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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

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ABSTRACT

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

1. Introduction

Schizophrenia is a common, chronic, heterogeneous neuropsychiatric illness with a lifetime prevalence of 1–4% (Bhugra, 2005; Saha et al., 2008). The core impairments of schizophrenia include both positive and negative symptoms, with cognitive decline considered to be a central pathology of the illness. 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 (Marwick and Hall, 2008; Green et al., 2012). Although some studies have shown that negative symptoms are more closely associated with dysfunction in facial emotion discrimination (Mandal et al., 1999; Kohler et al., 2003; Hofer et al., 2009), 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 (Suslow et al., 2003) and in neuroimaging studies employing various imaging modalities (Gur et al., 2002; Kosaka et al., 2002; Takahashi et al., 2004; Johnston et al., 2005). 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 (Gur et al., 2002; Kosaka et al., 2002; Takahashi et al., 2004; Johnston et al., 2005). 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

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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) (Schneider et al., 1995; Bediou et al., 2005; Pinkham et al., 2008). 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 (Michalopoulou et al., 2008; Mendrek et al., 2011). 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 (Gur et al., 2002; Whalley et al., 2009).

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 (Streit et al., 2001; Campanella et al., 2006; Caharel et al., 2007; Turetsky et al., 2007; Lynn and Salisbury, 2008; Wynn et al., 2008a; Lee et al., 2010).

In our previous studies (Lee et al., 2010; Jung et al., 2012), we found concrete evidence of emotion perception deficits in schizophrenia patients by investigating the characteristics of ERP components and their correlations with symptom severity scores. Both the amplitude and latency of N170 showed significant differences between schizophrenia patients and normal controls, and a statistically significant correlation was found between negative symptom scores and N170 latency in female schizophrenia patients. To our knowledge, however, no previous studies have focused on the correlation between ERP source activations during facial emotion discrimination tasks and the severity of schizophrenia symptoms, which might provide important temporal and spatial information for understanding the underlying mechanisms of schizophrenia.

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

2. Methods

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 years (mean ± SD), 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 (Kay et al., 1987). 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 (e.g. major depressive disorder and anxiety disorder) 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 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.

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” (Lee et al., 2004), which consists of emotional faces rated from 1 (minimum) to 8 (maximum). In this study, six color images (3 male and 3 female) 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

Table 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
Antipsychotic drug dosage (chlorpromazine equivalents, mg)	391.30 ± 97.30
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[a]	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

[a] One missing data exists.

2200 ms, which made the length of the total experiment approximately 15 min.

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. We followed a mathematically-established procedure to remove the error effects of the EOG (Semlitsch et al., 1986). The data was divided into epochs lasting from −300 ms to 1000 ms from the stimulus onset. Only epochs answered correctly were included in the analysis. If any signal at electrodes other than M1 and M2 exceeded ±70 μV, it was regarded as a physiological artifact and the corresponding epoch was rejected from the analysis. Baseline correction was done by subtracting the mean activity prior to the stimulus onset (during the period from −300 ms to 0 ms). The signal was bandpass filtered at 1–30 Hz with a steepness of 24 dB/octave for ERP analysis (Rousselet et al., 2005; Wynn et al., 2008a).

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) of all participants (Lee et al., 2010; Jung et al., 2012) and based on previous similar studies (Streit et al., 1999; Onitsuka et al., 2006; Blau et al., 2007; Turetsky et al., 2007; Wynn et al., 2008b): 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.

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 (Pascual-Marqui, 2002; Wagner et al., 2004). sLORETA assumes that 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 (Knott et al., 2009), P100 (Saavedra et al., 2012), N170 (Babiloni et al., 2010), and P300 (Sumiyoshi et al., 2009; Bae et al., 2011).

In this study, we used the open sLORETA software to estimate the source distribution (Pascual-Marqui, 2002). 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 gray matter (Mazziotta et al., 2001; Fuchs et al., 2002). The solution space was composed of 6238 voxels with 5-mm resolution. The source image for each ERP was reconstructed for a time window of (mean ERP latency) ± (1 standard deviation) for each emotion following the same procedure described in our previous study (Jung et al., 2012). The time ranges used for each ERP source imaging are listed in Table 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/PO3/POZ/PO4/PO6/PO8, O1/OZ/O2.

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, we tested statistical significance using a non-parametric permutation test. The voxel activations were randomly shuffled 10,000 times, and the correlation was calculated for each randomization to obtain the correlation distribution of each voxel (Nichols and Holmes, 2002). 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.

3. Results

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. The accept rates of each emotion condition were 73.22 ± 20.98% (neutral), 88.17 ± 16.42% (happy), and 87.62 ± 23.15% (fear). Grand averaged ERPs from designated electrodes are shown in Fig. 1, and detailed amplitude and latency values for the four ERP components and other demographic data are presented in Table 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 [$F(2,48) = 2.994$, $p = 0.62$].

3.2. Brain regions correlated with positive symptoms

3.2.1. Neutral face stimuli

PANSS positive scores were negatively correlated with four source activation clusters of the P100 component (Fig. 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 (Fig. 2(b)) and around the medial frontal gyrus (BA10, $r = -0.657$) for the N250 component (Fig. 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.

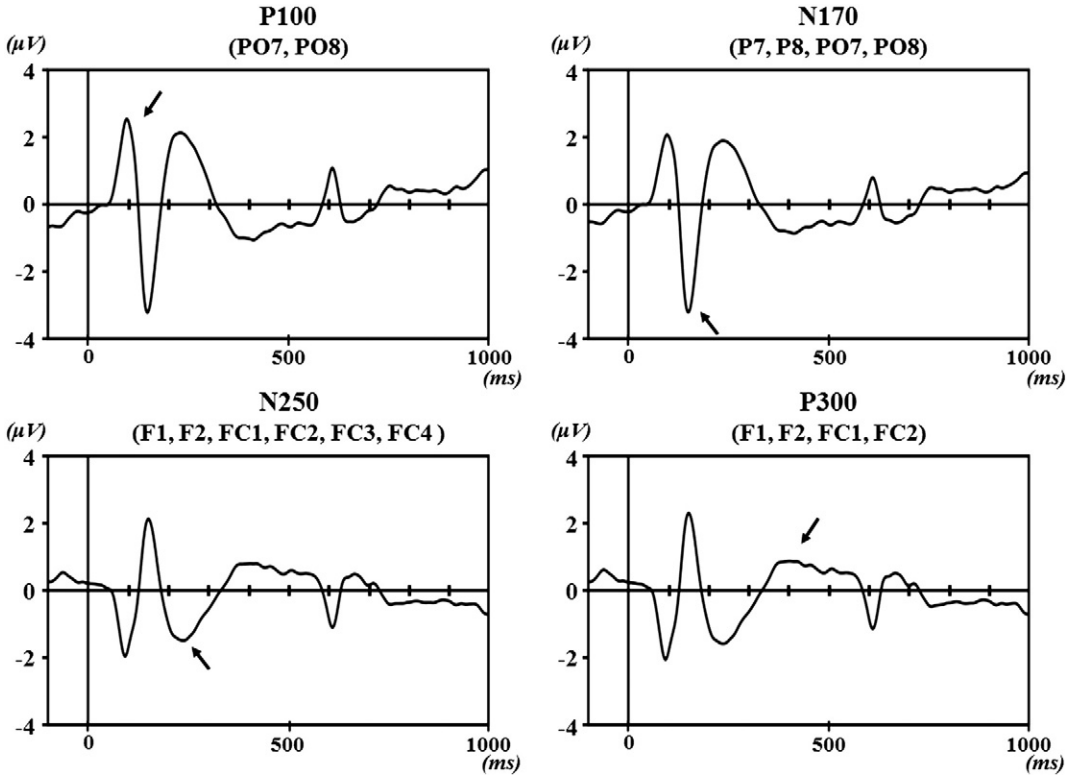

Fig. 1. A representative plot of four ERP components (P100, N170, N250, and P300) of their respective electrode site; (left top panel) grand average ERP of PO7 and PO8 electrodes representing P100 component; (right top panel) grand average ERP of P7, P8, PO7, and PO8 electrodes representing N170 component; (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.

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 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, $r = -0.685$) (Supplementary Fig. 2(a)). However, later components such as the N170, N250, or P300 did not show any source clusters significantly correlated with PANSS scores.

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 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, $r = -0.643$) (Supplementary Fig. 4(a)). N170 source activation in the middle frontal gyrus (BA 40, $r = -0.591$) showed significant negative correlation with positive symptom scores (Supplementary Fig. 4(b)). N250 and P300 source activation did not show meaningful correlations with PANSS positive scores.

3.3. Brain regions correlated with negative symptoms

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, $r = -0.693$): Supplementary Fig. 1(a)) and one cluster in the N250 component (middle frontal gyrus (BA 10, $r = -0.600$): Supplementary Fig. 1(b)). No clusters were significantly correlated with PANSS scores in the N170 or P300 components.

3.3.2. Fearful face stimuli

For fearful face stimuli, the source activity of P100 has shown that 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, $r = -0.722$) (Supplementary Fig. 3(a)). No significant correlations were found between later components, such as N170, N250, or P300, and source activities.

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, $r = -0.688$) (Supplementary Fig. 5(a)) showed strong negative correlation with PANSS negative scores, but no additional correlations were found for other regions or components.

4. Discussion

Our study investigated the relationships between symptomatic scores and voxel-based source activations of ERP components during facial emotion recognition. PANSS positive scores formed source clusters that were negatively correlated with P100 source activation in the left temporo-parietal regions regardless of emotion type: clusters showing maximum correlation were located in the inferior parietal lobule (BA 40), precentral gyrus (BA 6), precuneus (BA 31), insular (BA 13), supramarginal gyrus (BA50), middle temporal gyrus (BA 37), and sub-gyral (BA 37). In later components (N170 and N250), PANSS positive scores were significantly correlated with source clusters in the middle or medial frontal gyrus (BA 10) for neutral and

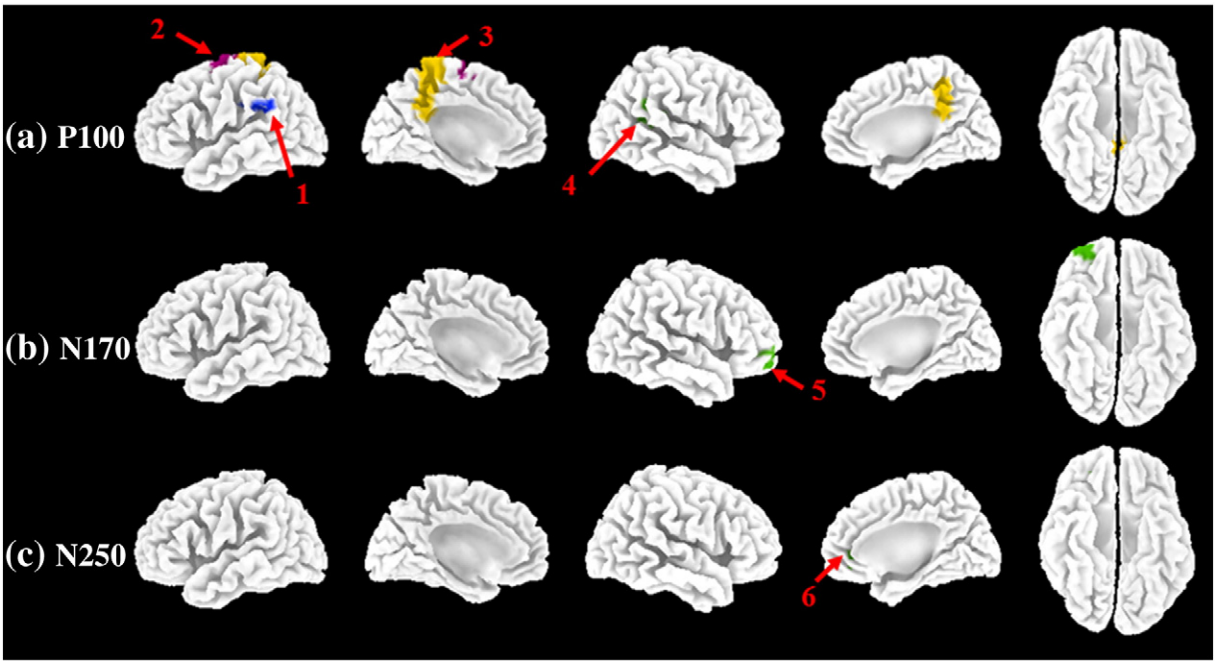

Fig. 2. Significant correlations between positive PANSS scores and source activity of (a) P100, (b) N170, and (c) N250 during neutral condition. Different colors within the same ERP indicate different clusters.

happy emotional faces. PANSS negative scores were highly correlated with clusters centering in the middle temporal gyrus (BA 37, 39), subgyral (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 (Fig. 3(a,b,c)).

The face perception model proposed by Haxby et al. (2000) 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 our study, 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. (2000). 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 through 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 (Farrow et al., 2001; Adolphs and Spezio, 2006). 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 face stimuli (Johnston et al., 2005; Michalopoulou et al., 2008) and fearful face stimuli (Michalopoulou et al., 2008). The decreased activation in the left temporal gyrus might indicate abnormal early visual perception causing failure to transmit accurate information (Foxe et al., 2001; Butler and Javitt, 2005), which can further lead to difficulties in judging the emotional information of the stimuli (Adolphs, 2009).

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, we 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 (Fusar-Poli et al., 2009; Li et al., 2010). Schizophrenia patients also show a decreased activation in the right frontal areas, especially during implicit emotion discrimination tasks (Li et al., 2010). Based on our results, it can be said that neuronal activity of the right frontal lobe declines as positive symptoms get 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 (Archer et al., 1994; Edwards et al., 2002; Bediou et al., 2005; Amminger et al., 2011). 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

Table 2
Brain regions showing significant correlation between 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
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

PANSS: Positive and Negative Syndrome Scale, *r*: correlation coefficient, BA: Brodmann area.

results with those from our previous study (Jung et al., 2012) 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 indicate 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 (Skuse et al., 2003; Li et al., 2010).

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 (Fig. 3). The left fusiform gyrus has been reported as an area which shows significantly reduced activation during facial emotion processing in schizophrenics (Quintana et al., 2003; Das et al., 2007). Also, studies have reported volume reduction of the fusiform area (Lee et al., 2002; Witthaus et al., 2009) in schizophrenia patients. Considering that the fusiform area is known to be a generator of P100 and N170 components (Herrmann et al., 2005), studies reporting decreased amplitudes of such early ERP components (Herrmann et al., 2004; Campanella et al., 2006; Lynn and Salisbury, 2008) in schizophrenia patients seem consistent with the decreasing activation trend of the fusiform areas. However, our 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 (Herrmann et al., 2004; Campanella et al., 2006; Onitsuka et al., 2006; Lynn and Salisbury, 2008; Lee et al., 2010). Given that negative emotion processing seems to be a trait pathology of schizophrenia patients (Bediou et al., 2007), abnormal N170 processing could also be a trait pathology of schizophrenia patients that is independent of symptom severity (Kayser et al., 2012) or disease stage (Kim et al., 2010; Amminger et al., 2011).

Summarizing our findings, the negative correlation between PANSS scores and source activation in early stages of face emotion processing was formed broadly in temporal regions and parietal regions. The regions showing negative correlation with positive and negative PANSS scores match with regions included in the core system (Haxby et al., 2000), which suggest 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 (Beauregard et al., 2001; Phan et al., 2002; Phillips et al., 2003; Ochsner and Gross, 2005) where the limbic system (especially amygdala) has been proposed to process emotional feature in extended system (Haxby et al., 2000). 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. Our results suggest that the areas showing correlation with the symptom scores are formed in posterior regions (temporoparietal areas as Haxby et al. (2000) proposed) in early stages and move forward to the frontal lobe in later stages, according to the areas related in face emotional processing.

In this study, we highlighted the areas which showed significant correlation between the source activation and symptom severity. Since we did not contrast the source activity difference between the schizophrenia group and normal control group, it might be questioned whether it is meaningful to investigate the correlation between source activation and symptom severity for cortical areas that did not show group differences. To address this issue, we present three different scenarios. Fig. 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

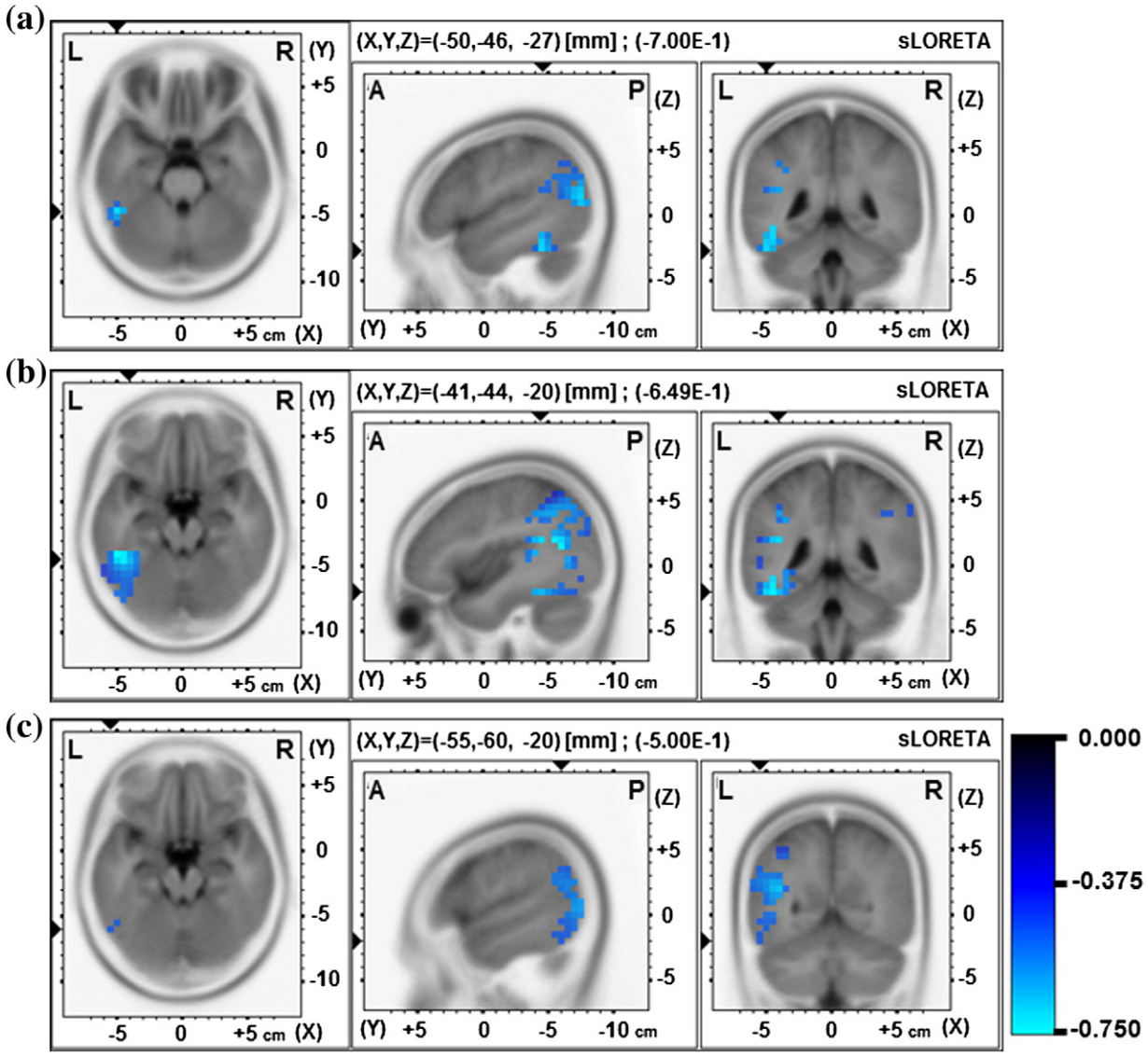

Fig. 3. Significant negative correlations between negative symptom scores and left fusiform gyrus of P100 source imaging when schizophrenia patient is viewing (a) neutral, (b) fearful, and (c) happy faces.

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 (Fig. 4(a)), we have 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 our previous finding (Jung et al., 2012), where we 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 (Fig. 4(b)), we 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 be used not only 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 our 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 symptom 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 Fig. 4(c). Our idea was that even though a 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

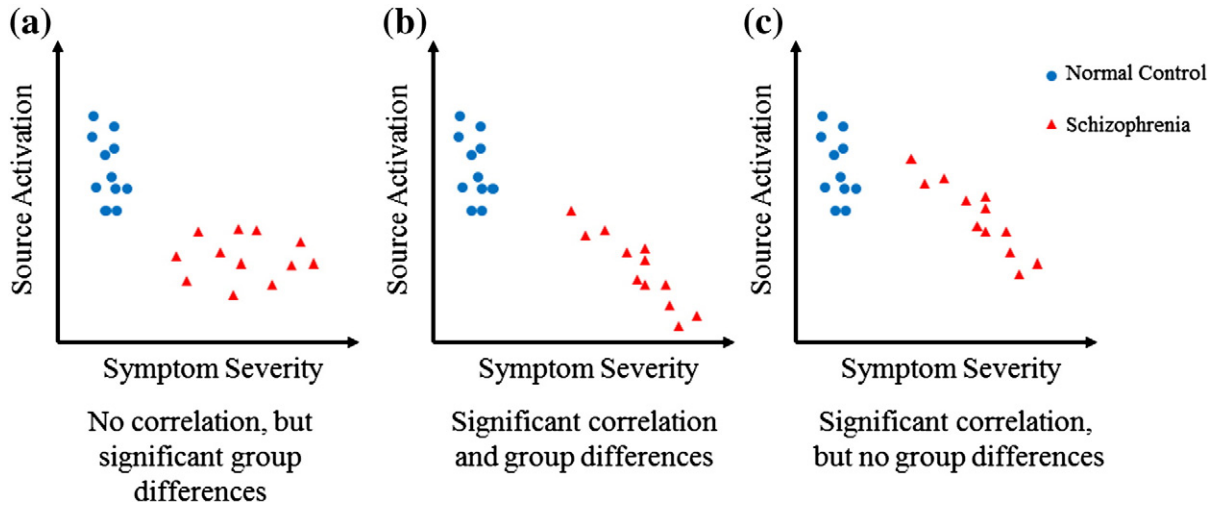

Fig. 4. Schematic illustrations on the relationship between the symptoms severity and source activation of each individual. Each dot and triangle indicates the individual measurement of normal control and schizophrenia, respectively. Three different scenarios are presented: (a) significant group difference but no correlation; (b) significant group difference and significant correlation, (c) significant correlation but no group difference.

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.

However, the current study has some limitations. First, all of our patients were on anti-psychotic medication. Even though we have 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 (Andreasen, 1982), some meaningful correlation between the positive symptoms and brain areas activation could be diluted. Second, our task does not distinguish areas that are involved only in facial affect processing, because our 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 we have asked participants to press a button when they encountered fearful or happy faces to check whether they were concentrating on the experimental task, there are possibilities that they might use a different strategy to press a button by neglecting neutral face stimuli, which might influence our 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 into 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.

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

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Contributors

Do-Won Kim designed the study and wrote the manuscript. Seung-Hwan Lee designed the study and wrote the protocol. Do-Won Kim and Han-Sung Kim produced the ERP waves and calculated the current source densities from data set. Chang-Hwan Im supervised the study process and manuscript writing. All authors contributed to and have approved the final manuscript.

Conflict of interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.10.025.

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