Association between antidepressant treatment response and EEG alpha: current source density (CSD) spectral measures at rest and time-frequency (TF) measures during a novelty oddball

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Introduction

EEG alpha rhythm has been used as a neurophysiological measure of activation, ranging from relaxation at rest to task-related local cortical synchronization or desynchronization. Although the topographic capacity of high density EEG is limited by volume conduction, it is enhanced by CSD transformation, which provides reference-free measures that represent the neuronal generator pattern underlying alpha. CSD-based frequency principal components analysis (CSD-fPCA) of resting EEG has identified posterior, condition-dependent (eyes closed-minus-open) alpha as a predictor of treatment response to serotonergic antidepressants.[3] Serotonergic and dual treatments (serotoner-gic plus bupropion, an NDRI) did not differ as both responder groups showed greater posterior alpha. However, this study tested only a limited number of patients treated with bupropion alone. Moreover, task-related alpha also varies during the performance of behavioral tasks, and these changes may be quantified as event-related spectral perturbations (ERSP). The present 67-channel EEG study combined task-related (novelty oddball) and resting CSD alpha measures obtained from depressed patients prior to treatment with a serotonergic antidepressant (n = 77) or bupropion alone (n = 23).

Methods

Participants. Depressed patients (n = 127; 60 male; age 38.3 ±11.8 yrs) and healthy adults (n = 114; 54 male; 31.2 ±10.0 yrs) with no history of any psychopathology or neurological disorder.

Novelty Oddball Task. An auditory novelty oddball task [5] consisted of eight 50-trial blocks of 300-ms tones (10 ms rise and fall time) and novel sounds (100-400 ms duration) presented in pseudorandom order (1000 ms SOA). Unique novel sounds (e.g., animals, instruments; p = .12) were intermixed with frequent nontargets (350 Hz; p = .76) and infrequent targets (500 Hz; p = .12) presented binaurally at 85 dB SPL. Subjects responded 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. As previously detailed [2], ERPs were recorded from 67 scalp sites (ActiView; BioSemi). Continuous EEG data were blink corrected using a spatial, singular value decomposition (NeuroScan). Stimulus-locked epochs (1200 ms, 200 ms prestimulus baseline) were extracted and screened for electrolyte bridges [7]. Channels containing 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 low-pass filtered at 12.5 Hz (-24 dB/octave) and baseline-corrected.

CSD-tPCA for Novelty Oddball Task. 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; 48441 observations = [241 subjects x 3 conditions x 67 sites]) followed by Varimax rotation [13].

CSD-fPCA for Resting EEG. EEG epochs (2 s; 75% overlap) were transformed to CSD, tapered using a Hanning window, and padded with zeros (1 s at each end) to yield a FFT-transformed spectral resolution of .25 Hz. Amplitude (RMS power) spectra were averaged over all artifact-free epochs for each condition and subject and submitted to fPCA [3, 12].

CSD-tfPCA in Novelty Oddball Task. ERSPs and corresponding baseline spectra were obtained from CSD-transformed stimulus-locked epochs (-200 to 800 ms) for each electrode, condition (target, nontarget, novel) and participant (N = 241) using EEGlab [14]. For comparability to prior work, ERSP matrices (-70 to 800 ms; 1 to 50 Hz) and baseline spectra were based on FFT-derived log power spectra. Grand mean ERSPs were computed and separately plotted for control and patient groups, and were compared to the time courses of the corresponding averaged CSD and CSD-tPCA loadings waveforms. Analogous to the tPCA and fPCA decompositions, CSD-ERSP matrices were vectorized (88 x 50 = 4400 variables) and characterized by PCA (i.e., CSD-tfPCA).

Association of ERSP plots with CSD-tfPCA factors. Our prior CSD-tPCA [2] identified a component unique to novel stimuli, termed novelty vertex source (NVS; Fig. 1), which was reduced in depressed patients. This a priori knowledge was exploited to delineate the relationship of the ERSP plots with the resulting tfPCA factors by comparing CSD-tfPCA solutions stemming from the complete topo-graphy or after restricting the ERSP data to midline sites or Cz alone.

Statistical methods. 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. *Treatment* (serotonergic, bupropion), treatment *response* (responder, nonresponder), and *gender* were between-factors in these ANOVAs. The Beck Depression Inventory (BDI) measure of pretreatment depression was used as a covariate because BDI was correlated with condition-dependent alpha at rest and post-stimulus ERD.

Results

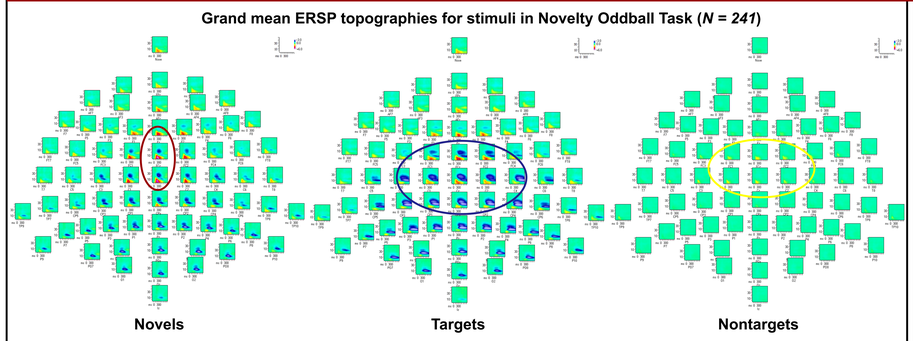


Fig. 4. Grand mean ERSP topographies (N = *241*). For **Novels**, the ERSP follows the time course of the novelty P3, beginning with a prominent low-frequency (alpha and below) ERS that is maximal at central regions at latencies corresponding to the novelty vertex source (NVS [2]; red oval). The ERS is followed by a somewhat more broadly-distributed beta ERD, and a posterior alpha ERD. For **Targets**, an anterior midline ERS is also observed, although it is less pronounced than for novels, while the subsequent beta ERD is more pronounced and persists to longer latencies. The posterior alpha ERD is also enhanced compared to novels, and is robust at centroparietal sites, stretching to frontocentral sites (i.e., consistent with both posterior alpha and central mu; blue oval). For **Nontargets**, prominent task-related ERSPs were not observed, although evidence of low amplitude ERS corresponding to auditory N1 can be detected (yellow oval) .

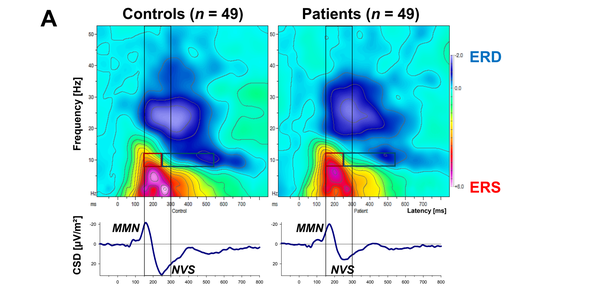
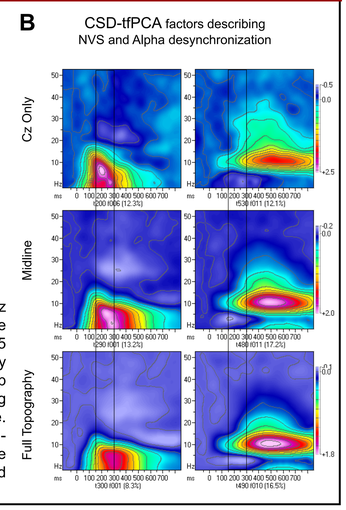


Fig. 5. A. Grand mean ERSPs and CSDs corresponding to NVS. Novelty CSDs at Cz consisted of a sink/source pair at 175/265 ms (peak-to-peak corresponds to a half-cycle sinusoid of 5.6 Hz). An event-related synchronization (ERS) across low frequencies (<15 Hz) closely corresponds to this transition, consistent with trial-by-trial ERPs, followed by an event-related desychronization (ERD) at and above alpha frequencies. Group differences are evident below 15 Hz, affecting both ERS and ERD, thereby supporting the hypothesized association between the NVS and a composite alpha/theta measure. **B.** CSD-tfPCA solutions across all conditions at Cz replicate the ERS related to the trial-to-trial ERP, as well as the subsequent alpha ERD. When a more representative topography is provided, the prominence of the ERD increases, contrasting the broad distribution of alpha against the sharp localization of the NVS.



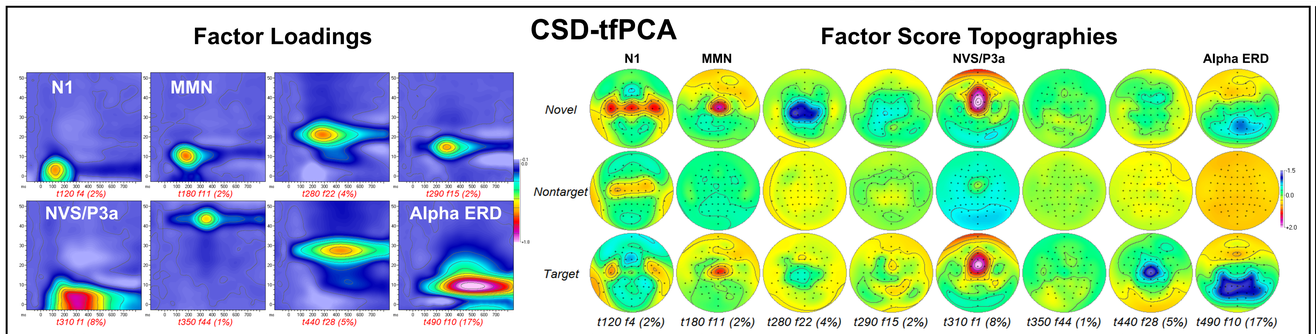


Fig. 6. CSD-tfPCA solution (N = 241). Factors are sorted by peak latency, showing all high-variance factors with a loadings peak < 500 ms. Factor lables (in red below loadings surfaces) jointly indicate latency (*t*) and frequency (*f*) of the loadings peak (e.g., *t120 f4* peaks at 120 ms, 4 Hz). The solution identified factors associated with prominent ERS peaks corresponding to the latency of N1, MMN, and NVS/P3a (cf. Figs. 1 and 4). The corresponding factor score topographies illustrate the condition-dependency of these time-frequency components, which compactly describe and quantify the data underlying the ERSP topographies shown in Fig. 4, justifying additional mnemonics (N1, MMN, NVS/P3a, Alpha ERD) to indicate their putative functional properties. The factor identified as Alpha ERD unambiguously quantified alpha desynchronization at 7-12.5 Hz in the latency range of 350-700 ms, showing a posterior topography for novels and targets, but not nontargets (note bilateral extension into central regions for targets) .

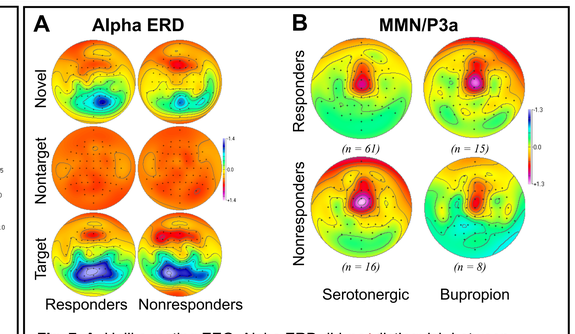


Fig. 7. A. Unlike resting EEG, Alpha ERD did ***not*** distinguish between responders and nonresponders. **B.** However, there was a prominent treatment by response interaction (p = .015) for ERS following infrequent novels and targets along the frontocentral midline at alpha and theta frequencies at latencies corresponding to mismatch detection (i.e., pooled MMN and NVS/P3a factors).

Conclusions

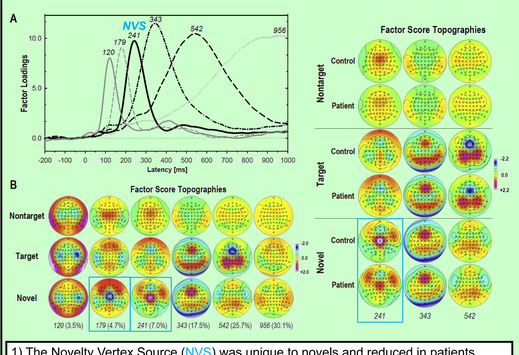
1. **Resting alpha is *predictive* of a positive outcome to treatment with serotonergic or nonserotonergic (NDRI) antidepressants.**
2. **Despite a comparable topography, task-related baseline alpha is *selective* for bupropion response.**
3. **Alpha ERD has a posterior topography for targets and novels, extends to central sensorimotor regions for targets, and is absent for nontargets, but is *not* related to treatment response.**
4. **Frontocentral midline synchronization following infrequent novels and targets at latencies corresponding to MMN and NVS/P3a was greater for serotonergic nonresponders than responders, but patients treated with bupropion showed the opposite difference (i.e., greater ERS in group in which psychomotor slowing has also been found).**

Medial frontocentral and posterior mechanisms are differentially predictive of treatment response to pharmacologic antidepressants

Fig. 8. A. CSD-fPCA solution for log prestimulus baseline power. Alpha factor score topographies (bottom) are comparable to those from resting EEG (cf. Fig. 3). **B.** Repeated measures ANOVA revealed a significant treatment by response interaction (p < .05) for posterior alpha: Bupropion responders (n = 15) showed markedly less alpha than nonresponders (n = 8), while serotonergic responders and nonresponders did not differ.

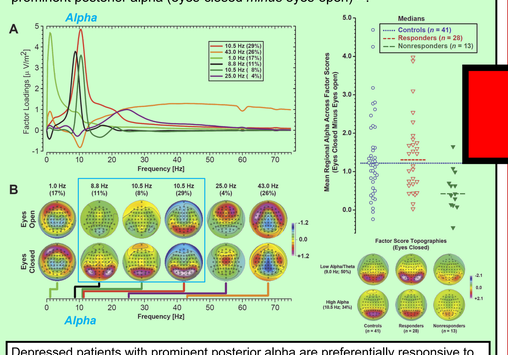
Previous CSD-PCA Findings for Major Depressive Disorder

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



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.

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



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

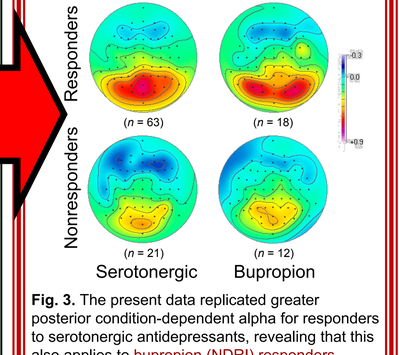


Fig. 3. The present data replicated greater posterior condition-dependent alpha for responders to serotonergic antidepressants, revealing that this also applies to bupropion (NDRI) responders.

Table 1. Factor Intercorrelations.

		MMN ERS			NVS/P3a ERS			Alpha ERD (minus ERS)		
		bTcov	cmod12	vMMN	tMMN	nMMN	vP3a	tP3a	nP3a	vAlphaM	tAlphaM	nAlphaM
bTcov (tf baseline alpha)	Pearson Correlation	1.000	-.315	-.328	-.287	-.392	.002	.054	.033	.447	.524	.004
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.973	.401	.608	.000	.000	.948
	N	241	238	241	241	241	241	241	241	241	241	241
cmod12 (resting cond-dep alpha)	Pearson Correlation	-.315	1.000	.117	.180	.157	.148	.147	.169	-.045	-.095	.024
	Sig. (2-tailed)	.000	.000	.071	.005	.015	.023	.024	.009	.493	.142	.718
	N	238	238	238	238	238	238	238	238	238	238	238
Age [years]	Pearson Correlation	-.217	.043	.008	-.077	.040	-.200	-.225	-.293	.048	-.041	-.106
	Sig. (2-tailed)	.001	.506	.897	.236	.534	.002	.000	.000	.460	.523	.102
	N	241	238	241	241	241	241	241	241	241	241	241
RT	Pearson Correlation	-.151	-.053	-.017	-.026	.142	-.090	-.245	-.367	.048	-.067	.010
	Sig. (2-tailed)	.019	.420	.789	.689	.028	.162	.000	.000	.458	.303	.877
	N	241	238	241	241	241	241	241	241	241	241	241
Beck Depression Inventory	Pearson Correlation	-.175	.231	.104	.069	.176	.045	.003	-.066	-.134	-.097	-.061
	Sig. (2-tailed)	.007	.000	.110	.288	.007	.491	.962	.315	.040	.138	.351
	N	236	233	236	236	236	236	236	236	236	236	236
Beck Depression Inventory (patients only)	Pearson Correlation	-.098	.213	.005	-.069	.196	-.067	-.052	.048	-.221	-.152	.011
	Sig. (2-tailed)	.276	.018	.956	.445	.029	.455	.565	.598	.013	.091	.904
	N	125	123	125	125	125	125	125	125	125	125	125

CSD-tfPCA Intercorrelations (Eyes Closed)

		vMMN	tMMN	nMMN	vP3a	tP3a	nP3a	vAlphaM	tAlphaM	nAlphaM
TPCA_vMMN	Pearson Correlation	-.210	-.109	.164	-.232	-.262	.275	-.185	-.252	.074
	Sig. (2-tailed)	.001	.095	.012	.000	.000	.000	.004	.000	.254
	N	236	236	236	236	236	236	236	236	236
TPCA_vNVS	Pearson Correlation	.097	.131	-.030	.360	.276	.298	-.006	.080	-.006
	Sig. (2-tailed)	.138	.044	.643	.000	.000	.000	.925	.223	.922
	N	236	236	236	236	236	236	236	236	236
TPCA_vP3a	Pearson Correlation	.055	.125	-.010	.397	.372	.197	-.080	-.008	-.104
	Sig. (2-tailed)	.401	.056	.879	.000	.000	.002	.219	.897	.111
	N	236	236	236	236	236	236	236	236	236

tf baseline: Inversely related to closed-minus-open resting EEG alpha
Inversely related to ERS at MMN latencies (all conditions)
Positively related to alpha ERD for novels and targets (i.e., greater baseline => greater ERD)

resting EEG: Positively related to ERS at MMN and NVS/P3a latencies (**targets and nontargets**)
Not related to alpha ERD

Age: Inversely related to tf baseline alpha
Inversely related to ERS at NVS/P3a latencies (all conditions)

RT: **Inversely related to tf baseline alpha**
Positively related to ERS at latencies corresponding to MMN (**nontargets**) and NVS/P3a (**targets, nontargets**)

BDI: Inversely related to tf baseline alpha (**only when controls included**)
Positively related to closed-minus-open **resting** alpha
Positively related to ERS at MMN latencies for **nontargets**
Inversely related to alpha ERD for novels

Intercorrelations with novelty CSD-tPCA factors
•vMMN broad pattern of intercorrelation (all conditions)
•NVS only correlated with NVS/P3a factors (all conditions)
•P3a only correlated with NVS/P3a factors (all conditions)

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