Segregated Systems of Human Brain Networks

Gagan S. Wig¹,²,*

The organization of the brain network enables its function. Evaluation of this organization has revealed that large-scale brain networks consist of multiple segregated subnetworks of interacting brain areas. Descriptions of resting-state network architecture have provided clues for understanding the functional significance of these segregated subnetworks, many of which correspond to distinct brain systems. The present report synthesizes accumulating evidence to reveal how maintaining segregated brain systems renders the human brain network functionally specialized, adaptable to task demands, and largely resilient following focal brain damage. The organizational properties that support system segregation are harmonious with the properties that promote integration across the network, but confer unique and important features to the brain network that are central to its function and behavior.

The Simple Organization of Some Complex Networks

Either via deliberate engineering or natural development, most networks in nature, technology, and society exhibit patterns of interactions that are far from random [1]. Research on these complex networks (see Glossary) has revealed that many social, biological, and man-made networks exhibit organizational properties that support efficient design and resilience to perturbation [2]. Some of these properties are relatively easy to understand and appreciate. For example, networks often contain distinct and segregated subnetworks, and effective network function is supported by maintaining subnetwork segregation while simultaneously allowing integration across the subnetworks [3]. Excess in either direction can be harmful for a network. Too much interconnectedness between subnetworks can lead to rapid spreading of disease [4], and has rendered financial networks vulnerable to sudden crisis [5]. Conversely, too much segregation between subnetworks can result in their diminished interaction or isolation, as has been argued in reference to the increasing polarization of the network of US political interactions [6].

Descriptions of brain connectivity have long recognized the order in the seemingly chaotic network architecture of the brain [7,8]. Theoretical and applied research has highlighted the presence and importance of subnetwork segregation alongside global integration across the brain network, leveraging observations in both computational and non-human animal models [3,9]. Consideration of the relationship between network organization and network function has incorporated observations derived from human imaging to reveal the importance of network integration in human brain networks [10]. I bring together here a collection of recent human brain network observations that collectively demonstrate the importance of maintaining segregated subnetworks in the brain (for an effective summary of the initial observations documenting the presence of human brain subnetworks see [11]). In the sections that follow I reveal how the analysis of large-scale functional brain networks in humans has provided evidence for the benefits of subnetwork segregation. I also highlight how subtle deviations in the patterns that maintain segregated subnetwork organization can be disruptive to brain function and cognition, even in ostensibly healthy networks. In doing so, I will demonstrate how synthesizing

¹Center for Vital Longevity and School of Behavioral and Brain Sciences, The University of Texas at Dallas, Dallas, TX, USA
²Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, TX, USA

*Correspondence: gwig@utdallas.edu (G.S. Wig).
these recent and diverse observations illuminates our understanding of the brain, and generates unique and novel predictions about brain function and behavior.

Organizational Units of Networks
It is important to first review and establish how networks and their properties are formally analyzed. Progress in the science of complex networks and the mathematics of graph theory have provided brain researchers with a language and framework with which to both describe and interpret the organization of brain networks [12,13]. In its simplest form, a network consists of a collection of items or objects (nodes) and the pairwise relationships between them (edges). A consequence of this generality is that a network model can represent the interactions among collections of people, proteins, computers, neurons, or even verbs in a piece of literature [13]. Numerous descriptions have documented how network analysis has aided in understanding the patterns of connections among the nodes of numerous real-world networks [2,14]. While there are multiple measures and ways to quantify and describe the organization of a network and the interactions of its nodes, my focus here will be on the modular organization that is often revealed in networks [15,16]. A modular network exhibits a ‘clustering’ of its nodes into multiple distinct subnetworks. At a connectational level, the subnetworks exhibit dense connectivity among nodes within each of the subnetworks, and sparser connectivity between nodes in different subnetworks (Figure 1, Key Figure). Subnetworks can go by many names, and are often referred to as modules (not to be confused with Fodor’s concept of modules in cognitive psychology [17]), communities, or clusters. For consistency, I will use the term ‘community’ to refer to a subnetwork in the remainder of this article.

Before examining the specific examples of communities in brain networks, we should not only carefully consider the connectivity patterns that define community organization but also understand how this organization is vulnerable to disruption. As mentioned earlier, the pattern of connections required for exhibiting community organization is seemingly simple. Dense connectivity within communities allows nodes within each of the communities to easily interact with one another, while sparser connectivity between communities allows the communities to remain relatively independent from one another. This distinction in proportion of connections within versus between communities is a prerequisite for maintaining a necessary balance between functional segregation and global integration across a network [3]. Altering the connections that maintain community organization can not only be beneficial for network function (e.g., to promote greater interaction between communities that are distinct and/or carry out specialized functions within a network) but can also have unanticipated consequences which are sometimes undesirable. At one end of the spectrum, diminished connectivity between communities of a network can result in loss of important interactions between nodes across communities or even isolation of an entire community itself (i.e., disconnection); at the other end of the spectrum, excessive connectivity between network communities may result in the loss of compartmentalization or specialization of a community (Figure 1).

The Segregated Communities of a Brain Network Correspond to Functionally Specialized Brain Systems
Early application of network methods to measures of brain connectivity involved in vivo tracing and neurophysiological recordings in non-human animals [9,18–20]. Technological advances in non-invasive imaging have enabled the application of network analyses to anatomical and functional interactions of the human brain. At present, the spatial resolution of non-invasive brain imaging in humans predominantly limits network descriptions to the level of cortical brain areas and subdivisions of subcortical structures [21]. Reports of anatomical brain networks have been derived from estimates of region-to-region fiber bundles defined using mathematical models of magnetic resonance images sensitive to the diffusion of water [22]. Functional network descriptions have
been generated for multiple modalities of information (e.g., magnetoencephalography [23], electroencephalography [24], multunit recording [25]), although the majority of research has employed time-series correlation of the blood oxygen level-dependent (BOLD) signal, measured either during performance of goal-directed tasks (e.g., [26]) or during rest [27].

My focus here will largely be on the wealth of observations that have been obtained in human brain networks defined by resting-state functional correlations (RSFCs) of BOLD time-series. Regions that ‘coactivate’ with one another in the context of goal-directed tasks exhibit correlations of their lower-frequency BOLD time-series in the absence of task [27]. These statistical relationships are correlated with local field potentials (reviewed in [28]), providing evidence for a neural source of the correlated BOLD signals. RSFCs are statistically malleable on multiple timescales, not only over development and aging [29] but also in relation to changes in the processing demands of the brain at shorter timescales [30–32]. As such, RSFCs are hypothesized to reflect a statistical history of coactivation that are sculpted over the lifespan of the individual [21], and represent an important functional architecture that is distinct in part from its anatomical underpinnings [33]. Accordingly, network edges defined by RSFC represent statistical relationships between brain regions which should not be confused with physical connections. Although I will occasionally use the term ‘connection’ to refer to RSFC relationships, it is important to be mindful of this distinction as it has implications for interpreting the brain network observations that follow.

Examination of RSFC networks obtained from healthy younger adults reveals the presence of multiple distinct and distributed communities of interacting brain regions (Figure 2A). The spatial arrangement (topography) of these communities includes sets of brain regions that are anatomically proximal to one another as well as sets of brain regions that are distributed across the brain, highlighting the orthogonality between brain network topography and brain network topology. Although the labels that have been applied to RSFC communities have measured using functional magnetic resonance imaging which is sensitive to variation in the blood oxygen level-dependent (BOLD) signal over time. Segregation: the amount of partitioning between distinct communities of a network. Formally calculated as the difference in within-versus between-community connections, relative to the within-community connections [39]. Segregation is similar to the modularity measure but different in that it directly quantifies the proportions of both within- and between-community connections that are present in the network. Topography: the spatial arrangement of physical features across a map or location (e.g., areas in the brain). Topology: the physical arrangement of the nodes and edges of a network.

**Key Figure**

Differences in the Extent of Segregation Between a Network’s Communities Impacts Network Function.

![Diagram of network communities showing increasing and decreasing segregation](image)

**Figure 1.** The toy networks consist of nodes connected by edges and are grouped into multiple distinct communities. The middle panel depicts an exemplary network exhibiting a modular (or community-based) organization. Nodes are colored according to their community membership; the organization of nodes into distinct communities leads to distinctions in community function across the network. To the left of the middle panel, the loss of edges between nodes in different communities can prohibit interaction between communities and even isolate communities from the rest of the network, resulting in loss of community and node function (darker disconnected nodes indicate increased segregation of the corresponding communities). To the right of the middle panel, introduction of edges between nodes in different communities blurs the connectivity-based distinctions between communities, rendering the affected communities functionally indistinguishable from one another (lighter nodes indicate decreased segregation of the corresponding communities).
Figure 2. Resting-State Correlation Networks Are Organized Along Distinctions in Functional Systems of the Human Brain. (A) Resting-state network organization exhibits large-scale spatial organization in healthy young adults. This organization is highly consistent across different network partitioning methods including clustering (left [35]) and community-detection (right [34]). The subnetworks have been labeled according to their correspondence to functional distinctions, several of which are presented in (B). (B) A collection of resting-state subnetworks correspond to functionally distinct systems of the human brain. Visual/spatial attentional systems (dorsal visual/spatial attention in green and ventral visual/spatial attention in blue; [128]) and task control systems (frontal-parietal control system in yellow and cingulo-opercular control system in black [97]; figure adapted from [129]) as defined by analysis of task-evoked activity. The default system defined by task-induced deactivations of regional activity ([130]; figure adapted from [131]). Visual, auditory, and somatosensory/motor systems highlighted by regional distinctions in patterns of cyto- and myoarchitecture [132]. Inset boxes highlight the spatial correspondence between the colored outlines of regions from specific resting-state clusters and communities observed in (A) and each brain system. While the focus of the figures is largely on cortical regions and their system membership, functional systems also include different subdivisions of subcortical structures and the regions of the cerebellum. (C) A spring-embedding network depiction of young adult resting-state network organization representing interactions between brain regions [34]. In spring-embedded depictions, relationships between nodes are treated as attractive springs which serve to position nodes in space according to their patterns of connectivity. Resting-state functional correlation (RSFC) brain network communities are segregated from one another: nodes, representing brain regions, within a community are densely connected with one another, and nodes in different communities are sparsely connected with one another. Nodes are color-coded by their community membership as in the right panel of (A).

differed across reports, the pattern of organization has been largely consistent [34–36]. Furthermore, several of these RSFC-defined communities correspond to brain systems that have been revealed via the analysis of task-related signals and/or patterns of brain damage in patient populations, providing important evidence that the mathematically defined RSFC communities are biologically meaningful. These include systems dedicated to processing incoming sensory information and motor output (visual system, auditory system,
somatosensory/motor systems), and systems involved in more integrative or ‘associative’ processes (e.g., the frontal-parietal control system, the cingulo-opercular control system, the salience system, the dorsal and ventral attention systems, and the default system; Figure 2B). Conversely, the presence of other communities revealed by RSFC network analysis are more tenuous and have yet to be firmly aligned with an independently validated system of the brain. There is evidence that some of these ‘orphan’ communities may correspond to presently unspecified brain systems [37]; others may be a result of more complex network relationships (e.g., hierarchical organization [36]) or be related to systematic signal artifacts related to network construction [38]. Keeping in mind these latter sets of observations, I will use the term ‘community’ to refer to a group of brain regions that are densely connected (or correlated) to one another in a brain network graph, and I will use the term ‘system’ when referring to a group of brain regions that have been previously associated with a related and dissociable set of cognitive operations in the neuroscience literature.

Inherent in the organization of the RSFC brain network communities is a degree of segregation that can be readily viewed with appropriate data depiction (Figure 2C). Similarly to other real-world networks, healthy younger adult functional brain networks exhibit segregated communities (systems) of brain regions that are characterized by dense relationships among brain regions that belong to the same community, and sparser relationships between communities, signifying less interactions between them. Accumulating evidence is revealing the impact of altering the balance of connections (statistical relationships) either via naturally occurring biological processes or by direct manipulation of the network (e.g., either via unanticipated insult or changing demands on the brain). The emerging picture portrays how the segregation of brain systems promotes the function and capabilities of human brain networks.

**Segregated Systems Are Important for Brain Network Function**

Recent observations have begun to illuminate (i) how system segregation varies across individuals, (ii) the properties associated with maintaining segregated systems in brain networks, (iii) the consequence of disrupting this aspect of network organization, and (iv) the circumstances under which system segregation varies or is altered to support brain function and cognition. In the remaining sections I synthesize a collection of these observations and highlight how they generate novel predictions about brain function and organization.

**Variability Related to Age and Cognition**

There are circumstances when the patterns of connections that support segregated systems are naturally altered or vary across individuals. For example, the strength of RSFC connections within and between brain systems exhibits progressive differences across adulthood, even in the absence of disease (Figure 3A). Examination of connectivity patterns across the healthy adult lifespan has revealed that increasing age is associated with decreasing connectivity within systems and increasing connectivity between brain systems [39–46]. Differences in the number and strength of connections within and between systems can be summarized using metrics that quantify the degree of either modular organization or segregation of the brain network communities themselves (Box 1). Application of these measures to the adult lifespan confirms that increasing age is accompanied by decreasing segregation of brain systems, and also reveals that different types of functional systems exhibit different trajectories of age-related differences in system segregation, suggesting different maturational timelines for different systems (Figure 3B, C) [39].

At the other end of the spectrum of age, there is accumulating evidence for changes in the segregation of the functional systems of the brain during brain development, from infancy through young adulthood. While the organization of RSFC brain network communities in early infancy appears to be very different from that of young adults (e.g., being organized into more local,
Figure 3. Resting-State System Segregation Decreases Across the Healthy Adult Lifespan and Relates to Cognitive Ability. (A) Increasing age is associated with decreasing connectivity within brain systems, and with increasing connectivity between brain systems. Each dot represents the mean resting-state correlation value of an individual. (B) System segregation summarizes the separation of communities within the brain network of an individual. Increasing age is associated with decreasing segregation of brain systems (black dots and line). The segregation of association systems (yellow dots and line) exhibits a different pattern of age-related decreases relative to sensory/motor systems (magenta dots and line). The segregation of association systems exhibits an inflection point at ~50 years of age, suggesting more pronounced reductions in segregation of these systems from this age onwards. (C) Spring-embedding network diagrams depicting network organization of groups of individuals from four adult age cohorts. The arrow points to the visual system, which can be seen to exhibit progressive weakening of within-system connections across age (edges within the blue community are less densely packed with increasing age). The circle highlights the location of several association systems in each cohort. Increasing age is associated with decreasing segregation, and this pattern is accentuated in the ‘middle late’ and ‘older’ adults, consistent with the trends noted in (B). Nodes have been colored according to a system label as in the right panel of Figure 2A. (D) Each individual’s association system value is plotted in relation to a score reflecting their long-term episodic memory ability (the color of the dot represents the age cohort the individual belongs to). Greater segregation of association systems, quantified in resting-state networks, is associated with better long-term episodic memory ability, independently of age. Figures adapted from [39].

anatomically proximal groups), versions of some of the distributed functional systems of the adult brain may be detectable by the second year of life [47–50]. Recent evidence suggests that adult-like communities are in place by childhood ([51,52]; for discussion of related issues see [53]). Maturation from childhood and adolescence through young adulthood is accompanied by a complex pattern of alterations in RSFC relationships. Systems involved in associative operations exhibit increasing connectivity among regions within brain systems and decreasing connectivity between different brain systems (i.e., increasing segregation [52,54–56]), although there is also evidence that there may be unique trajectories of segregation with respect to both different age ranges and different associative systems [51]. Conversely, sensory/motor systems exhibit less differences in segregation over this timeframe [56]. Accordingly, childhood development appears to be broadly associated with the refinement of brain network organization, predominantly characterized by increasing segregation between functional systems involved in associative operations, which presumably relates to their increasing specialization of function.

Despite the somewhat mirrored patterns of system segregation between childhood development and adult aging, it is important to appreciate that distinct processes likely contribute to the progressive changes in brain network organization. Brain development in childhood is predominantly characterized by a phase of rapid learning about the environment that is concomitant with maturation of neuronal structure and function [57]. Learning naturally continues
Box 1. Network Measures are Summary Statistics

Measures of segregation and modularity are summary statistics of the organization of a network. The numbers themselves quantify the degree to which a network is divided into distinct communities, with higher values indicating stronger divisions between the network communities. In many networks the communities themselves are uncertain; there are numerous community-detection algorithms that try to detect the communities, and each algorithm optimizes specific partitioning features for specific purposes [127]. Some of these algorithms attempt to identify partitions of nodes in a way that maximizes the modularity measure.

Modularity is calculated as the fraction of edges that fall within the given communities of a network compared to the expected fraction if the connections were distributed at random across the network [16]. Segregation is calculated as the difference in mean within-versus between-community connections, relative to the mean within-community connections of a network (Segregation = \( \frac{\text{within}}{\text{between}} \)). This measure can be applied to networks where the edges are binary (unweighted) or have a strength associated with them (weighted), and is described further in [39]. Networks with higher modularity (and/or higher segregation) have greater separation between their communities. However, these summary measures alone do not entirely reveal the organization of a network. An appropriate understanding and subsequent interpretation of modularity and segregation (much like many other network summary measures) necessitates careful evaluation of the corresponding topology of the network communities (Figure 1).

Figure 1. Interpreting Measures of Network Modularity and Segregation Necessitates Examining the Topology of the Network Communities. Panels (A–C) depict multiple toy networks with distinct patterns of community organization. Nodes have been colored according to their community assignment as defined by a community detection algorithm [133]. Quantification of modularity (calculated as in [16]) or segregation (calculated as in [39]) reveals how both network measures can provide a summary statistic of the separation between network communities. Measures of modularity and segregation can occasionally differ given that their calculation summarizes related but different features of network organization. Importantly, networks with very different patterns of community organization can have equivalent summary statistics (e.g., network A and network B have equivalent segregation while network A and network C have equivalent modularity). Conversely, two networks that have qualitatively similar community composition can exhibit differences in measures of modularity or segregation owing to differences in their patterns of within- and between-community connectivity (i.e., compare network B and network C). Relatedly, differences in modularity or segregation can be due to multiple possible differences in the patterns of connections of each network (e.g., decreased segregation can be due to any one or more of the possible components of a network differing in their patterns of connections within/between communities). These important details of the community organization of a network will be missed or misunderstood if not directly examined.

through adult aging; however, this period of life is also accompanied by progressive degeneration of neuronal architecture and, presumably, alterations (compensation) that may offset the ensuing burdens [58,59]. These differing factors need to be considered when interpreting the similarity between curves that summarize (network) observations across the lifespan.
The evidence thus far suggests that, in both advanced aging and early development, there are age-related differences in the segregation of functional systems. Further, different systems exhibit different age-related trajectories in their patterns of segregation (e.g., the segregation of sensory/motor versus association systems across the lifespan; for an illustration of this in adult aging see Figure 3C). Accordingly, some of the described patterns parallel observations related to differences in maturation of cognitive ability across different domains (e.g., visual versus executive control, etc. [60]). Do differences in system segregation directly relate to cognitive function? Emerging evidence suggests a link between the segregation of specific brain systems, defined at rest, and particular cognitive abilities [39,56,61,62] (Figure 3D). Within healthy adults, increasing segregation of systems that mediate more integrative or associative operations (as opposed to sensory and motor systems) is associated with superior cognitive ability (i.e., long-term episodic memory, fluid processing); importantly, the relationship between system segregation and cognitive ability persists independently of the influence of age on both measures, providing support for the importance of maintaining segregated brain systems across the lifespan [39,63].

**Functional Specialization and Heterogeneity of Processing Roles**

It is hypothesized that a community-based network organization is central to the functional specialization of each brain system (e.g., Figure 2). This same organizing principle gives rise to functional specialization or compartmentalization in many non-brain networks, including airports in the air transportation network, individuals in a social network, and proteins in a metabolic network [64,65].

Network nodes are often labeled according to their community assignment; this categorization inherently emphasizes the homogeneity of both node connectivity and node function within a community. This generalization alludes to the redundancy in connectivity that is often present in networks, and which is beneficial in many situations. However, examining the patterns of node connections within a community often reveals heterogeneous patterns of connectivity across the nodes. Nodes occupy different topological positions within their respective communities; these differences can both mediate distinctions in the processing role of the node [64,66,67] and can also support the conservation of network ‘wiring’ costs when network edges represent physical connections [68]. For example, the connections of some nodes are diversely distributed across the network and interact with nodes in communities other than their own (connector nodes [69]); connector nodes often facilitate interaction between the segregated communities of a network. Conversely, other nodes exhibit connections that are limited to nodes in their own community (‘non-connector nodes’). Finally, there are additional patterns of connections that further differentiate nodes from one another (e.g., different types of hubs, peripheral nodes, etc. [64]). While these latter nuanced distinctions are also important, they are not central to the arguments of this report and I will therefore not focus on them.

The distinctions in the pattern of connections of a brain region have functional consequences [9,70]. In healthy young adult brains, nodes with RSFC-defined connections that span multiple brain systems (i.e., globally defined connector nodes) are engaged across a wide range of tasks (Figure 4A,B) [71,72]. The diverse connectivity of these connector nodes likely mediates a broader repertoire of function and/or allows them to flexibly integrate and transfer information between distinct functional systems. In support of this hypothesis, distinctions in patterns of node connectivity at rest (i.e., connector nodes vs non-connector nodes) have been shown to relate to distinguishable changes in activity and patterns of connectivity during task performance, wherein connector nodes exhibit involvement across a broader range of tasks relative to non-connector nodes, a property that is consistent with enacting task control [73].

Do differences in the system segregation across a brain network impact the functional distinctions of its community’s nodes? Observations in other domains of network science
Figure 4. Segregated Systems contain Nodes with Heterogeneous Functions. (A) Specific nodes in the fronto-parietal control (FPN) system exhibit greater “flexibility”, whereby their brain-wide RSFC patterns rapidly change in relation to variable task demands relative to other FPN nodes and nodes in other brain systems (adapted from [71]). (B) Resting-state functional correlation (RSFC)-defined connector nodes exhibit connectivity with multiple systems as compared to non-connector nodes whose connections are largely limited to their own system. Connector nodes are more active during tasks that engage multiple brain systems (right graph), providing evidence for their role in integration. Non-connector nodes do not exhibit this positive relationship (adapted from [72]). (C) Reduced system segregation results in decreased differences in functional activity between connector and non-connector nodes. Connector (pink nodes of middle panels) and non-connector nodes (black nodes of middle panels) are defined within each RSFC brain system (left panels). Connector nodes of a system exhibit greater connectivity with other brain systems and can be seen on the periphery of each system in the spring-embedding diagrams; in some cases the distinction in topology is difficult to view because of the 2D representation. (Right panel) The functional (BOLD) activity of each node is quantified during a semantic classification task and mapped onto RSFC network organization. In healthy young adults, connector (pink border on inset panel) and non-connector (black border on inset panel) nodes exhibit differing activation in systems relevant to semantic classification processing demands (i.e., the fronto-parietal control system; summarized in the bar graph). Older adults, who exhibit decreased segregation of their systems, demonstrate less distinctive activity across connector and non-connector nodes (adapted from [75]).

have demonstrated how alterations in community organization impact node function [74], and there is evidence consistent with this observation in human brain networks as well. Connector and non-connector nodes of the brain exhibit differing patterns and magnitudes of task-related activity in healthy young adults [75]. However, the connector versus non-connector distinctions in both patterns of connectivity and task-related activity are diminished in brain networks that exhibit less system segregation (e.g., in older age [75]) (Figure 4C). Collectively, these observations highlight the heterogeneity in node processing that is observed within functionally
specialized brain systems, and reveal how the unique functional roles of distinct nodes may be disrupted with alterations to the segregation of brain systems.

Resilience and Vulnerability to Damage
Brain networks that have segregated systems are resilient to particular types of disruption. System segregation can be advantageous when focal damage is inflicted on nodes whose connections are largely limited to other nodes within the same system. Examinations of patients who have suffered damage to a specific brain region (e.g., due to stroke) reveal RSFC alterations that are largely limited to the corresponding brain system of the damaged region [76] but can also include connectivity with regions in other brain systems when they are close topological neighbors of the damaged location [77,78]. However, in both of these circumstances the large-scale patterns of segregation across the brain network appear to remain largely unaltered. Accordingly, it seems that damage inflicted on a node within a segregated system can result in relatively contained malfunction of the corresponding system while leaving the integrity and function of other systems largely intact.

Importantly, maintaining segregated systems also renders brain networks vulnerable at specific spots; network-wide disruption can follow targeted damage to crucial parts of the brain network or when multiple distributed insults have compounded across the network [79]. When either of these types of damage occur in the brain, there is evidence that the segregation of systems across the brain network are affected. Damage inflicted at connector nodes, or locations that are hypothesized to serve a central role in the integration across distinct brain systems (i.e., hubs), has been shown to decrease measures of RSFC network segregation [80] and also result in widespread cognitive deficits [81]. Because damage to hub locations reduces measures of segregation, it appears that a previously unappreciated function of hub nodes may be in maintaining segregated systems in addition to facilitating integration between them [11]. Conversely, damage to multiple distributed sites also modifies the large-scale network organization of the brain in addition to having system-specific effects. Brain dysfunction that is widely distributed across multiple regions of the brain, either via neurodegeneration (e.g., Alzheimer’s disease [82]) or some forms of psychiatric illness (e.g., schizophrenia [83]), is associated with reduced segregation of brain systems. It is presently uncertain to what extent this multifocal damage associated with neurodegeneration or psychiatric illness is naturally biased towards RSFC connector nodes or hubs (e.g., [84,85], but also see [81]).

The preceding lines of studies together indicate that sudden or progressive damage to the brain, especially when inflicted at crucial connector or hub locations, is associated with increased RSFC between systems, or decreased segregation. The observation of de-segregation of resting-state functional networks contrasts with descriptions that highlight the disconnection of anatomical networks (i.e., white matter bundles) in relation to both disease [86] and age-related cognitive decline [87]. It remains to be determined whether there are brain regions and/or types of damage wherein the damage results in large-scale disconnection of the functional connectome (left side of Figure 1; e.g., for evidence that damage to the hippocampal formation may exhibit these types of effects see [88], also see [89,90]).

Finally, recent observations in patients undergoing cognitive training to remedy impairment following brain damage provide additional support for the necessity of system segregation in supporting cognition. Patients with higher baseline levels of RSFC segregation exhibit the greatest improvements with cognitive training, providing evidence that greater system segregation may be beneficial towards training-related modification of cognitive ability ([91]; also see [92]). In keeping with this, increased RSFC system segregation has also been shown to correlate positively with improvements in therapy, providing evidence for a role of system segregation in behavioral improvement associated with rehabilitation [93]. Altogether,
observations in patient populations have provided strong evidence for the importance of maintaining segregated systems in the brain and have provided evidence towards understanding the mechanisms by which system segregation may be altered.

**Adaptation to Processing Demands**

Dynamic networks can reconfigure in relation to changes to the processing demands placed on the network. Thus far I have focused on the community-based organization of so-called ‘stationary’ RSFC networks; this approach to network analysis identifies the presumed ‘baseline’ state of functional architecture, reflecting the longer-term history of coactivation between regions of the brain network [21]. However, there are multiple circumstances under which the community organization of the brain network exhibits dynamic changes at relatively short timescales that are distinct from longer-term changes related to age, damage, or disease as described above. These dynamic changes reveal how temporary changes, specifically decreases, in system segregation may be beneficial for network function.

Resting-state networks can be analyzed to reveal non-stationary patterns of organization [94] and there is an ongoing debate as to the source and significance of these dynamics (e.g., see [95] vs [96]). However, I will focus here on the dynamic brain network changes that accompany stimulus- and task-related processing. In the brain, processing demands vary at multiple timescales ranging from transient changes supporting moment-to-moment processing to more sustained changes that are in service of maintaining present goals or task sets [97]. Examination of changes in connectivity and community organization can also be contextualized with respect to this distinction in timescales. Functional connectivity can be estimated on a trial-by-trial basis with respect to differences in stimulus and task processing across trials [98,99]. Comparisons of the resultant network organization across the different trial types have demonstrated decreased system segregation, stemming from increased task-related connectivity between brain nodes in distinct brain systems, during processing related to successful recollection [100–102], visual-spatial attention [103], stimulus awareness [104], autobiographical planning [105], emotional and motivational processing [106], integration of information across input modalities [107], task preparation [108], and increased cognitive control [109,110]. Task-related functional connectivity has also been estimated across longer periods of time; the connectivity in these cases represents a combination of signals related to both moment-to-moment processing and also to more sustained changes in processing that extend across the epoch of task execution (e.g., [111,112]). Here, task-related connectivity has revealed decreased segregation of brain systems compared to brain networks defined during rest [113–117] (Figure 5A).

Three observations are important to highlight. First, across several of the aforementioned studies probing the impact of task-related processing on the segregation of brain systems, there is evidence that the decreasing segregation that accompanies task-related processing is specific to a combination of more general task-control regions (e.g., [73,110]) and regions in systems that are most relevant to the processing demands of the task (e.g., [100,116]). Second, measures of task-related system segregation have also been shown to predict task performance; however, in the context of task-based connectivity, lesser segregation has been associated with better performance [110,116–120] (Figure 5B). This negative relationship between segregation and online behavioral performance contrasts with the positive relationship reported between resting-state system segregation and offline measures of cognitive ability (e.g., [39]) (Figure 3D). Third, the reduced segregation of task-relevant brain systems that accompanies novel task performance subsides with continued practice, leading towards automaticity in some tasks [121,122] (Figure 5C), and providing additional evidence that the segregation of large-scale systems exhibit dynamic changes in relation to processing demands over shorter timescales.
Together these observations reveal a push–pull dichotomy in the balance of segregation and integration that characterizes the organization of communities in functional brain networks during rest versus during task. While greater resting-state system segregation is associated with superior cognitive ability, effective task performance is best accomplished by a reduction in segregation, or greater integration, of the task-relevant systems that support the processing goals of the task. This juxtaposition fits well with the proposal that resting-state correlations reveal a statistic of regional co-recruitment patterns across the history of task-related processing of an individual [21,123]. A novel hypothesis that extends from the resting-state and task-related system segregation observations is that resting-state community organization represents an optimized state that has minimized the neural and/or metabolic energy demands (see [28] for a relevant discussion) across the likely set of necessary task-related reconfigurations. Maintaining segregated brain systems at rest allows the brain to rapidly and flexibly reconfigure its distributed systems or individual brain areas in service of any imminent task-related processing goals. Effective task performance necessitates greater interactivity between processing nodes that are distributed across multiple brain systems; this is accomplished by the temporary de-segregation of the task-relevant components from their resting-state network organization (a process which may also result in greater segregation between otherwise highly connected components).

Central to our understanding of changes in system segregation and integration in relation to task-related processing is the question of what determines whether and how the brain network adjusts itself to satisfy processing demands. Are dynamic changes to the functional brain
network architecture controlled by specific brain network nodes, sets of nodes, or systems [73,124]? Recent work has also highlighted the role of ascending neuromodulatory systems [110] and differences in levels of arousal [125,126] in changes in system segregation not only during task execution but also in the absence of external task demands, respectively. Importantly, theories regarding network controllers and more widespread neuromodulatory state effects are not mutually exclusive. Understanding the mechanism that mediates dynamic network changes will likely require fusing these multiple pieces to elucidate how they relate to one another.

Concluding Remarks
Throughout this article I have reviewed the evidence that demonstrates the presence and importance of maintaining segregated functional systems in human brain networks. Numerous observations obtained in different populations, under different experimental paradigms, and employing varying methodological approaches, have converged to reveal how this simple property of brain network organization relates to unique and fundamental features of brain function.

Brain network science is still in its infancy, and examinations of the brain as a large-scale network are still addressing the primary challenges to describing the constituent elements of brain networks (i.e., nodes and edges) in a biologically meaningful and accurate way [21]. Debates on how best to model the brain as a large-scale network are abundant, and there seems to be almost as many approaches for parceling the brain and quantifying its relationships as there are observations about the organization of brain network communities. Despite the differences in approaches that have been used, it is important to point out that the basic principles put forth in the present review have been largely consistent across the recent reports. Continual refinement of existing methods and brain atlases will aid progress towards further understanding the properties and functions of segregated system organization in brain networks (see Outstanding Questions).

One of the exciting opportunities that comes with examining the network properties of the brain relates to the type of analysis that this framework affords. Given its quantification of interactions between distributed areas and systems across the expanse of the brain, large-scale network organization offers a potentially informative target for probing the influence of multiple factors (e.g., genetics, lifestyle, environment) and interventions (e.g., pharmaceutics, surgical) that may have network-wide impact and relationships. It is clear that effective brain network function necessitates a fine balance between maintaining distinct but interactive brain systems. Examining the properties and consequences of maintaining segregated large-scale brain systems promises to advance our understanding of the complexities of brain function and organization.

Acknowledgments
I thank members of my laboratory for the insightful discussions that influenced this review: Micaela Chan and Neil Savalia (who also both helped me to create the figures for this article), Liang Han, and Phillip Agers. In addition, I am grateful to the James S. McDonnell Foundation for supporting my research, and for S.K. Wig and her perfect timing.

References
1. Watts, D.J. and Strogatz, S.H. (1998) Collective dynamics of ‘small-world’ networks. Nature 393, 440–442
2. Strogatz, S.H. (2001) Exploring complex networks. Nature 410, 268–276
3. Tononi, G. et al. (1994) A measure for brain complexity: relating functional segregation and integration in the nervous system. Proc. Natl. Acad. Sci. U. S. A. 91, 5033–5037
4. Sala, A. and Monti, J.H. (2010) Dynamics and control of diseases in networks with community structure. PLoS Comput. Biol. 6, e1000796
5. Liu, Z. et al. (2015) Banking sector interconnectedness: what is it, how can we measure it and why does it matter? Bank Engl. Q. Bull. 55, 130–138
6. The Economist 5 December (2013), p. 48. United States of Amoeba
7. Mesulam, M.M. (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann. Neurol. 28, 597–613
8. Sejnowski, T.J. and Churchland, P.S. (1989) Brain and cognition. In Foundations of Cognitive Science (Posner, M., ed.), pp. 301–356, MIT Press
Trends in Cognitive Sciences

9. Fellerman, D.J. and Van Essen, D.C. (1991) Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex 1, 1–47
10. van den Heuvel, M.P. and Sporns, O. (2013) Network hubs in the human brain. Trends Cogn. Sci. 17, 683–696
11. Sporns, O. (2013) Network attributes for segregation and integration in the human brain. Curr. Opin. Neurobiol. 23, 160–171
12. Bullmore, E. and Sporns, O. (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198
13. Newman, M.E.J. (2003) The structure and function of complex networks. SIAM Rev. 45, 167–256
14. Wasserman, S. and Faust, K. (1994) Social network analysis: methods and applications, Cambridge University Press
15. Sporns, O. and Bietz, R.F. (2016) Modular brain networks. Annu. Rev. Psychol. 67, 613–640
16. Newman, M.E. (2008) Modularity and community structure in networks. Proc. Natl. Acad. Sci. U. S. A. 103, 8577–8582
17. Fodor, J.A. (1993) The Modularity of Mind: An Essay on Faculty Psychology. MIT Press
18. Scannell, J.W. et al. (1995) Analysis of connectivity in the cat cerebral cortex. J. Neurosci. 15, 1463–1483
19. White, J.G. et al. (1986) The structure of the nervous system of the nematode Caenorhabditis elegans. Philos. Trans. R. Soc. Lond. B Biol. Sci. 314, 1–340
20. Sporns, O. et al. (2000) Theoretical neuroanatomy: relating anatomical and functional connectivity in graphs and cortical connection matrices. Cereb. Cortex 10, 127–141
21. Wig, G.S. et al. (2011) Concepts and principles in the analysis of brain networks. Annu. N. Y. Acad. Sci. 1224, 128–146
22. Hagmann, P. et al. (2008) Mapping the structural core of human cerebral cortex. PLoS Biol. 6, e159
23. Stam, C.J. (2004) Functional connectivity patterns of human magnetoencephalographic recordings: a ‘small-world’ network? Neurosci. Lett. 355, 25–28
24. Micheloyannis, S. et al. (2006) Using graph theoretical analysis of multi channel EEG to evaluate the neural efficiency hypothesis. Neurosci. Lett. 402, 273–277
25. Schmiedt, M.S. et al. (2015) Emergence of rich-club topology and coordinated dynamics in development of hippocampal functional networks in vitro. J. Neurosci. 35, 5459–5470
26. Friston, K.J. et al. (1997) Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6, 218–229
27. Biswal, B. et al. (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34, 537–541
28. Raisch, M.E. (2015) The restless brain: how intrinsic activity organizes brain function. Philos. Trans. R. Soc. Lond. B Biol. Sci. 370, 20140172
29. Biswal, B.B. et al. (2010) Toward discovery science of human brain function. Proc. Natl. Acad. Sci. U. S. A. 107, 4734–4739
30. Lewis, C.M. et al. (2009) Learning sculpts the spontaneous activity of the resting human brain. Proc. Natl. Acad. Sci. U. S. A. 106, 17558–17563
31. Albert, N.B. et al. (2009) The resting human brain and motor learning. Curr. Biol. 19, 1023–1027
32. Stevens, W.D. et al. (2010) Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. Cereb. Cortex 20, 1997–2006
33. Petersen, S.E. and Sporns, O. (2015) Brain networks and cognitive architectures. Neuron 88, 207–219
34. Power, J.D. et al. (2011) Functional network organization of the human brain. Neuron 72, 665–678
35. Yeo, B.T. et al. (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 1125–1165
36. Doucet, G. et al. (2011) Brain activity at rest: a multiscale hierarchical functional organization. J. Neurophysiol. 105, 2753–2763
37. Gilmore, A.W. et al. (2015) A parietal memory network revealed by multiple MRI methods. Trends Cogn. Sci. 19, 534–543
38. Wig, G.S. et al. (2014) An approach for parcellating human cortical areas using resting-state correlations. Neuroimage 93, 276–291
39. Chan, M.Y. et al. (2014) Decreased segregation of brain systems across the healthy adult lifespan. Proc. Natl. Acad. Sci. U. S. A. 111, 6498–6503
40. Betzel, R.F. et al. (2014) Changes in structural and functional connectivity among resting-state networks across the human lifespan. Neuroimage 102, 345–357
41. Geerligs, L. et al. (2015) A brain-wide study of age-related changes in functional connectivity. Cereb. Cortex 25, 1987–1999
42. Song, J. et al. (2014) Age-related reorganizational changes in modularity and functional connectivity of human brain networks. Brain Connect. 4, 662–676
43. Shaw, E.E. et al. (2015) Functional connectivity in multiple cortical networks is associated with performance across cognitive domains in older adults. Brain Connect. 5, 505–516
44. Spreng, R.N. et al. (2016) Attenuated anticorrelation between the default and dorsal attention networks with aging: evidence from task and rest. Neurobiol. Aging 45, 149–160
45. Grady, C. et al. (2016) Age differences in the functional interaction among the default, frontoparietal control, and dorsal attention networks. Neurobiol. Aging 41, 159–172
46. Ferrera, L.K. et al. (2016) Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. Cereb. Cortex 26, 3851–3865
47. Gao, W. et al. (2013) The dynamic reorganization of the default-mode network during a visual classification task. Front. Syst. Neurosci. 7, 34
48. Gao, W. et al. (2011) Temporal and spatial evolution of brain network topology during the first two years of life. PLoS One 6, e25278
49. van den Heuvel, M.P. et al. (2015) The neonatal connectome during preterm brain development. Cereb. Cortex 25, 3000–3013
50. De Asis-Cruz, J. et al. (2015) Functional properties of resting-state networks in healthy full-term newborns. Sci. Rep. 5, 17755
51. Marek, S. et al. (2015) The contribution of network organization and integration to the development of cognitive control. PLoS Biol. 13, e1002328
52. Fair, D.A. et al. (2012) Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. Front. Syst. Neurosci. 6, 80
53. Grayson, D.S. and Fair, D.A. (2017) Development of large-scale functional networks from birth to adulthood: a guide to the neuroimaging literature. Neuroimage Published online February 1, 2017, http://dx.doi.org/10.1016/j.neuroimage.2017.01.079
54. Dosenbach, N.U. et al. (2010) Prediction of individual brain maturity using fMRI. Science 329, 1358–1361
55. Sattetherwaite, T.D. et al. (2013) Heterogeneous impact of motion on fundamental patterns of developmental changes in functional connectivity during youth. Neuroimage 83, 45–57
56. Gu, S. et al. (2015) Emergence of system roles in normative neurodevelopment. Proc. Natl. Acad. Sci. U. S. A. 112, 13681–13686
57. Casey, B.J. et al. (2000) Structural and functional brain development and its relation to cognitive development. Biol. Psychol. 54, 241–267
58. Heddlen, T. and Gabrieli, J.D. (2004) Insights into the aging mind: a view from cognitive neuroscience. Nat. Rev. Neurosci. 5, 87–96
59. Park, D.C. and Reuter-Lorenz, P. (2009) The adaptive brain: aging and neurocognitive scaffolding. Annu. Rev. Psychol. 60, 179–196
60. Craik, F.I. and Bialystok, E. (2006) Cognition through the lifespan: mechanisms of change. Trends Cogn. Sci. 10, 131–138
61. Nashiro, K. et al. (2017) Resting-state networks associated with cognitive processing show more age-related decline than those...
82. Yue, Q.M. et al. (2017) Brain modularity mediates the relation between task complexity and performance. J. Cogn. Neurosci. 29, 1532–1546
83. Han, L. et al. (2016) Functional parcellation of the cerebral cortex across the healthy adult lifespan using resting-state functional connectivity. NeuroImage 128, 1447–1463
84. Guimera, R. et al. (2005) The worldwide air transportation network: anomalous centrality, community structure, and cities’ global roles. Proc. Natl. Acad. Sci. U. S. A. 102, 7794–7799
85. Grinwad, M. and Newman, M.E. (2002) Community structure in social and biological networks. Proc. Natl. Acad. Sci. U. S. A. 99, 7821–7826
86. Deng, Y. et al. (2012) Molecular ecological network analyses. BMC Bioinformatics 13, 113
87. Haniger, L. et al. (2012) Rich club organization of macaque cerebral cortex and its role in network communication. PLoS One 7, e46497
88. Bullmore, E. and Sporns, O. (2012) The economy of brain network organization. Nat. Rev. Neurosci. 13, 336–349
89. Guimera, R. and Amaral, L.A. (2005) Cartography of complex networks: modules and universal roles. J. Stat. Mech. 2005, n07, P07057
90. Ungerleider, L.G. and Desimone, R. (1986) Projections to the superior temporal sulcus from the central and peripheral field representations of V1 and V2. J. Comp. Neurol. 248, 147–163
91. Cole, M.W. et al. (2013) Multi-task connectivity reveals flexible hubs for adaptive task control. Nat. Neurosci. 16, 1348–1355
92. Bertolero, M.A. et al. (2015) The modular and integrative functional architecture of the human brain. Proc. Natl. Acad. Sci. U. S. A. 112, E6798–E6807
93. Gratton, C. et al. (2016) Evidence for two independent factors that modify brain networks to meet task goals. Cell Rep. 17, 1276–1288
94. Turkina, E. et al. (2016) Structure and evolution of global cluster networks: evidence from the aerospace industry. J. Econ. Geogr. 16, 1211–1234
95. Chan, M.Y. et al. (2017) Resting-state network topology differentiates task signals across the adult life span. J. Neurosci. 37, 2734–2743
96. Nomura, E.M. et al. (2010) Double dissociation of two cognitive control networks in patients with focal brain lesions. Proc. Natl. Acad. Sci. U. S. A. 107, 12017–12022
97. Siegel, J.S. et al. (2016) Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. Proc. Natl. Acad. Sci. U. S. A. 113, E4367–E4376
98. He, B.J. et al. (2007) Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53, 905–918
99. Albert et al. (2000) Error and attack tolerance of complex networks. Nature 406, 378–382
100. Gratton, C. et al. (2012) Focal brain lesions to critical locations cause widespread disruption of the modular organization of the brain. J. Cogn. Neurosci. 24, 1275–1285
101. Warren, D.E. et al. (2014) Network measures predict neuropsychological outcome after brain injury. Proc. Natl. Acad. Sci. U. S. A. 111, 14247–14252
102. Biter, M.R. et al. (2014) Functional connectivity and graph theory in preclinical Alzheimer’s disease. Neurobiol. Aging 35, 757–768
103. Yang, G.J. et al. (2016) Functional hierarchy underlies preferential connectivity disturbances in schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 113, E219–E229
104. Crossley, N.A. et al. (2014) The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain 137, 2382–2395
105. Buckner, R.L. et al. (2009) Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer’s disease. J. Neurosci. 29, 1860–1873
106. Mesulam, M.M. (1998) From sensation to cognition. Brain 121, 1013–1052
107. O’Sullivan, M. et al. (2001) Evidence for cortical ‘disconnection’ as a mechanism of age-related cognitive decline. Neurology 57, 632–638
108. Henson, R.N. et al. (2016) The effects of hippocampal lesions on MRI measures of structural and functional connectivity. Hippocampus 26, 1447–1463
109. Misc, B. et al. (2014) A network convergence zone in the hippocampus. PLoS Comput. Biol. 10, e1003982
110. van den Heuvel, M.P. and Sporns, O. (2011) Rich-club organization of the human connectome. J. Neurosci. 31, 15775–15786
111. Arnemann, K.L. et al. (2015) Functional brain network modularity predicts response to cognitive training after brain injury. Neurology 84, 1568–1574
112. Gallen, C.L. et al. (2016) Modular brain network organization predicts response to cognitive training in older adults. PLoS One 11, e0169015
113. Duncan, E.S. and Small, S.L. (2016) Increased modularity of resting state networks supports improved narrative production in aphasia recovery. Brain Connect. 6, 524–549
114. Chang, C. and Glover, G.H. (2013) Time-frequency dynamics of resting-state brain connectivity measured with fMRI. Neuroimage 50, 81–98
115. Hutchinson, R.M. et al. (2013) Dynamic functional connectivity: promise, issues, and interpretations. NeuroImage 80, 360–378
116. Laurmann, T.O. et al. (2017) On the stability of BOLD fMRI correlations. Cereb. Cortex 27, 4719–4732
117. Dosenbach, N.U. et al. (2006) A core system for the implementation of task sets. Neuron 50, 799–812
118. Friston, K.J. (1994) Functional and effective connectivity in neuroimaging: a synthesis. Hum. Brain Mapp. 2, 56–78
119. Horowitz, B. et al. (1999) Neural modeling, functional brain imaging, and cognition. Trends Cogn. Sci. 3, 91–98
120. Fomito, A. et al. (2012) Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. Proc. Natl. Acad. Sci. U. S. A. 109, 12788–12793
121. Scheldieber, A.M. et al. (2014) Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. Sci. Rep. 4, 6431
122. King, D.R. et al. (2015) Recollection-related increases in functional connectivity predict individual differences in memory accuracy. J. Neurosci. 35, 1763–1772
123. Spadone, S. et al. (2015) Dynamic reorganization of human resting-state networks during visuospatial attention. Proc. Natl. Acad. Sci. U. S. A. 112, 8112–8117
124. Godinot, D. et al. (2015) Breakdown of the brain’s functional network modularity with awareness. Proc. Natl. Acad. Sci. U. S. A. 112, 3799–3804
125. Spreng, R.N. and Schacter, D.L. (2012) Default network modulation and large-scale network interactivity in healthy young and old adults. Cereb. Cortex 22, 2610–2621
126. Kinninson, J. et al. (2012) Network analysis reveals increased integration during emotional and motivational processing. J. Neurosci. 32, 8361–8372
127. Sassai, S. et al. (2016) Functional split brain in a driving/listening paradigm. Proc. Natl. Acad. Sci. U. S. A. 113, 14444–14449
128. Elmman, M. et al. (2012) Predicting errors from reconfiguration patterns in human brain networks. Proc. Natl. Acad. Sci. U. S. A. 109, 16714–16719
129. Cohen, J.R. et al. (2014) Quantifying the reconfiguration of intrinsic networks during working memory. PLoS One 9, e106636
130. Shine, J.M. et al. (2016) The dynamics of functional brain networks: integrated network states during cognitive task performance. Neuron 92, 544–554
131. Shiner, W.R. et al. (2012) Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb. Cortex 22, 158–165
112. Gonzalez-Castillo, J. et al. (2015) Tracking ongoing cognition in individuals using brief, whole-brain functional connectivity patterns. Proc. Natl. Acad. Sci. U. S. A. 112, 8762–8767
113. Krienen, F.M. et al. (2014) Reconfigurable task-dependent functional coupling modes cluster around a core functional architecture. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369, 20130526
114. Cole, M.W. et al. (2014) Intrinsic and task-evoked network architectures of the human brain. Neuron 83, 238–251
115. Mattar, M.G. et al. (2015) A functional cartography of cognitive systems. PLoS Comput. Biol. 11, e1004533
116. Westphal, A.J. et al. (2017) Episodic memory retrieval benefits from a less modular brain network organization. J. Neurosci. 37, 3523–3533
117. Cohen, J.R. and D’Esposito, M. (2016) The segregation and integration of distinct brain networks and their relationship to cognition. J. Neurosci. 36, 12083–12094
118. Meunier, D. et al. (2014) Modular structure of functional networks in olfactory memory. Neuroimage 95, 264–275
119. Stanley, M.L. et al. (2014) Changes in global and regional modularity associated with increasing working memory load. Front. Hum. Neurosci. 8, 954
120. Vatansever, D. et al. (2015) Default mode dynamics for global functional integration. J. Neurosci. 35, 15254–15262
121. Bassett, D.S. et al. (2015) Learning-induced autonomy of sensorimotor systems. Nat. Neurosci. 18, 744–751
122. Mohr, H. et al. (2016) Integration and segregation of large-scale brain networks during short-term task automatization. Nat. Commun. 7, 15217
123. Dosenbach, N.U. et al. (2008) A dual-networks architecture of top-down control. Trends Cogn. Sci. 12, 99–105
124. Gu, S. et al. (2015) Controllability of structural brain networks. Nat. Commun. 6, 8414
125. Becker, R. et al. (2016) Species-conserved reconfigurations of brain network topology induced by ketamine. Transl. Psychiatry 6, e786
126. Tagliazucchi, E. et al. (2013) Large-scale brain functional modularity is reflected in slow electroencephalographic rhythms across the human non-rapid eye movement sleep cycle. Neuroimage 70, 327–339
127. Fortunato, S. (2010) Community detection in graphs. Phys. Rep. 486, 75–174
128. Corbetta, M. and Shulman, G.L. (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215
129. Petersen, S.E. and Posner, M.I. (2012) The attention system of the human brain: 20 years after. Annu. Rev. Neurosci. 35, 73–89
130. Shulman, G.L. et al. (1997) Common blood flow changes across visual tasks. II. Decreases in cerebral cortex. J. Cogn. Neurosci. 9, 645–663
131. Raichle, M.E. and Mintun, M.A. (2006) Brain work and brain imaging. Annu. Rev. Neurosci. 29, 449–476
132. Brodmann, K. (1909) Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien Dargestellt auf Grund des Zellenbaues. J.A. Barth
133. Rosvall, M. and Bergstrom, C.T. (2008) Maps of random walks on complex networks reveal community structure. Proc. Natl. Acad. Sci. U. S. A. 105, 1118–1123