Schizophrenia Research 162 (2015) 269–275

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Preliminary evidence for reduced auditory lateral suppression in schizophrenia

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ARTICLE INFO

Article history:
Received 25 October 2014
Received in revised form 18 December 2014
Accepted 22 December 2014
Available online 10 January 2015

Keywords:
Event-related brain potentials
Inhibition
Sensory gating

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.

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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http://dx.doi.org/10.1016/j.schres.2014.12.032
0920-9964/

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 × 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 ($n = 18$)	Healthy control ($n = 20$)	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			$\chi^2 = 3.5$, $p > .05$
% Caucasian	50.0	60.0	
% 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) ($n = 19$)[a]	20.8 (8.0)		
Years of illness (SD) ($n = 19$)[a]	25.1 (13.7)		
Hospitalizations (SD) ($n = 16$)[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