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Brain network characteristics separating individuals at clinical high risk for psychosis into normality or psychosis

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ABSTRACT

We aimed to separate individuals at clinical high risk for psychosis (CHR) state into subgroups according to neurobiological characteristics using structural and functional network constructs and examine their clinical characteristics. Structural diffusion tensor imaging and resting-state functional magnetic resonance imaging were performed in 61 healthy controls (HC), 57 individuals at CHR and 29 patients with schizophrenia (SZ). The main outcome was a likelihood ratio calculated from measures of structural and functional network efficiencies, coupling strength of structural and functional networks, and a disease-specific data analysis, resulting in the most probable classification of CHR into HC or SZ. The likelihood ratios revealed that 33 individuals at CHR were likely similar to HC (CHR-HC), and the remaining 24 CHR individuals were similar to SZ (CHR-SZ). The CHR subgroups were comparable to each other in demographic characteristics and clinical symptoms. However, the verbal and executive functions of CHR-HC were similar to those of HC, and those of CHR-SZ similar to SZ. Additionally, CHR-SZ was more responsive to treatment than CHR-HC during the follow-up period. By combining structural and functional data, we could detect the vulnerable population and provide an active intervention in the early phase of the CHR state.

1. Introduction

Individuals at clinical high risk for psychosis (CHR) have been the focus of clinical research for the early detection and prevention of psychotic disorders since the 1990s (Kwon et al., 2012). Longitudinal observation of these individuals, however, showed that 36% of CHR individuals symptomatically remitted and 30% functionally recovered, whereas 30% converted to psychosis within 2 years (Schlosser et al., 2012). This tells us that a heterogeneous group of individuals are in the CHR state between the transient disturbance of mental state in youth and the prodromal stage of psychosis. If we can distinguish the individuals who will have remission or transitory nonpsychotic disorders from those who will undergo overt psychosis or persistent attenuated symptoms, then appropriate intervention in the early stage of non-specific mental distress would be possible, according to the staging model of prodromal prevention (Fusar-Poli et al., 2014).

Similar to a risk rating for cardiovascular disease or cancer, Cannon and colleagues (Cannon et al., 2016) developed a "risk calculator" for the personalized prediction of psychosis using clinical, demographic and cognitive measures and demonstrated clinical utility of this calculator (Carrión et al., 2016). In addition to these sets of clinical information, neurobiological measures can improve the individualized approach for detection and treatment in individuals at CHR. Recently, Clementz et al. (2016) reported a possible advantage of neurobiological versus clinical phenomenology for differentiating psychotic disorders. As one of the possible brain-based biomarkers, network models can provide insight into the basic structures and mechanisms that underlie mental illnesses (Park and Friston, 2013; Sporns, 2014). In patients with schizophrenia (SZ), structural and functional brain networks analyses revealed that the connection density among rich club hubs was significantly reduced, suggesting a disruption of global communication in this disease (van den Heuvel et al., 2013).

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We performed a combined structural and functional imaging study using network analysis in accordance with the disconnection model of SZ (Fornito et al., 2012). Structural networks represent anatomical configurations, whereas functional networks represent the interactions among the time series of neuronal activity (Sporns, 2014). A disease-specific data analysis, termed the *Healthy State Model* (*HSM*) (Nicolau et al., 2007; Nicolau et al., 2011), was adopted to measure the error or deviation from the normal state, as well as global and local efficiencies of the network and structural-functional coupling.

We aimed to obtain the most probable classification of individual clinical high risk for psychosis into a subgroup that is similar to healthy controls and the classification of the remaining individuals into another subgroup that is similar to patients with schizophrenia, according to structural and functional network constructs. We hypothesized that the resulting subgroups would represent the respective clinical and neurocognitive features of healthy controls or patients with schizophrenia.

2. Materials and methods

2.1. Participants and clinical assessments

The study sample consisted of 61 healthy controls (HC, aged 17–35), 57 individuals at CHR (aged 15–33) and 29 patients with SZ (aged 15–35) who participated in a study conducted at the Seoul Youth Clinic as part of the prospective and longitudinal investigation of CHR and SZ (Kwon et al., 2012). The CHR group was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Interview of Prodromal Symptoms (SIPS) (Jung et al., 2010), both of which were conducted by psychiatrists. Clinical course of CHR individuals was investigated over six months and one year after the enrollment using the SIPS. Patients with SZ were diagnosed in the first psychotic episode with an onset during the previous year using the SCID-I administered by psychiatrists. Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). The functional level was assessed using the Global Assessment of Functioning (GAF). The HC group was confirmed with the SCID-I Non-Patient Edition. Additional information about our participants is available in the Supplement). All subjects provided written informed consent, and parental consent was obtained for subjects younger than 18 years of age. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea.

2.2. Neurocognitive tests

Measures of attention included the Trail Making Test, Part A (TMT-A) and the digit span test. Intelligence quotient was measured using the short forms of the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS; verbal subtests, vocabulary and arithmetic; performance subtests, block design and picture arrangement). A verbal fluency test measured the spontaneous oral generation of words within a given time based on phonemic (phonological fluency) or semantic criteria (semantic fluency). Verbal memory was assessed using the immediate and delayed recall tests of the Korean version of the California Verbal Learning Test (K-CVLT), and visual memory was assessed using the Rey–Osterrieth Complex Figure Test (RCFT) with immediate and delayed scores. The Trail Making Test, Part B (TMT-B) and perseverative errors in the Wisconsin Card Sorting Test (WCST) were used to estimate executive functions. For the TMT and perseverative errors in the WCST, higher scores represented poor performance.

2.3. Imaging data acquisition and network construction

Diffusion-weighted images (DWIs) were acquired over 775s with diffusion gradients (b-factor 1000s/mm^2) along 64 non-collinear directions. One volume was acquired with no diffusion gradient (B0 image). Resting-state functional magnetic resonance imaging was applied over 418 s using a gradient echo-planar imaging sequence. For the other protocols and imaging data processing, see the Supplement.

To construct the structural network using fiber tracts, we registered an automated anatomical labeling (AAL) atlas (Tzourio Mazoyer et al., 2002) to the individual high-resolution T1-weighted image using a non-linear transformation matrix obtained from the segmentation steps in the SPM8 package (www.fil.ion.ucl.ac.uk/spm/). The individually fitted AAL map parcellates the brain into 82 cortical regions in the individual space. For the functional network, the whole brain was parcellated into 82 cortical and eight subcortical regions with the AAL atlas. Then, the functional network of each subject (R_{ij}) was computed using Pearson's correlation coefficients between the mean time series of the i-th and j-th regions-of-interest.

2.4. Network efficiency and structural-functional coupling

For the constructed structural and functional networks, we computed the global and local network efficiencies to examine both global and regional network characteristics (Rubinov and Sporns, 2010). We used non-zero elements to calculate structural network efficiencies and sparsity threshold S ($0.08 \le S \le 0.48$) to calculate the functional network efficiency. The structural and functional network efficiency was compared with those of 1000 random networks. For statistical comparisons of the functional network efficiency, the area under the curve (AUC) for all sparsity thresholds was calculated for each global and local efficiency. A structural-functional coupling between the non-zero edges of the structural network and their functional counterparts was obtained using the following procedure. All non-zero entries of the structural network were selected, rescaled to a Gaussian distribution, and correlated with their functional counterparts selected from the Fisher's r-to-z transformed functional network. This produced a single structural-functional coupling value for each brain network (Honey et al., 2009).

2.5. Healthy state modeling

To decompose the disease component from the individual data, we adopted the *Disease-Specific Genomic Analysis* method and applied it to the structural and functional network data (Nicolau et al., 2007; Nicolau et al., 2011). The HSM was initially introduced in a previous microarray data analysis (Nicolau et al., 2007). Previous studies have shown that this type of linear decomposition analysis can also be used for brain network analysis (Leonardi et al., 2013; Park et al., 2014; Kyeong et al., 2015).

Following a previously published method (Kyeong et al., 2015), the upper triangular part of a connection matrix of the network constructs was extracted and vectorized for each subject. The vectorized network data of each subject was stacked in rows and decomposed into normal and disease components through a disease-specific data analysis (Nicolau et al., 2007). Finally, we obtained the magnitude of the disease component in each subject (see Kyeong et al. (2015) for detailed equations).

2.6. Likelihood ratio

To estimate the extent of deviation in the structural and functional constructs of individuals at CHR, we determined the likelihood functions for the HC ($\boldsymbol{L}_{\mathbf{HC}}$) and SZ ($\boldsymbol{L}_{\mathbf{SZ}}$) groups by multiplying the probability density functions (PDFs) obtained from the distributions of the global and local network efficiencies of structural and functional networks, the structural-functional coupling, and the magnitude of the disease component from the HSM. These were combined into a likelihood ratio $\boldsymbol{R}_{\mathbf{SZ}} = \boldsymbol{L}_{\mathbf{SZ}}/(\boldsymbol{L}_{\mathbf{SZ}} + \boldsymbol{L}_{\mathbf{HC}})$. We set the decision boundary at a 0.5 likelihood ratio, in which <0.5 was assigned to the HC group and ≥0.5 was assigned to the SZ group.

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