

# Network Theory in Neuroscience

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## Synonyms

[Complex network theory in neuroscience](#); [Graph theory in neuroscience](#)

## Definition

Network theory is a branch of mathematics concerned with the analysis of the structure of graphs, the mathematical abstraction of networks. Since the beginning of the twenty-first century, it has become an applied discipline due to the availability of large datasets for social, technological, and biological systems. Although network theory was initially restricted to topological analysis, it has soon become a tool for understanding the emergence, functioning, and evolution of networks and the dynamical processes occurring on them. The application of network theory to neuroscience and, more specifically, to the analysis of brain structure and function represents a qualitatively different view of brain activity and brain-behavior mapping, shifting from a computerlike to a complex system vision of the brain, where networks are endowed with properties which stem in a nontrivial way from those of their constituent nodes. The network approach allows addressing an entirely new set of issues, such as detection and description of modularity and hierarchical structure, evaluation of efficiency and vulnerability, and structure-function relationships in healthy brains and disease.

## Detailed Description

### Background

The brain can be understood as a network of cells forming a massively parallel system, organized to carry out three major functions: computation, information transport, and communication among computational structures.

Brain tissue can be separated into gray matter (neurons) and white matter fibers connecting neurons (axons and dendrites). The human brain consists of roughly  $10^{10}$ – $10^{11}$  neurons. Each neuron has approximately  $10^4$  synapses, which directly connect it to other neurons. The total wiring in the human cortical gray matter is of the order of  $10^5$ – $10^6$  km, resulting in an overall neuronal potential bandwidth of the order of the terabit/second. Furthermore, the brain performs an estimated  $10^{15}$  synaptic operations per second, but only consumes around 12 W, thus achieving an operation/joule ratio several orders of magnitude higher than the fastest available microprocessors (Sarpeshkar 1997).

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On the other hand, powering the human adult brain accounts for ~20 % of resting energy consumption (~60 % in infants). Neuronal signal transmission through axons and synapses accounts for about 50 % of the brain's overall consumption (Laughlin and Sejnowski 2003), and due to the dense interconnected structure of its axons and synapses, the cortical gray matter uses more than 75 % of total energy consumption for signaling. The energy supply limits both the total size and the amount of information that can be transmitted within the brain at a time.

The brain achieves these impressively high levels of computational efficiency by adopting energy-efficient architectures, involving trimming of superfluous signals and the representation of information with energy-efficient codes, resulting in appropriate distribution of the signal in space and time (Laughlin and Sejnowski 2003).

### Brain Anatomy and Functional Activity

Human brain anatomy is characterized by networks of coupled neural systems across many spatial scales. Vertical structures divide the cortex into six main layers, within which basic computational units can somehow heuristically be defined as *minicolumns*, consisting of dense local interconnections between excitatory cells and inhibitory interneurons. Couplings between these local regions arise through sparse long-range excitatory projections, such as cortico-cortical fibers. These couplings facilitate large-scale integrative processes involving coordination between specialized networks.

Functional brain activity consists of transient episodes of synchronized/desynchronized activity between different parts of the brain (Breakspear 2002). Synchronization may facilitate integrative functions, by transiently binding together spatially distributed neural populations in parallel networks during sensory perception and information processing (Singer 1995; Miltner et al. 1999). Desynchronization may allow the brain to flexibly switch from one coherent state to another (Rodriguez et al. 1999). Asynchronous (nonlinear) couplings may also play an important role in functional integration, facilitating the creation of transient context-sensitive coherent neural assemblies between distant brain regions (Friston 2000).

### Brain Connectivity

A network representation arises naturally both for the brain's anatomy and its functional activity. Brain networks can be defined at different scales, from the micrometer scale to the millimeter or centimeter scale of system-level neural assemblies, corresponding to the spatial resolution of the brain imaging technique used to define them.

For anatomical brain networks, it is straightforward to identify nodes as neurons or cortical areas and edges with axons or fiber tracts. On the other hand, when considering *functional connectivity*, networks are defined where edges correspond to correlated activity at different brain regions. Finally, *effective connectivity* can be associated to networks with directed edges whenever activity at one node modulates activity at another node (Sporns et al. 2004).

The classical approach to brain connectivity reflects the two basic ingredients of early neuropsychology: localization of cognitive function into specialized brain modules and the role of connection fibers in the integration of various modules. Thus, the emphasis is on the *identity* of the particular nodes and links forming the networks, under the covert hypothesis that each node and each link provide a unique contribution to the structure and function of the brain. The general model is that of a computerlike box-and-arrow one: by and large, computations are carried out within nodes, with links essentially working as pipes in a hydraulic system. Connectivity analysis is typically used to validate simple models of a given aspect of brain activity, and networks with only a few nodes and links are considered. The overall meaning of a given network can be traced back to the sum of its

parts: an interpretation of a given connectivity pattern is in general proposed based upon the precise identity of its constituents' properties and on their known properties.

### The Complex Network Approach

Over the last decade, brain structure and function have started being investigated using *complex network theory* (Boccaletti et al. 2006; Newman 2010), a statistical physics approach to an old branch of pure mathematics: graph theory.

Graph theory studies the properties of the formal mathematical structures called graphs, which are representations of a set of objects where some pairs of objects are connected by links. Complex network theory focuses on how *real* networks are organized and aims at identifying the guiding rules behind observed structures and dynamics of observed networks. For instance, nodes and links can both be endowed with dynamical properties and resulting collective behaviors such as synchronization can be investigated. It is also possible to study processes using the network as their support.

The way nodes and links are connected is associated with a great number of topological and dynamical properties at all scales, from that of the node to that of the whole network, which eventually allow neuroscientists to address many hitherto unaddressed issues.

Behavioral dynamics and its transitions are naturally described in terms of rewiring processes and the evolution of quantifiable network properties. Thus, network theory endows brain scientists with a potentially very high number of associated metrics of brain structure and activity, and brain *organization* receives a quantitative characterization. Moreover, it allows finding similarities and differences in the organization of neural networks, in spite of considerable variability in size and surface shape of individual brains.

The complex network approach represents a *qualitatively* different view of brain activity and brain-behavior mapping. The brain is understood as a complex system, where relationships between a *great number* of constituent parts give rise to collective behaviors. The spirit of the statistical physics approach hinges on an understanding of observed network properties as macroscopic phenomena resulting from microscopic interactions among a great number of individual components. Thus, in this approach, the identity of nodes and links is somehow lost. The network, rather than well-specified nodes or links, is endowed with specific properties. In general, these network properties are not easily traced to their single nodes and links; rather, they *emerge* from the *statistical properties* of their components.

With respect to prior connectivity methods, the complex network approach presents a range of distinctive *advantages*: first, it affords a *multiscale* characterization of the brain's organization. Not only does network theory provide a description of network properties at microscopic, mesoscopic, and macroscopic scales, but it also naturally describes the *relationship across these scales*. Second, it allows handling complex relationships between brain structure, dynamics, and function. Third, it allows studying the brain as a biophysical machine and investigating a wide range of aspects of mechanistic brain functioning, including efficiency, resistance to failure, and synchronizability, which could not directly be addressed with connectivity techniques alone. Not only does network theory afford a quantitative description of directly observed states, but it also allows appraising the functional potential of healthy brains and the extent of the damage of those suffering from neurological or psychiatric pathologies.

Complex network theory therefore achieves three main *objectives*:

1. Singling out important anatomical and functional brain components

2. Characterizing general organizational principles of brain structure and function and as a consequence validating models of anatomical and functional brain organization, development, and pathology, as well as of cognitive function
3. Characterizing the brain, both anatomically and functionally, as a complex biophysical system whose constructive rules are subject to energetic constraints

## Tools

### What Is a Complex Network

A network consists of a group of  $N$  nodes (or vertices) connected through a set of  $L$  links (or edges). *Graph theory* focuses on the statistical properties of networks, mainly from a theoretical perspective. *Complex network theory* describes the analysis of real networks and the ways topological structure determines the dynamical processes occurring in networks. Most real networks have an organization that is neither regular nor random. Complex network theory studies the laws that govern network topology and dynamics, the rules that lead to the formation of these nonrandom patterns, how topology influences the dynamics on top of the network, and the interplay between dynamics and the evolution of the network structure (Boccaletti et al. 2006; Newman 2010).

### Building a Brain Network

The projection of experimental data onto a network is one of the most delicate steps in the application of network theory to the analysis of biological data. Both the nature (anatomical or functional) and the scale of observation constrain the way networks are reconstructed. The experimental technique used to record brain activity determines the size of the network and, ultimately, the information that can be extracted from it. Important methodological aspects of brain network reconstruction and possible pitfalls are still a subject of debate (Bialonski 2012; Zanin et al. 2012).

Brain networks can be classified into three main types: **anatomical, functional, and effective networks**.

**Anatomical networks** refer to the physical connections between neuronal elements, ranging from synapses between neurons to the grid of bundles between regions of interest (ROIs). We can define an anatomical network of connections at the scale we are interested in (or the scale given by experimental limitations): neurons, cortical columns, ROIs, or any parcellation of the brain with significant meaning. There exist different experimental techniques to trace the anatomical network of connections, which rely on both the scale and the organism being studied. For example, electron microscopy allowed extraction of the complete set of connections between neurons of the nematode *C. elegans* (White et al. 1986), the only living system whose nervous system has been fully mapped (Varshney et al. 2011). More recently, micro-optical sectioning tomography (MOST) has also revealed the connectivity of a mouse brain (Li et al. 2010). Both the anatomical networks of the cat (Scannell et al. 1999) and the macaque (Felleman and van Essen 1991) cortex have been extensively studied thanks to the data obtained from different histological studies, leading to a complete cortico-cortical network of  $N = 53$  cortical regions and  $L = 650$  connections in the cat (Scannell et al. 1999) and the reconstruction of the macaque visual area ( $N = 32$  and  $L = 305$ ) (Felleman and van Essen 1991). Diffusion tensor imaging (DTI) (Iturria-Medina et al. 2007; Gong et al. 2009) allowed reconstruction of the human brain anatomical network, with the limitation of inferring the fiber bundle orientation. The use of diffusion spectrum imaging (DSI) has overcome this constraint (Hagmann et al. 2008) allowing an anatomical reconstruction of the human brain anatomical network formed by up to  $N \sim 1,000$  nodes and  $L \sim 100,000$  links (Hagmann et al. 2007).

Although the anatomical networks provide a substrate for the dynamical processes occurring on them, they are not necessarily linked to the functional activity occurring between different brain regions. Anatomical and functional networks may differ depending on the specific cognitive process that an individual is carrying out: while at short time scales the anatomical network is essentially static, the functional network associated with the execution of a cognitive task is inherently dynamical.

**Functional networks** account for the neurodynamical interactions between neural regions. Functional connectivity measures statistical interdependence between the dynamics of all pairs of the network nodes without taking into account causal effects. The more correlated the activity between two regions, the higher the weight of the functional connections between them. Note that despite the fact that functional connectivity requires the existence of an underlying anatomical connection, both functional and anatomical networks do not necessarily need to resemble each other (as the map of road connections does not necessary reveal the traffic moving through them). As we will see, functional networks share common features between them, despite the fact that each network is task dependent.

There are different ways of measuring brain dynamics in order to later extract a functional network. Electroencephalography (EEG) and magnetoencephalography (MEG) measure, respectively, the electric and magnetic fields created by the neuronal activity. Despite high temporal resolution (in the order of milliseconds) in both techniques, the spatial resolution is low (several centimeters) which leads to a poor reconstruction of the real dynamics of the brain. In addition, recordings are extracranial in both methodologies, which leads to problems of volume conduction in the case of EEG and common sources in MEG. Functional magnetic resonance imaging (fMRI) on the contrary, which monitors the brain activity by measuring the blood oxygenation, leads to a high spatial resolution ( $\sim$  millimeters) paying the price of temporal resolution in the order of seconds.

Nevertheless, one of the main drawbacks of functional networks is the lack of directionality of their links. The fact that correlation does not imply causality leads to the necessity of defining an additional kind of brain networks. **Effective networks**, which are constructed from the analysis of the dynamical response of different brain sites, assign directionality to the links based on causality analysis (Büchel and Friston 2000). This kind of networks is the most mathematically demanding (Stephan and Friston 2007) but also the most accurate approximation to evaluate the real relations between brain sites.

## Definitions and Notations

Tables 1 and 2 summarize the main node and network parameters, together with their mathematical definitions and the underlying concepts. Table 1 contains those parameters that concern to the node, although averaging over the whole network would lead to the extension of the parameter to the network level. Table 2 contains those parameters that only apply to network as a whole.

## Important Parts of the Network

### Degree and Strength Distributions

The degree  $k$  of a node simply accounts for the number of connections a node has. The degree distribution  $p(k)$  of a network refers to the probability of finding a node  $i$  with a certain number of connections  $k$ . When links are directed, the degree distribution is split into two: the in-degree (incoming links) and the out-degree (outgoing links) distributions. If links have a certain weight, then the degree distribution is transformed into the strength distribution  $s(i)$ , being the strength of a node, the sum of its links' weights. The degree distribution is a delta function in the case of regular networks and a Poissonian distribution when networks are completely random. Nevertheless, real



**Table 1** *Mathematical definition of the most significant node parameters.* It is possible to translate the majority of these metrics to the network level by simply averaging over the all nodes of the network. See (Rubinov and Sporns 2010) for the adaptation of these parameters to weighted networks

Node parameter	Mathematical definition	Underlying concept
Degree $k(i)$ and strength $s(i)$	$k(i) = \sum_{j \in N} a_{ij}$ $s(i) = \sum_{j \in N} w_{ij}$ <p>where <math>a_{ij} = 1</math> if nodes <math>i</math> and <math>j</math> are connected and <math>a_{ij} = 0</math> otherwise. <math>w_{ij}</math> corresponds to the weights of the links in case they are considered</p>	The degree accounts for number of links a node has. The strength is the sum of weights $w_{ij}$ of the links arriving at a certain node (Amaral et al. 2000; Newman 2003)
Outreach $o(i)$	$o(i) = \sum_{j \in N} l_{ij} w_{ij}$ <p>where <math>l_{ij}</math> is the length of the link between nodes <math>i</math> and <math>j</math></p>	Sum of the link's weight $w_{ij}$ multiplied by the link's Euclidean length $l_{ij}$ (Buldú et al. 2011)
Eigenvector centrality $e_c(i)$	$e_c(i) = \sum_{j \in V(i)} e_c(j)$ <p><math>V(i)</math> being the set of neighbors of node <math>i</math></p>	A measure of node importance that takes into account the importance of the node's neighbor. It is equivalent to the eigenvector associated with the largest eigenvalue of the connectivity matrix (Newman 2010)
Shortest path $d$	Given two nodes $i$ and $j$ , the shortest path $d_{ij}$ is the minimum number of nodes to be visited when going from $i$ to $j$	Computes the minimum number of steps to go from one node to another (Newman 2010)
Clustering $C(i)$	$C(i) = \frac{2L_i}{k_i(k_i-1)}$ <p>where <math>L_i</math> is the number of links between neighbors of node <math>i</math></p>	It is related to the percentage of neighbors of a certain node that, in turn, are neighbors between them (Watts and Strogatz 1998). There exist other metrics that quantify the node clustering (Newman 2010)
Node betweenness $b(i)$	$b(i) = \sum_{j \neq k} \frac{n_{jk}(i)}{n_{jk}}$ <p>where <math>n_{jk}</math> is the number of the shortest paths between nodes <math>j</math> and <math>k</math> and <math>n_{jk}(i)</math> is the number of these paths that go through node <math>i</math></p>	Accounts for the number of the shortest paths between any node $j$ and $k$ of the network that cross node $i$ (Newman 2010)
Within-module degree $z(i)$	$z(i) = \frac{k_i(m_i) - k(m_i)}{\sigma_{k(m_i)}}$ <p>where <math>k_i(m_i)</math> is the degree of node <math>i</math> inside its community and <math>k(m_i)</math> and <math>\sigma_{k(m_i)}</math> are, respectively, the average and the standard deviation of the degree inside the community</p>	Measures the importance of a node inside its community (Guimerà and Amaral 2005)
Participation coefficient $p(i)$	$p(i) = 1 - \sum_m \left( \frac{k_i(m)}{k_i} \right)^2$ <p>where <math>k_i(m)</math> is the degree of node <math>i</math> inside community <math>m</math></p>	Evaluates the percentage of links that a node has to other communities (Guimerà and Amaral 2005)
Local efficiency $E_L(i)$	Computed as the global efficiency of the subnetwork $V(i)$ containing all neighbors of node $i$ (see definition of Global Efficiency in Table 2)	Accounts for the inverse of the shortest path of the neighborhood of a node $i$ when node $i$ has been deleted. It is a measure of local resilience (Latora and Marchiori 2001)

**Table 2** *Mathematical definition of the most extended network parameters.* These parameters only have a meaning when analyzing the network as a whole. There exists a translation of all of them to weighted networks (Rubinov and Sporns 2010)

Network parameter	Mathematical definition	Underlying concept
Assortativity $r$	$r = \frac{L^{-1} \sum_i j_i k_i - \left[ L^{-1} \sum_i \frac{1}{2}(j_i + k_i) \right]^2}{L^{-1} \sum_i \frac{1}{2}(j_i^2 + k_i^2) - \left[ L^{-1} \sum_i \frac{1}{2}(j_i + k_i) \right]^2}$ <p>where <math>-1 \leq r \leq 1</math> and <math>j_i</math> and <math>k_i</math> are the degrees of the nodes at the end of the <math>i_{th}</math> link, with <math>i = 1 \dots L</math></p>	Quantifies the degree correlation of the whole network. Assortative (disassortative) networks are those with positive (negative) degree correlations (Newman 2002)
Small-worldness $S$	$S = \frac{C/C_{ran}}{d/d_{ran}}$ <p>being <math>C(d)</math> and <math>C_{ran}(d_{ran})</math>, respectively, the clustering (shortest path) of the network and its randomized version</p>	It evaluates the ratio between the normalized network clustering and the normalized shortest path. The highest the $S$ , the more “small world” the network is (Humphries and Gurney 2008)
Synchronizability $r$ and $\lambda_2$	$r = \frac{\lambda_N}{\lambda_2} \text{ (class III)}$ $\lambda_2 \text{ (class II)}$ <p>where <math>\lambda_2</math> and <math>\lambda_N</math> are, respectively, the second smallest and the largest eigenvalues of the Laplacian matrix <math>L = K - A</math>, with <math>K</math> being a diagonal matrix containing the degree of the nodes and <math>A</math> the adjacency matrix</p>	It is related to the stability of the synchronized state of the network. The dynamical system and the kind of coupling determine the class (I, II, or III), which is related to the ability of the system to synchronize (Boccaletti et al. 2006)
Global efficiency $E_g$	$E_g = \frac{1}{N(N-1)} \sum_{i \neq j} \frac{1}{d_{ij}}$ <p>where <math>d_{ij}</math> is the shortest path between nodes <math>i</math> and <math>j</math></p>	Measures the harmonic mean of the inverse of the shortest paths between all nodes of the network (Latora and Marchiori 2001)
Modularity $Q$	$Q = \sum_{s=1}^{N_M} \left[ \frac{l_s}{L} - \left( \frac{d_s}{2L} \right)^2 \right]$ <p>where <math>l_s</math> and <math>d_s</math> are, respectively, the number of links inside community <math>s</math> and the average degree of the community. <math>N_M</math> is the total number of communities inside the network</p>	Evaluates how good is a given partition of the network into communities by comparing the density of links inside each community with that obtained in an equivalent random network (Newman 2006)

networks show a diversity of degree distributions, with the majority of them being broad, with long tails. Additionally, in many cases, they can be described with a power-law decay ( $p(k) \sim k^{-\gamma}$ ) (Newman 2003). In the case of the brain, different kinds of distribution have been reported depending on the spatial scale at which the system is analyzed, since the scale determines the number of nodes  $N$  and links  $L$  of the network which, in turn, constrains the width of the degree distribution. In cultured neural networks, the fact that neurons primarily connect through a random process leads to exponential distributions (Shefi et al. 2002). This kind of distribution is also reported in the in-degree and the out-degree of the anatomical connections of *C. elegans* nematode, the only living system with a whole reconstruction of its neural network (Amaral et al. 2000).

In human brain networks, the degree distribution strongly depends on the experimental technique used to acquire the data, the scale at which the system is observed, and the nature of the network that it is being analyzed (anatomical, functional, or effective). Hagmann et al. (2007) showed, by means of diffusion MRI, that a reconstruction of the anatomical brain network into 66 ROIs led to a degree distribution with an exponential decay. Later results (Hagmann et al. 2008) showed that though not having a power-law decay, a small group of hubs exists in both the degree and strength distributions.

These functional hubs have high betweenness centrality and act as connectors between the main structural modules.

If we take a look at functional networks, the diversity of degree distributions increases. Eguíluz et al. showed that functional brain networks obtained from fMRI data show scale-free distributions for different tasks (Eguíluz et al. 2005) which could be related to their resistance to failure, facility of synchronization, and fast signal processing (Lago-Fernandez et al. 2000). Van den Heuvel et al. (2008) also reported a scale-free distribution. Nevertheless, other results showed some discrepancies at the tail of the degree distribution, which was better fitted with an exponential decay leading to a power-law, exponentially truncated distribution (Achard et al. 2006a).

Altogether, no unique function seems to describe the degree distribution of brain networks. The number of nodes and links of the network strongly constrains the width of the distribution, together with the experimental technique used to obtain the data and the task performed during the recordings.

### Network Hubs and the Rich Club

Network hubs are those nodes with higher importance in the network structure. Different measures have been proposed to quantify the relevance of a node within a network. At a local scale, the node degree (or strength if the network is weighted) is a good approach for identifying hubs. If we take into account the global structure of the network, the *betweenness* and the *eigenvector centralities* are the most widely used indicators (Newman 2010). The former is related to the number of shortest paths that crosses a given node, while the second takes into account not only the number of connections but also the importance of the neighbors.

The existence of hubs in both anatomical and functional brain networks has been related to a reduction of the wiring cost of the network, since hubs behave as integrators and distributors of information through the network when combined with a few long-range connections to other brain modules. Several studies have focused on the identification of these hubs and their role inside their respective community (i.e., among the nodes tightly connected to them) and as connectors between different brain modules (Hagmann et al. 2008). The tracking of hub connectivity during aging has shown an alteration of both its importance within its community and its participation in other network modules (Meunier et al. 2009b). Interestingly, hub failure, quantified in terms of loss of connectivity, has been associated with the emergence of different brain diseases (Bassett et al. 2008).

A number of recent studies investigated the interconnections *between brain hubs* as a potential substrate for central integrative processes. In both the human and the macaque cerebral cortices, a largely consistent set of brain regions termed the *rich club* turns out to be more densely interconnected than expected based on comparisons to degree-preserving null models, with a large number of short communication paths connecting two or more rich club regions to each other (Colizza et al. 2006; Harriger et al. 2012; Van den Heuvel et al. 2012). In the human brain, the rich club spans regions including the superior parietal cortex, the precuneus, both the posterior and anterior cingulate cortices, and the insula (Van den Heuvel et al. 2012). The brain's rich club appears as a “super hub” where information converges from and is broadcast back to segregated communities and networks, allowing for integrated processing, offering a potential network substrate for the “global neuronal workspace” proposed in recent influential theories of cognition (Shanahan 2012).

### General Organizing Principles

Complex systems, of which the brain is an example *par excellence*, are typically characterized by structure at and within multiple scales and by a correspondence between topology and dynamical processes taking place on them. In the brain, it is clear that both topology and dynamics control



function. In turn, function retroacts, possibly at much longer time scales, to optimize network topology and brain dynamics, producing topological communities corresponding to functional subdivisions in the brain. Complex network theory is ideally suited to extract the general rules governing these spatiotemporal multiscale relationships.

### **Assortativity/Disassortativity**

*Assortativity* is a measure of the degree-degree correlations within a complex network. First introduced by Newman in the context of complex networks (Newman 2002), the assortativity parameter  $r$  (see Table 2 for a mathematical definition) computes the Pearson correlation coefficient for the nodes of the same degree. In assortative (*disassortative*) networks, nodes of the same (different) degree are prone to be connected, often leading to the appearance of a *rich club* where nodes of higher degree have connections to each other. Hagmann et al. (2008) also reported assortative mixing in the anatomical network of the human brain, showing that hubs are prone to connect to each other. Functional brain networks obtained from fMRI recordings during music listening and finger tapping were shown to be assortative (Eguíluz et al. 2005). Interestingly, the majority of biological networks seem to be disassortative, with clusters organized around local hubs (Newman 2010).

### **Motifs**

Motifs are structural organizations of small size (typically less than 10 nodes) that are overrepresented inside the topological structure of a complex network. Milo et al. (2002) showed that biological networks have certain building blocks, which they called motifs, which emerge as a consequence of an underlying function. The existence of motifs in brain networks reveals the existence of nonrandom rules for creating local connections, and the diversity of network motifs has been related to the enhancement of the processing capacities at the local level (Sporns and Kötter 2004; Sporns et al. 2007).

### **Modularity and Hierarchy**

The modularity of a network accounts for the existence of densely connected groups of nodes that lead to the formation of network communities. The detection of network communities has several difficulties (e.g., the absence of a perfect network partition, the overlap between communities, the coexistence of modules of different size) and has been a field of intense research during the last years (Fortunato 2010). In addition, it is common to observe a hierarchy in the modular organization which indicates that, at different scales, there exist different network partitions that, in turn, have hierarchical dependencies between them (Sales-Pardo et al. 2007; Meunier et al. 2010). Detecting and evaluating the modular structure of a brain network is a complex task, but it is mandatory since, first, it gives information about the well-known segregated activity of the brain and, second, part of the complexity of the dynamical processes occurring in the brain relies on the existence of network modules (Pan et al. 2010). Interestingly, anatomical networks exhibit a modular (Hilgetag et al. 2000) and hierarchical organization (Zamora-Lopez et al. 2010). Different community partition algorithms of anatomical networks have shown high correlations of the obtained communities with known functional localized areas in the human brain (Chen et al. 2008) and also allow identification of those regions that make the structural core of the network (Hagmann et al. 2008). But the wealth of this kind of analysis is increased when analyzing functional networks. A series of studies have tracked the modular structure of resting-state functional networks at different ages, showing an alteration of the connections between communities as a consequence of the aging process (Meunier et al. 2009b). A hierarchical organization of functional communities has also been reported in the

human brain (Meunier et al. 2009a), and it seems to indicate that the hierarchically modular structures facilitate the embedding of complex topologies into low-dimensional physical space (Bassett et al. 2010).

### Integration/Segregation

Consistent experimental and computational evidence shows that cognitive function requires an optimal balance between *global* integrative and *local* functionally specialized processes (Tononi et al. 1994, 1998; van Putten and Stam 2001). Cooperation between local and global processing was shown to be the basis of cooperative phenomena such as feature binding in gestalt-like perception, in which the emergence of a coherent percept from spatially distant stimuli is associated with synchronous responses of distant neuronal assemblies (Singer 1995).

An appropriate balance between these two tendencies has been shown to be necessary for efficient functioning, particularly in neural systems (Tononi et al. 1994); in fact, exceedingly segregated or integrated brains have been associated with various pathological conditions, e.g., autism (Just et al. 2004) or schizophrenia (Fletcher et al. 1999; Tononi et al. 1998).

It appears then that the functional organization of the human brain presents an essential trade-off: on the one hand, modules should be sufficiently independent to guarantee functional specialization and parallel computing. On the other hand, modules should be sufficiently connected to bind multiple sources of information to promote coordinated activity or coherent percepts.

### Small Worlds and Fractal Networks

**Small-World Property** Small-world structure, a particular topology combining high local clustering and short path length, has been suggested to represent a solution to the trade-off between module independence and specialization. The small-world property refers to a very small distance in a network's path length, as compared to the total number of network nodes. The idea of a small world appeared in 1929, in a short story by the Hungarian author Frigyes Karinthy called *Láncszemek* (*Chains*), and later made famous by Stanley Milgram's *six degrees of separation* experiment (Milgram 1967). Milgram's experiments showed that the average number of successive acquaintances (i.e., the distance) between any two individuals in a population of the order of billions is just six.

Small-world networks show a high local density of connections together with a short number of steps to go from one node to any other (Watts and Strogatz 1998). They are characterized by (i) a high clustering coefficient  $C$ , which measures the percentage of the first neighbors of one node that are, in turn, connected with each other, and (ii) by the existence of long-range connections that create shortcuts between distant regions of the network. On the other hand, scale-free networks are associated with a power-law degree distribution  $P(k) \sim k^{-\gamma}$ , where  $\gamma$  is the degree exponent; the average distance  $\bar{d}$  scales logarithmically with the network size as  $\bar{d} \sim \ln N$ . The scale-free nature of functional networks implies that there are always a small number of brain sites functionally connected to most other brain regions and that the number of these nodes is comparatively much larger in these networks than in randomly connected ones.

It has consistently been shown that brain anatomical networks have characteristically small-world properties of dense or clustered local connectivity with relatively few long-range connections mediating a short path length between any pair of neurons or regions in the network (Sporns et al. 2004; He et al. 2007; Hagmann et al. 2007). Similarly, human brain functional networks of coherent activity associated with the execution of cognitive tasks have also been associated with power-law or truncated power-law degree distributions (Eguíluz et al. 2005; Salvador et al. 2005; Achard et al. 2006b; Bassett et al. 2006; Achard and Bullmore 2007).

The small-world structure seems to be pervasive both across scales of brain activity and across species. Such a structure also characterizes functional cortical neuronal circuits in mammals (Song et al. 2005; Yu et al. 2008) and been identified in nervous systems as simple as that of the nematode *C. elegans* (Watts and Strogatz 1998).

The modifications of small-world structure in disease (Stam et al. 2007), in normal aging, and by pharmacological blockade of dopamine neurotransmission (Achard and Bullmore 2007) may be functionally interpreted in the light of theoretical studies showing that small-world architecture optimizes information processing (Strogatz 2001), facilitates synchronization (Bucolo et al. 2003) and rapid response and emergence of coherent oscillations (Lago-Fernandez et al. 2000), and confers resilience against pathological attack.

**Fractal Networks** Because complex systems typically exhibit structure at many scales, it is extremely interesting to understand the behavior of a complex network under a scale transformation and see the degree of similarity across scales. Fractality in a complex network can be identified in a manner similar to that of ordinary fractals, which are objects consisting of self-similar copies at all scales. In this process, the network is first covered with boxes. After optimally covering a network with boxes of a given diameter  $l_B$ , a renormalization transformation is applied where each box is replaced by a single node and the links of the original network are transferred to the renormalized one, so that original links between nodes belonging to different boxes constitute links between these boxes.

Under general conditions, the required number of boxes  $N_B$  scales with the box diameter  $l_B$  as  $N_B \sim l_B^{-\gamma_B}$  and  $\gamma_B$  is the fractal dimension of the network. Thus, fractality indicates a power-law scaling of the distances with network size, which is very different from the logarithmic dependence of small-world structures.

The dependence of  $N_B$  on  $l_B$  highlights two main families of networks: fractal networks, displaying power-law scaling with a finite-valued exponent  $\gamma_B$ , and non-fractal networks with a sharp exponential decay of  $N_B$  with  $l_B$  and an infinite fractal dimension  $\gamma_B \rightarrow \infty$ . Several experimental studies have shown that brain networks show hierarchical, fractal structures (Meunier et al. 2010; Bassett et al. 2010).

In fractal networks hubs tend to connect to small degree nodes and not to each other. In other words, hubs tend to stay away from each other. As a result, centrality is weakly correlated with degree: due to the repulsion between hubs, small degree nodes appear at all parts of the fractal network. Thus, their centralities can have both small and large values, and their average centrality is significantly larger, resulting in transport properties that are different from those of networks with different topological organizations. Fractality is closely related with modularity: the isolation of hubs allows considering that each box is built around a local hub, so that boxes ultimately roughly correspond to a module. By comparison to scale-free networks, fractal networks should be more stable to hub damage. The isolation of hubs from each other may provide an explanation of why most biological networks evolved toward a fractal behavior.

**Solving the Integration-Segregation Trade-Off: The Role of Weak Ties** Shortcuts generating small worlds and the persistence of modularity, a global property unrelated to local clustering, are intrinsically conflicting mechanisms. Clustering is a local quantity related to the immediate neighborhood of a node, while modularity is a global network property (Girvan and Newman 2002; Meunier et al. 2010; Fortunato 2010). Furthermore, the short distances of a small-world network are generally incompatible with strong modularity, which typically presents the properties of a “large

world” (Song et al. 2005, 2006; Radicchi et al. 2008; Rozenfeld et al. 2010) characterized by long distances.

Gallos et al. (2012) presented a possible solution to the seeming trade-off between integration and segregation: while strong ties within the brain are hierarchically organized into modules with “large-world” self-similar properties, the addition of weak ties overcomes the repulsion between hubs, rendering the network non-fractal and small world (Watts and Strogatz 1998). Remarkably, weak ties are organized in a way that maximizes information transfer with minimal wiring cost, suggesting a natural solution to the paradox of efficient information flow in the highly modular structure of the brain (Gallos et al. 2012).

### Topology and Dynamics

Topological aspects of brain anatomy and the dynamical processes taking place on them are mutually intertwined.

On the one hand, the topology of structural (anatomical) networks influences the dynamical processes (namely, synchronization) taking place within them (Boccaletti et al. 2006). The topology of brain connectivity was shown to be a control parameter guiding global brain dynamics through series of phase transitions corresponding to different observable patterns, so that a wide range of different behaviors can be accessed by varying coupling strengths (Jirsa and Kelso 2000). For instance, changes in the topology or synaptic strengths in the relevant networks can cause transitions between various regimes of activity (i.e., from normal to seizing to bursting) in models of epilepsy (Netoff et al. 2004). This has important implications for neural networks, where synaptic coupling strengths can change at all temporal and spatial scales due to learning processes and plasticity.

On the other hand, the synchronization process unveils the emergence of hierarchical neural communities at different time scales (Arenas et al. 2006). Simulations showed that brain dynamics exhibits a modular hierarchical organization, where clusters coincide with the topological community structure of anatomical networks (Zhou et al. 2006). It was also shown that in the presence of (neurophysiologically plausible) weak synchronization between distant brain regions, dynamical clusters of brain activity closely reflect topological communities of brain anatomy, as areas that are important for long-range information integration; neuroanatomical connectivity patterns are univocally associated with given functional complexity levels; and networks capable of producing highly complex functional dynamics share common structural motifs (Sporns et al. 2000, 2002).

**Synchronizability** Synchronization is one of the emerging dynamical processes, the understanding of which has benefited the most from network theory. The spectral analysis of the *adjacency* and *Laplacian* matrices of a network allows evaluation of the synchronization properties of the whole network and quantification of the stability of the synchronized state (Boccaletti et al. 2006; Arenas et al. 2008). The analysis of the eigenratio  $r = \lambda_N/\lambda_2$  (see section “Tools”) of the *Laplacian matrix* showed that functional networks obtained for brain activity at rest and during the execution of a finger tapping task have a synchronizability parameter indicating that brain activity lies at a critical point separating the coherent/incoherent state of the whole network (Bassett et al. 2006). Interestingly, pathological dynamics, such as those reported during epileptic seizures, lead to an alteration of the network synchronizability, which recovers its adequate value just after the epileptic episode (Schindler et al. 2008).

### Mechanical Principles of Brain Organization

When considered as a biophysical system, it is clear that the brain faces harsh energetic constraints limiting its computational capabilities (Laughlin and Sejnowski 2003), and that is influenced by its

interactions with the environment and a range of potential sources of damage (as a result of trauma or degenerative damage). Correspondingly, it is interesting to understand how the brain faces its inherent trade-off between its information processing and transmission functions and the huge energetic costs that these suppose and how it prospers, withstands, or collapses in response to exogenous and endogenous events.

While understanding the general organizational principles of brain structure and function goes a long way into explaining the strategies that the brain uses to manage its economic dilemma in an optimal way (Bullmore and Sporns 2012), network theory provides valuable tools that allow for directly and quantitatively addressing this issue and through which insight as to how the brain would respond to various sources of attack can be gathered.

### Efficiency

In the general context of complex networks, the concept of efficiency has been related to the ability of traveling through a network with the minimum number of steps. Latora and Marchiori introduced a parameter called *global efficiency* corresponding to the inverse of the shortest paths between any pair of nodes of the network (Latora and Marchiori 2001).

The concept of efficiency of a brain network relies both on the cost of creating and maintaining the network and the performance in executing a given task. It is important to see that such a metric is essentially tantamount to a topological distance, so that, when used in the context of brain networks, it would be wrong to interpret it as a quantifier of biological efficiency and of the ability of a given anatomical or functional network to perform a certain task.

Studies on the anatomical network of the *C. elegans* showed that the sparse structure of connections between neurons (only 5 % of the total number of possible links) leads to a reasonably high global efficiency, resulting in a high-performance background for information transfer (Latora and Marchiori 2001). Different studies have shown that, in brain anatomical networks, both the number of steps between any pair of nodes in the network (Kaiser and Hilgetag 2006) and the physical cost of their placement in a three-dimensional space (Bassett et al. 2010) are reasonably close to their optimal value.

Interestingly, the dynamical nature of functional networks allows them to adapt the trade-off between cost and efficiency during cognitive processes. Functional networks can enhance their efficiency during a demanding cognitive process, paying the price of an extra cost and recovering the initial (and more “economical”) state after finalizing the task (Kitzbichler et al. 2011).

Another fact that reinforces the hypothesis of the existence of a cost-efficiency balance in the brain is the analysis of impaired networks. The emergence of brain diseases appears to shift the whole network either to regimes with much higher costs, as is the case in schizophrenia (Lynall et al. 2010), or to organizations with low efficiency, for instance in Alzheimer’s disease (Stam et al. 2007).

### Robustness

The robustness of a network is related to the impact of node/link deletion in the topological structure of the network (Cohen and Havlin 2010) and is classically quantified by measuring the deviations of the network parameters resulting from these deletions. The specific topology of a network determines its robustness. For example, scale-free networks maintain fairly well their structural properties when random failures are introduced in the network but turn out to be extremely fragile when hubs are the object of an attack (Albert et al. 2000). Anatomical networks of the cat and macaque showed a robustness similar to that of scale-free networks (Kaiser et al. 2007) due to the existence of hubs and the omnipresent modular structure of brain networks (Kaiser and Hilgetag 2004).



Counterintuitively, an increase in the network robustness is not necessarily associated with better performance of a brain network. For example, in the case of childhood-onset schizophrenia, the analysis of resting-state functional networks showed a decrease in the modular behavior of the network resulting in a more integrated structure and as a consequence an increased robustness to targeted attacks (Alexander-Bloch et al. 2010).

### **Modulating Network Properties**

**Temporal Evolution** The fact that brain networks are in continuous evolution demands that different analyses from those performed on static network properties be used. Specifically, what is needed is a perspective that would focus not only on the topology of the network but also on how it evolves in time. Interestingly, even in the absence of external stimulation, brain activity shows significant fluctuations in the network connectivity (Hutchison et al. 2012) with corresponding consequences in the topology of the functional network. At the fastest scales, functional networks emerge, evolve, and disappear according to the specific requirements of a given cognitive process. Several works have dealt with the evolution of functional brain networks (De Vico Fallani et al. 2008; Dimitriadis et al. 2010) showing that new information can be obtained when looking at the temporal evolution of functional networks. For example, Valencia and colleagues showed that during visual stimulation, the functional network maintains its small-world configuration, while, at the same time, functional connectivity is varying in time and frequency; network reconfiguration is also reported at larger time scales (Valencia et al. 2008). Bassett et al. followed the structure of functional networks during a learning process and demonstrated that the flexibility of the network topology is strongly correlated with the amount of learning in future sessions (Bassett et al. 2011). If we consider aging as the largest time scale that can be analyzed in the brain, again clear signs of reorganization are reported. While childhood is related to more disordered functional networks with progressive increase in small-worldness (Boersma et al. 2011), a subsequent evolution toward a hierarchical modular structure has been reported, which seems to be optimized in maturity. Nevertheless, as aging advances the modular structure and its hierarchy are lost (Meunier et al. 2009b), showing the importance of this particular kind of configuration in the optimal functioning of brain networks.

**Brain Diseases** Graph theoretical measures have proven to represent good indicators of the emergence and evolution of a series of brain diseases, an aspect that renders them of enormous practical application. The emergence of brain dysfunction can be quantified using network metrics, which are altered in a disease-specific way (Stam and van Straaten 2012). For example, during epileptic seizures, functional brain networks become more regular, modifying their degree distribution and losing part of their modular structure (Ponten et al. 2007; Kaiser and Hilgetag 2010). On the contrary, functional networks of schizophrenic patients become more random, with a consequent decrease of both the normalized clustering coefficient and shortest path (Micheloyannis et al. 2006). Mild cognitive impairment, a condition which sometimes evolves into Alzheimer's dementia, also shows increased functional network randomness, but in this case it is associated with increased network synchronization and a propensity to enhance long-range connections (Buldú et al. 2011). Network analysis of Alzheimer's disease indicates a disconnection syndrome leading to an increased shortest path and decreased network clustering, both leading to a severe impairment of the desirable properties afforded by small-world networks (Stam et al. 2009).

## Future Lines of Investigation

Complex network theory has undoubtedly started opening new avenues on the understanding of brain networks. Still, some aspects of this methodology have yet more to offer as new lines of investigation open in the coming years. Four main lines seem to have a particularly promising future:

**Quantitative Modeling of the Fundamental Principles of System-Level Brain Functioning** One of the merits of network theory is its ability to relate the topological structure of real networks to the processes occurring in them. It is possible to implement different network models which reproduce experimental observations or test new hypotheses with the aim of investigating the guiding rules behind the emergence, functioning, and evolution of anatomical and functional brain networks (Vértes et al. 2012). These models cannot be directly borrowed from other technological or biological fields and should contain the particular constraints of brain networks.

**Predicting the Behavior and Evolution of Brain Networks** The fact that both anatomical and functional networks are in continuous evolution leads to the conclusion that we should pay attention not only to the observed network but also its future stages. Models that predict the evolution of a network would provide a fundamental contribution of complex network theory to the understanding of brain functioning.

**Controlling and Targeting the State of the Network** Control and targeting of complex technological networks are two well-studied issues (Liu et al. 2011). Nevertheless, the application of these concepts to biological systems is a pristine field. Identification of those nodes that guide the behavior (or evolution) of a network and drive its dynamics would be of great interest in pathologies such as epilepsy.

**Classification of Brain Networks** There is now some evidence showing that network metrics are robust enough quantifiers of brain activity to be used as features capable of distinguishing healthy from pathological behavior (Zanin et al. 2012). Ultimately, network theory should help in the identification of the signatures of pathology in a selective way and in the comparison and classification of anatomical and functional networks, thus lending a hand in the early detection of brain neurodegenerative diseases or in the monitoring of a healthy aging.

## Cross-References

- [Brain Imaging: Overview](#)
- [Connectivity Analysis in Normal and Pathological Brains](#)
- [Connectome, \*C. elegans\*](#)
- [Information Theory: Overview](#)

## References

- Achard S, Bullmore E (2007) Efficiency and cost of economical brain functional networks. *PLoS Comput Biol* 3:17
- Achard S, Duke T, Bullmore E (2006a) Adaptive reconfiguration of fractal small-world human brain functional networks. *Proc Natl Acad Sci U S A* 103:19518–19523

- Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E (2006b) A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci* 26:63–72
- Albert R, Jeong H, Barabási AL (2000) Error and attack tolerance of complex networks. *Nature* 406:378–382
- Alexander-Bloch AF, Gogtay N, Meunier D, Birn R, Clasen L, Lalonde F, Lenroot R, Giedd J, Bullmore ET (2010) Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. *Front Syst Neurosci* 4:147
- Amaral LAN, Scala A, Barthélemy M, Stanley HE (2000) Classes of small-world networks. *Proc Natl Acad Sci U S A* 97:11149–11152
- Arenas A, Díaz-Guilera A, Pérez-Vicente CJ (2006) Synchronization reveals topological scales in complex networks. *Phys Rev Lett* 96:114102
- Arenas A, Díaz-Guilera A, Kurths J, Moreno Y, Zhou C (2008) Synchronization in complex networks. *Phys Rep* 469:93–153
- Bassett DS, Meyer-Lindenberg A, Achard S, Duke T, Bullmore E (2006) Adaptive reconfiguration of fractal small-world human brain functional networks. *Proc Natl Acad Sci USA* 103:19518–19523
- Bassett DS, Bullmore ET, Verchinski BA, Mattay VS, Weinberger DR et al (2008) Hierarchical organization of human cortical networks in health and schizophrenia. *J Neurosci* 28:9239–9248
- Bassett DS, Greenfield DL, Meyer-Lindenberg A, Weinberger DR, Moore SW, Bullmore ET (2010) Efficient physical embedding of topologically complex information processing networks in brains and computer circuits. *PLoS Comput Biol* 6:e1000748
- Bassett DS, Wymbs N, Porter MA, Mucha P, Carlson JM, Grafton ST (2011) Dynamic reconfiguration of human brain networks during learning. *Proc Natl Acad Sci USA* 108:7641–7646
- Bialonski S (2012) Inferring complex networks from time series of dynamical systems: pitfalls, misinterpretations, and possible solutions. *arxiv:1208.0800*
- Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang D (2006) Complex networks: structure and dynamics. *Phys Rep* 424:175–308
- Boersma M, Smit DJ, de Bie HM, Van Baal GC, Boomsma DI, de Geus EJ, Delemarre-van de Waal HA, Stam CJ (2011) Network analysis of resting state EEG in the developing young brain: structure comes with maturation. *Hum Brain Mapp* 32:413–425
- Breakspear M (2002) Nonlinear phase desynchronization in human electroencephalographic data. *Hum Brain Mapp* 15:175–198
- Büchel C, Friston KJ (2000) Assessing interactions among neuronal systems using functional neuroimaging. *Neural Netw* 13:871–882
- Bucolo M, Fazzino S, La Rosa M, Fortuna L (2003) Small-world networks of fuzzy chaotic oscillators. *Chaos Solitons Fractals* 17:557–565
- Buldú JM, Bajo R, Maestú F, Castellanos N, Leyva I, Gil P, Sendiña-Nadal I, Almendral JA, Nevado A, del Pozo F, Boccaletti S (2011) Reorganization of functional networks in mild cognitive impairment. *PLoS One* 6:e19584
- Bullmore E, Sporns O (2012) The economy of brain network organization. *Nat Rev Neurosci* 13:336–348
- Chen ZJ, He Y, Rosa-Neto P, Germann J, Evans AC (2008) Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. *Cereb Cortex* 18:2374–2381

- Cohen R, Havlin S (2010) Complex networks: structure, robustness, and function. Cambridge University Press, Cambridge
- Colizza V, Flammini A, Serrano MA, Vespignani A (2006) Detecting richclub ordering in complex networks. *Nat Phys* 2:110–115
- De Vico Fallani F, Latora V, Astolfi L, Cincotti F, Mattia D, Marciani MG, Salinari S, Colosimo A, Babiloni F (2008) Persistent patterns of interconnection in time-varying cortical networks estimated from high-resolution EEG recordings in humans during a simple motor act. *J Phys A* 41:224014
- Dimitriadis SI, Laskaris NA, Tsirka V, Vourkas M, Micheloyannis S, Fotopoulos S (2010) Tracking brain dynamics via time-dependent network analysis. *J Neurosci Methods* 193:145–155
- Eguíluz VM, Chialvo DR, Cecchi GA, Baliki M, Apkarian AV (2005) Scale-free brain functional networks. *Phys Rev Lett* 94:018102
- Felleman DJ, van Essen DC (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex* 1:1–47
- Fletcher P, McKenna J, Friston K, Frith C, Dolan R (1999) Abnormal cingulate modulation of fronto-temporal connectivity in schizophrenia. *Neuroimage* 9:337–342
- Fortunato S (2010) Community detection in graphs. *Phys Rep* 486:75–174
- Friston KJ (2000) The labile brain. I. Neuronal transients and nonlinear coupling. *Philos Trans R Soc Lond B* 355:215–236
- Gallos LK, Makse HA, Sigman M (2012) A small world of weak ties provides optimal global integration of self-similar modules in functional brain networks. *Proc Natl Acad Sci USA* 109:2825–2830
- Girvan M, Newman MEJ (2002) Community structure in social and biological networks. *Proc Natl Acad Sci USA* 99:7821–7826
- Gong G, He Y, Concha L, Lebel C, Gross DW, Evans AC, Beaulieu C (2009) Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. *Cereb Cortex* 19:524–536
- Guimerà R, Amaral LAN (2005) Functional cartography of complex metabolic networks. *Nature* 433:895–900
- Hagmann P, Kaurant M, Gigandet X, Thiran P, Wedeen VJ, Meuli R, Thiran JP (2007) Mapping human whole-brain structural networks with diffusion MRI. *PLoS One* 2:e597
- Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol* 6:e159
- Harriger L, van den Heuvel M, Sporns O (2012) Rich club organization of macaque cerebral cortex and its role in network communication. *PLoS One* 7:e46497
- He Y, Chen ZJ, Evans AC (2007) Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* 17:2407–2419
- Hilgetag CC, Burns GAPC, O'Neill MA, Scannell JW, Young MP (2000) Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. *Philos Trans R Soc Lond B* 355:91–110
- Humphries MD, Gurney K (2008) Network ‘small-world-ness’: a quantitative method for determining canonical network equivalence. *PLoS One* 3:e0002051
- Hutchison RW, Womelsdorf T, Gati JS, Everling S, Menon RS (2012) Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques. *Hum Brain Mapp* 34:2154–2177

- Iturria-Medina Y, Canales-Rodríguez EJ, Melie-García L, Valdés-Hernández PA, Martínez-Montes-E, Alemán-Gómez Y, Sánchez-Bornot JM (2007) Characterizing brain anatomical connections using diffusion weighted MRI and graph theory. *Neuroimage* 36:645–660
- Jirsa VK, Kelso JAS (2000) Spatiotemporal pattern formation in neural systems with heterogeneous connection topologies. *Phys Rev E* 62:8462–8465
- Just M, Cherkassky V, Keller TA, Minshew N (2004) Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain* 127:1811–1821
- Kaiser M, Hilgetag CC (2004) Edge vulnerability in neural and metabolic networks. *Biol Cybern* 90:311–317
- Kaiser M, Hilgetag CC (2006) Nonoptimal component placement, but short processing paths, due to long- distance projections in neural systems. *PLoS Comput Biol* 2:e95
- Kaiser M, Hilgetag CC (2010) Optimal hierarchical modular topologies for producing limited sustained activation of neural networks. *Front Neuroinform* 4:8
- Kaiser M, Martin R, Andreas P, Young MP (2007) Simulation of robustness against lesions of cortical networks. *Eur J Neurosci* 25:3185–3192
- Kitzbichler MG, Henson RNA, Smith ML, Nathan PJ, Bullmore ET (2011) Cognitive effort drives workspace configuration of human brain functional networks. *J Neurosci* 31:8259–8270
- Lago-Fernandez LF, Huerta R, Corbacho F, Siguenza JA (2000) Fast response and temporal coherent oscillations in small-world networks. *Phys Rev Lett* 84:2758–2761
- Latora V, Marchiori M (2001) Efficient behavior of small-world networks. *Phys Rev Lett* 87:198701
- Laughlin SB, Sejnowski TJ (2003) Communication in neural networks. *Science* 301:1870–1874
- Li A, Gong H, Zhang B, Wang Q, Yan C, Wu J, Liu Q, Zeng S, Luo Q (2010) Micro-optical sectioning tomography to obtain a high-resolution atlas of the mouse brain. *Science* 330:1404–1408
- Liu YY, Slotine JJ, Barabási AL (2011) Controllability of complex networks. *Nature* 473:167–173
- Lynall ME, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U, Bullmore ET (2010) Functional connectivity and brain networks in schizophrenia. *J Neurosci* 30:9477–9487
- Menzies L, Achard S, Chamberlain SR, Fineberg N, Chen CH, del Campo N, Sahakian BJ, Robbins TW, Bullmore E (2007) Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain* 130:3223–3236
- Meunier D, Lambiotte R, Fornito A, Ersche K, Bullmore ET (2009a) Hierarchical modularity in human brain functional networks. *Front Neuroinform* 3:37
- Meunier D, Achard S, Morcom A, Bullmore ET (2009b) Age-related changes in modular organization of human brain functional networks. *Neuroimage* 44:715–723
- Meunier D, Lambiotte R, Bullmore ET (2010) Modular and hierarchically modular organization of brain networks. *Front Neurosci* 4:200
- Micheloyannis S, Pachou E, Stam CJ, Breakspear M, Bitsios P, Vourkas M, Erimaki S, Zervakis M (2006) Small-world networks and disturbed functional connectivity in schizophrenia. *Schizophr Res* 87:60–66
- Milgram S (1967) The small-world problem. *Psychol Today* 1:61–67
- Milo R, Shen-Orr S, Itzkovitz S, Kashtan N, Chklovskii D, Alon U (2002) Network motifs: simple building blocks of complex networks. *Science* 298:824–827
- Miltner WHR, Braun C, Arnold M, Witte H, Taub E (1999) Coherence of gamma-band EEG activity as a basis of associative learning. *Nature* 397:434–436
- Netoff TL, Clewley R, Arno S, Keck T, White JA (2004) Epilepsy in small-world networks. *J Neurosci* 24:8075–8083



- Newman MEJ (2002) Assortative mixing in networks. *Phys Rev Lett* 89:208701
- Newman MEJ (2003) The structure and function of complex networks. *SIAM Review* 45:167–256
- Newman MEJ (2006) Modularity and community structure in networks. *Proc Natl Acad Sci USA* 103:8577–8696
- Newman MEJ (2010) *Networks: an introduction*. Oxford University Press, New York
- Pan RK, Chatterjee N, Sinha S (2010) Mesoscopic organization reveals the constraints governing *Caenorhabditis elegans* nervous system. *PLoS One* 5:e9240
- Ponten SC, Bartolomei F, Stam CJ (2007) Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clin Neurophysiol* 118:918–927
- Radicchi F, Ramasco JJ, Barrat A, Fortunato S (2008) Complex networks renormalization: flows and fixed points. *Phys Rev Lett* 101:148701
- Rodriguez E, George N, Lachaux J-P, Martinerie J, Renault B, Varela FJ (1999) Perception's shadow: long distance synchronization of human brain activity. *Nature* 397:430–433
- Rozenfeld HD, Song C, Makse HA (2010) The small world-fractal transition in complex networks: a renormalization group approach. *Phys Rev Lett* 104:025701
- Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 52:1059–1069
- Sales-Pardo M, Guimerà R, Moreira AA, Amaral LAN (2007) Extracting the hierarchical organization of complex systems. *Proc Natl Acad Sci USA* 104:15224–15229
- Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E (2005) Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb Cortex* 15:1332–1342
- Sarpeshkar R (1997) Efficient precise computation with noisy components: extrapolating from an electronic cochlea to the brain. Unpublished doctoral dissertation, California Institute of Technology
- Scannell JW, Burns GAPC, Hilgetag CC, O'Neil MA, Young MP (1999) The connectional organization of the cortico-thalamic system of the cat. *Cereb Cortex* 9:277–299
- Schindler KA, Bialonski S, Horstmann MT, Elger CE, Lehnertz K (2008) Evolving functional network properties and synchronizability during human epileptic seizures. *Chaos* 18:033119
- Shanahan M (2012) The brain's connective core and its role in animal cognition. *Philos Trans R Soc B* 367:2704–2714
- Shefi O, Golding I, Segev R, Ben-Jacob E, Ayali A (2002) Morphological characterization of in vitro neuronal networks. *Phys Rev E* 66:021905
- Singer W (1995) Putative functions of temporal correlations in neocortical processing. In: Koch C, Davis J (eds) *Large-scale neuronal theories of the brain*. MIT Press, Cambridge, pp 202–237
- Song C, Havlin S, Makse HA (2005) Self-similarity of complex networks. *Nature* 433:392–395
- Song C, Havlin S, Makse HA (2006) Origins of fractality in the growth of complex networks. *Nat Phys* 2:275–281
- Sporns O, Kötter R (2004) Motifs in brain networks. *PLoS Biol* 2:1910–1918
- Sporns O, Tononi G, Edelman GM (2000) Connectivity and complexity: the relationship between neuroanatomy and brain dynamics. *Neural Netw* 13:909–922
- Sporns O, Tononi G, Edelman GM (2002) Theoretical neuroanatomy and the connectivity of the cerebral cortex. *Behav Brain Res* 135:69–74
- Sporns O, Chialvo DR, Kaiser M, Hilgetag CC (2004) Organization, development and function of complex brain networks. *Trends Cogn Sci* 8:418–425

- Sporns O, Honey CJ, Kötter R (2007) Identification and classification of hubs in brain networks. *PLoS One* 2:e1049
- Stam CJ, van Straaten ECW (2012) The organization of physiological brain networks. *Clin Neurophysiol* 123:1067–1087
- Stam CJ, Jones BF, Nolte G, Breakspear M, Scheltens P (2007) Small-world networks and functional connectivity in Alzheimer’s disease. *Cereb Cortex* 17:92–99
- Stam CJ, de Haan W, Daffertshofer A, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW, Scheltens P (2009) Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer’s disease. *Brain* 132:213–224
- Stephan KE, Friston KJ (2007) Models of effective connectivity in neural systems. In: Jirsa VK, McIntosh AR (eds) *Handbook of brain connectivity*. Springer, Berlin, pp 303–325
- Strogatz SH (2001) Exploring complex networks. *Nature* 410:268–271
- Tononi G, Sporns O, Edelman GM (1994) A measure, of brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci USA* 91:5033–5037
- Tononi G, Edelman GM, Sporns O (1998) Complexity and coherency: integrating information in the brain. *Trends Cogn Sci* 2:474–484
- Valencia M, Martinerie J, Dupont S, Chavez M (2008) Dynamic small-world behavior in functional brain networks unveiled by an event-related networks approach. *Phys Rev E* 77:050905(R)
- Van den Heuvel MP, Starn CJ, Boersma M, Hulshoff Pol HE (2008) Small-world and scale-free organization of voxel based resting-state functional connectivity in the human brain. *Neuroimage* 43:528–539
- Van den Heuvel MP, Kahn R, Goni J, Sporns O (2012) A high-cost, high efficiency backbone for global brain communication. *Proc Natl Acad Sci USA* 109:11372–11377
- van Putten MJAM, Stam CJ (2001) Application of a neural complexity measure to multichannel EEG. *Phys Lett A* 281:131–141
- Varshney LR, Chen BL, Paniagua E, Hall DH, Chklovskii DB (2011) Structural properties of the *Caenorhabditis elegans* neuronal network. *PLoS Comput Biol* 7:e1001066
- Vértes PE, Alexander-Bloch AF, Gogtay N, Giedd JN, Rapoport JL, Bullmore ET (2012) Simple models of human brain functional networks. *Proc Natl Acad Sci USA* 109:5868–5873
- Watts D, Strogatz S (1998) Collective dynamics of ‘small-world’ networks. *Nature* 393:440–442
- White JG, Southgate E, Thomson JN, Brenner S (1986) The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philos Trans R Soc Lond B* 314:1–340
- Yu S, Huang D, Singer W, Nikolic D (2008) A small world of neuronal synchrony. *Cereb Cortex* 18:2891–2901
- Zamora-Lopez G, Zhou C, Kurths J (2010) Cortical hubs form a module for multisensory integration on top of the hierarchy of cortical networks. *Front Neuroinform* 4:1
- Zanin M, Sousa P, Papo D, Bajo R, García-Prieto J, del Pozo F, Menasalvas E, Boccaletti S (2012) Optimizing functional network representation of multivariate time series. *Sci Rep* 2:630
- Zhou C, Zemanová L, Zamora G, Hilgetag CC, Kurths J (2006) Hierarchical organization unveiled by functional connectivity in complex brain networks. *Phys Rev Lett* 97:238103

## Further Reading

- Barabási AL, Albert R (1999) Emergence of scaling in random networks. *Science* 286:509–512
- Bonifazi P, Goldin M, Picardo MA, Jorquera I, Cattani A, Bianconi G, Represa A, Ben-Ari Y, Cossart R (2009) GABAergic hub neurons orchestrate synchrony in developing hippocampal networks. *Science* 326:1419–1424

- Braitenberg V, Schüz A (1998) A statistics and geometry of neuronal connectivity. Springer, Berlin
- Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10:186–198
- Reijneveld JC, Ponten SC, Berendse HW, Stam CJ (2007) The application of graph theoretical analysis to complex networks in the brain. *Clin Neurophysiol* 118:2317–2331
- Sporns O, Zwi JD (2004) The small world of the cerebral cortex. *Neuroinformatics* 2:145–162