Complex brain networks: graph theoretical analysis of structural and functional systems

Ed Bullmore[*‡] *and Olaf Sporns*[§]

Abstract | Recent developments in the quantitative analysis of complex networks, based largely on graph theory, have been rapidly translated to studies of brain network organization. The brain's structural and functional systems have features of complex networks — such as small-world topology, highly connected hubs and modularity — both at the whole-brain scale of human neuroimaging and at a cellular scale in non-human animals. In this article, we review studies investigating complex brain networks in diverse experimental modalities (including structural and functional MRI, diffusion tensor imaging, magnetoencephalography and electroencephalography in humans) and provide an accessible introduction to the basic principles of graph theory. We also highlight some of the technical challenges and key questions to be addressed by future developments in this rapidly moving field.

Graph theory
A branch of mathematics that deals with the formal description and analysis of graphs. A graph is defined simply as a set of nodes (vertices) linked by connections (edges), and may be directed or undirected. When describing a real-world system, a graph provides an abstract representation of the system's elements and their interactions.

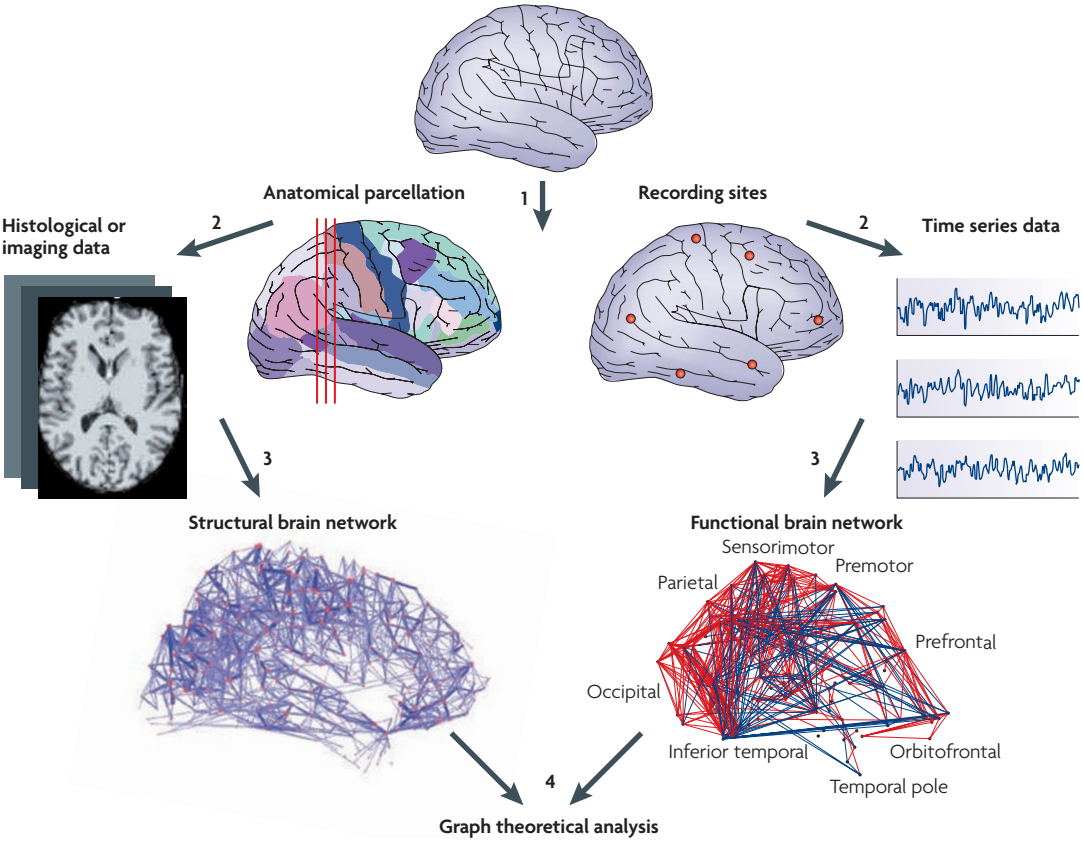
*University of Cambridge, Behavioural & Clinical Neurosciences Institute, Department of Psychiatry, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK.
‡GlaxoSmithKline, Clinical Unit Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK.
§Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana 47405, USA.
Correspondence to E.B.
e-mail: etb23@cam.ac.uk
doi:10.1038/nrn2575
Published online
4 February 2009

We have known since the nineteenth century that the neuronal elements of the brain constitute a formidably complicated structural network[1,2]. Since the twentieth century it has also been widely appreciated that this anatomical substrate supports the dynamic emergence of coherent physiological activity, such as phase-locked high-frequency electromagnetic oscillations, that can span the multiple spatially distinct brain regions that make up a functional network[3,4]. Such networks are thought to provide the physiological basis for information processing and mental representations[5–9]. In this article, we focus on graph theoretical approaches to the analysis of complex networks that could provide a powerful new way of quantifying the brain's structural and functional systems (BOX 1).

Since the mid 1990s, developments in our understanding of the physics of complex systems[10–12] have led to the rise of network science[13] as a transdisciplinary effort to characterize network structure and function. In this body of literature, complexity arises in the macroscopic behaviour of a system of interacting elements that combines statistical randomness with regularity[14]. The ascendancy of network science has been driven by the growing realization that the behaviour of complex systems — be they societies, cells or brains — is shaped by interactions among their constituent elements. The increasing availability and tractability of large, high-quality data sets on a wide range of complex systems[15–17] has led to a fundamental insight: substantively different complex systems often share certain key organizational principles, and these can be quantitatively characterized by the same parameters (BOX 2). In other words, many complex systems show remarkably similar macroscopic behaviour despite profound differences in the microscopic details of the elements of each system or their mechanisms of interaction.

One example of an apparently ubiquitous macroscopic behaviour in complex systems is the small-world phenomenon[18] (BOX 3). Recently, small-world architectures have been found in several empirical studies of structural and functional brain networks[19–22] in humans and other animals, and over a wide range of scales in space and time; small-worldness is naturally therefore a key topic for this Review. However, discovering that brain networks are small-world networks is only the first step towards a comprehensive understanding of how these networks are structurally organized and how they generate complex dynamics. In network science, methodological advances allow us to quantify other topological properties of complex systems — such as modularity[23], hierarchy[24], centrality[25] and the distribution of network hubs[26,27] — many of which have already been measured in brain networks. There have also been significant efforts to model the development or evolution of complex networks[28], to link network topology to network dynamics, and to explore network robustness

Box 1 | **Structural and functional brain networks**



Structural and functional brain networks can be explored using graph theory through the following four steps (see the figure):

- Define the network nodes. These could be defined as electroencephalography or multielectrode-array electrodes, or as anatomically defined regions of histological, MRI or diffusion tensor imaging data.
- Estimate a continuous measure of association between nodes. This could be the spectral coherence or Granger causality measures between two magnetoencephalography sensors, or the connection probability between two regions of an individual diffusion tensor imaging data set, or the inter-regional correlations in cortical thickness or volume MRI measurements estimated in groups of subjects.
- Generate an association matrix by compiling all pairwise associations between nodes and (usually) apply a threshold to each element of this matrix to produce a binary adjacency matrix or undirected graph.
- Calculate the network parameters of interest in this graphical model of a brain network and compare them to the equivalent parameters of a population of random networks.

Each step entails choices that can influence the final results and must be carefully informed by the experimental question. At step 1, parcellation schemes can use prior anatomical criteria or be informed by the functional connectivity profiles of different regions. Several such parcellation schemes may be available and can affect network measures[147]. In most magneto-encephalography and electroencephalography studies, network nodes are equivalent to individual electrodes or sensors, but networks could also be based on reconstructed anatomical sources. However, some reconstruction algorithms will determine the brain location of each source by minimizing the covariance between sensors, which has major effects on the configuration of functional networks. At step 2, a range of different coupling metrics can be estimated, including measures of both functional and effective connectivity. A crucial issue at step 3 is the choice of threshold used to generate an adjacency matrix from the association matrix: different thresholds will generate graphs of different sparsity or connection density, and so network properties are often explored over a range of plausible thresholds. Finally, at step 4 a large number of network parameters can be quantified (BOX 2). These must be compared with the (null) distribution of equivalent parameters estimated in random networks containing the same number of nodes and connections. Statistical testing of network parameters may best be conducted by permutation- or resampling-based methods of non-parametric inference given the lack of statistical theory concerning the distribution of most network metrics.

Most graph theoretical network studies to date have used symmetrical measures of statistical association or functional connectivity — such as correlations, coherence and mutual information — to construct undirected graphs. This approach could be generalized to consider asymmetrical measures of causal association or effective connectivity — such as Granger causal[148,149] or dynamic causal[66] model coefficients — to construct directed graphs. It is also possible to avoid the thresholding step (step 3) by analysing weighted graphs that contain more information than the simpler unweighted and undirected graphs that have been the focus of attention to date. Structural brain network image is reproduced from REF. 59. Functional brain network image is reproduced, with permission, from REF. 70 © (2006) Society for Neuroscience.

Complex network
An informal description of a network with certain topological features, such as high clustering, small-worldness, the presence of high-degree nodes or hubs, assortativity, modularity or hierarchy, that are not typical of random graphs or regular lattices. Most real-life networks are complex by this definition, and analysis of complex networks therefore forms an important methodological tool for systems biology.

Adjacency matrix
An adjacency matrix indicates the number of edges between each pair of nodes in a graph. For most brain networks, the adjacency matrix is specified as binary — that is, each element is either 1 (if there is an edge between nodes) or 0 (if there is no edge). For undirected graphs the adjacency matrix is symmetrical.

and vulnerability — topics that are likely to become increasingly relevant in relation to neuroscience.

In this article, we describe and discuss the expanding interface between systems neuroscience and the physics of complex networks. We review the existing empirical data on topological and dynamical properties of structural and functional brain networks, and ask what this literature tells us about how structural networks shape functional brain dynamics. Space limitations prevent us from providing coverage of all animal models, *in vitro*

Box 2 | **Network measures**

A network is defined in graph theory as a set of nodes or vertices and the edges or lines between them. Graph topology can be quantitatively described by a wide variety of measures, some of which are discussed here. It is not yet established which measures are most appropriate for the analysis of brain networks. The figure shows a schematic diagram of a brain network drawn as a directed (left) and an undirected (right) graph; both structural and functional networks can be either directed or undirected (BOX 1).

Node degree, degree distribution and assortativity

The degree of a node is the number of connections that link it to the rest of the network — this is the most fundamental network measure and most other measures are ultimately linked to node degree. The degrees of all the network's nodes form a degree distribution[15]. In random networks all connections are equally probable, resulting in a Gaussian and symmetrically centred degree distribution. Complex networks generally have non-Gaussian degree distributions, often with a long tail towards high degrees. The degree distributions of scale-free networks follow a power law[90]. Assortativity is the correlation between the degrees of connected nodes. Positive assortativity indicates that high-degree nodes tend to connect to each other.

Clustering coefficient and motifs

If the nearest neighbours of a node are also directly connected to each other they form a cluster. The clustering coefficient quantifies the number of connections that exist between the nearest neighbours of a node as a proportion of the maximum number of possible connections[18]. Random networks have low average clustering whereas complex networks have high clustering (associated with high local efficiency of information transfer and robustness). Interactions between neighbouring nodes can also be quantified by counting the occurrence of small motifs of interconnected nodes[150]. The distribution of different motif classes in a network provides information about the types of local interactions that the network can support[48].

Path length and efficiency

Path length is the minimum number of edges that must be traversed to go from one node to another. Random and complex networks have short mean path lengths (high global efficiency of parallel information transfer) whereas regular lattices have long mean path lengths. Efficiency is inversely related to path length but is numerically easier to use to estimate topological distances between elements of disconnected graphs.

Connection density or cost

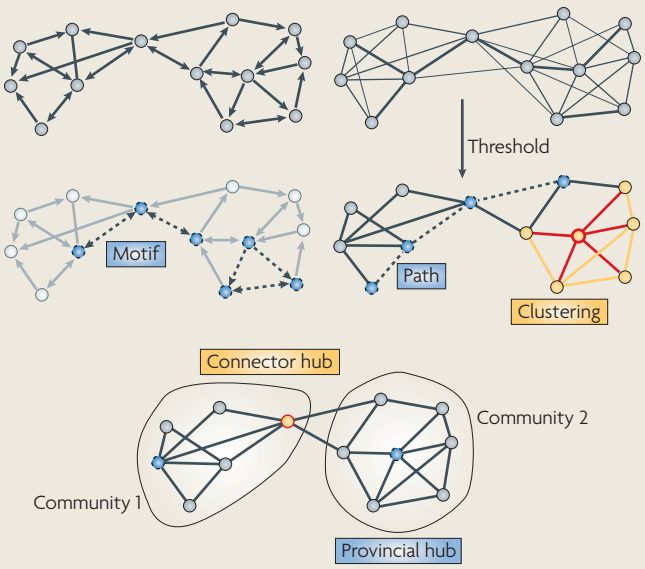
Connection density is the actual number of edges in the graph as a proportion of the total number of possible edges and is the simplest estimator of the physical cost — for example, the energy or other resource requirements — of a network.

Hubs, centrality and robustness

Hubs are nodes with high degree, or high centrality. The centrality of a node measures how many of the shortest paths between all other node pairs in the network pass through it. A node with high centrality is thus crucial to efficient communication[151]. The importance of an individual node to network efficiency can be assessed by deleting it and estimating the efficiency of the 'lesioned' network. Robustness refers either to the structural integrity of the network following deletion of nodes or edges or to the effects of perturbations on local or global network states.

Modularity

Many complex networks consist of a number of modules. There are various algorithms that estimate the modularity of a network, many of them based on hierarchical clustering[23]. Each module contains several densely interconnected nodes, and there are relatively few connections between nodes in different modules. Hubs can therefore be described in terms of their roles in this community structure[27]. Provincial hubs are connected mainly to nodes in their own modules, whereas connector hubs are connected to nodes in other modules.



Box 3 | **Random, scale-free and small-world networks**

In random graphs each pair of nodes has an equal probability, *p*, of being connected[152]. Large random graphs have Gaussian degree distributions (BOX 2). It is now known that most graphs describing real-world networks significantly deviate from the simple random-graph model.

Some networks (including the Internet and the World Wide Web) have degree distributions in the form of a power law: that is, the probability that a node has degree *k* is given as $Prob(k) \sim k^{-\lambda}$. In biological systems, the degree exponent λ often ranges between 2 and 3, and the very gradual ('heavy-tail') power law decay of the degree distribution implies that the network lacks a characteristic scale — hence such networks are called 'scale-free' networks. Barabási and Albert[90] demonstrated that scale-free networks can originate from a process by which each node that is added to the network as it grows connects preferentially to other nodes that already have high degree. Scale-free networks are unlikely if the attachment of connections is subject to physical constraints or associated with a cost[15]. Therefore, physically embedded networks, in which nodes have limited capacity for making connections, often do not have pure power law degree distributions but may instead demonstrate exponentially truncated power law degree distributions, which are associated with a lower probability of very high degree nodes.

Originally described in social networks[153], the 'small-world' property combines high levels of local clustering among nodes of a network (to form families or cliques) and short paths that globally link all nodes of the network. This means that all nodes of a large system are linked through relatively few intermediate steps, despite the fact that most nodes maintain only a few direct connections — mostly within a clique of neighbours. Small-world organization is intermediate between that of random networks, the short overall path length of which is associated with a low level of local clustering, and that of regular networks or lattices, the high-level of clustering of which is accompanied by a long path length[18]. A convenient single-number summary of small-worldness is thus the ratio of the clustering coefficient to the path length after both metrics have been standardized by comparing their values to those in equivalent random networks[154]. Evidence for small-world attributes has been reported in a wide range of studies of genetic, signalling, communications, computational and neural networks. These studies indicate that virtually all networks found in natural and technological systems have non-random/non-regular or small-world architectures and that the ways in which these networks deviate from randomness reflect their specific functionality.

preparations and human studies that have contributed to this endeavour: we necessarily focus on what we consider to be some representative examples of graph theoretical research in brain networks, with an emphasis on studies of the human brain. We thus consider the implications of complex brain networks for an understanding of neuropsychiatric disorders and conclude with some general remarks about the evolution of scale-invariant topology in brain networks and some key future challenges for this emerging field.

Structural brain networks

Topological and physical properties of structural networks. The anatomical configuration of brain networks, ranging from inter-neuronal connectivity to inter-regional connectivity, has long been a focus of empirical neuroscience. Network analysis, and in particular graph theory (BOX 4), offers new ways to quantitatively characterize anatomical patterns. According to graph theory, structural brain networks can be described as graphs that are composed of nodes (vertices) denoting neural elements (neurons or brain regions) that are linked by edges representing physical connections (synapses or axonal projections). Although graph theory emphasizes topological connectivity patterns, the topological and physical distances between elements in brain networks are often intricately related[29]. Neurons and brain regions that are spatially close have a relatively high probability of being connected, whereas connections between spatially remote neurons or brain regions are less likely[30–32]. Longer axonal projections are more expensive in terms of their material and energy costs[33]. It has been suggested that the spatial layout of neurons or brain regions[34,35] is economically arranged to minimize axonal volume. Thus, conservation of wiring costs is likely to be an important selection pressure on the evolution of brain networks.

Mapping structural networks in animal models. Tracing individual neuronal processes has been a long-standing technological challenge, and few structural brain networks have been mapped at cellular resolution. Serial reconstruction of electron microscopy sections allowed the complete connection matrix of the nematode *Caenorhabditis elegans* to be visualized[36]. Currently, this is the only nervous system to have been comprehensively mapped at a cellular level, and it was the first to be described as a small-world network[18]. In larger brains, combinations of physiological and anatomical techniques have allowed patterns in neuronal connections to be identified, leading to the identification of neuronal microcircuits[37] and the formulation of probabilistic connection rules[30]. Small-world properties have been demonstrated in biologically accurate models of cellular networks in the reticular formation of the vertebrate brainstem[38]. Reconstruction of cellular networks in the mammalian neocortex from multielectrode activity recordings has revealed several highly nonrandom features of connectivity[39], including a tendency for synaptic connections to be reciprocal and clustered. A promising approach for mapping connectivity involves the stochastic expression of several fluorescent proteins[40], and this may ultimately deliver a complete map of the cellular interconnections of an entire brain[41].

Histological dissection and staining, degeneration methods and axonal tracing have been used to map cerebral white matter connections. The pathways identified by these methodologies have formed the basis for the systematic collation of species-specific anatomical connection matrices, including those for the macaque visual cortex[42] and the cat thalamocortical system[43]. Network analyses of such data sets demonstrated high clustering of functionally related areas with short average path lengths[44–46], hallmarks of a small-world architecture. Clusters identified by network analysis map on to known functional subdivisions of the cortex[43]. Long-distance cortical projections facilitate short-path communication despite increasing axonal volume[47]. The cortical networks of several mammalian species also consistently demonstrated an overabundance of motif classes associated with network modularity and functionally diverse circuitry[48,49].

Mapping structural networks in the human brain. Several attempts have been made to map the structural networks of the human brain, also known as the human connectome[50], at the scale of brain regions. One

Connectivity
In the brain, connectivity can be described as structural, functional or effective. Structural connectivity denotes a network of anatomical links, functional connectivity denotes the symmetrical statistical association or dependency between elements of the system, and effective connectivity denotes directed or causal relationships between elements.

Microcircuit
A neuronal network composed of specific cell types and synaptic connections, often arranged in a modular architecture and capable of generating functional outputs.

Connectome
The complete description of the structural connections between elements of a nervous system.

Box 4 | **Origins of graph theory**

Graph theory is rooted in the physical world[155]. In 1736, Euler showed that it was impossible to traverse the city of Königsberg's seven bridges across the river Pregel exactly once and return to the starting point. To prove this conjecture, Euler represented the problem as a graph, and his original publication[156] is generally taken to be the origin of a new branch of mathematics called graph theory. In the middle of the nineteenth century, the analysis of electrical circuits and the exploration of chemical isomers led to the discovery of additional graph theoretic concepts[149]. Today, graph theory pervades many areas of science.

Significant progress in graph theory has come from the study of social networks[157]. One prominent experiment[153] tracked paths of acquaintanceship across a large social network and found that even very large networks could be traversed, on average, in a small number of steps. Although this 'small-world' phenomenon quickly captured the public imagination, its origins remained obscure until its association with specific types of connectivity was demonstrated (BOX 3). The dual discoveries of small-world[18] and scale-free[90] networks launched the modern era of graph theory, which now extends into biology and neuroscience. Neural systems have long been described as sets of discrete elements linked by connections. Nonetheless, graph theory has essentially only been applied to neuroscience in the past 10 years.

Diffusion tensor imaging
(DTI). An MRI technique that takes advantage of the restricted diffusion of water through myelinated nerve fibres in the brain to map the anatomical connectivity between brain areas.

Diffusion spectrum imaging
An MRI technique that is similar to DTI, but with the added capability of resolving multiple directions of diffusion in each voxel of white matter. This allows multiple groups of fibres at each location, including intersecting fibre pathways, to be mapped.

Cortical parcellation
A division of the continuous cortical sheet into discrete areas or regions; Brodmann's division of the cortex into areas defined by their cytoarchitectonic criteria is the most famous but not the only parcellation scheme.

Neuronographic measurements
Recordings of epileptiform electrical activity at specific sites in the cortex following topical application of a pro-convulsive drug to a distant cortical site; rapid propagation of electrical activity from stimulation to recording sites implies that the sites are anatomically connected.

Functional MRI
(fMRI). The detection of changes in regional brain activity through their effects on blood flow and blood oxygenation (which, in turn, affect magnetic susceptibility and tissue contrast in magnetic resonance images).

Electroencephalography
(EEG). A technique used to measure neural activity by monitoring electrical signals from the brain, usually through scalp electrodes. EEG has good temporal resolution but relatively poor spatial resolution.

Magnetoencephalography
(MEG). A method of measuring brain activity by detecting minute perturbations in the extracranial magnetic field that are generated by the electrical activity of neuronal populations.

study derived structural connection patterns from cross-correlations in cortical thickness or volume across individual brains, which might indirectly indicate the presence of corticocortical pathways[51,52]. Graph analysis revealed small-world attributes and the existence of local communities of brain regions. A more detailed analysis[53] of the modularity or community structure of connection data sets derived from cortical thickness correlations revealed significant overlap between anatomical network modules and functional systems in the cortex.

Human brain structural networks have also been mapped using diffusion imaging and tractography. A map of 70–90 cortical and basal brain grey matter areas was constructed using diffusion tensor imaging (DTI) and analysed using methods from graph theory[54,55]. The network exhibited high clustering and short path length, and contained motif classes similar to those identified from tract-tracing data[48]. Several areas, including the precuneus, the insula, the superior parietal cortex and the superior frontal cortex, were found to have high 'betweenness centrality' and thus to constitute putative hubs. Another study that mapped connections between 78 cortical regions using DTI also identified several hub regions, including the precuneus and the superior frontal gyrus[56].

Due to limitations in the model that is used to infer fibre bundle orientation, DTI has difficulty detecting crossing fibre bundles. Diffusion spectrum imaging can overcome this limitation by reconstructing multiple diffusion directions in each voxel[57] and was used to build cortical connection matrices between 500–4,000 homogeneously distributed regions of interest[58]. Again, network analyses revealed the small-world architecture of the cortical network. A more extensive analysis of 998 region-of-interest networks obtained from 5 participants[59] identified structural modules interconnected by highly central hub regions. When considering multiple network measures (including node degree, connection strength and centrality), a particular set of brain regions located predominantly in the posterior medial cortex, including portions of the posterior cingulate and the precuneus, was highly and densely interconnected, forming a structural core[59].

Although they differ in terms of their experimental methodology and cortical parcellation, most of these studies reveal highly clustered large-scale cortical networks, with most pathways existing between areas that are spatially close and functionally related. These clusters or modules are interlinked by specialized hub regions, ensuring that overall path lengths across the network are short. Most studies identified hubs among parietal and prefrontal regions, providing a potential explanation for their well-documented activation by many cognitive functions. Particularly notable is the prominent structural role of the precuneus[55,56,59], a region that is homologous to the highly connected posteromedial cortex in the macaque[60]. The precuneus is involved in self-referential processing, imagery and memory[61], and its deactivation is associated with anaesthetic-induced loss of consciousness[62]. An intriguing hypothesis suggests that these functional aspects can be explained on the basis of its high centrality in the cortical network.

Functional brain networks

Although analysing structural networks helps us to understand the fundamental architecture of inter-regional connections, we must also consider functional networks directly to elucidate how this architecture supports neurophysiological dynamics. Despite considerable heterogeneity in the methodological approaches, there is an encouraging degree of convergence between studies of functional brain networks. The first such study used a set of neuronographic measurements of the propagation of epileptiform activity following localized applications of strychnine to the macaque cortex[63]. This demonstrated a pattern of functional connections between cortical areas that was consistent with a small-world network. As we discuss below, these findings have been extended by studies based on functional MRI (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) or multielectrode array (MEA) data.

Although such studies based on graph theory are the focus of this Review, we note that other methods to investigate brain functional systems have recently been developed, including mathematical models of effective connectivity between regions. Effective connectivity models, such as structural equation modelling[64,65], dynamic causal modelling[66] or Granger causality[67], involve estimating the causal influence that each element of a system exerts on the behaviour of other elements. Thus, measures of effective connectivity

between multiple regions can be used to generate a directed graph, which can then be topologically described using graph theory. However, the functional network studies reviewed below have all been based on undirected graphs, derived from simpler measures of functional connectivity or symmetrical statistical association between brain regions. The key point is that, in principle, graph theory could be applied to an association matrix of either functional or effective connectivity measures, to generate either undirected or directed graphs, respectively, although all neuroscientific studies to date have in fact been based on measures of functional connectivity.

Mapping functional networks using fMRI. The first graph theoretical study of fMRI data measured the partial correlations of resting-state blood oxygen level-dependent (BOLD) signals between 90 cortical and subcortical regions and reported small-world properties of the resulting whole-brain networks[68]. Almost simultaneously, another study reported small-world properties of functional networks derived from a set of activated voxels in fMRI data; this voxel-level network was also reported to have a scale-free degree distribution[69]. Subsequently, small-world properties, with parameter values similar to those previously reported in topological studies of cat and macaque anatomical connectivity matrices[50], were confirmed in a low-frequency (0.03–0.06 Hz) whole-brain network derived from wavelet correlations between regional mean time series[70]. The high-degree nodes or hubs of this network were mostly regions of multimodal association cortex, and the degree distribution was an exponentially truncated power law[70]. Other studies have explored the community structure of fMRI networks using a hierarchical cluster analysis[68,71,72] and shown that functionally and/or anatomically related brain regions are more densely interconnected, with relatively few connections between functional clusters, again echoing prior work on anatomical connectivity matrices. The high density of connections between functionally related regions increases the clustering coefficient of the graph, whereas the long-range connections between different modules or clusters, even though they are relatively few in number, keep the path length low. Thus, the small-world architecture of a brain functional network is closely related to its modularity[72].

There are several other metrics for quantifying small-world architecture in brain functional networks. Studies in statistical physics[73,74] have shown that path length is inversely related to the global efficiency of a network for the transfer of information between nodes by multiple parallel paths, and that global efficiency is easier to estimate than path length when studying sparse networks. Furthermore, the clustering coefficient can be regarded as a measure of the local efficiency of information transfer, or of the robustness of the network to deletion of individual nodes. The structural network of the macaque brain was found to have high global and local efficiency and to be sparsely connected[73,74]. Thus, the macaque cortex has 'economical small-world' properties: it has high global efficiency of parallel information transfer and high local fault tolerance for relatively low connection density.

These concepts were translated to the analysis of resting-state fMRI data acquired from young and elderly adults[75], using the wavelet correlation (a measure of the association between time series in a specific frequency band) to estimate the functional connectivity between regional BOLD time series endogenously oscillating in the frequency interval 0.06–0.1 Hz (for a more detailed review of the rationale for wavelet analysis in fMRI, see REF. 76). In younger adults, functional brain networks demonstrated small-world properties over a broad range of connection densities or 'costs'. Relatively sparse networks were associated with maximum cost efficiency. The older age group also showed evidence of small-world properties, but had significantly reduced cost efficiency: they had to be relatively over-connected to provide the efficiency of parallel information transfer seen in a younger brain network. The suggestion that aging is associated with changes in the economical small-world properties of brain functional networks converges with studies that show differences in attentional and default-mode networks between children and young adults[77]. Normal processes of brain maturation and senescence might thus be reflected in quantifiable changes in functional network topology.

Mapping functional networks using electrophysiological techniques. When comparing the results of fMRI studies to results obtained using electrophysiological techniques (EEG, MEG or MEA), many aspects of the data clearly differ. fMRI has good spatial resolution (on the order of millimetres) but poor temporal resolution (on the order of seconds), restricting the measurable bandwidth to approximately 0.001–0.5 Hz, and fMRI measures activation-related haemodynamics rather than neuronal activity *per se.* All electrophysiological methods measure neuronal activity more directly and have better temporal resolution, with bandwidths typically of 1–100 Hz, but they often have worse spatial resolution (on the order of millimetres or centimetres for MEG and EEG) or less complete anatomical coverage (in the case of MEA) than fMRI. Another point of difference is that the nodes of a network derived from fMRI data will be anatomically localized regions or voxels of the image, whereas the nodes of a network derived from MEG or EEG data could be the surface sensors or recording electrodes. However, we can compare the topologies of networks derived from these different data sets by invoking a general operating principle of complex network analysis: microscopically distinct systems can be informatively compared in terms of their macroscopic organization using graph theory.

Functional connectivity between pairs of electrodes has been estimated using a measure of generalized synchronization[78], and then thresholded to generate functional networks, in several studies of EEG or MEG data sets. This has shown that small-world topology is represented at many frequency intervals[79] and can be related to cognitive performance and normal aging[80]. An alternative approach used the wavelet correlation to estimate frequency-dependent functional connectivity between MEG sensors, again revealing that many topological and

Multielectrode array
(MEA). A technique for simultaneously measuring the electrical activity of local neuronal populations or single neurons, usually in tissue slices or cell cultures *in vitro*.

Association matrix
A matrix that represents the strength of the association between each pair of nodes in a graph. Association between nodes can be quantified by many continuously variable metrics, such as correlation or mutual information. Either functional or effective connectivity measures can be used to construct an association matrix.

Blood oxygen level-dependent (BOLD) signals
Changes in magnetic susceptibility and MRI tissue contrast that are indirectly indicative of underlying changes in spontaneous or experimentally controlled brain activation.

Default-mode network
A set of brain regions, including medial frontal and posterior cingulate areas of the cortex, that are consistently deactivated during the performance of diverse cognitive tasks.

dynamic properties of brain functional networks were conserved across frequencies[81]. This timescale invariance of wavelet correlations and the brain functional network parameters derived from them is a theoretically predictable corollary of the long-range autocorrelations of neurophysiological time series[82–84].

Conservation of functional network properties. There have been fewer studies of functional networks in non-human species. In anaesthetized rats, fMRI has been used to demonstrate small-world and modular properties of whole-brain functional networks[85]. A recent study considered functional coupling between pairs of cortical neurons, measured by multiunit electrodes, in the visual cortex of the anaesthetized cat[86]. Most of the properties of these neuronal-interaction networks could be accounted for by the pairwise correlations between electrodes[87,88], and the networks had small-world properties with some highly connected (hub) neurons. The small-world organization of functional networks at a cellular level has also been described on the basis of MEA recordings from *in vitro* cultures of cortical networks[89]. These results indicate that small-worldness might be a conserved property of brain functional networks over different species and spatial scales.

Preliminary evidence suggests that other topological properties of brain functional networks, such as the degree distribution, might also be conserved over spatial and temporal scales. Many large networks exhibit scale-free power law degree distributions[90] indicative of the existence of highly connected nodes (BOX 3). Some studies of functional brain networks carried out at high spatial resolution (single voxels in fMRI) have provided evidence of scale-free organization[69,91]. However, in other studies of functional networks derived from fMRI and MEG data sets over a wide range of frequency intervals[70,81], the empirical degree distribution conforms to an exponentially truncated power law, implying that the probability of a highly connected node or hub is greater than in an equivalent random network but less than would be expected in a scale-free network. Truncated power law degree distributions have also been reported from analysis of anatomical networks derived from structural MRI data in humans[55], and from analysis of functional networks derived from MEA data in cats[86]. These distributions are typical of physically embedded networks, such as the global air-transportation network, in which the maximum degree is limited by physical considerations such as the finite capacity of any node to receive connections[27]. The reasons for the differences between these findings and reports of scale-free properties are currently unknown; however, it is notable that pure power law scaling of the degree distributions of human brain functional networks has only been reported by voxel-level analysis, whereas exponentially truncated power laws have been reported by region-level analysis. The form of the degree distribution could be affected by spatial interpolation, and other pre-processing steps applied before the construction of functional networks and the standardization of such methodological procedures will be important in elucidating the impact of anatomical resolution on the extent to which power law scaling of the degree distribution is truncated at high degree.

Structure–function relations in brain networks

How do functional brain networks emerge from structural brain connectivity? Structural maps indicate that each neural node maintains a specific pattern of structural connections with other nodes. Different nodes often have different functionalities, such as specific response preferences to sensory stimuli. From a network perspective, the functionality of an individual neural node is partly determined by the pattern of its interconnections with other nodes in the network[92]: nodes with similar connection patterns tend to exhibit similar functionality[36]. Although functional properties are expressed locally, they are the result of the action of the entire network as an integrated system. Structural connectivity places constraints on which functional interactions occur in the network.

Structural and functional connectivity in cellular networks undergo dynamic changes. The degree to which synaptic connectivity is modified in the adult brain is highly debated. Although some evidence suggests that mammalian cellular networks are continually remodelled[93], other evidence indicates that most synaptic spines are stable[94]. Changes in neuronal connectivity necessitate homeostatic mechanisms to ensure functional stability[95]. Multielectrode recording data suggest that cellular functional networks exhibit transient synchronization[96] and metastable dynamics[97]. These changes occur within seconds, and it seems possible that even more rapid transitions and network reconfigurations may take place[33]. These observations of relatively slow structural modifications accompanied by faster changes in functional linkages pose major unresolved questions regarding functional stability in neural circuits.

It is currently unknown whether large-scale cortical networks in the adult brain undergo structural modifications on fast timescales. Most of the changes that have been observed were associated with aging, disease progression or experience-dependent plasticity. By contrast, patterns of functional connectivity between brain regions undergo spontaneous fluctuations and are highly responsive to perturbations, such as those that are induced by sensory input or cognitive tasks, on a timescale of hundreds of milliseconds. These rapid reconfigurations do not affect the stability of global topological characteristics[81,98]. On longer timescales of seconds to minutes, correlations between spontaneous fluctuations in brain activity[99–101] form functional networks that are particularly robust. For example, a set of posterior medial, anterior medial and lateral parietal brain regions comprises the default mode network[102,103].

The persistence of functional networks associated with the brain's resting state provides an opportunity to investigate how much of the pattern of functional connections is determined by underlying structural networks. Observations from a single cortical slice[104], structural imaging of fibre bundles linking components of the default network[105], and direct comparisons of structural and functional connectivity in the same cohort

Metastable dynamics
Transitions between marginally stable network states; these transitions can occur spontaneously or as a result of weak external perturbations.

Resting state
A cognitive state in which a subject is quietly awake and alert but does not engage in or attend to a specific cognitive or behavioural task.

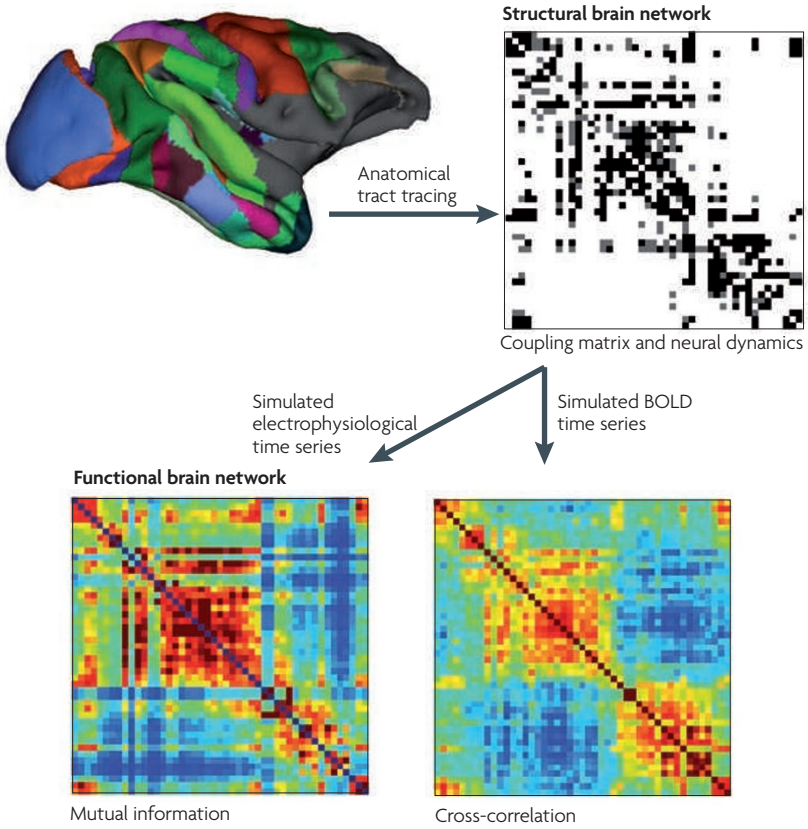


Figure 1 | **Computational modelling of structural and functional brain networks.** Computational models have been used to demonstrate how dynamic patterns arise as a result of interactions between anatomically connected neural units. Shown is how such a model is generated and used. A structural brain network derived from anatomical data serves as a matrix of coupling coefficients that link neuronal nodes, the activities of which unfold through time. This time evolution is governed by physiologically motivated dynamic equations. In the example shown, the surface of the macaque cortex was subdivided into 47 areas (nodes) and a structural brain network linking these nodes was compiled from anatomical tract-tracing data. The dynamic equations were derived from a model of large neuronal populations, the parameters of which were set to physiological values[109]. Data from computer simulations then yield functional brain networks. Such networks are derived from measures of association between the simulated time series — for example, an information theoretic measure such as the mutual information (computed on voltage–time data) or cross-correlations in neural activity that are computed from simulated blood oxygen level-dependent (BOLD) data. These matrices can then be thresholded to yield binary networks from which network measures can be derived. The fact that both structural and functional networks are completely specified in the model facilitates their comparative analysis. The structural brain network panel is reproduced, with permission, from REF. 109 © (2007) National Academy of Sciences. The rest of the figure is modified, with permission, from REF. 158 © (2009) Academic Press.

of participants[63,106,107] suggest that structural connections are highly predictive of functional connections. Indirect interactions can account for additional functional linkages. Such indirect connections can lead to discrepancies between structural and functional connectivity; however, current evidence suggests that topological parameters are generally conserved between structural and functional networks.

Computational models offer a complementary method to investigate structure–function relations in brain networks. Several studies have used empirically derived structural brain networks to specify the wiring between neural units, which then results in spatially patterened dynamic interactions (FIG. 1). The covariance structure of the endogenous activity generated by these neural units yields a functional network that can be generated by computer simulations or in some cases analytically[108]. This strategy has been used to determine the effects of structural topology on functional networks and dynamics. Simulation studies of large-scale cortical networks demonstrated the emergence of complex spatiotemporal structure in neural correlations at multiple timescales[109], as well as realistic patterns of modelled BOLD resting-state correlations that depend on the topology[109] and time delays[110] in the structural coupling matrix. The topology of structural and functional networks was identical when functional connectivity was estimated from long time samples, but functional networks estimated on shorter time samples or at higher frequencies were less strongly constrained by the structural wiring diagram[109]. Likewise it has been shown that the modularity of structural networks can determine the hierarchical organization of functional networks[111,112] and may be important for generating diverse and persistent dynamic patterns[113]. In a computational model of phase synchronization between coupled neurons, patterns of local versus global synchronization were found to depend strongly on the balance between high clustering and short path length in the connectivity of the network[114]. Computational studies have also begun to determine the effects of functional activity on structural topology. It has been shown that an initially random wiring diagram can evolve through synaptic plasticity to a functional state characterized by a small-world topology of the most strongly connected nodes and by self-organized critical dynamics[115].

These findings indicate that the brain's structural and functional networks are intimately related and share common topological features, such as modules and hubs (FIG. 2). Although most studies provide support for the idea that structural networks determine some aspects of functional networks, especially at low frequencies or over long time periods, it is less clear how the structural topology both supports the emergence of fast and flexibly reconfigured functional networks and is itself remodelled by function-related plasticity on a slower timescale.

Clinical and translational aspects

Since the work of pioneers such as Wernicke, Meynert and Dejerine, it has been appreciated that many neurological and psychiatric disorders can be described as dysconnectivity syndromes[116]. The emergence of symptoms or functional impairment in these disorders can be theoretically related to the disruption or abnormal integration of spatially distributed brain regions that would normally constitute a large-scale network subserving function.

Using network properties as diagnostic markers. One application of complex-network theory in this context is to provide new measures to quantify differences between patient groups and appropriate comparison groups. Several studies have reported that the parameters of

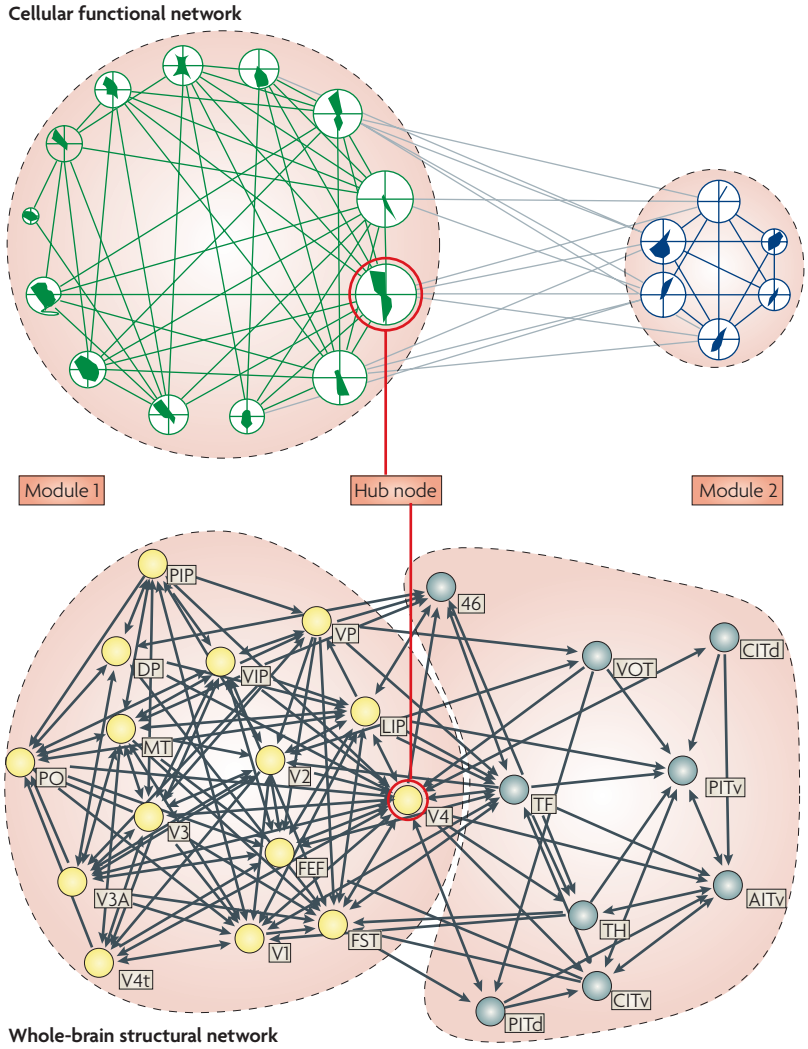


Figure 2 | **Cellular and whole-brain networks demonstrate consistent topological features.** The top panel shows a cellular functional network constructed from multi-electrode-array recordings made in the anaesthetized cat; each node (represented by a circle) corresponds approximately to one neuron and the connections represent high functional connectivity between neurons[86]. The different coloured nodes constitute separate clusters or modules. The plots in each circle illustrate cellular responses to stimuli of different orientations, and the circle size corresponds to the degree (number of functional connections) of each node. The bottom panel shows a whole-brain structural network constructed from histological data on the macaque cortex; each node corresponds to a brain area and the connections represent axonal projections between areas[49]. The network has two main modules, shown here with yellow and grey circles corresponding to mostly dorsal and ventral visual regions, respectively. Both networks exhibit the small-world attributes of high clustering and short path length (see BOX 3); both have an exponentially truncated power law degree distribution (see BOX 2), associated with the existence of high-degree 'hubs' (V4 in the anatomical network); and both have a community structure characterized by sparse connectivity between modules (each module is enclosed by stippled lines) and linked by hubs (nodes circled in red). AITv, anterior inferotemporal ventral area; CITd, central inferotemporal dorsal area; CITv, central inferotemporal ventral area; DP, dorsal preluneate area; FEF, frontal eye field; FST, floor of superior temporal area; LIP, lateral intraparietal area; MT, middle temporal area; PIP, posterior intraparietal area; PITd, posterior inferotemporal dorsal area; PITv, posterior inferotemporal ventral area; PO, parieto-occipital area; TF, area TF; TH, area TH ;V1–4, visual cortical areas 1–4; VIP, ventral intraparietal area; VOT, ventral occipitotemporal area; VP, ventral posterior area. The top panel is reproduced, with permission, from REF. 86 © (2008) Oxford University Press. The bottom panel is reproduced from REF. 49.

brain networks derived from fMRI, EEG or structural MRI data are altered in patients with schizophrenia or Alzheimer's disease (AD).

In an fMRI study of AD, clustering was significantly reduced at a global level (in whole-brain networks operating at frequencies below 0.1 Hz) and at a local level (in both hippocampi), and global clustering was able to discriminate AD patients from age-matched comparison subjects with high specificity and sensitivity, implying that the loss of small-world network properties might provide a clinically useful diagnostic marker[117]. In a comparable EEG study, path length in beta band (15–35 Hz) functional networks was significantly increased in patients with AD. Importantly, the variability of cognitive function across both control and AD groups was negatively correlated with path length, providing direct evidence that functional-network topology can be related to variation in cognitive performance[118]. A third MEG study of resting-state functional networks confirmed a degradation of small-world attributes in patients with AD and suggested that this effect is due to disease-related changes at highly connected network hubs[119]. However, in a fourth study that used between-subject covariation in regional measures of cortical thickness to infer anatomical networks from a large structural MRI data set, global clustering was significantly increased in patients with AD and there were abnormalities in the topological configuration of crucial, high-centrality nodes in regions of the multimodal association cortex[120].

Schizophrenia has been investigated by comparable approaches. The economical small-world properties of low-frequency functional networks derived from fMRI data were shown to be impaired in patients with schizophrenia[121]. Studies that used EEG to measure synchronization likelihood or nonlinear interactions between cortical nodes found that the clustering and path-length parameters of functional networks were closer to their values in random graphs for patients with schizophrenia than for comparison subjects[122,123]. Anatomical networks derived from inter-regional covariation of grey matter density in structural MRI data showed differences in the hierarchy and assortativity of multimodal and transmodal cortical subnetworks in healthy volunteers, suggesting that these major divisions of the cortex may have developed according to different growth rules or evolved to meet different selection criteria. Topological abnormalities in people with schizophrenia included a reduced hierarchy of multimodal cortex (FIG. 3). The schizophrenic group's networks also exhibited relatively long physical distances between connected regions, compatible with inefficient axonal wiring[124].

Thus, there is convergent evidence from methodologically disparate studies that both AD and schizophrenia are associated with abnormal topological organization of structural and functional brain networks. However, there are also inconsistencies between existing studies — for example, clustering is reportedly increased in the structural networks[120] but decreased in the functional networks of patients with AD[117] — which might be attributable to the clinical heterogeneity of the

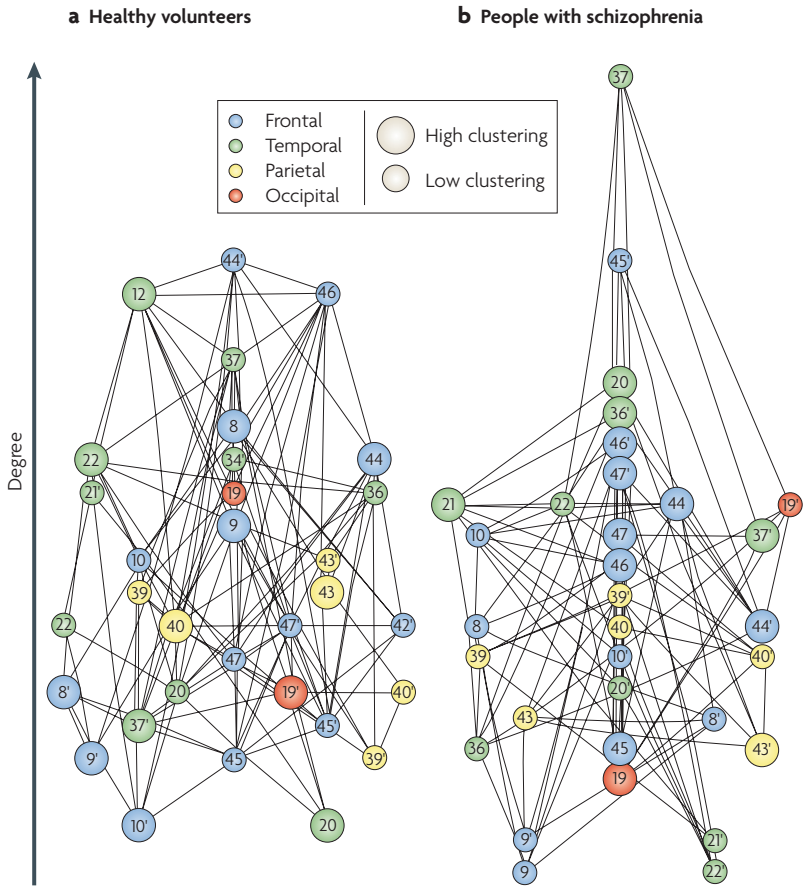


Figure 3 | **Disease-related disorganization of brain anatomical networks derived from structural MRI data.** In both parts, the nodes (circles) represent cortical regions and the connections represent high correlation in grey matter density between nodes. The nodes are arranged vertically by degree and are separated horizontally for clarity of representation. The numbers indicate approximate Brodmann area, and the prime symbols (′) denote left-sided regions. The clustering coefficient of each node, a measure of its local connectivity, is indicated by its size: nodes with high clustering are larger. **a** | The brain anatomical network of the healthy volunteers has a hierarchical organization characterized by low clustering of high-degree nodes[24]. **b** | The equivalent network constructed from MRI data on people with schizophrenia shows loss of this hierarchical organization — high-degree nodes are more often highly clustered. Figure is reproduced, with permission, from REF. 124 © (2008) Society for Neuroscience.

patient groups as well as to the differences in imaging and analytic methods. Some of these differences may perhaps be resolved by studies combining network measurements on structural and functional neuroimaging data acquired on the same patients. It also seems likely that evidence for network abnormalities in other neuropsychiatric disorders and conditions (such as epilepsy[125–127], attention-deficit hyperactivity disorder[128] or spinal cord injury[129]) will accumulate as the disorders are increasingly investigated from this perspective.

Understanding the pathogenesis and treatment of brain disorders from a network perspective. Many psychiatric disorders are highly heritable and are likely to represent the clinical outcome of aberrations in the formation of large-scale networks *in utero* or during early postnatal life. Measures of network topology may be worth investigating as intermediate phenotypes, or endophenotypes, that indicate the genetic risk for a neuropsychiatric disorder; however, network metrics have not yet been adopted for this purpose. A study of healthy twin pairs has shown that classical small-world metrics on brain functional networks derived from EEG data have high heritability[130], a necessary prerequisite for their candidacy as disease endophenotypes. Another study of graph theoretical measures of anatomical networks derived from inter-regional correlations in cortical-thickness MRI measurements on a sample of normal twins, singletons and singleton siblings of twins showed that genetically determined frontoparietal networks had small-world properties[131]. Network metrics are arguably more attractive as intermediate phenotypes than local measures of brain (dis)organization, because computational models of network development are often available to test mechanistic hypotheses for how an observed profile of anatomical or functional dysconnectivity in a mature network might have been generated by earlier developmental abnormalities[24,132].

Another example of how empirical and computational approaches can be usefully combined is provided by studies that have 'lesioned' anatomical or functional network models — for example, by deleting nodes or connections — to explore how acute and focal damage could affect the overall performance of brain networks[70,133,134]. Networks can be lesioned by random deletion of nodes or edges, or by targeted attack on the highest-degree nodes in the network. The vulnerability of the network to damage is assessed by comparing its topological or dynamical behaviour after the lesioning to its intact behaviour. Different network topologies confer different vulnerabilities to the effects of random or targeted attack. For example, scale-free networks are robust to random error but highly vulnerable to deletion of the network hubs. Brain functional networks with an exponentially truncated power law degree distribution were found to be less vulnerable to attack than scale-free networks[70]. In an anatomically informed computational model, deletion of hub nodes produced widespread disruptions of functional connectivity[53,134] that were consistent with effects reported in focal human brain lesions[135,136]. Computational lesioning of network models was also used to explore the functional consequences of a gradual and precisely specified disease process: the elimination of long-range projections and the sprouting of short-range connections in a model of epileptogenesis in the rat dentate gyrus[137]. The topology of the normal or non-epileptic dentate gyrus became relatively over-connected and dynamically hyperexcitable as a result of cellular changes previously described in relation to temporal lobe epilepsy. Other studies of models of temporal lobe epilepsy have shown loss of small-world topology in cellular networks during hypersynchronized bursting[138] and have shown that variation of small-world topological and synaptic properties of a computational model can cause transitions between normal, bursting and seizing behaviours[139].

It is also conceivable that network analysis can be used to further our understanding of the therapeutic effects of pharmacological or psychological therapies.

Assortativity
A measure of the tendency for nodes to be connected to other nodes of the same or similar degree.

Endophenotype
A quantifiable biological marker of the genetic risk for a neuropsychiatric disorder.

Dopaminergic drugs can modulate measures of functional connectivity in animal and human fMRI[140,141] and MEG recordings[142], suggesting that drug effects might be quantifiable in terms of altered functional network topology. This has been confirmed directly in a study which demonstrated that a dopamine D2 receptor antagonist impaired the economical small-world properties of human brain fMRI networks[75]. Future work might include efforts using graph theoretical measures to quantify how therapeutically effective treatments remediate topologically sub-optimal network configurations in patients.

Conclusions and prospects

It is clear that certain aspects of the organization of complex brain networks are highly conserved over different scales and types of measurement, across different species and for functional and anatomical networks. The archetypal brain network has a short path length (associated with high global efficiency of information transfer), high clustering (associated with robustness to random error), a degree distribution compatible with the existence of hubs, and a modular community structure. Furthermore, anatomical networks are sparsely connected, especially between nodes in different modules, and the 'wiring length' (the physical distance that connections span) is close to minimal. This profile of topological and geometric properties is typical not just of brain networks but also of many other complex networks, including transport systems and intracellular signalling pathways[17,73]. Why might this be so?

A parsimonious hypothesis is that many spatially embedded complex networks have evolved to optimize the same set of competitive selection criteria — high efficiency of information transfer between nodes at low connection cost — or to achieve an optimal balance between functional segregation and integration that yields high complexity dynamics[14]. If wiring cost was exclusively prioritized the network would be close to a regular lattice, whereas if efficiency was the only selection criterion the network would be random. The existence of a few long-range anatomical connections can deliver benefits in terms of efficiency and could arguably account for the evolution of economical small-world properties in brain networks at all scales[20,51]. This hypothesis needs to be more directly explored and tested, perhaps using evolutionary algorithms in computational models of brain network selection[48].

A key issue for the future will be to consolidate our understanding of how functional networks interact with their structural substrates. At low frequencies, or over long time periods, there are reasons to expect that functional networks should be highly isomorphic with underlying structural networks[84,109]. But clearly function can be adaptive over much shorter timescales than structure. We need to understand more about the non-stationarity or metastability[143] of brain functional networks. How does functional network topology change over time? Do functional networks exist in a dynamically critical state at some or all frequency intervals[144–146]? What constraints on the itinerancy of network dynamics are imposed anatomically and how does the long-term history of functional activity in a network feed back on the development and remodelling of the anatomical connections between nodes?

A related question concerns how the parameters of complex brain networks relate to cognitive and behavioural functions. One can make an intuitively reasonable claim that high clustering favours locally specialized processing whereas short path length favours globally distributed processing; but the empirical evidence is currently almost non-existent. This will probably be a key focus of future work that might be combined with further studies of clinical disorders or cohorts at different stages of normal development.

The emerging field of complex brain networks raises a number of interesting questions and provides some of the first quantitative insights into general topological principles of brain network organization. The fundamental growth in the statistical mechanics of complex networks, and the power and elegance of graph theoretical analysis, suggests that this approach will play an increasingly important part in our efforts to comprehend the physics of the brain's connectome.

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Acknowledgements
E.B. was supported by a Human Brain Project grant from the National Institute of Mental Health and the National Institute of Biomedical Imaging & Bioengineering. The Behavioural & Clinical Neurosciences Institute in the University of Cambridge is supported by the Wellcome Trust and the Medical Research Council (UK). O.S. was supported by the JS McDonnell Foundation.

Competing interests statement
The authors declare competing financial interests: see web version for details.

FURTHER INFORMATION
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