이학박사학위논문

조현형 인격장애
: 임상 특성 및
휴지기 뇌 기능적 연결성 연구

Altered resting state networks
in schizotypal personality disorder

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Altered resting state networks in schizotypal personality disorder

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To the Faculty of the

Department of Brain and Cognitive Sciences

At

Seoul National University

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Ji-Won Hur

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Abstract

Altered resting state networks in schizotypal personality disorder

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Introduction: Schizotypal personality disorder (SPD) shares genetic susceptibilities and clinical features with schizophrenia. Despite growing interest for resting functional connectivity networks of schizophrenia, to date, little is known about the presumably abnormal resting–connectivity networks of SPD. The current study aimed to examine the resting–state default mode network (DMN) functional connectivity in individuals with schizotypal personality disorder using functional MRI.

Methods: Twenty–five individuals with SPD and 39 HC underwent 3T resting-state functional scans. The connectivity analysis was performed by (1) Region of Interest (ROI)–to–ROI and (2) seed–to–voxel analysis.

(1) We examined the functional connectivity between eighteen a priori ROIs of the DMN, a set of the most dominant and intrinsic resting state functional network.

(2) To assess the abnormalities of connectivity built between the DMN components and the rest of the brain, seed-to-voxel connectivity estimations were also applied to the functional data.

We also investigated associations between the features of resting-state networks and individual psychopathology.

Results: Interactions among ROIs in the DMN significantly differed between the two groups. During resting state, the SPD group exhibited increased functional connectivity between the left middle frontal gyrus and both the bilateral posterior cingulate cortices and left parahippocampal gyrus. Additionally, connectivity between the right angular gyrus and bilateral posterior cingulate cortices was decreased in the SPD compared to the HC group. Seed–based correlation analysis revealed increased functional connectivity between the frontal lobe and the seed region, the posterior cingulate cortex. The altered temporal connectivity was significantly correlated with clinical symptoms.

Conclusions: Individuals with SPD showed hyperconnectivity in the frontal region and parahippocampal gyrus during resting state and may partially represent a crucial psychopathology of SPD. These findings support the idea that SPD is located at the lower end of schizophrenia spectrum disorders, maintaining distance from schizophrenia.

Keywords**:** schizotypal personality disorder, functional connectivity, default mode network, resting state, social dysfunction.

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Contents

Page

List of Figures

Page

List of Tables

Page

Introduction

- Loneliness has followed me my whole life. Everywhere. In bars, in cars, sidewalks, stores, everywhere. There's no escape. I'm God's lonely man.

(Movie, 'Taxi Driver (1976)')

The movie 'Taxi driver' has been praised as accurate portrayal of schizotypal personality disorder (SPD) (Hyler, 1988). The main character exhibits ideas of reference, magical thinking, cognitive distortions, poor reality testing, a markedly eccentric appearance, asociality, and alienation. He expresses the experience of social alienation that arises from living in a world where he is not understood, and where he cannot understand.

SPD first appeared in the Diagnostic and Statistical Manual of Mental Disorders in 1980 (APA, 1980), and the latest diagnostic guidelines, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (APA, 2013), treat it as a schizophrenia spectrum disorder. The DSM-5 defines SPD as "a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts." In addition to a disturbed self-experience and magical or paranoid thinking, which are dominant symptoms in most schizophrenia spectrum disorders, odd mannerisms, speech or appearance, social anxiety and social withdrawal are also salient in SPD. This pathology is particularly evident when self–boundary disturbances, paranoid ideation, or

peculiar interests are unexpectedly challenged by consensual accepted notions of reality (Dickey et al., 2005).

Contemporary neuroimaging approaches have identified the neural correlates of the self-experiences and social cognitive processes that had been studied for many decades by self–report and experimental methods (Jack et al., 2013; Kühn and Gallinat, 2013; Raballo and Parnas, 2011). Specifically, an increasing number of studies have determined that *resting-state networks* are essential for and intrinsic to introspective mental processes. Remarkably, in normal populations, these resting-state networks are activated during periods of waking rest, but they are deactivated during goal–directed behavior (Raichle and Snyder, 2007). These intrinsic networks may thus offer simple but empirically sound insights about brain functioning without the need for administering intricately designed tasks or subjecting patients to excessive cognitive loads (Malaspina et al., 2004; van de Ven et al., 2013; Zhou et al., 2007). The *default mode network* (DMN) is now considered the most representative. It has been suggested that the DMN plays a key role in ego functioning, monitoring, and attentional processing during social situations. It is known that this network includes the cingulate cortex, precuneus, anterior cingulate cortex, angular gyrus, parahippocampal gyrus, and hippocampus (McKiernan et al., 2003). Current research suggests that altered connectivity in the DMN was revealed from individuals at high risk for psychosis to patients with schizophrenia (Mannell et al., 2010; Orliac et al., 2013; Rotarska-Jagiela et al., 2010; Shim et al., 2010; Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009). These studies suggest that failure of the modulation function of the DMN may contribute to

misperceptions of the self-boundary, thought disorders, and even social and neurocognitive dysfunction (Woodward et al., 2011).

The traits associated with schizotypal personality disorder (e.g., psychotic symptoms, abnormal self-experiences, and social deficits) are more likely to be observed in individuals with schizophrenia (Rossi and Daneluzzo, 2002), their relatives (Fanous et al., 2001; Kendler and Gardner, 1997), individuals in the prodromal phase of schizophrenia (Fenton and McGlashan, 1989; Raine, 2006) and those at risk for psychosis than in normal population (Fanous et al., 2007; Johnstone et al., 2005). However, whether schizotypal traits decrease the risk for psychosis or facilitate the transition to this state remains controversial (Widiger, 2012; Woods et al., 2009). Therefore, it is important to define the psychopathophysical markers of SPD to understand its relationship to actual schizophrenia. However, to our knowledge, research on SPD is limited. Moreover, no resting-state functional connectivity analyses related to SPD have been performed to date.

The present study examined resting-state functional connectivity using functional magnetic resonance imaging (fMRI) to compare SPD and healthy control groups. We hypothesized that data on resting–state functional connectivity would reveal disorder-specific changes in the SPD group. We used both region of interest (ROI)–based and seed-region-based analyses to explore altered functional connectivity in SPD. The ROI-based analysis provided results in terms of the classic brain regions of interest, whereas the seed–region–based analysis showed the unique, disease-specific alterations in terms other than predetermined ROIs (Delmonte et al., 2013; Unschuld et al., In press). Finally, we examined the

clinical implications of altered functional connectivity in SPD based on correlation analysis. We hypothesized that the network measures extracted from ROIs or seed regions would correspond with clinical measures reflecting schizotypal personality pathology.

Materials and Methods

Participants

Twenty-five individuals with SPD (19 men, six women; mean age: 22.88 ± 3.52 years) and 39 healthy controls (30 men, nine women; mean age: 22.18 ± 2.47 years) participated in this study. Subjects were recruited via postings, bulletin board advertisements, and word of mouth. Based on the innovative advertisements used in recruiting individuals with SPD in prior research (Dickey et al., 1999), we used the following message to recruit potential participants: *A brain-imaging study being conducted by researchers at Seoul National University is looking for people who believe in or experience hallucinatory experiences, telepathy, sixth sense, or déjà vu and feel uncomfortable in situations involving getting along with others. The aim of the study is to contribute to a better understanding of a specific type of personality.*

The initial subject pool included 250 individuals who responded to the above advertisement (advertisement). Prospective participants were screened by phone (telephone screen), and 185 were ineligible because they did not respond to the telephone call or did not meet the minimum criteria (at least four of the criteria for SPD in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision) (APA, 2000). The remaining 65 participants were asked to schedule a clinic visit to complete a structured interview to determine their eligibility for participation in the study. The Structured Clinical Interview for DSM-IV (SCID)–Axis I, –non–patient, and –Axis II were administered by a

clinically licensed psychiatrist or psychologist to confirm the diagnosis as well as to rule out previous or current probable psychotic disorders (First et al., 1995; First et al., 1996). Participants were included in the SPD group only when two raters agreed substantially on the diagnosis of SPD. The exclusion criteria were a DSM-IV diagnosis of a psychotic disorder, current or past neurological disorders, medical illnesses affecting the central nervous system, and a history of using antipsychotics. A flowchart showing the recruitment process and numbers of potential participants involved at each stage of the study is presented in Figure 1. Healthy control (HC) subjects were recruited via Internet advertisement and completed a telephone screen, a structured interview, clinical and neurocognitive assessments, and a brain imaging scan.

Of the 65 subjects who completed clinical interviews to determine eligibility for membership in the SPD group, 31 met at least five of the nine criteria for a diagnosis of SPD. Six of these 31 individuals were excluded due to a previous or current bipolar disorder, not otherwise specified (n = 4), brief psychotic disorder (n = 1), or transition to actual schizophrenia prior to completing fMRI scanning (n = 1). Finally, 25 participants were enrolled in the SPD group. Individuals in this group had a mean of 0.4 additional personality disorders: paranoid (n = 5); schizoid, borderline, antisocial, avoidant, dependent, or obsessive-compulsive (n = 1, each). Several members of the SPD group also met criteria for depressive disorder (n = 3), obsessive–compulsive disorder (n = 2), or post-traumatic stress disorder (n = 1).

HC subjects had no personal or family history of psychiatric disorders and no neurological disorders. The SPD and HC groups were matched for age,

sex, socioeconomic status, educational level, estimated IQ according to the Korean version of the Wechsler Adult Intelligence (Kim et al., 1994) and handedness.

All subjects provided written informed consent for this study, which was approved by the Institutional Review Board of Seoul National University. Every participant was compensated, and all were individually informed about the research results.

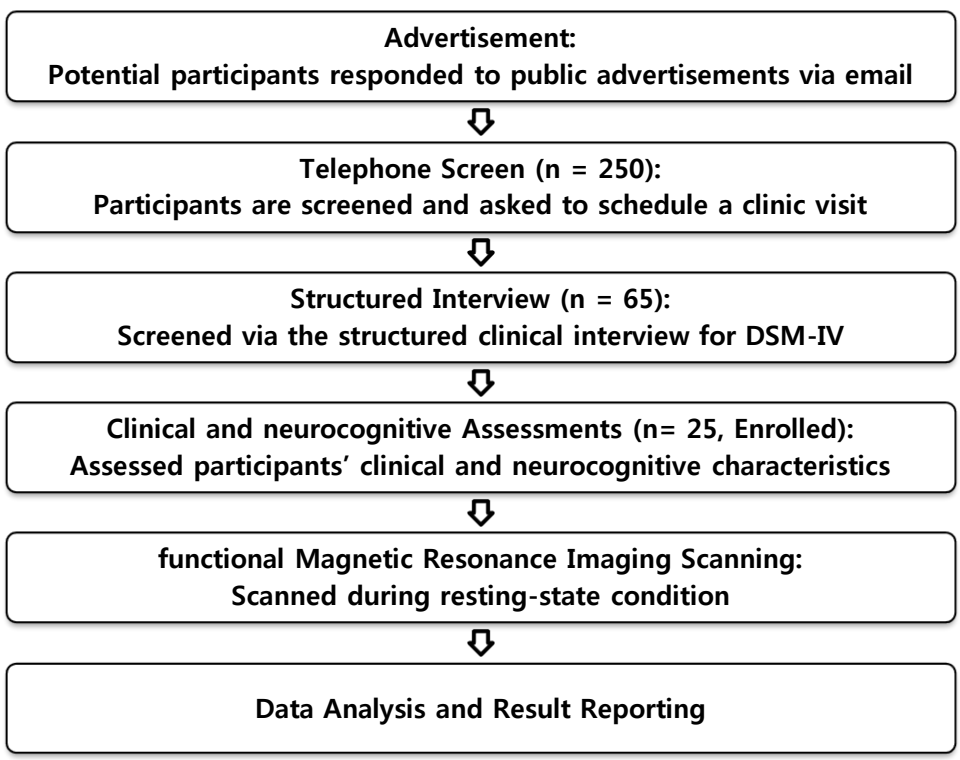

Figure 1. Flowchart of the recruitment process for schizotypal personality disorders through the study.

Clinical Measurements

To rate clinical symptoms, we used the Positive and Negative Syndrome Scale (PANSS; three dimensions of positive, negative, and general symptoms), the Scale for the Assessment of Positive Symptoms (SAPS; four distinct positive symptoms: hallucinations, delusions, bizarre behavior, and thought disorder), and the Scale for the Assessment of Negative Symptoms (SANS; five distinct negative symptoms: flat affect, alogia, avolition, anhedonia–asociality, and attention) (Andreasen and Olsen, 1982; Kay et al., 1987). To assess the range and severity of schizotypal traits, all subjects completed the Schizotypal Personality Questionnaire-Korean Version (SPQ-K) (Moon et al., 1997; Raine, 1991), a 74-item self-report questionnaire addressing cognitive–perceptual (ideas of reference, magical thinking, unusual perceptual experiences, paranoid ideation), interpersonal (social anxiety, no close friends, constricted affect, paranoid ideation), and disorganization (odd behavior, odd speech) factors, which have been supported by confirmatory factor analyses.

MRI Acquisition and preprocessing

Imaging was conducted on a Siemens 3T Magnetom Trio Tim syngo MR scanner (Siemens, Malvern, PA) with 12–channel head coil. T2*–weighted echo planar functional images (EPI) were acquired in an interleaved order with repetition time (TR) = 3.5 s, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 240 mm, voxel size = 1.9 × 1.9 × 3.5, 3.5-mm slice thickness, 0.7-mm gap, and 35 slices covering the whole brain. To obtain reference images

for analysis, T1-weighted anatomical images were also acquired with repetition time (TR) = 1670 ms, echo time (TE) = 1.89 ms, flip angle (FA) = 9°, field of view (FOV) = 250 mm, voxel size = 1 × 1 × 1 mm, and 1-mm slice thickness prior to the fMRI session. During the fMRI session, participants were asked to lie still and relax. All subjects were asked to refrain from drinking caffeinated beverages for at least 6 hours preceding their imaging session for purposes of standardization, and they were confirmed to be awake at the start and conclusion of the trial.

Image preprocessing was performed using the SPM8 software package (Statistical Parametric Mapping 8; http://www.fil.ion.ucl.ac.uk/spm/software/). Each trial consisted of 116 time points. The initial four images were discarded for signal stabilization. Scans were slice-time corrected to the first slice in each TR. Functional data were then realigned and unwarped, co-registered with the anatomical gray matter, and spatially normalized into standard stereotactic space using the Montreal Neurological Institute (MNI) template (http://www.mni.mcgill.ca/). Furthermore, voxel size was resampled to 3 × 3 × 3-mm isotropic resolution and smoothed with a full-width half-maximum (FWHM) Gaussian kernel of 6 × 6 × 6 mm on the space domain.

Functional Connectivity Analysis

The functional connectivity analysis was performed using the Conn toolbox of SPM8 (http://www.nitrc.org/projects/conn). To focus on the specificity of gray matter signals and to regress out physiological noise, such as white matter, cerebrospinal fluid signals, and other noise artifacts, a temporal band-pass filter

(0.008–0.09 Hz) and the anatomical component-based noise-correction method (CompCor) were applied.(Behzadi et al., 2007) Six head-motion parameters (three rotation and three translation) were also regressed out. Functional connectivity estimates were then generated by correlating the blood-oxygen-level-dependent (BOLD) time course extracted from each of the regions of the ROI–to–ROI or seed–to–voxel maps during the resting state. Correlation coefficients were converted into *z*–scores using Fisher's *r*–to–z transformation to allow for second-level general linear model (GLM) analyses.

Thus, images from the first-level results (correlation maps and *z*–maps) provided both (1) ROI–to–ROI and (2) seed-to-voxel connectivity maps for each selected source for each subject.

(1) To define ROI–to–ROI functional connectivity in the SPD and HC groups, we used 18 functional network templates composed of nine dorsal and nine ventral DMN regions from the Stanford FIND lab (http://findlab.stanford.edu/functional_ROIs.html. One of original 10 ventral DMN regions, the right lobule IX, was excluded due to the limitations of the cerebellar hemispheric image obtained from some participants) as ROIs (Shirer et al., 2012) (Fig. 2). The 18 ROIs were anatomically defined. Results were thresholded at a false-discovery rate (FDR) correction of $P < .05$ *(*P_{FDR} *corrected* < 0.05).

(2) We then applied the seed-driven approaches to define the obscured functional relationships among entire structures. The locations of the 6–mm diameter spherical seeds (the posterior cingulate cortex (MNI

coordinates, −8, −56, 26) and the ventral medial prefrontal cortex (0, 26,−18)) were based on *a priori* regions known for their specificity during the resting state in previous studies with either HCs or individuals with schizophrenia (Alonso-Solís et al., 2012; Menon and Uddin, 2010; Mingoia et al., 2012; Uddin et al., 2009; Uddin et al., 2011). Thus, the seeds were independent from our data. The average *z*-maps of the two seed regions were calculated. For the whole brain, significant clusters were thresholded using an *P*–value height threshold of 0.001 (uncorrected) with an extent threshold of a whole-brain family–wise error (FWE) correction of $P < .05$ *(*P_{FWE} *corrected* < 0.05).

Clinical Symptom Correlation

(1) DMN – based analysis parameters; *global efficiency*

When an individual's functional connectivity map was converted into a binary graph, the nodes and edges of the graph represented ROIs and functional connectivity, respectively. In this study, *global efficiency* was treated as a property of functional networks to explore correlations with clinical symptoms (Whitfield-Gabrieli et al., 2009). When the shortest absolute path length between *i*th node and the *j*th node is min[$L_{i,j}$}, the mean shortest absolute path length of a node is:

$$L_i = \frac{1}{N-1} \sum_{i \neq j \in G} \min\{L_{i,j}\} \ ,$$

and the global efficiency of a node is the inverse of the harmonic mean of shortest path between each pair of nodes within the DMN. Therefore, the computational formulation is as follows (Latora and Marchiori, 2001):

$$E_{\text{global}} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{i,j}}$$

Each individual's map had a global efficiency of 18 at the 18 ROIs. Generally, structurally sound and effective networks have increased global efficiency. However, topologically random graphs also have high levels of global efficiency (Achard and Bullmore, 2007). It has further been shown that global efficiency is increased by <1% in schizophrenia (Lynall et al., 2010).

(2) Mean connectivity values from seed regions

The mean connectivity values from seed regions used for analyses of correlations with clinical measurements were calculated. The Region of Interest extraction tool (http://web.mit.edu/swg/rex/rex.m) was used to extract mean connectivity values from the functional connectivity map showing group differences for each subject.

Results

Demographic and Clinical Characteristics

We found no group differences in age, sex, socioeconomic status (SES), handedness, estimated IQ, or education (Table 1). Table 1 also shows the clinical characteristics of the SPD group as measured by the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS), and self–report Schizotypal Personality Questionnaire (SPQ).

Table 1. Demographic and clinical characteristic for SPD and HC groups

Variable	**SPD (n=25)**	**HC (n=39)**	**Statistics**	
			***t* / x^2**	***P***
Age (years)	22.88 ± 3.52	22.18 ± 2.47	-0.94	n.s.
Sex (male/female)	19/6	30/9	0.93	n.s.
SES_paticipant (I/II/III/IV/V)	0/8/9/4/4	1/16/18/3/1	5.83	n.s.
SES_parental (I/II/III/IV/V)	1/10/7/6/1	0/15/17/7/0	5.05	n.s.
Handedness (R/L/A)	19 / 5 / 1	35 / 3 / 1	0.32	n.s.
Estimated IQ (K–WAIS)	115.00 ± 12.55	120.18 ± 7.59	1.86	n.s.
Education (years)	14.64 ± 1.60	14.69 ± 1.10	0.14	n.s.
SPQ total score	33.96 ± 12.41	5.69 ± 5.53	-10.73	<.001
PANSS total score	50.84 ± 10.98	n.a.		
PANSS_Positive symptoms	13.32 ± 4.13			

PANSS_Negative symptoms	11.24 ± 5.28	
PANSS_General symptoms	27.08 ± 5.66	
SAPS	18.76 ± 10.48	n.a.
SAPS_Hallucinations	3.92 ± 3.33	
SAPS_Delusions	8.92 ± 5.48	
SAPS_Bizarre Behavior	3.24 ± 2.79	
SAPS_Thought disorder	2.72 ± 3.47	
SANS	15.64 ± 15.64	n.a.
SANS_Affective flattening	5.48 ± 5.43	
SANS_Alogia	0.72 ± 1.97	
SANS_Avolition–apathy	3.36 ± 5.13	
SANS_Anhedonia–asociality	5.88 ± 6.77	
SANS_Attention	1.04 ± 1.79	

Mean ± S.D. SPD, Schizotypal personality disorder; HC, Healthy control; SES, Socioeconomic status, Five SES were identified ranging from highest (I) to lowest (V); R/L/A, Right/Left/ Ambidexter; K–WAIS, Korean–Wechsler Adult Intelligence Scale; PANSS, Positive and Negative Syndrome Scale; SAPS/ SANS; Scale for the Assessment of Positive / Negative Symptoms; SPQ, Schizotypal Personality Questionnaire; n.s, not – significant; n.a., not – applicable

Functional Brain Connectivity Analyses

ROI–to–ROI approach

When compared with HCs, the SPD group showed three ROIs with higher resting-state functional connectivity (P_{FDR} *corrected* < 0.05): the left middle frontal gyrus, the bilateral posterior cingulate cortices, and the left parahippocampal gyrus. Additionally, the functional connectivity between the right angular gyrus and bilateral posterior cingulate cortices was decreased in the SPD compared with the HC group (Table 2). No significant differences between

the groups were observed in the remaining networks. Between-group comparisons in the ROI–to–ROI analysis are illustrated in Figure 3.

Seed based analyses

Compared with HCs, the SPD group showed multiple areas with increased resting-state functional connectivity (height threshold of $P < 0.001$ with an extent threshold of P_{FWE} *corrected* <.05). The SPD group showed an even greater increase in connectivity with the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex (MNI coordinates, -04, +38, +24) when the posterior cingulate cortex was used as a seed region. Figures 4 and 5 show the connectivity patterns for the seed regions. This seed–based analysis did not reveal any other increased connectivity in the DMN of HC compared with SPD participants.

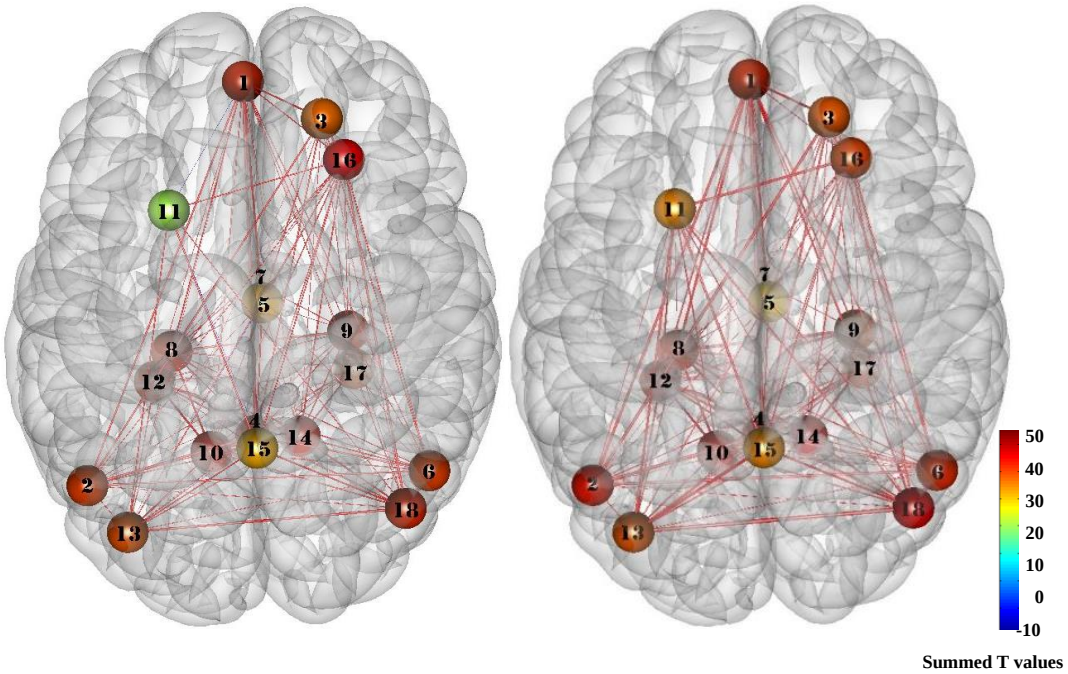

Figure 2. Definition of 18 ROIs within Default Mode Network.
(A) Positive network map in healthy control (HC) and (B) in schizotypal personality (SPD) groups (Top View).

dorsal Default Mode Network (dDMN)	Brodmann Areas
1. Medial Prefontal C, Anterior Cingulate C, Orbitofrontal C	9,10,24,32, 11
2. Left Angular G	39
3. Right Superior Frontal G	9
4. Posterior Cingulate C, Precuneus	23,30
5. Midcingulate C	23
6. Right Angular G	39
7. Left and Right Thalamus	N/A
8. Left Hippocampus	20,36,30
9. Right Hippocampus	20,36,30
ventral Default Mode Network (vDMN)	**Brodmann Areas**
10. Left Retrosplenial C, Posterior Cingulate C	29,30,23
11. Left Middle Frontal G	8,6
12. Left Parahippocampal G	37,20
13. Left Middle Occipital G	19,39
14. Right Retrospenial C, Posterior Cingulate C	30,23
15. Precuneus	7,5
16. Right Superior Frontal G, Middle Frontal G	9,8
17. Right Parahippocampal G	37,30
18. Right Angular G, Middle Occipital G	39.19

http://findlab.stanford.edu/functional_ROIs.html
C, Cortex; G, Gyrus

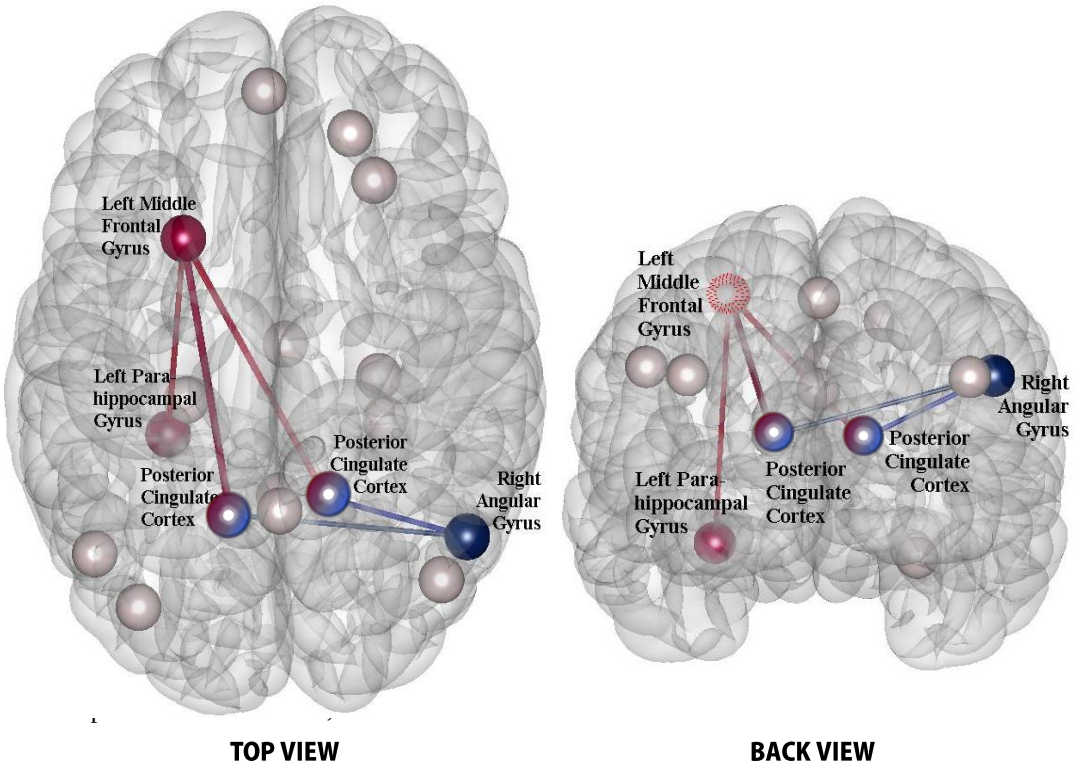

Figure 3. Default mode functional connectivity that differ between SPD and HC groups based on correlation within 18 ROIs (Group comparison, P_{FDR} *corrected*<0.05).

Red lines: functional connectivity was higher in SPD; whereas for blue lines: connectivity was lower in SPD

Table 2. Between-group ROI-to-ROI analysis results for default mode network

ROI 1	ROI 2	Group Difference (t – value)
Hyperconnectivity in schizotypal personality disorder		
Left Middle Frontal Gyrus	Left Parahippo-campal Gyrus	3.05*
	Left Posterior Cingulate Cortex	4.63***
	Right Posterior Cingulate Cortex	3.84***
Hyperconnectivity in healthy controls		
Right Angular Gyrus	Left Posterior Cingulate Cortex	−3.41*
	Right Posterior Cingulate Cortex	−3.16*

*P<0.05; **P<0.01; ***P<0.001

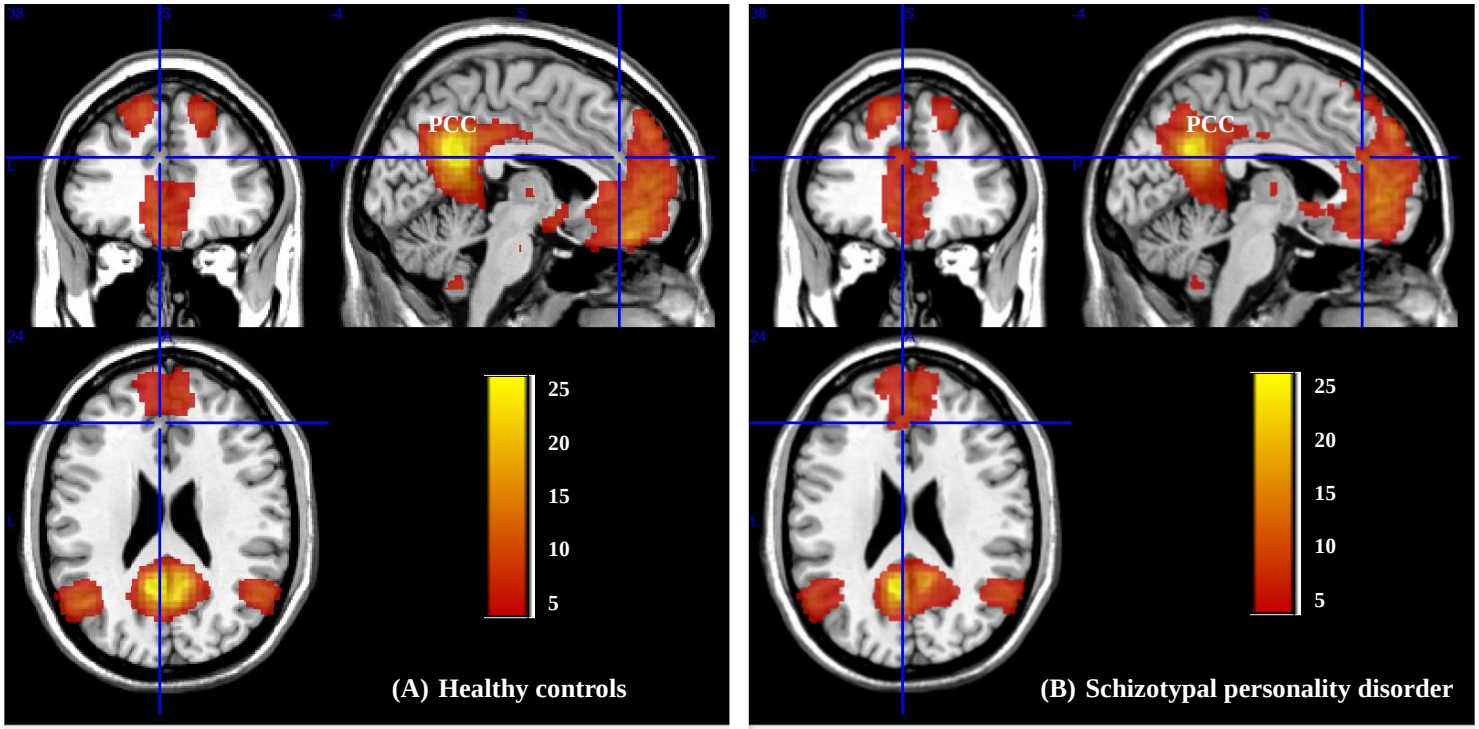

Figure 4. Functional connectivity maps from the posterior cingulate cortex (PCC) seed for subjects (A) Healthy controls (B) Schizotypal personality disorder (SPD). (B) depicts frontal lobe activation in the SPD (MNI coordinates, -04, +38, +24). The statistics and illustration of group differences are provided in figure 5 and table 3.

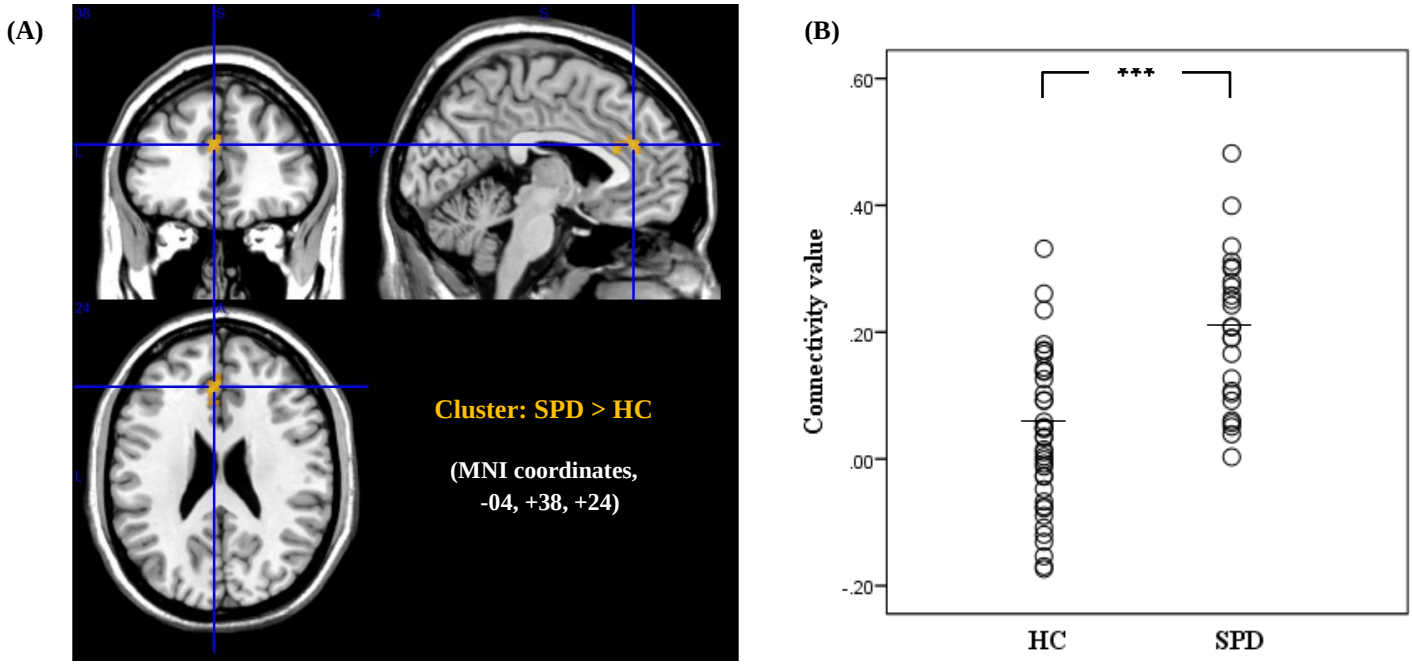

Figure 5. Hyperconnectivity in schizotypal personality disorder (SPD) relative to the healthy control (HC) during resting state using the posterior cingulate cortex (height threshold of $P < 0.001$ with an extent threshold of FWE correction of $P < .05$)**.** (A) Group differences of resting state functional connectivity (B) Group differences of connectivity strength with posterior cingulate cortex seed z-maps

Table 3. Brain regions exhibiting higher connectivity with the posterior cingulate cortex in SPD compared with HC group.

MNI coordinates (*x, y, z*)	Cluster size	Brain region	*cluster* P_{FWE}
(-04, +38, +24)	125	Dorsolateral Prefrontal Cortex, Dorsal Anterior Cingulate Cortex	0.001

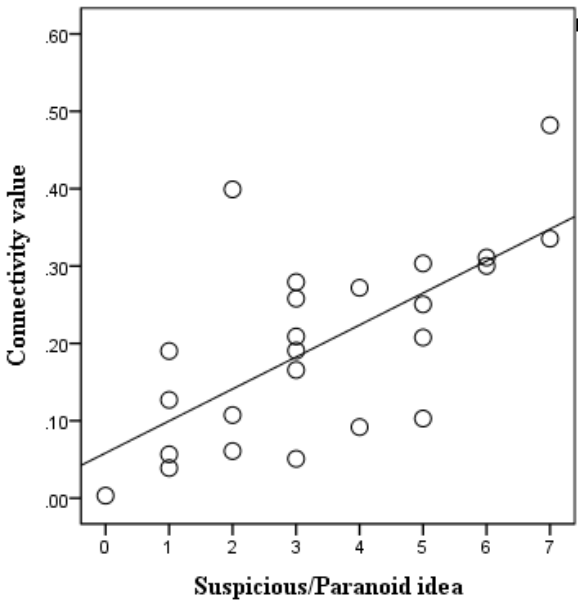

Figure 6. Correlation between z – value and suspicious/ paranoid idea of schizotypal personality questionnaire

Correlation between connectivity and clinical measurements in SPD

Correlation analyses revealed that the *global efficiency* in the angular gyrus of the SPD group was associated with scores on the SAPS_delusion subscale (*Spearman's rho* = –.51, *P* = .009). Connectivity in left PCC was related to scores on the PANSS_general symptom subscale (*rho* = .54, *P* = .005) and the SAPS behavioral subscale (*rho* = .53, *P* = .007). Connectivity in the parahippocampal gyrus was associated with the SAPS_thought disorder subscale (*rho* = .53, *P* = .006) (Fig. 7). The temporal connectivity (*z*-value) between significant regions was associated with the SPQ_suspicious/paranoid ideation subscale (*rho* = .53, *P* < .006) (Fig. 6).

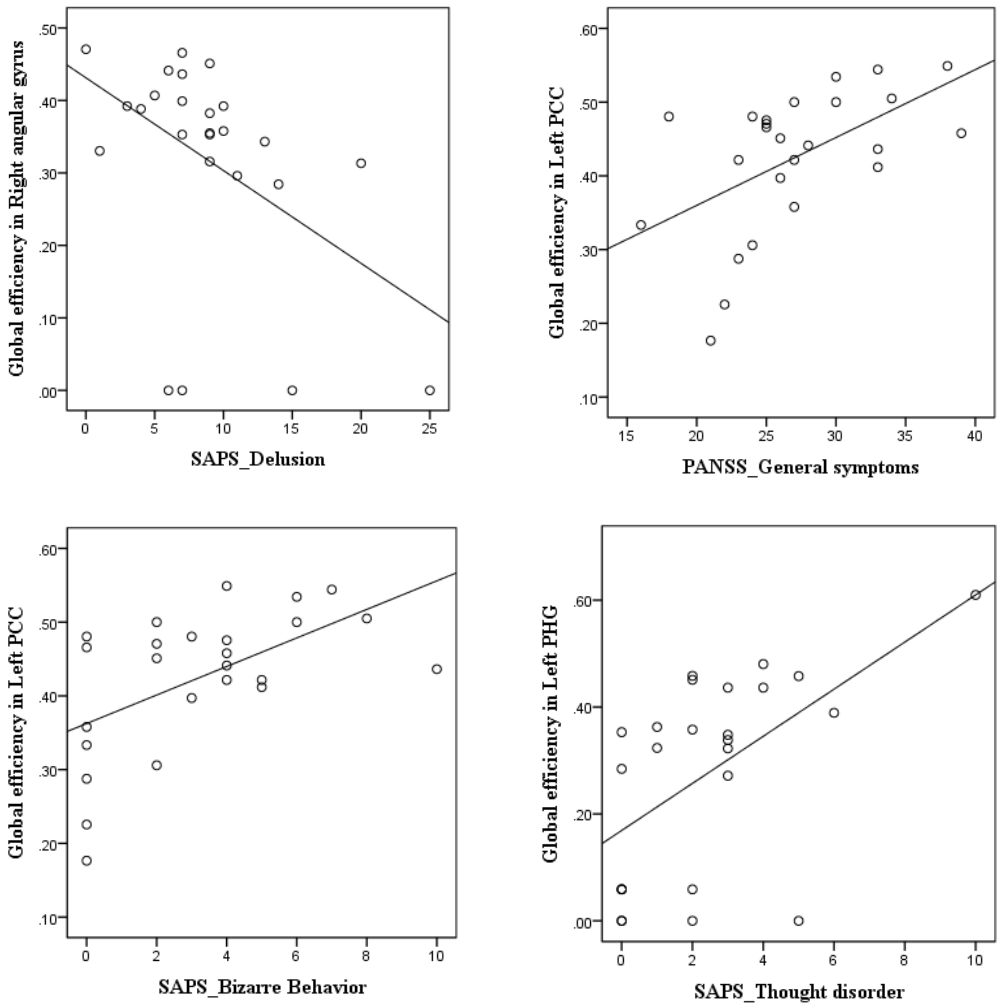

Figure 7. Correlation analyses between connectivity measures in ROIs and clinical data in schizotypal personality disorder group (PCC, Posterior cingulate cortex; PHG, Parahippocampal gyrus; PANSS, Positive and Negative Syndrome Scale; SAPS; Scale for the Assessment of Positive Symptoms)

Discussion

This study identified alterations in the default mode network (DMN) related to the psychopathology associated with schizotypal personality disorder (SPD) using resting-state connectivity analyses. To our knowledge, this is the first study to explore functional connectivity during the resting state in SPD. Individuals with SPD are disconnected from reality and simultaneously stand at the edge of psychosis. Their interests and ideas about themselves and others differ from those of other people. Thus, we believed that an analysis of resting-state connectivity, which relates to sense of self, social cognition, and even to psychosis (Jack et al., 2013; Malaspina et al., 2004; Mitchell, 2006; Shad et al., 2011) could provide clinical insights into SPD. Our findings revealed alterations in resting-state functional connectivity involving increased connectivity in the frontal regions and parahippocampal gyrus of individuals with SPD. Most brain regions showing connectivity anomalies in SPD individuals are the same as those identified in previous studies demonstrating altered DMN in schizophrenia (Whitfield-Gabrieli et al., 2009). Additionally, the global efficiency of DMN components and the strength of connectivity were markedly related to the clinical symptoms of SPD.

Specifically, individuals with SPD demonstrated greater connectivity between the left middle frontal gyrus and the bilateral posterior cingulate

cortices and left parahippocampal gyrus. Although no consensus has been reached about whether the connectivity of the middle frontal gyrus is increased or decreased in individuals with schizophrenia spectrum disorders compared with HCs, it is clear that anomalies in middle frontal gyrus connectivity exist in schizophrenia and that those are correlated with psychotic symptoms (Camchong et al., 2011; Whitfield-Gabrieli et al., 2009). Even the relatives of patients with schizophrenia exhibited increased resting-state connectivity in middle frontal gyrus (Garrity et al., 2007). Thus, many researchers have argued that understanding activation in the middle frontal gyrus during the resting state may be critical to elucidating the pathology of schizophrenia spectrum disorders. Consideration of the role of the middle frontal gyrus and posterior cingulate cortex in self-reference, internal thoughts, and monitoring clarifies the clinical implications of alterations in the DMN in schizophrenia spectrum disorders (Gusnard et al., 2001; Qin and Northoff, 2011). Many previous studies have also found that individuals with schizophrenia spectrum disorders who exhibit hyperconnectivity in the DMN may be prone to cognitive symptoms, social dysfunction, and reality-testing deficits (e.g., blurring the boundary between internal thoughts and the external environment) (Anselmetti et al., 2007; Whitfield-Gabrieli et al., 2009). Predictably, we found a significant change in the connectivity between the middle frontal gyrus and the posterior cingulate cortex. We also found a significant correlation between the global connectivity of the left posterior cingulate cortex and bizarre behavior and general psychopathology in individuals with SPD. That is, abnormalities in connectivity may consistently reflect the clinical features of

schizophrenia spectrum disorders.

Contrary to previous schizophrenia research (Benetti et al., 2009; White et al., 2008; Zhou et al., 2008) , connectivity in the parahippocampal gyrus was increased and connectivity in the angular gyrus was reduced in the resting state in the SPD relative to HC. The enhanced parahippocampal connectivity and reduced connectivity in the right angular gyrus in SPD are similar to anomalies in DMN connectivity associated with childhood autism (Kennedy and Courchesne, 2008; Lynch et al., 2013; Monk et al., 2009). One of the key roles of the parahippocampus is integrating and filtering the multimodal information transmitted from the cortex. Therefore, it has been suggested that the hyperconnectivity of the parahippocampal gyrus in the resting state is linked with inter- and intrapersonal cognitive processes in autism (Bar et al., 2008; White et al., 2008). Furthermore, we found that the long–range connections (global efficiency) of the parahippocampal gyrus were significantly correlated with the presence of thought disorders in the SPD group. Thus, increased parahippocampal connectivity may contribute to the ways in which individuals with autism or with SPD characterized by eccentric and unique interests or mannerisms communicate with internal and external environments. Interestingly, a number of studies have recently focused on the overlap between schizotypal and autistic symptomatology (Barneveld et al., 2011; Dinsdale et al., 2013; Hurst et al., 2007; Konstantareas and Hewitt, 2001). Additional studies with patients with schizophrenia and those with autism spectrum disorder may provide more evidence about the psychopathology shared by these mental illnesses. It is also notable that the

left parahippocampal region is genetically correlated with all other inherited DMN components. In turn, the parahippocampal connectivity within the DMN can be considered an endophenotype for mental illnesses (Glahn et al., 2010). Hence, it seems that different parahippocampal connectivity patterns between SPD and schizophrenia may reflect a divergent dimension of pathophysiology for these disorders.

In the seed-based analysis of the SPD group, the key hub of the DMN, the posterior cingulate cortex, demonstrated hyperconnectivity with the remaining regions of the brain, especially the dorsolateral prefrontal regions. Evidence about whether the DMN connectivity is increased or decreased in schizophrenia has been controversial for decades. However, most recent studies have identified increased intrinsic functional connectivity in those with schizophrenia and their unaffected first-degree relatives (Liu et al., 2012; Unschuld et al., In press; Whitfield-Gabrieli et al., 2009; Woodward et al., 2011). Additionally, our findings demonstrate that resting-state hyperconnectivity, which has been commonly located between the posterior cingulate cortex and the prefrontal cortex, may relate to scores on the suspicious/paranoid ideation subscale of the SPQ. Buckner (2013) recently offered an intriguing suggestion about the link between DMN abnormalities and psychotic symptoms. He proposed that the hyperconnectivity of the DMN may misdirect attentional resources when patients with schizophrenia try hard to interpret the ambiguous or neutral information originating in internal/external stimuli. Therefore, the altered frontoparietal control systems and over–engaged DMN observed in schizophrenia spectrum disorders may

contribute to abnormal information processing (Whitfield-Gabrieli et al., 2009). In this context, our findings seem to support the possibility that increased resting–state connectivity may relate to the neuronal underpinnings of thought disorders or social deficits, the core feature of schizophrenia spectrum disorders.

On the one hand, some researchers have suggested that excessive and inefficient resting-state networks in schizophrenia spectrum disorders may reflect compensatory reactions to the neural changes accompanying failures in cognitive processing and social functioning (Unschuld et al., In press). That is, disorder-specific functional connectivity may compensate for impairments in inhibitory processes, consequent dysregulation, and disruptions to the hierarchical prefrontal organization of patients. Such attempts at compensation within the brain may, of course, be either functional or dysfunctional in terms of their ability to deal with real or imaginary daily problems. In their systematic review of structural imaging results in SPD, Fervaha and colleagues (2013), also described "larger–than–normal prefrontal volume" as potentially reflective of a "neurocompensatory reserve" in SPD. Many structural or functional MRI findings of prominently increased or preserved frontal lobe volume or metabolic rates in SPD (Asami et al., 2013; Buchsbaum et al., 2002; Hazlett et al., 2008; Suzuki et al., 2005), have already raised the possibility of structural or functional compensatory mechanisms in this disorder. Although the results may need to be interpreted with caution, However, it is important to note that not all individuals with SPD will develop schizophrenia (Widiger, 2012). Thus, additional studies will be necessary to

identify relationships between structural and functional systems and their potential role in SPD.

The present study provides insight into resting–state functional networks in SPD; however, we also need to consider one limitation of the present study. That is, we did not perform direct comparisons between SPD and schizophrenia. There have been conflicting perspectives on the role of schizotypal personality traits as risk versus preventive factors in regard to the conversion to psychosis (Skodol, 2012). Further study is needed to determine the differences in the functional network patterns between schizophrenia and SPD. If prominent intergroup differences exist, the roles of the brain systems that underpin schizophrenia versus SPD should be elucidated.

In summary, individuals with SPD showed altered functional connectivity across five of the 18 ROIs of the DMN and increased connectivity between the dorsolateral prefrontal functional and posterior cingulate cortex. The hyperconnectivity in the frontal lobe and parahippocampal gyrus seems to reflect a possible neurobiological phenotype of SPD who are restless to agonize over and organize the internal and external stimuli. Furthermore, the relationships between the connectivity measures in altered brain regions and the psychopathology associated with SPD may be useful for understanding the busy and confused world of those with this disorder. We also believe that the present results justifies optimism about the resting-state network map, which functions as a potential guide to a more accurate clinical understanding of the characteristics of individuals with SPD, who occupy a lonely phenomenological space near that occupied by

individuals with schizophrenia.

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국문초록

조현형 인격장애
: 임상 특성 및 휴지기 뇌 기능적 연결성 연구

허지원

조현형 인격장애는 조현병과 유전적 특성을 공유하면서도 생애 전반에 걸쳐 지속적이며 안정적으로 조현형 인격 특유의 임상적 특성을 유지하는 것으로 알려져 있다. 휴지기 뇌 기능적 연결성 이상성은 조현 스펙트럼 환자의 자기 및 대인지각 문제를 비롯한 정신증적 특성과 관련이 있는 것으로 알려져 있으나 현재까지 조현형 인격장애를 대상으로 한 해당 연구는 많지 않은 편이다. 이에 본 연구에서는 기능적 자기공명영상법을 이용하여 조현형 인격장애 환자의 휴지기 뇌 기능적 연결성에 대해 탐색하고자 하였다. 휴지기에 활성화되는 영역의 연결성이 집단 간의 차이를 보일 것이며 유의한 차이를 보인 뇌

영역의 연결성 특징은 조현형 인격장애군의 임상적 특성과 상관을 보일 것이라는 가설을 설정하였다.

실험에 동의한 조현형 인격장애군 25명과 일반대조군 39명이 연구에 참여하였으며, 두 집단의 성별, 나이, 지능 및 교육연한은 통계적으로 유의한 차이를 보이지 않았다. 3.0T 자기공명영상장치를 이용하여 휴지기 동안의 기능적 자기공명영상 데이터를 획득하여 기능적 연결성에 대한 분석을 진행하였고, 이때 얻어진 연결성 데이터와 조현형 인격장애군의 임상적 평가결과 간 관계를 파악하기 위해 상관분석을 실시하였다.

결과는 다음과 같다. 첫째, 신경과 및 정신과적 질환이 배제된 일반인구에서 나타나는 휴지기 뇌 연결성을 특징짓는 18개 해부학적 관심영역 (region of interest, ROI)을 바탕으로 두 집단의 관심영역 간 상관분석 (ROI – to – ROI analysis)을 실시한 결과, 조현형 인격장애군에서 좌측 중전두회 (middle frontal fyrus) 와 좌측 해마방회 (parahippocampal gyrus), 그리고 좌측 중전두회와 양측 후측대상회 (posterior cingulate cortex) 간 연결성이 대조군에 비해 증가되어 있는

것으로 나타났다. 또한 인격장애군에서 양측 후측대상회와 우측 각회 (angular gryus) 간 연결성은 낮아져 있었다.

둘째, 관심영역 간 상관성 뿐 아니라 인격장애군의 전반적인 휴지기 뇌 연결성의 변화를 확인하고자, 휴지기 뇌 활성화 상태에서 핵심적 기능을 담당한다고 알려진 후측대상회와 복내측전전두피질을 구형의 씨앗영역 (seed region)으로 설정하여 씨앗영역 상관분석 (Seed – to – voxel analysis)을 실시하였다. 그 결과, 상기 씨앗영역은 배외측 전전두피질 (Dorsolateral prefrontal cortex)과 그 기능적 연결성이 강화되어 있는 것으로 확인되었다. 해당 씨앗영역 분석결과는 관심영역 분석에서 후측대상회와 전측 영역 간 상관이 높아져 있는 결과와 유사성을 보인다.

셋째, 관심영역 상관분석에서 집단간 차이를 보인 일부 영역들의 연결성 수준은 조현형 인격군의 사고장애 및 일반적 정신과적 증상과 유의한 상관을 보였다.

본 논문에서는 조현형 인격군의 휴지기 뇌 기능성 연결성의 이상성을 확인하였으며 이들 이상성은 임상적 특이성과도 관련이 있는 것으로

보인다. 특히 전두영역 과연결성 등 조현병 환자군에서 확인되는 휴지기 뇌 연결성 이상성과 유사한 맥락을 보이고 있으면서도 해마방회와 관련한 연결성 결과는 상반된 양상을 보이는 등, 조현 스펙트럼 장애에 속하면서도 조현병과는 다른 경과를 보이는 조현형 인격장애를 이해하는 데 본 연구가 유의한 시사점을 제공할 수 있을 것으로 보인다.

핵심어: 조현형인격장애, 뇌 기능적 연결성, 휴지기, 대인관계기능.

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이학박사학위논문

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: 임상 특성 및
휴지기 뇌 기능적 연결성 연구

Altered resting state networks
in schizotypal personality disorder

2014년 2월

서울대학교 대학원

뇌인지과학과

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Altered resting state networks in schizotypal personality disorder

Advisor: Jun Soo Kwon

A dissertation submitted in partial fulfillment of the requirement

for the degree of

DOCTOR OF PHILOSOPHY

To the Faculty of the

Department of Brain and Cognitive Sciences

At

Seoul National University

By

Ji-Won Hur

Thesis Committee:

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Abstract

Altered resting state networks in schizotypal personality disorder

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Department of Brain and Cognitive Sciences

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Introduction: Schizotypal personality disorder (SPD) shares genetic susceptibilities and clinical features with schizophrenia. Despite growing interest for resting functional connectivity networks of schizophrenia, to date, little is known about the presumably abnormal resting–connectivity networks of SPD. The current study aimed to examine the resting–state default mode network (DMN) functional connectivity in individuals with schizotypal personality disorder using functional MRI.

Methods: Twenty–five individuals with SPD and 39 HC underwent 3T resting-state functional scans. The connectivity analysis was performed by (1) Region of Interest (ROI)–to–ROI and (2) seed–to–voxel analysis.

(1) We examined the functional connectivity between eighteen a priori ROIs of the DMN, a set of the most dominant and intrinsic resting state functional network.

(2) To assess the abnormalities of connectivity built between the DMN components and the rest of the brain, seed-to-voxel connectivity estimations were also applied to the functional data.

We also investigated associations between the features of resting-state networks and individual psychopathology.

Results: Interactions among ROIs in the DMN significantly differed between the two groups. During resting state, the SPD group exhibited increased functional connectivity between the left middle frontal gyrus and both the bilateral posterior cingulate cortices and left parahippocampal gyrus. Additionally, connectivity between the right angular gyrus and bilateral posterior cingulate cortices was decreased in the SPD compared to the HC group. Seed–based correlation analysis revealed increased functional connectivity between the frontal lobe and the seed region, the posterior cingulate cortex. The altered temporal connectivity was significantly correlated with clinical symptoms.

Conclusions: Individuals with SPD showed hyperconnectivity in the frontal region and parahippocampal gyrus during resting state and may partially represent a crucial psychopathology of SPD. These findings support the idea that SPD is located at the lower end of schizophrenia spectrum disorders, maintaining distance from schizophrenia.

Keywords**:** schizotypal personality disorder, functional connectivity, default mode network, resting state, social dysfunction.

Student number**:** 2009-31229

Contents

Page

List of Figures

Page

List of Tables

Page

Introduction

- Loneliness has followed me my whole life. Everywhere. In bars, in cars, sidewalks, stores, everywhere. There's no escape. I'm God's lonely man.

(Movie, 'Taxi Driver (1976)')

The movie 'Taxi driver' has been praised as accurate portrayal of schizotypal personality disorder (SPD) (Hyler, 1988). The main character exhibits ideas of reference, magical thinking, cognitive distortions, poor reality testing, a markedly eccentric appearance, asociality, and alienation. He expresses the experience of social alienation that arises from living in a world where he is not understood, and where he cannot understand.

SPD first appeared in the Diagnostic and Statistical Manual of Mental Disorders in 1980 (APA, 1980), and the latest diagnostic guidelines, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (APA, 2013), treat it as a schizophrenia spectrum disorder. The DSM-5 defines SPD as "a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts." In addition to a disturbed self-experience and magical or paranoid thinking, which are dominant symptoms in most schizophrenia spectrum disorders, odd mannerisms, speech or appearance, social anxiety and social withdrawal are also salient in SPD. This pathology is particularly evident when self–boundary disturbances, paranoid ideation, or

peculiar interests are unexpectedly challenged by consensual accepted notions of reality (Dickey et al., 2005).

Contemporary neuroimaging approaches have identified the neural correlates of the self-experiences and social cognitive processes that had been studied for many decades by self–report and experimental methods (Jack et al., 2013; Kühn and Gallinat, 2013; Raballo and Parnas, 2011). Specifically, an increasing number of studies have determined that *resting-state networks* are essential for and intrinsic to introspective mental processes. Remarkably, in normal populations, these resting-state networks are activated during periods of waking rest, but they are deactivated during goal–directed behavior (Raichle and Snyder, 2007). These intrinsic networks may thus offer simple but empirically sound insights about brain functioning without the need for administering intricately designed tasks or subjecting patients to excessive cognitive loads (Malaspina et al., 2004; van de Ven et al., 2013; Zhou et al., 2007). The *default mode network* (DMN) is now considered the most representative. It has been suggested that the DMN plays a key role in ego functioning, monitoring, and attentional processing during social situations. It is known that this network includes the cingulate cortex, precuneus, anterior cingulate cortex, angular gyrus, parahippocampal gyrus, and hippocampus (McKiernan et al., 2003). Current research suggests that altered connectivity in the DMN was revealed from individuals at high risk for psychosis to patients with schizophrenia (Mannell et al., 2010; Orliac et al., 2013; Rotarska-Jagiela et al., 2010; Shim et al., 2010; Skudlarski et al., 2010; Whitfield-Gabrieli et al., 2009). These studies suggest that failure of the modulation function of the DMN may contribute to

misperceptions of the self-boundary, thought disorders, and even social and neurocognitive dysfunction (Woodward et al., 2011).

The traits associated with schizotypal personality disorder (e.g., psychotic symptoms, abnormal self-experiences, and social deficits) are more likely to be observed in individuals with schizophrenia (Rossi and Daneluzzo, 2002), their relatives (Fanous et al., 2001; Kendler and Gardner, 1997), individuals in the prodromal phase of schizophrenia (Fenton and McGlashan, 1989; Raine, 2006) and those at risk for psychosis than in normal population (Fanous et al., 2007; Johnstone et al., 2005). However, whether schizotypal traits decrease the risk for psychosis or facilitate the transition to this state remains controversial (Widiger, 2012; Woods et al., 2009). Therefore, it is important to define the psychopathophysical markers of SPD to understand its relationship to actual schizophrenia. However, to our knowledge, research on SPD is limited. Moreover, no resting-state functional connectivity analyses related to SPD have been performed to date.

The present study examined resting-state functional connectivity using functional magnetic resonance imaging (fMRI) to compare SPD and healthy control groups. We hypothesized that data on resting–state functional connectivity would reveal disorder-specific changes in the SPD group. We used both region of interest (ROI)–based and seed-region-based analyses to explore altered functional connectivity in SPD. The ROI-based analysis provided results in terms of the classic brain regions of interest, whereas the seed–region–based analysis showed the unique, disease-specific alterations in terms other than predetermined ROIs (Delmonte et al., 2013; Unschuld et al., In press). Finally, we examined the

clinical implications of altered functional connectivity in SPD based on correlation analysis. We hypothesized that the network measures extracted from ROIs or seed regions would correspond with clinical measures reflecting schizotypal personality pathology.

Materials and Methods

Participants

Twenty-five individuals with SPD (19 men, six women; mean age: 22.88 ± 3.52 years) and 39 healthy controls (30 men, nine women; mean age: 22.18 ± 2.47 years) participated in this study. Subjects were recruited via postings, bulletin board advertisements, and word of mouth. Based on the innovative advertisements used in recruiting individuals with SPD in prior research (Dickey et al., 1999), we used the following message to recruit potential participants: *A brain-imaging study being conducted by researchers at Seoul National University is looking for people who believe in or experience hallucinatory experiences, telepathy, sixth sense, or déjà vu and feel uncomfortable in situations involving getting along with others. The aim of the study is to contribute to a better understanding of a specific type of personality.*

The initial subject pool included 250 individuals who responded to the above advertisement (advertisement). Prospective participants were screened by phone (telephone screen), and 185 were ineligible because they did not respond to the telephone call or did not meet the minimum criteria (at least four of the criteria for SPD in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision) (APA, 2000). The remaining 65 participants were asked to schedule a clinic visit to complete a structured interview to determine their eligibility for participation in the study. The Structured Clinical Interview for DSM-IV (SCID)–Axis I, –non–patient, and –Axis II were administered by a

clinically licensed psychiatrist or psychologist to confirm the diagnosis as well as to rule out previous or current probable psychotic disorders (First et al., 1995; First et al., 1996). Participants were included in the SPD group only when two raters agreed substantially on the diagnosis of SPD. The exclusion criteria were a DSM-IV diagnosis of a psychotic disorder, current or past neurological disorders, medical illnesses affecting the central nervous system, and a history of using antipsychotics. A flowchart showing the recruitment process and numbers of potential participants involved at each stage of the study is presented in Figure 1. Healthy control (HC) subjects were recruited via Internet advertisement and completed a telephone screen, a structured interview, clinical and neurocognitive assessments, and a brain imaging scan.

Of the 65 subjects who completed clinical interviews to determine eligibility for membership in the SPD group, 31 met at least five of the nine criteria for a diagnosis of SPD. Six of these 31 individuals were excluded due to a previous or current bipolar disorder, not otherwise specified (n = 4), brief psychotic disorder (n = 1), or transition to actual schizophrenia prior to completing fMRI scanning (n = 1). Finally, 25 participants were enrolled in the SPD group. Individuals in this group had a mean of 0.4 additional personality disorders: paranoid (n = 5); schizoid, borderline, antisocial, avoidant, dependent, or obsessive-compulsive (n = 1, each). Several members of the SPD group also met criteria for depressive disorder (n = 3), obsessive–compulsive disorder (n = 2), or post-traumatic stress disorder (n = 1).

HC subjects had no personal or family history of psychiatric disorders and no neurological disorders. The SPD and HC groups were matched for age,

sex, socioeconomic status, educational level, estimated IQ according to the Korean version of the Wechsler Adult Intelligence (Kim et al., 1994) and handedness.

All subjects provided written informed consent for this study, which was approved by the Institutional Review Board of Seoul National University. Every participant was compensated, and all were individually informed about the research results.

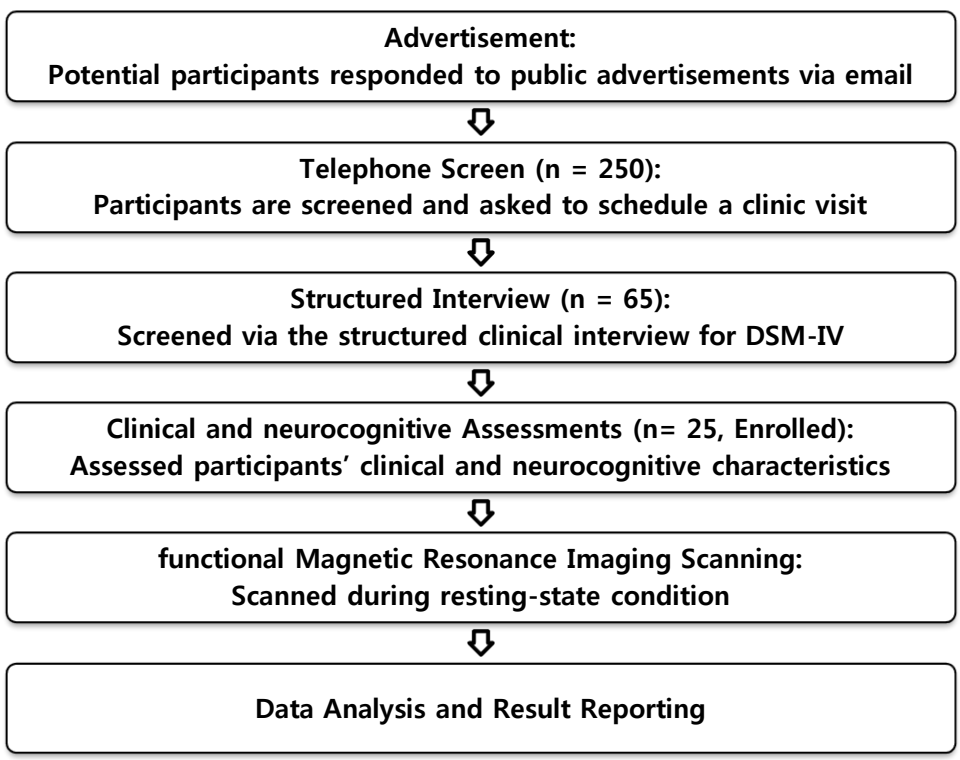

Figure 1. Flowchart of the recruitment process for schizotypal personality disorders through the study.

Clinical Measurements

To rate clinical symptoms, we used the Positive and Negative Syndrome Scale (PANSS; three dimensions of positive, negative, and general symptoms), the Scale for the Assessment of Positive Symptoms (SAPS; four distinct positive symptoms: hallucinations, delusions, bizarre behavior, and thought disorder), and the Scale for the Assessment of Negative Symptoms (SANS; five distinct negative symptoms: flat affect, alogia, avolition, anhedonia–asociality, and attention) (Andreasen and Olsen, 1982; Kay et al., 1987). To assess the range and severity of schizotypal traits, all subjects completed the Schizotypal Personality Questionnaire-Korean Version (SPQ-K) (Moon et al., 1997; Raine, 1991), a 74-item self-report questionnaire addressing cognitive–perceptual (ideas of reference, magical thinking, unusual perceptual experiences, paranoid ideation), interpersonal (social anxiety, no close friends, constricted affect, paranoid ideation), and disorganization (odd behavior, odd speech) factors, which have been supported by confirmatory factor analyses.

MRI Acquisition and preprocessing

Imaging was conducted on a Siemens 3T Magnetom Trio Tim syngo MR scanner (Siemens, Malvern, PA) with 12–channel head coil. T2*–weighted echo planar functional images (EPI) were acquired in an interleaved order with repetition time (TR) = 3.5 s, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 240 mm, voxel size = 1.9 × 1.9 × 3.5, 3.5-mm slice thickness, 0.7-mm gap, and 35 slices covering the whole brain. To obtain reference images

for analysis, T1-weighted anatomical images were also acquired with repetition time (TR) = 1670 ms, echo time (TE) = 1.89 ms, flip angle (FA) = 9°, field of view (FOV) = 250 mm, voxel size = 1 × 1 × 1 mm, and 1-mm slice thickness prior to the fMRI session. During the fMRI session, participants were asked to lie still and relax. All subjects were asked to refrain from drinking caffeinated beverages for at least 6 hours preceding their imaging session for purposes of standardization, and they were confirmed to be awake at the start and conclusion of the trial.

Image preprocessing was performed using the SPM8 software package (Statistical Parametric Mapping 8; http://www.fil.ion.ucl.ac.uk/spm/software/). Each trial consisted of 116 time points. The initial four images were discarded for signal stabilization. Scans were slice-time corrected to the first slice in each TR. Functional data were then realigned and unwarped, co-registered with the anatomical gray matter, and spatially normalized into standard stereotactic space using the Montreal Neurological Institute (MNI) template (http://www.mni.mcgill.ca/). Furthermore, voxel size was resampled to 3 × 3 × 3-mm isotropic resolution and smoothed with a full-width half-maximum (FWHM) Gaussian kernel of 6 × 6 × 6 mm on the space domain.

Functional Connectivity Analysis

The functional connectivity analysis was performed using the Conn toolbox of SPM8 (http://www.nitrc.org/projects/conn). To focus on the specificity of gray matter signals and to regress out physiological noise, such as white matter, cerebrospinal fluid signals, and other noise artifacts, a temporal band-pass filter

(0.008–0.09 Hz) and the anatomical component-based noise-correction method (CompCor) were applied.(Behzadi et al., 2007) Six head-motion parameters (three rotation and three translation) were also regressed out. Functional connectivity estimates were then generated by correlating the blood-oxygen-level-dependent (BOLD) time course extracted from each of the regions of the ROI–to–ROI or seed–to–voxel maps during the resting state. Correlation coefficients were converted into *z*–scores using Fisher's *r*–to–z transformation to allow for second-level general linear model (GLM) analyses.

Thus, images from the first-level results (correlation maps and *z*–maps) provided both (1) ROI–to–ROI and (2) seed-to-voxel connectivity maps for each selected source for each subject.

(1) To define ROI–to–ROI functional connectivity in the SPD and HC groups, we used 18 functional network templates composed of nine dorsal and nine ventral DMN regions from the Stanford FIND lab (http://findlab.stanford.edu/functional_ROIs.html. One of original 10 ventral DMN regions, the right lobule IX, was excluded due to the limitations of the cerebellar hemispheric image obtained from some participants) as ROIs (Shirer et al., 2012) (Fig. 2). The 18 ROIs were anatomically defined. Results were thresholded at a false-discovery rate (FDR) correction of $P < .05$ *(*P_{FDR} *corrected* < 0.05).

(2) We then applied the seed-driven approaches to define the obscured functional relationships among entire structures. The locations of the 6–mm diameter spherical seeds (the posterior cingulate cortex (MNI

coordinates, −8, −56, 26) and the ventral medial prefrontal cortex (0, 26,−18)) were based on *a priori* regions known for their specificity during the resting state in previous studies with either HCs or individuals with schizophrenia (Alonso-Solís et al., 2012; Menon and Uddin, 2010; Mingoia et al., 2012; Uddin et al., 2009; Uddin et al., 2011). Thus, the seeds were independent from our data. The average *z*-maps of the two seed regions were calculated. For the whole brain, significant clusters were thresholded using an *P*–value height threshold of 0.001 (uncorrected) with an extent threshold of a whole-brain family–wise error (FWE) correction of $P < .05$ *(*P_{FWE} *corrected* < 0.05).

Clinical Symptom Correlation

(1) DMN – based analysis parameters; *global efficiency*

When an individual's functional connectivity map was converted into a binary graph, the nodes and edges of the graph represented ROIs and functional connectivity, respectively. In this study, *global efficiency* was treated as a property of functional networks to explore correlations with clinical symptoms (Whitfield-Gabrieli et al., 2009). When the shortest absolute path length between *i*th node and the *j*th node is min[$L_{i,j}$}, the mean shortest absolute path length of a node is:

$$L_i = \frac{1}{N-1} \sum_{i \neq j \in G} \min\{L_{i,j}\} \ ,$$

and the global efficiency of a node is the inverse of the harmonic mean of shortest path between each pair of nodes within the DMN. Therefore, the computational formulation is as follows (Latora and Marchiori, 2001):

$$E_{\text{global}} = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{i,j}}$$

Each individual's map had a global efficiency of 18 at the 18 ROIs. Generally, structurally sound and effective networks have increased global efficiency. However, topologically random graphs also have high levels of global efficiency (Achard and Bullmore, 2007). It has further been shown that global efficiency is increased by <1% in schizophrenia (Lynall et al., 2010).

(2) Mean connectivity values from seed regions

The mean connectivity values from seed regions used for analyses of correlations with clinical measurements were calculated. The Region of Interest extraction tool (http://web.mit.edu/swg/rex/rex.m) was used to extract mean connectivity values from the functional connectivity map showing group differences for each subject.

Results

Demographic and Clinical Characteristics

We found no group differences in age, sex, socioeconomic status (SES), handedness, estimated IQ, or education (Table 1). Table 1 also shows the clinical characteristics of the SPD group as measured by the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS), and self–report Schizotypal Personality Questionnaire (SPQ).

Table 1. Demographic and clinical characteristic for SPD and HC groups

Variable	**SPD (n=25)**	**HC (n=39)**	**Statistics**	
			***t* / x^2**	***P***
Age (years)	22.88 ± 3.52	22.18 ± 2.47	-0.94	n.s.
Sex (male/female)	19/6	30/9	0.93	n.s.
SES_paticipant (I/II/III/IV/V)	0/8/9/4/4	1/16/18/3/1	5.83	n.s.
SES_parental (I/II/III/IV/V)	1/10/7/6/1	0/15/17/7/0	5.05	n.s.
Handedness (R/L/A)	19 / 5 / 1	35 / 3 / 1	0.32	n.s.
Estimated IQ (K–WAIS)	115.00 ± 12.55	120.18 ± 7.59	1.86	n.s.
Education (years)	14.64 ± 1.60	14.69 ± 1.10	0.14	n.s.
SPQ total score	33.96 ± 12.41	5.69 ± 5.53	-10.73	<.001
PANSS total score	50.84 ± 10.98	n.a.		
PANSS_Positive symptoms	13.32 ± 4.13			

PANSS_Negative symptoms	11.24 ± 5.28	
PANSS_General symptoms	27.08 ± 5.66	
SAPS	18.76 ± 10.48	n.a.
SAPS_Hallucinations	3.92 ± 3.33	
SAPS_Delusions	8.92 ± 5.48	
SAPS_Bizarre Behavior	3.24 ± 2.79	
SAPS_Thought disorder	2.72 ± 3.47	
SANS	15.64 ± 15.64	n.a.
SANS_Affective flattening	5.48 ± 5.43	
SANS_Alogia	0.72 ± 1.97	
SANS_Avolition–apathy	3.36 ± 5.13	
SANS_Anhedonia–asociality	5.88 ± 6.77	
SANS_Attention	1.04 ± 1.79	

Mean ± S.D. SPD, Schizotypal personality disorder; HC, Healthy control; SES, Socioeconomic status, Five SES were identified ranging from highest (I) to lowest (V); R/L/A, Right/Left/ Ambidexter; K–WAIS, Korean–Wechsler Adult Intelligence Scale; PANSS, Positive and Negative Syndrome Scale; SAPS/ SANS; Scale for the Assessment of Positive / Negative Symptoms; SPQ, Schizotypal Personality Questionnaire; n.s, not – significant; n.a., not – applicable

Functional Brain Connectivity Analyses

ROI–to–ROI approach

When compared with HCs, the SPD group showed three ROIs with higher resting-state functional connectivity (P_{FDR} *corrected* < 0.05): the left middle frontal gyrus, the bilateral posterior cingulate cortices, and the left parahippocampal gyrus. Additionally, the functional connectivity between the right angular gyrus and bilateral posterior cingulate cortices was decreased in the SPD compared with the HC group (Table 2). No significant differences between

the groups were observed in the remaining networks. Between-group comparisons in the ROI–to–ROI analysis are illustrated in Figure 3.

Seed based analyses

Compared with HCs, the SPD group showed multiple areas with increased resting-state functional connectivity (height threshold of $P < 0.001$ with an extent threshold of P_{FWE} *corrected* <.05). The SPD group showed an even greater increase in connectivity with the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex (MNI coordinates, -04, +38, +24) when the posterior cingulate cortex was used as a seed region. Figures 4 and 5 show the connectivity patterns for the seed regions. This seed–based analysis did not reveal any other increased connectivity in the DMN of HC compared with SPD participants.

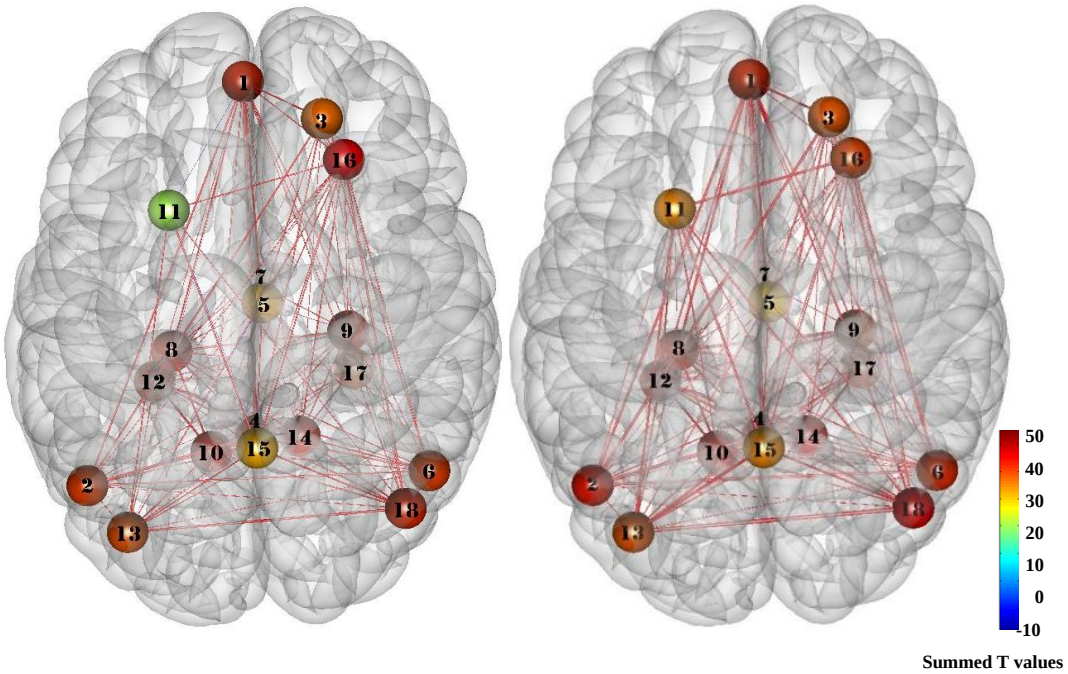

Figure 2. Definition of 18 ROIs within Default Mode Network.
(A) Positive network map in healthy control (HC) and (B) in schizotypal personality (SPD) groups (Top View).

dorsal Default Mode Network (dDMN)	Brodmann Areas
1. Medial Prefontal C, Anterior Cingulate C, Orbitofrontal C	9,10,24,32, 11
2. Left Angular G	39
3. Right Superior Frontal G	9
4. Posterior Cingulate C, Precuneus	23,30
5. Midcingulate C	23
6. Right Angular G	39
7. Left and Right Thalamus	N/A
8. Left Hippocampus	20,36,30
9. Right Hippocampus	20,36,30
ventral Default Mode Network (vDMN)	**Brodmann Areas**
10. Left Retrosplenial C, Posterior Cingulate C	29,30,23
11. Left Middle Frontal G	8,6
12. Left Parahippocampal G	37,20
13. Left Middle Occipital G	19,39
14. Right Retrospenial C, Posterior Cingulate C	30,23
15. Precuneus	7,5
16. Right Superior Frontal G, Middle Frontal G	9,8
17. Right Parahippocampal G	37,30
18. Right Angular G, Middle Occipital G	39.19

http://findlab.stanford.edu/functional_ROIs.html
C, Cortex; G, Gyrus

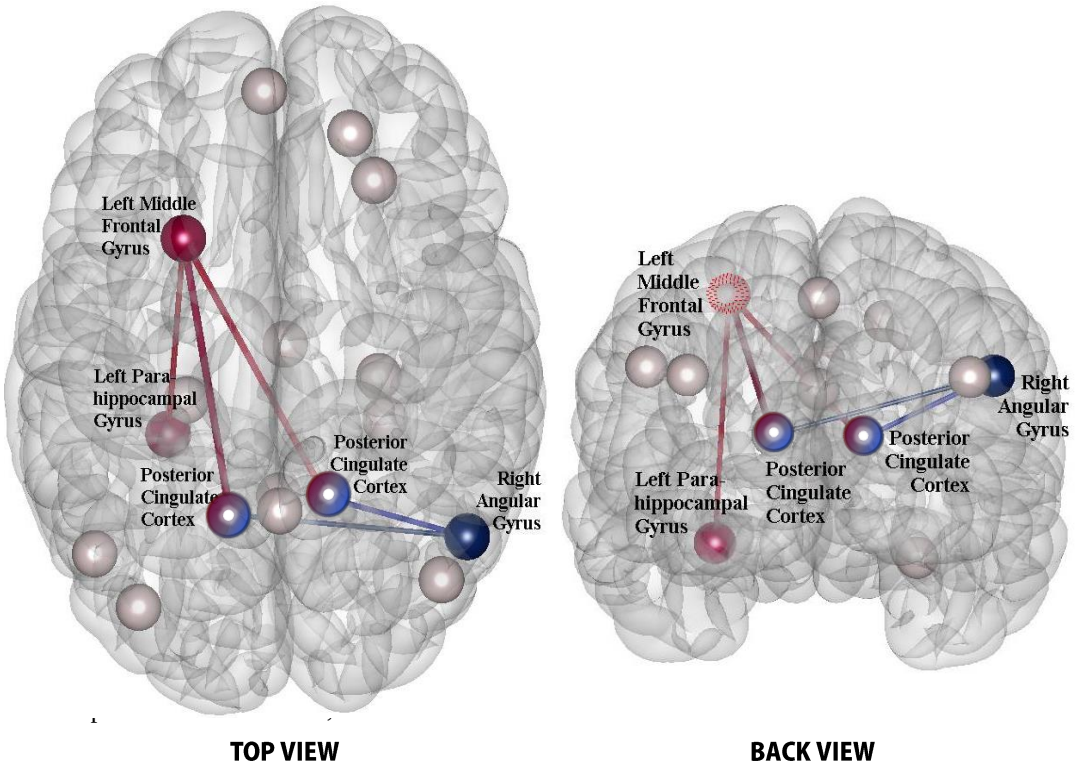

Figure 3. Default mode functional connectivity that differ between SPD and HC groups based on correlation within 18 ROIs (Group comparison, P_{FDR} *corrected*<0.05).

Red lines: functional connectivity was higher in SPD; whereas for blue lines: connectivity was lower in SPD

Table 2. Between-group ROI-to-ROI analysis results for default mode network

ROI 1	ROI 2	Group Difference (t – value)
Hyperconnectivity in schizotypal personality disorder		
Left Middle Frontal Gyrus	Left Parahippo-campal Gyrus	3.05*
	Left Posterior Cingulate Cortex	4.63***
	Right Posterior Cingulate Cortex	3.84***
Hyperconnectivity in healthy controls		
Right Angular Gyrus	Left Posterior Cingulate Cortex	−3.41*
	Right Posterior Cingulate Cortex	−3.16*

*P<0.05; **P<0.01; ***P<0.001

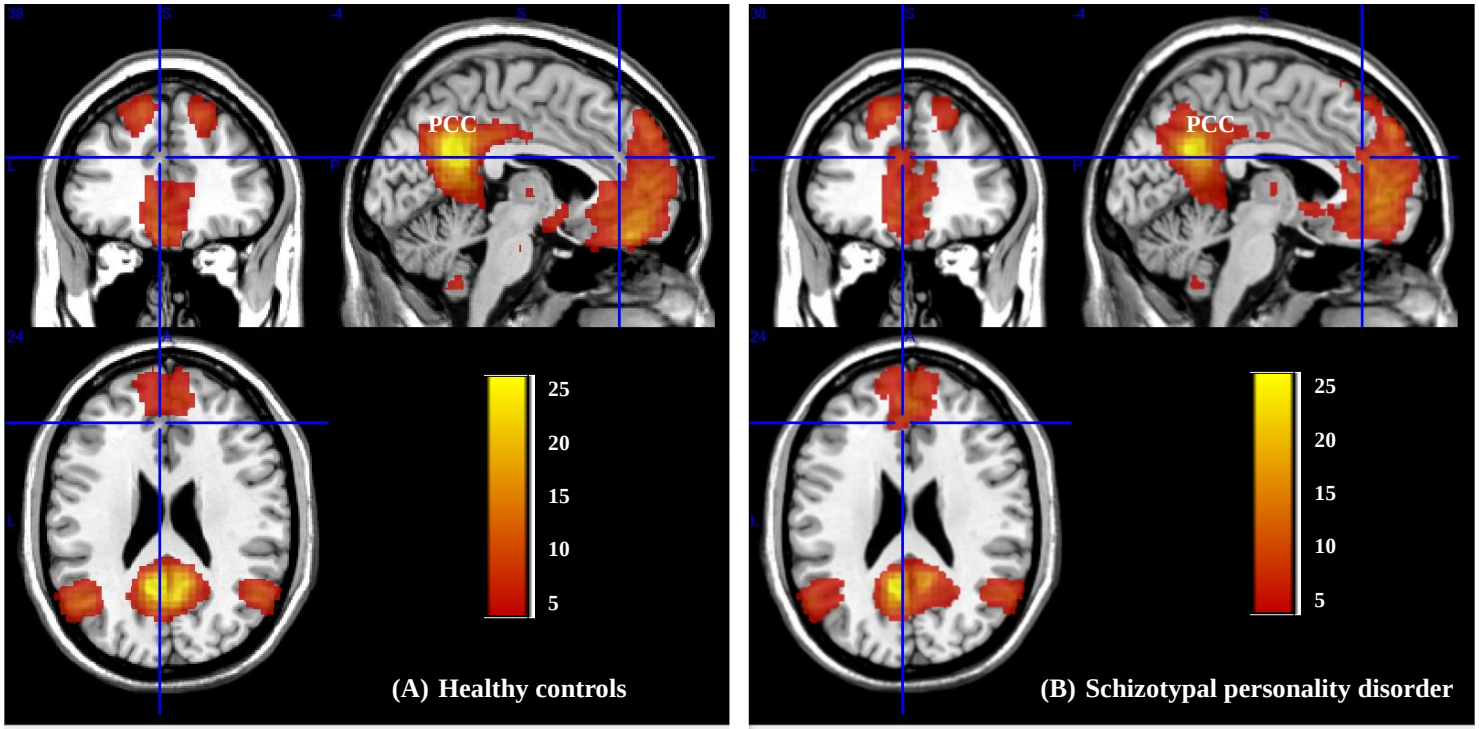

Figure 4. Functional connectivity maps from the posterior cingulate cortex (PCC) seed for subjects (A) Healthy controls (B) Schizotypal personality disorder (SPD). (B) depicts frontal lobe activation in the SPD (MNI coordinates, -04, +38, +24). The statistics and illustration of group differences are provided in figure 5 and table 3.

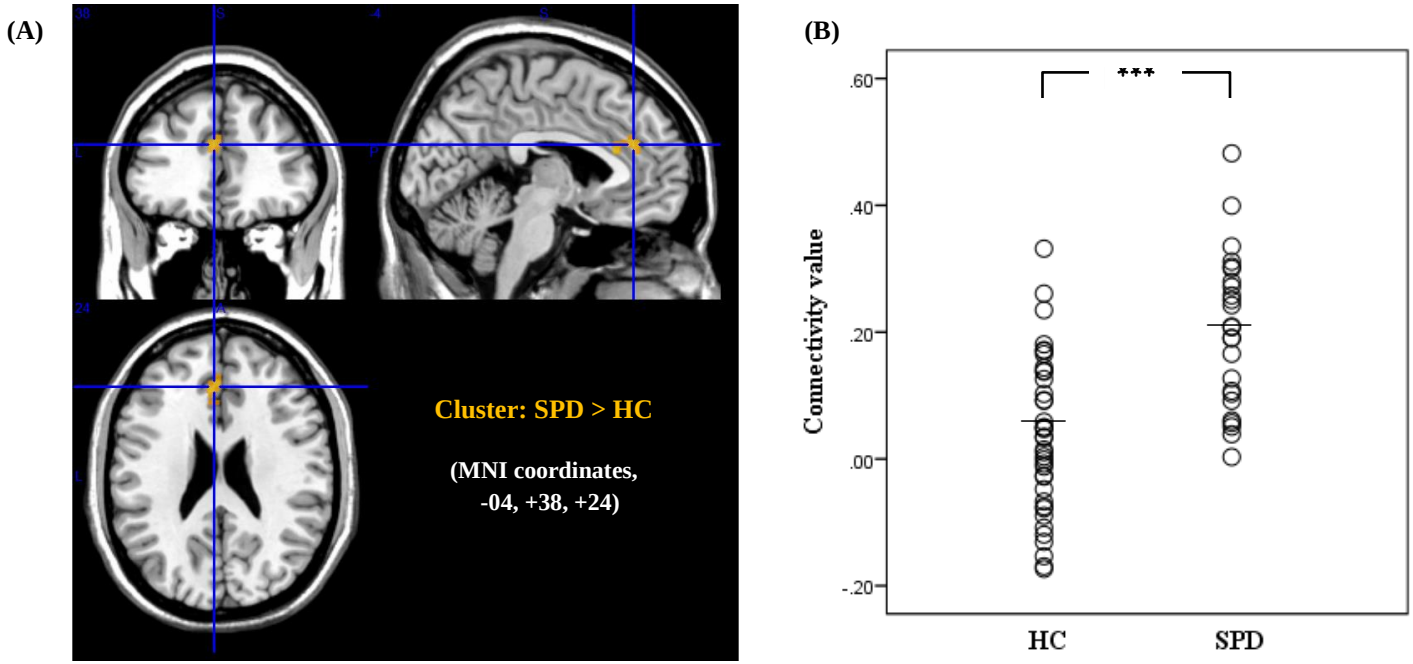

Figure 5. Hyperconnectivity in schizotypal personality disorder (SPD) relative to the healthy control (HC) during resting state using the posterior cingulate cortex (height threshold of $P < 0.001$ with an extent threshold of FWE correction of $P < .05$)**.** (A) Group differences of resting state functional connectivity (B) Group differences of connectivity strength with posterior cingulate cortex seed z-maps

Table 3. Brain regions exhibiting higher connectivity with the posterior cingulate cortex in SPD compared with HC group.

MNI coordinates (*x, y, z*)	Cluster size	Brain region	*cluster* P_{FWE}
(-04, +38, +24)	125	Dorsolateral Prefrontal Cortex, Dorsal Anterior Cingulate Cortex	0.001

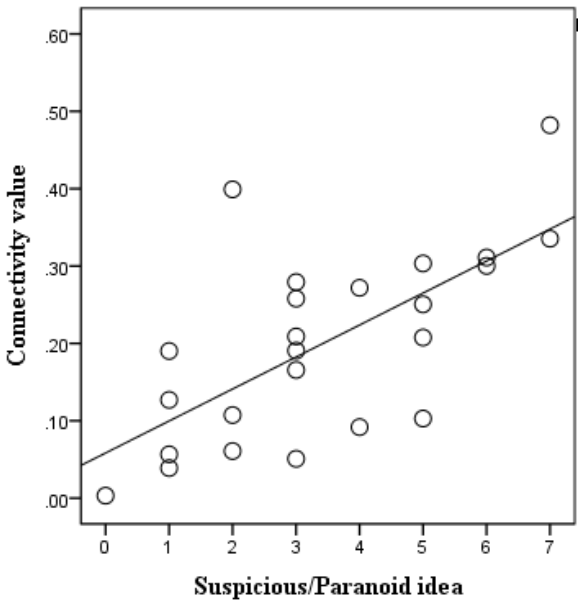

Figure 6. Correlation between z – value and suspicious/ paranoid idea of schizotypal personality questionnaire

Correlation between connectivity and clinical measurements in SPD

Correlation analyses revealed that the *global efficiency* in the angular gyrus of the SPD group was associated with scores on the SAPS_delusion subscale (*Spearman's rho* = –.51, *P* = .009). Connectivity in left PCC was related to scores on the PANSS_general symptom subscale (*rho* = .54, *P* = .005) and the SAPS behavioral subscale (*rho* = .53, *P* = .007). Connectivity in the parahippocampal gyrus was associated with the SAPS_thought disorder subscale (*rho* = .53, *P* = .006) (Fig. 7). The temporal connectivity (*z*-value) between significant regions was associated with the SPQ_suspicious/paranoid ideation subscale (*rho* = .53, *P* < .006) (Fig. 6).

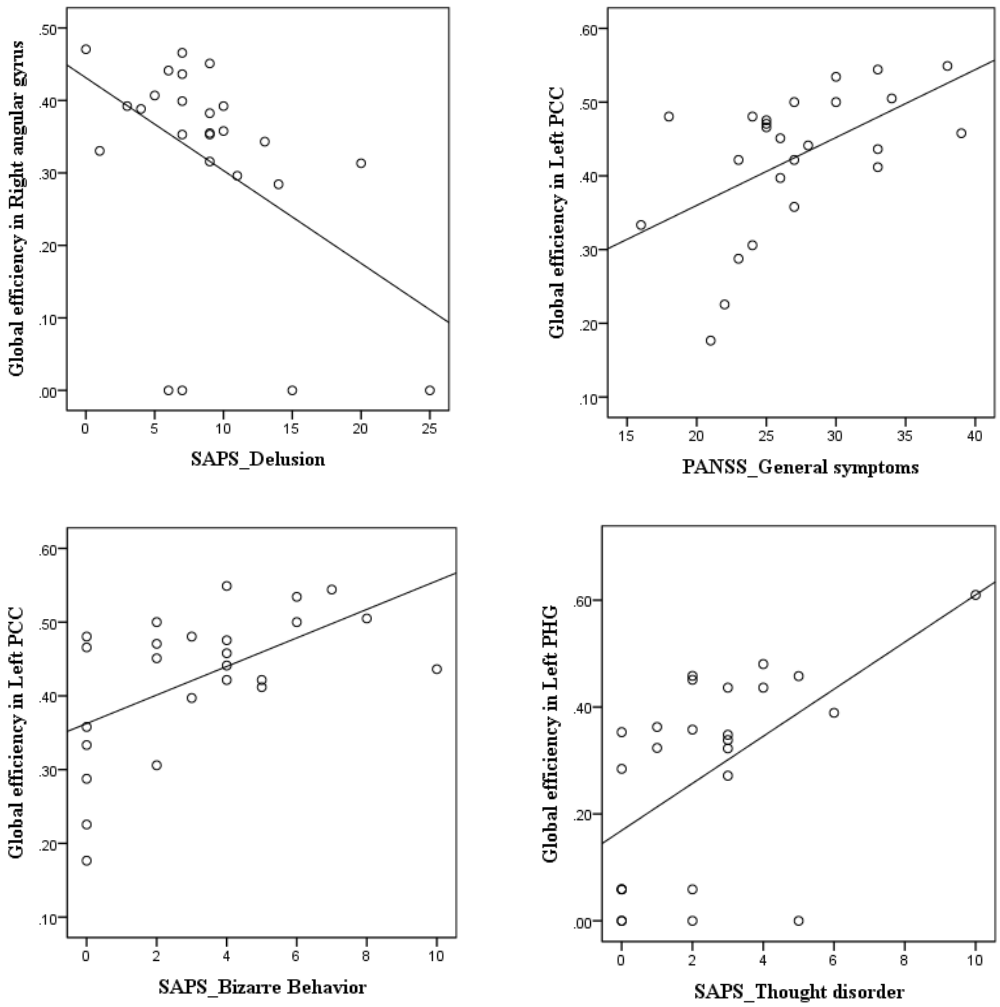

Figure 7. Correlation analyses between connectivity measures in ROIs and clinical data in schizotypal personality disorder group (PCC, Posterior cingulate cortex; PHG, Parahippocampal gyrus; PANSS, Positive and Negative Syndrome Scale; SAPS; Scale for the Assessment of Positive Symptoms)

Discussion

This study identified alterations in the default mode network (DMN) related to the psychopathology associated with schizotypal personality disorder (SPD) using resting-state connectivity analyses. To our knowledge, this is the first study to explore functional connectivity during the resting state in SPD. Individuals with SPD are disconnected from reality and simultaneously stand at the edge of psychosis. Their interests and ideas about themselves and others differ from those of other people. Thus, we believed that an analysis of resting-state connectivity, which relates to sense of self, social cognition, and even to psychosis (Jack et al., 2013; Malaspina et al., 2004; Mitchell, 2006; Shad et al., 2011) could provide clinical insights into SPD. Our findings revealed alterations in resting-state functional connectivity involving increased connectivity in the frontal regions and parahippocampal gyrus of individuals with SPD. Most brain regions showing connectivity anomalies in SPD individuals are the same as those identified in previous studies demonstrating altered DMN in schizophrenia (Whitfield-Gabrieli et al., 2009). Additionally, the global efficiency of DMN components and the strength of connectivity were markedly related to the clinical symptoms of SPD.

Specifically, individuals with SPD demonstrated greater connectivity between the left middle frontal gyrus and the bilateral posterior cingulate

cortices and left parahippocampal gyrus. Although no consensus has been reached about whether the connectivity of the middle frontal gyrus is increased or decreased in individuals with schizophrenia spectrum disorders compared with HCs, it is clear that anomalies in middle frontal gyrus connectivity exist in schizophrenia and that those are correlated with psychotic symptoms (Camchong et al., 2011; Whitfield-Gabrieli et al., 2009). Even the relatives of patients with schizophrenia exhibited increased resting-state connectivity in middle frontal gyrus (Garrity et al., 2007). Thus, many researchers have argued that understanding activation in the middle frontal gyrus during the resting state may be critical to elucidating the pathology of schizophrenia spectrum disorders. Consideration of the role of the middle frontal gyrus and posterior cingulate cortex in self-reference, internal thoughts, and monitoring clarifies the clinical implications of alterations in the DMN in schizophrenia spectrum disorders (Gusnard et al., 2001; Qin and Northoff, 2011). Many previous studies have also found that individuals with schizophrenia spectrum disorders who exhibit hyperconnectivity in the DMN may be prone to cognitive symptoms, social dysfunction, and reality-testing deficits (e.g., blurring the boundary between internal thoughts and the external environment) (Anselmetti et al., 2007; Whitfield-Gabrieli et al., 2009). Predictably, we found a significant change in the connectivity between the middle frontal gyrus and the posterior cingulate cortex. We also found a significant correlation between the global connectivity of the left posterior cingulate cortex and bizarre behavior and general psychopathology in individuals with SPD. That is, abnormalities in connectivity may consistently reflect the clinical features of

schizophrenia spectrum disorders.

Contrary to previous schizophrenia research (Benetti et al., 2009; White et al., 2008; Zhou et al., 2008) , connectivity in the parahippocampal gyrus was increased and connectivity in the angular gyrus was reduced in the resting state in the SPD relative to HC. The enhanced parahippocampal connectivity and reduced connectivity in the right angular gyrus in SPD are similar to anomalies in DMN connectivity associated with childhood autism (Kennedy and Courchesne, 2008; Lynch et al., 2013; Monk et al., 2009). One of the key roles of the parahippocampus is integrating and filtering the multimodal information transmitted from the cortex. Therefore, it has been suggested that the hyperconnectivity of the parahippocampal gyrus in the resting state is linked with inter- and intrapersonal cognitive processes in autism (Bar et al., 2008; White et al., 2008). Furthermore, we found that the long–range connections (global efficiency) of the parahippocampal gyrus were significantly correlated with the presence of thought disorders in the SPD group. Thus, increased parahippocampal connectivity may contribute to the ways in which individuals with autism or with SPD characterized by eccentric and unique interests or mannerisms communicate with internal and external environments. Interestingly, a number of studies have recently focused on the overlap between schizotypal and autistic symptomatology (Barneveld et al., 2011; Dinsdale et al., 2013; Hurst et al., 2007; Konstantareas and Hewitt, 2001). Additional studies with patients with schizophrenia and those with autism spectrum disorder may provide more evidence about the psychopathology shared by these mental illnesses. It is also notable that the

left parahippocampal region is genetically correlated with all other inherited DMN components. In turn, the parahippocampal connectivity within the DMN can be considered an endophenotype for mental illnesses (Glahn et al., 2010). Hence, it seems that different parahippocampal connectivity patterns between SPD and schizophrenia may reflect a divergent dimension of pathophysiology for these disorders.

In the seed-based analysis of the SPD group, the key hub of the DMN, the posterior cingulate cortex, demonstrated hyperconnectivity with the remaining regions of the brain, especially the dorsolateral prefrontal regions. Evidence about whether the DMN connectivity is increased or decreased in schizophrenia has been controversial for decades. However, most recent studies have identified increased intrinsic functional connectivity in those with schizophrenia and their unaffected first-degree relatives (Liu et al., 2012; Unschuld et al., In press; Whitfield-Gabrieli et al., 2009; Woodward et al., 2011). Additionally, our findings demonstrate that resting-state hyperconnectivity, which has been commonly located between the posterior cingulate cortex and the prefrontal cortex, may relate to scores on the suspicious/paranoid ideation subscale of the SPQ. Buckner (2013) recently offered an intriguing suggestion about the link between DMN abnormalities and psychotic symptoms. He proposed that the hyperconnectivity of the DMN may misdirect attentional resources when patients with schizophrenia try hard to interpret the ambiguous or neutral information originating in internal/external stimuli. Therefore, the altered frontoparietal control systems and over–engaged DMN observed in schizophrenia spectrum disorders may

contribute to abnormal information processing (Whitfield-Gabrieli et al., 2009). In this context, our findings seem to support the possibility that increased resting–state connectivity may relate to the neuronal underpinnings of thought disorders or social deficits, the core feature of schizophrenia spectrum disorders.

On the one hand, some researchers have suggested that excessive and inefficient resting-state networks in schizophrenia spectrum disorders may reflect compensatory reactions to the neural changes accompanying failures in cognitive processing and social functioning (Unschuld et al., In press). That is, disorder-specific functional connectivity may compensate for impairments in inhibitory processes, consequent dysregulation, and disruptions to the hierarchical prefrontal organization of patients. Such attempts at compensation within the brain may, of course, be either functional or dysfunctional in terms of their ability to deal with real or imaginary daily problems. In their systematic review of structural imaging results in SPD, Fervaha and colleagues (2013), also described "larger–than–normal prefrontal volume" as potentially reflective of a "neurocompensatory reserve" in SPD. Many structural or functional MRI findings of prominently increased or preserved frontal lobe volume or metabolic rates in SPD (Asami et al., 2013; Buchsbaum et al., 2002; Hazlett et al., 2008; Suzuki et al., 2005), have already raised the possibility of structural or functional compensatory mechanisms in this disorder. Although the results may need to be interpreted with caution, However, it is important to note that not all individuals with SPD will develop schizophrenia (Widiger, 2012). Thus, additional studies will be necessary to

identify relationships between structural and functional systems and their potential role in SPD.

The present study provides insight into resting–state functional networks in SPD; however, we also need to consider one limitation of the present study. That is, we did not perform direct comparisons between SPD and schizophrenia. There have been conflicting perspectives on the role of schizotypal personality traits as risk versus preventive factors in regard to the conversion to psychosis (Skodol, 2012). Further study is needed to determine the differences in the functional network patterns between schizophrenia and SPD. If prominent intergroup differences exist, the roles of the brain systems that underpin schizophrenia versus SPD should be elucidated.

In summary, individuals with SPD showed altered functional connectivity across five of the 18 ROIs of the DMN and increased connectivity between the dorsolateral prefrontal functional and posterior cingulate cortex. The hyperconnectivity in the frontal lobe and parahippocampal gyrus seems to reflect a possible neurobiological phenotype of SPD who are restless to agonize over and organize the internal and external stimuli. Furthermore, the relationships between the connectivity measures in altered brain regions and the psychopathology associated with SPD may be useful for understanding the busy and confused world of those with this disorder. We also believe that the present results justifies optimism about the resting-state network map, which functions as a potential guide to a more accurate clinical understanding of the characteristics of individuals with SPD, who occupy a lonely phenomenological space near that occupied by

individuals with schizophrenia.

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국문초록

조현형 인격장애
: 임상 특성 및 휴지기 뇌 기능적 연결성 연구

허지원

조현형 인격장애는 조현병과 유전적 특성을 공유하면서도 생애 전반에 걸쳐 지속적이며 안정적으로 조현형 인격 특유의 임상적 특성을 유지하는 것으로 알려져 있다. 휴지기 뇌 기능적 연결성 이상성은 조현 스펙트럼 환자의 자기 및 대인지각 문제를 비롯한 정신증적 특성과 관련이 있는 것으로 알려져 있으나 현재까지 조현형 인격장애를 대상으로 한 해당 연구는 많지 않은 편이다. 이에 본 연구에서는 기능적 자기공명영상법을 이용하여 조현형 인격장애 환자의 휴지기 뇌 기능적 연결성에 대해 탐색하고자 하였다. 휴지기에 활성화되는 영역의 연결성이 집단 간의 차이를 보일 것이며 유의한 차이를 보인 뇌

영역의 연결성 특징은 조현형 인격장애군의 임상적 특성과 상관을 보일 것이라는 가설을 설정하였다.

실험에 동의한 조현형 인격장애군 25명과 일반대조군 39명이 연구에 참여하였으며, 두 집단의 성별, 나이, 지능 및 교육연한은 통계적으로 유의한 차이를 보이지 않았다. 3.0T 자기공명영상장치를 이용하여 휴지기 동안의 기능적 자기공명영상 데이터를 획득하여 기능적 연결성에 대한 분석을 진행하였고, 이때 얻어진 연결성 데이터와 조현형 인격장애군의 임상적 평가결과 간 관계를 파악하기 위해 상관분석을 실시하였다.

결과는 다음과 같다. 첫째, 신경과 및 정신과적 질환이 배제된 일반인구에서 나타나는 휴지기 뇌 연결성을 특징짓는 18개 해부학적 관심영역 (region of interest, ROI)을 바탕으로 두 집단의 관심영역 간 상관분석 (ROI – to – ROI analysis)을 실시한 결과, 조현형 인격장애군에서 좌측 중전두회 (middle frontal fyrus) 와 좌측 해마방회 (parahippocampal gyrus), 그리고 좌측 중전두회와 양측 후측대상회 (posterior cingulate cortex) 간 연결성이 대조군에 비해 증가되어 있는

것으로 나타났다. 또한 인격장애군에서 양측 후측대상회와 우측 각회 (angular gryus) 간 연결성은 낮아져 있었다.

둘째, 관심영역 간 상관성 뿐 아니라 인격장애군의 전반적인 휴지기 뇌 연결성의 변화를 확인하고자, 휴지기 뇌 활성화 상태에서 핵심적 기능을 담당한다고 알려진 후측대상회와 복내측전전두피질을 구형의 씨앗영역 (seed region)으로 설정하여 씨앗영역 상관분석 (Seed – to – voxel analysis)을 실시하였다. 그 결과, 상기 씨앗영역은 배외측 전전두피질 (Dorsolateral prefrontal cortex)과 그 기능적 연결성이 강화되어 있는 것으로 확인되었다. 해당 씨앗영역 분석결과는 관심영역 분석에서 후측대상회와 전측 영역 간 상관이 높아져 있는 결과와 유사성을 보인다.

셋째, 관심영역 상관분석에서 집단간 차이를 보인 일부 영역들의 연결성 수준은 조현형 인격군의 사고장애 및 일반적 정신과적 증상과 유의한 상관을 보였다.

본 논문에서는 조현형 인격군의 휴지기 뇌 기능성 연결성의 이상성을 확인하였으며 이들 이상성은 임상적 특이성과도 관련이 있는 것으로

보인다. 특히 전두영역 과연결성 등 조현병 환자군에서 확인되는 휴지기 뇌 연결성 이상성과 유사한 맥락을 보이고 있으면서도 해마방회와 관련한 연결성 결과는 상반된 양상을 보이는 등, 조현 스펙트럼 장애에 속하면서도 조현병과는 다른 경과를 보이는 조현형 인격장애를 이해하는 데 본 연구가 유의한 시사점을 제공할 수 있을 것으로 보인다.

핵심어: 조현형인격장애, 뇌 기능적 연결성, 휴지기, 대인관계기능.

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