Complex network measures of brain connectivity: Uses and interpretations

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ABSTRACT

Brain connectivity datasets comprise networks of brain regions connected by anatomical tracts or by functional associations. Complex network analysis—a new multidisciplinary approach to the study of complex systems—aims to characterize these brain networks with a small number of neurobiologically meaningful and easily computable measures. In this article, we discuss construction of brain networks from connectivity data and describe the most commonly used network measures of structural and functional connectivity. We describe measures that variously detect functional integration and segregation, quantify centrality of individual brain regions or pathways, characterize patterns of local anatomical circuitry, and test resilience of networks to insult. We discuss the issues surrounding comparison of structural and functional network connectivity, as well as comparison of networks across subjects. Finally, we describe a Matlab toolbox (http://www.brain-connectivity-toolbox.net) accompanying this article and containing a collection of complex network measures and large-scale neuroanatomical connectivity datasets.

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Introduction

Modern brain mapping techniques—such as diffusion MRI, functional MRI, EEG, and MEG—produce increasingly large datasets of anatomical or functional connection patterns. Concurrent technological advancements are generating similarly large connection datasets in biological, technological, social, and other scientific fields. Attempts to characterize these datasets have, over the last decade, led to the emergence of a new, multidisciplinary approach to the study of complex systems (Strogatz, 2001; Newman, 2003; Boccaletti et al., 2006). This approach, known as complex network analysis, describes important properties of complex systems by quantifying topologies of their respective network representations. Complex network analysis has its origins in the mathematical study of networks, known as graph theory. However, unlike classical graph theory, the analysis primarily deals with real-life networks that are large and complex—neither uniformly random nor ordered.

Brain connectivity datasets comprise networks of brain regions connected by anatomical tracts or by functional associations. Brain networks are invariably complex, share a number of common features with networks from other biological and physical systems, and may hence be characterized using complex network methods. Network characterization of structural and functional connectivity data is increasing (Bassett and Bullmore, 2006, 2009; Stam and Reijneveld, 2007; Bullmore and Sporns, 2009) and rests on several important motivations. First, complex network analysis promises to reliably (Deuker et al., 2009) quantify brain networks with a small number of neurobiologically meaningful and easily computable measures (Sporns and Zwi, 2004; Achard et al., 2006; Bassett et al., 2006; He et al., 2007; Hagmann et al., 2008). Second, by explicitly defining anatomical and functional connections on the same map of brain regions, network analysis may be a useful setting for exploring structural–functional connectivity relationships (Zhou et al., 2006; Honey et al., 2007, 2009). Third, comparisons of structural or functional network topologies between subject populations appear to reveal presumed connectivity abnormalities in neurological and psychiatric disorders (Stam et al., 2007, 2009; Bassett et al., 2008; Leistedt et al., 2009; Ponten et al., 2009; Wang et al., 2009b).

In this article, we provide a non-technical introduction to complex network analysis of brain connectivity and outline important conceptual issues associated with its use. We begin by discussing the construction of structural and functional brain connectivity networks. We then describe the most commonly used measures of local and global connectivity, as well as their neurobiological interpretations. We focus on recently developed network measures (Boccaletti et al., 2006; Costa et al., 2007b) and provide a freely available Matlab toolbox, containing these measures, as well as their weighted and directed variants (Table A1). Finally, we discuss some of the issues associated with comparing structural and functional connectivity in the same subject and comparing connectivity patterns between subjects.

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Note that while we concentrate on the analysis of large-scale connectivity, our discussion is equally applicable to smaller scale connectivity, with appropriate redefinitions. For instance, small-scale brain networks could consist of neurons linked by synapses or of cortical columns linked by intercolumnar connections.

Construction of brain networks

A network is a mathematical representation of a real-world complex system and is defined by a collection of nodes (vertices) and links (edges) between pairs of nodes (Fig. 1). Nodes in large-scale brain networks usually represent brain regions, while links represent anatomical, functional, or effective connections (Friston, 1994), depending on the dataset. Anatomical connections typically correspond to white matter tracts between pairs of brain regions. Functional connections correspond to magnitudes of temporal correlations in activity and may occur between pairs of anatomically unconnected regions. Depending on the measure, functional connectivity may reflect linear or nonlinear interactions, as well as interactions at different time scales (Zhou et al., 2009). Effective connections represent direct or indirect causal influences of one region on another and may be estimated from observed perturbations (Friston et al., 2003).

Fig. 2 shows illustrative anatomical, functional, and effective connectivity networks, adapted from the study by Honey et al. (2007). The anatomical network represents large-scale connection pathways between cortical regions in the macaque, as collated from histological tract tracing studies. Functional and effective connectivity networks were constructed from time series of brain dynamics simulated on this anatomical network. The functional network represents patterns of cross-correlations between BOLD signals estimated from these dynamics. The effective network represents patterns of causal interactions, as computed with transfer entropy, a measure of directed information flow. All networks are represented by their connectivity (adjacency) matrices. Rows and columns in these matrices denote nodes, while matrix entries denote links. The order of nodes in connectivity matrices has no effect on computation of network measures but is important for network visualization (Fig. 2A).

The nature of nodes

The nature of nodes and links in individual brain networks is determined by combinations of brain mapping methods, anatomical parcellation schemes, and measures of connectivity. Many combinations occur in various experimental settings (Horwitz, 2003). The choice of a given combination must be carefully motivated, as the nature of nodes and links largely determines the neurobiological interpretation of network topology (Butts, 2009).

Nodes should ideally represent brain regions with coherent patterns of extrinsic anatomical or functional connections. Parcellation schemes that lump heterogeneously connected brain regions into single nodes may be less meaningful. In addition, a parcellation scheme should completely cover the surface of the cortex, or of the entire brain, and individual nodes should not spatially overlap. The use of MEG and EEG sensors may be problematic in this regard, given that sensors may detect spatially overlapping signals and are generally not aligned with boundaries of coherent regions (Ioannides, 2007).

Networks constructed using distinct parcellation schemes may significantly differ in their properties (Wang et al., 2009a) and cannot, in general, be quantitatively compared. Specifically, structural and functional networks may only be meaningfully compared, if these networks share the same parcellation scheme (Honey et al., 2009).

The nature of links

In addition to the type of connectivity (anatomical, functional or effective) and measure-specific (e.g., time scale) features of connectivity, links are also differentiated on the basis of their weight and directionality.

Binary links denote the presence or absence of connections (Fig. 2A), while weighted links also contain information about connection strengths (Figs. 2B, C). Weights in anatomical networks may represent the size, density, or coherence of anatomical tracts, while weights in functional and effective networks may represent respective magnitudes of correlational or causal interactions. Many recent studies discard link weights, as binary networks are in most cases simpler to characterize and have a more easily defined null model for statistical comparison (see below). On the other hand, weighted characterization usually focuses on somewhat different and complementary aspects of network organization (e.g., Saramaki et al., 2007) and may be especially useful in filtering the influence of weak and potentially non-significant links.

Weak and non-significant links may represent spurious connections, particularly in functional or effective networks (Figs. 2B, C—top panels). These links tend to obscure the topology of strong and significant connections and as a result are often discarded, by applying an absolute, or a proportional weight threshold (Figs. 2B, C—bottom panels). Threshold values are often arbitrarily determined, and networks should ideally be characterized across a broad range of thresholds. Independently, all self-connections or negative connections (such as functional anticorrelations) must currently be removed from the networks prior to analysis. Future network methods may be able to quantify the role of negative weights in global network organization.

Links may also be differentiated by the presence or absence of directionality. Thus, anatomical and effective connections may conceptually be represented with directed links. Unfortunately, current neuroimaging methods are unable to directly detect anatomical or causal directionality. On the other hand, directed anatomical networks constructed from tract tracing studies (e.g., Fig. 2A) indicate the existence of a large proportion of reciprocal connections in the cortex, which provides some validity for the use of undirected anatomical networks. Directed patterns of effective connectivity may be inferred from changes in functional activity that follow localized perturbations.

Measures of brain networks

An individual network measure may characterize one or several aspects of global and local brain connectivity. In this section, we describe measures that variously detect aspects of functional integration and segregation, quantify importance of individual brain regions, characterize patterns of local anatomical circuitry, and test resilience of networks to insult. Fig. 3 illustrates some basic concepts underlying these measures, while Table A1 contains mathematical definitions of all measures.

Network measures are often represented in multiple ways. Thus, measures of individual network elements (such as nodes or links) typically quantify connectivity profiles associated with these elements and hence reflect the way in which these elements are embedded in the network. Measurement values of all individual elements comprise a distribution, which provides a more global description of the network. This distribution is most commonly characterized by its mean, although other features, such as distribution shape, may be more important if the distribution is nonhomogeneous. In addition to these different representations, network measures also have binary and weighted, directed and undirected variants. Weighted and directed variants of measures are typically generalizations of binary undirected variants and

therefore reduce to the latter when computed on binary undirected networks.

To illustrate the different representations and variants of a network measure, we consider a basic and important measure known as the *degree*. The degree of an individual node is equal to the number of links connected to that node, which in practice is also equal to the number of neighbors of the node. Individual values of the degree therefore reflect importance of nodes in the network, as discussed below. The degrees of all nodes in the network comprise the *degree distribution*, which is an important marker of network development and resilience. The mean network degree is most commonly used as a measure of *density*, or the total "wiring cost" of the network. The directed variant of the degree distinguishes the number of inward links from the number of outward links, while the weighted variant of the degree, sometimes termed the strength, is defined as the sum of all neighboring link weights.

It is important to note that values of many network measures are greatly influenced by basic network characteristics, such as the number of nodes and links, and the degree distribution. Consequently, the significance of network statistics should be established by comparison with statistics calculated on null-hypothesis networks. Null-hypothesis networks have simple random or ordered topologies but preserve basic characteristics of the original network. The most commonly used null-hypothesis network has a random topology but shares the size, density and binary degree distribution of the original network (Maslov and Sneppen, 2002). Note, however, that this network may have a different weighted degree distribution, especially if the weight distribution is nonhomogeneous.

Measures of functional segregation

Functional segregation in the brain is the ability for specialized processing to occur within densely interconnected groups of brain regions. Measures of segregation primarily quantify the presence of such groups, known as clusters or modules, within the network. Measures of segregation have straightforward interpretations in anatomical and functional networks. The presence of clusters in anatomical networks suggests the potential for functional segregation in these networks, while the presence of clusters in functional networks suggests an organization of statistical dependencies indicative of segregated neural processing.

Simple measures of segregation are based on the number of triangles in the network, with a high number of triangles implying segregation (Fig. 3). Locally, the fraction of triangles around an individual node is known as the *clustering coefficient* and is equivalent to the fraction of the node's neighbors that are also neighbors of each other (Watts and Strogatz, 1998). The mean clustering coefficient for the network hence reflects, on average, the prevalence of clustered connectivity around individual nodes. The mean clustering coefficient is normalized individually for each node (Table A1) and may therefore be disproportionately influenced by nodes with a low degree. A classical variant of the clustering coefficient, known as the *transitivity*, is normalized collectively and consequently does not suffer from this problem (e.g., Newman, 2003). Both the clustering coefficient and the transitivity have been generalized for weighted (Onnela et al., 2005) and directed (Fagiolo, 2007) networks.

More sophisticated measures of segregation not only describe the presence of densely interconnected groups of regions, but also find the exact size and composition of these individual groups. This composition, known as the network's *modular structure* (community structure), is revealed by subdividing the network into groups of nodes, with a maximally possible number of within-group links, and a minimally possible number of between-group links (Girvan and Newman, 2002). The degree to which the network may be subdivided into such clearly delineated and nonoverlapping groups is quantified by a single statistic, the *modularity* (Newman, 2004b). Unlike most other network measures, the optimal modular structure for a given network is typically estimated with optimization algorithms, rather than computed exactly (Danon et al., 2005). Optimization algorithms generally sacrifice some degree of accuracy for computational speed. One notable algorithm (Newman, 2006) is known to be quite accurate and is sufficiently fast for smaller networks. Another more recently developed algorithm (Blondel et al., 2008) performs much faster for larger networks and is also able to detect a hierarchy of modules (the presence of smaller modules inside larger modules). Both of these algorithms have been generalized to detect modular structure in weighted (Newman, 2004a) and directed (Leicht and Newman, 2008) networks. Other algorithms detect overlapping modular network structure, and hence acknowledge that single nodes may simultaneously belong in multiple modules (e.g., Palla et al., 2005).

Figure 2A shows the modular structure of the anatomical connectivity network of a large portion of the macaque cortex, while Figs. 2B and C shows functional and effective networks reordered by this modular structure. These anatomical modules correspond to groups of specialized functional areas, such as the visual and somatomotor regions, as previously determined by physiological recordings. Anatomical, functional, and effective modules in this network show extensive overlap.

Measures of functional integration

Functional integration in the brain is the ability to rapidly combine specialized information from distributed brain regions. Measures of integration characterize this concept by estimating the ease with which brain regions communicate and are commonly based on the concept of a path. Paths are sequences of distinct nodes and links and in anatomical networks represent potential routes of information flow between pairs of brain regions. Lengths of paths consequently estimate the potential for functional integration between brain regions, with shorter paths implying stronger potential for integration. On the other hand, functional connectivity data, by its nature, already contain such information for all pairs of brain regions (Fig. 2B —top panel). Paths in functional networks represent sequences of statistical associations and may not correspond to information flow on anatomical connections. Consequently, network measures based on functional paths are less straightforward to interpret. Such measures may be easier to interpret when information about anatomical connections is available for the same subjects (e.g., Honey et al., 2009).

The average shortest path length between all pairs of nodes in the network is known as the *characteristic path length* of the network (e.g., Watts and Strogatz, 1998) and is the most commonly used measure of functional integration. The average inverse shortest path length is a related measure known as the *global efficiency* (Latora and Marchiori, 2001). Unlike the characteristic path length, the global efficiency may be meaningfully computed on disconnected networks, as paths between disconnected nodes are defined to have infinite length, and correspondingly zero efficiency. More generally, the characteristic path length is primarily influenced by long paths (infinitely long paths are an illustrative extreme), while the global efficiency is primarily influenced by short paths. Some authors have argued that this may make the global efficiency a superior measure of integration (Achard and Bullmore, 2007). Note that measures such as the characteristic path length and the global efficiency do not incorporate multiple and longer paths, which may significantly contribute to integration in larger and sparser networks (Estrada and Hatano, 2008).
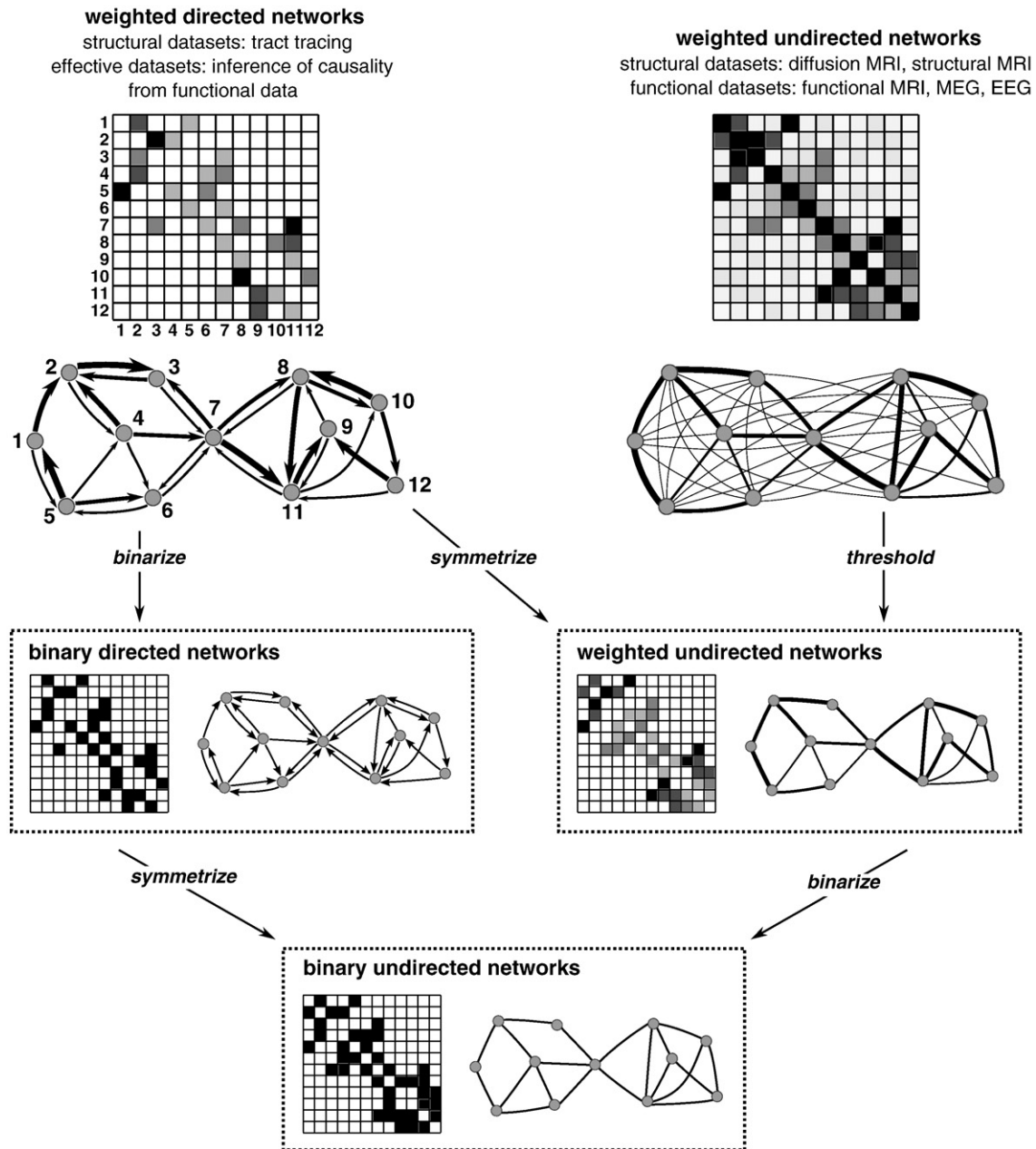
Fig. 1. Construction of brain networks from large scale anatomical and functional connectivity datasets. Structural networks are commonly extracted from histological (tract tracing) or neuroimaging (diffusion MRI) data. Functional networks are commonly extracted from neuroimaging (fMRI) or neurophysiological (EEG, MEG) data. For computational convenience, networks are commonly represented by their connectivity matrices, with rows and columns representing nodes and matrix entries representing links. To simplify analysis, networks are often reduced to a sparse binary undirected form, through thresholding, binarizing, and symmetrizing.

Paths are easily generalized for directed and weighted networks (Fig. 3). While a binary path length is equal to the number of links in the path, a weighted path length is equal to the total sum of individual link lengths. Link *lengths* are inversely related to link *weights*, as large weights typically represent strong associations and close proximity. Connection lengths are typically dimensionless and do not represent spatial or metric distance.

The structural, functional, and effective connectivity networks in Fig. 2 differ in their values of the global efficiency. Structural and effective networks are similarly organized (Honey et al., 2007) and share a high global efficiency. In comparison, functional networks have weaker connections between modules, and consequently a lower global efficiency.

Small-world brain connectivity

Anatomical brain connectivity is thought to simultaneously reconcile the opposing demands of functional integration and segregation (Tononi et al., 1994). A well-designed anatomical network could therefore combine the presence of functionally specialized (segregated) modules with a robust number of intermodular (integrating) links. Such a design is commonly termed small-world and indeed appears to be a ubiquitous organization of anatomical connectivity (Bassett and Bullmore, 2006). Furthermore, most studies examining functional brain networks also report various degrees of small-world organization. It is commonly thought that such an organization reflects an
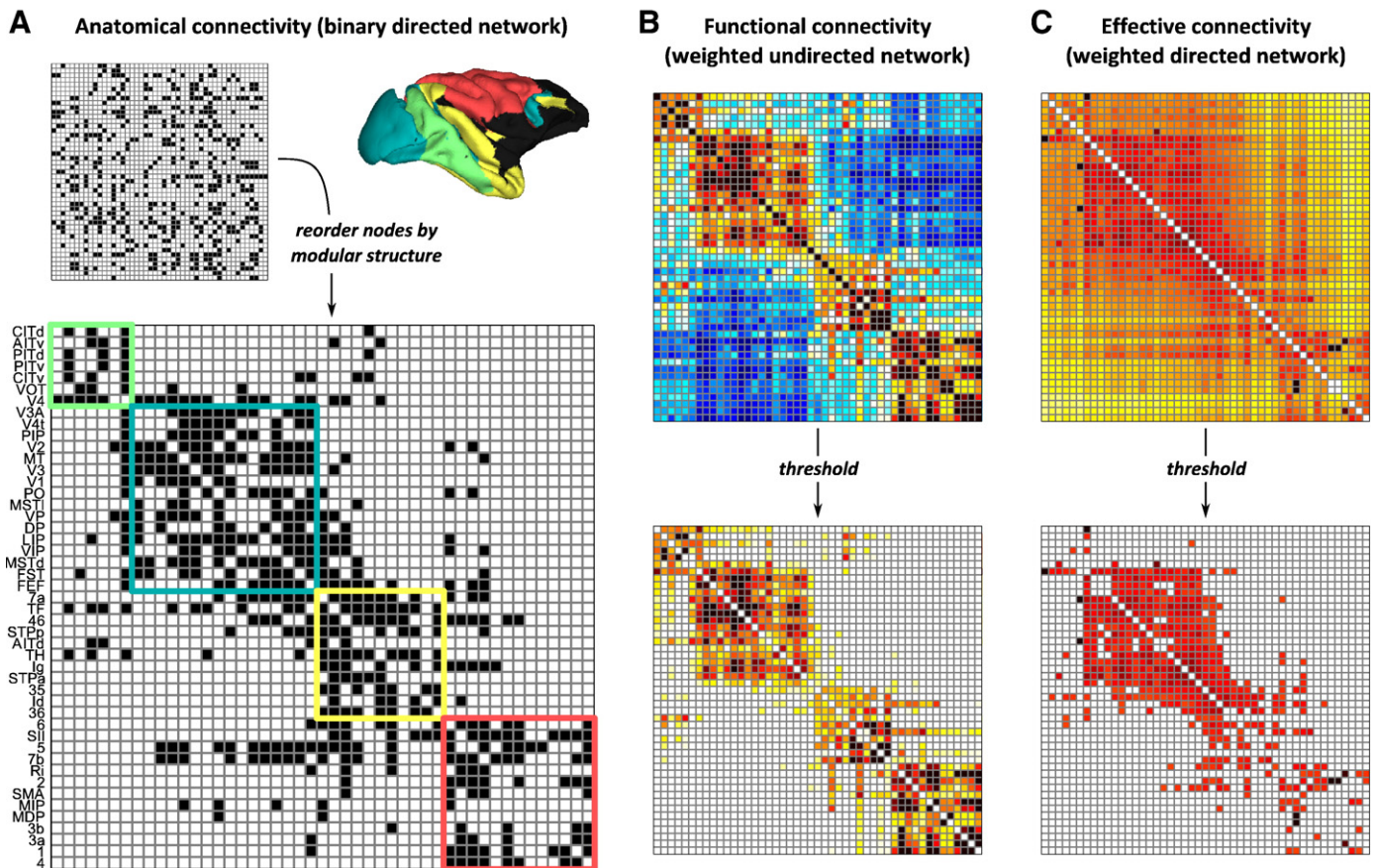
Fig. 2. Illustrative anatomical, functional, and effective connectivity networks. (A) Large-scale anatomical connection network of the macaque cortex. This network includes the ventral and dorsal streams of visual cortex, as well as groups of somatosensory and somatomotor regions. Network modules representing these groups, form largely contiguous (color-coded) anatomical regions. Area names and abbreviations are provided in the supporting information. (B, top) Functional connectivity network, representing cross-correlation of the regional BOLD signal, as estimated from simulated neural mass model dynamics. Warm colors represent positive correlations, while cool colors represent negative correlations. (B, bottom) The same network, thresholded by removing negative and self-self correlations. (C, top) Effective connectivity network, constructed by computing inter-regional transfer entropy, from the simulated fast time-scale dynamics. (C, bottom) The same network, thresholded to preserve the strongest connections, of the same number as in the structural network. See Honey et al. (2007) for a further exploration of these networks.

optimal balance of functional integration and segregation (Sporns and Honey, 2006). While this is a plausible hypothesis, the somewhat abstract nature of functional paths (see above) makes interpretation of the small-world property less straightforward in functional networks. A more complete understanding of the relationship between brain dynamics and functional connectivity will help to clarify this issue.

Small-world networks are formally defined as networks that are significantly more clustered than random networks, yet have approximately the same characteristic path length as random networks (Watts and Strogatz, 1998). More generally, small-world networks should be simultaneously highly segregated and integrated. Recently, a measure of *small-worldness* was proposed to capture this effect in a single statistic (Humphries and Gurney, 2008). This measure may be useful for snapshot characterization of an ensemble of networks, but it may also falsely report a small-world topology in highly segregated, but poorly integrated networks. Consequently, this measure should not in general be regarded as a substitute for individual assessments of integration and segregation.

Anatomical and effective networks in Fig. 2 are simultaneously highly segregated and integrated, and consequently have small-world topologies. In comparison, the functional network is also highly segregated but has a lower global efficiency, and therefore weaker small-world attributes.

Network motifs

Global measures of integration and segregation belie a rich repertoire of underlying local patterns of connectivity. Such local patterns are particularly diverse in directed networks. For instance, anatomical triangles may consist of feedforward loops, feedback loops, and bidirectional loops, with distinct frequencies of individual loops likely having specific functional implications. These patterns of local connectivity are known as (anatomical) motifs (Fig. 3). The significance of a motif in the network is determined by its frequency of occurrence, usually normalized as the *motif z-score* by comparison with ensembles of random null-hypothesis networks (Milo et al., 2002). The frequency of occurrence of different motifs around an individual node is known as the *motif fingerprint* of that node and is likely to reflect the functional role of the corresponding brain region (Sporns and Kotter, 2004). The frequency of occurrence of different motifs in the whole network correspondingly represents the characteristic motif profile of the network.

Functional activations on a local anatomical circuit may at any given time utilize only a portion of that circuit. This observation motivated the introduction of *functional motifs*, defined as possible subsets of connection patterns embedded within anatomical motifs (Sporns and Kotter, 2004). Functional motif significance may be optimally characterized by weighted
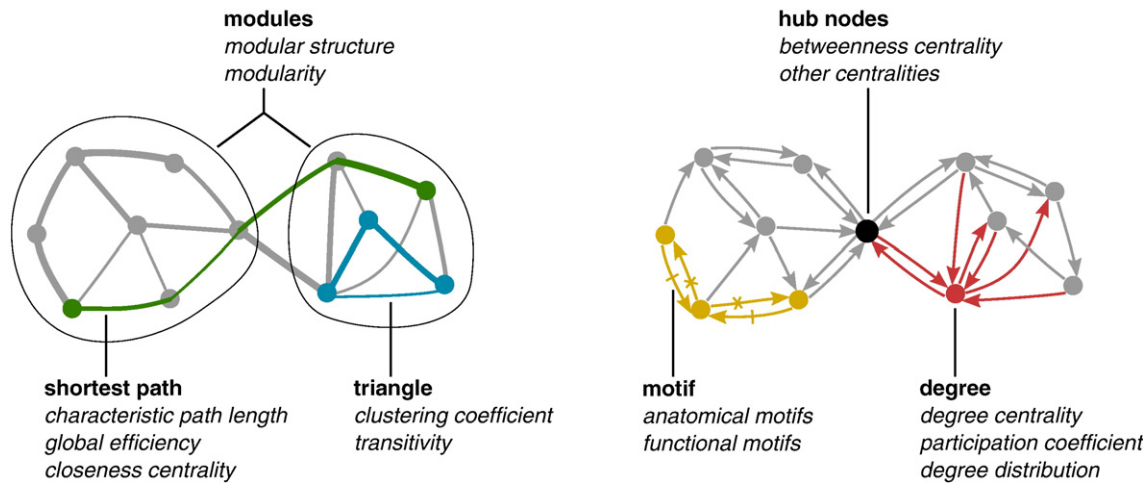
Fig. 3. Measures of network topology. An illustration of key complex network measures (in italics) described in this article. These measures are typically based on basic properties of network connectivity (in bold type). Thus, measures of integration are based on shortest path lengths (green), while measures of segregation are often based on triangle counts (blue) but also include more sophisticated decomposition into modules (ovals). Measures of centrality may be based on node degree (red) or on the length and number of shortest paths between nodes. Hub nodes (black) often lie on a high number of shortest paths and consequently often have high betweenness centrality. Patterns of local connectivity are quantified by network motifs (yellow). An example three-node and four-link anatomical motif contains six possible functional motifs, of which two are shown—one motif containing dashed links, and one motif containing crossed links.

measures of motif occurrence, known as the *motif intensity*, and the *motif intensity z-score* (Onnela et al., 2005). Motif intensity takes into account weights of all motif-comprising links and may therefore be more sensitive in detecting consistently strong functional configurations.

There is a source of possible confusion in motif terminology. Motifs ("structural" and "functional") were initially considered only in the context of anatomical brain networks (Sporns and Kotter, 2004). However, motif measures may also be meaningfully applied to some effective connectivity networks. On the other hand, motifs are generally not used in the analysis of undirected networks, due to the paucity of local undirected connectivity patterns.

Measures of centrality

Important brain regions (hubs) often interact with many other regions, facilitate functional integration, and play a key role in network resilience to insult. Measures of node centrality variously assess importance of individual nodes on the above criteria. There are many measures of centrality, and in this section, we describe the more commonly used measures. We also note that motif and resilience measures, discussed in other sections, are likewise sometimes used to detect central brain regions.

The *degree*, as discussed above, is one of the most common measures of centrality. The degree has a straightforward neurobiological interpretation: nodes with a high degree are interacting, structurally or functionally, with many other nodes in the network. The degree may be a sensitive measure of centrality in anatomical networks with nonhomogeneous degree distributions.

In modular anatomical networks, degree-based measures of within-module and between-module connectivity may be useful for heuristically classifying nodes into distinct functional groups (Guimera and Amaral, 2005). The *within-module degree z-score* is a localized, within-module version of degree centrality (Table A1). The complementary *participation coefficient* assesses the diversity of intermodular interconnections of individual nodes. Nodes with a high within-module degree but with a low participation coefficient (known as provincial hubs) are hence likely to play

an important part in the facilitation of modular segregation. On the other hand, nodes with a high participation coefficient (known as connector hubs) are likely to facilitate global intermodular integration.

Many measures of centrality are based on the idea that central nodes participate in many short paths within a network, and consequently act as important controls of information flow (Freeman, 1978). For instance, *closeness centrality* is defined as the inverse of the average shortest path length from one node to all other nodes in the network. A related and often more sensitive measure is *betweenness centrality*, defined as the fraction of all shortest paths in the network that pass through a given node. Bridging nodes that connect disparate parts of the network often have a high betweenness centrality (Fig. 3). The notion of betweenness centrality is naturally extended to links and could therefore also be used to detect important anatomical or functional connections. The calculation of betweenness centrality has been made significantly more efficient with the recent development of faster algorithms (Brandes, 2001; Kintali, 2008).

Weighted and directed variants of centrality measures are in most cases based on weighted and directed variants of degree and path length (Table A1).

Measures of centrality may have different interpretations in anatomical and functional networks. For instance, anatomically central nodes often facilitate integration, and consequently enable functional links between anatomically unconnected regions. Such links in turn make central nodes less prominent and so reduce the sensitivity of centrality measures in functional networks. In addition, path-based measures of centrality in functional networks are subject to the same interpretational caveats as path-based measures of integration (see above).

Measures of network resilience

Anatomical brain connectivity influences the capacity of neuropathological lesions to affect functional brain activity. For instance, the extent of functional deterioration is heavily determined by the affected anatomical region in a stroke, or by the capacity of anatomical

connectivity to withstand degenerative change in Alzheimer's disease. Complex network analysis is able to characterize such network resilience properties directly and indirectly.

Indirect measures of resilience quantify anatomical features that reflect network vulnerability to insult. One such feature is the *degree distribution* (Barabasi and Albert, 1999). For instance, complex networks with power-law degree distributions may be resilient to gradual random deterioration, but highly vulnerable to disruptions of high-degree central nodes. Most real-life networks do not have perfect power–law degree distributions. On the other hand, many networks have degree distributions that locally behave like a power–law—the extent to which these distributions fit a power–law may hence be a useful marker of resilience (Achard et al., 2006). Another useful measure of resilience is the *assortativity coefficient* (Newman, 2002). The assortativity coefficient is a correlation coefficient between the degrees of all nodes on two opposite ends of a link. Networks with a positive assortativity coefficient are therefore likely to have a comparatively resilient core of mutually interconnected high-degree hubs. On the other hand, networks with a negative assortativity coefficient are likely to have widely distributed and consequently vulnerable high-degree hubs. Related measures of assortativity computed on individual nodes include the *average neighbor degree* (Pastor-Satorras et al., 2001) and the recently introduced *local assortativity coefficient* (Piraveenan et al., 2008). Individual central nodes that score lowly on these measures may therefore compromise global network function if disrupted. Weighted and directed variants of assortativity measures are based on the respective weighted and directed variants of the degree (Barrat et al., 2004; Leung and Chau, 2007).

Direct measures of network resilience generally test the network before and after a presumed insult. For instance, patients with a progressive neurodegenerative disease may be imaged over a longitudinal period. Alternatively, insults may be computationally simulated by random or targeted removal of nodes and links. The effects of such lesions on the network may then be quantified by characterizing changes in the resulting anatomical connectivity, or in the emergent simulated functional connectivity or dynamical activity (e.g., Alstott et al., 2009). When testing resilience in such a way, it is prudent to use measures that are suitable for the analysis of disconnected networks. For instance, the global efficiency would be preferable to the characteristic path length as a measure of integration.

Network comparison

Complex network analysis may be useful for exploring connectivity relationships in individual subjects or between subject groups. In individual subjects, comparisons of structural and functional networks may provide insights into structural–functional connectivity relationships (e.g., Honey et al., 2007). Across subject populations, comparisons may detect abnormalities of network connectivity in various brain disorders (Bassett and Bullmore, 2009). The increased emphasis on structure–function and between-subject comparisons in studies of brain networks will require the development of accurate statistical comparison tools, similar to those in cellular and molecular biology (Sharan and Ideker, 2006). Preliminary steps have already been taken in this direction (Costa et al., 2007a). Here we discuss some general issues associated with network comparison.

Differences in density between anatomical and functional networks make global comparisons between these networks less straightforward. Functional networks are likely to be denser than anatomical networks, as they will typically contain numerous connections between anatomically unconnected regions (Damoiseaux and Greicius, 2009). These differences in density are likely to become more pronounced in larger, more highly resolved networks, as anatomical connectivity in such networks becomes increasingly sparse, while functional connectivity remains comparatively dense. Notably, comparisons between anatomical and functional modular structure (e.g., Zhou et al., 2006) remain meaningful despite differences in density. Other factors that may affect comparisons of network topology include degree and weight distributions.

The nontrivial relationship between structural and functional brain connectivity and the consequent interpretational difficulties of some functional measures (see above) make between-subject comparisons of functional networks difficult. The significance of such comparisons will become more obvious with increased knowledge about causal relationships between brain regions, as mediated by direct anatomical connections. The development of a detailed anatomical map of the human brain is an important step in this direction (Sporns et al., 2005).

Brain connectivity analysis software

Multiple network analysis software packages are freely available on the Web. These packages include command-line toolboxes in popular languages, such as Matlab (Gleich, 2008) and Python (Hagberg et al., 2008), as well as standalone graphical user interface software (Batagelj and Mrvar, 2003; NWB-Team, 2006). Some of these packages are especially suitable for the analysis of large networks containing thousands of nodes, while others have powerful network visualization capabilities.

To accompany this article, we developed a freely available and open source Matlab toolbox (http://www.brain-connectivity-toolbox.net). A number of features distinguish our toolbox from most other software packages. Our toolbox includes many recently developed network measures, which are discussed in this article, but are not yet widely available. In addition, we provide weighted and directed variants for all our measures—many of these variants are likewise not yet available in other software. In addition to these features, the toolbox provides functions for network manipulation (such as thresholding) and includes algorithms for generating null-hypothesis networks of predetermined (random, ordered and other) topologies. Finally, the toolbox contains datasets for large scale neuroanatomical networks of the mammalian cortex of several species. The open source nature of our toolbox allows researchers to customize individual functions for their needs, and to incorporate functions into larger analysis protocols.

Conclusion

Complex network analysis has emerged as an important tool for characterization of anatomical and functional brain connectivity. We described a collection of measures that quantify local and global properties of complex brain networks. The accompanying brain connectivity toolbox allows researchers to start exploring network properties of complex structural and functional datasets. We hope that the brain mapping community will be able to benefit from and contribute to these tools.

Acknowledgments

Appendix A.

Table A1
Mathematical definitions of complex network measures (see supplementary information for a self-contained version of this table).

Measure	Binary and undirected definitions	Weighted and directed definitions
Basic concepts and measures		
Basic concepts and notation	N is the set of all nodes in the network, and n is the number of nodes. L is the set of all links in the network, and l is number of links. (i, j) is a link between nodes i and j, $(i, j \in N)$. a_{ij} is the connection status between i and j: $a_{ij} = 1$ when link (i, j) exists (when i and j are neighbors); $a_{ij} = 0$ otherwise ($a_{ii} = 0$ for all i). We compute the number of links as $l = \sum_{i,j \in N} a_{ij}$ (to avoid ambiguity with directed links we count each undirected link twice, as a_{ij} and as a_{ji}).	Links (i, j) are associated with connection weights w_{ij}. Henceforth, we assume that weights are normalized, such that $0 \le w_{ij} \le 1$ for all i and j. l^w is the sum of all weights in the network, computed as $l^w = \sum_{i,j \in N} w_{ij}$. Directed links (i, j) are ordered from i to j. Consequently, in directed networks a_{ij} does not necessarily equal a_{ji}.
Degree: number of links connected to a node	Degree of a node i, $$k_i = \sum_{j \in N} a_{ij}.$$	Weighted degree of i, $k_i^w = \sum_{j \in N} w_{ij}$. (Directed) out-degree of i, $k_i^{out} = \sum_{j \in N} a_{ij}$. (Directed) in-degree of i, $k_i^{in} = \sum_{j \in N} a_{ji}$.
Shortest path length: a basis for measuring integration	Shortest path length (distance), between nodes i and j, $$d_{ij} = \sum_{a_{uv} \in g_{i \leftrightarrow j}} a_{uv},$$ where $g_{i \leftrightarrow j}$ is the shortest path (geodesic) between i and j. Note that $d_{ij} = \infty$ for all disconnected pairs i, j.	Shortest weighted path length between i and j, $d_{ij}^w = \sum_{a_{uv} \in g_{i \leftrightarrow j}^w} f(w_{uv})$, where f is a map (e.g., an inverse) from weight to length and $g_{i \leftrightarrow j}^w$ is the shortest weighted path between i and j. Shortest directed path length from i to j, $d_{ij}^{\rightarrow} = \sum_{a_{ij} \in g_{i \rightarrow j}} a_{ij}$, where $g_{i \rightarrow j}$ is the directed shortest path from i to j.
Number of triangles: a basis for measuring segregation	Number of triangles around a node i, $$t_i = \frac{1}{2} \sum_{j,h \in N} a_{ij} a_{ih} a_{jh}.$$	(Weighted) geometric mean of triangles around i, $t_i^w = \frac{1}{2} \sum_{j,h \in N} (w_{ij} w_{ih} w_{jh})^{1/3}$. Number of directed triangles around i, $t_i^{\rightarrow} = \frac{1}{2} \sum_{j,h \in N} (a_{ij} + a_{ji})(a_{ih} + a_{hi})(a_{jh} + a_{hj})$.
Measures of integration		
Characteristic path length	Characteristic path length of the network (e.g., Watts and Strogatz, 1998), $$L = \frac{1}{n} \sum_{i \in N} L_i = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \ne i} d_{ij}}{n - 1},$$ where L_i is the average distance between node i and all other nodes.	Weighted characteristic path length, $L^w = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \ne i} d_{ij}^w}{n - 1}$. Directed characteristic path length, $L^{\rightarrow} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \ne i} d_{ij}^{\rightarrow}}{n - 1}$.
Global efficiency	Global efficiency of the network (Latora and Marchiori, 2001), $$E = \frac{1}{n} \sum_{i \in N} E_i = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \ne i} d_{ij}^{-1}}{n - 1},$$ where E_i is the efficiency of node i.	Weighted global efficiency, $E^w = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \ne i} (d_{ij}^w)^{-1}}{n - 1}$. Directed global efficiency, $E^{\rightarrow} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \ne i} (d_{ij}^{\rightarrow})^{-1}}{n - 1}$.
Measures of segregation		
Clustering coefficient	Clustering coefficient of the network (Watts and Strogatz, 1998), $$C = \frac{1}{n} \sum_{i \in N} C_i = \frac{1}{n} \sum_{i \in N} \frac{2t_i}{k_i(k_i - 1)},$$ where C_i is the clustering coefficient of node i ($C_i = 0$ for $k_i < 2$).	Weighted clustering coefficient (Onnela et al., 2005), $C^w = \frac{1}{n} \sum_{i \in N} \frac{2t_i^w}{k_i(k_i - 1)}$. See Saramaki et al. (2007) for other variants. Directed clustering coefficient (Fagiolo, 2007), $C^{\rightarrow} = \frac{1}{n} \sum_{i \in N} \frac{t_i^{\rightarrow}}{(k_i^{out} + k_i^{in})(k_i^{out} + k_i^{in} - 1) - 2\sum_{j \in N} a_{ij} a_{ji}}$.
Transitivity	Transitivity of the network (e.g., Newman, 2003), $$T = \frac{\sum_{i \in N} 2t_i}{\sum_{i \in N} k_i(k_i - 1)}.$$ Note that transitivity is not defined for individual nodes.	Weighted transitivity*, $T^w = \frac{\sum_{i \in N} 2t_i^w}{\sum_{i \in N} k_i(k_i - 1)}$. Directed transitivity*, $T^{\rightarrow} = \frac{\sum_{i \in N} t_i^{\rightarrow}}{\sum_{i \in N} \left[(k_i^{out} + k_i^{in})(k_i^{out} + k_i^{in} - 1) - 2\sum_{j \in N} a_{ij} a_{ji} \right]}$.
Local efficiency	Local efficiency of the network (Latora and Marchiori, 2001), $$E_{loc} = \frac{1}{n} \sum_{i \in N} E_{loc,i} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j,h \in N, j \ne i} a_{ij} a_{ih} [d_{jh}(N_i)]^{-1}}{k_i(k_i - 1)},$$ where $E_{loc,i}$ is the local efficiency of node i, and $d_{jh}(N_i)$ is the length of the shortest path between j and h, that contains only neighbors of i.	Weighted local efficiency*, $E_{loc}^w = \frac{1}{2} \sum_{i \in N} \frac{\sum_{j,h \in N, j \ne i} \left(w_{ij} w_{ih} [d_{jh}^w(N_i)]^{-1} \right)^{1/3}}{k_i(k_i - 1)}$. Directed local efficiency*, $E_{loc}^{\rightarrow} = \frac{1}{2n} \sum_{i \in N} \frac{\sum_{j,h \in N, j \ne i} (a_{ij} + a_{ji})(a_{ih} + a_{hi}) \left([d_{jh}^{\rightarrow}(N_i)]^{-1} + [d_{hj}^{\rightarrow}(N_i)]^{-1} \right)}{(k_i^{out} + k_i^{in})(k_i^{out} + k_i^{in} - 1) - 2\sum_{j \in N} a_{ij} a_{ji}}$.

Table A1 (*continued*)

Measure	Binary and undirected definitions	Weighted and directed definitions
Modularity	Modularity of the network (Newman, 2004b), $$Q = \sum_{u \in M}\left[e_{uu} - \left(\sum_{v \in M} e_{uv}\right)^2\right],$$ where the network is fully subdivided into a set of nonoverlapping modules M, and e_{uv} is the proportion of all links that connect nodes in module u with nodes in module v. An equivalent alternative formulation of the modularity (Newman, 2006) is given by $Q = \frac{1}{l}\sum_{i,j \in N}\left(a_{ij} - \frac{k_i k_j}{l}\right)\delta_{m_i,m_j}$, where m_i is the module containing node i, and $\delta_{m,mj} = 1$ if $m_i = m_j$, and 0 otherwise.	Weighted modularity (Newman, 2004), $Q^w = \frac{1}{l^w}\sum_{i,j \in N}\left[w_{ij} - \frac{k_i^w k_j^w}{l^w}\right]\delta_{m_i,m_j}$. Directed modularity (Leicht and Newman, 2008), $Q^{\rightarrow} = \frac{1}{l}\sum_{i,j \in N}\left[a_{ij} - \frac{k_i^{out} k_j^{in}}{l}\right]\delta_{m_i,m_j}$.
Measures of centrality Closeness centrality	Closeness centrality of node i (e.g. Freeman, 1978), $$L_i^{-1} = \frac{n-1}{\sum_{j \in N, j \neq i} d_{ij}}.$$	Weighted closeness centrality, $\left(L_i^w\right)^{-1} = \frac{n-1}{\sum_{j \in N, j \neq i} d_{ij}^w}$. Directed closeness centrality, $\left(L_i^{\rightarrow}\right)^{-1} = \frac{n-1}{\sum_{j \in N, j \neq i} d_{ij}^{\rightarrow}}$.
Betweenness centrality	Betweenness centrality of node i (e.g., Freeman, 1978), $$b_i = \frac{1}{(n-1)(n-2)} \sum_{\substack{h,j \in N \\ h \neq j, h \neq i, j \neq i,}} \frac{\rho_{hj}(i)}{\rho_{hj}},$$ where ρ_{hj} is the number of shortest paths between h and j, and $\rho_{hj}(i)$ is the number of shortest paths between h and j that pass through i.	Betweenness centrality is computed equivalently on weighted and directed networks, provided that path lengths are computed on respective weighted or directed paths.
Within-module degree z-score	Within-module degree z-score of node i (Guimera and Amaral, 2005), $$z_i = \frac{k_i(m_i) - \overline{k}(m_i)}{\sigma^{k(m_i)}},$$ where m_i is the module containing node i, $k_i(m_i)$ is the within-module degree of i (the number of links between i and all other nodes in m_i), and $\overline{k}(m_i)$ and $\sigma^{k(m_i)}$ are the respective mean and standard deviation of the within-module m_i degree distribution.	Weighted within-module degree z-score, $z_i^w = \frac{k_i^w(m_i) - \overline{k}^w(m_i)}{\sigma^{k^w(m_i)}}$. Within-module out-degree z-score, $z_i^{out} = \frac{k_i^{out}(m_i) - \overline{k}^{out}(m_i)}{\sigma^{k^{out}(m_i)}}$. Within-module in-degree z-score, $z_i^{in} = \frac{k_i^{in}(m_i) - \overline{k}^{in}(m_i)}{\sigma^{k^{in}(m_i)}}$.
Participation coefficient	Participation coefficient of node i (Guimera and Amaral, 2005), $$y_i = 1 - \sum_{m \in M}\left(\frac{k_i(m)}{k_i}\right)^2,$$ where M is the set of modules (see modularity), and $k_i(m)$ is the number of links between i and all nodes in module m.	Weighted participation coefficient, $y_i^w = 1 - \sum_{m \in M}\left(\frac{k_i^w(m)}{k_i^w}\right)^2$. Out-degree participation coefficient, $y_i^{out} = 1 - \sum_{m \in M}\left(\frac{k_i^{out}(m)}{k_i^{out}}\right)^2$. In-degree participation coefficient, $y_i^{in} = 1 - \sum_{m \in M}\left(\frac{k_i^{in}(m)}{k_i^{in}}\right)^2$.
Network motifs Anatomical and functional motifs	J_h is the number of occurrences of motif h in all subsets of the network (subnetworks). h is an n_h node, l_h link, directed connected pattern. h will occur as an anatomical motif in an n_h node, l_h link subnetwork, if links in the subnetwork match links in h (Milo et al., 2002). h will occur (possibly more than once) as a functional motif in an n_h node, $l_h' \geq l_h$ link subnetwork, if at least one combination of l_h links in the subnetwork matches links in h (Sporns and Kotter, 2004).	(Weighted) intensity of h (Onnela et al., 2005), $$I_h = \sum_u \left(\Pi_{(i,j) \in L_{h^u}} w_{ij}\right)^{\frac{1}{l_h}},$$ where the sum is over all occurrences of h in the network, and L^{h^u} is the set of links in the uth occurrence of h. Note that motifs are directed by definition.
Motif z-score	z-Score of motif h (Milo et al., 2002), $$z_h = \frac{J_h - \langle J_{\text{rand},h}\rangle}{\sigma^{J_{\text{rand},h}}},$$ where $\langle J_{\text{rand},h}\rangle$ and $\sigma^{J_{\text{rand},h}}$ are the respective mean and standard deviation for the number of occurrences of h in an ensemble of random networks.	Intensity z-score of motif h (Onnela et al., 2005), $z_h^I = \frac{I_h - \langle I_{\text{rand},h}\rangle}{\sigma^{I_{\text{rand},h}}}$, where $\langle I_{\text{rand},h}\rangle$ and $\sigma^{I_{\text{rand},h}}$ are the respective mean and standard deviation for the intensity of h in an ensemble of random networks.
Motif fingerprint	n_h node motif fingerprint of the network (Sporns and Kotter, 2004), $$F_{n_h}(h') = \sum_{i \in N} F_{n_h,i}(h') = \sum_{i \in N} J_{h',i},$$ where h' is any n_h node motif, $F_{n_h,i}(h')$ is the n_h node motif fingerprint for node i, and $J_{h',i}$ is the number of occurrences of motif h' around node i.	n_h node motif intensity fingerprint of the network, $F_{n_h}^I(h') = \sum_{i \in N} F_{n_h,i}^I(h') = \sum_{i \in N} I_{h',i}$, where h' is any n_h node motif, $F_{n_h,i}^I(h')$ is the n_h node motif intensity fingerprint for node i, and $I_{h',i}$ is the intensity of motif h' around node i.

Table A1 (*continued*)

Measure	Binary and undirected definitions	Weighted and directed definitions
Measures of resilience		
Degree distribution	Cumulative degree distribution of the network (Barabasi and Albert, 1999), $$P(k) = \sum_{k'\geq k} p(k'),$$ where $p(k')$ is the probability of a node having degree k'.	Cumulative weighted degree distribution, $P(k^w) = \sum_{k'\geq k^w} p(k')$, Cumulative out-degree distribution, $P(k^{out}) = \sum_{k'\geq k^{out}} p(k')$. Cumulative in-degree distribution, $P(k^{in}) = \sum_{k'\geq k^{in}} p(k')$.
Average neighbor degree	Average degree of neighbors of node i (Pastor-Satorras et al., 2001), $$k_{nn,i} = \frac{\sum_{j\in N} a_{ij} k_j}{k_i}.$$	Average weighted neighbor degree (modified from Barrat et al., 2004), $$k_{nn,i}^w = \frac{\sum_{j\in N} w_{ij} k_j^w}{k_i^w}.$$ Average directed neighbor degree*, $$k_{nn,i}^{\rightarrow} = \frac{\sum_{j\in N}(a_{ij}+a_{ji})(k_i^{out}+k_i^{in})}{2(k_i^{out}+k_i^{in})}.$$
Assortativity coefficient	Assortativity coefficient of the network (Newman, 2002), $$r = \frac{l^{-1}\sum_{(i,j)\in L} k_i k_j - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i+k_j\right)\right]^2}{l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i^2+k_j^2\right) - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i+k_j\right)\right]^2}.$$	Weighted assortativity coefficient (modified from Leung and Chau, 2007), $$r^w = \frac{l^{-1}\sum_{(i,j)\in L} w_{ij} k_i^w k_j^w - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}w_{ij}(k_i^w+k_j^w)\right]^2}{l^{-1}\sum_{(i,j)\in L}\frac{1}{2}w_{ij}\left((k_i^w)^2+(k_j^w)^2\right) - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}w_{ij}(k_i^w+k_j^w)\right]^2}.$$ Directed assortativity coefficient (Newman, 2002), $$r^{\rightarrow} = \frac{l^{-1}\sum_{(i,j)\in L} k_i^{out} k_j^{in} - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i^{out}+k_j^{in}\right)\right]^2}{l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left((k_i^{out})^2+(k_j^{in})^2\right) - \left[l^{-1}\sum_{(i,j)\in L}\frac{1}{2}\left(k_i^{out}+k_j^{in}\right)\right]^2}.$$
Other concepts		
Degree distribution preserving network randomization.	Degree-distribution preserving randomization is implemented by iteratively choosing four distinct nodes $i_1, j_1, i_2, j_2 \in N$ at random, such that links $(i_1,j_1), (i_2,j_2) \in L$, while links $(i_1,j_2), (i_2,j_1) \notin L$. The links are then rewired such that $(i_1,j_2), (i_2,j_1) \in L$ and $(i_1,j_1), (i_2,j_2) \notin L$, (Maslov and Sneppen, 2002). "Latticization" (a lattice-like topology) results if an additional constraint is imposed, $|i_1+j_2| + |i_2+j_1| < |i_1+j_1| + |i_2+j_2|$ (Sporns and Kotter, 2004).	The algorithm is equivalent for weighted and directed networks. In weighted networks, weights may be switched together with links; in this case, the weighted degree distribution is not preserved, but may be subsequently approximated on the topologically randomized graph with a heuristic weight reshuffling scheme.
Measure `of network small-worldness.	Network small-worldness (Humphries and Gurney, 2008), $$S = \frac{C/C_{rand}}{L/L_{rand}},$$ where C and C_{rand} are the clustering coefficients, and L and L_{rand} are the characteristic path lengths of the respective tested network and a random network. Small-world networks often have $S \gg 1$.	Weighted network small-worldness, $S^w = \frac{C^w/C_{rand}^w}{L^w/L_{rand}^w}$. Directed network small-worldness, $S^{\rightarrow} = \frac{C^{\rightarrow}/C_{rand}^{\rightarrow}}{L^{\rightarrow}/L_{rand}^{\rightarrow}}$. In both cases, small-world networks often have $S \gg 1$.

All binary and undirected measures are accompanied by their weighted and directed generalizations. Generalizations that have not been previously reported (to the best of our knowledge) are marked with an asterisk (*). The Brain Connectivity Toolbox contains Matlab functions to compute most measures in this table.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.10.003.

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