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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 deficits (ASP) 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.

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5.2. Contributors

DFS designed the study and wrote the protocol. BAC, JL, 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.

5.3. Conflicts of interest

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

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Keywords

EEG; Auditory; Perception; Midcingulate; N2; Sustained Potential

1. Introduction

Perceptual deficits have been recognized as a hallmark of schizophrenia since the initial classification of the disorder by Kraepelin more than 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 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 and colleagues (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 participated in this study. 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 mm³ 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 skull, inner skull, and grey-white matter boundary (Dale et al., 1999). The latter was used to generate a cortically-constrained source space; the others to generate a 3-shell boundary element model for calculation of the forward model.

2.4. Electroencephalography

EEG was recorded with a 72-channel Active2 system (BioSemi), including 64 channels placed according to the 10–20 system, FT7, TP7, FT8, TP8, left and right mastoid, EOG (below right eye), and nose tip. The online bandpass was DC–104 Hz (24 dB/octave) digitized at 512 Hz. Using EEGLab (Delorme and Makeig, 2004), a high-pass filter (0.5 Hz, 12 dB/octave) was applied to remove DC offsets and skin potentials. Data were then inspected and channels with excessive noise were removed and interpolated. Independent components analysis (ICA, AMICA algorithm) was then used to remove ocular artifacts.

Sensor-level analyses were performed using BrainVision Analyzer2 (Brain Products GMBH). Data were re-referenced to averaged mastoids and 1500-ms epochs were extracted, including a 100-ms pre-stimulus baseline. To isolate the ASP, data were low-pass filtered (1.5 Hz, 12 dB/octave) prior to trial segmentation. ASP mean amplitude was measured from the average response between 250–1050 ms after initial tone onset. This latency window was chosen as it captures the entirety of the sustained response in the ASP while omitting the upslope and downslope of the response. For N2 measurement, 350-ms epochs were extracted separately for initial, middle, and final tones, including 20-ms pre-stimulus baseline periods for each. After baseline-correction, epochs containing signals $\pm 50 \mu\text{V}$ were rejected for ASP and N2 response measurements. No significant group differences in trial count were present (p 's > 0.1; FE (initial tone/middle tone/final tone) = 293/293/291 $\pm$ 65/66/66 trials; Controls = 282/282/283 $\pm$ 17/15/14). N2 responses were measured from low-pass filtered average responses (20 Hz, 24 dB/octave) between 280–330 ms after stimulus onset.

Source-level analyses were performed using MNE software (Gramfort et al., 2014). Data were re-referenced, segmented, baseline-corrected, and low-pass filtered using the same parameters listed above to isolate the ASP. A noise covariance matrix was calculated from the individual epochs using the 100-ms baseline period prior to stimulus onset. Standard 10–20 EEG sensor locations were fit to the structural data using `mne_analyze` (Gramfort et al., 2014) and custom MATLAB scripts. Possible source locations were constrained to the gray/white matter boundary. The forward solution for this source space was constructed using three-layer Boundary Element Models (BEMs) with the linear collocation approach (Mosher et al., 1999). The forward solution matrix and the data were whitened using the noise

covariance matrix (Lin et al., 2006). A linear inverse operator was then calculated using the noise covariance matrix and the whitened forward solution, and applied to the whitened EEG data using a loose orientation constraint (0.6). The current estimates were then normalized to baseline, resulting in a dSPM statistic for each cortical location (Dale et al., 2000). Finally, dSPM values were averaged between 250–1050 ms after initial tone onset for identification of ASP source locations and measurement of source-level ASP amplitudes. For presentation of group-level source distributions, source data were morphed to the FreeSurfer average brain using `mne_make_movie` and averaged across subjects in MATLAB.

2.5. Data Analysis

Group demographics were compared using t-tests and chi-squared tests where appropriate. Sensor-level ASP and N2 amplitudes were compared over six frontocentral sites (FC1, FCz, FC2, F1, Fz, or F2) using separate ANOVAs. Group (FE or control) was the between-subjects factor, while chain (F or FC) and laterality (left, central, or right) were within-subjects factors. N2 amplitude modulation was analyzed two ways: first, ANOVA was used as described above with serial tone position (1st, 2nd, or 3rd) entered as a third within-subjects factor; second, N2 modulation index was calculated as the difference between N2 amplitude in response to the 2nd tone and the average of N2 responses to the initial and final tones at electrode FCz. This modulation index was compared between groups using Student's t-test. For all within-subject statistics, Huynh-Feldt epsilon was used to correct for violations of sphericity. All simple effects were analyzed using Bonferroni-corrected alpha. ASP source locations were identified using a threshold of $p < 0.001$ and amplitudes were measured from anatomically-defined regions that contained the bulk of the source-level activity, including auditory cortex (Heschel's gyrus and planum temporale) and mid-cingulate cortex (MCC), bilaterally (see Figure 2). These source locations were also examined for the N2 response to determine the degree to which ASP regions of activation were involved in generation of the N2 and to examine group differences in regional N2 activity. Regional source amplitudes were averaged across vertices in left/right hemispheres and compared between groups using 2 (group) x 2 (source location) ANOVA. Pearson correlations were assessed between N2 (first and final) and ASP amplitudes, between ASP source and sensor amplitudes, and between sensor-/source-level ASP amplitudes and clinical and neuropsychological measures, separately for FE participants and controls. Results were considered significant at $p < 0.05$.

3. Results

Sensor-level ASP amplitude was reduced by 43% (0.8 SD) in FE compared to controls (FE: -0.61 ± 0.13 μ V; controls: -1.04 ± 0.12 μ V; $F_{(1,42)} = 6.20$; $p = 0.017$; Figure 1a and 1b). There were no other main effects or interactions for sensor-level comparisons of ASP amplitude. At the cortical surface, ASP sources were identified in auditory cortex and MCC, bilaterally (Figure 2). Statistical comparisons of ASP source amplitudes revealed a significant interaction of group and source location ($F_{(1,26)} = 5.78$; $p = 0.024$), where group differences were detected within responses localized to MCC (FE: 1.76 ± 0.37 ; controls: 2.28 ± 0.69 ; $t_{(26)} = -2.16$; $p = 0.043$), but not auditory cortex ($p > 0.1$). MCC amplitudes were significantly

greater than auditory cortex amplitudes for both groups (FE; $t_{(13)} = -3.85$; $p = 0.002$; controls: $t_{(13)} = -7.26$; $p < 0.001$).

N2 was not significantly different between groups (main effect and interactions p 's > 0.1 ; Figure 1a, 1c, and 1d). However, N2 response amplitude was significantly different between tones ($F_{(2,84)} = 16.28$; $p < 0.001$), with greater (more negative) N2 response to initial tones (mean $\pm$ SEM = -1.05 ± 0.17) compared to intermediate (-0.11 ± 0.10 ; $F_{(1,42)} = 23.99$; $p < 0.001$) and final tones (-0.70 ± 0.13 ; $F_{(1,42)} = 5.12$; $p = 0.029$), and greater N2 response to final tones compared to intermediate tones ($F_{(1,42)} = 15.18$; $p < 0.001$). There were no differences in N2 amplitude between initial and final tones ($p > 0.1$). Average N2 modulation index was 24% (0.2 SD) greater for controls than FE participants, but this difference was not significantly significant between groups ($t_{(42)} = 0.72$; $p > 0.1$). At the cortical surface, N2 sources were also identified in auditory cortex and MCC, bilaterally, along with additional activation of dorsolateral prefrontal cortex, superior parietal cortex, and medial and lateral aspects of temporal lobe, including hippocampus (Figure 3). For source-level comparisons of N2 within auditory cortex and MCC, we again identified a significant difference between tones ($F_{(2,84)} = 4.00$; $p = 0.027$), with greater N2 response to initial tones (2.61 ± 0.16) compared to intermediate (2.16 ± 0.14 ; $F_{(1,42)} = 11.77$; $p = 0.002$) and final tones (2.23 ± 0.15 ; $F_{(1,42)} = 4.08$; $p = 0.054$), but no difference between intermediate and final tones ($p > 0.1$). Source-level N2 activations across regions were significantly greater in controls than FE (main effect of group: $F_{(1,26)} = 6.08$; $p = 0.021$); however, a significant interaction was found between group and source location ($F_{(1,26)} = 6.24$; $p = 0.019$), where group differences were again detected within responses localized to MCC (FE: 2.51 ± 0.11 ; controls: 3.29 ± 0.23 ; $t_{(26)} = -3.02$; $p = 0.007$), but not auditory cortex ($p > 0.1$). MCC amplitudes were significantly greater than auditory cortex amplitudes for both groups (FE; $t_{(13)} = -6.56$; $p < 0.001$; controls: $t_{(13)} = -11.43$; $p < 0.001$).

Correlations between source-level activity in MCC and auditory cortex were significant for controls ($r = 0.86$; $p < 0.001$), but not FE ($r = 0.52$, $p > 0.1$). Sensor-level ASP amplitude was correlated with both MCC (controls: $r = -0.59$; $p = 0.027$; FE: $r = -0.52$; $p = 0.056$) and auditory cortex activities (controls: $r = -0.55$; $p = 0.041$; FE: $r = -0.60$; $p = 0.024$). Further, initial-tone N2 amplitude correlated with source-level ASP responses in MCC ($r = -0.51$; $p = 0.060$) and auditory cortex ($r = -0.56$; $p = 0.039$) in controls, but not FE (p 's > 0.1).

ASP amplitude did not correlate with neuropsychological or symptom measures in this study (p 's > 0.1). Further, no correlations were found between N2 amplitude and neuropsychological measures. However, we did find significant correlations in healthy controls between final-tone N2 responses and the total MCCB score ($r = -0.55$; $p = 0.006$), as well as Reasoning and Problem Solving ($r = -0.57$; $p = 0.004$) and Social Cognition ($r = -0.42$; $p = 0.043$) subscales of the MCCB.

4. Discussion

Auditory object segmentation responses were identified in healthy controls, with larger N2 responses to initial and final tones compared to intermediate tones, and an ASP that persisted for the duration of the object. In our previous series of experiments, we identified

deficits in these neurophysiological indices of auditory object segmentation in long-term schizophrenia (Coffman et al., 2016). Here, we have extended these findings to individuals who are more than 13 years earlier in the course of the disease, at the first episode of psychosis. These results indicate that schizophrenia-related reductions in ASP amplitude measured at the scalp can be detected even at first episode using a simple passive auditory task. Additionally, source analysis of the ASP based on individual realistic head models indicated that the sources of ASP's lie in bilateral auditory cortex and MCC, and that ASP amplitude reductions in FE participants were driven primarily by reduced cortical activity in MCC.

The results presented here provide further evidence of auditory object segmentation deficits in schizophrenia; however, N2 modulation deficits previously identified in individuals with long-term schizophrenia were not detected in FE participants. Notable differences in N2 modulation were found between FE and controls in this study, but these differences did not reach the threshold for statistical significance. An important aspect of objects in both the auditory and visual system is the presence of edges. In visual scene analysis, spatial edges are the most informative, while in ASA, temporal edges are more important to delineate object boundaries (Chait et al., 2008). Enhanced N2 potentials in response to initial and final tones in repeating discrete auditory patterns such as those presented here may represent this type of temporal edge detection. Here, we identified significant reduction of ASP, indicating deficits in auditory object perception and/or analysis, but not N2 modulation, indicating that temporal edge detection is still relatively intact in FE participants. This pattern of results may indicate a progressive decline in function that is most clearly evident with compounding deficits across multiple levels of processing. Next steps will be to investigate ASP in individuals at high risk for developing schizophrenia prior to first psychotic break to determine if ASP reductions predict the development of psychosis.

Our source models indicate that the ASP is generated in bilateral auditory cortex and MCC, including posterior dorsal anterior cingulate cortex. Resting-state connectivity between these regions, along with posterior insula and thalamus, has been previously demonstrated with functional magnetic resonance imaging (fMRI), suggesting that these regional responses may indicate network-level activity (Damoiseaux et al., 2006). Further, MCC has been linked to learning and decision making, and is a core node of both the auditory network and the salience network (Ham et al., 2013). ASP and N2 in MCC, but not AC, were reduced in FE compared to matched controls, and amplitude of ASP activity in AC was correlated with MCC activity more strongly in controls than FE. Schizophrenia-related connectivity impairments exist within and between these networks (Orliac et al., 2013; Palaniyappan and Liddle, 2012; Sigmundsson et al., 2001), and MCC impairment has been specifically linked to negative and cognitive symptom severity in schizophrenia (Sabri et al., 1997). Thus, MCC dysfunction may be at the heart of ASP reductions in schizophrenia, and may be a key component of aberrant perceptual organization, negative symptoms, and cognitive dysfunction. Although we did not find correlations between ASP and clinical/neuropsychological variables in this study, correlations observed in our previous experiments along with known links between MCC deficits and schizophrenia symptoms suggest that MCC deficits observed at first psychotic episode may predict negative symptoms later in the disease. Longitudinal studies are needed to determine if an early

deficit in amplitude of the ASP, and particularly sustained activity in MCC, is related to later decline in function.

In summary, we confirm auditory object segmentation deficits observed in our previous experiments and demonstrate that these deficits are observable early in the disease course. Neurophysiological indices of auditory segmentation were reduced by more than 40%, while indices of temporal edge detection were relatively preserved. Localization of auditory segmentation response deficits to MCC provides further evidence of MCC dysfunction as a key component of schizophrenia. Altogether, this study supports the construct validity of the ASP and suggests that the ASP may be useful as an index of early MCC dysfunction in schizophrenia. More generally, these findings suggest that indices of late perceptual processing may provide more powerful biomarkers of disease presence than indices of early sensory processing.

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Figure 1. Broadband event-related potential (ERP) responses and auditory segmentation potentials (ASPs) for healthy controls and first-episode schizophrenia participants (FE)
A. Broadband (0.5–20 Hz) ERP responses at electrode FCz showing individual auditory evoked potentials for controls (black) and FE (red). **B.** ASP responses at electrode FCz for controls (black) and FE (red). Music notes and corresponding vertical lines represent tone onset times in panels A and B. **C and D.** Broadband (0.5–20 Hz) ERP responses to individual tones for (C) healthy controls and (D) FE participants, illustrating significant N2 modulation effects for each participant group.

Figure 2. Source analysis of auditory segmentation potentials (ASPs) for healthy controls (black) and first-episode schizophrenia participants (FE, red)

A. Regions of interest used in analysis of the ASP and N2. **B.** Maps of cortical activity localized from ASP responses are shown, with controls responses shown in upper panels and FE in lower panels. The lateral surface is shown in the left panels to illustrate auditory cortex activity localization, and the medial surface is shown in the right panels to illustrate mid-cingulate cortex (MCC) activity localization. **C and D.** Source time courses are shown for average response across bilateral auditory cortex locations (**C**) and bilateral MCC (**D**).

Figure 3. Maps of cortical activity localized from auditory N2 responses for healthy controls (upper) and first-episode schizophrenia participants (FE, lower), for responses to each stimulus condition (S1, S2, and S3).

Table 1**Participant characteristics**

Descriptive and inferential statistics are reported for the full participant sample, as well as the subset of participants included in source analysis (listed in parentheses). Significant p-values are bolded. All other differences are non-significant ($p > 0.05$).

		Mean±SD			
		Patients	Controls	<i>t</i> / χ^2	<i>p</i>
<u>Sociodemographic data</u>					
Age (years)	22.8±4.7 (23.1±5.4)	24.5±5.3 (21.3±1.9)	−1.1 (−1.2)	0.279 (0.258)	
Sex (M/F)	15/5 (10/4)	17/7 (9/5)	0.1 (0.2)	0.757 (0.686)	
Participant SES	32.0±13.3 (33.1±14.6)	35.6±10.2 (33.9±9.6)	−1.0 (−0.2)	0.322 (0.868)	
Parental SES	43.8±14.7 (48.8±12.3)	50.4±9.9 (54.6±7.5)	−1.7 (−1.5)	0.109 (0.137)	
Education (years)	13.0±2.1 (13.3±2.5)	14.7±1.6 (14.4±1.4)	−2.9 (−1.4)	0.007 (0.179)	
<u>Neuropsychological Tests</u>					
WASI IQ	107.9±15.1 (109.5±17.1)	106.0±9.0 (107.4±10.0)	0.5 (0.4)	0.632 (0.700)	
MCCB–Processing speed	46.2±16.8 (47.5±18.3)	49.0±7.4 (51.6±7.4)	−0.7 (−0.8)	0.502 (0.442)	
MCCB–Attention	41.5±12.6 (41.6±14.3)	48.5±6.9 (48.6±7.6)	−2.2 (−1.6)	0.033 (0.118)	
MCCB–Working memory	42.3±13.8 (47.6±14.7)	43.8±11.3 (46.9±10.1)	−0.4 (−0.1)	0.699 (0.882)	
MCCB–Verbal learning	43.8±12.3 (44.9±13.7)	50.7±8.9 (49.6±9.6)	−2.1 (−1.0)	0.042 (0.310)	
MCCB–Visual learning	42.0±12.8 (42.1±13.1)	45.2±7.4 (45.8±6.2)	−1.0 (−0.9)	0.328 (0.358)	
MCCB–Reasoning	48.1±11.1 (47.8±12.3)	49.4±7.6 (51.8±6.1)	−0.4 (−1.1)	0.678 (0.291)	
MCCB–Social cognition	45.7±12.0 (48.7±10.9)	53.6±7.4 (53.6±7.1)	−2.6 (−1.4)	0.015 (0.175)	
MCCB–Total	41.1±14.7 (42.9±16.3)	47.5±7.7 (49.2±7.1)	−1.7 (−1.3)	0.094 (0.203)	
<u>Symptoms</u>					
PANSS–General	39.1±7.1 (40.8±7.1)	-			
PANSS–Negative	17.0±5.2 (17.3±6.0)	-			
PANSS–Positive	20.7±5.0 (21.9±5.2)	-			
PANSS–Total	76.8±14.6 (79.9±15.7)	-			
SANS	30.8±7.7 (30.4±8.6)	-			
SAPS	16.1±9.3 (18.2±9.9)	-			
<u>Psychosocial functioning</u>					
UPSA–B–Finance	41.6±5.6 (36.9±6.4)	-			
UPSA–B–Communication	36.9±6.3 (42.2±5.8)	-			
UPSA–B–Total	78.6±7.9 (79.1±8.0)	-			
<u>Medication data</u>					
Cpz. equivalent dose (mg)	274±176 (236±185)	-			
Medicated [*] /unmedicated	11/9 (7/7)	-			

^{*} Of the 11 medicated participants, 10 were prescribed Risperidol and 1 was prescribed Aripiprazole.