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Early- and late-latency gamma auditory steady-state response in schizophrenia during closed eyes: Does hallucination status matter?

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HIGHLIGHTS

- Early-latency gamma auditory steady-state responses are diminished in schizophrenic subjects and do not depend on hallucination status when recorded with closed eyes.
- Late-latency gamma responses do not differ between healthy and schizophrenic subjects and do not depend on hallucination status when recorded with closed eyes.
- Frequency of early-latency gamma is related to negative symptoms, whereas delayed build-up of entrainment is related to hallucination prevalence.

ABSTRACT

Objectives: Auditory steady-state responses are larger in patients experiencing auditory verbal hallucinations (AVH) than in never hallucinating subjects (NH) when recorded with open eyes. Compensatory effects were shown for schizophrenic patients when recorded with closed eyes. This effect has not been evaluated in respect to hallucination status.
Methods: Gamma responses to 40 Hz stimulation were recorded in 15 AVH patients, 25 healthy controls and 11 NH patients with closed eyes. Mean and peak evoked amplitude and phase-locking index, peak time and maximal frequency were extracted for early- and late-latency responses and compared between groups.
Results: Phase-locking of early, but not late-latency gamma was diminished in schizophrenic patients independently on hallucination status. Peak entrainment time was delayed in hallucinating patients. Magnitude and frequency of early-latency response correlated to negative symptoms.
Conclusions: In AVH patients, entrainment at gamma frequency was "normal" when eyes were closed. In contrast to never hallucinating subjects, entrainment to stimulation was delayed in AVH. The early-latency gamma response, standing for early sensory stimulus processing, on the contrary, was impaired in SZ irrespective of prevalence of hallucinations and was not modulated by subjects' general state; however its magnitude might be related to the expression of negative symptomatology.
Significance: Evaluation of auditory entrainment in both open eyes and closed eyes conditions is informative. Frequency and timing information of both early-latency and late-latency responses helps to uncover different aspects of impairment in schizophrenia patients.

1. Introduction

The auditory steady-state response (ASSR) – a response to periodic stimulation – has been proposed to serve as one of the biological markers of schizophrenia, being consistently impaired in the disorder (O'Donnell et al., 2013). The response to gamma range stimulation has been employed both to evaluate global synchronization of

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neural activity with the external environment (Light et al., 2006; Koenig et al., 2012; Tada et al., 2014) and the integrity of auditory circuits (Teale et al., 2003; Brenner et al., 2009; Spencer et al., 2009; Hamm et al., 2011).

Several state-related factors modulate 40 Hz ASSRs, such as controlled changes in general arousal (Jerger et al., 1986; Linden et al., 1987; Cohen et al., 1991; Griskova et al., 2007), activation level (Griskova-Bulanova et al., 2009; Griskova et al., 2011) and attentional demands (Ross et al., 2004; Skosnik et al., 2007; Gander et al., 2010). Moreover, state-sensitivity of 40 Hz ASSRs has been shown for schizophrenia, where the phase-locking index increased with eyes closure in the patients (Griskova-Bulanova et al., 2013). From the symptom prevalence perspective, it is known that phase-locked measures of 40 Hz ASSR positively correlated to positive symptoms/hallucinations during open eyes condition, i.e. were increased in subjects with higher hallucination scores (Spencer et al., 2008, 2009). Hallucinations, in turn, were shown to last longer in closed eyes as compared to open eyes condition (Angelopoulos et al., 2011), suggesting a potential state-related modulation.

The main sources of 40 Hz ASSRs (Herdman et al., 2002; Kuriki et al., 2013; Pantev et al., 1996) are in the primary auditory cortex (PAC) – the area where alterations have been described in hallucinating patients on different levels: ERPs (Hubl et al., 2007), fMRI (Dierks et al., 1999), quantifiers of brain structure (Hubl et al., 2010), or in non-invasive brain stimulation studies combined with metabolic measures (Kindler et al., 2013). In healthy subjects, activity in the auditory cortex was shown to be modulated by eyes-closure (Zou et al., 2015; Qin et al., 2013; Yuan et al., 2014).

Thus, it is relevant to evaluate state-related effects on phase-locked measures in hallucinating subjects and to contrast it to never hallucinating patients. The data set from Koenig et al. (2012) with thoroughly selected patient groups offered an opportunity to evaluate stimulus-locked response parameters and contrast never hallucinating and hallucinating patients, comparing both groups to matched controls.

We re-analyzed the dataset from Koenig et al. (2012) in a phase-locked to stimulus manner assessing both phase-locking and amplitude, to make it comparable to previous studies, where synchronization has been defined as the stability of the relation between stimulus onset and EEG phase (e.g. Spencer et al., 2009; Uhlhaas and Singer, 2010) in contrast to the phase-locking among all active regions at a given frequency (Koenig et al., 2012). Additionally we addressed both the early part of the 40 Hz response (referred to as early-latency gamma, 0–100 ms) and the late-entrainment related part of ASSRs (referred to as late-latency gamma, 200–300 ms). This was rarely done in clinical samples (Light et al., 2006; Tada et al., 2014), although as suggested by Ross et al. (2005), the two types of activity reflect activation of distinct neural networks (Ross et al., 2005) and thus can provide additional clinically relevant information.

2. Methods

2.1. Subjects

The initial sample, as described in Koenig et al. (2012) consisted of 26 healthy controls, 18 patients with schizophrenia and AVH, and 11 patients with schizophrenia without AVH. Due to technical reasons, data from one HC and 3 AVH subjects could not be used. The final sample was composed of 15 AVH, 25 HC and 11 NH patients. The main inclusion criteria and symptoms assessment procedures are described in Koenig et al. (2012) in detail. Briefly, the AVH group was defined by hearing voices at least 4 times/week for the last 4 weeks and perceiving AVH in every of their acute exacerbation of schizophrenia, but not necessarily during the time of measurement. The NH group was defined by the absence of any report of AVH, neither at time of investigation nor in any of their prior episodes. The demographical and clinical data of the final sample are presented in Table 1. PANSS (Kay et al., 1987) and CGI (NIH, 1970) were used to assess psychopathologic symptoms severity. Hallucinations were rated using the Oulis Auditory Hallucinations Rating Scale (Oulis et al., 1995) that measures 25 clinical characteristics of auditory hallucinations based on observer ratings. The character of the hallucinations fulfilled the criteria of the Schneiderian first-rank symptoms of voices referring to the patient in the second or third person or in the form of a commentary (Schneider, 1959).

The investigation was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Canton of Bern, Switzerland. All subjects gave their prior written informed consent.

2.2. Experimental setup and EEG recording

The recordings were made 24 h after the psychopathological assessment. 74 silver/silver chloride electrodes were placed at the subject's head at standard positions; 2 additional electrodes were placed below each eye. Cz served as recording reference. The subject was comfortably seated in an electrically and sound-shielded recording chamber.

Auditory stimulation consisted of trains of 1 ms rectangular pulses given at a rate of 20, 30 and 40 Hz (20 and 30 Hz not analyzed here) presented thru a loudspeaker set to 84 dB. Each train lasted 500 ms, followed by 700 ms of silence. For each frequency, 150 trials were presented, resulting in a 3 min block; blocks were randomly assigned. Subjects were instructed to close their eyes, sit still and pay no special attention to the tones. During the experiment, the EEG was continuously digitized (512 Hz sampling rate, 0.3–70 Hz bandpass) using Neurofax system (JE 209A; Nihon Kohden, Japan) and stored using a BrainScope EEG system (M&I, Prague, Chech Republic). The entire recording lasted about 10 min.

2.3. Data preprocessing

All EEG data was submitted to an ICA-based correction of eye-movements (Delorme et al., 2007), recomputed to average reference, and periods with remaining artifacts were eliminated by visual inspection. Channels containing excessive artifacts were interpolated (Perrin et al., 1989). To eliminate line-noise, the Cleanline plugin for EEGLAB was used. As the number of epochs is crucial for phase-locking measures, we have used only first 70 epochs (−100 to 600 ms) of each subject to ensure each group would have an equal number of epochs.

Table 1
Demographic and clinical data of the study sample.

		AVH	NH	HC	*p*-values
Age	Mean	40.47	38.45	35.20	
	SD	9.88	4.32	10.56	
PANSS positive	Mean	24.50	18.73	–	0.03
	SD	5.26	7.30		
PANSS negative	Mean	20.27	20.18	–	ns
	SD	6.23	8.24		
PANSS total	Mean	78.33	73.36	–	ns
	SD	21.02	15.28		
Hallucinations score	Mean	5.47	1.00	–	<0.0001
	SD	0.92	0.00		
Antypsychotics, CPZ	Mean	382.60	465.50	–	ns
	SD	300.28	417.36		