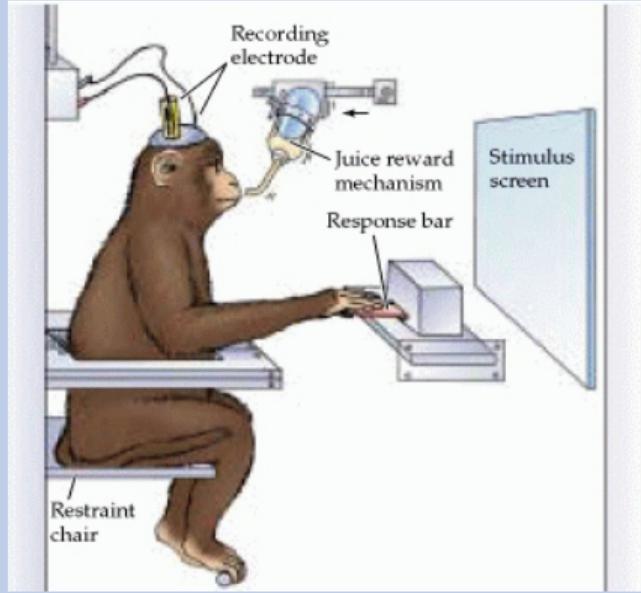
I'M ALWAYS WRONG
ABOUT EVERYTHING.
WHAT CAN I DO TO
FIX THAT?



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



Dopamine and prediction error

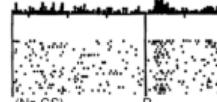


A Neural Substrate of Prediction and Reward

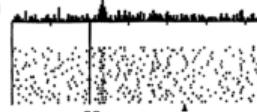
Wolfram Schultz, Peter Dayan, P. Read Montague*

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

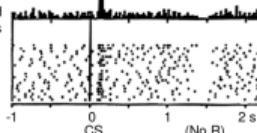
No prediction
Reward occurs



Reward predicted
Reward occurs



Reward predicted
No reward occurs



Schultz, Dayan, Montague 1997, Science

Q&A Joshua Gordon Psychiatry needs more mathematics

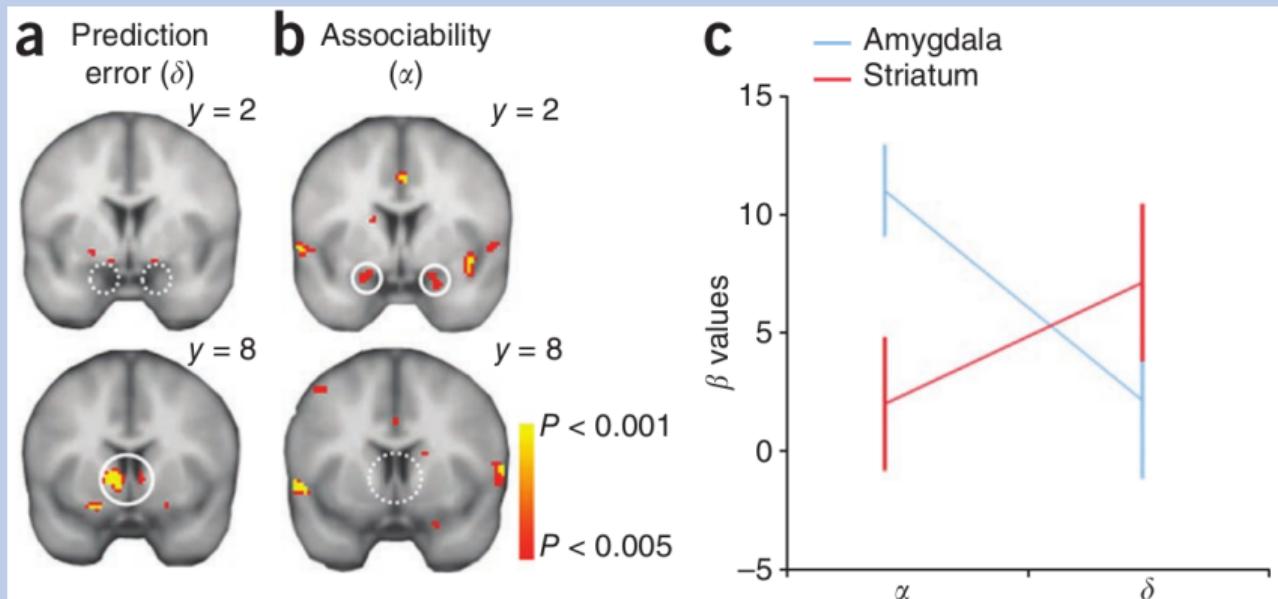
The US National Institute of Mental Health (NIMH) has a new director. On 12 September, psychiatrist Joshua Gordon took the reins at the institute, which has a budget of US\$1.5 billion. He previously researched how genes predispose people to psychiatric illnesses by acting on neural circuits, at Columbia University in New York City. His predecessor, Thomas Insel, left the NIMH to join Verily Life Sciences, a start-up owned by Google's parent company Alphabet, in 2015. Gordon says that his priorities at the NIMH will include "low-hanging clinical fruit, neural circuits and mathematics — lots of mathematics", and explains to *Nature* what that means.

Abbott 2016, *Nature*

- To study the algorithmic level (the how?) we need math
- Can capture latent variables (not observable from behavior)
- Observable behavior often not specific enough for psychiatric diseases



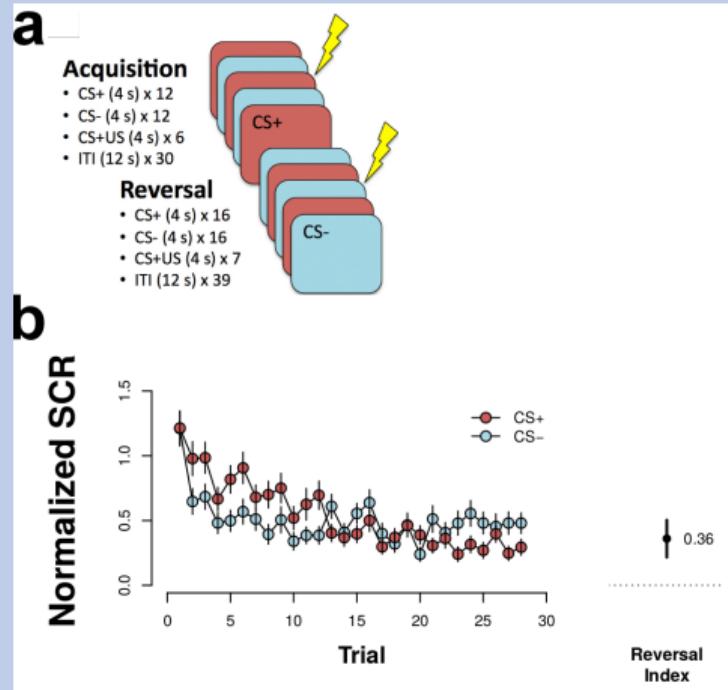
A computational approach to fear reversal learning



Li et al. 2011, Nat Neurosci



Fear learning in combat veterans



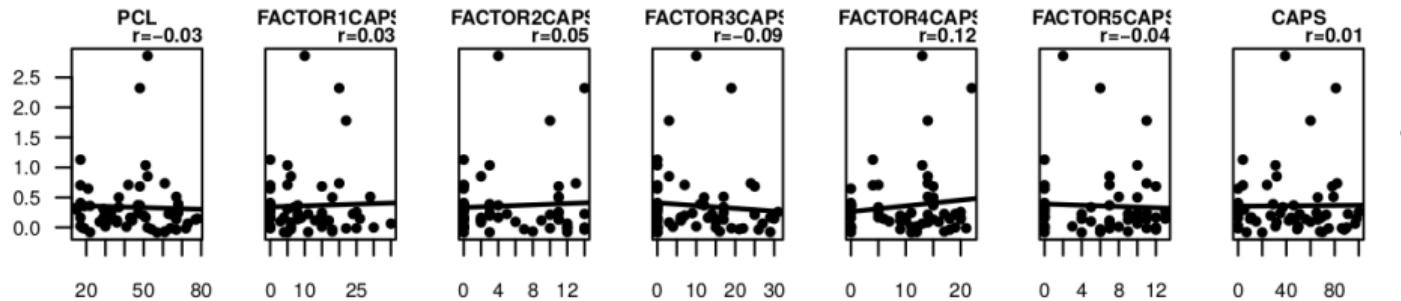
- 52 veterans with and without PTSD
- Fear learning during fMRI scan
- Computational approach: modeling the learning process

Homan et al., in revision



Why computational?

Reversal Learning



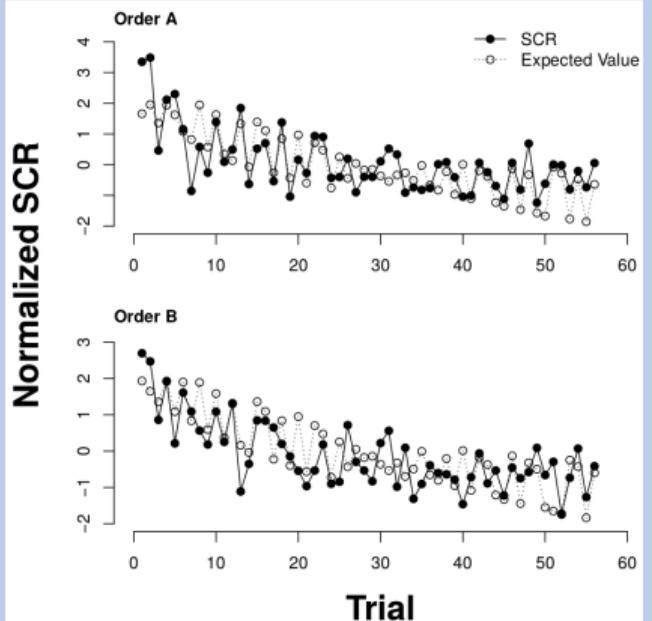
VCC|PTSD



Modeling fear learning behavior: learning from surprise

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

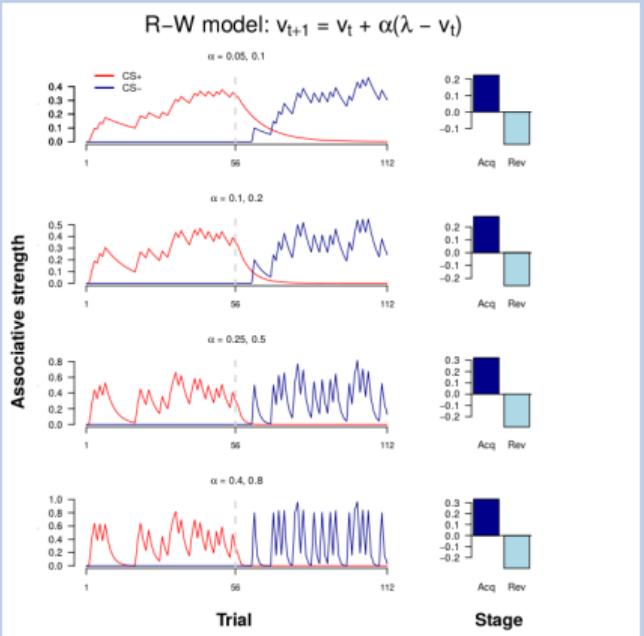
$$\delta_n = r_n - V_n(x_n)$$



Homan et al., in revision



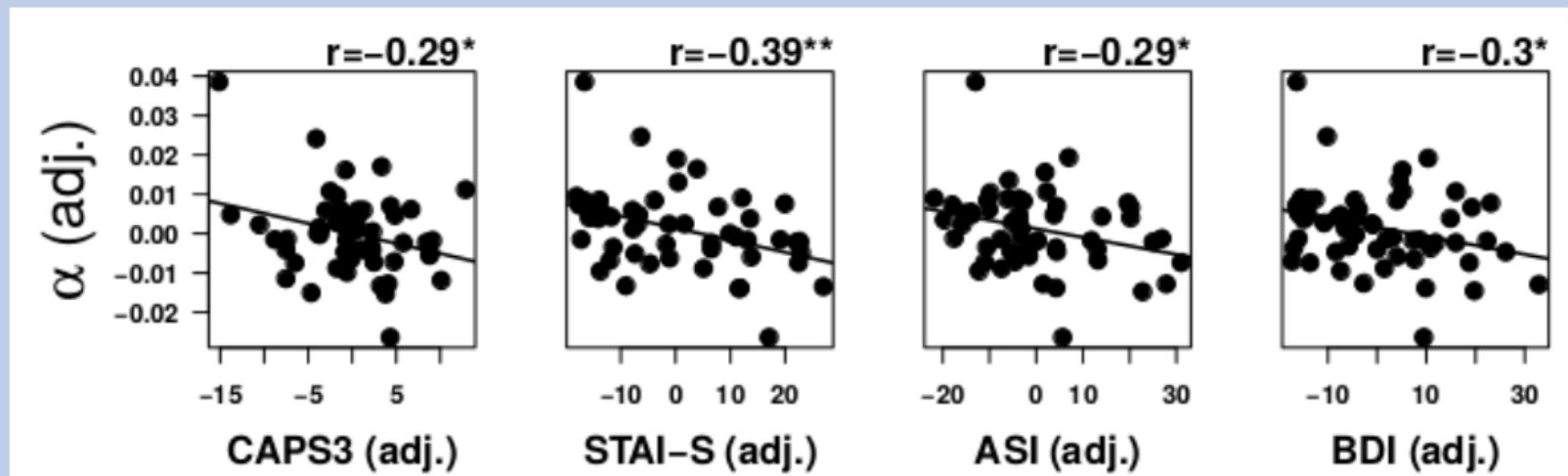
The learning rate determines the volatility of the behavior



Homan et al., in revision



Model predictions correlate with PTSD symptoms

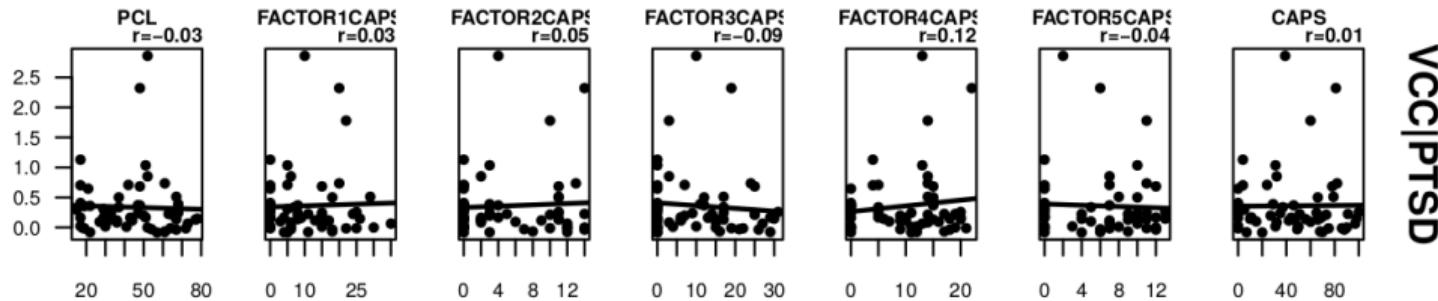


Homan et al., in prep.



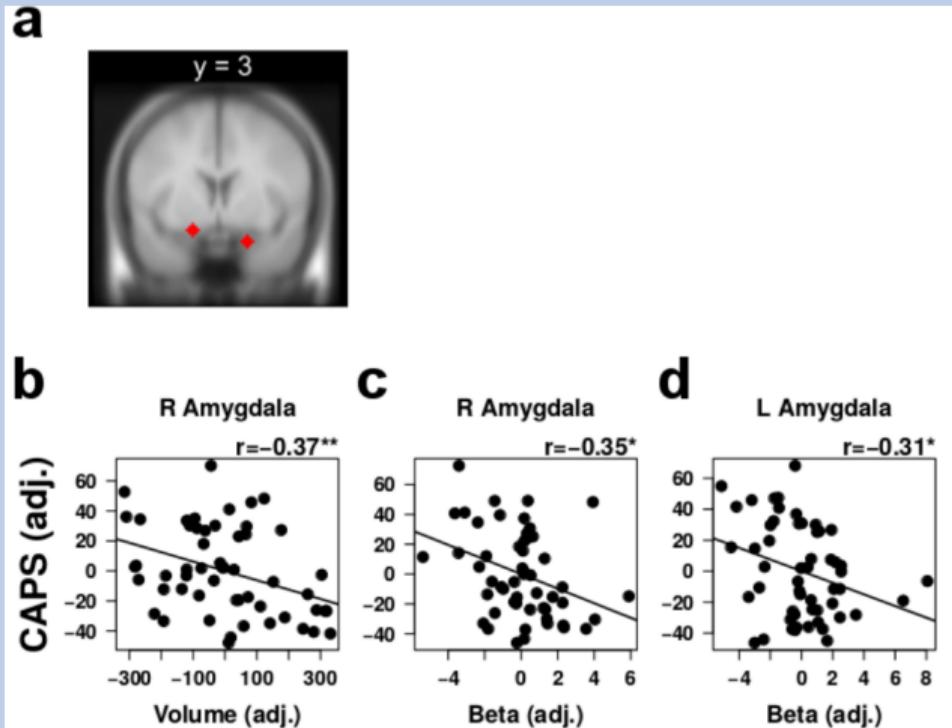
... whereas the observed behavior does not!

Reversal Learning





Amygdala computations contribute to PTSD symptoms



Homan et al., in revision



Summary

- Amygdala appears to play a key role in PTSD
- 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

- Daniela Schiller
- Jingchu Hu

Yale School of Medicine

- Ifat Levy
- Ilan Harpaz-Rotem
- John Krystal
- Stephen Southwick

University of Zurich

- Dominik Bach

Beijing Normal University

- Jian Li

NYU

- Candace Raio

University of Edinburgh

- David Carmel