Alterations of functional connectivity network related to working memory in ultra-high risk for psychosis and first-episode schizophrenia

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ABSTRACT

Alterations of functional connectivity network related to working memory in ultra-high risk for psychosis and first-episode schizophrenia

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Higher cognitive functions require functional interactions between multiple specialized neuronal networks in the brain. Disturbances in functional connectivity have been proposed as a major pathophysiological mechanism for schizophrenia (SPR). In the present study, functional connectivity networks were explored using small-worldness and synchronization likelihood (SL) during a working memory task. Thirteen first-episode SPR patients, 11 UHR individuals, 13 healthy controls were recruited. EEG data were collected during a verbal 0- and 2-back task in all participants. For SL, there was significantly different pattern of change in UHR subjects and SPR patients as the working memory load varied (significant working memory load by group interaction, theta: $p<0.001$, $F=21.768$; alpha: $p<0.001$, $F=22.779$; beta: $p<0.001$, $F=30.318$, and gamma: $p<0.001$, $F=17.452$). Specifically, while SL significantly decreased as the working memory load increased in the controls (theta: $p=0.017$, alpha: $p=0.003$, beta: $p=0.004$, gamma: $p=0.005$), these working memory load effect was not observed in UHR subjects. In SPR patients, SL was significantly higher than controls or UHR during the 0-back task, but decreased as the working memory load increased (significant working memory load effect, theta: $p<0.001$, alpha: <0.001, beta: <0.001, gamma: <0.001). For small-worldness, a trend of

the group effect was seen in the theta band (p=0.088, F=2.616), with decreased small-worldness in SPR patients compared to controls (p=0.031) as resulted from the pairwise comparisons. In correlation analyses, increased SL in UHR subjects was associated with lower working memory performance, lower neurocognitive function and more severe symptoms. These findings collectively support the disconnection hypothesis of schizophrenia and suggest an alteration of functional connectivity in the prodromal phase. These changes may be associated with impairments in functional trimming needed for modular specialization of brain networks for higher cognitive demands.

Key words : ultra-high risk, functional connectivity, schizophrenia, small-world, synchronization likelihood

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I. INTRODUCTION

During the recent years, disturbances in functional connectivity between different brain regions have been proposed as a major pathophysiological mechanism for schizophrenia (SPR)[1-3]. Histological, biochemical, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and bioelectrical studies demonstrate the dysfunctional connectivity associated with cognitive disorganization of SPR[4-8]. Functional connectivity or interactions in the brain have often been studied using synchronization likelihood (SL). Synchronization means that the state of one system is a function of the state of the other system[9]. Sensitive to both linear and nonlinear synchronization between signals, SL gives more accurate information about functional interactions than linear measures such as coherence[10].

A further approach to investigating the functional connectivity of the neuronal network is the graph theoretical approach. This approach explores the topographical characteristics of the network, offering a unique window into the

balance of local and distributed interactions occurring in the brain[11]. Graphs are characterized by two parameters: a cluster coefficient which is a measure of the local interconnectedness and a characteristic path length which is an indicator of overall connectedness. A "small-world" network, which is a near-optimal organization with highly efficient information processing, is characterized by a combination of strong local clustering and a short characteristic path length (an index of global integration)[12-13]. In healthy controls, small-world properties of the brain networks were consistently demonstrated across the different age groups[13-18]. In contrast, brain pathology such as SPR changes the network structure. Using the EEG time series, small-world properties were decreased in SPR patients compared to healthy subjects during a working memory task[19-20]. Also, functional MRI studies revealed similar findings in SPR patients during rest[21-22]. These findings demonstrate a failure of functional integration within different brain regions that may partially account for the deficits in cognition and behavior of SPR.

Evidence suggests that neurobehavioral deficits may be present prior to the emergence of frank psychotic illness[23]. Behaviorally, studies of prodromal and genetic-high-risk subjects report cognitive impairments such as the working memory deficit[24-27]. However, whether the abnormalities of functional integration that is hypothesized to underlie the cognitive deficits in SPR are already present prior to the onset of the psychosis is still unknown. Studying those at ultra-high risk (UHR) for psychosis may provide a view at the perhaps ongoing pathophysiological changes of functional integration in the illness.

Furthermore, the effect of cognitive loading must be taken into account to investigate the underlying neural mechanisms of cognitive deficits in SPR. In previous studies of healthy individuals, it has been reported that variations in the cognitive demand such as the working memory loading is accompanied by characteristic changes in the mean level of functional connectivity between neural networks. With increased cognitive loading, changes in functional

connectivities may be different in SPR patients and perhaps UHR individuals from that of healthy controls. Moreover, disruptions of interregional brain connectivity may lead to the failure of functional integration with the brain in SPR. So far, however, little is known about the stability or the changes of functional integration under different cognitive demands in SPR and UHR individuals.

In the present study, first-episode SPR patients, UHR individuals and healthy controls were recruited to explore the functional integration of brain networks with varying degrees of the working memory load. Two important parameters that reflect the properties of the functional brain networks were employed: SL, which represents the strength of the functional connectivity between different brain regions, and the small-worldness, which represents the efficiency of the global/local structure of the brain functional network. On the basis of previous studies, the following hypotheses were formulated and investigated: mainly, I hypothesized that there may be alterations of small-world topographical properties in SPR patients under the working memory load, while small-world properties may be preserved in UHR individuals due to continuous adjustments through reconfiguration of brain networks. In addition, patterns of functional connectivity with varying degrees of working memory load were also investigated. I hypothesized that changes in functional connectivity strength, as measured by SL, will be different in UHR subjects and SPR patients compared to healthy controls.

II. MATERIALS AND METHODS

1. Participants

Thirteen first-episode SPR patients and 11 UHR individuals were recruited from the psychiatric outpatient clinic of Severance Hospital, Yonsei University Medical Center. Inclusion criteria for the UHR subjects were based on the Structured Interview for Prodromal Syndromes (SIPS)[28]. The SIPS rating scale was developed specifically for use in UHR populations and assesses the presence, type, severity, frequency and duration of prodromal symptoms as well as the degree of distress from the symptoms. Those who met the clinical criteria defined in the Criteria of Prodromal Symptoms[28] were invited to enter the study. Briefly, the Criteria of Prodromal Symptoms require that individuals meet at least one of the following three clinical criteria: (1) for brief intermittent psychotic state (BIPS): emerging psychotic symptoms with spontaneous remission in less than 1 week; (2) for attenuated positive symptom state (APS) : sub-threshold delusional unusual thoughts and sub-threshold hallucinatory perceptual abnormalities; or (3) for genetic risk and deterioration state (GRDS) : genetic risk for SPR (first-degree relative with schizophrenia spectrum disorder and/or schizotypal personality disorder) plus a functional decline in the past year equivalent to a drop in global assessment of function of 30 percent sustained for at least 1 month. First-episode SPR patients were limited to those who have experienced their first psychotic episode within the past 3 years. SPR patients were interviewed and diagnosed by experienced psychiatrists on the basis of DSM-IV criteria for SPR through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). All subjects were screened according to the DSM-IV diagnostic criteria using the SCID upon entry to the program.

Thirteen healthy controls were recruited through internet advertisements. Age, gender, and education level were matched among the UHR subjects, SPR patients and the controls. Any participants with a past or current diagnosis for

any Axis I disorder or a family history of psychotic illnesses, past or current drug abuse/dependence, neurological disorder (including traumatic brain injury and epilepsy) or mental retardation were excluded from the healthy control group. All healthy control subjects were unmedicated at the time of the study.

2. Measures

A. Working memory task

All participants performed the verbal 0- and 2-back task. Eight Korean letters were used as stimuli. Each letter on a given trial appears at one of eight spatial locations. For the 0-back task, participants must decide if a stimulus on each trial matches a stimulus that appeared in the previous trial. For the 2-back task, participants must decide if a stimulus matches a stimulus that occurred 2 trials previously. Each stimulus was presented for 300 msec, with an inter-stimulus interval of 2700 msec.

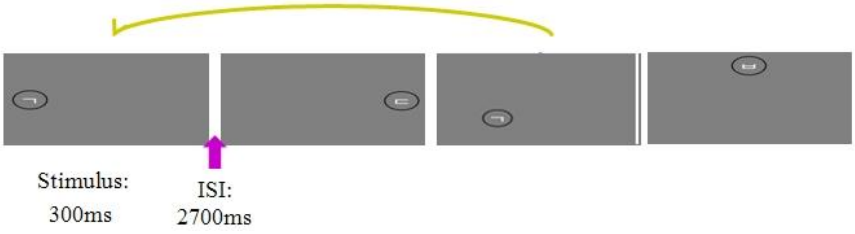

Fig 1. Example trials of a 2-back task. ISI: inter-stimulus interval.

B. Neurocognitive function

A comprehensive neuropsychological battery, including attention and working memory, visual memory, verbal memory and executive function, was performed to test neurocognitive function. The tests were applied after clinical stabilization of acute psychotic symptoms in first-episode SPR patients. The

neurocognitive domains were calculated as a composite score of global neurocognitive function.

C. Symptom severity

The symptom severities of the clinical groups were assessed with the Scale for the Assessment of Negative Symptoms (SANS)[31] and the Scale for the Assessment of Positive Symptoms (SAPS)[32]. Severities of depression and anxiety were assessed with Hamilton Rating Scale for Depression (HAM-D)[33] and Hamilton Rating Scale for Anxiety (HAM-A)[34].

3. EEG recording and analyses

EEG measurements were taken from the scalp using a SynAmps2 DC-amplifier and a 10/20 layout 64-channel Quik-cap electrode placement system (Neuroscan Inc., USA). EEGs were recorded from 64 electrodes (standard 10/20 system based) at a sampling rate of 1,000 Hz. Linked mastoid was used for reference. The impedance of each electrode was maintained below 10 kOhm. We used Matlab 7.4.0 (MathWorks, USA) with the eeglab toolbox[35] to preprocess and analyze the data.

The SL between all pairs of electrodes was calculated for the EEG frequency bands (theta: 3~8 Hz, alpha: 8~12 Hz, beta: 12~30 Hz, gamma: 30~80 Hz). Graph theoretical analysis was based on the full matrix of all possible pair wise combination of electrodes. The SL matrix was converted into a graph by choosing a threshold T, and the graph theoretical measures (cluster coefficient: Cp and characteristic path length: Lp) were derived from this binary graph. Briefly, Cp (cluster coefficient) is an index of a local efficiency of networks, and Lp (characteristic path length) is an index of a global efficiency of networks. We calculated the Cp, Lp as well as the ratios Cp/Cran and Lp/Lran where Cran and Lran denote the values of Cp and Lp for appropriate ordered and random reference graphs, for K=4, 5, 6 where K is the average number of edges per

vertex[14]. The small-worldness of a graph is expressed in the small-world index *sigma*, expressing the level of small-worldness of a graph as a ratio between Cp/Cran and Lp/Lran[17].

4. Statistical analyses

All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS Inc., Chicago, Illinois). A one-way analysis of variance (ANOVA) was used to test group differences in demographic and clinical variables. ANOVA was also used to compare working memory performance and neuropsychological measures. Statistical comparisons of SL, Cp, Lp and σ (small-worldness) were achieved using the repeated measures ANOVA for each frequency band, with WM load (0-back and 2-back task) as the within-subjects factor and the three groups (controls, UHR and SPR) as the between-subjects factors. Post-hoc analyses were performed to explore the significant group differences. Pearson's correlations were used to assess the association between functional connectivity measures and clinical variables, behavioral measures as well as neurocognitive domains. Significance level was set at $p<0.05$. Bonferroni correction was applied for multiple comparisons.

III. RESULTS

1. Demographics and clinical characteristics

Demographics and clinical characteristics of the participants are presented in Table 1. Men consisted 48.7% of the participants, with a similar proportion across groups (χ^2=3.284, p=0.194). Mean age was 19.77 years (S.D. 2.52), with no group differences (F(2,35)=0.292, p=0.749). No differences were found in education years and IQ among the three groups (F(2,35)=1.064, p=0.256; F=2.265, p=0.121, respectively). There were no group differences in depression or anxiety severity between UHR and SPR (t(22)=1.803, p=0.088; t(22)=1.522, p=0.145, respectively).

For symptom severity, SPR patients showed significantly higher scores on the SAPS total scores compared to UHR subjects (t(22)=-4.190, p<0.001). There were no differences between the two groups in SANS total scores.

Table 1. Demographics and clinical characteristics

	Healthy controls (n=13)	UHR (n=11)	SPR (n=11)	P
Sex (%) Male	5(38.5%)	8(72.7%)	5(38.5%)	0.194[a]
Female	8(61.5%)	3(27.38%)	8 (61.5%)	
Age (year)	20.15 (2.41)	19.38 (2.93)	19.77 (2.31)	0.749
Education years	12.92 (1.66)	12.23(1.54)	12.15 (1.21)	0.356
IQ	106.18(6.82)	101.00(12.95)	94.90 (15.76)	0.121
SANS	–	26.92 (13.93)	27.08(13.24)	0.977
SAPS	–	9.69(8.28)	20.23(12.30)	0.017*
HAM-D	–	12.18(6.11)	7.11(6.43)	0.088
HAM-A	–	14.91(8.88)	8.44(10.11)	0.145

Mean values presented with standard deviation in parenthesis.

UHR: ultra-high risk for psychosis, SPR: schizophrenia, SANS: Scale for the Assessment of Negative Symptoms, SAPS: Scale for the Assessment of Positive Symptoms, HAM-D: Hamilton Rating Scale for Depression, HAM-A: Hamilton Rating Scale for Anxiety.

[a]Comparison by χ^2 test. All other comparisons were analyzed by ANOVA or t-tests.

2. Behavioral data

No differences were seen in the 0-back performance among the three groups ($F(2, 35)=0.258$, $p=0.774$), but there were significant group differences in the 2-back performance ($F(2, 35)=3.981$, $p=0.029$), as measured by the hit rate. Post-hoc analyses revealed that SPR patients performed significantly worse compared to controls during the 2-back ($p=0.026$) (Fig 2).

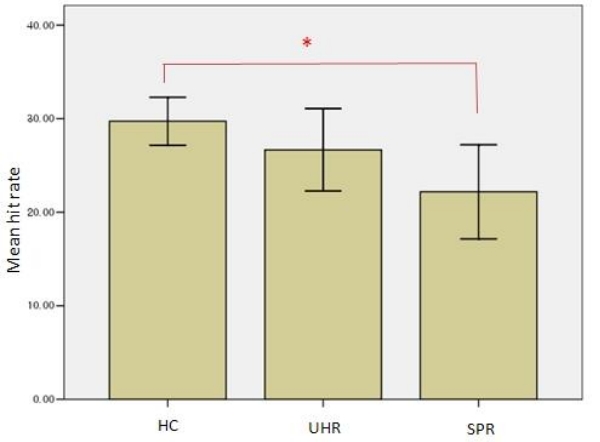

Fig 2. Comparison of mean verbal 2-back hit rate in the three groups. HC (healthy controls), UHR (ultra-high risk) and SPR (schizophrenia). Error bars indicate 95% of the confidence interval. * indicates significant group differences from the post-hoc analyses.

3. Small-world properties

There was no significant main working memory load effect or load by group interaction for small-worldness, as measured by S, in all frequency bands. A trend of the group effect was seen in the theta band ($F(2, 34)=2.616$, $p=0.088$), with decreased small-worldness in SPR patients compared to controls ($p=0.031$) in pairwise comparisons.

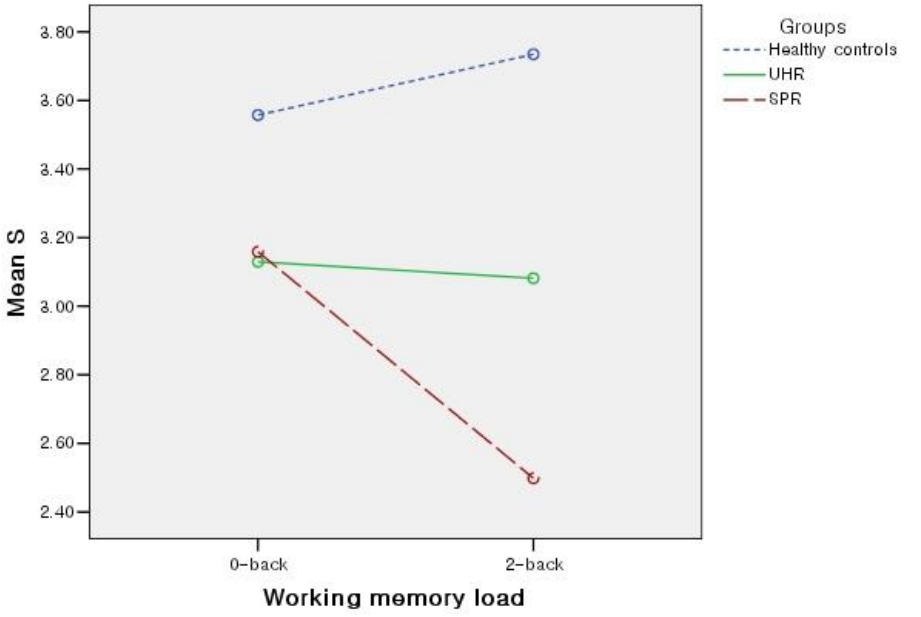

Fig 3. Comparison of small-worldness (S: sigma) of the theta band according to working memory load in the three groups. UHR: ultra-high risk for psychosis, SPR: schizophrenia.

4. Synchronization likelihood

A. Main effect of working memory load

There was a significant main WM load effect (theta: $F(2,34)=66.26$, $p<0.0017$; alpha: $F(2,34)=98.690$, $p<0.001$; beta: $F(2,34)=103.297$, $p<0.001$, and gamma: $F(2,34)=46.845$, $p<0.00$), with lower SL during the 2-back. When analyzed separately, significant group differences were seen in each condition. During the 0-back task, SPR patients showed significantly higher SL compared to UHR subjects and the controls in the theta (SPR vs. UHR: $p<0.001$, SPR vs. HC: $p<0.001$), alpha (SPR vs. UHR: $p<0.001$, SPR vs. HC: $p<0.001$) and beta bands (SPR vs. UHR: $p<0.042$, SPR vs. HC: $p=0.001$), while SL for the gamma band

was higher in SPR patients compared only to healthy controls (p=0.006). During the 2-back task, UHR subjects showed significantly higher SL compared to SPR (alpha: p=0.023, beta: p=0.001, and gamma: p<0.001) and controls (alpha: p=0.007, beta: 0.012, and gamma: p=0.004) in the alpha, beta and gamma bands.

B. Main effect of group

There was also a significant main effect of group in all frequency bands (theta: F(2,34)=5.417, p=0.009; alpha: F(2,34)=9.998, p<0.001; beta: F(2,34)=3.676, p=0.036, and gamma: F(2,34)=3.676, p=0.036). Within each group, a significant decrease in SL during the 2-back task compared to 0-back was seen in healthy controls (theta: p=0.017, alpha: p=0.003, beta: p=0.004, gamma: p=0.005) and SPR patients (theta: p<0.001, alpha: <0.001, beta: <0.001, gamma: <0.001).

C. Working memory load by group interaction effect

There was a significant WM load by group interaction in all frequency bands (theta: F(2,34)=21.768, p<0.001; alpha: F(2,34)=22.779, p<0.001; beta: F(2,34)=30.318, p<0.001, and gamma: F(2,34)=17.452, p<0.001). In a separate 2-by-2 repeated measures ANOVAs, there was a significant load by group interaction between healthy controls and SPR patients (theta: F(1,24)=37.519, p<0.001; alpha: F(1,24)=34.247, p<0.001; beta: F(1,24)=39.380, p<0.001, and gamma: F(1,24)=23.289, p<0.00), as well as between UHR subjects and SPR patients (theta: F(1,22)=30.499. p<0.001; alpha: F(1,22)=42.432, p<0.00; beta: F(1,22)=64.797, p<0.001, and gamma: F(1,22)=30.970, p<0.001), but not between UHR subjects and the controls.

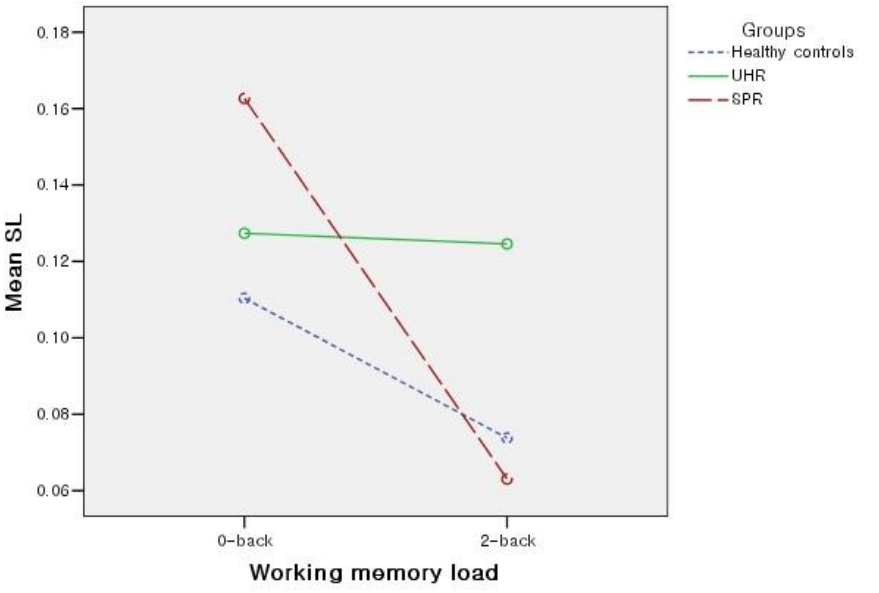

Fig 4. Comparison of synchronization likelihood (SL) of the gamma band according to working memory load in the three groups. UHR: ultra-high risk for psychosis, SPR: schizophrenia.

5. Correlation analyses

With behavioral measures, UHR subjects showed a negative correlation between the 2-back performance and SL of the gamma band. In contrast, 2-back performance in SPR was positively correlated with SL in the gamma band. There were no correlations with 0-back performance and any of the graph parameters in both groups.

With neurocognitive domains, UHR subjects showed negative correlations of theta synchronization during the 0-back with global neurocognitive scores ($p=0.016$, $r=-0.733$) (Fig 4). In SPR, small-worldness of the theta band and the gamma band during the 0-back task positively correlated with global neurocognitive scores (theta: $r=0.636$, $p=0.039$; gamma: $r=0.672$, $p=0.024$).

During the 2-back, theta synchronization positively correlated with global neurocognitive scores in SPR patients (r=0.779, p=0.005).

In relation to symptom severity, theta synchronization during both the 0-back and 2-back task positively correlated with SANS total scores in UHR subjects (0-back: p=0.033, r=0.641, and 2-back: r=0.666, p=0.013). Alpha synchronization during 0-back in UHR positively correlated with SANS total scores (p=0.002, r-0.817) and SAPS total scores (p=0.032, r=0.644).

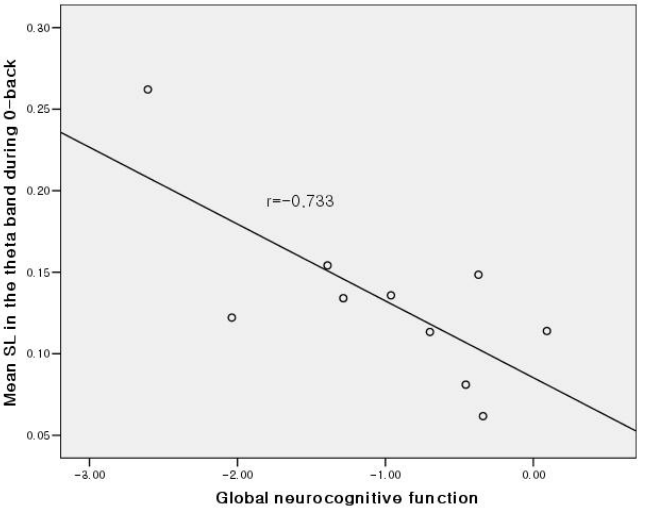

Fig 5. Correlation between mean synchronization likelihood (SL) in the theta band during the 0-back task and global neurocognitive function scores in UHR subjects.

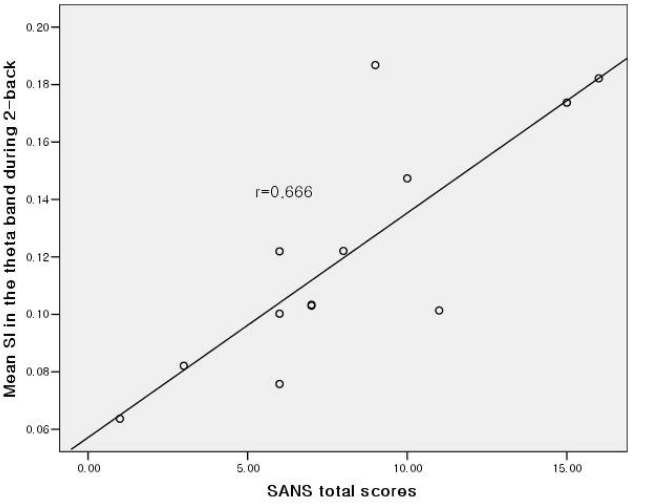

Fig 6. Correlation between mean synchronization likelihood (SL) in the theta band during the 2-back task and SANS total scores in UHR subjects. SANS: Scale for the Assessment of Negative Symptoms.

IV. DISCUSSION

In the present study, changes in the functional neuronal network in relation to the varying degrees of the working memory load were investigated in first-episode SPR patients, UHR individuals and the controls. The main finding was that small-world properties were preserved during 0- and 2-back tasks, while a trend of the group effect was seen in the theta band with decreased small-worldness in SPR patients compared to controls. For functional connectivity, SL according to working memory load was significantly different among the three groups. More specifically, while the strength of the functional connectivity significantly decreased with working memory load in the controls, this effect was not observed in UHR subjects. In SPR patients, functional connectivity strength was significantly higher than the controls or UHR individuals during the 0-back task but steeply decreased under the working memory load.

Findings of the current study can be linked to the results of previous studies in which small-world properties and connectivity strength were explored under various conditions. In a study comparing children and young adults, Supekar et al. demonstrated that, although the brains of children and young adults showed similar small-world organizations, the patterns of interregional functional connectivity differed significantly[38]. The findings suggested that connectivity rewiring through the process of over-connectivity followed by pruning occurs at the system level as well as the neuronal level, helping to maintain optimal organizations in the developing brain through reconfiguration and remodeling. Intriguingly, another study showed that a similar pattern emerges in adults under different levels of the working memory load[39]. While small-world properties were conserved throughout the different working memory loads, the connectivity strength decreased as the working memory load increased, although with a different connectivity measures. The authors suggested that a task-specific "functional trimming", conceptually similar to the anatomical pruning witnessed during development, may be needed for higher cognitive demands[39]. Similar to anatomical pruning, it is hypothesized that functional trimming is needed for greater modular specialization of cognitive faculties. Thus, under the emergent cognitive demand, functional connectivity strength may be decreased while small-world architecture may be maintained. The present study adds further evidence supporting this hypothesis.

In UHR subjects, the patterns of change in functional connectivity strength across the working memory load were significantly different, while the small-world network architecture was preserved. In particular, the functional connectivity strength of UHR individuals was not decreased as that of healthy controls when the working memory function was demanded. Although speculative, the finding may suggest abnormalities of functional trimming of connectivities needed for specialization of brain networks for adequate working memory function. The results from the correlation analyses are in accordance

with this speculation. Lower working memory performance and higher symptom severity were associated with higher functional connectivity strength, which may reflect less functional trimming.

Surprisingly, SPR patients showed higher functional connectivity strength than UHR subjects or the controls during the 0-back task. Collectively with the above findings, the increased SL of SPR patients may represent ineffective network connectomes due to pruning abnormalities of unused synapses. As the working memory load increases, however, the network may ultimately fail to make adequate functional connections among the overabundant synaptic connections. This may lead to a steeply decreased pattern of SL demonstrated in SPR patients. Evidence from other lines of research also supports the hypothesis of aberrant brain maturation process of synaptogenesis and pruning in SPR. Psychosis nearly always emerges in late adolescence or early adulthood, which is in accordance with the period of significant brain maturation. Although the changes in human cortical development during this period are not yet fully understood, studies in the non-human primate brain demonstrated that refinements of circuits, including pruning of excitatory synapses, proliferation of inhibitory synapses, occur during this period[41-43]. In longitudinal population-based studies, much earlier developmental problems, such as a history of delayed developmental milestone in the first year, are evident in SPR patients[44]. Moreover, genetic studies indicate an overlap of genetics of SPR with that of autism and other neurodevelopmental disorders[45-46], with implication of neurodevelopmental genes involved in neuronal proliferation, migration, or synapse formation[47].

There are several limitations to the present study. First, there are potential disadvantages of using scalp EEG signals such as problems with volume conduction, coarse spatial resolution and influence of reference electrodes. However, noisy reference would decrease, not increase group differences, supporting the robustness of the present findings. Furthermore, comparison

between groups using same procedures is expected to diminish these disadvantages. Still, the properties of scalp EEG signals are yet limited in direct evaluation of deep brain regions that may be associated with working memory. Other methods that can supplement these potential disadvantages will be helpful to strengthen the findings of this study. Second, most of the SPR patients included in the study were on antipsychotics medication. One cannot completely exclude the potential effects of medications, but the direction of the effects have been reported to be "restorative" or improving neurophysiological functioning in previous studies[3-4]. More importantly, there were no significant correlations between the chlorpromazine-equivalent medication doses and the graph parameters in the current study. Lastly, while the present study attempts to investigate the underlying brain mechanisms in the course of the illness, the design is still a cross-sectional one. In future studies, a within-subject comparison of network parameters in a longitudinal study will be needed to further confirm the putative hypothesis related to abnormal neurodevelopmental processes in SPR.

V. CONCLUSION

The small-world properties were preserved across the working memory load, while patterns of functional connectivity strength were distinctively different among SPR patients, UHR individuals and healthy controls. The current findings suggest abnormalities in functional trimming needed for modular specialization of brain networks under higher cognitive demands in SPR patients. Although the topographical network structure is yet maintained, alterations of functional connectivity are present from the prodromal phase of the illness. Collectively, the current findings support the neurodevelopmental hypothesis of SPR.

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ABSTRACT(IN KOREAN)

고위험군 및 초발 정신분열병 환자의 작업기억 관련 뇌 기능적 연결성의 변화

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정 경 운

고차원적 인지 기능은 뇌신경회로망의 다양한 영역의 기능적 연결을 필요로 한다. 이러한 기능적 회로의 이상은 정신분열병의 주된 병리 기전으로 제시되어 왔으며, 최근 다양한 뇌영상 연구 등에서 관련된 결과들이 발표되고 있다. 본 연구에서는 정신증의 고위험군과 초발 정신분열병 환자들을 대상으로 작업기억을 수행하는 동안 뇌신경회로망의 네트워크 구조를 비교하였다. 11명의 고위험군 환자, 13명의 정신분열병 환자, 13명의 대조군을 대상으로 0-back 과제 및 2-back 과제를 시행하면서 뇌파를 측정하였으며, 뇌신경회로망의 동기화 척도인 synchronization likelihood(SL)와 네트워크 구조의 최적화 정도를 측정하는 small-worldness를 비교하였다. 연구 결과, 작업기억능력의 부하가 증가함에 따른 SL의 변화 패턴은 군에 따라 유의미하게 달랐다. 특히, 대조군에서는 작업기억능력의 부하가 증가함에 따라 SL이 감소한 반면, 이러한 변화는 고위험군에서는 관찰되지 않았다. 정신분열병 환자군에서는 0-back 과제 시 SL이 대조군 및 고위험군에 비해 유의미하게 높았고, 작업기억능력의 부하가 증가하자 유의미하게 SL이 감소하였다. Small-worldness의 경우, 작업기억능력의 부하에 따른 유의미한 차이가 없었으나, 쎄타 밴드에서 정신분열병 환자군이 정상대조군이나 고위험군에 비하여 small-worldness가 낮은

경향성을 보였다. 본 연구결과는 정신분열병의 병인 기전과 관련하여 기능적 뇌연결성 이상의 역할을 지지하며, 전구기 때에도 기능적 뇌연결성의 이상이 있음을 시사한다.

핵심되는 말 : 고위험군, 기능적 연결성, 정신분열병, 네트워크 분석, 동기화