An EEG Biomarker for Predicting Placebo Response in Major Depressive Disorder: Development and Validation Across Open-Label and Double-Blind Trials

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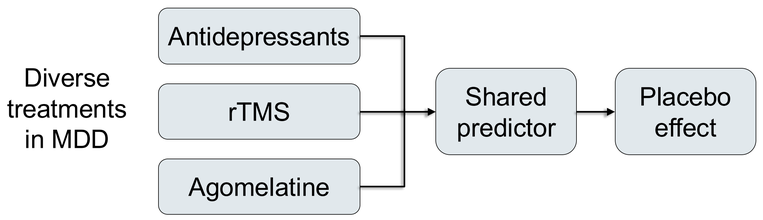
1. Introduction

- Placebo Response in Major Depressive Disorder (MDD) Clinical Trials
  - **High placebo response** is a major challenge in MDD trials, obscuring true drug effects and complicating data interpretation.
  - **No validated biomarker** exists for reliably predicting placebo responsiveness in patients with MDD.
- Developing an EEG-based Biomarker for Predicting Placebo Response
  - Electroencephalography (EEG) is a non-invasive, cost-effective tool that captures brain activity linked to placebo-related processes.
  - This study aims to **develop and validate an EEG biomarker capable of prospectively predicting placebo response.**
  - Such a biomarker could help reduce trial variability and improve detection of true drug effects (see poster S104 for details).

2. Methods

Training Dataset

- Pooled data from open-label MDD trials (**N=589**):
  - FDA-approved antidepressants (N=260)
  - Repetitive transcranial magnetic stimulation (rTMS; N=252)
  - Agomelatine (N=77)
- **Hypothesized that a shared predictor across diverse treatments would approximate a placebo effect.**



Predictive Model Development

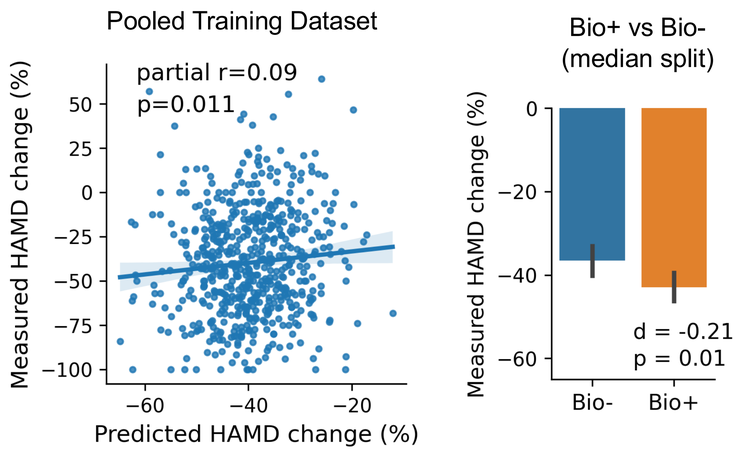
- Utilized baseline resting-state EEG features.
- Normalized EEG features by age and sex and standardized within trials.
- Predicted treatment response defined by percentage changes in Hamilton Depression Rating Scale (HAMD-17) scores at treatment completion.
- Optimized through cross-validation within the pooled training dataset.

Validation of Model Generalizability

- Used two independent datasets (total **N=317**):
  - Open-label trial of the investigational antidepressant **ALTO-100** (N=135)
  - Double-blind randomized controlled trial (**EMBARC**)
    - Sertraline (N=83)
    - Placebo (N=99)
- Evaluated predictive performance using:
  - Partial correlation, adjusted for age, sex, and baseline severity
  - Mixed Models for Repeated Measures (MMRM) with median split based on model predictions

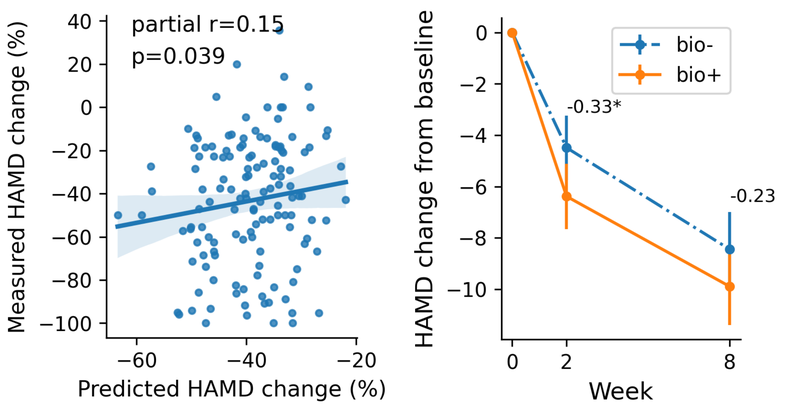
3. Cross-Validation Performance

- Identified a biomarker with significant cross-validation predictions on the pooled training dataset, suggesting a shared predictor across diverse interventions.



4. Test on Open-Label ALTO-100 Trial

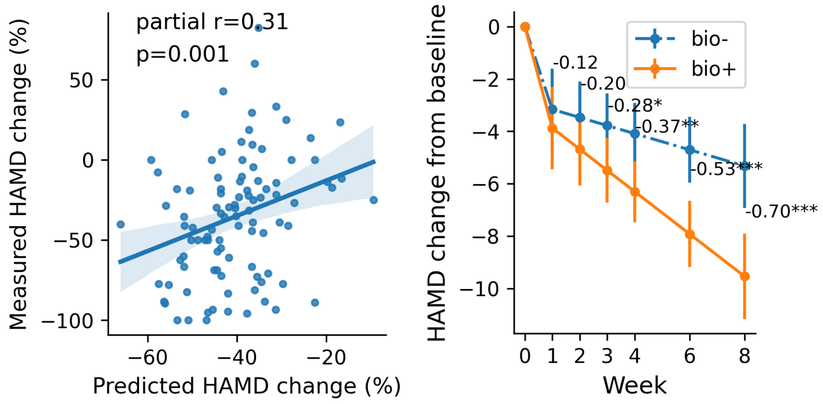
- This identified biomarker demonstrated generalizability in predicting ALTO-100 response.



*$p < 0.05$

5. Test on EMBARC Placebo Data

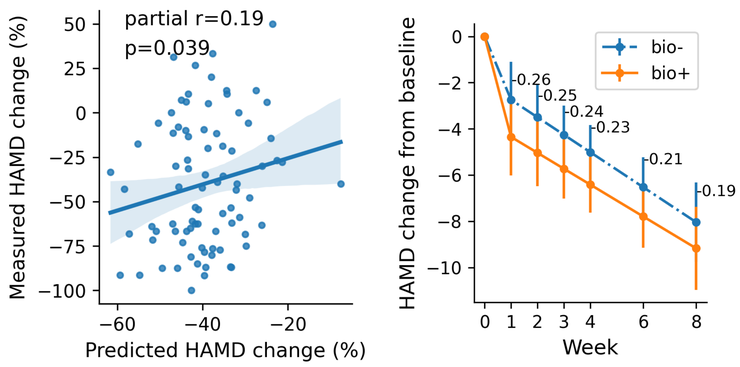
- The biomarker further demonstrated its capability in predicting placebo response.



* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

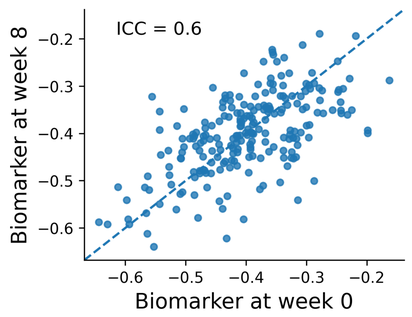
6. Test on EMBARC Sertraline Data

- The biomarker also yielded significant predictions for sertraline treatment response.



7. Biomarker Test-retest Reliability

Biomarker from Healthy Control Data
Recorded 8 Weeks Apart (N = 225)



ICC: Intraclass Correlation Coefficient

8. Demographic/Clinical Associations

- No consistent correlation between the biomarker and demographic/clinical variables.

Dataset	Age (r)	Sex (r)	BMI (r)	Baseline HAMD (r)	On Baseline Medication (r)
Antidepressants	-0.09	0.02	-0.12	0.01	-0.02
rTMS	-0.04	0.04	-0.06	0.02	-0.05
Agomelatine	0.12	-0.21	-0.14	-0.10	N/A
ALTO-100	0.12	0.13	0.00	0.05	0.07
EMBARC placebo	0.03	-0.17	-0.04	-0.08	0.13
EMABRC sertraline	0.03	-0.24	-0.22	-0.02	-0.02

9. Conclusions

- We developed and validated an EEG-based biomarker capable of predicting treatment response across multiple interventions and independent datasets.
- Its ability to predict the placebo response suggests that it reflects general treatment responsiveness.
- This biomarker may be useful for identifying high placebo responders in MDD clinical trials.

10. Acknowledgments

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