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Neural basis for inferring false beliefs and social emotions in others among individuals with schizophrenia and those at ultra-high risk for psychosis

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ABSTRACT

Inferring beliefs and social emotions of others has different neural substrates and possibly different roles in the pathophysiology of different clinical phases of schizophrenia. The current study investigated the neural basis for inferring others' beliefs and social emotions, as individual concepts, in 17 subjects at ultra-high risk for psychosis (UHR), 16 patients with schizophrenia and 20 healthy controls. Brain activity significantly differed from normal in both the left superior temporal sulcus (STS) and the inferior frontal gyrus (IFG) in the schizophrenia group while inferring others' beliefs, whereas those of UHR group were in the middle of those in the schizophrenia and healthy-control groups. Brain activity during inferring others' social emotions significantly differed in both the left STS and right IFG among individuals at UHR; however, there was no significant difference in the schizophrenia group. In contrast, brain activity differed in the left IFG of those in both the schizophrenia and UHR groups while inferring social emotion. Regarding the difference in direction of the abnormality, both the UHR and schizophrenia groups were characterized by hyper-STS and hypo-IFG activations when inferring others' beliefs and emotions. These findings might reflect different aspects of the same pathophysiological process at different clinical phases of psychosis.

1. Introduction

Social cognitive impairments among people with schizophrenia are consistently observed across distinct phases of illness (Green et al., 2012) and are considered an important determinant of prognosis and functional outcome (Fett et al., 2011; Horan et al., 2012; Schmidt et al., 2011; Smith et al., 2015). Therefore, this phenotype has received attention as a promising treatment target and surrogate endpoint of clinical trials (Green et al., 2013; Green and Penn, 2013; Kern et al., 2013; Olbert et al., 2013). Among deficits across social cognitive domains (Savla et al., 2013), deficits in inferring others' mental statuses, known as theory of mind (ToM) have been emphasized in light of their relationship to some specific schizophrenia symptoms (Bora and Pantelis, 2013). These symptoms include delusions of persecution and of reference, third-person auditory hallucinations, thought disorder and negative symptoms (Frith, 1992; Ventura et al., 2013, 2015).

Inferring others' mental statuses can be separated into two distinct subcomponents: inferring others' beliefs and emotions (Shamay-Tsoory, 2011; Vollm et al., 2006; Zaki and Ochsner, 2012). Previous studies have suggested that there are distinct neural bases underlying the deficits of inferring beliefs and those of inferring emotions in patients with schizophrenia (Derntl et al., 2012; Harvey et al., 2013; Modinos et al., 2010). A limited number of studies have investigated the neural bases of these deficits using single functional magnetic resonance imaging (fMRI) tasks in the same participants (Benedetti et al., 2009; Lee et al., 2010). Statistical methods and the subsequent results vary between studies. These studies suggest altered function in right superior temporal regions of participants with schizophrenia during the inference of others' belief and/or emotions (Benedetti et al., 2009; Lee et al., 2010). However, these studies used different stimuli in their psychological tasks between inferring beliefs and emotions to

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Table 1
Clinical and demographic characteristics of the study participants.

	Individuals with UHR[a] (n=17)		Patients with schizophrenia (n=16)		Healthy Controls (n=20)		F Tests or *t*-Tests or χ^2	
Variable	Mean	SD	Mean	SD	Mean	SD	F or t value	*P*
Age	22.4	4.1	25.5	6.5	24.7	4.3	1.7	0.19
Male/Female	8 / 9		12/4		13/7		χ^2=2.8	0.24
Self socioeconomic status[b]	2.9	1.3	3.3	1.4	2.0	0.9	6.2	0.004*
Parental socioeconomic status[b]	2.2	0.9	2.4	0.6	2.1	0.4	1.1	0.34
Estimated IQ[c]	109.0	10.0	108.7	8.9	105.0	9.1	1.0	0.36
Handedness[d]	86.7	17.2	91.3	16.6	93.8	17.7	0.8	0.46
Antipsyochotic dose[e] (mg/day)	157.2	218.0	408.0	376.2			2.4	0.025*
Age of Onset (year)			23.1	6.1				
Duration of untreated illness (weeks)			21.8	27.9				
Duration of illness (months)			29.6	48.1				
Positive and Negative Syndrome Scale								
Positive symptoms	13.3	3.6	14.3	4.6			0.7	0.48
Negative symptoms	16.7	6.9	17.0	5.2			0.1	0.89
General psychology	31.1	5.9	33.6	9.3			0.9	0.36
Delusional Behavior	7.8	2.1	9.3	4.0			1.3	0.20
Global Assessment of Functioning	48.9	11.6	46.6	16.9			0.5	0.65

[a] Ultra high-risk for schizophrenia.
[b] Assessed using the Hollingshead scale. Higher scores indicate lower status.
[c] Estimated from scores on the Japanese Adult Reading Test.
[d] Assessed using the Edinburgh Inventory. > 0 indicates right-handed.
[e] Based on chlorpromazine equivalents.
* $P < 0.05$.

examine their neural bases. Thus, the contrasts in these studies may not precisely differentiate the neural basis for the inference of others' emotions or beliefs. It is important to be able to distinguish whether these two deficits have independent neural bases and different relationships to functional outcomes, to provide evidence for their potential use as biomarkers in future therapeutic studies. In our recent study, we demonstrated the presence of differences in the neural correlates for each subcomponent together with their potential for use as therapeutic targets (Aoki et al., 2014).

Individuals who eventually develop psychotic disorders, such as schizophrenia, often suffer initially from several social and/or cognitive deficits. Individuals presenting with these deficits but not meeting full criteria for schizophrenia are thought to be at ultra high risk (UHR) for schizophrenia. Some of these UHR individuals will go on to develop schizophrenia. Therefore, investigating neural differences between individuals at UHR and those with schizophrenia may provide insight into the neural basis of the development and progression of the disorder (Pantelis et al., 2009). In fact, we have previously reported implicit differences in the functional and neuroanatomical correlates of the clinical stages of psychosis in brain regions such as the inferior frontal, superior temporal and medial prefrontal cortices (Iwashiro et al., 2012; Natsubori et al., 2014a, 2014b; Suga et al., 2010; Yamasue et al., 2004).

UHR individuals have demonstrable deficits in ToM, and neuroimaging studies have reported abnormalities in corresponding brain regions (Lee et al., 2013; Schurz et al., 2014). However, no study has yet examined the neural correlates that distinguish the processes of inferring others' beliefs from that of inferring others' emotions in people with schizophrenia or UHR. Given that there are abnormalities in ToM brain regions that are dependent on clinical stage in patients with schizophrenia and given that UHR individuals show cognitive ToM deficits, we hypothesized the presence of clinical stage-dependent functional abnormalities in patients with schizophrenia or UHR.

The current study employed an event-related fMRI task design to investigate brain activity related to the processes of inferring others' beliefs and emotions in response to the same stimuli in patients with schizophrenia and in those at UHR. We employed a modified psychological paradigm (based on the Sally-Ann task, a first-order false-belief task (Aoki et al., 2014)), which was recently developed by our research group, to identify different neural correlates of inferring others' beliefs and emotions. This task presents a situation in which one person has cheated the other. The one who cheated gloats after successfully deceiving the other, who is frustrated. The emotions in this task are therefore social emotions rather than basic emotions. Based on the previous literature outlined above, we predicted that brain regions such as the inferior frontal, superior temporal and medial prefrontal cortices would be associated with the inference of others' mental states. We also hypothesized that these neural correlates would be related to schizophrenia symptoms.

2. Methods

2.1. Participants

We enrolled 53 right-handed Japanese participants in this study. Handedness was evaluated using the Edinburgh Handedness Inventory (Oldfield, 1971). The recruitment site, inclusion/exclusion criteria for each diagnosis, and the clinical and demographic assessment methods were the same as those used in our previous studies (Iwashiro et al., 2012; Koike et al., 2013; Natsubori et al., 2014a, 2014b). Briefly, the inclusion criteria for UHR were aged 15–30 years and a diagnosis of UHR for psychosis based on the Structured Interview for Prodromal Symptoms (SIPS) (Kobayashi et al., 2007; Miller et al., 1999). Schizophrenia was diagnosed using the Structured Clinical Interview for the Diagnostic (SCID-1) and Statistical Manual of Mental Disorders, Fourth Edition, Axis I Disorders, Clinical Version (First et al., 1997). Psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) within 14 days (7dayts before and 7days after MRI scan). The clinical group comprised 33 participants, of which 17 individuals were at UHR and 16 had schizophrenia. Among the UHR participants, 11 had attenuated positive symptom syndrome (APSS), one had brief intermittent psychotic syndrome (BIPS), three had genetic risk and deterioration syndrome (GRDS), one had APSS and GRDS, and one had BIPS and APSS. These diagnoses were based on the SIPS criteria. Another participant had comorbid schizophreniform disorder. No UHR participants had any other comorbid psychiatric diagnoses. Antipsychotics were prescribed for nine participants at UHR and for all participants