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Aberrant within- and between-network connectivity of the mirror neuron system network and the mentalizing network in first episode psychosis

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ABSTRACT

Introduction: It has been suggested that the mentalizing network and the mirror neuron system network support important social cognitive processes that are impaired in schizophrenia. However, the integrity and interaction of these two networks have not been sufficiently studied, and their effects on social cognition in schizophrenia remain unclear.

Methods: Our study included 26 first-episode psychosis (FEP) patients and 26 healthy controls. We utilized resting-state functional connectivity to examine the a priori-defined mirror neuron system network and the mentalizing network and to assess the within- and between-network connectivities of the networks in FEP patients. We also assessed the correlation between resting-state functional connectivity measures and theory of mind performance.

Results: FEP patients showed altered within-network connectivity of the mirror neuron system network, and aberrant between-network connectivity between the mirror neuron system network and the mentalizing network. The within-network connectivity of the mirror neuron system network was noticeably correlated with theory of mind task performance in FEP patients.

Conclusion: The integrity and interaction of the mirror neuron system network and the mentalizing network may be altered during the early stages of psychosis. Additionally, this study suggests that alterations in the integrity of the mirror neuron system network are highly related to deficient theory of mind in schizophrenia, and this problem would be present from the early stage of psychosis.

1. Introduction

Schizophrenia is a debilitating psychiatric disorder, and its major pathophysiology is characterized by widespread dysconnectivity among brain regions (Pettersson-Yeo et al., 2011; Li et al., 2017). As it has become increasingly clear that abnormality in a single region cannot explain the entire range of impairments in schizophrenia, and many studies have therefore focused on networks that interact with one another and subserve a variety of neural processes (Calhoun et al., 2009). This approach is in accordance with the long-established "disconnection hypothesis" of schizophrenia (Friston, 1998; Friston and Frith, 1995; Stephan et al., 2009). As it has been demonstrated that resting-state networks also reflect networks involved in specific cognitive processes (Smith et al., 2009), and as some core networks have been identified in healthy individuals, studies have adopted networks beyond the default mode network to examine altered resting-state functional connectivity in schizophrenia (Repovs et al., 2011). In particular, a recent innovative study revealed abnormalities in resting-state functional connectivity in schizophrenia using an a priori-defined mirror neuron system (MNS) network and mentalizing network (Schilbach et al., 2016).

The MNS network and the mentalizing network are networks known to be involved in theory of mind, a domain of social cognition that refers to the ability to attribute intentional mental states of one's self and others (Frith and Frith, 2006; Uddin et al., 2007; Spunt and Lieberman, 2012). The ability to mentalize can be explained with an

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integrative model that incorporates low-level embodied processes, supported by the MNS, and higher-level reflective inference, subserved by the mentalizing system: low-level embodied processes may provide a pre-reflective intuition on another person's emotion or mental state, while higher-level reflective inference allows explicit inference based on social knowledge (Keysers and Gazzola, 2007). A meta-analytic study suggested that these two networks are functionally and anatomically distinct (van Overwalle and Baetens, 2009), yet other studies have suggested that these networks cooperate in attributing mental states (Lombardo et al., 2010; Spunt and Lieberman, 2012).

Theory of mind is a social cognitive domain that has consistently been reported to be associated with a pronounced deficit in schizophrenia patients (Green et al., 2015). Therefore, the two networks putatively involved in theory of mind—the mirror neuron system network and the mentalizing network—are of special interest in schizophrenia. Although some studies have independently reported mirror neuron deficit (for review, see Mehta et al., 2014) and mentalizing system impairment in schizophrenia (Lee et al., 2011; Dodell-Feder et al., 2014), substantial research on the relationship between these networks in schizophrenia is still lacking. Moreover, since how networks integrate and segregate is an important aspect of cognitive maturation (Fair et al., 2007; Fair et al., 2008), and schizophrenia is known to involve neurodevelopmental deficits during the course of the illness (Fatemi and Folsom, 2009), the integrity of the two networks and the interaction between them are of interest in investigations of schizophrenia, particularly when the networks of interest are known to be functionally and anatomically distinct (van Overwalle and Baetens, 2009) but interact (Lombardo et al., 2010; Spunt and Lieberman, 2012).

While most studies of brain networks in schizophrenia, including the study on the MNS network and the mentalizing network (Schilbach et al., 2016), have involved chronic schizophrenia patients, studies on first episode psychosis (FEP) patients may provide insight to aid in minimizing the effect of illness chronicity, chronic medication or institutionalization, and chronically deficient social function. Particularly, as the networks of interest are involved in important social function, chronically impaired social function due to chronic symptoms may have induced a compounding effect in previous studies on chronic schizophrenia.

This study therefore aims to focus on the within- and between-network connectivity of the MNS network and the mentalizing network and to examine whether such indices can potentially explain theory of mind deficits in FEP patients. Our hypotheses were two-fold: first, we hypothesized that FEP patients would show aberrant connectivity in the MNS network and the mentalizing network; second, we hypothesized that impaired integrity and interactions of the two networks would explain aberrant theory of mind in FEP.

2. Material and methods

2.1. Subjects

This study included a total of 52 participants (FEP, $n = 26$; healthy control (HC), $n = 26$) who were group matched for age, sex, handedness, and education. Among the 40 FEP subjects recruited from Seoul Youth Clinic (Kwon et al., 2010) of Seoul National University Hospital during the period of June 2010 to August 2016, subjects with structural and functional MRI data and theory of mind task scores were selected for inclusion in the present study. After checking the quality of the MRI data, subjects with head motion exceeding the voxel size were excluded.

Details on the subject characteristics are elaborated in the Supplementary materials.

2.2. Theory of mind story task

The theory of mind story task was administered to the participants as part of a larger battery of neuropsychological tests, including the Korean version of the Weschler Adult Intelligence Scale (K-WAIS). The task includes the Korean version of the Strange Story task (Chung et al., 2008; Happé, 1994). In this task, the participants were provided with stories and questions that were prepared to measure theory of mind of the participant. Each story was designed to reflect various aspects of theory of mind, such as double bluff, white lie, persuasion, and misunderstanding.

2.3. fMRI data acquisition and preprocessing

All structural and functional MR images were acquired with a Siemens 3T Trio MRI scanner (Siemens Magnetom Trio, Erlangen, Germany). Detailed descriptions of the acquisition parameters are provided in the Supplementary material.

The first four EPI images were discarded allowing for magnetic field saturation. Then, prior to further analysis, the remaining 112 EPI functional volumes were preprocessed. The CONN toolbox v17a (Whitfield-Gabrieli and Nieto-Castanon, 2012; https://www.nitrc.org/projects/conn) was used for preprocessing and further processing. The images were first realigned and unwarped to correct for head movement, and underwent slice-timing correction. Then, the functional images were coregistered to T1-weighted structural images. The images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) partitions and were spatially normalized to the Montreal Neurological Institute (MNI) template. Motion artifact was detected using ART (Artifact Detection Tools)-based scrubbing method. Spatial smoothing with 6-mm full-width half-maximum (FWHM) isotropic Gaussian kernel was applied. After preprocessing, signals from white matter and CSF, motion realignment parameters and their first derivatives were regressed out using aCompCor strategy (Behzadi et al., 2007), and so were motion outlier volumes detected during ART-based outlier detection. Then, linear detrending and band-pass filtering ($0.008 < f < 0.09$) were applied.

2.4. Region of interest (ROI) selection

The MNS network and the mentalizing network ROIs were obtained according to the MNI coordinates described by Schilbach et al. (2016) (see Table 1). This study adopted the MNS network from a meta-analysis of neuroimaging studies on action observation and action imitation (Caspers et al., 2010) and the mentalizing network from a meta-analysis of neuroimaging studies on social cognition and the

Table 1
"Centers of Gravity" of the mirror neuron system network and the mentalizing network. (Taken from Caspers et al., 2010, Schilbach et al., 2012 and Schilbach et al., 2016)

Macroanatomical location	MNI coordinates		
	x	y	z
Mirror neuron system network			
Left IFG (BA 44)	−56	8	28
Right IFG (BA 44)	58	16	10
Left SMA	−1	16	52
Left IPS/IPL	−38	−40	50
Right IPL	51	−36	50
Left MTG	−54	−50	10
Left V5	−52	−70	6
Right V5	54	−64	4
Right FG	44	−54	−20
Mentalizing network			
Left precuneus	−6	−54	24
Left DMPFC	−2	52	14
Right TPJ	52	−62	16
Left TPJ	−46	−66	18

Note: IFG, inferior frontal gyrus; BA, Brodmann area; SMA, supplementary motor area; IPS, intraparietal sulcus; IPL, inferior parietal lobe; MTG, middle temporal gyrus; V5, extrastriate visual area; FG, fusiform gyrus; DMPFC, dorsomedial prefrontal cortex; TPJ, temporo-parietal junction; MNI, Montreal Neurological Institute.

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