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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.