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Auditory event-related potentials and alpha oscillations in the psychosis prodrome: Neuronal generator patterns during a novelty oddball task

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ABSTRACT

Prior research suggests that event-related potentials (ERP) obtained during active and passive auditory paradigms, which have demonstrated abnormal neurocognitive function in schizophrenia, may provide helpful tools in predicting transition to psychosis. In addition to ERP measures, reduced modulations of EEG alpha, reflecting top-down control required to inhibit irrelevant information, have revealed attentional deficits in schizophrenia and its prodromal stage. Employing a three-stimulus novelty oddball task, nose-referenced 48-channel ERPs were recorded from 22 clinical high-risk (CHR) patients and 20 healthy controls detecting target tones (12% probability, 500 Hz; button press) among nontargets (76%, 350 Hz) and novel sounds (12%). After current source density (CSD) transformation of EEG epochs (−200 to 1000 ms), event-related spectral perturbations were obtained for each site up to 30 Hz and 800 ms after stimulus onset, and simplified by unrestricted time–frequency (TF) principal components analysis (PCA). Alpha event-related desynchronization (ERD) as measured by TF factor 610–9 (spectral peak latency at 610 ms and 9 Hz; 31.9% variance) was prominent over right posterior regions for targets, and markedly reduced in CHR patients compared to controls, particularly in three patients who later developed psychosis. In contrast, low-frequency event-related synchronization (ERS) distinctly linked to novels (260–1; 16.0%; mid-frontal) and N1 sink across conditions (130–1; 3.4%; centro-temporoparietal) did not differ between groups. Analogous time-domain CSD-ERP measures (temporal PCA), consisting of N1 sink, novelty mismatch negativity (MMN), novelty vertex source, novelty P3, P3b, and frontal response negativity, were robust and closely comparable between groups. Novelty MMN at FCz was, however, absent in the three converters. In agreement with prior findings, alpha ERD and MMN may hold particular promise for predicting transition to psychosis among CHR patients.

1. Introduction

For most individuals affected by schizophrenia, the first onset of symptoms is preceded by a prodromal period characterized by attenuated psychotic symptoms, anxiety, social and role dysfunction, and affective symptoms (Häfner et al., 2003). Early recognition of individuals who later develop psychosis holds the promise of preventing or delaying onset through early intervention (e.g., Corcoran et al., 2010). However, despite considerable efforts in studying individuals at clinical high risk (CHR) for psychosis (see Fusar-Poli et al., 2013, for a recent review), little is known about the underlying pathophysiology of emerging psychosis.

1.1. Neurophysiologic abnormalities in the psychosis prodrome

A multitude of neurophysiologic abnormalities have been documented in schizophrenia (e.g., Luck et al., 2011), some of which may potentially be used as translational biomarkers for drug discovery (e.g., Javitt et al., 2008). These abnormalities include electroencephalography (EEG) measures obtained in the time domain, notably event-related potentials (ERPs) that index neuronal functions ranging from early sensory (e.g., P1, N1) to late cognitive (e.g., P3) processing, or in the frequency domain, including power spectra that index attentional control (e.g., alpha) or binding of perceptual features (e.g., gamma). Initially, high expectations had been placed in the almost ubiquitous reduction of P3 amplitude, which has been associated with negative symptoms and may serve both as a state and trait marker of schizophrenia (e.g., Mathalon et al., 2000); however, a decrease in P3 amplitude is not specific to the disorder and is often observed, for example, in alcoholism, depression, bipolar disorder, or Alzheimer's disease (e.g., Ford, 1999). Still, P3 reductions and other neurophysiologic deficits have also been observed in unaffected relatives and first-episode patients

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(e.g., Bramon et al., 2005; Ford, 1999; Hirayasu et al., 1998; Michie, 2001; Turetsky et al., 2000; van der Stelt et al., 2005; Winterer et al., 2003), suggesting that certain electrophysiologic measures may be candidate risk biomarkers that may identify individuals at risk for schizophrenia (e.g., Luck et al., 2011).

A promising line of research has recently implicated various neurophysiologic measures obtained during active and passive *auditory* paradigms as potential tools in predicting transition to psychosis (Atkinson et al., 2012; Bodatsch et al., 2011; Frommann et al., 2008; Higuchi et al., 2013; Jahshan et al., 2012; Koh et al., 2011; Murphy et al., 2013; Shaikh et al., 2012; van der Stelt et al., 2005; van Tricht et al., 2010). Interestingly, while cognitive impairments in schizophrenia are typically studied with visual paradigms (e.g., Barch and Smith, 2008; Barch et al., 2009, 2012), neurophysiologic abnormalities are often more common or more pronounced in the auditory than visual modality (e.g., Egan et al., 1994; Ford et al., 1994; Ford, 1999; Kayser et al., 2009; Pfefferbaum et al., 1989). Deficits in auditory mismatch negativity (MMN), a preattentive measure of auditory change detection, have rather consistently been found in schizophrenia (e.g., Javitt et al., 2008; Michie, 2001), and this electrophysiologic measure has been considered a promising biomarker candidate to indicate transition to psychosis (e.g., Luck et al., 2011).

In one of the first neurophysiologic studies of psychosis risk, van der Stelt et al. (2005) employed an auditory target detection (oddball) task and found that CHR patients ($n = 10$) had reduced P3 amplitudes at parietal, centroparietal and central scalp sites when compared with age- and sex-matched controls. In other cross-sectional studies, Bramon et al. (2008) and Özgürdal et al. (2008) reported moderately reduced P3 in CHR patients ($n = 35$ and $n = 54$, respectively) when compared to controls, and Frommann et al. (2008) observed a widespread reduction of P3 in a large sample of CHR patients studied during an early ($n = 50$) or late ($n = 50$) initial prodromal state. In a longitudinal design, van Tricht et al. (2010) observed reduced target P3b in 18 CHR patients who later developed psychosis. Although none of these studies reported a reduction of auditory N1 amplitude in CHR patients, several cross-sectional studies observed reductions in MMN, showing that CHR individuals had reduced MMN amplitude to deviant tones differing from standard 1000-Hz tones in stimulus duration (Atkinson et al., 2012; Hsieh et al., 2012; Jahshan et al., 2012; Murphy et al., 2013; Shin et al., 2009). Studies that directly compared individuals with or without subsequent transition to psychosis found MMN reductions to be more severe or only present in those patients who later developed psychosis (Bodatsch et al., 2011; Higuchi et al., 2013; Shaikh et al., 2012). Brockhaus-Dumke et al. (2005) found only a non-significant MMN reduction in CHR patients, which was intermediate between controls and schizophrenia patients. As in schizophrenia, MMN deficits in CHR patients appear to be more robust for deviations in tone duration rather than pitch, and may also only be present in low but not high functioning patients (Hay et al., 2013).

Atkinson et al. (2012) also reported that an early P3 subcomponent with a frontocentral distribution, termed P3a, was reduced in CHR individuals, but this deficit was unrelated to MMN reductions. Reduced amplitudes of duration MMN and P3a have also been found in 17 first-episode patients, underscoring the potential phenotype value of both EEG measures (Hermens et al., 2010). Of interest, Salisbury et al. (2002) found reduced MMN to deviations in pitch for chronic schizophrenia ($n = 16$) but not for 21 first-episode patients, suggesting that MMN to deviations of tone duration reflect different aspects of neurophysiological processing. Notably, most of this ERP research in schizophrenia and CHR patients has relied on standard two-tone paradigms, but P3a is particularly evident to perceptually novel distractors embedded in a series of frequent nontarget and infrequent target stimuli, and has therefore been termed novelty P3 (Polich, 2007). In such a three-stimulus oddball task (Friedman et al., 1993), novelty P3 and P3b can be readily distinguished by their topographic differences (mid-frontocentral vs. mid-parietal maximum) *and* condition dependencies. Although a novelty oddball paradigm has previously been employed in schizophrenia using ERP (e.g., Mathalon et al., 2010) or functional magnetic resonance imaging (fMRI) measures (e.g., Laurens et al., 2005), with the former study failing to observe differential deficits of P3a and P3b and the latter suggesting that patients less efficiently divide processing resources between detecting and responding to the task-relevant target tones and reorienting and ignoring task-irrelevant novel sounds, to our knowledge, there are no such studies involving CHR patients.

In recent years, there has also been an increasing interest in abnormal neural oscillations in schizophrenia (e.g., Uhlhaas et al., 2008; Uhlhaas and Singer, 2010). Stimulus-induced or event-related changes in ongoing rhythmic EEG activity substantially contribute to the observed ERP components (e.g., Gruber et al., 2005; Makeig et al., 2002; Sauseng et al., 2007). Neurophysiologic techniques involving EEG or magnetoencephalography (MEG) provide high-temporal resolution and are therefore ideal for assessing oscillatory activation. However, the averaging process underlying ERPs generally prevents the study of neural oscillations (e.g., Pfurtscheller and Lopes da Silva, 1999). Several spectral decomposition approaches allow the study of event-related EEG oscillations that are poorly represented or absent in ERPs (e.g., Roach and Mathalon, 2008, for a review). Most of the time–frequency EEG research in schizophrenia has focused on high-frequency (i.e., beta and gamma) modulations (e.g., Ford et al., 2008; Spencer et al., 2003, 2004; Uhlhaas and Singer, 2010). Nonetheless, low-frequency modulations involving alpha and theta bands are associated with working memory, attention, inhibition and top-down cognitive control (Uhlhaas and Singer, 2010, for a review), functional domains that are the hallmark of cognitive impairments in schizophrenia (e.g., Barch and Smith, 2008).

Few studies in schizophrenia and individuals at risk have investigated reductions of alpha or theta activity as a function of cognitive performance. Among them, Higashima et al. (2007), using an auditory oddball paradigm, found that healthy controls showed a relative reduction in alpha power to targets compared with nontargets that was markedly reduced in schizophrenia patients. This reduction was unrelated to the observed reduction of P3 amplitude in patients, suggesting that alpha desynchronization indexes a different aspect of cognitive processing. More recently, a magnetoencephalography study by Koh et al. (2011) reported diminished alpha event-related desynchronization to target tones in 17 CHR individuals, which was intermediate between that of schizophrenia patients ($n = 10$) and healthy controls ($n = 18$).

1.2. The present study

Given prior evidence of P3a and/or P3b (e.g., Atkinson et al., 2012; Frommann et al., 2008) and alpha event-related desynchronization (Koh et al., 2011) abnormalities in CHR patients, we sought to study these time and time–frequency measures concurrently in a novelty oddball paradigm (Bruder et al., 2009). We employed a generic strategy for ERP analysis, which combines current source density (CSD) transformations of surface potentials with principal components analysis (PCA) to yield data-driven and physiologically-meaningful component estimates (e.g., Kayser and Tenke, 2003, 2006a, 2006b). This approach improves on conventional ERP analysis by obtaining unique ERP component measures that are independent of the EEG recording reference (cf. Kayser and Tenke, 2010), while also having an unambiguous polarity and sharper topography (Tenke and Kayser, 2012). This approach also addresses the spatial smearing of the EEG at scalp by volume conduction, which may lead to spurious EEG coherence (e.g., Fein et al., 1988; Guevara et al., 2005; Roach and Mathalon, 2008; Schiff, 2005), although these issues have an even wider impact on EEG spectral analysis (cf. Fig. 1 in Tenke and Kayser, 2005). For these reasons, the present study extends the temporal (e.g., Kayser and Tenke, 2006a) and frequency (e.g., Tenke and Kayser, 2005) CSD-PCA approach to time–frequency EEG analysis in an effort to confirm the MEG findings of Koh et al. (2011), which are also, by virtue of the imaging technique, unaffected