Auditory Event-Related Potentials (ERP) and Alpha Oscillations in the Psychosis Prodrome: Neuronal Generator Patterns During a Novelty Oddball Task

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Introduction

- Prior research suggests that event-related potentials (ERPs) obtained during active and passive *auditory* paradigms may be helpful in predicting transition to psychosis.
- ERP abnormalities in **schizophrenia patients** and **individuals at clinical high risk (CHR) for psychosis** included:
  - mismatch negativity (MMN), a pre-attentive measure of auditory change detection (e.g., Michie 2001; Atkinson et al 2012)
  - P3 amplitude (e.g., Ford 1999; van der Stelt et al 2005)
- Recent research also suggests abnormal neural oscillations in schizophrenia, with a focus on high-frequency (i.e., beta and gamma) modulations (e.g, Ford et al 2008; Spencer et al 2003, 2004; Uhlhaas & Singer, 2010).
- However, low-frequency modulations involving alpha and theta bands are associated with working memory, attention, inhibition and top-down cognitive control, that is, functional domains that are the hallmark of cognitive impairments in schizophrenia.
- Event-related alpha desynchronization (ERD) to target tones has been reduced in schizophrenia (Higashima et al 2007) and CHR patients (Koh et al 2011).
- The dependency of surface potentials on an **EEG reference** (e.g., linked mastoids, average) and the **definition and measurement** of appropriate **ERP and spectral EEG components** limit the value of neurophysiological measures (e.g., Kayser & Tenke 2003; Tenke & Kayser 2005, 2012).
- However, these limitations can be overcome by combining *reference-free* **current source density (CSD)** transformations and *unrestricted* **principal components analysis (PCA)** to identify relevant, data-driven components (Kayser &Tenke 2006a,b).

Objective:

- **examine a cohort of CHR patients and closely-matched healthy controls during an auditory *novelty* oddball task, which yields prominent ERP-CSD components, including N1, MMN, novelty P3, and P3b** (Tenke et al 2010)
- **expand the CSD-PCA approach from the time (ERP) to the time-frequency (ERSP) domain to identify neuronal generator patterns underlying distinct alpha oscillations**
- **evaluate whether CHR patients exhibit reduced alpha ERD and/or novelty MMN, and whether these measures are of value for predicting transition to schizophrenia**

Participants

Means, standard deviations (SD), and ranges for demographic and clinical variables

	Prodromal Patients (*n* = 22; 7 female)			Healthy Controls (*n* = 20; 7 female)				
Variable	Mean	SD	Range	Mean	SD	Range	*F*	*p*
Age (years)	21.5	3.6	13 - 27	21.7	3.3	16 - 27		
Education (years)	13.7	2.2	9 - 18	14.4	1.8	12 - 18		
Handedness (LQ) [a]	68.9 [b]	34.6	-40 - 100	79.4 [c]	49.3	-100 - 100		
SOPS positive [d]	11.3	4.3	4 - 20	0.6	0.8	0 - 2	98.1	<.0001
SOPS negative [d]	12.5	6.0	3 - 27	1.1	1.7	0 - 6	53.5	<.0001
SOPS disorganization [d]	6.8	3.3	1 - 14	0.3	0.7	0 - 2	60.7	<.0001
SOPS general [d]	8.1	4.2	0 - 14	0.5	1.1	0 - 4	63.5	<.0001
SOPS modified GAF [d]	46.8	6.4	38 - 60	83.8	7.0	68 - 95	279.9	<.0001

Note. Only *F* ratios with $p < .10$ are detailed ($df = 1, 38$). [a] Laterality quotient (Oldfield 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed). [b] $n = 19$. [c] $n = 16$. [d] *Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms* (SIPS/SOPS; Miller et al 2003) subscales (possible range): positive symptoms (0 - 30); negative symptoms (0 - 36); disorganization symptoms (0 - 24); general symptoms (0 - 24); modified global assessment of function score (0 - 100).

Novelty Oddball Task

- following prior studies (e.g., Fabiani & Friedman 1995; Bruder et al 2009; Tenke et al 2010), nontarget and target tones (300 ms duration, 350 Hz and 500 Hz frequency, 76% and 12% probability) interspersed with unique novel sounds (e.g., animals, musical instruments, etc.; 100–400 ms duration, 12% probability) were binaurally presented in pseudorandom order (1000 ms stimulus onset asynchrony; headphones at 85 dB SPL)
- a total of 400 trials was distributed over 8 blocks of 50 trials
- each block consisting of 38 nontargets, 6 targets, and 6 novels
- participants were instructed to press a button as quickly as possible when, and only when, they heard the target tone
- response hand was counterbalanced across blocks

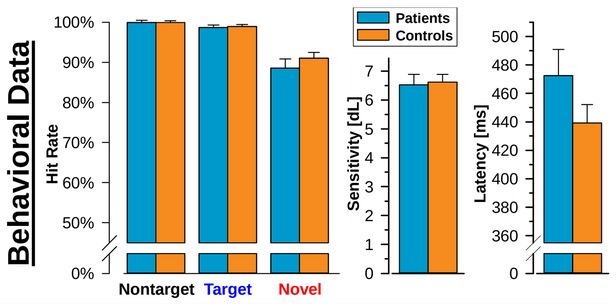
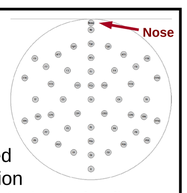


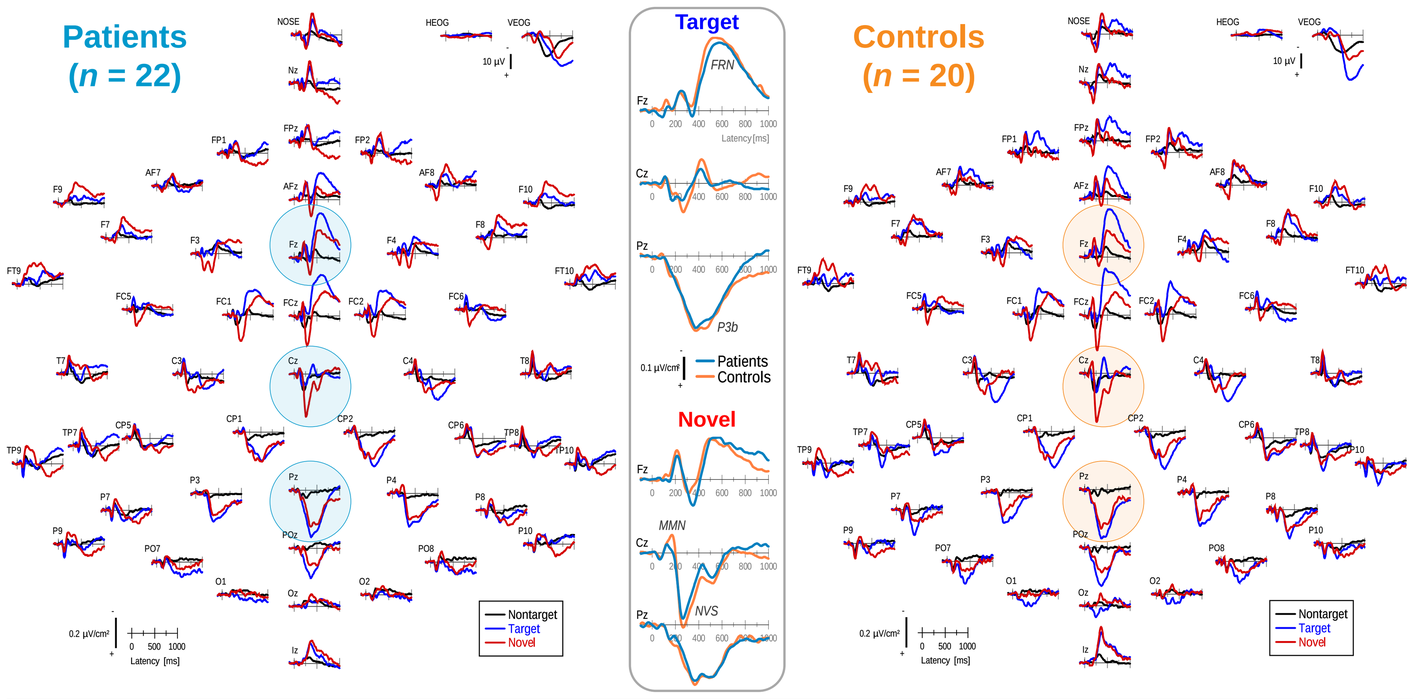
Fig. 1. Mean (SEM) percentage of correctly detected/rejected stimuli, the corresponding *d'*-like sensitivity measures d_L (no response bias; cf. Snodgrass & Corwin 1988), and response latency to targets. Statistics: Participants performed well on this task, and there were no significant differences between **prodromal patients** and **healthy controls** in any of these performance measures (all $F_{[1,38]} \leq 2.54$, all $p \geq .12$).

EEG/ERP Recording and Analysis

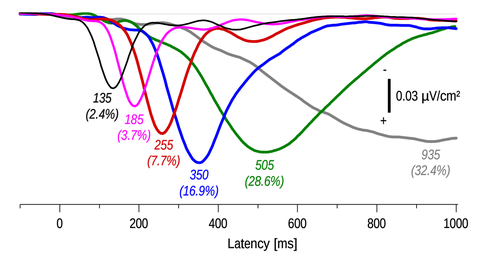


- EEG recorded from 49 scalp sites (nose reference, .01-30 Hz band pass, 200 samples/s)
- **spatial SVD blink reduction** (continuous EEG)
- **1200 ms epochs** (200 ms pre-stimulus)
- ERP averages (artifact-free trials) low pass filtered at 12.5 Hz (-24 dB/oct.), 100 ms baseline correction
- ***reference-free* current source densities (CSD)** (spherical splines surface Laplacian; Perrin et al 1989) computed for each ERP and EEG epoch (sharpen topographies, eliminate volume-conducted activity)
- **CSD-tPCA:** CSD-transformed ERPs submitted to ***unrestricted* temporal principal components analysis (tPCA)** [211 variables = stimulus-locked samples –100 to 1000 ms; 6174 observations = 42 *Subjects* x 49 *Recording Sites* x 3 *Conditions*], followed by Varimax rotation of covariance loadings (Kayser & Tenke 2003, 2006a,b)
- **CSD-tfPCA**: CSD-based event-related spectral perturbations (ERSP; Makeig 1993) obtained from CSD epochs via FFT power spectra (zero-padding ratio of 8) relative to the pre-stimulus baseline (Tenke & Kayser 2005; Tenke et al 2012); normalized ERS/ERD measures, reduced via bilinear interpolation to 30-by-82 matrices to reflect spectral (1 to 30 Hz) and temporal (-10 to 800 ms) ranges of interest, were rearranged as a vector by concatenating the time vectors for each frequency and submitted to ***unrestricted* time-frequency PCA (tfPCA)** [2460 variables = 30-by-82 ERD/ERS values; 6174 observations as above], followed by Varimax rotation of covariance loadings
- identify and measure **neuronal generator patterns** underlying novelty oddball ERPs and ERSPs from **meaningful, high-variance CSD factors** previously identified (Tenke et al 2010) or unambiguously related to alpha ERS or alpha ERD (Koh et al 2011)
- submit factor scores to **repeated measures ANOVA** with *group* (patients, controls) and *gender* (male, female) as between-subjects factors, and *condition* (target, novel) as a within-subjects factor (*hemisphere* and *site* to reflect CSD topography)

A Current Source Densities (CSD)



B CSD-tPCA Waveforms (Factor Loadings)



C CSD-tPCA Topographies (Factor Scores)

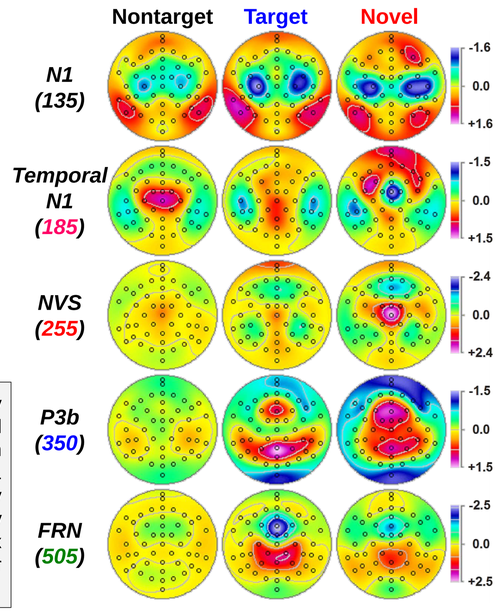
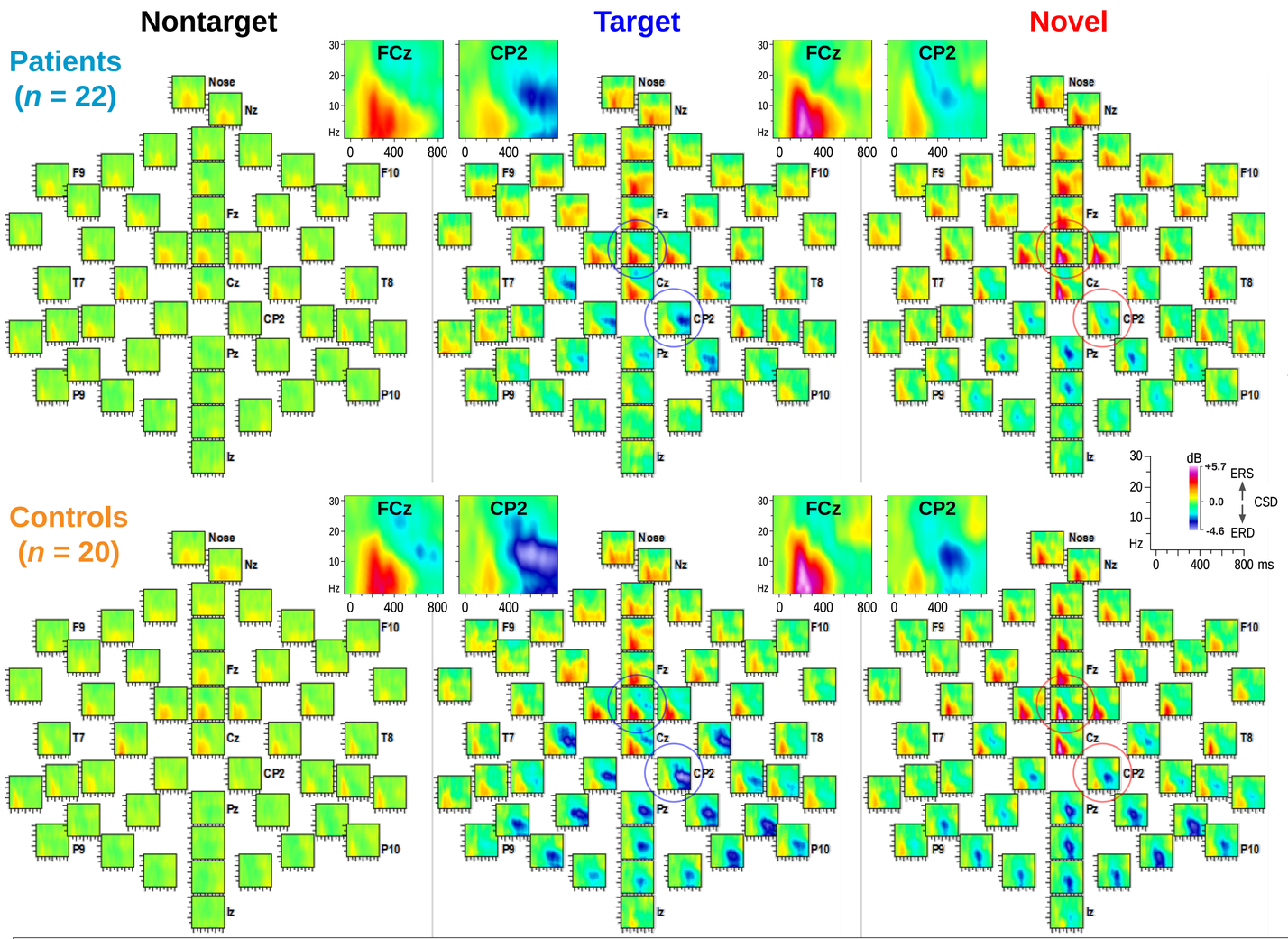
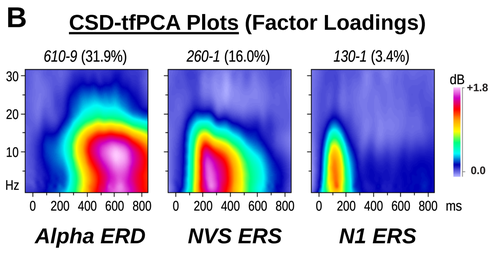


Fig. 2. (**A**) Grand mean surface Laplacian (CSD) waveforms for **CHR patients** and **healthy controls** revealing distinct CSD components, which included: novelty vertex source (NVS) and MMN for novels at site Cz; P3 source for targets at Pz (P3b); mid-frontal response negativity (FRN) for targets at Fz. Horizontal and vertical electrooculograms (EOG) are shown before blink correction. (**B**) Factor loadings of the first six temporal PCA (tPCA) factors (with explained variance) extracted from the time-locked CSD waveforms ($N = 42$). Factor labels reflect the peak latency [ms] of the factor loadings. (**C**) CSD factor score topographies corresponding to N1 sink (135 ms peak latency of factor loading), temporal N1 sink (185 ms), novelty vertex source (NVS; 255 ms), P3b source (350 ms), and frontal response negativity (FRN; 505 ms) comparing nontarget, target and novel stimuli (pooled across all 42 participants). Statistics: No significant group main effects were observed for any CSD component. However, the greater **MMN sink** for novels than targets at vertex (factor ***temporal N1*** [*185*]) was less robust for **patients** than **controls** (Group x Condition, $F_{[1,38]} = 4.29$, $p = .045$). Furthermore, the greater response-related centroparietal source for targets than novels (factor ***FRN*** [*505*]) was less robust for **patients** than **controls** (Group x Condition, $F_{[1,38]} = 4.13$, $p = .049$).

A Event-Related Spectral Perturbations (ERSP)



B CSD-tfPCA Plots (Factor Loadings)



C CSD-tfPCA Topographies (Factor Scores)

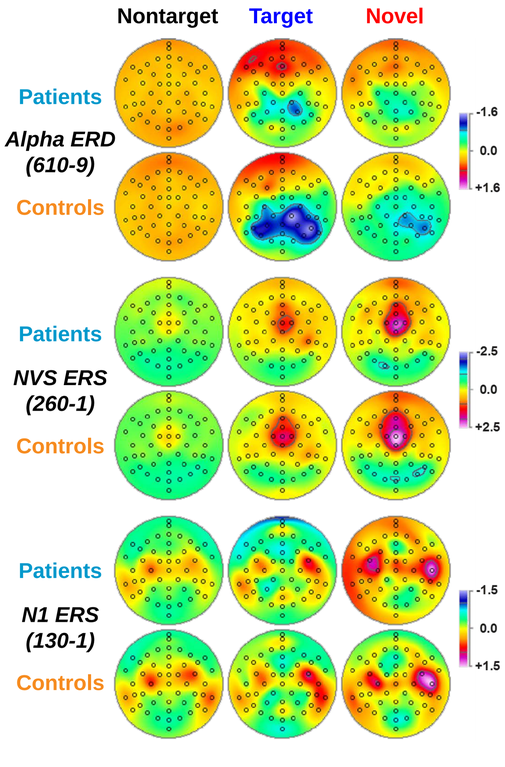


Fig. 3. (**A**) Grand mean surface Laplacian (CSD) event-related spectral perturbation (ERSP) plots (-10 to 800 ms; 1 to 30 Hz) at all 49 recording sites for **CHR patients** (top) and **healthy controls** (bottom) for each condition (nontarget, target, novel). Distinct event-related synchronization (ERS) for target and novel stimuli between 100 and 400 ms is evident for both groups at anterior sites (maximum at FCz). In contrast, event-related desynchronization (ERD) is most prominent for target stimuli between 400 and 800 ms over posterior sites (maximum at CP2), and appears to be reduced for patients compared to controls. (**B**) Factor loadings of three alpha-related time-frequency PCA (tfPCA) factors (with explained variance) extracted from the time-frequency CSD matrices ($N = 42$). Factor labels reflect both peak latency [ms] and peak frequency [Hz] of the factor loadings. (**C**) CSD factor score topographies corresponding to alpha event-related desynchronization (ERD; factor *610-9*), novelty vertex source (NVS) event-related synchronization (ERS; factor *260-1*), and N1 sink ERS (factor *130-1*) comparing nontarget, target and novel stimuli for 22 patients and 20 controls. Statistics: **Patients** had significantly reduced ***alpha ERD*** at right lateral centroparietal and parietal-occipital sites compared to **controls** (Group, $F_{[1,38]} = 5.63$, $p = .02$; Group x Hemisphere, $F_{[1,38]} = 9.26$, $p = .0005$). In contrast, there were no significant effects involving group for ***NVS ERS*** at mid-frontocentral or ***N1 ERS*** at lateral frontocentral and temporoparietal sites.

Observations for CHR Individuals with Transition to Psychosis

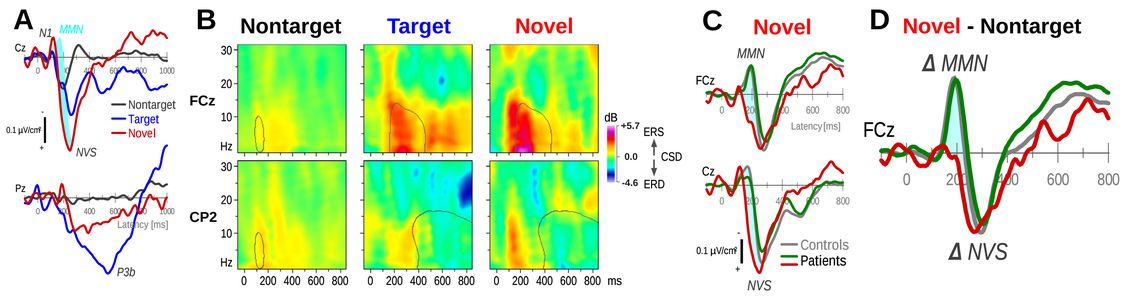


Fig. 4. (**A**) CHR individuals who developed threshold psychosis within a 4-year follow-up period ($n = 3$) had a prominent P3b source for targets at Pz and novelty vertex source (NVS) at Cz indicating robust condition effects, although the novelty MMN, which partially overlaps and follows N1 sink for the overall sample, is absent (cf. marked ***MMN*** area). (**B**) CSD-ERSP plots revealed that alpha ERD is virtually absent in converters, and alpha- and theta-related ERS associated with N1 and NVS is substantially reduced (contour lines depict tfPCA factor loadings [50% maximum; cf. Fig. 3B]). (**C**) Compared to **healthy controls** (gray lines) and CHR patients without (**nonconverters**; green lines) transition to psychosis, **converters** (red lines) lack the MMN sink preceding NVS for novels. (**D**) This reduction is particularly evident from the novel-minus-nontarget difference CSDs at FCz, which reveal a robust ***novelty MMN*** for **controls** and **nonconverters**, whereas ΔMMN is absent for three **converters**. Statistics: To better quantify these observations, and for descriptive purposes only, a post-hoc ANOVA was computed for ***novelty MMN*** (tPCA factor ***185*** at midfrontocentral sites) with 3 **converters**, 19 **nonconverters** and 20 **controls** as the only between-subjects factor, which confirmed greater MMN for novels than targets in **nonconverters** and **controls**, but not in **converters** (Group x Condition, $F_{[2,39]} = 6.73$, $p = .003$). Likewise, ***alpha ERD*** differed significantly between these groups (Group, $F_{[2,39]} = 3.56$, $p = .04$), stemming from a significant difference between **converters** and **controls** (Group, $F_{[1,39]} = 5.77$, $p = .02$), a marginal difference between **nonconverters** and **controls** ($F_{[1,39]} = 3.00$, $p = .09$), but no significant difference between **converters** and **nonconverters** ($F_{[1,39]} = 2.26$, $p = .14$). These parametric statistics were corroborated by the Approximate Degrees of Freedom (ADF) test, a robust multivariate *F* statistic for mixed designs when cell variances are heterogenous (Lix & Keselman 1995).

Summary and Conclusions

- Despite comparable novelty oddball task performance (Fig. 1), event-related desynchronization (ERD), as obtained by a *reference-free* time-frequency approach (CSD-tfPCA), was markedly reduced over right posterior regions for targets in CHR patients compared to healthy controls (Fig. 3).
- In contrast, low-frequency event-related synchronization (ERS) distinctly linked to novels (mid-frontal) and N1 sink across conditions (centro-temporoparietal) did not differ between groups (Fig. 3).
- Analogous time-domain measures (CSD-tPCA), replicating prior findings (Tenke et al 2010) and consisting of N1 sink, novelty mismatch negativity (MMN), novelty vertex source (NVS), novelty P3, P3b, and frontal response negativity (FRN), were robust and closely comparable between groups (Fig. 2).
- Novelty MMN and alpha ERD were virtually absent in three CHR patients who developed threshold psychosis (Fig. 4).
- The available preliminary data from three converters (Fig. 4) is extremely encouraging as this suggests that, in agreement with prior findings (e.g., Koh et al 2011; Atkinson et al 2012), alpha ERD and MMN may hold particular promise for predicting transition to psychosis among CHR patients.
- Event-related modulation of alpha has been hypothesized to reflect inhibitory cortical control (e.g., Uhlhaas & Singer 2010), with reduced alpha ERD indicative of impaired task-related coordination of cortical networks (Klimesch et al 2007), thereby implicating cognitive deficits of top-down processing (Koh et al 2011). Interestingly, another recent MEG study (Popov et al 2012) found that alpha ERD normalized in schizophrenia after cognitive training and was associated with improved verbal memory performance.

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