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

Inga Griskova-Bulanova^{1,2}, Daniela Hubl³, Claudia van Swam³, Thomas Dierks³, Thomas Koenig³

¹ Department of Neurobiology and Biophysics, Vilnius University, Vilnius, Lithuania

² Republican Vilnius Psychiatric Hospital, Vilnius, Lithuania

³ Translational Research Center, University Hospital of Psychiatry, University of Bern, Switzerland

***Corresponding Author**

Inga Griskova-Bulanova

Department of Neurobiology and Biophysics

Vilnius University

M. K. Ciurlionio 21/27,

LT-03101 Vilnius

Lithuania

Tel.: +37067110954

Fax: +37052398216

E-mail: i.griskova@gmail.com

inga.griskova-bulanova@gf.vu.lt

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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 40Hz 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 hallucinations status. Peak entrainment time was delayed in hallucinating patients. Magnitude, phase-locking 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 have been 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 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 40Hz 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 et al., 2009; Griskova-Bulanova et al., 2011) and attentional demands (Ross et al., 2004; Skosnik et al., 2007; Gander et al., 2010). Moreover, state-sensitivity of 40Hz 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 40Hz ASSR positively correlated to positive symptoms/hallucinations and ASSRs during open eyes condition, i.e. were increased in subjects with higher hallucination scores (Spencer et al., 2008; Spencer et al., 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 40Hz 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-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 40Hz response (referred to as early-latency gamma, 0-100ms) 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 24h 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 1ms rectangular pulses given at a rate of 20, 30 and 40 Hz (20Hz and 30Hz not analyzed here) presented thru a loudspeaker set to 84 dB. Each train lasted 500ms, followed by 700 ms of silence. For each frequency, 150 trials were presented, resulting in a 3 min block for each frequency, presented in randomly assigned blocks. 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 (512Hz sampling rate, 0.3–70Hz bandpass) using Neurofax system (JE 209A; Nihon Kohden, Japan) and stored using a BrainScope EEG system (M&I, Prague, Czech 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 600ms) of each subject to ensure each group would have an equal number of epochs.

Off-line analysis was performed in EEGLAB and ERPWAVELAB for Matlab© (Delorme and Makeig, 2004; Mørup et al., 2007). A wavelet transformation (WT; complex Morlet wavelet from Matlab© Wavelet Toolbox; frequencies represented from 10 to 80 Hz, 1 Hz intervals between each frequency) was performed. Details of the event-related measures - evoked amplitude (EA, corresponding to wavelet-transformed evoked potential, and representing phase-aligned amplitude measure) and inter-trial phase coherence, (termed phase-locking index (PLI)) can be seen in (Mørup et al., 2007).

2.4. Data analysis

First, we calculated the mean PLI and EA at the Fz electrode by averaging the data over the 0-100ms and 200-500ms periods within a trial.

Then decomposition employing non-negative multi-way factorization (NMWF), as implemented in ERPWAVELAB[®] toolbox (Mørup et al., 2007), was performed in a manner shown being useful for ERPs and ASSRs before (Arnfred et al., 2008; Griskova et al., 2011) that resulted in extraction of three characteristics (signatures) of the measure of interest: the time of the maximal entrainment within a defined time range, the frequency of the entrainment and the value of the measure (peak PLI/EA). As it was shown before for ASSRs (Griskova et al., 2009; Griskova-Bulanova et al., 2011), the search in a frequency window of 30-50Hz was performed for a single component for the early part of the response (referred to as early-latency gamma, 0-100ms) and the late-entrainment related part of ASSRs (referred to as late-latency gamma, 200-500 ms).

Statistical evaluation was performed in SPSSv20 (SPSS Inc., Chicago, Illinois, USA). Mean and peak EA and PLI values and corresponding peak time and frequency estimates were subjected to ANOVAs with group (AVH vs NH vs HC) as a factor separately for each time

period. Post-hoc comparisons were performed using a Bonferroni method and adjusted P values are reported.

The Pearson correlation coefficient (two tailed, $P < 0.05$) was used to evaluate the relationship between early-latency and late-latency response parameters and clinical measures (positive symptoms, negative symptoms, total score as measures by PANSS (Kay et al., 1987), hallucination score as measured by Oulis Auditory Hallucinations Rating Scale (Oulis et al., 1995) and medication dosage in CPZ equivalents) without applying corrections for multiple tests as the analyses were considered exploratory in nature.

3. Results

Figure 1 shows grand-average ASSRs to 40Hz stimulation from the Fz electrode in three groups of subjects: auditory verbal hallucination group, non-hallucinating and healthy controls.

The decompositions gave evidence of consistent activity: the early-latency gamma responses were maximal over the Fz electrode. This was also the case for the late-latency gamma responses, confirming previous studies (f .e. Roach et al., 2013). Means and standard deviations for each measure of each group (peak time, frequency and mean/peak PLI/EA measures) are depicted in Figure 2 for early-latency gamma and late-latency gamma responses.

3.1. Early-latency gamma response

The group factor was significant for mean EA of the early-latency gamma response ($F_{2,48}=6.254$, $p=0.004$) and mean PLI ($F_{2,48}=9.453$, $p<0.001$), being largest in the HC group as compared to AVH group (EA: $p=0.05$; PLI: $p=0.006$) and NH group (EA: $p=0.007$; PLI: $p=0.001$). However, no effect of group could be identified for peak EA ($F_{2,48}=1.433$, $p=0.25$) or peak PLI ($F_{2,48}=2.327$, $p=0.12$).

The peak time of EA ($F_{2,48}=1.433$, $p=0.25$) and PLI ($F_{2,48}=0.257$, $p=0.78$) was not different between the groups. Also the peak frequency of the entrainment did not depend on the group: EA ($F_{2,48}=1.057$, $p=0.36$); PLI ($F_{2,48}=1.368$, $p=0.26$).

3.2. Late-latency gamma response

The effect of group was not significant for either mean EA ($F_{2,48}=0.234$, $p=0.79$) or mean PLI ($F_{2,48}=0.163$, $p=0.85$) in response to 40Hz. Peak EA ($F_{2,48}=0.543$, $p=0.59$) and peak PLI ($F_{2,48}=0.456$, $p=0.64$) were not different between groups.

A significant effect of group was estimated for peak time of EA ($F_{2,48}=3.781$, $p=0.03$), post-hoc tests revealing longer time to maximal entrainment in the AVH group as compared to HC ($p=0.03$). This effect was not evident for peak time of the PLI ($F_{2,48}=0.138$, $p=0.87$).

Peak frequency of the entrainment did not differ between groups neither as measured for EA ($F_{2,48}=1.203$, $p=0.31$), nor for PLI ($F_{2,48}=0.069$, $p=0.93$).

3.3. Correlations to psychopathology

Positive symptoms. The peak PLI of early-latency gamma in response to 40Hz tended to positively correlate to positive symptoms ($r=0.36$, $p=0.08$).

Negative symptoms. Mean early-latency EA negatively correlated to negative symptoms ($r=-0.51$, $p=0.008$). The same trend was observed for the early-latency mean PLI ($r=-0.35$, $p=0.08$) (Figure 3, A). The frequency of the early-latency gamma negatively correlated to negative symptoms ($r=-0.41$, $p=0.04$ for EA and $r=-0.47$, $p=0.02$ for PLI) (Figure 3, B).

Total PANSS. None of the measures correlated to the total PANSS scores.

Hallucination score. The peak time of the EA of late-latency gamma correlated to the hallucination score ($r=0.49$, $p=0.01$) (Figure 3, C).

Medication. Mean PLI of late-latency gamma positively correlated to medication dose ($r=0.42$, $p=0.04$). A marginal correlation was observed for the corresponding EA measure ($r=0.36$, $p=0.08$) (Figure 3, D).

4. Discussion

Our results are based upon studying the early and late gamma activity signatures (mean and peak values of phase-locking index and evoked amplitude values and corresponding peak time and frequency of maximal activity) in response to periodic stimulation at 40Hz in two

groups of schizophrenic patients differing in their hallucination status and a group of healthy controls. The present study showed that the phase-locked measures of the late-latency gamma, resembling entrainment to 40Hz stimulation, did not differ between never hallucinating patients with schizophrenia, patients with auditory verbal hallucinations and healthy controls, when recordings were performed with closed eyes. The phase-locking of early gamma activity in response to 40Hz stimulation was diminished in patients irrespective of their hallucination status as compared to controls, confirming prior observations. Time of peak entrainment and maximal frequency of early gamma provided clinically relevant information.

The PLI was selected as the primary measure, as it is the least sensitive to noise (Kalcher and Pfurtscheller, 1995; Griskova et al., 2009; Rojas et al., 2011; Tan et al., 2015) and the most reliable (McFadden et al., 2014) parameter among other ASSR measures. Moreover, the reduction of PLI and evoked amplitude of gamma responses in schizophrenia on the group level is a consistent finding (Light et al., 2006; Rass et al., 2012; Tsuchimoto et al., 2011), with some data suggesting larger responses in subjects with auditory verbal hallucinations (Spencer et al., 2008; Spencer et al., 2009).

Reanalyzing data from Koenig et al. (2012), obtained during closed eyes condition, in a phase-locked to stimulus manner we showed that only early-latency gamma activity was reduced in schizophrenia patients; measures of AVH patients were not different from NH patients, but were lower than in healthy controls (Perez et al., 2013; Roach and Mathalon, 2008; Roach et al., 2013).

No significant differences in the late-latency gamma, resembling entrainment, could be seen between both groups of patients and controls. This observation is line with the results of Griskova-Bulanova et al. (2013): eyes closure increased both PLI and evoked amplitude of late-latency gamma in schizophrenia (Griskova-Bulanova et al., 2013), but had no effect in healthy subjects (Griskova-Bulanova et al., 2011). When evaluating patients based on their history of hallucinations, evoked amplitude and phase-locking index of late-latency gamma (either mean or peak values) were not different between controls and NH patients, suggesting increase in these measures in NH subjects. However, the AVH group did not differ in these measures from controls and NH group. As can be seen from Spencer et al. (2009) and Spencer et al. (2008), patients with higher levels of AVH already show higher phase-locked ASSRs in the eyes-open

condition (probably not different from that of healthy controls, based on (Spencer et al., 2009, Figure 4)), whereas the response is reduced in non-hallucinating subjects. The observation of Spencer et al. (2009) was explained by the presence of aberrant oscillatory synchronization in PAC of AVH subjects, being hyperexcitable independently of the external stimulation (Spencer et al., 2009). Taking into account the more impaired sensory gating (i.e. inability to filter out irrelevant stimuli) in patients with a history of hallucination (Smith et al., 2013; Smucny et al., 2013) and differences in the connectivity of the DMN between AVH and NH subjects (Kindler et al., 2015; Chang et al., 2015), it is possible that eyes closure might have an effect in NH group but not in AVH group. Our results thus suggest that the hyperexcitability in AVH was not modified by general subjects' state. However, it should be mentioned that a recent study by Hirano et al. (Hirano et al., 2015) did not show a correlation between phase-locked measures to 40Hz stimulation and hallucination scores (recording conditions not specified).

An earlier study failing to show differences in 40 Hz ASSR between schizophrenia and controls (Hong et al., 2004) related the results to the effect of medication, suggesting that atypical antipsychotics caused increases of 40Hz ASSRs. We have obtained a positive correlation (uncorrected P values) between mean late-latency gamma PLI and a marginal positive correlation between measures of late-latency gamma and the CPZ equivalent doses. The sample was mainly on atypical antipsychotics and in AVH group 2 subjects and in NH group 4 subjects were using clozapine at higher doses. As suggested by Spencer et al. (2009), the results of Hong et al. (2004) might be related to the application of clozapine that causes enhancement of the NMDA system. Thus, we cannot exclude potential effect of medication in the present study. The application of non-conventional feature extraction techniques (Morup et al., 2006) allowed identifying several clinically relevant aspects. Firstly, the peak time measure appeared to be informative: peak time of the evoked amplitude to 40Hz stimulation separated AVH subjects from healthy subjects and the measure was positively correlated to the hallucination scores in the patients, indicating a delayed-build up with more prevalent hallucinations. It is difficult to discuss this observation, as timing of the entrainment is rarely assessed. However, the absence of differences between NH and controls is in line with the only study assessing peak latency: Light et al.(2006) did not find differences between patients with schizophrenia and controls for 40Hz (Light et al., 2006). The delayed entrainment in AVH would suggest a slowing of the process, thus being in agreement with previous studies suggesting that the (dys-) functioning of the PAC

is an important aspect in the emergence of AVH (Dierks et al., 1999; Hubl et al., 2007; Hubl et al., 2010; Kindler et al., 2013).

Another important aspect was related to the frequency of individual gamma activity: the frequency of the early component to 40Hz stimulation correlated inversely with negative symptoms, suggesting that more impaired subjects showed responses at lower frequencies when stimulated with 40Hz. This result should be taken with caution, as corrections for multiple tests were not applied. However, this observation is in line with a recent study by Arnfred et al. (2015), where increased self-disorder scores were associated with lower frequency of response-specific gamma activity to proprioceptive right hand stimulation (Arnfred et al., 2015). The observed pattern is also in agreement with Noh et al. (2010), where the dynamical switching between beta and gamma bands in SZ patients was reduced and negatively correlated with the negative symptoms. The authors suggested this might be responsible for the critical mechanism that bridges phenomenological characteristics and the symptoms of schizophrenia (Noh et al., 2010). This is substantiated by our negative correlation between early-latency EA/PLI values and negative symptoms, being in line with the previously shown association between inability to gate beta activity and negative symptoms (Smucny et al., 2013).

Overall, it is not common to evaluate both the early part of the response and the late entrainment phase. In the study by Light et al. (2006) patients with schizophrenia showed reduced responses both during the early phase (1-100ms) and at later stages (100-500ms) (Light et al., 2006). Recently, Tada et al. (2014) showed that different patterns of impairment - intact early-latency (0–100 ms) and reduced late-latency (200–500 ms) ASSRs - distinguished an ultra-high schizophrenia risk group from healthy controls (Tada et al., 2014). With our data, we showed that early-latency and late-latency gamma in response to 40Hz is differently affected by clinical state and modulated by general subjects' state, thus giving support for the results of Ross et al. (2005) on the different nature of these activities. Roach et al. (2014) recently suggested that despite the fact that 40 Hz ASSR and early-latency gamma response measures seem to be largely independent, they do not appear to provide unique information about auditory gamma oscillation phase consistency abnormalities in schizophrenia. Our observation provides further insight into the question, suggesting the evaluation of both early-latency and late-latency gamma would provide more clinically relevant information.

It should be mentioned that several prior studies on network level evaluation suggested that ASSR response is altered in hallucinating patients: Koenig et al. (2012) by means of induced global field synchrony identified that 40Hz stimulation partly disrupts ongoing activity in networks representing auditory input (Koenig et al., 2012). Ying et al. (2015) showed that there are more synchronous oscillations that cover a long distance on the cortex but a less efficient network for patients with auditory hallucinations (Ying et al., 2015). Thus, in the context of network integration, 40Hz ASSR seems impaired in AVH subjects. Recently Hirano et al. (2015) demonstrated that spontaneous gamma activity was increased during auditory steady-state stimulation in patients with schizophrenia, correlating positively with the prevalence of hallucinations and negatively with PLI values. This suggests that an interaction between ongoing and evoked oscillations occurred. PLI and EA measures can be considered as indexing stimulus representation – starting with early sensory processes (early-latency gamma at 0-100ms) and resulting in the engagement of task-domain specific neural populations in a tightly stimulus-related fashion (late-latency gamma at 200-500ms). Gamma oscillations during sensory tasks are thought to be related to local processing and encode the stimuli as a discrete object with recognizable features (Eckhorn et al., 1988; Tallon-Baudry and Bertrand, 1999; Kottlow et al., 2012).

Summarizing prior findings and current results, it seems that in patients with AVH, the tightly stimulus-related representation of 40 Hz auditory stimulus as indexed by entrainment is “normal” when eyes are open (Spencer et al. 2008; Spencer et al., 2009) and remains “normal” when eyes are closed, in contrast to NH subjects, where impairment is evident in open eyes only and “normalization” occurs in closed eyes. The early-latency gamma, standing for early sensory stimulus processing, on the contrary, is impaired in schizophrenia irrespective of prevalence of hallucinations and is not modulated by subjects’ general state; however its magnitude might be related to the expression of negative symptomatology.

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Figure Legends

Figure 1. Time-frequency plots of PLI in response to 40Hz stimulation (40Hz ASSR) from patients with auditory verbal hallucinations (AVH), healthy controls (HC) and non-hallucinating patients (NH).

Figure 2. Means and SDs of the measures of evoked amplitude and phase-locking index from three groups of subjects. * $p < 0.05$, ** $p < 0.01$

Figure 3. Illustrative correlations obtained for parameters of evoked amplitude and phase-locking index of early-latency and late-latency gamma and clinical variables.

Figure 1

Figure 2

EVOKED AMPLITUDE

EARLY-LATENCY GAMMA

LATE-LATENCY GAMMA

PHASE-LOCKING INDEX

EARLY-LATENCY GAMMA

LATE-LATENCY GAMMA

Figure 3

EARLY-LATENCY GAMMA

LATE-LATENCY GAMMA

Table 1. Demographic and clinical data of the study sample.

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