

# A Circuits-First Approach to Mental Illness

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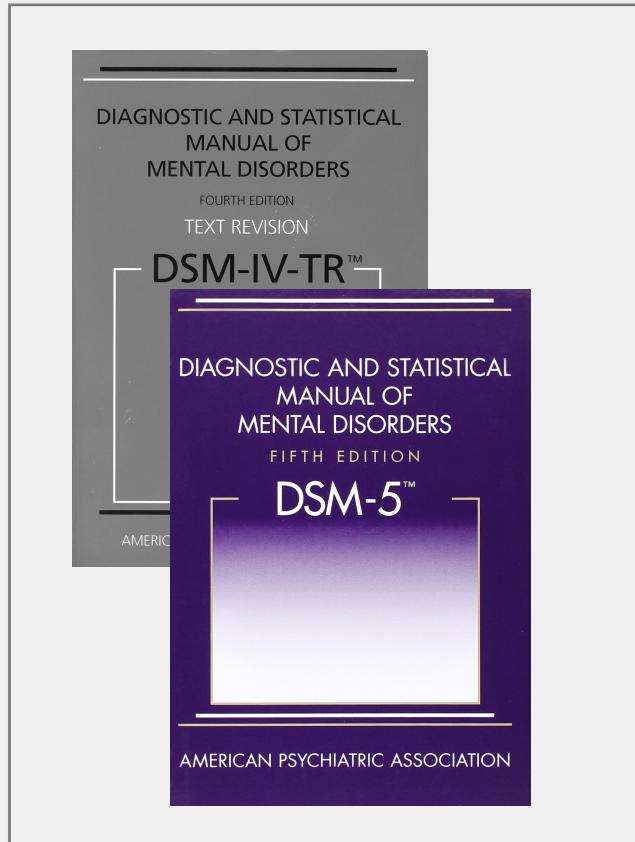
# Disclosures

Salary: Alto Neuroscience

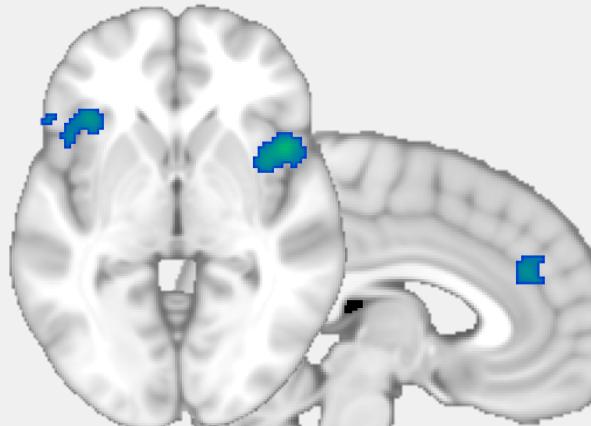
Equity: Alto Neuroscience, Mindstrong Health, Akili Interactive



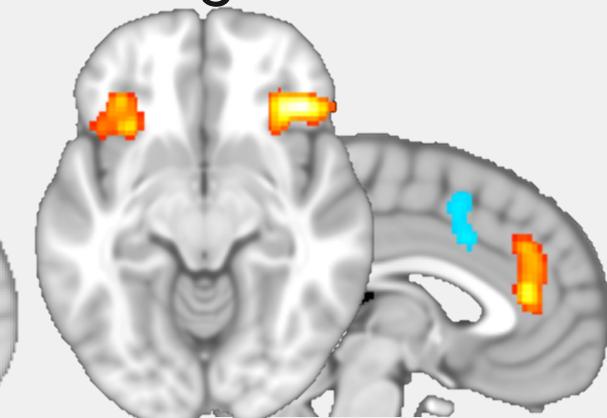
# Key Conceptual Evolutions: From Clinical to Brain Measures



Brain structure



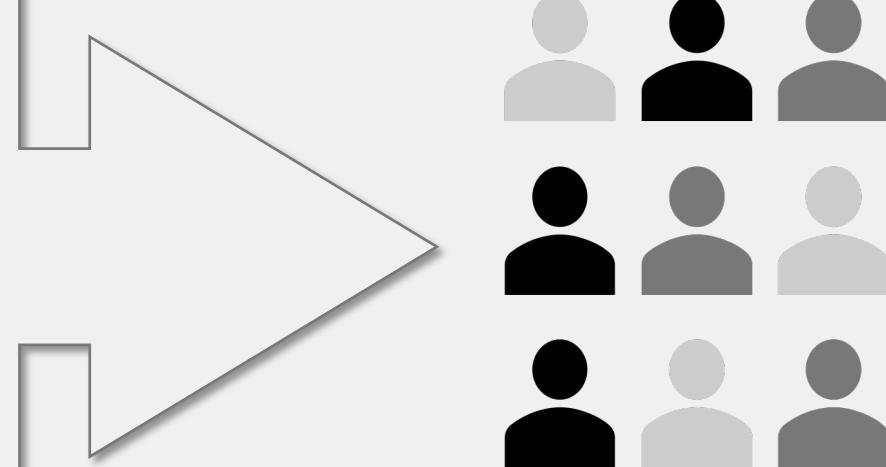
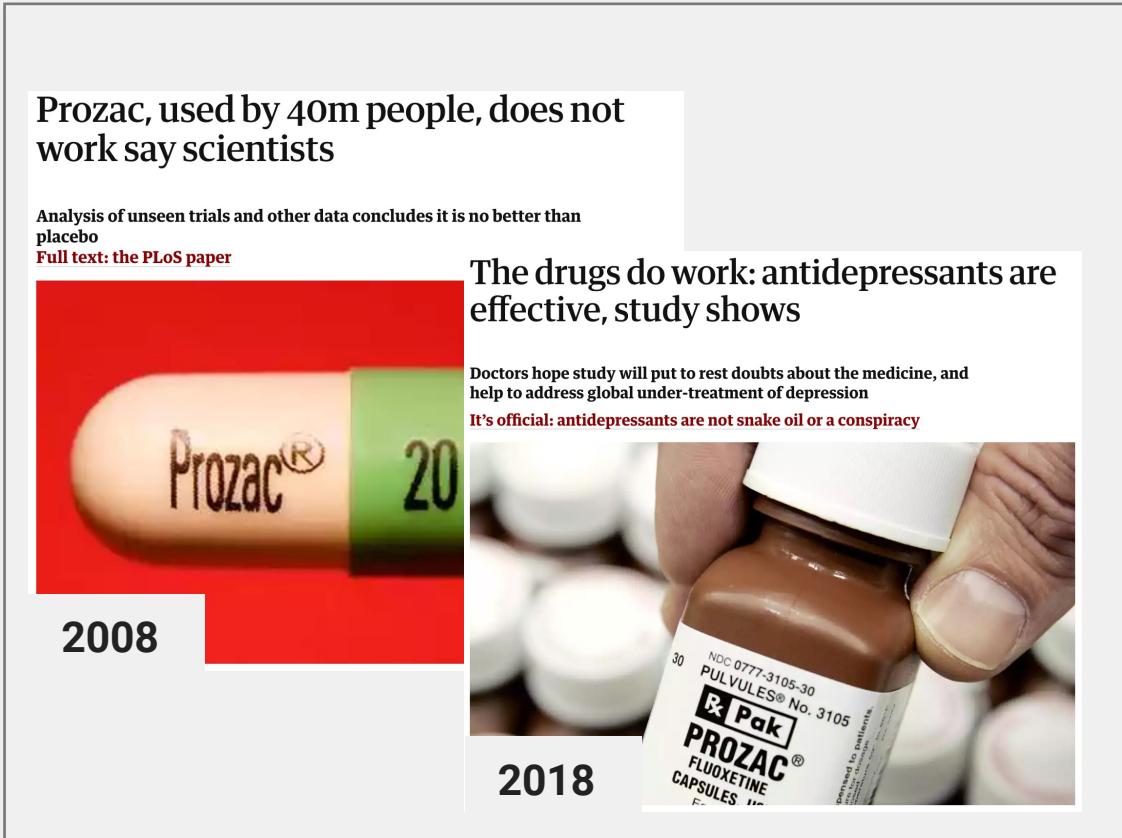
Cognitive tasks



Studying single disorders with brain imaging revealed more commonalities than differences between groups



# Key Conceptual Evolutions: From Averages to Precision Psychiatry?



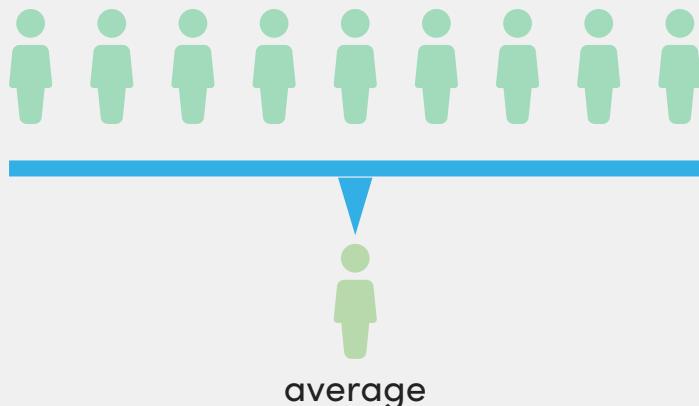
What if the drugs have worked, but we've thought about mental illness the wrong way?



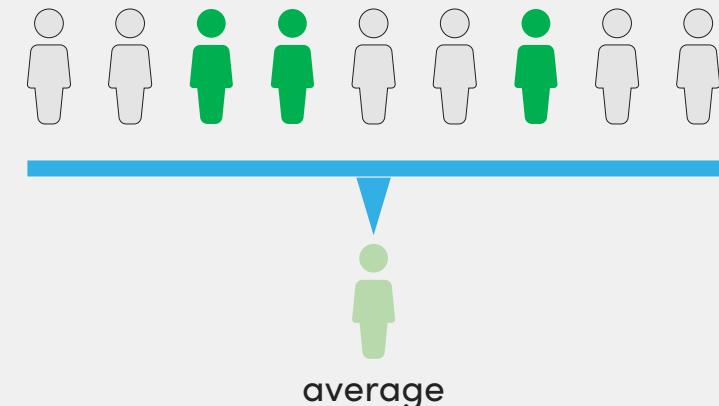
# A Precision Approach Requires Re-Orienting Our Thinking and Studies

Two alternative perspectives on small average effects:

Treatments have small effects



Only a minority respond well

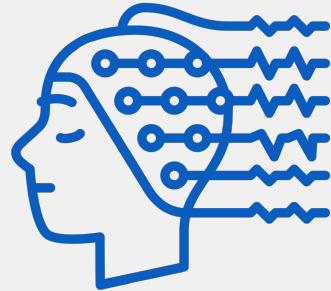


VS.

....but, for a precision approach to work, these differences cannot be due to random chance



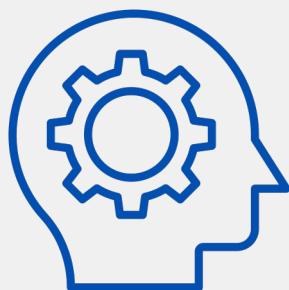
# A Central Biomarker Focus on Brain Circuits



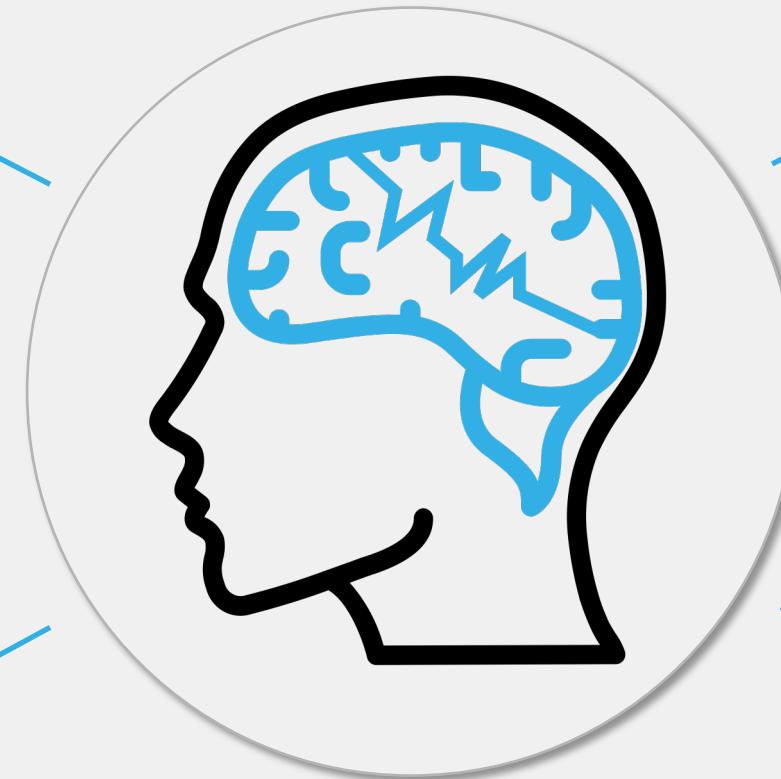
EEG  
(historically, fMRI)



Wearables



Behavior



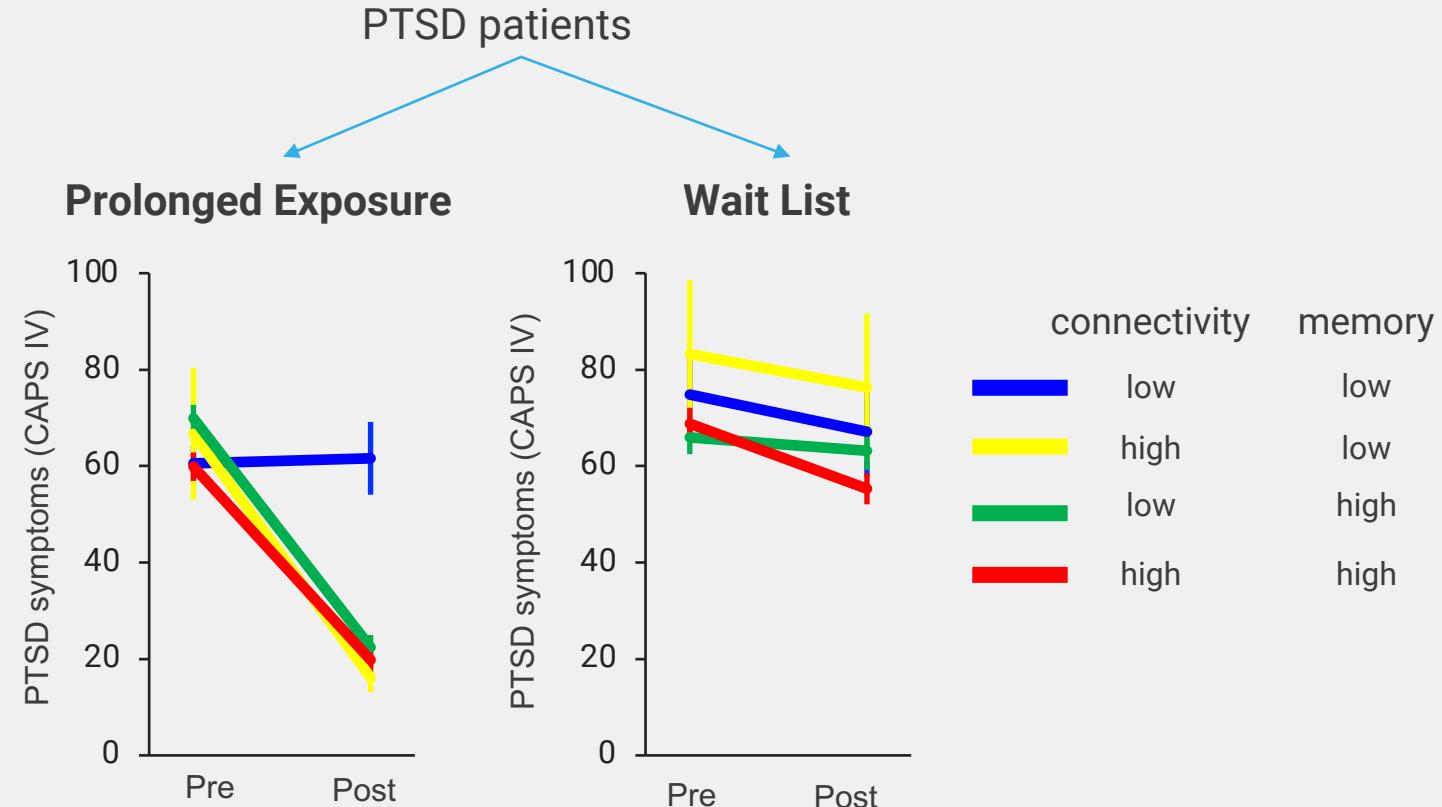
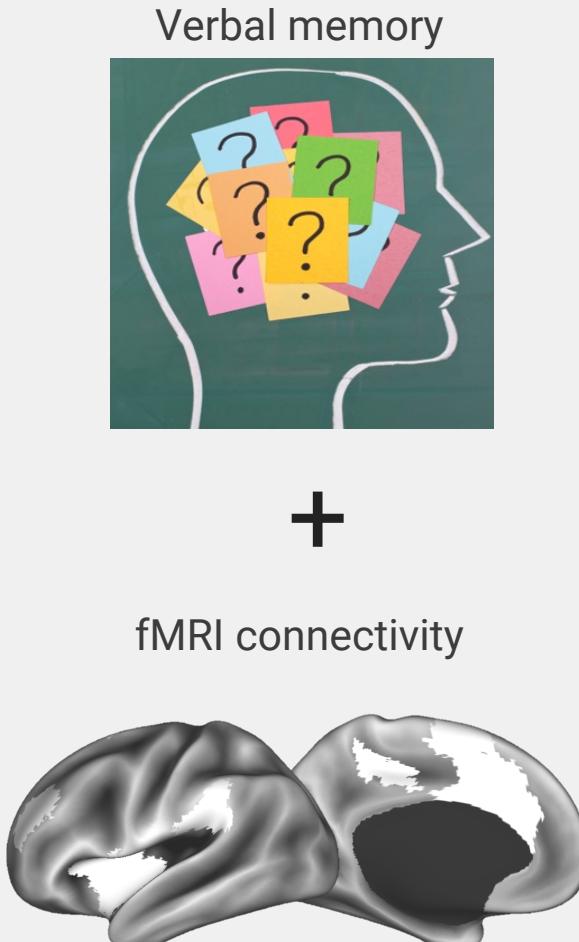
A biomarker **can be as simple as** reaction time, an EEG pattern, or how much a patient sleeps – **or a combination** of these factors.



Genetics



# Behavior and Brain Connectivity Predict Psychotherapy Outcome

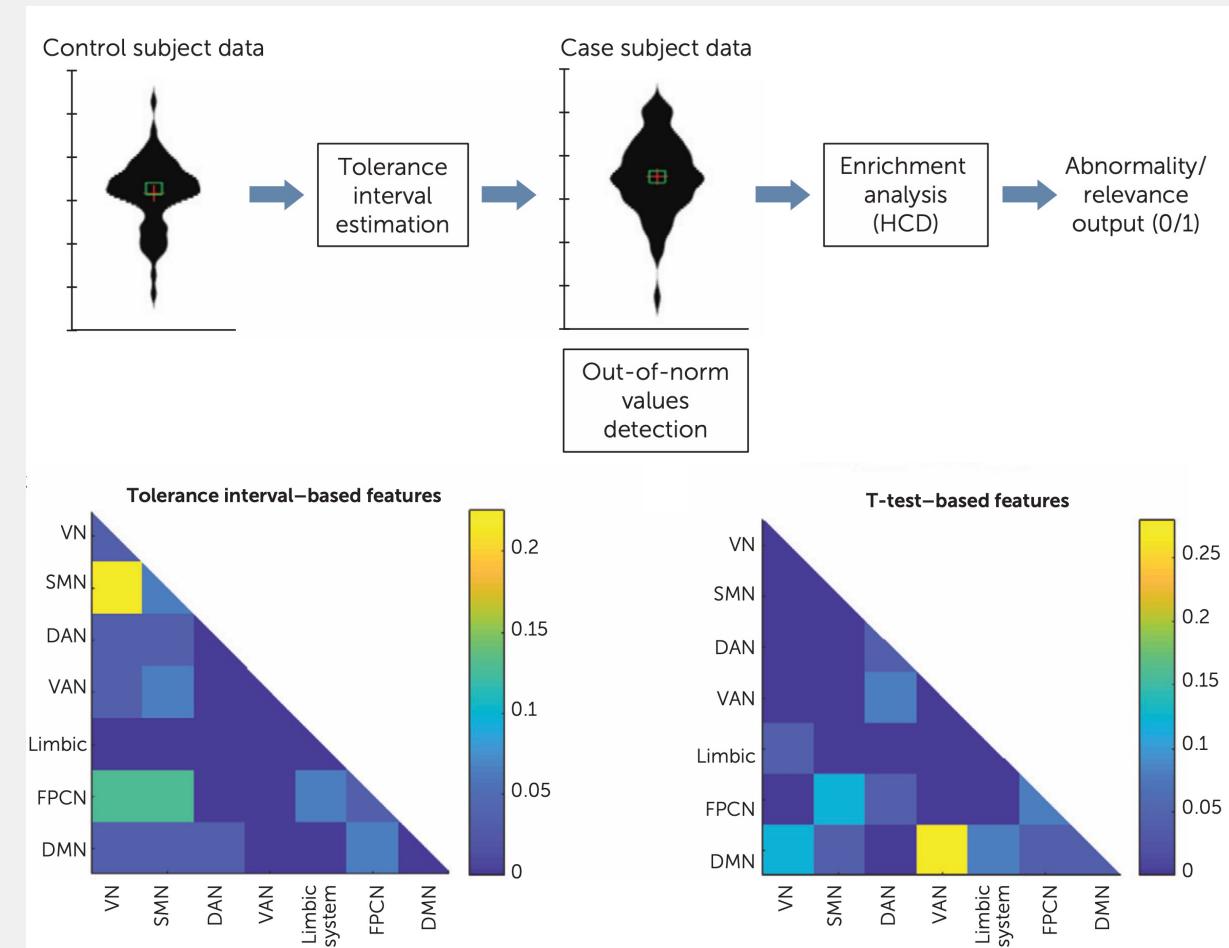
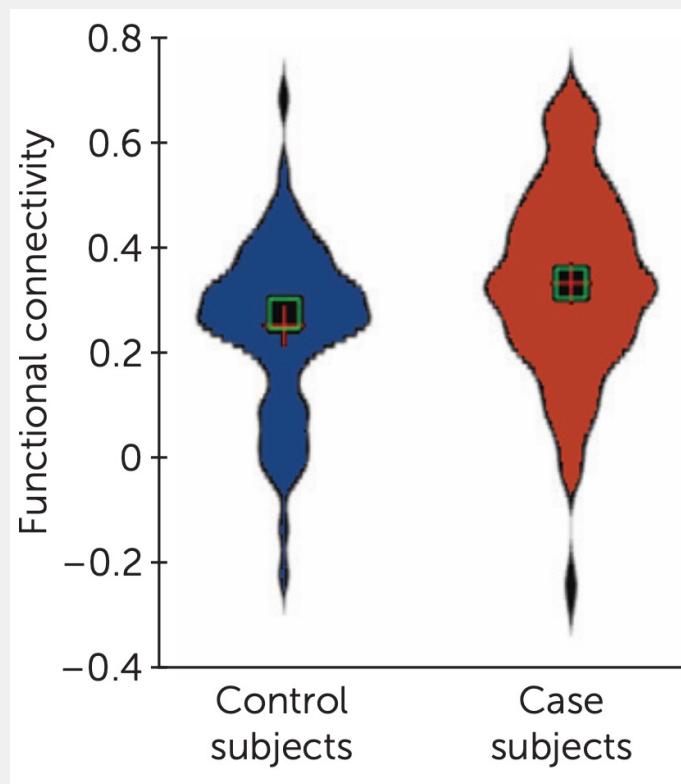


Etkin et al., *Science Translational Medicine*, 2019



# Patient-Control Differences Also Exist As Individual-Level Differences

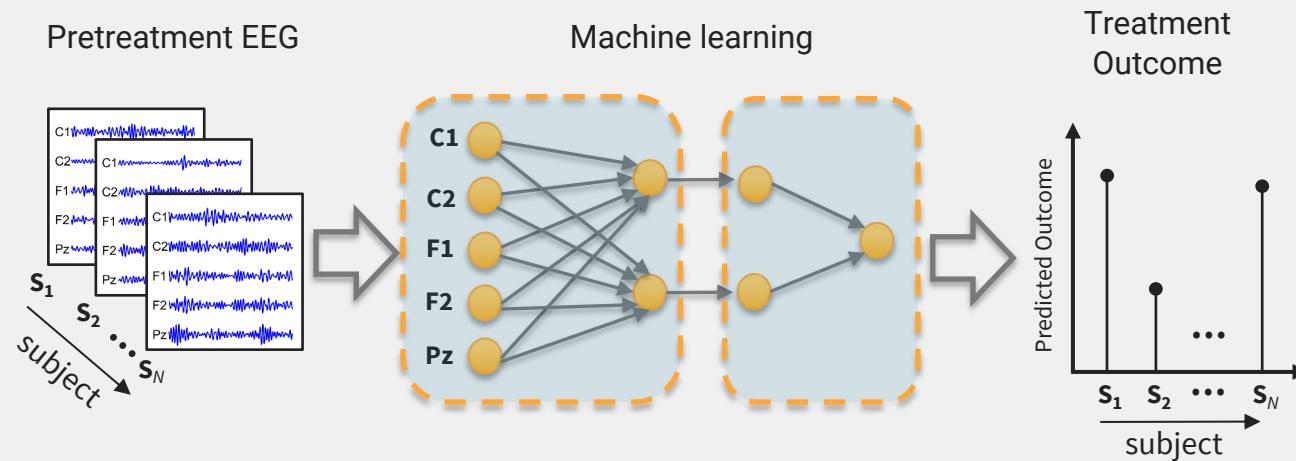
**Biotyping:** A few patients may have anomalous signals not seen in controls



# Machine Learning Enables Robust Discovery and Scalable Biomarkers

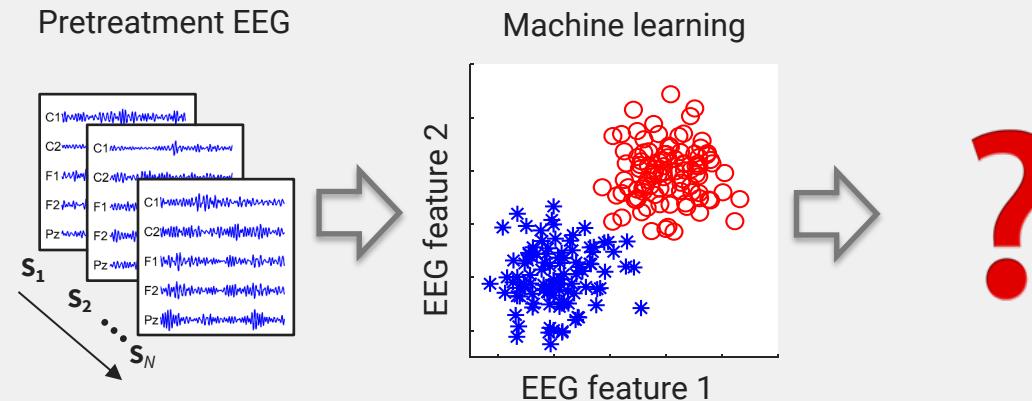
## Supervised:

- Known clinical targets
- Heterogeneity in treatment outcomes



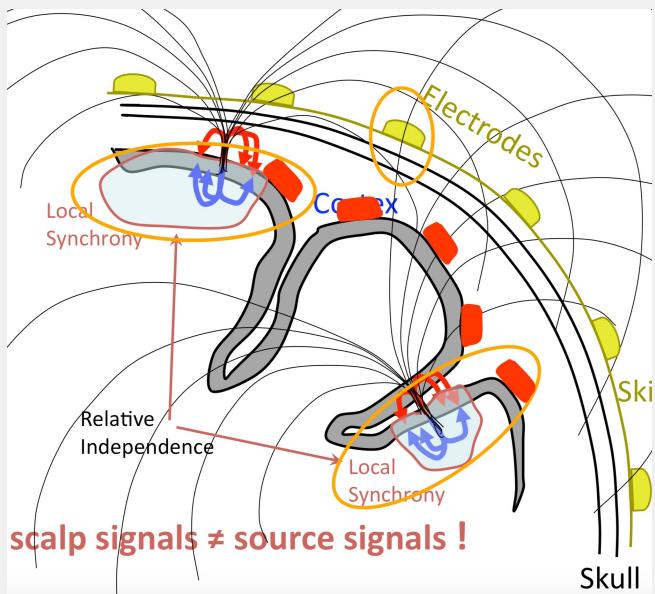
## Unsupervised:

- Heterogeneity in biology itself
- Challenge is aligning with clinical targets

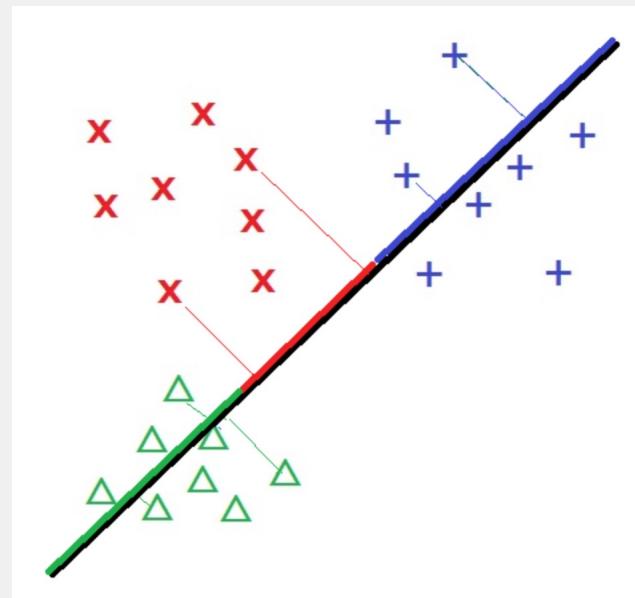


# Challenges of EEG Machine Learning

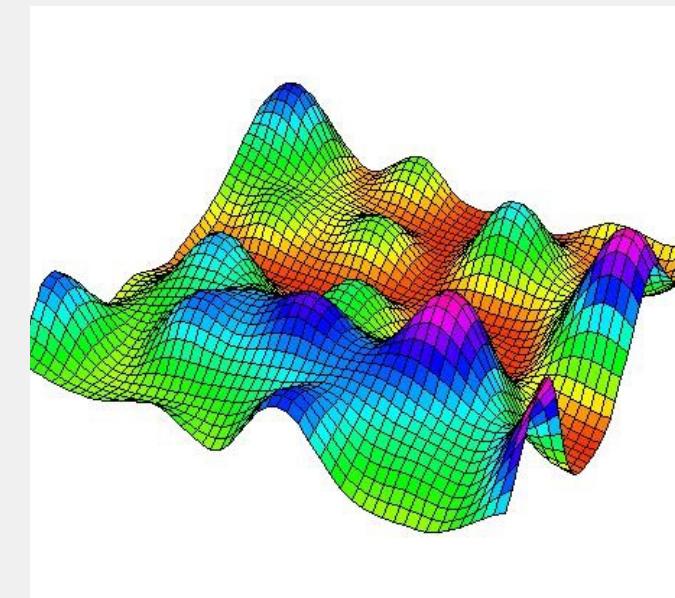
volume conduction



dimensionality reduction

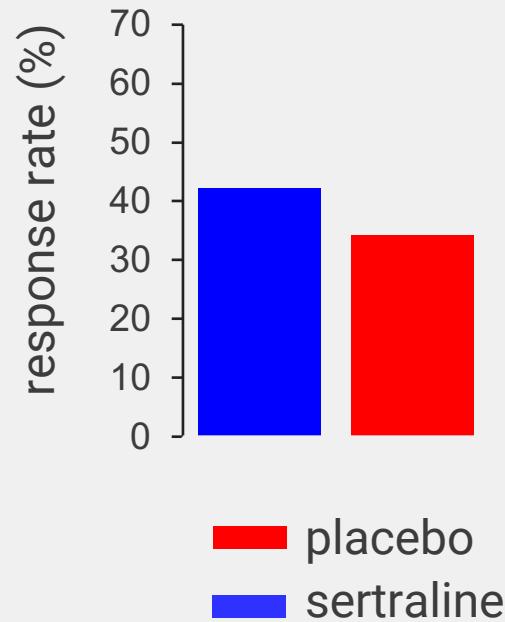


optimization



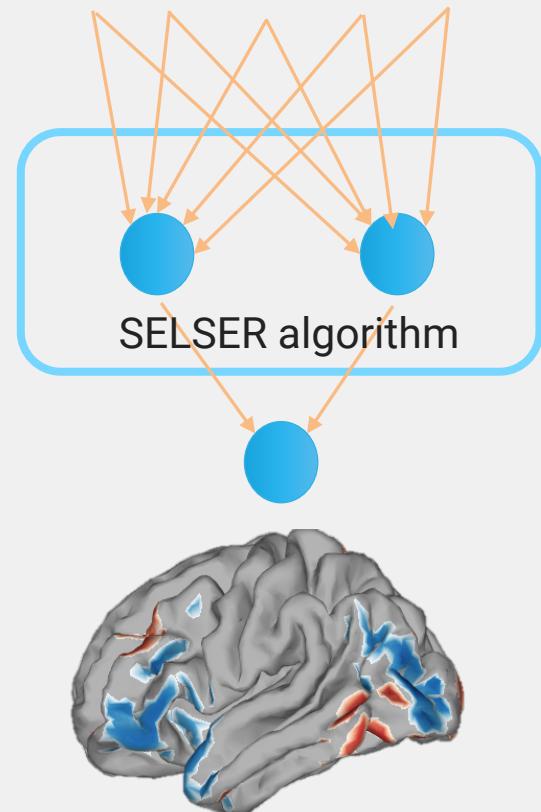
# EEG Predicts Who Will Respond to an Antidepressant Vs. Placebo

EMBARC study  
all-comers: small effect size



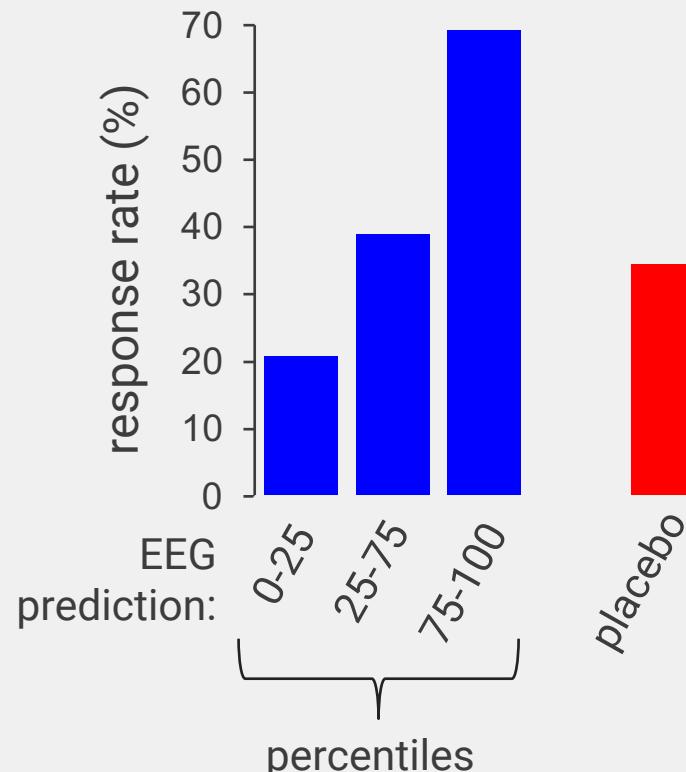
Fonzo et al., *Nature Human Behavior*, 2019

EEG spatial covariance matrices



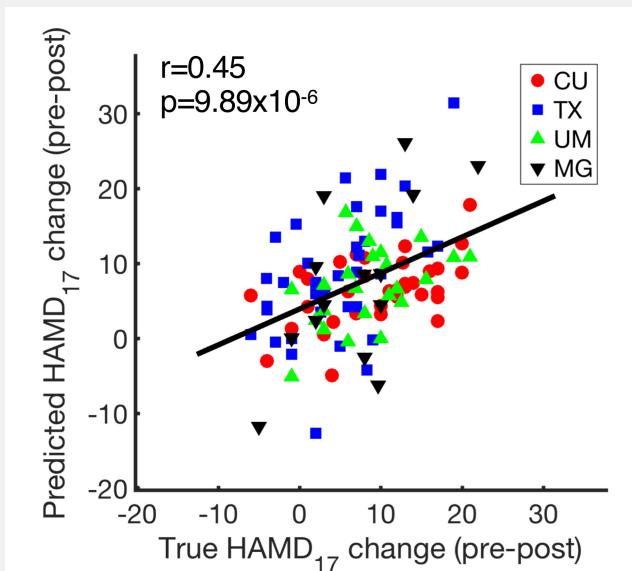
Wu et al., *Nature Biotechnology*, 2020

split based on sertraline EEG signature

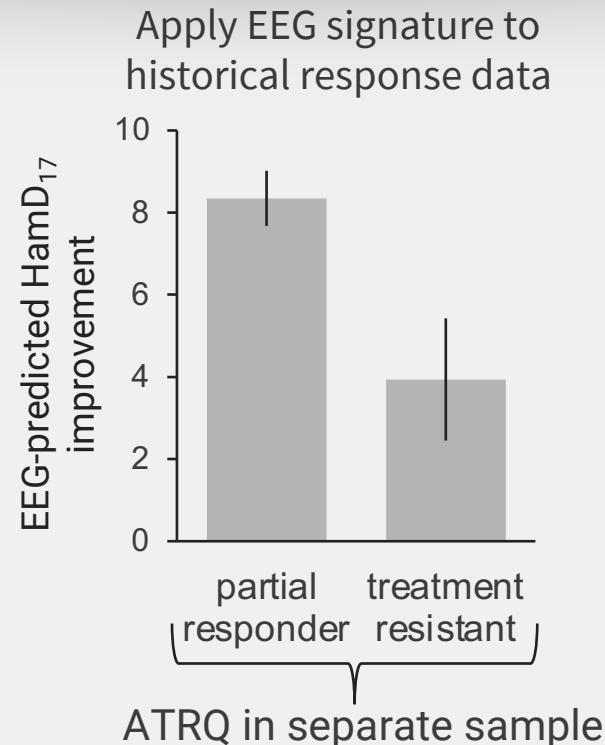


# The treatment-Predictive Pattern Is Robust and Informative

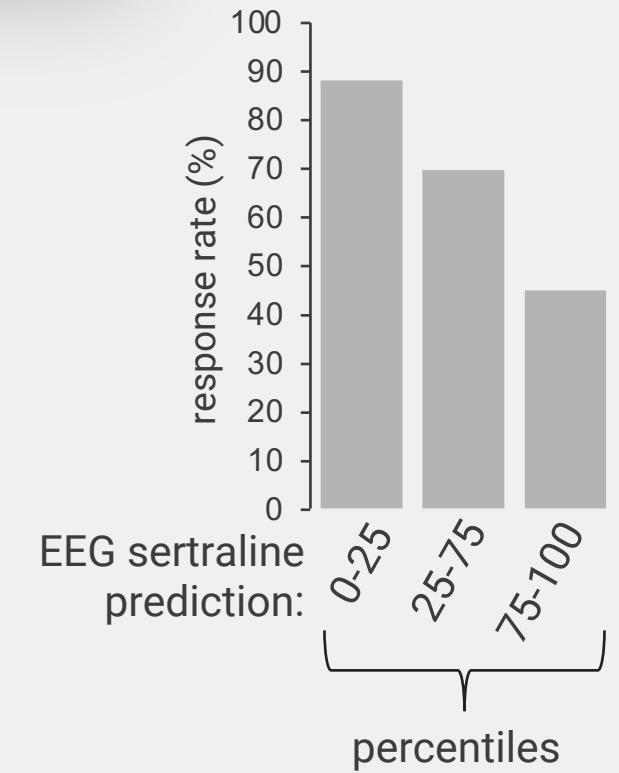
Trained model on data from three geographic sites and tested on the 4<sup>th</sup> site (also, each site had different EEG systems)



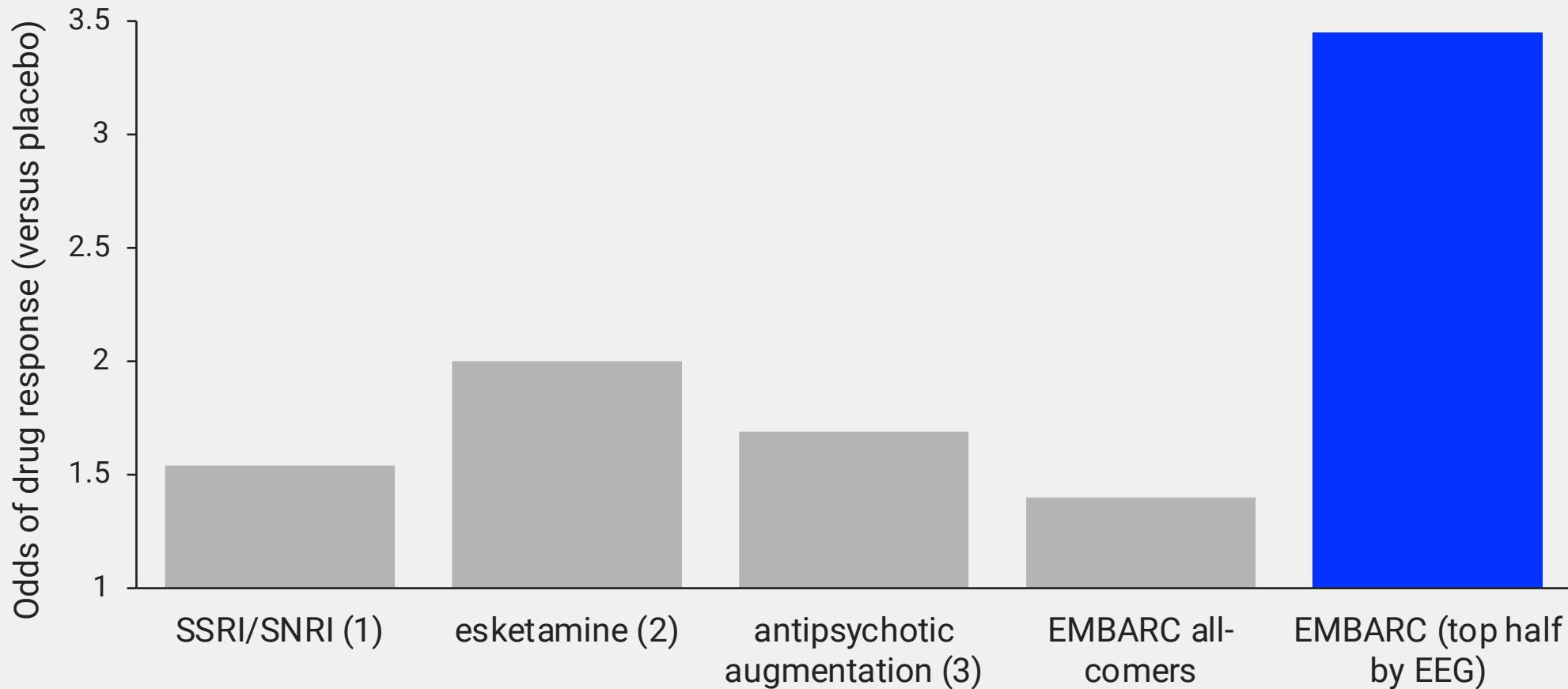
Can further test clinical significance by seeing if the sertraline EEG pattern relates to other outcomes



Apply EEG signature to 1 Hz rTMS data



# Clear Benefit of Using Biomarkers Over Traditional All-Comer Approaches



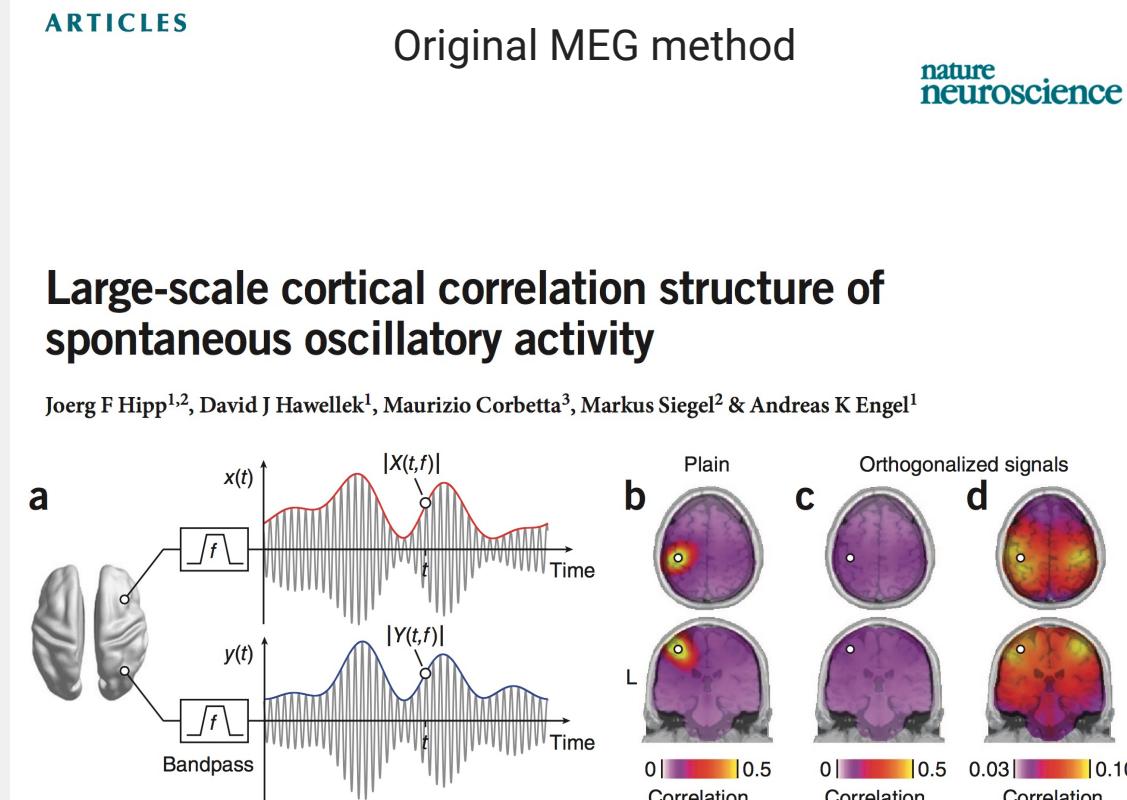
<sup>1</sup> Cipriani, *Lancet*, 2018

<sup>2</sup> Papakostas, *J Clin Psych*, 2020

<sup>3</sup> Nelson, *Am J Psych*, 2009

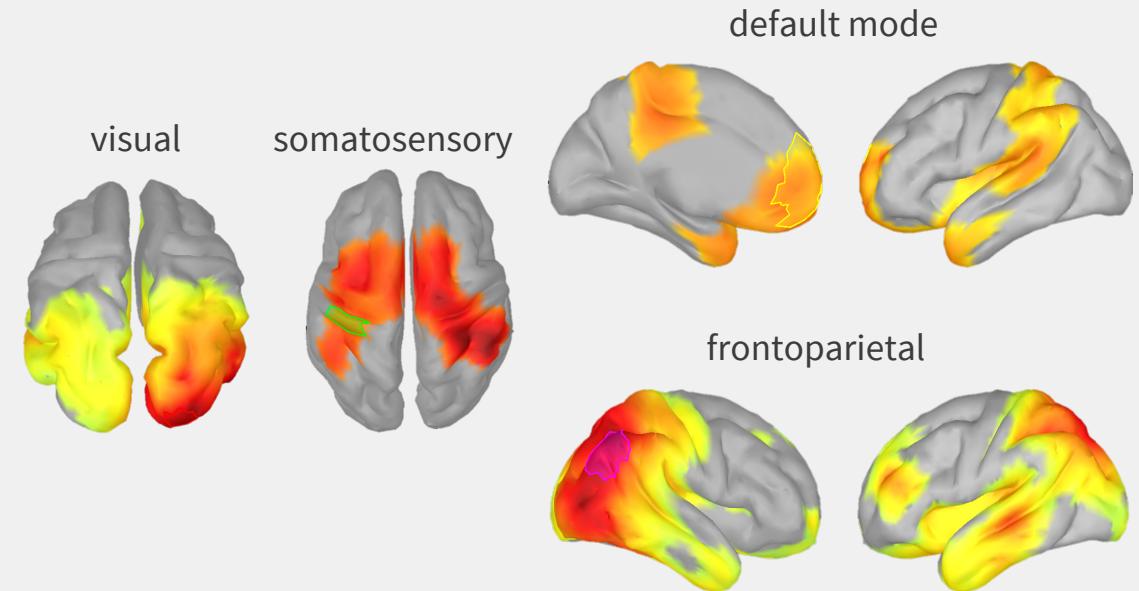


# Resting-State Network Connectivity With EEG



Hipp et al., *Nature Neuroscience*, 2012

Orthogonalized power envelope connectivity reveals fMRI-like networks using EEG data

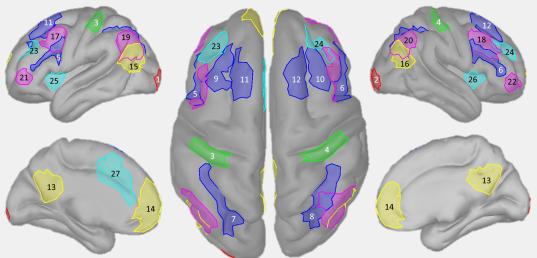


Toll et al., *American Journal of Psychiatry*, 2020

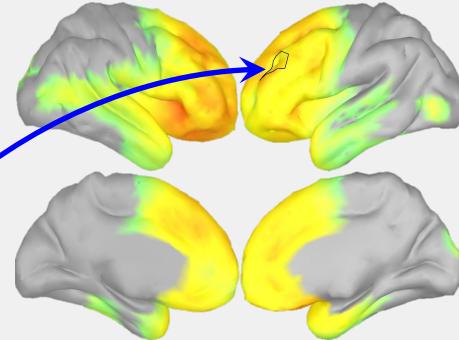


# EEG Connectomic Profile of PTSD and Cognitive Deficits

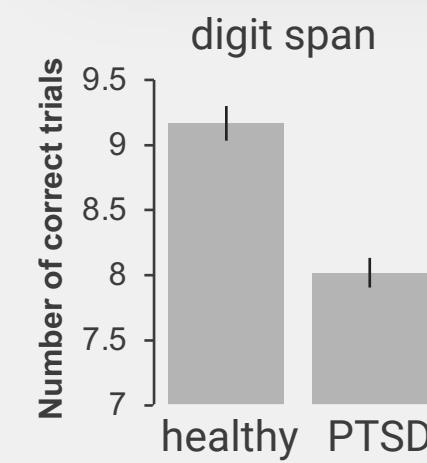
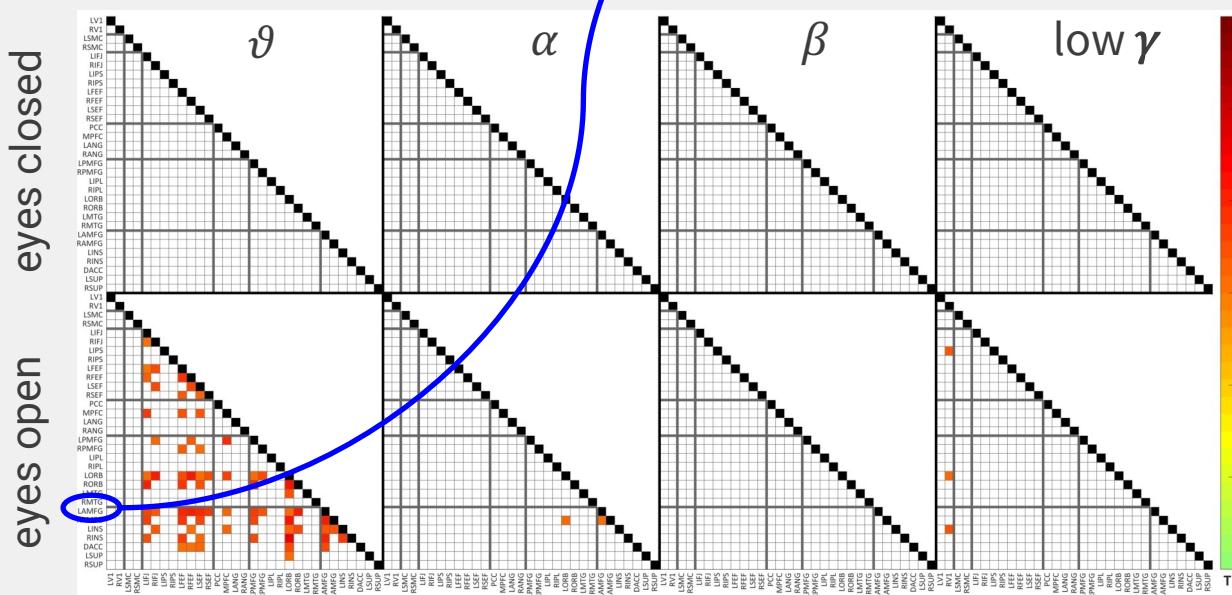
Network ROIs:



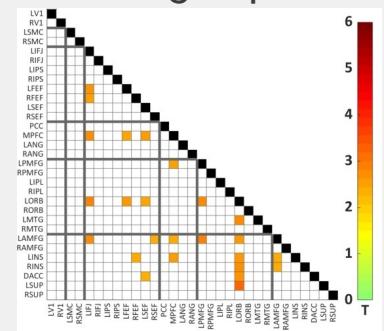
Healthy > PTSD



Reduced prefrontal  $\vartheta$  connectivity is related to worse cognition



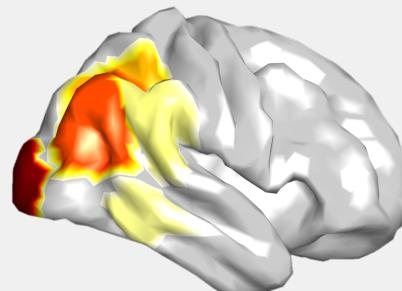
$\vartheta$  connectivity vs digit span



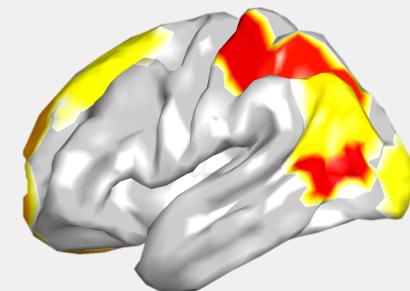
# EEG Connectivity Predicts and Tracks Antidepressant Outcomes

Power envelope connectivity analyses on EMBARC data:

Connectivity moderating outcome with sertraline vs placebo:

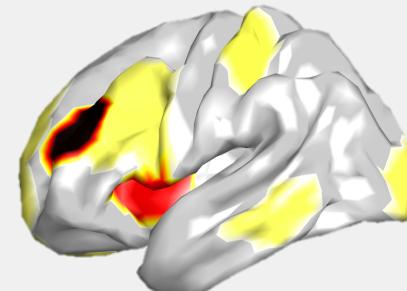


Eyes closed  $\alpha$

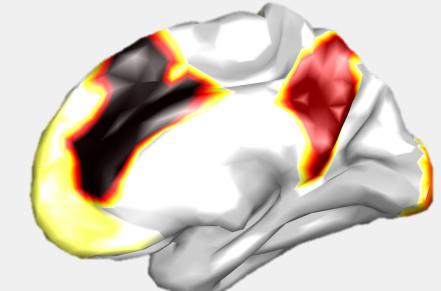


Eyes closed  $\gamma$

Connectivity change (at 1 week) with sertraline vs placebo:



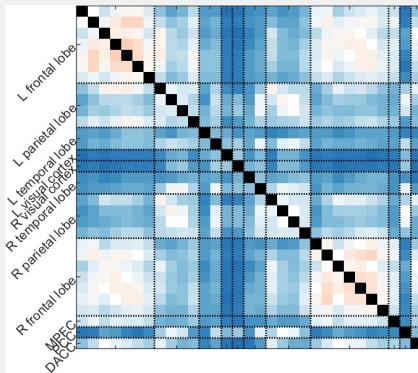
Eyes closed  $\alpha$



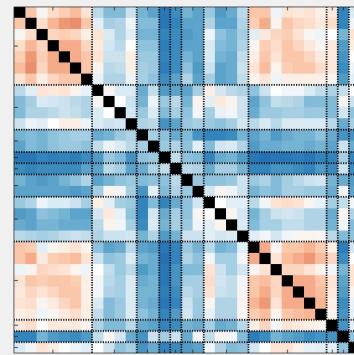
# Unsupervised Machine Learning Reveals Two EEG Connectivity Patient Biotypes

## EEG connectivity matrices:

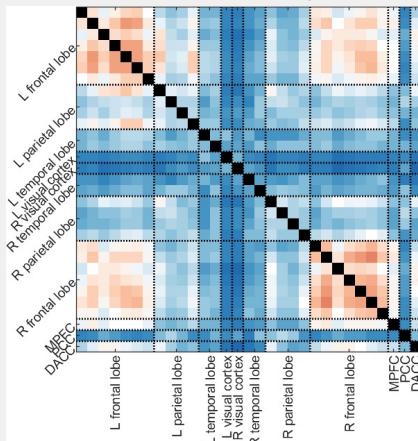
All patients (no biotyping)



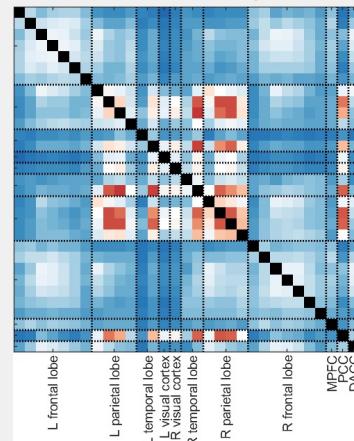
Healthy



Patients: biotype 1



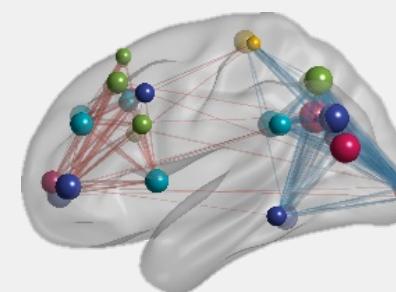
Patients: biotype 2



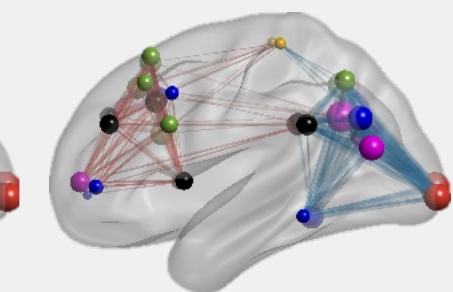
- Four independent datasets: 2 with MDD, 2 with PTSD

- >90% accuracy identifying biotypes when training models on three datasets and testing on the 4<sup>th</sup> (and works across EEG setups)

MDD cohort #1

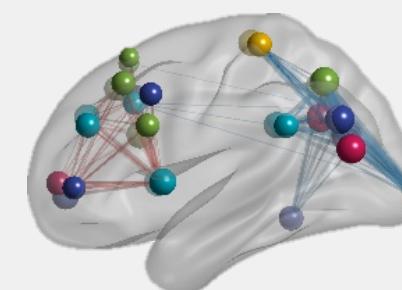


MDD cohort #2

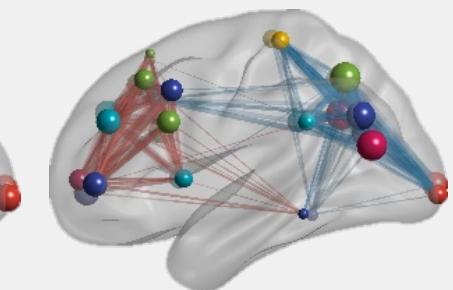


## Connectivity differences between biotypes:

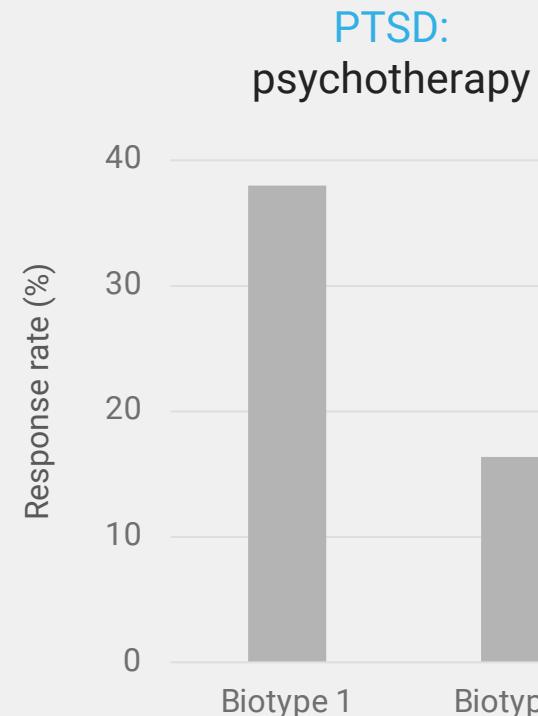
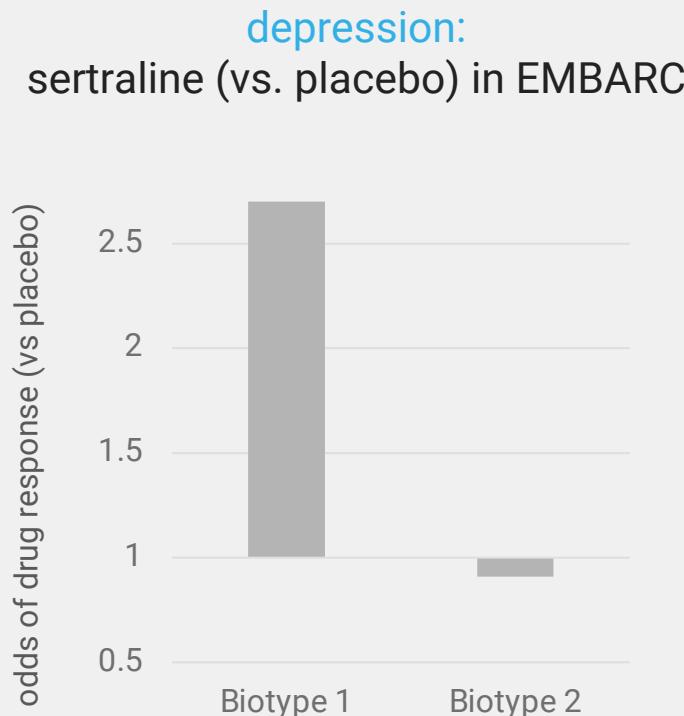
PTSD cohort #1



PTSD cohort #2



# EEG-Defined Patient Subtypes Have Transdiagnostic Clinical Relevance

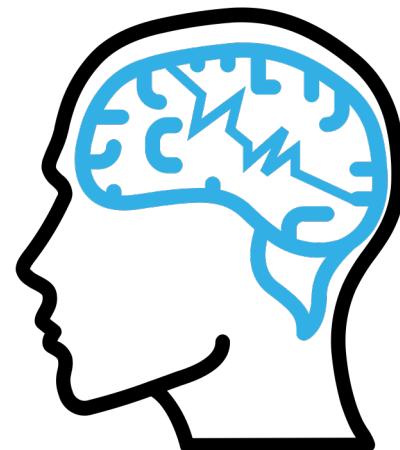


- Sample of veterans receiving prolonged exposure or cognitive processing therapy in the VA (PTSD cohort #2 in prior slide)
- Outcome predicted significantly in **two independent cohorts** ( $N's=72, 63$ )
- Prediction is **independent of therapy type**

Biotype 2 appears to be less responsive to standard-of-care treatments

# A Path Has Now Been Defined for Achieving Precision Medicine for the Brain

Brain-based biomarker platform,  
enabled by machine learning



Novel treatments targeting key  
brain circuits and functions



# Precision Medicine for the Brain is Here

More info on our approach soon

For updates

Email: amitetkin@altoneuroscience.com

Twitter: @amitetkin

