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Research article

40 Hz auditory steady-state response in schizophrenia: Sensitivity to stimulation type (clicks versus flutter amplitude-modulated tones)

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ABSTRACT

Auditory steady-state response (ASSR) at 40 Hz has been proposed as a potential biomarker for schizophrenia. The ASSR studies in patients have used click stimulation or amplitude-modulated tones. However, the sensitivity of 40 Hz ASSRs to different stimulation types in the same group of patients has not been previously evaluated. Two stimulation types for ASSRs were tested in this study: (1) 40 Hz clicks and (2) flutter-amplitude modulated tones. The mean phase-locking index, evoked amplitude and event-related spectral perturbation values were compared between schizophrenia patients (n = 26) and healthy controls (n = 20). Both stimulation types resulted in the observation of impaired phase-locking and power measures of late (200–500 ms) 40 Hz ASSR in patients compared to healthy controls. The early-latency (0–100 ms) 40 Hz ASSR part was diminished in the schizophrenia group in response to clicks only. The late-latency 40 Hz ASSR parameters obtained through different stimulation types correlated in healthy subjects but not in patients. We conclude that flutter amplitude-modulated tone stimulation, due to its potential to reveal late-latency entrainment deficits, is suitable for use in clinical populations. Careful consideration of experimental stimulation settings can contribute to the interpretation of ASSR deficits and utilization as a potential biomarker.

1. Introduction

Auditory steady-state responses (ASSRs) test the ability of thalamocortical and local cortical circuits to produce synchronous activity at certain frequencies as a response to repetitive external stimulation [1–3]. An impaired ASSR (reduced power and phase-locking) at 40 Hz has been proposed as a potential biomarker for schizophrenia [4,5]. Previous studies in psychiatric populations have used relatively consistent stimulation parameters for eliciting ASSRs. The most commonly utilized parameters have been 30–50 Hz click stimulation or amplitude-modulated 1000 Hz tones of 500–1000 ms. Stimulation with such parameters would lead to the elicitation of deficient 40 Hz ASSRs in schizophrenic patients [2,6,7], first-degree relatives [8,9], and in those at high risk for developing schizophrenia [10].

Thuné et al., in their meta-analysis based on studies in clinical patient populations, have revealed no effects of stimulation type on 40 Hz ASSR impairments in schizophrenia [5]. However, in patient groups the frequency [11,12] and the length [13,14] of stimulation were shown to be important factors modulating ASSR parameters. Similarly, data from healthy subjects demonstrated stimulus-related effects on ASSR measures, for example, the attentional impact [15] and variable test-retest characteristics [16]. Nevertheless, to the best of our knowledge, the effect of different stimulation settings in the same group of patients has not been previously evaluated. Importantly, according to Thuné et al., careful consideration of experimental parameters can optimize ASSR applications [5]. This would have implications for the interpretation of ASSR deficits, ASSR refinement and ASSR utilization as a biomarker in future research.

We aimed to examine the sensitivity of 40 Hz ASSR changes in patients with schizophrenia to the stimulation type used to elicit the responses. The 40 Hz click stimulation (as the "conventional" way to elicit a 40 Hz ASSR in patients [6–8]) and flutter-amplitude modulated tones (FAMs) [15] (as a novel way to elicit a 40 Hz ASSR) were used. Importantly, FAMs were perceived by our recent study participants as more pleasant than clicks [15]; thus, FAM application could be expanded to patient populations where known increased perceptual

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sensitivity to auditory stimuli is known [17,18]. Additionally, both the early part of the ASSRs (referred to as early-latency gamma, 0–100 ms) and the late entrainment-related part of ASSRs (referred to as late-latency gamma, 200–500 ms) were evaluated, as these are generated by different networks [19] and might be differently affected by psychopathology [10,20].

We hypothesized that both the early-latency and late-latency gamma responses of 40 Hz ASSRs would be impaired in patients independently of stimulation conditions. We also expected that the measures of 40 Hz ASSRs in response to click stimulation would correlate with the measures of 40 Hz ASSRs in response to FAM stimulation in both healthy controls and patients.

2. Methods

2.1. Subjects

Twenty six inpatient males from the Republican Vilnius Psychiatric Hospital (mean age, 42 years, SD 11 years) and 20 healthy male volunteers (mean age, 38 years, SD 14 years) participated in the study. Patients were diagnosed with paranoid schizophrenia (ICD-10, mean illness duration 17 years, SD 12 years) and interviewed using the Positive and Negative Syndrome Scale (PANSS) [21]. The mean positive symptom score was 21.77 (SD 5.87); the mean negative symptom score was 28.77 (SD 5.56); the mean total score was 49.54, (SD 12.07); and the mean general symptom score was 99.88 (SD 21.27). The treatment at the time of recruitment was based on antipsychotic medication, which was typically a combination of haloperidol with atypical neuroleptics (mean chlorpromazine equivalent 692.23 mg, SD 310.38) and diazepam. Subjects with a history of organic illnesses, head trauma, and alcohol/substance abuse (except tobacco) were excluded. The study was approved by the hospital's Bioethics Committee, and all study subjects gave informed consent.

2.2. Stimulation

Two ASSR stimulation paradigms were tested: (1) click stimuli and (2) FAMs (a detailed description of the stimulation settings is presented in Voicikas et al. [15]). The click stimulation trial consisted of 20 identical 1.5 ms bursts of white noise. For FAMs, the carrier was 440 Hz and the modulating envelope was 40 Hz. The schematic representation of the stimuli is plotted in Fig. 1A. Trials of clicks and FAMs lasted 500 ms with the inter-stimulus interval set within 700–1000 ms. Sounds were presented binaurally through Beyer dynamic DT-1350 headphones (Beyerdynamic GmbH & Co, Heilbronn, Germany) with the sound pressure level of both sounds adjusted to 60 dBA by using a DVM 401 decibel meter (Velleman, Fort Worth, Texas, USA). Each stimulus type was presented 150 times resulting in ~3 min of stimulation per paradigm. Study participants were instructed to watch a silent documentary movie on a screen in front of them and ignore incoming auditory stimuli.

2.3. EEG recording

The electrical brain activity was continuously recorded with a Galileo Mizar Sirius computerized electroencephalogram system (EBNeuro, Florence, Italy). Earlobe electrodes served as a recording reference. The ground electrode was attached at the Fpz location. Impedance was kept below 20 kΩ, and the sampling rate was set at 512 Hz. EEG from nine Ag/AgCl electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) were subjected to further analysis.

2.4. EEG processing

The off-line EEG data processing was performed in EEGLAB and ERPWAVELAB for MatLab© [22,23]. The power-line noise was removed using multi-tapering and Thomas *F*-statistics as implemented in CleanLine plugin for EEGLAB. The epochs of −100 ms before stimulus onset until 600 ms post-stimulus were created and re-referenced to the average reference. The excessively noisy epochs were determined by visual inspection and rejected. The data were baseline-corrected to the mean of the pre-stimulus period. A wavelet transformation (complex Morlet wavelet from Matlab© Wavelet Toolbox, frequencies from 10 to 80 Hz and 1 Hz intervals between each frequency) was performed. The phase-locking index (PLI, corresponding to the phase consistency over epochs), evoked amplitude (EA, corresponding to the time–frequency transformed evoked potential) and event-related spectral perturbation (ERSP, corresponding to the average power over epochs) of 40 Hz ASSRs were computed. The details on the calculation of the measures are presented in Mørup et al. [23]. Measures were averaged for F3, Fz, F4, C3, Cz, and C4 electrodes, resembling the strongest response.

2.5. Data analysis

We focused on the early (referred to as early-latency gamma, 0–100 ms) and late part of ASSRs (referred to as late-latency gamma, 200–500 ms), following a previously used analysis approach [20,24]. Mean PLI, EA and ERSP measures were obtained by averaging values along the 38–42 Hz frequency window separately for 0–100 ms and 200–500 ms time ranges. Statistical evaluation was performed in SPSSv20 (SPSS Inc., Chicago, Illinois, USA). RM-ANOVA with stimulus type (click vs FAM) and time period (early vs late) as within-subject factors, and group (controls vs patients) as between-subject factor was performed for each measure separately, followed by independent sample *T*-tests to assess group difference for each stimulation type. For correlation analyses among ASSR parameters (early- and late-latency PLI, EA and ERSP) in response to FAMs and clicks Pearson's correlation coefficients and corresponding *p* values were calculated.

Similarly, Pearson's correlation was used for correlation analyses among ASSR parameters (early- and late-latency PLI, EA and ERSP) and clinical variables (the mean positive symptom score, the mean negative symptom score, the mean total score, the mean general symptom score and medication).

3. Results

The grand-averaged time-frequency plots of PLIs, EAs and ERSPs for both stimulus types in the patient group and healthy controls are presented in Fig. 1B. The means and SDs of the mean PLI, EA and ERSP values for the early-latency and late-latency gamma are plotted in Fig. 1C.

RM-ANOVA on PLIs, EAs and ERSPs indicated significant effect of group (lower measures in patients; PLI: $F_{1,44} = 10.606$, $p = 0.002$, partial $\eta^2 = 0.19$; EA: $F1_{,44} = 11.371$, $p = 0.002$, partial $\eta^2 = 0.21$, ERSP: $F_{1,44} = 10.808$, $p = 0.002$, partial $\eta^2 = 0.20$), time (lower measures during the early phase; PLI: $F_{1,44} = 68.642$, $p < 0.010$, partial $\eta^2 = 0.61$; EA: $F_{1,44} = 130.420$, $p < 0.001$, partial $\eta^2 = 0.75$, ERSP: $F_{1,44} = 130.420$, $p < 0.001$, partial $\eta^2 = 0.75$) and time*group interaction (PLI: $F_{1,44} = 4.466$, $p = 0.04$, partial $\eta^2 = 0.09$; EA: $F_{1,44} = 7.476$, $p = 0.009$, partial $\eta^2 = 0.15$, ERSP: $F_{1,44} = 10.546$, $p = 0.002$, partial $\eta^2 = 0.19$). Further, to evaluate responses to each stimulus type separately and compare between experimental groups, we performed independent sample *T*-tests. The results of the *T*-tests are presented in Table 1. The early-latency measures were diminished in the schizophrenia group in response to click stimulation only. The late-latency measures were lower in patients for both click and FAM stimulation. We evaluated the correlation between responses to clicks and FAMs (results presented in Table 1): measures during the early ASSR part did not reveal correlation between clicks and FAMs in both controls (except ERSPs) and patients; during the late-part of the response, phase-locked measures of clicks and FAMs correlated in the healthy group only. We did not find any relationship between the early-latency