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Involvement of the dorsolateral prefrontal cortex and superior temporal sulcus in impaired social perception in schizophrenia

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ABSTRACT

Background: Schizophrenia is a mental disorder characterized by impairments in diverse thinking and emotional responses, which are related to social perception dysfunction. This fMRI study was designed to investigate a neurobiological basis of social perception deficits of patients with schizophrenia in various social situations of daily life and their relationship with clinical symptoms and social dysfunction.
Methods: Seventeen patients and 19 controls underwent functional magnetic resonance imaging, during which participants performed a virtual social perception task, containing an avatar's speech with positive, negative or neutral emotion in a virtual reality space. Participants were asked to determine whether or not the avatar's speech was appropriate to each situation.
Results: The significant group × appropriateness interaction was seen in the left dorsolateral prefrontal cortex (DLPFC), resulting from lower activity in patients in the inappropriate condition, and left DLPFC activity was negatively correlated with the severity of negative symptoms and positively correlated with the level of social functioning. The significant appropriateness × emotion interaction observed in the left superior temporal sulcus (STS) was present in controls, but absent in patients, resulting from the existence and absence of a difference between the inappropriate positive and negative conditions, respectively.
Conclusions: These findings indicate that dysfunction of the DLPFC-STS network may underlie patients' abnormal social perception in various social situations of daily life. Abnormal functioning of this network may contribute to increases of negative symptoms and decreases of social functioning.

1. Introduction

Schizophrenia is a mental disorder characterized by impairment in thinking and emotional responses. Clinical symptoms including positive, negative and disorganized symptoms as well as various cognitive deficits lead to social dysfunction, such as ineffective social interaction, poor social skills and the inability to remain employed (Boden et al., 2009; Weinberg et al., 2009). Social dysfunction in schizophrenia may be lifelong and predictive of longer hospitalization (Olfson et al., 2011). In particular, deficits in social cognition including social perception have been linked to poor functional outcome in schizophrenia (Mancuso et al., 2011). Social perception involves the ability to identify social roles, rules and context and to make inferences about complex or ambiguous social situations (Green et al., 2008; Penn et al., 2002). Social perception is the first step in social cognition, and it is further involved in processes of organizing behavioral responses directly or indirectly (Norman, 2002), suggesting that abnormal behaviors observed in schizophrenia may be initiated by impaired social perception.

To understand social perception, previous researchers have used various stimuli. Human faces are frequently used stimuli because they are the basic component of social perception and provide diverse information for social communication (Kanwisher et al., 1997; Marwick and Hall, 2008). Patients with schizophrenia have deficits in both face and facial affect recognition with less accurate and slower responses than control participants (Green and Phillips, 2004; Hooker and Park, 2002),

Abbreviations: fMRI, functional magnetic resonance imaging; DLPFC, dorsolateral prefrontal cortex; STS, superior temporal sulcus; DMPFC, dorsomedial prefrontal cortex; TPJ, temporo-parietal junction; DSM-IV-TR, Diagnostic and Statistical Manual, 4th Edition, Test-Revised; RPM, Raven's progressive matrices; SAS, Social Anhedonia Scale; PANSS, Positive and Negative Syndrome Scale; SC-LFS, Strauss–Carpenter Level of Functioning Scale; TE, echo time; TR, repetition time; BOLD, blood oxygen level dependent.

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and they have functional abnormalities in the fusiform gyrus during the facial information processing (Quintana et al., 2003). Another useful method is biological motion. Patients with schizophrenia have impaired gaze discrimination with longer reaction time and hyper-perception (Franck et al., 2002; Tso et al., 2012) and often show difficulties in discriminating biological motion due to abnormalities in the superior temporal sulcus (STS) and inferior parietal lobe (Kim et al., 2011b; Spencer et al., 2013; Thakkar et al., 2014). In particular, the STS is involved in understanding other people's actions and intentions (Pelphrey et al., 2004) and has been considered to be one of the core regions for the interaction of social perception and emotional processing (Kramer et al., 2010; Norris et al., 2004).

While perceiving others' behaviors in social situations, patients with schizophrenia show dysfunction in the intention network, including the dorsomedial prefrontal cortex (DMPFC) and temporo-parietal junction (TPJ) (Bara et al., 2011; Walter et al., 2009). In addition, patients with schizophrenia have shown aberrant responses in the occipital and temporal regions while processing situational pictures as social cues (Bjorkquist and Herbener, 2013), marked decreases in dorsolateral prefrontal cortex (DLPFC) activation during audiovisual integration (Szycik et al., 2009), and ventral premotor dysfunction during video-watching (Ebisch et al., 2013; Park et al., 2009). Particularly, given that the DLPFC plays an important role in cognitive control in social situations (Weissman et al., 2008), DLPFC hypofunction may be a leading factor regarding dysfunctional social perception in patients with schizophrenia.

Despite the accumulation of vast amount of knowledge, social perception remains an actively studied area because of its complexity and diversity. More complex social situations have been increasingly needed to discover how the brain works with a plethora of stimuli. Since the 1990s, several behavioral studies have used social situations as a stimulus. The examples are the social feature recognition test (Corrigan et al., 1996) and the social cue recognition videotaped test (Corrigan and Nelson, 1998), demonstrating that patients with schizophrenia are less accurate in situational feature recognition or social cue recognition than controls. Recently, it has been reported that these deficits in social perception may be related to abnormal eye gaze in interactive social situations (Choi et al., 2010). However, complex social situations have never been used in a functional magnetic resonance imaging (fMRI) study. It therefore remains unclear how the brain mechanism of deficits in social perception underlies the experiences of patients with schizophrenia in their daily lives. This unclear mechanism can be addressed by an fMRI study using a virtual reality task reflecting social perception in daily lives, as virtual reality provides an immersive environment simulating complex social situations (Choi et al., 2010; Han et al., 2009). In fact, virtual reality tasks using avatars have been used to assess patients' behavioral and emotional characteristics objectively and to train patients to cope effectively with various social situations (Kim et al., 2008).

This fMRI study was designed to investigate a neurobiological basis of social perception deficits in schizophrenia using social situations that patients would face in their daily lives. For these purposes, we developed a virtual social perception task in which participants were asked to determine the appropriateness of various ways of speech in different social situations. In this study using dynamic stimuli and functional outcome measures, we hypothesized that patients with schizophrenia would show altered activation in various social perception-related regions including the prefrontal cortex and STS, and that the degree of altered activation would be correlated with the clinical and social functioning scale scores.

2. Methods

2.1. Participants and clinical measurements

Seventeen patients with schizophrenia and 19 healthy control subjects participated in this study. All patients met the DSM-IV-TR criteria for schizophrenia without other comorbid psychiatric disorders and were taking antipsychotics with a mean chlorpromazine-equivalent dosage of 503.3 ± 226.4 mg. The Structural Clinical Interview for DSM-IV (First et al., 1996) was used for the diagnosis of schizophrenia in patients, who were recruited in the psychiatric outpatient clinic, and the exclusion of any psychiatric disorders in controls, who were recruited by poster advertisements. Any subjects with a past or present history of medical or neurological illness or with left-handedness were excluded. After a complete description of this study was presented, all subjects gave written informed consent to the protocols, which were approved by the local institutional review board.

Participants' general intellectual ability was measured by the Raven's progressive matrices (RPM) (Raven, 1990), and the ability to experience pleasure from social stimuli was measured by the Social Anhedonia Scale (SAS) (Chapman et al., 1976). In addition, the clinical status of each patient was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for the severity of schizophrenic symptoms and the Strauss–Carpenter Level of Functioning Scale (SC-LFS) (Strauss and Carpenter, 1972) for various domains of social functioning such as social contacts, useful work and fullness of life.

2.2. Experimental design

Participants performed the virtual social perception task during fMRI scanning. As shown in Fig. 1, social situations were created in a virtual reality space in which an avatar made conversation with someone. Participants were asked to determine whether or not the avatar's speech was appropriate to the situation by pressing a corresponding button. The task consisted of 126 experimental trials; there were 21 real-life situations that each included six different conditions. The avatar's speech was either well or poorly matched to the situation, in 63 appropriate and 63 inappropriate conditions, respectively, and was emotionally positive, negative or neutral, in 42 positive, 42 negative, and 42 neutral conditions, respectively. The trials were presented randomly in an event-related design. Each trial consisted of listening to the avatar's speech for 3 s, followed by 1 s of silence during which participants were expected to respond, and seeing a screen with a cross on a black background for 1 s. Null events were added in varying durations of 0.625 to 7.5 s, and the total session time was approximately 14 min.

2.3. MRI acquisition and analysis

The fMRI experiment was conducted on a research-dedicated, whole-body, 1.5 T MRI system (Sigma Eclipse; GE Medical Systems, Milwaukee, WI, USA) using a standard quadrature, bird-cage head coil. Functional images were obtained using an echo planar imaging sequence (matrix size = 64 × 64, number of slices = 30, slice thickness = 5 mm, spatial resolution = 3.75 × 3.75 × 5 mm^3, TE = 22 ms, TR = 2.5 s, field of view = 240 mm, flip angle = 90°). High-resolution anatomical images were obtained using a gradient echo sequence (matrix size = 256 × 256, number of slices = 115, slice thickness = 1.5 mm, spatial resolution = 0.94 × 0.94 × 1.5 mm^3, TE = 1.8 ms, TR = 8.5 ms, field of view = 240 mm, flip angle = 12°) after the functional scans.

Images were preprocessed using SPM8 (Welcome Institute of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm), and bad slices were detected and discarded using ArtRepair software (Mazaika et al., 2005). After correcting for differences in slice acquisition time and head motion, the functional images were co-registered to the T1-weighted image. The co-registered images were spatially normalized using the transformation functions, which were obtained by normalizing the T1-weighted image to the standard T1 template using nonlinear transformation. These normalized images were smoothed by a Gaussian kernel of 8 mm full-width-half-maximum. A high-pass filter (128 s) was applied on the image time series to eliminate low frequency signals.

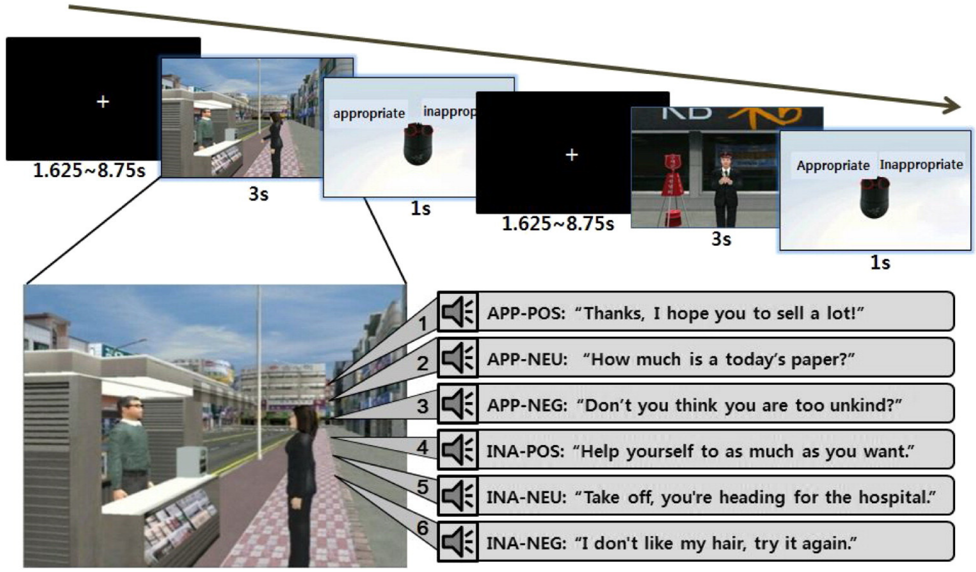

Fig. 1. An example of the experimental stimuli. In a scene of "at the kiosk," a woman says something to a storekeeper for 3 s. As shown on the right side, there are six different trials per scene. In the appropriate positive condition (APP-POS), her statement ("Thanks. I hope you to sell a lot!") is positive and well matched with the situation. On the other hand, in the inappropriate positive condition (INA-POS), she says "Help yourself to as much as you want," and this statement is positive, but unmatched with the situation. Four other trials included the appropriate negative (APP-NEG), inappropriate negative (INA-NEG), appropriate neutral (APP-NEU), and inappropriate neutral (INA-NEU) conditions. Twenty other scenes with six conditions were used to express diverse social situations.

Functional data were analyzed using a general linear model. To exclude activities related to the processing of neutral emotion, individual contrast maps were generated by contrasting positive or negative emotional events with neutral ones at the first-level analysis. The resulting set of contrast images were then entered into a second-level analysis using a flexible factorial model. The activation maps for the main effects and interactions were analyzed by a 2 (group: patients and controls) × 2 (appropriateness: appropriate and inappropriate) × 2 (emotion; positive and negative) flexible factorial model. In addition, the appropriateness × emotion interaction was analyzed in each group. For the comparison between trial types, activation was determined by uncorrected p values of less than 0.001 with a cluster extent threshold of 20 voxels and by corrected p value of less than 0.05 after the false discovery rate across the entire brain.

Finally, to ascertain the clusters related to task performance, a region of interest correlation analysis was performed. Based on our hypothesis that patients with schizophrenia would show altered activation in the prefrontal cortex and STS during social perception, we selected two clusters in the DLPFC identified by the result of the group × appropriateness interaction and the STS identified by the appropriateness × emotion interaction under each group. The % BOLD signal changes of the clusters were obtained using MarsBaR version 0.41 (http://marsbar.sourceforge.net/) and then non-parametric correlation analyses between cluster activities and clinical scales in each group were done at a significance level of p-values less than 0.05. In these correlation analyses, the duration of illness and chlorpromazine equivalent dose were used as covariates for the patient group.

2.4. Statistical analysis of the behavioral data

Demographic and clinical characteristics were compared between groups with independent-sample *t*-tests and chi-square tests. Accuracy and reaction time were analyzed using linear mixed model. The main and interaction effects of group, appropriateness, and emotion were included as fixed effects. In the post hoc analysis the least square means of 3 emotions were estimated by the MIXED procedure at appropriate or inappropriate.

3. Results

3.1. Participants' characteristics and behavioral performances

As shown in Table 1, patients and controls did not significantly differ in age, sex and educational level. However, patients showed lower general intellectual ability ($p < 0.05$) and higher social anhedonia scores ($p < 0.05$) than controls.

Accuracy and reaction time are shown in Table 2. The main effect of accuracy was found for group ($F_{1,203} = 27.37$, $p < 0.001$), but not for appropriateness and emotion. Post hoc analyses revealed that patients answered less correctly than controls ($p < 0.001$). The interaction effect was found for the appropriateness × emotion ($F_{2,203} = 3.26$, $p < .05$). The statistic power for these positive results was 0.9 and 0.7 ($\alpha = 0.05$) with >95% confidence interval in the group effect and appropriateness × emotion interaction effect of accuracy, respectively. The mean differences between emotions for appropriate speech were 0.48 (positive and neutral), 13.84 (positive and negative), and 13.36 (negative and neutral). For inappropriate speech, however, the mean differences between emotions were −0.30, −6.76, and −6.46, respectively. No significant interaction effect was found for group × appropriateness or group × emotion, and group × appropriateness × emotion. For reaction time, there were no significant main or interaction effects.

3.2. Imaging findings

Imaging results of the main effects for group, appropriateness, and emotion are provided in Supplementary Table 1. On an analysis of functional neuroimaging, data of three patients and one control were excluded due to a quality problem as bad slices were discarded using ArtRepair software. The main effect of group was found in a variety of the neocortical and subcortical regions, including the various prefrontal gyri, various temporal gyri, STS, supramarginal and angular gyrus, precuneus and cuneus, globus pallidus, and cerebellum. The main effect of appropriateness was found in the relatively restricted regions, including the inferior frontal gyrus, middle temporal gyrus and precuneus. The main effect of emotion was also restricted to the precentral gyrus, middle temporal gyrus, caudate, and cerebellum.

Table 1
Demographic information about patients with schizophrenia and controls.

	Patients ($n = 17$)	Controls ($n = 19$)	χ^2/t	P
Age (years)	31.0 ± 6.1	28.21 ± 4.2	−1.609	0.117
Sex (male/female)	11/6	12/7	0.009	0.923
Education level (years)	13.8 ± 1.6	14.6 ± 3.0	1.006	0.321
Intelligence quotient	98.7 ± 15	109.1 ± 12	2.270	0.030
Social anhedonia scale (0–40)	13.4 ± 6.2	8.8 ± 3.9	−2.581	0.016
PANSS				
Positive	17.1 ± 3.7			
Negative	17.3 ± 4.5			
General	32.6 ± 8.4			
SC–LFS (0–36)	20.8 ± 5.5			
Duration of illness	10.9 ± 6.9			
Chlorpromazine equivalent dosage of antipsychotics (mg)*	503.3 ± 226.4			

PANSS, Positive and Negative Syndrome Scale; SC–LFS, Strauss–Carpenter Level of Functioning Scale.
* The medicine was amisulpride (2), aripiprazole (3), clozapine (3), haloperidol (1), olanzapine (3), paliperidone (1), quetiapine (1), and risperidone (4).

As presented in Table 3, the group × appropriateness interaction was exhibited in the left DLPFC, right precentral gyrus and left supramarginal gyrus. In the post hoc test for the *a priori* regions, as shown in Fig. 2, left DLPFC activity in the appropriate condition was not significantly different between the two groups, whereas left DLPFC activity in the inappropriate condition was significantly lower in patients than in controls ($t = 2.6$, $p < 0.05$). Correlation analysis revealed that left DLPFC activity in the inappropriate condition was negatively correlated with the PANSS negative scores ($r = -0.650$, $p < 0.05$) and positively correlated with the SC-LFS scores ($r = 0.691$, $p < 0.05$), but not with any other scale scores. A group × emotion interaction was not found in any region.

An appropriateness × emotion interaction was observed in various brain regions including the right DMPFC, left DLPFC, left STS, right superior temporal gyrus, several occipital regions, and right cerebellum. An appropriateness × emotion interaction in each group indicated that different regions were involved. In particular, as shown in Fig. 3, an appropriateness × emotion interaction in the left STS was found in controls, but not in patients. Post hoc analysis revealed that left STS activity in patients was significantly higher in the appropriate negative condition than in the appropriate positive condition ($t = -3.1$, $p < 0.01$), but not significantly different between the inappropriate negative and inappropriate positive conditions. Left STS activity in controls was also significantly higher in the appropriate negative condition than in the appropriate positive condition ($t = -2.1$, $p < 0.05$), but significantly lower in the inappropriate negative condition than in the inappropriate positive condition ($t = 3.9$, $p < 0.01$).

4. Discussion

In the present study, we investigated the brain mechanisms involved in perceiving appropriateness and emotion in social situations. Using the MR-compatible virtual reality system, we presented diverse social situations to participants. Previously, our research group demonstrated that such a virtual reality system was useful in assessing social perception of patients with schizophrenia as well as normal subjects (Kim et al., 2007). In the diverse social situations of daily lives, participants differently responded according to the conditions. Particularly, low accuracy in the appropriate negative condition suggests that both patients and controls might consider negative events to be unfamiliar and uncomfortable because bad news and unlucky events happen less often than ordinary ones and occur suddenly, and thus both groups might perceive situations with neutral or positive contents as being relatively more comfortable and natural. In contrast, high accuracy for inappropriate negative speech suggests that such a condition seems to make both groups feel awkward.

Table 2
The accuracy and reaction time for the virtual social perception task (mean ± standard deviation).

	Patients (n = 17)		Controls (n = 19)	
	Appropriate	Inappropriate	Appropriate	Inappropriate
Accuracy (%)				
Positive	71.43 ± 30.91	63.31 ± 37.86	89.72 ± 10.07	82.21 ± 32.06
Neutral	69.75 ± 28.02	61.06 ± 33.77	90.48 ± 9.12	84.96 ± 30.21
Negative	58.82 ± 28.07	67.79 ± 31.25	74.44 ± 28.58	91.23 ± 16.21
Reaction time (ms)				
Positive	722.88 ± 291.65	704.26 ± 244.07	672.25 ± 324.75	691.77 ± 330.59
Neutral	676.69 ± 280.83	722.01 ± 235.16	685.49 ± 336.77	663.87 ± 332.05
Negative	784.25 ± 239.88	705.85 ± 286.88	727.74 ± 336.22	655.22 ± 330.45

The most characteristic group difference while experiencing the social situations was found in the left DLPFC. Significantly decreased activity in the left DLPFC was found during the inappropriate condition in patients compared to controls. Previous studies have recognized that the DLPFC plays an important role in various cognitive processes (Liu et al., 2004; MacDonald et al., 2000). Typically, this region is engaged in cognitive flexibility when people face new and unexpected situations to restructure knowledge in multiple ways (Kim et al., 2011a; Gu et al., 2008) and in abstract thinking when regarding situations in general and symbolic modes (Harrow et al., 1974). The role of the DLPFC in cognitive control has been shown in social situations of inconsistent conditions (Weissman et al., 2008). Therefore, our finding of DLPFC hypoactivity in patients suggests that impairment in perceiving socially unusual situations may stem from dysfunction in cognitive control. This view is supported by previous findings that patients with schizophrenia expressed cognitive rigidity in real life (Han et al., 2012) and abnormal abstract thinking, which was associated with impaired DLPFC function (Berman et al., 1988).

In addition, our study showed that DLPFC activity in patients had a negative correlation with the severity of negative symptoms and a positive correlation with the level of social functioning. Decreased metabolic activity in the DLPFC has been considered to be a core feature related to the predominance of negative symptoms in schizophrenia (Potkin et al., 2002; Wolkin et al., 1992). Cortical volumetric abnormalities in the DLPFC and disruption of the white matter tracts connecting to the DLPFC have also been regarded as a major feature of deficit schizophrenia, which is characterized by the presence of primary and enduring negative symptoms (Fischer et al., 2012; Voineskos et al., 2013). Deficit schizophrenia has been associated with greater impairment in cognitive ability and social cognition (Cohen et al., 2007; Csukly et al., 2014; Volpe et al., 2012). In particular, negative symptoms include an inclination toward stereotyped thinking (Piskulic and Addington, 2011) and are closely related to social functioning (Hunter and Barry, 2012). Therefore, DLPFC hypoactivity-related cognitive inflexibility may lead to social dysfunction in patients with schizophrenia (Carrion et al., 2011; Hunter and Barry, 2012). Taken together, DLPFC dysfunction in schizophrenia

Table 3
Brain regions showing the significant interaction effect of group, appropriateness, and emotion.

	Regions (BA)	Voxels	MNI Coordinates			*F*
			x	*y*	*z*	
Group × Appropriateness						
	Dorsolateral prefrontal cortex (8)*	25	−22	44	36	15.2
	Precentral gyrus (6)	80	50	−4	40	22.8
	Supramarginal gyrus (40)	23	−58	−40	36	14.4
Group × Emotion						
	None					
Appropriateness × Emotion						
	Dorsomedial prefrontal cortex (8)*	79	8	32	48	17.1
		58	0	56	30	16.5
	Dorsolateral prefrontal cortex (9)*	22	−46	8	26	16.5
		39	−56	20	28	14.5
	Superior temporal sulcus (22)*	107	−56	−18	−2	20.0
	Superior temporal gyrus (22)	21	48	−50	2	14.2
	Inferior occipital gyrus (17)*	418	−10	−98	−6	29.7
	Fusiform gyrus (37)*	651	−52	−64	−18	22.4
	Cuneus (17)	30	28	−78	10	17.4
	Cerebellum*	489	36	−66	−22	19.5
Appropriateness × Emotion in patients						
	Cerebellum	60	−44	−50	−22	27.0
Appropriateness × Emotion in controls						
	Superior temporal sulcus (22)*	110	−56	−18	−4	30.2
	Lingual gyrus (18)	242	−12	−90	−8	23.6
	Cuneus (17)	61	28	−78	10	20.0
	Cerebellum	33	10	−82	−32	17.4

Presented regions had a threshold of uncorrected $p < 0.001$ and more than 20 voxels. *Regions which survived after false discovery rate corrected $p < 0.05$.

may reflect a deficit in cognitive control during social perception, which contributes to negative symptoms and decreased social functioning.

Another region showing a noteworthy feature was the left STS, in which the interaction effect between appropriateness and emotion was present in controls, but absent in patients. In the appropriate condition, both groups showed significantly higher left STS activity in response to negative speech than to positive speech. This feature of activity may be connected to the behavioral observation that accuracy for appropriate speech was significantly lower in negative speech than in positive speech. The STS is activated by passive viewing of biological motion (Puce et al., 1998), and is further engaged in analyzing the intentions of observed biological motions (Lahnakoski et al., 2012; Pelphrey et al., 2004). STS activity tends to be increased in unexpected compared to expected situations (Ahmed and Vander Wyk, 2013). In the appropriate situations of our experiment, positive speech appeared to be experienced as typical, in contrast to the perception of negative speech as

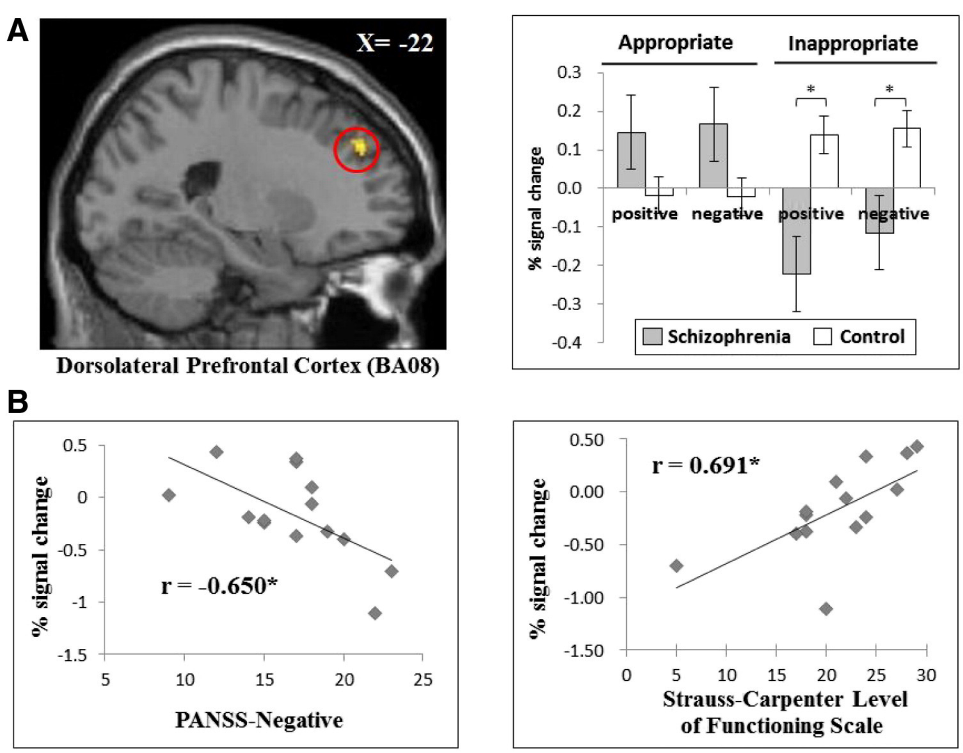

Fig. 2. (A) Dorsolateral prefrontal cortex (DLPFC) activity showing the interaction of group × appropriateness and the comparison of DLPFC activity in each condition between patients and controls, and (B) correlations of DLPFC activity in the inappropriate condition with the severity of negative symptoms and the level of social functioning (*$p < .05$).

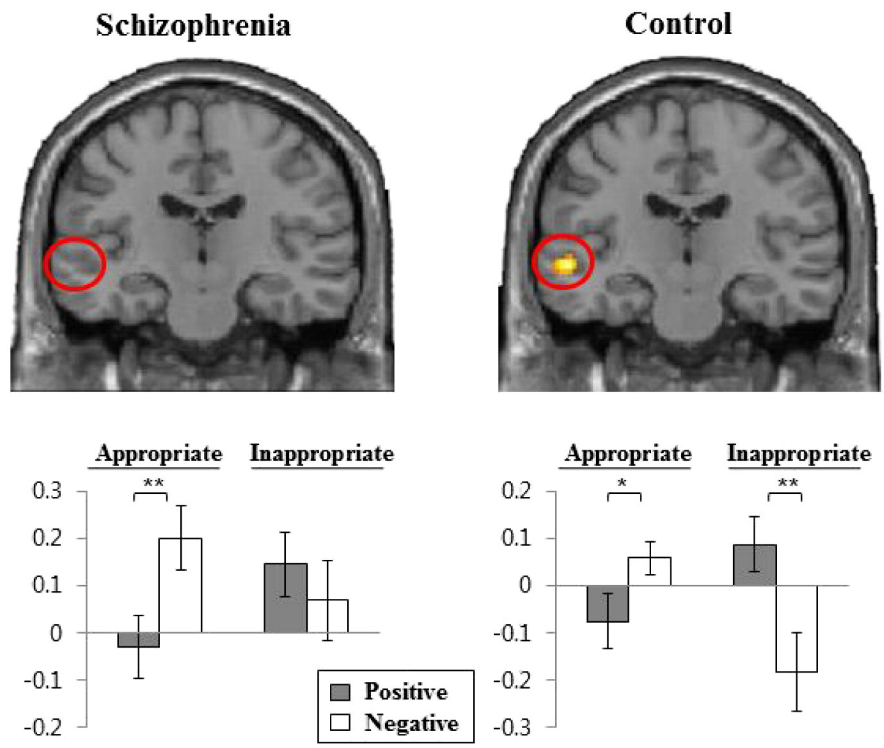

Fig. 3. Left superior temporal sulcus activity showing the interaction of appropriateness and emotion that exists only in controls, and the comparison of signal changes in the superior temporal sulcus based on conditions in each group (* $p < .05$, ** $p < .01$).

being a relatively uncommon occurrence. This situational unusualness of appropriate but negative speech might have led to the discrepancy in response accuracy and STS activity, with both patients and controls acting in a similar fashion under this appropriate condition. In the inappropriate condition, however, controls demonstrated significantly higher STS activity in response to positive speech than to negative speech, whereas patients showed no difference between the two conditions. This reverse finding in controls led to an interaction effect between appropriateness and emotion in the left STS, which is consistent with the previous notion that the STS plays a key role in the interactive processing of social and emotional information (Norris et al., 2004). Given that STS activity is sensitive to the congruency between observed action and emotion (Wyk et al., 2009), the different STS features between the appropriate and inappropriate conditions in controls may be additional evidence for the role of this region in analyzing the intention of others. Furthermore, the absence of this conditional difference in patients seems consistent with their difficulties in discriminating biological motion (Kim et al., 2011b; Spencer et al., 2013; Thakkar et al., 2014). Consistently, our research group has recently reported that patients with schizophrenia did not show normal STS hyperactivity in a socially interactive situation that was designed to simulate social rejection (Lee et al., 2014), supporting the presence of patients' deficits in the perception of social acts.

In contrast to our expectations, MPFC activity was not significantly different between patients and controls in our study. The MPFC has been regarded as a representative brain region in the theory of mind network together with the STS (Bosia et al., 2012). In particular, the MPFC has been implicated in mentalization, such as making inferences about others' intentions and mental states, and attributions of emotions to self and others (Frith and Frith, 1999; Ochsner et al., 2004). The absence of a positive finding in this region could be attributed to a characteristic of our task for measuring social perception in daily life that might recruit cognitive control or cognitive flexibility rather than mentalization. In other words, our social perception task may provoke activation of the DLPFC-STS network rather than the MPFC-STS network. Dysfunction of the DLPFC-STS network is striking in the salient stimuli such as inappropriate situations, though there is no direct evidence of connectional dysfunction between these two regions in our findings. However, since abnormal connectivity between the DLPFC and STS is important in individuals with autism spectrum disorder (Wicker et al., 2008), it is possible that impaired connectivity between the two regions may underlie social perception dysfunction in patients with schizophrenia. This interpretation is supported by another report on schizophrenia, which demonstrated the inferior frontal gyrus-STS disconnection during the processing of metaphoric gestures (Straube et al., 2014).

There are some limitations in our study. The generalizability of our results may be limited due to the relatively small sample size. Because all patients in our study were medicated and we did not evaluate the side effects of the antipsychotic medications, the effects of the antipsychotics could not be excluded from the results. Further studies including drug-naïve patients need to be done to avoid the confounding effects of medication. Another limitation is that social functioning was assessed only by the SC-LFS. Many social functioning scales, which greatly vary in terms of the number and types of domains, have been used for schizophrenia studies (Burns and Patrick, 2007). The SC-LFS includes domains of interpersonal and occupational function but has a weakness in personal domains. In addition, although cognitive control or flexibility was considered to be an important factor in social perception, executive functions were not evaluated. Given that there was a significant difference in general intelligence between patients and controls, executive functions would be different between the two groups and this difference could affect the performances.

In summary, we investigated the neural basis of social perception dysfunction in daily life of patients with schizophrenia and its relationship with their clinical symptoms and social functioning. The results provide useful information on the important role of the DLPFC in social perception and its relationship with negative symptoms and social dysfunction in patients with schizophrenia. The findings also affirm the key role of abnormal STS activity in social perception dysfunction in schizophrenia. These results suggest the possibility that dysfunction of the DLPFC-STS network may underlie patients' abnormal social perception in various social situations of daily life.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2014.12.006.

Contributors

SHC and JJK designed the study. SHC, HL and YSS collected the original imaging data. JES, YSS and DPJ managed and analyzed the imaging data. JES and JJK wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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