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ORIGINAL PAPER

Source Activation of P300 Correlates with Negative Symptom Severity in Patients with Schizophrenia

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Abstract It is well known that the P300 amplitude is reduced in schizophrenia patients, which may reflect the pathophysiology and symptom severity of schizophrenia, particularly related to negative symptoms. However, the relationship between the underlying neural generator of the P300 and symptomatic outcomes are not yet fully understood. This study aimed to verify the abnormal P300 of schizophrenia in terms of its source activation to and further examine the relationship between reduced source activation and symptom severity of patients. For this purpose, the P300 was recorded from 34 patients with schizophrenia and matched healthy controls using an auditory oddball paradigm. We found that the P300 amplitude of schizophrenia patients was significantly decreased along the midline electrodes and both bilateral temporal areas compared with healthy controls. In comparing the source activation between the two groups, schizophrenia patients showed decreased source activation predominantly over the left hemisphere, including the cingulate, inferior occipital gyrus, middle occipital gyrus, middle temporal gyrus, posterior cingulate, precuneus, and superior occipital gyrus. Furthermore, we found that the decreased activation of the contrasted areas showed significant negative correlation with PANSS negative symptom scores in the middle temporal gyrus, posterior cingulate, precuneus, and superior occipital gyrus. Our findings suggest that the reduced P300 source activation in schizophrenia might reflect deficits in fronto-temporal-parietal circuit.

Keywords Schizophrenia · Biomarker · Negative symptom · P300 · Source activity

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Introduction

The P300 is an endogenous event-related potential (ERP) that shows a positive deflection of 300–450 ms after the stimulus. The most classic way of eliciting the P300 is to use an 'oddball paradigm' during which the subject attends to a randomly presented, infrequent target stimuli interspersed among frequent stimuli. The elicited amplitude and latency of the P300 is accepted as a signifier of the integrity of the information processing functioning of the brain, especially stimulus evaluation or categorization processing (Kaustio et al. 2002; Santosh et al. 1994).

Abnormality in the auditory-elicited P300 component is one of the most replicated findings in schizophrenia. Most studies report reduced amplitude and prolonged latency of the P300 component in schizophrenia patients along the midline electrodes (Braff and Light 2004; St Clair et al. 1989; Sekihara et al. 2005; Lim et al. 2010), or over the left temporal area (Higashima et al. 2003; Yamasue et al. 2004; Bleich-Cohen et al. 2012; Havermans et al. 1999; Mccarley et al. 1993). These abnormalities in the P300 have been found not only in chronic schizophrenia patients, but also in those with first-episode schizophrenia (Weinberger 1988; Ziauddeen et al. 2011; Anderson et al. 2002; Wolkin et al. 1992;

Salisbury et al. 1998) and those who are clinically at-risk for psychosis (Kaustio et al. 2002; Santosh et al. 1994), suggesting that the P300 may be a fundamental indicator in explaining the pathophysiology of schizophrenia.

Despite the usefulness of P300 in schizophrenia, it is not conclusive whether the P300 abnormality of schizophrenia has to be related with their clinical symptoms. Most studies have reported that the P300 amplitude is correlated with negative symptom scores (Eikmeier et al. 1992; Ford et al. 1992; Liu et al. 2004; Pfefferbaum et al. 1989; Strik et al. 1993; Turetsky et al. 1998), although others have revealed a significant relationship with positive symptomatic scores (Egan et al. 1994; Higashima et al. 2003) or no correlation (Blackwood et al. 1987; St Clair et al. 1989). Such inconsistent findings might be due to the heterogenic characteristics of schizophrenia (Boutros et al. 2013; Galderisi and Maj 2009; Galderisi et al. 2009), but also might reflect a different contributions of distinct neural sources which are responsible for positive and negative symptoms. However, considering that the P300 amplitude recorded on the scalp is an attenuated signal of distinct neural sources, investigating the relationship between the P300 source activation and the symptomatic outcomes of schizophrenia will give us more insight on which brain area relates to the symptomatic outcome of schizophrenia. Therefore, to better understand the abnormal P300 and symptoms of schizophrenia, further studies are needed to investigate the actual neural sources and psychotic symptoms of the disease.

Conventional functional neuroimaging modalities such as functional magnetic resonance imaging (fMRI) cannot be used to unveil the underlying neuronal sources of the P300 due to their poor temporal resolutions relative to EEG. EEG, however, also has its drawbacks; it has a relatively low temporal resolution compared to fMRI. Although there are methods combining two neuroimaging modalities, such as EEG–fMRI multimodal imaging, one of the cost efficient options to enhance spatial and temporal resolution is to use EEG source imaging. The spatial resolution of EEG can be substantially improved by mapping the scalp potential distribution onto the underlying cortical source space using source imaging methods. For example, low-resolution brain electromagnetic tomography (LORETA) is a well-established method (Pascual-Marqui et al. 2002) and has been compared to results from intracranial recording (Lantz et al. 1997). Using LORETA, the P300 source areas of healthy controls appear to be widespread over the prefrontal cortex, cingulum, parietal lobe, and temporal lobe (Winterer et al. 2001).

Studies contrasting P300 source activation differences between schizophrenia and healthy controls using LORETA have found a significant reduction of neural sources, mostly over the left hemisphere and including the middle frontal gyrus, precuneus, precentral gyrus, and superior temporal gyrus (Higuchi et al. 2008; Kawasaki et al. 2007; Pae et al. 2003; Sumiyoshi et al. 2006; Wang et al. 2010; Winterer et al. 2001). However, only a few studies have investigated the relationship between source activation and clinical symptoms. For instance, (Kawasaki et al. 2007) found that the current densities of the superior temporal gyrus and the medial frontal regions are negatively correlated with both the positive and negative subscale scores of schizophrenia patients. More recently, (Wang et al. 2010) found that activations in the left insula, superior temporal gyrus, and postcentral gyrus are negatively correlated with the total score of the positive and negative syndrome scale (PANSS) of first-episode schizophrenia patients. These results suggest that the reduced activation of the P300 in schizophrenia may be related to symptomatic scores; however, extant studies have included either no control group (Kawasaki et al. 2007) or a relatively small sample size (Wang et al. 2010). Therefore, more independent investigations between the P300 source activation and symptom scores of schizophrenia are needed.

In the present study, we investigated the source activation difference between schizophrenia patients and healthy controls. Moreover, we focused on the relationship between significant source activation differences and the clinical symptoms of schizophrenia. We used a standardized LORETA (sLORETA) for source localization, which is superior in temporal resolution and has fewer localization errors than the original LORETA. The main objectives of the current investigation were: (1) compare the auditory oddball-elicited P300 component between schizophrenia patients and healthy controls, (2) contrast the underlying cortical source activation that contributes to P300 activation, and (3) characterize the relationship between clinical symptoms of schizophrenia and brain regions that differ between groups.

Methods

Participants

Thirty-four patients with schizophrenia and an equal number of healthy controls were recruited for this study. Patients were 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 (First et al. 1997). Patients with no history of central nervous system disease, alcohol or drug abuse, electroconvulsive therapy, mental retardation, or head injury with loss of consciousness were selected for the study. Psychiatric symptoms were evaluated using the PANSS (Kay et al. 1987).

The patient group consisted of 14 males and 20 females with a mean age of 33.91 ± 13.30 years, and the mean duration of illness was 51.88 ± 68.64 months. All patients were taking atypical antipsychotic medications (olanzapine, $n = 15$ and risperidone, $n = 19$), and on stable dosages of medications. Healthy controls (20 males and 14 females) were recruited from the local community though local newspapers and posters. Healthy controls were initially screened to exclude those with neurological disorders, head injury, personal or family history of psychiatric illness, alcohol abuse, or any circumstances that might affect cognitive functioning or cause hearing loss. After the initial screening, healthy controls were interviewed using the SCID for DSM-IV Axis II Disorders (First and Gibbon 1997). Potential subjects who met criteria for any disorders were excluded at this stage.

All participants had normal or corrected-to-normal vision and were right-handed. Participants' auditory functioning was examined using a 512-Hz tuning fork to ensure that no subjects with hearing impairment were included. All participants were instructed in the details of the study and signed a written consent form that was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital. Demographic data for all participants and the clinical symptom scores of the schizophrenia group are listed in Table 1.

ERP Recording and Analysis

The auditory oddball paradigm was used as the stimulation protocol. Participants were seated in a comfortable chair in front of a monitor with a fixation cross displayed in the middle. The auditory stimulus was delivered using MDRD-777 headphones (Sony, Tokyo, Japan) at 85 dB SPL in a sound-attenuated room. Stimuli consisted of pure tones at 1,000 Hz for standard tones and 1,500 Hz for the target tone. The tone duration was 100 ms each, with rise and fall times of 10 ms. A total of 400 auditory stimuli were presented in random order, with the target stimulus occurring at a 15 % chance. Participants were instructed to press a button promptly in response to target tones. The interval between stimuli was 1,500 ms. Before the paradigm, the participants completed a practice block of 20 stimuli to confirm that they understood the instructions.

Table 1 Demographic data of schizophrenia patients and healthy controls

	Schizophrenia patients	Healthy controls	*p*
Cases (*N*)	34	34	
Gender (male/female)	14/20	20/14	0.225
Age (years)	33.91 ± 13.30	34.74 ± 13.16	0.798
Illness duration (months)	51.88 ± 68.64		
Dosage of antipsychotics (chlorpromazine equivalents, mg)	511.10 ± 398.22		
Positive and negative syndrome scale (PANSS)			
Positive score	20.70 ± 7.00		
Negative score	19.03 ± 6.45		
General score	42.67 ± 11.00		
Total score	82.36 ± 21.49		

EEGs were recorded using a NeuroScan SynAmps amplifier (Compumedics USA, El Paso, TX, USA) with a headcap mounted with AgCl electrodes according to a modified 10-20 electrode scheme. We used E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) for accurate synchronization between the stimulus and EEG recordings. We recorded from 62 scalp positions (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, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, and CB2). Additional electrodes were placed above and below the right eye for vertical electrooculogram recording and at the outer canthus of each eye for horizontal electrooculogram recording. EEG data were recorded with a 1-to-100 Hz bandpass filter at a sampling rate of 1,000 Hz. The signals were referenced to both mastoids where the ground electrode was placed on the forehead. Impedance between the electrodes and scalp was maintained below 5 kΩ during the entire recording session.

EEG data were preprocessed using Scan 4.3 software (Compumedics USA, El Paso, TX, USA). Gross artifacts such as movement artifacts were rejected by visual inspection of the recording by a trained person with no prior information regarding the data origin. Artifacts related to eye movement or eye blinks were removed using an established mathematical procedure (Semlitsch et al. 1986). Data were then filtered using a 1-to-30 Hz bandpass filter and epoched from 100 ms pre-stimulus to 900 post-stimulus. Only correctly responded epochs were used for analysis. The selected epochs were subtracted from the average value of the prestimulus interval for baseline correction. If any remaining epochs contained significant physiological artifacts (amplitude exceeding ±75 μV) in any single cortical electrode sites, they were excluded from further analysis. Only artifact-free epochs were averaged across trials and participants for ERP analysis. The number of epochs used for analysis did not significantly differ between the two groups (schizophrenia patients: 54.76 ± 10.18, healthy controls: 58.03 ± 5.69; $p = 0.109$). P300 peaks were evaluated on the midline electrodes (Fz, Cz, and Pz) and also the bilateral temporal lobes (T7 and T8),

defined by a maximum amplitude between 300 and 450 ms post-stimulus (Jung et al. 2012; Kochi et al. 1996; van der Stelt et al. 2005).

Source Localization of P300 Activity Using sLORETA

Source analysis of the P300 components was performed using sLORETA software, which calculates a particular solution of the non-unique EEG inverse solution (Pascual-Marqui 2002). The sLORETA algorithm is based on the assumption that neighboring voxels tend to activate synchronously with each other. A three-layer realistic head model based on the MNI 152 template provided by the Brain Imaging Center, Monteral Neurological Institute (Fuchs et al. 2002) was used in the sLORETA software to solve the inverse problem. The source space in the software was restricted to cortical gray matter and hippocampus, and was divided into a total of 6239 5 mm cubic voxels. The time frame used to calculate the P300 source images were defined using the mean P300 latency ±2 standard deviations in each group in order to consider different peak latency variations between schizophrenia patients (283–512 ms) and healthy controls (273–445 ms) (Jung et al. 2012).

Statistical Analysis

Age and gender were tested using an independent *t* test and a Chi square test to verify homogeneity between the two groups. Between groups comparison of sLORETA images was done using a statistical non-parametric mapping method (SnPM) that was provided by the sLORETA software. Estimated voxel activation was averaged throughout the calculated time frame and tested voxel-by-voxel with an independent *t* test for the 6239 voxels, followed by adjustments for multiple comparisons.

To further investigate the relationship between clinical scales and the regions that showed significant group differences in P300 source activations, correlations between symptoms scores and activation were calculated. The source activation in regions showing significant group differences was averaged within each structure. This averaged activity of each region-of-interest was then correlated with clinical scores. To exclude false-positive relationships between symptom scores and ROI activity in such a large comparison, we applied permutation testing (Coutanche et al. 2011; Lee et al. 2013) to assess whether the correlation value of each voxel was greater than that which would have occurred by chance. Null distributions of the correlation coefficient were calculated for each voxel by independently shuffling the source activations 10,000 times. The original correlation coefficient was then tested based on each individual null distribution with a significance level of 0.05. We reported only the correlation coefficients which were found to be significant after the permutation test.

Results

Demographic Data and Behavioral Results

Demographic data for participants are listed in Table 1. The schizophrenia group and healthy controls did not differ in gender distribution ($p = 0.225$) or age ($p = 0.798$). For the auditory oddball task, the correct response rate of the schizophrenia group was 91.69 ± 12.76 %, which was significantly lower than of the healthy controls (97.66 ± 4.73 %, $p = 0.014$).

The P300 Component

The grand average ERP waveforms of the electrodes are presented in Fig. 1. The amplitudes of the P300 components were significantly decreased in schizophrenia patients compared with healthy controls in Fz (5.26 ± 4.57 vs. 9.02 ± 3.68, $p = 0.001$), Cz (6.50 ± 4.74 vs. 9.82 ± 4.60, $p = 0.005$), Pz (6.58 ± 4.04 vs. 8.92 ± 4.12, $p = 0.021$), T7 (4.37 ± 2.60 vs. 5.88 ± 2.62, $p = 0.020$), and in T8 (4.67 ± 2.90 vs. 6.50 ± 2.48, $p = 0.007$). The inter-hemispheric differences (T7-T8) between schizophrenia patients and healthy controls did not differ between groups (−0.30 ± 2.06 vs. −0.63 ± 1.64, $p = 0.488$). Although the amplitude differed between groups, the latency of the P300 components did not differ between groups across all electrodes (Fz: 359.73 ± 51.40 vs. 351.67 ± 22.08 ms, $p = 0.404$; Cz: 357.14 ± 46.33 vs. 364.73 ± 44.32 ms, $p = 0.493$; Pz: 378.65 ± 58.03 vs. 366.41 ± 44.40 ms, $p = 0.332$; T7: 349.82 ± 28.24 vs. 348.06 ± 29.08 ms, $p = 0.800$; T8: 355.26 ± 30.98 vs. 345.59 ± 29.44 ms, $p = 0.191$).

The P300 amplitude of the Fz electrode was negatively correlated with the negative symptom score of the PANSS in schizophrenia patients ($r = -0.353$, $p = 0.044$). There was no significant correlation between the P300 amplitude and PANSS positive or general scores, duration of illness, or dosage of antipsychotic medication. The P300 latency also had no significant correlation with symptom scores, duration of illness, or dosage of antipsychotic medication.

Group Comparisons of sLORETA

Group comparisons of sLORETA source imaging revealed that the source densities of the cingulate (BA 31), inferior occipital gyrus (BA 18), middle occipital gyrus (BA 19), middle temporal gyrus (BA 19), posterior cingulate (BA 31), precuneus (BA 31), and superior occipital gyrus

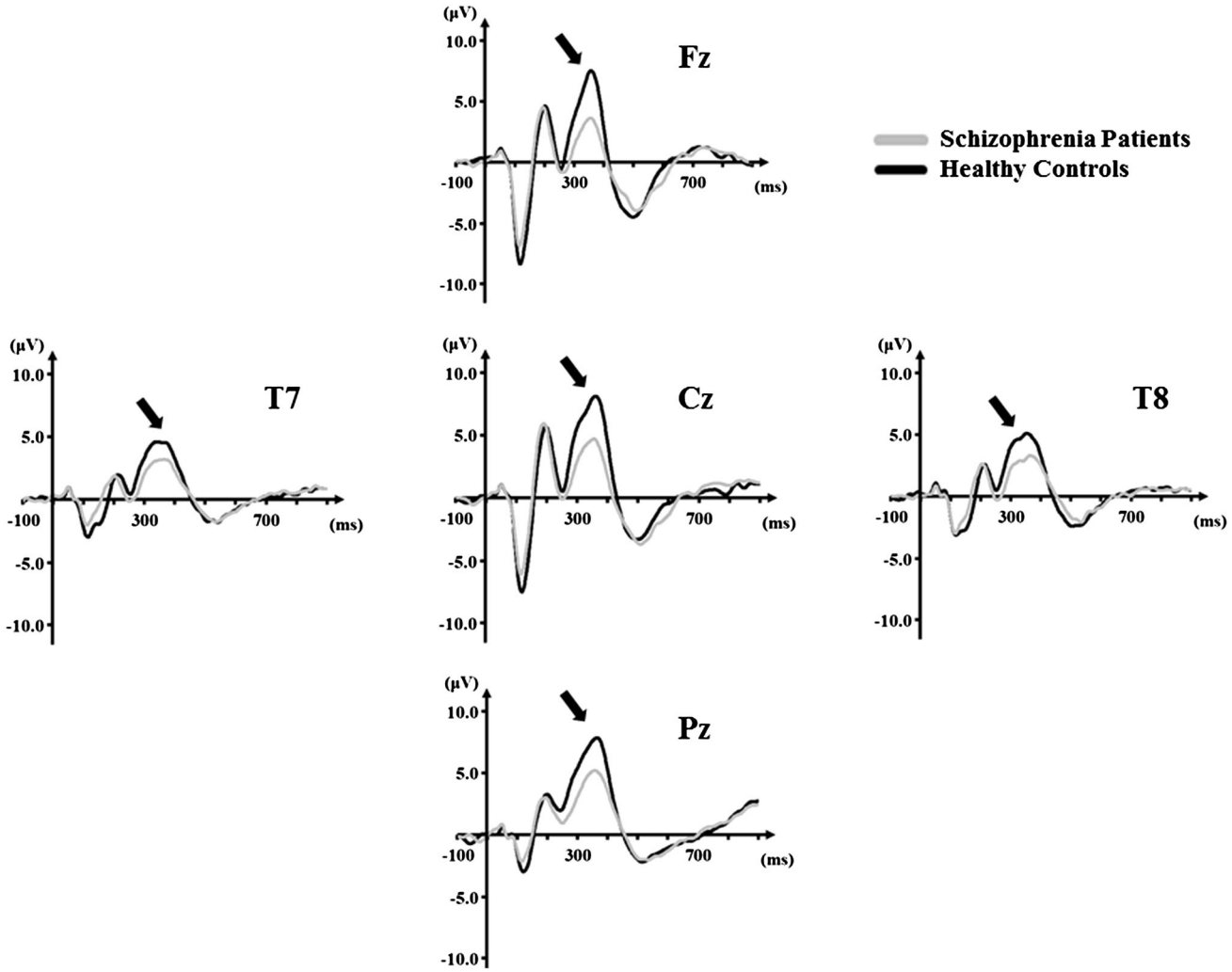

Fig. 1 Grand average ERP waveforms of schizophrenia patients (*gray line*) and healthy controls (*black line*) from the following electrodes: Fz, Cz, Pz, T7, and T8. The *arrow* indicates the P300 component

(BA 19) were decreased in schizophrenia patients compared with healthy controls ($p < 0.05$; Table 2; Fig. 2). Detailed information on the statistical values and the voxel coordinates are listed in Table 2 and illustrated in Fig. 2.

Correlation Analysis Between sLORETA Source Densities and PANSS Scores

There was a significant relationship between brain areas that showed significant group differences and PANSS subscale scores. Negative scores on the PANSS were inversely related to the source activity of the middle temporal gyrus ($r = -0.371$, $p = 0.034$), posterior cingulate ($r = -0.359$, $p = 0.040$), precuneus ($r = -0.432$, $p = 0.012$) and superior occipital gyrus ($r = -0.429$, $p = 0.013$). However, there was no significant relationship with the cingulate ($r = -0.124$, $p = 0.491$), inferior occipital gyrus ($r = -0.126$, $p = 0.483$), or middle occipital gyrus ($r = -0.171$, $p = 0.342$). There was also no relationship between the amount of source activity and other subscale scores (PANSS positive, general, and total). Correlations between ROI source activation and each PANSS subscale scores are listed in Table 3.

Since PANSS negative subscale includes cognitive (Difficulty in abstract thinking, N5) and disorganization (Stereotyped thinking, N7) items, we have further investigated the relationship using subscales concerning negative symptoms (Blunted affect, N1; Emotional withdrawal, N2; Poor rapport, N3; Social withdrawal, N4; Lack of spontaneity N6). The negative factor subscale was found to be more significant than using the Negative PANSS score (middle temporal gyrus, $r = -0.444$, $p = 0.010$; posterior cingulate, $r = -0.435$, $p = 0.012$; precuneus, $r = -0.505$, $p = 0.003$; superior occipital gyrus, $r = -0.500$, $p = 0.003$; Fig. 3).

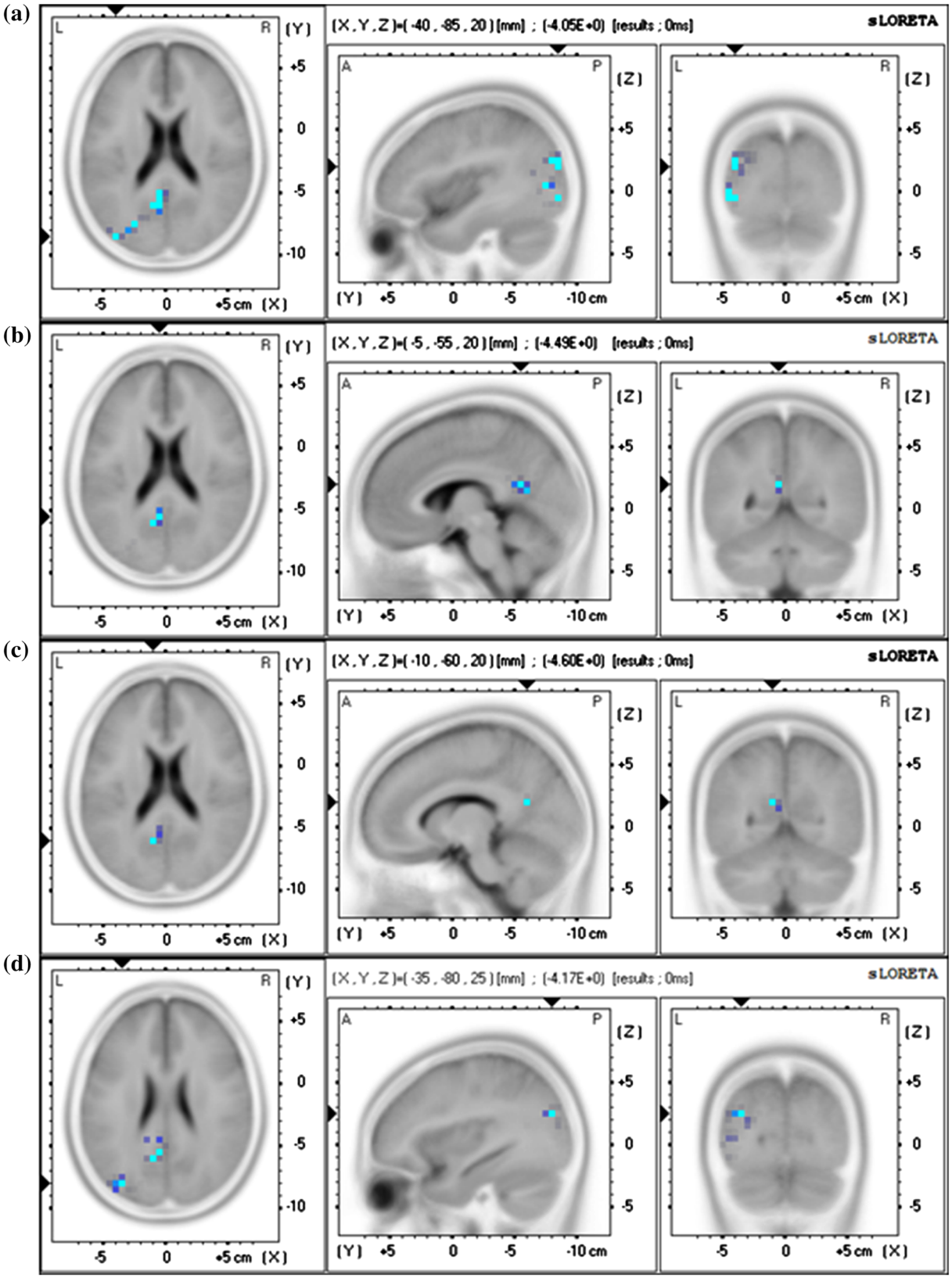

Fig. 2 Source activation differences between schizophrenia and healthy controls in selected regions: **a** middle temporal gyrus, **b** posterior cingulate, **c** precuneus, and **d** superior occipital gyrus

Table 2 Regions showing significant P300 source activation differences between groups

ROI (structure)	BA	MNI coordinates			Talairach coordinates			*t*
		X	Y	Z	X	Y	Z	
Cingulate	31	−15	−45	25	−15	−42	25	−4.03*
Inferior occipital gyrus	18	−40	−85	−5	−40	−83	0	−4.09*
Middle occipital gyrus	19	−45	−85	−5	−45	−83	0	−4.23*
Middle temporal gyrus	19	−40	−85	20	−40	−81	23	−4.05*
Posterior cingulate	31	−5	−55	20	−5	−52	21	−4.49*
Precuneus	31	−10	−60	20	−10	−57	21	−4.60**
Superior occipital gyrus	19	−35	−80	25	−35	−76	27	−4.17*

Voxels showing maximum difference in the same structure are listed. Source activation of the listed areas was significantly decreased in schizophrenia patients

** $p < 0.01$; * $p < 0.05$

Table 3 Correlation coefficients between the average source activation of each significant structure and positive, negative, general, and total PANSS scores

ROI (structure)	Positive *r*	Negative *r*	General *r*	Total *r*
Cingulate	0.175	−0.124	−0.081	−0.019
Inferior occipital gyrus	0.180	−0.127	−0.077	−0.017
Middle occipital gyrus	0.164	−0.171	−0.076	−0.035
Middle temporal gyrus	−0.067	**−0.371***	−0.144	−0.205
Posterior cingulate	−0.046	**−0.359***	−0.118	−0.182
Precuneus	−0.126	**−0.432***	−0.143	−0.239
Superior occipital gyrus	−0.116	**−0.429***	−0.135	−0.231

Significant relationships are indicated by bold text

* $p < 0.05$

Discussion

In this study, we examined differences in the P300 amplitude, latency and source activation between schizophrenia patients and healthy controls. We also investigated the correlation between the P300 current source density and the symptom severity of schizophrenia patients. We found that schizophrenia patients show reduced P300 amplitude and reduced left-hemispheric source activation compared with healthy controls. The reduced source areas of schizophrenia patients relative to healthy controls occurred in the cingulate, inferior occipital gyrus, middle occipital gyrus, middle temporal gyrus, posterior cingulate, precuneus, and superior occipital gyrus. Furthermore, schizophrenia patients also showed a negative correlation between the source activity of the middle temporal gyrus, posterior cingulate, precuneus, and superior occipital gyrus areas and negative symptom severity.

Our findings of reduced amplitude of the P300 along the midline electrodes and left temporal areas are in agreement with previous findings in schizophrenia patients (Bramon et al. 2004; Jeon and Polich 2001). Also our results showed a significant negative correlation between frontal P300 amplitude and negative symptom scores which have replicated previous results (Eikmeier et al. 1992; Pfefferbaum et al. 1989; Strik et al. 1993; Turetsky et al. 1998). The P300 amplitude is known to indicate the ability to allocate a sufficient amount of resources to a task, such as context updating process or memory storage (Ford 1999). Nonetheless, as we mentioned in the introduction, the P300 amplitude measured on the scalp surface shows inconsistent findings, such as correlation with positive scores (Egan et al. 1994; Higashima et al. 2003), or no significant correlation at all (Blackwood et al. 1987; St Clair et al. 1989).

Concerning the laterality of the findings, some studies have reported left dominant P300 reduction in schizophrenia patients (Bruder et al. 1999; Faux et al. 1993; Salisbury et al. 1998), some of the others stated symmetrical reduction of P300 on both temporal areas (Michie et al. 1990; Stefansson and Jonsdottir 1996; Umbricht et al. 1998). The current study seems to show symmetrical reduction of P300 amplitude; the P300 amplitude in both electrodes (T7, T8) showed significant reduction, however, the inter-hemispheric differences did not show statistical differences between groups in amplitude level.

Even though the laterality of the P300 amplitude was not found in the current study, we found a significant reduction in the left-hemispheric regions. The neuronal activation of the P300 and found reduced activation in left temporal regions, including the cingulate, inferior occipital gyrus, middle occipital gyrus, middle temporal gyrus, posterior cingulate, precuneus, and superior occipital gyrus. Considering that the bilateral prefrontal cortex, the temporal lobe, cingulum, the parieto-occipital junction, inferior parietal cortex, and the superior parietal cortex may be generators of the P300 (Anderer et al. 1998; Volpe et al. 2007; Wang et al. 2003; Winterer et al. 2001), the reduced P300 amplitude of the midline electrodes and

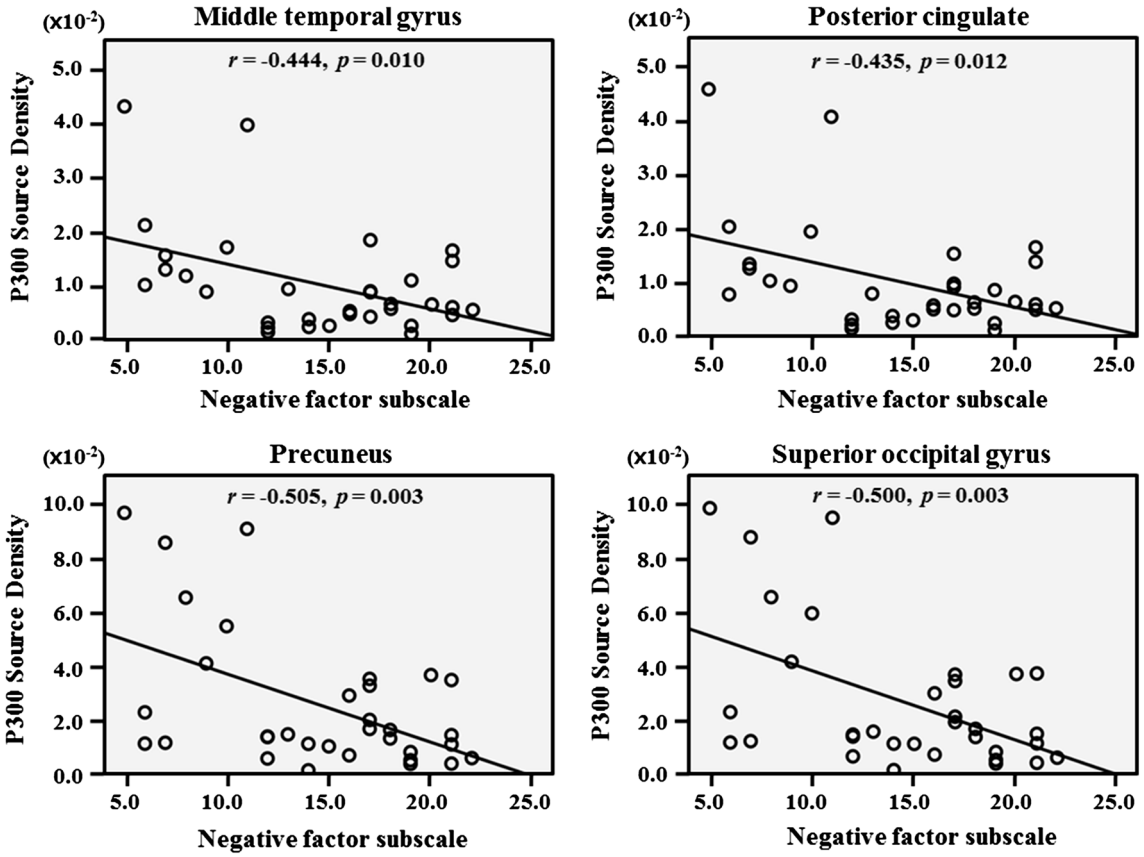

Fig. 3 Scatter plots and least *squares* regression *lines* indicating the relationship between the average P300 source density in the middle temporal gyrus, posterior cingulate, precuneus, and superior occipital gyrus and negative factor subscale

source activation in temporal-parietal regions in our study signifies a dysfunctional fronto-temporo-parietal network in schizophrenia patients (Turetsky et al. 1998; Wang et al. 2003). Our data suggests that the left hemispheric deficits of the P300 component are more sensitively reflected to P300 source activity than P300 amplitude.

Our finding corresponds with those of previous studies that have found reduced source activation in the superior temporal gyrus, middle temporal gyrus, precuneus, and temporo-parietal junction of chronic schizophrenia patients (Wang et al. 2003; Winterer et al. 2001) and also in first-episodic schizophrenia patients (Wang et al. 2010). Additionally, MRI studies have consistently reported reduced gray matter volume in the temporal lobe of schizophrenia patients MRI (Ziauddeen et al. 2011; Crow 1990; Shenton et al. 1992). Also, findings show reduced activation in the occipital lobe which are not consistent with the literature; however, some of the studies using EEG (Strik et al. 1994), or multimodal methods (Calhoun et al. 2006; Wolf et al. 2008) found similar reduced activation in the occipital cortex. Our finding of a left hemispheric deficit in schizophrenia patients converges with previous studies reporting the same deficit with auditory hallucinations (Barta et al. 1990), thought disorders (Pearlson 1997), abnormal speech recognition (Yamasue et al. 2004), diminished functional connectivity (Bleich-Cohen et al. 2012), and glutamatergic dysfunction (Deakin et al. 1989). Collectively, considering the results of other studies reporting reduced P300 amplitude, source activities, and structural anomalies of the left temporal lobe, the abnormal structure or functioning of the left temporal lobe seems to contribute to the pathophysiology of schizophrenia.

Extant studies focusing on the relationship between left temporal lobe source activation and symptom severities of schizophrenia have shown significant correlation with Brief Psychiatric Rating Scale (BPRS) total score in chronic and first-episodic schizophrenia patients (Kawasaki et al. 2007; Wang et al. 2010). In the current study, we also found a significant negative correlation between negative scores on the PANSS and areas of reduced activation, including the middle temporal gyrus. This finding converges with the results of the majority of previous studies, which also reported a negative correlation between the P300 amplitude and negative symptoms of schizophrenia (Eikmeier et al. 1992; Ford 1999; Liu et al. 2004; Pfefferbaum et al. 1989; Strik et al. 1993; Turetsky et al. 1998). In particular, accounting for the results of Higuchi et al. (2008), which found enhanced activation in the temporal areas of patients

using olanzapine that were also correlated with improvements in negative symptoms, both frontal lobe and temporal regions appear to have a close relationship with the negative symptoms of schizophrenia. Our results suggest that the temporal lobe contributes to the negative symptoms of schizophrenia, in addition to the frontal lobe contribution reported in previous researches (Weinberger 1988; Ziauddeen et al. 2011; Anderson et al. 2002; Wolkin et al. 1992).

Compared with the studies of Kawasaki et al. (2007) and Wang et al. (2010), one strength of our study is that we used more accurate source imaging. For instance, both studies used LORETA to estimate the source current density, which calculated the source in each 7 mm cubic voxel. In comparison, sLORETA is known to have less localization bias (Sekihara et al. 2005) and uses a denser head model of 5 mm cubic voxels. In addition, we considered the latency differences between the groups instead of the broad time interval used for source imaging (i.e. 200–500 ms). Thus, our results reflect more precise neural activation during the P300 response.

Although we carefully considered the experimental design and procedure, some limitations should be noted. First, the head model used for source estimation was made using a normal head model, which does not consider individual anatomical differences. Second, since it has been shown that cortical source activity is influenced by antipsychotic medication (Higuchi et al. 2008; Sumiyoshi et al. 2009; Sumiyoshi et al. 2006), our results must be interpreted considering the effect of such medications. Lastly, since the gender ratio did not perfectly match in this study, the results must be interpreted with caution since there are reports that schizophrenia might have potential gender differences in ERP findings (Josiassen et al. 1990; Turetsky et al. 1998).

In this study, we examined the left hemispheric neuronal sources that are responsible for reduced P300 amplitude in schizophrenia patients. The source activation of the corresponding areas showed a significant negative correlation with negative symptom scores. We conclude that source activity reduction in the left hemisphere, especially in the temporal area, is highly related to the pathophysiology of schizophrenia, which may be used as a biomarker reflecting the symptom severity of schizophrenia patients.

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