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Abnormal, affect-specific modulatory effects on early auditory processing in schizophrenia: Magnetoencephalographic evidence

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ABSTRACT

Abnormalities in the perception and identification of emotions have frequently been reported in schizophrenia. Hemodynamic neuroimaging studies found functional abnormalities in cortical and subcortical brain circuits that are involved in normal affective processing, but the temporal dynamics of abnormal emotion processing in schizophrenia remain largely elusive. To investigate this issue, we recorded early auditory evoked field components by means of whole-head magnetoencephalography that were in response to emotion-associated tones in seventeen patients with schizophrenia and in seventeen healthy, matched controls. Forty-two click-like tones (conditioned stimuli; CS) acquired differential emotional meaning through an affective associative learning procedure by pairing each CS three times with either pleasant, unpleasant or neutral auditory scenes. As expected, differential affect-specific modulation in patients vs. controls was evident, starting at the auditory N1m onset latency of approximately 70 ms, extending to 230 ms. While controls showed the expected enhanced processing of emotion associated CS, patients revealed an inverted pattern with reduced processing of arousal, when compared to neutral stimuli, in the right prefrontal cortex. The present finding suggests impairments in the prioritization of emotionally salient vs. non-salient stimuli in patients with schizophrenia. Dysfunction in higher cognitive processes and behavior in schizophrenia may therefore reflect dysfunction in fundamental, early emotion processing stages.

1. Introduction

Abnormalities in emotion perception and identification have frequently been reported in schizophrenia (Phillips et al., 2003). In several studies, schizophrenic patients show impaired recognition of facial emotion (Mueser et al., 1997; Edwards et al., 2001; Whittaker et al., 2001; Morris et al., 2009), most consistently in the identification of negative affect (Bell et al., 1997; Edwards et al., 2002). Moreover, ambiguous or neutral emotional stimuli were identified as more threatening by schizophrenic patients than stimuli that depicted overt fear or threat (Phillips et al., 2000). Although only few studies have investigated emotional processing effects for other sensory modalities, there is evidence for deficient identification of affect in speech/affective prosody (Murphy and Cutting, 1990) and of unpleasant odors (Crespo-Facorro et al., 2001).

Hemodynamic neuroimaging studies have shown functional abnormalities in cortical and subcortical circuits that are involved in affective processing (Phillips et al., 2003). Patients with schizophrenia show less affect-specific modulation in response to emotionally salient stimuli, particularly in the amygdala (Schneider et al., 1998; Gur et al., 2002; Taylor et al., 2002), the prefrontal cortex (PFC; Paradiso et al., 2003; Takahashi et al., 2004) and sensory-specific brain regions (Taylor et al., 2002; Paradiso et al., 2003). However, the temporal dynamics of deficient emotion processing in schizophrenia remain largely unknown.

Studies with healthy subjects that employ whole-head magnetoencephalography (MEG) or high-density electroencephalography (EEG) suggest that affective processing of visual stimuli already occurs at very early latencies and argue that these rapid cortical emotion processes play an important role (Pessoa and Adolphs, 2010). To investigate electrophysiological correlates of early emotion processing, affective *MultiCS conditioning* was introduced by our group (Bröckelmann et al., 2011; Steinberg et al., 2012; Steinberg et al., 2013). While classical affective conditioning typically uses one neutral stimulus (conditioned stimulus, CS) that becomes associated with an unconditioned stimulus (US) within several contingent CS–US pairings and acquires the power to elicit a conditioned response (CR) that was previously evoked by US presentation, MultiCS conditioning involves multiple complex stimuli

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(e.g., faces or tones) per affective category that acquire emotional meaning within a few associative learning trials.

MultiCS conditioning revealed affect-specific, amplified processing of CS faces that were associated with an unpleasant, rather than a neutral, US between 60 and 90 ms after stimulus-onset (visual C1m component; Steinberg et al., 2012). For auditory processing, these effects were already evident in the P20–50 m component but were strongest in the N1m component (Bröckelmann et al., 2011). Notably, the PFC was consistently activated as part of a distributed, modality-independent cortical network (Steinberg et al., 2013).

Here, we adopted the MultiCS conditioning procedure that was used by Bröckelmann et al. (2011) to analyze auditory evoked fields (AEFs) in response to multiple distinct click-like tones (CS) by MEG before and after three contingent pairings, with an equal number of pleasant, unpleasant, or neutral auditory scenes (UCS) in patients with schizophrenia and matched controls. The low demands on task performance, as well as on cognitive and explicit learning capacities, allowed for a valid comparison of patients with schizophrenia and gender-matched, age-matched and education-matched controls, regarding differences in early emotion processes by means of the MultiCS conditioning paradigm.

We hypothesized that there would be abnormalities in affect-specific modulation of click-tone processing after emotional learning in patients. Abnormalities should manifest as altered differential responsiveness to emotionally salient stimuli at early processing stages (Rockstroh et al., 2006). Regarding the predominant N1 effects of auditory motivated attention in a healthy sample (Bröckelmann et al., 2011), the prevalent deficits of directed attention in the auditory N1 of schizophrenic patients (e.g., Gallinat et al., 2002) and the model with networks of directed and motivated attention being closely linked (e.g., Steinberg et al., 2013), we expected a neural correlate of early emotional dysfunction in the N1m time-window (70–130 ms).

2. Methods

2.1. Participants

Seventeen inpatients with schizophrenia, recruited from the Department of Psychiatry of the University Hospital of Muenster, and seventeen healthy control subjects who were individually matched for age, gender, years of education and handedness (Table 1) were investigated. Subjects gave written informed consent to the protocol, which was approved by the local Ethics Committee (protocol 2006-351-f-S), according to the Declaration of Helsinki.

All of the participants had normal hearing that was assessed by individual hearing threshold determination. Thirty-two participants were right-handed, and two were left-handed. All of the patients met the criteria in the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000) for schizophrenia (SCID-I, Structured Clinical Interview for DSM-IV). Diagnoses were confirmed by a chart review and a consultation with the treating clinician. The mean duration of illness was 66.6 months (SD = 74.3), and at the time of testing, all of the patients were stabilized after having an acute psychotic episode with moderate psychopathology scores (Positive And Negative Syndrome Scale (PANSS), Kay et al., 1987; see Table 1). All but one patient received atypical antipsychotic medication (chlorpromazine equivalent dosage: mean = 674.2 mg/day, SD = 326.6; amisulpride: $N = 1$, aripiprazole: $N = 2$, clozapine: $N = 3$, olanzapine: $N = 4$, quetiapine: $N = 6$, risperidone: $N = 5$, sertindole: $N = 4$, ziprasidone: $N = 1$; typical neuroleptics: perazine: $N = 1$; combination of neuroleptics: $N = 12$) at stable doses for at least two weeks before scanning. Dimensions of hallucinations and delusions were assessed with the Psychotic Symptom Rating Scales (PSYRATS; Haddock et al., 1999). One patient suffered from intermittent acoustic hallucinations but did not experience any form of hallucination at the time of the MEG scanning. Intellectual performance was screened with the WAIS-R vocabulary test (Wechsler Adult Intelligence Scale; German version by Tewes, 1991).

Exclusion criteria for both groups included having neurological disorders, brain damage, serious head injury, substance abuse or dependence, or any contraindication for the MEG/MRI scanning. Control subjects with any lifetime history of a psychiatric disorder (SCID-I) or any first-degree relative with a psychotic disorder were excluded from the study.

2.2. Stimulus material and experimental procedure

2.2.1. Conditioned stimuli (CS)

Conditioned stimuli included a set of 42 natural tones that were generated by striking different hard materials (metal, glass, etc.) against each other, trimmed to a length of 20 ms and normalized regarding loudness. Despite their brief duration and the overall homogeneity of the stimulus set, all of the tones showed distinct physical properties and could be instantaneously differentiated.

2.2.2. Unconditioned stimuli (UCS)

As unconditioned stimuli, 14 highly-arousing unpleasant (UCS^{neg}), 14 highly-arousing pleasant (UCS^{pos}) and 14 low-arousing neutral (UCS^{neut}) sounds were selected from the International Affective Digitized Sounds system (IADS, Bradley and Lang, 2000) and trimmed to a length of 6 s. The selection was based on ratings of hedonic valence (means: $UCS^{neg} = 2.3 < UCS^{neut} = 4.9 < UCS^{pos} = 7.0$) and emotional arousal (means: $UCS^{neg} = 7.2 > UCS^{neut} = 4.3 < UCS^{pos} = 7.0$) on

Table 1
Demographic and clinical characteristics of all of the subjects.

	Schizophrenic patients ($N = 17$), mean (SD)	Control subjects($N = 17$), mean (SD)	Statistics	p
Age (years)	27.9 (7.7)	27.5 (6.9)	$t_{(32)} = -0.165$	0.870[a]
Sex (male:female)	7:10	7:10	$\chi^2_{(1)} = 1.059$	0.303[a]
Education (years)	12.1 (1.4)	12.2 (1.4)	$t_{(32)} = 0.245$	0.808[a]
WAIS-R[b]	20.1 (5.2) ($N = 15$)	24.4 (5.0)	$t_{(30)} = 2.360$	0.025
Duration of illness (months)	66.6 (74.3)	–	–	–
Chlorpromazine equivalent daily dosage (mg/day)	674.2 (326.6)	–	–	–
PANSS[c] total score	68.7 (10.0)	–	–	–
PANSS positive score	14.4 (2.7)	–	–	–
PANSS negative score	18.3 (5.3)	–	–	–
PANSS general psychopathology	35.3 (4.9)	–	–	–

[a] Patients and controls were matched according to age, sex and education.
[b] Wechsler Adult Intelligence Scale (German version by Tewes, 1991).
[c] Positive and Negative Syndrome Scale for schizophrenia (Kay et al., 1987).