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Emotional context restores cortical prediction error responses in schizophrenia

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ABSTRACT

The mismatch negativity (MMN) deficit in schizophrenia is a consistently replicated finding and is considered a potential biomarker. From the cognitive neuroscience perspective, MMN represents a cortical correlate of the prediction error, a fundamental computational operator that may be at the core of various cognitive and clinical deficits observed in schizophrenia. The impact of emotion on cognitive processes in schizophrenia is insufficiently understood, and its impact on basic operators of cortical computation is largely unknown. In the visual domain, the facial expression mismatch negativity (EMMN) offers an opportunity to investigate basic computational operators in purely cognitive and in emotional contexts. In this study, we asked whether emotional context enhances cortical prediction error responses in patients with schizophrenia, as is the case in normal subjects. Therefore, seventeen patients with schizophrenia and eighteen controls completed a visual sequence oddball task, which allows for directly comparing MMN components evoked by deviants with high, intermediate and low emotional engagement. Interestingly, patients with schizophrenia showed pronounced deficits in response to neutral stimuli, but almost normal responses to emotional stimuli. The dissociation between impaired MMN and normal EMMN suggests that emotional context not only enhances, but restores cortical prediction error responses in patients with schizophrenia to near-normal levels. Our results show that emotional processing in schizophrenia is not necessarily defect; more likely, emotional processing heterogeneously impacts on cognition in schizophrenia. In fact, this study suggests that emotional context may even compensate for cognitive deficits in schizophrenia that are, in a different sensory domain, discussed as biomarkers.

1. Introduction

Schizophrenia is associated with a broad range of cognitive deficits in domains including memory function, global cognitive functioning, language, executive function, and attention (Fioravanti et al., 2012; Heinrichs and Zakzanis, 1998). Impairments in these domains are well described on both the behavioral and the neuroimaging level (Kraguljac et al., 2013; Mesholam-Gately et al., 2009). Cognitive impairments in schizophrenia are suggestive of a global information-processing deficit because they are not restricted to any specific neurocognitive domain. Friston (2005) proposed the hierarchical cortical model of predictive coding in which the cortical information-processing stream is best described by the brains constant endeavors to reduce mismatches between bottom-up sensory inputs and top-down expectations (i.e. prediction errors) to generate a realistic model of the environment (Friston, 2005). Therefore, it has been suggested that the prediction error represents a basic cognitive operator that may principally underlie neurocognitive processes and that is impaired in schizophrenia. The hypothesis of prediction error and related predictive coding models provide, among other theories, a framework that can potentially elucidate why neurocognitive processes are impaired in schizophrenia.

In schizophrenia, predictive coding deficits have been linked to reward and salience processing deficits (Murray et al., 2008), repetition suppression deficits (Rentzsch et al., 2015), delusional thoughts (Corlett et al., 2007), paranoid delusions, hallucinations, passivity experience (Blakemore et al., 2000; Horga et al., 2014), circular inferences (Jardri and Deneve, 2013) and altered sense of agency (Voss et al.,

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2010). Impaired prediction error computation in schizophrenia thus seems to be at the core of various cognitive and clinical deficits observed in schizophrenia.

In the predictive coding framework, the mismatch negativity (MMN) is regarded as a correlate of the prediction error that occurs when top-down expectations conflict with bottom-up sensory inputs (Friston, 2005). In addition to prediction error-related impairments on the clinical and the cognitive level, deficits of MMN signals are therefore, not surprisingly, a prominent feature observed in schizophrenia. Despite some negative findings of MMN deficits in schizophrenia (e.g. Kathmann et al., 1995; Salisbury et al., 2002) and in schizophrenia-spectrum psychosis (Salisbury et al., 2017), MMN abnormalities in the auditory modality have been described in schizophrenia with large consistency suggesting a deficient auditory information processing mechanism (Butler et al., 2012; Erickson et al., 2016; Fisher et al., 2012; Salisbury et al., 2002; Umbricht and Krljes, 2005). In addition, deficits of MMN computation are also present in individuals at high risk for schizophrenia and in patients experiencing acute exacerbation of their illness (Fisher et al., 2012; Fisher et al., 2014; Perez et al., 2014). Moreover, deficits of auditory MMN have been shown to predate the onset of the illness (Bodatsch et al., 2011; Shaikh et al., 2012). In addition, deficits of auditory MMN in schizophrenia also correlate with poorer employment, less independent living, worse social perception (Wynn et al., 2010), and cognitive impairments (Baldeweg and Hirsch, 2015). Abnormal MMN signals are thus discussed as a potential biomarker of schizophrenia (Light and Naatanen, 2013; Light and Swerdlow, 2015; Naatanen et al., 2015).

While MMN in the auditory modality is well-studied in schizophrenia, only few studies have investigated the impaired generation of visual MMN (vMMN) in patients with schizophrenia (Farkas et al., 2015; Neuhaus et al., 2013; Urban et al., 2008). All of these studies report deficits of MMN responses to deviant visual stimuli, suggesting a computational deficit that is not restricted to the auditory modality but rather reflects a supra-modal deficit in the cortical network architecture in schizophrenia.

In healthy controls, only few studies have investigated the impact of emotional context on cortical prediction error responses and suggest enhanced cortical and striatal prediction errors by using emotional stimulus material in various paradigms (Bratec et al., 2015; Robinson et al., 2013; Vogel et al., 2015; Watanabe et al., 2013). Enhanced prediction errors may suggest a facilitated processing stream of emotionally salient face expressions, which may be explained by their importance in social interactions (Adolphs, 2003).

In schizophrenia, the effects of emotion on cognitive processes in general and on predictive coding in particular are, at best, insufficiently understood. Although emotional processing deficits in schizophrenia have been described extensively in the literature (Li et al., 2010; Tremeau and Antonius, 2012), research on emotion processing in schizophrenia also has produced mixed findings (Holt, 2016; Llerena et al., 2012; Taylor et al., 2012). This inconsistency between studies may, among other reasons, arise from the specific extent to which each study disentangled emotional processes from cognitive operations that are also triggered by employing emotional stimulus material. Thus, fully understanding emotional processing in schizophrenia represents a challenge that is still to be overcome; in this context, a promising approach to promote our understanding of emotion processing in schizophrenia is to investigate the impact of emotion on basic cognitive operators, such as the prediction error.

Therefore, this study aims to investigate the influence of emotional context on prediction error responses in schizophrenia. Given that earlier studies in healthy controls have shown that emotional context may facilitate cortical prediction error responses and suggest that the processing of emotional stimuli employs a different cortical network when compared to the processing of neutral stimuli (Kimura et al., 2011; Li et al., 2012; Vogel et al., 2015), our study may provide insight into the magnitude of MMN deficits in schizophrenia.

The present study therefore aimed at characterizing the specific impact of emotion on vMMN as a prediction error correlate in schizophrenia patients compared with healthy controls. We extracted the expression-related visual MMN (EMMN), as evoked by emotional and neutral faces. To control for differences in physical properties between stimuli, we applied a sequence oddball paradigm, where the sequence of a male and a female face was established as the standard sequence. In the experimental phase, this standard sequence was sporadically replaced by sequences with a second face that deviated in identity, affective expression (i.e. fearful), or both, which allowed for dividing our participant's neurophysiological responses into categories associated with low (sequence deviant), high (emotional deviant), and intermediate relative emotional engagement (emotional sequence deviant).

2. Methods

2.1. Participants

Seventeen patients diagnosed with schizophrenia (14 men, 3 women) and eighteen controls (15 men, 3 women) participated in this study. The groups were matched for sex and age (±2 years). One patient with schizophrenia was excluded from analysis because of excessive technical artifacts. Demographic and neuropsychological characteristics of the sample are summarized in Table 1.

All patients were recruited at the Department of Psychiatry, Charité University Medicine Berlin, Campus Benjamin Franklin. All patients met DSM-IV criteria for schizophrenia and had no comorbid psychiatric disorder except for nicotine abuse/dependence. Exclusion criteria were (i) current illicit drug abuse, (ii) a history of severe neurological or medical disorder, and (iii) age below 18 or above 65 years. Symptom severity was assessed by board-certified psychiatrists using the Positive And Negative Syndrome Scale (PANSS): positive 17.24 (±4.8); negative 21.62 (±4.3); general 40.32 (±7.5). Control subjects were recruited using internet advertisements. Exclusion criteria (i)–(iii) as well as (iv) any history of psychiatric disorders according to DSM-IV and (v) a family history of psychiatric illness were applied.

Prior to commencement of the study, participants gave written informed consent and completed a battery of questionnaires, which is specified under *neuropsychological profile* in the supplementary material. All participants were right-handed, as assessed with the Edinburgh Handedness inventory, and had normal or corrected-to-normal vision.

Table 1
Sample description.

Measure	Schizophrenia ($N = 17$)	Controls ($N = 18$)	p
Age [years]	31.94 (7.5)	30.67 (6.5)	n.s.
Age range [years]	20–45	21–43	–
Education [years]	14.47 (3.2)	17.11 (2.5)	0.01
Proportions questions tale correct	0.76 (0.13)	0.77 (0.17)	n.s.
Accuracy button click	0.98 (0.03)	0.99 (0.02)	n.s.
FTND	2.00 (2.5)	0.83 (1.9)	n.s.
DST 2 min	57.88 (16.1)	76.94 (12.5)	<0.001
IQ			
MWTB [verbal IQ]	107.24 (13.5)	112.83 (12.9)	n.s.
LPS [non-verbal IQ]	111.18 (5.8)	114.28 (10.8)	n.s.
EHI [laterality index]	83.47 (20.8)	80.67 (16.9)	n.s.
IRI			
Perspective taking	17.00 (4.3)	18.11 (3.7)	n.s.
Fantasizing	14.12 (5.9)	15.72 (4.2)	n.s.
Empathic concern	17.06 (4.0)	19.67 (3.1)	0.04
Personal distress	12.82 (4.7)	12.06 (6.5)	n.s.

All values are mean values with standard deviation in parenthesis. Between-group differences were assessed by *t*-tests for independent samples. DST 2 min, Digit Symbol Test, 2 min version; EHI, Edinburgh Handedness Inventory; FTND, Fagerström Test for Nicotine Dependence; IRI, Interpersonal Reactivity Index; IQ, intelligence quotient; LPS, Leistungsprüfsystem; MWTB, Mehrfachwortschatztest; n.s., not significant at $p = 0.05$.

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