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Elementary sensory deficits in schizophrenia indexed by impaired visual mismatch negativity☆

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ABSTRACT

Introduction: Mismatch negativity (MMN) is an automatic brain response to unexpected events. It represents a prediction error (PE) response, reflecting the difference between the sensory input and predictions. While deficits in auditory MMN are well known in schizophrenia, only few studies investigated impairments in predictive visual processing in schizophrenia. These studies used complex stimuli such as motion direction and emotional facial expressions. Here we studied whether automatic predictive processing of elementary features such as orientation is also impaired in 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. 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.
Results: We found significant mismatch responses in healthy controls but not in patients in the prefrontal and occipital–parietal regions in the 90–200 ms interval. Furthermore patients showed significantly decreased deviant minus standard difference waveforms relative to controls in the same regions with moderate to large effect sizes.
Conclusions: Our findings demonstrate that predictive processing of unattended low-level visual features such as orientation is impaired in schizophrenia. Our results complement reports of sensory deficits found in tasks requiring attentive processing and suggest that deficits are present in automatic visual sensory processes putatively mediated by glutamatergic functioning.

1. Introduction

1.1. Glutamate theory of schizophrenia

Schizophrenia is a severe and complex mental disorder with progressive cognitive deficit. The glutamate hypothesis has been suggested as the neural underpinning of the psychological impairments (Javitt et al., 1993; Humphries et al., 1996; Javitt, 2012; Javitt et al., 2012), and it provides a complementary theory to the dopamine hypothesis of schizophrenia (Egerton and Stone, 2012; Poels et al., 2014). The glutamate hypothesis was initially based on a set of clinical, neuropathological, and, later, genetic findings pointing at a hypofunction of glutamatergic signaling via N-Methyl-D-Aspartate Glutamate Receptor (NMDA) receptors in schizophrenia. Research using NMDA receptor antagonists ketamine and phencylidine demonstrated that not only positive and negative symptoms but cognitive deficits can be triggered by these agents (Umbricht et al., 2000).

1.2. Prediction errors and the aberrant salience theory of schizophrenia

MMN is generated when an unexpected, deviant event occurs in a regular repeating pattern of standard stimuli (Naatanen and Kahkonen, 2009). Mismatch negativity is thought to be a prediction error, i.e., the difference between bottom-up sensory input and top-down predictions, based on prior events (Todd et al., 2012; Stefanics et al., 2014). Electrophysiological studies showed that the NMDA receptor antagonists, such as ketamine (Ehrlichman et al., 2008; Gil-da-Costa et al., 2013), ethanol (He et al., 2013) or MK-801 (Tikhonravov et al., 2008), which can trigger symptoms of schizophrenia in healthy subjects, also decrease the MMN signal. According to the aberrant salience theory patients with schizophrenia have difficulties suppressing irrelevant information, and attach more importance to irrelevant stimuli (Morris et al., 2013). That is, delusions have been proposed to be secondary phenomena arising from a failure to explain away sensory prediction errors (Kapur, 2003) which in turn might lead to a

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compensatory increase in the precision of higher-level beliefs (Murray et al., 2008; Corlett et al., 2011; Adams et al., 2013). Accordingly, Nelson et al. (2014) and Todd et al. (2012) proposed that aberrant salience in schizophrenia is based on the attenuated mismatch negativity response.

1.3. Using MMN to predict psychosis

Decreased auditory MMN (Brockhaus-Dumke et al., 2005; Atkinson et al., 2012; Solis-Vivanco et al., 2014) and its magnetic counterpart (Shin et al., 2009) have been found in patients in their first episode of psychosis as well as individuals at high risk for psychosis. Furthermore, there is increasing evidence from longitudinal electrophysiological studies that MMN can be useful to predict the onset of psychosis. Converters to psychosis have significantly reduced auditory MMN amplitudes relative to non-converters at baseline (Higuchi et al., 2013; Nagai et al., 2013; Perez et al., 2014), indicating that MMN may have the potential to predict conversion to psychosis (Bodatsch et al., 2011; Sumiyoshi et al., 2013).

1.4. Previous results in MMN research—hypotheses

The mismatch negativity was thought to be primarily an auditory phenomenon (Naatanen et al., 2001), however, recently a substantial amount of evidence accumulated showing that automatic predictive mechanisms operate in the visual modality too (Kimura, 2012; Stefanics et al., 2014). Thus, the overwhelming majority of MMN studies in schizophrenia applied auditory stimuli (Farley et al., 2010; Naatanen et al., 2012; Escera et al., 2014; Witten et al., 2014), while only a few clinical studies used visual MMN (Kimura, 2012). To our knowledge only three previous studies used visual MMN and reported deficits of the mismatch response in patients with schizophrenia (Urban et al., 2008; Csukly et al., 2013). These studies applied rare changes in higher-level attributes of unattended stimuli, such as motion direction (Urban et al., 2008) or facial emotions (Csukly et al., 2013) to elicit the automatic visual mismatch response. Several previous investigations requiring attentive stimulus processing found deficits in facial expression recognition (Morris et al., 2009; Komlosi et al., 2013) and motion detection (Li, 2002; Kim et al., 2006) in schizophrenia. Visual MMN deficits though raise the possibility that the differences found by these studies are, at least in part, results of a more general visual deficit in predictive sensory processes in schizophrenia reflected by the attenuated visual MMN response.

Several studies demonstrated perceptual deficits in schizophrenia (Butler et al., 2008) indicating impairments in early sensory visual processing in schizophrenia (Silverstein and Keane, 2011). For example, Rokem et al. (2011) found that patients with schizophrenia have broader orientation tuning curves than healthy controls suggesting deficits at lower levels of the visual system. It is not known whether predictive mechanisms are affected in early visual processes or not. Therefore our primary aim was to investigate whether predictive processing of low-level visual features such as orientation is impaired in schizophrenia. To explore whether deficits are present in the processing of elementary visual features here we used rare changes in orientation of Gabor patches to elicit MMN. Prior studies reported reliable vMMN response to orientation deviants (Astikainen et al., 2004;2008; Kimura et al., 2009; Czigler and Sulykos, 2010; Takacs et al., 2013) in healthy subjects, therefore we used a simple oddball paradigm where we varied the probabilities of Gabor patches with different orientations. Our hypothesis was that the mismatch response to rare orientation changes will be reduced in the patients compared to controls.

A prior auditory MMN study reported that the amplitude of the MMN response correlated with Global Assessment of Functioning (GAF) score in schizophrenia (Light and Braff, 2005). However, other auditory MMN studies did not observe a relationship between the mismatch response and clinical, psychopathologic, or treatment variables (Umbricht et al., 2003). Regarding visual MMN, a study by Urban et al. (2008) found an association between vMMN impairments and lower level of functioning in patients with schizophrenia, and in our previous vMMN study (Csukly et al., 2013) we observed a relationship between the amplitude of the mismatch response and emotion recognition performance, a clinically relevant variable, both in patients with schizophrenia and healthy controls. To investigate whether vMMN evoked by orientation deviants is relevant to the illness, we calculated correlations between vMMN amplitude and clinical variables.

2. Materials and methods

2.1. Ethics statement

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, Budapest, Hungary, and participants gave their written informed consent before the procedures. The experiments were carried out in full compliance with the Helsinki Declaration.

2.2. Subjects

Twenty-eight patients (16 males, mean age 37.7 ± 8.4 years) and twenty-seven healthy controls (15 males, mean age 38.2 ± 10.6 years) were recruited for the study. As shown in Table 1 groups did not differ in age and education ($p > 0.05$). All participants were right-handed with the exception of one left-handed and one ambidextrous patient and two left-handed healthy controls. All participants had normal or corrected-to-normal vision.

Selection criteria were no history of any central nervous system disease, mental retardation, epileptic seizure, substance dependence or substance abuse in the past 3 months, no history of head injury with loss of consciousness more than 10 min and for healthy controls no history of any psychiatric disease. A global severity index of >114 on the Symptom Checklist—90-R, (Derogatis and Melisaratos, 1983) according to a Hungarian population sample (Unoka et al., 2004), was an additional exclusion criteria for controls in order to exclude subjects with high risk for psychiatric disorders. No subjects were excluded from the control group based on these criteria.

Patients were recruited from the Department of Psychiatry and Psychotherapy of the Semmelweis University, Budapest, Hungary, from both the inpatient (n = 14) and outpatient units (n = 14). All patients met the criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Axis I Disorders (American Psychiatry Association, 1994). Psychiatric symptoms on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) were evaluated by a trained psychiatrist. At the time of testing all patients took antipsychotic medication, the mean Chlorpromazine equivalent dose (Gardner et al., 2010) was 731 mg/day (SD = 322). Demographic information for both groups and clinical characteristics of the schizophrenia group are presented in Table 1.

Table 1
Demographic information for both study groups and clinical characteristics of the schizophrenia group (CPZ = chlorpromazine equivalent dose; PANSS = Positive and Negative Symptoms Scale).

	Schizophrenia group	Control group	Statistics	p Value
Gender (male/female)	16/12	15/12	$Chi^2 = 0.07$	n.s.
Age	37.71 (8.42)	38.21 (10.59)	$t = 0.84$	n.s.
Education [a]	2.86	3.18	$F = 1.65$	n.s.
Illness duration (years)	11.7 (7.23)	–		
In-/outpatient	14/14	–		
CPZ equivalent dose	731 (322)	–		
PANSS total score	81.3 (20.44)	–		

[a] 1 = elementary school; 2 = high school; 3 = polytechnic; 4 = college/university.

2.3. Stimuli and procedure

Visual stimuli were presented on a computer screen (Fig. 1). On each stimulus panel four identical Gabor patches were presented in the upper-left, upper-right, lower-left and lower-right quadrants of the monitor. Each patch subtended by 7.7° visual angle horizontally and vertically. A black fixation cross was presented in the center. The distance of the center of the Gabor patches from the fixation cross subtended 4.4° visual angle horizontally and 3.8° vertically.

Stimuli appeared on a dark-grey background at a viewing distance of 0.5 m. Stimulus duration was 200 ms. The stimulus onset asynchrony (SOA) was randomized between 650 and 680 ms. The fixation cross was continuously present on the screen.

In one of two experimental blocks Gabor patches of horizontal orientation were presented as frequent standards and vertical patches as rare deviants. Since the processing of low frequency visual stimuli may be impaired in schizophrenia due to deficits in the magnocellular tracts (Butler and Javitt, 2005), we applied high frequency Gabor patches (5 cycle/degree) similarly to previous investigations (Friedman et al., 2012). 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. Since attention is known to alter brain responses in the range of vMMN (Czigler and Csibra, 1990; Kenemans et al., 1993), we applied a primary task (Stefanics et al., 2014) that was independent of the Gabor patches to prevent participants from attending to the oddball stimuli. Similarly to our previous experiments (Stefanics et al., 2012; Csukly et al., 2013) the central fixation cross consisted of a longer and a shorter line. From time to time, the cross flipped with a mean frequency of 11 flips per minute (SD = 3). Participants were required to quickly and accurately respond to cross flips with a button press.

2.4. EEG recording and processing

EEG was recorded from DC with a low-pass filter at 100 Hz using a BioSemi ActiveTwo amplifier (Metting van Rijn et al., 1990). The high-density electrode caps had 128 equidistant channels that covered the whole head. Electrooculogram (EOG) electrodes were placed below the left and above the right external canthi to monitor eye movements. Data sampling rate was 1024 Hz. Built-in and self-developed Matlab functions (MathWorks, Natick, MA) as well as the freeware EEGLAB toolbox (Delorme and Makeig, 2004) were used for off-line data analyses. EEG was re-referenced to the common average potential and filtered off-line between 0.1 and 30 Hz using zero-phase shift Butterworth filter. The removal of muscle and eye movement artifacts in EEG and EOG channels was performed by fully automatic software driven method (Mognon et al., 2011) using independent component analysis (ICA).

Based on previous vMMN studies in patients with schizophrenia (Urban et al., 2008; Csukly et al., 2013) we analyzed the ERPs in three occipito-parietal and three prefrontal regions of interests (ROI). Epochs of 100 ms before to 600 ms after the onset of patch stimuli were extracted. ERPs were averaged within ROIs, separately for each stimulus condition and study group. Deviant minus standard differential responses were calculated by subtracting ERPs to horizontal standard stimuli from ERPs to horizontal deviant stimuli, and ERPs to vertical standard stimuli were subtracted from responses to vertical deviants. Afterwards responses to deviant and standard stimuli were collapsed across orientations to form a set of standard and a set of deviant responses. ERPs overlapping with a cross flip or responses to it were excluded from the analysis.

According to previous studies (Czigler et al., 2004; Urban et al., 2008; Kreegipuu et al., 2013), including which used orientation deviants (130–190 ms (Czigler and Sulykos, 2010); 100–150 ms and 200–250 ms (Kimura et al., 2009)), we expected to find visual mismatch negativity in the 90–200 ms time windows. Brain responses were analyzed with repeated measures analysis of variance (ANOVA) with study group, stimulus type, region and their interaction as independent factors.

3. Results

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 ($F(5, 53) = 2.45$, $p < 0.05$).

This interaction was analyzed further using post hoc t-tests. The differences between deviant and standard stimuli (i.e. the amplitude of the

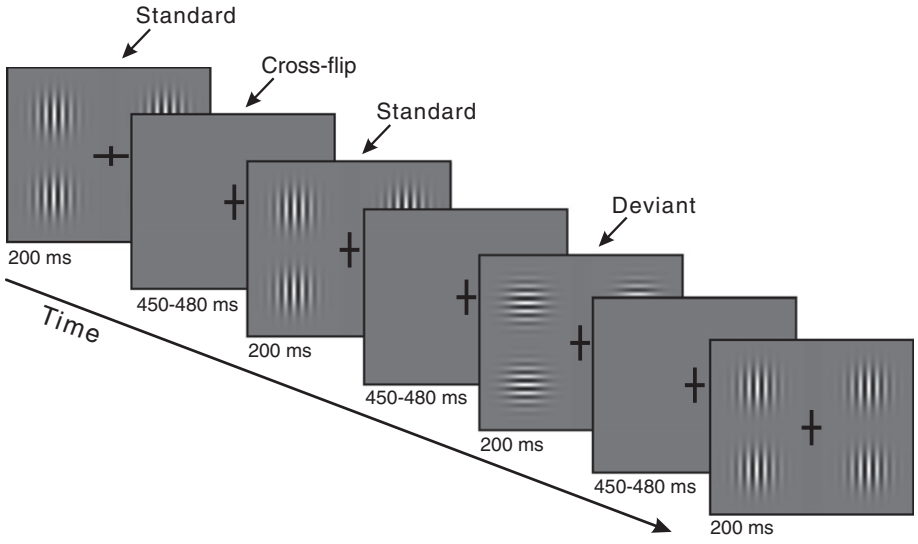

Fig. 1. Schematic illustration of the experimental paradigm and distractor task. An oddball sequence of Gabor patches was presented while participants attended a central fixation cross and responded to occasional cross-flips with pressing a button. Gabor patches were presented for 200 ms followed by an inter-stimulus interval (ISI) randomized between 450 and 480 ms. In one of two experimental blocks horizontal striped Gabor patches were presented as frequent standards and vertical striped patches as rare deviants, whereas in the other block stimulus probabilities were swapped.

Table 2
Differences between deviant and standard stimuli (i.e. the amplitude of the MM signal), group differences and corresponding effect sizes in terms of Cohen's d. Significant differences between deviant and standard stimuli are marked with *; significant group differences are marked with **.

	Deviant vs. standard				Between group difference in mismatch signal	
	Control group		Schizophrenia group			
Region of interest (ROI)	LSMean (SE)	p Value	LSMean (SE)	p Value	Effect size (Cohen's d)	p Value
Prefrontal left	0.20 (0.07)	0.008*	−0.02 (0.07)	0.765	0.54	0.054
Prefrontal right	0.22 (0.08)	0.011*	−0.10 (0.08)	0.211	0.77	0.007**
Prefrontal sagital	0.27 (0.11)	0.016*	−0.08 (0.11)	0.459	0.62	0.033**
Parieto-occipital left	−0.22 (0.07)	0.002*	0.06 (0.07)	0.411	0.72	0.011**
Parieto-occipital right	−0.26 (0.06)	<.001*	−0.02 (0.06)	0.750	0.77	0.007**
Parieto-occipital sagital	−0.30 (0.08)	<.001*	−0.01 (0.08)	0.910	0.68	0.019**

MM signal), group differences and corresponding effect sizes in terms of Cohen's d are provided in Table 2. In order to correct for Type I errors the Hochberg correction for multiple comparisons was used (Hochberg, 1988; Hochberg and Benjamini, 1990). After correction for multiple comparisons, we found significant difference between standard and deviant mismatch 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. 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 (Table 2) due to the posterior negativity and anterior positivity effect.

Fig. 2 shows grand mean ERPs in each ROIs for standard and deviant stimuli, as well as mismatch responses for healthy controls and patients.

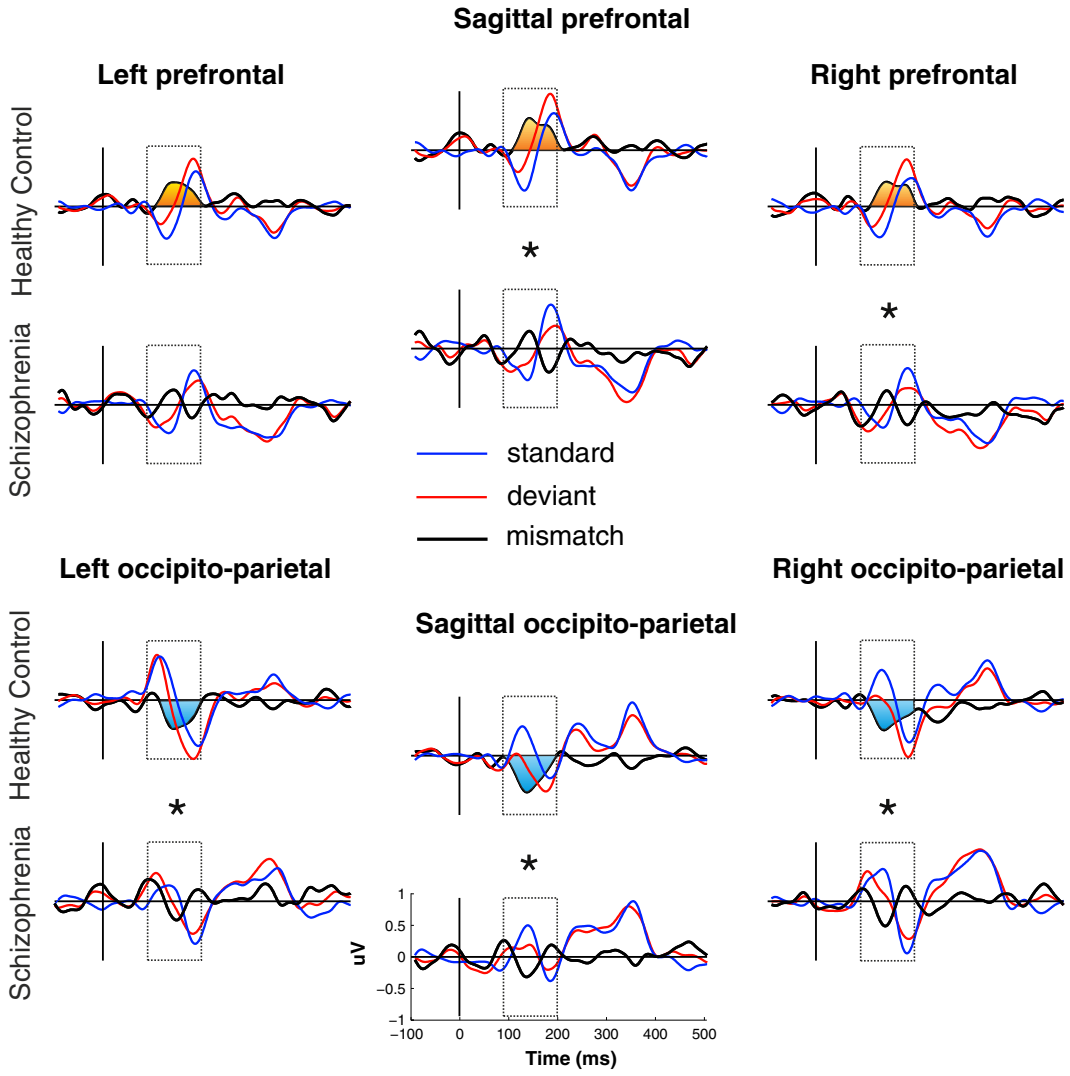

Fig. 2. Grand average ERPs for the standard (blue line) and the deviant stimuli (red line), and the mismatch response (black line) from the six ROIs in the two study groups. Dotted line rectangles indicate intervals of amplitude measurements. Areas under the curves of the significant posterior negative and anterior positive mismatch response observed only in the Healthy Control group are marked with blue and orange, respectively. Significant differences between study groups are marked with *.

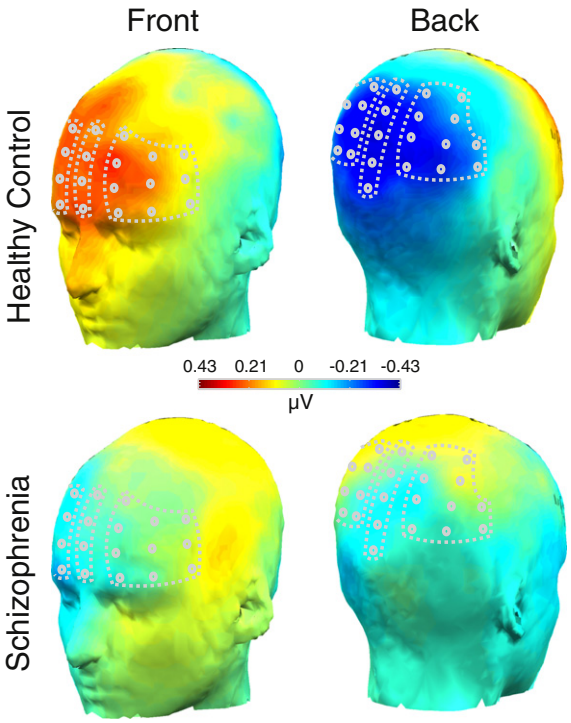

Fig. 3. Head plots of deviant minus standard mismatch responses in the 90–200 ms interval in the two study groups. Potential amplitude is color coded as shown in colorbar. Regions of interests (ROIs) and electrodes used for amplitude measurements are marked with grey.

Fig. 3 shows scalp distributions of the mismatch responses for both study groups in the 90–200 ms time window.

Correlations between clinical variables such as age, illness duration, PANSS scores (Kay et al., 1987), antipsychotic doses in terms of CPZ equivalents (Gardner et al., 2010), functionality as measured by PSP (Personal and Social Performance) (Morosini et al., 2000) and mismatch responses are provided in Table 3. We found no correlations between the studied parameters and vMMN after correction for multiple testing.

During the experiment participants responded to cross flips with pressing a button. There was a significant difference between study groups in accuracy and in reaction time. However hit rate was above 90% for both study groups; controls (97.4% SD = 3.4) significantly outperformed ($F(1,46) = 5.67$, $p = 0.02$) patients with schizophrenia (94.0% SD = 6.3). Furthermore the mean reaction time was significantly longer ($F(1,46) = 6.46$, $p = 0.01$) in the patient group (561 ms, SD = 372 ms), than in the healthy control group (478 ms, SD = 266 ms).

4. Discussion

Several studies demonstrated that visual sensory processing is impaired in schizophrenia (Butler et al., 2008; Javitt, 2009). For example, patients with schizophrenia have broader orientation tuning curves than healthy controls (Rokem et al., 2011) indicating deficits at lower levels of the visual hierarchy. Attentive processing of higher level attributes such as motion (Li, 2002; Brenner et al., 2003; Kim et al., 2006; Chen, 2011) and facial emotion perception (Morris et al., 2009; Brittain et al., 2012; Komlosi et al., 2013) are also impaired in schizophrenia. Studies using the auditory mismatch negativity revealed remarkable differences between patients with schizophrenia and healthy controls (Umbricht and Krljes, 2005) indicating deficits in automatic auditory predictive processing. However, only a few studies focused on automatic predictive stimulus processing in the visual modality in schizophrenia. Previous studies using vMMN revealed deficits in automatic predictive processing of motion (Urban et al., 2008) or facial emotion (Csukly et al., 2013) indicating that deficits observed in tasks requiring attentive stimulus processing might be caused at least partly by deficits in automatic predictive processes. To explore whether such deficits are also present at lower levels of the visual hierarchy, in the present study we applied a passive visual oddball paradigm where we used rare changes in orientation of simple Gabor patches to elicit MMN. Since processing of low frequency visual stimuli is impaired in schizophrenia due to magnocellular deficits (Butler and Javitt, 2005), we applied high frequency Gabor patches.

To avoid confounding attentional effects on the processing of change in orientation of the parafoveally presented Gabor patches, we applied an independent detection task in the center of the visual field. Although in this task controls outperformed patients, the high hit rates in both groups (>94%) suggest that the task engaged attention in both groups effectively.

Following prior studies we analyzed the mismatch response in the 90–200 ms time windows. In the control group we found a significant mismatch response in all three prefrontal and all three occipito-parietal regions in line with prior studies where anterior positive and posterior negative mismatch responses have been observed (Stefanics and Czigler, 2012; Cleary et al., 2013; Files et al., 2013). In the schizophrenia group no significant mismatch response was found in any of the regions. Significantly decreased deviant minus standard differential waveforms were found in the schizophrenia group relative to healthy controls in the sagittal and right prefrontal and in all three occipito-parietal regions. The effect sizes are large (0.62–0.77), and reached their maximum in the right prefrontal and occipito-parietal regions.

These findings are consistent with previous results (Urban et al., 2008; Csukly et al., 2013), where reduced mismatch waveforms were detected in patients with schizophrenia in similar time windows, and with a similar scalp distribution. The observed scalp distribution of the

Table 3
Correlation between mismatch signals and the demographic and clinical parameters (CPZ = chlorpromazine equivalent dose; PANSS = Positive and Negative Symptoms Scale; PSP = Personal and Social Performance).

		Age	PANSS			PSP	CPZ	Illness duration
			Total	Positive	Negative			
Prefrontal Left	Pearson's coefficient	−0.03	−0.02	0.09	−0.09	−0.12	0.13	0.06
	p Value	0.85	0.91	0.67	0.68	0.57	0.56	0.78
Prefrontal Right	Pearson's coefficient	−0.04	0.04	0.08	−0.01	−0.27	0.41	0.26
	p Value	0.76	0.85	0.72	0.95	0.19	0.05	0.23
Prefrontal Sagital	Pearson's coefficient	−0.09	0.03	0.11	−0.08	−0.19	0.32	0.19
	p Value	0.53	0.88	0.61	0.71	0.38	0.13	0.37
Parieto-occipital Left	Pearson's coefficient	0.10	−0.23	−0.27	−0.09	0.29	−0.22	0.08
	p Value	0.45	0.27	0.20	0.67	0.17	0.30	0.70
Parieto-occipital Right	Pearson's coefficient	0.07	−0.31	−0.44	−0.10	0.28	−0.37	0.01
	p Value	0.59	0.15	0.03	0.63	0.18	0.07	0.97
Parieto-occipital Sagital	Pearson's coefficient	0.08	−0.20	−0.27	−0.12	0.37	−0.22	−0.03
	p Value	0.56	0.34	0.20	0.58	0.08	0.31	0.89

vMMN is consistent with bilateral posterior dipolar sources projecting their negative and positive poles to the posterior and anterior scalp, respectively. Such a generator structure would be in line with recent reports (e.g., Susac et al., 2014) where neuromagnetic sources of the vMMN evoked by a change in spatial frequency, a low-level stimulus feature, were localized in the occipital cortex. Alternatively, frontal generators might have contributed to the observed anterior positivity, and visual sources to the posterior negativity. Given that no task was associated with the stimuli that evoked the mismatch response, a high degree of frontal engagement seems less likely, although some prior studies reported vMMN generators in frontal areas, too (Kimura et al., 2012; Li et al., 2012; Stefanics and Czigler, 2012; Csukly et al., 2013).

Hierarchical predictive coding theory suggests that both visual and higher level areas such as the prefrontal cortex play a role in mismatch processes, where prediction error responses are generated at lower levels are passed on to higher levels to update predictions, and predictions generated at higher levels are conveyed to lower levels to suppress prediction errors (Friston, 2005; Corlett et al., 2011; Kimura, 2012; Adams et al., 2013; Stefanics et al., 2014). Assuming that the mismatch response observed in healthy subjects at frontal and posterior regions in our study corresponds to such bottom-up and top-down processes, respectively, the decreased mismatch response at frontal and posterior regions in the schizophrenia group may indicate impairments in both processes.

In this study we examined potential relationships between the MMN and patients' age, antipsychotic medication, symptom severity, illness duration and functional outcome and we found no significant correlations. This is in line with prior studies which failed to find correlations between MMN and antipsychotic medication (Korostenskaja and Kahkonen, 2009), and symptom severity or illness duration (Umbricht and Krljes, 2005; Todd et al., 2013). However, Urban et al. (2008) found an association between vMMN impairments and lower level of functioning in patients with schizophrenia, but recent studies applying visual paradigms did not replicate this finding (Csukly et al., 2013; Neuhaus et al., 2013).

5. Limitations

In this study a relative good compliance was expected from the participants due to the complex and long lasting EEG measurements, therefore patients with higher symptom severity were not included. We examined only medicated patients, and found no correlation between MMN and antipsychotic dose. We cannot exclude that low variance in symptom severity due to our inclusion criteria might have caused or contributed to the lack of correlation between the mismatch signals and the PANSS scores.

We reversed the probabilities of the standard and deviant stimuli between the two experimental blocks. This is an effective method to control for effects that might arise due to physical differences between stimuli. However, it does not control for potential refractoriness effects, i.e., effects arising merely due to the frequent presentation of the standard. Therefore we cannot exclude the possibility that refractoriness effects contributed to the observed deviant vs. standard difference. Such effects can be controlled for by applying an equiprobable control condition (see e.g., Astikainen et al., 2008, 2013; Kimura et al., 2009; Li et al., 2012; Susac et al., 2014). We suggest that future studies should consider using equiprobable controls whenever possible instead of swapping stimulus probabilities between oddball blocks.

6. Conclusions

In this study we observed significant mismatch responses to rare changes in orientation of Gabor patches in occipito-parietal and prefrontal regions in healthy controls. In patients with schizophrenia no mismatch responses were detected in any of the studied regions indicating an impairment in automatic predictive processing of low-level visual processes. The deviant minus standard difference waveforms were significantly decreased in the patient group in five out of six regions. Our current findings indicate the impairment of predictive processing of a very simple stimulus feature, namely orientation. This result complements prior studies where decreased vMMN was observed in response to changes in higher level stimulus attributes such as movement or facial expressions, indicating that impairments in automatic sensory/perceptual predictive mechanisms are likely to be present at multiple levels of the visual processing hierarchy.

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Contributors

K.F. organized the measurements, recorded data, and wrote the manuscript. G.S. designed the study with G.C., and contributed to the analysis of data, and the writing of the manuscript. C.M. recorded data, and contributed to the writing of the manuscript. G.C. designed the study, wrote the protocol, analyzed data, contributed to the writing of the manuscript, and supervised the study.

Conflict of interest

The authors declare that they have no conflict of interest

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