

Measuring Brain Connectivity & Neurotransmission for Neuropsychiatric Investigations

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Cocchi, Sukhi Shergill, Charlotte
Horne, Read Montague*



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Models of the Brain



“Normative models describe how an optimal system would work given the goals. They describe ‘what’ the brain is trying to do.”



“Process models are about the mechanisms, thus describing ‘how’ it is done.”

Models of the Brain



Normative

- Maximise Reward
- Maximise Efficiency
- Minimise Surprise (Free Energy)
- Infer causal structure of world (The Bayesian Brain)
- Retain Representations in working memory

Process

- Reinforcement learning with Rescorla-Wagner Model
- Dynamic Programming via Temporal Difference
- Infomax
- Predictive Coding
- Variational message passing
- Stable and distinct firing patterns, E/I Balance

A Rewarding World



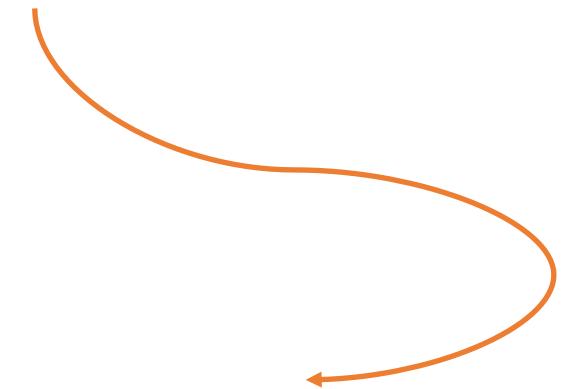
For Decision
Making



A Reward/Loss Environment



Employing Dopaminergic and
Serotonergic Signalling to Shape
Choice



The Free Energy Principle – becoming a model of your world



Minimise Free Energy

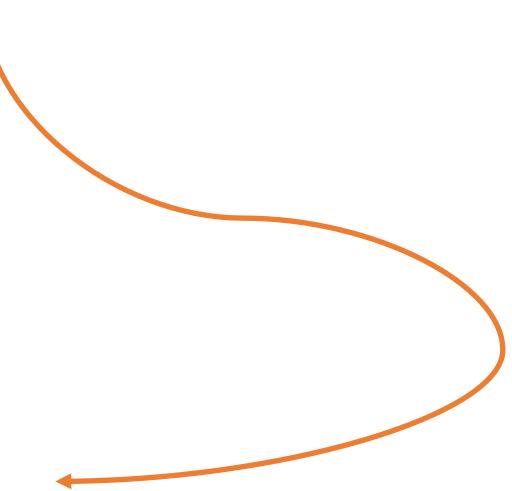
For Discrete State
Space Models



Taxi or Subway?



Via Variational Bayes



Outline

Models of the world & your
interaction with them

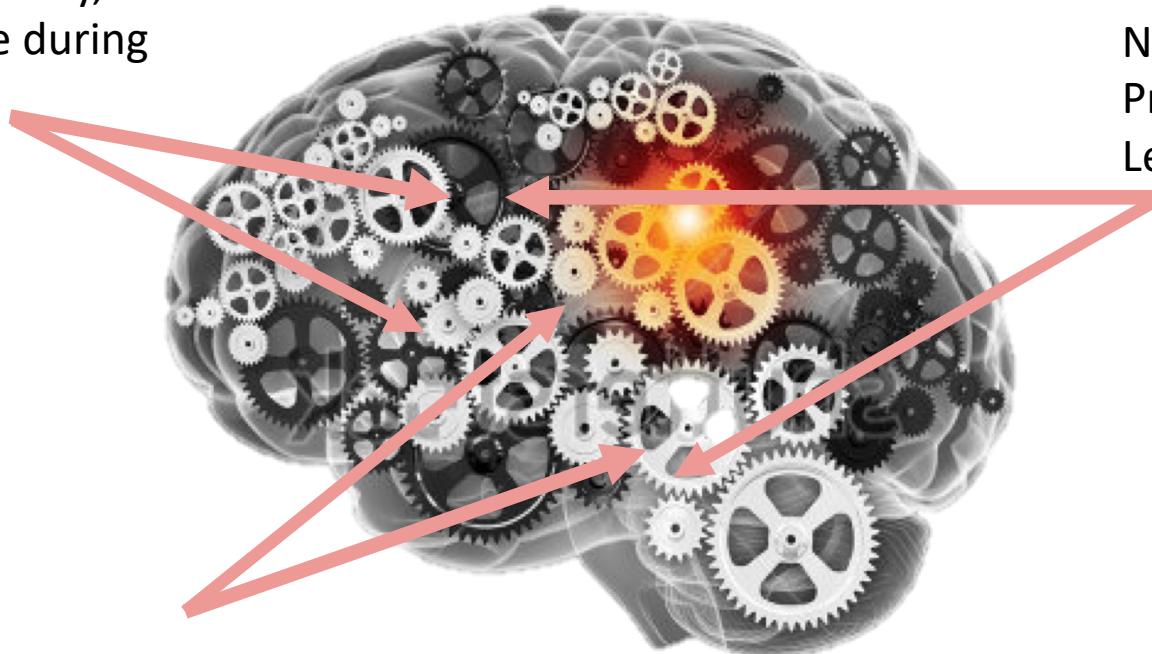


Outline

Models of the world & your
interaction with them

Insula – Cingulate Connectivity,
Anxiety & the Microbiome during
fear conditioning

Noradrenergic Responses, Cortical
Projections & Flexible Model
Learning



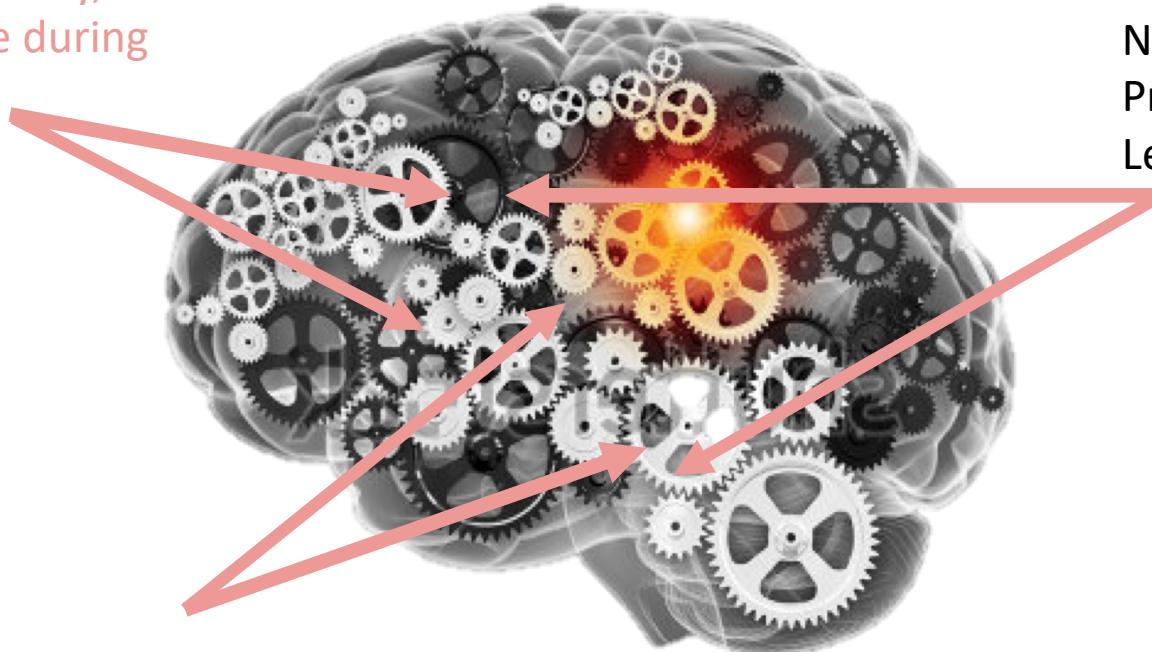
VTA & Striatal Dopamine & Serotonin
In PD & Cortical Connectivity in Schizophrenia subtypes

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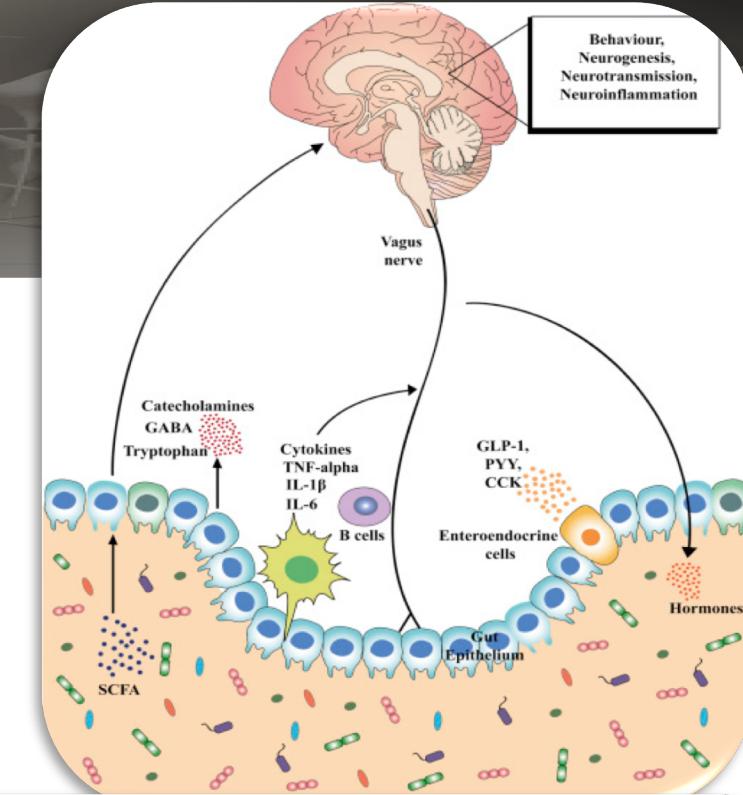
Noradrenergic Responses, Cortical Projections & Flexible Model Learning



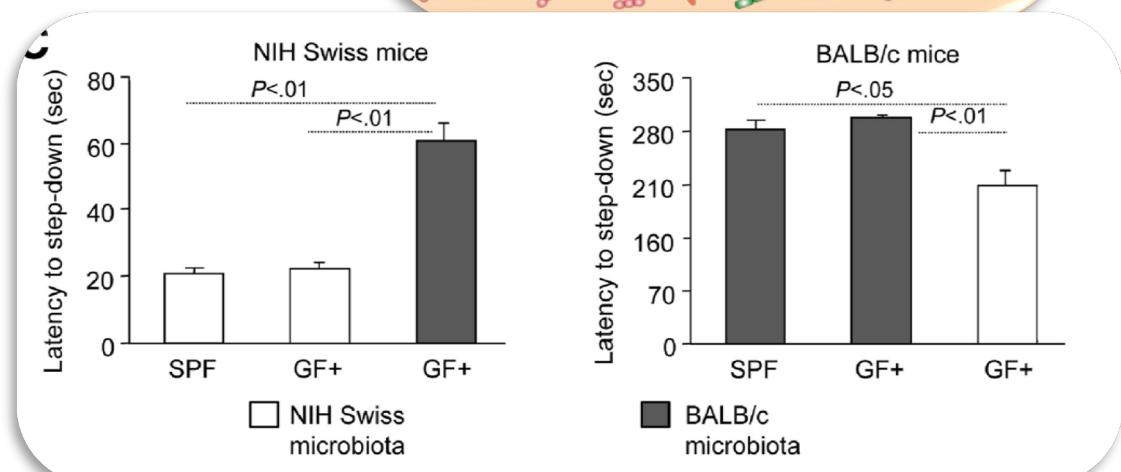
VTA & Striatal Dopamine & Serotonin
In PD & Cortical Connectivity in Schizophrenia subtypes

Microbiome Effects of Brain Connectivity (Caitlin Hall, Luca Cocchi)

- 1-2 Kg microbes, mainly bacteria
- Large co-morbidity of depression/anxiety with gut disorders (Inflammatory Bowel Disease – 65%, vs 45% in other chronic health samples)
- Putative pathways : Neuro – hormonal – immuno, bi-directional
- Major chronic disorders of the gut, (inflammatory bowel disease, coeliac disease) associated with dysbiosis
- Germ-free mice exhibit increased anxiety responses
- Colonization of germ-free NIH Swiss mice with BALB/c microbiota reduced exploratory behavior



Foster, et al, 2017



Bercik et al. 2011

Fear Conditioning with Reversal

Session 1 (120 min)

N = 38 Health and Neurocognitive Assessments

Provide stool sample kit

Session 2 (90 min)

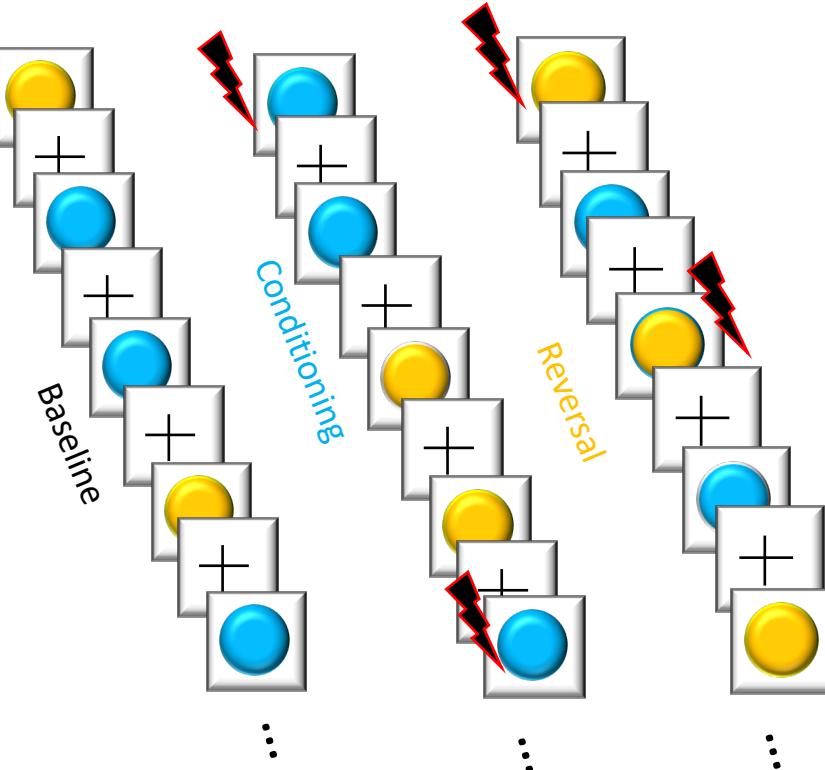
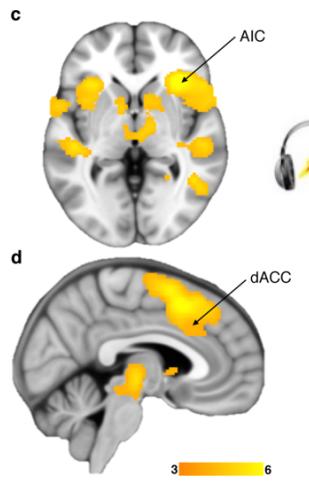
Return sample

T1

Resting-state fMRI

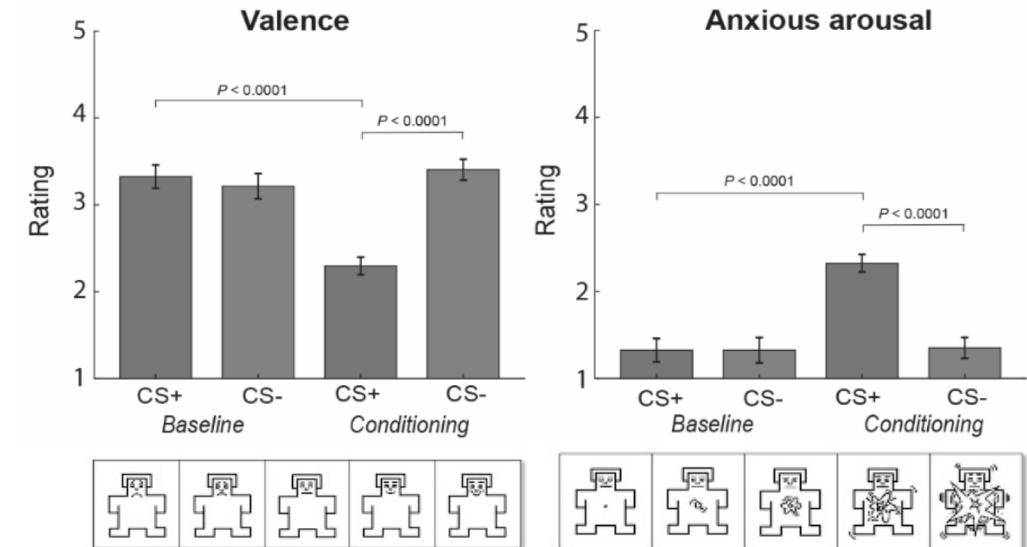
Fear conditioning fMRI task

Extended Fear Network
under Aversive Sounds



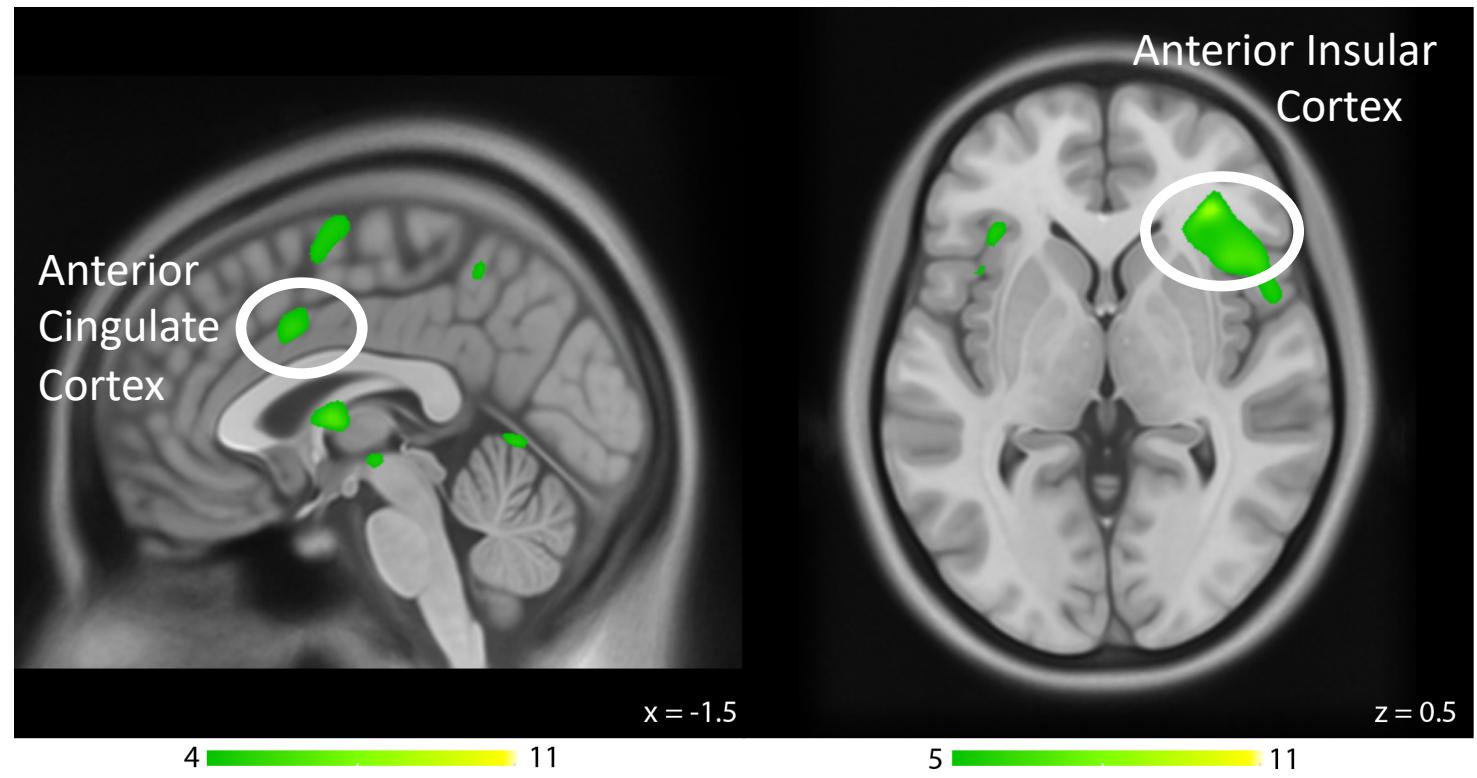
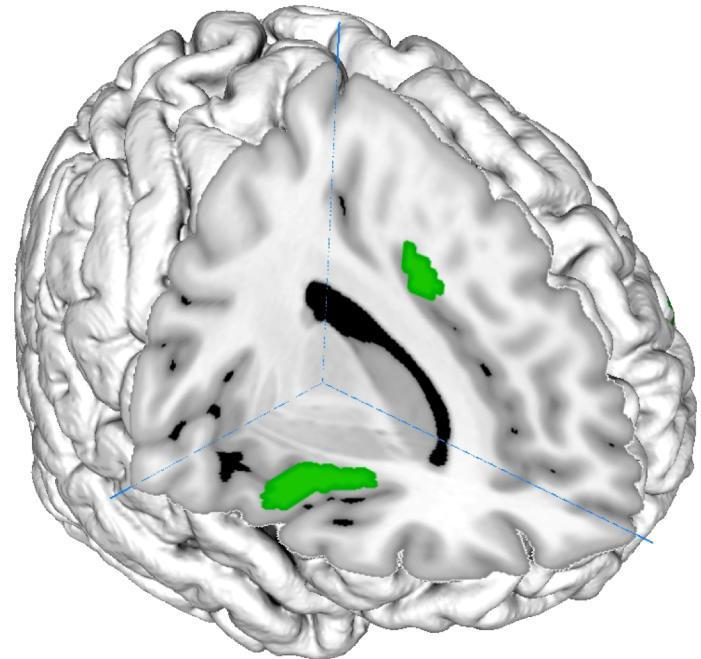
Harrison et al., (2015, 2017)

Subjective in-scanner ratings



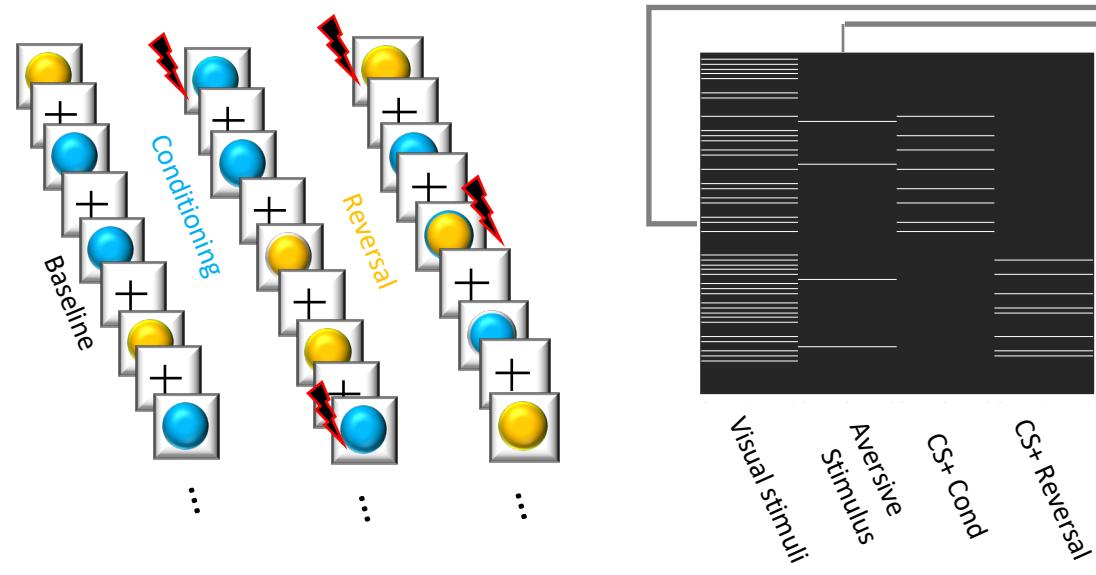
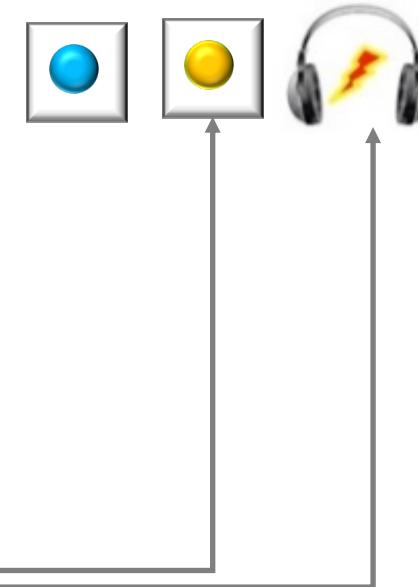
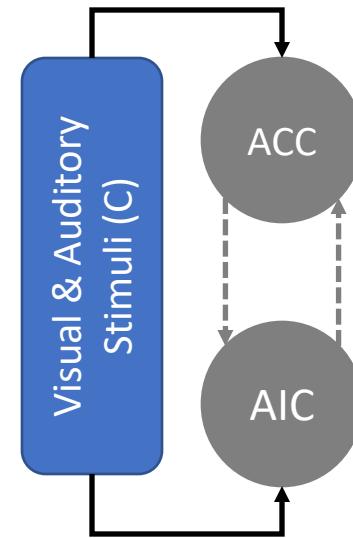
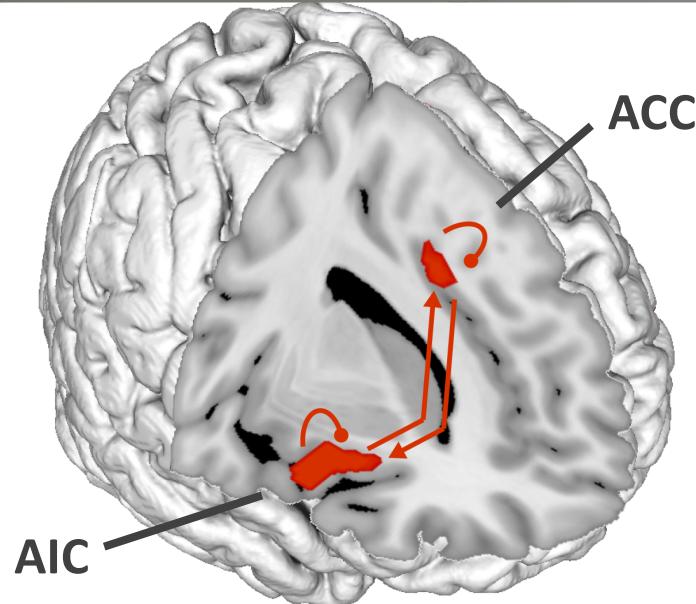
Mass Univariate Results

CS+ > CS-



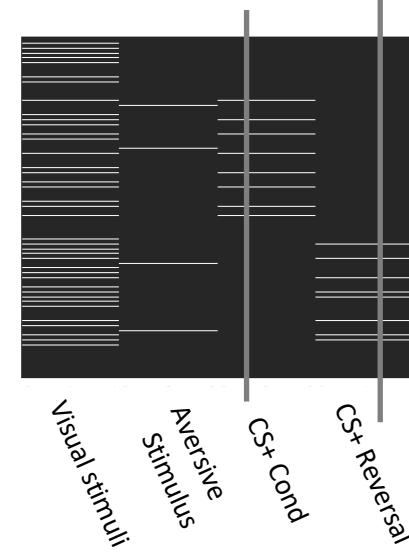
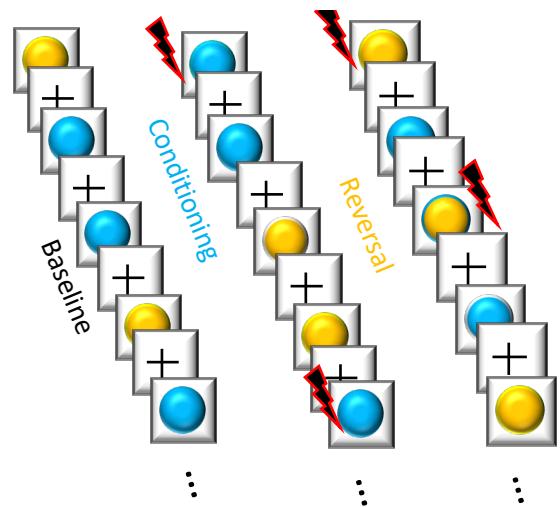
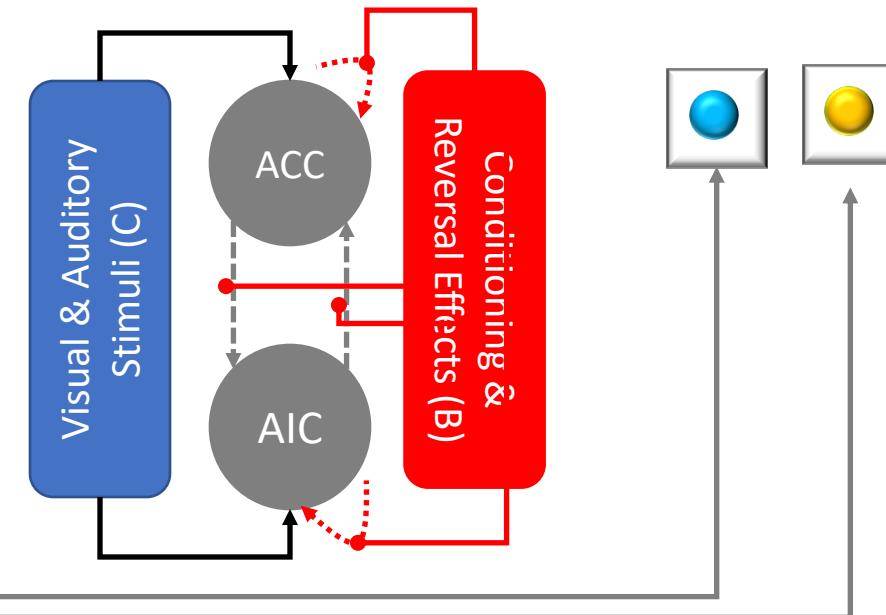
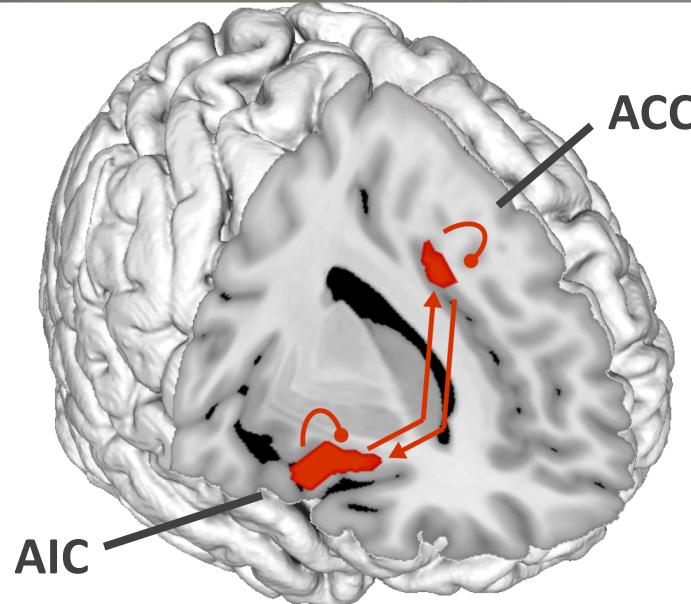
Neural correlates of fear conditioning. Significant group level activation of fear conditioning response, including the anterior cingulate cortex (ACC, left) and right anterior insular cortex (AIC, right). Results correspond to $P_{\text{FWE}} < 0.05$ at cluster level.

Connectivity Hypotheses for DCM

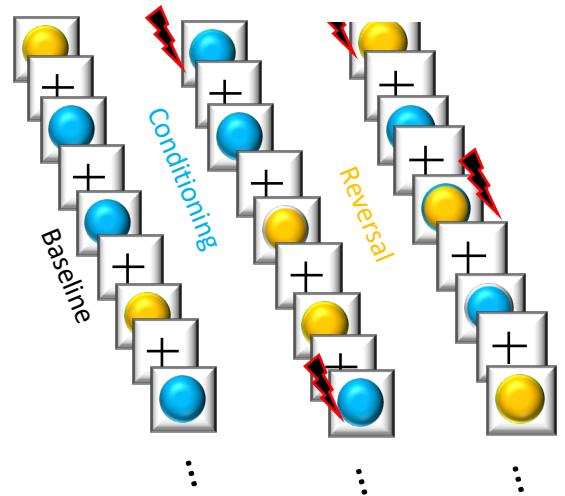
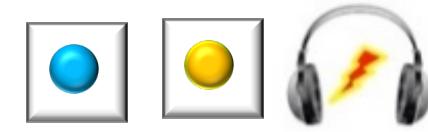
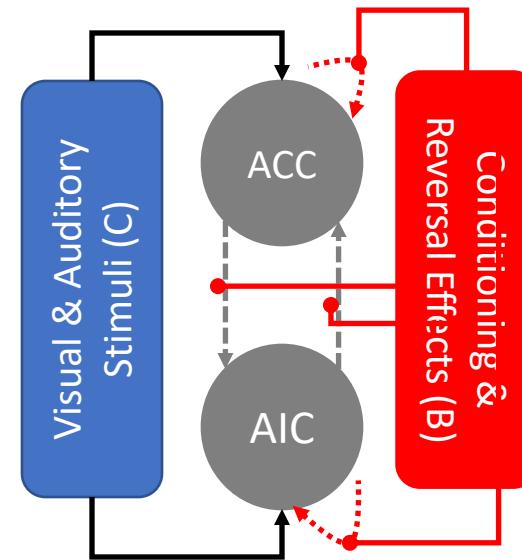
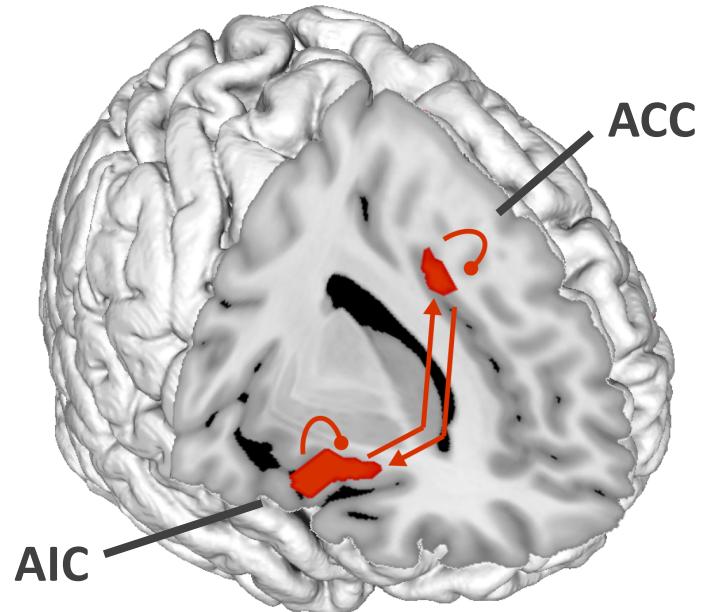


visual stimuli
aversive stimulus
CS+ Cond
CS+ Reversal

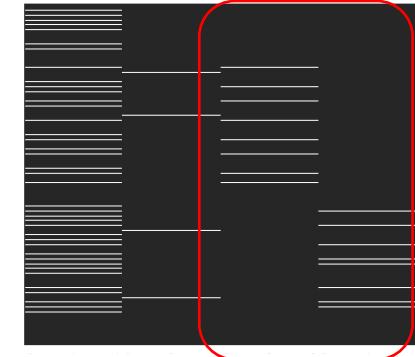
Connectivity Hypotheses for DCM



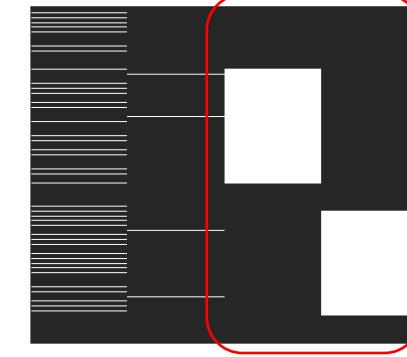
Connectivity Hypotheses for DCM – event or persistent anxiety?



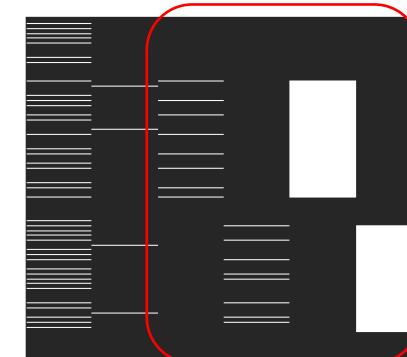
Bayesian Model Comparison



Model 1. Fear-related events

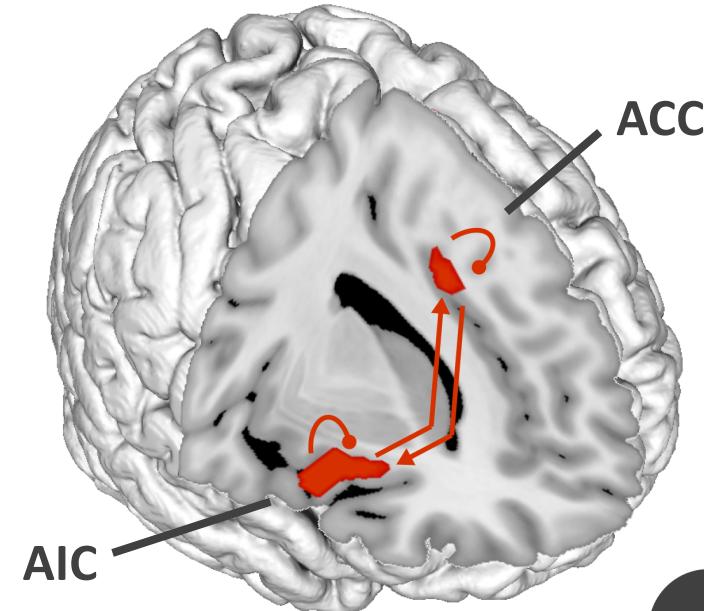
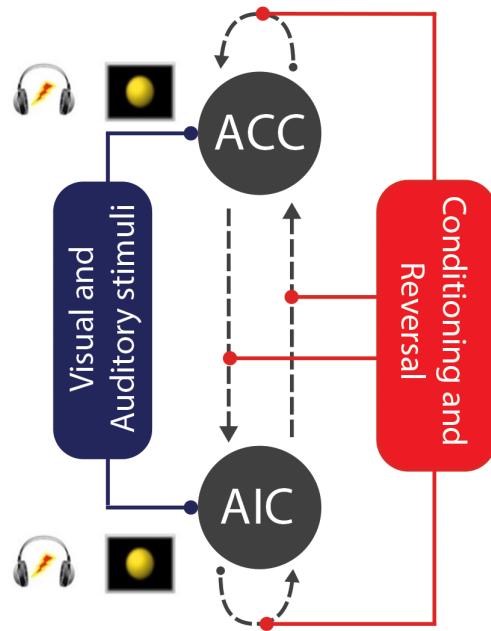


Model 2. Block-related events

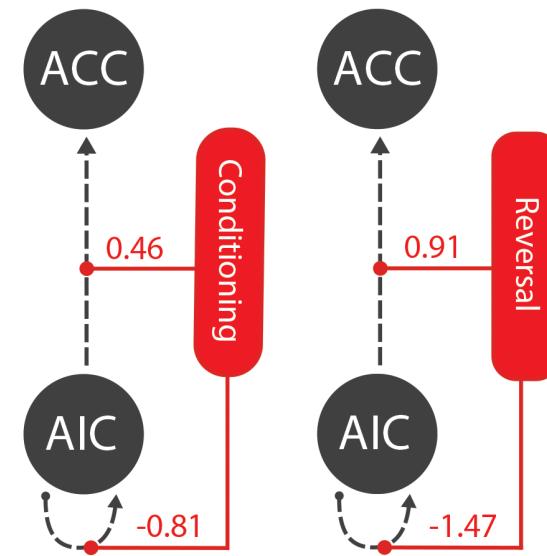
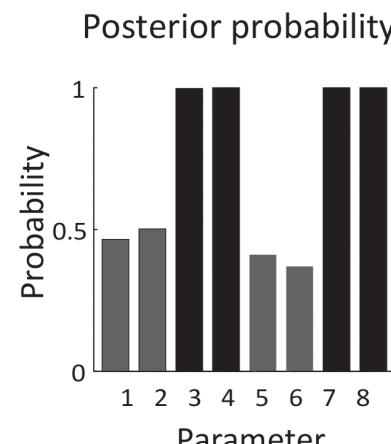
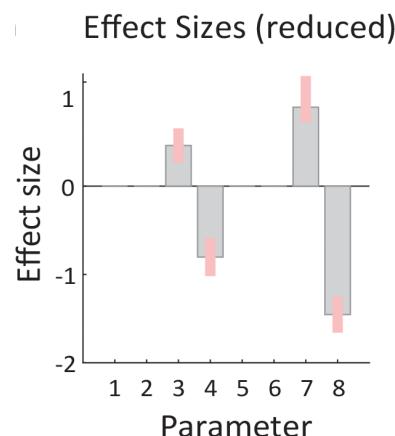
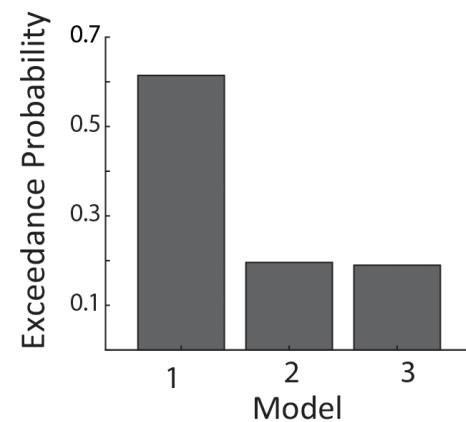


Model 3. Fear and block-related events

Modulation by fear-provoking stimulus

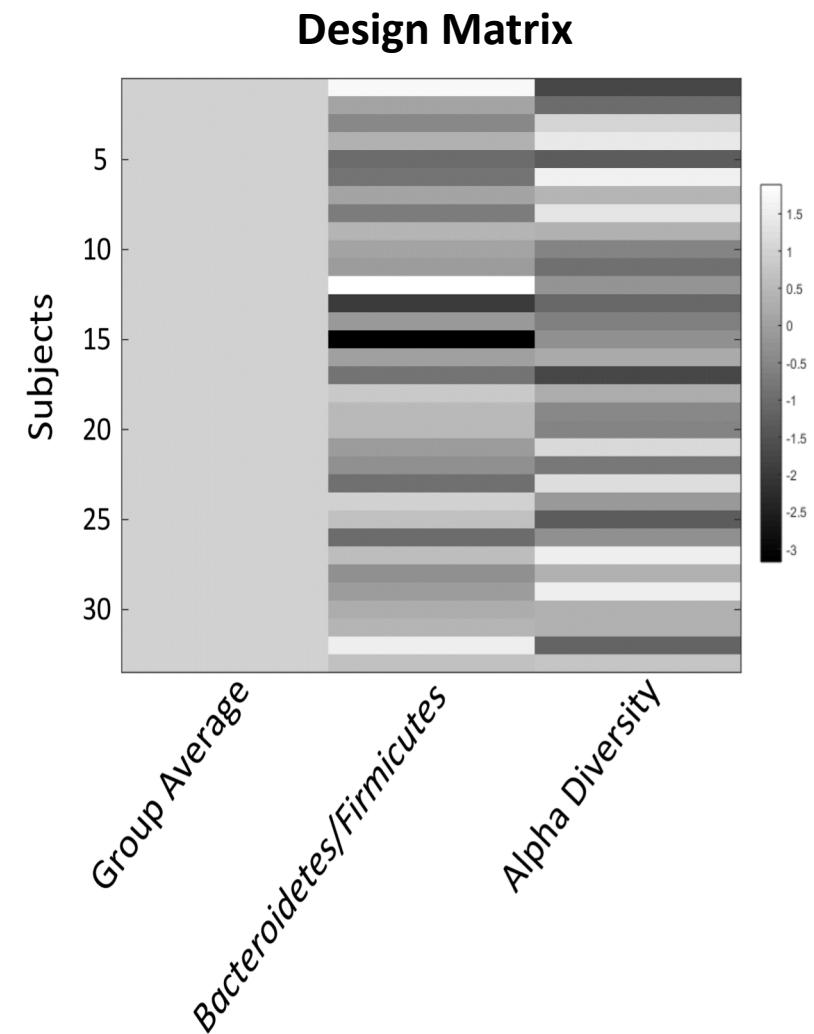
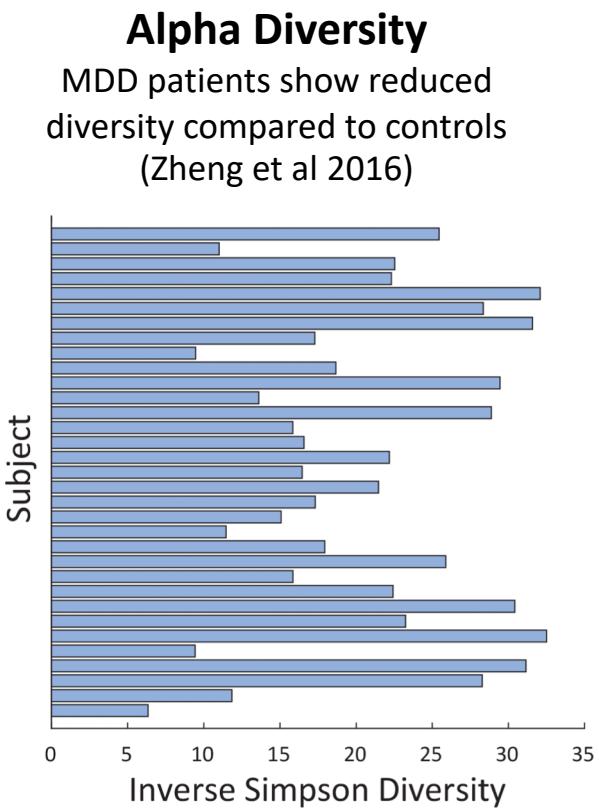
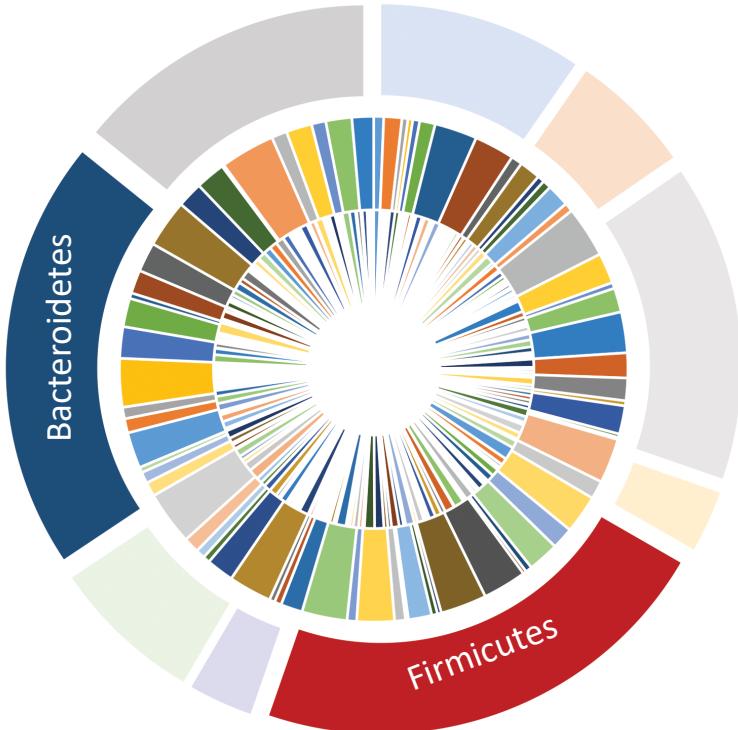


Bayesian Model Comparison



Gut Samples

Bacteroidetes/Firmicutes (associated with low BMI, rodent studies showed trends towards low B/F Ratio associated with heightened stress responses (Wong et al. 2016)



Parametric Empirical Bayes

$$\theta^{(2)} = \eta + \varepsilon^{(3)}$$



Priors on second level parameters

Second level



$$\theta^{(1)} = \Gamma^{(2)}(\theta^{(2)}) + \varepsilon^{(2)}$$

Between-subject error

Second level (linear) model

First level



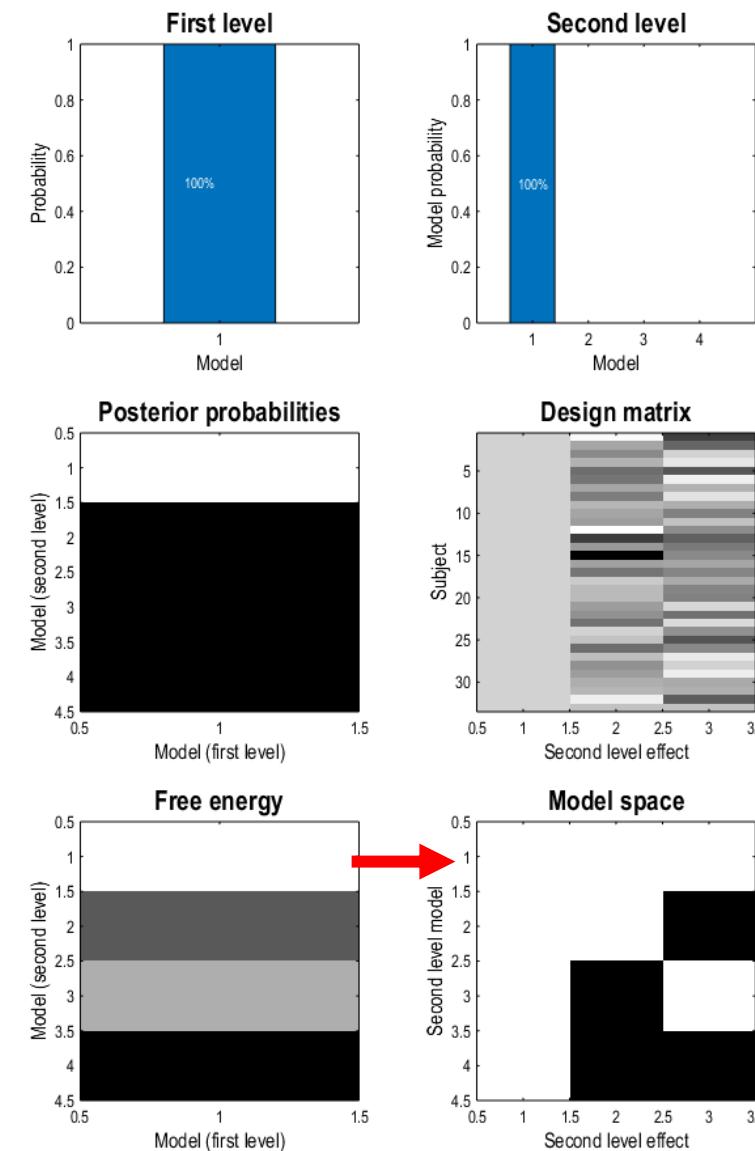
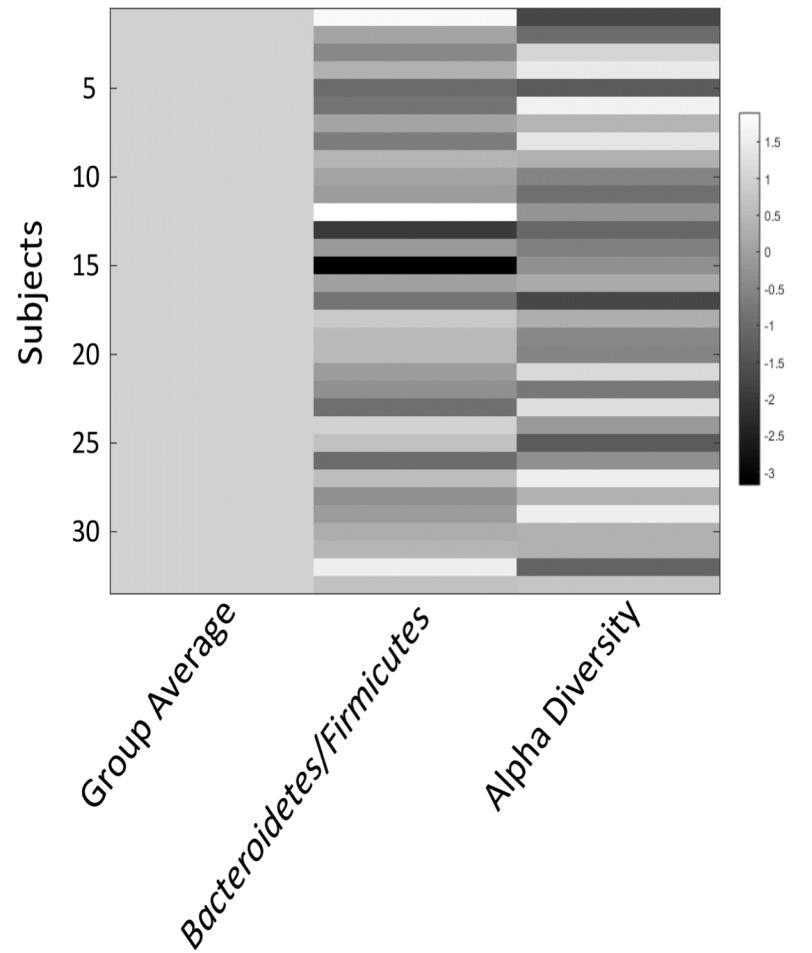
$$y = \Gamma_i^{(1)}(\theta^{(1)}) + \varepsilon^{(1)}$$

Measurement noise

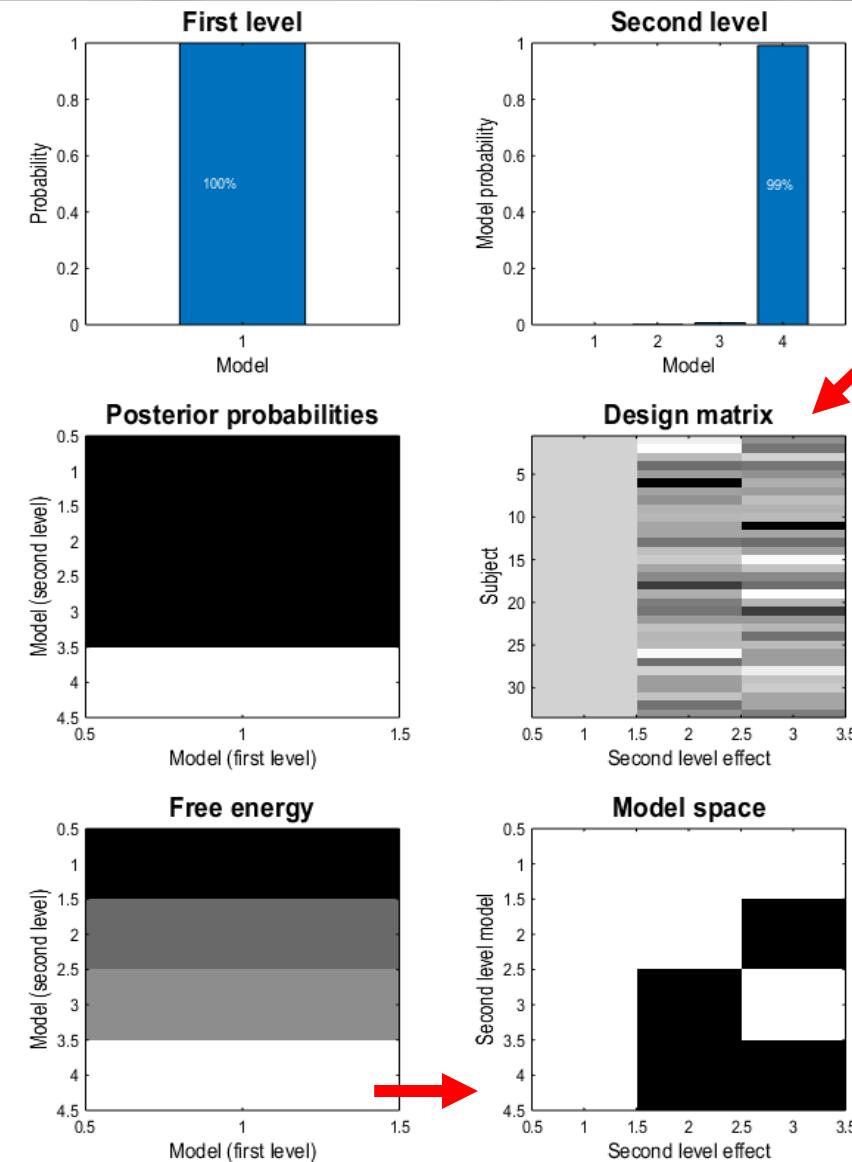
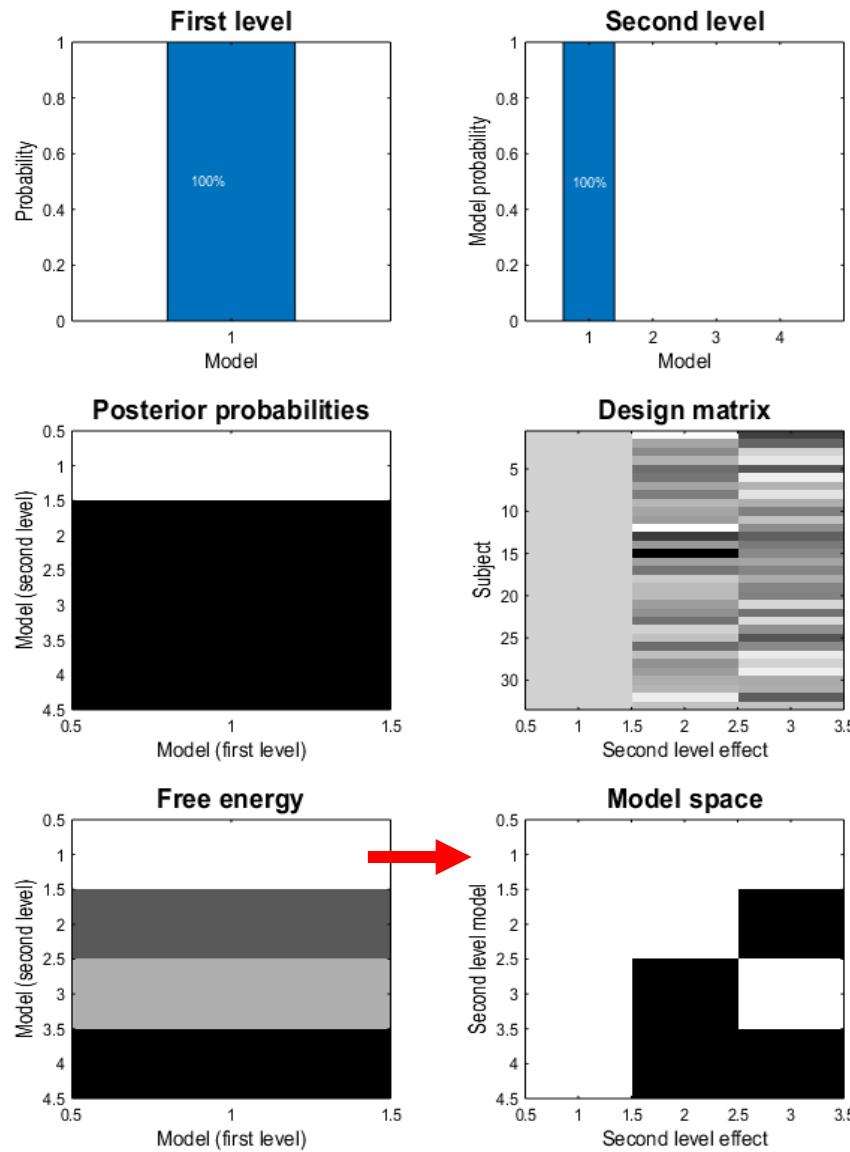
DCM for subject i

Parametric Empirical Bayes

2nd Level Design Matrix

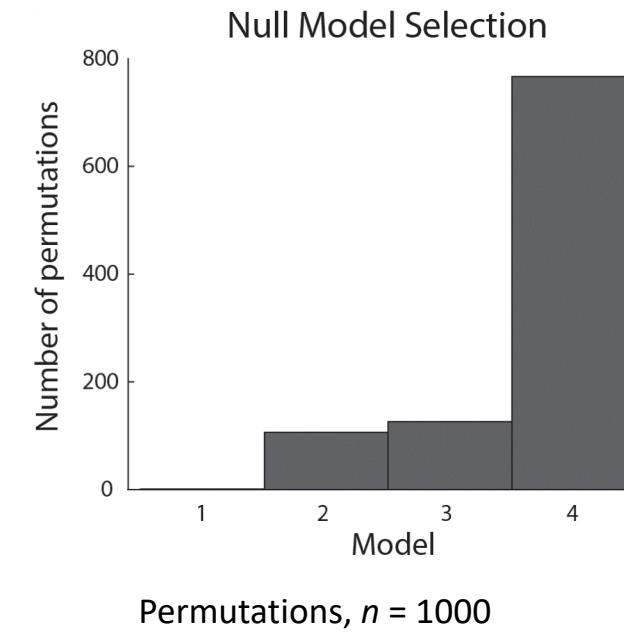
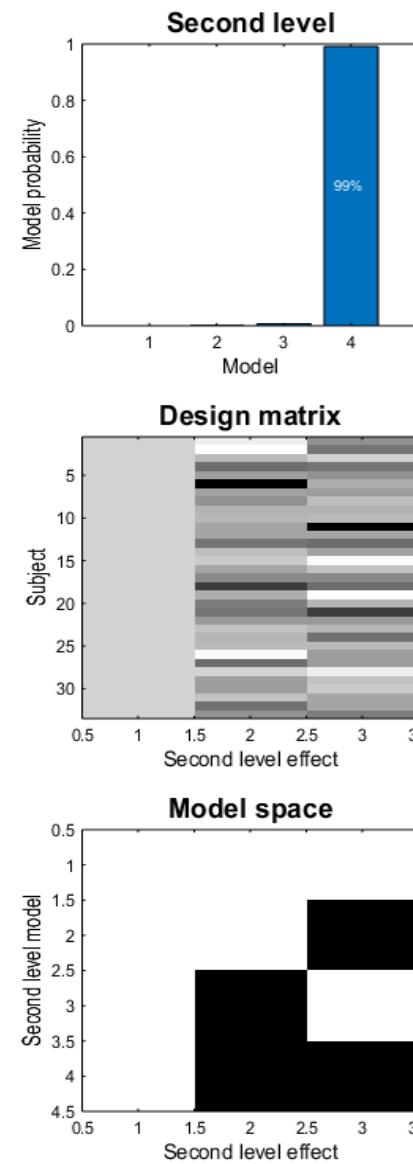
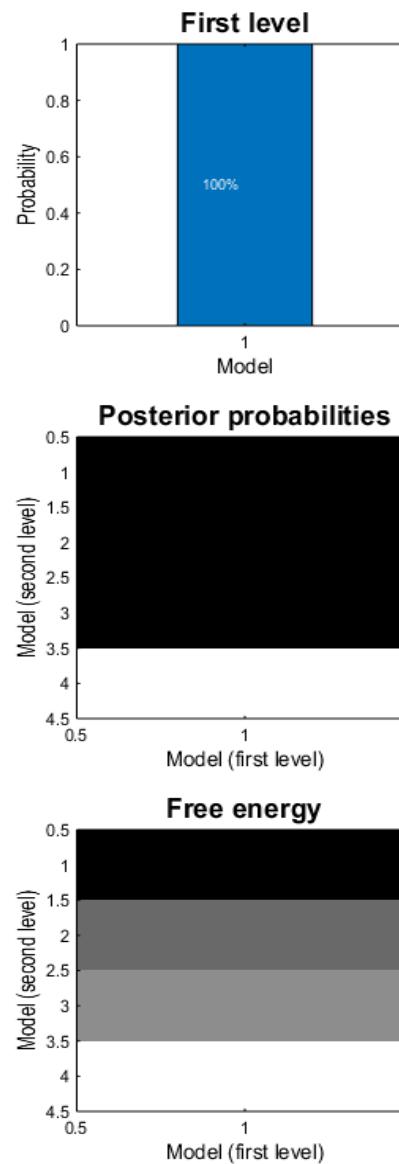


Parametric Empirical Bayes (Surrogate Testing)

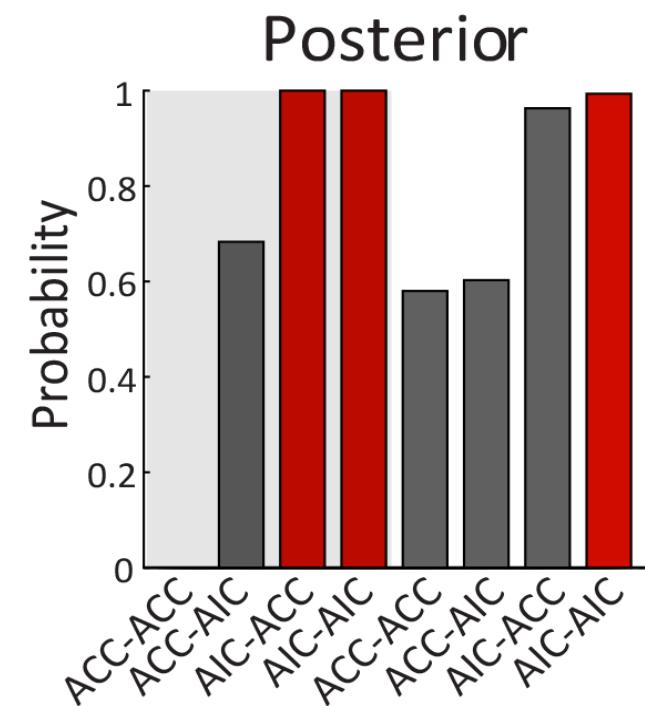
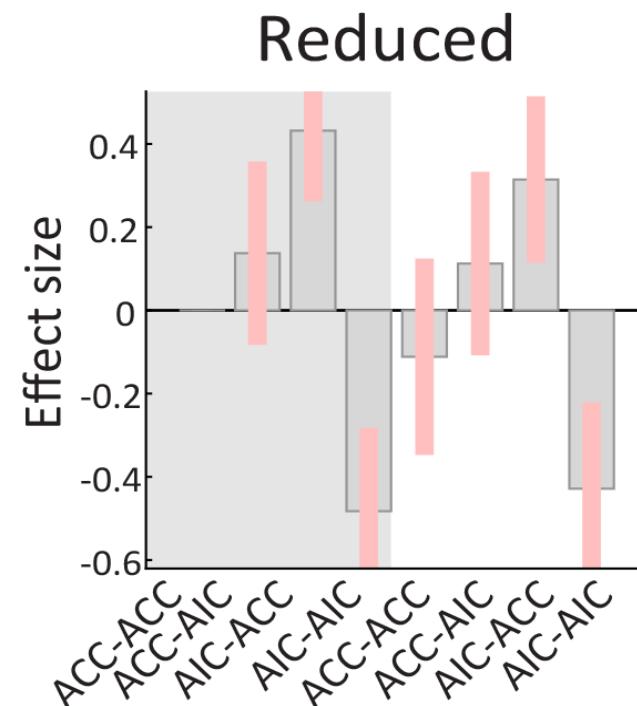
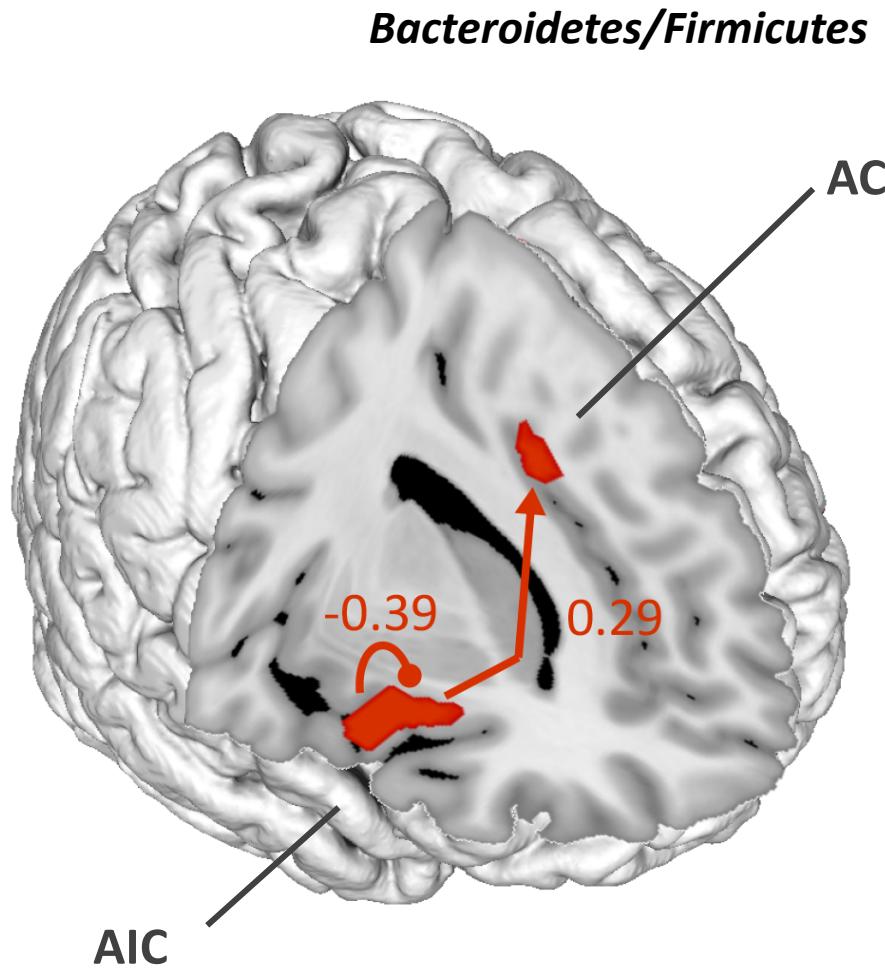


Shuffle Entries in Design Matrix

Parametric Empirical Bayes (Surrogate Testing)

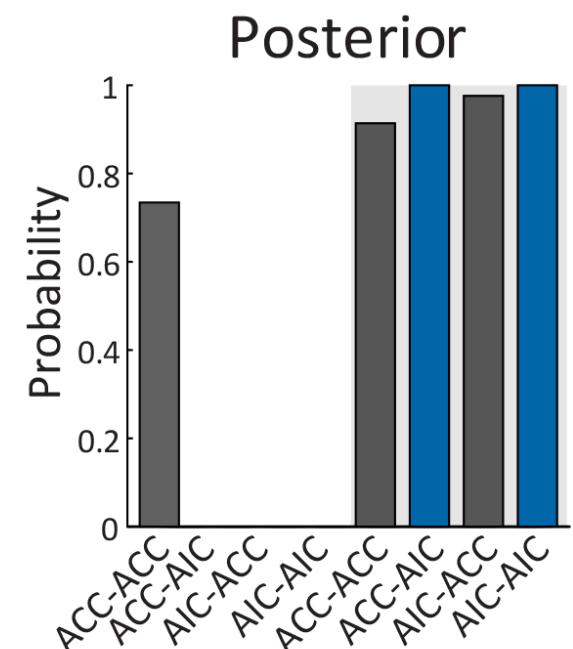
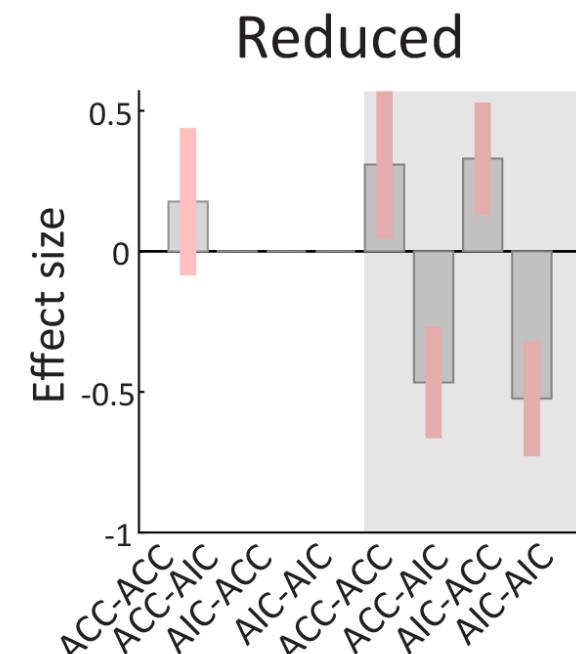
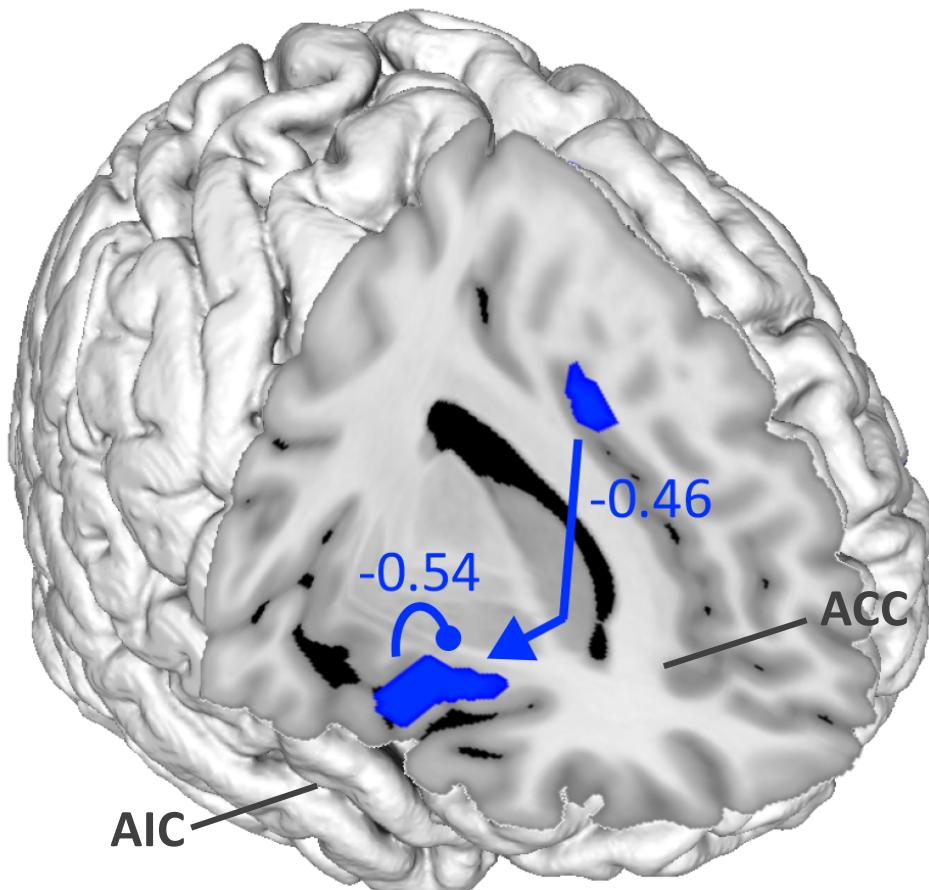


Effect of Ratio of Bacteroidetes/Firmicutes



Effect of Alpha Diversity

Alpha Diversity (Inverse Simpson)



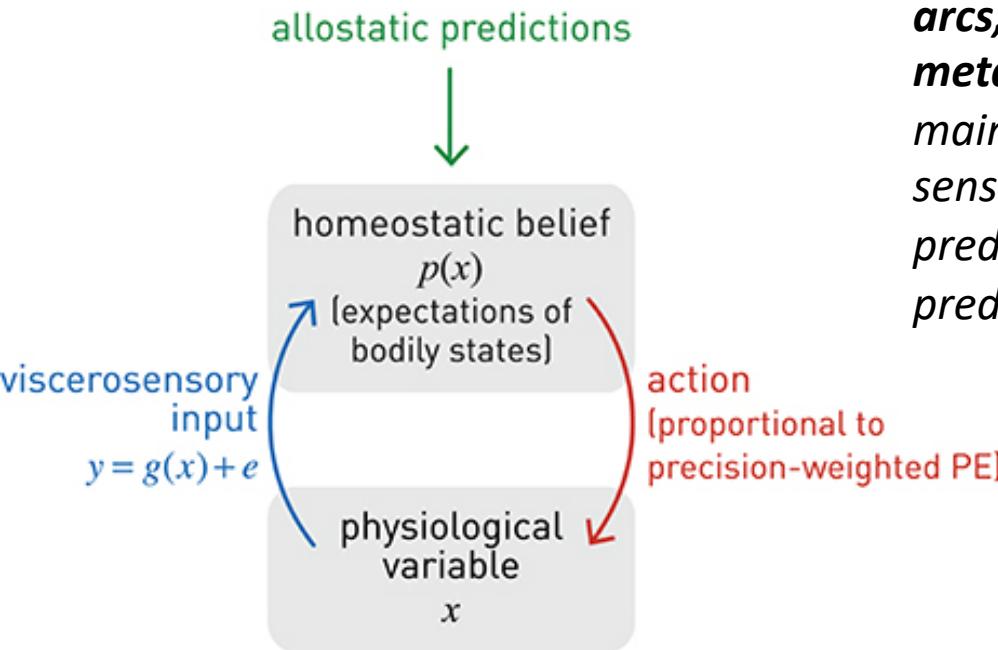
Conditioning

Reversal

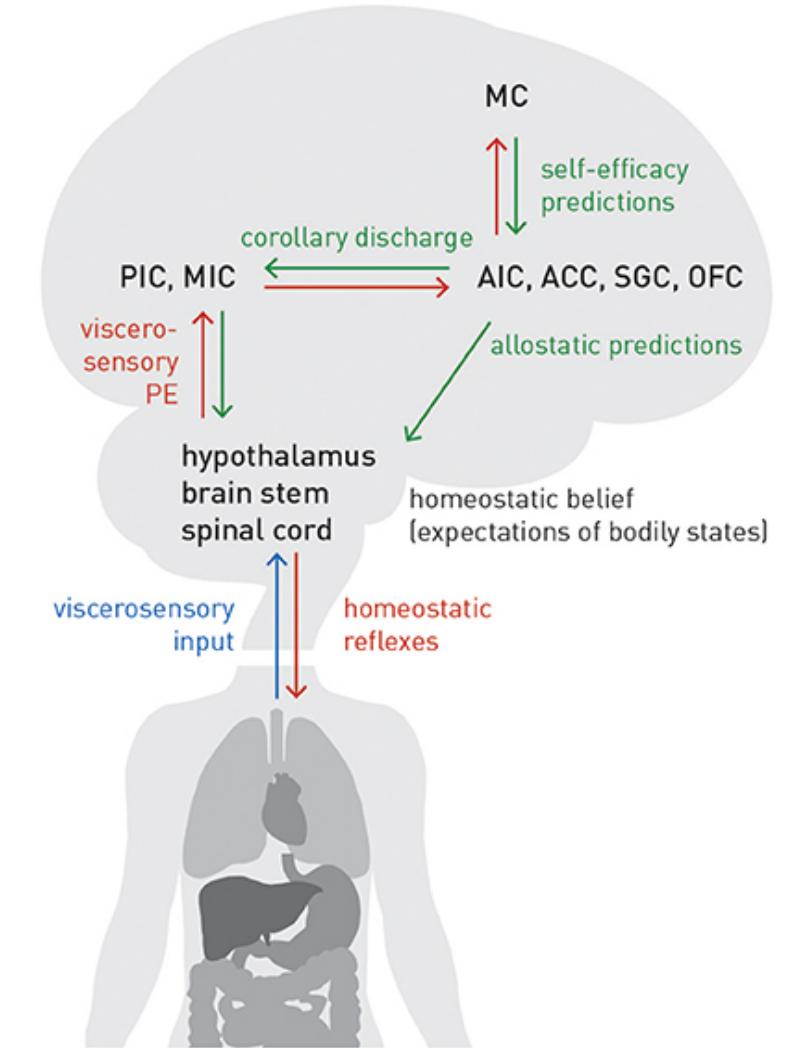
A putative framework for interpretation (Stephan et al 2016)

Allostatic Self-efficacy: A Metacognitive Theory of Dyshomeostasis-Induced Fatigue and Depression

Klaas E. Stephan^{1,2,3*}, Zina M. Manjaly^{1,4}, Christoph D. Mathys², Lillian A. E. Weber¹, Saeed Palwal¹, Tim Gard^{1,3}, Marc Tittgemeyer³, Stephan M. Fleming², Helene Hakkar¹, Anil K. Seth⁴ and Frederike H. Petzschner¹



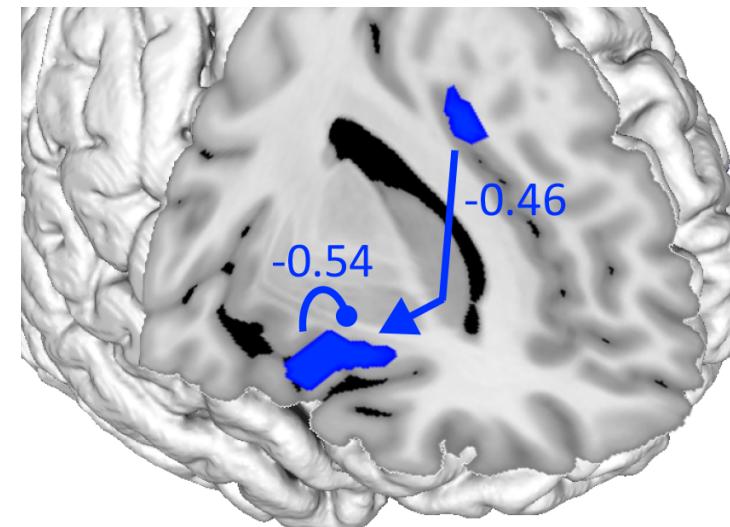
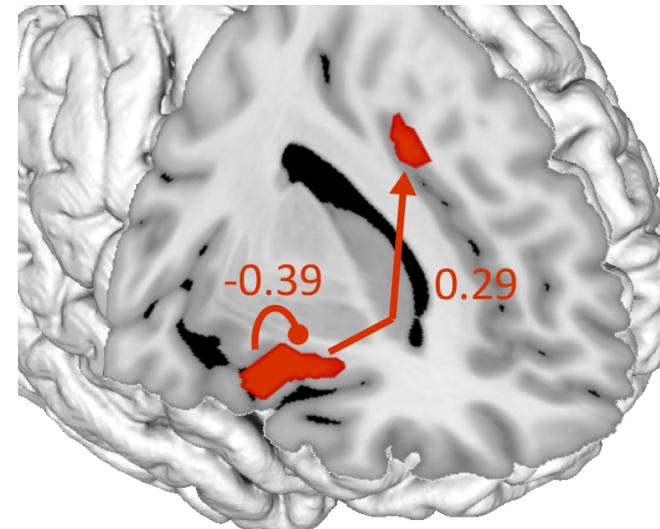
Proposed circuit for interoception and allostatic regulation of homeostatic reflex arcs, together with a metacognitive layer (MC). See main text for details. Blue lines: sensory inputs; red lines: prediction errors; green lines: predictions.



Gut Associations with Brain Connectivity

Gut ratio associated with increased “prediction error signalling”?

i.e. For threatening stimuli to be explained away/processed by ACC



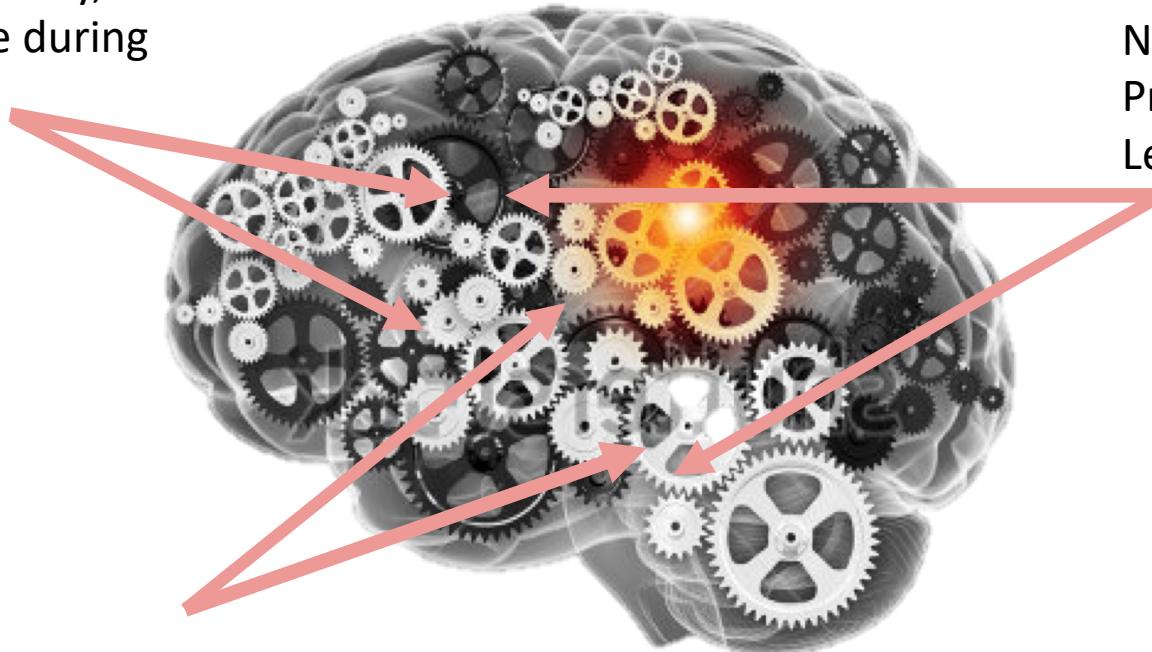
Diversity of the Microbiome – known to have positive health effects associated with more efficient ‘explaining away’?

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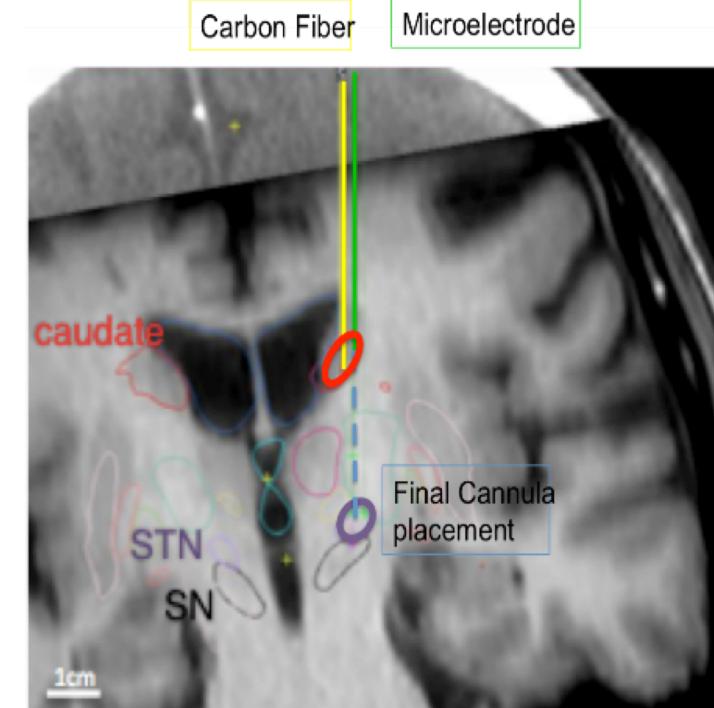
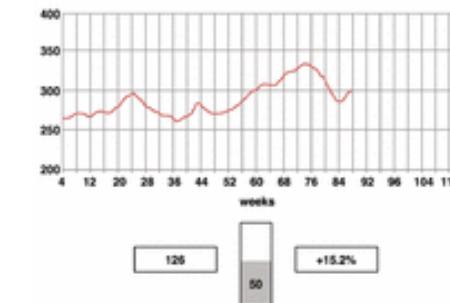
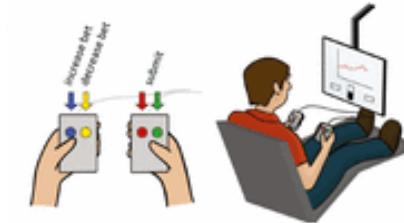
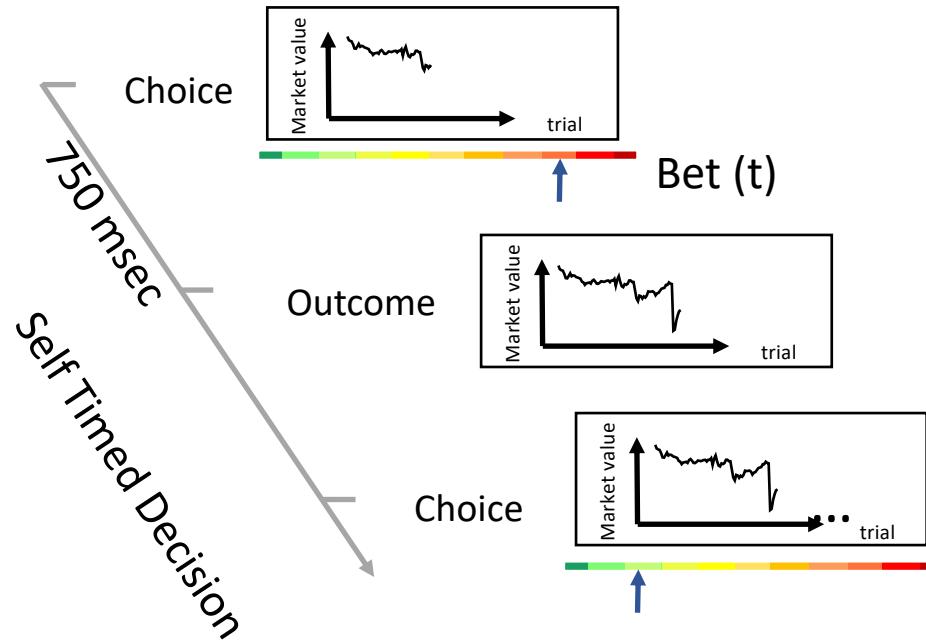
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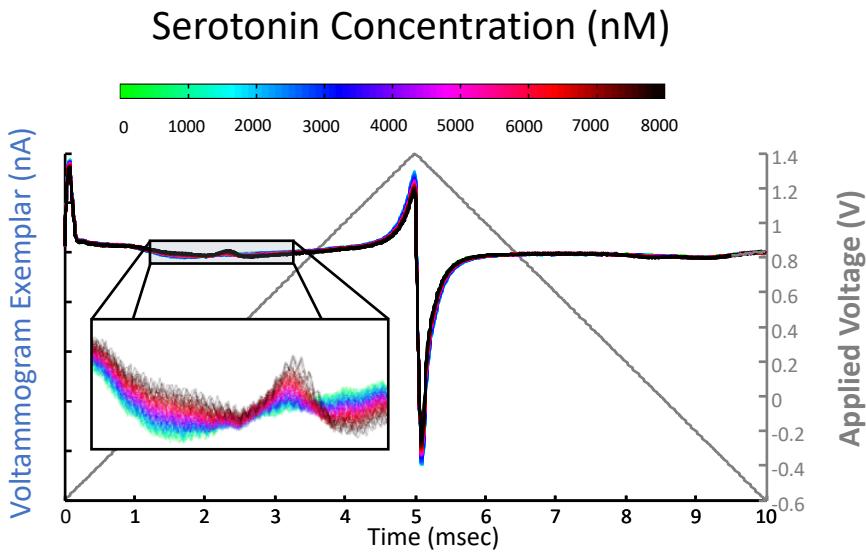
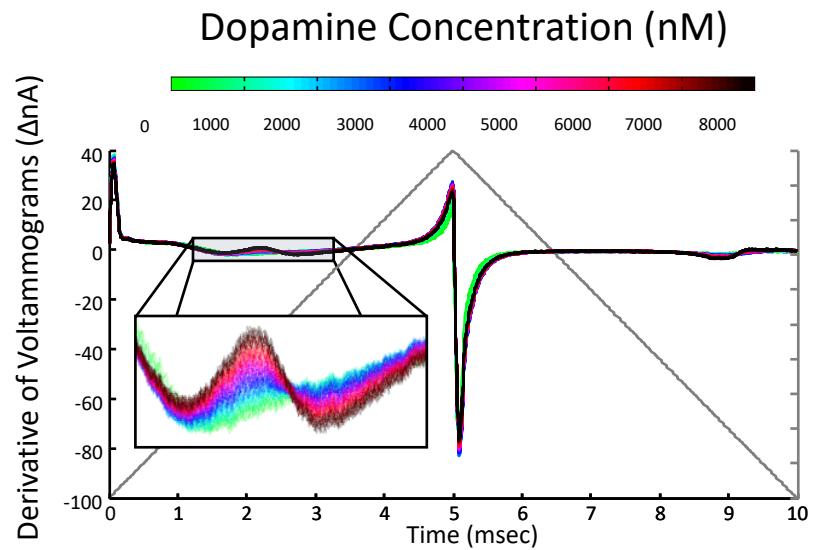
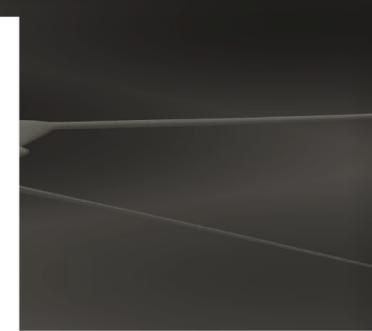
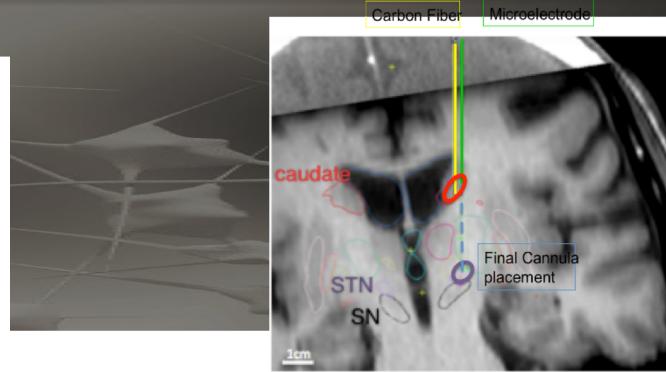
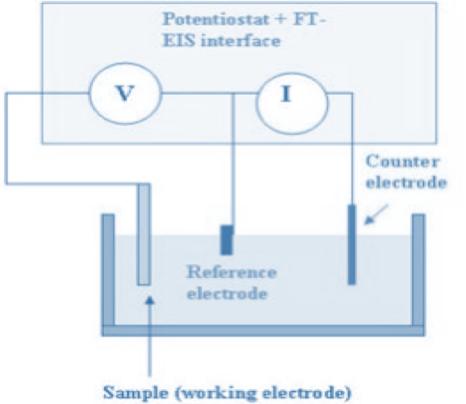
Measuring Serotonin & Dopamine in the striatum ... In Humans using voltammetry



With Read Montague VT/UCL & Stephen
Tatter Wake Forest

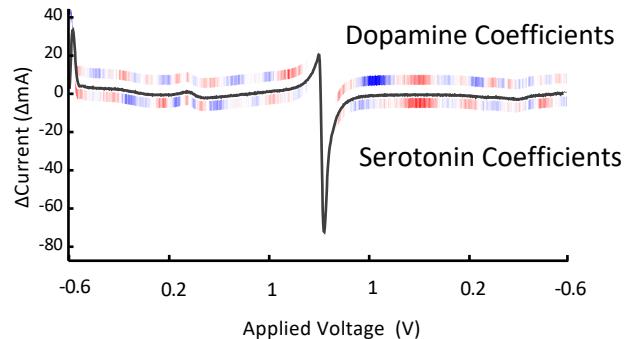
Measuring Chemicals Human Voltammetry

'OILRIG'

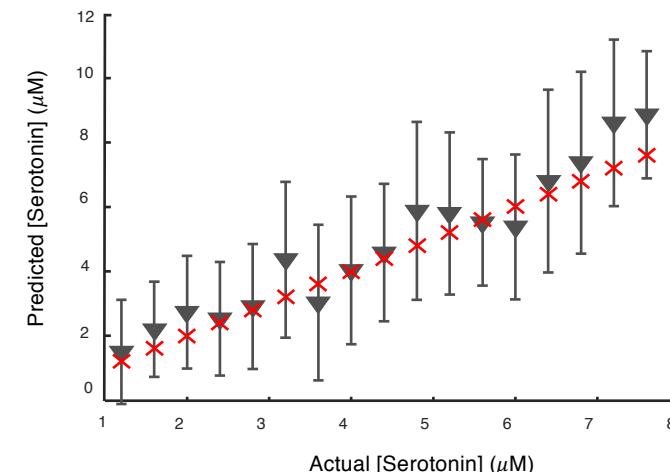
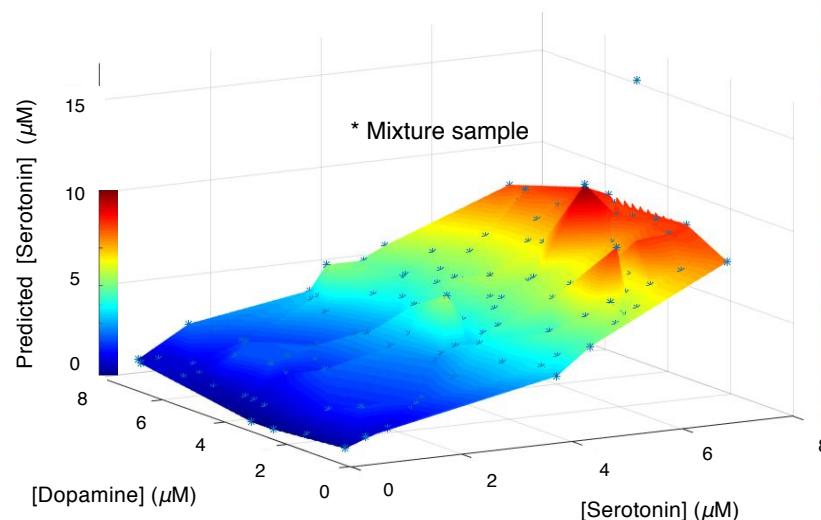
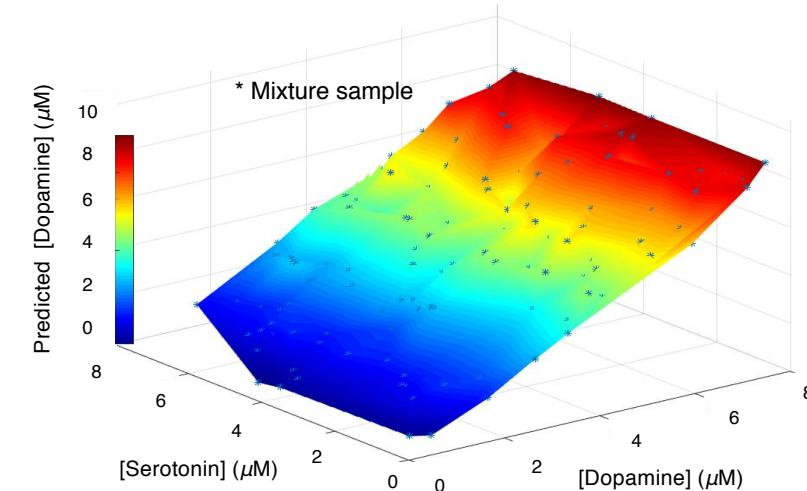
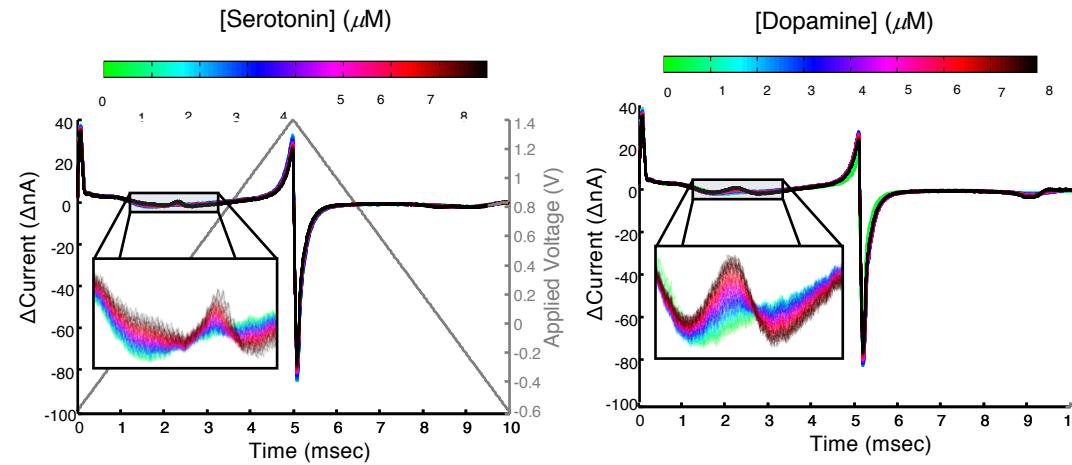


LASSO

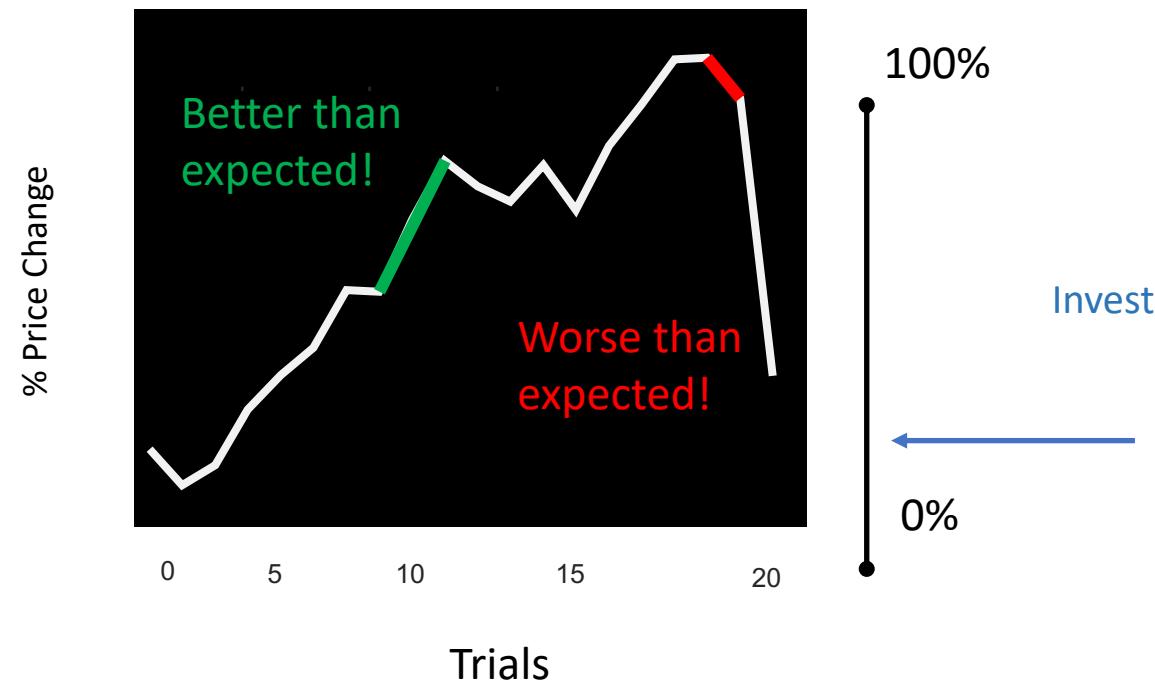
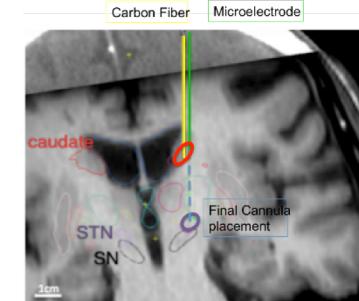
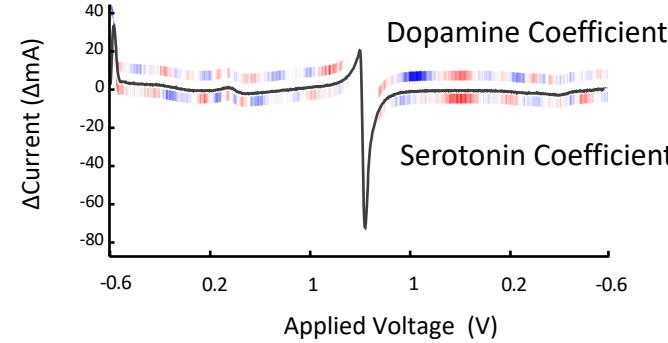
$$\hat{\beta} = \operatorname{argmin}_{\beta} \frac{1}{2} \|Y - X\beta\|_F^2 + \lambda \sum_{k=1}^p \|\beta_k\|_2$$



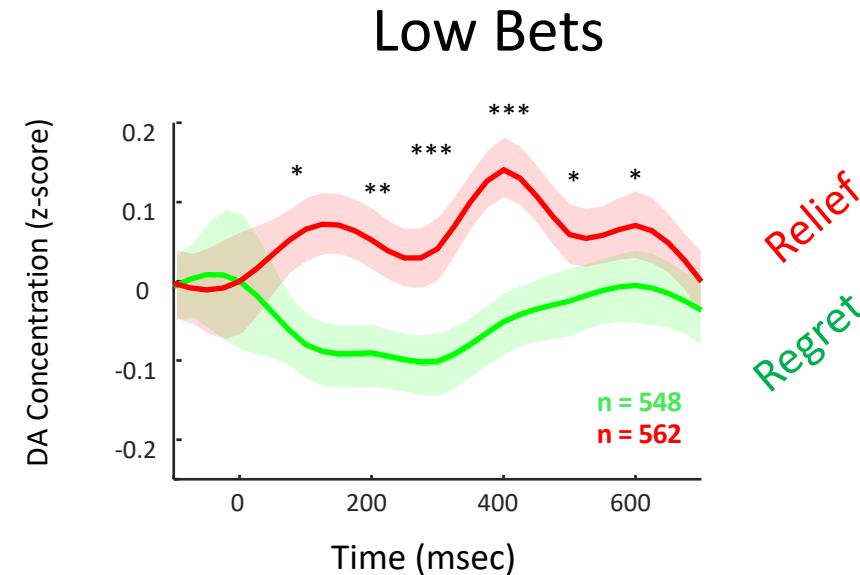
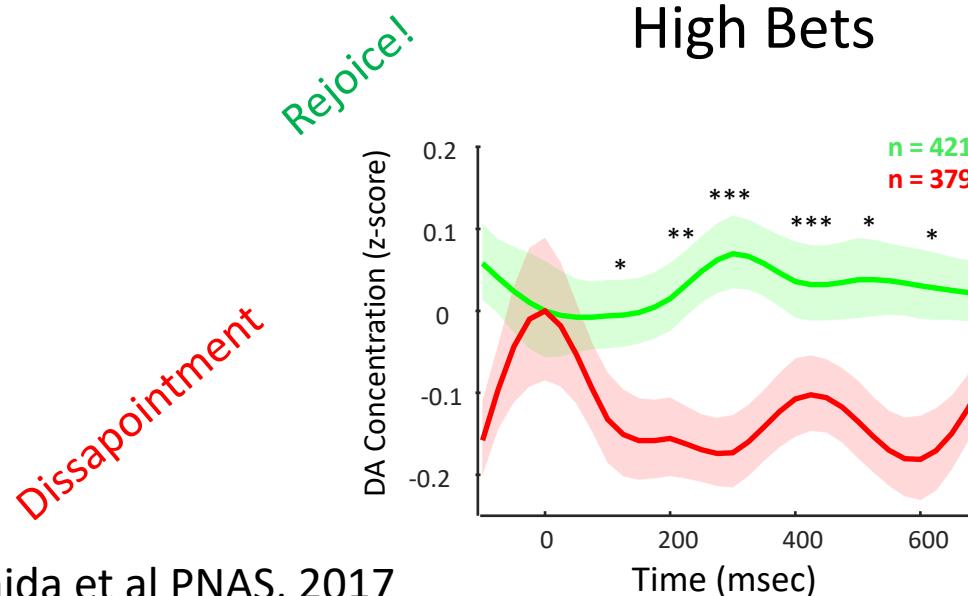
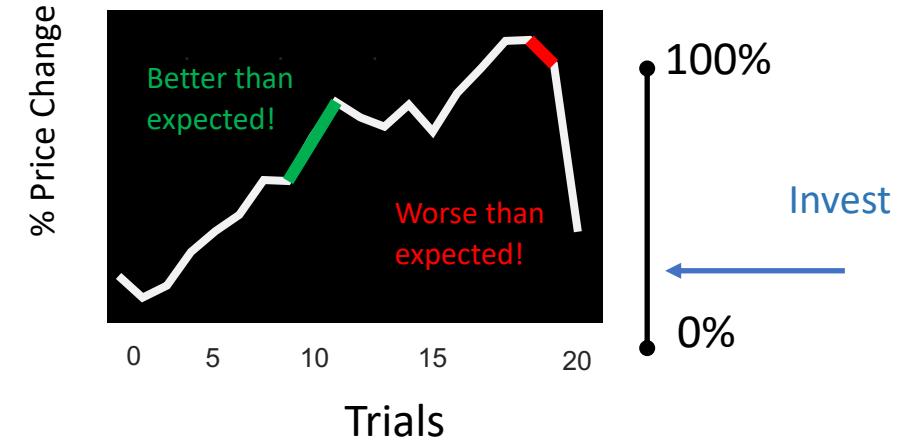
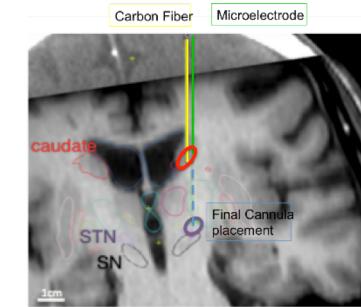
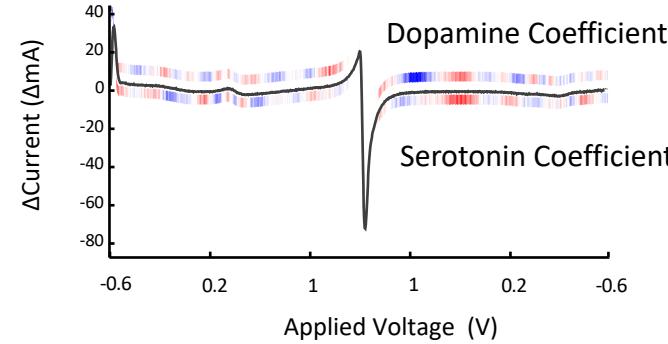
Human Voltammetry: Separating Chemicals



Does Dopamine encode Reward Prediction Errors?



Does Dopamine encode Reward Prediction Errors?



Negative Reward Prediction Errors?

SEROTONIN & DOPAMINE

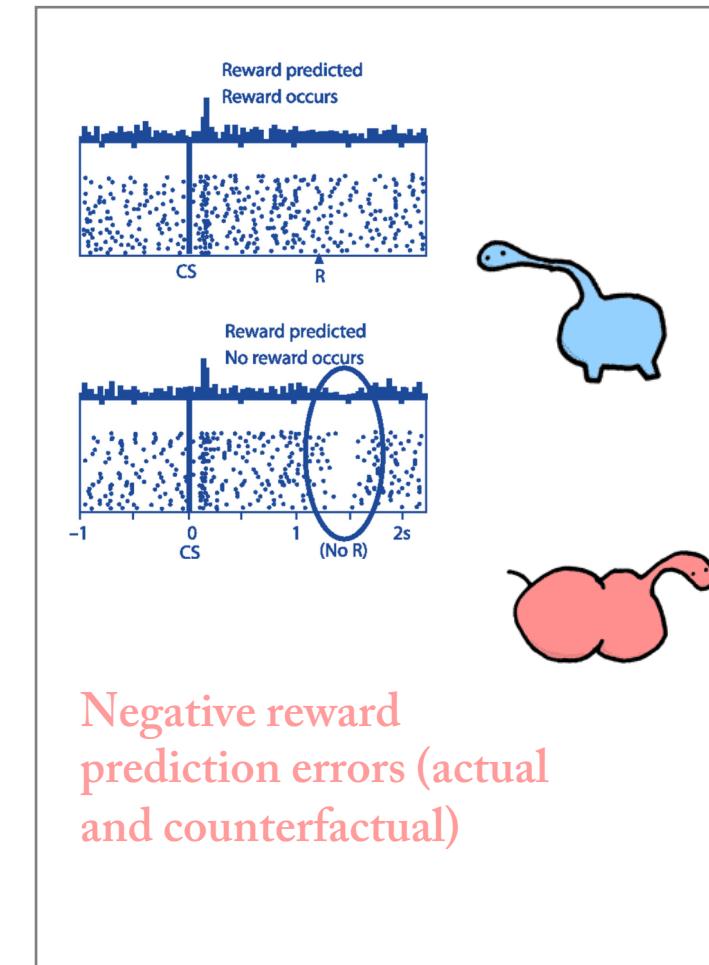
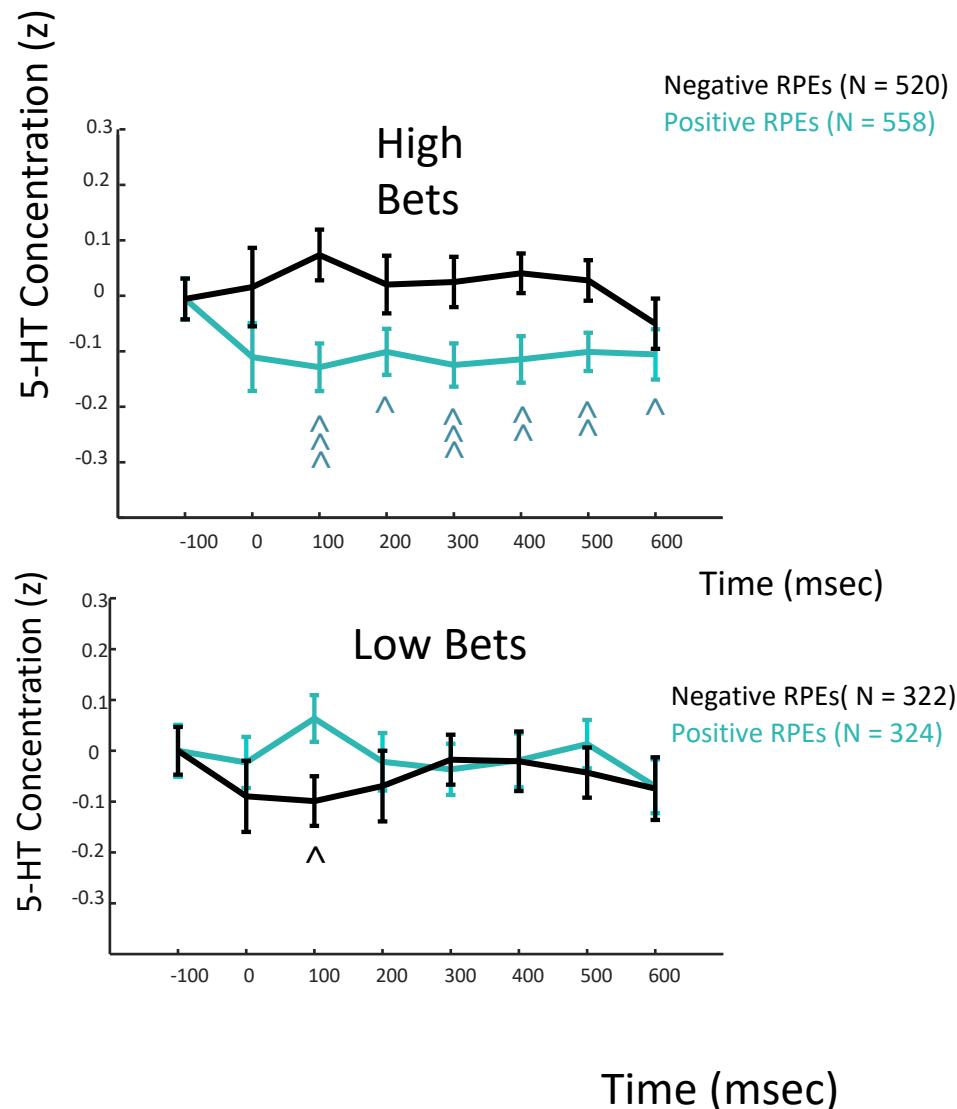


Technically, the only two things
you enjoy



- Serotonin Serves as an Opponent to Dopamine (Dayan & Daw)
- Related to Patience, Behavioural Inhibition (Doya)
- 5-HT can act as a “False Transmitter” from DA terminals (Danny)

Reacting to negative prediction errors



And Shaping Action Selection

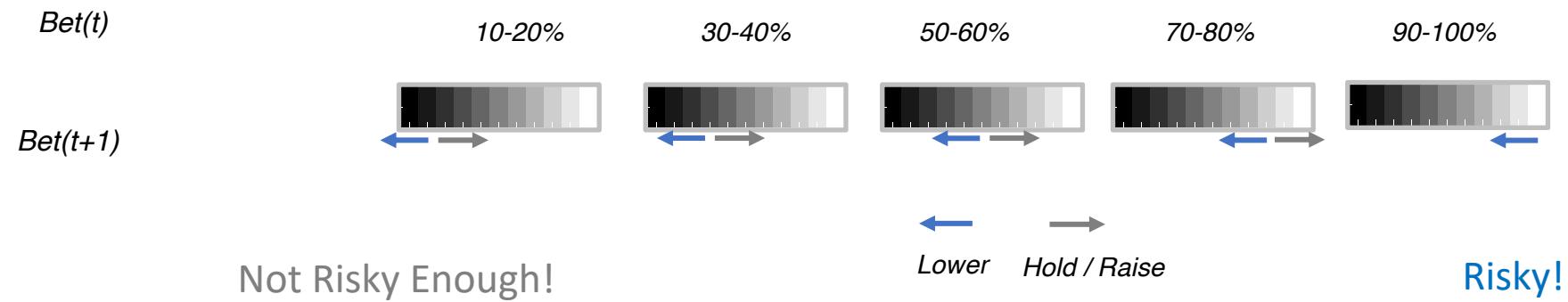
Reacting to negative reward prediction errors & behavioral inhibition

- Previous Investment, ‘How much did I just risk’: ... I’m changing my bet

And Shaping Action Selection

Reacting to negative reward prediction errors & behavioral inhibition

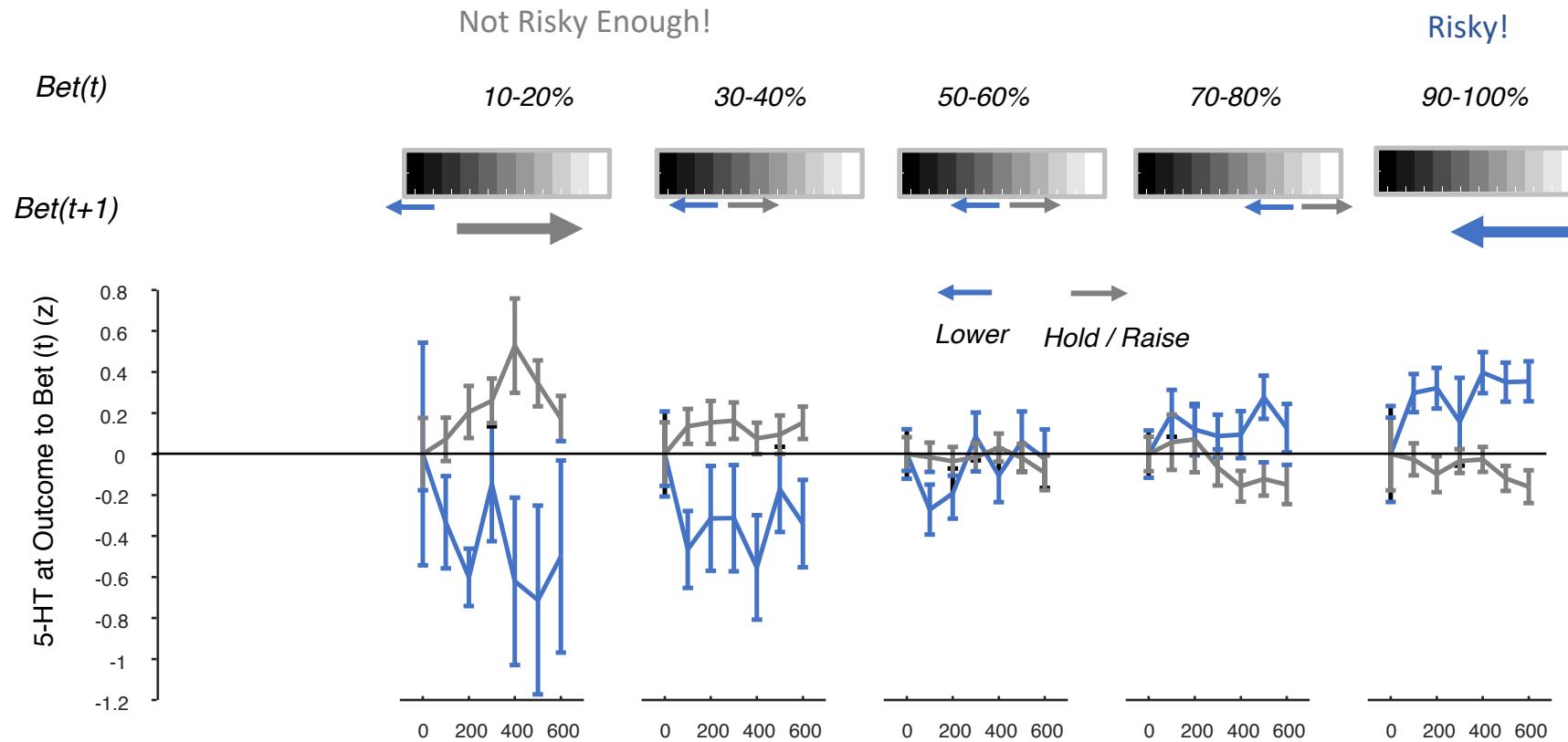
- Previous Investment, ‘How much did I just risk’: ... I’m changing my bet



And Shaping Action Selection

Reacting to negative reward prediction errors & behavioral inhibition

- Previous Investment, 'How much did I just risk': ... I'm changing my bet



Signalling from Midbrain to Striatum

Dopamine

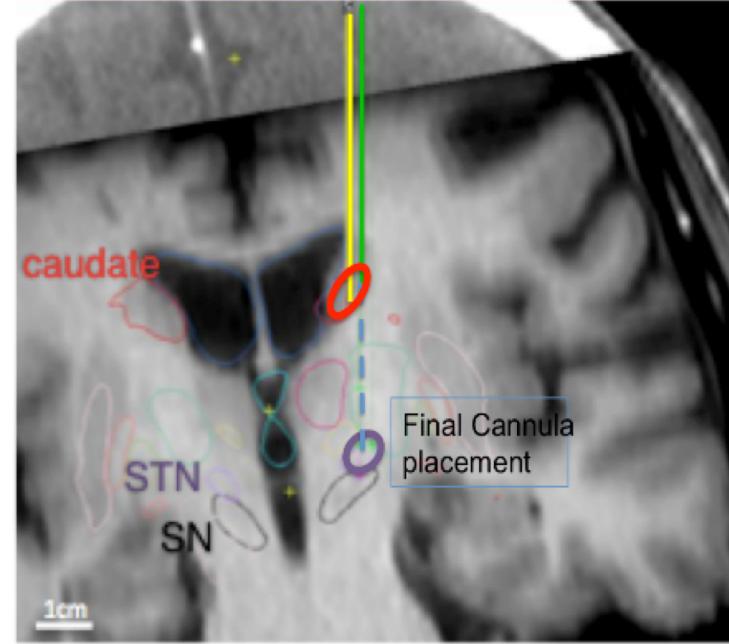
Peaks for Positive
Reward
Prediction Errors
& ‘Dips’ for
Negative Reward
Prediction Errors

Serotonin

Negative reward
prediction errors
(actual and
counterfactual)

+

The mother
hen:
*It's okay, you can go
with them... just not
too far*



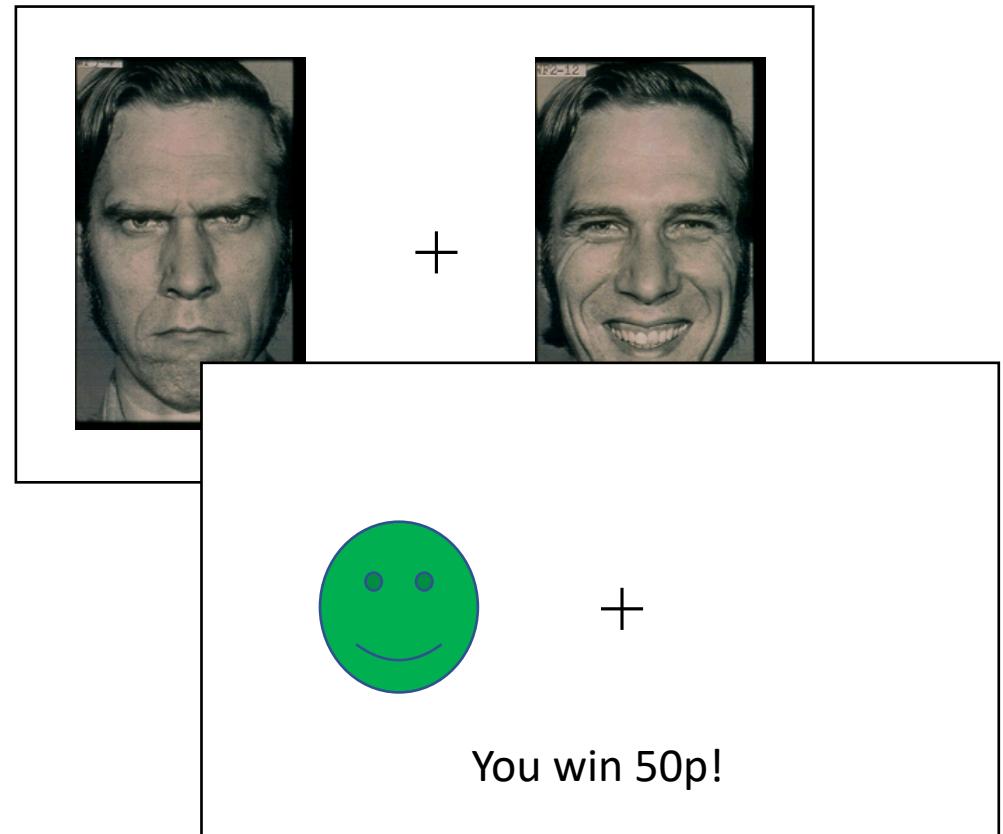
Aberrant Dopamine Signalling in Schizophrenia & Reward Learning

SZ patients show reduced RPE signalling compared to HC (Grandin et al 2011). This has been associated with a ‘drowning’ of phasic DA signals.

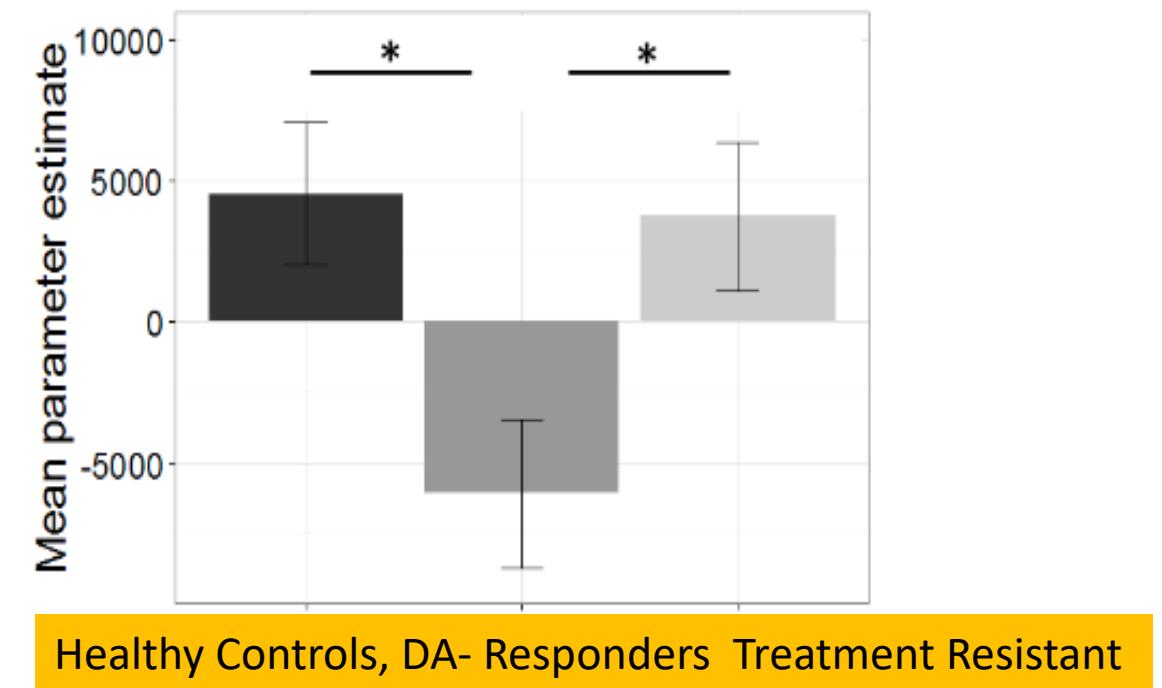
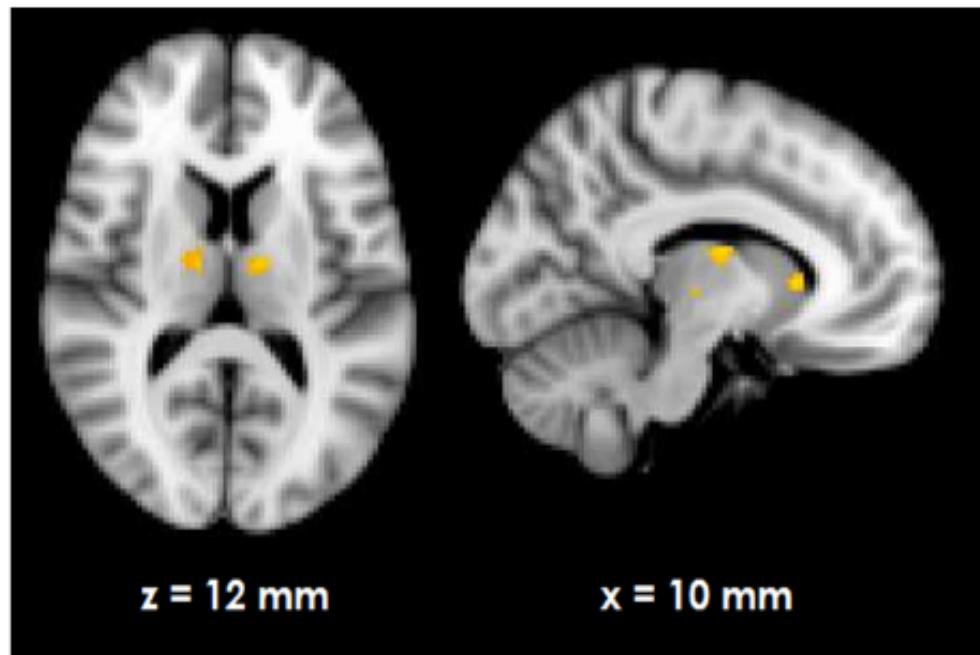
Two-thirds of patients with schizophrenia respond to dopaminergic antagonists, one third remain refractory

“Faces task”

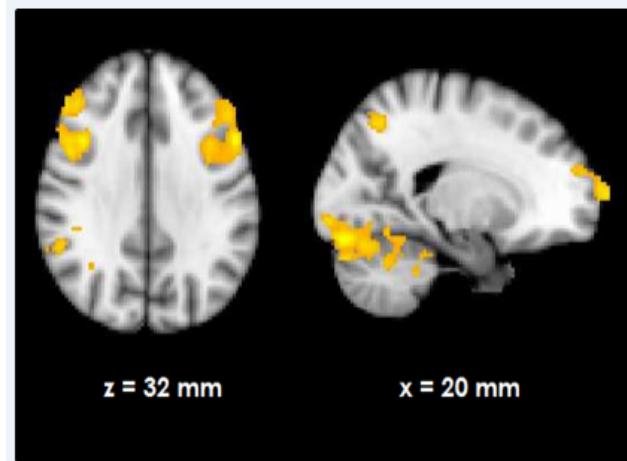
(Vanes et al, 2018; Averbeck & Duchaine, 2009)



Patients Resistant to Dopamine Medications present intact RPEs

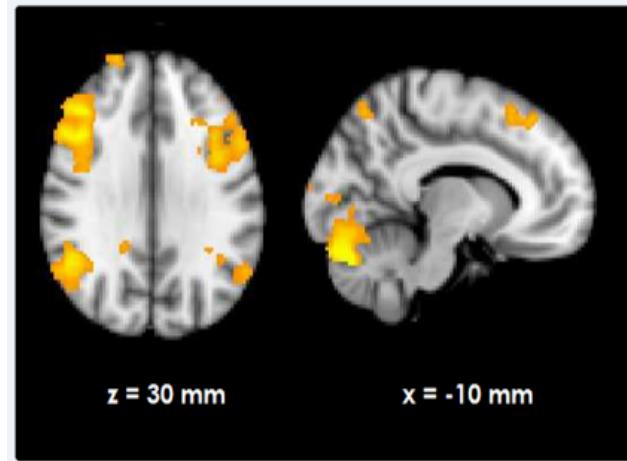


Healthy
Controls

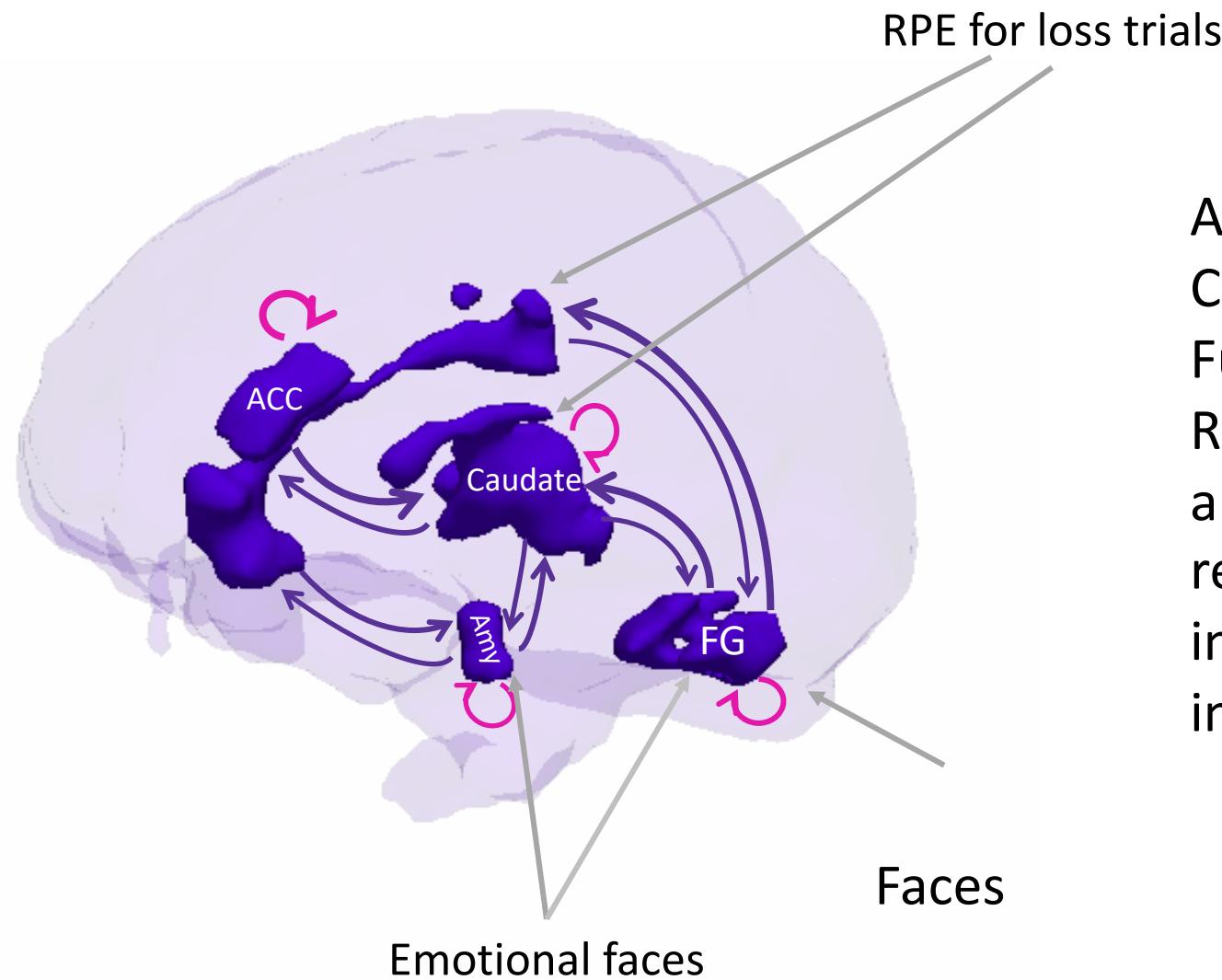


Vanes et al, 2018

Treatment Resistant



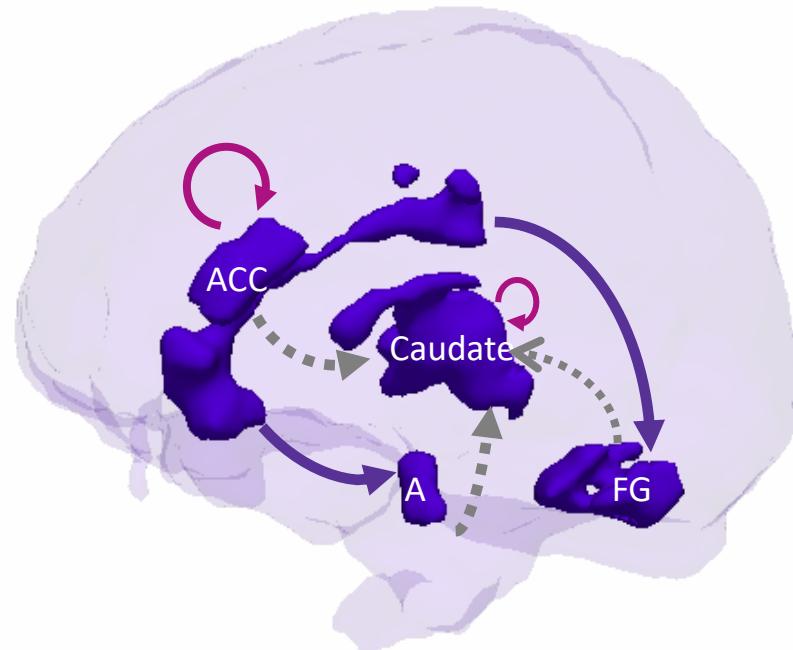
Connectivity Differences in Schizophrenia Subtypes (Horne, Shergill)



A DCM comprising Anterior Cingulate, Caudate, Amygdala & Fusifom Gyrus in Healthy Controls Reveals Bidirectional Interactions amongst sensory & learning regions – along with bilateral interactions with 'control' regions in the cingulate

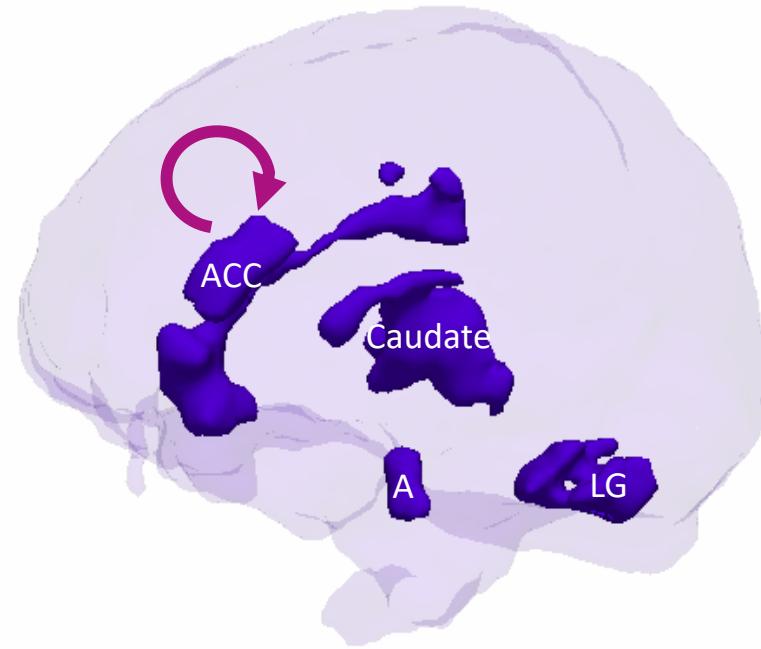
Connectivity Differences in Schizophrenia Subtypes (Horne, Shergill)

Responds to Dopamine Blockade



- Altered Intrinsic Effective Connectivity in ACC
- Altered Intrinsic Effective Connectivity in Caudate
- Increased Top-down 'control'/'predictions' to cortical processing
- Decreased Effective Connectivity from Cingulate & Sensory Regions to Caudate

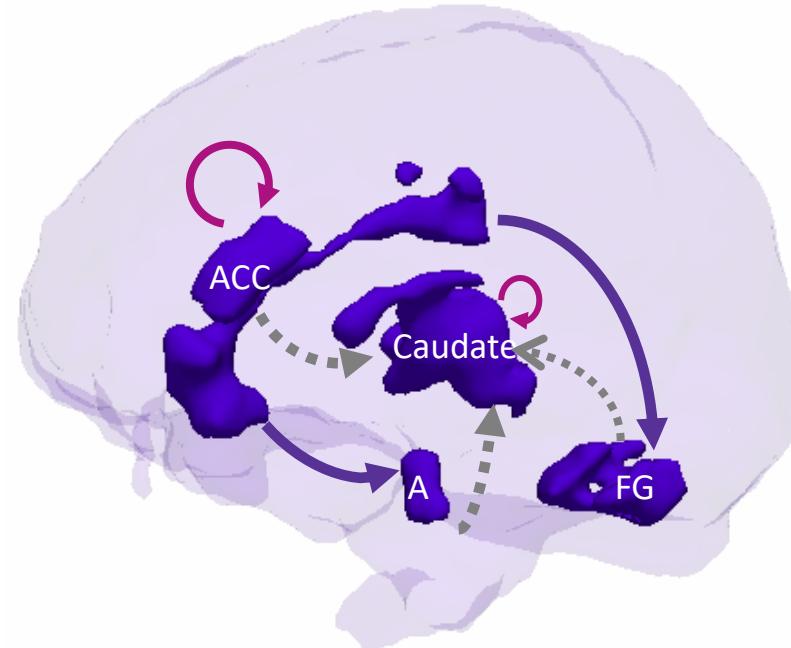
Does Not Respond to Dopamine Blockade



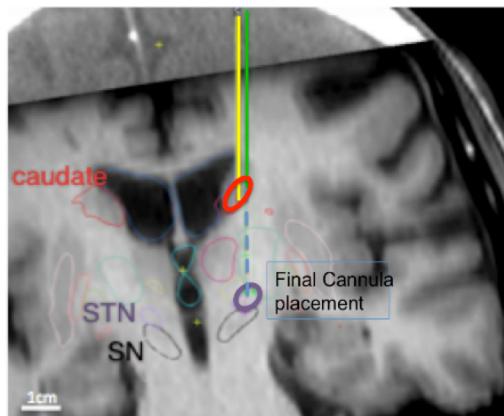
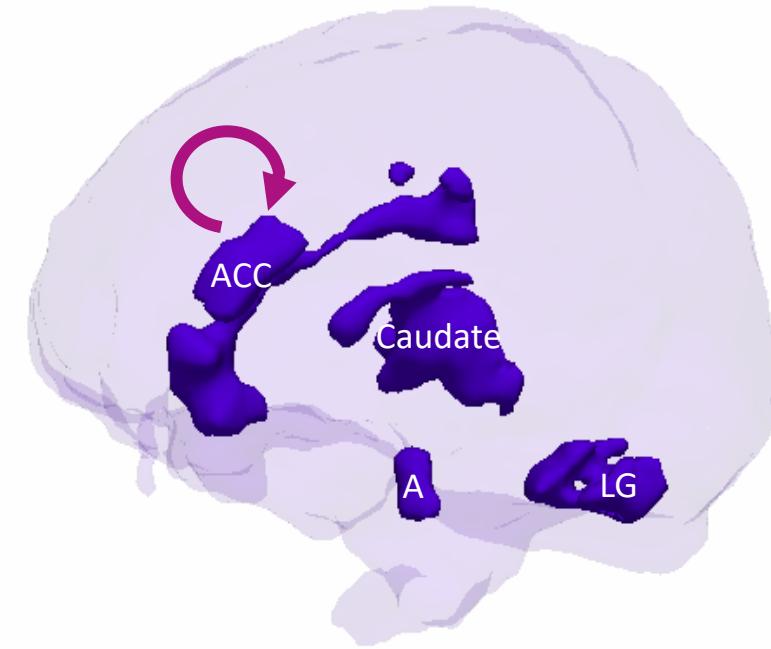
- Altered Intrinsic Effective Connectivity in ACC
- This non-responsive subtype comprises a different pathophysiological mechanisms
- What task/regions would indicate their pathology/treatment response

A Prognostic? Why use a DCM?

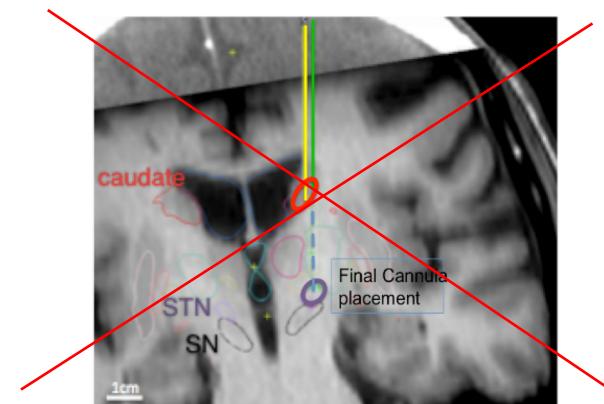
Responds to Dopamine Blockade



Does Not Respond to Dopamine Blockade



But! Confounded by
drug state: Need to
test these findings on
drug naïve patients

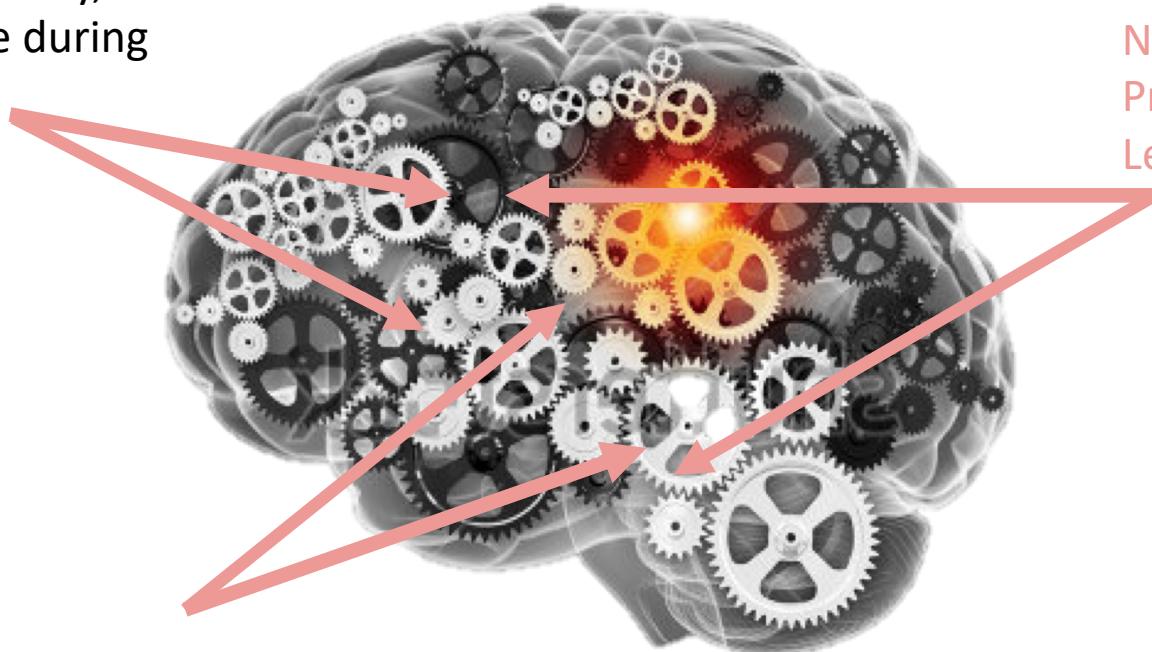


Outline

Models of the world & your interaction with them

Insula – Cingulate Connectivity,
Anxiety & the Microbiome during
fear conditioning

Noradrenergic Responses, Cortical Projections & Flexible Model Learning



VTA & Striatal Dopamine & Serotonin
In PD & Cortical Connectivity in Schizophrenia subtypes

Discrete Domain Active Inference: Free Energies into the Future

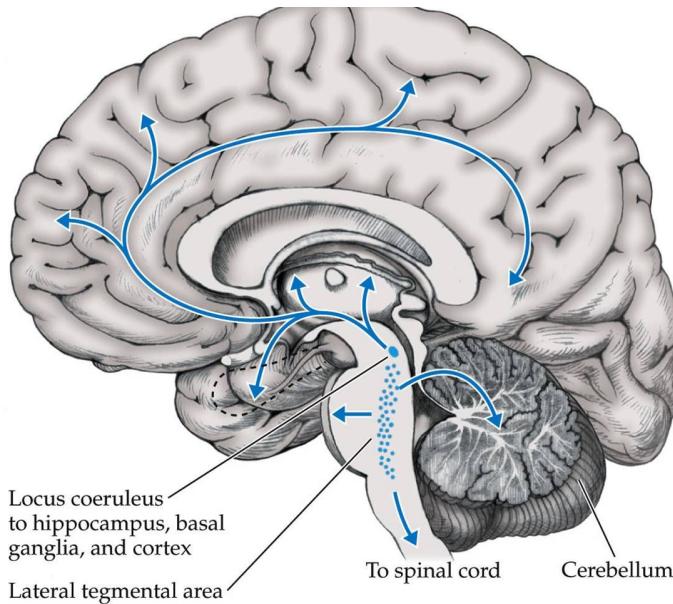
Noradrenaline:

Network Reset (Bouret & Sara)

Explore Exploit

Tonic Phasic (Aston-Jones & Cohen)

Unexpected Uncertainty (Yu & Dayan)



Biological Psychology 6e, Figure 4.4

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Friston et al, 2014; Fitzgerald et al, 2014; Schwartenbeck et al, 2015

A POMDP for Decision Making...

The hidden state of the Cabinet

Priors on outcomes: C



Soft Brexit

o1

Remain

o2



Hard Brexit

o3

Hidden States to
Outcomes : A

s1

Pragmatic

s2

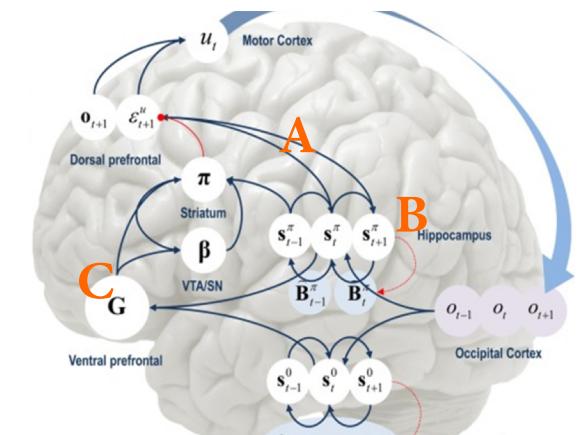
Pro Europe

s3

Eurosceptic

Hidden
States to
Hidden
States: B

Theresa's Choice ... Policy 1: π = Assemble Cabinet & Business Leaders



Choose Policy 1

Priors on outcomes: C



Soft Brexit



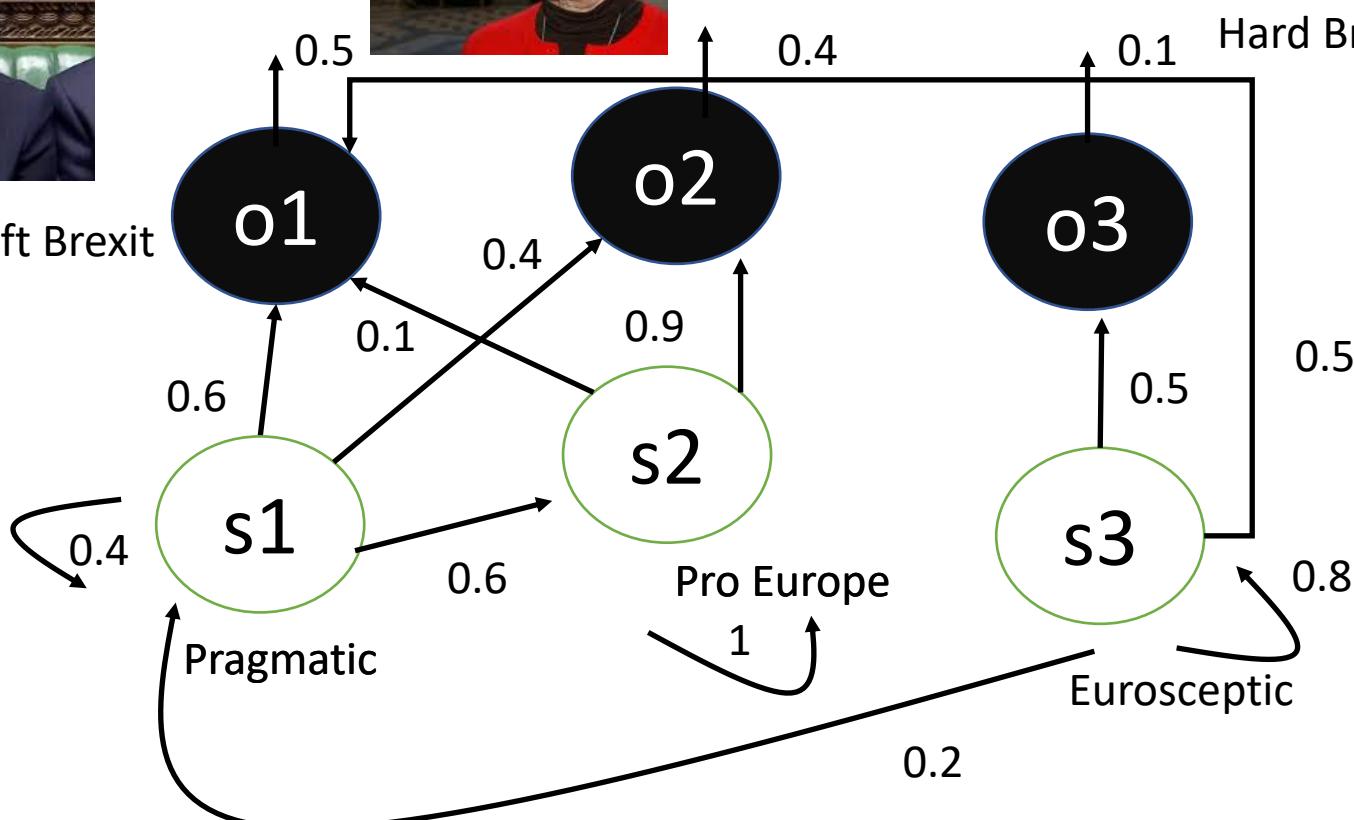
Remain



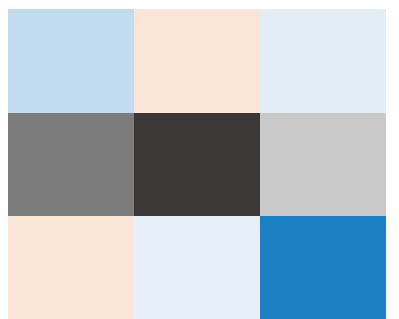
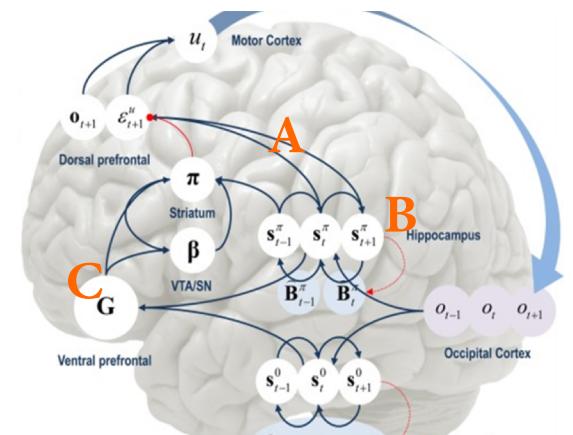
Hard Brexit

Hidden States to Outcomes : A

Hidden States to Hidden States: B



Theresa's Choice ... Policy 1: π = Assemble Cabinet & Business Leaders



Choose Policy 2

Priors on outcomes: C



Soft Brexit

o1



Remain



Hard Brexit

Hidden States to
Outcomes : A

s1

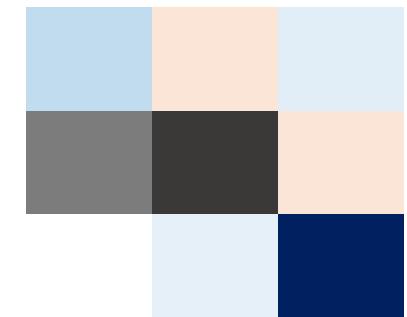
Pragmatic

s2

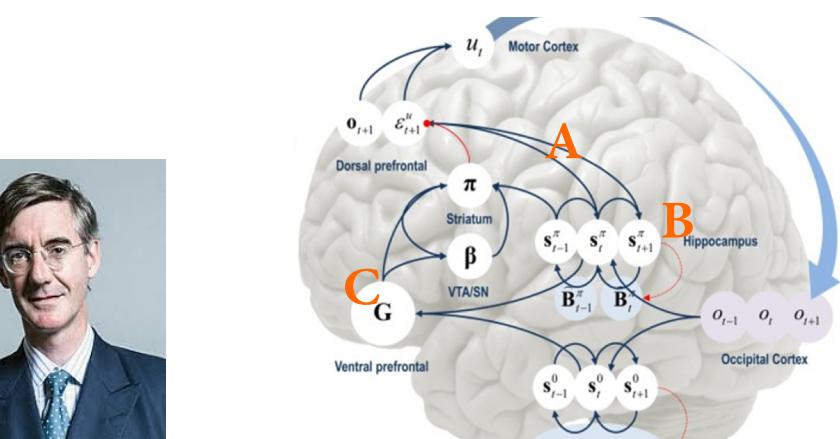
Hidden
States to
Hidden
States: B

s3

Eurosceptic



Theresa's Choice ... Policy 2: π = Assemble Members of the Opposition



Choose Policy 2

Priors on outcomes: C



Soft Brexit



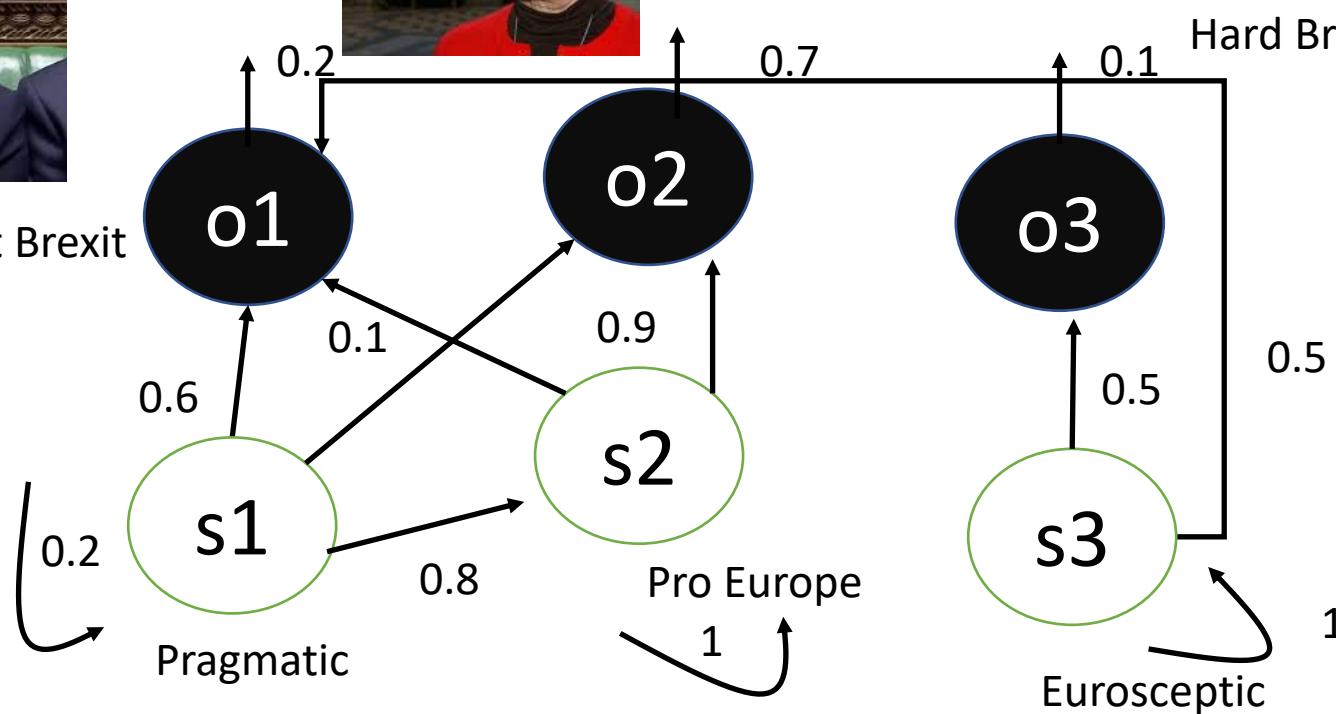
Remain



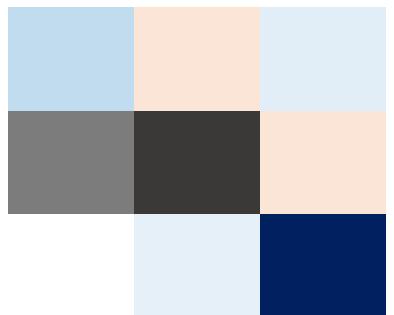
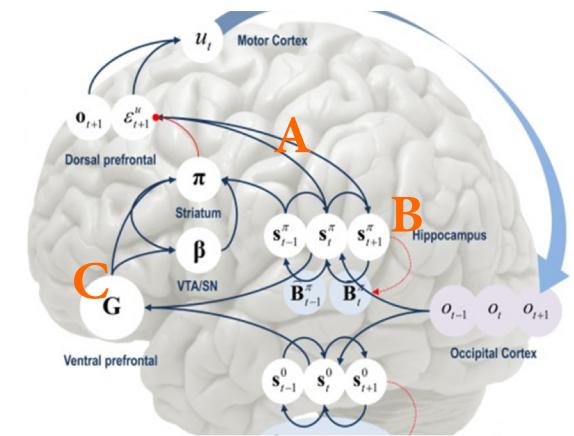
Hard Brexit

Hidden States to Outcomes : A

Hidden States to Hidden States: B



Theresa's Choice ... Policy 2: π = Assemble Members of the Opposition



Learning from Choices

Priors on outcomes: C



Soft Brexit



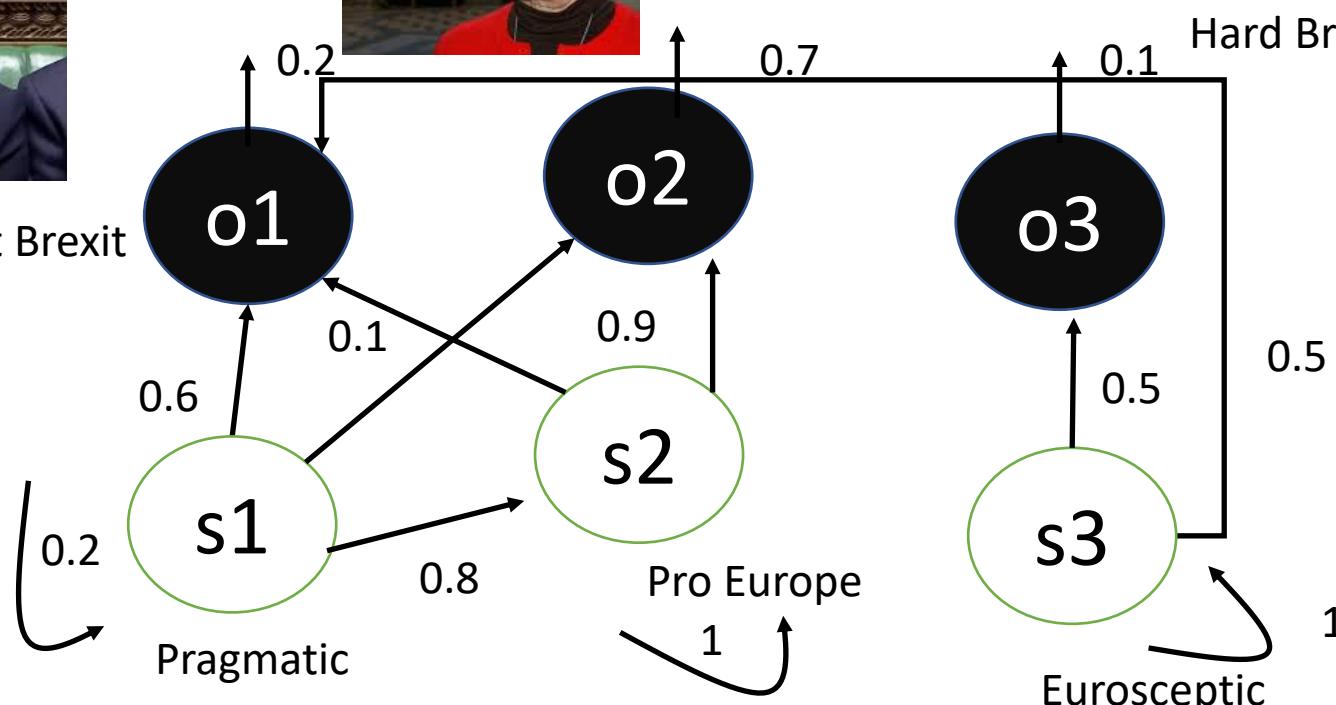
Remain



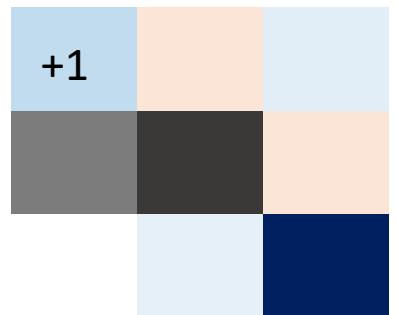
Hard Brexit

Hidden States to Outcomes : A

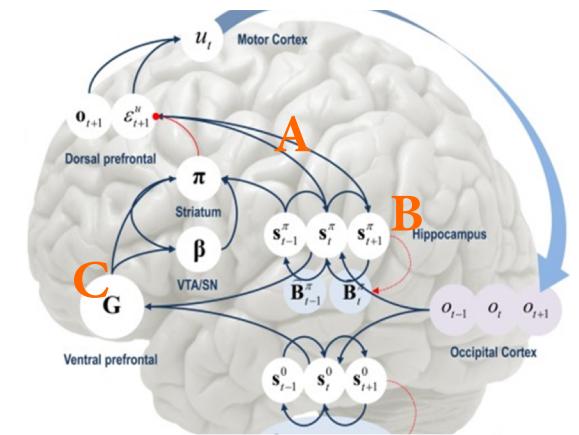
Hidden States to Hidden States: B



Add one & Renormalize



Theresa's Choice ... Policy 2: π = Assemble Members of the Opposition



Learning from Choices

Priors on outcomes: C



Soft Brexit



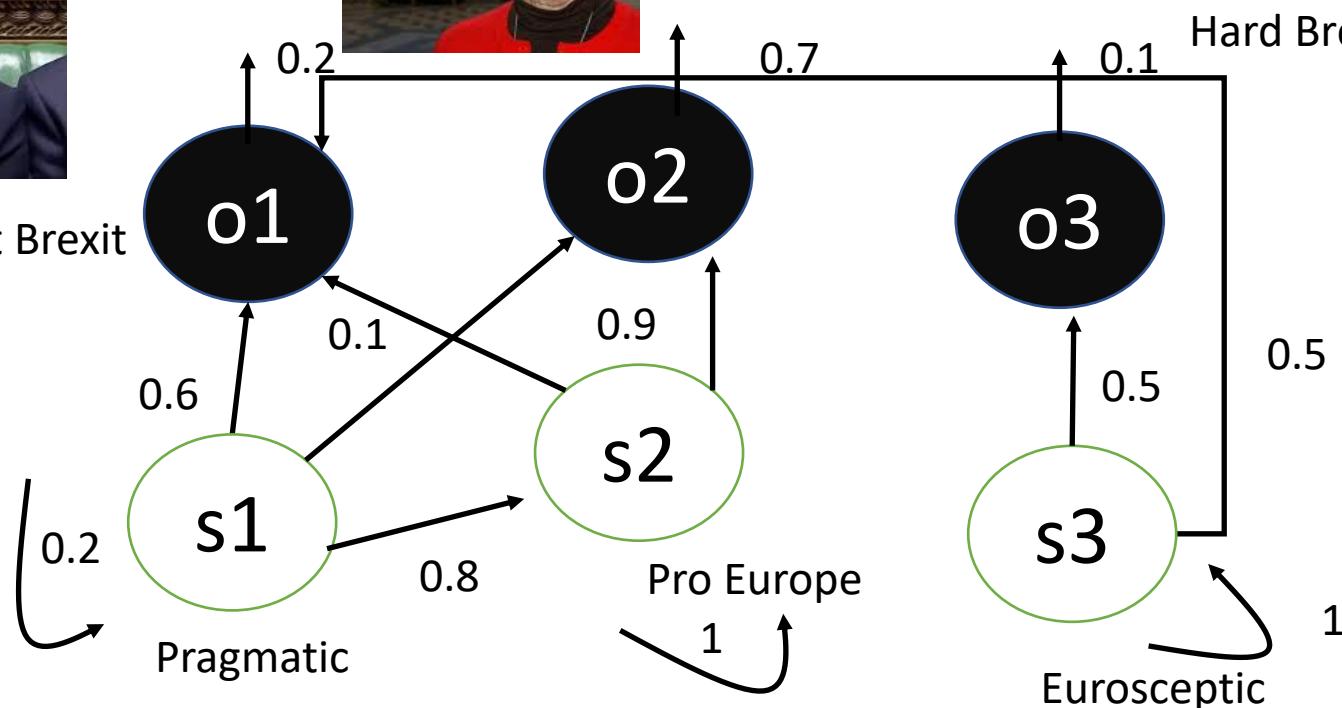
Remain



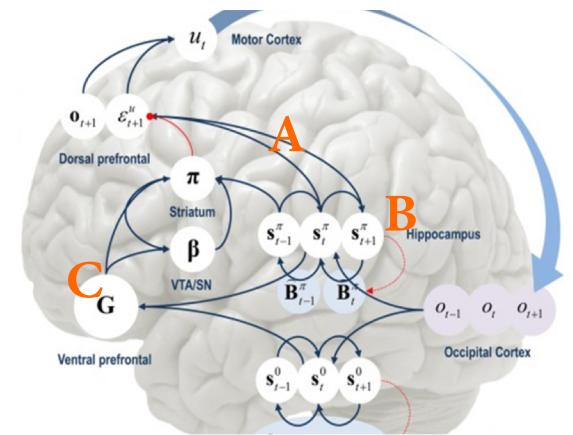
Hard Brexit

Hidden States to Outcomes : A

Hidden States to Hidden States: B



Theresa's Choice ... Policy 2: π = Assemble Members of the Opposition



Add one & Renormalize



Unexpected changes in hidden states (s) following action selection

Priors on outcomes: C



Soft Brexit



Remain

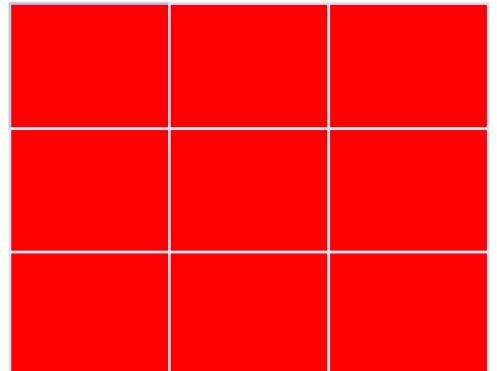
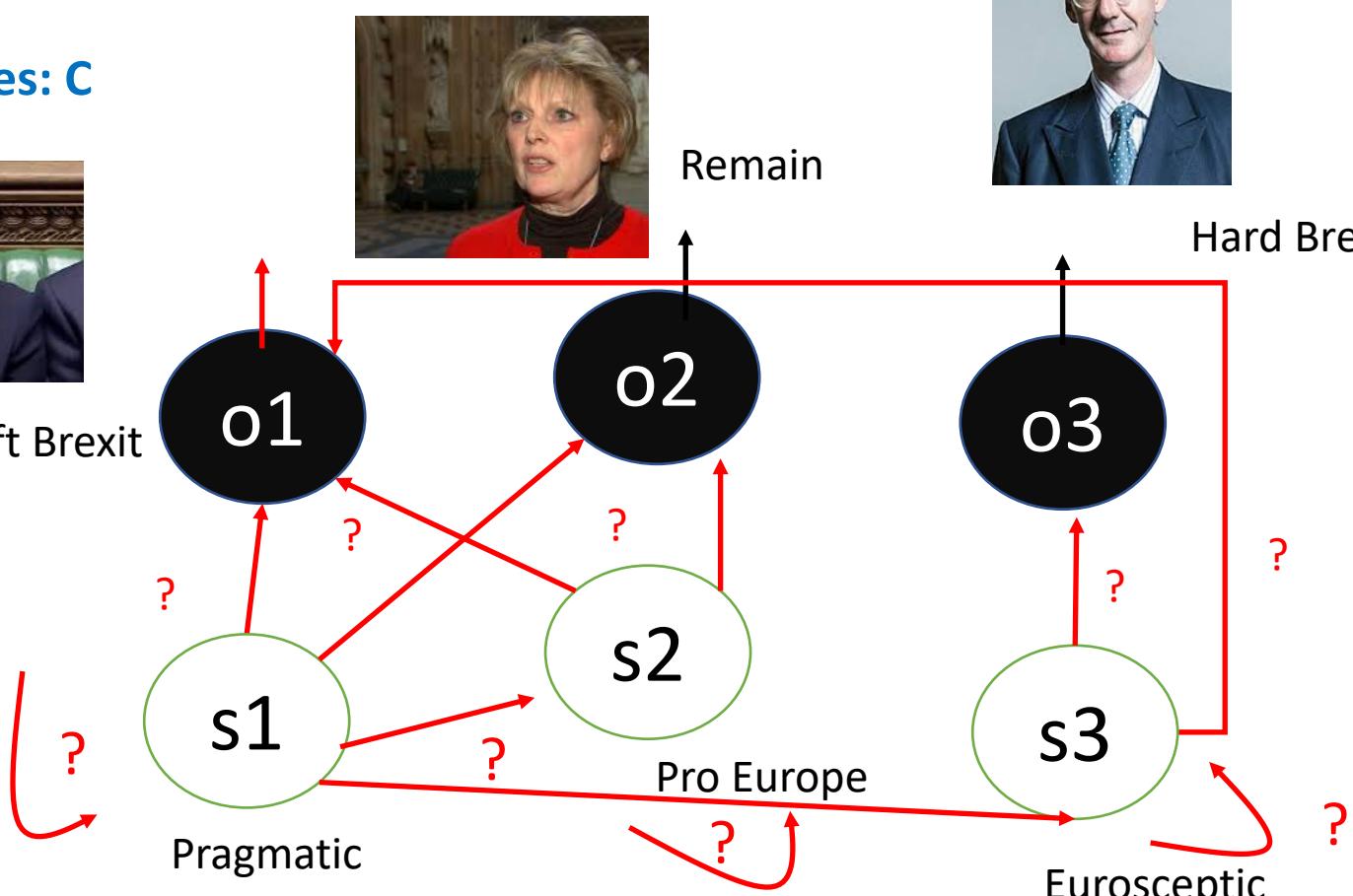


Hard Brexit



Hidden States to Outcomes : A

Hidden States to Hidden States: B



A Scaffold for Variational Inference



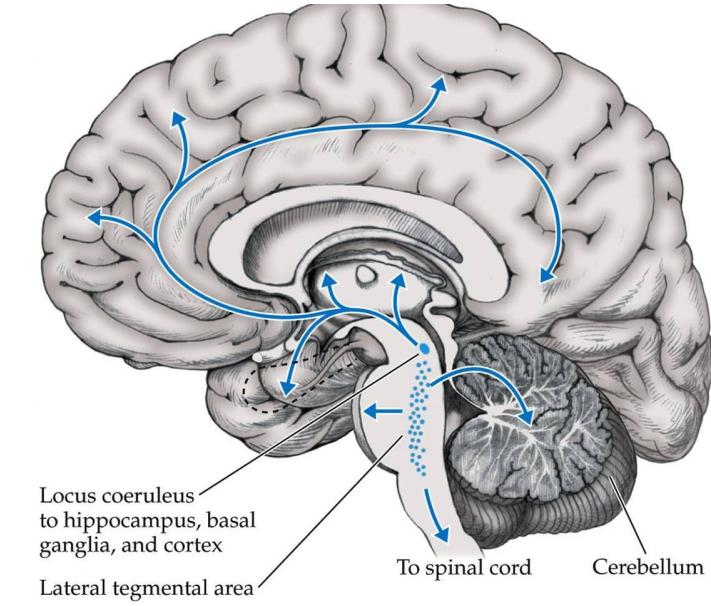
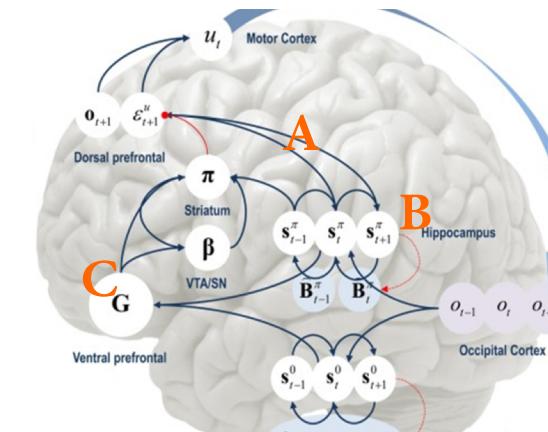
RESEARCH ARTICLE

Locus Coeruleus tracking of prediction errors optimises cognitive flexibility: An Active Inference model

Anna C. Sales^{1*}, Karl J. Friston², Matthew W. Jones¹, Anthony E. Pickering^{1,3}, Rosalyn J. Moran^{1,4}

Using information from the real world, the agent minimises free energy in two ways: by adjusting the parameters of the generative model itself, and by picking actions that it believes will be associated with the lowest free energy. This allows the agent to both optimise the model and change its action plans.

Sales, Friston, Jones, Pickering, Moran, PloSCB 2019



Biological Psychology 6e, Figure 4.4

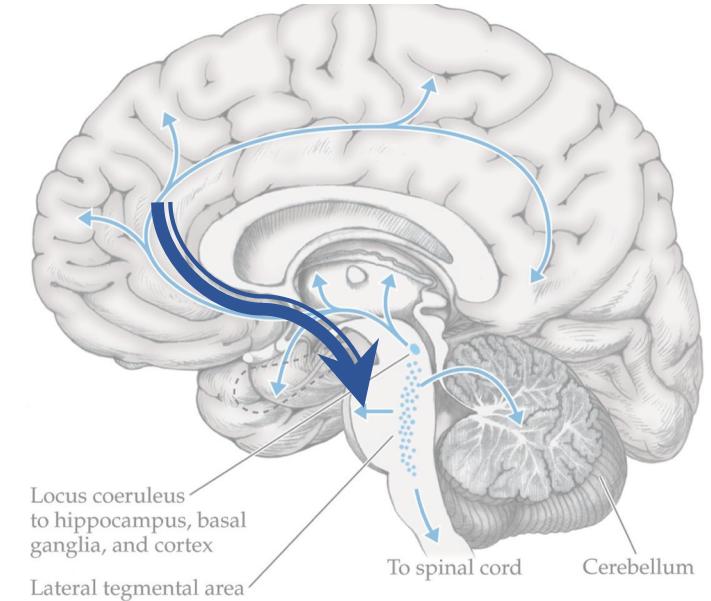
© 2010 Sinauer Associates, Inc.

State Action Prediction Errors: Drivers of LC

$$SAPE(t) = \sum_{\tau} D[S(t)||S(t - 1)]$$

To LC: Kullback-Leibler divergence between Bayesian Model Average (BMA) distributions at successive time steps. Mathematically, this reflects the degree of belief updating induced by each new observation.

Sales, Friston, Jones, Pickering, Moran, PloSCB 2019



Biological Psychology 6e, Figure 4.4

Breaking Models: Effects of LC



$$b = b + ST$$

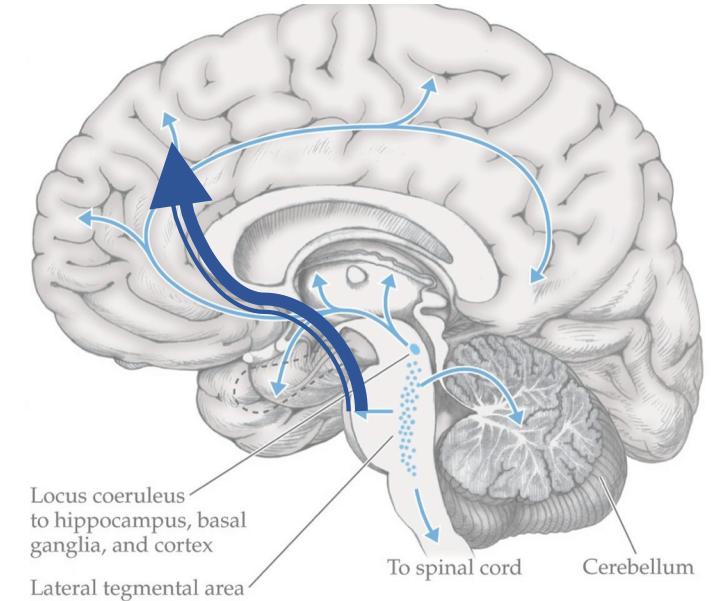
Update of Dirichlet parameters

$$b = b + ST - \frac{(b - 1)}{\alpha}$$

Adaptive Update of Dirichlet parameters

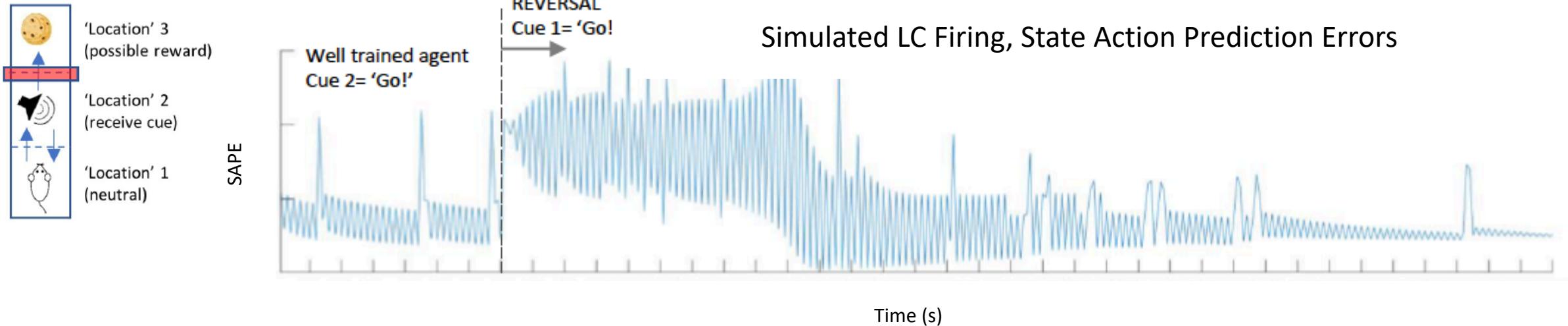
$$\alpha = \alpha_{min} + \frac{\alpha_{max}}{e^{k(SAPE-m)}}$$

From LC: A brief but large state-action prediction error ‘boosts’ the impact of a recent experience upon the agent’s model of the world. This occurs by temporarily **increasing the attrition of existing, experience dependent parameters** encoding environmental contingencies.

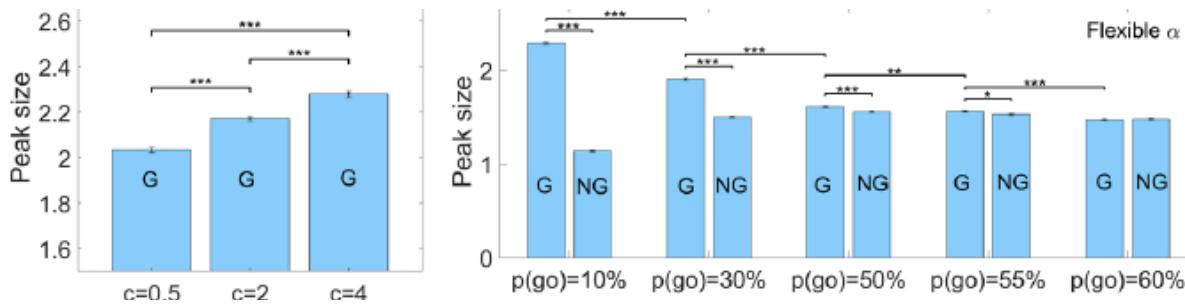


Biological Psychology 6e, Figure 4.4

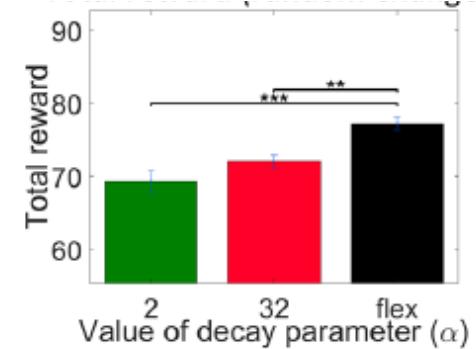
Firing of LC from Model Consistent with Rodent Literature



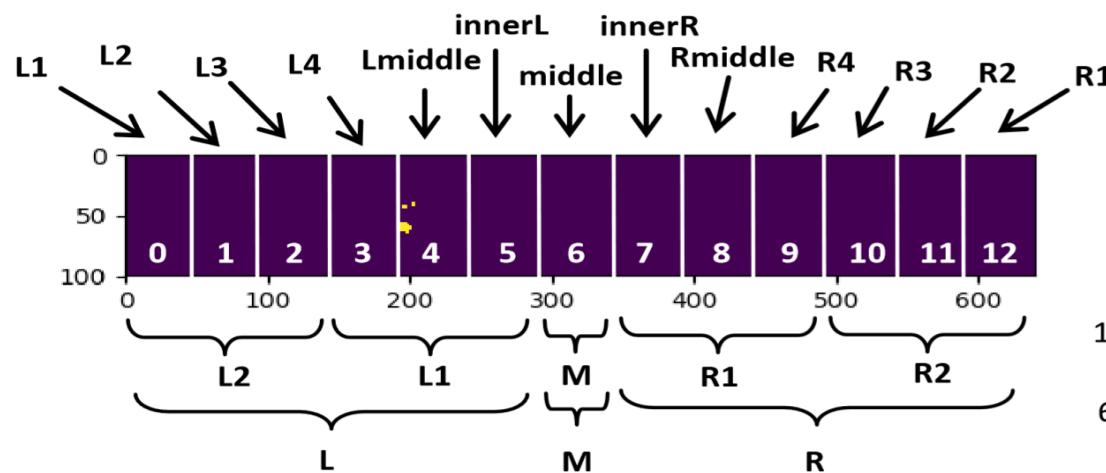
Simulated Peak Response & Relative Peak Responses for Different Contingencies



Simulated Behaviour with 'Optimal' Model Rebuilding

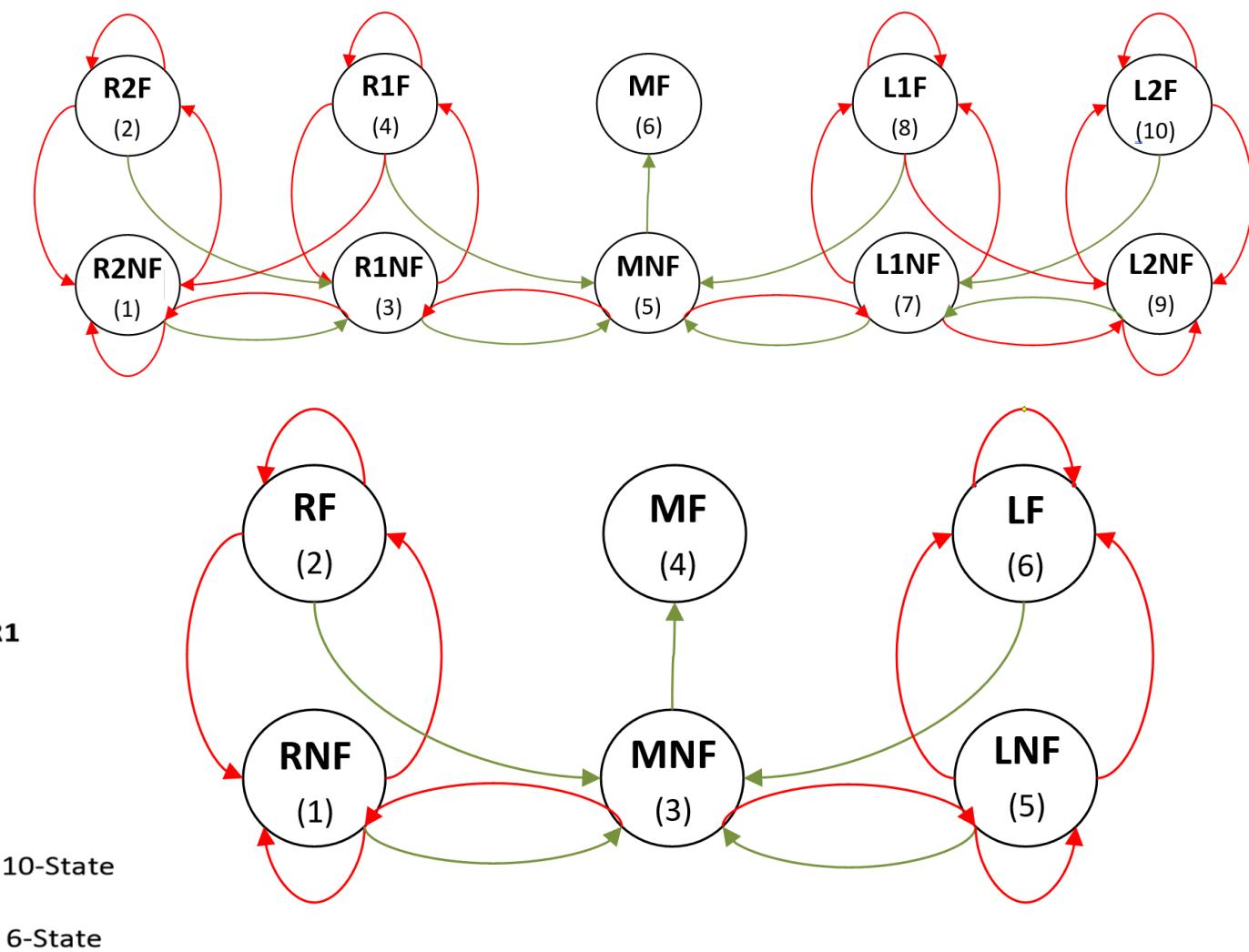


A Game of Doom for Human Play

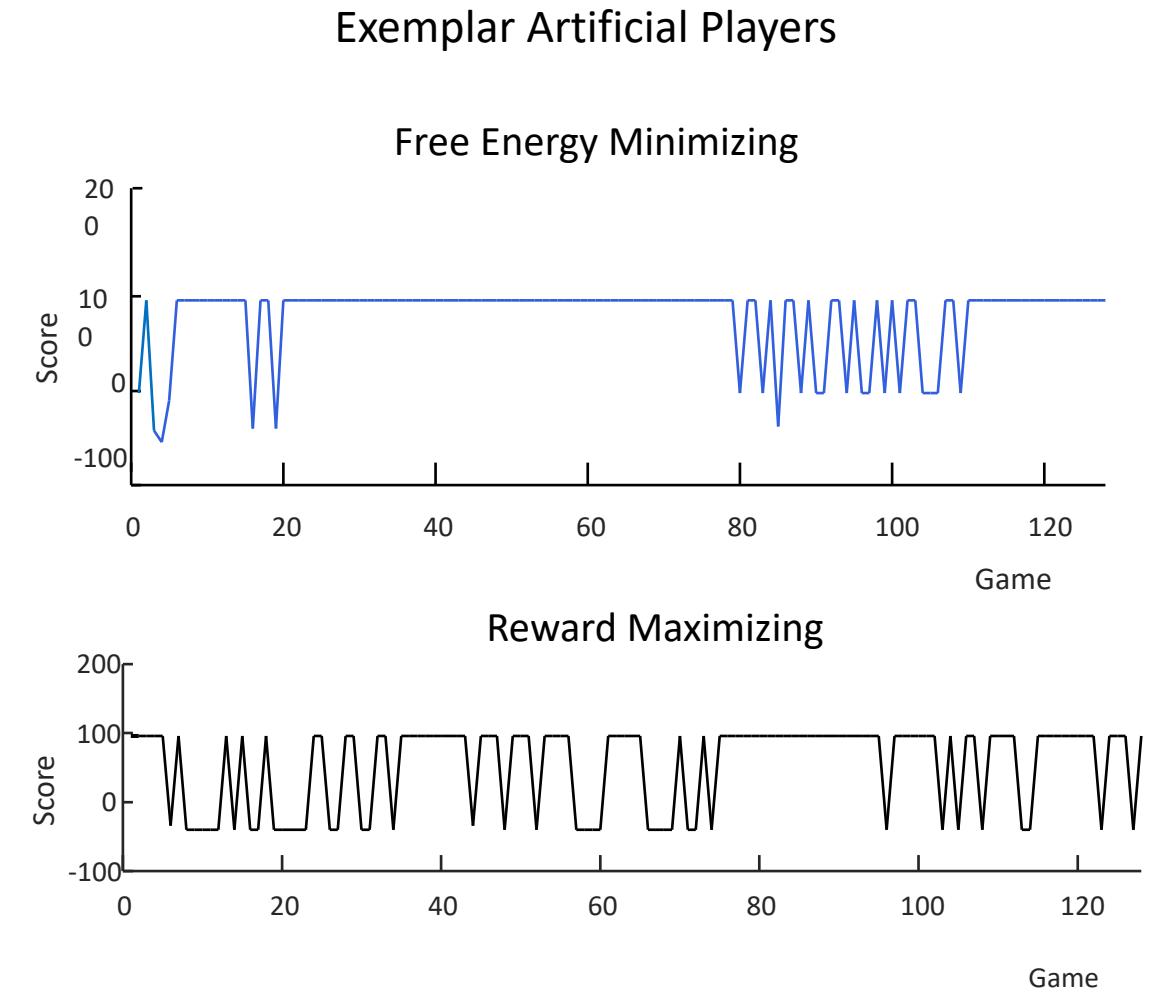
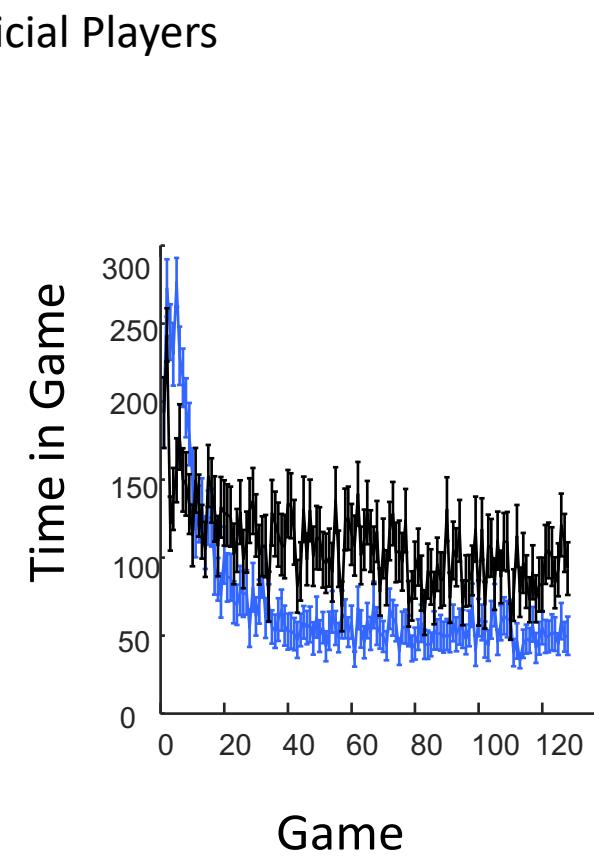
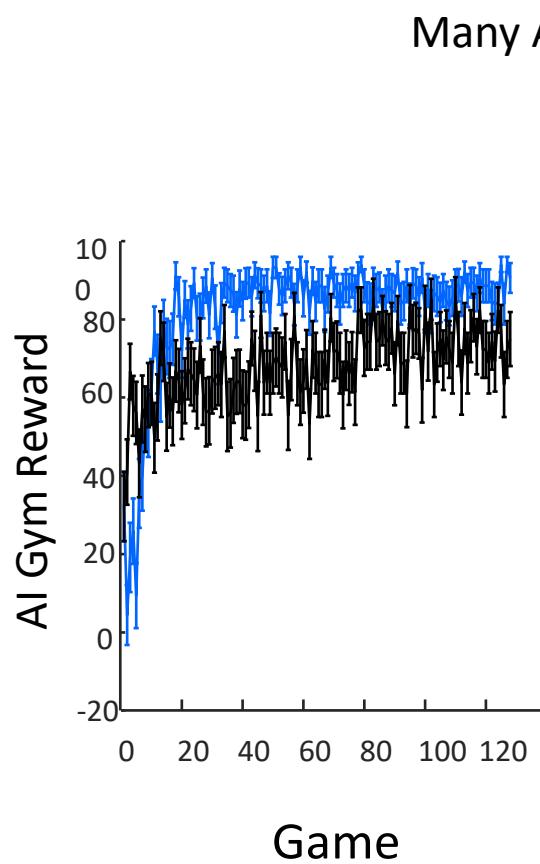


B: Transitions
among
Hidden States

$\pi = \text{fire}$
 $\pi = \text{move left}$
 $\pi = \text{move right}$



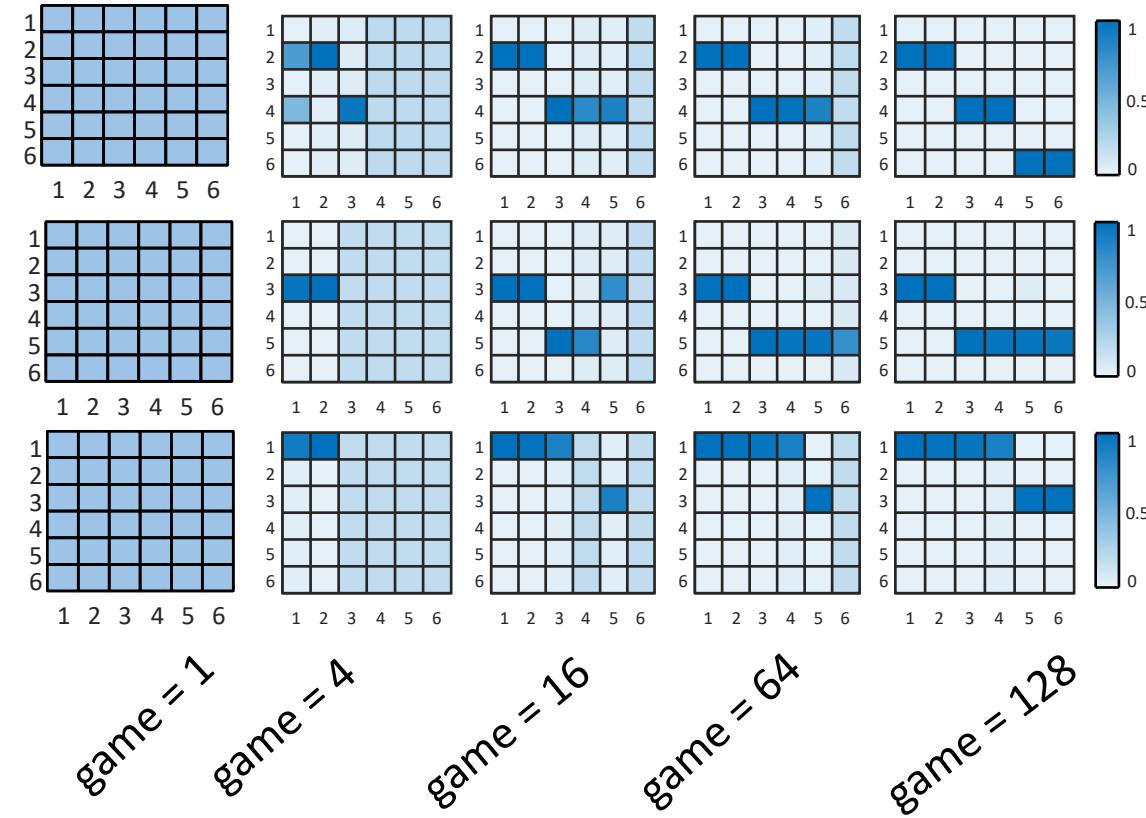
AI vs RL



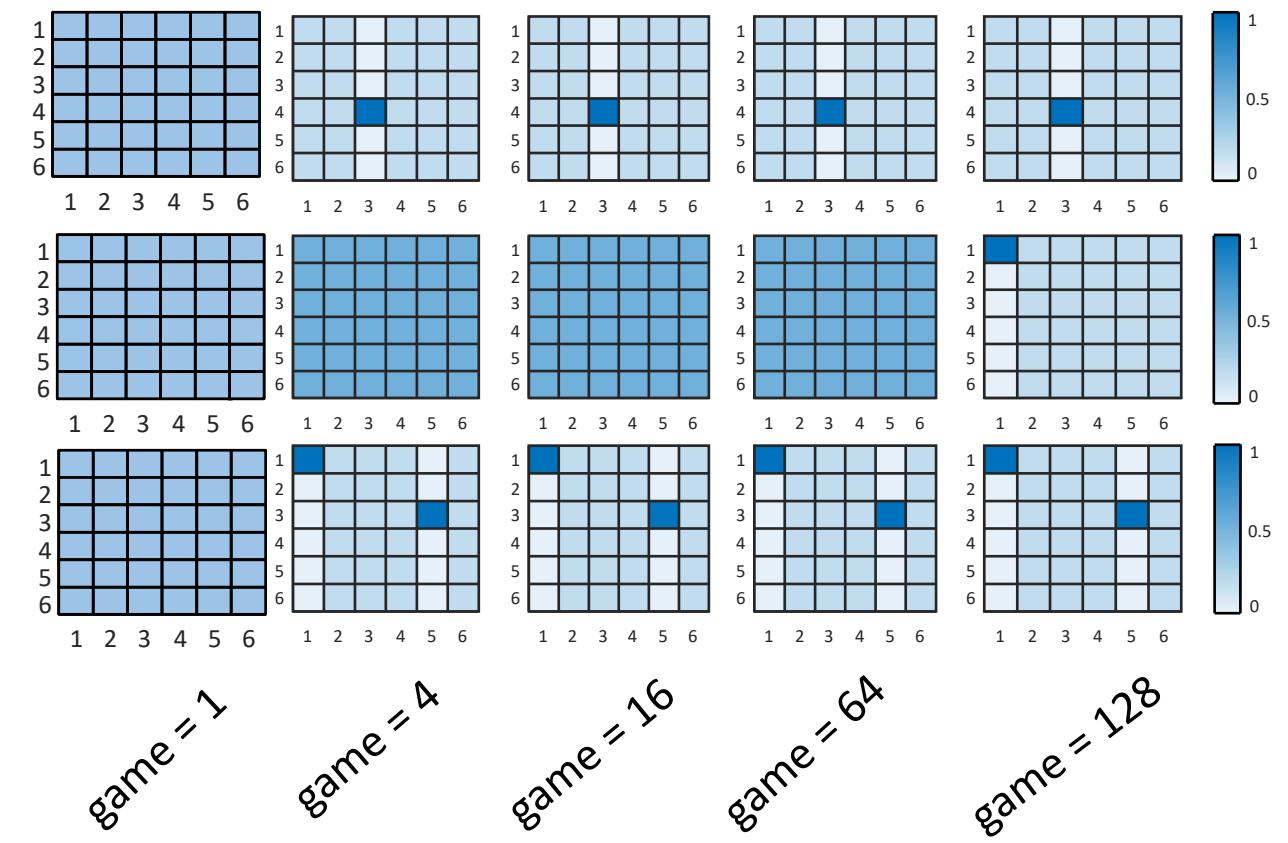
— Free Energy Minimizing
— Reward Maximizing

Reward-based Agent fails to learn the structure of the world

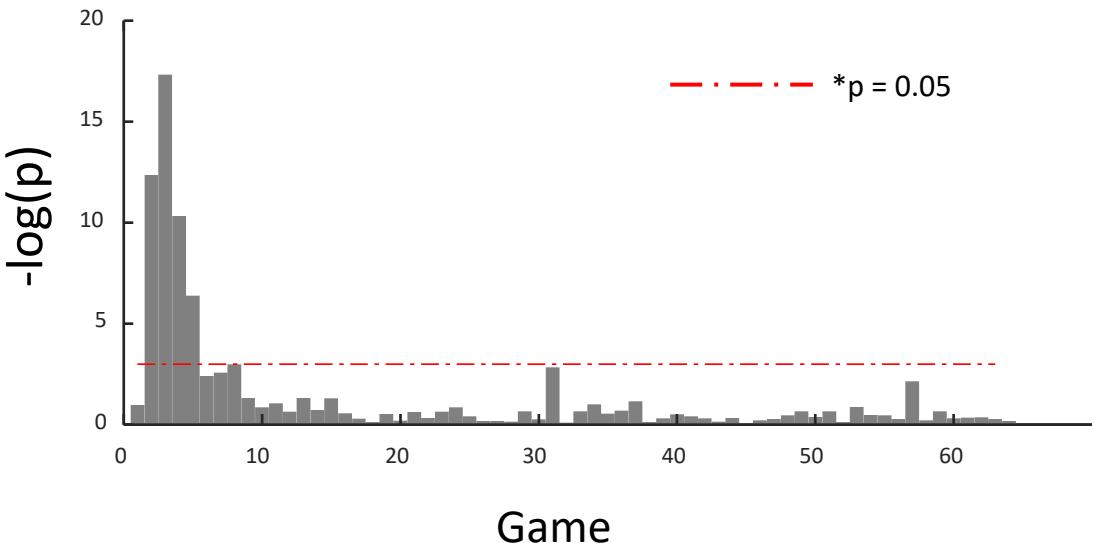
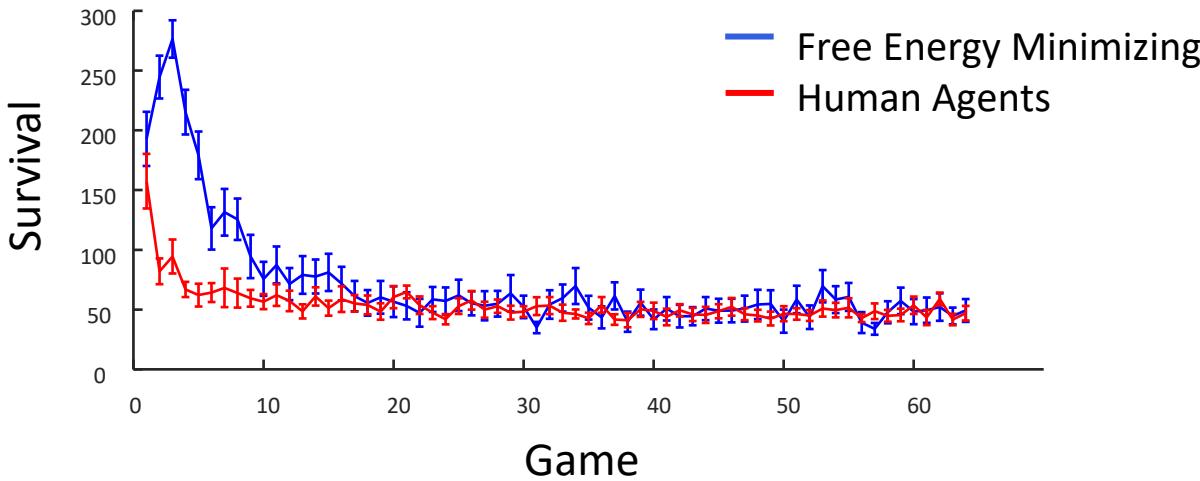
Decisions under Expected Free Energy & Inference



Decisions under Reward & Inference



Can we beat the human?

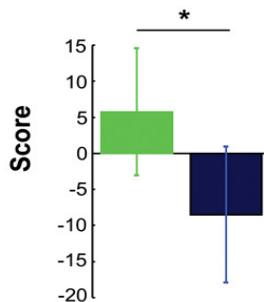
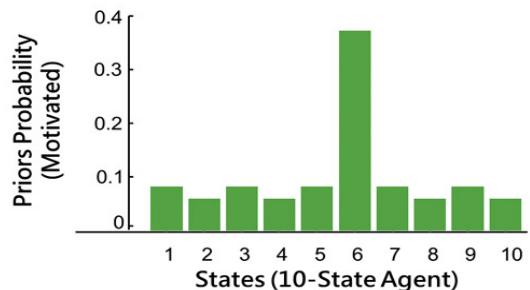


Man vs Machine

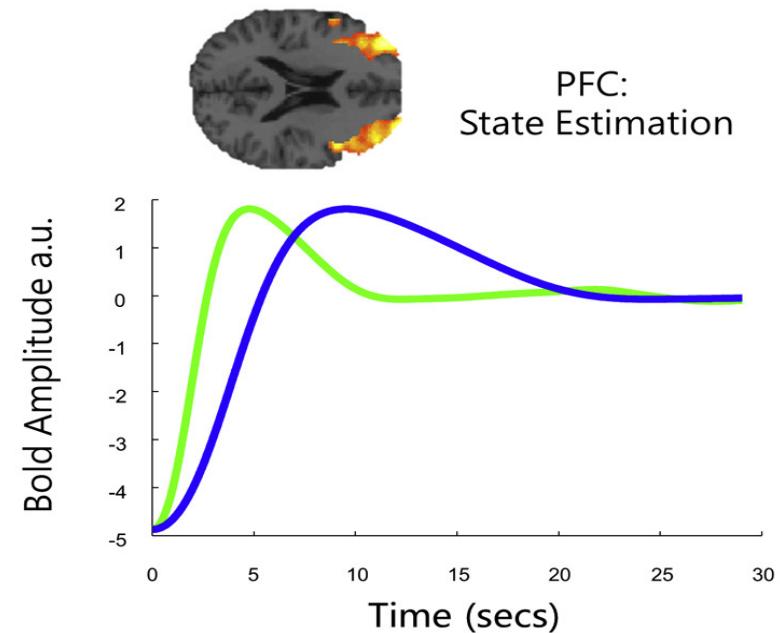
-When starting from a flat model - no.... but it Catches up quickly (by game 8, $p > 0.05$)
- The Human Comparison of a 'flat model' – "The following three buttons on the keyboard you can use to play the game, We will not tell you which button performs which action."
- $N = 18$
- Ages 22-30 ($n=10$) and 55-63 ($n=8$) recruited from Dept of Engineering Mathematics, University of Bristol, staff and students

Motivation/ Anhedonia

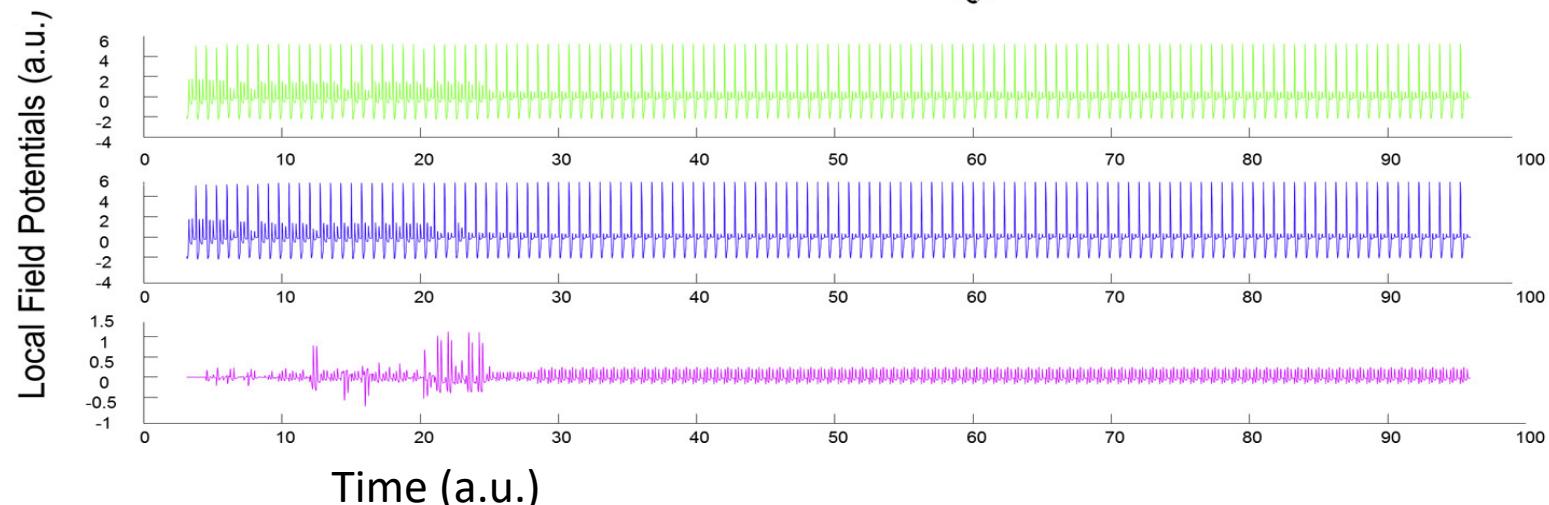
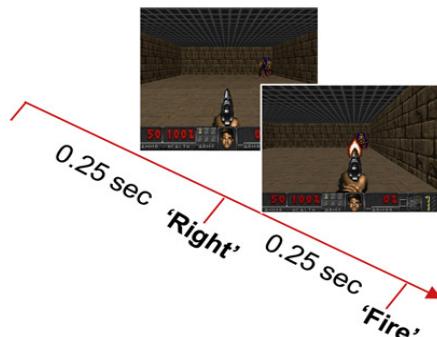
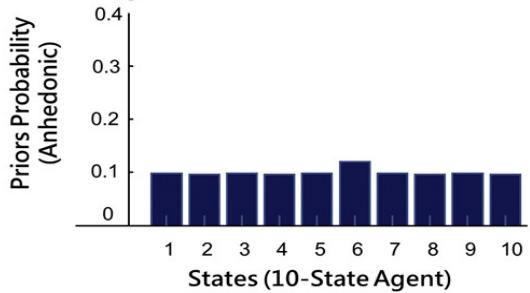
Motivated



PFC:
State Estimation



Anhedonic



Conclusions

Models of the world & your interaction with them

Insula – Cingulate Connectivity,
Anxiety & the Microbiome during
fear conditioning

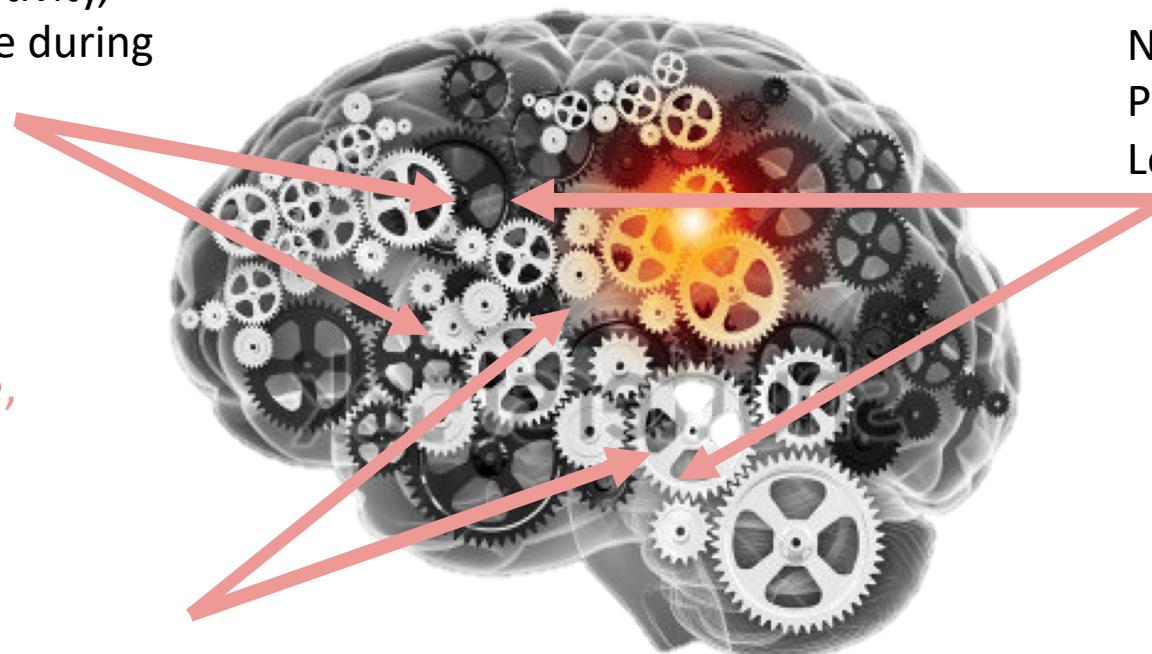
Bad Gut: Less prediction/top-down control of insula response, anxiously appraising all stimuli?

VTA & Striatal Dopamine & Serotonin
In PD & Cortical Connectivity in Schizophrenia subtypes

Noradrenergic Responses, Cortical Projections & Flexible Model Learning

Too much/too little NA:
Heightened model rebuilding or unable to adapt internal model to changed environmental contingencies

In Schizophrenia: Noisy Models of Reward Selection (and probably more generally for action selection), But refractory patients do not show this effect



Thank you

Mael Cullen

Ashley Tyrer

Anna Sales

Jamie Thackrer

Nicole Himmelstoß (University of Salzburg)

Elena Paci

Valeria Olivia

Berk Merza

Caitlin Hall (QIMR, Brisbane)

Karl Friston, *UCL*

Read Montague, *VT, UCL*

Klaas Enno Stephan, *ETH and University of Zurich*

Mkael Symmonds, *Oxford University*

Chris Wyatt, *VT*

Simon Rushton, *University of Cardiff*

David Marshall, *University of Cardiff*

Sukhi Shergill, *IOPPN, KCL*

Charlotte Horne, *IOPPN, KCL*

Luca Cocchi *QIMR, Brisbane*



Engineering and Physical Sciences
Research Council

