Clinical Decision Support in Psychiatry Using Brain-Based Measures

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Center for Precision Mental Health
Stanford University

Outline

- Part I: Circuit-based treatment selection
  - Reward circuit: retrospective findings
  - Prospective trial
  - Clinical implementation
- Part II: Foundation models for neuroimaging
  - Learning a representation from all scans
  - Predicting treatment response
  - Next steps

Heterogeneity of depression

- MDD: any 5 of 9 symptoms
- 1,030 distinct symptom profiles in 3,703 patients

Patient A
Depressed mood
Sleeping 12 hours a day
Increased appetite, weight gain
Psychomotor slowing

Patient B
Loss of interest
Insomnia
Decreased appetite, weight loss
Agitation

→ Same diagnosis, same first-line treatment.

Fried & Nesse, *J Affect Disord*, 2015

Current treatment approach



Psychiatric interview structured around DSM criteria

Treatment based on DSM

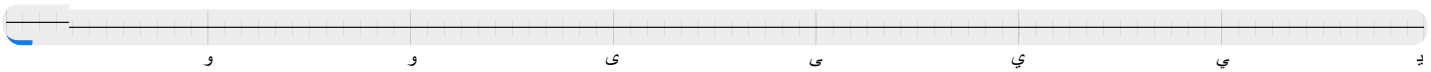
Trial period ~7 weeks

Fail to respond

Try another treatment

Only ~33% chance of treatment success

Current process **avg 7 years**



Ahn et al., *Biol Psychiatry*, 2025
Rush et al., *Am J Psychiatry*, 2006

Current treatment approach



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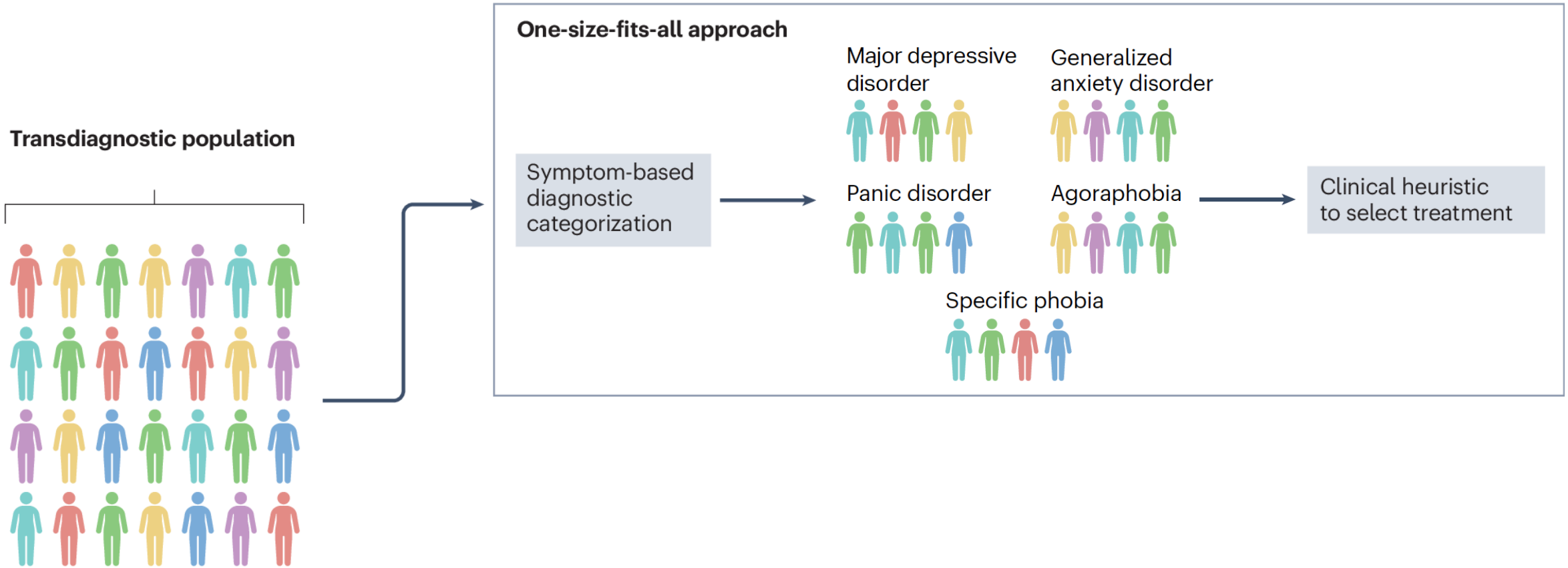
Current process **avg 7 years**

- Major Depressive Disorder — APA 2019, ACP 2023
- Generalized Anxiety Disorder — NICE 2011
- Social Anxiety Disorder — ADAA 2014, BAP 2014
- Panic Disorder — APA 2009, NICE 2011
- Posttraumatic Stress Disorder — VA/DoD 2023
- Obsessive-Compulsive Disorder — APA 2007

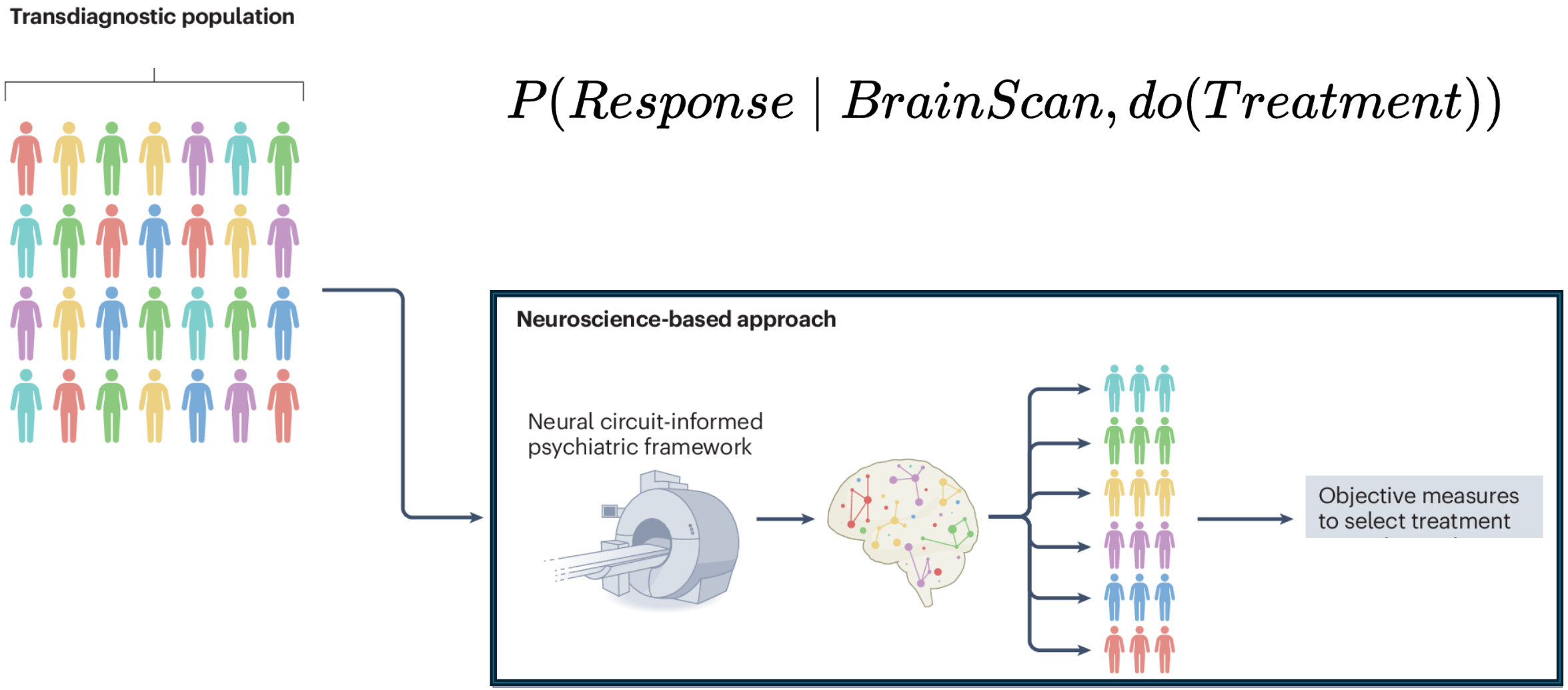
SSRI / SNRI

Same first-line agent class for all six diagnoses

Ahn et al., *Biol Psychiatry*, 2025
Akiki et al., *Nat Comp Sci*, 2025



Akiki et al., *Nat Rev Neurosci*, 2024
Insel & Cuthbert, *Science*, 2015



Akiki et al., *Nat Rev Neurosci*, 2024
Akiki et al., *Nat Comp Sci*, 2025

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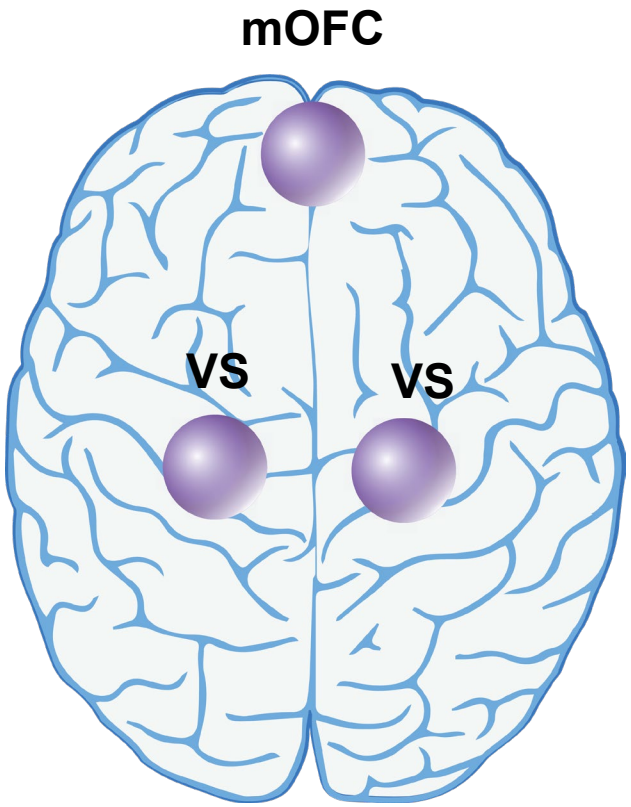
Anhedonia in depression

- Loss of interest or pleasure; one of the two cardinal criteria for MDD
- Often the symptom patients describe as most disabling
- Associated with a poorer response to first-line antidepressants
- Anhedonia symptom severity does not predict which treatment will work

→ **The symptom is the output of a circuit; measure the circuit instead**

Treadway & Zald, *Neurosci Biobehav Rev*, 2011
Uher et al., *Psychol Med*, 2012

Reward Circuit

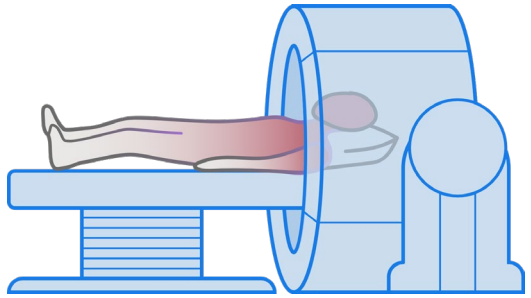


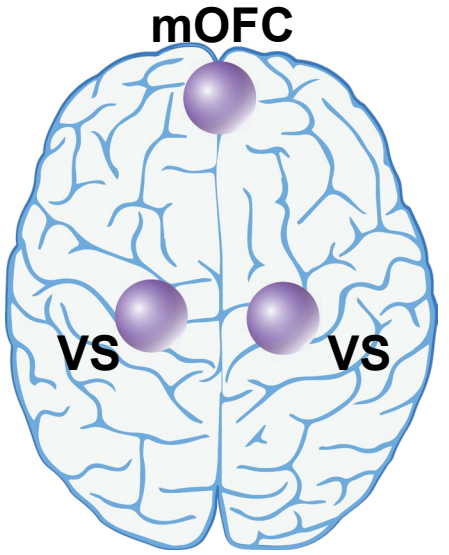
mOFC: subjective value
Multiple neuromodulatory systems

Ventral striatum: motivation, reward learning
Dopamine-dominant modulation

Russo et al, *Nat Rev Neurosci*, 2013
Berridge et al, *Neuron*, 2015

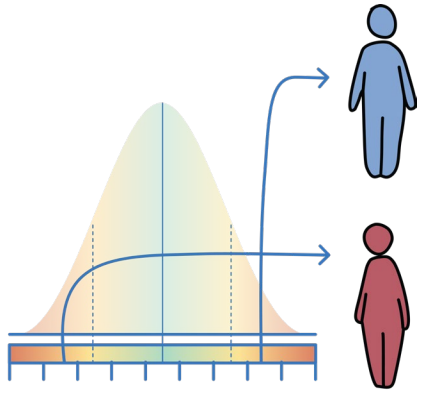
Experimental Design





fMRI Task: Happy-vs-neutral faces





Activation expressed as z-scores vs. matched healthy controls

→ Deviation in either direction may be clinically meaningful

Does pre-treatment reward circuit activity predict treatment outcomes?

Goldstein-Piekarski et al, *Biol Psychiatry*, 2022
Akiki et al, *ACNP*, 2026

Sample characteristics

iSPOT-D

n=1008

Treatments:

- Escitalopram
- Sertraline
- Venlafaxine

ENGAGE

n=108

Treatments:

- Behavioral Therapy

  [Behavioral Activation + Problem Solving Therapy]

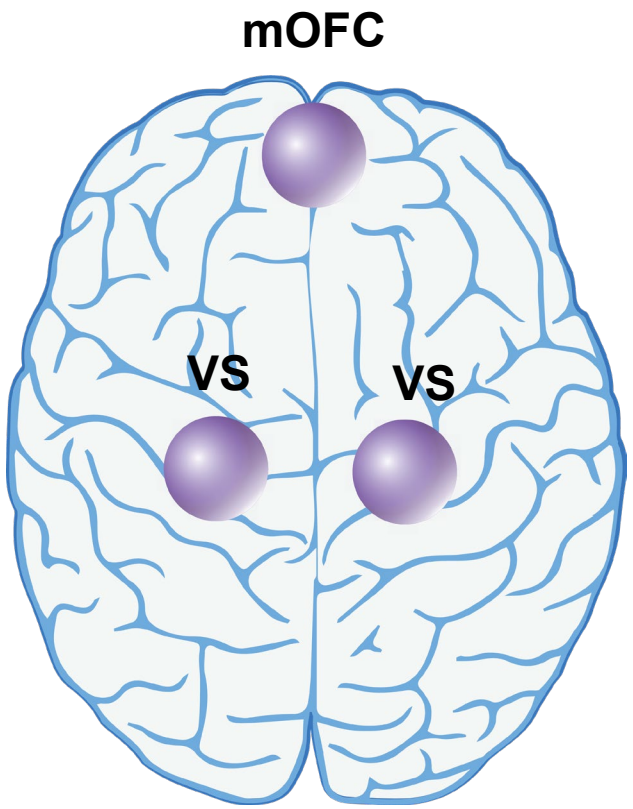
- Treatment as usual

Combined sample with imaging: N=287

Williams et al., *Behav Res Ther*, 2018
Grieve et al., *Trials*, 2013

Circuit deviation predicts treatment outcome

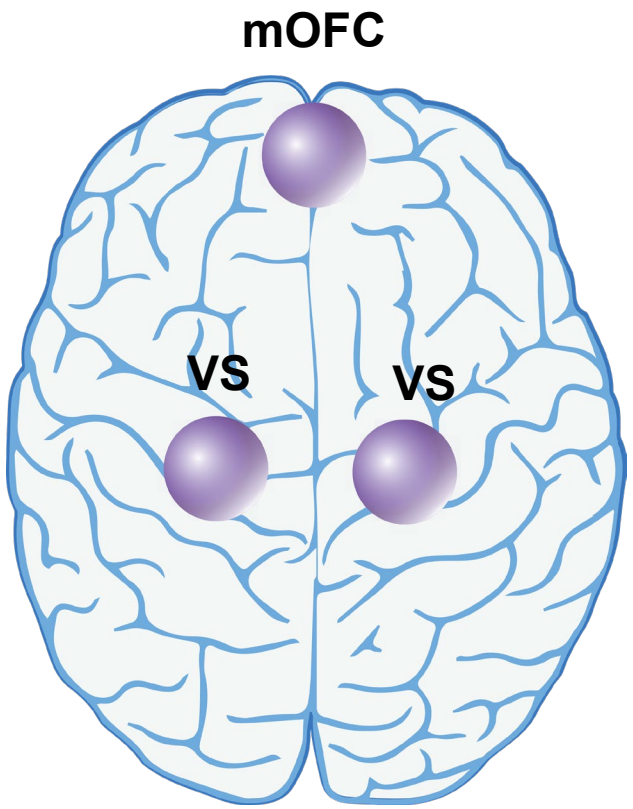
Odds ratios per 1 SD deviation from the healthy norm



Deviation from healthy norm	SSRI (escitalopram, sertraline)	Behav. Therapy (BA + PST)
mOFC <u>below</u> reference	**OR 0.29** lower odds of response	–
Ventral striatum <u>above</u> reference	**OR 0.70** lower odds of remission	**OR 2.48** higher odds of remission

Circuit deviation predicts treatment outcome

Odds ratios per 1 SD deviation from the healthy norm



Dopamine Agonist Treatment
LIMITED CASE SERIES
(5 patients)

Deviation from healthy norm	SSRI (escitalopram, sertraline)	Behav. Therapy (BA + PST)	Pramipexole
mOFC **below** reference	**OR 0.29** lower odds of response	–	**Improved**
Ventral striatum **above** reference	**OR 0.70** lower odds of remission	**OR 2.48** higher odds of remission	**Improved**

Stanford

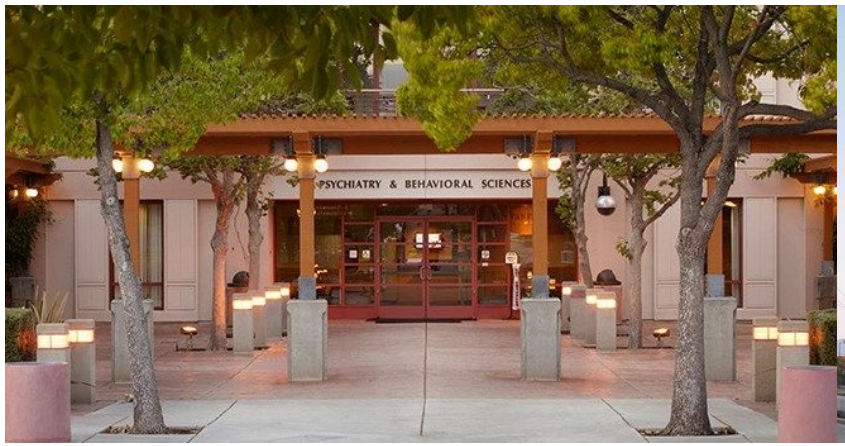
Precision Psychiatry Clinic

Stanford HEALTH CARE

STANFORD MEDICINE

STANFORD

Center for Precision Mental Health







Ongoing pramipexole trial



Stratified Pharmacological Approaches for Regulating Circuit-Level Effects

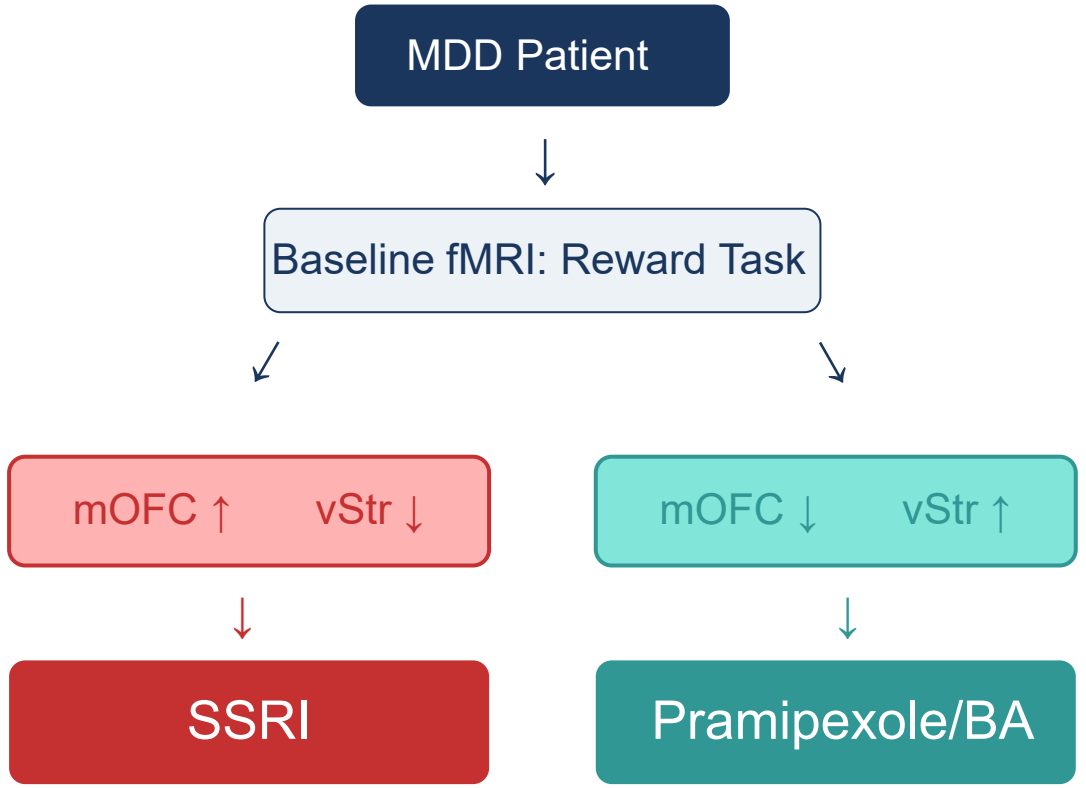
A prospective trial (target n=60)
Pramipexole monotherapy x 8 weeks
Moderate-to-severe MDD
Prespecified hypothesis: baseline reward circuit abnormality predicts response

NCT07022405

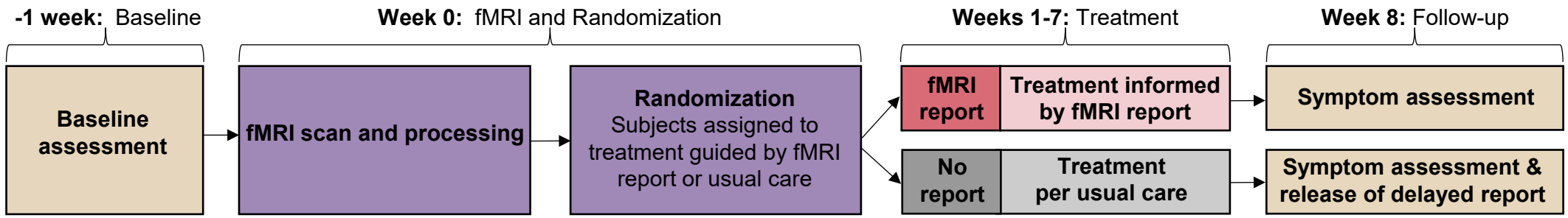
Toward circuit-guided Clinical Decision Support

If results hold:

- Baseline reward circuit imaging could identify likely SSRI non-responders before a failed trial
- Patients with VS hyperactivation could be routed to dopaminergic approaches earlier
- Baseline scan could inform which treatment to try first



Comparative effectiveness trial



- Baseline fMRI for all
- Randomized 1:1 to fMRI-Guided Treatment vs. Standard Care
- Question:
  Does using the fMRI report to guide treatment improve outcomes?

Expanding the range of therapeutics

- Pramipexole → Reward circuit
- Guanfacine → Cognitive control circuit
- Lurasidone → Salience circuit

…

SPARCLE

ACE-D STUDY



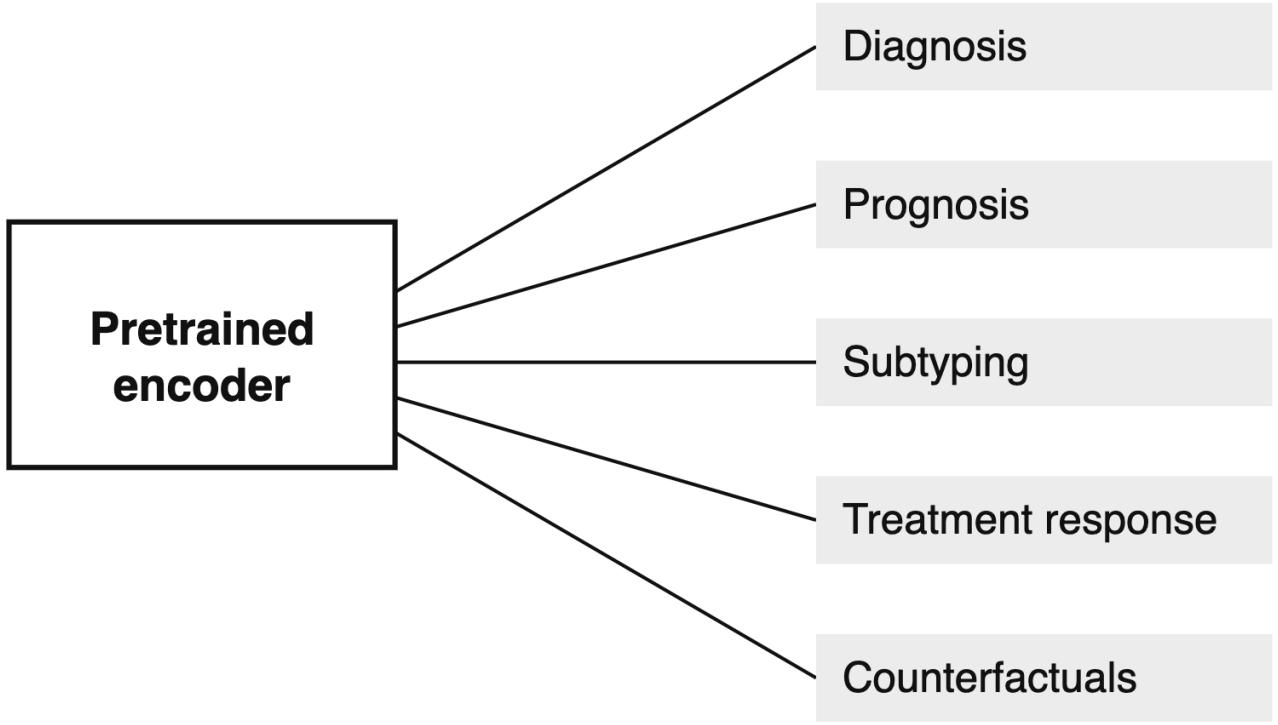
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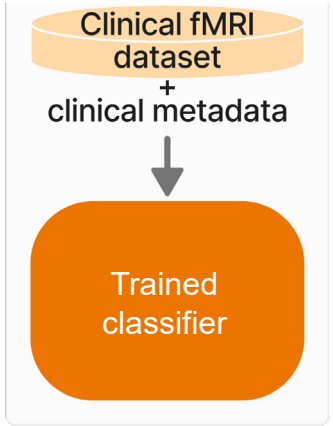
Foundation Model

“a model that is trained on broad data that can be adapted to a wide range of downstream tasks”

R. Bommasani et al., *arXiv*, 2021

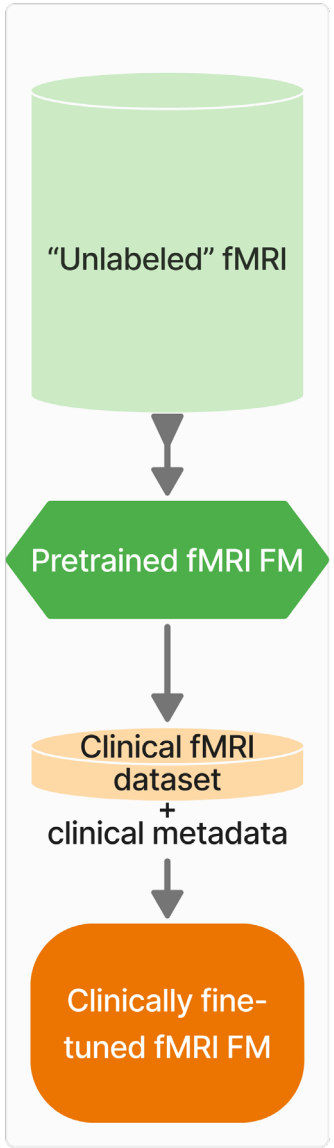


Conventional machine learning for treatment response prediction



100s of scans

Foundation model for neuroimaging

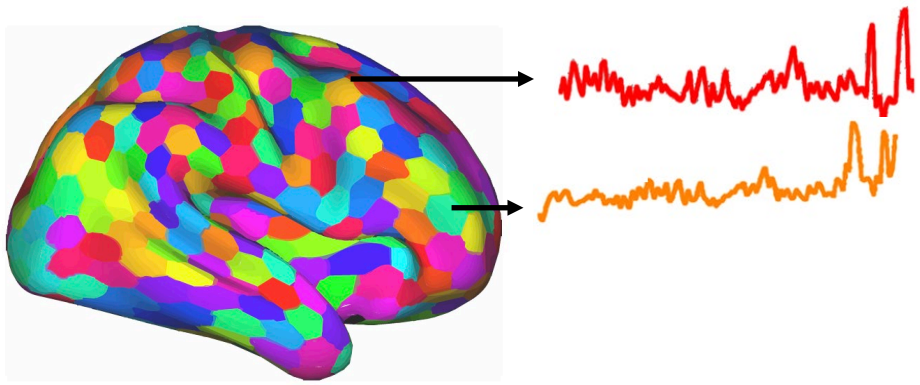


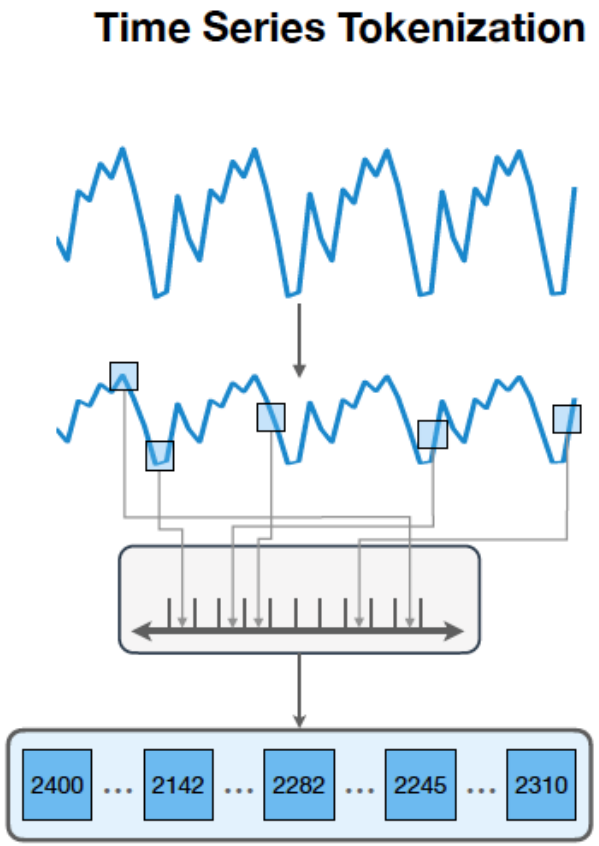
Thousands of scans

100s of scans

Adapting foundation models to neuroimaging

Unlike text, neuroimaging data has no natural token





Input:

Parcellated fMRI (Schaefer 400 + Tian)

432 regions × T tokens

Encoder:

Factored spatiotemporal transformer

Ansari et al, TMLR, 2024

Transdiagnostic datasets

Study	N	Design	Treatment
iSPOT	1,480 (incl. healthy controls)	RCT	Sertraline, Escitalopram, Venlafaxine
Twins	1,741	Observational	None/Naturalistic
RAD	382	Observational	None/Naturalistic
HCPDES	333	Observational	None/Naturalistic
Family	308	Community	None/Naturalistic
ENGAGE / ENGAGE2	236	Intervention	Behavioral Therapy, Treatment as Usual
TMS	105	Treatment trial	TMS
BIG	29	Treatment trial	Guanfacine
RADAT	22	Treatment trial	…
…	…	…	…

Williams et al., Behav Res Ther, 2018; Williams et al., BMC Psychiatry, 2021; Williams et al., BMC Psychiatry, 2016
Tozzi et al., NeuroImage, 2020; Hack et al., Nat Mental Health, 2025; Williams et al., Trials, 2011

In prep

Four-stage “curriculum learning” pipeline

1

Unsupervised Pretraining

Learn what a brain state is

2

Supervised Training

Cross Sectional

Learn what depression looks like now

3

Supervised Training

Longitudinal

Learn what clinical change looks like

4

Evaluation

Response & Remission

→ Each stage uses progressively more specific clinical data

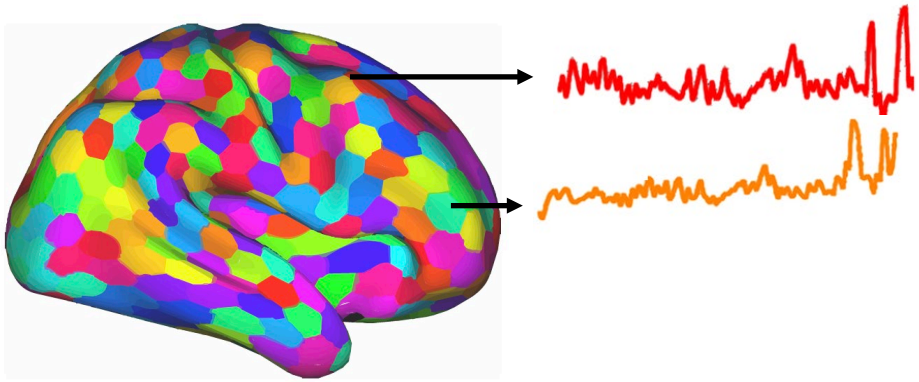
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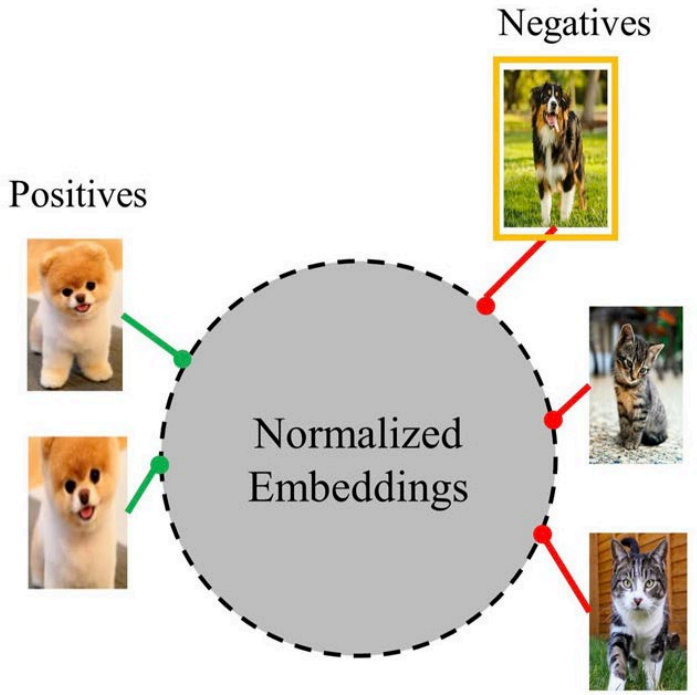
Unsupervised pretraining

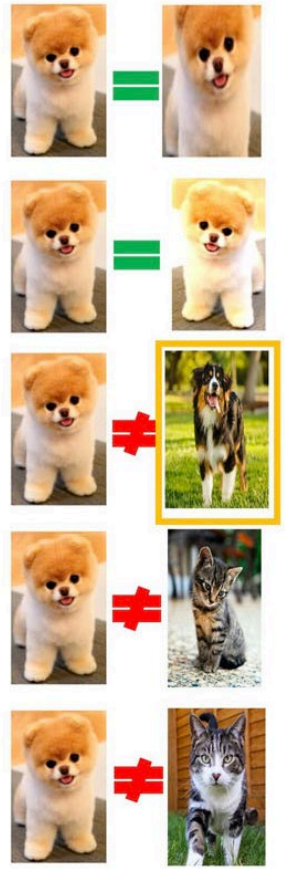
Contrastive objective

Same-individual, different fMRI scans → positive pair

Different individual → negative pair





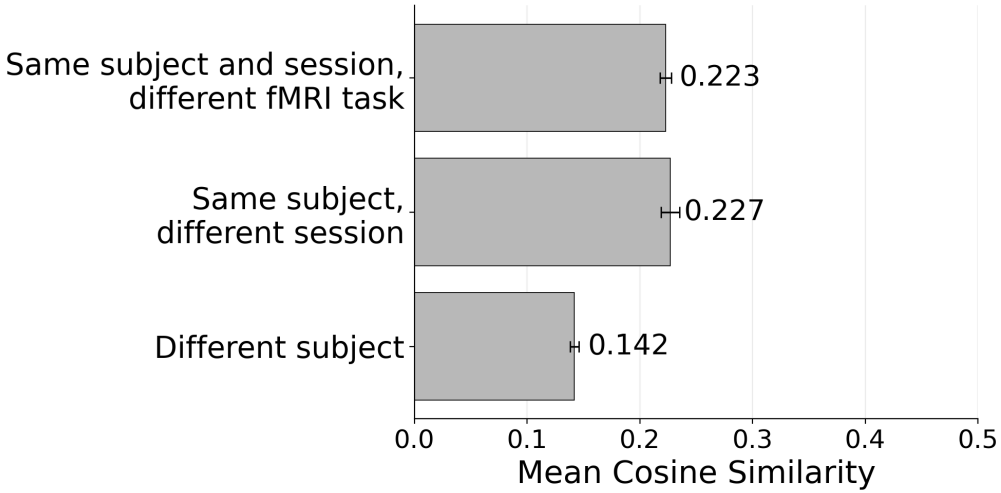


In prep

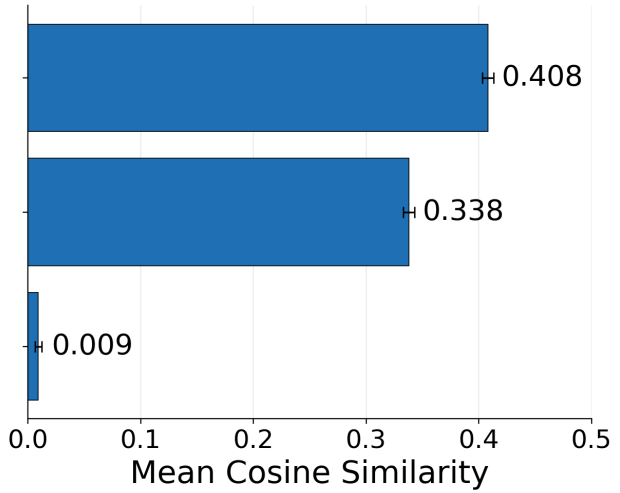
Unsupervised pretraining

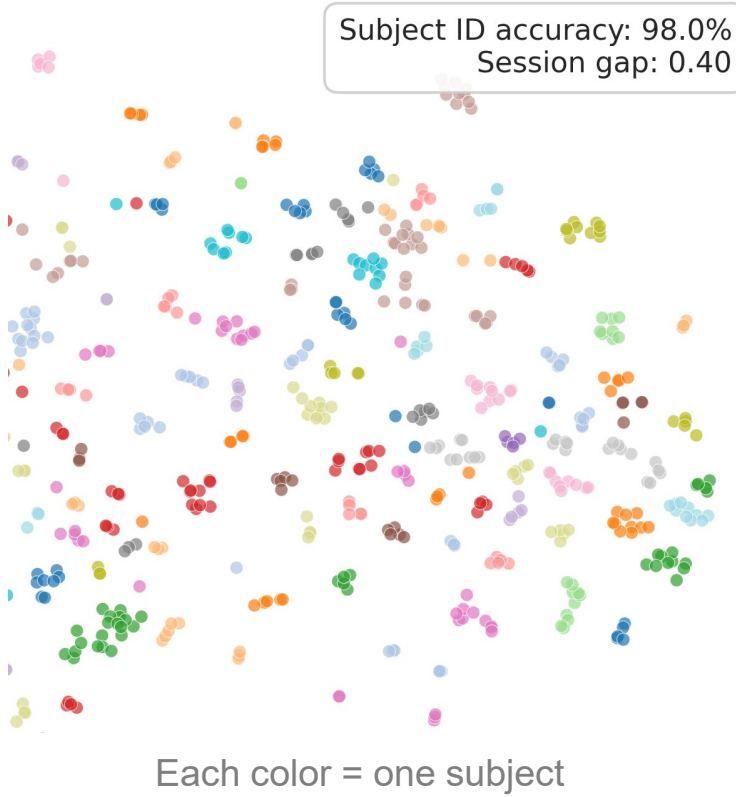
Contrastive objective

Before pretraining



After pretraining





Each color = one subject

→ **Representations are approximately task-invariant**

In prep

Supervised training

Adding clinical information to the representation

Cross-sectional training

Start from the pretrained encoder

- Add a supervised objective: predict depression severity at the time of the scan (cross sectional)
- About 84% of scans have a severity label

→ push clinical information into the representation that the contrastive objective alone would not capture

Longitudinal training

- Add a second objective: predict change in depression severity over follow-up (longitudinal)
- Change z-scored and adjusted for baseline severity
- About 49% of scans have longitudinal change data

→ teach the model what a clinical trajectory looks like

Scans without labels still contribute to the earlier stages.

In prep

Evaluation protocol

Response and Remission



Freeze Encoder

No further training
Representations are fixed



Extract

Representations for held-out participants (no session leakage)



Probe

Logistic regression



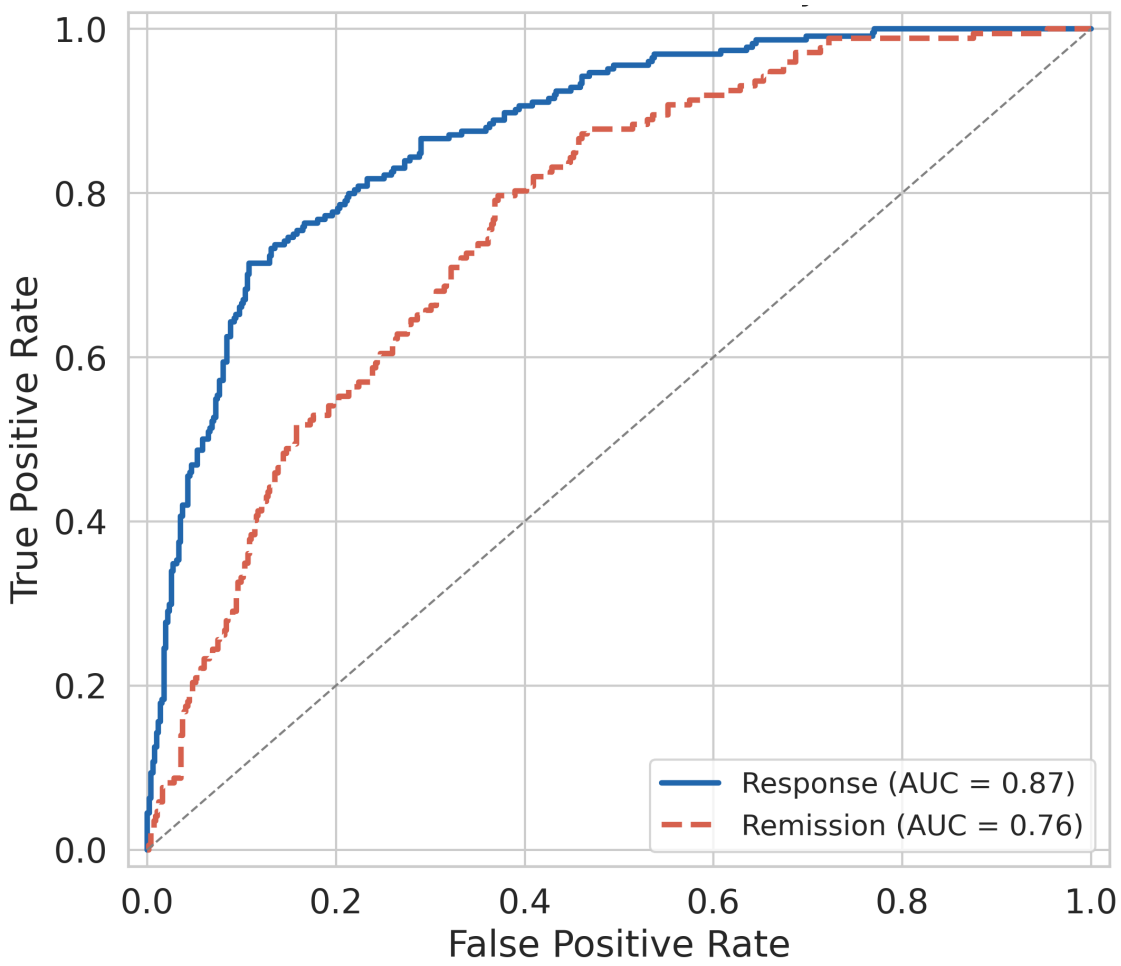
Validate

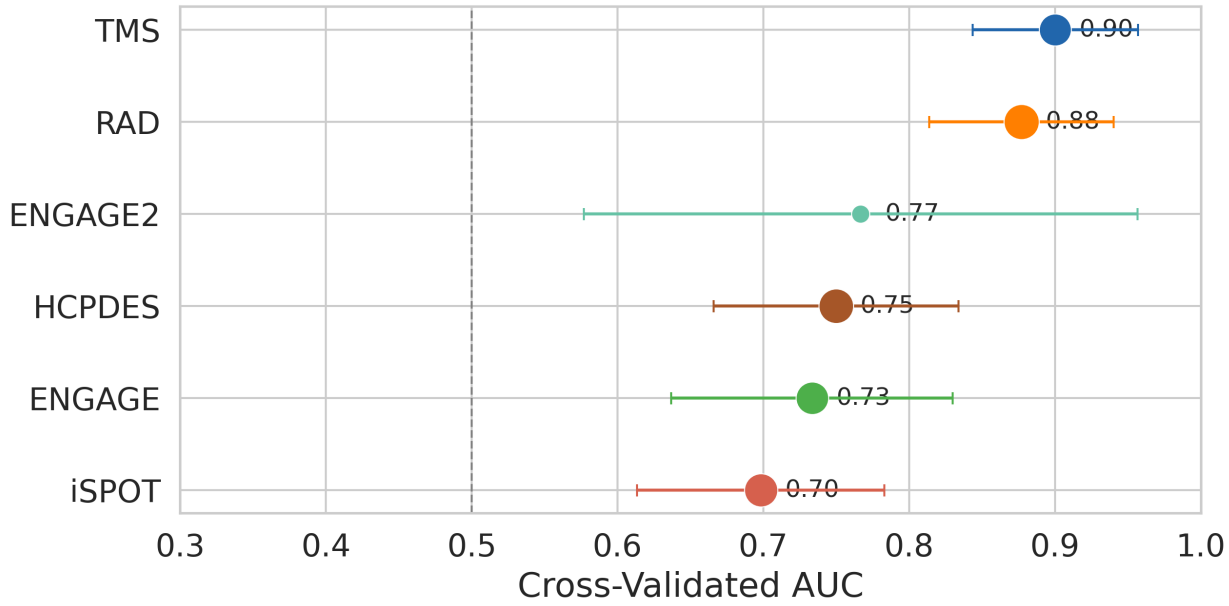
Group 5-Fold on SubjectID
AUC for response / remission

In prep

Evaluation results

Response and Remission (5-fold CV)





In prep

Next steps

Prospective validation

- Predictions made before treatment; clinicians blinded (SPARCLE, ACE-D)

Comparative effectiveness trial

- Does access to the circuit report improve outcomes? Randomize the report, not the treatment

Treatment-specific vs. prognostic signal

- Test on randomized arms; treatment × representation interaction

More trials, more treatments

- Every additional trial adds a treatment we can predict for, and more training data

Acknowledgments

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Trevor Hastie
Olu Ajilore

Stanford | Center for Precision Mental Health



https://stanfordpmhw.com/postdoctoral-research

akiki@stanford.edu

NIH National Institute of Mental Health

National Center for PTSD
POSTTRAUMATIC STRESS DISORDER

Stanford HEALTH CARE

K23MH139900
U01MH136062

Appendix



Psychiatric interview structured around DSM criteria

Current Treatment Approach

Treatment based on DSM

Trial period ~7 weeks

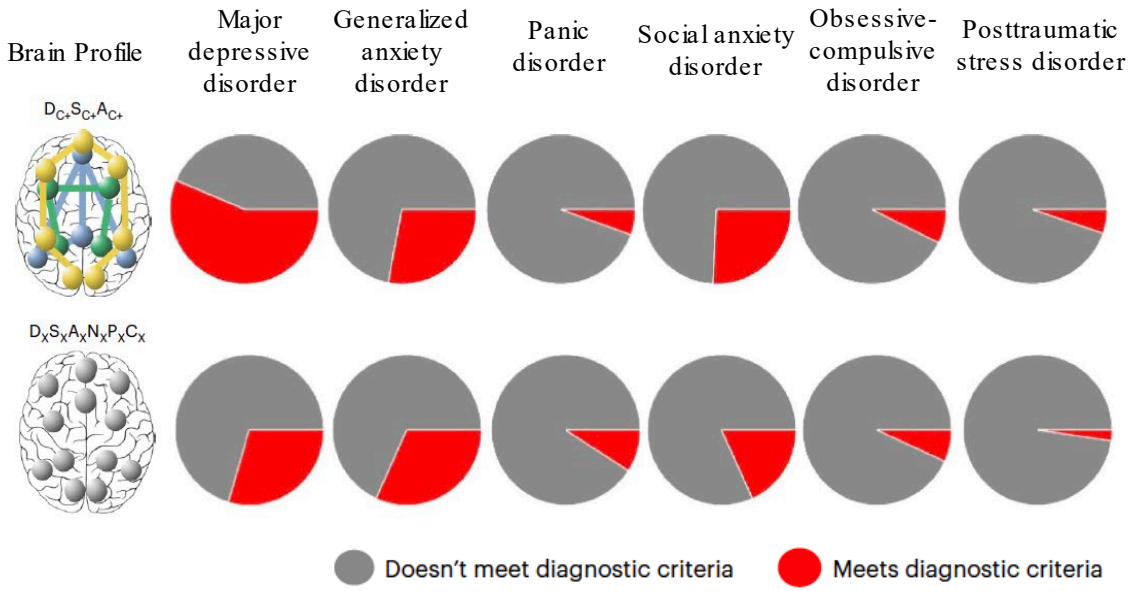
Fail to respond

Try another treatment

Only ~33% chance of treatment success

Current process avg 7 years

Additionally, DSM labels do not align with brain biology



Tozzi et al., Nature Med, 2024



Psychiatric interview structured around DSM criteria

Current Treatment Approach

Treatment based on DSM

Trial period ~7 weeks

Fail to respond

Try another treatment

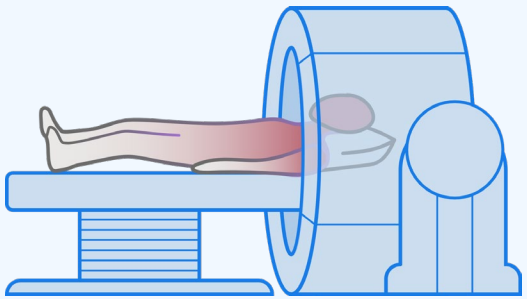
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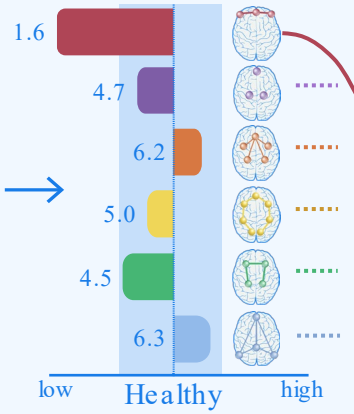
Precision approach avg 7 weeks

Neurobiologically-informed Diagnostic and Treatment Approach

fMRI scan

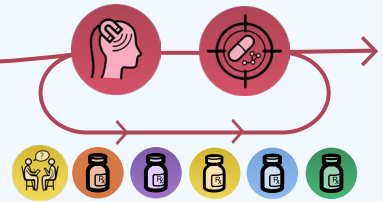


Circuit evaluation



Treatment decisions brain-based assessment

Most likely to respond



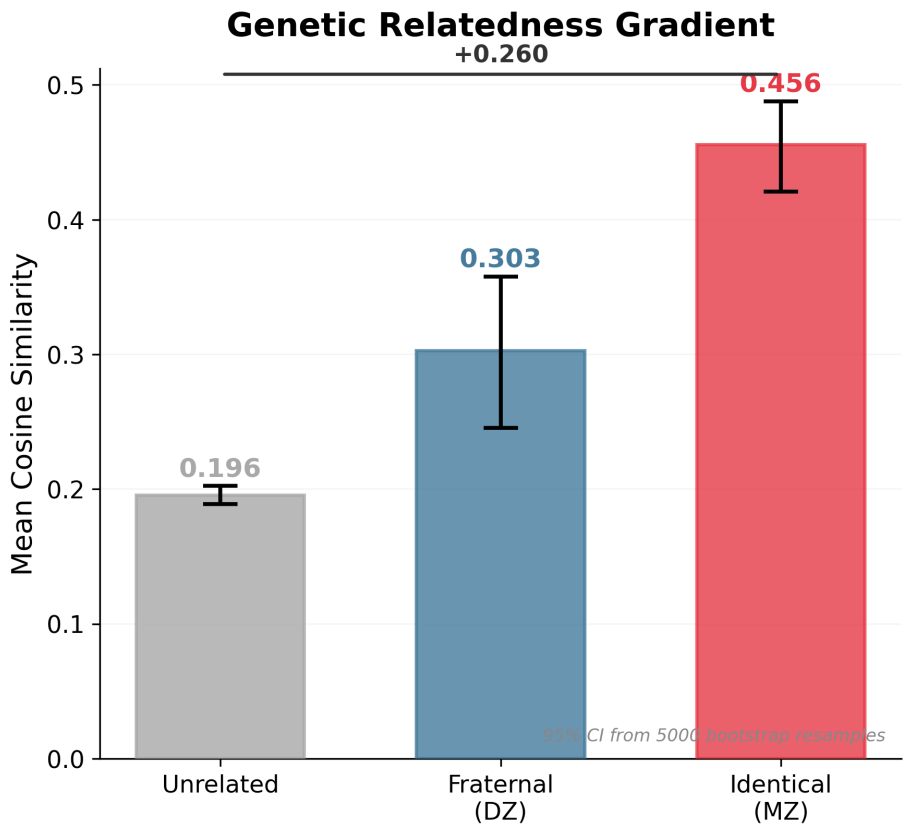
Available treatments

Rapidly improve first treatment success

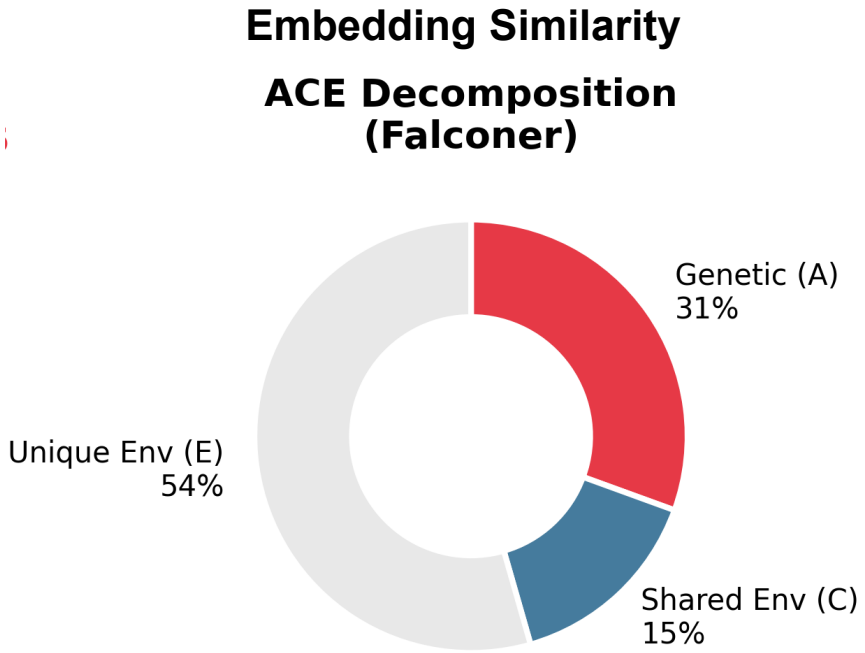
Ahn et al., Biol Psychiatry, 2025
Tozzi et al., Nature Med, 2024
Akiki et al., Nature Comp Sci, 2026

Unsupervised pretraining

Twin cohort

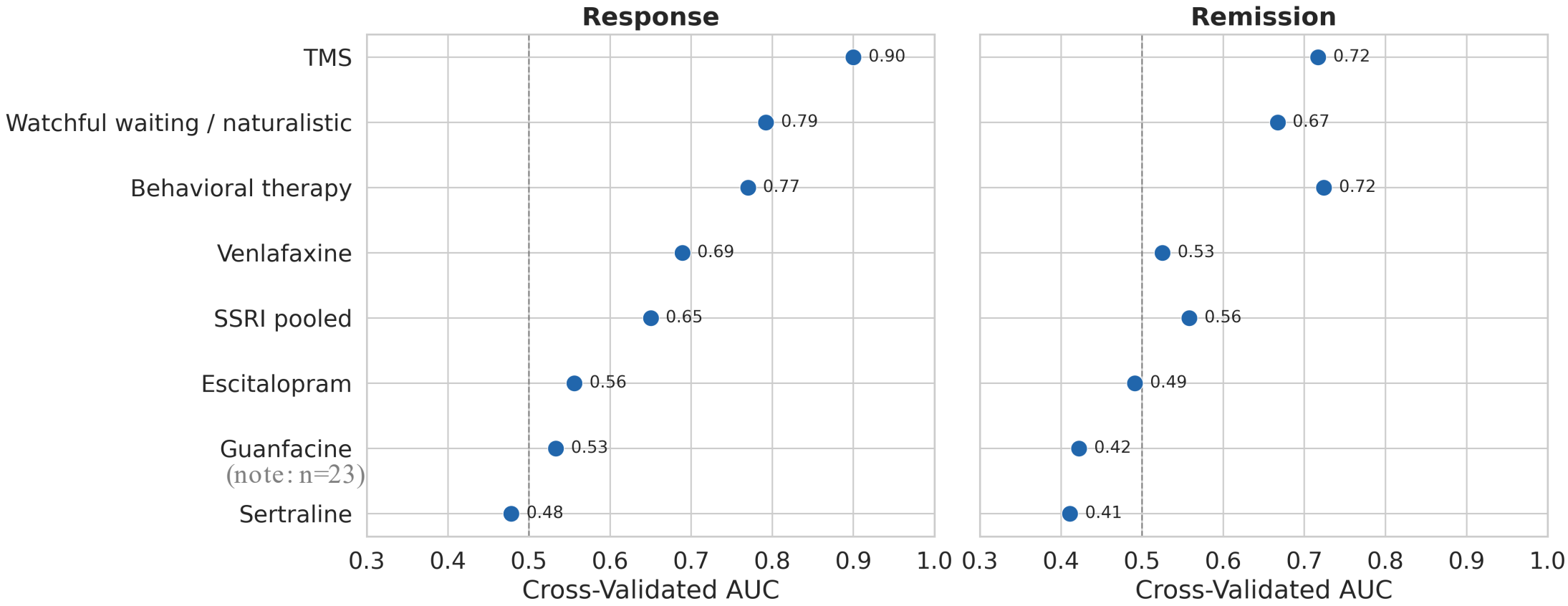


n=259



In prep

Evaluation by therapy

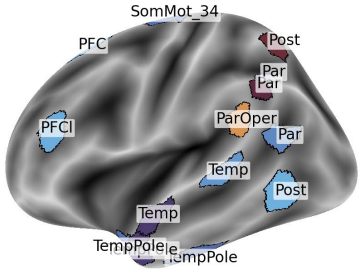


Interpretability analysis: Gradient saliency

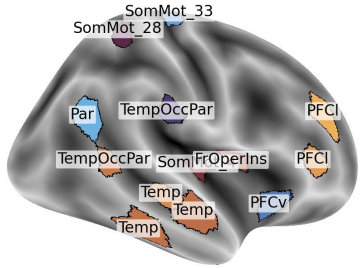
Depression severity

Top 10% ROIs by |gradient|, colored by directionality: anxiety severity

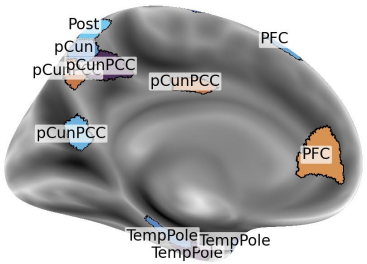
LH Lateral



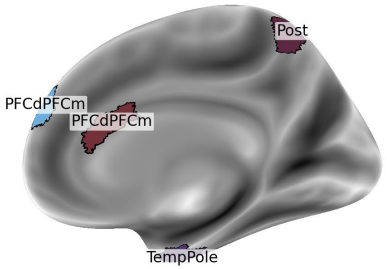
RH Lateral



LH Medial



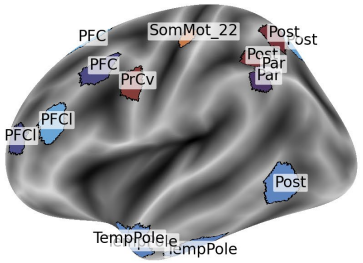
RH Medial



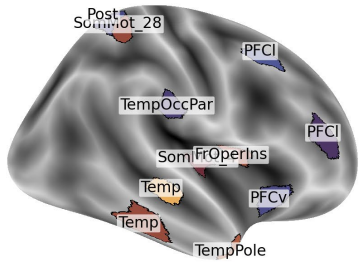
Anxiety severity

Top 10% ROIs by |gradient|, colored by directionality: depression severity

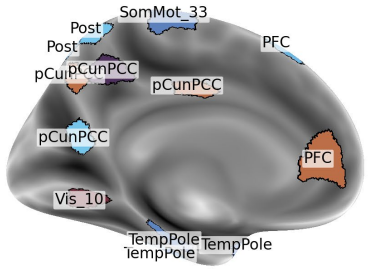
LH Lateral



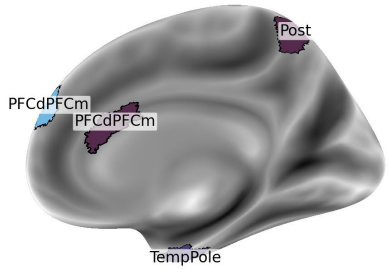
RH Lateral

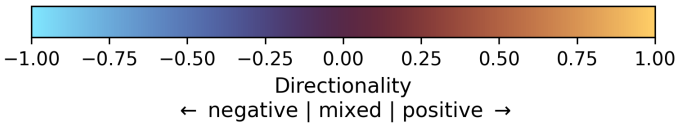


LH Medial



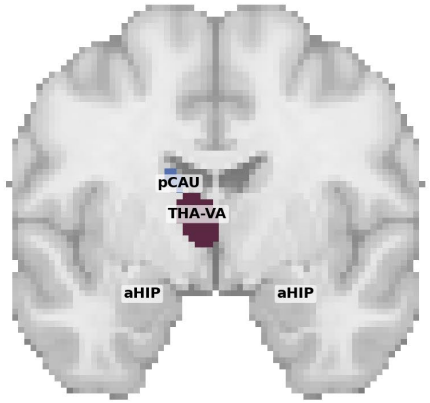
RH Medial



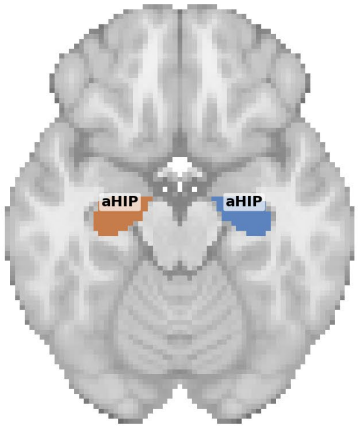


Interpretability analysis: Gradient saliency

Depression severity

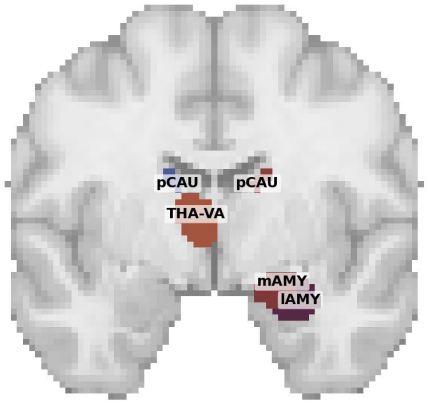


y=-4

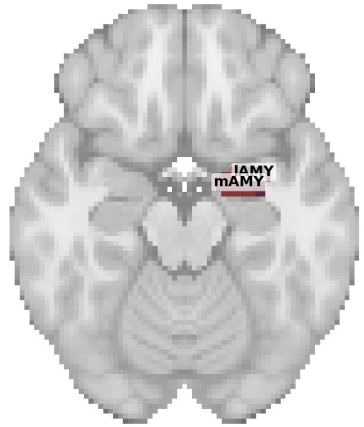


z=-18

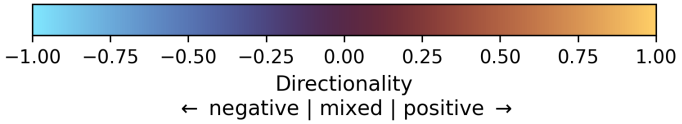
Anxiety severity



y=-4

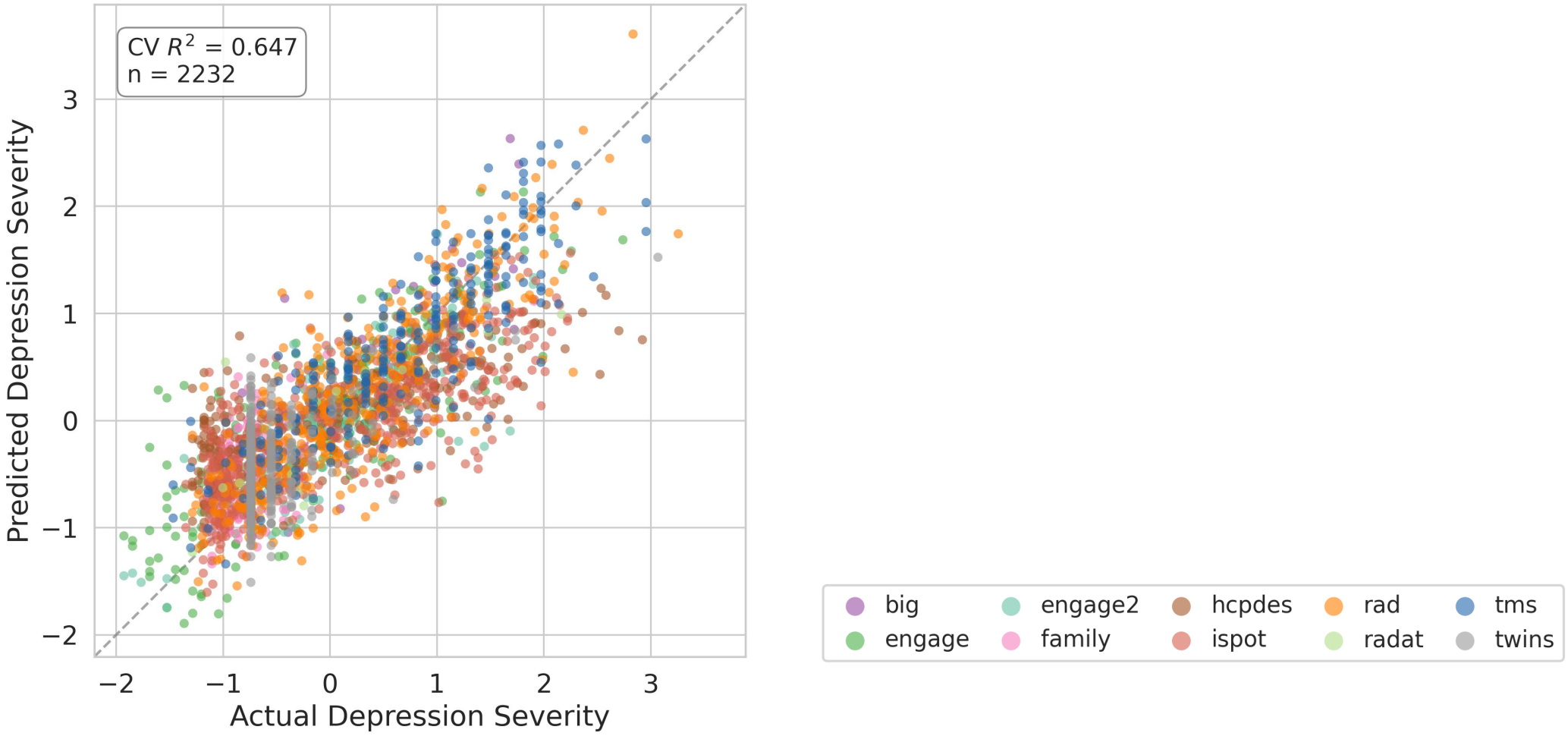


z=-18



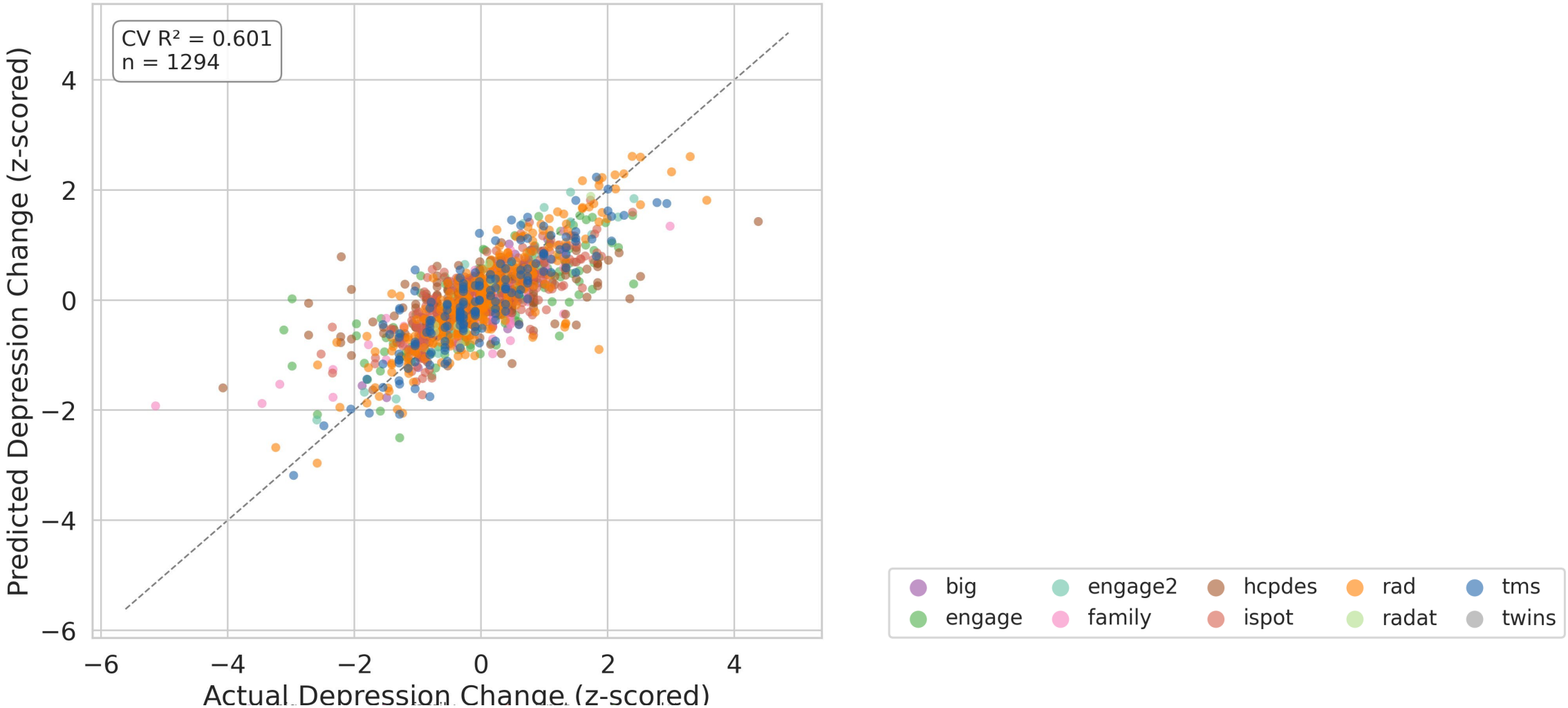
Stage 2: Intermediate training

“What depression looks like” (cross-sectionally)



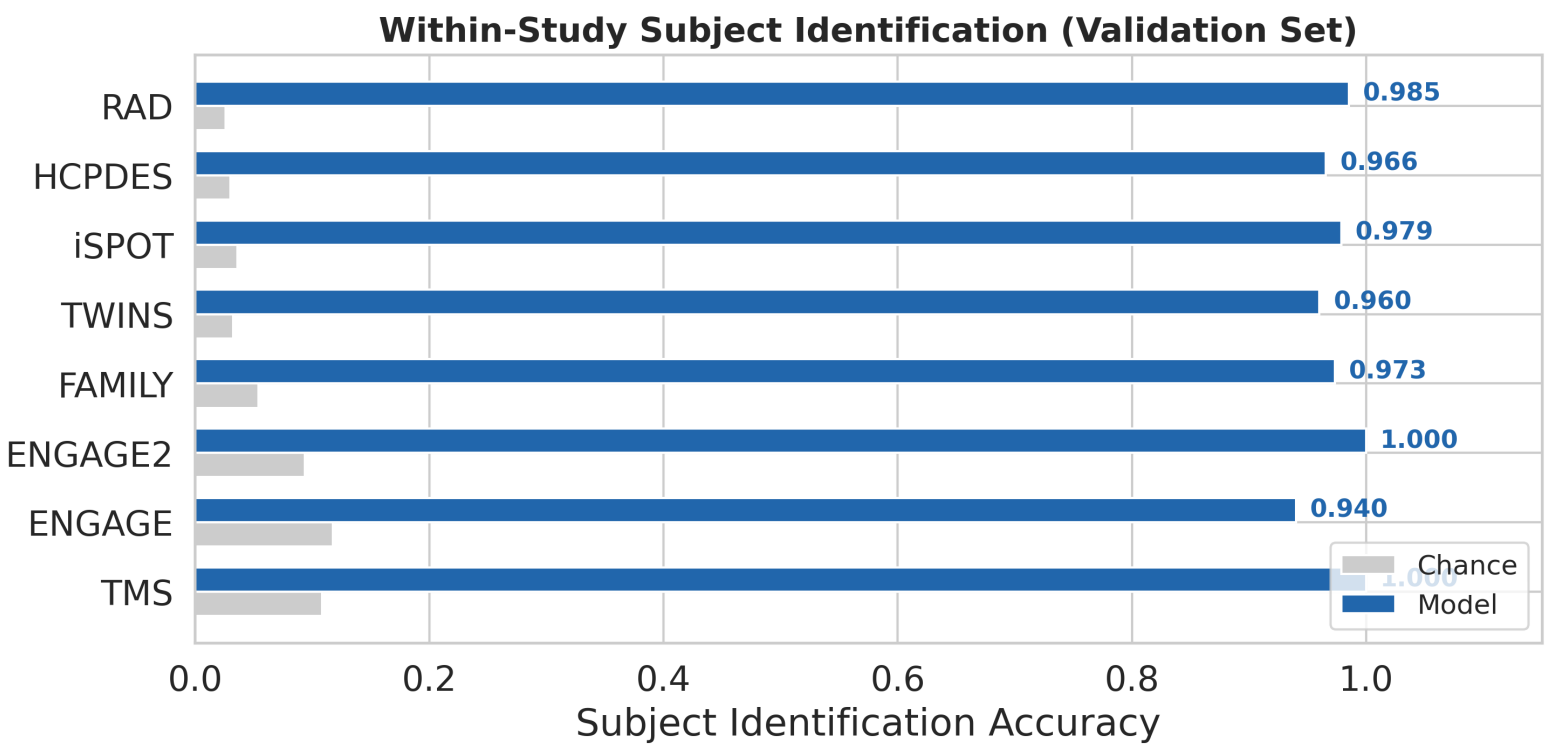
Stage 3: Fine-tuning

"What symptom change looks like" (longitudinally)



Stage 1: Unsupervised pretraining

Contrastive objective





```
$ python3 NeuroFomo_Inference.py models/neurofomo_20250902.pkl embeddings/subject_4721.npy --age 34
```



NeuroFomo v0.2

Loading model: models/neurofomo_20250902.pkl
Subject embedding: embeddings/subject_4721.npy
Feature completeness: 94.2%

Predicted probability of response:

escitalopram: 0.42
sertraline: 0.30
tms: 0.42
behavioral therapy (pst-ba): 0.51
watchful waiting: 0.21
venlafaxine: 0.73