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EDITORIAL

Graph-based network analysis in schizophrenia

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Abstract

Over the last few years, many studies have been published using modern network analysis of the brain. Researchers and practical doctors alike should understand this method and its results on the brain evaluation at rest, during activation and in brain disease. The studies are noninvasive and usually performed with elecroencephalographic, magnetoencephalographic, magnetic resonance imaging and diffusion tensor imaging brain recordings. Different tools for analysis have been developed, although the methods are in their early stages. The results of these analyses are of special value. Studies of these tools in schizophrenia are important because widespread and local network disturbances can be evaluated by assessing integration, segregation and several structural and functional properties. With the help of network analyses, the main findings in schizophrenia are lower optimum network organization, less efficiently wired networks, less local clustering, less hierarchical organization and signs of disconnection. There are only about twenty five relevant papers on the subject today. Only a few years of study of these methods have produced interesting results and it appears promising that the development of these methods will present important knowledge for both the preclinical signs of schizophrenia and the methods' therapeutic effects.

INTRODUCTION

Schizophrenia is characterized by the disintegration of thought processes and emotional responsiveness. Bleuler coined the term "schizophrenia," describing it as a group of diseases[1]. Early brain damage and genetic, psychological and social factors appear to be the main elements of the disease's expression. Diagnosis is established with the use of certain criteria based on the DSM-IV diagnostic tools. The symptomatology of schizophrenia is widely divergent and there is evidence for multiple processes and disturbances in the "group of schizophrenias". After decades of research, it is evident that widely dispersed brain circuits are implicated, mainly circuits of the dorsal and dorsolateral prefrontal cortex and cortical areas of the temporal lobe[2]. Numerous magnetic resonance imaging (MRI) and tractography or diffusion tensor imaging (DTI) studies did not reveal anatomical findings characteristic of schizophrenia[3,4]. In a greater population-based MRI study, gray matter reductions and white matter deficits were found to be widespread in schizophrenics. Simultaneously, gray matter excesses were observed bilaterally in the basal ganglia, anterior cingulate and medial orbitofrontal cortices. Additionally, cerebrospinal fluid excesses were evident in the ventricles[5]. A relationship between

structural and functional connectivity has been suggested by several authors[6]. Disturbances in structural connectivity are directly related to functional connectivity. The latter is expressed in abnormal patterns of neurophysiological oscillations, especially in high frequency bands seen in the electroencephalogram (EEG) and magnetoencephalogram (MEG)[7,8]. Disturbance of these high frequency oscillations is indicative of abnormal neural synchrony as the result of a "disconnection syndrome" in schizophrenia. In recent years, attempts have been made to study connectivity and network organization using tools derived from graph theory. With these tools, brain network analyses can be performed noninvasively using bioelectrical signals or MRI.

NETWORK ANALYSIS OF THE BRAIN

Modern network analyses of the brain using tools derived from graph theory assess anatomical, functional and effective connectivity, as well as their local or widespread properties. The information from such analyses is related to the integration and segregation of brain networks at rest and during several activations. A graph, a mathematical representation of the network, consists of vertices, i.e., the nodes corresponding to brain regions and edges representing connections or statistical dependencies between nodes. Several parameters characterize the graphs and present information about their potential behavior and connection topologies. The first use of graph theory to study networks of neurons was the nervous system of the roundworm *Caenorhabditis elegans* or *C. elegans*, which is the only animal with a completely known neuronal wiring diagram. This worm has exactly 302 neurons and all neuronal connections have been recorded. The organization of this neuronal network was found to have the optimum functional properties, i.e., the so-called small world network (SWN). This organization corresponds to graphs with optimum segregation and integration: local bindings are tightening and connection to remote points is easy, with few and/or easy steps[9]. In SWNs, the average distance between two vertices is similar to the random networks', increasing logarithmically with the number of vertices[10] (Figure 1).

Several measures characterize the graphs. The cluster coefficient and path length are between the commonly used parameters. The clustering coefficient of a vertex is the probability that its neighbor vertices are also connected to each other. The average of all of the clustering coefficients (C) of a graph is a measure of the local structure of the graph. The path length expresses the paths or the ease with which the information travels from one vertex to remote vertices. The average of the path lengths is the path length (L) of the graph. This average expresses the global interaction of the network.

Low L means easy communication between remote vertices. The degree of a vertex is the number of edges and the average of all of the degrees is the degree (K) of the whole graph. The degree distribution P (K) is the probability that a randomly chosen node has the degree K. Local and global efficiency, which are analogous to C and L, express segregation and integration. Using C and L or local and global efficiency, it is possible to detect whether or not a SWN organization exists. In that case, C is high and L is low; local and global efficiency are high. Many studies have shown that SWN organization is a healthy optimum organization in the brain from which deviations are detected in pathologies, such as ADD, AD, schizophrenia and epilepsy. An additional interesting graph metric is centrality, or betweenness centrality, which measures the number of short paths between any two nodes that pass through this node and identifies hubs, i.e., the nodes with high degree; modularity, i.e., a measure of the organization in modules with high clustering; and hierarchy, i.e., a measure of the way that hubs are connected in space.

Table 1 List of graph theoretical studies in schizophrenia

Study	Method	Parameters
2006: Micheloyannis *et al*[61]	EEG	C, L, SWN
2008: Basset *et al*[17]	MRI, MEG	SWN, efficiency
2008: Liu *et al*[67]	fMRI	C, L, Eloc, Eglob, K, SWN
2009: Rubinov *et al*[64]	EEG	C, L, SWN
2009: Basset *et al*[66]	MEG	Cost efficiency
2010: Wang *et al*[77]	fMRI	SWN, efficiency
2010: van den Heuvel *et al*[40]	DTI	C, L, SWN
2010: De Vico Fallani *et al*[62]	EEG	Network density, degree
2010: Lynall *et al*[68]	fMRI	SWN, efficiency, hierarchy, degree dist, connectivity strength and diversity
2010: Alexander-Bloch *et al*[69]	fMRI	Modularity
2011: Jalili *et al*[65]	EEG	Degree, node strength, SWN, Eglob, modularity, centrality
2011: Zalesky *et al*[70]	DTI	SWN, nodal degree, C, L, efficiency
2011: Fornito *et al*[25]	fMRI	C, L, SWN, efficiency
2011: Yu *et al*[71]	fMRI	C, L, Eloc, Eglob, SWN
2011: Lord *et al*[79]	fMRI	Betweenness centrality, degree centrality, L
2011: Weiss *et al*[86]	MEG	Network cost
2011: Yu *et al*[78]	fMRI	K, C, L, Eglob, Eloc
2011: Wang *et al*[75]	DTI	SWN, Cost, Eloc, Eglob
2012: Ma *et al*[72]	fMRI	C, L, centrality
2012: He *et al*[76]	fMRI	K, C, L, Eloc, Eglob
2012: Alexander-Bloch *et al*[74]	fMRI	Modularity
2012: Alexander-Bloch *et al*[73]	MRI	Network connection distance
2012: Shi *et al*[80]	MRI, DTI	SWN, modularity, centrality, connection distance

EEG: Electroencephalogram; MRI: Magnetic resonance imaging; MEG: Magnetoencephalographic; DTI: Diffusion tensor imaging; fMRI: Functional MRI; SWN: Small world network; C: Clustering coefficients; L: Path length; K: Degree K.

Brain networks in health

The first use of graph theoretical network analysis in humans was performed with MEG signals in healthy individuals[11] (Table 1). It was found that the lower and higher frequency bands displayed the features of SWN. A vast body of literature has accumulated using network

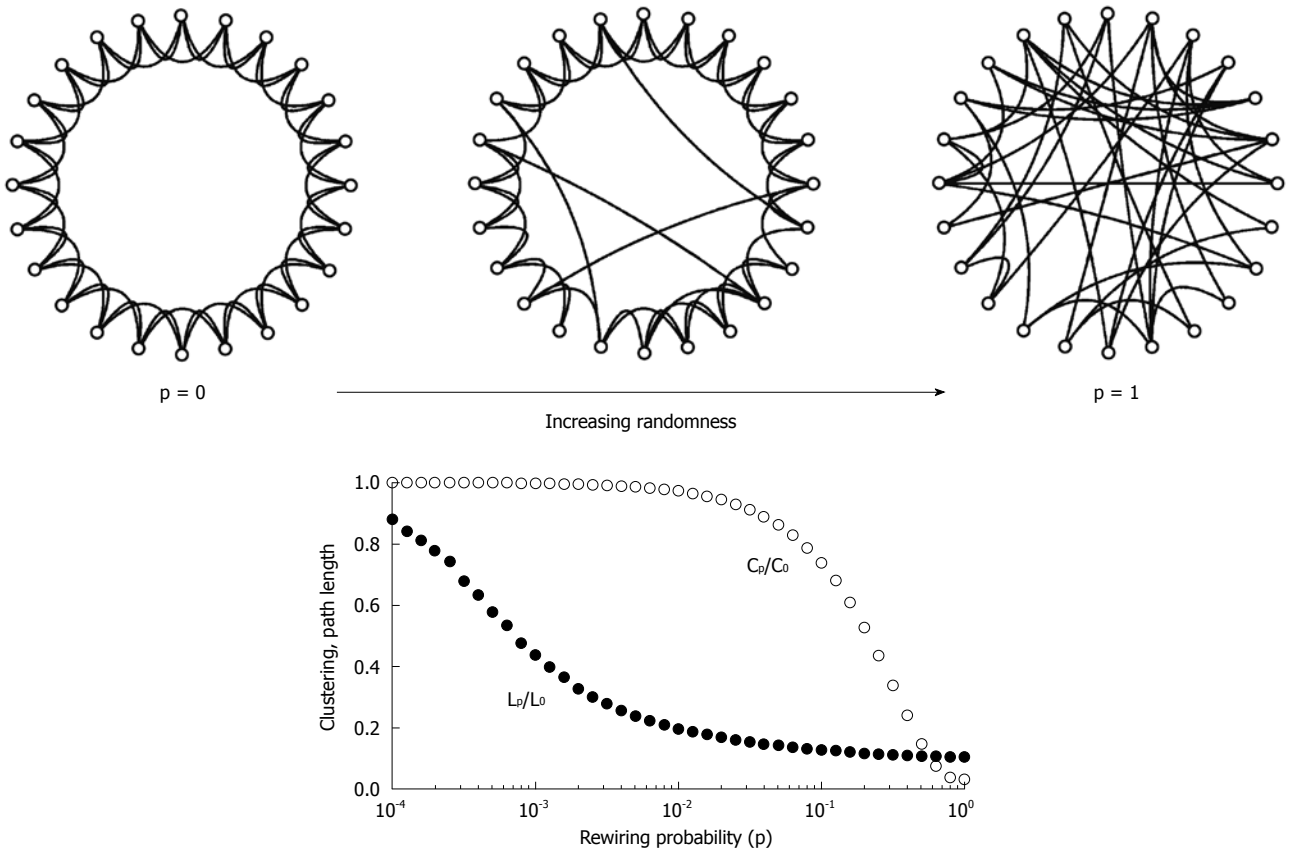

Figure 1 The Watts-Strogatz model of the small world. The network at the upper left corner represents a ring lattice with circular boundary conditions. Starting from this configuration, connections are randomly rewired with given rewiring probability p. For p = 0 (no rewiring), the network retains its regular lattice topology. For p = 1, the network is completely random, and all lattice-like features have disappeared. Intermediate values of p result in networks that consist of a mixture of random and regular connections. The plot at the bottom shows the clustering coefficient Cp and the path length Lp, both normalized by their values for the regular network (P0, L0). Note that there is a broad range for the rewiring probability p when networks have clustering similar to the regular network's clustering and a path length similar to the random network's path. Within this range, networks exhibit small-world attributes. Data computed following the procedure is described in Watts and Strogatz (66), with networks consisting of 1000 nodes and 10 000 edges (data points represent averages of 400 rewiring steps)[85].

analysis in health, at rest or during several tasks. The main characteristic of the brain network analysis is the SWN. As in other SWNs in the brain, this structure could be simultaneously scale-free with connectivity distribution following a power law. Connectivity distribution following a truncated power law distribution seems more possible. This architecture means that there is a modular organization (with clusters) and simultaneously optimized fast processing[12]. Nodes of brain networks (neurons or groups of neurons) can have different degrees. High-degree nodes are the hubs. Nodes can be organized in small subgroups consisting of only a few nodes having similar functions. These are the motifs. Clusters or modules are parts of a network with many connections between them and few connections to the other parts of the network; these clusters subserve similar brain functions[13]. Modularity corresponds to local segregation of the network (Figure 2). Another important feature of brain network organization is hierarchy. Hierarchy characterizes the structural and functional organization of neural networks and can be seen as the encapsulation of smaller elements in larger ones, a behavior that is recursive of fractal development[14].

Construction of brain graphs

There are several methods of constructing brain graphs to study parameters and visualize brain networks. Graphs can be constructed from EEG or MEG and MRI. For microelectrode recordings, the nodes of the graph are the microelectrodes. For EEG or MEG recordings, the electrodes or sensors are the nodes. Because volume conduction of electrical activity influences the electrodes, if nodes are taken from the sources under each sensor from the cortex, they give more accurate values for the construction of graphs. Adequate estimation of the sources can be performed with several softwares[15]. The edges are taken to be the correlations between nodes estimated using linear or nonlinear methods. The connections between nodes can be binarized or weighted, directed or not. Binarized connections are the simplest form, but for functional or effective connectivity estimation, weights or causal relationships between nodes must be considered[12].

The methods of construction of the graphs from MRI differ (Figure 3). Regions corresponding to Brodman areas can be taken as nodes. The automated anatomical labeling template is often used to find the nodes

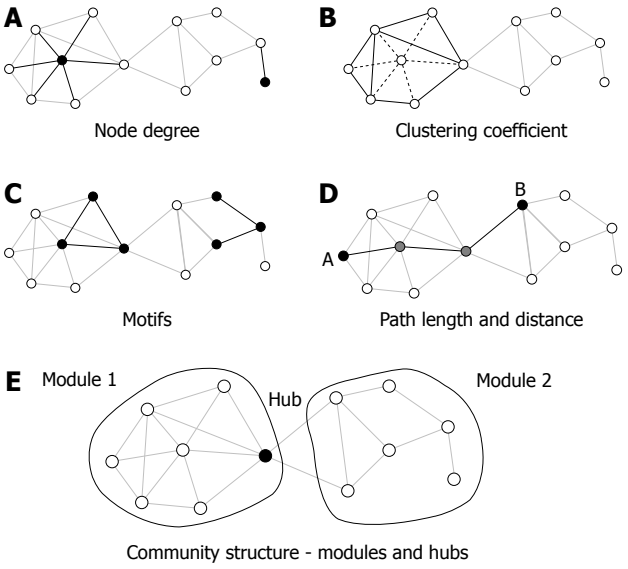

Figure 2 Key graph measures and their definitions. The measures are illustrated in a rendering of a simple undirected graph with 12 nodes and 23 edges. A: Node degree corresponds to the number of edges attached to a given node, which are shown here for a highly connected node (left) and a peripheral node (right); B: The clustering coefficient is shown here for a central node and its six neighbors. These neighbors maintain eight out of 15 possible edges for a clustering coefficient of 0.53; C: Each network can be decomposed into subgraphs of motifs. The plot shows two examples of two different classes of three-node motifs; D: The distance between two nodes is the length of the shortest path. Nodes A and B connect in three steps through two intermediate nodes (shown in gray). The average of the finite distances for all node pairs is the graph's path length; E: The network forms two modules interconnected by a single hub node[85].

for the MRI graphs[16]. The other possibility is to take nodes with equal numbers of voxels covering the whole brain[17]. An additional possibility is to construct and assess structural graphs using DTI to find the nodes and edges. Strong co-variation between cortical regions is assumed to be related to connectivity and the trophic effects of neurons. Thus, the cortical thickness or volume of multiple cortical regions can be taken as the different nodes[17,18]. The EEG or MEG signals or the time series of voxels or brain regions in MRI are used to construct an association matrix as a weighted network. They can be transformed into a binary matrix in which a threshold is used; values above one threshold exist and below another do not.

Normal brain network organization

Using EEG signals, it becomes evident that numerous neurophysiological parameters show heritability[19]. During the last several years, brain networks were studied for heritability. This methodology is important because network organization indicates brain function ability[20-22]. In EEG studies, synchronization likelihood (showing linear and nonlinear dependencies between signals), clustering coefficient, path length and small-worldness showed heritability in a great number of twins[23,24]. In a functional MRI (fMRI) study in monozygotic and dizygotic twins, the genetic influence was more evident in special regions[25].

Normal brain network organization is characterized by high clustering (existence of motifs, modules and high-degree nodes, i.e., hubs) and short path length, expressing the SWN architecture with high efficiency and organized for optimum economy and cost[26]. The SWN architecture shows differences between hemispheres and gender, as demonstrated in an fMRI study[27,28]. A fMRI study[29] found that there was a difference between men and women. Women had shorter path length and higher clustering. A DTI tractography study showed that local efficiency was higher in females[30]. Women show greater overall cortical connectivity and more efficient networks[31].

Two additional important characteristics of normal brain network organizations are modularity and hierarchy. These traits characterize not only neural networks but also most complex systems, such as biological, economic, social networks and the internet[14,32]. The achievement of this brain organization is revolutionary[33]. Structural and functional modular organization has been demonstrated analyzing anatomical and BOLD fluctuations from resting-state fMRI[34,35]. In accordance with other studies, the modular organization influence segregation and integration, high information processing and network robustness[32]. Hierarchy, the other neural network characteristic, is considered recursive of fractals[29], i.e., the network organization shows a self-similar organization. It can be visible in spatial, temporal and topological scales[36-38]. The small nervous system of C. elegans, as well as other animals and human brains, show hierarchical modularity represented by an economical wiring diagram[37]. The existence of hubs, i.e., high-degree nodes, is important for the normal function of brain networks. These hubs have a central position for efficient integration of information across the network. The hubs have above-average connections, low clustering coefficients, low path length to other nodes and a high level of betweenness centrality[39,40].

The SWN, as well as the modular organization and widespread interconnections, shows changes during several brain functions, depending on the accuracy of executive task performance and general intelligence[21,29,41]. During working memory, individuals with higher education showed lower SWN organization according to the neural efficiency hypothesis, i.e., the lower-educated needed more effort, producing more efficient network organization, as expressed by a higher SWN index[41]. Cognitive effort breaks modularity depending on effort, as shown during working memory of difficulties[21]. In a study of learning in short or longer intervals (minutes, hours, days), dynamic changes in modularity were detected[42]. A study of graph characteristics using bioelectrical signals during visual working memory maintenance found that α and β bands showed a memory-load-dependent scale-free SWN behavior[43]. Returning to graph theoretical tools and fMRI, it was found that during working memory, connectivity strength decreased as working memory load increased[44]. Intelligence is related to brain network or-

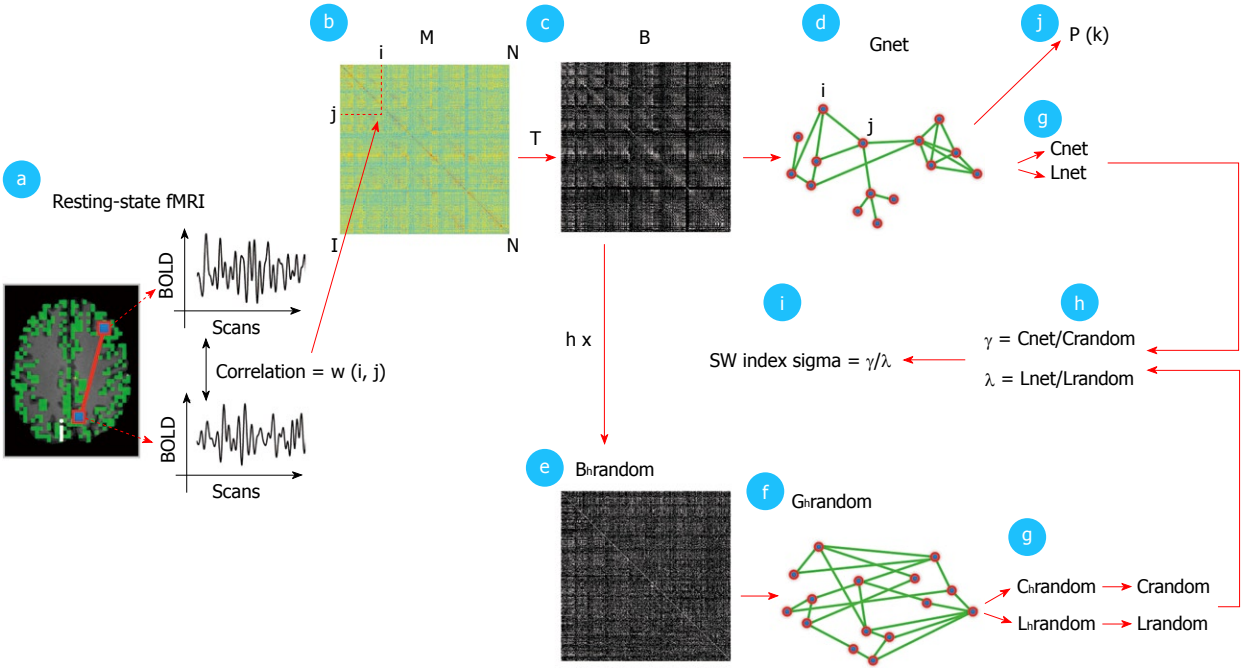

Figure 3 Detailed schematic illustration of the graph analysis. The first step (panel a) consisted of calculating the temporal zero-lag correlations between the filtered functional magnetic resonance imaging BOLD time-series of all voxels, which was believed to reflect inter-voxel functional connectivity. The computed correlations were represented as a correlation matrix M, with cell M (i, j) holding the level of functional connectivity between voxel i and voxel j (panel b). M was thresholded with a threshold T (panel c), resulting in a binary connectivity matrix B, representing an unweighted graph Gnet (panel d). T varied between 0 and 0.7 (with steps of 0.05) and a range of fixed k between 4000 and 20. For each fixed k, M was thresholded with a computed T that corresponded exactly to a connectivity degree of k for that particular individual dataset. Next, B was randomized (panel e) to create a random graph Grandom with a similar connectivity distribution P (k) as Gnet but a random organization of connections. Also, h random graphs were formed per Gnet. From Grandom and Gnet, the graph characteristics Cnet, Lnet, Crandom, Lrandom were computed (panel g). Crandom and Lrandom were created by averaging the clustering-coefficient and path length of the h random graphs. Next, γ and λ were computed, as defined as Cnet/Crandom and Lnet/Lrandom (panel h). The small-world index sigma was computed as the ratio between γ and λ (SW index, panel i) expressing the small-worldness of Gnet. In addition, the connectivity distribution P (k) of Gnet was computed (panel j). Finally, the individually computed graph characteristics were averaged over the group of subjects and the group averaged connectivity distribution P (k) was fitted with a power-law function to examine a possible scale-free organization of the functionally connected human brain[36].

ganization. Higher scores on intelligence tests are related to greater global efficiency of the brain anatomical networks, as found in a diffusion tensor tractography study using graph theoretical tools[45]. Three recent functional connectivity studies using fMRI, high-density resting state EEG or MEG had similar findings, demonstrating the correlation between global efficiency and intelligence performance[20,22,29].

In children, the long distant connections (edges) are weak in contrast with stronger short-distance edges. During development, short-distance connections weaken, while the long-distance connections increase in strength[46-49]. The SWN architecture already exists in the 1st month of life[48] and this organization seems to assume higher values in adults[50]. Modular organization changes greatly in elderly people compared with the young and middle-aged. The old showed a decrease in the connector ratio and inter-module connections[51]. In another study, older people showed a decrease in the inter-modular organization frontal and an increase in the posterior and central modules[35]. Additionally, there are age-related task-dependent effects. In a study of language perception, age-related declines in global efficiency were found[52]. During mathematical thinking, the $\alpha 2$ band showed a degree of SWN disorganization in adults compared to children, whereas β and γ bands showed lower synchronization and lower SWN organization[53]. Recently published reviews are helpful to understand the normal organization and development[54-58]. Existing studies related to network development are not sufficient to provide a conclusive and detailed picture. It is important to collect more details in the future to define first signs of disturbance in the development of brain diseases, such as schizophrenia.

BRAIN NETWORKS IN SCHIZOPHRENIA

There is a vast body of literature related to neuroanatomical abnormalities and connectivity in schizophrenia[59,60]. Brain network disturbances began to be studied in 2006, providing many interesting findings and sparking the hope that in a few years, we will understand more about schizophrenia and the signs of its onset. Because network analysis offers information about integration, segregation, connectivity and overall organization of brain networks, it promises an interesting approach to schizophrenia. The first studies using network analysis in schizophrenia were performed assessing SWN organization. In 2006, the first paper related to schizophrenia and SWN was published. The authors recorded electroencephalographic signals using 29 electrodes in which the nodes and the edges

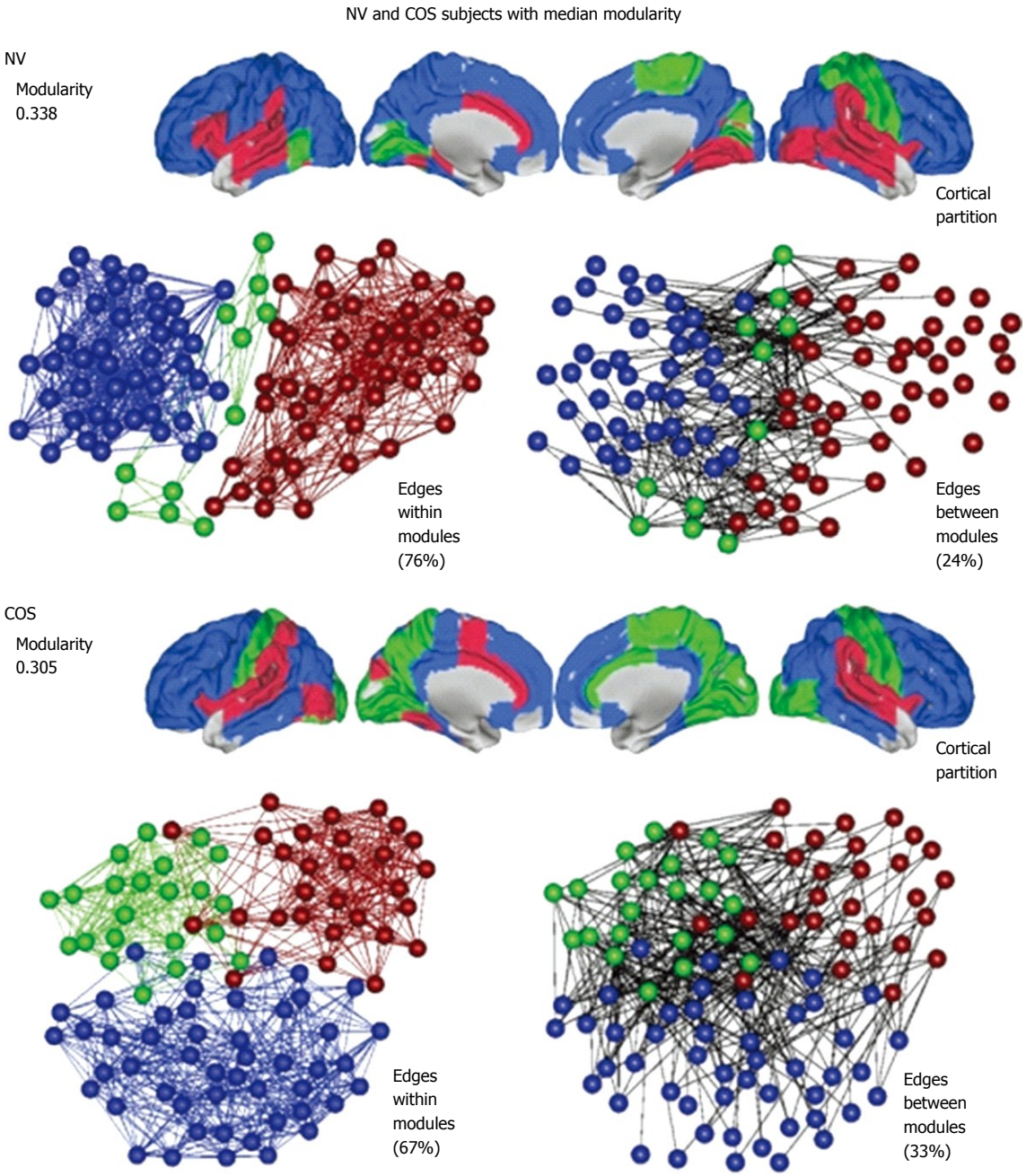

Figure 4 An illustration of modularity using representative brain networks from a childhood-onset schizophrenia population and a control (NV) population. At a local threshold of 0.22 topological cost, the modular partition is shown for the median NV subject (above) and the median childhood-onset schizophrenia (COS) subject (below). Each module is assigned a specific color and the modular structure of each subject is illustrated in three different ways. The cortical partition shows the anatomical location of modules, while the left-hand topological plot shows the density of intra-modular edges between nodes in different modules[69].

were estimated with a linear and nonlinear estimator in 20 stabilized, functional schizophrenics and 20 healthy controls. Undirected binary graphs were constructed and the clustering coefficient, path length and SWN index were evaluated at rest and during a working memory test separately in all frequency bands. Disrupted patterns of functional integration were found for $\alpha 1$, $\alpha 2$, β and $\gamma 1$ bands in schizophrenics during working memory in comparison to controls. The SWN pattern was lower in patients[61]. The same material was later analyzed with spectral analysis, coherence and construction of graphs from the coherence, and high-resolution EEG and graphs. These analyses showed the SWN disruption and, additionally, signs of hypofrontality with an asymmetry[62,63]. In another study with EEG signal recordings at rest, 40 young schizophrenics and 40 controls were estimated using a nonlinear method and the nonlinear correlation matrices were converted to weighted graphs. Clustering coefficient, path length and central hubs were evaluated. Schizophrenics showed the lower clustering and shorter path lengths indicative of lower SWN organization. The centrality of hubs was also lower in schizophrenics. These findings are indicative of a disturbance toward the randomization of schizophrenics' networks[64].

Another study used two methods of measuring between electrode values and several graph parameters of EEG signals in 14 schizophrenics and 14 controls. The correlation between electrodes was assessed using partial and non-partial cross-correlations that complemented one another. Graphs were constructed and graph parameters were measured for small-worldness, vulnerability, modularity, assortativity and synchronizability[65]. The small-worldness was reduced in schizophrenics, indicative of lower segregation and integration. The modularity index was also lower in schizophrenic patients, indicative of the lower segregation properties of their networks. This reduced modularity was more evident in the β band. Vulnerability and assortativity showed that resilience in schizophrenics was lower. The normal networks show assortative construction, while nodes with high degree tend to link with other nodes with high degree. The vulnerability shows the size of the drop in performance when a node is removed. Both of these parameters differed in patients who indicated lower resilience, except for the γ band, which showed less vulnerability in comparison to controls. Additionally, widespread synchronizability was lower in patients in the θ, α, β and γ bands. All of these differences in the components of schizophrenics' brain networks are indicative of the networks' failures in schizophrenic patients.

Bassett *et al*[66] recorded magnetoencephalographic signals from 29 healthy individuals and 28 schizophrenics performing a working memory task. The nodes were the 275 channels of the MEG. These authors used mutual information (sensitive to linear and nonlinear association) between wavelet coefficients for each pair of channels to construct graphs at each MEG band in the range between 1 and 60 Hz, and they estimated efficiency in relationship to cost, i.e., the cost-efficiency of networks' different frequency bands (connection cost estimated by the mutual information). The normal organization of brain networks maximizes efficiency for minimum cost. In this study, the schizophrenics showed reduced maximal cost-efficiency in relationship to normal individuals in the β-frequency band (15-30 Hz). There are indices that this band is a coordination frequency for large-scale networks, such as the networks for the working memory. This was more evident on nodes in the left lateral parietal and frontal areas related to working memory function.

With MRI, including tractography, network construction can include cortical and subcortical structures. Several studies in schizophrenia have been performed using MRI. Liu *et al*[67] studied SWN behavior in schizophrenics using fMRI. fMRI reveals information about the activities of cortex and subcortical structures. Liu *et al*[67] used a well-known "automated anatomical labeling" method to define 90 regions as nodes[18]. Partial correlation was used to assess between-node connectivity. Partial correlation matrices were used to construct binary undirected graphs and their parameters were compared between patients and healthy controls. The schizophrenics showed lower small-worldness in relationship to the normal controls with a lower degree of connectivity, lower strength of connectivity, lower clustering coefficient and longer path length. Additionally, there was a negative correlation between SWN index and duration of the disease. Topological estimations showed frontal, parietal and temporal functional alterations. These findings indicate the reduction of information processing more evident in the more chronic cases. Another study[68] using fMRI adds more indices towards disorganization of networks in schizophrenia, although the basic characteristic of the normal network organization, i.e., the small-worldness, is reduced but not totally disrupted, as found in other studies. Resting-state fMRI was acquired over 17 min in 12 schizophrenics and 15 healthy individuals. Seventy-two cerebral regions were used as nodes to construct undirected graphs in the 0.06-0.125 Hz frequency interval using wavelet correlation matrices. Using the wavelet correlation (a linear estimator) and wavelet mutual information (a linear and nonlinear estimator), the functional connectivity strength and diversity for each of the 72 nodes was assessed. In schizophrenia, the strength of functional connectivity was reduced and several brain regions showed increased diversity of functional connectivity. It is important to mention that while several studies show a reduction in functional connectivity, other studies have shown regional increased connectivity. Clustering was lower for most patients' cortical nodes and node degree was reduced in some places and increased in others. High-degree hubs and lower-degree nodes are more probable in healthy individuals. Interestingly, an additional finding shows that schizophrenics have a great robustness to random attack (removal of nodes). Alexander-Bloch *et al*[69] studied modules of resting-state fMRI in 13 cases of childhood-onset schizophrenia and 19 healthy individuals. Modularity is an important property of complex systems, such as the brain. Modules were defined as groups of brain regions with fMRI time series that are similar to each other and are dissimilar from other groups.

Abnormal modularity (dysmodularity) was found in schizophrenic patients (Figure 4), suggesting that it is a sign of developmental disturbance. The clustering coefficient was also reduced in this study, while complementary measures of global efficiency and robustness were increased.

In another detailed fMRI-graph theoretical study of 203 people with schizophrenia and 259 health controls, the authors used partial correlation to measure the between all possible pairs of node values[17]. The nodes were extracted from cortical thickness measurements, as these measurements are strongly correlated between regions that are axonally connected. This method has been used in several studies in recent years. From these partial correlation values, binary graphs were constructed and topological, as well as distant, metrics were evaluated. The analyses included cortical and subcortical structures at global, divisional and regional scales, including unimodal, multimodal and transmodal divisions of the cerebral cortex. Firstly, the common graph parameters

were calculated, i.e., the node degree, hierarchy, assortativity, connection distance, centrality and identified hubs. Hubs with high hierarchy have high total connectivity but low local connectivity. With assortativity, the existence of assortative or disassortative networks is estimated. The former is characterized by connections between nodes with the same degree. Thus, high-degree nodes (hubs) are likely to be connected to each other. In the disassortative networks, the hubs are not connected to each other. The connection distance represents a special or topological property of the network. The centrality measure is used to identify hubs. Altogether, in this study, detailed network analyses were performed, thereby contributing important knowledge of the organization of normal and schizophrenics' brains. The multimodal network showed a hierarchical organization in normal brains in which frontal hubs with low clustering dominated, whereas the transmodal network was assortative. In schizophrenics, the multimodal network showed reduced hierarchy, loss of frontal hubs and emergence of non-frontal hubs and increased connection distance. To explain these findings, the authors speculate that the network pattern of schizophrenia is a neurodevelopmental disturbance.

Zalesky *et al*[70] constructed graphs of 74 schizophrenics and 37 healthy controls using whole-brain tractography. By assessing corticocortical connectivity through tractography and calculating the graph parameters node degree, small-worldness, efficiency, path length and clustering, it was possible to extract valuable information. Neural fiber tract connectivity was assessed using tractography. The graph constructed had a total of 82 nodes for each individual, corresponding to 82 distinct gray-matter regions. Pairs of nodes were interconnected if they were joined by a link *via* a sufficient number of streamlines, as detected by tractography. This direct assessment of connectivity revealed impaired connectivity in three regionally distinct groups of nodes: medial frontal, parietal/occipital and left temporal. The patients showed disconnection in cingulum and corpus calosum findings understood from previous studies. The occipital nodes showed the greatest disruption. The antero- and postero-medial components of the default mode network were also affected at a high degree. Network organization as expressed by the graph parameters showed several impairments in schizophrenia. The nodal degree was reduced, indicative of sparse interconnections. Network efficiency and small-worldness in patients were also reduced. It is interesting that in non-schizophrenic subjects, the intelligence quotient showed a linear association to the clustering coefficient, path length and global efficiency. This correlation was not found in patients with schizophrenia. In summary, this study showed disconnection and disorganization in schizophrenics' brains. Recently, a few more studies were performed related to resting state using fMRI. Yu *et al*[71] used ICA and fMRI to determine a set of maximally specially independent brain networks and then graph theory methods. Small-worldness, clustering coefficient, path length, local and global efficiencies were altered in schizophrenia, in comparison to healthy controls. Ma *et al*[72] used ICA and fMRI and graph construction with the help of mutual information. Schizophrenic patients showed lower small worldness at rest. Alexander-Bloch *et al*[69,73,74] with collaborators published three articles related to modularity, anatomical distance and population differences in network community structure in health and childhood onset schizophrenia using fMRI. In schizophrenics, both modularity and the modular community were quantitatively disturbed. Another interesting finding was that there was reduced strength of functional connectivity over short distances and it could be a sign of excessive "pruning" of short-distance functional connectivity in schizophrenia. Wang *et al*[75] used diffusion tracking tractography to construct weighted anatomical networks of the brain in 79 schizophrenics and 96 controls. It was found that the anatomical networks of the patients showed decreased global efficiency, the small world network was disrupted in schizophrenia and the regional efficiency of the prefrontal cortex and the paralimbi/limbic regions were affected in patients.

A number of studies examined regional brain disturbances in schizophrenia. From previous studies, it is known that frontal and temporal gray matter show decreased integrity in schizophrenics. For this reason, van den Heuvel *et al*[40] studied these regions and their capacity to communicate with other brain regions in 40 patients and 40 healthy controls. These researchers constructed weighted graphs using DTI and magnetic transfer imaging, which shows the myelin transmitting information related to the normal function of axons. The graph's nodes were defined by the tractography and automated anatomical label template parcellating the brain into 108 unique regions. The strength of the existing connections between nodes was taken as the measure of average level of magnetic transfer imaging to calculate the weighted connections. The graph parameters assessed were clustering coefficient; path length, small-worldness, connectivity strength, which shows how strong each node is connected to the rest of the network, and betweenness centrality, which shows how centrally a node is located in the network. Hubs were identified. The patients showed decreased network connectivity of frontal and temporal areas. The magnetic transfer imaging that shows myelination in white matter revealed reduction diffusely across the frontal lobe. Increased path length was higher in the frontal, temporal and occipital regions, which are indicative of reduced global efficiency. The frontal hubs have less betweenness centrality, i.e., fewer remote connections, and are less efficient in patients. Bassett *et al*[17], as well as Lynall *et al*[68], also discovered impairment of the role of frontal hubs. Small-worldness was reduced but preserved. The reduced efficiency of frontal and temporal regions, together with the lower efficiency of frontal hubs, is of importance to the impairment of cognitive processes in schizophrenics. Additional studies related to regional brain dysfunction were performed by Yu and Ma: Yu *et al*[71] found that the network parameters extracted using ICA

and graph theory were disturbed in frontal, parietal and occipital areas; Ma *et al*[72] found disturbances in motor regions, cerebellum and parietal regions.

To examine connectivity and neural network disturbances during a cognitive task performance, Fornito *et al*[25] studied 23 first episode schizophrenics and 23 controls. They examined brain connectivity and network disturbances during a cognitive task performance as an indicator of weaknesses of cognitive disturbances in the disease. In this study, functional connectivity was measured between 78 brain nodes with a β series correlation technique examining region-wise and edge-wise connectivity, clustering coefficient, path length, local efficiency, global efficiency and small-worldness. The cognitive task used was the AX-Continuous Performance Task, which has been used previously as a clinical test in schizophrenia to examine frontal lobe function. fMRI recordings and functional connectivity were event-related, while whole-brain networks were constructed. Results showed connectivity deficits in the cognitive task in frontoparietal regions, which occur in addition to generalized impairment of connection between the frontal regions and the rest of the brain. This study is indicative of widespread, but especially frontal, dysfunction in schizophrenia. He *et al*[76] studied working memory in schizophrenics and found aberrant BOLD activations and disrupted functional connectivity during the task. An additional study assessed disturbances during cognition in schizophrenia-combined activation and functional evaluation, i.e., structural activation during a cognitive task, as well as network functional evaluation during the same task using graph theoretical tools[77]. The cognitive task was a memory task (episodic memory-for-context task). One hundred and twenty well-known words were used. During the recall phase, fMRI was recorded in 23 schizophrenics and 33 healthy controls. The cortical functional activation during the performance of the memory task showed a similar pattern in schizophrenia and healthy controls. Using more strength criteria ($P < 0.001$), the schizophrenics showed decreased activation in the bilateral prefrontal cortex, as well as the inferior and middle occipital gyrus, thalamus and caudate. Patients showed gray matter reduction in the left medial prefrontal cortex, occipital cortex, temporal pole and bilateral insula. The network measures showed SWN configuration in both groups but with reduced local efficiency in patients. Importantly, between the two groups, there were differences in the number of hubs and a few differences in their location. That several network hubs were located in different regions in schizophrenics could be the result of gray matter volume reduction in certain areas in patients. For the same reason, the normal patients had more hubs than the schizophrenics. Altogether, this structural and functional study shows important differences between normal controls and schizophrenics during the memory cognitive task. Another fMRI study was undertaken to examine the temporal lobe during an auditory oddball task in 20 schizophrenics and 20 healthy controls[78]. The authors evaluated connectivity and network properties during the cognitive task. It is known that in schizophrenia, P300 amplitude (oddball response) is reduced. Auditory cortex activation is also reduced in schizophrenics, as shown in fMRI studies. This study intended to examine the oddball differences between schizophrenics and normal controls more precisely. Firstly, the top 95 task-related voxels were detected separately on the left and right using independent component analysis during the auditory oddball task. Using partial correlation to construct graphs, clustering coefficient, shortest path length, local and global efficiency, and small worldness were subsequently evaluated. Independent-component analysis showed, as expected, the most task-related components on both temporal lobes. SWN was preserved in both sides and both groups but it was lower in patients who showed longer short path length and lower global efficiency on the left side. Thus, temporal lobe task-related dysfunction with a significant asymmetry was detected. He *et al*[76] estimated working memory in 35 schizophrenics using fMRI. They found that during working memory, the patients showed lower clustering coefficient and less local efficiency. During an auditory oddball task, Ma *et al*[72] found lower small-worldness in schizophrenic patients.

Crucial to treating schizophrenia are not only the study of the disease after the development of the symptoms but also the evaluation of at-risk individuals. Evaluation of the progress of the disease and the therapeutic effects are also important. Brain network analysis is a new method in this effort. Thus, these important evaluations are sparse, in contrast to many previous studies using clinical, neurophysiological and MRI methods. In one study[79], at-risk mental-state individuals were examined in comparison to healthy controls during a verbal fluency task performance that recruits frontal lobe networks. The study used functional MRI and graph theoretical tools to assess brain networks during the task. The network metrics used were network density (as a measure of total network connectivity), global average path length and global betweenness-centrality, indicating the compactness of the network. Because executive function and information processing are disconnected in schizophrenia and in at-risk mental states, in this study, the assessment was concentrated in the anterior cingulated cortex function. Nineteen regions of interest in this area were selected in 22 healthy people and 33 individuals in the prodromal stage of the disease. Global connectivity, as assessed by partial correlations as well as efficiency, showed no group differences. In contrast, in the cingulated region, the at-risk subjects showed a reduction in topological centrality. This finding is indicative that the disturbance exists prior to the disease in the region that supports executive functions. In an interesting study, Shi *et al*[80] estimated the brain networks of 26 neonates at high risk for schizophrenia. They showed impaired global efficiency, lower path length and lower connection distance. These findings were indicative of brain alteration in neonates at genetic risk for schizophrenia.

Conclusions and future implications

A literature search related to schizophrenia retrieves more than 100 000 papers (in Scopus, 127 770). From the time

that schizophrenia was acknowledged as a disease of the brain, several methods have been used to study the brains of schizophrenics and their relatives. Research on schizophrenia is still notably active. During the last 20 years, many structural MRI studies of schizophrenia have been performed. These have provided more knowledge than the previous (postmortem) anatomical studies related to structural and functional organization of the brains of schizophrenics. The main structural findings are gray-matter abnormalities primarily located in the frontoparietal, frontotemporal and anterior limbic regions, as well as enlargement of the ventricles[59,81]. DTI imaging visualizes connections in the white matter[4,79]. These studies, especially the DTI, are in their infancy and exhibit methodological problems. Nevertheless, widespread disconnectivity is supported by several fMRI and DTI studies in parallel with neurophysiological studies[7,82,83]. In schizophrenia, there is neither a characteristic anatomical finding nor a local disturbance. Disconnectivity is found in schizotypy and in the general population[82]. In ultra-high-risk for psychosis individuals, MRI studies have shown abnormalities in the prefrontal, temporal and anterior cingulated cortices. Attempts have been made to use MRI to find biomarkers with which to access the development of the disease, but valid results have not been reached[84]. This search for biomarkers is especially difficult because the progression of the disease produces more severe morphological brain abnormalities[5].

The modern network theory intends to provide answers to many questions related to structural and functional disturbances in the disease of schizophrenia. In just a few years, this method revealed many interesting findings. It was found that the networks of schizophrenics' brains are less efficiently wired, show less small-worldness, are less clustered and are less hierarchically organized. In short, network disturbances in schizophrenia are indicative of abnormal connectivity, abnormal integration and segregation, lower cost-efficiency and abnormal modularity. It is less probable to find high-degree hubs and there are signs of developmental disturbances in the brains of schizophrenics. All of these findings have been extracted in the last 10 years. In parallel with schizophrenia, other brain diseases, such as autistic disorders, Alzheimer's disease, depression and epilepsy, have been studied with these methods. These findings indicate that the modern method is promising. More studies are needed to clarify several questions about the disease, its pre-clinical signs and treatment effects.

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