Investigation on Impaired Facial Affect Processing of Schizophrenia Using Electroencephalogram (EEG)

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Abstract

Investigation on Abnormal Cognitive Function of Schizophrenia Patients Using Electroencephalogram (EEG)

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Abnormal social function is one of the most frequently reported symptoms of schizophrenia. Especially, a large number of behavioral studies have shown that schizophrenia patients show deficit in perceiving gender, age, mood, or intention through the opponent's face. With behavioral studies alone, however, it is difficult to interpret the underling malfunction of the brain that causes such deficits. Recently,

increasing number of neuroscientists started to investigate this abnormality of schizophrenia patients using various types of neuroimaging methods, such as positron emission topography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalogram (MEG), and electroencephalogram (EEG). Although the researchers have collected some evidences which might support the deficits, the fundamental principle that causes malfunction in identifying facial features in schizophrenia still remains unknown. Therefore, more studies need to be done to infer the neural basis of abnormal face recognition in schizophrenia.

The principle aim of this dissertation is to investigate abnormal social functions of schizophrenia using EEG, especially focusing on impaired facial affect recognition. A series of analyses are performed to contrast out the underlying neurophysiological difference between schizophrenia and normal controls throughout the dissertation. For an in-depth investigation, the author has analyzed clinical EEG data not only using conventional electrode-level analysis (time-frequency analysis or synchronization analysis) but also applying more sophisticated methods based on cortical source imaging. Furthermore, correlation between cortical sources during face affect recognition and clinical symptom scores of schizophrenia has been investigated to interpret the underlying neural correlates of different symptoms of schizophrenia. EEG data were recorded from twenty-five schizophrenia patients and age-matched normal controls using a facial affect recognition task. Pictures expressing three different facial emotions (neutral, fearful, and happy) were randomly

presented to the participants. The participants were instructed to respond by pressing a button when pictures with emotional faces were presented.

Using the recorded EEG signal, the author first investigated gamma-band activity (GBA) and its phase synchrony in schizophrenia patients in neutral face stimuli. The spectral power and phase synchrony in the frequency band from 30 to 55 Hz were analyzed in midline electrodes (FCz, Cz, CPz, Pz, and POz). Repeated-measures ANOVA revealed that the GBA was lower in schizophrenia patients than in normal controls. GBA was significantly lower in the schizophrenia patients than in the normal controls at around 700–800 ms at the FCz electrode. The frontal (FCz) and central (Cz) GBA were significantly correlated with the number of hospitalization, and the negative symptoms of schizophrenia, respectively. A significant main effect was also found in location and time. The phase synchronization was significantly lower at 200–300 ms in the schizophrenia patients than in the normal controls.

As the second step of analysis, the author has implemented standardized low-resolution brain electromagnetic tomography (sLORETA) to compare the source activation between schizophrenia and normal controls. The cortical sources were estimated for four face-related ERP components (P100, N170, N250, and P300) and compared between two groups 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 fearful stimulus. 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.

Lastly, the author performed an investigation to reveal the relationship between cortical sources during face affect recognition and clinical symptoms scores of schizophrenia. 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 24 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. The current analysis demonstrated 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.

In summary, the author has made a full investigation on abnormal facial affect recognition of schizophrenia to reveal the neurophysiological differences and the pathogenesis of schizophrenia. The results indicate that schizophrenia patients have a broad impairment during face recognition in terms gamma-band activation, phase-coherence and cortical sources, and their symptoms affect independent brain regions.

Key Words: schizophrenia, electroencephalography (EEG), Positive and Negative Syndrome Scale (PANSS), positive symptoms, negative symptoms, face affect recognition, fearful emotion, event-related potential (ERP), P100, N170, N250, P300, gender, gamma-band activity (GBA), phase coherence, cortical source imaging, standardized low-resolution electromagnetic tomography (sLORETA), correlation, clinical symptoms, functional connectivity

Chapter 1: Introduction

Schizophrenia is a common, chronic, heterogeneous neuropsychiatric illness with a lifetime prevalence of 1–4 % [1, 2]. The core impairments of schizophrenia include both positive and negative symptoms, with cognitive decline considered to be a central pathology of the illness.

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 [3]. Especially, facial affect perception is an important aspect of social cognition which allows us to recognize the emotion or intention using opponent's facial expression. It has been repeatedly reported that schizophrenia patients have deficits in social cognitive function [4].The ability to recognize and discriminate facial emotions is reported to be impaired compared to normal controls than in schizophrenia patients [5-7]. Furthermore, it has been suggested that general deficits in facial affect processing are associated with symptoms severity and reduced social functioning in these patients [8-10]. However, there are also studies which claim that face affect recognition deficits is not a core symptom of schizophrenia. It was suggested that patients with schizophrenia could also perform affect recognition tasks at near-normal abilities [11].

Recently, an increasing number of neuroscientist investigated the abnormal facial affect processing of schizophrenia patients using various neuroimaging modalities since it is possible to estimate the neuronal activation with satisfactory accuracy by using appropriate signal processing techniques [12]. For instance, electroencephalogram (EEG) is one of the representative neuroimaging modalities that have been widely used in neuroimaging studies. EEG is able to measure the spontaneous or evoked neural activity on the scalp surface by placing multiple electrodes on the scalp surface. The advantages of EEG are that it needs relatively less efforts to record neuronal signals, requires low maintain cost, and has a superior temporal resolution compared to other modalities such as functional magnetic resonance imaging (fMRI). Modern EEG used in schizophrenia researches has a reasonable spatial resolution as signals can be recorded simultaneously from up to 256 electrode sites.

Studies using EEG have revealed that the recorded signals from the scalp surface are highly related to the brain responses elicited by specific stimuli, memory processes or other cognitive processes. One of the typical findings is the event-related potential (ERP), which is a time-locked response of the brain that occurs at a specific time after an external stimuli or an internal event. Various ERP components are now well-understood, which are closely related with sensory perception or higher-cognitive functions [13-15]. Time-frequency analysis is also a prevalent method to observe the change of frequency components over time. Frequency components of

EEG are known to be highly correlated with various brain functions such as sleep, memory retrieval, and long-range communication between distinct brain areas. More recently, development of source imaging methods made it possible to accurately estimate the current density of the cortical source space from scalp recordings. The biggest advantage of EEG source imaging is that it is possible to estimate neural sources relatively easily and noninvasively, without losing the high temporal resolution of EEG.

For decades, an increasing number of neuroscientists are adding neurological evidences to better understand the abnormal social behaviors of schizophrenia patients using EEG. For instance, studies using ERP have shown that schizophrenia patients show reduced ERP amplitude when facing facial stimuli [7, 16]. Reduced amplitude or prolonged latency of face-related ERP components seems to be associated with the clinical symptom scores of schizophrenia. A recent study using high-frequency activity of schizophrenia patients during face-related processing has reported reduced gamma band power activation compared to normal controls which may reflect the deficit in coordination of neural activity in schizophrenia patients [17]. Other studies using cortical source imaging have shown consistent findings of reduced activation related to face-recognition or emotion processing in various brain areas such as amygdala, fusiform face area, temporal lobe, and frontal sides [18]. Reduced gray-matter volume of the fusiform face area revealed via

magnetic resonance imaging (MRI) also provided strong evidences on impaired social functioning of schizophrenia [19, 20].

Although many studies have focused on revealing the pathogenesis of schizophrenia using neuroimaging studies, the findings are rather fragmentary or even confusing across studies. Furthermore, the relationship between clinical outcomes and neurophysiological findings seems to be still unclear to draw any concrete conclusions. The heterogeneous characteristics of schizophrenia and the wide spectrum of impairments could be the main cause of the inconsistent findings between studies. Thus, a comprehensive analysis using various state-of-the-art analysis methods could contribute to explain the impaired face emotion recognition of schizophrenia patients.

The main objective of this dissertation is to conduct a comprehensive investigation on face emotion recognition of schizophrenia patients using EEG analyses. Hierarchical analyses from sensor-level to source-level are done to put more neurophysiological evidence on impaired face-emotion recognition of schizophrenia patients. Furthermore, relationship between neurological findings and symptom severity are also investigated and discussed.

For this purpose, the author have applied various signal processing methods and analysis techniques using the recorded EEG signal throughout the dissertation;

from sensor level analysis (i.e. time-frequency analysis, sensor-level connectivity analysis) to source level analysis (i.e. source imaging analysis, connectivity analysis between sources), and investigated the relationship between neurological findings and symptom severity (i.e. correlation analysis between source activation and clinical symptoms scores).

This dissertation consists of 7 chapters. First, the author introduces basic knowledge of electroencephalogram and schizophrenia throughout Chapter 2 and Chapter 3. Chapter 2 will include the brief information of neurophysiological sources, introduction to principles of electroencephalogram, and conventional analysis methods. Chapter 3 contains brief knowledge on schizophrenia; symptomatic features and diagnosis criteria of schizophrenia, and summary on recent findings of abnormal face perception in schizophrenia patients.

Throughout the rest of the dissertation, the author will contrast the difference between schizophrenia patients and normal controls from the perspective of facial affect recognition. Twenty-five schizophrenia patients and matched normal controls were recruited for the study. The EEG signals were recorded while the participants were performing facial affect recognition task, which was originally established for a conventional ERP study. The signals were preprocessed to eliminate and suppress noise components, and some of the patient's data were dropped out due

to poor signal quality. The ERP results are will not be mentioned with importance, since it is not the major coverage of this dissertation

In Chapter 4, the author will perform several sensor-level analyses, which is focused on the gamma-band activity and connectivity during face affect discrimination task. Since the gamma band activation is known to be responsible for long-range communication between distinct brain regions, it will be appropriate to compare the gamma band activation with normal controls. The main purpose of the chapter is to explain abnormal facial affect recognition by decreased connectivity between distinct brain areas in schizophrenia during task compared to normal controls. The author applied time-frequency analysis to observe the fast-varying changes in high-frequency band power during task. The difference between schizophrenia and normal controls in sensor-level connectivity will be also contrasted using phase-locking value (PLV), which is considered to be appropriate to investigate task-induced changes in long range synchronization of neural activity.

Chapter 5 will impose source localization methods to exam fundamental differences in terms of cortical source activity. First, the author will compare neural activity during facial emotion discrimination task using standardized low-resolution brain electromagnetic tomography (sLORETA), which is one of the reliable methods for localizing EEG and ERP electrical activity. sLORETA source activities of four ERP components (P100, N170, N250, and P300), which is known to be related to face

processing, will be compared between schizophrenia patients and healthy controls in response to fearful, happy, and neutral facial expressions. The author will contrast also contrast the effect of gender in source activities.

In Chapter 6, the author investigates the relationship between symptom scores of schizophrenia and the source activation. Previous studies suggest that the impairment of facial affect recognition is more influenced by the negative symptom of schizophrenia patients. However, considering the heterogenic characteristic, the author hypothesized that positive and negative symptoms are affected together resulting an overall decline in facial affect recognition, rather than a symptom category alone. To validate the hypothesis, twenty-three schizophrenia patients and their source estimations using sLORETA were calculated on four ERP components (P100, N170, N250, and P300). All voxels of the estimated source image were correlated with the symptom severity scores of each individual, measured using Positive and Negative Syndrome Scale (PANSS). Voxels showing significant relationship were contrasted and clustered in response to three emotional facial expressions; fearful, happy and neutral. Chapter 6 introduces the full testing procedure and verifies the hypothesis with the outcome.

The results of each analysis will be integrated and reviewed in the discussion section of each chapter. Chapter 7 will summarize the result and discussion and discuss about the limitation and future works and conclude this dissertation.

Chapter 2: Basics of Electroencephalogram (EEG)

In this chapter, a brief introduction on EEG and its underlying neuronal sources are provided to help the readers to understand this dissertation. Section 2.1 describes how neuronal sources generate measureable signals. Section 2.2 covers more detailed information on EEG and how the signals are recorded. Finally, Section 2.3 introduces technical details on conventional analysis methods such as event-related potential, rhythmic activity, source imaging, and functional connectivity.

2.1. Neurophysiological Basis

The human brain is the center of the nervous system which takes charge of all human functions in daily life, i.e. perception, motor control, cognitive functions, etc. The brain communicates and processes information in a sophisticated and well-organized manner using electrical and chemical signals. These signals are elicited from highly specialized information-processing units called neurons. The cell body and dendrites of the neurons are concentrated in the gray matter (almost over 90%), which the largest part of cerebral cortex that forms the surface of the brain. The left side of Figure 2.1 shows the coronal section of the brain, where the gray matter is depicted in dark violet. The neurons in cerebral cortex are also called pyramidal cells

(or neurons) and they are aligned parallel to each other and tend to align perpendicular to the cortical surface (Figure 2.1, right).

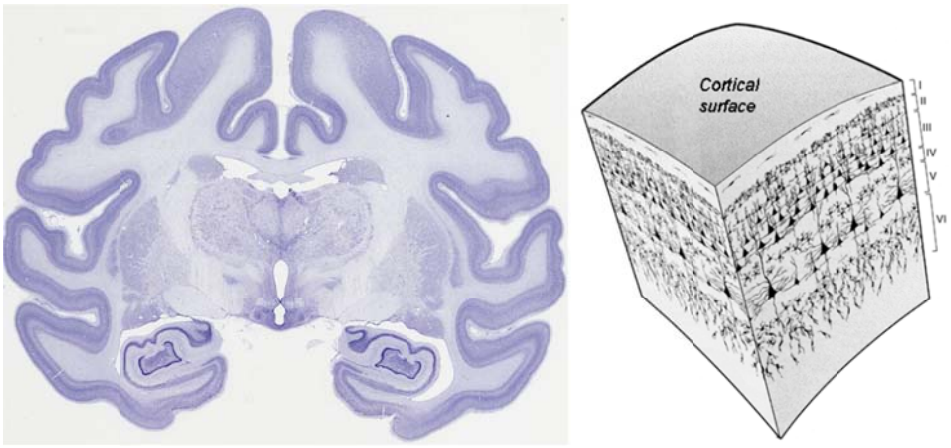

Figure 2.1. The coronal section of the human brain (left, http://brainmaps.org). A schematic figure showing the alignment of the cortical neurons, which are perpendicular to the cortical surface (right, http:// http://www.acbrown.com).

The typical structure of the neuron includes the soma (cell body), dendrites and axon (Figure 2.2). Dendrites are branched fibers, which are interconnected with other neuron's axon via a junction called the synapse. Synapse is a specialized structure where the information is transferred from one neuron to another, via chemical or electrical signals. When an action potential is elicited from the action hillock of the soma, the electrical signal runs down from the soma to the axon terminal and opens voltage-gated Ca++ channel. The channel releases neurotransmitters to the synaptic cleft. The responding receptors to these

neurotransmitters are concentrated on the opposite side of the synaptic cleft, which is equivalent to the dendrite of the following neuron. Once the receptors bind with the neurotransmitters, the influx of ions to the dendrite causes inhibitory or excitatory post-synaptic potential (depending on the type of the neurotransmitter), which will be integrated to the soma of the next neuron.

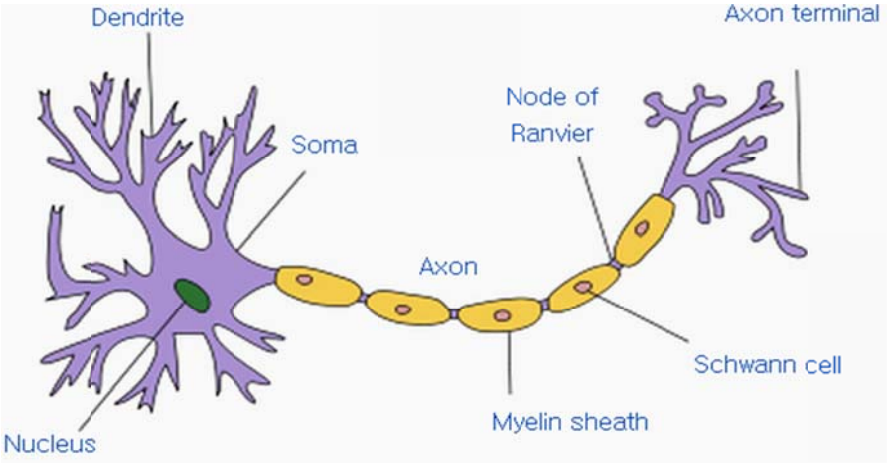

Figure 2.2. Schematic illustration of a typical neuron. (http://www.wikipedia.org/)

This way of information transmission leads to two kinds of potential changes in neuron as that may contribute to record brain signals: action potential and post-synaptic potential (caused by chemical transmission between synapses). Compared to the large and rapid electrical discharge of action potential, the post-synaptic potential is rather slow in time and low in amplitude (Figure 2.3). However, it is believed that most measureable extracranial fields are generated not by action potentials, but by post-synaptic potentials. It is because action potentials are not very

likely to occur synchronously in large number of neurons to generate enough potential to be recorded on the scalp surface. On the contrary, post-synaptic potentials are weak compared to action potential: however, if numerous pyramidal neurons at a certain cortical region are synchronously activated, the summation of post-synaptic potential is able to form a unidirectional current that is responsible for the measureable signal from the surface of the head.

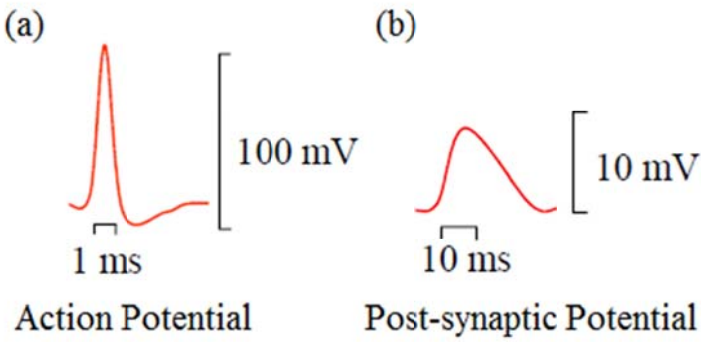

Figure 2.3. A schematic time course of (a) action potential and (b) excitatory post-synaptic potential.

2.2. Electroencephalogram (EEG)

The brain electrical activity of human was first obtained in 1924 by a German psychiatrist Hans Berger (1873-1941) beginning with the discovery of the "alpha waves" in human (Figure.2.4). After the finding of EEG, tremendous development of hardware technologies and software methodologies has been introduced to reveal the nature of human brain: however, the basic principle of EEG remains unchanged.

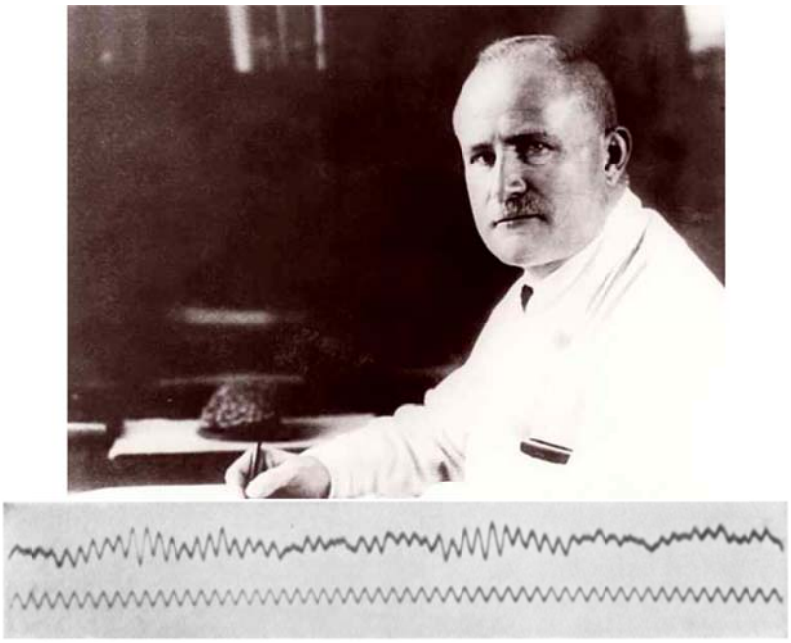

Figure 2.4. The first recording of human EEG was done by Hans Berger (top). The recording on the bottom represents EEG samples from his publication which he named 'alpha rhythm' (with a sinusoidal rhythm of approximately 10 Hz).

EEG has its advantage in high-temporal resolution, relatively low cost for installation and maintenance compared to other noninvasive neuroimaging tools such as magnetoencephaolgram (MEG), functional magnetic resonance imaging (fMRI), and near infrared spectroscopy (NIRS). EEG has played an important role not only to investigating the cortical activity of healthy humans but also to investigate patients with severe neurological and neuropsychological disorders such as schizophrenia, Alzheimer's disease, Parkinson's disease, and epilepsy.

EEG records an electrical potential difference over short period of time between pairs of electrodes attached to the surface of the head. Since EEG records the potential difference, it needs at least two electrodes to obtain one EEG signal. The electrode can be attached on the scalp surface directly above the interested brain region; or following the standard configurations such as international 10-20 electrodes system (Figure 2.5). The 10-20 electrode system has been widely used as an international standard, which attaches 19 electrodes in a near-uniform distribution at 10 % and 20 % fractions of distances between anatomical landmarks of the skull. More subdivisions between the landmarks are possible (i.e. 5 %) in order to place more electrodes to increase the spatial resolution. It is able to record up to 256 electrodes simultaneously for EEG: however, more than 32 electrodes are considered to be satisfactory for fundamental analyses.

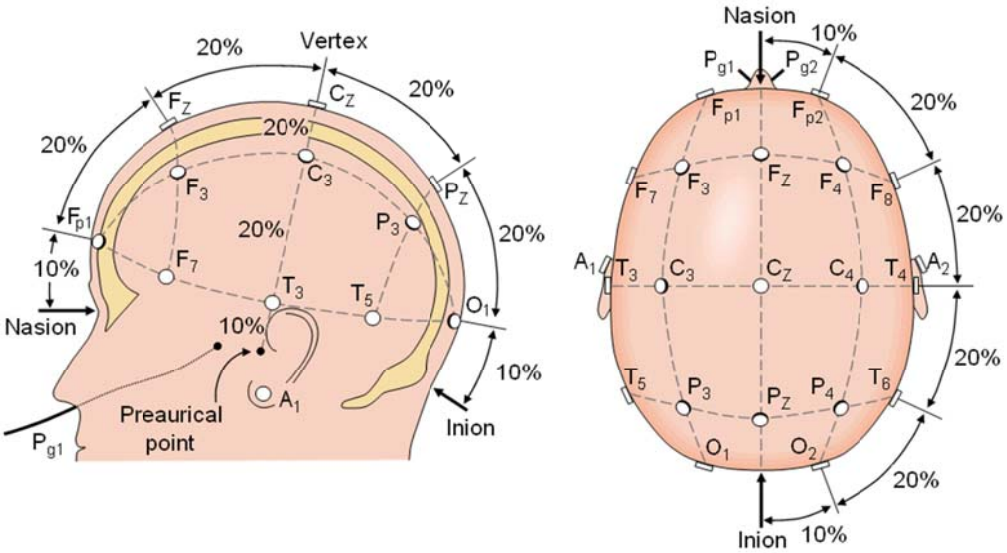

Figure 2.5. The international 10-20 electrode system seen from left and above the head.

As mentioned in the previous section, the recorded signals are mostly post-synaptic potentials elicited synchronously in a certain cortical area. However, the electrical potentials are blurred and distorted due to the electrical conductivity difference between the scalp and the cortical surface. Especially when treating EEG signals, it always has to be considered that the skull has a poor conductivity, nearly 16 times less than the scalp or the brain. Therefore, the recorded signal of an electrode is not fully responsible for the cortices directly under the electrode, but a summation of attenuated and distorted signals from nearby regions.

2.3. Conventional Analysis using EEG

Many researches have utilized EEG to investigate the functioning of human brain. Considering that the recorded EEG contains severe artifacts compared to relatively small amplitude, proper signal analysis methodology needs to be introduced to contrast out meaningful findings. In this section, the author introduces conventional analysis methods that are widely used for EEG analysis.

2.3.1. Event-Related Potential (ERP)

One of the oldest and fundamental analysis methods among EEG studies is event-related potential (ERP). ERP is a neural signal that reflects coordinated neural network activity, generally a direct resultant of a specific event. The ERP is not usually visible in raw signals due to background fluctuation of the brain and other noises. To observe ERP component with respect to a certain event, the signal needs to be ensemble-averaged with respect to the onset of the repetitive stimuli. Since the random (background) noise or signals are assumed to be uncorrelated and independent to the event, they approach to zero as more trials are being averaged. Meanwhile, time- or stimulus-locked components increase its signal-to-noise ratio (SNR) as more trials are being averaged. With sufficient number of repeated trials, only stimulus-locked component remains while other random fluctuations will be nearly zero-out. A resulting waveform might include several positive or negative ERP

components, which is referred to by a letter P/N depending on the polarity of the component (positive/negative) followed by numbers indicating either the latency in milliseconds or the component's ordinal position in the waveform. For instance, P300 ERP component is a positive deflection that peaks roughly 300 ms after stimulus onset. Figure 2.6 is a schematic diagram showing how to calculate an ERP waveform from EEG epochs and a representative ERP waveform including five ERP components (P1, P2, P3, N1, and N2).

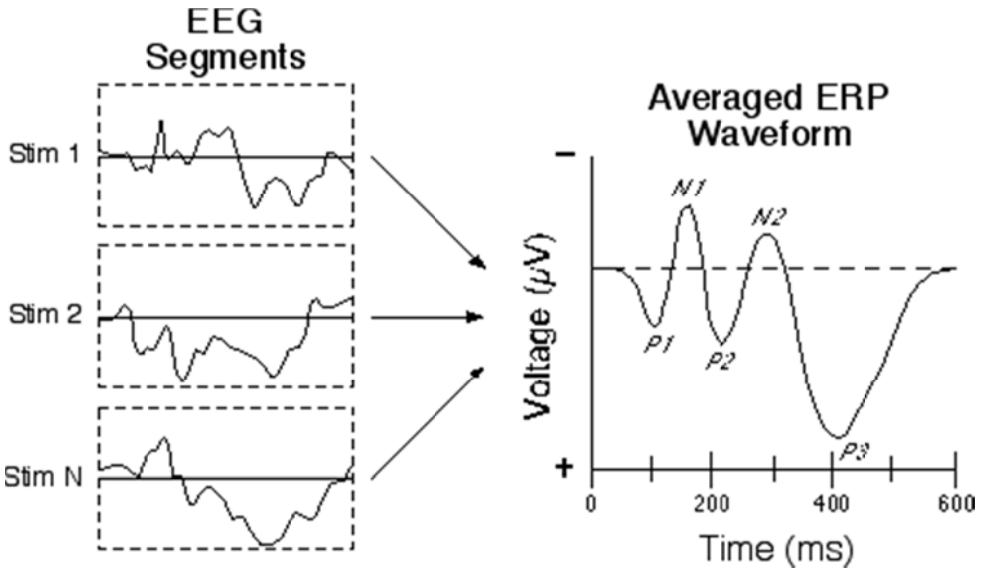

Figure 2.6 A schematic diagram of how to observe ERP components from EEG segments (epochs). (http://www.erpinfo.org)

2.3.2. Rhythmic Activity

The EEG records the synchronous activity of underlying cortical neurons depending on the various state of the brain. Development of hardware configuration and software methodology has provided clear and easy way to observe such rhythmic activation using frequency analysis. The recorded signal on the scalp surface falls in to several rhythmic oscillations at different frequencies: delta (1-3 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (15-30 Hz), and gamma (30-100 Hz). It has been well established that these frequency bands reflects different states of brain functioning (Figure 2.7).

Briefly, delta band is the slowest wave component with biggest amplitude that is known to be associated with deepest sleep stages (3 and 4). Theta rhythm is found to be highly related with spatial navigation, creative states, or when conducting working memory task. Alpha band is one of the most well studied rhythmic activities in human EEG, which is easily observable on the parieto-occipital region related to visual perception. The beta rhythm has been revealed to associate with normal waking consciousness and motor behavior. Lastly, gamma activity is the fastest brain oscillation, which originally thought as measurement noise. However, recent investigations offer that the high-frequency oscillation in the gamma band is an essential feature which is related with higher cognitive functions or communication between distinct cortical areas.

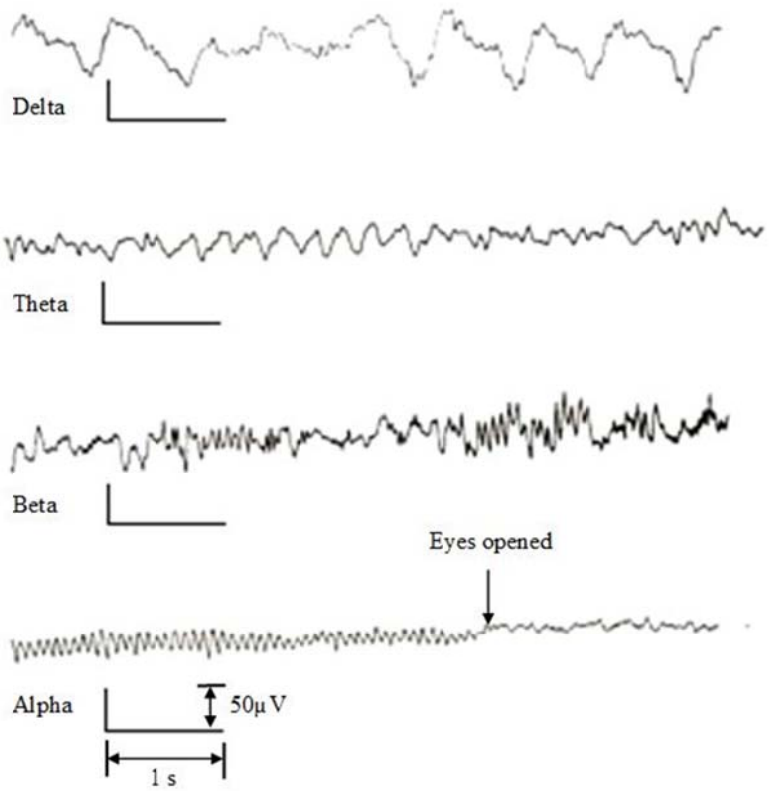

Figure 2.7 A sample illustration of different frequency bands of EEG [21]. Note that the alpha band dramatically decreases after eye opens.

2.3.3. Source Imaging Methods

As emphasized several times before, the EEG does not pick up the cortical activation directly underneath the recording electrode. Especially due to the attenuated and distorted signal characteristics, it is difficult to link the findings from the cortical surface to the actual cortical area. To overcome this limitation of EEG, various numerical methods have been developed to locate the source of the recorded EEG. However, due to the limited number of recording channels on the scalp surface and a huge number of unknown variables to estimate the source, it is difficult to estimate unknown variables reliably. Therefore, the EEG inverse problem is an ill-posed problem with non-unique and unstable solution. There are various methods to remedy the situation, which introduces different assumptions to model source activations. In this dissertation, the author has used an inverse algorithm called standardized low-resolution electromagnetic tomography (sLORETA) [22]. The solution of sLORETA is based on one simple assumption; “the activity at any one neuron must be very similar to the neighboring neuron”. The estimated source activation using ‘maximum synchronization’ assumption has been verified to be reasonably accurate in many independent studies [23]. An example of estimated cortical sources is illustrated in Figure 2.8 using an open software package downloadable in http://www.uzh.ch/keyinst/loreta.htm.

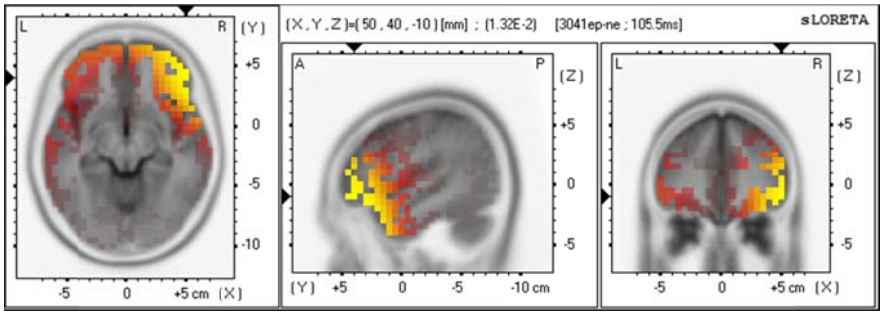

Figure 2.8 An example of estimated source activation using standardized low-resolution electromagnetic tomography (sLORETA) that shows maximum neural activation in right frontal area.

2.3.4. Connectivity Analysis

Traditional "activation studies" are focused on the pattern of activation or activation differences between conditions or participant groups. Besides traditional analysis introduced in the previous section, the connectivity analysis between brain regions has gained significant interest between neuroscientists to understand the brain as an integrated network. As the brain does not function in parts of distinct regions but cooperates in a sophisticated manner, it is reasonable to investigate such interconnection ("functional connectivity") between distinct brain areas. For such purpose, fundamental concepts to investigate connectivity have been successfully tested in EEG signals such as correlation, coherence, phase coherence, phase locking value, or phase synchronization index. Figure 2.9 shows a schematic illustration of a connectivity analysis. The connectivity of both figures are calculated with phase

locking value during cognitive test were the red line indicates significant synchronization between distinct electrodes (Figure 2.9(a)) or between distinct brain regions (Figure 2.9(b)). Such measures were able to contrast highly connected brain areas during a certain task, which provides more evidence about how distinct brain areas work simultaneously as a system. Moreover, neuroscientists recently started to apply measures based on graph theory to understand the brain as a network. Measures provided by Graph theory is able to characterize the structure of the brain network, for instance, finding the hub of the brain network, quantifying the efficiency of the network structure, or even dividing the network structure into smaller sub-networks. The advantage of such connectivity or graph measures is that it is able to compare the connection patterns or network structure between subjects or even groups, which is suitable to investigate the abnormal functional connectivity of patients with psychological illness, such as schizophrenia, Alzheimer's disease, or epilepsy.

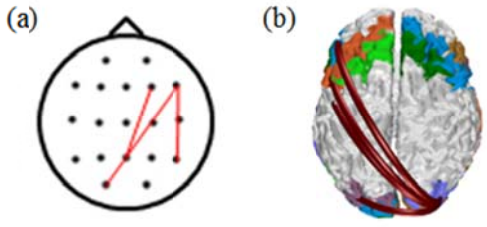

Figure 2.9 A schematic illustration of connectivity analysis: (a) electrode-level connectivity between distinct electrodes marked as dots, (b) source-level connectivity. The red line indicates significant connectivity between connected areas.

Chapter 3: Schizophrenia

In Chapter 3, the author delivers brief background knowledge on schizophrenia over three subsections. Section 3.1 covers the features of schizophrenia, and their signs and symptoms. The typical criterion used for diagnosis schizophrenia is introduced in the second section. Section 3.3 reviews abnormal facial affect processing in schizophrenia and related neuroimaging studies.

3.1. Signs and Symptoms of Schizophrenia

Schizophrenia is one of the most severe and chronic forms of mental illness, which roughly 1-4 % of world population suffers. By reason of the complex contribution between genetic and environmental factors, the pathogenesis of schizophrenia remains still unclear. Since there is no evident biomarker or definitive test to diagnosis schizophrenia or convince the severity of the illness, the diagnosis still relies on well-trained psychiatrist's counseling.

Schizophrenia could be clinically confusing because it affects to a broad spectrum of brain functions, and even shares common symptoms with other mental illnesses. Due to the heterogenic characteristic of schizophrenia, the signs and

symptoms of schizophrenia seem to be complicated and diverse; however, due to constant effort of investigators, the characteristics of schizophrenia has been simplified and categorized. Among those signs and symptoms, some evident and common signs and symptoms of the disease are used to diagnose schizophrenia, which doesn't seem to be influenced by cultural background and distinct from other mental diseases.

The core impairment of schizophrenia patients are reported as to have abnormal mental features (positive symptoms) such as hallucination and delusions, or absence of normal features (negative symptoms), including blunted affect and emotions, lack of motivation, and poverty of speech. Positive symptoms are considered *positive* in the sense that they were not present to be in with, but emerged with the onset of the illness. As opposed to positive psychotic symptoms, negative symptoms reflect the disappearance of certain abilities, mostly emotions and drives that are typically present. They include absence of normal emotional expressions in faces and gestures, reduction in normal thoughts and speech, and reduction in desire for social and familial connections. Generally, schizophrenia is also associated with social and occupational dysfunction, and defect in interpreting the emotions and intentions of others [24].

3.2. Diagnosis of Schizophrenia

Schizophrenia is a mental illness without a diagnostic test. There is no blood, urine test or biopsy that makes a definitive diagnosis of schizophrenia. Furthermore, due to the heterogenic characteristic of schizophrenia, it makes more difficult to distinguish schizophrenia from other mental illness that shares common clinical outcomes. The current psychiatric classification system of schizophrenia is based on their clinical symptomatology. One of the systems which are widely used is The Diagnostic and Statistical Manual of Mental Disorders fourth revised edition (DSM-IV) [25], which defines the criteria to categorize patients with schizophrenia. The following Table 3.1 introduces the criteria to diagnosis schizophrenia:

Table 3.1 Diagnostic criteria for schizophrenia and associated disorders based on Diagnostic and statistical manual of mental disorders fourth edition (DSM-IV)

A. **Characteristic symptoms**: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated) : (1) delusions (2) hallucinations (3) disorganized speech (4) (e.g., frequent derailment or incoherence) (5) grossly disorganized or catatonic behavior (6) negative symptoms, i.e., affective flattening, alogia, or avolition

Note : Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. **Social/occupational dysfunction**: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. **Duration**: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal (symptomatic of the onset) or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. **Schizoaffective and Mood Disorder exclusion**: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive Episode, Manic Episode, or Mixed Episode have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. **Substance/general medical condition exclusion**: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. **Relationship to a Pervasive Developmental Disorder**: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

3.3. Facial Affect Deficit in Schizophrenia

Deficits in schizophrenia patients, characterized by lower performance in face recognition or facial affect recognition, have been reported both in behavioral studies [26] and in neuroimaging studies employing various imaging modalities. In this sub-section, summary of the recent findings in abnormal facial affect recognition using various imaging studies is introduced.

3.3.1. ERP Studies

Studies using electroencephalogram (EEG) has identified four major event-related potential (ERP): P100, N170, N250 and P300; which is related to facial information processing. The P100 ERP is believed to indicate the successful recognition and categorization of stimuli as well as luminance and contrast. The deficits in this component in schizophrenia patients have been observed using several nonface stimuli [27-31]. The abnormality of P100 components in schizophrenia, however, seems to be controversial. Several researches have reported no distinct difference between normal subject during facial affect processing [7, 32, 33], whereas concurrent researches have shown an abnormal P100 response [34, 35].

The N170 component is a response showing a greater peak to the human face than to other objects [32, 36] and known as to indicate the earliest stage of facial

structure encoding [37, 38]. N170 in schizophrenia patients has been reported to show reduced N170 amplitude during face and facial affect processing [7, 32, 33]. Moreover, recent studies have found that N170 is associated not only with facial structure encoding [32], but also while processing facial emotional expressions [7, 35, 36, 39, 40].

The N250 component is known as to process the emotional content of a face, especially ones which are familiar [41-43]. Findings regarding the N250 component are not fully understood among the literatures in schizophrenia patients. Reduced N250 amplitude at frontal electrode sites were found in schizophrenia patients compared to normal controls during facial emotional processing task [44, 45]. On the contrary, other researchers have suggested that these reduced outcomes are secondary flow-on effects of broader deficits in the structural encoding of faces [7, 33].

The P300 ERP is hypothesized to reflect the stage of affect encoding stage of the facial emotional component [46, 47]. A general deficit in P300 ERP was shown by Turetsky et al. [7], which shown significant reduced amplitude across all emotion valences in schizophrenia patients than in controls. Among the emotions, the negative emotional targets were found to be significantly smaller than those generated by positive emotional targets in patients with schizophrenia [48].

3.3.2. fMRI Studies

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 [18]. The perception of fearful faces is associated with the functional activation of corticolimbic structures, which are altered in individuals with schizophrenia [33, 49-51]. However, the areas involved in impaired facial affect processing by schizophrenia patients remain controversial.

3.3.3. Correlation with Clinical Symptoms

Studies on facial emotion processing, which is an aspect of social cognition, have demonstrated that schizophrenia patients have defects in interpreting the emotions and intentions of others [24, 52]. Although some studies have shown that negative symptoms are more closely associated with dysfunction in facial emotion discrimination [53-55], the different neural correlates of facial emotional processing with respect to negative and positive symptoms have not yet been studied.

Previous fMRI studies have also 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) [56-58]. They have reported significant negative correlations between negative symptom scores and activations in the left superior temporal gyrus and prefrontal area during facial emotion processing [59, 60]. 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 [61, 62].

Chapter 4: Dysfunctional Gamma Band Activity and Phase-Synchrony in Schizophrenia Patients

4.1. Research Background

Synchronous oscillatory neural activity is a possible candidate mechanism for the coordination of neural activity between and within functionally specialized brain regions [63, 64]. It is known that the coordination of distributed neural activity is dysfunctional in schizophrenics [65-67].

There are several studies showing face processing disturbance in schizophrenia patients and possible neural structures underlying this deficit [32, 36, 68]. They revealed that schizophrenia patients, compared with normal controls, have smaller fusiform gyrus volume and lower amplitude of N170 components with wider neuropsychological impairments. Recent electrophysiological studies have demonstrated that functional communication between distinct brain regions during neural activity relies on the oscillatory synchronization of gamma and beta frequency bands [69]. Furthermore, other recent findings have suggested that the gamma-band activity (GBA) in the human EEG is related to higher cognitive processes [32, 64, 70-72].

Several studies have shown that GBA is related to face and facial emotional processing in normal individuals [72-77]. Anaki et al. [73] reported that induced GBA at around 150–250 ms at midline centroparietal area in healthy persons was higher while viewing an upright or familiar face than an inverted or unfamiliar one. They insisted that the effect of face inversion was found in lower gamma frequency (25–50 Hz), whereas familiarity affected amplitudes in higher gamma frequency band (50–70 Hz). Zion-Golumbic and Bentin [75] revealed that increased GBA (25–45 Hz) was elicited in undergraduate students at midline parieto-occipital area at around 200–300 ms by full faces, but not by scrambled faces. However, they did not find significant findings in high GBA (55–70 Hz). Another study also revealed increased GBA in the middle posterior electrode cluster (Pz, POz, and Oz) at around 300 ms during face processing [76]. Rodriguez et al. [74] who applied ambiguous visual stimuli (perceived either as faces or as meaningless shapes) reported that GBA was prominent at −230 ms and −800 ms and only face perception induced long distance pattern of gamma synchronization. The enhanced GBA is also observed at occipital electrode sites in healthy subjects viewing emotional faces in rotating figures [78]. Meanwhile, Matsumoto et al. [77] revealed that GBA at the Cz and Pz electrodes for negative emotional faces at around 400–450 ms was higher in nonalexithymic subjects than in alexithymic subjects.

Face and facial emotional processing are important research areas because

they are closely involved with social cognition, deficits of which may underlie the decreased functional outcomes of schizophrenia patients. To the best of the author's knowledge, there is currently only one published study on GBA for face-related processing in schizophrenia [17]; the study reported the deficits in Gestalt perception in schizophrenia patients were associated with reduced phase synchrony in the band (20–30 Hz), whereas induced spectral power in the band (40–70 Hz) was mainly intact. But they found schizophrenia patients are impaired in the long-range synchronization of neural responses, which may reflect a core deficit in the coordination of neural activity. GBA in schizophrenia patients processing real human faces is thus worthy of evaluation. Furthermore, face structural processing and emotional processing should be assessed separately since they are likely to involve different brain resources.

In this chapter, the author hypothesized that the schizophrenia patients will show the decreased GBA and gamma synchronization during the face structural processing compared to the normal controls. As a first stage of exploration about GBA dysfunction of face processing in schizophrenia patients, this study has examined the face structural processing while viewing emotionally neutral face.

4.2. Methods

4.2.1. Participants

Twenty-five patients with schizophrenia and 25 normal controls were recruited for this study. The schizophrenia patients were recruited from the Psychiatry Department of Inje University Ilsan Paik Hospital, and they were diagnosed based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Psychiatric Disorders [79]. Their psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) [80]. 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 of stable state and taking atypical antipsychotic medication (olanzapine, n = 12 and risperidone, n= 13).

Normal controls were recruited from the local community through local newspapers and posters. An initial screening interview excluded subjects if they had any identifiable neurological disorder or head injury, any personal history of psychiatric disease, and a family history of psychiatric illness. After the initial screening, potential normal controls were interviewed using the Structured Clinical Interview for DSM-IV Axis II Psychiatric Disorders [25], and were excluded if they had any of these disorders. All subjects had normal or corrected-normal vision and

were right-handed. Handedness was 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 are given in Table 4.1, which indicates that there were no significant group differences in gender distribution, age, and education.

Table 4.1 Demographic data and symptom ratings for schizophrenia patients and normal controls. The antipsychotics dosage was converted to chlorpromazine equivalents. Data are mean ± SD values.

	Schizophrenia patients (n = 25)	Normal Controls (n = 25)	p
Age (years)	34.6 ± 12.6	38.9 ± 12.4	0.225
Males : Females	12:13	12:13	1.000
Education duration (years)	12.5 ± 2.5	12.9 ± 3.0	0.605
Illness duration (years)	6.1 ± 5.6		
Number of hospitalizations	1.8 ± 1.5		
PANSS			
Total score	82.4 ± 24.8		
Negative score	18.6 ± 7.2		
Positive score	20.6 ± 7.6		
Antipsychotics dosage (mg)	398 ± 103		

4.2.2. Procedures

Participants were presented with two types of human face: emotional (happy and fearful) and neutral. The presented images were selected from the "Chaelee face," which is a standardized set of pictures of a Korean face [81]. The pictures of faces comprised the whole face structure including the hair. The luminance and contrast were made the same in all of the images. Stimuli were presented on a 17-inch (approx. 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 time of sequence of an event was 2000–2200 ms, and this was changed randomly in each trial so as to avoid habituation. The entire recording session for each subject lasted approximately 15 min.

All participants were requested to push a button using their right thumb when they saw an emotional face; recognition of emotional faces requires greater cognitive processing than that of neutral faces in this task. Since the aim of this

chapter was to examine face structural processing, the author only analyzed data obtained from the subjects while viewing neutral faces.

4.2.3. EEG Recording

Stimulus presentation and data synchronization with the EEG were accomplished with E-Prime (Psychology Software Tools, Pittsburgh, USA). The EEG was synchronized to the onset of face stimulus presentation. EEG activity was recorded and amplified 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 band-pass 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. EEG data were re-referenced offline to an average reference. Gross movement artifacts were removed by visual inspection. Eye blinks were removed from the data using established mathematical procedures [82]. Trials were rejected if they included significant physiological artifacts (amplitude exceeding ±70 μV) at any site over all 64 electrode

sites. After artifact removal, baseline correction was conducted by subtracting the mean of 300 ms of prestimulus data from the poststimulus data for each trial. Data were then epoched to 300 ms prestimulus and 1000 ms poststimulus.

All participants showed a sufficient number of accepted event-related potential (ERP) epochs for neutral faces, and the averaged acceptance rate did not differ significantly between the groups [schizophrenia patients 96.1 % (accepted epoch n = 94.1) vs. normal control 92.3% (accepted epoch n = 89.0), p = 0.06].

4.3.4. Time-Frequency Analysis

Event-related spectral perturbation (ERSP) analysis which measures the dynamic change of spectral power over time has been increasingly used in EEG studies to observe narrow-band event-related desynchronization and synchronization [83-85]. In this chapter, ERSP was calculated using functions implemented in a well-known MATLAB toolbox EEGLAB (http://sccn.ucsd.edu/eeglab/) [83]. The ERSP maps were calculated using the short-time Fourier Transform method. The spectral power was computed for every 5 ms by a Hanning window of 250 ms and the results were averaged across all trials. After the calculation of the average spectral power for each subject, the average baseline (−300～0 ms) power was subtracted from each spectral estimate, which resulted in the baseline-normalized ERSP maps. The time–

frequency map of each midline channel (FCz, Cz, CPz, Pz, and POz) was obtained by averaging the ERSP values across all epochs and subjects.

The choice of midline electrodes was based on previous study findings. Most of the previous studies using the cortical EEG method have found that the GBA was mainly higher at the midline cortical area for face-related processing [72, 73, 75, 77]. One intracranial EEG study of epileptic patients found a higher GBA in the face-specific fusiform gyrus [86]. However, other cortical EEG studies have failed to find any significant lateral GBA. Furthermore, the author did not analyze the FPz, Fz, and Oz electrodes because these electrodes can be easily contaminated by muscle artifacts [87]. Here, the author focused on and discuss the recordings from five midline channels (FCz, Cz, CPz, Pz, and POz).

4.2.5. Phase Synchrony Analysis

To determine the degree of synchronization between the activations of two components, the author computed event-related phase coherence (ERPCOH) between two channels. The event-related phase cross-coherence is defined by :

$$ERPCOH^{a,b}(f,t) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k^a(f,t)F_k^b(f,t)^*}{\left|F_k^a(f,t)F_k^b(f,t)^*\right|}$$

where *f* and *t* represent frequency and time window centered at time *t*, respectively, *a* and *b* represent two selected channels, and *n* is the number of epochs. $F_k^a(f,t)$ is the spectral estimate of channel *a* for a *k*th trial and was calculated by short-time Fourier transform with the same parameters used for the ERSP calculation. $F_k^b(f,t)^*$ is the complex conjugate of $F_k^b(f,t)$ and $\|\cdot\|$ operator represents the complex norm. ERPCOH has a value between 0 and 1, where 0 indicates complete absence of phase synchronization between two signals *a* and *b* at a given frequency *f* in the time window centered on *t*; whereas 1 indicates perfect synchronization. For the sake of simplicity, the author chose 19 electrodes (Fp1, Fp2, Fz, F3, F7, F4, F8, Cz, C3, T7, C4, T8, Pz, P3, P7, P4, P8, O1, and O2) based on the international 10–20 electrodes system. For the visualization of meaningful synchrony between the channels, lines were connected between two electrodes only when the ERPCOH between the electrodes showed statistically significant increment or decrement ($p < 0.0003$, Bonferroni-corrected two-tailed t-tests) compared to the baseline activity [17].

4.2.6. Statistical Analysis

A map of differences in GBA between schizophrenia patients and normal controls was produced. By visual inspection, the discernible area of GBA differences was examined statistically. The data were analyzed by repeated-measures ANOVA with group (patients vs. controls) as the between-subjects factor, and time [three time

windows: 0–100 ms (30–33 Hz), 250– 300 ms (34–38 Hz), and 700–800 ms (40–45 Hz)], and location (five electrodes: FCz, Cz, CPz, Pz, and POz) as the within-subjects factors. The Greenhouse–Geisser epsilon value was obtained in all cases in which the repeated-measures data failed the sphericity test (Greenhouse and Geisser, 1959). When a significant effect was found, the Bonferroni-corrected t-test for multiple comparisons was applied. The number of t-test was five, which the author considered to calculate the resulting threshold. The threshold of significant synchrony lines ($p < 0.0003$, two-tailed t-tests) was chosen by Bonferroni correction while considering that there were a total of 171 synchrony lines. The Spearman correlation coefficient was calculated between GBA and symptomatic and demographic variables.

4.3. Results

4.3.1. Behavioral Data

Hit rate was defined as the percentage of correct responses. There were no significant differences in hit rate for happy (89.4 ± 15.4 vs. 91.2 ± 18.8, $t = -0.338$, $p = 0.737$) and fearful faces (88.9 ± 21.5 vs. 81.9 ± 32.6, $t = 0.811$, $p = 0.422$) between schizophrenia patients and normal controls. However, the false alarm rate for neutral faces was significantly higher in schizophrenia patients than in normal controls (23.2 ± 21.1 vs. 6.7 ± 9.9, $t = 3.175$, $p = 0.004$).

4.3.2. Spectral Power of the Gamma Band

The difference map, in which the ERSP map of the schizophrenia patients is subtracted from that of the normal controls, revealed three time windows of GBA: 0–100 ms (30–33 Hz), 250–300 ms (34–38 Hz), and 700–800 ms (40– 45 Hz). These time windows became the focus of this study. Figure 4.1 depicts the GBA values of the three time windows at five midline electrodes, and Figure 4.2 shows the ERSP map at three prominent electrodes (FCz, Cz, and CPz).

Repeated-measures ANOVA revealed a significant main effect for group [$F(1, 48) = 7.95$, $p = 0.007$], location [$F(4, 45) = 13.661$, $p = 0.000$], and time [$F(2,$

47) = 3.692, p = 0.029]. Furthermore, there was a significant interaction between time and location [$F(8, 41) = 4.799$, $p = 0.000$; Figure 4.1].

In the 0-to-100 ms time window the author found that the GBA was significantly higher in the normal controls than in the schizophrenia patients, especially at the POz region ($t = -2.279$, uncorrected $p = 0.027$; Figure 4.1). However, this effect disappeared after Bonferroni correction. In the 250-to-300 ms time window the author found that the GBA was significantly higher in the normal controls than in the schizophrenia patients, especially at the CPz region ($t = -2.047$, uncorrected $p = 0.046$, Figure 4.1). This effect also disappeared after Bonferroni correction. In the 700-to-800 ms time window, a Bonferroni corrected t-test revealed that GBA was significantly higher in the normal controls than in the schizophrenia patients, especially at the FCz region ($t = -3.215$, corrected $p = 0.01$; Figure 4.2).

4.3.3. Phase Synchrony of the Gamma Band

The synchrony lines have displayed in Figure 4.3. The normal controls showed increased synchrony lines among the frontal, temporal, and parieto-occipital electrodes from 100 ms, peaking at the 200-to-300 ms time window. Compared with normal controls, schizophrenia patients exhibited weak patterns of significant synchrony lines. All subjects did not produce any decreased synchrony lines. Group comparisons of phase coherence between two groups were analyzed using chi-square

statistics for each time bin [88]. The result showed that the phase coherence distribution is significantly different between the groups across time bins ($\chi^2_{(4)} = 18.8$; $p = 0.0008$).

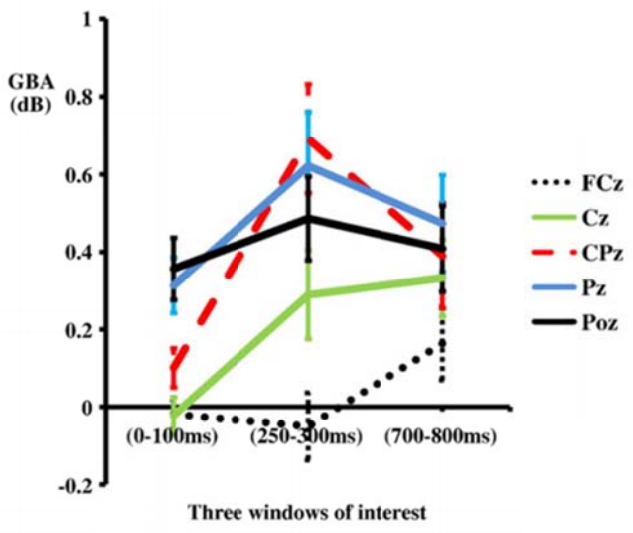

Figure 4.1 Comparison of gamma-band activity (GBA) between schizophrenia patients and normal controls. Patterns of GBA in three windows of interest at five electrodes sites from all subjects (schizophrenia patients and normal controls). The GBA was highest at the occipital electrode (POz) in the period 0–100 ms, and at frontal electrode (FCz) in the period 700–800 ms. The standard errors were presented.

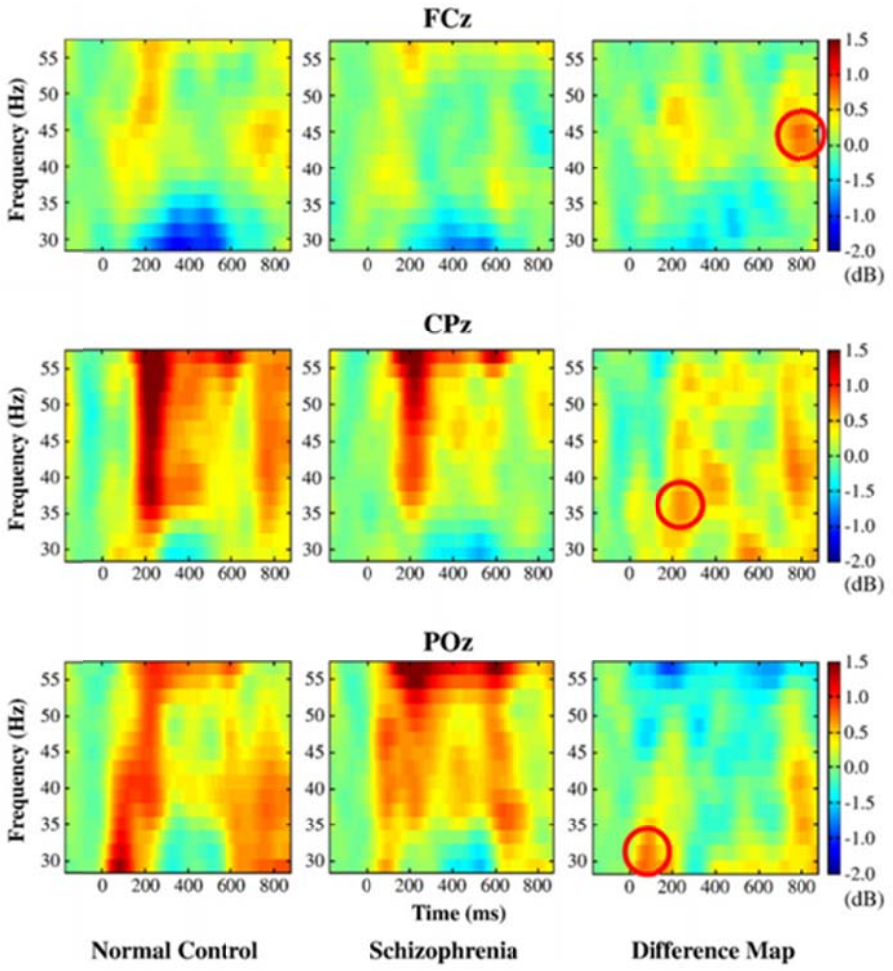

Figure 4.2 Event-related spectral perturbation (ERSP) from electrodes FCz, CPz, and POz. The difference map was calculated by subtracting the schizophrenia ERSP map from that of the normal controls. Red circles indicate the three windows of interest for which there are significant differences between normal controls and schizophrenia patients. After Bonferroni-corrected t-tests, only the FCz region (corrected $p = 0.01$) remained as a significantly activating region in the normal controls relative to the schizophrenia patients.

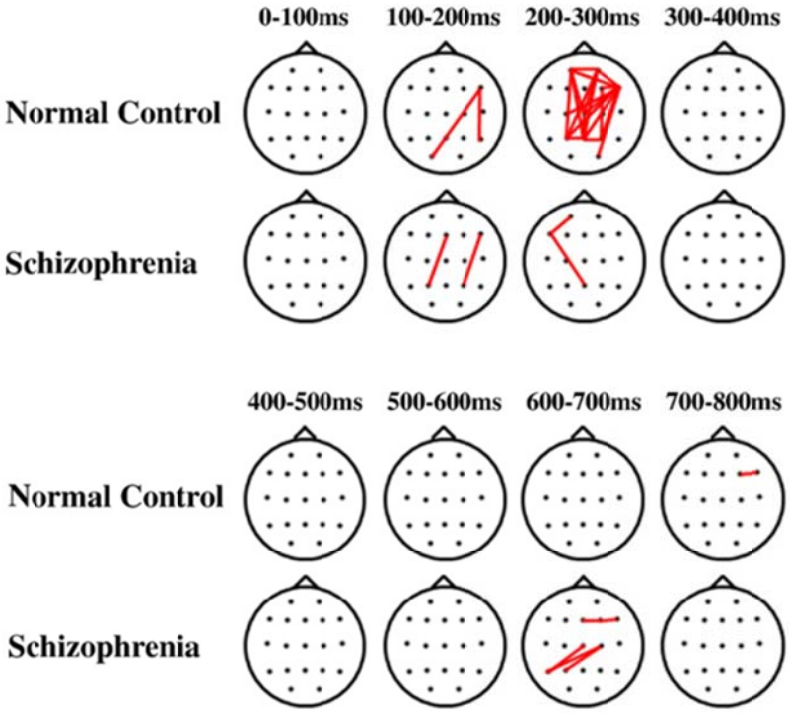

Figure 4.3 Topography of phase synchrony for neutral face processing. Synchrony between electrodes is indicated by lines, which are drawn only where there is a synchrony value beyond a two-tail probability of $p < 0.0003$. Gamma-band phase synchronization was significantly increased (red) at 200–300 ms, and was lower in schizophrenia patients than in normal controls.

4.3.4. Induced GBA or Evoked GBA

The question of whether the observed GBA is induced or evoked was addressed by calculating the mean inter-trial PLVs for each subject during this period [75]. The PLV is bounded between 0 and 1. A PLV of 1 corresponds to perfect phase-locking. The results confirmed that low level of PLVs were present during the time window of interest in all participants (at POz between 0–100 ms, mean = 0.11, SD = 0.03; at CPz between 250–300 ms, mean = 0.19, SD = 0.08; at FCz between 700–800 ms, mean = 0.10, SD = 0.03). These GBAs can therefore be regarded as being induced.

4.4. Discussion

The goal of the chapter was to clarify the characteristics of face structural processing in schizophrenia patients by analyzing the spectral power and phase synchronization of the gamma band. The author found three windows of interest among the midline electrodes from the data set, and found that the GBA was significantly lower in schizophrenia patients than in normal controls.

Even though the author found interesting GBA dysfunction at around 0–100 ms at POz and at around 200–300 ms at CPz, these GBA differences disappeared after Bonferroni correction. So, the author concentrated on the third time window (700–800 ms, 40–45 Hz) which has still shown the significant difference after considering multiple comparisons.

The author also found increased GBA at around 700–800 ms at the FCz region. Rodriguez et al. [74] reported that two gamma peaks appear at around 800 ms and 230 ms after seeing a "Mooney" face. However, no previous study has demonstrated frontal GBA during facial processing. The predominant frontal GBA at this late period may be associated with postperceptual top-down processing of faces. The relatively decreased frontal GBA observed in schizophrenia patients might reflect decreased frontal-lobe function during face processing (Figure 4.1). There existed the scarcity of theoretical knowledge about the specific cognitive mechanisms normally

involved in face processing during this interval. Thus, the author's finds need to be further evaluated in future study.

Detailed spatiotemporal information is provided by the regional distribution of GBA and phase synchrony over the scalp (Figure 4.3). The pattern of gamma activity first occurred at around 100–200 ms, peaked at around 200–300 ms, and reappeared at around 600–800 ms. These findings are similar to those of Uhlhaas et al. [17] demonstrating that gamma activity peaked at around 300–400 ms when normal controls processed Mooney faces. There is some debate as to whether the gamma synchrony computed from scalp EEGs is the result of spurious synchronization resulting from volume conduction [89]. However, the author's results show that multiple significant synchronies were established between distant electrodes. It is thus conceivable that distant synchronization could result from a powerful deep source that diffuses widely over the scalp. The average reference can produce artificial GBA. However, in the present data, referencing the present data linked to the mastoid did not affect the statistical significance of topographic effects regarding ERPs and GBA. The author can therefore conclude that the GBA he measured was not significantly produced from reference-related artifacts.

The author has found that the GBAs of frontal, central and parietal areas were negatively correlated with the score for negative symptoms on the PANSS, and the number of hospitalization in schizophrenia patients. The current results suggest

that the GBA during face structural processing is reduced in schizophrenia patients with dominant negative symptoms as well as the higher number of hospitalization. The significant correlations found only at 700–800 ms would suggest dysfunctional top-down processing in schizophrenia patients, and a functional relationship between GBA and schizophrenia patients.

The analysis of this chapter has a limitation: all of the schizophrenia patients were taking antipsychotic medications and the author are unable to exclude the drug effects on the author's findings. However, the current data still revealed that there is a deficit in the GBA and synchrony during the processing of neutral human faces in schizophrenia patients. In addition, the results from neutral face can be influenced, at least in part, by emotional content of the paradigm and/or inhibition of motor response to low probability neutral stimuli. However, as you can see in Figure 4.2, the baseline activities of gamma were well stabilized. It could be evidenced that the current data contain neutral face processing without confounding effects of emotional content of the paradigm and/or inhibition of motor response to low probability neutral stimuli. Even though the author cannot know what kind of emotion the schizophrenia patients perceived when they did the false alarm for neural faces, no significant association between GBA and false alarm rate indicated that inhibition (no-go) during processing of neutral stimuli had minimal effects on GBA in this study.

Chapter 5: Reduced Source Activity of Event-Related Potentials in Schizophrenia Patients

5.1. Research Background

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 accumulated ERP data indicating that, in general, four ERP components are related to facial affect processing: P100, N170, N250, and P300 [7, 45, 90-92].

Although deficits in the P100 component associated with facial affect processing have not been typically reported in schizophrenia patients [7, 32, 33], some studies have demonstrated an abnormal P100 response [34, 35]. Recent studies have also noted reduced N170 amplitude in schizophrenia patients during face and facial affect processing [7, 32, 33, 91]. The N170 component is associated with not only facial structure encoding [32], but also facial emotional expressions [7, 35, 40, 91]. 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 [93, 94], the posterior inferior temporal gyrus, and the lingual gyrus [95]. Pegna et al. [96] 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 [44, 45]. However, other researchers have found normal N250 responses in schizophrenia patients [7, 33]. The P300 component is hypothesized to reflect the affect-encoding stage in the processing of emotions [47]. Schizophrenia patients are reported to exhibit smaller P300 responses or emotional stimuli than healthy controls [7].

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 [22]. 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 [97]. Standardized LORETA (sLORETA) has recently been introduced, whereby localization inference is based on images of standardized current density [23, 98]. Esslen et al. [93] 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 [99, 100]. And several factors, including genetic, hormonal and psychosocial factors, were involved in gender difference in schizophrenia patients [101-103]. An interesting gender effect was recently found in response to facial affect recognition tasks. Kempton et al. [104] 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. [105] showed gender differences in the brain response to affective scenes both with and without humans in them. In the previous ERP study of Lee et al. [91], they 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 chapter, the author 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, the author hypothesized that there would a gender effect in facial affect processing.

5.2. Methods

5.2.1. Subjects

Twenty-three patients with schizophrenia (age: 32.2 ± 10.1 years, 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 [79]. Their psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS; [80]. 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 [25], 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 5.1, which indicated that there were no significant group differences in gender distribution, age, or education.

Table 5.1 Demographic data and symptom ratings for 23 schizophrenia patients and 24 healthy controls. Data are mean ± SD values.

	Schizophrenia patients (n = 23)	Normal controls (n = 24)	p
Age (years)	32.2 ± 10.1	38.0 ± 11.9	0.077
Males:females	12:11	12:12	1.000
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

5.2.2. 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 [81]. 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, the author 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 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 carryover 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.

5.2.3. 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 band-pass 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 re-referenced offline to an average reference. Gross movement artifacts were removed by visual inspection. Eye blinks were removed from the data using established mathematical procedures [82]. 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 band-pass filtered at 1–30 Hz [45, 106] with a steepness of 24 dB/octave and then epoched to 300 ms prestimulus and 1000 ms poststimulus.

5.2.4. 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 (Figure 5.1). 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 previous work of Lee et al. [91] in which the maximum electrical potentials were detected in visual inspection of the topographic map (Figure 5.2(a)). However, stricter selection criteria were applied for ERP data in the present study compared to previous study [91]. 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, the author 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.

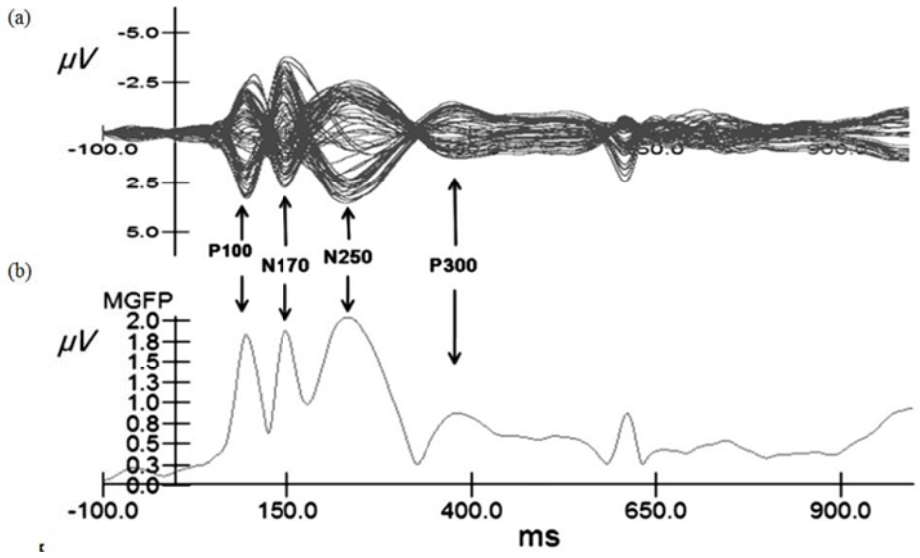

Figure 5.1 (a) Butterfly map and (b) mean global field potential of whole event-related potential (ERP) components from schizophrenia patients and healthy controls. Four identifiable peaks (P100, N170, N250, and P300) were detected.

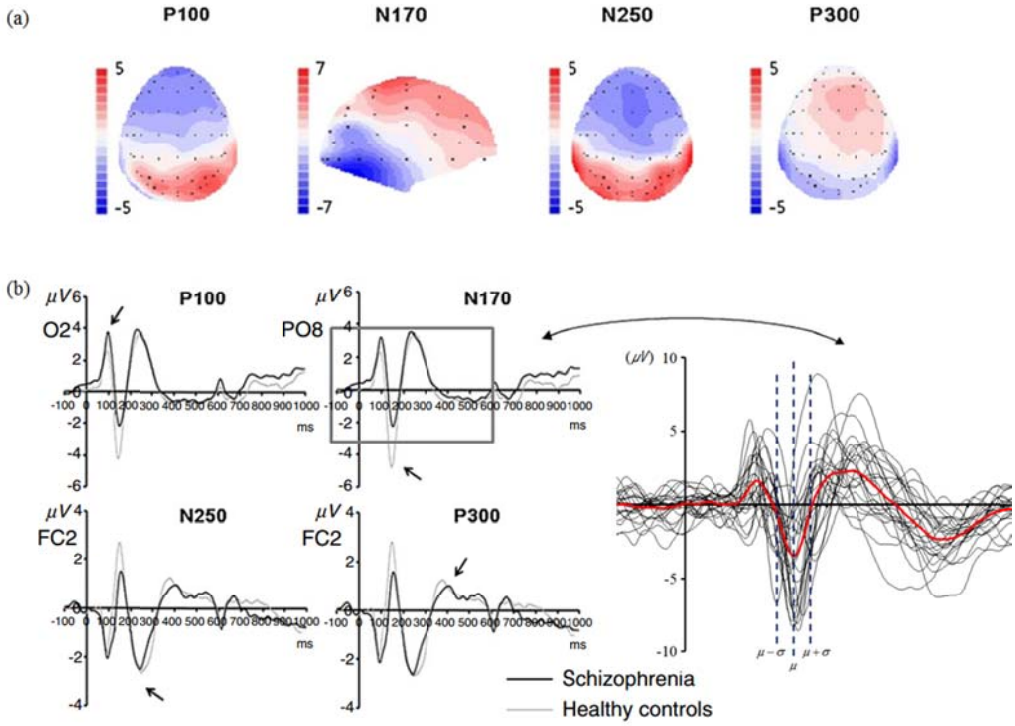

Figure 5.2 (a) Two-dimensional scalp topographic maps. Each map shows maximal activating areas on the cortical area. (b) Schematic example of 4 ERP components for all subjects and defining the analysis interval for the N170 ERP component. The red line is the average waveform. The interval was decided from one standard deviation prior (μ−σ) to one standard deviation after (μ+σ) the mean latency (μ) of the group.

5.2.5. Source Localization of the ERP Activity using sLORETA

The source activations of ERP components were compared using sLORETA inverse solution method [22, 98]. 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 [22], 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 [98]. 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 (Figure 5.2(b)). 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, the author 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 [98, 107]. The source space is divided into 6239 voxels in 5 mm resolution, restricted to the cortical gray matter and hippocampus.

5.2.6. 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 [108] 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 the author 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.

5.3. Results

5.3.1. 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).

5.3.2. 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 [$F(2, 86) = 16.524$, $p < 0.001$]. 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 [$F(2, 86) = 18.416$, $p < 0.001$]. 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 5.2 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, therefore, the author did not explore or discuss them further.

Table 5.2 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

5.3.3. 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 5.3).

Table 5.3 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
	Insular (right)	40	15	5
	Inferior frontal gyrus (right)	45	20	5
Male NC vs female HC	No significant difference			

5.3.3.1. Between Group Comparisons

The level of activations at the middle frontal gyrus and inferior frontal gyrus area was lower in schizophrenia patients than in healthy controls (Figure 5.3; $p < 0.05$, 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 (Figure 5.4; $p < 0.05$, two-tailed test). A corresponding comparison for the female subjects of two groups did not yield any significant differences.

5.3.3.2. 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 gyrus areas were significantly lower in male schizophrenia patients than in female schizophrenia patients (Figure 5.5; $p < 0.05$, two-tailed test).

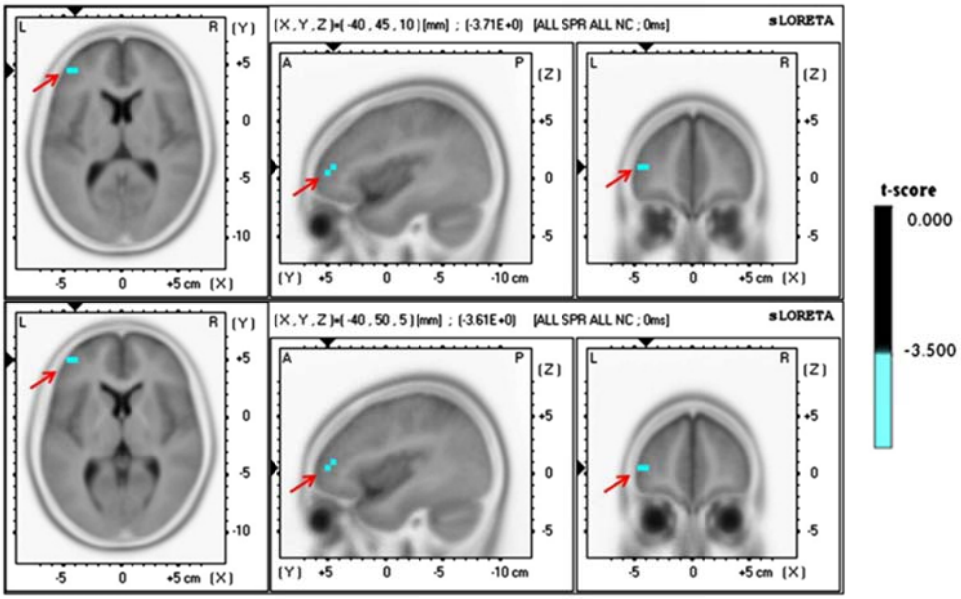

Figure 5.3 Comparison of ERP source activity for N170 in response to fearful faces between schizophrenia patients and healthy control subjects. The areas marked blue show significantly lower activation in the middle frontal gyrus and the inferior frontal gyrus, respectively ($p < 0.05$, one-tailed).

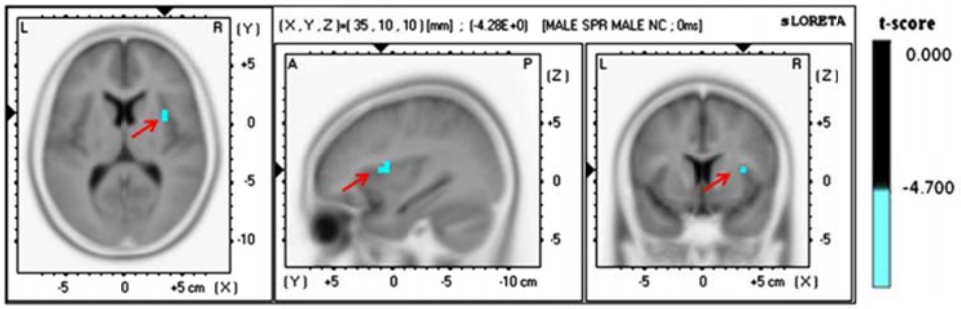

Figure 5.4 Comparison of ERP source activity for N170 in response to fearful faces between male schizophrenia patients and male healthy control subjects. The areas marked blue shows significantly lower activation in the insula ($p < 0.05$, two-tailed).

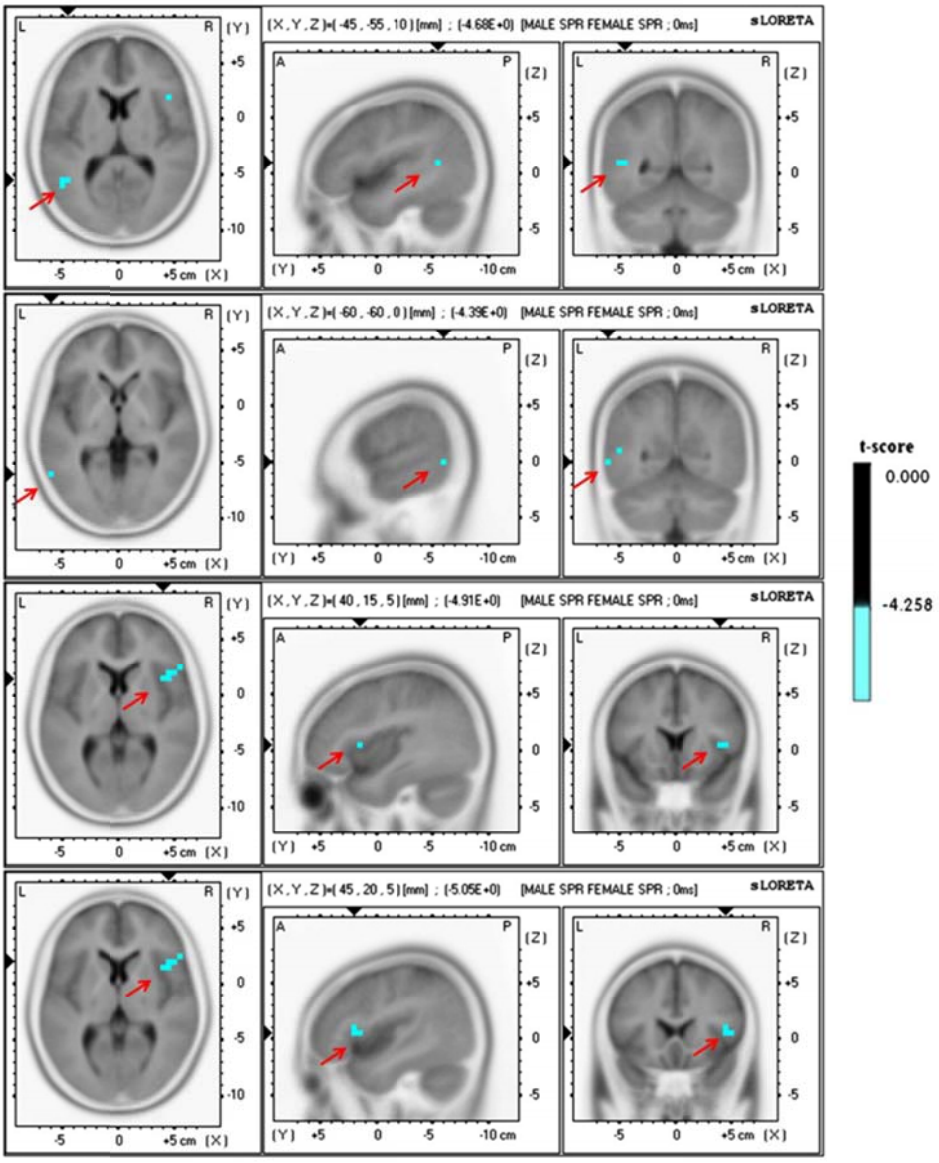

Figure 5.5 Comparison of ERP source activity for N170 in response to fearful faces between male and female schizophrenia patients. The areas showing a maximum difference were the superior temporal gyrus, the middle temporal gyrus, the insula, and the inferior frontal gyrus, respectively ($p < 0.05$, two-tailed).

5.3.4. 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 [109]. 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 5.3) 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

5.3.5. 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.

5.4. Discussion

In the present study, the author 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. Using the same data, Lee et al. [91] reported interesting ERP findings that differentiate schizophrenia patients from healthy controls in response to affective facial stimuli. Even though this temporal information of ERP amplitudes is relevant for defining the disturbed cognitive processing, here the author 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 the current 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 [7,

32, 33]. 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 [110]. 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 the 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 [57, 111]. Furthermore, patients with higher negative symptoms scores were characterized by deficits in recognizing fear emotion [112]. It was recently found that the amplitude of the N170 response to fearful faces is decreased in schizophrenia patients [112, 113]. 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.

The author 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 (Figure 5.3). 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 [114]. In LORETA source localization study, Esslen et al. [93] 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. [115] found prominent activation in the left inferior frontal gyrus during unconscious processing of emotional faces. Also, Blair and Curran [116] found that the right orbital cortex was activated when subjects were viewing angry faces, while Nakamura et al. [117] 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 [118] and mirror neuron function [119]. 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.

The author also found reduced source activities of the insula in male schizophrenia patients when compared with male healthy controls or female schizophrenia patients (Figure 5.4 and 5.5). 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 [120], 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 [121]. Various studies using structural and functional imaging, and cytoarchitectural methods have found insular abnormalities in schizophrenia [122-126]. 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 [122, 123]. It has recently been suggested that the insula plays an important role in integrating cognitive and affective processing [127]. This 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 (Figure 5.5). 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 (Figure 5.4).

Many functional imaging papers reported activation in temporal areas during affective processing [93, 128, 129]. A review paper by Haxby et al. [128] revealed that superior temporal sulcus was involved in perceiving emotional face expressions. Pizzagalli et al. [129], using LORETA, found that bilateral occipito-temporal regions, including lingual and fusiform gyri and extending to inferior temporal gyri, were activated males during facial affect recognition tasks [104], and viewing painful stimuli [105]. Scholten et al. [130] 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 [131] and disruption of hypothalamic sexual dimorphism [101] 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 the 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, the author did not implement non-facial control stimuli of a similar perceptual complexity. Given that there are already many ERP-related reports comparing facial and non-facial stimuli, comparing ERP responses of facial with non-facial stimuli seems to be redundant and beyond the scope of this study. The author

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, the current results are suggesting that ERP source imaging can be a useful method in studying altered affective facial processing in schizophrenia patients.

In summary, the author 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, the 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.

Chapter 6: The Relationship between Symptom Severity Scores and Cortical Activation

6.1. Research Background

Recently, impairment of social cognitive function has been repeatedly reported in schizophrenia patients. Studies on facial emotion processing, which is an aspect of social cognition, have demonstrated that schizophrenia patients have defects in interpreting the emotions and intentions of others [24, 52]. Although some studies have shown that negative symptoms are more closely associated with dysfunction in facial emotion discrimination [53-55], the different neural correlates of facial emotional processing with respect to negative and positive symptoms have not yet been studied.

Deficits in schizophrenia patients characterized by lower performance in face recognition or facial affect recognition have been reported both in behavioral studies [26] and in neuroimaging studies employing various imaging modalities [33, 61, 132, 133]. 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.

These studies have demonstrated significant differences in the activation patterns between patients and controls, which included cortical regions in the medial prefrontal cortex, occipital gyrus, and temporal gyrus, as well as subcortical structures such as the amygdala, hippocampus, and fusiform gyrus [33, 61, 132, 133]. 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) [56-58]. They have also reported significant negative correlations between negative symptom scores and activations in the left superior temporal gyrus and prefrontal area during facial emotion processing [59, 60]. 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 [61, 62].

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. Four major event-related potential (ERP) components have been identified as associated with face structural and affect recognition processing: P100, N170, N250, and P300. All these components have been reported as having abnormal amplitudes or latencies in schizophrenia patients compared to normal controls [7, 34, 35, 40, 44, 45, 91].

In previous studies [91, 134], the author 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 the author's 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 the author's 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. The author 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.

6.2. Methods

6.2.1. 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 [80]. All participants were stable, right-handed, with normal or corrected-to-normal vision. Participants with a history of central nervous system disease, alcohol or drug abuse, electroconvulsive therapy, mental retardation, head injury with loss of consciousness, or any other symptoms that might affect the experiment were excluded from the study. All subjects were taking atypical antipsychotics (olanzapine, $n = 11$; risperidone, $n = 12$). The demographic data of the participants are presented in Table 6.1. 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.

Table 6.1 Demographic data and symptom rating of 23 schizophrenia patients. Peak amplitudes are the mean peak amplitude and its standard deviation for each emotion. The latencies indicate the time range used for sLORETA source imaging, which was the range of the mean latency ± 1 SD. Data given are mean ± standard deviation values. (PANSS: Positive and Negative Syndrome Scale, sLORETA: standardized low-resolution brain electromagnetic tomography)

	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		
PANSS total score	81.8 ± 25.8		
Positive score	20.2 ± 7.8		
Negative score	18.7 ± 7.4		
Peak Amplitude	Neutral	Fear	Happy
P100 (μV)	2.88 ± 1.42	3.36 ± 1.93	3.84 ± 2.21
N170 (μV)	-3.52 ± 2.60	-3.47 ± 2.66	-3.23 ± 3.08
N250 (μV)	-1.80 ± 0.98	-2.59 ± 1.30	-2.63 ± 1.11
P300 (μV)	1.51 ± 0.95	2.03 ± 1.28	1.16 ± 1.04
Latencies for sLORETA	Neutral	Fear	Happy
P100 (*ms*)	91–116	90–116	92–119
N170 (*ms*)	142–183	143–181	146–183
N250 (*ms*)	215–259	216–264	216–258
P300 (*ms*)	334–413	332–425	336–425

6.2.2. 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°. The provided facial stimuli were categorized into two types: emotional (either happy or fearful) or neutral faces. The participants were asked to concentrate on facial stimuli and discriminate the facial emotion which is presented in the center of the monitor. They were asked to press a button with their right thumb only when they encountered emotional faces (happy or fearful). The facial images used for the current study were selected from a Korean standardized facial image set named “Chaelee face” [81], which consists of emotional faces rated from 1 (minimum) to 8 (maximum). In this study, six color images with maximum intensity were selected for each emotion (happy, fearful, and neutral; eighteen images in total). The images showed the entire face of the person, including hair. The contrast and luminance of the pictures were adjusted to an equal level.

Facial stimuli were presented as 288 randomly ordered pictures, with an equal probability for each emotion (96 neutral faces, 192 emotional faces). 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.

6.2.3. 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 electrodes were attached according to a modified 10-20 configuration. 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. E-Prime (Psychology Software Tools, Pittsburgh, PA, USA) was used to synchronize the exact stimulus onset with the recorded signal.

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. The author followed a mathematically-established procedure to remove the error effects of the EOG [82]. 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 band-pass filtered at 1–30 Hz with a steepness of 24 dB/octave for ERP analysis [45, 106]. 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 [91]: 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.

6.2.4. Source Localization using sLORETA

Standardized low-resolution brain electromagnetic tomography (sLORETA) is one of representative source localization methods for solving the EEG inverse problem [22, 135]. sLORETA assumes the source activation of a voxel is similar to that of the surrounding voxels (maximum likelihood) for calculating a particular solution, and applies an appropriate standardization of the current density. sLORETA

has been used in various studies to investigate which brain areas participate in the generation of ERP components such as P50 [136], P100 [137], N170 [138], P300 [139, 140].

In this study, the author used the open sLORETA software to estimate the source distribution [22]. 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 [98, 107]. The solution space was composed of 6239 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 Chapter 5. The time ranges used for each ERP source imaging are listed in Table 6.1. In the present analysis, 60 channels were used for the sLORETA source imaging: FP1 / FPz / FP2, AF3 / AF4, F7 / F5 / F3 / F1 / Fz / F2 / F4 / F6 / F8, FT7 / FC5 / FC3 / FC1/ FCz / FC2 / FC4 / FC6 / FT8, T7 / C5 / C3 / C1 / Cz / C2 / C4 / C6 / T8, TP7 / CP5 / CP3 / CP1 / CPz / CP2 / CP4 / CP6 / TP8, P7 / P5 / P3 / P1 / Pz / P2 / P4 / P6 / P8, PO7 / PO5 / POZ / PO4 / PO6 / PO8, O1 / OZ / O2.

6.2.5. 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, the author 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 [141]. 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.

6.3. Results

6.3.1. Behavioral Test and ERP Components

The average PANSS scores of the subjects were 20.2 ± 7.8 and 18.7 ± 7.4 for positive and negative symptoms, respectively. Grand averaged ERPs from designated electrodes are shown in Figure 6.1, and detailed amplitude and latency values for the four ERP components and other demographic data are presented in Table 6.1.

One-way ANOVA analysis revealed that the peak amplitudes (μV) of P100 [$F(2, 65) = 1.436$, $p = 0.245$], N170 [$F(2,66) = 0.073$, $p = 0.930$], and P300 [$F(2,66) = 0.131$, $p = 0.878$] had no difference among the different emotions (neutral, fearful, and happy). However, the peak amplitude of N250 showed significant difference among emotions [$F(2,66) = 3.894$, $p = 0.025$]. Post-hoc analysis found that the amplitude for neutral emotions was larger than for happy emotions [-1.80 ± 0.98 vs. -2.63 ± 1.11, $p = 0.048$ (Bonferroni corrected)]. The hit rates were 73.22 ± 20.97 for neutral faces, 87.62 ± 23.14 for fearful faces, and 88.17 ± 16.42 for happy faces, which showed no significant differences [$F(2,48) = 2.994$, $p = 0.62$].

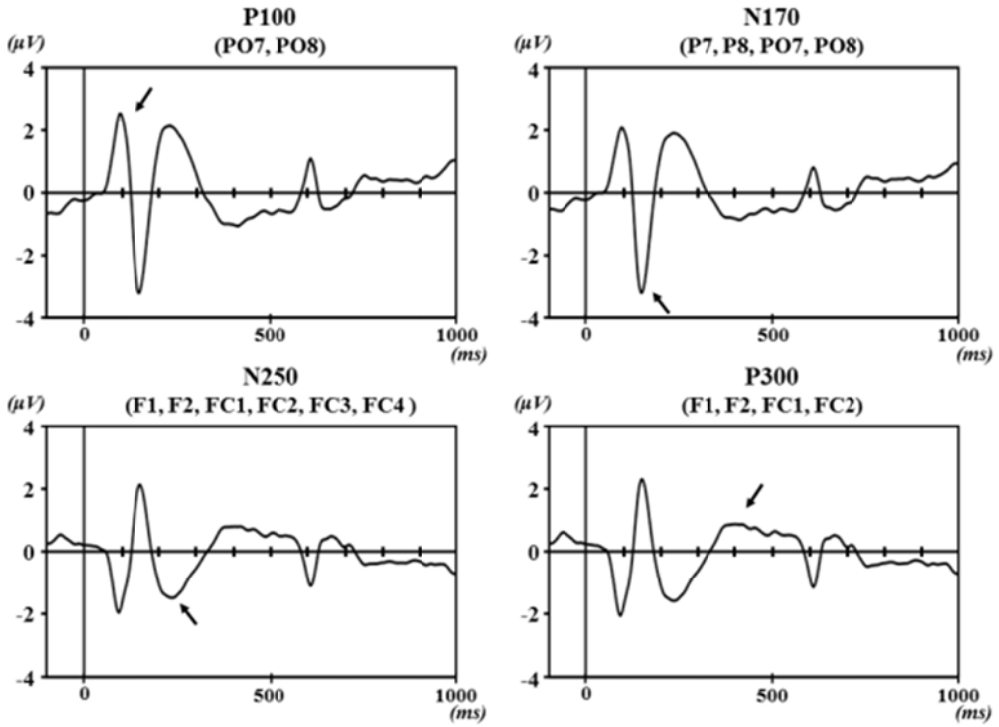

Figure 6.1 A representative plot of four ERP components (P100, N170, N250, and P300) of their respective electrode site; (left top panel) grand average ERP of PO7 and PO8 electrodes representing P100 component; (right top panel) grand average ERP of P7, P8, PO7, and PO8 electrodes representing N170 component; (left lower panel) grand average ERP of F1, F2, FC1, FC2, FC3, and FC4 electrodes representing N250 component; (right lower panel) grand average ERP of F1, F2, FC1, and FC2 electrodes representing P300 component.

6.3.2. Brain Regions Correlated with Positive Symptoms

6.3.2.1. Neutral face stimuli

PANSS positive scores were negatively correlated with four source activation clusters of the P100 component (Figure 6.2(a)): the inferior parietal lobule (BA 40, r = -0.647), precentral gyrus (BA 6, r = -0.639), precuneus (BA 31, r = -0.662), and insula (BA 13, r = -0.616). Source activation clusters around the middle frontal gyrus (BA 10, r = -0.607) for the N170 component (Figure 6.2(b)) and around the medial frontal gyrus (BA10, r = -0.657) for the N250 component (Figure 6.2(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 (Table 6.2).

6.3.2.2. Fearful face stimuli

Meaningful relationships between positive symptom severity and source activation during fearful face perception were found only in the P100 component (Table 6.2). The PANSS positive score was negatively correlated with seven distinct clusters covering the supramarginal gyrus (BA 40, r = -0.625), precentral gyrus (BA 6, r = -0.616), inferior parietal lobule (BA 40, r = -0.581), middle temporal gyrus (BA 37, r = -0.579), insular (BA 13, r = -0.595), middle temporal gyrus (BA 37, r = -0.536), and precuneus (BA 31, r = -0.685) (Appendix A.2(a)). However, later

components such as the N170, N250, or P300 did not show any source clusters significantly correlated with PANSS scores.

6.3.2.3. Happy face stimuli

The strongest negative correlation was found in the inferior parietal lobule (BA 40, r = -0.664) between PANSS positive scores and P100 source activation (Table 6.2). The P100 source activities also had significant negative correlations with PANSS positive scores in the supramarginal gyrus (BA 40, r = -0.593), superior frontal gyrus (BA 6, r = -0.581), middle frontal gyrus (BA 9, r = -0.570), and precuneus (BA 31, r = -0.643) (Appendix A.4(a)). N170 source activation in the middle frontal gyrus (BA 40, r = -0.591) showed significant negative correlation with positive symptom scores (Appendix A.4(b)). N250 and P300 source activation did not show meaningful correlations with PANSS positive scores (Table 6.2).

6.3.3. Brain Regions Correlated with Negative Symptoms

6.3.3.1 Neutral face stimuli

PANSS negative scores showed significant correlation with two source clusters in the P100 component (sub-gyral (BA 37, r = -0.702) and middle temporal gyrus (BA 39, r = -0.693): Appendix A.1(a)) and one cluster in the N250 component (middle frontal gyrus (BA 10, r = -0.600): Appendix A.1(b)). No clusters were

significantly correlated with PANSS scores in the N170 or P300 components (Table 6.3).

6.3.3.2 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), inferior parietal lobule (BA 40, r = -0.523), and inferior frontal gyrus (BA 9, r = -0.722) (Appendix A.3(a)). No significant correlations were found between later components, such as N170, N250, or P300, and source activities (Table 6.3).

6.3.3.3 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) (Appendix A.5(a)) showed strong negative correlation with PANSS negative scores, but no additional correlations were found for other regions or components (Table 6.3).

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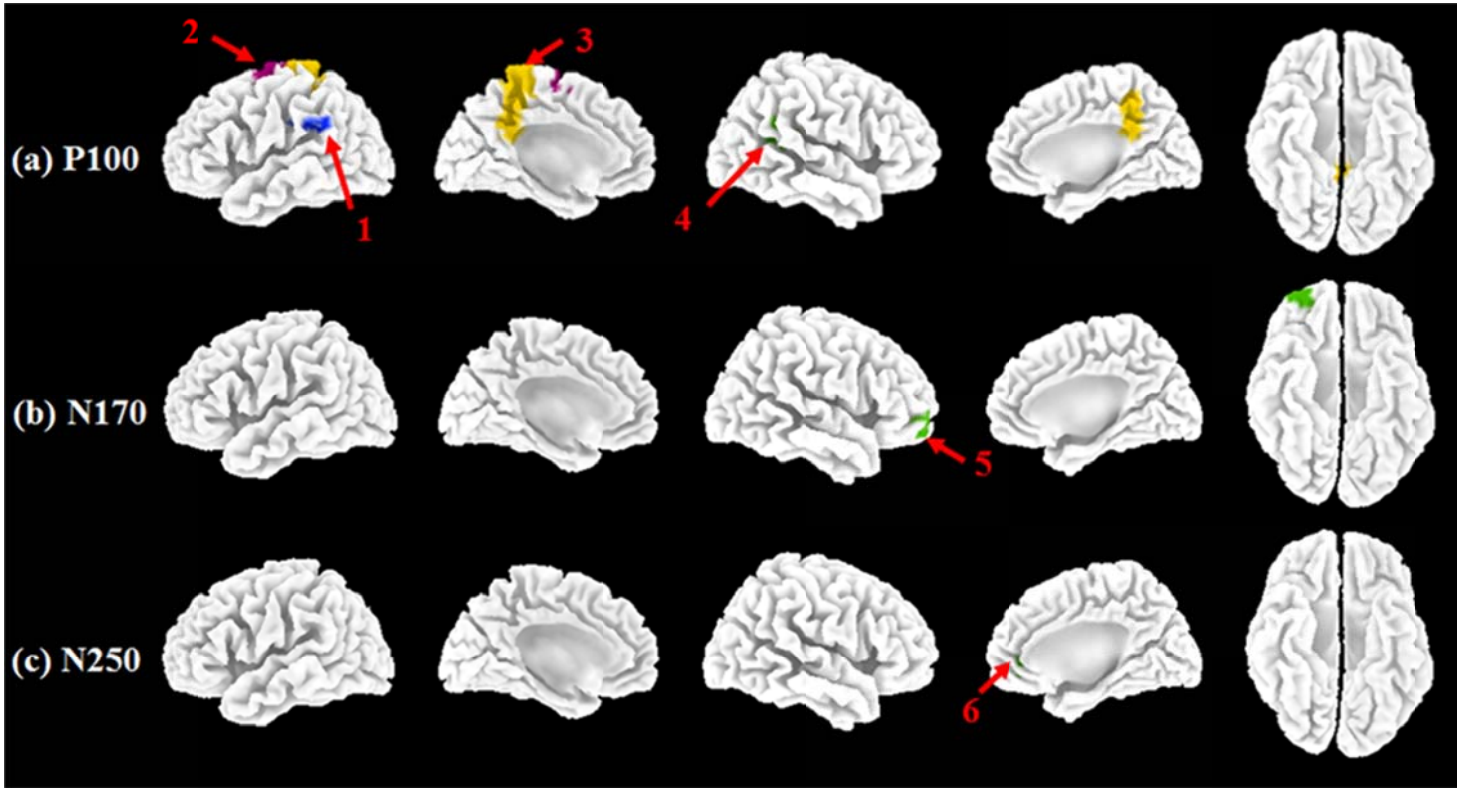

Figure 6.2 Significant correlations between positive PANSS scores and source activity of (a) P100, (b) N170, and (c) N250 during neutral condition. Different colors within the same ERP indicate different clusters.

Table 6.2 Brain regions showing significant correlation between Positive PANSS scores and ERP source imaging in neutral, fearful, and happy stimulus conditions. Maximum correlation values (*r*) and their respective regions with MNI coordinates are listed for each cluster unit.

PANSS	Emotion	ERP	Cluster	*r*	Structure (Brodmann Area)	MNI of maximum		
						X	*Y*	*Z*
Positive	Neutral	P100	1	-0.647	Inferior Parietal Lobule (BA 40)	-50	-35	35
			2	-0.639	Precentral Gyrus (BA 6)	-15	-20	70
			3	-0.662	Precuneus (BA 31)	-15	-50	35
			4	-0.616	Insula (BA 13)	40	-45	20
		N170	5	-0.607	Middle Frontal Gyrus (BA 10)	35	60	-5
		N250	6	-0.657	Medial Frontal Gyrus (BA 10)	20	45	0
	Fear	P100	1	-0.625	Supramarginal Gyrus (BA 40)	-55	-40	30
			2	-0.616	Precentral Gyrus (BA 6)	-15	-20	70
			3	-0.581	Inferior Parietal Lobule (BA 40)	40	-35	35
			4	-0.579	Middle Temporal Gyrus (BA 37)	-50	-40	-15
			5	-0.595	Insula (BA 13)	40	-45	20
			6	-0.536	Middle Temporal Gyrus (BA 37)	-45	-65	-5
			7	-0.685	Precuneus (BA 31)	-10	-50	30
	Happy	P100	1	-0.664	Inferior Parietal Lobule (BA 40)	-45	-35	35
			2	-0.593	Supramarginal Gyrus (BA 40)	50	-50	20
			3	-0.581	Superior Frontal Gyrus (BA 6)	-15	-15	70
			4	-0.570	Middle Frontal Gyrus (BA 9)	55	5	40
			5	-0.643	Precuneus (BA 31)	-15	-50	35
		N170	6	-0.591	Middle Frontal Gyrus (BA 10)	35	40	25

Table 6.3 Brain regions showing significant correlation between Negative PANSS scores and ERP source imaging in neutral, fearful, and happy stimulus conditions. Maximum correlation values (*r*) and their respective regions with MNI coordinates are listed for each cluster unit.

PANSS	Emotion	ERP	Cluster	*r*	Structure (Brodmann Area)	MNI of maximum		
						X	*Y*	*Z*
Negative	Neutral	P100	1	-0.702	Sub-Gyral (BA 37)	-45	-45	-15
			2	-0.693	Middle Temporal Gyrus (BA 39)	-50	-75	15
		N250	3	-0.600	Middle Frontal Gyrus (BA 10)	30	50	0
	Fear	P100	1	-0.532	Inferior Parietal Lobule (BA 40)	60	-40	45
			2	-0.523	Inferior Frontal Gyrus (BA 9)	55	10	35
			3	-0.722	Inferior Temporal Gyrus (BA 37)	-50	-40	-20
	Happy	P100	1	-0.688	Middle Temporal Gyrus (BA 39)	-40	-65	20

6.4. Discussion

In this chapter, the author 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 6.3).

The face perception model proposed by Haxby et al. [128] divides the neural system that participates in face perception into two systems: a core system and an extended system. Visual analysis of facial configuration is mainly processed in the core system, which involves the inferior occipital gyri, superior temporal sulcus, and

lateral fusiform gyrus. After the initial analyses of visual features, more delicate processing, including prelexical speech perception, emotion, spatially directed attention, and personal identification, is done by the extended system. The brain areas participating in emotion discrimination are believed to be the amygdala, insula, and limbic system. It is evident that deficits in any of these systems could lead to abnormal facial emotion perception, but the relationships among the deficits and symptoms are not clear.

In this chapter, PANSS positive scores were mainly associated with activation in the left temporo-parietal regions during early visual perception. In particular, these regions were found to be negatively correlated with early component activation (P100), regardless of the emotion. These findings imply that positive symptoms affect facial structural processing, which occurs relatively early, and also suggest that this early facial processing is not related with facial emotion. Though the significant correlation between PANSS positive scores and P100 activation is found over both the core and extended systems, the brain regions with strong correlation with PANSS positive scores are more predominantly found in the core system, which is consistent with the theory of Haxby et al. [128]. These regions are the left temporal areas and bilateral parietal regions, such as the superior temporal gyrus (BA 13), middle temporal gyrus (BA 39), supramarginal gyrus, and inferior parietal (BA 40), representing deficits in the core system. On the other hand, correlations with the limbic systems, such as precuneus and insular (BA 31, 13), constitute evidence of

reduced activity in the extended system. The temporal lobe is known to play an important role in early visual perception, especially in interpreting the "what" features though the ventral stream of the visual pathway. In addition, the temporal lobe is highly interconnected with other brain regions, such as the precuneus, frontal lobe, and limbic system, to form an interface between emotion and cognition [142, 143]. The hypoactivation that may occur in the left middle temporal gyrus or left superior temporal gyrus in schizophrenia patients compared to normal controls has been repeatedly reported in previous studies with neutral stimuli [33, 60] and fearful face stimuli [60]. The decreased activation in the left temporal gyrus might indicate abnormal early visual perception causing failure to transmit accurate information [144, 145], which can further lead to difficulties in judging the emotional information of the stimuli [146].

PANSS positive symptom scores were also negatively correlated with activations of the right middle frontal gyrus (BA 10) and right medial frontal gyrus (BA 10) including the right superior frontal gyrus, in N170 and N250 ERP components during both neutral and happy conditions. In the fearful condition, however, the author did not find any significant relationships with later ERP components (N170, N250, and P300). Involvements of these frontal regions are common in facial emotion processing, almost regardless of the emotional elements, in normal controls [18, 147]. Schizophrenia patients also show a decreased activation in the right frontal areas, especially during implicit emotion discrimination tasks [147].

Based on the current results, it can be said that neuronal activity of the right frontal lobe declines as positive symptoms gets worse. However, absence of a relationship between PANSS positive symptom scores and activations in the right frontal lobe during the fearful condition suggest that fear processing deficit could be a trait pathology rather than a state-dependent pathology of schizophrenia patients. Altered fearful emotion perception is shown not only in chronic schizophrenia patients but also in ultra-high risk schizophrenia and first-episode schizophrenia patients [57, 148-150]. Thus, the involvement of brain areas processing negative emotions could be altered from the beginning of the psychosis, rather than worsening throughout the progression of the illness. Combining the current results with those from the previous study [134] which reported reduced ERP source activity for N170 in response to fearful faces in middle and inferior frontal gyrus activation, it can be said that the frontal lobe function for neutral and happy face processing could be degraded by the increased positive symptom severity in schizophrenia patients, whereas deficits in fearful face processing could be a generalized pathology of schizophrenia patients regardless of positive symptom severity.

Taken together, these findings on the strong negative correlation between PANSS positive scores and neural activations in temporal, parietal, and frontal areas indicates a general decline in function, affecting both core and extended systems of face processing. These regional activation patterns are also compatible with a recently promoted concept that schizophrenia patients show sparse activation throughout the

ventral temporal-basal ganglia-prefrontal cortex, called the integrated social cognitive network [147, 151].

PANSS negative scores were associated with activations in the left parieto-temporal areas, especially including the left fusiform gyrus in all emotional conditions of P100. Interestingly, significant correlations were found only in the P100 component (Figure 6.3). The left fusiform gyrus has been reported as an area which shows significantly reduced activation during facial emotion processing in schizophrenics [152, 153]. Also, studies have reported volume reduction of the fusiform area [19, 154] in schizophrenia patients. Considering that the fusiform area is known to be a generator of P100 and N170 components [94], studies reporting decreased amplitudes of such early ERP components [32, 35, 40] in schizophrenia patients seem consistent with the decreased activation trend of the fusiform areas. However, the current results did not show any significant correlation between negative symptoms and N170 activity. These results may suggest that negative symptoms affect the earliest neural processing (P100) rather than later processing. Even though N170 occurs in a relatively early phase, it could be a part of both structural and emotional components of facial processing [32, 35, 36, 40, 91]. Given that negative emotion processing seems to be a trait pathology of schizophrenia patients [155], abnormal N170 processing could also be a trait pathology of schizophrenia patients that is independent of symptom severity [156] or disease stage [148, 157].

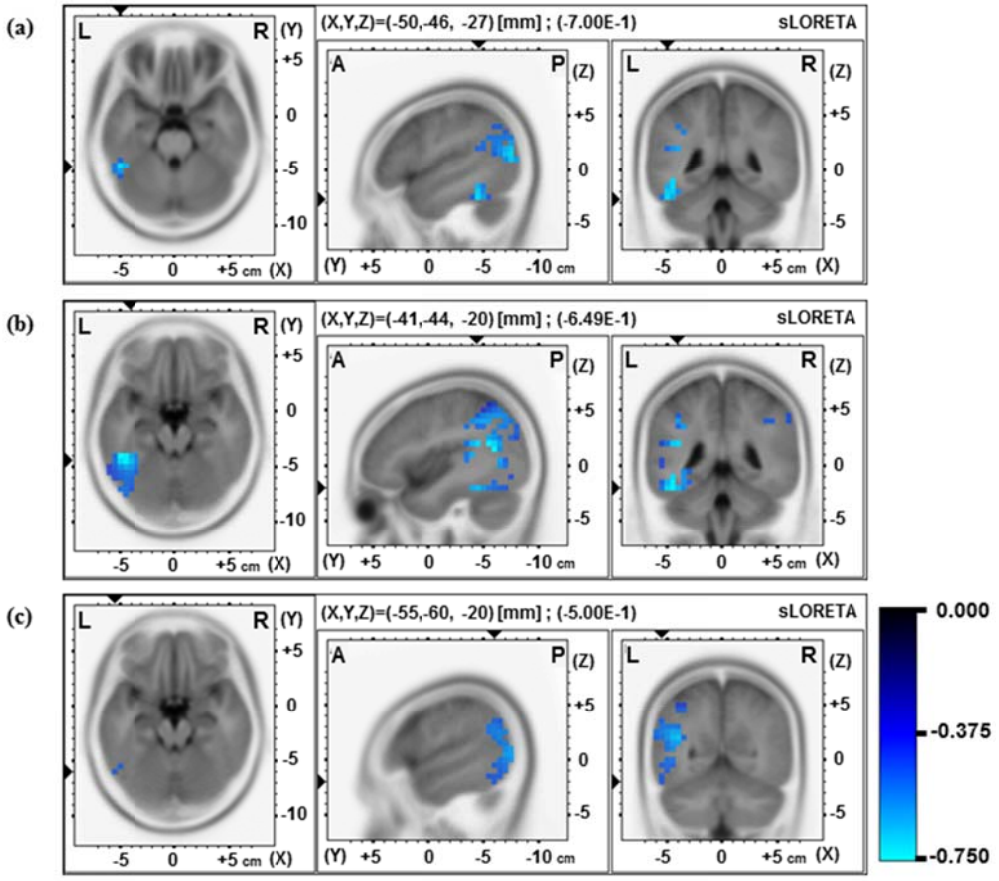

Figure 6.3 Significant negative correlations between negative symptom scores and left fusiform gyrus of P100 source imaging when schizophrenia patient is viewing (a) neutral, (b) fearful, and (c) happy faces.

Summarizing the 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 [128], which suggests that the symptoms are highly correlated with impaired visual processing of faces in the early stages. In later stages, the regions with strong negative correlation with symptom scores moved to frontal lobe. The frontal lobe is known to form a high relationship with the cortical limbic system [158-161] where the limbic system (especially amygdala) has been proposed to process emotional feature in extended system [128]. Thus the negative correlation in these areas seems to indicate impaired top-down processing of schizophrenia patients while processing facial emotional components in later stages. The results suggest that the areas showing correlation with the symptom scores are formed in posterior regions (temoproparietal areas as Haxby et al. proposed [128]) in early stages and moves forward to frontal lobe in later stages, according to the areas related in face emotional processing.

In this study, the author highlighted the areas which showed significant correlation between the source activation and symptom severity. Since the author did not contrast the source activity difference between schizophrenia group and normal control group, it might be questioned whether it is meaningful to investigate the correlation between source activation and symptoms severity for cortical areas that

did not show group differences. To address this issue, the author will present three different scenarios. Figure 6.4 illustrates the relationship between the symptom severity (x-axis) and source activation of a single voxel (y-axis: this can be any other index such as the amplitude or latency of a specific ERP component) of each individual. Normal controls are expressed as blue dots, while red triangle indicates schizophrenia patients. Since the normal controls have an intact physical/psychological condition, they do not spread horizontally; however, individual differences should exist among the normal controls, which are illustrated as vertical spreading of blue dots. Compared to normal controls, red triangles representing schizophrenia patients will spread out horizontally depending on each individual's symptom score but will also spread out vertically due to the individual difference.

On the left figure (Figure 6.4(a)), the author illustrated a case in which the group difference is found, but no relationship between the source activity and the severity is found. The example shows that source activation of schizophrenia patients is decreased compared to the normal controls; however, the decreased source activation does not seem to have a significant correlation with the symptoms severity. This corresponds to the case of previous findings from the author [134], where the author found reduced source activation in middle frontal gyrus between a schizophrenia group identical to the current study and a matched normal control group, but no significant correlation was found between the reduced source activity

and the symptom severity of schizophrenia patients. Such decreased source activity can be used as a trait maker, because the source activity of that area seems to be decreased from the early stage or the onset of the illness regardless of the symptom severity. In the middle figure (Figure 6.4(b)), the author illustrated the second scenario in which both the decreased source activation and significant negative correlation were found. In this case, the source activation at the specific voxel could not only be used as a trait marker to discriminate schizophrenia patients from normal controls, but also as a state maker indicating the severity of symptom in the schizophrenia population.

To the best to the author's knowledge, all studies investigating differences in source activations between groups or correlations between source activation and symptom severity in schizophrenia fell into the two scenarios introduced above. Previous approaches first highlighted the group differences, and then investigated the correlation between the activation showing significant group difference and the symptoms severity score. However, there is also a remaining possibility that the source activations that do not show significant difference between groups can be strongly correlated with the symptom severity as depicted in Figure 6.4(c). The author's idea was that even though the source activation did not show a statistically significant group difference, the activation can be used as a state marker indicating the symptom severity of schizophrenia and thus needed to be taken into account as an

important neurological maker for characterizing the underlying neural substrate of schizophrenia. In summary, the main goal of the current study was to investigate the relationship between source activities and symptom severity, including the source activations that were not contrasted in group comparison but showed a strong correlation with symptom severity.

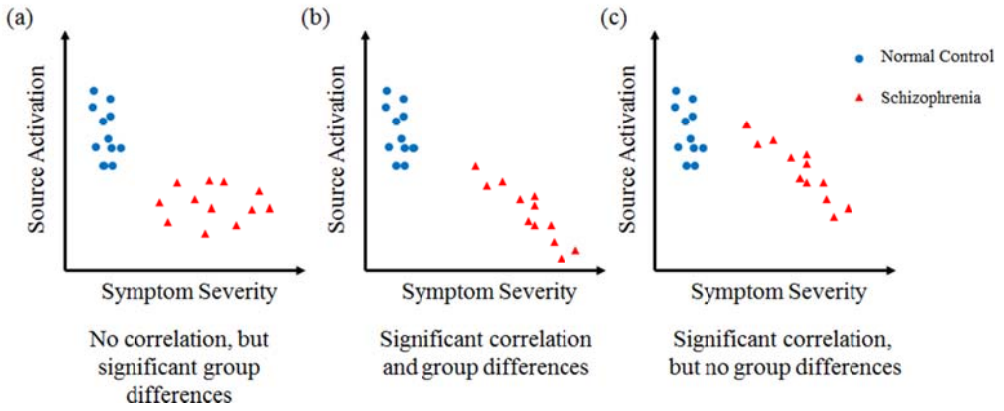

Figure 6.4. A schematic illustration on relationship between the symptoms severity and source activation of each individual. Each dot or triangle indicates the individual measurement of normal control or schizophrenia, respectively. Three different scenarios are illustrated; (a) where groups show significant group differences with absent correalation; (b) where both significant correlation and groups different exists; and (c) where no group difference were found but has a significant correlation.

However, the current study has some limitations. First, all of the patients were on anti-psychotic medication. Even though the author has found no significant effect between the dosage of antipsychotics and any ERP variable, there are no clear answers about whether the medication may affect the source current density. Note that since antipsychotic medications are effective on positive symptoms [162], some meaningful correlation between the positive symptoms and brain areas activation could be diluted. Second, the task does not distinguish areas that are involved only in facial affect processing, because the current paradigm does not include non-facial stimulus as a control. In addition, source activations of later ERP components showed fewer correlations with symptom severity, compared to early ERP components. This may be in part because the source space of sLORETA is mostly restricted to cortical gray matter, not capturing the activations of deep brain structures. Since deep brain structures, such as the amygdala and limbic system of the extended system, mainly participate during the later processes of facial emotion processing, the correlations with deep brain activation could not be examined in this study. Although the author asked participants to press a button when they encountered fearful or happy faces to check whether they were concentrating on the experimental task, there is possibilities that they might use a different strategy to press a button by neglecting neutral face stimuli, which might influence the results. In future studies, a modified paradigm for instructing the participants to provide different responses to different emotional stimuli needs to be developed. In addition, it must be taken account that it is unclear whether the ERP solely reflects face perception and facial emotion processing or

rather it may reflect the internal emotion of the subjects provoked by the picture, which may be attained by empathy.

This chapter investigated the relationship between source activation during facial emotion processing and symptom severity of schizophrenia patients. The author 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. The current 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.

Chapter 7: Conclusion

In this dissertation, various neurophysiological abnormalities were contrasted which puts more evidence to explain decreased facial affect recognition of schizophrenia. Furthermore, relationships between symptomatic scores of schizophrenia and source activity were highlighted, where distinct brain areas associated to face affect processing were significantly correlated.

The main findings of the current dissertation are as follows: 1) reduced gamma-band activation (GBA) in midline electrodes and less connectivity between electrodes, 2) reduced source activation in middle frontal gyrus and inferior frontal gyrus in schizophrenia patients, and activation differences between genders, 3) Positive and Negative PANSS scores separately correlate with distinct brain areas during face emotion recognition.

In Chapter 4, the author has shown that the altered face processing in schizophrenia patients is due to disconnections between distinct brain regions. The reduced gamma band activation seems to indicate that the top-down processing of schizophrenia patients are impaired comparing to normal controls. To the author's best knowledge, no study has investigated dysfunctional GBA in schizophrenia patients viewing pictures of real human faces. The current findings are in line with the

previous studies that used ambiguous figures of faces, which also suggested a deficit of cognitive face processing in schizophrenia patients. Combining such findings could be potentially used as a biomarker to contrast schizophrenia from normal controls in terms of altered gamma band activation and connectivity.

The study introduced in Chapter 5 has its originality by comparing the source activations of face-related ERP components between different emotion components. There are many ERP studies published which contrasts between non-facial stimuli and facial or between emotional faces. Not a lot of the studies compares source activation between emotions, and rarely does gender comparisons. Since little has been investigated about neural correlates associated with gender differences, the present result highlights the importance of gender difference in affective facial processing in schizophrenia. It should be addressed that the results also could be used as a potential biomarker to diagnose schizophrenia using cortical source activations.

In Chapter 6, the author has investigated the relationship between source activation during facial emotion processing and symptom severity of schizophrenia patients. The author evaluated voxel-based correlations between the source activities of the four ERP components measured using sLORETA source imaging method and symptom severity based on PANSS scores, which is a novel method different from traditional ROI-based comparison. The author has revealed clearer relationships between positive and negative symptoms and source activity, thus identifying which

regions of the brain are affected by each symptom. The current result suggested that altered face-emotion processing of schizophrenia patients might be caused by the combined effects of positive and negative symptoms affecting different areas of the brain. Also, the methodological approach of the study has its novelty which could be applied to other paradigms to further investigate the relationship between clinical sources and schizophrenia, or to other patient groups to reveal their relationship between clinical symptoms and source activation.

For further investigation, the following topics can be addressed. First, since there is no clear test to diagnose schizophrenia or the symptom severity of schizophrenia, a quantitative diagnosis based neurophysiological measures could help to evaluate and track the symptom severity of schizophrenia and further assist to establish treatment program or strategy for antipsychotic dose administration. Second, using patients individual MRI could infer more accurate information about the source activation differences. The current study used a standard head model which is made by averaging a satisfactory amount of individual MRI. Considering that the shape of the head and brain is different from person to person, the estimated source activity might contain localization errors which can be crucial in some extreme cases. However, the amount of more information that we can obtain by individual MRI versus the cost of expensive imaging tools and time-consuming analysis process has to be seriously considered. Lastly, the results could be used to narrow down the field-of-view of the fMRI to observe hemodynamic changes in high temporal resolution. If

the field-of-view of the fMRI images are restricted to the areas that showed significant correlations with symptoms scores or activation differences, the images could be obtained in more faster rate, thus, the temporal dynamics could be investigated using fMRI. It might be helpful to find new or consistent findings to explain the impaired facial affect processing of schizophrenia patients, however, it must be take into account that the neuronal activation in not directly correlated with hemodynamic responses.

In summary, the author has investigated the facial affect processing deficit in schizophrenia patients using EEG recordings by applying various state-of-the-art analysis methodologies. Based on the results, the author reconfirmed that impaired facial affect processing is one of the prominent symptom of schizophrenia patients. The author hopes that the results from this dissertation will contribute to find fundamental features that cause face recognition abnormalities of schizophrenia.

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Appendix

Appendix A: Correlation cluster maps showing clusters with significant correlation between PANSS scores and sLORETA source activity during face-emotional recognition, which is not suggested in Chapter 6. For the exact brain structures and its respective MNI coordinates, refer to Table 6.2 and 6.3.

Figure A.1. Significant correlations between negative PANSS score and source activity of (a) P100, and (b) N250 component during neutral condition. Different colors within the same ERP indicate different clusters.

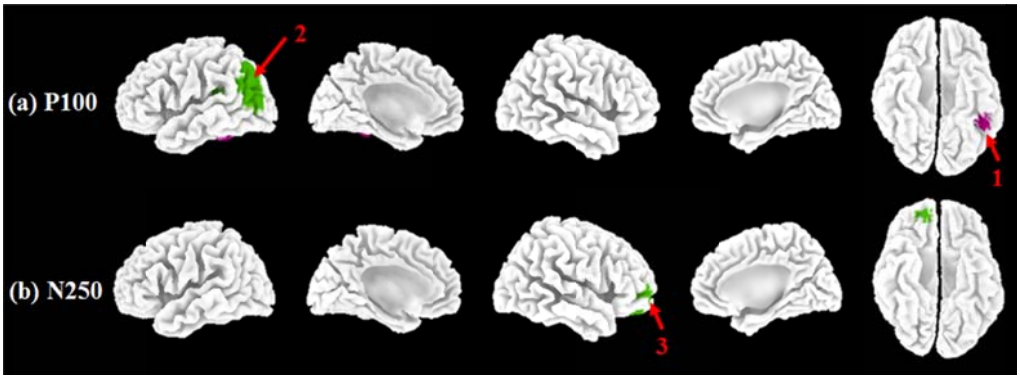


Figure A.2. Significant correlations between positive PANSS score and source activity of (a) P100 component during fear condition. Different colors within the same ERP indicate different clusters.

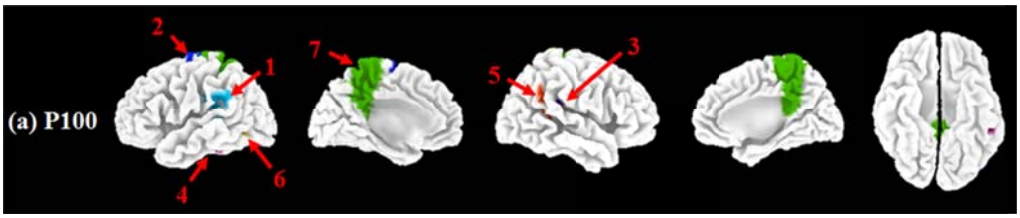


Figure A.3. Significant correlations between negative PANSS score and source activity of (a) P100 component during fear condition. Different colors within the same ERP indicate different clusters.

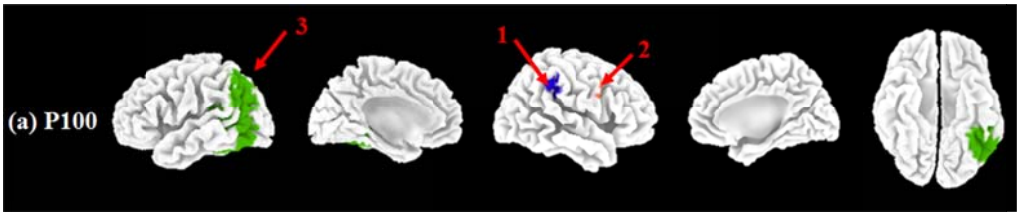


Figure A.4. Significant correlations between positive PANSS score and source activity of (a) P100, and (b) N170 component during happy condition. Different colors within the same ERP indicate different clusters.

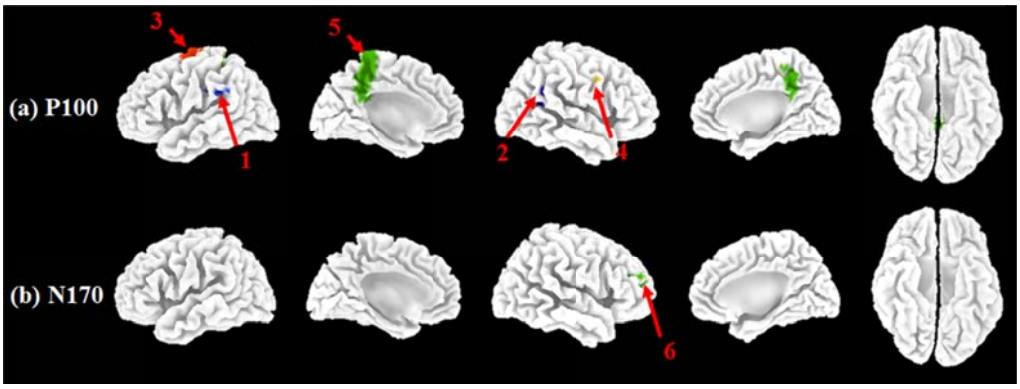
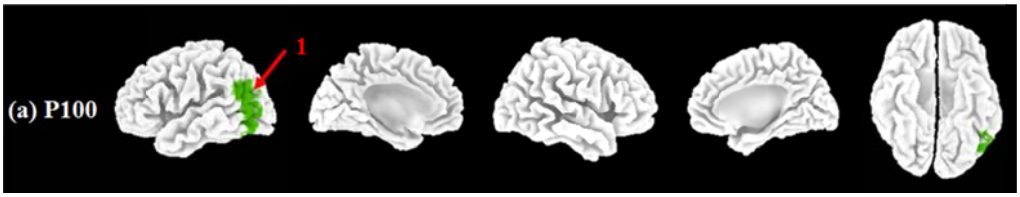


Figure A.5. Significant correlations between negative PANSS score and source activity of (a) P100 component during happy condition. Different colors within the same ERP indicate different clusters.



Curriculum Vitae

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RESEARCH INTERESTS

- Development of neurophysiologic biomarkers to **diagnose neuropsychiatric diseases** (e.g. Alzheimer's disease, anxiety disorder, schizophrenia, post-traumatic stress disorder, etc.)
- **Brain Computer Interfaces(BCI)** based on EEG or NIRS
- **Analysis of brain signals** using advanced signal processing methods
- **Paradigm development** for cognitive neuroscience

EDUCATION

- **Integrated M.S/Ph. D. course** 2008.03 ~ present
  Department of Biomedical Engineering, Yonsei University
- **Bachelor's Degree** 2002.03 ~ 2008.02
  Department of Biomedical Engineering, Yonsei University

SKILLS

EEG/MEG/NIRS signal processing

- Event related potential(ERP), Time-frequency analysis, Connectivity analysis
- Source localization methods (sLORETA, SPM, EEGLab, CURRY, BrainSuite etc.)
- Nonlinear synchronization methods; GFS, GSI, Omega Complexity

Full experimental procedure using EEG/NIRS

- Solid background knowledge and experiment on designing experiments for cognitive neuroscience, Brain-Computer Interface(BCI), and clinical experiments
- Various experiment to execute full experiment procedure – experimental design, execute experiment, signal processing, pattern classification, and statistical analysis

Language

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Programming

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ACADEMIC EXPERIENCE

Teaching Assistant; Yonsei University

Computer Programming (C++)	2009.09 ~ 2009.12
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Engineering Mathematics II	2009.03 ~ 2009.06

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PROFESSIONAL EXPERIENCE

• Computational Neuroengineering Laboratory, Hanyang University	2011. 03 ~ present
• Computer Aided Biomedical Engineering, Yonsei University	2011. 03 ~ present
• Researcher, Clinical Emotion and Cognition Research Laboratory, Department of Psychiatry, Ilsan Paik Hospital	2009. 08 ~ present
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PUBLICATIONS

Peer-reviewed International Journal Papers

13. **Do-Won Kim**, Han-Sung Kim, Seung-Hwan Lee, and Chang-Hwan Im, "Positive and negative symptom scores are correlated with activation in different brain regions during facial emotion perception in schizophrenia patients: A voxel-based sLORETA source activity study," *Schizophr. Res.*, in revision
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Non-SCI and Domestic Papers

3. **Do-Won Kim**, Jun-Chang Lee, Young-Min Park, In-Young Kim, and Chang-Hwan Im, "Auditory brain-computer interfaces (BCIs) and their practical applications," *Biomed. Eng. Lett*., vol. 2, no. 1, pp. 13-17, 2012.
2. **Do-Won Kim**, Young-Jin Jung, Chang-Hwan Im, "Influence of Modeling Errors in the Boundary Element Analysis of EEG Forward Problems upon the Solution Accuracy," *J. Biomed. Eng. Res.*, vol. 30, no. 1, pp. 10-17, 2009. 02.
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PATENTS

Registered Patents

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Abstract in Korean

뇌파를 이용한 조현병의 얼굴 감정 인식 장애 연구

연세대학교 대학원

의공학과

김도원

조현병은 망상, 환각, 비정상적인 말과 행동, 대인관계 회피, 정서적 둔감 등의 증상과 더불어 사회적 기능(social function)에 장애를 일으키는 정신질환이다. 그 중 사회적 기능 장애는 상대방의 얼굴을 통하여 상대방의 나이, 성별을 추정하거나 표정을 통하여 감정을 읽는 능력이 정상인보다 결핍된 증상을 말한다. 특히 얼굴 감정 인식 능력의 저하는 조현병 환자의 대인 간 의사소통에서 상대방의 감정상태나 의도를 파악하는 데 큰 영향을 미쳐 상대방의 정확한 의도를 파악하지 못하게 되며 환자들이 원만한 대인관계 및 사회적 활동을 유지하는데 어려움을

초래한다. 이러한 장애는 행동연구뿐만 아니라 뇌전도 (EEG), 뇌자도 (MEG), 기능성자기공명영상(fMRI), 양자방출단층촬영(PET) 등의 다양한 뇌 영상 기법을 통하여 신경생리학적인 관점에서도 조명이 되었지만, 연구간의 일관성 있는 결론이 도출되고 있지 않아 그 기전이 아직 밝혀지지 않았다.

따라서 본 학위 논문에서는 조현병 환자들의 안면 표정 인식 장애의 기전을 밝히는 데 이바지하고자 다양한 뇌파분석기법을 이용하여 그 신경생리학적인 기전을 연구하였다. 이러한 신경생리학적인 기전을 연구하기 위하여 조현병 환자 25 명과 정상대조군 25 명을 대상으로 피험자들이 안면표정인식 검사를 수행할 때, 시간 분해능이 우수한 뇌파를 측정하여 1) 감마 대역 활성화와 전극 단위의 연결성 비교, 2) 뇌 전류원의 활성화 정도 비교, 3) 뇌 전류원의 활성화 정도와 조현병 환자들의 임상증상과의 연관관계를 연구하여 그 기전을 심층적으로 규명하고자 한다.

안면표정인식은 약 1 초 이내에 무의식적으로 이루어지는 과정으로 다양한 뇌 영역들이 빠르고 순차적으로 활성화 되는 것으로 알려졌다. 안면표정인식 중에 다양한 뇌 영역들이 어떻게 연결성을 형성하는지에

관한 정상군 연구는 다수가 존재하나 조현병 환자를 이용한 연구들은 실제 얼굴이 아닌 게슈탈트 자극을 이용한 연구밖에 이루어지지 않았다. 따라서 조현병 환자들이 실제 얼굴 사진을 이용한 안면표정인식 과제를 수행할 때 뇌 영역 간 연결성에 어떤 차이를 보이는지 연구하기 위하여 뇌 영역 간 의사소통에 관여한다고 알려진 감마파의 활성화와 위상 동기화를 측정하여 비교하였다. 그 결과 조현병 환자들에게서 전두엽의 전극에서 유의미한 감마파 감소세를 보였으며, 위상 동기화도 유의미하게 떨어지는 것으로 나타났다. 본 연구는 조현병 환자을 대상으로 실제 얼굴 자극을 이용하여 안면표정인식 과제를 연구한 최초의 사례로 환자들에게서 전두엽에서의 감마파 감소와 전극 간 연결성 이상을 규명한 데에 의의를 가진다.

조현병의 안면표정인식 중 뇌 활성화 비교 연구는 일반적으로 fMRI 를 이용하여 수행되어 오고 있지만, 시간 분해능이 낮아서 1 초 이내에 이루어지는 안면표정인식에 관여하는 영역을 관찰하기 어려워서 안면표정인식 과정 중 어느 시점에 이상이 있는지 결론짓기 어렵다. 따라서 본 연구에서는 우수한 시간 분해능을 가지는 뇌파를 이용하여 대뇌 피질의 활성화를 추정하고 비교해봄으로써 차이 나는 위치뿐만 아니라 안면표정인식의 어느 과정에서 차이가 나는지 추정해보고 한다. 우선 안면표정인식 과정 중 발생하는 네 개의 사건유발전위(event-related

potential)의 뇌 전류원을 계산하여 비교하였다. 그 결과, 조현병 환자들에게 공포 자극이 주어졌을 때 N170 성분이 유발되는 시점에서 중전두회(middle frontal gyrus)와 하전두회(inferior frontal gyrus)에서 유의미하게 뇌 전류원의 활성화가 감소하는 것을 확인하였다. 추가로 조현병 남자들은 정상인 남자들에 비하여 동일 시간대의 뇌섬(insular)부위의 활성화가 감소하였지만, 여자 피험자들 간에는 차이를 보이지 않았다. 두 군 간에서 차이를 보이는 뇌 영역들은 감정 처리나 감정 이입에 관여하는 부위로써 정상군보다 해당 기능들이 잘 이루어지지 않는다는 것을 시사한다. 본 연구에서는 최초로 안면표정인식에 관련된 모든 사건유발전위의 전류원을 비교해봄으로써 기존 연구들에서 조명하지 않은 안면표정인식 과정 중 어느 시점에서 두 군 사이에 유의미한 차이를 보이는지 조명하였다.

조현병의 안면표정인식 과제 중 뇌 전류원의 활성화의 감소는 일반적으로 조현병의 증상 심각도와 연관이 있다고 알려졌다. 일반적으로 이러한 상관관계를 연구할 때는 두 군 사이의 뇌 활성화가 차이 나는지 확인한 후에 유의미한 차이를 보이는 영역에 대해서만 그 관계를 연구해 왔다. 하지만 이러한 방법은 실제로 증상과 높은 상관성을 가지고 있지만, 군 간 차이에서 유의미한 차이를 보이지 않는 부위들을 간과하게 된다.

따라서 본 연구에서는 안면표정인식 과정 중에서 유발된 사건 유발전위들을 이용하여 구해진 대뇌 피질의 모든 전류원들과 조현병 환자들의 양성 및 음성 증상과의 관계를 연구하기 위한 새로운 방법을 제안하였다. 연구에 사용된 조현병 환자들의 임상 증세는 양성 및 음성 증후군 척도(Positive and Negative Syndrome Scale; PANSS)의 양성 척도와 음성 척도를 사용하였다. 우선 역문제를 통해 구해진 각 복셀 전류원과 조현병의 양성 및 음성 증상과 상관관계를 계산하였으며 비모수 치환검정(non-parametric permutation test)을 통하여 통계적으로 유의미한 관계를 맺는 복셀만을 선별한 후 인접한 복셀들은 하나의 집합체로 나타내었다. 그 결과 초기 사건유발전위인 P100 전류원들은 양성증상과는 측두회 (temporal gyrus) 영역 등에서 강한 음의 상관관계를, 음성증상과는 방추모양표면영역 (fusiform face area) 영역 등에서 강한 음의 상관관계를 맺는 것으로 나타났다. 또한, 일부 자극의 후기 사건유발전위에서는 감정 처리와 높은 상관관계를 맺는 중전두회(middle frontral gyrus)나 내측전두회(medial frontal gyrus)에서 음의 상관관계가 나타남을 확인하였다. 본 연구는 안면감정인식 장애가 조현병의 양성과 음성 증상이 각각 뇌의 서로 다른 부위에 영향을 미치는 것을 확인하였으며 조현병의 이상적 (heterogeneous)인 특징을 잘 반영하는 것으로 보인다.

본 학위 논문에서는 조현병의 안면표정인식검사 도중의 뇌파 데이터를 이용하여 1) 감마 대역 활성화와 전극 단위의 연결성 분석, 2) 뇌 전류원의 활성화 정도 비교, 3) 뇌 전류원의 활성화 정도와 조현병 환자들의 임상증상과의 연관관계를 규명하여 조현병의 안면표정인식 장애를 신경생리학적으로 이해할 수 있는 새로운 결과들을 제시하였다. 본 학위 논문에서 보인 조현병과 정상대조군과 유의미한 차이가 나는 감마대역의 활성화 감소, 연결성의 감소, 뇌 전류원의 활성화의 감소, 임상증상과의 연관관계 등을 이용하여 조현병을 뇌파로 진단할 수 있는 새로운 지표를 개발하는 데 쓰일 수 있을 것으로 기대된다. 특히 뇌 전류원의 활성화 정도와 임상증상과 연관관계를 보는 새로운 방법론은 다른 작업 과제에 적용하거나 다른 정신질환에 시험함으로써 조현병 또는 다른 정신질환의 기전을 밝히는데 많은 이바지 할 수 있을 것으로 예상한다.

핵심 되는 말: 조현병, 얼굴 감정 인식 장애, 뇌파, 양성 및 음성 증후군 척도(PANSS), 양성 증상, 음성 증상, 임상증상, 사건유발전위, 감마파, 위상 동기화, 기능적 연결성, 뇌 전류원 이미징, 역문제, 정신 질환 진단, 바이오마커,