Computational approaches to avoid relapse after antidepressant discontinuation

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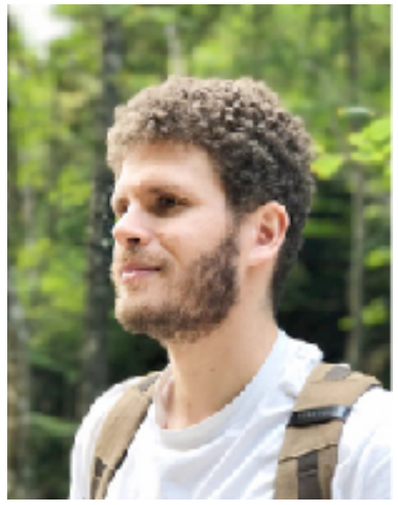
- Marius Tröndle
- Erich Seifritz
- **Klaas Enno Stephan**
- **Henrik Walter**
- Julia Wenzel





Molecular Imaging Network Zurich

Deutsche Forschungsgemeinschaft

Depression - a chronic disorder

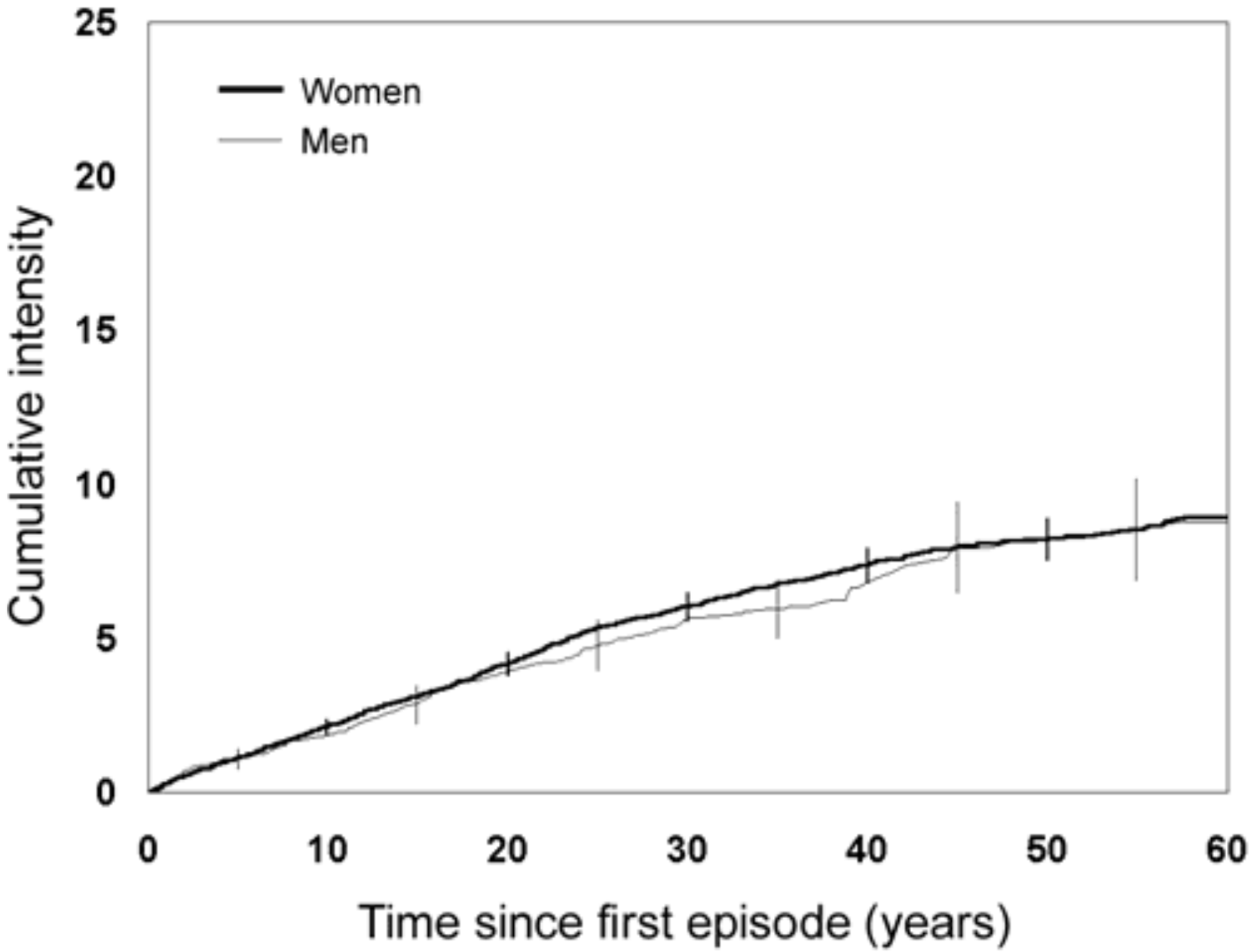
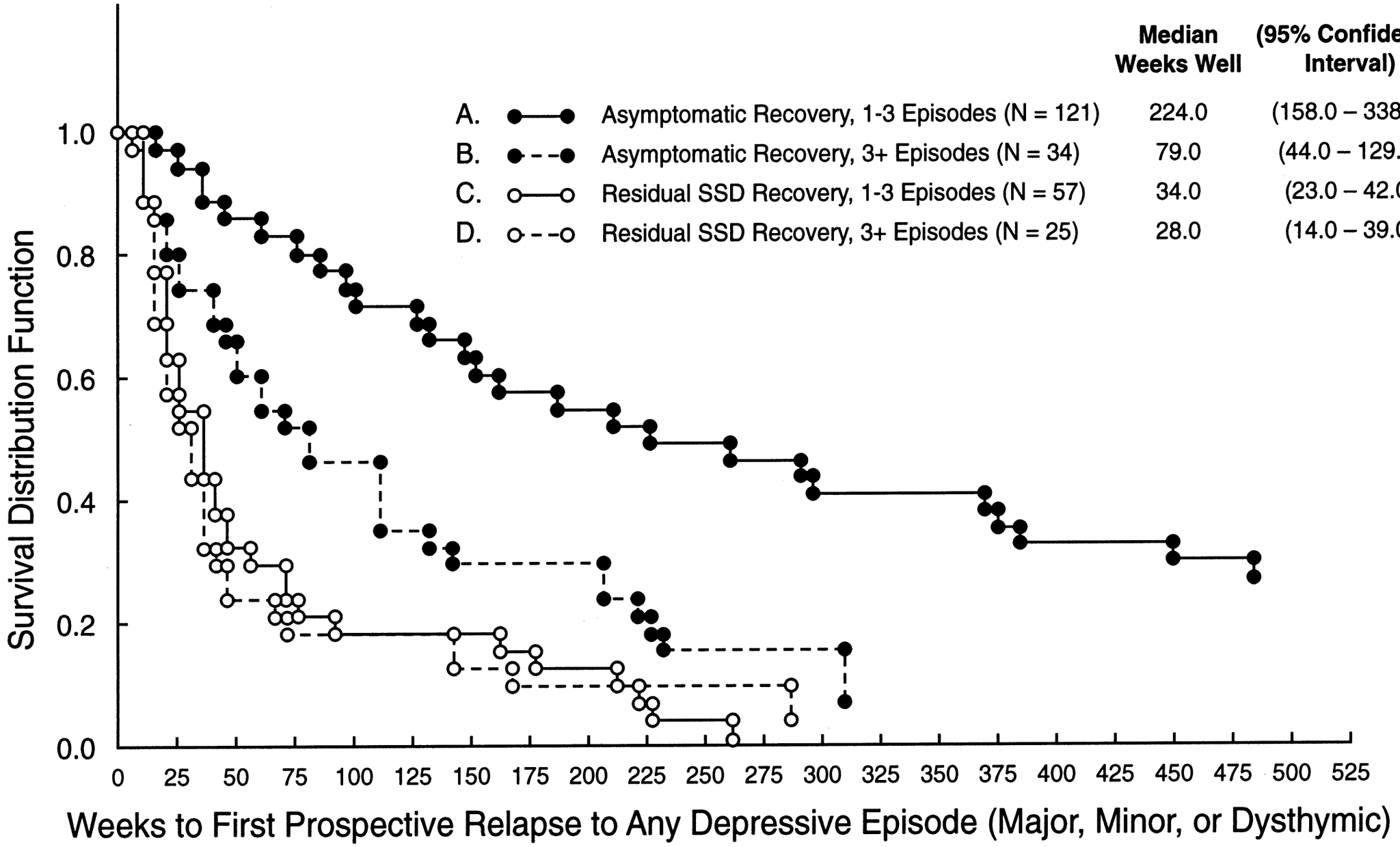


Fig. 4 Major depressive disorders

Angst et al., 2003

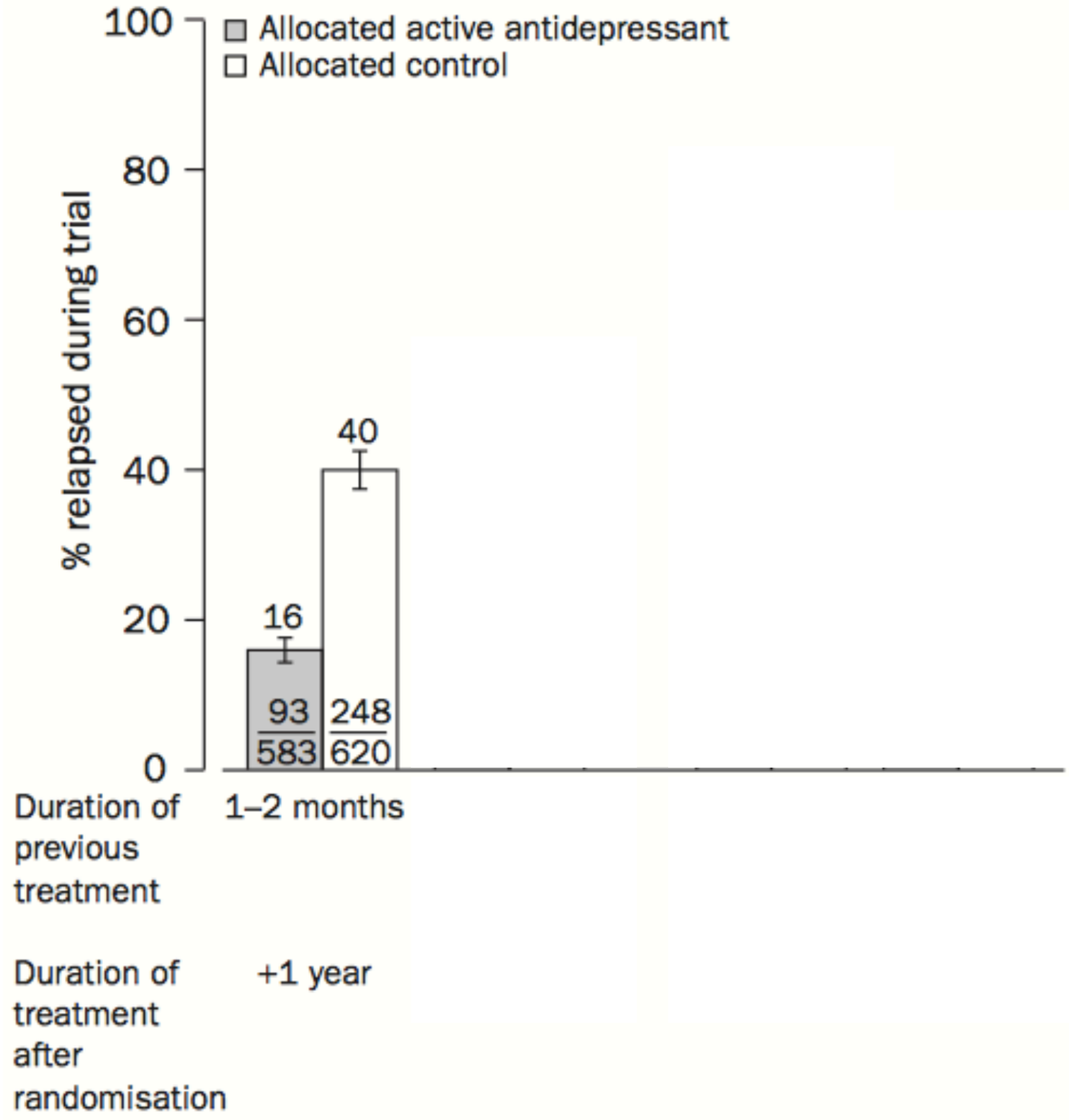
Relapse



Subsyndromal medication > Symptom-free medication

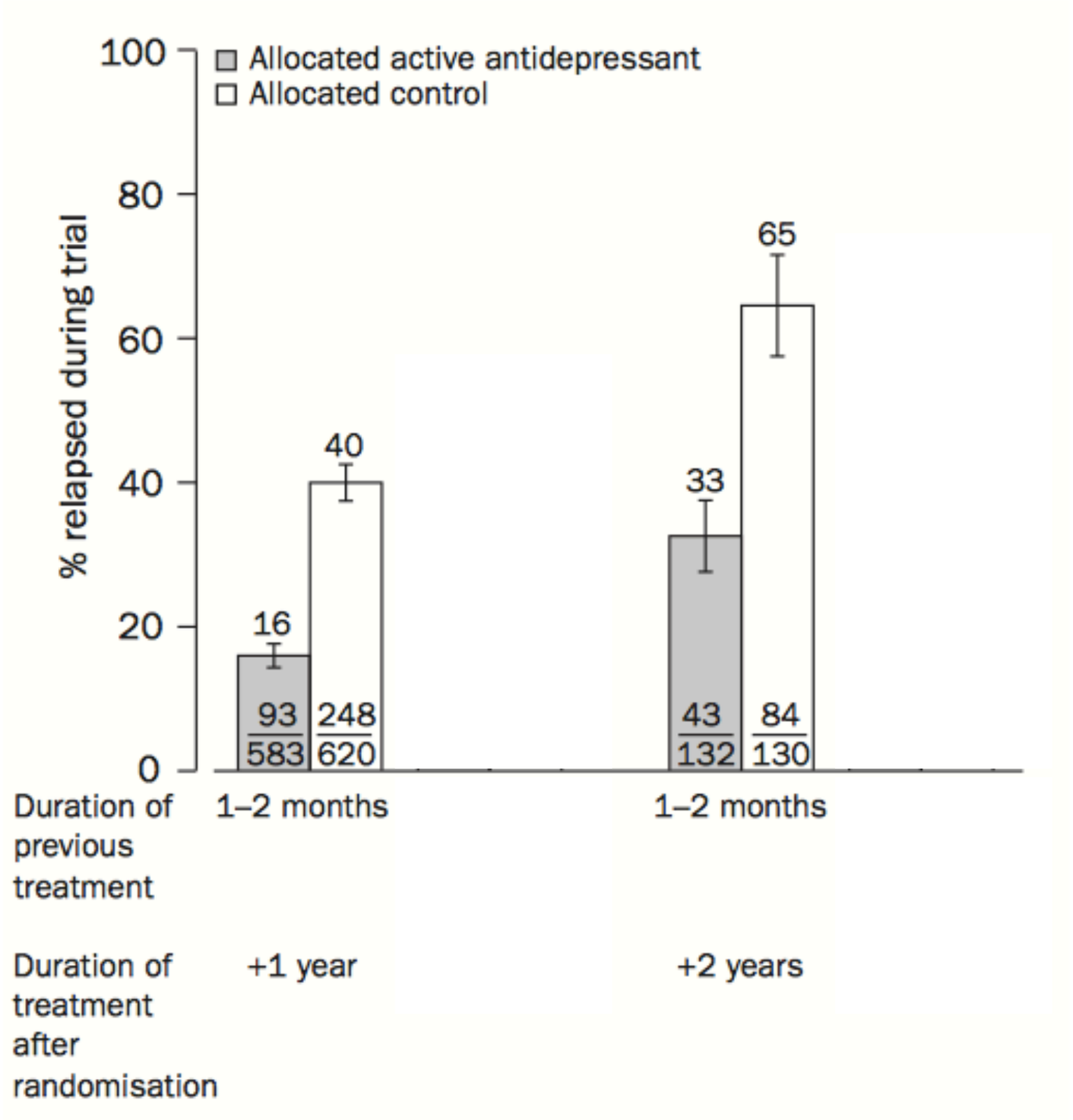
Judd et al. 1998

Antidepressant discontinuation



Geddes et al., 2003; Viguera et al., 1998

Antidepressant discontinuation



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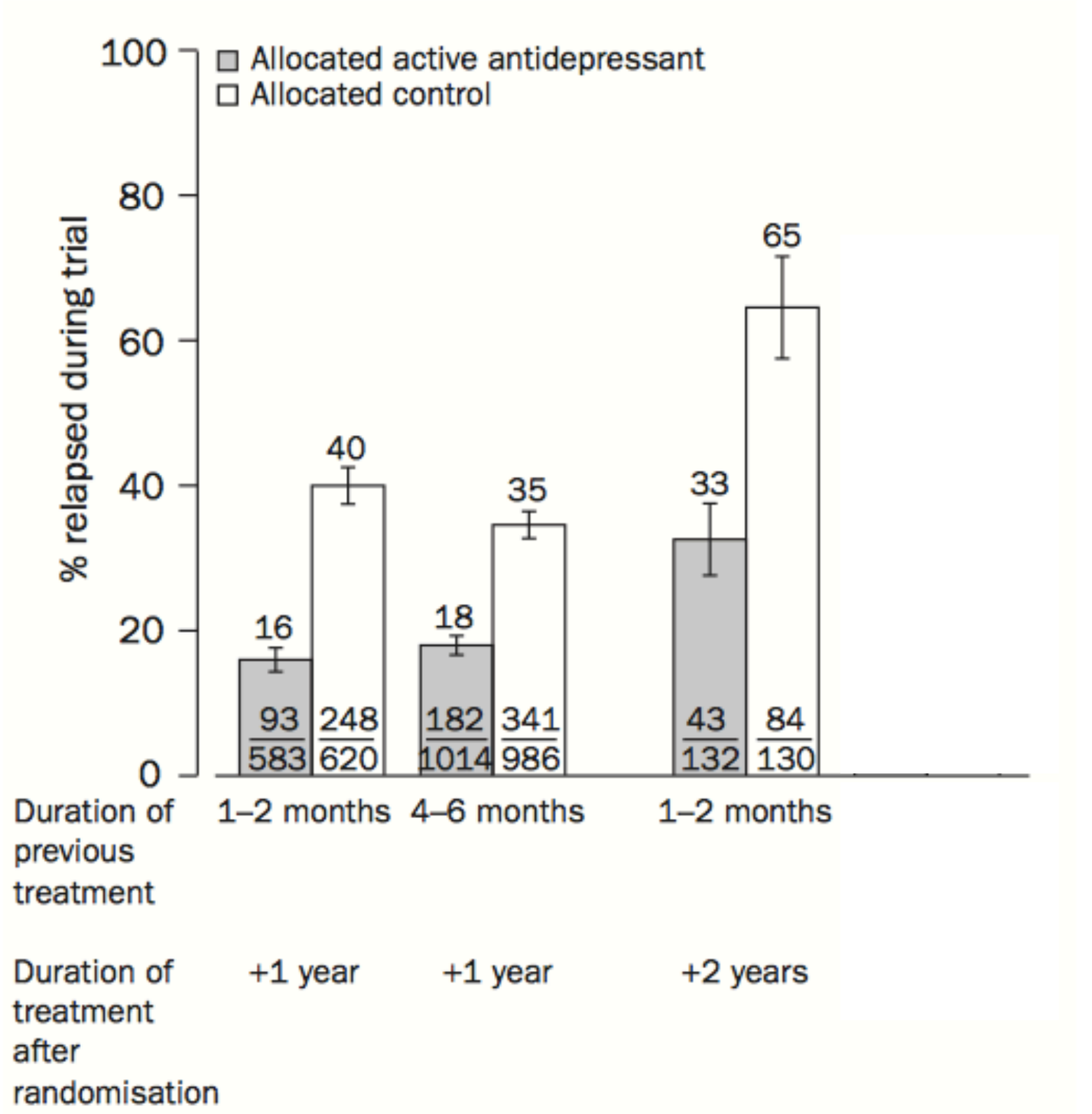

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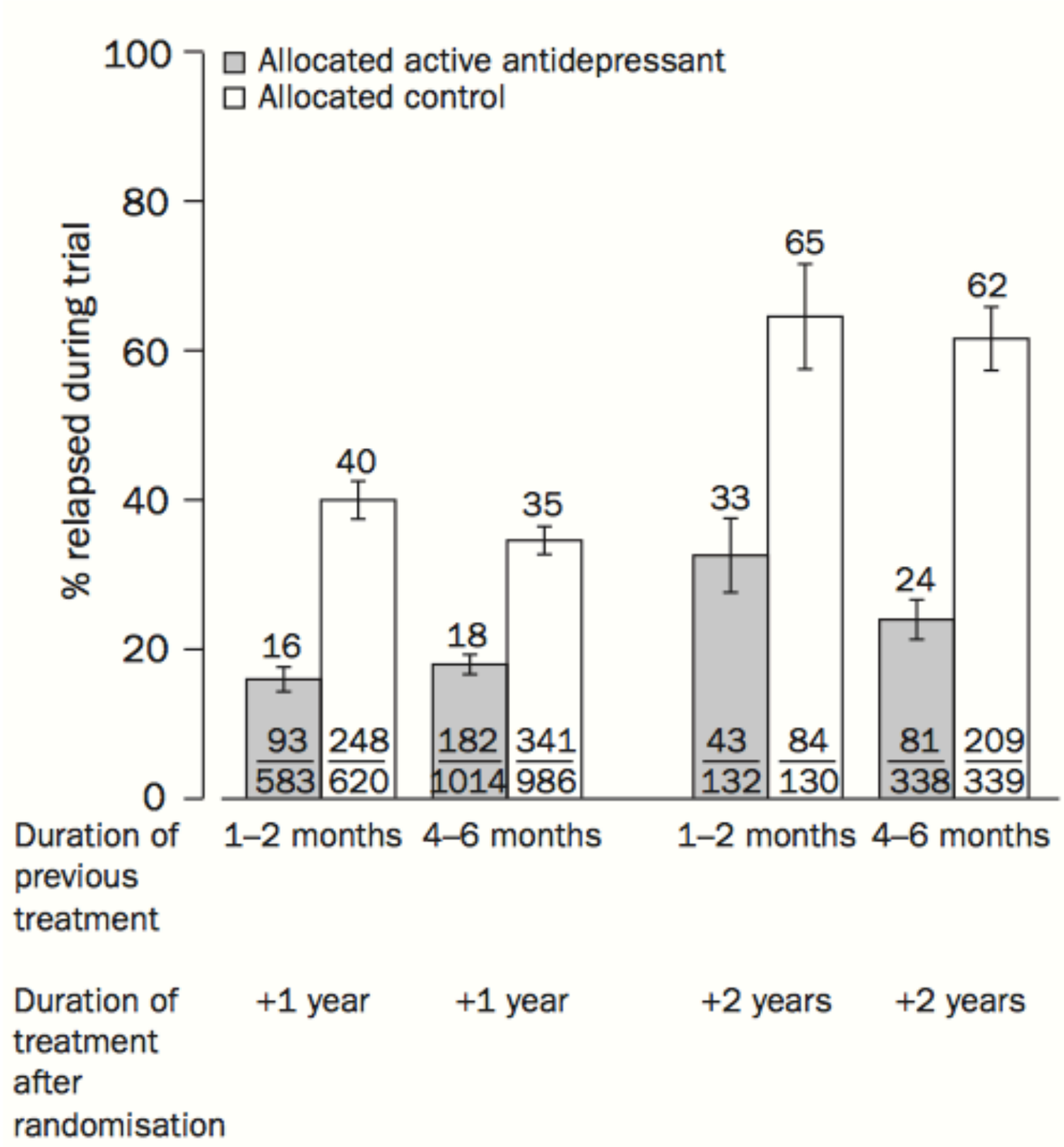
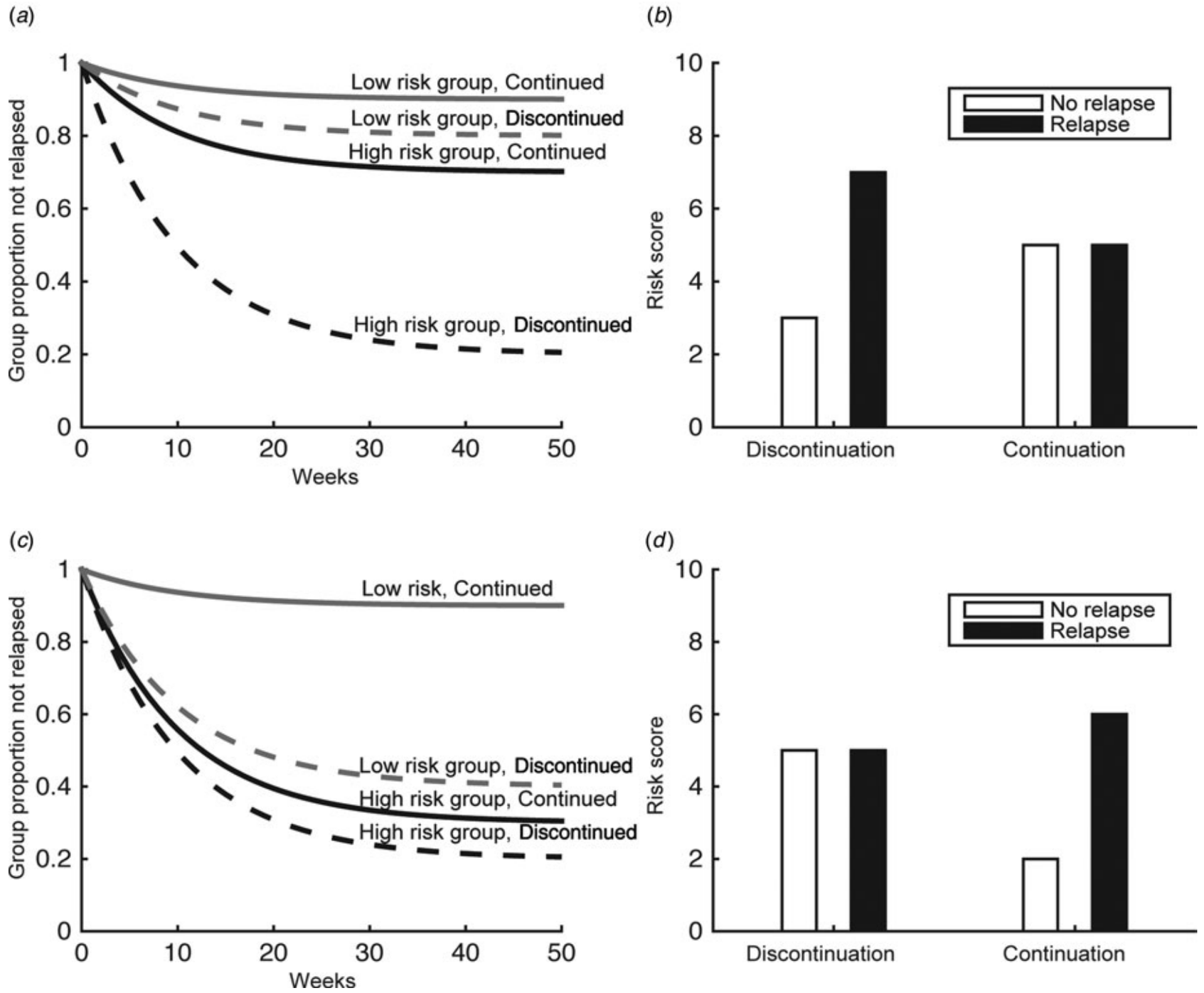


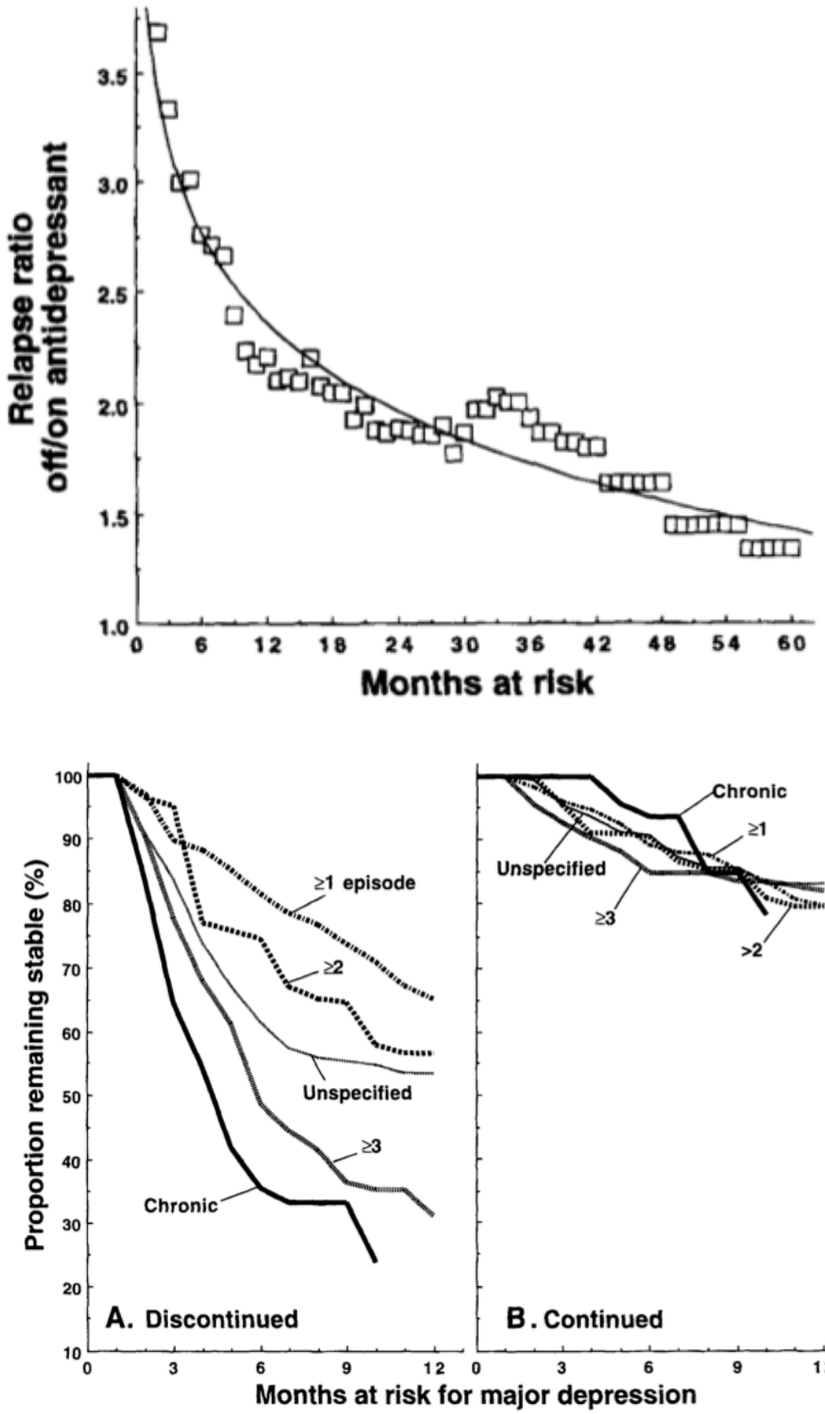
Geddes et al., 2003; Viguera et al., 1998

Risk scores



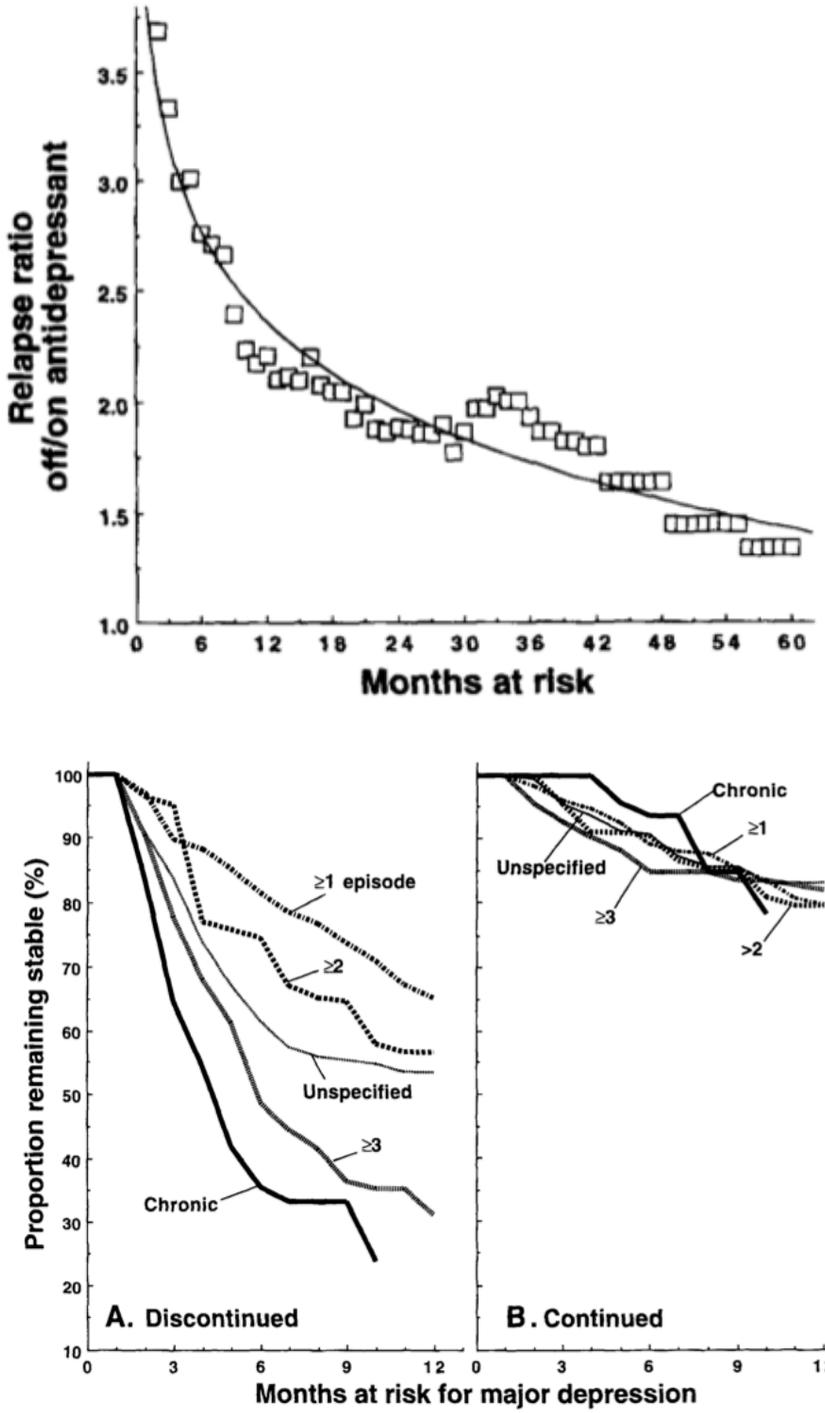
Berwian et al., 2017 Psychol Med

Number of episodes



Viguera et al., 1998; Kaymaz et al. 2008

Number of episodes



Data Synthesis: Data were collected from 30 trials with 4890 participating patients. The overall reduction of relapse risk in the maintenance phase was highly significant for both SSRIs (OR = 0.24, 95% CI = 0.20 to 0.29) and TCAs (OR = 0.29, 95% CI = 0.23 to 0.38) over 1 year of follow-up of maintenance treatment. The prophylactic effect appeared to be constant over the length of the continuation phase. Recurrent episode patients experienced less protection from antidepressants over the maintenance phase (OR = 0.37, 95% CI = 0.31 to 0.44) than single episode patients (OR = 0.12, 95% CI = 0.06 to 0.26).

Conclusions: Antidepressants robustly reduce relapse risk in the maintenance phase, regardless of a number of clinical and pharmacologic factors. There is evidence, however, that with increasing number of episodes, patients develop a relative resistance against the prophylactic properties of antidepressant medication.

Viguera et al., 1998; Kaymaz et al. 2008

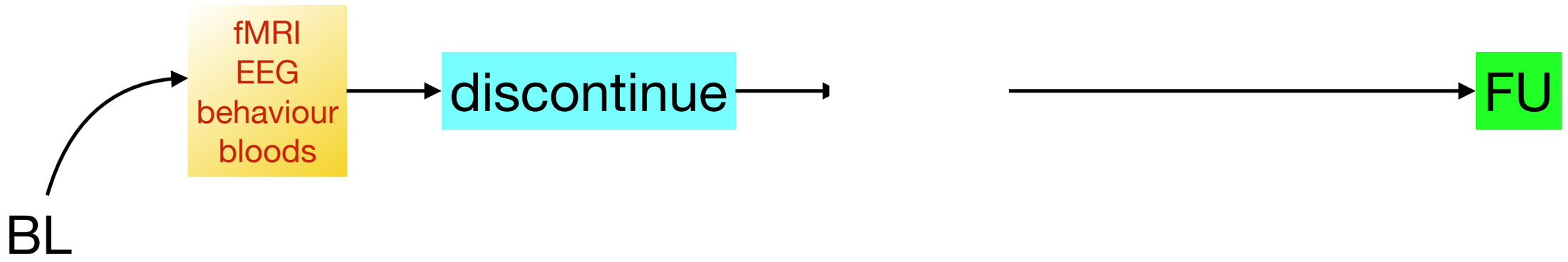
Systematic review

- Only 13 looked at predictors of relapse after discontinuation

Predictor	Number of studies with sign. predictor	Number of studies without sign. predictor
Demographics		
Age	0	3
Gender	0	5
Race and ethnicity	1	0
Symptoms		
Neurovegetative symptoms	1	1
Residual Symptoms	0	4
Residual Symptoms: phobic anxiety	0	1
Clinical predictors		
Chronicity and age of onset	0	3
Severity at onset	0	2
Number of prior episodes	0	4
Subtype	1	1
Response pattern	**2**	1
Comorbidities		
Anxiety	1	1

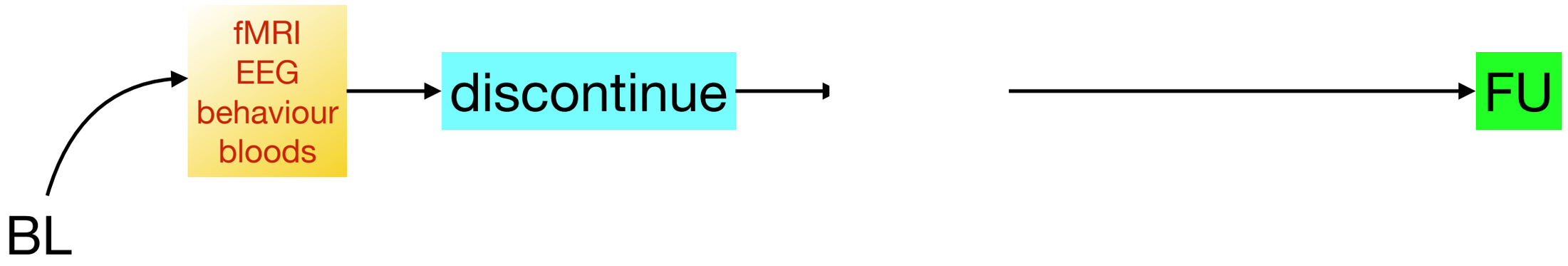
Berwian et al., 2016

AIDA Study



AIDA Study

- MDD who have remitted on ADM



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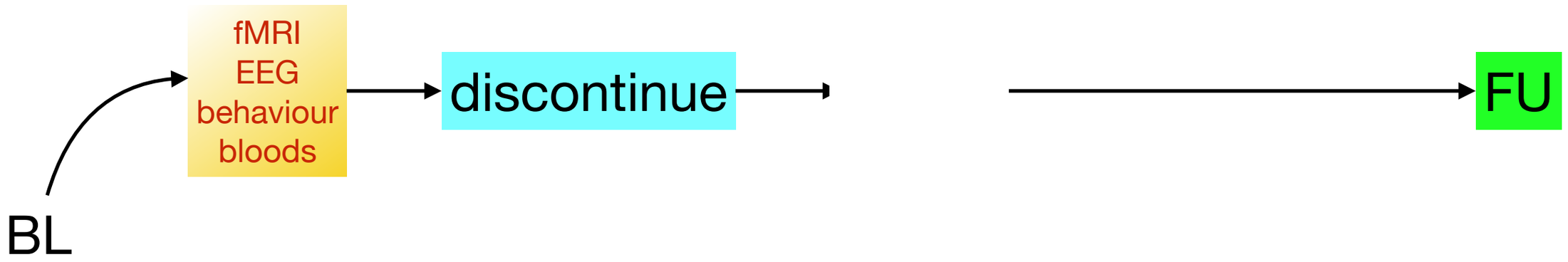

- Relapse associations & prediction (T1)

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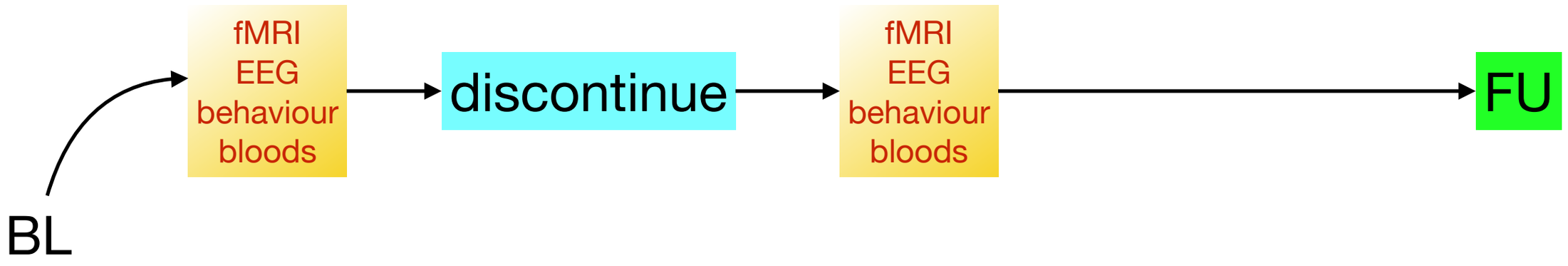

- Relapse associations & prediction (T1)
- Effect of discontinuation (T x group)

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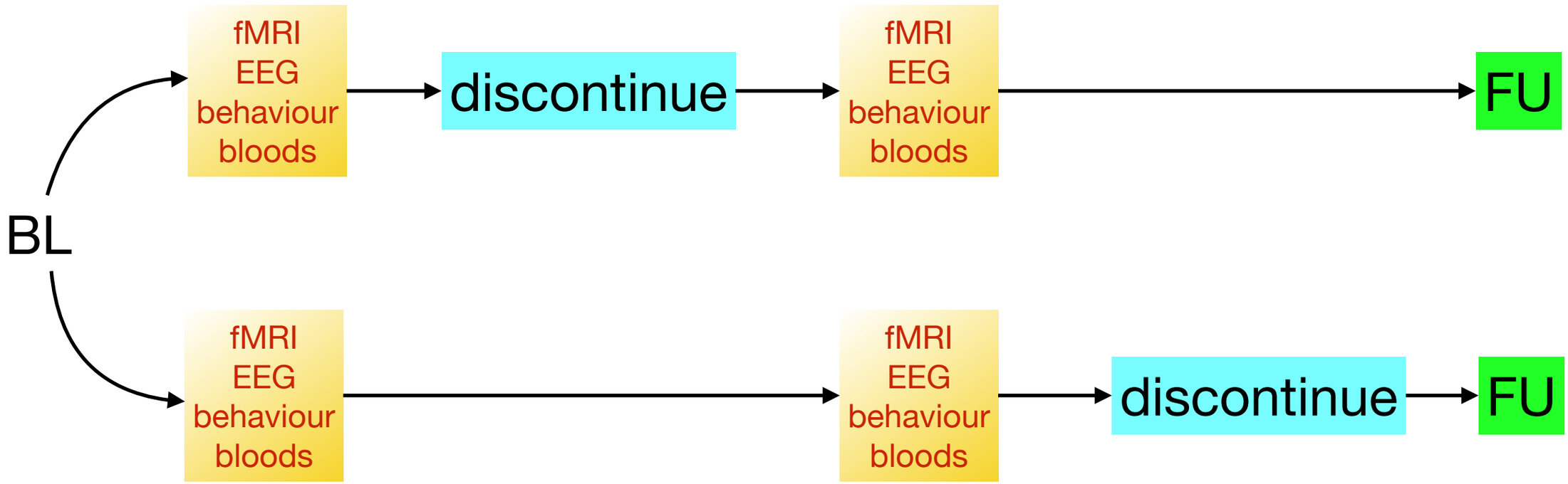

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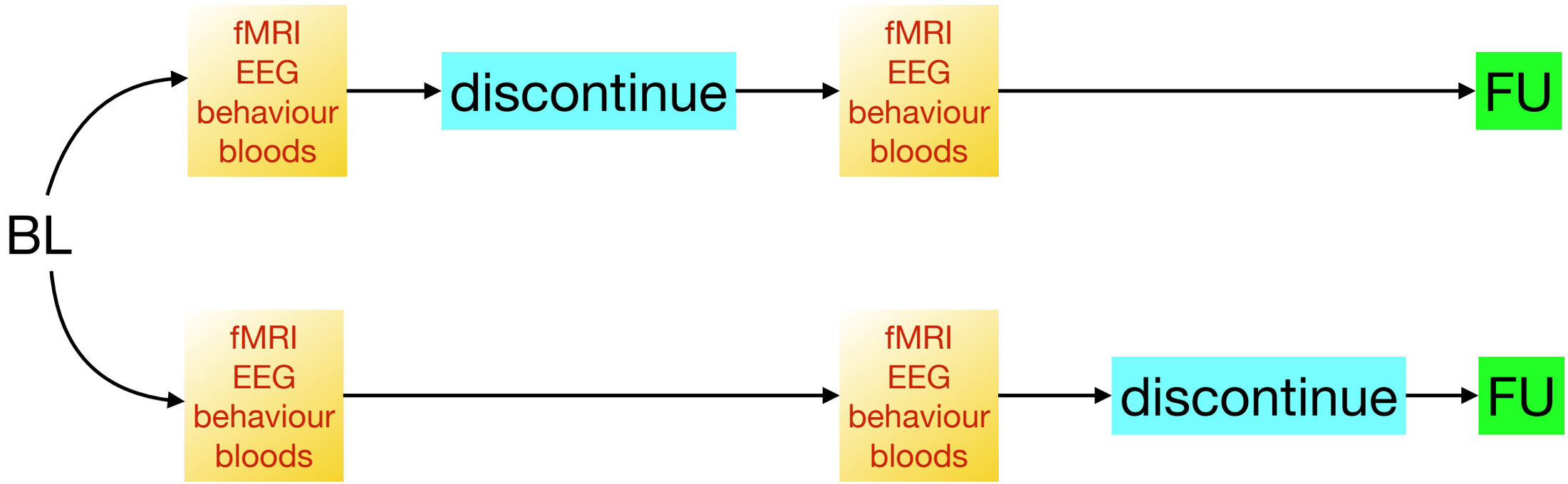

- Relapse associations & prediction (T1)
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- Effect of discontinuation on relapse (T x group x relapse)

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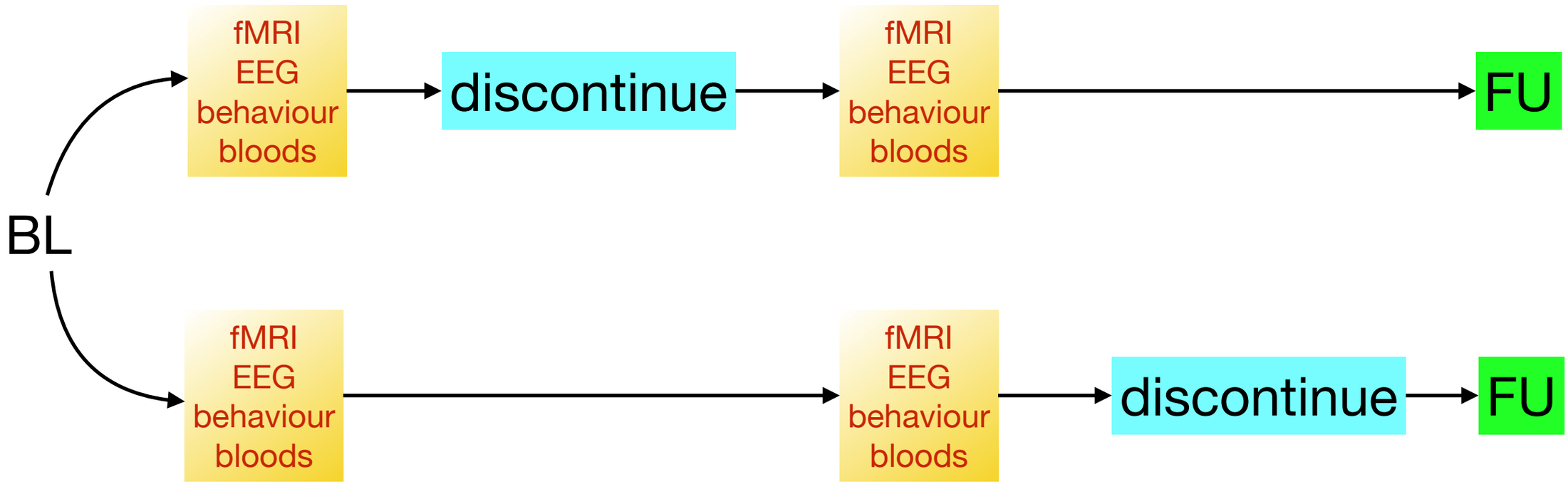
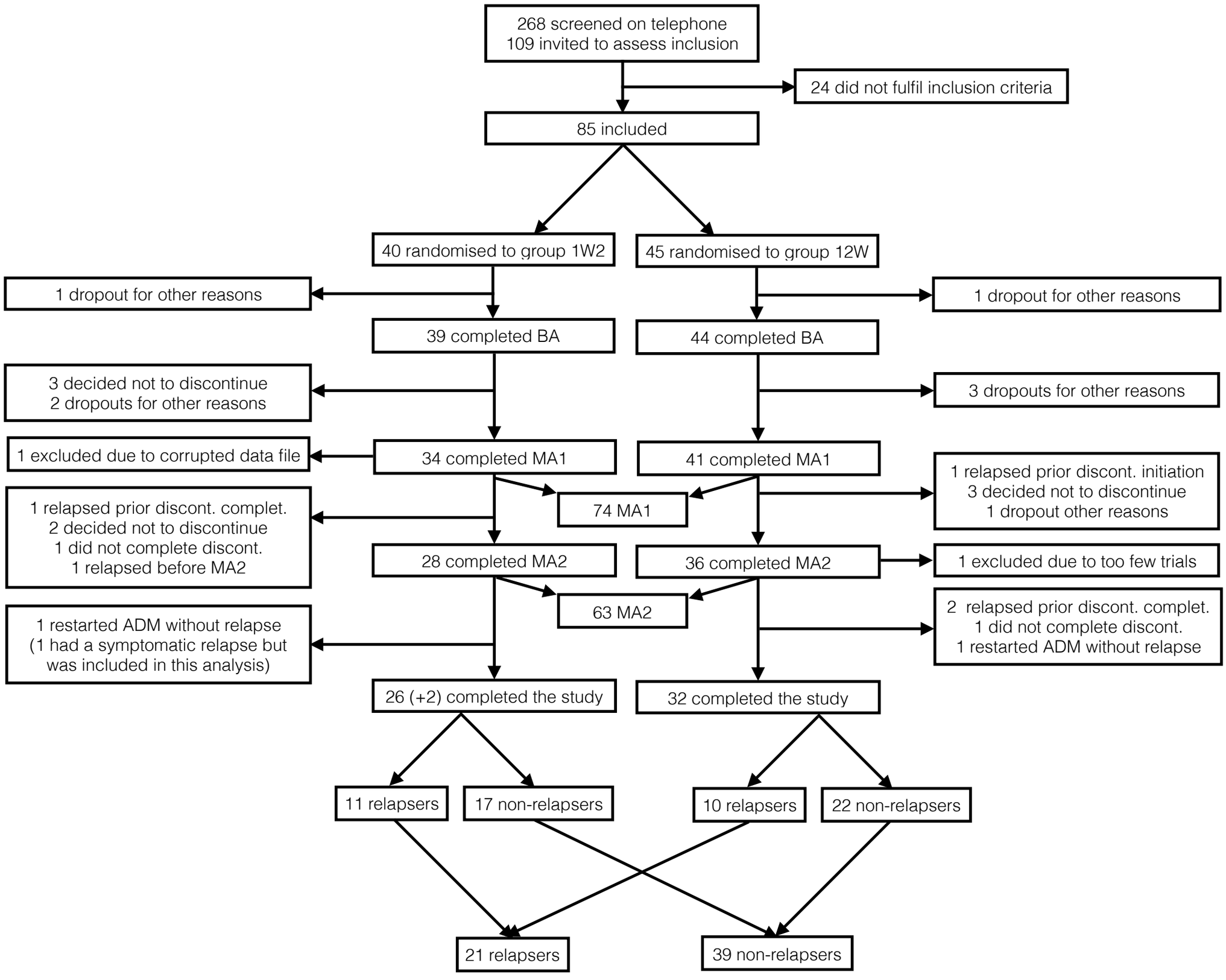
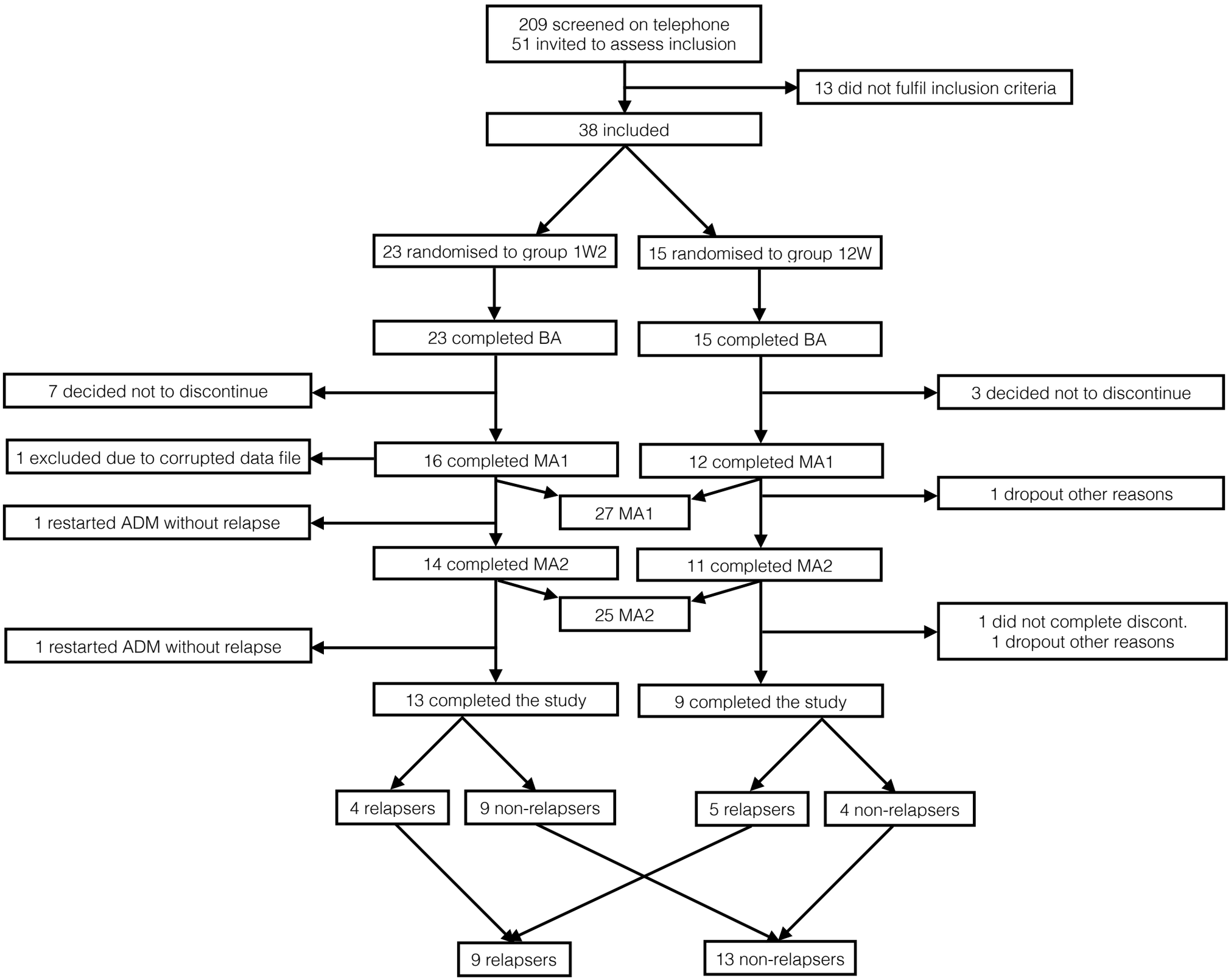


- Relapse associations & prediction (T1)
- Effect of discontinuation (T x group)
- Effect of discontinuation on relapse (T x group x relapse)
- Disease effect - T1 pat vs HC

Main sample - Zurich

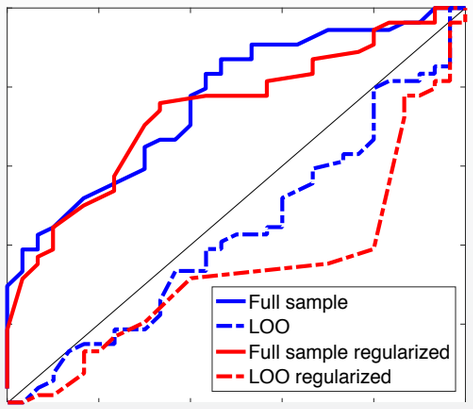


Second sample - Berlin

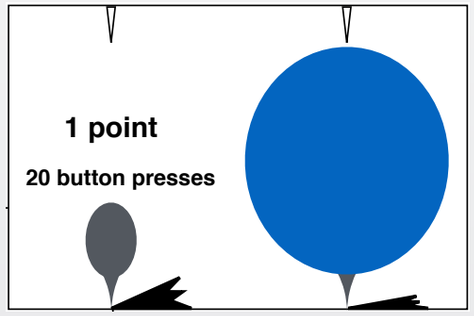


Outline

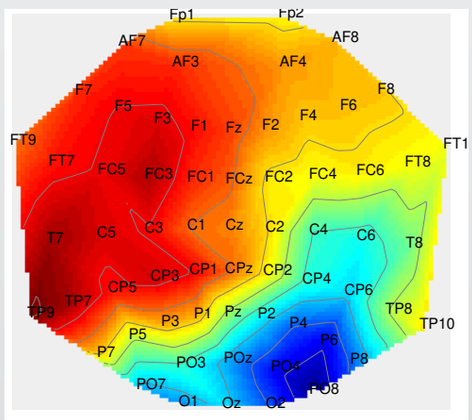
Prediction



Clinical variables

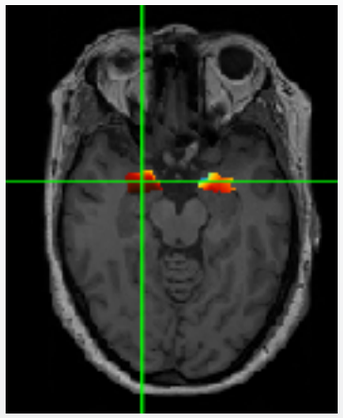


Effort

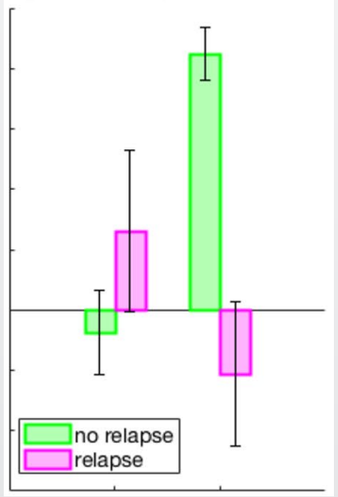


EEG Emotion reactivity

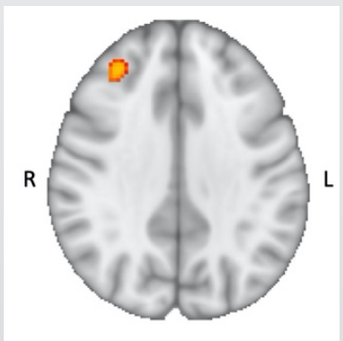
Mechanism



Amygdala Reactivity

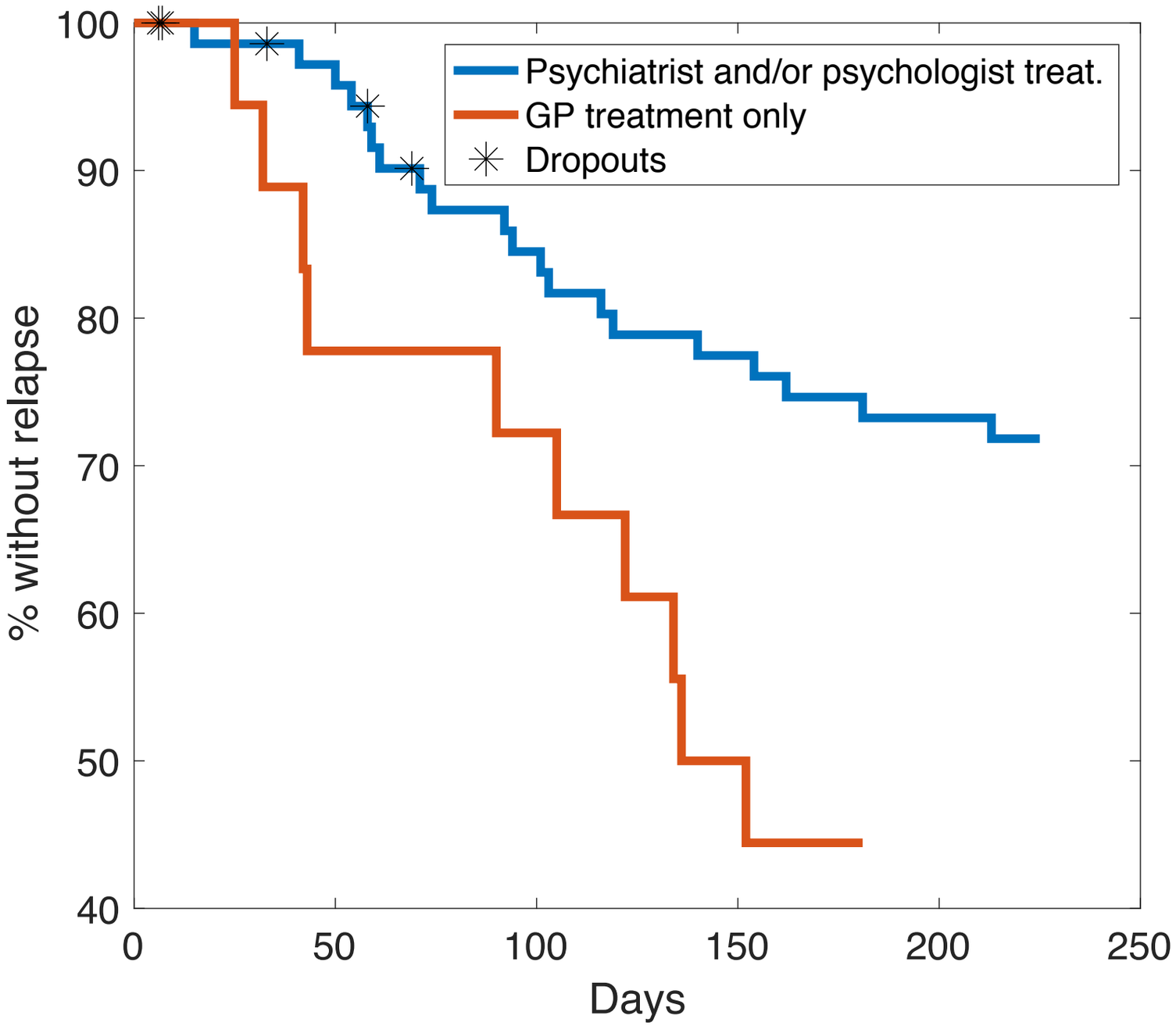


dlPFC-PCC Connectivity

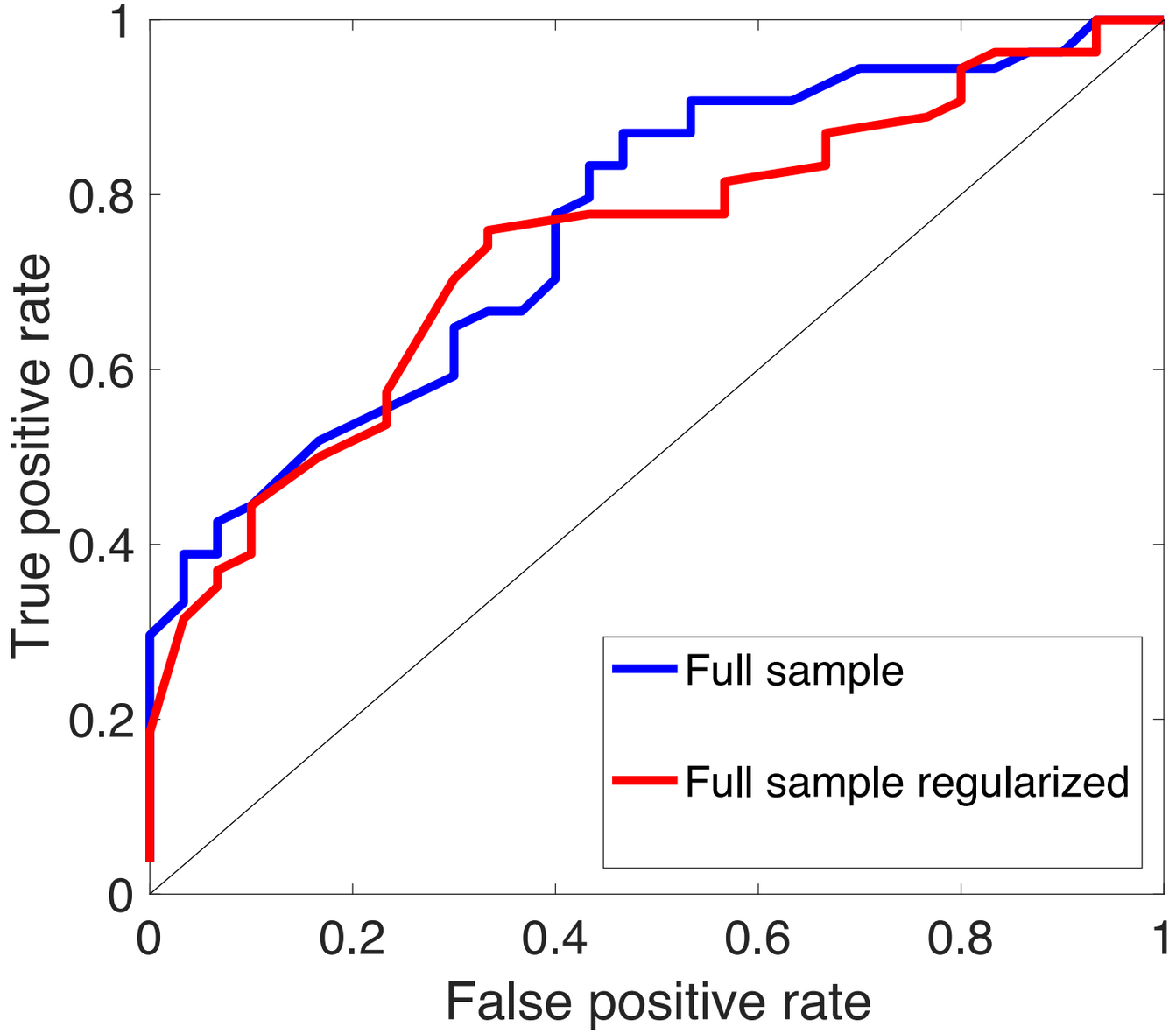


Memory

Prediction: treatment provider



Predicting Relapse



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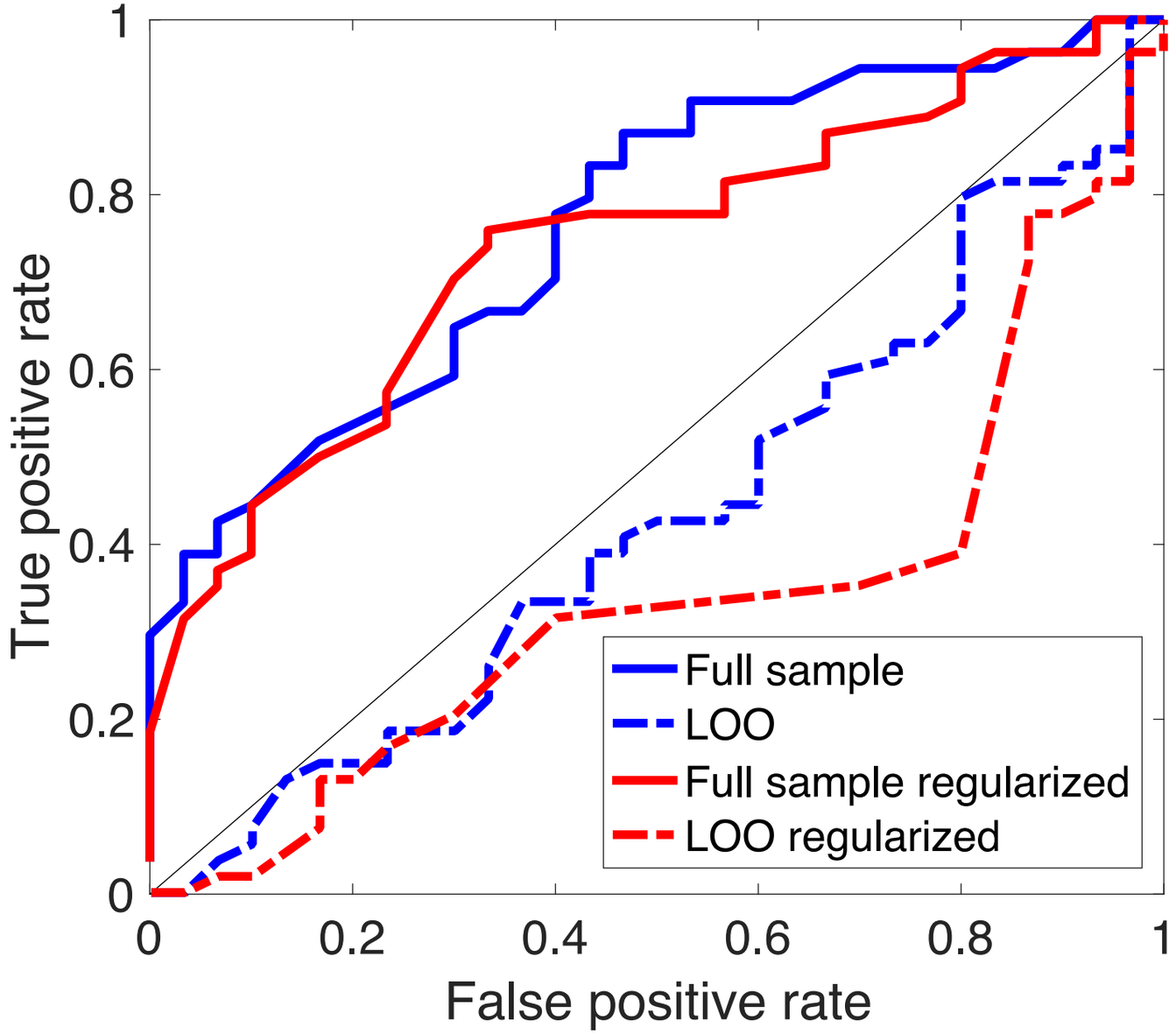
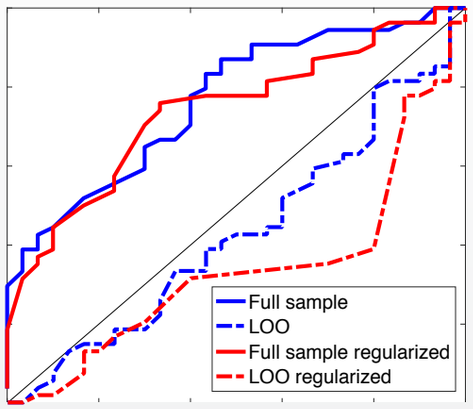


Outline

Prediction



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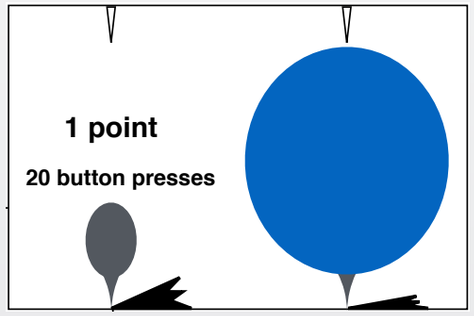
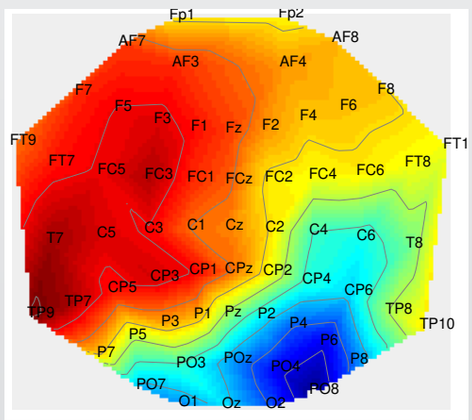


Effort



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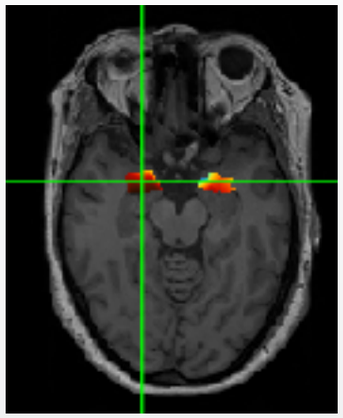

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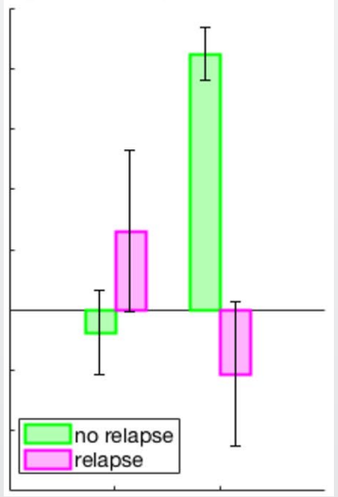

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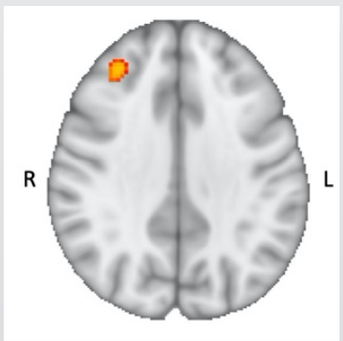

Memory

MDD in ICD-10

- **depressed mood** to a degree that is definitely abnormal for the individual, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least 2 weeks.

- **loss of interest or pleasure** in activities that are normally pleasurable;

- **decreased energy** or increased fatiguability.

- Very high negative predictive value

TABLE 1. Sensitivity, Specificity, OR, PPV and NPV of Alternative Symptom Criteria for Major Depressive Disorder ($N = 1523$)[a]

Symptom	Sensitivity %	Specificity %	OR	PPV %	NPV %
Depressed mood	92.9	82.4	61.2	86.3	90.6
Loss of energy or diminished drive	**97.6**	**55.3**	**50.1**	**72.3**	**95.0**
Loss of energy	87.2	68.4	14.8	76.8	81.8
Diminished drive	**88.2**	**69.9**	**17.3**	**77.8**	**83.2**
Diminished interest/pleasure or diminished drive	**94.2**	**66.4**	**32.2**	**77.0**	**90.6**
Diminished interest/pleasure	80.6	87.8	29.7	88.7	79.1
Diminished drive	**88.2**	**69.9**	**17.3**	**77.8**	**83.2**

- At the heart of psychotherapy
  - Behavioural activation

McGlinchey et al., 2006

Anhedonia

Individuals may report feeling less interested in hobbies, “not caring anymore”, or not feeling any enjoyment in activities that were previously considered pleasurable […]. Family members often notice social withdrawal or neglect of pleasurable avocations (e.g. a formerly avid golfer no longer plays, a child who used to enjoy soccer finds excuses not to practice). In some individuals there is a significant reduction from previous levels of sexual interest or desire.

DSM-5, APA

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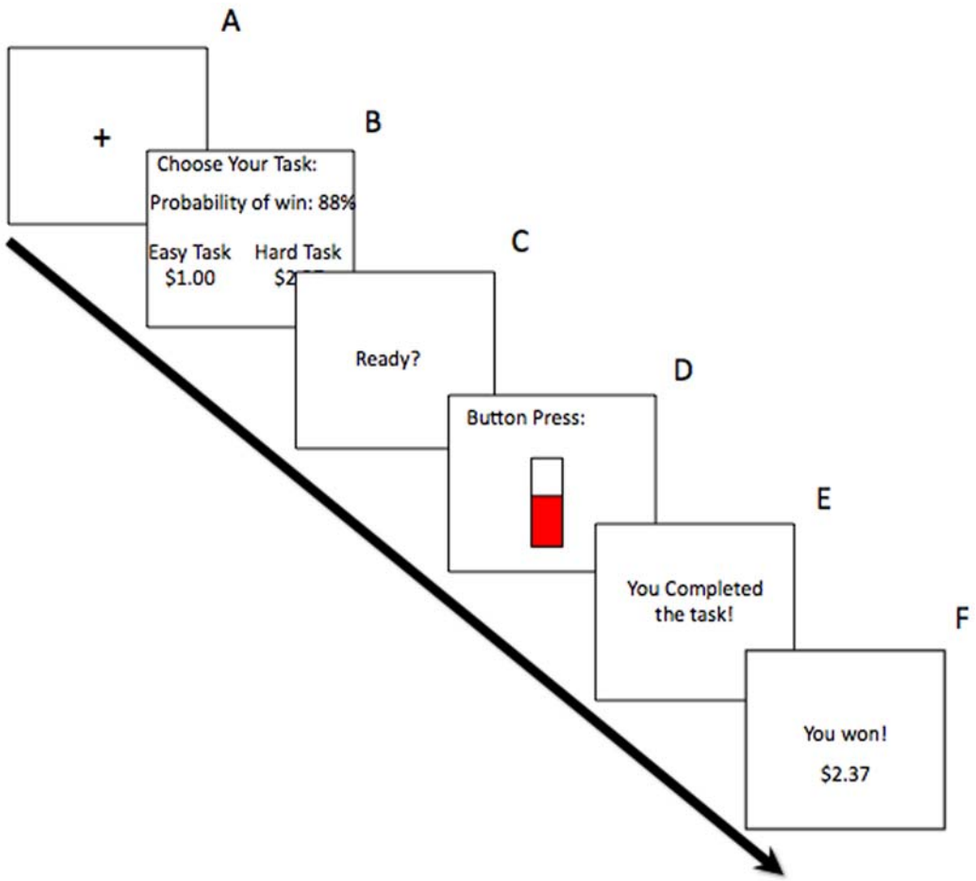
DSM-5, APA

Effort and reward in MDD



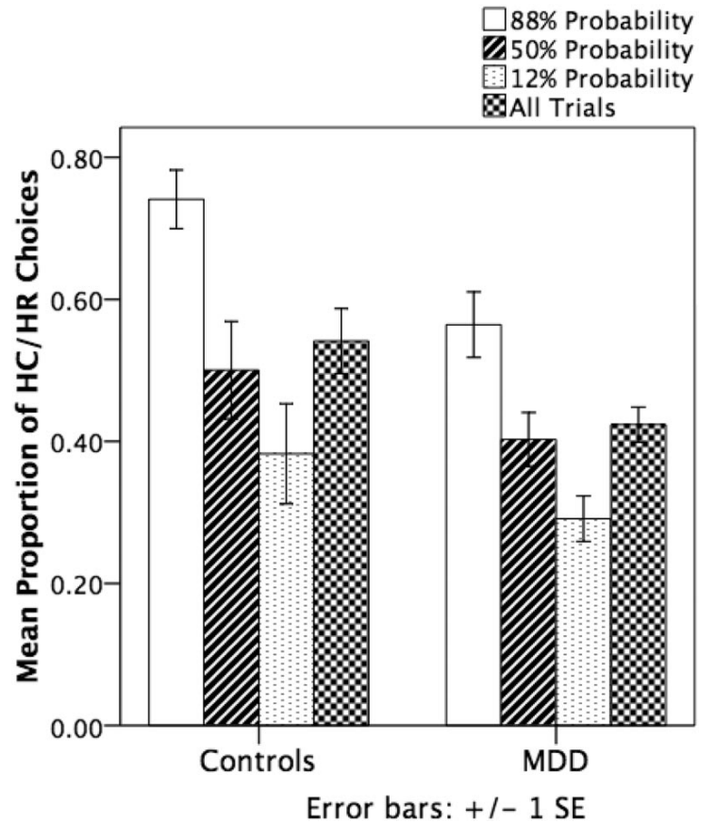


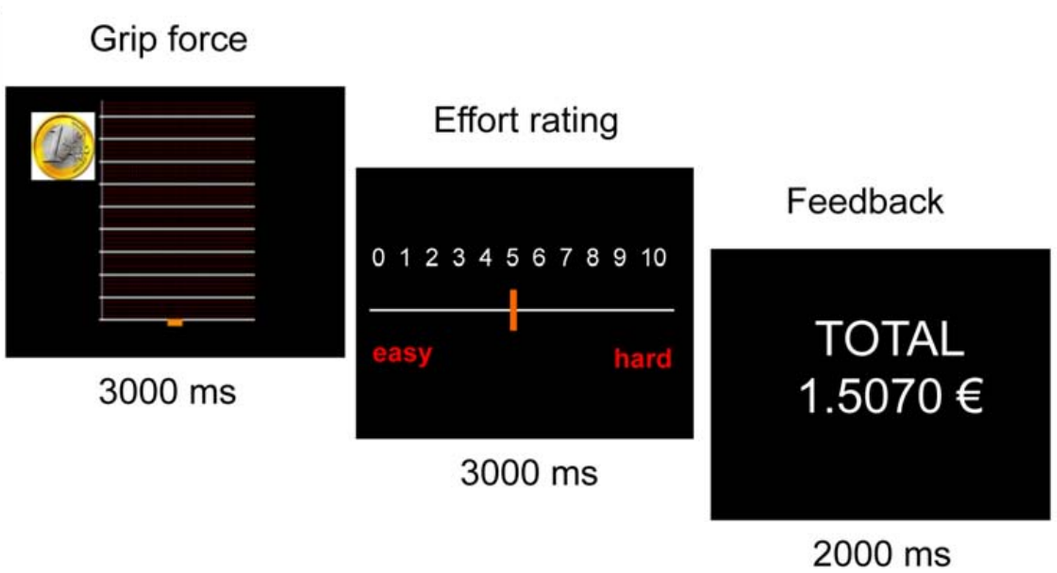
Table 3. Correlations between self-report measures and proportion of hard-task choices.

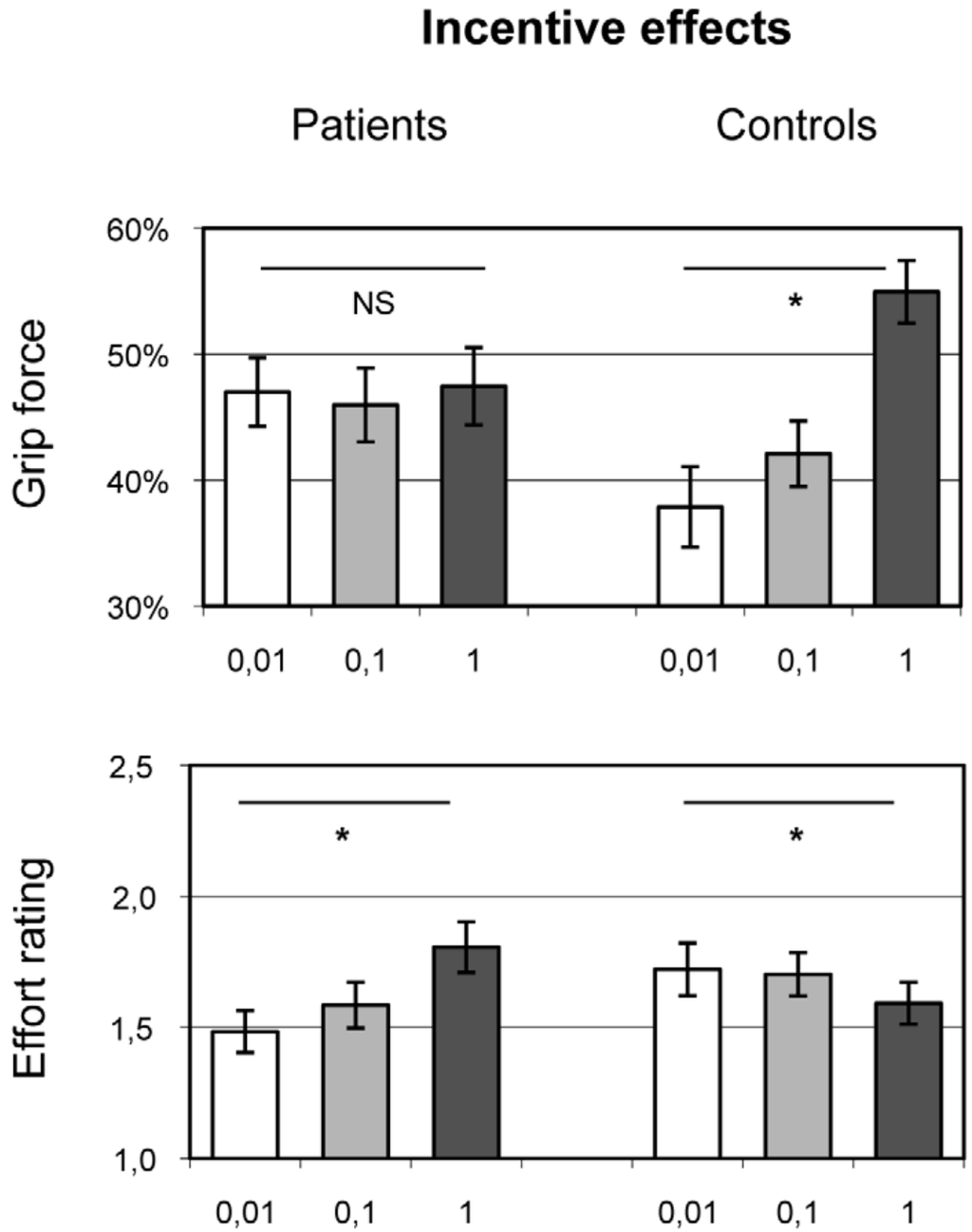
Variable	Proportion of Hard Task Choices		
	88%	50%	12%
Chapman Anhedonia Scales	−0.05	−.28*	−0.22
Beck Depression Inventory (BDI)	−0.29*	−0.16	0.11
BDI - Anhedonia Subscale	−0.31*	−0.22	0.09
BDI - Melancholy Subscale	−.34*	−.34*	0.05
SHAPS	0.16	0.13	−0.01
PANAS Postive Affect (PA)	−0.08	−0.19	−0.22
PANAS Negative Affect (NA)	0.03	−0.32*	−0.05

*$p<.05$. With $N=60$, correlations as low as $r=.36$ have 80% power.
doi:10.1371/journal.pone.0006598.t003

Treadway et al., 2009 PLoS One, Treadway et al., 2012 J Abnorm Psychol

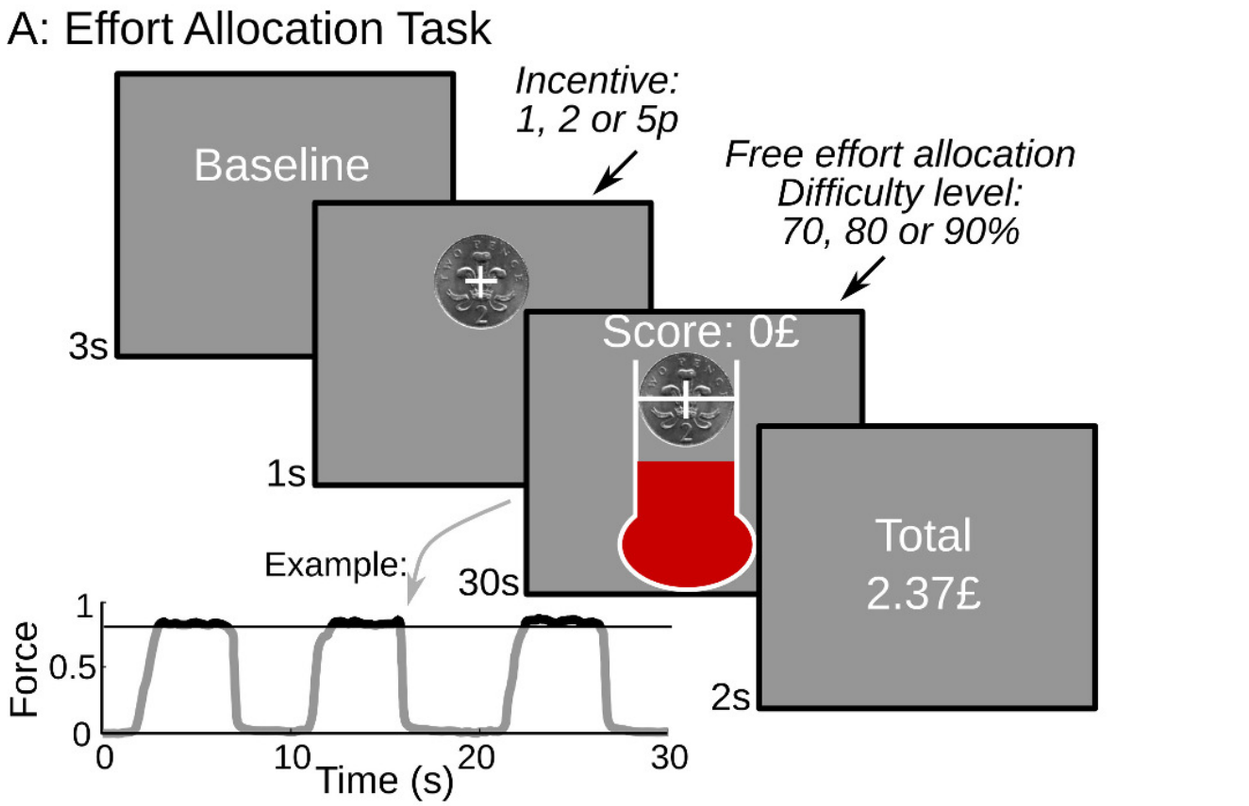
MDD affects subjective effort

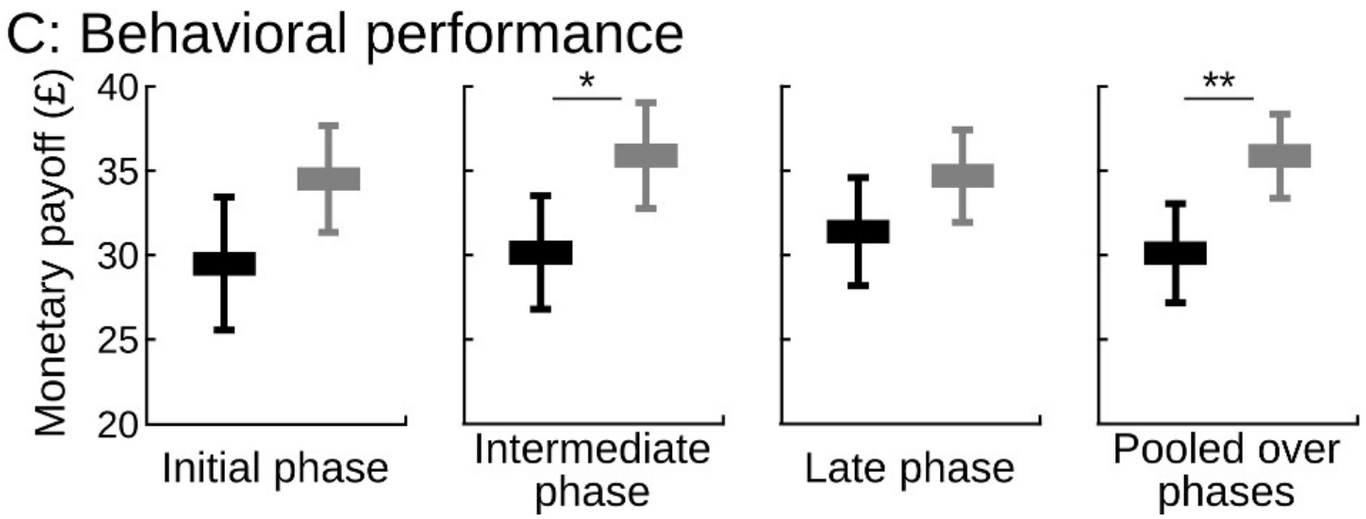




Clery-Melin et al. 2011 PLoS One

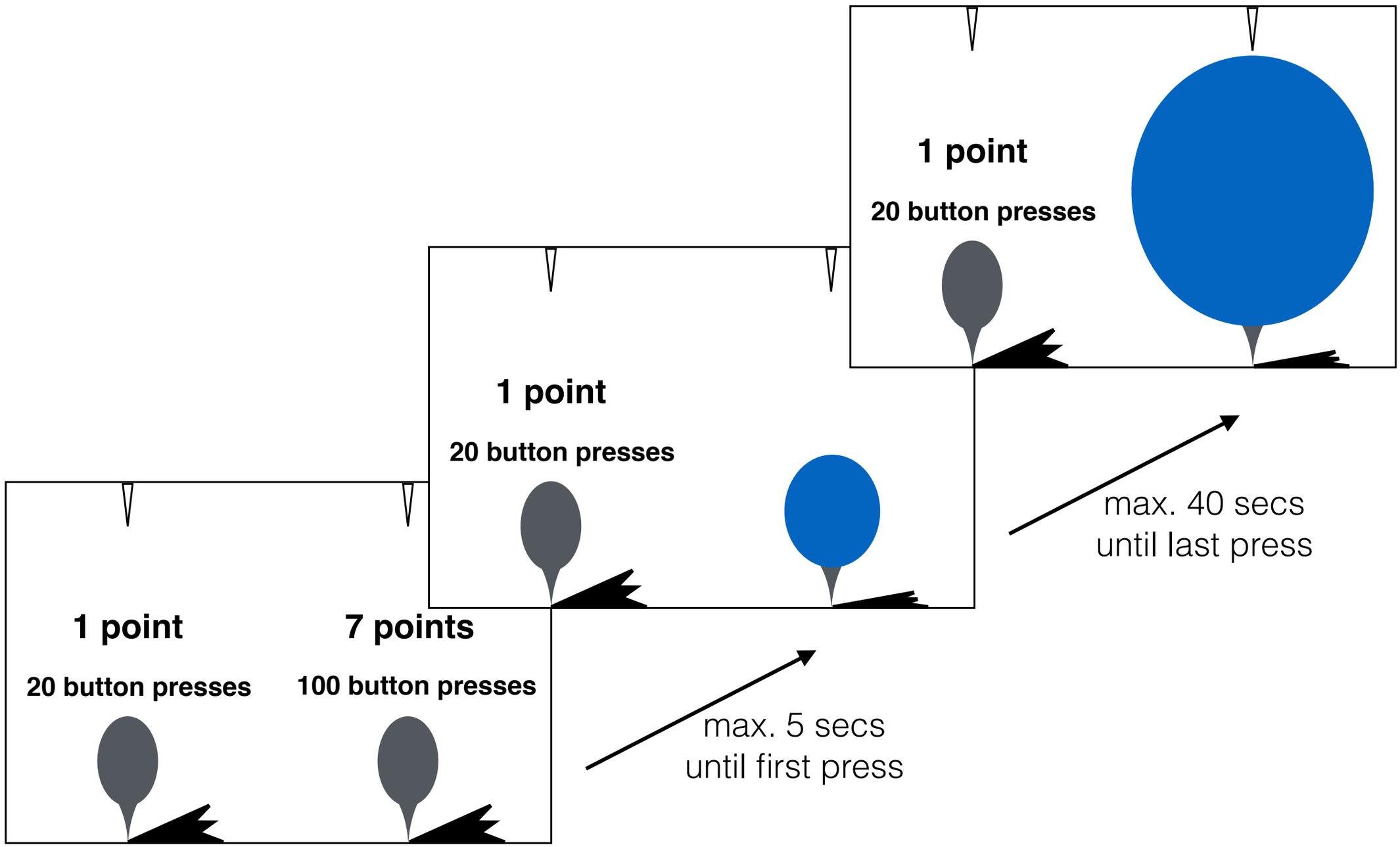
SSRIs and effort





Meyniel et al., 2015

Effort for rewards



After Gold et al., 2012 Arch Gen Psych

Raw choice data

Patients n=73
Controls n=33

Berwian et al., JAMA Psych 2020

Raw choice data

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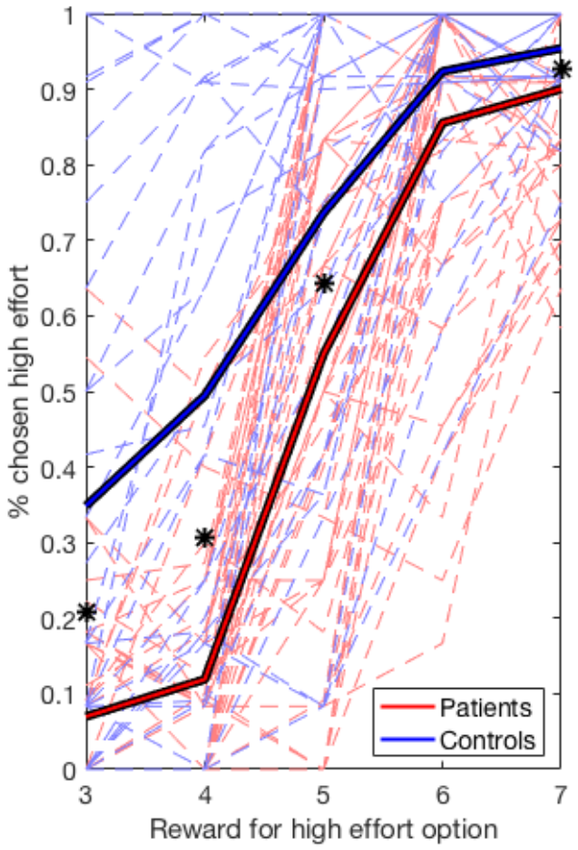
Controls n=33

p<0.001



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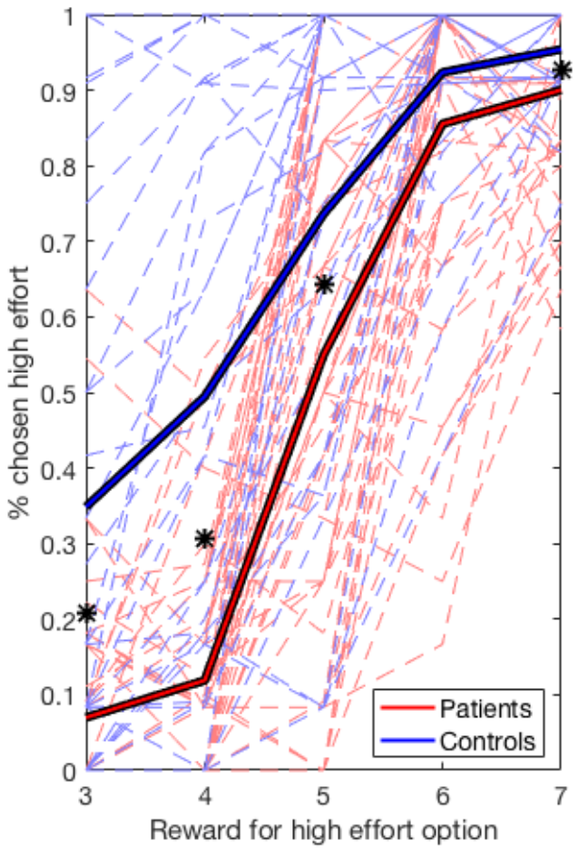
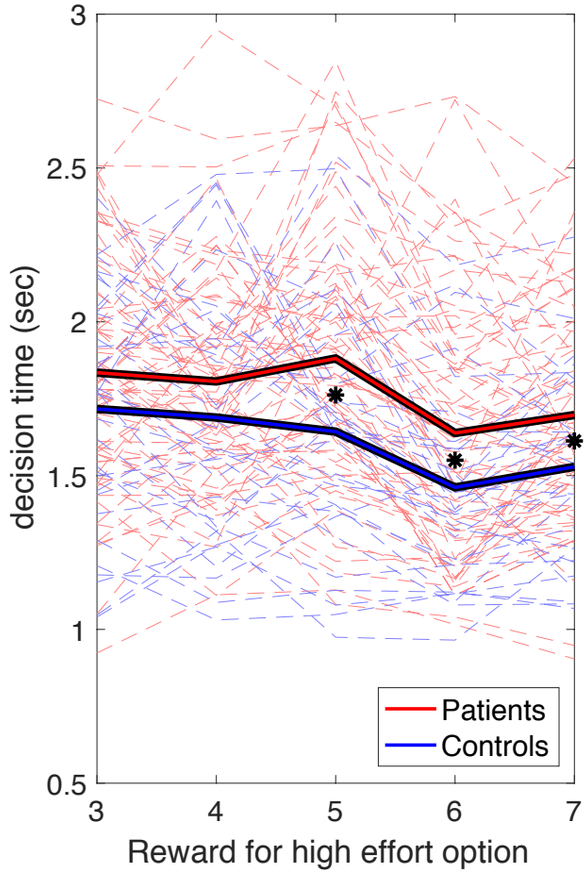


p<0.015



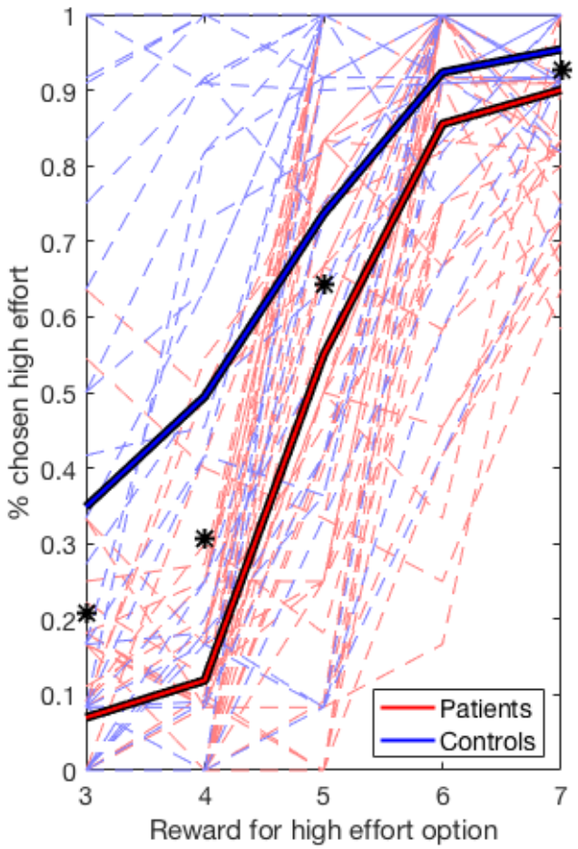
Berwian et al., JAMA Psych 2020

Raw choice data

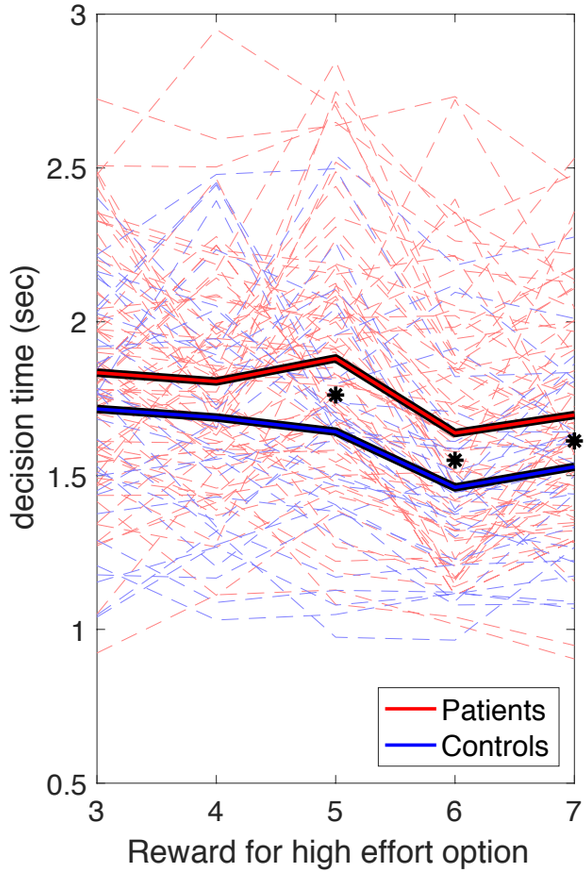
Patients n=73
Controls n=33

No relapse n=37
Relapse n=21

p<0.001



p<0.015

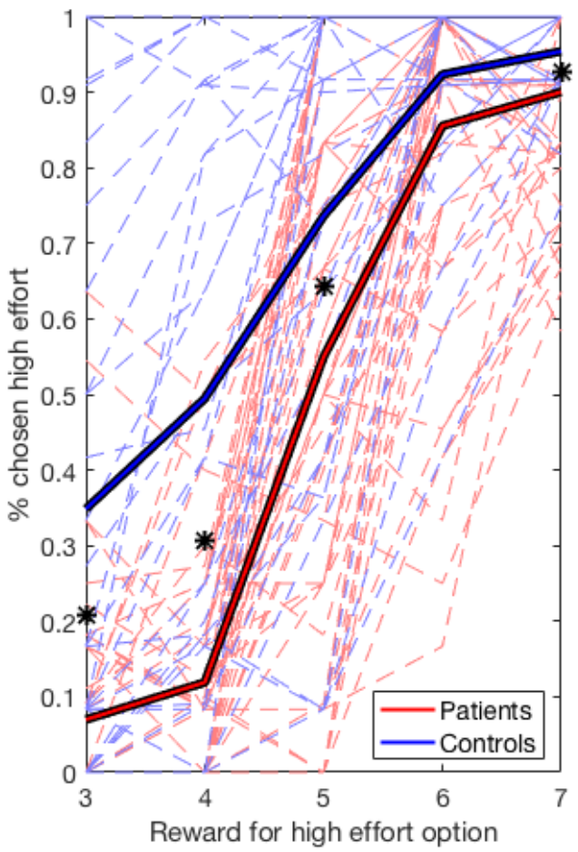


Berwian et al., JAMA Psych 2020

Raw choice data

Patients n=73 No relapse n=37
Controls n=33 Relapse n=21

p<0.001



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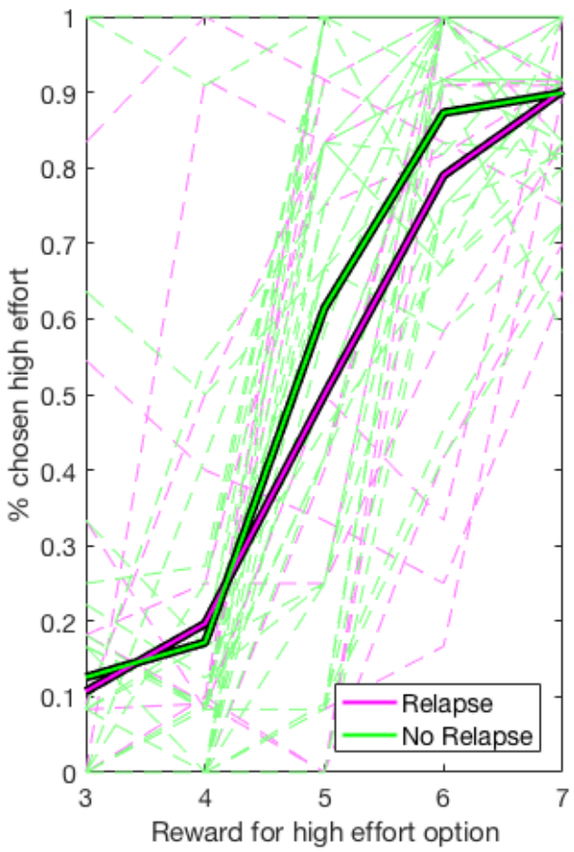

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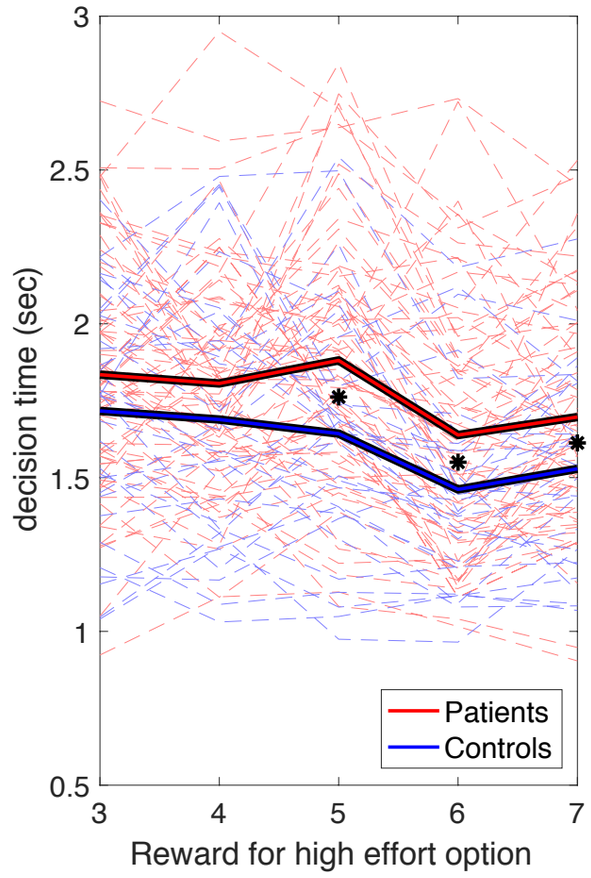

Berwian et al., JAMA Psych 2020

Raw choice data

Patients n=73 No relapse n=37
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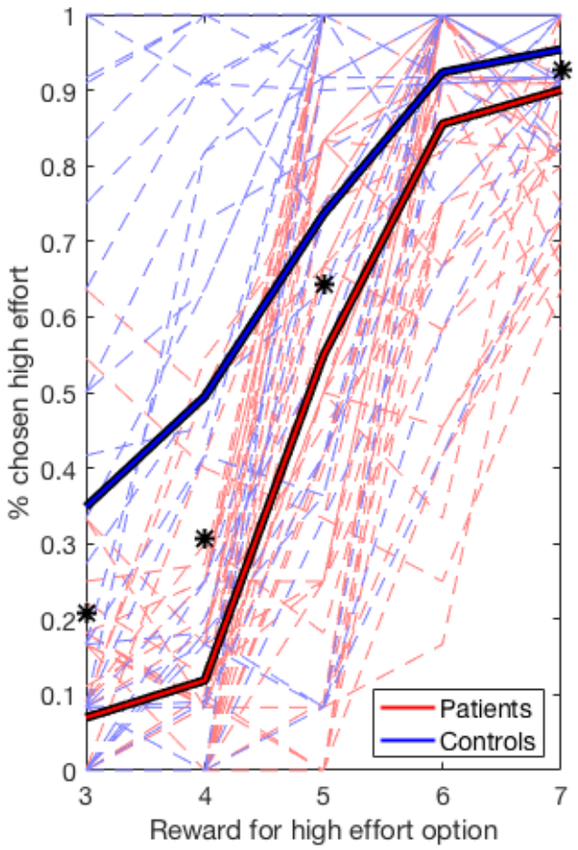
p<0.001



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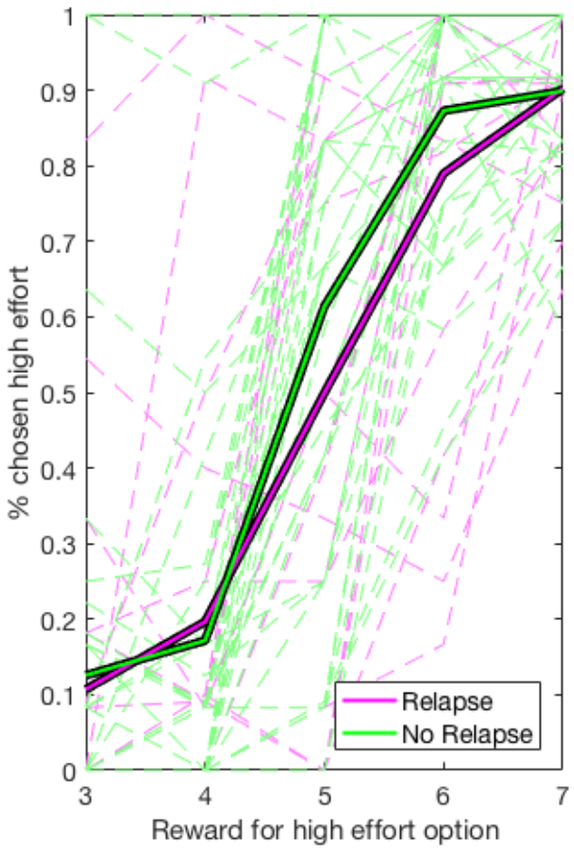

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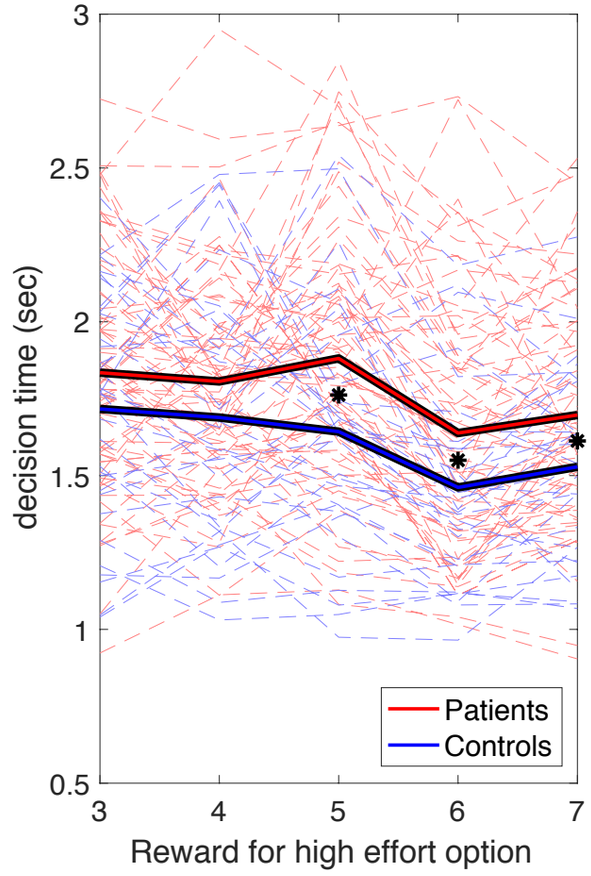
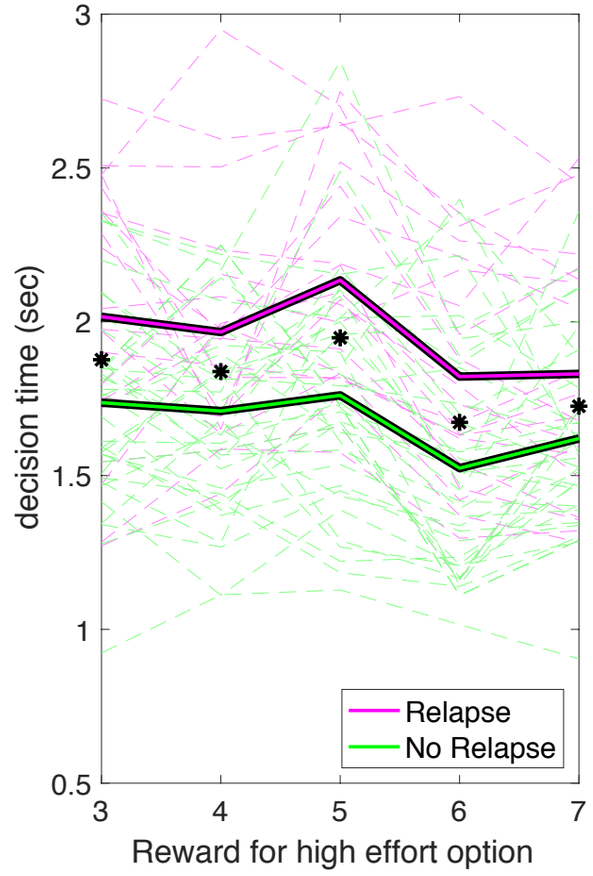


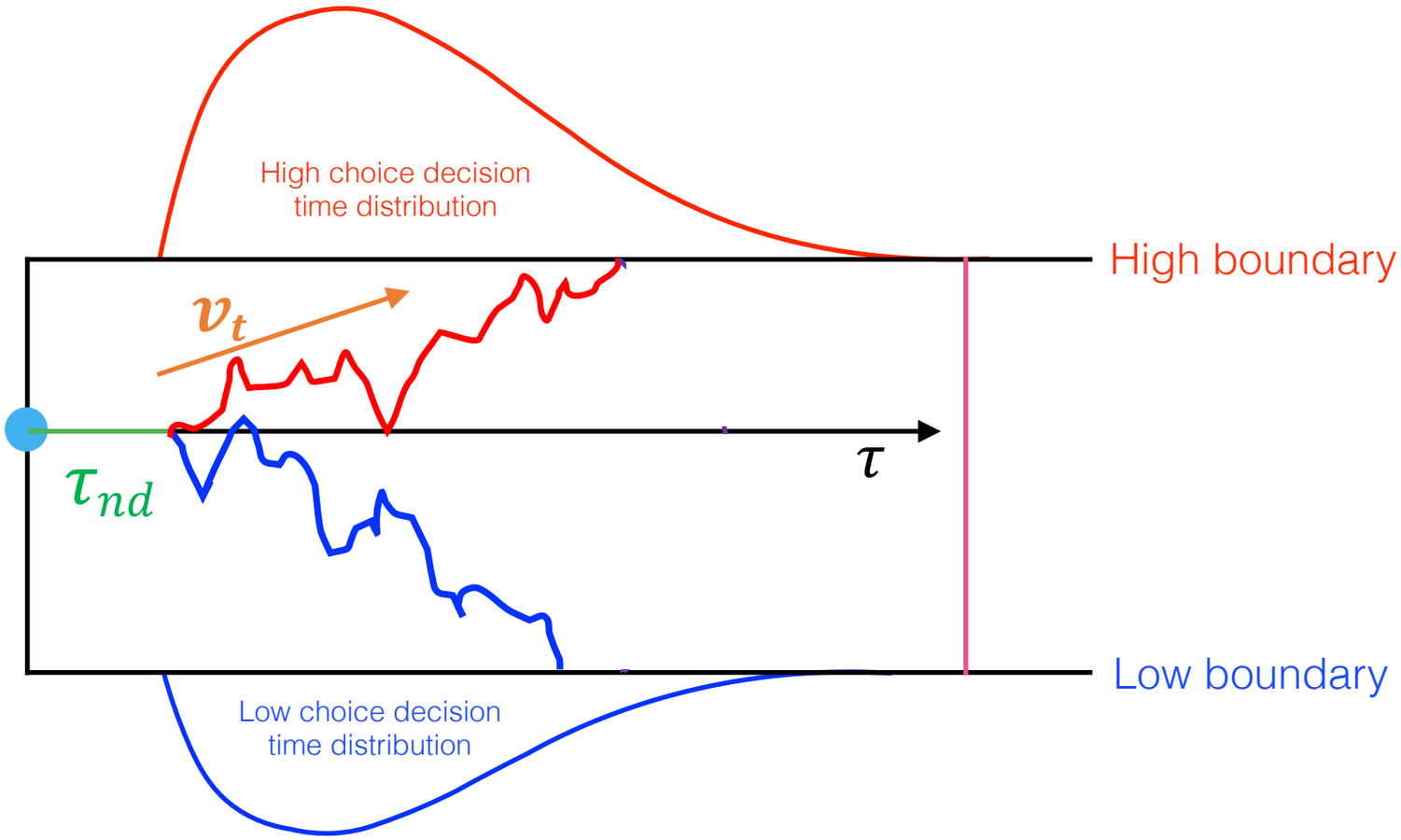
p<0.001



Berwian et al., JAMA Psych 2020

Drift-diffusion models

- Capture choices & reaction times



Berwian et al., JAMA Psych 2020

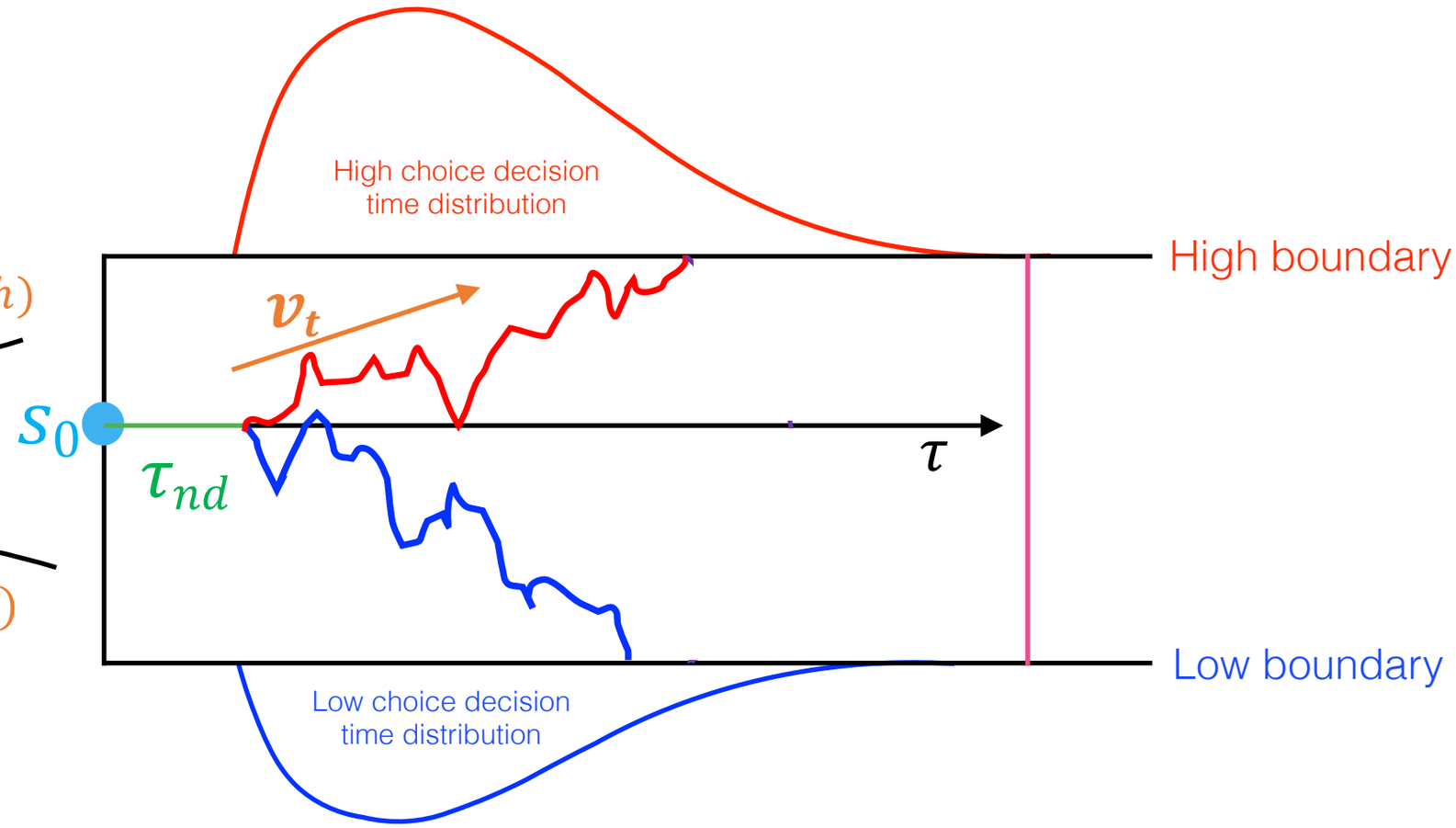
Drift-diffusion models

- Capture choices & reaction times

$$V_t(h) = \beta_{rew} * r(h_t) - \beta_{eff} * e(h)$$

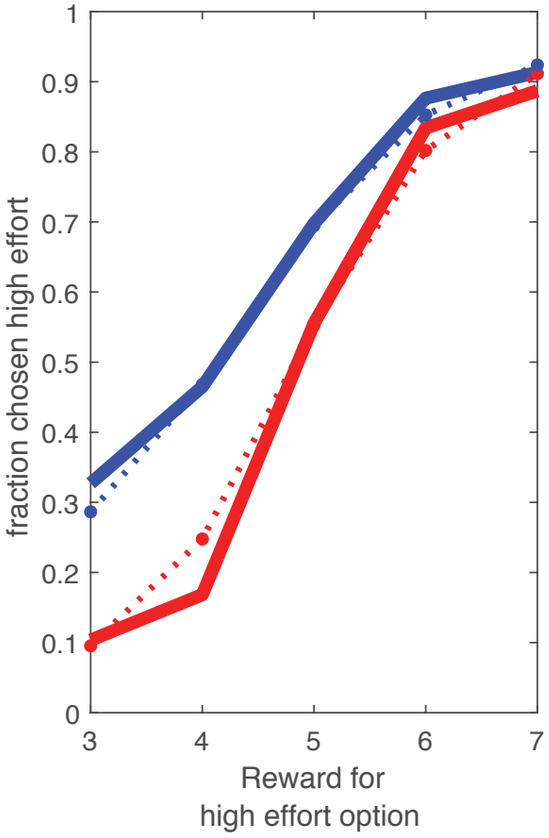
$$\boldsymbol{v_t} = \boldsymbol{V_t(h) - V(l)}$$

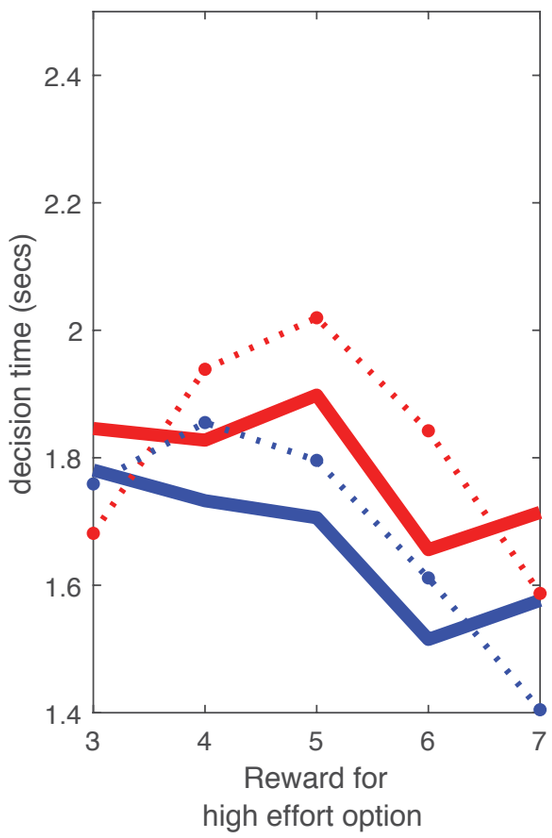
$$V(l) = \beta_{rew} * r(l) - \beta_{eff} * e(l)$$

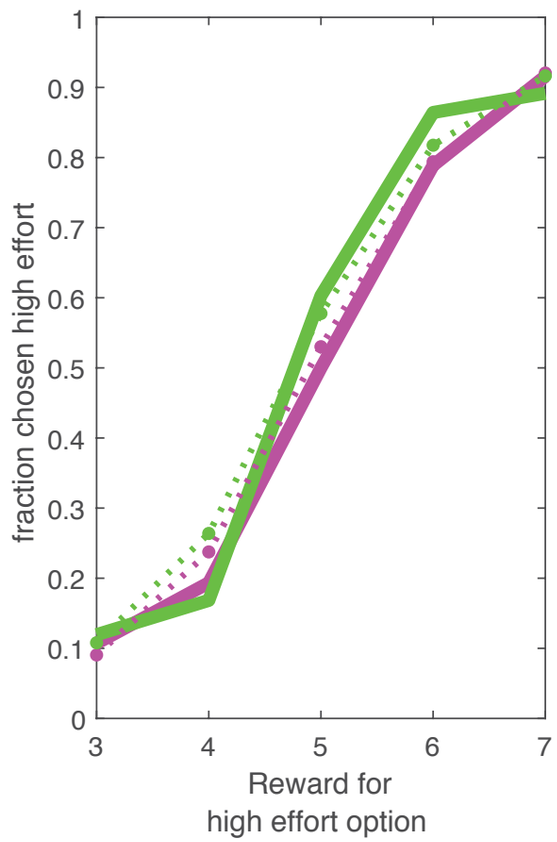


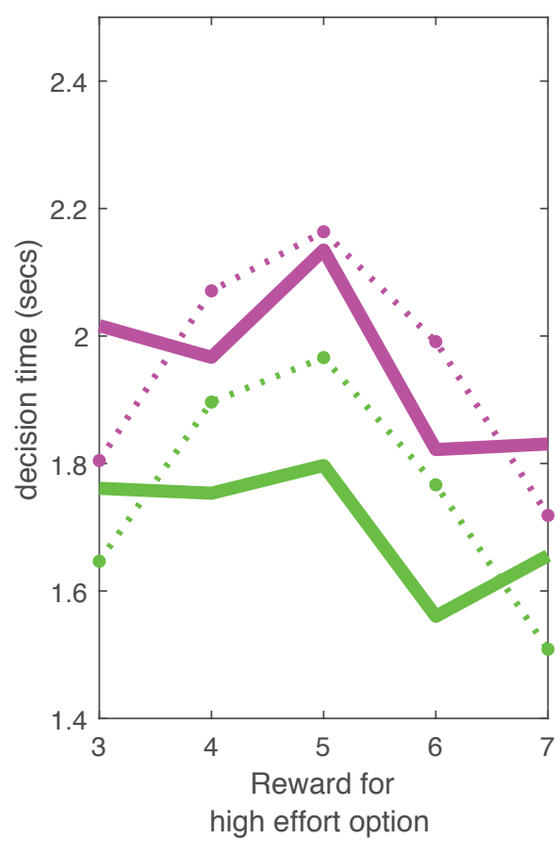
Berwian et al., JAMA Psych 2020

Systematic failure to fit patients









Berwian et al., JAMA Psych 2020

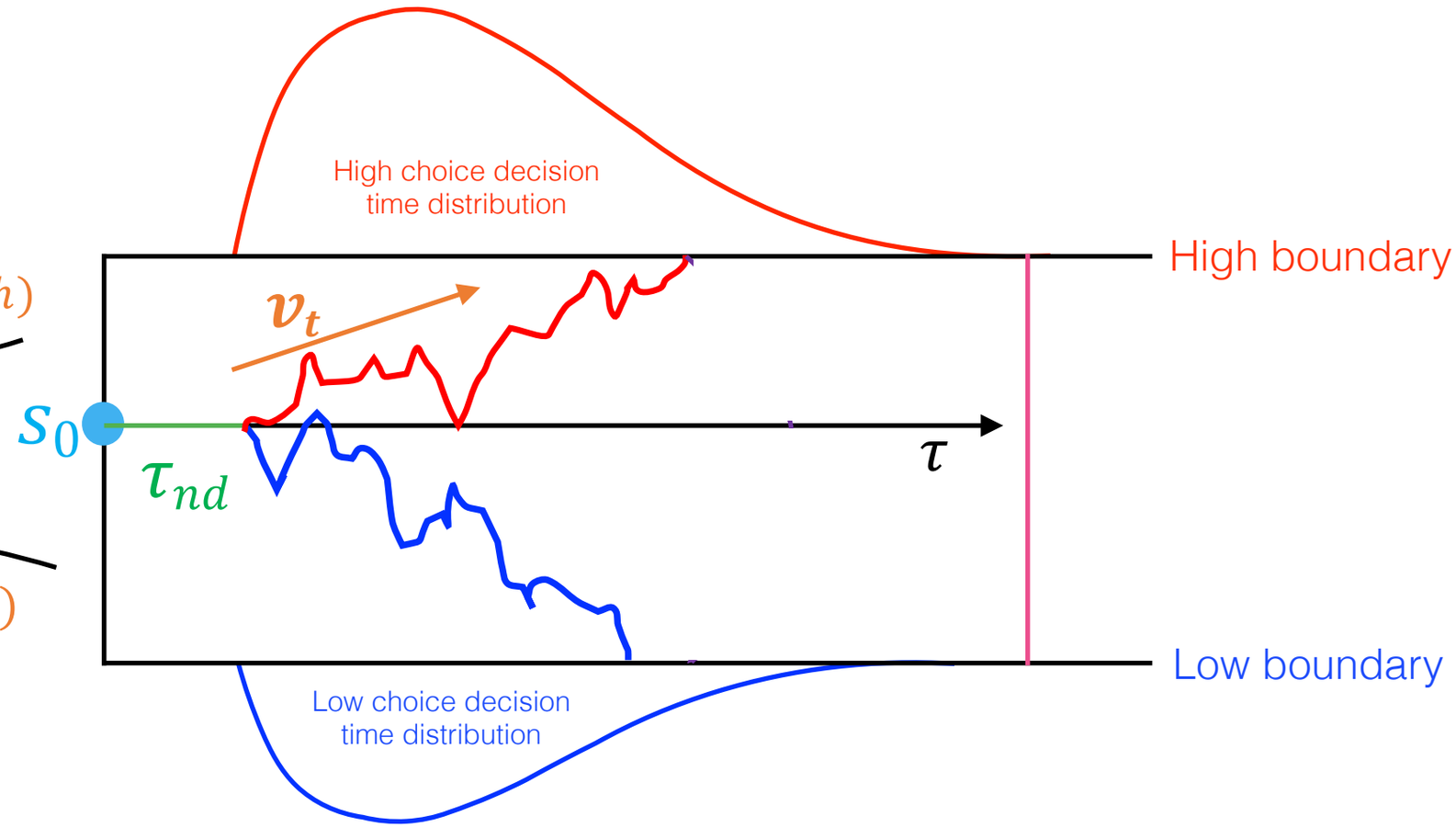
Drift-diffusion models

- Capture choices & reaction times

$$V_t(h) = \beta_{rew} * r(h_t) - \beta_{eff} * e(h)$$

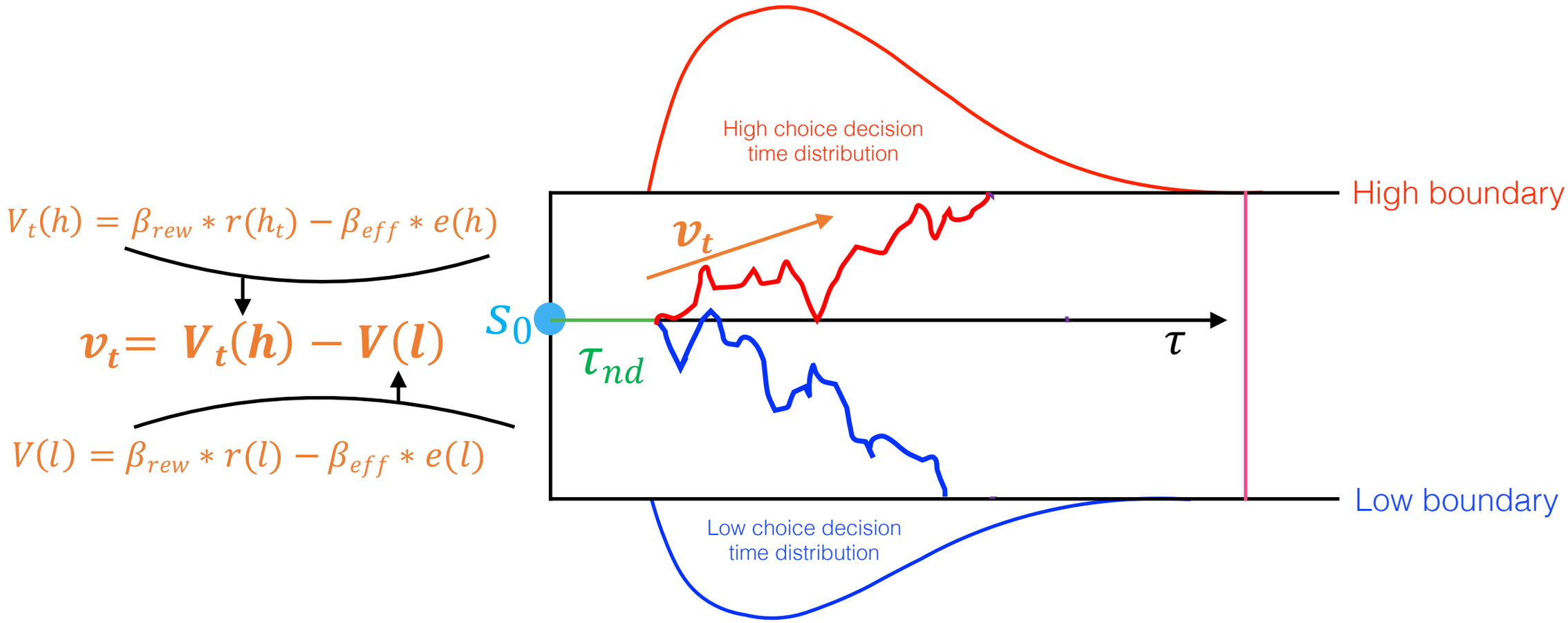
$$\boldsymbol{v_t} = \boldsymbol{V_t(h) - V(l)}$$

$$V(l) = \beta_{rew} * r(l) - \beta_{eff} * e(l)$$



Drift-diffusion models

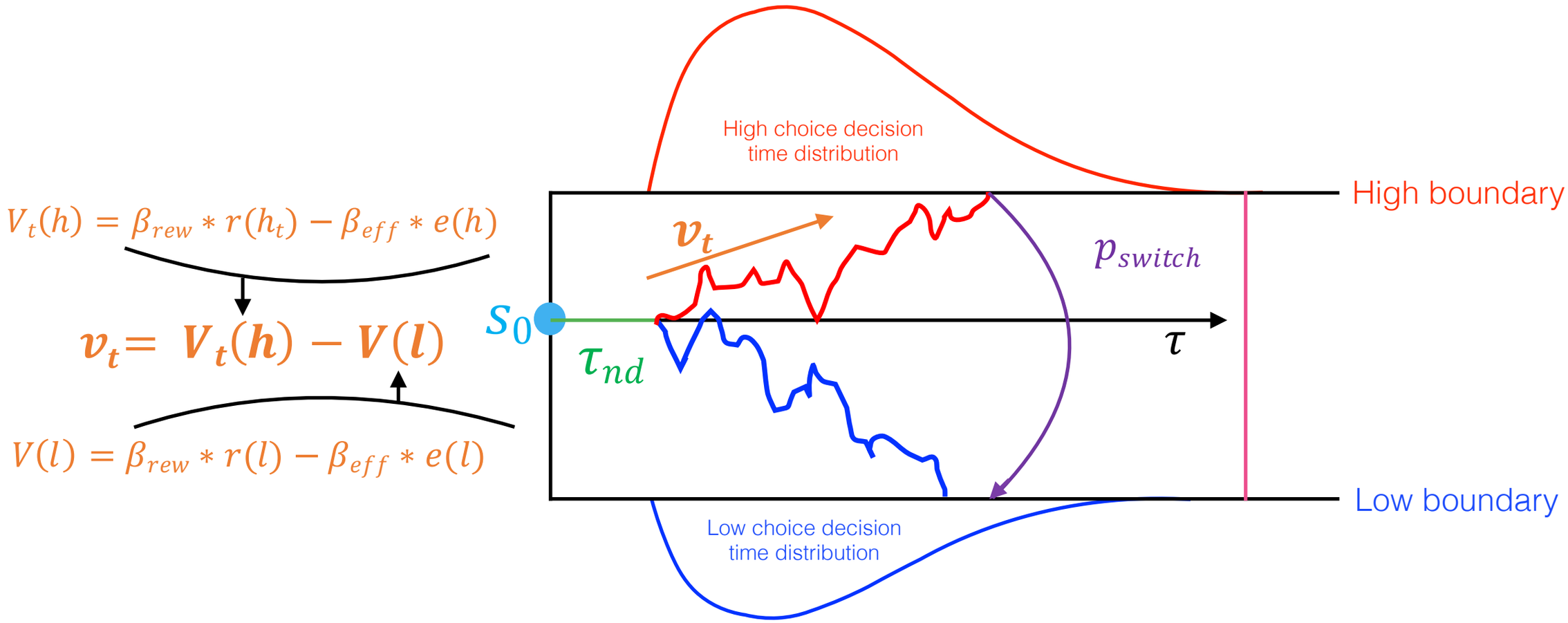
- Capture choices & reaction times



$$p(a, t, p_{\text{switch}}) = \begin{cases} p(\text{higheffort}, t)(1 - p_{\text{switch}}) & \text{if high effort} \\ p(\text{loweffort}, t) + p_{\text{switch}} p(\text{higheffort}, t) & \text{if low effort} \end{cases}$$

Drift-diffusion models

- Capture choices & reaction times

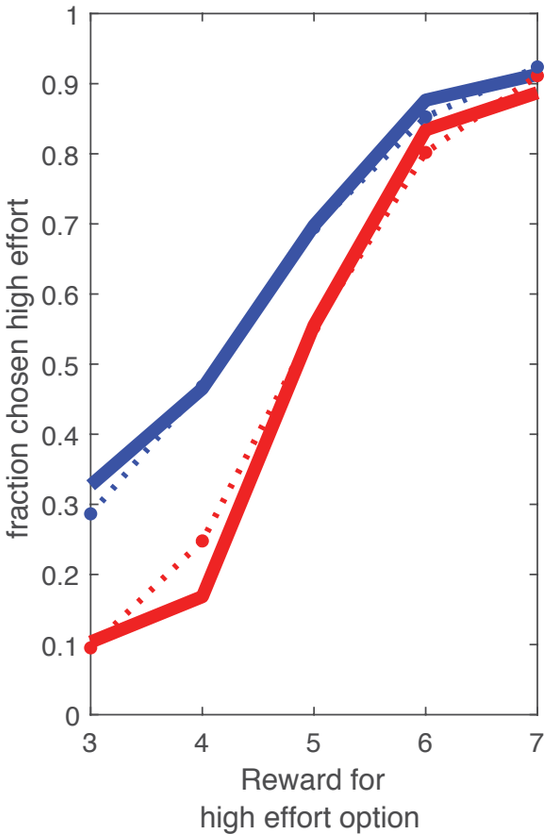


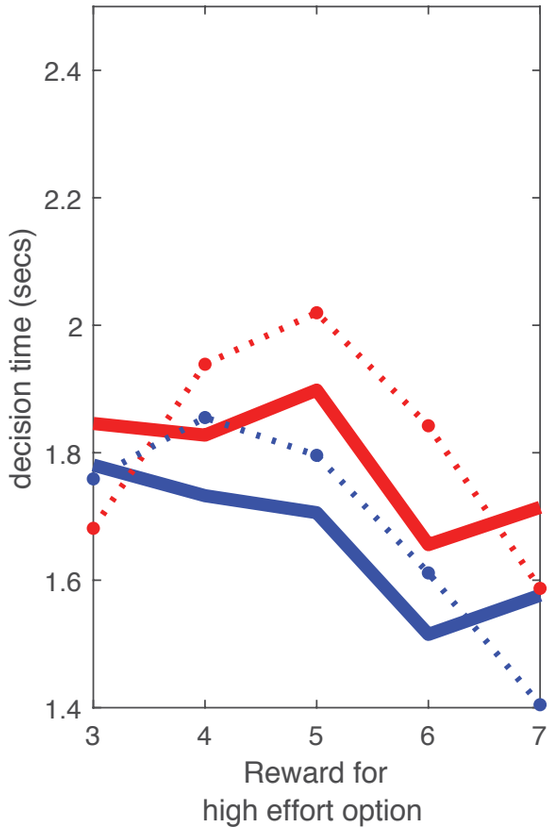
$$p(a, t, p_{\text{switch}}) = \begin{cases} p(\text{higheffort}, t)(1 - p_{\text{switch}}) & \text{if high effort} \\ p(\text{loweffort}, t) + p_{\text{switch}} p(\text{higheffort}, t) & \text{if low effort} \end{cases}$$

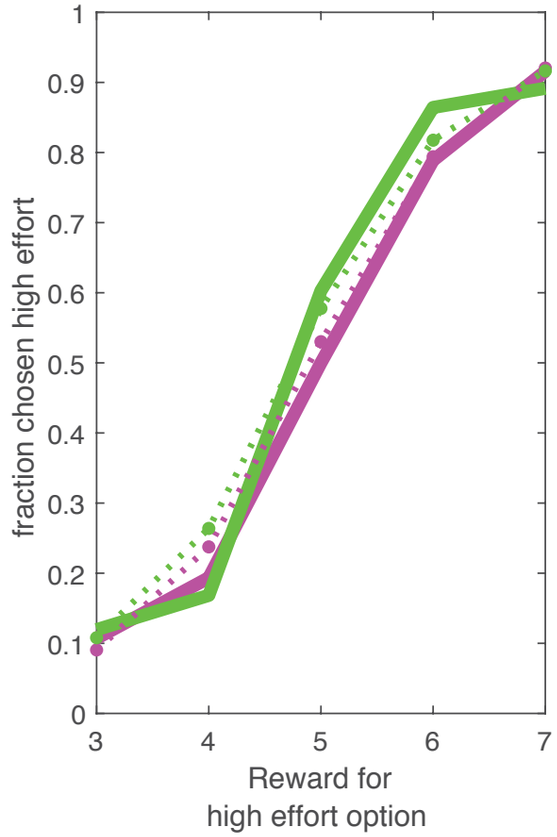
Systematic failure to fit patients

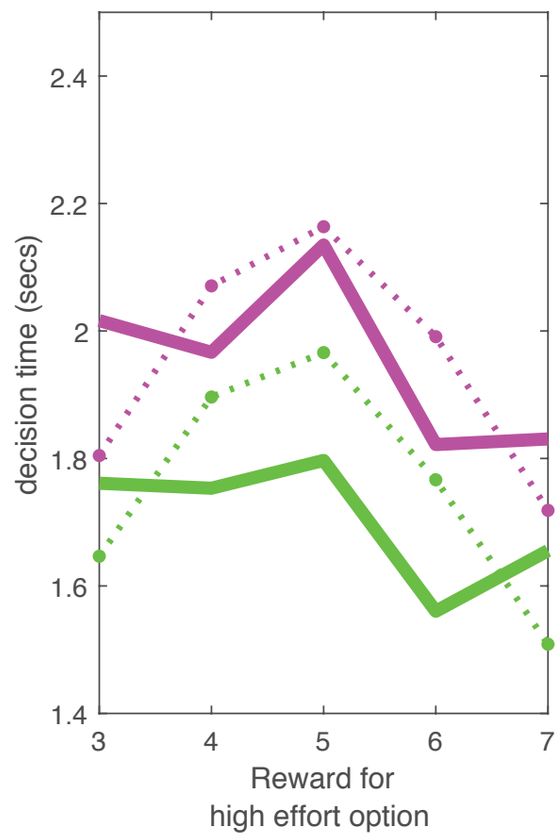
Patients
Controls

Relapse
No Relapse





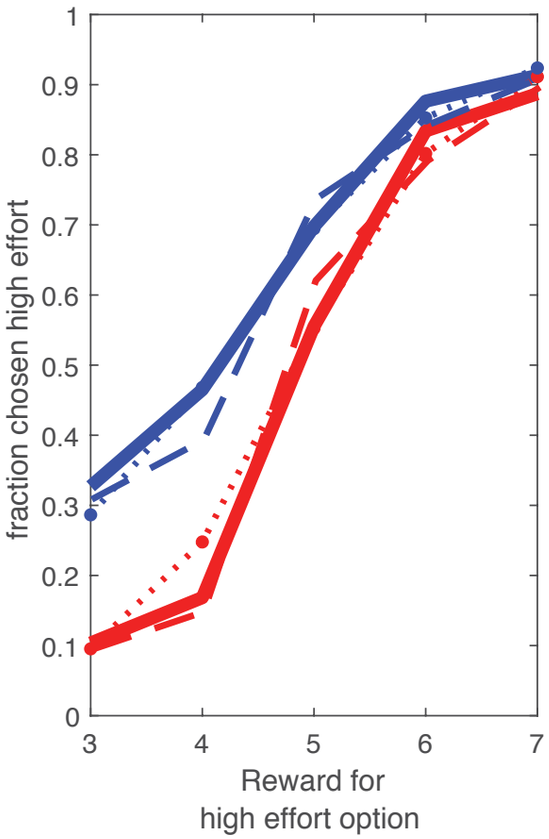


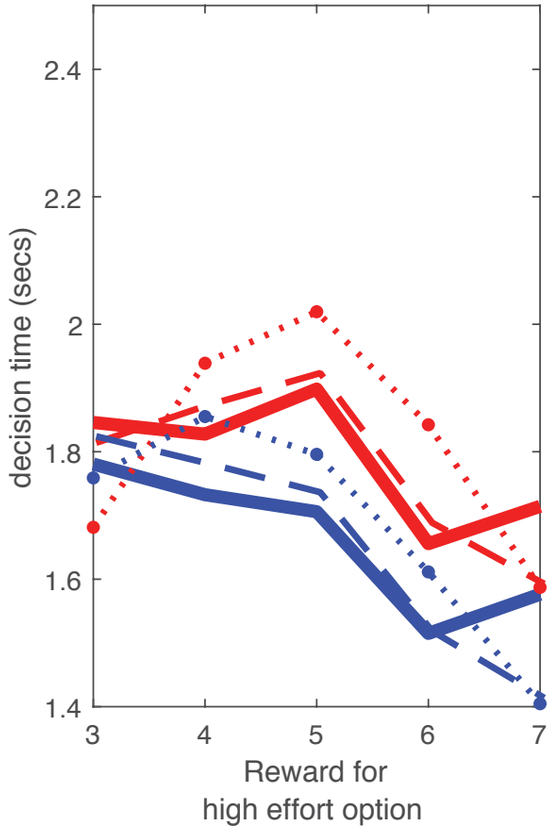


Berwian et al., JAMA Psych 2020

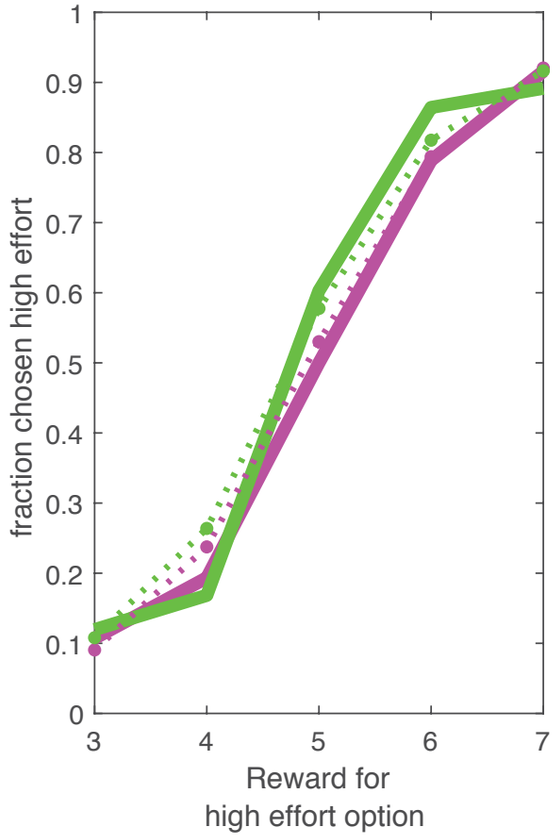
Systematic failure to fit patients

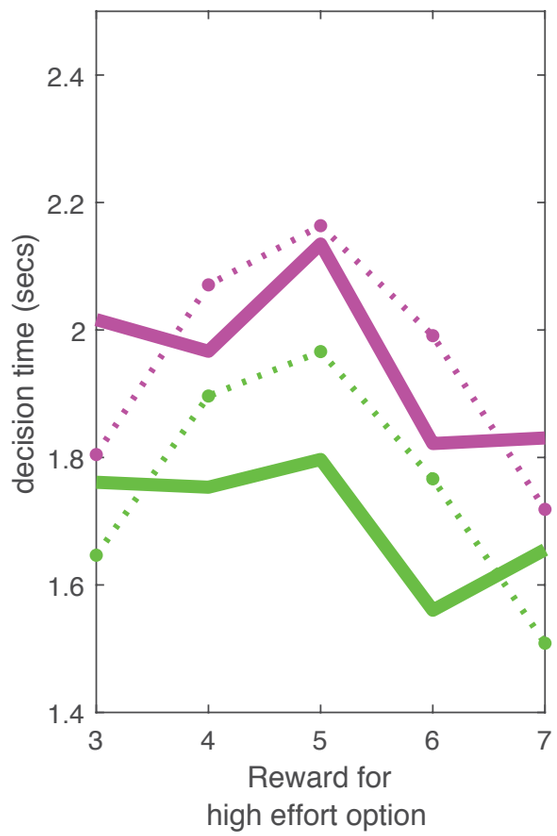
Patients
Controls





Relapse
No Relapse



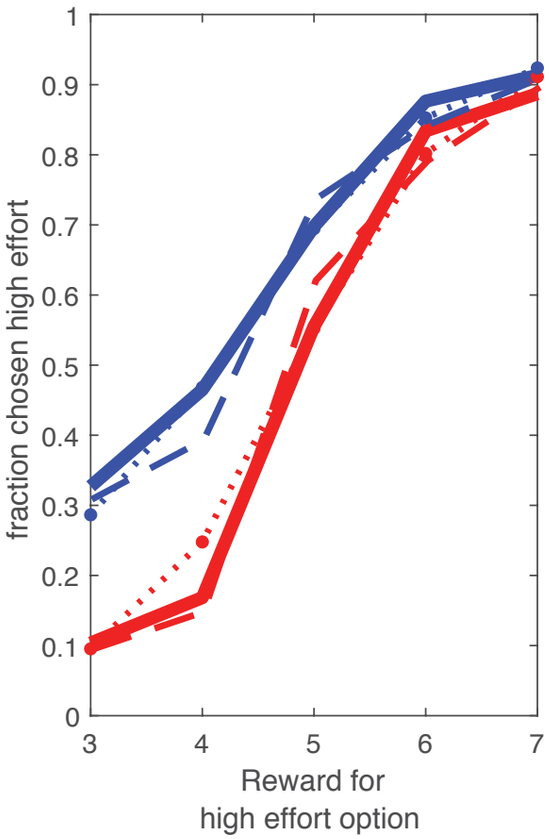


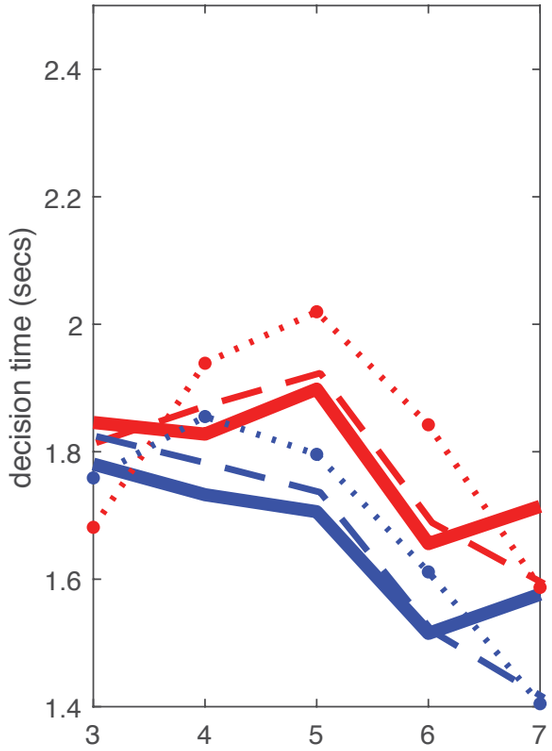
Berwian et al., JAMA Psych 2020

Systematic failure to fit patients

Patients

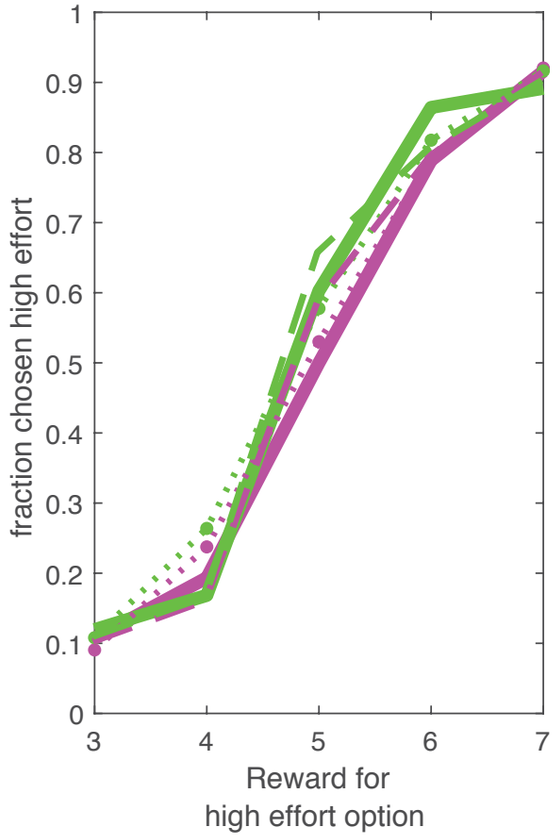
Controls

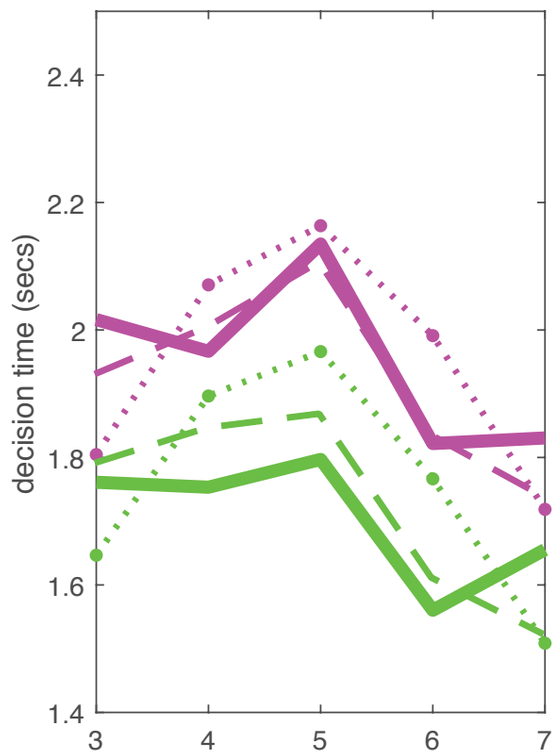




Relapse

No Relapse

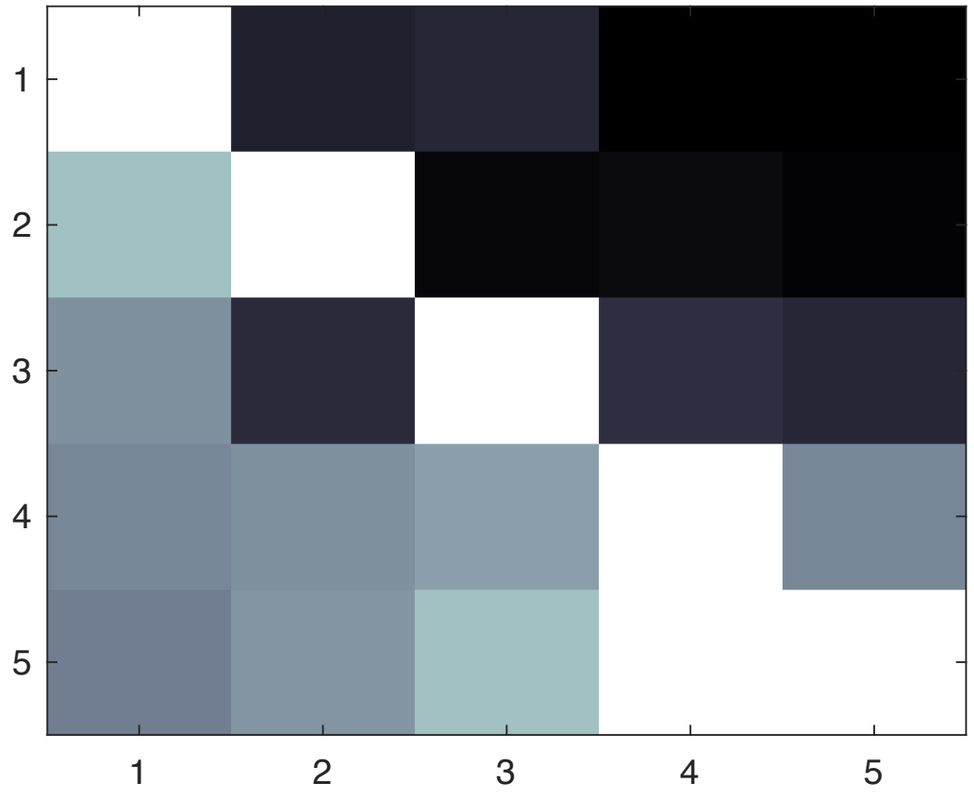




Berwian et al., JAMA Psych 2020

Can we recover the model?

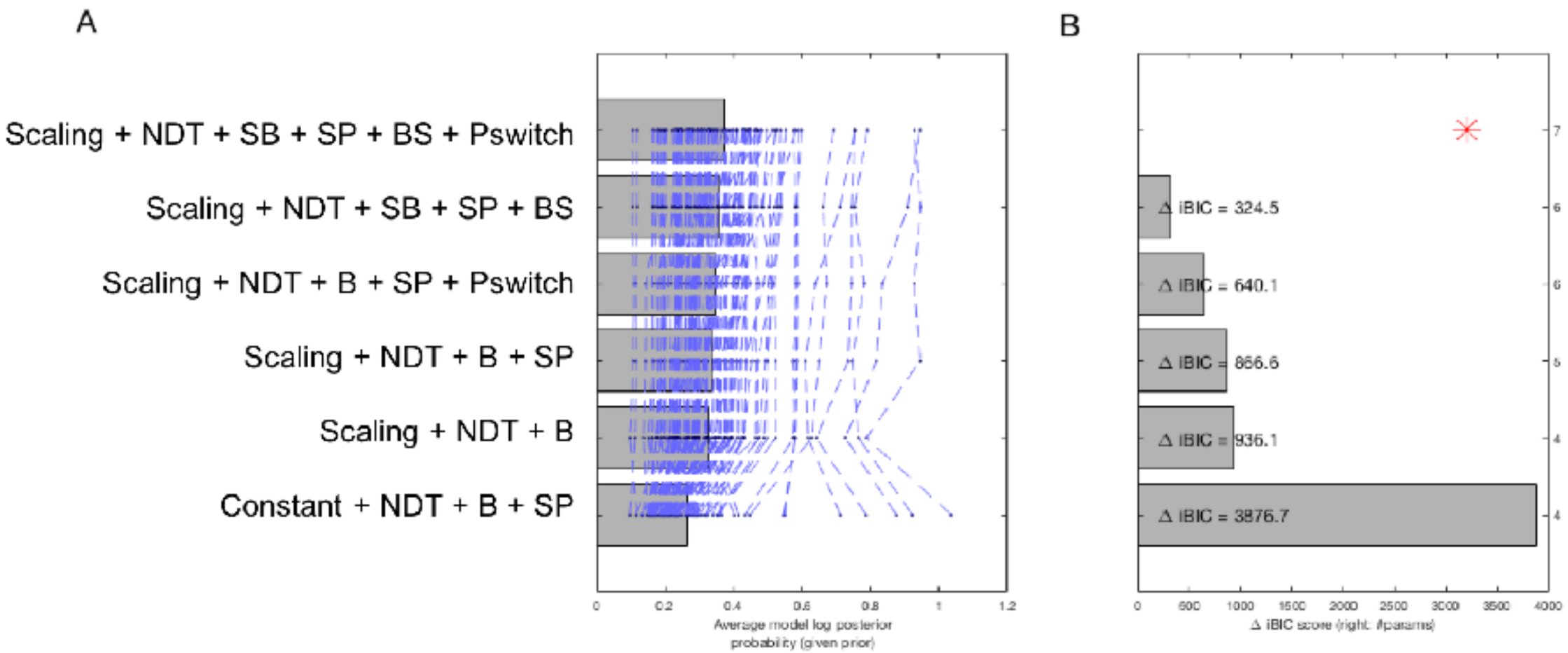
True model



Inferred model

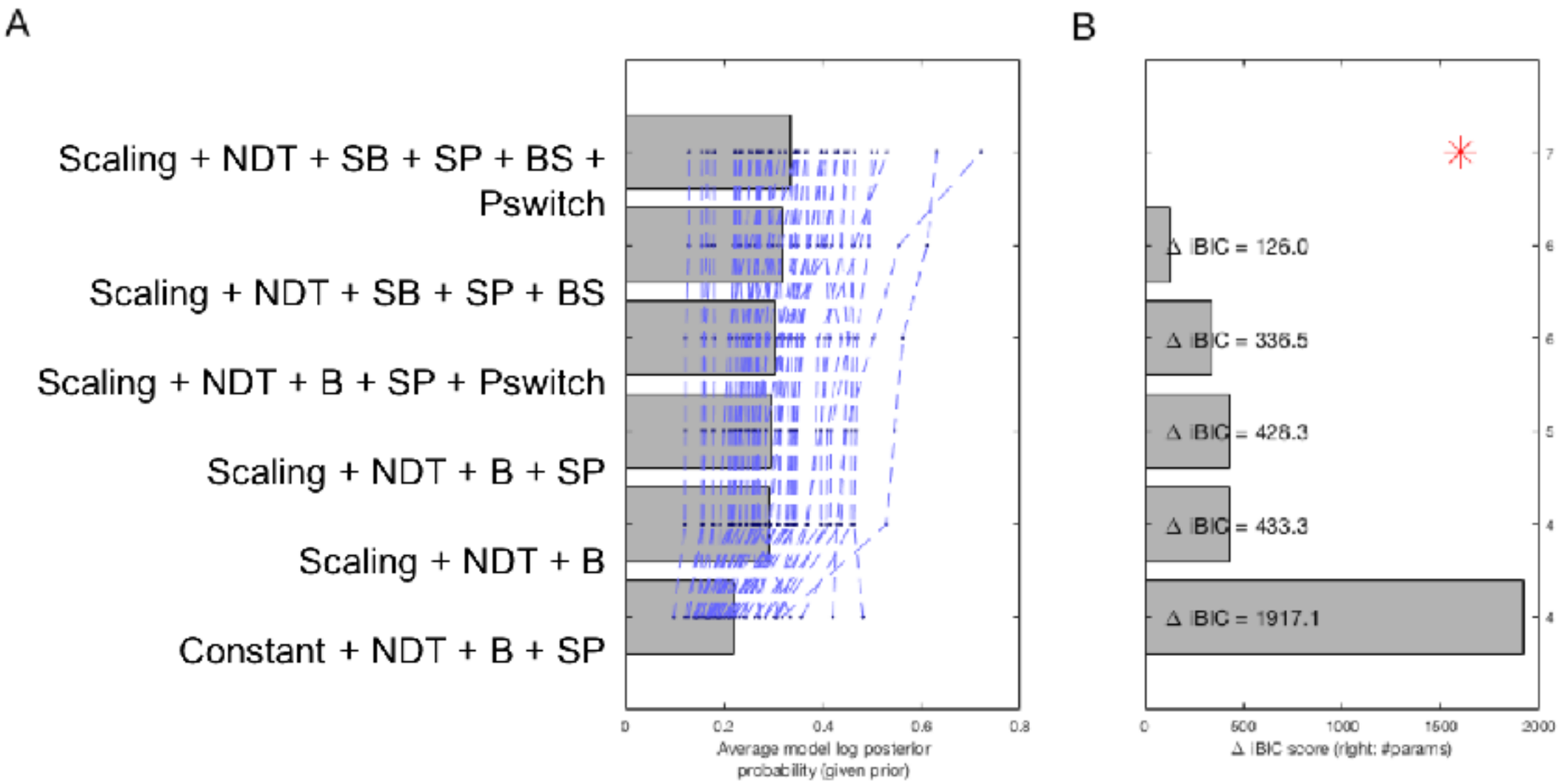
Berwian et al., JAMA Psych 2020

Model comparison



Berwian et al., JAMA Psych 2020

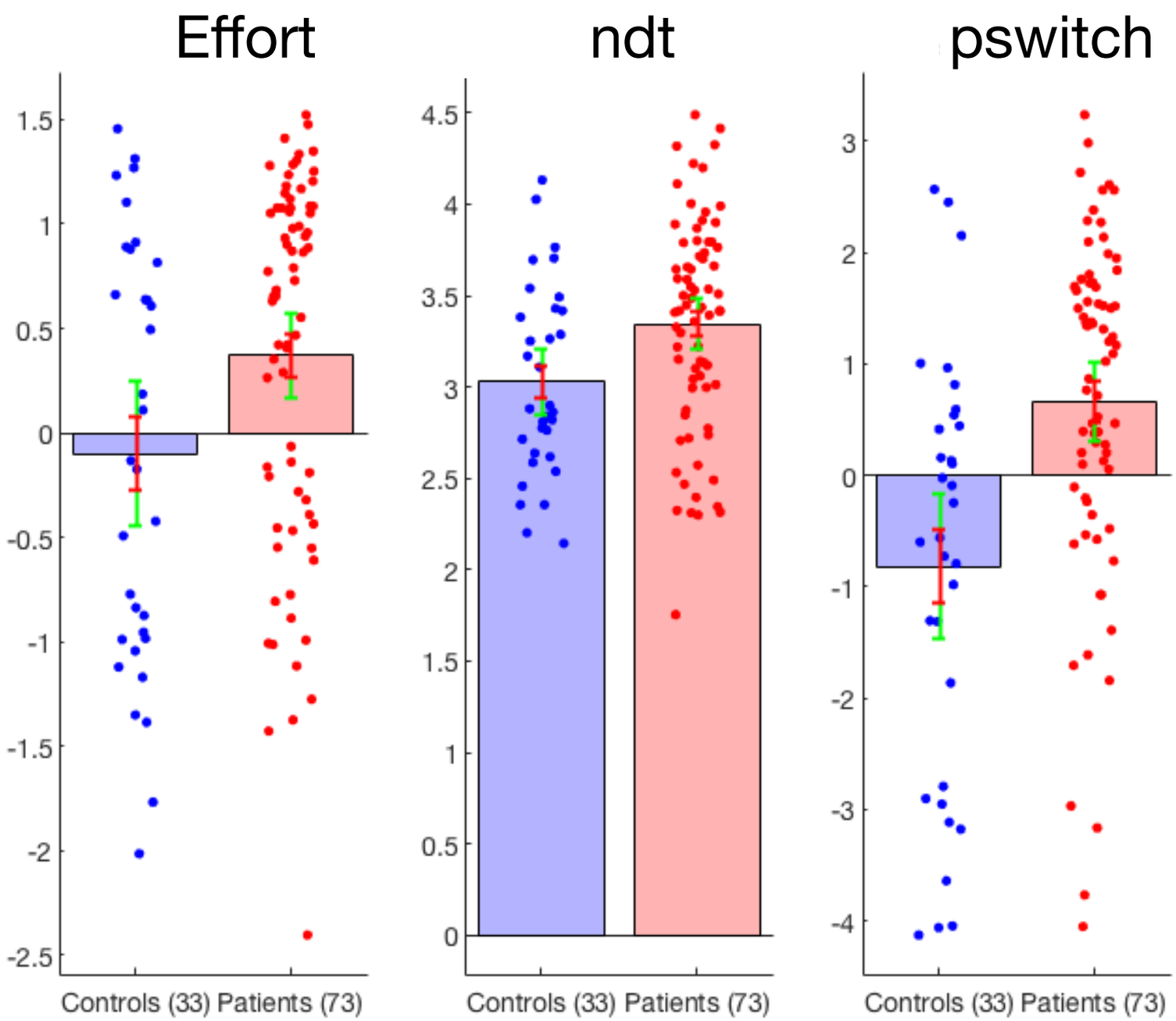
Model comparison replication



Berwian et al., JAMA Psych 2020

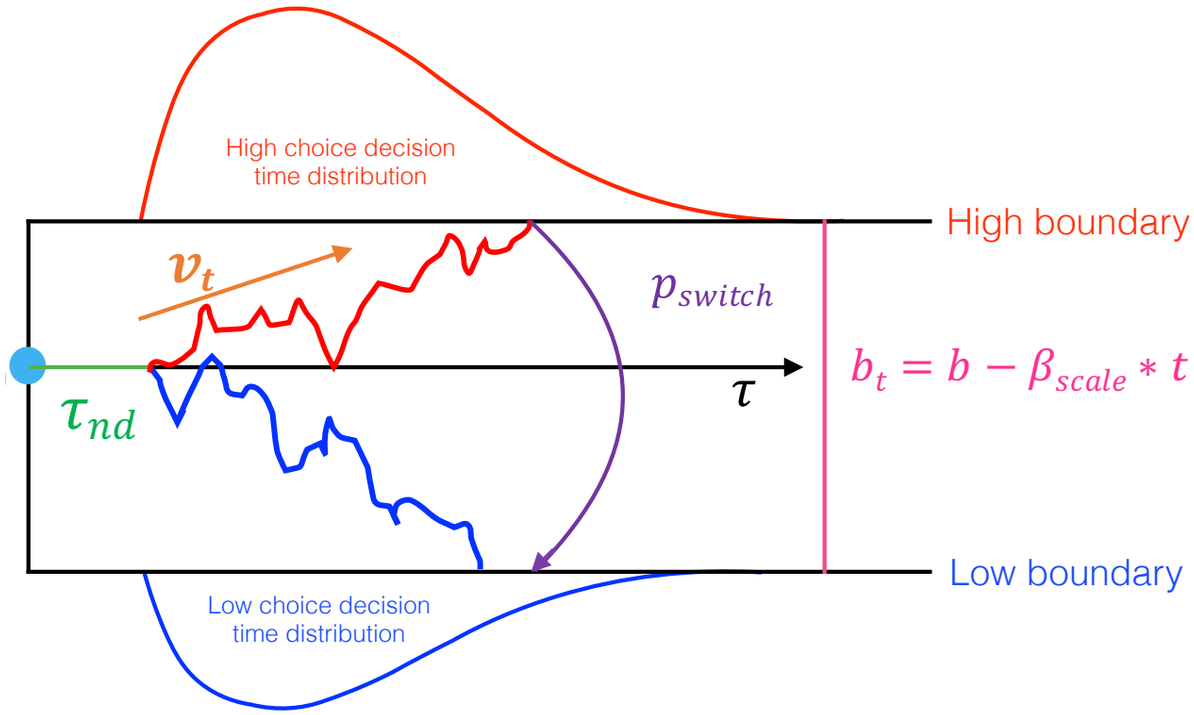
Change of mind after remission?

Patients
Vs
Controls



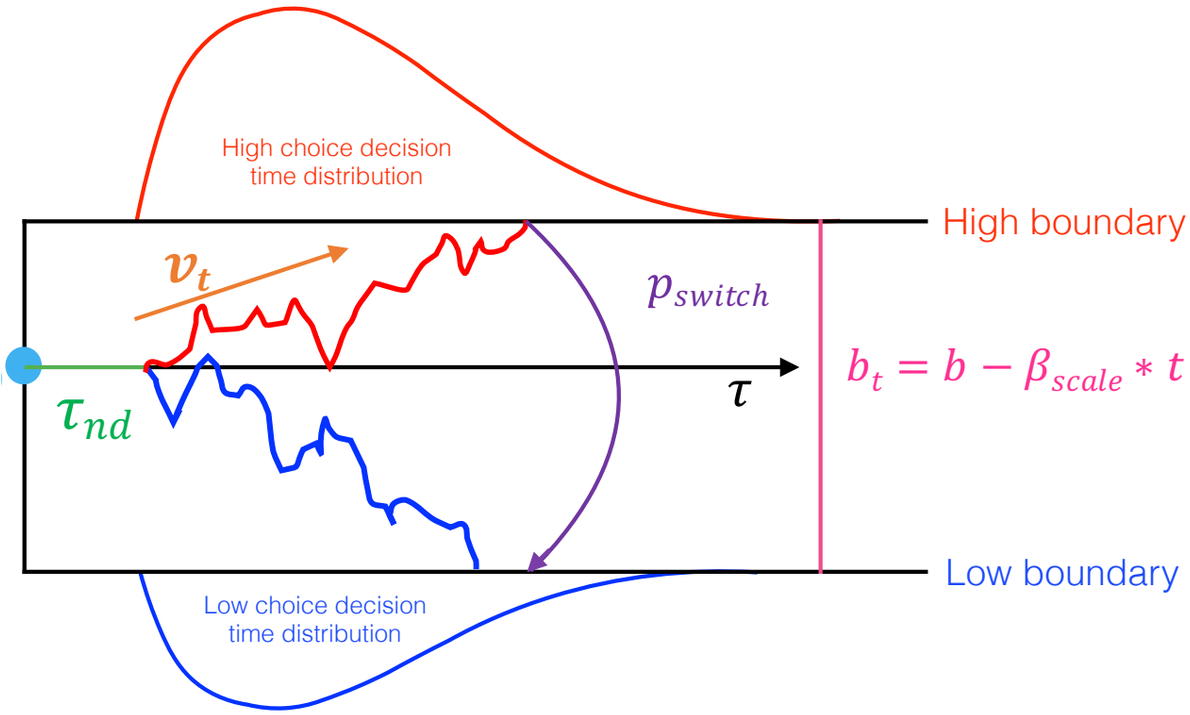
p=0.0177 p=0.0094 p<0.0001

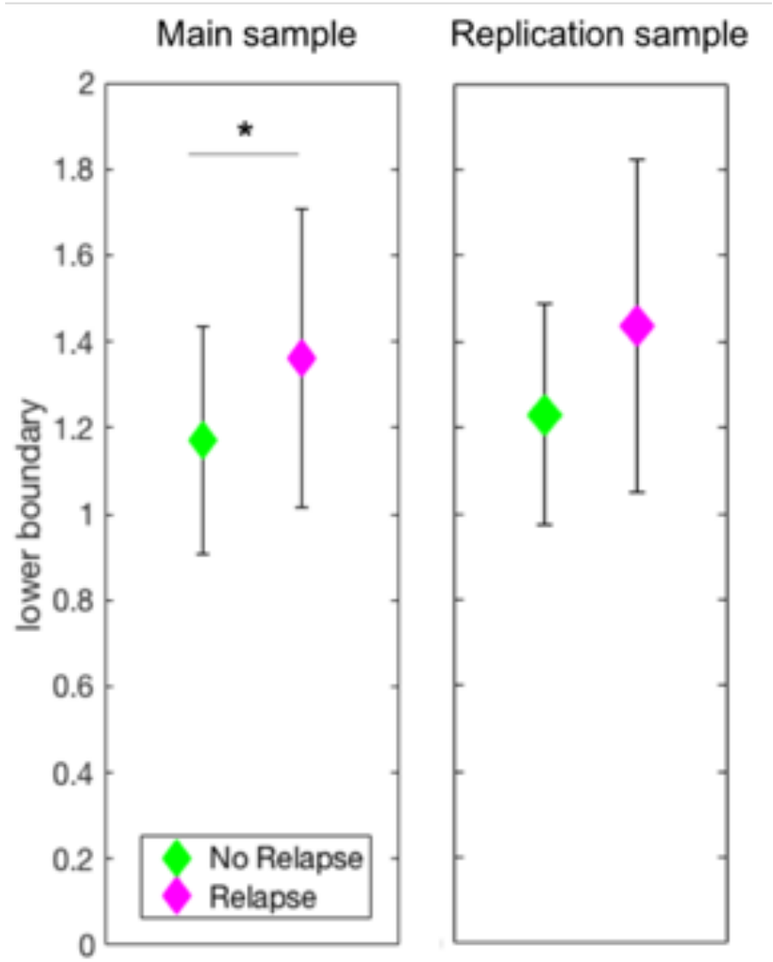
Boundary for actions and relapse



Berwian et al., JAMA Psych 2020

Boundary for actions and relapse

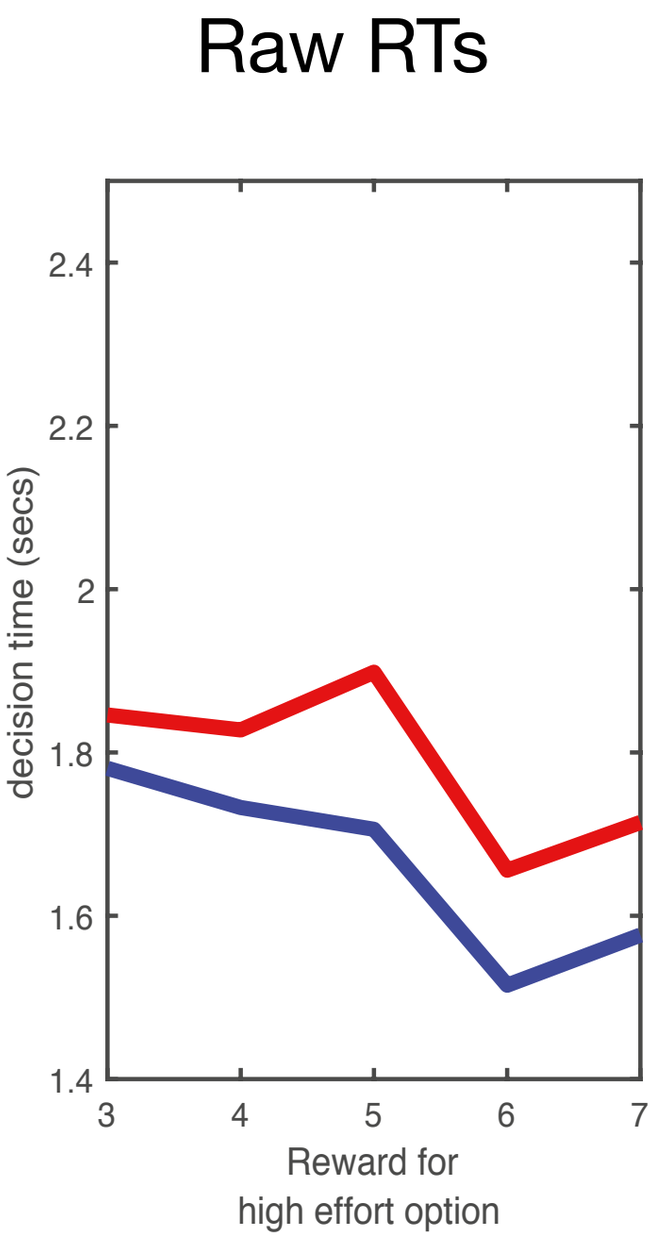




p=0.021

Berwian et al., JAMA Psych 2020

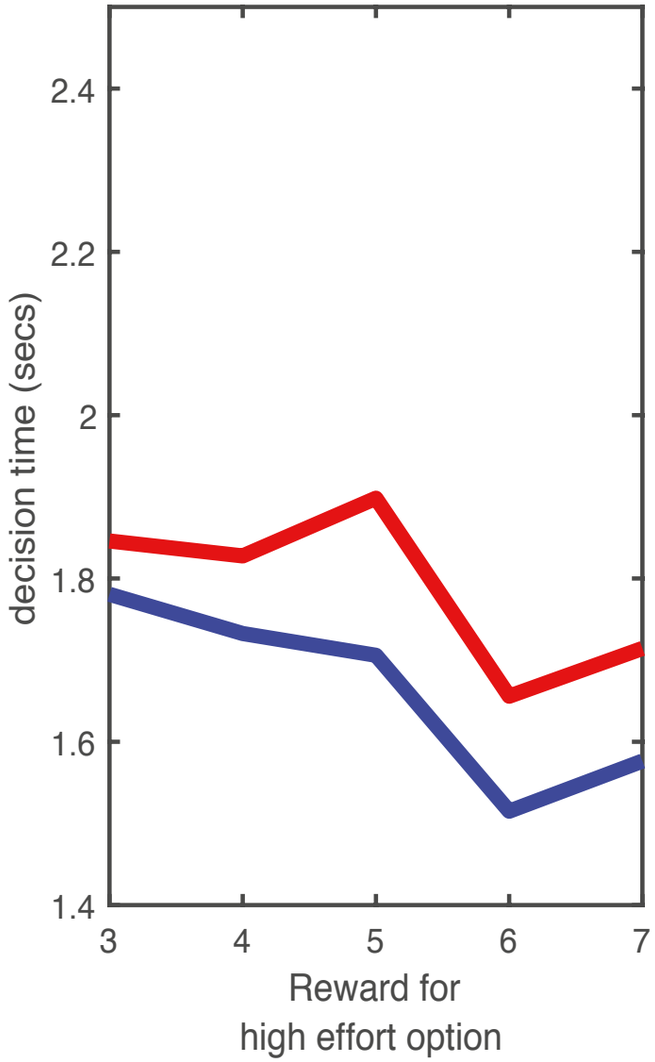
Prediction?



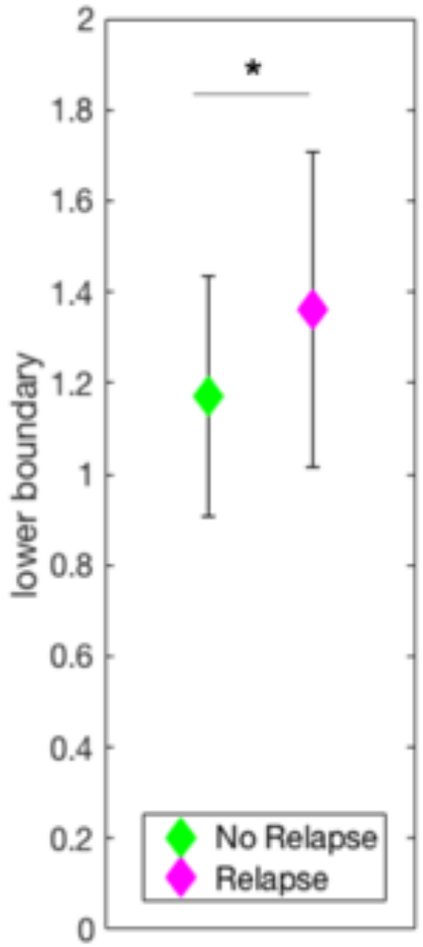
Berwian et al., JAMA Psych 2020

Prediction?

Raw RTs

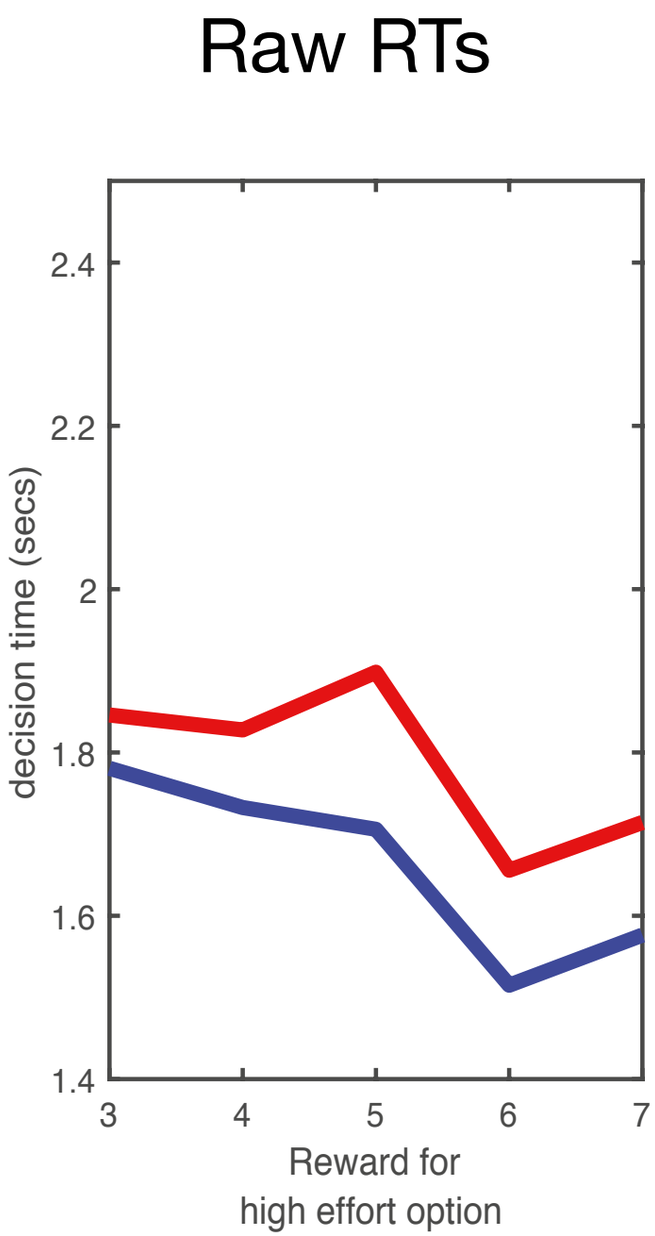


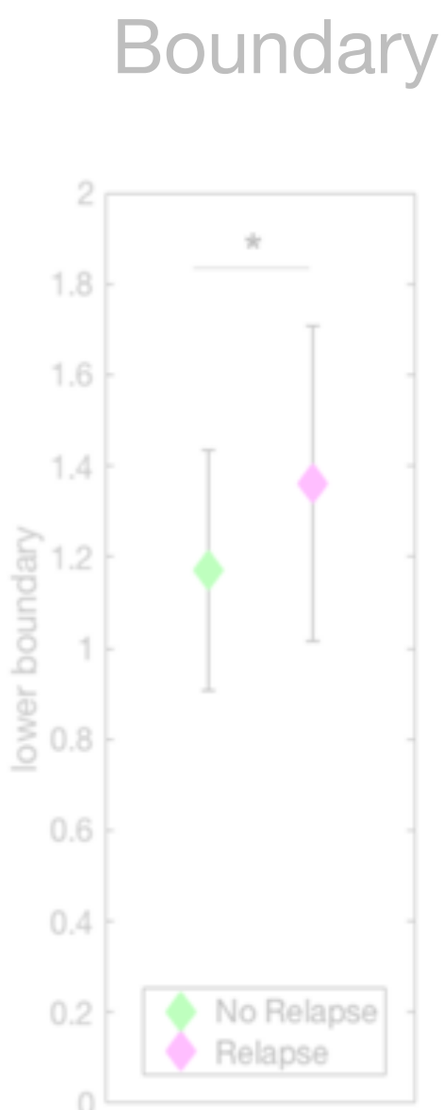
Boundary

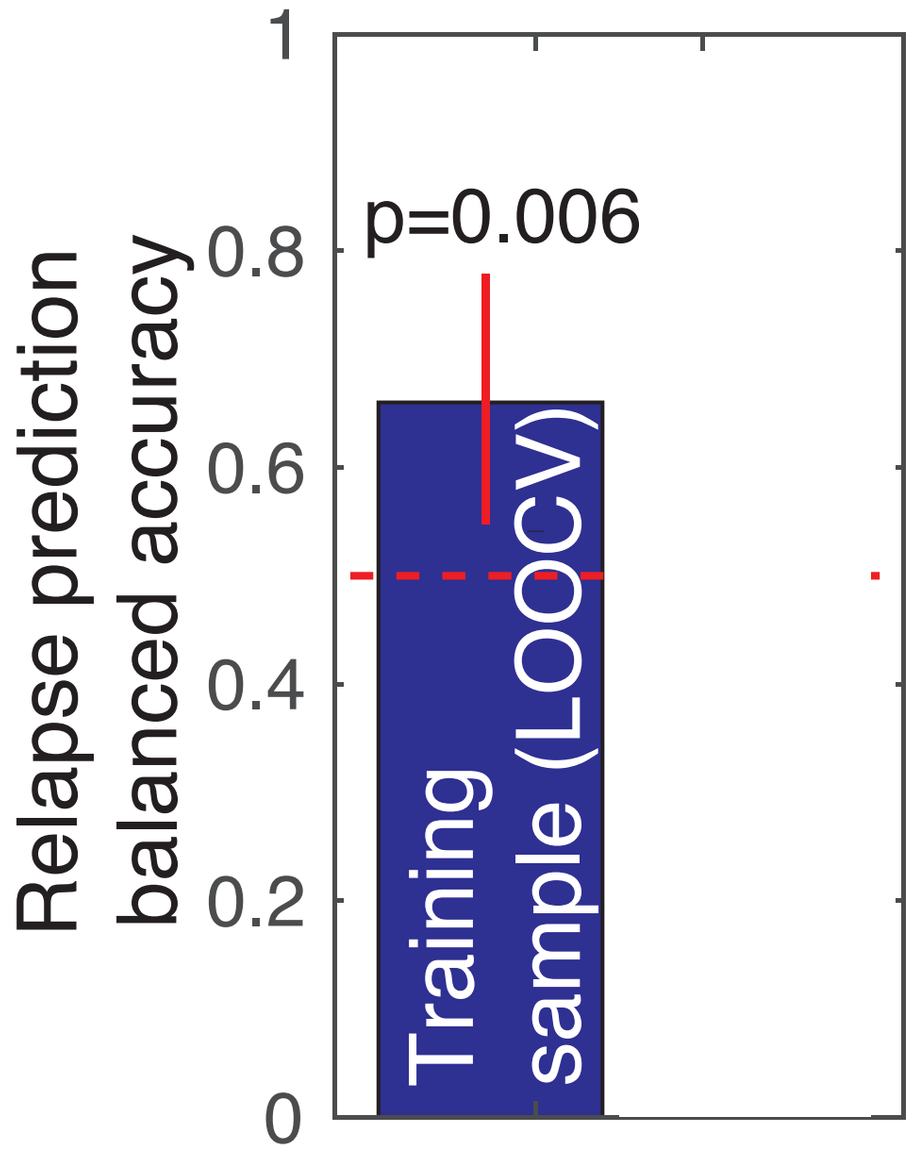


Berwian et al., JAMA Psych 2020

Prediction?

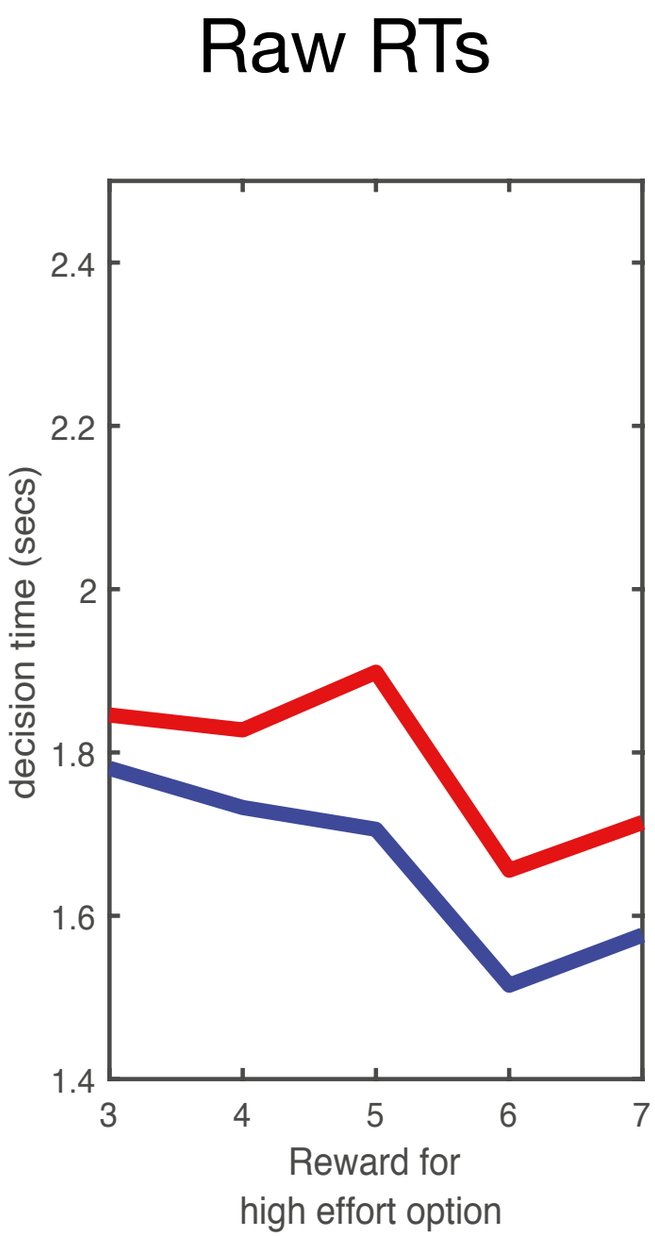


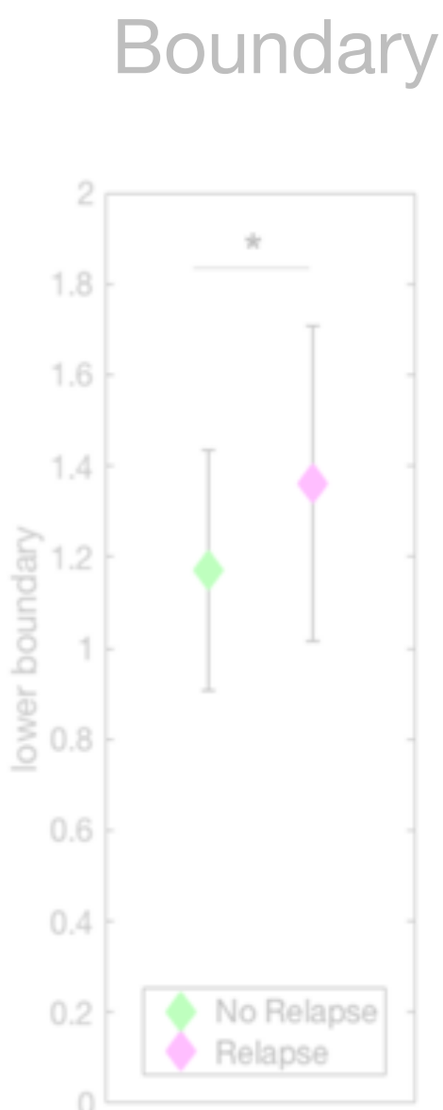


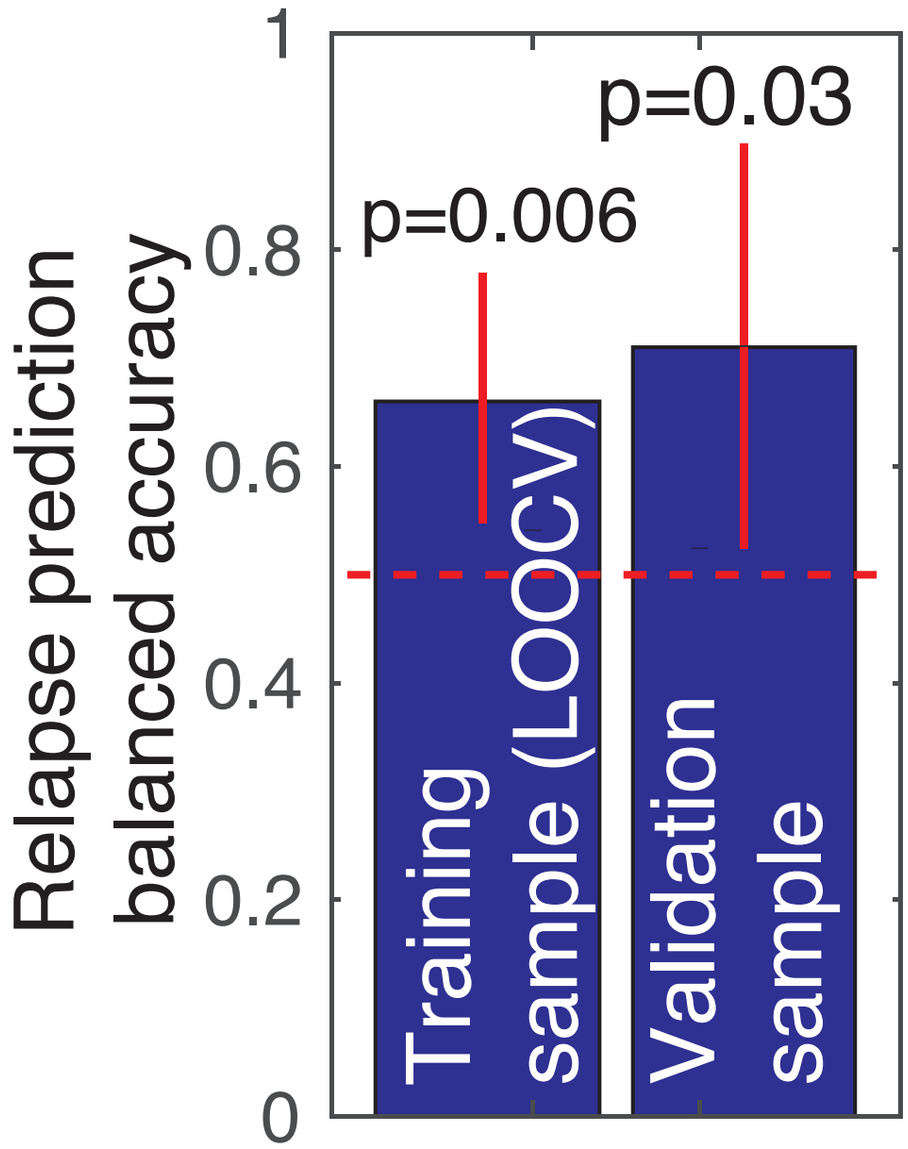


Berwian et al., JAMA Psych 2020

Prediction?

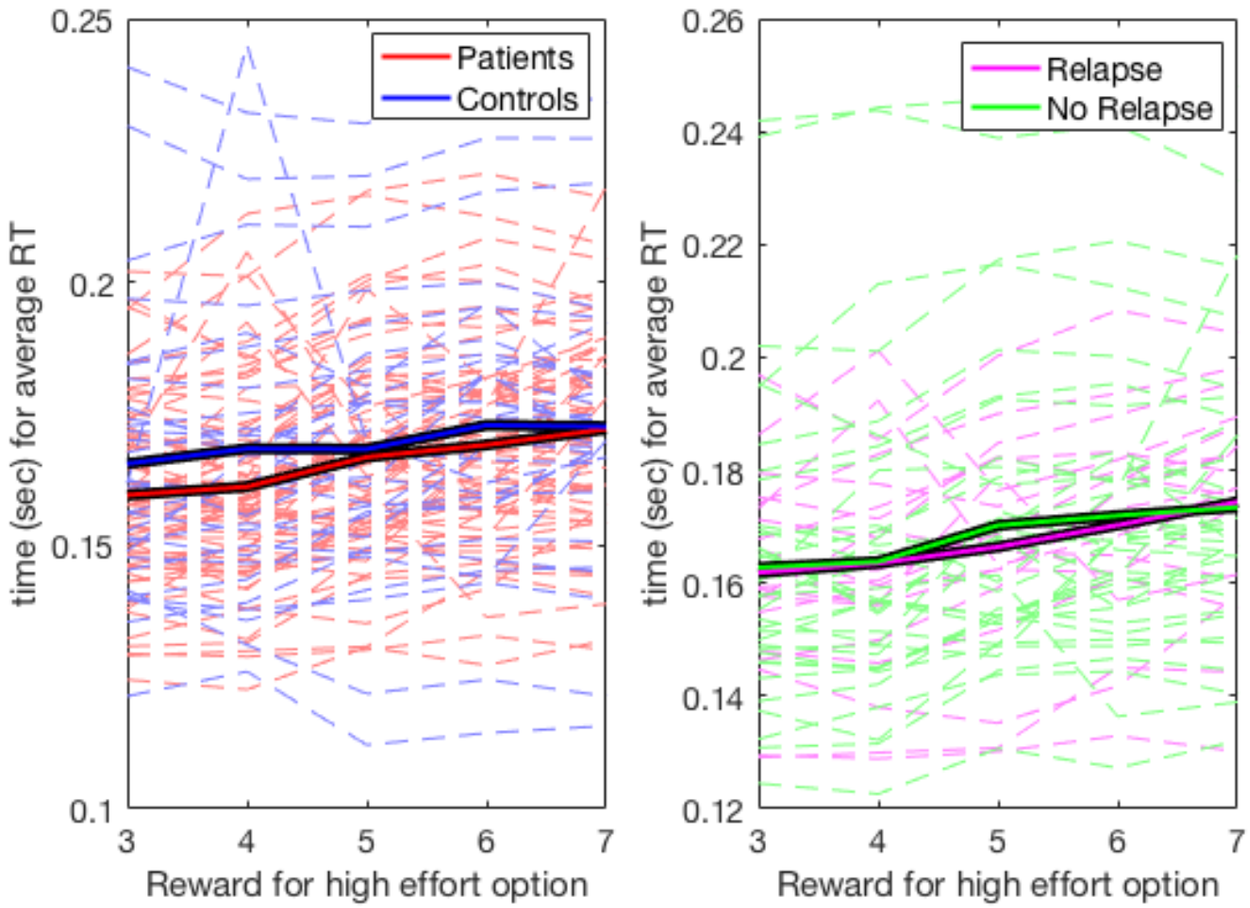






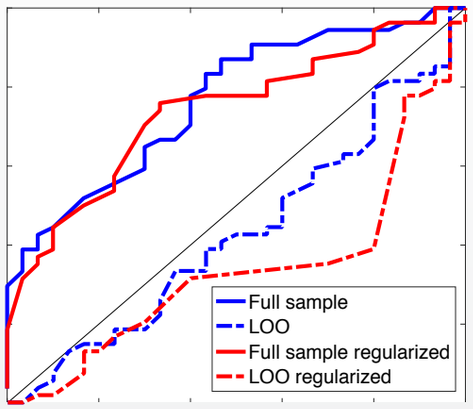
Berwian et al., JAMA Psych 2020

Actual effortful behaviour

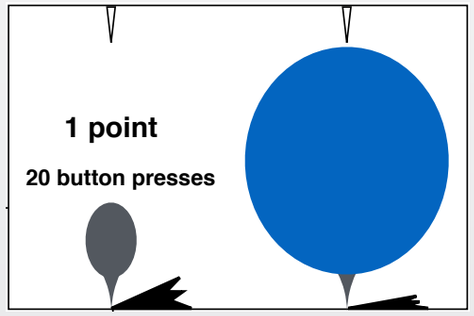


Outline

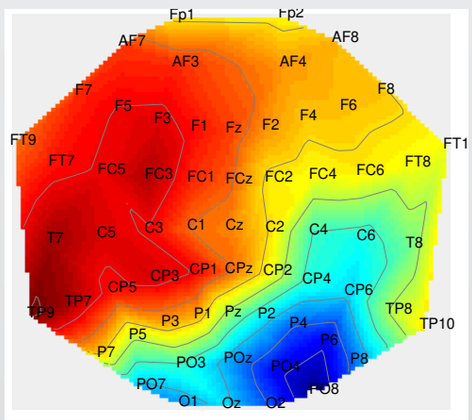
Prediction



Clinical variables

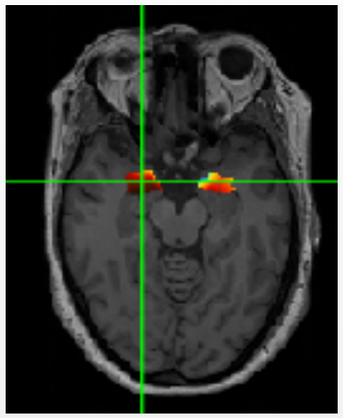


Effort

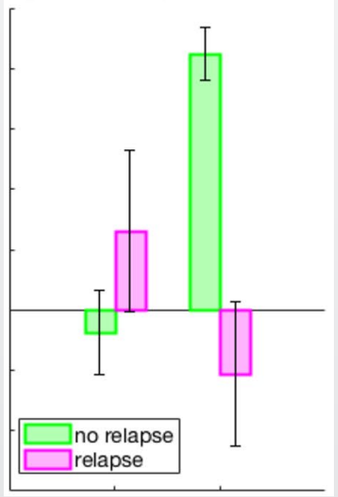


EEG Emotion reactivity

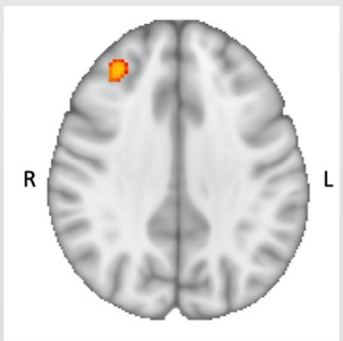
Mechanism



Amygdala Reactivity



dlPFC-PCC Connectivity



Memory

Mood reactivity

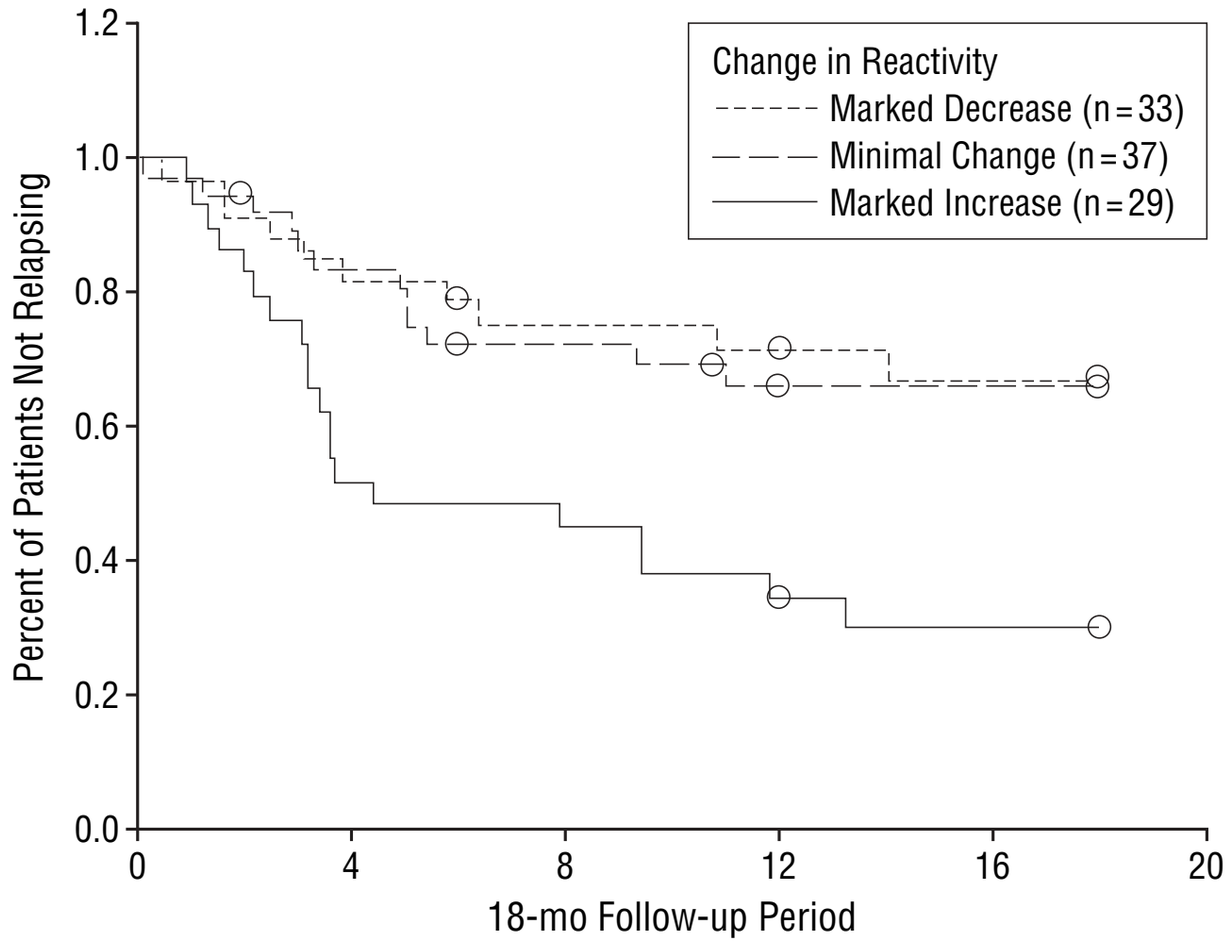
Sad mood

↓

Dysfunctional attitudes

↓

Maintenance?



Segal et al., 2006, 2010

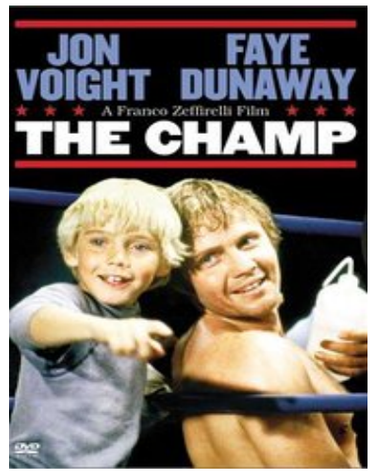
Neuroimaging

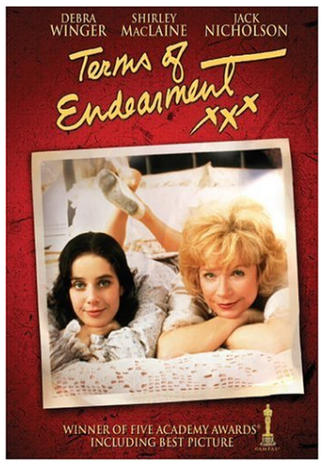
Neutral

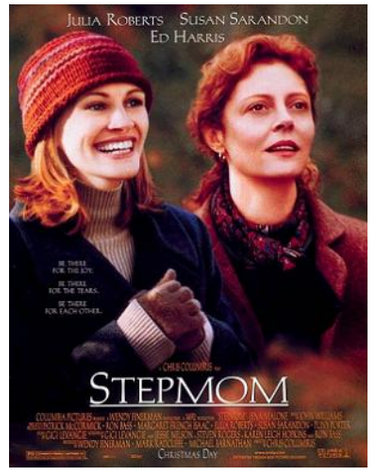
Sad

Neutral

Sad



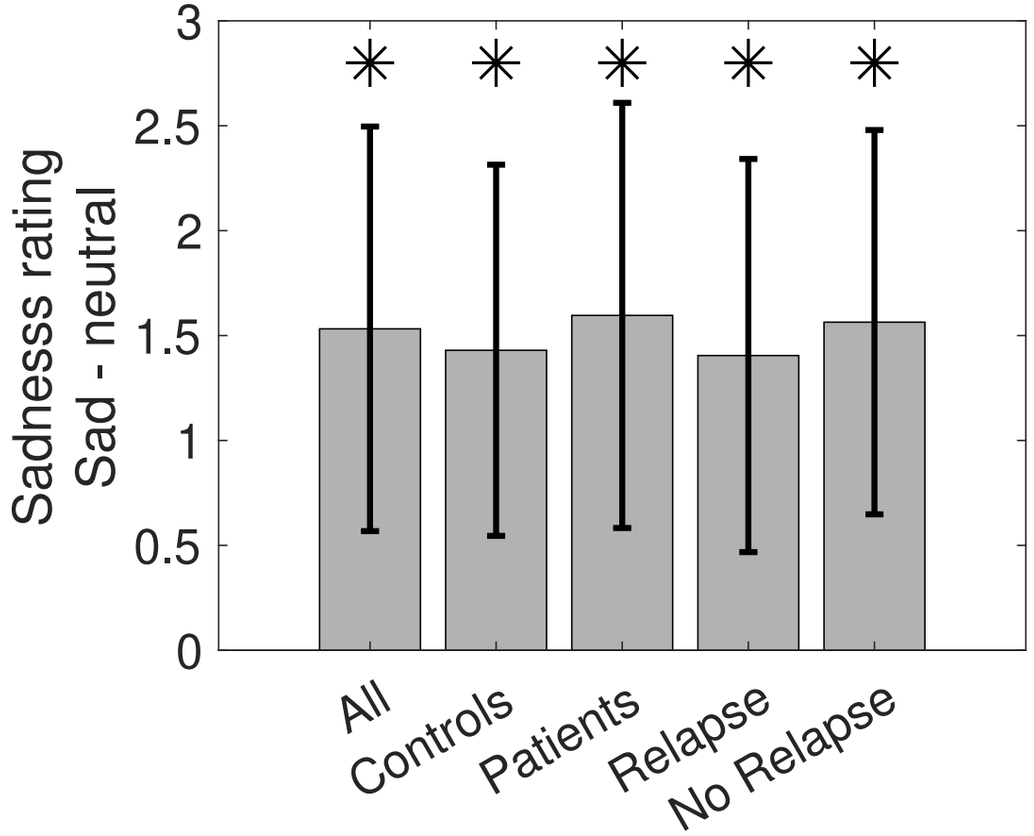




Farb et al., 2011

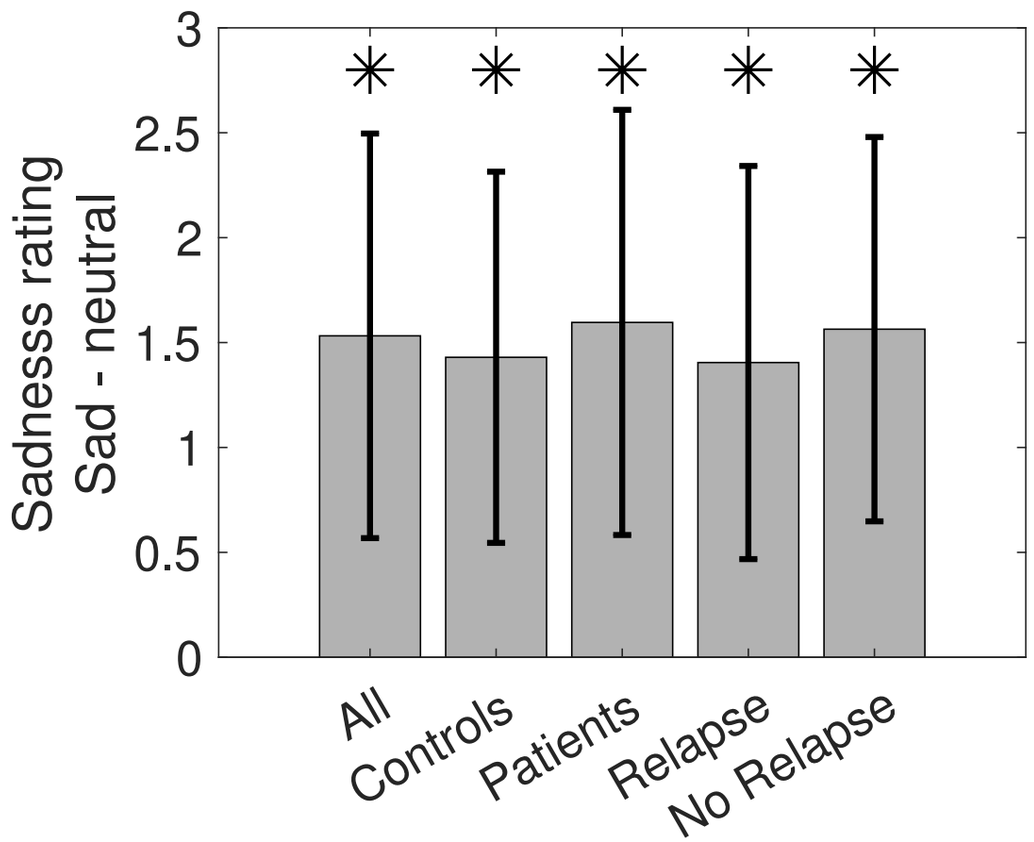
Sadness

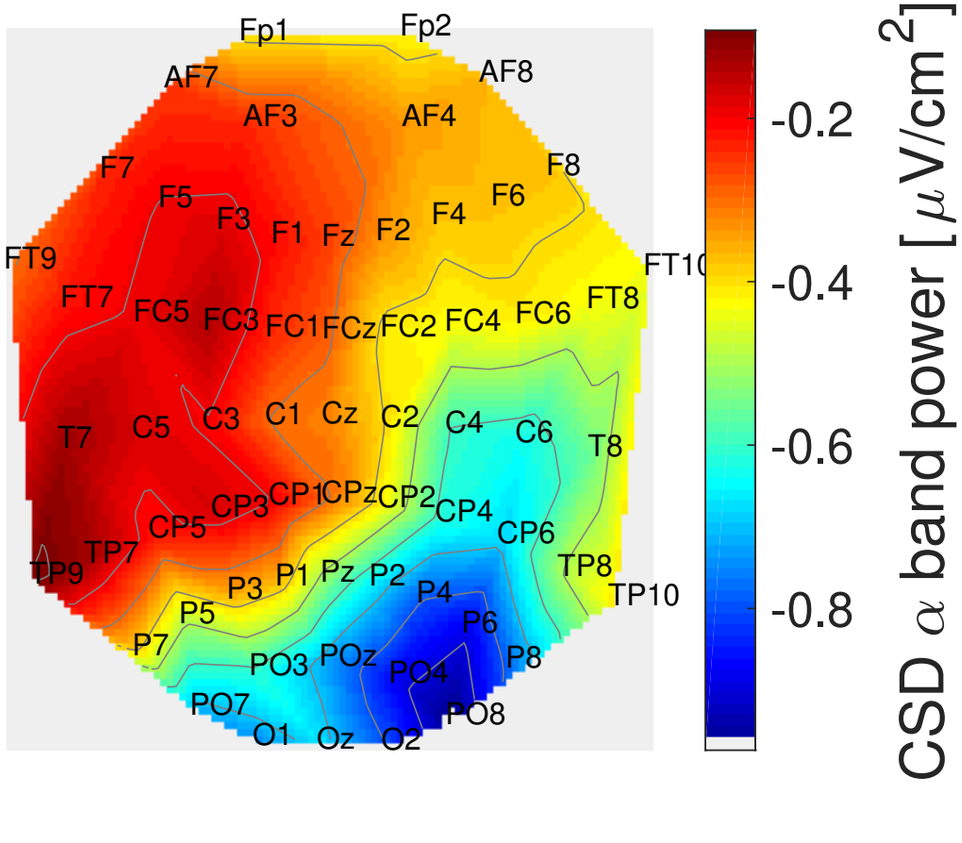
Marius Tröndle



Sadness

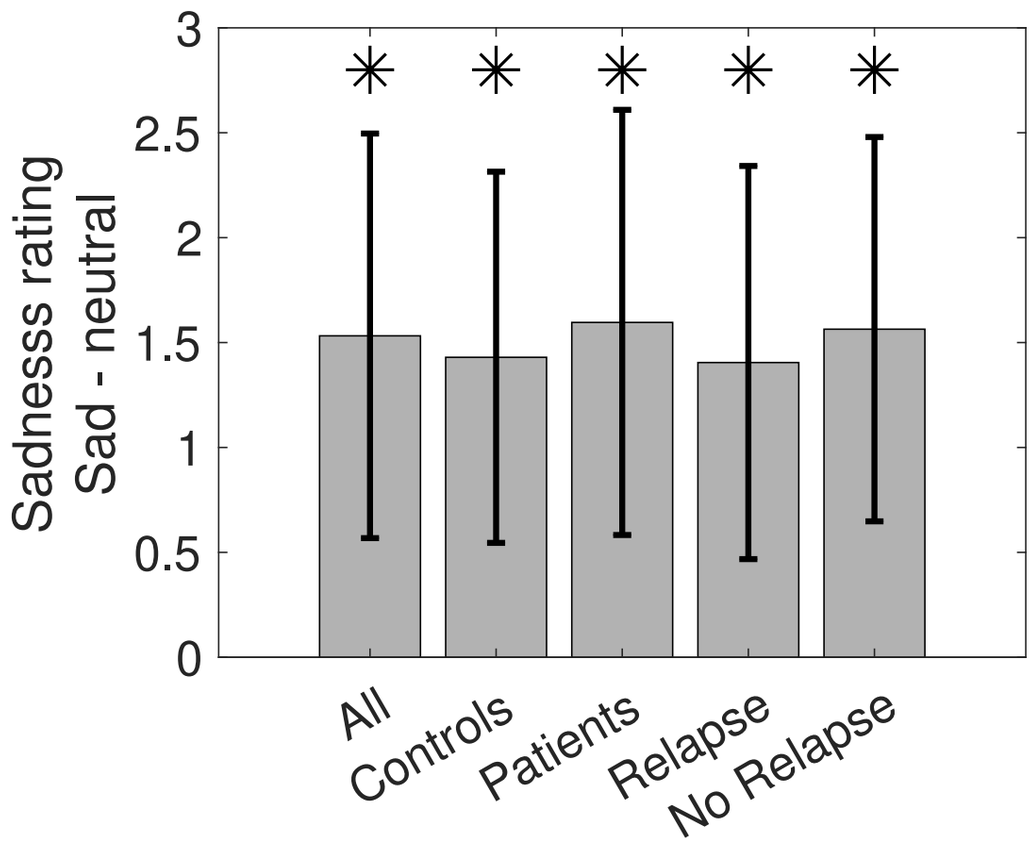
Marius Tröndle

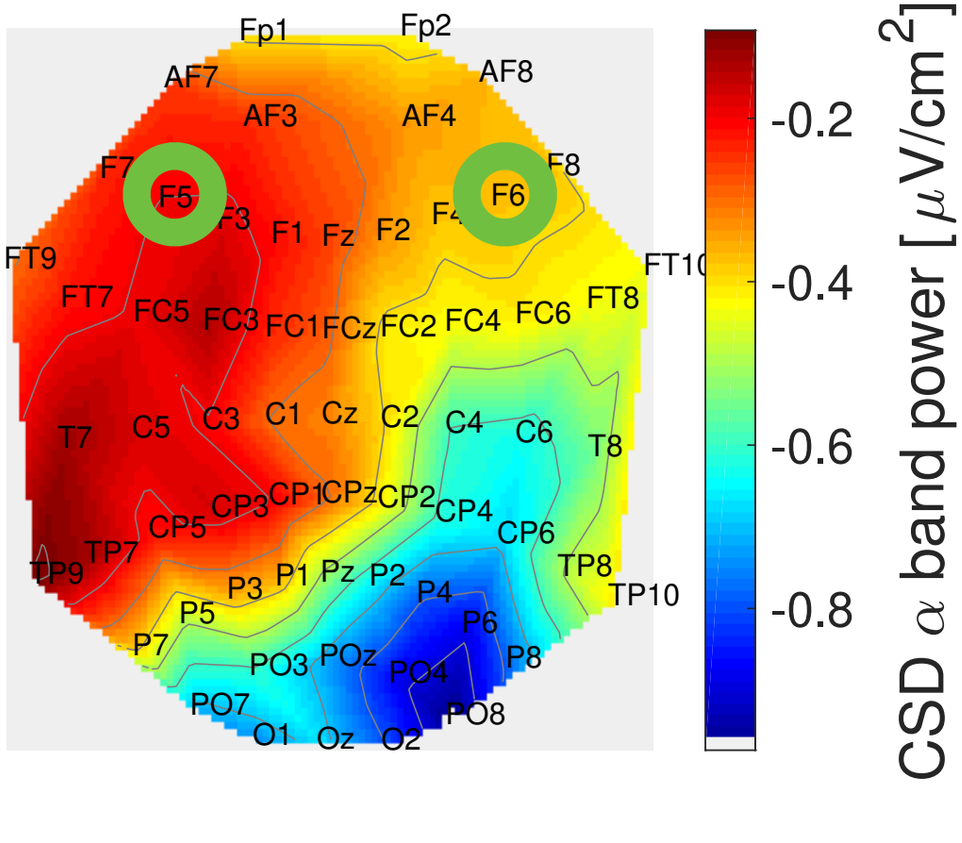




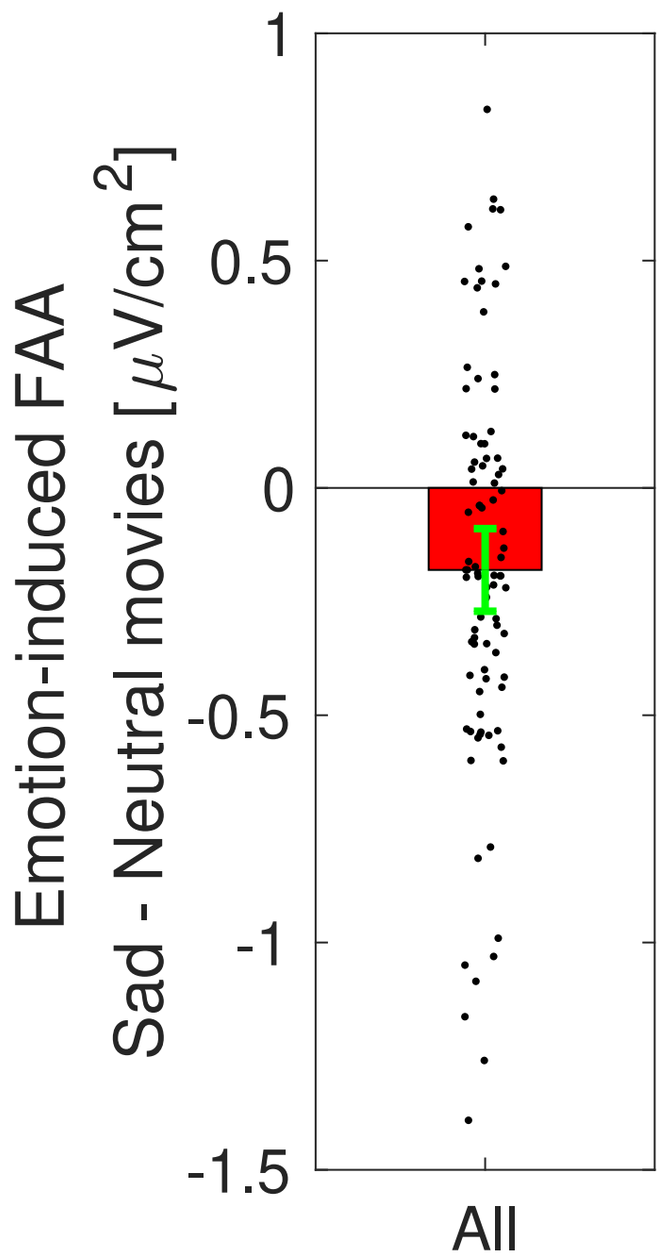
Sadness

Marius Tröndle



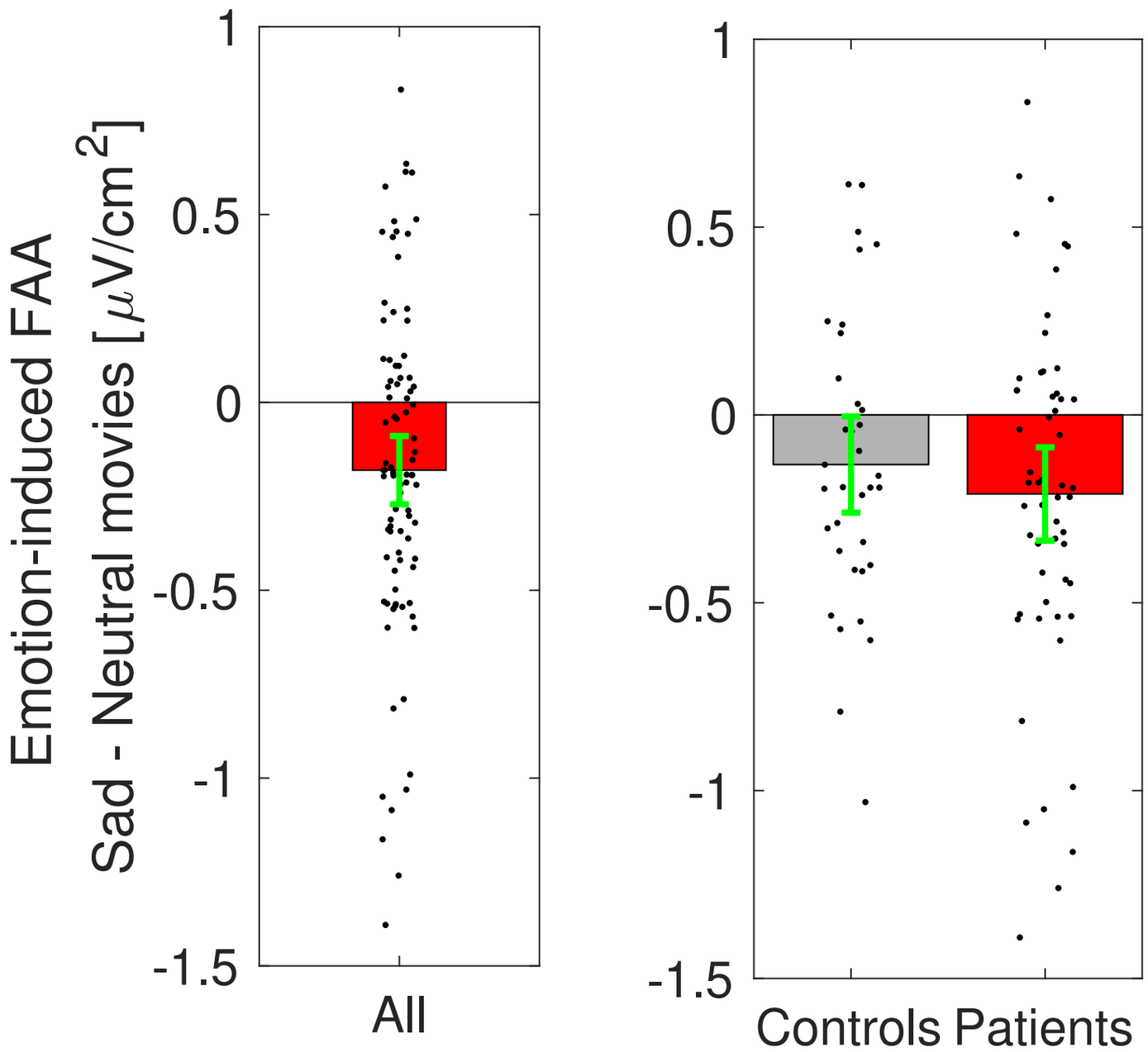


Emotion reactivity - relapse



p=0.0002

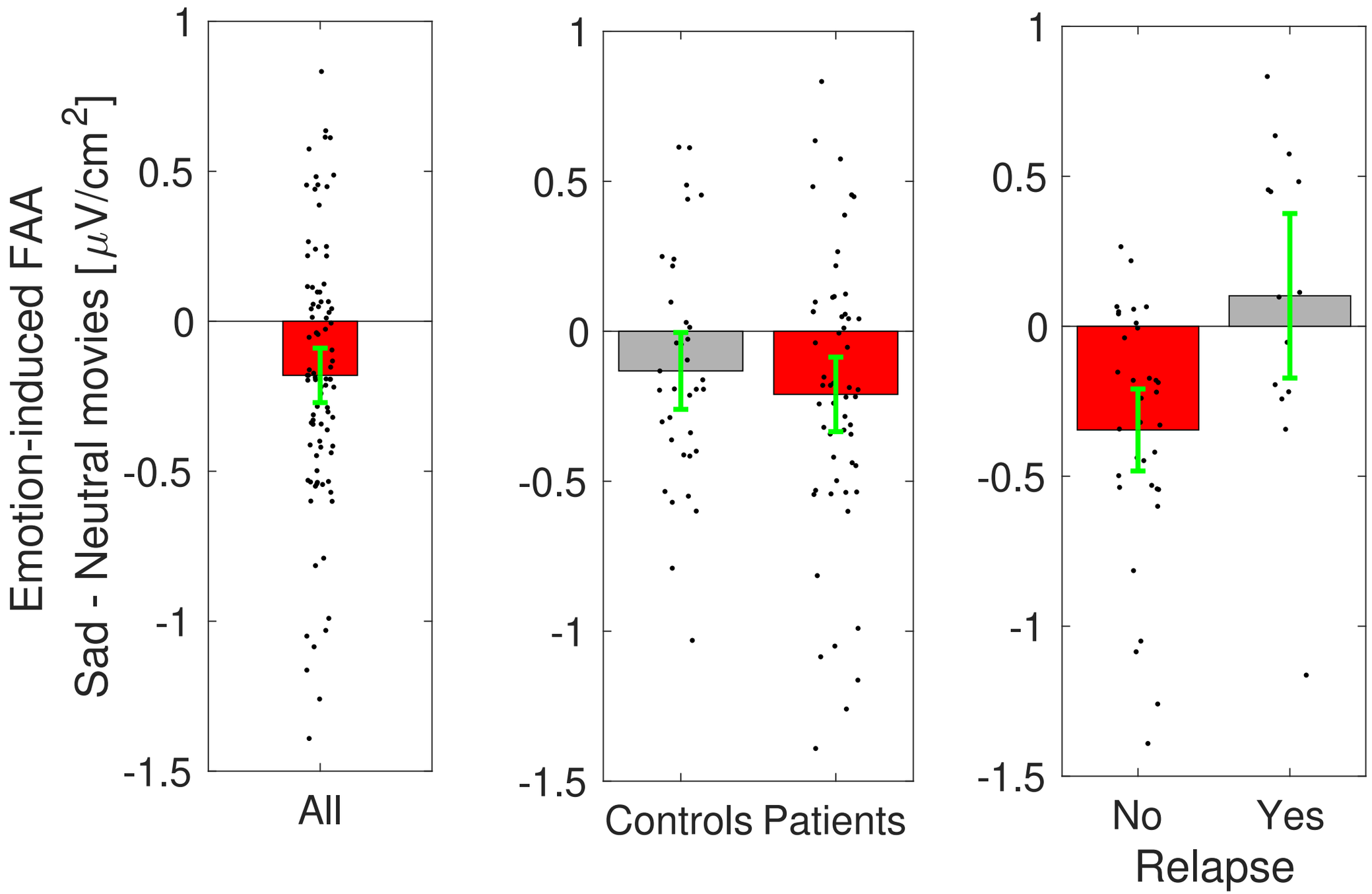
Emotion reactivity - relapse



p=0.0002

p=0.44

Emotion reactivity - relapse

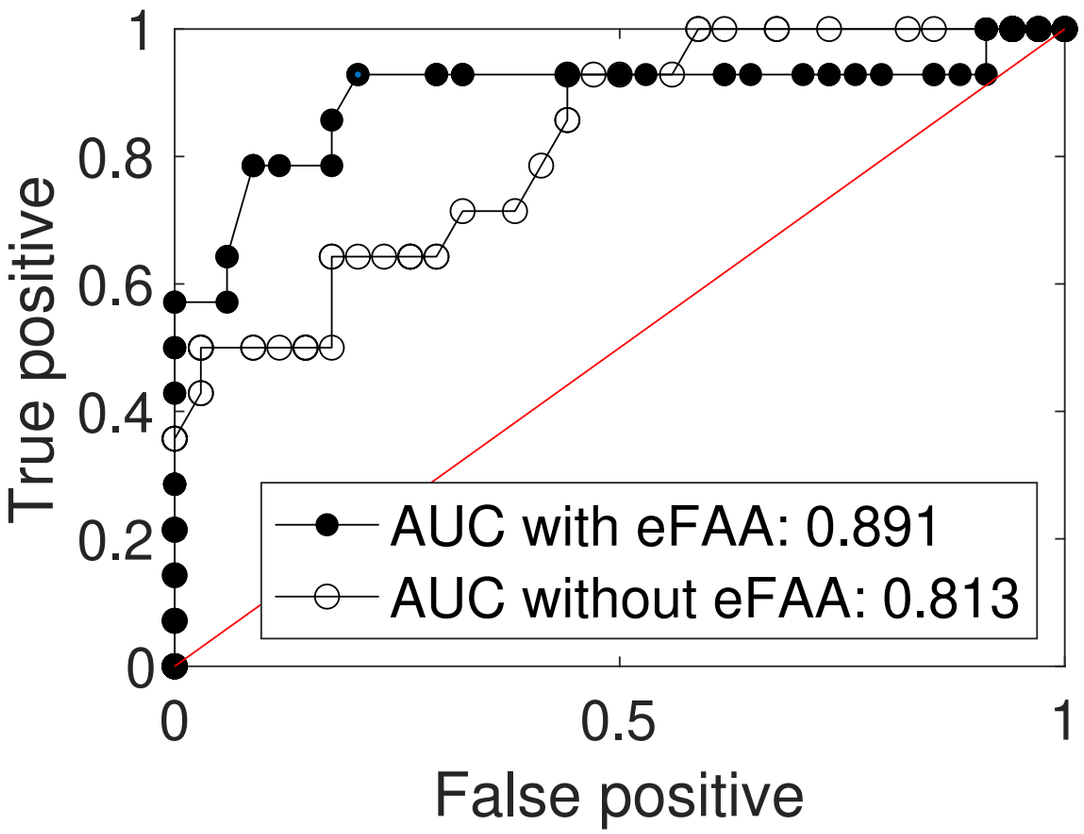


p=0.0002

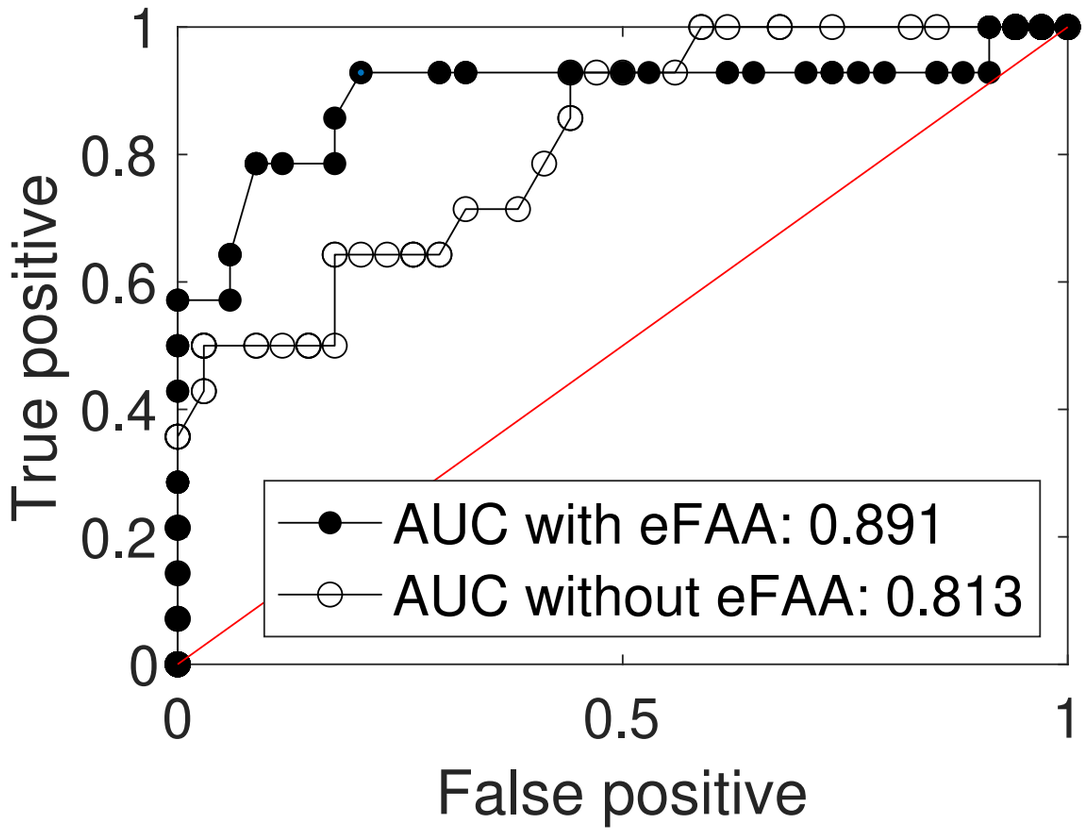
p=0.44

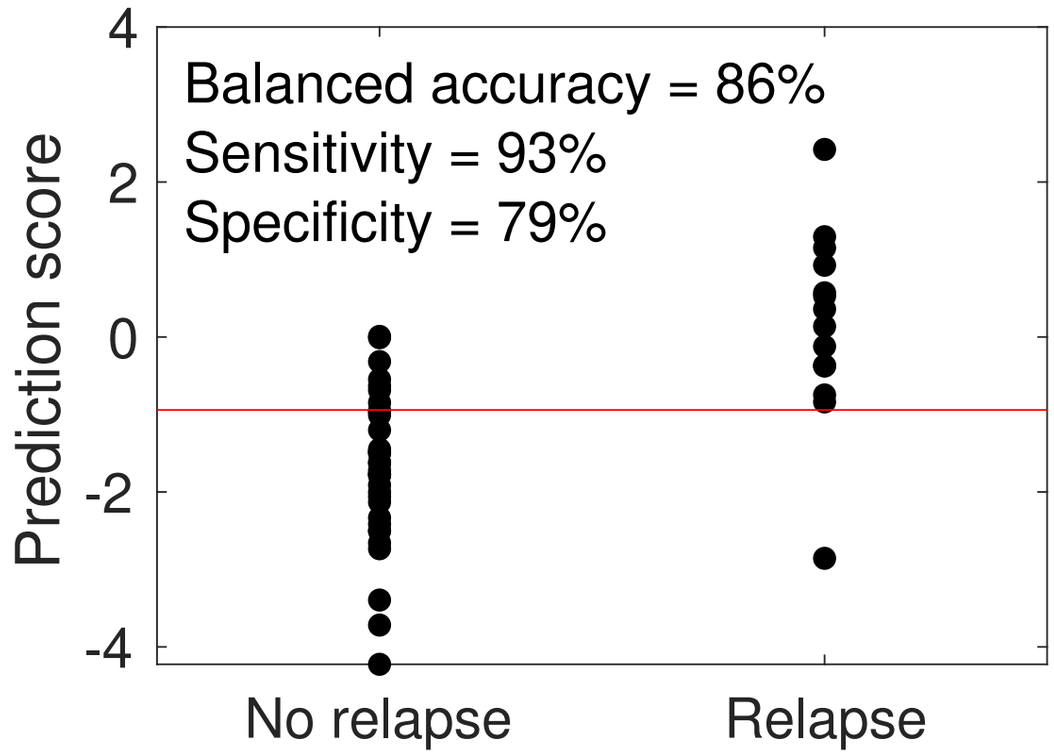
d'=0.9
p=0.003

Added value?


True positive
False positive
0
0.2
0.4
0.6
0.8
1
0
0.5
1
AUC with eFAA: 0.891
AUC without eFAA: 0.813

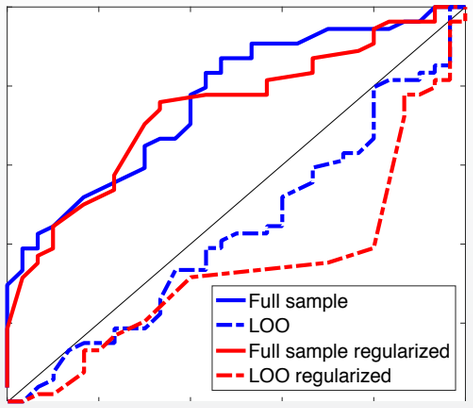
Added value?


True positive
False positive
0
0.2
0.4
0.6
0.8
1
0
0.5
1
AUC with eFAA: 0.891
AUC without eFAA: 0.813

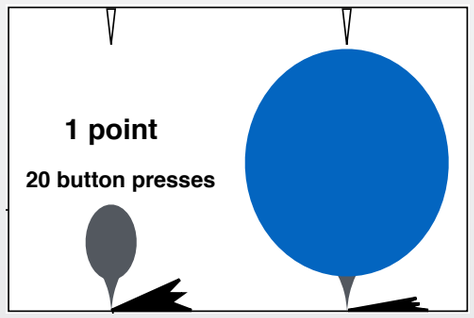

Balanced accuracy = 86%
Sensitivity = 93%
Specificity = 79%
Prediction
4
2
0
-2
-4
No relapse
Relapse

Outline

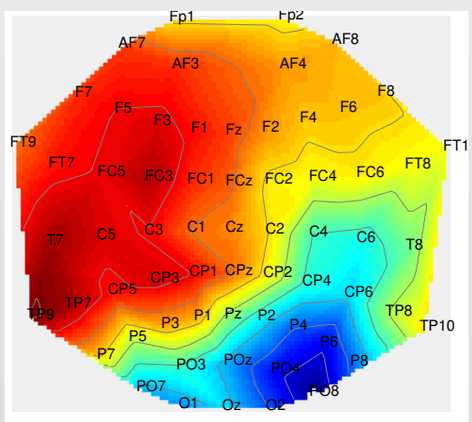
Prediction



Clinical variables

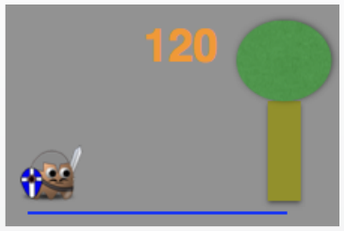


Effort

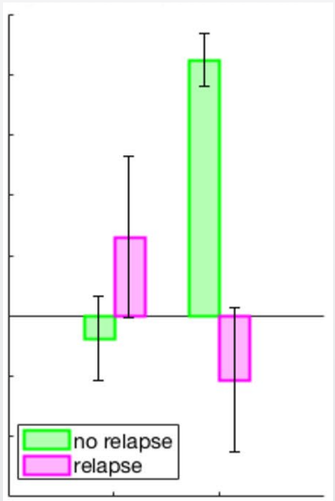


EEG Emotion reactivity

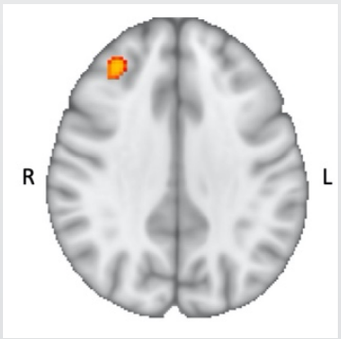
Mechanism



Vigour



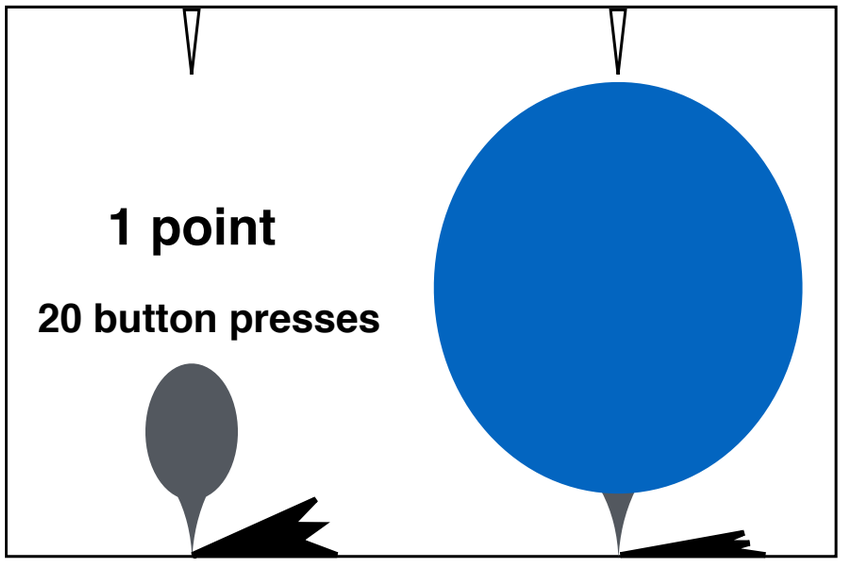
Amygdala Reactivity



dlPFC-PCC Connectivity

Memory

Effort



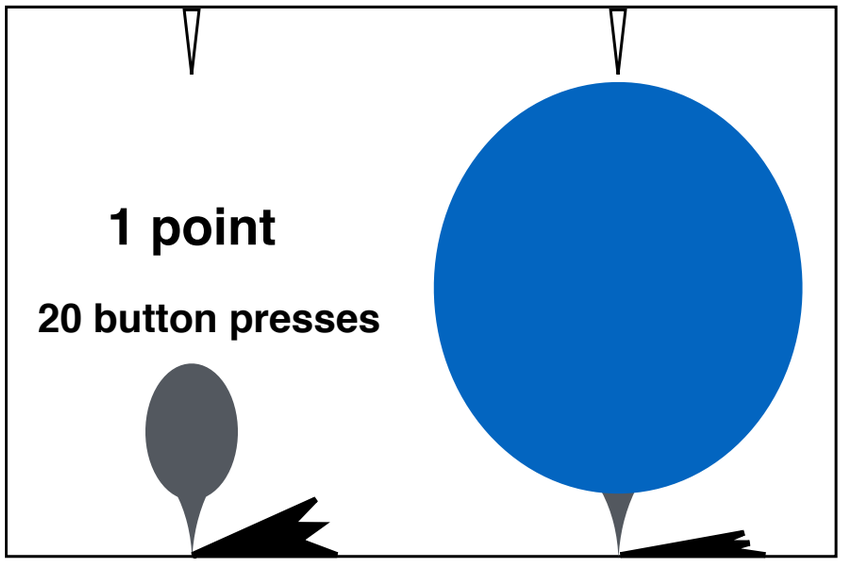
Decision variables did not change with discontinuation.

Trend-level change in vigour.

p=0.059

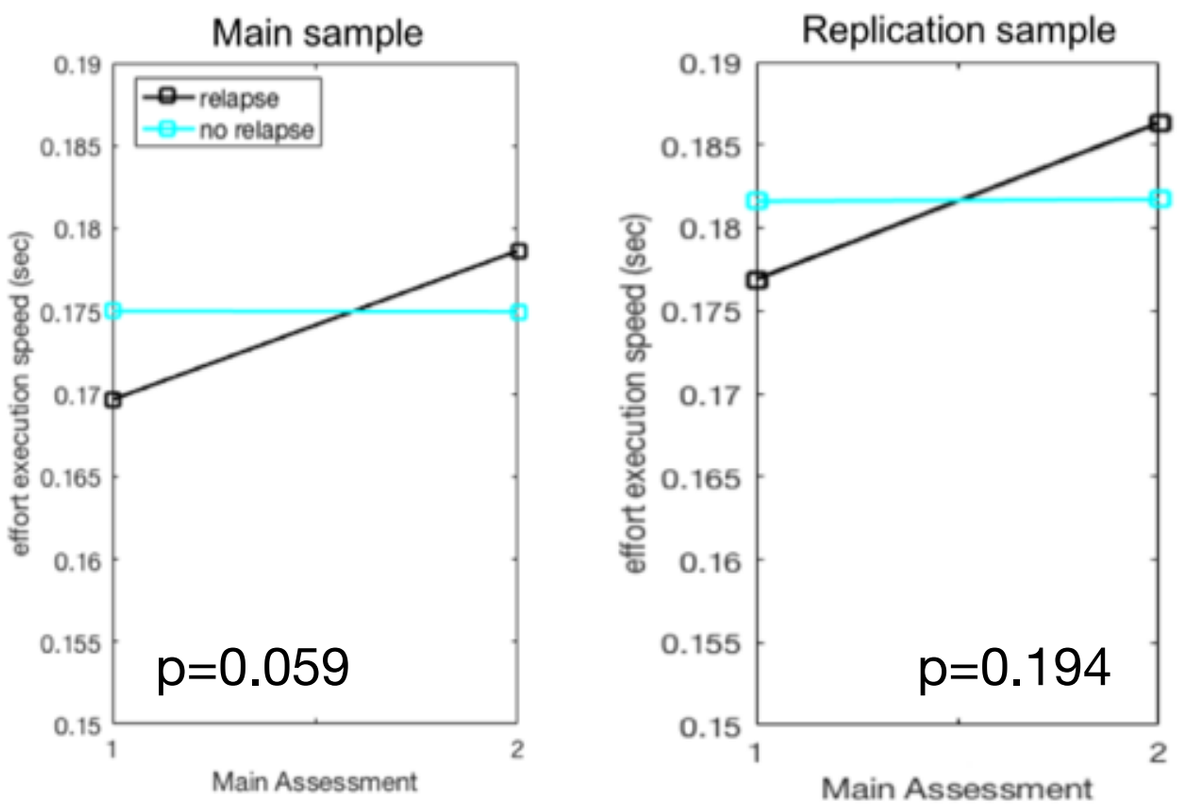
p=0.194

Effort

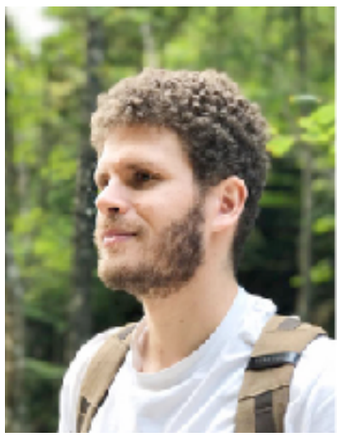


Decision variables did not change with discontinuation.

Trend-level change in vigour.

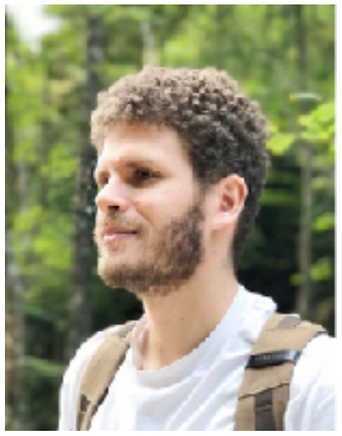


Choice, foraging and vigour



Evan Russek

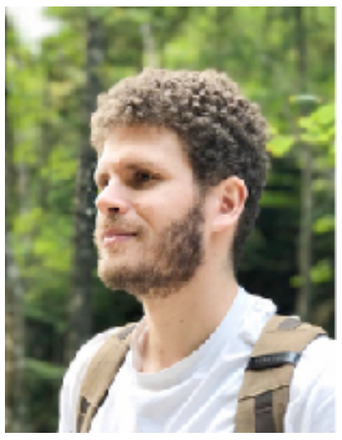
Choice, foraging and vigour



Evan Russek

Foraging

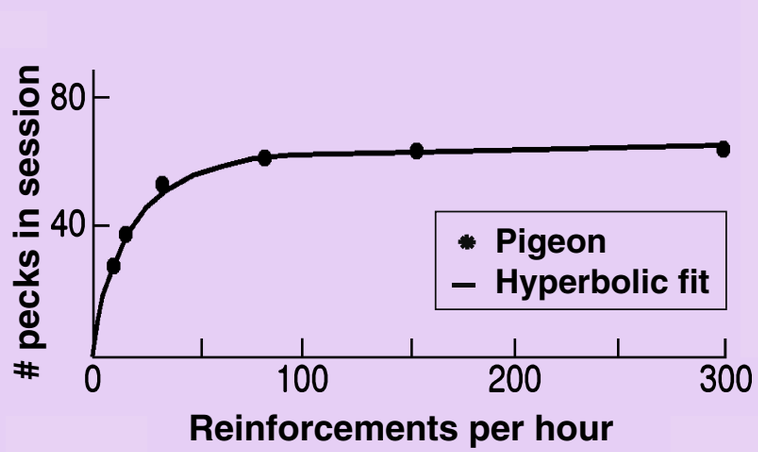
Choice, foraging and vigour



Evan Russek

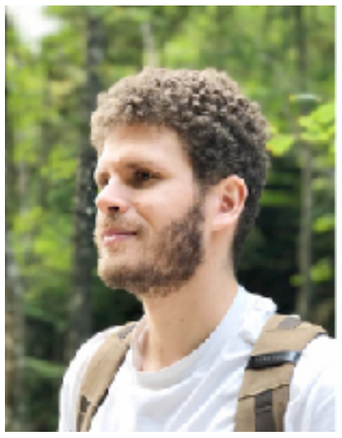
Foraging

Vigour



Niv, Daw, Dayan 2007 Psychopharmacology

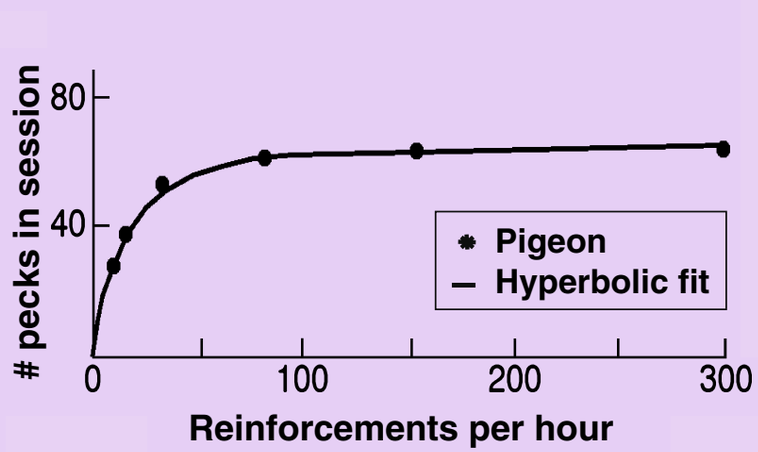
Choice, foraging and vigour



Evan Russek

Foraging

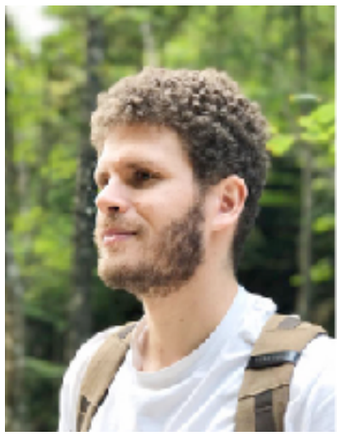
Vigour



Niv, Daw, Dayan 2007 Psychopharmacology

Average reward rate ρ

Choice, foraging and vigour



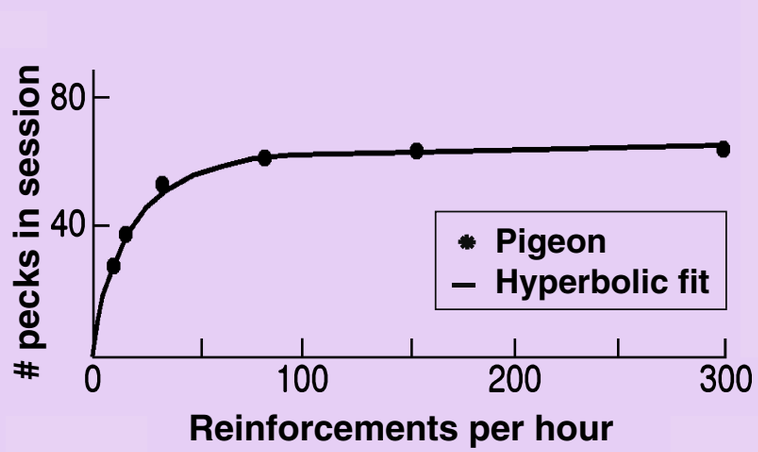
Evan Russek

Foraging

MVT

$$\frac{\mathbb{E}[r]}{\tau} < \rho$$

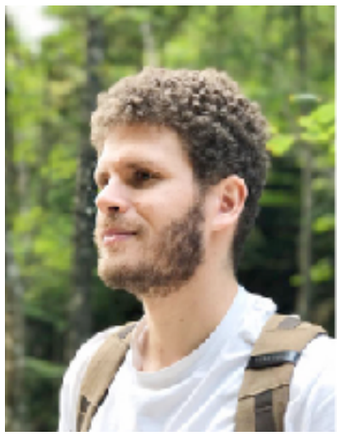
Vigour



Niv, Daw, Dayan 2007 Psychopharmacology

Average reward rate ρ

Choice, foraging and vigour



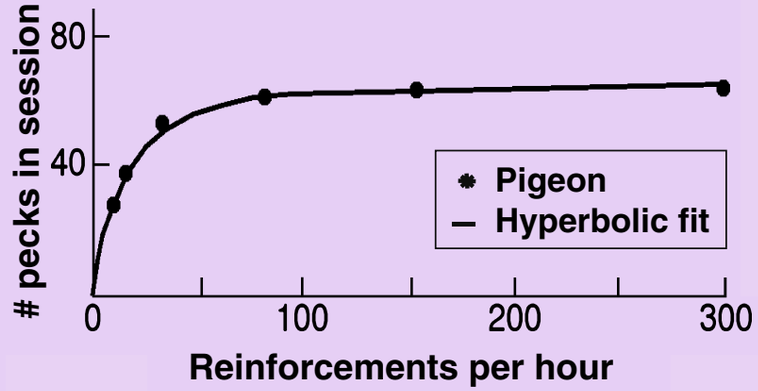
Evan Russek

Foraging

MVT

$$\frac{\mathbb{E}[r]}{\tau} < \rho$$

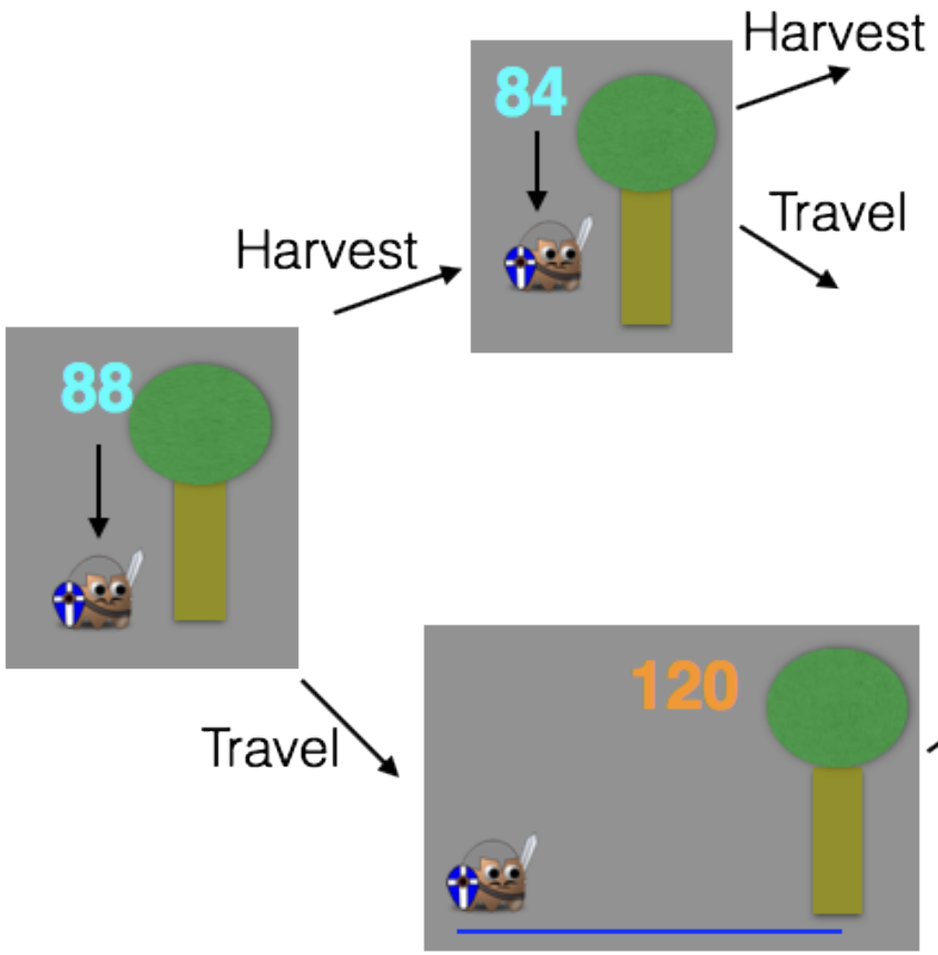
Vigour $\propto \sqrt{\frac{1}{\rho}}$



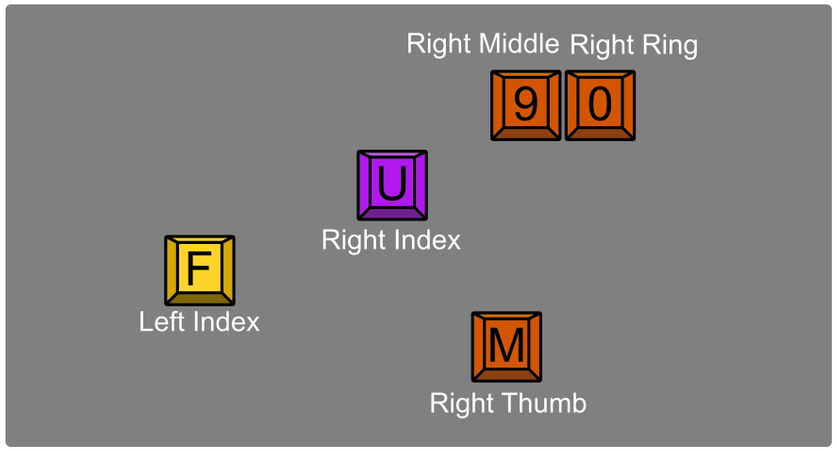
Niv, Daw, Dayan 2007 Psychopharmacology

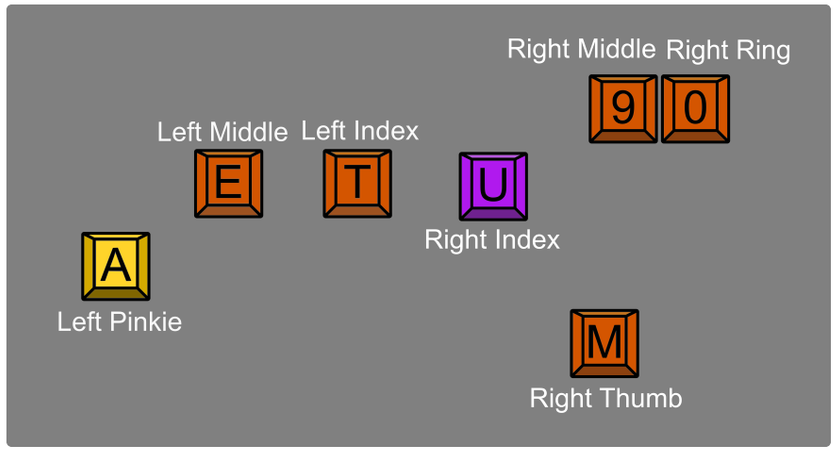
Average reward rate ρ

Effortful foraging task



Press travel key repeatedly to reach new tree





Different average rates

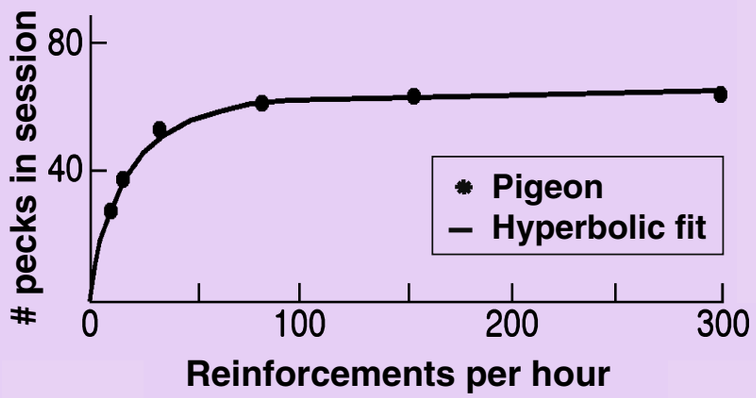
Foraging

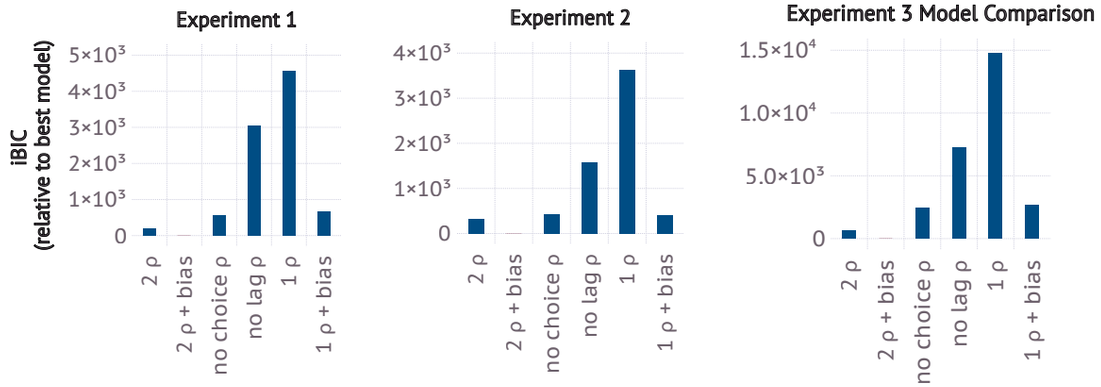
MVT

$$\frac{\mathbb{E}[r]}{\tau} < \rho$$

Average reward rate ρ

Vigour $\propto \sqrt{\frac{1}{\rho}}$

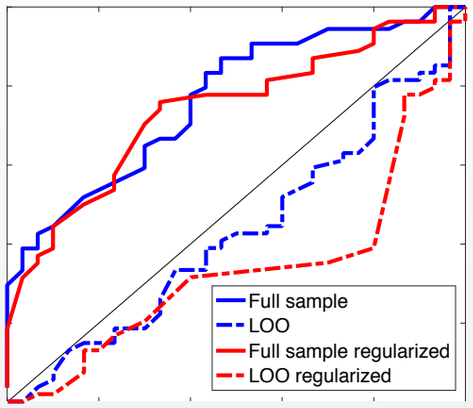




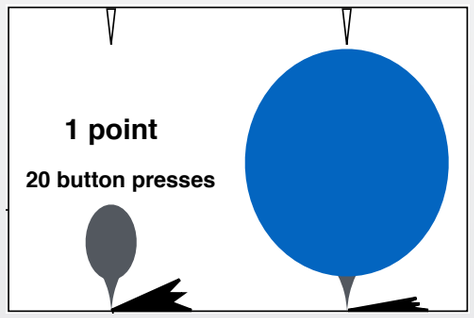
Vigour and foraging choice are driven by different average reward rate estimates

Outline

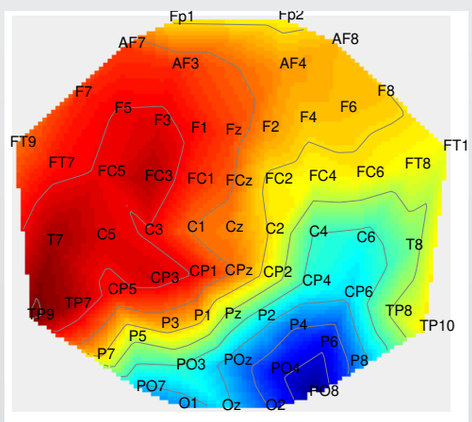
Prediction



Clinical variables

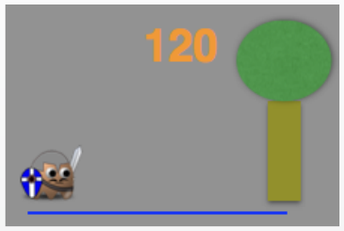


Effort

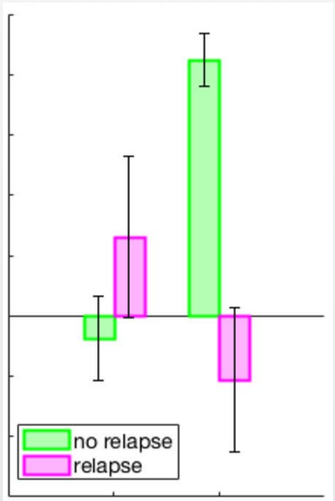


EEG Emotion reactivity

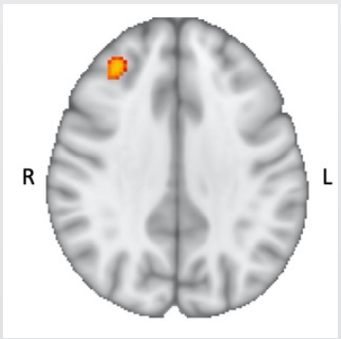
Mechanism



Vigour



Amygdala Reactivity

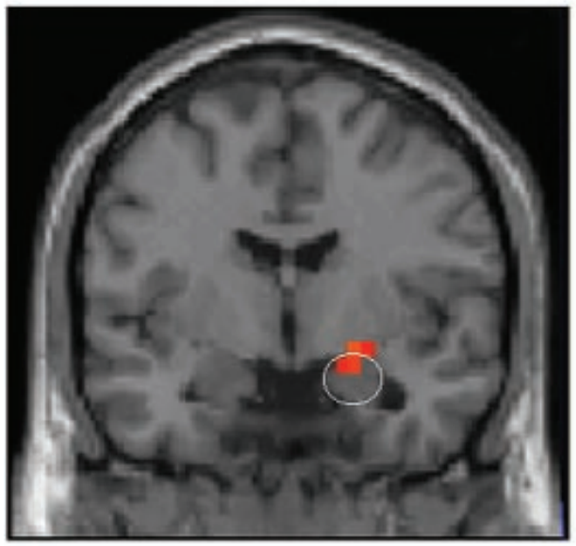


dlPFC-PCC Connectivity

Memory

Amygdala reactivity

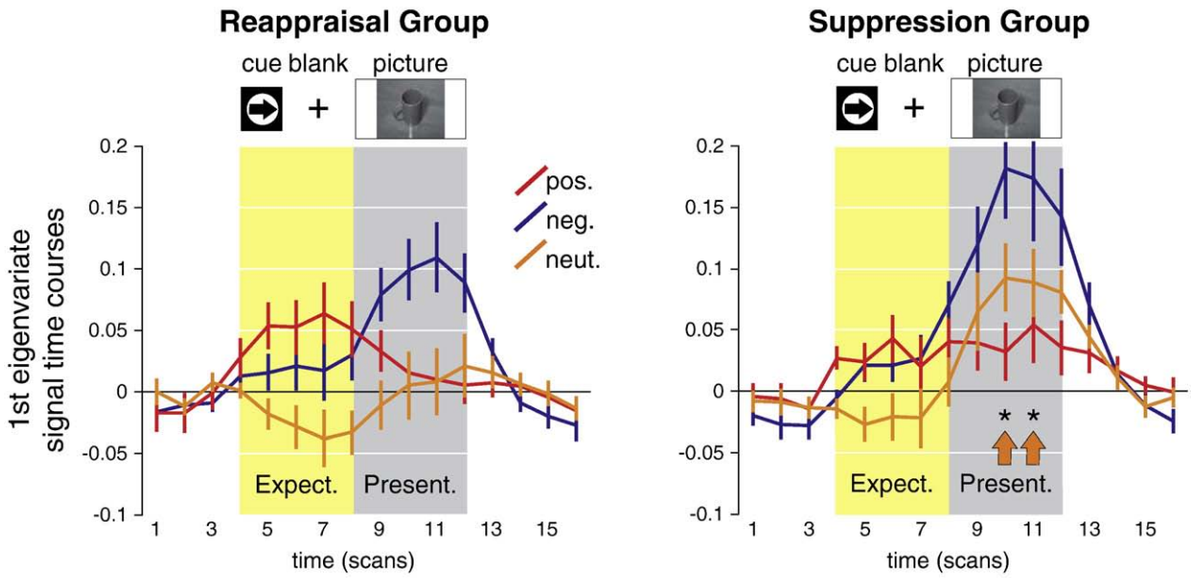
5HTTLPR variation



First Cohort
(N = 14)

Hariri et al., 2002 Science

Habitual emotion regulation

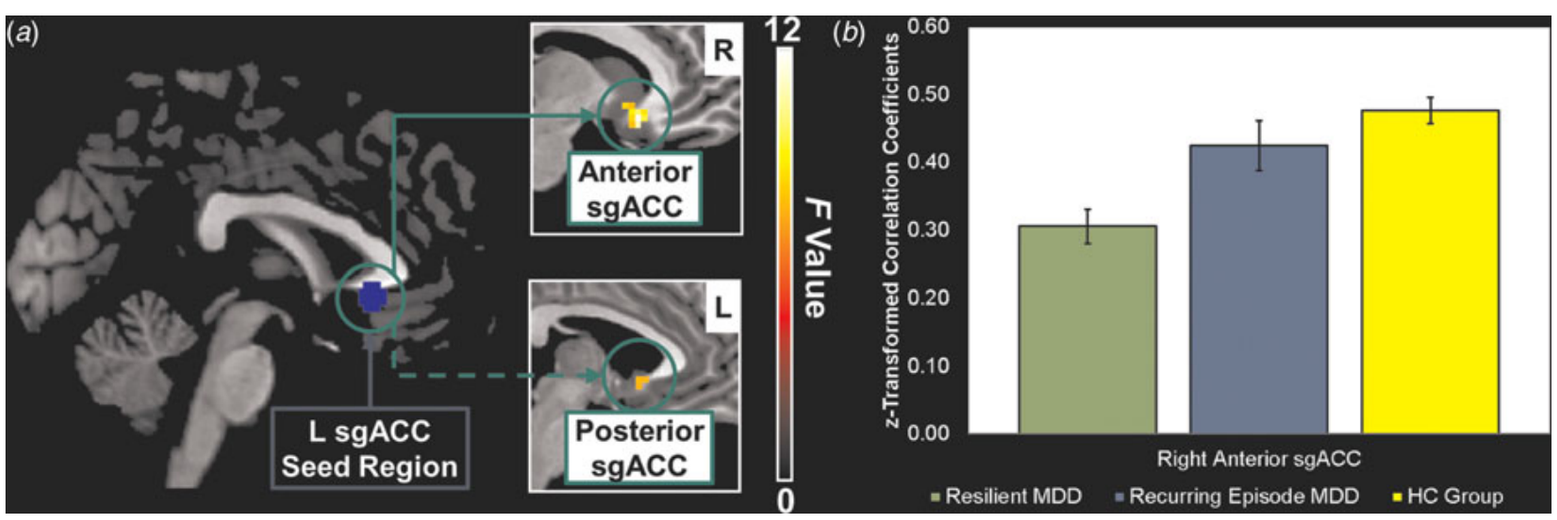


Abler et al., 2010 J. Neurosci

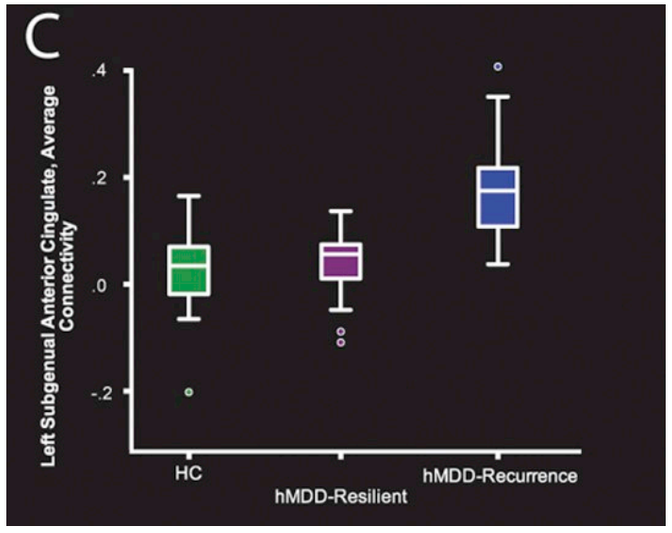
Slide omitted

Resting-state fMRI

- In MDD, see abnormalities in
  - Default mode network
  - Reduced connectivity CEN and SN
- Relapse



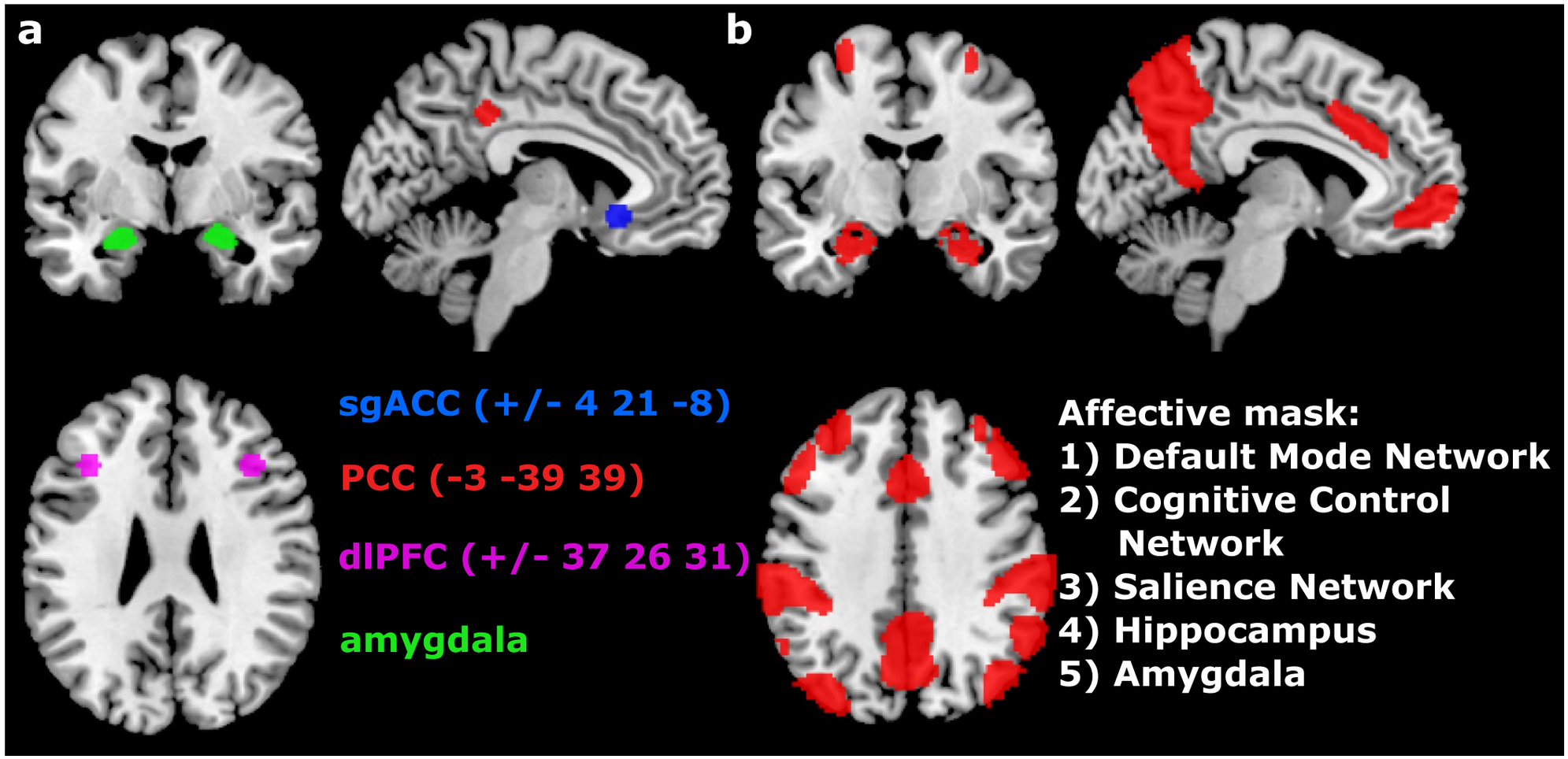
Workman et al., 2017 Psychol Med



Langenecker et al., 2018 Neuroim Clin

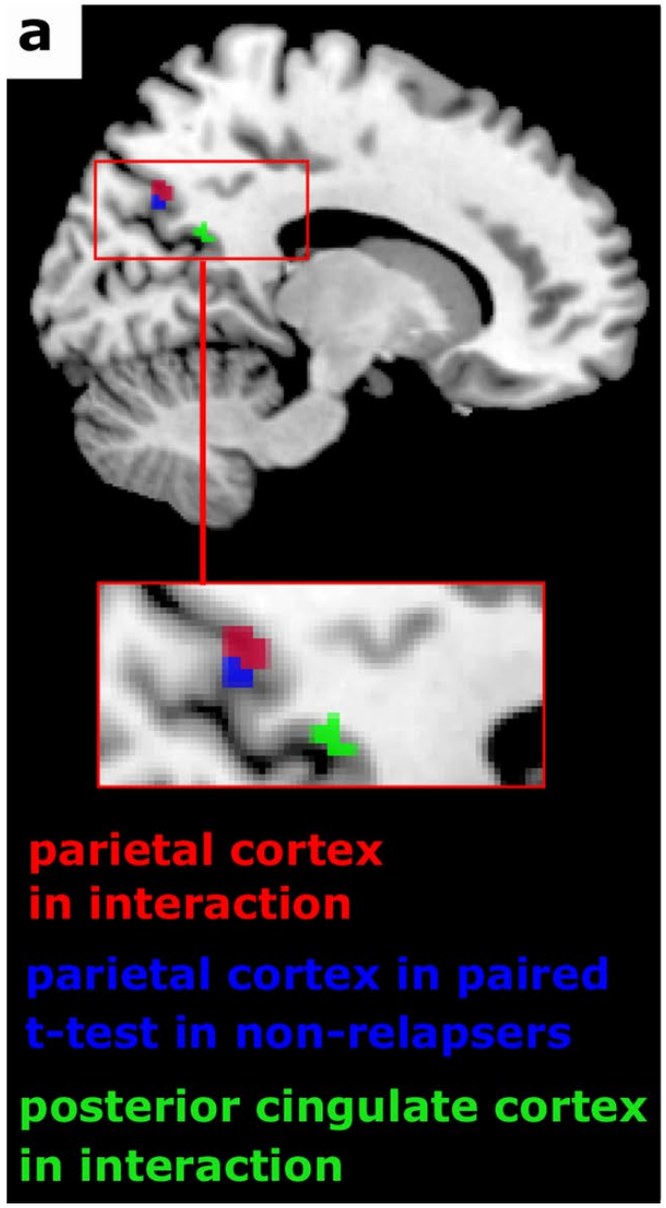
Kaiser et al., 2015 JAMA Psych;

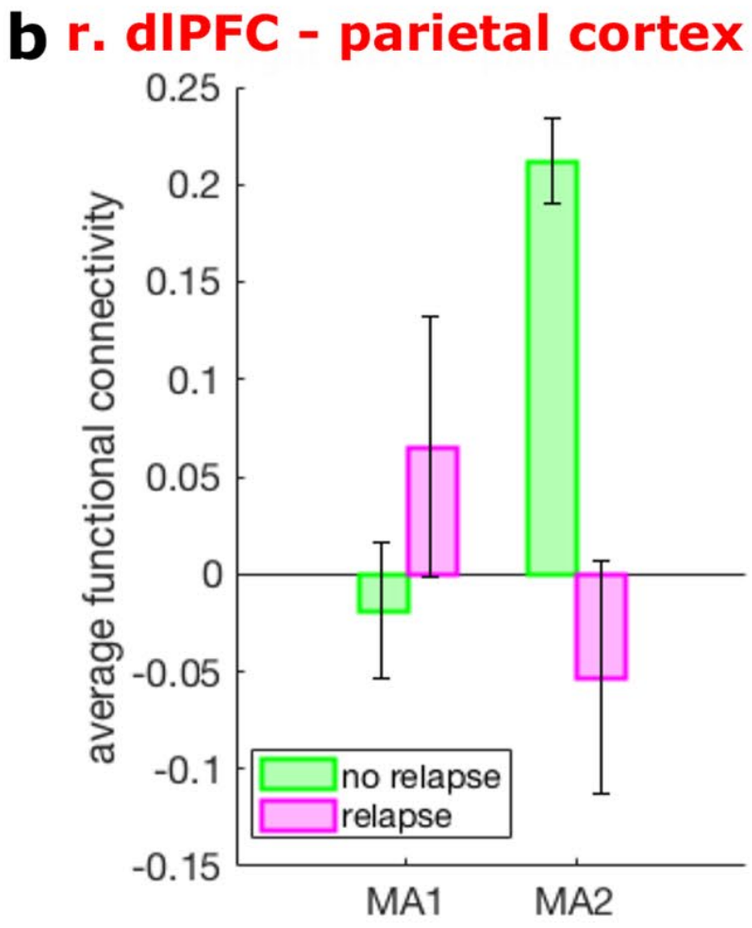
- Seed-based approach
- Connectivity to affective mask

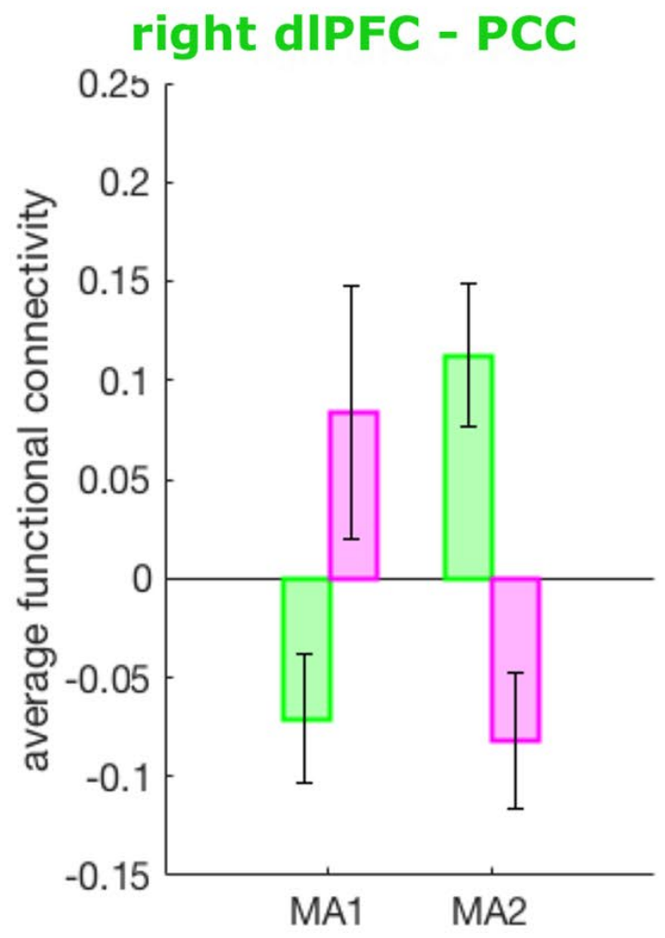


Berwian et al., 2020 Sci Reports

Relating discontinuation to relapse

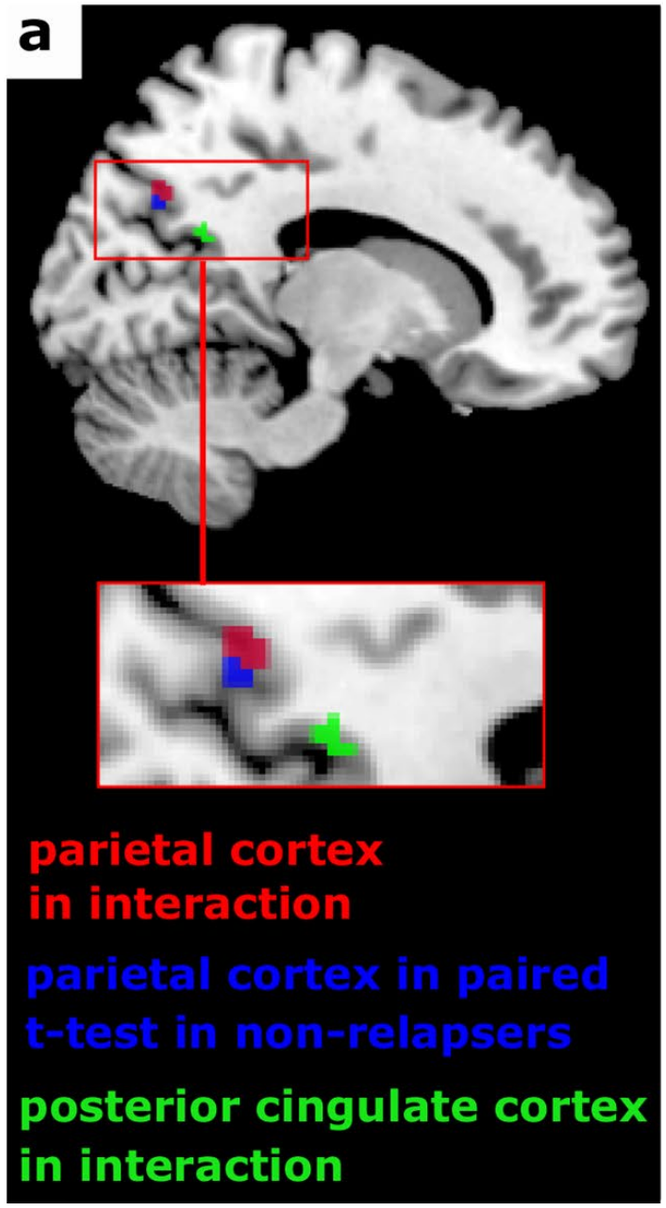


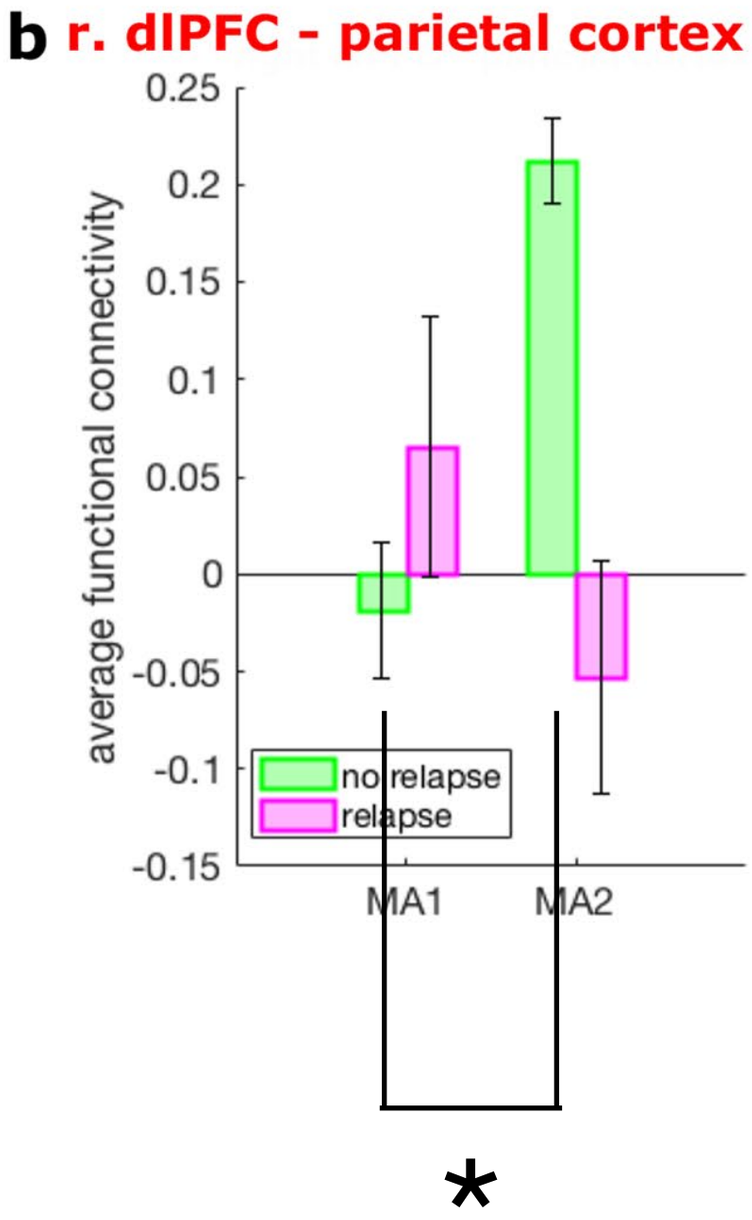


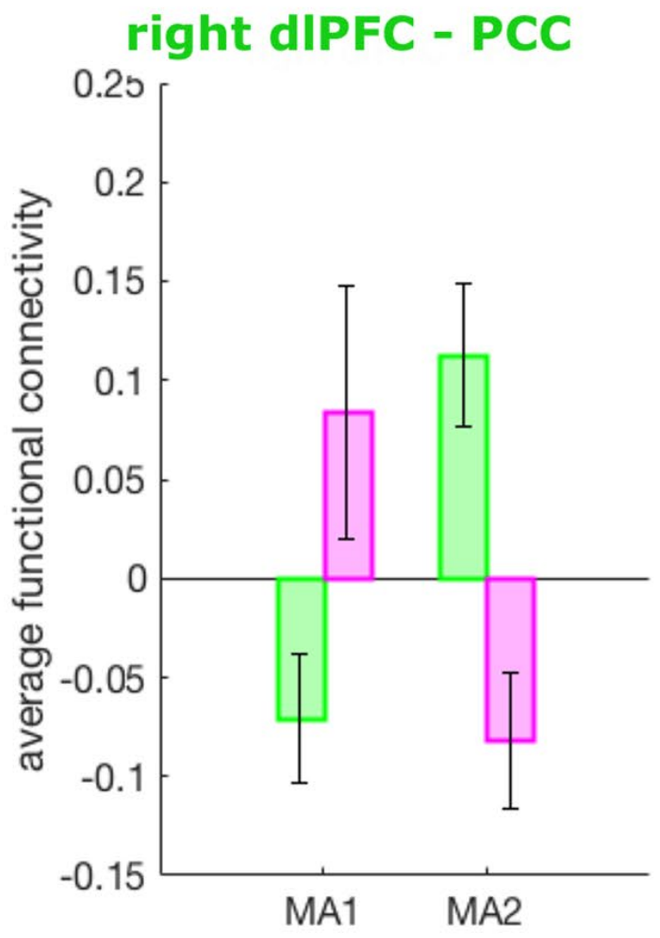


Berwian et al., 2020 Sci Reports

Relating discontinuation to relapse







Berwian et al., 2020 Sci Reports

Episodic memory

- Clinically often impaired in depression
- Highly dependent on hippocampus
  - HC volume reductions in MDD
- Heterogeneous findings re neural activity
- Erk et al. task

Kuehn, Erk et al., submitted

Episodic memory

- Clinically often impaired in depression
- Highly dependent on hippocampus
  - HC volume reductions in MDD
- Heterogeneous findings re neural activity
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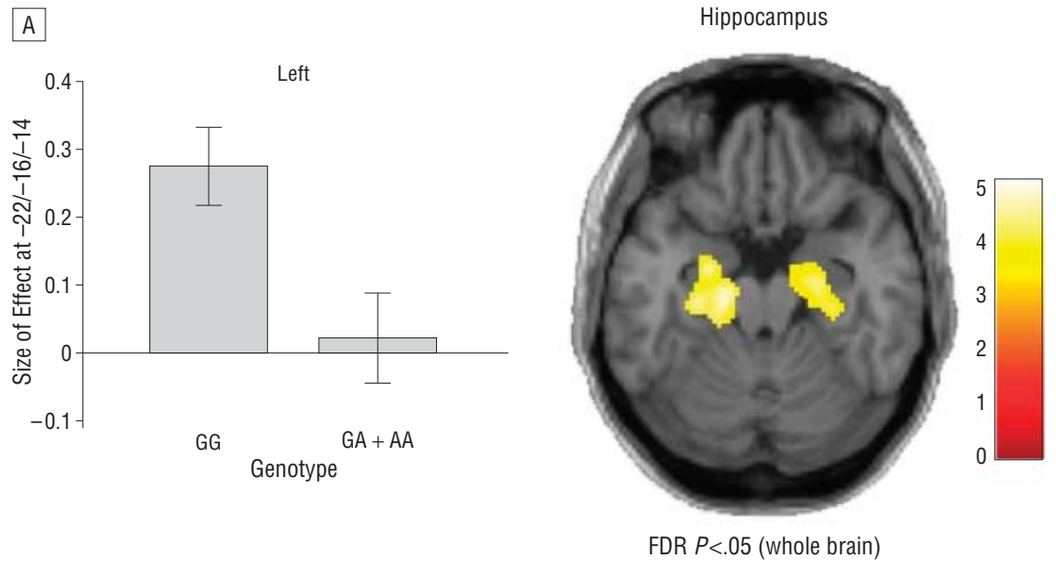

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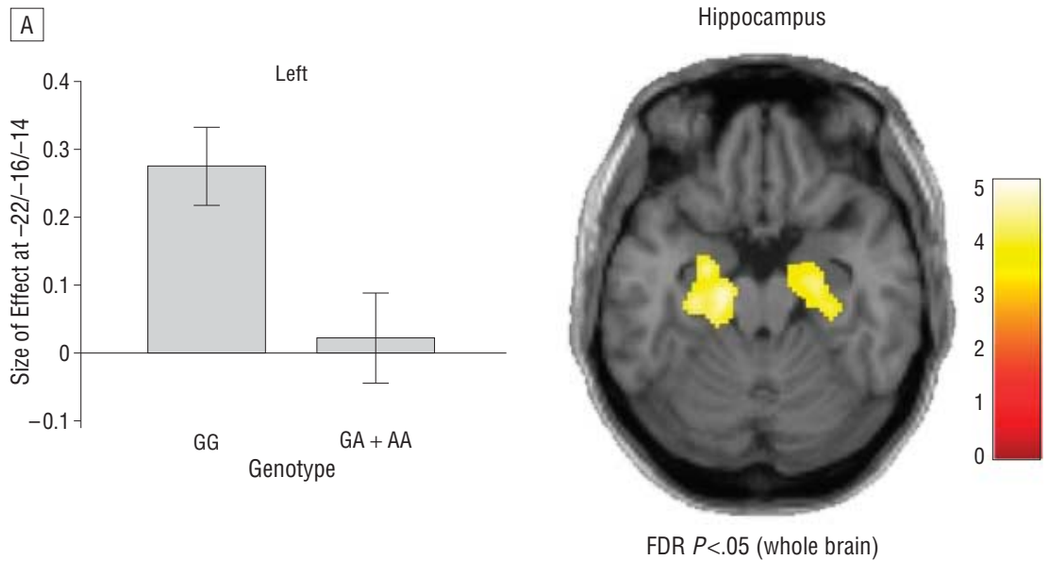

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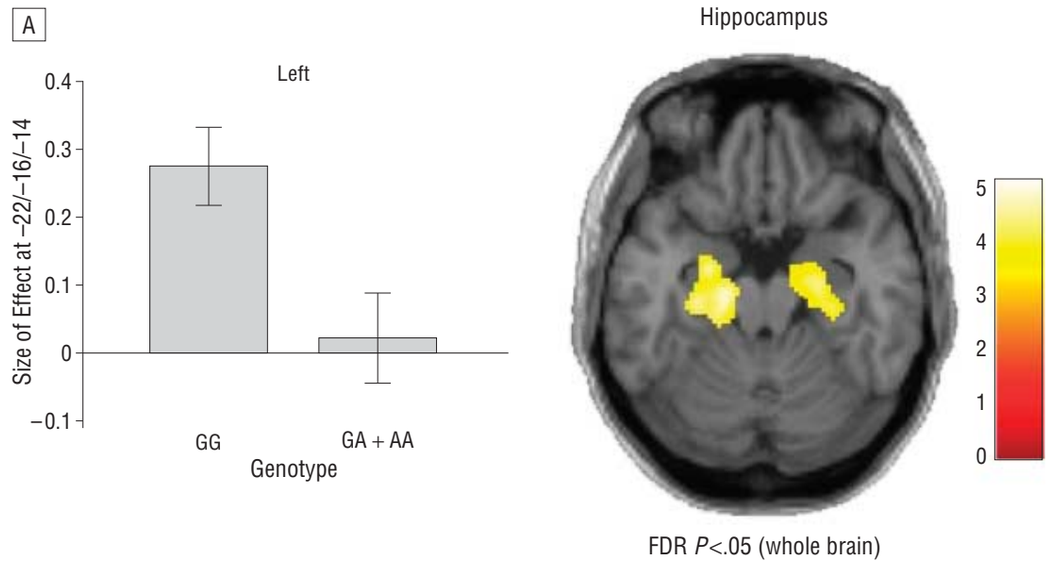

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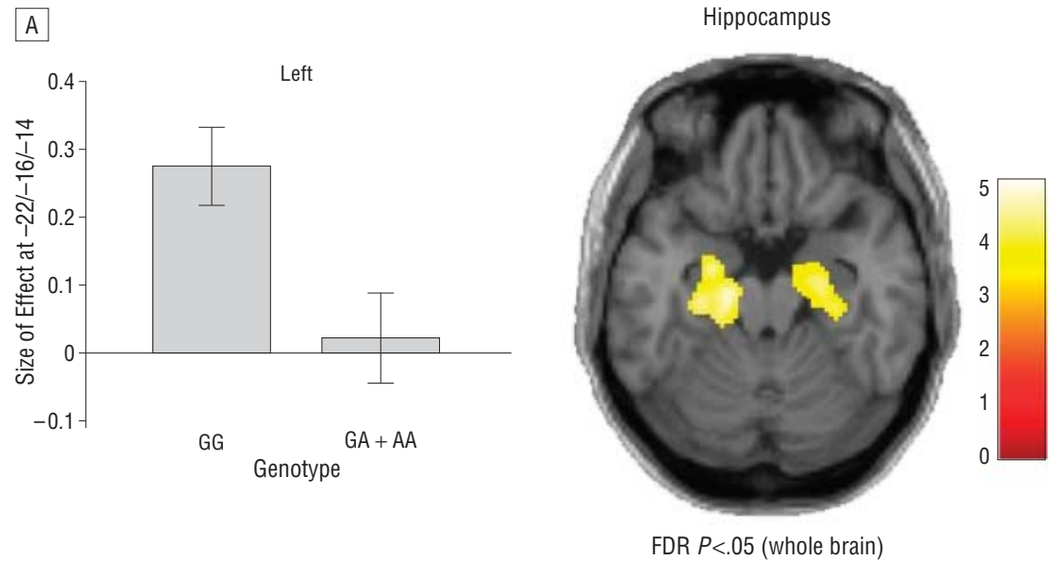

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Slide omitted

Summary

- Remitted, medicated state
  - Ambivalence in effort-related decisions

- Predictive risk factors for relapse after discontinuation
  - Slower effort-related decision-making
  - Flatter sadness-induced alpha power

- Discontinuation effect
  - Reduced vigour
  - dlPFC compensatory memory recruitment

- How does discontinuation result in relapse?
  - Amygdala hyper-reactivity
  - Connectivity dlPFC - PCC

Outlook

- Relapse after discontinuation is predictable
  - Important clinically
  - Effort & affective reactivity

- Discontinuation has identifiable behavioural and neurobiological signatures, some of which relate to relapse
  - Vigour, amygdala reactivity and connectivity

- Can we get closer?
  - Use MEG and fast inference of decision-making algorithms in combination with 5HT manipulations

Thought biases

- Think of driving fast

Russek et al., in prep.

Thought biases

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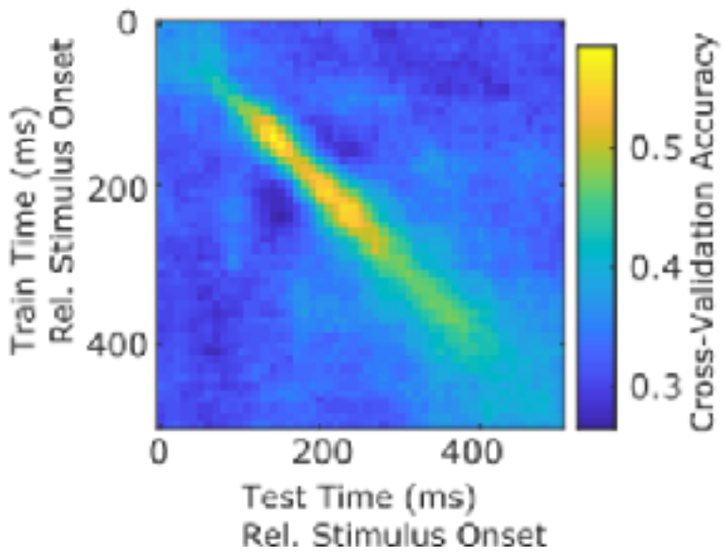

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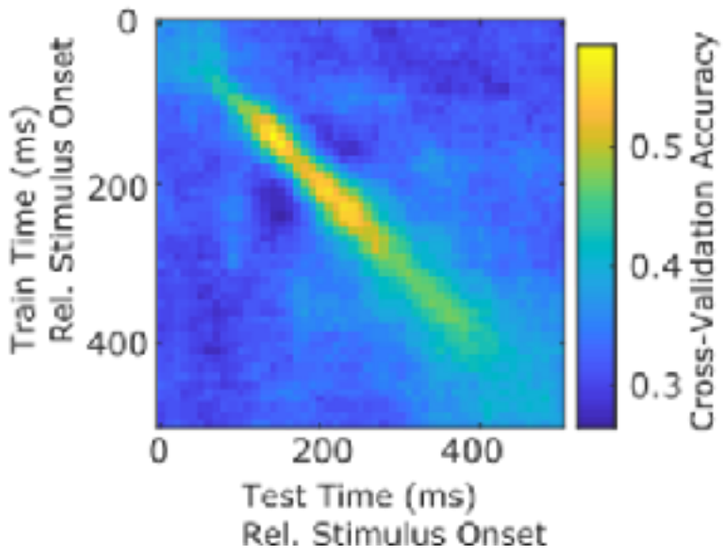

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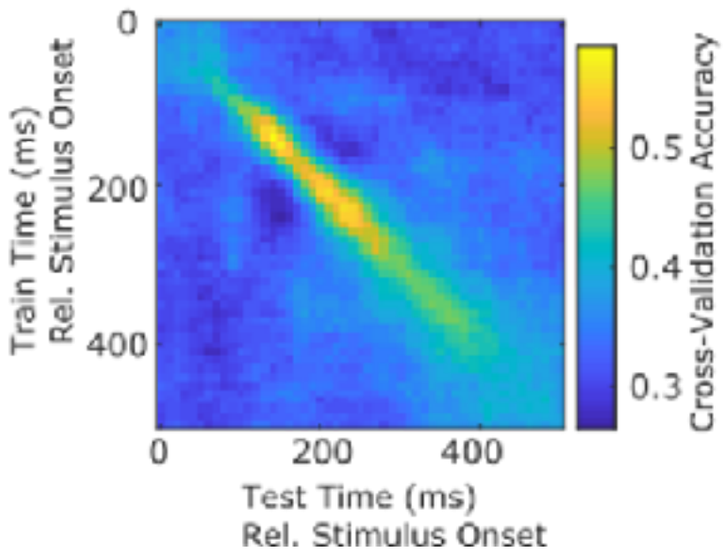

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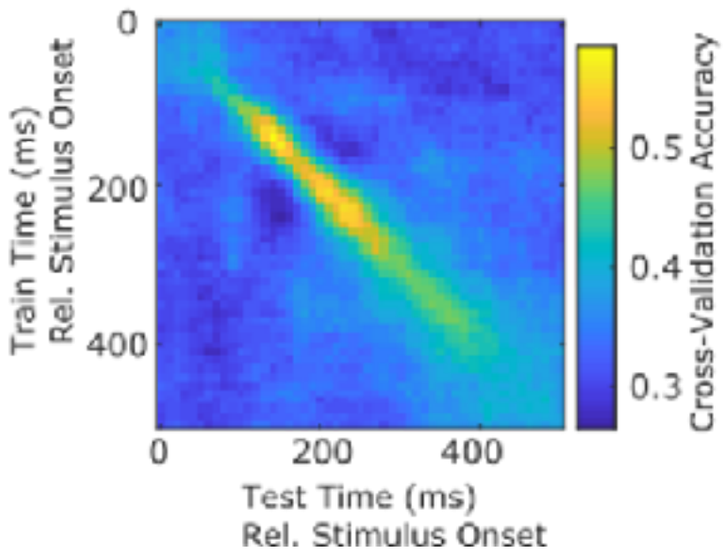

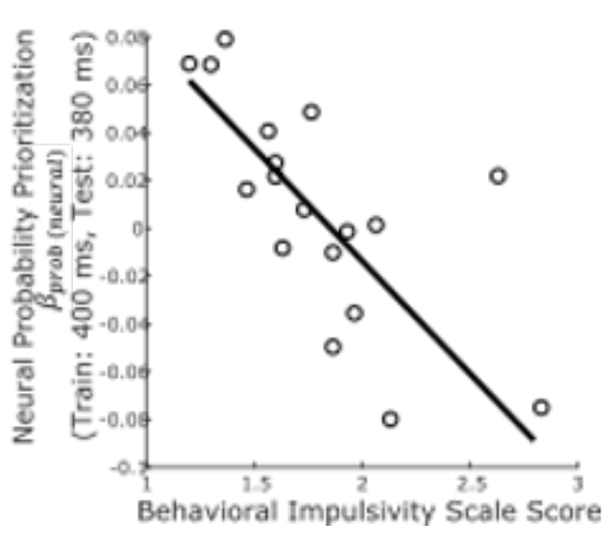

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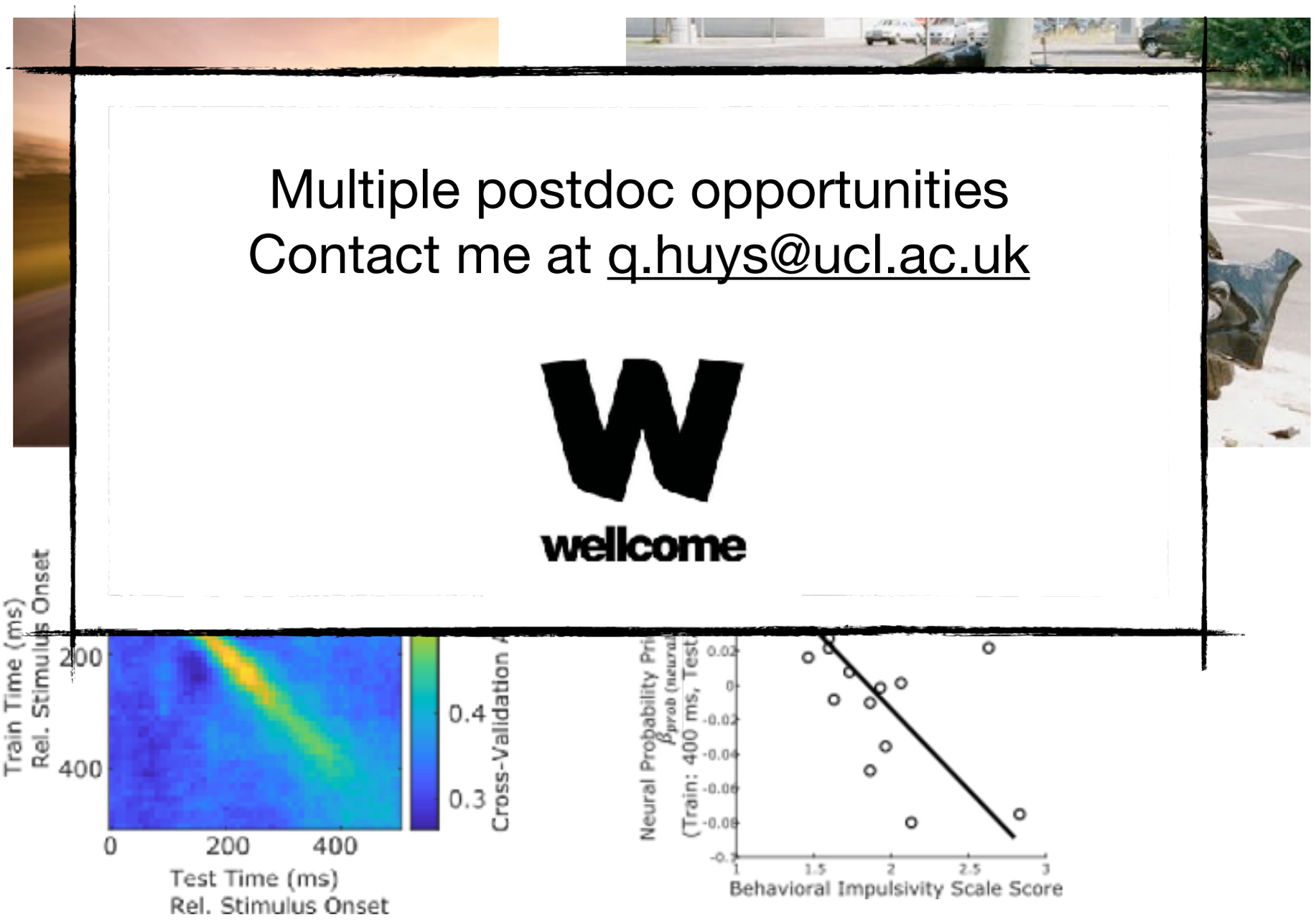

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