Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care: The EMBARC Data Repository and Machine Learning Based EEG Biomarkers

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Disclosures

Relevant to this presentation: Dr. Detke is a consultant to Neumarker, Inc.

Other Potential Financial Conflicts of Interest over the last 2 years:

Adial Pharmaceuticals (consultant)

Amgen (consultant)

Catalys Pacific (consultant)

CliniLabs (advisory board)

K2X (investor, advisor)

Goldman Sachs (consultant)

Lighthouse Pharma (co-founder; equity)

Neumora (consultant, equity)

Negev Labs (consultant)

NIH BluePrint NeuroTherapeutics Program (consultant)

Osmol Therapeutics (consultant)

Context: Reality, Challenges, Unmet Needs and Goals for CNS Treatment Development

Reality:

- >90% of CNS drug development programs fail.
- Compared to other therapeutic areas, 50% lower success rate, 30% longer development timelines

Challenges:

- High placebo response rates
- Clinical and biological heterogeneity

Unmet needs:

- Adequate, objective, actionable "predictive" biomarkers to:
  - Identify responsive subtypes to include in clinical trials
  - Identify high placebo responders to exclude from clinical trials

Goals:

- Reduce risk of trial failures
- Reduce cost of trials
- Reduce time to patients with unmet needs

Unfortunately: "The literature on biomarkers for treatment response is largely based on secondary analyses of studies designed to answer primary questions of efficacy, rather than on a planned systematic evaluation of biomarkers for treatment decision." Petkova, 2017.

What to do next: Data Consortium approach!!

NIMH-funded Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design

Background:

- No biological or clinical marker had demonstrated sufficient ability to match individuals to efficacious treatment for MDD
- Goal: Develop biosignatures developed from the systematic exploration of multiple biological markers, which might optimize treatment selection for individuals (moderators) and provide early indication of ultimate treatment response (mediators)
- Multi-site, placebo-controlled 8-week randomized clinical trial of sertraline (stage 1)
- Standardized assessment of biomarkers across and replicable quality control methods
- **NIMH-funded, the data were made available in a public scientific repository.**
- Other studies had similar goals (iSPOT, PreDICT) but lacked a placebo control arm.

Hypotheses:

- Clinical moderators included anxious depression, early trauma, gender, melancholic and atypical depression, anger attacks, Axis II disorder, hypersomnia/fatigue, and chronicity of depression.
- Biological moderator and mediators included cerebral cortical thickness, task-based fMRI (reward and emotion conflict), resting connectivity, diffusion tensor imaging (DTI), arterial spin labeling (ASL), **electroencephalography** (**EEG**), cortical evoked potentials, and behavioral/cognitive tasks.

Results:

- Recruitment began July 29, 2011, and was completed December 15, 2015.
- There was a failure to separate sertraline and placebo (p=.065) but a trove of biomarker data.

Trivedi, M., et al., 2016, J Psych Research; 78 11-23. https://doi.org/10.1016/j.jpsychires.2016.03.001

EMBARC – Some Examples of the Fruits of the Labor

The EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study has yielded several significant publications across various biomarker domains. Here are some notable examples:

1. Neuroimaging Biomarkers:

- **Early-Treatment Cerebral Blood Flow Change as a Predictive Biomarker of Antidepressant Treatment Response: Evidence from the EMBARC Clinical Trial**
- *Summary:* Response to 8-week placebo treatment was associated with increased CBF in temporal cortex and reduced CBF in postcentral region at 1 week. CBF response in these brain regions was significantly correlated with improvement in HAMD score in the placebo group. Cambridge University Press

2. Genetic and Genomic Biomarkers:

- **A Brain-Enriched circRNA Blood Biomarker Can Predict Response to SSRI Antidepressants**
- *Summary:* Identifies a circular RNA biomarker in blood that predicts response to SSRI antidepressants, but not bupropion or placebo. bioRxiv

3. Biochemical Biomarkers:

- **Statistical Analysis Plan for Stage 1 EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) Study**
- *Summary:* Outlines the statistical analysis plan for identifying biochemical and other biomarkers predictive of antidepressant response in the EMBARC study. Europe PMC

EMBARC – Fruits of the Labor, cont'd

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4. Imaging and Cognitive Task Biomarkers:

- **Patterns of Pretreatment Reward Task Brain Activation Predict Antidepressant Response in the EMBARC Trial**
- *Summary:* Pretreatment brain activation patterns during reward tasks can predict antidepressant response (R^2 = .48 for sertraline, R^2 = .34 for bupropion, R^2 = .28 for placebo. Biological Psychiatry Journal

5. EEG Biomarkers:

- **Cortical Connectivity Moderators of Antidepressant vs Placebo Treatment Response in Major Depressive Disorder**
- *Summary:* Observed moderation by connections within and between widespread cortical regions—most prominently parietal—for both the antidepressant and placebo groups. Greater alpha-band and lower gamma-band connectivity predicted better placebo outcomes and worse antidepressant outcomes. Lower connectivity levels in these moderating connections were associated with higher levels of anhedonia. JAMA Psych

In summary, these publications provide insights into the diverse biomarker research conducted within the EMBARC study, contributing to the understanding of personalized treatment approaches for depression.

Combining EEG and AI/ML*: A Novel Biomarker Technology and the Vision Behind

- Scalp EEG technology coupled with AI/ML to generate subtypes and predict individual drug response
  - EEG offers the most direct, convenient, and inexpensive measurement of brain activity.
  - EEG is noninvasive for patients, relatively painless, and reasonably quick; it is very widely available and relatively inexpensive.
  - AI/ML may be a key to accelerate progress, as the large amount of data generated in an EEG is impossible to thoroughly analyze using conventional methods.
  - Potentially becomes routine brain measurement in psychiatry and neurology (The "EKG of Neuropsychiatry")

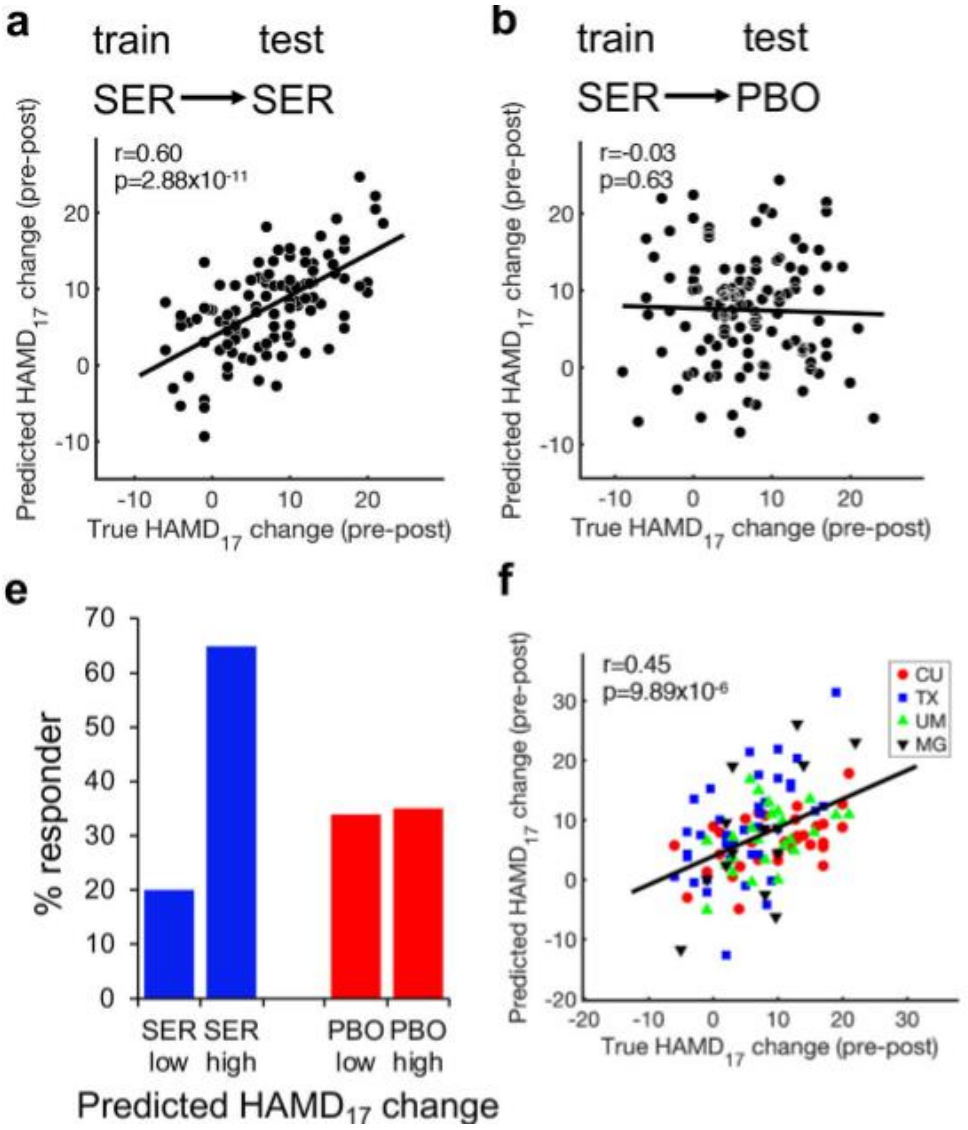
- Connectivity-centric biomarker approach
  - The pathophysiology of many CNS disorders is due to alterations in functional connectivity of neural networks
  - "Neurons that fire together wire together"

*Given the rise in AI/ML capabilities in recent years, perhaps not even considered in EMBARC conception prior to 2011

EEG signature developed using AI/ML predicts antidepressant response in major depression

- Designed a latent-space machine learning algorithm tailored for resting-state electroencephalography (rsEEG) and applied it to data from the largest imaging-coupled, placebo-controlled antidepressant study (n=309; EMBARC).
- Symptom improvement was robustly predicted in a manner both specific for the antidepressant sertraline (versus placebo) and generalizable across different study sites and EEG equipment.
- This sertraline-predictive EEG signature generalized to two depression samples, wherein it reflected general antidepressant medication responsivity, and related differentially to repetitive transcranial magnetic stimulation (rTMS) treatment outcome.
- Figure at right shows that model trained on sertraline predicts sertraline response, but not placebo. Using a median split on predicted HAMD change, the predicted high responder group had a much greater % of responders on sertraline vs. the low responder group, but there was no difference for placebo.

Wu, 2020



Developing an EEG-Based Model for Predicting Response to Antidepressant Medication (also AI/ML, also in open-label)

- This study developed a predictive model using EEG data from 2 independent cohorts of participants with depression: 1) Canadian Biomarker Integration Network in Depression (CAN-BIND) and 2) the EMBARC consortium.
- CAN-BIND participants received an 8-week treatment regimen of escitalopram treatment (10-20 mg).
- The model achieved a balanced accuracy of 64.2% during internal validation with CAN-BIND.
- During external validation with EMBARC, the model achieved a balanced accuracy of 63.7%.

Schwartzmann, 2023

This demonstrates that EEG-AI/ML modelling can predict responses to two SSRIs, one in an open-label study, suggesting that clinical treatment responses may also be amenable to similar modelling.

Methodological Considerations for Collecting EEGs from EMBARC

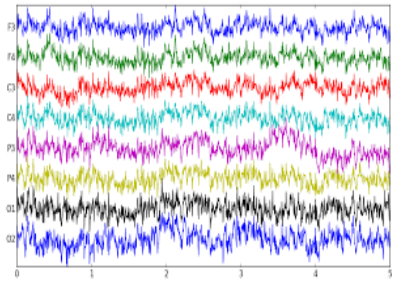
1. Variety of EEG data were collected, allowing maximum utilization of the clinical data, for example
    a. Resting state EEG, eye close, eyes open
    b. ERP, auditory oddball task, emotional conflict task
    c. LDAEP
2. Multi-site EEG collected, allowing cross site validation
3. Sizable single site sample size, allowing modeling building using single site data, and cross site validation
4. High channel count EEG, enabling tools from (simple) power density analysis to (advanced) channel connectivity analysis
5. Multi-omic data repository, including EEG, MRI, fMRI, Genomic data … allowing cross correlation of various modalities
6. EEG and MRI in combination allowing source location
7. Some longitudinal EEG, i.e. week 0 and week 1 (would be nicer to have endpoint EEG data collected)

Requirements: EEG Data Collection and ML Data Processing

Scalp EEG, direct measurement of brain activity (cerebral cortex) with high time resolution.

Standardized, mature, easy to use, and FDA approved brain imaging modality.

Highly accessible brain imaging technology at fractional cost compared to MRI or fMRI.



EEG Signal Preprocessing → **Connectome feature extraction** → **Machine Learning Platform** → **Treatment Outcome Prediction**

Patient Subtyping AI Platform

Treating EEG as an antenna array.

Capturing millisecond time resolution connectome features.

Model Development: Unsupervised Fully Blind Process

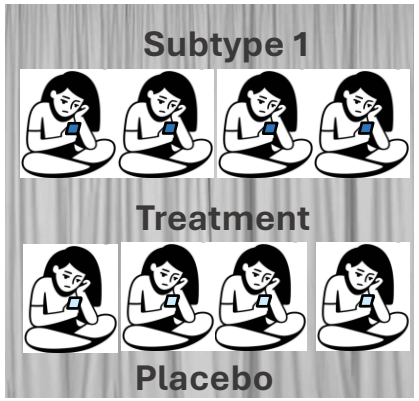
Whole patient group, fully blind

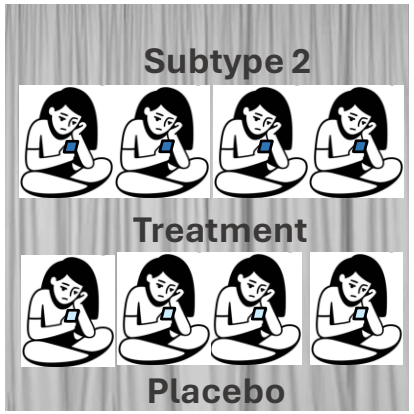
Baseline EEG Data only

Novel Analytic Platform

Clustered into subtypes, still fully blind

Reveal and Evaluate





Treatment and placebo subjects revealed, treatment results mapped, clustering results evaluated

Discovery of MDD/SSRI Biomarkers and Key Findings

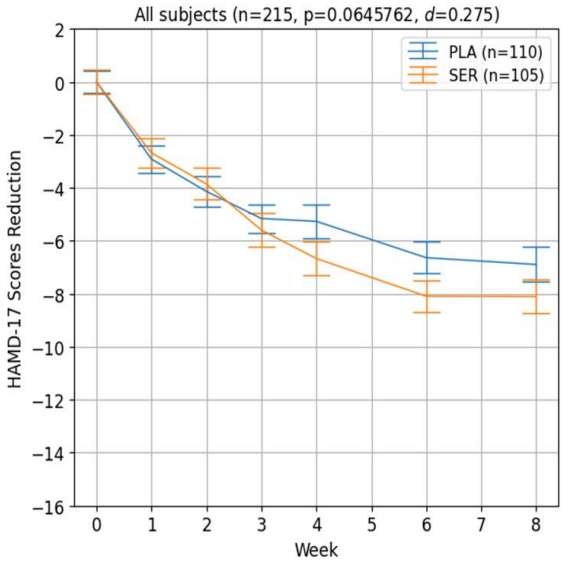
1. **Drug Responder Subtype** with large effect size, Cohen's d=1.24
2. **Non-responder Subtype** with Cohen's d=0.23
3. **"High Placebo Responder" Subtype**, p=0.0003, d=-1.45

   Eliminating Subtype 3 could significantly enhance success rate

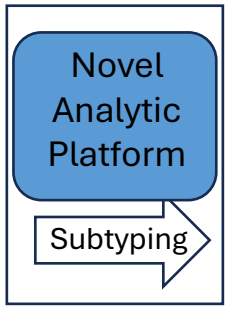
3. **Also Adverse Drug Responder Subtype**

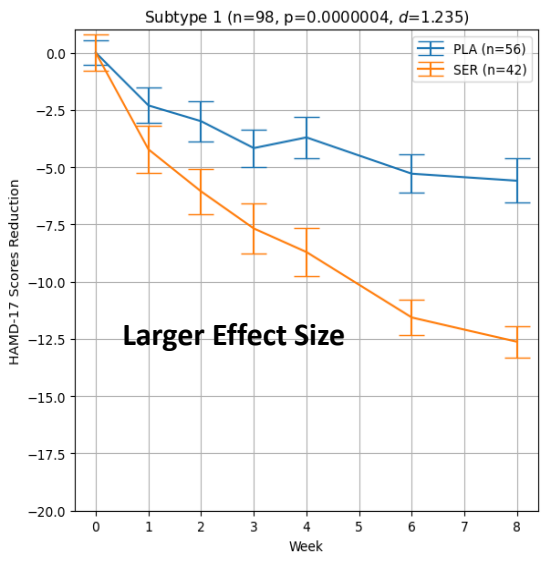
   Drug response even worse than "normal" placebo response

   These patients should not be treated with Sertraline

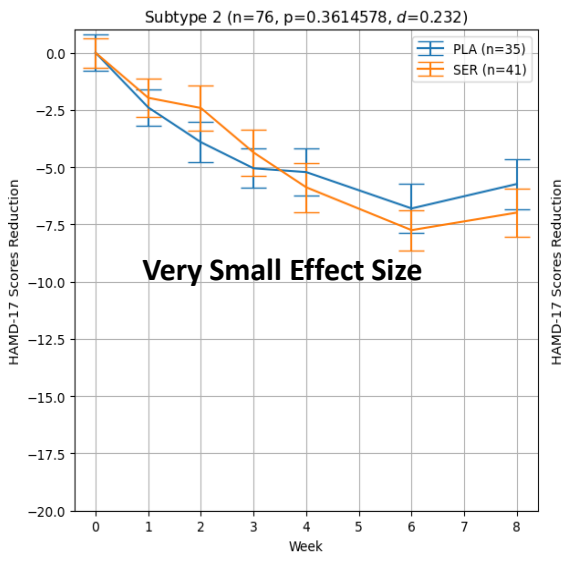


Full Cohort (n=215)

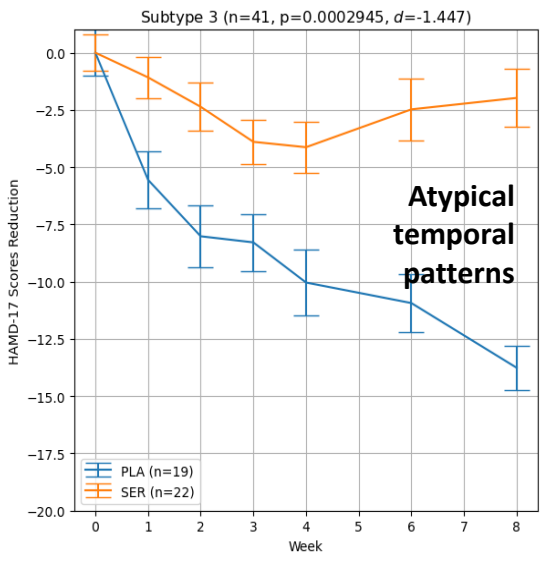




Subtype 1 (n=98) Responder Subtype



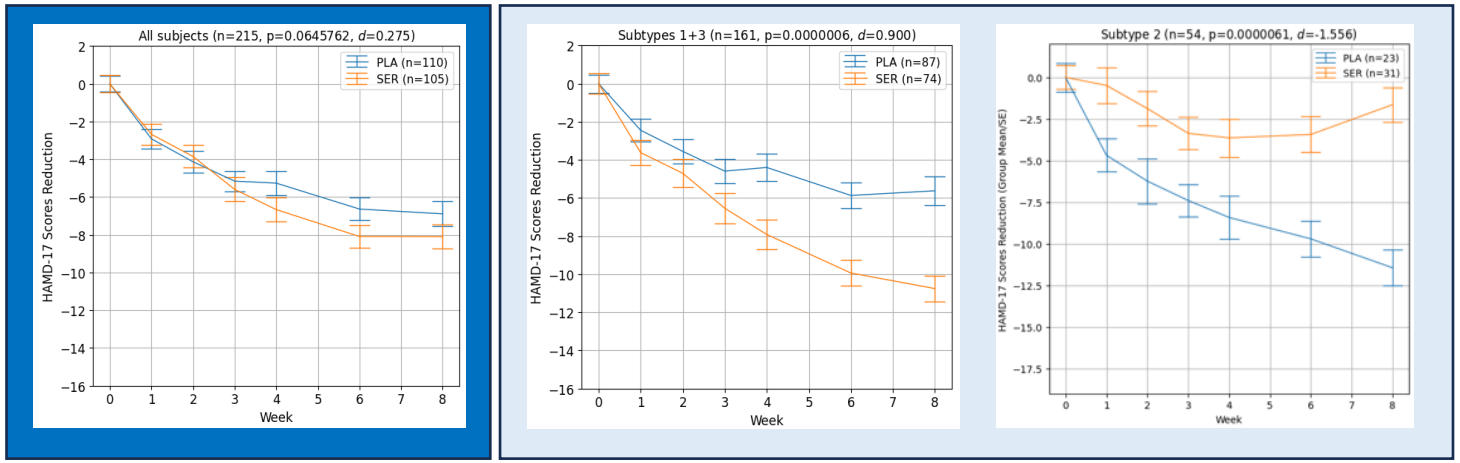
Subtype 2 (n=76) Non-Responder Subtype



Subtype 3 (n=41) High Placebo Responder Subtype

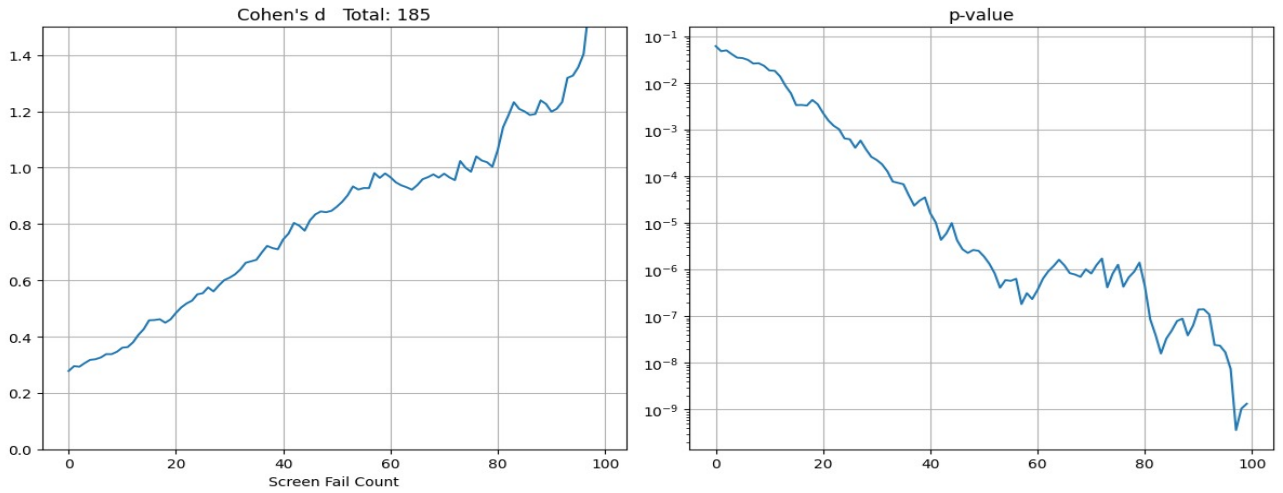
Li, et al., 2024. Poster presentation, ISCTM Autumn Conference

One Approach for RCTS: Exclude High Placebo Response Subtype



- Screen fail High Placebo Responder Subtype (subtype 3, n=41), using baseline EEG data
- Retain subtype 1 and 2, Cohen's d = 0.90, n=161 (75%)

Effect size driven screen fail strategies



Cross Site Validation

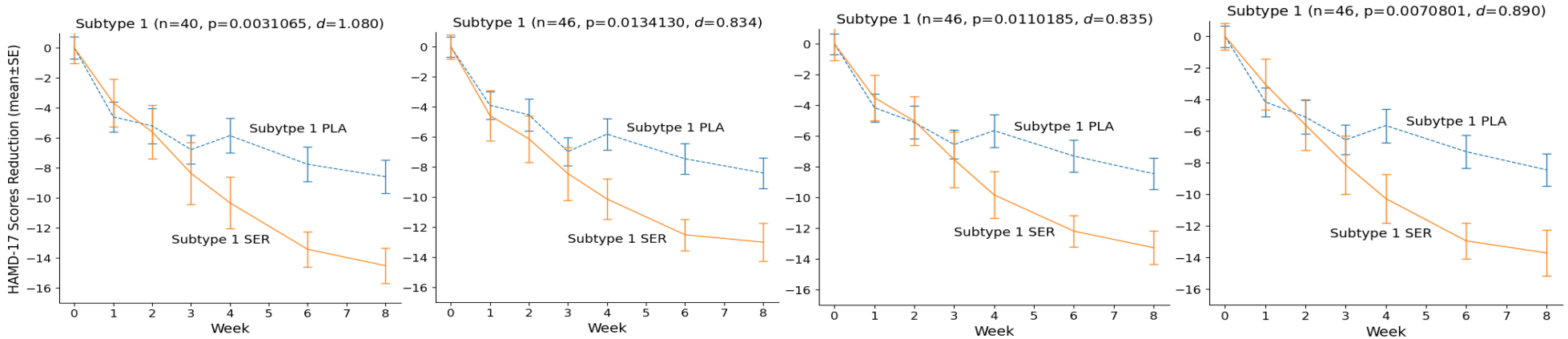
- Leverage the design of EMBARC trial: each site is stratified with sizable samples
- Use data from various sites to train AI model, find biomarker, apply the model prospectively on the same target site.
- Achieved robust predictive power with Cohen's d > 0.8
- Achieved unrivaled membership consistency

Model trained with CU data
Applied to CU data.

Model trained with TX data,
Applied to CU data

Model trained with UM data,
Applied to CU data

Model trained with TX and UM data
Applied to CU data



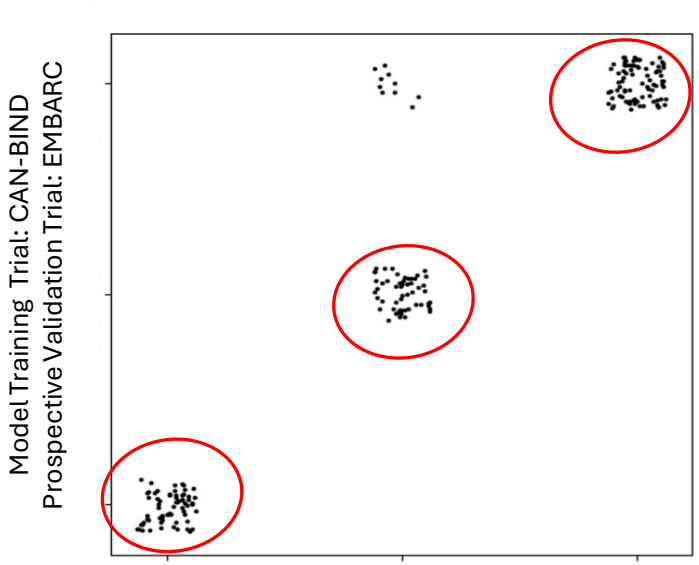
Li, et al., 2024. Poster presentation, ISCTM Autumn Conference

Validation & Generalizability – Cross Trial Membership Consistency

Greater than 90% subtyping consistency between two independent trials

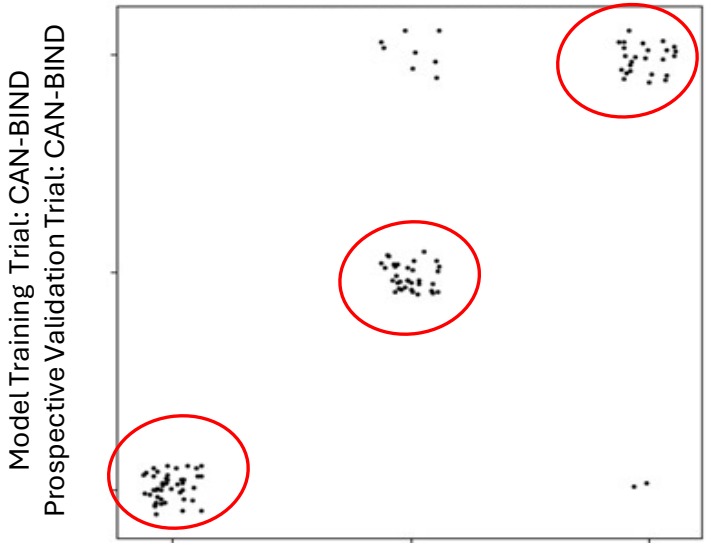
Trial I: EMBARC
Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care

Trial II: CAN-BIND
The Canadian Biomarker Integration Network in Depression



Model Training Trial: EMBARC Eyes-Close
Prospective Validation Trial: EMBARC

Rand Score 0.94, Consistency 95.3%



Model Training Trial: EMBARC
Prospective Validation Trial: CAN-BIND

Rand Score 0.91, Consistency 91.2%

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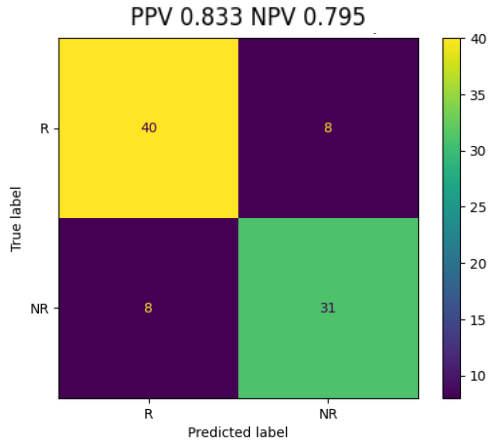
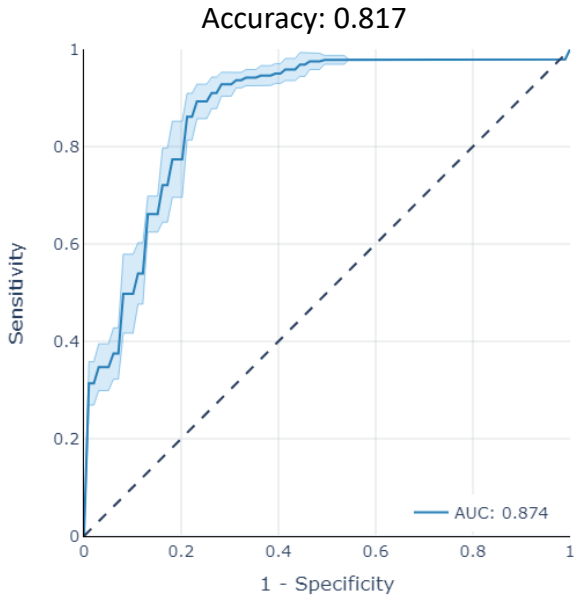
Application of the model to sertraline arm only – potential clinical application

Classification Model Results

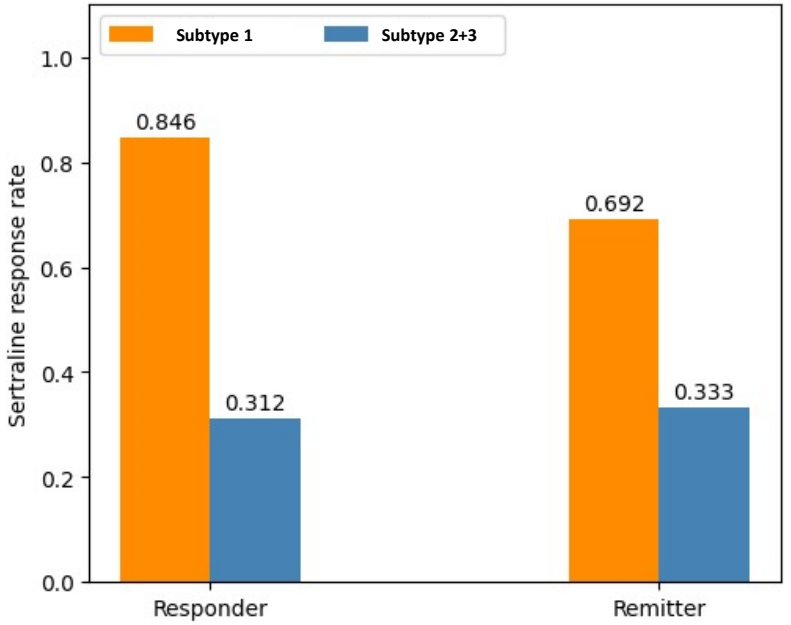




	Response (50% reduction)
Sensitivity	83.3%
Specificity	79.5%

- **Value in clinical practice**
  - Enhance patient response prediction apx. 35% -> 80+%
  - Earlier assessment of efficacy?
  - Shorten patient suffering from ineffective treatment
  - Minimize disability
  - Reduce healthcare costs from ineffective treatment

Cluster Model Results



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Next Steps

- Seek further databases to attempt replication of EMBARC sertraline data
- Seek further EEG (and other) data on other antidepressant trials
- Consider other therapeutic areas and/or diseases likely to have value added by EEG biomarkers
    - Treatment-resistant Depression
    - Epilepsy
- An important question for any of these models is how broadly do they generalize:
    - Would the sertraline model only apply to sertraline? All SSRIs? All antidepressants? Etc.
    - This will only be resolved with more data, careful assessment of replications, etc.