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Review

Can structure predict function in the human brain?

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ABSTRACT

Over the past decade, scientific interest in the properties of large-scale spontaneous neural dynamics has intensified. Concurrently, novel technologies have been developed for characterizing the connective anatomy of intra-regional circuits and inter-regional fiber pathways. It will soon be possible to build computational models that incorporate these newly detailed structural network measurements to make predictions of neural dynamics at multiple scales. Here, we review the practicality and the value of these efforts, while at the same time considering in which cases and to what extent structure does determine neural function. Studies of the healthy brain, of neural development, and of pathology all yield examples of direct correspondences between structural linkage and dynamical correlation. Theoretical arguments further support the notion that brain network topology and spatial embedding should strongly influence network dynamics. Although future models will need to be tested more quantitatively and against a wider range of empirical neurodynamic features, our present large-scale models can already predict the macroscopic pattern of dynamic correlation across the brain. We conclude that as neuroscience grapples with datasets of increasing completeness and complexity, and attempts to relate the structural and functional architectures discovered at different neural scales, the value of computational modeling will continue to grow.

Contents

Introduction

The brain is composed of anatomically distinct elements interconnected by a dense web of structural links. This structural network shapes how neural dynamics—the processes underlying human cognitive function—unfold over time. Structure–function relationships are pervasive in biology and range in scale from the folding of proteins up to the biomechanics of mammalian skeletons. Structure invariably informs and constrains biological function. In what ways does structure predict function in the human brain? We review evidence at microscopic and macroscopic scales, and frame an answer from the perspectives of network theory and computational modeling.

Large-scale computational models now combine neuroanatomical and physiological connectivity data with unprecedented comprehensiveness and detail. What can these models tell us about the relationship

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between anatomical connectivity and dynamic interactions that develop upon the network over time?

The question gains in significance because of the accumulation of highly resolved neural connectivity data recorded from individual participants. Until the recent arrival of noninvasive diffusion imaging techniques, mapping of human brain connectivity depended largely on gross dissection or on postmortem histology. These methods left large gaps in our understanding of the structural substrate of cognition. The comprehensive description of human brain connectivity—the connectome (Sporns et al., 2005)—has now become a feasible scientific goal. The availability of detailed large-scale connectivity data offers the opportunity to understand the links between brain structure and brain function at the regional level, and parallel approaches to mapping the connectivity of single neurons will facilitate a more complete understanding of the functioning of local neural circuits.

The paper is structured as follows. In the second section we define key terms such as "structural connectivity" and "functional connectivity", we make a distinction between two levels of brain organization, and we introduce the computational framework of network modeling approaches. The third section addresses the structure–function relationships observed among individual neurons and among small populations of neurons. We examine the evidence for precise and patterned synaptic targeting, and the potential role of such precise structure in local circuit dynamics. In the fourth section we review the evidence for a link between structure and function at the large scale. We focus on empirical studies of spontaneous and task-evoked neural interactions. We further review how structure–function relationships depend on the spatiality of the brain and how they change across time, or as a consequence of local or distributed network damage. Throughout, we attempt to establish links between empirical findings and results of network analysis and computational modeling. We close with some considerations of empirical and modeling developments in the near future.

Definitions, scales, and models

When asking whether "structure" determines "function" in a given context it is necessary to specify one's usage of the key terms. In the present context, we take "structure" to refer to the spatial and topological arrangement of connections between neuronal elements. The notion of "function" is more delicate. By the "function" of a particular neuron or brain region we do not refer to the set of behavioral or psychological functions (e.g. attention, memory) subserved by a given neural circuit or system, but rather to the kinds of dynamics (e.g. coherent oscillation, long-range temporal autocorrelation) typically exhibited within the active circuit. This definition focuses on the relationship between the structure of a neural circuit and its dynamic repertoire. This relationship, while often indirect, is nonetheless closer than that between anatomical structure and organismic behavior, which takes place within a social and ecological context.

For discursive purposes, we will draw a (somewhat arbitrary) distinction between the micro and macro scale. We take macroscopic neural structure to be that which is seen with current neuroimaging technology (e.g., magnetic resonance imaging), at a maximal spatial resolution of voxels with a size of several cubic millimeters. Network structure at this scale is a combination of long-range intra-regional horizontal fibers, as well as the sets of fiber bundles or fasciculi linking neuronal populations inter-regionally. Microscopic neural structure is defined as everything more fine-grained than the macroscopic scale, from the radial groupings of neurons in sensory cortices down to the level of individual spines. At this microscopic scale, network structure is composed of inter-neuronal connections mediated by single axons and synapses. The simple micro–macro scheme we employ here may also be refined to recognize important "mesoscale" circuitries encompassing hundreds to thousands of neurons (Ingber and Nunez, 1990; Freeman, 2000).

In neuroimaging, the metabolic signals measured in an individual voxel are a complex aggregate of all micro-scale activity within that locale. One could argue that all dynamics observed at the macroscopic scale are reducible to those seen at this microscopic level. While it has not been unambiguously demonstrated that macroscopic neural signals have an "emergent" functional role, it is known that signals aggregated across heterogeneous populations of thousands or millions of neurons can be directly and precisely associated with online behavior (e.g. Miller et al., 2009a) and that they can exert modulatory feedback on the spiking of their constituent neurons (e.g. O'Keefe & Recce, 1993). It is also the case that very large populations of single neurons simply cannot, at present, be individually and simultaneously recorded. Hence, we advocate an inclusive and multi-scale approach to the characterization of brain networks (Breakspear and Stam, 2005), cognizant of the fact that local circuits exist within an ecology of large-scale processes that feed back into the microscopic domain, and that whole-brain contrast maps arise from exquisite local circuitry that is invisible to magnetic resonance imaging.

In this paper we use the terms "structural connectivity" and "functional connectivity" according to their standard usage in the neuroimaging literature. Structural connectivity (SC) refers to macroscopic structural linkage, as obtained, for instance, from long-range tract tracing or diffusion imaging tractography. Functional connectivity (FC) refers to the statistical dependence between time series describing the neural dynamics at distinct locations in the brain (Friston, 1994). Both SC and FC can be recorded and estimated with a broad array of methods, many of which allow the representation of SC and FC datasets as connection or adjacency matrices (Bullmore and Sporns, 2009) amenable to quantitative analysis and modeling.

In examining the evidence for a relationship between structure and function, we make reference to computational models of both microscopic and macroscopic neurodynamics. These models embody assumptions about the intrinsic dynamics of neuronal elements or nodes, and also about the pattern and strength of connectivity between nodes. In most of the examples discussed in this review, models primarily serve to generate high-dimensional neural dynamics at micro or macro scales, and thus allow the exploration of rules and principles that translate structural into functional connectivity (Breakspear and Jirsa, 2007; Breakspear and Knock, 2008; Knock et al., 2009). Such models can be assessed and refined according to whether they produce patterns of functional connectivity that match those observed empirically. A long-term goal of these modeling endeavors is to identify a mapping between dynamic network states and cognitive processes.

Thinking inside the voxel: Structure and function of neural circuits

Ten cubic millimeters of human cerebral cortex—the approximate volume of a standard fMRI voxel—contains on the order of 10^5 neurons and 10^9 synapses (Pakkenberg and Gundersen, 1997). In human sensory cortices, such a voxel will typically contain between 10 and 40 functional domains (assuming each domain has a diameter between 300 and 600 μm). Functional domains are constituted by sets of neurons that show similar responses to variations in somatic, auditory or visual stimulation (Mountcastle, 1997). While the existence of such functional domains is undisputed (Hubel, 1978), there has been some disagreement as to whether the boundaries of functional domains correspond to the boundaries of any clearly defined anatomical units. It is unclear, for example, whether cortical columns have distinct anatomical boundaries (Douglas and Martin, 2007), whether they are purposefully composed of "minicolumns" (Mountcastle, 1997), and whether they represent an essential feature

of cortical computation that is shared across many species (Horton and Adams, 2005).

In visual cortex, functional domains have long been known to exist in correspondence to, among other properties, the ocular dominance and orientation preference of groups of neurons. Anatomical and physiological evidence suggests that longer range intra-regional connections (>0.5 mm from the labeled soma) occur in patches (Fig. 1), with a preference to connect neurons with similar receptive field properties (Gilbert and Wiesel, 1983; Malach et al., 1993; Bosking et al., 1997; Angelucci et al., 2002). Importantly, neurons with similar tuning properties are likely to be co-active, even during spontaneous activity, i.e. under "resting-state" conditions (Tsodyks et al., 1999; Kenet et al., 2003). As a result, structural and functional connectivity should be expected to correspond quite strongly within any millimetric patch of visual cortex imaged at a spatial resolution coarser than the width of a pyramidal dendrite bundle (~23 μm; Peters and Sethares, 1996).

Although ordered functional domains are clearly observable in sensory cortices, it is not yet known precisely which structural regularities underlie these dynamical phenomena. Early studies of local synaptic connectivity in the cerebral cortex suggested that patterns of connectivity were essentially probabilistic functions of distance (Sholl, 1953; Uttley, 1955; Braitenberg and Schüz, 1998). In such random network models a heavy burden is placed on learning and synaptic modification to achieve functional specialization. More recent theoretical and computational research has advanced the concept of local circuits as "computational reservoirs" that can be trained to accommodate a variety of functional roles (Maass et al., 2002; Buonomano and Maass, 2009; Sussillo and Abbott, 2009). So long as the neural reservoir has sufficient built-in complexity (i.e., is capable of rich dynamics) a large variety of input–output mappings can be realized (Bertschinger and Natschläger, 2004), including the approximation of intricate time-varying functions, but rules that link specific synaptic patterns to specific input–output transformations are yet to be described (e.g. Häusler et al., 2009).

However, several recent lines of evidence point to the existence of highly non-random structural features in cortical circuits. Connections among specific neuronal cell types are more prevalent than expected by chance (Thomson and Bannister, 2003; Stepanyants et al., 2004), with important functional outcomes. For instance, selective connections among GABA-ergic cells might allow them to exert focused control over principal cells in neocortex (Hestrin and Galarreta, 2005). Applying the idea of network motifs (Milo et al., 2002) to connection data extracted from *in vitro* cortical recordings, Song et al. (2005) found that a subset of interaction configurations were more prevalent than expected by chance. These specific patterns may provide a structural skeleton or backbone that enhances the regularity of dynamic firing patterns. A range of other intra-regional correlation patterns and their presumed structural bases have recently been reviewed by Kohn et al. (2009).

Modeling studies support the notion that specific, ordered patterns of connectivity are associated with particular dynamical outcomes. Binzegger et al. (2009) have examined the relationship between dynamic stability and the wiring topology within a modeled columnar circuit. The ability of neurons to synchronize their firing patterns also depends on the topology of their structural connectivity, and the coexistence of local and long-range connections appears to facilitate this dynamic process (e.g. Masuda and Aihara, 2004; Buzsáki et al., 2004). Other models have demonstrated that network topology and neural dynamics are mutually interdependent once mechanisms of neuroplasticity, which mold connection topology in an activity-dependent manner, are taken into account (Rubinov et al., 2009).

Connectivity also plays a role in shaping the temporal organization of neural activity. Roopun et al. (2008) have investigated the relationship between microcircuit topology and the generation of nested rhythms. Another recent modeling study, using networks of Hodgkin-Huxley neurons, showed that a specific three-node motif, previously identified as characteristic of inter-areal cortical connectivity (Sporns and Kötter, 2004; Sporns et al., 2007) promotes zero-lag synchronization despite the presence of significant conduction delays (Vicente et al., 2008). This model and others (Ostojic et al., 2009) highlight the relationship between neural connectivity and time-dependent correlations among cells.

Another form of structural organization with clear functional consequences is point-to-point topography (Thivierge and Marcus, 2007). This pattern is found in all primary sensory areas of cortex and

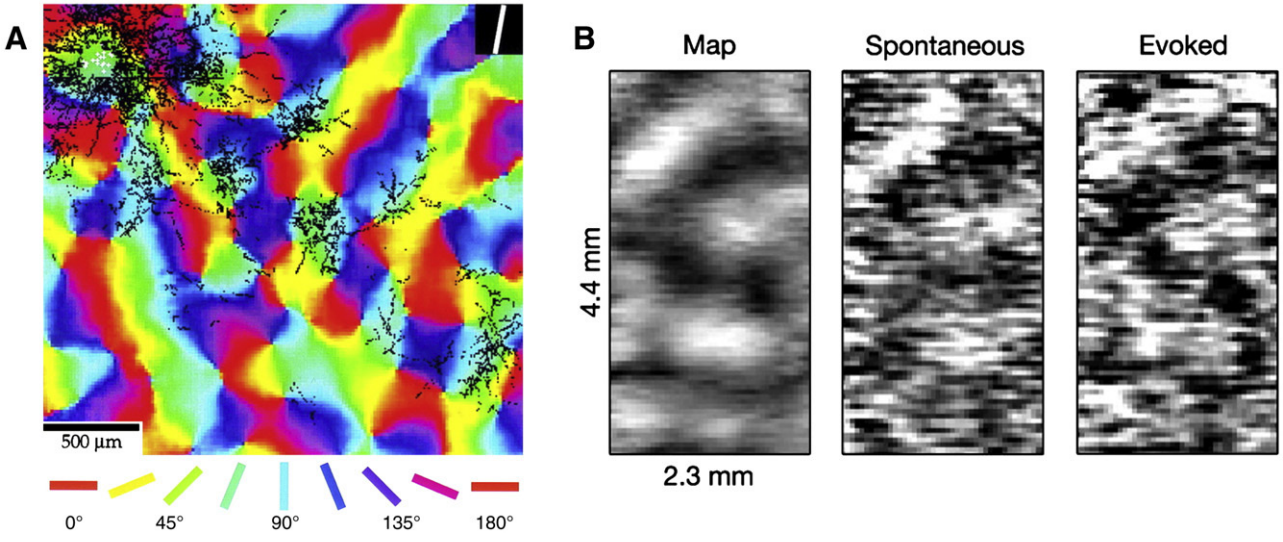

Fig. 1. Structure–function relationship at the cellular scale. (A) Overlay of an orientation preference map, optically recorded from the striate cortex of the tree shrew, and the bouton distribution after injection of an anatomical tracer into a site located at the upper left (Bosking et al., 1997). The orientation preference at the tracer injection site is shown in the upper right hand corner. Note boutons nearby the injection site are found within all orientation preferences, while boutons farther away are preferentially located in similar orientations. Reproduced from Bosking et al. (1997), with permission. (B) Spontaneous and evoked orientation-selective responses in visual cortex. Orientation map, and two individual frames obtained from optical recordings of neural activity in area 18 of the cat. The middle panel shows a single frame obtained during a spontaneous recording session (no visual stimulus was presented) and the panel on the right shows a single frame recorded during the presentation of a grating with vertical orientation. Note the similarity between all three panels, particularly the spontaneous and evoked response patterns. From Kenet et al. (2003), reproduced with permission.

serves to preserve relationships among representations at the periphery. In the visual system, for instance, inputs from the retina activate areas of striate cortex such that features of an image represented close together on the retina will activate nearby regions of cortex. This form of topography is sufficiently precise that different portions of visual space occupy separate anatomical positions within the dendritic tree of individual midbrain neurons (Bollmann and Engert, 2009). Topographic representations also allow, in principle, for a range of information processing mechanisms to be implemented using short-range circuitry: rapid feature detection by feedforward pooling is one example (e.g. Serre et al., 2007) and information propagation by traveling waves is another (Rubino et al., 2006).

The pattern of local synaptic connectivity found in the human nervous system is likely shaped by a combination of numerous biological and computational constraints, as well as stochastic growth processes. Conservation of wiring length and volume (Chklovskii et al., 2002; Buzsáki et al., 2004), the efficiency of short average path lengths (Kaiser and Hilgetag, 2006), and the value of an explicit topographic neural representation of behavioral repertoire (Graziano and Aflalo, 2007) are all principles that may influence the arrangement of synaptic connectivity. Random variations in molecular gradients and axonal pathfinding (Mortimer et al., 2009) or in axo-dendritic interactions (Lichtman and Smith, 2008) during neural development are also likely contributors. Jointly, these processes mold synaptic circuits to achieve specific dynamics and processing capabilities. Importantly, models have suggested that identical dynamical outcomes can be achieved on the basis of distinct sets of synaptic parameters and circuit mechanisms (Prinz et al., 2004), an example of network degeneracy (Tononi et al., 1999). Therefore, while the evidence does suggest that many uniquely specified structure–function relationships are manifest within local circuits, the assertion that a given structure is necessary or sufficient for a specific dynamical or behavioral outcome may not always be warranted.

Independently of what organizational principles best describe local neural wiring, it is clear that the activity of local circuits has consequences for more global aspects of neural dynamics (Breakspear and Stam, 2005). Small changes in local circuit properties—both at the functional and anatomical levels—can have a large impact on the activity of broader networks in which they are embedded. Next, we examine the relationship between connectivity and dynamics at the large scale.

From single voxels to the whole brain: Structure and function of large-scale systems

The analysis of spontaneous neural dynamics offers an opportunity to measure the aggregate level of relation between structural and functional connectivity in a relatively task-neutral manner. Several studies have performed a combined analysis of structural connectivity (SC) derived from diffusion imaging and tractography, and functional connectivity (FC) derived from spontaneous fluctuations of the BOLD response (reviewed in Damoiseaux and Greicius, 2009). The first such study examined SC and FC within a single axial slice (Koch et al., 2002), and reported that the presence of strong SC tended to imply the presence of strong FC, but that strong FC could also regularly be observed between structurally unconnected regions. Subsequent studies have employed larger coverage and different parcellation schemes, with generally consistent results. Using a parcellation of the cortex into approximately 1000 equal-sized regions of interest, Hagmann et al. (2008) and Honey et al. (2009) reported robust correlations between the strengths of SC and FC across the entire cortical surface (Fig. 2). This correlation persisted after potential confounds such as spatial proximity between regions were taken into account, and indirect structural connections were found to account for some proportion of the functional connectivity observed between node pairs lacking direct linkage. A more fine-grained analysis, carried out by Skudlarski et al. (2008) also reported a robust SC–FC correlation after performing a voxel-by-voxel SC–FC comparison across almost the entire extent of the cerebral gray matter.

More focused analyses of specific brain systems confirmed that functionally connected sets of brain regions tended to be structurally linked. The default mode network (DMN) is comprised of a set of brain regions, including the posterior cingulate and precuneus, lateral parietal cortex and elements of medial prefrontal cortex that are jointly activated and linked by FC in the resting state (Raichle et al., 2001; Greicius et al., 2003). Several studies have reported the presence of structural pathways between some core components of the DMN (Greicius et al., 2009), as well as between components of several distinct resting state networks, including the DMN (Van den Heuvel et al., 2009a). Zhang et al. (2008) mapped resting-state BOLD signal correlations between human thalamus and cortex and noted significant agreement between BOLD correlations and connectional anatomy within the same cortical hemisphere. Vincent et al. (2007) found that cortical patterns of coherent spontaneous BOLD fluctuations in anesthetized macaque monkey were similar to those of anatomical connectivity derived from tract tracing studies.

Evidence for a correspondence between SC and FC in a task-related setting comes from the work of Stephan et al. (2009), who demonstrated that models of "effective connectivity" (i.e. causal interactions) in lexical and spatial task performance in fMRI are improved when the priors on the inter-regional coupling parameters are informed by SC data. SC–FC linkages may also account for individual variations in behavior and cognition. Several studies have pointed to correlations between FC and behavioral and cognitive measures obtained during task performance. These relationships have emerged in studies focusing on single functional connections (Hampson et al., 2006) as well as global network measures related to the efficiency of information flow (Van den Heuvel, 2009b).

Taken together, these studies support the idea that structural connections, when present, are highly predictive of the presence and strength of functional connections. However, structural connections cannot reliably be inferred on the basis of observed functional coupling, since strong functional connections may also exist between regions that are not directly anatomically linked. Recent successes in relating empirical structural to functional connectivity should not lead to the mistaken conclusion that their relationship is simple or even trivial. Van Dijk et al. (2009) have recently reviewed the optimal methodological parameters for FC acquisition, with a focus on the utility of FC measurement in connectomics.

It is hoped that a more refined understanding of this structure–function relationship will emerge from computational models of endogenous neural activity. Honey et al. (2007) investigated the SC–FC relationship in a large-scale model of the macaque monkey cortex, consisting of neural mass oscillators based on physiological characteristics of cortical neuronal populations (Breakspear et al., 2003) that were coupled by a structural network describing the segregated regions and interregional pathways of macaque cortex. Spontaneous neural activity in the model exhibited patterns of transient synchronization and functional connectivity on multiple time scales. The availability of SC from diffusion MRI (Hagmann et al., 2008) allowed an extension of the model to the scale of the entire human cerebral cortex (Honey et al., 2009). Functional connectivity patterns were derived from cross-correlations of synthetic BOLD time series data. Comparison of these modeled patterns to the empirically obtained functional connectivity revealed significant similarity (Fig. 3). The presence and strength of a structural link was predictive of the presence and strength of a functional connection in both model and data.

Modeling studies by Ghosh et al. (2008) and Deco et al. (2009) investigated the role of noise and conduction delays in shaping large-scale neural dynamics, and noted that both of these factors critically effected the dynamical outcomes, including the presence and the relative phases of <0.1 Hz rhythms. In all studies, FC was found to be

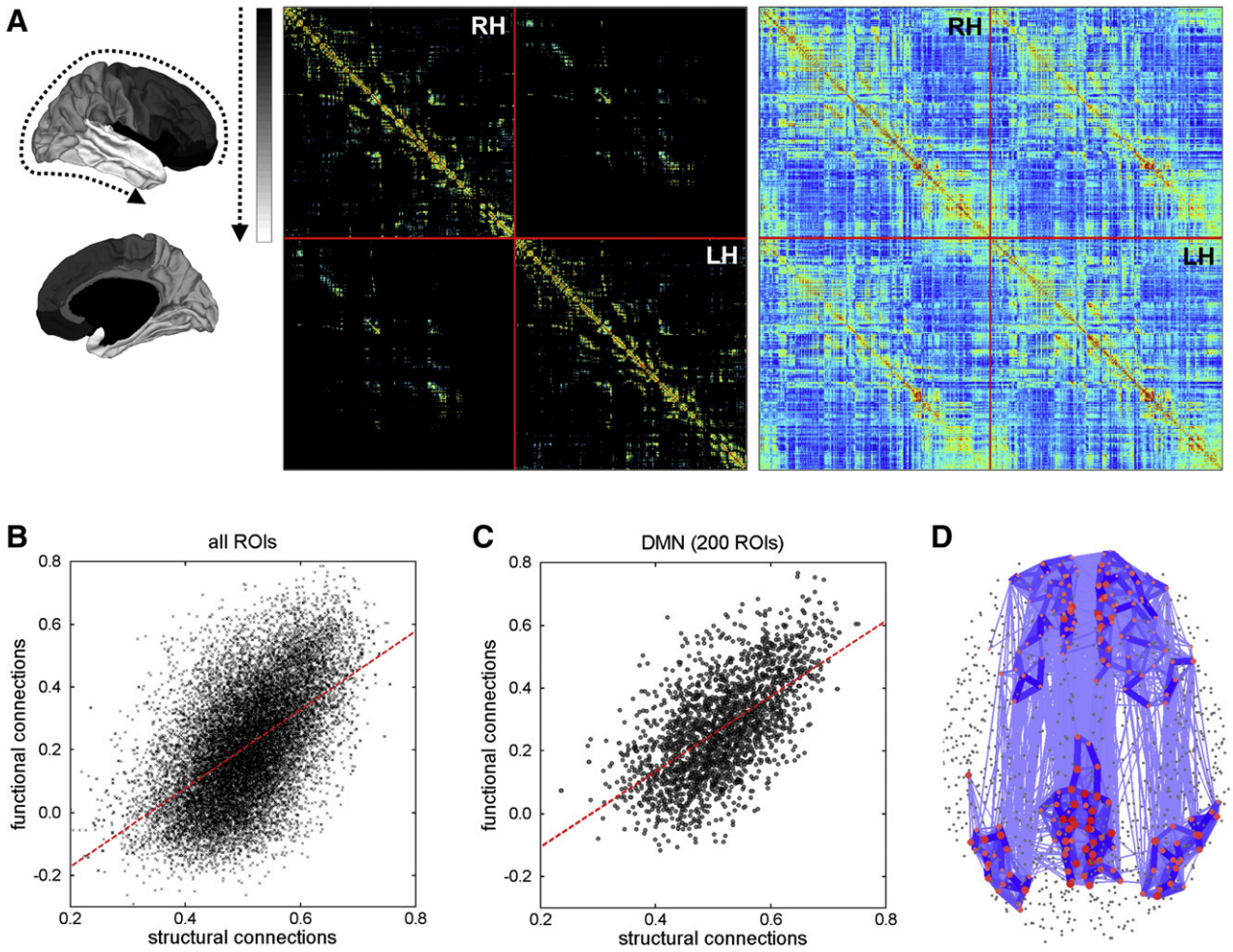

Fig. 2. Direct comparison of structural and functional connectivity in the human brain. (A) Structural connectivity derived from diffusion imaging (Hagmann et al., 2008; Honey et al. 2009) and resting-state functional connectivity derived with functional neuroimaging (Honey et al., 2009), from the same set of five participants. Maps show connectivity among 998 ROIs in an anterior–posterior–temporal arrangement to emphasize spatial organization. (B) Scatter plot of structural connections and corresponding functional connections ($r = 0.54$, $p \ll 10^{-6}$). (C) Scatter plot of structural connections and corresponding functional connections ($r = 0.61$, $p \ll 10^{-6}$) for the 200 ROIs that form the default mode network. These 200 ROIs were derived by seeding the DMN in the posterior cingulate/precuneus (PCC), medial frontal cortex, and lateral parietal cortex and selecting the 200 ROIs that were most strongly functionally correlated with these seed regions. (D) Location of the 200 DMN ROIs and their structural interconnections. Note the presence of dense pathways between the medial frontal cortex and the PCC as well as lateral parietal cortex, as well as the relative absence of connections between the lateral parietal cortex and the precuneus (see also Van den Heuvel et al., 2009a). All data shown here represent averages over all five participants and are replotted from Honey et al. (2009).

dynamically rich and diverse, forming a "functional repertoire" of FC patterns that was explored during spontaneous neural activity (see Fig. 1). An extension of large-scale models of the human brain to networks of millions of thalamic and cortical spiking neurons (Izhikevich and Edelman, 2008), each parameterized into 1 of 15 distinct types and connected in accordance with diffusion imaging-inferred connection maps, also generated rich spatiotemporal patterns that resembled rhythmic neural activity in the resting brain.

Taken together, these modeling studies reinforce the idea that SC and FC are related. However, they also suggest that the degree of their correspondence depends on spatial resolution and time scales. The relationship is particularly robust for functional networks obtained at low frequencies (as in resting state fMRI) and over long sampling periods (on the order of minutes). At higher frequencies and within shorter time windows, FC fluctuates in a complex pattern, reflective of the rich underlying dynamics. Thus, we should not think of the brain's endogenous neural activity as a static time-invariant pattern of interneuronal or interregional coupling. Spontaneous dynamics allow for rapid reconfigurations of functional interactions at fast time scales of hundreds of milliseconds, and these reconfigurations are manifestly necessary for internal cognitive control (e.g. Fries, 2005) and environmentally responsive behavior (Bassett et al., 2006).

Network models of structural and functional connectivity

Network topology of SC and FC

Network concepts have been used to define principles of the structural and functional organization of the cerebral cortex for many decades. The "mosaic organization" of the cortex into specialized regions that become functionally integrated during perception and cognition (Zeki, 1978; Zeki and Shipp, 1988), as well as the idea that large-scale connectivity in the primate brain is structurally (Felleman and Van Essen, 1991) and functionally (Mesulam, 1998) organized into multiple processing streams and forms a hierarchy. More recently, the arrival of quantitative network modeling and analysis (Sporns et al., 2004; Bullmore and Sporns, 2009) has provided well-defined, internally consistent, and methodologically flexible tools with which to characterize and report hierarchy (Reid et al., 2009), informational efficiency (Achard and Bullmore, 2007), small-world connectivity (Sporns and Zwi, 2004; Bassett and Bullmore, 2006), modularity (Chen et al., 2008; Meunier et al., 2009), and hub structure (Hagmann et al., 2008; Buckner et al., 2009) in brain network data. Topological analyses of brain network have been carried out on MR imaging data as well as on electrophysiological

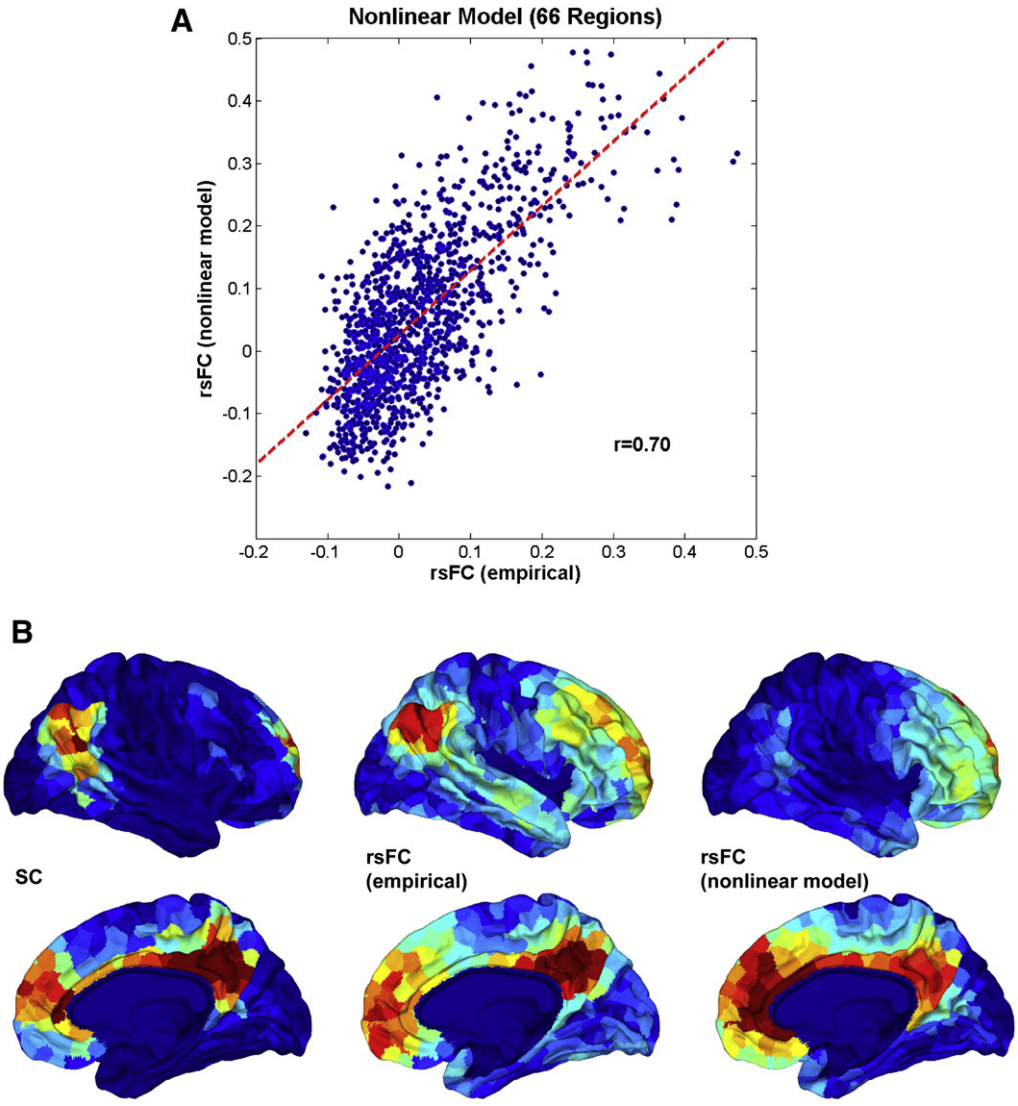

Fig. 3. Modeling and predicting functional connectivity. (A) Direct comparison of empirical resting state functional connectivity and modeled functional connectivity, across all brain regions (Honey et al., 2009). (B) Cortical surface maps for structural connectivity (SC), empirical resting-state functional connectivity (rsFC) and modeled functional connectivity. The maps were created by placing seeds in the PCC, medial frontal and lateral parietal cortex. Note substantial agreement between modeled and empirical FC along the cortical midline, but some mismatch in the lateral parietal cortex. Data replotted from Honey et al. (2009).

recordings (e.g. Stam, 2004; Stam et al., 2007). The motivation for topologically characterizing brain networks is manifold. Most importantly for our present discussion, graph-theoretic measures can be used to summarize the properties of both SC and FC datasets, enabling the direct comparison of structural and functional network architecture.

If structural and functional connectivity are indeed related we might expect to see correspondences between their network topologies. Several studies have documented common architectural features such as small-world attributes, and the existence of modules and hubs. For example, structural hubs in the posterior medial cortex (Hagmann et al., 2008; Gong et al., 2009) correspond to hubs in resting-state fMRI FC networks (Buckner et al., 2009). The shared small-world organization of structural and functional networks allows for economical wiring and communication costs, and it also promotes efficient neural processing by ensuring short communication distances, as well as diverse and complex network dynamics (Sporns et al., 2000). A more recent neural mass modeling study by Ponten et al. (2009) emphasizes that the path length and clustering properties of FC networks do not necessarily vary smoothly with the parameters of the underlying coupling matrix.

When assessing and interpreting the statistics that characterize SC and FC networks, it is worth bearing in mind that the methods used to acquire SC and FC empirically may influence the observed network features (Rubinov and Sporns, 2010). Because of the nature of the correlation coefficient, for example, it will commonly be the case that FC is transitive. In other words, strong FC between A and B as well as between A and C is associated with an increased probability of strong FC between B and C, and a greater degree of clustering in FC networks than expected in the simplest null models.

Spatiality in the SC–FC relationship

As we consider brain regions that are increasingly distant from one another, we find that both SC and FC are, on average, diminished. It is important to analytically account for this systematic spatial variation in SC and FC patterns, because the inter-regional distance may mediate a large portion of the covariation between SC and FC. Notably, in the two studies that examined the role of distance (Skudlarski et al., 2008; Honey et al., 2009) it was observed, that although distance contributed significantly to the SC–FC correlation,

the SC–FC relationship nevertheless remained highly significant in even once inter-regional distance was included as a covariate in their correlation analyses.

Although controlling for distance is an important component of the analysis of SC–FC, caution should be exercised when interpreting the results of such a manipulation. The cerebral cortex essentially forms a two-dimensional sheet, and the observed prevalence of connections linking spatially proximate regions (e.g. Young, 1992) results in a "lattice-like" topology. Hence, the notions of "network proximity" and "spatial proximity" are intertwined. When one is "controlling" for distance, one typically aims to correct for spurious sources of covariation between SC and FC, i.e. sources of covariation other than those arising from direct neural interactions. But many such instances of "spurious" FC can ultimately be demonstrated to arise from SC. For example, FC between adjacent portions of cortex may arise from traveling wave activity across the cortical surface (e.g., Lubenov and Siapas, 2009) or from common thalamic innervation. However, in both cases, the spatiality of the FC profile arises from a structural basis which also displays spatial autocorrelation: the traveling waves are likely mediated by lattice-like horizontal connections within the cortical gray matter and the spatial autocorrelation in thalamocortical drive is likely a result of reciprocal and near-neighbor feedback SC between thalamus and cortex. The anatomical network of the brain is spatially embedded, and this fundamental physical property induces some neighbor-to-neighbor FC at many spatial scales.

SC and FC over time

One would expect that fast fluctuations of FC will occur during spontaneous and task-evoked activity while plasticity and development are accompanied by slower and mutually interdependent changes in SC and FC. Computational models of large-scale neural dynamics suggest that rapid changes in FC can occur in the course of spontaneous activity, even while SC remains unaltered (e.g. Honey et al., 2007; Ghosh et al., 2008; Deco et al., 2009). Detailed analysis of electromagnetic and fMRI time series data suggests that functional coupling between remote sites in the brain undergoes continual and rapid fluctuations (Linkenkaer-Hansen et al., 2001; Stam and de Bruin, 2004; Freyer et al., 2009), possibly indicative of a complex dynamic regime (Kitzbichler et al., 2009). Fluctuations in FC may result from intermittency or metastability created by the shape of the system's high-dimensional attractor (Tsuda, 2001; Breakspear, 2002). Transitions in dynamic states of a large-scale neural system may thus occur spontaneously, even in the absence of any overt stimulus. While these computational studies, as well as many reports in the electrophysiological literature, are suggestive of a high degree of dynamic variability over periods of a few seconds, fMRI resting-state patterns aggregated over a many minutes have proven to be both reliable and robust (Damoiseaux et al., 2006). A comprehensive study (Shehzad et al., 2009) examined the reliability of individual functional connections and the consistency of functional networks measured with fMRI within the adult brain. Based on a comparison of scans separated by less than an hour and by as much as 16 months apart, the authors concluded that functional connectivity was a moderately reliable quantity over these timescales, and noted that the more highly reliable functional connections were also more likely to be linked to the default-network and to be positive rather than negative correlations. Honey et al. (2009) also examined inter-scan reliability, and noted that, although FC did appear to be a reliable quantity, the variability in FC across runs was greater than would be expected if the underlying random variables describing fMRI time-series were static, subject only to variability induced by sample size effects. They suggested that some of this excess might result from fluctuations in FC that were occurring at a time-scale more rapid than that at which FC can be measured in fMRI. Recent electrophysiological recordings from the default mode network in humans (Miller et al., 2009b) not only firmly establish the neuronal origin of task-related BOLD decreases in the DMN, but also demonstrate a methodology that can soon be used to more precisely quantify the ongoing fluctuations in large-scale spontaneous FC.

Functional connectivity undergoes significant changes in the course of learning (McIntosh et al., 2003), stimulation-induced cortical reorganization (Rounis et al., 2006), and neuroplasticity (Canals et al., 2009). A significant and unresolved question is the extent to which SC is invariant in the adult brain, and whether large-scale FC measurements might be used to detect specific, localized changes in SC generated by ongoing synaptic plasticity associated with, e.g. learning. Recent results from diffusion imaging studies suggest that SC, even at a large scale, is plastic (Scholz et al., 2009) and these structural changes may produce changes that are measurable using functional neuroimaging.

The study of developmental change can powerfully inform our understanding of both SC and FC, as well as their relationship with one another and with distinct behavioral capacities. The pruning of over-proliferated synapses, which begins in human visual cortex at approximately 1 year of age and continues through adulthood, is a critical element of cerebral development (Huttenlocher, 1990). Between the ages of approximately 5 and 20 years, the ratio of gray matter to white matter (as measured using tissue classification of MR images) is found to decrease, as axonal myelination and cytoarchitectural maturation proceed at different rates across the cortex (Gogtay et al., 2004). While diffusion-imaging based SC mapping is yet to be systematically assessed across the course of human brain development, several cross-sectional studies have examined the developmental trajectories of FC (Fair et al., 2007; Fair et al., 2009; Supekar et al., 2009). Fair et al. compared groups of children (7–9 years old) and young adults (21–31 years old), and reported that FC between nearby regions decreased in the course of development, while long-range FC increased. Additionally, Fair et al. (2008) observed that the FC of regions within the default system was quite different between the child and adult groups: the default system FC in children lacked its long-range intra-hemispheric rostro-caudal connections. Combined with findings that the DMN appears to be absent in human neonates (Fransson et al., 2007), these results indicate that FC is substantially altered in parallel with the diverse biological and behavioral changes that constitute human development.

Structural damage and functional deficits

The functional consequences of network damage are a central concern in network studies of technological, social and natural systems. Building on these approaches, the analysis of brain network damage and the assessment of resulting functional deficits promise to open new avenues to understanding human brain damage and disease.

Lesions are perturbations of structural brain networks that have physiological effects. One way to gauge the possible consequences of localized brain lesions is to model the effects of deleting subsets of nodes and edges on the structure and function of the remaining brain. Several such studies have been carried out on structural networks of the mammalian cerebral cortex (Young et al., 2000; Honey and Sporns, 2008) and have reported non-local consequences of local lesions. More abstract network studies have examined the vulnerability of structural networks to the deletion of single nodes and edges (Kaiser and Hilgetag, 2004; Kaiser et al., 2007), with the authors concluding that damage to nodes and edges of high centrality is particularly deleterious. Consistent with these earlier studies, lesions of highly central regions had the largest effects on FC in the remaining brain in a recent model of human brain dynamics (Alstott et al., 2009). For example, deletion of structural hubs along the cortical midline or in the vicinity of the temporoparietal junction disrupted FC not only in the immediate vicinity of the lesion, but also between pairs of remote brain regions (Fig. 4).

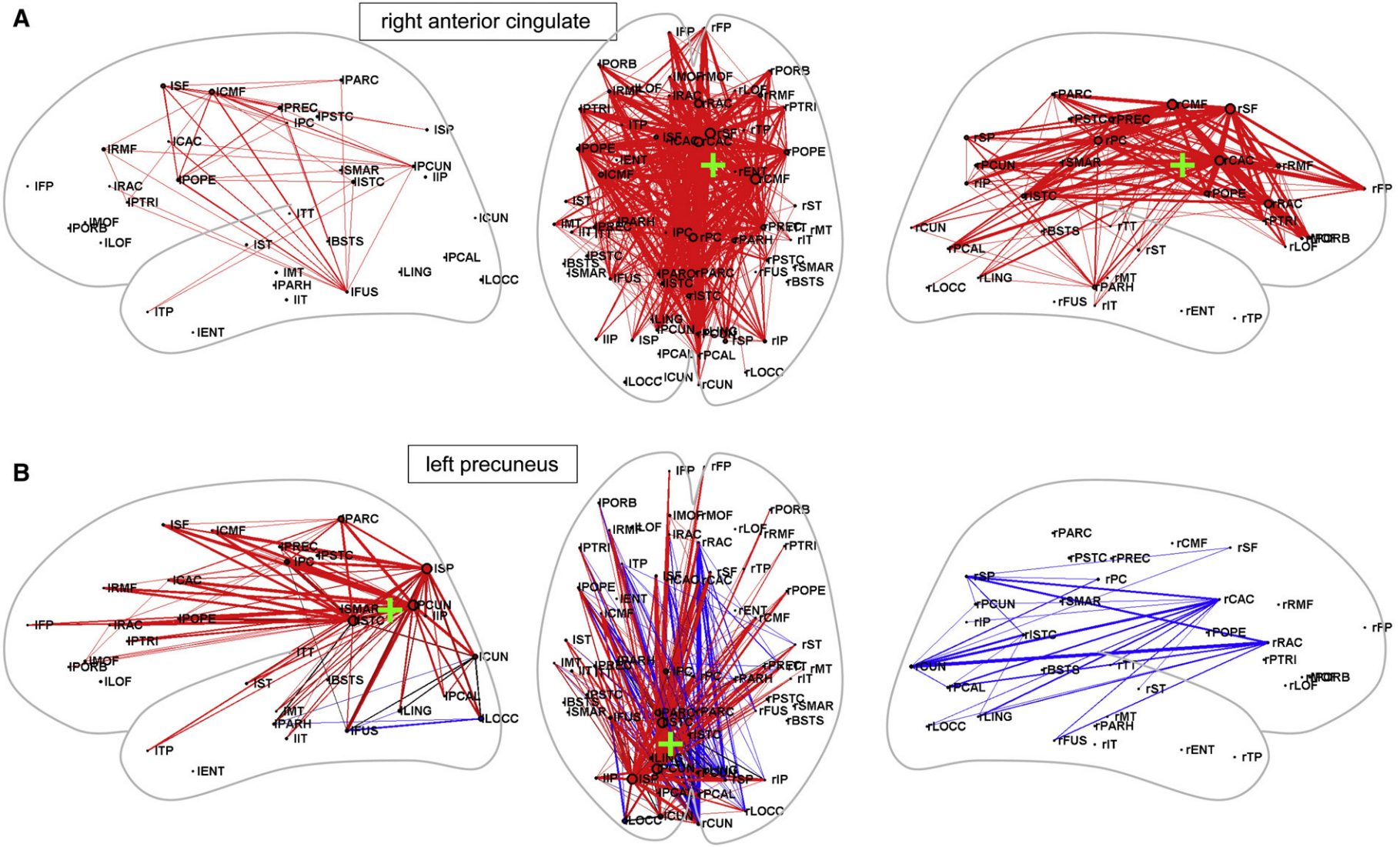

Fig. 4. Dynamic consequences of lesions in a model of the human brain. Lesions were centered approximately at the location of the green cross, comprising about 5% of the cortical surface around the right anterior cingulate cortex (A) and the left precuneus (B). Functional connections across the brain that were significantly changed (increased = blue, decreased = red) are shown in a dorsal view of the brain (middle plots) as well as within the left and right hemispheres alone. Note that both lesions, while located in only one hemisphere, result in disruptions of functional connectivity in both ipsilateral and contralateral hemispheres. Reproduced from Alstott et al. (2009).

Studies of functional networks in patients with structural lesions and specific cognitive deficits support this model. He et al. (2007a) examined FC in patients exhibiting spatial neglect following a stroke in the right cerebral hemisphere. Acute disruptions of FC located outside of the primary lesion site-in regions involved in spatial attention-were found to be strongly correlated with an impairment of attentional processing. These results support a network approach to understanding complex neurological disorders such as spatial neglect and document the contributions of nonlocal lesion effects to disruptions of behavior and cognition (He et al., 2007b). Further direct evidence for an acute change in FC following a disruption of SC is provided by the study of Johnston et al. (2008) who analyzed pre- and post-surgical functional images acquired from a young patient who underwent callosotomy. In this individual, inter-hemispheric FC was largely abolished, and intra-hemispheric was largely unaltered acutely post-surgically.

Several neurodegenerative or neuropsychiatric disorders may be traced to disturbances in SC that become functionally expressed in disturbances of brain dynamics. The literature on changes in SC and FC in neuropsychiatric conditions is a complex and expanding field, and we refer the reader to reviews by Buckner et al. (2008), Greicius (2008) and Bassett and Bullmore (2009) for more complete coverage.

Promising recent results come from the study of Alzheimer's disease (AD) and the associated, potentially prodromal syndrome of Mild Cognitive Impairment (MCI). The intrinsic and extrinsic FC of DMN regions is found to be diminished in patients with AD (Greicius et al., 2004; Wang et al., 2007) and MCI (Sorg et al., 2007). Importantly, areas of increased amyloid deposition in healthy and potentially pre-MCI elderly individuals exhibited abnormal task-related BOLD signal in DMN regions (Sperling et al., 2009). In parallel, it has been demonstrated that white matter anisotropy is altered in the vicinity of the DMN in patients with amnesic MCI (Bai et al., 2009). Ideally, future work will combine these metrics of pathology in a single population of AD patients so that the interconnections between them can be better understood. There appears to be substantial utility for FC and SC measurements in the diagnosis (and potentially the prognosis) of AD.

The link to SC and FC in other neuropsychiatric disorders is definitive. The SC and FC signatures of schizophrenia do not appear to be localized to any small subset of brain regions (e.g. Micheloyannis et al., 2006). Some studies implicate DMN regions (Garrity et al., 2007), while others have reported changes in aggregate network topological properties (Bassett et al., 2008; Liu et al., 2008). There has been some inconsistency in the findings of the field (Greicius, 2008) and it is unclear whether this is a consequence of the intricacy of the disorder or of methodological differences across groups. Diminutions of FC magnitude have been detected in ADHD (Castellanos et al., 2008) as well as autism (Kennedy and Courchesne, 2008; Monk et al., 2009), whereas increased FC, in particular between DMN regions and the subgenual cingulate, has been reported in cases of depression (Greicius et al., 2007).

For all of these disorders, further progress in the characterization of SC pathology is needed. An unanswered question of major clinical relevance is whether it is more diagnostic to measure FC in the resting state or under task conditions designed to elicit differentiating pathology-linked behavior (Jones et al., 2009). Understanding whether and to what extent task-free and task-focused protocols measure a common “underlying” FC is also an important basic research question, because its answer informs us as to which aspects of FC are reflective of the present behavioral state, and which aspects are more persistent, and therefore potentially reflective of the functional architecture within which large-scale neurodynamics and behavior must evolve. An important recent paper (Smith et al., 2009) indicates that many of the functional networks detected in spontaneous activity are also expressed in functional activations patterns across diverse task settings.

Conclusions

Rapid advances in recording and data processing methods are beginning to yield structural and functional connection maps of brain networks at multiple scales and with unprecedented accuracy and resolution. Connectome datasets will facilitate a far clearer understanding of the relationship between structure and function in the human brain. Initial results are encouraging, in that many of the characteristics of functional brain dynamics can be traced to structural patterns in connectivity. In this sense structure does predict function, by shaping neural dynamics among cells and brain regions. However, as our models become more complete, incorporating both local and global connectivity data, our expectations of them must increase.

The next generation of models must make quantitative predictions of—and must be tested against—not only the aggregate correlation structure of neural dynamics in large populations, but also of dynamical properties (such as the power spectrum) of individual nodes. As the connective data becomes available to model multi-synaptic circuits organized between cells of different types in distinct cortical layers, our models must capture these interactions. Finally, the detailed predictions of rapid changes in micro-scale dynamics must then be related to the slowly changing patterns of functional connectivity observed using neuroimaging.

At present, we cannot definitively specify the extent to which structure shapes function within human brain networks, because the structural networks remain to be fully characterized at both micro and macro scales, and because we are only now beginning to quantitatively and empirically test the predictions of large network models. What is clear, based on the studies we have reviewed, is that as we undertake the considerable task of organizing and interpreting novel datasets, computational modeling and network approaches will be indispensable in our search for structure–function relationships across the multiscale architecture of the human brain.

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References

Achard, S., Bullmore, E., 2007. Efficiency and cost of economical brain functional networks. PLoS Comput. Biol. 3, e17.
Alstott, J., Breakspear, M., Hagmann, P., Cammoun, L., Sporns, O., 2009. Modeling the impact of lesions in the human brain. PLoS Comput. Biol. 5, e1000408.
Angelucci, A., Lebitt, J.B., Walton, E.J.S., Hipe, J.M., Bullier, J., et al., 2002. Circuits for local and global signal integration in primary visual cortex. J. Neurosci. 22, 8633–8646.
Bai, F., Zhang, Z., Watson, D.R., Yu, H., Shi, Y., et al., 2009. Abnormal integrity of association fiber tracts in amnestic mild cognitive impairment. J. Neurol. Sci. 278, 102–106.
Bassett, D.S., Bullmore, E.T., 2006. Small-world brain networks. Neuroscientist 12, 512–523.
Bassett, D.S., Meyer-Lindenberg, A., Achard, S., Duke, T., Bullmore, E.T., 2006. Adaptive reconfiguration of fractal small-world human brain functional networks. Proc. Natl. Acad. Sci. U. S. A. 103, 19518–19523.
Bassett, D.S., Bullmore, E.T., Verchinksi, B.A., Mattay, V.S., Weinberger, D.R., Meyer-Lindenberg, A., 2008. Hierarchical organization of human cortical networks in health and schizophrenia. J. Neurosci. 28, 9239–9248.
Bassett, D.S., Bullmore, E.T., 2009. Human brain networks in health and disease. Curr. Opin. Neurol. 22, 340–347.
Bertschinger, N., Natschläger, T., 2004. Real-time computation at the edge of chaos in recurrent neural networks. Neural Comput. 16, 1413–1436.
Binzegger, T., Douglas, R.J., Martin, K.A., 2009. Topology and dynamics of the canonical circuit of cat V1. Neural Netw. 22 (8), 1071–1078.
Bollmann, J.H., Engert, F., 2009. Subcellular topography of visually driven dendritic activity in the vertebrate visual system. Neuron 61, 895–905.
Bosking, W.H., Zhang, Y., Schofield, B., Fitzpatrick, D., 1997. Orientation selectivity and the arrangement of horizontal connections in tree shrew striate cortex. J. Neurosci. 17, 2112–2127.
Braitenberg, V., Schüz, A., 1998. Statistics and Geometry of Neuronal Connectivity. Springer, Berlin.
Breakspear, M., 2002. Nonlinear phase desynchronization in human electroencephalographic data. Hum. Brain Mapp. 15, 175–198.

Breakspear, M., Terry, J., Friston, K., 2003. Modulation of excitatory synaptic coupling facilitates synchronization and complex dynamics in a biophysical model of neuronal dynamics. Network Comput. Neural. Syst. 14, 703–732.
Breakspear, M., Stam, C.J., 2005. Dynamics of a neural system with a multiscale architecture. Phil. Trans. Roy. Soc. B. 360, 1051–1074.
Breakspear, M., Jirsa, V., 2007. Neuronal dynamics and brain connectivity. In: McIntosh, A.R., Jirsa, V.K. (Eds.), Handbook of Brain Connectivity. Springer, Berlin.
Breakspear, M., Knock, S., 2008. Kinetic models of brain activity. Brain Imaging Behav. 2, 270–288.
Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N.Y. Acad. Sci. 1124, 1–38.
Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., 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.
Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10, 186–198.
Buonomano, D.V., Maass, W., 2009. State-dependent computations: spatiotemporal processing in cortical networks. Nat. Rev. Neurosci. 10, 113–125.
Buzsáki, G., Geisler, C., Henze, D.A., Wang, X.J., 2004. Interneuron diversity series: circuit complexity and axon wiring economy of cortical interneurons. Trends Neurosci. 27, 186–193.
Canals, S., Beyerlein, M., Merkle, H., Logothetis, N.K., 2009. Functional MRI evidence for LTP-induced neural network reorganization. Curr. Biol. 19, 398–403.
Castellanos, F.X., Margulies, D.S., Kelly, A.M.C., Uddin, L.Q., Ghaffari, M., et al., 2008. Cingulate–precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol. Psychiatry 63, 332–337.
Chen, Z.J., He, Y., Rosa-Neto, P., Germann, J., Evans, A.C., 2008. Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. Cereb. Cortex 18, 2374–2381.
Chklovskii, D.B., Schikorski, T., Stevens, C.F., 2002. Wiring optimization in cortical circuits. Neuron 34, 341–347.
Damoiseaux, J.S., et al., 2006. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. U. S. A. 103, 13848–13853.
Damoiseaux, J.S., Greicius, M.D., 2009. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct. Funct. 213, 525–533.
Deco, G., Jirsa, V., McIntosh, A.R., Sporns, O., Kötter, R., 2009. Key role of coupling, delay, and noise in resting brain fluctuations. Proc. Natl. Acad. Sci. U. S. A. 106, 10302–10307.
Douglas, R.J., Martin, K.A.C., 2007. Mapping the matrix: the ways of neocortex. Neuron 56, 226–238.
Fair, D.A., Dosenbach, N.U.F., Church, J.A., Cohen, A.L., Brahmbhatt, S., et al., 2007. Development of distinct control networks through segregation and integration. Proc. Natl. Acad. Sci. U. S. A. 104, 13507–13512.
Fair, D.A., Cohen, A.L., Dosenbach, N.U., Church, J.A., Miezin, F.M., et al., 2008. The maturing architecture of the brain's default network. Proc. Natl. Acad. Sci. U. S. A. 105, 4028–4032.
Fair, D.A., Cohen, A.L., Power, J.D., Dosenbach, N.U.F., Church, J.A., et al., 2009. Functional brain networks develop from a "local to distributed" organization. PLoS Comput. Biol. 5, e1000381.
Felleman, D.J., van Essen, D.C., 1991. Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex 1, 1–47.
Fransson, P., Skiold, B., Horsch, S., Nordell, A., Blennow, M., et al., 2007. Resting-state networks in the infant brain. Proc. Natl. Acad. Sci. U. S. A. 104, 15531–15536.
Freeman, W., 2000. Neurodynamics. Springer Verlag, London, An Exploration in Mesoscopic Brain Dynamics.
Freyer, F., Aquino, K., Robinson, P.A., Ritter, P., Breakspear, M., 2009. Bistability and non-Gaussian fluctuations in spontaneous cortical activity. J. Neurosci. 29, 8512–8524.
Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn. Sci. 9, 474–480.
Friston, K.J., 1994. Functional and effective connectivity in neuroimaging: a synthesis. Hum. Brain Mapp. 2, 56–78.
Garrity, A.G., Pearlson, G.D., McKiernan, K., Lloyd, D., Kiehl, K.A., Calhoun, V.D., 2007. Aberrant "default mode" functional connectivity in schizophrenia. Am. J. Psychiatry 164, 450–457.
Ghosh, A., Rho, Y., McIntosh, A.R., Kotter, R., Jirsa, V.K., 2008. Noise during rest enables the exploration of the brain's dynamic repertoire. PLoS Comput. Biol. 4, e1000196.
Gilbert, C.D., Wiesel, T.N., 1983. Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. J. Neurosci. 9, 2432–2442.
Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., et al., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. U. S. A. 101, 8174–8179.
Gong, G., He, Y., Concha, L., Lebel, C., Gross, D.W., et al., 2009. Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. Cereb. Cortex 19, 524–536.
Graziano, M.S.A., Aflalo, T.N., 2007. Mapping behavioral repertoire onto the cortex. Neuron 56, 239–251.
Greicius, M.D., 2008. Resting-state functional connectivity in neuropsychiatric disorders. Curr. Opin. Neurol. 21, 424–430.
Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U. S. A. 100, 253–258.
Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl. Acad. Sci. U. S. A. 101, 4637–4642.
Greicius, M.D., Flores, B.H., Memon, V., Glover, G.H., Solvason, H.B., et al., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol. Psych. 62, 429–437.
Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F., 2009. Resting state functional connectivity reflects structural connectivity in the default mode network. Cereb. Cortex 19, 72–78.
Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., et al., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol. 6, e159.
Hampson, M., Driesen, N.R., Skudlarski, P., Gore, J.C., Constable, R.T., 2006. Brain connectivity related to working memory performance. J. Neurosci. 26, 13338–13343.
Häusler, S., Schuch, K., Maass, W., 2009. Motif distribution and computational performance of two data-based cortical microcircuit templates. J. Physiol. (Paris) 103, 73–87.
He, B.J., Snyder, A.Z., Vincent, J.L., Epstein, A., Shulman, G.L., et al., 2007a. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53, 905–918.
He, B.J., Shulman, G.L., Snyder, A.Z., Corbetta, M., 2007b. The role of impaired neuronal communication in neurological disorders. Curr. Opin. Neurol. 20, 655–660.
Hestrin, S., Galarreta, M., 2005. Electrical synapses define networks of neocortical GABAergic neurons. Trends Neurosci. 28, 304–309.
Honey, C.J., Sporns, O., 2008. Dynamical consequences of lesions in cortical networks. Hum. Brain Mapp. 29, 802–809.
Honey, C.J., Kötter, R., Breakspear, M., Sporns, O., 2007. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc. Natl. Acad. Sci. U. S. A. 104, 10240–10245.
Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., et al., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl. Acad. Sci. U. S. A. 106, 2035–2040.
Horton, J.C., Adams, D.L., 2005. The cortical column: a structure without a function. Phil. Trans. R. Soc. B. 360, 837–862.
Hubel, W., 1978. Anatomical demonstration of orientation columns in macaque monkey. J. Comp. Neurol. 77, 361–380.
Huttenlocher, P.R., 1990. Morphometric study of human cerebral cortex development. Neuropsychologia 28, 517–527.
Ingber, L., Nunez, P.L., 1990. Multiple scales of statistical physics of the neocortex: application to electroencephalography. Math Comput. Model. 13, 83–95.
Izhikevich, E.M., Edelman, G.M., 2008. Large-scale model of mammalian thalamocortical systems. Proc. Natl. Acad. Sci. U. S. A. 105, 3593–3598.
Johnston, J.M., Vaishnavi, S.N., Smyth, M.D., Zhang, D., He, B.J., et al., 2008. Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. J. Neurosci. 28, 6453–6458.
Jones, T.B., Bandettini, P.A., Kenworthy, L., Case, L.K., Milleville, S.C., et al., 2009. Sources of group differences in functional connectivity: an investigation applied to autism spectrum disorder. Neuroimage 49, 401–414.
Kaiser, M., Hilgetag, C.C., 2004. Edge vulnerability in neural and metabolic networks. Biol. Cybern. 90, 311–317.
Kaiser, M., Hilgetag, C.C., 2006. Nonoptimal component placement, but short processing paths, due to long-distance projections in neural systems. PLoS Comput. Biol. e95, 2.
Kaiser, M., Robert, M., Andras, P., Young, M.P., 2007. Simulation of robustness against lesions of cortical networks. Eur. J. Neurosci. 25, 3185–3192.
Kenet, T., Bibitchkov, D., Tsodyks, M., Grinvald, A., Arieli, A., 2003. Spontaneously emerging cortical representations of visual attributes. Nature 425, 954–956.
Kennedy, D.P., Courchesne, E., 2008. The intrinsic functional organization of the brain is altered in autism. Neuroimage 39, 1877–1885.
Kitzbichler, M.G., Smith, M.L., Christensen, S.R., Bullmore, E., 2009. Broadband criticality of human brain network synchronization. PLoS Comput. Biol. 5, e1000314.
Knock, S.A., McIntosh, A.R., Sporns, O., Kötter, R., Hagmann, P., Jirsa, V.K., 2009. The effects of physiologically plausible connectivity structure on local and global dynamics in large scale brain models. J. Neurosci. Methods 183, 86–94.
Koch, M.A., Norris, D.G., Hund-Georgiadis, M., 2002. An investigation of functional and anatomical connectivity using magnetic resonance imaging. Neuroimage 16, 241–250.
Kohn, A., Zandvakili, A., Smith, M.A., 2009. Correlations and brain states: from electrophysiology to functional imaging. Curr. Opin. Neurobiol. 19, 434–438.
Lichtman, J.W., Smith, S.J., 2008. Seeing circuits assemble. Neuron 60, 441–448.
Linkenkaer-Hansen, K., Nikouline, V.V., Palva, J.M., Ilmoniemi, R.J., 2001. Long-range temporal correlations and scaling behavior in human brain oscillations. J. Neurosci. 21, 1370–1377.
Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., et al., 2008. Disrupted small-world networks in schizophrenia. Brain 131, 945–961.
Lubenov, E.V., Siapas, A.G., 2009. Hippocampal theta oscillations are travelling waves. Nature 459, 534–539.
Maass, W., Natschläger, T., Markram, H., 2002. Real-time computing without stable states: a new framework for neural computation based on perturbations. Neural. Comput. 14, 2531–2560.
Malach, R., Amir, Y., Harel, M., Grinvald, A., 1993. Relationship between intrinsic connections and functional architecture revealed by optical imaging and in vivo targeted biocytin injections in primate striate cortex. Proc. Natl. Acad. Sci. 90, 10469–10473.
Masuda, N., Aihara, K., 2004. Global and local synchrony of coupled neurons in small-world networks. Biol. Cybern. 90, 302–309.
McIntosh, A.R., Rajah, M.N., Lobaugh, N.J., 2003. Functional connectivity of the medial temporal lobe relates to learning and awareness. J. Neurosci. 23, 6520–6528.
Mesulam, M.M., 1998. From sensation to cognition. Brain 121, 1013–1052.
Meunier, D., Achard, S., Morcom, A., Bullmore, E., 2009. Age-related changes in modular organization of human brain functional networks. Neuroimage 44, 715–723.

Micheloyannis, S., Pachou, E., Stam, C.J., Breakspear, M., Bitsios, P., et al., 2006. Small-world networks and disturbed functional connectivity in schizophrenia. Schizophr. Res. 87, 60–66.
Miller, K.J., Zanos, S., Fetz, E.E., den Nijs, M., Ojemann, J.G., 2009a. Decoupling the cortical power spectrum reveals real-time representation of individual finger movements in humans. J. Neurosci. 29, 3132–3137.
Miller, K.J., Weaver, K.E., Ojemann, J.G., 2009b. Direct electrophysiological measurement of human default network areas. Proc. Natl. Acad. Sci. U. S. A. 106, 12174–12177.
Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., et al., 2002. Network motifs: simple building blocks of complex networks. Science 298, 824–827.
Monk, C.S., Peltier, S.J., Wiggins, J.L., Weng, S.J., Carrasco, M., et al., 2009. Abnormalities of intrinsic functional connectivity in autism spectrum disorders. Neuroimage 47, 764–772.
Mortimer, D., Feldner, J., Vaughn, T., Vetter, I., Pujic, Z., et al., 2009. A Bayesian model predicts the response of axons to molecular gradients. Proc. Natl. Acad. Sci. U. S. A. 106, 10296–10301.
Mountcastle, V.B., 1997. The columnar organization of the neocortex. Brain 120, 4701–4722.
O'Keefe, J., Recce, M.L., 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 317–330.
Ostojic, S., Brunel, N., Hakim, V., 2009. How connectivity, background activity, and synaptic properties shape the cross-correlation between spike trains. J. Neurosci. 29, 10234–10253.
Pakkenberg, B., Gundersen, H.J.G., 1997. Neocortical neuron number in humans: effect of sex and age. J. Comp. Neurol. 384, 312–320.
Peters, A., Sethares, C., 1996. Myelinated axons and the pyramidal modules in monkey primary visual cortex. J. Comp. Neurol. 365, 232–255.
Ponten, S.C., Daffertshofer, A., Hillebrand, A., Stam, C.J., 2009. The relationship between structural and functional connectivity: graph theoretical analysis of an EEG neural mass model. NeuroImage. doi:10.1016/j.neuroimage.2009.10.049.
Prinz, A.A., Bucher, D., Marder, E., 2004. Similar network activity from disparate circuit parameters. Nat. Neurosci. 7, 1345–1352.
Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 98, 676–682.
Reid, A.T., Krumnack, A., Wanke, E., Kötter, R., 2009. Optimization of cortical hierarchies with continuous scales and ranges. Neuroimage 47, 611–617.
Roopun, AK., Kramer, MA, Carracedo, LM, Kaiser, M, Davies, CH, Traub, RD, Kopell, NJ, Whittington, MA, 2008. Period concatenation underlies interactions between gamma and beta rhythms in neocortex. Front. Cell Neurosci. 2, 1 doi:10.3389/neuro.03.001.2008.
Rounis, E., Stephan, K.E., Lee, L., Siebner, H.R., Pesenti, A., et al., 2006. Acute changes in frontoparietal activity after repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in a cued reaction time task. J. Neurosci. 26, 9629–9638.
Rubino, D., Robbins, K.A., Hatsopoulos, N.G., 2006. Propagating waves mediate information transfer in the motor cortex. Nat. Neurosci. 9, 1549–1557.
Rubinov, M., Sporns, O., van Leeuwen, C., Breakspear, M., 2009. Symbiotic relationship between brain structure and dynamics. BMC Neurosci. 10, 55.
Rubinov, M., Sporns, O., 2010. Propagating waves mediate information transfer in the motor cortex. Neuroimage 52, 1063–1073.
Scholz, J, Klein, MC, Behrens, TEJ, Johansen-Berg, H, 2009. Training induces changes in white-matter architecture. Nat. Neurosci. doi:10.1038/nn.2412.
Serre, T., Oliva, A., Poggio, T., 2007. A feedforward architecture accounts for rapid categorization. Proc. Natl. Acad. Sci. U. S. A. 104, 6424–6429.
Shehzad, Z, Kelly, AMC, Reiss, PT, Gee, DG, Gotimer, K, et al., 2009. The resting brain: unconstrained yet reliable. Cereb. Cortex. doi:10.1093/cercor/bhn256.
Sholl, D.A., 1953. Dendritic organization in the neurons of the visual and motor cortices of the cat. J. Anat. 87, 387–406.
Skudlarski, P., Jagannathan, K., Calhoun, V.D., Hampson, M., Skudlarska, B.A., et al., 2008. Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. Neuroimage 43, 554–561.
Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., et al., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106, 13040–13045.
Song, S., Sjöström, P.J., Reigl, M., Nelson, S., Chklovskii, D.B., 2005. Highly nonrandom features of synaptic connectivity in local cortical circuits. PLoS Biol. 3, e68.
Sorg, C., Riedl, V., Mühlau, M., Calhoun, V.D., Eichele, T., et al., 2007. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 104, 18760–18765.
Sperling, R.A., LaViolette, P.S., O'Keefe, K., O'Brian, J., Rentz, D.M., et al., 2009. Amyloid deposition is associated with impaired network function in older persons without dementia. Neuron 63, 178–188.
Sporns, O., Tononi, G., Edelman, G.M., 2000. Theoretical neuroanatomy: relating anatomical and functional connectivity in graphs and cortical connection matrices. Cereb. Cortex 10, 127–141.
Sporns, O., Kötter, R., 2004. Motifs in brain networks. PLoS Biol. 2, 1910–1918.
Sporns, O., Chialvo, D., Kaiser, M., Hilgetag, C.C., 2004. Organization, development and function of complex brain networks. Trends Cogn. Sci. 8, 418–425.
Sporns, O., Zwi, J., 2004. The small world of the cerebral cortex. Neuroinformatics 2, 145–162.
Sporns, O., Tononi, G., Kötter, R., 2005. The human connectome: a structural description of the human brain. PLoS Comput. Biol. 1, 245–251.
Sporns, O., Honey, C.J., Kötter, R., 2007. Identification and classification of hubs in brain networks. PLoS ONE 2, e1049.
Stam, C.J., 2004. Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci. Lett. 355, 25–28.
Stam, C.J., de Bruin, E.A., 2004. Scale-free dynamics of global functional connectivity in the human brain. Hum. Brain Mapp. 22, 97–109.
Stam, C.J., Jones, B.F., Nolte, G., Breakspear, M., Scheltens, P., 2007. Small-world networks and functional connectivity in Alzheimer's disease. Cereb. Cortex 17, 92–99.
Stepanyants, A., Tamás, G., Chklovskii, D.B., 2004. Class-specific features of neuronal wiring. Neuron 43, 251–259.
Stephan, K.E., Tittgemeyer, M., Knösche, T.R., Moran, R.J., Friston, K.J., 2009. Tractography-based priors for dynamic causal models. Neuroimage 47, 1628–1638.
Supekar, K., Musen, M., Menon, V., 2009. Development of large-scale functional brain networks in children. PLoS Biol. 7, e1000157.
Sussillo, D., Abbott, L.F., 2009. Generating coherent patterns of activity from chaotic neural networks. Neuron 63, 544–557.
Thivierge, J.P., Marcus, G.F., 2007. The topographic brain: from neural connectivity to cognition. Trends Neurosci. 30, 251–259.
Thomson, A.M., Bannister, A.P., 2003. Interlaminar connections in the neocortex. Cereb. Cortex 13, 5–14.
Tononi, G., Sporns, O., Edelman, G.M., 1999. Measures of degeneracy and redundancy in biological networks. Proc. Natl. Acad. Sci. U. S. A. 96, 3257–3262.
Tsodyks, M., Kenet, T., Grinvald, A., Arieli, A., 1999. Linking spontaneous activity of single cortical neurons and the underlying functional architecture. Science 286, 1943–1946.
Tsuda, I., 2001. Towards an interpretation of dynamic neural activity in terms of chaotic dynamical systems. Behav. Brain Sci. 24, 793–847.
Uttley, A.M., 1955. The probability of neural connexions. Proc. R. Soc. B. 144, 229–240.
Van den Heuvel, M.P., Mandl, R.C.W., Kahn, R.S., Hulshoff Pol, H.E., 2009a. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum. Brain Mapp. 30, 3127–3141.
Van den Heuvel, M.P., Stam, C.J., Kahn, R.S., Hulshoff Pol, H.E., 2009b. Efficiency of functional brain networks and intellectual performance. J. Neurosci. 29, 7619–7624.
Van Dijk, K.R., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2009. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103 (1), 297–321.
Vicente, R., Gollo, L.L., Mirasso, C.R., Fischer, I., Pipa, G., 2008. Dynamical relaying can yield zero time lag neuronal synchrony despite long conduction delays. Proc. Natl. Acad. Sci. U. S. A. 105, 17157–17162.
Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., et al., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83–86.
Wang, K., Liang, M., Wang, L., Tian, L., Zhang, X., et al., 2007. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. Hum. Brain Mapp. 28, 967–978.
Young, M.P., 1992. Objective analysis of the topological organization of the primate cortical visual system. Nature 358, 152–155.
Young, P.Y., Hilgetag, C.C., Scannell, J.W., 2000. On imputing function to structure from the behavioural effects of brain lesions. Philos. Trans. R. Soc. Lond., B. Biol. Sci. 355, 147–161.
Zeki, S.M., 1978. Functional specialization in the visual cortex of the rhesus monkey. Nature 274, 423–428.
Zeki, S., Shipp, S., 1988. The functional logic of cortical connections. Nature 335, 311–317.
Zhang, D., Snyder, A.Z., Fox, M.D., Sansbury, M.W., Shimony, J.S., et al., 2008. Intrinsic functional relations between human cerebral cortex and thalamus. J. Neurophysiol. 100, 1740–1748.