Characterization of N1/P2 Loudness Dependency by Temporal Principal Components Analysis of Current Source Density (CSD-PCA): Prediction of Treatment Response in Depressed Patients

Craig E. Tenke[1,2], Jürgen Kayser[1,2], Nathan A. Gates[1], Daniel M. Alschuler[1], Christopher J. Kroppmann[1], Shiva Fekri[1], Jonathan W. Stewart[2,3], Patrick J. McGrath[2,3], Gerard E. Bruder[1,2]

[1] Division of Cognitive Neuroscience, New York State Psychiatric Institute, New York, NY;
[2] Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY;
[3] Depression Evaluation Service, New York State Psychiatric Institute, New York, NY

49th Annual Meeting of the
Society of Psychophysiological Research (SPR)
in Berlin, Germany, October 21 - 24, 2009

Poster available in high resolution at
http://psychophysiology.cpmc.columbia.edu/mmedia/spr2009/AIM.pdf

http://psychophysiology.cpmc.columbia.edu

Abstract

Auditory EP loudness dependency (LDAEP) shows promise as a predictor of clinical response in depressed patients treated with serotonin agonists. Quantification of LDAEP used N1/P2 peak-to-peak differences and inverse models of N1 corresponding to primary auditory cortex generators (e.g., BESA, LORETA). Reference-free unrestricted Varimax CSD-PCA (covariance matrix) offers a conservative, model-independent alternative. Auditory 72-channel ERPs (BioSemi) were recorded from 23 healthy adults and 15 depressed patients listening to 40-ms, 1000-Hz pure binaural tones (1600-2100 ms ISI) at five, equiprobable intensities (60-100 dB SPL). Subsequently, patients began treatment with an SSRI, NDRI, or both antidepressants, and were assessed for treatment response after 4-12 weeks (7 remitters; 8 nonremitters). An N1 factor (116 ms peak latency) with a tangentially-oriented sink/source topography consistent with activation of auditory cortex showed a robust, monotonic association with intensity. Whereas the loudness dependency of this sink was greater for remitters than for nonremitters, who did not differ from controls, only overall N1 sink was significantly greater for remitters. The P2 factor (226 ms; midline source topography) showed intensity effects that were less robust, while a radial temporal lobe N1 sink (167 ms) and a temporal lobe P3 source (351 ms) failed to show consistent effects. Thus, CSD-PCA offers a concise, but conservative, characterization of LDAEP generators, and may be of clinical value for predicting response to antidepressants.

MH036295 and MH066597

Methods

Participants. 23 healthy adults (age = 32±9 y; 11 female) with no history of any psychopathology or neurological disorder. 15 patients (medication-free MDD; age = 37±11 y; 11 female) were recruited from a double-blind clinical trial comparing SSRI (escitalopram), NDRI (bupropion), and dual therapy (both). Patients were subsequently classified as remitters (n = 7) or nonremitters (n = 8) based on post-treatment Hamilton Ratings (<= 7 criterion).

Intensity modulation. Subjects sat quietly with their eyes opened and fixated on a cross while binaural tones (1000 Hz, 40 ms duration with 10 ms rise and decay time) were presented at varying levels of intensity (e.g., Hegerl & Juckel, 1993). Tones were presented in pseudorandomized order via TDH-49 headphones at five intensities (60, 70, 80, 90, 100 dB SPL) with interstimulus intervals ranging from 1600 – 2100 ms. Each stimulus intensity was repeated 100 times (i.e., 5 stimulus intensities = 500 trials).

ERP recordings. ERPs were recorded from 72 scalp sites (ActiView; BioSemi), using an active recording reference composed of sites PO1 (common mode sense) and PO2 (driven right leg), and rereferenced to nose offline. Continuous data were exported to Neuroscan format using Polyrex (Kayser, 2003). Amplifier drift was eliminated by padding the beginning of the file and applying a rectangular high-pass filter (10 s time constant).

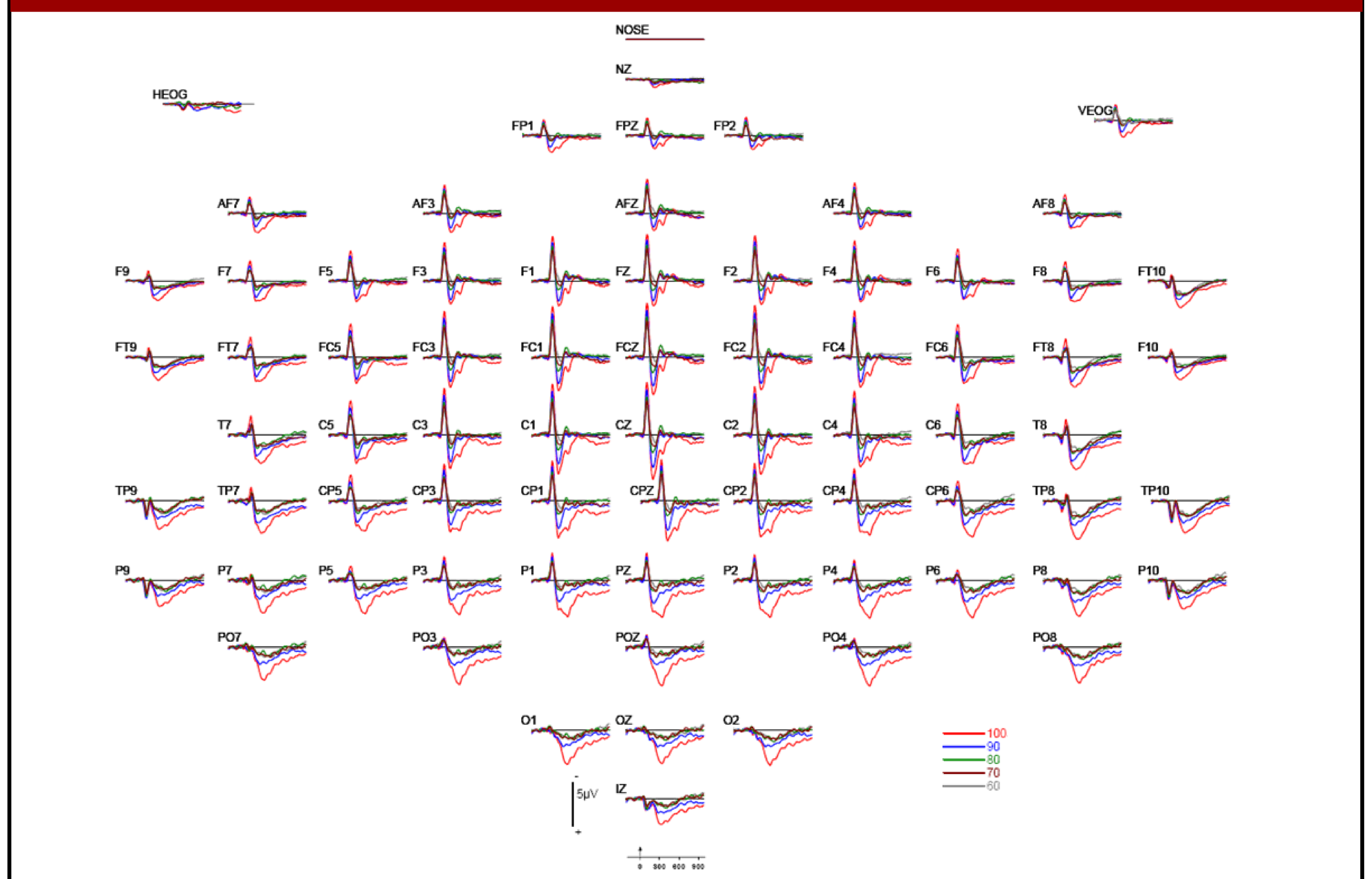
Continuous EEG was blink corrected using a spatial, singular value decomposition (NeuroScan). Stimulus-locked epochs (1200 ms, 200 ms prestimulus) were extracted and screened for electrolyte bridges (Tenke & Kayser, 2001). Channels containing amplifier drift, residual eye activity, muscle or movement-related artifacts or noise for any given trial were identified using a reference-free approach (Kayser & Tenke, 2006c), and replaced by spherical spline interpolations (Perrin et al., 1989) when possible. ERP averages were then low-pass filtered at 12.5 Hz (-24 dB/octave) and finally baseline-corrected using the 200 ms preceding stimulus onset.

ERPs were averaged for each stimulus intensity. For the purpose of intensity modulation, the tangentially-oriented N1 generator within the superior temporal gyrus in the vicinity of primary auditory cortex is uniquely important (Hegerl & Juckel, 1993; Mulert et al., 2002). Although CSD-PCA dissociates this tangential N1 generator from a radially-oriented, temporal lobe subcomponent of N1 (temporal N1 factor; cf. Kayser & Tenke 2006a,b), we examined all components of interest in the course of our analytic approach.

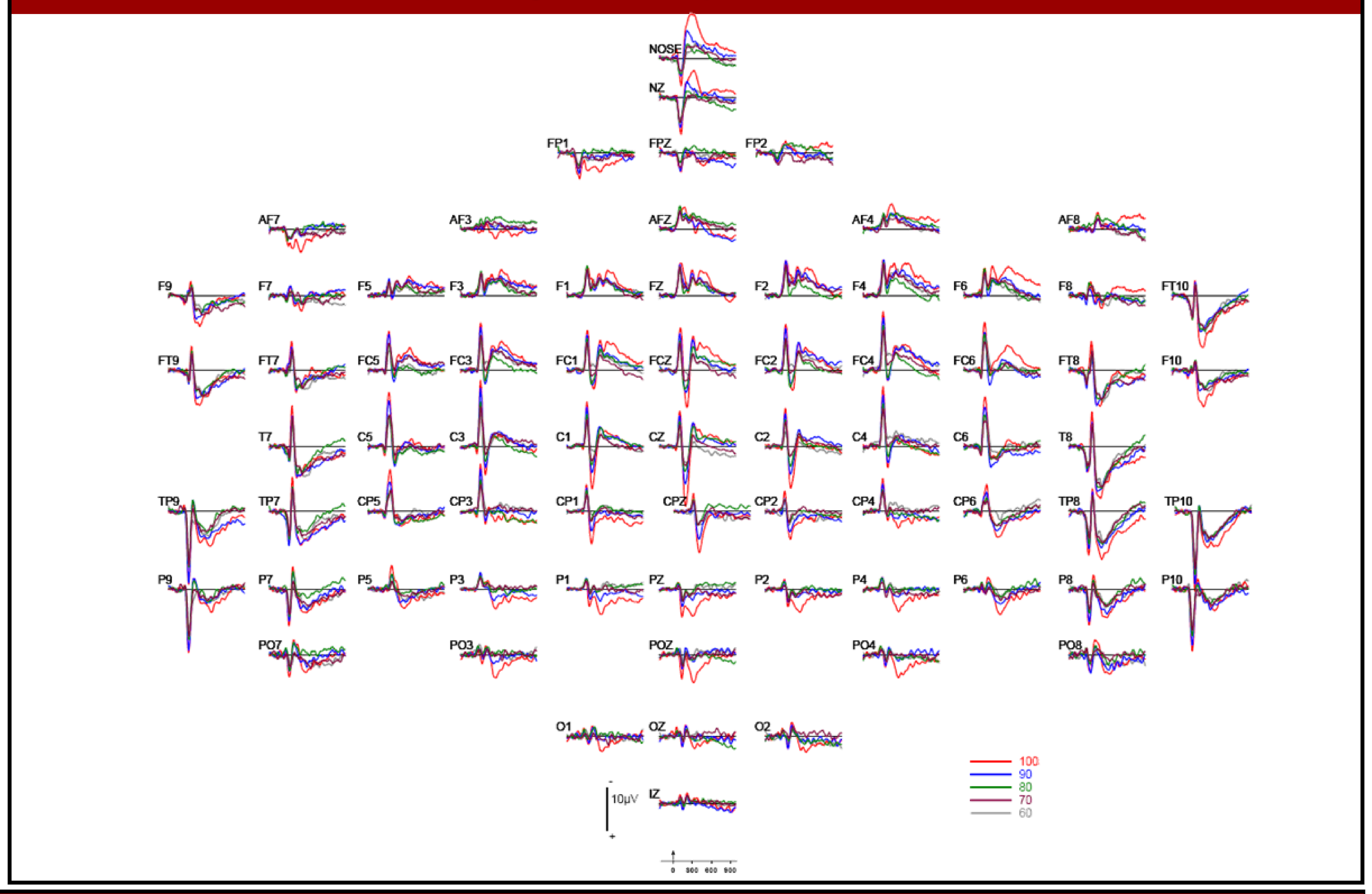
CSD-PCA. Reference-free CSD waveforms (spherical spline Laplacian; Perrin et al., 1989) were computed from ERP averages to sharpen topographies, eliminate volume-conducted contributions from distant regions, and quantify underlying current generators (Kayser & Tenke, 2006a,b; Tenke & Kayser, 2005). CSDs were submitted to unrestricted Varimax-PCA (covariance matrix; 308 variables = samples -200..1000 ms; 13680 observations = 38 Subjects x 5 Conditions x 72 Sites; cf. Kayser & Tenke, 2003).

Statistical tests. For factors of interest, factor scores were submitted to repeated measures ANOVA at selected sites (C3/C4 for N1 sink; T7/8 for temporal N1 sink; Cz for P2) using the Generalized Linear Model of SPSS 17. Within-subjects factors were *Condition* (100, 90, 80, 70, 60 dB) for midline regions (e.g., vertex), plus *Hemisphere* (right/left) for sites off the midline (Greenhouse-Geisser as needed). Between-subject factors were *Group* (Control, Remitter, Nonremitter), with *Gender* (male, female) as a control factor, and *Age* as a covariate. Findings from these selected sites were confirmed using complete hemitopographies, as extracted from factor score topographies using hemispatial PCA (cf. Tenke et al., 2008).

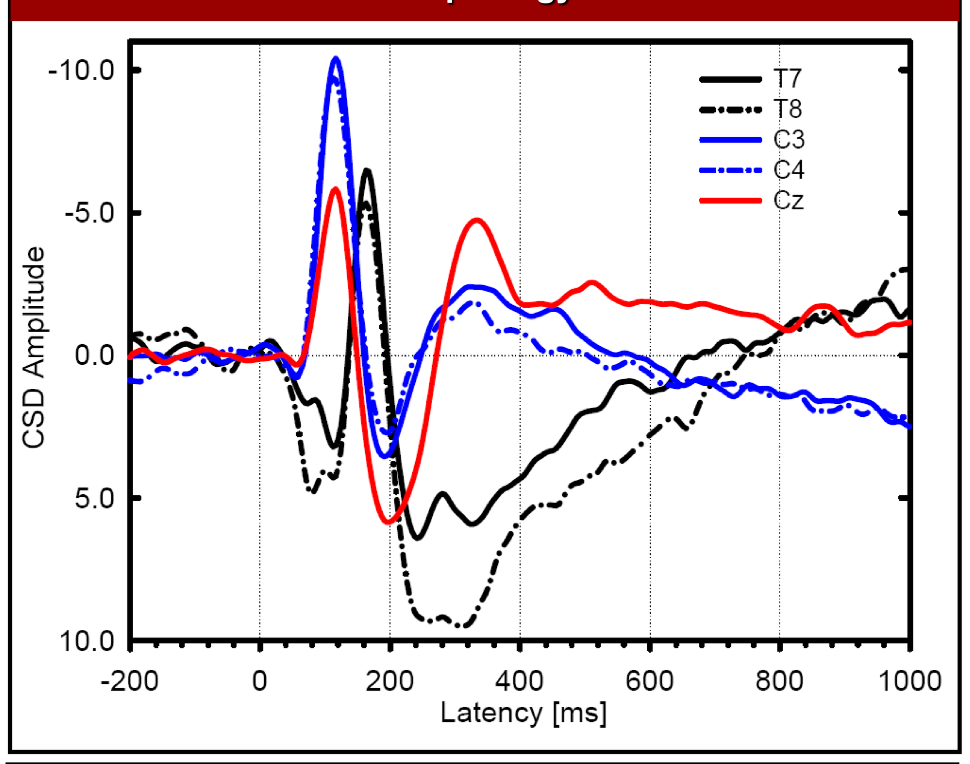
I. Nose-referenced ERP averages for five stimulus intensities



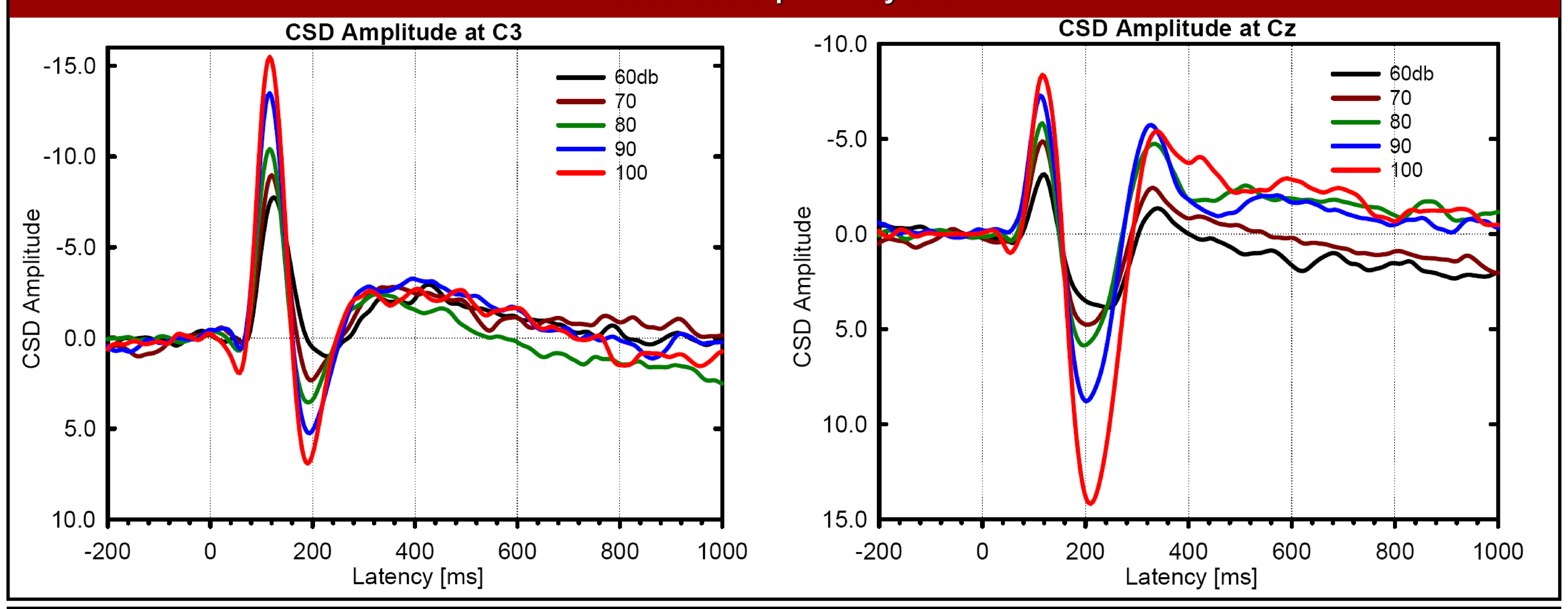
II. Corresponding CSD averages for five stimulus intensities



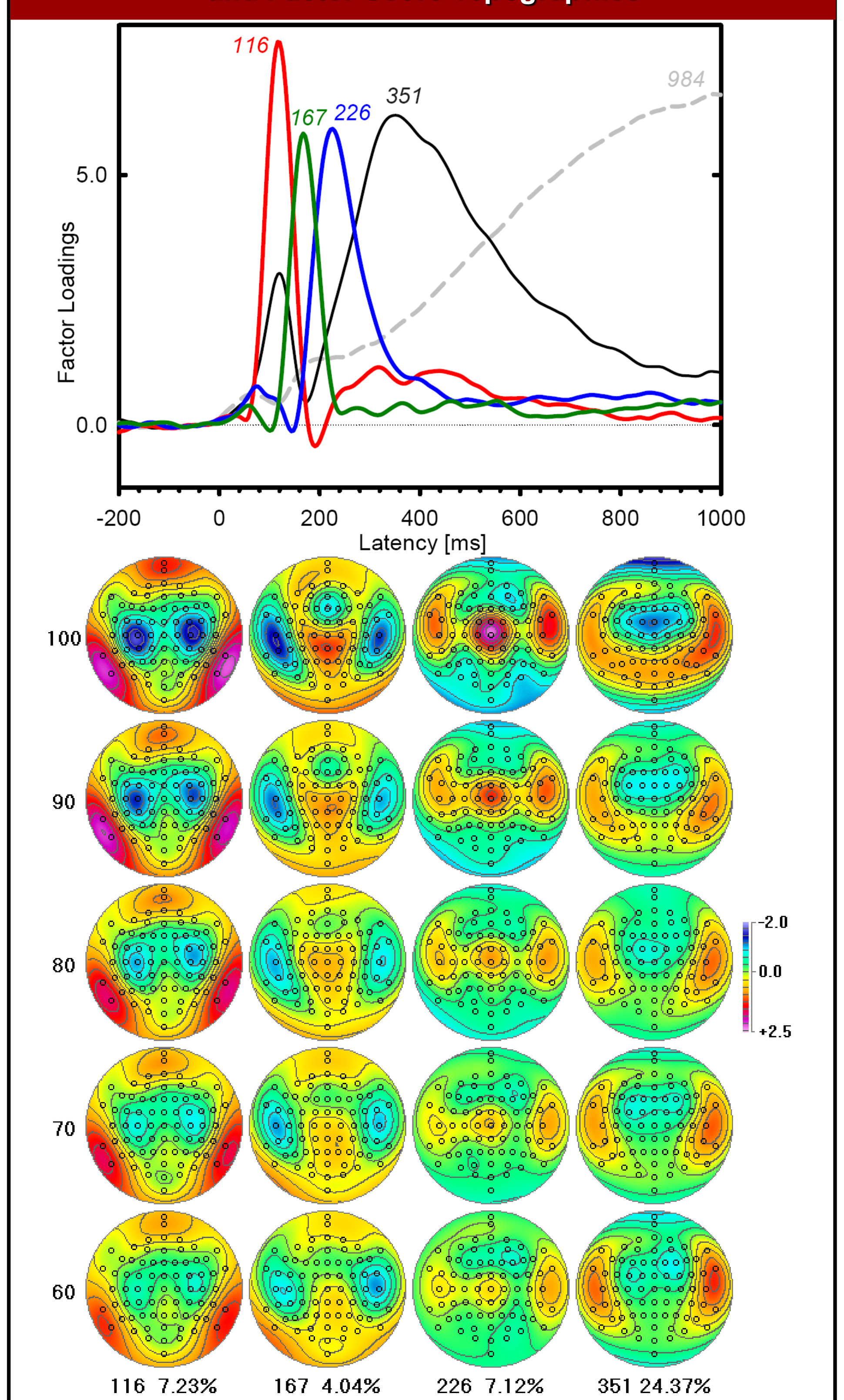
III. CSD morphology at 80 dB



IV. Loudness dependency of CSD

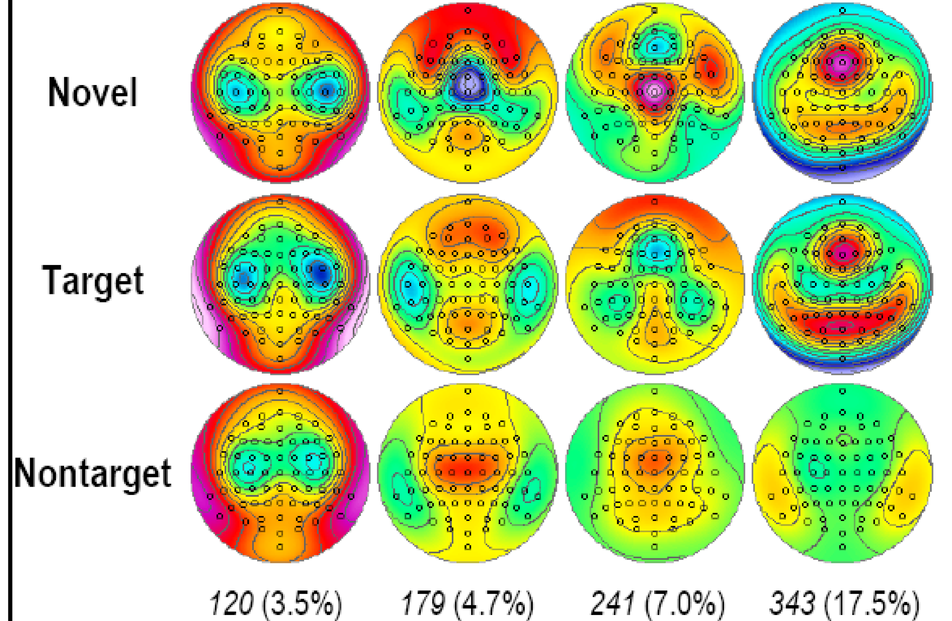


V. Varimax Rotated Factor Loadings and Factor Score Topographies



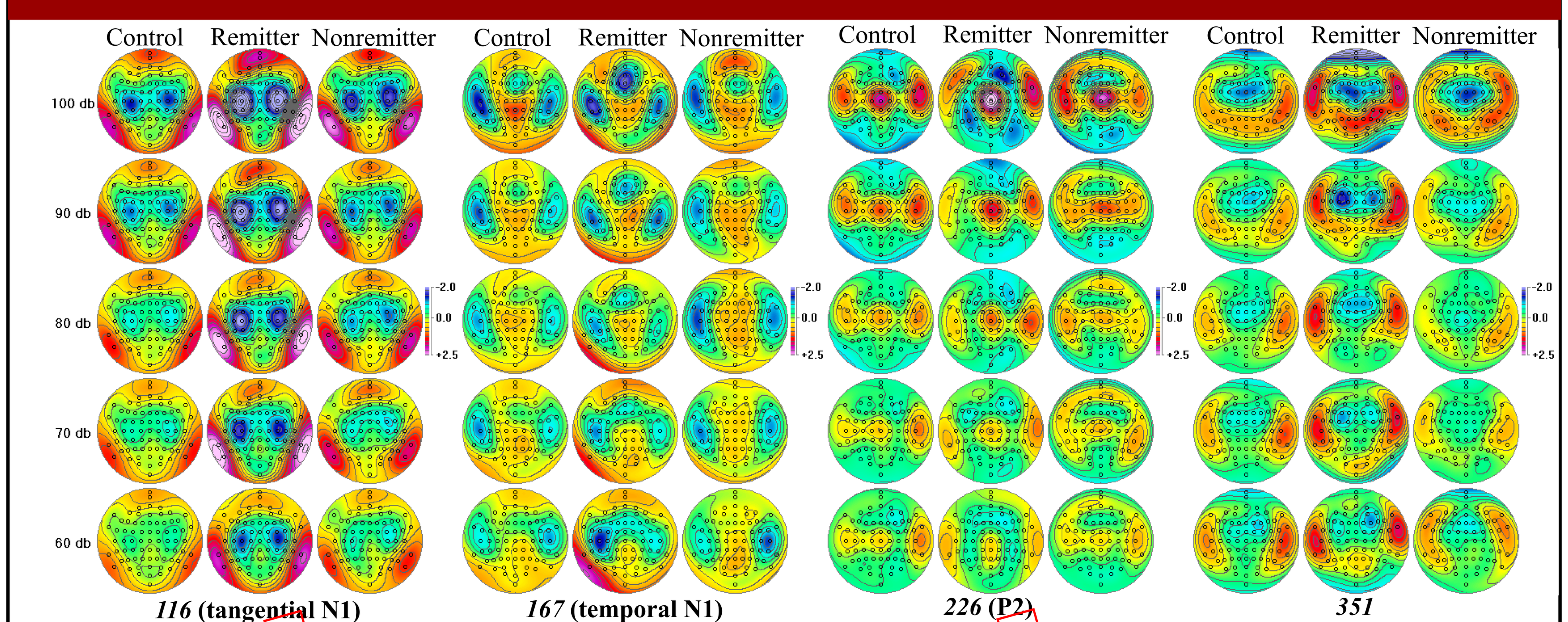
PCA factor loadings waveforms and factor score topographies for 5 factors with largest variance contributions, and averaged factor score topographies for each stimulus intensity (arranged by peak latency).

VI. Corresponding Novelty Oddball Factors

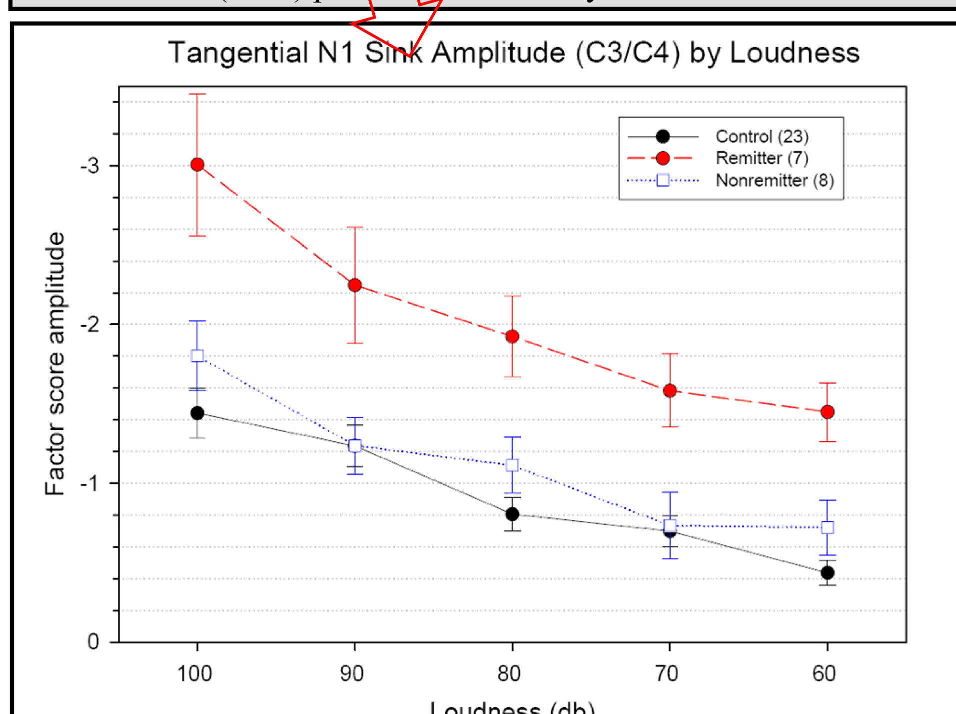


Despite differences in stimulus properties and task requirements, CSD-PCA factors are consistent with those observed in an auditory novelty oddball task, but without parietal P3b (Tenke et al., in press).

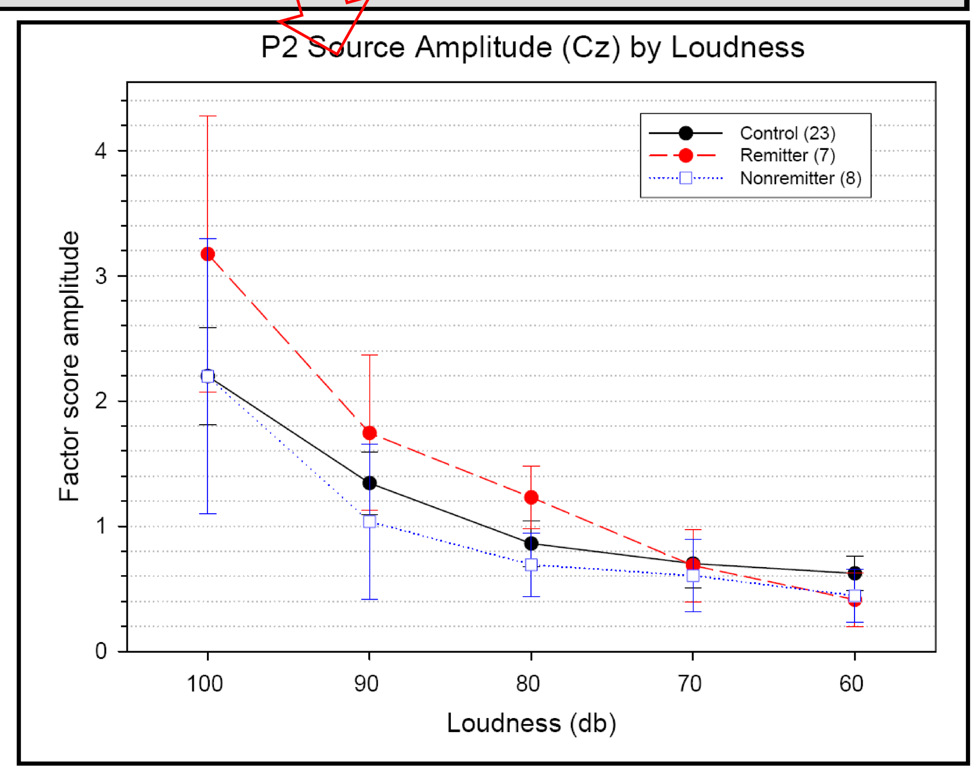
VII. Group differences for factors of interest



All groups showed loudness dependency for (tangential) N1, with the largest overall response and greatest slope for Remitters. In contrast, the loudness dependency and group difference for the vertex P2 source were prominent only for the loudest stimuli, reminiscent of the Novelty Vertex Source (NVS) produced in a novelty oddball task.



Group effect: F(2,31)=4.107 p=.026



References

Hegerl, U., & Juckel, G. (1993). Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. *Biol. Psychiatry*, *33(3)*, 173-187.

Kayser, J. (2003). Polygraphic Recording Data Exchange - PolyRex. Version 1.2 (Build 2.1). Psychophysiological Laboratory, Department of Biopsychology, New York State Psychiatric Institute (http://psychophysiology.cpmc.columbia.edu/Software/PolyRex).

Kayser, J., Tenke, C.E. (2003). Optimizing PCA methodology for ERP component identification and measurement: theoretical rationale and empirical evaluation. *Clin. Neurophysiol., 114*, 2307-2325.

Kayser, J., Tenke, C.E. (2006a). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: I. Evaluation with auditory oddball tasks. *Clin. Neurophysiol.*, *117(2)*, 348-368.

Kayser, J., Tenke, C.E. (2006b). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. *Clin. Neurophysiol.*, *117(2)*, 369-380.

Kayser, J., Tenke, C.E. (2006c). Electrical distance as a reference-free measure for identifying artifacts in multichannel electroencephalogram (EEG) recordings. *Psychophysiology*, *43*, S51.

Mulert, C., Juckel, G., Augustin, H., & Hegerl, U. (2002). Comparison between the analysis of the loudness dependency of the auditory N1/P2 component with LORETA and dipole source analysis in the prediction of treatment response to the selective serotonin reuptake inhibitor citalopram in major depression. *Clin. Neurophysiol.*, *113(10)*, 1566-1572.

Perrin F, Pernier J, Bertrand O, Echallier JF (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalogr. Clin. Neurophysiol., 72(2)*, 184–187 [Corr. EEG 02274, 1990].

Tenke, C.E., Kayser, J. (2001). A convenient method for detecting electrolyte bridges in multichannel electroencephalogram and event-related potential recordings. *Clin. Neurophysiol.*, *112*, 545-550.

Tenke, C.E., Kayser, J. (2005). Reference-free quantification of EEG spectra: combining current source density (CSD) and frequency principal components analysis (fPCA). *Clin. Neurophysiol.*, *116*, 2826-2846.

Tenke, C.E., Kayser, J., Shankman, S.A., Griggs, C.B., Leite, P., Stewart, J.W., Bruder, G.E. (2008). Hemispatial PCA dissociates temporal from parietal ERP generator patterns: CSD components in healthy adults and depressed patients during a dichotic oddball task. *Int. J. Psychophys., 67*, 1-16.

Tenke, C.E., Kayser, J., Stewart, J.W., Bruder, G.E. (in press). Novelty P3 reductions in depression: characterization using principal components analysis (PCA) of current source density (CSD) waveforms. *Psychophysiology*.

Conclusions

- Tangential N1 sink amplitude is monotonically related to stimulus intensity
- Tangential N1 sink amplitude is greater for Remitters than Nonremitters and Controls
- A steeper P2 source slope for Remitters than Nonremitters did not attain significance
- Vertex P2 source characterizes loud (i.e., salient) stimuli, reminiscent of the Novelty Vertex Source
- CSD-PCA offers a concise, conservative characterization of LDAEP generators, and may be of clinical value for predicting response to antidepressants