

Contributions and challenges for network models in cognitive neuroscience

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The confluence of new approaches in recording patterns of brain connectivity and quantitative analytic tools from network science has opened new avenues toward understanding the organization and function of brain networks. Descriptive network models of brain structural and functional connectivity have made several important contributions; for example, in the mapping of putative network hubs and network communities. Building on the importance of anatomical and functional interactions, network models have provided insight into the basic structures and mechanisms that enable integrative neural processes. Network models have also been instrumental in understanding the role of structural brain networks in generating spatially and temporally organized brain activity. Despite these contributions, network models are subject to limitations in methodology and interpretation, and they face many challenges as brain connectivity data sets continue to increase in detail and complexity.

A substantial body of evidence from both anatomical and physiological studies supports the idea that cognitive processes depend on interactions among distributed neuronal populations and brain regions^{1–3}. The identification of neural substrates of cognition is aided by methods allowing the identification of significant spatial or temporal patterns in brain activity—for example, through exploratory multivariate statistical techniques such as independent component analysis or multivariate pattern analysis^{4,5}. Increasingly, experiments aiming to localize regions that are differentially activated across tasks are complemented by observations of anatomical and functional relationships among such regions. The latter approach is driven by methodological developments in neuroimaging that have enabled the noninvasive mapping of structural and functional brain connectivity^{6,7}. Data on brain connectivity can be rendered in the form of network models^{8–10}: essentially, simplified representations of brain systems as sets of neural elements and their interconnections. Such network models allow the application of a quantitative theoretical framework for the objective and data-driven analysis of network attributes associated with specific aspects of human brain structure and function.

What insights and conceptual advances have been achieved so far, and what are some of the methodological and interpretational pitfalls of the network approach? This article takes a critical look at some of the advantages and limitations of network models in cognitive neuroscience. The article surveys applications of networks in descriptive accounts of brain organization, their utility for clarifying the relation of localized and distributed aspects of cognitive function and their growing role as a basis for computational models of brain activity. Finally, the article identifies future challenges and

opportunities for network-based approaches in the study of brain organization and function.

Network models describe brain organization

The growth of network approaches in neuroscience has not occurred in isolation but has largely followed parallel advances in the analysis and modeling of complex systems in a range of scientific disciplines¹¹, including other areas of biology, such as proteomics, cell metabolism and ecology. Rooted in a branch of mathematics called graph theory, network models represent complex systems as sets of discrete elements (nodes) and their mutual relationships (edges) that can be summarized in the form of a connection matrix. The relations of nodes and edges define the network's topology, amenable to descriptive analysis through a broad array of measures that probe local and global aspects of network organization¹². **Figure 1** illustrates several of the most widely applied measures, including node degree, clustering, modularity and centrality. Broadly, brain networks fall into two different categories. Structural networks represent anatomical wiring diagrams, while functional networks are derived from estimates of interactions among time series of neuronal activity. The distinct neurobiological substrates of structural and functional networks demand careful consideration when applying network methodologies. For example, because structural networks describe anatomical connections, they are well-suited to measures that capture aspects of neuronal signaling or communication along structural paths. In contrast, functional networks represent patterns of correlations that do not necessarily coincide with direct neuronal communication (see below).

An important first step toward constructing a network model from brain data involves the definition of nodes and edges. Node definition is relatively unambiguous at the neuronal scale. However, at the large scale of whole-brain data sets, node definition requires partitioning or parcellation of the brain into regions or areas that are internally coherent according to anatomical or functional criteria, an issue that is of fundamental importance in network science¹³. Parcellation remains particularly challenging in cerebral cortex¹⁴, where many strategies have been pursued, including random partitioning of

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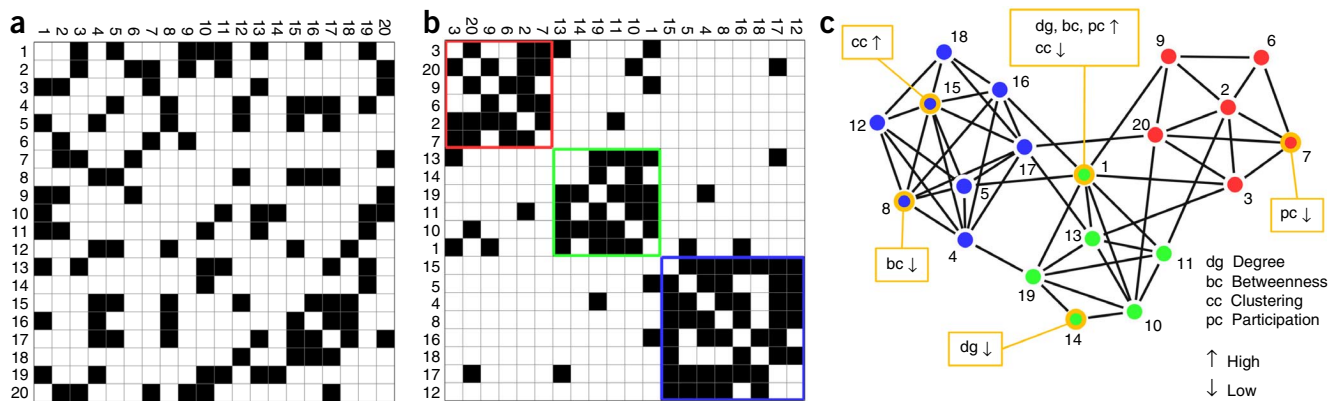


Figure 1 Network concepts and terminology. These diagrams introduce some of the key terms in network models. (a) A connection matrix summarizing binary pairwise relations among 20 nodes. These relations express the presence (black) or absence (white) of a symmetric connection. (b) The same matrix as shown in a, but with the nodes reordered according to an optimal modularity partition. Three network modules are shown (red, green, blue). (c) Spring-embedded two-dimensional network diagram of the network summarized in a, b, with module assignments indicated by node color. Various nodes are highlighted, according to various network measures. For example, node 1 stands out because of its high degree (number of connections), betweenness centrality (placement on many of the network's short paths), and participation coefficient (connections broadly distributed across network modules). The node also has low clustering, as most of its topological neighbors are mutually unconnected. Other nodes with high clustering (node 15), low betweenness (node 8), low degree (node 14) and low participation coefficient (node 7) are indicated.

gray-matter voxels into equal-sized clusters and strategies that use cytoarchitectonics or anatomical landmarks. Particularly promising are data-driven approaches based on the detection of boundaries in structural or functional connectivity profiles¹⁵, region-growing and clustering methods¹⁶, or a combination of connectivity and activation-based partitioning criteria¹⁷. In the context of combined analyses of structural and functional networks, it is clearly advantageous to derive a single parcellation that can be applied across modalities. However, the extent to which different parcellation approaches can produce convergent results across anatomical and functional networks remains unknown.

Once nodes are defined, relations among nodes can be represented as edges (connections). Across the two domains of structural networks and functional networks, a host of edge measures are available, each suited to answer specific empirical questions. In structural networks, the coarsest information is conveyed by binary adjacency matrices that report only the presence or absence of a connection. More detailed analyses have employed labeling density¹⁸ or, in the case of diffusion imaging, density of tractography streamlines, connection probabilities or indices of myelination status to estimate connections weights, although anatomical interpretations remain unclear¹⁹. Functional networks are constructed from neuronal time series and express their statistical dependencies. In functional magnetic resonance imaging (fMRI), cross-correlation remains a useful measure expressing the similarity of time courses, despite a known propensity to link structurally unconnected nodes²⁰. Alternative measures such as partial correlations or Bayes nets have been proposed²¹. Regardless of the edge measure employed, interpreting network data should take into account that even the most sensitive anatomical or functional measure of connectivity can only provide a limited view of the underlying neurobiological substrate.

Methodological issues associated with the definition of nodes and edges in brain network data sets are important to consider because the use of different parcellation schemes in conjunction with many variants of measures of anatomical or functional connections can lead to inconsistencies across studies. For example, because parcel boundaries are not aligned with connectivity profiles, atlas-based or random node partitions may result in spatial blurring of network connections.

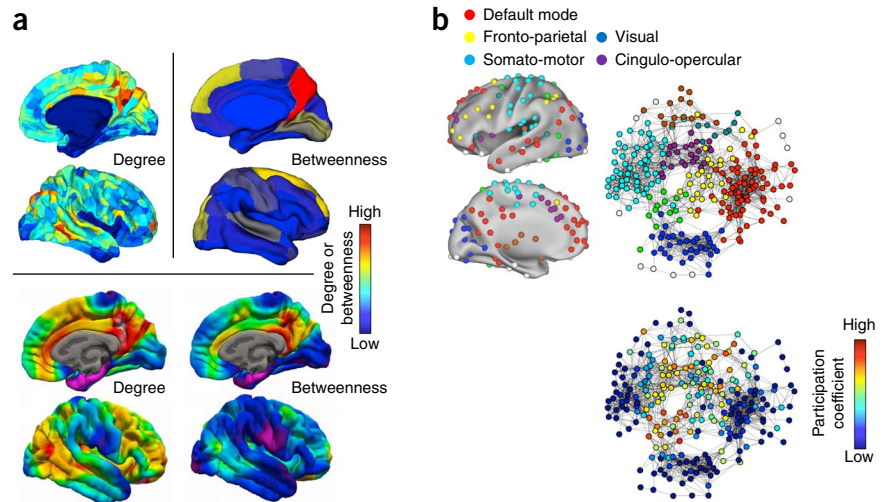
Overcoming this limitation would require a data-driven parcellation strategy based on measures of connectional homogeneity that can be uniformly applied across the brain. In another example, comparative studies have shown that the spatial scale of the nodal parcellation affects subsequent network analyses²². One way in which this issue has been addressed involves network construction and analysis across different parcellation schemes and spatial scales²³ to identify network attributes that are robustly expressed. Indeed, it appears that many qualitative characteristics of network structure are relatively stable across different parcellations²⁴.

Node and edge definition represent examples of methodological issues that arise as brain networks are constructed from observational data. Other such issues relate to data quality (for example, spatiotemporal resolution, tractography and fMRI de-noising strategies), statistical models for estimating node interactions, limited observational data, group averaging and network comparison. For example, network estimation (and hence subsequent analysis) may be susceptible to noisy data acquisition or subtle biasing effects due to physiological state or head motion. These issues surrounding network definition are not limited to human neuroimaging but extend to invasive studies in model organisms, where even the most sensitive anatomical or physiological techniques can be subject to measurement noise or sampling biases.

Despite these methodological issues, studies of brain networks using a variety of parcellations and edge definitions, acquired using different hardware and preprocessing and across numerous participant cohorts, have converged on a set of fundamental attributes of human brain organization^{8,9} that are largely consistent with those found in nonhuman primates. Examples include network hubs, highly connected nodes that are centrally placed in the network's global topology (Fig. 2). Network analysis can identify such hubs with descriptive measures such as node degree or centrality, or through perturbation by probing for points of vulnerability. Several structural network studies of the human cerebral cortex have converged on a restricted set of regions that include the precuneus, anterior and posterior cingulate cortex, insula and portions of the superior frontal, temporal and lateral parietal cortex as putative network hubs^{25–28}. Most of these regions had previously been

Figure 2 Network hubs and modules.

(a) Examples of network hubs coming from studies of structural brain networks. Despite differences in acquisition sites, imaging protocols, parcellations, edge metrics and network measures, there is broad agreement across studies in identifying parts of the medial parietal cortex, cingulate cortex, superior frontal cortex, prefrontal cortex and temporal cortex as network hubs. Panels show maps of node degree and betweenness, with high centrality indicated by hot colors (red, orange). Adapted from refs. 25 (top left), 26 (top right) and 27 (bottom). (b) An example of a partition of the cerebral cortex into network communities (modules) based on functional connectivity derived from resting-state fMRI. Top, the topographic distribution of major resting-state networks. Bottom, the same spring-embedded network layout as at top, but with the nodes color-coded according to their participation coefficient. Notably, participations coefficients for visual, somato-motor and default mode networks are low, indicating a less central placement of their constituent network nodes. In contrast, nodes belonging to the fronto-parietal and cingulo-opercular networks have high participation coefficients, which is suggestive of a role as functional network hubs. Adapted from ref. 89; see also ref. 33.



classified as multimodal (transmodal or heteromodal) association regions, on the basis of their diverse and complex response profiles. Descriptive network analyses add an important new dimension to these earlier findings in that they reveal a structural basis for multimodality in the topology of inter-regional projections. Data-driven network analysis has opened new avenues toward comparative studies of brain hubs across species²⁹, as well as in studies of individual differences, development and disease states.

Another important contribution of descriptive network models has been in the identification of network communities or modules (Fig. 2). Intrinsic or resting-state functional MRI has revealed a set of distributed components or ‘resting-state networks’ (RSNs)⁷ whose constituent regions exhibit coherent signal fluctuations resulting in high internal functional connectivity. RSNs can be detected with seed-based correlations³⁰, independent component analysis³¹, connectivity-based cluster analysis³² and network-based community detection³³. An advantage of the network approach is that it not only yields a partitioning of the brain into components but also offers further insights into RSN intrinsic organization and interconnectivity. First, network approaches have revealed not only the topography of RSN components but also their mutual network relations³³—for example, demonstrating that the frontoparietal control network is pivotal in balancing activity between default and attention networks³⁴. Second, network approaches naturally lend themselves to multimodal analysis across the domains of structural and functional networks, and such analyses have shown robust structure–function relationships in individual RSNs^{35,36} and whole-brain network data^{37–39}. Third, quantitative network-based approaches can estimate the strength with which individual regions associate with their own network community—for example, through measures of participation⁴⁰, cluster stability^{40,41} and consensus clustering⁴²—thus providing information on regional roles in neural processing within and across communities.

A caveat in descriptive network analysis concerns the use of simple global measures such as ‘small-worldness’. The discovery of the widespread occurrence of small-world architectures in complex systems⁴³ has led to important findings in brain networks regarding the trade-off between an abundance of highly clustered (short-distance) connections and specific (long-distance) ‘shortcuts’ that

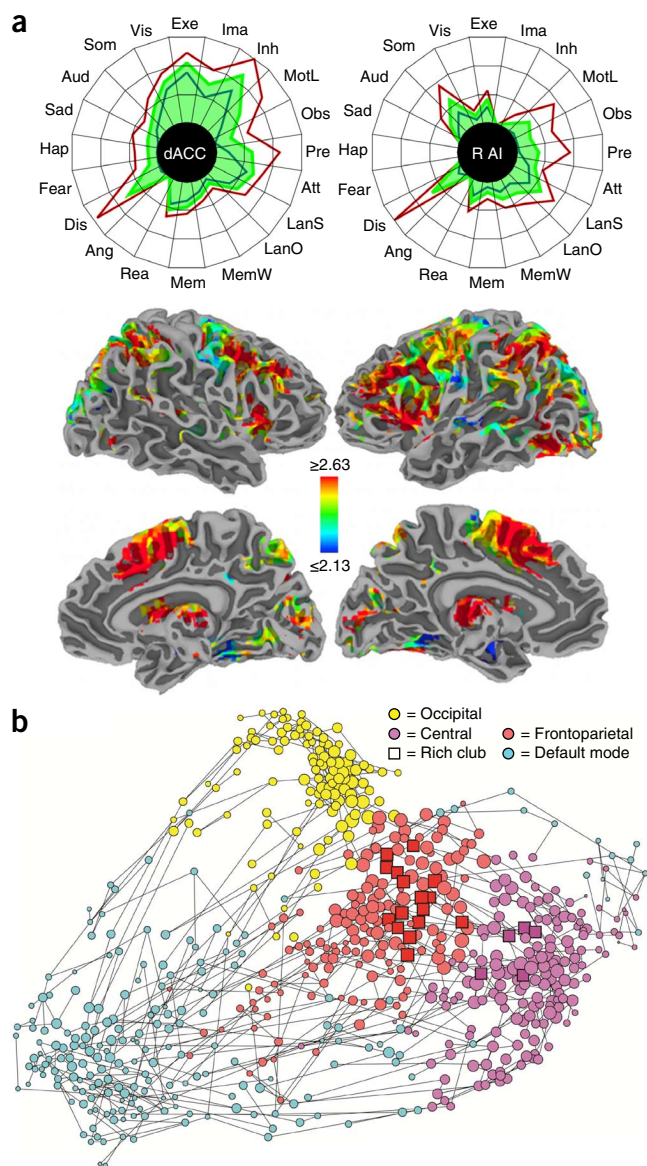
enable efficient communication^{44,45}. Indeed, global network measures capture important characteristics related to overall signaling capacity or clustered organization. Nevertheless, exclusive reliance on global measures when performing comparisons of networks across individuals, participant cohorts or time points may only provide limited insight. For example, differences in small-worldness, clustering or efficiency arising in group comparisons may be due to any number of differences in network topology. Such differences in global measures become more informative when they are supplemented by more detailed analyses that pinpoint specific network elements—for example, through the use of more fine-grained local measures of network topology—as well as with the application of statistically sound tools for network comparison⁴⁶.

In summary, despite unsolved issues in the construction of brain networks from anatomical and/or functional data, descriptive studies have offered insights into basic principles of brain organization. A major contribution of descriptive network models is that they allow the objective identification and quantification of local and global network attributes, thus paving the way for characterizing networks across individuals, developmental stages and disease states. Descriptive network models profit from continuous dialog with empirical data: as models, they make predictions about the functioning of neural systems that must come under the scrutiny of further empirical observation. Even in cases where network models may be viewed as confirmatory of known aspects of brain function and physiology, such models take an important additional step by establishing links between observed brain responses and features of network topology. In so doing, network models place anatomical and physiological attributes of neurons and brain regions in the context of fundamental rules and principles of network science.

Networks unify localized and distributed brain function

The struggle between localized and distributed accounts of brain function has been a major theme in the history of cognitive neuroscience. While extensive evidence points to the existence of functionally specialized and anatomically segregated areas and circuits, there is a growing body of work demonstrating the importance of connections and integrative processes for coherent cognitive and behavioral outcomes. By addressing how connectivity mediates both

Figure 3 Diversity of regional activation patterns. (a) Top, regional diversity profiles (functional fingerprints) for the dorsal anterior cingulate cortex (dACC) and the right-hemispheric anterior insula (R AI). Cognitive or behavioral task domains are arranged around a circle. The green line refers to the involvement of the region in each domain, according to a large database⁵² of task-based fMRI activation studies; red and blue lines indicate upper and lower bounds of the estimate. Task domains: Exe, execution-action; Ima, imagination-action; Inh, inhibition-action; MotL, motor learning-action; Obs, observation-action; Pre, preparation-action; Att, attention-cognition; LanS, language semantics-cognition; LanO, language other-cognition; MemW, working memory-cognition; Mem, memory-cognition; Rea, reasoning-cognition; Ang, anger-emotion; Dis, disgust-emotion; Fear, fear-emotion; Hap, happiness-emotion; Sad, sadness-emotion; Aud, audition-perception; Som, somesthesia-perception; Vis, vision-perception. Bottom, a map of functional diversity across the cortical surface, computed as the Shannon entropy across task domains. Higher entropy indicates greater diversity. Color bar represents Shannon entropy values. Adapted from ref. 54. (b) Spring-embedded network layout of a functional coactivation network compiled from the same fMRI database⁵² used in a. Modules of the coactivation network, several of which correspond to known resting-state networks (see Fig. 2), are color-coded. In addition, square nodes indicate members of a highly interconnected rich club (see Fig. 4) embedded within the coactivation network. Note the strong involvement of the frontoparietal network in the rich club. Adapted from ref. 53.



segregation and integration, network approaches not only reconcile these seemingly opposing perspectives, they also suggest that their coexistence is fundamental for brain function⁴⁷.

One of the main underpinnings of the network approach is that it places great importance on patterns of connectivity for creating functional differences between network elements⁴⁸. Studies of large-scale structural brain networks have shown consistent relationships between the topology of projections and physiological responses of brain regions^{49,50}. Along the same lines, similarities in connectivity profiles have been widely deployed in approaches to cortical parcellation^{14,15,17}. Going beyond predicting functional similarities on the basis of connection profiles or 'fingerprints', network models also make predictions about which nodes and edges are central for network communication or most strongly influence system dynamics; that is, they allow the identification of structural network elements that are specialized for carrying out integrative function.

Important links between network architecture and functional specialization have come from comparisons of resting-state fMRI and patterns of regional task-related coactivation. Comparative studies have shown that RSNs measured in the resting brain strongly resemble sets of regions that are coactivated across a wide range of cognitive and behavioral tasks⁵¹. Further studies showed that most RSNs are associated with specific behavioral or cognitive domains and that these associations are strongest for unimodal networks and more diffuse for networks involved in higher cognitive processes⁵². In related approaches, network communities corresponding to specific cognitive domains were also found in a matrix expressing the similarity of regional activation profiles across a large set of task-related activation studies⁵³, and individual regions as well as networks were found to be associated with distinct 'functional fingerprints'⁵⁴ (Fig. 3). Jointly, these findings demonstrate robust relationships between network architecture and functional specialization as established in fMRI activation studies. These findings are consistent with the idea that the topography of RSNs reflects a history of coactivation and common recruitment during task-evoked activity¹⁴.

Network approaches have also been applied to data sets acquired with electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings. The high temporal resolution of these techniques

offers a unique opportunity for linking changes in network interactions to transitions between cognitive states. MEG studies have revealed fast reconfigurations of functional brain networks in sensorimotor coordination⁵⁵, and specific topological attributes of MEG networks were found to be correlated with task performance in working memory⁵⁶. Other studies have shown that MEG and EEG cortical networks display distinct patterns of organization in different frequency bands, with network attributes expressed at frequencies related to task condition⁵⁷. Greater cognitive effort was found to be associated with MEG functional networks that were less clustered and less modular, owing to the emergence of functional connections linking distributed brain regions⁵⁸. Integrative processes across distributed regions and networks have also been studied using band-limited power correlations in resting MEG recordings, which can be mapped to temporal fluctuations in anatomically distinct RSNs⁵⁹. Changes in interactions among several RSNs were found to involve functional connectivity with a specific set of network nodes, especially the posterior cingulate cortex and precuneus⁶⁰, lending further support to the idea that integrative processes have a distinct anatomical substrate.

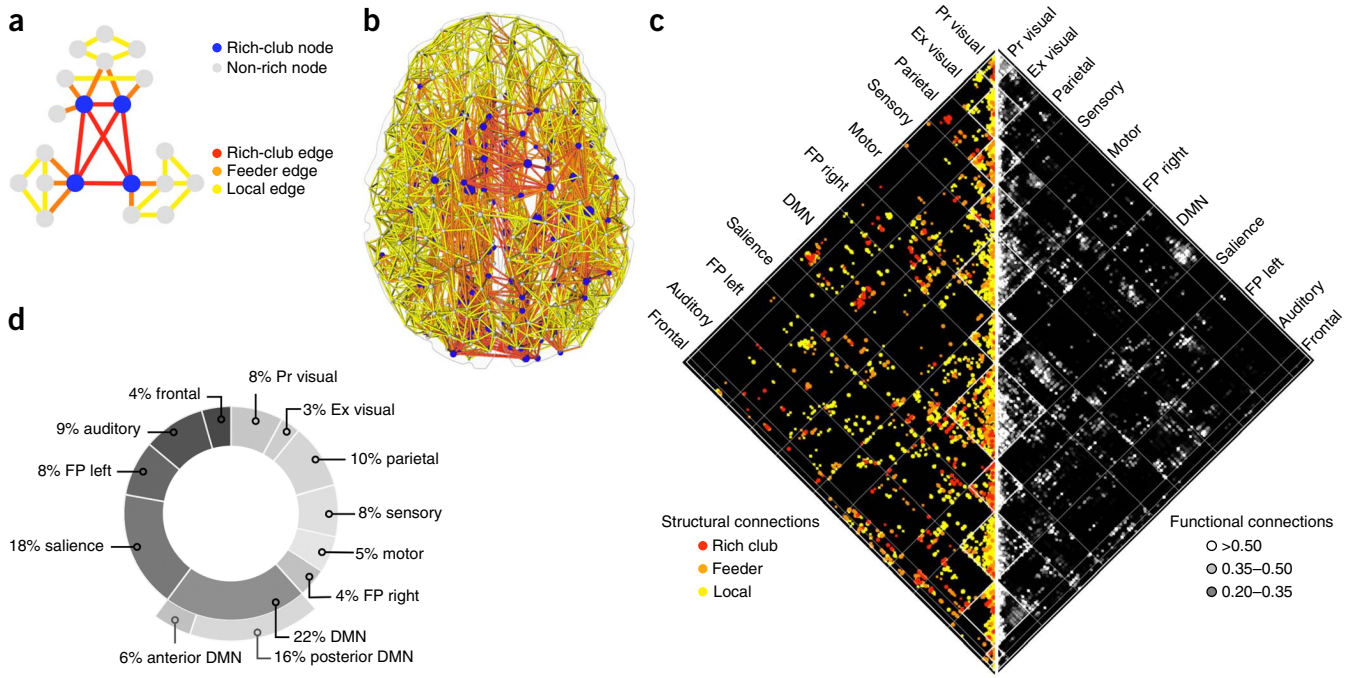


Figure 4 Rich-club and functional modules. **(a)** A schematic diagram of a network with high-degree rich-club nodes (blue) that are also highly connected among one another. Connections among rich-club nodes are so-called rich-club edges (red), while connections linking rich-club nodes to non-rich nodes are labeled feeder edges (orange) and connections among non-rich-club nodes are local edges (yellow). **(b)** Spatial layout of rich club nodes and connections. Rich-club nodes are widely dispersed across all main anatomical subdivisions of cortex. **(c)** Connection matrix of structural connections acquired with diffusion tensor imaging (left triangle) and strong (Pearson's $R > 0.2$) resting-state functional connections derived from fMRI recordings (right triangle), averaged across a group of 75 healthy volunteers. The 1,170 network nodes are arranged according to functional modules, derived from independent component analysis and corresponding to 11 resting-state networks. Pr visual, primary visual; Ex visual, extrastriate visual; FP, frontoparietal; DMN, default mode network. **(d)** Distribution of rich-club nodes (derived from structural connectivity) in relation to resting-state networks (derived from functional connectivity), expressed as proportions across RSNs. Adapted from ref. 67.

Several recent studies have deployed network analysis to identify neural substrates of multimodal integration. One approach, called stepwise functional connectivity analysis⁶¹, tracks paths from unimodal (visual, auditory, motor) cortex to increasingly multimodal (higher order cognitive) regions. Paths were found to converge on a single multimodal network, including portions of the superior parietal cortex, anterior insula, dorsal anterior cingulate and dorsolateral prefrontal cortex. The topological arrangement of this network is consistent with a central role in interconnecting and integrating activity across otherwise unconnected subdivisions of unimodal cortex. Another approach attempts to identify patterns in the temporal evolution of network communities over the course of sensorimotor learning⁶². Regional differences in the stability of module assignments suggested that, as learning progresses, unimodal (visual, motor) cortices maintain their module memberships (and hence functional associations), whereas the module memberships of multimodal association areas are substantially more labile and subject to change. These results point to a mode of functional organization combining a stable (unimodal) temporal core with a more variable (multimodal) periphery⁶³, the latter essential for modulating task- and learning-dependent interactions among network communities. A convergent set of results identified temporal signatures of functional integration across RSNs in a restricted set of multimodal association areas⁶⁴.

Other studies have suggested a putative structural network basis for integrative processing. In the human brain, regions with high degree tend to be highly connected among one other, forming a coherent sub-network ('rich club')⁶⁵ (Fig. 4), also found in nonhuman primates⁶⁶.

Combined structural and functional network analysis demonstrated that this subnetwork spans all RSNs, suggesting that it is central to cross-RSN network communication⁶⁷. Similar topological arrangements were found in cat cortex⁶⁸ and macaque cortex, with hubs cross-linking all structural⁶⁶ and functional modules⁶⁹. Taken together, these applications of network models to structural and functional connectivity data suggest that integration in large-scale brain networks is supported by a set of specialized brain regions that transiently orchestrate interactions between functional modules or RSNs.

In summary, network models have been instrumental in revealing how patterns of structural and functional connections promote the interplay between segregated and integrated processing. A core theme is that of network communities or modules associated with specific domains of behavior and cognition that become functionally linked in resting and task-evoked brain activity. Building on established models of brain activation, network models add important insights by revealing patterns of interactions and by allowing the application of quantitative measures of network topology. Network models offer a theoretical framework that naturally encompasses both local and global processes and thus resolves the long-standing conflict between localized and distributed processing.

Networks are important for models of brain dynamics

Going beyond their utility as descriptive tools to characterize brain organization, network models, specifically structural networks, are an important ingredient of computational models that can simulate and predict observed brain activity. Indeed, the mechanistic role of

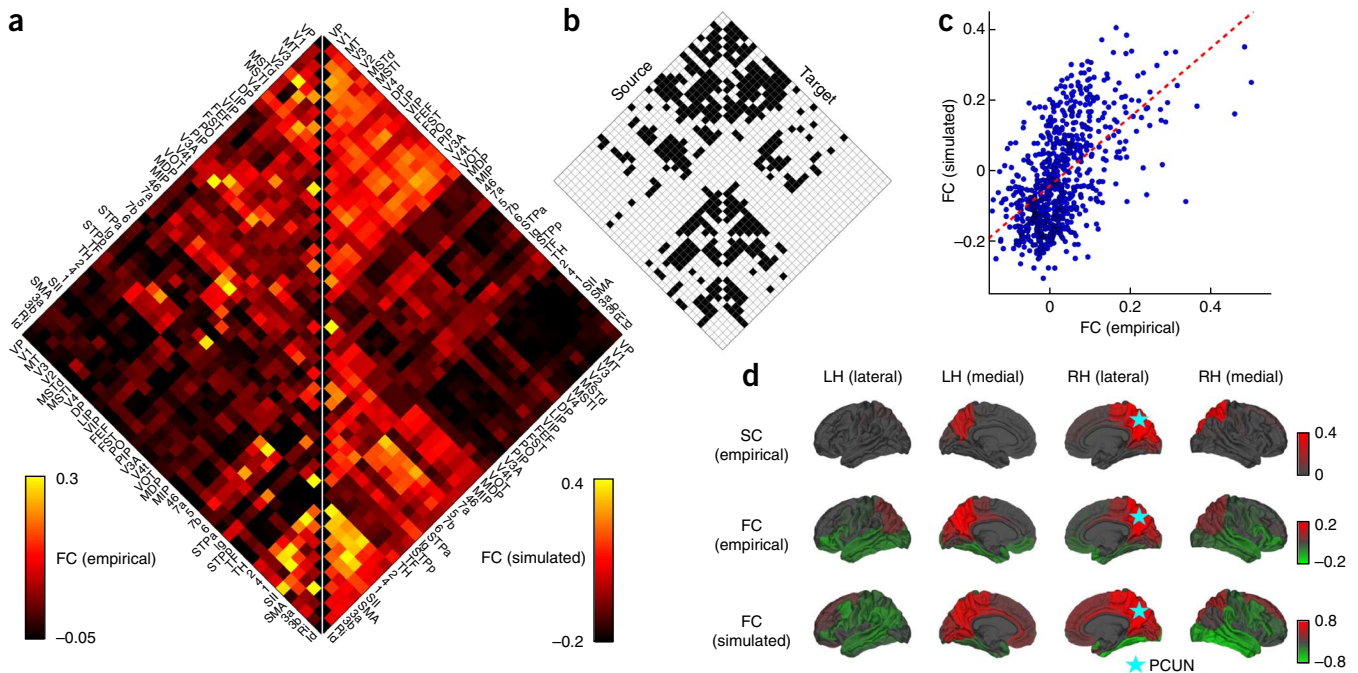


Figure 5 Network models of brain dynamics. **(a)** Comparison of empirical (left triangle) and simulated (right triangle) functional connectivity (FC) among 39 regions of macaque cerebral cortex, derived from a standard parcellation of the macaque cortical surface (see ref. 100 for full region names). Empirical data represent averages of multiple fMRI sessions across two monkeys. Simulated data are derived from a computational network model of spontaneous neural dynamics implemented on the structural connectivity shown in **b**. Functional connectivity is expressed as the Pearson correlation among empirical or simulated fMRI regional time courses. **(b)** Corresponding matrix of directed structural connectivity derived from tract tracing studies. **(c)** Scatter plot of empirical versus simulated functional connectivity, indicating a significant relationship ($R = 0.55$, $P < 0.001$). **a–c** adapted from ref. 70. **(d)** Seed plots of structural connectivity (SC), empirical functional connectivity and simulated functional connectivity, for a dynamic network model of human resting-state fMRI. Seeds are placed in the right hemisphere precuneus (PCUN). Empirical data are from ref. 25, **d** adapted from ref. 100.

structural brain networks for shaping brain dynamics is a key rationale for mapping the human connectome. Informed by comprehensive data on structural brain connectivity, computational network models offer unique tools for establishing links between structure and function, a key challenge in many complex biological systems.

Typical examples of such computational network models are instantiated as sets of state equations that specify the biophysics of neuronal elements or populations—for example, their membrane conductances or mean firing levels—and sets of coupling terms that specify which neuronal elements are structurally linked; for example, an anatomical connection matrix. The dynamics generated by such models consists of neural time series that can be represented as functional networks and analyzed using the same tools and approaches applied to empirical data. A main purpose of the modeling approach is to explain and predict empirically observed brain dynamics, with the model serving as a test bed for identifying essential ingredients in model form and parameters. If models are relatively simple, a large number of such models can be tested and rigorous criteria of model selection can be applied.

All such models rest on the assumption that structural connectivity shapes brain dynamics and hence functional connectivity. Several lines of empirical evidence support this view. Combined analyses of structural and functional networks obtained from resting brain fMRI have shown that the presence and strength of structural connectivity between two nodes is correlated with the strength of their mutual functional connectivity³⁸. Functional connectivity between structurally unconnected node pairs can be partially predicted by indirect structural paths^{38,70}. Distributed components of several RSNs have been shown to be linked by anatomical connections^{35,36},

and variations in the strengths of such connections are reflected in variations of functional connectivity⁷¹. Direct intervention—for example, through callosotomy—has shown that the integrity of anatomical pathways is essential for maintaining interhemispheric functional connectivity⁷² and that spared connections may contribute to compensatory processes⁷³. Importantly, the crucial role of structural networks in shaping functional connectivity has been demonstrated not only at the large scale of whole-brain networks but also at mesoscopic⁷⁴ and microscopic scales⁷⁵.

Building on a long tradition of structurally based dynamic brain models, structural network data from nonhuman primates and humans has been used to design anatomically and physiologically realistic models of spontaneous, resting brain activity (Fig. 5). The role of structural connections in shaping the spatiotemporal patterns observed in resting-state functional connectivity was demonstrated in a model of macaque cerebral cortex⁷⁶, later shown to exhibit substantial agreement with empirical data⁷⁰. When informed by a human structural connectivity matrix, a similar model was able to generate patterns of functional connectivity that matched empirical observations³⁸. Other models emphasized the roles of conduction delays and noise for generating realistic resting brain dynamics⁷⁷. Extensions of this modeling framework include forecasting the functional effects of brain lesions⁷⁸, modeling the progression of degenerative brain disease⁷⁹ and deriving analytic models to predict functional connectivity^{80–82}.

An important contribution of computational network models relates to the nature of temporal fluctuations in the topology of functional networks. While models demonstrated robust relationships between structural and functional networks that emerge over

long-time averages (several minutes) of observation, functional networks obtained on shorter time scales were found to be considerably more variable⁷⁶, giving rise to the idea that functional networks form a ‘dynamic repertoire’ that is constantly rehearsed in the resting state. Nonstationarity in functional couplings has since been found in empirical data⁸³ and is becoming a new focus of investigation in resting-state fMRI. While the origin of these fluctuations in empirically measured functional connectivity is still largely unknown, the appearance of similar temporal patterns in computational models may indicate that multistability and critical behavior arising from system dynamics are important.

An important topic not extensively covered in this review concerns the role of network models for mapping causal dependencies among neural events, summarized as networks of ‘effective connectivity’⁸⁴. Detecting patterns of effective connectivity involves the formulation of appropriate neural models that combine biophysically based nodal dynamics and an anatomically based coupling structure, followed by model inversion and inference⁸⁵. By taking into account information on patterns of structural brain connectivity to reduce the dimensionality of the problem, such models are becoming increasingly capable in estimating large-scale (potentially whole-brain) networks of effective connectivity⁸⁶.

As this brief survey has shown, network models are important not only as descriptive tools but also as important ingredients in computational (generative) models of complex brain dynamics. The models suggest that the topology of structural connections, in conjunction with the biophysics of neural elements, provides a structural basis for observed neural response patterns. Such models also have clear limitations, as a full account of neural responses must include additional factors, such as neuromodulation, exogenous perturbations due to sensory input or task state, and coupling of brain to environment. Nevertheless, network models are indispensable for providing mechanistic accounts of how neural elements activate and organize into functional networks.

Future challenges and opportunities

Some challenges facing network approaches to cognitive neuroscience have already been discussed, including those involving data acquisition and network definition. Other challenges involve interpreting network measures across the two domains of brain structure and function, relating network attributes more directly to neural computation, integrating networks across spatial scales and tracking network dynamics across time. Implicit in all these challenges are opportunities for moving beyond current formulations and applications of network models.

Network measures can be subject to intrinsic computational or mathematical limitations. For example, a widely used measure of modularity is prone to a spatial resolution limit that biases the scale of detected network communities⁸⁷. Overcoming this limitation, more sophisticated multiscale methods for extracting network modules have been proposed⁸⁸, and such methods are beginning to be applied in brain network studies^{63,81}. It should also be noted that many network measures make implicit assumptions about what it is that they express about a given real-world system. For example, network paths are conceptually straightforward in structural networks but may be problematic in correlation (functional) networks owing to the nature of the edge metric. In another example, the use of node degree as an index of centrality in functional networks may be subject to measurement bias, as it tends to co-vary with the size of network communities⁸⁹. Finally, lesioning of functional networks to assess robustness or vulnerability may give unreliable results because the

primary effect of any real-world lesion is the disruption of a structural network, followed by system-wide compensatory effects and readjustments of functional couplings involving functional connections between regions remote to the lesion site^{73,78,90}.

Much work remains in the area of relating network models more explicitly to cognition and neural computation. Large-scale network analysis of structural and functional connectivity offers only limited insight into the mechanisms by which neuronal systems compute—that is, the rules underlying the transformation and encoding of neural response patterns in both local and distributed circuits. This limitation partially reflects the strong focus of many network studies on task-free or resting brain functional connectivity. Future work is needed to broaden the range of applications of network models to stimulus-driven and task-evoked functional connectivity. Examples of network models applied to specific cognitive operations include mapping of large-scale networks involved in interhemispheric coordination⁹¹, memory recollection⁹² and visual attention⁹³. A series of studies employing connectivity-based analyses has focused on the central role of prefrontal cortex⁹⁴ and the fronto-parietal network⁹⁵ as flexible hub regions in cognitive control. Closer links to neural computation will also emerge as network models are extended to the meso- and microscale, revealing links between network topology and computation in local neuronal populations and microcircuits. The latter development has been impeded by a lack of precisely measured microscale connective data, a limitation that will likely soon be overcome.

Another challenge relates to tracking networks across time. The challenge encompasses slow changes across the lifespan and changes due to experience or plasticity, as well as rapid spontaneous fluctuations and evoked reconfigurations in the course of behavior. On slow time scales, developmental growth models⁹⁶ and generative models⁸⁰ are beginning to identify some of the key ingredients that shape the spatial arrangement and topology of networks. On fast time scales, EEG and MEG studies have long demonstrated moment-to-moment reconfigurations of large-scale networks during rest and task conditions, and such network dynamics have recently come into sharper focus in fMRI also. Analysis and modeling of networks whose topology changes through time is an active area of research in network science^{97,98}, and initial applications of these advanced network methods to the brain include community detection based on network dynamics⁹⁹.

A final challenge relates to the growing need to map neural activity and connectivity across multiple spatial and temporal scales. Network models are well positioned to address this challenge, as one of their main advantages is their applicability across scales, ranging from neuronal and synaptic networks at the micrometer and millisecond scales all the way to whole-brain networks imaged at much coarser resolutions. This naturally encourages the construction of network models along nested spatial and temporal dimensions. Furthermore, computational network models are important for establishing links between fast neural activity measured at finer scales and slow bulk activation measured at coarser scales, informed by comprehensive and co-registered multiscale data. In humans, given the limitations of present-day neuroimaging technology, new methods for noninvasive tracing of connections and recording of neural activity are urgently needed, a grand challenge that is poised to take center stage in future brain mapping initiatives.

As these and other challenges for network models are beginning to be addressed, one of the areas that will benefit the most is concerned with characterizing biological substrates of brain and mental disorders. The appeal of network approaches for diagnosing, monitoring and

managing disease states of the brain has several origins. First, convergent findings across many studies suggest that most, perhaps all, brain diseases are associated with specific disturbances of network connectivity, and the detection of such disturbances may enable the development of diagnostic tools or biomarkers. Second, the placement of brain connectivity as an ‘intermediate phenotype’ positioned between genetics and behavior renders it an attractive target for studies that link networked systems across levels, from molecules to neurons and brain systems, and into the social environment. Finally, the availability of comprehensive data sets on brain networks, as well as data on brain metabolism and gene expression, opens possibilities of asking an entirely new set of questions regarding the interaction of connectivity with brain physiology and genomics, including its dysregulation as a possible trigger of brain disorders.

Conclusions

The application of network models in cognitive neuroscience has provided insights into anatomical and functional brain organization, revealed the importance of connectivity in functional specialization and integrative processing, and shown how the architecture of structural links among neural elements shapes their functional interactions. Methodological and interpretational limitations exist as a result of uncertainties in data recording and network definition. Bearing in mind these limitations, a major appeal of network models is that they establish a firm link from neuroscience to a rapidly expanding theoretical framework for understanding complex networked systems. Given the natural fit of network approaches with the structure and function of nervous systems and the rapid proliferation of brain network data across the discipline, sophisticated and neurobiologically based network models will likely become indispensable tools for deeper understanding of the neural substrates of cognition.

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