Rev. Neurosci., Vol. 22(5): 551–563, 2011 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/RNS.2011.039

Graph theoretical analysis of human brain structural networks

Chun-Yi Zac Lo[1], Yong He[2] and Ching-Po Lin[1,3,*]

[1] Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan
[2] State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China
[3] Brain Connectivity Laboratory, Institute of Neuroscience, National Yang-Ming University, Taipei, Taiwan

*Corresponding author
e-mail: cplin@ym.edu.tw

Abstract

There is a growing interest in exploring the connectivity patterns of the human brain. Specifically, the utility of noninvasive neuroimaging data and graph theoretical analysis have provided important insights into the anatomical connections and topological pattern of human brain structural networks *in vivo*. This review focuses on recent methodological and application studies, utilizing graph theoretical approaches, on brain structural networks with structural magnetic resonance imaging (MRI) and diffusion MRI. These studies showed many nonrandom properties of structural brain networks, such as small-worldness, modularity, and highly connected hubs. Importantly, topological organization of the networks shows changes during normal development, aging, and neuropsychiatric diseases. Network structures have also been found to correlate with behavioral or cognitive functions, which imply their associations with functional dynamics. These advances not only help us to understand how the healthy human brain is structurally organized, but also provide a novel insight into the biological mechanisms of brain disorders. Future studies will involve the combination of structural/diffusion MRI and functional MRI, to realize how the structural connectivity patterns of the brain underlie its functional states, and will explore whether graph theoretical analysis of structural brain networks could serve as potential imaging biomarkers for disease diagnosis and treatment.

Keywords: connectome; graph theory; magnetic resonance imaging; modularity; small-world; structural brain networks.

Introduction

The human brain is a highly dense neural architecture, which is structurally organized into complex networks of fiber bundles with the capacity for information generation, segregation, and integration. To understand the dynamic processing of the human brain, an important issue in neuroscience, is to map the connection pattern of the human brain (known as the 'human connectome') with the elements and connections in different levels, such as at microscale (e.g., single neurons), mesoscale (e.g., a group of neurons), and macroscale (e.g., distinct brain regions) (Sporns et al., 2005; Sporns, 2011). With structural connectivity, the human connectome represents the organization of the neuronal elements, which are structurally linked, and shows the network architecture in specific constraints on brain dynamics. Nowadays, noninvasive neuroimaging modalities, including structural magnetic resonance imaging (MRI) and diffusion MRI, have been widely used to measure the structural characteristics of the human brain. Through these techniques, the structural human connectome can be established by mapping the anatomical connectivity between distinct regions. By further modeling the human brain as a complex network, graph theoretical analysis provides an important framework to explore the architecture of the human connectome involving the information propagation in the nervous system. Researchers have found many nonrandom topological properties of brain networks such as small-worldness, efficiency, modularity, and network hubs (Bassett and Bullmore, 2006, 2009; Bullmore and Sporns, 2009; He and Evans, 2010; Stam, 2010; Wang et al., 2010; Wen et al., 2011a). These approaches provide a network-level representation for investigation of the human brain in a global view. Recently, structural brain networks have demonstrated that the topological patterns correspond with specific biological characteristics such as development (Hagmann et al., 2010; Fan et al., 2011) and gender (Gong et al., 2009a; Lv et al., 2010; Yan et al., 2010). Moreover, it has been suggested that many neurological and psychiatric disorders can be described as dysconnection syndromes (Catani and Ffytche, 2005). The topology of the brain connectome has a major potential impact for our understanding of brain alterations, either damage or reorganization in diseases (Petrella, 2011). Abnormal topological organization, with disruption of structural connectivity in disorders, may be related to impairment of cognitive functions or behaviors. The architecture of the brain networks may serve as a potential imaging biomarker for disease diagnosis or evaluation of treatment response (Bullmore and Sporns, 2009; He et al., 2009a; He and Evans, 2010). Focusing on the growing interest in the brain connectome, in this review, we summarized recent advances for the topological organization of human brain structural networks, in health and diseases, revealed by neuroimaging modalities with graph theoretical approaches.

Graph theoretical approaches

A network can be described as a graph, which is composed of a set of nodes (vertices) that are connected by edges (connections). The edges can be directed (edges are directed from one

node to another) or undirected (no direction for each edge), and additionally can be unweighted (all edges have the same weight of 1) or weighted (edges have different strengths). The complex structural brain network can be reconstructed by linking the regions-of-interest of the cerebral cortex (nodes) with the structural connections (edges). The present review focuses on only undirected brain networks.

Graph theory is a mathematical analysis framework that represents the topological characteristics of complex networks, for the communication of nodes connected by edges. Several key points of network metrics are described in the following perspectives. More detailed descriptions of graph theory have been reported (Boccaletti et al., 2006). In general, the clustering coefficient and the shortest path length are two basic measurements for each graph to quantify local and global architectures (Watts and Strogatz, 1998). The clustering coefficient of a network is the average of the clustering coefficient over all nodes. In detail, the clustering coefficient of a node is defined as the ratio of the existing connections to all possible connections of neighboring nodes that are connected directly to this node (Strogatz, 2001). This characteristic indicates the extent of local cliquishness or interconnectivity for information transfer in a network (Watts and Strogatz, 1998; Latora and Marchiori, 2001). The path length between a pair of nodes is defined as the sum of the edge lengths along this path. The shortest path length for a network is defined as the average of minimum path lengths for each pair of nodes, which quantifies the ability for information propagation in parallel. Of note, these two measurements can classify the network architectures into regular, small-world, and random networks (Watts and Strogatz, 1998). Importantly, the most efficient model is the small-world network, which is characterized by a high extent of local interconnectivity and small path length linking individual network nodes (Watts and Strogatz, 1998). In practice, a real network can be examined to be the small-world model, by comparing the clustering coefficient and shortest path length with those of matched random networks. That is, a small-world network not only has higher local transitivity, but also the approximately equivalent shortest path length compared with random networks. On the other hand, the path length can also approach the efficiency for a network (Latora and Marchiori, 2001). Global and local efficiencies conceptually correspond to the shortest path length and clustering coefficient, respectively (Latora and Marchiori, 2003). Specifically, the global efficiency of a network is the inverse of the harmonic mean of the shortest path length between each pair of nodes within the network, which represents the transfer speed of parallel information for a network. That is, the shorter the path length is, the more efficient the network will be. The local efficiency of one node is the global efficiency of the subnetwork that which is composed by its directly connected neighbors (not including itself) and the local efficiency of a network is the average of the local efficiency of each node. The local efficiency reflects how much the network is fault tolerant and how well the information is transferred within the neighbors of a given node. Alternatively, a network with both high local and global efficiencies, is considered to be a small-world network (Latora and Marchiori, 2001, 2003; Gong et al., 2009a; He et al., 2009b).

Another way to quantify the organization of a network is modularity. Many complex networks consist of a number of modules, which are organized into modular or community structures. Modularity refers to the construction of a network by modules of linked nodes that are densely inter-connected together and relatively sparsely connected to the nodes in other modules (Newman, 2006). Currently, there are various optimized algorithms with different advantages which can be used to describe the modularity (Fortunato, 2010). For example, a widely used method for module detection is proposed by Newman and Girvan (2004), which depends on the importance of edges to find the optimized modules. Detecting the composition of modules in a structural brain network, which represents the groups of components connected anatomically, can help us to realize how nodes are clustered and whether those modules are responsible for specific cognitive functions (Meunier et al., 2010).

In addition, the network properties for a node can also be described by nodal characteristics such as degree (or strength in weighted networks), nodal efficiency, and betweenness centrality. The nodal degree/strength is the sum of all binary/weighted edges of one node, which measures the single nodal connectivity to the rest of the nodes in a network. The nodal efficiency for each node is the inverse of mean harmonic shortest path length between this node and all other nodes in a network (Achard and Bullmore, 2007). This metric indicates the ability of the node for communicating to the other nodes within the network. The betweenness centrality of a node is the count of the shortest paths between any pair of nodes that have to pass through this node (Freeman, 1977). These nodal metrics can also be used to determine the hub nodes in the networks. A node with high degree, efficiency or betweenness can be considered as a hub (He et al., 2007; Hagmann et al., 2008; Gong et al., 2009b).

Structural brain networks

One of the key issues in studying the structural brain connectome is node definition of the human cerebral cortex, which has usually been defined by pre-parcellated regions such as automated anatomical labeling (AAL) (Tzourio-Mazoyer et al., 2002) and automatic nonlinear imaging matching and anatomical labeling (ANIMAL) (Collins et al., 1995). The other important issue is the construction of a structural connection matrix to characterize the connectivity between regions. Recently, morphometry-based and white matter (WM) connections via structural MRI and diffusion MRI have been used to construct the networks of structural connectivity in the human brain *in vivo*. The following description and Figure 1 show the concept for structural network construction.

Gray matter (GM) networks

With structural MRI, gray matter (GM) morphology of the brain has demonstrated that the interregional statistical associations in cortical measurements provide important structural or functional connectivity in the human brain (Lerch et al.,

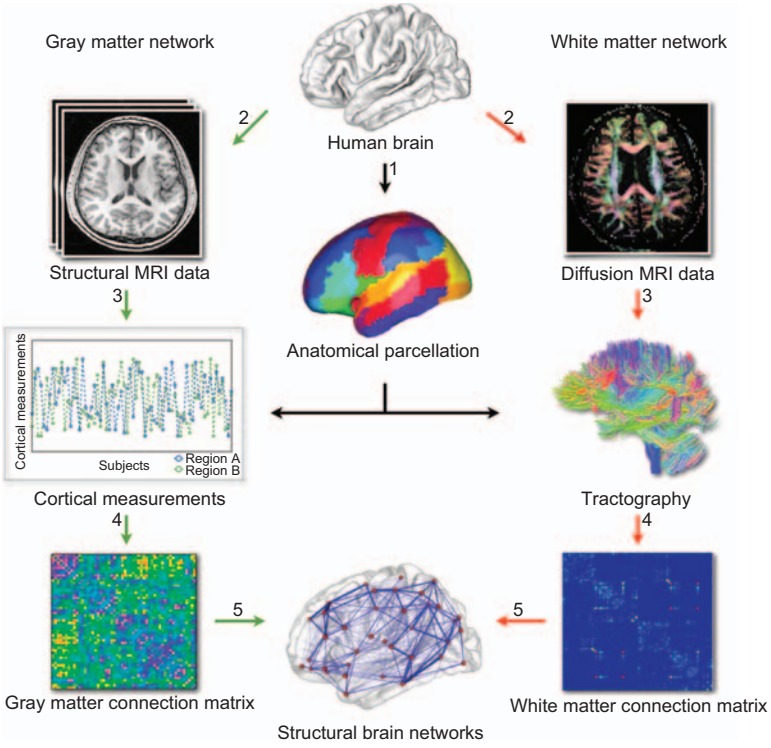

Figure 1 The framework for the construction of structural brain network.
The definition of network nodes: (1) the parcellation of cerebral cortex into anatomical distinct regions. The definition of network edges: the green arrows and red arrows, respectively, indicate the procedure for gray matter and white matter network construction, (2) the structural or diffusion MR image acquisition, (3) cortical measurement (left) or diffusion-based tractography (right), (4) construction of a connection matrix by interregional correlation of cortical measurements (left) or diffusion-based tractography (right), (5) graph theoretical analysis.

2006). The correlation of morphological measurements (e.g., volume, thickness, or surface area) between cortical regions across subjects, has been represented as a morphometric connectivity to map the connection matrix (He et al., 2009a). That is, an edge between two regions will be established if the measurements are highly correlated. With these approaches, He et al. (2007), first utilizing interregional cortical thickness correlations, demonstrated that the GM network of the human brain follows a small-world configuration, implying that the structural brain architecture has high clustering and short path length. Subsequently, Chen et al. (2008) showed that the GM network consists of six modules that are likely to be associated with specific brain functions such as strategic/executive, auditory/language, sensorimotor, visual, and mnemonic processing. Bassett et al. (2008), using interregional volumetric correlations, indicated that the classical divisions of cortex (multimodal, unimodal, and transmodal) have some distinct topological attributes, and that all divisions have a small-world model with efficient wiring. Moreover, they also indicated that the multimodal network has a hierarchical organization, whereas the transmodal network is assortative. Sanabria-Diaz et al. (2010) demonstrated that the GM brain network, derived from surface area metrics, also has a small-world organization, whereas the topological parameters are different from those of cortical thickness based GM network.

White matter (WM) networks

For the white matter (WM) neural pathway, the recent diffusion MRI, involving diffusion tensor imaging (DTI), diffusion spectrum imaging (DSI), and q-ball imaging (QBI), is a unique technique that can be used to probe direction-dependent diffusivity of water molecules *in vivo* to reflect the microstructural tissue status and orientations. Neural tractography (so-called fiber tracking) by propagating the orientation information in each voxel, has demonstrated its ability to map WM trajectories (Mori and van Zijl, 2002). By linking the distinct regions with fiber tracts, it is possible to reveal WM anatomical connections and map the whole brain connectivity. Topological patterns of the human brain WM networks have been recently investigated through diffusion-MRI based tractography, which provides a novel method to study the efficiency of brain communication (Iturria-Medina et al., 2007). Hagmann et al. (2007) showed the first capability of revealing brain anatomical topology based on DSI tractography, and demonstrated the small-world architecture of the human brain. The WM networks that have major structural cores within the posterior medial and parietal cerebral cortex (Figure 2A), and contain six modular structures, were then examined (Hagmann et al., 2008). Gong et al. (2009b), exploiting a group based WM network with DTI tractography

from 80 healthy subjects, showed that the major hub regions of the human brain are predominately located in association with cortices connecting the long-range fiber pathways (Figure 2B). With different schemes of WM network constructions, Zalesky et al. (2010b) showed broadly consistent topological patterns of WM networks constructed with DTI and QBI from the same subjects, but quite different topological properties of WM networks with different parcellation scales.

These important studies, using graph theoretical analysis to investigate the structural network of the human brain, opened a new field for investigating structural topology involving the information processing ability of brain. Nowadays, the attributes of structural brain connectomes have been widely studied in multiple domains, to show a convincing perspective in neuroscience. See Table 1 for recent literatures of structural brain networks reviewed in this article.

Structural brain networks in normal population

To date, studies focusing on sex dimorphism, development, and aging with graph theoretical analysis have revealed specific topological characteristics of structural brain networks in a normal population.

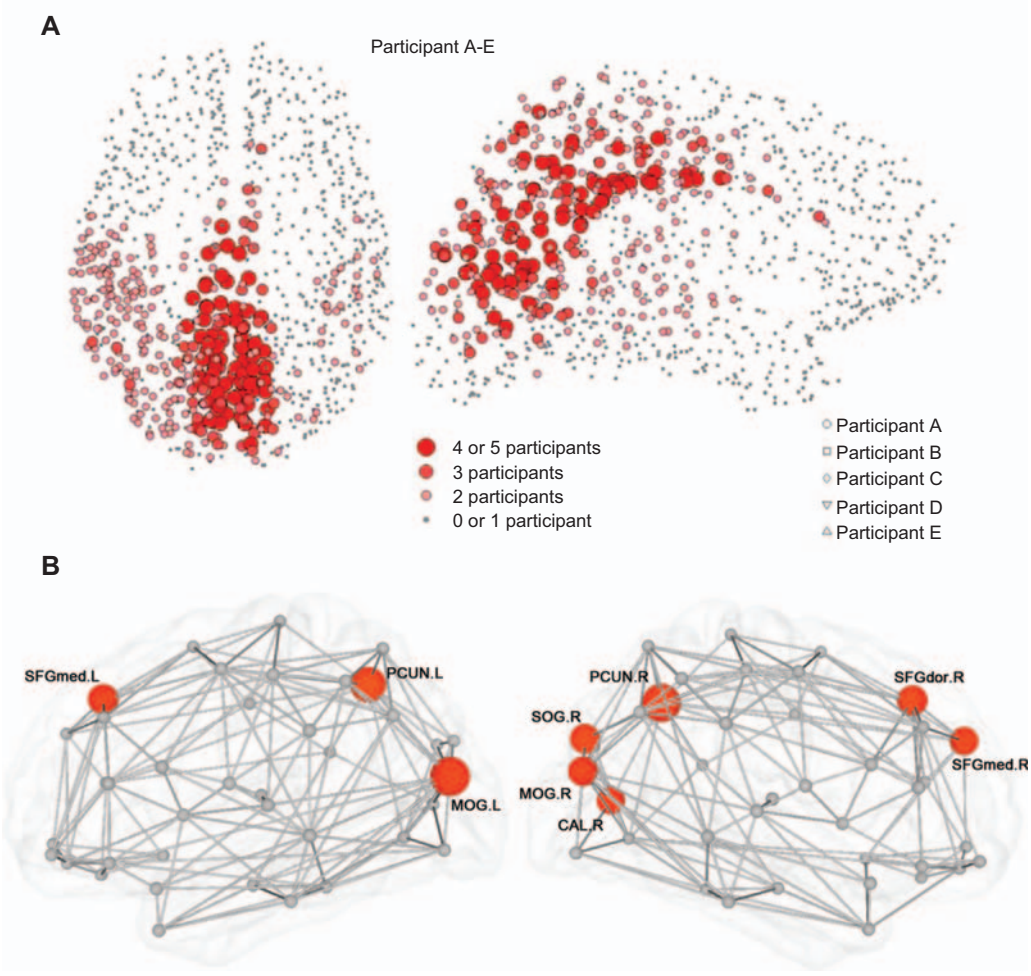

Figure 2 Major hub distribution in WM networks of the human brain.
Note that the principle hubs in WM networks in both studies are predominately located in the posterior medial and parietal cortical regions. (A) Average network core across all five participants in (Hagmann et al., 2008), which were derived by k-core decomposition of a binary connection matrix obtained by thresholding the high-resolution fiber densities, such that a total of 10 000 connections remain in each participant. Nodes are plotted according to their core number, counted backwards from the last remaining core. (B) Node betweenness centrality map on the human cerebral cortex. According to the AAL template (Tzourio-Mazoyer et al., 2002), the cerebral cortex was parcellated into 78 regions (39 regions per hemisphere), each representing a node in the anatomical cortical network. Regions were mapped into an average cortical surface obtained from ICBM152 according to their normalized betweenness centrality values. The color bar indicating the range of normalized node betweenness is shown on the right. Hub regions identified in this study are marked on the map. For the abbreviations of the regions, see Gong et al. (2009b).

Table 1 Graph theoretical analysis of structural brain network studies.

Study	Population	No. of subjects	Nodal definition	No. of nodes	Edge definition	Network type	Imaging
He et al. (2007)	Normal	124	ANIMAL	54	Pearson's correlations of GM thickness	B	sMRI
Chen et al. (2008)	Normal	124	ANIMAL	54	Pearson's correlations of GM thickness	B	sMRI
Sanabria-Diaz et al. (2010)	Normal	186	AAL, Jacob	82, 56	Partial correlations of GM surface area, GM thickness	B	sMRI
Hagmann et al. (2007)	Normal	2	Random generated	500~4000	Streamline WM tractography	W	DSI
Hagmann et al. (2008)	Normal	5	Freesurfer, random generated	66, 998	Streamline WM tractography	W	DSI
Gong et al. (2009b)	Normal	80	AAL	78	Streamline WM tractography	B	DTI
Zalesky et al. (2010b)	Normal	3	AAL, random generated	82, 500~4000	Streamline WM tractography	B	DTI, QBI
Vaessen et al. (2010)	Normal	6	Brodmann area	111	Probabilistic WM tractography	B	DTI
Bassett et al. (2011a)	Normal	7	AAL, HO, LPBA40	54~720	Streamline WM tractography	B, W	DTI, DSI
Fan et al. (2011)	Development	28	AAL	90	Pearson's correlations of GM volume	B	sMRI
Hagmann et al. (2010)	Development	30	Freesurfer, random generated	83~258	Streamline WM tractography	W	DSI
Zhu et al. (2010)	Aging	Young=428, Elder=374	AAL	90	Partial correlations of GM volume	B	sMRI
Chen et al. (2011)	Aging	Young=102, Elder=97	AAL	78	Pearson's correlations of GM thickness	W	sMRI
Wu et al. (2011)	Aging	Young=551, Middle=560, Elder=372	AAL	90	Pearson's correlations of GM volume	B	sMRI
Wen et al. (2011b)	Aging	342	Freesurfer	68	Streamline WM tractography	B, W	DTI
Gong et al. (2009a)	Aging, gender	95	AAL	78	Probabilistic WM tractography	W	DTI
Lv et al. (2010)	Gender	Young=90, Elder=94	ANIMAL	54	Partial correlations of GM thickness	W	sMRI
Yan et al. (2010)	Gender	73	AAL	78	Streamline WM tractography	W	DTI
Iturria-Medina et al. (2010)	Lateralization	Human=11, Macaque=1	LVE00a	90	Probabilistic WM tractography	W	DTI
Li et al. (2009)	Intelligence	79	AAL	90	Streamline WM tractography	B, W	DTI
Hänggi et al. (2011)	GCS	NC=24, GCS=24	Freesurfer	154, 2366	Pearson's correlations of GM thickness	W	sMRI
He et al. (2008)	AD	NC=97, AD=92	ANIMAL	54	Partial correlations of GM thickness	B	sMRI
Yao et al. (2010)	MCI, AD	NC=98, MCI=113, AD=91	AAL	90	Pearson's correlations of GM volume	B	sMRI
Lo et al. (2010)	AD	NC=26, AD=30	AAL	78	Streamline WM tractography	W	DTI
Wee et al. (2011)	MCI	NC=17, MCI=10	AAL	90	Streamline WM tractography	W	DTI
He et al. (2009b)	MS	NC=330	ANIMAL	54	Pearson's correlations of GM thickness	B	sMRI
Shu et al. (2011)	MS	NC=39, MS=39	AAL	90	Streamline WM tractography	W	DTI
Bassett et al. (2008)	Sch	NC=259, Sch=203	Brodmann area	104	Partial correlations of GM volume	B	sMRI
van den Heuvel et al. (2010)	Sch	NC=40, Sch=40	AAL	108	Streamline WM tractography	W	DTI
Zalesky et al. (2011)	Sch	NC=32, Sch=74	AAL	82	Streamline WM tractography	B	DTI
Bernhardt et al. (2011)	TLE	NC=47, TLE=112	ANIMAL	52	Pearson's correlations of GM thickness	B	sMRI
Raj et al. (2010)	TLE	NC=30, TLE=27	Freesurfer	68	Disease progression path of GM thickness	W	sMRI
Crofts et al. (2011)	Stroke	Patients=9	HOA	56	Probabilistic WM tractography	W	DTI
Shu et al. (2009)	Blindness	NC=17, Blindness=17	AAL	90	Streamline WM tractography	B	DTI

GCS, grapheme-color synesthesia; AD, Alzheimer's disease; MCI, mild cognitive impairment; MS, multiple sclerosis; Sch, schizophrenia; TLE, temporal lobe epilepsy; GM, gray matter; WM, white matter; ANIMAL, automatic nonlinear imaging matching and anatomical labeling; AAL, automated anatomical labeling; HOA, Harvard–Oxford atlas; LBPA, LONI probabilistic brain atlas; B, binary; W, weighted; sMRI, structural MRI; DSI, diffusion spectrum imaging; DTI, diffusion tensor imaging; QBI, q-ball imaging.

Development/aging

The characterization of time-dependent changes of brain systems can help us to understand brain development and aging (Power et al., 2010). Given that the mature human brain has structurally been optimally organized into a complex network (Hagmann et al., 2007; He et al., 2007; Bassett et al., 2008; Chen et al., 2008; Hagmann et al., 2008; Gong et al., 2009b), studying the topological patterns of large-scale structural brain network in a global level across a lifespan may provide more intellections for the developing process of brain organization. In addition to brain development, some studies focusing on normal aging of structural brain networks have been reported.

With morphometry-based connections, Fan et al. (2011), using longitudinal data from 28 healthy subjects at the early ages of 1 month, 1 year, and 2 years, showed that the GM networks of early brains have the small-world topology and modular organization, and that the efficiency of the brain network increases with brain development. In a normal aging study, Zhu et al. (2010), exploiting younger (age range: 44–48 years) and older (age range: 64–68 years) cohort data, found that there are lower global efficiencies and higher clustering coefficients in the GM networks of the older cohort compared with the younger cohort. The brain networks of the older cohort have reduced hemispheric asymmetry, and some cortical regions, such as the hippocampus and insula, have lower nodal centrality. Chen et al. (2011), investigating young (age range: 20–27 years) and aging (age range: 60–94 years) groups, indicated that the GM network of the aging group has a significantly reduced modularity with reduced intra-/inter-module connectivity in modules corresponding to the executive function and the default mode network of young adults. Wu et al. (2011) reported that small-world efficiency and node betweenness of the GM networks revealed a U- or inverted U-shape model tendency among young (age range: 18–40 years), middle (age range: 41–60 years), and aging (age range: 61–80 years) groups. They also found that the modular organization of structural brain networks was similar between the young and middle age groups, but quite different from the elder group.

For WM networks in development, Hagmann et al. (2010) demonstrated that the nodal strength and efficiency increase, and the clustering coefficient decreases with age in WM networks of the late developing brain (age range: 2–18 years). Moreover, this study also indicated that the structural connectivity is positively correlated with functional connectivity, which strengthened with age. For normal aging, Gong et al. (2009a) demonstrated that the overall cortical connectivity and the local efficiency in the brain WM network, is reduced with age (age range: 19–85 years). They also found that the negative age effect on nodal efficiency was mainly localized to regions in the parietal and occipital cortex, whereas the positive age effect concentrated on regions in the frontal and temporal cortex. Wen et al. (2011b), exploiting the association between cognitive functions and the attributes of structural brain networks from 342 healthy elders (age range: 72–92 years), showed that the processing speed, visuospatial, and executive functions are associated with the global efficiency of structural brain networks, and that many regions (59 regions out of 68) including most of the frontal and temporal cortices, have decreased nodal efficiency with age. This study also indicated that there are significant correlations between the nodal efficiency of specific cortical regions and certain specific cognitive functions, e.g., the higher the nodal efficiency of the superior frontal gyrus and posterior cingulate cortex in the WM network, the better the executive functions. Moreover, this work identified that, for the first time, regional anatomical connectivity maps relate to processing speed and visuospatial and executive functions in the elders.

Sex difference/lateralization

Sexual dimorphism has been indicated in GM and WM (Sowell et al., 2007; Cheng et al., 2009; Chou et al., 2011). In a morphometry-based study, Lv et al. (2010) reported that there are significant gender-related differences of cortical thickness in the frontal, parietal and occipital lobes. However, there was no gender-related statistical difference in additional graph theoretical analysis of GM networks. In WM networks, Gong et al. (2009a) showed that female brains have greater overall connectivity and local and global efficiencies than males. Yan et al. (2010) indicated that the local efficiency in female brains is higher than in male brains, and they found a correlation between sex and brain size, in that smaller brains showed higher local efficiency in females but not in males.

For brain lateralization, it has been demonstrated that the human brain is asymmetrical in terms of structure and function (Toga and Thompson, 2003). Iturria-Medina et al. (2010) showed the asymmetry of brain GM networks, where the right hemisphere is significantly more efficient and interconnected than the left hemisphere. Interestingly, they found that the left hemisphere presents more central or indispensable regions for the whole-brain structural network than the right hemisphere. On the otherhand, it has also been suggested that functional asymmetry of the human brain is correlated with gender, such as language function (Kansaku et al., 2000). Tian et al. (2011), utilizing resting-state functional MRI (rs-fMRI), indicated that the right hemispheric network has a higher normalized clustering coefficient, but the left hemispheric network has a lower clustering coefficient in males, compared with females. Although structural asymmetry of the human brain has been shown (Iturria-Medina et al., 2010), no study has reported gender-linked lateralization of structural brain networks.

Others

In a normal population, there are also some special topics of interest to investigate in graph theoretical analysis. Recently, investigators using graph theoretical analysis showed that structural brain networks are related to intelligence and grapheme-color synesthesia (GCS). Li et al. (2009) reported that people with higher scores on intelligence tests have greater global efficiency in brain WM networks, and found that the shortest path length and global efficiency are associated with intelligence scores. In GCS, Hänggi et al. (2011) indicated

a globally significant, different structural network topology in synesthetes. Compared with nonsynesthetes, the GM networks in synesthetes have reduced small-worldness, increased clustering, increased degree, and decreased betweenness centrality. In their study, the hierarchical modularity analysis also revealed increased intramodular and intermodular connectivity of the intraparietal sulcus in GCS.

Structural brain networks in clinical population

In recent years, many investigators have shifted the focus of brain abnormalities from regional to global view on structural brain networks, to understand brain alterations by diseases, and to look for potential biomarkers for diseases.

Alzheimer's disease and mild cognitive impairment

The atrophy of GM in the medial temporal, posterior cingulate/precuneus and lateral temporo-parietal structures is associated with Alzheimer's disease (AD) (Dickerson and Sperling, 2005; Salmon et al., 2008). Neural degeneration in specific WM tracts has also been observed, including corpus callosum, posterior cingulate fasciculus, and thalamic connections (Zarei et al., 2010). In a global view, alterations of structural brain networks with morphometry-based connectivity in AD were first demonstrated by He et al. (2008); significant decreased cortical thickness intercorrelations between the bilateral parietal regions and increased intercorrelations in several cortical regions, involving the lateral temporal and parietal cortex, and the cingulate and medial frontal cortex regions, were indicated (Figure 3). Importantly, they showed that the AD GM networks have abnormal small-world architecture, with higher clustering coefficients and longer shortest path lengths compared with healthy controls, implying that they favor a regular configuration in AD networks. Since mild cognitive impairment (MCI) is often considered to be a prodromal phase of AD, Yao et al. (2010), using interregional volumetric correlations to compare the GM networks of the MCI patients, AD patients, and matched healthy controls, demonstrated that AD networks have the largest clustering coefficient and longest shortest path length in the 3 groups, and that MCI networks have intermediate characteristics. However, significant differences in these two network metrics were only found between AD and healthy controls, indicating the transitional stage in MCI. AD-related alterations in WM networks have been also studied (Lo et al., 2010), showing that the AD networks not only have the longer shortest path length and decreased global efficiency, but also reduced nodal efficiency predominantly located in the frontal regions (Figure 4). Moreover, they showed that reduced topological properties are associated with specific memory-related scores in patients. In the most recent study, the combination diffusion indices and topological patterns of WM networks have been used to classify MCI patients (Wee et al., 2011). The clustering coefficient of each node (brain region) was extracted as the features for classification with support vector machine, and the results showed that accuracy of the classification is 88.9% for detecting brain abnormalities in MCI patients. Given the alterations of topological attributes in AD and MCI patients, network metrics may be potential biomarkers for early diagnosis and therapeutic interventions of AD. With graph theoretical analysis, functional imaging studies also indicated AD-related alterations of topological patterns in functional networks (see He et al., 2009a for AD networks review).

Multiple sclerosis

The impairment of multiple sclerosis (MS) arises predominantly from impaired neuronal conduction due to WM lesions, and is also associated with morphological abnormalities in GM (Rovaris et al., 2005; Filippi et al., 2010). Using morphometric connections and graph theoretical analysis, the overall efficiency of structural brain networks was reduced with the total WM lesion loads (TWMLL), and the nodal efficiency also was found to be decreased in several brain regions such as the insula and the precentral gyrus (He et al., 2009b). In WM networks, Shu et al. (2011) indicated that the global and local efficiencies are disrupted in MS patients, and that these metrics are also associated with disease duration and TWMLL. Notably, in the collected subset of MS patients with visual deficit, the distribution of regions with reduced nodal efficiency was similar to results derived from analysis in all collected patients, but the most significantly reduced nodal efficiency was located in the left superior occipital gyrus, suggesting that the topological changes of the WM networks could be associated with specific behavior deficits in the MS patients. These two studies provide evidence for the association of the decline of information processing in structural brain networks and WM lesions for MS patients.

Schizophrenia

In the first GM network study in schizophrenia, Bassett et al. (2008) indicated that the brain GM networks of schizophrenia patients have an abnormal multimodal network organization, with reduced hierarchy, the loss of frontal and the emergence of nonfrontal hubs, and increased connection distance. In WM networks, van den Heuvel et al. (2010) indicated that the overall networks reveal no difference in their tested metrics between schizophrenia patients and healthy controls. However, the regions with increased shortest path length were found in the frontal and temporal lobes in patients, especially of bilateral inferior or superior frontal cortex and temporal pole regions. Notably, the weights of edges in their study were defined with magnetic transfer ratio and fractional anisotropy for different weighted network constructions. Zalesky et al. (2011) demonstrated that the average nodal degree and network efficiency were significantly reduced in WM networks of the patients. Moreover, this study further identified an impaired network that interconnected medial frontal regions and several regions of parietal/occipital lobes in the patients using network-based statistic analysis, which is based on the principles underpinning traditional cluster-based thresholding of statistical parametric maps (Zalesky et al., 2010a).

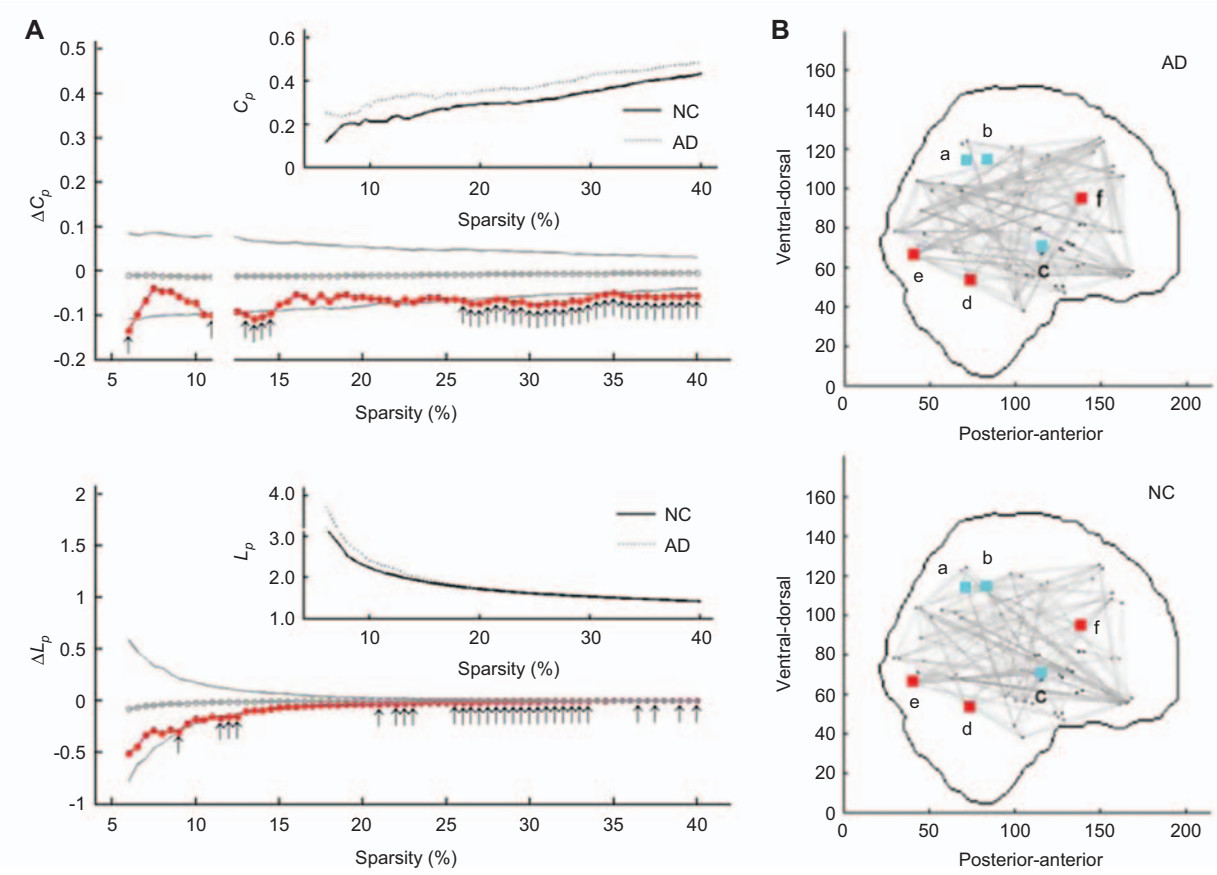

Figure 3 Topological alterations of gray matter networks in Alzheimer's disease (AD).
(A) Between-group differences in clustering coefficient (C_p) and shortest path length (L_p) as a function of sparsity. The upper graph shows the differences (red circles) in the C_p between the controls and AD patients as a function of sparsity thresholds. The gray lines represent the mean values (open circles) and 95% confidence intervals of the between-group differences obtained from 1000 permutation tests at each sparsity value. The arrows indicate a significant (p<0.05) difference in C_p between the two groups. Note that AD patients (dotted lines) show larger C_p values in the brain networks than controls (solid lines) over a wide range of thresholds (inset). The lower graph shows the differences (red circles) in the L_p between the controls and AD patients as a function of sparsity thresholds. The gray lines represent the mean values (open circles) and 95% confidence intervals of the between-group differences obtained from 1000 permutation tests at each sparsity value. The arrows indicate a significant (p<0.05) difference in L_p between the two groups. Note that AD patients (dotted lines) show larger L_p values in the brain networks than controls (solid lines) over a wide range of thresholds (inset). (B) Regions showing significant AD-related changes in betweenness were mapped to anatomical space in the control (upper panel) and AD (lower panel) groups. Regions showing AD-related decreases are colored in cyan, and regions showing AD-related increases are colored in red. Black lines represent the links of the networks. Note that these results were obtained from the brain networks with a sparsity of 13%. NC, normal controls.

Epilepsy

It has been shown that the GM networks in temporal lobe epilepsy (TLE) have increased shortest path length and clustering coefficient, altered distribution of network hubs, and higher vulnerability to targeted attacks than healthy controls (Bernhardt et al., 2011), which suggested the reorganization process in TLE. The longitudinal analysis in their work additionally demonstrated that network alterations intensify over time. Moreover, they also showed the high reproducibility of network parameters across random subsamplings, which proved their consistent findings. In a different kind of network-level analysis in TLE, Raj et al. (2010) used cortical thickness and curvature measurements to derive disease progress and constructed the brain network with the progression paths (not intercorrelation of volumetric measurements). They also proposed a new network measurement 'pickiness', which involves entropy, complexity, and exponential decay. With the network approaches for classifying a given structural MRI into normal or TLE, the classifier showed better accuracy (93%) than the non-network classifier (73%).

Others

There are some specific, important topics of using graph theoretical approaches to explore brain damage or alterations. Crofts et al. (2011) demonstrated that the WM networks

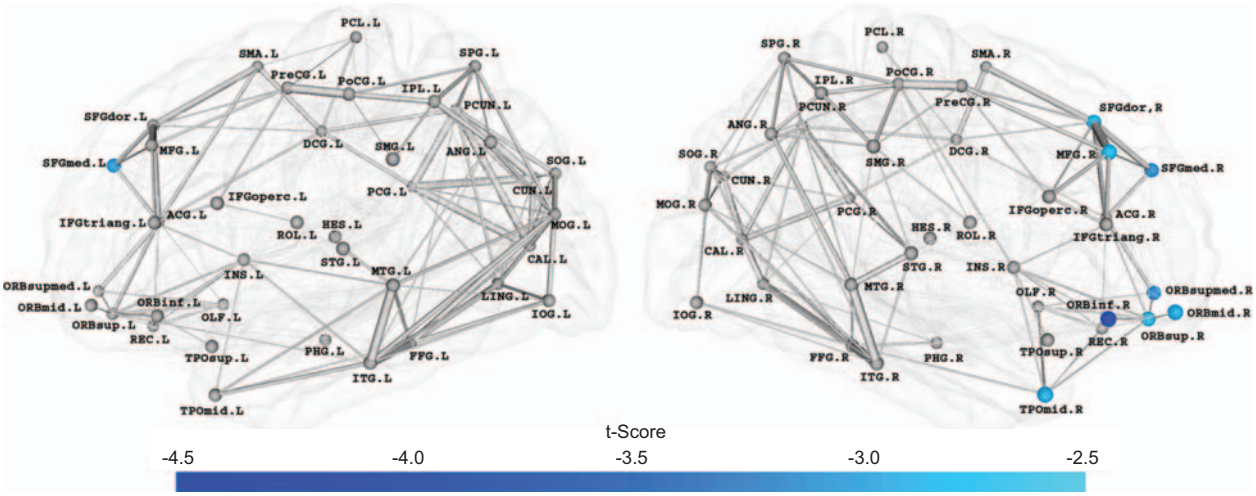

Figure 4 Regions with significant differences in nodal efficiency between Alzheimer's disease and normal controls.
The brain regions showing significant group difference in nodal efficiency are mapped onto the cortical surfaces at the lateral view. Notably, the network shown here was constructed by averaging the anatomical connection matrices of all subjects. The nodal regions are located according to their centroid stereotaxic coordinates. The edge widths represent the strengths of the connections between nodes. The statistical criterion for between-group differences was set at $p<0.05$ (false discovery rate-corrected). The color bar represents t values of group comparison after removing the effects of age and sex. For the abbreviations of the regions, see Lo et al. (2010).

in stroke patients have a reduced communicability (similar with shortest path length but involving all possible paths between regions, Estrada and Hatano, 2008) in regions surrounding the lesions in the affected hemisphere. In addition, they found that the communicability of homologous locations in the contralesional hemisphere was reduced for a subset of these regions. From blind subjects (mean age: 22 years, blinded within the first year of life) and matched healthy controls, Shu et al. (2009) showed that the WM networks of blindness have a decreased degree of connectivity, reduced global efficiency, and increased characteristic path length, especially in the visual cortex with disrupted attributes. They also indicated that motor or somatosensory functions in related regions have increased connectivity and efficiency, suggesting experience-dependent compensatory.

Methodological issues and future perspectives

Some consistent topological characteristics of structural brain networks, such as small-worldness, modular structures, and core regions, have been demonstrated by utilizing the neuroimging techniques with graph theoretical analysis. In this review, recent advances have shown the structural connectivity patterns of the human brain in normal and clinical populations such as development, aging, and neuropathology diseases, however, these are still in early stages. There are many challenging issues and further considerations for studies of human brain structural networks.

Nodes and edges are the most basic components of the structural brain network; there is a lack of a gold standard for the construction of brain networks. Various parcellation schemes, either predefined atlases or random parcellation, can be used to define the nodes for the brain network. In previous studies, different predetermined anatomical templates such as Brodmann's areas (Brodmann, 1909), AAL (Tzourio-Mazoyer et al., 2002), and ANIMAL (Collins et al., 1995) have been widely used to construct the brain networks; the random parcellation of brain regions has also been used to investigate the brain networks in different spatial scales (Table 1). Structural and functional brain networks that are constructed with different parcellation schemes, have significantly different topological properties (Wang et al., 2009; Hayasaka and Laurienti, 2010; Sanabria-Diaz et al., 2010; Zalesky et al., 2010b). Therefore, the node definition for network construction is important, since the topological organization is quite different with different parcellation schemes. On the other hand, the definition of edges for the construction of structural brain network depends on the image processing and the connectivity methods. It has been demonstrated that different definitions of edges for structural brain networks may cause the constructed networks to present different topological properties (Iturria-Medina et al., 2010; Sanabria-Diaz et al., 2010). Moreover, for weighted networks, the edge's weight, which expresses the strength of the connection between nodes, may represent different meanings with different usages. For example, the weight of the WM network for each edge may be assigned by fiber number, fiber length, or probability, which may reflect the fiber density, path distance, or chance of connectivity, respectively. These various methods are important factors in representing the properties of the brain connectivity and should be carefully selected for suitable use during network construction and further analysis.

The tests of stability and reproducibility for network metrics of the brain are also important. More systematic analyses

of brain networks in this topic are necessary, since only a few studies have identified the consistent topological features when evaluating the network metrics with multiple tests. Vaessen et al. (2010) indicated that the WM network construction exhibits high reproducibility of small-world metrics with DTI-based tractography, which is reconstructed from a different image acquisition such as the number of gradient direction and gradient strength. Bassett et al. (2011a) also showed high reproducibility and low variability of network metrics for WM networks which were constructed with DTI and DSI. The evaluations provide robust attributes of graph theoretical analysis, which may help us investigate structural brain networks for longitudinal studies.

For further consideration, an interesting question is, how do the structural brain networks relate to individual characteristics? In a twin study, Schmitt et al. (2008) showed that the associations of cortical thickness among regions are genetically mediated in the frontoparietal and occipital networks. However, no study demonstrated the relationship between topological patterns and phenotype. Li et al. (2009) found that the global efficiency of WM networks had a strong correlation with intelligence quotient. This finding has also been found in the functional brain network which was constructed with rs-fMRI (van den Heuvel et al., 2009). Moreover, in a recent fMRI study, Bassett et al. (2011b) indicated the modularity changes of functional brain network during human learning, which shows the brain reconfiguration. Accordingly, further investigations for the relationship between structural brain network organization and individual characteristics, may provide the insight into brain plasticity and flexibility. For the clinical population, the network topology may be also a characteristic that can be used for diagnosis. The network metrics have been used to classify clinical patients such as MCI patients (Wee et al., 2011) and TLE patients (Raj et al., 2010), suggesting that the potential features of diseases might be revealed by the network organization. On the other hand, combination of different neuroimaging techniques to probe the functional and structural connectivity may help us know how information processing is associated with the underlying brain structure. It has been suggested that functional connectivity may reflect the structural connections (Damoiseaux and Greicius, 2009). Hagmann et al. (2008) showed that there is a high correlation between structural connectivity and functional connectivity which were derived from DSI and rs-fMRI. Subsequently, Honey et al. (2009) indicated that the structural brain networks have similar topological features with functional network, implying a close association between structural and functional connections. This application has also been applied into a development study, which showed that the structural connectivity is highly correlated with functional connectivity, which strengthened by age (Hagmann et al., 2010). The integration of different modalities may provide a more straightforward understanding of the association of the structural and functional brain networks for the connectivity of brain organization.

To reveal the highly complex structural organization of the human brain, more methodological problems need to be solved. Individual variances or different methods of network construction may affect the network topological patterns that revealed controversial properties in previous studies. The GM network, which presents cortical thickness correlations between brain regions, may only reflect partial WM connections (Gong et al., unpublished). Since the WM network shows more directly structural connections, the combination of the GM and WM networks is consequential to study the structural connectivity of the human brain. However, to what extent can the WM network reveal the structural organization of the human brain? Previous WM network studies, that utilized streamline-tractography with DTI instead of DSI or QBI to construct WM networks, faced some general problems such as fiber crossing or fiber kissing within a voxel. The streamline-tractography is also sensitive to noise and has propagation errors, so that the resultant network is also dependent on image quality. The probabilistic tractography may reduce these effects on network constructions. Previously, the tractography of diffusion MRI has shown its ability to reconstruct the fiber bundles from animals (Lin et al., 2001, 2003) or phantoms (Fillard et al., 2011). The evaluation of the reliability of WM connectivity with animal diffusion data, such as DTI, QBI, and DSI, is also an important issue to be investigated. Moreover, the combination of graph theoretical analysis and a detailed dissection approach with an animal model may help us realize the expression of the topological properties of the brain. To account for highly individual variance across subjects, the collection and distribution of large-scale neuroimaging data for investigations of the human connectome are important and necessary. Several public neuroimaging databases such as 'Human Connectome Project' (http://www.humanconnectomeproject.org), 'Alzheimer's Disease Neuroimaging Initiative (ADNI)' (http://www.adni-info.org/), and 'Open Access Series of Imaging Studies (OASIS)' (http://www.oasis-brains.org/) have become recently available, and offer further systematical investigations of the human brain connectome in normal and clinical populations.

Conclusion

Graph theoretical analysis applied to neuroimaging data, offers a powerful way to explore the topological organization of human structural brain networks. The topological characteristics of structural brain networks, not only represent how the brain is structurally organized, but also shed light on brain flexibility, which provides novel insights into the reconfiguration of the brain in multiple domains. Focusing on structural brain networks with recent advances of neuroimaging techniques and analytical approaches, further research is needed to confirm and identify the pattern of structural connectivity of the human brain, and to investigate whether and how the brain structure network may constrain the functional integration. The accomplishments summarized in this review, show a new aspect to realize the organizational mechanisms of the brain and its interaction with functional dynamics.

References

Achard, S. and Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. PLoS Comput. Biol. *3*, e17.

Bassett, D.S. and Bullmore, E. (2006). Small-world brain networks. Neuroscientist *12*, 512–523.

Bassett, D.S. and Bullmore, E.T. (2009). Human brain networks in health and disease. Curr. Opin. Neurol. *22*, 340–347.

Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R., and Meyer-Lindenberg, A. (2008). Hierarchical organization of human cortical networks in health and schizophrenia. J. Neurosci. *28*, 9239–9248.

Bassett, D.S., Brown, J.A., Deshpande, V., Carlson, J.M., and Grafton S.T. (2011a). Conserved and variable architecture of human white matter connectivity. Neuroimage *54*, 1262–1279.

Bassett, D.S., Wymbs, N.F., Porter, M.A., Mucha, P.J., Carlson, J.M., and Grafton, S.T. (2011b). Dynamic reconfiguration of human brain networks during learning. Proc. Natl. Acad. Sci. USA *108*, 7641–7646.

Bernhardt, B.C., Chen, Z., He, Y., Evans, A.C., and Bernasconi, N. (2011). Graph-Theoretical Analysis Reveals Disrupted Small-World Organization of Cortical Thickness Correlation Networks in Temporal Lobe Epilepsy. Cereb. Cortex. doi:10.1093/cercor/bhq291.

Boccaletti, S., Latora, V., Moreno, Y., Chavez, M., and Hwang, D.U. (2006). Complex networks: structure and dynamics. Physics Reports *424*, 175–308.

Brodmann, K. (1909). Vergleichende lokalisationslehre der grobhirnrinde. Barth: Leipzig.

Bullmore, E. and Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. *10*, 186–198.

Catani, M. and Ffytche, D.H. (2005). The rises and falls of disconnection syndromes. Brain *128*, 2224–2239.

Chen, Z.J., He, Y., Rosa-Neto, P., Germann, J., and Evans, A.C. (2008). Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. Cereb. Cortex *18*, 2374–2381.

Chen, Z.J., He, Y., Rosa-Neto, P., Gong, G., and Evans, A.C. (2011). Age-related alterations in the modular organization of structural cortical network by using cortical thickness from MRI. Neuroimage *56*, 235–245.

Cheng, Y., Chou, K.H., Decety, J., Chen, I.Y., Hung, D., Tzeng, O.J., and Lin, C.P. (2009). Sex differences in the neuroanatomy of human mirror-neuron system: a voxel-based morphometric investigation. Neuroscience *158*, 713–720.

Chou, K.H., Cheng, Y., Chen, I.Y., Lin, C.P., and Chu, W.C. (2011). Sex-linked white matter microstructure of the social and analytic brain. Neuroimage *54*, 725–733.

Collins, D.L., Holmes, C.J., Peters, T.M., and Evans, A.C. (1995). Automatic 3-D model-based neuroanatomical segmentation. Hum. Brain. Mapp. *3*, 190–208.

Crofts, J.J., Higham, D.J., Bosnell, R., Jbabdi, S., Matthews, P.M., Behrens, T.E., and Johansen-Berg, H. (2011). Network analysis detects changes in the contralesional hemisphere following stroke. Neuroimage *54*, 161–169.

Damoiseaux, J.S. and Greicius, M.D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct. Funct. *213*, 525–533.

Dickerson, B.C. and Sperling, R.A. (2005). Neuroimaging biomarkers for clinical trials of disease-modifying therapies in Alzheimer's disease. NeuroRx *2*, 348–360.

Estrada, E. and Hatano, N. (2008). Communicability in complex networks. Phys. Rev. E. Stat. Nonlin. Soft Matter Phys. *77*, 036111.

Fan, Y., Shi, F., Smith, J.K., Lin, W., Gilmore, J.H., and Shen, D. (2011). Brain anatomical networks in early human brain development. Neuroimage *54*, 1862–1871.

Filippi, M., Rocca, M.A., Benedict, R.H., DeLuca, J., Geurts, J.J., Rombouts, S.A., Ron, M., and Comi, G. (2010). The contribution of MRI in assessing cognitive impairment in multiple sclerosis. Neurology *75*, 2121–2128.

Fillard, P., Descoteaux, M., Goh, A., Gouttard, S., Jeurissen, B., Malcolm, J., Ramirez-Manzanares, A., Reisert, M., Sakaie, K., Tensaouti, F., et al. (2011). Quantitative evaluation of 10 tractography algorithms on a realistic diffusion MR phantom. Neuroimage *56*, 220–234.

Fortunato, S. (2010). Community detection in graphs. Physics Reports *486*, 75–174.

Freeman, L.C. (1977). A set of measures of centrality based on betweenness. Sociometry *40*, 35–41.

Gong, G., Rosa-Neto, P., Carbonell, F., Chen, Z.J., He, Y., and Evans, A.C. (2009a). Age- and gender-related differences in the cortical anatomical network. J. Neurosci. *29*, 15684–15693.

Gong, G., He, Y., Concha, L., Lebel, C., Gross, D.W., Evans, A.C., and Beaulieu, C. (2009b). Mapping anatomical connectivity patterns of human cerebral cortex using *in vivo* diffusion tensor imaging tractography. Cereb Cortex *19*, 524–536.

Hagmann, P., Kurant, M., Gigandet, X., Thiran, P., Wedeen, V.J., Meuli, R., Thiran, J.-P., and Sporns, O. (2007). Mapping human whole-brain structural networks with diffusion MRI. PLoS ONE *2*, e597.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., and Friston, K.J. (2008). Mapping the structural core of human cerebral cortex. PLoS Biol. *6*, e159.

Hagmann, P., Sporns, O., Madan, N., Cammoun, L., Pienaar, R., Wedeen, V.J., Meuli, R., Thiran, J.-P., and Grant, P.E. (2010). White matter maturation reshapes structural connectivity in the late developing human brain. Proc. Natl. Acad. Sci. USA *107*, 19067–19072.

Hänggi, J., Wotruba, D., and Jancke, L. (2011). Globally altered structural brain network topology in grapheme-color synesthesia. J. Neurosci. *31*, 5816–5828.

Hayasaka, S. and Laurienti, P.J. (2010). Comparison of characteristics between region-and voxel-based network analyses in resting-state fMRI data. Neuroimage *50*, 499–508.

He, Y. and Evans, A. (2010). Graph theoretical modeling of brain connectivity. Curr. Opin. Neurol. *23*, 341–350.

He, Y., Chen, Z.J., and Evans, A.C. (2007). Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. Cereb. Cortex *17*, 2407–2419.

He, Y., Chen, Z., and Evans, A. (2008). Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease. J. Neurosci. *28*, 4756–4766.

He, Y., Chen, Z., Gong, G., and Evans, A. (2009a). Neuronal networks in Alzheimer's disease. Neuroscientist *15*, 333–350.

He, Y., Dagher, A., Chen, Z., Charil, A., Zijdenbos, A., Worsley, K., and Evans, A. (2009b). Impaired small-world efficiency in structural cortical networks in multiple sclerosis associated with white matter lesion load. Brain *132*, 3366–3379.

Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., and Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl. Acad. Sci. USA *106*, 2035–2040.

Iturria-Medina, Y., Canales-Rodríguez, E.J., Melie-García, L., Valdés-Hernández, P.A., Martínez-Montes, E., Alemán-Gómez,

Y., and Sánchez-Bornot, J.M. (2007). Characterizing brain anatomical connections using diffusion weighted MRI and graph theory. Neuroimage *36*, 645–660.

Iturria-Medina, Y., Fernández, A.P., Morris, D.M., Canales-Rodríguez, E.J., Haroon, H.A., Pentón, L.G., Augath, M., García, L.G., Logothetis, N., Parker, G.J.M., et al. (2010). Brain hemispheric structural efficiency and interconnectivity rightward asymmetry in human and nonhuman primates. Cereb. Cortex *21*, 56–67.

Kansaku, K., Yamaura, A., and Kitazawa, S. (2000). Sex differences in lateralization revealed in the posterior language areas. Cereb. Cortex *10*, 866–872.

Latora, V. and Marchiori, M. (2001). Efficient behavior of small-world networks. Phys. Rev. Lett. *87*, 198701.

Latora, V. and Marchiori, M. (2003). Economic small-world behavior in weighted networks. Eur. Phys. J. B. Condensed Matter Complex Syst. *32*, 249–263.

Lerch, J.P., Worsley, K., Shaw, W.P., Greenstein, D.K., Lenroot, R.K., Giedd, J., and Evans, A.C. (2006). Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. Neuroimage *31*, 993–1003.

Li, Y., Liu, Y., Li, J., Qin, W., Li, K., Yu, C., and Jiang, T. (2009). Brain anatomical network and intelligence. PLoS Comput Biol *5*, e1000395.

Lin, C.P., Tseng, W.Y., Cheng, H.C., and Chen, J.H. (2001). Validation of diffusion tensor magnetic resonance axonal fiber imaging with registered manganese-enhanced optic tracts. Neuroimage *14*, 1035–1047.

Lin, C.P., Wedeen, V.J., Chen, J.H., Yao, C., and Tseng, W.Y. (2003). Validation of diffusion spectrum magnetic resonance imaging with manganese-enhanced rat optic tracts and *ex vivo* phantoms. Neuroimage *19*, 482–495.

Lo, C.-Y., Wang, P.-N., Chou, K.-H., Wang, J., He, Y., and Lin, C.-P. (2010). Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. J. Neurosci. *30*, 16876–16885.

Lv, B., Li, J., He, H., Li, M., Zhao, M., Ai, L., Yan, F., Xian, J., and Wang, Z. (2010). Gender consistency and difference in healthy adults revealed by cortical thickness. Neuroimage *53*, 373–382.

Meunier, D., Lambiotte, R., and Bullmore, E.T. (2010). Modular and hierarchically modular organization of brain networks. Front Neurosci. *4*, 200.

Mori, S. and van Zijl, P.C. (2002). Fiber tracking: principles and strategies – a technical review. NMR Biomed. *15*, 468–480.

Newman, M.E. and Girvan, M. (2004). Finding and evaluating community structure in networks. Phys. Rev. E. Stat. Nonlin. Soft Matter Phys. *69*, 026113.

Newman, M.E.J. (2006). Modularity and community structure in networks. Proc. Natl. Acad. Sci. USA *103*, 8577–8582.

Petrella, J.R. (2011). Use of graph theory to evaluate brain networks: a clinical tool for a small world? Radiology *259*, 317–320.

Power, J.D., Fair, D.A., Schlaggar, B.L., and Petersen, S.E. (2010). The development of human functional brain networks. Neuron *67*, 735–748.

Raj, A., Mueller, S.G., Young, K., Laxer, K.D., and Weiner, M. (2010). Network-level analysis of cortical thickness of the epileptic brain. Neuroimage *52*, 1302–1313.

Rovaris, M., Gass, A., Bammer, R., Hickman, S.J., Ciccarelli, O., Miller, D.H., and Filippi, M. (2005). Diffusion MRI in multiple sclerosis. Neurology *65*, 1526–1532.

Salmon, E., Lekeu, F., Bastin, C., Garraux, G., and Collette, F. (2008). Functional imaging of cognition in Alzheimer's disease using positron emission tomography. Neuropsychologia *46*, 1613–1623.

Sanabria-Diaz, G., Melie-Garcia, L., Iturria-Medina, Y., Aleman-Gomez, Y., Hernandez-Gonzalez, G., Valdes-Urrutia, L., Galan, L., and Valdes-Sosa, P. (2010). Surface area and cortical thickness descriptors reveal different attributes of the structural human brain networks. Neuroimage *50*, 1497–1510.

Schmitt, J.E., Lenroot, R.K., Wallace, G.L., Ordaz, S., Taylor, K.N., Kabani, N., Greenstein, D., Lerch, J.P., Kendler, K.S., Neale, M.C., et al. (2008). Identification of genetically mediated cortical networks: a multivariate study of pediatric twins and siblings. Cereb. Cortex *18*, 1737–1747.

Shu, N., Liu, Y., Li, J., Li, Y., Yu, C., and Jiang, T. (2009). Altered anatomical network in early blindness revealed by diffusion tensor tractography. PLoS One *4*, e7228.

Shu, N., Liu, Y., Li, K., Duan, Y., Wang, J., Yu, C., Dong, H., Ye, J., and He, Y. (2011). Diffusion tensor tractography reveals disrupted topological efficiency in white matter structural networks in multiple sclerosis. Cereb. Cortex. doi, 10.1093/cercor/bhr039.

Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., Xu, D., Zhu, H., Thompson, P.M., and Toga, A.W. (2007). Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb. Cortex *17*, 1550–1560.

Sporns, O. (2011). The human connectome: a complex network. Ann. NY Acad. Sci. *1224*, 109–125.

Sporns, O., Tononi G., and Kötter, R. (2005). The human connectome: a structural description of the human brain. PLoS Comput. Biol. *1*, e42.

Stam, C.J. (2010). Characterization of anatomical and functional connectivity in the brain: a complex networks perspective. Int. J. Psychophysiol. *77*, 186–194.

Strogatz, S.H. (2001). Exploring complex networks. Nature *410*, 268–276.

Tian, L., Wang, J., Yan, C., and He, Y. (2011). Hemisphere- and gender-related differences in small-world brain networks: a resting-state functional MRI study. Neuroimage *54*, 191–202.

Toga, A.W. and Thompson, P.M. (2003). Mapping brain asymmetry. Nat. Rev. Neurosci. *4*, 37–48.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage *15*, 273–289.

Vaessen, M.J., Hofman, P.A.M., Tijssen, H.N., Aldenkamp, A.P., Jansen, J.F.A., and Backes, W.H. (2010). The effect and reproducibility of different clinical DTI gradient sets on small world brain connectivity measures. Neuroimage *51*, 1106–1116.

van den Heuvel, M.P., Stam, C.J., Kahn, R.S., and Hulshoff Pol, H.E. (2009). Efficiency of functional brain networks and intellectual performance. J. Neurosci. *29*, 7619–7624.

van den Heuvel, M.P., Mandl, R.C.W., Stam, C.J., Kahn, R.S., and Hulshoff Pol, H.E. (2010). Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. J. Neurosci. *30*, 15915–15926.

Wang, J., Wang, L., Zang, Y., Yang, H., Tang, H., Gong, Q., Chen, Z., Zhu, C., and He, Y. (2009). Parcellation-dependent small-world brain functional networks: a resting-state fMRI study. Hum. Brain Mapp. *30*, 1511–1523.

Wang, J., Zuo, X., and He, Y. (2010). Graph-based network analysis of resting-state functional MRI. Front Syst. Neurosci. *4*, 16.

Watts, D.J. and Strogatz, S.H. (1998). Collective dynamics of'small-world' networks. Nature *393*, 440–442.

Wee, C.-Y., Yap, P.-T., Li, W., Denny, K., Browndyke, J.N., Potter, G.G., Welsh-Bohmer, K.A., Wang, L., and Shen, D. (2011). Enriched white matter connectivity networks for accurate identification of MCI patients. Neuroimage *54*, 1812–1822.

Wen, W., He, Y., and Sachdev, P. (2011a). Structural brain networks and neuropsychiatric disorders. Curr. Opin. Psychiatry 2*4*, 219–225.

Wen, W., Zhu, W., He, Y., Kochan, N.A., Reppermund, S., Slavin, M.J., Brodaty, H., Crawford, J., Xia, A., and Sachdev, P. (2011b). Discrete neuroanatomical networks are associated with specific cognitive abilities in old age. J. Neurosci. *31*, 1204–1212.

Wu, K., Taki, Y., Sato, K., Kinomura, S., Goto, R., Okada, K., Kawashima, R., He, Y., Evans, A.C., and Fukuda, H. (2011). Age-related changes in topological organization of structural brain networks in healthy individuals. Hum. Brain Mapp. doi: 10.1002/hbm.21232.

Yan, C., Gong, G., Wang, J., Wang, D., Liu, D., Zhu, C., Chen, Z.J., Evans, A., Zang, Y., and He, Y. (2010). Sex- and brain size-related small-world structural cortical networks in young adults: a DTI tractography study. Cereb. Cortex.

Yao, Z., Zhang, Y., Lin, L., Zhou, Y., Xu, C., and Jiang, T. Initiative AsDN (2010). Abnormal cortical networks in mild cognitive impairment and Alzheimer's disease. PLoS Comput. Biol. *6*, e1001006.

Zalesky, A., Fornito, A., and Bullmore, E.T. (2010a). Network-based statistic: identifying differences in brain networks. Neuroimage *53*, 1197–1207.

Zalesky, A., Fornito, A., Harding, I.H., Cocchi, L., Yücel, M., Pantelis, C., and Bullmore, E.T. (2010b). Whole-brain anatomical networks: does the choice of nodes matter? Neuroimage *50*, 970–983.

Zalesky, A., Fornito, A., Seal, M.L., Cocchi, L., Westin, C.-F., Bullmore, E.T., Egan, G.F., and Pantelis, C. (2011). Disrupted axonal fiber connectivity in schizophrenia. Biol. Psychiatry *69*, 80–89.

Zarei, M., Patenaude, B., Damoiseaux, J., Morgese, C., Smith, S., Matthews, P.M., Barkhof, F., Rombouts, S.A., Sanz-Arigita, E., and E., Jenkinson, M. (2010). Combining shape and connectivity analysis: an MRI study of thalamic degeneration in Alzheimer's disease. Neuroimage *49*, 1–8.

Zhu, W., Wen, W., He, Y., Xia, A., Anstey, K.J., and Sachdev, P. (2010). Changing topological patterns in normal aging using large-scale structural networks. Neurobiol. Aging. doi: 10.1016/j.neurobiolaging.2010.06.022.

Recevied May 23, 2011; accepted July 5, 2011; previously published online August 24, 2011

Chun-Yi Zac Lo is a PhD candidate at the Department of Medical Imaging and Radiological Sciences, National Yang-Ming University, Taiwan. He obtained his bachelor's and master's degrees in Biomedical Engineering from Chung Yuan Christian University, Taiwan, in 2005 and 2007. He has worked on medical image processing since 2003. As a key member in the Brain Connectivity Lab, his current research focuses on the diffusion MRI based white matter tractography and the applications of human brain connectome.

Dr. Yong He obtained his PhD in pattern recognition from the Chinese Academy Sciences in 2005 and was a postdoctoral research fellow in neuroimaging and brain connectivity between 2005 and 2007 at the Montreal Neurological Institute, McGill University. Since January 2008, he is an Investigator at the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University. His research interests are in the methodology and applications of human brain connectome using structural MRI, diffusion MRI and resting-state fMRI. He has served on the organizing, reviewing and program committees of several international conferences (OHBM, MICCAI and MIAR). He is currently an editor of Brain Connectivity and PLoS ONE. To date, he has authored or co-authored 60 peer-reviewed journal articles.

Dr. Ching-Po Lin obtained his PhD in diffusion MRI technique from the Department. of Electrical-Engineering, National Taiwan University (NTU) in 2002 and was a postdoctoral research fellow for neuroimaging and related applications between 2002 and 2004 at NTU-EE and NTU-Hospital. Since February 2004 and 2009, he has been an assistant professor and an associate professor, respectively, at the Institute of Neuroscience, National Yang-Ming University. Has set up a Brain Connectivity Lab, dedicated to the methodology of diffusion MRI and the applications to neuroscience and neuropsychiatric disorders. He has served on the program committee of Organization for Human Brain Mapping between 2010 and 2011. He is currently an associate editor of Brain Connectivity. To date, he has authored or co-authored 50 peer-reviewed journal articles.