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Event-Related Potentials Demonstrate Deficits in Acoustic Segmentation in Schizophrenia

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Abstract

Segmentation of the acoustic environment into discrete percepts is an important facet of auditory scene analysis (ASA). Segmentation of auditory stimuli into perceptually meaningful and localizable groups is central to ASA in everyday situations; for example, separation of discrete words from continuous sentences when processing language. This is particularly relevant to schizophrenia, where deficits in perceptual organization have been linked to symptoms and cognitive dysfunction. Here we examined event-related potentials in response to grouped tones to elucidate schizophrenia-related differences in acoustic segmentation. We report for the first time in healthy subjects a sustained potential that begins with group initiation and ends with the last tone of the group. These potentials were reduced in schizophrenia, with the greatest differences in responses to first and final tones. Importantly, reductions in sustained potentials in schizophrenia patients were associated with greater negative symptoms and deficits in IQ, working memory, learning, and social cognition. These results suggest deficits in auditory pattern segmentation in schizophrenia may compound deficits in many higher-order facets of the disorder.

Keywords

schizophrenia; auditory perception; negative symptoms; EEG; N2; sustained potential

1. Introduction

Separation of acoustic events into discrete percepts, or auditory scene analysis (ASA), is accomplished through *segregation* of multiple sources/streams, *integration* of concomitant

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Contributors

DFS designed the study and wrote the protocol. BAC and TKM performed the statistical analyses. BAC, DFS, and SMH interpreted findings. BAC wrote the first draft of the paper. All authors contributed to the critical revision of the manuscript and approved the final version.

Conflicts of interest

All other authors declare that they have no conflicts of interest.

acoustic elements, and *segmentation* of stimuli within a stream into auditory objects (Bregman, 1990). Segmentation of stimuli into perceptually meaningful objects is crucial in everyday situations; for example, the separation of discrete words from continuous language. Neurophysiological studies using event-related potentials (ERPs) suggest acoustic segmentation in auditory cortex is not dependent upon attention (Näätänen et al., 2001). Atienza and colleagues (2003) demonstrated that the mismatch negativity (MMN) ERP can be reduced or eliminated by changing temporal relationships *between* tone sets, thereby eliminating the perception of discrete auditory objects. Sussman and Gumenyuk (2005) also showed that temporal relationships *within* tone sets can affect whether tones are grouped as objects. Further, MMN is also elicited when established patterns are violated in auditory groups, such as changes in the number of tones (Salisbury et al., 2012; Van Zuijen et al., 2004, Rudolph et al., 2015), or pitch relationships between tones (Saarinen et al., 1992). Although these studies clearly demonstrate effects of acoustic segmentation, a more direct measure is needed which does not rely on pattern deviation.

Segmentation is relevant to schizophrenia, where deficits in perceptual organization are related to poor functional outcome (Uhlhaas & Silverstein, 2005). Schizophrenia patients have pronounced deficits in working memory and attention (Silver et al., 2003; Nuechterlein et al., 2004), which are central to ASA (Scott, 2005). Also, schizophrenia patients are slower to learn visual sequences in a serial reaction time task (Adini et al., 2015). Behavioral and electrophysiological evidence suggests impairment in the ability to perceptually *segregate* auditory streams in schizophrenia (Weintraub et al., 2012; Ramage et al., 2012); however, effects of schizophrenia on electrophysiological indices of *segmentation* of acoustic patterns into auditory objects has not been studied. In this paper, we identify the electrophysiological correlates of acoustic *segmentation* in healthy subjects and identify deficits in these measures in schizophrenia.

In behavioral studies of auditory pattern recognition, tones presented in first and last positions in a pattern are more easily recognized than intermediate tones (Macken et al., 2004; Mondor et al., 2004). Additionally, single-neuron recordings from primary and secondary auditory cortex in the cat have identified neurons that preferentially respond to tones in first and last positions (McKenna et al., 1989). We hypothesized that ERP amplitudes to first and last tones in a group would differ from responses to intermediate tones, and that ERP indices of segmentation would be reduced in schizophrenia. Deficits in visual perceptual organization exist in schizophrenia (Uhlhaas & Silverstein, 2005), but little is known about the perception of auditory groups. As deficits in other electrophysiological signs of auditory perceptual processes are prominent in schizophrenia (Salisbury et al., 2010; Javitt et al., 2009a; Foxe et al., 2011), we expected the same for ERP indices of acoustic segmentation.

2. Materials and Methods

2.1. Participants

Twenty-five individuals with schizophrenia (Sz) and 22 healthy control subjects (HC) participated in this study. One Sz participant was excluded from analysis (N=46, see section 2.5). Subjects were matched for age, gender, and parental social economic status (Table 1).

Subjects had normal hearing as assessed by audiometry and received \$50 for participation. The study was approved by the University of Pittsburgh IRB.

2.2. Procedures

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. In Experiment 1, six tones (75 dB, 50 ms pips, 5 ms rise/fall times, 330 ms SOA) were presented, with an initial 1.5 kHz tone, followed by 5 tones increasing in pitch in 0.5 kHz steps (final tone pitch = 4 kHz). Sets were separated by 800 ms. Deviant trials (10%) where the final tone decreased in pitch were also presented, but are not discussed here. In Experiment 2, an additional 6 tones were presented with decreasing pitch, resulting in a 12-tone “scale” pattern that began and ended with the same 1.5 kHz tone. Deviant trials (10%) in which the first six tones repeated were presented but are not discussed here. Prior to EEG recording, either 100 (Experiment 1) or 67 standard groups (Experiment 2) were presented to aid participants’ perception of auditory objects.

2.3. Assessments

Schizophrenia 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), Scale for Assessment of Negative Symptoms (SANS), and the brief UCSD Performance-based Skills Assessment (UPSA-B; for psychosocial functioning) by an expert diagnostician (Table 1). All participants completed the MATRICS (Nuechterlein et al., 2008), the Wechsler Abbreviated Scale of Intelligence (WASI), and the 4-factor Hollingshead Scale to measure socioeconomic status (SES) of the participant and his/her parents. Sz also completed the Brief Assessment of Cognition in Schizophrenia (BACS) (Table 1).

2.4. EEG Recording

EEG was recorded with a 72-channel Active2 system (BioSemi), comprising 70 scalp sites (including both mastoids), 1 site below the right eye, and 1 site at the nose tip referenced to a common mode sense site (near PO1). The online bandpass was DC to 104 Hz (24 dB/octave) digitized at 512 Hz. Off-line processing used BESA6 (BESA GMBH) and BrainVision Analyzer2 (Brain Products GMBH). First, using BESA, data were inspected and channels with excessive noise were interpolated. EEG was filtered between 0.5–20 Hz. Independent components analysis (ICA) was then used to isolate/remove eye-blinks and horizontal eye movements. In BrainVision Analyzer2, data were re-referenced to averaged mastoids and epochs were extracted (Experiment 1: 2400 ms; Experiment 2: 4400 ms), including a 100 ms pre-stimulus baseline. After baseline-correction, epochs containing signals $\pm 50 \mu\text{V}$ were rejected. No significant group differences in trial count were present (p 's > 0.1; Experiment 1: HC: 381 ± 59 trials; Sz: 365 ± 86 ; Experiment 2: HC: 382 ± 136 ; Sz: 328 ± 145). We detected a prominent sustained negative potential (SP) in the ERP waveform that lasted throughout the duration of the tone group (see below); therefore, transient ERPs (i.e. P1, N1, P2, and N2) were measured from the average waveform after applying a 1.5 Hz high-pass filter. Peak latencies and mean amplitudes were calculated between 45–75 ms (P1), 90–120 ms (N1), 150–200 ms (P2), or 280–330 ms (N2). Only mean N2 amplitude

comparisons are reported here, as other transient ERP measures were unrelated to group segmentation. Sustained Potential (SP) was measured from the average waveform after applying a 1.5 Hz low-pass filter. SP mean amplitude was calculated between 330 ms after the first tone to 330 ms after the last tone.

2.5. Data Analysis

One univariate outlier (Sz) > 3 SD from the mean was detected (amplitude of both the initial tone N2 and SNP was > 3 SD above the mean) and this subject was removed from the dataset prior to analysis. Group demographics were compared using t-tests and chi-squared tests where appropriate. N2 and SP amplitude were compared over six frontocentral sites (FC1, FCz, FC2, F1, Fz and F2) using separate ANOVAs. Group (HC or Sz) was the between subjects factor, while chain (F or FC) and laterality (1, z, or 2) were within-subjects factors. For N2 amplitude, serial tone position (Experiment 1: 1st–6th; Experiment 2: 1st–12th) was entered as a third within-subjects factor. Huynh-Feldt epsilon was used to correct for violations of sphericity. Significant effects of serial tone position were followed by planned pairwise comparisons: (1) first tone vs. all other positions and (2) last tone vs. all other positions. All simple effects were analyzed using Bonferroni-corrected alpha.

Pearson correlations were assessed between N2 (first, final, and average over intermediate tones) and SP amplitudes, as well as between these ERP amplitudes and clinical and neuropsychological measures, separately for HC and Sz . Due to high correlation between Experiments 1 and 2 ($r^2 > 0.5$) and to reduce the number of comparisons, response amplitudes were combined into summary variables by taking the mean amplitude across experiments. Due to the exploratory nature of these comparisons, results were considered significant at $p < 0.05$.

3. Results

3.1. Experiment 1

ERPs evoked by tone sequences were first examined in HC to identify responses that differed as a function of serial tone position (Figure 1b). N2 was significantly different across serial tone positions ($F_{5,105} = 6.10$; $p < 0.001$), with increased N2 to the first and final tones compared to all intermediate tones (Figure 1d). We further identified a sustained negative potential (SP) that began shortly after presentation of the first stimulus and persisted throughout the duration of the tone sequence (Figure 1f). N2 scalp distribution and dipole model localization were consistent with a ventrolateral prefrontal source (Figure S1a), while SP was consistent with an anterior temporal source (Figure S2a).

N2 and SP amplitudes for HC were next compared to those of Sz . ERPs in Sz had a similar morphology to those of healthy controls, with clear N1 and N2 responses following each tone, and SPs beginning after the first tone and persisting for the duration of the pattern (Figure 1c). Sz N2 responses were not different across serial positions (group $\times$ serial position: $F_{5,220} = 2.52$; $p = 0.039$; simple effect of serial position in Sz : $p > 0.1$; Figure 3a). N2 amplitude was reduced in Sz for responses to the first ($p < 0.001$) and final tone ($p < 0.001$) [Complete ANOVA statistics can be found in Table S1]. SPs were also smaller in Sz

($F_{1,44}=8.91$; $p=0.005$; Figure 3c). Thus, Sz did not modulate N2 response to the first and final tones to the same degree and tone patterns did not elicit SPs of the same magnitude as HC.

3.2. Experiment 2

HC N2 and SP followed a similar pattern in Experiment 2 (Figure 2b). N2 was again consistent with a ventrolateral prefrontal source (Figure S1b), and SP was again consistent with an anterior temporal source (Figure S2b). N2 differed across serial tone positions ($F_{11,231}=5.70$; $p<0.001$), with increased N2 to the first and final tones compared to all intermediate tones (Figure 2d).

Effects of serial tone position on N2 amplitude were again reduced in Sz (group $\times$ serial position; $F_{11,484}=2.27$; $p=0.017$; Figure 3b). Although Sz N2 amplitudes in Experiment 2 varied by serial tone position ($F_{11,253}=2.70$; $p=0.006$), N2 to the final tone was not different from other tones in the group (pairwise comparisons; $p's>0.05$), and N2 to the first tone only significantly differed from one other tone in the sequence. As in Experiment 1, N2 amplitude to the final tone was reduced compared to HC ($p<0.001$) [Complete ANOVA statistics can be found in Table S2]. SPs in Experiment 2 were again smaller in Sz ($F_{1,44}=6.873$; $p=0.012$; Figure 3c).

3.3. Correlations between ERPs

For HC, SP was correlated with N2 to the first tone ($r=0.62$; $p=0.002$; Figure 4a) and final tone ($r=0.67$; $p=0.001$; Figure 4b), but not intermediate tones ($r=0.11$; $p>0.1$; Figure 4c). For Sz, SP was correlated with N2 to the final tone ($r=0.47$; $p=0.021$; Figure 4a), but not to the first tone ($r=0.13$; $p>0.1$; Figure 4b) or the intermediate tones ($r=-0.29$; $p>0.1$; Figure 4c).

3.4. Correlations with clinical and neuropsychological measures

No significant relationships were identified between N2 and clinical measures in Sz or neuropsychological measures in either group. SP was correlated with IQ in HC ($r=-0.47$; $p=0.026$) and Sz ($r=-0.53$; $p=0.007$; Figure 5a), where larger SP was related to greater IQ. In Sz, SP amplitudes were also correlated with negative symptoms ($r=0.48$; $p=0.023$, Figure 5b), BACS scores ($r=-0.56$; $p=0.008$, Figure 5c), and the working memory ($r=-0.58$; $p=0.006$, Figure 5d), verbal learning ($r=-0.50$; $p=0.022$, Figure 5e), visual learning ($r=-0.44$; $p=0.044$, Figure 5f), and social cognition ($r=-0.56$; $p=0.008$, Figure 5g) scales of the MCCB.

4. Discussion

We report for the first time putative acoustic segmentation effects in HC, reflected in modulation of N2 to first and last tones within perceptual groups and an SP that begins with auditory group initiation and ends following the last tone of the group. Both N2 modulation and SP amplitude were reduced in Sz. These novel results demonstrate that presenting groups of tones related to each other in timing and pitch results in characteristic differences in ERP response amplitude between tones in the group and links an objective neurobiological measure to acoustic segmentation dysfunction in schizophrenia.

The N2 ERP is traditionally seen as an index of stimulus classification (Folstein & Van Petten, 2008); however, Allison et al. (1999) demonstrated a relationship between N2 and object perception. Letter sequences of recognizable nouns, but not random letter sequences, and pictures of complex objects (e.g. butterflies), but not scrambled pictures, produced an N2 response. Also, in studies of hierarchically-organized visual stimulus processing, N2 responses are larger when attending to global object form compared to local features (Heinze et al., 1998). Here N2 response appears to signify object perception in the auditory modality.

SPs are most commonly seen in response to long-duration sounds or rapidly-presented tones with SOA < 200 ms (Picton et al., 1978; Keceli et al., 2012). Here we presented discrete tones with SOA of 330 ms, more than 60% longer than the 200 ms threshold. SPs have also been highlighted in auditory stream segregation studies (Snyder et al., 2006), with evidence suggesting that sustained activity arises from higher-order cortical areas (Seifritz et al., 2002) and may indicate preference of neuronal firing (Wang et al., 2005). In this study, SPs were correlated with N2 responses to first and final tones, but not intermediate tones, suggesting that both N2 modulation and SP amplitude index auditory object perception. Thus, SPs identified in this study may indicate higher-level processes such as pattern matching, and reduced SPs in schizophrenia could signify reduced acoustic segmentation.

Deficits in sequence learning have been identified in behavioral studies of visual patterns in long-term (Adini et al., 2015; Marvel et al., 2007; Exner et al., 2006) and first episode schizophrenia (Pedersen et al., 2008; Exner et al., 2006). Although auditory sequence segmentation is somewhat different from visual pattern sequence learning, we believe these findings reflect similar physiological disturbances related to grouping of stimuli into solitary perceptual units. Furthermore, deficits in the N2 ERP have long been reported in schizophrenia, and are related to reductions in temporal lobe grey matter in the disorder (O'Donnell et al., 1993). In this context, deficits in N2 enhancement for initial and final tones in schizophrenia may result from deficits in feedforward excitation in the auditory cortex, which has been linked to reduced volumes of pyramidal soma in deep layer 3 of secondary auditory cortex in the disorder (Sweet et al., 2003; Sweet et al., 2004).

SP amplitudes were also strongly correlated with measures of cognitive function in schizophrenia patients. Some of these measures, such as working memory and attention, are closely related to pattern learning and/or identification. For example, pattern learning relies on the temporary maintenance and integration of former components of the pattern during perception of latter components. Deficits in local inhibitory processes within the prefrontal cortex are known to exist in schizophrenia (Lewis et al., 2005; Woo et al., 1997), and have been implicated in working memory deficits (Wang et al., 2004). It is also possible that auditory cortex circuit abnormalities (Sweet et al., 2004, 2009) are related to the segmentation deficits observed here. Additionally, SP amplitude was correlated with negative symptoms. This is particularly relevant to the recent body of literature suggesting that abnormal low-frequency electrophysiological responses may be characteristic of Deficit Syndrome, a subgroup of schizophrenia patients with primary and persistent negative symptoms (for a review, see Boutros et al., 2014). We propose that sensory deficits in perceptual organization undermine the foundation for more complex processing, in terms of

intellectual and social functioning, and may be important to understanding the phenomenology of schizophrenia. Future studies will compare patients who meet criteria for Deficit Syndrome to those experiencing predominantly positive symptoms in order to determine whether these results are specific to this patient subgroup.

While the results presented here are novel and significant, some caveats should be taken into consideration. Certainly, the findings need to be replicated in larger samples and in different stages of the disease. To the extent that our hypothesis is correct, the N2 and SP effects should be observed to other acoustic patterns within auditory streams. Although we believe that the N2 and SP index auditory object perception, we have not measured these effects behaviorally. Future studies should examine behavioral indices of object perception and correlate these measures with the ERP findings seen here. Additionally, due to the exploratory nature of these analyses, reported correlations with neuropsychological and clinical measures were examined without corrections for multiple comparisons. These should be confirmed using *a priori* hypothesis testing in future studies.

In summary, we report for the first time that N2 and SP in response to tone sets index the perception of discrete groups of stimuli, and that these responses are impaired in schizophrenia patients. Segmentation is an important part of auditory perception, a known area of deficit in schizophrenia. Reduction of the N2 and SP responses is indicative of deficits in acoustic segmentation in schizophrenia, and strong correlations between SP amplitude and negative symptoms, social functioning, and neurocognitive measures indicates the potential compounding effect of poor perceptual processes on later complex human behavior (Javitt, 2009b).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Analysis of event-related potentials (ERPs) in Experiment 1

(A) A schematic depiction of an individual trial is shown in the top panels. Timing of individual tones is further represented by dashes at the top of panels B–G to orient the reader. Grand-averaged, unfiltered ERPs recorded over medial frontal electrodes are shown in (B–C), followed below by high-pass filtered (>1.5 Hz) grand-averaged ERPs (D–E), and low-pass filtered (<1.5 Hz) grand-averaged ERPs (F–G). N1 and N2 responses to the first and final tones are highlighted to orient the reader (arrows). N2 amplitudes were extracted from shaded areas in high-pass filtered ERPs (D–E). Sustained potential amplitudes were extracted from shaded areas low-pass filtered ERPs (F–G). ERPs from healthy controls are shown in left panels and ERPs from schizophrenia patients are shown in right panels.

Channels from which average ERP waveforms were calculated are shown at the top right corner of the figure.

Figure 2. Analysis of event-related potentials (ERPs) in Experiment 2

(A) A schematic depiction of an individual trial is shown in the top panels. Timing of individual tones is further represented as dashes at the top of panels B–G to orient the reader. Grand-averaged, unfiltered ERPs recorded over medial frontal electrodes are shown in (B–C), followed below by high-pass filtered (>1.5 Hz) grand-averaged ERPs (D–E), and low-pass filtered (<1.5 Hz) grand-averaged ERPs (F–G). N1 and N2 responses to the first and final tones are highlighted to orient the reader (black arrows). N2 amplitudes were extracted from shaded areas in high-pass filtered ERPs (D–E). Sustained potential amplitudes were extracted from shaded areas low-pass filtered ERPs (F–G). ERPs from healthy controls are shown in left panels and ERPs from schizophrenia patients are shown in right panels.

Figure 3. Mean ERP amplitudes by group and serial position of tones within (A and C) Experiment 1 and (B and D) Experiment 2

Error bars represent standard error of the measurement. Asterisks denote statistical significance, corrected for multiple comparisons. Healthy control subjects are shown in black, while schizophrenia patients are shown in grey.

Figure 4. Scatterplots showing correlations between mean sustained potential and N2 amplitudes
 Data points for healthy controls are shown with filled circles, and schizophrenia patients are shown with open circles. Trend lines and enlarged data points are shown for correlations that reached statistical significance ($p < 0.05$), with trends for healthy controls shown by solid lines, and schizophrenia patients shown by dashed lines.

Figure 5. Scatterplots showing correlations between mean sustained potential amplitude and clinical measures

Data points for healthy controls are shown with filled circles, and schizophrenia patients are shown with open circles. Trend lines and enlarged data points are shown for correlations that reached statistical significance ($p < 0.05$), with trends for healthy controls shown by solid lines, and schizophrenia patients shown by dashed lines.

Table 1**Participant characteristics**

Mean values are reported with standard deviations in parentheses.

	Patients	Controls
<u>Socio-demographic data</u>		
N	24	22
Age (years)	35.5 (8.7)	32.4 (10.8)
Sex (M/F)	17/7	13/9
Education (years) ***	13.1 (2.4)	15.8 (2.7)
Participant SES ***	29.9 (14.0)	45.2 (10.7)
Parental SES	34.9 (15.3)	41.7 (9.5)
WASI IQ	101.6 (13.3)	107.6 (11.2)
Age at onset (years)	21.4 (7.8)	
Duration of illness (years)	14.0 (6.9)	
<u>Clinical data (T-scores)</u>		
PANSS – Positive symptoms	42.2 (8.4)	
PANSS – Negative symptoms	47.9 (10.2)	
PANSS – Total	44.3 (7.6)	
BACS ***	35.6 (12.6)	52.3 (11.7)
MCCB – Processing speed ***	34.1 (12.1)	54.5 (10.3)
MCCB – Attention **	37.4 (12.7)	49.2 (7.8)
MCCB – Working memory *	37.3 (11.7)	45.0 (6.9)
MCCB – Verbal learning ***	35.9 (8.5)	53.4 (9.2)
MCCB – Visual learning *	37.7 (11.6)	45.0 (8.9)
MCCB – Reasoning/Problem solving *	45.3 (10.9)	51.8 (7.1)
MCCB – Social cognition ***	35.3 (13.8)	53.4 (7.7)
MCCB – Total ***	30.7 (13.3)	50.4 (7.2)
<u>Medication data</u>		
Chlorpromazine equivalent dose (mg)	529 (292)	
Medicated/unmedicated	23/1	

Asterisks represent significant differences between groups (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). All other differences are non-significant with $p > 0.1$.