Differential Alterations of Auditory Gamma Oscillatory Responses Between Pre-Onset High-Risk Individuals and First-Episode Schizophrenia

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Abstract

Alterations in gamma-band auditory steady-state response (ASSR) are the most robust finding of abnormal neural oscillations in patients with first-episode (FES) and chronic schizophrenia. Gamma-band ASSRs may indicate GABAergic interneuron dysfunction. Nevertheless, it is unknown whether abnormal gamma-band ASSRs are present before the onset of psychosis. Subjects were 15 ultra-high-risk (UHR) individuals, 13 FES patients, and 21 healthy control (HC) subjects. We performed electroencephalogram recordings and measured ASSRs in each group as they were presented with click trains at 20, 30, and 40 Hz. We then conducted time-frequency analyses and calculated intertrial phase coherence and event-related spectral perturbation. The time course of gamma-band ASSRs showed significantly different features among groups. Compared with the HC group, the UHR group was characterized by intact early-latency (0–100 ms) and reduced late-latency (300–500 ms) ASSRs. In contrast, both early- and late-latency ASSRs were significantly reduced in the FES group. Gamma-band ASSRs were correlated with clinical symptoms and attentional functioning in FES (|r| > 0.70). These results suggest differential alterations of gamma-band ASSRs between UHR and FES groups. The late-latency ASSR alteration may represent a biomarker for early detection of psychosis, while the early-latency ASSR abnormality may develop through the onset of psychosis.

Key words: auditory steady-state response, electroencephalogram, gamma oscillations, schizophrenia, ultra-high risk

Introduction

The gamma oscillation is a useful biological marker that indexes cognitive dysfunction in schizophrenia (Fries 2009; Minzenberg et al. 2010). Cortical gamma oscillations result from synaptic interactions between parvalbumin-positive γ-aminobutyric acid (GABA)-ergic interneurons and pyramidal neurons (Cardin et al. 2009; Sohal et al. 2009). Abnormalities in cortical neurons, including parvalbumin-positive GABAergic interneurons, have been observed in postmortem brains of individuals with schizophrenia (Hashimoto et al. 2008; Moyer et al. 2012). Therefore, investigating gamma oscillations may help to understand GABAergic interneuron dysfunction in these patients with schizophrenia (Gonzalez-Burgos and Lewis 2008; Fisahn et al. 2009).

Electroencephalography (EEG) and magnetoencephalography (MEG) studies have reported abnormal gamma oscillations in...
patients with schizophrenia (Uhlhaas and Singer 2010; Sun et al. 2011). The auditory steady-state response (ASSR) has been thought to be the most robust finding of abnormal gamma oscillations in schizophrenia. The ASSR is an electrophysiological response entrained to both the frequency and phase of rapid, periodic auditory stimuli (Galambos et al. 1981; Brenner et al. 2009). In humans, the ASSR is most evident when stimuli are presented in the gamma frequency range (30–50 Hz) (Galambos et al. 1981).

Recent studies have focused on early stages of schizophrenia (Kasai et al. 2003; Takahashi et al. 2009; Andreasen et al. 2011; Jahshan et al. 2012) because early detection and intervention may improve functional outcomes (Marshall et al. 2005) and even prevent the onset of psychosis. Several clinical criteria have been developed to identify people who have a high risk for developing psychosis (Cannon et al. 2008; Ruhrmann et al. 2010), and the condition defined by these criteria is termed ultra-high risk (UHR). It remains unclear when the deficits in ASSR appear through the stages of psychosis. Previous studies have reported that chronic schizophrenia (Kwon et al. 1999; Brenner et al. 2003; Light et al. 2006; Tasele et al. 2008; Vierling-Claassen et al. 2008; Tsuchimoto et al. 2011; Kirihara et al. 2012) and first-episode schizophrenia (FES) patients (Spencer et al. 2008; Wilson et al. 2008) have clear deficits in the gamma-band ASSR. To our knowledge, however, no studies have investigated gamma-band ASSR in UHR individuals.

Furthermore, analyzing the time course of the gamma-band ASSR might help to reveal abnormalities in neural circuits during the early stages of psychosis. Ross et al. (2002) suggested that the ASSR can be decomposed into a “transient gamma-band response” (gamma-band response in 0–100 ms) and a “steady-state response” (gamma-band response in 250–500 ms) because these components show distinct stimulus-dependent characteristics. This finding suggests that different neural circuits contribute to the ASSR at early and late latencies, and that these ASSR components may be affected differently in the early stages of psychosis.

Our research question was to clarify whether the gamma-band ASSR was altered in UHR individuals. We also compared the time course of gamma-band ASSR between UHR individuals and patients with FES. We hypothesized that an overall reduction of the gamma-band ASSR would be present in patients with FES, and that latency-specific ASSR alterations might be present in UHR individuals.

**Materials and Methods**

**Subjects**

A total of 49 subjects participated in this study. These subjects were divided into the following three groups: 1) 15 subjects (9 males) who met UHR criteria, 2) 13 patients with FES (8 males), and 3) 21 healthy control (HC) subjects (11 males). This study was approved by the ethical committee of the University of Tokyo (approval No. 629-3, 2226-3). Written informed consent was obtained from all subjects after they were given a complete explanation of the study.

UHR subjects and patients with FES were recruited from the University of Tokyo Hospital as part of the Integrated Neuroimaging Studies in Schizophrenia Targeted for Early Intervention and Prevention (IN-STEP) project (Koike et al. 2011, 2013; Iwashiro et al. 2012). All subjects were between 15 and 40 years of age. All UHR subjects were seeking medical care, and most of them were recruited from the outpatient unit for early intervention at the University of Tokyo Hospital (http://plaza.umin.ac.jp/arms-ut). Our recruitment method was described in detail in a previous report (Koike et al. 2013). Here, we briefly summarize the methods that are relevant to this study.

We used the Structured Interview for Prodromal Symptoms (SIPS) to select UHR subjects. Subjects who met criteria for attenuated psychotic symptoms (APS), brief intermittent psychotic symptoms (BIPS), and genetic risk and deterioration (GRD) were selected for the study (Miller et al. 1999; Kobayashi et al. 2007). APS was defined by the onset of subthreshold psychotic symptoms, or worsened subthreshold psychotic symptoms within 12 months. BIPS was defined by the occurrence of psychotic episodes within 3 months that were too short and infrequent to be considered the Presence of Psychotic Symptoms criteria. GRD was defined by a greater than 30% decrease in the Global Assessment of Functioning (GAF) score within 12 months, and having a first-degree relative diagnosed with psychosis and/or schizotypal personality disorder using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association 1994). Among the 15 UHR subjects, we identified 9 with APS, 2 with APS and GRD, 2 with GRD, 1 with BIPS, and 1 with APS and BIPS.

Patients with FES were diagnosed using DSM-IV (American Psychiatric Association 1994) criteria, and were included in the present study if they demonstrated continuous psychotic symptoms within the past 24 months, without previously demonstrating psychotic symptoms.

HC subjects were screened with the Mini-International Neuropsychiatric Interview (Sheehan et al. 1998) to rule out psychiatric disorders. Healthy subjects were excluded from the study if they had a history of psychiatric illness, or a history of Axis I disorders in their first-degree relatives.

For all subjects, the exclusion criteria were as follows: 1) neurological illness at any point in their lifetime, 2) traumatic brain injury with any cognitive consequences or loss of consciousness for more than 5 min, 3) a history of electroconvulsive therapy, 4) low estimated premorbid intelligence quotient (IQ; below 70), 5) previous alcohol abuse or dependence, and 6) previous continuous substance use or substance use disorder. Prior to entering the study, we confirmed that all participants could detect 1000-Hz tones at 30 dB using the audiometric testing.

We assessed the functioning and symptoms in all UHR and FES group subjects using the GAF scale (American Psychiatric Association 1994) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987). Separate raters were involved in conducting assessments of the PANSS, the Brief Assessment of Cognition in Schizophrenia (BACS), and EEG. Experienced psychiatrists assessed clinical symptoms and functioning with PANSS and GAF, respectively. The inter-rater reliability of clinical assessments was 0.857 (Cronbach alpha). Well-trained psychologists assessed cognitive functions with BACS, and EEG recordings and analyses were conducted by researchers with expertise in EEG. EEG recordings were obtained within 1 month of the clinical assessments.

The clinical characteristics for all study participants are presented in Table 1. We observed no difference among the 3 groups in terms of sex ratio, age, and estimated IQ, as measured with the Japanese version of the National Adult Reading Test (Matsuoka et al. 2006). Antipsychotic doses were significantly higher in the FES group than in the UHR group. In the UHR group, 6 subjects received second-generation antipsychotic medications and 5 received benzodiazepines. The mean antipsychotic dose for those UHR participants who were treated with antipsychotics was 262.8 mg/day. All patients in the FES group received second-generation antipsychotic medications, with one also receiving sulpiride.
Table 1 Demographic characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>UHR</th>
<th>FES</th>
<th>Statistic</th>
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<tbody>
<tr>
<td>N (sex ratio M/F)†</td>
<td>21 (11/10)</td>
<td>15 (9/6)</td>
<td>13 (8/5)</td>
<td>χ² = 0.35, P = 0.84</td>
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<tr>
<td>Mean ageb</td>
<td>22.4 (3.3)</td>
<td>22.1 (4.0)</td>
<td>24.5 (5.9)</td>
<td>F₂,46 = 1.24, P = 0.30</td>
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<tr>
<td>premorbid IQb,c</td>
<td>109.5 (7.7)</td>
<td>105.9 (8.3)</td>
<td>107.1 (8.5)</td>
<td>F₂,45 = 0.92, P = 0.41</td>
</tr>
<tr>
<td>PANSS total</td>
<td>59.6 (11.4)</td>
<td>65.8 (23.3)</td>
<td>t₂60 = -0.91, P = 0.37</td>
<td></td>
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<tr>
<td>Positive</td>
<td>13.4 (3.8)</td>
<td>14.1 (5.9)</td>
<td>t₂60 = -0.37, P = 0.72</td>
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<tr>
<td>Negative</td>
<td>15.3 (5.5)</td>
<td>17.9 (7.5)</td>
<td>t₂60 = -1.08, P = 0.29</td>
<td></td>
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<tr>
<td>General</td>
<td>30.9 (5.8)</td>
<td>33.8 (11.8)</td>
<td>t₂60 = -0.83, P = 0.42</td>
<td></td>
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<tr>
<td>GAF</td>
<td>51.1 (10.2)</td>
<td>38.8 (12.4)</td>
<td>t₂60 = 2.88, P = 0.008</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic dosed</td>
<td>105.1 (187.1)</td>
<td>489.7 (434.1)</td>
<td>t₂60 = -3.12, P = 0.004</td>
<td></td>
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<tr>
<td>Benzo diazepine*</td>
<td>5.2 (12.7)</td>
<td>6.1 (8.2)</td>
<td>t₂60 = -0.22, P = 0.83</td>
<td></td>
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<tr>
<td>DOT (months)</td>
<td></td>
<td>6.1 (6.6)</td>
<td></td>
<td></td>
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<tr>
<td>BACS composite</td>
<td>0.002 (0.57)</td>
<td>-1.12 (0.73)</td>
<td>t₂60 = 4.63, P &lt; 0.001</td>
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<tr>
<td>Verbal memory</td>
<td>0.09 (0.87)</td>
<td>-1.03 (1.20)</td>
<td>t₂60 = 2.85, P = 0.008</td>
<td></td>
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<tr>
<td>Working memory</td>
<td>0.32 (1.01)</td>
<td>-0.35 (1.00)</td>
<td>t₂60 = 1.77, P = 0.09</td>
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<tr>
<td>Motor speed</td>
<td>-0.58 (1.23)</td>
<td>-2.40 (0.79)</td>
<td>t₂60 = 4.57, P &lt; 0.001</td>
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<tr>
<td>Verbal fluency</td>
<td>-0.04 (0.62)</td>
<td>-0.48 (0.53)</td>
<td>t₂60 = 1.98, P = 0.06</td>
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<tr>
<td>Attention</td>
<td>0.34 (1.13)</td>
<td>-1.06 (0.70)</td>
<td>t₂60 = 3.84, P = 0.001</td>
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<td>Executive function</td>
<td>-0.12 (1.07)</td>
<td>-1.38 (1.83)</td>
<td>t₂60 = 2.26, P = 0.03</td>
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Note: All values are shown as mean (standard deviation).

FES, first-episode schizophrenia; UHR, ultra-high risk; HC, healthy controls; IQ, intelligence quotient; PANSS, positive, negative, and general psychopathology scale scores; GAF, global assessment of functioning; DOT, duration of antipsychotic treatment for psychosis; BACS, brief assessment of cognition in schizophrenia.

†χ² test.
‡One-way ANOVA otherwise, t-tests were used. P < 0.05 was considered significant.
§One subject with FES was not measured for premorbid IQ.
¶Based on chlorpromazine equivalent (mg/day).
‖Based on diazepam equivalent (mg/day).

Auditory Stimuli and Procedures

Employment of the ASSR paradigm on each subject is described as follows (Kwon et al. 1999; Light et al. 2006). Briefly, subjects sat in a comfortable chair, in a quiet, shielded room and were instructed to relax with their eyes opened. Subjects received auditory stimuli presented binaurally through inserted earphones (Multi Trigger System, Medical Try System, Tokyo, Japan). The auditory stimuli were click sounds (80 dB, 1 ms) presented in a comfortable chair, in a quiet, shielded room and were instructed to relax with their eyes opened. Subjects received auditory stimuli presented binaurally through inserted earphones (Multi Trigger System, Medical Try System, Tokyo, Japan). The auditory stimuli were click sounds (80 dB, 1 ms) presented in a single block containing 200 trains, and each subject was presented with 3 blocks. The intertrain interval was 500 ms.

EEG Recordings and Analyses

EEGs were recorded at 64 electrode sites using the Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR, USA). Electrode impedances were kept below 50 kΩ, and data were sampled at 250 Hz using a system acquisition filter (0.1–100 Hz). The reference electrode was located at the vertex. We used EEGLAB (Delorme and Makeig 2004) to perform off-line analyses, and continuous EEG data were re-referenced to an average reference. A high-pass filter (1 Hz) and a notch filter (50 Hz) were applied to the EEG data to remove artifacts. EEG data were segmented from −250 to 750 ms, relative to the stimulus onset. Independent component analysis was used for eye blink correction, and epochs exceeding ±100 μV at any electrode were rejected. Importantly, numbers of artifact-free epochs did not differ significantly among groups. [One-way analysis of variance (ANOVA), 20 Hz: F₂,46 = 0.99, P = 0.38, 30 Hz: F₂,46 = 1.59, P = 0.22, 40 Hz: F₂,46 = 0.06, P = 0.94] The mean number of epochs for each group were as follows: HC (20 Hz: 186, 30 Hz: 184, 40 Hz: 184), UHR (20 Hz: 191, 30 Hz: 192, 40 Hz: 185), and FES (20 Hz: 188, 30 Hz: 181, 40 Hz: 186). We neither observed significant main effects for frequency (F₂,92 = 1.05, P = 0.36) and group (F₂,46 = 0.84, P = 0.44) nor a group-by-frequency interaction (F₂,92 = 1.02, P = 0.40).

We performed time–frequency analyses with a short-term Fourier transformation, and then calculated the event-related spectral perturbation (ERSP) and intertrial phase coherence (ITC). The ERSP indicates event-related changes in power relative to a prestimulus baseline, while the ITC indicates phase consistency across trials, and ranges between 0 (random phase across trials) and 1 (identical phase across trials). We used ERSP and ITC as measures of power and phase, respectively, because these parameters provide information about the temporal dynamics of ASSR. Decreases of ERSP and/or ITC reflect reduced neural responses to auditory steady-state stimulation.

Neurocognitive Battery

We used the BACS-Japanese version (BACS-J) to assess cognitive function in UHR subjects and patients with FES. The BACS-J measures 6 cognitive subdomains, including verbal memory, working memory, motor speed, verbal fluency, attention, and executive function (Keefe et al. 2004; Kaneda et al. 2007). The BACS-J was used previously as a valid cognitive assessment tool for both UHR subjects and patients with FES. We administered the BACS-J to 5 HC subjects (3 men and 2 women). However, the number of HC subjects was insufficient for comparisons to the patient group; therefore, the data were not presented.

Statistical Analysis

First, we calculated the mean ITC and ERSP at the frontocentral electrode site (FCz) by averaging the data over the first 500 ms within a trial (0–500 ms), and for each frequency range (20 Hz: 16–25 Hz; 30 Hz: 26–35 Hz; 40 Hz: 36–45 Hz). We focused our analysis at FCz because the most prominent ASSR was found at this
The ITC and the ERSP were analyzed separately using a repeated-measures ANOVA using the ASSR stimulation frequencies (20, 30, 40 Hz) as within-subjects factors, and groups (UHR, FES, HC) as between-subjects factors. We used the Greenhouse-Geisser epsilon adjustment whenever appropriate.

For time-course analyses, we calculated the mean ITC and ERSP for each 100-ms epoch (Light et al. 2006; O'Donnell et al. 2004). A repeated-measures ANOVA was performed separately with time blocks (0–100, 100–200, 200–300, 300–400, and 400–500 ms) as within-subjects factors and groups (UHR, FES, HC) as between-subjects factors with Greenhouse-Geisser epsilon adjustment. Post hoc Tukey's honestly significant difference tests were performed for significant main effects. For all ANOVAs, we set the threshold for statistical significance at P < 0.05.

Correlations between EEG measures (40-Hz ITC and ERSP; early-latency (mean score across 0–100 ms) and late-latency (300–400 ms)) and clinical/cognitive variables and medication dosage (both chlorpromazine and diazepam equivalents) were tested in UHR and FES groups, respectively. We used Spearman's rank correlation coefficient (two tailed, P < 0.05) without applying corrections for multiple tests because the analyses were considered exploratory in nature.

**Results**

**Intertrial Phase Coherence**

Figure 1 shows the grand average time–frequency maps for ITC at FCz in each stimulation frequency for each group.

A repeated-measures ANOVA showed a significant main effect of frequency (F<sub>2,46</sub> = 221.95, P < 0.001), and a significant group-by-frequency interaction (F<sub>4,92</sub> = 3.73, P = 0.02). Further analyses showed a significant difference among the 3 groups with 40-Hz stimuli (F<sub>2,46</sub> = 3.85, P = 0.03), but not with 20-Hz (F<sub>2,46</sub> = 0.43, P = 0.66) or 30-Hz stimuli (F<sub>2,46</sub> = 0.03, P = 0.97). Thus, we focused our remaining analyses on the ITC response to 40-Hz stimulation.

The time course of the 40-Hz ITC showed different features among groups (Fig. 2). To quantitatively analyze the time course of ITC, we performed a repeated-measures ANOVA and found a significant main effect for time (F<sub>4,184</sub> = 62.14, P < 0.001) and group-by-time interaction (F<sub>8,184</sub> = 5.85, P < 0.001). ANOVAs in each time block revealed a significant main effect for group in the 0- to 100-ms (F<sub>2,46</sub> = 3.49, P = 0.04), 200- to 300-ms (F<sub>2,46</sub> = 4.36, P = 0.02), 300- to 400-ms (F<sub>2,46</sub> = 5.66, P = 0.006), and 400- to 500-ms (F<sub>2,46</sub> = 5.10, P = 0.01) time blocks. In the 0- to 100-ms block, post hoc tests revealed a significant reduction of 40-Hz ITC in the FES group compared with the UHR group (P = 0.03). In the 200- to 300-ms block, post hoc tests revealed a significant reduction of 40-Hz ITC in the FES group compared with the HC group (P = 0.03). In the 300- to 500-ms blocks, post hoc tests revealed a significant reduction of 40-Hz ITC in both the FES (300–400 ms: P = 0.02; 400–500 ms: P = 0.03) and UHR groups (300–400 ms: P = 0.02; 400–500 ms: P = 0.03) compared with the HC group.

**Event-Related Spectral Perturbation**

Figure 3 shows the grand average time–frequency maps for ERSP at FCz in each stimulation frequency for each group. Consistent
with the ITC data, a repeated-measures ANOVA showed a significant main effect of frequency \( (F_{2,92} = 65.74, P < 0.001) \) and a group-by-frequency interaction \( (F_{4,92} = 4.15, P = 0.007) \). Further analyses showed no significant differences among the 3 groups with 20-Hz \( (F_{2,46} = 0.17, P = 0.85) \) or 30-Hz stimuli \( (F_{2,46} = 0.98, P = 0.38) \), but did show significant differences among the 3 groups with 40-Hz stimuli \( (F_{2,46} = 5.80, P = 0.006) \). As with our ITC analysis, we focused our remaining analyses on the ERSP response to 40-Hz stimulation.

The time course of the 40-Hz ERSP was analyzed in the same manner as the 40-Hz ITC (Fig. 4). A repeated-measures ANOVA showed a significant main effect for time \( (F_{4,184} = 43.38, P < 0.001) \) and a significant group-by-time interaction \( (F_{8,184} = 4.00, P = 0.004) \). ANOVAs in each time block revealed a significant main effect for group in the 200- to 300-ms \( (F_{2,46} = 6.12, P = 0.004) \), 300- to 400-ms \( (F_{2,46} = 7.40, P = 0.002) \), and 400- to 500-ms \( (F_{2,46} = 5.29, P = 0.009) \) time blocks. Post-hoc tests revealed a significant reduction of 40-Hz ERSP in both the FES (200–300 ms, \( P = 0.005 \); 300–400 ms, \( P = 0.003 \); 400–500 ms, \( P = 0.01 \)) and UHR groups (200–300 ms, \( P = 0.05 \); 300–400 ms, \( P = 0.02 \); 400–500 ms, \( P = 0.05 \)) compared with the HC group. There was no difference between FES and UHR groups for any time block.

Neurocognitive Functions

BACS-J composite scores were significantly impaired in the FES group when compared with scores for the UHR group \( (P < 0.001) \). Among the 6 BACS-J subdomains, we observed several significant decreases in the FES group compared with the UHR group.
Compared with the UHR group, we found that verbal memory ($P = 0.008$), motor speed ($P < 0.001$), attention ($P = 0.001$), and executive function ($P = 0.03$) were impaired in the FES group (Table 1).

Correlations with Clinical and Neurocognitive Variables

In the FES group, we observed that the late-latency 40-Hz ITC ($r_s = -0.73$, $P = 0.004$) and the late-latency 40-Hz ERSP ($r_s = -0.70$, $P = 0.008$) were significantly correlated with the PANSS score for general psychopathology. Among the neurocognitive functions examined, we found that attention was significantly correlated with the late-latency ITC ($r_s = 0.75$, $P = 0.003$) and late-latency ERSP ($r_s = 0.76$, $P = 0.003$) (Fig. 5).

In the UHR group, the early-latency 40-Hz ERSP was significantly correlated with the PANSS score for positive symptoms ($r_s = -0.53$, $P = 0.04$) and general psychopathology ($r_s = -0.70$, $P = 0.004$). All findings of correlational analyses are shown in Supplementary Table 1.

Effect of Medication Dosage

We observed that gamma-band ASSRs (40-Hz ITC and ERSP; early-latency [mean score across 0–100 ms] and late-latency [300–400 ms]) and medication dosage (antipsychotics and benzodiazepine) were not significantly correlated (antipsychotics: $|r_s| < 0.45$, $P > 0.09$ for UHR, $|r_s| < 0.28$, $P > 0.35$ for FES; benzodiazepine: $|r_s| < 0.17$, $P > 0.53$ for UHR, $|r_s| < 0.48$, $P > 0.10$ for FES). We also found no significant differences of gamma-band ASSRs between UHR individuals with antipsychotic medication and those without antipsychotic medication (Supplementary Figs 1 and 2).

Discussion

The present study shows gamma-band ASSR deficits in UHR individuals. Furthermore, the UHR group was characterized by intact early-latency (0–100 ms) and reduced late-latency (300–500 ms) gamma-band ASSRs. In contrast, both early- and late-latency ASSRs were significantly reduced in the FES group. Furthermore, early-latency ASSR indices were significantly correlated with clinical symptoms in UHR individuals, while late-latency ASSR indices accounted for substantial proportions of variance (i.e., 56–58%) in clinical symptoms and attentional functioning in patients with FES. The correlation between deficits in gamma-band ASSR and attentional deficits is important because attentional deficits are associated with functional outcome (Keefe et al. 2006). Moreover, deficits in gamma-band ASSR may underlie attentional deficits that lead to poor functioning in patients with schizophrenia.

To our knowledge, this study is the first to investigate the gamma-band ASSR in UHR individuals. Many studies have reported reduced gamma-band ASSR in cases of chronic schizophrenia (Kwon et al. 1999; Brenner et al. 2003; Light et al. 2006; Teale et al. 2008; Vierling-Claassen et al. 2008; Tsuchimoto et al. 2011; Kirihara et al. 2012). A few studies have reported similar reductions in patients with FES (Spencer et al. 2008; Wilson et al. 2008). Previous reports have shown correlations between oscillatory measures and cognition in patients with chronic schizophrenia (Light et al. 2006; Kirihara et al. 2012). These findings also suggest that oscillatory measures may underlie cognitive deficits in schizophrenia.

Recent studies have revealed dynamic brain changes in early stages of schizophrenia (Kasai et al. 2003; Salisbury et al. 2007). Several researchers suggest that these brain changes may be associated with development of the cerebral cortex during adolescence (Uhlhaas and Singer 2011; Kasai 2013). In healthy subjects, gamma-band ASSR has been shown to increase from childhood to adolescence (Rojas et al. 2006) but decrease during young adulthood (Cho et al. 2015). This dynamic change of
gamma-band ASSR during adolescence and young adulthood is thought to reflect maturation of GABAergic inhibitory interneurons that may be associated with the pathophysiology of schizophrenia (Hashimoto et al. 2009; Hofman and Lewis 2011). Brain maturation is not only limited to childhood and adolescence, but continues to occur through to young adulthood. In fact, the brain, especially phylogenetically newer cortical areas such as the prefrontal cortex, continues to mature up to age 30 (Sowell et al. 2003). Gamma oscillations also shows dynamic changes during adolescence and young adulthood, and these changes may reflect maturation of neural circuits (Uhlhaas et al. 2009). Therefore, alterations of gamma oscillations may be associated with disruptions in neural circuit development and the risk of psychosis. However, future prospective studies will be needed to investigate this hypothesis.

In this study, we found alterations of gamma-band ASSRs and revealed a correlation between gamma-band ASSRs and attentional functioning. These findings suggest that normal development of gamma oscillations during adolescence is important for the normal development of cognitive functions.

This study is also the first to show latency-specific alterations of gamma-band ASSRs in the early stages of schizophrenia. Ross et al. (2002) investigated the ASSR with various stimulus parameters and suggested that a “transient gamma-band response” (0–100 ms) might differ from a “steady-state response” (250–500 ms). Our study showed a reduction of early-latency gamma-band ASSRs in the FES group and a reduction of late-latency gamma-band ASSRs in UHR and FES groups. These findings suggest that the early gamma-band response may be reduced after the onset of psychosis, whereas the late gamma-band response may be impaired before the onset of psychosis. Light et al. (2006) reported that patients with chronic schizophrenia showed a reduction in the gamma-band ASSR at all time ranges; this finding may be consistent with our results.

In the current study, deficits in late-latency gamma-band ASSRs were associated with worse clinical symptoms and cognitive deficits in patients with FES. Thus, deficits in late-latency gamma-band ASSRs may reflect pathological processes of schizophrenia. It should be noted that we observed a statistically significant correlation between early-latency gamma-band ASSRs and clinical symptoms in the UHR group. However, since we did not find significant reductions of this index in the group as a whole, this correlation may not have clinical relevance. Further longitudinal studies are needed to clarify the characteristics of early and late gamma-band responses in the early stages of schizophrenia.

There are some limitations to our study. First, the patients in this study were medicated. A previous study reported that patients with schizophrenia that were medicated with a new generation of antipsychotics had significantly increased 40-Hz EEG synchronizations (Hong et al. 2004). Other studies, however, have failed to find evidence that medication affects the gamma-band ASSR (Light et al. 2006; Spencer et al. 2008; Tsuchimoto et al. 2011). It should be noted that these previous studies, along with our current study, were not designed to investigate the potential effects of medication on gamma-band ASSRs. However, while it remains possible that medication might affect gamma-band ASSRs, our correlational analyses between EEG measures and medication dosage revealed no significant correlations. We also found no significant differences of gamma-band ASSRs between UHR individuals with antipsychotic medication and those without antipsychotic medication. Because of our small sample size and study design, these findings are not sufficient to exclude potential medication effects. However, Supplementary Figures 1 and 2 suggest that if antipsychotic medications were to have any effect on gamma-band ASSR, medications would not decrease but increase their value, which would tend to obscure group differences rather than to accentuate such differences. Therefore, reduced gamma-band ASSR in UHR individuals is considered to be not due to antipsychotic medication. Taken together, these findings suggest that medication had little effect on gamma-band ASSRs. Further studies will be needed to completely elucidate this issue. Second, this study was a cross-sectional study. The findings in this study suggest that the early gamma-band response may be reduced after the onset of psychosis, whereas the late gamma-band response may be impaired before the onset of psychosis. A cross-sectional study, however, is insufficient for this conclusion. Therefore, further longitudinal studies are needed to confirm these findings.

In conclusion, we found that the gamma-band ASSR was altered in UHR individuals, which indicates a presumably prodromal stage of schizophrenia. Moreover, time course analyses suggest that early gamma-band responses may be reduced after the onset of psychosis (FES), whereas the late gamma-band response may be impaired before the onset of psychosis (UHR). These findings indicate that gamma-band ASSR may be a useful biomarker in early stages of schizophrenia. Using animal models of the gamma-band ASSR in future studies may help to reveal the mechanisms underlying GABAergic neural network abnormalities (Amann et al. 2010; Vohs et al. 2012).

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes
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References
prospective longitudinal study of first-episode schizophrenia. Biol Psychiatry. 70:672–679.


