Neuroscience and Biobehavioral Reviews 77 (2017) 286–300

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Small-world human brain networks: Perspectives and challenges

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ARTICLE INFO

Keywords:
Brain modelling
Connectome
Graph theory
Modularity
Small-world

ABSTRACT

Modelling the human brain as a complex network has provided a powerful mathematical framework to characterize the structural and functional architectures of the brain. In the past decade, the combination of non-invasive neuroimaging techniques and graph theoretical approaches enable us to map human structural and functional connectivity patterns (i.e., connectome) at the macroscopic level. One of the most influential findings is that human brain networks exhibit prominent small-world organization. Such a network architecture in the human brain facilitates efficient information segregation and integration at low wiring and energy costs, which presumably results from natural selection under the pressure of a cost-efficiency balance. Moreover, the small-world organization undergoes continuous changes during normal development and ageing and exhibits dramatic alterations in neurological and psychiatric disorders. In this review, we survey recent advances regarding the small-world architecture in human brain networks and highlight the potential implications and applications in multidisciplinary fields, including cognitive neuroscience, medicine and engineering. Finally, we highlight several challenging issues and areas for future research in this rapidly growing field.

1. Introduction

The human brain is a formidably complex system, in which approximately 86 billion neurons (Azevedo et al., 2009) interact through approximately 150 trillion synapses (Pakkenberg et al., 2003). Explaining the emergent coherent brain function unfolding on complicated structural pathways is a great challenge for neuroscientists. Recently, there has been an explosion of studies modelling the brain as complex networks that consist of neural units (e.g., neurons and brain regions) linked by structural connectivity (i.e., structural wiring) or functional connectivity (i.e., coherent temporal activities) (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009, 2012; Craddock et al., 2013; He and Evans, 2010; Park and Friston, 2013; Reijneveld et al., 2007). The characterization of the human brain from a network perspective provides a comprehensive understanding of the structural and functional architectures of the human brain. Mapping and quantifying the connectivity patterns of the human brain (i.e., the human connectome) have become important topics in the field of neuroscience (Kelly et al., 2012; Sporns et al., 2005; Van Essen et al., 2012).

To date, significant progress has been made in neuroimaging technologies, such as electroencephalography (EEG), magnetoencephalography (MEG) and multi-modal magnetic resonance imaging (e.g., structural MRI, diffusion MRI and functional MRI), which enable non-invasive mapping of the human connectome. Graph theory-based network analysis helps demonstrate the intrinsic topological organization of human brain networks, such as small-worldness, modular organization and highly connected or centralized hubs (Bullmore and Sporns, 2009, 2012; He and Evans, 2010; Kaiser, 2011; Meunier et al., 2010; van den Heuvel and Sporns, 2013b). The small-world model is of special interest when describing human brain networks, because it supports efficient information segregation and integration with low energy and wiring costs, and it is well suited for complex brain dynamics (e.g., a high rate of information transmission) (Watts and Strogatz, 1998). Recent studies indicate that the small-world topological organization of brain networks undergoes changes during development and ageing (Cao et al., 2016b; Collin and van den Heuvel, 2013; Gao et al., 2016), as well as in the case of brain disorders (Dai and He, 2014; Filippi et al., 2013; Fornito and Bullmore, 2015; Fornito et al., 2012b; Gong and He, 2015; Stam, 2014; Xia and He, 2011), and that these changes provide novel insights into the biological mechanisms in health and disease. Moreover, advances in small-world brain models

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http://dx.doi.org/10.1016/j.neubiorev.2017.03.018
Received 7 December 2016; Received in revised form 19 January 2017; Accepted 31 March 2017
Available online 05 April 2017

may spur innovations in engineering, thereby enabling the design of more-efficient and more-powerful chips, computers and other devices than what existed previously (Bassett et al., 2010; Eliasmith et al., 2012; Furber, 2016; Machens, 2012; Merolla et al., 2014; Rueckert, 2016).

This review primarily focuses on the recent advances in small-world human brain networks, through the utility of non-invasive neuroimaging data and graph theory-based network analysis. The remaining sections are organized as follows. Section 2 provides background on human brain network analyses and the small-world model, including the construction of brain networks and graph theoretical approaches. Section 3 summarizes recent small-world human brain network studies using empirical or theoretical approaches. Sections 4–6 discuss the potential implications and applications in multidisciplinary science, such as cognitive neuroscience, medicine and engineering. Finally, Section 7 highlights challenging issues and areas for future research in this rapidly growing field.

2. Background

2.1. Brain network construction

Diverse biological, technological and social systems can be modelled as networks, which consist of a set of nodes that represent the constituent units of the system, and edges that denote the interactions between nodes (Barabási, 2011; Boccaletti et al., 2006). For example, in the World Wide Web, the nodes may be webpages, whilst the edges may be the hyperlinks between them. In brain networks, the nodes can be neurons, neuronal populations or brain regions, depending on the spatial scales of interest, and the edges represent the structural or functional connectivity that links the nodes. To date, most in vivo human brain network studies have primarily focused on the large-scale networks of brain regions, which can be constructed as follows (Fig. 1):

(1) Node definition. Nodes can be defined in various ways according to the neuroimaging data considered (Fig. 1a), such as EEG electrodes, MEG sensors or reconstructed brain sources of EEG/MEG signals using biophysical models (Lopes da Silva, 2004). In MRI studies, regions of interest may be defined according to anatomical landmarks (Tzourio-Mazoyer et al., 2002), functional significances (Dosenbach et al., 2010; Power et al., 2011), connectivity profiles (Cohen et al., 2008; Craddock et al., 2012; Fan et al., 2016), multi-modal parcellation (Glasser et al., 2016) and random parcellation (Zalesky et al., 2010), as well as a single imaging voxel with a high spatial resolution (~millimetres) (Hayasaka and Laurienti, 2010; Liang et al., 2013; Liao et al., 2013; Valencia et al., 2009) (Fig. 1b) . In most cases, brain networks involve tens to hundreds of nodes, with the exception of voxel-wise brain networks that comprise at least thousands of nodes (i.e., voxels). Notably, it is still an open question regarding how to choose the most appropriate node definition while addressing a specific scientific question (Bullmore and Bassett, 2011; Kaiser, 2011; Rubinov and Sporns, 2010; Sporns, 2014). In general, structurally constrained schemes are preferred used in structural network studies, whereas functional defined schemes are preferred in functional network studies. When exploring the structure–function relationship, the parcellations obtained through multi-modal neuroimaging data or randomized parcellations may serve as appropriate candidates. Besides, cross-validation using different parcellations is encouraged to address whether the findings are not driven by a specific brain parcellation.

(2) Edge definition. The structural and functional connectivity of the human brain may be inferred through in vivo neuroimaging techniques (Fig. 1c). In general, structural connectivity refers to the anatomical pathways between brain regions, which form a biological route for information transfer and communication. Specifically, by using diffusion MRI to measure the anisotropic diffusion of water molecules in brain tissues, structural connectivity may be inferred as the interregional white matter fibre tracts reconstructed through deterministic or probabilistic tractography methods (Behrens et al., 2003; Mori et al., 1999; Parker et al., 2003). Additionally, structural connectivity can also be defined as the structural covariance inferred from the across-individual covariation of regional morphological measurements (e.g.,

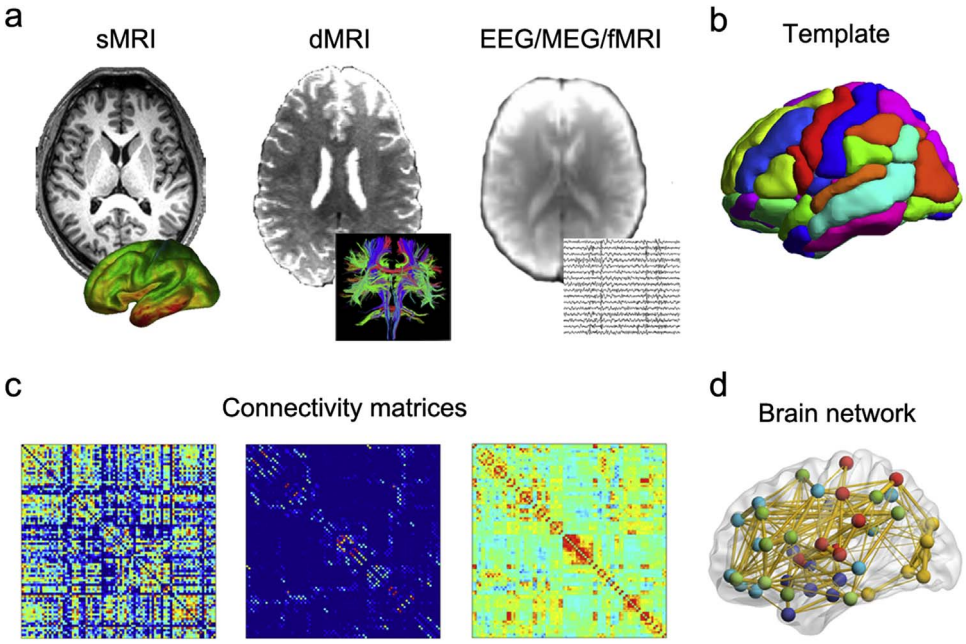

Fig. 1. Illustration of brain network construction. (a) Multi-modal neuroimaging data used for the estimation of structural and functional connectivity, including structural MRI (left), diffusion MRI (middle) and EEG, MEG and functional MRI data (right). sMRI, structural MRI; dMRI, diffusion MRI; fMRI, functional MRI; EEG, electroencephalography; MEG, magnetoencephalography. (b) Brain template used for the node definition. The brain nodes can be defined in a variety of ways, such as EEG electrodes, MEG sensors, anatomical and/or functional information-based divisions, random divisions and imaging voxels. (c) Structural and functional connectivity matrices representing the relationship between each pair of nodes. The structural connectivity can be inferred as across-individual covariation in regional morphological measures observed by structural MRI (left) or white matter fibre tracts reconstructed from diffusion MRI (middle). The functional connectivity between two nodes is estimated as the statistical coherence between the nodal time courses observed by EEG, MEG or functional MRI (right). (d) Visualization of the human brain network using the BrainNet Viewer package (Xia et al., 2013).

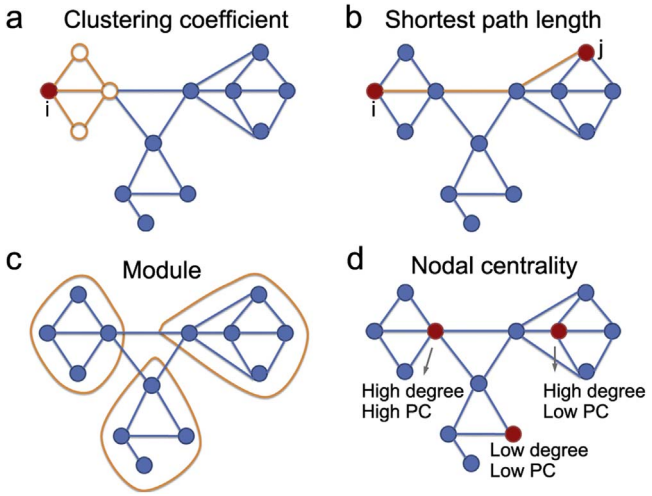

Fig. 2. Summary of small-world related metrics. (a) The clustering coefficient of a node reflects the closeness of the connections between its neighbouring nodes. The clustering coefficient of a network equals the average clustering coefficient across all the nodes in the network. (b) The shortest path length between two nodes denotes the number of edges that must be transferred from one node to another. The characteristic path length of a network is defined as the average shortest path lengths across all possible pairs of nodes in the network. (c) Modules in a network refer to a group of nodes with dense intra-group connections and sparse between-group connections. Each module is indicated by a yellow circle. (d) Nodal centrality measures. Nodal degree denotes the number of edges directly attached to a node. "High degree" and "Low degree" indicate a node with many or few connections, respectively. Nodal participation coefficient (PC) indicates the distribution of its connections among different modules. "High PC" and "Low PC" indicate that the node tends to connect the nodes in different or the same modules, respectively.

cortical thickness or grey matter volume) measured from structural MRI (Alexander-Bloch et al., 2013; Evans, 2013; He et al., 2007; Lerch et al., 2006). The structural covariance between two nodes is defined based on statistical similarity; thus, it may exist between region pairs in the absence of direct axonal connectivity. Functional connectivity is typically defined as the interregional statistical coherence, such as the synchronization likelihood or Pearson's correlation, between time series recorded by EEG, MEG or functional MRI (fMRI) (Friston, 1994). Compared with fMRI, electrophysiological recordings of EEG and MEG can obtain brain activities at a higher temporal resolution (~100 Hz) at the expense of spatial resolution. Most often, functional connectivity is estimated when the subject is at rest in the absence of specific cognitive demands, which is thought to reflect the intrinsic functional organization of the brain (Biswal et al., 1995; Fox and Raichle, 2007). Recently, there is growing interest in understanding the brain's functional connectivity patterns and topological reorganization by building graph models of brain networks during task performance (Medaglia et al., 2015; Sporns, 2014; Liang et al., 2016).

Once structural or functional connectivity among nodes are obtained, we usually employ a threshold to exclude weak or spurious connections potentially induced by noisy signals, and subsequently construct a binary or weighted brain network (Fig. 1d). The connection density of a network is defined as the number of existing edges in the network normalized by the maximal possible number of edges, which reflects the wiring cost of the network. The other topological properties of brain networks (see Section 2.2) can be quantitatively characterized by graph theoretical approaches.

2.2. Graph theoretical approaches

Graph theory is an old branch of mathematics concerning the pairwise relationship between objects. It can be traced back to the Leonhard Euler's solution to the Königsberg Bridge Problem in 1736 (Euler, 1736). In this context, a graph is a set of vertices or nodes connected by links, arcs or edges. In the middle of the nineteenth century, graph theory underwent further developments with the analysis of electrical circuits and chemical isomers. Today, graph theory has been used to quantify complex relations in diverse fields, such as genetic and neuronal networks in biology, electrical power grids in infrastructure, the Internet in communication, integrated circuits in computer science and collaborations in social interaction (Boccaletti et al., 2006; Schweitzer et al., 2009; Watts and Strogatz, 1998). It is useful for solving many types of practical problems. For example, graph theory can be used to design very large-scaled integrated computer circuits to achieve an optimized balance between the wiring costs and communication efficiency among processing elements (Bassett et al., 2010; Landman and Russo, 1971; Stroobandt, 1999).

Using graph theory, a network with *N* nodes can be represented by an *N-by-N* adjacency matrix, in which the nonzero elements reflect the presence or strength of an edge between two nodes. A graph may be categorized as directed or undirected, depending on whether the edges between nodes contain directional information (e.g., causal interaction). A graph can also be classified as weighted or binary, depending on whether the edges between nodes are assigned different strengths. For example, in weighted white matter structural networks, interregional connectivity derived from diffusion MRI may be weighted according to different information, such as fibre length, fibre number, fractional anisotropy or connectivity probability (Fornito et al., 2013; Zhong et al., 2015). Since the landmark concept in the "Human Connectome" (Sporns et al., 2005), studies of complex human brain networks using a graph theoretical approach have undergone explosive growth. To date, most human brain network studies have focused on undirected networks due to the technical and methodological limitations in direction inference. Once we have established an adjacency matrix of a brain network, we can assess the topological properties of the network using the metrics developed in graph theory. Here, we briefly introduce several small-world related metrics (Fig. 2), the details of which can be found in Boccaletti et al. (2006), Rubinov and Sporns (2010) and Watts and Strogatz (1998).

(*1) Small-world Measures*: Watts and Strogatz (1998) pointed out that many biological, social and technical networks are neither completely random nor completely regular, instead showing a "small-world" architecture with a distinctive combination of high clustering coefficient and short characteristic path length.

The clustering coefficient measures the tendency to which the neighbouring nodes of a node are interconnected, reflecting the extent of local cliquishness. The clustering coefficient of a node can be defined in many ways (Boccaletti et al., 2006; Bolanos et al., 2013; Rubinov and Sporns, 2010) and in binary, undirected networks it is often defined as the ratio of the number of existing edges between its neighbouring nodes to the maximal possible number of edges between them (Fig. 2a). The clustering coefficient of a network equals the average clustering coefficients across all nodes in the network. The characteristic path length of a network is defined as the average shortest path lengths across all possible pairs of nodes in the network, which reflects the capability for global information integration. The shortest path length, namely, the distance, between two nodes in a binary network is defined as the minimal number of edges that must be transferred from one node to another (Fig. 2b). Notably, the definition of clustering coefficient and shortest path length can be extended to weighted networks (Boccaletti et al., 2006; Rubinov and Sporns, 2010).

Based on these two measures, a network can be classified as regular (high local clustering and long path length), random (low local clustering and short path length) or small-world (high local clustering and short path length) lying somewhere between regular and random networks (Fig. 3). To diagnose the small-worldness of a real network, a commonly used method is to compare the clustering coefficient and characteristic path length in the real network with those in matched random networks (Maslov and Sneppen, 2002; Zalesky et al., 2012). A small-world network can be quantified with a higher clustering coefficient (i.e., normalized version > 1) and a comparable character-

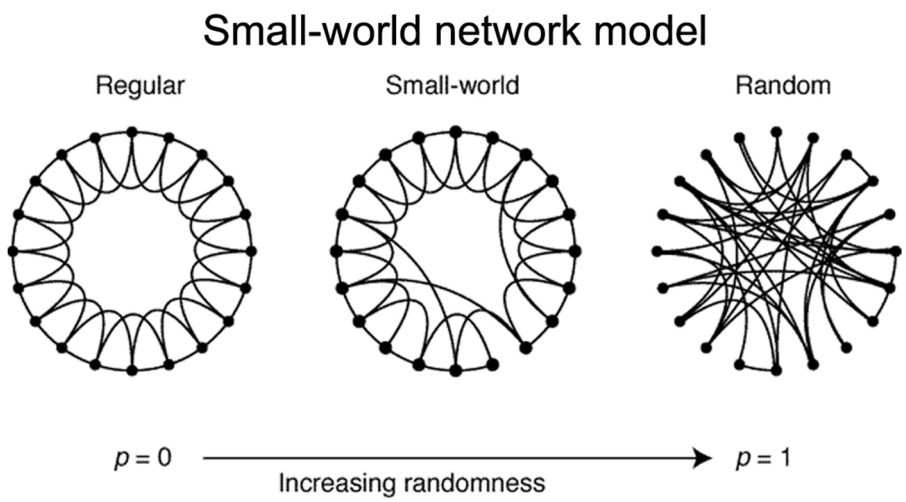

Fig. 3. Small-world network model. A regular network (left) with regular connections exhibits a high clustering coefficient and a long characteristic path length. In contrast, a random network (right) with random connections exhibits a low clustering coefficient and a short characteristic path length. A small-world network (middle) exhibits an intermediate property between regular (left) and random (right) networks, in which a large number of short-range connections coexist with a few long-range connections. Thus, the small-world network exhibits a high clustering coefficient and a short characteristic path length.
Source: Reproduced from Watts and Strogatz (1998).

istic path length (i.e., normalized version ~1), leading to a small-worldness index larger than one (Humphries and Gurney, 2008; Humphries et al., 2006). From the aspect of information transmission, a high clustering coefficient indicates high efficiency for local information transfer, and a shorter path length indicates higher efficiency in global information transmission. Thus, a small-world network exhibits high local efficiency and global efficiency in information communication, accompanied with low wiring costs (i.e., sparse connections) (Latora and Marchiori, 2001), which provides a concrete conception of the 'economic small-world'.

Notably, in the past decade the quantification of small-world properties in complex networks have been improved in various aspects, including defining a new small-worldness index through separately comparing network clustering to matched regular lattices and path length to matched random networks (Telesford et al., 2011), developing new clustering coefficients and path lengths for weighted graphs (Bolanos et al., 2013; Rubinov and Sporns, 2010) and establishing a novel metric called small-world propensity accounting for variations in network density and connection strengths (Muldoon et al., 2016). Incorporating these newly developed metrics into future brain network studies could further extend and/or revise the previous knowledge regarding small-world brain network findings.

(2) Modularity and Hub: From the view of mathematics, a small-world network needs not be modular and a modular organization needs not be small-world. However, when considering the infrastructure in the real brain network, researchers have demonstrated that the small-world topology is usually accompanied by the presence of a modular structure and hub nodes (Bullmore and Sporns, 2009; He and Evans, 2010; Meunier et al., 2010; Sporns, 2013; van den Heuvel and Sporns, 2013b). These well-organized structures ensure the optimal balance of information segregation and integration, and support the small-world configuration of the brain network.

Modules (also referred to as communities) in a network denote groups of nodes that possess dense intra-group connections and sparse inter-group connections (Fig. 2c). The dense intra-module connections increase the local clustering and thus facilitate information specialization within the specific module, while the sparse inter-module connections serve as shortcuts to reduce the characteristic path length of the network and enhance the global information integration. Therefore, a modularly organized system generally exhibits a small-world organization, but the converse is not always true. Currently, numerous algorithms have been established to detect modular organization (i.e., modules, communities or clusters) in brain networks (Fortunato, 2010; Meunier et al., 2010; Newman, 2004; Sporns and Betzel, 2016). Most often, the modular partition of a network is probed by optimizing the modularity index, which characterizes the difference between the actual number of intra-module connections and the expected number by chance (Sporns and Betzel, 2016).

Hub nodes are identified as nodes with a high nodal centrality, which indicates the importance of the nodes in the network. The nodal degree, k, is the simplest and best-known measure of nodal centrality, and denotes the number of edges directly attached to a node (Fig. 2d). The degree distribution $P(k)$ of a network indicates the proportion of nodes that have a degree k. For example, a scale-free network has a power-law degree distribution, which allows the presence of several nodes possessing a disproportionately high degree (Barabasi and Albert, 1999). A rich club architecture is formed if the highly-connected hub nodes exhibit dense inter-connectivity, which enables efficient and robust information signalling in the network (van den Heuvel et al., 2012). Moreover, the nodal centrality can be quantified via other aspects, such as nodal efficiency, betweenness and eigenvector (Boccaletti et al., 2006; Liang et al., 2013; Rubinov and Sporns, 2010; Zuo et al., 2012).

In brain networks, modules typically refer to anatomically connected or functionally related regions, and hub nodes are typically defined as highly centralized regions. Given a module partition, the hub nodes may be further classified as either connector hubs or provincial hubs according to the participation coefficient, which indicates their connecting patterns across modules (Guimera et al., 2005; He et al., 2009; Power et al., 2013). Connector hubs with a high participation coefficient tend to distribute their edges in different modules, whereas provincial hubs with a low participation coefficient primarily connect nodes in the same module.

3. Small-world human brain networks

3.1. Small-world topology of human brain networks

The small-world architecture is robustly demonstrated in large-scale human brain structural networks regardless of the imaging modalities (Fig. 4, top and middle). Using structural MRI, the small-world property was first identified in the population-level structural covariance network of young healthy adults, based on the interregional covariation in the cortical thickness (He et al., 2007) and other morphological

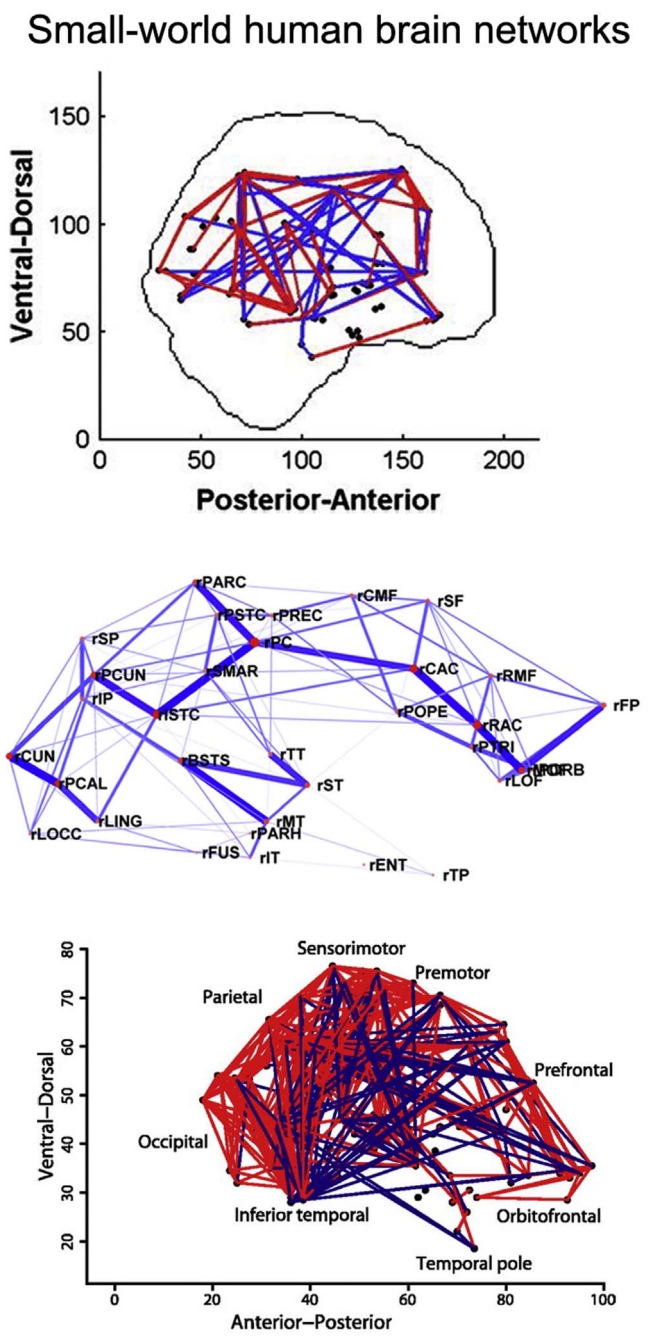

Fig. 4. Small-world human brain networks of healthy adults, including the structural covariance network (top), the white matter structural network (middle) and the functional network (bottom). Nodes are placed in order according to their anatomical positions in the brain. In the top and bottom panels, red and blue connections denote short-distance (Euclidean distance < 75 mm) and long-distance (Euclidean distance > 75 mm) connections, respectively.

Source: Top panel reproduced from He et al. (2007); middle panel reproduced from Hagmann et al. (2008); bottom panel reproduced from Achard et al. (2006).

measures, such as the grey matter volume (Bassett et al., 2008) and surface area (Sanabria-Diaz et al., 2010). Recently, small-world properties have also been identified in individual structural covariance networks based on a novel intracortical similarity approach (Tijms et al., 2012). Through diffusion MRI, Hagmann et al. (2007) characterized the individual white matter connectivity patterns (~500 to 4000 nodes), and demonstrated small-world organization for two individuals. To date, many studies have investigated the topological organization of structural networks through different methodological approaches (e.g., imaging sequences, node definitions and edge definitions), and small-world architecture is consistently demonstrated at both individual and population levels (Bullmore and Sporns, 2009; Gong et al., 2009; Iturria-Medina et al., 2008; Lo et al., 2011). The small-world organization in the human brain extends previous observations in the neural network of the nematode *Caenorhabditis elegans* (Watts and Strogatz, 1998) and brain networks of the mouse (Oh et al., 2014; Rubinov et al., 2015), cat and macaque (Hilgetag et al., 2000; Hilgetag and Kaiser, 2004; Sporns and Zwi, 2004), which suggests a general wiring principle for brain network organization across species and spatial scales.

Compatible with structural brain networks, small-world attributes are observed in human brain functional networks extracted from different neuroimaging modalities (Fig. 4, bottom), regardless of the network construction strategies used (e.g., node definitions and edge definitions) (Achard et al., 2006; Bullmore and Sporns, 2009; Eguiluz et al., 2005; Micheloyannis et al., 2006; Reijneveld et al., 2007; Salvador et al., 2005; Stam, 2004; Valencia et al., 2009; Wang et al., 2009a). Notably, functional connectivity is typically estimated using long-term coherence in brain activities measured via fMRI, EEG or MEG, which implicitly assumes that it is temporally constant during the recording (Biswal et al., 1995; Fox and Raichle, 2007; Friston, 1994). A small-world property is reported for brain networks during rest or task states at different spatial scales that range from voxel-wise brain networks (~millimetres) (Eguiluz et al., 2005; Valencia et al., 2009) to regional-level brain networks (~centimetres) (Achard et al., 2006; Salvador et al., 2005; Wang et al., 2009a), as well as at different frequency bands of interest (Achard et al., 2006; Micheloyannis et al., 2006; Salvador et al., 2005; Stam, 2004), thus indicating a complicated spatiotemporal pattern for functional organization.

All this evidence suggests that human brain networks are structurally and functionally well organized in an optimized small-world fashion (Fig. 4). This facilitates information specialization in local clustering regions and promotes information integration across spatially distributed brain regions at low costs. However, distinct from the relatively fixed patterns of structural connectivity, the functional connections exhibit a rich repertoire of configurations. Interregional functional connections will flexibly change on a time scale of seconds to minutes to meet potential or ongoing cognitive demands during task performance (Bassett et al., 2011; Braun et al., 2015; Cole et al., 2013) and even spontaneously fluctuate in the resting state without external task demands (Allen et al., 2014; Calhoun et al., 2014; Chang and Glover, 2010; Hutchison et al., 2013a; Kang et al., 2011; Liao et al., 2015). The temporal fluctuations of functional connections may be partially attributable to mental state shifts (Allen et al., 2014) and physiological signals (Chang et al., 2013b). However, the dynamic reconfiguration of brain organization during rest may more likely reflect the intrinsic brain activity, as supported by empirical observations in anaesthetized macaques controlled for consciousness level changes (Hutchison et al., 2013b) and by computational models naturally free from physiological artefacts (Deco et al., 2011, 2013; Haimovici et al., 2013; Hansen et al., 2015). Interestingly, during the spontaneous reconfigurations of functional networks, small-world topology with low connectivity densities has been preserved (Liao et al., 2015), and the global efficiency of the brain networks was found to sporadically increase to reduce the metabolic demands (Zalesky et al., 2014). These features reflect a dynamic balance between information segregation and integration during rest.

Exploring the relationship between small-world structural and functional architectures is crucially important for understanding the brain mechanism underlying cognition and behaviour (Park and Friston, 2013; Wang et al., 2015). At the connection level, numerous studies have demonstrated that region pairs that possess direct white matter structural connectivity often exhibit functional connectivity (Greicius et al., 2009; Liao et al., 2015; van den Heuvel et al., 2009a), and the functional connectivity strength is positively associated with the structural connectivity strength (Hagmann et al., 2008; Honey et al., 2009; Liao et al., 2015; van den Heuvel et al., 2009a). Largely

consistent patterns have been identified between intrinsic task-free functional connectivity and the across-individual structural covariance in morphological measures (Hosseini and Kesler, 2013; Seeley et al., 2009; Segall et al., 2012). At the network level, the functional and structural networks of the brain share typical topological properties, such as small-worldness, modular architecture and the presence of hubs (Bullmore and Sporns, 2009, 2012; Wang et al., 2015). However, despite the close relationship between the structural and functional networks, their topological properties cannot be quantitatively inferred from each other by a simple one-to-one correspondence. For example, functional connectivity may exist between regional pairs without direct structural connectivity (Honey et al., 2009; Liao et al., 2015), which may be mediated by indirect structural pathways (Adachi et al., 2012; Goni et al., 2014; Honey et al., 2009) or by collective characteristics of whole-brain structural networks (e.g., common efferents) (Adachi et al., 2012). Furthermore, the functional connections and their topological organization dynamically change at a time scale of seconds to minutes (Calhoun et al., 2014; Chang and Glover, 2010; Hutchison et al., 2013a), which makes the inference of functional networks from relatively fixed structural substrates more difficult. The intricate relationship between structural and functional connectivity requires further investigation.

3.2. Relationship with modular organization and brain hubs

In brain networks, the small-world structure is typically accompanied by modular organization and the presence of hubs (Bullmore and Sporns, 2012; He and Evans, 2010; Meunier et al., 2010; Sporns, 2013; van den Heuvel and Sporns, 2013b). In modular brain networks, dense connections within the same module facilitate local information segregation, and sparse connections between modules ensure efficient global information integration. Given a modular architecture, the coexistence of hub regions facilitates information transmission across modules in a collaborative manner.

The modular organization in human brain structural networks was initially demonstrated by Chen et al. (2008) and was found to be consistent with previous findings in the anatomical networks of macaque and cat cortices (Bassett and Bullmore, 2006; Bassett and Bullmore, 2016; Harriger et al., 2012; Hilgetag et al., 2000; Modha and Singh, 2010). Six modules were identified in a structural covariance network based on across-individual covariation in cortical thickness, which largely overlapped with known functional systems, such as the visual, sensorimotor and auditory systems (Chen et al., 2008). In human brain white matter structural networks obtained from diffusion MRI, topological modules tend to be anatomically localized, such as the four unilateral modules (i.e., lateralized frontal and temporoparietal modules) and two bilateral modules observed by Hagmann et al. (2008). The modular organization is also demonstrated in large-scale human brain functional networks obtained from resting-state fMRI (Bertolero et al., 2015; He et al., 2009; Meunier et al., 2010; Power et al., 2011; Valencia et al., 2009) or slow EEG and MEG rhythms (Chavez et al., 2010; Tagliazucchi et al., 2013). The functional modules typically consist of anatomically connected or functionally related regions, and they exhibit good spatial correspondence with functional modules during task performance or prior task-defined systems, such as visual, sensorimotor, default-mode, frontoparietal task control and attention systems (Bertolero et al., 2015; Crossley et al., 2013; Power et al., 2011). This modularized organization of the human brain ensures the performance of a single module with less influence on other modules, and it simultaneously enables the reuse and adaptability of the existing brain function to meet the changing environments (Meunier et al., 2010). In a recent study, Bertolero et al. (2015) discerned multiple cognitive components across 77 cognitive tasks by performing an author-topic hierarchical Bayesian model. They demonstrated that the functional modules during rest may serve a discrete and autonomic cognitive function, which is compatible with the workspace theory in psychology (Fodor, 1983). In workspace theory, mental function is speculated to be divided into sub-functions or function modules, and consciousness-effortful tasks may recruit more sub-functions (Kitzbichler et al., 2011). Furthermore, several studies have indicated that human brain modules exhibit a hierarchical organization, namely, nested modules at several topological levels (Bassett et al., 2008, 2010; Ferrarini et al., 2009; Meunier et al., 2009b; Salvador et al., 2005). The modular and hierarchical modular organization in the human brain not only reduces the wiring costs but also allows high efficiency, adaptability and flexibility as well as rich nonlinear brain dynamics (Hilgetag and Hutt, 2014; Meunier et al., 2010; Moretti and Munoz, 2013). However, the mechanism that underlies the divergent spatial layouts of structural and functional modules requires further elucidation.

Numerous studies on human brain structural and functional networks have demonstrated that the node degree distribution of the networks follows a heavy-tailed distribution, such as an exponentially truncated power law (Achard et al., 2006; Bassett et al., 2008; Gong et al., 2009; Hayasaka and Laurienti, 2010; He et al., 2007, 2009; Hosseini and Kesler, 2013; Iturria-Medina et al., 2008; Valencia et al., 2009; Wang et al., 2009a) or a power-law (Eguiluz et al., 2005; van den Heuvel et al., 2008), indicating the existence of several highly connected hub regions. In addition to degree centrality, several other nodal centrality measures (e.g., betweenness, efficiency and eigenvector) have been used to identify brain hubs (Gong et al., 2009; Liang et al., 2013; van den Heuvel and Sporns, 2013b; Zuo et al., 2012). Although the spatial distributions of hubs vary across different centrality measures, we can discern several convergent hubs across studies. These highly connected or highly central hubs are primarily located at the heteromodal or unimodal association cortex and are thought to be critical to global information integration. The most-consistent hubs are predominantly located in the posterior medial cortex (e.g., precuneus and posterior cingulate cortex) and superior frontal cortex for structural networks (Bassett et al., 2008; Gong et al., 2009; Hagmann et al., 2008; He et al., 2007), and in default-mode areas (e.g., precuneus and medial prefrontal cortex) for functional networks (Achard et al., 2006; Buckner et al., 2009; Liang et al., 2013; Liao et al., 2013; Zuo et al., 2012). Both structural and functional studies indicate that highly connected hubs are often densely interconnected with one another and form a ‘core’ (Hagmann et al., 2008) or ‘rich-club’ architecture (Cao et al., 2014b; van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011; Zhao et al., 2015). This architecture involves long-distance neural pathways (van den Heuvel et al., 2012) and thus maintains effective information integration across spatially distributed regions (Cao et al., 2014b; van den Heuvel et al., 2012; van den Heuvel and Sporns, 2013a). Interestingly, an increasing attention has been devoted to assessing the functional roles of regions by estimating the spatial layout of their connections among different modules, using the participation coefficient metric (Guimera et al., 2005; Hagmann et al., 2008; He et al., 2009; Power et al., 2013). In functional networks, connector hubs with a high participation coefficient are found to be adjacent to the articulation points of multiple modules (Power et al., 2013) and associated with multiple cognitive functions (Bertolero et al., 2015), which reflects their potential roles in inter-module information coordination and integration.

3.3. Formation and degeneration of small-world organization

In terms of evolution, economic small-world organization with high local clustering and a short path length is a ubiquitous feature for neural systems across species, ranging from the microscopic *C. elegans* connectome (Watts and Strogatz, 1998) to the mesoscopic mouse connectome (Oh et al., 2014; Rubinov et al., 2015) to the macroscopic brain networks of cats, macaques and humans (Bassett and Bullmore, 2016; Bullmore and Sporns, 2009; He and Evans, 2010). Furthermore, the presence of structural modules and a rich club organization are consistently observed in the neural network of *C. elegans* (Bassett et al.,

2010; Towlson et al., 2013) and in drosophila (Shih et al., 2015), mouse (Rubinov et al., 2015), cat (de Reus and van den Heuvel, 2013; Hilgetag et al., 2000; Hilgetag and Kaiser, 2004), macaque (Harriger et al., 2012; Hilgetag et al., 2000; Hilgetag and Kaiser, 2004) and human (Chen et al., 2008; Hagmann et al., 2008; van den Heuvel and Sporns, 2011) brain structural networks. The conservation of these topological properties across species suggests an evolutionarily preserved mechanism for the anatomical network architecture of nervous systems (Bassett and Bullmore, 2016; van den Heuvel et al., 2016). Using resting-state fMRI, a recent study indicated the conservation of rich-club functional organization and default mode-like networks across mouse, macaque and human brains (Stafford et al., 2014), whereas in primates, highly connected nodes are more strongly inter-connected, and the default-mode network covers additional areas in the posterior cingulate cortex. These unique and important variations between species are indicative of the adaptive network organization for high-order cognition function.

The development and ageing of the human connectome during the lifespan provide important models to ascertain the formation and degeneration of small-world human brain networks and are also instructive for understanding brain functions in healthy and diseased states. Small-world organization is present as early as approximately 30 gestational weeks in preterm human brain structural and functional networks (Cao et al., 2016a; van den Heuvel et al., 2015) and is preserved across infancy, childhood, adolescence, adulthood and old age (Bullmore and Sporns, 2009; Cao et al., 2016b; Collin and van den Heuvel, 2013; Gao et al., 2016). Of note, the small-world organization continuously adjusts and changes during development and ageing, while structural and functional networks exhibit distinct trajectories. Specifically, the structural networks undergo significant increases in both local segregation and global integration during the third trimester (van den Heuvel et al., 2015) and reach an adult-like small-world modular organization at birth (Huang et al., 2015; van den Heuvel et al., 2015; Yap et al., 2011). During postnatal development from infancy to adulthood, the small-world organization of the structural networks undergoes subtle refinements, with increases in local and global efficiency (Hagmann et al., 2010; Huang et al., 2015; Zhao et al., 2015). For functional networks, the small-world organization exhibits a shift towards a more regular configuration with enhanced segregation during prenatal development, and it exhibits a clearly different modular and hub architecture at birth compared with adults (Cao et al., 2016a; Fransson et al., 2011; Gao et al., 2011; van den Heuvel et al., 2015). Functional networks after birth have also been demonstrated to exhibit rapid increases in local segregation and global integration in the first two years (Gao et al., 2011), and they are reorganized into a more integrated architecture through a “local to distributed” transformation from childhood to adulthood (Fair et al., 2009; Gu et al., 2015; Satterthwaite et al., 2013). It is worthy to note that head motion may affect the age-related changes in functional network segregation during development in youth (Satterthwaite et al., 2013). During ageing, both the structural and functional brain networks exhibit a shift towards a more localized organization with decreased inter-modular (Cao et al., 2014b; Meunier et al., 2009a; Wu et al., 2012; Zhao et al., 2015) and long-distance (Andrews-Hanna et al., 2007; Cao et al., 2014a) connections. Existing studies demonstrate that the structural and functional networks exhibit substantial overlap in the neonate's brain (van den Heuvel et al., 2015), and their coupling is strengthened during development (Hagmann et al., 2010). However, the intricate structure–function relationship during the lifespan and the associated microstructure basis remain largely unknown.

3.4. Why brain networks are expected to be ‘small-world’

Given the prevalence of small-world modular brain organization across species and their persistence across the human lifespan, it is important to understand the mechanism underlying the formation of small-world characteristics. The accumulated evidence suggests that the formation of small-world organization, accompanied by a modular structure and hubs, is the outcome of natural selection to satisfy the balance between the low cost of neuronal resources and the high efficiency of information transmission (Bassett and Bullmore, 2006; Bullmore and Sporns, 2012; Chen et al., 2013; Meunier et al., 2010; Samu et al., 2014).

The human brain is spatially embedded within the limited volume of the skull. The long-distance connections connecting spatially distant regions show higher wiring and metabolic costs in comparison with those connecting anatomically adjacent regions (Bullmore and Sporns, 2012). Theoretical modelling studies suggest that the brain regions preferentially connect with anatomically adjacent regions to reduce the overall costs, and they simultaneously require the presence of a few long-distance connections to reduce information transmission relay (Bullmore and Sporns, 2012; Chen et al., 2013; Karbowski, 2001; Sik et al., 1995; Vertes et al., 2012). Consistent with theoretical studies, several empirical studies have confirmed that the connecting strength or probability between two nodes in the human brain decreases with interregional distance in both structural and functional networks, and dominant short-distance connections coexist with a few long-distance connections (Hagmann et al., 2007; He et al., 2007; Salvador et al., 2005). Importantly, there are several brain hubs involving long-distance connections, which substantially promotes global information integration at the expense of high costs (Liao et al., 2013; Sepulcre et al., 2010; van den Heuvel et al., 2012). The frequently reported truncated power law degree distribution is a reasonable model for spatially embedded brain networks; it allows the presence of brain hubs, but prevents the appearance of very expensive hubs with an extremely large number of connections.

Notably, in addition to the cost-efficiency balance, theoretical models regarding the formation mechanisms of brain networks indicate that, other factors (e.g., functional significances of the topology) should also be taken into account to fully capture the brain network topology (Chen et al., 2013; Kim and Kaiser, 2014; Vertes et al., 2012). From the perspective of network dynamics, recent theoretical studies based on empirical data have indicated that small-world brain structural networks support rich dynamical behaviours and adaptive functions, such as rapid spreading and integration of information (Misic et al., 2015), spontaneous transitions of functional connectivity patterns (Ghosh et al., 2008; Hansen et al., 2015), and the presence of critical states for fast responses to external demands (Deco and Jirsa, 2012; Deco et al., 2013; Haimovici et al., 2013). These dynamic characteristics are important for the realization of complex brain cognition and behaviour. Additionally, the modular and hierarchical modular organization in the human brain facilitates high adaptability and flexibility for cognitive function and increased evolvability (Meunier et al., 2010; Sporns and Betzel, 2016). Correspondingly, in recent empirical studies, the small-world architecture has been shown to emerge in both structural and functional networks of cultured neurons initiated from random configurations (de Santos-Sierra et al., 2014; Downes et al., 2012; Schroeter et al., 2015; Teller et al., 2014), which further highlights the importance of small-world organization for the survival of neural systems. These empirical and theoretical findings extend the previous understanding (Bassett and Bullmore, 2006; Meunier et al., 2010) and suggest that future studies taking into account different functional significances of the small-world organization may provide valuable insights into the working mechanism of the brain.

4. Cognitive implications and physiological basis of small-world brain networks

4.1. Cognitive implications

Our understanding of the brain mechanisms underlying cognition and behaviour has substantially advanced, thanks to the combination of non-invasive neuroimaging techniques and graph theoretical ap-

proaches (Medaglia et al., 2015; Park and Friston, 2013; Pessoa, 2014; Petersen and Sporns, 2015; Sporns, 2014). In addition to traditional task-activation paradigms, the brain network framework enables the investigation of the neurobiological mechanisms that underlie human cognition and behaviour from the perspective of interregional coordination (Medaglia et al., 2015; Pessoa, 2014; Sporns, 2014). Since small-world organization supports efficient information segregation and integration, which are essential for human brain function, small-world related metrics are supposed to be associated with individual cognitive performance. Consider intelligence as an example. An early review that summarized 37 structural and functional neuroimaging studies indicated that individual intelligence involves spatially distributed regions (Jung and Haier, 2007), suggesting the potential importance of interregional interactions. In terms of network analysis, an increasing number of studies regarding young adult brain networks indicate that the small-world organization of both structural and intrinsic functional networks contributes to individual intellectual performance (Langer et al., 2012; Li et al., 2009; van den Heuvel et al., 2009b). Higher intelligence quotient scores correspond to shorter characteristic path lengths of the brain network, which indicates a positive contribution of global efficiency to intellectual performance. In addition, the nodal centrality of several brain regions (i.e., the parietal and frontal areas) is found to be related to intellectual ability, which is largely consistent with previous task-evoked regions (Jung and Haier, 2007). Recently, a cross-sectional study has indicated that the non-verbal intelligence of preadolescent children also exhibits a strong positive correlation with the global efficiency of structural networks (Kim et al., 2016). These findings extend the previous parieto-frontal integration theory (Jung and Haier, 2007) and further demonstrate that human intellectual performance involves the efficient integration of spatially distributed regions. A better understanding of the relationship between small-world brain architectures and intellectual performance may be instructive for the device design in artificial intelligence.

Recently, increasing attention has been devoted to the dynamic changes of small-world functional networks during task performance. During various cognitive tasks, functional connection patterns have been demonstrated to modulate flexibly in order to meet cognitive demands while maintaining the small-world modular organization (Bassett et al., 2006, 2011; Braun et al., 2015; Fornito et al., 2012a; Liang et al., 2016; Valencia et al., 2008). During the dynamic reconfiguration, the frontal and parietal areas, which contain several highly connected hub regions, are found to play important roles by adjusting their brain-wide connectivities, especially those between different modules (Braun et al., 2015; Cole et al., 2013). Consider the working memory task as an example. The inter-module integration of the brain network tended to increase with increasing cognitive loads (Braun et al., 2015; Kitzbichler et al., 2011; Liang et al., 2016), and the flexibility and integration of between frontal systems were correlated with the working-memory performance (Braun et al., 2015). Interestingly, recent functional MRI or EEG studies have found an increase in the modularity (i.e., decrease in global integration) of functional networks for non-rapid eye movement sleep, which exhibits a decreasing level of consciousness compared with wakefulness (Boly et al., 2012; Tagliazucchi et al., 2013). These findings across different cognitive tasks or mental states suggest a potential positive correlation between the cognitive load/consciousness level and the global integration capability of brain networks, which requires additional evidence in the future.

4.2. Physiological basis of brain network organization

The brain exhibits high energy consumption. Although the adult human brain represents approximately 2% of the body mass, it consumes 20% of the body's total energy (Raichle, 2006). Nevertheless, the relationship between the small-world brain network organization and the metabolic demands needs to be further elucidated. Recent studies suggest that functional modules/systems at rest exhibit distinct metabolic features related to aerobic glycolysis (Vaishnavi et al., 2010) and regional cerebral blood flow (Liang et al., 2013), which may be modulated according to task demands (Liang et al., 2013). In addition, brain hub regions exhibit high metabolic requirements, such as cerebral blood flow (Hagmann et al., 2008; Liang et al., 2013; Varkuti et al., 2011) and glucose metabolism (Liang et al., 2013; Tomasi et al., 2013). The high metabolic requirements of brain hubs and the rich club architecture may be trade-offs for efficiently integrating the brain network as a whole (Collin et al., 2014; van den Heuvel et al., 2012). Therefore, the dynamic small-world organization of brain networks with time-varying modules and hubs may be related to the energy expenditure in real time. Moreover, the topological properties (e.g., degree, clustering coefficient and shortest path length) of the macaque connectome are related to its microscopic neuroarchitectonics (Scholtens et al., 2014), indicating a microscopic biological substrate for macroscopic topological organization. Recent studies suggest that the small-world related network topologies in structural networks (Duarte-Carvajalino et al., 2012), structural covariance networks (Schmitt et al., 2008) and functional networks (Fornito et al., 2011; Smit et al., 2008) are highly heritable. The gene co-expression signature has also been demonstrated for functional modules in the human brain (Richiardi et al., 2015) as well as the axonal connectivity (Richiardi et al., 2015) and structural hubs (Fulcher and Fornito, 2016) in the mouse connectome, which further suggests a genetic control over brain structural and functional organization. In the future, the incorporation of multiple-modal information, including metabolic measurements, histological information and genetic signatures will further enhance our understanding of the formation and development of small-world human brain networks.

5. Disorganization of small-world brain networks in neurological and psychiatric disorders

Strong evidence demonstrates that nearly all neurological and psychiatric diseases exhibit not only focal abnormalities but also the disconnection features (Bassett and Bullmore, 2009; Dai et al., 2015; Filippi et al., 2013; Fornito and Bullmore, 2015; Fornito et al., 2012b, 2015; Gong and He, 2015; Reijneveld et al., 2007; Stam, 2014; Xia and He, 2011). These disconnections typically involve widespread regions, indicating an altered coordination among spatially distributed regions. In particular, discerning changes of small-world attributes in human brain networks provides novel insights into the physiological mechanisms of brain diseases. Altered small-world organization has been demonstrated in several psychiatric and neurological diseases. For example, convergent evidence in attention deficit hyperactivity disorder (ADHD) has demonstrated that the functional and structural brain networks exhibit more-regular configurations with higher local clustering and/or decreased global efficiency, suggesting a delayed development of brain structure and function (Fig. 5a) (Cao et al., 2013, 2014a, 2016b; Wang et al., 2009b). In schizophrenia, most studies suggest that the functional brain networks exhibit a shift towards a randomized architecture with reduced local segregation (Fig. 5b) (Alexander-Bloch et al., 2010; Kambeitz et al., 2016; Skudlarski et al., 2010; van den Heuvel and Fornito, 2014). In Alzheimer's disease, a chronic neurodegenerative disorder, most studies have found that functional and structural networks tend to shift towards the regular configuration with a decreased global efficiency in information transmission, despite inconsistent findings observed across studies (Bai et al., 2012; Dai and He, 2014; He et al., 2008; Liu et al., 2014; Lo et al., 2010; Stam et al., 2007; Zhao et al., 2012). These distinct trends of small-worldness alterations (i.e., tendency to be more regular or random) suggest potentially different neurobiological substrates underlying neurological and psychiatric diseases. Moreover, even with deviation in the same direction, different diseases may exhibit distinct small-world features. Consider schizophrenia and depression as examples. Although the

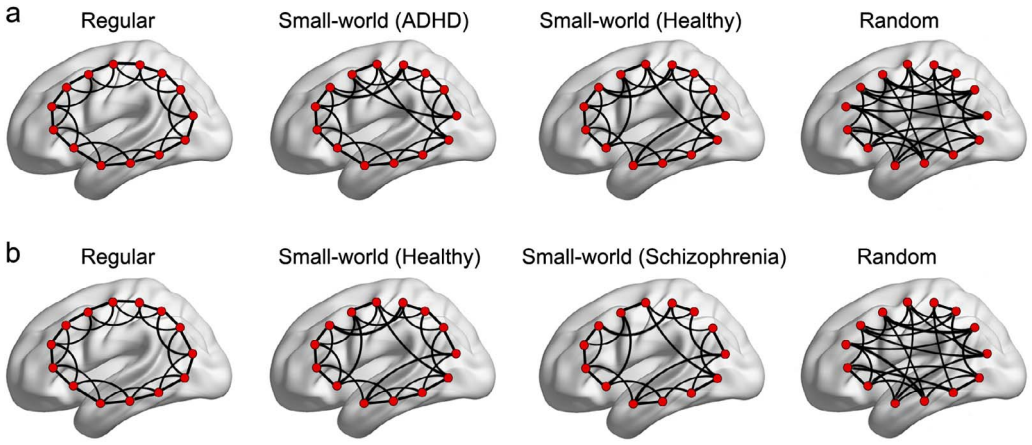

Fig. 5. Small-world models for two brain diseases: ADHD (a) and schizophrenia (b). The brain networks in ADHD and schizophrenia exhibit a disrupted small-world organization in comparison with healthy controls. For ADHD, convergent studies suggest that the structural and functional networks exhibit a shift towards regular configurations with decreased global efficiency. For schizophrenia, the functional networks are found to shift towards random configurations with reduced local clustering. ADHD, attention deficit hyperactivity disorder. *Source*: (a) Reproduced from Cao et al. (2014a). (b) Reproduced according to the finding of a meta-analysis (Kambeitz et al., 2016).

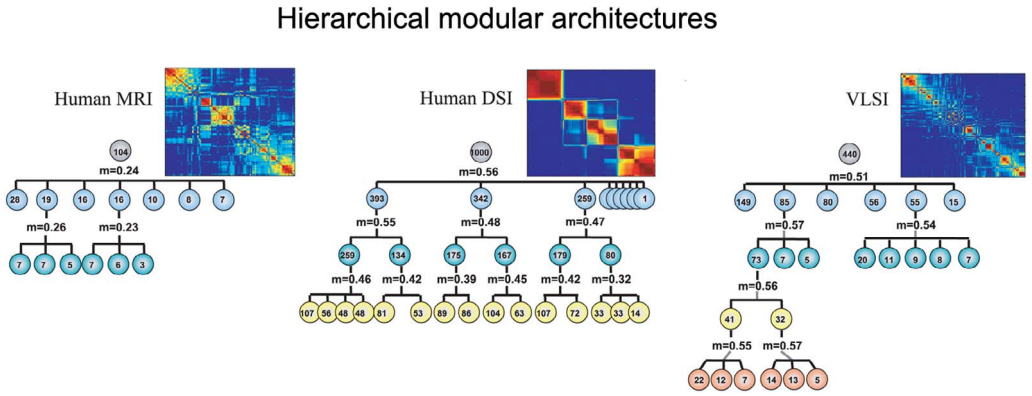

Fig. 6. Hierarchical architectures of the human brain structural covariance network (left), the white matter structural network (middle) and a very large-scale integrated circuit (right). DSI, diffusion spectrum imaging; VLSI, very large-scale integrated.
Source: Reproduced from Bassett et al. (2010).

functional networks of both diseases are found to exhibit a shift towards randomization, the functional networks tend to exhibit a reduced local segregation for schizophrenia (Kambeitz et al., 2016; van den Heuvel and Fornito, 2014) and an increased global efficiency for depression (Gong and He, 2015; Zhang et al., 2011). Thus, characterizing the brain network alterations at both global and local levels can provide comprehensive insights into the understanding of network dysfunctional mechanisms in diseases. Alterations in small-world attributes, particularly localized abnormal regions/connections, may serve as potential biomarkers for early detection, diagnosis and treatment evaluation (Filippi et al., 2013; Gong and He, 2015; Stam, 2014; Worbe, 2015).

Notably, most of current studies mainly explored the small-world network alterations in specific disorders using a single neuroimaging modality of a small sample. With the fusion of multi-modal imaging data, brain disorders can be systematically characterized in both structural and/or functional network abnormality at global, system and regional/connectional levels, thus greatly improving the understanding of brain–behaviour relationship. In addition, the increasing availability of open-access dataset and the accumulating literature provide a unique opportunity to quantify the disease-related changes across large populations with higher statistical power. Intriguingly, recent meta-analyses of grey matter lesions have highlighted that although the impaired regions are disease dependent, the structural hub regions are more likely to exhibit lesions across various neuropsychiatric disorders (Crossley et al., 2014), and three lesion regions are consistently identified across six psychiatric diseases (Goodkind et al., 2015), which indicates shared neurobiological substrates across diseases. The common alterations across diseases and disease-specific alterations in small-world properties should be further investigated in the future with the increasing availability of large-sample multi-modal neuroimaging data of brain disorders.

6. Implications of small-world brain networks in engineering

The human brain is a complicated information processing system that involves the input, encoding, storage, retrieval, processing and output of a vast amount of information. The small-world modular organization of the human brain facilitates high efficiency in information transmission with low wiring and energy costs (Bassett and Bullmore, 2006; Bullmore and Sporns, 2012; Watts and Strogatz, 1998). Like brain networks, many other systems that involve information processing also follow a small-world organization with a hierarchical modular topology. Examples include electrical power grids, the Internet and very large-scale integrated circuits (Bassett et al., 2010; Boccaletti et al., 2006; Lancichinetti et al., 2010; Meunier et al., 2010). Bassett et al. (2010) demonstrated that the number of connections and the number of nodes within a topological/spatial partition follow a Rentian power law for human brain networks (Fig. 6, left and middle), for the neural network of *C. elegans*, and for large-scale integrated circuits (Fig. 6, right), despite the varying power exponents of different systems. These well-established scaling relationships across systems reflect the trade-off between maximizing the topological complexity and minimizing the wiring costs. An exploration of the quantitative

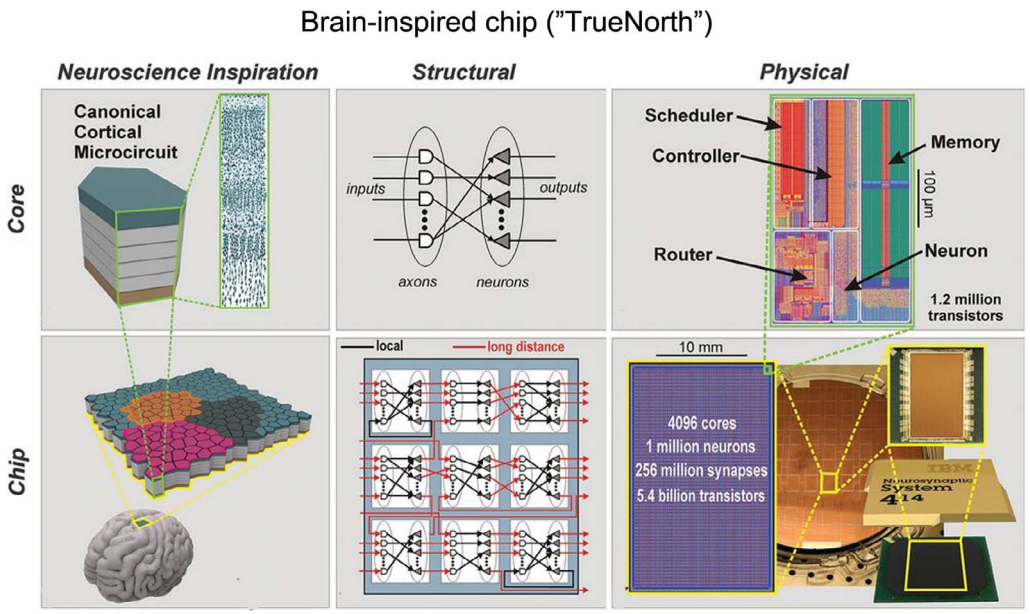

Fig. 7. Architecture of a brain-inspired chip called 'TrueNorth'. Left panels show the canonical cortical circuit in the two-dimensional sheet-like cortical cortex of a macaque brain. Middle panels display the structures of a neurosynaptic core and a chip comprising multiple cores. Right panels show the physical layouts of a neurosynaptic core and a chip comprising 4096 cores.
Source: Reproduced from Merolla et al. (2014).

similarities and differences in topological organization between the brain networks and other systems may shed light on the unique working mechanism of the human brain as well as promote the design of other information processing systems, such as brain-like computing (Furber, 2016; Rueckert, 2016).

The small-world modular organization of the brain has recently provided important implications in the field of engineering, such as the design of digital devices and artificial intelligence systems (Eliasmith et al., 2012; Machens, 2012; Merolla et al., 2014). Inspired by the sheet-like architecture of the cortical cortex, IBM and co-operators built a million spiking-neuron integrated functional digital chip (named 'True-North') (Fig. 7), which comprises a network of 4096 neurosynaptic cores linked by long-distance connections (Merolla et al., 2014). This brain-like chip is efficient, scalable and flexible, and it operates with a power density of 20 mW/cm^2, which is significantly lower than that of the traditional central processing unit (50–100 W/cm^2). Another representative example is a recent 2.5-million-neuron computational model of a functioning brain (called 'Spaun') that embeds empirical constraints on the neurons and the synaptic responses in the model, and mimics the communication between different cortical regions (Eliasmith et al., 2012). This model is able to perform various behavioural tasks in response to visual inputs and, in turn, may provide novel insights into the neural mechanisms that underlie the basic cognitive functions. However, despite great progress in brain-like computing in the last few years, we should note that several issues must be taken into account (Furber, 2016; Machens, 2012; Rueckert, 2016), such as the high energy requirement for the large-scale neural simulation of Spaun. Many refinements are desired for brain-like architectures to make them more comparable with the brain, such as the plasticity of the structural connectivity, the adaptability and flexibility of brain functions and the low energy expenditure in comparison with computer devices.

7. Challenges and future perspectives

In this article, we have discussed recent advances regarding small-world human brain networks and their formation, degeneration and alterations, as well as their potential implications and applications. Current studies have made important progress in understanding the working mechanism of small-world human brain networks and the neurobiological basis that underlies brain disorders; however, several major issues deserve further attention and investigation.

One of these is how to characterize the small-world organization of the human connectome at a higher spatial resolution. Until now, most studies have investigated the topological organization of human brain networks at a macroscopic level (Bullmore and Sporns, 2009, 2012; Bullmore and Bassett, 2011; Craddock et al., 2013; He and Evans, 2010; Park and Friston, 2013; Reijneveld et al., 2007; Stam, 2014). It is valuable to develop novel techniques to non-invasively map the human brain structure and functional connectivity at a finer spatial scale (e.g., neural circuit or cortical column at the mesoscopic level) in an effort to comprehensively understand the working mechanism of the human brain. We should note that once the human connectome is available at the mesoscopic level, the storage, management and processing of huge amounts of information embedded in the networks will pose great challenges to computing platforms.

Secondly, the accumulated evidence suggests that the functional brain networks undergo spontaneous reconfigurations at a temporal scale of seconds to minutes, even during rest (Calhoun et al., 2014; Chang and Glover, 2010; Hutchison et al., 2013a). The small-world organization, the modular structure and the hub regions temporally fluctuate over time, which reflects a dynamic balance between information segregation and integration (Allen et al., 2014; Betzel et al., 2016; Jones et al., 2012; Liao et al., 2015). Several recent studies have demonstrated that brain network dynamics are associated with the white matter structural connectivity (Liao et al., 2015; Shen et al., 2015; Zhang et al., 2016), neurophysiological (e.g., EEG) associates (Chang et al., 2013a; Tagliazucchi et al., 2012; Zhang et al., 2016) and some putative molecular mechanisms, including N-methyl-D-aspartate receptor (Braun et al., 2016), norepinephrine (Safaai et al., 2015) and glucose metabolism (Liang et al., 2013; Tomasi et al., 2013). However, the neurophysiological and biochemical mechanisms underlying these dynamic changes and their relationship with cognitive function require further research.

Thirdly, previous studies highlight that the topological properties between the structural and functional networks cannot be derived from each other through a simple one-to-one correspondence (Park and Friston, 2013; Wang et al., 2015). In particular, the aberrations of

small-world organization in brain diseases may exhibit opposite trends between structural and functional networks, such as randomization for functioning and regularization for structure in schizophrenia (van den Heuvel and Fornito, 2014). The intricate structure-function relationship in the topological organization should be further explored. We should note that computational modelling may provide mechanistic insights via the simulation of brain activities according to the known empirical data (Deco et al., 2013; Gonzalez-Castillo and Bandettini, 2015; Honey et al., 2009), such as large-scale neuronal modelling of brain function (Markram et al., 2015).

Fourthly, individual differences in the small-world organization of the human connectome require further investigation (Kelly et al., 2012). Individual cognition and behaviour vary dramatically across individuals, perhaps due to individual differences in brain structure and function, such as the regional cytoarchitecture (Eickhoff et al., 2005), cortical morphology (Hill et al., 2010) and task-evoked activations (Frost and Goebel, 2012), as well as intrinsic functional connectivity profiles (Finn et al., 2015; Gao et al., 2014; Liu et al., 2016; Mueller et al., 2013). Considering the importance of small-world organization for brain functioning, future studies could be conducted to ascertain how small-world brain networks vary across individuals, their potential cognitive implications and whether they may serve as brain fingerprints for individual identification.

Fifthly, the emergent trend of worldwide neuroimaging data sharing is greatly advancing the development of the human connectome (Eickhoff et al., 2016; Laird et al., 2011; Poldrack and Gorgolewski, 2014; Poldrack and Poline, 2015; Poline et al., 2012; Van Essen et al., 2012). More than 40 repositories and datasets have already been initiated to share large neuroimaging data of the healthy populations and those with brain disorders. Examples are the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org/fcpClassic/FcpTable.html) and the ADHD-200 Sample (http://fcon_1000.projects.nitrc.org/indi/adhd200) included in the NITRC image repository (Kennedy et al., 2016) as well as the Human Connectome Project (Van Essen et al., 2012). Large aggregated datasets or meta-analyses across studies can lead to robust and convincing conclusions regarding the small-world organization of the human brain, thereby resulting in meaningful knowledge of brain structural and functional architectures, their inter-subject variability as well as of the neurobiological substrates underlying neuropsychiatric diseases.

Finally, the developments of human connectome and computer science are closely linked and may reinforce each other. Huge amounts of information will be involved in the further developments of small-world human connectome mentioned above, the handling of which raises high requirements to hardware and software platforms in computer science, such as graphic processing units for image construction in real time (Ugurbil et al., 2013) and for fast mapping of human connectome (Boubela et al., 2016; Hernandez et al., 2013; Wang et al., 2013). In turn, unveil how brain function emerges on the hierarchical modular structure can promote the design of more-economic and more-efficient chips, integrated circuits, artificial intelligence systems and other computer devices.

Author contributions

X. L. and Y. H. designed research and wrote the manuscript; A. V. V. revised the manuscript.

Acknowledgments

We would like to thank Dr. Miao Cao and Dr. Yuhan Chen for valuable discussions. This work was supported by the National Natural Science Foundation of China[grant numbers 81620108016, 91432115, 31521063 and 11205041], the China Postdoctoral Science Foundation [grant 2016T90056], Beijing Municipal Science & Technology Commission [grants numbers Z161100000216152 and Z151100003915082], Changjiang Scholar Professorship Award (Award No T2015027), and the Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning [grant number CNLYB1307].

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