Network attributes for segregation and integration in the human brain

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Network studies of large-scale brain connectivity have begun to reveal attributes that promote the segregation and integration of neural information: communities and hubs. Network communities are sets of regions that are strongly interconnected among each other while connections between members of different communities are less dense. The clustered connectivity of network communities supports functional segregation and specialization. Network hubs link communities to one another and ensure efficient communication and information integration. This review surveys a number of recent reports on network communities and hubs, and their role in integrative processes. An emerging focus is the shifting balance between segregation and integration over time, which manifest in continuously changing patterns of functional interactions between regions, circuits and systems.

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Introduction

Recent years have seen a sharp increase in empirical and theoretical studies of networks as models of complex systems. In neuroscience, the rising interest in brain networks is driven by the increasing availability of network data on the structure and function of neural systems. Such networks or graphs, described as collections of nodes (neurons, regions) and edges (connections, pathways) can be analyzed with a wide array of quantitative tools and methods (Figure 1) [1–7]. Importantly, network science not only provides intuitive and analytically powerful approaches for data analysis and modeling, it also offers a comprehensive theoretical framework for understanding the biological basis of brain function [8]. This framework bridges and unifies the domains of neuroanatomy ('structural connectivity' [9]) and brain dynamics ('functional and effective connectivity' [10]) by linking neuronal operations

(measured empirically or generated computationally) to an underlying anatomical substrate.

This review article surveys a selection of recent studies on large-scale brain networks, mostly obtained from noninvasive imaging of the human brain. What these studies have in common is that they use network approaches to gain insight into the basis of integrative brain function. Structural connections are fundamental in this regard because they allow neural elements to coordinate their activity into coherent dynamic states that support cognition and behavior. To achieve such coherent dynamics, structural networks shape the flow of information between local regions of the brain to accomplish two distinct goals (Figure 1): firstly they promote functional segregation by forming local network communities that are intrinsically densely connected and strongly coupled; and secondly they promote functional integration by enabling global communication between communities through network hubs. The balance between segregation and integration is essential for the operation of distributed networks underlying cognitive function [11,12]. The remainder of this review will survey recent studies that have identified network architectures and mechanisms that promote segregation, integration, and their dynamic interplay.

Segregation: network communities

Functional segregation refers to neuronal processing carried out among functionally related regions arranged within modules. In networks such modules correspond to 'communities' defined by high density of connectivity among members of the same community and low density of connections between members of different communities. This arrangement of connections tends to generate statistical dependence of neural signals within modules and statistical independence between modules, and hence promotes functional segregation. Network communities can be objectively detected with a broad spectrum of network measures and algorithms [13] which reveal not only their composition, but also their interconnections and dependencies. Virtually all studies of brain networks have demonstrated interlinked communities that form a partly decomposable modular architecture. Such architectures are hallmarks of complex systems [14] and are thought to be of fundamental importance for understanding mental processing and cognition [15]. In the brain, hierarchies of linked communities span across several levels including brain regions, functional circuits and large-scale networks.
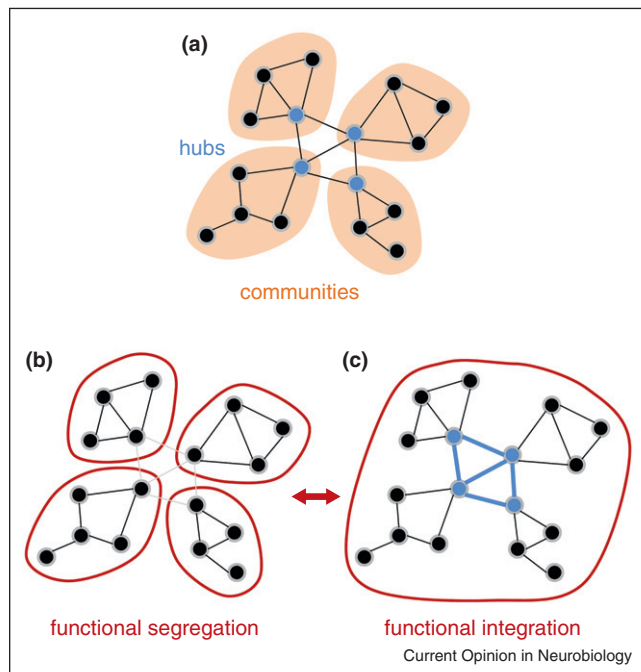
Communities and hubs, segregation and integration. **(a)** Schematic diagram showing a set of nodes and edges arranged into a network comprised four network communities (orange) interconnected by highly connected and highly central network hubs (blue). Note that network hubs are linked by structural connections. If these connections are denser than predicted by a degree-preserving random model, these hubs are said to form a 'rich club'. **(b)** Functional segregation indicated by strong functional coupling within communities (red) with little or no functional coupling across communities. **(c)** Functional integration indicated by globally strong functional coupling, including strong information flow across network hubs and their mutual interconnections (blue).

All network studies must begin with a definition of the network's nodes and edges [2]. In brain networks, nodes are variously taken to be individual voxels, randomly selected and uniformly distributed voxel clusters, or brain regions whose boundaries are defined either on the basis of gray matter boundaries, anatomical landmarks, functional task-evoked activations, or connectivity profiles. The initial step of node definition is particularly crucial for studies of cerebral cortex where the detection of anatomically and/or functionally coherent regions remains challenging [16]. Until now, the majority of studies have defined network nodes based on voxels or atlas-based partitions. More recent studies have devised data-driven regional parcellation strategies based on myelination patterns [17] and connectivity profiles [18–20]. Particularly promising are multimodal approaches, for example combining resting-state functional connectivity with data on task-related activations [21••] (Figure 2a) or with meta-analytic coactivation analysis [22], or combining boundary detection in structural and functional brain networks [23]. The latter approach capitalizes on the notion that if structural connections determine regional functional specialization, then regions with an internally coherent structural connection profile should also exhibit coherent functional responses. Some recent studies have lent support to this notion. Paralleling earlier reports [19], a recent study of cingulate cortex found mutual agreement between partitions detected with anatomical and functional parcellation strategies [24]. A study of the temporoparietal junction first identified anatomical subdivisions based on differences in their structural connectivity profiles and then determined their patterns of functional connectivity across the brain [25]. Similarly, a clustering algorithm applied to resting-state fMRI connectivity data was used to detect regional subdivisions with distinct functional connectivity profiles in the human orbitofrontal cortex [26]. Multimodal parcellation of the human insula [27] by clustering data on task activation, resting-state functional connectivity and gray matter structure revealed a consistent partition into subregions associated with different cognitive and behavioral processes. These studies highlight the power of connectivity-based approaches to identify functionally distinct regions.

As some of these examples indicate, parcellation studies aiming at the detection of clusters or modules in structural and/or functional connectivity often result not only in the definition of regional subdivisions but also to the mapping of functional circuits interconnecting different sets of spatially distributed regions. For example, an analysis of resting-state functional connectivity patterns revealed several subdivisions within the human precuneus, each of which participated in a different set of functional circuits linking distant regions of the cortex [28]. Employing a similar clustering approach to functional connectivity patterns of the default mode network suggested that the network can be subdivided into structural components and intrinsic circuits that are associated with different mental processes [29]. More recently, cluster analysis of resting-state functional connectivity in macaque cingulate cortex was used to identify a number of component networks, each putatively associated with distinct subdomains of cognitive function [30]. What these studies have in common is that they use network-based clustering techniques to delineate 'networks of regions' comprising anatomically distinct functional circuits that are associated with different cognitive domains.

Various decomposition or clustering approaches (based on independent component analysis, seed-based connectivity, or graphs) applied to whole-brain resting-state fMRI data have revealed that spontaneous BOLD signal fluctuations are organized into a set of distinct large-scale components, often identified as 'resting-state networks' (RSNs) or intrinsic connectivity networks (to better reflect their role in task-states). Analyses of structural

Figure 2
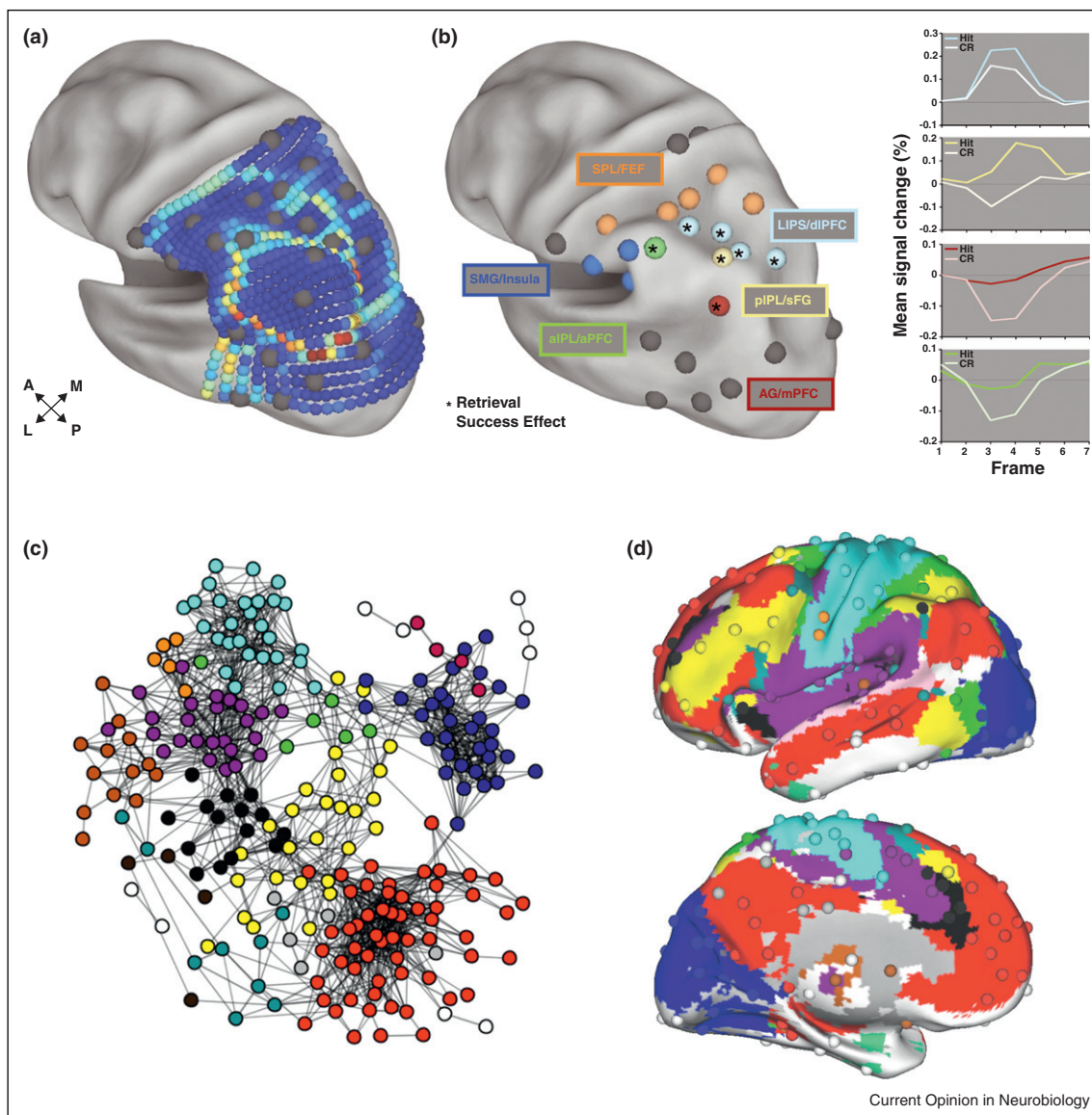
Regional parcellation and definition of network communities. **(a)** The left panel shows the mapping of boundaries based on variations in the connectivity profile of resting-state fMRI. Hot colors indicate discontinuities of these profiles indicative of putative regional boundaries, while cool colors indicate regions with relatively stable connectivity profiles. Peaks of stability are indicated by gray spheres and denote the centers of putative cortical regions. **(b)** These peaks are displayed again in this panel and are colored according to their membership in network communities. Time courses on the right show functional activation patterns (of the regions marked with an asterisk) observed during memory retrieval tasks. Note that regions belonging to different network communities identified based on resting-state data exhibit distinct functional activation patterns. **(c)** A network of resting-state functional connectivity, estimated across a set of cortical regions. The network was formed by retaining the top 4% of the strongest connections and is displayed using a layout algorithm optimized for visualizing graph structure in 2 dimensions. A detection algorithm was used to identify network communities, and nodes are colored according to their community membership. **(d)** Spheres on the surface of the right hemisphere of the cortex correspond to the locations of the regions forming the graph in panel **(c)** and their colors correspond to their community membership. The surface color is derived from a parallel network community analysis derived from a voxel-wise graph. Communities correspond closely to resting-state networks. Panels **(a)** and **(b)** are modified and reproduced from [21[••]]. Panels **(c)** and **(d)** are modified and reproduced from [33[••]].

and functional connectivity have shown that RSNs form networks that are intrinsically anatomically connected [31,32]. Several recent studies have attempted to create comprehensive maps of RSNs across the human brain. Using network-based community detection, a recent study described consistent sets of subgraphs (corresponding to modules or RSNs) in whole-brain networks constructed from a novel regional parcellation as well as a modified voxel-wise graph that excluded short-range functional couplings [33[••]] (Figure 2b). Using

independent component analysis, another study identified a total of 23 RSNs, arranged into a nested hierarchy along two main branches corresponding to brain systems associated with intrinsic and extrinsic processing [34]. Using a clustering algorithm, a third study derived a partition into 17 components, consistently identified in a discovery and replication data set [35••]. All three studies were able to draw clear relationships between the functional anatomy of the detected components, clusters or communities, and functional systems that are defined on the basis of task-evoked coactivation. This relationship between task-free and task-derived components is in agreement with meta-analyses of fMRI activation studies and RSNs, which have demonstrated associations between anatomically distinct RSNs and specific behavioral and cognitive domains [36].

Until now, only a small number of studies have directly examined how functional components or RSNs are related to each other. Most clustering techniques, including independent component analysis, generally assign regions or nodes to a single cluster, but do not provide information on the stability of these assignments, on possible overlap between clusters (including the possibility that regions or nodes belong to more than one cluster), or on how these clusters are interconnected. New methodological developments in network science, for example involving link-based communities [37] and consensus clustering [38], may soon offer a new perspective on brain network organization. One future focus is likely on network hierarchies. Some studies have provided evidence for hierarchical organization of brain regions in structural networks (e.g. [39]) and of RSNs in functional networks (e.g. [34]). Hierarchical organization of RSNs was explicitly examined in a recent study [40] which applied a data-driven clustering algorithm to resting-state fMRI time series. The analysis detected a number of multi-cluster solutions with clusters (corresponding to RSNs) that were hierarchically arranged. Some portions of the cortex exhibited uncertain cluster assignments, representing areas of overlap between otherwise segregated networks. Future studies are needed to test if these areas of overlap are involved in linking RSNs, perhaps through network hubs (see next section).

The emerging picture suggests that brain networks generally exhibit complex community structure, encountered with some consistency across studies and methods in both structural and functional domains. It appears that this community structure defines a hierarchy of individual brain regions, linking regions into functional circuits, and large-scale networks corresponding to RSNs. There are many open questions: Are all brain regions demarcated by equally sharp anatomical and functional boundaries? What is the relationship of structural network communities to functional components or RSNs? How do RSNs communicate with each other, and does such communication take place continuously or intermittently? Answering this last question will require a deeper understanding of integration and the role of network hubs.

Integration: network hubs

Integrative processes in networks can be viewed from at least two different perspectives, one based on the efficiency of global communication and another on the ability of the network to integrate distributed information. A widely used measure of global communication efficiency in networks [41] essentially captures the average length of the shortest communication paths between any two nodes. However, this measure is often found to be maximized in networks with random topology, that is networks that do not have pronounced community structure and hence allow for very little segregated information. In addition, direct paths for global communication do not provide a means for information integration, generally thought to involve the convergence and joint processing of specialized information derived from diverse sources. Recent studies of structural brain networks have revealed two important network attributes that jointly promote the integration of information: the existence of highly connected and highly central brain regions representing 'network hubs', and a high propensity for these network hubs to be mutually interconnected.

Hub nodes in structural networks can be defined on a number of (often correlated) criteria, including the number of connections they maintain (their degree), the number of paths they contribute to (their betweenness centrality), or their connection diversity relative to a given modular partition [42]. Using one or several of these metrics, several recent studies of networks derived from diffusion imaging and tractography [43,44,45•] have identified specific cortical regions as putative hubs, with some of them aggregated into a highly resilient structural core [46]. While the detection of hub nodes in structural networks rests on the 'ground truth' of the brain's wiring, hubs in functional networks are less clearly defined and are dependent on recording parameters and methodology. Various approaches have been used to define functional hubs [47], most prominently among them the local density of strong functional connections [48,49]. A comparison of different measures for characterizing the functional centrality of brain regions demonstrated that each of them tends to highlight different aspects of local and global information flow, with significant differences in the ranking of regions across different measures [50]. The difficulty to unambiguously define functional network hubs strongly argues for the importance of putting dynamic observations on a firm structural basis, by adding data on underlying anatomical connections and modeling structure–function relations.

New avenues for characterizing functional hubs involve the use of activation and connectivity data obtained from resting-state and task-evoked fMRI recordings [51•], as

well as probing for regions of convergence of multiple connectivity paths traced in functional networks [52•] (Figure 3a). A measure of weighted degree centrality [53] was used to characterize the resting-state level of global connectivity of brain regions including several that were previously identified as 'cognitive control regions' in MRI activation data [51•]. These regions, including portions of the lateral prefrontal cortex, were indeed found to be highly ranked in terms of global connectivity, and their level of connectivity was found to be predictive of individual differences in cognitive performance. A different study [52•] used a novel approach called 'stepwise functional connectivity' to identify a central multimodal integration network based on resting-state data. By placing seed nodes in unimodal cortex and then tracking paths of increasing lengths across the functional network, this technique allows for detecting regions where unimodal influences converge onto putative multimodal integration centers. Regions identified by using this approach included the superior parietal cortex, dorsolateral prefrontal cortex, the dorsal anterior cingulate, the parietal operculum, and portions of the anterior insula. While the characterization of

functional hubs continues to be an area that is still in flux, these and other studies appear to point toward a convergent set of brain regions involved in functional integration.

The role of structural network hubs for maintaining global network integrity has been examined in computational models that link structure (connectivity) to function (dynamics). These models consistently show that network damage of hub regions leads to structural disconnection causing disruption or loss of functional connectivity. Some early studies have investigated network damage in large-scale simulations of spontaneous neural activity and their associated BOLD signal fluctuations unfolding in an empirically measured structural brain network [54,55]. Damage to the structural network, for example the loss of specific brain regions and their associated structural connections, resulted in disrupted patterns of functional connectivity, and the spatial extent and magnitude of the disruption was partly accounted for by the centrality of the lesion site. Empirical studies of human brain lesions support the predictions of these computational models regarding long-distance and

Figure 3
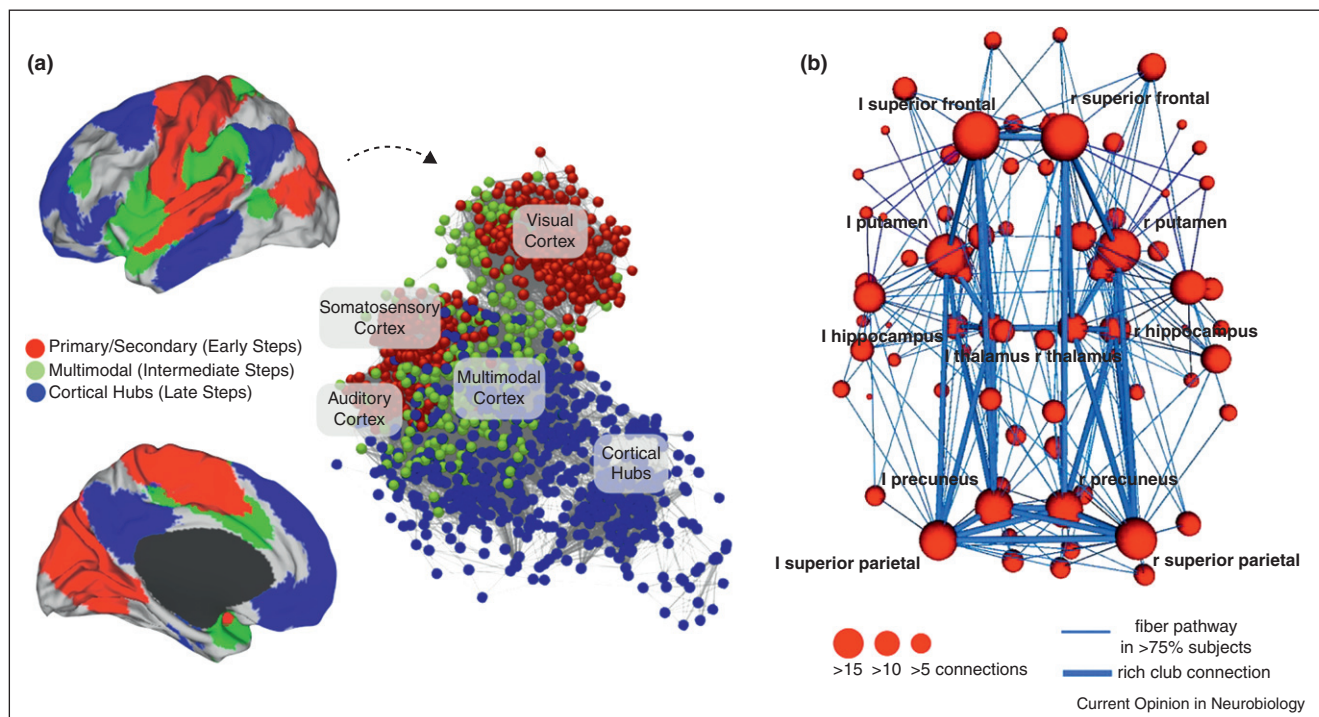
Identifying network for global integration. **(a)** A cortical map of primary/secondary regions, multimodal regions and cortical hubs, derived from a stepwise functional connectivity analysis of resting-state data. The analysis proceeds by placing seeds in primary sensory and motor regions and then tracing strong functional connections in multiple steps. These steps converge onto multimodal cortex and finally on highly central cortical hubs. A corresponding network diagram is shown on the right. **(b)** A spatial plot of brain regions and their structural connections estimated from diffusion imaging and tractography. Positions of spheres correspond to the region's center-of-mass anatomical coordinates and their size corresponds to their number of connections. Rich club regions were identified based on mutual connection density and a statistical comparison to an appropriate random null model. Connections between rich club regions are shown as thick blue lines and connections from rich club regions to other regions of the brain are shown as thin blue lines (other pathways are not shown). Note the distributed locations of rich club regions, their bilateral symmetry and prominent long-distance interregional pathways. Panel **(a)** modified and reproduced from [52•], and panel **(b)** modified and reproduced from [60••].

distributed effects on functional connectivity [56] and greater magnitude of effects following lesions of network hubs [57]. More recent modeling studies have confirmed the impact of structural disconnection on disturbances of functional connectivity, and have examined possible implications for brain disorders such as schizophrenia [58] and neurodegenerative conditions [59].

A number of recent studies have focused on the interconnections between brain hubs as a potential substrate for central integrative processes. An important aspect of the structural organization of the human connectome is the existence of a prominent 'rich club' [60••] (Figure 3b), defined as a set of highly connected and highly central nodes that are more densely interconnected than expected based on comparisons to degree-preserving null models [61]. The cortical rich club included parts of the superior parietal cortex, the precuneus and posterior cingulate cortex, the anterior cingulate cortex, and the insula. A largely consistent set of homologous regions has been identified in an analysis of the rich club in macaque cerebral cortex derived from tract tracing data [62]. An analysis of short communication paths across the human and macaque cortex revealed that a large number of such paths travel through rich club regions and involve connections linking two or more rich club regions to one another [62,63]. This finding suggests that the brain's rich club attracts and disseminates a large proportion of global communication, thus serving to integrate information across segregated communities and networks. The analysis also suggests that these significant functional benefits come at a cost to the brain's economy [64]. While enabling high efficiency in global communication, rich club connections tend to span long distances and thus consume valuable resources of brain volume, material and energy.

The brain's rich club or 'connective core' may be an essential prerequisite for enabling neural processes underlying cognitive integration that become engaged in the coupling of neural resources relevant to sensorimotor processes, in response to different attentional demands, and in the course of both short-term and long-term memory [65]. The topologically central position of the core or rich club ensures the convergence and divergence of information and allows for its integrated processing. Rich club connectivity offers a potential network substrate for a 'global neuronal workspace', a key component of recent theories of higher cognition and consciousness [66,67]. Future work is needed to investigate the role of rich club regions and connections in brain disorders affecting integrative processes, and their development across the life span.

Segregation and integration across time and task: network dynamics

To date, most studies of structural or functional brain networks have built on static descriptions of network matrices, which represent a simple summary of brain structure and dynamics sampled over longer time spans. However, structural connections and (on a much faster time scale) functional connections are in constant flux and change across time, both in the course of spontaneous and task-evoked neural activity. The emerging picture is that of a truly 'restless brain' [68], and a number of recent studies have refocused attention on fluctuations in brain networks across time, that is on 'network dynamics'. Network dynamics explicitly refers to changes in the configuration of network nodes and edges across time.

Numerous studies have documented reconfigurations of functional connectivity with changing conditions of sensory input, task or cognitive load [69] and in the course of learning [70]. More specifically, several recent studies have linked differences in cognitive state to differences in integrative or cooperative processing [71,72] and errors in task performance to failure in appropriately reconfiguring functional networks [73]. But dynamic changes in functional connectivity are not only found to accompany changes in task or input — they also appear to occur spontaneously in the resting brain. In most fMRI studies, it has been common practice to derive resting-state functional connectivity from long samples of spontaneous BOLD fluctuations processed into a single matrix of cross-correlations. In such matrices, the strength of functional couplings among nodes (estimated from the similarity of their time courses) is represented as a single coefficient summarizing data collected over several minutes of brain activity. However, computational models of spontaneous activity unfolding in large-scale neural systems strongly suggest that structural connections can shape functional interactions on multiple (short and long) time scales [74], even in the absence of any overt endogenous or exogenous processes driving fluctuations in connectivity. Windowed analysis of simulated functional connectivity revealed large variations in coupling strengths as well as variations in nodal network metrics such as centrality. More recently, empirical studies of resting-state fMRI have documented nonstationarities in functional couplings among remote brain regions [75], and these findings have been confirmed and extended across the human, macaque, and rat brain [76•,77•,78] (Figure 4). Ongoing RSN dynamics across the mammalian species studied to date hints at evolutionarily preserved mechanisms, and recording under the presence of anesthesia suggests that the spontaneous relationships are not solely a consequence of conscious, cognitive processing and attention shifts. Windowing of resting-state data sets allows the characterization of nonstationary couplings among network modules in terms of 'dwell times', and it has been suggested that differences in functional connectivity seen in clinical conditions may be due to alterations in nonstationary temporal fluctuations [79]. In related work, a temporal ICA analysis approach leveraging recent methodological developments that allow

Figure 4
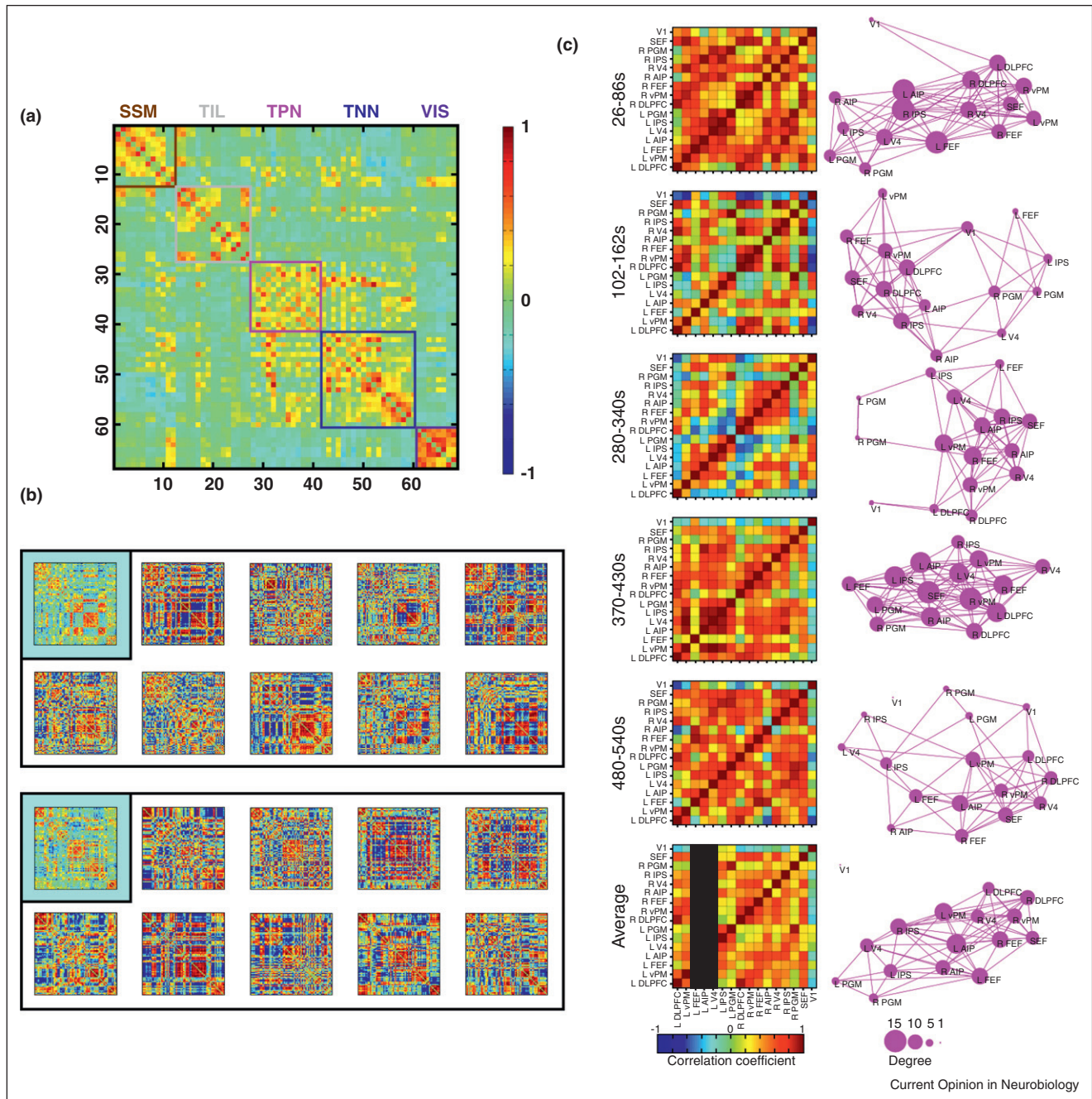
Nonstationarities and network dynamics. **(a)** A matrix representation of a 68-node fully connected (unthresholded) resting-state fMRI network, averaged across 892 subjects each with 90 graphs estimated from 33 s of data. Community detection reveals five modules (SSM, somatic sensory-motor network; TIL, temporal/insular/limbic network; TPN, task-positive network; TNN, task-negative network; VIS, visual network). **(b)** Average matrix (upper left) and individual frames from each subject's time course. Videos of a corresponding sliding window analysis are contained in the supplementary information of ref. [78]. **(c)** Changes in network structure across time in a single human subject, for 16 regions forming an oculomotor network. The matrix and network plots at the bottom refer to a long-time average (12 min) while the other plots display 60-s windows of the same run. Note significant fluctuations in correlation-strengths and node centrality expressed here as the node degree. Panels **(a)** and **(b)** are modified and reproduced from [79], panel **(c)** is modified and reproduced from [76•].

higher fMRI sampling rates has identified multiple 'temporal functional modes' [80•]. These modes define network components not by way of spatial decomposition, but rather on the basis of coherent temporal fluctuations across time, allowing for spatial overlap of nodes within modes. Approaches such as these may allow new insights into patterns of stationarity and nonstationarity. In parallel to these findings in fMRI data, several studies have reported pronounced nonstationarities in resting-state electromagnetic recordings, for example in measurements of MEG signal power [81] and in synchronization patterns in EEG networks [82,83].

Network dynamics represents one of the most important new frontiers in the study of brain connectivity. Recent evidence points to significant fluctuations of connectivity and networks across multiple time scales, ranging from milliseconds to seconds and involving spontaneous dynamics as well as transitions that are input-related or task-related. Functional (and effective) connectivity is increasingly regarded as highly time-dependent. These observations raise a number of questions: Are patterns of network dynamics recorded in the resting brain related to sequences of network states that accompany specific tasks? Is there a finite set of patterns of functional connectivity (a 'functional repertoire') supporting cognition, and is this repertoire continually revisited in the resting brain? Do dynamic reconfigurations of functional connectivity respect or break regional and/or community boundaries? What is responsible for the nonstationarity of functional couplings? Answering these questions involves a number of empirical and analytic challenges. As these challenges are beginning to be addressed, the dynamic nature of brain connectivity will likely come into sharper focus.

Conclusions

Numerous studies, only a fraction of which have been included in this brief overview, have documented network attributes such as communities and hubs that accommodate and promote segregation and integration of neural information. What future developments are to be expected? The emerging picture may be one of an increasingly dynamic and flexible multiscale network model, where regions, circuits and communities are demarcated by boundaries of varying degrees of sharpness and temporal stability, and are arranged into nested hierarchies. In such a model, regions, circuits and communities join and separate as dynamic links form and dissolve, spontaneously and in response to varying cognitive demands. An important focus of future studies will likely be on temporal fluctuations in network attributes for segregation and integration of information.

Acknowledgement

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