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Visual mismatch negativity among patients with schizophrenia

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Abstract

Event related potentials (ERPs) provide an insight into sensory and cognitive processes in health and disease. Studies of an ERP negative amplitude deflection elicited by a change in a series of auditory stimuli is known as mismatch negativity (MMN). The generation of MMN is impaired in schizophrenia. Its deficit is associated with lower everyday functioning and may be also interpreted as the marker of progression in schizophrenia.

MMN elicited by visual stimuli (vMMN) was described by several research teams, but it has not been investigated in schizophrenia as yet. Using a motion-direction paradigm, we elicited visual MMN in 24 patients with schizophrenia and schizoaffective disorder. The vMMN was computed as differences in areas under curve of visual ERPs to standard and deviant motion-direction stimuli recorded from midline derivations at the interval of 100–200 ms. They were compared between groups of patients with schizophrenia and healthy controls. The significantly smaller vMMN indicated an impaired generation of mismatch negativity in patients with schizophrenia. In secondary analyses there was an association of vMMN impairment among patients with higher dose of medication, lower level of functioning and the presence of deficit syndrome. This impairment appears analogous to the impairment of MMN in the auditory domain and is probably related to early visual information processing. Its relationship to cognitive functioning of patients with schizophrenia deserves further attention.

Keywords: Schizophrenia; Event related potentials; Mismatch negativity; Visual mismatch negativity; Information processing

1. Introduction

Schizophrenia is associated with a disorder of information processing (Callaway and Naghdi, 1982) manifested by cognitive dysfunction (Sharma and Antonova, 2003). Cognitive dysfunction has been studied by neuropsychological (Albus et al., 2006; Bilder et al., 2000; Caspi et al., 2003), psychophysiological and also by electrophysiological means (Braff and Light, 2004). Event related potentials (ERPs) are brain's electrophysiological responses to sensory stimuli and they may serve for the investigation of attentional and preattentional sensory and cognitive processes.

Over the preceding decade, one important focus of electrophysiological research in schizophrenia became "mismatch negativity" (MMN). Mismatch negativity is a negative deflection in event related potentials (ERP) to

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infrequent non-standard (deviant) stimuli that differ from preceding standard stimulation. This early ERP component was first described in the auditory modality (Näätänen et al., 1978). It is thought to reflect automatic detection of change in the early stage of auditory processing (Näätänen and Winkler, 1999). Investigation of MMN is non-invasive, inexpensive, and can be done quickly (Näätänen, 2003). Its reproducibility is comparable with that of neuropsychological testing (Light and Braff, 2005).

Insufficient formation of MMN in patients with schizophrenia has been first described in early nineties (Shelley et al., 1991). More than sixty studies have been published on the relationship between MMN and schizophrenia since then. Most studies found that patients with schizophrenia, irrespective of medication status, had lower MMN amplitudes than healthy controls (Umbricht and Krljes, 2005). MMN has been linked to echoic memory (working memory for sounds) and NMDA neurotransmission (Javitt et al., 1996; Umbricht et al., 2000). The auditory MMN reduction in patients with schizophrenia is associated with global functional impairment (Light and Braff, 2005). Reduction of MMN in chronic schizophrenic patients is associated with the reduction of gray matter volume in Heschl's gyrus of the temporal lobe (Salisbury et al., 2007). Because the first episode patients with schizophrenia appear to have no detectable impairment of MMN (Salisbury et al., 2002), the deficient auditory MMN has been also interpreted as a marker of a progression in schizophrenia.

Most studies of MMN done so far were related to auditory stimuli. There were reports of an analogy to auditory MMN in somatosensory (Kekoni et al., 1997), visual (Tales et al., 1999; Kremláček et al., 2001; Czigler et al., 2007), and olfactory modalities (Krauel et al., 1999).

Although the presence and significance of MMN in the visual modality (vMMN) has been a matter of some controversy, there are a number of studies that support the possibility of memory-based automatic detection of deviance in the visual system (Pazo-Alvarez et al., 2003).

Recently, a study was published on the vMMN impairment in Alzheimer's Disease (Tales and Butler, 2006). To our knowledge, there is no report on the vMMN among patients with schizophrenia as yet. The objective of our study is to test the presence of the impaired generation of mismatch negativity after visual motion stimuli among patients with schizophrenia and schizophrenia related psychosis. We report on vMMN data in a group of patients treated for schizophrenia in a cross sectional study with matched control subjects.

Table 1
Demographic and clinical data of patients (N=24)

	Mean	SD	Median	Range
Age (years)	27.9	9.25	26	19–61
Duration of schizophrenia (years)	7.1	10.04	1.0	1–44
Number of hospitalisations	3.4	1.75	4.0	1–6
Antipsychotic dose (N=23) (mg/day in chlorpromazine equivalents)	366	257	400	100–1100

Table 2
Distribution of antipsychotic treatment

	Antipsychotic	No. of patients
Second generation antipsychotics (SGA)	Olanzapine	10
	Clozapine	5
	Risperidone	2
	Others*	4
First generation antipsychotics (FGAs)	Haloperidol	2
	Others**	3
SGA and FGA combinations***		4

*Ziprasidone, quetiapine, aripiprazole and amisulpiride.
**Flupentixol, fluphenazin enathate, pimoside.
***All combinations were SGA and FGA combinations.

2. Methods

2.1. Participants

We report data on 24 patients with the diagnosis of schizophrenia and schizoaffective disorder who consented to participate. Screening and recruitment took place at the units of a University affiliated Psychiatric Clinic. The clinical and diagnostic assessment was performed by experienced psychiatrists in accordance with Diagnostic Criteria for Research, Classification of Mental and Behavioral Disorders (ICD-10, 1993).

ERP recordings were performed at the Electrophysiological Laboratory of the Department of Pathophysiology of the Charles University Faculty of Medicine.

The patients with the presence or history of vision disorders, neurological disorders and comorbid psychiatric disorders were excluded. The age and sex matched controls for each patient were recruited from students and staff of the University School of Medicine. There were 19 males and 5 females among the patients. Demographic and clinical data of the patients are in

Table 1. The patients were diagnosed as schizophrenia paranoid type in 13 subjects, other types of schizophrenia in 6 patients, schizoaffective psychosis in 4 participants. The single patient with schizophreniform disorder was later rediagnosed as schizophrenia. All patients except for one were on antipsychotic medication at the time of the electrophysiological measurements. The antipsychotics used for their treatment are in Table 2. The mean dose in chlorpromazine equivalents was 350 mg/day (range 0–1100, SD= 262 mg/day).

All subjects with schizophrenia were assessed by Global Assessment of Functioning (GAF) (DSM-IV, 2000) and Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989) by a trained psychiatrist.

All procedures had been explained to patients as well as to control subjects and they all signed Informed Consent. The study was approved by the Ethics Committee of the Charles University Faculty of Medicine in Hradec Králové.

2.2. Procedures

2.2.1. Stimuli

The test paradigm was specifically designed to elicit the visual MMN and was based on a similar study by Tales et al. (1999). It involved presenting a standard stimulus 88% of the time and a random deviant stimulus 6% of the time. In order to prevent the subjects from paying attention to deviant stimuli, they were asked to respond to a random target stimulus that was presented

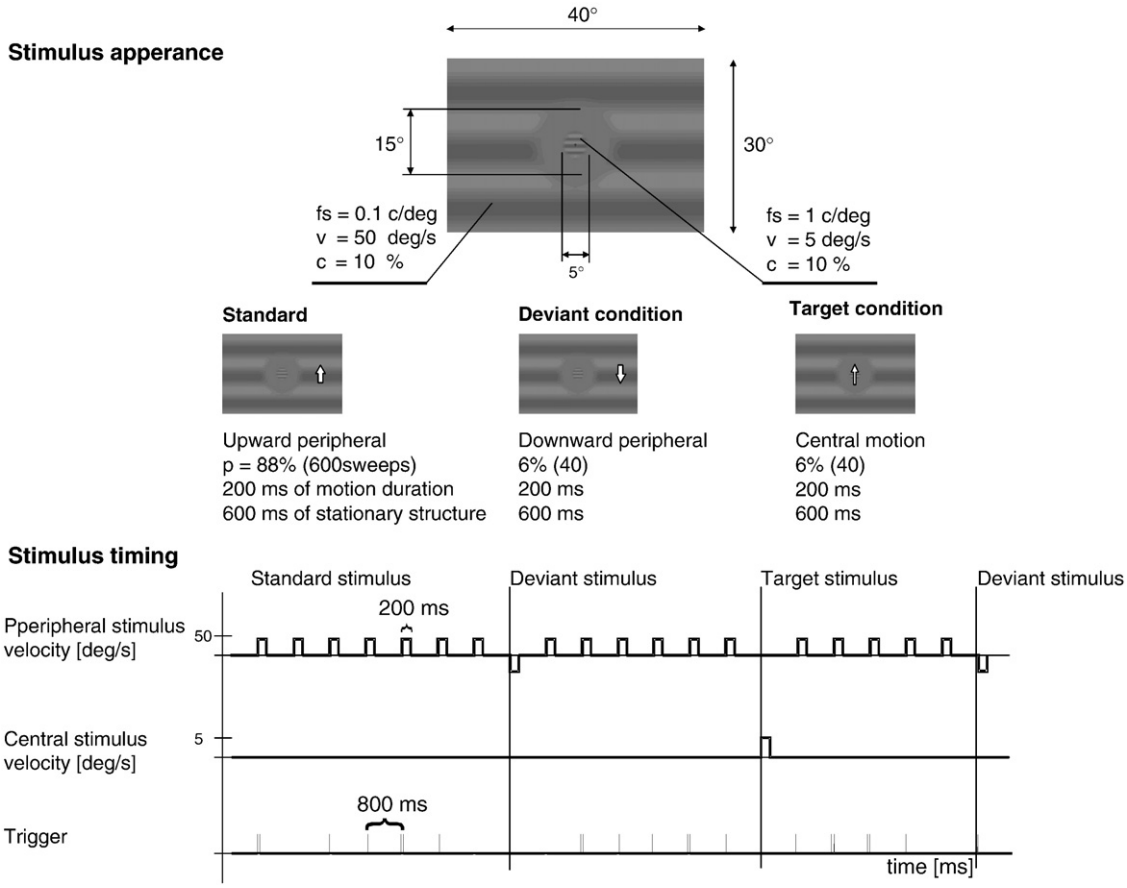

Fig. 1. The figure presents the design and properties of stimuli. The screen with stimuli is in the upper part of the figure. The white arrows in the middle part of the figure demonstrate the direction of the motions in particular stimuli and their order. E.g. the standard condition consisted of the motion of a peripheral stimulus (horizontal grating outside the central 15° of the visual field) moving upwards with a velocity of 50°/s for 200 ms. The pattern remained stationary for a period of 600 ms between stimuli. The other stimuli are displayed in the similar fashion. The stimulus timing diagrams are in the lower part of the figure and show the sequence of events during the recording procedure. The used abbreviations: velocity — *v*; spatial frequency — sf, luminancy contrast (Michelson) — *c*; probability of stimulus occurrence — *p*.

in the central visual field 6% of the time. The subjects had to press a handheld button whenever the target stimulus appeared.

The stimuli consisted of two low contrast (10%) horizontal sinusoidal gratings: one with a spatial frequency (0.1 c/°) outside the central 15° of the field, and a second one with a spatial frequency (1 c/°) inside the central 5°. The standard and deviant stimuli were presented as fast motion (50°/s) in the peripheral visual field. The standard stimulus consisted of 200 ms of upward motion, the deviant stimulus was the downward motion of the same duration. The inter- stimulus interval was 600 ms of stationary pattern (the stimulus onset asynchrony was 800 ms). Fig. 1 presents the spatial and temporal parameters of the stimuli. The stimuli were exposed on a 21 in. computer monitor IIyama with a frame rate of 70 frames per second. The monitor was driven by the program developed in the laboratory (Kremláček et al., 1999). The screen subtended a visual field of 42° × 30° at a 0.5 m viewing distance. The mean stimulus luminance was 17 cd/m^2.

2.2.2. ERP measurements

The ERP acquisition was performed in a darkened, sound attenuated, electromagnetically shielded room with a background luminance of 1 cd/m^2. The subjects sat in a comfortable reclining chair with a head support. They were instructed to fix the centre of the stimulus field. Correct fixation was checked via a CCD camera. Responses were recorded from six unipolar electrode derivations used in the laboratory (Kremláček et al., 2006). The active electrodes were positioned at FZ, CZ, PZ, OZ and at two lateral temporo-occipital locations placed 5 cm to the right and to the left of OZ (OR and OL, respectively). The right earlobe (A2) served as the reference. The signal amplifier (Contact Precision Instruments—PSYLAB, System 5) had a bandwidth of 0.3–

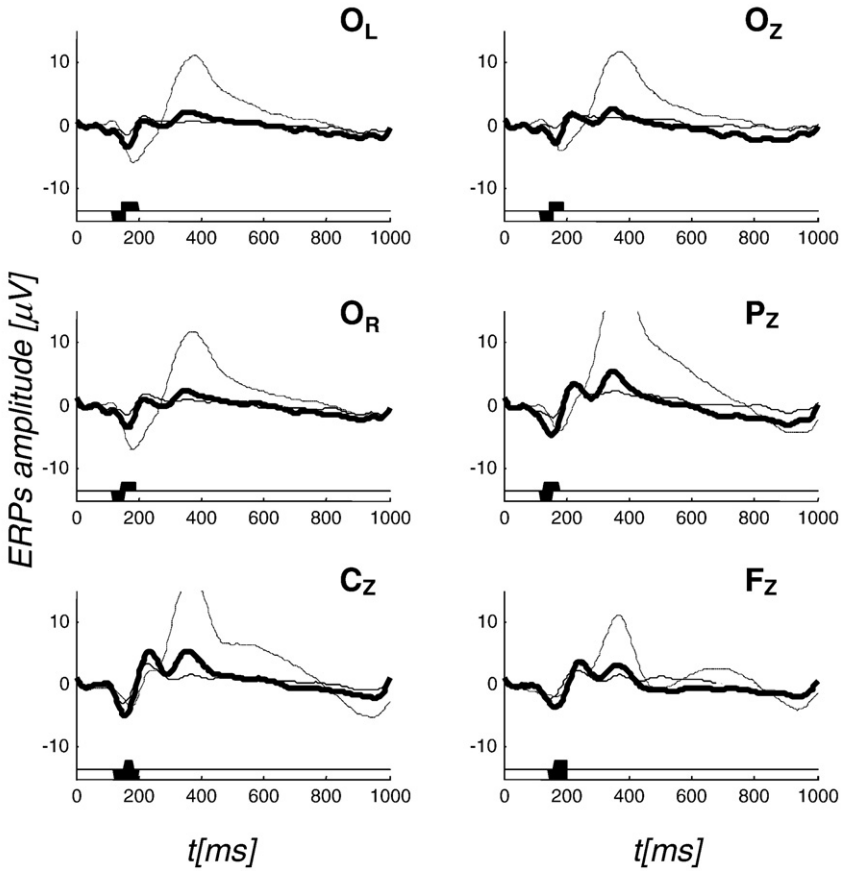

Fig. 2. The grand averages of ERPs to the target stimuli (dashed line), deviant stimuli (solid thick curve) and standard stimuli (solid thin curve). The grand averages represent mean response from 24 control subjects. The derivation of recorded responses is indicated in the right corner of each appropriate plot. The significant differences between ERPs to standard and deviant stimuli are displayed as the black area at the bottom part of each plot. The vMMN was statistically significant in all derivations.

100 Hz. The responses were sampled at a rate of 500 Hz and selectively averaged off-line. Each subject underwent four recording sessions each consisting of 170 stimulus presentations; 150 standard, 10 deviant and 10 target. Ten responses from each of the three stimuli were recorded. The pseudorandom selection of ten standard responses was determined in advance and was maintained for all sessions. For each stimulus condition 40 single ERP sweeps were averaged. The DC level was specified as the mean value of the first 15 samples (30 ms) of each sweep and the DC component was removed before averaging. The averaged signal was digitally filtered by a low pass filter with a cut-off frequency 30 Hz.

2.3. Analyses

Statistical analysis of the recordings was based on the difference between the ERPs elicited by standard and deviant stimuli. This difference represents visual MMN that has been described at different intervals in various studies (for review see Pazo-Alvarez et al., 2003). It appears to vary with the methodology: We inspected visually grand averages of vMMN in controls and subjects with schizophrenia and found the interval of maximal inter-group difference at 100–200 ms, which is analogous to the auditory MMN interval. Area under curve (AUC), computed as integral of the vMMN, approached to zero for similar ERP responses to standard and deviant stimuli and had negative values for more negative ERP to deviant stimuli. The AUC differences between the group of patients and healthy controls were assessed by *T*-test for paired measures. For the exploratory secondary analyses Pearson´s correlations were used. Also, subgroups of patients were generated by median split of variables "duration of schizophrenia", "GAF score" and "mean dose of antipsychotics" and by division according to absence (SDS score = 0) or presence (SDS score > 0) of the deficit syndrome. *T*-tests of differences

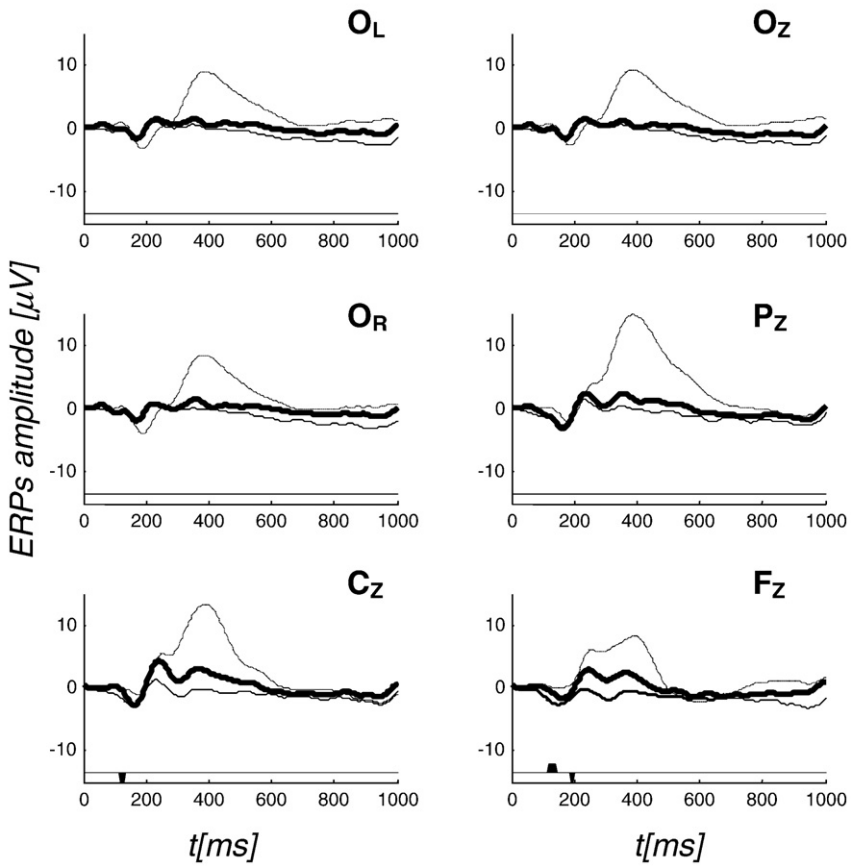

Fig. 3. The grand averages of ERPs to the target stimuli (dotted curve), deviant stimuli (solid thick curve) and standard stimuli (solid thin curve). The grand averages represent mean response from 24 patients. For description of the figure layout see the legend of Fig. 2. As opposed to the control group, in group of patients the vMMN appears only in the frontal derivation.

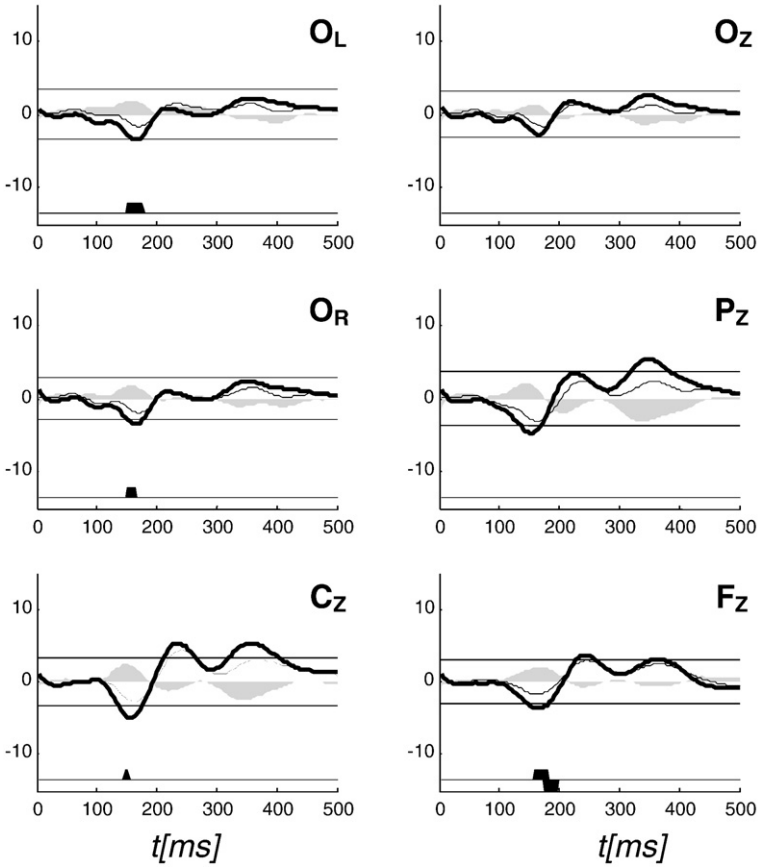

Fig. 4. Comparison of grand averages of ERPs to the deviant stimuli in the group of control subjects (solid thick curve) and the group of patients (solid thin curve). The gray filling marks the difference between responses of controls and patients. The difference was computed by subtracting the area under curve (AUC) after standard stimuli from the AUC after deviant stimuli.

between vMMN values of patients and matched controls in those subgroups were performed.

3. Results

3.1. Differences in responses to deviant motion-direction stimuli in patients and controls

In all subjects with schizophrenia and controls the artefact-free ERPs to motion-direction stimuli were recorded.

The grand averages of event related potentials for different stimuli at all the recording sites in the group of controls are provided in Fig. 2. The corresponding recordings the group of patients are in Fig. 3. The comparison of ERP grand averages to the deviant stimuli between the groups of patients and controls is in Fig. 4.

AUC differences between average responses to deviant and standard stimuli at the 100–200 ms interval are summed up in Table 3 for both groups. They stand for the measure of visual MMN, in analogy to a similar phenomenon in auditory modality.

The positive or higher values of differences in the group of patients correspond with the expectation of smaller negative deflection to deviant stimuli (vMMN

Table 3
The visual mismatch negativity in patients and controls

Interval	Derivation	AUC (μV*/ms)=[AUC deviant stimuli]−[AUC standard stimuli]				
		Patients (N=24)		Controls (N=24)		p
		Mean	SD	Mean	SD	
100–200 ms	O_Z	0.72	51.65	−33.85	59.86	0.048
	O_R	−0.64	48.29	−33.07	61.64	0.049
	P_Z	−3.27	56.20	−44.97	57.52	0.025
	C_Z	16.86	70.26	−23.56	67.02	0.061
	F_Z	30.69	65.14	−24.21	62.28	0.011

deficit) in comparison to control volunteers. The group differences between visual MMN of patients and controls were significant in all the occipital, parietal and frontal midline derivations. The difference failed significance at CZ derivation.

3.2. The associations of vMMN impairment in schizophrenia with other variables

The correlational matrix did not reveal any significant correlations of vMMN with age and the total GAF score.

There were significant Pearson's correlations in CZ and FZ derivations with the daily dose (in mg of chlorpromazine equivalents) of antipsychotics ($r=0.54$; $p=0.006$ in both leads).

There was also a significant correlation with severity coding of deficit syndrome in SDS and vMMN value in FZ ($r=0.55$; $p=0.004$).

3.3. The vMMN impairment in subgroups of patients generated by the median split of clinically relevant variables

3.3.1. Duration of schizophrenia

The significant difference in vMMN between controls and patients with the duration of schizophrenia 3 years and longer was present in midline FZ ($t=2.64$, $p=0.001$) derivation. There were no significant differences in vMMN between controls and patients with the duration of schizophrenia shorter than 3 years.

3.3.2. Total score of global assessment of functioning

There were no significant differences in vMMN amplitude between controls and patients among patients with the GAF score higher than the median, i.e. 74. The differences were retained only in patients with lower level of functioning as indicated by GAF score in the lower half of the range. The differences in patients with low GAF score patients were significant in Ol ($t=2.32$, $p=0.040$), PZ ($t=3.19$, $p=0.008$), CZ ($t=2.33$, $p=0.039$) and FZ ($t=3.05$, $p=0.010$) derivations.

3.3.3. Daily dose of antipsychotics

The significant differences in vMMN between controls and patients were present in midline PZ ($t=2.54$, $p=0.03$), CZ ($t=2.18$, $p=0.04$) and FZ ($t=2.08$, $p=0.04$) derivations in the subgroup of patients with the daily dose of antipsychotic above the median of 375 mg of chlorpromazine equivalent. The subgroup with the daily antipsychotic dose bellow the median retained the significant difference in vMMN only in Fz derivation ($t=2.27$, $p=0.044$).

3.3.4. Presence of the deficit syndrome

In this post hoc analysis, the patients were grouped according to the presence or absence of deficit syndrome in schizophrenia as indicated by the SDS scale. The group of patients ($N=11$) with the present deficit syndrome had significantly different vMMN response in comparison to controls in PZ ($t=3.03$, $p=0.012$), CZ ($t=2.24$, $p=0.048$) and FZ ($t=4.17$, $p=0.001$) derivations. There were no significant differences in vMMN response among patients with the absent deficit syndrome ($N=13$).

4. Discussion

We detected significant deficit in the generation of negative amplitude deflection in visual ERPs induced by deviant stimulus among patients with schizophrenia in comparison to healthy controls. It was consistently detected in the latency range of approximately 100–200 ms since the deviant stimulus. The peak amplitude change was in the midline frontal derivation. To our knowledge, this is the first report of an impairment of the vMMN in patients with schizophrenia.

The existence of an analogous ERP phenomenon in the visual domain was disputed. However, a comprehensive review of studies concludes that there are viable candidates for the role of visual counterpart to MMN (Pazo-Alvarez et al., 2003), if the paradigm allows for the control of visual attention. Our data appear to confirm an analogy in the impairment of automatic sensory information processing among patients with schizophrenia in the auditory and visual domain.

The characteristics of our experimental population approximately correspond with the average characteristics of other MMN studies in the auditory domain. Our results are in agreement with the descriptions of MMN presence in the later stage of schizophrenia. MMN may be considered as a state marker that corresponds to a neurodegenerative period in the course of the disorder. Our post hoc pairwise comparisons of means in median split subgroups suggest that the significant differences between patients and controls are in patients with primary deficit syndrome and lower GAF scores who are also treated with higher dose of antipsychotic drugs and tend to have a longer duration of the illness.

There are some limitations to our results. In order to argue for a preattentive and automatic sensory information process in vMMN, it is crucial to control for conscious attention in the test paradigm. We believe that

this has been adequately resolved by employing the target stimulus requiring response and attention in the course of the standard-deviant stimuli paradigm (Kremláček et al., 2001). However, the necessity to fixate attention during recording session on the attention binding target task limits the admission of patients to subjects capable of collaboration.

Another limitation is the fact that all except one patient were receiving psychotropic medication during the test. Most patients were on second generation antipsychotics, including clozapine. Although it has been known that D2 or 5 HT2 antagonists do not influence the size of MMN in the auditory domain (Umbricht et al., 1998; Chen et al., 1999) and medication did not influence the group results in a MMN study (Catts et al., 1995), it remains to be established whether this is true also in visual MMN. The median split of chlorpromazine equivalents in our study resulted in groups with different degree of vMMN impairment. Because this is true also about the duration of hospitalization and deficit/non-deficit division of the experimental group, we believe that the difference is due more to the clinical state of patients rather than their dose of antipsychotics.

MMN is the part of an ERP that is manifested in the border area between the early sensory component of ERPs and the cognitive component, that is context sensitive and reflects attentional and memory processes. Auditory MMN belongs to cognition related phenomena, however the significance of analogous visual phenomena is uncertain. The analogy with the auditory ERP requires an attempt at explanation.

MMN in the auditory domain has been hypothesised to be related to working memory and NMDA neurotransmission. The preattentive automatic detection of change requires the comparison of neuronal memory representations with the incoming stimuli. It may be thought of as a working memory component that serves the purpose of automatic cognitive pre-filtering of sensory information before it hits the conscious attention. This is compatible with the concept of auditory MMN as an index of NMDA related echoic memory encoding mechanism related to NMDA receptor functioning (Javitt et al., 1995, 1996). The association of MMN with working memory is consistent with a study in which auditory memory trace in healthy volunteers and MMN lasted similar periods of time and had similar sensitivity to masking with different stimuli (Winkler and Näätänen, 1992).

Patients with schizophrenia have also a deficit in the generation of the early negative peak of evoked potential preceding MMN — the N1 waveform (Ford et al., 2001). This finding supports the hypothesis that schizophrenia is characterized by a disturbance of sensory information processing at very early stages. The deficits in visual processing of schizophrenia patients may result from dysfunction of the magnocellular visual pathway (Butler et al., 2005). It provides for a quick, orientation in visual cues and provides elementary filtering of stimuli for later cognitive processing at the level of brain sensory pathways. The magnocellular system operates normally in a non-linear amplification mode mediated by NMDA glutamatergic receptors (Butler et al., 2005). The pattern of event related potential reduction observed in schizophrenia is consistent with patterns of visual dysfunction typically observed following infusion of *N*-methyl-D-aspartate antagonists into lateral geniculate nucleus or primary visual cortex. Thus deficits in magnocellular processing might be indicative of *N*-methyl-D-aspartate receptor dysfunction, consistent with recent neurochemical theories of schizophrenia.

The results of our vMMN study suggest that there is a deficit in generation of mismatch negativity induced by deviant visual motion stimuli among patients with schizophrenia. The smaller MMN may reflect a deficit in preattentive processing of sensory information during the early component of visual event related potentials. The origin and stability of the visual MMN deficit and its relationship to cognitive functions require further study.

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Contributors

Aleš Urban, Jan Kremláček and Jan Libiger had conceived and designed the study and wrote the manuscript. Jan Kremláček was responsible for recording and processing of electrophysiological data and for the statistical analysis. Jiří Masopust evaluated the patients and provided clinical data.

Conflict of interest

There is no conflict of interest of contributing authors.

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