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Small-world networks in individuals at ultra-high risk for psychosis and first-episode schizophrenia during a working memory task

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HIGHLIGHTS

- Small-world network during working memory was investigated using the EEG.
- Small-worldness is reduced in first-episode schizophrenia and intermediate in UHR.
- Suboptimal network integration is suggested in schizophrenia pathophysiology.

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ABSTRACT

Disturbances of functional interaction between different brain regions have been hypothesized to be the major pathophysiological mechanism underlying the cognitive deficits of schizophrenia. We investigated the small-world functional networks in individuals at ultra-high risk (UHR) for psychosis, first-episode schizophrenia (FESPR) patients, and healthy controls. All participants underwent the electroencephalogram during a control task and a working memory (WM) task. Small-world properties of the theta band were reduced in FESPR relative to controls during the WM task. Small-worldness of the UHR during the WM task exhibited intermediate value between that of controls and FESPR. These results imply that the suboptimal organization of the brain network may play a pivotal role in the schizophrenia pathophysiology.

1. Introduction

Schizophrenia is a chronic mental disorder with impairments in multiple cognitive domains including the working memory (WM) [18,29]. Underlying these cognitive impairments, disturbances in functional interaction between different brain regions have been hypothesized [5,6,11]. A method of graph theoretical analysis investigating the so-called "small-world network" may offer valuable information in exploring this hypothesis. Characterized by a high clustering coefficient (an index of local clustering), and a short path length (an index of global integration), the small-world network reflects an optimal network topology for functional segregation and integration to maximize information processing efficiency between brain regions [1,45,46,51]. Using the electroencephalography (EEG), small-world properties were found to be decreased in schizophrenia patients compared to healthy subjects during a WM task [38,40]. It has also been demonstrated that decreased small-worldness is associated with lower cognitive

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function in healthy subjects [20]. Together, it has been suggested that the suboptimal small-world network may play an important role underlying the cognitive impairments of schizophrenia [38,40].

Evidence suggests that cognitive deficits may be present not only in the first episode of schizophrenia but also prior to the emergence of frank psychotic symptoms. The 'putative' prodromal, ultra-high-risk for psychosis (UHR), subjects show cognitive impairments such as WM deficits [8,15,16,30,32]. In search of underlying neural dynamics, previous studies of small-world networks during cognitive tasks were limited in that subjects were chronic, multi-episode schizophrenia patients [38,40]. The only small-world network study reported of first-episode patients explored the network properties during the resting state [41]. Furthermore, small-world network architecture in UHR subjects has not yet been investigated. Studying the small-world topology associated with cognitive function in first episode schizophrenia (FESPR) and those at UHR may provide an important insight at the ongoing pathophysiological alterations of network integration.

In the present study, we investigated the small-world network properties in UHR subjects, FESPR patients, and healthy controls (HC) during a WM task. Based on previous reports [38,40], we hypothesized that the small-worldness will also be reduced in FESPR during the WM task. Since neurocognitive impairments are reported to be present before the frank onset of psychotic symptoms, we also hypothesized that small-world properties will be altered in UHR subjects, but to a lesser degree compared to FESPR patients.

2. Materials and methods

2.1. Participants

Twelve FESPR, 13 UHR, and 13 HC subjects participated. Inclusion of UHR subjects was based on the Criteria of Prodromal Symptoms from the Structured Interview for Prodromal Syndromes (SIPS) [39], requiring that individuals meet at least one of the following three clinical criteria: (1) brief intermittent psychotic syndrome ($n = 4$), (2) attenuated positive prodromal syndrome ($n = 12$), or (3) genetic risk and deterioration syndrome ($n = 2$), in which the genetic risk is determined if the subject has a first degree relative with any psychotic disorder and/or the subject meets the DSM-IV Schizotypal Personality Disorder criteria. FESPR patients were limited to those who have experienced their first psychotic episode within the past 3 years and have taken antipsychotic medications for less than 12 months. HC were recruited through internet advertisement. The diagnosis of FESPR and screening of HC were performed using the Structured Clinical Interview for DSM-IV [21,22]. Any participants with a past or current diagnosis for any Axis I disorder, past or current drug abuse/dependence or neurological disorders were excluded from the HC group. Symptom severities of the clinical groups were assessed with the Scale for the Assessment of Negative Symptoms (SANS) [3] and the Scale for the Assessment of Positive Symptoms (SAPS) [4]. A comprehensive neurocognitive battery was performed, from which a global neurocognitive composite score was calculated according to the procedure of our previous study [32]. The neurocognitive battery was not administered in 2 HC, 1 UHR and 2 FESPR patients. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board of Severance Hospital and Severance Mental Health Hospital.

2.2. Experimental task

For the WM condition, the verbal 2-back task was used (see detail, Kim et al.) [32]. It is one of the most widely used methods to assess WM, requiring components of maintenance, monitoring, updating and manipulation of information [7]. Briefly, 8 Korean letters were used as stimuli, appearing at one of 8 spatial locations. Participants determined whether a stimulus on each trial matches a stimulus that appeared in the second-to-previous trial, regardless of location. In the control condition (simple vigilance task) using the same stimuli, participants were instructed to press a button when a certain target letter appeared, regardless of location. Each stimulus was presented for 300 ms, with 2700 ms inter-stimulus interval. There were a total of 120 trials consisting of 34 (28%) target and 86 (72%) non-target stimuli.

2.3. EEG recording

EEG measurements were recorded using a 64-channel cap and a 10/20 electrode placement system (Neuroscan Inc., USA) at a sampling rate of 1000 Hz (SynAmps2 DC-amplifier). Linked mastoid was used for reference. The impedance was maintained below 10 k Ohm. Matlab 7.4.0 (MathWorks, USA) with the EEGLAB toolbox [19] was used for preprocessing and analysis. Two EEG data from the control condition in UHR were cracked and could not be analyzed.

2.4. Data analysis

Synchronization likelihood (SL) between all pairs of electrodes was calculated for the frequency bands (theta: 3–8 Hz, alpha: 8–12 Hz, beta: 12–30 Hz, gamma: 30–80 Hz). Average SL for each person was computed to an average of 4 epochs. Based on the full matrix of all possible pairwise combination of electrodes, SL matrix was converted into a graph by choosing a threshold T. Graph theoretical measures (clustering coefficient: C_p and characteristic path length: L_p) were derived. Thresholds were chosen in such a way that the resulting graphs of the different groups have an equal mean degree K. Ratios C_p/C_{ran} and L_p/L_{ran} were computed [44], and the small-world index was defined as a ratio between C_p/C_{ran} and L_p/L_{ran} [28].

2.5. Statistical analysis

Behavioral data were screened for outliers using Tukey's hinges, and, when possible, outliers were included after a winsorizing procedure [27]. Following data cleaning, all variables except the hit rate of the control task had acceptable skewness statistics (<1.0). One-way ANOVA and t-tests were used to test group differences except for the hit rate of the control task for which Kruskal–Wallis test was used. Pearson's correlations were used to explore the relationship of small-worldness of the theta band to neurocognitive scores and symptom severities. Bonferroni corrections were used to control accumulation of α error. The level of significance was defined as $p < 0.05$.

3. Results

As shown in Table 1, there were no between-group differences in demographics and clinical characteristics except the global neurocognitive composite scores and positive symptom severity. FESPR demonstrated lower neurocognitive scores compared to HC ($p = 0.026$). There were no significant differences in neurocognitive scores of UHR with that of other groups (UHR vs. HC: $p = 0.087$; UHR vs. FESPR: $p = 1.00$). Behavioral performance did not differ among groups for both the control task (Chi square of Kruskal–Wallis test = 0.89, df = 2, $p = 0.640$; hit rate (%) for HC = 95.7 ± 6.8, UHR = 96.5 ± 9.2, FESPR = 97.6 ± 3.5) and WM task ($F(2,35) = 2.39$, $p = 0.107$; hit rate (%) for HC = 83.9 ± 9.4), UHR = 70.6 ± 30.3, FESPR = 70.1 ± 16.1).