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Reduced auditory segmentation potentials in first-episode schizophrenia

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ABSTRACT

Auditory scene analysis (ASA) dysfunction is likely an important component of the symptomatology of schizophrenia. Auditory object segmentation, the grouping of sequential acoustic elements into temporally-distinct auditory objects, can be assessed with electroencephalography through measurement of the auditory segmentation potential (ASP). Further, N2 responses to the initial and final elements of auditory objects are enhanced relative to medial elements, which may indicate auditory object edge detection (initiation and termination). Both ASP and N2 modulation are impaired in long-term schizophrenia. To determine whether these deficits are present early in disease course, we compared ASP and N2 modulation between individuals at their first episode of psychosis within the schizophrenia spectrum (FE, N = 20) and matched healthy controls (N = 24). The ASP was reduced by >40% in FE; however, N2 modulation was not statistically different from HC. This suggests that auditory segmentation (ASP) deficits exist at this early stage of schizophrenia, but auditory edge detection (N2 modulation) is relatively intact. In a subset of subjects for whom structural MRIs were available (N = 14 per group), ASP sources were localized to midcingulate cortex (MCC) and temporal auditory cortex. Neurophysiological activity in FE was reduced in MCC, an area linked to aberrant perceptual organization, negative symptoms, and cognitive dysfunction in schizophrenia, but not temporal auditory cortex. This study supports the validity of the ASP for measurement of auditory object segmentation and suggests that the ASP may be useful as an early index of schizophrenia-related MCC dysfunction. Further, ASP deficits may serve as a viable biomarker of disease presence.

1. Introduction

Perceptual deficits have been recognized as a hallmark of schizophrenia since the initial classification of the disorder by Kraepelin >100 years ago (Kraepelin, 1987). They are present before emergence of psychotic symptoms (Cornblatt and Erlenmeyer-Kimling, 1985; Davidson et al., 1999), persist throughout life (Rund, 1998), and are related to functional outcome (Niendam et al., 2006; Uhlhaas and Silverstein, 2005). Neurophysiology of auditory perceptual deficits in schizophrenia has traditionally been characterized by reduced auditory event-related potentials (ERPs), such as P50 and N100 (Javitt, 2009), and reductions in mismatch negativity (MMN), which has been linked to functional outcome and disease burden (Klosterkötter et al., 2001; Light and Braff, 2005). MMN appears with the presentation of stimuli that deviate from an established/predicted pattern of physical sound characteristics such as pitch and duration, independent of attention to the stimuli being presented. MMN reductions have been heavily studied over the past 20 years, and converging evidence suggests that reductions in the MMN develop over the disease course in schizophrenia. Yet, deficits in MMN responses to pitch changes are not identified at first psychotic episode in schizophrenia (Haigh et al., 2017). It is thus unclear if pitch MMN is suitable as a pre-psychosis biomarker of disease presence. However, deficits in MMN response to deviation from temporal expectancy (i.e. tone duration) seem to be somewhat more reliable at first psychotic episode, suggesting that deficits in predictive modeling of temporal parameters may suffer prior to deficits in modeling of frequency (Haigh et al., 2017). In recent years, more complex auditory perceptual paradigms have been investigated in an attempt to identify such a biomarker. For example, MMN can be detected in response to deviation from complex pattern rules, such as changes in the number of tones (Haigh et al., 2016; Rudolph et al., 2015; Salisbury, 2012), or pitch relationships between tones (Saarinen et al., 1992; Zuijen et al., 2004). Importantly, this type of deviance detection relies on the perceptual organization of auditory patterns in the auditory scene. To detect complex pattern deviance, the brain must first identify relationships among pattern elements and segment the auditory scene into distinct auditory objects. Representations of auditory objects are then used as a predictive model to be validated or revised upon presentation of subsequent auditory objects. More generally, auditory objects are

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important for downstream processing of auditory information in association with the other senses, and for guiding behavior (Nelken et al., 2014).

The process of segmenting the auditory scene into discrete auditory objects, termed auditory scene analysis (ASA), is a late perceptual process accomplished through segregation of multiple sound sources, integration of concomitant acoustic elements, and grouping of patterned auditory sequences into auditory objects (Bregman, 1994). All of these facets are disrupted in long-term schizophrenia, as demonstrated by studies of auditory stream segregation (Ramage et al., 2012; Silverstein et al., 1996; Weintraub et al., 2012) and acoustic pattern segmentation based on rhythmic regularities (Coffman et al., 2016). Using ERPs, we recently identified two reliable neurophysiological correlates of auditory object segmentation in subjects passively listening to acoustic patterns. First, N2 amplitude is greater (more negative) in response to initial and final sequence elements compared to medial elements of the auditory object (Coffman et al., 2016). The N2 is an ERP occurring approximately 200 ms after stimulus onset that traditionally reflects stimulus classification. In the context of acoustic pattern segmentation, N2 amplitude modulation for initial and final elements of the auditory object may reflect the identification of object initiation and termination/closure, termed auditory object "edge" detection by Chait et al. (2008). Second, healthy subjects show a reliable sustained ERP in response to groups/patterns of auditory stimuli that persists for the duration of the pattern before returning to baseline shortly thereafter (Coffman et al., 2016). This response, which we now label the auditory segmentation potential (ASP), is correlated with auditory edge detection (N2 modulation) and intellectual function (IQ) (Coffman et al., 2016). We hypothesize that the ASP represents the segmentation of auditory objects from patterned acoustic stimuli in the auditory scene, and that deficits in this response will be identifiable early in the disease course, at first episode of psychosis.

The ASP is closely related to other auditory-evoked sustained responses that have been previously identified. Sustained potentials in response to long-duration single tones were among the earliest auditory-evoked potentials to be identified (Köhler et al., 1952). These responses occur when tone duration is longer than 600 ms, and normally co-occur with onset and offset potentials (N1/P2 complex) that track the edges of the auditory tone burst (Picton et al., 1978a, 1978b). Interestingly, sustained potentials elicited by long-duration tones are facilitated if participants are instructed to attend the duration, but not the intensity or warble of the tones, suggesting a role in temporal expectancy (Picton et al., 1978b). Further, sustained potentials/fields have also been identified in response to abutting short-duration tone pips, and these potentials/fields are enhanced when regular frequency patterns are presented (Auksztulewicz et al., 2017; Barascud et al., 2016; Southwell et al., 2017). The ASP is similar to these previously-identified sustained responses in that (1) the ASP is generated in response to auditory objects with long duration, but the stimuli used to elicit the ASP are not themselves sustained, and (2) it is generated in response to predictable patterns of stimulation, but the tone pip sequences used to generate the ASP are not abutting. Rather, stimuli presented with long (280 ms) inter-stimulus interval (ISI) and even longer (750 ms) inter-trial interval (ITI), giving the perception of temporally-discrete groups of temporally-distinct tones.

We previously reported reductions of the ASP and the initial/final tone N2 response in schizophrenia in two experiments of sequential auditory pattern perception (Coffman et al., 2016). Here, we extend these findings by examining the neurophysiology of auditory pattern perception in individuals at their first episode of schizophrenia-spectrum psychosis. Further, we implemented an auditory pattern task in this study that is of significantly shorter duration compared to our previous experiments and utilizes patterns that are recognizable only by temporal regularity and not by frequency pattern. This abbreviated auditory pattern task was used in order to improve the clinical utility of the neurophysiological responses identified here as tools for early identification of auditory perceptual deficits. Further, we collected structural MRI in a subset of participants to afford distributed source modeling of the ASP based on individual realistic head models.

2. Materials and methods

2.1. Participants

Participants included 20 individuals within six months of their initial contact with clinical services for help seeking at their first episode of psychosis within the schizophrenia spectrum (FE) and 24 healthy control subjects. T1-weighted structural MRIs were acquired for 14 FE and 14 controls, permitting analysis of cortical source activity. In both the overall sample and the smaller subsample of subjects with available MRIs, groups were matched for age, gender, IQ, and parental social economic status (Table 1).

All participants completed the MATRICS Cognitive Consensus Battery (MCCB) and the Wechsler Abbreviated Scale of Intelligence (WASI). The 4-factor Hollingshead Scale was used to measure socioeconomic status (SES) of the participants and their parents (Table 1). All participants had normal hearing as assessed by audiometry, at least nine years of education, and an estimated IQ over 85. None of the participants had a history of concussion or traumatic brain injury with sequelae, history of alcohol or drug addiction, detox in the last five years, or neurological or psychiatric comorbidity. Participants received $50 for participation. The study was approved by the University of Pittsburgh IRB.

Schizophrenia-spectrum diagnosis was confirmed approximately six months after completing the experiment (≥6 months after initial clinical interview). Ten FE were diagnosed with schizophrenia (paranoid = 8, undifferentiated = 2), two with schizoaffective disorder (depressed subtype), five with psychotic disorder not otherwise specified (NOS), and three were lost to follow-up resulting in a final diagnosis of schizophreniform disorder. Diagnosis was based on the Structured Clinical Interview for DSM-IV (SCID-P). Symptoms were rated using the Positive and Negative Symptom Scale (PANSS), Scale for Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS). Psychosocial functioning was assessed using the brief UCSD Performance-based Skills Assessment (UPSA-B) (Table 1). All tests were conducted by an expert diagnostician. FE participants were medicated and moderately symptomatic.

2.2. Procedures

Electroencephalography (EEG) was recorded while participants watched a silent video. Binaural tones created with Tone Generator (NCH) were presented using Presentation (Neurobehavioral Systems) over Etymotic 3A insert earphones, with loudness (75 dB) confirmed by sound meter. Trials consisted of groups of three tones (450 trials [1350 tones], 1 kHz, 50 ms pips with 5 ms rise/fall times, 330 ms stimulus onset asynchrony [SOA], and 280 ms inter-stimulus interval (ISI)) separated by a 750 ms inter-trial interval (ITI). Thus, the duration of the auditory sequence (from onset to offset) was 710 ms. Deviant four-tone trials (50 trials) were also presented, but are not discussed here. These trials had the same physical characteristics as frequent trials (frequency, duration, SOA, ITI), but contained an extra fourth tone.

2.3. Magnetic resonance imaging

For a subset of participants, a T1-weighted structural MRI was obtained for anatomic localization of the ASP response. Contiguous slices were acquired in the sagittal plane with 1 mm^3 voxel resolution (TR/TE/TI(ms) = 2530/1.74, 3.6, 5.46, 7.32/1260, 7° flip angle, 256 × 256 × 176 acquisition matrixes, FOV = 256 × 256 mm, GRAPPA acceleration factor = 2). Using FreeSurfer (Dale et al., 1999), MRI volumes were segmented into triangular surface meshes representing the scalp, outer

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