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Olfaction in the psychosis prodrome: Electrophysiological and behavioral measures of odor detection

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ABSTRACT

Smell identification deficits (SIDs) are relatively specific to schizophrenia and its negative symptoms, and may predict transition to psychosis in clinical high-risk (CHR) individuals. Moreover, event-related potentials (ERPs) to odors are reduced in schizophrenia. This study examined whether CHR patients show SIDs and abnormal olfactory N1 and P2 potentials. ERPs (49 channels) were recorded from 21 CHR and 20 healthy participants (13 males/group; ages 13–27 years) during an odor detection task using three concentrations of hydrogen sulfide (H_2S) or blank air presented unilaterally by a constant-flow olfactometer. Neuronal generator patterns underlying olfactory ERPs were identified and measured by principal components analysis (unrestricted Varimax) of reference-free current source densities (CSD). Replicating previous findings, CSD waveforms to H_2S stimuli were characterized by an early N1 sink (345 ms, lateral–temporal) and a late P2 source (600 ms, mid-frontocentroparietal). N1 and P2 varied monotonically with odor intensity (strong > medium > weak) and did not differ across groups. Patients and controls also showed comparable odor detection and had normal odor identification and thresholds (Sniffin' Sticks). However, olfactory ERPs strongly reflected differences in odor intensity and detection in controls, but these associations were substantially weaker in patients. Moreover, severity of negative symptoms in patients was associated with reduced olfactory ERPs and poorer odor detection, identification and thresholds. Three patients who developed psychosis had poorer odor detection and thresholds, and marked reductions of N1 and P2. Thus, despite the lack of overall group differences, olfactory measures may be of utility in predicting transition to psychosis among CHR patients.

1. Introduction

Schizophrenia is a chronic illness with an onset of symptoms typically occurring early in life (i.e., during young adulthood). Before a first onset of psychosis, a prodromal period occurs in over 70% of schizophrenia cases (Häfner et al., 2003), which is characterized by attenuated psychotic symptoms, anxiety, social and role dysfunction, and affective symptoms. In the hope of reducing morbidity and preventing or delaying onset through early intervention, current efforts aim at identifying young people at risk during this prodromal stage (e.g., Corcoran et al., 2010; Fusar-Poli et al., 2012b). Little is known, however, about the underlying pathophysiology of emerging psychosis. A large multisite study (Cannon et al., 2008) that followed individuals at clinical high risk (CHR) for psychosis for 2.5 years reported that certain clinical characteristics assessed at baseline predicted psychosis, including genetic risk with recent functional decline, positive symptom severity, social impairment and substance abuse; however, no psychophysiological measures were included. These findings are consistent with previous studies which identified as predictors poor role function, earlier onset, and longer duration and greater severity of prodromal symptoms (Amminger et al., 2006; Haroun et al., 2006; Yung et al., 2004). Although less impaired than schizophrenia, CHR patients have generalized neuropsychological deficits (Brewer et al., 2006; Hawkins et al., 2004; Woodberry et al., 2010), and verbal memory deficits may be a predictor of psychosis (Brewer et al., 2005; Lencz et al., 2006; Woodberry et al., 2010). A promising line of research has recently implicated various electrophysiologic measures obtained during active and passive auditory paradigms as helpful tools in predicting transition to psychosis (Atkinson et al., 2012; Bodatsch et al., 2011; Frommann et al., 2008; Koh et al., 2011; Shaikh et al., 2012; van der Stelt et al., 2005; van Tricht et al., 2010). However, only smell identification deficits have been shown to discern whom among high-risk cases will specifically develop schizophrenia and its spectrum disorders (Brewer et al., 2003), which is in agreement with evidence showing that impairments in odor identification are present before individuals develop psychotic symptoms (Woodberry et al., 2010). Moreover, a cross-sectional study found that CHR individuals were

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impaired not only in odor identification but also in odor discrimination, with both deficits being comparable to schizophrenia patients (Kamath et al., 2011).

1.1. Olfactory deficits in schizophrenia

Deficits of olfactory function are common in schizophrenia, affecting threshold sensitivity, discrimination and identification of odors (e.g., reviewed by Moberg et al. (1999) and Moberg and Turetsky (2003)). Although olfactory abnormalities have also been found in several neurological diseases (Barresi et al., 2012) and other psychiatric disorders (Buron & Bulnena, 2013; Schecklmann et al., 2013), most research in this area has been performed in schizophrenia (Atanasova et al., 2008). Studies using psychophysical measures of odor identification have consistently demonstrated that schizophrenia patients, when compared to healthy controls, have a robust impairment in correctly naming or identifying different odors (Cohen et al., 2012a; Kamath et al., 2011). This deficit in odor identification is not due to increased odor detection threshold (Moberg et al., 2006), the findings for which have been less consistent (Martzke et al., 1997; Moberg et al., 1999; Purdon and Flor-Henry, 2000). Moreover, it has been suggested that smell identification deficits are relatively specific to schizophrenia (Hurwitz et al., 1988) and its negative symptoms (Malaspina and Coleman, 2003), including in young people with psychotic disorders (Corcoran et al., 2005), which cannot be accounted for by cognitive impairment (Seidman et al., 1991, 1997), socioeconomic status, smoking or medication (Coleman et al., 2002; Malaspina and Coleman, 2003; Turetsky et al., 2003b). Interestingly, unaffected relatives of schizophrenia patients also showed poorer smell identification (Kopala et al., 2001; Turetsky et al., 2008) and elevated odor thresholds, which were intermediate between patients and controls (Roalf et al., 2006). Although these data suggest a genetic component, there has been some controversy about the extent to which olfactory identification deficits may constitute a meaningful, broader vulnerability marker of schizophrenia pathology (Cohen et al., 2012a,b; Turetsky et al., 2012).

Given the functional anatomy of human olfactory pathways (e.g., Martzke et al., 1997; Seubert et al., 2013), olfactory deficits likely originate from brain structures in medial temporal lobe regions and orbitofrontal and dorsolateral prefrontal cortex linked to olfactory as well as cognitive and emotional disturbances in schizophrenia (e.g., Atanasova et al., 2008), and may help elucidate limbic system dysfunctions (Moberg et al., 2003). Thus, decreased olfactory threshold sensitivity in schizophrenia patients was associated with reduced volume in the perirhinal, but not entorhinal, region of the anterior ventromedial temporal lobe (Turetsky et al., 2003b), and both patients and their healthy relatives had reduced olfactory bulb volumes compared to healthy controls (Turetsky et al., 2003c). Also, Rupp et al. (2005) reported that poorer olfactory discrimination in schizophrenia patients was related to smaller hippocampal volumes, but not volumes in the orbitofrontal region. However, given that olfactory deficits have been observed across several neuropsychiatric and neurodegenerative disorders, including Parkinson's and Alzheimer's disease, it has been proposed that some aspects of impaired odor processing may share a common dopaminergic pathology, which may affect neurotransmission in the olfactory bulbs (Schecklmann et al., 2013). This is of particular interest given the refined dopamine hypothesis of schizophrenia (e.g., Howes and Kapur, 2009) and evidence that dopaminergic abnormalities precede psychosis onset (Egerton et al., 2013; Howes et al., 2011).

Nonetheless, reports of behavioral deficits in olfactory function and structural abnormalities in the olfactory system in schizophrenia offer limited insights into the relevant brain activity. Recent functional magnetic resonance imaging (fMRI) evidence in healthy adults suggests that odor identification, as opposed to smelling of nonidentified odors, is specifically associated with activity of entorhinal cortex and hippocampus (Kjelvik et al., 2012), but it remains to be seen whether these structures can be linked to smell identification deficits in schizophrenia. While functional imaging methods (e.g., PET, SPECT, fMRI) have shown decreased activation in schizophrenia in limbic as well as frontal and temporal regions in response to olfactory cues (e.g., Crespo-Facorro et al., 2001; Malaspina et al., 1998; Schneider et al., 2007), only electrophysiological correlates of information processing, with far greater temporal resolution, can provide direct, 'real-time' measures of olfactory function in schizophrenia and its risk states. Because event-related potentials (ERPs) trace the sequence of information processing by indexing neuronal activity, ERP components (e.g., N1, P2, P3), time-locked to the onset of sensory events, reflect brain activity representative of the underlying neurophysiologic processes associated with successive stages of stimulus information processing. These characteristics, in combination with their cost-effectiveness and development of advanced data analytic techniques, have been recognized as offering unique opportunities to identify and study translational biomarkers in schizophrenia (e.g., Javitt et al., 2008).

1.2. Neurophysiologic abnormalities in the psychosis prodrome

There is ample evidence of neurophysiologic abnormalities in schizophrenia and unaffected relatives for processing auditory or visual stimuli, although prominent ERP reductions, such as the decrease in P3 amplitude, are not specific to schizophrenia (e.g., Ford, 1999; Javitt et al., 2008; Winterer et al., 2003). Of relevance for high risk studies, P3 amplitude reduction has elements of being both a state and trait marker of schizophrenia (e.g., Mathalon et al., 2000). In CHR patients, several studies have reported abnormalities of auditory P3 amplitude (e.g., Frommann et al., 2008; van Tricht et al., 2010; van der Stelt et al., 2005) and duration mismatch negativity (e.g., Atkinson et al., 2012; Bodatsch et al., 2011; Shaikh et al., 2012), as well as for visual ERPs during recognition of facial affect (e.g., Wölwer et al., 2012), which has been linked to odor identification in schizophrenia (Kohler et al., 2007).

In contrast to electrophysiologic studies probing the auditory and visual modality, olfactory ERPs have rarely been used due to methodological challenges linked to the precise timing of odor stimulation (e.g., Lorig, 2000), but the limited evidence suggests that abnormal olfactory ERPs may be a vulnerability marker for schizophrenia. Compared to healthy controls, schizophrenia patients showed reduced N1 and P2 amplitudes to three different concentrations of hydrogen sulfide (H_2S) despite similar ratings of odor intensity (Turetsky et al., 2003a), and similar reductions of N1 (left nostril only) and P2 (bilaterally) were observed in first degree relatives of patients with schizophrenia (Turetsky et al., 2008). Moreover, family members had increased odor detection thresholds for the left nostril, and showed poorer odor identification for both nostrils as measured by the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al., 1984), thereby supporting smell identification deficit as a candidate endophenotype for schizophrenia (Brewer et al., 2003). Using an odor detection task with two concentrations of H_2S, we replicated and extended olfactory ERP findings for schizophrenia patients (Kayser et al., 2010). The patients ($n = 32$) showed regional amplitude reductions of N1 over inferior frontotemporal sites and of P2 over medial parietal sites, despite patients having similar odor detection performance as healthy controls ($n = 35$).

Olfactory ERPs have not yet been evaluated in CHR patients, namely help-seeking young people with attenuated psychotic symptoms and/or functional decline in the context of genetic risk. For "persons at risk" identified within a sample of 948 young adults who scored in the uppermost deciles on German scales for physical anhedonia and/or perceptual aberration, Becker et al. (1993) reported a reduction in P1/N1 peak-to-peak amplitude at vertex after left nostril stimulation with H_2S. However, although this early study provided some evidence for an abnormality in processing of odor stimuli