Small-world brain networks in schizophrenia

Mingli LI[1,2], Zhuangfei CHEN[3], Tao LI[1,2]*

Summary: Over the last decade the combination of brain neuroimaging techniques and graph theoretical analysis of the complex anatomical and functional networks in the brain have provided an exciting new platform for exploring the etiology of mental disorders such as schizophrenia. This review introduces the current status of this work, focusing on the topological properties of human brain networks – called 'small-world brain networks' – and on the disruptions in these networks in schizophrenia. The evidence supporting the findings of reduced efficiency of information exchange in schizophrenia both within local brain regions and globally throughout the brain is reviewed and the potential relationship of these changes to cognitive and clinical symptoms is discussed. Finally we propose some suggestions for future research.

Schizophrenia is a severe mental disorder characterized by positive symptoms (delusions, hallucinations and other thought disturbances), negative symptoms (apathy, social withdrawal and other behaviors), cognitive impairments, and emotional dysregulation. Despite more than a century of research, the pathophysiological mechanisms that result in schizophrenia remain unknown, presumably because of the incredible complexity of the human brain.[1] The intensive study of the structure and function of complex systems in nature – 'network science'[2] – may provide insights that can be applied to the study of the brain and, thus, improve our understanding of mental disorders like schizophrenia. Network science describes the topological properties of complex networks in terms of the characteristics of 'small-world architecture', 'centrality,' 'hierarchy,' 'modularity,' and 'distribution of network hubs'. When applied to the brain, these hypothesized small-world properties may enable the cortical network to process information globally and locally with maximal efficiency. This article briefly reviews the current understanding of the small-world network of the brain and then focuses on recent studies about the relationship between disruptions of the small-world brain network and schizophrenia.

1. Attributes of the small-world network

The 'small-world network' is one of the three basic types of networks: 'regular networks,' 'small-world networks, 'and 'random networks.' Networks are usually described in terms of two specific properties: the clustering coefficient of the nodes, and the path lengths between the nodes. High levels of local clustering of the nodes of a network (i.e., a high 'clustering coefficient') reflect high efficiency of local information transfer; short path lengths between pairs of nodes in the network reflect high global efficiency of parallel information transfer. As shown in Diagram A in Figure 1, in regular networks each node is only directly connected to its nearest nodes: this results in many short-distance connections and no long-distance connections, a high clustering coefficient and a long average path length between pairs of nodes. As shown in Diagram C of Figure 1, in a random network the probability of any two nodes having a direct connection is equal (regardless of distance) so there is a low level of local clustering and a short average path length between

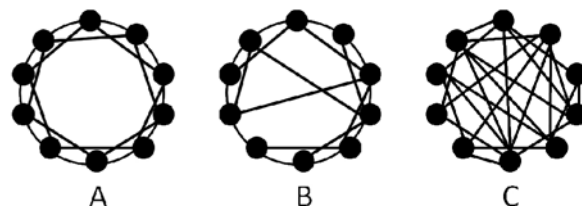**Figure 1. Three basic types of small-world networks**

Diagram A represents a 'regular network' with a high level of clustering and a long path length between different nodes; Diagram B represents a 'small-world network' with a high level of local clustering and relatively short path lengths between different nodes; Diagram C represents a 'random network' with low local clustering and very short path lengths between different nodes.

[1]Mental Health Center and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

[2]State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

[3]Faculty of Medicine, Kunming University of Science and Technology, Kunming, Yunan Province, China

*Correspondence: xuntao26@hotmail.com

pairs of nodes. The organization of the small-world network (Diagram B in Figure 1) is intermediate between that of the regular network and the random network: it combines high levels of local clustering among nodes and relatively short paths that link all nodes of the network. These features of both segregated and integrated information processing in small-world networks result in high global and local efficiency of parallel information processing, sparse connectivity and low wiring costs.[3]

2. The human brain as a small-world network

Electroencephalography (EEG), magnetoencephalography (MEG), and magnetic resonance imaging (MRI) are the most commonly employed technologies for studying the anatomical and functional connectivity of the human brain in vivo.

2.1 The small-world anatomical brain network

Cross-correlational of cortical thickness or volume and tractography are the most common methods for assessing the structural topography of small-world networks in the human brain. He and colleagues[4] were the first to investigate the distribution of small-world anatomical networks in the human brain; they did this by analyzing MRI results of whole brain cortical thickness mapping in 124 healthy subjects. Subsequently, Bassett and colleagues[5] analyzed inter-regional covariation of gray matter volume in the MRI data of 259 healthy volunteers to identify the small-world network of the human brain.Using diffusion-weighted MRI and graph theory analysis, Iturria-Medina and colleagues[6] found that human brain anatomical networks had higher local efficiency and lower global efficiency than predicted by random networks. Similar results were found using diffusion tensor imaging (DTI) tractography.[7,8] These studies indicate that the human brain has the attributes of small-world anatomical networks. Moreover, the DTI studies also reported that the organization of the brain anatomical network was affected by age, sex and brain size: overall cortical connectivity decreases with aging; females have greater local and global efficiencies; and higher local efficiency is associated with smaller brain size in females but not in males.[7,8] These results provide insight about age-related and sex-related differences in cognition and behavior. Other studies with twins and siblings suggest that the relationship of the characteristics of small-world networks to brain cortical thickness is genetically mediated.[9]

2.2 The small-world functional brain network

Functional magnetic resonance imaging (fMRI), EEG and MEG are often used to explore the topological properties of functional brain networks in vivo. Generally speaking, fMRI has good spatial resolution but poor temporal resolution while EEG and MEG – which measure neuronal activity more directly – have better temporal resolution but poorer spatial resolution. Consistent with results from anatomical studies, data about functional connectivity obtained using these different functional neuroimaging techniques also suggest that the functional brain network has the properties of a small-world network.

Using resting-state fMRI (rsfMRI), Salvador and colleagues were the first to demonstrate the small-world network properties of the functional human brain. Defining 90 brain regions of interest as nodes (based on the Automated Anatomical Labeling [AAL] atlas) and using partial correlations of blood oxygenation level dependent (BOLD) time series between each region to identify connections (edges), small-world characteristics (including local clustering and short mean path length) were demonstrated by an undirected graph that was derived from the mean partial correlation matrix; these characteristics were compatible with prior results for nonhuman cortical anatomy.[10] Subsequent rsfMRI studies investigated the properties of the functional human brain network using different nodes in mesoscale (voxel-based parcellation)[11] or in macroscale (70 regions of interest [ROIs] using the ANIMAL-atlas,[12] or 90 ROIs using the AAL-atlas[13]). Results from the various rsfMRI studies consistently found that brain functional networks had robust small-world properties regardless of the nodes selected. Moreover, task-related fMRI studies also find robust small-world network properties that are consistent for different types of tasks, for different types of subjects, and at different scales of analysis.[14-16]

As mentioned above, although EEG and MEG have less spatial resolution than fMRI, they directly measure neuronal activity and provide a better temporal assessment of brain activity so the synchronization between pairs of electrodes can be used to evaluate functional connectivity. The synchronization pattern for both low (<8 Hz) and high (>30 Hz) frequency bands assessed using MEG indicate much higher clustering coefficients than those for random networks and path lengths intermediate between those of ordered or random graphs;[17] these results confirm the small-world network characteristics of the functional brain network. Moreover, twin studies that used resting-state EEG to explore the heritability of small-world networks in the brain compared the affinity of monozygotic twins, dizygotic twins and siblings and found that 46 to 89% of individual differences in the clustering coefficient and 37 to 62% of individual differences in path length are heritable across various frequency bands: this suggests that small-world organization might be a marker of genetic differences in brain organization.[18]

EEG studies also suggest that intelligence is related to small-world characteristics.[19,20] The small-world network connections between brain areas are well-organized in subjects with limited education who are engaged in working memory tasks, suggesting that use

of the more optimal small-world configuration during cognitive tasks might compensate for their lower cognitive abilities.[21]

In brief, a large number of studies demonstrate the existence of small-world properties in human anatomical and functional brain networks. These studies also show that these properties are heritable, related to cognition, and affected by age and sex.

3. Schizophrenia and the small-world brain network

Bleuler described the core symptom of schizophrenia as 'psychic splitting' and implied that brain dysconnection might be the underlying pathophysiological mechanism of schizophrenia.[22] Several decades later, Friston reemphasized the dysconnection hypothesis of schizophrenia to support and explain the relationship between core schizophrenia symptoms, impaired synaptic plasticity, and dysconnectivity between brain regions.[23] The rapid development of neuroimaging technologies over the last decade has generated new information that directly addresses this issue. The current consensus is that schizophrenia is related to a relatively widespread, altered functional connectivity between the frontal cortex and posterior regions.[24] The use of graph theory to assess the brain as a complex network helps map the diverse topological properties of the human connectome and provides insight into the altered connectomics of schizophrenia.

3.1 Do the properties of small-world networks also exist in schizophrenia?

Accumulating evidence demonstrates that the small-world characteristics of the human brain result in high global and local efficiency of parallel information processing for low connection costs and maintain a balance between local processing and global integration of information. Does this basic organizational property also exist in the brains of patients with mental disorders and neurological diseases? Numerous studies have found that the brain network organization of patients with Alzheimer's disease,[25,26] epilepsy,[27] attention deficit hyperactivity disorder,[28] autism spectrum disorder,[29] and schizophrenia[16,19,30-32] also exhibit the small-world properties of high local and global efficiency; thus, despite deficits in the topological metrics of the brain networks of persons with psychiatric and neurological illnesses, the basic small-world network is conserved.[33] Researchers have speculated that the small-world architecture of the brain might help reduce the loss of network functionality in individuals who experience developmental, neurological or psychiatric diseases.[13]

3.2 Disrupted small-world networks in schizophrenia

Small-world network properties exist in patients with schizophrenia, but specific topological metrics are altered. Decreased clustering and decreased local efficiency are consistently reported in schizophrenia for both anatomical networks[5] and functional networks (assessed using rsfMRI[30,34] and task-related fMRI[16,35]). The decreased clustering coefficient reflects abnormalities in inter-regional connectivity and in the efficiency of local information transfer. Studies of structural brain networks in patients with schizophrenia that use DTI[36] or combine DTI with magnetization transfer ratio magnetic resonance imaging[37] or rsfMRI[32] report longer path lengths and lower global efficiency; these results suggest slower interactions between interconnected brain regions and a decreased ability to integrate local information. Taken together, the decreased local and global efficiency identified in the studies suggest a disrupted balance between local processing and global integration of information in schizophrenia.

Most studies report a decreased clustering coefficient and a longer mean path length in schizophrenia, but some studies have the opposite result. For example, increased clustering coefficients were found at most of the selected nodes (identified by group-independent component analysis) in an fMRI study that used functional network connectivity maps which were constructed based on partial correlation analysis of the time courses of the identified nodes.[32] A relatively large study with 79 patients with schizophrenia and 96 age and gender matched healthy controls that used diffusion tensor tractography[36] found no difference in the local efficiency of the brain anatomical network between patients and controls. Another study that assessed the functional brain network in persons with first-episode schizophrenia using fMRI during a cognitive control task[31] also found no change in local efficiency. Other studies fail to confirm the reported decreased global efficiency for small-brain networks in schizophrenia: one study found increased global efficiency during resting-state functional connectivity,[30] and another found unchanged global efficiency in a task-related fMRI.[16]

These discrepant findings may be due to confounding. First, different parcellation schemes and graph building methods were used including independent components based graphs, brain regions based graphs and voxel based graphs. Second, the sample sizes in most studies were relatively small (about 30 subjects); larger samples may be needed to provide more robust and consistent findings. Third, the timing of disease episodes and the duration of illness may influence the results: one study of first-episode schizophrenia found unchanged local efficiency[31] and another study of brain functional networks in schizophrenia found that longer duration of illness is associated with smaller clustering coefficients, lower connectivity, lower global and local efficiency, and longer path lengths.[34] Finally, treatment with antipsychotic medication and progression of the illness may affect the efficiency of global and local brain networks.[38] For example, Fornito and colleagues have speculated that

the global network topology of patients is relatively intact during their first psychotic episode but subsequently deteriorates with progression of the illness.[31]

3.3 The relationship between disrupted small-world networks and clinical symptoms in schizophrenia

Exploring the relationship between disrupted small-world networks and clinical symptoms in schizophrenia can help delineate the mechanisms via which changes in the topological structural characteristics of the brain network can result in the clinical manifestation of illness. For example, deficits in working memory – a core neuropsychological dysfunction in schizophrenia[39]— have been associated with changes in the functionality of brain networks. When presented a working memory task of medium difficulty, fMRI assessments find that the functional brain networks of patients with schizophrenia have a lower clustering coefficient and lower local efficiency than those of healthy controls; moreover, the decreased indicators are associated with longer reaction times.[35] This less clustered structure and lower efficiency of task-related networks might be one of the factors causing impaired working memory in schizophrenia.

Wang and colleagues found that the global and local efficiency of anatomical networks in schizophrenia were negatively correlated to positive symptom scores, negative symptom scores and total scores of the Positive and Negative Syndrome Scale (PANSS, the most widely used instrument to assess the symptoms of schizophrenia); this suggests that more severe psychotic symptoms are associated with lower efficiency of brain networks.[36] Studies of functional brain networks in schizophrenia have found the negative symptom score on the PANSS is negatively correlated with global efficiency and positively correlated with the mean path length.[32] Thus, disturbances in the integration and segregation of information, as revealed by the disruption of small-world anatomical and functional brain networks, might underlie the abnormal psychotic symptoms observed in schizophrenia. However, other studies have not replicated these findings of a correlation between the topological indicators of brain networks and the clinical severity of schizophrenia.[34,37,40]

4. Summary and future directions

Numerous studies have shown that the anatomical and functional brain networks of patients with schizophrenia retain the basic properties of small-world brain networks seen in healthy individuals; they also show that there are characteristic alterations in the topological metrics of patients' small-world brain networks. Some of these studies go further to suggest that disruptions in the small-world brain networks of patients with schizophrenia contribute to anomalous information transfer and are associated with the severity of clinical symptoms. It remains unclear whether the altered characteristics of small-world brain networks in schizophrenia is a 'state' or a 'trait'; further studies are needed to clarify this important issue.

There are a number of other suggestions for future studies. First, larger sample sizes are needed to generate more robust results and to allow comparisons between subgroups of subjects. Second, to reduce the potential confounding introduced by medication use and illness progression, studies should preferentially enroll first-episode, drug-naïve patients. Third, longitudinal studies are needed to monitor changes in the small-world characteristics of brain networks during the progression and treatment of schizophrenia. Fourth, studies that integrate assessment of anatomical and functional brain networks are needed to assist in the understanding of the interaction between the two networks. Fifth, most current studies use undirected and unweighted graph methods to model the small-world brain network in schizophrenia; using directed and weighted graph methods could provide more information and more accurate models. The promising connectivity models for building a directed graph that have been proposed should also be formally assessed: structural equation modeling,[41] dynamic causal modeling,[42-44] and Granger causality.[45,46] Further studies could utilize these new models to explore the brain network of schizophrenia.

We believe that improved experimental designs and more powerful graph theoretical analyses will continue to expand our knowledge of brain networks and eventually identify the pathological mechanisms underlying schizophrenia.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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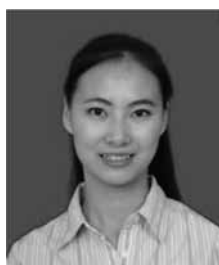
Mingli Li received her Bachelor's degree in clinical medicine in 2007 and her Ph.D. in Medical Science in 2012 from Sichuan University. She currently works as an Associate Researcher in the Research Center of the Mental Health Department of the West China Hospital at Sichuan University. The focus of her research is on the neuroimaging of mental disorders.