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Source activation during facial emotion perception correlates with positive and negative symptoms scores of schizophrenia*

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Abstract— **Schizophrenia is one of the most devastating of all mental illnesses, and has dimensional characteristics that include both positive and negative symptoms. One problem reported in schizophrenia patients is that they tend to show deficits in face emotion processing, on which negative symptoms are thought to have stronger influence. In this study, four event-related potential (ERP) components (P100, N170, N250, and P300) and their source activities were analyzed using EEG data acquired from 23 schizophrenia patients while they were presented with facial emotion picture stimuli. Correlations between positive and negative syndrome scale (PANSS) scores and source activations during facial emotion processing were calculated to identify the brain areas affected by symptom scores. Our analysis demonstrates that PANSS positive scores are negatively correlated with major areas of the left temporal lobule for early ERP components (P100, N170) and with the right middle frontal lobule for a later component (N250), which indicates that positive symptoms affect both early face processing and facial emotion processing. On the other hand, PANSS negative scores are negatively correlated with several clustered regions, including the left fusiform gyrus (at P100), most of which are not overlapped with regions showing correlations with PANSS positive scores. Our results suggest that positive and negative symptoms affect independent brain regions during facial emotion processing, which may help to explain the heterogeneous characteristics of schizophrenia.**

I. Introduction

Deficits in schizophrenia patients characterized by lower performance in face recognition or facial affect recognition have been reported both in behavioral studies [1] and in neuroimaging studies employing various imaging modalities [2-3]. For instance, a number of functional magnetic resonance imaging (fMRI) studies have compared the differences in hemodynamic responses during facial emotion processing between schizophrenia patients and healthy control subjects. In this area of research, investigating the correlation between neuronal activations and symptom scores is of importance in order to understand the heterogeneous characteristics of schizophrenia and to interpret the pathological differences between positive and negative symptoms. Previous fMRI studies have demonstrated a significant correlation between Positive and Negative Syndrome Scale (PANSS) scores and behavioral outcomes (e.g., illness duration, age at onset, antipsychotic dose, and social functioning scores) [4-6], and also significant negative correlations between negative symptom scores and activations in the left superior temporal gyrus and prefrontal area during facial emotion processing [7-8]. However, these studies have not shown consistent results regarding the relationship between hemodynamic responses and symptoms during facial emotion processing, with some studies reporting no significant correlation between regional activations and symptoms [2].

Since facial emotion processing is a complex cognition process that requires participation by multiple brain regions in a sophisticated sequential manner in a short period of time, it is likely that the inconsistent findings of fMRI studies are due to the low temporal characteristics of fMRI. Compared to other neuroimaging techniques, scalp electroencephalogram (EEG) has superior temporal resolution, which makes it possible to track temporal changes in the underlying neuronal activity.

In our previous studies [9-10], we found concrete evidence of emotion perception deficits in schizophrenia patients by investigating the characteristics of ERP components and their correlations with symptom severity scores. Both the amplitude and latency of N170 showed significant differences between schizophrenia patients and normal controls, and a statistically significant correlation was found between negative symptom scores and N170 latency in female schizophrenia patients. To our knowledge, however, no previous studies have focused on the correlation between ERP source activations during facial emotion discrimination tasks and the severity of schizophrenia symptoms, which might provide important temporal and spatial information for understanding the underlying mechanisms of schizophrenia.

As an extension of our previous study, the current study investigates the relationship between the source activations of four ERP components (P100, N170, N250, and P300) during facial affect perception and positive/negative symptom severity in schizophrenia patients. We evaluated voxel-based correlations between the source activities of the four ERP components measured using standardized low-resolution electromagnetic tomography (sLORETA) and symptoms severity based on PANSS scores, with the ultimate goal of revealing clearer relationships between positive and negative symptoms and source activity, thus identifying which regions of the brain are affected by each symptom.

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II. METHODS

A. Participants

A total of 23 schizophrenia patients were recruited for the current study. The mean age of the participants was 32.2 ± 10.1 (mean ± SD) years, and 11 were female. All participants had been diagnosed with schizophrenia based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), Axis I Psychiatric Disorders. To measure the severity of symptoms according to psychopathologic syndromes, all participants were diagnosed using the PANSS. All participants were stable, right-handed, with normal or corrected-to-normal vision. All subjects were taking atypical antipsychotics (olanzapine, n = 11; risperidone, n = 12). The demographic data of the participants are presented in Table 1. The study was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital. After a complete explanation of the study to the participants, their written consent was obtained prior to the study.

B. Stimuli and Experimental Paradigm

The participants were seated in a comfortable chair, facing a 17-inch CRT monitor in a sound-attenuated room. The monitor was located at 1 m in front of the participants, allowing for maximum visual angle of 4° × 4°. Facial stimuli were presented as 288 randomly ordered pictures, with an equal probability for each emotion (96 neutral faces, 192 emotional faces). The facial images used for the current study were selected from a Korean standardized facial image set named "Chaelee face" [11]. Each trial started with a fixation cross presented on the middle of the screen for 100 ms, then a black screen was presented for 500 ms. Next, the facial image was displayed for 500 ms as a stimulus, and the screen returned to black for a random interval of 900-1100 ms to prevent habituation. Each epoch took from 2000 to 2200 ms, which made the length of the total experiment approximately 15 minutes. They were asked to press a button with their right thumb only when they encountered emotional faces (happy or fearful).

C. EEG recording and ERP analysis

EEG signals were recorded using NeuroScan SynAmps (Compumedics USA, El Paso, TX, USA) with 64 Ag-AgCl electrodes mounted in a Quick Cap. The ground and reference electrodes were placed on the forehead and Cz, respectively. A pair of electrodes was attached above and below the right eye to record the vertical electrooculogram (EOG), and another pair was attached at the outer canthus of each eye to record the horizontal EOG. The sampling rate was set at 1000 Hz. The recorded EEG was bandpass filtered online with cutoff frequencies of 1 Hz and 100 Hz.

The recorded EEG was preprocessed using Scan 4.3 to reduce various artifacts. The raw signal was re-referenced to an average reference. The re-referenced signal was visually inspected by a clinician to reject sections with gross artifacts, and these were excluded from the main analyses. The data was divided into epochs lasting from -300 *ms* to 1000 *ms* from the stimulus onset.

TABLE I. DEMOGRAPHIC DATA AND SYMPTOM RATING OF 23 SCHIZOPHRENIA PATIENTS.

	Schizophrenia (n = 23)
Age (years)	32.2 ± 10.1
Male, female	12, 11
Education duration (years)	12.8 ± 2.1
Number of hospitalizations	1.7 ± 1.4
Duration of illness (years)	5.2 ± 4.9
Antipsychotic drug dosage (mg)	391.30 ± 97.30
PANSS total score	81.8 ± 25.8
Positive score	20.2 ± 7.8
Negative score	18.7 ± 7.4

a. Antipsychotic drugs dosages are chlorpromazine equivalents.
b. PANSS: Positive and Negateive Syndrome Scale

We followed a mathematically-established procedure to remove the error effects of the EOG [12]. If any signal at electrodes other than M1 and M2 exceeded ±70 μV, it was regarded as a physiological artifact and the corresponding epoch was rejected from the analysis. Baseline correction was done by subtracting the mean activity prior to the stimulus onset (during the period from -300 ms to 0 ms). The signal was bandpass filtered at 1–30 Hz with a steepness of 24 dB/octave for ERP analysis.

Each signal was then averaged to identify the four ERP components associated with facial emotion processing: P100, N170, N250, and P300. The criteria for identifying each ERP peak and latency were established based on the mean global field potential (MGFP) over the scalp topography in all participants: the P100 component had the maximum positive potential from 50 to 150 ms after the stimulus onset at electrodes PO7 and PO8; N170 had the largest negative peak in ERP amplitude from 120 to 220 ms at P7/PO7 and P8/PO8; N250 had the biggest negative potential in F1/FC1/FC3 and F2/FC2/FC4 at a latency of 150 to 350 ms; and the P300 component had the largest positive peak at electrodes F1/FC1 and F2/FC2 from 300 to 450 ms post stimulus.

D. Source localization using sLORETA

In this study, we used the open sLORETA software to estimate the source distribution [13]. For each individual's ERP signals, sLORETA was used to compute the cortical distribution of the standardized source current density of each ERP component. The lead field matrix was computed using a realistic head model segmented using the MNI152 standard template, in which the three-dimensional solution space was restricted to only the cortical grey matter. The solution space was composed of 6238 voxels with 5-mm resolution. The source image for each ERP was reconstructed for a time window of (mean ERP latency) ± (1 standard deviation) for each emotion following the same procedure described in our previous study [9].

D. Correlation between PANSS scores and source activation

For each individual voxel, Pearson's correlation between sLORETA source activation and PANSS positive/negative scores was calculated. To avoid false positive relationships, we tested statistical significance using a non-parametric permutation test. The voxel activations were randomly shuffled 10,000 times, and the correlation was calculated for each randomization to obtain the correlation distribution of

each voxel. The significance of the correlation value of each voxel was tested using each correlation distribution at a significance level of 0.05. After the correlation maps were generated, voxels with significant correlations were classified as clusters. Voxels were classified into the same cluster when both of the following criteria were satisfied: 1) the voxel should have at least one nearby (including diagonal directions) voxel which is significant; and 2) each cluster should include more than three voxels. Therefore, one or two isolated voxels were regarded as outliers.

III. Results

A. Brain regions correlated with positive symptoms

1) Neutral face stimuli

PANSS positive scores were negatively correlated with four source activation clusters of the P100 component (Figure 1.(a)): the inferior parietal lobule (BA 40, r = -0.647, p = 0.002), precentral gyrus (BA 6, r = -0.639, p = 0.003), precuneus (BA 31, r = -0.662, p = 0.002), and insula (BA 13, r = -0.616, p = 0.004). Source activation clusters around the middle frontal gyrus (BA 10, r = -0.607, p = 0.004) for the N170 component (Figure 1.(b)) and around the medial frontal gyrus (BA10, r = -0.657, p = 0.002) for the N250 component (Figure 1.(c)) also showed significant negative correlation with PANSS positive scores. There was no significant correlation between the source activation of the P300 component and PANSS scores.

2) Fearful face stimuli

Meaningful relationships between positive symptom severity and source activation during fearful face perception were found only in the P100 component. The PANSS positive score was negatively correlated with seven distinct clusters covering the supramarginal gyrus (BA 40, r = -0.625, p = 0.002), precentral gyrus (BA 6, r = -0.616, p = 0.004), inferior parietal lobule (BA 40, r = -0.581, p = 0.007), middle temporal gyrus (BA 37, r = -0.579, p = 0.006), insular (BA 13, r = -0.595, p = 0.005), middle temporal gyrus (BA 37, r = -0.536, p = 0.012), and precuneus (BA 31, r = -0.685, p = 0.002). However, later components such as the N170, N250, or P300 did not show any source clusters significantly correlated with PANSS scores.

3) Happy face stimuli

The strongest negative correlation was found in the inferior parietal lobule (BA 40, r = -0.664, p = 0.002) between PANSS positive scores and P100 source activation. The P100 source activities also had significant negative correlations with PANSS positive scores in the supramarginal gyrus (BA 40, r = -0.593, p = 0.006), superior frontal gyrus (BA 6, r = -0.581, p = 0.006), middle frontal gyrus (BA 9, r =-0.570, p = 0.008), and precuneus (BA 31, r = -0.643, p = 0.002). N170 source activation in the middle frontal gyrus (BA 40, r = -0.591, p = 0.006) showed significant negative correlation with positive symptom scores. N250 and P300 source activation did not show meaningful correlations with PANSS positive scores.

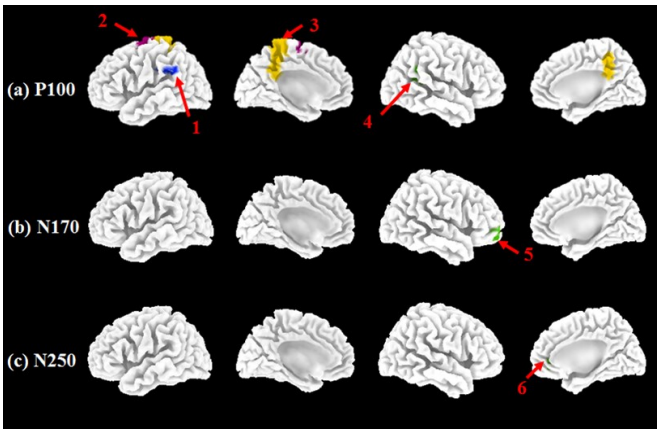

Figure 1. Significant correlations between positive PANSS scores and source activity of (a) P100, (b) N170, and (c) N250 during neutral condition. Different colors within the same ERP indicate different clusters.

B. Brain regions correlated with negative symptoms

1) Neutral face stimuli

PANSS negative scores showed significant correlation with two source clusters in the P100 component (sub-gyral (BA 37, r = -0.702, p < 0.001) and middle temporal gyrus (BA 39, r = -0.693, p = 0.001)) and one cluster in the N250 component (middle frontal gyrus (BA 10, r = -0.600, p = 0.005)). No clusters were significantly correlated with PANSS scores in the N170 or P300 components.

2) Fearful face stimuli

For fearful face stimuli, the source activity of P100 has shown strong negative correlations were found in three distinct brain regions: the inferior temporal lobule (BA 37, r = -0.532, p = 0.012), inferior parietal lobule (BA 40, r = -0.523, p = 0.014), and inferior frontal gyrus (BA 9, r = -0.722, p < 0.001). No significant correlations were found between later components, such as N170, N250, or P300, and source activities.

3) Happy face stimuli

Negative symptom scores were negatively correlated with P100 source activation when patients viewed happy faces. A P100 source cluster in the middle temporal gyrus (BA 39, r = -0.688, p = 0.001) showed strong negative correlation with PANSS negative scores, but no additional correlations were found for other regions or components.

IV. Discussion

Our study investigated the relationships between symptomatic scores and voxel-based source activations of ERP components during facial emotion recognition. PANSS positive scores formed source clusters that were negatively correlated with P100 source activation in the left temporo-parietal regions regardless of emotion type: clusters showing maximum correlation were located in the inferior parietal lobule (BA 40), precentral gyrus (BA 6), precuneus (BA 31), insular (BA 13), supramarginal gyrus (BA50), middle temporal gyrus (BA 37), and sub-gyral (BA 37). In later components (N170 and N250), PANSS positive scores were significantly correlated with source clusters in the

middle or medial frontal gyrus (BA 10) for neutral and happy emotional faces. PANSS negative scores were highly correlated with clusters centering in the middle temporal gyrus (BA 37, 39), sub-gyral (BA 37), inferior parietal lobule (BA40), and inferior frontal gyrus (BA 9) for the early component (P100), and the left fusiform gyrus was always included in each cluster (Figure 2 (a,b,c)).

Summarizing our findings, the negative correlation between PANSS scores and source activation in early stages of face emotion processing were formed broadly in temporal regions and parietal regions. The regions showing negative correlation with positive and negative PANSS scores matches with regions included in the core system [14], which suggests that the symptoms are highly correlated with impaired visual processing of faces in the early stages. In later stages, the regions with string negative correlation with symptom scores moved to frontal lobe. Our results suggest that the areas showing correlation with the symptom scores are formed in backside (temoroparietal areas as Haxby et al. (2000) proposed) and move forward to frontal lobe, which reflects top down processing in face emotional perception [14].

V. Conclusion

The present study investigated the relationship between source activation during facial emotion processing and symptom severity of schizophrenia patients. We found meaningful negative correlation between PANSS positive scores and source activity in temporo-parietal regions during the early stages of visual processing, regardless of the emotional component. PANSS positive scores were also correlated with frontal cortex activity during later components (N170 and N250) for the neutral and happy conditions, but not for the fearful condition. These relationships show that dysfunction of the integrated social cognitive network in schizophrenics is highly related to the progress of the positive symptoms of schizophrenia. Moreover, this absence of positive symptom correlation in the fearful condition suggests that altered fearful emotion perception could be a trait pathology of schizophrenia. Finally, the left fusiform gyrus, a region important to early face processing, showed negative correlation with PANSS negative scores in the P100 components, regardless of emotion type. It also suggests that fusiform gyrus dysfunction could be a trait pathology in schizophrenia patients. Our results suggest that altered face-emotion processing of schizophrenia patients is caused by the combined effects of positive and negative symptoms affecting different areas of the brain.

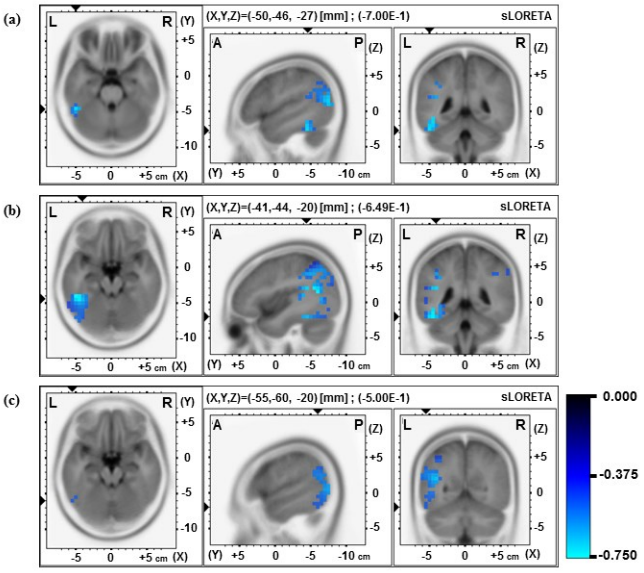

Figure 2. Significant negative correlations between negative symptom scores and left fusiform gyrus of P100 source imaging when schizophrenia patient is viewing (a) neutral, (b) fearful, and (c) happy faces.

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