



Preliminary evidence for reduced auditory lateral suppression in schizophrenia



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ABSTRACT

Background: Well-documented auditory processing deficits such as impaired frequency discrimination and reduced suppression of auditory brain responses in schizophrenia (SZ) may contribute to abnormal auditory functioning in everyday life. Lateral suppression of non-stimulated neurons by stimulated neurons has not been extensively assessed in SZ and likely plays an important role in precise encoding of sounds. Therefore, this study evaluated whether lateral suppression of activity in auditory cortex is impaired in SZ.

Methods: SZ participants and control participants watched a silent movie with subtitles while listening to trials composed of a 0.5 s control stimulus (CS), a 3 s filtered masking noise (FN), and a 0.5 s test stimulus (TS). The CS and TS were identical on each trial and had energy corresponding to the high energy (recurrent suppression) or low energy (lateral suppression) portions of the FN. Event-related potentials were recorded and suppression was measured as the amplitude change between CS and TS.

Results: Peak amplitudes of the auditory P2 component (160–260 ms) showed reduced lateral but not recurrent suppression in SZ participants.

Conclusions: Reduced lateral suppression in SZ participants may lead to overlap of neuronal populations representing different auditory stimuli. Such imprecise neural representations may contribute to the difficulties SZ participants have in discriminating complex stimuli in everyday life.

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1. Introduction

Individuals with schizophrenia (SZ) have auditory frequency discrimination deficits (Javitt et al., 1997; Rabinowicz et al., 2000), which are likely to impact real-world auditory functioning. Importantly, auditory deficits in SZ are found not only for frequency discrimination tasks but also for intensity discrimination (Bach et al., 2011) and cue localization tasks (Perrin et al., 2010). Deficits also appear for more complex auditory tasks that require precise encoding of sensory features (Cienfuegos et al., 1999; Leitman et al., 2005; Micoulaud-Franchi et al., 2011; Gold et al., 2012; Ramage et al., 2012; Weintraub et al., 2012; Wu et al., 2012; Kantrowitz et al., 2013). Similarly, direct brain measurements in SZ show reduced amplitude of auditory cortical responses to various sound properties (Clementz et al., 1997; Michie et al., 2000; Salisbury et al., 2002; Bramon et al., 2004; Jansen et al., 2004; Light and Braff, 2005; Spencer et al., 2008; Hall et al., 2011a,b); reduced gray matter volumes in auditory cortex (Hirayasu et al., 2000; Kasai

et al., 2003); and abnormal microscopic characteristics of auditory cortex (Sweet et al., 2003; Deng and Huang, 2006).

Here, we assess whether reduced effectiveness of lateral suppression should be considered a candidate for explaining some auditory deficits. *Lateral suppression* is the reduced responsiveness of one set of neurons as a result of the prior activation of neighboring neurons. Likewise, *recurrent suppression* is the reduced responsiveness of a set of neurons as a result of these same neurons being active recently. Lateral suppression is thought to be a mechanism that leads to smaller populations of neurons being active in response to any given acoustic stimulus (Chen and Jen, 2000; Wang et al., 2002) and for a shorter amount of time (Wehr and Zador, 2003). This is advantageous because the smaller the population and the more abrupt its response, the less overlap there will be with neural populations representing other stimuli, which should support better auditory discrimination. Thus, disruption of lateral suppression could be a candidate mechanism for explaining some of the discrimination deficits observed in SZ as resulting from excessive overlap in neural representations for different sounds.

Many previous studies showed less reduction of auditory responses when tones and clicks are repeated in SZ, relatives of those with SZ, and in bipolar disorder (Clementz et al., 1998; Boutros et al., 2004; Olincy and Martin, 2005; Rojas et al., 2007). However, these prior studies have not separately measured lateral and recurrent suppression

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because the repeated stimuli have been identical in frequency content. One magnetoencephalography (MEG) study did show that alternation of tones with different frequencies resulted in less suppression of the N1 response in SZ (Rojas et al., 2007), consistent with a lateral suppression deficit.

To measure lateral and recurrent suppression in SZ, we recorded event-related brain potentials (ERPs) while presenting stimuli similar to those used in previous MEG studies (Okamoto et al., 2004; Pantev et al., 2004). The stimuli have energy in alternating frequency bands, which should activate neurons sensitive to those frequencies and suppress activity of neighboring frequencies (for lateral suppression) and the originally stimulated neurons (for recurrent suppression). We predicted that individuals with SZ would show less lateral suppression than healthy controls. Previous studies using this type of paradigm reported lateral and recurrent suppression of the N1 response, an index of auditory sensory memory and pitch processing (Pantev et al., 1989; Lu et al., 1992; Näätänen and Winkler, 1999) that we expect to show suppression deficits in lateral suppression (cf. Rojas et al., 2007). However, it is also possible that other components such as P2 will show suppression deficits in SZ because prior MEG studies only reported findings for N1, but the P2 is an index of spectral processing and therefore might also reflect frequency-dependent suppression (Shahin et al., 2005, 2007; Snyder et al., 2006, 2009).

2. Experimental/materials and methods

2.1. Participants

This research study was approved by the Institutional Review Board at the University of Nevada, Las Vegas and written informed consent was obtained from all participants before starting study procedures.

Participants included 18 individuals diagnosed with SZ (1 schizoaffective) and 20 healthy controls (HCs) free of any psychiatric diagnosis. Demographics for each group and illness characteristics for SZ participants are shown in Table 1; there were no significant between-group differences on self-reported gender, ethnicity, or handedness. The SZ group reported significantly fewer years of education and had significantly lower IQ scores.

All HC participants were recruited from the community at large and all SZ participants were recruited through an outpatient community mental health center. Most had normal hearing for their age, as assessed using a GSI-17 audiometer using headphones. A few individuals at the upper end of the age range had mild to moderate hearing loss as expected for their age (all were ≤ 40 dB HL from 250 to 1000 Hz, and ≤ 50 dB HL from 2000 to 4000 Hz). Overall, the SZ group (16.56 dB) had higher dB levels (i.e., worse hearing) than the control group (11.05 dB) on the hearing test, $F(1,36) = 6.81, p < .05$; however, there was no group \times frequency interaction ($p = .534$), which is not consistent with differences in age-related hearing loss between groups, which was our main concern due to the inclusion of middle-aged participants. Alternatively, it is possible that those with SZ had more difficulty detecting the tones in the hearing test due to attention or other cognitive problems. For this reason and also to avoid depleting our statistical power, we decided not to use the hearing test performance as a covariate in analyses below.

Inclusion criteria for all participants included being between the ages of 18 and 65 years. Exclusion criteria included history of electroconvulsive therapy, neurological disorder or a medical condition with known effects on CNS function, diagnosis of alcohol or drug abuse or dependence within the last 12 months, alcohol or drug use within the last 24 h, and use of medications that would affect auditory function, other than medications prescribed to treat schizophrenia. Healthy controls were also excluded if they reported a first- or second-degree relative with a psychiatric diagnosis.

Table 1

Demographic and clinical information for participants.

	Schizophrenia (<i>n</i> = 18)	Healthy control (<i>n</i> = 20)	Between group differences
General information			
Age in years (SD)	46.6 (12.1)	40.2 (15.3)	$t = 1.45, p > .05$
% Females	31.3	35.0	$\chi^2 = .06, p > .05$
% Right handed	81.3	90.0	$\chi^2 = 1.38, p > .05$
Years of education (SD)	11.8 (2.4)	15.5 (1.8)	$t = -5.36, p < .001$
IQ (SD)	78.6 (13.9)	104.4 (12.2)	$t = -6.09, p < .001$
Ethnic distribution			
% Caucasian	50.0	60.0	$\chi^2 = 3.5, p > .05$
% African American	37.5	25.0	
% Hispanic/Latino	6.3	5.0	
% Pacific Islander	6.3	0	
% Asian American	0	5.0	
% Other	0	5.0	
Current psychiatric medication			
Chlorpromazine equivalent in mg (SD)	1102.98 (889.79)		
% Antipsychotics	77.8		
% Typical	11.1		
% Atypical	77.8		
% Mood stabilizer	50.0		
% Antidepressant	27.8		
% Lithium	5.6		
% No medication	0.0		
% No information	16.7		
Other patient information			
Age in years at onset (SD) (<i>n</i> = 19) ^a	20.8 (8.0)		
Years of illness (SD) (<i>n</i> = 19) ^a	25.1 (13.7)		
Hospitalizations (SD) (<i>n</i> = 16) ^a	3.6 (1.6)		

^a Value of *n* represents the number of SZ participants with endorsed information.

2.2. Stimuli and design

Auditory stimuli were generated off-line in Matlab (The MathWorks, Inc., Natick, MA). Individual trials consisted of a 0.5 s control stimulus (CS), a 3 s (duration including 20 ms rise/fall times) filtered masking noise (FN), and finally a 0.5 s test stimulus (TS). There were also 0.5 s silences before and after the FN. Trials were separated by 2.5 s of silence resulting in a total trial onset to onset time period of 7.5 s. As shown by examining the spectral profiles of the stimuli in Fig. 1, the FN was filtered to have high energy in the range of 0.25–1.4 kHz (top of Fig. 1), equally spaced by half an octave via Fourier filtering of white noise (bottom of Fig. 1). On each trial, the CS and TS were identical 0.5 s (duration including 12.5 ms rise/fall times) complex tones with energy corresponding to high energy or pass-band (recurrent suppression) and low energy or stop-band (lateral suppression) portions of the FN, as depicted in the middle panels of Fig. 1. The pass-band tones were composed of energy centered at 0.7, 1.0, 1.4, 2.0, and 2.8 kHz, and the stop-band tones were composed of energy centered at 0.59, 0.83, 1.19, 1.66, and 2.39 kHz. Trials were separated into 6 blocks (presented in fixed order) of 80 trials randomized independently for each block (40 pass-band trials and 40 stop-band trials) for a total of 480 trials (240 pass-band trials and 240 stop-band trials).

2.3. Procedures

All individuals in the SZ group had a clinical diagnosis of schizophrenia, which was confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) (First et al., 2002) and review of medical records. The SCID was also used to rule out psychiatric diagnosis in the HC group. Current IQ was assessed using the Vocabulary and

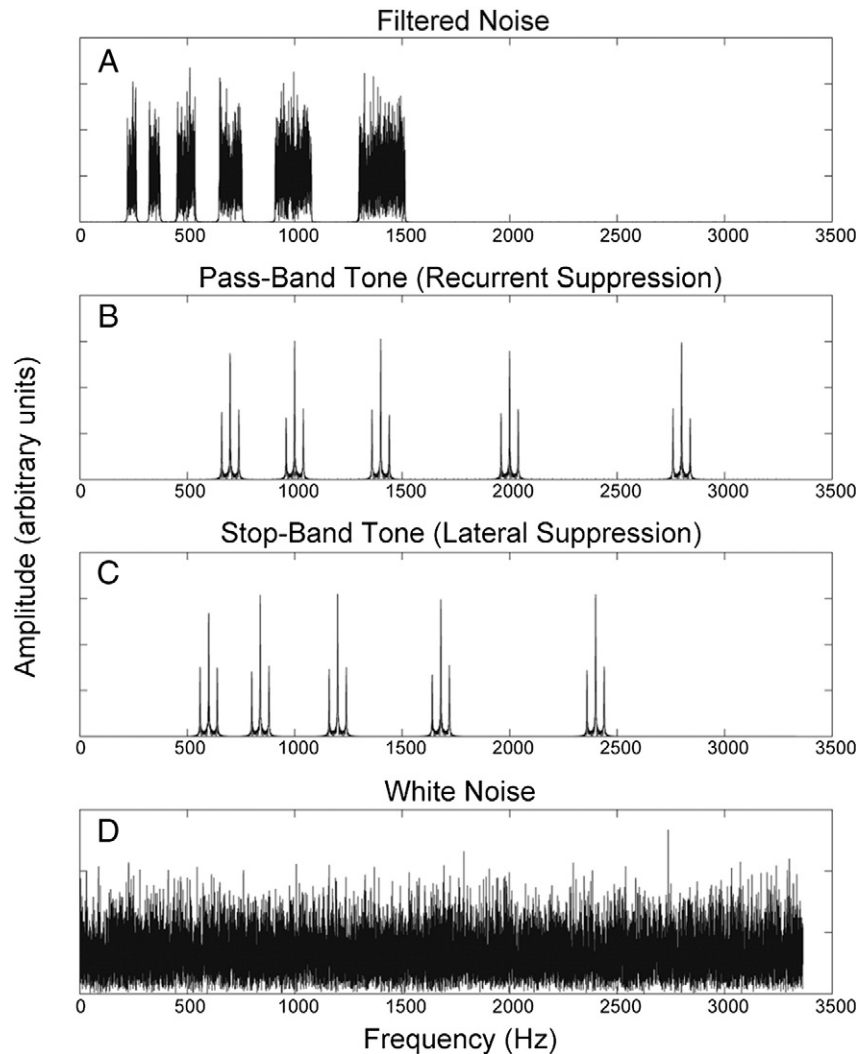


Fig. 1. Amplitude spectra of stimuli. Depiction of the amplitude spectra used for stimuli differentiating Recurrent versus Lateral suppression. A) Filtered noise. B) Pass-band tone with energy corresponding to bands of high energy in the filtered noise to measure recurrent suppression. C) Stop-band tone with energy corresponding to bands of low energy in the filtered noise to measure lateral suppression. D) Depiction of white noise prior to filtering.

Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997; Ringe et al., 2002). Medication use was confirmed via medical records and/or information provided by mental health professionals providing treatment for the SZ participants. The aforementioned procedures were not always completed on the same day of testing as many participants had recently participated in a related study by our group. Psychiatric symptom severity was assessed prior to experimental testing on the same day using the Calgary Depression Rating Scale (Addington et al., 1990), Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), and Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1981).

All stimuli were presented at a listening level of ~80 dB SPL. Throughout the experimental portion of the study, participants were seated comfortably in a single-walled sound-attenuated room (Industrial Acoustic Corp, Bronx, NY). Breaks of unlimited time were provided between the 6 blocks of EEG recording.

EEG data were recorded on an array of 72 Ag–AgCl electrodes using the Biosemi ActiveTwo system (<http://www.biosemi.com>). This system uses Common Mode Sense (CMS) and Driven Right Leg (DRL) passive electrodes serving as grounds by creating a feedback loop (see <http://www.biosemi.com/faq/cms&drl.htm>). Electrodes were placed at 64 points based on a 10/20 system within a Biosemi electrode cap and 8 points below the hairline. 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 hairline, 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. EEG signals were digitized continuously (512-Hz sampling rate, 104-Hz bandwidth). During EEG recording, participants watched a silent movie with subtitles while passively listening to suppression trials binaurally over ER3A insert earphones (Etymotic Research, Inc., Elk Grove Village, IL). Participants were asked to ignore the sound stimuli, and to avoid moving their eyes, head, or other body parts while the sounds were being played.

2.4. EEG data analysis

All EEG data processing and extraction of ERP measures were done using BESA 5 Software (BESA GmbH, Gräfelfing, Germany). ERPs were measured by averaging EEG epochs from 500 ms before to 1000 ms after the stimulus onset for each stimulus condition (CS, TS), suppression condition (Recurrent, Lateral) and electrode site separately, and re-referencing off-line to the average of all electrodes not adjacent to the eyes. Epochs contaminated by artifacts (amplitude > 150 μ V, gradient > 75 μ V, low signal < .01 μ V) were automatically rejected

prior to averaging. Ocular artifacts (blinks, saccades, smooth movements) were corrected automatically with a spatial filtering method (Ille et al., 2002). A minimum of 35% of epochs was accepted for each condition in each participant (average of 178 epochs per condition for SZ and 208 epochs per condition for HCs). Epochs were digitally bandpass filtered to attenuate frequencies below 1 Hz (6 dB/octave attenuation, forward) and above 20 Hz (24 dB/octave attenuation, zero phase).

To extract components of interest, ERPs were baseline corrected by subtracting the mean of the portion 50 ms prior to each CS and TS epoch. We then calculated grand-averaged ERP waves between conditions of interest for each group. Using these grand averages, we chose latency windows for both groups showing clear N1 (90–155 ms), P2 (160–260 ms), and N2 (260–375 ms) waveform components and maximal difference between groups. Analyses included six frontocentral (Cz, C1, C2, FCz, FC1, FC2) electrode locations because these regions

are typically used to measure auditory ERP sources arising from the primary and secondary auditory cortices in sources tangentially oriented relative to the temporal portion of the scalp. Additionally, these electrode sites allowed us to compare the effects of scalp regions; frontocentral electrode peak amplitudes were averaged in sets of two, representing the left hemisphere (FC1, C1), central/midline (FCz, Cz), and right hemisphere (FC2, C2) scalp regions and these averages were used for all analysis. ERPs were plotted for these frontocentral electrodes, as well as the P9 and P10 (mastoid) electrodes in order to verify polarity reversal, consistent with sources in auditory cortex.

Peak amplitudes for the six frontocentral electrodes were submitted to a mixed-design analysis of variance (ANOVA) with group (SZ, HC) as a between-subjects factor, and scalp region (left, central, right) and suppression (CS, TS) as within-subjects factors. All ANOVAs were performed separately for each suppression type (Recurrent, Lateral). The degrees of freedom were adjusted using the Greenhouse–Geisser ϵ

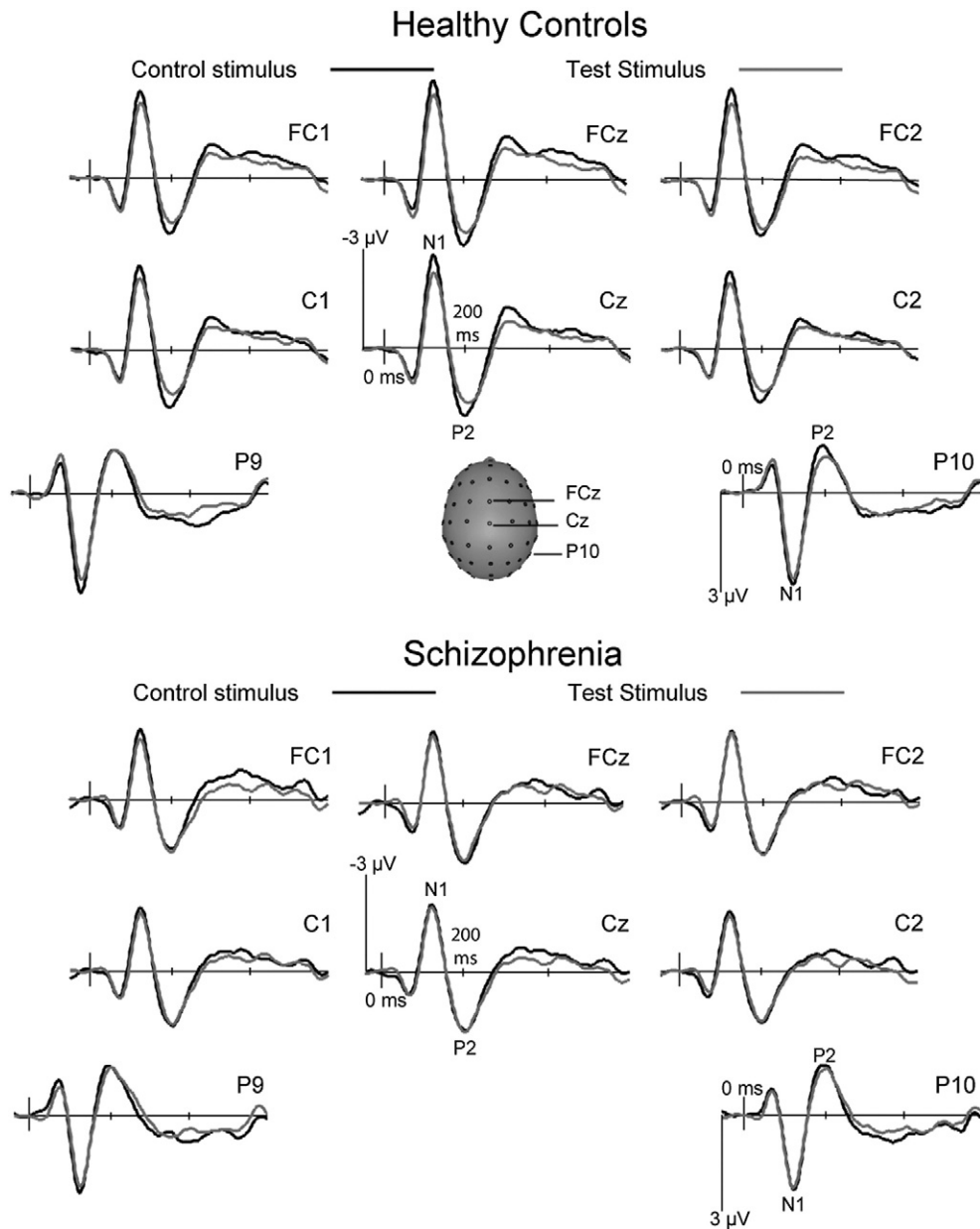


Fig. 2. Lateral suppression. Auditory ERPs to the stop-band tones for the control and test stimuli (i.e., before and after hearing the filtered noise) in healthy controls and those with schizophrenia at six fronto-central electrodes and the two mastoid electrodes. Note the reversal of polarity of the N1 and P2 response as well as the N1 and P2 suppression when comparing fronto-central and mastoid electrodes.

and all reported probability estimates were based on the reduced degrees of freedom. A suppression index (SI) was created for use in correlational analysis for each component where a significant group \times suppression interaction was found; SI was calculated as $(CS - TS) / CS$ (larger values represent greater suppression) using the amplitude averaged over the six frontocentral electrodes.

2.5. Correlation analysis

To determine whether there was a relationship between ERP responses and the symptom ratings on the BPRS, SAPS, or SANS, SI measures and symptom ratings were entered into simple correlation analyses. To avoid inflating the rate of Type I errors, only symptoms of particular interest were considered (Overall SAPS, auditory hallucinations, voices commenting, voices conversing, global rating of hallucinations; Overall SANS, Global ratings of affective flattening, avolition, anhedonia–asociality, and attention; Overall BPRS, and hallucinatory

behavior). Finally, to determine whether any group differences in ERP responses could be explained by age, years of education, or IQ, we ran correlations between these variables.

3. Results

3.1. Lateral suppression

As shown in Fig. 2 for lateral suppression, there was a significant main effect of suppression of all components in the frontocentral electrodes of the HC group [$N1: F(1,36) = 6.41, p < .05$; $P2: F(1,36) = 5.84, p < .05$; $N2: F(1,36) = 8.29, p < .01$], and the pattern of lateral suppression reversed polarity at mastoid electrodes (P9 and P10). No significant main effects of group were found for any components (all $p > .10$). Most importantly, there was a significant suppression by group interaction for P2 amplitudes over the frontocentral electrodes ($F(1,36) = 6.39, p < .05$), indicating reduced lateral suppression in SZ. However,

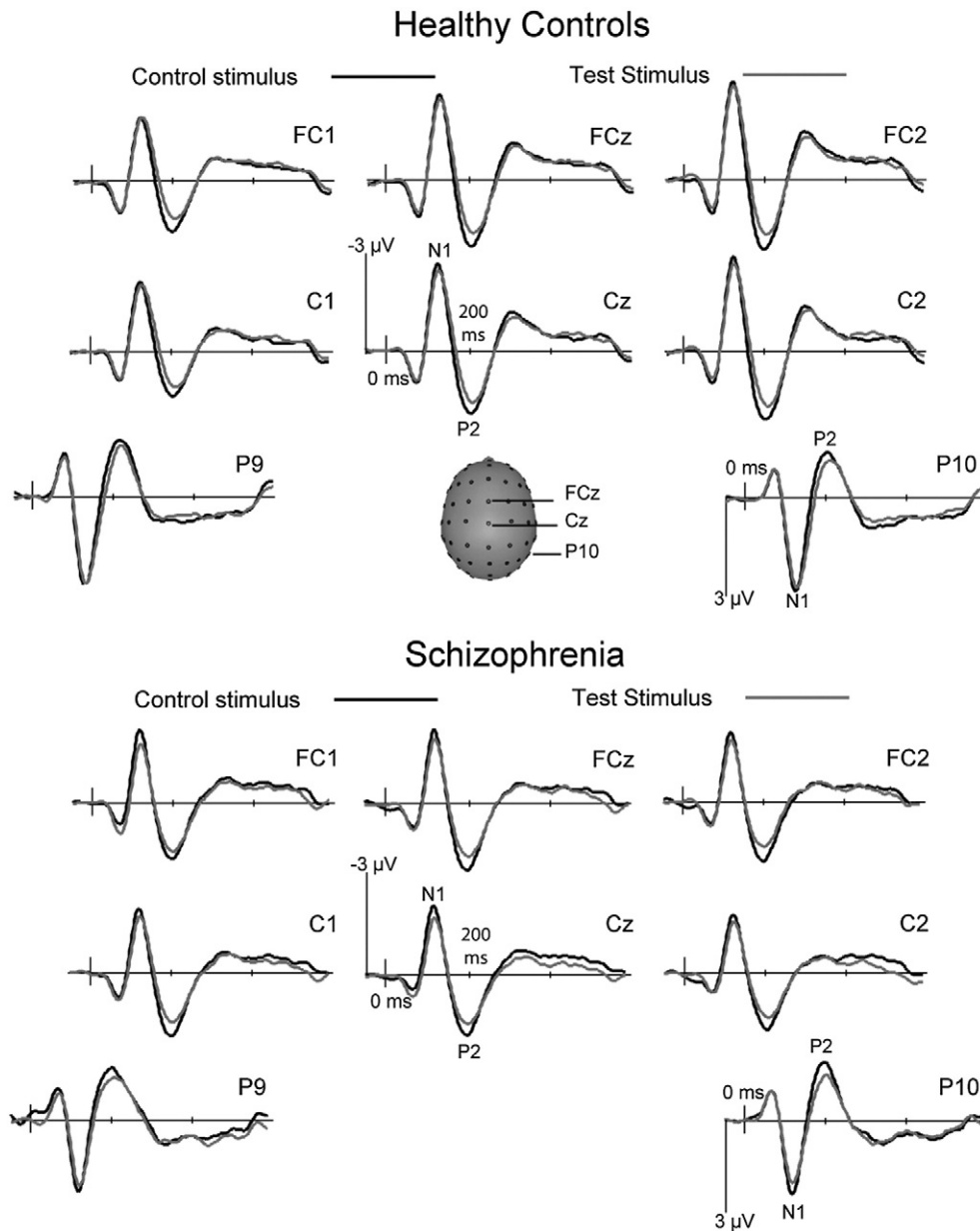


Fig. 3. Recurrent suppression. Auditory ERPs to the pass-band tones for the control and test stimuli (i.e., before and after hearing the filtered noise) in healthy controls and those with schizophrenia at six fronto-central electrodes and the two mastoid electrodes. Note the reversal of polarity of the N1 and P2 response as well as the P2 suppression when comparing fronto-central and mastoid electrodes.

N1 and N2 did not show an interaction between suppression and group ($p > .3$).

Significant effects of scalp region for all components in the frontocentral electrodes [N1: $F(2,72) = 11.34, p < .001$; P2: $F(2,72) = 26.78, p < .001$; N2: $F(2,72) = 11.42, p < .001$] indicated greater amplitude in the central electrodes as compared to the left and right lateral electrodes ($p < .005$ for all comparisons). There was a significant interaction between hemispheric region and group for the N2 component ($F(2,72) = 9.10, p < .001$) because the greater amplitude in the central electrodes compared to the right and left hemispheres was seen only in the HC group.

3.2. Recurrent suppression

As shown in Fig. 3, there was significant recurrent suppression of the P2 component ($F(1,36) = 10.02, p < .005$) that was not present in the N1 or N2 components [N1: $F(1,36) = 2.68, p = .11$; N2: $F(1,36) = .94, p = .34$]. As with lateral suppression, the P2 recurrent suppression reversed polarity in the mastoid electrodes (see Fig. 3). There was a significant effect of group on N2 component amplitudes ($F(1,36) = 5.44, p < .05$), indicating an overall decreased amplitude in the SZ group; this was not found in any other components [N1: $F(1,36) = 3.30, p = .08$; P2: $F(1,36) = .06, p = .81$]. Unlike with lateral suppression, however, there were no interactions between suppression and group for any of the components ($p > .4$ for N1, P2, and N2). Finally, there was a significant effect of scalp region for all components [N1: $F(2,72) = 16.18, p < .001$; P2: $F(2,72) = 23.08, p < .001$; N2: $F(2,72) = 12.30, p < .001$], indicating greater amplitude in the central electrodes as compared to the left and right hemispheres ($p < .001$ for all comparisons).

3.3. Symptom correlations

Global overall affective flattening was negatively associated with P2 lateral SI in the SZ group ($r(16) = -.48, p < .05$). No other symptom or demographic variable correlated with SI.

4. Discussion

As predicted, individuals with SZ exhibited significantly reduced lateral suppression of the P2 component as compared to the HC group, while recurrent suppression of the P2 was preserved. Our results show that the measure of lateral suppression we used is a promising tool for understanding auditory deficits in SZ. Future studies with larger sample sizes should therefore be conducted in order to search for correlations between P2 lateral suppression and auditory discrimination abilities and positive symptoms such as auditory hallucinations. It would also be important to determine whether P2 lateral suppression is reduced in first-episode SZ, in first-degree relatives, or in those scoring high on schizotypy scales, in order to rule out medication effects and to determine whether P2 lateral suppression reduction is an endophenotype (Braff et al., 2007).

The finding that lateral suppression of auditory ERPs is reduced in SZ is consistent with previous studies showing less suppression of auditory responses in SZ after repeated clicks or tones (Clementz et al., 1998; Boutros et al., 2004; Olincy and Martin, 2005; Rojas et al., 2007), and studies showing reduced suppression of responses to self-produced speech in auditory cortex of those with SZ (Ford et al., 2001; Ford and Mathalon, 2005). However, the current study is among the first to our knowledge (also see Rojas et al., 2007) showing that lateral suppression in particular is impaired in SZ, which is an important finding because lateral suppression is likely to be a neurophysiological capability that is vital for more precise coding of auditory features (Chen and Jen, 2000; Wang et al., 2002). The finding of impaired P2 lateral suppression in particular could be related to the fact that P2 is particularly involved in processing spectral information in healthy individuals (Shahin et al.,

2005, 2007; Snyder et al., 2006, 2009). Thus, this impairment should be considered a candidate for explaining at least some of the widely reported auditory deficits observed in SZ. Future studies should therefore replicate our findings with larger sample sizes and if possible better control for medication, education, and IQ effects by testing people with SZ experiencing their first hospitalization and appropriately matched controls.

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Contributors

All authors contributed to designing the study and writing the protocol. Erin Ramage, David Weintraub, Sally Vogel, Griffin Sutton, Erik Ringdahl and Joel Snyder managed the literature searches and analyses. Erin Ramage, David Weintraub, Sally Vogel, Griffin Sutton, Erik Ringdahl, 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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