Principal Components Analysis (PCA) of Time-Frequency (TF) Measures Derived from Current Source Density (CSD) Reveal a Direct Link between EEG Alpha and the Reduced Novelty Response in Major Depression

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Introduction

Despite a long history, the investigation of clinical depression using task-related, cognitive event-related potentials (ERPs) and quantitative EEG measures at rest have produced two distinct lines of research with little, if any, overlap in theory or findings. Whereas both literatures are typically limited by uncertainties attributable to volume conduction, a surface Laplacian (or CSD) transformation provides reference-free ERP/EEG measures that are closer to the underlying neuronal generators [1]. Using a CSD-PCA approach, we recently reported a sharply localized novelty vertex source (NVS) component that is unique to novel stimuli and substantially reduced in depressed patients [2]. In another study, condition-dependent (eyes open vs. closed) posterior EEG alpha predicted antidepressant treatment response [3]. Moreover, the novelty ERP response is itself associated with alpha- and theta-coupling to slower rhythms (delta) [4]. This convergence of temporal and spectral findings in clinical depression suggest that CSD-based TF measures may be identifiable with the NVS.

Methods

Participants. Depressed patients (*n* = 49; 22 male; age 35.8 ±10.7 yrs) and healthy adults (*n* = 49; 23 male; 31.0 ±10.6 yrs) with no history of any psychopathology or neurological disorder.
Novelty Oddball Task. An auditory novelty oddball task was implemented on a Neuroscan STIM system using stimuli developed for this task) [5]. Eight 50-trial blocks consisted of 300-ms tones (10 ms rise and fall time) and novel sounds (100-400 ms duration) that were presented in pseudorandom order (1000 ms SOA). Unique novel sounds (i.e., animal sounds, musical instruments, environmental sounds; p = .12) were intermixed with a frequent nontarget tone (350 Hz; p = .76) and an infrequent target tone (500 Hz; p = .12). All stimuli were presented binaurally over headphones at 85 dB SPL. Subjects were instructed to focus their eyes on a fixation cross displayed on a computer monitor, and to respond with a button press as quickly as possible when, and only when, they heard the infrequent target tone (response hand counterbalanced across blocks).
ERP Recordings. ERP methods and results were detailed in [2]. ERPs were recorded from 67 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 [6]. 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 [7]. 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 [8], and replaced by spherical spline interpolations [9] 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.
CSD-tPCA. Reference-free CSD waveforms (spherical spline Laplacian [9]) were computed from ERP averages to sharpen topographies, eliminate volume-conducted contributions from distant regions, and quantify underlying current generators [1,10-12,16]. CSDs were submitted to unrestricted PCA using the covariance matrix (308 variables = samples -200 to 1000 ms; 19698 observations = [98 subjects x 3 conditions x 67 sites]) followed by Varimax rotation [13]. For each PCA factor of interest, factor scores were submitted to repeated measures ANOVA using within-subjects factors electrode *site* and *condition* (nontarget, target, novel) for midline regions (e.g., vertex), and *hemisphere* (right/left) for sites off the midline.

ERSP of Novelty CSD

ERSP of Novelty CSD. A CSD-tfPCA of the ERSP may be applied to the complete set of all sites and experimental conditions, yielding factor score topographies consistent with those produced by temporal [10,11] and spectral [12] PCA of CSD waveforms. Time-locked EEG epochs for each of the 98 participants were transformed to reference-independent CSD [16] and iteratively imported into EEGlab [14]. To retain comparability with previous work from our lab using FFT-derived power spectra, a Matlab program was developed to compute an ERSP matrix (< 400 ms; < 30 Hz) for any given site, condition and subject. Mean ERSPs were then computed for control and patient groups, plotted, and compared with the timecourse of the corresponding averaged CSD waveforms (Fig. 3).
CSD-tfPCA of ERSP of Novels at Cz. Initially, the present analysis was restricted to a single site (Cz, vertex) and condition (novel stimuli) because summarizing the vertex CSD for all novel trials was deemed crucial for the study of depression [2]. The set of CSD-ERSP matrices for 98 subjects were remapped as data vectors and characterized and simplified by unrestricted PCA with Varimax rotation [13]. This approach was preferred to a mutiple-stage simplification (i.e., time and frequency) because of its simplicity and ease of interpretation, recognizing the ability of PCA to identify spectral and/or temporal processes that belong together, and is closely analogous to the joint (simultaneous) extraction of stimulus- and response-locked components [15].
Generalized CSD-tfPCA of Novelty ERSP. Ultimately, the complete set of all CSD ERSP data (67-channels; 98 participants; target, nontarget, and novel) was employed using this CSD-tfPCA approach.

Results

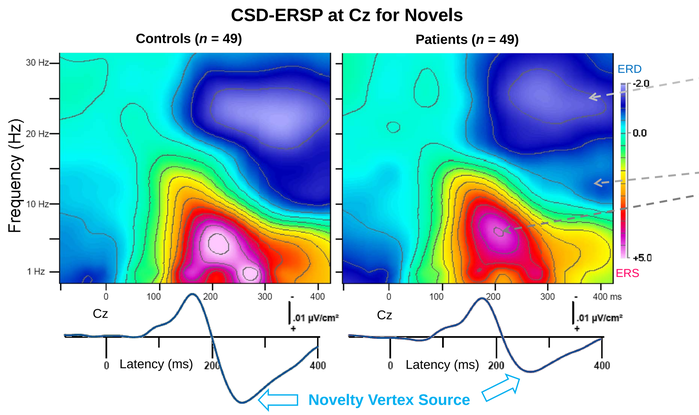


Fig. 3. Grand Mean CSD-ERSPs at Cz for Controls and Patients. The averaged novelty CSD waveform (bottom) consists of a sink/source pair peaking at 175/265 ms (peak-to-peak corresponds to a half-cycle sinusoid of 5.6 Hz; from [3]). The group-averaged ERSPs (top color maps) show a close correspondence with the intervening peak-to-peak transition, which is associated with a primary ERSP maximum (red). The precisely time-locked event-related synchronization (ERS; green-to-red transition) across all frequencies below 15 Hz is therefore consistent with trial-by-trial ERPs. In contrast, at longer latencies the ERS is replaced by an event-related desychronization (ERD; blue) at and above alpha frequencies. Differences between patients (right) and controls (left) are prominent below 15 Hz and take the form of both an initial difference in ERS, followed by an ERD difference, thereby supporting the hypothesized association between the Novelty Vertex Source and a composite alpha/theta measure.

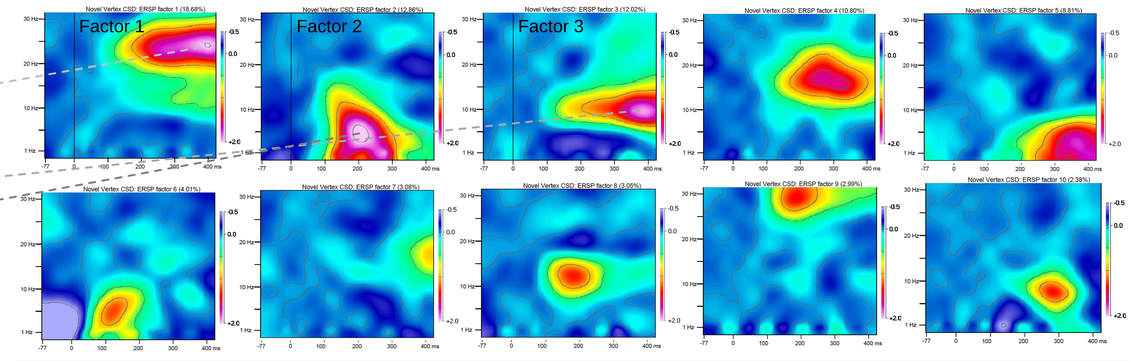


Fig. 4. CSD-tfPCA of ERSP at Cz for Novels. Factor loadings of the first ten novelty vertex CSD-tfPCA factors (79% explained variance). The first three factors are sufficient for a concise description of the grand mean CSD ERSP. The earliest of these component (Factor 2: theta maximum; 12.9% variance) reflects the ERS that closely matches the timing the novelty ERP (175-300 ms after stimulus onset). The other two factors reflect a subsequent ERD (i.e., red maxima for factors 1 and 3 correspond to blue minima in Fig. 3) at beta (Factor 1: 25 Hz; 18.7%) and alpha (Factor 3: 10 Hz; 12.0%) frequencies. The early theta ERS factor did not distinguish between depressed patients and controls (Mann-Whitney U = 1014; z = -1.325; *p* = .19), although the difference for the subsequent alpha desynchronization was suggestive (U = 949; z = -1.787; *p* = .07). However, theta and alpha factors jointly separated the two groups (U = 985; z = -2.171; *p* = .03).

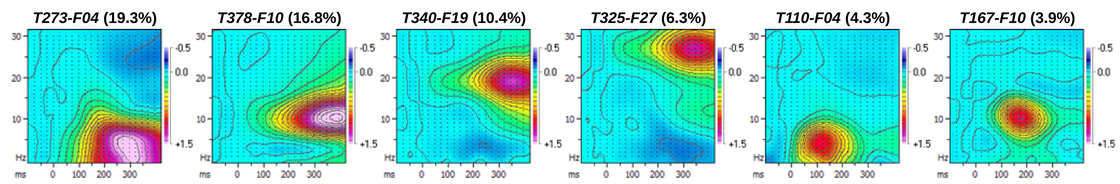


Fig. 5. Generalized CSD-tfPCA (67 sites; nontarget, target, novel). Factor loadings of the first six novelty vertex CSD-tfPCA factors (61% ERSP variance). The first three factors are sufficient for a concise description of the grand mean CSD ERSP. This factors structure differs from that of Fig. 4 by incorporating the entire topography and all three conditions.

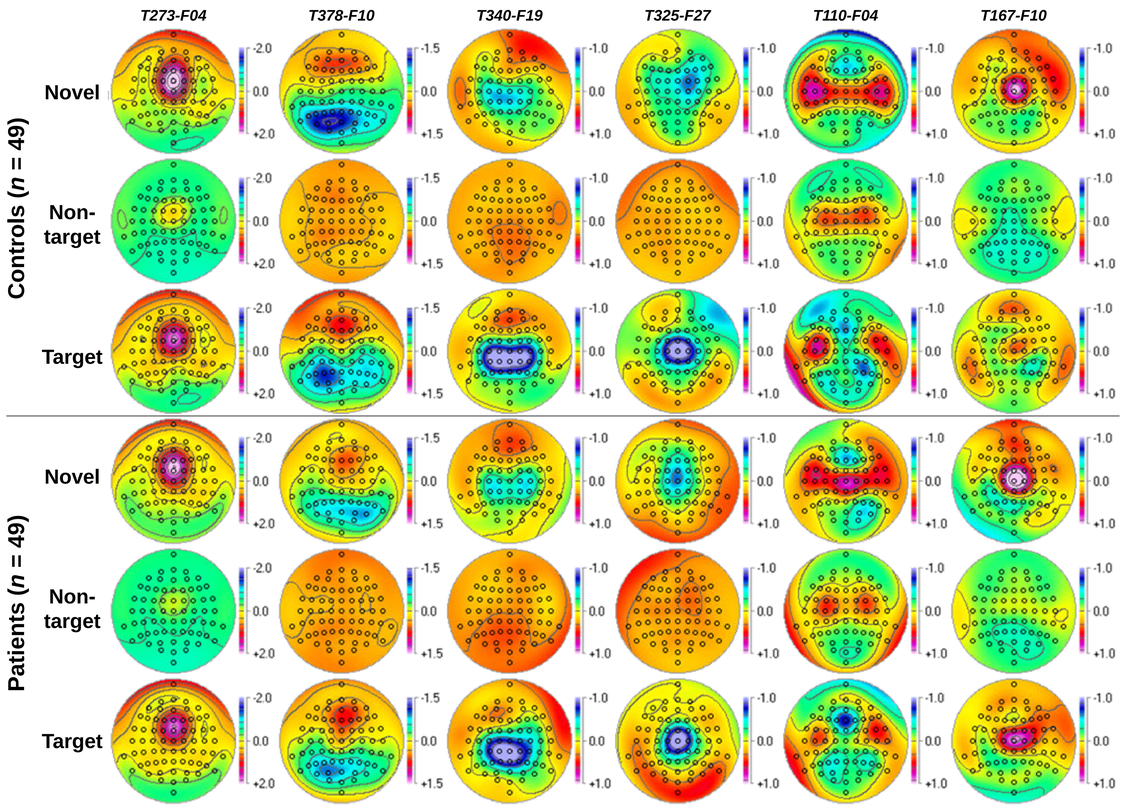


Fig. 6. Factor Score Topographies. The most prominent CSD-tfPCA factor (*T273-F04*: 273 ms peak latency; 4 Hz peak frequency) had a loadings peak latency comparable to the NVS (265 ms), but its midline topography was further anterior, pronounced for targets, and not reduced in patients. A subsequent component (*T378-F10*: 378 ms; 10 Hz) had a posterior topography identifiable as posterior alpha desynchronization for both novels and targets that was greatest over the left hemisphere for controls (particularly for targets), but markedly reduced in patients compared to controls. However, an earlier midline component (*T167-F10*: 167 ms; 10 Hz) represented alpha synchronization that was most robust for novels and patients. Although this TF component corresponded to the mismatch negativity (MMN) latency peak to novels (175 ms), groups did not differ in MMN.

Summary and Conclusions

- **The enhanced early vertex alpha synchronization in depressed patients following salient, but task-irrelevant, distracters is associated with subsequent reductions in both the *novelty vertex source* and in the subsequent reduction in condition-dependent, *posterior alpha desynchronization* following novel sounds.**
- **These findings thereby provide a *common framework* for interpreting tonic and event-related alpha abnormalities in major depression.**
- **CSD-tfPCA shows promise as a useful integrative tool for identifying and characterizing better predictors of antidepressant treatment outcomes.**
- **CSD-tfPCA is a comprehensive approach for dealing with the temporal and spectral processes underlying the trial-by-trial event-related EEG.**
- **Being based on CSDs, these results directly reflect neuronal current generator patterns, and are not confounded by errors and artifacts related to the recording reference or volume conduction that plague all voltage measures of the EEG.**

Previous CSD-PCA Findings for Major Depressive Disorder

Fig. 1. Novelty Oddball Task ERPs: Patients show reduced NVS [2].

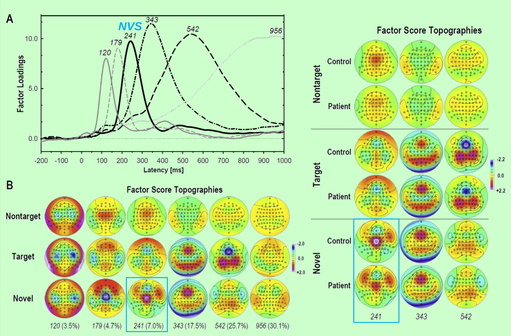
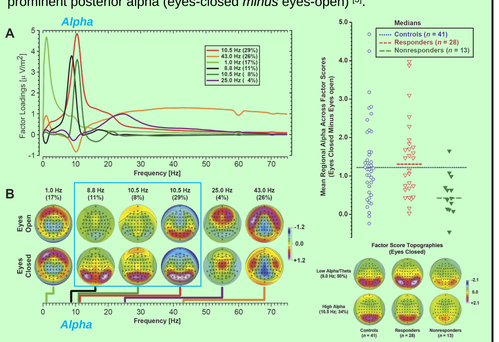


Fig. 2. Resting EEG: Responders to serotonergic antidepressants show prominent posterior alpha (eyes-closed *minus* eyes-open) [3].



1) The Novelty Vertex Source (NVS) was unique to novels and reduced in patients.
2) CSD-tPCA yields a concise, reference-free summary of ERP current generators.

Depressed patients with prominent posterior alpha are preferentially responsive to treatment with serotonergic antidepressants.

References

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