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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 $= 64 \times 64$, number of slices = 30, slice thickness = 5 mm, spatial resolution $= 3.75 \times 3.75 \times 5$ 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 $= 256 \times 256$, number of slices = 115, slice thickness = 1.5 mm, spatial resolution $= 0.94 \times 0.94 \times 1.5$ 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.