EDITORIAL

Electroencephalographic Biomarkers for Predicting Antidepressant Response

New Methods, Old Questions

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Medication selection in depression still relies primarily on trial and error, frustrating both patients and clinicians. Diagnostic tests that predict treatment response in advance could facilitate an informed approach and reduce suffering. Ideally, those tests would directly measure brain function. The primary research test of brain function, functional magnetic resonance imaging (fMRI), is too expensive to scale to routine care. Electroencephalography (EEG), however, is comparatively inexpensive and fast and could be made available in many settings. Plus, as a direct measure of localized brain activity, EEG is ideal for dissecting the connections between neurotransmission, symptoms, and pharmacologic response.

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Unfortunately, prior EEG studies violated cardinal principles of biomarker discovery: (1) adequate high-quality training data, (2) appropriate feature selection, and (3) cross-validation. Cross-validation refers to the evaluation of a prediction model on data that were not used to create the model. It is an essential step in any modern biomarker study and ties closely to data adequacy.[1] Biomarker studies often use small, single-site samples, introducing bias and inflating effect sizes. A recent meta-analysis found that no published EEG biomarker met standards for clinical reliability in predicting antidepressant response, largely owing to poor methods.[2]

In this issue of *JAMA Psychiatry*, Rolle et al[3] attempt to overcome those limitations, reporting pretreatment EEG connectivity markers modulating response to sertraline hydrochloride or placebo. They leverage a large, quality-controlled data set from the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study. The EMBARC trial spanned 221 participants across 4 sites, with EEG recorded using different techniques at each site, increasing generalizability. The data are freely available online, increasing reproducibility. With this larger sample, Rolle et al[3] were able to explore a broader space of potential biomarkers using a data-driven rather than hypothesis-driven analysis. They applied linear mixed-effect modeling, a powerful regression approach for high-dimensional data.

In multisite, multi-instrument studies, aligning the data set so the same marker is similarly measured across sites is difficult. Rolle et al[3] approached that alignment by bringing the scalp EEG data to "source space"—inferring the current in the underlying cerebral cortex from the observed scalp voltages. The challenge is that, with a limited number of scalp electrodes, an infinite number of brain patterns could produce the observed EEG, depending on one's assumptions about the conductivity of bone, skin, and cerebrospinal fluid. Precise localizations require a high-resolution head MRI for each patient and registration of EEG electrode positions to that MRI—technical requirements that cannot scale to clinical practice. Rolle et al[3] thus performed all analyses on a template brain, leveraging sample size to compensate for potential source-localization errors. Rolle et al[3] further attempted to align their EEG predictors with the fMRI literature, which emphasizes resting-state functional connectivity (ie, depression as a network illness).[4] Connectivity analysis in EEG is hindered by volume conduction–electrical signal correlations that are not caused by information traveling along axons, but by direct electrical conduction through the cerebrospinal fluid. Rolle et al[3] adapted a technique called power envelope connectivity, which removes most volume conduction from EEG connectivity estimates.[5] They then computed EEG connectivity between regions of interest defined by a prior fMRI study.

From this data-driven, fMRI-informed analysis, Rolle et al[3] identified multiple connections that correlated with the 8-week slope of symptom improvement (treatment moderators). These connections were most common in the alpha band and the eyes-closed resting condition. Surprisingly, these moderators did not involve frontal regions commonly implicated in depression, but predominately connected the temporal, occipital, and parietal lobes. Alpha has been associated with default mode network activity,[6] which one might expect to increase during eyes-closed rest, but the implicated regions are not part of the traditional default mode network. This finding may be explained by the other surprising finding of this study: most of the significant moderating effects predicted placebo response, not active sertraline response. In that light, the connectivity moderators might represent mechanisms of placebo response, that is, a sensitivity to self-perception. The authors also suggest a possible connection to reward processing and anhedonia. Interestingly, region-to-region connectivity features were better correlates of treatment outcomes than were advanced graph-theoretic metrics that summarized each region's overall connectedness. This finding is surprising, given that multiple depression therapies are believed to work by altering the connectivity of hubs within affective networks.[7] Similarly, none of the identified features changed during treatment, a puzzling disconnect between moderation and mechanism.

Interpretation of the results found by Rolle et al[3] is limited by some of their analytic choices. First, they modeled each

EEG feature separately, rather than attempting to fit multiple modulators, that is, a penalized multivariate regression. As such, some of the selected features may be redundant or correlated with each other. Second, although they reference predictors of treatment response, the primary term analyzed is the EEG × treatment × time interaction—a slope, not a response end point. That is, the identified EEG features inform on the speed of a patient's improvement during 8 weeks of acute treatment, but not on the ultimate level of improvement. Similarly, the primary analysis did not dichotomize patients into responders and nonresponders and compute prediction values, which would have better aligned the study with past literature.[2] A secondary analysis, provided in the supplement, did perform classical response prediction, with effect sizes that were mostly near the canonical small effect size of 0.2. That is, even for the predictors that replicate, their ability to explain response variance may be quite modest. Third, and most important, depression is a heterogeneous signal. Electroencephalographic-based prediction models, such as the model by Rolle et al,[3] attempt to fit a function between resting-state brain activity and a similarly heterogeneous treatment response. This simplification facilitates reporting, but may obscure critical neuronal and psychopathologic subtypes.

An essential step in all data-driven modeling is cross-validation, or out-of-sample testing. In cross-validation, a subset of the data is used to train or fit a predictive model, and the model is then evaluated on held-out data it has never seen. This prevents overfitting, a tendency for predictive models to be very good on their training data set at the expense of generalizability. Cross-validation has, unfortunately, been mostly absent from the EEG biomarker literature.[2] Rolle et al[3] report cross-validation of their moderating connectivity features in the supplement. The analysis suggests that many of the observed features may not be fully stable. When the data set was split into 5 separate subsets, most predictors were significant in 3 or fewer of those subsets. Given this instability, validation in a fully independent data set (eg, another large depression study such as iSPOT-D [International Study to Predict Optimized Treatment for Depression][8]) is a critical next step. iSPOT-D includes both sertraline and other serotonin-targeted medications as interventions, which may identify whether the sertraline-predictive findings of Rolle et al[3] are consistent across medications and populations.

Even with those limitations, the study by Rolle et al[3] is a large step forward for EEG biomarker research. It is one of the first reports in this field to apply modern statistical practice, and through doing so demonstrates how much we still have to learn. It introduces a broader community to the potential of the EMBARC data set, which is now readily available for further data mining. Finally, the power envelope connectivity method may have value in a range of studies, from biomarkers to basic science. New tools such as these hold much promise for someday improving the precision of clinical practice.

ARTICLE INFORMATION

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