Schizophrenia Research 147 (2013) 326–330

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Evidence for impaired visual prediction error in schizophrenia

Andres H. Neuhaus [a,*], Emily S.L. Brandt [a], Terry E. Goldberg [b], John A. Bates [b], Anil K. Malhotra [b]

[a] Department of Psychiatry and Psychotherapy, Charité University Medicine, Campus Benjamin Franklin, Berlin, Germany
[b] Department of Psychiatry Research, Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, Glen Oaks, NYC, USA

ARTICLE INFO

Article history:
Received 1 August 2012
Received in revised form 8 March 2013
Accepted 4 April 2013
Available online 26 April 2013

Keywords:
Mismatch negativity
Event-related potential
Oddball
Schizophrenia
Predictive coding
Prediction error

ABSTRACT

Background: Mismatch negativity (MMN) is regarded a prediction error signal that is deficient in schizophrenia in the auditory modality. If, however, MMN reflects a general computational signal of the cortex, then MMN should be also deficient in the visual modality in schizophrenia patients.
Methods: Twenty-two schizophrenia patients and 24 matched healthy controls finished a visual oddball task while high-density electroencephalogram was recorded. Visual mismatch negativity was computed as a surrogate marker of prediction error.
Results: Visual MMN, as measured over posterior extra-striate cortical areas, was significantly reduced in schizophrenia at about 300 ms post stimulus. Standardized mean difference was −.98, corresponding to a large effect size.
Conclusions: A posterior visual MMN deficit in schizophrenia is demonstrated for the first time. Our results tentatively suggest a supra-modal MMN deficit in schizophrenia and thus argue in favor of reduced prediction error estimation in schizophrenia.

1. Introduction

Schizophrenia is associated with a variety of clinical symptoms such as auditory hallucinations, paranoid delusional thoughts, disorganized thinking, or disturbances of self. Apart from these clinical features, schizophrenia is regularly associated with deficits in a broad range of cognitive domains including working memory, selective attention, reward and salience processing, or theory of mind that can be measured both on the behavioral and the systems, i.e. neuroimaging, level (e.g. Murray et al., 2008; Minzenberg et al., 2009; Sparks et al., 2010; Pedersen et al., 2012). This overarching symptom constellation is suggestive of a basic processing deficit that integrates these observations into a coherent cognitive model of the disease.

From a computational neuroscience perspective, the diversity of deficits observed in schizophrenia can be explained by a disruption of network architecture (Liu et al., 2008) or by a deficient global processing algorithm. While disrupted neural networks are well in line with the disconnection hypothesis of schizophrenia (Camchong et al., 2011), a deficient global processing algorithm remains hypothetic. Recently, the predictive coding hypothesis has been proposed as a unifying theory of cortical computational function (Friston, 2005). This theory posits that our brain is a hierarchically organized system where bottom-up sensory experience is compared with top-down predictions on every level of the hierarchy. Mismatches between sensory information and prediction, i.e. prediction errors, are then processed throughout the cortical hierarchy in order to minimize prediction error and to obtain a realistic model of the environment. Predictive coding has become a dominant theory in the reward and salience processing literature (Schultz et al., 1997; Matsumoto and Hikosaka, 2009). Regarding schizophrenia, a growing body of research has associated predictive coding deficits with deficient reward and salience processing (Murray et al., 2008), with delusional thoughts (Corlett et al., 2007), auditory hallucinations and passivity experience (Blakemore et al., 2000), and altered sense of agency (Voss et al., 2010). A recent computational study suggests that reduced network connectivity may result in prediction error disequilibrium, thus linking disconnection and predictive coding theories into a coherent framework that may be of great importance for schizophrenia (Yamashita and Tani, 2012).

An elegant way to measure mismatches between prediction and expectation is offered by analyzing the mismatch negativity (MMN), an event-related potential (ERP) that signals prediction error (Garrido et al., 2008; Wacongne et al., 2012). In the auditory modality, MMN deficits constitute a long-standing and firmly established finding in schizophrenia research (Umbricht and Krljes, 2005; Butler et al., 2012; Fisher et al., 2012) that even predates illness onset (Bodatsch et al., 2011; Shaikh et al., 2012). By definition, however, the prediction error model is not confined to a specific sensory modality, but should operate supra-modally, so findings of auditory MMN should directly translate into, e.g., the visual modality. In fact, a visual MMN has been identified approximately 200 to 400 ms after deviant stimuli at inferior posterior scalp sites, i.e. in close topographical proximity to the visual areas (Woods et al., 1992; Tales et al., 1999; Stagg et al., 2004; Kimura et al.,

* Corresponding author at: Department of Psychiatry and Psychotherapy, Charité University Medicine Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany. Tel.: +49 30 8445 8412; fax: +49 30 8445 8393.
E-mail address: andres.neuhaus@charite.de (A.H. Neuhaus).

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.04.004

2012). According to the theory of a deficient prediction error model in schizophrenia, we hypothesized to find posterior visual MMN deficits in schizophrenia. We investigated visual MMN and neighboring negative component N1 and N2 with a strong a priori spatiotemporal hypothesis based on previous normative studies using an established oddball paradigm in schizophrenia.

2. Methods

2.1. Subjects

Twenty-four schizophrenia patients (11 women, 13 men) participated in this study. They met DSM-IV criteria for schizophrenia and had no psychiatric disorder other than schizophrenia and nicotine abuse/dependence. Current drug abuse as determined by urine toxicology led to exclusion from the study. None of the included patients had a history of severe medical disorder or severe neurological disorder. Two of 24 schizophrenia patients had to be excluded from analysis because of technical artifacts (N = 1) and low accuracy (N = 1). Of the remaining 22 schizophrenia patients (10 women, 12 men), mean age was 40.67 ± 11.3 years (range 23–57 years), mean duration of illness was 16.53 ± 11.3 years, and mean number of episodes was 2.73 ± 2.0. Mean chlorpromazine equivalent was 186.34 ± 159.2 mg/d. Mean Global Assessment of Functioning (GAF) score was 33.5 ± 13.4, mean Brief Psychiatric Rating Scale (BPRS) score was 57.27 ± 8.2. All patients were recruited from the outpatient clinic of the Zucker Hillside Hospital, North Shore-Long Island Jewish Health System.

Twenty-four healthy subjects (11 women, 13 men) recruited via newspapers served as controls. They were screened for mental and physical health and were excluded when meeting the criteria of psychiatric disorders according to DSM-IV as determined by structured clinical interviews. Further reasons for exclusion were a family history of psychiatric illness, medical or neurological disorders, or intake of psychotropic drugs as confirmed by urine toxicology before participating in the study. Mean age was 37.96 ± 7.3 years (range 25–50 years).

All participants were right-handed and had normal or corrected-to-normal vision. All subjects gave written informed consent before participating in our study. This study was approved by the North Shore-Long Island Jewish Health System Institutional Review Board and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

2.2. Procedure and task design

Subjects were seated in a reclined chair and were instructed to visually fixate a cross on a computer monitor. Our visual oddball paradigm consisted of a pseudo-randomized presentation of 240 standard and 60 target stimuli (probability 0.20; stimulus onset asynchrony 1200 ms). Stimuli were presented as white letters on a black background for 100 ms at a medium intensity level on a computer monitor 1 m in front of the subjects, where “O” served as standard and “X” as target (deviant) stimulus, respectively. Subjects were instructed to respond to target stimuli by pressing a response button with the right index finger as fast and as accurately as possible.

2.3. EEG data acquisition and analysis

EEG was collected with 64 Ag/Ag–Cl electrodes according to the extended international 10/20 system using an electrode cap. Additional electrodes were placed at left and right mastoids, at the outer canthus of the left eye, below the left eye, and at the tip of the nose. A ground electrode was placed on the forehead. Electrode impedances were kept below 5 kΩ. All channels were referenced to the tip of the nose. EEG was recorded with a Neuroscan SynAmps (El Paso, TX, US) and continuously digitized at a sampling rate of 500 Hz. During acquisition, EEG data were band-pass filtered from 0.05 to 100 Hz. Offline ERP analysis was conducted with Brain Vision Analyzer 1.05 (Brain Products, Munich, Germany). Ocular artifact correction was performed using an independent component analysis approach (Jung et al., 2000). Data were then re-referenced to common average, digitally filtered at 20 Hz low pass, and remaining artifacts (80 μV at any electrode) were marked for later removal. Data were segmented according to stimulus class and relative to stimulus onset (200 ms pre-stimulus to 800 ms post-stimulus). After final automated artifact rejection and baseline correction, the remaining artifact-free and correctly responded trials (within 100–1000 ms post-stimulus) were averaged per subject and experimental condition.

Individual ERP averages were used to construct N1 to standard stimuli, N2 to deviant stimuli and MMN by subtracting the waveforms elicited by standards from those elicited by deviants. For all components, two regions of interest (ROI) were defined that included inferior temporal-occipital electrodes P5, P7, PO5, PO7 (left hemisphere) and P6, P8, PO6, PO8 (right hemisphere). To avoid circular analyses (Kriegeskorte et al., 2009; Vul et al., 2009), electrode values within one ROI were averaged for each component, thus forming three visual components per group and hemisphere. Peaks were automatically determined as baseline-to-peak-amplitudes with a visual control post hoc to verify correct peak identification. N1 was determined as a negative peak at a latency of 130–230 ms post standard stimuli. N2 was picked as a negative peak at 260–400 ms following deviant stimuli. MMN was measured as a negative peak at 250–350 ms in the difference ERP condition. MMN signals were visually inspected for polarity inversion at mastoid electrodes.

Analyses were based on a mean of 198.79 ± 34.5 standard segments for controls and 165.95 ± 65.6 for schizophrenia patients ($p < .05$). Mean number of deviant segments was 52.25 ± 8.3 for controls and 41.35 ± 14.0 for schizophrenia patients ($p < .01$).

2.4. Data analysis

Statistical analyses were done with IBM SPSS version 19 (Armonk, NY, US). Demographic data, behavioral data, and number of utilized ERP segments were analyzed with t-tests for independent samples or chi-squared tests, as appropriate. N1, N2, and MMN amplitudes were analyzed separately using a repeated measures analyses of covariance entering hemisphere (left, right) as within-subjects factor, group (schizophrenia, control) and sex (female, male) as between-subjects factors, and age as co-variate. Partial eta squared and standardized mean difference served as estimators of effect sizes. Pearson rank correlations were performed using post hoc Bonferroni correction. For all tests, alpha was set at $p < .05$.

3. Results

3.1. Behavioral results

Mean reaction time for button presses to deviant stimuli was 217.12 ± 32.6 ms for controls and 236.07 ± 25.6 ms for schizophrenia patients (no significant difference). Mean accuracy was significantly higher in controls (97.78 ± 4.9%) than in schizophrenia patients (86.67 ± 16.2%; $p < .01$).

3.2. ERP results

Fig. 1 illustrates grand averaged ERP responses to standard and deviant stimuli as well as visual MMN waveforms for each hemisphere along with current source density maps at the components' respective latencies. Temporal-occipital areas of maximum negativity largely correspond to the a priori ROI definitions that involve electrodes P5,