Prospective Replication and Application of an EEG-based Placebo Response Prediction Biomarker in Randomized Controlled Trials in Depression

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1. Introduction

- Managing placebo response remains a significant challenge in randomized controlled trials (RCTs).
- This is particularly problematic in trials targeting psychiatric conditions such as major depressive disorder (MDD), which are prone to higher placebo response.
- Accounting for subject level placebo responses may reduce the risk of trial failure and enhance the detection of true treatment effects.
- We developed and validated an electroencephalography (EEG)-based biomarker to predict nonspecific response (placebo); see poster S86 for details.
- Here, we prospectively validated this biomarker in the ALTO-100 Phase 2b placebo arm.
- We then evaluated whether the placebo biomarker could be used to enhance the detection of treatment effects in two independent RCTs in MDD.

2. Method

Several **prospective analyses** were conducted in **independent datasets**:

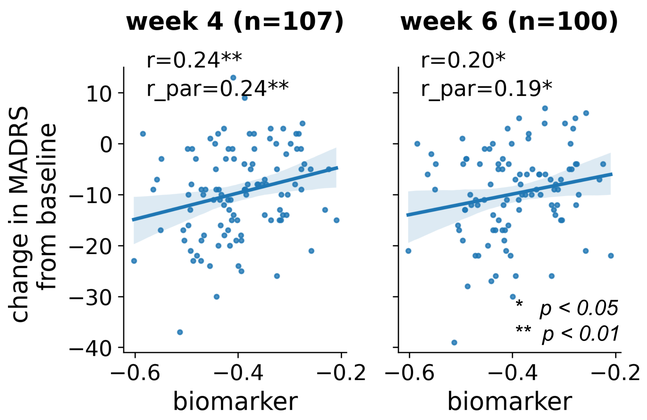
- Prospective replication in ALTO-100 RCT placebo arm
  - Pearson and partial correlations, controlling for age, sex, and baseline severity, were assessed between biomarker predictions and observed clinical change. The one-sided p-value and correlation coefficients are reported given the directional hypothesis.
  - The MMRM effect size is estimated within the placebo treatment group, with participants stratified by the median split of the biomarker value.
- Use of the placebo biomarker to enhance the drug-placebo effect size in RCTs.
  - Examined whether weighting by the predicted placebo response influenced the drug–placebo effect size using the MMRM framework.
- Pre-specified analyses on patients included:
  - ALTO-100 placebo arm all-comers across those that had EEG collected (N =111; 74 poor memory and 37 good memory patients).
  - EMBARC (N = 208): HAM-D >= 14, including sertraline and placebo arms.
  - ALTO-100 (N = 140): poor memory subpopulation, including drug and placebo arms.
  - The primary analysis population in ALTO-100-phase 2b trial was MDD patients with poor cognition.
  - This analysis includes only the subset of patients with available EEG.

Table 1. Demographic details of the patient subgroups included

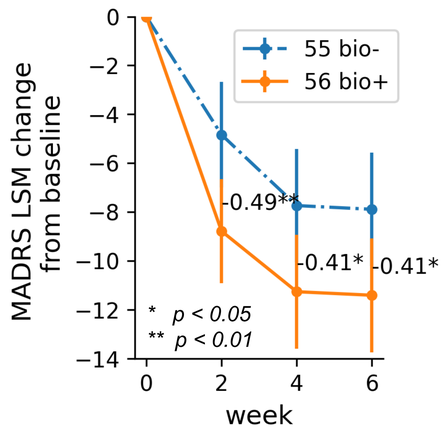
	Arm	Age (mean ± std)	Sex (M/F)	Count (n)
ALTO-100 phase 2b (NCT05712187)	drug	43.7 ± 12.8	30/36	66
	placebo	44.7 ± 12.5	29/45	74
EMBARC (NCT01407094)	drug	37.1 ± 12.6	30/68	98
	placebo	36.9 ± 13.7	40/70	110

3. Prospective validation in the ALTO-100 Phase 2b placebo arm

- In the ALTO-100 placebo arm, the biomarker significantly predicted MADRS change scores, with partial correlations of 0.29 (p=0.001), 0.24 (p=0.006), and 0.19 (p=0.029) at weeks 2, 4, and 6, respectively.

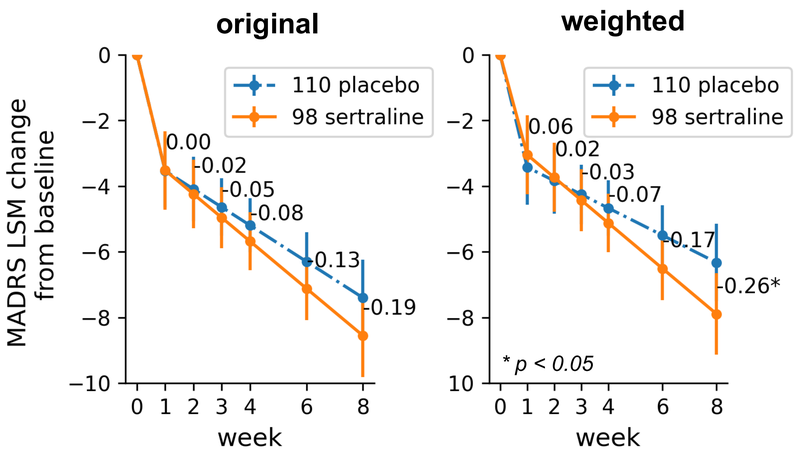


- The estimated effect size from the MMRM analysis within the placebo arm, stratified by a median split was Cohen's d=0.49 at week 2, d=0.41 at Week 4, and d=0.41 at week 6.



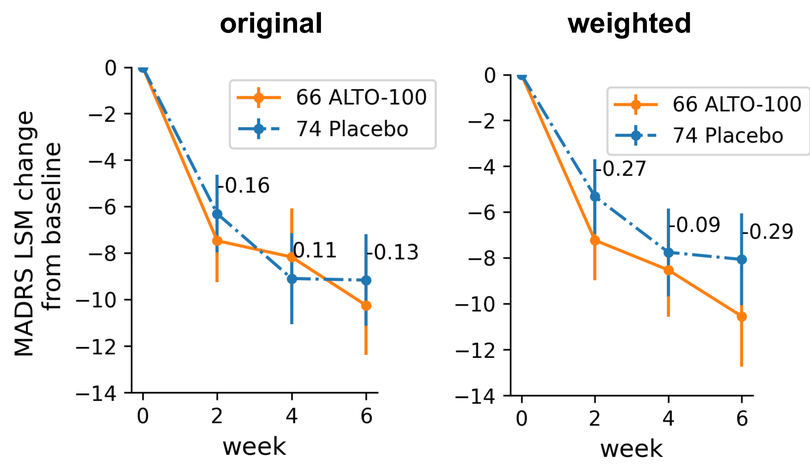
4. Use of the placebo biomarker enhanced the drug-placebo difference in the EMBARC RCT

- Incorporating the biomarker predictions as sample weights increased the effect size from 0.19 to 0.26 at the primary endpoint at week 8. Here, the time is modeled as continuous variable in MMRM to improve statistical power.

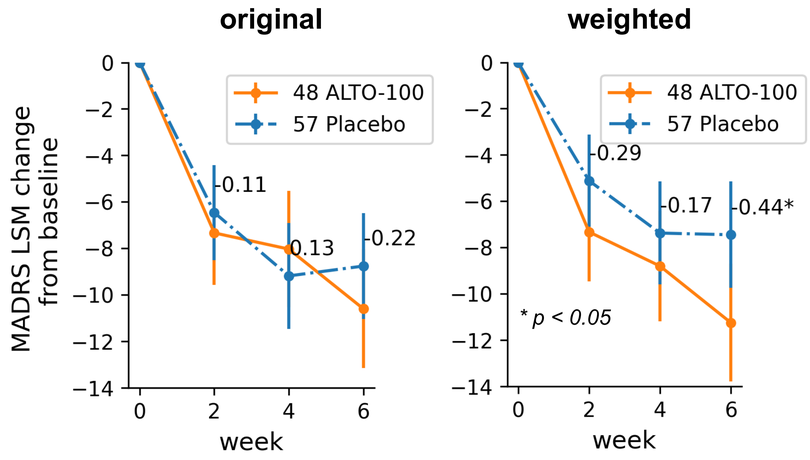


5. Use of the placebo biomarker enhanced the drug- placebo difference in the ALTO-100 Phase 2b RCT

- Incorporating the placebo biomarker predictions as sample weights in an MMRM increased the ALTO-100 vs. placebo effect size from 0.13 to 0.29 at the primary endpoint (week 6) within the primary outcome poor memory population.
- These analyses included patients that were identified as non-compliant based on blood sample analyses.



- Removing three sites with high levels of non-compliance increased the effect size to 0.22 without correction. Applying sample weights within this subpopulation further boosted the effect size to 0.44.



7. Conclusions

- We prospectively replicated an EEG-based biomarker that predicts nonspecific response (i.e., placebo).
- We then demonstrated that treatment effect sizes in two RCTs are enhanced when accounting for individual differences in predicted placebo response.
- This demonstrates the utility of such biomarkers to improve detection of true drug effects in RCTs.

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