Graph theoretical modeling of brain connectivity

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Purpose of review

In recent years, there has been an explosion of studies on network modeling of brain connectivity. This review will focus mainly on recent findings concerning graph theoretical analysis of human brain networks with a variety of imaging modalities, including structural MRI, diffusion MRI, functional MRI, and EEG/MEG.

Recent findings

Recent studies have utilized graph theoretical approaches to investigate the organizational principles of brain networks. These studies have consistently shown many important statistical properties underlying the topological organization of the human brain, including modularity, small-worldness, and the existence of highly connected network hubs. Importantly, these quantifiable network properties were found to change during normal development, aging, and various neurological and neuropsychiatric diseases such as Alzheimer's disease and schizophrenia. Moreover, several studies have also suggested that these network properties correlate with behavioral and genetic factors.

Summary

The exciting research regarding graph theoretical analysis of brain connectivity yields truly integrative and comprehensive descriptions of the structural and functional organization of the human brain, which provides important implications for health and disease. Future research will most likely involve integrative models of brain structural and functional connectivity with multimodal neuroimaging data, exploring whether graph-based brain network analysis could yield reliable biomarkers for disease diagnosis and treatment.

Keywords

fMRI, graph theory, human connectome, modularity, small world, tractography

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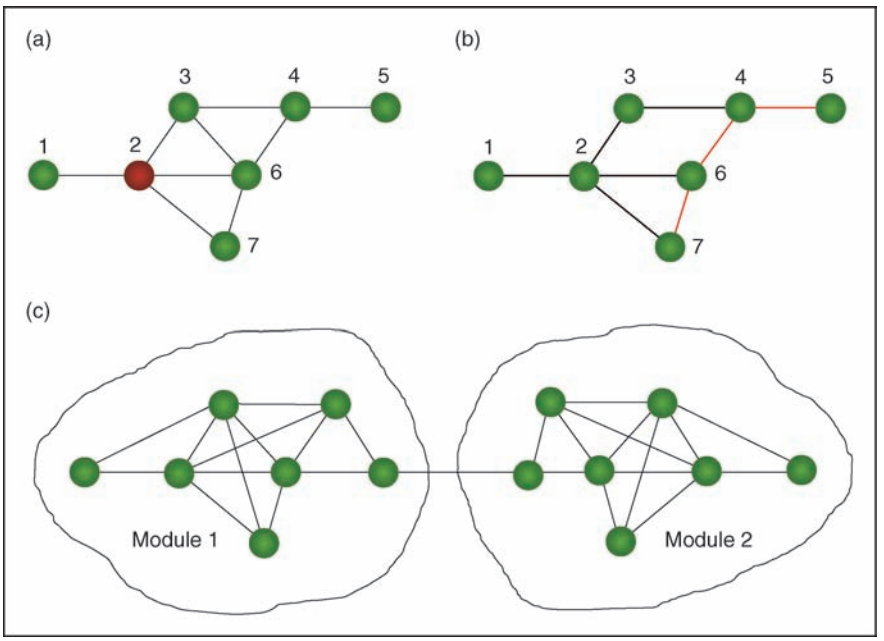
Introduction

The human brain is structurally and functionally organized into complex networks allowing the segregation and integration of information processing. In the past decade, researchers have demonstrated that by combining a variety of different imaging technologies [e.g. structural MRI, diffusion MRI, functional MRI (fMRI), and EEG/MEG] with sophisticated analytic strategies such as structural equation modeling [1], dynamic causal modeling [2], and partial least squares [3], it is possible to noninvasively map the patterns of structural and functional connectivity of the human brain (known as the human connectome [4••,5]). Specifically, by modeling the brain as a complex network, graph theoretical analysis provides an uncomplicated but powerful mathematical framework for characterizing topological properties of the brain networks such as modularity, efficiency, and hubs (see [6,7••,8•,9•] for recent reviews of graph analysis in healthy and diseased brains). In this review, we will summarize recent progress in the graph theoretical analysis of brain networks derived from multimodal imaging techniques, focusing mainly on areas of ongoing research and application.

Structural and functional connectivity of the brain

Structural and functional connectivity are the two main types of brain connectivity. Structural brain connectivity represents structural associations among different neuronal elements, which includes both the morphometric correlation and true anatomical connectivity [7••,8•,9•]. The former can be obtained by examining the statistical interdependencies of morphological descriptors (e.g. cortical thickness, gray matter volume, and surface area) between brain regions from structural MRI data. The latter can be obtained by examining the white matter fiber connections among gray matter regions from diffusion MRI data. Functional brain connectivity represents functional associations among brain regions and can be obtained by measuring the temporal correlations

Figure 1 Illustrations of network measures



(a) Clustering coefficient of node 2. The panel shows an example of a graph composed of seven nodes and nine edges. The dots represent nodes and the lines represent edges linking the nodes. Node 2 (red color) has four immediate neighbors indicated by nodes 1, 3, 6, and 7 (green colors). The clustering coefficient of node 2 is the number of existing connections (i.e., 3–6 and 6–7) among the node's neighbors divided by all of their possible connections (i.e. 1–3, 1–6, 1–7, 3–6, 3–7, and 6–7), which is 2/6 (i.e. 1/3). (b) The characteristic path length between nodes 5 and 7. There are many different kinds of ways between nodes 5 and 7, but the shortest path length (i.e. characteristic path length) is 3, indicated by red lines. (c) Modular structure. There are two modules in the graph in which connections within modules are much denser than between them.

between spatially remote neurophysiological events from fMRI and EEG/MEG data [10]. Once the brain connectivity information is extracted from the neuroimaging data, graph theoretical approaches can be further applied to model brain networks and analyze their underlying topological properties.

Graph theoretical approaches

Graph theory is a natural framework for the mathematical representation of complex networks. Recently, graph theory has attracted considerable attention in brain network research because it provides a powerful way to quantitatively describe the topological organization of brain connectivity. According to the theory, the brain can be depicted as graphs composed of nodes representing regions or voxels and edges representing structural or functional connectivity among the nodes. A graph can be undirected or directed as well as unweighted (binary) or weighted. Several key network metrics are introduced as follows. See [11] for a detailed review of graph theory.

The clustering coefficient and characteristic path length are two basic measurements of a network [12]. The clustering coefficient of a network is the average of the clustering coefficients over all nodes in the network, where the clustering coefficient of a node is the number of existing connections among the node's immediate neighbors divided by all of their possible connections (Fig. 1). It quantifies the extent of local cliquishness or local efficiency of information transfer of a network. The characteristic path length of a network is the average minimum number of connections that link any two nodes of the network (Fig. 1). It quantifies global efficiency (in terms of inverse path length) or the capability for parallel information propagation of a network. The two metrics can be used to distinguish different classes of network such as regular, small-world, and random networks. A small-world network has a shorter characteristic path length than a regular network (high clustering and long path lengths) but a greater local interconnectivity than a random network (low clustering coefficient and short path lengths). The small-world model is attractive for complex brain networks, as it not only supports both specialized/modularized and integrated/distributed information processing but also maximizes the efficiency of information transfer at a relatively low wiring cost [12]. Another important network metric is the modularity, which identifies modules of linked nodes that work together to achieve distinctive functions [11]. Connections are usually denser within modules than between them (Fig. 1). Detecting and characterizing modules of the brain can allow us to identify groups of anatomically

and/or functionally associated components that may subserve specific behavioral functions.

In a network, the nodal characteristics can be measured by several metrics such as the degree, efficiency, and betweenness centrality [11]. The degree of a node is the number of all links for the node. The efficiency of a node is the mean of the inverse of the minimum path length between the node and all other nodes in the network. The betweenness centrality of a node is the number of shortest paths between any two nodes that run through the node. These nodal metrics can be used to identify network hubs.

Human brain structural networks

The network of structural connectivity in the human brain *in vivo* can be constructed by using both structural MRI and diffusion MRI.

Structural MRI

Structural MRI supplies rich information on the brain morphology. Numerous structural MRI studies have demonstrated that there are correlated changes in gray matter morphology (e.g. cortical thickness and volume) between various anatomically or functionally linked areas [13,14]. The notion of morphological correlations has been widely used to study correlated evolution in mammalian brain structures [15] or to infer structural connectivity between regions in the human brain [13]. Using cortical thickness measurements derived from structural MRI, He *et al.* [16] constructed a human whole-brain structural network at a macroscopic level by computing the interregional thickness correlations across populations and found that the resultant network exhibits a 'small-world' topology (high clustering and short path lengths) and contains a set of network hubs predominantly located in heteromodal association cortical regions. In a subsequent study, Chen *et al.* [17•] showed that the structural brain network has a modular structure closely overlapping with known functional domains such as auditory/language, strategic/executive, sensorimotor, visual, and mnemonic processing. In a twin study, Schmitt *et al.* [18••] showed not only that the associations of cortical thickness among regions are genetically mediated in the frontoparietal and occipital networks but also that the mediated relationships follow a small-world principle. In addition to the cortical thickness measurements, other morphological descriptors such as gray matter volume and surface area have also been used to study brain structural networks. By analyzing the interregional correlations of gray matter volume, Bassett *et al.* [19••] found that multimodal cortical networks have a hierarchical organization dominated by frontal hubs, whereas transmodal and unimodal cortical networks are less hierarchically organized, suggesting different topological organization for different cortical divisions. Recently, Sanabria-Diaz *et al.* [20•] showed that structural brain networks derived from cortical thickness and surface area measurements have distinct topological attributes indicated by significant differences in network parameters (e.g. clustering coefficient, path length, and local and global efficiency), which is suggestive of distinct properties of the interaction or different aspects of the same interaction (mechanical, anatomical, and chemical) between brain structures.

Several structural MRI studies have applied morphology-based network models to the study of brain diseases such as Alzheimer's disease, schizophrenia, and multiple sclerosis. He *et al.* [21••] showed that Alzheimer's disease patients had abnormal topological organization in the whole-brain structural networks, such as increased clustering and path lengths as well as reduced betweenness centrality in temporal and parietal regions. These changes suggest a shift to more local processing and a disrupted structural integrity of the larger-scale brain systems. Bassett *et al.* [19••] showed that schizophrenia patients are associated with abnormal topology in the multimodal brain network characterized by a reduced hierarchy, an increased connection distance, and the loss of frontal hubs. More recently, He *et al.* [22••] showed that the small-world efficiency of structural brain networks in multiple sclerosis was disrupted in a manner proportional to the extent of total white matter lesions and that regional efficiency reductions were mainly located in the insula and precentral gyrus as well as the prefrontal and temporal association cortical regions.

Diffusion MRI

Recent advances in diffusion MRI and tractography methods have facilitated the noninvasive mapping of structural networks in the human brain at an individual level. Deterministic 'streamline' tractography allows us to infer the continuity of fiber bundles from voxel to voxel [23]. In contrast, probabilistic tractography allows us to compute the connectivity probabilities rather than the actual white matter pathways between voxels [24]. Several previous studies involving diffusion tensor imaging (DTI) and diffusion spectrum imaging have utilized the deterministic tractography methods to construct human whole-brain structural connectivity networks by exploring the density or existence of fiber connections between anatomically and/or functionally related brain regions [25••,26••]. Similar to those of morphology-based brain structural networks, the diffusion MRI-based networks were also found to exhibit small-world attributes. Two recent studies by diffusion-weighted MRI have utilized probabilistic diffusion tractography methods to construct human whole-brain structural networks by characterizing

the interregional connectivity probabilities. Not surprisingly, graph analysis also revealed small-world topology and high efficiency in those brain networks [27••,28]. Notably, these diffusion MRI-based studies have consistently demonstrated that human brain structural networks contain a particular set of highly connected areas located predominantly in the posterior medial and parietal cortices.

Several diffusion MRI studies have also explored whole-brain structural connectivity patterns in different populations. Using DTI tractography, Li *et al.* [29•] showed that higher intelligence quotient scores are associated with larger global efficiency in the brain networks, suggesting an association between the structural organization of the brain and intelligence performance. Also using DTI tractography, Shu *et al.* [30•] showed that early blind subjects are associated with decreased connectivity degree and global efficiency in the structural brain networks, particularly in the visual cortex. However, increased connections were detected in the motor or somatosensory areas. These results imply a topological re-organization of structural brain connectivity in the specific population with early visual deprivation. Recently, Gong *et al.* [27••] showed that the local efficiency of structural brain networks constructed from diffusion-weighted MRI decreases with age (from 19 to 85 years) and that there is also a shift of regional efficiency from the parietal and occipital to the frontal and temporal neocortex in older brains (Fig. 2). Interestingly, they also showed that female brains have greater overall connectivities and higher efficiencies than male brains. These results provide insight into the understanding of age-related and sex-related differences in cognition and behavior.

Human brain functional networks

The network of functional connectivity in the human brain *in vivo* can be constructed by fMRI and EEG/MEG.

Functional MRI

fMRI utilizes changes in cerebral blood flow and oxygen consumption in order to detect neuronal activity. With intermediate temporal (seconds) and spatial (mm) resolutions, fMRI has recently attracted considerable attention for the graph analysis of brain networks. Several fMRI studies have consistently demonstrated that brain functional networks (region-based and voxel-based levels) in healthy individuals have small-world topologies, high efficiencies at a low wiring costs, and highly connected hub regions that are mainly located in the association cortical regions [31,32,33••,34,35••,36]. Particularly, several recent studies using resting-state fMRI have shown that the brain functional networks have an intrinsically cohesive modular (community) structure in which the connections between regions are much denser within each module than between them and, more importantly, that those modules are mainly composed of functionally and/or anatomically related brain regions [33••,37,38•] (Fig. 3).

Using resting fMRI and graph theoretical analysis, van den Heuvel *et al.* [39•] showed a significantly negative correlation between the path length of brain networks (voxel level) and intelligence quotient, that is, more efficiently connected brains correspond to higher levels of intellectual performance. Furthermore, most pronounced effects were found predominantly in the frontal and parietal regions, which have been known to be where the structural [25••,26••] and functional [35••] hubs are located. These results suggest that human cognitive ability is likely to be related to the topological architecture of the brain functional network.

Several fMRI studies have utilized graph-based network models to examine age-related changes in the functional connectivity patterns of the human brain. Using a large fMRI dataset (210 individuals: 66 aged 7–9 years; 53 aged 10–15 years; 91 aged 19–31 years), Fair *et al.* [40••] showed that the small-world measurements of brain functional networks composed of 34 predefined brain regions were constant over age. In contrast, module assignments change over age: modules in children are predominantly arranged by anatomical proximity, whereas modules in adults predominantly reflect functional relationships. This suggests a dynamic developmental trajectory of brain functional network topology. Supekar *et al.* [41••] reported that both children (7–9 years) and young adults (19–22 years) have similar 'small-world' topological organization of their whole-brain functional networks but differ significantly

Figure 2 (*Continued*)
(a) The schematic image processing for the construction of the cortical weighted network. The brain template masks in diffusion MRI space for one subject (top of left panel) are shown. Each color represents a cortical region. The connectivity probability using diffusion MRI tractography (bottom of left panel) was determined. The yellow–red color represents the resulting probability (yellow > red) from the left precuneus (marked as blue) to the other voxels. The regional probability matrix from the probabilistic tractography is shown for the same subject. Each row or column represents one cortical region. (b) The age effect on the local and global efficiency of the cortical networks. A significant age effect was observed for the integrated local efficiency (left panel), but the integrated global efficiency showed no significant age effect (right panel). Notably, all results here were calculated after adjusting for the effects of brain size and sex, using a general linear model. (c) The spatial distribution of cortical regions, showing a significant age effect ($P < 0.05$, false discovery rate-corrected) on the integrated regional efficiency. The color represents the *t*-statistic of the age effect that was calculated from the general linear model. Each identified region was marked out. Notably, the negative age effect was mainly distributed in the parietal and occipital cortex, whereas the positive age effect was localized only in the frontal and temporal cortex. Reproduced with permission from [27••].

Figure 2 Construction of structural brain networks by diffusion MRI tractography and age-related changes in network efficiency

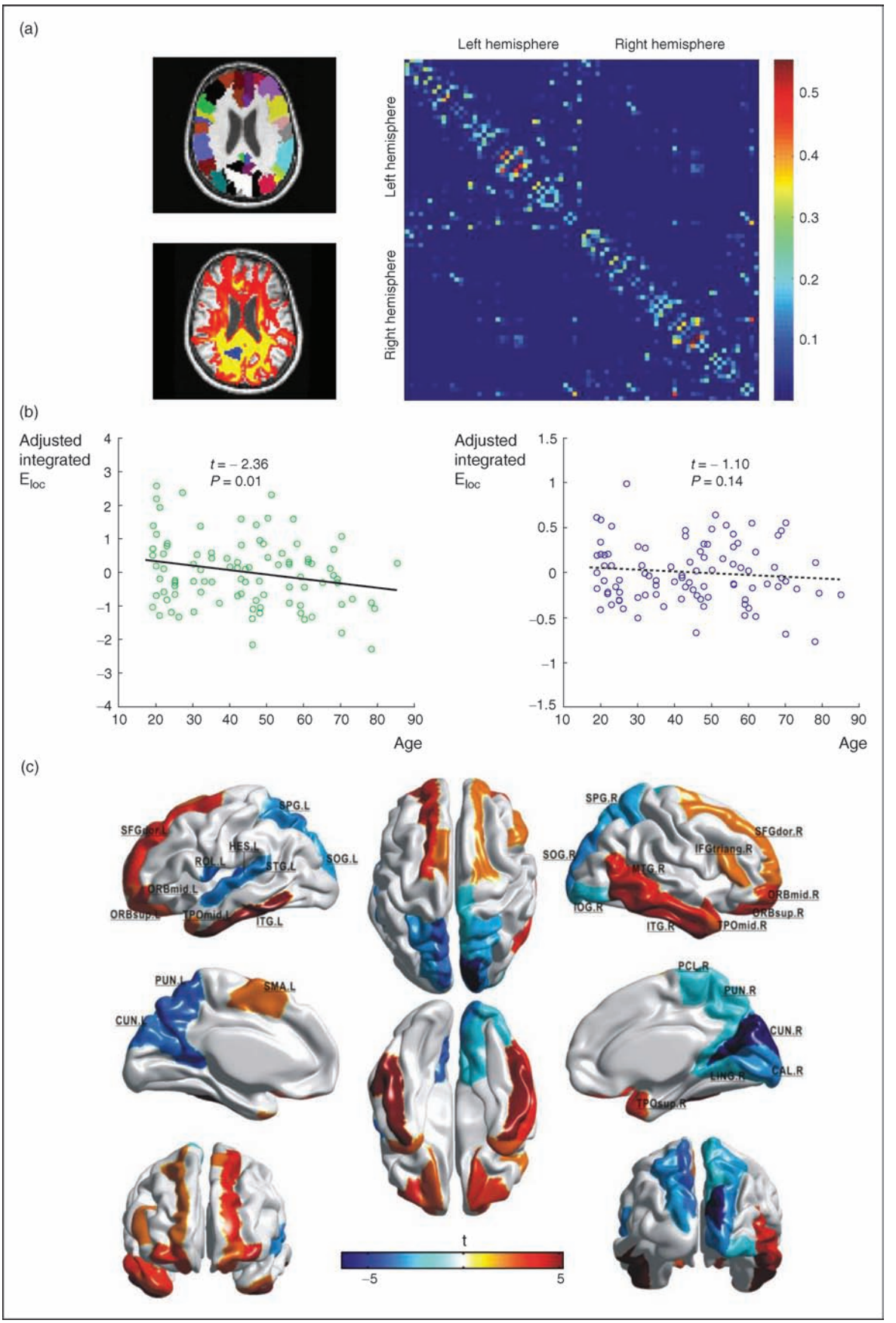
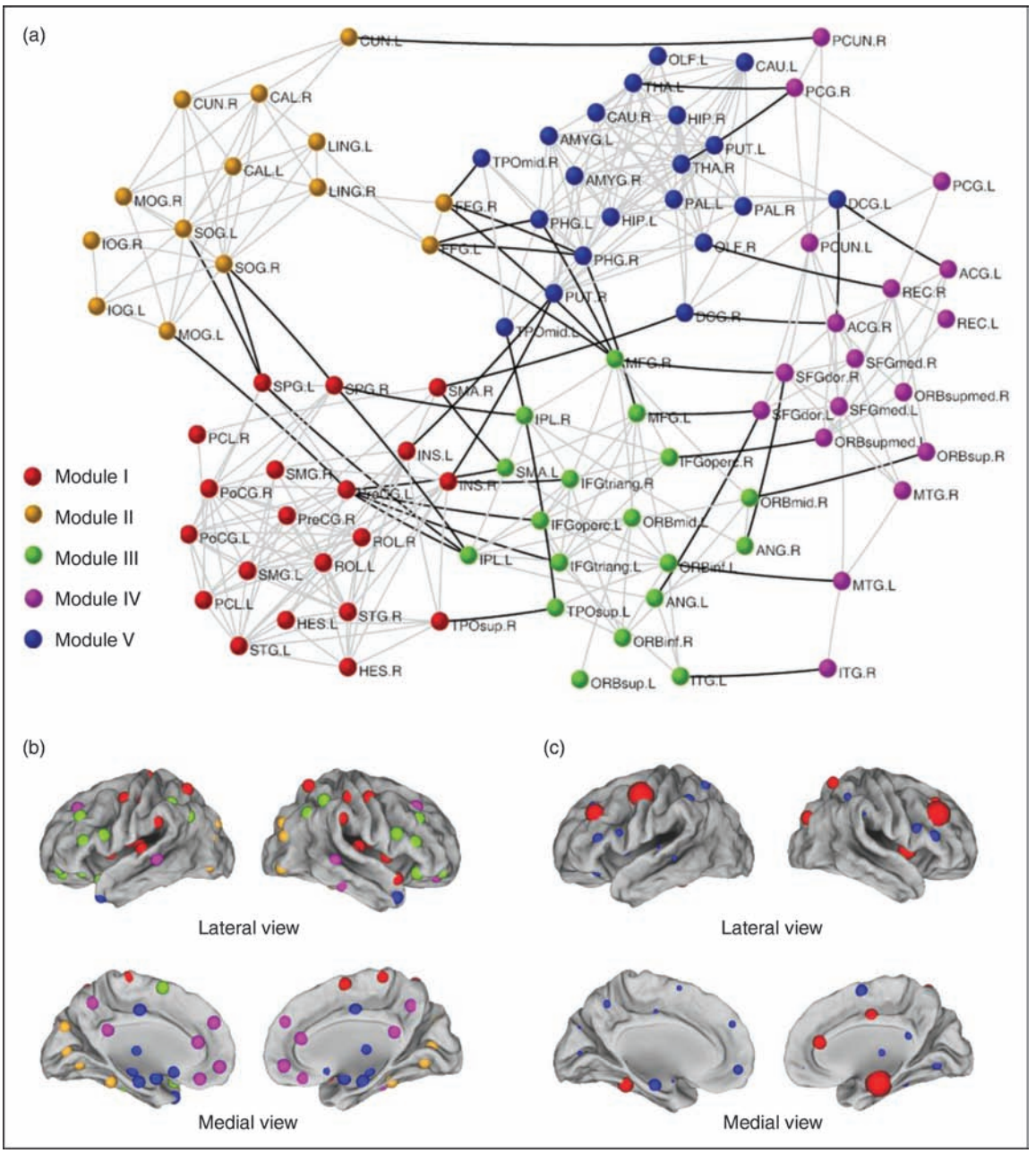


Figure 3 The modular structure and hubs of the human brain functional network by resting fMRI



(a) The modular architecture of the human brain functional network. Five functional modules were identified in the brain functional network derived from resting fMRI data and represented by five different colors. The geometric distance between two brain regions on the drawing space approximates the shortest path length between them. The network is visualized with the Pajek software package (http://vlado.fmf.uni-lj.si/pub/networks/pajek/) using a Kamada–Kawai layout algorithm. The intramodule and intermodule connections are shown in the gray and dark lines, respectively. (b) Surface and anatomical representation of the modular architecture of the human brain functional network. All of the 90 brain regions are marked by different color spheres (different colors represent distinct network modules) and are further mapped onto the cortical surfaces at the lateral, medial, and top views, respectively, using the Caret software (http://brainvis.wustl.edu). Notably, the regions are located according to their centroid stereotaxic coordinates. For visualization purposes, the subcortical regions are projected to the medial cortical surface according to their y and z centroid stereotaxic coordinates. (c) The global hubs with high topological centralities in the human brain functional networks. The surface visualization of all 90 brain regions is shown, with node sizes indicating their relative node betweenness centrality, N^{bc}. Regions with $N^{bc} >$ mean + SD are considered to be hubs (red colors), and otherwise they are considered to be nonhubs (blue colors). Reproduced with permission from [33••].

in their hierarchical organization and interregional connectivity, with a reduction in short-range connectivity and a strengthening of long-range connectivity, suggesting a process of greater functional segregation but weaker functional integration in children. Achard and Bullmore [42] showed that brain functional networks derived from resting fMRI had significantly reduced efficiency in older adults than in young adults. In a subsequent study on the same dataset [38•], the older group was also found to have a reduced number of intermodular connections to frontal modular regions but an increased number of connector nodes in posterior and central modules. Wang *et al.* [43•] showed that the brain functional networks of older adults were associated with an increased shortest path length and a reduction in the long-range connections during the performance of memory tasks, thereby providing insight into age-related declines in cognitive functions.

During the past 2 years, there has also been increasing attention focused on the application of graph-based network models of resting fMRI in brain diseases. Supekar *et al.* [44•] reported that Alzheimer's disease patients had reduced clustering in the brain functional networks, indicative of disrupted local neighboring connectivity. Liu *et al.* [45•] showed that various topological measurements, such as the clustering coefficient and the global and local efficiency, were reduced in the brain networks of schizophrenia patients as compared with controls, and the reduction was negatively correlated with the illness duration. Wang *et al.* [46•] showed that boys with attention-deficit/hyperactivity disorder had increased local efficiency in the brain functional networks, with nodal efficiency changes in the prefrontal and temporal regions. These changes could reflect a compensatory recruitment or a developmental delay in brain topological organization in this disorder. Liao *et al.* [47•] showed that patients with mesial temporal lobe epilepsy were associated with smaller clustering coefficients and shorter path lengths, indicating a more random-like configuration in the brain functional networks of the patients. Nakamura *et al.* [48•] illustrated that patients with traumatic brain injury had reduced connectivity strength and increased small-world attributes from 3 months to 6 months postinjury, suggestive of a network recovery following severe brain injury.

EEG/MEG

In contrast to fMRI, which is based on a neurovascular signal, noninvasive in-vivo human electrophysiology with EEG or MEG measures the changes in the electromagnetic field related to neuronal activity at a high temporal resolution (milliseconds) but a poor spatial resolution (cm). In the past year, several studies have applied EEG/MEG techniques to the graph analysis of brain functional networks under healthy and clinical conditions. For example, an MEG study [49•] reported that the cost efficiency of a brain functional network correlated positively with task performance (working memory) and specifically with the cost efficiency of nodes in the left lateral frontal and parietal regions. An EEG study [50] showed that young adults had decreased clustering and increased path lengths in the brain functional networks as compared with children. In Alzheimer's disease, a graph theoretical analysis of a resting-state MEG network [51••] revealed decreased clustering coefficients and path lengths, with a preferential decrease in connections between highly connected network hubs, a result that was compatible with a previous fMRI-based brain network study in Alzheimer's disease [44•]. Interestingly, a resting-state EEG study [52••] reported similar changes in the brain functional network topology in Alzheimer's disease patients but observed changes in the opposite direction (increased clustering and path lengths) in patients with frontotemporal dementia, suggesting a different pathophysiology. However, it is worth noting that these findings are inconsistent with those shown in a previous structural MRI study demonstrating increased clustering and shortest path lengths in structural brain networks in Alzheimer's disease [21••]. The discrepancies could be attributable to different imaging modality, population size, network node, and edge definitions applied in these studies. Graph theoretical analysis of brain networks based on EEG/MEG data has been also applied to other diseases such as schizophrenia [49•,53], epilepsy [54], and depression [55].

Future perspectives

Graph-based network analysis represents the state-of-the-art methodology in brain connectivity; however, there are many challenging issues in this new field that need to be addressed.

Whole-brain structural and functional connectivity can be modeled as networks with different neuroimaging modalities. During the network construction, the definition of nodes and edges is a critical step. Previous studies using structural, functional, and diffusion MRI have demonstrated that network nodes can be defined using both anatomical and/or functional brain atlases and image voxels, but the resultant networks exhibited significantly different topological properties [20•,56•,57•,58•]. Moreover, some studies have confined the network to the cerebral cortical system, namely only considering cortical regions as network nodes [16,18••,20•,21••,22••,25••–27••], whereas others allow for connectivity to deep gray matter structures such as the thalamus and striate cortex [31,32,33••,41••,42,43•–48•,56•]. Likewise, the definition of network edges depends on the selection of different image preprocessing and connectivity metrics

[6,19••,20•,21••,25••,26••,31,32,33••,34,35••,37,38•]. Given the lack of a gold standard for the definition of network nodes and edges, researchers still need to take care when choosing the right network representation of the brain connectivity to ensure the appropriate use of network analysis.

The stability and reproducibility of graph metrics are also important for brain network analysis. A recent DTI study [59•] reported a high reproducibility of small-world metrics in the structural brain networks derived from different image acquisition parameters such as the number of gradient directions and gradient strength. A high reproducibility of graph metrics across different task states and subjects was also reported in the brain functional networks derived from MEG and fMRI data [33••,35••,60••]. Thus, graph-based brain network analysis could be both practical and feasible for longitudinal studies, but more systematic evaluation is still necessary.

Another area of expansion is in the combination of different imaging modalities to determine the relationship of the structural and functional connectivity of the brain. Several previous studies have shown that the strength of intrinsic functional connectivity derived from resting fMRI positively correlated with the strength of structural connectivity measured with diffusion MRI [61]. With the aid of computational modeling, Honey *et al.* [62••] showed that the system-level properties of functional brain networks can be partly accounted for by the properties of the underlying structural network, implying topological correlations of structural and functional networks. The combination of multimodal imaging techniques of the future will provide integrative information to map the patterns of brain connectivity that underlie cognition and behaviors in humans.

The collection and distribution of large-scale neuroimaging data are important and necessary for the noninvasive mapping of the structural and functional connectivity of the human brain. There are currently a few publicly available neuroimaging databases, for example, *fMRIDC* (http://www.fmridc.org), *NIHPD* (http://www.bic.mni.mcgill.ca/nihpd/), *OASIS* (http://www.oasis-brains.org), *ADNI* (http://www.adni-info.org), *FBIRN* (http://www.birncommunity.org), *BrainMap* (http://www.brainmap.org), *BrainScape* (http://www.brainscape.org), and '1000 Functional Connectomics Project' dataset (http://www.nitrc.org/projects/fcon_1000/). These databases offer excellent opportunities for systematically investigating the network modeling of brain connectivity in health and disease and for facilitating knowledge-sharing and collaboration among the scientific community.

Conclusion

The accumulating body of evidence suggests that graph theoretical analysis of neuroimaging data offers a powerful way to understand the topological principles of brain networks in the normal adult, in development and with aging and disease. It is clear that more research is needed to allow comprehensive and reliable descriptions for patterns of structural and functional brain connectivity. These efforts are opening up new avenues of research into organizational mechanisms of the brain that will be of interest for all basic scientists and clinical researchers.

Acknowledgements

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 433–434).

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