Spectral Analysis of P300 Generation in Depression and Schizophrenia

Key Words
Event-related potentials
P300
Frequency bands
Amplification factors
Depression
Schizophrenia

Abstract
In the past it was reported in several studies that both depressive and schizophrenic patients exhibit reduced P300 amplitudes compared to healthy controls. In order to elucidate the underlying mechanisms of spectral P300 generation, we analysed P300 responses in depression and schizophrenia by a frequency based approach. Herefore, the amplification (poststimulus/prestimulus) of spectral power in different frequency bands was evaluated for non-target and target epochs. Generally, we found that P300 responses are accompanied by a pronounced frequency amplification in the delta and theta range. For the depressive patients we detected only under target condition a statistically significant reduction of alpha and gamma amplification compared to controls. In contrast to this, we observed a highly significant reduction of delta amplification in schizophrenic patients, under both target and non-target conditions.

Introduction
The P300 component of event-related potentials is elicited after unexpected, task-relevant stimuli requiring a motor response or cognitive decision [1, 2]. The P300 wave is usually interpreted as a manifestation of short-term memory processing related to context updating [3, 4]. Its amplitude is related to the subjective probability and task relevance of the eliciting events and is supposed to reflect the amount of resources allocated to the processing of the stimulus [5]. A common setting for P300 experiments is the so-called 'oddball paradigm', where frequent (non-target) and infrequent (target) stimuli are presented to a subject who has been instructed to concentrate on the target events. The P300 response results from averaging the target trials, whereby the spontaneous background EEG, which is not phase-locked, is eliminated.

It is a common finding for schizophrenic subjects that the average P300 amplitude measure is reduced compared to prestimulus baseline [6–10]. Ward et al. [11, 12] interpreted this phenomenon as an expression of allusive thinking, since they recognized reduced P300 responses in normal subjects with increased conceptual looseness. On the other hand, the majority of studies report a reduced P300 amplitude also in depressive disorder [10, 13–16], although this effect seems to be less robust. The psychopathology and clinical signs of schizophrenia and depression nevertheless are very different. Schizophrenics depict perceptual abnormalities and an impairment of contents and forms of thoughts, whereas depressives are characterized...
by a loss of interest, difficulties in concentrating and psychomotor retardation. Therefore, we supposed that the mechanisms responsible for altered P300 generation might be of a different nature in these two diagnostic groups.

Basar [17] introduced the idea of investigating evoked and event-related potentials by analyzing the degree of amplification of different frequency components in post-stimulus EEG compared to prestimulus values [18, 19]. The amplification was quantified by calculating band-specific peak amplitudes in poststimulus versus prestimulus EEG yielding the so-called enhancement factors. This kind of analysis reveals information about resonant activity and excitability of EEG fundamental frequency components. It could be demonstrated that the P300 response is accompanied by a prominent frequency enhancement in the delta and theta range [20, 21]. In the present investigation we analysed the band-specific amplification factors of P300 responses for depressive and schizophrenic patients versus controls. Amplification factors were calculated from single trial quotients of poststimulus divided by prestimulus power values. We hypothesized that this frequency-related approach might reveal different mechanisms underlying reduced P300 responses in schizophrenia and depression.

Materials and Methods

Subjects

We investigated 16 right-handed acute schizophrenic inpatients (11 male, 5 female) aged between 21 and 56 years (mean = 31 ± 9 years) and 14 healthy controls matched for gender and age (mean = 32 ± 9 years). The depressive group consisted of 12 inpatients (5 male, 7 female) with depressive episodes aged between 20 and 61 years (mean = 40 ± 14 years). 12 healthy subjects matched for gender and age (mean = 38 ± 11 years) served as controls. Patients were diagnosed according to DSM-III-R criteria by the consensus of 2 experienced senior psychiatrists. A physical examination revealed neither any current or past history of alcohol dependence nor any serious medical illness. No hearing deficits were found. None of the patients had been on medication for the last 3 months. All testing was performed between 10 a.m. and noon. During ERP recording the subjects were instructed to close their eyes and to count the infrequent target stimuli as well as to press a button in response to them. All subjects gave their written informed consent prior to the participation in the study.

Experimental Design

EEG was recorded from the electrode positions Fz, Cz and Pz with A2 (mastoid) as reference electrode according to the 10-20 system. Horizontal EOG recordings were measured using electrodes at the outer canthi of the right and left eye. Vertical EOG was recorded from electrodes placed above and below the right eye. All electrode impedances were below 5 kΩ. Analog recording bandpass was 0.16 Hz (time constant = 1.0 s) to 70 Hz (rolloff = 3 dB/oct). Data were digitized with a sampling frequency of 1,000 Hz (200 Hz digital low pass filter with =45 dB/oct rolloff; 12 bit ADC; 512 data points pre- and poststimulus). Subjects were presented with 269 non-target stimuli (probability = 0.9, sine-wave tone of 1,500 Hz) and 31 target stimuli (probability = 0.1, sine-wave tone of 2,000 Hz). The intensity of both stimuli was 80 dB SPL with a duration of 500 ms. Interstimulus intervals were randomly distributed between 1.0 and 1.5 s. The sequence of stimuli was constant across subjects. For control purposes subjects were instructed to press a button in case of recognition of a target tone. Each single trial was scanned off-line by a computer algorithm in order to reject trials showing a saturation of the ADC or with ocular artifacts (EOG amplitude exceeding 75 μV).

Spectral Amplification Factors

Target respectively non-target epochs were divided into poststimulus (512 ms) and prestimulus (512 ms) intervals. For each target and non-target epoch the spectral power density was calculated separately for the prestimulus and the poststimulus interval. Power densities were based on FFTs with cosine windowing in the time domain. Now, the quotients from poststimulus power estimates divided by prestimulus power estimates were calculated. The spectral amplification factors (SAF) were defined by the n-th root of the products (geometric average) of these quotients over target (T) respectively non-target (NT) epochs. The rule guarantees that averaging of inverse quotients yields an amplification factor of 1.

\[
SAF = \left( \prod_{i=1}^{n} \frac{\text{power(poststim,}_i \cdot (T/NT)\text{epoch}}{-\text{power(prestim,}_i \cdot (T/NT)\text{epoch}}} \right)^{\frac{1}{n}}
\]

\[
= \left( \frac{\text{power(poststim,}_1 \cdot (T/NT)\text{epoch}}{-\text{power(prestim,}_1 \cdot (T/NT)\text{epoch}}} \cdot \frac{\text{power(poststim,}_2 \cdot (T/NT)\text{epoch}}{-\text{power(prestim,}_2 \cdot (T/NT)\text{epoch}}} \cdots \right)^{\frac{1}{n}}
\]

n = Number of target respectively non-target epochs.

Spectral amplification factors were based on the following definition of frequency bands: total band: 0.5–45 Hz; delta: 0.5–3.5 Hz; theta: 3.5–7.5 Hz; alpha: 7.5–15 Hz; beta: 15–30 Hz; gamma: 30–45 Hz. Discrete Fourier transform of intervals of 512 ms duration gives a frequency resolution of 1.95 Hz. Therefore, in reality several discrete frequencies contributed to the spectral bands, e.g. delta (1.95 Hz), theta (3.90 Hz, 5.86 Hz), alpha (7.81 Hz, 9.77 Hz, 11.72 Hz, 13.67 Hz), etc. Altogether, 12 amplification factors were obtained for each subject, 6 for the target condition and 6 for the non-target condition.

Statistical Analysis

Statistical analysis was performed in three main steps:

(1) For the combined group of control subjects related to the depressive and schizophrenic patients a multivariate analysis of variance (MANOVA) and subsequent univariate analyses of variance (ANOVA) with the 6 spectral amplification factors as independent measures were performed (SAS procedure glm). Dependent factors were stimulus, with the two possible values ‘target’ and ‘non-target’, and the factor position specifying the electrode position Fz, Cz or Pz. Subsequently, for the factor position analyses of contrasts were calculated, where each electrode position was separately tested against the two other positions.
(2) The prestimulus power values (averaged over target and non-target epochs together) were analysed by MANOVA and subsequent ANOVAs for the depressive patients versus controls and for the schizophrenic patients versus controls. The power values corresponding to the 6 different frequency bands served as independent measures. Dependent factors were group (depressives/controls) respectively schizophrenics/controls) and position (Fz, Cz, Pz).

(3) By MANOVA and subsequent ANOVAs the spectral amplification factors under target respectively non-target condition were statistically evaluated for the depressive and schizophrenic patients. Again, the independent measures were given by the spectral amplification factors for the 6 different frequency bands and dependent factors were defined as group (depressives/controls respectively schizophrenics/controls) and position (Fz, Cz, Pz).

For all statistical analyses a cutoff significance level of p = 0.05 was employed.

Results

Qualitative Description of the Results for Control Subjects

Figure 1 shows a single target epoch, which was filtered in the delta, alpha, beta and gamma range, as required for the calculation of the amplification factors. The stimulus was applied at the 0-msec marking. Obviously, a pronounced reinforcement occurs in the delta and theta range. Only a slight amplification can be observed in the alpha range. On the other hand, in the beta and gamma range no reinforcement occurs and even a reduction of amplitudes can be detected in the time interval between 250 and 400 ms, which is the time region of the P300 deflection.

Mean values and standard deviations of the spectral amplification factors for all control subjects and target versus non-target conditions are illustrated in figure 2. The values are related to electrode position Cz. For the total frequency band only a small amplification was calculated for the non-target epochs (SAF = 1.17), whereas a pronounced amplification can be observed for the target condition (SAF = 2.16). The largest difference between the target and non-target condition appears in the delta range with an average non-target SAF of 1.90, but an average target SAF of 7.71. The standard deviation of the target SAFs is large (5.15). A pronounced difference between average target and non-target SAFs also appears in the theta range (non-target SAF = 1.29; target SAF = 2.75), with a much smaller variability of the target SAFs (standard deviation of target SAFs = 1.30) compared to the delta range. In the alpha band a slight reinforcement can be observed for the target epochs (average SAF = 1.28), whereas no amplification was found for the non-target responses (average SAF = 0.98). For the beta and gamma range, no pronounced reinforcement of amplitudes can be detected for the non-target, as well as for the target epochs (average SAFs; beta (non-target) = 0.96, beta (target) = 0.94, gamma (non-target) = 1.00, gamma (target) = 1.09). Since the amplification factors were calculated from the complete prestimulus respectively poststimulus intervals (512 ms), amplitude reductions in the time region of the P300 deflection, which were observed for the single target epoch (fig. 1), do not manifest in the beta and gamma SAFs.
Results of Analyses of Variance

(1) MANOVA of spectral amplification factors for the control subjects (table 1) revealed a highly significant differentiation between non-target and target trials (factor stimulus; p < E−8). ANOVAs for the band-specific SAFs yielded significant effects of the total band (p < E−9), as well as for delta, theta and alpha SAFs. For the partial frequency bands the best differentiation between non-target and target epochs was obtained for the SAFs of the delta (p < E−10) and theta band (p < E−9). A much smaller significant effect was found for the alpha band (p = 0.004). For the beta and gamma band, no significant discrimination between non-target and target epochs was observed.

A significant MANOVA effect was also detected for the factor position (p = 0.01), whereas no interaction between stimulus and position was calculated. ANOVAS revealed effects related to the electrode position for the SAFs of the total band (p = 0.003), the theta band (p = 0.003) and the alpha band (p = 0.006). Subsequent analyses of contrast delivered that total, theta and alpha SAFs for electrode position Fz can significantly be distinguished from the two other positions. The same is the case for position Pz, but not for Cz. With respect to the electrode-specific average SAF values, this means that the spectral amplification factors for the total, theta and alpha band monotonically decrease from position Fz to Cz to Pz.

(2) Concerning prestimulus power values a significant MANOVA effect for the factor group (table 2) was found for depressives versus controls (p = 0.006), as well as for schizophrenics versus controls (p = 0.0002). ANOVAs for the individual frequency bands (table 3) revealed a significant increase of the gamma power for the depressives compared to controls (p = 0.005), and a significant reduc-
Table 2. Illustration of significant MANOVA results (factor group) for the different frequency bands

<table>
<thead>
<tr>
<th></th>
<th>Depressives vs. controls</th>
<th>Schizophrenics vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestimulus power</td>
<td>p = 0.006 (λ = 0.740)</td>
<td>p = 0.0002 (λ = 0.721)</td>
</tr>
<tr>
<td>Amplification factors</td>
<td></td>
<td></td>
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<tr>
<td>Non-target</td>
<td>-</td>
<td>p = 0.003 (λ = 0.784)</td>
</tr>
<tr>
<td>Target</td>
<td>p = 0.007 (λ = 0.678)</td>
<td>p = 0.0001 (λ = 0.660)</td>
</tr>
</tbody>
</table>

(λ stands for Wilk’s lambda).

Table 3. Illustration of significant ANOVA results (factor group) for the different frequency bands

<table>
<thead>
<tr>
<th></th>
<th>Depressives vs. controls</th>
<th>Schizophrenics vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestimulus power</td>
<td>↑ gamma (p = 0.005; F₁,63 = 8.59)</td>
<td>↓ theta (p = 0.002; F₁,63 = 10.34)</td>
</tr>
<tr>
<td>Amplification factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-target</td>
<td>-</td>
<td>↓ delta (p &lt; E–5; F₁,83 = 23.53)</td>
</tr>
<tr>
<td>Target</td>
<td>↓ alpha, ↓ gamma (p = 0.002, 0.04; F₁,63 = 10.54, 4.43)</td>
<td>↓ delta (p = 0.0006; F₁,83 = 12.81)</td>
</tr>
</tbody>
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↑ means significant increase, ↓ means significant decrease.

For depressives and controls under non-target condition no significant effects were found for the factor group (tables 2, 3). On the other hand, under target condition a significant MANOVA group effect was observed (p = 0.007). Subsequent ANOVAs yielded reductions of the spectral amplification factors of the alpha (p = 0.002) and gamma band (p = 0.04) for the depressives compared to controls. No interactions between group and electrode position were detected.

For the schizophrenics and controls significant MANOVA group effects were found under non-target (p = 0.003), as well as under target condition (p = 0.0001). In both cases, subsequent ANOVAs yielded significant reductions of the SAFs of the delta band (non-target condition: p < E–5; target condition: p = 0.0006). Again, no group × position interactions were calculated.

All healthy subjects correctly counted and marked the less frequent target trials. The average rate for pressing the button when a non-target stimulus appeared could be neglected because it was so low (range: 0–1; mean = 0.2 ± 0.4). Schizophrenics had a higher overall rate of incorrect button pressing (range 0–14; mean = 3.5 ± 4.5) and so did depressives (range 0–19; mean = 2.2 ± 3.4).

A direct comparison between the depressive and schizophrenic patients revealed a reduced alpha amplification for the depressives (p = 0.001) under target condition, and a reduced delta amplification for the schizophrenics (p = 0.01) under non-target condition (but not under target condition). Anyhow, since the two diagnostic groups were quite different in age and gender, the direct comparison should be interpreted with caution.

Discussion

The aim of the present study was to elucidate the mechanisms underlying altered P300 generation in schizophrenia and depression by a frequency-based approach. For this purpose, we evaluated spectral amplification factors for different frequency bands under target and non-target condition. As Basar [17] pointed out, the amplification of certain EEG frequencies during generation of evoked or event related potentials can be understood as a frequency-specific synchronisation and phase coupling between individual neural cell assemblies rather than as a frequency amplification within the assemblies. In this sense the P300 wave seems to represent a phase-reordered continuation of the prestimulus EEG. An increase of P300 relevant frequencies in the prestimulus EEG consequently should result in increased P300 target response. This idea is supported by the findings of Intriligator and Polich [22], who reported a positive correlation between background EEG spectral power and P300 amplitude with the strongest relationship in the delta, theta and alpha1 range. In this context, spectral amplification factors allow a frequency specific analysis of P300 responses taking into account background EEG effects. As a general result we found that target responses can be differentiated best from non-target trials by the amplification factors for the delta and theta band. This means that auditory P300 responses in comparison to 'plain' evoked potentials are accompanied by a pronounced frequency
amplification in the delta and theta range, which is in accordance with the strong correlation between background EEG and P300 responses observed for these frequency bands [22]. Similar results were previously reported by Basar et al. [20] and Basar-Eroğlu et al. [21], who supposed that delta and theta responses might be correlates of selective attention and decision making. We moreover observed that the theta and alpha amplification decreases from the anterior to the posterior medial region.

The comparison between spectral amplification factors of depressive respectively schizophrenic subjects versus controls revealed two completely different patterns. For the depressive patients, we found no alteration of the non-target responses, but a reduced spectral amplification of the alpha and gamma band under target condition. On the other hand, we observed a pronounced reduction of delta amplification for the schizophrenic patients under both non-target and target conditions. The amplification factors were evaluated by the geometric average of individual single-trial amplification values. Therefore, diminished SAFs cannot be deduced from a higher variability of single trial latencies. Anyhow, several earlier studies failed to find experimental evidence that a higher variability of single trial P300 latencies contributes to a decreased average P300 amplitude in schizophrenic [6, 7, 23] or depressive patients [13, 14, 24].

Since the P300 response was found to be generally accompanied by a delta, theta and alpha amplification, diminished alpha reinforcement of target responses in depressive patients respectively reduced delta reinforcement in schizophrenic patients are compatible with smaller P300 amplitudes reported for the two diagnostic groups [10]. The decrease of gamma SAFs possibly relies on a compensatory effect related to the increased prestimulus gamma power observed in depressive patients. Alpha and gamma SAF reductions were detected only under target condition in the depressive subjects, which might be a functional correlate to the loss of interest and difficulty in concentrating seen in those patients. On the other hand, amplification values remained unaltered compared to controls under non-target condition, which could mean, that plain auditory information processing (related to evoked potentials) is not impaired in depressive disorder.

In contrast to this, schizophrenic patients exhibited a highly significant reduction of delta amplification factors under both non-target and target conditions. This could imply that in schizophrenia not only selective P300 processing, but also plain evoked potential processing is severely disturbed, which in the extreme may lead to perceptual abnormalities and hallucinations. Basar-Eroğlu et al. [21] compared the frequency-specific responses under an omitted stimulus paradigm and a common oddball paradigm. Both paradigms include focused attention and signal detection, but the oddball experiment additionally involves matching for target recognition and decision making. Comparison of the two paradigms revealed a pronounced increase of the delta response for the oddball paradigm. Basar et al. [18] analysed evoked potentials caused by stimuli at the hearing threshold, where subjects are supposed to be involved in decision making, and similarly found a very pronounced response in the delta range. Hence, they concluded that delta amplification is essential for sensory matching and decision making. In this context, the highly significant reduction of delta amplification, which we detected in schizophrenic patients, might reflect a severe impairment of sensory matching and decision making related to the distractability and deficits in selective attention, which are clinically observed in schizophrenia.

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References

