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Evidence for stimulus-general impairments on auditory stream segregation tasks in schizophrenia

Erin. M. Ramage [1], David M. Weintraub [1], Daniel N. Allen, Joel S. Snyder*

Department of Psychology, University of Nevada, 4505 Maryland Parkway, Mail Stop 5030, Las Vegas, NV 89154-5030, USA

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ABSTRACT

Background: Auditory impairments in schizophrenia have been demonstrated previously, especially for tasks requiring precise encoding of frequency, although it is unclear the extent to which they have difficulty using pitch information and other cues to segregate sounds. We determined the extent to which those with schizophrenia have difficulty using pitch information and other auditory cues to segregate sounds that are presented sequentially.

Methods: Ten participants with schizophrenia and nine healthy/normal control participants completed a battery of tasks that tested for the ability to perform sequential auditory stream segregation using pitch, amplitude modulation, or inter-aural phase difference as cues to segregation.

Results: All three sequential segregation tasks showed reduced tendency for those with schizophrenia to perceive segregated sounds, compared to control participants.

Conclusions: These findings extend prior research by demonstrating a general impairment on sequential sound segregation tasks in schizophrenia, and not just on tasks that require precise encoding of frequency. Together, the pattern of results provide evidence that auditory impairments in schizophrenia result from selective abnormalities in neural circuits that carry out specific computations necessary for stream segregation, as opposed to an impairment in processing specific cues.

1. Background

It is well established that individuals with schizophrenia (SZ) have auditory abnormalities. For example, SZ reduces the ability to discriminate sounds on the basis of frequency, a deficit that cannot easily be accounted for by differences in attention or sensory memory (Javitt et al., 1997). People with SZ also have abnormal categorical perception of speech sounds (Cienfuegos et al., 1999) and reduced ability to use the melody of a speaker's voice to understand the meaning of sentences (Leitman et al., 2005, 2010). Importantly, the latter finding of impaired speech prosody judgments was accounted for by impairments in frequency discrimination, suggesting that high-level perceptual difficulties might arise from basic sensory encoding problems. Consistent with this suggestion, studies indicate abnormal structure and function of the auditory cortex in SZ. Reduced gray matter volume of primary and secondary auditory cortex is present even in SZ at first hospitalization, especially in left-hemisphere structures (Kasai et al., 2003) and reduced cortical responses to frequency change appear within the first two years after first hospitalization (Salisbury et al., 2007).

Recently, we provided evidence for deficits in SZ for precise frequency encoding using an auditory stream segregation task (Weintraub et al., in press), in which participants listen to sequentially presented low (A) and high (B) pure tones and silences (–) in a repeating ABA pattern and judge whether the tones were perceived as one stream in a galloping rhythm (ABA-ABA) or two segregated streams with isochronous rhythms (A-A- and B-B-B-B) (Bregman and Campbell, 1971; Snyder and Alain, 2007). A main cue that influences the ability to hear two segregated streams (or "streaming") is the frequency separation between the A and B tones (Δf). In healthy individuals, streaming is more likely to occur as Δf increases. In comparison to controls, however, people with SZ show less increase in perception of two streams as Δf values increased (Weintraub et al., in press). Electrophysiological responses from auditory cortex that were recorded during the stream segregation task also showed reduced tendency to increase in amplitude with increased Δf, suggesting that the perceptual difficulties in SZ were occurring at a basic sensory encoding level of processing (Weintraub et al., in press).

* Corresponding author. Tel.: +1 011 702 895 4692; fax: +1 011 702 895 0195.
E-mail address: joel.snyder@unlv.edu (J.S. Snyder).
[1] These authors contributed equally.

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The study of auditory stream segregation ties abnormalities in the auditory system with everyday situations in which individuals with SZ have difficulty. In natural environments, the ability to segregate sounds arising from multiple sources, such as the speech of one individual from another as well as from background noise (e.g., cars honking, dogs barking), is paramount to successful social interactions, a domain clearly impaired in SZ (Edwards et al., 2002). Because the ability to segregate sounds is very important in everyday listening situations, addressing questions about the nature of this ability in SZ may provide insights into basic mechanisms that contribute to ecologically relevant listening deficits. Such investigations will also help clarify findings of prior studies that suggest normal stream segregation in SZ (Bourdet et al., 2003).

The main goal of the current study was to determine whether stream segregation deficits in SZ were limited to cases in which pure-tone frequency was the cue for hearing two streams. If auditory deficits in SZ are primarily due to poor encoding of frequency or pitch, sound segregation on the basis of other cues might offer opportunities for those with SZ to take advantage of redundant cues in the environment to discriminate separate sound sources. However, previous behavioral evidence showed that people with SZ have deficits in processing other acoustic cues such as intensity, duration, and spatial location (Bach et al., 2011; Davalos et al., 2003; Elvevag et al., 2003; Penney et al., 2005; Perrin et al., 2010). Additionally, electrophysiological evidence has shown reduced cortical responses of the mismatch negativity (MMN) response in SZ (Michie, 2001); the MMN is elicited when deviant changes in stimulus characteristics are detected within a backdrop of repeated standard sounds. These reduced MMN responses have been reported due to changes not only in frequency (Todd et al., 2008), but also intensity and duration (Michie, 2001; Todd et al., 2008), the latter even preceding onset of psychosis (Atkinson et al., 2012). Taken together, reduced perception of changes in sound intensity, duration, and spatial location, as well as reduced allocation of neural resources in response to changes in intensity and duration, suggest individuals with SZ have deficits in processing acoustic cues other than frequency. How deficits in processing these acoustic cues may affect sound segregation in SZ has not yet been studied; thus, it remains to be seen whether there are general difficulties with streaming, regardless of the available segregation cues. In the current study, we assess streaming in control and SZ participants using cues that have been shown previously to facilitate segregation in healthy individuals: complex-tone fundamental frequency, amplitude-modulation frequency, and inter-aural phase difference (Grimault et al., 2002; Schadwinkel and Gutschalk, 2010; Vliegen et al., 1999).

2. Materials and methods

2.1. Participants

This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and following a protocol approved by an Institutional Review Board at the University of Nevada, Las Vegas. Ten individuals with SZ (7 Undifferentiated, 2 Residual, 1 Schizoaffective) and nine healthy controls participated in the study. Table 1 contains demographic information for each group. Groups had similar mean ages, although there were more females in the control group; however, there were no significant gender differences on any of the tasks within either group. For the SZ group, nine of the ten were taking atypical antipsychotics and one was taking a typical antipsychotic. All participants exhibited normal hearing for their age (<30 dB HL from 250 to 1000 Hz, <40 dB HL from 2000 to 8000 Hz).

Table 1
Demographic characteristics for the SZ and healthy control groups.

	SZ ($n = 10$)	Healthy control ($n = 9$)
Demographic information		
Age (SD)	44.0 (10.2)	45.3 (7.5)
% Females	30.0%	66.7%
Current psychiatric medication		
% Antipsychotics (typical)	10.0%	
% Antipsychotics (atypical)	90.0%	
Current treatment ($n = 8$)[a]		
% Outpatient treatment	100%	
% Inpatient treatment	0%	
Other illness information		
Age at onset (SD) ($n = 9$)[a]	19.1 (8.2)	
Duration of illness (SD) ($n = 9$)[a]	25.2 (12.7)	
# Hospitalizations (SD) ($n = 7$)[a]	3.7 (1.9)	

[a] Value of n represents the number of SZ participants with endorsed information.

SZ participants were recruited through a community mental health center. 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 or neurological disorder, a medical condition with known effects on central nervous system function, diagnosis of alcohol or drug abuse or dependence within the last 12 months, alcohol or drug use within the last 24 h, or use of medications that would affect neurological or cognitive function, other than those medications prescribed to treat SZ.

Diagnosis of SZ was established by clinically trained graduate student assistants using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First et al., 2002), and information from mental health professionals providing treatment to these individuals. Control participants were screened for inclusion and exclusion criteria via self-report during a telephone interview. Symptom ratings were not collected on the day of testing as part of this investigation; however the Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) was collected as part of a previous study one week to 15 months prior ($M = 4.33$, $SD = 4.40$). After complete description of the study to participants, written informed consent was obtained.

2.2. Stimuli

Complex-tone fundamental frequency, amplitude-modulation frequency, and inter-aural phase difference have each been shown to be helpful cues for perceiving streaming (Grimault et al., 2002; Schadwinkel and Gutschalk, 2010; Vliegen et al., 1999) and so the A and B tones used in the current study were developed to differ by varying amounts on one of these three stimulus dimensions. Table 2 shows the various stimulus values for the A and B tones for each of the three stimulus dimensions.

In the complex-tone fundamental frequency condition, A and B tones were complex tones of different fundamental frequencies that consisted of only harmonics in the 800–1600 Hz frequency range, in order to yield tones that differed predominantly in terms of perceived pitch with minimal differences in the distribution of energy in the spectral domain. The A tone always had a fundamental frequency of 100 Hz, and consisted of the harmonics 800, 900, 1000, 1100, 1300, 1400, 1500, and 1600 Hz. The B tones had fundamental frequencies of 141, 200, and 400 Hz (i.e., 0.5, 1, and 2 octaves above the A tone fundamental, respectively), and consisted of the following sets of harmonics, respectively: 846, 987, 1128, 1269, and 1551 Hz; 800, 1000, 1200, and 1400 Hz; and 800, 1200, and 1600 Hz. To generate each complex tone, these four sets of sine waves were averaged together (as opposed to summing) in order to generate sounds of roughly equal intensity.

Table 2
Stimulus values of A and B tones.

	Stimulus dimension		
	Fundamental frequency	Amplitude modulation frequency	Inter-aural phase difference
Small difference			
A tone	100 Hz	100 Hz	−500 μsec
B tone	141 Hz	141 Hz	−250 μsec
Medium difference			
A tone	100 Hz	100 Hz	−500 μsec
B tone	200 Hz	200 Hz	0 μsec
Large difference			
A tone	100 Hz	100 Hz	−500 μsec
B tone	400 Hz	400 Hz	+500 μsec

In the amplitude-modulation frequency condition, the A and B tones were 1000 Hz sine tones multiplied by a sinusoidal modulation window to yield pure tones that had the same carrier frequency but different modulation frequencies. The A tone always had a modulation frequency of 100 Hz, and the three B tones had modulation frequencies of 141, 200, and 400 Hz (i.e., 0.5, 1, and 2 octaves above the A tone modulating frequency), respectively.

In the inter-aural phase difference condition, the A and B tones were 300 Hz sine tones in which the onset of the tone was delayed in one ear relative to the other by varying amounts. The A tone always had a −500 μsec phase difference, meaning the tone was presented in the left ear 500 μsec earlier than in the right ear. The three B tones had phase differences of −250, 0, and +500 μsec, respectively. It should be noted that the largest phase difference of +500 μsec was perceived by participants as being rather similar to the A tone, and thus resulted in less perception of two streams than expected. The reason for this is that despite the large difference in onset time between tones in the left and right ear, the resulting phase difference was such that the waveforms in the two ears were perfectly inverted with respect to each other for both the A and B tones. This phase inversion for the A and B tones apparently made the tones difficult to segregate from each other. However, we did not exclude this condition from the analysis because it still allowed us to examine differences between groups in overall amount of streaming.

Auditory stimuli were generated in Matlab (The MathWorks, Inc., Natick, MA) and consisted of pure tones (100 ms in duration, including 10 ms rise/fall time) presented binaurally through Sennheiser HD 280 headphones (Sennheiser Electronic Corporation, Old Lyme, CT) at 70 dB SPL. Each of the three stimulus types was presented in separate blocks in the following order: Block 1 used complex-tone fundamental frequency; Block 2 used amplitude-modulation frequency; and Block 3 used inter-aural phase difference. Within each block, 20 trials were presented for each level of stimulus difference (see Table 2) and these trials were presented in random order. Each trial consisted of a 6.72 s sequence of tones with an intertrial interval of 3 s. Stimulus sequences consisted of 14 repeating ABA-patterns where A represents a tone with a lower stimulus value, B a tone with a higher stimulus value, and − a silence. Between blocks, participants could rest for as long as they liked.

2.3. Procedures

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 and at the end of each 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. Participants were instructed to listen to each sound sequence without any expectation of hearing one or two streams, and to simply allow their perception to occur naturally without bias. Prior to beginning the experimental trials, participants completed a block of practice trials that was typically five trials long but lasted until they could sufficiently distinguish between the two percepts.

2.4. Data analysis

The effect of stimulus difference on perception was calculated as the proportion of trials that each participant reported hearing two separate streams for each trial type. To determine if there were differences in perception between the groups, these proportions were entered into mixed-model analyses of variance with stimulus difference (small, medium, and large) as a within-subjects factor and group (SZ, control) as a between-subjects factor, separately for each type of stimulus. The degrees of freedom were adjusted using the Greenhouse–Geisser ε (reported for each within-subject effect) and all reported probability estimates were based on the reduced degrees of freedom. To investigate relations between streaming and auditory hallucinations in SZ participants only, a mixed-model analysis of variance was used with stimulus difference as the within-subjects factor and auditory hallucination status (marked or severe auditory hallucinations AND some degree of voices vs. no or questionable auditory hallucinations) as the between-subjects factor.

3. Results

As shown in Fig. 1, as stimulus difference between the A and B tones increased there was a general increase in the likelihood of hearing two streams for both groups for the fundamental frequency, amplitude modulation frequency, and inter-aural phase difference conditions. An exception was the inter-aural phase difference condition in which streaming increased from the small to the medium but decreased from the medium to large phase difference (see Materials and methods for further explanation of the reasons for this effect). Nevertheless, the main effect of stimulus difference was significant for fundamental frequency, $F(2,34) = 95.66$, $p < .001$, $\eta_p^2 = 0.849$, $\varepsilon = 0.98$, amplitude modulation frequency, $F(2,34) = 22.75$, $p < .001$, $\eta_p^2 = 0.572$, $\varepsilon = 0.80$, and inter-aural phase difference, $F(2,34) = 14.86$, $p < .001$, $\eta_p^2 = 0.466$, $\varepsilon = 0.76$. There was also a main effect of group in each condition, due to control participants reporting more perception of streaming than participants with SZ for fundamental frequency, $F(1,17) = 5.59$, $p < .05$, $\eta_p^2 = 0.247$, amplitude modulation frequency, $F(1,17) = 11.10$, $p < .005$, $\eta_p^2 = 0.395$, and inter-aural phase difference, $F(1,17) = 8.70$, $p < .01$, $\eta_p^2 = 0.338$, respectively. In addition to the main effects of stimulus difference and group, there was also an interaction between these two factors for the fundamental frequency condition only, $F(2,34) = 4.20$, $p < .025$, $\eta_p^2 = 0.198$, $\varepsilon = 0.98$. As seen in Fig. 1, this interaction occurred because the control group reported hearing two streams more often than the SZ group when the stimulus difference was medium, but no such differences were present when stimulus differences were small or large.

Post-hoc comparison of those experiencing marked or severe auditory hallucinations (SAPS Item 1, rating of 4 or 5) with mild or worse voices (SAPS Items 2 or 3, rating 2 or greater) (with AHs, $n = 6$) vs. those with no or questionable auditory hallucinations (without AHs, $n = 4$) with no voices (rating of 0 on both Items 2 and 3) within the SZ group revealed a significant interaction between inter-aural phase difference and auditory hallucination status $F(2,16) = 19.38$, $p < .001$, $\eta_p^2 = 0.708$, $\varepsilon = 0.91$. This interaction

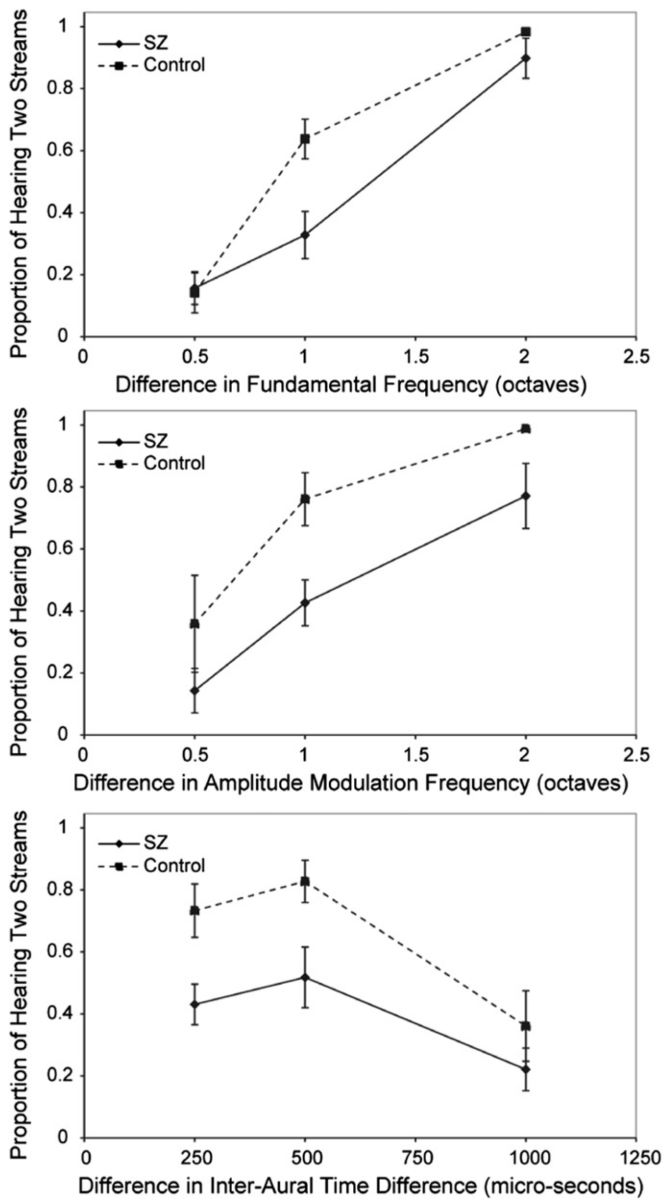

Fig. 1. Behavioral results: Effects of stimulus difference on proportion of streaming for schizophrenia ($n = 10$) and control participants ($n = 9$) for each of the three stimulus dimensions on which A and B tones could differ.

occurred due to reduced reports of streaming in the SZ participants with AHs as compared to those without AHs when the stimulus difference was medium. No significant findings in either the fundamental frequency or the amplitude modulation frequency conditions were found between auditory hallucination groupings.

4. Discussion

The results clearly demonstrate that individuals with SZ have reduced likelihood of hearing two segregated streams compared to control participants, regardless of whether the stimuli differ with regard to fundamental frequency, amplitude-modulation frequency, or inter-aural phase. These findings extend our other study, in which participants with SZ reported less streaming when alternating tones differed only in pure-tone frequency (Weintraub et al., in press). In that study, sensory-evoked brain responses arising from auditory cortex mirrored this group difference by showing less streaming-related neural modulations in the SZ group compared to controls. Considered together, these behavioral and sensory-evoked brain response differences suggested that streaming deficits in SZ were most likely due to abnormalities in sensory-level processing of sound frequency. Thus, the current results extend the previous findings by showing that stream segregation deficits in SZ are not confined to cases in which simple frequency processing is critical to hearing two streams. Rather, the current results suggest that the computations that enable perceptual segregation of sequential sounds coming from different sources (Bregman and Campbell, 1971; Snyder and Alain, 2007) may be operating abnormally in individuals with SZ, regardless of which stimulus dimension is being used to compute perception. Another possibility, however, is that the encoding of many stimulus features in the auditory system of individuals with SZ is impaired and that this results in reduced streaming using a wide variety of cues.

Our previous study on streaming in SZ and the current study conflict with previous findings that suggest individuals with SZ might not have stream segregation deficits (Bourdet et al., 2003). However, this conflict may be explained by differences in the stream segregation tasks used in our studies and the Bourdet et al. study. Perhaps most importantly, the frequency differences between the tones used by Bourdet et al. were much larger than the medium frequency difference we have observed to yield the largest difference in segregation between our groups. Also, Bourdet et al. used a task that was an indirect measure of streaming (temporal irregularity detection), as opposed to the direct one that we have used (reporting “one stream” vs. “two streams”). This latter difference between studies is less likely to explain the different findings, because indirect and direct measures of streaming typically yield similar patterns of results (e.g., compare Roberts et al., 2008; Rogers and Bregman, 1993, 1998). We did not directly address this matter so it would be important to measure streaming indirectly in individuals with SZ and controls, but using stimulus differences between A and B tones that we have shown to yield robust group differences.

Although the current study did not measure brain activity during the streaming tasks, prior neurophysiological studies of streaming with fundamental frequency and inter-aural time differences (Gutschalk et al., 2007; Schadwinkel and Gutschalk, 2010) suggest that abnormalities in auditory cortical processing underlie the streaming deficits with the acoustic cues examined here. In particular, the studies by Gutschalk et al. demonstrate that frequency-based streaming and streaming with cues other than frequency are accomplished using similar neurocomputational mechanisms, most likely by the activation of distinct neural populations responding to the A and B tones. As the acoustic difference between A and B tones becomes larger, this likely activates populations of neurons that are more segregated (non-overlapping), leading to greater perception of two separate streams. For example, this is particularly suited for frequency cues due to the tonotopic organization of the auditory cortex (Hartmann and Johnson, 1991; Snyder and Alain, 2007), where neurons tuned to particular frequencies are organized according to frequency. One mechanism that might help explain frequency-based stream segregation deficits in schizophrenia is lateral inhibition, or a decrease in neural activity for neurons adjacent to those previously activated. Lateral inhibition is important for maintaining the sharp tuning curves that allow precise encoding of frequency in the auditory cortex (Wang et al., 2002). Given the inhibitory abnormalities seen in schizophrenia (Benes and Berretta, 2001; Lewis et al., 2005), reduced lateral inhibition is a good candidate for abnormalities in stream segregation. Another possible mechanism of stream segregation is forward masking, the suppression of neural responses to tones that occurs as a result of preceding tones (Fishman et al., 2001; Bee and Klump, 2004). A forward-masking effect similar to that described with frequency differences has also been shown in amplitude-modulated stimuli (Wojtczack and Viemeister, 2005), although its effect on the perception of stream segregation is unknown. Thus, further investigation of basic auditory processes such as lateral inhibition and forward masking in schizophrenia as well as their association with perception of streaming is needed.

While there is a possibility that higher-order cognitive impairments could account for the reduced perception of stream segregation found in this study, previous research has shown that neither attention nor sensory memory can fully account for other auditory impairments seen in schizophrenia, such as frequency discrimination deficits (Javitt et al., 1997). Thus, it is likely that basic auditory processing mechanisms necessary for the perception of sequential stream segregation can better account for the observed impairments. However, future research could directly address this issue by statistically controlling for attention and working memory performance in a larger sample of participants.

In a post-hoc analysis comparing participants in the SZ group with and without auditory hallucinations (AHs), those with AHs reported reduced stream segregation when the inter-aural phase difference was medium, suggesting a link between more severe clinical symptoms and an impaired ability to utilize cues from stimulus differences that are more ambiguous. This finding is interesting in relation to a previous study by Hoffman et al. (1999) reporting that SZ participants with AHs had a reduction in the ability to repeat speech with background babble from narrative passages in an ongoing fashion relative to those without AHs. However, the current study did not find any differences according to hallucination group on the fundamental-frequency or the amplitude-modulation tasks. Thus, it is possible that the link between hallucinations and perception is specific to only some auditory cues or that the finding is not robust, the latter being of particular concern given the small sample size and the time delay between the symptom ratings and the streaming tasks.

Despite the robust effect sizes found in this study, the small sample size precluded examination of how the current results may have been influenced by a number of important clinical variables, such as medication effects and disease chronicity; therefore, future studies should assess these factors in larger samples. For example, there is a mixed set of findings regarding the effects of antipsychotic medications on physiological measures related to auditory function (Kumari et al., 1999; Leumann et al., 2002; Rosburg et al., 2008; Umbricht et al., 1998). However, it is not clear how these findings translate into perceptual changes, thus emphasizing the need for investigation of auditory perception in drug-naïve individuals with schizophrenia.

Given this study's findings of impaired stream segregation in schizophrenia, it would be important to measure the ability for individuals with SZ to perform segregation tasks that more closely approximate real-world listening situations, such as a speech in noise task (e.g., Bilger et al., 1984), and the relationship of these tasks with clinical symptoms in order to determine whether there is an actual deficit that would likely impact real-world function (cf. Wynn et al., 2010). It would also be essential to assess other simple segregation tasks, in particular those that require segregation of concurrently presented sounds (e.g., Assmann and Summerfield, 1994; Moore et al., 1985), because this is the other main type of segregation that is thought to be required to perform segregation in real-world settings.

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Contributors

All authors contributed to designing the study and writing the protocol. Erin Ramage, David Weintraub, and Joel Snyder managed the literature searches and analyses. Erin Ramage, David Weintraub, and Joel Snyder undertook the statistical analysis, and Joel Snyder wrote the first draft of the manuscript. Daniel Allen supervised all participant recruitment, screening, and informed consent. All authors edited and approved the final manuscript prior to submission.

Conflict of interest

No conflicts of interest are pronounced by any authors of this study.

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