Aberrant cerebro-cerebellar functional connectivity and its phenomenological manifestation in individuals at ultra-high risk for psychosis and with first-episode schizophrenia

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Directed by Professor Suk Kyoon An

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This certifies that the Doctoral Dissertation of Minji Bang is approved.

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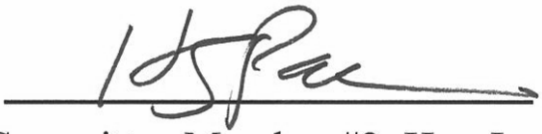

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Minji Bang

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ABSTRACT

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From a phenomenological perspective, *ipseity* disturbances have been suggested as the fundamental psychopathology of schizophrenia; however, the underlying neural mechanisms remain unclear. Here, we investigated the cerebro-cerebellar default mode network (DMN) connectivity during rest and its association with *ipseity* disturbances in individuals at ultra-high risk (UHR) for psychosis and patients with first-episode schizophrenia (FES). Thirty-three UHR individuals, including eight converters, 18 FES patients, and 56 healthy controls underwent functional magnetic resonance imaging during rest at baseline. All UHR participants were assessed for conversion to overt psychosis every month

during a follow-up period. Seed-based functional connectivity analyses using the cerebellar DMN seeds were performed, followed by between-group comparisons. Correlation analyses were conducted to examine the relationship between the cerebro-cerebellar functional connectivity and the self-reported severity of *ipseity* disturbances in the UHR and FES groups, respectively. Compared to healthy controls, converted UHR and FES participants showed decreased functional connectivity between the cerebellum and the right anterior prefrontal cortex, left presupplementary motor area, and precuneus, whereas UHR participants without conversion showed comparable functional connectivity to healthy controls. Furthermore, the degree of the cerebellar functional connectivity with several cerebral regions was significantly associated with more-severe *ipseity* disturbances in the respective groups of UHR and FES participants. Our findings support the notion that schizophrenia is a disorder of *ipseity*, which appears to be associated with aberrant cerebro-cerebellar functional connectivity. These results also imply that the underlying neuropathological changes associated with *ipseity* disturbances can be detected in UHR individuals who will later develop schizophrenia spectrum psychosis. Such aberrations in cerebro-cerebellar networks may help to predict future psychosis in UHR individuals, thus providing an opportunity to apply early interventions to prevent the onset of schizophrenia spectrum psychosis.

Key words: schizophrenia, ultra-high risk for psychosis, cerebellum, default mode network, *ipseity*, phenomenology

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I. INTRODUCTION

The current diagnosis of schizophrenia in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) is based on a description of the observable and measurable features of psychopathology. Nevertheless, this diagnosis does not capture the true nature of schizophrenia, since the DSM only describes the minimum criteria, which are reliable but do not have guaranteed validity.[1]

Over the past few years, studies have begun to explore subjective self-experiences to determine the fundamental psychopathology of schizophrenia from a phenomenological perspective.[2-5] Subjective experiences of the self, also known as the minimal self or *ipseity*, constitute the most basic levels of our

experiences, which normally remain "in the tacit background" of conscious awareness.[6-8] However, once *ipseity* is disturbed, individuals no longer experience themselves or their surroundings in a usual way. These anomalous changes are conceptualized as hyperreflexivity (heightened awareness toward some aspects of oneself that normally remain pre-reflective) and diminished self-presence (decreased feeling of being a subject of everyday experiences), which lead to disruptions in the cognitive-perceptual experiential field.[6,7] Such anomalous self-experiences have been found to be selectively aggregated in schizophrenia spectrum disorders,[9-12] and already present in the prodrome of schizophrenia.[13-15] Moreover, higher levels of anomalous self-experiences reportedly predict diagnostic conversion to overt psychosis in genetic[16] and clinical high-risk individuals.[15] These findings suggest that *ipseity* disturbances are a phenomenological manifestation of the core pathogenesis of schizophrenia. Nonetheless, the neural mechanisms responsible for the anomalous self-experiences currently remain unclear.

Recent neuroimaging studies have demonstrated that the cortical midline structures are functionally relevant to self-referential processing.[17] These areas substantially overlap with the default mode network (DMN), which is active when attention is allocated to intrinsic feelings and thoughts.[18] The DMN is known to mediate a broad range of self-related mental operations: integration of self-relevant information from the inner and outer world,[19] self-referential mental simulations and judgments,[20] autobiographical memory retrieval,[21] self-other representations,[22] and perspective taking of others.[21,23] Given this relevance of the DMN to self-referential mental activities, the DMN has been postulated to be a

neural correlate of *ipseity*.[24] However, mental operations mediated by the DMN are not purely pre-reflective but instead, are accompanied by higher cognitive aspects of the self. Because the sense of *ipseity* is immediately and automatically given to oneself without conscious awareness,[25] it is necessary to consider a more implicit mechanism of self-referential processing to investigate the neural underpinning of *ipseity* itself.

The sense of *ipseity* is closely related to the sense of agency and the sense of ownership,[6,25] which are generated by comparing the predicted outcome of our intention to the actual feedback from movement.[26,27] Based on neuroimaging findings,[28,29] the cerebellum is considered the center of this comparator system, operating as an internal model that represents the implicit dynamics of movements and thoughts.[30,31] As the internal model becomes more sophisticated throughout our lives, motor and cognitive schemas become more stable, thus enabling us to experience a pre-reflective feeling of control over our own body and mind.[32] Given that *ipseity* is a solid referential point in the field of first-person experiences, the cerebellum has been hypothesized to play an important role in the sense of *ipseity*.[33] Therefore, investigating cerebro-cerebellar connectivity within the DMN may better disclose the pre-reflective aspect of the self, which appears to be mediated not only via the cerebral DMN but also through coordination with the cerebellum.

Aberrant functional connectivity in the cerebral DMN has been repeatedly found in patients with schizophrenia; however, the findings vary across studies. Although the most common finding is hyperconnectivity of the cerebral DMN,[18,34] multimodal neuroimaging studies have identified both structural and

functional disruptions of the cerebral DMN in schizophrenia.[35,36] Regarding the cerebro-cerebellar DMN, decreased connectivity was found in patients with chronic schizophrenia,[37] while a mixed pattern of connectivity was also found in patients with first-episode schizophrenia.[38,39] Based on the functional relevance of the cerebral DMN to self-referential processing, the above findings have been interpreted as reflecting a state of preoccupation with one's own inner world.[18] However, given the functional organization between the cerebral DMN and the cerebellum as an internal model,[40] aberrant cerebro-cerebellar connectivity may be related to the disturbances of pre-reflective self-experiences in schizophrenia, although the link between them has not yet been empirically examined. Since it is known that *ipseity* disturbances can be detected more precisely prior to psychotic elaborations,[5,41] examining the disturbances in individuals at ultra-high risk (UHR) for psychosis may help to reveal the true gestalt of schizophrenia as a disorder of *ipseity*. Moreover, UHR individuals have an advantage of being relatively less contaminated by secondary morbidity due to advances illness, as well as FES patients do. Although some recent studies have reported that the functional connectivity of the cerebro-cerebellar DMN was increased in genetic high-risk[38,39] and UHR[42] individuals compared to that in healthy individuals, differences between converters and non-converters were not investigated. Therefore, further investigations are needed to specify what neurobiological mechanisms are related to the conversion risk in UHR individuals and their relevance to *ipseity* disturbances from a phenomenological perspective.

The aim of the present study was to investigate the cerebro-cerebellar DMN functional connectivity and its association to *ipseity* disturbances across healthy

controls, UHR individuals with and without conversion to overt psychosis, and FES patients. A resting-state functional magnetic resonance imaging (fMRI) paradigm was chosen to evaluate implicit and pre-reflective experiences of the self in the absence of specific thoughts or external stimuli. We first hypothesized that UHR individuals and FES patients would show aberrant functional connectivity within the cerebro-cerebellar DMN when compared to healthy controls. More specifically, converted UHR individuals were expected to show a similar pattern of aberrant functional connectivity with schizophrenia, whereas non-converters were not. Finally, we predicted that aberrant cerebro-cerebellar DMN connectivity would be associated with the severity of *ipseity* disturbances in UHR individuals and FES patients.

II. MATERIALS AND METHODS

1. Participants

Thirty-three UHR individuals, including eight converters, 18 patients with FES and 56 healthy controls (HCs) participated in the present study. UHR and FES participants were recruited from the Clinic FORYOU of the Green Program for Recognition and Prevention of Early Psychosis (GRAPE) project at Severance Hospital of the Yonsei University Health System in Seoul, Republic of Korea.[43,44] The present study was reviewed and approved by the Institutional Review Board of Severance Hospital of the Yonsei University Health System. All participants, including a parent for participants who were younger than 18 years, provided written informed consent after the procedures had been fully explained.

All participants were assessed for psychiatric disorders using the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-IV).[45,46] Participants with a current or past diagnosis of neurological disorders, traumatic brain injury, or intellectual disability (IQ < 70) were excluded. After a diagnostic interview, HCs with any current or past history of psychiatric illness and UHR individuals with a current or past history of major psychiatric disorders with psychotic features were also excluded. Patients with schizophrenia were diagnosed based on the DSM-IV criteria.[47] First episode was defined as a new onset of overt psychotic symptoms, which are sufficient in duration and severity for the diagnosis of schizophrenia. Only patients with less than 36 months of illness were included in the present study; the mean duration of illness in FES participants was 16.4 months (standard deviation [SD] = 11.6 months, median = 16.0 months,

interquartile range [IQR] = 7.5−27.0 months, range: 1−36 months). The diagnosis of UHR individuals was made based on the Structured Interview for Prodromal Syndromes (SIPS; version 4.0).[48] Each UHR participant met at least one of the following three criteria: (1) attenuated positive prodromal syndrome (APPS; n = 32), (2) brief intermittent psychotic syndrome (BIPS; n = 5) and (3) genetic risk and deterioration syndrome (GRDS; n = 6).

The clinical characteristics and severity of symptoms in UHR and FES participants were assessed using the Scale for the Assessment of Negative Symptoms (SANS)[49] and Scale for the Assessment of Positive Symptoms (SAPS).[50] One converter and eight non-converters in UHR participants and all FES participants were taking atypical antipsychotic medications at the time of fMRI scanning. Table 1 shows the demographic and clinical profiles of the participants.

Table 1. Demographic and clinical profiles of the participants[1]

	HCs (n = 56)	UHR-NC (n = 25)	UHR-C (n = 8)	FES (n = 18)	Statistics	
					Test	*p*-value
Age (years)	20.5 (3.1)	20.3 (4.7)	20.9 (2.9)	21.4 (6.0)	$F(3, 103) = 0.31$	0.818
Sex (male/female)	28/28	16/9	6/2	8/10	$\chi^2(3) = 3.45$	0.327
Education (years)	13.4 (1.9)	12.6 (1.9)	13.3 (1.6)	12.6 (2.5)	$F(3, 103) = 1.30$	0.278
SIPS[2]						
Positive symptoms		12.8 (3.3)	12.9 (3.5)		t=-0.07	0.947
Negative symptoms		11.6 (6.2)	13.3 (4.1)		t=-0.69	0.494
Disorganized symptoms		3.7 (2.4)	3.6 (3.3)		t=0.03	0.980
General symptoms		6.2 (3.8)	6.0 (4.1)		t=0.11	0.914
SANS, summary score[3]		5.4 (3.9)	6.9 (3.9)	7.9 (4.5)	$F(2, 47) = 1.90$	0.161
SAPS, summary score[3, *]		3.5 (2.2)	3.3 (1.8)	6.7 (3.0)	$F(2, 47) = 9.92$	< 0.001
Medication status (medicated/unmedicated)		8/17	1/7	18/0		
Chlorpromazine equivalent dose (mg/day)[51]		132.9 (146.6)	195 (NA)	428.0 (283.0)		

[1] Mean values are presented with standard deviations in parentheses.

[2] Data from two non-converter are missing.

[3] Data from one non-converter are missing.

[*] Post-hoc comparisons: UHR-NC vs. UHR-C: $p > 0.999$, UHR-NC vs. FES: $p < 0.001$, UHR-C vs. FES: $p = 0.006$

HCs, healthy controls; UHR-NC, ultra-high risk individuals without conversion; UHR-C, ultra-high risk individuals with conversion; FES, first-episode schizophrenia; SIPS, Structured Interview for Prodromal Syndromes[48]; SANS, Scale for the Assessment of Negative Symptoms[49]; SAPS, Scale for the Assessment of Positive Symptoms[50]; NA, not applicable.

2. Assessment of *ipseity* disturbances

To assess the *ipseity* disturbances, all participants completed the eight-item schizophrenia-specific subscale of the Frankfurt Complaint Questionnaire (FCQ-S; see Appendix), which has been shown to be diagnostically specific to schizophrenia.[52] Although the FCQ is primarily utilized for assessing basic symptoms, that is, the subtle and subjectively experienced disturbances in affect, cognition, perception, and motor abilities,[5] these basic symptoms largely overlap with anomalous self-experiences and thus have been used to index the severity of the *ipseity* disturbances in previous studies.[8,53] The statements of the FCQ-S can be conceptually divided into two categories: "sensomotoric irritations (items 11, 14, 63, and 81)" and "avoidance behavior (items 15, 90, 93, and 94)."[52] The items describing sensomotoric irritations may correspond to operative hyperreflexivity which refers to a sudden conscious awareness of phenomena that normally remain tacit and pre-reflective.[6] On the other hand, the items on avoidance behavior seem to be a behavioral counterpart of diminished self-presence, which refers to a decreased feeling of being affected by the cognitive-perceptual world.[6] Because such disturbances are no longer implicit in the experiential field, they can be detected by self-reported ratings. Participants answered each item with either yes (1) or no (0), and the total score was calculated as the sum of the eight items, which ranged from 0 to 8. The internal consistency (Cronbach's α) of the FCQ-S was 0.737 in the present study.

3. Assessment of conversion to overt psychosis in UHR participants

UHR participants were re-assessed every month during a follow-up period

(median = 14.2 months, IQR = 7.1−28.9 months, range: 1−94.0 months) to determine whether they had developed schizophrenia spectrum psychosis. There were included six UHR participants, who were followed up for less than six months (all non-converters). Conversion to overt psychosis was confirmed according to the DSM-IV criteria for psychotic disorders (schizophrenia, schizoaffective disorder, delusional disorder, and psychotic disorder not otherwise specified [NOS]),[47] which corresponded to the criteria of the Presence of Psychotic Syndrome (POPS) from the SIPS.[48]

Eight out of 33 UHR participants (24.2%) were found to develop schizophrenia spectrum psychosis. Five participants were diagnosed with schizophrenia, one with delusional disorder, and the other two with psychotic disorder NOS. Among the eight converters, four participants converted within 12 months of enrolment, three participants converted between 12 and 24 months after enrolment, and one participant converted 27.1 months after enrolment. The Kaplan-Meier estimates of conversion risk are 31.0% (95% confidence interval [CI]: 11.4–50.6%) at two years and 38.7% (95% CI: 16.2–61.2%) at the end of the last follow-up.

4. Neuroimaging data acquisition

Functional and structural MRI data were acquired using a three-Tesla scanner (Intera Achieva; Philips Medical System, Best, The Netherlands). All participants underwent a 5.5-min resting-state scan, during which they were instructed to stay quietly with their eyes closed, without moving, sleeping, or focusing on any specific thought. Blood oxygen level-dependent (BOLD) images

were obtained using a T2*-weighted gradient echo-planar imaging (EPI) sequence (repetition time [TR] = 2000 ms; echo time [TE] = 30 ms; flip angle = 90˚; matrix = 80 × 80; voxel size = 2.75 × 2.75 × 4 mm^3; field-of-view [FOV] = 220 mm; 31 interleaved slices without slice gap). High-resolution structural images were subsequently acquired using a three-dimensional T1-weighted turbo field echo (TFE) sequence (TR = 9.7 ms; TE = 4.6 ms; flip angle = 8˚; matrix = 256 × 256; voxel size = 0.859 × 0.859 × 1.2 mm^3; FOV = 220 mm; 180 slices).

5. Image preprocessing

Resting-state functional images were preprocessed using Statistical Parametric Mapping (SPM12; Wellcome Trust Center for Neuroimaging, London, UK), implemented in MATLAB (Mathworks Inc., Natick, MA, USA). The first five images of each participant were discarded to ensure steady-state magnetization. The remaining images underwent standard preprocessing steps, including correction of acquisition time delays between different slices, correction for head motion by realigning all consecutive volumes to the first image of the session, and co-registration of T1-weighted images to the first EPI data using the non-linear registration algorithm. The nonlinear co-registration algorithm was used to minimize image distortions in the EPI sequence by maximizing normalized mutual information between the first EPI and T1-weighted images over second-order B-spline basis functions. Co-registered T1-images were used to spatially normalize functional EPI into Montreal Neurological Institute (MNI) template space by using a non-linear transformation in SPM12. The functional volumes were resampled to a voxel dimension of 2 ×

2×2 mm^3.

The fMRI time courses were processed by (1) regressing out the effects of six rigid motions and their derivatives, and three principal components from the white matter and the cerebrospinal fluid mask, which were segmented using SPM12; (2) despiking based on the median absolute deviation; and (3) high-pass filtering up to 0.009 Hz.[54-57] Since it is known that serious motion effects can be a major confounder in the functional connectivity analysis,[54,58-62] despiking, as one of the censoring procedures,[59] was performed to mitigate such motion effects. To describe the amount of movements in our data, the framewise displacement (FD) that measures the sum of the absolute values of the derivatives from the translational and rotational motion estimates were calculated for each participant. There was no significant difference in the FD values among the four groups (FES: mean ± SD = 0.23 ± 0.18; UHR-C: mean ± SD = 0.22 ± 0.04; UHR-NC: mean ± SD = 0.23 ± 0.09; HCs: mean ± SD = 0.22 ± 0.07; $F[3, 103] = 0.11$, $p = 0.955$). Low-pass filtering was not applied since a growing number of studies have reported information over the 0.1 Hz.[63-66] All procedures were performed using in-house multimodal brain network analysis software, MNET (Multimodal brain NETwork analysis toolbox; Yonsei University, Seoul, Republic of Korea; http://neuroimage.yonsei.ac.kr/mnet).

6. Connectivity analysis

A seed-based functional connectivity map was calculated for each participants using cerebellar seeds from left (MNI: -32, -79, -31) and right Crus I (MNI: 29, -78, -32), which have been found to be functionally connected to the

cerebral DMN in 1,000 healthy individuals.[40] Seed regions were defined as 2-mm radius spheres, and the mean time series of each region was extracted. Correlation maps for each participant were created by calculating the Pearson's correlation coefficients between the time series of the seed regions and that of other voxels in the brain. The resulting correlation maps were converted to *z*-values using Fisher's *r*-to-*z* transformation. To obtain an overall functional connectivity of the cerebro-cerebellar DMN, *z*-maps from each cerebellar seed were averaged, resulting in one mean connectivity map for each participant. Before the statistical analyses, data were smoothed using a Gaussian filter with a 6-mm full-width at half-maximum (FWHM).

One-sample *t*-tests were respectively conducted for HCs, UHR participants with conversion (UHR-C) and without conversion (UHR-NC), and FES participants to identify significant correlations with the cerebellar DMN seeds. Explicit masks were created by applying a voxel-level family-wise error (FWE) rate of $p < 0.05$ to correct for multiple comparisons over the whole brain. By combining the masks of each group, one single explicit mask that included all of the significant voxels from the four groups was created.

To examine significant between-group differences, the functional connectivity map for each participant was entered into an analysis of covariance (ANCOVA) model with age and sex as covariates. Statistical significance was defined by the clusters surviving the voxel-level threshold of $p < 0.005$ (uncorrected) and the cluster-level extent threshold of $p < 0.05$ (cluster size $\geq$ 196 voxels) generated with Monte Carlo simulations using the 3dClustSim program (January 2016 version), implemented in Analysis of Functional NeuroImages

software (AFNI; the National Institute of Mental Health, Bethesda, MD, USA; https://afni.nimh.nih.gov/afni). To minimize the problems related to the underestimation of the group smoothness,[67] the group residuals from the general linear model were used to calculate the group smoothness. Post-hoc tests for each significant cluster were corrected for multiple comparisons using the Bonferroni correction. To examine the association between the functional connectivity maps and the FCQ-S scores, correlation analyses were performed for the UHR and FES groups, respectively. Three UHR-NC and 2 FES participants were excluded from these analyses owing to missing data for the FCQ-S. Age and sex were added as covariates in the analyses. Statistical significance was set using the same methods as mentioned above (single voxel $p < 0.005$, cluster size ≥ 277 voxels [two-tailed]).

7. Statistical analysis

The demographic and clinical profiles of the HCs, UHR-NC, UHR-C, and FES participants were compared using one-way analyses of variance, independent *t*-tests, and chi-square tests. Post-hoc analyses were adjusted for multiple comparisons with the Bonferroni correction. Statistical significance was set at $p < 0.05$, and a *p*-value greater than 0.05 but less than 0.10 was accepted to indicate a trend toward statistical significance. All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS23; IBM Corp., Armonk, NY, USA).

III. RESULTS

1. Functional connectivity of the cerebellar seeds

The resting-state functional connectivity of the cerebellar DMN seeds is shown in Figure 1. In each group, the cerebellar seed regions were significantly correlated with major components of the cerebral DMN, including the medial prefrontal and posterior cingulate cortices.

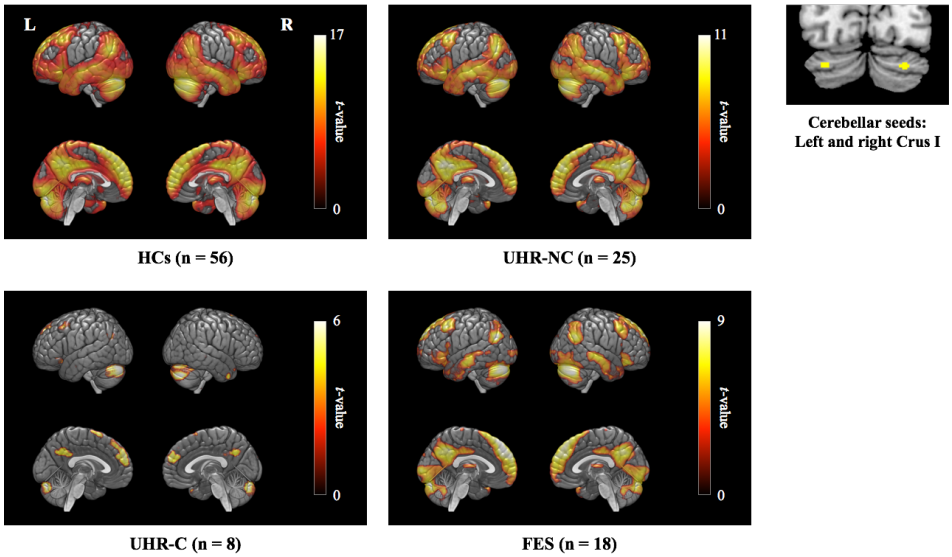

Figure 1. Resting-state functional connectivity of the cerebellar default mode network seeds.

HCs, healthy controls; UHR-NC, ultra-high risk individuals without conversion; UHR-C, ultra-high risk individuals with conversion; FES, first-episode schizophrenia.

2. Group differences in the cerebro-cerebellar functional connectivity

An ANCOVA revealed significant differences in functional connectivity between the cerebellum and several cerebral regions including the right anterior prefrontal cortex (aPFC), left presupplementary motor area (pre-SMA), and precuneus (Figure 2A). Post-hoc analyses of the regions identified in the ANCOVA were shown in Figure 2B. A decreasing tendency in the cerebellar functional connectivity with these regions was noted from HCs to UHR-NC, to UHR-C, and then to FES participants.

Compared to HCs, significantly decreased cerebellar functional connectivity with the right aPFC and precuneus was found in both UHR-C (right aPFC: p = 0.039; precuneus: p = 0.005) and FES participants (right aPFC: $p < 0.001$; precuneus: $p < 0.001$). Compared to UHR-NC participants, FES participants also showed significantly reduced cerebellar connectivity with the precuneus (p = 0.007), while UHR-C participants showed a trend-level reduction (p = 0.092). The functional connectivity between the cerebellum and the left pre-SMA was significantly decreased in FES participants, compared to that in HCs ($p < 0.001$). Besides, there were trend-level differences between UHR-C participants and HCs ($p = 0.090$), and between FES and UHR-NC participants ($p = 0.067$). Table 2 lists the cerebral regions showing significant differences in functional connectivity with the cerebellum among the four groups.

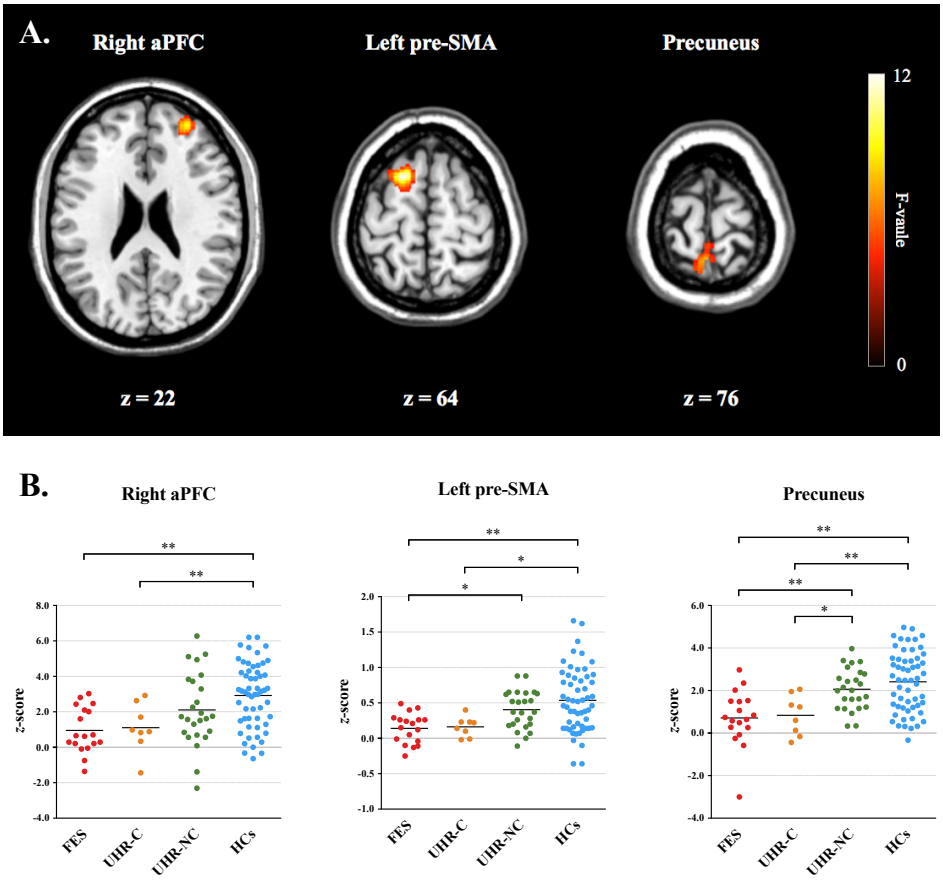

Figure 2. **(A)** Cerebral regions showing significant group differences in the ANCOVA model. **(B)** Post-hoc comparisons within significant clusters among the four groups.

* $p < 0.10$, ** $p < 0.05$ (Bonferroni-corrected).

ANCOVA, analysis of covariance; aPFC, anterior prefrontal cortex; pre-SMA, presupplementary motor area; HCs, healthy controls; UHR-NC, ultra-high risk individuals without conversion; UHR-C, ultra-high risk individuals with conversion; FES, first-episode schizophrenia.

Table 2. MNI coordinates of cerebral regions showing significantly decreased functional connectivity with the cerebellum in the ANCOVA model

Region	BA	Cluster size	MNI coordinates			Statistics	
			x	y	z	F	Peak *z*-score
Left presupplementary motor area	6	438	-16	12	64	11.58	4.69
Right anterior prefrontal cortex	10	357	30	52	24	8.84	4.02
			32	60	16	6.53	3.32
Precuneus	7	247	-2	-50	76	7.38	3.60
			-8	-60	72	6.51	3.32
			0	-42	76	5.73	3.05

MNI, Montreal Neurological Institute; ANCOVA, analysis of covariance; BA, Brodmann area.

Because there were six UHR-NC participants who were followed up less than six months, their distribution patterns of the cerebellar functional connectivity with significant cerebral clusters in the entire group of UHR participants were checked using dot plots, to support their neurobiological closeness to the other UHR-NC participants (Figure 3). The distribution of the cerebellar functional connectivity with the precuneus in six UHR-NC participants with short-term follow-up tended to be closer to that in the other UHR-NC participants, whereas the distribution of the cerebellar functional connectivity with the right aPFC and left pre-SMA showed no specific distribution pattern.

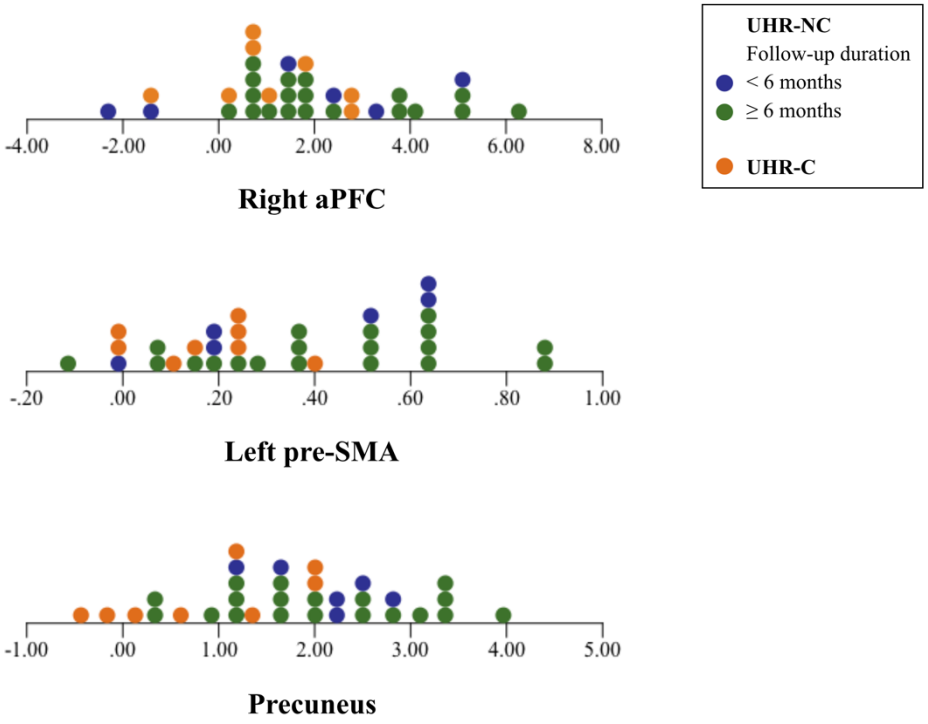

Figure 3. Dot plots of the cerebellar functional connectivity with significant cerebral clusters in the entire group of UHR participants.

aPFC, anterior prefrontal cortex; pre-SMA, presupplementary motor area; UHR-NC, ultra-high risk individuals without conversion; UHR-C, ultra-high risk individuals with conversion.

3. Associations with *ipseity* disturbances

Compared to HCs, UHR-C and FES participants had *ipseity* disturbances that were more severe (FES: mean ± SD = 1.8 ± 1.8; UHR-C: mean ± SD 2.3 ± 2.4; UHR-NC: mean ± SD = 1.1 ± 1.2; HCs: mean ± SD = 0.4 ± 0.8; $F[3, 96] = 9.37$, $p < 0.001$; Figure 4). The group means for UHR-C and FES participants were comparable to those for schizophrenia patients which were reported by Maß et al.[52]

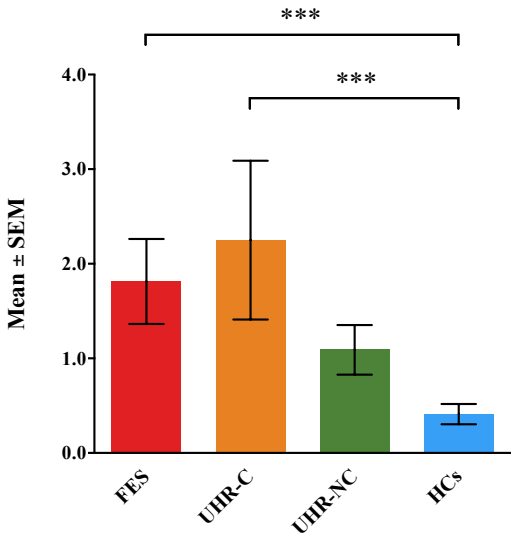

Figure 4. The mean FCQ-S scores of the four groups.

*** $p < 0.001$ (Bonferroni-corrected).

FCQ-S, the eight-item schizophrenia-specific subscale from the Frankfurt Complaint Questionnaire; SEM, standard error of the mean; HCs, healthy controls; UHR-NC, ultra-high risk individuals without conversion; UHR-C, ultra-high risk individuals with conversion; FES, first-episode schizophrenia.

In the entire group of UHR participants (n = 30), the severity of *ipseity* disturbances, as indexed by the FCQ-S, was negatively correlated with the functional connectivity between the cerebellum and the right pre-SMA (Figure 4; shown in blue). In the FES group (n = 16), the FCQ-S scores were positively correlated with the functional connectivity between the cerebellum and the left inferior parietal lobule (IPL), posterior cingulate cortex (PCC), dorsomedial prefrontal cortex (dmPFC), and left caudate nucleus (Figure 5; shown in red). Table 3 lists all regions of significant correlations in the UHR and FES group.

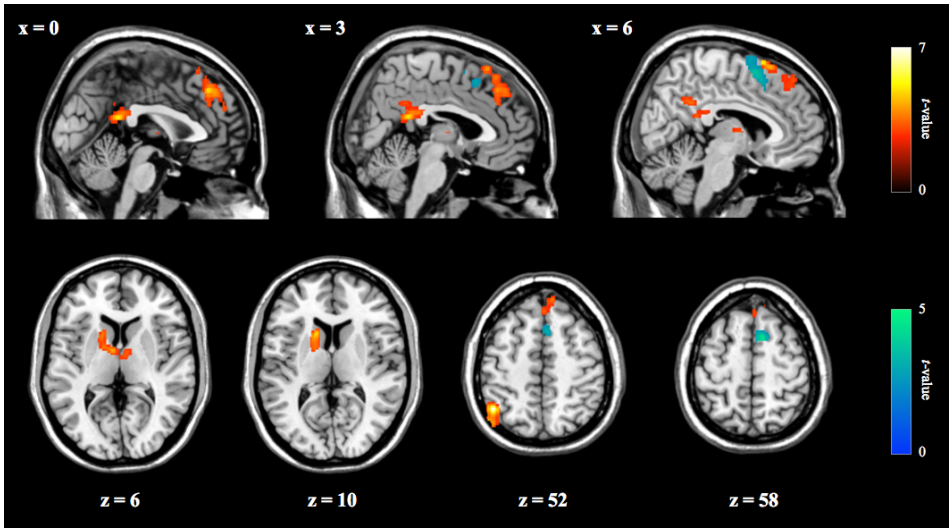

Figure 5. Cerebral regions showing significant correlations with the FCQ-S scores in the respective groups of UHR (n = 30; shown in blue; negative correlation) and FES participants (n = 16; shown in red; positive correlation).
FCQ-S, the eight-item schizophrenia-specific subscale from the Frankfurt Complaint Questionnaire; UHR, ultra-high risk for psychosis; FES, first-episode schizophrenia.

Table 3. MNI coordinates of cerebral regions showing significant correlations between the cerebro-cerebellar connectivity and the FCQ-S scores in the respective groups of UHR and FES participants

Region	BA	Cluster size	MNI coordinates			Statistics	
			x	y	z	T	Peak *z*-score
UHR participants (n = 30) – negative correlation							
Right presupplementary motor area	6	384	10	10	58	4.42	3.78
			10	6	70	3.67	3.26
			4	16	52	3.52	3.16
FES participants (n = 16) – positive correlation							
Left inferior parietal lobule	40	540	-46	-58	52	7.00	4.34
			-52	-74	44	5.07	3.64
			-48	-58	34	4.41	3.34
Posterior cingulate gyrus	31	301	0	-44	20	5.14	3.67
			12	-56	36	4.14	3.20
Dorsal medial prefrontal cortex	8	600	6	16	68	5.13	3.66
			0	36	44	5.03	3.62
			-10	44	30	4.66	3.45
Left caudate nucleus	-	308	-16	14	10	5.04	3.63
			-16	0	8	4.39	3.33
			-8	-2	6	4.39	3.33

MNI, Montreal Neurological Institute; FCQ-S, the eight-item schizophrenia-specific subscale from the Frankfurt Complaint Questionnaire; UHR, ultra-high risk for psychosis; FES, first-episode schizophrenia; BA, Brodmann area.

IV. DISCUSSION

To our best knowledge, this is the first study to investigate resting-state functional connectivity of the cerebro-cerebellar DMN and its association with *ipseity* disturbances in UHR and FES participants. Compared to HCs, UHR-C and FES participants showed significantly weaker functional connectivity between the cerebellum and the right aPFC, left pre-SMA, and precuneus, whereas UHR-NC participants did not. Furthermore, the degree of the cerebellar functional connectivity with several cerebral regions was significantly associated with more-severe *ipseity* disturbances in the entire group of UHR participants and FES group, respectively. These findings imply that aberrant cerebro-cerebellar connectivity may be related to the fundamental pathogenesis of schizophrenia as a disorder of *ipseity*.

Decreased functional connectivity between the cerebellar DMN seeds and several cerebral regions including the right aPFC, left pre-SMA, and precuneus was observed in UHR-C and FES participants compared to in HCs. This finding is globally in line with previous studies showing functional disruptions between the cerebellum and cerebral cortices in patients with schizophrenia.[37,68-70] On the other hand, our finding is partially inconsistent with previous studies showing not only decreased, but also increased cerebro-cerebellar functional connectivity in patients with first-episode schizophrenia.[38,39] This discrepancy may be explained by complex interactions between the developmental and pathogenetic dynamics of the brain. Because the early pathogenesis of schizophrenia is closely intertwined with the neurodevelopmental process of myelination and neural pruning during adolescence and young adulthood,[71,72] patterns of functional

connectivity in the prodromal and early stages of the disease may be heterogeneous; however, reduced myelination and excessive pruning eventually lead to disruptions of the functional organization of the brain in schizophrenia.[73] It is noteworthy that UHR participants who later developed schizophrenia spectrum psychosis showed a pattern of aberrant functional connectivity that was similar to that identified in FES participants in the present study. There were some reports of increased cerebral-cerebellar functional connectivity in healthy siblings of patients with schizophrenia, which were proposed to reflect an endophenotype of schizophrenia.[38,39] However, it is also possible that these findings of increased functional connectivity may reflect protective or compensatory efforts for the underlying vulnerability of the brain to maintain its normal function in genetic high risk individuals,[74-76] given that a majority of siblings never develop overt psychosis in life even with genetic vulnerabilities. In addition, although one previous study reported increased cerebro-cerebellar functional connectivity in UHR individuals,[42] the functional connectivity of UHR individuals with conversion and without conversion were not separately investigated. Because it is known that there is a qualitative difference between this two group of UHR individuals, our findings of decreased functional connectivity between the cerebellum and the right aPFC, left pre-SMA, and precuneus in UHR-C and FES participants may reflect the fundamental pathogenetic changes, which is specifically related to the risk of schizophrenia.

Cerebellar functional connectivity with the precuneus was more decreased in UHR-C and FES participants than it was in UHR-NC participants and HCs. The precuneus, as a part of the posterior DMN, has been found to be involved in

various kinds of self-related processing including recollection of prior experiences and attribution of them to oneself,[77] self-related intentional causality processing,[78] and the experience of agency.[79] Previous neuroimaging studies have reported that both functional and structural abnormalities of the precuneus are closely associated with lack of insight in patients with schizophrenia.[80,81] Insight in schizophrenia is conceptualized as consisting of two dimensions: awareness of illness and attribution of illness.[82] Based on previous findings in functional neuroimaging studies,[83,84] lack of insight into illness is mediated by the self-reflection network which includes the precuneus as one of the core regions. In a phenomenological context, it has been suggested that *ipseity* disturbances destabilize those two dimensions of insight by distorting one's first-person perspective on experiences of oneself and its surroundings.[85] Nonetheless, UHR individuals usually hold full insight into their anomalous self-experiences, while patients with schizophrenia do not.[5] This implies that the impairment in attributing one's first-person experiences to oneself may facilitate the emergence of overt psychotic symptoms. Then, the current finding of decreased functional connectivity between the cerebellum and the precuneus in UHR-C and FES participants may suggest that disruptions of the neurobiological mechanism underlying insight accelerate psychotic elaborations of *ipseity* disturbances and that the functional connectivity between the cerebellum and the precuneus reflects a clinical risk state for schizophrenia.

The functional connectivity between the cerebellum and the left pre-SMA was significantly decreased in FES participants, while UHR-C participants showed a trend-level of decrease compared to HCs. Although this region is not a

major component of the DMN, the current finding is not surprising given the functional association between the pre-SMA and the cerebellar Crus I.[40] The pre-SMA is known as a source of the "readiness potential," which reflects the preparation of a voluntary action prior to conscious intention.[86] This readiness signal contributes to the neural representation of the "desired state" of the self.[27] On the other hand, the cerebellum helps produce error signals by comparing the "desired state" and "predicted future state" from the internal model, and then tacitly attributing agency to oneself when error signals are cancelled out.[27,29,87] Through this series of processes, our intentions are linked to actual perceptual-motor performance, thereby enhancing the integrated feeling of control.[86] Hence, the decreased cerebellar connectivity with the pre-SMA that was observed in FES participants may implicate disruptions in this comparator system, perhaps interrupting the ability to experience the self as one's own agency in a pre-reflective way.[25-27]

Decreased cerebellar connectivity with the right aPFC was found in UHR-C and FES participants compared to in HCs. The aPFC is involved in higher-level cognitive functions, particularly the explicit processing of internally generated thoughts.[88,89] Indeed, patients with schizophrenia exhibit difficulties in turning their attention away from their own inner thoughts and feelings,[18] although this impairment has also found in other psychiatric disorders such as depressive disorders.[18] Thus, the current finding of decreased functional connectivity between the cerebellum and the right aPFC in UHR-C and FES participants may be a secondary reaction that occurs when people are engaged in introspection or "reflective hyperreflexivity," to cope with more fundamental anomalous self-

experiences.[90] However, such efforts seem less effective and even maladaptive for them, as reflected in the disrupted functional connectivity between the cerebellum and the right aPFC.

The associations we identified between the cerebro-cerebellar functional connectivity and the severity of *ipseity* disturbances in the respective groups of UHR and FES participants further support the role of the cerebro-cerebellar network in experiencing the pre-reflective aspect of the self. Correlation analyses showed significant associations between the cerebro-cerebellar functional connectivity and the FCQ-S scores in the UHR and FES groups respectively, while the pattern of the associations was different according to the clinical state. UHR participants showed a negative correlation between the FCQ-S scores and the cerebellar functional connectivity with the right pre-SMA. This finding may further support the functional link between the cerebellum and the pre-SMA in experiencing the self as one's own agency. On the other hand, FES participants showed positive correlations between the FCQ-S scores and the cerebellar functional connectivity with several cerebral regions including the dmPFC, PCC, left IPL and left caudate nucleus. There has been some evidence that a functional reorganization occurs after psychotic elaborations in patients with schizophrenia.[91-93] Although the cerebellar functional connectivity with those regions was not significantly different in the between-group comparisons, it has been widely known that those regions show functional aberrations in patients with schizophrenia.[18,34,94] In particular, the dmPFC and PCC are major functional subdivisions of the cerebral DMN.[19] They are mainly involved in a higher cognitive level of self-related processing; the dmPFC is related to conflict

monitoring and response selection,[95] while the PCC and adjacent precuneus are engaged in autobiographical memory retrieval.[96] The associations between the FCQ-S scores and the cerebellar functional connectivity with the dmPFC and PCC may directly reflect a maladaptive struggle to cope with *ipseity* disturbances in FES participants. Unlike UHR participants who did not reach the threshold for overt psychosis, FES participants seem to be engaged in hyper-reflection to find out acceptable meanings of their anomalous experiences; such maladaptive hyper-reflection may facilitate the emergence and formation of delusions and hallucinations. Therefore, our findings on the associations between the cerebro-cerebellar functional connectivity and *ipseity* disturbances in the respective groups of UHR and FES participants may provide a link between the phenomenology and neuropathogenesis of schizophrenia.

The present study has several limitations. First, because of the small sample size of the UHR-C group (n = 8), a generalization of the current findings may be limited. However, although a replication with more participants is required, the present study provides a novel insight into the neural basis of *ipseity* disturbances in schizophrenia. Second, the follow-up duration of UHR participants, which ranged from 1 to 94.0 months, was various among them. Since some of the UHR-NC participants (6 out of 25) were followed up for less than 6 months, there is a chance that these individuals will convert to overt psychosis later. Nonetheless, the cerebellar functional connectivity with the precuneus in UHR-NC participants with short-term follow-up tended to be closer to that in the other UHR-NC participants. Therefore, our main results would not be greatly affected by the variation of follow-up periods, although it is necessary to be cautious when

interpreting the results. Third, some UHR (1 out of 8 UHR-C and 8 out of 25 UHR-NC) and all FES participants were taking atypical antipsychotic medications. Some studies have suggested that antipsychotic medications may reduce the functional connectivity of the brain in schizophrenia,[97,98] while other studies state that this is not always the case.[99,100] Given the complex effects of antipsychotic medications on the functional connectivity of the brain, it is unclear how much neuronal activity is affected by the medications. Fourth, the instrument used to assess the *ipseity* disturbances in this study was a self-report questionnaire. Further studies using semi-structured, objective assessment instruments, such as the Examination of Anomalous Self-Experience (EASE)[41] may help reveal more comprehensive information about the neurobiological aspects of *ipseity* disturbances. Finally, because the present study was designed as a baseline comparison, the temporal trajectories of the functional connectivity changes from the ultra-high risk state to overt psychosis could not be investigated; thus, additional longitudinal studies are needed to examine this issue. However, baseline findings are still meaningful, as they provide clues about the conversion risk at the time of the initial evaluation in UHR individuals.

V. CONCLUSION

In conclusion, our findings of aberrant cerebro-cerebellar functional connectivity in both converted UHR and FES individuals and its association with *ipseity* disturbances support the notion that schizophrenia is a disorder of *ipseity*. These findings also imply that the underlying neuropathological changes associated with *ipseity* disturbances can be detected in UHR individuals who will later develop schizophrenia spectrum psychosis. In the near future, the neuromodulation strategies that target the cerebro-cerebellar circuits could potentially be a novel method of treating schizophrenia and preventing conversion to overt psychosis in UHR individuals.

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APPENDIX

The eight-item schizophrenia-specific subscale of the Frankfurt Complaint Questionnaire (FCQ-S)

11	When walking, I am sometimes conscious of every step.
14	It happened that people's faces looked unusual, almost distorted or displaced to me.
15	My sexual needs have diminished.
63	It often happens that I don't see things as a whole, but only parts, e.g., of a face, a row of houses.
81	Sometimes a movement goes on by itself, and I cannot stop at once.
90	I am reluctant to read, because I have so much trouble to grasp the meaning correctly.
93	I withdraw from people, because I have so much trouble to follow conversations.
94	If someone uses long sentences, it is particularly difficult for me to grasp the meaning.

ABSTRACT (IN KOREAN)

정신증 고위험군 및 초발 조현병 환자에서의 대뇌-소뇌 간 기능적 연결성 손상 및 현상학적 징후

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방 민 지

현상학적 관점에서 바라본 조현병의 근본적인 정신병리는 *ipseity*의 손상일 것이라고 여겨지나, 아직까지 이에 대한 신경학적 기전은 아직 밝혀지지 않았다. 이 연구에서는 정신증 고위험군 및 초발 조현병 환자를 대상으로 휴지기에서 대뇌-소뇌 디폴트 모드 네트워크(default mode network; DMN)의 기능적 연결성과 *ipseity* 손상 사이의 관련성을 규명하고자 하였다. 8명의 정신증 이환군을 포함한 33명의 정신증 고위험군, 18명의 초발 조현병 환자군 및 56명의 정상 대조군을 대상으로 기저 시점에서 휴지기 기능적 뇌자기공명영상을 촬영하였으며, 정신증 고위험군에서 정신증 이환 여부를 확인하기 위해 추적관

찰 기간 동안 1개월 간격으로 임상적 평가를 시행하였다. 이후 기저 시점의 휴지기 기능적 뇌자기공명영상에서 소뇌 DMN 영역을 시드(seed)로 설정하여 대뇌와의 기능적 연결성 분석을 시행하고, 소뇌 DMN 영역과 유의한 연결성을 보인 대뇌 영역을 중심으로 각 그룹의 대뇌-소뇌 기능적 연결성을 비교하였다. 정신증 고위험군 및 초발 조현병 환자군 각각에 대해서는 대뇌-소뇌의 기능적 연결성과 자가 보고를 통해 측정한 *ipseity* 손상의 심각도 간 상관 분석을 시행하였다. 연구 결과, 정신증에 이환된 고위험군 및 초발 조현병 환자군에서는 오른쪽 앞 이마앞엽 피질(anterior prefrontal cortex), 왼쪽 전보조운동영역(presupplementary motor area), 그리고 쐐기앞소엽(precuneus)과 소뇌와의 기능적 연결성이 정상 대조군에 비해 저하된 소견을 보였다. 이에 반해, 정신증에 이환되지 않은 고위험군은 정상 대조군과 비교하여 대뇌-소뇌의 기능적 연결성에 차이가 없는 것으로 나타났다. 상관 분석에서는 정신증 고위험군 및 초발 조현병 환자군 각각에서 몇몇 영역의 대뇌-소뇌 간 기능적 연결성 및 *ipseity* 손상의 심각한 정도 사이에 유의한 상관성이 관찰되었다. 이 연구의 결과는 조현병이 *ipseity*의 장애라는 사실을 뒷받침하며, 그 기저에는 대뇌-소뇌의 기능적 연결성 손상이 있음을 보여준다. 또한 *ipseity* 손상과 관련된 신경병리적 변화는 조현병-스펙트럼 장애로 이환되기 이전의 고위험군 단계에서 미리 발견될 수 있음을 시사한다. 이러한 대뇌-소뇌 네트워크의 이상은 정신증 고위험군에서 미래의 정신증 이환 여부를 예측하는데 도움을 줄

수 있으며, 조현병-스펙트럼 장애로의 이환을 막는 조기 개입을 가능하게 할 것으로 기대된다.

핵심되는 말: 조현병, 정신증 고위험군, 소뇌, 디폴트 모드 네트워크, *ipseity*, 현상학