

## Special Issue: The Connectome – Feature Review

## Network hubs in the human brain

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Virtually all domains of cognitive function require the integration of distributed neural activity. Network analysis of human brain connectivity has consistently identified sets of regions that are critically important for enabling efficient neuronal signaling and communication. The central embedding of these candidate ‘brain hubs’ in anatomical networks supports their diverse functional roles across a broad range of cognitive tasks and widespread dynamic coupling within and across functional networks. The high level of centrality of brain hubs also renders them points of vulnerability that are susceptible to disconnection and dysfunction in brain disorders. Combining data from numerous empirical and computational studies, network approaches strongly suggest that brain hubs play important roles in information integration underpinning numerous aspects of complex cognitive function.

## The central role of integrative processes and communication

Since the beginning of modern neuroscience, the brain has generally been viewed as an anatomically differentiated organ whose many parts and regions are associated with the expression of specific mental faculties, behavioral traits, or cognitive operations [1]. The idea that individual brain regions are functionally specialized and make specific contributions to mind and cognition is supported by a wealth of evidence from both anatomical and physiological studies as well as from noninvasive neuroimaging. These studies have documented highly specific cellular and circuit properties, finely tuned neural responses, and highly differentiated regional activation profiles across many regions of the human brain, including the cerebral cortex. Functional specialization has become one of the enduring theoretical foundations of cognitive neuroscience.

Specialization alone, however, cannot fully account for most aspects of brain function. Mounting evidence suggests that integrative processes and dynamic interactions across multiple distributed regions and systems underpin cognitive processes as diverse as visual recognition [2], language [3], cognitive control [4], emotion [5], and social

## Glossary

**Brain connectivity:** description of structural or functional connectivity between brain network elements (i.e., brain regions, neurons).

**Centrality:** measures of the relative importance of a node or edge within the overall architecture of a network. Several centrality metrics have been proposed, including (among many others) degree, betweenness, closeness, eigenvector, and pagerank centrality.

**Clustering:** the tendency of small groups of nodes to form connected triangles. Many triangles around a central node imply that the connected neighbors of the node are also neighbors of each other, forming a cluster or clique.

**Community:** in networks, communities refer to modules, densely interconnected sets of nodes.

**Connection matrix:** a summary of all pairwise associations (connections) between network nodes, rendered in the form of a square matrix.

**Connection:** a connection expresses the existence and/or strength of a relationship, interaction, or dependency between two nodes in the network. Connections can be binary or weighted and they can be directed or undirected. Connections are also referred to as edges.

**Connectome:** a comprehensive network map of the anatomical connections of a species’ nervous system.

**Connector hub:** a high-degree network node that displays a diverse connectivity profile across several different modules in a network.

**Core:** a group of nodes that share a large number of mutual connections, rendering them resistant to damage. Cores are identified by using a recursive procedure that prunes away weakly connected nodes.

**Degree:** the number of edges attached to a given node.

**Directed network:** a network comprising directed connections (edges).

**Edge:** a term for a network connection.

**Functional connectivity:** measured as the statistical dependence between the time series of two network nodes (e.g., brain regions, neurons).

**Graph:** a mathematical description of a network, comprising a collection of nodes and a collection of edges.

**Hub:** a node occupying a central position in the overall organization of a network.

**Module:** a group of nodes that maintain a large number of mutual connections and a small number of connections to nodes outside their module.

**Parcellation:** a subdivision of the brain into anatomically or functionally distinct areas or regions.

**Participation coefficient:** a graph-theoretical measure that expresses the distribution of edges of a node across all modules in a network.

**Provincial hub:** a high-degree network node that mostly connects to nodes within its own module.

**Resting-state network:** a set of brain regions that show coherent functional connectivity during task-free spontaneous brain activity.

**Rich-club organization:** the propensity of a set of high-degree nodes in a network to be more densely interconnected than expected on the basis of their node degree alone.

**Scale-free organization:** a network with a degree distribution that follows a power-law function.

**Shortest path length:** the shortest path length between two nodes reflects the minimal number of links that have to be crossed to travel from one node to another node in the network.

**Small-world organization:** a network that shows a level of clustering higher than that observed in random networks and an average shortest path length that is equal to that observed in random networks.

**Structural connectivity:** a description of the anatomical connections between network nodes (i.e., brain regions, neurons); for example, reconstructed anatomical projections derived from diffusion MRI, directed anatomical pathways derived from neural tract tracing, or synaptic connections between individual neurons.

**Undirected network:** a network comprising undirected connections (edges).

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cognition [6]. What is the neural substrate that enables integration of distributed neural information and thus the emergence of coherent mental and cognitive states? Two aspects of brain organization appear particularly important. First, integration depends on neural communication among specialized brain regions, unfolding within a network of interregional projections [7–10], which gives rise to large-scale patterns of synchronization [11,12] and information flow [13] between connected elements. Second, important integrative functions are performed by a specific set of brain regions and their anatomical connections. These regions are capable of complex and diverse responses (multimodal or transmodal regions [14]), are placed at higher levels within a cortical hierarchy [15], and represent focal points of convergence or divergence of more specialized neural information ('confluence zones' [16,17]).

The brain's anatomical and functional organization can be approached from the perspective of complex networks [18–21]. Embracing network science as a theoretical framework for brain connectivity (see [Glossary](#)), numerous studies have begun mathematically to describe neural systems in terms of graphs or networks comprising nodes (neurons and/or brain regions) and edges (synaptic connections, interregional pathways). The comprehensive network map of the nervous system of a given organism, its connectome [22,23], represents a structural basis for dynamic interactions to emerge between its neural elements. A principal aim of connectome studies is to unravel the architecture of brain networks and to explain how the topology of structural networks shape and modulate brain function. Network science or 'graph theory' can be used to elucidate key organizational features of the brain's connectome architecture and to make predictions about the role of network elements and network attributes in brain function. There is strong convergence across many studies indicating that connectomes as diverse as the cellular network of the nematode *Caenorhabditis elegans* and the human cerebral cortex combine attributes that promote modularity (specialization) with attributes that ensure efficient communication (integration). The latter include network elements that are often referred to as network hubs, generally characterized by their high degree of connectivity to other regions and their central placement in the network.

The goal of this review is to examine the concept of network hubs in the context of brain data, with respect to their central placement in the overall network structure and their putative role in neural communication and integrative brain function. We begin with a brief overview of various network measures that can be used to detect potential candidates for network hubs in human and animal brain data sets. We then provide a survey of current empirical results on hub structure in connectome networks, with a focus on structural and functional networks. We discuss several recent findings of network studies that highlight the central role of these candidate hubs in both the healthy and diseased brain. Integrating across methodology and empirical findings, we offer a conceptual framework that examines potential functional roles of neural hubs from the perspective of network science,

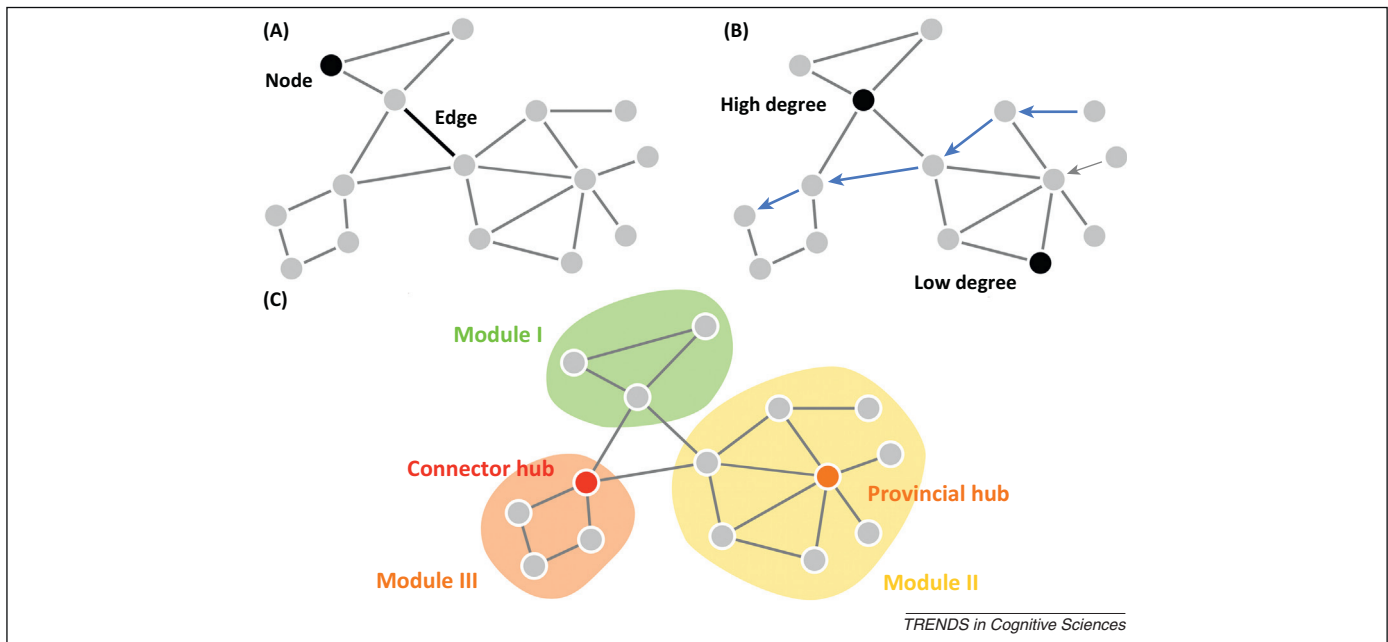
especially in the context of network models of communication, integration, and information flow. The review concludes with a reflection on some of the new insights that network models have contributed to our understanding of the neural substrates that enable complex brain function.

### Methodological aspects: detection and classification of hubs in brain networks

Brain networks can be mathematically described as graphs, essentially comprising sets of nodes (neuronal elements) and edges (their interconnections) whose pairwise couplings are summarized in the network's connection matrix and whose arrangement defines the network's topology ([Figure 1](#)). The extraction of brain networks from human imaging data as well as the many opportunities and limitations of graph-based approaches have been the subject of numerous recent reviews [20,24–28]. One appealing aspect of graph models is that graph theory offers a vast array of objective data-driven measures to characterize the topology of networks, many of which have originally been defined in other disciplines [29–31]. An important subset of these measures identifies network elements (nodes or edges) that are likely to have a strong influence on communication and information integration and thus on the global function of the network.

#### Hub detection: centrality, modularity, and interconnections

Within the framework of network science, nodes that are positioned to make strong contributions to global network function are generally referred to as network hubs. Hubs can be detected using numerous different graph measures, most of which express aspects of node centrality [32,33] ([Figure 1](#)). The simplest graph measure used for identifying hubs is the node degree, also called degree centrality, which is equal to the number of edges that are maintained by each node. Many real-world networks, including biological systems, have been shown to exhibit 'heavy-tailed' degree distributions, with a small number of elements exhibiting a high connectivity degree. Although node centrality simply counts relationships, measures like eigenvector centrality or pagerank centrality favor nodes that connect to other highly central nodes, a property that can be computed from the graph's eigenvector decomposition [34]. A more global aspect of centrality is captured by considering the layout of short communication paths among nodes. Closeness centrality corresponds to the average distance (the length of the shortest paths) between a given node and the rest of the network. Betweenness centrality [35] expresses the number of short communication paths that a node (or edge) participates in. Yet another set of measures, including for example vulnerability [36] and dynamic importance [37], attempts to assess the impact of node (or edge) deletion with respect to global network communication or synchronization by comparing graph metrics before and after node (or edge) deletion. Although no single measure is both necessary and sufficient for defining network hubs, rankings of nodes according to different criteria of centrality are often highly correlated. Hence, it is often advantageous to detect hubs by aggregating rankings across different measures



**Figure 1.** Basic network attributes. (A) Brain networks can be described and analyzed as graphs comprising a collection of nodes (describing neurons/brain regions) and a collection of edges (describing structural connections or functional relationships). The arrangement of nodes and edges defines the topological organization of the network. (B) A path corresponds to a sequence of unique edges that are crossed when traveling between two nodes in the network. Low-degree nodes are nodes that have a relatively low number of edges; high-degree nodes (often referred to as hubs) are nodes that have a relatively high number of edges. (C) A module includes a subset of nodes of the network that show a relatively high level of within-module connectivity and a relatively low level of intermodule connectivity. 'Provincial hubs' are high-degree nodes that primarily connect to nodes in the same module. 'Connector hubs' are high-degree nodes that show a diverse connectivity profile by connecting to several different modules within the network.

[33,38,39]. Several centrality measures, including betweenness and vulnerability, can also be applied to identify highly central network edges.

An increasingly important approach to defining network hubs builds on their role in integrating network communities or modules [40,41]. Network communities are sets of nodes that are more densely linked among each other than with nodes in other communities, and various algorithms and metrics for detecting network modules are available. Network communities are important descriptors of brain network organization and have proved useful in mapping functional networks in resting [42] and task-evoked coactivation studies [43]. Once an optimal module partition has been identified, each node's pattern of connections relative to this partition can be quantified. The participation coefficient [44] is based on the diversity of a node's connection profile. Among high-degree nodes, the participation coefficient differentiates hubs that primarily link nodes within a single module ('provincial hubs') from others that predominantly link nodes across different modules ('connector hubs') [44]. Low-degree nodes that predominantly connect to nodes in their own module and hence exhibit a low participation coefficient are classified as 'peripheral nodes'. Other proposed approaches are based on an assessment of the placement of brain regions (i.e., nodes) into multiple functional modules or functional networks [45].

Once candidate network hubs have been identified, an important additional question concerns their mutual interconnections. Specifically, it may be of interest to determine whether hub nodes are more highly interconnected than predicted by chance (i.e., predicted by a random null model that preserves node degrees but destroys global topology).

Such collectives of high-degree nodes and their interconnecting edges are referred to as a 'rich club' [46], a network attribute that tends to further boost the influence of its members by facilitating their mutual interactions. A related concept is that of the structural core [47], determined by a process of recursive pruning of nodes of increasing degree that reveals subsets of nodes that are highly resilient by virtue of being densely interconnected.

#### *Hubs in structural and functional networks*

Patterns of brain connectivity can be recorded using various anatomical or physiological methods that respectively yield structural and functional brain networks. These two domains of brain networks differ in the way they are constructed and they express different aspects of the underlying neurobiological reality. This fundamental distinction becomes important when interpreting network data of neural systems, including putative hubs. 'Structural networks' describe anatomical connectivity, which tends to be relatively stable on shorter time scales (seconds to minutes) but may be subject to plasticity at longer time scales (hours to days). Importantly, edges in structural networks correspond to physical (axonal, synaptic) links that form the biological infrastructure for neuronal signaling and communication. By contrast, 'functional networks' are derived from statistical descriptions of time series data, which in resting-state functional MRI (fMRI) studies are often represented as linear (Pearson) cross-correlations. These statistical estimates are highly time dependent, modulated by stimuli and task context, and exhibit significant non-stationary fluctuations even at rest [48]. Edges in functional networks thus do not represent anatomical connections and should not be interpreted as such. For

example, direct comparisons of structural and functional networks obtained in register have shown that functional connectivity, especially when estimated via cross-correlation, links many structurally unconnected node pairs [49–51] and is prone to transitivity, which leads to a propensity for ‘over-connection’ and high clustering [52].

In the context of this review, it is especially important to note that functional connections do not relay neuronal signals; rather, functional connections are a reflection of signaling and communication events that unfold within the underlying structural network. Hence, although all hub measures described above are meaningful when applied to structural networks, the interpretation of hubs derived from functional networks based on measures like degree [53] or betweenness centrality is less straightforward. One possible promising approach that appears applicable across both structural and functional networks is to define hubs based on the network’s community structure.

### Empirical results: candidate hubs in the structural and functional connectome

#### Structural hubs

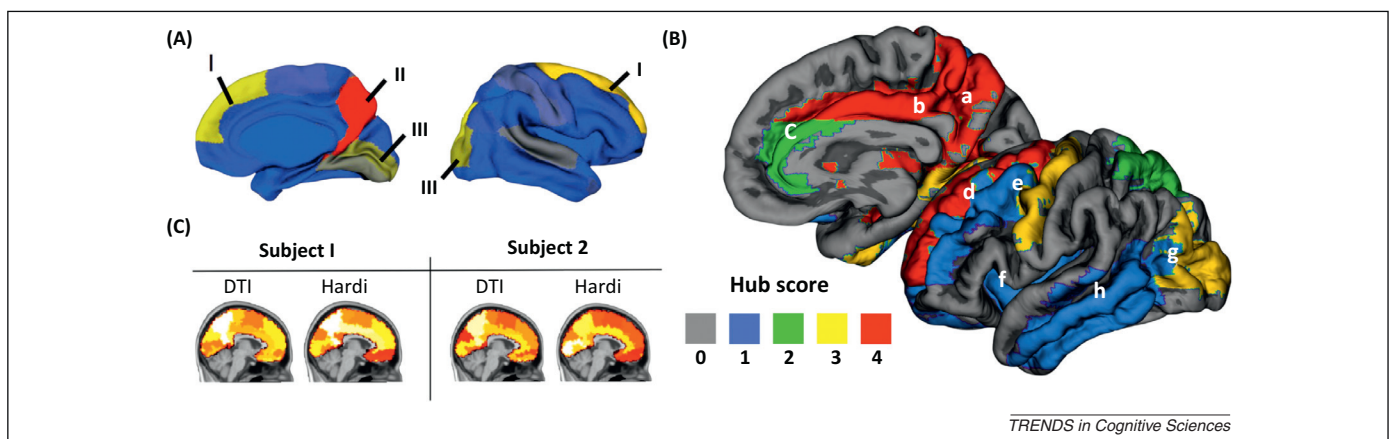
Compiling macroscale connectome maps of the human brain from diffusion imaging data, several studies have noted the existence of a specific set of hub regions (Figure 2). Network analyses have consistently identified the precuneus, anterior and posterior cingulate cortex, insular cortex, superior frontal cortex, temporal cortex, and lateral parietal cortex as densely anatomically connected regions with a central position in the overall network [38,54–62], using various graph measures. For example, a structural vulnerability analysis suggested an important role for the precuneus, insular, superior parietal, and superior frontal regions in global communication processes [62]. A similar central role for the precuneus and superior frontal gyrus emerged from applying measures of node degree and betweenness centrality [61].

Ranking of brain regions according to their score on multiple centrality metrics (e.g., degree, betweenness, and closeness centrality) confirmed a central network position for the medial parietal, frontal, and insular regions [38,55,56,59,63,64], findings shown to be consistent across different cortical and subcortical parcellations.

These network-based classifications of structural brain hubs are consistent with classic work on the functional importance of these medial parietal, frontal, and insular regions. Electrophysiological recordings have long reported the involvement of cortical association areas in various cognitive tasks, classifying them as transmodal or heteromodal areas that are involved in a broad range of cognitive processes [14]. Network analysis now suggests that the integrative and diverse properties of these regions are due to their central embedding within the connection topology of the brain, which is in line with the idea that functional properties of regions are shaped by their ‘connectional fingerprint’ [65].

Recent observations have suggested that structural brain hubs are not only highly connected with the rest of the brain, but also maintain a high number of anatomical connections among each other. Examining the level of connectivity of hub nodes, graph analytical studies of structural brain networks have noted that brain hub regions are more densely interconnected than predicted on the basis of their degree alone, hence giving rise to the formation of a densely interconnected ‘core’ [63,66] or rich club [54,57,64,67,68]. Rich-club organization of neural hubs may have important functional consequences by boosting the robustness of inter-hub communication and promoting efficient communication and functional integration across the brain.

Besides dense anatomical connectivity, several other structural and functional aspects of neural architecture classify these candidate hub regions as exceptional or ‘rich’ (Box 1). Structural network hubs and their associated connections occupy disproportionately high levels of wiring



**Figure 2.** Empirical results on structural hubs. Collected findings on structural hubs in the human cerebral cortex, derived from diffusion imaging data. (A) A centrality map showing the distribution of betweenness centrality scores across cortical regions, identifying the dorsal superior prefrontal cortex (I), the precuneus (II), and the superior and medial occipital gyrus (III) as highly central regions. (B) A group-averaged cortical map of an accumulated score of nodes belonging to the highest-ranking nodes across several graph metrics (e.g., degree centrality, shortest path length, betweenness centrality), identifying the precuneus (a), posterior cingulate cortex (b), anterior cingulate cortex (c), superior frontal cortex (d), dorsolateral prefrontal cortex (e), and insular cortex (f) as well as regions of the occipital (g) and superior and middle temporal gyrus (h) as central brain regions. (C) Illustrates the consistency of structural hub classification (by distribution of node degree scores) between two subjects (subject 1 and subject 2) and two acquisition methods (diffusion tensor imaging [DTI], high-angular resolution diffusion imaging [HARDI]). (A) Adapted and reproduced from [61], (B) adapted and reproduced from [38], (C) adapted and reproduced from [60].



### Box 1. The ‘richness’ of hubs

Both theoretical and empirical observations have led to the hypothesis that the architecture of neural systems is shaped by a trade-off between the optimization of wiring cost and the efficiency of neural communication [112,146,155,156]. In the context of such a trade-off, structural hub nodes have been noted to represent a high-cost feature of brain connectivity, due to their dense connection patterns. In addition to a high level of physical connectivity, several other aspects may classify hub regions as exceptional or ‘rich’ elements of neural architecture. For example, hub connections have been noted to link regions over long distances, thus accounting for a disproportionately large share of the brain’s total wiring length [54,144]. In addition, in humans, hub connections tend to exhibit a high level of wiring volume and high levels of white matter organization [69], aspects that may confer several important advantages for neural communication, including more direct communication paths, shorter transmission delays, and higher levels of robustness [146]. On the more microscopic level, cellular studies have reported that putative hubs like cortical association areas exhibit greater spine density compared with primary unimodal regions [157]. These cost-related and complex attributes of macroscopic and microscopic connectivity, combined with the high rate of neural processing and information flow across hubs, are likely to impose high demands on the metabolic activity of hub regions [69,112]. Several studies monitoring cortical blood flow and the metabolic activity of brain regions have indeed ranked cortical hubs among the metabolically most active areas of the cortex [158,159]. Further observations have suggested that hub regions display distinct developmental trajectories [108], that they show high levels of variability across individuals [160], and that their level of cost-efficient wiring is under strong genetic control [98].

In all, hubs tend to constitute a ‘high-cost, high-value’ attribute of neural architecture. High levels of macroscopic wiring volume, elaborate white matter microstructure, high spine density, and high energy consumption make hub regions a high-cost feature of brain architecture, but this high cost is offset by the functional benefits that hub nodes and connections confer on neural communication and information integration in the brain [69,112].

volume, are among the most metabolically active regions in the brain, and display complex cellular and microcircuit properties [69]. Jointly, these distinctive attributes of network hubs may be indicative of differences in their local physiology, energy metabolism, and neural processing that set them apart from other, less-central network elements.

Structural hubs have been identified not only in the human brain but also in several other mammalian species and by different data-collection methodologies (Box 2 and Figure 3). The location of network hubs within the cerebral cortex has been remarkably consistent, with graph analyses of human, macaque, and cat brain networks converging on a set of high-degree regions in the parietal, frontal, and insular cortices [56,57,70–74]. High-degree ‘hub neurons’ have also been shown to be present in the neuronal network of *C. elegans*, suggesting that the existence of network hubs may be a universal feature of connectome organization across many, if not all species with a central nervous system. This universality may be related to obligatory trade-offs between wiring cost, spatial and metabolic constraints, and optimization of network performance [69,75].

#### Functional hubs

In addition to the classification of hubs on the basis of anatomical connectivity, numerous studies have also examined the existence of ‘functional hubs’ derived from

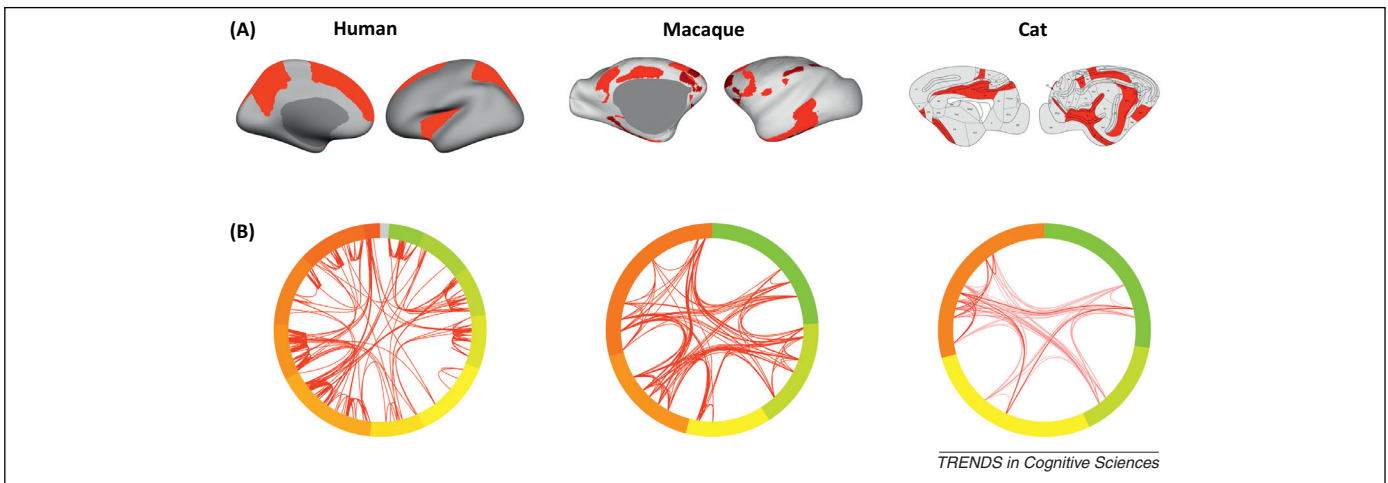
### Box 2. Brain hubs across species

The presence of highly connected and highly central hub nodes has been established in virtually all brain networks across a wide range of species, ranging from the mammalian [32,61,63,67,73,143,161], rodent [162], and avian [163] brain to cellular networks in the zebrafish larva [164], the fruit fly *Drosophila* [165], and the nematode *Caenorhabditis. elegans* [166,167]. Early anatomical studies reported on the existence of a small number of cortical regions in the macaque (including occipital area 19, parietal area 7a, the posterior cingulate, frontal area 46A, and the superior temporal gyrus [10]) and the cat cortex (including the cingulate gyrus CGa, CGp, parietal area 7, frontal/temporal areas 35 and 36, and the prefrontal and insular Ia and Ig cortex [168]) that showed a dense and widespread level of connectivity. More recent graph-theoretical analysis identified various hub regions in the parietal, temporal, and prefrontal cortex of the macaque and the cat cortex that were not only densely connected to the rest of the brain but also centrally positioned with respect to short communication paths [32]. Other studies have confirmed the central placement of medial frontal and parietal regions in the macaque [169] and the cat cortex [70,71], suggesting potential homologies in cortical hub organization across mammalian species [67]. A recent study, directly comparing the spatial location of structural hubs across human, chimpanzee, and macaque cortex [56] identified the medial parietal, cingulate, insular, and ventromedial frontal cortices as densely connected hub regions in all three primate species.

In addition to the presence of central hubs in mammalian species, recent studies have reported rich club organization in several neural systems see Figure 3 in main text, first in the cat neocortex [70–72] and subsequently in the human [54,64] and macaque [144] cortex, the avian brain [163], and *C. elegans* [167]. It appears that the existence of hub nodes and rich clubs is a universal feature of connectome organization across many species.

networks of dynamical interactions between brain regions (Figure 4). Several studies have been conducted on voxel-wise or region-wise functional connectivity matrices, measuring the density or ‘concentration’ of the local and global functional connectivity of network regions. These studies have suggested a strong focus of functional interactions in the ventral and dorsal precuneus, posterior and anterior cingulate gyrus, ventromedial frontal cortex, and inferior parietal brain regions (e.g., [76–79]). The spatial locations of these functional cortical hubs suggest significant overlap with subregions of the default mode network [80].

More recent approaches to detection of functional hubs tend to focus on the characterization of the functional heterogeneity of cortical regions. These methods involve an assessment of the level of coactivation of regions across a wide range of cognitive tasks [43], the participation of cortical hubs in multiple functional domains [81], and an examination of the layout of functional paths within the network’s functional connectivity pattern [82]. The latter study used a ‘step-wise connectivity’ approach tracing information pathways originating from unimodal (e.g., visual, auditory, and motor) regions to higher-order cognitive regions. Regions classified as multimodal and functional hubs included the superior parietal and superior frontal cortex and the anterior and posterior cingulate gyrus as well as portions of the anterior insula, all regions that are part of cognitive resting-state networks such as the default mode and salience-processing networks. Other approaches have aimed to elucidate the heterogeneous character of functional hubs by examining the participation of cortical regions across multiple functional networks



**Figure 3.** Hubs across mammalian species. Collated findings of recent studies showing consistency of cortical hub and rich-club organization across human, macaque, and cat species. **(A)** Cortical maps of hub regions (in red) in the three examined species (left: group-averaged human map, low resolution shown, 34 cortical regions; middle: macaque, 242 cortical regions; right: cat, 65 cortical regions per hemisphere), predominantly overlapping the medial parietal cortex (precuneus/posterior cingulate), cingulate cortex, medial and lateral superior frontal cortex, anterior cingulate cortex, lateral superior parietal cortex, and insular cortex. **(B)** The set of connections spanning between hub nodes (in red) in a circular graph, with the nodes along the ring ordered according to their module assignment, reflecting a structural or functional partitioning of the cortex. This illustrates that hub nodes participate in most functional and structural domains and that white matter pathways (derived from either diffusion imaging or tract tracing) between hub regions strongly contribute to intermodule connections. Data in (A) and (B) adapted and reproduced from [57,67,144].

[79] or the level of overlap between different functional domains [83]. Primary regions (e.g., primary motor, visual, and auditory cortex) were found to predominantly participate in a single or a small number of functional networks, whereas putative hub regions including portions of the medial superior frontal cortex, anterior cingulate cortex, and precuneus/posterior cingulate gyrus were found to participate in multiple functional networks.

The capacity adaptively to link and interact with a highly diverse set of brain regions is a hallmark of ‘flexible network hubs’ and adds the important dimension of time and temporal variability to the definition of functional hub regions. Looking across multiple tasks, recent fMRI studies identified a set of frontoparietal brain regions that participate in various cognitive tasks [43,84,85] whose functional connectivity patterns can be rapidly updated in different task contexts [84]. Studies examining the non-stationary properties of functional interactions of brain regions with magnetoencephalography (MEG) further support a central network role for medial parietal regions. For example, examination of the dynamical synchronization patterns of cortical regions during resting-state MEG recordings show the posterior cingulate cortex to display a high level of cross-network interactions [86], suggesting that this region may serve as a central and flexible network hub.

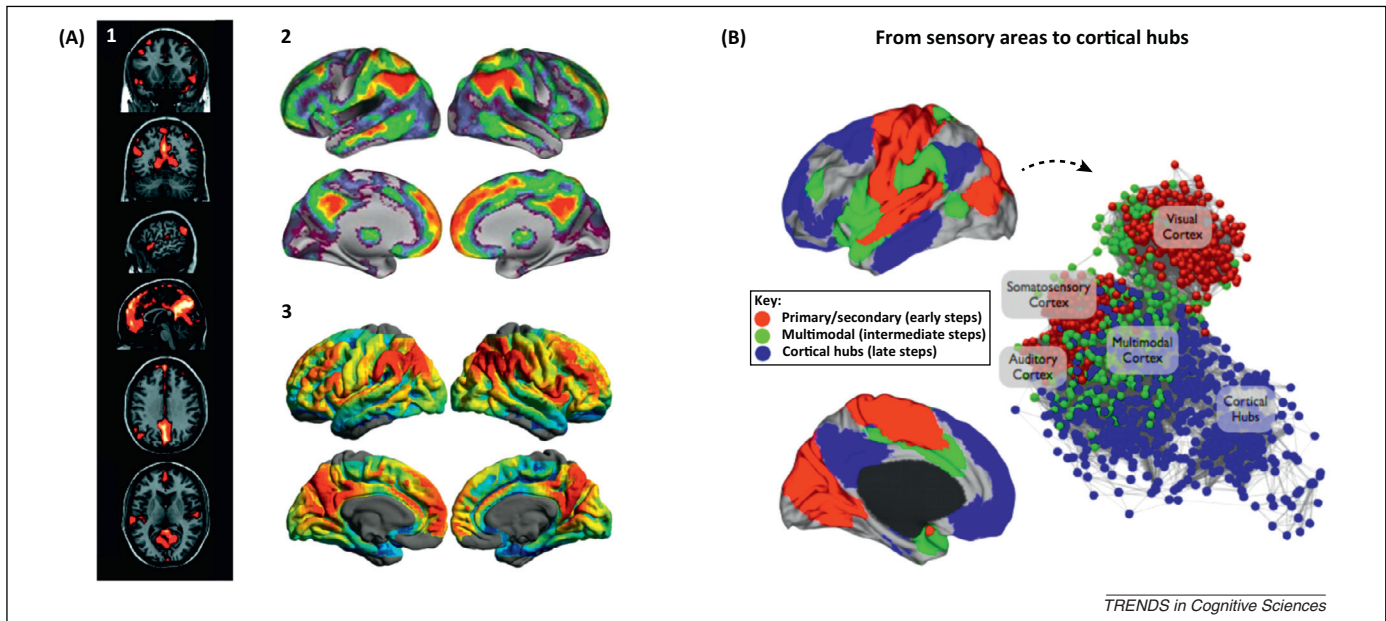
In many studies, the detection of functional hubs is based on graph analysis of functional networks derived from estimates of pair-wise statistical relationships, often simply expressed in terms of correlation coefficients between recorded time series of neuronal or hemodynamic signals [e.g., MEG, electroencephalography (EEG), fMRI resting-state recordings]. Given the wide range of recording empirical approaches and analysis methods, the identification of functional hubs depends on the methodology used for estimating network edges as well as the graph metrics used to express ‘functional centrality’ [78]. For example, some studies have noted high spatial overlap

of functional hubs with regions of the default mode network [79,80,87,88], suggesting a central role for the default mode network in the overall network structure. Others have, however, noted that a high level of functional connectivity of these regions may be due to local interactions within the default mode network [89] and that, more generally, the level of functional degree of a region may be biased by the size of the functional network that a region participates in [53].

#### *Individual differences and development of hubs*

Individual variations in the connectivity profile and level of functional coupling of cortical hubs have been linked to individual differences in intelligence [90–93], performance in different cognitive domains [94], differences in inter-hemispheric integration [95], and individual differences in personality traits [96]. For example, the communication efficiency of medial parietal and prefrontal hub regions has been related to different subscales of intelligence [91] and the level of global connectivity of frontal hub regions was found to predict individual variations in cognitive control and intellectual performance [94]. Furthermore, subtle differences in the functional connectivity profile of a core set of medial parietal and cingulate functional hubs have been associated with inter-subject variability in personality traits such as neuroticism, extraversion, motivation, empathy, and future-oriented thinking [96]. Twin studies have suggested that the topology of functional connectivity in the adult and child brain is highly heritable [97–100], particularly at regions that show a high functional connectivity density [98]. Other studies have demonstrated a strong genetic influence on the structural integrity of long-range white matter tracts, with effects on modulating intellectual performance [101].

Connectome studies across the human life span are beginning to shed light on patterns in the development of network attributes, including the spatial embedding and functional role of brain hubs [102–104]. Cross-sectional



**Figure 4.** Empirical results on hubs derived from functional studies. Findings of a selection of studies examining functional hub formation in human cerebral cortex derived from resting-state functional MRI (fMRI) studies. **(A)** Collated results of three selected resting-state fMRI studies (A-1, A-2, A-3), reporting a high density of functional connectivity in the precuneus/posterior cingulate cortex, lateral inferior parietal cortex, medial orbitofrontal cortex, and medial superior frontal cortex. **(B)** A cortical map resulting from a step-wise connectivity analysis of functional brain networks derived on the basis of resting-state fMRI recording. Following the connections of a functional network step by step starting in primary regions, cortical regions were classified as primary/secondary (first steps, red), multimodal (intermediate steps, green), or cortical hub regions (late steps, blue) based on their position in the traced functional paths. The corresponding network diagram is shown on the right, with nodes colored according to their classification. A-1 adapted and reproduced from [107], A-2 adapted and reproduced from [80], A-3 adapted and reproduced from [78]. (B) Adapted and reproduced from [82].

developmental studies have suggested that structural hubs emerge relatively early during brain development, with connectivity of medial posterior cingulate, frontal, and insular regions already present in the postnatal infant [105] as well as the young child brain [106], but in a relative immature functional state [107] and with functional hubs largely confined to primary visual and motor regions [107]. From childhood to adolescence, hub regions remain relatively stable whereas their interactions with other parts of the network undergo developmental changes [106,108–110] (see also Menon, this issue). For example, the strength of functional interactions between frontal hubs and distributed frontal, parietal, and temporal cortical regions increases from childhood to adolescence [108], including connections within a frontoparietal network implicated in cognitive control. These observations are in line with other data reporting an increase in functional connectivity among association areas [110] as well as a transition from a spatially localized to a more globally distributed functional network organization through brain development [42]. Sex-related differences in hormone levels have been suggested to influence the developmental patterns of white matter brain connectivity during adolescence. For example, high levels of luteinizing hormone have effects on the white matter microstructure of the central cingulate gyrus/cingulum bundle, middle temporal regions, and corpus callosum fiber pathways [111], potentially influencing the efficacy of white matter projections.

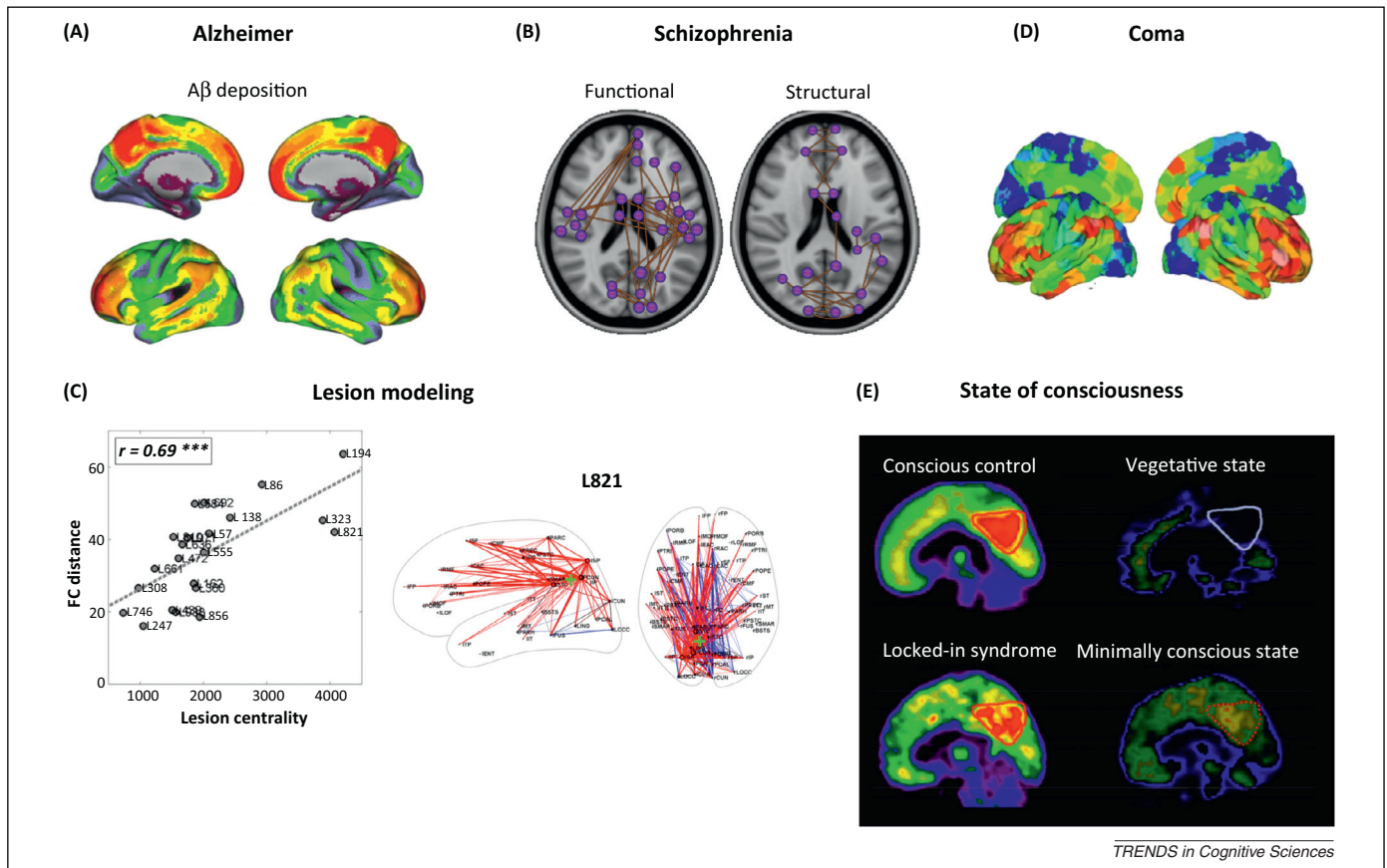
Taken together, these studies suggest that both genetic and environmental factors contribute to subtle individual variation in the development of connectivity that impact the structural and functional connection patterns of hubs, which in turn has an impact on individual variation in

cognition and behavior. Going beyond normal individual variation, abnormal developmental patterns of brain and hub connectivity have been suggested to play an important role in the etiology of neurodevelopmental brain disorders.

#### Hubs in brain dysfunction

Abnormal anatomical connectivity and functioning of hub regions has been hypothesized to relate to behavioral and cognitive impairment in several neurological and psychiatric brain disorders [80,112–114] (Figure 5). For example, analyses of structural and functional connectivity in schizophrenia have shown reduced frontal hub connectivity [38,92,115–118] and disturbed rich club formation in patients [119,120] as well as their offspring [105], which provides empirical evidence for the long-standing dysconnectivity hypothesis of the disease [116]. Developmental studies have reported altered intramodular and intermodular connectivity of densely connected limbic, temporal, and frontal regions in children with autism [121]. Furthermore, childhood-onset schizophrenia has been associated with a disrupted modular architecture [122], together with disturbed connectivity of network connector hubs in multimodal association cortex [123]. In late aging, network analyses applied to neurodegenerative conditions such as Alzheimer's disease [124–127] and frontotemporal dementia (FTD) [128] have indicated the involvement of, respectively, medial parietal and frontal regions in the etiology of these disorders, regions that have high spatial overlap with network hubs. Computational network studies have further hypothesized an important role for the brain's highly connected nodes in the spread of neurodegenerative disease effects within and between functional networks [113,129–132].





**Figure 5.** Hubs in brain disease. (A) A cortical map of amyloid-beta deposition in Alzheimer's disease patients, suggesting a strong involvement of functional hub regions in disease pathology. (B) A functional (left) and structural (right) subnetwork of the most strongly affected connections and regions in schizophrenia (for a review, see [116]). Nodes notably overlap with structural and functional connectivity hubs. (C) Results of a lesion-modeling study simulating the dynamic functional effects of structural damage to specific nodes of the network. Lesion centrality (left) was found to significantly correlate with severity of functional disruption (i.e., cumulative changes in functional connectivity across the brain). The image on the right illustrates increases (blue) and decreases (red) of functional connectivity as a result of structural damage to a highly central portion of cortex located in medial parietal regions of the network (lesion L821). (D) Disrupted functional connectivity in comatose patients, with red regions (overlapping the location of lateral parietal and frontal functional hubs) indicating decreased functional centrality in patients compared with controls. (E) Collated findings from positron emission tomography (PET) data exhibiting the highest levels of metabolism in precuneus/posterior cingulate hub regions in healthy controls ('conscious control') and in patients with a locked-in syndrome, and decreasing levels of precuneus/posterior cingulate metabolism associated with decreasing levels of conscious awareness (from minimally conscious to vegetative state). (A) Adapted and reproduced from [80], (B) adapted and reproduced from [116], (C) adapted and reproduced from [152], (D) adapted and reproduced from [138], (E) adapted and reproduced from [136].

Empirical findings of focal damage as a result of lesions or traumatic injury to cortical network hubs have shown pronounced effects on behavioral and cognitive brain functioning. Focal brain lesions located at cortical regions overlapping functional connector hubs, which play a central role in connecting different functional modules, have been reported to result in widespread disruption of the modular organization of the functional brain network [133]. Furthermore, cognitive decline as a result of traumatic brain injury was found to be associated with white matter damage and reduced integrity of functional brain networks after injury, with particularly strong effects following focal damage to the posterior and anterior cingulate cortex [134,135]. Damage to long-distance connections that are implicated in intermodular communication [57,73] was found to be related to disruptions of network function and cognitive outcome [134].

Several other studies have also reported disruption of connectivity of cortical hub regions in neurological conditions that involve diminished or reduced levels of conscious awareness. Measurements of the regional metabolism of cortical regions derived from positron emission tomography

(PET) data across different stages of coma indicated decreases in metabolic activity in parietal precuneus and posterior cingulate hub regions, with the strongest effects observed in patients in a totally non-responsive vegetative state; the effects are less pronounced in patients who showed remaining levels of awareness [136,137]. Further observations suggest a potential random reorganization of functional hubs in comatose patients [138], with persisting levels of functional connectivity correlated with levels of remaining consciousness in vegetative and minimal consciousness states [139,140].

### Conceptual framework: role of hubs in communication and integration

#### Hubs and network communication

The status of candidate hub regions and their connections as influential network elements rests on their central embedding in the brain's network. This notion implies that neural hubs derive their influence from their strong participation in dynamic interactions due to neuronal signaling that is, from their central role in neuronal communication processes unfolding within the structural



network. The concept of brain hubs is therefore closely linked to an assessment of network communication. An important goal of network analysis is to infer patterns of communication on the basis of network topology, particularly by focusing on the layout of short paths across the network and on the centrality of nodes relative to these paths.

Pursuing this approach, numerous studies of brain networks have focused on network elements that enable efficient signal transmission and information flow along short communication paths. Consistently, network analysis in macroscopic brain networks has suggested that structural and functional hubs play a central role in global brain communication [32,57,61,63,67,141]. The relationship of hub organization and individual differences in cognitive performance [90,91,93] underscores their importance for promoting neural communication and integration in the healthy brain. An interesting corollary of the involvement of hub regions in a disproportional number of communication paths is that this not only makes them focal points of neural communication, but may also render them potential neural ‘bottlenecks’ of information flow, possibly defining capacity limits in cognitive processing [66,142]. Capacity limits due to hubs may not only set upper bounds for neural integration but may also be essential for the chaining or serializing of mental operations [66].

Disruption of brain communication may also be an important factor in brain and mental disorders. Viewed from a network perspective, brain and mental disorders result from disturbances of patterns of structural and functional connectivity. Based on network models of brain function, disturbances of hub regions or their interconnections are likely to cause severe impairments due to their influential role in global integrative processes. Indeed, as discussed above, disease-related disruptions of hub nodes and hub connections are associated with numerous manifestations of brain dysfunction [112] (see also Rubinov and Bullmore, this issue).

Several limitations of current models of network communication should be mentioned. First, current large-scale models of communication in the human brain capture only inter-regional projections (accounting for only a small proportion of all neural connectivity) and do not include networks of local circuits. Local processing of neural signals is undoubtedly an important aspect of brain communication because it involves the transformation and recoding of neural messages at each node of the network. Second, it should be noted that current graph-based analyses of communication cannot fully predict dynamic (i.e., time-varying) patterns of communication. Factors influencing the dynamics of neuronal time series such as local firing rates of neurons and/or level of activity, external inputs or task demands, coherent phase relationships, or synaptic efficacy are generally not incorporated into current graph analyses. Furthermore, some sets of nodes may preferentially engage in neural communication processes whereas others may do so only rarely or never. More sophisticated studies of neural communication would benefit from multimodal imaging or the joint recording of anatomical networks and neuronal time series, ideally at the level of neuronal spike or population activity. To

be applicable in the human brain, the latter will require the development of entirely new methods for the noninvasive observation of brain dynamics. Third, and related to the previous point, many graph-based analyses of network communication operate on the assumption that network nodes connect along the most efficient (i.e., topologically shortest) paths. However, this assumption implies that such paths are accessible and that path length is the dominant criterion for path selection. Determining whether short paths are indeed privileged in this regard would require more detailed neurophysiological studies that track actual network paths of information flow. We would note that most of these limitations are not intrinsic to network models, but rather reflect our ignorance and lack of data on the detailed anatomy and specific patterns of dynamic interactions in brain networks. Once such data become available, more capable and realistic network models of communication can be designed and empirically tested.

### *Hubs as sources and sinks*

Tract tracing and other invasive methods for measuring anatomical connections in non-human species allow insight into the directionality of neuronal pathways and have revealed a high incidence of nonreciprocal inter-regional projections [143]. Studies examining the total sum of afferent and efferent connections of hub regions in such data sets have suggested that some cortical hub regions maintain an unequal balance of incoming and outgoing projections. This imbalance suggests a potential role for these cortical hub regions as neural communication ‘sources’ and ‘sinks’. Analysis of the macroscopic macaque brain network identified several hub regions including portions of frontal and paracingulate cortex as net receivers (i.e., neural sinks), whereas hubs in the cingulate, entorhinal, and insular cortex have been identified as net emitters (i.e., neural sources) [144]. This distribution of structural hubs is consistent with reports on the inferred directionality of functional interactions in the human brain, categorizing hubs in medial regions – including posterior cingulate, precuneus, and medial frontal cortex – as ‘driven hubs’ and central brain regions of attentional networks – including dorsal prefrontal, posterior parietal, visual, and insular cortex – as ‘driving hubs’ [109,145]. A more direct assessment of hubs as sources or sinks in the human brain requires new methodologies for detecting the directionality of anatomical projections or of dynamic information flow *in vivo*.

### *Hub connections*

The central position of brain hubs in neural systems is further underscored by the proposed role of their connections (edges) in neural signaling and communication [57,67,69,71]. Some recent studies have taken an ‘edge-centric’ perspective on network architecture by focusing on the influence of edges on network organization rather than focusing on the role of nodes. These studies have consistently shown a highly central position of hub-related edges within the overall network. For example, edges linking hub nodes to each other, together with edges linking hub nodes to non-hub nodes, comprise a large proportion of all

spatially long-distance connections, absorb a large proportion of all shortest communication paths in neural systems, and display a high level of communication efficacy [54,67,144]. Dense connections between cortical hubs may thus promote short communication relays, efficient neural communication, and robustness of inter-hub communication. Short paths have been suggested to confer several advantages on communication in neural systems, including shorter transmission delays, reduced interference and noise during communication [146], and faster synchronization [68]. Short communication paths have long been regarded as a defining feature of ‘small-world’ networks, which combine high clustering with short path length due to the placement of a small number of random long-distance shortcuts among locally connected nodes. Going beyond this classical small world, hub models of brain connectivity suggest that these shortcuts are not randomly placed within the network’s architecture, but rather aggregate at hub nodes [54].

The widespread spatial distribution of hubs and the aggregation of shortcuts involving hub edges may be seen as a potential anatomical backbone for global brain communication, centralizing synchronization [147] and offering the anatomical infrastructure to route information flow efficiently between brain regions [54]. Consistent with this idea, studies combining estimates of macroscopic structural connectivity derived from diffusion imaging and estimates of functional connectivity derived from resting-state fMRI recordings have revealed a disproportionately strong presence of hub connections among white matter pathways linking different structural modules and functional resting-state networks, thus suggesting an important role of hub edges in intermodular neural communication [57,67]. Computational studies further underscore a central role of hub edges in global communication, showing a disproportional impact of damage to hub edges on the modularity structure and functional dynamics of the system [64,68,119].

#### *Hubs and cross-modal integration*

Neuronal communication occurring within the structural network is a critical prerequisite for brain function. With hub nodes and their connections attracting and disseminating a large number of all neural communication paths, brain hubs and their connections, as a system, have been hypothesized as a convergent structure for integration of information, together forming a putative anatomical substrate for a functional ‘global workspace’. Such a workspace is hypothesized as a cognitive architecture in which segregated functional systems can share and integrate information by means of neuronal interactions, with an important role for pathways that link central regions and constitute a global workspace. Closely related to the notion of global workspace, the ‘connective core hypothesis’ [66] suggests that interconnected hub regions that are topologically central offer an important substrate for cognitive integration, not only for broadcasting and dynamic coupling of neural signals but also by offering an ‘arena for dynamic cooperation and competition’ among otherwise segregated information [148].

The network basis of the global workspace or connective core may correspond to projections crosslinking hubs into a coherent rich club network that spans multiple modalities. Supporting this idea, cross-modal analyses of structural and functional human brain connectivity have noted the strong presence of hub regions across areas of the cortex in which multiple functional domains overlap [67,79,149], forming ‘confluence zones’ or ‘convergence zones’ of neural interactions [57,107]. Network analyses employing overlapping node community detection algorithms, which allow nodes to participate in multiple modules, reveal a strong involvement of hub nodes in intermodular connectivity [67], consistent with the idea that hub edges crosslink multiple functional domains [57,81,82]. A network of dense, intermodular, and reciprocal hub connections bridging different functional domains and spanning functionally heterogeneous brain regions may thus form a promising anatomical substrate for neural integration and competition in the brain.

#### *Hubs in computational models of brain dynamics*

The availability of structural connectivity maps in conjunction with biophysical models simulating the dynamic behavior of neural populations has enabled the construction of computational models of large-scale brain networks. Several such models have suggested that hubs play key roles in enabling high levels of functional diversity and functional synchronization between cortical regions. For example, a model of spontaneous neural activity incorporating a synchrony-based activity-dependent rewiring rule showed that highly central hub nodes engaged on more variable or noisy dynamics, resulting in a higher likelihood of structural rewiring [150]. A computational model of synchronization in the cat cortex has demonstrated that highly connected network hub nodes and their connections dominate the dynamical organization of the system, playing key roles in the transition from desynchronized to centrally synchronized dynamics [68]. Other neural models estimating the theoretical levels of functional configurations across numerous toy networks have shown the emergence of the highest functional diversity in networks with a scale-free hub architecture compared with other types of network architecture (e.g., random, regular or small-world networks) [147,151]. Finally, network models predict lesions to hub nodes and hub edges to be among the most disruptive for overall network organization and functioning, effects that appear to overlap with empirical observations of focal brain damage (see section on hubs in brain dysfunction and Figure 5). Furthermore, computational vulnerability analyses, modeling the effects of anatomical lesions on overall network structure and neural dynamics, have shown disproportional effects of damage to cortical hubs and hub connections on the modularity structure [57] and functional dynamics of the network [152,153]. Jointly, these computational simulations indicate network hubs as loci of high variability and plasticity in conjunction with an important role in maintaining the cortical synchronization, modularity structure, and functional dynamics of the network at a system level.

### Box 3. Outstanding questions

- What is the most sensitive and reliable way to detect network hubs?
- To what extent can structural network models of the brain predict the location of functional hubs?
- Do hub nodes differ from non-hubs in their gene-expression and metabolic profiles?
- What are the developmental mechanisms through which hub regions emerge?
- To what extent do hubs form global sources and sinks of neural activity?
- Which brain and mental disorders can be understood as 'disorders of brain network communication'?
- Are brain hubs potential 'hot spots' for developing new diagnostic biomarkers or attractive targets for therapeutic intervention?

### Concluding remarks

Complex cognitive operations emerge from the coordinated activity of large neuronal populations in distributed brain networks. Network theory identifies several highly connected and highly central hub regions and predicts that these network hubs and their connections play key roles in the integration of information and in efficient neuronal signaling and communication in the brain. Network analysis tools applied to structural and functional human connectome data provide a data-driven computational framework for detecting brain network hubs and for examining their variation across individuals, their development across time, and their roles in brain disorders. Numerous open questions remain to be addressed (Box 3). Importantly, future conceptual progress will depend on close dialog between theoretical network models and empirical studies of network function. For example, the central placement of hub nodes and edges in network models makes specific predictions about the neural substrate of integrative brain function. These predictions can be tested by manipulating (stimulating or silencing) specific network elements through modern interventional techniques followed by observation of functional consequences. Another important avenue may include the development of neurobiologically realistic computational models to simulate the dynamics of neural systems, which will allow for a more systematic and in-depth examination of the putative function of brain hubs in neural communication and integration. Network approaches to neuroscience are currently accelerating at a rapid pace, propelled by the availability of 'big data' [154], an expanding computational infrastructure, and the formation of large-scale research consortia and initiatives focused on mapping brain connectivity. As these developments unfold, it seems certain that the study of brain network hubs will remain an enduring theme in the quest to better understand the complex function of the human brain.

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