Loudness Dependency of Auditory Evoked Potentials (LDAEP) as a Differential Predictor of Antidepressant Treatment Response in Major Depressive Disorder (MDD): Results from the Sertraline/Placebo-Controlled EMBARC Study

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Poster available in high resolution at *http://psychophysiology.cpmc.columbia.edu/mmedia/SoBP2018/LDAEP-EMBARC.pdf*

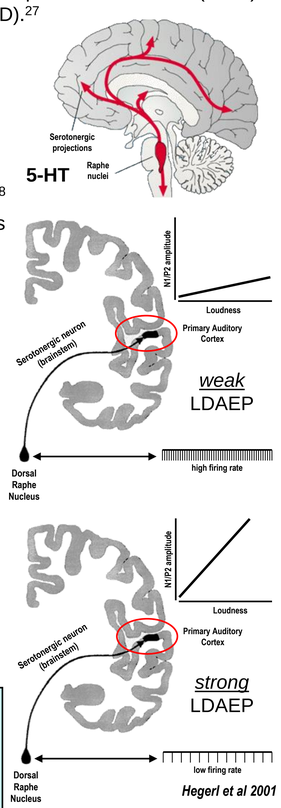
EMBARC — Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care

Abstract

Background: Loudness-dependent auditory evoked potentials (LDAEP), a monotonic increase of N1/P2 amplitude with increasing tone intensity, has promise as a predictor of clinical treatment response with serotonin agonists in MDD. LDAEP was therefore included in a comprehensive array of putative clinical and biological moderators of treatment effect (rate of change in depressive symptoms across randomized SSRI or placebo treatment [Tx]) in the multisite project *Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care* (EMBARC). **Methods:** MDD patients (baseline $HAMD_{17}$ ≥ 15, 78 sertraline, 86 placebo) who completed Stage 1 (8-wk) provided baseline 72-channel ERPs to 1000-Hz tones at five intensities (60-100 dB). N1 activity attributable to primary auditory cortex (tangential dipole) was quantified using scalp current source density and temporal PCA. Multilevel analysis examined the association of N1 dipole amplitude, Tx, intensity, and rate of symptom change (slope of HAMD scores). **Results:** A significant Tx*intensity*symptom change interaction (p = .006) originated from an increasingly stronger association between larger N1 and better clinical response with increasing tone intensity for sertraline only, whereas this association was lower for placebo and did not vary with intensity. At the same time, a significant intensity*symptom change interaction (p = .003) confirmed that a steeper LDAEP N1 slope was linked to symptom improvement, independent of Tx. These effects remained after adding gender, age, and baseline HAMD as covariates to the regression model. **Conclusions:** Results confirm and extend prior findings, suggesting that LDAEP as a neurobiological marker may function both as a predictor of MDD treatment response and as a moderator of treatment effect.

Introduction

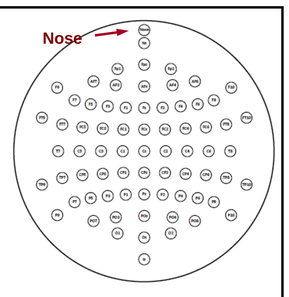
- The NIMH-funded, multi-site study ***Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC)*** seeks to identify baseline clinical, neuroimaging, electrophysiological, and behavioral predictors of differential treatment response for sertraline (SSRI) vs. placebo in major depressive disorder (MDD).[27]
- **Serotonergic (5-HT) neurons in dorsal raphe** modulate activity in **primary auditory cortex** by providing a stable, **tonic preactivation level**.
- In cats, **loudness dependence of auditory evoked potentials (LDAEP)** is inversely related to 5-HT activity in dorsal raphe nuclei.[8]
- A *high tonic firing rate* of serotonergic neurons in the raphe nuclei is related to a *weak* LDAEP, indicated by a shallow increase in N1/P2 evoked potential amplitude for louder stimuli.[5,6]
- In contrast, *low tonic firing* in the raphe is related to a *strong* LDAEP, indicated by a steep increase in N1/P2 evoked potential amplitude or louder stimuli.
- MDD patients with strong LDAEP responded better to an SSRI than those with weak LDAEP.[3,6,14,17,20-21; reviewed by 28]
- Several LDAEP studies reported *differential* prediction of clinical response to serotonergic and noradrenergic antidepressants.[9,15-16,18]
- Jaworska et al[7] found more responders than nonresponders had steep LDAEP slopes at baseline independent of treatment with an SSRI (escitalopram) or NDRI (bupropion).



Objective: Examine whether LDAEP is a differential predictor of clinical response to SSRI as opposed to Placebo in the EMBARC study

ERP Recording and Quantification

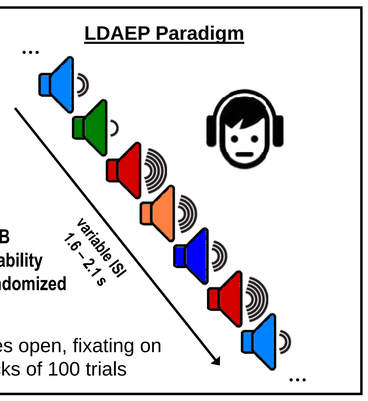
- EEG collected at 4 test centers with diverse hard- and software
- Data unified to common EEG montage and sample rate via **standardized analysis pipeline**see 26 for details
- ERPs for **72 scalp sites** referenced to nose
- 0.5-50 Hz band pass (-24dB/octave), 256 samples/s
- **Blink reduction** (continuous EEG) **via spatial SVD**
- Interpolated bipolar horizontal and vertical EOGs
- Horizontal eye artifacts (epoched EEG) by linear regressions of lateral differences (Fp2-Fp1, etc.)



- **1,000 ms epochs** (100 ms pre-stimulus baseline), 12.5 Hz low pass (-12dB/octave)
- Transform ERPs to **reference-free current source densities (CSD)** (spherical splines surface Laplacian[22]): sharpen topographies, eliminate volume-conducted activity[11-13,25]
- Temporally adjust CSDs by each participant's peak latency of N1 sink (~ 110 ms)[26]
- **CSDs** (Fig. 1) submitted to ***unrestricted* temporal principal components analysis (PCA)**, followed by Varimax rotation of covariance loadings[10-12]
- CSD-PCA (Figs. 2 and 3): identify and measure neuronal generator patterns underlying **activation of primary auditory cortex** (tangential N1 sink)

- Bihemispheric N1 sink min- and maxima determined from individual N1 sink topographies
- Most negative location within 12 frontocentral and centroparietal locations (F1, F3, F5, FC1, FC3, FC5, C1, C3, C5, CP1, CP3, CP5 for left hemisphere)
- Most positive location within an array of 7 lateral frontotemporal and temporoparietal locations (FT7, FT9, T7, TP7, TP9, P7, P9 for left hemisphere)
- Compute difference for an estimate of N1 sink dipole strength for each hemisphere
- N1 sink dipoles pooled across hemispheres for a single **N1 dipole amplitude** measure

Stimuli and Procedure



Participants sat quietly with their eyes open, fixating on a central cross during each of 5 blocks of 100 trials

Participants

Means, Standard Deviations (SD), and Ranges for Demographic and Clinical Variables

	Placebo (n = 86; 53 female, 62%)			SSRI (n = 78; 54 female, 69%)			
Variable	Mean	SD	Range	Mean	SD	Range	p
Age (years)	35.6	12.2	18 - 63	37.2	13.8	18 - 65	n.s.
Education (years)	15.4	2.5	9 - 22	14.9[b]	2.7	7 - 21	n.s.
EHI score [a]	73.2	45.7	-100 - 100	77.0	40.2	-100 - 100	n.s.
HAM-D [c]	19.4	3.3	15 - 27	14.9	3.4	15 - 28	n.s.

Note. [a] Laterality quotient[19] can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed). [b] n = 76. [c] *Hamilton Depression Rating Scale* ($HAMD_{17}$)[4].

- Enrolled at 1 of 4 test centers (**UT**: University of Texas South Western; **CU**: Columbia University; **MG**: Massachusetts General Hospital; **UM**: University of Michigan)
- Randomized to ***SSRI*** *(Sertraline)* or ***Placebo*** treatment
- $HAMD_{17}$ ≥ 15 at baseline
- LDAEP data collected at baseline (wk 0)
- Completed Stage 1 (8-wk treatment)

CSD Waveforms

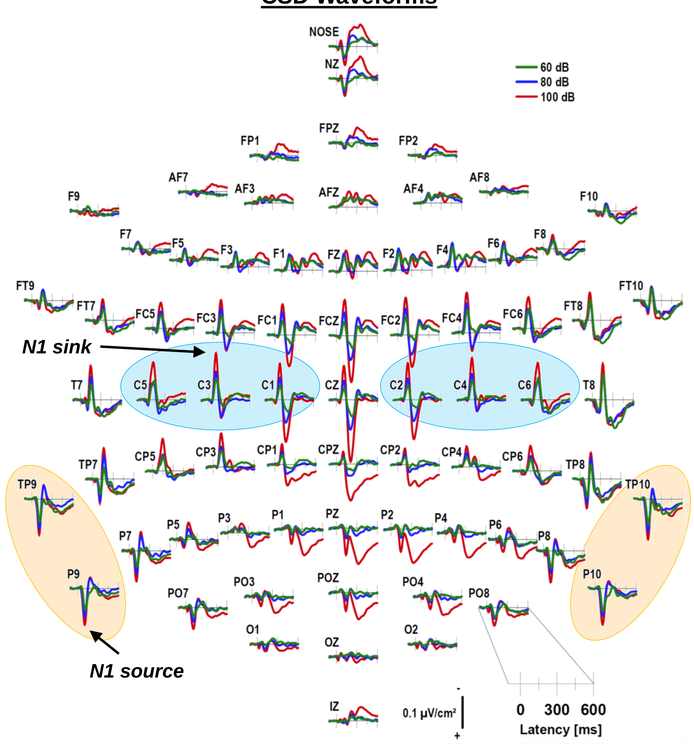


Fig. 1. Grand mean (N = 164) current source density (CSD) [µV/cm²] waveforms (-100 to 600 ms) for low (**60 dB**), medium (**80 dB**), and high (**100 dB**) loudness intensity at all 72 scalp recording locations. CSDs had been individually adjusted for N1 sink peak latency.[26]

CSD-PCA Factor Loadings

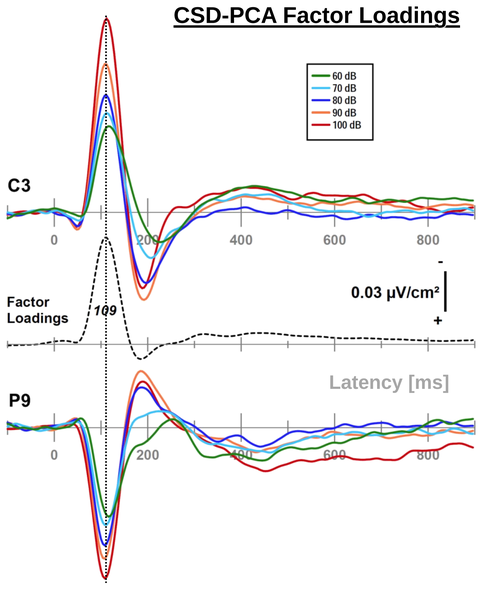


Fig. 2. Enlargements of CSD waveforms (see Fig. 1) at selected left central (C3) and left inferior-parietal (P9) sites comparing all five loudness intensities. The loadings of factor 109 corresponding to N1 sink are shown for comparison on the same scale.

CSD-PCA Factor Score Topographies

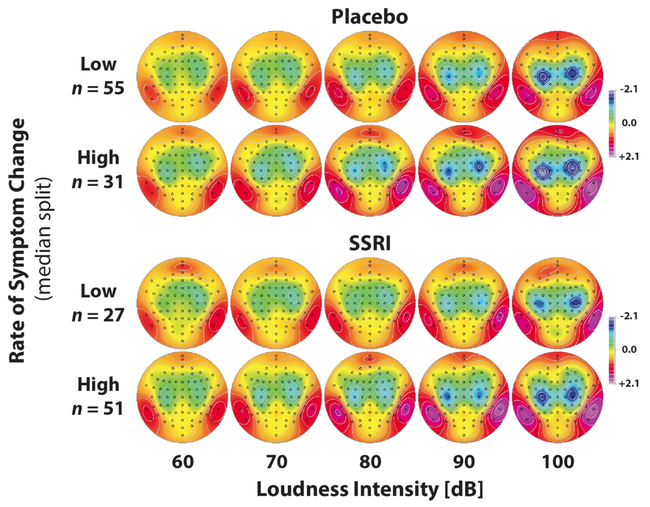


Fig. 3. N1 sink (factor ***109***) topographies, plotted separately for treatment (placebo, SSRI) x response (rate of symptom change; subgroups via median split, Fisher's Exact Test, p < 001), revealed bihemispheric sink-source dipoles across the Sylvian fissure consistent with primary auditory cortex activations. N1 sink dipoles showed monotonic increase with loudness intensity.

Multilevel Regression Analysis

- **LDAEP** considered a within-subjects measure (*N1 dipole* amplitude at 5 intensities [dB])
- **Clinical treatment outcome** defined as *Rate of Symptom Change* [slope of $HAMD_{17}$ scores during treatment (wks 0-4, 6, 8) estimated via a mixed effects model[23]]
- **2-level multilevel model** to account for N1 dipole measurements nested within participants by estimating a **random intercept** and **random slope for each participant** (unstructured covariance matrix, between-within method for *df*s)
- All variables either grand-mean centered (N1, dB, $S_x$change, age) or effect-coded (±1)
- ***Pseudo* R^2** (at each level) and ***semi-partial* R_β^2** (single effects)[2] used as effect sizes

- ***N1 dipole*** was modeled as a function of ***Treatment*** [Tx], ***Intensity*** [dB], ***Rate of Symptom Change*** [$S_x$change] (Figs. 4 and 5) with R as follows:

lme(N1 ~ Tx*dB*$S_x$change, random=~1|participant)

$R^2_{Level\ 1}$ = 0.134, $R^2_{Level\ 2}$ = 0.019
dB*$S_x$change, b = 0.011, SE = 0.004, $t_{(652)}$ = 3.00, p = 0.003, R_β^2 = 0.014
Tx*dB*$S_x$change, b = 0.010, SE = 0.004, $t_{(652)}$ = 2.73, p = 0.006, R_β^2 = 0.011

- Adding *sex*, *age*, and *baseline HAMD* as covariates did not change these effects:

lme(N1 ~ sex+age+$HAMD_{bl}$ + Tx*dB*$S_x$change, random=~1|participant)

- Effects were still preserved when adding *sex*, *age*, and *baseline HAMD* to the full model:

lme(N1 ~ sex*age*$HAMD_{bl}$*Tx*dB*$S_x$change, random=~1|participant)

$R^2_{Level\ 1}$ = 0.138, $R^2_{Level\ 2}$ = 0.012
dB*$S_x$change, b = 0.012, SE = 0.005, $t_{(624)}$ = 2.35, p = 0.019, R_β^2 = 0.009
Tx*dB*$S_x$change, b = 0.012, SE = 0.005, $t_{(624)}$ = 2.34, p = 0.020, R_β^2 = 0.009

Effect size conventions[1]: small R^2 = 0.02, medium R^2 = 0.13, large R^2 = 0.26

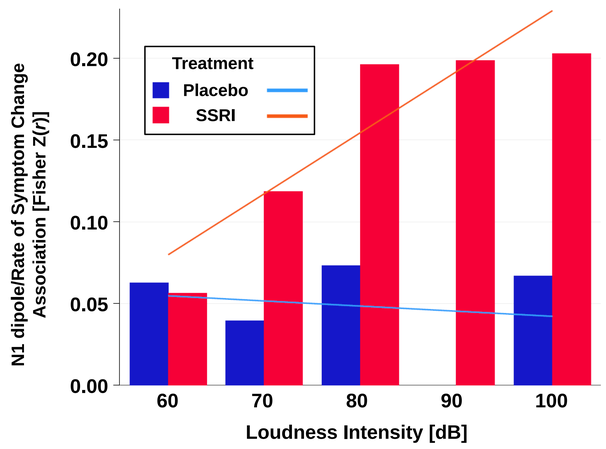


Fig. 5. Association between ***N1 dipole*** amplitude and ***rate of symptom change*** (Fisher-Z transformed Pearson's r) at each loudness intensity (see Fig. 4). Linear regression lines depict a monotonic increase with intensity of this association for SSRI, however, not for Placebo treatment groups.

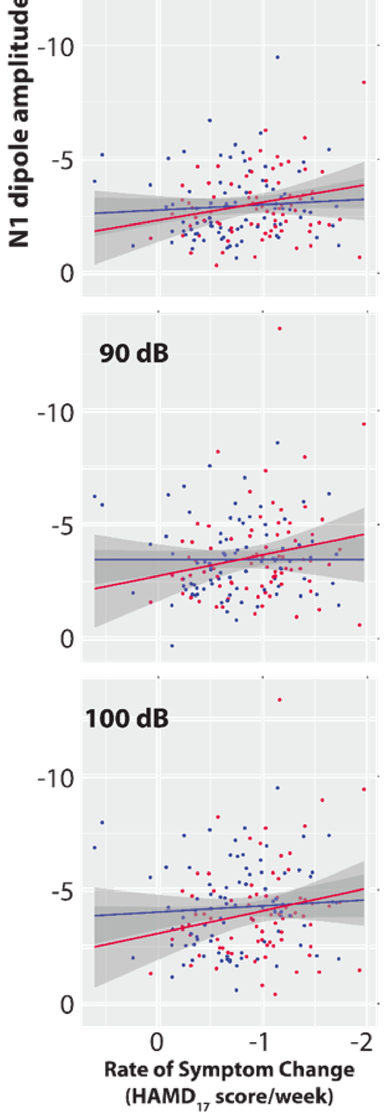


Fig. 4. Scatterplots of ***N1 dipole*** amplitude and ***rate of symptom change*** at each loudness intensity for **SSRI** and **Placebo** treatment arms. Note the change in the regression slope for SSRI with increasing intensity, whereas the slope remains shallow for Placebo across intensities.

Summary and Conclusions

- **Results confirm and extend prior findings indicating that stronger LDAEP is associated with better treatment outcome in MDD.[28]**
- **These findings further suggest that LDAEP is a biomarker that may function both as a predictor of MDD treatment response *and* as a moderator of treatment effect (i.e., differential prediction of response to SSRI vs. Placebo).**
- **In this regard, pretreatment LDAEP differs from pretreatment rostral ACC theta activity, which represented a nonspecific prognostic marker of treatment outcome in the same EMBARC sample.[24]**
- **However, given that effect sizes for the critical interactions involving *treatment arm*, *rate of symptom change*, and *loudness intensity* were small, clinical significance remains to be established.**

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