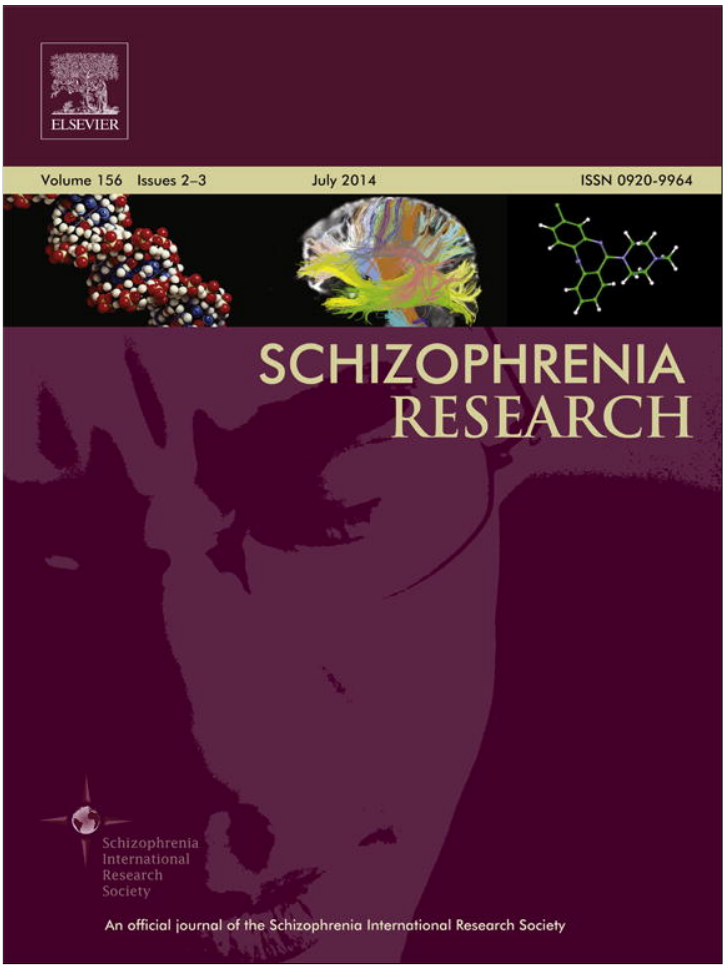

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Disruptions in small-world cortical functional connectivity network during an auditory oddball paradigm task in patients with schizophrenia

Miseon Shim [a,b], Do-Won Kim [a,b], Seung-Hwan Lee [b,c], Chang-Hwan Im [a,*]

[a] Department of Biomedical Engineering, Hanyang University, Seoul, Republic of Korea
[b] Clinical Emotion Cognition Research Laboratory, Goyang, Republic of Korea
[c] Psychiatry Department, Ilsan Paik Hospital, Inje University, Goyang, Republic of Korea

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ABSTRACT

P300 deficits in patients with schizophrenia have previously been investigated using EEGs recorded during auditory oddball tasks. However, small-world cortical functional networks during auditory oddball tasks and their relationships with symptom severity scores in schizophrenia have not yet been investigated. In this study, the small-world characteristics of source-level functional connectivity networks of EEG responses elicited by an auditory oddball paradigm were evaluated using two representative graph-theoretical measures, clustering coefficient and path length. EEG signals from 34 patients with schizophrenia and 34 healthy controls were recorded while each subject was asked to attend to oddball tones. The results showed reduced clustering coefficients and increased path lengths in patients with schizophrenia, suggesting that the small-world functional network is disrupted in patients with schizophrenia. In addition, the negative and cognitive symptom components of positive and negative symptom scales were negatively correlated with the clustering coefficient and positively correlated with path length, demonstrating that both indices are indicators of symptom severity in patients with schizophrenia. Our study results suggest that disrupted small-world characteristics are potential biomarkers for patients with schizophrenia.

1. Introduction

Each local brain region has its own functions and is connected with other brain regions both structurally and functionally, which facilitates information transfer among distant brain regions (Dosenbach et al., 2007; Friston, 2011). Information processing through the complex cortical functional network has been known to be impaired in patients with schizophrenia, which therefore has been suggested to be a disrupted cortical and subcortical network disorder. Among neuroimaging modalities, electroencephalography (EEG) has proved to be one of the most useful tools to investigate brain information processing. Previous EEG studies reported altered event-related potential (ERP) waveforms, disrupted functional connectivity, and reduced source activity for specific ERP components in patients with schizophrenia (Pascual-Marqui et al., 1999; Winterer et al., 2003b; Kayser et al., 2010). For example, reduced P300 amplitude and prolonged P300 latency have been consistently found in these patients (Potts et al., 1998; Mathalon, 2000; van der Stelt et al., 2005). Some studies also reported disrupted functional connectivity, particularly in the temporo-patietal junction and fronto-temporal connection (Friston and Frith, 1995; Schall et al., 1999; Lawrie et al., 2002; Wolf et al., 2007). EEG source imaging studies have shown reduced source activities at the left insular, left postcentral gyrus, and left temporal areas in patients with schizophrenia (Pae et al., 2003; Kawasaki et al., 2007; Wang et al., 2010).

Recently, an increased number of researchers have focused on changes in the cortical functional connectivity network, because alterations in the cortical connectivity network might provide clues to reveal the underlying neural mechanisms of schizophrenia. Many of these studies adopted graph theory to quantify global and local changes in the cortical functional connectivity network (Stam and Reijneveld, 2007; Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). In particular, the small-world network has been regarded as one of the most suitable models to elucidate information transfer in the human brain (Li et al., 2007; Bolanos et al., 2013). The small-world network is the middle ground between random network and regular network. The small-world network is characterized by a higher clustering coefficient than random networks and a shorter path length than regular networks, where the clustering coefficient and the path length reflect the amount of segregation of highly inter-connected units and the amount of integration of the whole network, respectively (Watts and Strogatz,

* Corresponding author at: Department of Biomedical Engineering, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul 133–791, Republic of Korea. Tel.: +82 2 2220 2322; fax: +82 2 2296 5943.
E-mail address: ich@hanyang.ac.kr (C.-H. Im).

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1998). Therefore, the small-world characteristics of the brain allow for more efficient information transfer among distant brain regions.

In previous EEG studies, patients with schizophrenia consistently showed disrupted small-world networks characterized by decreased clustering coefficients and prolonged path lengths in the resting state (Micheloyannis et al., 2006; Rubinov et al., 2009; Jalili and Knyazeva, 2011) and during the working memory task (Schinkel et al., 2011), compared to healthy control subjects. However, most EEG network analysis studies, including these examples, were based on sensor-level connectivity analysis. Therefore, these studies failed to report specific cortical regions that contribute to the disruption of the small-world cortical functional network in schizophrenia. This shortcoming was also noted by De Vico Fallani et al. (2010), who performed the first network analysis (node degree and network density) of EEG source-level functional connectivity in patients with schizophrenia during the 2-back working memory task. EEG topographies cannot be directly attributed to the underlying cortical regions, since sensors may contain information from multiple brain sources, some of which might overlap, and topographic maps are sometimes smeared out due to inhomogeneous conductivity distributions in the human head. This so-called "volume-conduction effect" can cause spurious connectivity between scalp EEG channels (Haufe et al., 2013), eventually leading to failure in identifying the region-specific changes in cortical functional connectivity networks. In addition, most previous studies also used binary (unweighted) functional networks for the estimation of small-worldness. The use of binary networks might lead to losses of information about interaction strength that might be useful to characterize small-world characteristics in patients with schizophrenia, because arbitrary threshold values are required to convert the original functional connectivity network into a binary network.

In the present study, the small-worldness of brain networks was evaluated using a source-level weighted functional connectivity network analysis. The use of source-level weighted network analysis allows for observing the alternation of small-world networks in specific local cortical regions as well as in the global brain network pattern. Moreover, the use of weighted networks is not only free from ambiguity in determining threshold values, but can also preserve the unique traits of the original network without distortion. Although a series of P300 EEG studies demonstrated that patients with schizophrenia generally show significant decreases in task performance and brain activity (Kügler et al., 1993; Polich and Kok, 1995; Pae et al., 2003; Kawasaki et al., 2007; Wang et al., 2010), to the best of our knowledge, auditory oddball tasks have not been used to investigate changes in small-world cortical functional networks in patients with schizophrenia. In addition, no previous studies have investigated the relationships between small-worldness and symptom severity of patients with schizophrenia. We hypothesized that the small-worldness of cortical functional connectivity networks would be disrupted during P300 processing of an auditory oddball task in patients with schizophrenia, and that the disrupted small-world characteristics would be correlated with symptom severity.

2. Methods

2.1. Participants

Thirty-four patients with schizophrenia (20 males and 14 females) and 34 healthy controls (14 males and 20 females) were recruited for this study from the Psychiatry Department of Inje University Ilsan Paik Hospital. Patients who had diseases of the central nervous system, medical histories of alcohol and drug abuse, experience with electrical therapy, mental retardation, or head injuries with loss of consciousness were excluded from the study by the initial screening interviews. The patients were diagnosed based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Psychiatric Disorders. Their psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Healthy controls were recruited from the local community through local newspapers and posters. After an initial screening using the same criteria, control subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis II Disorders (Gibbon et al., 1997). All subjects provided written informed consent, and the study protocol was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital. Table 1 presents the demographic data of patients and healthy controls.

2.2. EEG recording and pre-processing

The stimuli used for the auditory oddball paradigm were composed of target tones with 1500 Hz tone frequency and standard tones with 1000 Hz tone frequency. The duration of each stimulus was set to 100 ms, and rising and falling times were set to 10 ms. Four-hundred pure tone stimuli consisting of 15% target tones and 85% standard tones were presented in random order with an inter-stimulus interval (ISI) of 1500 ms. The participants were required to press a button when target tones were presented.

Scalp EEG data were recorded using a NeuroScan SynAmps2 amplifier (Compumedics USA, El Paso, TX, USA) from 62 Ag/AgCl scalp electrodes (FP1, FPZ, FP2, AF3, AF4, F7, F5, F3, F1, FZ, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCZ, FC2, FC4, FC6, FT8, T7, C5, C3, C1, CZ, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPZ, CP2, CP4, CP6, TP8, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO7, PO5, PO3, POZ, PO4, PO6, PO8, CB1, O1, OZ, O2, and CB2) evenly arranged in a head cap according to a modified 10–20 electrode system. The ground electrode was placed on the forehead and the reference electrodes were attached at both mastoids. The vertical electrooculogram (VEOG) channels were located above and below the right eye and the horizontal electrooculogram (HEOG) channels were placed on the outer canthus of each eye. EEG data were recorded with a 1 to 100 Hz band-pass filter at a sampling rate of 1000 Hz; with 60 Hz noise removed using a notch filter.

After recording EEGs, the data were processed using Scan 4.3 software (Compumedics USA, El Paso, TX, USA). Eye blink artifacts were corrected using a linear regression analysis for which correction coefficients were estimated from averaged maximal eye blinks in time domain (Semlitsch et al., 1986). We also rejected other gross artifacts by visual inspection done by one experienced person who was blind to the data origin. After artifact rejection, the data were band-pass filtered at 1 to 55 Hz and epoched from 100 ms before the target stimulus onset to 900 ms after the target stimulus onset. The epochs were rejected if they contained significant physiological artifacts (amplitude exceeding $\pm 75\ \mu V$) at any site over all electrodes. Among the 60 trials of target stimulus, the numbers of remaining epochs after artifact rejection were 53.09 ± 9.89 for normal controls and 47.59 ± 13.86 for patients with schizophrenia.

2.3. Source localization and connectivity

To estimate the source-level cortical functional connectivity network, time series of source activity were estimated using minimum-norm estimation (MNE), and the synchronization between each pair of cortical sources was estimated in terms of phase locking value (PLV). Values of clustering coefficient and path length were evaluated for individual cortical functional networks during an auditory oddball task, and then the correlations between the graph theoretical measures and the symptom severity scores were evaluated using Pearson's correlation analysis.

Source localization was performed using MNE implemented in eConnectome toolbox (Biomedical Functional Imaging and Neuroengineering Laboratory, University of Minnesota, Minneapolis, MN, USA) (He et al., 2011). A three-layer boundary element method (BEM) model constructed from the MNI 152 standard template was used to compute the leadfield matrix. Cortical current density values

Table 1
Demographic data of patients with schizophrenia and healthy controls.

	Schizophrenia patients	Healthy controls	p
Cases (*N*)	34	34	
Gender (male/female)	14/20	20/14	0.225
Age (years)	33.91 ± 13.30	34.74 ± 13.16	0.798
Education	13.59 ± 9.06	13.97 ± 13.10	0.827
Illness duration (months)	51.88 ± 68.64		
Dosage of antipsychotics (chlorpromazine equivalents, mg)	511.10 ± 398.22		
Positive and Negative			
Syndrome Scale (PANSS)			
Positive score	20.70 ± 7.00		
Negative score	19.03 ± 6.45		
General score	42.67 ± 11.00		
Total score	82.36 ± 21.49		

at 7,850 cortical vertices were evaluated for every time point of each epoch. After estimating the cortical current density distribution at every time point, 314 dipole sources were extracted as evenly as possible from the original cortical surface model (Fig. 1). The time series data at each of the 314 cortical locations were band-pass filtered and divided into five frequency bands (alpha (8–12 Hz), beta1 (12–18 Hz), beta2 (18–22 Hz), beta3 (22–30 Hz) and gamma (30–55 Hz)) (Koenig et al., 2001; Park et al., 2008). Lower frequency bands such as delta (1–4Hz) and theta (4–8Hz) were not considered in the analysis because only one or two full cycles of these frequency components were included in the analysis time window (500 ms), which might cause significant biases in the phase locking analysis results.

PLV was used to quantify the functional connectivity between all possible pairs of cortical regions of interest (Lachaux et al., 1999). The time interval was set from 0 to 500 ms after the target stimulus onset, which includes the P300 component that showed significant changes in schizophrenia in our previous ERP study (Kim et al., 2013). We selected the PLV as the measure of synchronization because the PLV ranges from 0 to 1, and thus can be directly used to stand for the connection strength in the weighted network analysis without any further modifications.

2.4. Network analysis

In this study, we performed weighted network analysis based on graph theory. A network is composed of several nodes, which are connected to each other by edges. The weighted clustering coefficient quantifies the functional segregation of a network, and the path length quantifies the functional integration of the network. The detailed definitions of these terms can be found in a well-organized review article (Rubinov and Sporns, 2010). To compare the characteristics of the observed network and the random networks, 1,000 surrogate graphs were created by randomly reshuffling weights (De Haan et al., 2009). The clustering coefficient was evaluated for each node (denoted as local level results), and then averaged across all cortical regions of interest (denoted as global level results). Since path length is defined only at the global level, 'local-level' path length values are not available (Watts and Strogatz, 1998).

2.5. Statistical analysis

The cortical network characteristics at the global level between patients with schizophrenia and healthy controls were investigated for each frequency band using independent *t*-test without multiple comparisons (Micheloyannis et al., 2006; Stam and Reijneveld, 2007; de Haan et al., 2009). At the local level, group differences were tested with independent *t*-test without multiple comparisons (Jalili and Knyazeva, 2011; Wang et al., 2012). When significant differences were found in the network measures between two groups, additional correlation analyses were performed to investigate the relationships between the network measures and the symptom severity scores in schizophrenia (Stam and Reijneveld, 2007; Stam et al., 2009). The psychopathology symptom severity score (PANSS) was divided into five factors: negative, positive, cognitive, excitement, and depression (Lindenmayer et al., 1995). The five factors are explained in a more detail in Table 2.

3. Results

3.1. Global level differences of cortical functional networks

The global level values of clustering coefficient and path length are summarized in Table 3. The clustering coefficient was significantly reduced in patients with schizophrenia compared to healthy controls in

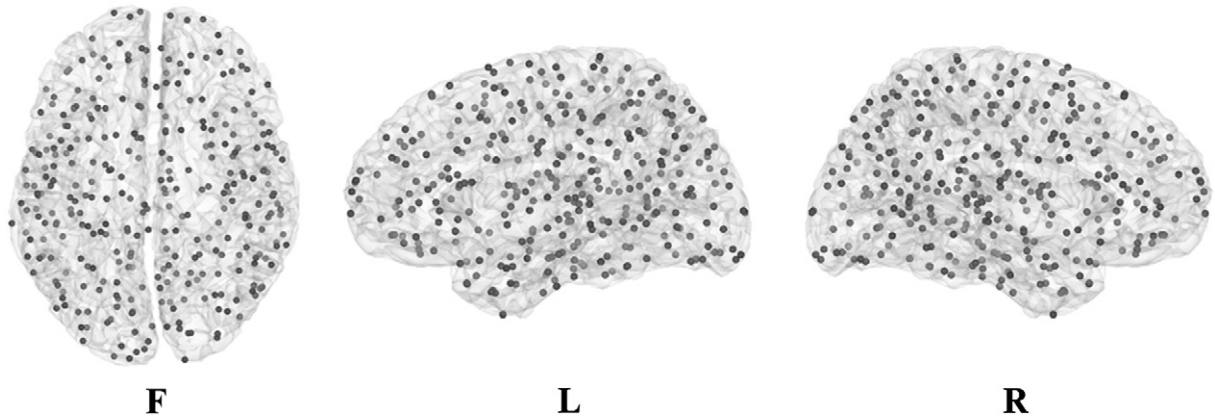

Fig. 1. Distribution of the 314 cortical vertices extracted from the original cortical surface model, which were used for the connectivity analyses. 'F', 'L', and 'R' represent front view, left view, and right view, respectively.

Table 2
Five factors of psychiatric symptoms in the PANSS score.

Negative	Emotional withdrawal, apathetic social withdrawal, lack of spontaneity, poor rapport, blunted affect, active social avoidance
Positive	Hallucinations, stereotyped thinking
Cognitive	Poor attention, mannerisms and posturing, conceptual disorganization, difficulty in abstract thinking, disorientation
Excitement	Excitement, poor impulse control, hostility, uncooperativeness
Depression	Anxiety, guilt feelings, depression and tension

the beta1 band (0.419 ± 0.026 vs. 0.434 ± 0.017; t = −2.820; confidence interval (c.i.) = −0.026 ~ −0.005; $p = 0.006$). In addition, the path length was significantly longer in schizophrenia patients than healthy controls in the beta1 band (2.720 ± 0.249 vs. 2.563 ± 0.197; t = 2.886; c.i. = 0.048 ~ 0.266; $p = 0.005$) and beta2 band (2.420 ± 0.179 vs. 2.310 ± 0.190; t = 2.474; c.i. = 0.021 ~ 0.199; $p = 0.016$).

3.2. Local level difference of cortical functional network

Since the global level values of clustering coefficient was significantly different between patients with schizophrenia and healthy controls only in the beta1 band, the local level differences of the clustering coefficients in the beta1 band were investigated. The clustering coefficients of schizophrenia were decreased in frontal and temporal–parietal regions ($p < 0.01$). Fig. 2 shows differences of clustering coefficients between two groups, represented by node color (blue represents decreased clustering coefficients in patients with schizophrenia) and the node size, which represents the p-value. Note that path length does not have a local-level value.

3.3. Correlation analysis between network measures and symptomatic scores

The relationships between network measures and symptom severity scores were investigated. The correlation analyses were applied only to pairs of frequency bands and network measures that showed significant differences between two groups (clustering coefficient in beta1 band; path length in beta1 and beta2 bands). Clustering coefficient showed negative correlations with the negative component ($r = -0.408$, $p = 0.019$; Fig. 3A) and cognitive component ($r = -0.389$, $p = 0.027$; Fig. 3C) in beta1 band. However, path length was positively correlated with the negative component ($r = 0.381$, $p = 0.029$; Fig. 3B) and cognitive component ($r = 0.392$, $p = 0.024$; Fig. 3D) only in the beta1 band. No significant correlations were found between network measures and other sub-components. Table 4 presents the results of correlation analyses.

4. Discussion

This study is the first to investigate the network characteristics of cortical functional connectivity during an auditory oddball paradigm task in patients with schizophrenia. Our major findings were: (1) clustering coefficient is significantly lower and path length is significantly longer in patients with schizophrenia than healthy controls during P300 processing of the auditory oddball paradigm task; (2) the local clustering coefficients of patients with schizophrenia were decreased in frontal and temporal–parietal regions; and (3) negative correlations were found between the clustering coefficient and the negative and cognitive components of PANSS, whereas positive correlations were found between the path length and the same components of PANSS.

4.1. Global level and local level network

Small-world networks are generally characterized by clustering coefficient and path length (Micheloyannis et al., 2006; Liu et al., 2008; Bullmore and Sporns, 2009). Clustering coefficient represents how strongly each node is connected with its neighbors, whereas path length represents how well the network nodes are communicating with each other. Therefore, decreased clustering coefficient represents loose coupling among network nodes (brain areas), and prolonged path length implies inefficient connections (delayed information transfer) between brain regions during information processing.

According to previous fMRI studies, decreased clustering coefficients were commonly observed in frontal, temporal and occipital areas in patients with schizophrenia (Li et al., 2007; Liu et al., 2008; Lynall et al., 2010; Yu et al., 2011b; Wang et al., 2012). In the present study, clustering coefficients were significantly decreased in frontal and temporal–parietal areas in patients with schizophrenia, compared to healthy subjects, corresponding well with previous fMRI results. Traditionally, schizophrenia has been suggested to be a fronto-temporal network dysfunctional disorder (Schall et al., 1999; Lawrie et al., 2002; Wolf et al., 2007). Our local-level results are in line with this well-established concept of schizophrenia pathology.

The global level network analysis results showed decreased clustering coefficient and prolonged path length during an auditory oddball paradigm, which were also observed in previous sensor level small-world network analyses that used EEG data recorded during the resting state or a working memory task (Micheloyannis et al., 2006; Rubinov et al., 2009). All of results, including ours, explain the pathophysiological background underscoring why the latency of P300 in schizophrenia is generally longer than in healthy controls (Karoumi et al., 2000), because disruptions of small-world network characteristics, especially prolonged path length, imply slower information processing and less efficient information transfer.

Table 3
Mean clustering coefficient and path length in each frequency band, averaged over all cortical vertices of interest. Bold letters represent significant differences between patients with schizophrenia (denoted by SPR) and normal controls (denoted by NC).

Frequency band	Clustering coefficient			Path length		
	SPR	NC	t-Statistics (p-value)	SPR	NC	t-Statistics (p-value)
Alpha (8–12 Hz)	0.474 ± 0.029	0.480 ± 0.027	−0.979 (0.331)	2.447 ± 0.213	2.353 ± 0.231	1.748 (0.085)
Beta1 (12–18 Hz)	**0.419 ± 0.026**	**0.434 ± 0.017**	**−2.820 (0.006**)**	**2.720 ± 0.249**	**2.563 ± 0.197**	**2.886 (0.005**)**
Beta2 (18–22 Hz)	0.491 ± 0.026	0.497 ± 0.020	−1.037 (0.303)	**2.420 ± 0.179**	**2.310 ± 0.190**	**2.474 (0.016*)**
Beta3 (22–30 Hz)	0.400 ± 0.025	0.400 ± 0.027	−0.089 (0.919)	2.820 ± 0.253	2.745 ± 0.253	1.185 (0.240)
Gamma (30–55 Hz)	0.332 ± 0.028	0.338 ± 0.021	−0.932 (0.355)	3.192 ± 0.280	3.088 ± 0.248	1.634 (0.107)

** $p < 0.01$.
* $p < 0.05$.

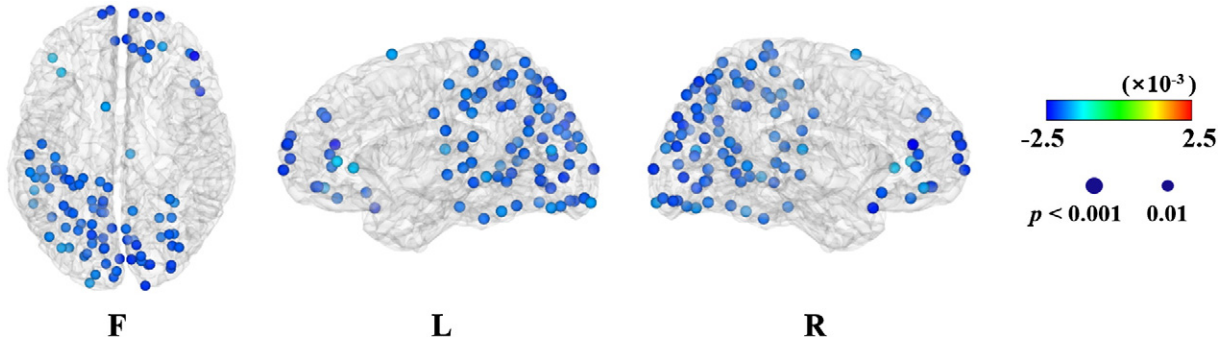

Fig. 2. The differences of clustering coefficients between schizophrenia and healthy control estimated at the local level: the clustering coefficients of schizophrenia were significantly decreased in frontal and temporal–parietal areas. The colors of circles represent the differences of clustering coefficients and the sizes of the circles the *p*-values. 'F', 'L', and 'R' represent front view, left view, and right view, respectively.

4.2. The relationships between graph-theoretical measures and psychiatric symptom factors

Correlations between network measures (other than small-worldness) and symptom scores were reported in previous studies (Yu et al., 2011a; Wang et al., 2012), whereas some other studies did not find significant relationships between symptomatic scores and network measures (Micheloyannis et al., 2006; Liu et al., 2008). Wang et al. (2012) found that global efficiency has a negative correlation and path length has a positive correlation with negative symptom score. Yu et al. (2011a) also reported that both the global efficiency and local efficiency have negative correlations with negative, positive, and total symptom scores of PANSS. Interestingly, both studies (Yu et al., 2011a; Wang et al., 2012) reported correlations between negative symptomatic scores and network measures. In the present study, the clustering coefficient and the path length also showed positive and negative correlations with negative factor, respectively, supporting the hypothesis that that the negative symptom in patients with schizophrenia might be closely associated with the disruption of cortical functional connectivity networks. Only the beta1 frequency band showed correlations with negative factor both in clustering coefficient and path length, which coincide well with previous studies that reported close relationships between EEG beta band powers and negative symptoms in schizophrenia (Harris et al., 1999; Gschwandtner et al., 2009).

Recently, some studies of patients with schizophrenia reported significantly reduced beta-band synchronization and absolute power compared to healthy controls during cognitive tasks (Uhlhaas et al., 2006, 2008). Considering that beta-band activity is closely related to top-down and bottom-up processes involved in cognitive functions (Engel and Fries, 2010), the reduced cortical activity in beta band might reflect cognitive deficits in patients with schizophrenia. Meanwhile, the P300 ERP component evoked by an auditory oddball paradigm is thought to

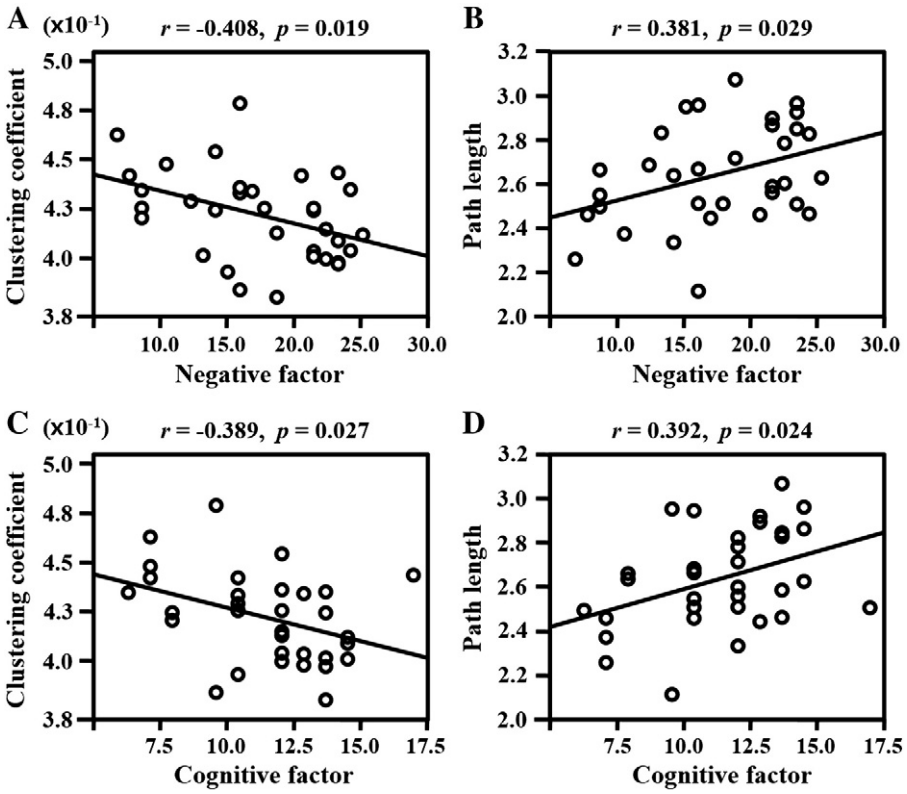

Fig. 3. The relationships between small-world network measures in the beta1 band (12–18 Hz) and psychiatric symptom scores (refer to Table 4). 'Negative factor' and 'cognitive factor' represent negative and cognitive symptom factors, respectively.

Table 4
The relationships between five factors and global-level small-world network measures in the beta1 band (12–18 Hz). Significant relationships are marked as bold letters. '*r*' represents Pearson correlation coefficient.

Network measures	Negative		Positive		Cognitive		Excitement		Depression	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Clustering coefficient	**−0.408**	**0.019***	−0.108	0.550	**−0.389**	**0.027***	−0.243	0.173	−0.215	0.230
Path length	**0.381**	**0.029***	0.126	0.485	**0.392**	**0.024***	0.266	0.135	0.133	0.461

** $p < 0.01$.
* $p < 0.05$.

be associated with cognitive processes such as attention allocation and immediate memory (Polich, 2012). Therefore, altered P300 characteristics such as reduced peak amplitude, prolonged latency, and reduced cortical source activity are widely believed to reflect cognitive impairments in patients with schizophrenia (Friston and Frith, 1995; Polich and Kok, 1995; Mathalon et al., 2000; Pae et al., 2003; Winterer et al., 2003a; van der Stelt et al., 2005; Kawasaki et al., 2007; Wang et al., 2010; Polich, 2012; Kim et al., 2014). In the present study, we found that cognitive factor of PANSS scale in patients with schizophrenia have negative and positive correlations with the clustering coefficient and the path length, respectively, in the beta1 frequency band. These findings suggest that disorganized small-world cortical functional networks during auditory oddball tasks might also reflect cognitive decline in patients with schizophrenia.

4.3. Limitations

There are some limitations in the present study. First, our patient sample did not control for the possible confounding effects of antipsychotic drugs. Second, participants did not perform neuropsychological tests to evaluate cognitive function. Thus, our results might be insufficient to explain the direct relationships between cognitive function and small-world network characteristics in patients with schizophrenia.

Despite these limitations, our results are meaningful considering that our study was the first attempt to analyze the source-level small-world network in schizophrenia using an auditory oddball task. Our results demonstrate that source-level network analysis of EEG signals elicited by an auditory oddball P300 paradigm provides information on dysfunctional cortical network characteristics and also might be used as potential diagnostic biomarkers in patients with schizophrenia. More validation studies are still needed to use small-world network measures as practical diagnostic biomarkers, for example, longitudinal studies, test–retest reliability check, and validation with more numbers of patients, all of which we would like to perform in our future studies.

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Contributors

Miseon Shim designed the study and wrote the manuscript. Seung-Hwan Lee designed the study and wrote the protocol. Do-Won Kim produced the ERP waves and calculated the current source densities from the data set. Chang-Hwan Im supervised the study process and manuscript writing. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest.

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