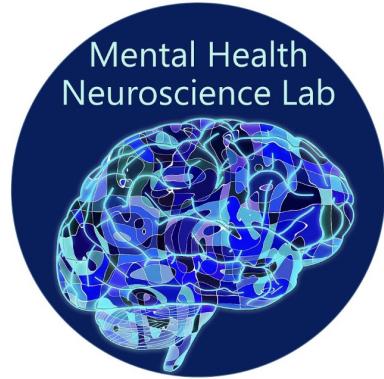




MRC Cognition
and Brain
Sciences Unit



UNIVERSITY OF
CAMBRIDGE



Identifying & exploring novel treatment targets in computational psychiatry *from psychotherapy to brain-body interactions*

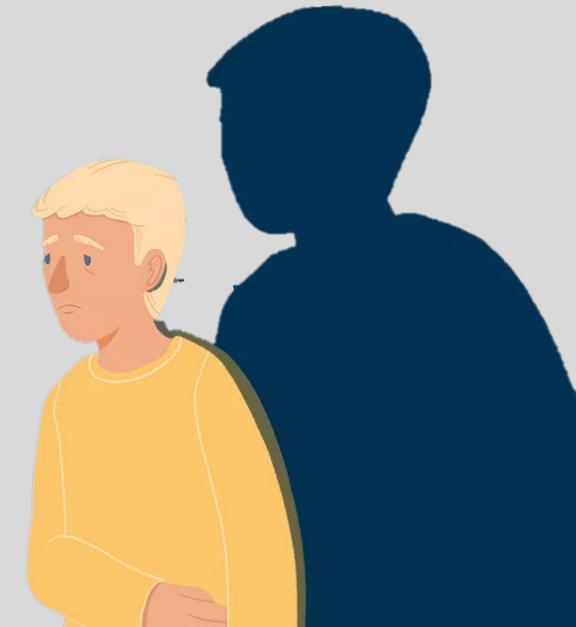
Camilla Nord

MRC Programme Leader, MRC Cognition and Brain Sciences Unit, University of Cambridge

Assistant Professor of Cognitive Neuroscience, Department of Psychiatry

@camillalnord

The fundamental challenge of mental health treatment today



Two crucial questions to solve this challenge

1. What do effective mental health treatments actually *do*?

- *Pressing need to understand treatment mechanisms – across treatment modalities*

2. What are the *missing variables* in our understanding and treatment of mental health disorders?

- *Signals from the body (gut, circadian rhythm, metabolic health...)*
- *Interoception– the brain's sense and interpretation of bodily state*

Two crucial questions to solve this challenge

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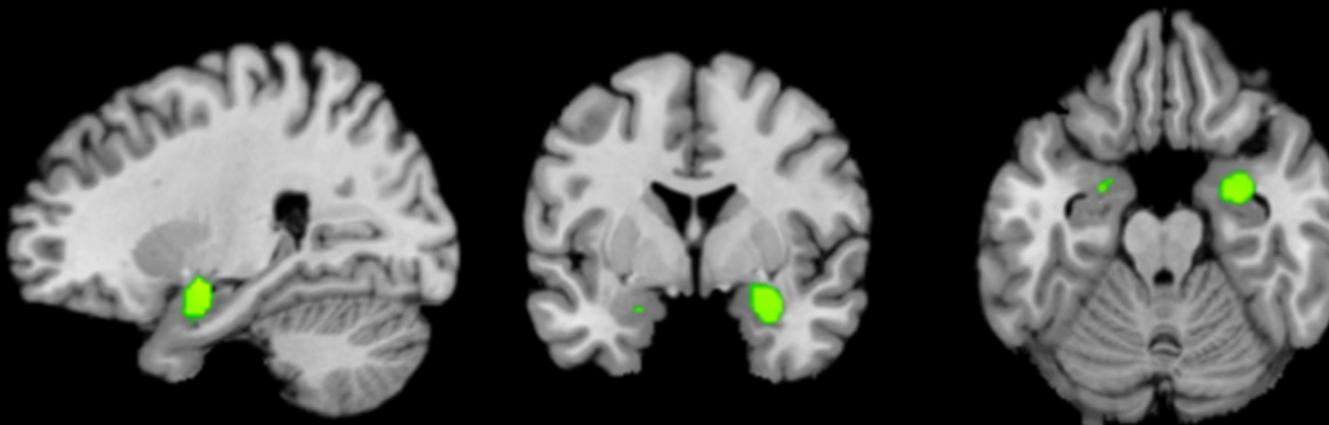
- *Signals from the body (gut, circadian rhythm, metabolic health...)*
- *Interoception– the brain's sense and interpretation of bodily state*



What do effective mental health treatments actually *do*?



N=343

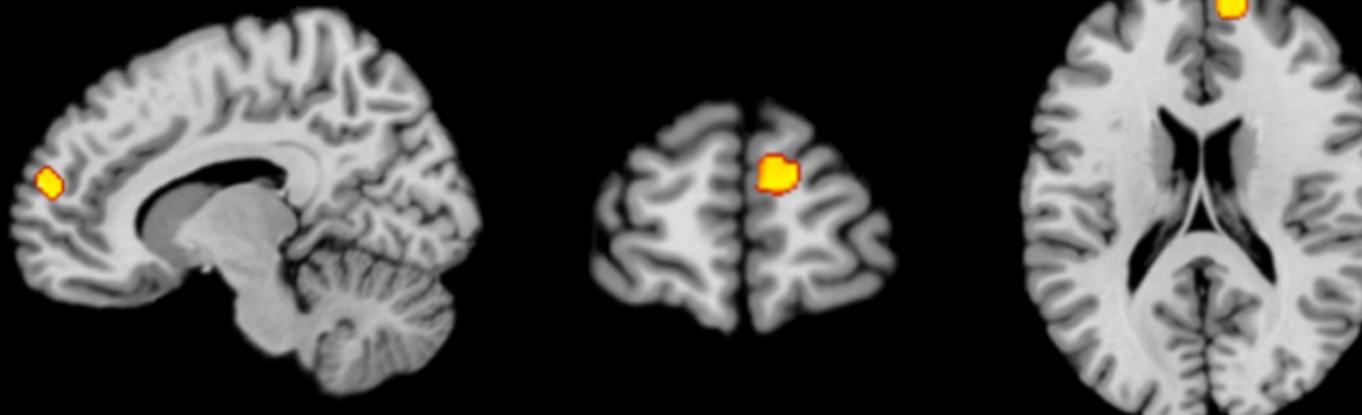


■ *Amygdala changes after pharmacotherapy (SSRI + SNRI)*

■ *mPFC changes after psychotherapy*

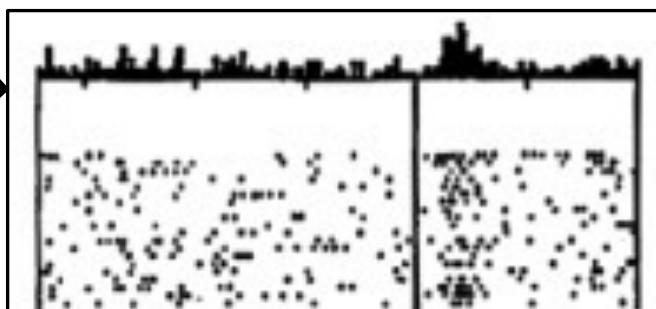
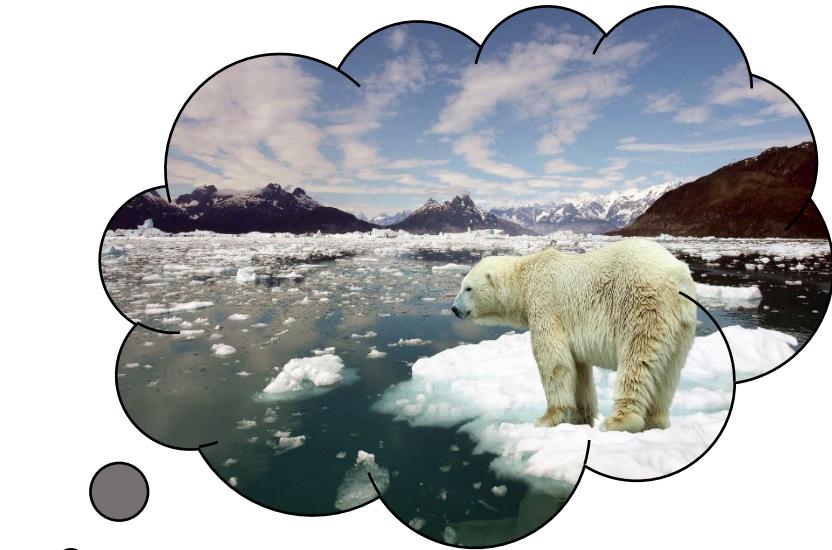


N=276





What do effective mental health treatments actually *do*?



What do effective mental health treatments actually *do*?



Quentin Dercon

- 995 participants, UK census-matched for age, sex, and history of psychiatric diagnosis
- **Half randomised to practice cognitive distancing during probabilistic reward learning**
 - Pre-registered analyses using single and dual learning rate reinforcement learning models



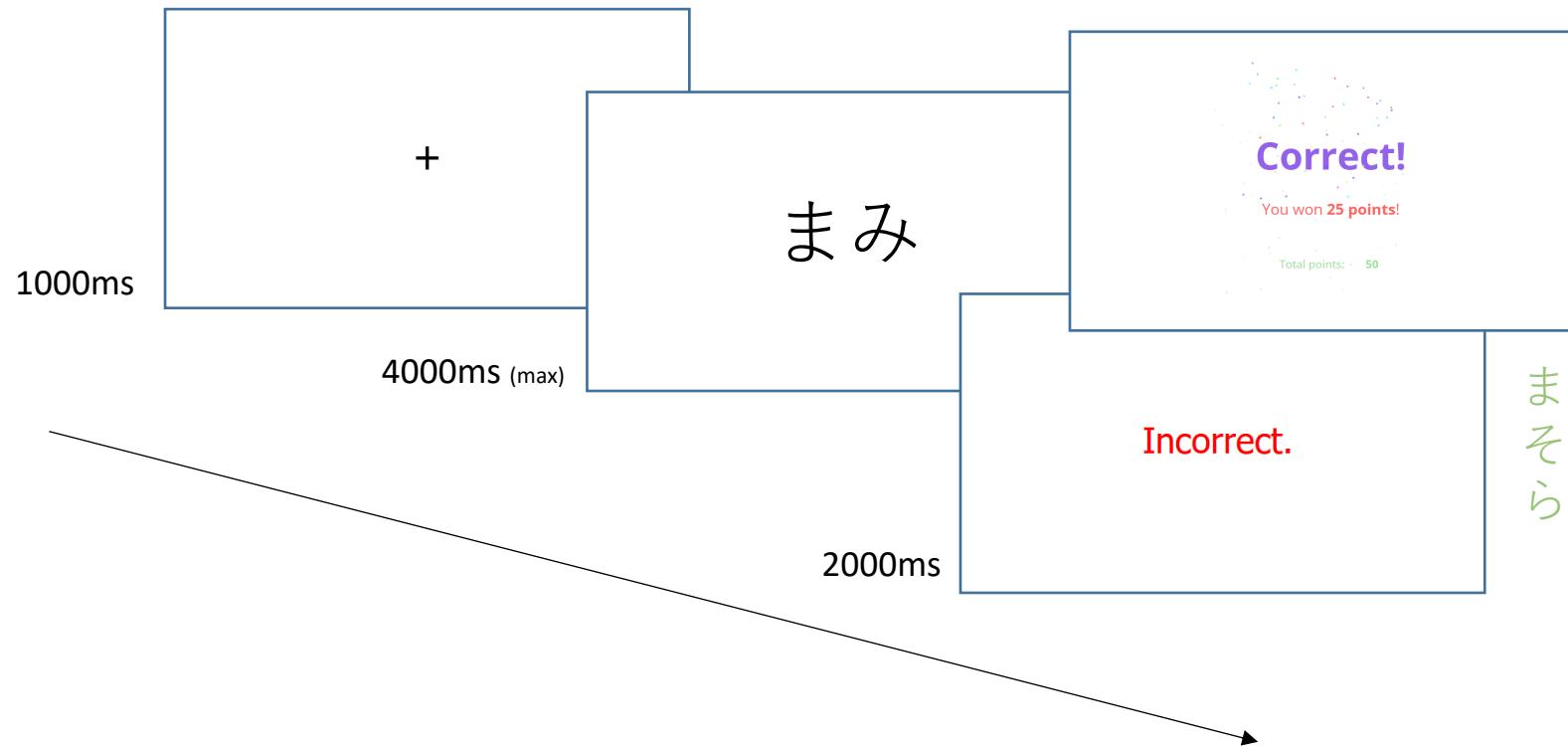
Sara Mehrhof





What do effective mental health treatments actually *do*?

training phase: 6 blocks of 60 trials (exactly 20 of each pair, randomised and counterbalanced)



→ **Distancing group**
trained to “try to take a step back” from immediate reactions to feedback, to view events from a less emotional perspective.
Reminded every trial.

Frank *et al.* (2004), *Science*; ²Frank *et al.* (2007), *PNAS*;



What do effective mental health treatments actually *do*?

Choices fit to two standard models:

- QL model with a single learning rate:

$$Q_{t+1}(s_t, a_t) = Q_t(s_t, a_t) + \alpha \delta_t$$

- Extended QL model with two learning rates: α_{gain} and α_{loss}

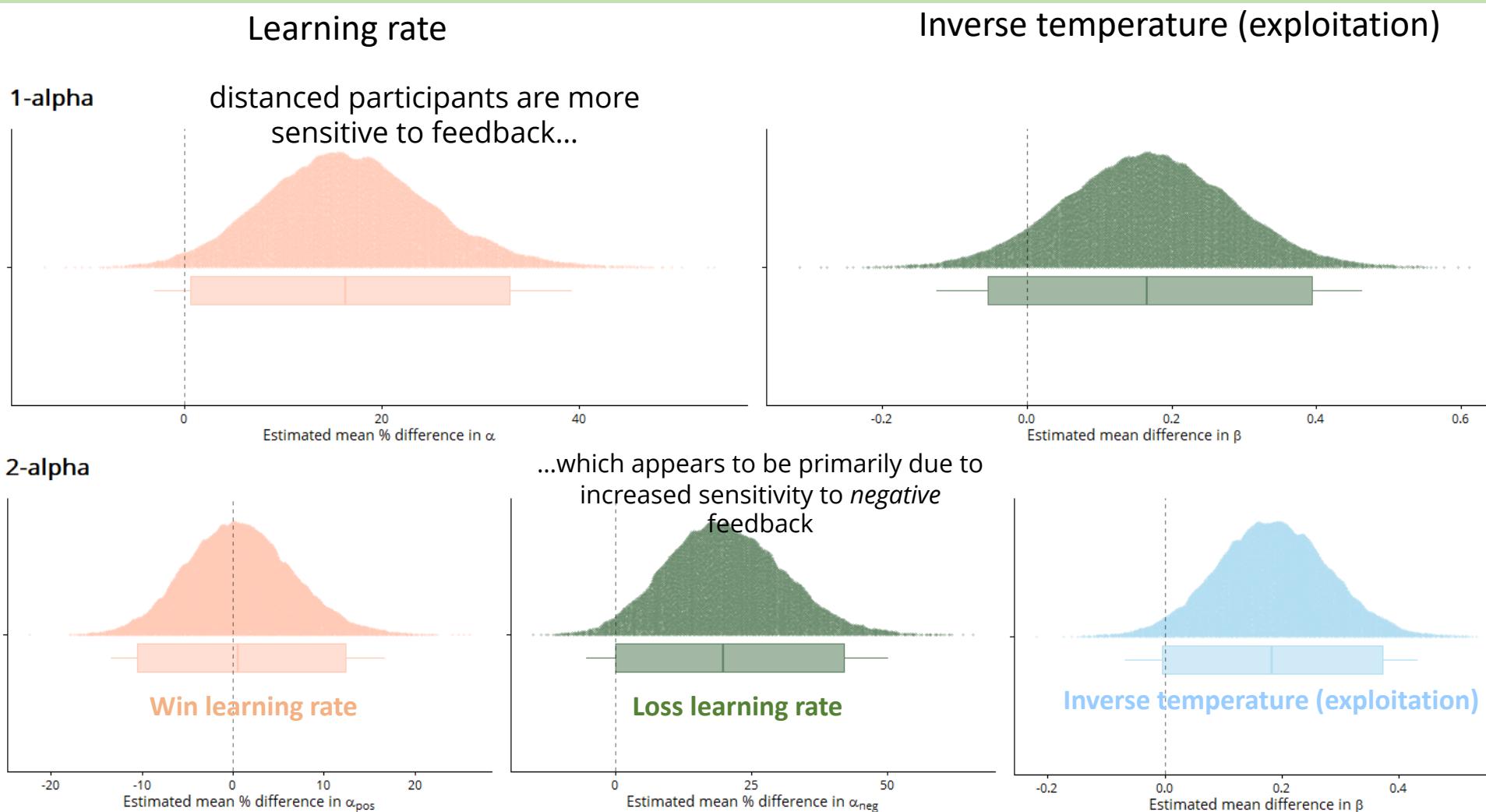
→ higher α_{loss} can be interpreted as an **increased sensitivity to recent negative feedback**

→ higher α_{gain} values suggest **increased sensitivity to recent positive feedback**

- **Both models also fit inverse temperature** → has higher β/β' can be interpreted as **improved clarity of choice values**



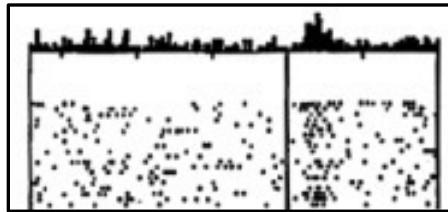
What do effective mental health treatments actually *do*?



Bayesian GLMs adjusted for age, sex, digit span



Summary: What do effective mental health treatments actually *do*?



Psychological therapy vs. antidepressant medication

- Potentially – a distinct anatomical basis, but overlapping network

Ingredient of therapy (cognitive distancing):

- Improves clarity of choice values (β/β')
- Increases learning from negative information (α'_{loss})

→ Does therapy improve adaptive
(non-catastrophic) responses to
failures?

Two crucial questions to solve this challenge

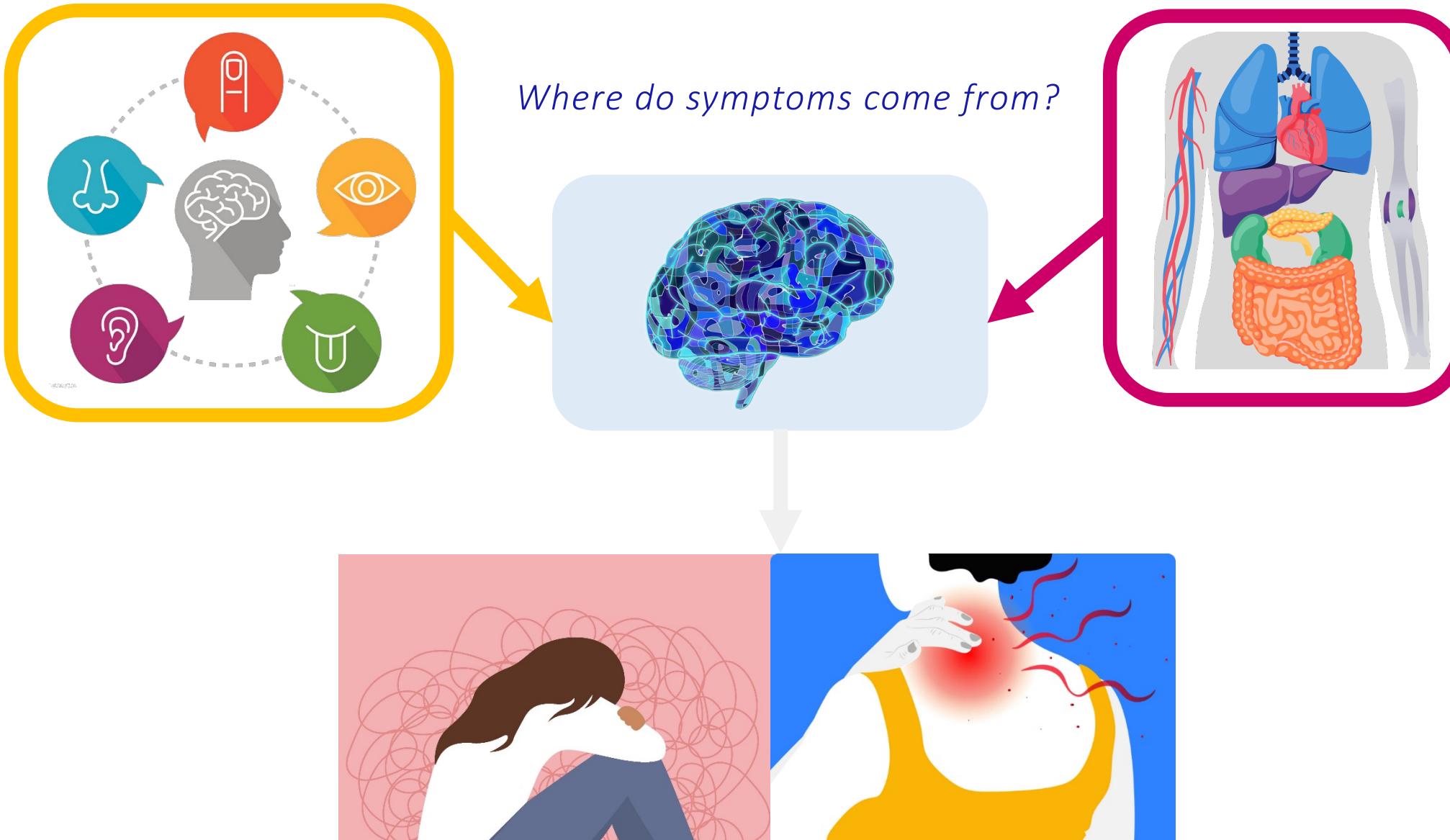
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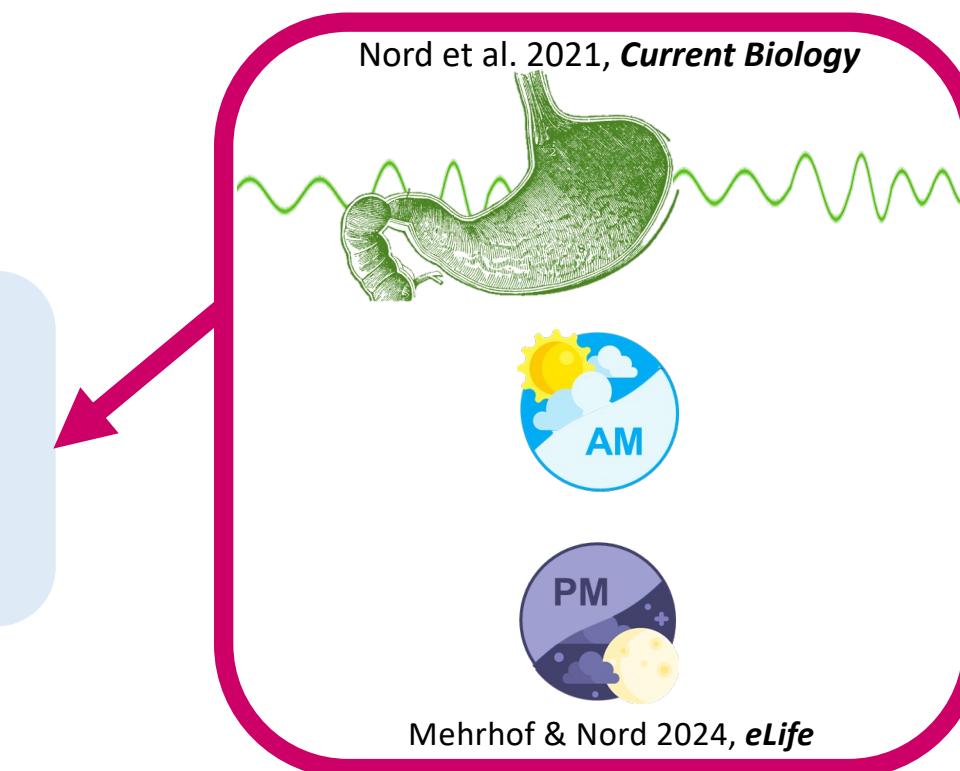
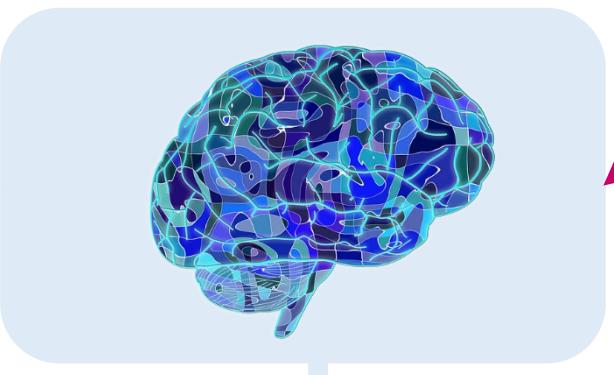
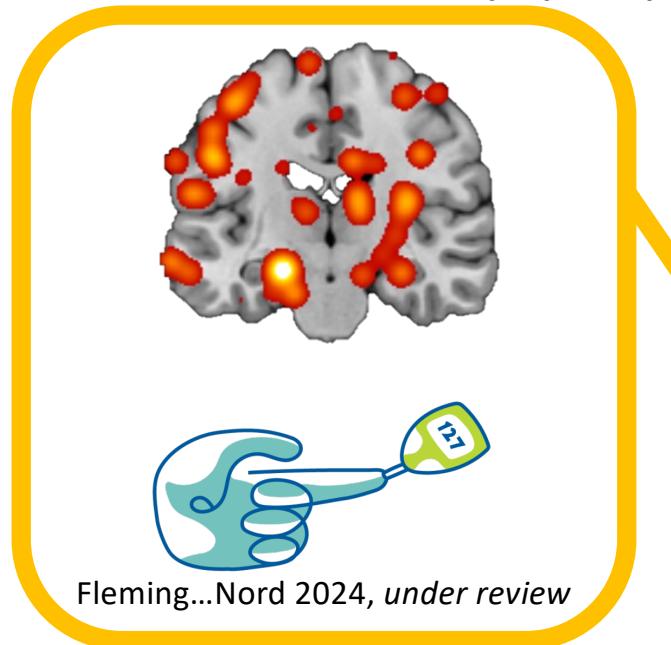
What are the *missing variables* in our understanding and treatment of mental health disorders?





missing variables in our understanding and treatment of mental health disorders?

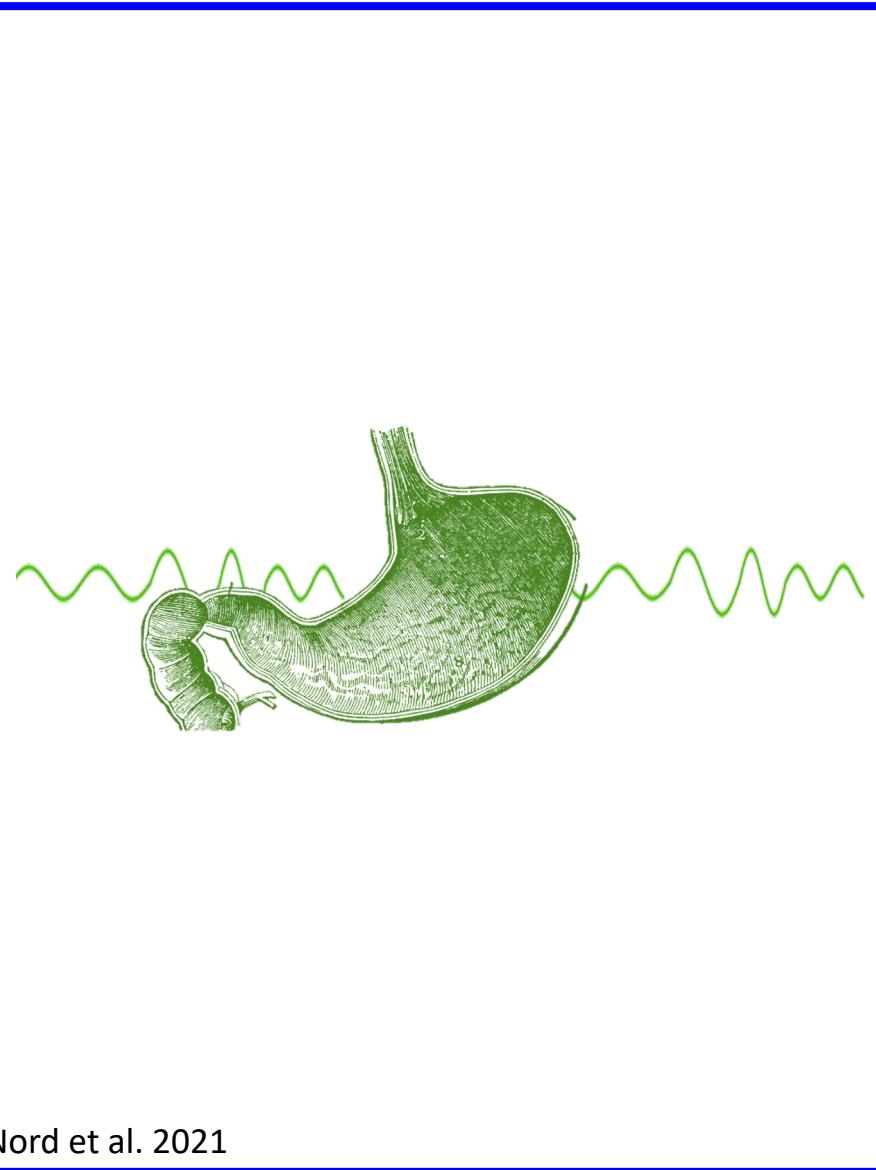
Nord, et al. 2021, *American Journal of Psychiatry*



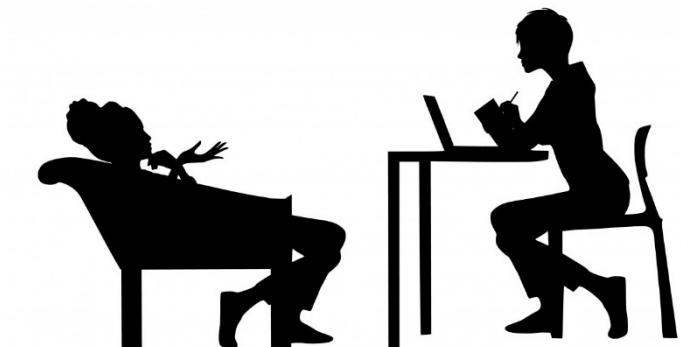
missing variables in our understanding and treatment of physical health?



What are the *missing variables* in our understanding and treatment of mental health disorders?



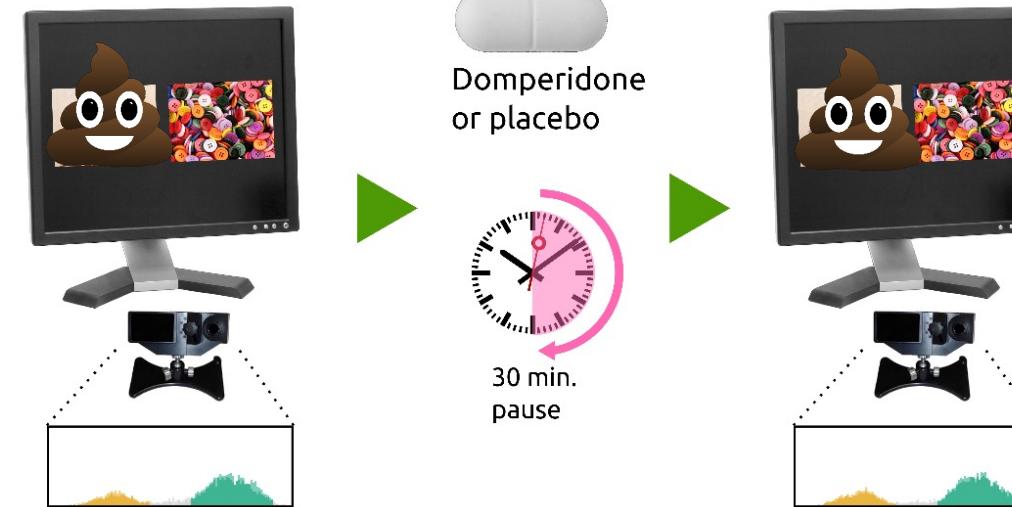
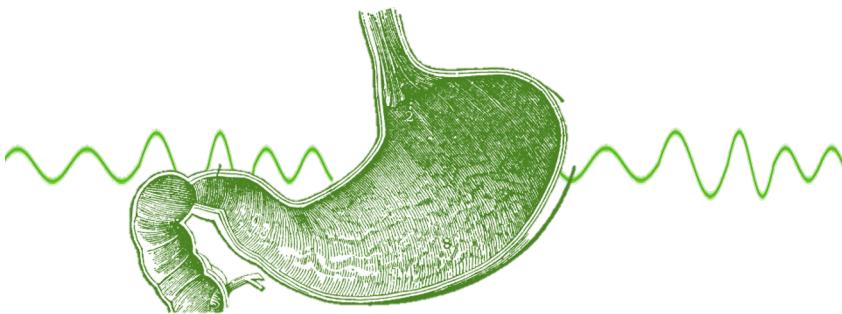
Nord et al. 2021



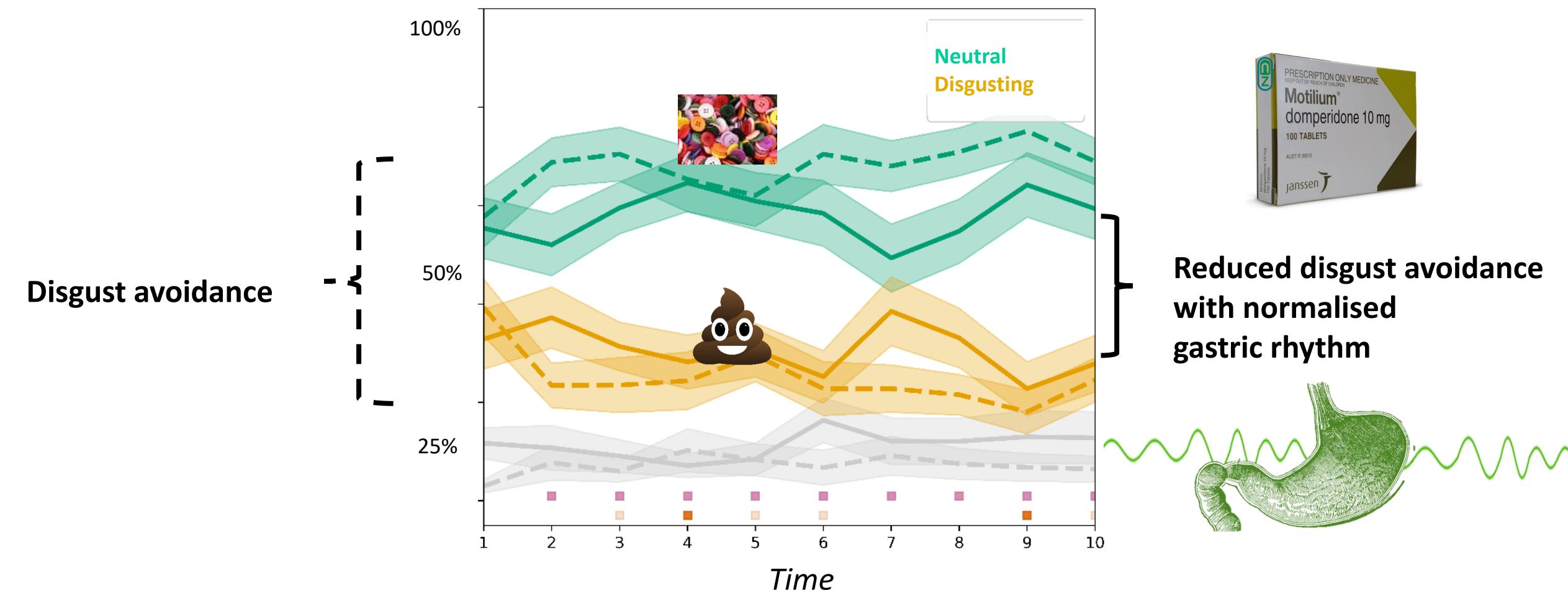
Power & Dalgleish 1997

Dalmaijer et al. 2020

What are the *missing variables* in our understanding and treatment of mental health disorders?



What are the *missing variables* in our understanding and treatment of mental health disorders?

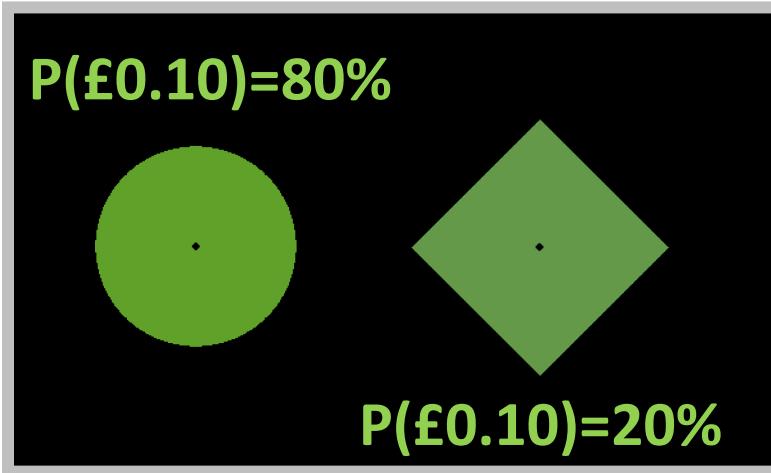


But if domperidone is a dopamine receptor antagonist, and dopamine is involved in reward processing....

Couldn't some have snuck into the brain and affected learning/rewards/incentivised exposure?



- From pharmacological studies on where domperidone deposits in the body/brain, seems extremely unlikely
- But just in case....



- D2/D3 receptor antagonists reliably affect reinforcement learning
- Tested effects of domperidone reinforcement learning (computational and non-computational analyses)

$$(1) v_{A,i} = v_{A,i-1} + \eta(R_{i-1} - v_{A,i-1})$$

MODEL (1): one learning rate (η) for rewards and no-rewards

$$(2) v_{A,i} = \begin{cases} v_{A,i-1} + \eta_{win}(R_{i-1} - v_{A,i-1}), & \text{if } R_{i-1} > 0 \\ v_{A,i-1} + \eta_{lose}(R_{i-1} - v_{A,i-1}), & \text{otherwise} \end{cases}$$

MODEL (2): two learning rates: for rewards and no-rewards

$$(3) P(A)_i = \frac{\exp(\beta v_{A,i})}{\exp(\beta v_{A,i}) + \exp(\beta v_{B,i})}$$

Softmax (3) to fit choice temperature parameter (β)

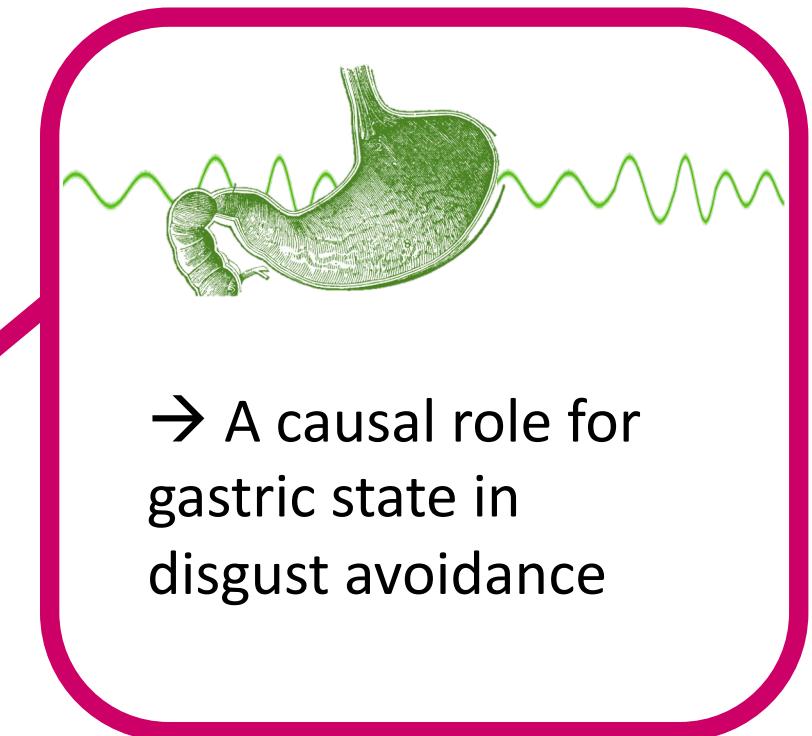
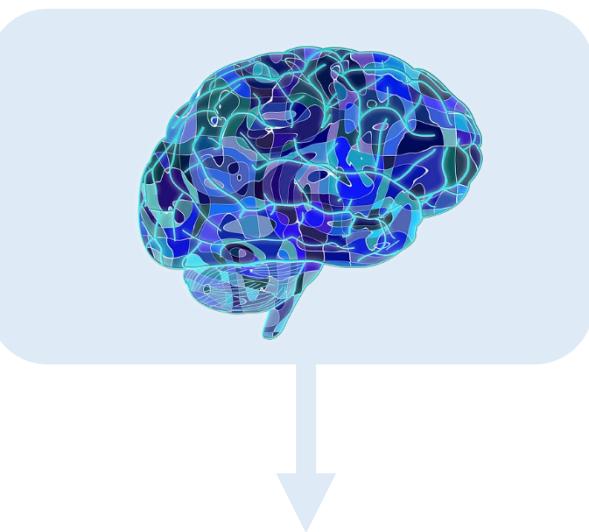
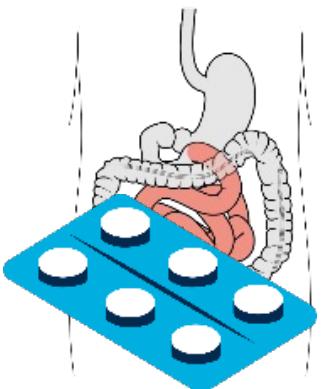
→ No effect of domperidone on reinforcement learning

	drug		phase		drug*phase		Evidence for null model	
	β	p	β	p	β	p	ER_0	BF_{01}
P(win)	0.366	0.131	0.213	0.379	-0.442	0.197	38.60	1921.70
η	0.190	0.366	0.138	0.510	-0.118	0.692	107.02	5327.99
β	0.202	0.398	0.216	0.366	-0.017	0.960	32.42	1614.17
η_{win}	0.380	0.150	0.189	0.473	-0.085	0.821	13.66	680.07
η_{lose}	0.204	0.355	0.068	0.759	0.013	0.968	60.62	3018.00
$\beta_{win/lose}$	-0.003	0.992	0.094	0.729	0.016	0.967	80.07	3986.27

- Frequentist: No main effects of drug (domperidone or placebo), phase (pre- vs. post-administration), or interaction on non-computational ($p(win)$) or computational parameters
- Bayesian: Null model 14-5000 times more likely to explain data (AIC and BIC)

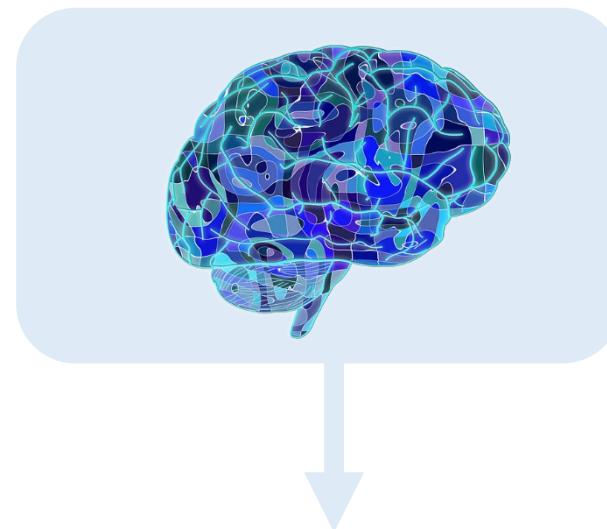
What are the *missing variables* in our understanding and treatment of mental health disorders?

- Potential visceral route for treating maladaptive pathological disgust?
- But disgust avoidance is also learned...



Nord et al. 2021, *Current Biology*

Circadian rhythm as a missing variables in our
understanding of **motivational syndromes**



Sara Mehrhof



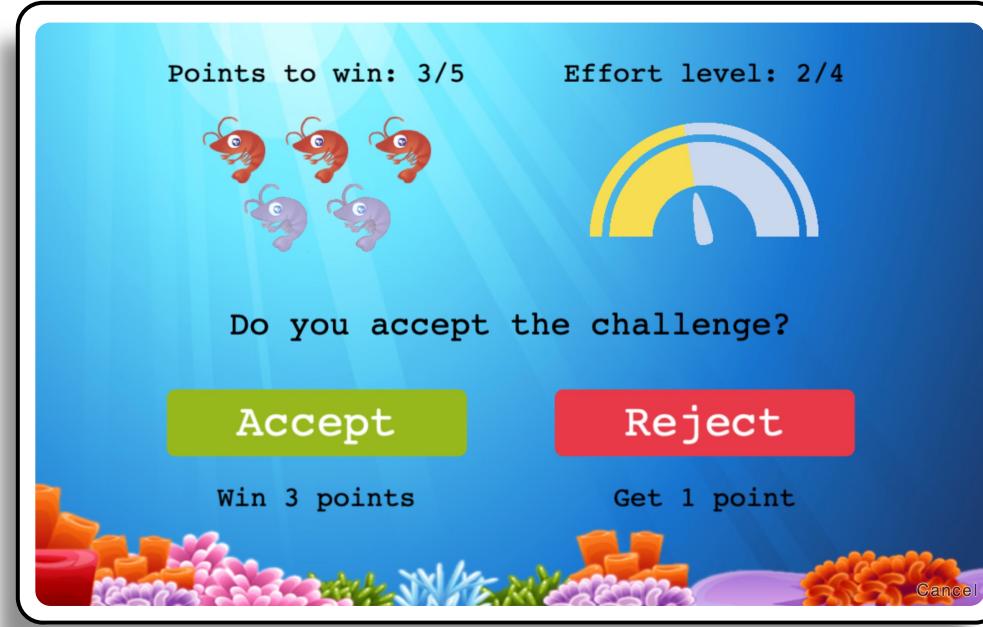


Sara Mehrhof

N=995
Demographics

Effort-based
decision-making

Self-report
questionnaires



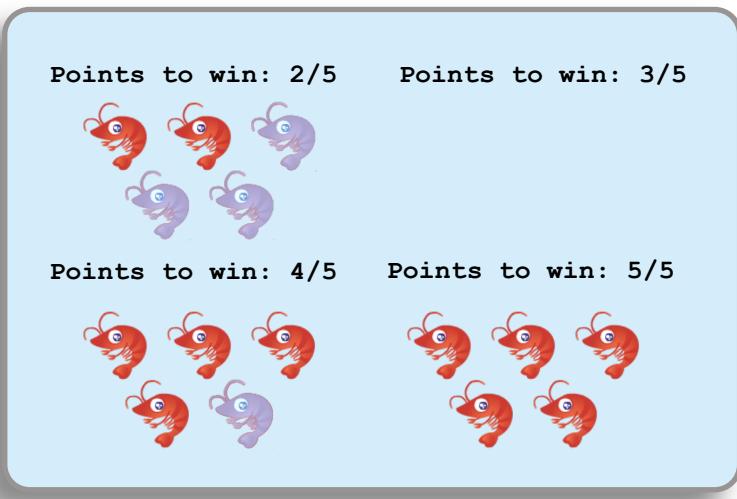
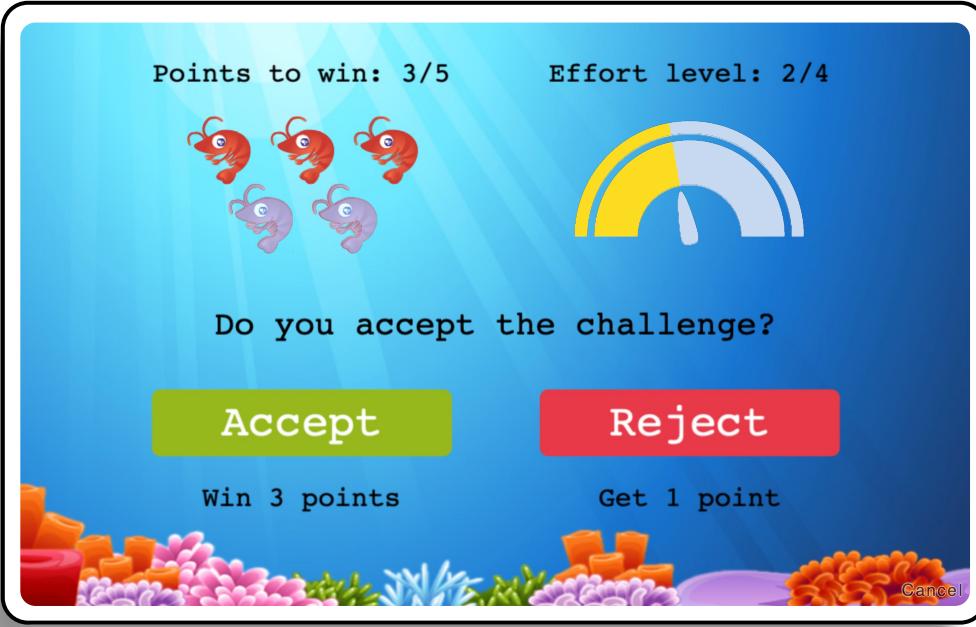


Sara Mehrhof

Demographics

Effort-based decision-making

Self-report questionnaires





Demographics

Effort-based
decision-making

Self-report
questionnaires

Dimensional ('transdiagnostic') measures

- Anhedonia (SHAPS, DARS)
- Apathy (AES)
- Circadian rhythm (MEQ, MCTQ)

Categorical measures

- Currently depressed vs.
healthy controls (M.I.N.I.)
- Early, intermediate, or late
chronotype (MEQ, MCTQ)



Sara Mehrhof



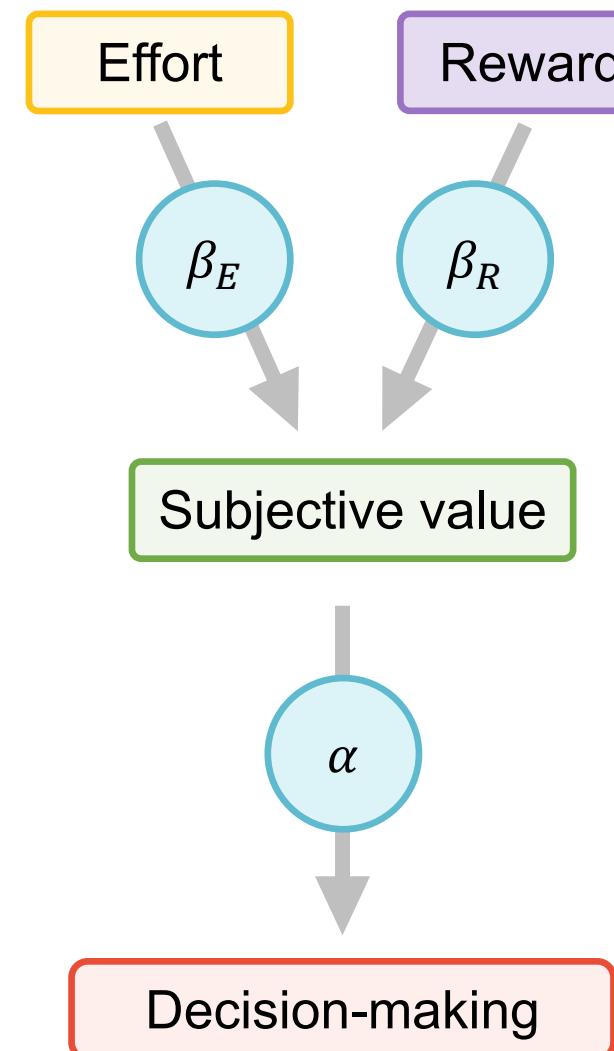
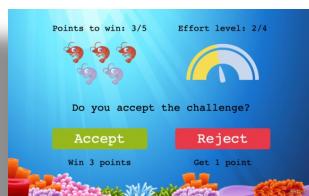


Transdiagnostic
symptoms

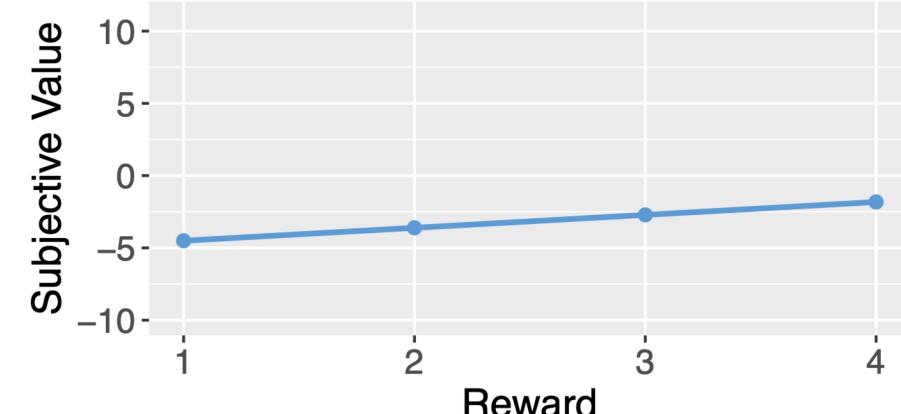
Circadian measures



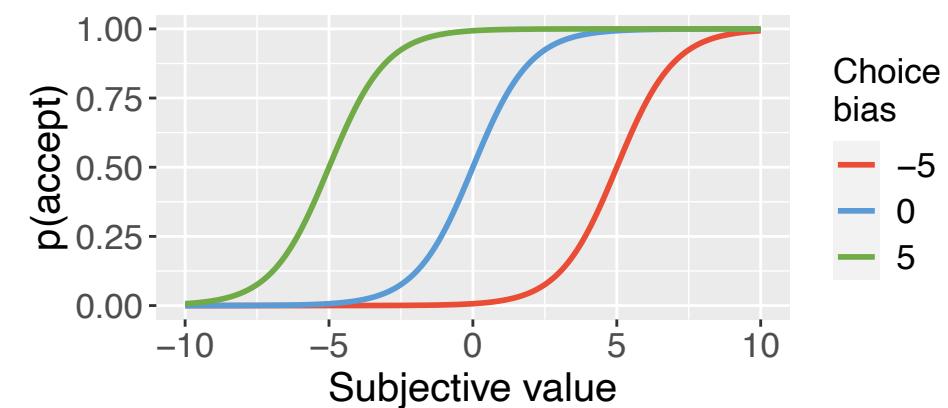
Effort-based
decision-making



$$SV = (\beta_R \cdot R) - (\beta_E \cdot E^2)$$



$$p(\text{accept}) = \frac{1}{1 + e^{-(\alpha + SV)}}$$

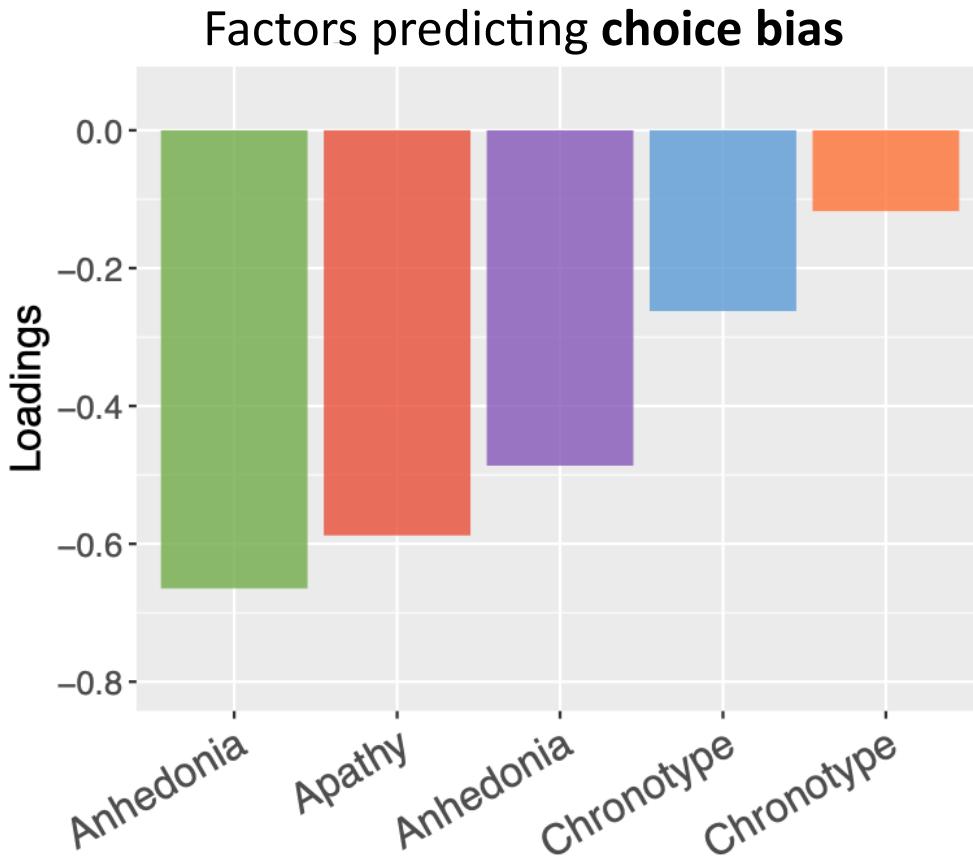




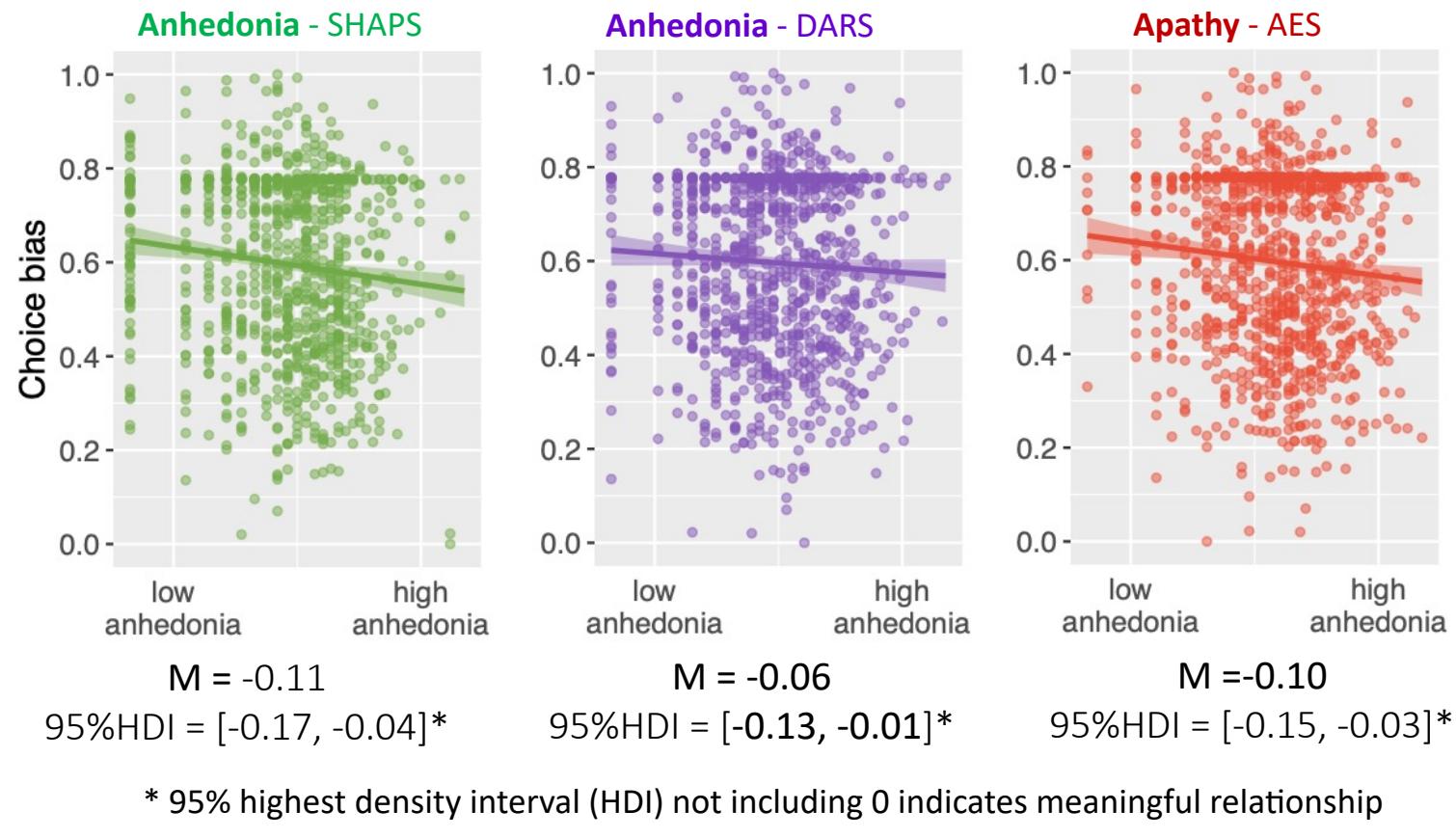
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→ Lower tendency to exert effort for reward ('choice bias') predicted by higher anhedonia & apathy

- PLS regression → modelling parameters predicted by self-report measures simultaneously



- Bayesian GLMs



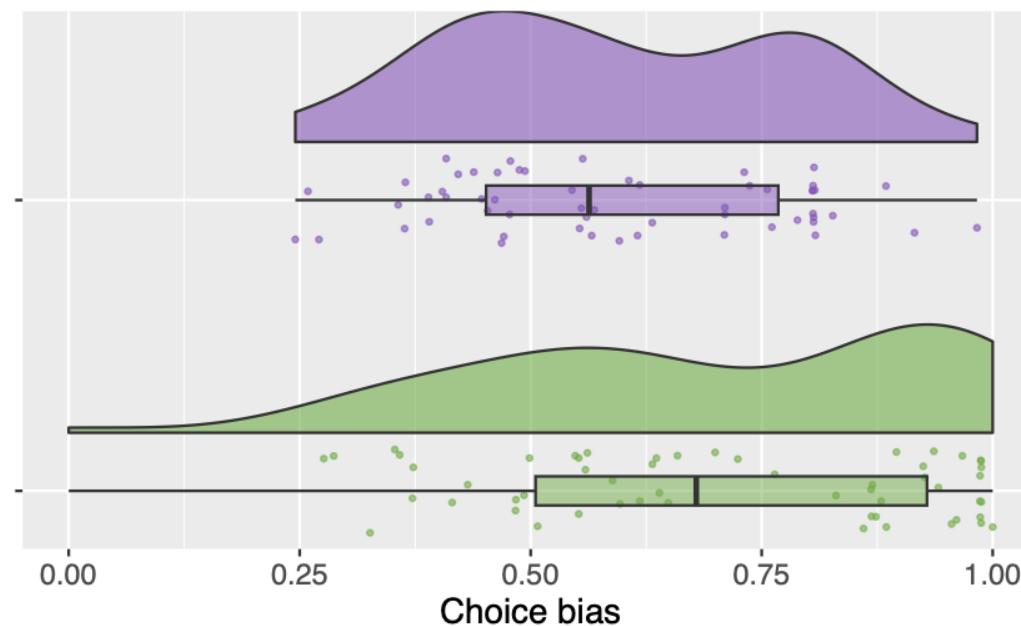


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→ Replicated blunted choice bias in sample meeting criteria for current major depressive episode

N=56 currently depressed participants

N=56 age- and gender-matched controls



$$M=-0.172, 95\% \text{ HDI} = [-0.28, -0.08]^*$$



Sara Mehrhof

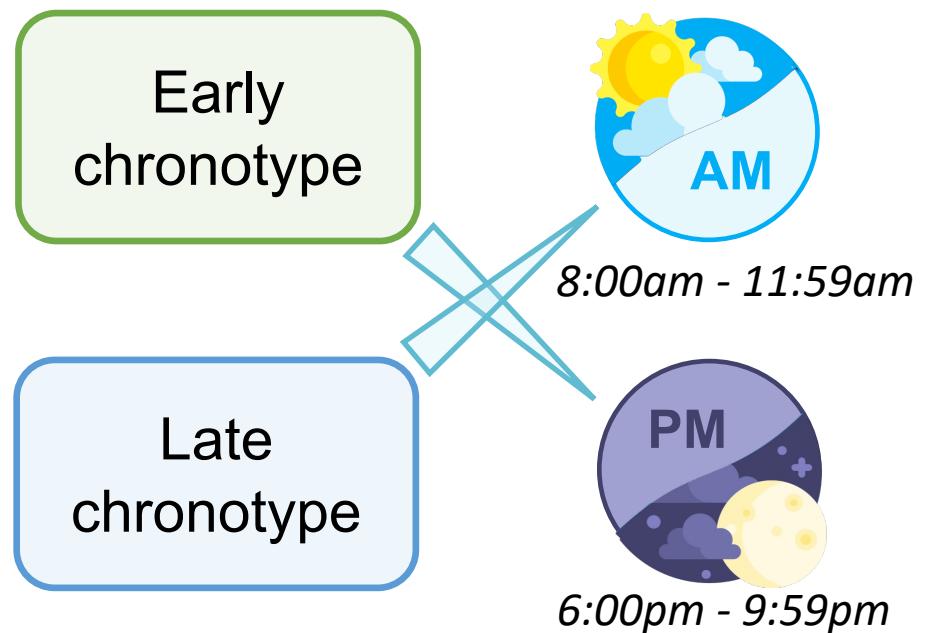
But is there a missing variable?

Early chronotype
N = 90 (9.39%)

Intermediate chronotype
N = 761 (79.43%)

Late chronotype
N = 77 (8.37%)

Additional pre-registered data collection

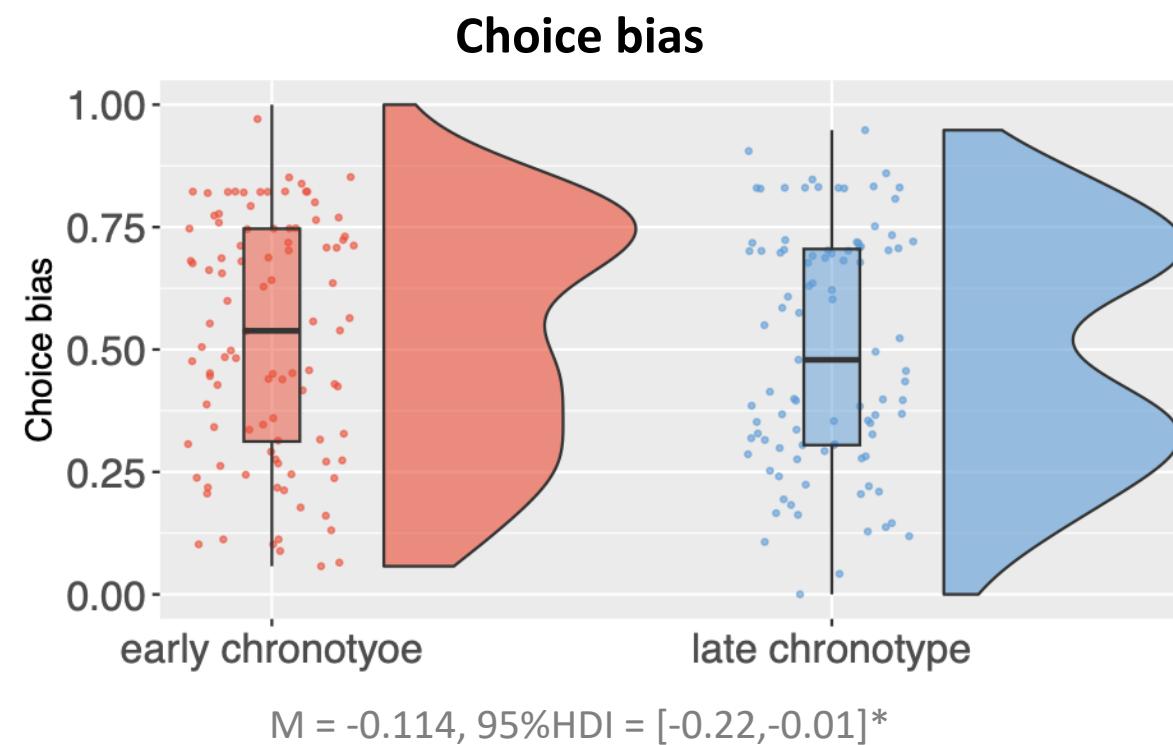




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→ Late chronotype reduces tendency to exert effort for reward (choice bias)

Sample: n = 100 early and 95 late chronotypes

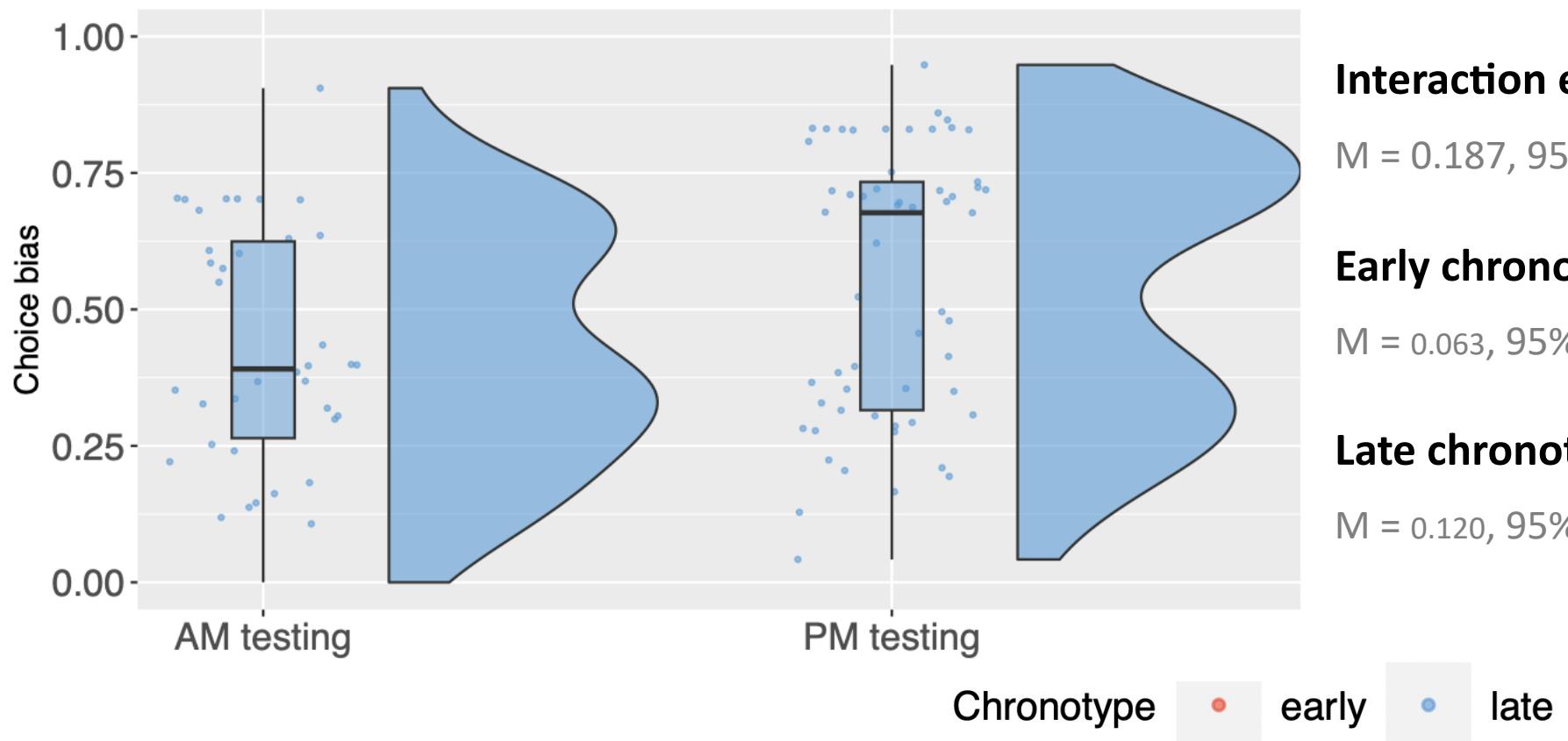




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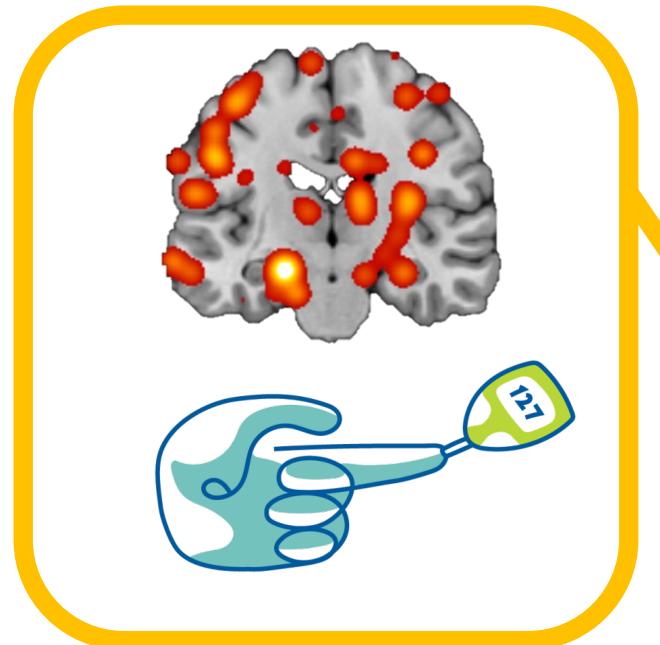
→ Late chronotype reduces choice bias—but only in the morning!

Sample: n = 100 early and 95 late chronotypes



* 95% highest density interval (HDI) not including 0 indicates meaningful relationship



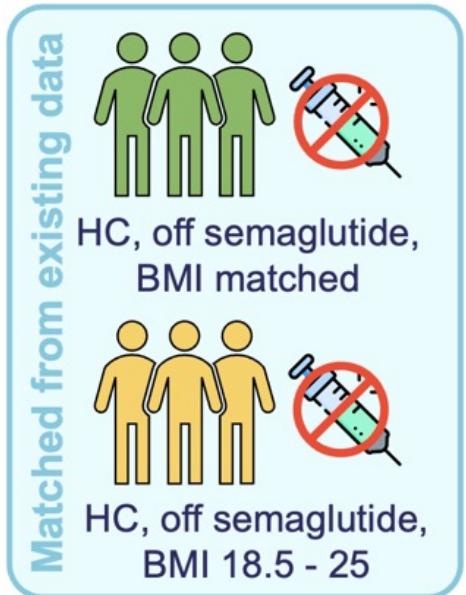
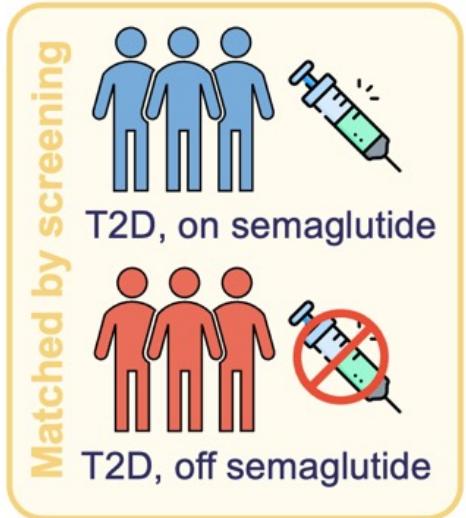


missing variables in our understanding
and treatment of physical health?



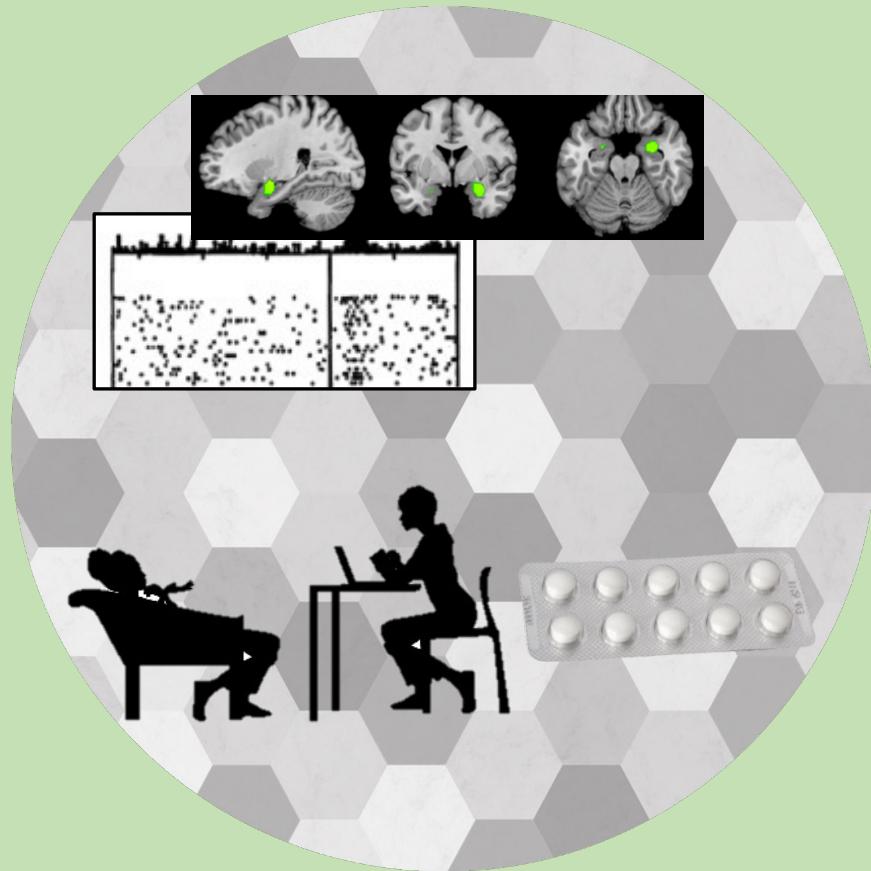
Sara Mehrhof

Beyond mental health.....

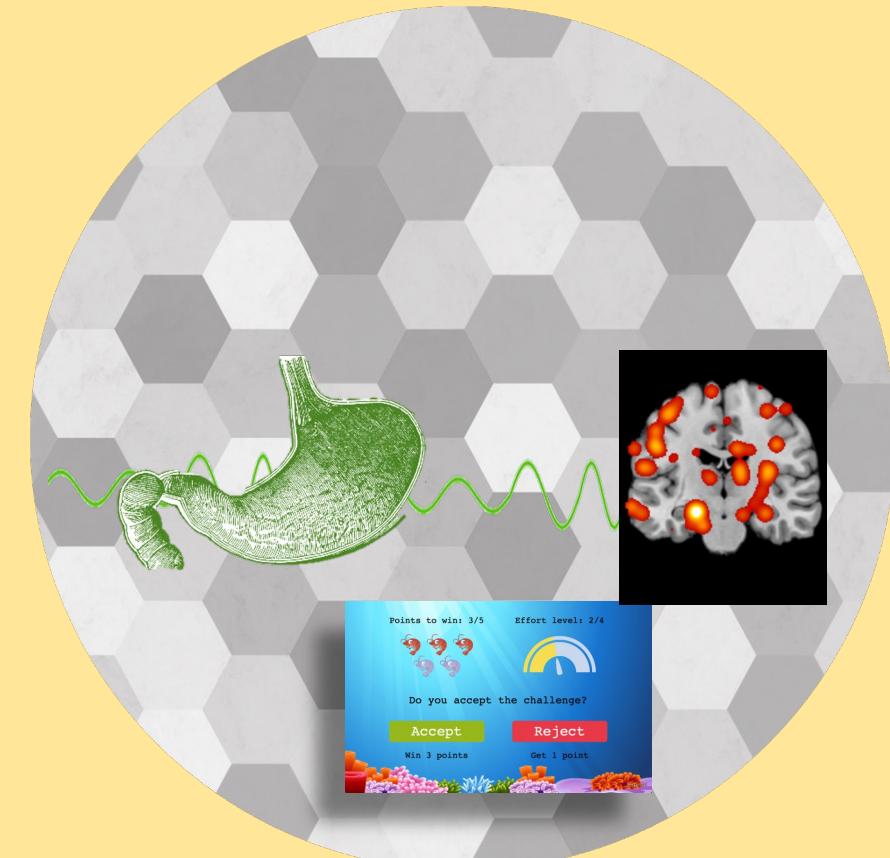


How do we get from here to precision mental health?

Unmask treatment mechanisms –
across treatment modalities

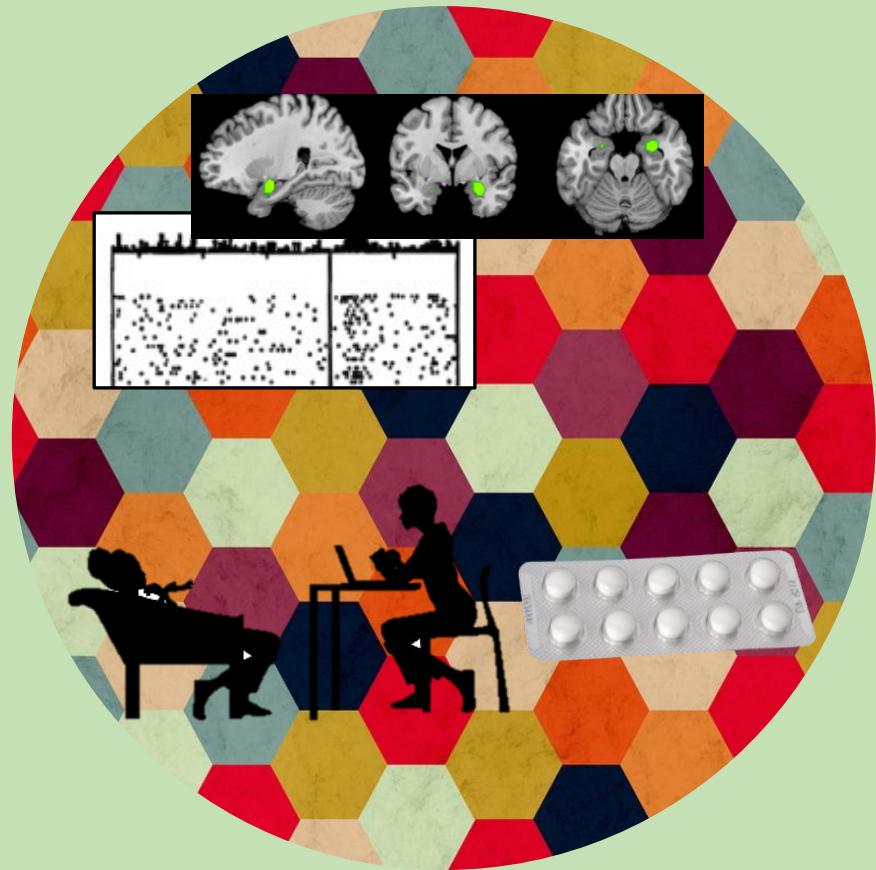


Discover disorder mechanisms –
across traditional diagnostic nosology

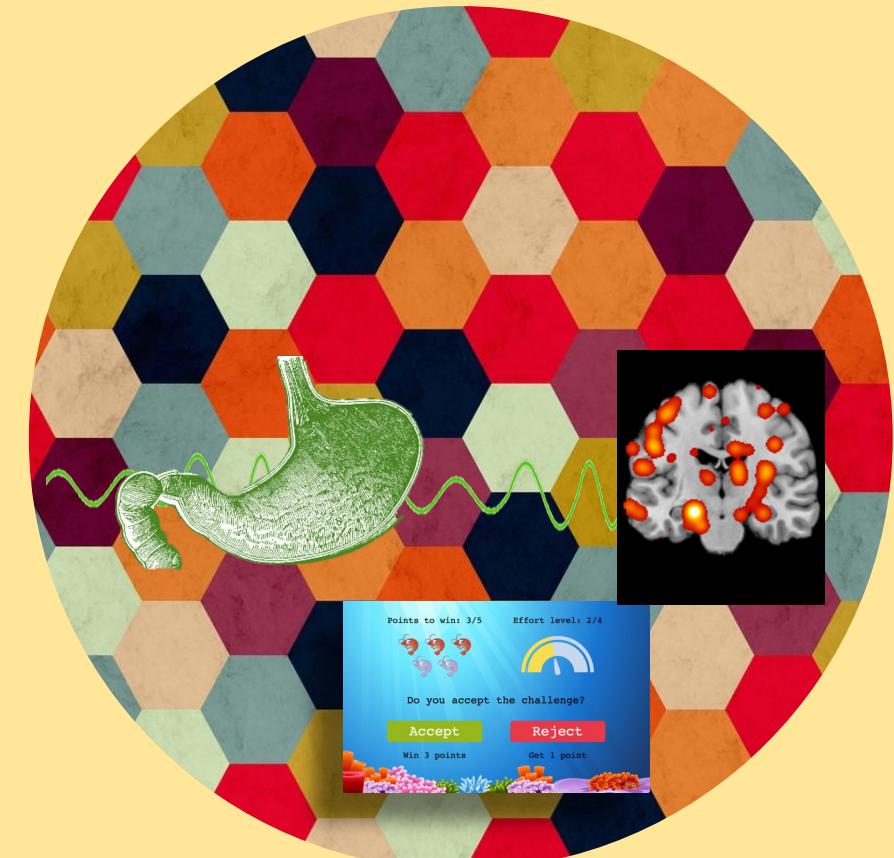


How do we get from here to precision mental health?

Unmask treatment mechanisms –
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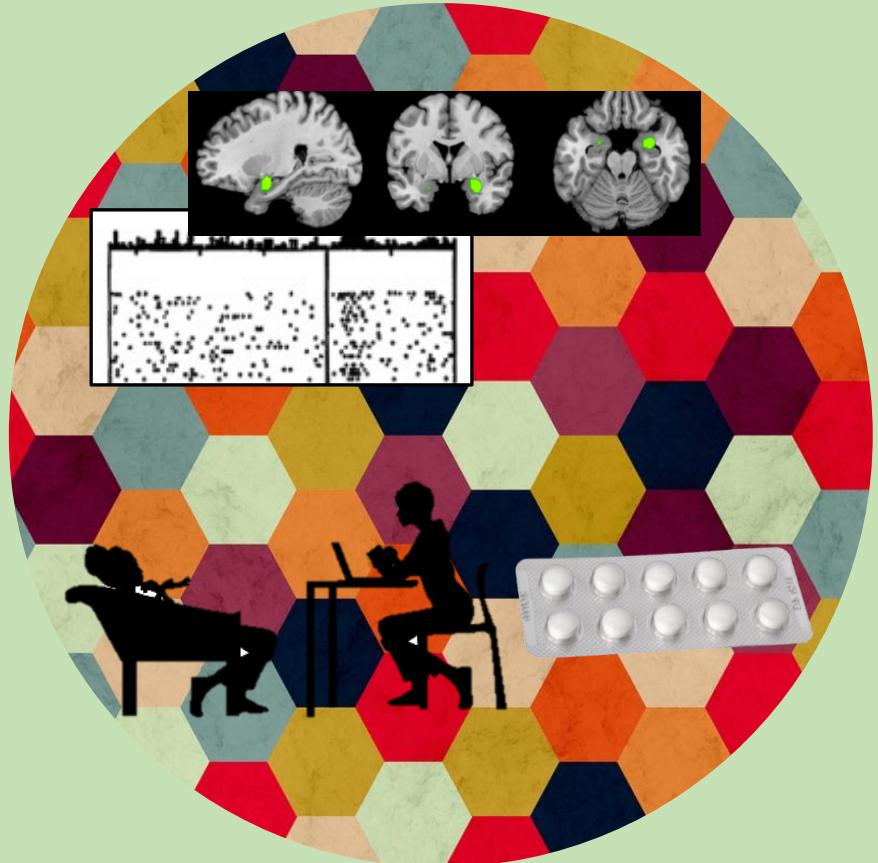


Discover disorder mechanisms –
across traditional diagnostic nosology



An example area for innovation

Unmask treatment mechanisms –
across treatment modalities



nature mental health

Analysis

<https://doi.org/10.1038/s44220-023-000>

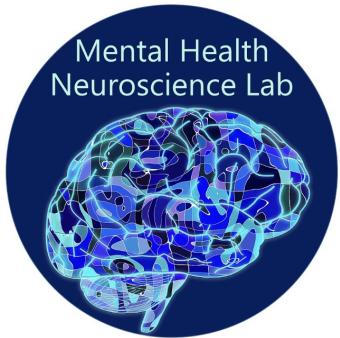
A transdiagnostic meta-analysis of acute augmentations to psychological therapy



Ketamine-like drug for depression gets UK licence

Psychiatrists divided on 'game-changing' esketamine due to potential for addiction





Thank you!



Dr Hugo Fleming



Sara Mehrhof



Dr Lydia Hickman



Gabriel Mackie



Annalise Whines



Alicia Smith



Emily Bagley



Quentin Dercon
(UCL)



Isabel Lau

Thank you to collaborators

Edwin Dalmaijer
Sarah Garfinkel
Tim Dalgleish
Anna Bevan
Caitlin Hitchcock
Diego Pizzagalli
Rebecca Lawson
Tim Sandhu
Jon Roiser

Funders



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AXA
Research Fund

... and thanks to the Zurich Computational Psychiatry Course

JAMA Psychiatry | Original Investigation

Reevaluating the Efficacy and Predictability of Antidepressant Treatments A Symptom Clustering Approach

Adam M. Chekroud, MSc; Ralitsa Gueorguieva, PhD; Harlan M. Krumholz, MD, SM; Madhukar H. Trivedi, MD;
John H. Krystal, MD; Gregory McCarthy, PhD

nature
neuroscience

Adults with autism overestimate the volatility of the sensory environment

Rebecca P Lawson¹⁻³ , Christoph Mathys^{1,4-6} & Geraint Rees^{1,2} 

Insistence on sameness and intolerance of change are among the diagnostic criteria for autism spectrum disorder (ASD), but little research has addressed how people with ASD represent and respond to environmental change. Here, behavioral and pupillometric

Biological
Psychiatry

Archival Report

Modeling Avoidance in Mood and Anxiety Disorders Using Reinforcement Learning

Anahit Mkrtchian, Jessica Aylward, Peter Dayan, Jonathan P. Roiser, and Oliver J. Robinson

Psychopharmacology (2024) 241: 47–962
<https://doi.org/10.1007/s00213-023-06521-5>

ORIGINAL INVESTIGATION



Insight into differing decision-making strategies that underlie cognitively effort-based decision making using computational modeling in rats



Neuroscience and Biobehavioral Reviews

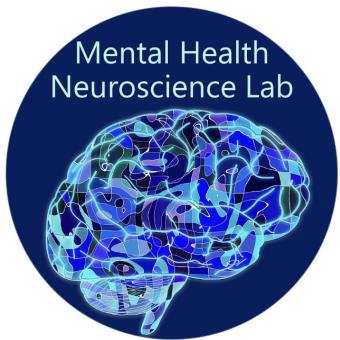
journal homepage: www.elsevier.com/locate/neubiorev

Review article

Comprehensive review: Computational modelling of schizophrenia

Vincent Valton^{a,b,1}, Liana Romaniuk^b, J. Douglas Steele^c, Stephen Lawrie^b, Peggy Seriès^{a,*}





Thank you!



Dr Hugo Fleming



Sara Mehrhof



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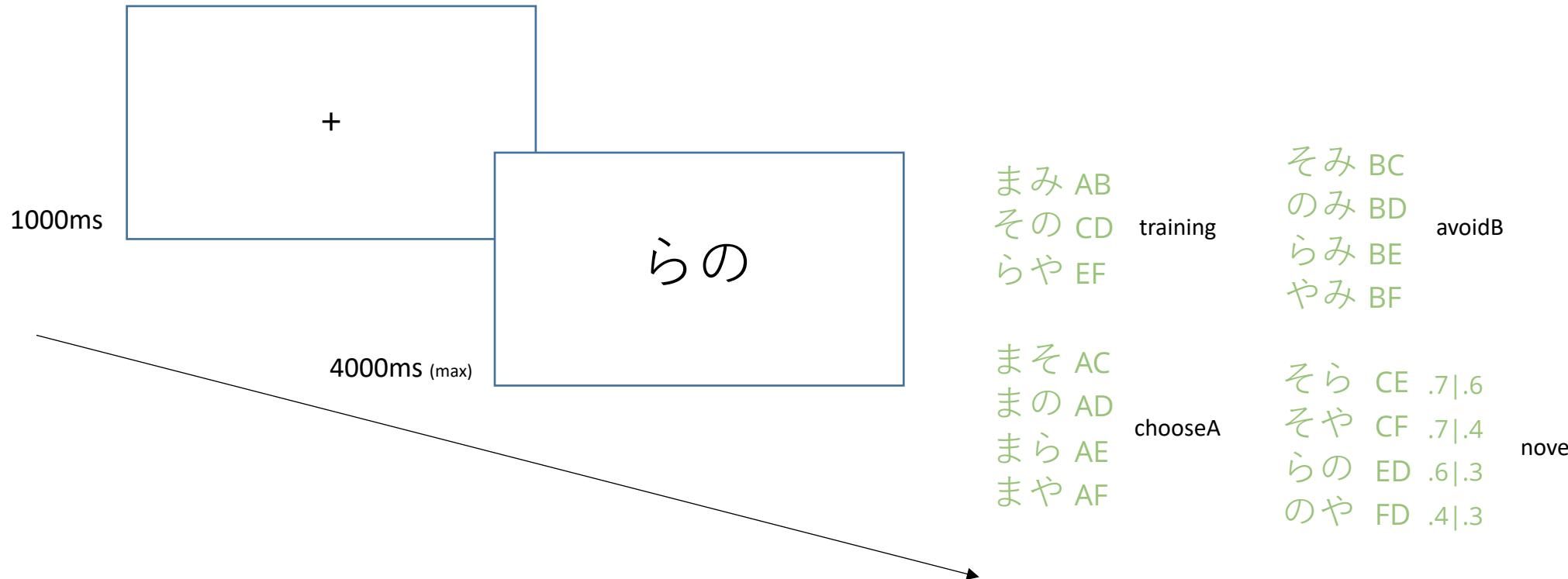


AXA
Research Fund

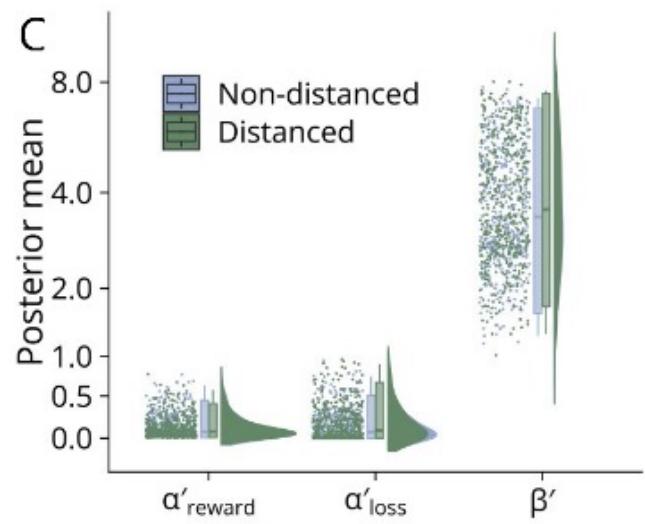
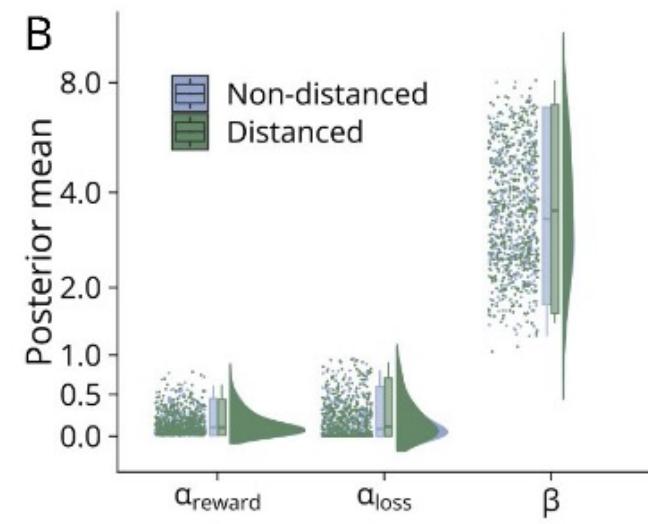
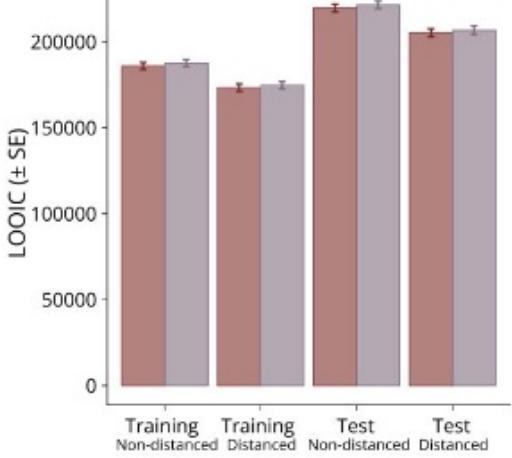
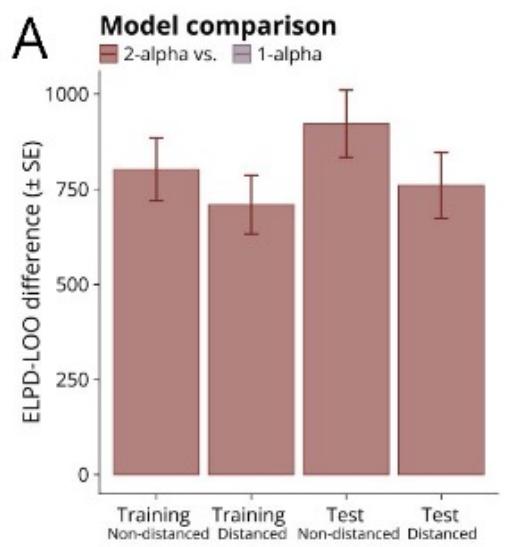


How does psychological therapy work?

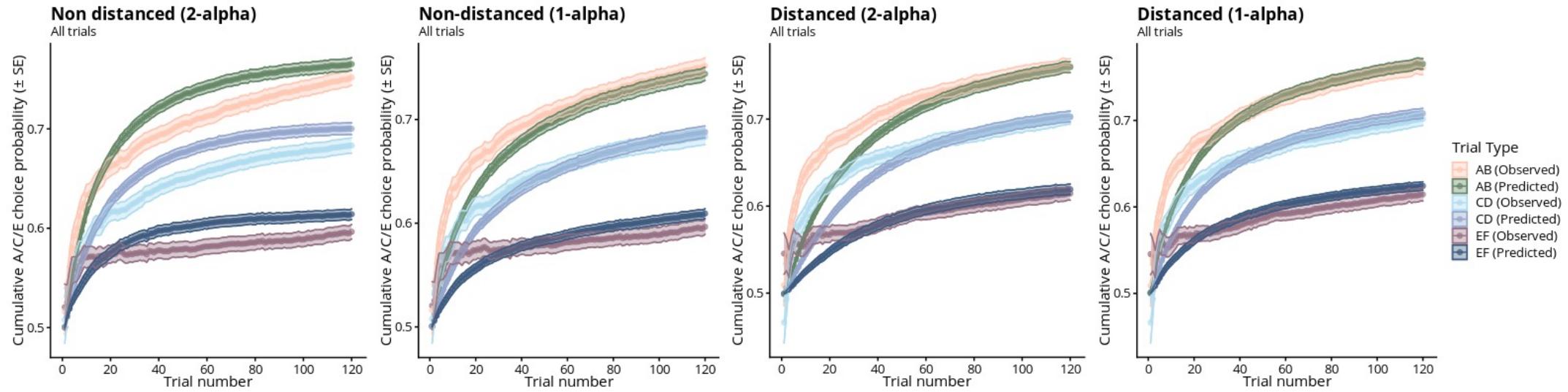
test phase: 60 trials – 4 of each of the 15 possibilities



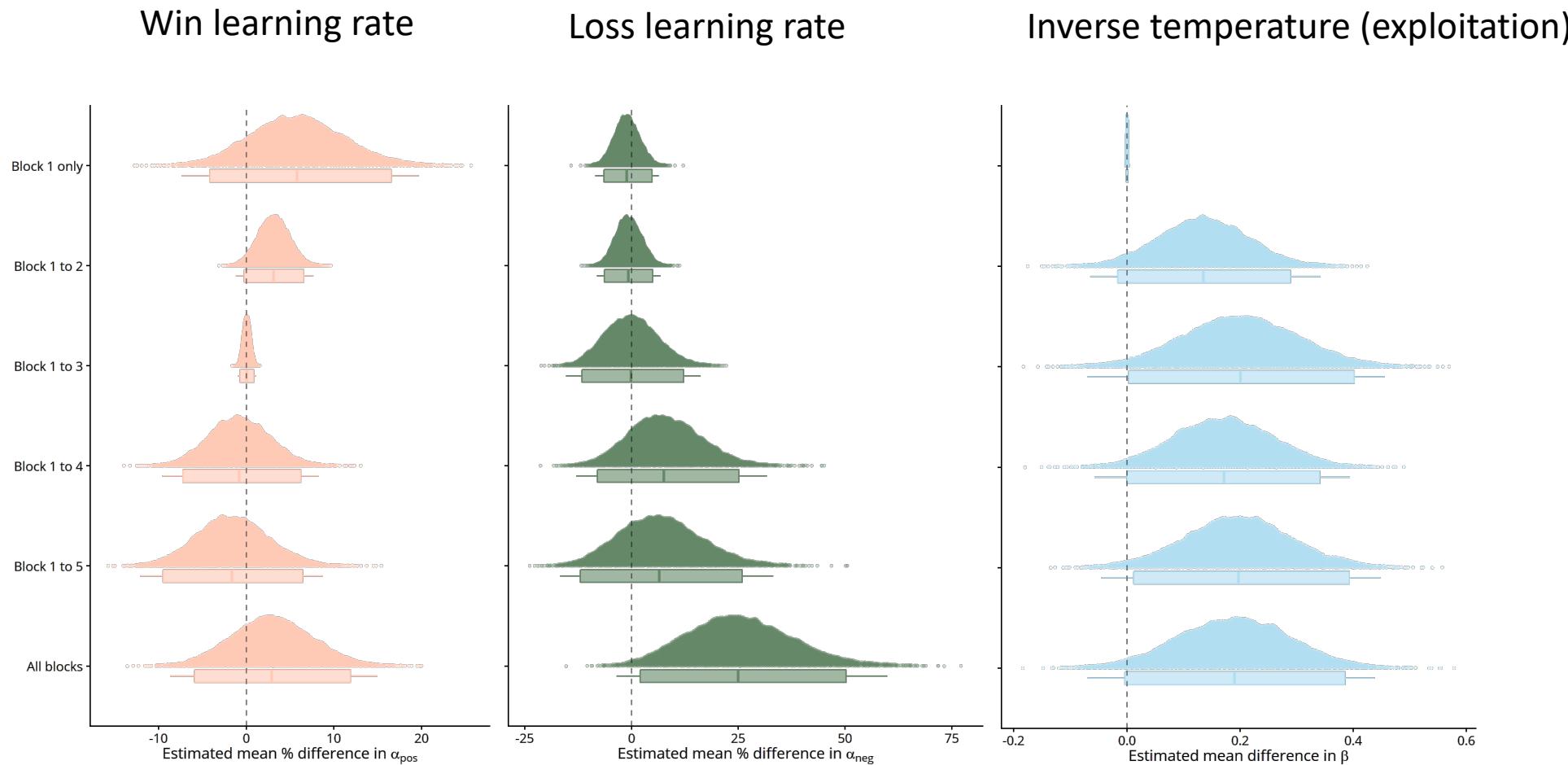
¹Frank et al. (2004), Science; ²Frank et al. (2007), PNAS



model FITTING & CHECKS

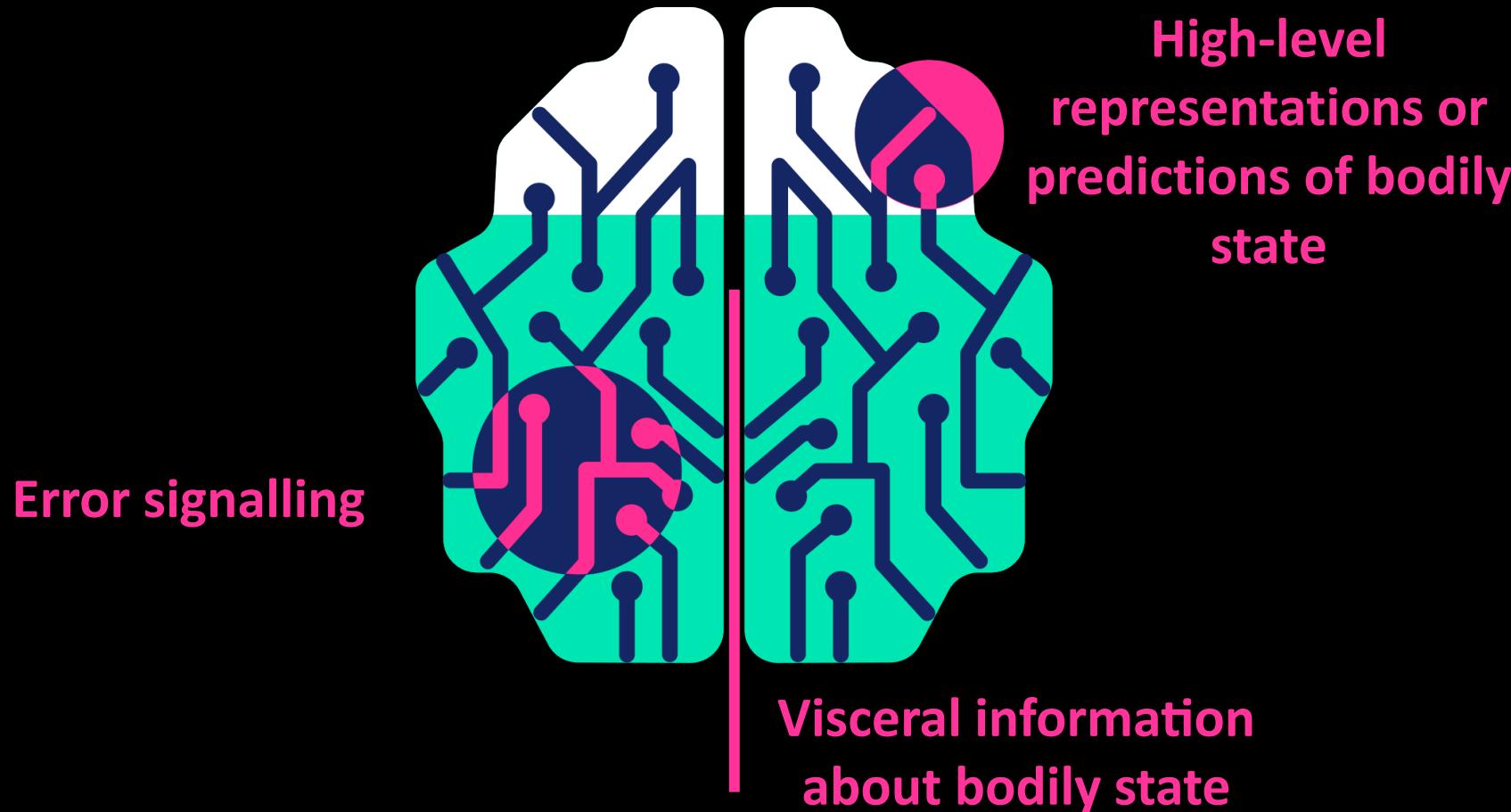


- models checked in a number of ways, including:
 - posterior predictive checks:
 - the estimated parameters at every iteration are used to generate predictions for the choice at each trial, and then compared to the observed data
 - parameter recovery:
 - we simulate data from the models using a random sample of parameter values, and then fit the models to see if we can “recover” the parameter values that went in



- the difference in α_{neg} only appears to emerge towards the end of training, while difference in β is more consistent

What are the *missing variables* in our understanding and treatment of mental health disorders?

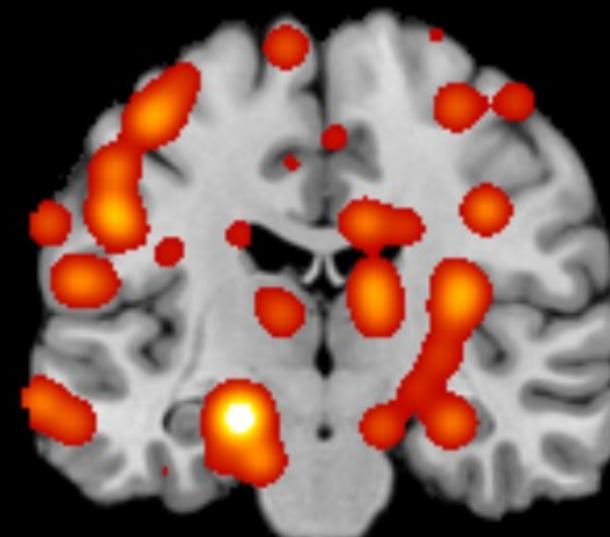


→ Do psychiatric disorders show a **common locus of disruption?**

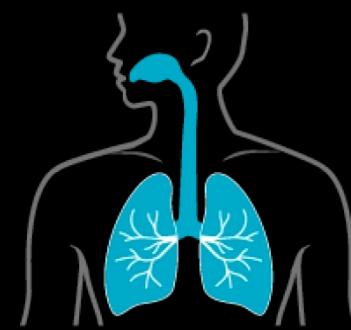
Missing variable: a common disruption in interoception across psychiatric disorders?



N=1226 (patients vs controls)
(anxiety disorders, affective disorders, eating disorders, addictions, etc.)



heartbeat counting > sound counting (e.g.)

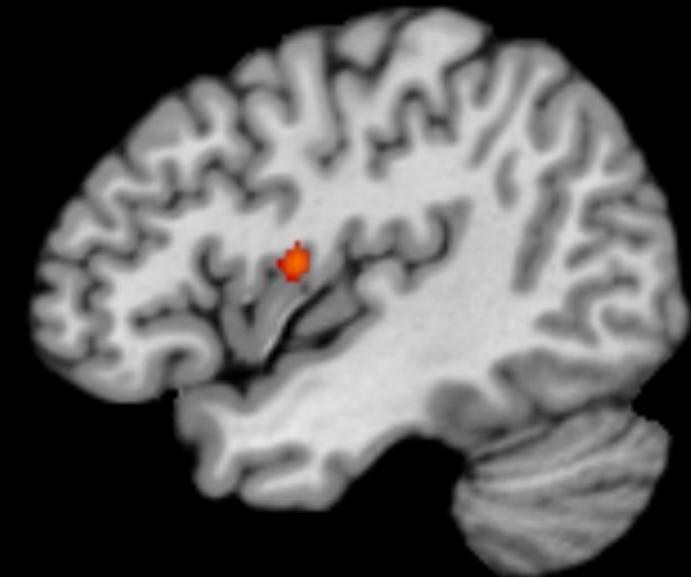
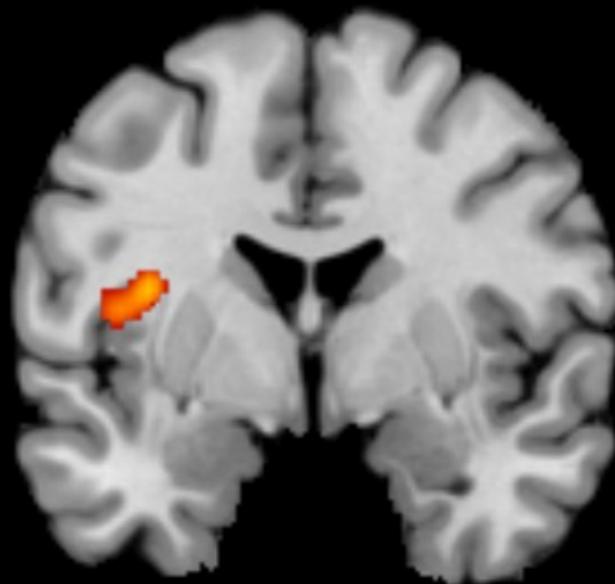
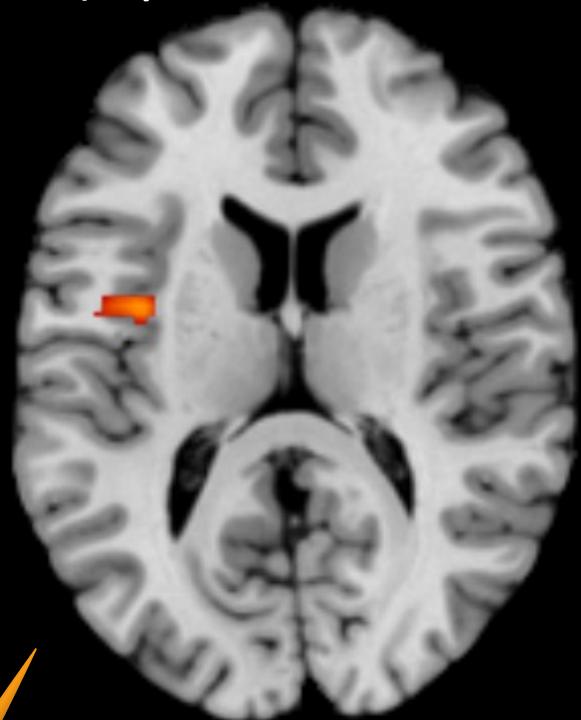




Missing variable: a common disruption in interoception across psychiatric disorders?



(bipolar disorder, anxiety, major depression, remitted anorexia, schizophrenia)



left dorsal mid-insula (BA 13)

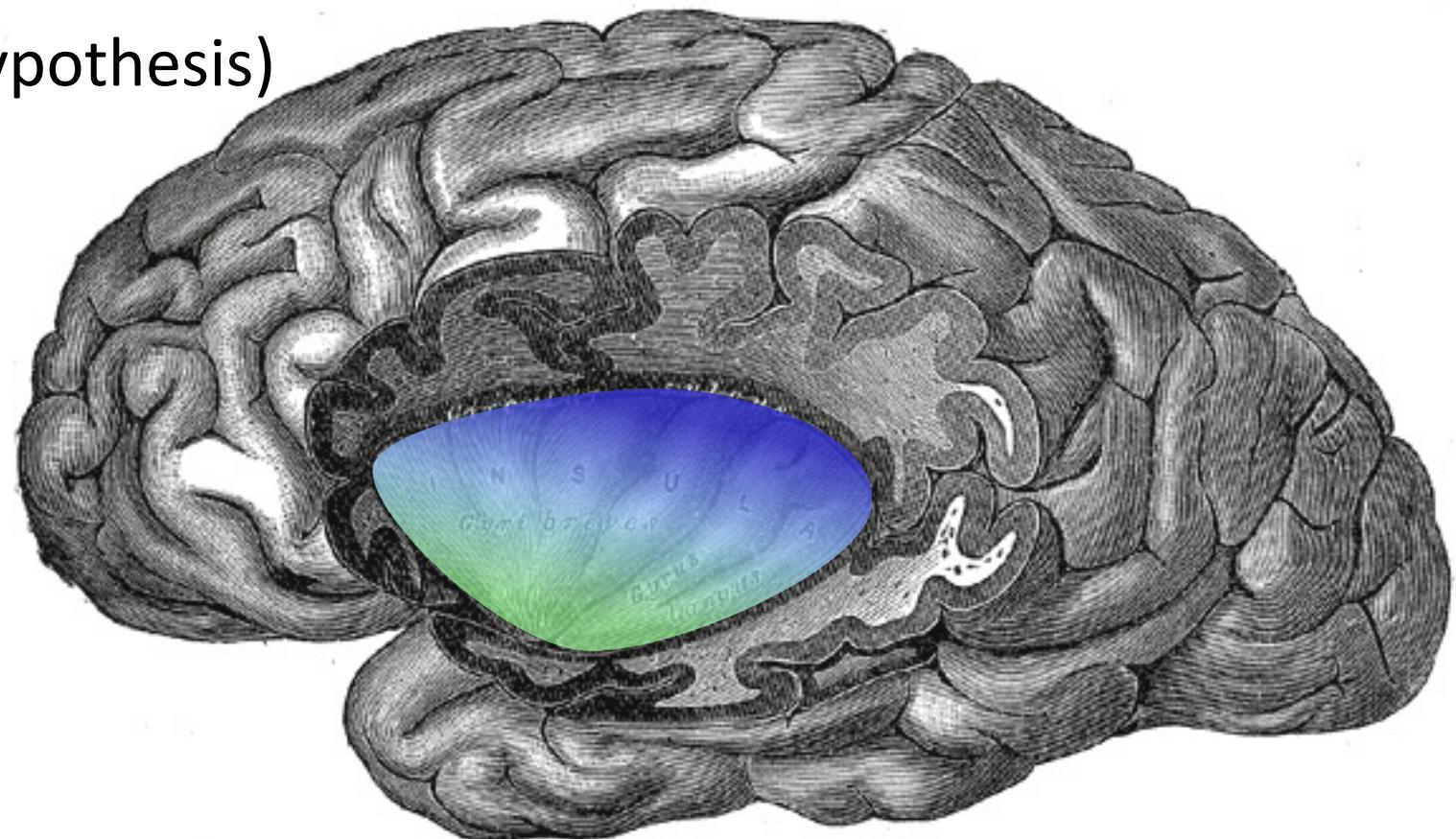
$Z=4.47, p<0.05$ FWE cluster-corrected



Missing variable: a common disruption in interoception across psychiatric disorders?

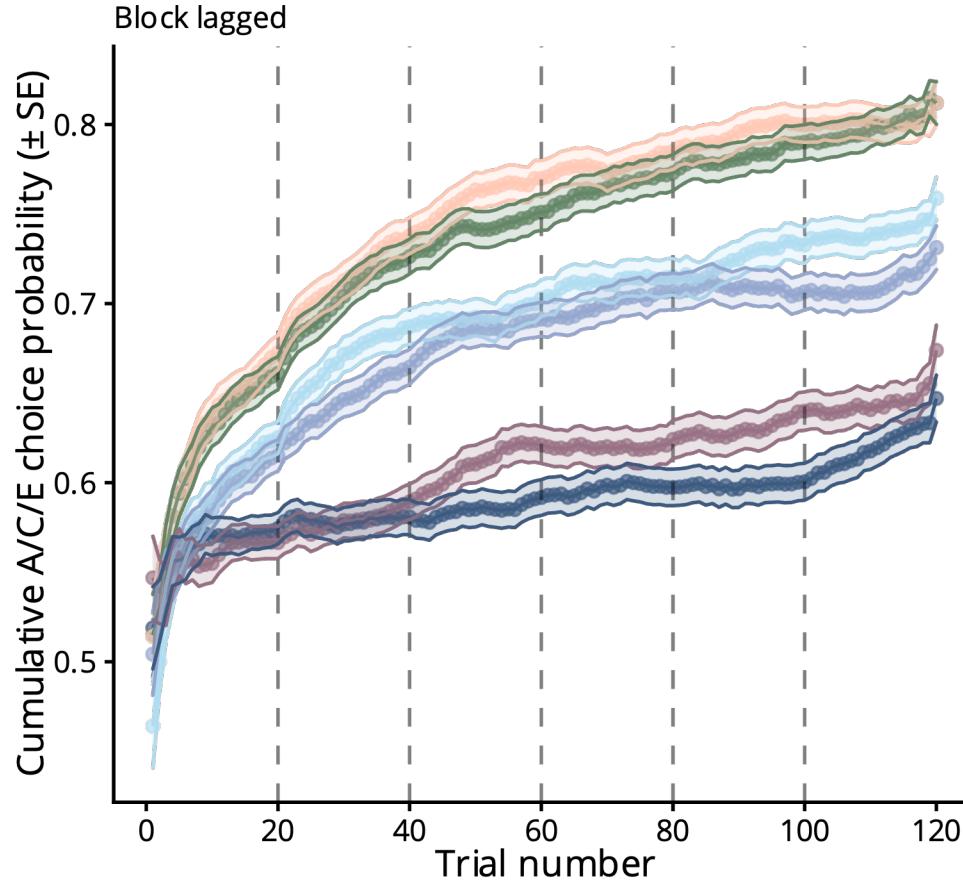
Why the dorsal mid-insula? (Hypothesis)

- Agranular – anterior insula
- Dysgranular – mid-insula
- Granular – posterior insula





How does psychological therapy work?

Training performance**Training performance**