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Organization, development and function of complex brain networks

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Recent research has revealed general principles in the structural and functional organization of complex networks which are shared by various natural, social and technological systems. This review examines these principles as applied to the organization, development and function of complex brain networks. Specifically, we examine the structural properties of large-scale anatomical and functional brain networks and discuss how they might arise in the course of network growth and rewiring. Moreover, we examine the relationship between the structural substrate of neuroanatomy and more dynamic functional and effective connectivity patterns that underlie human cognition. We suggest that network analysis offers new fundamental insights into global and integrative aspects of brain function, including the origin of flexible and coherent cognitive states within the neural architecture.

Complex networks, in a range of disciplines from biology to physics, social sciences and informatics, have received significant attention in recent years [1–3]. What can an investigation of network structure and dynamics contribute to our understanding of brain and cognitive function? In our review, we address this question by highlighting a series of recent studies of complex brain networks and by attempting to identify promising areas and questions for future experimental and theoretical inquiry.

Networks are sets of nodes linked by connections, mathematically described as GRAPHS ([4–6]; see Glossary). The nodes and connections may represent persons and their social relations [7], molecules and their interactions [8], or web pages and hyperlinks [9], often numbering in the thousands or millions. What makes such networks complex is not only their size but also the interaction of architecture (the network's connection topology) and dynamics (the behavior of the individual network nodes), which gives rise to global states and 'emergent' behaviors. Recent work across a broad spectrum of complex networks has revealed common organizational principles (Box 1). In many complex networks, the non-linear dynamics of individual network components unfolds within network topologies that are strikingly irregular, yet non-random. In many networks, clusters of nodes segregate into tightly

coupled neighborhoods, but maintain very short DISTANCES among nodes across the entire network, giving rise to a small world within the network [10]. The degree to which individual nodes are connected forms a distribution that, for many but not all networks, decays as a power law, producing a SCALE-FREE architecture characterized by the existence of highly connected nodes (hubs) [11].

What about the brain? Nervous systems are complex networks *par excellence*, capable of generating and integrating information from multiple external and internal sources in real time. Within the neuroanatomical substrate (structural connectivity), the non-linear

Glossary: Graph theory and networks

For the following definitions of graph theory terms used in this review we essentially follow the nomenclature of ref. 4 (see also [27] for additional definitions and more detail). A Matlab toolbox allowing the calculation of these and other graph theory measures is available at <http://www.indiana.edu/cortex/connectivity.html>.

Adjacency (connection) matrix: The adjacency matrix of a graph is a $n \times n$ matrix with entries $a_{ij} = 1$ if node j connects to node i , and $a_{ij} = 0$ if there is no connection from node j to node i .

Characteristic path length: The characteristic path length L (also called 'path length' or 'average shortest path') is given by the global mean of the finite entries of the distance matrix. In some cases, the median or the harmonic mean can provide better estimates.[10]

Clustering coefficient: The clustering coefficient C_i of a node i is calculated as the number of existing connections between the node's neighbors divided by all their possible connections. The clustering coefficient ranges between 0 and 1 and is typically averaged over all nodes of a graph to yield the graph's clustering coefficient C .[10]

Connectedness: A connected graph has only one component, that is a set of nodes, for which every pair of nodes is joined by at least one path. A disconnected graph has at least two components.

Cycle: A cycle is a path that links a node to itself.

Degree: The degree of a node is the sum of its incoming (afferent) and outgoing (efferent) connections. The number of afferent and efferent connections is also called the 'in-degree' and 'out-degree', respectively.

Distance: The distance between a source node j and a target node i is equal to the length of the shortest path.

Distance matrix: The entries d_{ij} of the distance matrix correspond to the distance between node j and i . If no path exists, $d_{ij} = \text{infinity}$

Graph: Graphs are a set of n nodes (vertices, points, units) and k edges (connections, arcs). Graphs may be undirected (all connections are symmetrical) or directed. Because of the polarized nature of most neural connections, we focus on directed graphs, also called digraphs.

Path: A path is an ordered sequence of distinct connections and nodes, linking a source node j to a target node i . No connection or node is visited twice in a given path. The length of a path is equal to the number of distinct connections.

Random graph: A graph with uniform connection probabilities and a binomial degree distribution. All nodes have roughly the same degree ('single-scale').

Scale-free graph: Graph with a power-law degree distribution. 'Scale-free' means that degrees are not grouped around one characteristic average degree (scale), but can spread over a very wide range of values, often spanning several orders of magnitude.

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Box 1. Complex networks: small-world and scale-free architectures

For any number of n nodes and k connections, a RANDOM GRAPH (see Glossary) can be constructed by assigning connections between pairs of nodes with uniform probability. For many years, random graphs (Figure 1a) have served as a major class of models for describing the topology of natural and technological networks. However, although random graphs have yielded numerous and often surprising mathematical insights [5], they are probably only poor approximations of the connectivity structure of most complex systems.

Classical experiments [71] first revealed the existence of a small world in large social networks. Small worlds are characterized by the prevalence of surprisingly short PATHS linking pairs of nodes within very large networks. In a seminal paper [10], Watts and Strogatz demonstrated the emergence of small world connectivity in networks that combined ordered lattice-like connections with a small admixture of random links (Figure 1b). Combining elements of order and randomness, such networks were characterized by high degrees of local clustering as well as short path lengths, properties shared by genetic, metabolic, ecological and information networks [1–3].

The nodes in random graphs have approximately the same DEGREE (number of connections). This homogeneous architecture generates a normal (or Poisson) degree distribution. However, the degree distributions of most natural and technological networks follow a

power law [11], with very many nodes that have few connections and a few nodes (hubs) that have very many connections (Figure 1c). This inhomogeneous architecture lacks an intrinsic scale and is thus called SCALE-FREE. Scale-free networks are surprisingly robust with respect to random deletion of nodes, but are vulnerable to targeted attack on heavily connected hubs [45], which often results in disintegration of the network. A corollary of this finding is that the connection topology of scale-free networks cannot be efficiently captured by random sampling, as most nodes have few connections and hubs will tend to be under-represented. Sampling is thus a crucial issue for determining if brain networks have scale-free topology.

Systematic investigations of large-scale [32–35] and intermediate-scale [35,36] structural cortical networks have revealed small-world attributes, with path lengths that are close to those of equivalent random networks but with significantly higher values for the clustering coefficient. At the structural level, cortical networks either do not appear to be scale-free [35] or exhibit scale-free architectures with low maximum degrees [44], owing to saturation effects in the number of synaptic connections, which prevent the emergence of highly connected hubs. Instead, functional brain networks exhibit power law degree distributions as well as small-world attributes [52,62].

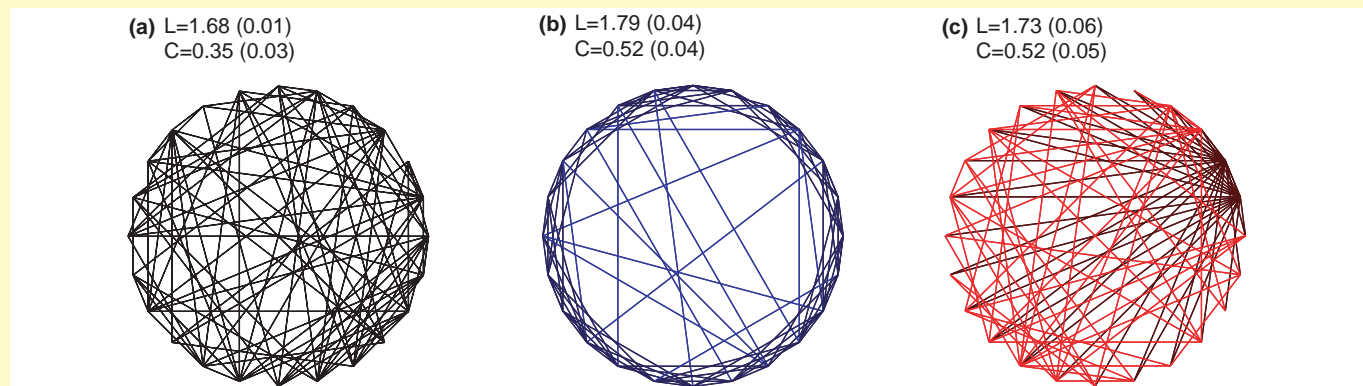


Figure 1. Structure of random, small-world and scale-free networks. All networks have 24 nodes and 86 connections with nodes arranged on a circle. The characteristic path length L and the clustering coefficient C are shown (mean and standard deviation for 100 examples in each case; only one example network is drawn). (a) Random network. (b) Small-world network. Most connections are among neighboring nodes on the circle (dark blue), but some connections (light blue) go to distant nodes, creating short-cuts across the network. (c) Scale-free network. Most of the 24 nodes have few connections to other nodes (red), but some nodes (black connections) are linked to more than 12 other nodes. For comparison, an ideal lattice with 24 nodes and 86 connections has $L = 1.96$ and $C = 0.64$.

dynamics of neurons and neuronal populations result in patterns of statistical dependencies (functional connectivity) and causal interactions (effective connectivity), defining three major modalities of complex brain networks (Box 2). Human cognition is associated with rapidly changing and widely distributed neural activation patterns, which involve numerous cortical and sub-cortical regions activated in different combinations and contexts [12–15]. Two major organizational principles of the cerebral cortex are functional segregation and functional integration [16–18], enabling the rapid extraction of information and the generation of coherent brain states. Which structural and functional principles of complex networks promote functional segregation and functional integration, or, in general, support the broad range and flexibility of cognitive processes?

In this review we examine recent insights gained about patterns of brain connectivity from the application of novel quantitative computational tools and theoretical models to empirical datasets. Whereas many studies of single neuron networks have revealed their complex morphology

and wiring [19], our focus is on the large-scale and intermediate-scale networks of the cerebral cortex, allowing us to examine links between neural organization and cognition arising at the ‘systems’ level. We divide this review into three parts, devoted in turn to the organization (structure), development (growth) and function (dynamics) of brain networks.

Structural organization of cortical networks

Most structural analyses of brain networks have been carried out on datasets describing the large-scale connection patterns of the cerebral cortex of rat [20], cat [21,22], and monkey [23] – structural connection data for the human brain is largely missing [24]. These analyses have revealed several organizational principles expressed within structural brain networks. All studies confirmed that cerebral cortical areas in mammalian brains are neither completely connected with each other nor randomly linked; instead, their interconnections show a specific and intricate organization. Methodologically, investigations have used either graph theoretical

Box 2. Brain connectivity: structural, functional and effective

Anatomical connectivity is the set of physical or structural (synaptic) connections linking neuronal units at a given time. Anatomical connectivity data can range over multiple spatial scales, from local circuits to large-scale networks of inter-regional pathways. Anatomical connection patterns are relatively static at shorter time scales (seconds to minutes), but can be dynamic at longer time scales (hours to days); for example, during learning or development.

Functional connectivity [72] captures patterns of deviations from statistical independence between distributed and often spatially remote neuronal units, measuring their correlation/covariance, spectral coherence or phase-locking. Functional connectivity is time-dependent (hundreds of milliseconds) and 'model-free', that is, it measures statistical interdependence (mutual information) without explicit reference to causal effects. Different methodologies for measuring brain activity will generally result in different statistical estimates of functional connectivity [73].

Effective connectivity describes the set of causal effects of one neural system over another [72]. Thus, unlike functional connectivity, effective connectivity is not 'model-free', but requires the specification of a causal model including structural parameters. Experimentally, effective connectivity can be inferred through perturbations, or through the observation of the temporal ordering of neural events. Other measures, estimating causal interactions can also be used (e.g. [52]).

Functional and effective connectivity are time-dependent. Statistical interactions between brain regions change rapidly reflecting the participation of varying subsets of brain regions and pathways in different cognitive tasks [12–15], behavioral or attentional states [65], awareness [14], and changes within the structural substrate related to learning [74]. Importantly, structural, functional and effective connectivity are mutually interrelated. Clearly, structural connectivity is a major constraint on the kinds of patterns of functional or effective connectivity that can be generated in a network. Structural inputs and outputs of a given cortical region, its connective fingerprint [28], are major determinants of its functional properties. Conversely, functional interactions can contribute to the shaping of the underlying anatomical substrate, either directly through activity (covariance)-dependent synaptic modification, or, over longer time scales, through affecting an organism's perceptual, cognitive or behavioral capabilities, and thus its adaptation and survival.

approaches, or multivariate methods to extract statistical structure by clustering or scaling techniques [25].

Structural contributions of individual areas and motifs

At the local level, simple statistical measures ('network participation indices', [26]) can be used to characterize inputs and outputs of individual areas. These measures include an area's IN-DEGREE and OUT-DEGREE, and its 'transmission' coefficient, defined as the relative number of efferents to afferents. Such measures allow identification of highly connected nodes (hubs) and provide an initial functional characterization of areas as either (mainly sending) 'broadcasters' or (mainly receiving) 'integrators' of signals. For macaque visual cortex [23], the average efferent/afferent ratio is close to 1, with a standard error of 0.4 [25], indicating that brain regions tend to engage in cooperative ('give-and-take') information-processing.

The 'matching index' captures the pairwise similarity of areas in terms of their specific afferents and efferents from other parts of the network [25,27]. One of the central assumptions of systems neuroscience is that the functional roles of brain regions are specified by their inputs and outputs. In agreement with this concept, one finds

that pairs of areas with high matching index also share functional properties [25]. In general, the 'connective fingerprint' of a cortical area can serve as an indicator of its functional contribution to the overall system [28].

On the next higher level of organization – neural circuits linking small sets of connected brain areas – the approach of motif analysis can be used to identify patterns of local interconnections that occur with a significantly higher frequency in real networks than in randomized networks of the same size [29,30,31]. Biological and technological networks contain several characteristic motifs, such as 'feedforward loops' and 'bi-parallel pathways'. A systematic analysis of motifs in brain networks revealed a small number of characteristic motifs shared among several examples of cortical networks (O. Sporns and R. Kotter, in preparation), potentially indicating common modes of information processing.

Large-scale connection patterns

Graph theoretical analysis of large-scale connection patterns of cat and monkey has revealed characteristic properties, several of which are shared across neural systems and species (see also Box 1). All large-scale cortical connection patterns (ADJACENCY MATRICES) examined so far exhibit small-world attributes with short PATH LENGTHS and high CLUSTERING COEFFICIENTS [32–35] (Figure 1a). These properties are also found in intermediate-scale connection patterns generated by probabilistic connection rules, taking into account metric distance between neuronal units [35,36]. This suggests that high clustering and short path lengths can be found across multiple spatial scales of cortical organization. The quantitative analysis of structural connection patterns using graph theory tools provides several insights into the functioning of neural architectures. In-degree and out-degree specify the amount of functional convergence and divergence of a given region (see above), whereas the clustering coefficient measures the degree to which the area is part of a local collective of functionally related regions. The path length between two brain regions captures their potential 'functional proximity'. If no path exists, no functional interaction can take place.

Various global connectivity features of cortical networks have been described and characterized with the help of multivariate analysis techniques, such as multi-dimensional scaling or hierarchical cluster analyses [25]. For example, streams of visual cortical areas have been identified that are segregated functionally [37] as well as in terms of their inputs, outputs and mutual interconnections [38]. Topological sequences of areas might provide the layout for signaling pathways across cortical networks [39]. Alternatively, hierarchies of cortices can be constructed, based on the laminar origin and termination patterns of interconnections [23,40].

To identify the clusters which are indicated by the high clustering coefficients of cortical networks, a computational approach based on evolutionary optimization was proposed [32]. This stochastic optimization method delineated a small number of distinctive clusters in global cortical networks of cat and macaque [32] (e.g. Figure 1b)

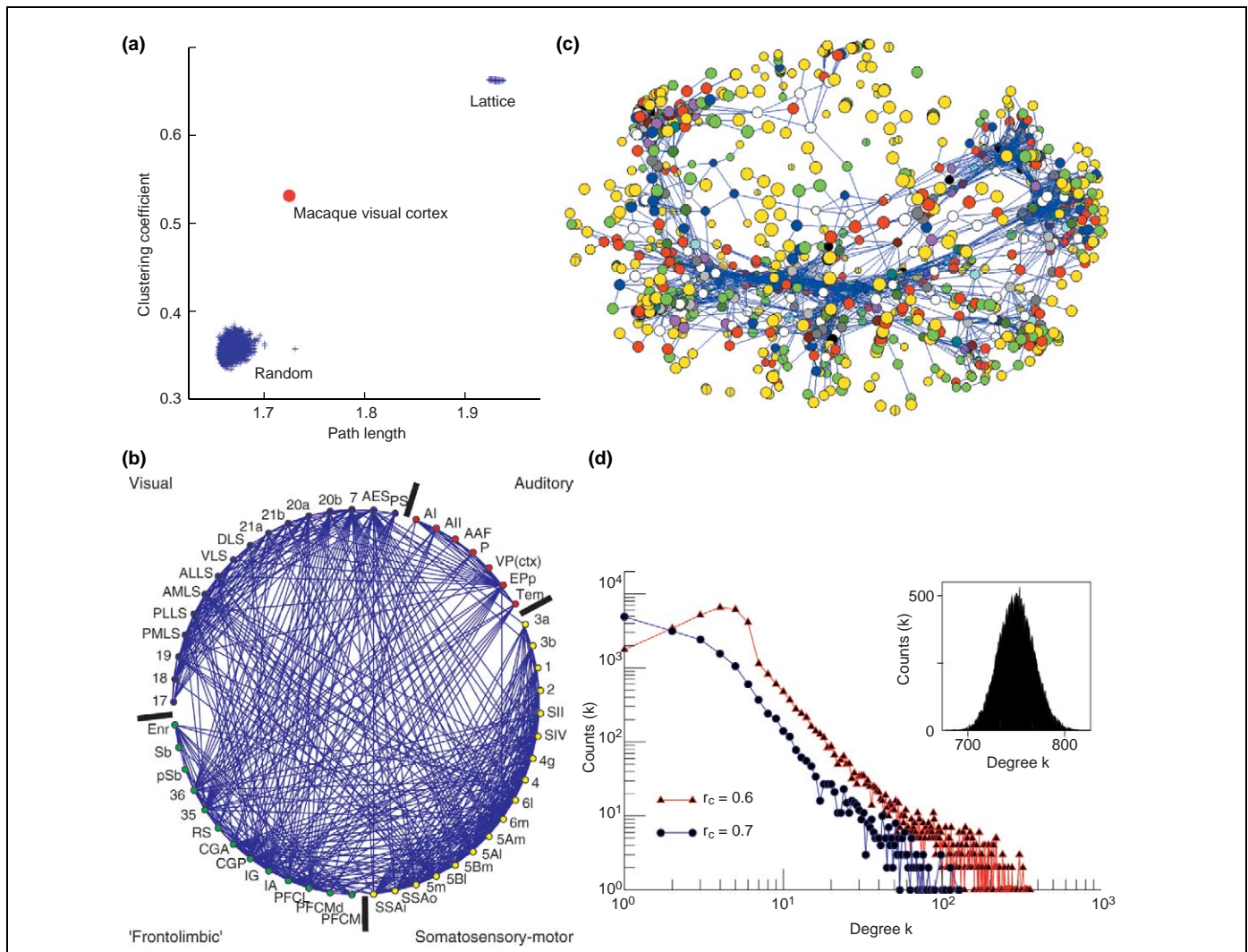


Figure 1. Small-world and scale-free structural and functional brain networks. (a) Characteristic path length and clustering coefficient for the large-scale connection matrix (see Glossary) of the macaque visual cortex (red) (connection data from [23], results modified from [35]). For comparison, 10 000 examples of equivalent random and lattice networks are also shown (blue). Note that the cortical matrix has a path length similar to that for random networks, but a much greater clustering coefficient. (b) Cluster structure of cat corticocortical connectivity, based on [32] and visualized using Pajek (<http://vlado.fmf.uni-lj.si/pub/networks/pajek/>). Bars indicate borders between nodes in separate clusters. Cortical areas were arranged around a circle by evolutionary optimization, so that highly inter-linked areas were placed close to each other. The ordering agrees with the functional and anatomical similarity of visual, auditory, somatosensory-motor and frontolimbic cortices. (c) A typical functional brain network extracted from human fMRI data (from [52]). Nodes are colored according to degree (yellow=1, green=2, red=3, blue=4, other colours >4). (d) Degree distribution for two correlation thresholds. The inset depicts the degree distribution for an equivalent random network (data from [52]).

as well as primate prefrontal cortex [41]. The algorithm could be steered to identify clusters that no longer contained any known absent connections, and thus produced maximally interconnected sets of areas. The identified clusters largely coincided with functional cortical subdivisions, consisting predominantly of visual, auditory, somatosensory-motor, or frontolimbic areas [32]. On a finer scale, the clusters identified in the primate visual system closely followed the previously proposed dorsal and ventral visual streams, revealing their basis in structural connectivity patterns.

In networks composed of multiple distributed clusters, inter-cluster connections take on an important role. It can be demonstrated that these connections occur most frequently in all shortest paths linking areas with one another [42]. Thus, inter-cluster connections can be of particular importance for the structural stability and efficient working of cortical networks. The degree of

CONNECTEDNESS of neural structures can affect the functional impact of local and remote network lesions [43], and this property might also be an important factor for inferring the function of individual regions from lesion-induced performance changes. Indeed, the cortical networks of cat and macaque are vulnerable to the damage of the few highly connected nodes [44] in a similar way that scale-free networks react to the elimination of hubs [45]. Random lesions of areas, however, have a much smaller impact on the characteristic path length.

Network growth and development

The physical structure of biological systems often reflects their assembly and function. Brain networks are no exception, containing structures that are shaped by evolution, ontogenetic development, experience-dependent refinement, and finally degradation as a result of brain injury or disease.

Box 3. Growing complex networks: local rules and global design

Local spatial growth rules...

To understand how various developmental factors affect functional specializations of brain networks, it is helpful to consider biologically inspired models based on known constraints of neural development. Previous algorithms for the generation of random and scale-free networks (see Box 1) constitute unlikely growth algorithms, as they ignore the fact that cortical networks develop in space. Preferential attachment [2], for instance, would establish links to hubs independent of their distance. In biological networks, however, long-distance connections are rare, in part because the concentration of diffusible signaling and growth factors decays with distance. Accounting for this constraint, a spatial growth model was presented [46] in which growth starts with two nodes, and a new node is added at each step. The establishment of connections from a new node u to one of the existing nodes v depends on the distance $d(u,v)$ between nodes, that is, $P(u,v) = \beta e^{-\alpha d(u,v)}$. This spatial growth mechanism can lead to networks with similar clustering coefficients and characteristic path lengths as in cortical networks when growth limits are present, such as extrinsic limits imposed by volume constraints. Lower clustering results if the developing model network does not reach the spatial borders and path lengths among areas increase [47]. By comparison, a preferential attachment model might yield

similar global properties, but fails to generate multiple clusters, as found in cortical networks.

...and global network design

Can local spatial growth rules yield the known corticocortical topology? In addition to similar global properties, defined by clustering coefficient and characteristic path length, the generated networks also exhibit wiring properties similar to the macaque cortex, whose network and wiring distribution is shown in Figure 1. This supports the idea that the likelihood of long-range connections among cortical areas of the macaque decreases with distance [47]. Total wiring length both in the cortical and spatially grown networks lies between benchmark networks in which connections are randomly chosen, and in which only the shortest-possible connections are established. The (few) long-range connections existing in the biological networks might constitute shortcuts, ensuring short average paths with only few intermediate nodes. Thus, the minimization of this property might compete with global wiring length minimization. As a by-product, the short-distance preference for inter-area connections during spatial growth can lead to optimal component placement [75] without the need of a *posteriori* optimization.

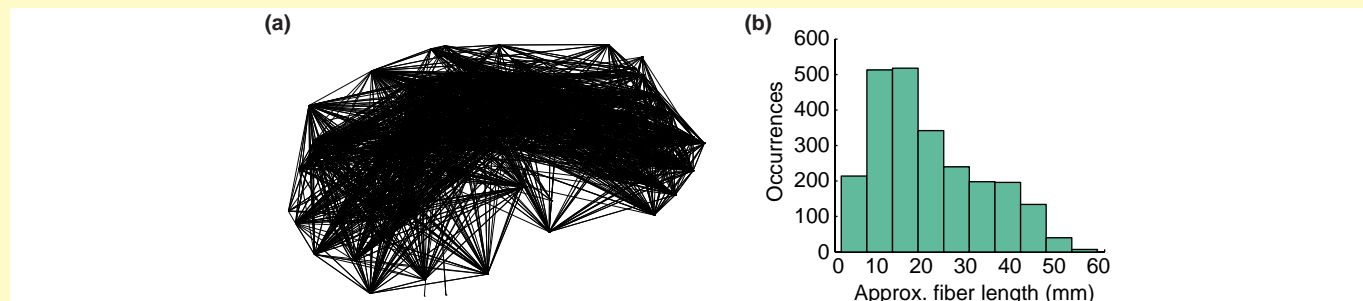


Figure 1. Connectivity and idealized wiring lengths of the macaque cortex. (a) Cortex with associated long-range connectivity among areas (based on Ref. [23]). The connection matrix represents data of three different studies obtained from the CoCoMac database (<http://cocomac.org/home.htm>). Node positions were calculated by surface coordinates using corresponding parcellation schemes within the Caret software (<http://brainmap.wustl.edu/caret/>). (b) Distribution of approximate fiber length as calculated by the direct Euclidian distance between the average spatial positions of brain areas. Note that the layout of areas on the cortical sheet might impose limits on the distribution of distances among areas. Nevertheless, the figure indicates that some cortical projections can reach considerable length. (Redrawn from [47].)

Intuitively plausible growth mechanisms have been proposed for the large classes of small-world [10] and scale-free networks [11]. Such topological algorithms, however, are not biologically realistic and do not represent good models for the development of cortical networks (Box 3). Alternative developmental algorithms were proposed recently that acknowledge spatial constraints in biological systems, while also yielding different types of scale-free and small-world networks [46,47]. It will be an important challenge to refine these computational models by drawing on the wealth of data available from studies in developmental neurobiology [48], to reproduce the specific organization of cortical networks.

Especially intriguing is the role that experience might play in network growth. Although the same complement of connections appears to exist in different individuals of a species, the density of specific cortical fiber pathways can vary substantially between individual brains [49]. It is currently not clear whether this variability is partly attributable to activity-dependent processes. If so, it might be described by recent approaches that couple changes in connection topology to the dynamical evolution of connection weights [50].

Functional networks and neural dynamics

Scale-free functional brain networks

Dodel [51] developed a deterministic clustering method that combines cross-correlations between fMRI signal time courses, and elements of graph theory to reveal brain functional connectivity. Image voxels form nodes of a graph, and their temporal correlation matrix forms the weight matrix of the edges between the nodes. Thus a network can be implemented based entirely on fMRI data, defining as 'connected' those voxels that are functionally linked, that is correlated beyond a certain threshold r_c . A set of experiments examined the resulting functional brain networks [52], obtained from human visual and motor cortex during a finger-tapping task. Over a wide range of threshold values r_c the functional correlation matrix resulted in clearly defined networks with characteristic and robust properties (Figure 1c). Their degree distribution (Figure 1d) and the probability of finding a link versus metric distance both decay as a power law. Their CHARACTERISTIC PATH LENGTH is short (similar to that of equivalent random networks), although the clustering coefficient is several orders of magnitude larger. Scaling and small-world properties persisted across different

tasks and within different locations of the brain. In contrast to other biological networks [53], the relative independence of clustering and degree of individual nodes in these examples of brain functional networks indicated an absence of hierarchical organization.

Using correlations to derive functional brain networks from fMRI datasets has several known limitations. Transitivity in correlations could contribute to an artificial increase in the clustering coefficient, suggesting the use of more stringent correlation measures such as partial directed coherence (PDC, [54]). The use of PDC or other measures of causality might allow the extraction and analysis of effective networks (see Box 2) associated with human cognitive function.

Relationship between structural connectivity and functional dynamics

Neural dynamics unfolding within a structural substrate gives rise to patterns of functional and effective connectivity (Box 2). These patterns exhibit characteristic features of segregation and integration, which can quantitatively be captured using multivariate and hierarchical information-theoretical measures [16,33,34]. Optimization analyses have demonstrated that a high level of complexity (defined as the co-expression of functional segregation and functional integration [16]) is strongly associated with the emergence of small-world attributes, high proportions of CYCLES and minimized wiring length in structural connection patterns [33]. Such architectures also promote high levels of information integration [55] and the formation of an integrated 'dynamic core', a potential neural correlate of higher cognition and consciousness [56,57].

The relation of structural connectivity patterns to resulting neuro-dynamical states has been investigated in detailed computer simulations of cortical networks with heterogeneous [58] and spatially patterned [36] connection topologies. Different connection topologies generated different modes of neuronal dynamics [34,36]. Locally clustered connections with a small admixture of long-range connections exhibited robust small-world attributes [35,36], while conserving wiring length, and gave rise to functional connectivity of high complexity with spatially and temporally highly organized patterns. These computational studies suggest the hypothesis that only specific classes of connectivity patterns (structurally similar to cortical networks) support short wiring, small-world attributes, clustered architectures, high complexity, and possibly metastable dynamical states [59], and an abundance of dynamical transients [60].

A recent proposal suggests that the continual integration and redistribution of neuronal impulses represents a critical branching process ([61]; see also [62,63]), giving rise to sequences of propagating spikes forming neuronal avalanches. In the critical regime, the branching parameter expressing the ratio of descendant spikes from ancestor spikes is found to be near unity, such that a triggering event causes a long chain of spikes that neither dies out quickly (subcriticality) nor grows explosively (supercriticality). Slice preparations of rat cortex operate at or near criticality, generating neuronal avalanches with

a size distribution following a power law [61]. Importantly, criticality is found to be associated with maximal information transfer [61] and thus high efficacy of neuronal information processing. The relationship between criticality and complexity or specific structural connection patterns is still unknown.

Within functional brain imaging, approaches such as Structural Equation Modeling (SEM, [15,64,65]) or, more recently, Dynamic Causal Modeling (DCM, [66]) have successfully related brain activation patterns to a changing functional 'load' of structural connections. Despite the relative scarcity of structural connection data for the human brain, these approaches have great potential for revealing distributed functional and effective networks underlying human cognition.

Conclusion: links between complex networks and cognition

Highly evolved neural structures like the mammalian cerebral cortex are complex networks that share several general principles of organization with other complex interconnected systems. These principles reflect systematic and global regularities in the structural interconnections and functional activations of brain areas. The work reviewed in this article has suggested some emerging links between network organization and cognition, illuminating the structural basis for the coexistence of functional segregation (modularity) and functional integration, for the rapid generation and transfer of information, and for the robustness of brain networks and their failure following damage.

Small-world attributes and the occurrence of highly clustered connection patterns appear to represent a general organizational principle found throughout many large-scale cortical networks. What are the potential functional implications of this mode of connectivity? The connectivity clusters found in cat and rhesus monkey cortex tend to follow functional subdivisions of these brains [32,38]. The groups of areas delineated by clustering are also broadly similar to clusters of semi-functional, neuronographic interactions [67]. Thus, it appears that structural clustering shapes at least some cortical activation patterns. Clustering implies short path lengths between cluster elements. But path lengths between any two cortical areas are already very short (typically, cortical areas are connected directly or via just one or two intermediate areas [32,33]), so it is not immediately clear why direct connections between areas within a cluster provide additional benefits. The answer may have to do with the signal transformations that are carried out by cortical areas. Although they might be helpful to eliminate noise from irrelevant sources, too many intermediate transformations might interfere with the capacity of brain areas to cooperate on a specialized task (an idea expressed in the context of consciousness [68]). In addition, failures of edges or nodes within clusters can be compensated for more easily, as nearby nodes share similar (matching) afferent and efferent connections.

Apart from functional cooperation, clustering might achieve three main purposes. First, the distributed cluster structure of cortical systems is ideal for creating a balance

Box 4. Questions for future research

- What are the best experimental approaches to generate large and comprehensive connective datasets for neural systems, especially for the human brain?
- What is the time scale for changes in functional and effective connectivity that underlie perceptual and cognitive processes?
- Are all cognitive processes carried out in distributed networks? Are some cognitive processes carried out in more restricted networks, whereas others recruit larger subsets?
- Does small-world connectivity reflect developmental and evolutionary processes designed to conserve or minimize physical wiring, or does it confer other unique advantages for information processing?
- What is the relationship between criticality, complexity and information transfer?
- Is the brain optimized for robustness towards lesions, or is such robustness the by-product of an efficient processing architecture?
- What is the role of hubs within scale-free functional brain networks?
- How can scale-free functional networks arise from the structural organization of cortical networks?

between functional segregation and integration, resulting in functional connectivity of high complexity [33], while conserving wiring length. Second, the close association of areas within clusters lends itself to efficient recurrent processing. Closed feedback loops among areas are very likely to occur, given the high frequency of reciprocal connections [23,26,33] and abundance of short cycles [33] in cortical systems. Finally, the clustered organization of cortical networks might support synchronous processing [47,69] or efficient information exchange [70], as demonstrated in other types of small-world networks.

Currently, the links between complex networks and cognition are still tentative and more such links are likely to emerge as empirical and theoretical research progresses. Although many questions remain open (see Box 4) we anticipate that our future understanding of human cognitive function will benefit from converging studies of the connectivity pattern of the human brain and of complex networks.

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