

# Application of Evoked Response Audiometry To Schizophrenia For Specifying 40-Hz Aberrant Gamma Oscillations In A Real-World Clinical Setting

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## Research Article

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# Abstract

Gamma oscillations probed using auditory steady-state response (ASSR) are promising clinical biomarkers that may address novel therapeutic interventions for schizophrenia. Optimizing clinical settings for these biomarker-driven interventions will require a quick and easy assessment system of gamma oscillations in psychiatry. ASSR has been used in clinical otolaryngology for evoked response audiometry (ERA) to judge hearing loss by focusing on the phase-locked response detectability in an automated analysis system. Herein, a standard ERA system was applied to evaluate the brain pathophysiology of patients with schizophrenia with 40-Hz ASSR. The 40-Hz ASSR in the ERA system showed excellent detectability of the phase-locked response in healthy subjects, which sharply captured the deficits of the phase-locked response caused by aberrant gamma oscillations in individuals with schizophrenia. These findings reveal the availability of the ERA system in specifying patients who have aberrant 40-Hz gamma oscillations. The ERA system may have a potential to serve as a real-world clinical setting for upcoming biomarker-driven therapeutics in psychiatry.

## Introduction

Gamma oscillations whose impairments have been predominantly shown in the prefrontal cortex as in schizophrenia are promising clinical biomarkers that may address novel therapeutic interventions for schizophrenia<sup>1-7</sup>. They are neural rhythmic fluctuations of the gamma frequency range (30–200 Hz) that are commonly captured by electroencephalogram (EEG) or magnetoencephalography<sup>2,8</sup>. The gamma oscillations play a role in information processing in higher-order brain functions (e.g., perception, attention, and working memory). Hence, various kinds of sensory and cognitive stimuli elicit gamma oscillations in the associated brain regions<sup>2,6,8</sup>. The auditory steady-state response (ASSR) is sustained neural entrainment to periodic auditory stimuli that can be used to stably measure the gamma oscillations by using the stimuli temporally modulated at gamma frequency ranges. ASSR potentials in humans are largest when the periodic auditory stimuli are presented at the frequency of approximately 40 Hz<sup>9</sup>. Previous ASSR studies have shown that the 40-Hz gamma oscillations are highly impaired in patients with schizophrenia<sup>10</sup>.

The impaired 40-Hz gamma oscillations implicate abnormal functional interaction between parvalbumin-positive GABAergic neurons and pyramidal neurons in the prefrontal cortex of schizophrenia<sup>11-13</sup>. Considering the evidence of rodent studies that the cortical parvalbumin-positive GABAergic neurons are the generator of gamma oscillations<sup>14,15</sup>, the parvalbumin-positive GABAergic neurons could be the primary target to treat the impaired gamma oscillations<sup>16</sup>. Based on the findings of postmortem brain studies that the cortical parvalbumin-positive GABAergic neurons are impaired in the prefrontal cortex of patients with schizophrenia<sup>1,17</sup>, GABAergic compounds have been challenged to compensate for the dysfunction of the GABAergic neurons in patients with schizophrenia<sup>18-20</sup>. A compound for modulating the Kv3.1 activity, a potassium channel involved in the firing of parvalbumin-positive GABAergic neurons<sup>21</sup>, has been developed to treat schizophrenia<sup>22</sup> based on the finding of the prefrontal reduction of this

channel protein in schizophrenia<sup>23</sup>. However, given the heterogeneous nature of schizophrenia, the therapeutic target of such compounds may be optimal for several, but not all patients with schizophrenia<sup>24,25</sup>. Given that the gamma oscillations have the potential to detect such targeting pathophysiology among patients with schizophrenia, a simple system with automated analysis of gamma oscillations will be required for optimizing clinical settings in psychiatry.

ASSR is currently used in clinical otolaryngology for evoked response audiometry (ERA) with medically approved devices. The ASSR in the ERA system is performed using the automated analysis, which is designed to judge hearing loss by focusing on the phase-locked response detectability. These devices are globally available at many hospital facilities, where the established clinical protocol for measurements ensures the reproducibility of the ASSR results. Furthermore, the 40-Hz ASSR is the testing condition in ERA for awake adults, which is preset in the devices with a stimulus rate of around 40 Hz. The ERA system has such an advanced utility for clinical applications of 40-Hz ASSR in psychiatry. Thus, this study examined the availability of a standard device for ERA to detect brain pathophysiology of schizophrenia with the 40-Hz ASSR.

## Results

### Phase-locked/nonphase-locked response

The phase-locked (A) and nonphase-locked (B) representative responses in the 40-Hz ASSR with the preset stimulus are shown in Fig. 1. All of the measurements conducted thrice in the healthy subjects demonstrated a phase-locked response in both the preset and basic stimuli, whereas the nonphase-locked response was demonstrated in several patients with schizophrenia by the preset (14 patients) and basic (10 patients) stimuli. The details for the occurrence of the phase- and nonphase-locked responses are described in Table 1.

### Clinical variables in patients with and without nonphase-locked responses

No significant differences were found between patients with nonphase-locked responses (nonphase-locked group) and without nonphase-locked responses (all phase-locked group) both in the preset and basic stimuli of the 40-Hz ASSR (Table 2).

### Number of trials to achieve phase-locked response

The nonphase-locked response, which was statistically judged not to phase-lock within 64 trials, was assigned the maximum trial number of 64 to statistically analyze the number of trials to achieve the phase-locked response. Significant increases were noted in the number of trials to achieve the phase-locked response in patients with schizophrenia [preset (mean  $\pm$  SD = 35.5  $\pm$  17.4) and basic (31.0  $\pm$  15.9)] compared with healthy subjects [preset (20.2  $\pm$  3.8) and basic (20.3  $\pm$  3.3)] in both stimuli [preset ( $t = 5.3$ ,  $df = 74$ ,  $P < 0.0001$ ) and basic ( $t = 4.0$ ,  $df = 74$ ,  $P = 0.0001$ )] (Fig. 2a).

# Response amplitude

The response amplitude of the 40-Hz ASSR did not significantly differ between patients with schizophrenia [preset ( $0.35 \pm 0.26 \mu\text{V}$ ) and basic ( $0.35 \pm 0.16 \mu\text{V}$ )] and healthy subjects [preset ( $0.38 \pm 0.12 \mu\text{V}$ ) and basic ( $0.36 \pm 0.11 \mu\text{V}$ )] in both stimuli [preset ( $t = 0.72$ ,  $df = 74$ ,  $P = 0.47$ ) and basic ( $t = 0.43$ ,  $df = 74$ ,  $P = 0.67$ )] (Fig. 2b). In addition, no significant differences were observed between patients with nonphase-locked responses [preset ( $0.34 \pm 0.36 \mu\text{V}$ ) and basic ( $0.34 \pm 0.18 \mu\text{V}$ )] and those without nonphase-locked responses [preset ( $0.35 \pm 0.19 \mu\text{V}$ ) and basic ( $0.35 \pm 0.15 \mu\text{V}$ )] in both stimuli [preset ( $t = 0.08$ ,  $df = 36$ ,  $P = 0.94$ ) and basic ( $t = 0.28$ ,  $df = 36$ ,  $P = 0.78$ )].

## Test–retest reliabilities of the ASSR measurements

Excellent ICCs were observed among the three ASSR measurements both in the number of trials to achieve the phase-locked response (0.92 for preset stimulus and 0.89 for basic stimulus) and in the response amplitude (0.94 for preset stimulus and 0.91 for basic stimulus).

## Discussion

The current study proposed an approach using the automated ERA system to specify individual patients with schizophrenia who have severely impaired 40-Hz gamma oscillations. The 40-Hz ASSR in the ERA system, which showed excellent detectability of the phase-locked response in healthy subjects, sharply captured the nonphase-locked responses in individuals with schizophrenia both in the preset (AM + FM at 46 Hz rate) and basic (AM at 40 Hz rate) auditory stimuli (Table 1). Further clinical investigation on the 40-Hz ASSR showed no significant differences in clinical variables between patients with and without the nonphase-locked responses in both stimuli (Table 2). This finding conversely suggests the usefulness of 40-Hz ASSR in specifying patients with aberrant gamma oscillations who may be difficultly designated using current clinical contexts. The advanced utility of the ERA system in the real-world clinical setting suggests its potential utility in real-world clinical applications in psychiatry. The global ERA system is suitable for extensive clinical trials to recruit patients compatible with novel treatments to improve the 40-Hz gamma oscillation abnormalities. These biomarker-driven treatments can be expanded into clinical practices, where the established clinical procedure of the ASSR ensures the reproducibility of results among the global facilities. Thus, the globally advanced ERA system could significantly enhance the utility of 40-Hz ASSR in efforts to develop novel and targeted treatments to ameliorate the impaired gamma oscillations in psychiatry.

The ASSR with the nonphase-locked response comprised nonphase-aligned trials that prevented the identification of phase-locked response as represented in Fig. 1b. These nonphase-aligned activities were potentially occurring at a similar amplitude level as the normal phase-locked activities (Fig. 1a, 1b). Thus, the response amplitude of the 40-Hz ASSR did not significantly differ between patients with schizophrenia and healthy subjects as shown in Fig. 2b despite patients having poor phase-locked responses (Fig. 2a). Previous studies reported aberrant gamma oscillations that have heightened induced (stimulus-induced nonphase-locked) gamma activities accompanied by a reduced phase-locking of 40-Hz

ASSR in patients with schizophrenia<sup>26,27</sup>. These aberrant gamma oscillations may be linked with those shown as the prevailing nonphase-aligned trials during the 40-Hz ASSR experiment in this study. In addition, the results of the current study showed that nonphase-locked responses were observed more frequently in the preset stimulus compared with the basic one in patients with schizophrenia. A major difference between the preset and basic stimuli is the fluctuation of the tone induced by the FM. A previous study exhibited similar abnormalities in ASSR between the 40- and 45-Hz rate in patients with schizophrenia<sup>28</sup> although other differences in the modulated rate (46 vs. 40 Hz) between the two stimuli were observed. The complex tone stimulation in which the FM component was added to the AM may be more sensitive than the AM only to the neural entrainment dysfunction in patients with schizophrenia. The FM detection is generally crucial for speech perception especially under noisy conditions (e.g., the presence of competing voices)<sup>29</sup>. The FM variation in the 40-Hz ASSR may be worth exploring in further studies to probe the abnormal speech perception that has been reported in patients with schizophrenia<sup>30,31</sup>.

This is an initial application study of the ERA system to evaluate impaired 40-Hz gamma oscillations, the brain functional abnormality, in schizophrenia. Further investigations will be required to optimize this automated assessment system into clinical psychiatry. Firstly, the Audera system defines the nonphase-locked response for the cases that did not reach phase-locked response within 64 trials. This cutoff criterion to define nonphase-locked response needs to be scrutinized while clinical tests with the ERA system progress in psychiatry. Secondly, the influence of the methodological difference between the ERA system and the previous ASSR studies in schizophrenia needs to be characterized. The ERA system uses continuous auditory tone stimuli, while previous studies for schizophrenia have used discrete ones. The continuous tone stimuli have an advantage that can shorten the measurement time, which helps the examinee to avoid falling asleep, a confounding factor to decrease the amplitude of the 40-Hz ASSR<sup>32</sup>. The ERA system can easily enhance the overlay of epochs up to hundreds of times in a short period for reliably judging the phase-locked response with another ingenuity of using short epochs for overlay. Instead, the ERA system provides only single summary results for the frequency domain activity. The discrete tone stimuli allow time-frequency decomposition analysis, which is currently the standard analytical method in schizophrenia research<sup>33</sup>. This analysis provides collateral information such as transient onset/offset responses<sup>34</sup> and time course of the response in the discrete tones<sup>35-38</sup>. On the other hand, the kinds of parameters available to analyze the gamma oscillations are limited in the ERA device software, and the ERA system does not store the EEG recordings needed for detailed analysis of ASSR. Further development of the software will be required for a comprehensive understanding of the pathophysiology encircling the impaired 40 Hz gamma oscillations in schizophrenia.

In summary, the availability of the ERA system, which has the potential for a global platform of real-world clinical settings in psychiatry, was revealed to specify aberrant 40-Hz gamma oscillations in patients with schizophrenia. Given that schizophrenia is a heterogeneous disease whose pathophysiology is shared with other psychiatric diseases such as bipolar disorder<sup>25,34,39</sup>, the ERA system may be used adjunctively with other biomarkers to biologically classify schizophrenia and related disorders by seeking the optimal

therapeutic target with the 40-Hz ASSR. Further clinical challenges with the 40-Hz ASSR in the ERA system will be warranted to construct a solid biomarker for the target treatment in the concept of the biological classification of schizophrenia and related disorders.

## Methods

### Subjects

This study recruited 38 patients with schizophrenia (20 men and 18 women) aged between 27 and 68 years old (mean  $\pm$  SD =  $46.2 \pm 11.2$ ) and 38 case-matched healthy subjects (20 men and 18 women) aged between 24 and 67 years ( $46.7 \pm 10.9$ ) from Kindai University Hospital and Izumigaoka Hospital. Each patient was diagnosed based on the DSM-5 criteria. Clinical symptoms and social functioning were assessed using the Brief Psychiatric Rating Scale (BPRS)<sup>40</sup> and the Global Assessment of Functioning (GAF), respectively. Clinical information was obtained from the clinical psychiatrists in charge of each patient based on detailed clinical observations during hospitalization and/or long-term follow-up during outpatient treatment. Diagnosis and clinical assessments were verified by two research psychiatrists who were blinded to the ASSR data. None of the patients had a history of auditory disorders, neurological disorders, head trauma, electroconvulsive therapy, or substance/alcohol abuse. However, all patients were administered antipsychotics. The clinical variables of the patients were as follows: illness duration,  $22.8 \pm 12.0$  years; chlorpromazine-equivalent antipsychotic dose,  $945.1 \pm 896.5$  mg/day; and GAF score,  $34.1 \pm 16.1$ . The BPRS item scores were categorized into a four-dimensional model according to a previous report<sup>41</sup>:

(1) Thinking disturbance (hallucinatory behavior, unusual thought content, and conceptual disorganization):  $6.1 \pm 4.2$ .

(2) Withdrawal/retardation (emotional withdrawal, blunted affect, and motor retardation):  $5.1 \pm 4.0$ .

(3) Hostile/suspiciousness (hostility, suspiciousness, and uncooperativeness):  $2.8 \pm 2.9$ .

(4) Anxious/depression (anxiety, guilt feelings, and depressive mood):  $2.9 \pm 2.3$ .

The latter report confirms that Thinking Disturbance and Withdrawal–Retardation reflect positive and negative symptoms, respectively<sup>42</sup>. The healthy subjects had no history of psychiatric, neurological, or auditory disorders. This study was approved by the Ethics Committee of the Kindai University Faculty of Medicine, and carried out in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. A complete description of the study was provided and written informed consent was obtained from all the participants.

### ASSR measurements

The ASSR was performed with a medical ERA device, Audera (Grason-Stadler Inc., Eden Prairie, MN, USA) following technical protocol with minor modification. The Audera device usually tests one ear at a time with the TIP-50 insert phones (Grason-Stader Inc.). In this study, the tube from the insert phone for the left ear was replaced with a bifurcated tube to binaurally present the tones. The bifurcated tube was placed

so as not to touch the body or the clothing to avoid any interfering noises. The EEG was sampled from an electrode placed on the forehead around the middle point between the Fz and Fpz of the International 10–20 system. The electrodes on the left earlobe and the low forehead around the Fpz served as the reference and the ground electrodes, respectively. The electrode impedances were  $< 5$  kOhms. The 40-Hz ASSR potentials were evoked by two kinds of auditory stimuli with intensity levels at 70 dBHL. These two stimuli are the continuous sine wave tones with a carrier frequency (CF) of 1,000 Hz, which have (1) mixed modulation (100% amplitude plus 10% frequency modulations) at 46 Hz, where a sinusoidal change of the tone volume between 0 and 70 dB and a fluctuation of the CF tone between 900 and 1,100 Hz occur at the rate of 46 Hz or (2) 100% amplitude modulation, where the tone volume sinusoidally changes between 0 and 70 dB at the rate of 40 Hz. The former is the preset stimulus in Audera for the 40-Hz ASSR that is used for awake adults, whereas the latter is one of the basic stimuli that have been used, although as discrete tones, for ASSR studies in schizophrenia<sup>27,28</sup>. The preset stimulus was slightly modulated from the basic stimulus to increase the ASSR potentials by adding frequency modulation<sup>43</sup>. The (1) preset and (2) basic stimuli were presented thrice to each subject in a counterbalanced manner. The subjects were instructed to sit and relax on the chair and keep their eyes closed and remain motionless during ASSR measurements to avoid muscular artifact generation. The subjects were asked to open their eyes during a brief break between the three measurements to avoid falling asleep during the subsequent measurement.

## Data acquisition

The presence or absence of the phase-locked response was automatically determined by the statistical algorithm adopted in the Audera system. First, the system serially segmented the continuous EEG sample during the tone stimulation into epochs in every few cycles of the sine wave tones. Every 10 epochs were then overlaid as trials. Each trial was analyzed using a fast Fourier transform to calculate the amplitude and phase in the frequency domain corresponding to the modulation frequency. These outcomes were reported as vectors (Fig. 1). Moreover, the statistical algorithm applied phase coherence squared (PC2) to estimate the phase coherence between the trials and the modulation frequency. The PC2 value was statistically evaluated using a circular variance to test for a 97% confidence criterion resulting in phase-locked response detection. The PC2 value was updated during the measurement each time a new trial was added, and the system algorithm automatically terminated the stimulation and the data sampling when the response was detected or when the response could not be reasonably detected within 64 trials. The latter case was defined as the nonphase-locked response in this study. The minimum number of trials to achieve the phase-locked response was 16, which represents the evaluation of 160 sampling epochs. The maximum number of trials was 64, which resulted in the evaluation of 640 sampling epochs in total. The time taken to run one measurement ranges 31–98 s, according to the number of trials between a minimum of 16 and a maximum of 64. To support the evaluation of the 40-Hz gamma oscillations with the presence/absence of the phase-locked response, additional parameters were selected: (1) the number of trials to achieve the phase-locked response, which was displayed as the number of vectors in Fig. 1, and (2) the response amplitude (root mean square voltage; in microvolts) of

the 40-Hz ASSR, which was calculated as the mean length of the vectors. The results of three measurements for both parameters were averaged for each of the stimuli for each subject.

## Statistics

The occurrence of the nonphase-locked response was compared between patients with schizophrenia and healthy subjects using Fisher's exact test. The clinical variables were compared between patients with and without nonphase-locked responses using binary logistic regression. The numbers of trials to achieve the phase-locked response and the response amplitude were compared between two groups using unpaired *t*-tests. The test–retest reliabilities for the three ASSR measurements were examined in the total cohort of patients and healthy subjects using average-measure intraclass correlation coefficients (ICCs) as previously described<sup>44</sup> in terms of the number of trials to achieve the phase-locked response and the response amplitude. All statistical tests were two-tailed, and the threshold for the significance of *P* values was set at 0.025 (0.05/2) by the Bonferroni correction because two different stimuli were tested in this study. SPSS version 25.0 (IBM Inc., Armonk, NY, USA) was used for the statistical analyses.

## Declarations

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### Author Contributions

M.Y. designed the study. M.Y. and F.H. collected the ASSR data. A.T. and S.O. obtained the clinical data of patients with schizophrenia. M.Y. managed the analyses. M.Y. wrote the manuscript. O.S. interpreted the data and supervised this study. All authors contributed to and have approved the final manuscript.

### Competing Interests

The authors declare no competing interests.

### Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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## Tables

**Table 1. Occurrence of the phase-locked and nonphase-locked responses in thrice measurements of 40-Hz ASSR.**

| ASSR            |                                     | Occurrence of responses for phase-locked/nonphase-locked |     |     |     | Fisher's exact test |
|-----------------|-------------------------------------|--|-----|-----|-----|---------------------|
|                 |                                     | 3/0  | 2/1 | 1/2 | 0/3 |                     |
| Preset stimulus | Healthy subjects, n = 38            | 38   | 0   | 0   | 0   | < 0.0001            |
|                 | Patients with schizophrenia, n = 38 | 24   | 5   | 5   | 4   |                     |
| Basic stimulus  | Healthy subjects                    | 38   | 0   | 0   | 0   | 0.001               |
|                 | Patients with schizophrenia         | 28   | 3   | 4   | 3   |                     |

**Table 2. Comparison of clinical variables between all phase-locked and nonphase-locked groups in schizophrenia.**

| 40-Hz ASSR                           | All phase-locked <sup>a</sup> | Nonphase-locked <sup>b</sup> | P value |
|--------------------------------------|-------------------------------|------------------------------|---------|
| Preset stimulus                      |                               |                              |         |
| Number of cases (male/female)        | 24 (12/12)                    | 14 (8/6)                     |         |
| Age, y, mean ± SD                    | 44.0 ± 11.1                   | 51.4 ± 9.1                   | 0.03    |
| Illness duration, y                  | 20.3 ± 11.8                   | 27.1 ± 11.4                  | 0.83    |
| GAF                                  | 35.9 ± 15.5                   | 31.1 ± 17.2                  | 0.3     |
| BPRS, four-dimensional model         |                               |                              |         |
| Thinking disturbance <sup>c</sup>    | 5.0 ± 3.3                     | 8.1 ± 4.8                    | 0.52    |
| Withdrawal/retardation <sup>d</sup>  | 4.5 ± 3.4                     | 5.9 ± 4.9                    | 0.71    |
| Hostile/suspiciousness               | 2.6 ± 2.9                     | 3.0 ± 2.9                    | 0.18    |
| Anxious/depression                   | 2.7 ± 2.3                     | 3.2 ± 2.4                    | 0.13    |
| Antipsychotics <sup>e</sup> , mg/day | 700 ± 99                      | 1388 ± 336                   | 0.04    |
| Basic stimulus                       |                               |                              |         |
| Number of cases (male/female)        | 28 (16/12)                    | 10 (4/6)                     |         |
| Age, y, mean ± SD                    | 45.0 ± 11.3                   | 51.5 ± 8.1                   | 0.1     |
| Illness duration, y                  | 21.3 ± 12.3                   | 27.0 ± 10.7                  | 0.78    |
| GAF                                  | 35.0 ± 16.1                   | 31.6 ± 16.4                  | 0.6     |
| BPRS, four-dimensional model         |                               |                              |         |
| Thinking disturbance                 | 5.4 ± 3.2                     | 8.3 ± 5.8                    | 0.48    |
| Withdrawal/retardation               | 4.5 ± 3.3                     | 6.7 ± 5.3                    | 0.22    |
| Hostile/suspiciousness               | 2.8 ± 3.1                     | 2.6 ± 2.3                    | 0.55    |
| Anxiety/depression                   | 2.9 ± 2.3                     | 2.8 ± 2.3                    | 0.83    |
| Antipsychotics, mg/day               | 901 ± 183                     | 1099 ± 223                   | 0.71    |

<sup>a</sup>The group of patients who had the phase-locked responses in all three measurements (patients without nonphase-locked responses).

<sup>b</sup>The group of patients who had nonphase-locked responses, at least one in three measurements (patients with nonphase-locked responses).

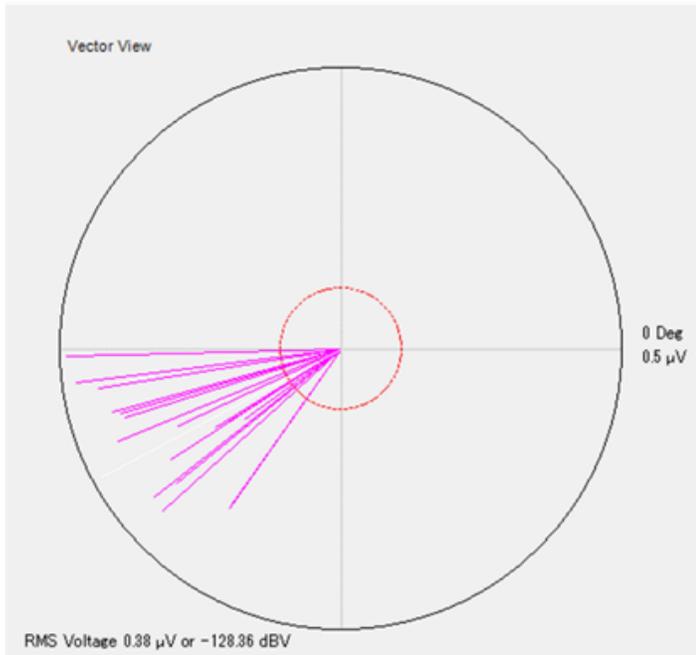
<sup>c</sup>Positive symptoms.

<sup>d</sup>Negative symptoms.

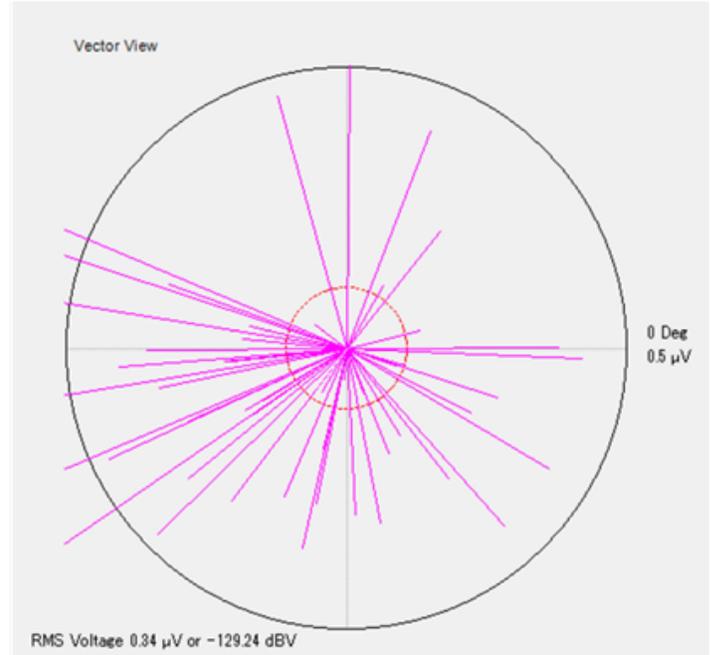
<sup>e</sup>Chlorpromazine equivalent dose.

## Figures

**a. Phase-locked response**



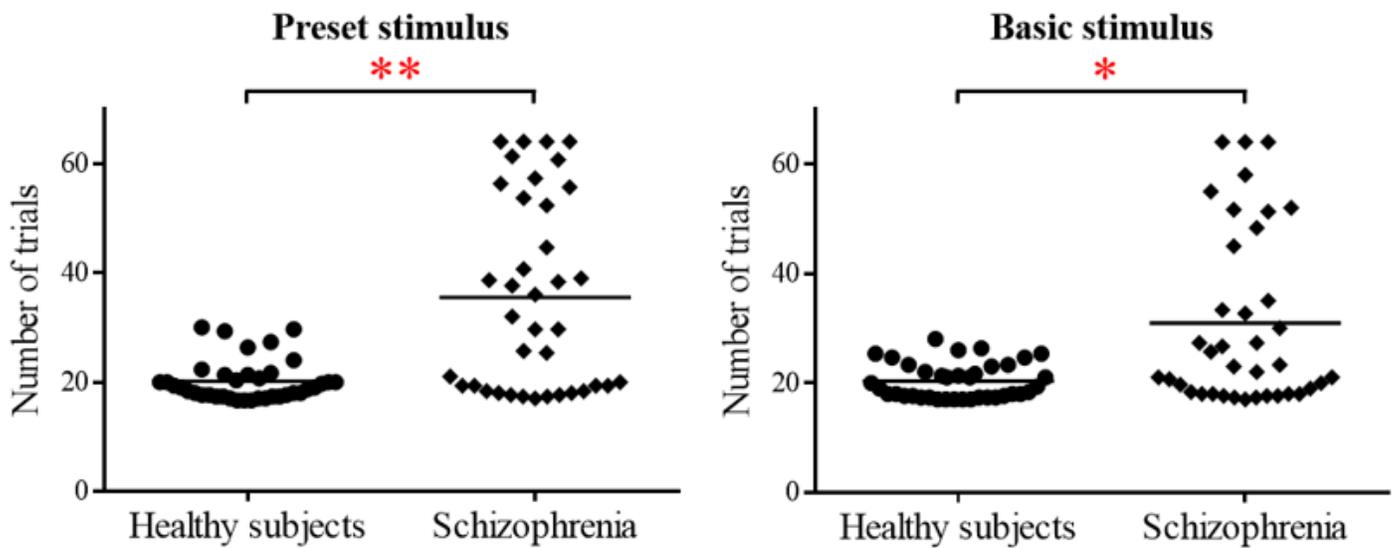
**b. Nonphase-locked response**



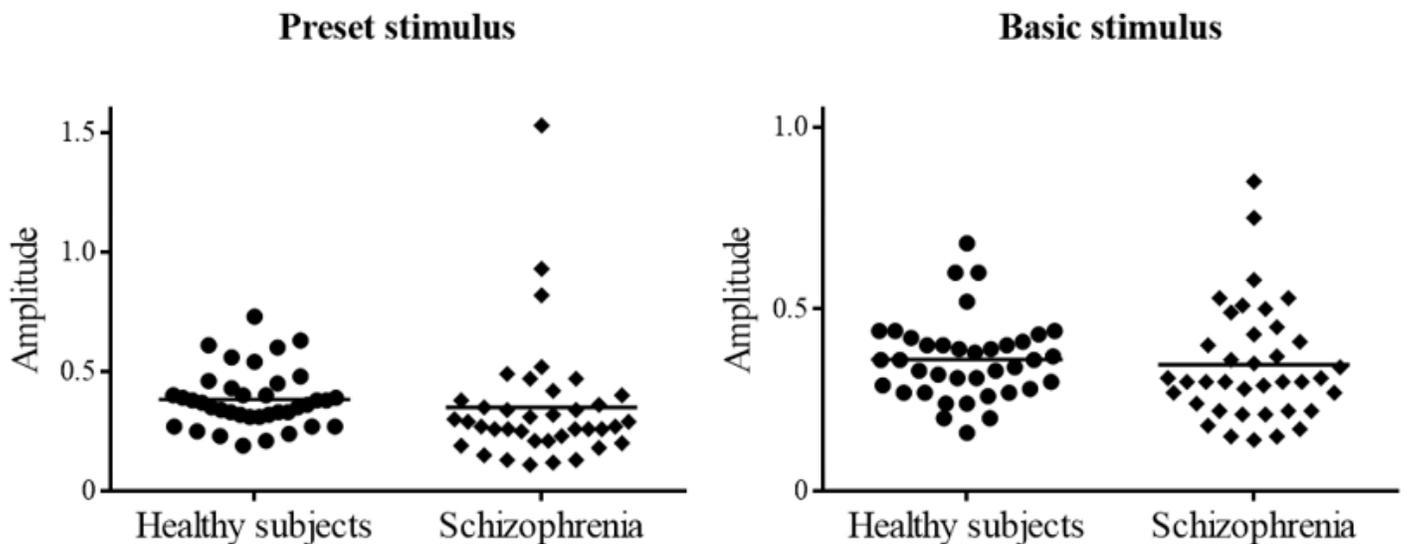
**Figure 1**

Representative responses in the 40-Hz ASSR in the automated ERA system. The representative phase-locked (a) and nonphase-locked (b) responses in the 40-Hz ASSR with the preset stimulus in the ERA system. a and b are cases of a healthy participant and a patient with schizophrenia, respectively. Each vector in the diagram, which was created by each trial during the auditory stimulus, represents the phase and the amplitude of EEG activity corresponding to the tone modulation frequency rate. The phase angle of the vectors corresponds to the time delay between the presentation of the stimulus and the neural response of trials. The cross-trial phase consistency of the vectors determines the phase-locked or nonphase-locked response. While all trials are aligned in the same range in a, the nonaligned trials that prevent the identification of phase-locked response are seen in b. The mean length of the vectors represents the response amplitude (root mean square voltage, in microvolts) of the ASSR.

**a. Number of trials to achieve phase-locked response**



**b. Total amplitude**



**Figure 2**

Trends to achieve the phase-locked response and the 40-Hz ASSR potentials. a Significant differences were observed in the number of trials conducted to achieve a phase-locked response between patients with schizophrenia and healthy subjects in the 40-Hz ASSR with preset (left) and basic (right) stimuli. \*\* $P < 0.0001$ , \* $P = 0.0001$ . b No significant differences were observed in the total amplitudes of the 40-Hz ASSR with preset (left) and basic (right) stimuli between patients with schizophrenia and healthy subjects.