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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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default mode network (Schilbach et al., 2012). Spherical ROIs with 5 mm radii centred on the given MNI coordinates were created.

2.5. fMRI data first-level analysis

We measured the functional connectivity of the regional mean time series of each ROI of the MNS network and the mentalizing network. Pearson's correlation (bivariate) analyses were performed to estimate the connectivity of each connection among the ROIs of the MNS network and the mentalizing network. The correlation coefficients were subsequently transformed into Fisher's z scores to represent the functional connectivity of each connection of each subject.

2.6. fMRI data second-level analysis: within- and between-network connectivity indices and pairwise connectivity values

Within- and between- network connectivity indices were obtained by averaging the z scores for all ROI pairs within and between each network. Group comparisons of the indices between patients and controls using independent t-tests were performed. Functional connectivity values of individual connections within each network and between the two networks were also group-compared using independent t-tests. The results of the statistical tests were FDR-corrected for multiple comparisons.

2.7. Correlation analyses between theory of mind performance and functional connectivity indices

Correlation between theory of mind performance, and the within- and between-functional connectivity indices was examined. Such correlation analyses were also performed on theory of mind performance and individual pairwise functional connectivity values that showed significant group differences. Due to the skewed distribution of theory of mind task scores, Spearman's correlations were assessed in FEP patients and in HCs, respectively. FDR correction for multiple comparisons was applied.

3. Results

3.1. Subject characteristics

The demographical and clinical characteristics of each group of subjects are summarized in Table 2. There were no significant differences in age, sex, handedness and education between groups ($p > .05$); however, some difference in IQ was noted (average IQ of FEP patients = 102.54, average IQ of HCs = 108.92; $t = 2.07$, $p = .044$). Among FEP patients, 21 were under medication at the time of data acquisition, and 5 were drug-naïve. The mean olanzapine-equivalent dose of antipsychotic drug intake of FEP patients, calculated based on Gardner et al. (2010), was 9.6 ± 8.26 mg/day. All medicated subjects were taking atypical antipsychotics.

Table 2
Demographic and clinical characteristics of the subjects.

	FEP (n = 26)	Control (n = 26)	Statistics (χ^2 or t)	p value
Demographic variables				
Age (y)	23.77 ± 5.95	22.62 ± 5.29	−0.74	.463
Sex (M/F)	12/14	11/15	−0.08	.780
Handedness (L/R)	3/23	2/24	−0.22	.638
Estimated IQ	102.54 ± 10.89	108.92 ± 11.34	2.07	.044
Education	13.27 ± 2.01	14.08 ± 1.62	1.59	.117
Clinical variables				
PANSS Total	66.54 ± 11.36			
PANSS Positive	16.42 ± 4.16			
PANSS Negative	16.19 ± 4.36			
PANSS General	33.92 ± 6.38			
GAF	49.00 ± 9.48			
Medication (medicated/drug-naïve; average olanzapine-equivalent dose in mg/day)	21/5 (9.6)			

Note: PANSS, the Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning scale.

3.2. Theory of mind story task results

The average theory of mind story task score for FEP patients was 20.35 ± 2.51, while that of HCs was 23.00 ± 1.57. HCs performed significantly better than FEP patients in the theory of mind task ($t = 4.56$, $p < .001$).

3.3. Group differences in the within- and between-network connectivity indices

While there was no significant group difference in the within-network connectivity index of the mentalizing network, FEP patients showed a significantly lower within-network connectivity index of the MNS network than HCs ($t = 4.07$, $p < .001$). FEP patients also had a significantly lower between-network connectivity index ($t = 3.65$, $p = .001$).

3.4. Group differences in pairwise functional connectivity values within and between the networks

Fig. 1 shows correlation matrices of the functional connections for each group. Group comparisons using independent t-tests indicated that several connections within the MNS network showed altered connectivity in FEP patients compared to controls (see Fig. 2, Table 3). On the other hand, no significant group differences in the connectivity values of connections within the mentalizing network were found. There were some connections between the two networks that showed significant group differences (see Table 3).

3.5. Correlation between functional connectivity indices and theory of mind story task score

Having examined the correlation between theory of mind task scores and each functional connectivity indices in FEP patients, a negative correlation between theory of mind Story Total score and the within-network connectivity of the MNS network at the marginal level of significance was noticed ($\rho = -.55$, uncorrected $p = .004$, FDR-corrected $p = .050$; Fig. 3). No meaningful correlation between functional connectivity indices and Theory of Mind Story Task score was observed in HCs.

4. Discussion

In this study, we assessed aberrant within- and between-network connectivity of the MNS network and the mentalizing network in psychotic patients with a duration of illness of less than a year. Also, we investigated individual connections that comprise the MNS network and the mentalizing network using ROI-to-ROI functional connectivity analysis. Additionally, we examined the correlation between these connectivity indices and theory of mind performance in the patient group. Our results demonstrated altered within-network connectivity of the MNS network and between-network connectivity of the MNS and mentalizing network in FEP patients. There were also some individual connections within the MNS network and between the MNS and mentalizing network that showed group differences in the connectivity values, which would explain the alteration in the within- and between-network indices. Moreover, the within-network connectivity of the

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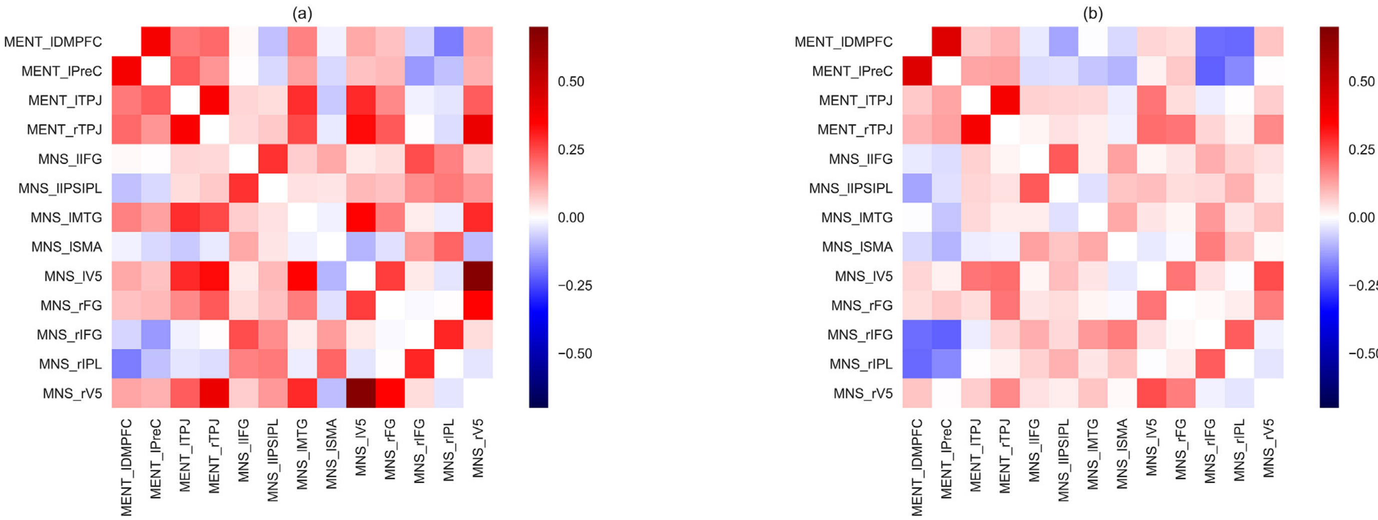

Fig. 1. Correlation matrices of the functional connections of the mirror neuron system network and the mentalizing network, each for the patient group and the control group. (a) Correlation matrix of the functional connections of the control group; (b) correlation matrix of the functional connections of the patient group. Note: MNS, the mirror neuron system network; MENT, the mentalizing network; r, right; l, left; IFG, inferior frontal gyrus; 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; PreC, precuneus; TPJ, temporo-parietal junction.

MNS network was noticeably correlated with theory of mind performance in FEP patients. To our knowledge, this is the first study to investigate the integrity and interaction of the MNS network and the mentalizing network and to directly examine the correlation between those indices and social cognitive performance in FEP.

Our results showed that within-network connectivity of the MNS network was significantly reduced in FEP patients, and that some connections within the MNS network showed group difference in their connectivity values. These results indicate that there is underlying neural impairment within the network that supports MNS function, and that the integrity of the MNS network as a network separable from other networks of the brain is deficient in FEP patients. The results of our study on reduced within-network connectivity and altered individual connectivity of the MNS are in line with the results of previous studies on mirror neuron dysfunction (for review, see Mehta et al., 2014) and on the resting-state functional connectivity of the MNS and the

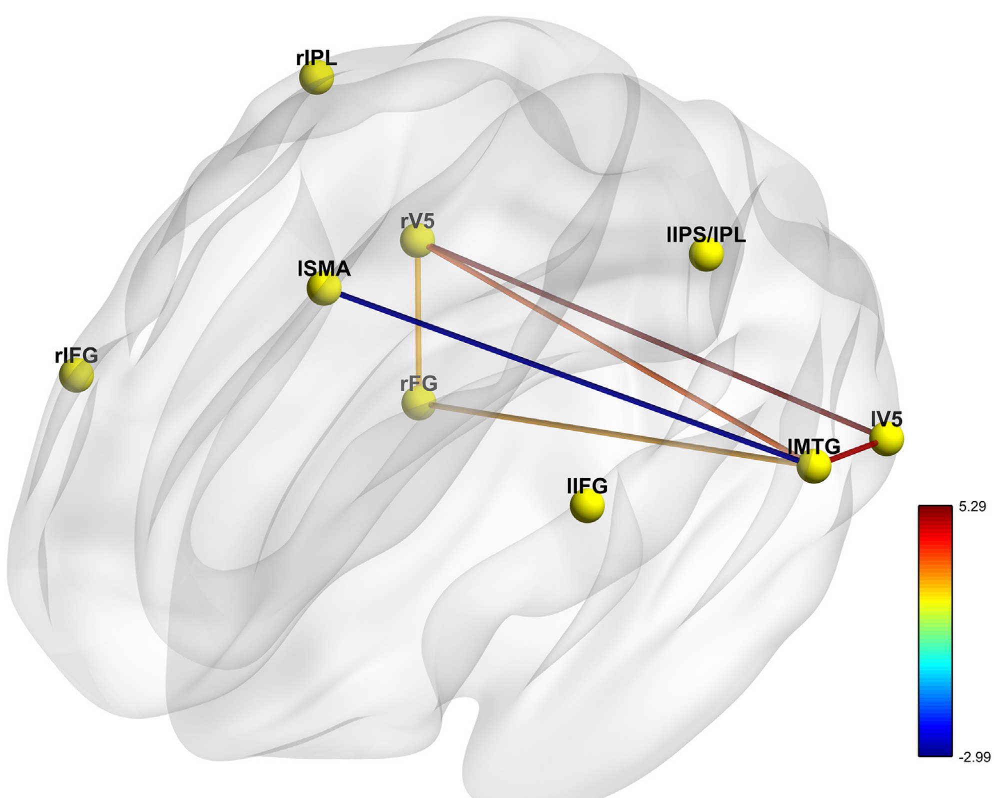

Fig. 2. Connections of the MNS network that showed altered connectivity values in FEP patients. Note: r, right; l, left; IFG, inferior frontal gyrus; SMA, supplementary motor area; IPS, intraparietal sulcus; IPL, inferior parietal lobe; MTG, middle temporal gyrus; V5, extrastriate visual area; FG, fusiform gyrus. The colours of the edges represent the *t* statistics of independent *t*-tests of connectivity values between the FEP group and the HC group. The figure was visualized with the BrainNet Viewer.

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Table 3
Functional connectivity within and between the mirror neuron system network and the mentalizing network that showed group differences between FEP patients and HCs.

Connectivity	Fisher's *z* of FEP	Fisher's *z* of HC	*t*	*p*
Within the mirror neuron system network				
Left MTG – left SMA	0.117 ± 0.156	−0.019 ± 0.172	−2.99	.032
Left MTG – left V5	0.037 ± 0.198	0.347 ± 0.244	5.02	.000
Left MTG – right FG	0.012 ± 0.173	0.179 ± 0.226	2.98	.032
Left MTG – right V5	0.079 ± 0.175	0.293 ± 0.243	3.64	.008
Right V5 – right FG	0.180 ± 0.209	0.347 ± 0.214	2.85	.038
Right V5 – left V5	0.241 ± 0.266	0.680 ± 0.330	5.29	.000
Between the mirror neuron system network and the mentalizing network				
Left MTG – left DMPFC	−0.003 ± 0.213	0.174 ± 0.213	3.00	.030
Left MTG – left Precuneus	−0.082 ± 0.221	0.129 ± 0.264	3.12	.027
Left MTG – left TPJ	0.053 ± 0.267	0.290 ± 0.231	3.41	.019
Left MTG – right TPJ	0.023 ± 0.196	0.251 ± 0.279	3.40	.019
Right V5 – right TPJ	0.160 ± 0.221	0.401 ± 0.294	3.34	.019

Note: SMA, supplementary motor area; MTG, middle temporal gyrus; V5, extrastriate visual area; FG, fusiform gyrus; TPJ, temporoparietal junction; IFG, inferior frontal gyrus; DMPFC, dorsomedial prefrontal cortex; FEP, first episode psychosis; HC, healthy control. *p* values were FDR-adjusted for multiple comparisons.

mentalizing system in chronic schizophrenia patients (Schilbach et al., 2016). The result of our study of FEP patients supplement the results of the previous study that dysconnectivity of the MNS network in schizophrenia is not an effect of illness chronicity or chronic decrease in social function but may be a characteristic of schizophrenia from the early stages of the illness.

Furthermore, we examined the correlation between the functional connectivity indices and theory of mind performance in FEP patients. Our sample of FEP patients, consistent with previous studies on mentalizing deficits in FEP (Inoue et al., 2006; Bertrand et al., 2007; Koelkebeck et al., 2010; Achim et al., 2012) showed significant dysfunction in theory of mind. This study is unique compared with previous studies in that we adopted a Strange Story task, a naturalistic theory of mind task that assesses diverse yet conceptually connected situations (Happé, 1994). The theory of mind deficit in schizophrenia has been considered to have clinical and therapeutic implications, as it predicts functional outcome better than symptoms and neurocognitive deficits (Bora et al., 2009; Lam et al., 2014) and is considered a key target for new interventions and psychosis treatments (Green et al., 2004; Green et al., 2008). Therefore, we sought to explain the theory of mind deficient in FEP patients with altered functional connectivity indices of the networks involved in mentalizing.

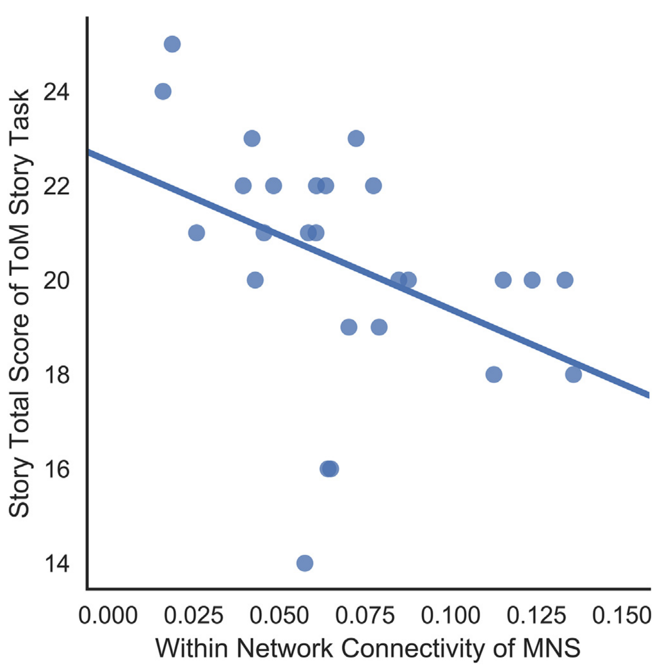

Fig. 3. Correlation between theory of mind story task scores and within-network connectivity of the MNS network.

Interestingly, the decreased within-network connectivity of the MNS network in FEP patients was noticeably negatively correlated with theory of mind performance. One possible explanation for this seemingly contradictory phenomenon is that relatively stronger within-network connectivity of the MNS network in those with lower theory of mind performance may have originated from unsuccessful compensation for their deficient theory of mind. The results of group comparisons of the functional connectivity values of the MNS network indicate that the MNS network is deficient in FEP patients; among the patients, those with deficient theory of mind would have overused such defective MNS network as a mean of compensation to their impaired theory of mind performance. This explanation is in part supported by the result of our analysis that the control group did not show a significant correlation between theory of mind performance and within-network functional connectivity of the MNS network. Because HCs do not have deficient MNS network and do not need a compensatory mechanism, no significant correlation would have been shown between the two indices. Indeed, those with deficient social functioning showing increased connectivity within the MNS network is not an entirely unexpected finding: a previous study on autism spectrum disorder, a neurodevelopmental disorder that share similarities with schizophrenia such as significant impairments in social behaviour and understanding (Kanner, 1965; Eack et al., 2017), reported that the within-network connectivity of the MNS network was positively correlated with social symptom score—that is, autistic patients showed more severe social symptoms as the within-network connectivity of the MNS network increased (Fishman et al., 2014).

On the other hand, among mentalizing network ROIs, there was no group difference in the connectivity values of each connection comprising the network. Furthermore, no significant group difference in within-network connectivity was noticed. These results suggest that the mentalizing network is relatively unaffected in early psychosis. Along with the results of the previous study of chronic schizophrenia (Schilbach et al., 2016), which reported some altered connectivity of the mentalizing network in schizophrenia, it can be suggested that the mentalizing network becomes affected during the course of a chronic illness or as an effect of chronic medication. Integrating these results with the previously discussed results on aberrant MNS networks, in early psychotic patients with near-normal intelligence, theory of mind performance deficits may be primarily due to impairments in low-level, pre-reflective intuition subserved by the MNS network rather than higher-level inferential processes. However, as some studies on theory of mind of chronic schizophrenia patients suggest dysfunction of the mentalizing system (Lee et al., 2011; Dodell-Feder et al., 2014), it is difficult to expect that the mentalizing system would remain unaffected even in the chronic stage of illness.

Our analysis of the between-network connectivity between the MNS network and the mentalizing network suggests that these two networks are overly segregated in FEP. While it has been proposed that the MNS and the mentalizing system cooperate in social functioning (Keysers and Gazzola, 2007; Lombardo et al., 2010; Spunt and Lieberman, 2012), reduced between-network connectivity suggests that such an interaction may be impaired, leading to the characteristic social dysfunction of schizophrenia.

A previous study that examined the between-network connectivity of several networks, such as the default mode network, the frontal-parietal network, the cingulo-opercular network, and the cerebellar network also reported decreased between-network connectivity among several networks (Repovs et al., 2011). In line with the results of this previous study, the results of our study support the "disconnection hypothesis" of schizophrenia, which claims that the core pathophysiology of schizophrenia lies in the failure to properly integrate

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distinct brain regions (Friston and Frith, 1995). Furthermore, our study supports the claim that impairment of functional integration is more fundamental in schizophrenia as a disconnection syndrome than functional specialization (Friston, 1998). Our results suggest diminished within- and between-network connectivity of networks involved in social cognitive processes, indicating that proper integration of these networks as networks distinct from other networks is lacking and the proper interactions necessary for proper functioning are impaired.

Our study has several limitations. A considerable portion of the FEP patients were medicated when resting-state fMRI was acquired. Because antipsychotics are known to alter resting-state functional connectivity in schizophrenia patients (Lui et al., 2010), medication may have been a confounding factor in our study. However, no significant correlation was observed between the functional connectivity indices and the olanzapine-equivalent dose of antipsychotics in FEP patients. Also, although the effect of substance abuse or dependence other than nicotine was controlled by including it in the exclusion criteria for our sample, nicotine use was not quantified in this study, and therefore its effect could not be taken into account. Furthermore, our sample size was limited, and the FEP patient sample was heterogeneous. Though most of the patients were diagnosed with schizophrenia, some were diagnosed with schizoaffective disorder ($n = 3$), schizophreniform disorder ($n = 2$), or brief psychotic disorder ($n = 1$).

Taken together, our results suggest that the within-network connectivity of the MNS network and the between-network connectivity of the MNS and mentalizing network are diminished in FEP, and the alteration in the within-network connectivity of the MNS may be related to functional compensation for deficient theory of mind. These results imply that the integrity and interaction of the MNS network and the mentalizing network are impaired in schizophrenia. Furthermore, these impairments are present from the early stages of psychosis, indicating that they may not be the effect of chronic impairment in social function or illness chronicity. Overall, this study is in agreement with the disconnection hypothesis of schizophrenia, which states that the main pathophysiology of schizophrenia lies in improper functional integration among brain regions.

Conflict of interest

All authors have declared that there are no conflicts of interest in relation to the subject of this article.

Contributors

Author Eugenie Choe, Jun Soo Kwon and Tae Young Lee designed the study and wrote the protocol.

Author Eugenie Choe and Tae Young Lee wrote the manuscript.

Author Eugenie Choe, Tae Young Lee, Youngwoo Bryan Yoon, Minah Kim, Ji-Won Hur, Kang-Ik K. Cho, supported the analysis, interpretation and manuscript revision.

All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.03.024.

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