Electrophysiological examination of mismatch negativity and emotional processing in schizophrenia

Doctoral theses

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INTRODUCTION

Schizophrenia is a heterogenous, intensively studied disease with unclear etiology. Several fields of science are focusing on schizophrenia because its relatively high prevalence with severe symptoms and impact on quality of life.

According to the dysconnection hypothesis of schizophrenia, the main problem is the disturbance of functional and anatomical connections of neurons between and within brain regions. The hypothesis integrates every symptoms of the disease, including positive, negative, cognitive and psychomotor symptoms, and the results of the genetic, neuroimaging and electrophysiological studies.

Electrophysiological methods are widely used for studying information processing and dysconnection. In the present study we used electrophysiological methods.

The importance of our first paradigm, mismatch negativity (MMN) is that it is one of the most reproducible difference between the normal population and schizophrenia, and is still a potential biomarker.

While deficits in auditory MMN are well known in schizophrenia, only a few studies investigated impairments in predictive visual processing in schizophrenia. In this work I studied whether automatic predictive processing of elementary features is also impaired in schizophrenia.

The second study is also embedded in the theoretical framework of dysconnectivity, where we also used visual stimulus presentation. In this part we studied another disturbed function, emotional processing in schizophrenia with electrophysiological methods. In the second study we measured the change in beta desynchronization, which represents the neuronal connectivity, during presentation of images with different emotional content.

OBJECTIVES

In the present study we have analysed more aspects of electrophysiological data of schizophrenic patients and healthy controls.

During the analysis of mismatch negativity, our aim was to answer the following questions:

1. Is there a difference in mismatch negativity in case of elemental visual (spatial orientation) changes between schizophrenic patients and control group?
2. Is there any connection between supposed decrease in mismatch negativity and the symptom severity and psychosocial functioning of patients with schizophrenia?

During the analysis of emotional processing, our aim was to answer the following questions:

1. Is there a difference in beta desynchronisation during visual emotional content presentation between schizophrenic patients and control group?
2. Is there any connection between supposed difference and the symptom severity and psychosocial functioning of patients with schizophrenia?

METHODS

Altogether 28 patients with schizophrenia and 27 healthy controls matched in age, gender and education participated in the study. EEG was recorded using 128 channels in the two experimental blocks.

Visual stimuli were presented on a computer screen, stimuli appeared on a dark-grey background at a viewing distance of 0.5 m. We used Presentation 13.0 software for stimuli presentation. Built-in and self-developed Matlab functions as well as the freeware EEGLAB toolbox were used for off-line data analyses. Before statistical analysis we preprocessed the EEG data.

Using an oddball paradigm, horizontal stripes of Gabor patches were presented as frequent standards and vertical stripes as rare deviants in one block. Stimulus probabilities were swapped in the other block. Mismatch responses were obtained by subtracting responses to standard from those to deviant stimuli. We applied high frequency Gabor patches (5 cycle/degree) similarly to previous investigations. The standard stimulus occurred five times often than deviant. In the other block the standard and deviant conditions were swapped. The sequence of the two blocks was counterbalanced between subjects. A total of 100 deviant and 500 standard stimuli were presented in each block. We analyzed the ERPs in three occipito-parietal and three prefrontal regions of interests.

Brain responses were analyzed with repeated measures analysis of variance (ANOVA) with study group, stimulus type, region and their interaction as independent factors. Group differences and corresponding effect sizes presented in terms of Cohen's d. Interaction was analyzed further using post hoc t-tests. In order to correct for Type I errors the Hochberg correction for multiple comparisons was used.

In the second study a total of 180 pictures were presented from the International Affective Picture System (IAPS) of these, 60 depicted pleasant, 60 neutral and 60 unpleasant scenes. Each picture was presented for 800 ms, and preceded by a fixation cross. This was a passive paradigm, and no response was needed by the subjects. The channels were divided into 5 regions of interest: a frontocentral, two temporal, and two parieto-occipital regions. Stimulus-related low beta (12–16 Hz) activity changes were measured by the event-related spectral perturbation (ERSP), which provides a 2-D representation of mean change in spectral power (in dB) from baseline.

The different effects on ERSP were tested by three-way analyses of variance (ANOVA). To investigate the interactions, post-hoc pairwise contrasts were conducted. Since between-group comparisons were evaluated, Hochberg correction for multiple comparisons was applied. The associations of PSP and PANSS scoreswith ERSPwere investigated by partial Pearson correlation adjusted for the effect of age.

RESULTS

Between group comparison of mismatch negativity

The main effect of study group was not significant (F (1, 53)= 0.2; p = 0.66), the difference between regions reached marginal significance (F (5, 53) = 2.25; p = 0.06; the maximum value was detected in the sagittal occipital-parietal region), while the interaction between study group and region was significant (F (5, 53) = 2.45, p b 0.05).

After correction for multiple comparisons, we found significant difference between standard and deviantmismatch responses in the control group in all regions, while in the patient group these responses did not reach significance in any of the regions. The differences between study groups were significant in all regions except in the left prefrontal region after correction (right prefrontal Cohen's d = 0.77, p = 0.007, sagittal prefrontal Cohen's d = 0.62, p = 0.033, left paritetooccipital Cohen's d = 0.72, p = 0.011, right parietooccipital Cohen's d = 0.77, p = 0.007, sagittal parietooccipital Cohen's d = 0.68, p = 0.019).

It is worth noting that the study group main effect was not significant because the direction of difference between groups was reversed in the anterior and posterior regions due to the posterior negativity and anterior positivity effect.

We found no correlations between clinical variables such as age, illness duration, PANSS scores, antipsychotic doses in terms of CPZ equivalents, functionality as measured by PSP and mismatch responses after correction for multiple testing.

Between group comparison of low beta desynchronisation negativity

A beta desynchronization (ERD) was observable both in low beta ERD, and in high beta ERD in both study groups, in all regions and to all conditions.

There was a significant main effect of study group ($F(1,53) = 4.9$, $p = 0.03$) on beta ERD in the 300–800 ms time window, indicating stronger ERD in controls relative to patients, while the main effect of stimulus condition and the interactions of study group with stimulus condition and region were not significant.

In the 900–1100 ms timeframe the main effect of study group was significant on beta ERD ($F(1,53)=10.8$, $p=0.002$), indicating stronger ERD in controls relative to patients. A significant main effect of stimulus condition ($F(2,53) = 5.9$, $p =$

0.005) was also detected indicating a stronger low beta ERD to negative relative to neutral ($t = 3.3$, $df = 53$, $p = 0.002$) and positive ($t = 2.4$, $df = 53$, $p = 0.02$) stimulus conditions, Moreover region had a significant effect on beta ERD ($F(4,53) = 35.7$, $p < 0.0001$) with maximum beta ERD in the right parieto-occipital region in both study groups.

While the largest difference were found between study groups in the right temporal and parieto-occipital regions for negative stimulus condition, the correlations between low beta ERD and clinical parameters were also analyzed in these regions in the patient group. Low beta ERD correlated significantly with PANSS negative score in both time windows in the right parieto-occipital (300-800 ms: Pearson $r = 0.58$, $p = 0.002$; 900-1100 ms: Pearson $r = 0.48$, $p = 0.02$), and in the right temporal regions (300-800 ms: Pearson $r = 0.5$, $p = 0.01$; 900-1100 ms: Pearson $r= 0.39$, $p= 0.05$) for the negative stimulus condition. Higher negative symptom severity was associated with decreased beta ERD.

In the first timeframe the PANSS positive subscore showed significant relationship with low beta ERD indicating that higher positive symptom severity was associated with decreased beta ERD to negative stimuli (right parieto-occipital region: Pearson r = 0.42, p = 0.03; right temporal region: Pearson r = 0.44, p = 0.03).

Social functioning as measured by the PSP was also associated significantly with low beta ERD in the patient group. The PANSS negative subscore and the PSP showed very strong negative correlation (Pearson $r = -0.69$, $p = 0.0009$) indicating worse functioning in patients with more severe negative symptoms.

Conclusions

The two parts of this study are focusing on the different aspects of visual perception and information processing, in order to explore more details in information processing disturbances in schizophrenia. In summary, both lower and higher levels of central nervous system structures involved in visual perception are impaired in schizophrenia compared to control persons.

Decreased mismatch negativity refers a deficit in lower level of visual progessing, during simple visual predictive coding process. This is in line with previous study results, applied more complex stimuli, such as motion or emotional facial expressions, indicating that the impairment of the sensory prediction process affects several levels of visual perception in schizophrenia.

Decreased mismatch negativity and decreased beta desynchronisation during negative emotional content stimuli presentation both refers to disturbances of difference detection betwee relevant and irrelevant information.

Both processes play a role in prediction coding and directing attention to important content. The systemic explanation may be the abnormal brain interconnections and related synaptic dysfunction.

Differences in correlation with clinical variables indicate that the degree of reduction in visual mismatch negativity - if schizophrenia has been established - has less correlation (trait marker) with symptom severity and illness duration, while the decrease in beta desynchronization is more pronounced during negative emotional stimuli presentation when the negative symptoms are more severe (state marker for the negative symptoms).

The presented results are consistent with previous literature data and point out that mismatch negativity is also present at the elemental levels of visual modality, emotional processing disturbance can be well investigated at the oscillation level (ERSP), and both can be interpreted in the context of the dysconnection hypothesis of schizophrenia.

PUBLICATION RELATED TO THE DISSERTATION

Farkas K, Stefanics G, Marosi C, Csukly G. Elementary sensory deficits in schizophrenia indexed by impaired visual mismatch negativity. Schizophr Res; 166(1-3) pp. 164-170. (2015) IF: 4.453

Csukly G, **Farkas K**, Marosi C, Szabo A. Deficits in low beta desynchronization reflect impaired emotional processing in schizophrenia. Schizophr Res; 171(1-3) pp. 207-214. (2016) IF: 4.453

OTHER PUBLICATION

Farkas K, Siraly E, Szily E, Csukly G, Rethelyi J. [Clinical characteristics of 5 hospitalized 3,4-methylenedioxypyrovalerone (MDPV) users]. Psychiatr Hung; 28(4) pp. 431-439. (2013)