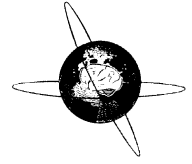




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Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing

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Abstract

Objective: Integration of sensory information by cortical network binding appears to be crucially involved in target detection. Studies in schizophrenia using functional and diffusion tensor neuroimaging, event-related potentials and EEG coherence indicate an impairment of cortical network coupling in this disorder. Previous electrophysiological investigations in animals and humans suggested that gamma activity (oscillations at around 40 Hz) is essential for cortical network binding. Studies in medicated schizophrenia provide evidence for a reduced gamma activity in the context of auditory stimulus processing. This is the first investigation of oscillatory activations in the gamma-band in an auditory oddball paradigm in unmedicated schizophrenic patients.

Methods: EEG gamma-band responses (GBRs) of 15 drug-free schizophrenic patients and 15 age- and gender-matched healthy controls were compared. A wavelet transform based on Morlet wavelets was employed for the calculation of oscillatory GBRs.

Results: In response to standard stimuli, early evoked GBRs (20–100 ms), which are supposed to reflect auditory cortex activation, did not show significant group differences. However, schizophrenic patients showed reduced evoked GBRs in a late latency range (220–350 ms), particularly after target stimuli. This deficit occurred over right frontal scalp regions. Furthermore, significant correlations were observed between oscillatory GBRs and clinical parameters in schizophrenic patients.

Conclusions: The results are consistent with a relative preserved stimulus processing in the auditory cortex as reflected by the early GBR. The reduced late GBR is compatible with an abnormal interaction within a frontal lobe network, as was postulated by previous neuroimaging studies.

Significance: The present study provides evidence for disturbed processing within frontal cortical regions in unmedicated schizophrenic patients as indicated by reduced evoked EEG GBRs.

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Keywords: Schizophrenia; Gamma; EEG; Event-related potential; Frontal lobe; Binding

1. Introduction

A basic question in brain function research is how the manifold parallel neuronal activations, necessary to process even a simple sensory stimulus, are integrated and bound together. For example, in an auditory oddball task, early stimulus classification has to be integrated with attention,

working memory, response selection, and motor output within a time range of milliseconds. This is known as the binding problem (Engel et al., 2001; Singer and Gray, 1995). The temporal binding model assumes that integrative processes in the brain are closely related to precisely synchronized activity of different neurons within the same, or between different cortical areas. Synchrony was shown to enhance the salience of neural responses because correlated discharges (synchrony) have a stronger impact on neuronal populations than temporally disorganized inputs (Alonso et al., 1996; Singer, 1999). According to the binding

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concept, neuronal populations in a cortical network that are already synchronized entrain other neurons to become part of the same overall assembly which corresponds to the incorporation of some content (e.g. stimulus) into a broader context (decision making and response).

Synchrony of electromagnetic activity across a broad frequency spectrum has been demonstrated to be related to cortical information processing (Bressler et al., 1993; Winterer et al., 1999). A major focus of interest have been high frequency oscillations in the gamma-band (30–80 Hz, mainly around 40 Hz), which apparently play a crucial role in the integration of cortical processes (Basar-Eroglu et al., 1996; Joliot et al., 1994; Senkowski and Herrmann, 2002). It has been shown that oscillatory gamma-band responses (GBRs) can be synchronized over short and large distances, and thereby showing a distinct temporal relation to the underlying cerebral activity (Schurmann et al., 1997). Furthermore, GBRs have been related to various sensory and cognitive processes in widespread cortical regions including perceptual and associative learning (Gruber et al., 2002; Miltner et al., 1999), sensory/motor integration (Murthy and Fetz, 1992; Salenius et al., 1996), object representation (Tallon-Baudry and Bertrand, 1999) and selective attention processes (Fries et al., 2001; Herrmann and Knight, 2001).

With regard to schizophrenia, measurable neurophysiological correlates of regional and inter-regional synchrony are of major interest. This is because there are a number of indications that anatomical and functional connectivity is critically disturbed in schizophrenic patients. For instance, evidence exists that the demyelination of subfrontal white matter, which is thought to result in a disturbance of regional interaction, can be accompanied by psychotic symptoms (Hyde et al., 1992). Furthermore, diffusion tensor imaging (DTI), a relatively new technique assessing the integrity and possibly connectivity of white matter fibers in vivo, provided evidence for a disruption in the white matter of the prefrontal cortex (Buchsbau et al., 1998), the posterior corpus callosum (Foong et al., 2000) and the uncinate fasciculus, which is the most prominent white matter tract connecting temporal and frontal brain regions (Kubicki et al., 2002). In line with this, functional neuroimaging and electrophysiological studies in schizophrenia suggest abnormalities in the interaction, i.e. functional connectivity or coherence between a number of brain areas, notably between prefrontal and temporal lobe structures (Fletcher et al., 1999; Ford et al., 2002; Friston and Frith, 1995; Norman et al., 1997; Winterer et al., 2003a). These studies focused on the interaction of regions, i.e. usually multisynaptic macrocircuits, rather than on deficits in isolated cortical areas. It is therefore of interest that recent work in schizophrenic patients also suggested a disturbance of synchrony in local prefrontal and temporal lobe microcircuits (Winterer et al., 2003b, 2004).

So far, it is not well understood at which time point in the information processing stream deficits of synchrony or

functional connectivity are most prominent in schizophrenia illness. Measuring task-related oscillatory GBRs may provide a new insight in the temporal aspects of regional and inter-regional information processing. GBRs can be roughly classified in *early* sensory oscillations with a likely origin in sensory areas, for example the auditory cortex (Pantev et al., 1991), and in *late* cognitive gamma responses which are intrinsically generated (Basar et al., 2001)—presumably from continuous large-scale cortical interactions (Engel and Singer, 2001; Varela et al., 2001). In this context, gamma activity was seen as a correlate of the binding of sensory cortical areas with high-order cortical networks (Basar et al., 2001; Schutt and Basar, 1992). Previous investigations in schizophrenic patients described disturbed GBRs during auditory oddball paradigm (Haig et al., 2000; Lee et al., 2001) in response to trains of clicks with varying repetition frequency (Kwon et al., 1999), and in response to ‘Gestalt’ stimuli (Spencer et al., 2003). The results suggest a decrease in the ability of neural networks to support synchronous neural activity, particularly at 40 Hz (for a recent review see Lee et al., 2003). The deficit in auditory stimulus processing was observed in the early (Lee et al., 2001; <100 ms post-stimuli) and the late gamma activities (Haig et al., 2000; 200–400 ms post-stimuli). However, since neuroimaging studies provided evidence that antipsychotic medication may enhance inter-regional connectivity in schizophrenia (Dolan et al., 1995), the results of previous studies may comprise some therapeutic effects because the included patients were treated with antipsychotics. The present study investigated GBRs in an auditory oddball paradigm in 15 drug-free schizophrenic patients and 15 age- and gender-matched healthy controls. With regard to local and inter-regional pathophysiology in schizophrenia we tested the following hypotheses:

- (a) Cortical network processing is disturbed at early stages of information processing in schizophrenic patients. We expect to find abnormal early GBRs (at around 20–100 ms) in the primary auditory cortex.
- (b) Impaired network processing in patients with schizophrenia also occurs at later stages of information processing. Therefore, we also expect to find decreased late GBRs (>200 ms).

2. Methods

2.1. Subjects

The study was approved by the Ethics Committee of the Benjamin-Franklin-University Hospital of the Free University of Berlin. All subjects gave written informed consent after the procedure was fully explained to them.

2.2. Schizophrenic patients

Fifteen patients (4 females, 11 males, 28.4 ± 11.0 years) of the Department of Psychiatry, Benjamin-Franklin-University Hospital, Berlin, who met DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994) were enrolled in the investigation. The diagnosis of schizophrenia was determined by a structured interview (SCID-I) (First et al., 1996) and the consensus of the attending physician and a senior house officer. The diagnostic subgroups were: paranoid schizophrenia (295.3 $n = 7$), disorganized schizophrenia (295.1 $n = 3$) and undifferentiated schizophrenia (295.9 $n = 5$). Clinical ratings were performed within 24 h of the EEG-recording session shortly after admission and before the initiation of any treatment. Patients were rated on the 30-item Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Symptoms are rated from 1 (absent) to 7 (extreme). The classical 7-item PANSS positive and 7-item PANSS negative scores were computed. No patient was chronically hospitalized. Ten patients were drug-naive (all of them experienced their first psychotic episode), the other patients were drug-free (psychotropic agents) for more than 4 weeks. Exclusion criteria for patients were: significant cardiovascular, hepatic, renal, gastrointestinal, metabolic, or other systemic disease, concurrent psychiatric or neurological illness, organic mental disorder, seizure disorder, mental retardation, significant alcohol or substance abuse within the previous 12 months, Parkinson's disease, toxic central nervous system depression or any clinically relevant abnormalities in blood chemistry, or other laboratory tests. For further details, see Table 1.

2.3. Healthy controls

Healthy controls were recruited by newspaper advertisements and paid for their participation. All subjects were explored by a psychiatrist in the Department of Psychiatry, Free University Berlin. A structured interview was performed (mini-SCID) (Sheehan et al., 1998). Subjects were excluded when fulfilling the criterion of any axis I

diagnosis or were likely to have an axis II diagnosis (cluster A, B or C) according to DSM-IV criteria. Further reasons for exclusion were severe medical or neurological illness (e.g. Parkinson disease, ischemic brain insults, non-compensated hypothyroidism or diabetes mellitus), hearing disorder or intake of any psychotropic medication. In addition subjects were screened with respect to psychiatric diagnoses in the family. An axis I diagnosis in first-degree relatives was an exclusion criterion. An axis II disorder in first-degree relatives and/or an axis I and II disorders in second or higher degree relatives were documented. A subsample of the entire sample, i.e. 15 subjects (mean age 30.9 ± 9.2 years) matched with respect to age, sex, and handedness, was enrolled in the study.

2.4. Task and stimulation

Subjects had to perform an auditory oddball task with pseudo-randomized presentation of frequent non-targets (175 double-clicks with 500 ms inter-stimulus intervals (ISI), 1 ms square waves at 83 dB) and rare targets (55 sine-tones 1000 Hz, 83 dB SPL; 40 ms duration including 10 ms rise- and 10 ms fall time) with an overall ISI between 1.5 and 4.6 s presented binaurally by headphones. Targets had to be responded by a button press. The whole task took 12 min. Stimuli were generated by a PC-stimulator with Creative Labs SoundBlaster 16. Based on the known and stable transducer sensitivity of the headphones, calibration was performed by electrical AC voltage measurement at the headphones' terminals before beginning of the study. Stimulus levels are the absolute sound pressure levels of a continuous sinewave with a peak-to-peak amplitude equaling that of the referring stimulus.

2.5. Data acquisition

EEG-recordings were carried out in a sound-attenuated and electrically shielded room adjacent to the recording apparatus (Synamps-Neuroscan[®]; 500 Hz sampling rate; gain 75000). Subjects were seated with eyes closed in a slightly reclined chair with a head rest. EEG was recorded with 32 channels (Ag/AgCl electrodes) referenced to Cz. The electrodes were positioned according to the international 10/20 system with the additional electrodes FC1, FC2, FC5, FC6, T1, T2, CP5, CP6, PO9, PO10. Fpz was used as ground electrode. Analysis was performed using average reference (EOG, A1, A2 were not included in the average reference). Eye movements were recorded across an electrode which was placed 1 cm lateral to the left eye (Lo1). Electrode impedances were kept below 10 k Ω . Data were collected with a sampling rate of 500 Hz and an analogues filtered with a 0.16 Hz high-pass and a 100 Hz low-pass filter. Furthermore, data were off-line filtered using a notch-filter (frequency band 47.77–52.33 Hz (-3 dB)). Averaging epochs for event-related potentials (ERP) and EEG gamma activity were limited from 450 ms

Table 1
Characteristics of healthy subjects and schizophrenic patients (mean \pm standard deviation)

	Healthy controls	Schizophrenic patients
N (m/f)	15 (11/4)	15 (11/4)
Age (years)	30.9 ± 9.2	28.4 ± 11.0
Handedness (r/l/ambi)	13/1/1	14/1/0
Duration of illness (years)	–	4.6 ± 6.2
Age of onset (years)	–	23.9 ± 10.0
No. of episodes	–	1.9 ± 2.6
No. of hospitalizations	–	1.9 ± 1.6
PANSS positive score	–	23.6 ± 4.8
PANSS negative score	–	23.6 ± 7.4
PANSS global	–	44.2 ± 7.9

pre-stimulus to 800 ms after stimulus onset. For artifact suppression, trials were automatically excluded from averaging, if the standard deviation within a moving 200 ms time interval exceeded $30 \mu\text{V}$ in any one of the EEG channels and $40 \mu\text{V}$ in the Lo1 channel. We set a criterion of at least 30 valid trials for data analysis. After the automatic artifact rejection all trials were visually inspected and rejected if eye-movement artifacts or electrode drifts were visible. Baselines were computed based on a pre-stimulus 300–200 ms time window. This early baseline was chosen to avoid the temporal smearing of post-stimulus activity into the interval preceding the stimulus in the wavelet transform.

2.6. Data analysis

Mean reaction times for the target stimulus were calculated on the basis of the interval between stimulus onset and button press. Due to the physical differences of the standards and the target stimuli, we did not compare the physiological response to the two stimulus conditions directly. To avoid a loss of statistical power that is inherent when repeated measures ANOVAs are used to quantify multi-channel EEG data, P3-amplitudes and EEG gamma activity were pooled across selected electrode sites with 4 topographical regions of interest (ROIs): the left anterior region (LAR) was comprised of the electrode positions FP1, F3 and FC5. The left posterior region (LPR) included electrodes P3, T5 and O1. Corresponding ROIs were defined for the right hemisphere based on homologous electrode positions. The P3-component was measured as mean amplitude in the time interval between 250 and 400 ms. Fig. 2 shows the target ERPs of the ROI and midline electrodes for the patients with schizophrenia and matched healthy controls. In both groups, a positive target P3 after about 300–350 ms was evoked at posterior sites. A further negative deflection was found at anterior sites (in the averaged referenced data). Guided by previous work (Gallinat et al., 2002; Mulert et al., 2001), we chose the mean amplitudes of the Fz and the Cz electrode in a time interval between 100 and 150 ms in order to determine the amplitude of the N1 component.

For the analysis of the EEG gamma-activity a wavelet transform based on Morlet wavelets was employed. Details about Morlet wavelet analyses are described, for example, by Tallon-Baudry et al. (1998). For the analysis of GBRs we calculated wavelet transformations with a central frequency of 40 Hz ($f_0 = 40$). The duration ($2\sigma_t$) of the wavelet was 50 ms resulting in a spectral bandwidth ($2\sigma_f$) of 12.73 Hz. The spectral bandwidth is two times the standard deviation of the Gaussian kernel ($\sigma_f = (2\pi\sigma_t)^{-1}$). Two types of gamma activity were investigated: ‘evoked’ and ‘induced’ gamma activities. The two types of gamma activity differ in the way they are time-locked to experimental stimuli. Evoked gamma activity is strictly phase- and time-locked to the onset of an experimental condition. This gamma activity

starts at approximately the same latency after stimulus onset, for every repetition of the stimulus. Therefore, it adds up and is visible in the averaged ERP. For the calculation of evoked gamma activity we computed a wavelet transform on the average over single trials, i.e. the ERP. In contrast to the evoked gamma activity, induced gamma activity is not strictly phase-locked to the onset of an experimental condition. Induced gamma activity occurs after each stimulation but with a varying onset time and/or phase jitter. This activity usually cancels out in the averaged ERP. For the calculation of induced gamma activity we computed the sum of evoked and induced gamma activity in a first step by averaging the absolute values of the wavelet transforms of single trials. In other words, each single trial was first transformed, using a 40 Hz wavelet, and the absolute values of these transformations were averaged subsequently. To compute the induced gamma activity, we finally subtracted the evoked gamma activity from the sum of evoked and induced activities. The result of this subtraction is the induced gamma activity (details about this method have previously been described) (Herrmann and Knight, 2001; Herrmann et al., 1999). Induced and evoked gamma activities were computed separately for early (20–100 ms) and late (220–350 ms) latency ranges for the 4 ROIs.

2.7. Statistical analyses

Statistical calculations were carried out using SPSS for Windows (Release 10.0)[®]. Between-group comparisons of the dependent variables GBRs or the ERPs N1, P3 were performed with repeated measures ANOVAs using the between subject factor ‘group’ (healthy controls, patients with schizophrenia) and the within subject factor ‘ROI’ (right anterior, left anterior, right posterior, left posterior). In case of non-sphericity, all calculated ANOVAs were adjusted with the Greenhouse–Geisser epsilon correction for non-sphericity. ANOVA results were considered statistically significant when a two-tailed alpha < 0.05 was given.

3. Results

3.1. Reaction times and error rates

Mean reaction times in response to target stimuli did not differ significantly between schizophrenic patients (402 ± 148 ms) and healthy controls (379 ± 70 ms) ($F(1, 28) = 0.387$, $P = 0.539$). Patients made more errors (omitted button press on target stimuli) (mean $5.2 \pm 10.9\%$) as compared to healthy controls (mean $0.6 \pm 1.5\%$), but these differences were not statistically significant ($F(1, 28) = 2.77$, $P = 0.107$).

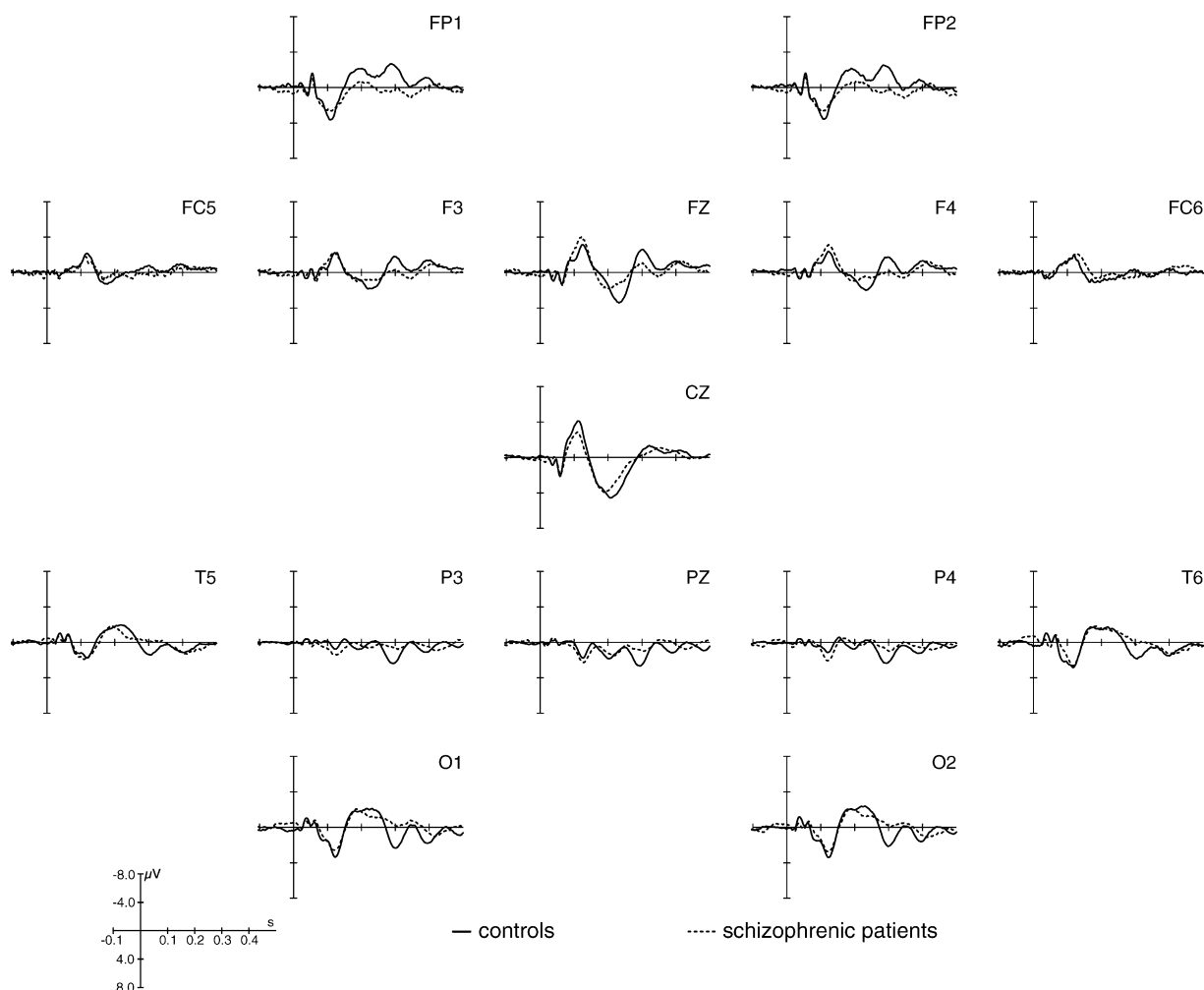


Fig. 1. ERPs (average referenced, 20 Hz low-pass filtered) for standard stimuli, averaged across 15 unmedicated schizophrenics (dotted line) and 15 age- and gender-matched healthy control subjects (solid line). No significant differences were found for early standard N1 amplitudes.

3.2. Analysis of event-related potentials (N1-, P3-component)

N1-component: The analysis of the N1-amplitudes (100–150 ms) at the midline electrodes Fz and Cz revealed no significant differences between healthy controls and schizophrenic patients in response to the standard stimuli (Fig. 1) and target stimuli (Fig. 2).

Target P3-component: The ANOVA for the P3-amplitude (250–400 ms) yielded a significant main effect of the factor ROI ($F(1.20, 33.47) = 18.10, P < 0.0001$), indicating a different phase of anterior (negative activations) and posterior (positive activations) regions. No significant main effect of the factor group was found ($F(1, 28) = 0, P < 0.9633$) but a significant group \times ROI interaction ($F(1.20, 33.47) = 4.99, P = 0.027$). *Post-hoc* ANOVAs for the 4 ROIs revealed lower (more negative) P3-amplitudes in healthy controls ($-3.20 \mu\text{V}$) as compared to patients ($-0.22 \mu\text{V}$) over right frontal scalp areas ($F(1, 28) = 4.89, P = 0.035$). Higher P3-amplitudes in healthy controls as compared to patients were observed

over the left ($F(1, 28) = 8.58, P < 0.007$) and the right posterior region ($F(1, 28) = 4.23, P = 0.049$).

3.3. Analysis of EEG oscillations (gamma activity)

Generally, the wavelet analysis revealed an increase of evoked gamma activity after stimulus onset of the standard and the target stimuli in both groups. However, there was no increase of induced gamma activity after stimulus onset in either group. Therefore, the analysis was restricted to evoked GBRs in an early (20–100 ms) and a late (220–350 ms) time interval. Due to the fact that baseline activations in a pre-stimulus time window between 300 and 200 ms were subtracted before data analysis, some post-stimulus activation showed a negative value. However, none of these negative activations differed significantly from baseline activity. We tested whether there are differences between drug-naive ($n = 10$) and drug-free ($n = 5$) patients. ANOVAs for the early and late time interval using the between subject factor ‘patient group’

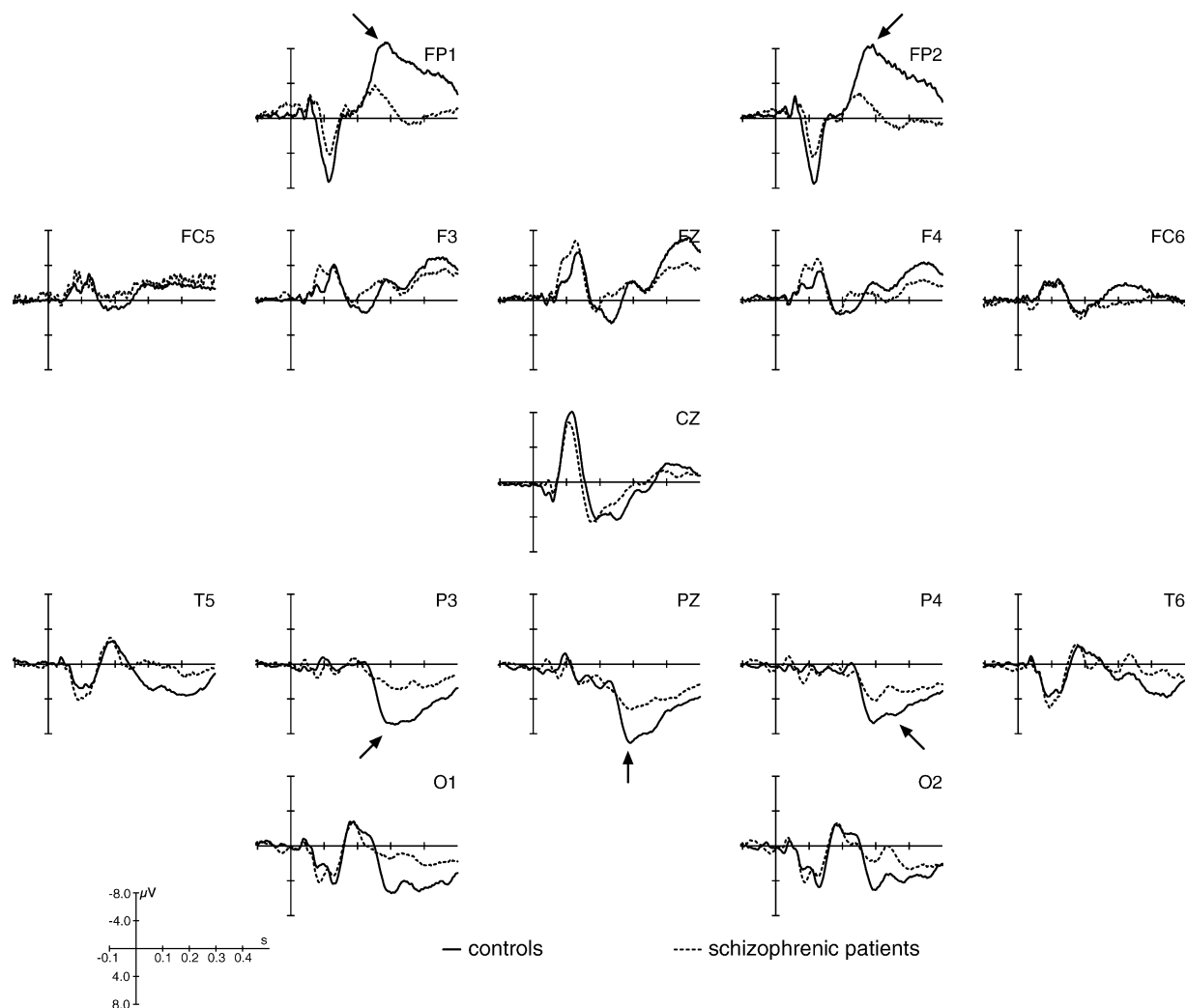


Fig. 2. ERPs (average referenced, 20 Hz low-pass filtered) for target stimuli, averaged across 15 unmedicated schizophrenics (dotted line) and 15 age- and gender-matched healthy control subjects (solid line). Notice the reduced amplitudes for patients with schizophrenia in a latency range of about 250–400 ms over anterior and posterior scalp regions.

(drug-naïve, drug-free) did not reveal significant effects on GBRs for the 4 ROIs.

Due to previous positive reports (Crawford et al., 2002), effects of smoking on GBRs were tested. In the present study significantly more smokers were found in the patients groups (9/15) as compared to controls (3/15; $\chi^2 = 5$, $df = 1$, $P < 0.025$). ANOVAs revealed higher early target GBRs in all 4 ROIs for smokers than for non-smokers [LAR: $F(1, 28) = 5.78$, $P = 0.028$; LAL: $F(1, 28) = 12.44$, $P = 0.001$; RPR: $F(1, 28) = 6.25$, $P = 0.019$; LPR: $F(1, 28) = 6.92$, $P = 0.014$]. No effects of the factor ‘smoking’ on late target GBRs and on early and late standard GBRs were observed.

Standard stimuli: No significant main effect of the factor group was found for the evoked GBRs in either the early latency range ($F(1, 28) = 0.84$, $P = 0.3679$), or the late latency range ($F(1, 28) = 0.11$, $P = 0.744$; Fig. 3).

Target stimuli: Fig. 4 shows evoked gamma activity at midline and ROI electrodes for healthy controls

and schizophrenic patients. In both groups, the highest peak of early target-gamma activity was found for the early time interval between 20 and 100 ms. An ANOVA for the early time interval revealed no significant main effects of the factor group ($F(1, 28) = 0.11$, $P = 0.744$) or the group \times ROI interaction ($F(2.71, 75.94) = 0.603$). We calculated an analysis of covariances (ANCOVA) using the between subject factor group (healthy controls, patients), the within subject factor ROI (right anterior, left anterior, right posterior, left posterior), and the covariate smoking (smoker, non-smoker). No effects of the factor group were found in this ANCOVA ($F(1, 27) = 1.16$, $P = 0.292$), indicating that the early target GBRs did not differ between subject groups. For the late time interval (220–350 ms), another ANOVA did not reveal significant effects of the factors group ($F(1, 28) = 0.19$, $P = 0.670$) or ROI ($F(2.70, 75.45) = 0.63$, $P = 0.597$). However, a significant group \times ROI interaction indicates that the late target-gamma activity

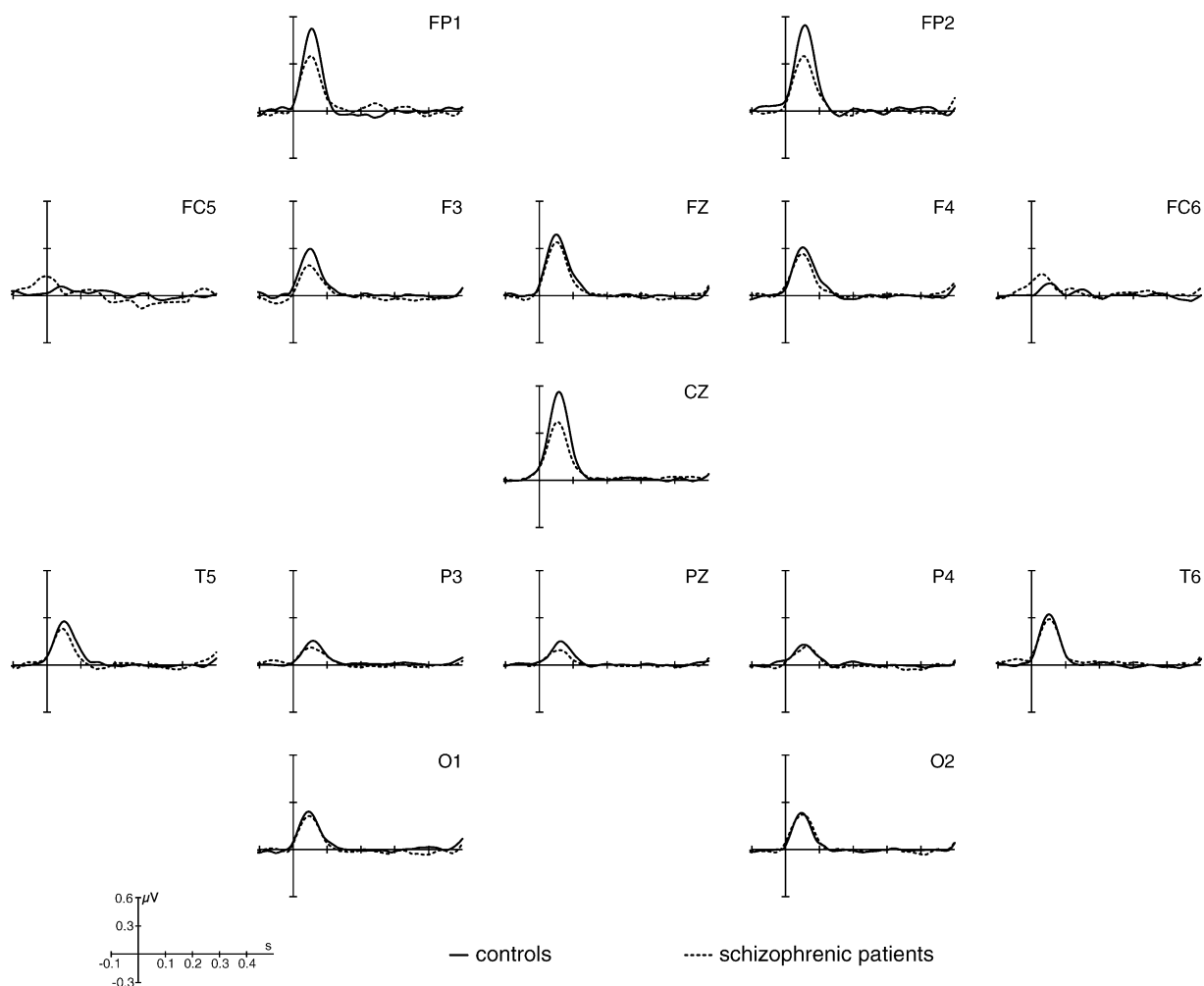


Fig. 3. Evoked gamma-band responses for standard stimuli, averaged across 15 unmedicated schizophrenics (dotted line) and 15 healthy control subjects (solid line). No significant differences were found between patients with schizophrenia and healthy control subjects.

differs at specific topographic regions between patients with schizophrenia and healthy control subjects ($F(2.70, 75.45) = 3.80$, $P = 0.016$). Post-hoc comparisons for the 4 regions separately yielded a significant higher gamma activity in healthy controls ($0.05 \mu\text{V}$) as compared to patients with schizophrenia ($-0.01 \mu\text{V}$) over right anterior scalp areas ($F(1, 28) = 6.63$, $P < 0.016$). No differences were observed over the other 3 scalp regions (Fig. 4).

3.4. Clinical data

A correlation analysis between late target gamma-responses, reaction times and clinical parameters was performed (see Table 2). Significant correlations between GBRs and reaction times were observed in healthy controls and schizophrenic patients. Late target gamma also showed a significant correlation with the duration of illness but not with number of episodes or the actual psychopathology in schizophrenic patients.

4. Discussion

This study investigated oscillatory responses in the EEG gamma-band during an auditory oddball paradigm. GBRs of 15 drug-free schizophrenic patients and 15 age- and gender-matched healthy controls were compared. As a main result, we found reduced evoked GBRs for patients in a late latency range between 220 and 350 ms for the target stimuli over right frontal scalp regions. In addition, significant correlations were observed between oscillatory GBRs and clinical parameters in schizophrenic patients. No group differences in GBR were found for the standard stimuli.

4.1. Gamma activity

In the present study we found that evoked and not induced gamma activity is related to the onset of an experimental condition. Evoked activity is defined as those oscillations which occur time- and phase-locked, whereas induced activity represents oscillations which occur without time- or phase-locking to the onset of an experimental stimulus.

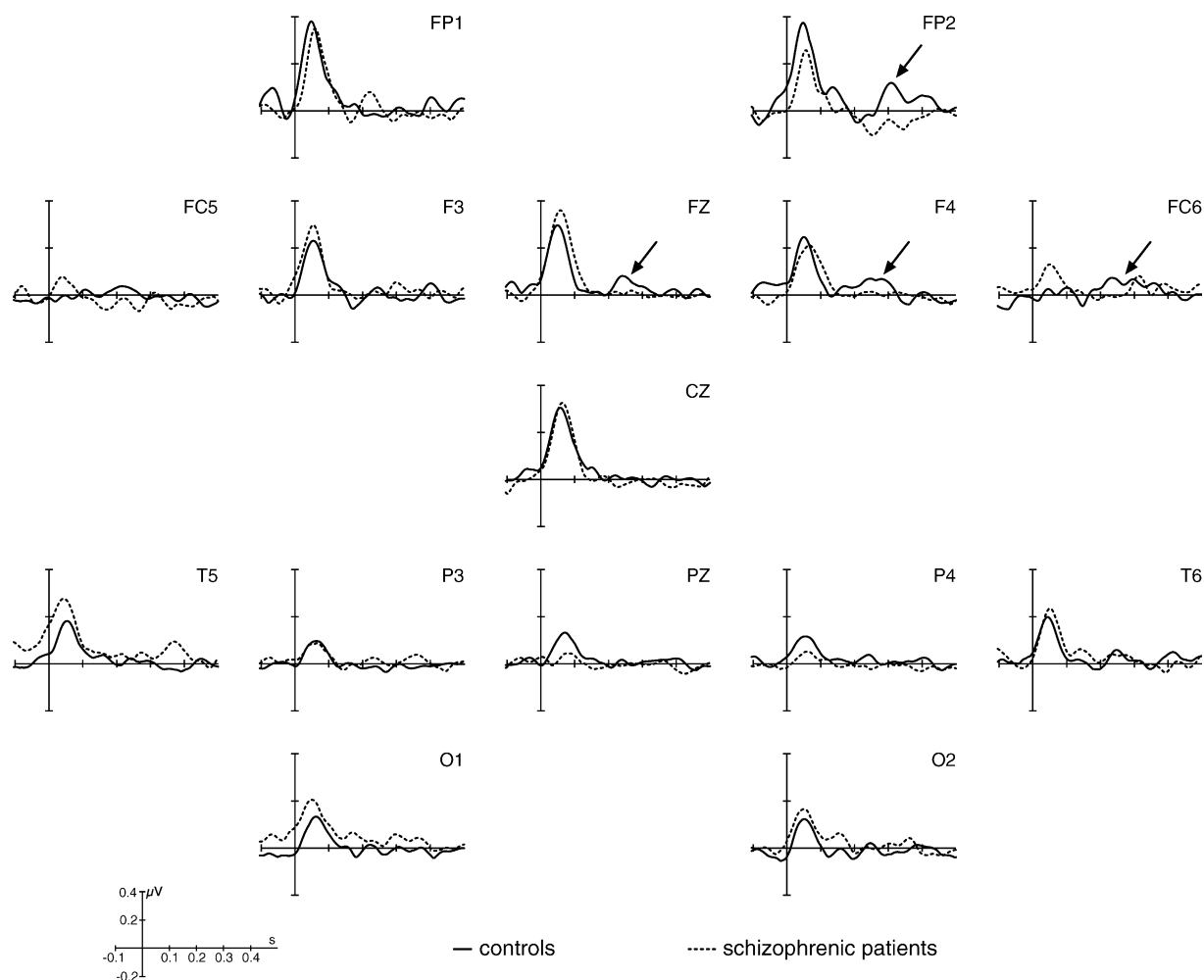


Fig. 4. Evoked gamma-band responses for target stimuli, averaged across 15 unmedicated schizophrenics (dotted line) and 15 healthy control subjects (solid line). Significant reduced gamma-band responses were found for patients with schizophrenia over anterior and anterior right scalp regions in a latency range between 220 and 350 ms. No significant differences were found in an earlier time range between 20 and 100 ms.

By using Gabor wavelet transformations, Gurtubay et al. (2001) systematically investigated GBRs in an auditory oddball paradigm. The authors reported strong early GBRs and smaller late GBRs for target stimuli, comparable with the GBRs in the present study. In addition, these authors found that early GBRs occur particularly as evoked activity which is well in line with the results of previous studies (Pantev et al., 1991; Tiitinen et al., 1994). Interestingly, Gurtubay et al. (2001) also reported an increase of evoked and induced GBRs in a later time interval (at about 360 ms). Although we did not find late induced GBRs, which also is in line with Fell et al. (1997), we found evoked GBRs with a comparable latency in the present study (at about 300 ms). Late evoked GBRs have also been reported by Haig et al. (1999). However, the precise role of late GBRs regarding evoked and induced activities remains to be explored in future studies.

4.2. Early evoked gamma activity

In response to the standard stimulus pronounced early GBRs were observed within the first 100 ms post-stimulus

in healthy controls and schizophrenic patients mainly over fronto-central scalp regions (Fig. 3). The time course of this activity is similar to 40 Hz oscillations observed in cats 100 ms after auditory stimulation (Basar et al., 2001; Schurmann et al., 1997). Barth, Sukov, and colleagues

Table 2

Pearson correlation coefficients between late evoked target gamma and clinical parameters in patients with schizophrenia ($n = 15$)

	Late gamma band response			
	Anterior		Posterior	
	Left	Right	Left	Right
Reaction time (controls)	0.536*	0.329	0.456 +	-0.018
Reaction time (patients)	-0.224	0.038	-0.304	-0.729**
Duration of illness	0.035	0.122	-0.428	-0.622*
No. of episodes	0.304	0.318	-0.321	-0.441
PANSS positive score	-0.044	0.109	0.132	-0.082
PANSS negative score	-0.120	-0.087	-0.188	-0.275

* $P < 0.05$; ** $P < 0.01$.

(Barth and MacDonald, 1996; Sukov and Barth, 2001) demonstrated in rats that this activity originates in the primary (AI) and secondary (AII) auditory cortex. Similar results were described in anesthetized macaque monkeys (Brosch et al., 2002). In line with the animal experiments, oscillatory GBRs in a latency range between 20 and 130 ms after auditory stimuli have been observed in humans using magnetoencephalography (Pantev et al., 1991). Dipole source analysis of this activity suggested a generation in the supratemporal plane, compatible with the localization of the auditory cortex (Tzourio et al., 1997). Due to the dipole localization, the early occurrence and the stimulus dependency, these oscillations were interpreted as a correlate of perceptual processing in the auditory cortex (Pantev et al., 1991).

Following this argumentation, the present results indicate that unmedicated schizophrenic patients have no obvious deficit in the early auditory information processing for simple auditory stimuli—neither in response to non-target nor in response to target stimuli. This is in line with the observation that the activity of the primary auditory cortex in schizophrenic patients is relatively preserved in response to simple sine-tones (Gallinat et al., 2002) and furthermore fits well with the normal ERP N1-amplitudes at midline electrodes in the present study. In addition, the result is compatible with functional imaging studies of auditory attention paradigms in schizophrenia (Holcomb et al., 2000). In terms of the temporal binding model, this suggests, that the binding signal, i.e. the integration of the salience of the auditory stimulus is not disturbed at the level of the primary auditory cortex in schizophrenia. Another interesting finding is the higher early target GBRs in smokers as compared to non-smoking subjects. This finding is in line with a study by Crawford et al. (2002) who also showed that smokers have higher evoked GBRs at an early latency. The authors interpreted their finding with the psychopharmacological effects of smoking. However, the factor smoking did not explain the GBR differences between schizophrenic patients and healthy control subjects in the present study.

4.3. Late evoked gamma activity

In response to the target tone, healthy subjects showed increased GBRs in a post-stimulus interval between 220 and 350 ms over right frontal scalp regions (Fig. 4). Similar late GBRs have been recorded in cats by utilization of omitted auditory stimuli as targets (Basar-Eroglu and Basar, 1991). The activity in healthy subjects does not seem to be a correlate of the early perceptual processing in the auditory cortex, because of its more frontal—instead of fronto-central—topography and the right-sided accentuation. This topography is difficult to explain by a bilateral activation of the primary auditory cortex with its fronto-centrally oriented neuronal generators (Gallinat et al., 2002). Furthermore, the occurrence is probably too late to be

generated in the auditory cortex, since AEPs generated in the primary auditory cortex (N1-, P2-component) mainly occur within 200 ms post-stimulus (Gallinat and Hegerl, 1994; Herrmann et al., 2002).

Taking into account these characteristics together with the occurrence in response to target stimuli, it is more likely that late target GBRs reflect processes such as selective attention, working memory, decision-making and motor response. These cognitive elements are involved in the oddball task within the first 400 ms after stimulus presentation (Holcomb et al., 2000; McCarthy et al., 1997; Winterer et al., 2001b) and have been subsumed under the term ‘executive functions’ (Vogt et al., 1992). Executive functions have been linked to the activation of the frontal lobe, which is in line with the occurrence of the late target GBRs over anterior scalp regions. In fact, several functional neuroimaging studies revealed the important role of the anterior cingulate cortex in selective attention paradigms (Posner and Dehaene, 1994; Tzourio et al., 1997), activation of the right DLPFC during working memory tasks (Jonides et al., 1993; McCarthy et al., 1994), and activity of the cingulate motor division, SMA and M1 area during motor reaction (Holcomb et al., 2000; Sugiura et al., 2001).

More importantly, executive functions are dependent on the interaction of these brain areas in the sense of network processing (Shallice, 1988; Stuss et al., 1995; Umiltà and Stablum, 1998). Cerebral networks have gained interest in brain research and neuroimaging studies that are focused on the global integration rather than isolated regional changes of the brain in response to psychological tasks in healthy subjects (Fletcher et al., 1995) and schizophrenia (Fletcher et al., 1999). In this context, temporal binding comes into play as an important component of network processing. Since binding was attributed to the phenomenon of synchronized GBRs (Singer and Gray, 1995), the late target GBRs in the present study may be interpreted as a correlate of frontal brain areas interaction. In schizophrenic patients, reduced late target GBRs over frontal scalp areas were observed as compared to healthy controls compatible with the hypothesis of a disturbed frontal lobe inter-regional connection in this disorder.

Focusing on the functional connection of brain areas, Fletcher et al. (1999) demonstrated a failure of the anterior cingulate cortex to modulate the prefronto-temporal interaction. The authors discussed that attention may have a modulatory role on the regional brain activity and the interactions between brain regions. This is in line with other observations that patients with schizophrenia are unable to make optimal use of fronto-cingulate systems in high-error tasks (Holcomb et al., 2000). In the present study, the time point of the late gamma deficit in schizophrenia (220–350 ms post-stimulus) fits well with an assumed deficit in network processing during the oddball paradigm because this paradigm requires a response which was observed within the first 400 ms post-stimulus. The correlation between target GBR and reaction time may

indicate that late GBRs reflect executive functions comprising selective attention, decision-making, motor control and others. Although the present data provide evidence for an abnormal interaction within a frontal network, no evidence for a disturbed interaction between frontal and temporal lobes was observed, contrary to some neuroimaging studies (Friston and Frith, 1995; Heckers et al., 1998; Meyer-Lindenberg et al., 2001; Winterer et al., 2003a). The normal early GBRs following target as well as non-target stimuli in this study indicate a preservation of the stimulus processing in the auditory cortex in schizophrenic patients. Because of this, the impaired late GBRs over frontal scalp regions cannot be a consequence of a reduced neuronal input signal from the temporal lobe auditory cortex. However, the results of the present study cannot rule out a fronto-temporal interaction deficit because (1) the employed paradigm may require less fronto-temporal interaction as compared to the memory retrieval task of Fletcher et al. (1999), (2) not all functional aspects of the temporal lobe (e.g. activity of the secondary auditory cortex) are reflected by the employed electrodes (for discussion see Gallinat et al., 2002), and (3) a long-range coupling like the fronto-temporal interaction may be rather represented by lower oscillation frequencies (i.e. beta band) (von Stein and Sarnthein, 2000; von Stein et al., 1999; Winterer et al., 2003a,b). Also, there is ample evidence that cortical synchronization of lower frequency oscillations in local prefrontal microcircuits is more dramatically disturbed in schizophrenia than in the gamma-frequency range (Winterer et al., 2004) and that fronto-temporal interaction may only be secondarily disturbed in schizophrenia resulting from primary local cortical dysfunction in the frontal and/or temporal lobe area (Winterer et al., 2003a).

The significant correlations between GBR and clinical parameters revealed some evidence that a more pronounced gamma deficit is associated with longer illness duration. Although, this association was observed for the posterior scalp regions only, the result is compatible with the view that a disturbed network processing is associated with a more severe course of the disease.

The present results differ to some extent from an earlier finding in schizophrenic patients in which higher GBRs over right frontal scalp regions were found (Haig et al., 2000). Furthermore, in this previous study, reduced left sided GBRs were observed contrary to the present results. Differences in clinical parameters, e.g. duration of illness (12.1 years in the study of Haig et al. as compared to 4.6 years in our patients) may account for this discrepancy. Another reason may be that the patients in the study of Haig et al. were medicated contrary to the present sample. Since dopaminergic neurotransmission modulate the frontal lobe activity (Gallinat et al., 2003) as well as the fronto-temporal interaction during cognitive tasks (Dolan et al., 1995) in schizophrenic patients, antipsychotic drugs may alter GBRs.

4.4. P3-component

Next to the GBR deficit, a reduced P3-amplitude was observed in schizophrenic patients as compared to controls which was first described by Roth and Cannon (1972) and replicated by several reports using different analysis methods (Gallinat et al., 2001, 2003; Roth et al., 1981; Winterer et al., 2001a). Interestingly, in the present data, a more pronounced left-than-right sided deficit of the P3-amplitude was observed in schizophrenic patients, compatible with other reports (Faux et al., 1988, 1993). This left-sided deficit was attributed to a more pronounced left sided temporal lobe histopathology and pathophysiology. In this context it is remarkable that no deficit of the left-sided GBRs were observed in the patients. Röschke et al. (1996) and Wagner et al. (2000) previously demonstrated that reduced P3-amplitudes in patients with schizophrenia are associated with fewer elicited single trial P3-amplitudes in patients. It might be that the reduced evoked GBRs in the present study were also related with a higher trial-to-trial variation of evoked GBRs in patients with schizophrenia. Because of the relatively low signal-to-noise ratio of GBRs on the single trial level, the variability of single trial GBRs was not analyzed in the present study. Future investigations should focus on the aspect of single trial variability and evoked GBRs.

The main findings of the present study were disturbed right frontal GBRs and a disturbed left posterior accentuated deficit of the P3-amplitude in unmedicated patients with schizophrenia. This indicates that the averaged low frequency responses (P3) and the high frequency gamma-response reflect different aspects of cerebral stimulus processing. Therefore, GBR may be an interesting new tool in schizophrenia research to investigate temporal network processing.

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References

- Alonso JM, Usrey WM, Reid RC. Precisely correlated firing in cells of the lateral geniculate nucleus. *Nature* 1996;383(6603):815–9.
- American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Barth DS, MacDonald KD. Thalamic modulation of high-frequency oscillating potentials in auditory cortex. *Nature* 1996;383(6595):78–81.

- Basar-Eroglu C, Basar E. A compound P300-40 Hz response of the cat hippocampus. *Int J Neurosci* 1991;60(3–4):227–37.
- Basar-Eroglu C, Struber D, Schurmann M, Stadler M, Basar E. Gamma-band responses in the brain: a short review of psychophysiological correlates and functional significance. *Int J Psychophysiol* 1996;24(1–2):101–12.
- Basar E, Basar-Eroglu C, Karakas S, Schurmann M. Gamma, alpha, delta, and theta oscillations govern cognitive processes. *Int J Psychophysiol* 2001;39(2–3):241–8.
- Bressler SL, Coppola R, Nakamura R. Episodic multiregional cortical coherence at multiple frequencies during visual task performance. *Nature* 1993;366(6451):153–6.
- Brosch M, Budinger E, Scheich H. Stimulus-related gamma oscillations in primate auditory cortex. *J Neurophysiol* 2002;87(6):2715–25.
- Buchsbaum MS, Tang CY, Peled S, Gudbjartsson H, Lu D, Hazlett EA, Downhill J, Haznedar M, Fallon JH, Atlas SW. MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. *NeuroReport* 1998;9(3):425–30.
- Crawford HJ, McClain-Furmanski D, Castagnoli Jr. N, Castagnoli K. Enhancement of auditory sensory gating and stimulus-bound gamma band (40 Hz) oscillations in heavy tobacco smokers. *Neurosci Lett* 2002;317:151–5.
- Dolan RJ, Fletcher P, Frith CD, Friston KJ, Frackowiak RS, Grasby PM. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* 1995;378(6553):180–2.
- Engel AK, Singer W. Temporal binding and the neural correlates of sensory awareness. *Trends Cogn Sci* 2001;5(1):16–25.
- Engel AK, Fries P, Singer W. Dynamic predictions: oscillations and synchrony in top-down processing. *Nat Rev Neurosci* 2001;2(10):704–16.
- Faux SF, Torello MW, McCarley RW, Shenton ME, Duffy FH. P300 in schizophrenia: confirmation and statistical validation of temporal region deficit in P300 topography. *Biol Psychiatry* 1988;23(8):776–90.
- Faux SF, McCarley RW, Nestor PG, Shenton ME, Pollak SD, Penhune V, Mondrow E, Marcy B, Peterson A, Horvath T, Davis KL. P300 topographic asymmetries are present in unmedicated schizophrenics. *Electroencephalogr Clin Neurophysiol* 1993;88(1):32–41.
- Fell J, Hinrichs H, Rösche J. Time course of human 40 Hz EEG activity accompanying P3 responses in an auditory oddball paradigm. *Neurosci Lett* 1997;235(3):121–4.
- Friston MB, Gibbon M, Spitzer RL, Williams JBW. User's guide for the SCID-I for DSM-IV axis I disorders-research version. New York: Biometrics Research; 1996.
- Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RS, Dolan RJ. Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. *Brain* 1995;118(2):401–16.
- Fletcher P, McKenna PJ, Friston KJ, Frith CD, Dolan RJ. Abnormal cingulate modulation of fronto-temporal connectivity in schizophrenia. *NeuroImage* 1999;9(3):337–42.
- Foong J, Maier M, Clark CA, Barker GJ, Miller DH, Ron MA. Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study. *J Neurol Neurosurg Psychiatry* 2000;68(2):242–4.
- Ford JM, Mathalon DH, Whitfield S, Faustman WO, Roth WT. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biol Psychiatry* 2002;51(6):485–92.
- Fries P, Reynolds JH, Rorie AE, Desimone R. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 2001;291(5508):1560–3.
- Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci* 1995;3(2):89–97.
- Gallinat J, Hegerl U. Dipole source analysis. Linking scalp potentials to their generating neuronal structures. *Pharmacopsychiatry* 1994;27(2):52–3.
- Gallinat J, Riedel M, Juckel G, Sokullu S, Frodl T, Moukhtieva R, Mavrogiorou P, Nisse S, Muller N, Danker-Hopfe H, Hegerl U. P300 and symptom improvement in schizophrenia. *Psychopharmacology (Berl)* 2001;158(1):55–65.
- Gallinat J, Mulert C, Bajbouj M, Herrmann WM, Schunter J, Senkowski D, Moukhtieva R, Kronfeldt D, Winterer G. Frontal and temporal dysfunction of auditory stimulus processing in schizophrenia. *NeuroImage* 2002;17(1):110–27.
- Gallinat J, Sander T, Bajbouj M, Schlattmann P, Xu K, Ferro EF, Goldman D, Winterer G. Association of the G1947A COMT (Val108/158Met) gene polymorphism with prefrontal P300 during information processing. *Biol Psychiatry* 2003;54(1):40–8.
- Gruber T, Muller MM, Keil A. Modulation of induced gamma band responses in a perceptual learning task in the human EEG. *J Cogn Neurosci* 2002;14(5):732–44.
- Gurtubay IG, Alegre M, Labarga A, Malanda A, Iriarte J, Artieda J. Gamma band activity in an auditory oddball paradigm studied with the wavelet transform. *Clin Neurophysiol* 2001;112(7):1219–28.
- Haig AR, De P V, Gordon E. Peak gamma latency correlated with reaction time in a conventional oddball paradigm. *Clin Neurophysiol* 1999;110(1):158–65.
- Haig AR, Gordon E, De Pascalis V, Meares RA, Bahramali H, Harris A. Gamma activity in schizophrenia: evidence of impaired network binding? *Clin Neurophysiol* 2000;111(8):1461–8.
- Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nat Neurosci* 1998;1(4):318–23.
- Herrmann CS, Knight RT. Mechanisms of human attention: event-related potentials and oscillations. *Neurosci Biobehav Rev* 2001;25(6):465–76.
- Herrmann CS, Mecklinger A, Pfeifer E. Gamma responses and ERPs in a visual classification task. *Clin Neurophysiol* 1999;110(4):636–42.
- Herrmann CS, Senkowski D, Maess B, Friederici AD. Spatial versus object feature processing in human auditory cortex: a magnetoencephalographic study. *Neurosci Lett* 2002;334(1):37–40.
- Holcomb HH, Lahti AC, Medoff DR, Weiler M, Dannals RF, Tamminga CA. Brain activation patterns in schizophrenic and comparison volunteers during a matched-performance auditory recognition task. *Am J Psychiatry* 2000;157(10):1634–45.
- Hyde TM, Ziegler JC, Weinberger DR. Psychiatric disturbances in metachromatic leukodystrophy. Insights into the neurobiology of psychosis. *Arch Neurol* 1992;49(4):401–6.
- Joliot M, Ribary U, Llinas R. Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. *Proc Natl Acad Sci USA* 1994;91(24):11748–51.
- Jonides J, Smith EE, Koeppel RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET. *Nature* 1993;363(6430):623–5.
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261–76.
- Kubicki M, Westin CF, Maier SE, Frumin M, Nestor PG, Salisbury DF, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Am J Psychiatry* 2002;159(5):813–20.
- Kwon JS, O'Donnell BF, Wallenstein GV, Greene RW, Hirayasu Y, Nestor PG, Hasselmo ME, Potts GF, Shenton ME, McCarley RW. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch Gen Psychiatry* 1999;56(11):1001–5.
- Lee KH, Williams LM, Haig A, Goldberg E, Gordon E. An integration of 40 Hz gamma and phasic arousal: novelty and routinization processing in schizophrenia. *Clin Neurophysiol* 2001;112(8):1499–507.
- Lee KH, Williams LM, Breakspear M, Gordon E. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. *Brain Res Rev* 2003;41:57–81.
- McCarthy G, Blamire AM, Puce A, Nobre AC, Bloch G, Hyder F, Goldman-Rakic P, Shulman RG. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proc Natl Acad Sci USA* 1994;91(18):8690–4.

- McCarthy G, Luby M, Gore J, Goldman-Rakic P. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *J Neurophysiol* 1997;77(3):1630–4.
- Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, Berman KF. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am J Psychiatry* 2001;158(11):1809–17.
- Miltner WH, Braun C, Arnold M, Witte H, Taub E. Coherence of gamma-band EEG activity as a basis for associative learning. *Nature* 1999;397(6718):434–6.
- Mulert C, Gallinat J, Pascual-Marqui R, Dorn H, Frick K, Schlattmann P, Mientus S, Herrmann WM, Winterer G. Reduced event-related current density in the anterior cingulate cortex in schizophrenia. *NeuroImage* 2001;13(4):589–600.
- Murthy VN, Fetz EE. Coherent 25- to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proc Natl Acad Sci USA* 1992;89(12):5670–4.
- Norman RM, Malla AK, Williamson PC, Morrison-Stewart SL, Helmes E, Cortese L. EEG coherence and syndromes in schizophrenia. *Br J Psychiatry* 1997;170:411–5.
- Pantev C, Makeig S, Hoke M, Galambos R, Hampson S, Gallen C. Human auditory evoked gamma-band magnetic fields. *Proc Natl Acad Sci USA* 1991;88(20):8996–9000.
- Posner MI, Dehaene S. Attentional networks. *Trends Neurosci* 1994;17(2):75–9.
- Röschke J, Wagner P, Mann K, Fell J, Grözing M, Frank C. Single trial analysis of event related potentials: a comparison between schizophrenics and depressives. *Biol Psychiatry* 1996;40:844–52.
- Roth WT, Cannon EH. Some features of the auditory evoked response in schizophrenics. *Arch Gen Psychiatry* 1972;27(4):466–71.
- Roth WT, Pfefferbaum A, Kelly AF, Berger PA, Kopell BS. Auditory event-related potentials in schizophrenia and depression. *Psychiatry Res* 1981;4(2):199–212.
- Salenius S, Salmelin R, Neuper C, Pfurtscheller G, Hari R. Human cortical 40 Hz rhythm is closely related to EMG rhythmicity. *Neurosci Lett* 1996;213(2):75–8.
- Schurmann M, Basar-Eroglu C, Basar E. Gamma responses in the EEG: elementary signals with multiple functional correlates. *NeuroReport* 1997;8(7):1793–6.
- Schutt A, Basar E. The effects of acetylcholine, dopamine and noradrenaline on the visceral ganglion of *Helix pomatia*. II. Stimulus evoked field potentials. *Comp Biochem Physiol C* 1992;102(1):169–76.
- Senkowski D, Herrmann CS. Effects of task difficulty on evoked gamma activity and ERPs in a visual discrimination task. *Clin Neurophysiol* 2002;113:1742–53.
- Shallice T. *From neuropsychology to mental structures*. Cambridge, UK: Cambridge University Press; 1988.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl 20):22–33.
- Singer W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* 1999;24(1):49–65.
- Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis. *Annu Rev Neurosci* 1995;18:555–86.
- Spencer KM, Nestor PG, Niznikiewicz A, Salisbury DF, Shenton ME, McCarley RW. Abnormal neuronal synchrony in schizophrenia. *J Neurosci* 2003;23(19):7407–11.
- Stuss DT, Shallice T, Alexander MP, Picton TW. A multidisciplinary approach to anterior attentional functions. *Ann N Y Acad Sci* 1995;769:191–211.
- Sugiura M, Kawashima R, Takahashi T, Xiao R, Tsukiura T, Sato K, Kawano K, Iijima T, Fukuda H. Different distribution of the activated areas in the dorsal premotor cortex during visual and auditory reaction-time tasks. *NeuroImage* 2001;14(5):1168–74.
- Sukov W, Barth DS. Cellular mechanisms of thalamically evoked gamma oscillations in auditory cortex. *J Neurophysiol* 2001;85(3):1235–45.
- Tallon-Baudry C, Bertrand O. Oscillatory gamma activity in humans and its role in object representation. *Trends Cogn Sci* 1999;3(4):151–62.
- Tallon-Baudry C, Bertrand O, Peronnet F, Pernier J. Induced γ -band activity during the delay of a visual short-term memory task in humans. *J Neurosci* 1998;18(11):4244–54.
- Tiitinen H, Sinkkonen J, May P, Naatanen R. The auditory transient 40-Hz response is insensitive to changes in stimulus features. *NeuroReport* 1994;6(1):190–2.
- Tzourio N, Massiou FE, Crivello F, Joliot M, Renault B, Mazoyer B. Functional anatomy of human auditory attention studied with PET. *NeuroImage* 1997;5(1):63–77.
- Umiltà C, Stablum F. Control processes explored by the study of closed-head-injury patients. In: Mazzoni G, Nelson TO, editors. *Metacognition and cognitive neuropsychology: monitoring and control processes*. Mahwah, NJ: Erlbaum; 1998. p. 37–52.
- Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2001;2(4):229–39.
- Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex* 1992;2(6):435–43.
- von Stein A, Sarnthein J. Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *Int J Psychophysiol* 2000;38(3):301–13.
- von Stein A, Rappelsberger P, Sarnthein J, Petsche H. Synchronization between temporal and parietal cortex during multimodal object processing in man. *Cereb Cortex* 1999;9(2):137–50.
- Wagner P, Röschke J, Grözing M, Mann K. A replication study on P300 single trial analysis in schizophrenia: confirmation of a reduced number of 'true positive' P300 waves. *J Psychiatr Res* 2000;34(3):255–9.
- Winterer G, Ziller M, Dorn H, Frick K, Mulert C, Dahhan N, Herrmann WM, Coppola R. Cortical activation, signal-to-noise ratio and stochastic resonance during information processing in man. *Clin Neurophysiol* 1999;110(7):1193–203.
- Winterer G, Egan MF, Radler T, Coppola R, Weinberger DR. Event-related potentials and genetic risk for schizophrenia. *Biol Psychiatry* 2001a;50(6):407–17.
- Winterer G, Mulert C, Mientus S, Gallinat J, Schlattmann P, Dorn H, Herrmann WM. P300 and LORETA: comparison of normal subjects and schizophrenic patients. *Brain Topogr* 2001b;13(4):299–313.
- Winterer G, Egan MF, Goldberg TE, Coppola R, Weinberger DR. Functional and effective frontotemporal connectivity and genetic risk for schizophrenia. *Biol Psychiatry* 2003a;54(11):1181–92.
- Winterer G, Egan MF, Raedler T, Sanchez C, Jones DW, Coppola R, Weinberger DR. P300 and genetic risk for schizophrenia. *Arch Gen Psychiatry* 2003b;60(11):1158–67.
- Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, Weinberger DR. Prefrontal broadband noise, working memory and genetic risk for schizophrenia. *Am J Psychiatry* 2004;161(3):490–500.