Structural and Functional Brain Networks: From Connections to Cognition

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REVIEW SUMMARY

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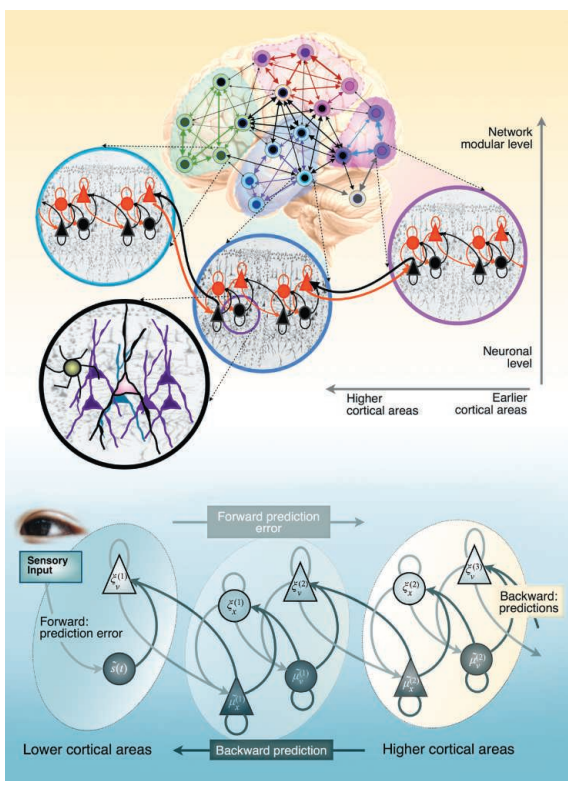
Background: The human brain presents a puzzling and challenging paradox: Despite a fixed anatomy, characterized by its connectivity, its functional repertoire is vast, enabling action, perception, and cognition. This contrasts with organs like the heart that have a dynamic anatomy but just one function. The resolution of this paradox may reside in the brain's network architecture, which organizes local interactions to cope with diverse environmental demands—ensuring adaptability, robustness, resilience to damage, efficient message passing, and diverse functionality from a fixed structure. This review asks how recent advances in understanding brain networks elucidate the brain's many-to-one (degenerate) function-structure relationships. In other words, how does diverse function arise from an apparently static neuronal architecture? We conclude that the emergence of dynamic functional connectivity, from static structural connections, calls for formal (computational) approaches to neuronal information processing that may resolve the dialectic between structure and function.

Advances: Much of our understanding of brain connectivity rests on the way that it is measured and modeled. We consider two complementary approaches: the first has its basis in graph theory that aims to describe the network topology of (undirected) connections of the sort measured by noninvasive brain imaging of anatomical connections and functional connectivity (correlations) between remote sites. This is compared with model-based definitions of context-sensitive (directed) effective connectivity that are grounded in the biophysics of neuronal interactions.

Recent topological network analyses of brain circuits suggest that modular and hierarchical structural networks are particularly suited for the functional integration of local (functionally specialized) neuronal operations that underlie cognition. Measurements of spontaneous activity reveal functional connectivity patterns that are similar to structural connectivity, suggesting that structural networks constrain functional networks. However, task-related responses that require context-sensitive integration disclose a divergence between function and structure that appears to rest mainly on long-range connections. In contrast to methods that describe network topology phenomenologically, model-based theoretical and computational approaches focus on the mechanisms of neuronal interactions that accommodate the dynamic reconfiguration of effective connectivity.

We highlight the consilience between hierarchical topologies (based on structural and functional connectivity) and the effective connectivity that would be required for hierarchical message passing of the sort suggested by computational neuroscience.

Outlook: In summary, neuronal interactions represent dynamics on a fixed structural connectivity that underlie cognition and behavior. Such divergence of function from structure is, perhaps, the most intriguing property of the brain and invites intensive future research. By studying the dynamics and self-organization of functional networks, we may gain insight into the true nature of the brain as the embodiment of the mind. The repertoire of functional networks rests upon the (hidden) structural architecture of connections that enables efficient hierarchical functional integration. Understanding these networks will require theoretical models of neuronal processing that underlies cognition.



Schematic of the multiscale hierarchical organization of brain networks. Brain function or cognition can be described as the global integration of local (segregated) neuronal operations that underlies hierarchical message passing among cortical areas, and which is facilitated by hierarchical modular network architectures.

ARTICLE OUTLINE

RELATED ITEMS IN *SCIENCE*

See the special section beginning on page 580.

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REVIEW

Structural and Functional Brain Networks: From Connections to Cognition

Hae-Jeong Park[1]* and Karl Friston[2]

How rich functionality emerges from the invariant structural architecture of the brain remains a major mystery in neuroscience. Recent applications of network theory and theoretical neuroscience to large-scale brain networks have started to dissolve this mystery. Network analyses suggest that hierarchical modular brain networks are particularly suited to facilitate local (segregated) neuronal operations and the global integration of segregated functions. Although functional networks are constrained by structural connections, context-sensitive integration during cognition tasks necessarily entails a divergence between structural and functional networks. This degenerate (many-to-one) function-structure mapping is crucial for understanding the nature of brain networks. The emergence of dynamic functional networks from static structural connections calls for a formal (computational) approach to neuronal information processing that may resolve this dialectic between structure and function.

One of the major challenges in neuroscience is to understand functional anatomy on the basis of its structural substrates, namely, neuronal circuits and connections. This challenge is not trivial, especially in higher brain systems, whose complexity increases exponentially with the number of neuronal elements. To explain the rich functionality that arises from a relatively fixed structure, neuroscientists have recently focused on the topology of brain networks by using analyses that have proven successful in sociology and systems biology (*1*).

Integration of Integration

To date, network analyses suggest that the organization of the brain's structural connections enable the efficient processing of information and thus supports complex brain functions. This structural organization is both modular and hierarchical; a module (subnetwork of the whole brain network) comprises multiple submodules (Fig. 1A).

In this structural hierarchy, the function of a module is to integrate and contextualize the more specialized functions of its submodules. For example, visual perception in the primary visual cortex V1 assimilates the diverse orientations detected by a multitude of ocular columns, which themselves integrate more basic neuronal operations, within each macrocolumn.

In this respect, brain function or cognition can be described as global integration of local integrators. To highlight this hierarchical aspect of neuronal architectures, we will use local integration instead of functional segregation or specialization (*2*). Local integration entails specialized functional processing mediated by short-range connections, intrinsic to a module at any scale, whereas global integration subserves higher cognition, facilitated by long-range connections, such as extrinsic corticocortical connections.

In both local and global integration, the integration within and between submodules depends on (hidden or unobserved) coupling parameters, such as connection strengths and timing. Therefore, understanding the true nature of neuronal interactions that underlie specific brain functions requires a formal theory of hierarchical integration based on neuronally plausible models with coupling parameters and a well-defined computational objective.

This brief review considers recent characterizations of large-scale brain networks and our current understanding of structure-function relationships from the perspective of network theory. We begin by introducing the concepts of nodes and edges in networks, explaining three types of connections (or edges) between nodes and describing in vivo neuroimaging methods for estimating brain connectivity. After reviewing the topology of structural brain networks, we then consider the convergence and divergence (context sensitivity) of structure-function mappings. Formally, this divergence complements cognitive degeneracy (*3*, *4*), in that the same structural connectivity can support many functions. To understand this flexible and pleiotropic organization, we then turn to the nature of message passing in these networks, in terms of information coding and computational modeling of integration. Last, we conclude with a brief outline of future directions.

Nodes and Edges and How They Are Measured

Network analysis for both structure and function in the brain starts with the identification of nodes as interacting units and their interconnections, called edges. Node identification usually involves parcellation of a spatially continuous cortical manifold into homogeneous and unique regions. Because homogeneity and uniqueness are generally defined with respect to function, identifying nodes is a key challenge for establishing structure-function mappings. In the past, node identification focused on cytoarchitectonics and macrostructures, but more recent schemes exploit the similarity of long-range structural or functional connectivity patterns [for details, see (*5*)].

In large-scale networks from in vivo neuroimaging, an edge can be defined by three types of connectivity: structural connectivity, for anatomical links; functional connectivity, for undirected statistical dependencies; and effective connectivity, for directed causal relationships among distributed responses (*6*) (Fig. 1B). This three-way categorization is not restricted to large-scale networks but also applies at mesoscopic and microscopic scales, although the precise definitions depend on the measurements and the models available at any particular scale.

Structural connectivity measured by using in vivo neuroimaging usually reflects large-range fiber bundles inferred from diffusion (or diffusion tensor) magnetic resonance imaging (MRI) (*7*). One can derive a structural brain network in terms of fiber bundles according to the regions they interconnect [e.g., (*8*, *9*)] (Fig. 2A). Structural connectivity based on diffusion MRI is however undirected and cannot differentiate between excitatory or inhibitory connections. This contrasts with structural connectivity based on tracing studies that can have different strengths or densities in either direction and in some instances be associated with excitatory or inhibitory postsynaptic effects.

Functional connectivity is generally inferred by the correlation between nodal activities on the basis of blood oxygenation level–dependent (BOLD) functional MRI (fMRI) or coherence in electro- or magnetoencephalogram (EEG/MEG) signals acquired during task performance or the resting state. In particular, resting-state fMRI has become an important basis for functional network analysis, after the discovery of spatially organized endogenous low-frequency fluctuations of BOLD signals (*10*).

Effective connectivity is defined as the influence one node (neuronal population) exerts over another, under a particular network model of causal dynamics. Effective connectivity is then inferred by using a model of neuronal integration. This usually involves estimating the model parameters (effective connectivity) that best explain observed BOLD or EEG/MEG signals. Although the neuronal model is generally constrained by structural connectivity, structural connectivity does not fully determine effective connectivity, which is dynamic (state-dependent) and changes with experimental context. Furthermore, in some models, effective connectivity can be polysynaptic and does not necessarily entail direct axonal connections. Effective connectivity is becoming increas-

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ingly important in the analysis of functional integration because the underlying model defines the mechanisms of neuronal coupling. We will return to this in a later section.

Recent studies of large-scale human brain networks have mostly had their bases in structural and functional connectivity, using in vivo neuroimaging. However, structural connectivity based on diffusion MRI cannot resolve intracortical or intrinsic connections. It is also potentially blind to weak long-range axonal connections, which may serve as weak ties for global integration (*11*, *12*). Conversely, functional connectivity (statistical dependencies) may exist between anatomically unconnected nodes, for example, synchronous activity in two (anatomically unconnected) nodes that is driven by common sources, polysynaptic connections, or other configurations of bidirectional circuits (*13*). Neither structural nor functional connectivity in large-scale networks specify the direction or sign (inhibitory or excitatory) of underlying directed (effective) connectivity.

Despite its many challenges, our current connectivity mapping ability is analogous to cartography in the Age of Exploration. The gross atlas, even if not comparable to Google Earth, delineated the boundary of the world, directed new explorations, and changed the world from an unfathomable entity into a tangible object, amenable to further charting and exploration. Likewise, technical advances in neuroimaging have led researchers to regard the human brain as a system that can be explored as a whole, leaving the details for the fullness of time.

Structural Organization

The analysis of network topology in the brain (*14*) highlights the principles underlying its organizational properties—such as efficient information passing, robustness, adaptability, resilience—and, more importantly, the divergent functionalities within a fixed structure. Many characterizations suggest that the structural architecture of the brain may reflect a compromise between wiring costs and the computational imperatives above (*15*). Structural brain networks exhibit small-worldness (*14*) and modularity (*15*). Small-worldness indicates a short average path length between all node pairs, with high local clustering, whereas modularity denotes dense intrinsic connectivity within a module but sparse, weak extrinsic connections between modules.

More recently, the rich-club phenomenon may offer a more cogent description of networks that facilitate dynamic and diverse brain functions (Fig. 1C), in which rich-club hubs (heavily connected nodes) are highly interconnected to promote global communication among modules (*16*). Rich-club organization is seen in a wide range of neuronal systems from the neuronal systems of *Caenorhabditis elegans* (*17*) and the macaque cerebral cortex (*18*) to the human brain (*16*). In humans, rich-clubs have been found to include the precuneus, superior frontal and superior parietal cortex, hippocampus, putamen, and thalamus (*16*) (Fig. 2B).

Several organizational properties of structural brain networks have been studied; for example, a computational modeling study showed a relatively

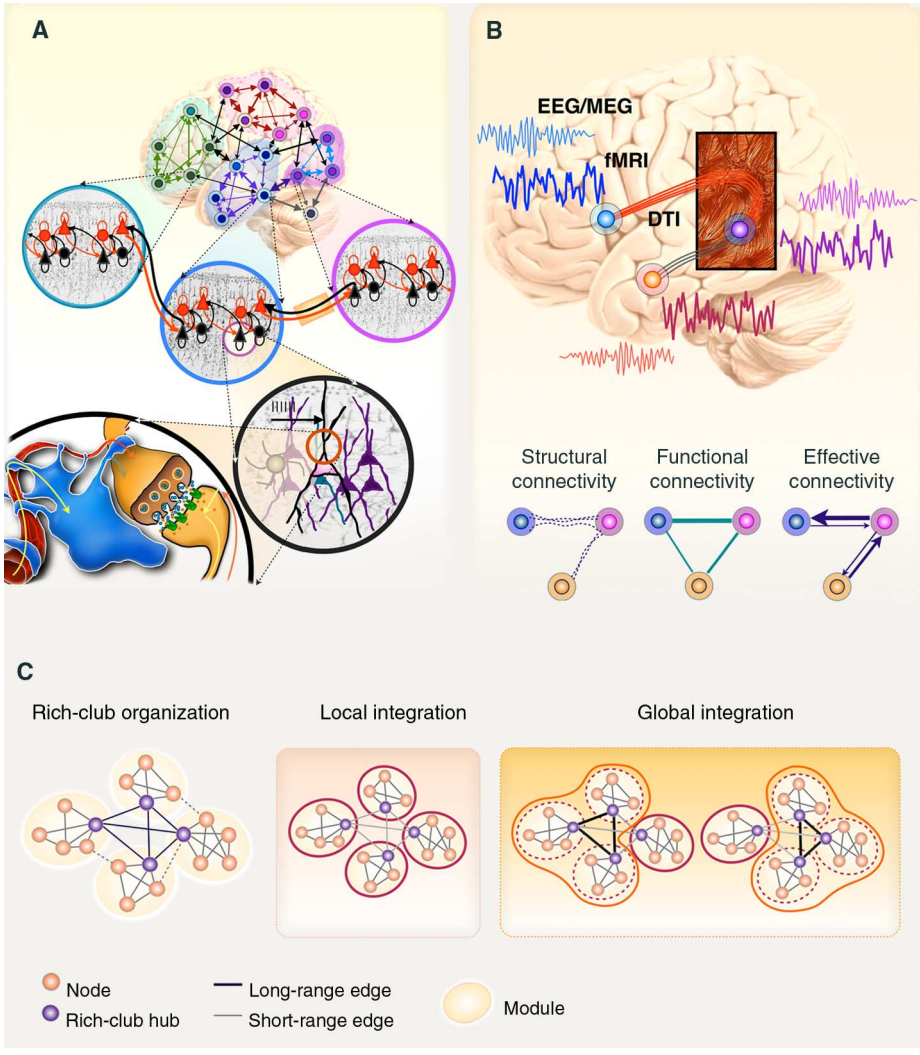

Fig. 1. Node, edge, and organization in the brain network. (**A**) Schematic of the multiscale hierarchical organization of brain networks: from neurons and macrocolumns to macroscopic brain areas. A network is composed of nodes and their links, called edges. A node, defined as an interacting unit of a network, is itself a network composed of smaller nodes interacting at a lower hierarchical level. (**B**) Depictions of "edges" in a brain network, as defined by three types of connectivity: structural, functional, and effective. Structural connectivity refers to anatomical connections and (macroscopically) is usually estimated by fiber tractography from diffusion tensor MRI (DTI). These connections are illustrated with broken lines in the bottom images. Functional and effective connectivity are generally inferred from the activity of remote nodes as measured by using BOLD-fMRI or EEG/MEG signals. Functional connectivity, defined by the correlation or coherence between nodes, does not provide directionality or causality and is therefore depicted without arrows. Because effective connectivity is estimated by using a model of neuronal interactions, it can evaluate directionality. This is illustrated by the one-sided arrows. Adjacency (or connectivity) matrices subserve graph theoretical analyses of brain systems and encode structural and functional connectivity between pairs of nodes. (**C**) Rich-club organization describes many aspects of the hierarchical (modular) brain. As shown in this (simplified) schematic, the brain is highly modular, with nodes integrated locally through strong short-range edges (thin gray lines). Rich-club hubs are densely interconnected among themselves (mainly through long-range edges in thick black lines). These hubs facilitate intermodular communication or global integration that may be contextualized via weaker long-range connections (dotted lines). Brain functions can be characterized by local integration within segregated modules for specialized functions and global integration of modules for perception, cognition, and action. Context-dependent global integration recruits a subset of modules with different configurations that nuances the collaboration between different modules. See also (*2*).

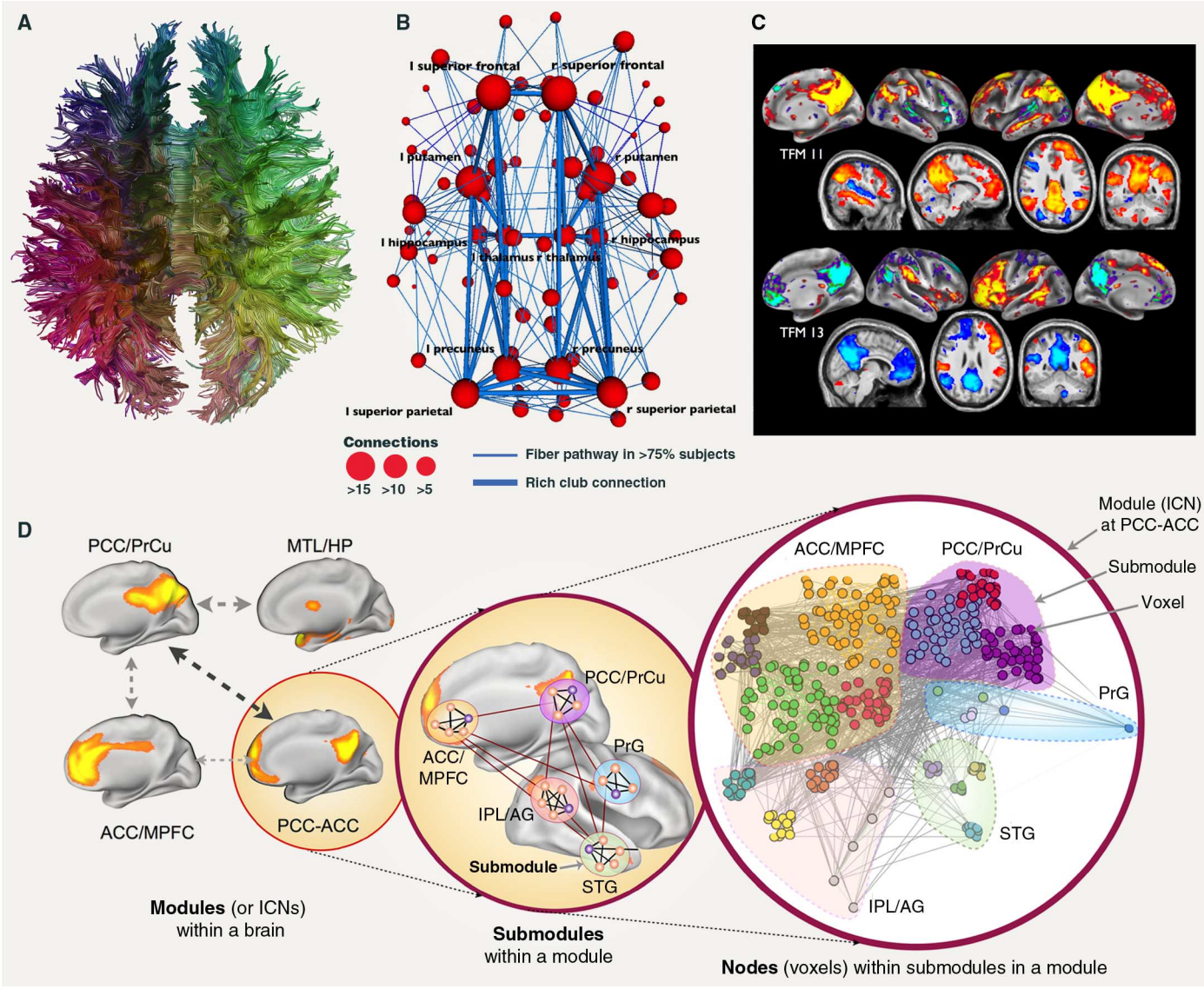

Fig. 2. Convergence: structural and functional brain network organization. (**A**) Whole-brain fiber bundles reconstructed from diffusion tensor MRI are colored according to their connection similarity (*8*). A structural brain network can be constructed by parcellating fibers according to the cortical or subcortical regions they interconnect. (**B**) The human brain's structural network constructed from diffusion tensor MRI (*16*) has rich-club hubs in the precuneus, superior frontal and superior parietal cortex, the subcortical hippocampus, putamen, and thalamus. Dark (thick) blue and light (thin) blue lines represent connections between rich clubs and connections from rich clubs to others, respectively. The sizes of the nodes reflect the number of their connections. (**C**) Repertoires of spatial modules have emerged from the analysis of spontaneous BOLD fluctuations in the brain at rest, i.e., ICNs that comprise clusters of nodes fluctuating synchronously. This figure shows two examples of temporal functional modes (TFMs, more detailed ICNs) derived from temporal independent component analysis of fast resting-state fMRI (*25*). TFMs often correspond to task-related neurocognitive modules. As an example, TFMs 11 and 13 are similar to the task-activated semantic network and the lateralized language network, respectively. (**D**) Hierarchical (modular) resting-state functional network. Changes in dynamic global coupling occur between the four ICNs (modules) associated with the default mode network (*26*). However, relatively stable coupling exists among the submodules (red lines within the second circle) within a given ICN, and highly stable local coupling is maintained among nodes within individual submodules (black solid lines within submodules in the second circle). The stability of connectivity estimated over a relatively long time period suggests that, at the level of the submodule, functional connectivity is closely related to the underlying structural connectivity, especially intracortical connectivity (which diffusion MRI cannot resolve). Note that ICNs show a hierarchical modularity: Submodules within ICNs are composed of hierarchically clustered voxels. This hierarchical modularity is neuronally plausible, considering the multiscale nature of neuronal circuits from micro- to macroscopic brain networks. See also (*21*). The ICNs displayed in this figure are networks located mainly in the posterior cingulate cortex and precuneus (PCC/PrCu), the anterior cingulate cortex and medial prefrontal cortex (ACC/MPFC), the posterior cingulate cortex and anterior cingulate cortex (PCC-ACC), and the medial temporal lobe and hippocampal formation (MTL/HP). Submodules within the PCC-ACC ICN in the second and the third circles are ACC/MPFC (node size, 6 mm by 6 mm by 6 mm, n = 188 nodes), PCC/PrCu (n = 104), inferior parietal lobe and angular gyrus (IPL/AG) (n = 52), precentral gyrus (PrG) (n = 7), and superior temporal gyrus (STG) (n = 25). Modified from (*8*) for (A) and from (*26*) for (D), and permitted to reproduce from (*16*) for (B) and from (*25*) for (C).

high resilience to random node removal (attack) (*19*). However, there appears to be a greater vulnerability and topological reorganization after damage to central hubs or rich clubs (*16*, *19*). In a study of schizophrenia, the connection density among rich-club hubs was significantly reduced (*20*), suggesting a disruption of global communication in this disease.

Although the rich-club phenomenon is consistent with hierarchical brain architectures (*21*), it largely has its basis in "strong" structural connectivity, measured with neuroimaging. In contrast to noninvasive human studies, recent tracing studies in the macaque brain suggest a denser connectivity matrix, with many "weak" long-range connections (*11*). These weak long-range connections may play an important role in hierarchically organized functional modules (*12*).

Despite differences in detail, the overall concept of modules (defined by dense short-range connections) that are integrated by relatively sparse long-range connections remains valid. We use the term rich-club phenomenon in this context, not as a mathematical definition. Notably, the modular, hierarchical, and rich-club–like brain organization may furnish the structural constraints under which functional connectivity emerges.

Structure Function Convergence

Like the Lake Isle of Innisfree, the resting brain was originally thought to be calm and peaceful. This view, however, ignores turbulent interactions beneath the surface. Although fMRI measures the "resting-state" brain, what is measured is restless (*22*). When endogenous fluctuations in resting-state BOLD signals are decomposed (by using independent component analysis), they reveal repertoires of spatial modules, that is, clusters of nodes fluctuating synchronously, called intrinsic connectivity networks (ICNs). Considerable correspondence can be found between ICNs and task-related neurocognitive modules (*23*, *24*). Some representative ICNs are the default mode network; dorsal attention network; executive control network; salience network; and sensorimotor, visual, and auditory systems (*22*). Analyses of faster resting-state fMRI further have revealed temporally independent functional modes (extended ICNs) (Fig. 2C), which map more precisely to task-evoked modules than conventional ICNs, some of which contain submodules overlapping with other modes (*25*).

Setting aside the many interesting questions about ICNs (e.g., why are ICNs not at rest when they are not needed?), we note that most ICNs incorporate two or more segregated submodules within and between hemispheres. A submodule (subnetwork) within an ICN comprises synchronously active

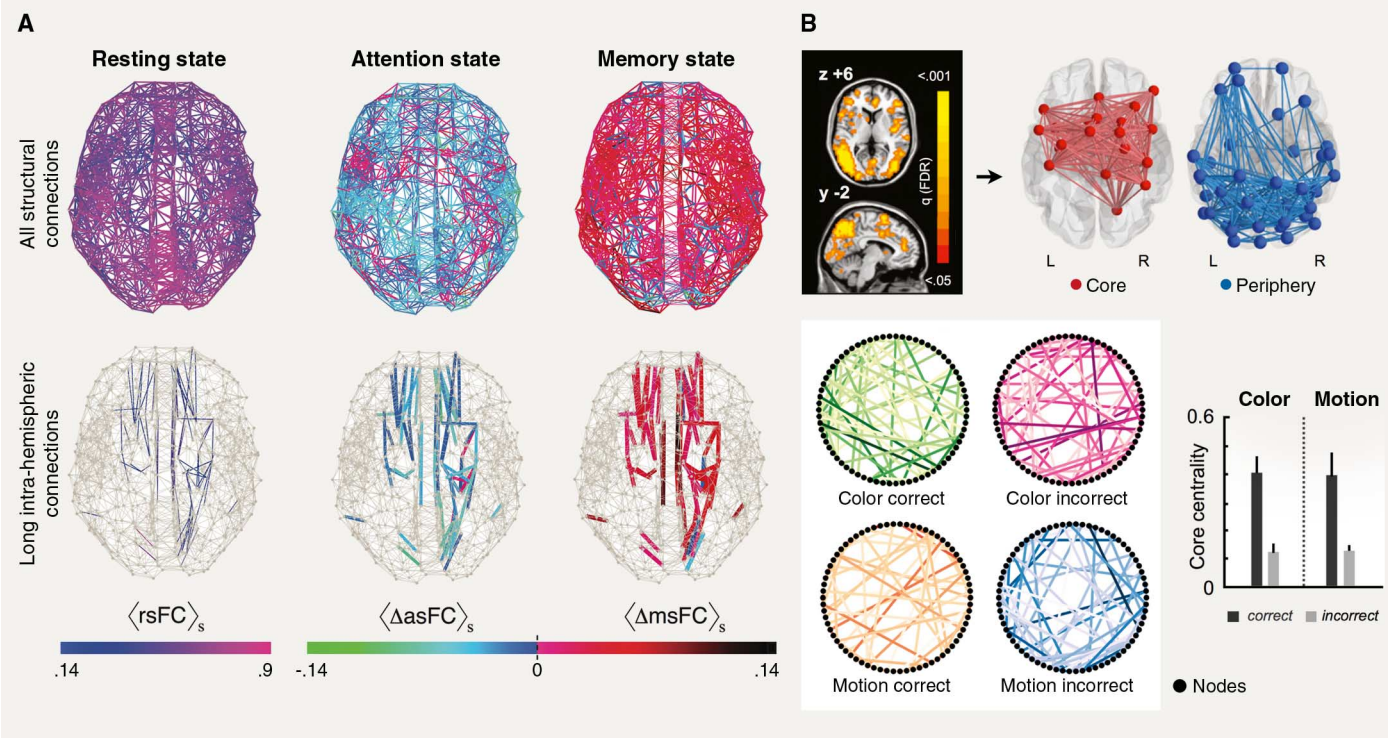

Fig. 3. Context-sensitive divergence. (**A**) Task-dependent reconfiguration of functional connectivity was found predominantly in long-range intrahemispheric connections (*31*). All structural connections (top row), especially long-range intrahemispheric connections (bottom row), are colored according to the functional connectivity during rest (rsFC, left column) and task-dependent deviations in functional connectivity from rest during attention (ΔasFC, middle column) and memory (ΔmsFC, right column). In the maps of intrahemispheric connections (bottom row), thicker lines in the resting state indicate stronger rsFC; thicker lines during attention indicate larger decreases in FC, and thicker lines during memory indicate larger increases in FC relative to rest, averaged across participants. An overall decrease in functional connectivity was observed during the attentional task, whereas a memory task elicited an overall increase of functional connectivity. Furthermore, the functional connectivity of long-range intrahemispheric pathways decreased to a greater degree during attentional demands and increased during the memory task, compared with the other subgroups of connections during task performance. This suggests that global integration by modulating long-range connectivity is crucial for task-dependent functions. (**B**) Functional MRI activations during the preparatory phase of a visual discrimination task for color and motion (*32*) were used as nodes for graph analysis (top left). FDR, false discovery rate. These nodes were decomposed into either core nodes (red in top middle) or peripheral nodes (blue in top right) according to their connection densities. Visual areas V4 (color processing) and V5/hMT (motion processing) were categorized as peripheral nodes. Functional networks during the preparatory period before either correct or incorrect responses for color and motion stimuli are shown in the bottom left (black dots in circle maps indicate nodes and colored lines for task-dependent functional connectivity). During both color and motion discrimination tasks, erroneous preparation trials had significantly lower core centrality, a global measure of the core's ability to integrate and control information flow (bottom right). This finding indicates that aberrant core-periphery interactions may be responsible for the incorrect responses in this study. Redrawn from (*31*) for (A) (courtesy of A. M. Hermundstad) and modified with permission from (*32*) for (B).

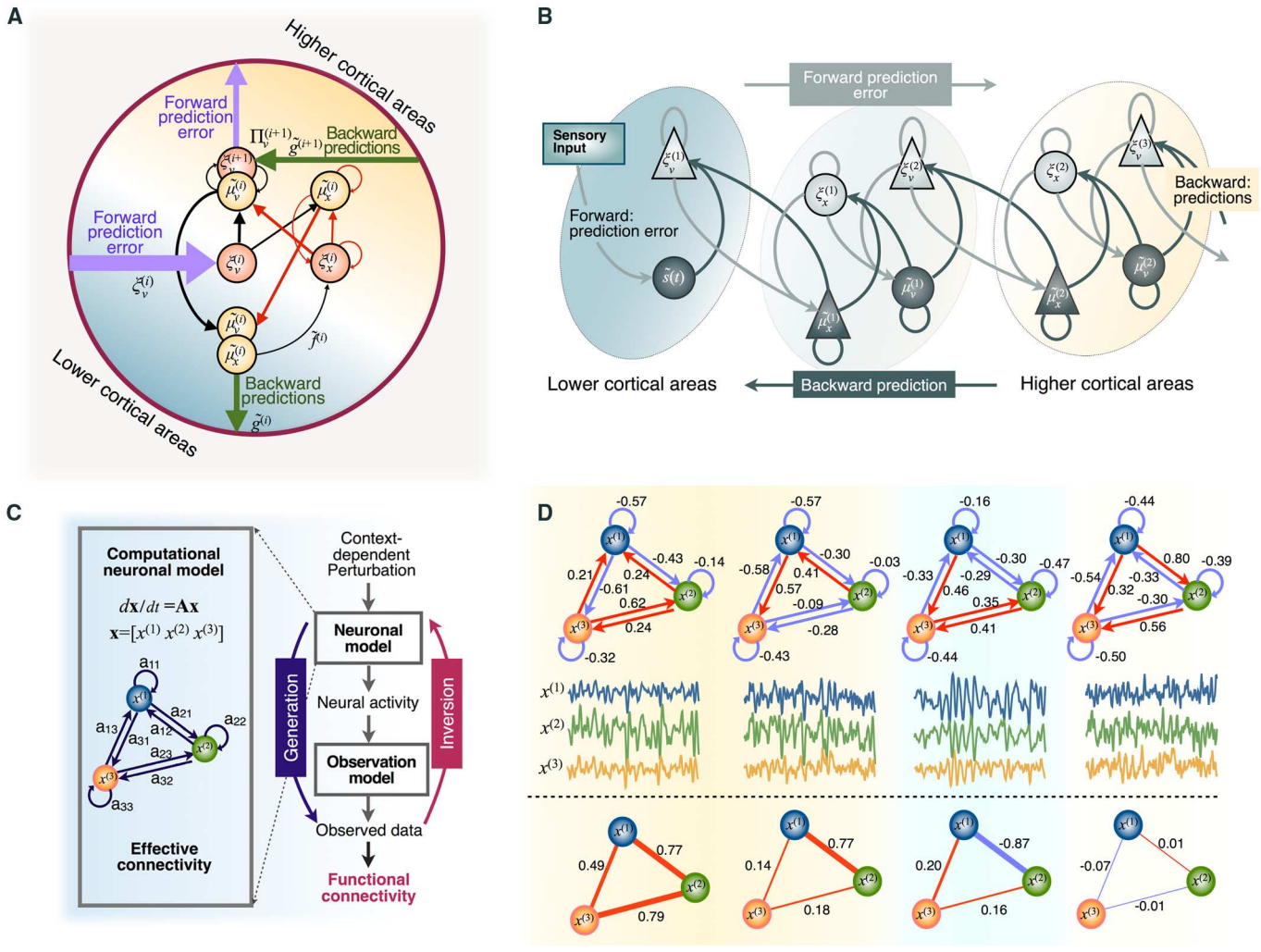

Fig. 4. Mechanisms and simulations of functional networks. (**A**) An example of a canonical microcircuit. A simplified canonical microcircuit (*36*) includes intrinsic connectivity (inhibitory and excitatory) and extrinsic forward and backward connectivity. Inhibitory connections are colored in red, and excitatory connections are in black. Unlike the simple role edges play in most current network analyses, a canonical microcircuit node is equipped with intrinsic connections and states. (**B**) A theory of predictive coding in the hierarchical brain network may explain what information is broadcast within the network and how edge strengths are adjusted (*39*). According to this theory, the brain entails a hierarchical generative model that is used to predict sensory or lower level input. The predictions of the generative model are adjusted at each hierarchical level until the prediction errors between sensory inputs and predictions are minimized. This prediction error minimization process is mediated by forward driving connections, delivering prediction errors (light arrows) from an earlier area to a higher area, and (modulatory) backward connections (dark arrows) that build context-sensitive predictions. Prediction errors for hidden causes and hidden states, at the *i*th level, $[\xi_v^{(i)}, \xi_x^{(i)}]$ are the weighted [by precisions, $\Pi_v^{(i)}, \Pi_x^{(i)}$] difference between conditional expectations about hidden causes and states $[\tilde{\mu}_v^{(i)}, \tilde{\mu}_x^{(i)}]$ and their predicted values. The ellipses correspond to nodes in a network. See (*39*) for details. (**C**) The neuronal mechanism, i.e., causal influences among nodes underlying observed data, is inferred via computational modeling, where parameters of a dynamic network model (e.g., effective connectivity) are estimated by using model inversion. During model inversion, the effective connectivity in the model is optimized to minimize errors between predicted signals and observed data, in a manner similar to the predictive coding theory for the brain in (B). In fMRI, the observation model represents the hemodynamic response to underlying neural activity. Functional connectivity of the observed data describes the undirected statistical dependencies among nodes. (**D**) Four simulations using a model with a linear differential equation for three nodes and four different sets of effective connectivity [top, based on the computational model in (C)], generating four sets of signals at each node (middle). The functional connectivity among nodes was evaluated by using correlation coefficients (bottom). Notably, effective connectivity with different signs and weights generated diverse functional connectivity patterns from an identical structural wiring; for example, different mechanisms but almost identical functional connectivity between nodes 1 and 2 emerged in the first and second simulations, whereas negative functional connectivity under the same structural connectivity resulted from the third simulation. As shown in the fourth simulation, the third node plays an important role in shaping the dynamics of nodes 1 and 2 as a modulator or a neuronal context, suppressing functional connectivity. These simulations address the importance of computational modeling for a mechanistic understanding of the brain network. Modified from (*36*) for (A) and from (*39*) for (B).

voxels, with a stable coupling that persists over time, although the coupling between different ICNs may be more dynamic and context-sensitive than the strong coupling among the nodes that comprise any given ICN (*26*, *27*) (Fig. 2D).

This enduring and tight synchrony can be attributed to local integration by short-range, strong-tied dense connectivity within the submodule. High-density local projections in the macaque brain characterized by using retrograde tracers support this notion [e.g., (*11*)].

Meanwhile, the coupling between submodules of an ICN is plausibly mediated by strong long-range structural connections, such as commissural fibers for bilateral submodules and longitudinal fibers within a hemisphere. For example, submodules of the default mode network appear to be interconnected through long-range fibers characterized with diffusion tensor MRI (*28*).

Clearly, functional connectivity depends on how it is measured, and correlations measured over shorter periods of time may themselves fluctuate. However, it is likely that functional connectivity over long time periods (5 to 10 min.) reflects underlying structural connectivity because functional connectivity measures the average statistical dependencies between two nodes over the measured period. In other words, functional connectivity is highly constrained by structural connectivity.

Simulation studies of the human brain network show that structural connectivity can predict resting-state functional connectivity (*29*). A study based on macaque brain connectivity also demonstrated that anatomical connectivity derived from axonal tract tracing provided a good explanation for resting-state functional connectivity (*30*). Inferring structural connectivity from resting-state functional connectivity may also be possible within subgroups of structural connections (*31*).

In this respect, resting-state functional connectivity may be more informative about short-range intracortical connectivity, which diffusion tensor MRI cannot resolve easily. Resting-state functional network analysis reveals a hierarchical modularity in brain networks (Fig. 2D) that is consistent with the multiscale nature of brain anatomy from the microscopic to the macroscopic (*21*). However, if structural connectivity determines functional connectivity, why is functional connectivity so context and state-dependent?

Structure Function Divergence

Comparisons of functional connectivity statistics during the performance of attention and memory tasks demonstrate that functional connectivity changes according to task, with an overall reduction for attention and an overall increase for memory (*31*). Moreover, long-range intrahemispheric connections show a larger decrease in functional connectivity during visual attention and a greater increase during memory task, compared with short-range connections (Fig. 3A). These results indicate that changes in global integration via long-range connections facilitate diverse cognitive functions and disclose its context sensitivity.

The importance of global integration for successful task performance was also documented in a study by using a color-or-motion judgment task. When perceptual areas were recruited for their specialized functions (for example, V4 for color perception), they were tightly integrated into the large-scale network topology (*32*). Crucially, aberrant interactions between nodes in the network's core and periphery predicted performance errors. This implies a strong link between behavioral performance and anticipatory reconfiguration of the topology of the network core (e.g., rich clubs) (Fig. 3B).

These studies suggest that the divergence between invariant structural connectivity and context-sensitive functional connectivity may be expressed more at the level of global integration of segregated modules than local integration within a module. In this respect, the rich-club architecture supports functional diversity by providing long-range interconnections among modules. These long-range connections are clearly flexible and facilitate diverse integration for various functional demands (*31*, *32*). Modulating synaptic gains or nonlinear synchronous interactions, or both, may underpin this versatility.

How global network architectures self-organize or reconfigure for specific tasks remains an open question. More investigations of task-specific functional topologies are required to answer this question. However, even with our current capabilities, it is clear that, for any one structural connectivity pattern, there are many possible patterns of functional connectivity. This should be of no surprise because one-to-many and many-to-one structure-function mappings are ubiquitous in systems biology, from molecular to the macroscopic level (*3*). In short, recent coarse-grained topological characterizations of structural and functional networks may not be sufficient to illuminate the dynamical mechanisms of functional integration.

From Phenomena to Mechanisms

What neuronal architectures support integration within and between submodules? What information is conveyed from one submodule to another during functional integration? Under what principle do submodules distribute incoming information within themselves, and how do their nodes remain integrated while doing so? At this point, these questions remain open; however, our current understanding of canonical neuronal circuits and their putative roles within the principles of brain functioning may shed some light on these questions.

Numerous attempts have been made to assimilate diverse anatomical and physiological findings into a canonical microcircuit, a model architecture of cortical processing at the millimeter scale (*33*–*35*). Recent formulations have considered extrinsic and intrinsic connections among excitatory and inhibitory populations specific to granular, supra-, and infragranular cortical layers (*36*) (Fig. 4A). In a hierarchical setting, extrinsic connections can be forward, backward, or lateral. Forward and backward connections emphasize driving and modulatory properties, respectively.

Canonical circuits of intrinsic connections are easily concatenated into a hierarchical network. In these architectures, a canonical microcircuit node does not function as a simple convergence of edges, as in most current network analyses, but is equipped with intrinsic connections and states. The intrinsic neuronal state, self-organized by intrinsic connections, is crucial for processing unexpectedly weak extrinsic input. For example, in the macaque monkey, the extrinsic lateral geniculate nucleus (LGN) input to V1, which is small (~1%) compared with the intrinsic inputs in V1 (~85%) (*11*), can drive V1 very efficiently because of state-dependent dynamics of V1 microcircuitry. In other words, recurrent connections within V1 may amplify feedforward input from LGN (*37*).

In the brain, like the Internet, information coding is as crucial as structural topology in reducing information transfer costs. In the Internet, coding is usually conducted offline before transmission (e.g., MPEG video compression). Neural information, however, is manipulated online, while traveling within and between subnetworks. For example, a visual impression in the primary visual cortex is transferred to the frontal cortex in a compact and abstract form that is comprehensible to the frontal cortex. This online coding may be conducted through dynamic integration of distributed nodes by adjusting edge strengths (i.e., connectivity) within the network.

What information is distributed within the network, and under what principle is it integrated by state-dependent (adjustable) edge strengths? One of the most appealing theories is predictive coding, which is supported by a growing body of evidence in neuroscience and theoretical neurobiology (*38*, *39*). In predictive coding, neuronal networks constitute a probabilistic generative model of incoming sensory input: Brain networks make top-down predictions about ascending input and then refine these predictions by minimizing prediction errors. Prediction tuning (or learning) is a process of adjusting the model parameters (e.g., edge strength) by changing synaptic efficacy. In a hierarchical setting (*36*), backward connections deliver predictions to lower levels, whereas forward connections convey prediction errors to upper levels (*39*) (Fig. 4B). Intrinsic states and edge strengths are recursively updated to produce better predictions at each level of the hierarchy. Under models like predictive coding, the directed edge strength corresponds to the effective connectivity of the network en-

gaged during a specific task. This sort of computationally informed modeling of neuronal message passing may provide an appealing and plausible explanation for the functional integration among hierarchical subnetworks.

Return to Reality: Modeling Links Gaps

In reality, no in vivo imaging to date can measure effective connectivity directly. Furthermore, effective connectivity can only be defined within an experimental or neuronal context (*40*), as realized many years ago in electrophysiology (*41*): "in particular, 'effective connectivity' may be only a subset of the actual structural connectivity since it deals only with connections and relations that are active during the time of measurement." This context sensitivity makes direct measurement of effective connectivity unattainable without a very carefully controlled neuronal context and an explicit model of neuronal interactions.

As in early electrophysiology studies [e.g., (*41*)], effective connectivity is quantified by estimating the parameters of biophysical or computational models from measured time series (Fig. 4, C and D). Several methods now exist to estimate directed connectivity on the basis of either phenomenological time series models, such as Granger causality, or realistic neuronal models, such as dynamic causal modeling (DCM). The pros and cons of these methods have been discussed elsewhere (*42*, *43*). DCM is a Bayesian identification scheme based on a model of neuronal interactions and an observation model (e.g., the hemodynamic model for fMRI) (*44*). This model-based approach is gradually being validated by animal and human studies, using EEG/MEG or fMRI, and is being used increasingly widely (*42*).

Because models are judged by their predictive validity, models of effective connectivity must be updated in light of new structural connectivity findings and empirical evaluations. Recent advances in microscopic techniques—such as microscopic tracing and imaging [e.g., (*45*)], a structural and molecular interrogation technique called CLARITY (*46*), and precise optogenetic stimulation—may allow us to refine our models for macroscopic functional imaging data. Crucially, because effective connectivity rests on structurally constrained network models to explain functional activity, computational modeling can serve as an interface between structure and function.

Getting Closer to Brain Network

This review has suggested that (i) the relationship between structure and function is an integration problem, (ii) the organization of structural networks supports local and global integration, (iii) the inherent context sensitivity of functional integration mandates a divergence of functional connectivity from structural connectivity, and (iv) understanding the dynamic configuration of connectivity will benefit from theoretically informed and realistic neuronal models.

However, our understanding of structure-function mapping at the network level is still in its infancy. We have only looked at a few aspects of brain networks with rather crude measurements. Some examples of the many topics reserved for future research include dynamic and transient-state functional networks (*47*), coordination of task-specific brain networks, reconfiguration of effective networks because of extrasynaptic neuromodulators (*48*), long-term modification of structural network for functional demands, and individual variations, particularly in neurological and neuropsychiatric disease. Toward these ends, effort should be devoted to constructing finer maps of structural connectivity, especially directed and weighted connectivity, by combining research from microscopic and macroscopic scales. Last, effective connectivity needs to be quantified by using more realistic computational modeling for both resting and task-induced states.

Function may deviate from structure to exhibit dynamic and contextualized behavior. Such divergence of function from structure is perhaps the most intriguing property of the brain and invites intensive future research. By studying the dynamics and self-organization of functional networks thereby enabled, we may gain insight into the true nature of the brain as the embodiment of the mind. The repertoire of functional networks will most likely emerge from the (hidden) structural architecture that enables the efficient global integration of local integrations.

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