Review

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Feature Review

Large-scale brain networks in cognition: emerging methods and principles

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An understanding of how the human brain produces cognition ultimately depends on knowledge of large-scale brain organization. Although it has long been assumed that cognitive functions are attributable to the isolated operations of single brain areas, we demonstrate that the weight of evidence has now shifted in support of the view that cognition results from the dynamic interactions of distributed brain areas operating in large-scale networks. We review current research on structural and functional brain organization, and argue that the emerging science of large-scale brain networks provides a coherent framework for understanding of cognition. Critically, this framework allows a principled exploration of how cognitive functions emerge from, and are constrained by, core structural and functional networks of the brain.

Large-scale brain networks and cognition

Much of our current knowledge of cognitive brain function has come from the modular paradigm, in which brain areas are postulated to act as independent processors for specific complex cognitive functions [1,2]. Accumulating evidence suggests that this paradigm has serious limitations and might in fact be misleading [3]. Even the functions of primary sensory areas of the cerebral cortex, once thought to be pinnacles of modularity, are being redefined by recent evidence of cross-modal interactions [4]. A new paradigm is emerging in cognitive neuroscience that moves beyond the simplistic mapping of cognitive constructs onto individual brain areas and emphasizes instead the conjoint function of brain areas working together as large-scale networks. The historical roots of this new large-scale network paradigm can be traced to Wernicke [5], Pavlov [6] and Luria [7]. More recently, important contributions have been made by a number of researchers, including Freeman [8], Edelman [9], Mountcastle [10], Goldman-Rakic [11], Mesulam [12], Bressler [13], McIntosh [14], Menon [15], Fuster [16] and Sporns [17].

This review describes recent developments in the emerging science of large-scale brain networks that are leading to a new understanding of the neural underpinnings of cognition by revealing how cognitive functions arise from interactions within and between distributed brain systems. It focuses on technological and methodological advances in the study of structural and functional brain connectivity that are inspiring new conceptualizations of large-scale brain networks. Underlying this focus is the view that structure–function relations are critical for gaining a deeper insight into the neural basis of cognition. We thus emphasize the structural and functional architectures of large-scale brain networks (Box 1). For this purpose, we

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Glossary

Blood-oxygen-level-dependent (BOLD) signal: measure of metabolic activity in the brain based on the difference between oxyhemoglobin and deoxyhemoglobin levels arising from changes in local blood flow.
Central-executive network (CEN): brain network responsible for high-level cognitive functions, notably the control of attention and working memory.
Default-mode network (DMN): large-scale network of brain areas that form an integrated system for self-related cognitive activity, including autobiographical, self-monitoring and social functions.
Diffusion-based tractography: class of noninvasive magnetic resonance imaging techniques that trace fiber bundles (white matter tracts) in the human brain *in vivo* based on properties of water molecule diffusion in the local tissue microstructure.
Dynamic causal modeling: statistical analysis technique based on bilinear dynamic models for making inferences about the effects of experimental manipulations on inter-regional interactions in latent neuronal signals.
Functional interdependence: statistical inter-relation of variables representing temporal changes in different network nodes.
Granger causality analysis (GCA): statistical method that, when applied to the brain, measures the degree of predictability of temporal changes in one brain area that can be attributed to those in another area.
Independent component analysis (ICA): computational technique that separates a multivariate signal into additive components based on the assumption that the components arise from statistically independent non-Gaussian sources.
Intrinsic connectivity network (ICN): large-scale network of interdependent brain areas observed at rest.
Large-scale: term referring to neural systems that are distributed across the entire extent of the brain.
Local field potential (LFP): electric potential generated in a volume of neural tissue by a local population of neurons. LFPs result from the flow of current in the extracellular space generated by electromotive forces operating across the cell membranes of neurons, principally at synapses.
Functional magnetic resonance imaging (fMRI): noninvasive neuroimaging method that measures BOLD signals in the brain *in vivo*.
Network: physical system that can be represented by a graph consisting of nodes and edges.
Network edge: component of networks that links nodes.
Network node: component of networks linked by edges.
Phase synchrony: tendency for two time series to exhibit temporal locking, or a constant relative phase relation, usually in a narrow frequency range.

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Box 1. The concept of brain networks

Brain networks can be defined based on structural connectivity or functional interdependence. The structural network organization of the brain is based on the anatomical linkage of its neurons. Neurons are connected locally by synapses from short axons, dendrites and gap junctions. Although neuronal populations throughout the brain have a variety of different internal circuitry configurations, they can be represented as network nodes if they have a uniquely identifiable local structural organization, a large-scale structural connectivity pattern or a local functional activity pattern that allows them to be distinguished from their neighbors.

Some (projection) neurons in the brain have long axons that synapse at a distance from the cell body. Long axon pathways that project from one neuronal population to another can be represented as network edges. If the pathway between two populations (A and B) consists of axons only from A to B or only from B to A, then the edge can be considered to be directed. If the pathway consists of axons in both directions, then the edge can be considered to be bidirectional. If the method used to identify edges in the brain does not establish directionality, the edges can be treated as being undirected.

The functional interdependence of brain network nodes refers to joint activity in different brain structures that is co-dependent under variation of a functional or behavioral parameter. Most methods yield non-zero values of functional interdependence in all cases, so true functional interdependence must depend on values that are significantly different from zero or significantly different between cognitive conditions.

review the use of basic terminology from network theory (Box 2) [18], which provides a standardized framework for comparison and contrast of current concepts of large-scale brain networks emerging from the fields of neuroanatomy, functional neuroimaging and cognitive electrophysiology.

Our review begins with structural architectures of large-scale brain networks. It details the ways in which structural nodes and edges are defined, and discusses the inference of function from structure. We then move on to large-scale functional brain network architectures, considering multiple ways of defining functional nodes and edges, and contrasting them with related structural measures. We discuss recent findings on the measurement of functional brain networks, focusing in particular on intrinsic core networks and their relation to structural networks. We further discuss the role of functional brain networks in psychopathology. We conclude that the large-scale network framework allows a more systematic examination of how cognitive functions emerge from, and are constrained by, core structural and functional networks of the brain. Finally, we suggest some directions in which we expect research in this field to proceed in the future.

Box 2. Graphs and networks

A graph is a mathematical entity consisting of a collection of nodes (vertices) and a collection of edges that connect pairs of nodes. Graphs are used to model pairwise relations between the nodes. A graph can be either directed, in which case the edges point from one node to another, or undirected, in which case the edges have no directionality. If an edge points in both directions between two nodes, it is bidirectional. In a directed graph, the node from which the edge points is called the initial node or tail, and the node to which it points is called the terminal node or head. A graph can also be weighted, in which case a numeric value is associated with every edge in the graph, or unweighted, in which case the edges are not distinguished by numeric value. A subgraph of a graph G is a graph for which the set of nodes is a subset of the set of nodes for G and the set of edges is a subset of the set of edges for G.

A network is a physical system with graph-like properties whereby the properties of the network correspond to the properties of the graph on which it is based. Networks are often characterized by their topology, which is the arrangement or configuration of the network elements. A subnetwork corresponds to a subgraph.

Large-scale structural brain networks

The neuroanatomical structure of large-scale brain networks provides a skeleton of connected brain areas that facilitates signaling along preferred pathways in the service of specific cognitive functions. It is important to identify the brain areas that constitute structural network nodes and the connecting pathways that serve as structural network edges to know which configurations of interacting areas are possible. In the past, large-scale structural brain networks were often schematized by two-dimensional wiring diagrams, with brain areas connected by lines or arrows representing pathways. Currently, more sophisticated network visualization and analysis schemes are being developed and used [19]. We focus here first on the principal methods used to define structural nodes and edges in the brain. We then consider some possible functional consequences of the structural organization of large-scale brain networks.

Nodes

The nodes of large-scale structural networks are typically considered to be brain areas defined by: (i) cytoarchitectonics; (ii) local circuit connectivity; (iii) output projection target commonality; and (iv) input projection source commonality. A brain area can be described as a subnetwork of a large-scale network; this subnetwork consists of excitatory and inhibitory neuronal populations (nodes) and connecting pathways (edges). Despite the complex internal structure of brain areas, it is often convenient, particularly in network modeling research, to treat them as unitary neural masses that serve as spatially undifferentiated (lumped) nodes in large-scale networks. The definition of nodes is undergoing progressive refinement as new methods are developed and understanding of structure–function relations in the brain evolves (see below).

Techniques used in recent years to determine structural nodes from neuroanatomical data include: (i) anatomical parcellation of the cerebral cortex using the Brodmann atlas; (ii) parcellation in standardized Montreal Neurological Institute (MNI) space using macroscopic landmarks in structural magnetic resonance imaging (sMRI) data [20]; (iii) subject-specific automated cortical parcellation based on gyral folding patterns [21]; (iv) quantitative cytoarchitectonic maps [22]; and (v) neurochemical maps showing neurotransmitter profiles [23] (Figure 1). Diverse tradeoffs arise in the use of these techniques, a major one being that of anatomical specificity versus extent of coverage across the brain. This problem is particularly acute for the cerebral cortex because the borders of most cortical regions cannot be reliably detected using macroscopic features from sMRI. The choice of spatial scale for nodal parcellation has important consequences for the determination of network connectivity [24]. Recent quantitative cytoarchitecture mapping techniques [22] yield a more fine-grained parcellation and refined set of nodes than the more classical, but still popular,

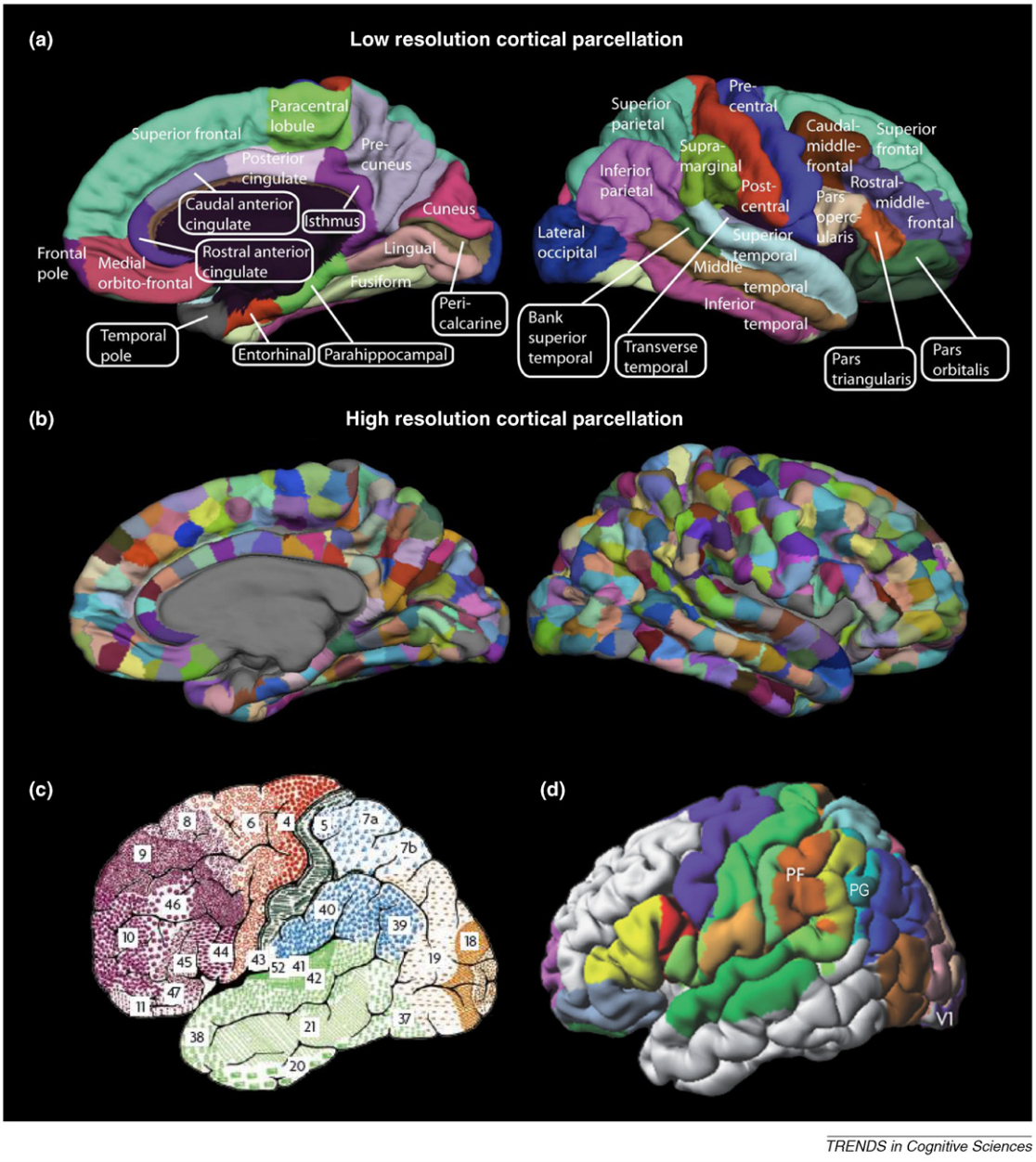

Figure 1. Identification of large-scale structural network nodes in the human brain by four methods currently in use. **(a)** Automated parcellation of a single subject's structural MR image into nodes based on the geometry of large sulcal landmarks. **(b)** High-resolution parcellation with arbitrary granularity. (Reproduced with permission from [35].) **(c)** Classical Brodmann atlas based on cytoarchitectonic features. **(d)** The Jülich–Düsseldorf cytoarchitectonic probabilistic brain atlas, based on observer-independent mapping of cortical areas in ten post-mortem brains. (Not all brain areas are currently covered in this scheme.) (Reproduced with permission from [160].)

Brodmann mapping scheme. Although newer methods offer a tighter link with the functional architecture of the brain, coverage currently exists for only a small set of cortical regions [25] and a wide swath of human prefrontal and temporal cortices have not yet been adequately mapped.

Most anatomical parcellation studies have focused on the cerebral cortex. Less attention has been paid to subcortical structures such as the basal ganglia and the thalamus, which have only been demarcated at a coarse level using sMRI. Brainstem systems mediating motivation, autonomic function and arousal have been poorly studied because they are notoriously difficult to identify using *in vivo* techniques. Nonetheless, it is important to identify these structures because they significantly influence cortical signaling and thus affect cognitive function. The demarcation of anatomical nodes by divergence and convergence patterns of structural connectivity is a recent technique that offers promise. Used to distinguish supplementary and pre-supplementary motor areas in the cortex [26], the technique has also been effective in discriminating individual thalamic nuclei [27].

Edges

The edges connecting brain areas in large-scale structural networks are long-range axonal-fiber (white matter) pathways. Network edges are directed because axonal fiber pathways have directionality from the somata to the synapses, and can be bidirectional when fiber pathways

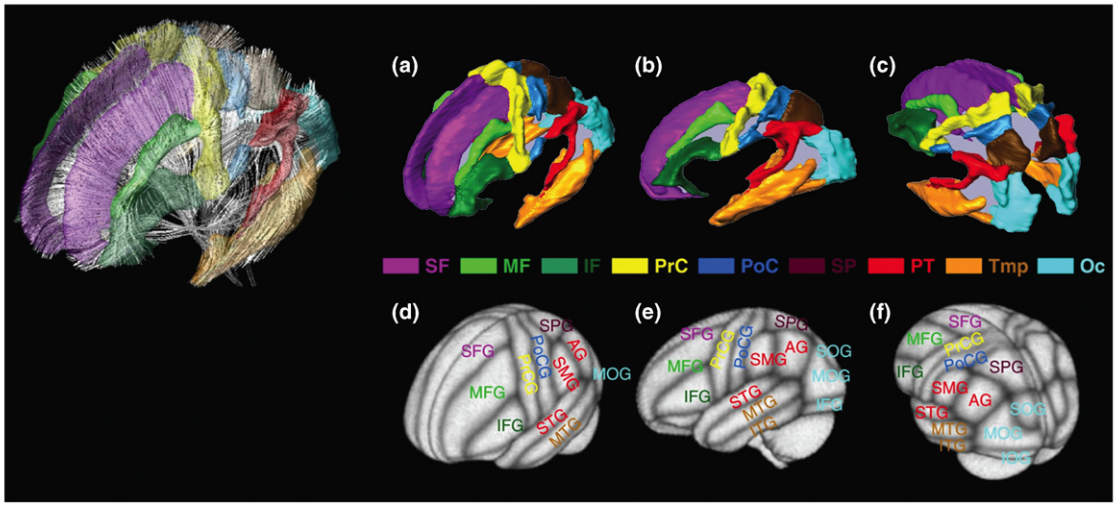

Figure 2. Identification of large-scale structural network edges in the human brain. Edges linking structural nodes were defined using diffusion tensor imaging. **Left:** individual fiber tracts. **Top row, right (a–c):** tract reconstruction and clustering showing three different orientations. **Bottom row, right (d–f):** relation to cortical nodes, shown from the same three orientations. (Reproduced with permission from [161].)

run in both directions between brain areas. Each brain area has a unique connection set of other areas with which it is interconnected [28,29]. Network edges have variable weights based on the number and size of axons in the pathways, and the number and strengths of functioning synapses at the axon terminals.

Three main approaches are currently used to trace axonal fiber pathways, and thus determine structural network edges. The first is autoradiographic tracing in experimental animals, historically the mainstay of neural tractography. In the macaque monkey, this technique has provided a rudimentary map of anatomical links between major cortical areas [30] and more recently has successfully detailed rostro–caudal and dorsal–ventral connectivity gradients between major prefrontal and parietal cortical areas [31]. It is difficult, however, to extrapolate from macaque connectional neuroanatomy to that of the human brain because the degree of pathway homology between macaque and human brains is not well understood. Methods using postmortem human brains to corroborate pathways identified in the macaque have yielded only limited knowledge about human brain connectivity because they are not consistently successful, are labor intensive and are often used to study only a few brain regions at a time [32].

The second approach uses diffusion-based magnetic resonance imaging methods, such as diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI), to determine major fiber tracts of the human brain *in vivo* by identifying the density of connections between brain areas (Figure 2). Good convergence between diffusion-based imaging and autoradiographic results has been reported [33], but the former has its own unique set of benefits and drawbacks. It has the advantage of being able to identify tracts in single human subjects, allowing replication and validation. It can also help to differentiate monosynaptic from polysynaptic connections, refine convergent and divergent projection zones, and better delineate and segregate anatomical areas [34]. However, it suffers from not being able to delineate feedforward and feedback connections between brain areas. Diffusion-based tractography of the entire human brain is still in its infancy, but rapidly evolving techniques are providing reliable estimates of the anatomical connectivity of several hundred cortical nodes [19,33,35]. With additional anatomical constraints on 'seeds' and 'targets' in diffusion-based tractography, it is increasingly possible to make closer links between projection zones and cytoarchitectonic maps [36] (Figure 3).

The third approach to mapping of network edges uses anatomical features such as local cortical thickness and volume to measure anatomical connectivity. In this approach, which has evolved during the same recent time period as DTI technology, interregional covariation in cortical thickness and volume across subjects is used to estimate connectivity [37,38]. Edges thus identified might not actually reflect axonal pathways and caution is required in interpreting the results. Nevertheless, networks identified using this approach have revealed stable graph-theoretic properties [39,40].

Recent studies have combined both node and edge detection to identify structural networks, either across the whole brain or within specific brain systems. At the whole-brain level, network nodes are determined by one of the parcellation methods described above, and then network edges are determined by DTI [41] or DSI [19]. If, however, structural network nodes are inferred from DTI or DSI patterns of convergence and divergence, nodes and edges cannot be independently identified. Within specific functional systems, such as for language or working memory, the nodes are constrained to lie within the system and then the edges are identified by diffusion-based tractography [42,43]. The use of cytoarchitectonic boundaries to define the nodes allows aspects of brain connectivity that are more closely linked to the underlying neuronal organization to be uncovered in parallel [44].

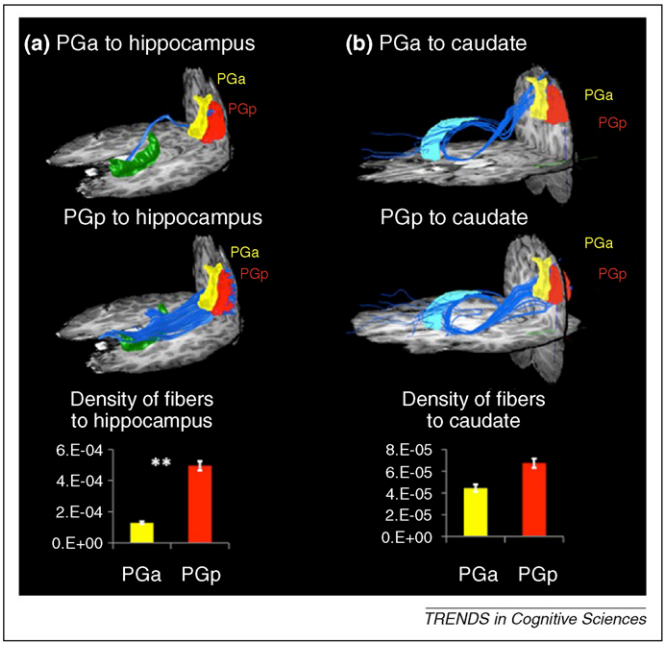

Figure 3. Distinct structural connectivity of cytoarchitectonically defined PGa and PGp regions of the human angular gyrus. **(a)** DTI tractography and density of fibers between the PGa and PGp and hippocampus. PGp shows greater structural connectivity with hippocampus than PGa does (**$P < 0.01$). **(b)** DTI tractography and density of fibers between PGa and PGp and the caudate nucleus. (Reproduced with permission from [44].)

Inferring function from structural networks

Large-scale structural networks provide an anatomical frame within which functional interactions take place [28,45]. At a minimum, knowledge of which brain areas are connected is necessary to know which functional interactions are possible. Beyond that, the patterning of structural network connectivity indicates which types of interaction are possible. Knowing that a cortical network has a small-world structure [46], for example, informs us of the expected functional interactions (many short-range and fewer long-range interactions). Knowing the hierarchical structural organization of sensory cortical networks can facilitate inferences about the functional activity flow patterns following sensory stimulation [47]. Knowing certain structural network features, such as node clustering or path length, divergence and convergence, provides important clues about the functional segregation and integration of network interactions [48]. Finally, knowing the differential transmission delays on different network edges can be important for predicting the dynamic patterning of network interactions.

A productive line of investigation into this question considers the repertoire of functional states that can possibly be generated by a given structural network architecture. Research on this issue suggests that brain networks have evolved to maximize the number and diversity of functional interaction patterns (functional motifs), while minimizing the number of structural connectivity patterns (structural motifs) [39].

With continuing improvement in methods for tracking, segmenting and classifying fiber tracts in the brain, further insights into the dependence of large-scale network function on network structure can be expected. However, a comprehensive understanding of network function will not necessarily follow from knowledge of large-scale structural networks. Large-scale functional networks, the topic of the next section, must be studied in their own right.

Large-scale functional brain networks

The primate brain has evolved to provide survival value to primate species by allowing individual species members to behave in ways that accommodate a wide variety of environmental contingencies, performing different behaviors under different sets of conditions. At each moment, a specific set of conditions must be analyzed by the perceptual apparatus of the brain and sets of percepts must be combined with learned concepts to create a 'solution' to the immediate problem of understanding the environment and acting appropriately. It is reasonable to assume that collections of interconnected brain areas act in concert to produce these solutions, as well as corresponding behaviors, and that they interact dynamically to achieve concerted action [49]. A large-scale functional network can therefore be defined as a collection of interconnected brain areas that interact to perform circumscribed functions.

Structural networks provide a complex architecture that promotes the dynamic interactions between nodes that give rise to functional networks. The connectivity patterns of structural networks, which vary with species [50], determine the functional networks that can emerge. Some functional networks, such as for language, depend on species-specific structural specializations [51], whereas others are common across species. The topological form of functional networks (which nodes are connected to which other nodes) changes throughout an individual's lifespan and is uniquely shaped by maturational and learning processes within the large-scale neuroanatomical connectivity matrix for each individual [52].

Large-scale functional networks in the brain exert coordinated effects on effector organs, subcortical brain structures and distributed cortical areas during a host of different cognitive functions. Component brain areas of large-scale functional networks perform different roles, some acting as controllers that direct the engagement of other areas [53] and others contributing specific sensory or conceptual content to network operations. For instance, coordinated prefrontal and posterior parietal control areas channel the flow of activity among sensory and motor areas in preparation for, and during, perceptuomotor processing [54–57].

Nodes

The characterization of functional networks in the brain requires identification of functional nodes. However, there is no commonly agreed definition of what constitutes a functional node in the brain. Historically, functional brain network nodes have been defined by inferences concerning the effects of brain lesions on cognitive function: when damage to a particular brain area impaired a cognitive function, that area was said to be a node in a network subserving that function.

Since the advent of advanced functional electrophysiological and neuroimaging methods, additional methodologies to define functional network nodes have become

available. A network node can be a circumscribed brain region displaying elevated metabolism in positron emission tomography (PET) recordings, elevated blood perfusion in functional magnetic resonance imaging (fMRI) recordings, or synchronized oscillatory activity in local field potential (LFP) recordings. Participation of a brain area in a large-scale functional network is commonly inferred from its activation or deactivation in relation to cognitive function. A group of brain areas jointly and uniquely activated or deactivated during cognitive function with respect to a baseline state can represent the nodes of a large-scale network for that function.

A major challenge is to determine how functional network nodes defined by different recording modalities are related, and how they relate to structural network nodes. From the network perspective, cognitive functions are carried out in real time by the operations of functional networks comprised of unique sets of interacting network nodes. For a brain area to qualify as a functional network node, it must be demonstrated that, in combination with a particular set of other nodes, it is engaged in a particular class of cognitive functions. Although it is not yet known how the various definitions of large-scale functional network nodes derived from different recording modalities are related, a possible scenario is that the elevated excitability of neurons within an area leads to elevated metabolic activity, which in turn causes an increase in local blood oxygen availability. The elevated excitability could also cause increased interactions between neurons within the area. Interactions between different populations can produce oscillatory activity and can have important functional consequences if, for example, the interactions lead to increased sensitivity of neurons within the area to the inputs that they receive.

Much of the work in the field of functional neuroimaging uses the fMRI blood-oxygen-level-dependent (BOLD) signal to identify the nodes of large-scale functional networks by relating the joint activation of brain areas to different cognitive functions. fMRI BOLD activation has revealed network nodes that are involved in such cognitive functions as attention [58], working memory [59], language [60], emotion [61], motor control [62] and time perception [63]. By contrast, nodes of a default-mode network (DMN), which are involved in self-monitoring functions, have been discovered by examining the joint deactivation of brain areas in relation to different goal-directed tasks [64–67].

Edges

The identification of functional network edges comes from different forms of functional interdependence (or functional connectivity) analysis, which assesses functional interactions among network nodes. The identification of network edges, like that of network nodes, is highly dependent on the monitoring methodology. Functional interdependence analysis can identify network edges from time series data in the time (e.g. cross-correlation function) or frequency (e.g., spectral coherence or phase synchrony measures) domain. In either domain, the analysis can use a symmetric measure, in which case significant interdependences are represented as undirected edges, or an asymmetric measure, in which case they are represented as directed edges [17]. Methods using directional measures include Granger causality analysis [57,68–72] and dynamic causal modeling [73,74].

Functional interdependences must be statistically significant for them to represent the edges of large-scale functional networks. Determination of thresholds for significance testing of network edges is often fraught with difficulty, and the particular method used for threshold determination can have an appreciable impact on the resulting large-scale network. Certain graph-theoretic measures, however, do not suffer from this problem because they take into account the full weight structure of the network [18].

Functional interdependence analysis has revealed large-scale functional network edges when applied to LFP [75–78] (Figure 4), combined LFP and multi-unit spiking [79,80], electrocorticographic (ECoG) [81–83], electroencephalographic (EEG) [84,85], magnetoencephalographic (MEG) [86] and fMRI BOLD [87,88] time series. As with functional network nodes, it is necessary to understand how large-scale functional network edges defined by different recording modalities are related. Fluctuations in

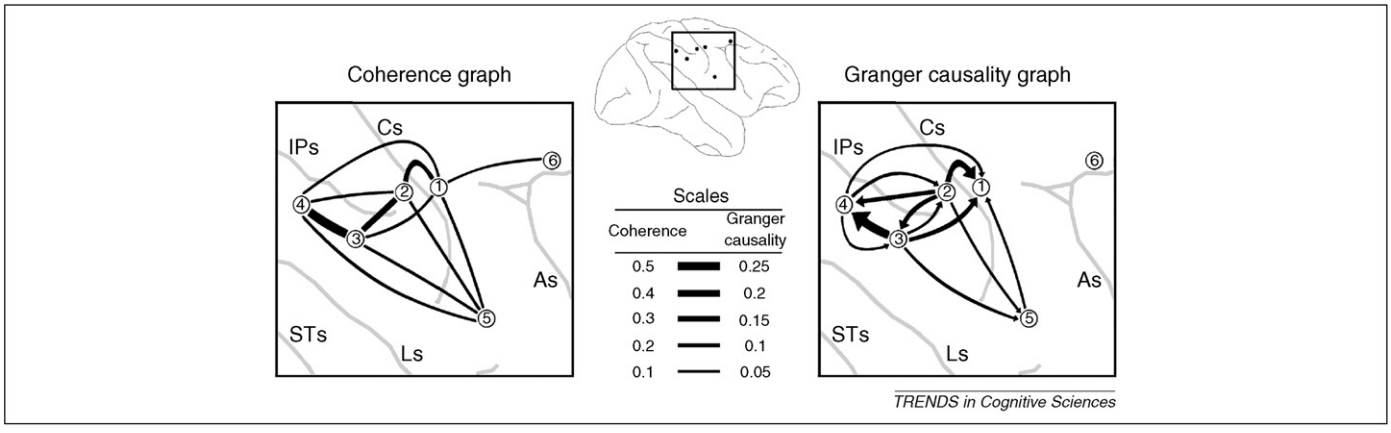

Figure 4. A large-scale sensorimotor network in the monkey cerebral cortex. Coherence (left) and Granger causality (right) graphs characterize the interactions of distributed neuronal populations in somatosensory and motor regions of the macaque monkey cerebral cortex. The determination of network organization was based on the observation of highly synchronized population oscillatory activity in the β frequency range (14–30 Hz) as the monkey maintained pressure on a hand lever while engaged in a visual discrimination task. (Reproduced with permission from [75].)

neuronal population activity at different time scales can control the time-dependent variation of engagement and coordination of areas in large-scale functional networks [52].

Network edges are possibly best represented by the correlation of time series fluctuations at different time scales, reflecting different functional network properties. The correlation of slow fluctuations at rest in fMRI BOLD signals possibly reflects slow interactions necessary to maintain the structural and functional integrity of networks [89], whereas the correlation of fast fluctuations could reflect fast dynamic coupling required for information exchange within the network [52].

On the basis of the local circuit organization of excitatory and inhibitory neuronal populations in the cortex and the ubiquitous reciprocal nature of interregional cortical transmission, it has been hypothesized that fast dynamic coupling is based on long-range phase synchrony of oscillatory neuronal population activity [90,91]. Phase synchrony has been found between extrastriate areas of the visual cortex during visual short-term memory maintenance [92], frontal, occipital and hippocampal areas during visual object processing [82], frontal, temporal, parietal and occipital areas during multisensory processing [93], and different widespread sets of cortical areas during different attention tasks [94]. Although these results suggest that long-range phase synchrony can serve as a dynamic mechanism underlying functional interactions in the brain, a systematic framework for the study of large-scale brain networks based on phase synchrony has not yet emerged, chiefly because the requisite electrophysiological recordings are typically restricted in terms of the number of brain areas that can be simultaneously sampled.

Functional interdependence has been observed across a range of time scales from milliseconds [80,95] to minutes [96,97]. Recent evidence suggests that slow intracranial cortical potentials are related to the fMRI BOLD signal [98]. It is possible that functional networks are organized according to a hierarchy of temporal scales, with structural edges constraining slow functional edges, which in turn constrain progressively faster network edges. Studies in both monkeys [99] and humans [100] support the existence of hierarchical functional organization across time scales.

Intrinsic functional brain networks

Functional interdependence analysis has often been used to investigate interactions between brain areas during task performance. Although task-based analyses have enhanced our understanding of dynamic context-dependent interactions, they often have not contributed to a principled understanding of functional brain networks. By focusing on task-related interactions between specific brain areas, they have tended to ignore the anatomical connectivity and physiological processes that underlie these interactions. We suggest that characterization of the intrinsic structural and functional connectivity of large-scale brain networks is necessary for a more systematic understanding of how they engender cognition.

In contrast to functional interdependence analyses of task-induced changes in interactions, intrinsic interdependence analysis focuses on large-scale brain organization independent of task processing demands [15]. Intrinsic interdependence analysis of fMRI data acquired from subjects at rest and unbiased by task demands has been used to identify intrinsic connectivity networks (ICNs) in the brain [101]. Characterization of large-scale functional networks in the resting state has the advantage of avoiding idiosyncrasies that might be present in certain cognitive tasks [102–104]. ICNs identified in the resting brain include networks that are also active during specific cognitive operations, suggesting that the human brain is intrinsically organized into distinct functional networks [105–108].

One key method for identifying ICNs in resting-state fMRI BOLD data is independent component analysis (ICA) [105], which has been used to identify ICNs involved in executive control, episodic memory, autobiographical memory, self-related processing and detection of salient events. ICA has revealed a sensorimotor ICN anchored in bilateral somatosensory and motor cortices, a visuospatial attention network anchored in intra-parietal sulci and frontal eye fields, a higher-order visual network anchored in lateral occipital and inferior temporal cortices, and a lower-order visual network [105,107]. This technique has allowed intrinsic (Figure 5), as well as task-related (Figure 6), fMRI activation patterns to be used for identification of distinct functionally coupled systems, including a central-executive network (CEN) anchored in dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC), and a salience network anchored in anterior insula (AI) and anterior cingulate cortex (ACC) [107].

A second major method of ICN identification is seed-based functional interdependence analysis [15,109]. Like ICA, this technique has been used to examine ICNs associated with specific cognitive processes such as visual orienting attention [106,110], memory [103] and emotion [111]. First, a seed region associated with a cognitive function is identified. Then, a map is constructed of brain voxels showing significant functional connectivity with the seed region. This approach has demonstrated that similar networks to those engaged during cognitive task performance are identifiable at rest, including dorsal and ventral attention systems [109] and hippocampal memory systems [112]. It has also revealed distinct functional circuits within adjacent brain regions: functional connectivity maps of the human basolateral and centromedial amygdala [113], for example, reproduce connectivity patterns observed using animal cyto-, myelo- and chemoarchitectural methods with remarkable fidelity [111].

Graph-theoretic studies of resting-state fMRI functional connectivity results [114,115] have suggested that human large-scale functional brain networks are usefully described as small-world [18,116]. Other graph-theoretic metrics such as hierarchy have been useful in characterizing subnetwork topological properties [117], but a consistent view of hierarchical organization in large-scale functional networks has yet to emerge.

Core functional brain networks

A formal characterization of core brain networks, anatomically distinct large-scale brain systems with distinct

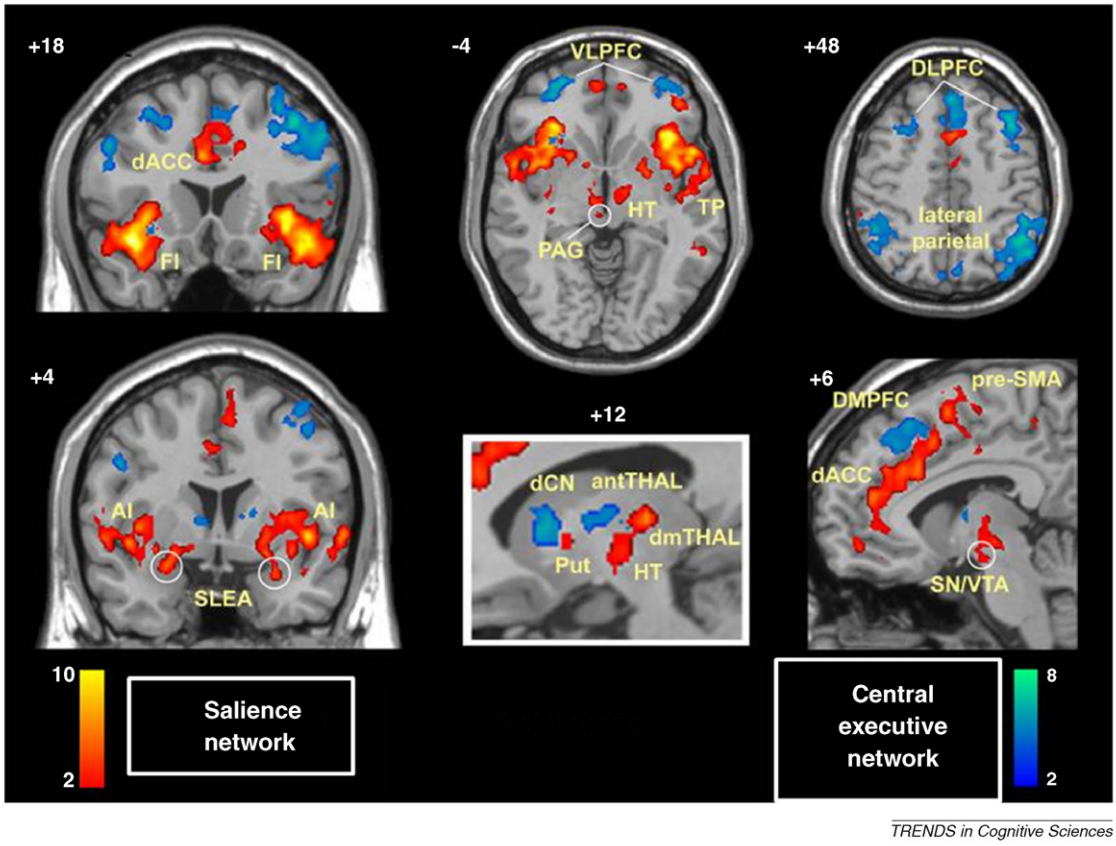

Figure 5. Two core brain networks identified using intrinsic physiological coupling in resting-state fMRI data. The salience network (shown in red) is important for monitoring the salience of external inputs and internal brain events, and the central-executive network (shown in blue) is engaged in higher-order cognitive and attentional control. The salience network is anchored in anterior insular (AI) and dorsal anterior cingulate cortices (dACC), and features extensive connectivity with subcortical and limbic structures involved in reward and motivation. The central-executive network links the dorsolateral prefrontal and posterior parietal cortices, and has subcortical coupling that is distinct from that of the salience network. (Reproduced with permission from [107].)

cognitive functions, was first reported by Mesulam [12]. In his view, the human brain contains at least five major core functional networks: (i) a spatial attention network anchored in posterior parietal cortex and frontal eye fields; (ii) a language network anchored in Wernicke's and Broca's areas; (iii) an explicit memory network anchored in the hippocampal–entorhinal complex and inferior parietal cortex; (iv) a face-object recognition network anchored in

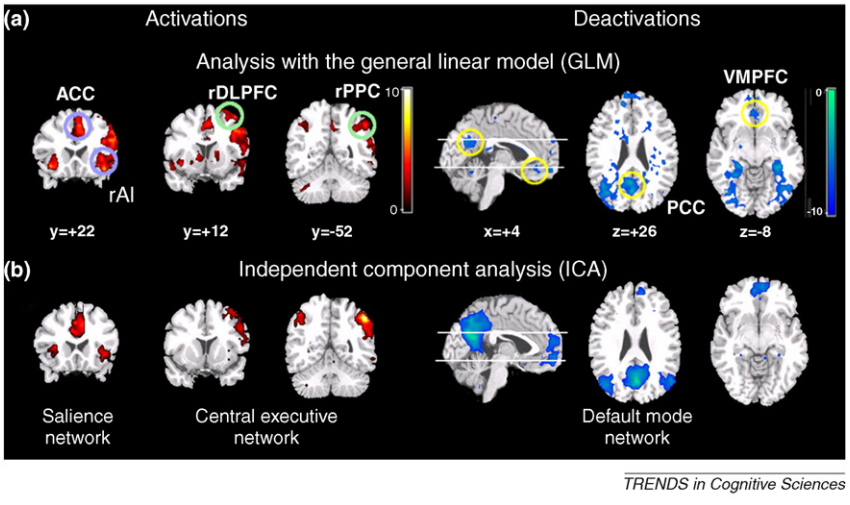

Figure 6. Three major functional networks in the human brain identified using converging methodologies. Task-related activation patterns in the central-executive and salience networks, and deactivation patterns in the default-mode network during an auditory event segmentation task. Activation and deactivation patterns can be decomposed into distinct subpatterns. **(a)** Analysis with the general linear model revealed regional activations (left) in the right AI and ACC (blue circles) and the DLPFC and PPC (green circles), and deactivations (right) in the ventromedial (VM)PFC and PCC. **(b)** Independent component analysis provided converging evidence of spatially distinct networks. From left to right: salience network (rAI and ACC), central-executive network (rDLPFC and rPPC), and default-mode network (VMPFC and PCC). (Reproduced with permission from [129].)

midtemporal and temporopolar cortices; and (v) a working memory-executive function network anchored in prefrontal and inferior parietal cortices. The nodes of these core networks have been inferred from fMRI activations during tasks that manipulate one or more of these cognitive functions. A full characterization of core functional brain networks, however, will require additional studies to validate the nodes of these networks by other criteria, to measure their edges, and to determine whether other core networks exist.

Major functional brain networks, and their composite subnetworks, show close correspondence in independent analyses of resting and task-related connectivity patterns [118], suggesting that functional networks coupled at rest are also systematically engaged during cognition. The important discovery that some core brain networks can be identified by the characterization of ICNs in subjects at rest has contributed to a more unified perspective on central neurocognitive operations. A prime candidate for consideration as a core brain network is the DMN, an ICN that shows extensive deactivation during cognitively demanding tasks [119] and increased activity during high-level social cognitive tasks [120]. Numerous studies have revealed activation and deactivation of various nodes of the DMN: the PCC during tasks involving autobiographical memory and self-referential processes [121], the medial PFC in social cognitive processes related to self and others [122], the MTL in episodic memory [123], and the angular gyrus in semantic processing [124]. These studies suggest that the functions of the DMN nodes are very different. However, when considered as a core brain network, the DMN is seen to collectively comprise an integrated system for autobiographical, self-monitoring and social cognitive functions [125], even though a unique task-based function cannot be assigned to each of its nodes. The concept of an integral DMN function is supported by observations that dynamic suppression of the entire network is necessary for accurate behavioral performance on cognitively demanding tasks [126,127].

Another candidate core brain network is the aforementioned salience network, comprised of cortical areas AI and ACC and subcortical areas including the amygdala, substantia nigra or ventral tegmental area and thalamus. It has been suggested that the salience network is involved in the orientation of attention to the most homeostatically relevant (salient) of ongoing intrapersonal and extrapersonal events [107,128] (Figure 5). In this light, a recent study examining the directional influences exerted by specific nodes in the salience network on other brain regions suggested that the AI plays a causal role in switching between the CEN and DMN [129], two networks that undergo competitive interactions across task paradigms and stimulus modalities (Figure 7) and are thought to mediate attention to the external and internal worlds, respectively.

A crucial open question concerning core brain networks is whether a given network can be said to support a specific cognitive function. The answer to this question for any network will depend on a deeper understanding of its input–output relations, its temporal dynamics and the ways in which it interacts with other networks. We use the salience network to illustrate this point. As described above, it has been suggested that this network mediates attention to the external and internal worlds [130]. To determine whether this network indeed specifically performs this function will require testing and validation of a sequence of putative network mechanisms that includes: (i) bottom-up detection of salient events; (ii) switching

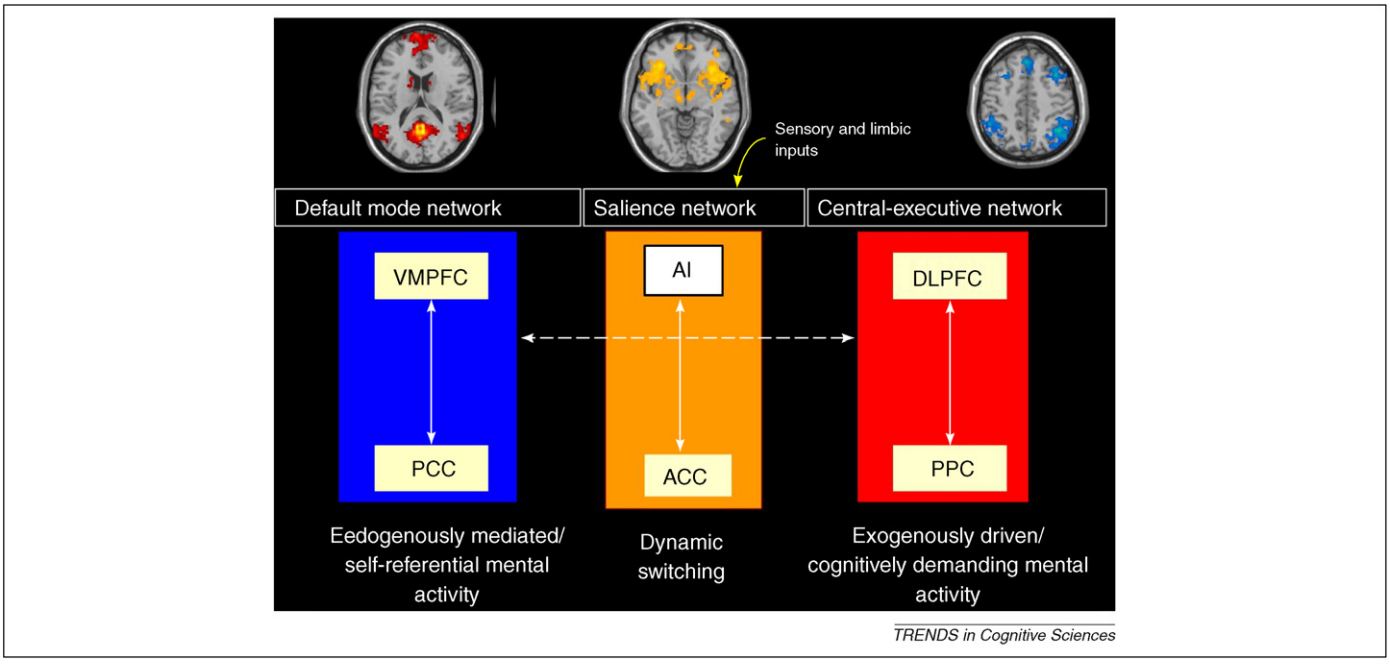

Figure 7. Multi-network switching initiated by the salience network. It is hypothesized that the salience network initiates dynamic switching between the central-executive and default-mode networks, and mediates between attention to endogenous and exogenous events. In this model, sensory and limbic inputs are processed by the AI, which detects salient events and initiates appropriate control signals to regulate behavior via the ACC and homeostatic state via the mid and posterior insular cortex. Key nodes of the salience network include the AI and ACC; the default-mode network includes the VMPFC and PCC; the central-executive network includes the DLPFC and PPC. (Based on [129] and [130].)

between other large-scale networks to facilitate access to attention and working memory resources when a salient event occurs; (iii) interaction of the anterior and posterior insula to modulate autonomic reactivity to salient stimuli; and (iv) strong functional coupling with the ACC to facilitate rapid access to the motor system. Such validation would help to establish cognitive sequelae associated with the salience network and provide novel insights into its role in mediating attention to the external and internal worlds.

Functional brain networks and psychopathology

The systematic exploration of large-scale functional brain networks is yielding not only parsimonious accounts of normal cognitive processes, but also novel insights into psychiatric and neurological disorders [131–133]. Abnormalities in intrinsic functional connectivity have been identified within the DMN in Alzheimer's disease [134,135] and in major depression [131], albeit in different network nodes. Abnormalities have been observed in the phase synchrony of oscillatory neuronal population activity [136] in relation to Alzheimer's disease [137], schizophrenia [138–140], autism [141–143], the manic phase of bipolar disorder [144] and Parkinson's disease [145]. Thus, impairment of functional network interactions might be common in psychiatric and neurological disorders, and observable by functional interdependence analysis of both oscillatory neuronal population and fMRI activity.

A particularly striking example of this new view of psychopathology comes from the finding, discussed above, that the AI is a critical node for initiation of network switching. This key insight reveals the potential for profound deficits in cognitive functioning should AI integrity or connectivity be compromised. AI hyperactivity has been implicated in anxiety disorders, suggesting that salience network hyperactivity can be pathological [146]. Individuals scoring high on the trait neuroticism, the tendency to experience negative emotional states, demonstrate greater AI activation during decision-making even when the outcome of the decision is certain [147]. It is possible that an appropriate level of AI activity is necessary to provide an alerting signal that initiates brain responses to salient stimuli. If so, pathology could result from AI hyperactivity, as in anxiety, or hypoactivity, as might be the case in autism [148]. Similarly, Uddin and Menon suggested that a large-scale brain network description can provide a parsimonious account of the recent neuroimaging literature on autism and that the AI is a key node in coordinating brain network interactions owing to its unique anatomy, function and connectivity [149]. Characterization of brain networks associated with this structure has helped to identify an important but neglected area of research in autism. A systematic investigation of the salience network could be important for better differentiation and characterization of neurodegenerative disorders such as Alzheimer's disease and different forms of frontotemporal dementia [133].

Finally, the central role played by large-scale networks in cognitive function and dysfunction is well illustrated by recent studies demonstrating that face perception is not the property of a single face-processing area in fusiform cortex, but rather of an extended network of visual, limbic and prefrontal cortical regions [150]. Impaired face perception in congenital prosopagnosia results from the degraded structural integrity of the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus, two fiber tracts that connect the fusiform gyrus with other face-processing network areas in anterior temporal and frontal cortices [151]. The fMRI response to faces in congenital prosopagnosic individuals is normal in the fusiform cortex, but not in the extended regions [152]. A decline in face perception with normal aging is also related to reduced structural integrity of the inferior fronto-occipital fasciculus [153].

Conclusions and future directions

We have reviewed emerging methods for the identification and characterization of large-scale structural and functional brain networks, and have suggested new concepts in cognitive brain theory from the perspective of large-scale networks. Although critical open questions remain (Box 3), the large-scale brain network framework described here offers a principled and systematic approach to the study of cognitive function and dysfunction [154,155].

Continued progress in understanding of cognitive function and dysfunction will depend on the development of new techniques for imaging structural and functional brain connectivity, as well as new methods for investigating dynamic interactions within and between networks. In the remainder of this section, we discuss important directions for future research and highlight areas in which progress is likely to occur.

Although we have reviewed studies that tend to map cognitive functions onto large-scale brain networks, we expect that attempts to equate individual brain networks with a set of cognitive functions could prove to be just as inadequate as attempts to equate single brain regions with specific cognitive functions. It is likely that the function of any cognitive brain network ultimately depends on its multidimensional context [156]. We predict that future studies will explicitly recognize the importance of context in the formation of large-scale functional networks, and will seek to determine the other factors contributing to context in addition to anatomical structure.

Box 3. Critical questions about cognition from the network perspective

- How does cognitive function emerge from large-scale brain networks?
- What mechanisms underlie the dynamic engagement and disengagement of brain areas responsible for the formation and dissolution of large-scale functional networks?
- How do different large-scale functional networks cooperate, compete and coordinate their activity during complex cognitive behavior?
- How does functional interdependence based on the fMRI BOLD signal relate to that based on synchronized oscillatory activity in neuronal population activity measured in LFP recording?
- Is knowledge constructed dynamically by large-scale functional networks?

In the same vein, although our review has emphasized studies based on the fMRI BOLD signal, our perspective does not imply a static view of large-scale brain networks. Rather, we view cognitive function as a dynamic process that is constrained by intrinsic structural connectivity and ongoing physiological processes. We anticipate that the future will increasingly bring more studies seeking to relate dynamic processes such as oscillatory phase synchrony to processes occurring at slower time scales. The growing tendency to combine EEG and fMRI recording modalities in the same study [157] represents a trend in this direction.

Many of the issues raised in this review, such as the problem of relating functional network edges existing at different time scales, are exceedingly difficult to address strictly by experimental means. Computational modeling is becoming increasingly important for studies of large-scale brain networks [158], and its importance is likely to grow even more in the future. In our view, for the foreseeable future computational modeling will represent the best means of reconciling large-scale brain networks identified by different recording modalities. A compelling example of the need for computational modeling is the problem of relating the effects of different types of neurons, neurotransmitters and neuromodulators on network node activity to neuroimaging results in which network nodes appear as unitary neural masses.

The potential value of computational modeling is also evident when considering that the prevalent view of large-scale brain networks as small-world networks is largely a static image [37,46,135]. Studies of small-world and other network properties provide insights into the network architecture and help to demarcate hierarchies. A challenge for cognitive neuroscience is to better understand how intrinsic hierarchies in brain networks influence cognition. Computational modeling could prove to be essential for understanding the dynamic interactions within small-world brain networks that are important for cognition.

Another direction for future research is ongoing refinement of the concept of a network node. As discussed in our review, this concept is derived from multiple structural and functional methodologies, and currently there is no clear consensus as to which is most relevant for cognitive neuroscience. We suggest that future development of methods to define cytoarchitectonic maps [23,44,111] might eventually satisfactorily address many critical questions regarding the functioning of large-scale network nodes.

Finally, it will be essential for future studies to critically address the ways in which network nodes and edges are constrained and reorganized by learning and development. It is to be expected that the boundaries of network nodes shift with learning and that prominent changes in network edges are even more likely. Consideration of individual variability will have important implications for understanding the changes in large-scale network function that occur during development. In adults, some expansion of node size is likely; however, changes in the strength of network edges are likely to be most critical for understanding of large-scale network changes during learning [159] and development [116].

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