

Reversal learning after exposure to combat trauma

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github.com/philiphoman/geneva2019

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A clinical vignette



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



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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



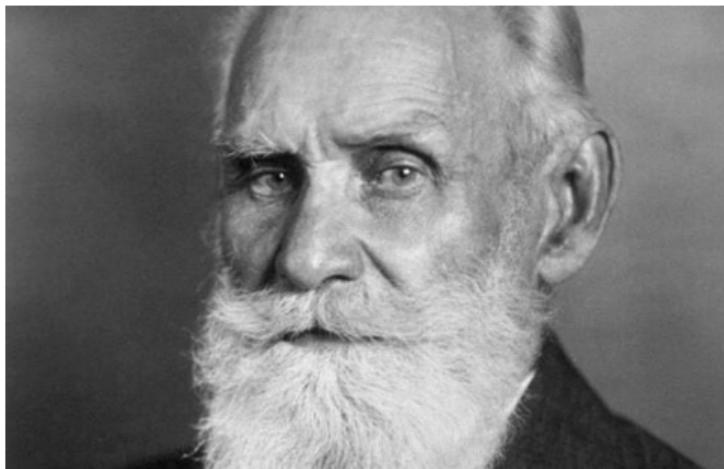
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- Explicit conditioning episode
- Conditioned fear response
- Primary symptoms:
 1. Re-experiencing
 2. Avoidance
 3. Hypervigilance
- Of trauma-exposed individuals, 10-30% develop PTSD
- Why?

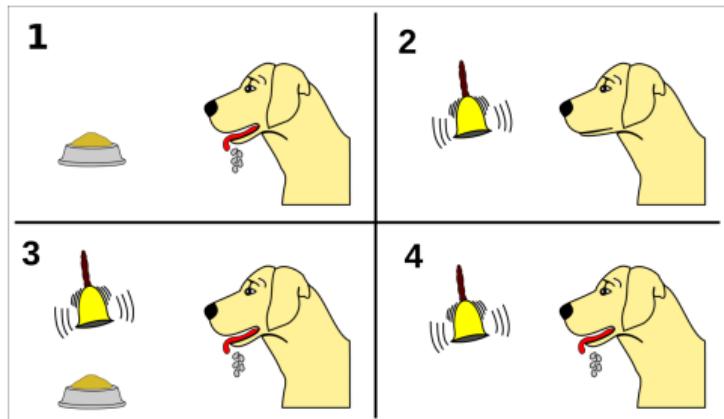
Learning by association



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Ivan Pavlov (1849 - 1936)

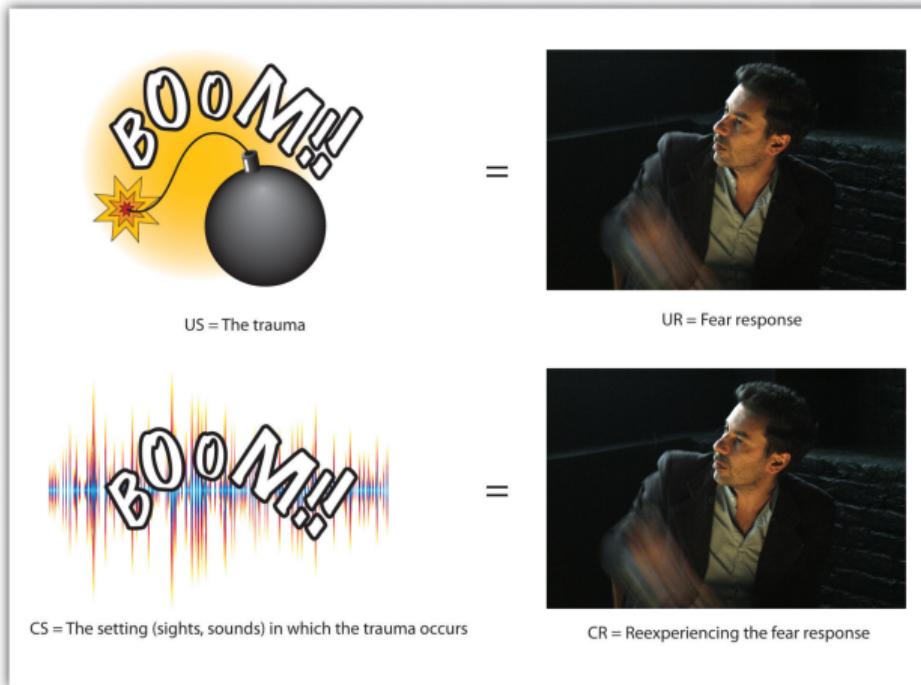


Credit: <https://www.psychestudy.com>



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Pavlovian fear conditioning



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

Posttraumatic stress disorder (PTSD)



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- 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

PTSD and fear conditioning



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Fear conditioning:

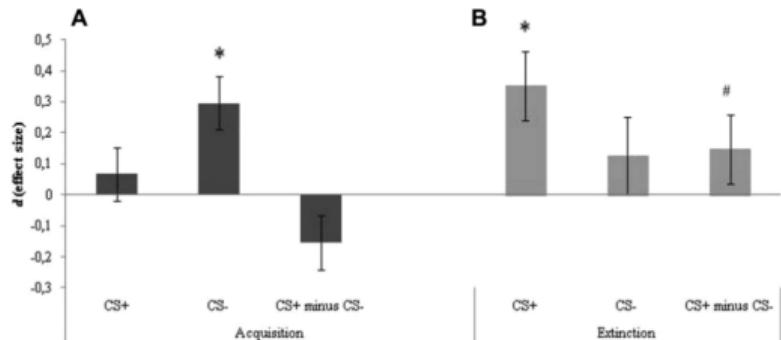
- Helps understand the pathophysiology
- Suggests a treatment (exposure therapy)

Fear conditioning and extinction in anxiety disorders



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



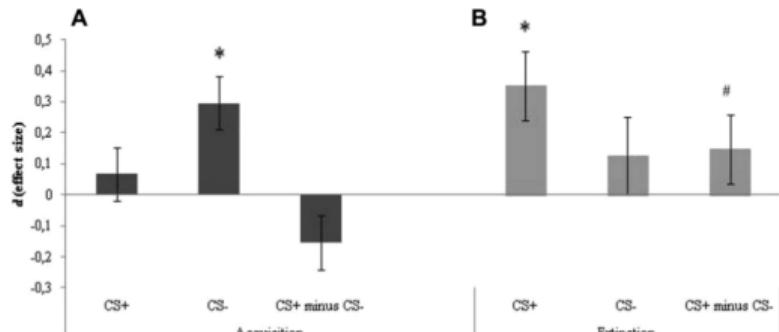
Duits et al. 2015, *Depress Anxiety*

Fear conditioning and extinction in anxiety disorders

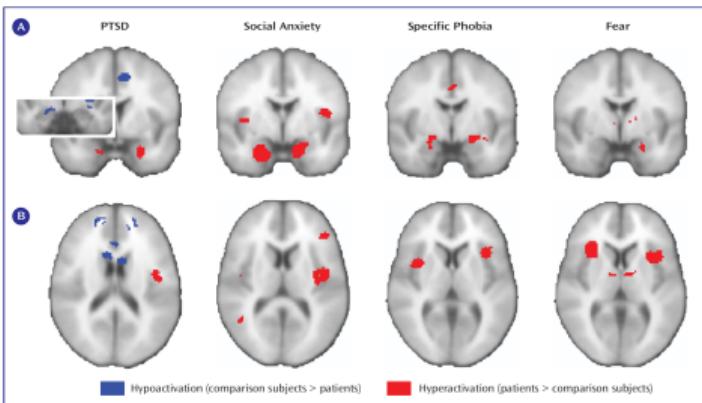


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Review: Updated Meta-Analysis of Fear Conditioning in Anxiety Disorders



Duits et al. 2015, Depress Anxiety



Etkin and Wager 2007, Am J Psychiatry



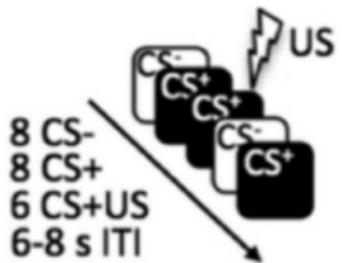
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Schiller et al. 2013, J Vis Exp



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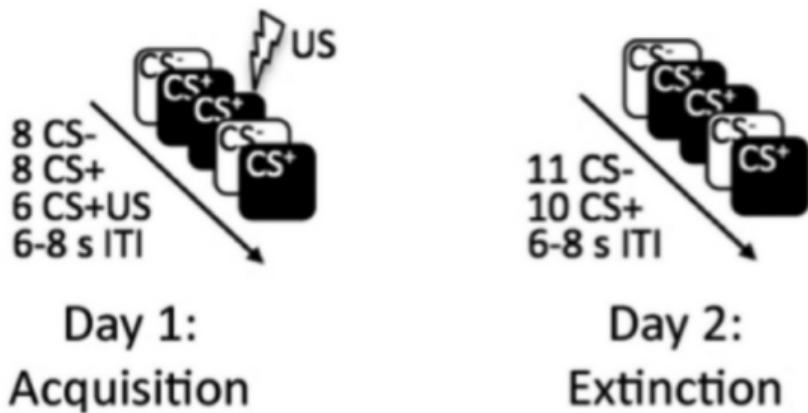


Day 1: Acquisition

Homan et al. 2017, Learn Mem



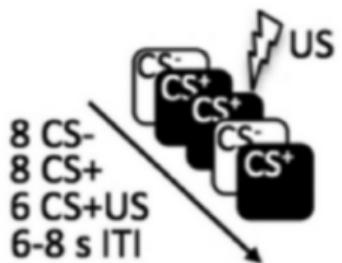
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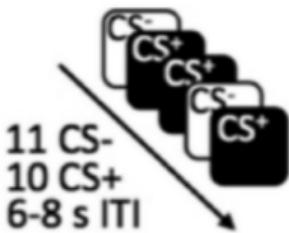
Homan et al. 2017, Learn Mem



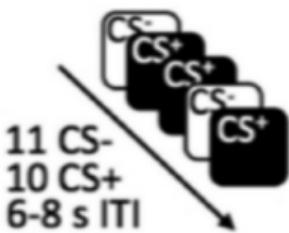
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Day 1:
Acquisition



Day 2:
Extinction



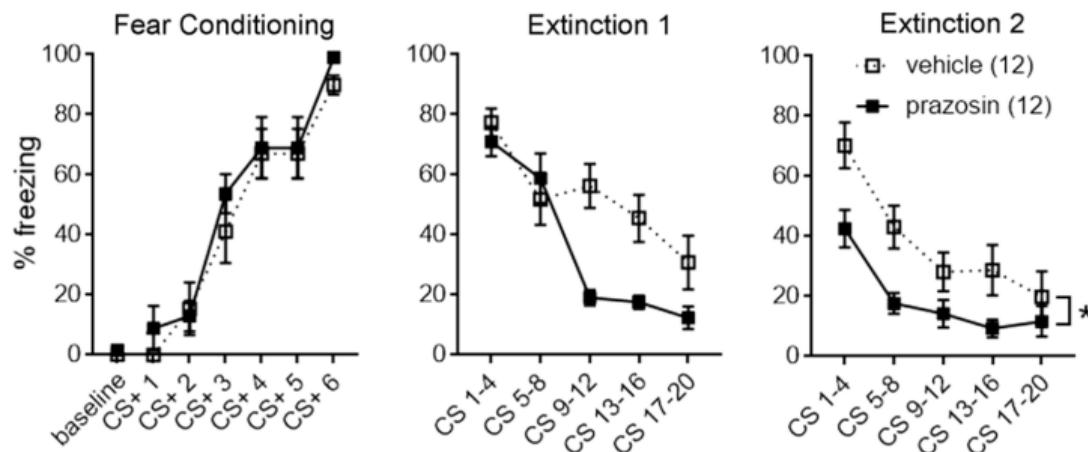
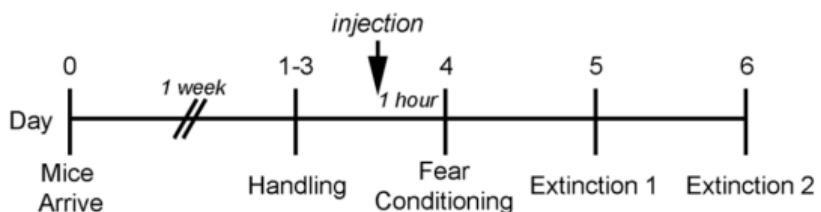
Day 3:
Re-Extinction

Homan et al. 2017, Learn Mem

Prazosin accelerates extinction in mice



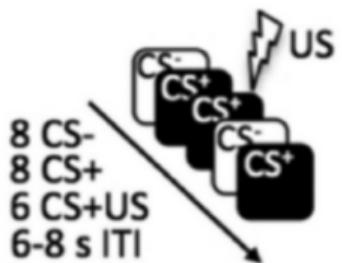
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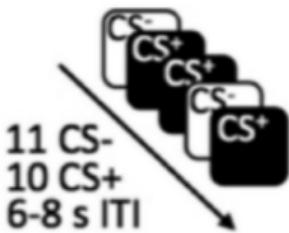
Lucas et al. 2019, Psychopharmacol



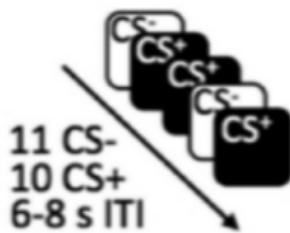
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Day 1:
Acquisition



Day 2:
Extinction

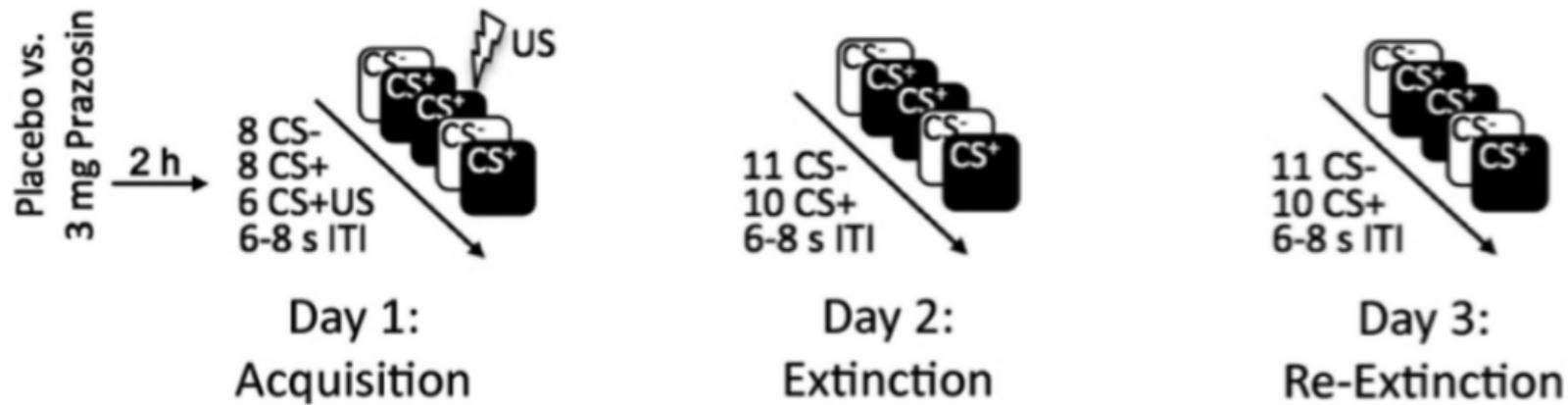


Day 3:
Re-Extinction

Homan et al. 2017, Learn Mem



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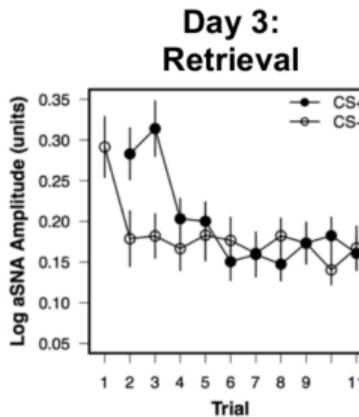
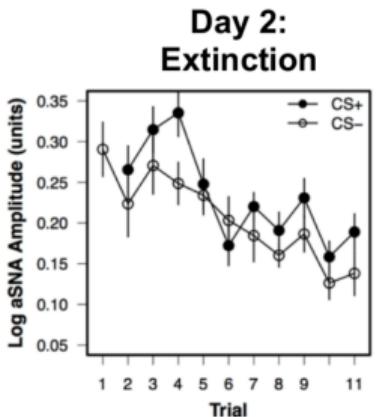
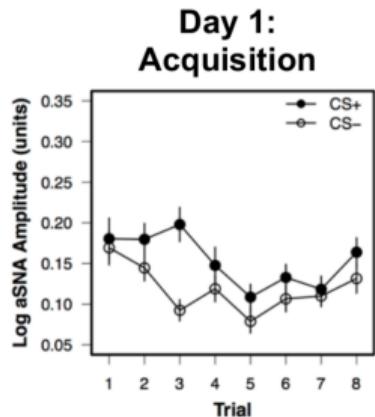


Homan et al. 2017, Learn Mem

Prazosin and fear extinction in humans



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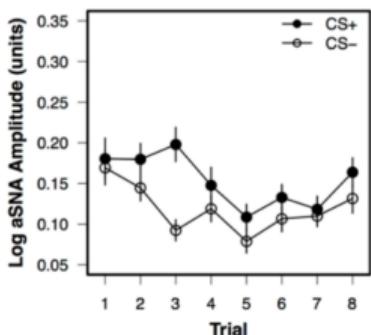
Placebo

Prazosin and fear extinction in humans

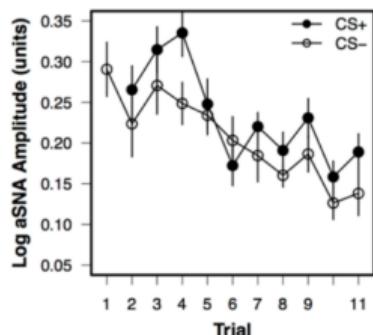


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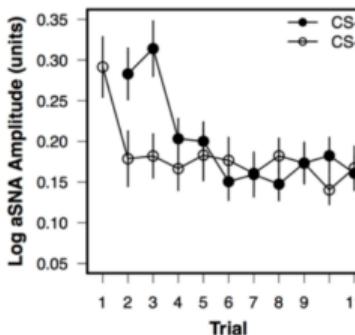
Day 1:
Acquisition



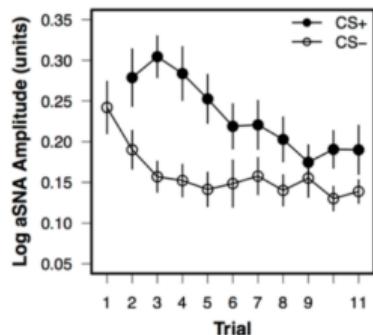
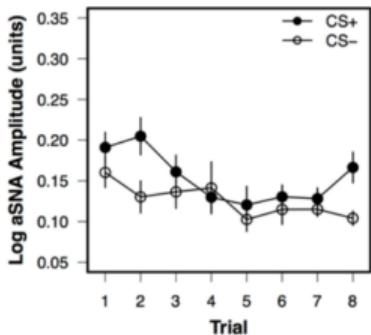
Day 2:
Extinction



Day 3:
Retrieval



Placebo

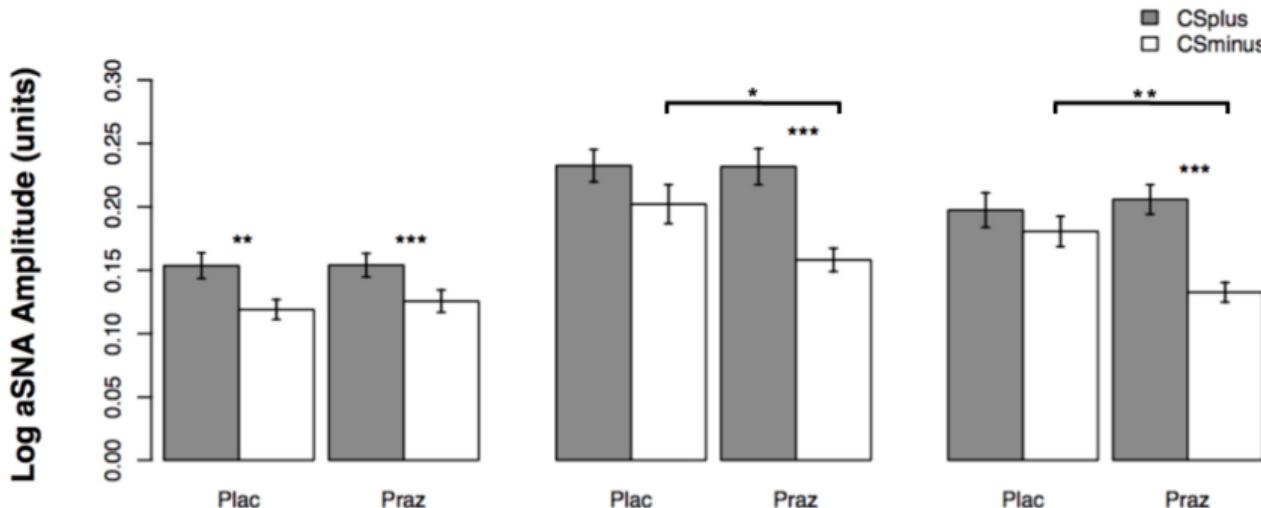


Prazosin

Prazosin and fear extinction in humans



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Homan et al. 2017, Learn Mem

Interim summary

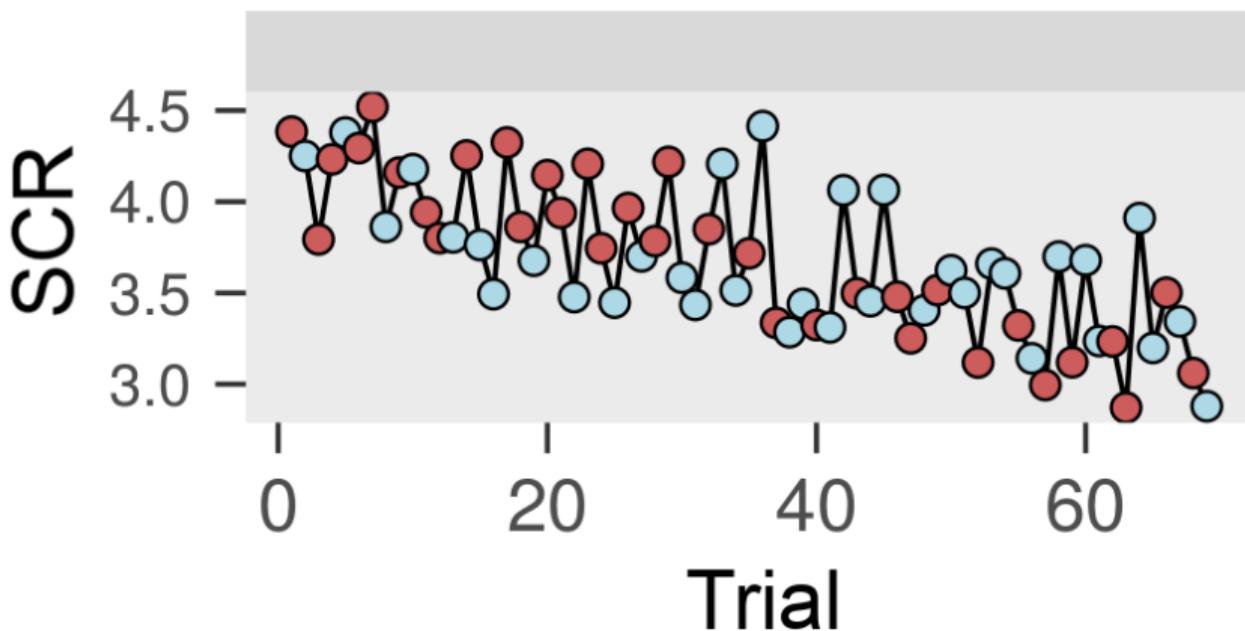


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- In theory: crucial role of fear learning and extinction in PTSD
- In practice: extinction effective, but difficult to enhance
- How can we do better?



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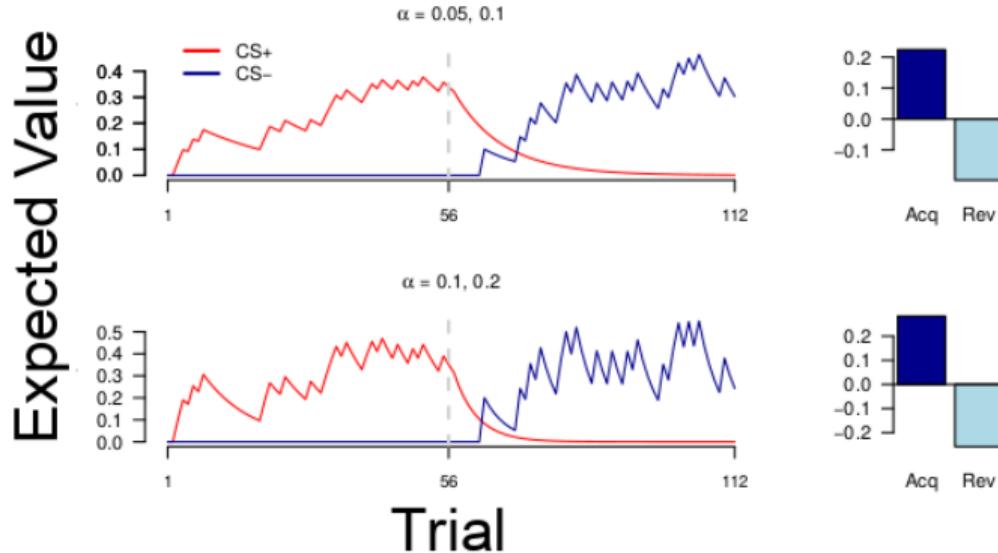
$$R-W \text{ model: } v_{t+1} = v_t + \alpha(\lambda - v_t)$$



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Modeling threat response trial-by-trial

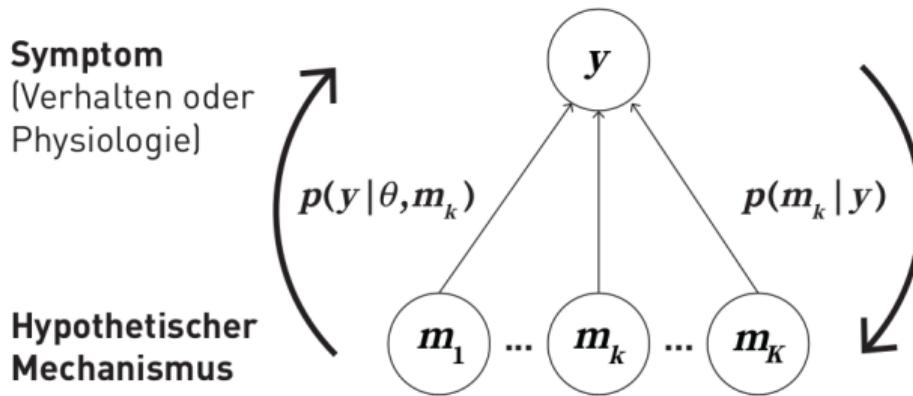
$$R-W \text{ model: } v_{t+1} = v_t + \alpha(\lambda - v_t)$$





Quantitative models

Differentialdiagnose durch Modellselektion



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

Stephan et al. 2017



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Image by Babil Kulesi from pixabay.com

Caveat



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G.E.P. Box (1919 - 2013)

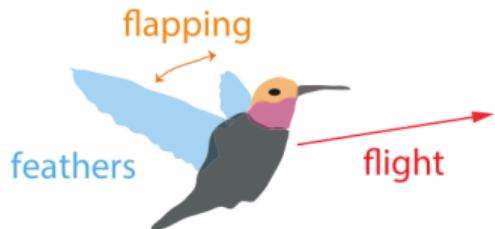
All models are wrong,
but some are useful.



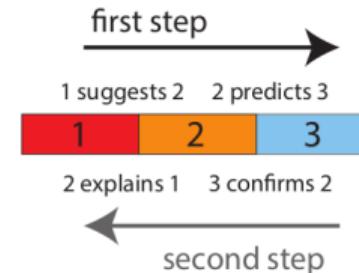
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Why we need behavior

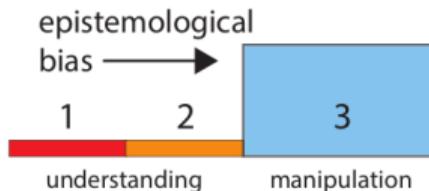
A



B



C



Krakauer et al. 2017, Neuron

Basic assumption



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With quantitative models we are closer to the
relevant disease mechanisms

Basic assumption



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Models will help us identify parameters for:

1. Differential diagnostics
2. Individual therapy

The reality?



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Clinically relevant findings in
Computational Psychiatry are scarce



Computational psychiatry

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From reinforcement learning models to
psychiatric and neurological disorders

Tiago V. Matos^{1,2} & Michael J. Fischl^{2,4}

Computational psychiatry

P. Read Montague^{1,2}, Raymond J. Dolan², Karl J. Friston² and Peter Dayan²

Computational approaches to psychiatry
Klaas Enno Stephan^{1,2,3} and Christoph Mathys³

Computational Psychiatry

Xiao-Jing Wang^{1,2,3,*} and John H. Krystal^{1,2,3}

Computational psychiatry: the brain as a phantastic organ

Karl J. Friston, Klaas Enno Stephan, Read Montague, Raymond J. Dolan

**Computational psychiatry: a Rosetta Stone linking the brain
to mental illness**

Philip N. Corlett, Paul C. Fletcher*

Translational Perspectives for Computational Neuroimaging

Klaas E. Stephan,^{1,2,3} Sandra Iglesias,¹ Jakob Heimola,¹ and Andreas G. Dimiceli¹

Computational psychiatry as a bridge from
neuroscience to clinical applications

Quentin J.M. Huys^{1,2,3}, Tiago V. Matos^{1,2} & Michael J. Fischl²

**Computational Psychosomatics and
Computational Psychiatry: Toward a Joint
Framework for Differential Diagnosis**

Frederike H. Petzschner, Lilian A.E. Weber, Tim Gard, and Klaas E. Stephan

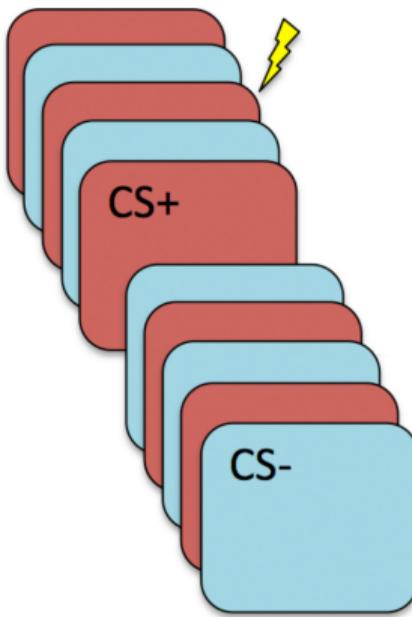
Stephan 2018

Beyond fear conditioning: reversal learning



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Acquisition



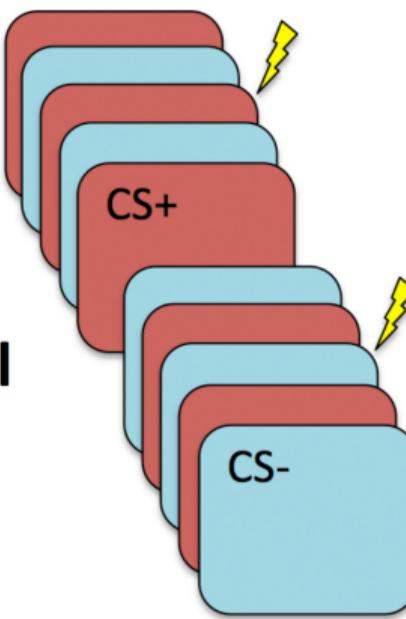
Homan et al. 2019, Nat Neurosci

Beyond fear conditioning: reversal learning

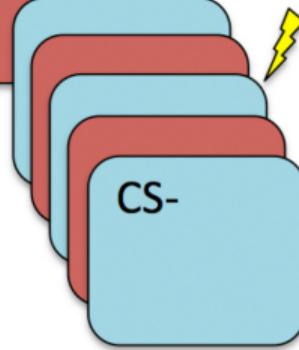


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Acquisition



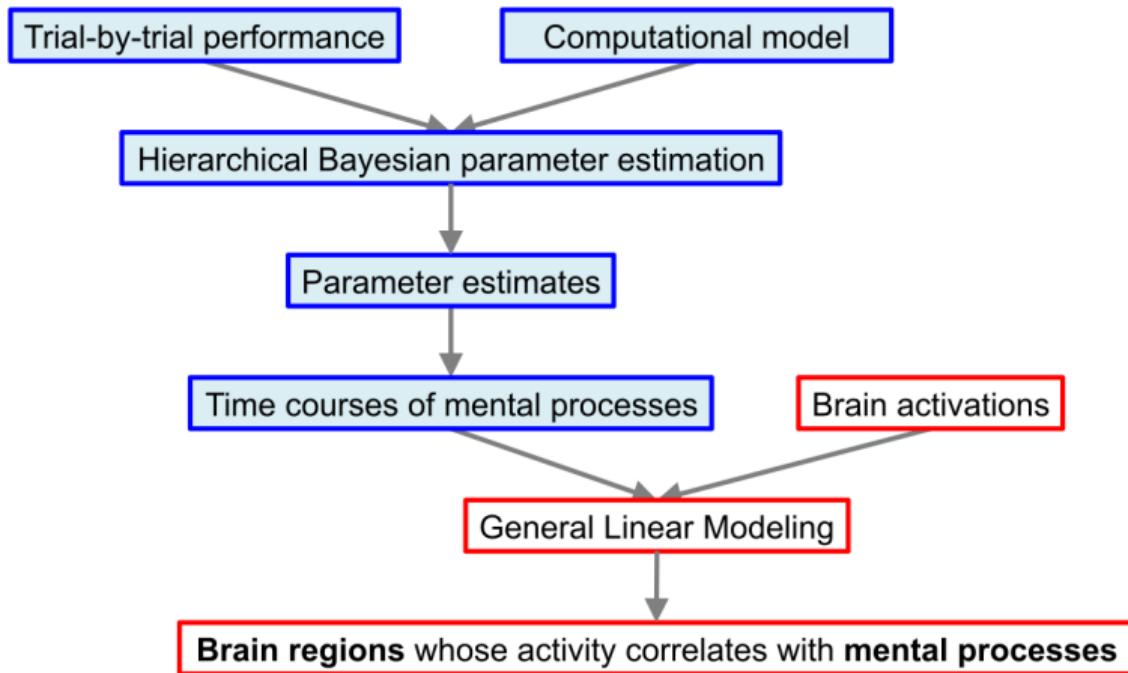
Reversal



Homan et al. 2019, Nat Neurosci



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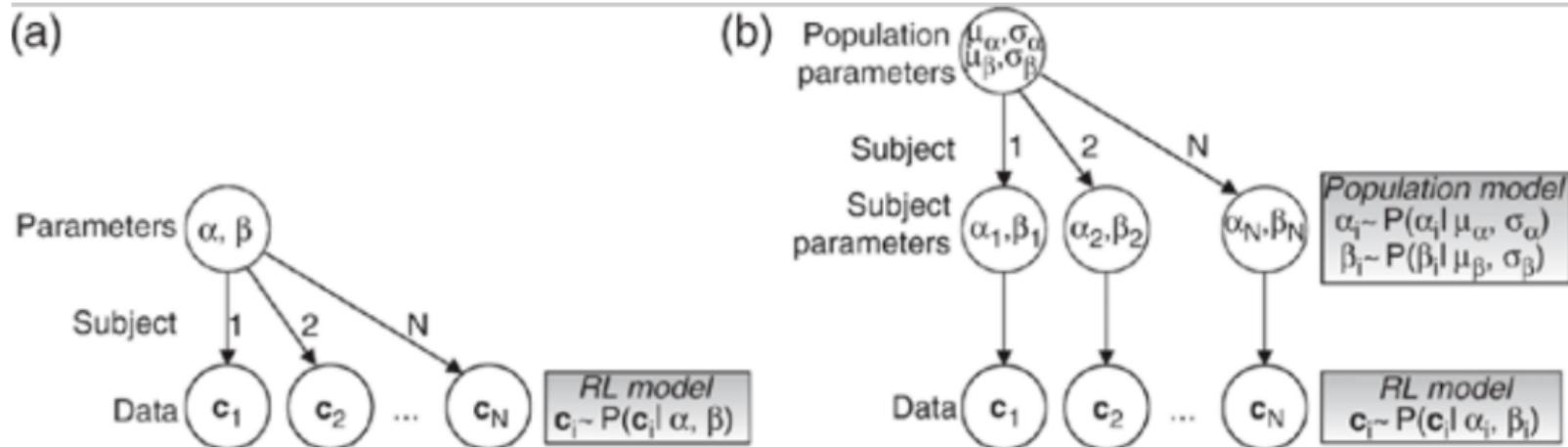


Ahn et al. 2017, Comp Psy

Hierarchical models



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Daw 2011

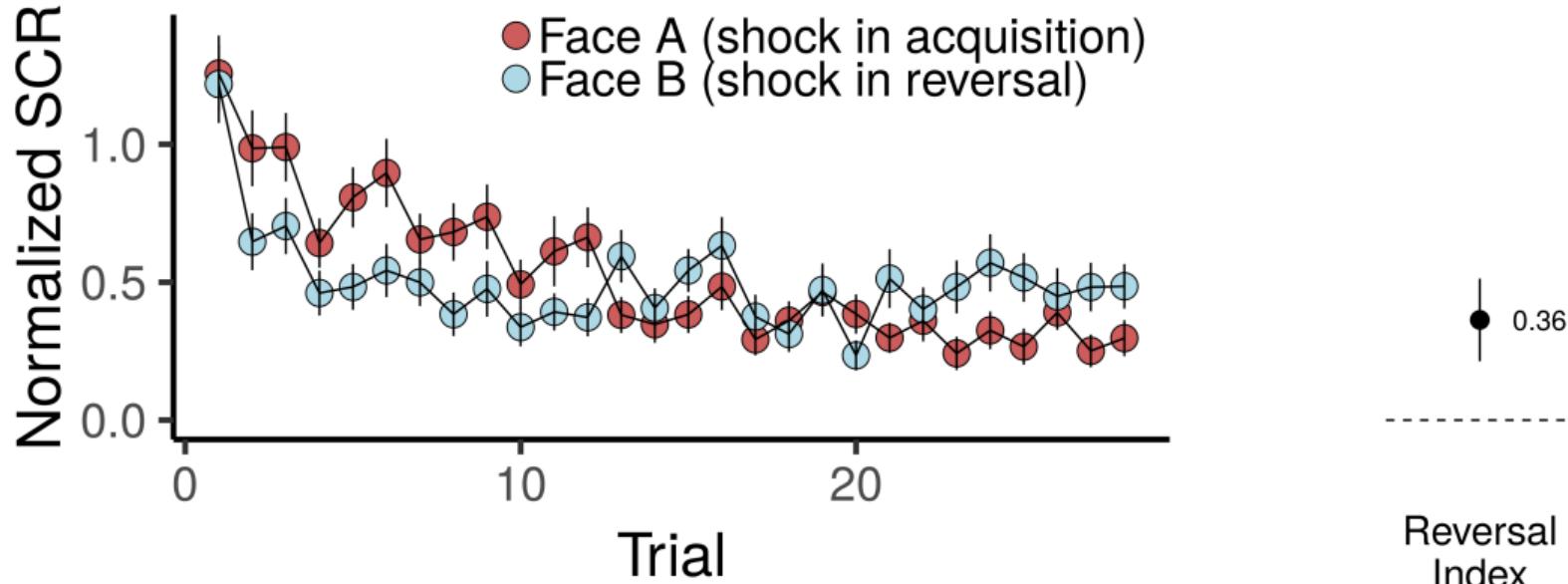


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Reversal learning in combat veterans



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Homan et al. 2019, Nat Neurosci



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Did reversal learning scale with symptoms?



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Did reversal learning scale with symptoms?

No! ($\beta = 0.02, P = 0.894$)



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Modeling threat responses: learning from surprise

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

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

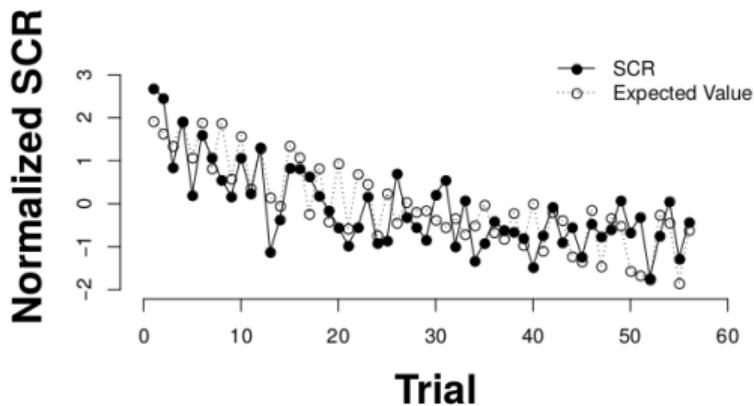
Modeling threat responses: learning from surprise



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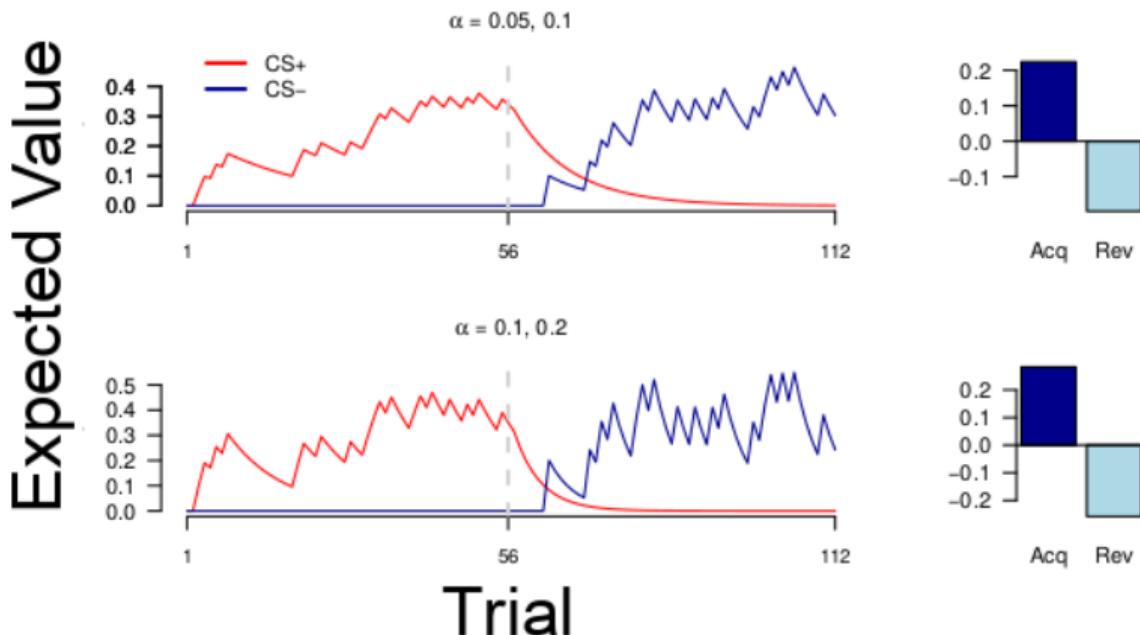
Homan et al. 2019, Nat Neurosci



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Learning rate and volatility

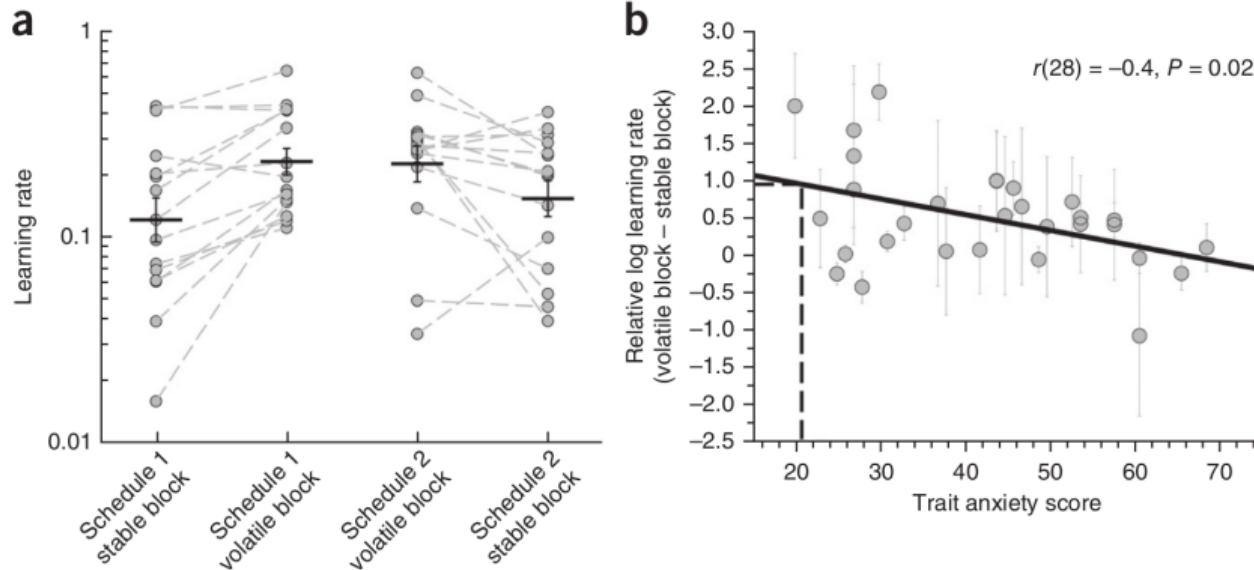
$$R-W \text{ model: } v_{t+1} = v_t + \alpha(\lambda - v_t)$$



Anxiety and volatility



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Browning et al., 2015, Nat Neurosci

Modeling fear learning behavior: surprise and attention



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

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

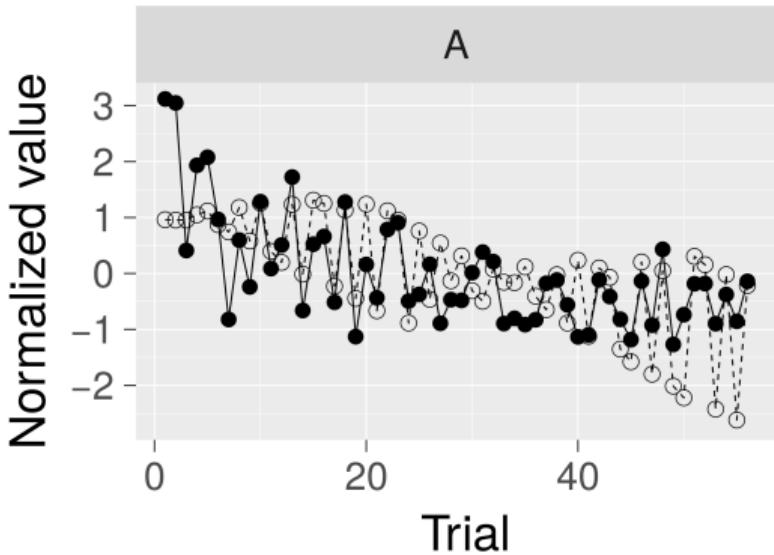
Modeling fear learning behavior: surprise and attention



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ZUCKER SCHOOL OF MEDICINE
AT HOFSTRA/NORTHWELL

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



Homan et al. 2019, Nat Neurosci



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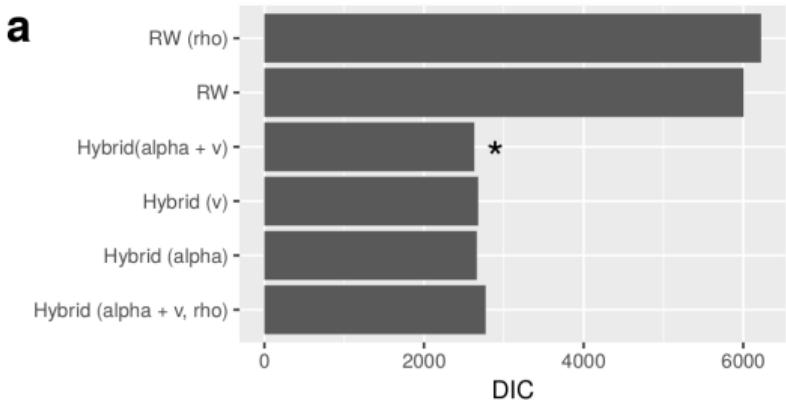


Image by Babil Kulesi from pixabay.com



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Model comparison

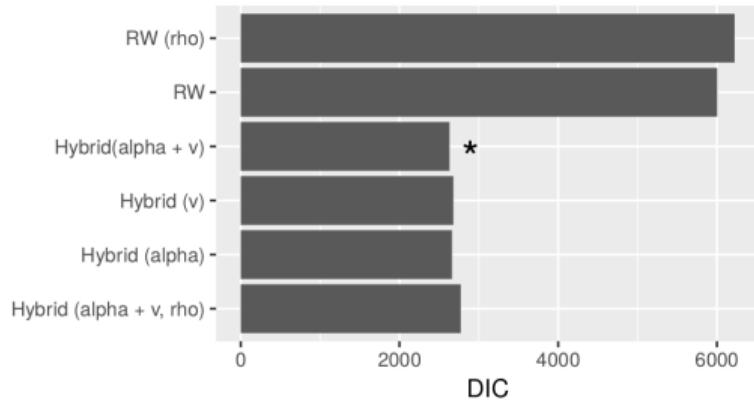


Homan et al. 2019, Nat Neurosci



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Model comparison



Homan et al. 2019, Nat Neuro

	-LL
RW(V)	507.25
Hybrid(V)	455.04
Hybrid(a)	461.34
Hybrid(a+V)	423.23

Li et al. 2011, Nat Neurosci

How does the winning model relate to PTSD symptoms?

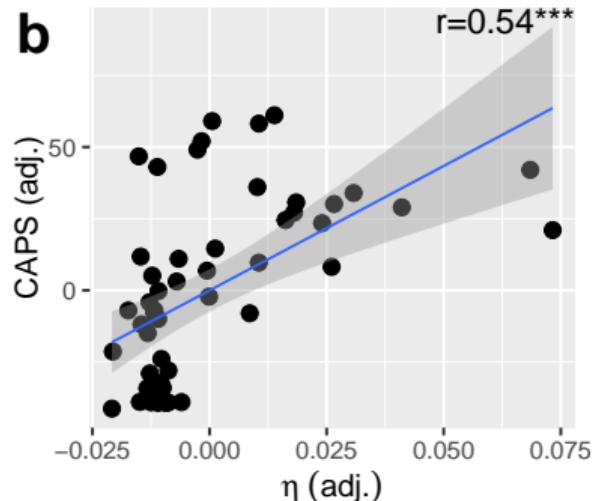
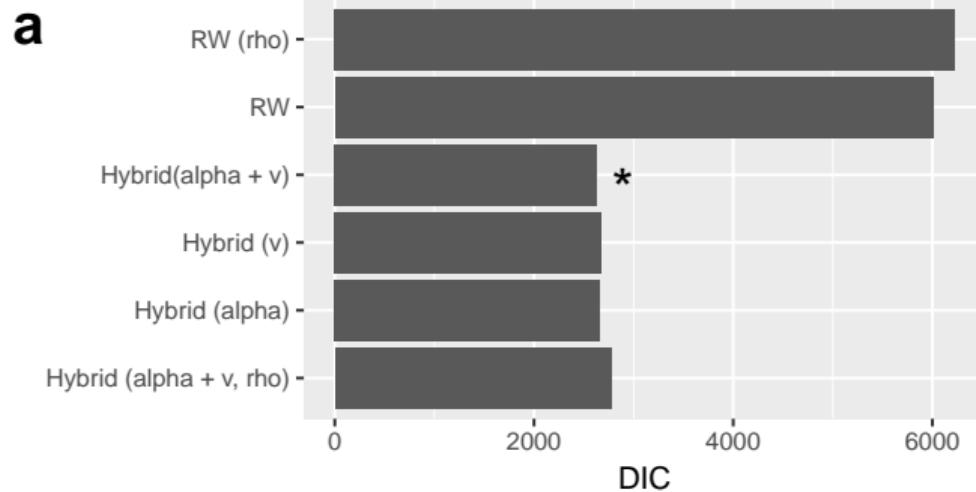


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How does the winning model relate to PTSD symptoms?



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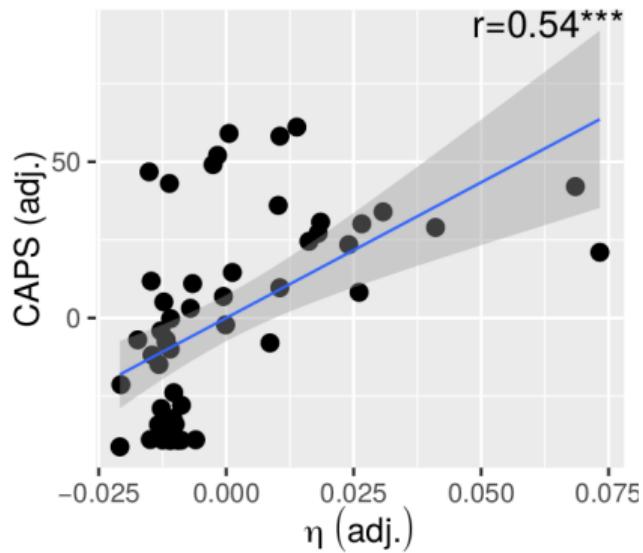


Homan et al. 2019, Nat Neurosci

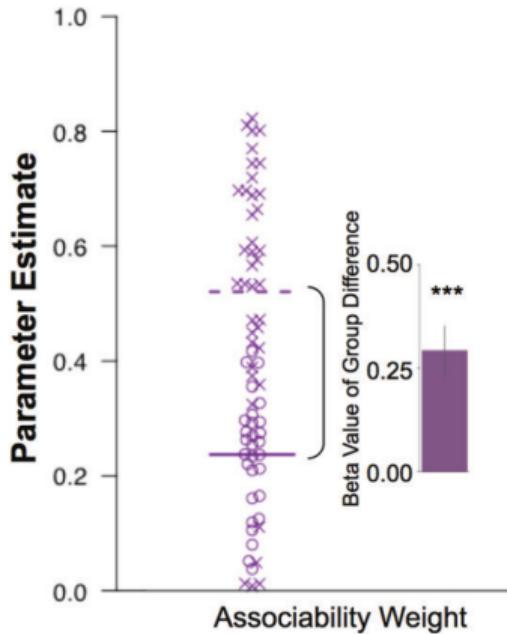
How does the winning model relate to PTSD symptoms?



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Homan et al. 2019, Nat Neurosci

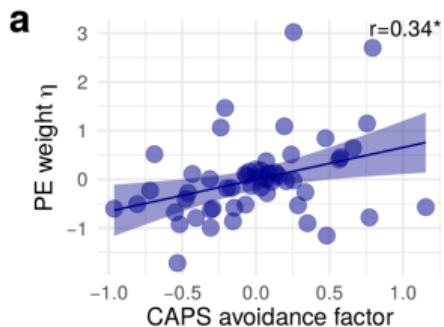


Brown et al. 2018, eLife



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Considering the 5 factors of PTSD

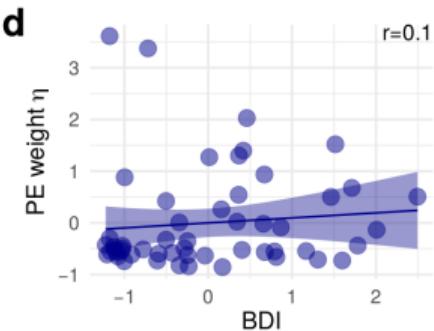
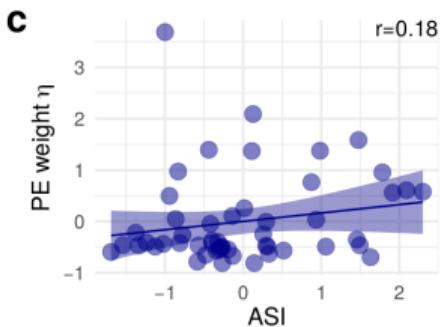
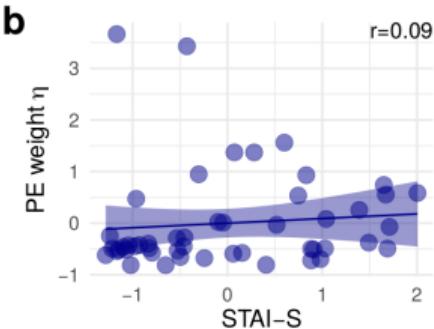
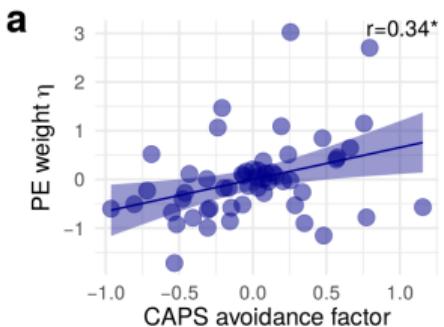


Homan et al., in prep.



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Considering the 5 factors of PTSD

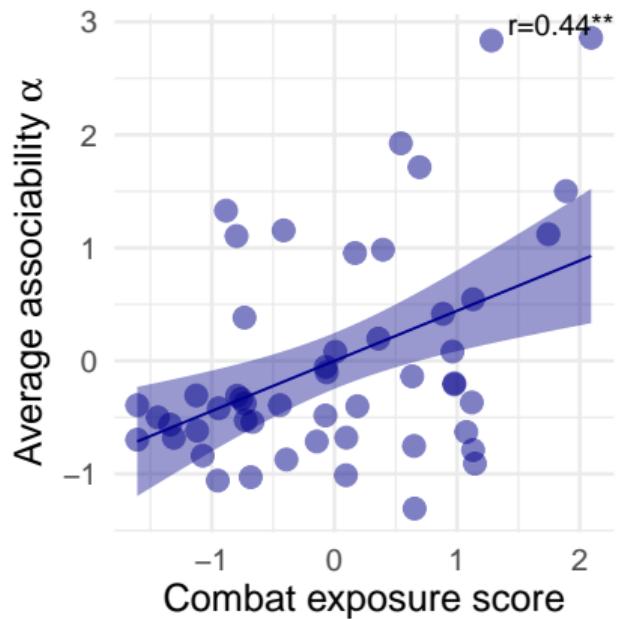


Homan et al., in prep.



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Combat exposure and associability



Homan et al., in prep.

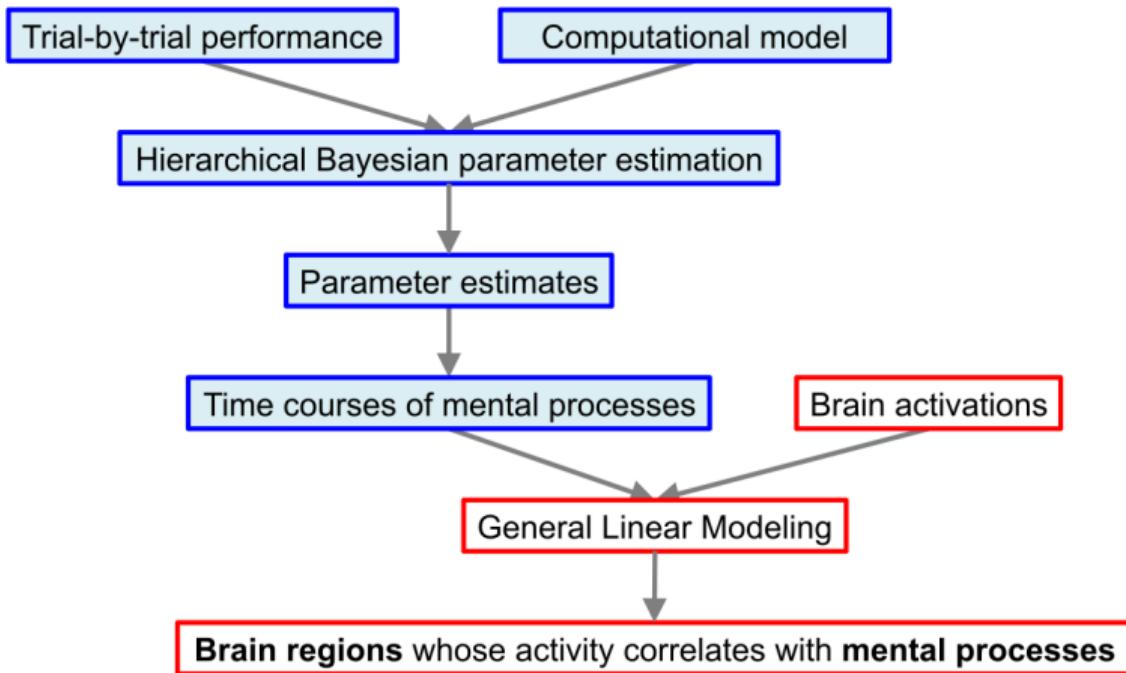


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How might the model be implemented in the brain?



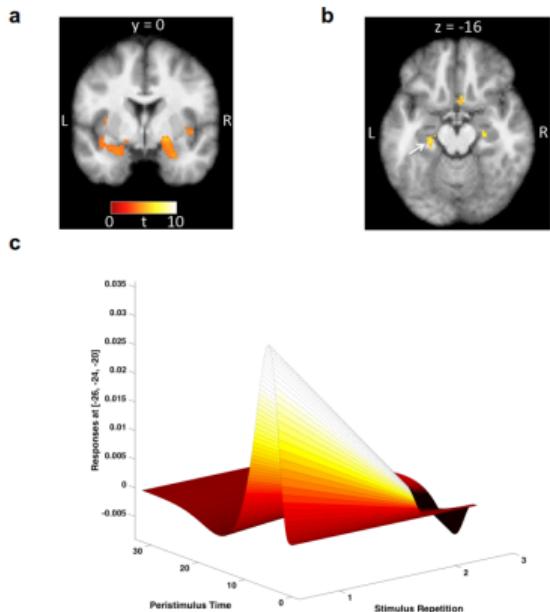
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Ahn et al. 2017, Comp Psy



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

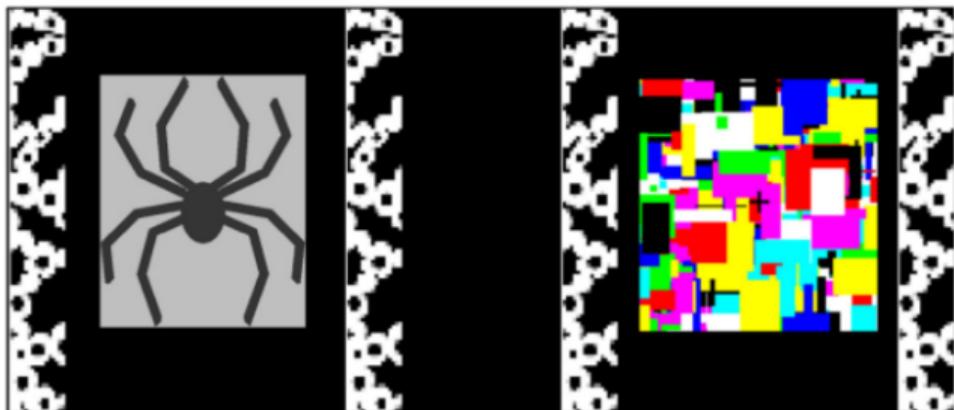
Homan et al. 2017, Neurobiol Learn Mem

Fear conditioning without conscious awareness



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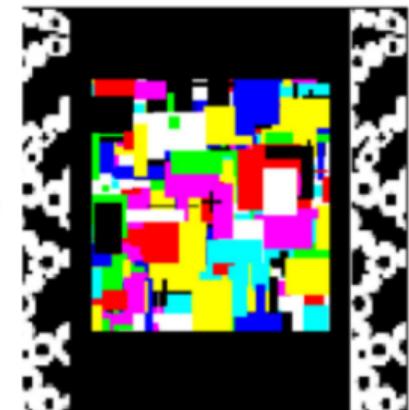
Shown (6 sec)



Left eye

Right eye

Percept



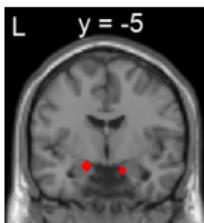
Homan et al. 2018, bioRxiv



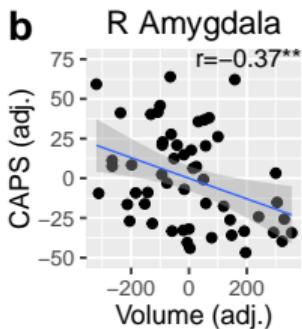
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Amygdala activity correlates with PTSD symptoms

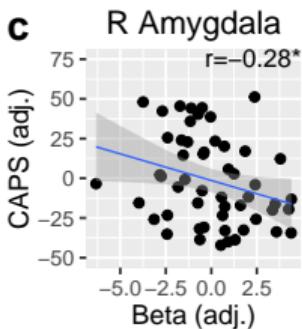
a



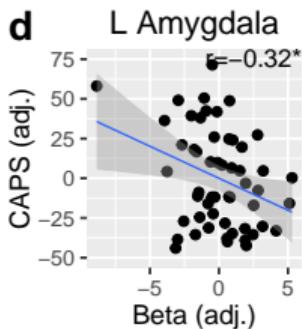
b



c



d

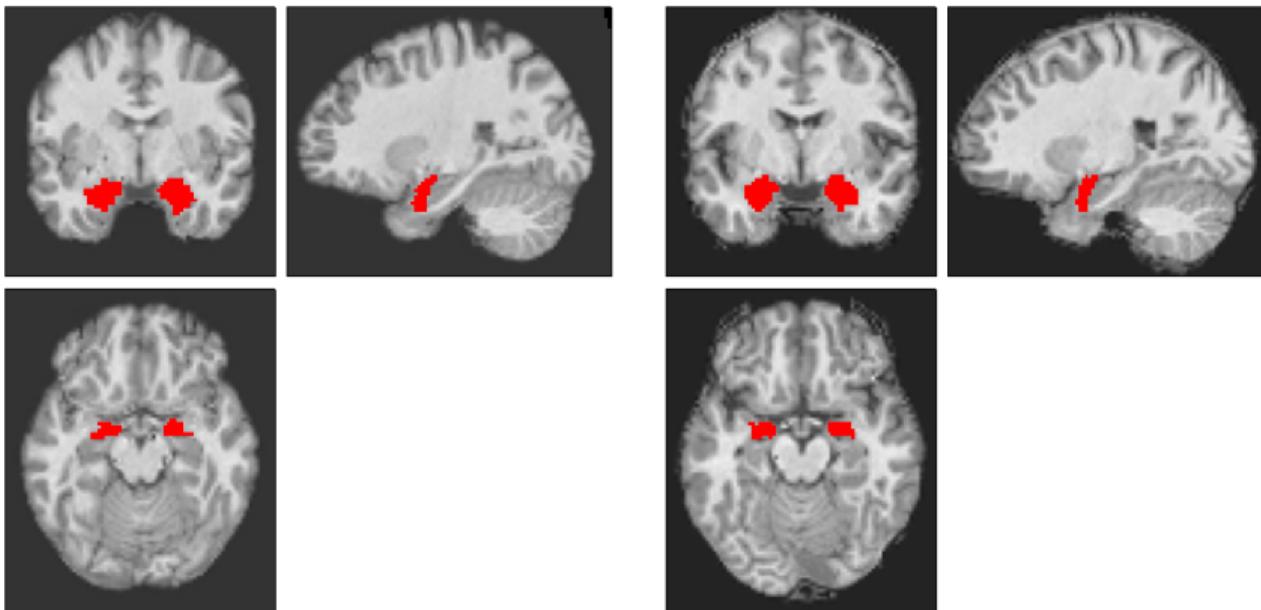


Homan et al. 2019, Nat Neurosci

Amygdala activity correlates with PTSD symptoms



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Homan et al. 2019, Nat Neurosci



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Summary

- Threat conditioning as a crucial mechanism for PTSD
- Informs treatment: exposure therapy
- Central role of amygdala: might encode expected aversive value
- Prediction error as a teaching signal computed in striatal neurons

Limitations



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- Cross sectional study
- Relatively small sample size ($N = 54$)
- Limited amount of trials ($N = 69$)



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What does all this mean for our patient?



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

Conclusion



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- Impact of trauma might be reflected by components of threat learning
- Would have been missed with conventional summary statistics
- May allow us to stratify patients to exposure treatment



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