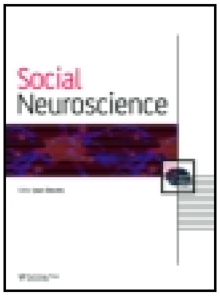

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Aberrant neural responses to social rejection in patients with schizophrenia

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Patients with schizophrenia often show abnormal social interactions, which may explain their social exclusion behaviors. This study aimed to elucidate patients' brain responses to social rejection in an interactive situation. Fifteen patients with schizophrenia and 16 healthy controls participated in the functional magnetic resonance imaging experiment with the virtual handshake task, in which socially interacting contents such as acceptance and refusal of handshaking were implemented. Responses to the refusal versus acceptance conditions were evaluated and compared between the two groups. Controls revealed higher activity in the refusal condition compared to the acceptance condition in the right superior temporal sulcus, whereas patients showed higher activity in the prefrontal regions, including the frontopolar cortex. In patients, contrast activities of the right superior temporal sulcus were inversely correlated with the severity of schizophrenic symptoms, whereas contrast activities of the left frontopolar cortex were positively correlated with the current anxiety scores. The superior temporal sulcus hypoactivity and frontopolar hyperactivity of patients with schizophrenia in social rejection situations may suggest the presence of mentalizing deficits in negative social situations and inefficient processes of socially aberrant stimuli, respectively. These abnormalities may be one of the neural bases of distorted or paranoid beliefs in schizophrenia.

Keywords: Social rejection; Social interaction; Schizophrenia; Superior temporal sulcus; Frontopolar cortex.

Patients with schizophrenia often have difficulties in returning to normal social life, even after improvements in psychotic symptoms, because they tend to have deficits in social cognition and skills (Pijnenborg et al., 2009). In particular, a deficit in the mentalizing ability or the theory of mind (ToM) explaining and predicting others' behaviors through attributing mental states is closely connected to the poor quality of life in patients with schizophrenia (Derks et al., 2012). They often show abnormal social interactions, mainly due to deficits in nonverbal communication and negative symptoms, which may be a contributing factor for their social exclusion (Kupper, Ramseyer, Hoffmann, Kalbermatten,

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& Tschacher, 2010; Lavelle, Healey, & McCabe, 2013).

Social rejection is a painful threat for patients with schizophrenia (Perry, Henry, Sethi, & Grisham, 2011), and can become a risk factor for suicide (Pompili et al., 2007). Social rejection occurs when an individual is deliberately excluded from a social relationship or social interaction (Eisenberger, Lieberman, & Williams, 2003). A person can be rejected on an individual basis or by an entire group. Furthermore, rejection can be either active, by bullying, teasing, or ridiculing, or passive, by ignoring a person, or giving the "silent treatment". Neural correlates of social rejection have been identified using a functional magnetic resonance imaging (fMRI) study with an interactive design, such as the "Cyberball" game, where participants play a ball-passing game with two other people, often presented as animated cartoon figures (Eisenberger et al., 2003). This paradigm revealed activations in the medial prefrontal cortex with the social exclusion conditions, probably due to self-evaluation processes and inferences of other's thoughts (Sebastian et al., 2011).

In the last decade, previous fMRI studies have shown that neural correlates of the ToM include the medial prefrontal cortex, orbital frontal cortex, posterior part of the superior temporal sulcus (pSTS), temporoparietal junction, anterior insula, and amygdala (Amodio & Frith, 2006; Frith & Frith, 2006). In particular, the medial prefrontal cortex is engaged in the experience and anticipation of physical pain (Porro, Cettolo, Francescato, & Baraldi, 2003) and the self-referential processing (Moran, Macrae, Heatherton, Wyland, & Kelley, 2006; Ochsner et al., 2005) as well as the mentalizing process. The pSTS and its adjacent region, the temporoparietal junction, form a core system for the detection of multimodal social acts (Van Overwalle & Baetens, 2009), perception of biological motions or gestures (Herrington, Nymberg, & Schultz, 2011), rapid identification of social threats (Kret, Denollet, Grèzes, & De Gelder, 2011), and attention to communicative cues (Materna, Dicke, & Thier, 2008). A growing body of research has also demonstrated that defective social cognitions in patients with schizophrenia are related to abnormal functions of the mentalizing system, including the medial prefrontal cortex and pSTS (Benedetti et al., 2009; Mier et al., 2010; Park et al., 2011).

Recent fMRI studies have suggested that the mentalizing system is crucially engaged in social interaction, together with the mirror neuron system for action understanding (Canessa et al., 2012; Van Overwalle & Baetens, 2009). Patients with schizophrenia often show abnormal social behaviors, such as increased interpersonal distance and decreased eye contact, in socially interactive conditions (Choi et al., 2010; Park et al., 2009). Therefore, an fMRI study that demands patients to interact with social partners may be an effective tool for exploring social problems in schizophrenia. An interactive neuroimaging study that investigates the neural mechanism of patients' experiences of social rejection is very important, as it may contribute to understanding the effects of social rejection and the ways of improving social interaction skills for their responses to possible social threats. An interactive approach is particularly important, especially for studying schizophrenia, because the affected patients are often socially excluded due to bizarre behaviors eliciting fear in others, a lack of social motivations, interaction difficulties, stigma, and deficits in social cognition (Lavelle et al., 2013). However, to date, few neuroimaging studies have reported the neural bases of social problems in schizophrenia using interactive approaches such as a Cyberball game (Gradin et al., 2012) and a trust game (Fett et al., 2012).

In order to emulate an actual experience of feeling social rejection in an interactive situation, the authors of the present study developed a virtual handshake task, and we reported that this task was effectively implemented in an fMRI setting (Ku, Lee, Kim, Kim, & Kim, 2012). Based on virtual reality technology, this task was designed so that participants could experience either social acceptance or rejection, depending on the success of their attempts to make a handshake with a virtual person in the system.

A handshake is a universal custom across cultures, through which people show happiness, express gratitude, offer congratulations, complete an agreement upon meeting, and reveal positive feelings for greeting or parting. Although there can be cultural and situational differences, most people extend a hand when others offer a hand for handshaking. Therefore, when one's attempts for handshaking are refused, people can feel a rather strong embarrassment, which may provoke a feeling of social rejection. An experimental study revealed that individuals who violated expectations increased uncertainty during social interactions and engendered threat responses in perceivers (Mendes, Blascovich, Hunter, Lickel, & Jost, 2007).

The current study was designed to investigate the neural responses to social rejection in schizophrenia using a virtual handshake task in an fMRI setting. This task provoked the experiences of social rejection passively, or by being ignored by the avatar. The medial prefrontal cortex and pSTS were of particular interest, as these regions have been consistently reported to be associated with the mentalizing processes, and as such, with the experiences of social rejection. We hypothesized that schizophrenia would be associated with aberrant activations of these two regions in response to the experiences of social rejection in an interactive situation.

METHODS

Participants

Participants consisted of 15 patients with schizophrenia (male = 10; mean age = 30.7 ± 6.6 years), who were recruited from an outpatient psychiatric clinic, and age-and sex-matched 16 healthy controls (male = 9; mean age = 27.4 ± 6.9 years), who were recruited from the community. The absence of comorbid psychiatric diagnoses of Axis I disorders in patients and the exclusion of any psychiatric disorder in controls were made by a trained psychiatrist using the Structural Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1996). All patients were medicated with conventional dosages of atypical (n = 14) or typical (n = 1) antipsychotics, and their mean chlorpromazine-equivalent dosage (Woods, 2003) was 499 ± 420 mg. All participants were right-handed, as assessed by the Annett Handedness Inventory (Annett, 1970). As presented in the demographic data of Table 1, the level of education and intellectual function assessed using Raven's Progressive Matrices (Raven, Sourt, & Raven, 1988) were significantly lower in the patient group than in the control group. Participants' anxiety was measured with the Interaction Anxiety Scale (IAS) for dispositional social anxiety (Leary, 1983) and with the State-Trait Anxiety Inventory (STAI) for current anxiety (state anxiety) and general anxiety susceptibility (trait anxiety) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Patients' schizophrenic symptoms were measured using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). The study was approved by the institutional review board, and written informed consent was obtained from all participants before the study began.

TABLE 1
Demographic data of participants

	Patients with schizophrenia (n = *15)*	*Healthy controls* (n = *16)*	χ^2/t	*P*
Age (years)	30.7 ± 6.6	27.4 ± 6.9	1.36	0.18
Sex (M/F)	10/5	9/7	0.35	0.55
Education (years)	13.3 ± 1.8	15.0 ± 1.7	−2.72	0.01
RPM (raw scores)	46.5 ± 8.6	52.5 ± 6.9	−2.14	0.04
Duration of illness (years)	7.7 ± 5.3			
PANSS				
Positive	16.2 ± 3.7			
Negative	15.4 ± 4.3			
General	28.9 ± 4.2			
IAS	39.7 ± 5.8	37.3 ± 6.8	1.07	0.29
STAI				
Trait	48.2 ± 10.9	45.6 ± 11.7	0.65	0.52
State	56.3 ± 10.5	49.0 ± 11.2	1.86	0.07

Note: RPM, Raven's Progressive Matrices; PANSS, Positive and Negative Syndrome Scale; IAS, Interaction Anxiety Scale; STAI, State-Trait Anxiety Inventory.

Task procedure

As shown in Figure 1, the patterned marker, MR-compatible camera (MRC Systems GmbH, Heidelberg, Germany) and fMRI-compatible head-mounted display (HMD; VisuaStim XGA, Resonance Inc., Northridge, CA, USA) were used to implement the virtual handshake task in the fMRI setting. In each task trial, a participant's task was to raise and lower the right hand to propose and finish the handshake, respectively, with a virtual avatar. To prevent head movement, the participant moved only the lower arm for the handshake. The participants were trained to offer the handshake to an avatar by raising their right hand when the avatar was shown on the screen. The MR-compatible camera was placed adjacent to the MR bed to capture an image of the patterned marker, which was attached to the participant's right hand. The camera sent the captured image to a computer, which detected and recorded the participant's hand motion so that the avatar responded to the participant's offer. The avatar's response was set to accept or refuse the handshake, which was referred to as "the acceptance condition" and "the refusal condition", respectively. In order to reduce a habitation to visual stimuli, we used four different accepting and four different refusing gestures (see Figure 1b). The accepting gestures were different in the bending angle of the upper body and the position of the left hand, whereas the refusing gestures differed in motions of the arms and head. The action time of the avatars was 3 seconds in all gestures. After the avatar responded, the trial finished if the participant lowered the right hand.

Because the start and finish of each trial were dependent on a participant's action, the duration varied and took an average of 6 seconds. The time when the participant raised and lowered the right hand was automatically recorded to be used as a regressor for the fMRI analysis. A total of 12 different avatars made one of the accepting or refusing gestures in each trial, and thus there were a total of 24 trials which consisted of 12 acceptance and 12 refusal conditions. A pair of trials of the same condition without

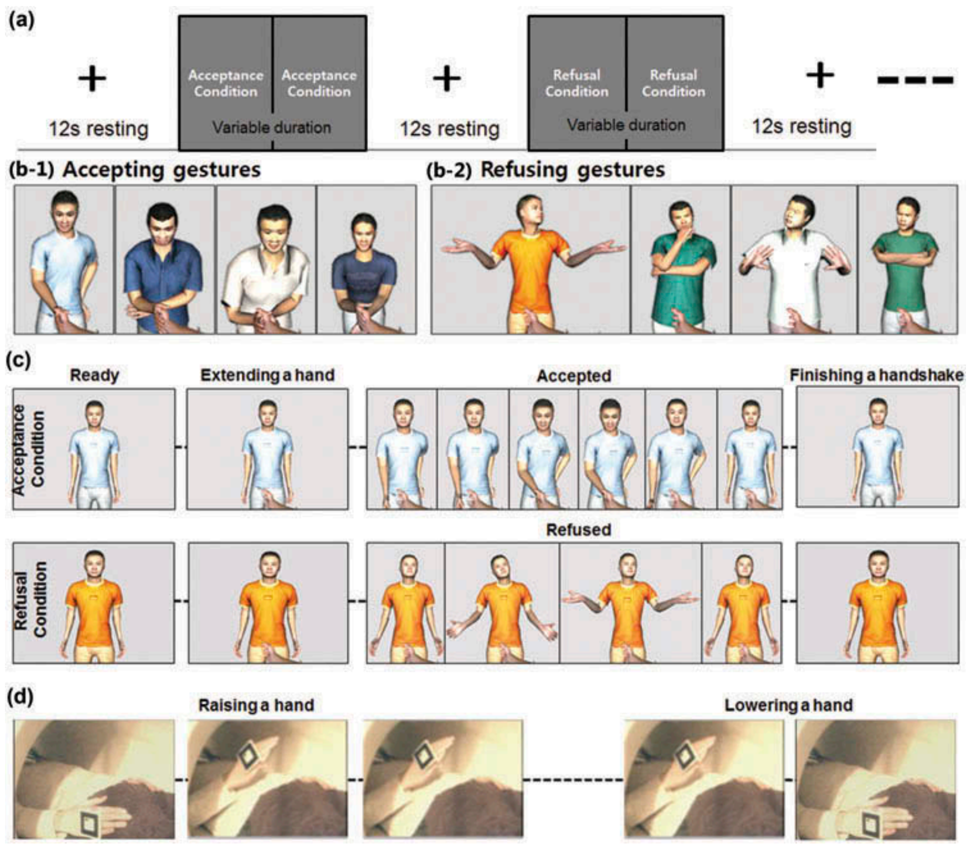

Figure 1. Task design for the fMRI experiment. The sequence of the experiment included pairs of trials and resting blocks (a). There were the two conditions according to the avatar's responses, and four different accepting and four different refusing gestures were used for each condition ((b-1) and (b-2)). A participant raised or lowered his/her right hand for handshaking with an avatar in each trial ((c) and (d)).

an interval was randomly repeated, and followed by a resting block of 12 seconds in duration. The task took approximately 300 seconds.

After the fMRI task, participants were asked to respond to the post-task questionnaires, which consisted of three questions regarding the task conditions: (1) "How much did you feel as if you were actually being refused by the avatar?"; (2) "How much did you feel as if you were actually being disliked by the avatar?"; and (3) "How much did you feel as if you were actually being threatened?" Each question was scored from 1 (not at all) to 5 (very much). Participants watched video clip including contents of acceptance or refusal conditions to be prohibited from responding with false memory.

Imaging data acquisition and data analyses

The fMRI experiments were conducted on a research-dedicated whole-body 1.5 T MRI system (Signa Eclipse, GE Medical Systems, Waukesha, WI, USA) using a standard quadrature birdcage head coil. Functional images were obtained using an echoplanar T2* gradient echo (matrix size = 64 × 64, field of view = 240 mm, slice thickness = 5 mm, echo time = 22 ms, repetition time = 2000 ms, flip angle = 90°, number of slices = 30). A series of high-resolution anatomical images was also acquired with a T1-weighted fast spoiled gradient-echo sequence (matrix size = 256 × 256, echo time = 1.8 ms, repetition time = 8.5 ms, field of view = 240 mm, slice thickness = 1.5 mm, flip angle = 12°, number of slices = 116) prior to the functional scans to serve as an anatomical underlay for the maps of brain activity.

Imaging data analysis was conducted with the Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/afni) software (Cox, 1996). The functional data for the first six time points were discarded to eliminate possible fMRI signal decay associated with magnetization reaching equilibrium. The remaining data were corrected regarding the slice timing and coregistered to the first remaining time sample to correct the effects of head movements during the task performance. Then, spike values were corrected in the three-dimensional plus time input dataset despike routine provided with the AFNI software. The spatial normalization was conducted to transform data into the Talairach space using the Montreal Neurological Institute N27 template (bilinear interpolation, 2 × 2 × 2 mm^3). Further processing included the spatial smoothing with a Gaussian filter with 8-mm full-width at half-maximum and detrending to remove constant and linear trends from the time series data. Individual brain activation maps were produced using a deconvolution routine provided in the AFNI software that contrasted stimulus periods with resting periods. For the deconvolution process to obtain the individual activation map, the regressor was generated in each participant on the basis of time needed for raising and lowering the right hand. The six-head movement parameters and global signal change covaried in order for the movements to be regressed out.

For the group analysis, paired sample *t*-tests were conducted between the acceptance and the refusal conditions to obtain a contrast image in each of the patient and control groups. Then, two sample *t*-test with the activity differences of the two conditions between the two groups was performed in order to examine the patient group's functional characteristics of the socially interactive situations. The regions which survived at uncorrected $p < .001$ and a cluster extent threshold of 80 mm^3 were considered for the interpretation. Then, the clusters which survived at family-wise error corrected $p < .05$ were reported to determine a crucial region. In order to test how regional brain activity was related to a participant's characteristics and responding, averaged regional activities were calculated in the identified regions of interest from the group comparison. Response times in each condition and the scores of the post-task questionnaires and anxiety scales were analyzed using paired *t*-test for the within-group comparison and Student's *t*-test for the between-group comparison, and Pearson correlations of regional activities with these scores and symptom severity were calculated in each group.

RESULTS

Behavioral responses

All participants successfully performed their tasks in all trials. Response time for raising the right hand after an avatar appeared was 1.62 ± 0.39 seconds in the control group and 2.05 ± 0.69 seconds in the schizophrenia group, which was significantly longer than in the control group (t = 2.09, p = .049). Response time for lowering the right hand after the avatar finished a motion was 1.29 ± 0.32 seconds during the acceptance condition and 1.48 ± 0.38 seconds during the refusal condition in the schizophrenia group, and 1.35 ± 0.26 and 1.69 ± 0.45 seconds, respectively, in the control group. Response time was significantly longer in the refusal condition than in the acceptance condition in both groups (control group, t = 2.77, p = .015; schizophrenia group, t = 3.29, p = .005), whereas the group difference was not significant in both conditions.

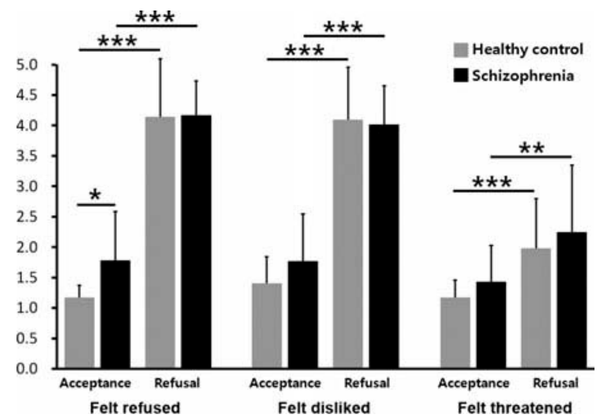

Figure 2. Subjective feelings after experiencing virtual handshake with accepting and rejecting avatars. The scores indicate a mean value across different gestures.
Notes: *$p < .05$; **$p < .01$; ***$p < .001$.

In the answers to the post-task questionnaire (Figure 2), the scores of the refused, disliked, and threatened feelings were significantly higher in the refusal condition than in the acceptance condition in both groups (control group, t = 11.74, $p < .001$; t = 11.01, $p < .001$; t = 4.50, $p < .001$, respectively; schizophrenia group, t = 9.00, $p < .001$; t = 8.68, $p < .001$; t = 3.13, p = .007, respectively). Regarding the acceptance condition, the schizophrenia group scored significantly higher in the refused feeling than the control group (t = 2.88, p = .011), but not in the disliked and threatened feelings. Regarding the refusal condition, there was no significant group difference in all feelings.

Imaging findings

As shown in Table 2, brain regions showing significantly increased activity in the refusal condition compared with the acceptance condition were the right pSTS and right thalamus in the control group, whereas

TABLE 2
Contrast results between the refusal and acceptance conditions in each group of healthy controls and patients with schizophrenia

		Coordinates			
Anatomical region	*Vol.(mm³)*	*X*	*Y*	*Z*	T_{max}
Healthy controls					
Refusal > acceptance					
Right superior temporal sulcus	144	67	−35	2	5.31
	136	43	−35	2	5.88
Right thalamus	112	9	−11	6	4.98
Refusal < acceptance					
No results					
Patients with schizophrenia					
Refusal > acceptance					
Left frontopolar ccortex	288	−23	57	0	5.96
Right middle frontal gyrus	136	37	31	32	5.43
Right superior frontal gyrus	120	21	11	56	5.13
Left anterior cingulate cortex	88	−11	39	6	6.01
Refusal < acceptance					
Right paracentral lobule	120	3	−39	64	−5.28
Right superior parietal lobule	344	19	−47	54	−5.20
Left superior parietal lobule	544	−19	−63	58	−7.00
	88	−23	−57	46	−4.79
Left fusiform gyrus*	1464	−21	−65	−10	−7.59

Notes: Significance was set at the level of uncorrected $p < .001$ and cluster size > 80 mm³ (*significant at the level of family-wise error corrected $p < .05$).

those were the frontal regions, including the left frontopolar cortex, right middle and superior frontal gyri, and left anterior cingulate cortex in the schizophrenia group. Brain regions showing significantly decreased activity in the refusal condition compared with the acceptance condition were not found in the control group, whereas those were multiple posterior regions, including the right paracentral lobule, bilateral superior parietal lobules, and left fusiform gyrus in the schizophrenia group.

In the group contrast of the refusal condition minus acceptance condition, compared with the control group, the schizophrenia group showed lower activities in multiple regions, including the right pSTS, right supramarginal gyrus, left middle cingulate cortex, bilateral insula, and left cerebellum (see Table 3). Conversely, higher activities in the schizophrenia group were found only in the left frontopolar cortex.

As shown in Figure 3, two significant correlations were found between the average contrast activities of the regions and the scores from the post-task questionnaires, IAS, STAI, and PANSS. In the schizophrenia group, contrast activities of the left frontopolar cortex showed a significant correlation with the current anxiety scores of the STAI (r = .72, p = .002),

TABLE 3
Group differences in the contrasts of the refusal-minus-acceptance condition

		Coordinates			
Anatomical region	*Vol.(mm³)*	*X*	*Y*	*Z*	T_{max}
Patients with schizophrenia < healthy controls					
Right superior temporal sulcus*	664	45	−39	6	5.27
Right supramarginal gyrus	200	37	−35	38	4.48
Left middle cingulate cortex	176	−5	−1	38	4.33
Right insula	112	31	−7	10	4.13
Leftiinsula	88	−33	5	2	5.02
Left cerebellum	168	−17	−77	−18	3.99
Patients with schizophrenia > healthy controls					
Left frontopolar cortex	96	−19	57	0	3.89

Notes: Significance was set at the level of uncorrected $p < .001$ and cluster size > 80 mm³ (*significant at the level of family-wise error corrected $p < .05$).

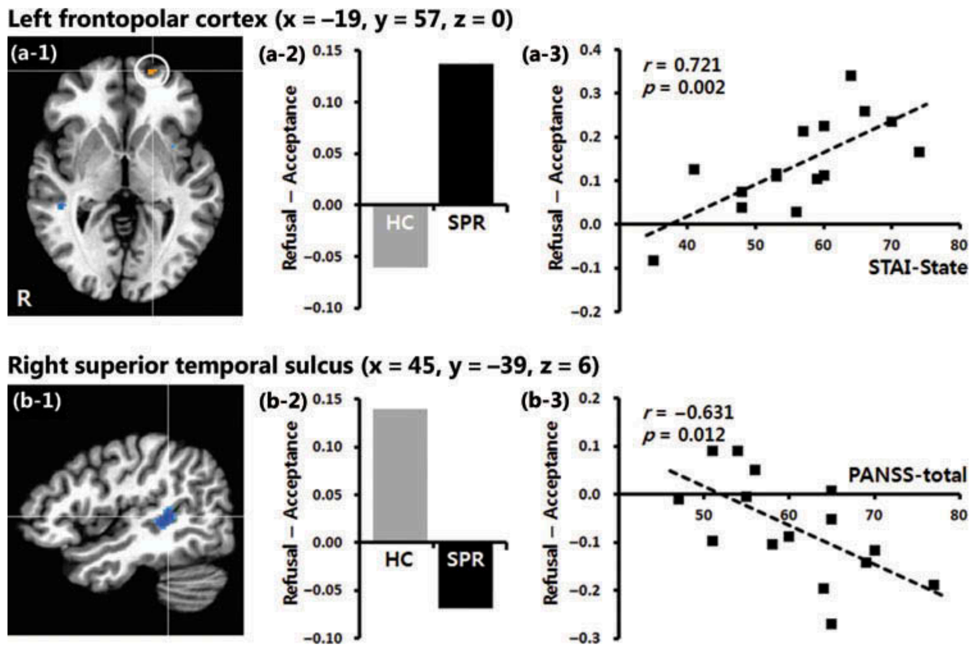

Figure 3. Regions identified in the group contrast of the refusal condition minus acceptance condition and correlations of their activities with clinical symptoms. The left frontopolar cortex (a-1) was the only region showing significantly higher contrast activity (a-2) in patients with schizophrenia (SPR) than in healthy controls (HC). Contrast activities of the left frontopolar cortex in patients with schizophrenia showed a significant correlation (a-3) with current anxiety scores of the Sitate-Trait Anxiety Inventory (STAI-State). The right superior temporal sulcus (b-1) was one of the regions showing significantly lower contrast activity (b-2) in patients with schizophrenia than in healthy controls. Contrast activities of the right superior temporal sulcus in patients with schizophrenia showed a significant inverse correlation (b-3) with total scores of the Positive and Negative Syndrome Scale (PANSS-total).

whereas the contrast activities of the right pSTS showed a significant inverse correlation with the total scores of the PANSS (r = −.63, p = .012). Other correlations with the schizophrenia group were not significant, and no significant correlations were found in the control group.

DISCUSSION

In this study investigating the neural responses to social rejection in schizophrenia using a virtual interactive setting, the refusal of a handshake successfully induced feelings of social rejection in both groups. These feelings were not significantly different between the two groups, but the neural responses were quite dissimilar; the refusal of a handshake activated the pSTS in the control group and the frontopolar cortex in the schizophrenia group. These findings support our hypothesis that in response to social rejection the mentalizing process would be operated in healthy controls, whereas an aberrant process would be intervened in patients with schizophrenia.

The control group showed more activities in the pSTS and thalamus during the refusal condition compared to the acceptance condition. The pSTS has been consistently reported as being involved in processing for mentalizing others' minds (Frith & Frith, 2006). In particular, the pSTS serves as a precursor to mind reading by mentally imitating others' behaviors from observations and eventually mirroring the mental states of others (Völlm et al., 2006). The thalamus is known to be involved in attempts to process social and emotional anticipation signals (Herwig, Kaffenberger, Baumgartner, & Jäncke, 2007; Kreifelts, Ethofer, Huberle, Grodd, & Wildgruber, 2010). Therefore, our findings of the pSTS and thalamus involvement in the control group support our expectation that feelings of social rejection in the refusal condition would stimulate the mentalizing process.

As confirmed with the post-task questionnaires, the refusal tasks provoked feelings of being rejected and disliked. This condition might have also produced embarrassments, with which the pSTS was engaged as a major region (Takahashi et al., 2004). In fact, the refusal condition is considered to be a salient stimulus, which is not usually experienced in everyday social life. The finding of pSTS involvement in the refusal condition is in accordance with previous studies, which have shown that the pSTS is recruited when the stimuli are socially salient (Sinke, Sorger, Goebel, & de Gelder, 2010; Wyk, Hudac, Carter, Sobel, & Pelphrey, 2009) or violate one's expectation (Pelphrey, Viola, & McCarthy, 2004). The result implies that the pSTS plays a role not only in interpreting biological motion-related stimuli but also in signaling socially salient stimuli, which should be considered based on one's own expectations.

Conversely, the schizophrenia group did not show any activation in the pSTS and thalamus during the refusal condition. Particularly, the group comparison showed that the refusal-related activities in the pSTS were significantly lower in the schizophrenia group than in the control group. This finding shows that patients with schizophrenia did not properly employ the mentalizing system in the interactive situation of social rejection. Previous behavioral studies had indicated that patients with schizophrenia were impaired, to varying degrees, in their ability to appropriately infer the beliefs, intentions, or feelings of others (Brüne, 2005; Frith & Corcoran, 1996). These deficits have been proposed to underlie specific symptoms of psychosis, such as delusions of persecution and reference, third-person auditory hallucinations, thought disorders, and negative symptoms. Additionally, a previous fMRI study using a video clip showed that abnormalities in the mentalizing process, including the involvement of the pSTS, might be a basis of paranoid delusion in schizophrenia (Park et al., 2011). Our correlation analyses showed that fewer activities in the pSTS were correlated with more severe schizophrenic symptoms. This is consistent with a previous finding that a structural deficit in the posterior part of the superior temporal region, including the pSTS, was associated with positive symptoms of schizophrenia (Kim et al., 2003). Therefore, an inability to properly employ the pSTS in the situation of social rejection may be connected with psychotic symptoms.

The post-task questionnaires revealed that the schizophrenia group reported higher refusal feelings to the acceptance responses than the control group. This peculiar schizophrenic behavior might also reflect a paranoid tendency. In fact, this could be the reason why multiple regions with higher activities in the acceptance condition, compared with the refusal condition, were observed in the schizophrenia group but not in the control group.

The refusal condition produced widespread prefrontal activations in the schizophrenia group. Several previous studies suggested that task-related hyperfrontality in schizophrenia might reflect inefficient functioning of the neural circuitry (Callicott et al., 2000; Manoach et al., 1999). In schizophrenia, task-related prefrontal dysfunctions have been mainly reported as hypoactivation but often hyperactivation as well, suggesting that an imbalanced system failure in adjusting the amount of local activities in the brain network should be the main concern of the pathophysiology of the illness (Schneider et al., 2007). Given that prefrontal activity shows load-dependent increase until the cognitive load goes beyond capacity (Johnson et al., 2006; Manoach, 2003), the refusal-related prefrontal activations in the schizophrenia group can be interpreted as the signal of the inordinate mental load evoked by the salient social stimuli.

As the frontopolar cortex was the only region which was observed to survive in the group comparison, the frontopolar load seemed to be particularly high in the schizophrenia group. The frontopolar cortex is a large complex structure which has been known to be involved in multiple-task coordination (Gilbert et al., 2006) and integration processes, including attention to environmental stimuli and self-generated representations (Burgess, Dumontheil, & Gilbert, 2007). A recent fMRI study suggested that the frontopolar dysfunction in schizophrenia might be related to a failure to integrate multiple cognitive processes that are necessary for insight (Raij, Riekki, & Hari, 2012). In particular, the lateral portion of the frontopolar cortex, the similar area the present study identified, was associated with interpersonal relation integrations, and played a role in the social domain (Raposo, Vicens, Clithero, Dobbins, & Huettel, 2011). Therefore, in the case of schizophrenia with excessive mental loads caused by social rejection, a considerable burden may be generated on this region, and this stressful condition may be a result of inefficient processing of social information. Our finding regarding the significant correlation between the frontopolar activity and the level of current anxiety also supports this explanation.

Regarding the behavioral responses, the schizophrenia group required more time to begin the task, but performed it well without missing any response. Since response time for lowering the hand showed no group difference, the delayed response of raising the hand in the schizophrenia group did not appear to be attributed to deficits in motor function. In the ambiguous state, before beginning the handshaking behavior in which participants did not know if the avatar accepted or refused their extending hand, the schizophrenia group may have had more reluctance because of more fear of social rejection. Although this possibility was not confirmed in the post-task questionnaires, the responses after finishing the task in the schizophrenia group could be different from the behaviors during the task performance because of denial or rejection feelings or cognitive deficits.

Unexpectedly, engagement of the medial prefrontal cortex during the refusal condition was not observed in the control group. This result may indicate that the refusal task did not provoke higher cognitive processing. Furthermore, despite multiple prefrontal activations in response to social rejection, the schizophrenia group showed no activation in the dorsomedial prefrontal cortex, which had been consistently reported to be engaged in the mentalizing process (Amodio & Frith, 2006; Mendes et al., 2007), suggesting that the multiple prefrontal activations did not stem from the mentalizing process.

The schizophrenia group showed social rejection-related activation in the pregenual region of the anterior cingulate cortex, which was considered to be a part of the affective division for the assessment of salience and regulation of emotional response (Bush, Luu, & Posner, 2000). The anterior cingulate cortex is most often provoked by Stroop paradigms, and an emotional Stroop task has been used as a functional probe for its affective division (Whalen et al., 1998). An fMRI study using an emotional Stroop paradigm reported that deficits in cognitive modulation over emotional interference in schizophrenia might be explained by a failure in suppression of the affective division of the anterior cingulate cortex (Park, Park, Chun, Kim, & Kim, 2008). This failure in suppressing the bottom–up processing of emotion during a cognitive–emotional interaction in schizophrenia might be related to an abnormal response of the affective division of the anterior cingulate cortex to the salient social rejection stimuli in the present study. This result can be linked to the previous report showing the differential role of the anterior cingulate cortex subdivisions while making social judgments, such as the dorsal part for expectancy violations and the ventral part for social feedback (Somerville, Heatherton, & Kelley, 2006).

The present study has several limitations. The patient and control groups were well matched in age and sex, but not in the level of education and cognitive ability. Although the acceptance condition was used as a control task, it could produce a "social reward" for some people and as such, may provoke some pleasure responses. In addition, conceiving a neutral condition in the handshaking situation is difficult. Another stimulus limitation is that the avatar in the virtual reality environment may look nonhuman or as a simple computer-generated figure. Being rejected by a nonhuman figure may produce somewhat different feelings of annoyance and discomfort from those of social rejection by a real person.

The usage of the virtual reality-based interactive approach is the strength of the present study. The interactive approaches have been employed in the studies of human social functions, including cooperation and competition with others (Decety, Jackson, Sommerville, Chaminade, & Meltzoff, 2004; King-Casas et al., 2005), interaction with a virtual character gazing at the subject (Schilbach et al., 2006), and reciprocal imitation through a double video system (Guionnet et al., 2012). Capturing dynamic mental states in actual social interactions may advance the understanding of human social behaviors by expanding the possibilities of scientific explanation (De Jaegher, Di Paolo, & Gallagher, 2010). Therefore, fMRI studies, like ours, using a dynamic task in which individuals are supposed to interact with social partners may be valuable for understanding normal and abnormal social behaviors.

In summary, the present study demonstrated that patients with schizophrenia showed hypoactivity in the pSTS and hyperactivity in the frontopolar cortex in the situation of social rejection. The abnormal pSTS hypoactivity implies that patients with schizophrenia could not appropriately recruit the mentalizing system in response to social rejection. The abnormal frontopolar hyperactivity is possibly a result of the socially aberrant stimuli, which required a very high cognitive load for integration. These findings can be helpful in understanding the aberrant brain characteristics of patients with schizophrenia in social situations and their distorted or paranoid beliefs.

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