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## Auditory stream segregation impairments in schizophrenia

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### Abstract

We used behavior and event-related potentials (ERPs) to examine auditory stream segregation in people with schizophrenia and control participants. During each trial, a context pattern was presented, consisting of low (A) and high (B) tones in a repeating ABA pattern, with a frequency separation ( $\Delta f$ ) of 3, 6, or 12 semitones. Next, a test ABA-pattern was presented that always had a 6-semitone  $\Delta f$ . Larger  $\Delta f$  during the context resulted in more perception of two streams and larger N1 and P2 ERPs, but less perception of two streams during the test pattern. These effects of  $\Delta f$  were smaller in schizophrenia. Individuals with schizophrenia also showed a reduced effect of prior perceptual judgments. Overall, the findings demonstrate that people with schizophrenia have abnormalities in segregating sounds. These abnormalities result from difficulties utilizing frequency cues in addition to reduced temporal context effects.

### Keywords

auditory cortex; auditory scene analysis; event-related potentials; tonotopic organization; context effects

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Schizophrenia is characterized by a wide range of symptoms and neurobehavioral deficits that result from diverse genetic and environmental factors. Abnormalities in the perception of auditory information are common in schizophrenia and have been demonstrated across a wide range of tasks. One well-documented finding is reduced performance on simple frequency-discrimination tasks (Javitt, Shelley, & Ritter, 2000; Javitt, Strous, Grochowski, Ritter, & Cowan, 1997; March, et al., 1999; Rabinowicz, Silipo, Goldman, & Javitt, 2000; Strous, Cowan, Ritter, & Javitt, 1995). Importantly, frequency-discrimination difficulties may contribute to impairments in more complex real-world skills such as categorical perception of speech (Cienfuegos, March, Shelley, & Javitt, 1999) or encoding speech prosody (Leitman, et al., 2005). Furthermore, impairments in auditory perception may have important relations with the underlying pathophysiology of the disorder, as they are accompanied by brain abnormalities in cortical regions associated with auditory processing. For example, event-related potential (ERP) and magnetoencephalographic (MEG) studies of auditory cortex have shown abnormal tonotopic organization (Rojas et al., 2002); abnormal processing of tone sequences containing alternating frequencies (Rojas, Slason, Teale, & Reite, 2007); and overall reduced amplitude of auditory brain responses (McCarley, Faux, Shenton, Nestor, & Adams, 1991; Shelley et al., 1991). Also, magnetic resonance imaging (MRI) studies have shown reduced gray matter volume in the superior temporal gyrus

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(STG), which contains primary and secondary auditory cortex (McCarley et al., 1999; Shenton, Dickey, Frumin, & McCarley, 2001).

Whether these functional and structural auditory abnormalities affect the ability to segregate sounds coming from different sources is unknown, despite the importance of sound segregation in real-world situations. In particular, it is not clear whether the difficulties in discriminating sound frequency would lead to problems segregating sounds because pure-tone frequency discrimination thresholds are typically smaller than thresholds for perceptually segregating tone patterns (Rose & Moore, 2005). The present study examines these matters in schizophrenia participants and control participants using an auditory stream segregation task. Auditory stream segregation is the phenomenon by which listeners perceptually organize sounds into one or more *streams*, where a stream can be thought of as a sequence of sounds emanating from a single source. Stream segregation is necessary during noisy social gatherings, such as when trying to segregate a friend's voice from background noise in order to have a meaningful conversation. In the laboratory, a cue that has been found to greatly increase the likelihood of perceiving multiple streams is the frequency separation ( $\Delta f$ ) between sequential sounds. Specifically, in a repeating sequence of low tones (A), a high tone (B), and silence (-) in an ABA-pattern, the likelihood of perceiving the low tones and high tones as separate streams (i.e., A---A---A--- and B---B---B---) increases as  $\Delta f$  increases. In contrast, a sequence with a small  $\Delta f$  is typically perceived as a single stream (i.e., ABA-ABA-ABA-) (see Figure 1).

The importance of  $\Delta f$  as a cue to streaming is likely to be a consequence of the tonotopic organization of the peripheral (Hartmann & Johnson, 1991) and central (Snyder & Alain, 2007b) auditory system. Specifically, alternating tone sequences with small  $\Delta f$  activate overlapping frequency-selective neurons in the auditory cortex and are consequently perceived as one stream; in contrast, sequences with large  $\Delta f$  activate two non-overlapping frequency-selective neuronal populations and are consequently perceived as two streams. Therefore, the non-overlapping neural populations activated by large  $\Delta f$  sequences should produce larger responses, as there will be less mutual suppression of the two neural populations. Support for this was provided by MEG and ERP studies showing changes in auditory cortical N1 and P2 components (Gutschalk et al., 2005; Snyder & Alain, 2007a; Snyder, Alain, & Picton, 2006; Snyder, Holder, Weintraub, Carter, & Alain, 2009), such that increases in  $\Delta f$  were coupled with increases in response amplitudes and these amplitude modulations correlated very strongly with perception of streaming.

To our knowledge, only one study has examined auditory stream segregation in schizophrenia (Bourdet, Brochard, Rouillon, & Drake, 2003). In this study, schizophrenia participants showed no streaming impairments compared to controls, as measured indirectly based on temporal change detection that should have been easier when two segregated streams were perceived. An alternative strategy for assessing streaming is to have participants directly report their perception. This task is particularly well suited for investigating streaming because it is possible to rapidly assess behavior, in contrast to indirect tasks that are often extremely time consuming and cognitively demanding. An additional limitation of the study by Bourdet and colleagues is that they used  $\Delta f$  values that were all larger than one octave. Such large values may be unable to reveal robust group differences.

In addition to low-level processes such as  $\Delta f$ -based segregation, streaming also involves higher-level aspects of auditory processing (for reviews, Moore & Gockel, 2002; Snyder & Alain, 2007b; Snyder, Gregg, Weintraub, & Alain, 2012), as indicated by context effects on perception of streaming. Specifically, the perception of streaming during a current pattern is greatly influenced by the previous  $\Delta f$  and the perception of previous patterns. When a

context ABA-pattern is presented with a variable  $\Delta f$ , followed by a test ABA-pattern, the larger the  $\Delta f$  during context, the less likely listeners hear the test pattern as two streams (Snyder, Carter, Hannon, & Alain, 2009; Snyder, Carter, Lee, Hannon, & Alain, 2008; Snyder, Holder, et al., 2009; Snyder & Weintraub, 2011). This effect of prior  $\Delta f$  is not due to a suppressive effect of the prior perceptual interpretation because when the  $\Delta f$  is kept constant during the context and test, perception of two streams at the end of the context actually results in listeners more likely to again report perceiving two streams compared to one stream during the test pattern. Thus, there are two separate context effects that can be observed in streaming, one that is due to the influence of prior  $\Delta f$  and another that is due to the prior percept. Studying these two implicit memory effects together should shed light on higher-level aspects of streaming.

To our knowledge, only one study has examined effects of context on auditory perceptual organization in schizophrenia (Silverstein, Matteson, & Knight, 1996). In this study, participants listened to a list of numbers spoken by a human speaker followed by an animal sound that could be perceived as either originating from the human or an animal. When the final sound was perceived as originating from the male speaker, recall of the list of numbers worsened compared to when it was perceived as originating from an animal. By instructing participants that the suffix actually originated from a separate source (an animal), the interfering effects of the final sound were reduced. However, this contextual manipulation had no effect on schizophrenia participants, demonstrating impaired use of context by schizophrenia participants.

The aim of the current study is to examine schizophrenia participants during a streaming task, using behavioral and ERP measures obtained with a recently studied paradigm that is able to simultaneously reveal the presence of abnormalities in  $\Delta f$ -based segregation and the use of context (Snyder, Holder, et al., 2009). In this paradigm, a trial consists of two sequences of ABA-patterns: 1) a context sequence with a variable  $\Delta f$ , and 2) a test sequence with a fixed 6-semitone  $\Delta f$  (Figure 1a). Examining perception and ERPs during the context can provide information about the use of the  $\Delta f$  cue for streaming. Given the low-level auditory abnormalities described above, schizophrenia participants were expected to experience less of an increase in perception of two streams with increasing  $\Delta f$  compared to controls during the context, and to show a smaller effect of  $\Delta f$  on N1 and P2 response amplitude. Additionally, examining the impact of the prior context on later perception during the test can provide information about the operation of context effects, a high-level aspect of streaming. Given their reduced effects of context on auditory perceptual organization (Silverstein, Matteson, & Knight, 1996), schizophrenia participants were expected to experience less of a decrease in perception of two streams with increasing prior  $\Delta f$  compared to controls during the test. Schizophrenia participants were also expected to experience a reduced effect of prior perception such that, compared to controls, they less often report the same percept during the test as reported for the preceding context when the  $\Delta f$  between context and test was constant.

## Methods

### Participants

Twenty-one participants with schizophrenia and twenty-two healthy controls participated in the study. Table 1 contains demographic information for each group. As indicated in Table 1, groups did not significantly differ on age, gender, ethnicity, or handedness as measured by self-report. However, the schizophrenia group had significantly fewer years of education and significantly lower IQ. For the schizophrenia group, seventeen participants were taking atypical antipsychotics, two participants were taking an additional typical antipsychotic, and two were not taking any antipsychotics. The behavioral data from two schizophrenia

participants and one healthy control were not included in the present report because these participants were unable to sufficiently understand the behavioral task. However, their ERP data displayed normal trends. Furthermore, previous work has shown that attention and other high-level factors do not greatly affect the ERP modulations we examined (Gutschalk et al., 2005; Snyder et al., 2006); rather the modulation of N1 and P2 are largely driven by  $\Delta f$  and thus reflect early frequency-based segregation of tones in auditory cortex. Thus, it is unlikely that the ERP data were compromised by poor task performance so the data were retained in the analysis. Demographic characteristics between groups did not change appreciably when these subjects were excluded. All participants exhibited normal hearing for their age (<30 dB HL from 250 to 1000 Hz, <40 dB HL from 2000 to 8000 Hz).

Schizophrenia participants were primarily recruited through an outpatient community mental health center, although two participants were recruited from the community. All control participants were recruited from the community. To be included in the study, all participants had to be between the ages of 18 and 65 years and have normal hearing. Additional exclusion criteria included history of electro-convulsive therapy; neurological disorder or a medical condition with known effects on CNS function; or diagnosis of alcohol or drug abuse or dependence within the last 12 months, alcohol or drug use within the last 24 hours, or use of medications that would affect the electroencephalogram (EEG), neurological or cognitive function, other than those medications that were prescribed to treat schizophrenia. Additionally, healthy controls were excluded if they reported during a standardized interview that they had a first- or second-degree relative diagnosed with a psychotic or affective disorder.

Diagnosis of schizophrenia was established using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002), review of medical records, and information provided by mental health professionals providing treatment for the participants. Severity of positive, negative and general psychiatric symptoms were assessed using the Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and Negative Symptoms (SANS) (Andreasen, 1984), Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), and Calgary Depression Rating Scale (Addington, Addington, & Schissel, 1990). Vocabulary and Block Design subtests from the Wechsler Adult Intelligence Scale 3<sup>rd</sup> edition (WAIS-III) (Wechsler, 1997) were used to estimate current IQ (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002). After complete description of the study to participants, written informed consent was obtained. An Institutional Review Board at the University of Nevada, Las Vegas approved the study's protocol, which is consistent with the Declaration of Helsinki.

## Stimuli

Auditory stimuli were generated in Matlab (The MathWorks, Inc., Natick, MA) and consisted of pure tones (50 ms in duration, including 10 ms rise/fall time) presented binaurally through ER3A headphones (Etymotic Research, Inc., Elk Grove Village, IL) at 70 dB SPL. Trials consisted of a 6.72 s context sequence, a 1.44 s silent interval, and a 6.72 s test sequence (Figure 1a). The intertrial interval was 3 s. Context and test sequences both consisted of 14 repeating ABA-patterns where A represents a low tone, B a high tone, and - a silence. The stimulus onset asynchrony between A and B tones within an ABA- cycle was 120 ms. The  $\Delta f$  between the low and high tones during the test sequence was always 6 semitones where A=300 Hz and B=424 Hz. During the context sequence, four of the following conditions could occur: (1) A=300 Hz, B=357 Hz ( $\Delta f$ =3 semitones), (2) A=300 Hz, B=424 Hz ( $\Delta f$ =6 semitones), (3) A=300 Hz, B=600 Hz ( $\Delta f$ =12 semitones), or (4) silence. Each context sequence was paired with the test sequence to make a total of 4 trial types. Each trial type occurred 40 times across 5 blocks. Between blocks, participants could

break for as long as they liked. Similar paradigms have been successfully used to study auditory stream segregation in healthy controls (Snyder, Holder, et al., 2009).

## Procedure

EEG signals were digitized continuously (512-Hz sampling rate, 104-Hz bandwidth) using a Biosemi ActiveTwo system (<http://www.biosemi.com>). EEG data were recorded on an array of 72 Ag-AgCl electrodes (512-Hz A/D rate), with a Common Mode Sense (CMS) active electrode and a Driven Right Leg (DRL) passive electrode serving as grounds (see <http://www.biosemi.com/faq/cms&drl.htm>), placed at 64 points based on a 10/20 system in a Biosemi electrode cap and 8 points below the hair line. Before EEG recording, conducting gel was applied to each electrode site with the cap on, and sintered Ag-AgCl pin-type electrodes were fit into place at each site in the cap. For the 8 points below the hair line, Ag-AgCl flat-type electrodes were attached using adhesive stickers. No abrading of the skin was performed. Voltage offsets were below 40 mV prior to recording, and the resting EEG was checked for any problematic electrodes prior to and throughout recording.

During the experiment, participants were seated comfortably in a single-walled sound-attenuated room (Industrial Acoustic Corp, Bronx, NY) and were asked to maintain fixation on a white cross, centered on a black background on a computer screen, throughout the experiment. Participants were asked to listen to the stimuli during EEG recording and to avoid moving their eyes, head, or any other body parts while the stimuli were being presented. At the end of each context and test sequence, participants indicated by pressing one of two buttons whether they heard a *galloping rhythm* (one stream) for the entire sequence or *two even metronomes* (two streams) at any point during the sequence (Figure 1b). Participants were told to let their perception occur naturally and to not bias their perception one way or the other. Prior to beginning the main experimental trials, participants completed a practice block that was typically 8 trials long but lasted until they could sufficiently distinguish between the two percepts. Similar procedures have been successfully used to study the ERP correlates of the effect of  $\Delta f$  in auditory stream segregation in healthy controls (Snyder, Holder, et al., 2009).

## Behavioral Data Analysis

To examine the effect of context  $\Delta f$  on perception during the context and test and whether this effect differed between groups, we calculated the proportion of trials that each participant reported hearing two streams during the context and test sequences separately for each trial type. The proportions of hearing two streams during the context were entered into a mixed-design ANOVA with context  $\Delta f$  (3, 6, 12 semitones) as a within-subjects factor and group (schizophrenia, control) as a between-subjects factor. A separate mixed-design ANOVA tested the effect of context  $\Delta f$  on perception during the test, with prior  $\Delta f$  (3, 6, 12 semitones) as a within-subjects factor and group as a between-subjects factor. A separate independent-samples t-test tested whether perception during test sequences following silent-context trials differed between groups.

To examine the effect of prior perception on later perception and whether this effect differed between groups, we examined only the stimulus condition in which the context and test had a  $\Delta f$  of 6 semitones. We calculated the proportion of trials in which participants reported hearing the same perception during the context and test (i.e., perceptual stabilization), separately for trials which context perception was reported as one stream or two streams and separately for the schizophrenia group and control group. These proportions were entered into one-sample t-tests to evaluate whether perceptual stabilization had occurred, defined by being significantly higher than 0.5 (i.e., more than 50% of the time). To examine whether the effect of prior perception was different between groups, the proportions were also



entered into a mixed-model ANOVA with prior perception (one stream, two streams) as a within-subjects factor and group as a between-subjects factor. Given that the schizophrenia group heard two streams less frequently overall, portion of streaming during the test sequences following silent-context trials was added as a covariate. For all ANOVAs, the degrees of freedom were adjusted using the Greenhouse-Geisser  $\epsilon$  and all reported probability estimates were based on the reduced degrees of freedom.

### EEG Data Analysis

ERPs during the context were measured by averaging EEG epochs for each stimulus condition and electrode site separately, and rereferenced to the average of all electrodes not adjacent to the eyes. Epochs contaminated by artifacts (amplitude  $> 120 \mu\text{V}$ , gradient  $> 75 \mu\text{V}$ , low signal  $< .10 \mu\text{V}$ ) were automatically rejected prior to averaging. Ocular artifacts (blinks, saccades, smooth movements) were corrected automatically with a Principal Component Analysis based method (Ille, Berg, & Scherg, 2002). Epochs were digitally bandpass filtered to attenuate frequencies below 1Hz (6 dB/octave attenuation, forward) and above 30Hz (24 dB/octave attenuation, zero phase). The number of epochs retained for analysis (on average 325 and 392 per condition for the schizophrenia and control groups, respectively) did not significantly differ between groups,  $F(1,42)=3.06$ ,  $p>.05$ . ERPs during the test are not reported because there was no stimulus manipulation during the test and the effects of the context were unreliable.

To examine the effect of  $\Delta f$  and whether this differed between groups, ERPs were baseline corrected by subtracting the mean of the portion 30 ms prior to the B-tone from each point in the epoch. Previous ERP research in healthy participants has shown that  $\Delta f$ -modulations in P1-N1-P2 amplitude are time locked to the B-tone of an ABA-pattern (Snyder & Alain, 2007a; Snyder et al., 2006; Snyder, Holder, et al., 2009). Furthermore, this period is short enough that it does not overlap with the preceding A-tone. We then calculated grand-averaged ERP difference waves between conditions of interest during the context sequences. These difference waves were only used to choose latency windows in the original waveforms for analysis that showed maximal difference between groups. Indeed, as shown below, the latency windows chosen were sufficient to reveal both  $\Delta f$ -related ERP modulations and robust group differences. The first ABA-pattern of each sequence was not analyzed because of the large onset response. The last ABA-pattern of each sequence was also not analyzed because the ERP data may have been contaminated by muscle-related or movement-related activity as participants were getting ready to make a response. All analyses included the following electrodes: FC3, C3, FC4, and C4 because these electrodes are typically used to measure auditory ERPs arising from the superior temporal plane of STG and also because they allowed us to compare the effects of hemisphere, which were apparent upon visual examination of the ERPs. It is unlikely that  $\Delta f$ -related ERP modulations measured at these sites reflect motor preparation activity given that behavioral responses were required for all non-silent sequences. Thus, motor preparation activity should be similar across conditions. Additionally, behavioral responses were not made until the end of a sequence following ERP measurements. Therefore, differences in  $\Delta f$ -related ERP modulations across conditions are unlikely to reflect differences in motor preparation. Mean amplitudes of the original ERP waves were averaged across electrode sites in the same hemisphere for each participant and submitted to a mixed-design ANOVA with group as a between-subjects factor and hemisphere (left, right) and  $\Delta f(3, 6, 12$  semitones) as within-subjects factors. For all ANOVAs, the degrees of freedom were adjusted using the Greenhouse-Geisser  $\epsilon$  and all reported probability estimates were based on the reduced degrees of freedom.

## Correlation Analysis

To determine whether there was a relationship between behavioral responses and ERP mean amplitudes, we first calculated the correlation between behavioral reports of streaming and ERP mean amplitudes for each individual participant. The mean behavioral responses at each  $\Delta f$  were correlated with the corresponding ERP mean amplitudes for each  $\Delta f$ , separately for each participant. This enabled us to evaluate whether on average the correlations across subjects were different than 0. Correlations were then entered into a one-sample t-test evaluating the hypothesis that the correlations were on average different from zero. This analysis was conducted for both groups together and separately and for both hemispheres together and separately. For negative-voltage ERPs, we expected to find a negative correlation such that as response mean amplitudes decreased (“increase in negativity”) proportion of streaming would increase. Likewise, for positive ERPs, we expected to find a positive correlation.

Next, we determined whether any of our group differences measured during test (prior  $\Delta f$  and prior perception) could be accounted for by impaired processing of  $\Delta f$  during context. To do this, we examined whether the effect of  $\Delta f$  correlated with the effect of prior  $\Delta f$  or prior perception in separate correlation analyses. For each participant, the effect of  $\Delta f$  was calculated as the slope of streaming measured during context as a function of  $\Delta f$ . The effect of prior  $\Delta f$  was calculated as the slope of streaming measured during test as a function of context  $\Delta f$ . The effect of prior perception was calculated as the difference between the proportion of stabilized trials and trials in which perception changed, for both context perceptions (one stream, two streams) separately. The differences for both context perceptions were then collapsed to give one measure of prior perception.

To determine whether there was a relationship between behavioral or ERP responses and symptom ratings on the BPRS, SAPS, or SANS for the schizophrenia group we first calculated slopes of ERP mean amplitudes as a function of  $\Delta f$  in addition to the behavioral slope. Slopes and symptom ratings were then entered into a correlation analysis. To avoid inflating the rate of Type I errors, only symptoms of particular interest were considered that included both global and individual item scores. Symptoms measures from the BPRS included the following: hallucinations and total score. Symptom measures from the SAPS included the following: auditory hallucinations, voices commenting, voices conversing, tactile hallucinations, olfactory hallucinations, visual hallucinations, global rating of hallucinations, global rating of delusions, and global rating of formal thought disorder. Symptom measures from the SANS included the following: global rating of affective flattening, global rating of avolition, global rating of anhedonia-associality, and global rating of attention. For brevity, only significant symptom rating correlations are reported. Finally, to determine whether any group differences in our behavioral or ERP measures could be explained by years of education or IQ, we calculated correlations between behavioral or ERP slopes and years of education or current IQ.

## Results

### Demographic Analyses

Given the differences between the schizophrenia and healthy control groups on years of education and current IQ, correlations were calculated between these variables and the behavioral and ERP measures. Neither years of education nor current IQ were significantly correlated with any of our behavioral or ERP measures, even without correcting for multiple comparisons, suggesting that behavioral nor ERP group differences were not accounted for by the observed differences in education or IQ (see Table 2).

## Effects of Current $\Delta f$

As shown in Figure 2, as  $\Delta f$  increased there was an increase in the likelihood of hearing two streams for both groups,  $F(2,76)=359.43$ ,  $p<.001$ ,  $\epsilon=.92$ ,  $\eta^2=.904$ ; however, the schizophrenia group was overall less likely to perceive two streams compared to controls,  $F(1,38)=24.44$ ,  $p<.001$ ,  $\eta^2=.391$ . Given that the schizophrenia group reported hearing two streams more often with increasing  $\Delta f$  suggests they understood the task and performed appropriately, and were not for example simply reporting the presence of two different frequencies within the same stream, which would likely have resulted in very high proportions of reporting two sounds even for the 3-semitone condition (cf. Javitt et al., 1997).

Analyses also showed that the groups were significantly different for all  $\Delta f$  levels. For the 3-semitone condition the schizophrenia group was slightly more likely to perceive two streams overall compared to controls,  $t(38)=2.17$ ,  $p<.05$ . This could reflect a small degree of response bias to report hearing two streams. However, for the 6- and 12-semitone conditions the schizophrenia group was less likely to perceive two streams overall compared to controls [ $\Delta f=6$ :  $t(38)=5.36$ ,  $p<.001$ ;  $\Delta f=12$ :  $t(38)=3.84$ ,  $p<.002$ ]. Importantly, there was a group  $\times$   $\Delta f$  interaction,  $F(2,76)=19.88$ ,  $p<.001$ ,  $\epsilon=.92$ ,  $\eta^2=.343$ , such that the effect of  $\Delta f$  was smaller in the schizophrenia group compared to controls. Although there were quadratic trends in the data of both groups, the interaction between the linear components was significant,  $F(1,38)=13.24$ ,  $p<.001$ ,  $\eta^2=.258$ .

For both groups, as  $\Delta f$  increased there was a marginally increased negativity in the ERP response to the ABA- pattern, likely to be an N1 component 80-150 ms after the B tone,  $F(2,82)=3.01$ ,  $p=.06$ ,  $\epsilon=.915$ ,  $\eta^2=.068$ . There was also an increased positivity, likely to be a P2 component 200-280 ms after the B tone,  $F(2,82)=11.46$ ,  $p<.001$ ,  $\epsilon=.919$ ,  $\eta^2=.218$  (Figure 3 and Figure 4). For both components, we found no main effect of group, [N1:  $F(1,41)=.32$ ,  $p>.50$ ,  $\eta^2=.008$ ; P2:  $F(1,41)=.03$ ,  $p>.80$ ,  $\eta^2=.001$ ] nor did we find a  $\Delta f \times$  group interaction [N1:  $F(2,82)=.06$ ,  $p>.90$ ,  $\epsilon=.915$ ,  $\eta^2=.001$ ; P2:  $F(2,82)=1.01$ ,  $p>.30$ ,  $\epsilon=.919$ ,  $\eta^2=.024$ ]. However, for both N1 and P2 mean amplitudes there was a significant hemisphere  $\times$   $\Delta f \times$  group interaction [N1:  $F(2,82)=4.57$ ,  $p<.02$ ,  $\epsilon=.859$ ,  $\eta^2=.10$ ; P2:  $F(2,82)=3.66$ ,  $p<.05$ ,  $\epsilon=.803$ ,  $\eta^2=.082$ ] such that the effect of  $\Delta f$  on ERP mean amplitude was smaller in the schizophrenia group in the right hemisphere for the N1 and smaller in the left hemisphere for the P2 (Figure 4). For both components, there was no main effect of hemisphere, [N1:  $F(1,41)=1.40$ ,  $p>.20$ ,  $\eta^2=.033$ ; P2:  $F(1,41)=.42$ ,  $p>.50$ ,  $\eta^2=.01$ ] nor was there a significant hemisphere  $\times$   $\Delta f$  interaction [N1:  $F(2,82)=2.25$ ,  $p>.10$ ,  $\epsilon=.859$ ,  $\eta^2=.052$ ; P2:  $F(2,82)=.19$ ,  $p>.70$ ,  $\epsilon=.803$ ,  $\eta^2=.005$ ].

The following correlations assess the relationship between cortical  $\Delta f$  encoding and perception of streaming (see Figure 5). When combining all participants from both groups, the correlations between proportion of hearing two streams and size of P2 mean amplitude were significantly greater than zero (mean  $r=0.39$ ,  $t(39)=3.69$ ,  $p<.001$ ), indicating a moderate relation between low-level ERPs and perception of streaming. For the schizophrenia group separately there was a non-significant trend for the P2 correlations to be greater than zero,  $r=0.25$ ,  $t(18)=1.87$ ,  $p=.078$ . For the control group separately, the P2 correlations were significantly greater than zero,  $r=0.51$ ,  $t(20)=3.25$ ,  $p<.005$ . Results were similar when hemispheres were examined separately. For N1, no mean correlations were significantly different from zero ( $p>.05$ ) for both groups together or separately and for both hemispheres together or separately, although the trends were in the expected direction.



### Effects of Prior $\Delta f$

As shown in Figure 6, as prior  $\Delta f$  increased there was a decrease in the likelihood of hearing two streams during a later test sequence for both groups,  $F(2,76)=42.01$ ,  $p<.001$ ,  $\epsilon=.778$ ,  $\eta^2=.525$ , as demonstrated in previous studies (Snyder, Carter, et al., 2009; Snyder, et al., 2008; Snyder, Holder, et al., 2009; Snyder & Weintraub, 2011). Consistent with the data from the context pattern presented above, the schizophrenia group was less likely to perceive two streams overall compared to controls,  $F(1,38)=23.27$ ,  $p<.001$ ,  $\eta^2=.38$ . Most importantly, there was a group x prior  $\Delta f$  interaction,  $F(2,76)=3.81$ ,  $p<.05$ ,  $\epsilon=.778$ ,  $\eta^2=.091$ , such that the effect of prior  $\Delta f$  was smaller in the schizophrenia group compared to controls. Although there were quadratic trends for  $\Delta f$  in both groups, the interaction involving the linear component was significant,  $F(1,38)=4.28$ ,  $p<.05$ ,  $\eta^2=.101$ . The effect of prior  $\Delta f$  was not significantly correlated with the behavioral effect of current  $\Delta f$  measured during the context, suggesting that the abnormal prior  $\Delta f$  effect cannot be simply attributed to impaired processing of  $\Delta f$  during the context sequences. Finally, the schizophrenia group reported less streaming compared to controls for test sequences following silent-context trials,  $t(38)=3.73$ ,  $p<.001$ , consistent with the overall main effects of group reported above.

### Effects of Prior Perception

As shown in Figure 7, both groups showed a significant likelihood of hearing one stream during the test sequence when the previous context sequence was also heard as one stream [schizophrenia:  $t(18)=4.26$ ,  $p<.001$ ; control:  $t(20)=3.47$ ,  $p<.003$ ]. A similar perceptual stabilization occurred when the prior perception was two streams, however, this was only marginally so for the schizophrenia group [schizophrenia:  $t(18)=1.70$ ,  $p=.10$ ; control:  $t(20)=8.39$ ,  $p<.001$ ]. Importantly, there was a significant main effect of group,  $F(1,37)=4.80$ ,  $p<.05$ ,  $\eta^2=.115$ , such that the effect of prior perception was smaller in the schizophrenia group compared to controls. There was no significant prior perception x group interaction,  $F(1,37)=.25$ ,  $p>.60$ ,  $\eta^2=.007$ , suggesting that the group difference reported above was the same whether the prior percept was one or two streams. This effect is solely attributable to the prior perception and not aspects of the prior stimulus because this effect was only examined for trials in which both the context and test had  $\Delta f$  values of 6 semitones. Additionally, the effect of prior perception was not significantly correlated with the behavioral effect of current  $\Delta f$  measured during the context, suggesting that the abnormal prior perception effect cannot be attributed to impaired processing of  $\Delta f$  during the context sequences.

### Symptom Correlations

For the schizophrenia group, proportion of hearing two streams was negatively correlated with commenting hallucinations,  $r(17)=-.62$ ,  $p<.01$ , tactile hallucinations,  $r(17)=-.59$ ,  $p<.01$ , and global ratings of attention,  $r(17)=-.63$ ,  $p<.01$ , as measured from the SAPS and SANS. There was a marginal correlation between slope of P2 mean amplitudes and global ratings of attention,  $r(19)=.42$ ,  $p=.056$ . One study has shown that attention to a stream alters its neural representation, as reflected by a sharpened tuning curve for neurons responding to the frequency of attended sounds during a stream segregation task (Yin, Ma, Elhilali, Fritz, & Shamma, 2007). However, it is unlikely that the correlations with attention reflect a failure to attend to the sequences given the P2 modulations observed here are not affected by attention (Snyder et al., 2006), and all participants responded to most trials on time (within a 1.44 s window) and in the expected direction (minus the two participants who failed to understand the task). Finally, smaller prior  $\Delta f$  effects on perception were associated with larger avolition ratings,  $r(17)=.47$ ,  $p<.05$ , as measured from the SAPS/SANS.

## Discussion

We found that schizophrenia participants were less likely to report hearing two streams with increasing  $\Delta f$ , compared to controls. This was coupled with a reduced effect of  $\Delta f$  in the right-hemisphere N1 and left-hemisphere P2 ERPs time locked to the B (high) tone. Given that N1 and P2 arise from sources in the superior temporal plane, it is likely that the observed group differences are due at least in part to sensory-level impairments in auditory cortical areas in schizophrenia participants that are critical for organization of sound based on frequency. Furthermore, the fact that we found no main effect of group differences in our ERP measures and instead found impairments that were lateralized to either hemisphere suggests that our results are not due to other factors within our schizophrenia group such as medication effects, inattention, fatigue, etc. Instead, our results likely do reflect a true sensory processing impairment. Such impairment has clear implications for how auditory cortex abnormalities negatively affect normal functioning in day-to-day life, which we discuss in more detail below.

This is the first study to provide evidence that auditory stream segregation is impaired in schizophrenia, in contrast with a previous study (Bourdet et al., 2003). It is possible that we obtained different results because of differences in stimuli and tasks. For example, their study used very large  $\Delta f$  levels, which may have been unsuitable for revealing robust group differences. Indeed, the largest group difference reported in our study was at the intermediate  $\Delta f$ . Also, they indirectly measured streaming using a temporal-irregularity detection task, whereas our study measured streaming more directly by asking participants to report their perceptual experience. However, this latter difference is less likely to be responsible for the different findings because indirect and direct measures of streaming typically lead to similar findings (Micheyl & Oxenham, 2010a).

The present results can be interpreted in terms of a place model of stream segregation (Hartmann & Johnson, 1991), which posits that alternating tone sequences with a small  $\Delta f$  will activate overlapping frequency-selective neuronal populations and consequently be perceived as one auditory object; likewise, sequences with a large  $\Delta f$  will activate non-overlapping frequency-selective neuronal populations and consequently be perceived as two auditory objects. As a consequence of this spatial distinctiveness in the brain, neural populations will interact less such that suppression (e.g., adaptation, forward suppression, lateral inhibition) of the ERP response to the B (high) tone caused by the preceding A (low) tone is reduced. The enhanced ERP mean amplitudes with increasing  $\Delta f$  in the present study is therefore likely due to distinct neural populations being activated by the A and B tones, respectively, leading to more summed activity at the scalp. Thus, the schizophrenia group's reduced N1 and P2 mean amplitude with increasing  $\Delta f$  likely reflects more overlap in frequency-selective neurons compared to controls. This is consistent with studies of schizophrenia participants showing abnormal tonotopic organization and impaired processing of multiple frequencies in MEG responses (Rojas et al., 2002; Rojas et al., 2007). The significant correlation between behavioral performance and P2 mean amplitude reported here is consistent with our previous work (Snyder & Alain, 2007a; Snyder et al., 2006), demonstrating a link between auditory cortical ERPs and perception of stream segregation. The results further suggest that the reduced effect of  $\Delta f$  on perception of streaming in schizophrenia is related to abnormalities in place coding in auditory cortex rather than higher-level factors. This interpretation also explains why the perceptual group differences were most evident for the 6-semitone condition and did not increase linearly. That is, the 3- and 12-semitone conditions used here might be unlikely to show large group differences because in both groups they might be expected to show similar amounts of overlap or separation, respectively. The 6-semitone condition, in contrast, might be more likely to show large group differences because of an intermediate amount of overlap at a

neural level. Nevertheless, the possibility that the reduced effect of  $\Delta f$  on perception and ERPs in the schizophrenia group actually reflect more cognitive-level factors, such as an attentional impairment, cannot be definitively ruled out without further studies.

It is noteworthy that in the present study, N1 abnormalities in schizophrenia were right-hemisphere lateralized and P2 abnormalities were left-hemisphere lateralized. These results were probably not due to differences in handedness between the schizophrenia and control groups, given that the groups had similar proportions of left- and right-handed individuals. The results are also unlikely to be due to medication because the majority of schizophrenia participants were taking antipsychotic medicines, which do not seem to affect auditory ERPs (Umbricht et al., 1998, 1999). However, given the poor spatial resolution of ERPs and the inherent ambiguities in performing source analysis due to the inverse problem (Luck, 2005), these findings of lateralized ERP abnormalities require replication with methods that are better at revealing hemispheric differences in auditory cortex such as MEG. Nevertheless, the left-lateralized P2 abnormality is consistent with MRI studies showing left-lateralized STG gray matter volume reductions (McCarley et al., 1999; Shenton et al., 2001). Additionally, similar left-lateralized deficits have been shown in neurophysiological studies of auditory components M50 (an MEG form of P50) (Thoma et al., 2003), N200 (O'Donnell et al., 1993), and P300 (McCarley et al., 2002; McCarley et al., 1993). Previous right-lateralized deficits, similar to the N1 reduction reported here, have also been found in schizophrenia participants, in the form of reduced auditory steady-state response amplitudes to 40 Hz amplitude modulated noise (Hamm, Gilmore, Picchetti, Sponheim, & Clementz, 2011; Mulert, Kirsch, Pascual-Marqui, McCarley, & Spencer, 2011). Finally, a recent study showed N1 abnormalities were larger in anterior electrode sites compared to posterior sites. In contrast, P2 abnormalities in first-hospitalized schizophrenia participants were larger in posterior electrode sites than anterior sites (Salisbury, Collins, & McCarley, 2010). These findings provide additional evidence for topographical differences in N1 and P2 abnormalities in schizophrenia. Thus, our results of lateralized N1 and P2 impairments are consistent with previous studies showing that there may be distinct right- and left-lateralized deficits in the auditory cortices of schizophrenia participants.

In addition to low-level impairments in processing  $\Delta f$  in schizophrenia participants, we also observed reduced influences of immediate prior contexts compared to controls. These results are of interest because effects of context are necessary for understanding perception in naturalistic situations, such as when trying to interpret an utterance in the context of previous utterances by the same speaker. These reduced effects of prior  $\Delta f$  and prior perception in schizophrenia were unlikely to arise simply from lower-level impairments because the reductions did not correlate with reductions in effects of current  $\Delta f$ . This is consistent with other research suggesting that cognitive impairments during an auditory perception task do not arise from low-level impairments (van der Stelt, Frye, Lieberman, & Belger, 2004; but see Leitman et al., 2010). Instead, these impairments likely reflect abnormalities within relatively high-level auditory areas that are not finely tuned to frequency (Snyder, Carter, et al., 2009) but are sensitive to rhythmic pattern (Snyder & Weintraub, 2011). Our findings are also consistent with previous research using visual, auditory, and language processing paradigms, which also showed that schizophrenia participants show a reduced tendency to be influenced by prior context (visual studies: Silverstein, Bakshi, Chapman, & Nowlis, 1998; Silverstein, Knight, et al., 1996; Uhlhaas, Phillips, Mitchell, & Silverstein, 2006; Uhlhaas & Silverstein, 2005; auditory studies: Ford, 1999; Ford et al., 2010; Ford, White, Lim, & Pfefferbaum, 1994; Niwa et al., 1992; van der Stelt et al., 2004; language studies: Condray, Steinhauer, Cohen, van Kammen, & Kasperek, 1999; Ditman & Kuperberg, 2007; Kuperberg, Kreher, Goff, McGuire, & David, 2006; Kuperberg, McGuire, & David, 1998; Mitchell et al., 1991; Strandburg et al., 1997). And our results also extend one previous study showing a reduced tendency for prior contextual

information to influence auditory perceptual organization (Silverstein, Matteson, et al., 1996). Thus, our findings strongly suggest that both low-level and high-level aspects of stream segregation are impaired in schizophrenia participants and therefore raise the important question of how these impairments affect functioning in real-world situations such as a noisy social setting. Our results further suggest that processing of contextual information is a general difficulty found in schizophrenia that is likely to impair their ability to make sense of complex real-world acoustic situations.

Future studies should continue to examine the extent to which sound segregation is impaired in schizophrenia. For example, studies have shown useful cues for stream segregation besides pure-tone frequency, such as fundamental frequency of complex tones (Vliegen & Oxenham, 1999), amplitude modulation (Grimault, Bacon, & Micheyl, 2002), and interaural time difference (Hartmann & Johnson, 1991). Given that individuals with schizophrenia have difficulty processing auditory cues other than frequency, including intensity (Bach, Buxtorf, Strik, Neuhoff, & Seifritz, 2011) and interaural time difference (Matthews, Todd, Budd, Cooper, & Michie, 2007), they might show a generalized impairment in stream segregation. Another important question is whether sound segregation impairments generalize to sounds played concurrently (Micheyl & Oxenham, 2010b). Finally, future studies should use tasks that more closely match real-world environments such as using tests that assess the ability to recognize spoken sentences in the presence of background noise (Bilger, Nuetzel, Rabinowitz, & Rzeczkowski, 1984). Abnormalities on speech in noise tests would suggest that sound segregation impairments in schizophrenia generalize to more natural settings.

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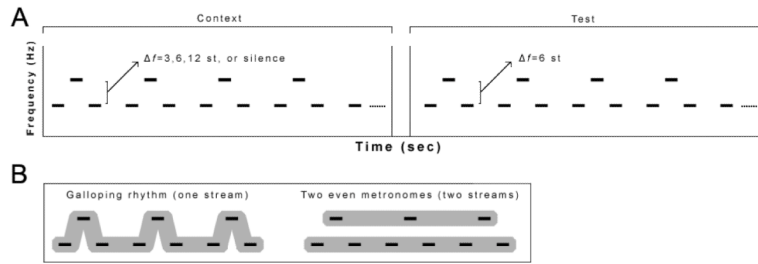
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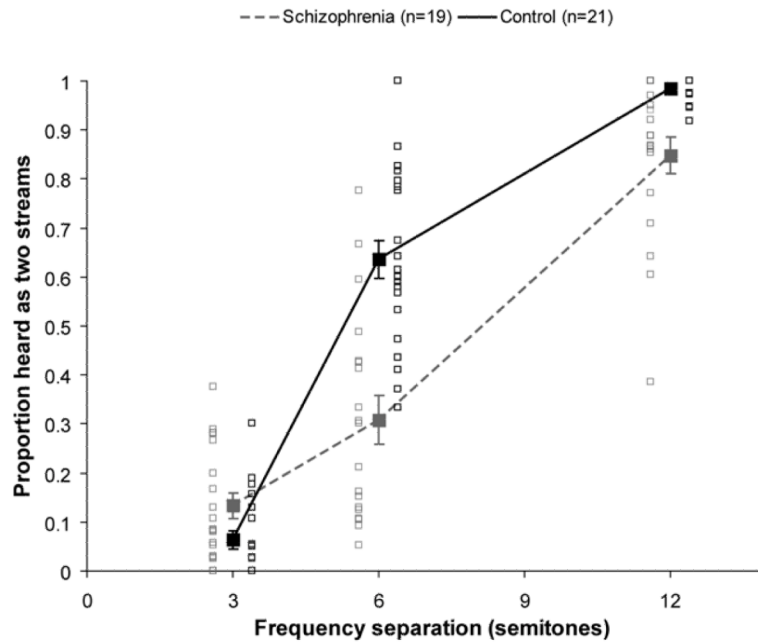
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**Figure 1.**

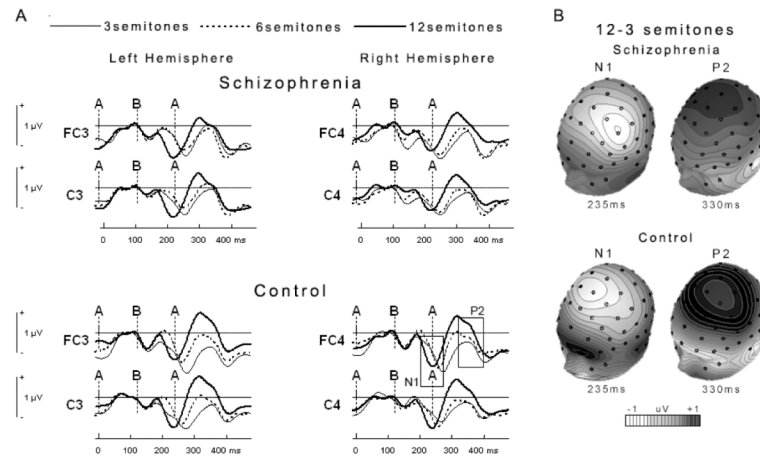
Stimulus design and perceptual organization. (A) Trials consisted of a 6.72 s context sequence, a 1.44 s silent interval, and a 6.72 s test sequence. Context and test sequences both consisted of 14 repeating ABA-patterns where A represents a low tone, B a high tone, and - a silence. The  $\Delta f$  between the low and high tones during the test sequence was always 6 semitones (st) where A=300 Hz and B=424 Hz. During the context sequence, four of the following conditions could occur: (1) A=300 Hz, B=357 Hz ( $\Delta f=3$  st), (2) A=300 Hz, B=424 Hz ( $\Delta f=6$  st), (3) A=300 Hz, B=600 Hz ( $\Delta f=12$  st), or (4) silence. Each context sequence was paired with the test sequence to make a total of 4 trial types. (B) Both context and test patterns could be heard as either a galloping rhythm (one stream) or two even metronomes (two streams).



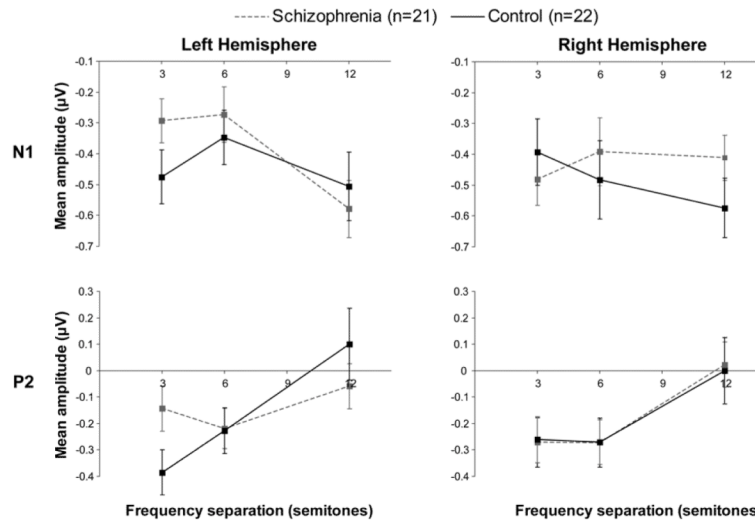
**Figure 2.**

Behavioral effects of current  $\Delta f$ . Effects of  $\Delta f$  on proportion of streaming. For both groups, there was a significant effect of  $\Delta f$  ( $p < .001$ ); however, the effect of  $\Delta f$  was smaller in the schizophrenia group than the control group ( $p < .001$ ). Grey boxes represent individual schizophrenia participants. Black boxes represent individual control participants. Note that boxes have been spaced apart on the x-axis for visual comparison purposes only. Error bars represent  $\pm 1$  SE.



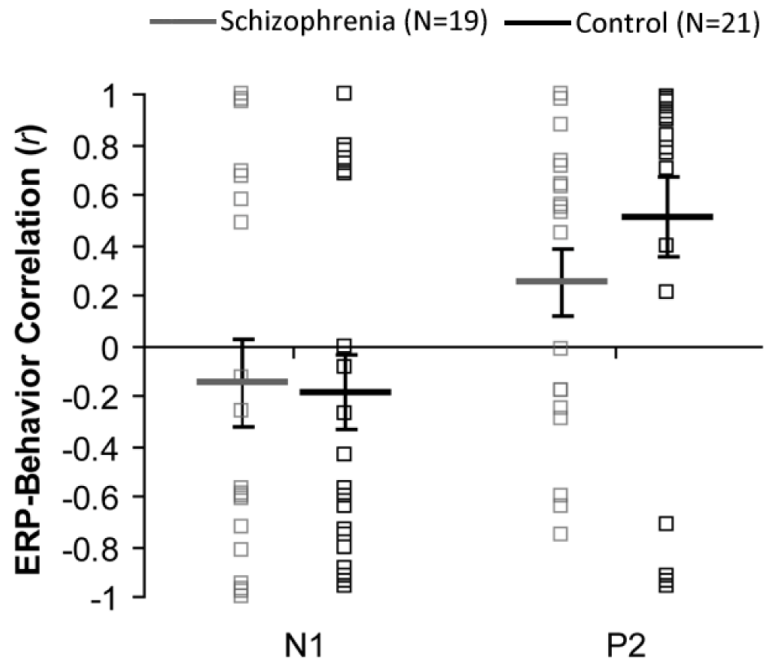


**Figure 3.** Event-related potential (ERP) results. Effect of  $\Delta f$  on ERPs time-locked to the B tone. For both groups, there was a marginally increased negativity ( $p=.06$ ), likely to be an N1 component 80-150 ms after the B tone and a significantly increased positivity ( $p<.001$ ), likely to be a P2 component 200-280 ms after the B tone. N1 and P2 components have been referenced in the bottom right panel. Boxed frames highlight the latency windows chosen for statistical analysis. These latency windows were chosen as they showed the largest difference between conditions and groups. Vertical lines with labels indicate tone onsets in the ABA pattern.

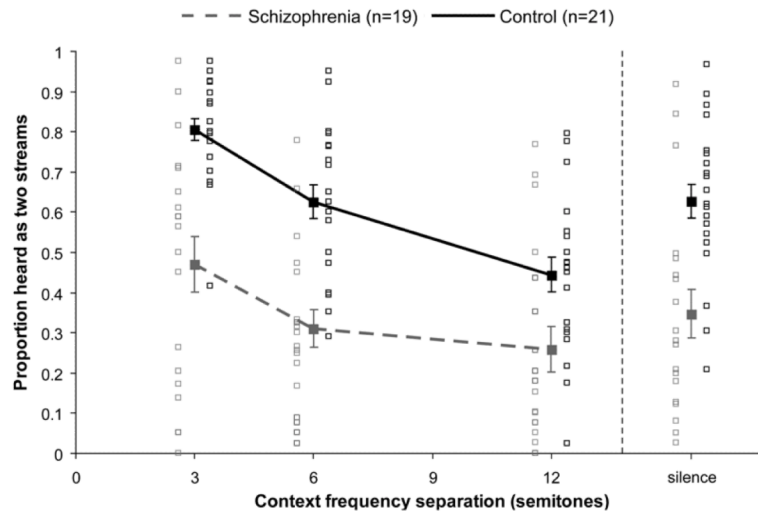


**Figure 4.**

(A) Event-related potential (ERP) results. Graph representation of the data presented in Figure 3 for the N1 and P2 ERPs separated by hemisphere. The effect of  $\Delta f$  was smaller in the schizophrenia group in the right hemisphere for the N1 ( $p < .02$ ) and smaller in the left hemisphere for P2 ( $p < .05$ ). Data for the N1 are mean amplitudes 80-150 ms after the B tone. Data for the P2 are mean amplitudes 200-280 ms after the B tone. Note the different mean amplitude scales for each component. Left hemisphere includes FC3 and C3 electrodes. Right hemisphere includes FC4 and C4 electrodes. Error bars represent  $\pm 1$  SE. (B) Topographies of difference waves for ERPs elicited when  $\Delta f$  is 12-3 semitones. Isopotential contours reflect  $0.05 \mu V$ /step.



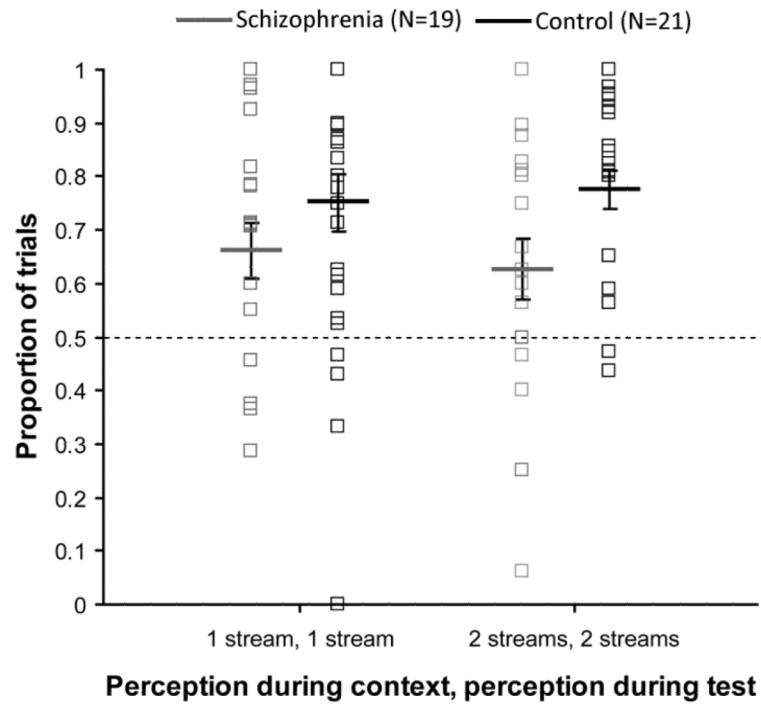
**Figure 5.** Brain-behavior correlations. Average correlations between participants' ERP mean amplitude modulations due to increased  $\Delta f$  and behavioral modulations of reporting two streams due to increased  $\Delta f$ , for the N1 and P2, respectively. Solid lines and boxes represent group averages and individual participants, respectively. Error bars represent  $\pm 1$  SE.



**Figure 6.**

Behavioral effects of prior  $\Delta f$ . For both groups, there was a significant effect of prior  $\Delta f$  ( $p < .001$ ), with less perception of two streams when the prior  $\Delta f$  was larger; however, the effect of prior  $\Delta f$  was smaller in the schizophrenia group compared to controls ( $p < .05$ ).

Additionally, the schizophrenia group reported less streaming compared to controls for test sequences following silent-context trials ( $p < .001$ ). Gray boxes represent individual schizophrenia participants. Black boxes represent individual control participants. Note that boxes have been spaced apart on the x-axis for visual comparison purposes only. Error bars represent  $\pm 1$  SE.



**Figure 7.**

Behavioral effects of prior perception. For both groups, there was a significant effect of prior perception ( $p < .001$ ), with a likelihood greater than chance of perceiving the same organization for consecutive patterns; however, the effect of prior perception was smaller in the schizophrenia group compared to controls ( $p < .04$ ). Solid lines and boxes represent group averages and individual participants, respectively. Averages reflect adjusted means from the ANCOVA analysis. Dotted horizontal line indicates the 50% proportion. Error bars represent  $\pm 1$  SE.



**Table 1**  
**Demographic characteristics for the schizophrenia and healthy control groups**

|                                   | Schizophrenia<br>(n=21) | Normal control<br>(n=22) | Between Group<br>Differences |
|-----------------------------------|-------------------------|--------------------------|------------------------------|
| Demographic Information           |                         |                          |                              |
| Age (SD)                          | 45.2 (12.1)             | 39.8 (12.0)              | $t=1.47, p=.15$              |
| % Females                         | 38                      | 50                       | $\chi^2=.62, p=.43$          |
| % Right Handed                    | 81                      | 100                      | $\chi^2=4.62, p=.10$         |
| Education (SD)                    | 11.8 (2.9)              | 14.6 (2.7)               | $t=-3.82, p<.001$            |
| IQ (SD)                           | 79.8 (13.2)             | 100.8 (12.0)             | $t=-5.42, p<.001$            |
| Ethnic Distribution               |                         |                          |                              |
| % Caucasian                       | 47.6                    | 63.6                     | $\chi^2=10.4, p=.10$         |
| % African American                | 33.3                    | 9.0                      |                              |
| % Hispanic / Latino               | 4.8                     | 13.6                     |                              |
| % Pacific Islander                | 4.8                     | 0                        |                              |
| % American Indian                 | 4.8                     | 0                        |                              |
| % Bi-racial                       | 4.8                     | 0                        |                              |
| % Other                           | 0                       | 13.6                     |                              |
| Current Psychiatric Medication    |                         |                          |                              |
| % Unmedicated                     | 9.5%                    |                          |                              |
| % Antipsychotics (typical)        | 9.5%                    |                          |                              |
| % Antipsychotics (atypical)       | 81.0%                   |                          |                              |
| Current Treatment (n=17) *        |                         |                          |                              |
| % Outpatient                      | 76.2%                   |                          |                              |
| % No Treatment                    | 4.8%                    |                          |                              |
| Other Patient Information         |                         |                          |                              |
| Age at Onset (SD) (n=19) *        | 20.8 (8.0)              |                          |                              |
| Duration of Illness (SD) (n=19) * | 25.1 (13.7)             |                          |                              |
| # Hospitalizations (SD) (n=16) *  | 3.6 (1.6)               |                          |                              |

\* =value of *n* represents the number of schizophrenia participants with endorsed information

**Table 2**  
**Correlation matrix for schizophrenia and control groups separately displaying Pearson Correlation ( $r$ ) and corresponding p-value ( $p$ ) for correlations between Education or IQ and the effect of current  $\Delta f$  on behavioral responses ( $\Delta f$ ), N1 ERP amplitudes (N1), P2 ERP amplitudes (P2), the effect of prior  $\Delta f$  on behavioral responses (Prior  $\Delta f$ ), or the effect of prior perception on behavioral responses (Prior Perception)**

| Schizophrenia              |              |              |              |                  |                  |  |
|----------------------------|--------------|--------------|--------------|------------------|------------------|--|
|                            | $\Delta f$   | N1           | P2           | Prior $\Delta f$ | Prior Perception |  |
| Education [ $r$ , ( $p$ )] | .201 (.410)  | .269 (.238)  | -.347 (.124) | -.326 (.173)     | -.296 (.219)     |  |
| IQ [ $r$ , ( $p$ )]        | -.174 (.475) | .082 (.722)  | -.120 (.604) | .022 (.929)      | .042 (.864)      |  |
| Control                    |              |              |              |                  |                  |  |
|                            | $\Delta f$   | N1           | P2           | Prior $\Delta f$ | Prior Perception |  |
| Education [ $r$ , ( $p$ )] | .031 (.894)  | -.150 (.515) | -.329 (.145) | -.065 (.780)     | .224 (.330)      |  |
| IQ [ $r$ , ( $p$ )]        | .086 (.711)  | -.098 (.673) | -.165 (.474) | -.105 (.651)     | .203 (.379)      |  |