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Modulations of functional connectivity in the healthy and schizophrenia groups during task and rest

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Abstract

Connectivity analysis using functional magnetic resonance imaging (fMRI) data is an important area, useful for the identification of biomarkers for various mental disorders, including schizophrenia. Most studies to date have focused on resting data, while the study of functional connectivity during task and the differences between task and rest are of great interest as well. In this work, we examine the graph-theoretical properties of the connectivity maps constructed using spatial components derived from independent component analysis (ICA) for healthy controls and patients with schizophrenia during an auditory oddball task (AOD) and at extended rest. We estimate functional connectivity using the higher-order statistical dependence, i.e., mutual information among the ICA spatial components, instead of the typically used temporal correlation. We also define three novel topological metrics based on the modules of brain networks obtained using a clustering approach. Our experimental results show that although the schizophrenia patients preserve the small-world property, they present a significantly lower small-worldness during both AOD task and rest when compared to the healthy controls, indicating a consistent tendency towards a more random organization of brain networks. In addition, the task-induced modulations to topological measures of several components involving motor, cerebellum and parietal regions are altered in patients relative to controls, providing further evidence for the aberrant connectivity in schizophrenia.

Keywords

Functional connectivity; graph theoretical analysis; spatial dependence; resting state; auditory oddball task; schizophrenia

1. Introduction

In the past two decades, the human brain as a complex system has been successfully analyzed using functional magnetic resonance imaging (fMRI). One of the most active areas in current fMRI research involves examining the functional connectivity, i.e., interactions among distributed regions. More interestingly, dysconnectivity or abnormal connectivity has been hypothesized as the major pathophysiological mechanism of various mental disorders, especially schizophrenia (Friston and Frith, 1995; Bullmore et al., 1997; Palmer et al., 2009; Stephan et al., 2009). Evidences for dysconnectivity in schizophrenia have been found between several brain regions (Lawrie et al., 2002; Honey et al., 2005; Liang et al., 2006; Zhou et al., 2007; Rotarska-Jagiela et al., 2010). For example, (Friston and Frith, 1995) discovered profound disruption of prefrontal-temporal interaction; (Rotarska-Jagiela et al., 2010) reported that schizophrenia patients showed aberrant connectivity in the default-mode network and decreased frontoparietal activity. Recently, further studies using graph-theoretical analysis methods suggested that patients with schizophrenia often present abnormalities in topological properties of the brain network connectivity, including small-worldness, efficiency and modularity (Liu et al., 2008; Bullmore and Sporns, 2009; Alexander-Bloch et al., 2010; Guye et al., 2010; Lynall et al., 2010; Wang et al., 2010; Zalesky et al., 2010; Yu et al., 2011b). For example, significantly decreased local and global efficiency in schizophrenia has been shown in a resting-state fMRI study (Liu et al., 2008); a reduced small-worldness in schizophrenic group has been reported in (Lynall et al., 2010). In general, most previous studies using graph-theoretical analysis methods have been conducted with participants during the resting state (van de Ven et al., 2004; Beckmann et al., 2005; De Luca et al., 2005; Jafri et al., 2008; Camchong et al., 2011; Yu et al., 2011b); while the topological properties of network connectivity as a function of task performance (Yu et al., 2011a; Rajapakse et al., 2006) and also the differences between task and rest have not been studied to the same degree. In this work, we examine the graph-theoretical properties of the brain network connectivity for the patients with schizophrenia and healthy controls during both an auditory oddball task (AOD) and an extended rest.

For fMRI data analysis, functional connectivity can be investigated using seed-based method that relies on temporal correlation between a few predefined seed regions of interest and other remaining regions (Biswal et al., 1995, 1997; Cordes et al., 2000, 2002; Moussa et al., 2011). However, the seed-based approach usually requires *prior* knowledge, for example an anatomical model, to determine the seed regions.

An alternative approach to estimate functional connectivity is using independent component analysis (ICA) (McKeown and Sejnowski, 1998). ICA, as applied to fMRI, separates data into a set of maximally independent components and associated time courses, where each component is a spatially distinct network containing *temporally coherent* voxels (Calhoun et al., 2001). Without an explicit *prior* knowledge, ICA provides a promising way to study connectivity on a multivariate level. Based on an ICA decomposition, functional connectivity is generally defined as the correlation between the ICA time courses (van de Ven et al., 2004; Jafri et al., 2008).

However, the time dimension of fMRI data and thus of the ICA time courses typically contain a significantly smaller set of samples relative to the spatial components (hundreds compared to tens of thousands). The inherent small sample size of time courses may reduce the accuracy of the computed statistics. Also, the second-order statistics such as correlation do not take full-order statistical information into account. We note that ICA uses diversity to take higher-order statistics into consideration. Based on its generative model, ICA also naturally takes temporal information into account by providing a clustering of spatial components through the temporal modulations. Hence, we measure the functional

connectivity using ICA spatial components and in terms of higher-order statistical dependence, instead of the typically used temporal correlation.

In this study, we examine the functional connectivity in patients with schizophrenia and healthy controls acquired during both an auditory oddball task (AOD) and an extended rest. We construct connectivity maps using the mutual information among the ICA spatial components and calculate the graph-theoretical metrics of these maps. We also define three novel metrics based on the modules of components obtained using our previously proposed clustering approach (Ma et al., 2011a). According to the dysconnectivity hypothesis in schizophrenia, we assume in our study that the graph-theoretical properties of the network connectivity observed in the healthy group would be altered in the schizophrenia group, not only at resting state but also during the AOD task. Our experimental results show that regardless of the brain activation states (AOD task versus rest), the connectivity networks derived from spatial dependencies in schizophrenia patients preserve the small-world property. However, patients present a significantly lower small-worldness during both AOD task and rest relative to controls, indicating a consistent tendency towards a more random network organization. These two groups also present some different task-induced changes in the topological features, for example healthy controls show higher efficiency in the motor regions during the AOD task than at rest while patients exhibit reverse trend. These altered connectivity modulations in patients during different activation states may provide further evidence for the cortical processing deficiency in schizophrenia.

2. Methods and materials

2.1. Participants and experimental design

Participants consisted of 28 healthy controls (HC, average age: 33 ± 13 ; range: 17–62) and 28 schizophrenia patients (SZ, average age: 38 ± 12 ; range: 19–59). Four patients and one control were left-handed. All patients had chronic schizophrenia and symptoms were also assessed by positive and negative syndrome scale (PANSS). The detailed demographic characteristics for participants are shown in Table I.

All participants were scanned during both an auditory oddball task (AOD) and an extended rest. For AOD task, participants were asked to detect infrequent target sounds within a series of standard and novel sounds. The task consisted of two 6.5-min scans. The standard stimuli (50-Hz tone) occurred with a probability of 0.80; the target (1000-Hz tone) and novel stimuli (nonrepeating random digital noise, e.g., tone sweeps and whistles) each occurred with a probability of 0.10. The stimulus duration was 200 ms with a 1000, 1500, or 2000 ms interval. The participants were instructed to respond to the target tones by pressing reaction time button with their right index finger as quickly and accurately as possible and not to respond to the non-target stimuli. An MRI compatible fiber-optic response device (Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses. All participants were able to perform task successfully during practice prior to the scanning session. For resting-state scan, participants were instructed to rest quietly with their eyes open and avoid falling into sleep. The scan consisted of one 5-min scan.

2.2. Image acquisition and preprocessing

All scans were acquired on a Siemens 3 T Allegra dedicated head scanner using single echo planar imaging with the following parameters: repeat time 1.5 s, echo time 27 ms, field of view 24 cm, 64×64 acquisition matrix, flip angle 70° , $3.75 \times 3.75 \times 4 \text{ mm}^3$ voxel size, 4 mm slice thickness, 1 mm gap, 29 slices, and ascending acquisition. Six “dummy” scans were acquired at the beginning to allow for longitudinal equilibrium, after which the paradigm was automatically triggered to start by the scanner.

The fMRI data were realigned with INRIalign (Freire et al., 2002), spatially normalized into the standard Montreal Neurological Institute (MNI) space and resampled to $3 \times 3 \times 3 \text{ mm}^3$, resulting in $53 \times 63 \times 46$ voxels.

2.3. Group spatial ICA for fMRI data

The goal of ICA as applied to fMRI data is to find a linear combination of the underlying components that are maximally spatially independent of each other. Consider an M -dimensional observed fMRI data set, denoted by $\mathbf{x}$, which is assumed to be generated as the following linear mixture model,

$$\mathbf{x} = \mathbf{A}\mathbf{s}$$

where $\mathbf{s} = [s_1, \dots, s_i, \dots, s_N]^T$ is the source vector whose element s_i is the i th spatial component and $\mathbf{A}$ is the M -by- N (usually $M > N$) mixing matrix with the i th column ($i = 1, \dots, N$) uniquely denoting the time course associated with component s_i . ICA decomposition of $\mathbf{x}$ can be achieved by estimating a demixing matrix $\mathbf{W} = \mathbf{A}^{-1}$ (when the permutation and scaling ambiguity are ignored) such that the invertible transformation $\mathbf{y} = \mathbf{W}\mathbf{x}$ is an estimate of $\mathbf{s}$. For individual components, we have $y_i = \mathbf{w}_i^T \mathbf{x}$, where $\mathbf{w}_i^T$ is the i th row of $\mathbf{W}$. Before applying this ICA model to fMRI data, we perform principal component analysis (PCA) to reduce the data dimension from M to N . According to the ICA linear mixture model, we note that the estimation of each spatial component is modulated by the corresponding time course. In our study, we demonstrate this modulation property through simulation experiments using the SimTB toolbox (Erhardt et al., 2011), which generates fMRI-like data.

As in (Calhoun et al., 2008), we perform group ICA (Calhoun et al., 2001) to decompose each of the resting-state and AOD task-related data sets into 60 spatial components and corresponding time courses. In fMRI analyses using ICA, typically 20–30 independent components are extracted. More recently, it has been noted that using high ICA model order, for example, 60 to 70 or higher, a more detailed and hence a more useful functional segmentation of brain can be achieved (Kiviniemi et al., 2009; Allen et al., 2010). Therefore, we perform the ICA decomposition at a relatively high model order to obtain 60 components. The spatial components and time courses for individual subjects are obtained using back-reconstruction of group-aggregated results. The ICA algorithm used in our study is the standard Infomax using sigmoid nonlinearity (Bell and Sejnowski, 1995), equivalently maximum likelihood ICA (Cardoso and Laheld, 1996), which works well in estimating super-Gaussian sources. We run the ICA algorithm 10 times with random initialization and bootstrapping using the ICASSO toolbox (<http://www.cis.hut.fi/projects/ica/icasso>) and we select all the components from the most reliable run based on the performance index proposed in (Ma et al., 2011a). After removing components related to cerebrospinal fluid (CSF) artifact, large edge effects and ventricles, we retain components of interest to construct the graph using spatial dependence among these components as functional connectivity.

2.4. Estimation of connectivity using spatial dependence

Instead of using temporal correlation between the ICA time courses, we estimate the brain connectivity using the higher-order statistical dependence among the ICA spatial components. Mutual information is an appropriate measure of statistical dependence, which takes full-order statistical information into account. In our study, we use a normalized form of mutual information, defined as follows (Dionisio et al., 2004),

$$\lambda(i, j) = (1 - \exp(-2\mathcal{I}(y_i; y_j)))^{1/2} \quad (1)$$

where y_i and y_j are two spatial components derived from ICA decomposition and $\mathcal{I}(y_i; y_j)$ is the mutual information between them. Note that $\lambda(\cdot, \cdot)$ is in the interval of $[0, 1]$ and a value of zero means completely independent. The functional connectivity matrix $\mathbf{I}$ for all components is constructed by assigning $\lambda(i, j)$ to the (i, j) th entry of $\mathbf{I}$. In our experiments, mutual information $\lambda(\cdot, \cdot)$ is estimated using a nonparametric kernel density approach (Moon et al., 1995).

2.5. Graph-theoretical analysis

Using (1), we construct the $N \times N$ undirected graph G which consists of N nodes (spatial components) and edges to connect nodes. To obtain an adjacency matrix for G , a threshold T is calculated as $\mu - \kappa\sigma$ and applied to G , here μ is the average connectivity of whole graph, σ is the variance and $\kappa \in \mathbb{R}$. An edge between two nodes is said to exist if $\lambda(i, j) > T$ and otherwise is eliminated from G . As the threshold decreases, i.e., increases, more and more edges are preserved and the graph becomes more and more dense.

To quantify the topological properties of the obtained graph, several graph parameters are calculated across a series of thresholds. The degree of the i th node, K_i , $i = 1, \dots, N$, is defined as the number of edges connected to this given node. The clustering coefficient of the i th node is the ratio of the number of existing edges to the number of all possible edges among K_i direct neighbors of this node:

$$C_i = \frac{E_i}{K_i(K_i - 1)/2}$$

where E_i is the number of existing edges among neighbors. Consequently, the average clustering coefficient of the whole graph, $C = \sum_{i=1}^N C_i / N$, can be calculated to quantify the cliquishness of graph and is associated with local efficiency of information transfer and robustness (Bullmore and Sporns, 2009). On a global scale, the mean shortest path length of a given node is defined as:

$$L_i = \frac{1}{N-1} \sum_{j \in G, j \neq i} L_{i,j}$$

where $L_{i,j}$ is the minimum number of edges that must be taken to join the i th and j th nodes. The average shortest path length of a graph is defined as $L = \sum_{i \in G} L_i / N$ to measure the global efficiency of communication among the nodes.

The small-world index is thus calculated by $\gamma = C/L$, where both C and L are normalized by the corresponding measures from the comparable random networks that have the same number of nodes and edges as the observed graph. This index is typically greater than one for small-world networks (Achard et al., 2006).

Besides, the graph architecture is also studied by identification of hubs, where a hub in one graph is the node with high centrality. The centrality for one individual node is defined as,

$$H_i = \sum_{p \neq q \neq i}^N \frac{E_{p,i,q}}{E_{p,q}}$$

where $E_{p,q}$ is the total number of shortest paths between the p th and q th node, and $E_{p,i,q}$ is the number of shortest paths passing through the i th node.

Using the component grouping scheme by mutual information based hierarchical clustering and hypothesis testing, functionally related modules in the brain can be identified automatically (Ma et al., 2011a). We thus define several topological metrics to quantify the connections within and between modules. For the i th node, we modify the clustering coefficient C_i as follows,

$$\tilde{C}_i = \frac{\tilde{E}_i}{K_i(K_i-1)/2}$$

where $\tilde{E}_i$ is the number of edges among all neighbors of the i th node and these neighbors belong to the same module with this node. For all nodes, the average of $\tilde{C}_i$, $i = 1, \dots, N$, denoted as $\tilde{C}$, is then calculated. In contrast to C which measures the local closeness in the whole graph, the metric $\tilde{C}$ quantifies the local cliquishness within functional modules in the graph.

Another metric for the i th node, denoted as K_i^{inner} , is defined as the number of inner-module edges connected to this node, where the inner-module edge connects to two nodes within the same module. Similarly, the inter-module edge in the graph is defined as the edge linking two nodes, which belong to different modules. We consequently calculate a ratio of numbers of inner- and inter-module edges as,

$$R = \frac{\sum_u^M E_u^{\text{inner}}}{\sum_{u,v}^M E_{u,v}^{\text{inter}}}$$

where M is the number of identified modules, E_u^{inner} is the number of inner-module edges within the u th module, $E_{u,v}^{\text{inter}}$ is the number of inter-module edges between the u th and v th modules. The higher the value of R , the more are the inner-module connections.

3. Experimental results

3.1. Simulations using fMRI-like data

In order to show that ICA decomposition takes temporal information into account when estimating the spatial components, we first generate a simulated fMRI AOD task-related data set using the SimTB toolbox (Erhardt et al., 2011). Total of 20 super-Gaussian sources are generated, including motor, auditory, frontal, parietal, visual, dorsal attention network (DAN), default mode network (DMN), ventricle and sub-cortical nuclei regions. Each source has 148×148 voxels and is independently rotated, translated, and contracted or expanded for each of 12 simulated subjects. Noise is added relative to a standard level of contrast-to-noise ratio (CNR) uniformly in the range [0.8,2] across all subjects. Time courses are simulated as the convolution of “neural” events with a canonical hemodynamic

response function, where each includes 150 time points at a sampling rate corresponding to 2 seconds. For each subject, time courses are scaled to have a peak-to-peak range of one. We specify the event magnitude of each time course for two less-overlapping sources: DAN and bilateral frontal regions (the spatial dependence between these two sources is relatively low, average value is 0.16 ± 0.001 for 12 subjects). In this way, the temporal correlation between these two original sources varies from 0.1 to 0.9.

After ICA decomposition, we calculate mutual information between the estimated DAN and bilateral frontal components. We find that as time courses become more correlated, the spatial dependence between components increases as well, providing support of using spatial dependence to measure functional connectivity.

3.2. Mutual information based network connectivity

We apply group ICA to the rest and AOD task fMRI data sets to obtain 60 components for each data set. We visually inspect all these spatial components and select a number of components of interest to ensure that these components of interest do not contain large edge effects or ventricles. We also use Talairach atlas (Talairach and Tournoux, 1988) to instruct the component selection. Other component selecting methods can be used here as well, for example using the approach proposed in (Allen et al., 2010) with a ratio of time course power spectra in low-frequency band and high-frequency band. Since the ICA networks are generally robust (Calhoun et al., 2008), we obtain a number of similar spatial components for the rest and AOD task-related data sets and finally retain 35 components of interest for the AOD data and 32 comparable components for the rest data. The slight difference in number of retained components, as well as for the two data sets, is due to the inherent variety of the brain networks, especially when extracting a large number of components. We calculate mutual information between all possible pairs of components for each subject in the healthy control (HC) and schizophrenia patient (SZ) groups. During AOD task, the average functional network connectivity for the HC group is 0.23 ± 0.04 ; while for the SZ group, the average connectivity is slightly higher (0.24 ± 0.04). In contrast to task-related networks, the resting-state networks for the HC group show a significantly decreased average connectivity (0.1 ± 0.04), while for the SZ group, the average value of network connectivity increases (0.29 ± 0.03), indicating altered interactions among networks in schizophrenia at rest. The average network connectivity from the HC and SZ groups also shows significant difference at rest ($p < 0.01$, uncorrected).

3.3. Topological properties of network connectivity

After ICA decomposition, we perform graph-theoretical analysis across a series of thresholds $T = \mu - \sigma$ using mutual information based network connectivity. We set κ in the range $[-0.2, 1]$ to ensure that we obtain connected graphs for all subjects in two groups. Further study using a local threshold as in (Alexander-Bloch et al., 2010) to ensure connected graph may be performed as well.

The topological properties (clustering coefficient and path length) for the HC and SZ groups and rest are shown in Fig. 1. When κ is small, for both groups, $C > 1$ and $L \approx 1$. As κ increases, more and more connections are retained and the graph for each group approaches to its comparable random network (the normalized clustering coefficient and path length are approximately equal to one). Therefore, both groups preserve small-world properties despite the activation level. We performed two-sample t -test between the HC group and the SZ group across a series of thresholds for the mean values of the graph-theoretical metrics, which is averaged over the 28 individual subjects in each group. Compared with the HC group, however, the SZ group presents slightly lower clustering coefficient C , longer path length L , and a significantly lower small-world index γ than the HC group ($p = 0.002$).

during the AOD task. While at rest, the SZ group retains the smaller clustering coefficient and smaller γ , but demonstrates significantly shorter path length than the HC group ($p = 0.03$). Furthermore, we observe that both the HC and SZ groups have significantly higher clustering coefficient and shorter path length when performing the AOD task than merely at rest ($p < 0.03$). At each threshold, we also performed two-sample t -test between the graph-theoretical metrics from individual subjects in two groups, as shown by black upper-triangles in Fig. 1.

Using the clustering approach in (Ma et al., 2011a), we identify $M = 9$ modules for each group during AOD task and rest, including modules related to motor, temporal, cerebellum, occipital, frontal, frontoparietal, precuneus, thalamus, insular regions. The modified clustering coefficient $\tilde{C}$, inner-module degree and inner-inter module edge ratio R are calculated across thresholds, as shown in Fig. 2. We find that compared to resting state, the HC group presents significant changes ($p < 0.05$) when performing AOD task: a higher local cliquishness within modules ($\tilde{C}$), an increased inner-module degree and a higher ratio R . For the HC group at rest, the values of metrics to quantify inner-module connections all decrease. However, the corresponding task-induced adjustments within functional modules in the SZ group are not as prominent as in the HC group.

3.4. Activation-induced modulations of individual components

For individual components, two-sample t -test is used across a set of thresholds to discover statistically significant differences in topological properties between two groups for task versus rest. We show the graph parameters at a typical threshold $\kappa = -0.1$ for 15 components in Fig. 4. The spatial maps for these components are shown in Fig. 3. For the HC group during AOD task, several task-related components (IC1, IC2, IC7, IC13, IC14 and IC15) demonstrate higher clustering coefficient (higher local efficiency) and most of them have higher degrees than those at rest. The components related to precuneus, left motor and left frontoparietal in the HC group show shorter path length (higher global efficiency) when performing AOD task, while with increased path length at rest. Also, for the HC group, IC6 has a higher local efficiency at rest than during task, which may indicate its inherent relationship with DMN. However, these modulations induced by task in the HC group are altered in the SZ group. For example, some task-related components, including motor (IC1 and IC13) and frontoparietal (IC14), present lower clustering coefficient during AOD task than at rest in the SZ group. In the SZ group, the component related to anterior-DMN (IC6) has a decreased local efficiency at rest; components of interest (IC3, IC7 and IC12) show a longer path length when performing AOD task.

Using centrality across thresholds, different components are identified as hubs in two groups for task versus rest, as shown in Fig. 5. For the HC group during AOD task, several task-related components, containing parietal, frontal, frontoparietal, left motor, and cerebellum regions, demonstrate a higher centrality, which is in agreement with previous findings and the predominant roles of these regions in fMRI studies (Bullmore and Sporns, 2009; Ma et al., 2011b). At rest, several components associated with DMN in the HC group are identified as hubs, such as anterior DMN and orbitofrontal components. While the SZ group utilizes different components to achieve efficient communication among networks in the brain not only at rest but also during AOD task. For the SZ group, components related to Globus pallidus, thalamus and caudate regions are identified as hubs during task, and components with inferior frontal and temporal pole regions are important for efficient interaction at rest, which is consistent with previous evidence in the anatomical connectivity study (Bassett et al., 2008). For a typical threshold $\kappa = -0.1$, the graphs for the HC and SZ groups during AOD task and rest are shown in Fig. 6.

3.5. Relationships between graph parameters and PANSS

For schizophrenia patients, we also calculate the partial correlation between the topological metrics and the symptoms (assessed by PANSS scales) using the patient age as the controlling variable. We find that during extended resting state, clustering coefficient is positively correlated with positive symptoms; path length is positively correlated with negative symptoms, as shown in Fig. 7. During AOD task, clustering coefficient consistently shows negative correlation with positive symptoms. We also examine the relationships between graph parameters and symptoms of schizophrenia for individual components. At the resting state, clustering coefficient of several components, including precuneus, visual, inferior frontal and motor components (IC3, IC8, IC9, IC13 and IC1), is positively associated with positive symptoms significantly; path length of left frontoparietal, inferior parietal and temporal components (IC14, IC13 and IC5) have significantly and consistently positive correlation with negative symptoms. While during the AOD task, we find that clustering coefficient of sensorimotor, visual, inferior/middle frontal, left frontoparietal, and inferior parietal components (IC7–IC10, IC13–IC15) has consistent negative correlation with positive symptoms across thresholds.

We divide patients into two subgroups, one with higher positive scores and another with lower positive scores. Similar division is also obtained based on negative scores. For each subgroup, we examine individual edges across subjects and retain those edges only missing at most for one patient. We subtract adjacency graph of the group with lower scale from the group with higher scale. The difference graphs for negative and positive scales at rest are shown in Fig. 8. We find that the networks from patients with lower negative PANSS scale contain a significantly larger number of connections than patients with higher negative scale; on the contrary, the networks from patients with lower positive PANSS scale have smaller number of connections than patients with higher positive scale. The difference for lower versus higher symptoms during task is not as clear as at rest (not shown here due to the space limitation).

4. Discussion

In this study, we decompose fMRI data sets acquired during an AOD task and extended resting state into a number of spatial components and associated time courses using group ICA. We measure the functional connectivity using the spatial dependence among the ICA components and construct undirected connectivity maps. Several topological properties of these maps are examined for task versus rest and compared between multiple healthy controls and patients with schizophrenia.

With or without a driving task, we find that the functional networks from both the HC and SZ groups preserve higher local and global efficiency than random networks, which is consistent with previous studies that report the small-world feature in the human brain (Stam and Reijneveld, 2007; Liu et al., 2008; Rubinov et al., 2009; Yu et al., 2011a). However, the normal brains show task-induced modulations to topological properties of network connectivity, which are altered in the brains with schizophrenia. During the AOD task, the SZ group shows slightly lower level of local connectedness, longer global processing length, and significantly lower small-worldness than the HC group. Consistent with previous studies (Stam and Reijneveld, 2007; Liu et al., 2008; Yu et al., 2011a), the differences of small-world metrics between two groups suggest that information interactions in the normal brains are more efficient at both local and global scales than in the brains with schizophrenia when performing a cognitive task. At rest, the SZ group preserves lower clustering coefficient and small-world index, but presents a significantly shorter path length than the HC group. The longer path length in the HC group may due to the adjusted connections between networks in order to adapt the brain to the resting state. As we mentioned, during the AOD task or at

rest, the SZ group demonstrates a significantly lower value of small-world index than the HC group, indicating a trend towards a more randomized organization in schizophrenia, thus providing further support to previous findings in an EEG study (Rubinov et al., 2009). We also observe significant differences in groups and tasks using our metrics based on the identified modules. When performing an AOD task, the healthy group presents a trend that nodes within the same module tend to connect to each other. On the contrary, the healthy group at rest reduces the intensity of connections within the functional modules. One possible reason for this decline may be conservation of energy in the cortex. However, the corresponding task-induced adjustment in the SZ group is not as significant as in the HC group.

In addition, the topological properties of the brain connectivity using the spatial dependence also show significant differences in several components of interest when performing the AOD task and at rest. We find that for the HC group the task-related components including sensorimotor, frontal and parietal regions present an increased local and global efficiency during the AOD task relative to at rest, indicating effective adjustments to connectivity topology induced by task in the normal brains. However, such task-related modulations are altered in the SZ group. We observe abnormal connectivity patterns in components including motor, DMN, precuneus and frontoparietal regions for the SZ group, which are consistent with previous findings in these regions (Danckert et al., 2004; Tan et al., 2006; Liu et al., 2008; Yu et al., 2011a).

For SZ group, we find interesting different relationships between graph parameters and PANSS scales at different activation levels. As defined, positive syndrome is composed of florid symptoms, such as delusions and hallucinations and negative syndrome is characterized by deficits in cognitive and social functions (Kay et al., 1987). We find that several components related to inferior parietal, left frontoparietal, temporal, precuneus and motor regions have significant contribution to the correlation between the graph-theoretical features and symptoms, which is in line with previous findings that different networks are involved with different symptoms of schizophrenia (Stephan et al., 2009; Rotarska-Jagiela et al., 2010; Woodward et al., 2011). During resting state, higher positive and negative symptoms are positively correlated with clustering co-efficient and path length. This result might indicate increased unusual interactions between the functional regions for patients with more severe positive symptoms and decreased normal functional connections in the brains of patients with more severe negative symptom. While during the AOD task, positive scales are negatively correlated with clustering coefficient. The correlation differences between the AOD data set and the resting-state data set may suggest symptom-related modulations to network connectivity and further study is required to verify. However, it is not clear why only positive symptoms but not negative symptoms have a consistent correlation with topological properties during an AOD task.

One limitation of the current study is that we calculated the small-world features based on a binary adjacency matrix. In future work, we may consider using the weighted topological properties. Secondly, we use a statistical significance level of $p < 0.05$ (uncorrected). An alternative way is using type I error control such as false discovery rate correction. We also do not rule out the potential influence of medication in the patients. We plan to study the schizophrenia patients before and after treatment. In addition, further investigation of the age effect to the graph-theoretical analysis is needed to supply more information since previous studies suggested a dynamic development trend of brain functional connectivity over age (Fair et al., 2009; Dosenbach et al., 2010). In further studies we may perform an analysis by grouping participants based on their age.

In summary, we examine the topological properties of both task-related and resting-state networks using spatial dependence as functional connectivity. Significant differences between the HC and SZ groups are found, including a more random organization in schizophrenia. Furthermore, we find significant differences in task modulations to functional connectivity between the extended resting state and the AOD task. Results in this work are, we believe, physiologically meaningful and may help us to better understand the underlying pathophysiology of schizophrenia as well as the brain system in the healthy brains. Future work involving classification between two groups may be performed based on the group differences found in the current study.

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ARTICLE HIGHLIGHTS

- Functional connectivity is quantified using higher-order spatial information
- Connectivity during task and rest is studied using graph-theoretical analysis
- Novel metrics are proposed based on the modules obtained using a clustering approach
- Meaningful task-induced modulations to connectivity are found in the healthy group
- Altered topological properties of connectivity are observed in schizophrenia patients

Fig. 1.

Average graph parameters and standard error across 28 subjects: (A) AOD, clustering coefficient; (B) AOD, path length; (C) resting state, clustering coefficient; (D) resting state, path length. Black triangle indicates that two groups have significant differences ($p < 0.05$) at a given threshold. HC: healthy controls; SZ: patients with schizophrenia.

Fig. 2.

Graph metrics based on identified modules: $\tilde{C}$ for subjects during (A) AOD task and (B) rest; inner-module degree during (C) AOD task and (D) rest; ratio of number of inner- and inter-module edges R during (E) AOD task and (F) rest.

Fig. 3.

Spatial maps for 15 individual components, $|Z| > 1.5$. Here we only show group maps for the AOD data set and three representative slices for each component due to the space limitation; similar maps are obtained for the rest data set.

Fig. 4.

Average graph parameters for 15 individual components which show significant group differences ($p < 0.05$) at a typical threshold $\kappa = -0.1$. The color of bar indicates the group and the height represents the value of relative parameter. Error bars correspond to standard error across 28 subjects.

Fig. 5. Identified hubs for (A) the HC group and (B) the SZ group during the AOD task; (C) the HC group and (D) the SZ group at rest, across thresholds. Here, we show the complete slices for each component to demonstrate the detailed differences between the two data sets and two groups. We display individual components using composite view such that one component is represented by one color. The maps are thresholded at $|Z| > 1.5$.

Fig. 6. Graph visualizations for (A) the HC group and (B) the SZ group during AOD task; (C) the HC group and (D) the SZ group during rest with a typical threshold $\kappa = -0.1$. The color of a node represents the belonging module; the number is component index (correspondence is made for two groups during AOD task and rest); the colored edge represents within-module connection and black edge represents between-module connection; the width of edge is the strength of connection, i.e., mutual information.

Fig. 7. Partial correlation between graph parameters and positive/negative PANSS scores with patient age as the controlling variable. *C*: clustering coefficient; *L*: path length; pos: positive scale of PANSS score; neg: negative scale of PANSS score.

Fig. 8.

Graph to show different edges for patients with high and low (A) negative PANSS score, (B) positive PANSS score, during resting-state. Each node represents one component. Blue line means the edge exists for patients with lower score and red lines means the edge exists for patients with higher score.

Table IDemographic and clinical characteristics of patients with schizophrenia ($n = 28$) and healthy controls ($n = 28$)

Variable	SZ	HC	<i>t</i> / <i>P</i> -value
Age	37.8 ± 12.3	32.7 ± 12.9	NS, 1.3/0.2
Percent male	82	68	NS, 1.2/0.2
NART, estimated IQ	105.3 ± 6.9	111.3 ± 8.3	NS, 1.5/0.2
PANSS			
Total	63.2 ± 16.6	NA	NA
Positive	15.8 ± 5.5	NA	NA
Negative	15.4 ± 5.6	NA	NA
Percent treated with atypical antipsychotic medication	100	NA	NA
Percent treated with antidepressants	43	NA	NA
Percent with some psychotic symptoms	67	NA	NA

SZ, schizophrenia; HC, healthy control; NS, non-significant; NART, national adult reading test; NA, non-applicable; Group comparisons are reported in the last column.