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Reduced source activity of event-related potentials for affective facial pictures in schizophrenia patients

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ABSTRACT

The ability to recognize facial affect is impaired in schizophrenia patients. This study compared source activities of the event-related potentials (ERPs) for affective facial pictures between schizophrenia patients and healthy controls. Twenty-three schizophrenia patients (11 females) and 24 healthy controls (12 females) were recruited. The standardized low-resolution brain electromagnetic tomography (sLORETA) source activities of four ERP components (P100, N170, N250, and P300) were compared between schizophrenia patients and healthy controls in response to fearful, happy, and neutral facial expressions. Group differences of sLORETA source activities were found only for the N170 component in response to the fearful face. Source activities in the middle frontal gyrus and inferior frontal gyrus were lower in schizophrenia patients compared to healthy controls. Source activity in the insula was lower in male schizophrenia patients compared to male healthy controls. Source activities in the superior temporal gyrus, middle temporal gyrus, insula and inferior frontal gyrus were lower in male compared to female schizophrenia patients. However, there was no gender difference on ERP source activities in the healthy controls. These results support the hypothesis that schizophrenia patients have reduced N170 current source density in response to fearful faces. The area exhibiting reduced current source density includes the frontal and temporal cortex. The present results suggest that there may be gender differences in facial affect processing in schizophrenia patients.

1. Introduction

Social cognition refers to the mental operations underlying social interactions, which include processes involved in perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others (Brothers, 1990). It has been known that schizophrenia patients have deficits in social cognitive function (Green et al., 2008). Facial affect perception is an important aspect of social cognition and there is an increasing interest on visual perception of facial affect in schizophrenia. The ability to recognize and discriminate facial emotions is reportedly impaired in schizophrenia patients (Turetsky et al., 2007; Im et al., 2008; Larøi et al., 2010). However it was suggested that patients with schizophrenia also perform affect-recognition tasks at near-normal abilities (Fiszdon and Johannesen, 2010). Furthermore, it has been suggested that general deficits in facial affect processing are associated with symptoms severity and reduced social functioning in these patients (Doop and Park, 2009; Bae et al., 2010; Johnston et al., 2010).

Many brain areas are involved in facial affect processing. However, the exact neurofunctional maps underlying facial affect processing are not well defined. A meta-analysis of functional MRI (fMRI) studies of emotional face processing revealed that fearful and happy faces are processed in different brain regions, with fearful faces activating predominantly the bilateral amygdala and fusiform gyrus, right cerebellum, left inferior parietal lobule, left inferior frontal, and right medial frontal gyrus, and happy faces activating predominantly the bilateral amygdala, left fusiform gyrus, and right anterior cingulate cortex (Fusar-Poli et al., 2009). The perception of fearful faces is associated with the functional activation of corticolimbic structures, which are altered in individuals with schizophrenia (Johnston et al., 2005; Gur et al., 2007; Fakra et al., 2008; Hall et al., 2008). However, the areas involved in impaired facial affect processing by schizophrenia patients remain controversial.

fMRI has a high spatial resolution that indicates neural substrates associated with dysfunctional facial processing in schizophrenia, but it cannot reveal delicate temporal changes in brain activity within less than a few seconds. In contrast, EEG and event-related potential (ERP) source imaging can detect these temporal changes. There are

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accumulated ERP data indicating that, in general, four ERP components are related to facial affect processing: P100, N170, N250, and P300 (Campanella et al., 2004; Turetsky et al., 2007; Rozenkrants and Polich, 2008; Wynn et al., 2008; Lee et al., 2010).

Although deficits in the P100 component associated with facial affect processing have not been typically reported in schizophrenia patients (Herrmann et al., 2004; Johnston et al., 2005; Turetsky et al., 2007), some studies have demonstrated an abnormal P100 response (Campanella et al., 2006; Caharel et al., 2007). Recent studies have also noted reduced N170 amplitude in schizophrenia patients during face and facial affect processing (Herrmann et al., 2004; Johnston et al., 2005; Turetsky et al., 2007; Lee et al., 2010). The N170 component is associated with not only facial structure encoding (Herrmann et al., 2004), but also facial emotional expressions (Campanella et al., 2006; Turetsky et al., 2007; Lynn and Salisbury, 2008; Lee et al., 2010). The main source area of this component is thought to be the fusiform gyrus, with additional activation in a more widely distributed network, including the occipital visual cortex (Esslen et al., 2004; Herrmann et al., 2005), the posterior inferior temporal gyrus, and the lingual gyrus (Shibata et al., 2002). Pegna et al. (2008) reported that source localization performed on the N170 component for fearful face has shown greater activation in extrastriate visual areas, particularly of the right hemisphere.

A smaller N250 response was reported in schizophrenia patients compared with healthy controls (Streit et al., 2001; Wynn et al., 2008). However, other researchers have found normal N250 responses in schizophrenia patients (Johnston et al., 2005; Turetsky et al., 2007). The P300 component is hypothesized to reflect the affect-encoding stage in the processing of emotions (Oliver-Rodríguez et al., 1999). Schizophrenia patients are reported to exhibit smaller P300 responses for emotional stimuli than healthy controls (Turetsky et al., 2007).

The low-resolution brain electromagnetic tomography (LORETA) inverse solution is one of the most reliable methods for localizing EEG and ERP electrical activity, which is associated with relatively low error rates (Pascual-Marqui et al., 2002). LORETA current source images obtained using 19 or more electrodes have been shown to provide good estimates of the localization of activated brain regions identified with fMRI (Mulert et al., 2004). Standardized LORETA (sLORETA) has recently been introduced, whereby localization inference is based on images of standardized current density (Fuchs et al., 2002; Pascual-Marqui, 2002). Esslen et al. (2004) used LORETA to identify the brain regions involved in emotional processing. Different emotions (happy, sad, angry, fearful, and disgust) evoked specific activation patterns in different brain regions, which changed over time. However, as yet there have been no ERP source-localization studies of the processing of human affective faces in schizophrenia patients.

Gender differences of schizophrenia patients have been widely reported (Roy et al., 2001; Abel et al., 2010). And several factors, including genetic, hormonal and psychosocial factors, were involved in gender difference in schizophrenia patients (Leung and Chue, 2000; Häfner, 2003; Goldstein et al., 2007). An interesting gender effect was recently found in response to facial affect recognition tasks. Kempton et al. (2009) found a gender effect on brain activations in the left amygdala and right temporal pole, with greater activation observed in females than in males. Proverbio et al. (2009) showed gender differences in the brain response to affective scenes both with and without humans in them. In our previous ERP study (Lee et al., 2010), we found that the ERP amplitudes in response to fearful face stimuli were reduced in male relative to female schizophrenia patients. Previous evidence prompted us to investigate the potential gender effect on the current source density of face-related ERP components in schizophrenia patients.

In the present study, we employed standardized LORETA (sLORETA) to localize the sources of ERP components associated with facial affect recognition in schizophrenia patients. It was hypothesized that schizophrenia patients would exhibit decreased source activities of ERP components for facial affect processing, and that these decreased source activities would be observed in the brain areas associated with emotional processing. Furthermore, we hypothesized that there would a gender effect in facial affect processing.

2. Materials and methods

2.1. Subjects

Twenty-three patients with schizophrenia (age = 32.2 ± 10.1 years, mean ± SD; 11 females) and 24 healthy controls (age = 38.0 ± 11.9 years, 12 females) were recruited for this study. The schizophrenia patients were recruited from the Psychiatry Department of Inje University Ilsan Paik Hospital, and were diagnosed based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Psychiatric Disorders (First et al., 1997a). Their psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). None of the patients had a history of central nervous system disease, alcohol or drug abuse, electroconvulsive therapy, mental retardation, or head injury with loss of consciousness. All patients were stable and taking atypical antipsychotics (olanzapine, $n = 11$; risperidone, $n = 12$).

Healthy controls were recruited through posters displayed in the hospital and advertisements in local newspapers. An initial screening interview was conducted by a board certified psychiatrist to exclude subjects if they had any identifiable psychiatric disorder, neurological disorder or head injury, a first-degree relative with schizophrenia, any personal history of psychiatric disease, a family history of psychiatric illness, or a history of arrest for violent behavior. After initial screening, potential healthy control subjects were interviewed with the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 1997b), and were excluded if they had any of these disorders.

All subjects had normal or corrected-to-normal vision and were right-handed, as determined by asking which hand the subject tended to use for writing and other precise motor skills. All subjects signed a written informed consent form that was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital prior to their participation in the study. The demographics of the two groups were given in Table 1, which indicated that there were no significant group differences in gender distribution, age, or education.

2.2. Procedures

Participants were presented with two types of human faces: emotional (fearful and happy) and neutral. The presented images were selected from the “Chaelee face”, which is a standardized set of color pictures of a Korean face (Lee et al., 2004). In this picture set, each actor or actress expresses seven facial emotions, each of which is presented in eight pictures with emotional intensities ranging from 1 (minimum) to 8 (maximum). For the ERP study, we selected pictures showing the maximum intensities of 3 emotions from 6 people, giving a total of 18 facial emotions: fearful (6 pictures), happy (6 pictures), and neutral (6 pictures). Each picture depicts the entire face, including the hair. The luminance and contrast were made the same in all of the images. Stimuli were presented on a 17-inch (approximately 43-cm) CRT monitor positioned 1 m in front of the participants, and which subtended a maximum visual angle of 4° × 4°.

Face stimuli were presented repeatedly in random order but at the same frequency of presentation for a total of 288 trials, comprising 96 neutral faces and 192 emotional faces. The trials started with a fixation cross presented for 100 ms followed by a black screen for 500 ms. Face stimuli were then presented for 500 ms and followed by a black screen displayed for 900–1100 ms; the total duration of each trial was 2000–2200 ms, and this was changed randomly in each trial so as to avoid habituation. The entire recording session for each

Table 1
Demographic data and symptom ratings for 23 schizophrenia patients and 24 healthy controls. Data are mean ± SD values. PANSS, Positive and Negative Syndrome Scale.

	Schizophrenia patients ($n=23$)			Healthy controls ($n=24$)		
Age (years)	32.2 ± 10.1			38.0 ± 11.9		0.077
Males:females	12:11			12:12		1.0
Education duration (years)	12.8 ± 2.1			13.0 ± 2.9		0.730
Number of hospitalizations	1.7 ± 1.4					
Illness duration (years)	5.2 ± 4.9					
PANSS total score	81.8 ± 25.8					
Negative score	18.7 ± 7.4					
Positive score	20.2 ± 7.8					
	Males ($n=12$)	Females ($n=11$)	P	Males ($n=12$)	Females ($n=12$)	p
Age (years)	28.5 ± 8.2	36.3 ± 10.7	0.063	38.5 ± 12.1	37.6 ± 12.2	0.855
Education duration (years)	12.6 ± 2.1	13.0 ± 2.2	0.650	13.4 ± 2.7	12.7 ± 3.2	0.540
Number of hospitalizations	1.3 ± 0.9	2.2 ± 1.8	0.120			
Illness duration (years)	3.5 ± 3.0	7.1 ± 6.0	0.078			
PANSS total score	78.7 ± 31.1	85.3 ± 19.4	0.552			
Negative score	18.8 ± 8.2	18.7 ± 6.8	0.994			
Positive score	18.4 ± 8.5	22.2 ± 6.8	0.256			

PANSS: Positive and Negative Syndrome Scale.

subject lasted approximately 15 min. All participants were requested to push a button using their right thumb when they saw an emotional face.

Emotional stimuli could produce carry-over effects if they are presented consecutively. In the present study, the possibility of carry-over effects were minimized by taking two steps: (1) by showing 96 neutral faces randomly among emotional faces, and (2) by using two group comparisons for processing of emotional face, thus balancing out potential carry-over effects.

2.3. EEG recording

Stimulus presentation and data synchronization with the EEG were accomplished with E-Prime (Psychology Software Tools, Pittsburgh, USA). EEG activity was recorded using a NeuroScan SynAmps amplifier (Compumedics USA, El Paso, TX, USA) and 64 Ag–AgCl electrodes mounted in a Quick Cap using a modified 10–20 placement scheme. The vertical electrooculogram (EOG) was recorded using two electrodes, one located above and one below the right eye. The horizontal EOG was recorded at the outer canthus of each eye. EEG data were recorded with a 1- to 100-Hz bandpass filter at a sampling rate of 1000 Hz. The ground electrode was placed on the forehead and the reference was located at electrode Cz. EEG data were initially processed using Scan 4.3. Before beginning the further analysis, EEG data were rereferenced offline to an average reference. Gross movement artifacts were removed by visual inspection. Eye blinks were removed from the data using established mathematical procedures (Semlitsch et al., 1986). Trials were rejected if they included significant physiological artifacts (amplitude exceeding ± 70 μV) at any site over all 62 electrode sites except for M1, and M2. After artifact removal, baseline correction was conducted by subtracting the mean of 300 ms before stimulus onset from the poststimulus data for each trial. Data were bandpass filtered at 1–30 Hz (Rousselet et al., 2005; Wynn et al., 2008) with a steepness of 24 dB/octave and then epoched to 300 ms prestimulus and 1000 ms poststimulus.

2.4. Determinant of target ERP components

The four ERP components were detected after calculating global field potentials and examining a butterfly map of all of the ERP data (Fig. 1A, B). The four ERP components were identified as follows: P100, the largest positive peak in the window of poststimulus from 50 to 150 ms; N170, the largest negative peak of mean amplitude in the window of poststimulus from 120 to 220 ms; N250, the largest negative peak of mean amplitude in the window of poststimulus from 150 to 350 ms; P300, the largest positive peak of mean amplitude in the window of poststimulus from 300 to 450 ms. The ranges of largest peaks were determined based on the our previous work (Lee et al., 2010) in which the maximum electrical potentials were detected in visual inspection of the topographic map (Fig. 1C). However, stricter selection criteria were applied for ERP data in the present study compared to our previous study (Lee et al., 2010). To exclude poor-quality data, ERP data with a sufficient number of accepted ERP epochs (average above 90%) for the three facial-affect stimuli were taken for further analysis. In addition, through behavioral performance, only the correctly hit epochs were used for ERP amplitude and sLORETA source-localization analysis.

ERP data were averaged for each participant according to the emotion on the presented face: fearful, happy, and neutral. The average number of epochs in each condition did not differ significantly between groups and genders. The numbers of accepted epochs were as follows:

1. Fearful face: male schizophrenia patients, 95.08 ± 2.99; female schizophrenia patients, 91.64 ± 5.48; male healthy controls, 84.67 ± 14.06; and female healthy controls, 89.25 ± 8.06; $F(3, 43) = 2.542$; $p = 0.069$.
2. Happy face: male schizophrenia patients, 95.25 ± 2.49; female schizophrenia patients, 91.36 ± 5.59; male healthy controls, 85.33 ± 12.70; and female healthy controls, 89.92 ± 6.66; $F(3, 43) = 2.618$; $p = 0.063$.
3. Neutral face: male schizophrenia patients, 96.25 ± 3.19; female schizophrenia patients, 92.55 ± 6.47; male healthy controls, 89.83 ± 7.94; and female healthy controls, 90.67 ± 8.96; $F(3, 43) = 1.990$; $p = 0.130$.

In the present analysis, we used the data from 60 electrodes: FP1/FPz/FP2, AF3/AF4, F7/F8, F5/F6, F3/F4, F1/Fz/F2, FT7/FT8, FC5/FC6, FC3/FC4, FC1/FCz/FC2, T7/T8, C5/C6, C3/C4, C1/Cz/C2, TP7/TP8, CP5/CP6, CP3/CP4, CP1/CPz/CP2, P7/P8, P5/P6, P3/P4, P1/Pz/P2, PO7/PO8, PO5/PO6, PO3/POz/PO4, and O1/Oz/O2.

2.5. Source localization of the ERP activity using sLORETA

The source activations of ERP components were compared using sLORETA inverse solution method (Fuchs et al., 2002; Pascual-Marqui, 2002). The differences of source activity between schizophrenia and healthy controls, and between female and male subjects were mainly explored in this study. sLORETA was developed by Pascual-Marqui

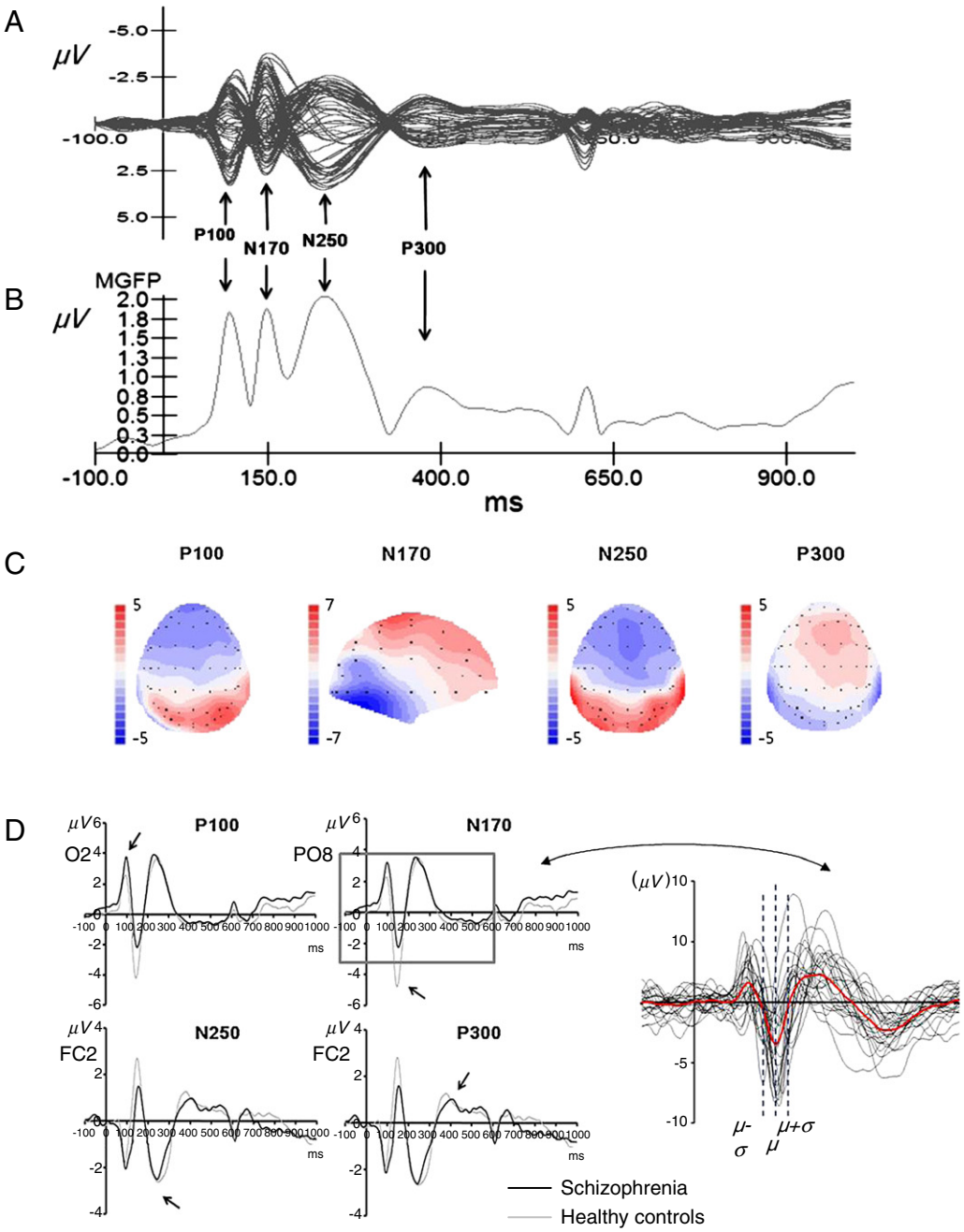

Fig. 1. A, B. Bufferfly map and mean global field potential of whole event-related potential (ERP) components from schizophrenia patients and healthy controls. Four identifiable peaks (P100, N170, N250, and P300) were detected. C. Two-dimensional scalp topographic maps. Each map shows maximal activating areas on the cortical area. D. Schematic example of 4 ERP components for all subjects and defining the analysis interval for the N170 ERP component. The red line is the average waveform. The interval was decided from one standard deviation prior ($\mu-\delta$) to one standard deviation after ($\mu+\delta$) the mean latency (μ) of the group.

(2002), and it computes a particular solution of the nonunique EEG inverse problem while assuming maximum synchronization between neighboring voxels, where the localization inference is based on images of the standardized current density (Fuchs et al., 2002). It doesn't require land mark, electrode position, and individual MRI data and supplies the standardized head model.

The mean latencies and standard deviation of individual ERP components from all participants were calculated. The window of interest (WOI) was defined as from one standard deviation prior to one standard deviation after the mean peak latency of each ERP (Fig. 1D). The mean latencies differed slightly by the type of affective facial picture and by the group. Since the strength of individual WOI analysis reflects peak amplitude power, which is useful for comparing two groups, we used WOIs that differed slightly from common broad WOIs to analyze the ERP source activity. In the fearful condition, WOIs were defined as follows in schizophrenia patients and healthy controls: P100, 90–116 ms vs. 94–116 ms, respectively; N170, 143–181 ms vs. 140–169 ms; N250, 216–264 ms vs. 222–275 ms; and P300, 332–425 ms vs. 335–412 ms. In the happy condition, WOIs were defined as follows in schizophrenia patients and healthy controls: P100, 92–119 ms vs. 89–115 ms, respectively; N170, 146–183 ms vs. 142–169 ms; N250, 216–258 ms vs. 215–271 ms; and P300, 336–425 ms vs. 336–420 ms. In the neutral face condition, WOIs were defined as follows in schizophrenia patients and healthy

controls: P100, 91–116 ms vs. 94–115 ms, respectively; N170, 142–183 ms vs. 140–167 ms; N250, 215–259 ms vs. 213–271 ms; and P300, 334–413 ms vs. 342–405 ms. Computations of the electric potential lead field were made with a realistic three-shell head model using the MNI 152 template provided by the Brain Imaging Center of the Montreal Neurological Institute (Mazziotta et al., 2001; Fuchs et al., 2002). The source space is divided into 6239 voxels in 5 mm resolution, restricted to the cortical gray matter and hippocampus.

3. Statistical analysis

The behavioral data and the ERP amplitudes were analyzed by separate repeated-measures ANOVA. For ANOVA analysis, group (schizophrenia and healthy controls) and gender (male and female) were applied as between-subjects factors, and stimulus type (fearful, happy, and neutral) as the within-subjects factor. Significant main effects and interactions were followed up by Bonferroni-corrected, pairwise comparisons. The Greenhouse–Geisser correction (Greenhouse and Geisser, 1959) was applied to adjust the degrees of freedom for nonsphericity (for simplicity, the uncorrected degrees of freedom are presented).

The source activation of the ERP waveform was calculated for each subject using a statistical nonparametric mapping method that was provided by the sLORETA toolbox. Voxel-by-voxel independent *t*-testing of each group was conducted. Statistical significance was assessed nonparametrically with a randomization test ($n=5000$) that corrects for multiple comparisons.

The regions showing significant differences in current source density between schizophrenia patients and healthy controls, as revealed by nonparametric analysis, were analyzed supplementally by traditional parametric analysis using repeated-measures ANOVA.

When we found significant differences in current source density between two groups, the spearman correlation was conducted to explore the relationship between the current source density and PANSS scores.

4. Results

4.1. Behavioral data

The hit rate was defined as the percentage of correct responses. The hit rate showed a significant group×stimulus interaction [$F(2, 66)=3.599$, $p=0.033$]. The hit rate did not differ significantly between schizophrenia patients and healthy controls for fearful faces (87.62 ± 23.14 vs. 84.47 ± 30.90; $t=-0.34$, $p=0.73$) or happy faces (88.17 ± 16.42 vs. 94.42 ± 12.18, respectively; $t=-1.32$, $p=0.19$), but it did differ significantly for neutral faces (73.22 ± 20.97 vs. 93.07 ± 10.37; $t=-3.73$, $p<0.001$).

There was no significant main or interaction effect of response latency between schizophrenia patients and healthy controls for fearful faces (805.33 ± 208.00 ms vs. 875.45 ± 187.15 ms) or happy (828.31 ± 217.04 ms vs. 897.11 ± 160.63 ms).

4.2. ERP amplitude analysis

Analysis of the P100 amplitude showed a significant main effect for gender [$F(1, 42)=6.922$, $p=0.012$] and stimuli [$F(2, 84)=7.807$, $p=0.002$]. However, there was no significant main effect for group [$F(1, 42)=2.962$, $p=0.093$], and no significant interactions.

Analysis of the N170 amplitude showed a significant main effect for group [$F(1, 43)=5.546$, $p=0.023$], and significant interactions for group×stimuli [$F(2, 86)=4.020$, $p=0.021$] and group×gender [$F(1,43)=8.850$, $p=0.005$]. However, there was no significant main effect for gender [$F(1, 43)=1.413$, $p=0.241$], or stimulus [$F(2, 86)=0.679$, $p=0.510$], and no further significant interactions.

Analysis of the N250 amplitude showed a significant main effect for stimulus [$F(2, 86)=16.524$, $p=0.000$]. However, there was no significant main effect for either group [$F(1, 43)=1.804$, $p=0.186$] or gender [$F(1, 43)=0.143$, $p=0.707$], and no further significant interactions.

Analysis of the P300 amplitude showed a significant main effect for stimulus [$F(2, 86)=18.416$, $p=0.000$]. However, there was no significant main effect for either group [$F(1, 43)=0.468$, $p=0.498$] or gender [$F(1, 43)=1.237$, $p=0.272$], and no significant interactions.

Table 2 lists the peak amplitudes of the P100, N170, N250, and P300 ERP components for fearful, happy, and neutral conditions in each group (schizophrenia patients and healthy controls). The N170 peak amplitude in response to fearful faces was significantly lower in schizophrenia patients than in healthy controls (-3.48 ± 2.66 vs. -5.17 ± 2.71; uncorrected $p=0.036$). The N170 peak amplitude in response to happy faces was significantly lower in schizophrenia patients than in healthy controls (-3.23 ± 3.08 vs. -5.46 ± 2.76; uncorrected $p=0.012$). There were no significant differences in other ERP peak amplitudes. N170 and N250 amplitudes were significantly lower in male than in female schizophrenia patients. These gender-related differences were not observed among the healthy controls.

The analysis of ERP amplitudes was not the major concern of the present study, and we therefore did not explore or discuss them further.

4.3. ERP source analysis

Statistical comparisons revealed that there was a significant difference between schizophrenia patients and healthy controls in the N170 component for fearful faces, but not for happy or neutral faces. Furthermore, the P100, N250, and P300 localities did not significantly differ between two groups for all three types of facial stimuli (Table 3).

4.3.1. Between group comparison

The level of activations at the middle frontal gyrus and inferior frontal gyrus area was lower in schizophrenia patients than in healthy controls (Fig. 2; $p<0.05$, one-tailed test). Comparison of the source activity between male subjects of two groups revealed differences in the insular areas. These areas were significantly less activated in schizophrenia patients than in healthy subjects (Fig. 3; $p<0.05$, two-tailed test). A corresponding comparison for the female subjects of two groups did not yield any significant differences.

4.3.2. Within-groups comparisons

Comparison between genders within the healthy control group revealed no differences. However, the levels of activation in the superior temporal gyrus, middle temporal gyrus, insula, and inferior frontal

Table 2
Peak amplitudes of the P100, N170, N250, and P300 components for fearful, happy, neutral facial affects between schizophrenia patients and healthy controls.

	Schizophrenia patients ($n=23$)	Healthy controls ($n=24$)	Uncorrected *p*
P100 (μV)			
Fearful	3.36 ± 1.93	2.39 ± 1.65	0.071
Happy	3.84 ± 2.21	2.94 ± 2.07	0.158
Neutral	2.88 ± 1.42	2.53 ± 1.54	0.422
N170 (μV)			
Fearful	-3.47 ± 2.66	-5.17 ± 2.71	0.036*
Happy	-3.23 ± 3.08	-5.46 ± 2.76	0.012*
Neutral	-3.52 ± 2.60	-4.86 ± 2.59	0.085
N250 (μV)			
Fearful	-2.59 ± 1.30	-2.73 ± 1.36	0.716
Happy	-2.63 ± 1.11	-3.21 ± 1.12	0.080
Neutral	-1.80 ± 0.98	-2.30 ± 1.23	0.130
P300 (μV)			
Fearful	2.03 ± 1.28	2.37 ± 1.16	0.342
Happy	1.16 ± 1.04	1.69 ± 1.02	0.794
Neutral	1.51 ± 0.95	1.65 ± 1.03	0.628

* $p<0.05$.

Table 3
The localization of the N170 ERP component for fearful face stimuli assessed by using sLORETA (standardized low-resolution brain electromagnetic tomography) source localization, as a function of groups (i.e., schizophrenia vs. healthy control, and male vs. female). The maximum Montreal Neurological Institute (MNI) coordinate is presented when the anatomical region has multiple MNI coordinates. SPR, schizophrenia group; HC, healthy control group.

Compared groups	Areas	MNI coordinate		
		X	*Y*	*Z*
All SPR vs. all HC ($p<0.05$, one-tailed)	Middle frontal gyrus (left)	−40	45	10
	Inferior frontal gyrus (left)	−40	50	5
Male SPR vs. male HC ($p<0.05$, two-tailed)	Insula (right)	35	10	10
Female SPR vs. female HC	No significant difference			
Male SPR vs. female SPR ($p<0.05$, two-tailed)	Superior temporal gyrus (left)	−45	−55	10
	Middle temporal gyrus (left)	−60	−60	0
	Insula (right)	40	15	5
	Inferior frontal gyrus (right)	45	20	5
Male HC vs. female HC	No significant difference			

gyrus areas were significantly lower in male schizophrenia patients than in female schizophrenia patients (Fig. 4; $p<0.05$, two-tailed test).

4.4. Supplementary parametric analysis for current source density

Evidence showed that parametric normative comparisons had lower false positive rates than the non-parametric tests in LORETA current source density analysis (Thatcher et al., 2004). Predetermined six regions in non-parametric analysis (right insular, left inferior frontal gyrus, right inferior frontal gyrus, left middle frontal gyrus, left superior temporal gyrus, and left middle temporal gyrus; Table 3) were regarded as regions of interest (ROI), and their current source densities were calculated through the sLORETA program using log transformation, and these values were analyzed by repeated measures ANOVA. Only group and gender-related interactions were commented in this analysis.

The significant group × gender × stimuli interaction was found only in N170 at left superior temporal gyrus [$F(2, 86)=5.133$, $p=0.008$], and left middle temporal gyrus [$F(2, 86)=7.577$, $p=0.001$]. In post hoc analysis, male schizophrenia patients, compared with female schizophrenia patients, showed significantly reduced current source density in left superior temporal (-0.01 ± 0.80 vs. 1.16 ± 0.48; $t=-4.14$, $p=0.000$), and in left middle temporal gyrus (0.16 ± 0.75 vs. 1.52 ± 0.65; $t=-4.56$, $p=0.000$) in response to the fearful stimuli, but not happy stimuli. The male healthy controls, compared with female healthy controls, did not show any significant difference of current source density for each stimulus on these regions. In other ERP components, there was no significant group × gender × stimuli interaction.

4.5. Correlation between the current source activities and PANSS scores

The spearman correlation was conducted to explore the relationship between the current source densities of insula, superior temporal gyrus, middle temporal gyrus, and inferior frontal gyrus and PANSS scores. However, there was no significant correlation between the current source densities and PANSS scores.

5. Discussion

In the present study, we investigated differences in the source activity of four ERP components (P100, N170, N250, P300) between schizophrenia patients and healthy control subjects in response to three types of affective face stimuli (fearful, happy, and neutral). Significant findings for the N170 component were observed only for the fearful face. Furthermore, interesting gender effects were revealed. Our group already reported interesting ERP findings that differentiate schizophrenia patients from healthy controls in response to affective facial stimuli (Lee et al., 2010). Even though this temporal information of ERP amplitudes is relevant for defining the disturbed

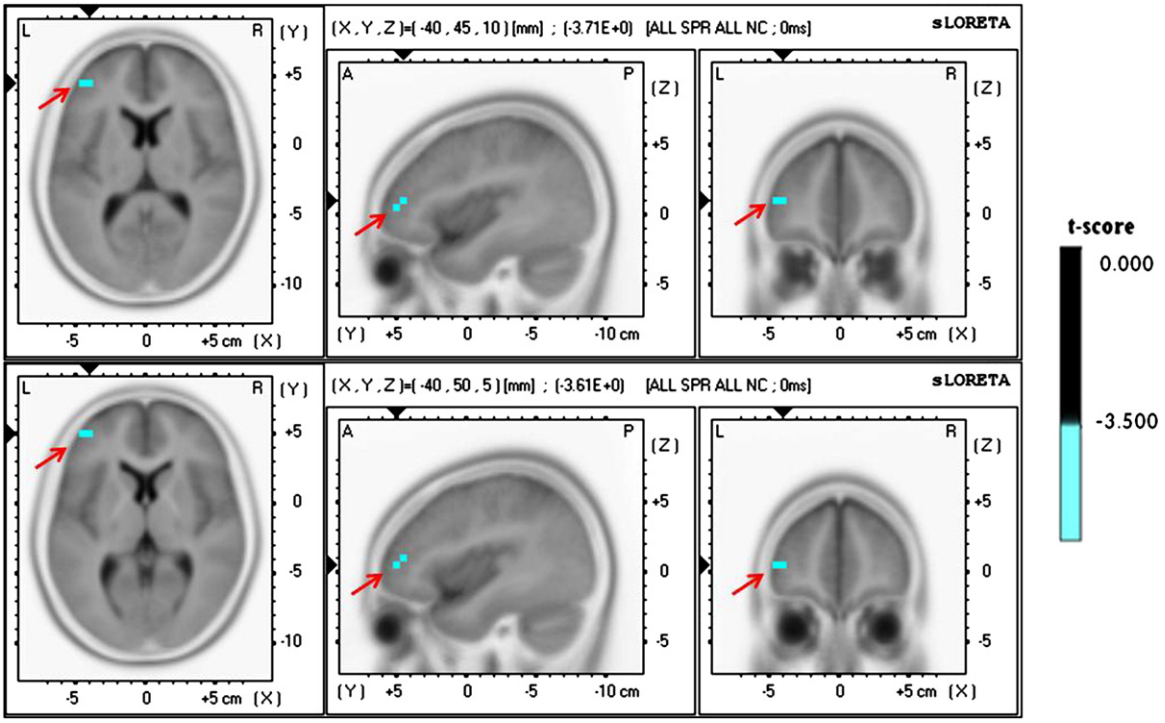

Fig. 2. Comparison of ERP source activity for N170 in response to fearful faces between schizophrenia patients and healthy control subjects. The areas marked blue show significantly lower activation in the middle frontal gyrus and the inferior frontal gyrus, respectively ($p<0.05$, one-tailed).

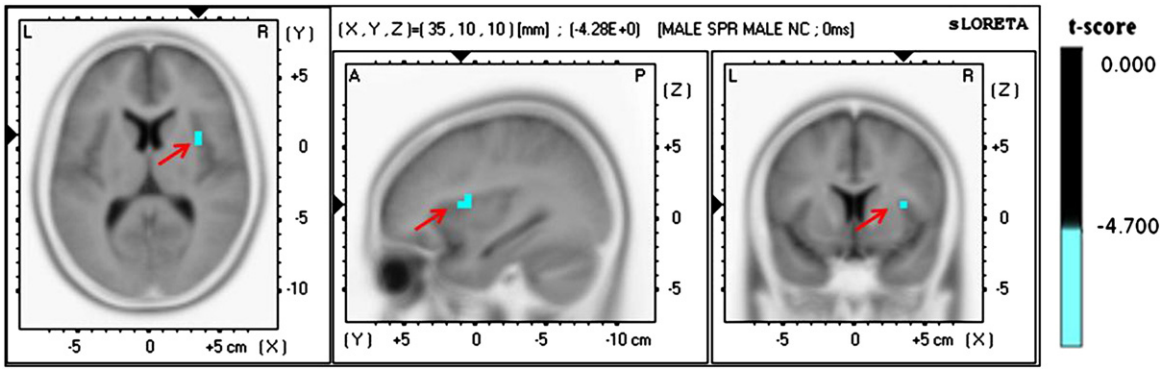

Fig. 3. Comparison of ERP source activity for N170 in response to fearful faces between male schizophrenia patients and male healthy control subjects. The areas marked blue shows significantly lower activation in the insula ($p<0.05$, two-tailed).

cognitive processing, here we focus on and discuss the source activity of each of the four ERP components.

In behavioral data, schizophrenia patients showed the increased rate of false positive responses to neutral faces. In the task, participants were asked to respond when emotional faces were presented. Thus, false positive responses to neutral faces suggested a failure to inhibit their response and our data indicated that schizophrenia patients had difficulty inhibiting their behavioral pattern.

A significant difference in current source density emerged only for the N170 elicited in response to fearful face. N170 deficits in schizophrenia patients during the processing of neutral or emotional faces have been reported previously (Herrmann et al., 2004; Johnston et al., 2005; Turetsky et al., 2007). It is thought that separate neurological mechanisms are responsible for the structural encoding of the face and the recognition of face. N170 is known to be associated with the structural encoding of the face. However, there is evidence implicating N170 not only in structural encoding but also in affective processing (Eimer and Holmes, 2007). The reduced current source density of the N170 component in response to fearful facial pictures could reflect decreased visual perception of emotionally negative stimuli in schizophrenia patients.

Furthermore, in our present study, the differences of current source density emerged only for fearful face, but not for other affective faces. It has been repeatedly reported that schizophrenia patients exhibit particular difficulty recognizing fearful faces (Bediou et al., 2005; Morris et al., 2009). Furthermore, patients with higher negative symptoms scores were characterized by deficits in recognizing fear emotion (van't Wout et al., 2007). It was recently found that the amplitude of the N170 response to fearful faces is decreased in schizophrenia patients (van't Wout et al., 2007; Norton et al., 2009). Deficits in the processing of fearful emotions may lead to misinterpretation of threat-related stimuli, which eventually results in the difficulties in social interactions experienced by schizophrenia patients.

We found that activation of the middle frontal gyrus and inferior frontal gyrus associated with the N170 component for fearful faces was lower in schizophrenia patients than in healthy control subjects (Fig. 2). There is extensive evidence showing that the frontal cortex is activated during affective processing. More specifically, the orbital and medial prefrontal parts were found to be predominantly involved in affective processing, while the lateral part was involved in cognitive functions (Fuster, 2001). In LORETA source localization study, Esslen et al. (2004) reported that both frontal lobes and a small area in the right temporal lobe were activated for fearful faces when the subjects were instructed to induce the same mood as expressed in the presented faces. Dolan et al. (1996) found prominent activation in the left inferior frontal gyrus during the unconscious processing of emotional faces. Also, Blair and Curran (1999) found that the right orbital cortex was activated when subjects were viewing angry faces, while Nakamura et al. (1999) found that the right inferior frontal cortex was activation when participants were asked to compare the emotional content of faces with their attractiveness. Furthermore, inferior frontal gyrus has been known to be implicated in the processing of empathy (Liakakis et al., 2011) and mirror neuron function (Molenberghs et al., 2011). Therefore, it can be argued that decreased activity of inferior frontal gyrus in response to fearful faces may be associated with a deficit in experiencing empathy and reduced activation of mirror neuron, which are typically characterized in schizophrenia patients.

We also found reduced source activities of the insula in male schizophrenia patients when compared with male healthy controls or female schizophrenia patients (Figs. 3 and 4). These findings suggest that the insula may play a central role in dysfunctional emotional face processing in male schizophrenia patients. Due to wide interconnectivity with corticolimbic areas, the insula has been of great interest in the investigation of psychiatric disorders. The insular cortex is involved in the processing of sensory perception and emotion (Nagai et al., 2007), and it plays a key role in affective processing as a result of its abundant connections with other association and primary sensory areas. The regulatory interactions between the extended limbic system, including the insula, and the amygdala is thought to be critical for affective processing (Stein et al., 2007). Various studies using structural and functional imaging, and cytoarchitectural methods have found insular abnormalities in schizophrenia (Crespo-Facorro et al., 2000; Shergill et al., 2000; Kasai et al., 2003; Pennington et al., 2008; Roiz-Santianez et al., 2010). Also, the area of the cortical surface and the volume of the gray matter of the insula were smaller in schizophrenia patients than in healthy controls (Crespo-Facorro et al., 2000; Kasai et al., 2003). It has recently been suggested that the insula plays an important role in integrating cognitive and affective processing (Berntson et al., 2011). Our present results suggest that the insula may play an important role in emotional processing in schizophrenia patients.

The source activity in processing N170 components for fearful faces was significantly lower in male than in female schizophrenia patients. This decreased activity was localized to the superior temporal gyrus, middle temporal gyrus, insula, and inferior frontal gyrus areas (Fig. 4). Meanwhile, the between-group comparisons within the same gender revealed deficits in N170 source activity in male schizophrenia patients compared to male healthy controls, but not in female subjects. This decreased activity was localized to the insular cortex (Fig. 3).

Many functional imaging papers reported activation in temporal areas during affective processing (Haxby et al., 2000; Pizzagalli et al., 2000; Esslen et al., 2004). A review paper by Haxby et al. (2000) revealed that superior temporal sulcus was involved in perceiving emotional face expressions. Pizzagalli et al. (2000), using LORETA, found that bilateral occipito-temporal regions, including lingual and fusiform gyri and extending to inferior temporal gyri, were activated

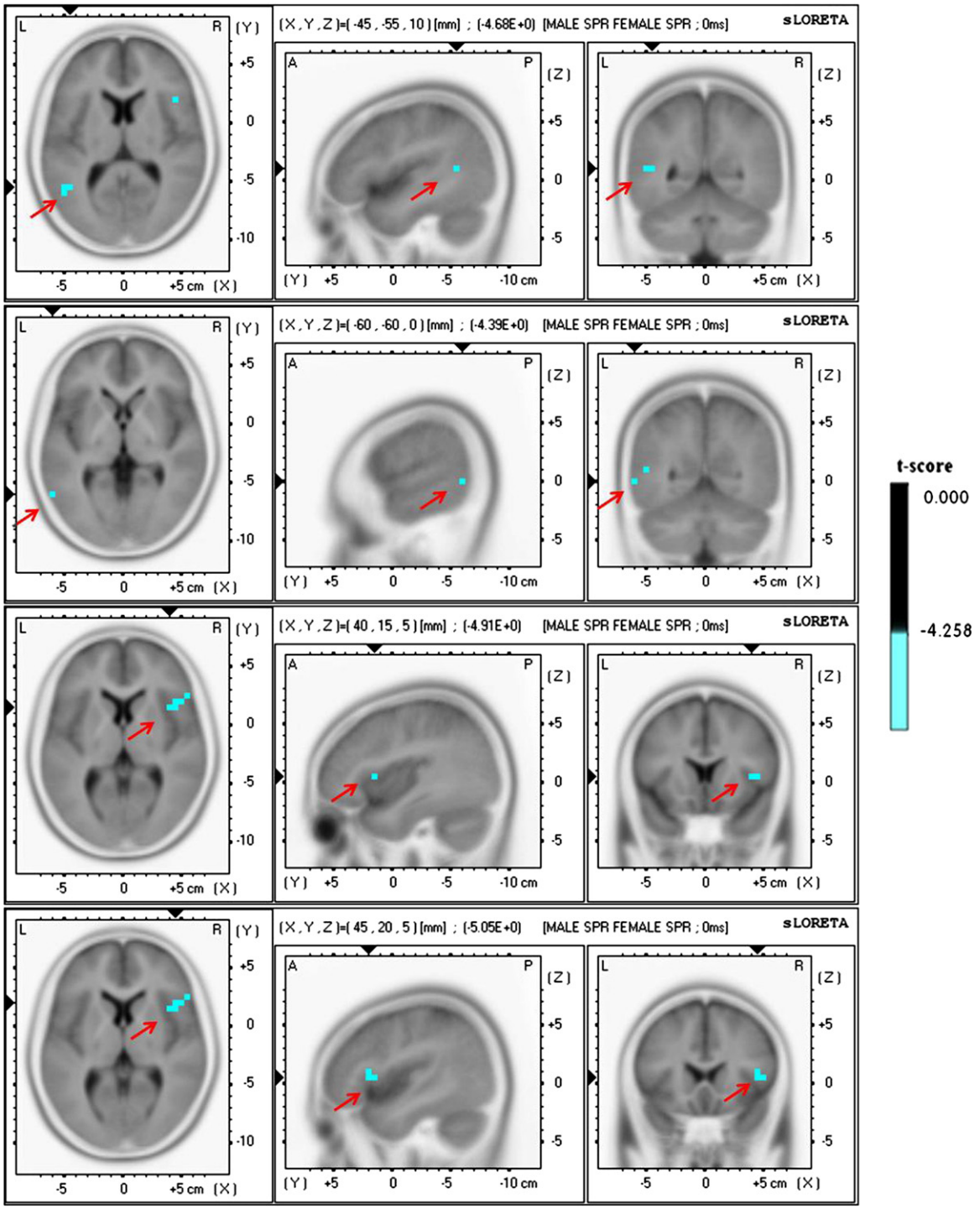

Fig. 4. Comparison of ERP source activity for N170 in response to fearful faces between male and female schizophrenia patients. The areas showing a maximum difference were the superior temporal gyrus, the middle temporal gyrus, the insula, and the inferior frontal gyrus, respectively ($p<0.05$, two-tailed).

in response to emotion-eliciting faces. Furthermore, visual memory is appeared to be associated with temporal areas which are interconnected with the lateral prefrontal cortex (Fuster, 2001). Taking together, it appears that facial affective processing depends on the coordination of multiple brain regions, rather than on the implication of a single brain area. Affective processing interacts with different cognitive processing such as attention and memory. Based on our study results, we suggest that reduced functional capacity of several brain structures such as frontal–insular–temporal gyrus in male schizophrenia patients may hinder them from integrating and coordinating different processing necessary to process fearful face stimuli.

The present study highlights the importance of gender differences in affective facial processing of schizophrenia patients. Little has been investigated about neural correlates associated with gender differences on facial affect processing. While there were no confirmatory findings of gender differences in cognitive function in schizophrenia patients (Bozikas et al., 2010), gender differences have been found for affective processing among schizophrenia patients, especially when they are asked to recognize facial expressions. Amygdala volume was reduced in male patients compared to female patients among subjects of early onset schizophrenia spectrum disorder (Frazier et al., 2008). Furthermore, activity of the amygdala was greater in females than in

males during facial affect recognition tasks (Kempton et al., 2009), and viewing painful stimuli (Proverbio et al., 2009). Scholten et al. (2005) found that female schizophrenia patients were better than male patients at recognizing negative facial emotions such as anger and disgust, but not at recognizing positive emotions such as happiness. Also, a neuroanatomical study revealed that reduction of hippocampal volume (Exner et al., 2008) and disruption of hypothalamic sexual dimorphism (Goldstein et al., 2007) were observed in male schizophrenia patients. These previous findings support the present findings of greater deficits in the emotional processing of male compared to female schizophrenia patients.

This study had some limitations. First, all of our patients were medicated at the time of testing. While the dosage of antipsychotics used was not correlated with any of the ERP variables, the medication may have affected the patients' cortical responses. Second, we did not implement nonfacial control stimuli of a similar perceptual complexity. Given that there are already many ERP-related reports comparing facial and nonfacial stimuli, comparing ERP responses of facial with nonfacial stimuli seems to be redundant and beyond the scope of our study. We instead focused on ERP components and their source densities in response to different facial emotions. Third, emotion valence (emotional versus neutral) with ERP correlates of motor response and no-go effects were potential confounders of ERP differences in this study. However, there was a significant difference in LORETA current density only to fearful facial stimuli; although subjects may need to concentrate more on neutral facial stimuli because they should not press the button when they see them, this appeared to have no significant effect on LORETA current density. In spite of all these limitations, our results are suggesting that ERP source imaging can be a useful method in studying altered affective facial processing in schizophrenia patients.

In summary, we found that schizophrenia patients have reduced current source density of N170 for fearful faces. These findings were not found in happy or neutral facial expressions. Also, there were no significant differences on current source density between groups in other ERP components (P100, N250, and P300) for all three facial affects. Schizophrenia patients showed reduced current source density of the N170 to fearful faces in middle frontal gyrus and inferior frontal gyrus. In addition, our results indicate that gender may be an important factor to be considered in affective facial processing of schizophrenia patients. Male schizophrenia patients showed reduced activation in insula, superior temporal gyrus, middle temporal gyrus and inferior frontal gyrus. To conclude, the source localization of the N170 component for fearful faces is sensitive to affective processing in schizophrenia patients, suggesting that it can be a useful biomarker to examine schizophrenia patients.

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The KOSEF had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Seung-Hwan Lee designed the study and wrote the protocol. Hyung-Tae Jung wrote the manuscript. Do-Won Kim and Sangrea Kim produced the ERP waves and calculated the current source densities from data set. Chang-Hwan Im undertook the sLORETA and the statistical analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest.

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