Reduced auditory evoked gamma band response and cognitive processing deficits in first episode schizophrenia

GREGOR LEICHT1, CHRISTINA ANDREOU1, NENAD POLOMAC1, CLARISSA LANIG1, DANIEL SCHÖTTEL2, MARTIN LAMBERT2 & CHRISTOPH MULERT1

1Department of Psychiatry and Psychotherapy, Psychiatry Neuroimaging Branch (PNB), University Medical Center Hamburg-Eppendorf, Hamburg, Germany, and 2Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Abstract

Objectives. Gamma-band oscillations (e.g., the early auditory evoked gamma-band response, aeGBR) have been suggested to mediate cognitive and perceptual processes by driving the synchronization of local neuronal populations. Reduced aeGBR is a consistent finding in patients with schizophrenia and high-risk subjects, and has been proposed to represent an endophenotype for the illness. However, it is still unclear whether this reduction represents a deficit in sensory or cognitive processes, or a combination of the two. The present study investigated this question by manipulating the difficulty of an auditory reaction task in patients with first-episode schizophrenia and healthy controls.

Methods. A 64-channel EEG was recorded in 23 patients with first-episode schizophrenia and 22 healthy controls during two conditions of an auditory reaction task: an easy condition that merely required low-level vigilance, and a difficult condition that placed significant demands on attention and working memory.

Results. In contrast to healthy controls, patients failed to increase aeGBR power and phase-locking in the difficult condition. In patients, aeGBR power and phase-locking indices were associated with working memory deficits.

Conclusions. The observed results confirm the applicability of aeGBR disturbances as a stable endophenotype of schizophrenia, and suggest a cognitive, rather than sensory, deficit at their origin.

Key words: schizophrenia, EEG, gamma, first episode, auditory

Introduction

Current pathophysiological theories assume that the cognitive deficits appearing in schizophrenia are a correlate of the disturbed coordination of distributed processes involving multiple brain areas (Friston 1999; Phillips and Silverstein 2003). Abnormalities in the synchronization of neural oscillatory activity are an important mechanism, through which this disturbed coordination is thought to occur (Uhlhaas and Singer 2010). In this context, high-frequency activity in the gamma-band range (30–100 Hz) has received increasing attention, for two reasons: first, gamma-band oscillations have been suggested to mediate cognitive and perceptual processes by driving the synchronization of local neuronal populations (Singer 1999; Engel et al. 2001; Canolty et al. 2006; Fries et al. 2007). Second, their generation depends on a closed microcircuit involving parvalbumin-positive GABAergic interneurons and glutamatergic pyramidal cells (Bartos et al. 2007; Sohal et al. 2009), which is disrupted in patients with schizophrenia and in pharmacological or genetic models of the illness (Gandal et al. 2012; Uhlhaas and Singer 2013).

The largest body of research on gamma-band oscillations in schizophrenia concerns evoked gamma-band responses associated with sensory stimuli. Patients with schizophrenia have been reported to display abnormalities in visually evoked gamma response (Spencer et al. 2003, 2004), or in visually evoked steady state potentials (Krishnan et al. 2005), indicating disturbed visual feature-binding processes. In the auditory domain, alterations have been detected during auditory oddball paradigms (Haig et al. 2000; Lee et al. 2001; Gallinat et al. 2004;
Symond et al. 2005; Roach and Mathalon 2008; Spencer et al. 2008a) and during auditory steady-state-stimulation (Kwon et al. 1999; Light et al. 2006; Spencer et al. 2008b; Teale et al. 2008; Vierling-Claassen et al. 2008; Wilson et al. 2008) in the gamma frequency range.

A particularly interesting feature of evoked gamma-band responses is that they do not only reflect sensory processes, but are also affected by cognitive functions such as attention or memory (Gurtubay et al. 2004; Tallon-Baudry et al. 2005; Cho et al. 2006; Herrmann et al. 2010). These top-down influences on even early stages of information processing are exemplified in the case of the early auditory evoked gamma-band response (aeGBR), which appears 25–100 ms upon the presentation of an evoked gamma-band response (aeGBR), which are exemplified in the case of the early auditory evoked gamma-band response (aeGBR), which appears 25–100 ms upon the presentation of an auditory stimulus (Tiitinen et al. 1993). Although the aeGBR originates in the primary auditory cortex (Pantev et al. 1991) and is modulated by sensory properties of the stimulus (Schadow et al. 2007), it also has an undisputable cognitive component, as its magnitude is strongly influenced by task difficulty (Mulert et al. 2007; Herrmann et al. 2010), and more specifically by attentional (Tiitinen et al. 1997) and (working-) memory processes (Herrmann et al. 2010). Indeed, an additional aeGBR generator has been localized in the medial prefrontal cortex and the dorsal anterior cingulate cortex (dACC), using both EEG-based source localization (Mulert et al. 2007; Leicht et al. 2010) and single trial EEG-fMRI coupling (Mulert et al. 2010).

Similarly to other evoked gamma-band responses, the aeGBR is reduced in schizophrenia. This deficit has been reliably replicated across all stages of the illness: first-episode (Taylor et al. 2013) and chronic patients (Roach and Mathalon 2008; Leicht et al. 2010), high-risk subjects (Perez et al. 2013), and symptom-free first-degree relatives of patients (Hall et al. 2011a; Leicht et al. 2011). This feature, in conjunction with their association with a biologically plausible mechanism of the illness (Tsuang et al. 1993), has established reduced aeGBR as a probable endophenotype for schizophrenia which could be of potential interest for future studies investigating glutamatergic treatment strategies, genetic mechanisms, or the prediction of transition to psychosis in high-risk individuals. However, it is still unclear whether this reduction represents a deficit in sensory (bottom-up), or cognitive (top-down) processes, or a combination of the two. Previous findings have not provided sufficient evidence regarding this point. Typically, the aeGBR is investigated in the context of auditory oddball tasks, in which subjects are asked to respond by button press only to non-frequent, deviant tones intermingled in a sequence of standard tones. Differences between patients with schizophrenia and controls have been reported both by investigating aeGBR to both non-target (standard) (Roach and Mathalon 2008; Taylor et al. 2013) and target (deviant) tones (Leicht et al. 2010). However, attentional and working-memory mechanisms are presumably relevant for both of these stimulus types, as all incoming tones need to be attended to and matched against a template for the task to be performed correctly. The present study aimed to elucidate the differential contributions of sensory and cognitive processes to aeGBR deficits in patients with first-episode schizophrenia. This was achieved by manipulating the difficulty of an auditory reaction task. Two conditions were applied, an easy condition that merely required a motoric reaction whenever a sensory stimulus was perceived, and a difficult condition consisting in a three-tone oddball paradigm that placed significant demands on attention and working memory. On one hand, if reduced aeGBR in patients results from sensory processing deficits, then it should be apparent in both conditions; on the other hand, if cognitive factors (also) contribute to reduced aeGBR, then the effect should (additionally) be more pronounced in the difficult than in the easy condition.

Method

Ethics statement

The present study was part of a larger project investigating resting-state and task-related brain connectivity in schizophrenia by means of EEG, MEG, and simultaneous EEG-fMRI, within the context of the Collaborative Research Centre 936 (“multi-site communication in the brain”, www.sfb936.net). The study was approved by the Ethics Committee of the Medical Association Hamburg the investigation was and carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all participants after the nature of the procedures had been fully explained.

Participants

Twenty-three patients with a first-episode of schizophrenia and 22 healthy controls participated in the study. First-episode status was defined as having received the first diagnosis and psychiatric treatment less than a year prior to study participation, and presence of psychotic symptoms in any form for no more than 5 years. Patients were recruited through the Psychosis Center of the Department of Psychiatry of the University Medical Center Hamburg-Eppendorf. Diagnosis of schizophrenia in patients was established with the Mini International Neuropsychiatric
Interview (Sheehan et al. 1998). Two patients and one healthy control had to be excluded from further analyses due to poor EEG data quality resulting in an insufficient number of trials suitable for analysis.

Exclusion criteria for all participants were current substance abuse or dependence, and presence of major somatic or neurological disorders. For healthy control subjects, additional exclusion criteria were any previous psychiatric disorder or treatment, and a family history of psychotic disorders. The presence of inclusion/exclusion criteria was assessed by means of a semi-structured interview conducted by a clinical psychiatrist or trainee with at least 4 years of clinical experience. Healthy controls were recruited from the community through advertisement and word-of-mouth.

The severity of clinical symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987); subscores for positive, negative, disorganization, excitement and distress symptoms were created according to a five-factor model of the PANSS (van der Gaag et al. 2006). Because participation in the original project included three to five neurophysiological testing sessions (EEG, MEG and simultaneous EEG-fMRI), it was not always possible to conduct clinical assessments close to the EEG session. Therefore, based on reported trajectories of antipsychotic treatment response (Case et al. 2011; Stauffer et al. 2011), clinical severity ratings were used for analyses only if they were separated from EEG analyses by no more than a week for acutely ill patients, or 2 months for stable patients (i.e., clinical stability as per medical record and no change in medication for at least 2 months prior to study participation). Thus, appropriate clinical ratings were available for 19 patients.

Participants of both groups also underwent neuropsychological testing with an extensive battery that included tests of: memory [Logical Memory subtests from the Wechsler Memory scale, revised (Wechsler 1987); Verbal Learning and Memory Test (Helmstaedter et al. 2001)]; attention [Digit span forward and Digit-Symbol-Coding of the Wechsler Adult Intelligence Scale-III (Wechsler 1997)]; working memory [Digit span backward and Letter-Number Sequencing of the Wechsler Adult Intelligence Scale (Wechsler 1997)]; visuomotor sequencing [Trail Making Test Parts A and B (Reitan and Wolfson 1985)]; letter fluency (Aschenbrenner et al. 2001). Neurocognitive performance data were available for 20 healthy controls and 17 patients. In all patients, neurocognitive data were collected within a week or within 2 months from EEG for acutely ill and stable patients, respectively. Given the relatively small sample size, only those tasks, for which an association with aeGBR indices could be expected based on previous literature, i.e., working memory and attention tasks (see Introduction), were included in analyses. This was done in order to minimize the number of variables included in correlational analyses reported below, and thereby reduce the risk of Type I errors.

The majority of patients were on antipsychotic medications at the time of EEG recording (atypical antipsychotics: n = 18; typical antipsychotics: n = 1; no psychotropic medication: n = 2). Moreover, seven patients were currently in treatment with antidepressants (either escitalopram or venlafaxine). No subjects were receiving benzodiazepines or anticholinergic agents. Demographic characteristics of the two groups, and clinical characteristics of patients, are presented in Table I. The groups were matched with respect to age, sex and educational level. All subjects had hearing better than 30 dB at a pitch of 1000 Hz.

Paradigm

We used two different difficulty levels of an auditory reaction task (Mulert et al. 2001) that had been earlier shown to increase aeGBR amplitude according to the level of difficulty (Mulert et al. 2007). Accordingly, the experiment consisted of two different runs during which tones varying in pitch (duration: 250 ms, generated using the Presentation software version 16.1) were presented via earphones at 85 dB SPL with pseudo-randomized interstimulus intervals (ISI: 2.5–7.5 s; mean 5.0 s). In the easy condition (EC), 80 tones at a pitch of 800 Hz had to be responded to per button-press with the left index finger. In the difficult condition (DC), 120 tones of different pitch (33% 800 Hz, 33% 1000 Hz and 33% 1200 Hz) had to be differentially responded to, by pressing a button with the left index finger following the low tone and with the right index finger following the high tone. No response was required for the 1000 Hz (middle) tone. Prior to each run, subjects were instructed to respond as fast and accurately as possible. Before the beginning of the measurement, a short test run was carried out. Reaction times (from stimulus onset until button press) and errors (incorrect response or no response within 2000 ms after stimulus presentation) were registered during the experimental run.

EEG recording

Recording took place in a sound-attenuated and electrically shielded room. Subjects were seated with their eyes open in a slightly reclined chair with a head rest and were asked to keep the eyes open and look at a fixation cross presented at a 19” computer monitor 1 m in front of them. The EEG was recorded at a sampling rate of 1000 Hz and an analog band-pass...
window starting 210-ms pre-stimulus in any channel were automatically rejected. After re-referencing to common average reference and baseline correction (using an interval of 210–10 ms pre-stimulus), averaged event-related potential (ERP) wave-shapes were computed. Only wave-shapes based on at least 35 segments were accepted.

Evoked gamma power and PLF

Using the BVA Software, evoked gamma power and phase-locking factor (PLF) were computed using a wavelet transformation [complex Morlet wavelet with the formula \( w(t) = A \exp(-t^2/2) \exp(i2\pi ct) \), Morlet parameter \( c = 5 \), Instantaneous Amplitude (Gabor Normalization), as used previously by other groups (Herrmann et al. 1999; Senkowski and Herrmann 2002) and our group (Mulert et al. 2007).

In order to reveal the phase-locked evoked gamma power, wavelet transformation was performed on averaged ERP wave-shapes. Layer-wise baseline correction was applied using a timeframe of 200 ms starting 210 ms prior to stimulus presentation. The frequency range from 20 to 80 Hz was divided into 30 frequency steps (distributed on a logarithmic scale) for each subject. For aeGBR peak detection, the wavelet layer with the central frequency of 40 Hz (frequency range 32–48 Hz) was extracted. Based on prior knowledge (Mulert et al. 2007, 2010; Leicht et al. 2010) the aeGBR-peak was defined as the highest value within the timeframe 30–100 ms post-stimulus at the electrode Cz.

PLFs were calculated by performing wavelet transformation (without layer-wise baseline correction) and extracting complex-phase information with all filter (0.1–1000 Hz) with 66 active electrodes mounted on an elastic cap (ActiCaps, Brain Products, Munich, Germany) using the Brain Vision Recorder software Version 1.10 (Brain Products, Munich, Germany). Electrodes were arranged according to a modified 10/10 system without electrodes at the positions FPz, F9, F10, T9, T10, CP3, CP4, P9, P10, PO7, PO8 and with additional electrodes at positions PO9 and PO10. Eye movements were recorded through four EOG channels (positioned at the outer canthi bilaterally and infra- and supraorbitaly on the right). An electrode at the FCz position was used as the reference, the electrode at position AFz served as ground. Impedances were always kept below 5 kΩ.

**EEG pre-processing**

Data analysis was carried out using Brain Vision Analyzer (BVA) Version 2.0 (Brain Products, Munich, Germany). The channels PO9 and PO10 were excluded from further analysis due to persistent muscle artefact contamination in most subjects. After band-pass filtering (1–100 Hz), topographic interpolation (spherical splines) of up to six channels was performed (mean number of interpolated channels: EC 0.52 ± 1.31; DC 0.60 ± 1.23; no significant differences between groups or conditions). Channels were selected for interpolation if more than 5% of data in the respective channel was affected by technical artifacts or muscle artifacts exceeding amplitudes of ±70 µV. The continuous EEG was segmented into epochs of 1400-ms starting 400 ms prior to the auditory stimulus. Segments including incorrect responses or amplitudes exceeding ±70 µV within a 410-ms window starting 210-ms pre-stimulus in any channel were automatically rejected. After re-referencing to common average reference and baseline correction (using an interval of 210–10 ms pre-stimulus), averaged event-related potential (ERP) wave-shapes were computed. Only wave-shapes based on at least 35 segments were accepted.

**Table I. Sociodemographic and clinical characteristics of the two participant groups.**

|                              | Healthy controls | Schizophrenia | \( T^{2/3} \) | \( P \) |
|------------------------------|------------------|---------------|----------------|-------|
| Gender (m/f)                 | 18/3             | 17/4          | 0.171          | 0.68  |
| Educational level            |                  |               | 1.732          | 0.42  |
| low (secondary school)       | 1                | 3             |                |       |
| middle (junior high school)  | 8                | 5             |                |       |
| high (general qualification for university entrance) | 12 | 13 | | |
| Age                          | 25.00 (5.6)      | 23.52 (5.0)   | 0.899          | 0.37  |
| Age of illness onset         | –                | 22.43 (5.4)   |                |       |
| Antipsychotic medication dose*| –              | 202.39 (179.0)|                |       |
| PANSS scores                 |                  |               |                |       |
| total                        | –                | 54.72 (15.1)  |                |       |
| positive                     | –                | 14.06 (6.8)   |                |       |
| negative                     | –                | 14.33 (5.0)   |                |       |
| disorganization              | –                | 14.89 (3.7)   |                |       |
| excitement                   | –                | 13.22 (4.5)   |                |       |
| distress                     | –                | 17.39 (6.5)   |                |       |

*Chlorpromazine equivalent dose (Woods 2003).
Results

Behavioural performance

With regard to reaction times, there was a significant main effect of group ($F = 9.56, P = 0.003, \eta^2_{\text{partial}} = 0.199$), while the condition×group interaction did not achieve significance ($F = 2.9, P = 0.098, \eta^2_{\text{partial}} = 0.067$). Follow-up $t$-tests revealed significantly longer reaction times in SZ compared to HC in both conditions, and in DC compared to EC in both groups (see Table II) – although the latter effect was tendentially more pronounced in patients.

With regard to error rates, the ANOVA revealed a significant condition×group effect ($F = 5.9, P = 0.019, \eta^2_{\text{partial}} = 0.129$). Follow-up $t$-tests revealed significantly higher error rates in SZ compared to HC in DC but not in EC, and significantly higher error rates in DC compared to EC in both groups (see Table II).

Evoked GBR power and PLF

Around 50 ms after stimulus presentation in both groups, an increase of evoked gamma activity was observed (see Figure 1) at electrode Cz. For scalp topographies please see Supplementary Figure 1 (Supplementary material to be found online at http://informahealthcare.com/doi/abs/10.3109/15622975.2015.1017605). With respect to the peaks of this evoked GBR power, a significant condition×group interaction applied to calculate robust confidence intervals of correlation coefficients. Bonferroni correction was applied to correct for multiple comparisons; however, due to the exploratory nature of these analyses, uncorrected results are also reported.

Statistical analyses

All statistical analyses were performed using the SPSS software package (21.0). In order to describe significant group×condition effects, repeated-measures ANOVAs with condition as the within-subject factor and group as the between-subject factor were conducted on the variables of interest. Significant results were followed-up by exploratory pairwise $t$-tests, using paired-tests to assess differences between conditions, and $t$-tests for independent samples to check for significant group differences; because of the small sample size, bootstrapping was performed in $t$-test analyses to adjust significance values based on estimates of the properties of the sampling distribution. For the comparison of the two groups on educational level and gender differences, the chi-square test was used. For ANOVAs, the partial eta squared ($\eta^2_{\text{partial}}$) is provided as an estimate of effect size (small: 0.01–0.06; moderate: 0.06–0.14; large: > 0.14); for $t$-tests, Pearson’s $r$ is provided (small: 0.1–0.3; moderate: 0.3–0.5; large: > 0.5).

In patients, exploratory correlational analyses (Spearman’s rho) were conducted between electrophysiological parameters on one hand and severity of clinical symptomatology, attention/working memory performance and medication dose (in chlorpromazine equivalents) on the other. Bootstrapping was applied to calculate robust confidence intervals of correlation coefficients. Bonferroni correction was applied to correct for multiple comparisons; however, due to the exploratory nature of these analyses, uncorrected results are also reported.
emerged \((F=4.3, P=0.045, \eta^2_{\text{partial}}=0.096)\). \(t\)-Tests revealed significantly diminished aeGBR power peaks in SZ compared to HC in DC but not in EC, and marginally increased aeGBR power peaks in DC compared to EC in HC but not in SZ (see Table III). There was no significant condition\(\times\)group effect concerning the latency of the aeGBR peaks at Cz (mean latencies: HC-DC: 73.7 ms, HC-EC: 74.4 ms, SZ-DC: 69.1 ms, SZ-EC: 69.6 ms).

Regarding the PLF, we observed a significant condition\(\times\)group interaction \((F=8.46, P=0.006, \eta^2_{\text{partial}}=0.175)\). Compared to HC, SZ showed significantly reduced PLF values in DC but not in EC. Follow-up \(t\)-tests revealed a significant increase of PLF values in HC during DC compared to EC; this effect was not present in SZ (see Figure 2).

Correlations with clinical and neuropsychological variables in the patient group

In the easy condition, there were negative correlations between PLF \((\rho=0.510, P=0.05, \text{CI} = -0.035–0.877)\) and evoked power \((\rho=0.600, P=0.02, \text{CI} = 0.0186–0.876)\) and the negative factor score, i.e., PLF and evoked power were lower in patients with higher negative symptom load. Moreover, a trend-wise significant correlation emerged between aeGBR evoked power and disorganized factor scores \((\rho=0.504, P=0.06, \text{CI} = 0.004–0.835)\). These correlations were not significant after Bonferroni correction.

No significant correlations were noted between chlorpromazine equivalents and either evoked aeGBR power or gamma PLF (all \(P>0.2\)).

Figure 1. Auditory evoked gamma-band response (aeGBR) power. Time-frequency-analyses of the timeframe 200 ms prior to the stimulus and 300 ms post-stimulus averaged over all subjects of healthy controls (HC, left column) and patients with schizophrenia (SZ, right column) for the difficult condition (DC, upper row) and the easy condition (EC, lower row). Scaling was uniform for both groups. The auditory evoked gamma-band response (aeGBR) can be seen as an increased activity at about 50 ms after stimulus presentation (dashed line) and in the frequency range around 40 Hz. In contrast to SZ, healthy subjects showed a significant increase of the aeGBR power in DC compared to EC.
Reduced gamma band response in early schizophrenia

393

Studies that have suggested a role of the aeGBR as an endophenotype for the illness (Hall et al. 2011b; Leicht et al. 2011; Perez et al. 2013). Importantly, aeGBR was reduced in patients compared to controls only in the cognitively more demanding condition, while it was not affected in the easy condition. Consistent with the latter finding, studies that assessed the aeGBR during passive P50 paradigms (reviewed in Taylor et al. 2013) have failed to observe abnormalities in patients with schizophrenia (although note that these paradigms use clicks instead of tones as auditory stimuli, which might lead to different gamma-band responses, cf. Taylor et al. 2013). The above suggest that the aeGBR reductions observed in patients with schizophrenia reflect deficits in cognitive, rather than sensory processes. In this sense, our findings are comparable to those of previous studies reporting a failure of patients with schizophrenia to enhance gamma-band activity in response to increased task demands in working memory paradigms (reviewed in Gandal et al. 2012). In line with this conclusion, a previous study by our group (Leicht et al. 2010) demonstrated decreased activity not only in the auditory cortex in patients with schizophrenia, but also in the dorsal ACC – a region suggested to be involved in functional interactions with the auditory cortex, as its activation correlates with task difficulty in auditory choice reaction paradigms (Mulert et al. 2007, 2008). In combination with the findings of post mortem studies pointing to parvalbumin-positive GABAergic interneuron abnormalities in the ACC in patients with schizophrenia (Kalus et al. 1997; Woo et al. 2004), the results of the present study used two auditory reaction tasks differing in difficulty, in order to investigate the relative contributions of sensory and cognitive processes to aeGBR deficits in patients with first-episode schizophrenia. There were no differences between patients and healthy controls in an easy condition dependent only on sensory processing and low-level vigilance. In contrast to healthy controls, though, patients failed to increase early evoked gamma power and phase-locking in response to a more cognitively demanding task. Power and phase-locking indices of the aeGBR in the easy condition showed weak associations with negative and disorganized symptoms in patients. There was also a significant correlation of aeGBR power in the easy condition with one measure of working memory.

This is the second study to report decreased aeGBR in first-episode patients, confirming that reported deficits in schizophrenia are not simply a result of chronicity and/or long-term effects of antipsychotic medication, which is in line with several previous studies that have suggested a role of the aeGBR as an endophenotype for the illness (Hall et al. 2011b; Leicht et al. 2011; Perez et al. 2013). Importantly, aeGBR was reduced in patients compared to controls only in the cognitively more demanding condition, while it was not affected in the easy condition. Consistent with the latter finding, studies that assessed the aeGBR during passive P50 paradigms (reviewed in Taylor et al. 2013) have failed to observe abnormalities in patients with schizophrenia (although note that these paradigms use clicks instead of tones as auditory stimuli, which might lead to different gamma-band responses, cf. Taylor et al. 2013). The above suggest that the aeGBR reductions observed in patients with schizophrenia reflect deficits in cognitive, rather than sensory processes. In this sense, our findings are comparable to those of previous studies reporting a failure of patients with schizophrenia to enhance gamma-band activity in response to increased task demands in working memory paradigms (reviewed in Gandal et al. 2012). In line with this conclusion, a previous study by our group (Leicht et al. 2010) demonstrated decreased activity not only in the auditory cortex in patients with schizophrenia, but also in the dorsal ACC – a region suggested to be involved in functional interactions with the auditory cortex, as its activation correlates with task difficulty in auditory choice reaction paradigms (Mulert et al. 2007, 2008). In combination with the findings of post mortem studies pointing to parvalbumin-positive GABAergic interneuron abnormalities in the ACC in patients with schizophrenia (Kalus et al. 1997; Woo et al. 2004), the results of the present study used two auditory reaction tasks differing in difficulty, in order to investigate the relative contributions of sensory and cognitive processes to aeGBR deficits in patients with first-episode schizophrenia. There were no differences between patients and healthy controls in an easy condition dependent only on sensory processing and low-level vigilance. In contrast to healthy controls, though, patients failed to increase early evoked gamma power and phase-locking in response to a more cognitively demanding task. Power and phase-locking indices of the aeGBR in the easy condition showed weak associations with negative and disorganized symptoms in patients. There was also a significant correlation of aeGBR power in the easy condition with one measure of working memory.

This is the second study to report decreased aeGBR in first-episode patients, confirming that reported deficits in schizophrenia are not simply a result of chronicity and/or long-term effects of antipsychotic medication, which is in line with several previous studies that have suggested a role of the aeGBR as an endophenotype for the illness (Hall et al. 2011b; Leicht et al. 2011; Perez et al. 2013). Importantly, aeGBR was reduced in patients compared to controls only in the cognitively more demanding condition, while it was not affected in the easy condition. Consistent with the latter finding, studies that assessed the aeGBR during passive P50 paradigms (reviewed in Taylor et al. 2013) have failed to observe abnormalities in patients with schizophrenia (although note that these paradigms use clicks instead of tones as auditory stimuli, which might lead to different gamma-band responses, cf. Taylor et al. 2013). The above suggest that the aeGBR reductions observed in patients with schizophrenia reflect deficits in cognitive, rather than sensory processes. In this sense, our findings are comparable to those of previous studies reporting a failure of patients with schizophrenia to enhance gamma-band activity in response to increased task demands in working memory paradigms (reviewed in Gandal et al. 2012). In line with this conclusion, a previous study by our group (Leicht et al. 2010) demonstrated decreased activity not only in the auditory cortex in patients with schizophrenia, but also in the dorsal ACC – a region suggested to be involved in functional interactions with the auditory cortex, as its activation correlates with task difficulty in auditory choice reaction paradigms (Mulert et al. 2007, 2008). In combination with the findings of post mortem studies pointing to parvalbumin-positive GABAergic interneuron abnormalities in the ACC in patients with schizophrenia (Kalus et al. 1997; Woo et al. 2004), the results of the present study used two auditory reaction tasks differing in difficulty, in order to investigate the relative contributions of sensory and cognitive processes to aeGBR deficits in patients with first-episode schizophrenia. There were no differences between patients and healthy controls in an easy condition dependent only on sensory processing and low-level vigilance. In contrast to healthy controls, though, patients failed to increase early evoked gamma power and phase-locking in response to a more cognitively demanding task. Power and phase-locking indices of the aeGBR in the easy condition showed weak associations with negative and disorganized symptoms in patients. There was also a significant correlation of aeGBR power in the easy condition with one measure of working memory.

This is the second study to report decreased aeGBR in first-episode patients, confirming that reported deficits in schizophrenia are not simply a result of chronicity and/or long-term effects of antipsychotic medication, which is in line with several previous studies that have suggested a role of the aeGBR as an endophenotype for the illness (Hall et al. 2011b; Leicht et al. 2011; Perez et al. 2013). Importantly, aeGBR was reduced in patients compared to controls only in the cognitively more demanding condition, while it was not affected in the easy condition. Consistent with the latter finding, studies that assessed the aeGBR during passive P50 paradigms (reviewed in Taylor et al. 2013) have failed to observe abnormalities in patients with schizophrenia (although note that these paradigms use clicks instead of tones as auditory stimuli, which might lead to different gamma-band responses, cf. Taylor et al. 2013). The above suggest that the aeGBR reductions observed in patients with schizophrenia reflect deficits in cognitive, rather than sensory processes. In this sense, our findings are comparable to those of previous studies reporting a failure of patients with schizophrenia to enhance gamma-band activity in response to increased task demands in working memory paradigms (reviewed in Gandal et al. 2012). In line with this conclusion, a previous study by our group (Leicht et al. 2010) demonstrated decreased activity not only in the auditory cortex in patients with schizophrenia, but also in the dorsal ACC – a region suggested to be involved in functional interactions with the auditory cortex, as its activation correlates with task difficulty in auditory choice reaction paradigms (Mulert et al. 2007, 2008). In combination with the findings of post mortem studies pointing to parvalbumin-positive GABAergic interneuron abnormalities in the ACC in patients with schizophrenia (Kalus et al. 1997; Woo et al. 2004), the results of the present

Table III. Electrophysiological measures and pairwise comparisons between groups and conditions.

|                     | Healthy controls | Schizophrenia |
|---------------------|------------------|---------------|
| **Evoked GBR power (µV²)** | Mean (SD) | Mean (SD) | T   | P*  | r** |
| Easy condition      | 0.08 (0.08) | 0.06 (0.05) | 0.71 | 0.52 | 0.11 |
| Difficult condition | 0.14 (0.15) | 0.08 (0.08) | 2.23 | 0.04 | 0.33 |
| **Phase locking factor** | Mean (SD) | Mean (SD) | T   | P*  | r** |
| Easy condition      | 0.27 (0.09) | 0.25 (0.06) | 0.88 | 0.40 | 0.14 |
| Difficult condition | 0.36 (0.15) | 0.24 (0.07) | 3.13 | 0.01 | 0.44 |

Significant values are displayed in bold, trends are displayed in italics.

* Adjusted based on 1000 bootstrapping samples.
** Pearson’s r (effect size).

Of the neuropsychological test scores, only Letter-Number-Span (a demanding test of working memory) was significantly correlated with aeGBR evoked power in the EC (rho = 0.711, P = 0.003, CI = 0.324–0.898). This correlation remained significant (P = 0.04) after correcting for multiple comparisons. A correlation between the same variables emerged at trend-level in the DC (rho = 0.487, P = 0.066, CI = 0.046–0.832); this trend disappeared after Bonferroni correction.
stimulus-related evoked responses ("signal"), but may additionally be affected by pre-stimulus gamma-band activity ("noise"), which has been consistently reported to be increased in patients with schizophrenia (Winterer et al. 2004; Hong et al. 2008; Spencer 2011). In fact, in a previous auditory steady-state stimulation study, total gamma-band power was correlated with baseline (pre-stimulus) gamma-band activity, whereas this was not the case for gamma-band phase-locking, suggesting the two measures are dissociable (Spencer 2011). Moreover, total gamma-band aeGBR is affected in chronic (Roach et al. 2013) but not first-episode patients with schizophrenia and prodromal subjects (Perez et al. 2013; Taylor et al. 2013) – in contrast to evoked aeGBR, which is consistently reduced across all stages of the illness (see Introduction). Thus, it is possible that different aspects of the gamma-band study could indicate a disturbed “gamma-modulated” functional interaction between the ACC and the auditory cortex in schizophrenia.

It is more difficult to reconcile the present results with reported reductions in the gamma-band auditory steady-state response (ASSR) in patients with schizophrenia (Kwon et al. 1999; Light et al. 2006), which does not depend on cognitive factors, but rather is assumed to reflect bottom-up neural synchronization. In a recent study (Roach et al. 2013), gamma-band ASSR and aeGBR phase-locking (and, to a lesser extent, total power) indices were significantly correlated in patients with schizophrenia as well as in healthy controls, suggesting that the two gamma-band responses are, at least partly, dependent on the same mechanisms. Contrarily, the ASSR involves a sustained elevation in total gamma-band power that does not necessarily reflect only stimulus-related evoked responses ("signal"), but may additionally be affected by pre-stimulus gamma-band activity ("noise"), which has been consistently reported to be increased in patients with schizophrenia (Winterer et al. 2004; Hong et al. 2008; Spencer 2011). In fact, in a previous auditory steady-state stimulation study, total gamma-band power was correlated with baseline (pre-stimulus) gamma-band activity, whereas this was not the case for gamma-band phase-locking, suggesting the two measures are dissociable (Spencer 2011). Moreover, total gamma-band aeGBR is affected in chronic (Roach et al. 2013) but not first-episode patients with schizophrenia and prodromal subjects (Perez et al. 2013; Taylor et al. 2013) – in contrast to evoked aeGBR, which is consistently reduced across all stages of the illness (see Introduction). Thus, it is possible that different aspects of the gamma-band
Reduced gamma band response in early schizophrenia

...features of schizophrenia (Harvey et al. 2010; Perez et al. 2013; Taylor et al. 2013), we observed no significant correlation of evoked aeGBR power or phase-locking with positive symptoms. The state-independency of these markers is consistent with the notion of an endophenotype (Gottesman and Gould 2003), although our results indicate a relationship between aeGBR measures and negative symptoms of schizophrenia. However, negative symptoms display much greater longitudinal stability than positive symptoms, and are often regarded as “trait” features of schizophrenia (Harvey et al. 2006). Interestingly, all of the studies that failed to observe correlations between gamma-band responses and positive symptoms used auditory oddball paradigms that engage attentional and working memory mechanisms. In contrast, several other studies that reported significant positive correlations between gamma-band responses and positive symptoms all used auditory steady-state stimulation paradigms.

Our finding of a significant correlation between aeGBR and working memory should be interpreted with caution, given the small sample size and the fact that it only applied to one of the two measures used to assess working memory. However, it is a plausible finding, given recent studies that suggest a relationship between working memory capacity and synchronized activity in the theta- and gamma-band range (reviewed in Haenschel 2011). A similar correlation was observed in a much larger patient sample in a previous study (Light et al. 2006). As the study in question used a passive auditory steady-state paradigm, the authors concluded that deficits in the early sensory processing of stimuli might lead to impaired working memory encoding in patients (Light et al. 2006). An alternative interpretation in the present study could be that aeGBR deficits reflected the poor performance of patients. However, this is rather unlikely, as the correlation of aeGBR with Digit-Number Span was observed in the easy rather than the difficult condition.

A limitation of the present study is that most patients were medicated at the time of testing. However, there was no significant correlation between antipsychotic medication dose and the aeGBR in the patients group, and medication status cannot generally explain similarities and differences in the findings of previous studies (see Hamm et al. 2012). Only one study (Hong et al. 2004) reported an association between antipsychotic medication type and the magnitude of the gamma-band response, which was higher in patients treated with second-generation antipsychotics compared to those treated with first-generation antipsychotics. As the majority of patients in the present study were on treatment with second-generation antipsychotics, it can be assumed that the effect of antipsychotic medication, if any, would have been to reduce differences in aeGBR between patients and healthy controls. A possible influence of the antidepressive treatment of seven patients with escitalopram or venlafaxin cannot be ruled out, although there are no correspondent reports and a serotonergic or noradrenergic influence on the generation of gamma-oscillations seems to be unlikely.

The DC compared to the EC involves both an increase of stimulus type variations and task demands (more than one response is required). Therefore, based on the present data, it is not possible to distinguish between these two possible reasons for the increase in aeGBR measures. However, we have explicitly investigated this question in a previous study with healthy subjects using the same paradigm as in the present study (Mulert et al. 2007): both an increase of stimulus type variation without increasing the number of different responses and an increase of the number of response options led to an increase of reaction times, error rates and participant’s subjective self-ratings of task difficulty and mental effort demands. According to that, the increase of cognitive demands in the DC compared to the EC at the bottom of the stronger gamma response is supposed to result from both an increase of stimulus type variation and an increase of response options.

In conclusion, evoked power and phase-locking of the early auditory gamma-band response were significantly reduced in a sample of first-episode patients with schizophrenia compared to healthy controls in a cognitively demanding auditory choice-reaction paradigm, whereas there were no differences between patients and controls in an easy version of the same...
task. aeGBR indices were not associated with symptomatology, but a possible correlation with working memory deficits was noted. This pattern of results confirms the applicability of aeGBR disturbances as a stable endophenotype of schizophrenia, and suggests a cognitive, rather than sensory, processing deficit at their origin.

Acknowledgments

Parts of this work were prepared in the context of Clarissa Lanig’s dissertation at the Faculty of Medicine, Universität Hamburg, Hamburg. This work has been supported by DFG, SFB 936 “Multi-Site Communication in the Brain”, project C6.

Statement of Interest

None to declare.

References

Aschenbrenner S, Tucha O, Lange KW. 2001. [Regensburger lexical fluency test]. Göttingen: Hogrefe.

Bartos M, Vida I, Jonas P. 2007. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. Nat Rev Neurosci 8:45–56.

Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, et al. 2006. High gamma power is phase-locked to theta oscillations in human neocortex. Science 313:1626–1628.

Case M, Stauffer VL, Ascher-Svanum H, Conley R, Kapur S, Kane JM, et al. 2011. The heterogeneity of antipsychotic response in the treatment of schizophrenia. Psychiatr Med 41:1291–1300.

Cho RY, Konecky RO, Carter CS. 2006. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. Proc Natl Acad Sci U A 103:19878–19883.

Engel AK, Fries P, Singer W. 2001. Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2:704–716.

Fries P, Nikolic D, Singer W. 2007. The gamma cycle. Trends Neurosci 30:309–16.

Friston KJ. 1999. Schizophrenia and the disconnection hypothesis. Acta Psychiatr Scand Suppl 395:68–79.

Gallinat J, Winterer G, Herrmann CS, Senkowski D. 2004. Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. Clin Neurophysiol 115:1863–1874.

Gandol MF, Edgar JC, Klook K, Siegel SJ. 2012. Gamma synchrony: towards a translational biomarker for the treatment-resistant symptoms of schizophrenia. Neuropharmacology 62:1504–1518.

Gottesman II, Gould TD. 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160:636–645.

Gurubay IG, Alegre M, Labarga A, Malanda A, Artieda J. 2004. Gamma band responses to target and non-target auditory stimuli in humans. Neurosci Lett 367:6–9.

Henschel C. 2011. Abnormalities in task-related neural network formation in schizophrenia. Acta Psychiatr Scand 123:96–97.

Haig AR, Gordon E, De Pascalis V, Meares RA, Bahramali H, Harris A. 2000. Gamma activity in schizophrenia: evidence of impaired network binding? Clin Neurophysiol 111:1461–1468.

Hall MH, Taylor G, Salisbury DF, Levy DL. 2011a. Sensory gating event-related potentials and oscillations in schizophrenia patients and their unaffected relatives. Schizophr Bull 37:1187–1199.

Hall MH, Taylor G, Sham P, Schulze K, Rübsjik F, Picchioni M, et al. 2011b. The early auditory gamma-band response is heritable and a putative endophenotype of schizophrenia. Schizophr Bull 37:778–787.

Hamm JP, Gilmore CS, Clementz BA. 2012. Augmented gamma band auditory steady-state responses: support for NMDA hypofunction in schizophrenia. Schizophr Res 138:1–7.

Harvey PD, Koren D, Reichenberg A, Bowie CR. 2006. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr Bull 32:250–258.

Helmstaedter C, Lendt M, Lux S. 2001. Verbal Lern- und Merkfähigkeitstest. Göttingen: Beltz Test GmbH.

Herrmann CS, Frund I, Lenz D. 2010. Human gamma-band activity: a review on cognitive and behavioral correlates and network models. Neurosci Biobehav Rev 34:981–992.

Herrmann CS, Mecklinger A, Pfeifer E. 1999. Gamma responses and ERPs in a visual classification task. Clin Neurophysiol 110:636–642.

Hong LE, Summerfelt A, McMahon R, Adami H, Francis G, Elliott A, et al. 2004. Evoked gamma band synchronization and the liability for schizophrenia. Schizophr Res 70:293–302.

Hong LE, Summerfelt A, Mitchell BD, McMahon RP, Wonodi I, Buchanan RW, et al. 2008. Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate. Arch Gen Psychiatry 65:1008–1016.

Kalus P, Sonitz D, Beckmann H. 1997. Altered distribution of parvalbumin-immunoreactive local circuit neurons in the anterior cingulate cortex of schizophrenic patients. Psychiatry Res 75:49–59.

Kay SR, Fiszbein A, Opler LA. 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276.

Krisnahan GP, Vohs JL, Hetrick WP, Carroll CA, Shekhar A, Bockbrader MA, et al. 2005. Steady state visual evoked potential abnormalities in schizophrenia. Clin Neurophysiol 116:614–624.

Kwon JS, O’Donnell BF, Wullenstein GV, Greene RW, Hirayasu Y, Nestor PG, et al. 1999. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. Arch Gen Psychiatry 56:1001–1005.

Lee KH, Williams LM, Haig A, Goldberg E, Gordon E. 2001. An integration of 40 Hz Gamma and phasic arousal: novelty and routinization processing in schizophrenia. Clin Neurophysiol 112:1499–1507.

Leicht G, Karch S, Karamatskos E, Giegling I, Moller HJ, Hegel U, et al. 2011. Alterations of the early auditory evoked gamma-band response in first-degree relatives of patients with schizophrenia: hints to a new intermediate phenotype. J Psychiatr Res 45:699–705.

Leicht G, Kirsch V, Giegling I, Karch S, Hantschk I, Moller HJ, et al. 2010. Reduced early auditory evoked gamma-band response in patients with schizophrenia. Biol Psychiatry 67:224–231.

Light GA, Hsu JL, Hsieh MH, Meyer-Gomes K, Sprock J, Swardlow NR, et al. 2006. Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. Biol Psychiatry 60:1231–1240.

Mulert C, Gallinat J, Pascual-Marqui R, Dorn H, Frick K, Schlattmann P, et al. 2001. Reduced event-related current density in the anterior cingulate cortex in schizophrenia. Neuroimage 13:589–600.
Reduced gamma band response in early schizophrenia

Spencer KM, Salisbury DF, Shenton ME, McCarley RW. 2008b. Gamma-band auditory steady-state responses are impaired in first episode psychosis. Biol Psychiatry 64:369–375.

Stauffer V, Case M, Kollack-Walker S, Ascher-Svanum H, Ball T, Kapur S, et al. 2011. Trajectories of response to treatment with atypical antipsychotic medication in patients with schizophrenia pooled from 6 double-blind, randomized clinical trials. Schizophr Res 130:11–19.

Symond MP, Harris AW, Gordon E, Williams LM. 2005. “Gamma synchrony” in first-episode schizophrenia: a disorder of temporal connectivity? Am J Psychiatry 162:459–465.

Tallon-Baudry C, Bertrand O, Henaff MA, Isnard J, Fischer C. 2005. Attention modulates gamma-band oscillations differently in the human lateral occipital cortex and fusiform gyrus. Cereb Cortex 15:654–662.

Taylor GW, McCarley RW, Salisbury DF. 2013. Early auditory gamma band response abnormalities in first hospitalized schizophrenia. Suppl Clin Neurophysiol 62:131–145.

Teale P, Collins D, Maharaj K, Rojas DC, Kronberg E, Reite M. 2008. Cortical source estimates of gamma band amplitude and phase are different in schizophrenia. Neuroimage 42:1481–1489.

Tiiainen H, May P, Naatanen R. 1997. The transient 40-Hz response, mismatch negativity, and attentional processes in humans. Prog Neuropsychopharmacol Biol Psychiatry 21: 751–771.

Tiiainen H, Sinkkonen J, Reinitkainen K, Alho K, Lavikainen J, Naatanen R. 1993. Selective attention enhances the auditory 40-Hz transient response in humans. Nature 364:59–60.

Tsung MT, Faroone SV, Lyons MJ. 1993. Identification of the phenotype in psychiatric genetics. Eur Arch Psychiatry Clin Neurosci 243:131–142.

Uhlhaas PJ, Singer W. 2010. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11:100–113.

Uhlhaas PJ, Singer W. 2013. High-frequency oscillations and the neurobiology of schizophrenia. Dialogues Clin Neurosci 15:301–313.

van der Gaag M, Hoffman T, Remijisen M, Hijman R, de Haan L, van Meijsel B, et al. 2006. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophr Res 85:280–287.

Vierling-Claassen D, Siekmeyer P, Stoffelbein S, Kopell N. 2008. Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. J Neurophysiol 99:2656–2671.

Wechsler D. 1987. Wechsler Memory Scale, Revised. New York: The Psychological Corporation.

Wechsler D. 1997. Wechsler Adult Intelligence Scale – Third Edition. San Antonio, TX: The Psychological Corporation.

Wilson TW, Hernandez OO, Asherin RM, Teale PD, Reite ML, Rojas DC. 2008. Cortical gamma generators suggest abnormal auditory circuitry in early-onset psychosis. Cereb Cortex 18:371–378.

Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, et al. 2004. Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. Am J Psychiatry 161:490–500.

Woo TU, Walsh JP, Benes FM. 2004. Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. Arch Gen Psychiatry 61:649–657.

Woods SW. 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 64:663–667.

Supplementary material available online

Supplementary Figure 1. Scalp topographies of the aeGBR.