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Stimulus train duration but not attention moderates γ-band entrainment abnormalities in schizophrenia

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ABSTRACT

Electroencephalographic (EEG) studies of auditory steady-state responses (aSSRs) non-invasively probe gamma-band (40-Hz) oscillatory capacity in sensory cortex with high signal-to-noise ratio. Consistent reports of reduced 40-Hz aSSRs in persons with schizophrenia (SZ) indicate its potential as an efficient biomarker for the disease, but studies have been limited to passive or indirect listening contexts with stereotypically short (500 ms) stimulus trains. An inability to modulate sensorineural processing in accord with behavioral goals or within the sensory environmental context may represent a fundamental deficit in SZ, but whether and how this deficit relates to reduced aSSRs is unknown. We systematically varied stimulus duration and attentional contexts to further mature the 40-Hz aSSR as biomarker for future translational or mechanistic studies. Eighteen SZ and 18 healthy subjects (H) were presented binaural pure-tones with or without sinusoidal amplitude modulation at 40-Hz. Stimulus duration (500-ms or 1500-ms) and attention (via a button press task) were varied across 4 separate blocks. Evoked potentials recorded with dense-array EEGs were analyzed in the time-frequency domain. SZ displayed reduced 40-Hz aSSRs to typical stimulation parameters, replicating previous findings. In H, aSSRs were reduced when stimuli were presented in longer trains and were slightly enhanced by attention. Only the former modulation was impaired in SZ and correlated with sensory discrimination performance. Thus, gamma-band aSSRs are modulated by both attentional and stimulus duration contexts, but only modulations related to physical stimulus properties are abnormal in SZ, supporting its status as a biomarker of psychotic perceptual disturbance involving non-attentional sensori-cortical circuits.

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1. Introduction

The generation of spatially coherent neural oscillations in the gamma-band (25–120-Hz) is believed necessary for establishing synchrony in local cell ensembles and carrying out essential cerebral cortical computations (Buzsaki, 2009; Uhlhaas and Singer, 2010). Gamma oscillations depend on local GABA-ergic interneuronal coordination (Gonzalez-Burgos and Lewis, 2008; Traub et al., 2004) and their disruption is hypothesized to link global cellular abnormalities in SZ (Curley and Lewis, 2012) to perceptual (Uhlhaas et al., 2006) and cognitive deviations prevalent in the disorder (Basar-Eroglu et al., 2007). Though externally and internally driven gamma oscillations are detectable and quantifiable at the scalp in humans with electro- and magnetoencepalography (E/MEG), the presence or nature of basic sensori-cortical gamma-band abnormalities in SZ exhibit inconsistency, including augmentations, reductions, and null effects across studies (Clementz and Blumenfeld, 2001; Hall et al., 2010; Hamm et al., 2012a; Moran and Hong, 2011; Spencer et al., 2004).

Auditory stimuli presented at a constant and rapid rate elicit steady-state responses (aSSRs), or sustained auditory neural entrainment, in the listener. Human aSSRs measured with E/MEG exhibit specific resonance in mid gamma-band frequencies [30–50-Hz, i.e. a stimulus every 20–33 ms (Galambos et al., 1981; Picton et al., 2003)], theoretically reflecting the propensity of cortical networks to oscillate in this frequency range (Brenner et al., 2009). Importantly, the 40-Hz aSSR exhibits enhanced signal-to-noise ratio versus background and transient gamma oscillations, affording a powerful tool in assessing the integrity of gamma-generating cortical circuitry.

Aside from the fact that hallucinations specifically in the auditory domain are a characteristic feature of SZ (Goodwin et al., 1971) and other psychoses (Baethge et al., 2005), SZ also typically display deficiencies in basic auditory processing and feature discrimination which are independent of higher-level cognitive dysfunction (Rabinowicz et al., 2000) and may reflect core pathology (Javitt and Freedman, 2015;

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Javitt, 2009). While it is known that both positive and negative symptomology covary with gamma-band aSSR magnitude (Hamm et al., 2011; Hirano et al., 2015), an understanding of the relationship between aSSR and basic auditory processing abnormalities has not been established in SZ. Because auditory processing is by nature a temporally precise modality and more sensitive to time perception abnormalities in SZ than e.g. vision (Carroll et al., 2008b), it follows that discordant neuronal synchrony at rapid timescales, such as the gamma aSSR, could theoretically relate to auditory perceptual difficulties.

A majority [at least 11 out of 14; see Brenner et al. (2009)] of investigations of 40-Hz aSSRs in SZ indicate reduction of entrainment related to the disease which is bilateral in auditory cortex (when measured with MEG; Oda et al., 2012; Teale et al., 2008; Vierling-claassen et al., 2008a, 2008b). The fact that different results also come from studies with different stimulus parameters is noteworthy. Hamm et al. (2011) demonstrated normal 40-Hz aSSRs in left hemisphere in SZ when stimulus trains were actively attended. Hamm et al. (2012b) showed augmented 40-Hz aSSRs with EEG during passive listening, and both studies utilized stimulus trains 2–3 times longer than most aSSR SZ reports. This pattern could suggest that SZ gamma abnormalities do not reflect a pure gamma generation deficit per se, but, rather, deficient interaction of sensory processing with environmental and/or behavioral context.

Interestingly, in psychiatrically healthy subjects (H) allocation of attention to 40-Hz auditory stimulus trains enhances aSSR amplitude (Ross et al., 2004; Saupe et al., 2009), although insufficient task difficulty may eliminate this relatively small effect (Griskova-Bulanova et al., 2011). The influence of attention on aSSR amplitude is unknown in SZ. The specific impact of stimulus train duration on aSSRs is far less frequently studied. Alpha-band visual steady-state entrainment abnormalities in SZ are known to differ as a function of train duration (Clementz et al., 2004). Treatment with NMDA-receptor antagonists (a well-established pharmacological model of psychosis; Javitt et al., 2012) enhances 40-Hz aSSRs in humans and rats when long duration trains are employed (Plourde et al., 1997; Vohs et al., 2012) while reducing 40-Hz aSSRs when more traditional 500 ms trains are used (Sivarao et al., 2013). Thus a systematic investigation of SZ gamma-band aSSR abnormalities across different sensori-behavioral contexts is necessary for understanding the neurophysiological underpinnings of and effectively refining this promising marker of psychotic pathology. If SZ reductions in aSSR power are dependent on contextual variables, or are abnormally modulated by behaviorally relevant or sensory conditions, aSSRs may index an auditory-contextual processing abnormality beyond and/or in addition to basic gamma-synchrony deficits. This would have implications for how gamma-band aSSR deficits are interpreted, further refined, and utilized as a biomarker in future research.

Given what has been demonstrated regarding top-down attribution of attention to basic auditory discrimination (Javitt and Freedman, 2015; Javitt et al., 2012; Rabinowicz et al., 2000), we expected that attentional context (inclusion of an auditory discrimination task) would similarly affect SZ and healthy aSSRs. Given findings from Hamm et al. and Clementz et al., along with dependencies of SZ sensory cortical abnormalities on, for example, inter-stimulus interval (Rosburg et al., 2008) and temporal contextual processing (Light and Näätänen, 2013), we expected SZ aSSR abnormalities to be less modulated by temporal context of the presented stimulus trains (compared to H), reflecting potentially deficient sensory gain control and/or cortical adaption to dense, repetitive stimulation. The current study specifically addressed whether stimulus duration (500 ms vs 1500 ms) and attentional context (inclusion of an auditory discrimination task) of the recording block influenced SZ gamma-band auditory neural entrainment. Additionally, aSSR measurements were regressed on auditory discrimination performance to test the hypothesis that gamma-band synchrony and, specifically, the aSSR biomarker reflects auditory perceptual dysfunction in SZ.

2. Methods

2.1. Subjects

Eighteen persons with DSM-IV SZ (Mean +/− SD: 45.6 +/− 8.3 years, 9 females) and 18 healthy persons (40.8 +/− 9.9 years, 7 females) participated. SZ were recruited through community advertisements and through outpatient services of the Medical College of Georgia (Georgia Regents University, Augusta, GA); healthy subjects were recruited from the community. SZ were diagnosed using the Structured Clinical Interview for DSM-IV (First and Gibbon, 1997). The Positive and Negative Syndrome Scale (PANSS) quantified severity and extent of symptomatology [(Kay et al., 1987) Table 1]. All subjects were free of substance use disorders in the 6 months prior to testing. SZ were chronic patients with typical age of illness onsets. Medication information is provided in the Supplement. All participants provided informed consent and were paid for their time. This study was approved by the Institutional Review Boards at University of Georgia and Georgia Regents University.

2.2. Stimuli

Four blocks of 130–165 tones (carrier pitches 500-, 1000-, or 2000-Hz; randomly ordered) were presented binaurally through Etymotic insert earphones (Etymotic Research, Elk Grove Village, IL) at 76 dB SPL with an average 3 s ISI (range 2.7–3.3 s) while participants sat in a dark room with eyes open and fixated on a small cross presented on a computer monitor. Tones were either sinusoidally amplitude modulated (Krishnan et al., 2009) at 40-Hz (90%; "standards") or unmodulated pure-tones (10%; "targets"). To the listener, "standards" resembled, for example, a phone ringing, while "targets" sounded like a smooth dial-tone. In 2 of the blocks, tones had a 500 ms duration (Kwon et al., 1999), while in the other 2 blocks each tone lasted 1500 ms (Hamm et al., 2012b). Further, in 2 of the blocks, participants were instructed to make a button press to "target" tones ("task" condition), while in the other 2 blocks participants were instructed to simply listen to the tones while fixating ("no-task" condition). Thus the 4 conditions were short-duration task, short-duration no-task, long-duration task, and long-duration no-task. Order of conditions was counter-balanced across subjects. Subjects' comprehension and ability to perform the task was confirmed prior to data collection.

2.3. EEG recording

EEG data were recorded vertex-referenced using a 256 sensor Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI, Eugene, OR). Sensor impedances were kept below 50 kO, as is standard when using high input impedance amplifiers. Data were sampled at 500-Hz with an analog filter bandpass of 0.1–200-Hz.

Table 1
Participant information. H, healthy control subjects; SZ, schizophrenia subjects; CPZ, chloropromazine; PANSS, Positive and Negative Syndrome Scale. (a) CPZ equivalents in mg. (b) symptom scores.

	H	SZ	Statistic	p-value
	39%	50%	$\chi 2[1] = 0.45$	.502
Female participants				
Age (years)	41 (25–54)	46 (25–55)	$t(34) = 1.56$	.126
Medication dosage[a]	–	207 (20–533)	–	–
PANSS positive[b]	–	13.7 (8–27)	–	–
PANSS negative[b]	–	14.8 (8–28)	–	–
PANSS general[b]	–	33.9 (17–64)	–	–
Number of trials				
Short no-task	117 (97–138)	111 (72–139)	$t(34) = 1.49$	.145
Short task	120 (97–139)	111 (74–149)	$t(34) = 1.77$	.090
Long no-task	94 (75–114)	87 (69–111)	$t(34) = 1.54$	.131
Long task	94 (75–113)	94 (76–110)	$t(34) = -0.16$	.878

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