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# Understanding Structural-Functional Relationships in the Human Brain: A Large-Scale Network Perspective

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## Abstract

Relating the brain's structural connectivity (SC) to its functional connectivity (FC) is a fundamental goal in neuroscience because it is capable of aiding our understanding of how the relatively fixed SC architecture underlies human cognition and diverse behaviors. With the aid of current noninvasive imaging technologies (e.g., structural MRI, diffusion MRI, and functional MRI) and graph theory methods, researchers have modeled the human brain as a complex network of interacting neuronal elements and characterized the underlying structural and functional connectivity patterns that support diverse cognitive functions. Specifically, research has demonstrated a tight SC-FC coupling, not only in interregional connectivity strength but also in network topologic organizations, such as community, rich-club, and motifs. Moreover, this SC-FC coupling exhibits significant changes in normal development and neuropsychiatric disorders, such as schizophrenia and epilepsy. This review summarizes recent progress regarding the SC-FC relationship of the human brain and emphasizes the important role of large-scale brain networks in the understanding of structural-functional associations. Future research directions related to this topic are also proposed.

## Keywords

functional connectivity, structural connectivity, module, rich club, graph theory, connectome

One of the most important and challenging questions in neuroscience is the elucidation of the relationship between the structure and function of large-scale brain systems—that is, how the structure of the neural connective network underlies cognitive functions. Current understanding emphasizes the notion that cognitive functions are derived from interactions within and between a distributed set of brain regions (Zeki and Shipp 1988; Mesulam 1990) and can be further described as global integrations of local specialized processing (Park and Friston 2013). Specifically, a new emerging paradigm in cognitive neuroscience has suggested that cognition results from the dynamic interactions of distributed brain areas that operate in large-scale networks, such as the networks of vision, motion, memory, and attention (Bressler 2002; Bressler and Menon 2010). The architecture of the structural connections shapes the functional interactions among the cerebral areas, giving rise to diverse functional networks. Thus, mappings of the spatial patterns of structural and functional brain interactions are opening a new avenue for understanding how the structural-functional relationship of the human brain underlies cognition and behavior.

Using current noninvasive multimodal imaging techniques and graph theory, researchers have been able to model the human brain as a complex network of interacting elements, or graph, and further characterize its topological

properties and underlying mechanisms. The characterization of structural and functional connectivity patterns of brain networks has been referred to as the concept of “connectomes” (Sporns and others 2005; Biswal and others 2010; Kelly and others 2012; Smith and others 2013). A handful of neuroimaging studies have demonstrated that the structural and functional networks, or connectomes, of the human brain share many important topologic features, including small-worldness, power-law degree distribution,

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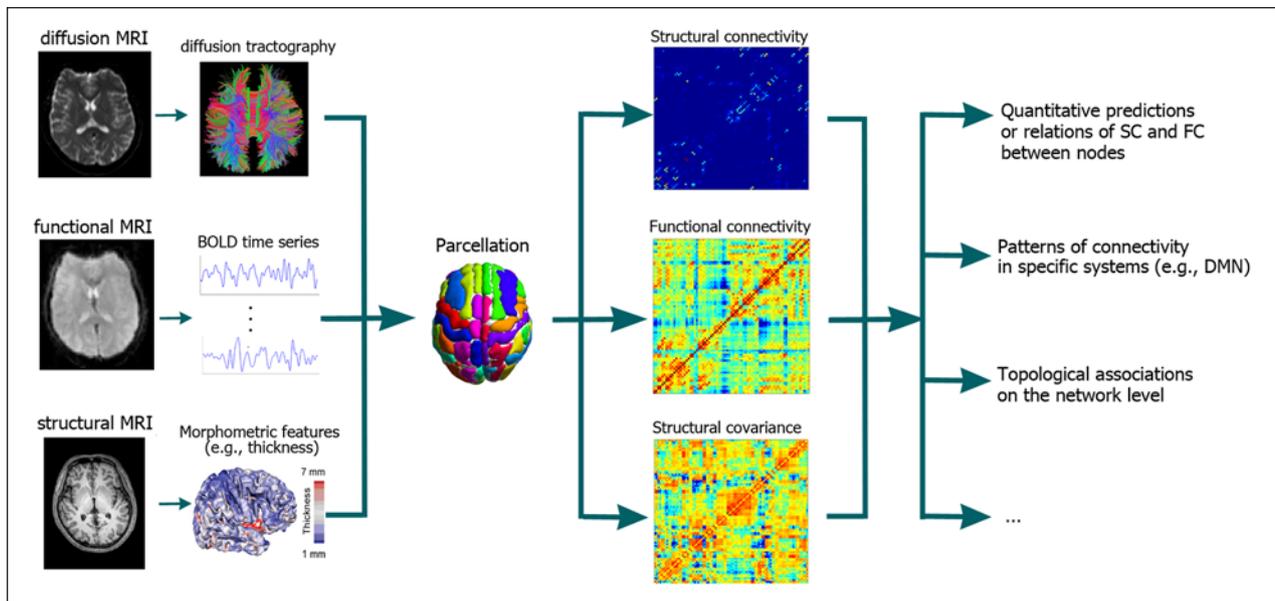
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**Figure 1.** A flowchart for constructing large-scale brain networks and exploring structural connectivity (SC)–functional connectivity (FC) associations. First, the brain networks can be constructed based on the concepts of SC, FC, and structural or functional covariance using the current noninvasive multimodal imaging technologies through the following steps: defining network nodes using a predefined regional parcellation atlas, estimating associations between nodes from neuroimaging data, and generating association matrices, including all pairwise associations between nodes. Then, the SC-FC relationship can be explored through different aspects, which includes quantitative predictions or relations of SC and FC between nodes, connectivity patterns in specific systems (e.g., default-mode network [DMN]), and topologic associations (local and global) on the network level. BOLD = blood oxygen–level dependent.

modularity, hierarchy, and the existence of highly connected hubs (for reviews, see Bullmore and Sporns 2009, 2012; He and Evans 2010; Filippi and others 2013). These findings suggest an intricate and tight relationship between the structural and functional networks of the human brain. Recent studies have provided direct evidence that the patterns of structural connectivity (SC) and functional connectivity (FC) in the brain are correlated. These studies included empirical analysis of interregional SC-FC couplings (Skudlarski and others 2008; Hagmann and others 2008; Honey and others 2009), network topologic organization (e.g., small world, community, rich club, and motifs) (Park and others 2008; Baria and others 2013; Alexander-Bloch and others 2013; Betzel and others 2013; van den Heuvel and Sporns 2013; Sporns and Kötter 2004; Adachi and others 2012; Shen and others 2012; Goñi and others 2014), and computational modeling of large-scale neuronal dynamics (Zhou and others 2006, 2007; Honey and others 2007, 2009; Izhikevich and Edelman 2008; Ghosh and others 2008; Deco and others 2009, 2013; Abdelnour and others 2014). Moreover, the SC-FC coupling is not constant but rather exhibits significant changes during normal development (Hagmann and others 2010) and brain diseases (Skudlarski and others 2010; Zhang and others 2011a; van den Heuvel and others 2013; Alstott and others 2009; Pons and others 2010).

In this review, we summarize the progress of the research into the relationship between the structural and functional connectivity of large-scale brain networks that has been made using both empirical data analysis and computational model studies. Figure 1 shows a flowchart for the construction of large-scale brain networks based on the concepts of SC and FC and explorations of SC-FC relationships in the human brain, using the current noninvasive multimodal imaging technologies. We first introduce the basic concepts of SC, FC, and the topologic characterization of brain networks. Next, we describe the studies of structural-functional association via direct SC-FC comparisons, or linking them in network topology analysis and computational modeling of large-scale neural dynamics. Furthermore, we discuss the evidence for the changes in SC-FC coupling in brain networks that occur across normal development and in disease. Last, we conclude with considerations about future research directions.

## Brain Connectivity and Large-Scale Brain Networks

### Structural Connectivity

Structural connectivity refers to the white matter anatomic connections that link different brain regions and can be

macroscopically estimated with current noninvasive diffusion imaging technologies, such as diffusion tensor imaging (DTI) and diffusion spectral imaging (DSI) (LeBihan 2003; Wedeen and others 2005), and computational tractography approaches, such as deterministic “streamline” tractography (Conturo and others 1999; Mori and van Zijl 2002; Catani and others 2002; Wakana and others 2004) and probabilistic diffusion tractography (Parker and Alexander 2005; Behrens and others 2007). SC typically reflects a map of the white matter fiber bundles and structural integrity of the brain. Several measures can be used to quantify SC properties, including fractional anisotropy, mean diffusivity, streamline counts, and probabilistic tractography. Based on the concept of SC, several recent studies have been able to establish human whole-brain structural networks with diffusion MRI tractography approaches (Hagmann and others 2007; Iturria-Medina and others 2008; Gong and others 2009). In addition, researchers have also examined structural covariance in morphologic measures (e.g., gray matter volume, cortical thickness, and surface area) among regions across subjects as an additional SC measure in the human brain (Mechelli and others 2005; Lerch and others 2006; He and others 2007).

### *Functional Connectivity*

The functional interactions of neural dynamics can be captured via functional and effective connectivity (Friston 1994). FC refers to the temporal correlations or statistical dependences between observed neurophysiologic events in spatially remote brain areas (Friston 1994) and can be measured with a broad range of linear (e.g., Pearson correlation) or nonlinear (e.g., synchronization likelihood and mutual information) methods. Moreover, FC does not provide directionality or causality of the functional interactions that link different neural elements. In contrast, effective connectivity describes the influence that one neural element exerts over another in a causal model and thus evaluates the directionality or causality of neural interactions (Friston 1994). Essentially, both functional and effective connectivity are generally derived from examinations of the relationships between time series of neural dynamics or activities between different regions that are obtained with a variety of neurophysiologic and neuroimaging techniques, such as electroencephalography/magnetoencephalography and fMRI.

Notably, resting-state fMRI (R-fMRI), a promising brain functional imaging technique, has used FC as a metric of functional integration to determine the intrinsic spatial patterns of coherent neural activity in spontaneous low-frequency blood oxygen–level dependent (BOLD) fluctuations (<0.1 Hz) (for a review, see Fox and Raichle 2007). The spatial patterns in synchronized spontaneous brain activity measured by R-fMRI occur not only in

local neuroanatomic subsystems (Biswal and others 1995; Lowe and others 2000; Hampson and others 2002; Greicius and others 2003) but also over the entire cortex of the brain (Salvador and others 2005; Achard and others 2006; He and others 2009). Interestingly, researchers also extended the standard concept of FC to functional covariance for the characterization of the spatial patterns of brain correlative activity through examining the covariance of functional measures (e.g., amplitude of low-frequency fluctuations) in BOLD signals across subjects (Zhang and others 2011b; Taylor and others 2012).

### *Large-Scale Brain Networks*

The brain is a dynamic complex network of interconnected neural units (neurons or regions) that spans multiple spatial and temporal scales. The networks of the brain can be classified into structural and functional networks based on the collections of brain regions (i.e., nodes) involved and the types of connections that link them (i.e., edges). The current advances of *in vivo* neuroimaging techniques have offered opportunities to map the structural and functional connectomes of the human brain at the macroscopic scales (voxel or regional based). In a large-scale brain network model, the nodes are usually determined by the parcellation of a spatially continuous cortical manifold into homogeneous and unique regions (Park and Friston 2013). However, it is difficult to define the nodes of brain networks at the macroscopic scale because agreements have not been reached regarding how to best define the constituent brain units (Craddock and others 2013; Sporns and others 2005). Different strategies of brain parcellation rely on cytoarchitectonics, macro-anatomic landmarks, and connectivity-based information (for a review, see Craddock and others 2013). Data-driven techniques can be used to subdivide the whole brain into areas, such as clustering (Yeo and others 2011; Craddock and others 2012), independent component analysis (Kiviniemi and others 2009; Yu and others 2011, 2012), or random parcellations (Hagmann and others 2007; Zalesky and others 2010). These different strategies of regional parcellation have generated different structural and functional atlases (for details, see Craddock and others 2013).

Edges can be defined by the concept of SC or FC that are derived from current *in vivo* brain imaging techniques (e.g., fMRI and diffusion MRI) with a wide range of measures. Notably, the technical limitations of the current *in vivo* neuroimaging methods can lead to false positives or false negatives when estimating the likelihood of connections (Damoiseaux and Greicius 2009; Johansen-Berg and Rushworth 2009; Murphy and others 2009). Moreover, different parcellation schemes for building brain networks may significantly influence the quantification of spatial and topologic features of both functional and structural

**Table 1.** Network Topologic Properties.

Topologic Properties	Descriptions
Degree (or strength)	Number of connections (sum of all connection weights) of a node
Hub	A topologically important node with high centralities (e.g., degree)
Rich club	A structural system composed of densely interconnected hubs that has a central role in generating globally efficient information flow
Motif	A family of connected graphs or networks consisting of $M$ vertices and a set of edges, referring to a rich repertoire of local connectivity patterns
Small-world	An economic topology with high clustering coefficient and short path length or both high global and local information efficiencies
Module	A subset of highly interconnected nodes that are relatively sparsely connected to nodes in other modules

For the details of definitions and descriptions, please refer to Bullmore and Sporns (2009, 2012), Rubinov and Sporns (2010), He and Evans (2010), and Meunier and others (2010).

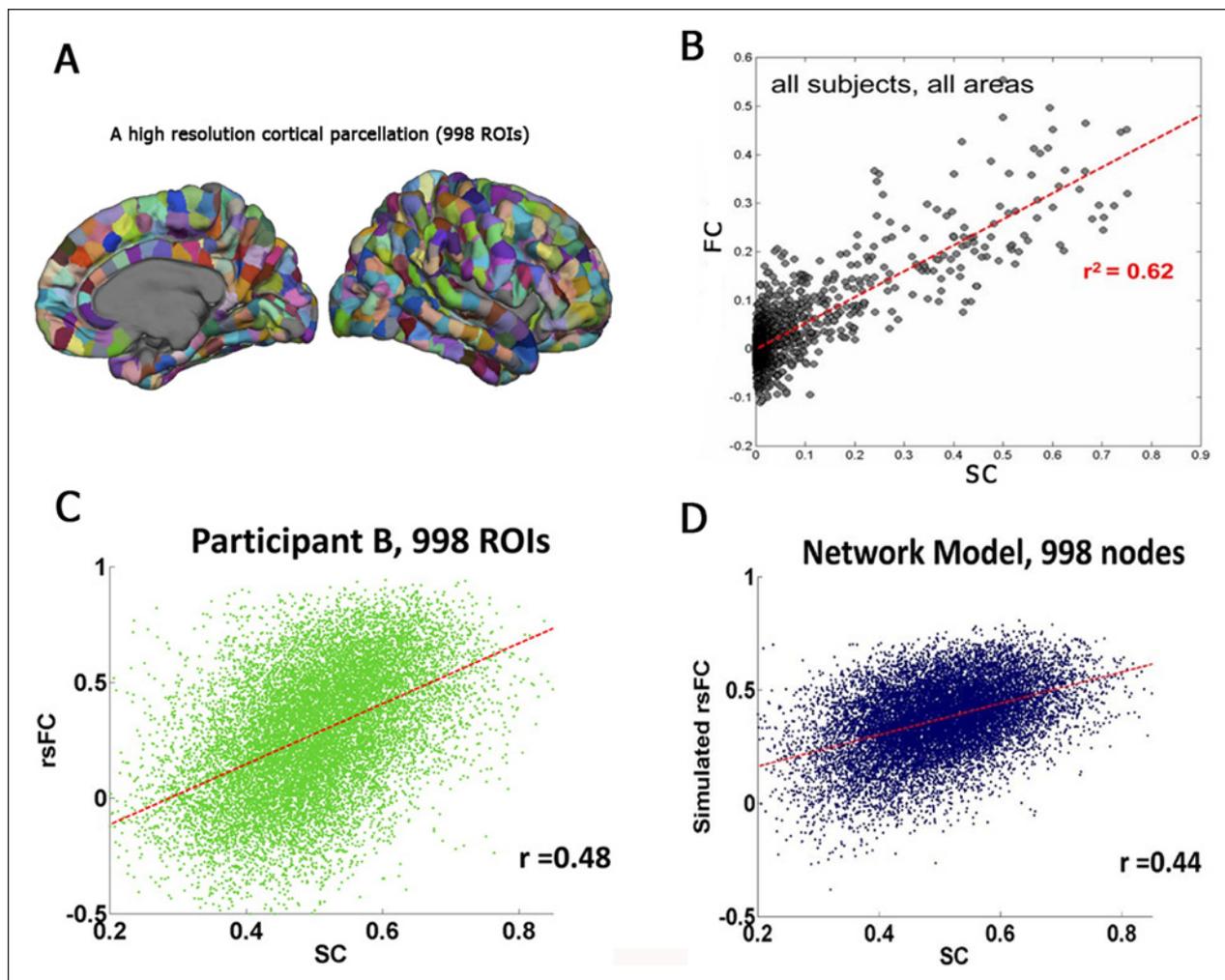
networks (Wang and others 2009; de Reus and van den Heuvel 2013; Fornito and others 2013). Nevertheless, the development of theories and technologies in neuroscience and complex network science has opened up a number of new opportunities to study the structure and function of the human brain at the systems level. Many important topologic properties have been demonstrated in large-scale brain networks using MRI, such as small-worldness (Eguíluz and others 2005; Salvador and others 2005; Achard and others 2006; He and others 2007; Gong and others 2009), modularity (Hagmann and others 2008; He and others 2009; Meunier and others 2009), rich club (van den Heuvel and Sporns 2011; Yu and others 2013; Cao and others 2014), motif (Iturria-Medina and others 2008; van den Heuvel and others 2012), and highly connected hubs (Achard and others 2006; He and others 2009; Hagmann and others 2008; Gong and others 2009) (for descriptions, see Table 1; for reviews, see Bullmore and Sporns 2009, 2012; He and Evans 2010; Filippi and others 2013). These approaches may impel the perspective of the large-scale human connectome to play a critical role in the establishment of structure–function association in humans.

## Structural Connectivity versus Functional Connectivity

Some studies have directly compared SC and FC between regions in resting-state brains and demonstrated robust

SC-FC correlations across the cerebral cortex. For example, Koch and others (2002) compared white matter SC with R-fMRI FC within a single axial slice of the human brain and reported that the regions that are linked by dense SC tend to also be strongly connected functionally. These authors also showed a positive correlation between the FCs and SCs of regions along the central sulcus. Subsequent studies have extended the examinations to the entire cerebral cortex at rest and produced generally consistent findings. For example, Skudlarski and others (2008) performed a voxel-by-voxel SC-FC comparison across the gray matter of nearly the whole brain and reported a strong similarity between the SC and FC maps in humans. Using both predefined anatomic parcellations of 66 regions and a high-resolution parcellation into 998 equal-sized regions, Hagmann and others (2008) and Honey and others (2009) reported robust correlations between the strengths of SC and FC across the whole cerebral cortex (Fig. 2). This overall SC-FC relationship has also been observed in the macaque cortex (Shen and others 2012; Honey and others 2007). These findings suggest that the resting-state FC patterns can reflect the underlying anatomic structure of the cerebral cortex. Furthermore, Hermundstad and colleagues (2013) proposed that several structural properties, including the length, number, and spatial location of white matter streamlines, are indicative of and can be inferred from the strengths of FCs between regions during both rest and task performance.

The correspondence of SC and FC has also been investigated in specific brain systems. Many studies have focused on the default-mode network (DMN), which includes the posterior cingulate cortex/precuneus, medial prefrontal cortex, inferior parietal cortex, and medial temporal lobe (Raichle and others 2001; Greicius and others 2003). Many R-fMRI studies have shown significant FC between DMN regions (Greicius and others 2003; Fox and others 2005). Studies have also employed DTI tractography to demonstrate direct structural connections between several core components of the DMN (Fig. 3) (Greicius and others 2009; van den Heuvel and others 2009; Honey and others 2009; Khalsa and others 2013). More interestingly, a recent study combining human fMRI and DTI data has shown that the key hubs (e.g., posterior cingulate cortex) in the DMN correspond well to DTI fiber-tracking results of the same subjects at a finer spatial scale (van Oort and others 2014). The high degree of correspondence between the SC and FC within specific systems has also been found in the oculomotor and primate somatosensory systems of anesthetized monkeys (Vincent and others 2007; Wang and others 2013) and in a large number of major functionally linked resting-state networks of the human brain that involve the executive control network, salience network, and primary motor and visual networks (van den Heuvel and others

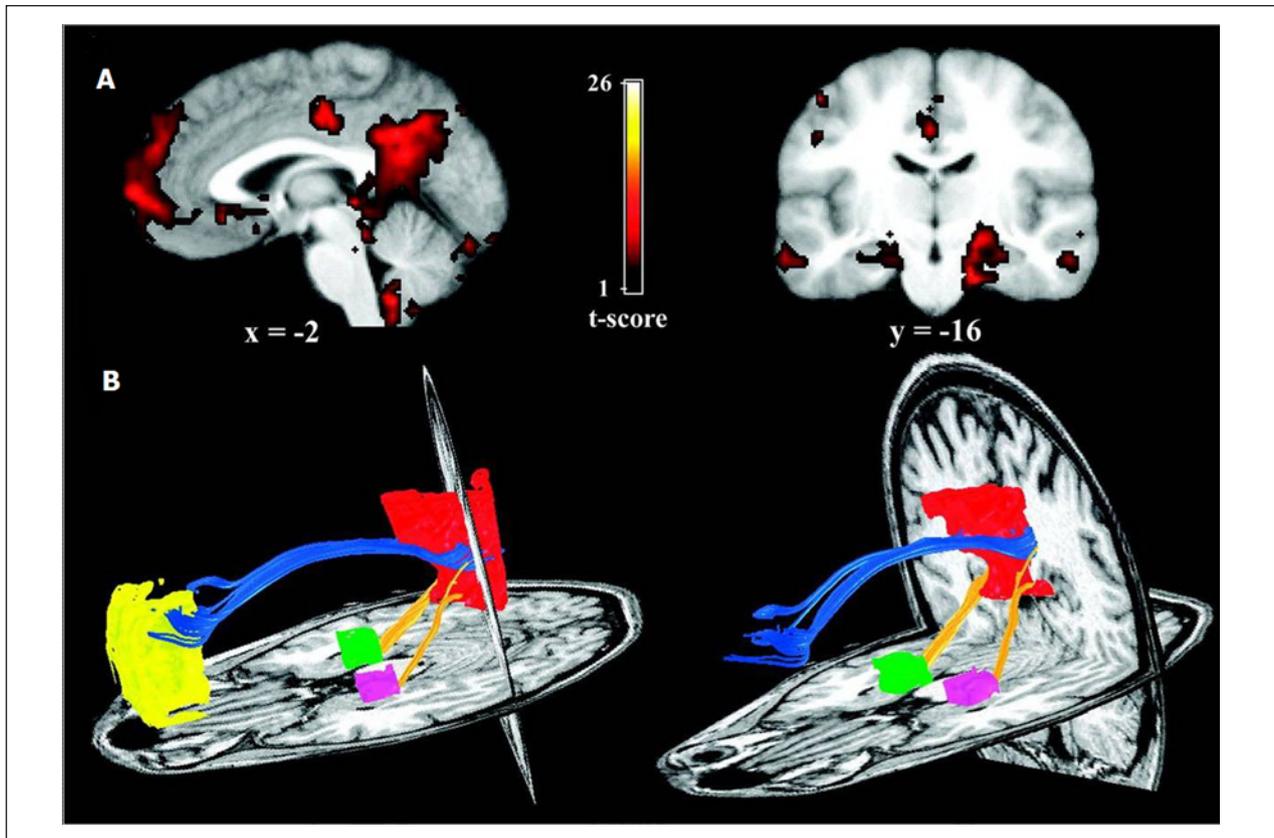


**Figure 2.** Overall structural connectivity (SC)–functional connectivity (FC) relationships in the human brain at rest. (A) A high-resolution parcellation with 998 regions of interest (ROIs) (Hagmann and others 2008). (B) Scatter plots of structural and functional connections averaged over all five participants for all ROIs in both hemispheres (Hagmann and others 2008). The result revealed a highly significant correlation between the strengths of FC and the SC ( $r^2 = 0.62, p < 10^{-10}$ ). (C) Scatter plot of the SC and resting-state FC for participant B (C) and simulated FC from a computational model (D) showing the edges with nonzero SCs (Honey and others 2009). In their work, a low-resolution parcellation of 66 cortical regions (33 per hemisphere) of varying size was first identified and matched across participants using an automated landmark-based algorithm (Desikan and others 2006). Next, the high-resolution parcellation (998 ROIs) was refined from the low-resolution surface partition with approximately equal sizes ( $1.5 \text{ cm}^2$ ). The figures were adapted from Hagmann and others (2008) and Honey and others (2009).

2009). In addition, studies using morphologic measurements (e.g., gray matter density, volume) have reported high spatial overlaps between the maps of structural covariance and resting-state FC in the human brain (Seeley and others 2009; Segall and others 2012). Regarding quantitative analysis, the first work that investigated SC-FC relations by Koch and colleagues (2002) has indicated a positive correlation between SC and FC in the sensorimotor system (around the central sulcus). Other studies have reported that the FC within specific systems, such as the DMN and the language networks, is strongly associated with the strength of SC or other metrics of the underlying white matter microstructures based

on the fractional anisotropy, mean diffusivity, and the radii of fiber bundles (van den Heuvel and others 2008; Teipel and others 2010; Khalsa and others 2013; Morgan and others 2009). Moreover, Horn and colleagues (2013) have found that the DMN in the human brain exhibits particularly high voxel-by-voxel SC-FC correlations (Fig. 4). Studies have also reported high levels of SC-FC coupling in the cortical rich-club system (Collin and others 2013; see Fig. 5B) and a portion of the structural core (Hagmann and others 2008).

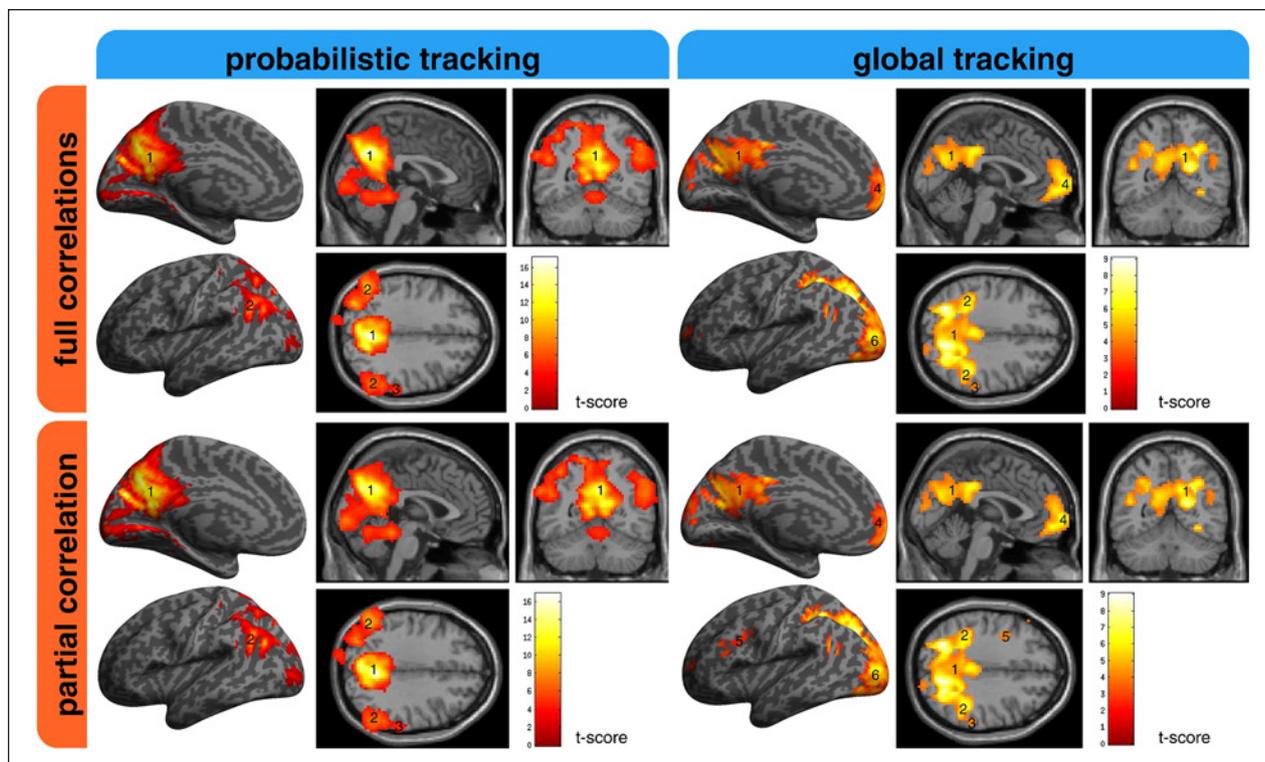
However, there are also divergences and discrepancies between SC and FC; for example, relatively fixed structural organizations can produce diverse functional



**Figure 3.** Functional connectivity reflects structural connectivity in the default-mode network (DMN). (A) Resting-state functional connectivity in the DMN is shown in a group of six subjects. The posterior cingulate cortex (PCC)/retrosplenial cortex (RSC) and medial prefrontal cortex (MPFC) clusters are best appreciated in the sagittal view. Prominent bilateral medial temporal lobe (MTL) clusters are observed on the coronal image (the left side of the image corresponds to the left side of the brain). (B) Diffusion tensor imaging (DTI) fiber tractography in a single subject demonstrates the cingulum bundle (blue tracts) that connects the PCC/RSC to the MPFC. The yellow tracts connect the bilateral MTL to the PCC/RSC. Note that, generally, the tracts from the MPFC enter the more rostral aspect of the PCC/RSC region of interest (ROI) corresponding to the PCC proper, whereas the tracts from the MTL enter the more caudal aspect of the PCC/RSC ROI corresponding to the RSC proper. The left and right columns show slightly different views of the same tracts to highlight the distinct entry points into the PCC/RSC. There are no tracts connecting the MPFC to the MTL. The figure was adapted from Greicius and others (2009).

network patterns (for a review, see Park and Friston 2013). First, strong FC might exist between regions without direct structural linkages (Koch and others 2002; Vincent and others 2007; Skudlarski and others 2008; Honey and others 2009; Adachi and others 2012; O'Reilly and others 2013). For example, within the DMN, the medial prefrontal cortex and the medial temporal lobe exhibit functional connectivity but may not share a direct anatomic connection (Greicius and others 2009). FC is also mediated by polysynaptic connections, common-source connections, and other configurations of bidirectional circuits (Skudlarski and others 2008; Adachi and others 2012; Shen and others 2012). Thus, we should emphasize that the relationship between SC and FC does not exhibit a simple one-to-one mapping; rather, this relationship is broadly correlated and complex. Second, studies have

further demonstrated that resting-state FC changes dynamically over time based on both resting-state fMRI scanning of human brains (Chang and Glover 2010; Allen and others 2014; for a review, see Hutchison and others 2013) and computational modeling of the primate neocortex (Honey and others 2007; Ghosh and others 2008; Deco and others 2009), although the underlying structural architecture is relatively fixed. The FC between structurally unconnected regions exhibits more variability than does the FC between areas with direct anatomic connections (Honey and others 2009). Third, both the patterns and strengths of FC can also change according to task demands or learning effects. For example, an overall decrease can occur during attention, and an overall increase can occur during memory relative to rest (Hermundstad and others 2013). In addition, functional modules can be adaptively



**Figure 4.** Group results of structural connectivity (SC)–functional connectivity (FC) correlations. Voxel-wise comparisons between each voxel's functional and structural connectivity to the rest of the brain were analyzed for each subject and analyzed using a *t*-test group analysis. Findings from spatial correlation analyses between one of the SC measures (probabilistic global fiber-tracking) and one of the FC measures (full or partial correlations) are shown. Areas in this figure are thresholded at  $P < .001$  and corrected for multiple comparisons on a cluster level ( $FWE < 0.05$ ). 1. Precuneus and adjacent posterior cingulate/retrosplenial cortex. 2. Bilateral inferior parietal lobe/angular gyrus. 3. Right supramarginal gyrus. 4. Bilateral medial prefrontal gyrus. 5. Left middle/inferior frontal gyrus. 6. Occipital pole. The figure was adapted from Horn and others (2013).

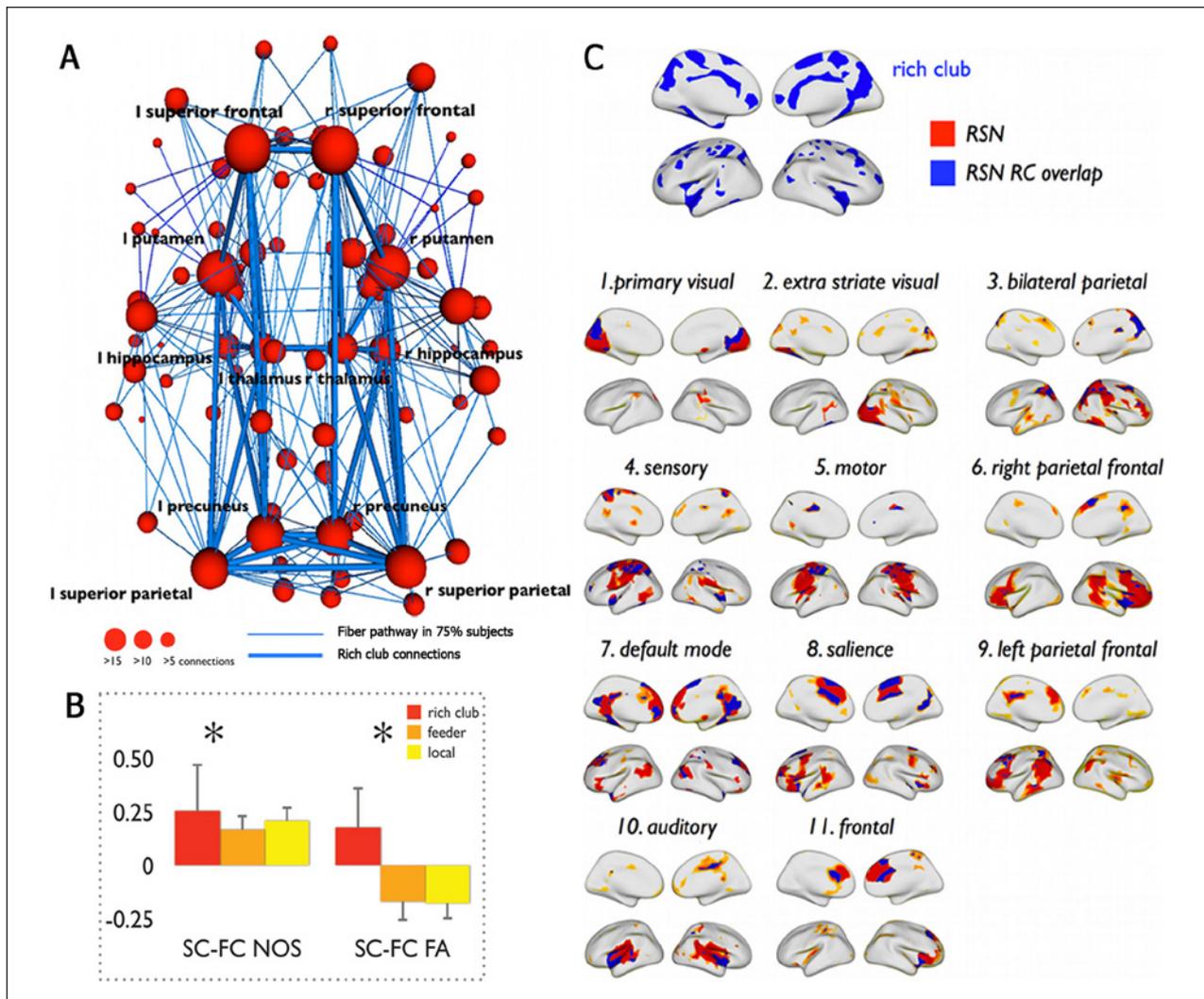
modulated over time during learning (Bassett and others 2011). Moreover, resting-state FC can also be modulated by prior experience or tasks during task-dependent resting states (Albert and others 2009; Lewis and others 2009; Hasson and others 2009; Wang and others 2012). Notably, the content sensitivity or flexibility of FC may partially account for the differences between structural and functional networks. Last, clinical studies present evidence that the normal interhemispheric FC can be widely preserved in the absence of major commissural fibers due to callosal agenesis (Tyszka and others 2011) or surgical lesions of the corpus callosum (Uddin and others 2008; Pizoli and others 2011; O'Reilly and others 2013), which suggests that the SC and FC metrics are not always related in a straightforward manner and that the FC exhibits stronger flexibility, variability, and plasticity.

In summary, SC and FC can be observed to display significantly robust relationships, but these relationships are broadly correlated and complex rather than always straightforward. Nevertheless, the SC that characterizes the underlying anatomic structure of the cerebral cortex

constrains and shapes the diverse patterns of FC, while the FC patterns can also reflect the SC architecture of the cerebral cortex.

### Structural-Functional Relationship in Network Topology

The human brain has been modeled as complex networks of SC and FC with shared topologic features, including small-worldness, power-law degree distributions, modularity, hierarchy, and the existence of highly connected hubs (for reviews, see Bullmore and Sporns 2009, 2012; He and Evans 2010; Filippi and others 2013). These organizational principles between the two large-scale brain networks of SC and FC may shed more light on the structural-functional relationship in the human brain. Recent studies have related SC to FC in the topology of large-scale networks in terms of both global and local topologic patterns. In general, it is necessary to investigate SC-FC mappings on the network level, in addition to the investigations that are limited to



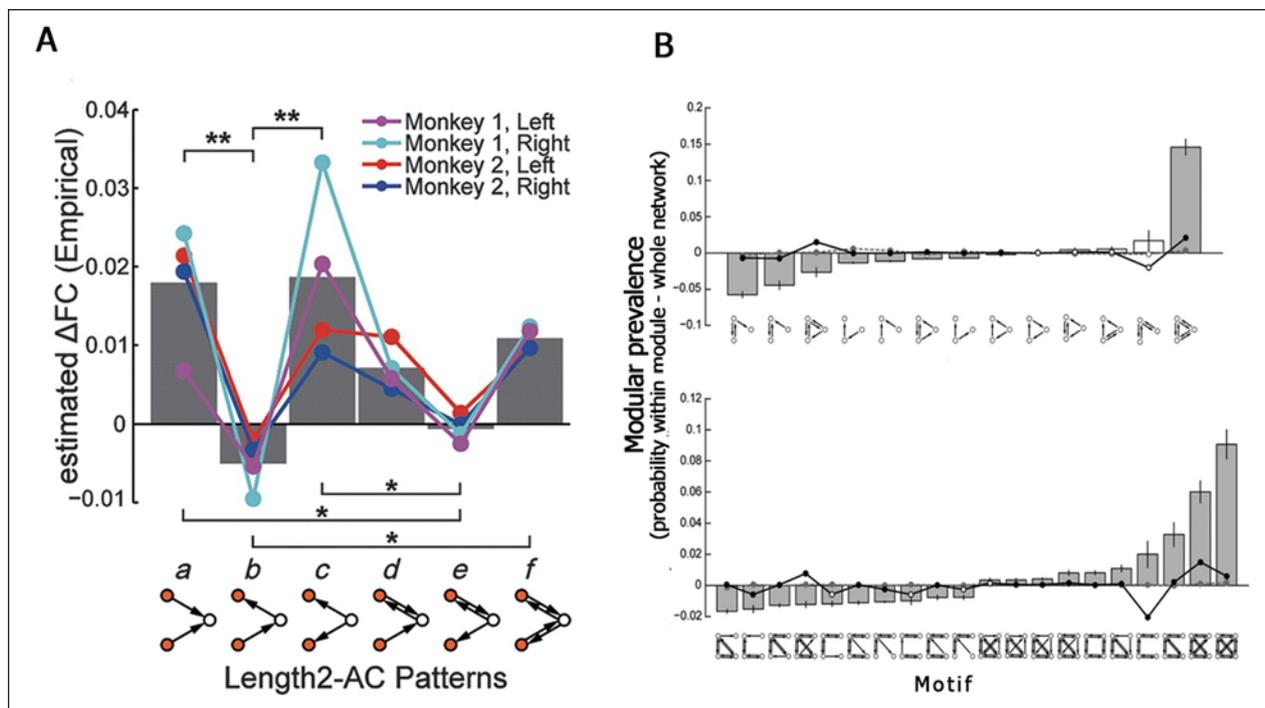
**Figure 5.** Network-level linking between structural connectivity (SC) and functional connectivity (FC) by rich-club structure.

(A) The rich-club structure in the structural networks of the human constructed from diffusion tensor imaging (van den Heuvel and Sporns 2011). The dark (thick) blue lines represent the connections between the rich clubs, and the light (thin) blue lines represent the connections from the rich clubs to other areas. The sizes of the nodes reflect their numbers of connections. (B) SC-FC couplings in rich-club, feeder, and local connections, with SC based on the number of streamlines (NOS) and on fractional anisotropy (FA). “Rich-club” connections, linking rich-club nodes to each other; “feeder” connections, linking rich-club nodes to non-rich-club nodes; and “local” connections, linking non-rich-club nodes to each other. Error bars express variation (standard deviations) of measures for each connection class over the group of subjects.  $*P < .05$  (permutation test; 10,000 permutations). (C) Spatial overlap of the rich-club and resting-state networks (RSNs) projected on the cortical surface. Note that parts of the surface assigned to an RSN are colored in red and blue, and the blue regions indicate overlaps between the RSN and the rich club (van den Heuvel and Sporns 2013). These findings suggest that the brain’s rich clubs serve as a macroscopic anatomic substrate that cross-links functional networks and thus play a critical role in the integration of information between functional modules. The figures were adapted from van den Heuvel and Sporns (2011, 2013) and Collin and others (2013).

one-to-one comparison (Adachi and others 2012; O’Reilly and others 2013).

Some investigations have directly compared the topologic properties of large-scale structural and functional brain networks. These studies have reported differences in the topologic properties (e.g., degree, modularity, centrality, clustering coefficient, and efficiency) of structural and functional networks both across the whole

human brain (Park and others 2008) and within different systems (i.e., unimodal, heteromodal, and limbic/paralimbic systems) (Baria and others 2013). In addition, differences in topologic properties have also been reported between the functional connectivity networks and structural covariance networks (using cortical thickness) in the human brain (Alexander-Bloch and others 2013).



**Figure 6.** Network-level linking between structural connectivity (SC) and functional connectivity (FC) by motif configurations. (A) The increment in FC per length2-AC (anatomical connection) varies with the direction of axonal projections (Adachi and others 2012). Here, this work adopted a multiple regression model (i.e.,  $y_i = \alpha + \sum_{j \in \{a, b, \dots, f\}} \beta_j n_j + \varepsilon_i$ , where  $y_i$  is the FC of area pair  $i$ ,  $n_j$  is the number of length2-AC patterns  $j$  [ $j \in \{a, b, \dots, f\}$ ] that connect area pair  $i$ ,  $\alpha$  is the constant term, and  $\varepsilon_i$  is the error term) to examine how the FCs of area pairs without direct SCs are dependent on the length2-AC patterns  $a$  to  $f$ , which is illustrated in the bottom panel. Two areas (orange circles) with no direct SC are connected via an intermediate area (white circle) (see Fig. 6A) and the arrows represent the directions of the axonal projections. Increment of FC due to each length2-AC pattern ( $\Delta FC_j$ ,  $j = \{a, b, \dots, f\}$ ) is defined as each of the six parameter estimates in the regression analysis. Gray bars indicate the mean values.  $**P < .01$  and  $*P < .05$ , Tukey's test following a three-way analysis of variance. The common efferent (a) and afferent (c) have significantly larger  $\Delta FC$  than the two-step serial relay (b). (B) Modular prevalence of motif classes with three (up) and four nodes (bottom). Average  $\pm$  SEM difference between the probabilities of the motif occurrences within the module and across the whole network (Shen and others 2012). Filled bars represent significant differences from 0 ( $t$ -test,  $P < .001$ ). Circular data points represent the average  $\pm$  SEM modular prevalence of the motif classes for 1000 null models within fixed-degree (gray dashed line) and fixed-connection length (black solid line) distributions. The filled circles represent significant differences from the observed in at least 75% of the null models ( $t$ -tests,  $P < .05$ ). For the four-node motif, only the top 10 most and least prevalent motif classes are shown. The bidirectional motif has a higher modular prevalence (the fully connected bidirectional motif has the highest), which suggests that this motif is more likely within functional modules than when the whole network is considered. These data suggest that functional modules are composed of dense, bidirectional structural connections and that functional communication between modules is supported by unidirectional connections via specific nodes. The figures were adapted from Adachi and others (2012) and Shen and others (2012).

Recent studies have attempted to characterize or identify putative causal relationships between SC and FC in terms of local topologic patterns. van den Heuvel and Sporns (2013) demonstrated that the cortical rich club, as a local system, plays a central role in the cross-linking of distinct functional modules in the human brain (Fig. 5A and C). Three recent studies highlight the existence of the rich-club organization in functional networks (Yu and others 2013; Cao and others 2014; Grayson and others 2014). Other studies have indicated that lower-level local properties (e.g., motif and local detours) of structural brain networks can constrain and predict both the strength and the

spatial patterns of FC (Sporns and Kötter 2004; Shen and others 2012; Goñi and others 2014). For example, Adachi and colleagues (2012) reported that FC varies with the patterns of the local structural motifs in the monkey cortex. More importantly, they further suggested that the FC between pairs of regions without direct SC depends more strongly on the motifs that have common afferents and efferents than those with serial relays (Fig. 6A). Moreover, Shen and colleagues (2012) reported that the properties (e.g., density, directionality, and symmetry) of local structural motifs could determine both structure of the global functional communities and intermodule communications

in the monkey cortex (Fig. 6B). Goñi and colleagues (2014) suggested that increases in the number of local detours along the shortest structural path could promote stronger FC between two regions in human brains.

Furthermore, studies have found causal relationships between the FC and global features of structural networks of the cerebral cortex. Some of these studies have shown that the functional community structure of resting-state activity is determined by the underlying anatomic architecture (Honey and others 2007; Shen and others 2012; Betzel and others 2013). Even the interregional FC is also substantially influenced by the global network features of the cortical architecture, not solely determined by interregional shortest connection patterns (Adachi and others 2012). These studies shed new light on the network-level cortical architecture that substantially shapes and generates the emergence of FC patterns between cerebral regions.

### Computational Models for Mapping Structural-Functional Connectivity Relationships

Computational models of large-scale neural dynamics offer opportunities to advance the theoretical understanding of the SC-FC relationship (for a review, see Deco and others 2011). First of all, nonlinear simulation models based on neural mass and field theories have attempted to model the spontaneous dynamics of each cortical region and to explore the coupling patterns of neural activities between regions under the constraints of fixed SC over the whole brain. For example, Honey and colleagues (2007) investigated the SC-FC relationships in a large-scale neural model of the macaque monkey cortex at multiple temporal scales. These authors found that the functional networks that were recovered over long time windows (minutes) largely overlapped with the underlying SC network, including the hubs and interregional connections. They also extended the model to the human cerebral cortex and found a significantly robust SC-FC correlation (Honey and others 2009). Zhou and colleagues (2006, 2007) proposed a multilevel model with weak couplings of the cat cortex; this model generated a hierarchical cluster organization of synchronization patterns that was similar to the anatomic topology. Other nonlinear modeling studies have emphasized the roles of local dynamics, signal transmission delays, and noise in shaping large-scale neural dynamics during spontaneous activity (Ghosh and others 2008; Deco and others 2009, 2011, 2013). Moreover, Izhikevich and Edelman (2008) developed a large-scale, anatomically detailed model of the mammalian thalamocortical system with millions of spiking neurons at the microscopic level, and the rich spatiotemporal patterns generated by this model resemble

those observed in resting-state FC studies of human brains. Finally, it should be noted that linear models have also been developed to explore the SC-FC relationship. Recently, Abdelnour and colleagues (2014) proposed a novel linear network model of brain dynamics based on graph diffusion, and this linear model appeared to be superior to previous nonlinear macroscopic approaches in capturing the brain's long-range second-order correlation structure that governs the relationship between FC and SC. Overall, these computational modeling studies provide theoretical understandings on the relationship between SC and FC from the viewpoint of brain dynamics or behaviors.

### Altered Structural-Functional Connectivity Relationships in Normal Development and Disease

Abnormalities or disruptions of SC or FC could primarily cause cognitive dysfunction, and both SC and FC dynamically evolve across the life span (for reviews, see Bullmore and Sporns 2009; Collin and van den Heuvel 2013). Studies have also reported evidence of alterations of the SC-FC relations during normal development and disease.

The SC-FC coupling globally strengthens with age rather than remaining constant, which suggests that direct white matter connectivity plays an increasingly important role in constraining brain-wide coherence and synchrony (Hagmann and others 2010). Along the anterior-posterior and other intrahemispheric tracts, such as the cingulum bundle and the fronto-occipital fasciculus, no significant correlations are observed between SC and FC in children, but such correlations can be observed in adults (Supekar and others 2010; Uddin and others 2011). Some functional connections within the DMN can precede the maturation of structural connectivity (Supekar and others 2010; Zielinski and others 2010). Moreover, Grayson and colleagues (2014) reported that the functional rich-club organization of the human brain strengthens and is modulated in adults.

Studies have also reported variations in SC-FC coupling in brain diseases. On one hand, decreased SC-FC couplings (or decouplings) could be observed in patients with schizophrenia (Skudlarski and others 2010), idiopathic generalized epilepsy (Zhang and others 2011a), and psychogenic nonepileptic seizures (Ding and others 2013). The strength of SC-FC coupling is significantly correlated with the clinical symptoms of schizophrenia (Skudlarski and others 2010), is negatively correlated with duration of epilepsy (Zhang and others 2011a), and can even differentiate psychogenic nonepileptic seizures patients from healthy controls with high sensitivity and specificity (Ding and others 2013). Moreover, a recent

study identified a negative correlation between the integrity of the uncinate fasciculus (which links the subgenual anterior cingulate cortex to the medial temporal lobe) and the FC of the subgenual anterior cingulate cortex with the bilateral hippocampus in major depressive disorder (but not in healthy subjects), and this negative structure-function relation is positively associated with depression severity (de Kwaasteniet and others 2013). On the other hand, stronger SC-FC couplings could also be observed in patients with schizophrenia (van den Heuvel and others 2013). A stronger correspondence between the patterns of the large-scale functional and structural covariance networks by measuring amplitude of low-frequency fluctuations and gray matter volume, respectively, was also observed in patients with idiopathic generalized epilepsy (Liao and others 2013). Moreover, the FC and SC could be observed to be consistently reduced within the DMN in mesial temporal lobe epilepsy (Liao and others 2011), while the interhemispheric FC and SC between the bilateral cuneus or anterior cingulate cortex were consistently increased in generalized tonic-clonic epilepsy (Ji and others 2014). These findings suggest that FC-SC coupling might be associated with different phenotypes of epilepsy. Finally, the interhemispheric FC could be preserved or reduced in conditions of callosal section (Johnston and others 2008; Uddin and others 2008; Pizoli and others 2011; O'Reilly and others 2013) and agenesis (Quigley and others 2003; Tyszka and others 2011).

Moreover, computational models have been used to investigate the effects of structural lesions and pathologies on the FC patterns of large-scale neural dynamics. For example, Alstott and colleagues (2009) reported that focal lesions in hub regions can result in large and widespread effects on the distributed spatial patterns of FC throughout the brain. Pons and colleagues (2010) combined modeling and human electroencephalography data to relate FC to SC in normal and pathologically aging brains and showed greater FC strengths at lower frequencies in mild cognitive impairment. This finding is consistent with experimental results. In summary, all of the relevant studies suggest a complex relationship between abnormal interaction patterns of brain connectivity and diseases or behaviors.

## Future Perspectives

The studies on the SC-FC relationship have accumulated valuable observations and set up the foundation for further investigations. In the near future, the study of SC-FC relationships in large-scale networks could include the following promising directions. First, it will be important to unveil the structural substrates of single FC across multiple levels, modules, and different frequency bands over the whole brain (as a hierarchical modular complex

system), particularly the substrates of FC without direct anatomic connections. The SC-FC relationship is essentially a dynamic organization over a complex structural network, and dynamic correlation can be influenced not only by the direct connection between two nodes but also between the inputs through higher order network neighbors. Therefore, a modeling study may be critical to reveal the possible mechanisms underlying SC-FC coupling and help to develop new tools for empirical analysis. Second, it is necessary to focus on constructing putative causal mappings between SC and FC in terms of topologic patterns (e.g., motif, rich-club, modular, and small-world patterns) across task and resting states. Third, it is important to determine the normal and aberrant trajectories of SC and FC and their interactions during network formation, development, and aging across the human life span. Such studies will be helpful for deepening our understanding of the dynamic structural-functional relationship. Fourth, it is also important to understand or model the evolutionary dynamics (e.g., task-rest transitions, learning procedures, nervous system formation, and development and disease) of the human brain with computational models of large-scale neural dynamics. Finally, current *in vivo* imaging technologies and data-processing procedures are limited by some factors—for example, noise in the BOLD signal and the lack of directionality and insensitivity to intracortical and weak long-range axonal connections of diffusion imaging. These factors may lead to some false positives and false negatives when estimating the likelihood of connections (Damoiseaux and Greicius 2009; Johansen-Berg and Rushworth 2009; Murphy and others 2009). Thus, it will be important to combine multiple imaging modalities (e.g., rest and task fMRI, structural MRI, and DTI/DSI) for data fusion such that the limitations of single modalities will be weakened and multi-integrated, or more complete observations of brain information can be obtained (Damoiseaux and Greicius 2009; Zhu and others 2013; Sui and others 2013). For example, combining fMRI and DTI can improve functional (Bowman and others 2012) and effective connectivity measures (Stephan and others 2009) and can even be used to generate an entirely new track-weighted FC map (Calamante and others 2013). On the whole, such studies may further our understanding of the structural-functional relationships and complexity of human brains in the future.

## Conclusions

This review summarizes recent progress in the understanding of the SC-FC relationship in the human brain that has been made using both empirical and computational studies in terms of the strengths of interregional connectivity and network topologic organization, and it

emphasizes the important role of large-scale brain networks in understanding the structural-functional associations in humans. We conclude that SC and FC are strongly related not only in terms of interregional connectivity but also in terms of the patterns of network topologic organizations. As a physical substrate, SC can constrain and shape FC patterns across both local and global scales. Moreover, this SC-FC coupling exhibits remarkable changes during development, normal aging, and disease. Advances in data analysis and in vivo neuroimaging promise to enable the creation of a huge and rich database that will provide opportunities to characterize human structural and functional connectomes at multiple levels in a reasonably accurate manner. The study of large-scale brain networks may open a door to unveiling the complex relationship between structure and function in the human brain that supports human cognition and diverse human behaviors. Nevertheless, the study of the SC-FC relationships in large-scale brain networks is still in its infancy, and much further work is needed to attain a more comprehensive understanding of them.

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