

A Circuits-First Approach to Mental Illness

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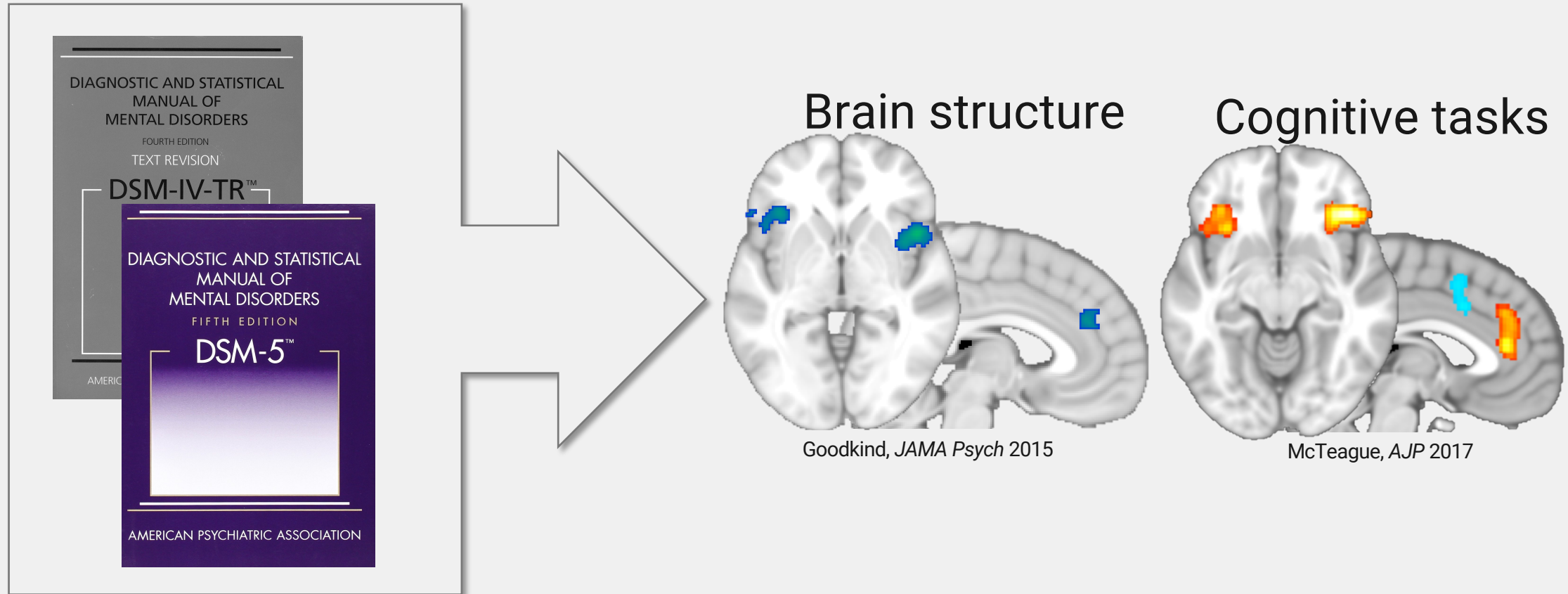
Disclosures

Salary: Alto Neuroscience

Equity: Alto Neuroscience, Mindstrong Health, Akili Interactive



Key Conceptual Evolutions: From Clinical to Brain Measures



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

Key Conceptual Evolutions: From Averages to Precision Psychiatry?

Prozac, used by 40m people, does not work say scientists

Analysis of unseen trials and other data concludes it is no better than placebo

Full text: [the PLoS paper](#)



2008

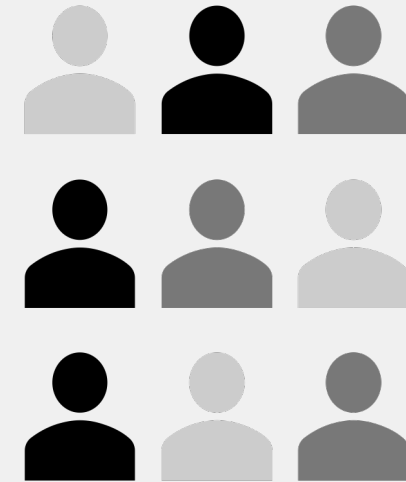
The drugs do work: antidepressants are effective, study shows

Doctors hope study will put to rest doubts about the medicine, and help to address global under-treatment of depression

It's official: antidepressants are not snake oil or a conspiracy



2018

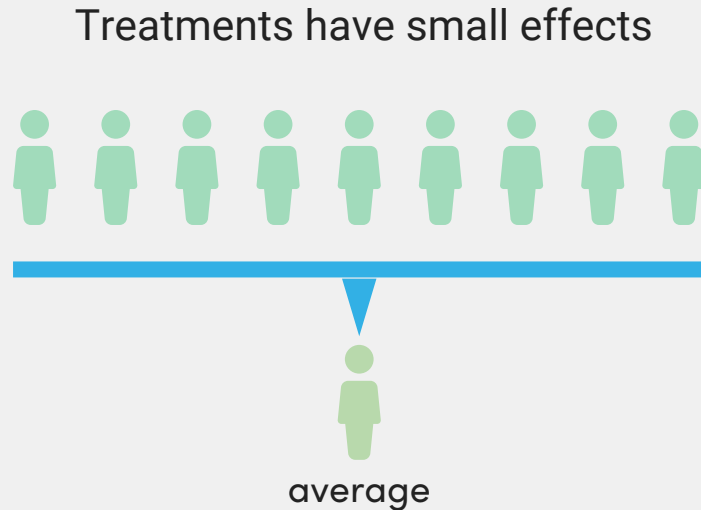


What if the drugs have worked, but we've thought about mental illness the wrong way?

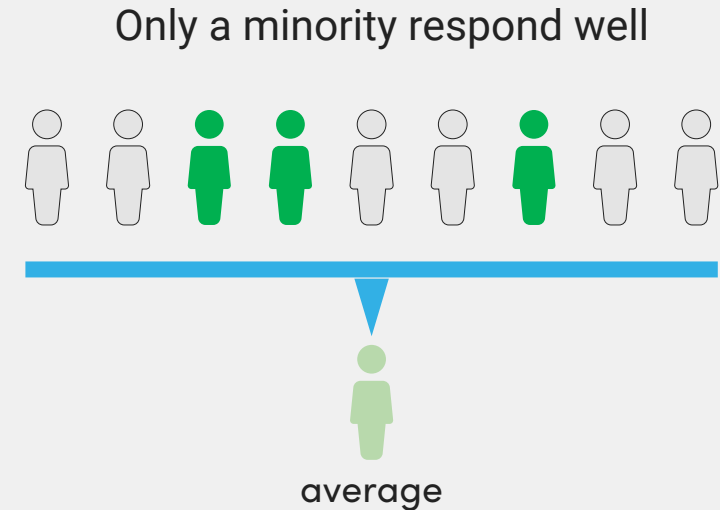


A Precision Approach **Requires Re-Orienting** Our Thinking and Studies

Two alternative perspectives on small average effects:



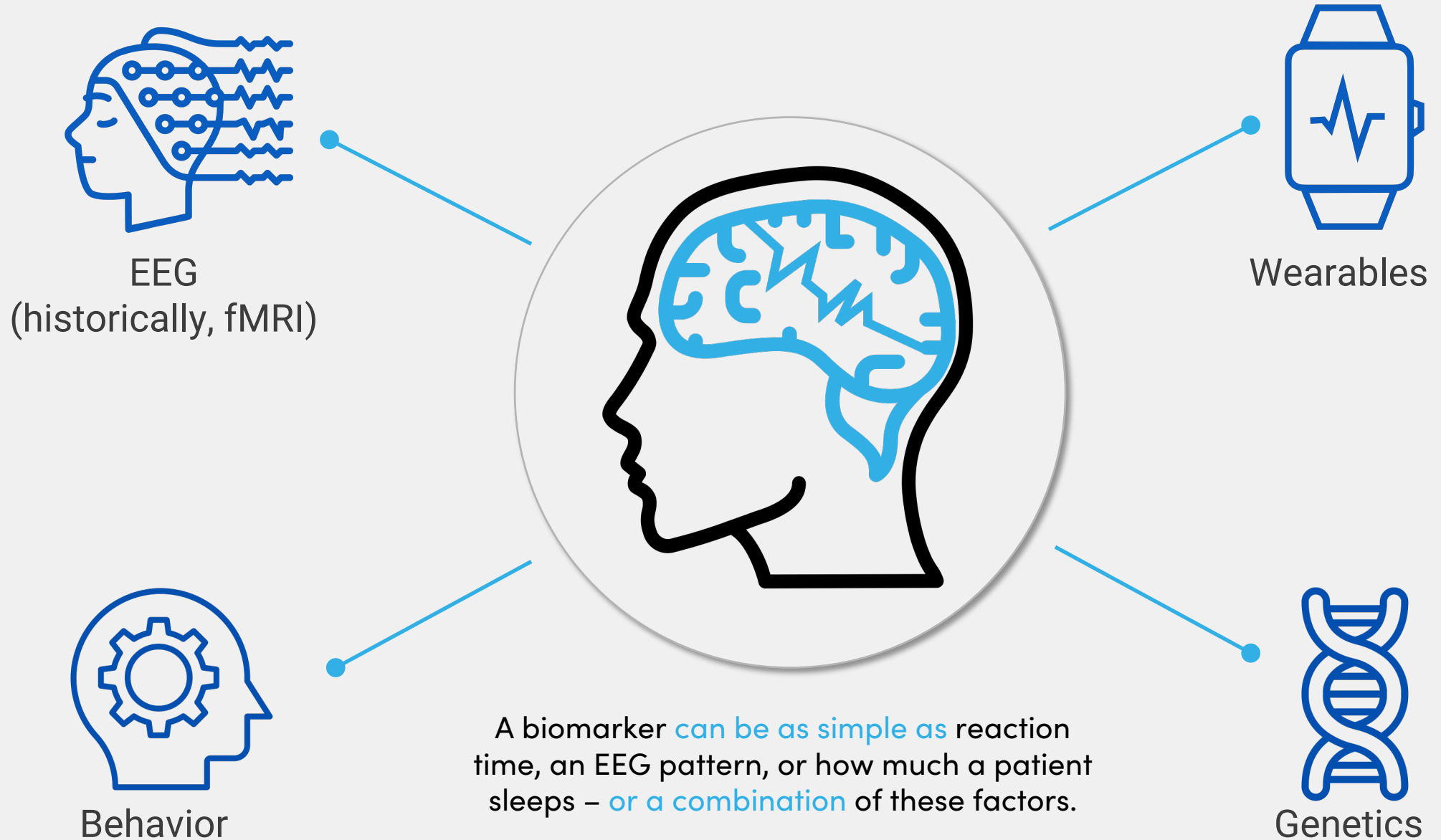
VS.



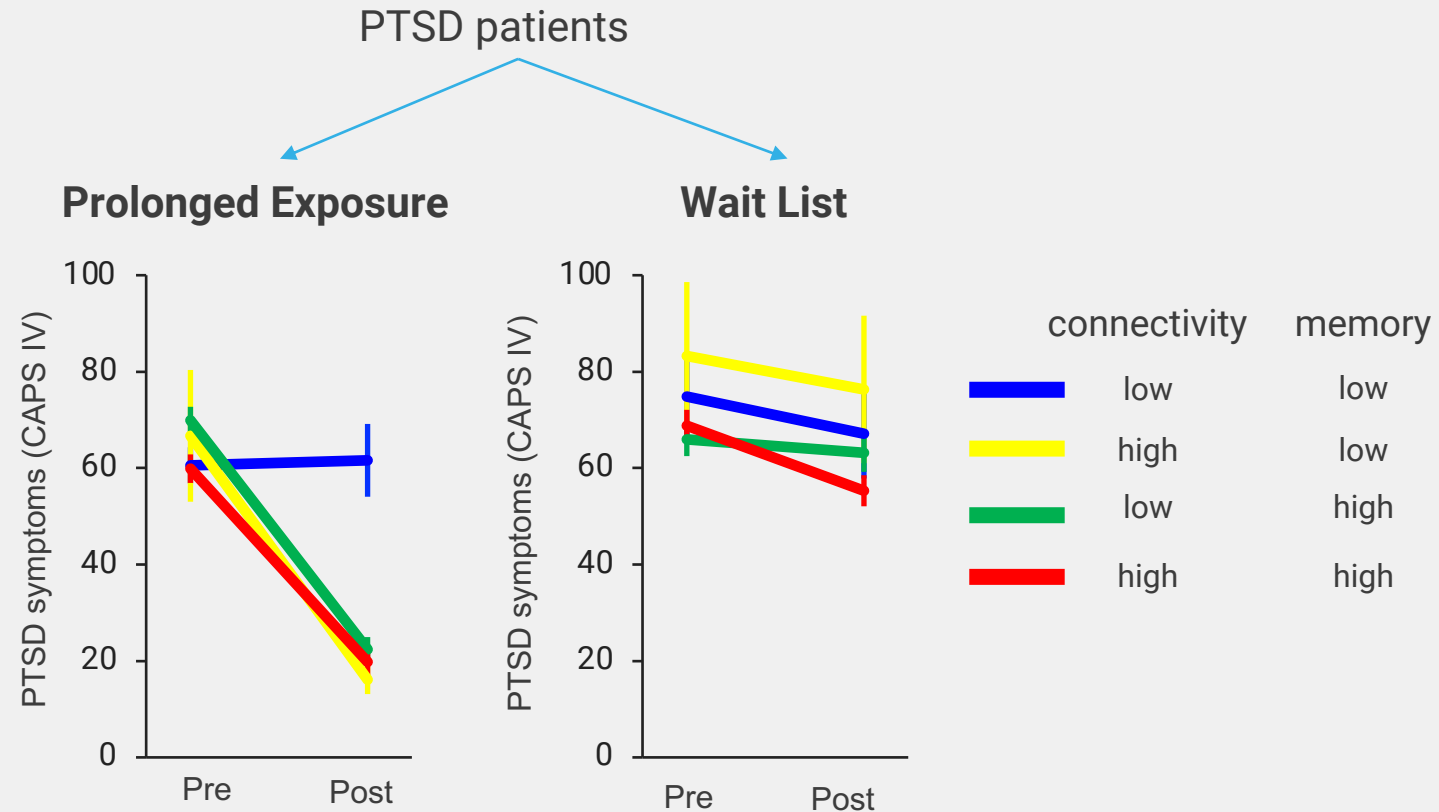
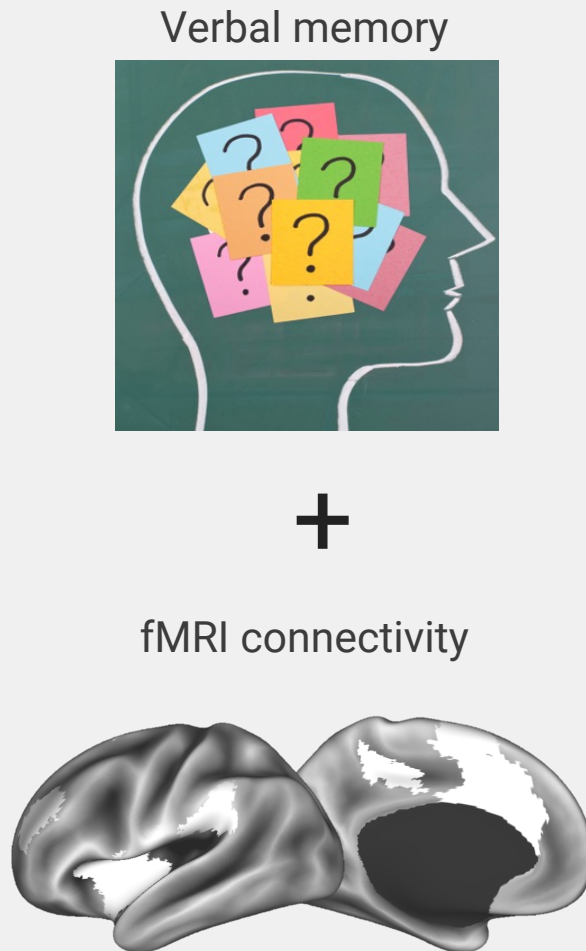
....but, for a precision approach to work, these differences cannot be due to random chance



A Central Biomarker Focus on Brain Circuits



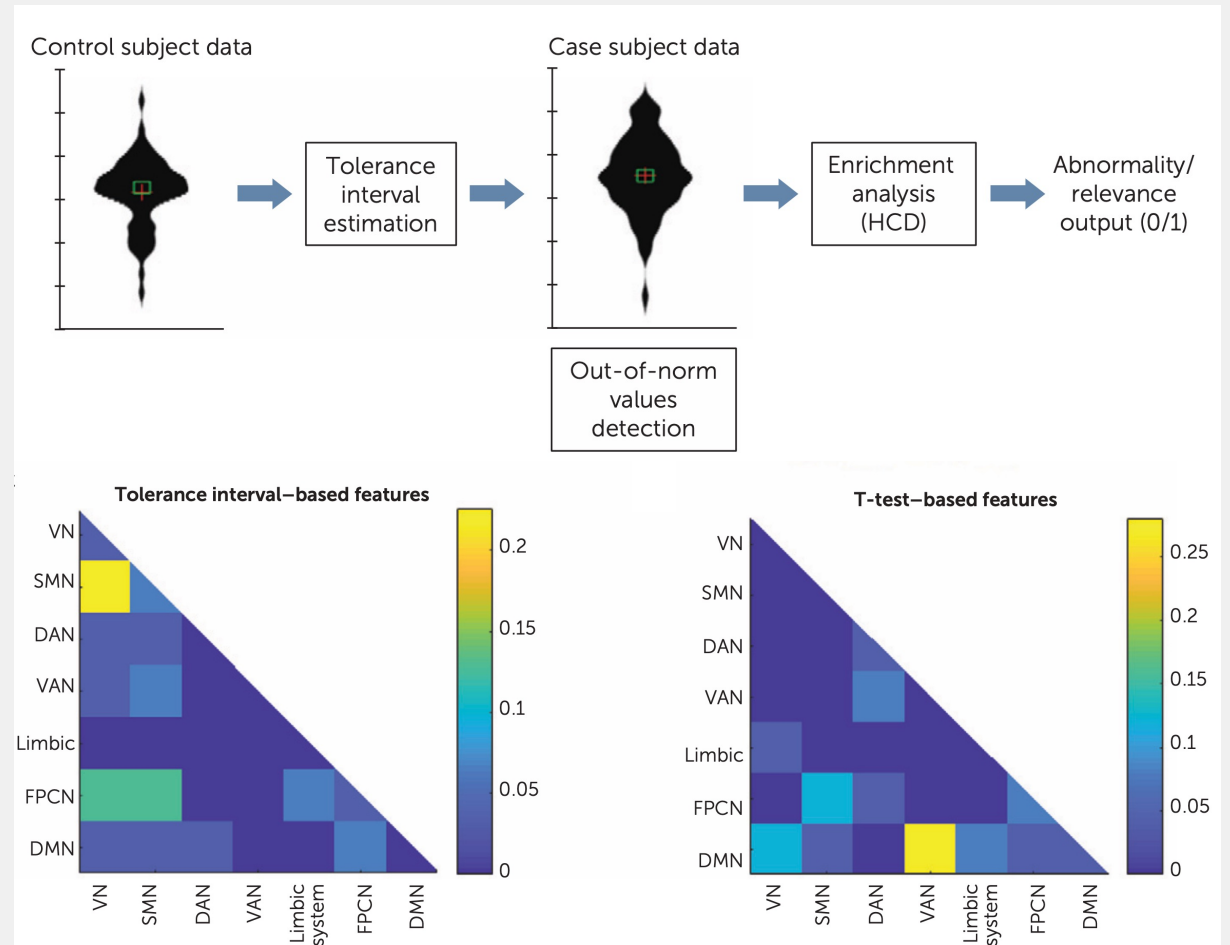
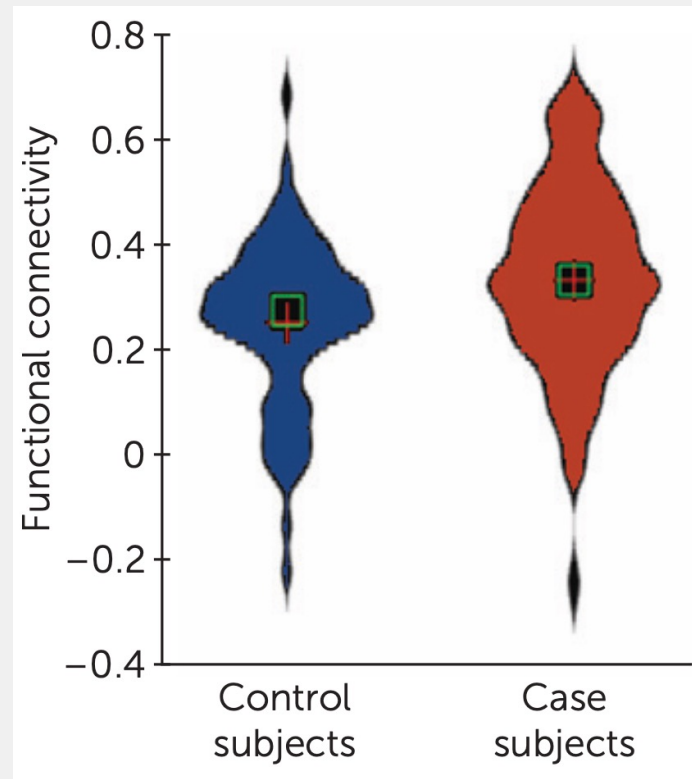
Behavior and Brain Connectivity Predict Psychotherapy Outcome



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

Patient-Control Differences Also Exist As Individual-Level Differences

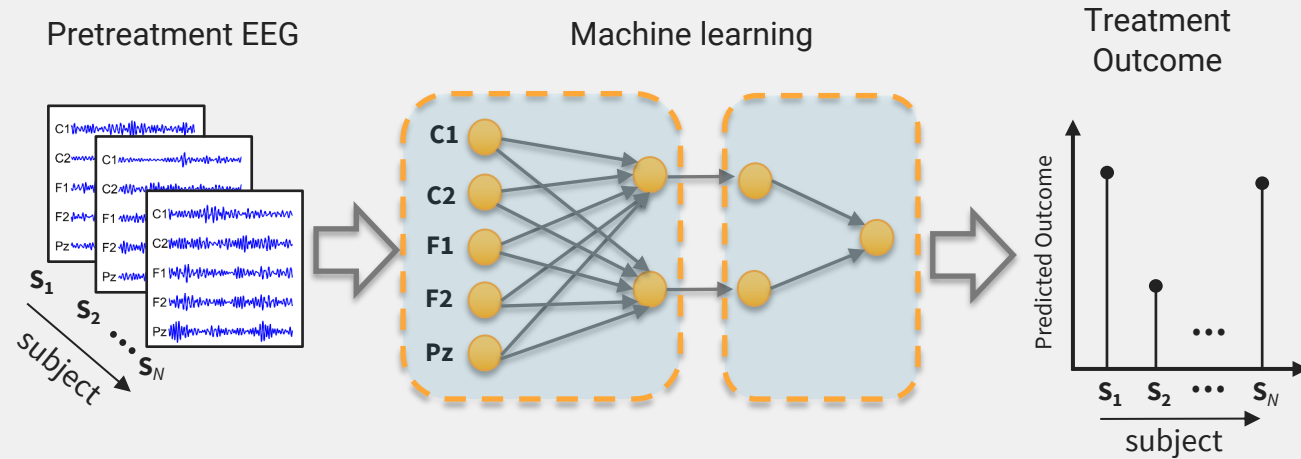
Biotyping: A few patients may have anomalous signals not seen in controls



Machine Learning Enables Robust Discovery and Scalable Biomarkers

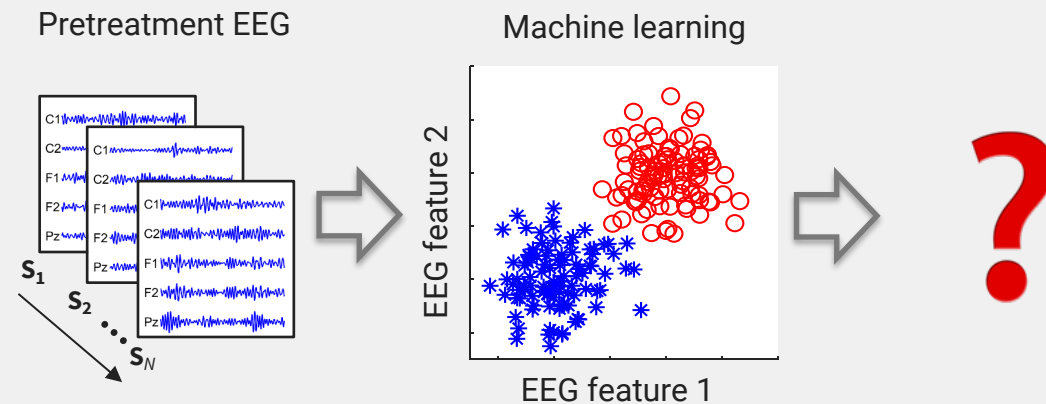
Supervised:

- Known clinical targets
- Heterogeneity in treatment outcomes



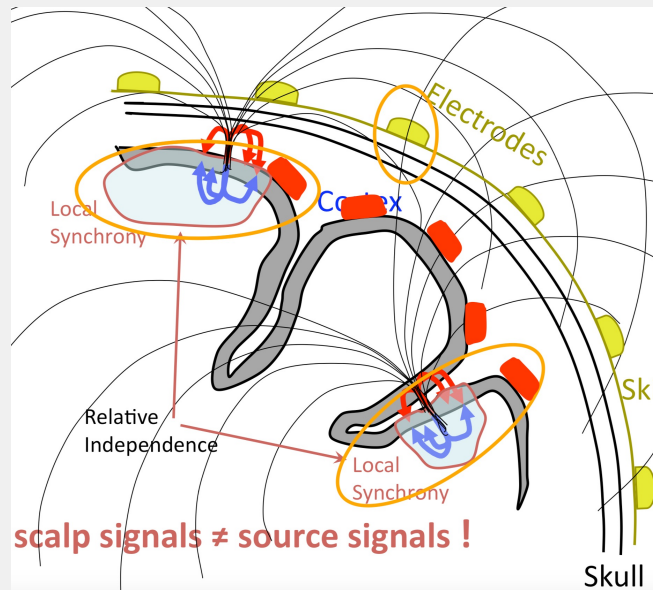
Unsupervised:

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

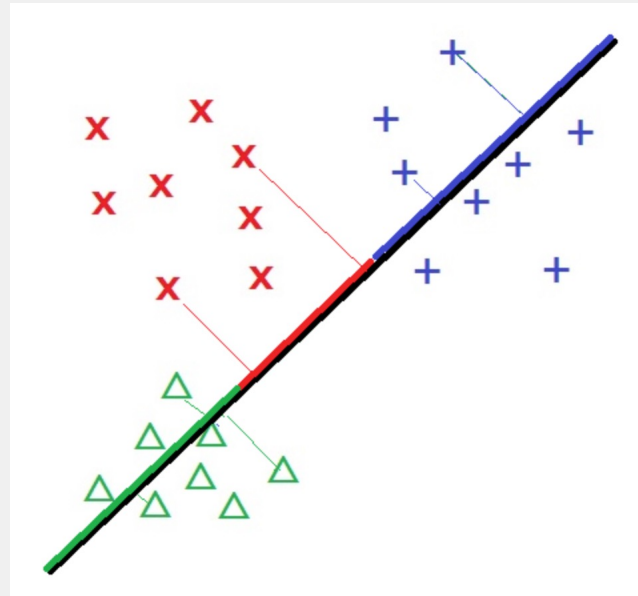


Challenges of EEG Machine Learning

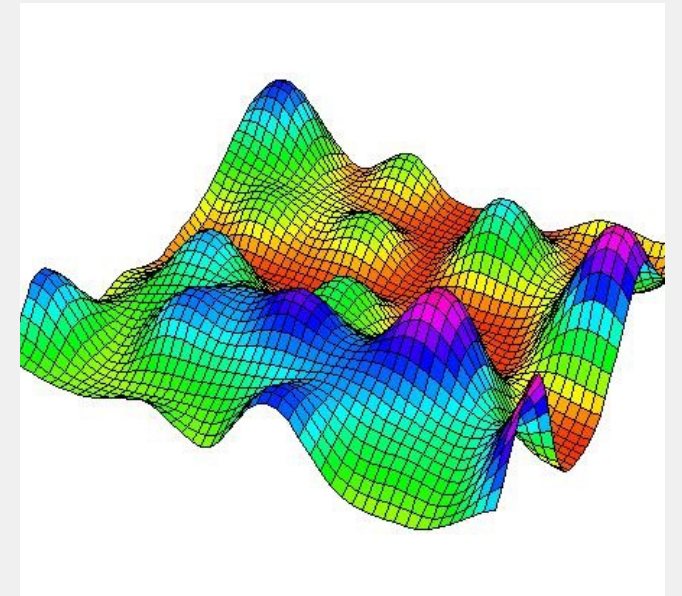
volume conduction



dimensionality reduction

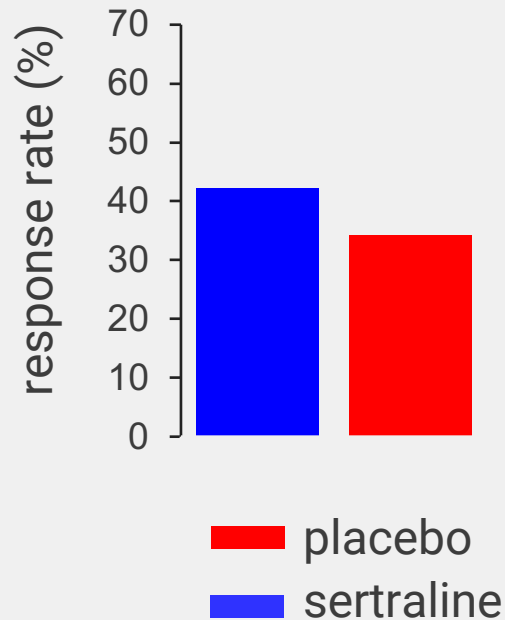


optimization



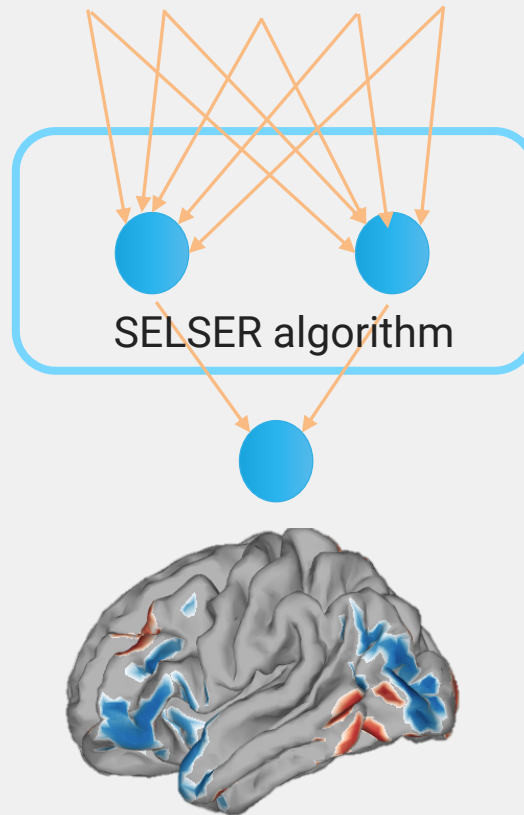
EEG Predicts Who Will Respond to an Antidepressant Vs. Placebo

EMBARC study
all-comers: small effect size



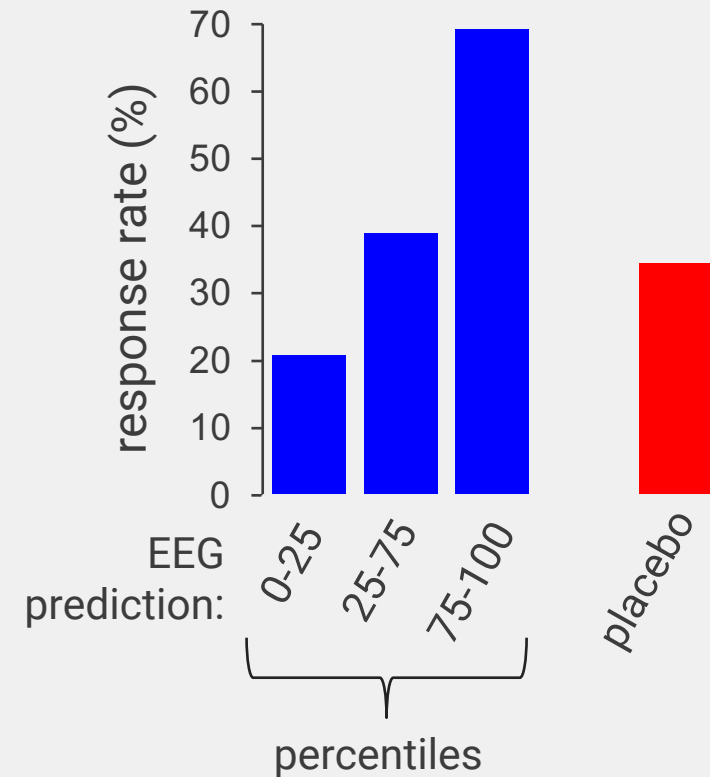
Fonzo et al., *Nature Human Behavior*, 2019

EEG spatial covariance matrices



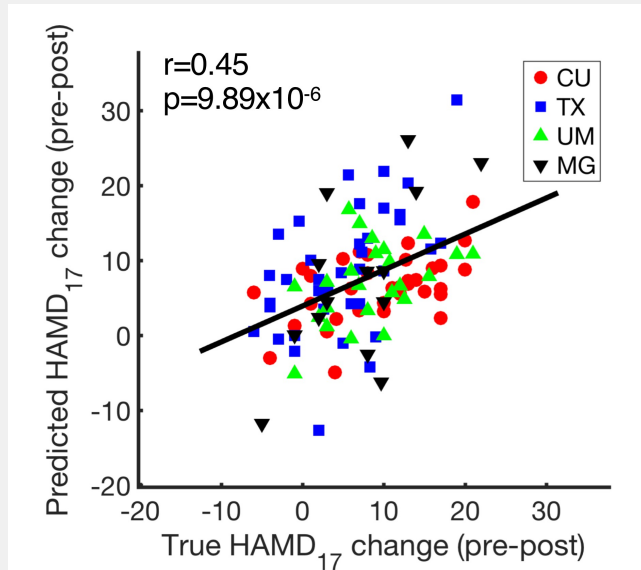
Wu et al., *Nature Biotechnology*, 2020

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 4th site (also, each site had different EEG systems)

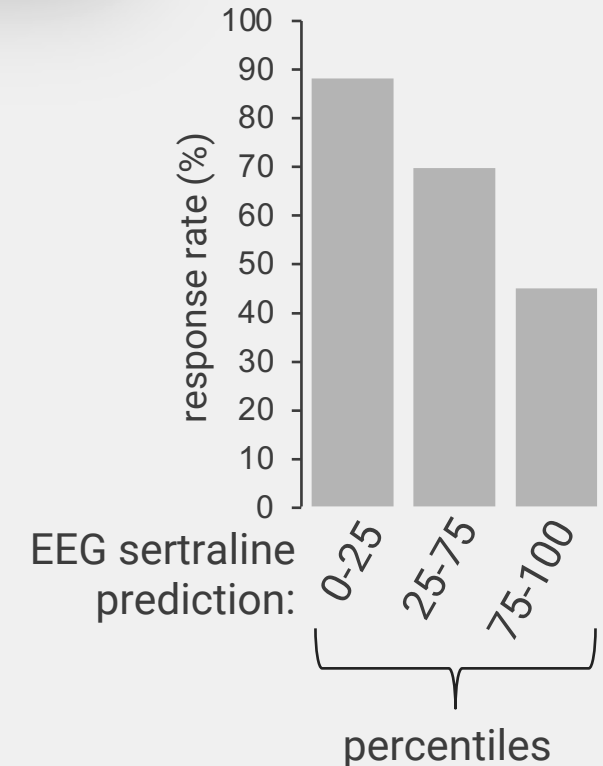
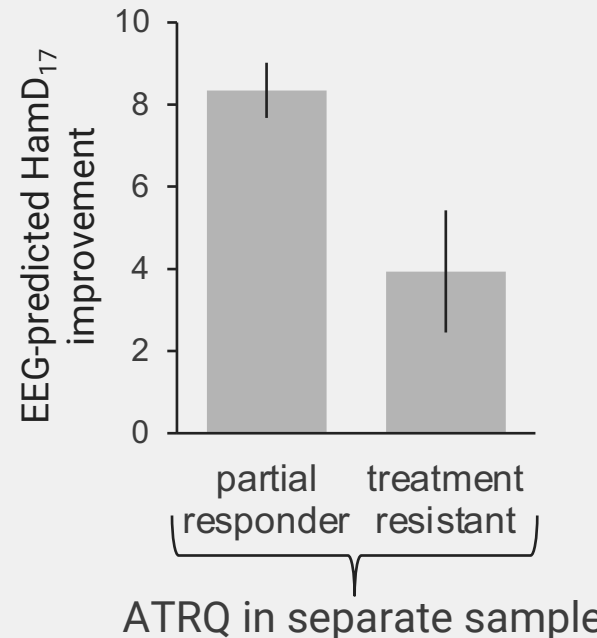


Can further test clinical significance by seeing if the sertraline EEG pattern relates to other outcomes

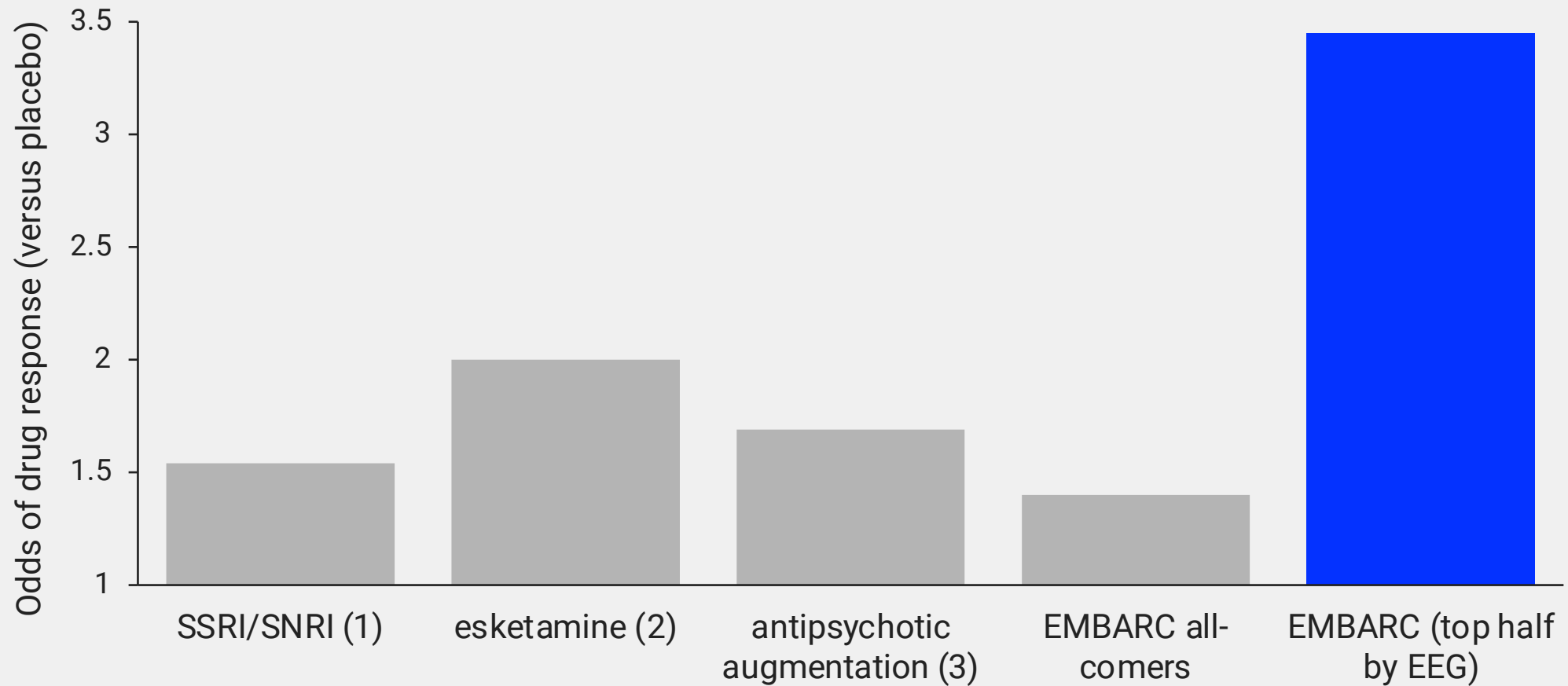
Apply EEG signature to 1 Hz rTMS data



Apply EEG signature to historical response data



Clear Benefit of Using Biomarkers Over Traditional All-Comer Approaches



¹ Cipriani, *Lancet*, 2018

² Papakostas, *J Clin Psych*, 2020

³ Nelson, *Am J Psych*, 2009



Resting-State Network Connectivity **With EEG**

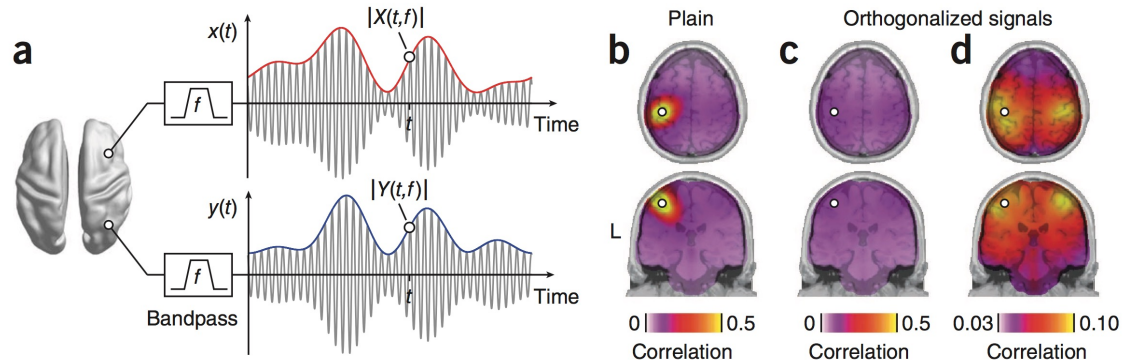
ARTICLES

Original MEG method

nature
neuroscience

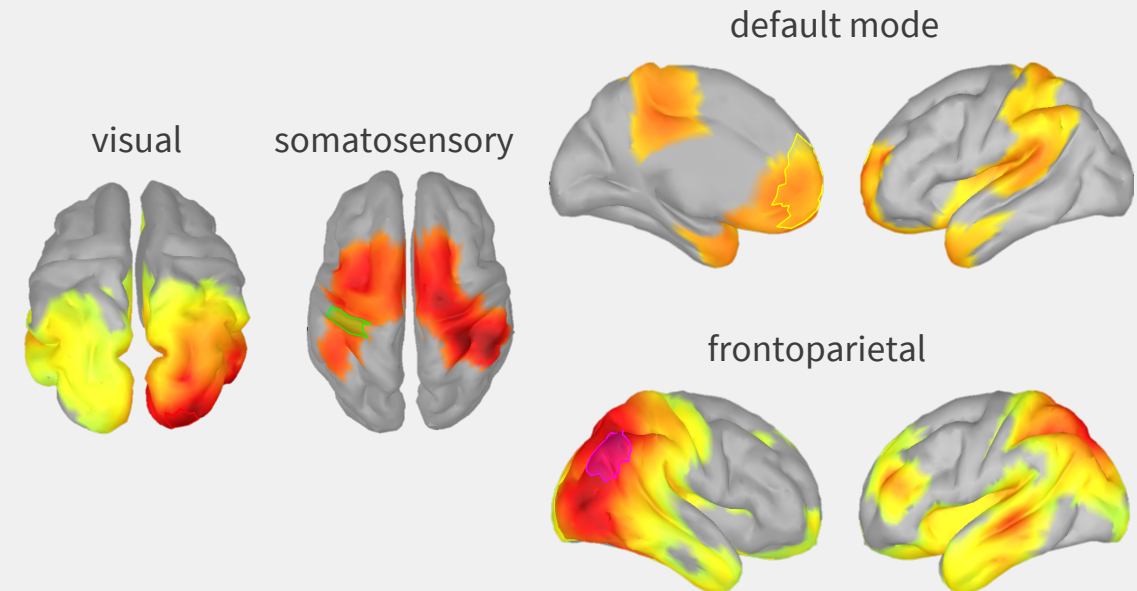
Large-scale cortical correlation structure of spontaneous oscillatory activity

Joerg F Hipp^{1,2}, David J Hawellek¹, Maurizio Corbetta³, Markus Siegel² & Andreas K Engel¹



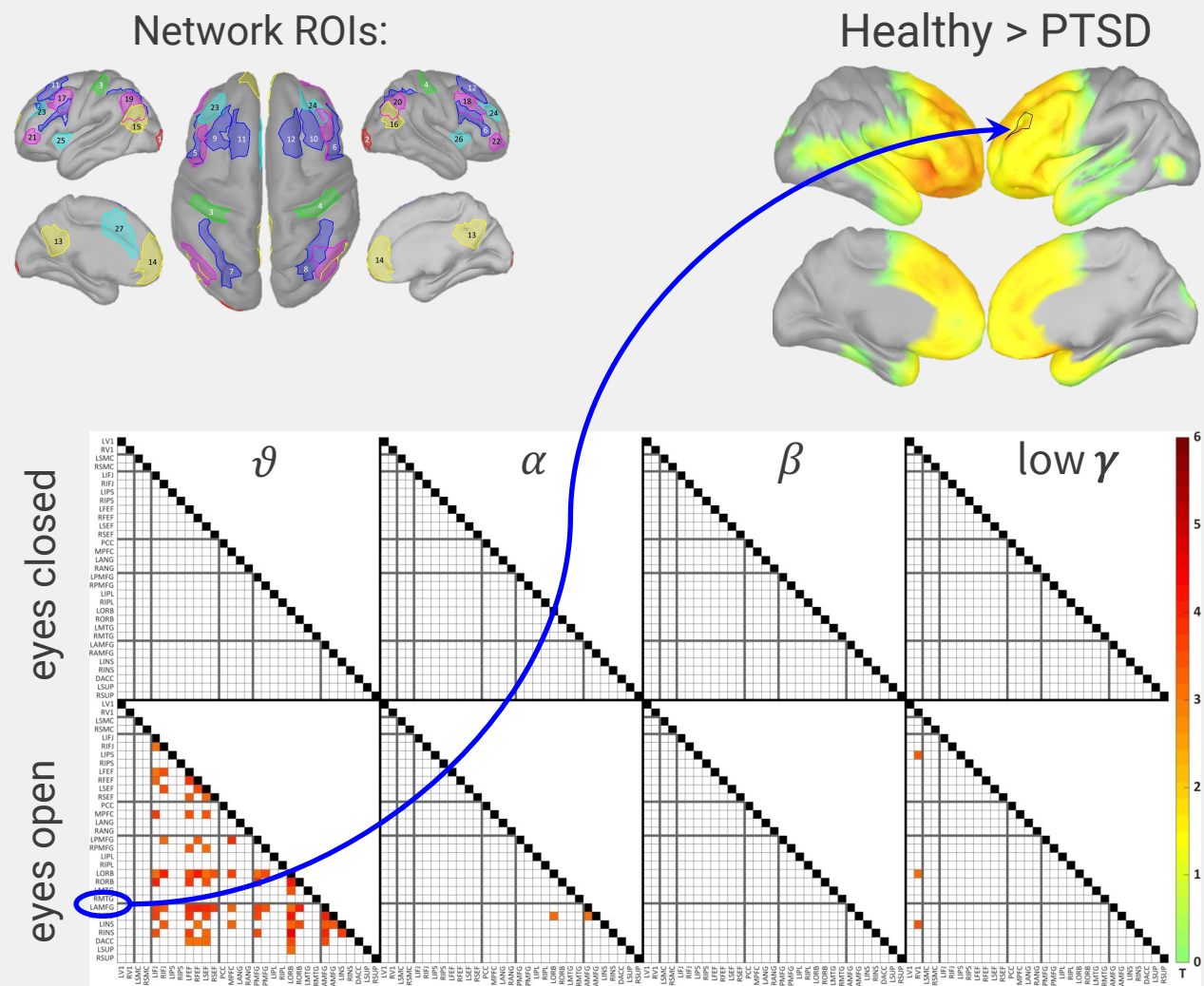
Hipp et al., *Nature Neuroscience*, 2012

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

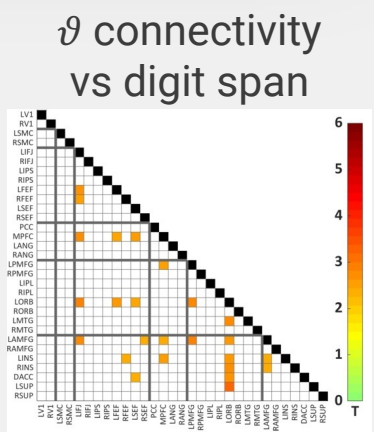
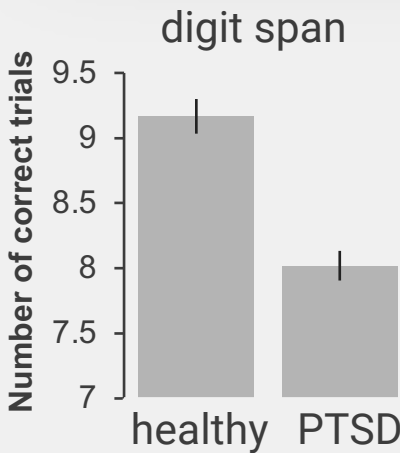


Toll et al., *American Journal of Psychiatry*, 2020

EEG Connectomic Profile of PTSD and Cognitive Deficits



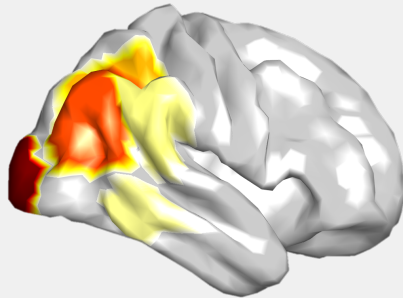
Reduced prefrontal θ connectivity is related to worse cognition



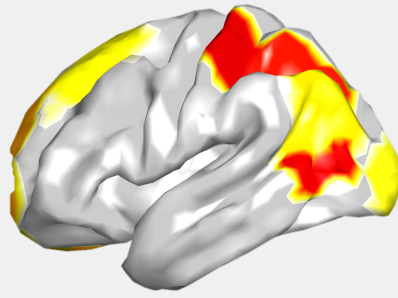
EEG Connectivity Predicts and Tracks Antidepressant Outcomes

Power envelope connectivity analyses on EMBARC data:

Connectivity moderating outcome with
sertraline vs placebo:

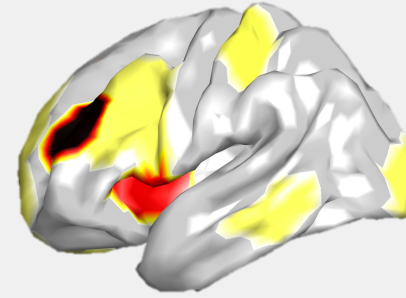


Eyes closed α

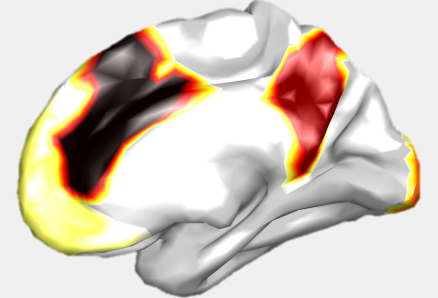


Eyes closed γ

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



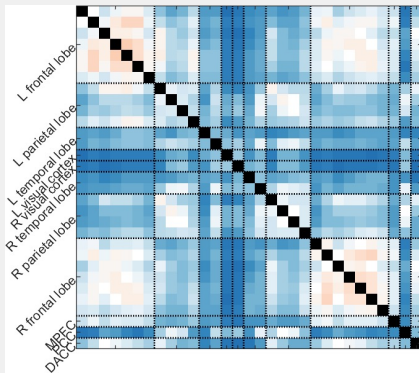
Eyes closed γ



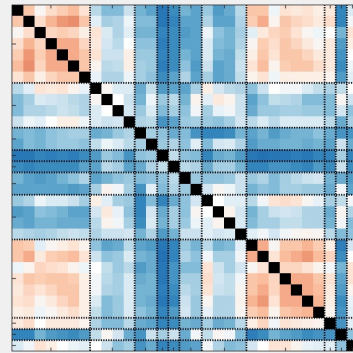
Unsupervised Machine Learning Reveals Two EEG Connectivity Patient Biotypes

EEG connectivity matrices:

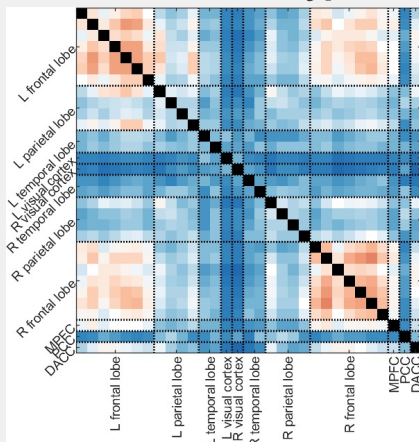
All patients (no biotyping)



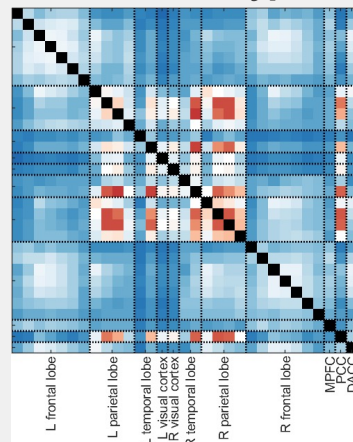
Healthy



Patients: **biotype 1**

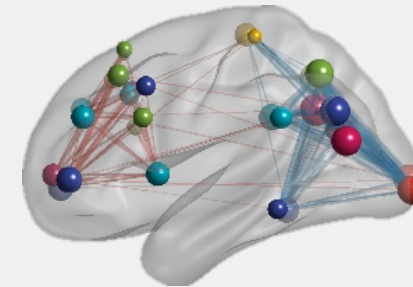


Patients: **biotype 2**

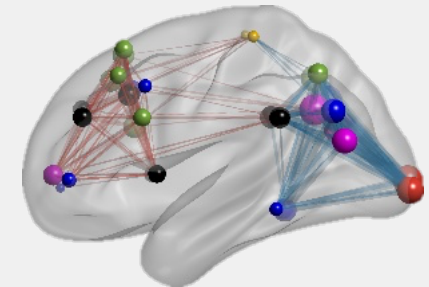


- Four independent datasets: 2 with MDD, 2 with PTSD
- **>90% accuracy identifying biotypes** when training models on three datasets and testing on the 4th (and works across EEG setups)

MDD cohort #1

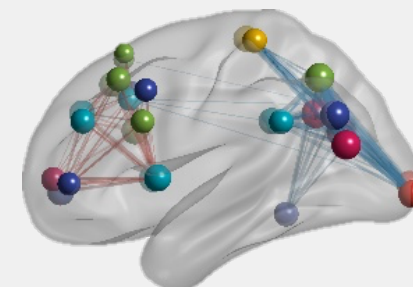


MDD cohort #2

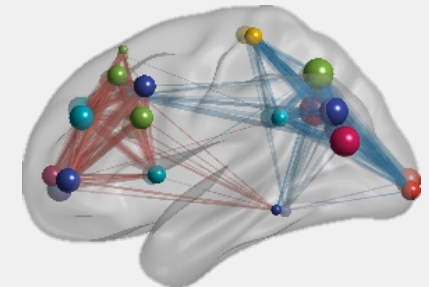


Connectivity differences
between biotypes:

PTSD cohort #1

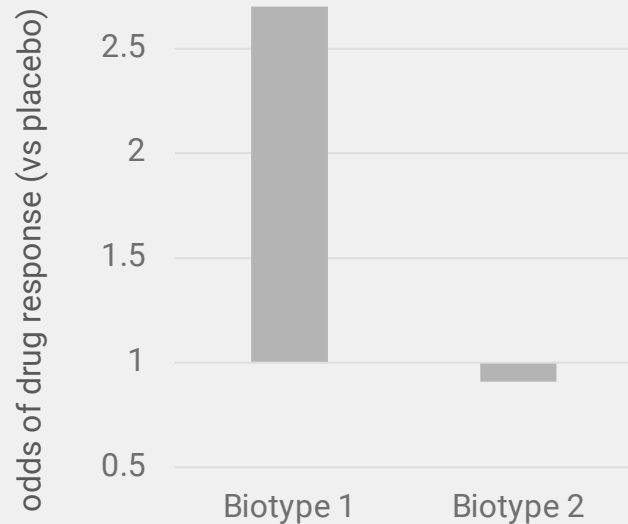


PTSD cohort #2

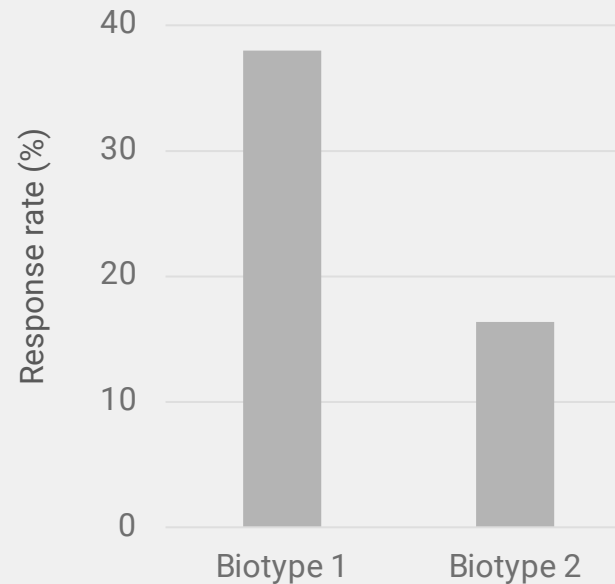


EEG-Defined Patient Subtypes Have Transdiagnostic Clinical Relevance

depression:
sertraline (vs. placebo) in EMBARC



PTSD:
psychotherapy



- 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](https://twitter.com/amitetkin)

