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Event-Related Theta Synchronization Predicts Deficit in Facial Affect Recognition in Schizophrenia

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Growing evidence suggests that abnormalities in the synchronized oscillatory activity of neurons in schizophrenia may lead to impaired neural activation and temporal coding and thus lead to neurocognitive dysfunctions, such as deficits in facial affect recognition. To gain an insight into the neurobiological processes linked to facial affect recognition, we investigated both induced and evoked oscillatory activity by calculating the Event Related Spectral Perturbation (ERSP) and the Inter Trial Coherence (ITC) during facial affect recognition. Fearful and neutral faces as well as nonface patches were presented to 24 patients with schizophrenia and 24 matched healthy controls while EEG was recorded. The participants' task was to recognize facial expressions. Because previous findings with healthy controls showed that facial feature decoding was associated primarily with oscillatory activity in the theta band, we analyzed ERSP and ITC in this frequency band in the time interval of 140–200 ms, which corresponds to the N170 component. Event-related theta activity and phase-locking to facial expressions, but not to nonface patches, predicted emotion recognition performance in both controls and patients. Event-related changes in theta amplitude and phase-locking were found to be significantly weaker in patients compared with healthy controls, which is in line with previous investigations showing decreased neural synchronization in the low frequency bands in patients with schizophrenia. Neural synchrony is thought to underlie distributed information processing. Our results indicate a less effective functioning in the recognition process of facial features, which may contribute to a less effective social cognition in schizophrenia.

Keywords: EEG, emotion recognition, ERSP, facial affect recognition, ITC, schizophrenia

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Deficits in facial expression perception have been shown to be closely related to psychosocial functioning and quality of life in schizophrenia (Kee, Green, Mintz, & Brekke, 2003). Because of their good temporal resolution, event related potential (ERP) paradigms have traditionally been used to explore the stages in the cascade of facial processing (for a review see Luo, Feng, He, Wang, & Luo, 2010). Several studies reported that patients with schizophrenia show deviations in face-evoked ERPs compared with healthy controls (Mandal, Pandey, & Prasad, 1998). Results, however, have been inconsistent and have been discussed in the context of the bottom-up or top-down view of emotional information processing. Based on specific ERP components related to facial emotion processing, such as amplitude differences of the face-specific N170, the N250, or the P300 in patients with schizophrenia versus controls, most studies suggest a deficit during the structural decoding of the face (N170) in patients (Ibáñez et al., 2012; Jung, Kim, Kim, Im, & Lee, 2012; Wolwer et al., 2012; Herrmann, Ellgring, & Fallgatter, 2004). However, some of the studies found deficits at a later phase, during decoding of facial affect features (Wynn, Lee, Horan, & Green, 2008). A possible explanation is offered by Turetsky et al. (2007), who showed that patients with schizophrenia demonstrate abnormalities in early

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visual decoding of facial features, which precedes the ERP response typically associated with facial affect recognition. They found that the variance of the P300 component was explained by the N170, and concluded that affect recognition deficits are secondary to faulty structural decoding of faces.

None of the above mentioned studies reported a relationship between electrophysiological measures of face decoding (N170) and emotion recognition performance. One possible explanation for the lack or limited correlations could be that the recognition tasks applied during EEG recordings were too simple, resulting in little variation in performance and in a statistical ceiling effect. To address this issue, in the present study an additional, more comprehensive and sensitive measure of facial emotion recognition was applied after the EEG recordings.

Furthermore, the failure to find a correlation between ERPs, such as the face-sensitive N170 and emotion recognition performance, could be attributable to the fact that conventional ERP analysis yields only a partial insight into the electrophysiological processes triggered by facial expressions since it captures only event-locked, but not event-induced activity (Makeig, 1993). The reason is that unlike evoked responses, induced activity is not phase-locked to the stimulus, and if a brain response to an event is not phase-locked across trials precisely enough, the potentially important induced activity will be averaged out. Accordingly, oscillatory changes "induced" by experimental events can be poorly represented in, or completely absent from, the time-domain features of the ERP "evoked" by the same events. To gain a full insight into the electrophysiological activity linked to facial affect recognition, in the present study both evoked and induced activity were analyzed by calculating the Event Related Spectral Perturbation (ERSP) during stimulus processing (Makeig, 1993). ERSP measures relative changes from the spectral power baseline, allowing the study of the time course of the EEG signal energy in specific frequency bands. The strength of phase-locking was assessed by calculating the phase-locking factor, the Inter Trial Coherence (ITC) (Makeig, Debener, Onton, & Delorme, 2004). ITC is a measure of consistency of relative phase at a given latency in response to environmental events and was reported to vary with task conditions in visual experiments(Delorme & Makeig, 2004; Freunberger, Klimesch, Doppelmayr, & Holler, 2007; Mishra, Martinez, Schroeder, & Hillyard, 2012). In other words, ITC measures the phase coherence across trials, but not across electrodes.

Based on previous animal and human studies, Buzsáki and Draguhn (2004) proposed that theta oscillations coordinate the firing of larger subunits of neurons and thus contribute to complex functions such as emotions. Empirical data from previous findings with healthy controls showed that facial feature decoding (Sakihara, Gunji, Furushima, & Inagaki, 2012) and emotion recognition (Balconi & Lucchiari, 2006) were associated with oscillatory activity in the theta band (4–7 Hz) in the 150–200 ms after stimulus presentation. In addition, a study of facial expression processing using MEG (Maratos, Mogg, Bradley, Rippon, & Senior, 2009) found differences in theta oscillations between fearful and neutral faces and proposed that theta oscillations play an important role in integrating activity within emotion-processing networks. Based on these results, we assumed that facial emotion recognition would be associated primarily with theta-band oscillations.

Only a few studies have examined oscillatory brain activity linked to emotion recognition in psychiatric conditions. Aftanas, Varlamov, Reva, and Pavlov (2003) found disrupted event related synchronization over the left hemisphere in patients with alexithymia compared with healthy controls when viewing affective pictures. Furthermore, a recent hypothesis put forward by Uhlhaas et al. (2011, 2010) suggests that aberrant development of neural oscillations during adolescence in schizophrenia may lead to impaired neural activation and temporal coding and thus lead to neurocognitive dysfunctions, such as deficits in facial affect recognition. A study by Ramos-Loyo et al. (2009) found decreased theta activity over central and frontal regions in patients with schizophrenia in a facial emotion recognition task. However, in this study neither the changes from baseline in oscillatory activity (synchronization) nor ITC were measured. To our knowledge the present investigation is the first to analyze the time course of induced and evoked theta oscillations and intertrial phase coherence in patients with schizophrenia during facial emotion recognition.

In the present investigation, fearful and neutral faces as well as nonface patches were presented to patients with schizophrenia and matched healthy controls while EEG was recorded. The participants' task was to recognize facial expressions and respond by depressing a button. An additional standardized facial emotion recognition task (Ekman & Friesen, 1976) was applied after the EEG recordings. The following hypotheses were tested:

1) We hypothesized that event-related theta synchronization induced by facial stimuli would predict overall facial affect recognition performance.

2) We expected patients with schizophrenia to exhibit decreased theta oscillatory amplitude and phase-locking to facial stimuli relative to healthy control subjects. Furthermore we expected the decreased ERSP and ITC in the schizophrenia group to be face-specific, that is, no or decreased difference in ERSP and ITC was expected to nonface stimuli between the two groups.

3) We hypothesized higher theta ERSP and ITC to facial expressions relative to nonfacial visual stimuli. Based on previous ERP studies (Blau, Maurer, Tottenham, & McCandliss, 2007; Eimer & Holmes, 2007) a difference in ITC and ERSP between neutral and fearful faces was also expected, however other studies reported no relationship between emotional content of the face and the N170 component (Ashley, Vuilleumier, & Swick, 2004; Eimer & Holmes, 2002).

Method

Subjects

Twenty-four patients meeting the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM–IV*; American Psychiatry Association, 1994) criteria for schizophrenia and 24 healthy controls were enrolled in the study. Healthy controls were individually matched to the patients by gender, age (±5 years), and years of education (±3 years), thus resulting in 24 matched pairs. With the exception of three left-handed patients and two

left-handed healthy controls, all participants were right-handed and had normal or corrected-to-normal vision. Participants did not receive payment for their participation and provided written informed consent after all procedures were fully explained according to study protocol approved by the Institutional Review Board of the Semmelweis University.

Patients were recruited from both the inpatient and outpatient units of the Department of Psychiatry and Psychotherapy of the Semmelweis University, Budapest. All patients were assessed on the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) by a trained psychiatrist or psychologist. All patients were taking antipsychotic medication at the time of testing. We convert all antipsychotic doses to chlorpromazine equivalents, using published equivalencies for oral conventional (American Psychiatric Association, 1997) and atypical antipsychotics (Woods, 2003). The exclusion criteria for patients with schizophrenia were any other *DSM–IV* Axis I disorder, any other central nervous system disease, mental retardation, history of head injury with loss of consciousness for more than 1 hour, and alcohol or drug abuse. Exclusion criteria for healthy controls included history of any psychiatric or neurological disease, mental retardation, history of head injury with loss of consciousness for more than one hour, and alcohol or drug abuse. Demographic information for both groups and clinical characteristics of the schizophrenia group are presented in Table 1.

Stimuli and Procedures

During EEG recordings, subjects were seated in a dimly lit, sound-attenuated room. Stimuli were presented on a computer screen at a viewing distance of approximately 50 cm using the Presentation 13.0 software (Neurobehavioral Systems, Inc.). The pictures were chosen from Ekman and Friesen's Face stimuli inventory (Ekman & Friesen, 1976). Nonfacial parts of the pictures (hair, background) were removed. Five female and five male faces were used, each displaying a neutral ($p = .4$) and a fearful expression ($p = .4$), yielding altogether 20 stimuli. Stimuli were presented for 200 ms, followed by a blank screen with a fixation cross until the participant's behavioral response. The interval between the response and presentation of subsequent stimulus varied randomly between 600 ms and 700 ms with a mean of 650 ms. As nonface control stimuli, phase-randomized patches were generated from the Ekman-faces that were presented for 200 ms with a probability of $p = .2$. To generate these nonface patches, faces were phase-randomized using the "Weighted mean phase (WMP) type phase scrambling" (Dakin, Hess, Ledgeway, & Achtman, 2002). As compared with other phase blending procedures that lead to nonmonotonicities in main image attributes (Rainer, Augath, Trinath, & Logothetis, 2001), the WMP blending procedure produces monotonic changes in statistics considered essential for phase representation: contrast and kurtosis/sparseness. These statistics have been known to be linked to the human perception of structure in images and shown to influence cortical activity. By using this procedure the nonface patch condition contained same visual information in the face stimuli, just "scrambled up."

Occasionally a schematic picture of an eye was presented to the participants for 1000 ms followed by a 1000-ms interval of a blank screen (no response was asked), giving them the chance to blink and thus to achieve reduction in blink-related artifacts during facial stimulus presentation (Diana, Van den Boom, Yonelinas, & Ranganath, 2011). Participants were instructed to respond as quickly and accurately as possible by pressing one of two buttons whenever they perceived the facial expression displayed as neutral, and the other button whenever they perceived the facial expression displayed as fearful. Figure 1 gives an overview of representative experimental trials.

The following clinical and emotion recognition measures were obtained from all participants before EEG recording: the SCL-90, a 90-item Symptom Checklist assessing general dimensions of psychopathology, and the Ekman-60 Test (Facial Expressions of Emotion – Stimuli and Tests, FEEST; Ekman P

Table 1
Demographic Data, Clinical Characteristics, and Behavioral Results[a]

Characteristic	Subjects with schizophrenia ($n = 24$)	Healthy control participants ($n = 24$)	Statistics	p value[b]
Age (years)	34.2 (10.3)	33.2 (9.8)	—	—
Education (years)	13.9 (2.2)	15.0 (2.6)	—	—
Gender (male/female)	13/11	13/11	—	—
Symptom Checklist 90 (Global Severity Index)	98.6 (66.6)	22.9 (23.5)	—	—
Duration of illness (years)	9.7 (7)	N/A	—	—
Chlorpromazine equivalent (mg)	601.9 (445.5)	N/A	—	—
Antipsychotic medication (atypical/typical)	23/1	N/A	—	—
PANSS total	59.4 (21.6)	N/A	—	—
PANSS positive	14.5 (6.0)	N/A	—	—
PANSS negative	15.1 (7.5)	N/A	—	—
Schizophrenia subtypes: Paranoid/Catatonic/Disorganized/Undifferentiated	13/2/6/3	N/A	—	—
Inpatients/Outpatients	9/15	N/A	—	—
FEEST[c]	79% (9.3)	85.9% (7.5)[d]	$t = 2.7$	0.01
Emotion recognition during EEG (overall)	91%	95%	$\chi^2 = 9.8$	0.002
Reaction time during EEG (overall)	747 ms (270)	639 ms (196)	$\chi^2 = 11.2$	0.001

[a] Continuous variables are characterized by mean (*SD*); categorical variables are represented by frequencies (n). [b] Level of significance: The difference between study groups was tested by unpaired t test for the FEEST. For emotion recognition, and reaction time during EEG, the differences were tested by Kruskal Wallis χ^2. [c] FEEST = Facial Expressions of Emotion – Stimuli and Tests (Ekman and Friesen, 1976). [d] $n = 21$ for control participants, as because of technical difficulties, 3 healthy control subjects' emotion recognition scores were not obtained.

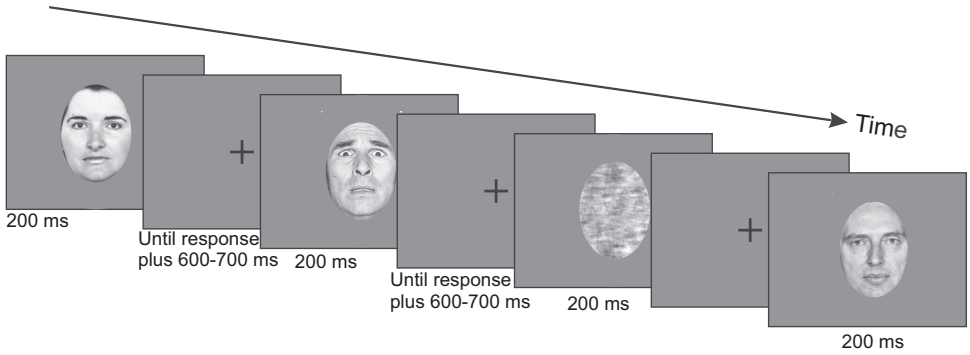

Figure 1. Stimuli and paradigm.

& Friesen WV, 1976), a computerized emotion recognition task, using stimuli from the Ekman and Friesen pictures of facial affect. Sixty pictures depicting the six primary emotions (anger, fear, disgust, happiness, sadness, and surprise) were presented in random order. Subjects were asked to pair the emotion displayed in each photograph with one of the six emotion labels displayed on the screen. This test was used to obtain a more sensitive measure of facial affect recognition, because the emotion recognition task which was used during the EEG had presented only neutral or fearful expressions.

Recordings

EEG was recorded from DC with a low-pass filter at 100 Hz using a high-density 128-channel BioSemi ActiveTwo amplifier (Metting van Rijn, Peper, & Grimbergen, 1990). The electrode cap covered the whole head with an equidistant-layout. Eye movements were monitored by two electrooculogram (EOG) electrodes placed below the left and above the right external canthi. Data were digitized at 24-bit resolution and a sampling rate of 512 Hz. Subsequent data analyses were carried out off-line by using the built-in functions of the EEGLAB toolbox (Delorme & Makeig, 2004) in Matlab (MathWorks, Natick, MA). Further statistical analyses were carried out using the SAS 9.2 software (SAS Institute, Inc.). EEG was rereferenced to the common average potential and filtered off-line between 0.1 and 100 Hz using zero-phase shift Butterworth filter. Epochs from 350 ms prestimulus to 800 ms poststimulus were extracted from the continuous EEG for further analysis and corrected for the prestimulus baseline. To avoid potential artifacts, epochs with a voltage exceeding ± 120 μV on any EEG or EOG channel were rejected from the analysis. Total trial number per each picture type (fearful and neutral) was 192. After artifact rejection, the average number of trials in the control group was 167 trials (SD = 20.6) and 168 trials (SD = 17.2) for the fearful and neutral condition, respectively. For patients with schizophrenia the mean trial number was 155 trials (SD = 26.7) and 156 trials (SD = 26.3) for fearful and neutral faces, respectively.

Data Analysis

Stimulus-related theta activity (4–7 Hz) changes were measured by the event-related spectral perturbation (ERSP), which provides a two-dimensional representation of mean change in spectral power (in dB) from baseline. Stimulus-locked evoked activity was measured by inter trial coherence (ITC), which provides a two-dimensional representation of strength (0 to 1) of the phase locking of the EEG signals to the time-locking events (Makeig et al., 2004). Furthermore, the N170 ERP component was also calculated.

To compute the ERSP and the ITC, baseline spectra are calculated from the EEG immediately preceding each event. The epoch is divided into brief, overlapping data windows, and a moving average of the amplitude spectra of these is created. Each of these spectral transforms of individual response epochs are then normalized by dividing by their respective mean baseline spectra. Normalized response transforms for many trials are then averaged to produce an average ERSP, plotted as relative spectral log amplitude on a time-by-frequency plane (Delorme & Makeig, 2004; see details in online Supplement 1).

Based on prior studies applying similar paradigms (Balconi & Lucchiari, 2006; Zhang, Wang, Luo, & Luo, 2012; Herrmann et al., 2004) to study facial emotion processing, the 140–200 ms time window (±30 ms around 170 ms) was selected for analysis. Several previous investigations applying concurrent ERP and fMRI measures, found that the principal sources of the electrophysiological activity of the brain in this time interval during facial expression processing are located in the fusiform face area, and the superior temporal sulcus (Sadeh, Podlipsky, Zhdanov, & Yovel, 2010; Iidaka, Matsumoto, Haneda, Okada, & Sadato, 2006; Horovitz, Rossion, Skudlarski, & Gore, 2004). Mean ERSPs, ITCs, and ERPs values were calculated by averaging across electrodes within regions of interest (ROIs). Supplemental Figures S1 and S2 show ERPS and ITC from 1 to 50 Hz in the different ROIs. ROIs were defined based on previous studies using similar paradigms and analysis methods (Knyazev, Slobodskoj-Plusnin, & Bocharov, 2009; Aftanas, Varlamov, Pavlov, Makhnev, & Reva, 2001). Electrode clusters selected for analyses are marked with black dots in black frames in Figure 2. The different effects on ERSP, ITC, and ERPs were tested by three-way analyses of covariance (ANCOVA) of study group (healthy control [HC] vs. schizophrenia [SZ]) × ROI (left and right frontal, central, left and right temporal, left and right occipital) × stimulus type (fear vs. neutral vs. nonface patches). To investigate the interactions, post hoc t tests were conducted. Because between-groups comparisons were evalu-

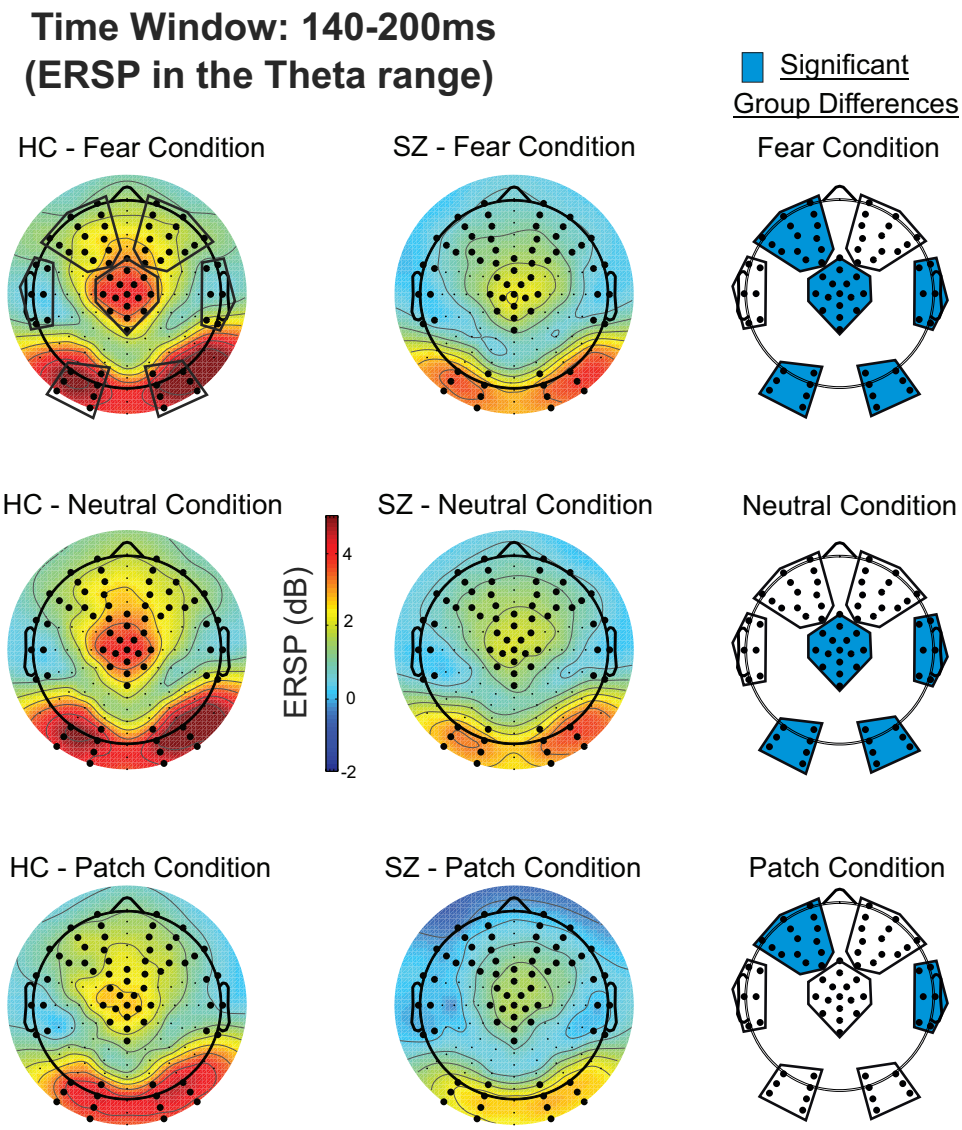

Figure 2. Scalp topography of the event-related spectral perturbation (ERSP) in the two study groups in the three experimental conditions. Electrode clusters selected for analyses (regions of interests) are marked with black dots in black frames in the upper-left scalp map. Regions with significant group differences are highlighted in blue in the third column. HC = Healthy Control Group; SZ = Schizophrenia Group.

ated over seven regions, Bonferroni correction for multiple comparisons was applied to the post hoc tests, and the alpha value was set to 0.05/7 = 0.007. The alpha value for a marginally significant difference was set to 0.1/7 = 0.014.

The associations of emotion recognition performance (as indexed by the FEEST) with ERSP, ITC, and ERPs were investigated by Pearson correlation. Relationship between ERSP, ITC, and emotion recognition performance during EEG was examined by Spearman correlation in both study groups separately. In the latter case the Spearman correlation was used, because the results of this recognition task was strongly left-skewed. All correlations were controlled for age, gender, and education by calculating partial correlations.

Results

Behavioral Results

Details of the behavioral tasks are summarized in Table 1. Control subjects significantly outperformed patients in both behavioral tests, namely on the emotion recognition task as indexed by the FEEST, and on the emotion recognition task during the EEG experiment. In the emotion task during EEG both groups showed a relatively high recognition rate of emotions (>90%). Controls had a significantly shorter reaction time (RT) during the emotion recognition task than patients with schizophrenia. As a result of technical difficulties three healthy control subjects' emo-

tion recognition scores were not obtained; thus, $n = 21$ control participants' data were entered in the between-groups comparison.

Stimulus-Related Changes in Theta Response and Correlations With Behavioral Results

Between group differences in evoked and induced theta amplitude (ERSP). A significant main effect of study group, $F(1, 46) = 10.9$, $p = .002$, was observed in evoked and induced theta response amplitude, which was caused by decreased theta power in patients with schizophrenia compared with healthy controls. A significant main effect of region, $F(6, 46) = 26.4$, $p < .0001$, was caused by the activity gradient Occipital > Central > Frontal > Temporal Right > Temporal Left pattern (all p values <0.007). A main effect of stimulus type, $F(2, 46) = 7.4$, $p = .002$, was caused by increased theta activity to faces relative to nonface patches (Fearful vs. Non-Face: $t = 3.8$, $p = .0004$; Neutral vs. Non-Face: $t = 3.7$, $p = .0006$), while no significant difference was found between fear and neutral faces ($t = 1.02$, $p = .31$).

There was a significant three-way interaction between study group, ROI, and condition, $F(12, 46) = 3$, $p = .004$. Post hoc tests revealed that theta activity was decreased in the patient group relative to the controls in the left frontal ($t = 3.0$, $p = .005$), central ($t = 3.5$, $p = .001$), right temporal ($t = 3.2$, $p = .002$), and both occipital regions (Left: $t = 2.8$, $p = .007$; Right: $t = 2.9$, $p = .005$) for the fear condition; in the central ($t = 4$, $p = .0002$), both occipital (Left: $t = 2.9$, $p = .006$; Right: $t = 2.8$, $p = .007$), and right temporal regions ($t = 3.0$, $p = .004$) for the neutral face condition; and in the left frontal ($t = 3.6$, $p = .0009$) and right temporal regions ($t = 2.9$, $p = .007$) for the nonface condition. The largest between-groups differences (1–1.2 in terms of Cohen's d) were detected over the central region for the neutral and fear conditions. Time course of the theta activity in the ROIs is shown in Figure 3.

Association between theta ERSP and behavioral results. Correlations between theta amplitude to fearful faces and emotion recognition performance as indexed by the FEEST were significant in both study groups in the left frontal (Controls: $r = .5$, $n = 21$, $p = .03$; Patients: $r = .54$, $n = 24$, $p = .01$), and right frontal ROIs (Controls: $r = .49$, $n = 21$, $p = .04$; Patients: $r = .54$, $n = 24$, $p = .01$). Correlations are shown in the top left and right panels in Figure 3. Emotion recognition correlated significantly with theta activity to neutral faces only in the patient group in the left (Controls: $r = .34$, $n = 21$, $p = .17$; Patients: $r = .62$, $n = 24$, $p = .003$) and right (Controls: $r = .41$, $n = 21$, $p = .09$; Patients: $r = .56$, $n = 24$, $p = .008$) frontal ROIs. All correlations were controlled for age, gender, and education.

Greater increases in theta activity were associated with higher emotion recognition rates in all cases (Figure 3). No significant association between ERSP to the nonface patch and emotion recognition was found in any of the ROIs ($p > .05$).

Correlations between emotion recognition performance during EEG recording and theta activity did not reach significance in any of the study groups ($p > .05$). Theta activity did not correlate significantly with symptom severity as indexed by the PANSS, nor with medication dose in Chlorpromazine Equivalents ($p > .05$).

Phase-Locking in the Theta Band

Between-groups differences in theta phase-locking (ITC). A significant main effect of study group, $F(1, 46) = 5.1$, $p = .03$, region, $F(6, 46) = 209$, $p < .0001$; Occipital > Central > Frontal > Temporal Right > Temporal Left (all p values <0.007), and stimulus type, $F(2, 46) = 5.7$, $p = .006$, was found. Patients with schizophrenia showed a decreased phaselocking relative to control subjects. ITC to faces was increased relative to nonface patches (Fearful vs. Non-Face: $t = 3$, $p = .005$; Neutral vs. Non-Face: $t = 2.6$, $p = .01$); furthermore, ITC to fearful faces was significantly increased relative to neutral faces ($t = 2.7$, $p = .01$).

There was a significant three-way interaction between study group, ROI, and condition, $F(12, 46) = 2.4$, $p = .02$. After performing post hoc tests and correction for multiple comparisons ITC decrease was marginally significant in the patient group over the central region for both face conditions ($n = 45$, Fearful: $t = 2.7$, $p = 0.009$; Neutral: $t = 2.6$, $p = 0.01$). *Between group differences were 0.79 and 0.77 in terms of Cohen's d* to fearful and neutral stimuli, respectively. In the other ROIs between-groups differences were not significant (uncorrected p values > 0.014).

Association between ITC and behavioral results. Emotion recognition performance as indexed by the FEEST correlated significantly with ITC to both face conditions over the left frontal ROI in the patient group (Fearful: $r = .54$, $n = 24$, $p = .01$; Neutral: $r = .49$, $n = 24$, $p = .02$), and over the right frontal ROI in the control group (Fearful: $r = .55$, $n = 21$, $p = .02$; Neutral: $r = .53$, $n = 21$, $p = .02$). In the control group emotion recognition performance correlated significantly with ITC to neutral face condition over the left temporal region, and showed a tendency with ITC to fearful face condition in the same region (Fearful: $r = .44$, $n = 21$, $p = .07$; Neutral: $r = .51$, $n = 21$, $p = .03$). All correlations were controlled for age, gender, and education.

In the control group, emotion recognition performance during the EEG recording and ITC to both face conditions correlated significantly over the right frontal region (Fearful: $r = .47$, $n = 21$, $p = .05$; Neutral: $r = .5$, $n = 21$, $p = .04$). In the patient group, emotion recognition performance during EEG recording correlated significantly with ITC to fearful face condition, and showed a tendency with ITC to neutral face condition over the right temporal region (Fearful: $r = .49$, $n = 24$, $p = .02$; Neutral: $r = .41$, $n = 24$, $p = .06$).

Stronger intertrial coherence (ITC) was associated with higher recognition rates in all cases. No significant association between ITC to the nonface patch and emotion recognition was found in any of the ROIs ($p > .05$). ITC did not correlate significantly with symptom severity as indexed by the PANSS, nor with medication dose in Chlorpromazine Equivalents ($p > .05$).

Between Group Differences in the n170 ERP Component, and Correlations With Emotion Recognition

The n170 component did not differ significantly between study groups, $F(1, 46) = 1.8$, $p = .19$. The two-way interaction of study group and stimulus condition was not related to the N170 component, $F(2, 46) = 0.5$, $p = .63$, nor was the study group and region two-way interaction, $F(6, 46) = 2.2$, $p = .06$, and the three-way interaction of study group, region, and stimulus condition, $F(12,$

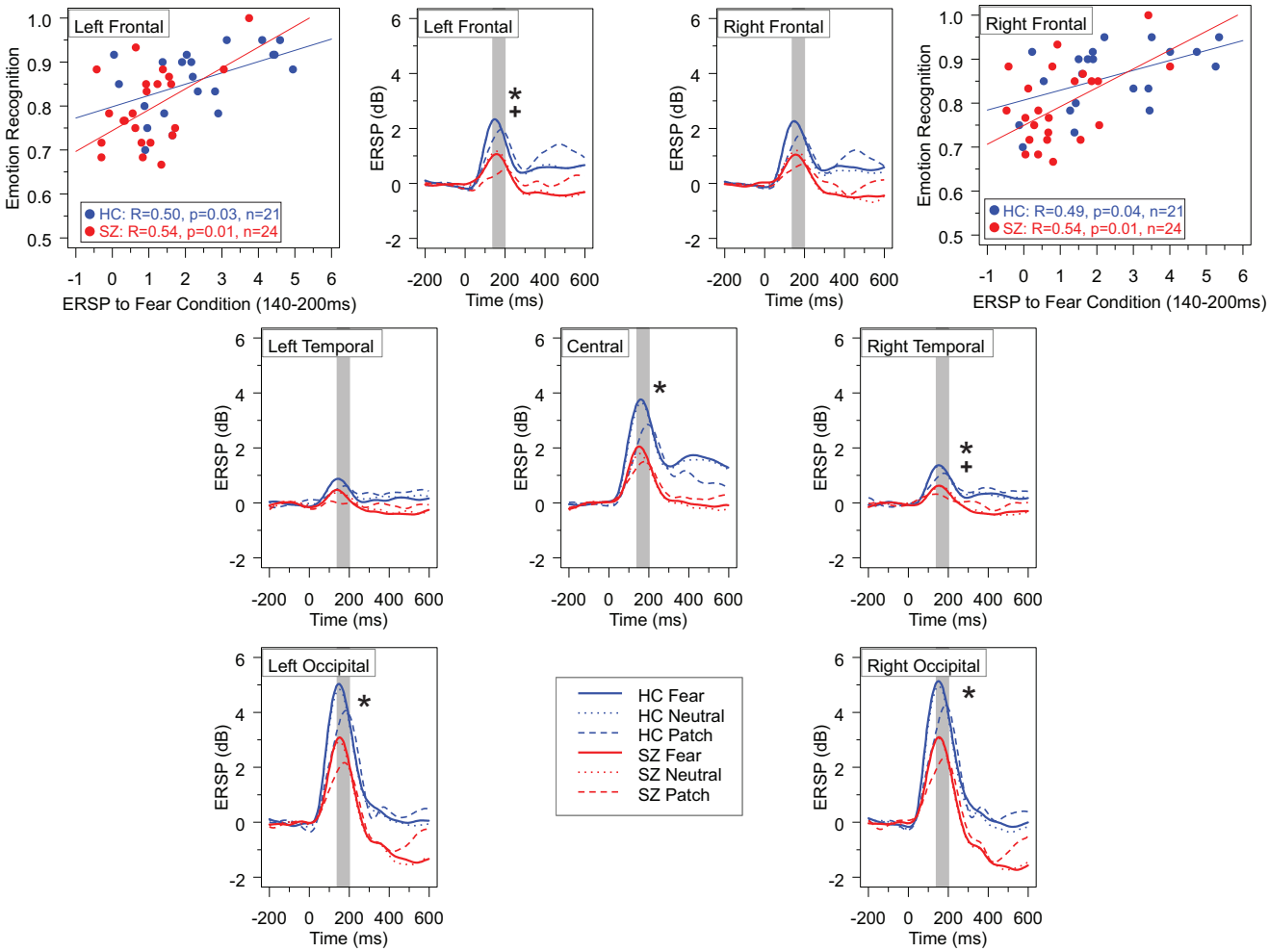

Figure 3. Between-groups differences in event-related theta spectral perturbation (ERSP) in the three conditions, and correlations between ERSP values at frontal regions and emotion recognition as indexed by the FEEST scores. Asterisks mark time windows in which significantly larger ERSP to face stimuli were found in the healthy control group compared with patients with schizophrenia. Crosses mark time windows in which significantly larger ERSP to nonface stimuli were found in the healthy control group compared with the patients. HC = Healthy Control Group; SZ = Schizophrenia Group.

46) = 0.8, $p = .62$. The time course of the ERPs in the ROIs is shown in Figure 5.

Emotion recognition performance as indexed by the FEEST correlated significantly with the n170 component to both face conditions over the left frontal ROI in the patient group (Fearful: $r = .52$, $n = 24$, $p = .02$; Neutral: $r = .49$, $n = 24$, $p = .02$), and with n170 to fear condition over the right frontal ROI in the patient (Fearful: $r = .53$, $n = 21$, $p = .01$) and in the control (Fearful: $r = .48$, $n = 21$, $p = .04$) groups. Furthermore, the emotion recognition performance in the patient group correlated significantly with the N170 ERPs to both face conditions over the central (Fearful: $r = .47$, $n = 24$, $p = .03$; Neutral: $r = .51$, $n = 24$, $p = .02$) and over the right occipital (Fearful: $r = .49$, $n = 24$, $p = .02$; Neutral: $r = .50$, $n = 24$, $p = .02$) regions. No significant association between ERPs to the nonface patch and emotion recognition was found in any of the ROIs ($p > .05$). All correlations were controlled for age, gender, and education.

Discussion

Our main findings are twofold: first, event-related theta activity and phase-locking in the 140–200 ms time interval predicted facial affect recognition performance both in controls and patients with schizophrenia; second, event-related changes in theta amplitude and phase-locking were significantly weaker in patients compared with healthy controls in the time interval of 140–200 ms post-stimulus.

Measures of event-related changes in induced and evoked theta oscillatory activity (ERSP) and phase-locking across trials (ITC) to fearful and neutral faces relative to nonface stimuli in the 140–200 ms time interval were significantly larger in both study groups over all ROIs. This result indicates that activity in the theta frequency range plays a prominent role in face-specific information processing in this time window (Rousselet, Husk, Bennett, & Sekuler, 2007). Furthermore we know from previous research

applying concurrent ERP and fMRI measures that electrophysiological activities in this time interval are mainly localized to the fusiform face area and the superior temporal sulcus (Sadeh et al., 2010; Iidaka et al., 2006; Horovitz et al., 2004), regions engaged in face and facial feature processing.

Both study groups showed a strong positive relationship between event-related theta activity changes and emotion recognition performance (as indexed by the FEEST) over the frontal regions (Figure 3). According to our hypothesis, such a relationship was observed only in response to facial stimuli; event-related theta activity to nonface patch stimuli was not associated with emotion recognition performance. A further positive correlation was found between emotion recognition performance and theta phase-locking (ITC) to facial stimuli over frontal and temporal regions; again, ITC to nonface patch stimuli was not associated with emotion recognition performance. These findings support the notion that effective facial emotion recognition requires stronger neural synchronization.

Overall, healthy controls showed significantly stronger event-related theta amplitude (ERSP) and phase-locking (ITC) in the theta band than schizophrenia patients. These findings are in line with previous investigations showing decreased neural synchroni-

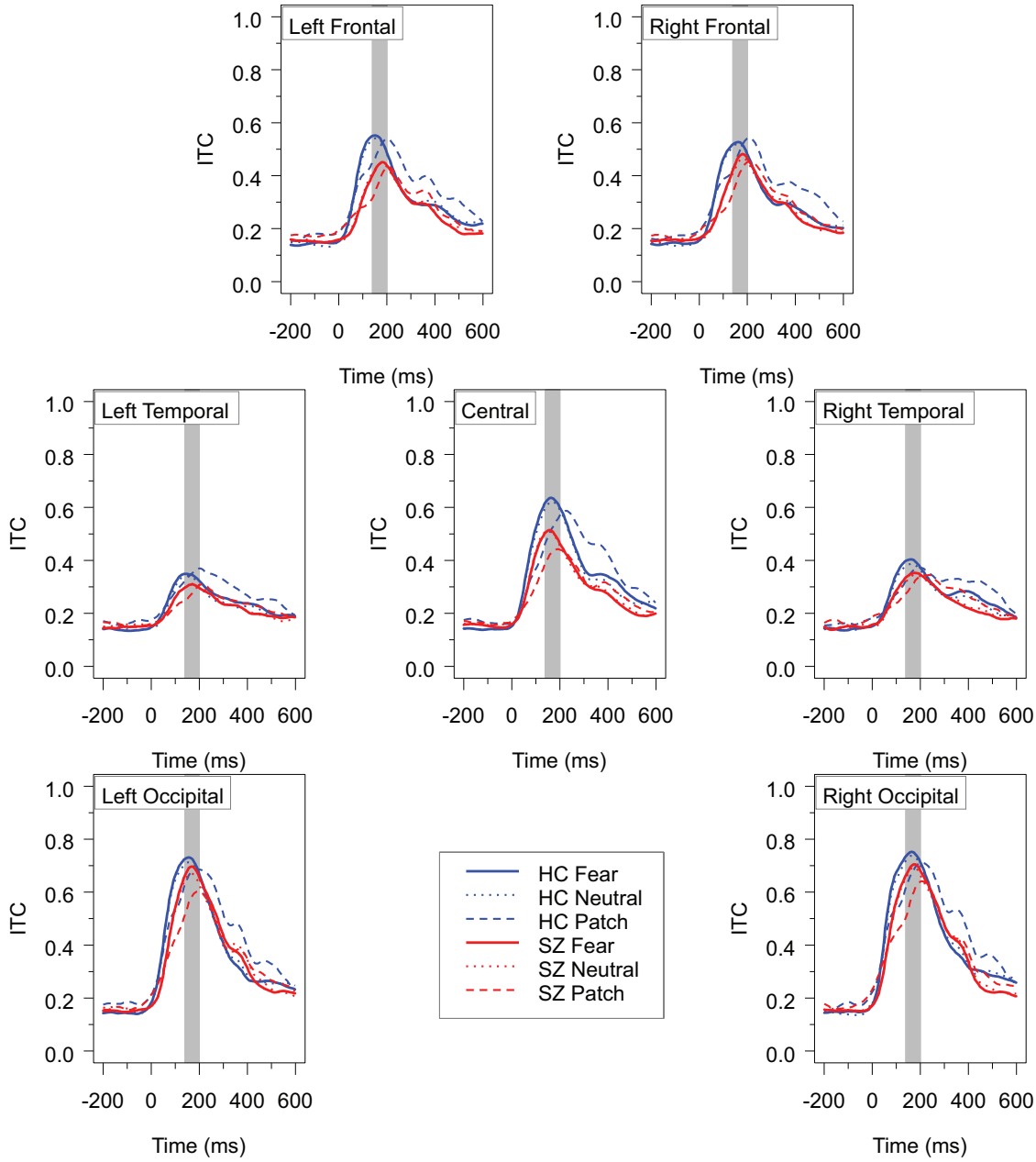

Figure 4. Between-groups differences in intertrial theta coherence (ITC) in the three conditions. HC = Healthy Control Group; SZ = Schizophrenia Group.

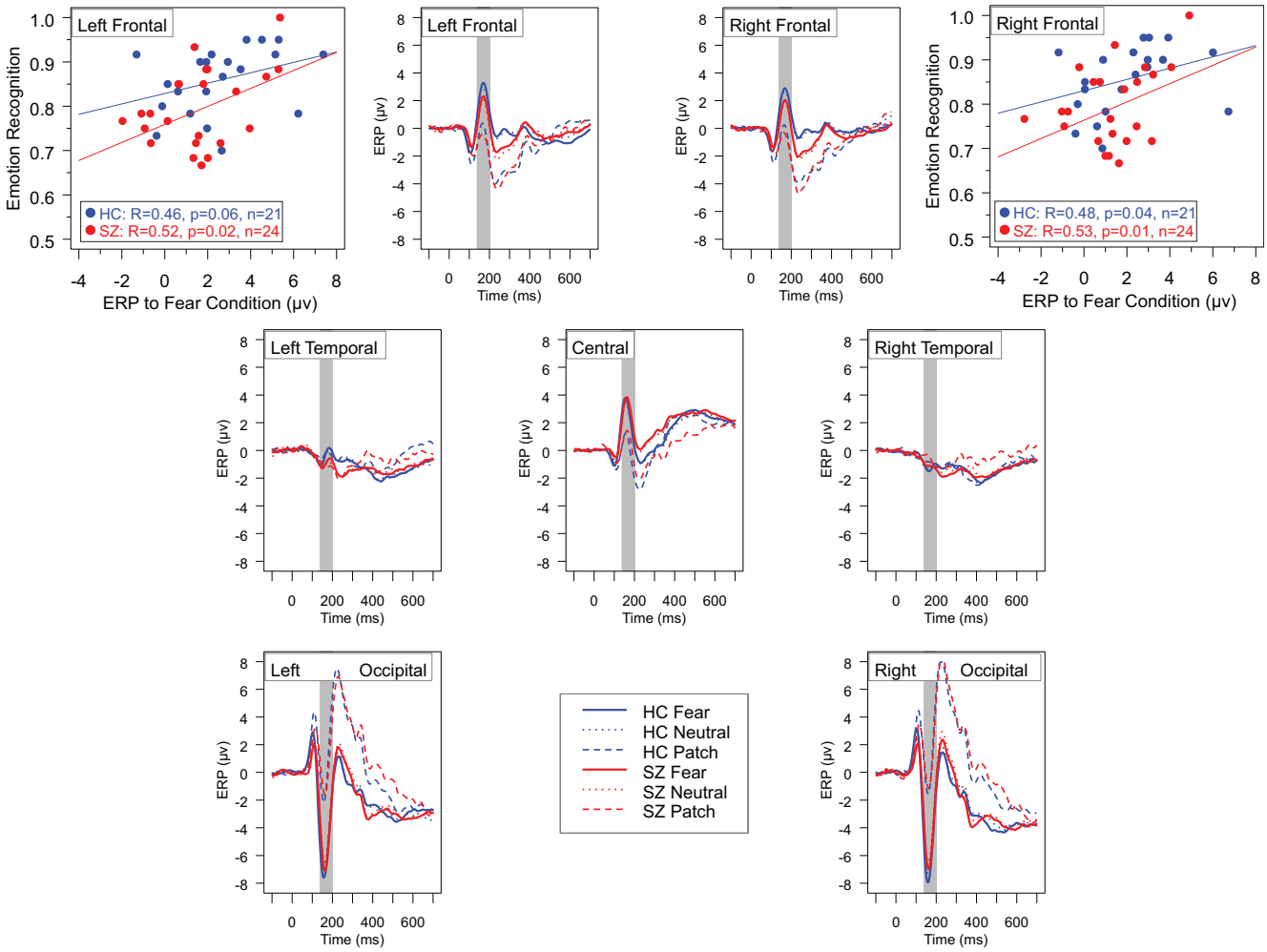

Figure 5. Between-group differences in event-related potentials (ERP) in the three conditions, and correlations between ERP values at frontal regions and emotion recognition as indexed by the FEEST scores. No significant between group differences in ERPs were detected in any regions. HC = Healthy Control Group; SZ = Schizophrenia Group.

zation in the lower frequency bands in patients with schizophrenia (Uhlhaas, Haenschel, Nikolic, & Singer, 2008; Doege et al., 2009; Shin et al., 2010). Furthermore, both animal (Buzsáki, 2002) and human studies (Jacobs, Kahana, Ekstrom, & Fried, 2007) suggest that low frequency oscillations coordinate the spiking of neurons, assemble large neuronal networks (Buzsáki & Draguhn, 2004; Stefanics et al., 2010), and thus contribute to complex functions, such as attention, memory, and recognition. Whereas high-frequency oscillations coordinate the firing of smaller subunits of neurons, theta oscillations are responsible for the coordination of larger ensembles of cells (Lisman & Buzsaki, 2008). According to this conceptual framework, stronger event-related theta activity and intertrial coherence in the present study may indicate a more effective functioning of brain regions in the recognition process of facial features and thus resulting in more efficient facial affect recognition.

Differences in evoked and induced theta amplitude between study groups were significant over central and both occipital regions only for face stimuli. In the right temporal and left frontal regions the differences between study groups were significant for both face and nonface stimuli (Figures 2–3). ERSP reached its maximum over the central and occipital regions in both groups, which is in line with previous findings (Güntekin & Basar, 2009). These regions showed between-groups differences only for the face-stimuli (Figure 2).

The largest between-groups differences (1–1.2 in Cohen's *d*) in theta response amplitude (ERSP) were detected to neutral and fearful faces over the central region. When theta phase-locking (ITC) was analyzed by region, the between-groups difference approached significance only in the central region, with a Cohen's *d* value of 0.8 (Figure 4). A decreased event-related theta response was observed in the schizophrenia group compared with healthy controls also for nonface patch stimuli in two regions. This finding is in line with previous studies reporting a general visual decoding deficit in schizophrenia (Dias, Butler, Hoptman, & Javitt, 2011; Javitt, 2009; Martínez et al., 2012), which may contribute to the

specific impairment seen in facial expression and emotion recognition.

Whereas phase-locking in the theta band was sensitive to the emotional valence of face stimuli, no difference in ERSP was found between fearful and neutral facial stimuli. Overall phase-locking was significantly higher to fearful faces than to neutral faces. This finding is in line with previous studies showing larger ERP amplitudes for emotional compared with neutral faces in the 140–200 ms time interval (Blau et al., 2007; Eimer & Holmes, 2007), which corresponds well to that of the N170 ERP component.

Some of the previous literature reported a reduction of N170 in schizophrenia (Ibáñez et al., 2012; Herrmann et al., 2004). However, in some of the studies the N170 component did not differ between study groups (Wynn et al., 2008; Streit, Wolwer, Brinkmeyer, Ihl, & Gaebel, 2001), which is in line with our findings. Nonetheless, our findings revealed a robust group difference in ERSP and ITC, which may indicate that these measures are more reliable indices of facial affect encoding impairments by capturing both event-locked and event-induced activity. Moreover, previous studies reported a lack of significant relationship between N170 amplitude and task performance. In the present study we found that all 3 measures (ERP, ERSP, ITC) of the N170 component to facial stimuli correlated significantly with emotion recognition performance. This might be attributable to the more comprehensive and sensitive measure of emotion recognition performance applied in the present study.

Neither ERSP nor ITC measures correlated significantly with the PANSS score or medication dose in chlorpromazine equivalents, which is in line with negative findings of a previous study applying an ERP paradigm (Herrmann et al., 2004). However, another study reported a modest correlation between the N170 amplitude and severity of positive psychotic symptoms (Campanella, Montedoro, Streel, Verbanck, & Rosier, 2006). The only study that analyzed brain oscillations in relation to facial emotion recognition in schizophrenia did not report any correlations with symptom severity or dose of medication (Ramos-Loyo, Gonzalez-Garrido, Sanchez-Loyo, Medina, & Basar-Eroglu, 2009). It is worth noting, however, that average PANSS scores were relatively low in the present study, indicating a chronic-stable mental state of the participating patients (Leucht et al., 2005), which might have limited our ability to find a correlation between symptom severity and theta oscillations. Further studies using a longitudinal design or the inclusion of patients with more severe psychotic symptoms are needed to explore this association further. With regard to medication, a common concern in imaging and electrophysiological studies of clinical populations is the potential influence of medication on results. In the current studies, all patients were receiving stable antipsychotic medication. Although in our studies no correlation was found between antipsychotic dose and electrophysiological measures, nonetheless, it cannot be ruled out that medication status may have played a role in differences seen in electrophysiological measures. However, previous investigations suggest that such effects are minimal (Berenbaum & Oltmanns, 1992; Horan, Wynn, Kring, Simons, & Green, 2010; Kring & Neale, 1996).

In the present investigation no positive stimuli were used, which limits the generalizability of our findings. The rationale for applying a negative emotion was that previous investigations found that in particular the processing of negative emotions are impaired in schizophrenia (Mandal et al., 1998), and the strongest correlation of the functional outcome occurred with the recognition of fear of (Brittain, Ffytche, & Surguladze, 2012). Furthermore, this impairment was found to be correlated with lower effective amygdale connectivity in schizophrenia (Mukherjee et al., 2012). The fact that in the present investigation no positive stimuli were used might limit the generalizability of our findings.

A link between event-related theta activity during face decoding and emotion recognition ability was found. Subjects who showed stronger event-related theta response and phase-locking performed better at recognizing basic emotional expressions, confirming that facial emotion recognition requires greater neural activation and temporal coding. Patients showed weaker event-related theta activity and phase-locking, which may contribute to the less effective social cognition in schizophrenia.

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