Negative Symptoms in Neuroleptic-naïve Patients with First-episode Psychosis Correlate with QEEG Parameters

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Abstract

Introduction: While several studies have shown an association of QEEG band power with negative symptoms in patients with schizophrenia, this has not yet been investigated in a sample with neuroleptic-naïve first-episode patients (NNFE) up to now. From literature we hypothesized delta (0.5–4 Hz) and theta (4–8 Hz) power to be augmented and alpha (8–12 Hz) power to be decreased with increased negative symptoms in NNFE.

Materials and methods: The sample consisted of 27 NNFE. Psychopathology was rated with the Scale for the Assessment of Negative Symptoms (SANS). EEG was recorded from 21 electrodes according to the 10/20 system. Spectral analysis was performed on mean power of 8 electrodes in seven frequency bands after artefact removal. Linear regressions were calculated with log transformed power as dependent and psychopathology as independent variable. We controlled for medication, drugs, age, sex, education and day time of EEG recording.

Results: A positive correlation of SANS global scorewith power in delta and theta frequency bands could be confirmed in NNFE. In the alpha1 (8–10 Hz) band we found no significant correlation with negative symptoms and in the alpha2 (10–12 Hz) band therewas a positive correlation with SANS (p=0.069). Beta1 (12–15 Hz) power also correlated positively with SANS.

Discussion: The present results confirm the correlation of negative symptoms with power of slow frequency bands. In addition to previous studies in chronic schizophrenia patients, the effect was shown in NNFE, which is compatible with augmented slow wave power being a marker for negative symptoms in psychosis.

1 Introduction

QEEG slow wave excess (delta and theta) is considered a robust organic sign of schizophrenia and has been found in medicated as well as in unmedicated patients (John et al., 1994; Boutros et al., 2008). Most studies also found a decrease in alpha power (Boutros et al., 2008) and reported a predominantly frontal localization of these effects (Wuebben and Winterer, 2001; Mientus et al., 2002).

As schizophrenic syndromes are clinically heterogeneous, the abnormalities might result from different etiologies. One major aspect within the phenomenological entity of "schizophrenia" is the occurrence of negative symptoms. Therefore, it is of interest to investigate the association negative symptoms with EEG spectral power variations as a physiological marker for this clinically observed phenomenon. Negative symptoms are consistently associated with increased slow wave activity (Gattaz et al., 1992; Gerez and Tello, 1995; Gerez and Tello, 1995; Harris et al., 1999; Winterer et al., 2000; Sponheim et al., 2000). The results for the alpha band are rather inconsistent: decreased alpha activity (Sponheim et al., 2000; Merrin and Floyd, 1996) as well as augmented alpha activity (Gerez and Tello, 1995) has been found in association with negative symptoms. Finally Harris et al., (1999) found increased beta band activity in relation to negative symptoms. For an overview, see Table 1.

Insert Table1

While slow wave excess in patients with stronger negative symptoms seems to be a stable result, other findings such as power alteration in the alpha band differ between studies. These differences in results might depend on the current illness state rather than the diagnosis itself, or even on medication or alertness.

This study aims to confirm the presence of slow wave augmentation in patients with negative symptoms in NNFE. This would underline this finding as being independent of neuroleptic medication on one hand. On the other hand it would be in favour of the hypothesis that the slow wave phenomenon has characteristics of a trait marker because it is already present in a very early stage of the disease.

Concerning the alpha and beta frequency ranges most studies found an alpha decrease. Therefore, our second hypothesis was an alpha decrease with augmented negative symptom score.

2 Materials and methods

2.1 Subjects

We recruited patients with a first episode of psychosis from the early Basel "Prediction and early detection of psychosis - a prospective multilevel approach" study, which aims to improve the early detection of psychosis. The multi-domain assessment approach used in this study covers psychopathological, neuropsychological, neurophysiological, and neuroimaging investigations. The study design and preliminary results of the study have been described in detail elsewhere (Riecher-Rossler et al., 2007).

Patients with suspected psychosis were referred from general practitioners, psychiatrists in private practice, and from the Psychiatric Outpatient Department of the University Hospital of Basel. Inclusion criteria were defined according to Yung et al. (1998) based on the Brief Psychiatric Rating Scale (BPRS). Patients with previously diagnosed schizophrenia, substance-induced psychosis, age below 18 years, inadequate knowledge of the german language, and intelligence below IQ of 70 were excluded.

We analyzed data of 27 (11 women and 16 men) neuroleptic-naïve first episode (FE) patients. Mean age was 32 (± 8.9 SD) years. The actual medication of the participants were: antidepressants (2 citalopram and 1 paroxetin) and benzodizepines (3 lorazepam, 1 oxazepam). The benzodiazepines were prescribed for sedation. 8 patients used cannabis. The ICD-10 diagnoses of our patients were as follows: 16 patients with "paranoid schizophrenia", 7 patients with "acute polymorphic psychotic disorder with symptoms of schizophrenia", 3 patients with "undifferentiated schizophrenia", and 1 patient with "hebephrenic schizophrenia". After complete description of the study to the subjects, written informed consent was obtained from all participants. The study was approved by the local ethics committee (Ethikkommission beider Basel, EKBB).

2.2 Psychopathological Ratings

Patients were rated with the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) which consists of five subscales that evaluate aspects of negative symptoms: alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attentional impairment. We calculated SANS global score by counting one point for every existent item. The mean SANS global score was 7.4 (standard deviation: 4.6, median: 8, minimum:0, maximum:18) and the variable was normally distributed.

2.3 EEG - Data Acquisition

Routine EEG recordings were performed in a quiet room with patient either sitting or lying in supine position with eyes closed; the recordings lasted about 20 minutes and included several episodes with opening and closing of eyes.

EEG data were digitally recorded with 21 gold cup electrodes placed according to the international 10/20 system. Impedances were kept below 5 kΩ. Amplifiers were calibrated using a 50 µV square pulse. Sampling frequency was 250 Hz with high- and low pass filters set to 0.5-120 Hz. All channels were referenced to linked ears. EEGs were recorded with Alliance Works for Windows NT^{TM}.

Raw EEG data were converted to European Data Format with Nicolet Data Converter.

The converted data were then read into Brain Vision Analyzer software (© Brain Products GmbH, Munich, Germany; BVA). With BVA we selected 19 electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz), recalculated the reference to average and set the high- and low pass (Butterworth) filters to 0.5 – 120 Hz. We then removed eyes open sequences that had been marked by the laboratory assistants during the recording with the tool "Segmentation" of BVA.

2.4 Artefact Rejection

To ensure a high validity of the analysis Boutros et al. (Boutros et al., 2008) recommend a minimum of 25 artefact free segments of 2 seconds duration. To conserve a maximum of EEG recording we developed a semi-automatic standard operating procedure (SOP) to remove artefacts. The procedure can be explained in three steps.

1. Visual inspection of the EEG recording was performed, obvious artefacts (e.g. electrode artefacts), except for those caused by eye movements, were manually removed with the tool "Raw Data Inspector" of BVA.

2. In order to remove well defined sources of artefact, an ICA (Independent Component Analysis) was performed with BVA. Once the independent time courses of different brain and artefact sources are extracted from the data, corrected EEG signals can be derived by eliminating the contributions of the artefactual sources. The ICA has been demonstrated to

reliably isolate artefacts due to horizontal and vertical eye movements, heart and to certain extent muscle or line noise (Jung et al., 2000).

3. In a last step the already corrected EEG was visually inspected by an experienced neurophysiologist who was blind to the patient's symptoms. He cut further artefacts not readily removed in steps 1 and 2 from the EEG recording: muscle, movement and electrode artefacts; patients with EEGs containing deeper sleep than stage A of Loomis et al. (1937) and with EEGs that showed EEG-identifiable pathologies (e.g. generalized epilepsy) were excluded.

After artefact-removal, EEG was divided in segments of two seconds. The remaining EEG recordings had a minimum length of 69 two-second-segments (over 2 minutes), an average of 172 (over 5 minutes) and a standard deviation of 45 segments.

2.5 Analysis and Statistics

Power was calculated with Fast Fourier Transformation (Hanning Window, 10% taper length) using Brain Vision Analyzer Software for 0.5 Hz bins from 0.5 Hz up to 30 Hz over 19 electrodes and then exported into R-Software (R Development Core Team, 2007) for statistical analysis.

The FFT output data over the 0.5 Hz bins were combined to delta (0.5-4 Hz), theta (4-8 Hz), alpha1 (8-10 Hz), alpha2 (10-12 Hz), beta1 (12-15 Hz), beta2 (15-25 Hz) and beta3 (25-30 Hz) bands. Analyses were performed on average power of the 8 electrodes used in the study of Gross et al. (1996) over the anterior half of the scalp (Fp1, F3, C3, Fz, Cz, Fp2, F4, C4) (other locations were not tested to keep the number of variables small). EEG variables were then log transformed to achieve normal distribution.

In a first step of data analysis we controlled for the following confounding factors: age, gender, education, day time of recording, use of tranquilizers, antidepressants, and cannabis

by calculating correlations of these confounders with the power in every band. Confounding factors that were significant at a conservative level of p < 0.1 were taken into account in the next step.

We then performed one linear regression analysis for every band. Power was used as dependent variable. The psychopathological ratings were taken as independent variables, and we controlled for the effect of the previously selected confounding factors by including them as further independent variables into the regression model of the band in which they were relevant. We then dropped non relevant explaining variables from the models using a stepwise backwards elimination procedure based on Akaike's information criterion (AIC) as it is implemented in the R software for statistical computing. However, in case the negative symptom variable was dropped by this automatic procedure we decided to leave it within the model because it is in the focus of interest of the actual study.

3 Results

The confounder analysis of step one revealed that day time of EEG recording is a relevant confounder in the delta (r = 0.34, p = 0.083), theta (r = 0.34, p = 0.085) and the alpha1 (r = 0.33, p = 0.096) bands. Only this variable was initially included in the regression models.

The regression analysis showed a significant effect of negative symptoms in the delta (p = 0.011), theta (p = 0.026) and beta1 (p = 0.009) and a trend (p = 0.069) in alpha2 bands. In these frequency-bands power increases in correlation with stronger negative symptoms. For details of regression models see Table2.

Insert Table 2

To facilitate comparison with results from other studies, we plotted the correlation (Spearman) of power in 0.5 Hz frequency bins with SANS global score instead of using predefined bands (Figure I).

Insert Figure 1

3.1 Additional confounding factor analysis

We had to initially preselect confounding factors to include in the statistical analysis to keep the number of variables small. However there is a danger that the confounding factors that did not correlate with power –as tested previously- could still have an effect of the results. Therefore we performed post hoc sensitivity analysis of the confounding factors including them one by one into the regression models: All additionally included confounding factors (including medication, age, gender, education and cannabis use) were dropped by a stepwise backwards elimination process and had no effect on the results of the paper.

Still, intake of benzodiazepines was especially problematic, since it was significantly related with the negative symptom score (t-test, p-value = 0.017). To additionally rule out the effect of benzodiazepine, we recalculated the effect of negative symptoms by excluding the 4 patients on benzodiazepines: We observed the same significant effects (in the delta, theta and beta1 bands) and also a trend in the alpha2 band in this reduced and more homogeneous sample (N = 23).

We applied the same methods for the patients with cannabis use: The correlation of cannabis use with the negative symptom scoring was close to zero (r = 0.07, p-value = 0.719). Excluding patients using cannabis on a regular basis (N = 20 patients left) we still found the same effects whereas the previously significant result in the theta band became a trend (p = 0.058) and the effect in alpha2 became significant (p = 0.04).

4 Discussion

This study shows increased power in the EEG frequency ranges from 0.5-8 Hz and from 10.5-15 Hz in correlation with negative symptoms in neuroleptic-naïve patients with a first episode of psychosis.

Several factors could potentially affect this result: The level of alertness influences the EEG frequency pattern but was controlled in this study by repeatedly opening and closing the eyes. Moreover, we tried to control for this effect by excluding EEG recordings with signs of sleep deeper than stage A of Loomis (1937) and by controlling for the time of day of the recording. Power in delta, theta and alpha1 correlates positively with progressing time of day of the EEG recording. This phenomenon is probably an expression of changes due to the circadian rhythm (Cajochen and Dijk, 2003). When adding this factor into the regression analysis the effect of negative symptoms was revealed to be more pronounced.

Another potential problem of this study is related to the muscle activity recorded by the EEG: As we wanted to conserve a maximum of segments, it was not always possible to remove muscle noise to 100 %. Due to this, one limitation of this study could be the effect of the remaining muscle artefacts. Surface EMG activity goes down as far as 12-15 Hz and overlaps with beta band (Gotman et al., 1975; O'Donnell et al., 1974). Goncharova et al. (2003) demonstrated that frontalis and temporalis muscle had maximum amplitude frontally from 20 to 30 Hz and temporally from 40 to 89 Hz. This means that delta, theta and alpha band results remain largely unaffected but there might be a chance for beta band results to be slightly influenced by muscle artefacts.

A further difficulty is of course the use of medication and cannabis, as psychoactive compounds affect the electrical brain activity in many ways (Wauquier, 2005). The results of this study were probably, even if slightly, contaminated by the use of different substances.

Since no chemical tests were performed simultaneously with EEG recordings, controlling statistically based on clinical data is the best available approximation to homogenous experimental setting. Therefore, one major limitation of this study was the use of benzodiazepines. Benzodiazepines are known to induce changes in the beta activity. The frequency and amplitude of these changes depend on various factors like age, type of medication and environmental conditions (Wauquier, 2005). The same accounts for the use of cannabis that has been shown to induce an alpha augmentation (Struve et al., 1999). However, with the additional post hoc exclusion of patients using benzodiazepines or cannabis described in the results section we assume that the observed changes in the power of theta and delta frequencies in relation to negative symptoms are not due to effects of benzodiazepines nor cannabis.

One of the strong aspects of this study is that we can rule out the effect of neuroleptic medication as all our patients were neuroleptic naive. Earlier studies with medication-free patients applied withdrawal periods between 24 hours and 2 weeks. Neuroleptics are known to influence EEG frequencies and their effects differ between substances (Wauquier, 2005). Additionally, little is known about the long term effects of neuroleptics on EEG frequencies (Wauquier, 2005), and therefore, having patients medication-free for a limited time period adapted to the pharmacokinetic properties of the substance may not be sufficient to control for all their effects.

Keeping these limitations and advantages of our study in mind, our first hypothesis derived from literature is supported: low frequency band power is linked with negative symptoms in neuroleptic-naïve schizophrenic patients with a first psychotic episode. For delta (0.5-4 Hz) our results are comparable to the studies of Gattaz et al. (1992), Harris et al. (1999), Sponheim et al. (2000), Winterer et al. (2000) and Gross et al. (2006); for theta (4-8 Hz) they are in line with the studies of Gerez and Tello (1995), Sponheim et al. (2000) and partly with Winterer et al. (2000).

Many studies (Boutros et al., 2008) reported group differences of healthy controls compared to schizophrenic patients in slow wave activity (δ and θ). The results of the present study and others (Gattaz et al., 1992; Gerez and Tello, 1995; Harris et al., 1999; Sponheim et al., 2000; John et al., 2007; Gross et al., 2006) point to the hypothesis that these group differences are mainly explainable by negative symptoms in schizophrenic patients. Correlation of slow wave activity with negative symptoms has consistently been found in schizophrenic patients while correlations with positive symptoms are a inconsistent result in literature (e.g. Omori et al. (1995) vs. Merrin et Floyd (1996)).

The second hypothesis derived from literature linking a decrease of alpha power with negative symptoms is not confirmed. Instead, we found positive correlations with negative symptoms, the opposite effects of our hypothesis, in the alpha2 (10-12 Hz, $p = 0.069$) and beta1 (12-15 Hz) bands in these patients in a very early stage of schizophrenia. While this is in contradiction to the studies of Merrin and Floyd (1996) and Sponheim et al. (2000), our results are similar to Gerez and Tello (1995) who found an alpha (7.5 -12.5 Hz) augmentation in patients in remission 2 years after a first episode of schizophrenia.

If we are allowed to speculate on the psychophysiological mechanisms we propose that both negative symptoms and altered cortical rhythms represent dysregulation of prefrontal and limbic circuits linking the basal ganglia, thalamus and cerebral cortex. Interestingly, altered cortical rhythms have observed also in dementia of parkinsons' disease which begins as a dysexecutive syndrome with some similarities to negative symptoms of schizophrenia, and which most likely results from malfunction of these circuits (Van Cott and Brenner (2005)).

To the best of our knowledge this is the first study on this topic with a pure sample of neuroleptic naïve first episode patients. The paper states that there is a correlation between negative symptoms and EEG power in delta, theta and beta1 frequency bands at a very early stage of the disease. While this correlation is found in the group, it is not possible to decide ultimately whether the observed phenomenon is a marker of state changing with symptom

strength in the individual or a diagnostic marker of the disease ("trait marker"). A clear differentiation between these two possibilities can be drawn only from repeated measures obtained from the same individuals at times of relative health and at times of increased symptoms. This would be a very interesting issue to address in the future.

Another interesting question is whether the observed phenonomenon is also present in the prodromal phase of the disease. In a next step, we will therefore investigate this question in individuals in an at-risk mental state for psychosis. In these individuals EEG might contribute to the identification of those, who are in the prodromal phase of schizophrenia with purely negative symptoms (Riecher-Rossler et al., 2007).

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