Reliability of Electrophysiological Predictors of Treatment Response in the EMBARC Study

Diego A. Pizzagalli[1], Craig E. Tenke[2,3], Jürgen Kayser[2,3], Pia Pechtel[1], Daniel Dillon[1], Crystal Cooper[4,#], Patricia Deldin[5,#], Maurizio Fava[6,#], Benji T. Kurian[4,#], Patrick McGrath[3,#], Ramin Parsey[7,#], Eva Petkova[8,#], Madhukar Trivedi[4,#], Myrna Weissman[2,#], Sarah Weyandt[4,#], Gerard Bruder[2,3]

[1] McLean Hospital/Harvard Medical School, [2] Columbia University, [3] New York State Psychiatric Institute, [4] UT Southwestern Medical Center, [5] University of Michigan, [6] Massachusetts General Hospital, [7]Stony Brook University, [8]New York University

Poster: T155

ABSTRACT

BACKGROUND. Three electrophysiological measurements have been prospectively associated with antidepressant treatment responses: the amplitude of loudness dependent auditory evoked potentials (LDAEP), EEG power in the alpha band, and theta current density localized to the rostral anterior cingulate cortex (rACC). However, the reliability of these measures has not been established. The current analyses evaluated the test-retest reliability of these EEG measures in healthy adults enrolled in the multi-site Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) project.

METHODS. Resting EEG (four min each eyes open and closed) and auditory event-related potentials (1000 Hz tones, five intensities from 60 to 100 dB) were collected from 40 healthy adults with a test-retest interval of about one week; 10 participants were assessed at each of the four EMBARC sites. EEG alpha and LDAEP measures of N1 dipole were quantified using principal components analysis of current source density (CSD) estimates. Low-resolution electromagnetic tomography (LORETA) was used for EEG source localization, and resting theta current density was extracted from a predefined rACC region-of-interest.

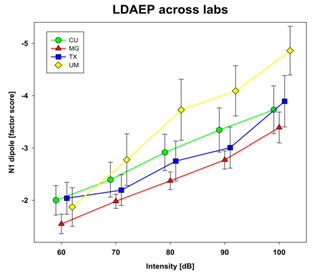
RESULTS. For the LDAEP, N1 dipole amplitudes increased monotonically along with tone intensity ($p < 0.001$), with no differences across sessions or centers. The overall reliability of N1 was high ($r = 0.87$; range: 0.70 to 0.98 across centers). For EEG alpha, there was a significant difference in posterior CSD alpha across centers ($p < 0.001$), with one center (MGH) showing lower alpha than the other three centers, and a center by session interaction ($p < 0.05$), with one center (Columbia) showing greater alpha in the second session. There was, however, no overall session effect and test-retest reliability was high ($r = 0.89$; range: 0.72 to 0.99 across centers. LORETA measures of theta activity localized to rACC required spatial smoothing to minimize differences across sites. Nevertheless, there was a significant center effect ($p < 0.001$), with one center (MGH) having higher current density than the others. There was, however, no significant difference between the two sessions with respect to rACC current density for each level of spatial smoothing, and test-retest reliability ranged from $r = 0.70$ to $r = 0.91$ for different levels of spatial smoothing.

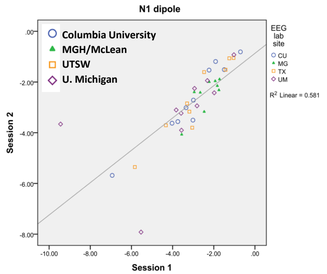
DISCUSSION. These findings demonstrate that CSD measures of N1 dipole loudness modulation, EEG alpha, and source-localized rACC theta activity can be obtained with good to excellent reliability in a multi-site study. These findings lay the foundation for investigating the predictive validity of these EEG markers with respect to treatment outcome in major depression.

SUPPORTED BY: NIMH grant 1U01MH010040

LOUDNESS DEPENDENCY AUDITORY EVOKED POTENTIAL

METHOD: For LDAEP, the main measure is the current source density (CSD) corresponding to N1 dipole amplitude at the five tone intensities (60-100 dB). We analyzed data for 38 controls with acceptable data in both sessions at the four sites [Columbia (CU), MGH/McLean (MG), UTSW (TX), and U. Michigan (MU)].



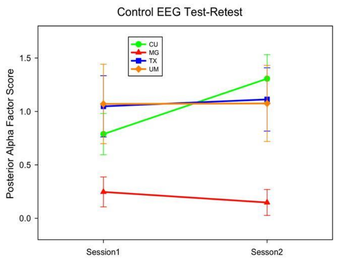


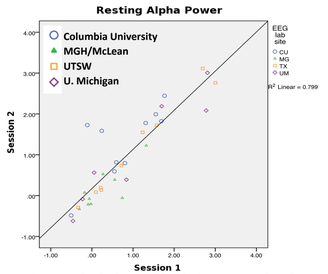
SITE CONSISTENCY: All sites showed the expected monotonic increase in N1 amplitude with increasing tone intensity. An ANOVA including *Site*, *Session*, and *Intensity* (five tone intensities) yielded the expected highly significant effect of *Intensity* ($p < .001$), but no significant difference in N1 amplitude across sessions or sites.

TEST-RETEST: The test-retest reliability for the N1 amplitude (averaged over intensity) was high across sites (Pearson $r = 0.87$; Spearman $r = 0.95$) and ranged from 0.70 to 0.98 for the individual sites.

RESTING ALPHA POWER

METHOD: Resting alpha power was measured at posterior electrode sites. We analyzed data for 35 controls with acceptable resting EEG data in both sessions.



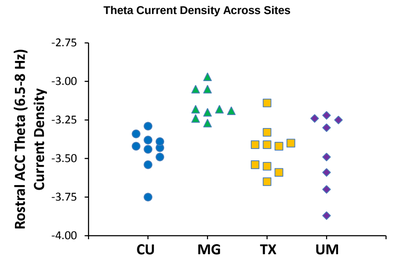


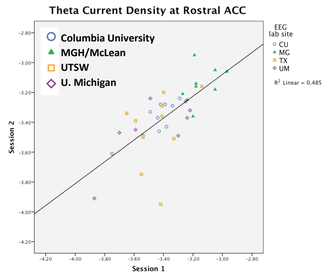
SITE CONSISTENCY: Three-way ANOVA entering *Site, Session, Condition* (eyes open, eyes closed) yielded the expected effect of *Condition* with alpha being greater with eyes closed. There was a significant effect of *Site* due to generally lower resting alpha power at the MG/MH site (red triangles), yet these remained well within the range from other three sites.

TEST-RETEST: Reliability of alpha was high across all sites ($r = 0.89$) with reliability within each site ranging from $r = 0.72$ to 0.99 for the individual sites. There was a significant *Session* by *Site* interaction reflecting a between-session difference in alpha at the Columbia site (blue circles), mainly driven by two outliers.

THETA CURRENT DENSITY at the ROSTRAL ACC

METHOD: Current density in rACC for the theta band (6.5-8 Hz) was calculated for 37 controls with acceptable data in both sessions at the four sites using three levels of smoothing: no/minimal spatial smoothing (TM00), intermediate smoothing (TM05), and highest smoothing (TM04).





SITE CONSISTENCY: TM04 smoothing produced the greatest consistency among sites. Despite the high degree of smoothing, a *Site* by *Session* mixed ANOVA still revealed a main effect of *Site* ($F(1,33) = 8.27$, $p < 0.001$).

TEST-RETEST: Across all subjects with Baseline and Week 1 data ($n = 37$), paired t-tests revealed no significant test-retest differences in rACC current density. In addition, Pearson correlations revealed highly significant test-retest correlations for all levels of smoothing ($r = 0.70$, $P < 10^{-6}$).

CONCLUSIONS

These findings demonstrate that CSD measures of N1 dipole loudness modulation, EEG alpha, and source-localized rACC theta activity can be obtained with good to excellent reliability in a multi-site study. Site should be entered as covariate in future analyses or intensity-normalizations should be implemented to norm data across the four sites. These findings lay the foundation for investigating the predictive validity of these EEG markers with respect to treatment outcome in major depression.

ESTABLISHING MODERATORS AND BIOSIGNATURES OF ANTIDEPRESSANT RESPONSE FOR CLINICAL CARE (EMBARC) PROJECT

Depression is a clinically and biologically heterogeneous disorder. Although many treatments are available, two-thirds of patients do not achieve remission with their first step treatment. To improve diagnostic and prescriptive efficiency, the EMBARC study is evaluating carefully selected clinical, behavioral and neurobiological markers to find a parsimonious composite predictor of treatment effectiveness. This multi-site study is employing a randomized, placebo-controlled, two-stage trial of three treatments for 400 participants with major depressive disorder. EMBARC is being conducted under joint leadership from Columbia University and University of Texas Southwestern Medical Center together with Massachusetts General Hospital, University of Michigan, University of Pittsburgh and McLean Hospital.