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Triple-Network Dysconnectivity in Patients With First-Episode Psychosis and Individuals at Clinical High Risk for Psychosis

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Objective In the triple-network model, the salience network (SN) plays a crucial role in switching between the default-mode network (DMN) and the central executive network (CEN). Aberrant patterns of triple-network connectivity have been reported in schizophrenia patients, while findings have been less consistent for patients in the early stages of psychotic disorders. Thus, the present study examined the connectivity among the SN, DMN, and CEN in first-episode psychosis (FEP) patients and individuals at clinical high risk (CHR) for psychosis.

Methods Thirty-nine patients with FEP, 78 patients with CHR for psychosis, and 110 healthy controls (HCs) underwent resting-state functional magnetic resonance imaging. We compared the SN, DMN, and CEN connectivity patterns of the three groups. The role of the SN in networks with significant connectivity differences was examined by mediation analysis.

Results FEP patients showed lower SN-DMN and SN-CEN (cluster-level F=5.83, false discovery rate [FDR] corrected-p=0.001) connectivity than HCs. There was lower SN-DMN connectivity (cluster-level F=3.06, FDR corrected-p=0.053) at a trend level in CHR subjects compared to HCs. Between HCs and FEP patients, mediation analysis showed that SN-DMN connectivity was a mediator between group and SN-CEN connectivity. Additionally, SN-CEN connectivity functioned as a mediator between group and SN-DMN connectivity.

Conclusion Aberrant connectivity between the SN and DMN/CEN suggests disrupted network switching in FEP patients, although CHR subjects showed trend-level SN-DMN dysconnectivity. Our findings suggest that dysfunctional triple-network dynamics centered on the SN can appear in patients in the early stages of psychotic disorders. **Psychiatry Investig 2022;19(12):1037-1045**

Keywords Clinical high risk; First-episode psychosis; Salience network; Schizophrenia; Triple-network connectivity.

INTRODUCTION

Brain networks seem to be activated not only when people perform cognitive tasks but also when they are at rest. Among the resting functional networks, the central executive network (CEN), salience network (SN), and default-mode network (DMN) seem to crucially influence human neurocognitive function.[1] When a new stimulus is detected, the SN activates, and as cognitive tasks are performed, the CEN is activated, while DMN activation is suppressed.[2] The triple-network model states that these three network connectivities are integrated with SN as a core modulator, where SN facilitates the switch between the CEN and DMN upon the performance of cognitive tasks or self-related thoughts. However, dysfunctional interactions among these three networks may create confusion in the assignment of salience to external versus internal events.[1] In a recent meta-analysis, dysconnectivity among these three networks was reported in chronic schizophrenia patients,[3] and this abnormal connectivity between the networks seemed to be associated with positive[4] and negative symptoms[5] of schizophrenia. Based on previous studies,[2,6,7] the dysfunctional connectivity among the SN, DMN, and CEN found in chronic schizophrenia patients emphasizes the

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role of the SN in the triple-network model of schizophrenia.[8,9]

However, patients with chronic schizophrenia are influenced by disease chronicity itself, as well as a long duration of antipsychotic usage and relatively old age. Therefore, it is important to examine patients who are in the early stage of psychosis, including first-episode psychosis (FEP) patients and individuals at clinical high risk (CHR) for psychosis. Although there are studies that examined connectivity among the SN, DMN, and CEN in FEP patients, networks that were identified as dysfunctional and the interconnectivity strength between them varied across the studies.[10-12] Furthermore, a small number of previous studies on the interconnectivity of these three networks in individuals at CHR for psychosis presented inconsistent interactions among the networks,[13,14] including a negative finding.[15] Thus, further research is needed to determine how triple-network connectivity is impaired in early psychosis patients.

The inconsistent results of previous studies regarding these three networks in the FEP[10-12] and CHR popluations[13-15] may be due to the a priori region-of-interest (ROI) method used in those studies. Since this ROI method requires an a priori hypothesis to analyze the connectivity of the brain, the regions of networks are predefined. In contrast, the independent component analysis (ICA) method identifies networks with a data-driven procedure,[16] which have an advantage in detecting networks that reflect the data of the study. One study investigated the interconnectivity among networks, including the SN, DMN, and CEN, using high-order ICA methods in FEP patients and found no significant triple-network dysconnectivity.[17] This may be because the study was not specific to an examination of the triple network, and the peak activation of the extracted SN was not in the anterior insula, which is considered a crucial part of the SN.[1,8,18] In individuals at CHR for psychosis, explicit investigations of triple-network dysconnectivity using the high-order ICA method have not yet been reported.

Therefore, we aimed to investigate whether triple-network dysconnectivity exists in patients with early psychoses, such as individuals with FEP and CHR, using the high-order ICA method. Considering the suggested importance of the modulating role of the SN within triple networks,[1,8,18] we performed mediation analysis to determine whether the SN plays a key role in the triple-network dysconnectivity of the patients. Based on previous studies indicating alterations in SN, CEN, and DMN connectivity in chronic schizophrenia patients,[2-8] we hypothesized triple-network dysfunctionality in both FEP patients and individuals at CHR for psychosis. In addition, considering the crucial role of the SN in the triple-network model,[1,8,9,18] we expected that SN interconnectivity among the networks would act as a mediator.

METHODS

Participants

A total of 39 patients with FEP, 78 subjects at CHR for psychosis, and 110 healthy controls (HCs) participated in this study. Resting-state functional magnetic resonance imaging (rs-fMRI) data from 39 FEP patients and 40 HCs were used in our previous study,[19,20] and data from 110 HCs were used in other studies.[21,22] FEP patients and individuals at CHR for psychosis were recruited from the Seoul Youth Clinic (www.youthclinic.org)[23] and the Department of Neuropsychiatry at the Seoul National University Hospital (SNUH). Using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I disorders (SCID-I), FEP patients had to be diagnosed with schizophreniform, schizophrenia, or schizoaffective disorder for less than 2 years to be considered for inclusion. The Positive and Negative Syndrome Scale (PANSS) was utilized to assess psychotic symptom severity in FEP patients. Individuals at CHR for psychosis were assessed with the validated Korean version of the Structured Interview for Prodromal Symptoms (SIPS)[24,25] and were recruited if they met the criteria for one of the three high-risk states: attenuated positive symptoms (APS), brief intermittent psychotic symptoms (BIPS), and genetic risk and deterioration (GRD). The Scale of Prodromal Symptoms (SOPS) was used to examine prodromal symptom severity in individuals at CHR for psychosis. HCs were recruited via internet advertisement. Potential HC subjects were screened using the SCID-I Non-Patient Edition (SCID-NP) and were excluded if they had any first- to third-degree biological relatives with a psychotic disorder. The common exclusion criteria for individuals in all groups were a diagnosis of substance abuse or dependence (except nicotine), neurological disease, a history of significant head injury, or intellectual disability (intelligent quotient [IQ] <70).

All participants agreed to provide written informed consent after receiving a full explanation of the study procedure in the previous prospective cohort study (IRB no. H-1110-009-380). For minors, participants and their parents provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of SNUH (IRB no. H-2109-042-1252).

Image acquisition and preprocessing

A Siemens 3T Magnetom Trio MRI scanner with a 12-channel head coil was used to obtain T1 and rs-fMRI image data. T1 images were acquired with the parameters of repetition time (TR)=1,670 ms, echo time (TE)=1.89 ms, field of view=250 mm, flip angle=9°, voxel size=1.0×1.0×1.0 mm^3, and

208 sagittal slices. Rs-fMRI images were obtained with the parameters of TR=3,500 ms, TE=30 ms, FOV=240 mm, flip angle=90°, voxel size=1.9×1.9×3.5 mm^3, 35 slices, and 116 volumes. Participants were told to close their eyes and be as still as possible during the image acquisition, which lasted for 6 minutes and 58 seconds.

We excluded subjects with head motion exceeding the criteria (translation >2.0 mm and rotation >2.0°), and data were preprocessed using CONN toolbox version 19c (www.nitrc.org/projects/conn) implemented in MATLAB version 2020a.[26] The images were realigned and unwarped for motion estimation and were processed by slice-timing correction. Then, outliers were detected through ART-based scrubbing. Then, the images were coregistered using structural and functional images, segmented on structural images and normalized to Montreal Neurology Institute (MNI) space. Finally, the images were smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

Independent component analysis

The GIFT toolbox (http://trendscenter.org/software/gift/) was used to extract intrinsic connectivity network components by performing a group-level spatial ICA. Principal component analysis (PCA) was performed for each subject's data reduction with 116 components, and the data were decomposed into 100 ICA components. Then, for stability analysis, the Informax algorithm was utilized to run ICA 10 times in ICASSO. Last, GIGA was selected for the back-reconstruction method to estimate subject-specific spatial maps and time courses.[27,28]

First, components were selected by inspecting whether peak activation existed in gray matter. Then, the network labeling tool in the GIFT toolbox was used to identify the networks for each component. For network identification, the Gordon atlas was utilized for the network mask.[29] After network labeling, spatial correlation analysis was performed to double check if the components corresponded to the Gordon template. The networks were confirmed as the DMN, SN, and CEN if the correlation coefficient value was above R >0.20.[30] Finally, the selected networks were visually inspected.

Statistical analyses

In the CONN toolbox, rs-fMRI data were denoised by using aCompCor, where five components of white matter and cerebrospinal fluid, and six motion parameters and first-order temporal derivatives were removed as confounding variables.[31] Linear detrending and bandpass filtering (0.008−0.09 Hz) were performed. ROIs were identified through ICA, and extracted time-series data were averaged across voxels in each ROI. Then, Pearson's correlation was performed between the time series data in each subject, and the resulting values were converted into z scores via Fisher-z transformation.

The threshold for statistical significance was set at $p<0.05$, and multivariate statistics were used to present clusters that had significant group differences.[32] To examine differences in between-network connectivities among the FEP, CHR, and HC groups, one-way analysis of covariance (ANCOVA) was performed while controlling for the effect of age and sex. To further examine significant functional connection abnormalities between two groups at a time, we conducted pairwise comparisons of functional network connectivity.

To investigate the causal effects of the SN in internetwork connectivity that showed significant differences in group comparison, post hoc analysis was conducted by using Andrew Hayes' PROCESS macro (www.processmacro.org) in SPSS Ver. 25.0 (IBM Corp., Armonk, NY, USA) to perform mediation analyses. We set the confidence interval (CI) percentage as 95% and the number of bootstrap samples as 5,000. Moreover, age and sex were included as covariates.

RESULTS

Demographic and clinical characteristics

The demographic and clinical data of the subjects are presented in Table 1. There was a significant difference in age ($F=13.699$, $p<0.001$) and sex ($\chi^2=9.704$, $p=0.008$) among the FEP patients, individuals at CHR for psychosis and HCs. The participants in the CHR group were the youngest, followed by participants in the FEP group and the HC group (FEP vs. HC, $p=0.224$; CHR vs. HC, $p<0.001$; FEP vs. CHR, $p=0.077$), and there were more females in the FEP group than in either of the other groups. Handedness did not differ among the three groups.

Resting-state functional connectivity

A total of 5 components were identified as a triple network: two components were designated as the DMN (labeled as anterior and posterior), two components were identified as the SN (labeled as SN1 and SN2), and one component was categorized as the CEN (Figure 1). Compared to HCs, FEP patients showed lower functional connectivity between SN1 and the anterior DMN (cluster level $F=5.83$, p-false discovery rate [FDR] corrected=0.001; connection level $t=-4.01$, $p<0.001$), between SN1 and the posterior DMN (cluster level $F=5.83$, p-FDR corrected=0.001; connection level $t=-2.72$, $p=0.007$), and between SN1 and the CEN (cluster level $F=5.83$, p-FDR corrected=0.001; connection level $t=-2.73$, $p=0.007$). Participants in the CHR group showed lower functional connectivity at a trend level between SN1 and the anterior DMN (cluster level $F=3.06$, p-FDR corrected=0.053; connection level t=

-2.99, p=0.003) and between SN1 and the posterior DMN (cluster level F=3.06, p-FDR corrected=0.053; connection level t=-2.42, p=0.016) compared to participants in the HC group. FEP patients and individuals at CHR for psychosis did not show a significant difference in functional connectivity (Figure 1 and Table 2).

Table 1. Demographic and clinical characteristics of FEP patients, individuals at CHR for psychosis, and HCs

	FEP (N=39)	CHR (N=78)	HCs (N=110)	Statistical analysis†	
				F/χ^2	p
Age (yr)	23.03±5.63	20.53±3.65	24.92±6.75	13.699	<0.001**
Sex (male/female)	17/22	57/21	69/41	9.704	0.008*
Handedness (right/left)	34/5	70/8	104/6	2.588	0.274
IQ	98.67±13.51	107.79±12.71	112.89±12.29	18.515	<0.001**
PANSS					
Positive symptoms	16.38±4.89				
Negative symptoms	16.97±4.85				
General symptoms	34.56±6.92				
SOPS					
Positive symptoms		9.82±3.76			
Negative symptoms		13.37±6.60			
Disorganization		4.04±2.78			
General symptoms		6.81±4.39			
GAF	46.54±9.96	51.86±9.72			

Data are presented as the mean±standard deviation. *p<0.05; **p<0.005; †analysis of variance if the variances were not equal; χ^2 analysis or Fisher's exact test for categorical data. FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control; IQ, intelligence quotient; PANSS, Positive and Negative Syndrome Scale; SOPS, Scale of Prodromal Symptoms; GAF, global assessment functioning

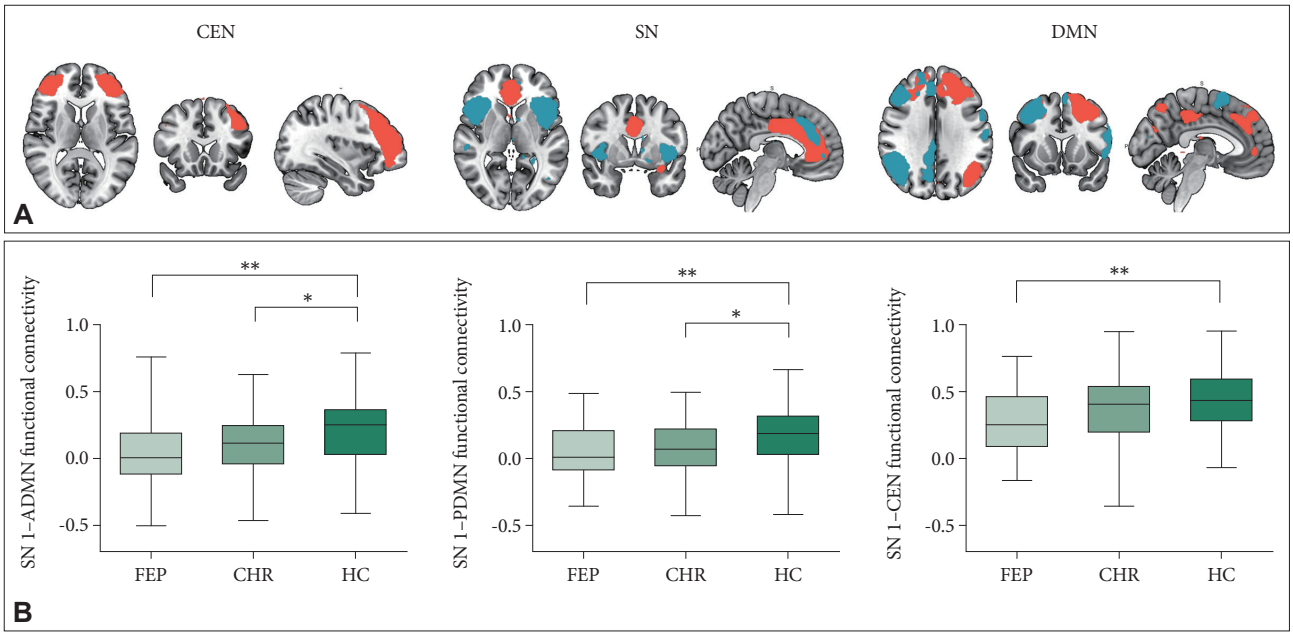

Figure 1. Extracted network mask and resting-state functional connectivity differences across participants in the FEP, CHR for psychosis, and HC groups. A: Extracted intrinsic connectivity networks are categorized into three different networks: the CEN, SN, and DMN. Each color presented in each network brain image represents a different component. The presented network had a threshold of T>4. B: Functional connectivity among networks for each group. The horizontal lines at each end of the vertical line indicate minimum and maximum values, and a horizontal line in the box indicates mean values. *indicates trend-level significance at cluster level FDR-corrected p=0.05; **indicates significance at the cluster level FDR-corrected p<0.005. CEN, central executive network; SN, salience network; DMN, default-mode network; ADMN, anterior default-mode network; FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control; PDMN, posterior default-mode network; FDR, false discovery rate.

Table 2. Comparison of internetwork connectivity across FEP patients, individuals at CHR for psychosis, and HCs

Brain network	Connectivity strengths			F	Cluster p-FDR corrected	T	p
	FEP	HCs	CHR				
FEP vs. HCs							
Cluster A				5.83	0.001**		
SN1–ADMN	0.033±0.255	0.213±0.217				-4.01	<0.001**
SN1–CEN	0.292±0.243	0.421±0.210				-2.73	0.007*
SN1–PDMN	0.042±0.199	0.156±0.223				-2.72	0.007*
SN2–CEN	0.151±0.191	0.230±0.208				-1.91	0.057
SN2–PDMN	0.306±0.214	0.251±0.224				1.48	0.139
SN2–ADMN	0.196±0.193	0.237±0.217				-0.73	0.463
Cluster B				1.10	0.296		
ADMN–CEN	0.593±0.228	0.670±0.249				-1.45	0.147
PDMN–CEN	0.642±0.286	0.679±0.246				-0.28	0.776
CHR vs. HCs							
Cluster C				3.06	0.053		
SN1–ADMN		0.213±0.217	0.112±0.218			-2.99	0.003**
SN1–PDMN		0.156±0.223	0.081±0.202			-2.42	0.016*
SN2–PDMN		0.251±0.224	0.275±0.227			0.84	0.401
SN1–CEN		0.421±0.210	0.388±0.238			-1.01	0.312
SN2–CEN		0.230±0.208	0.212±0.190			-0.46	0.646
SN2–ADMN		0.237±0.217	0.227±0.229			0.17	0.865
Cluster D				3.90	0.074		
ADMN–CEN		0.670±0.249	0.595±0.237			-1.85	0.065
PDMN–CEN		0.679±0.246	0.639±0.267			-0.66	0.507
FEP vs. CHR							
Cluster E				1.53	0.292		
SN1–CEN	0.292±0.243		0.388±0.238			-1.77	0.078
SN2–CEN	0.151±0.191		0.212±0.190			-1.43	0.153
SN1–ADMN	0.033±0.255		0.112±0.218			-1.43	0.153
SN2–ADMN	0.196±0.193		0.227±0.229			-0.82	0.413
SN2–PDMN	0.306±0.214		0.275±0.227			0.74	0.463
SN1–PDMN	0.042±0.199		0.081±0.202			-0.67	0.505
Cluster F				0.31	0.581		
PDMN–CEN	0.642±0.286		0.639±0.267			0.25	0.802
ADMN–CEN	0.593±0.228		0.595±0.237			0.08	0.938

Data are presented as the mean±standard deviation. *p<0.05; **p<0.005. FEP, first-episode psychosis; CHR, clinical high risk; HC, healthy control; SN, salience network; ADMN, anterior default-mode network; CEN, central executive network; PDMN, posterior default-mode network; FDR, false discovery rate

Mediation analysis

Since SN1 and DMN interconnectivity and SN1 and CEN interconnectivity showed significant differences in FEP patients when compared to the interconnectivity of HCs, mediation analysis was used to determine the role of the SN in these internetwork connectivities in FEP patients. Group was set as an independent variable, SN1 and anterior/posterior DMN connectivity strength was set as a dependent variable, and SN1 and CEN connectivity strength were set as mediators. As a result, SN1 and CEN connectivity acted as significant mediators between the group and SN1 and anterior/posterior DMN connectivity (indirect effect: -0.065, 95% BootCI [-0.119, -0.017]; indirect effect: -0.060, 95% BootCI [-0.117, -0.015]). Another mediation analysis was performed by set-

ting group as an independent variable, SN1 and CEN connectivity strength as a dependent variable and SN1 and anterior/posterior DMN connectivity strength as a mediator. This analysis also showed that the group and SN1 and CEN connectivity were significantly mediated by SN1 and anterior/posterior DMN connectivity (indirect effect: -0.085, 95% BootCI [-0.141, - 0.035]; indirect effect: -0.058, 95% BootCI [-0.103, -0.016]). The p value between the independent variable and dependent variable did not reach significance after mediation except when the dependent variable was set as SN1 and anterior DMN connectivity. However, the resulting p value was less significant than it was before the mediation analysis (Figure 2). Therefore, mediation analysis demonstrates that dysconnectivity between the SN and CEN and between the SN and DMN are mutually reinforcing.

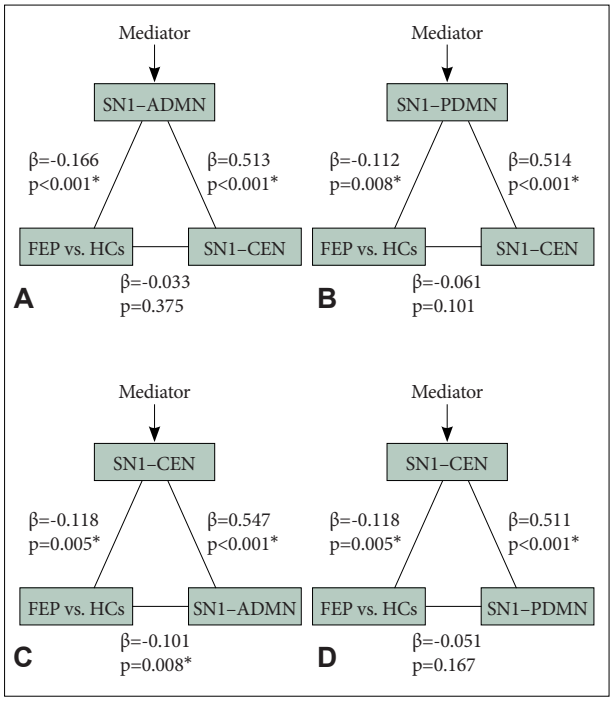

Figure 2. Mediation analysis between triple network connectivity in participants in the FEP group. A: Group (FEP and HCs) was set as an independent variable. Connectivity between SN1 and the ADMN was set as a mediator, and connectivity between SN1 and the CEN was set as a dependent variable. B: Group (FEP and HCs) was set as an independent variable. Connectivity between SN1 and the PDMN was set as a mediator, and connectivity between SN1 and CEN was set as a dependent variable. C: Group (FEP and HCs) was set as an independent variable. Connectivity between SN1–CEN was set as a mediator, and connectivity between SN1–ADMN was set as a dependent variable. D: Group (FEP and HCs) was set as an independent variable. Connectivity between SN1–CEN was set as a mediator, and connectivity between SN1–PDMN was set as a dependent variable. *indicates p<0.05, and β indicates the coefficient value. SN, salience network; ADMN, anterior default-mode network; FEP, first-episode psychosis; HC, healthy control; CEN, central executive network; PDMN, posterior default-mode network.

DISCUSSION

This study examined SN, DMN, and CEN interconnectivity in FEP patients, individuals at CHR for psychosis, and HCs by implementing a high-order ICA method to investigate the existence of dysconnectivity in the triple networks in early psychosis patients. Our results showed that, compared to HCs, FEP patients exhibited lower SN-DMN and SN-CEN functional connectivity and individuals at CHR for psychosis demonstrated lower SN-DMN functional connectivity at a trend level. Additionally, mediation analysis on functional network connectivity that had significant differences in FEP patients compared to that in HCs revealed that interconnectivity between the SN and DMN as well as between the SN and CEN both acted as mediators of one another. Overall, our findings not only suggest the existence of triple-network dysconnectivity but also indicate that the SN acts as a crucial mediating network in the early stage of psychotic disorders.

The triple-network model illustrates an interaction among the SN, CEN, and DMN and emphasizes the role of the SN in modulating between the CEN and DMN.[1,18] Previous studies reported triple-network abnormalities in chronic schizophrenia patients,[3,6,33] suggesting that dysfunctional interaction of the SN with the DMN and CEN may be a neural correlate of psychotic disorders.[8,34] The relationships between triple-network dysfunction and psychotic symptoms reported in those patients support the triple-network dysfunction theory of psychotic disorders.[2,4,5] In this study, we used the high-order ICA method to assess the inconsistencies across the previous triple-network studies on FEP patients that utilized a priori ROI methods; with our approach, we found that there was dysfunctional connectivity between the three networks of the triple-network model in FEP patients. However, unlike the current study results, a previous study by Anhøj et al.[17] that utilized high-order ICA reported no significant dysconnectivity between the triple networks in FEP patients. This discrepancy may be due to the difference in the set of networks investigated between the studies. Anhøj et al.[17] included overall cortical networks in group comparison analysis and did not focus on the triple networks, which may have led to subtle changes being missed in triple networks in early psychosis patients. Furthermore, while the region of our peak activation in the selected SN included the insular cortex, which is considered an important region of SN in many other studies,[1,8,18] the study by Anhøj et al.[17] did not. In our results, SN1, which showed a significant difference in connectivity between the CEN and DMN, had peak activation in the insular cortex. This may suggest that, in line with previous studies that highlighted the role of the insular cortex in the triple-network model, the SN, especially the insular cortex, may play an im-

portant part in the engagement between the CEN and DMN in FEP patients.

In addition, we found that the SN plays a central role in the triple-network dysconnectivity of FEP patients by demonstrating that both SN-DMN and SN-CEN dysconnectivity influenced one another via mediation analysis. Similar to our results, a recent study using dynamic causal modeling also showed disruption of the SN in interactions between the DMN and CEN in FEP patients.[35] Impaired SN connectivity could cause deficits in allocating saliency to external events or internal self-referential mental processes, and this confusion may contribute to the manifestation of psychotic symptoms in chronic schizophrenia patients.[9,34] The current study results suggest the existence of triple-network dysconnectivity centering around the dysfunctional SN modulation from the FEP state, as in chronic schizophrenia patients. However, further study examining the relationship between engagement and disengagement of the SN with the DMN and CEN and psychotic symptoms in FEP patients may help to elucidate how the model explains psychotic symptoms observed in early stages of schizophrenia.

Regarding individuals at CHR for psychosis, a small number of previous studies reported inconsistent results using the a priori ROI method. On the one hand, a study found hyperconnectivity between the SN and DMN,[14] and another study reported dysfunctionality in the three networks.[13] On the other hand, a recent meta-analysis study that investigated functional network dysconnectivity using ROIs within the DMN, CEN, and SN in individuals at CHR for psychosis reported no significant difference among the three networks.[15] In the current study, we utilized a high-order ICA method and found trend-level lower connectivity between the SN and DMN in individuals at CHR for psychosis than in HCs. The small effect size of the individuals at CHR for psychosis in the current study may be due to the characteristics of the at-risk state. First, individuals at CHR for psychosis experience attenuated psychotic symptoms, unlike FEP patients with overt psychotic symptoms, which may be a cause of the small effect size of triple-network dysfunction that is reported to be related to psychotic symptoms in schizophrenia patients.[4,5] Second, the heterogeneity of the participants in the CHR group,[36] consisting of individuals who later will transition to overt psychotic disorder and those who will not, may be another reason for the small effect size. According to Wang et al.,[37] only individuals at CHR for psychosis who later transitioned to psychotic disorder showed reduced connectivity in the SN and DMN. Considering that the transition rate in our individuals at CHR for psychosis from the Seoul Youth Clinic has been reported to be 32.6%,[38] the trend-level lower connectivity between the SN and DMN found in individuals at CHR for psychosis in the current study may be the result of the dilution effect of heterogeneous individuals at CHR for psychosis.

This study had several limitations. First, most of the FEP patients were taking antipsychotics at the time of fMRI data acquisition. Since antipsychotics seem to have an effect on functional connectivity,[12,39] we should not ignore the possible effect of antipsychotics when interpreting the current study results. Second, age and sex were not matched across the groups. Although we tried to control for age and sex by using these variables as covariates in every group comparison analysis, the results still need to be cautiously interpreted. Third, since it was a cross-sectional study, there was a limitation in the ability to show how functional connectivity changes as individuals at CHR for psychosis transition to having a psychotic disorder longitudinally. Furthermore, the lower DMN-SN connectivity found in participants in the CHR group was found only at a trend level. This may be due to the characteristics of the at-risk state, which are subthreshold psychotic symptoms and heterogeneity. Although we were unable to perform subgroup analysis between individuals at CHR for psychosis who transitioned and those who did not due to limited sample size, we may speculate that subgroup analysis may have helped to increase statistical power. Finally, we designed the present study specifically to investigate internetwork connectivity among the DMN, CEN, and SN using the triple-network model. However, it should be taken into a consideration that there are also whole-brain network studies that investigate not only networks included in the triple-network model but also other networks detectable by resting-state neuroimaging.

In conclusion, the current study results suggest the existence of triple-network dysconnectivity centering around SN dysfunction from the FEP state, as in chronic schizophrenia patients. In addition, we found triple-network dysconnectivity in individuals at CHR for psychosis to a lesser degree. Although the findings are somewhat speculative because of the cross-sectional study design, triple-network dysconnectivity may worsen as a patient's disorder progresses from a high-risk state to an overt psychotic disorder. Therefore, future longitudinal studies with large sample sizes are warranted to conclude whether triple-network dysconnectivity could be a marker reflecting the progression of early psychotic disorders. Overall, the present study results may help to draw conclusions from inconsistencies regarding triple-network dysconnectivity reported in early psychosis patients.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jun Soo Kwon, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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