Trends in Cognitive Sciences

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Review

Linking Structure and Function in Macroscale Brain Networks

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Structure–function relationships are a fundamental principle of many naturally occurring systems. However, network neuroscience research suggests that there is an imperfect link between structural connectivity and functional connectivity in the brain. Here, we synthesize the current state of knowledge linking structure and function in macroscale brain networks and discuss the different types of models used to assess this relationship. We argue that current models do not include the requisite biological detail to completely predict function. Structural network reconstructions enriched with local molecular and cellular metadata, in concert with more nuanced representations of functions and properties, hold great potential for a truly multiscale understanding of the structure–function relationship.

Highlights

The emergence of network neuroscience allows researchers to quantify the link between the organizational features of neuronal networks and the spectrum of cortical functions.

Current models indicate that structure and function are significantly correlated, but the correspondence is not perfect because function reflects complex multisynaptic interactions in structural networks.

Function cannot be directly estimated from structure, but must be inferred by models of higher-order interactions. Statistical, communication, and biophysical models have been used to translate brain structure to brain function.

Structure–function coupling is regionally heterogeneous and follows molecular, cytoarchitectonic, and functional hierarchies.

Structure and Function of Brain Networks

The relationship between structure and function is a central concept in natural sciences and engineering. Consider how the conformation of a protein determines its chemical properties and, ultimately, its biological function. The folding of the protein into a 3D structure promotes interactions among amino acids, allowing the protein to chemically interact with other molecules and endowing it with function. Conversely, disruption of the protein's structure results in loss of function. Tellingly, the protein is said to be denatured, highlighting the idea that changing its structure has fundamentally altered its natural function.

The function of the nervous system is analogously shaped by the structure and arrangement of neurons and neuronal populations. The complex network of synaptic projections forms a **hierarchy** (see Glossary) of nested and increasingly polyfunctional neural circuits that support perception, cognition, and action. Modern imaging technology permits high-throughput reconstruction of neural circuits across spatiotemporal scales and across species (Box 1). Through extensive international data sharing efforts, increasingly detailed reconstructions of the nervous system's connection patterns are available in humans and in multiple model organisms, including invertebrate [1], avian [2], rodent [3,4], and primate species [5,6]. These comprehensive wiring diagrams of the nervous system, termed **structural connectivity (SC)** networks or **connectomes**, represent the physical connections between neural elements [7].

The emergence of network neuroscience offers an opportunity to quantify and articulate the link between the organizational features of neuronal networks and the spectrum of cortical functions. SC networks possess distinctive and nonrandom attributes, including high local clustering and short path length, characteristic features of a small-world architecture [8]. Populations with similar functional properties tend to cluster together, forming specialized modules crosslinked by hub nodes with diverse connectional fingerprints [9,10]. The hubs of the networks are disproportionately interconnected with each other, forming a putative core [11] or 'rich club' [12], an architectural feature that potentially allows signals to be sampled and integrated from specialized modules [13]. Finally, brain networks are spatially embedded, with finite metabolic and material

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 https://doi.org/10.1016/j.tics.2020.01.008

Box 1. Measuring Structural Connectivity (SC) and Functional Connectivity (FC)

Modern imaging and tracing technology allows reconstruction of brain connectomes at multiple spatial and temporal scales (Figure I). Depending on the acquisition technique, network nodes may represent neurons, neuronal populations, or brain regions. Network edges represent either SC or FC, and their definition and interpretation depends on the imaging modality.

Diffusion-weighted MRI is the most extensively used noninvasive *in vivo* imaging method to measure macroscale SC between brain regions. Applying tractography algorithms on an individual's diffusion-weighted imaging data, SC can be defined as either the connection probability, the number of reconstructed streamlines, or the mean fractional anisotropy across streamlines between two brain regions. This family of techniques is subject to several important limitations, most notably systematic false positives and false negatives [131–133]. Reconstructions are also sensitive to methodological choices, such as the location of the initial seed points and tracking algorithm employed [134]. Tracing technologies, applied to postmortem samples, offer greater fidelity, finer spatial detail, and information about directionality of anatomical projections. Mesoscale methods reconstruct cellular connectivity by combining light microscopy with conventional or viral tracers. Microscale methods reconstruct individual synaptic contacts using electron microscopy.

MRI-based measures are also used to derive macroscale FC networks. FC is typically quantified by computing statistical associations between regional hemodynamic time courses recorded using resting state or task based fMRI. fMRI-based FC may primarily capture stable functional configurations, potentially limiting inferences about time-dependent functional interactions [135] (but see [136]). Other technologies, focusing on electromagnetic neural activity at the macroscale, offer greater potential to resolve time-dependent functional interactions, including electroencephalography, magnetoencephalography, and electrocorticography. At the microscale, numerous microelectrode recording techniques allow measurement of extracellular and intracellular electrical activity. Recent advances in calcium imaging with fluorescent indicators permits comprehensive *in vivo* measurement of action potentials across the entire brain in animal models [137].

Altogether, exciting technological advances yield estimates of anatomical projections and functional interactions over multiple levels of description. Many of the key insights from human MRI (imperfect correspondence between structure and function, relation with spatial proximity, etc.) can be replicated by tracing studies in animal models [138] and by electrophysiological methods [72]. At the same time, recent studies suggest that tracer-based structural networks do provide better overall predictive power compared with diffusion-based structural networks, primarily because they contain information about projection directionality [139,140]. How the structure–function relationship depends on measurement scale and technology is still not fully understood and more research is necessary to consolidate knowledge across subfields.

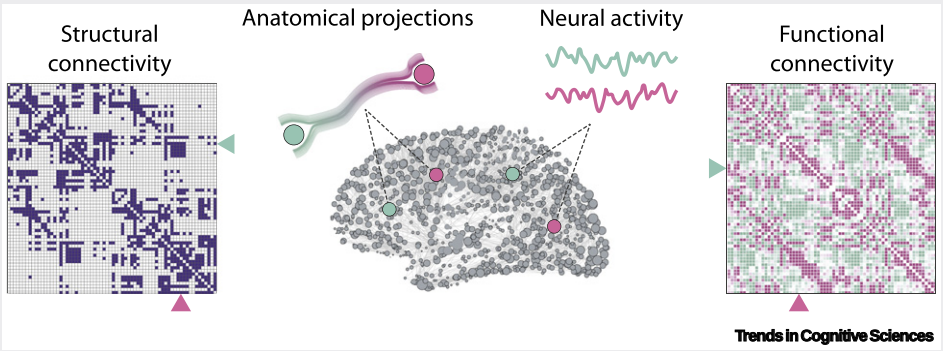

Figure I. Measuring Structural and Functional Connectivity. At the macroscale level, structural and functional networks are derived by first parcellating the brain into grey matter nodes. For structural connectivity networks, edges are defined by reconstructing white matter projections between network nodes. For functional networks, edges are defined by estimating statistical associations between node time courses.

resources [14], resulting in increased prevalence of shorter, low-cost connections [15,16]. These organizational attributes have been replicated across a range of species and tracing techniques, suggesting common organizational principles across phylogeny [17].

The architecture of SC networks imparts a distinct signature on neuronal coactivation patterns. Inter-regional projections promote signaling and synchrony among distant neuronal populations,

Glossary

Annotated graphs: also known as 'colored graphs', these are networks in which nodes are assigned one or more labels. In the case of the brain, these labels can be any local property and can be either discrete (e.g., cell type) or continuous (e.g., activity level).
Connectome: the complete set of neural elements and their physical connections. This object can be represented as a graph of nodes interconnected by edges.
Functional connectivity (FC): statistical associations between time courses of electromagnetic or hemodynamic neural activity. Associations may be estimated either across time or across individuals.
Hierarchy: the organization of the brain from primary sensorimotor to polysensory association areas. Increasing specialization of function along the hierarchy is thought to be supported by microcircuit properties, manifesting as topographic gradients of cytoarchitecture, gene expression, myelination, and connectivity.
Higher-order interactions: in a complex network, two nodes may interact directly via a shared connection, but also indirectly via common neighbors. These higher-order interactions, shaped by the topology of the network, preclude a simple one-to-one mapping between structural and functional connectivity.
Multiplexing: a family of methods by which multiple signals are transmitted over a shared medium. Thus, multiple modes of communication may simultaneously take place over the same network.
Neuromodulation: the influence exerted over neural dynamics by the ascending arousal system originating from the brainstem. subcortex and basal forebrain. By adjusting neural gain, the neuromodulatory system allows multiple types of functional interactions (i.e., functional connectivity patterns) to play out on the same underlying structural network.
Neuronal ensemble: a population of neurons so frequently involved in coordinated activity that they can be summarized as a single unit. Often used to represent discrete regions in biophysical, dynamical models of the brain.
Structural connectivity (SC): physical, material connections between

giving rise to coherent neural dynamics, measured as regional time series of electromagnetic or hemodynamic neural activity. Systematic coactivation among pairs of regions can be used to map **functional connectivity (FC)** networks. Over the past decade, these dynamics are increasingly recorded without task instruction or stimulation; the resulting 'intrinsic' or ' resting-state' FC is thought to reflect spontaneous neural activity [18]. Intrinsic FC patterns are highly organized [19–21], reproducible [22,23], and comparable with task-driven coactivation patterns [24,25]. The persistent and reproducible nature of brain activity during rest makes resting-state FC an ideal starting point to study structure–function relationships [26,27].

neural elements that support signal propagation. At the cellular level structural connectivity refers to axonal projections between individual neurons; at the macroscale level it refers to fibers connecting neuronal populations.

Here we synthesize the current state of knowledge linking structure and function in macroscale brain networks. We first show that direct one-to-one links between structure and function are limited and inherently obscured by the networked nature of the brain. We survey modern quantitative methods that move away from direct correlations between structure and function by conceptualizing function as emerging from **higher-order interactions** among multiple neuronal populations, with a focus on strengths, limitations, and commonalities. We posit that the next steps in understanding network-level structure–function relationships must take into account regional heterogeneity by enriching network reconstructions with microscale attributes, including transcriptomic, cytoarchitectonic, and neuromodulatory information. We close by highlighting emerging theories that macroscale structure–function relationships are not uniform across the brain, but vary in parallel with cytoarchitectonic and representational hierarchies.

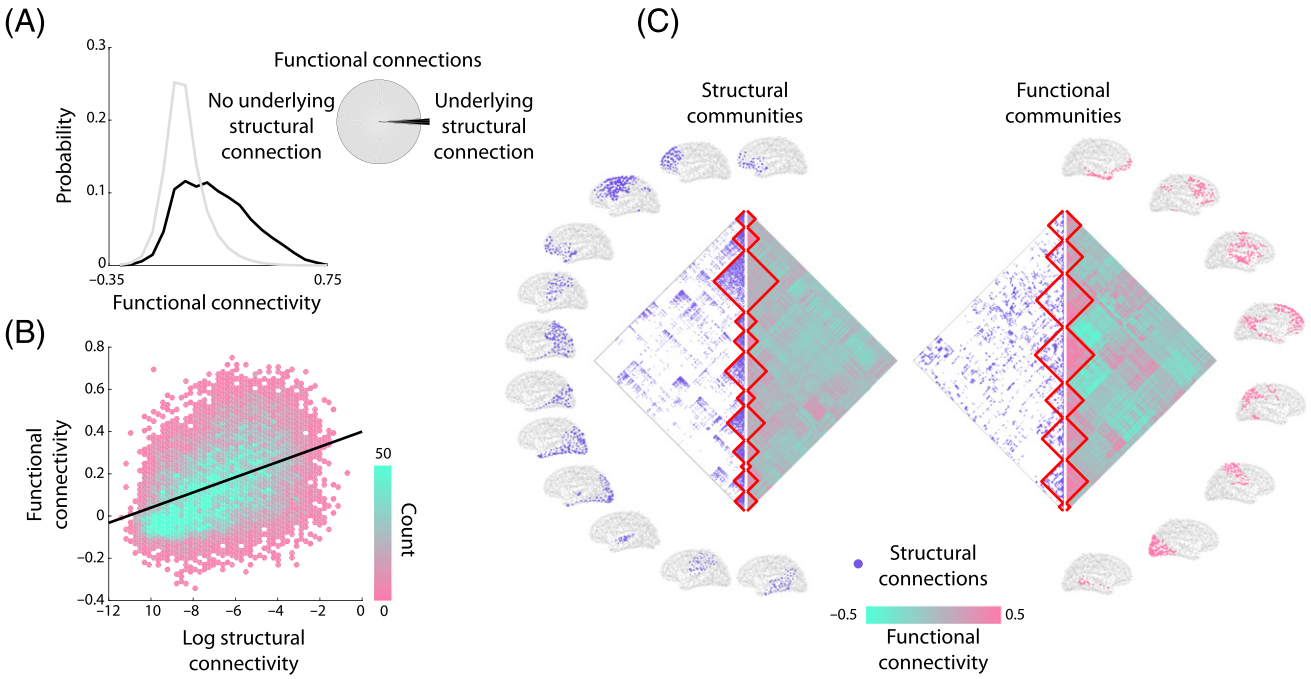

Figure 1. Imperfect Correspondence between Structural and Functional Connectivity. Despite considerable overlap, structure and function diverge both locally and globally. (A) Due to the sparse nature of structural connectivity, most functional connections are not supported by an underlying structural connection. Models of higher-order interactions are therefore necessary to make predictions about most functional connections. (B) In cases where a corresponding structural connection exists, there is a correlation between structural and functional connection weights, but these correlations are typically between $R = 0.3$ and $R = 0.7$. This means that even for this small class of connections, direct structural connectivity optimistically explains no more than 50% of the variance in functional connectivity. (C) Structure and function continue to diverge at the mesoscopic scale. Community detection for structural and functional networks typically yields different solutions; functional communities (resting state networks) tend to encompass spatially distributed systems with perceptual, cognitive, and affective relevance, while structural networks tend to be more spatially constrained.

An Imperfect Correspondence

Early studies emphasized correlations between structural and functional connection weights. Structural weights are correlated with functional weights [28], and nodes that are central to structural networks also tend to be central in functional networks [28]. Furthermore, structurally connected pairs of neural elements display greater FC than structurally unconnected pairs [28,29] (Figure 1A). More globally, many intrinsic functional networks, particularly the visual and somatomotor networks, are circumscribed by patterns of dense anatomical connectivity [29–31].

While SC and FC are significantly correlated, the correspondence is not perfect. Even the best-case estimates place the correlation at $R^2 \approx 0.5$ [28], which means that considerable variance (at least half) in functional connection weights is unexplained by a simple 1:1 correspondence with structure. The discrepancy widens in the case of functional connections between regions that are not structurally connected (Figure 1B). A particularly salient example is the case of homotopic functional connections between corresponding structures in the two hemispheres. These are typically the strongest subset of functional connections [32], but not all homotopic functional connections are supported by a direct underlying callosal projection [33], and strong homotopic functional connections may be observed even in individuals with no callosal connections [34–36]. These examples illustrate the simple point that sustained communication via indirect anatomical connections may manifest as strong FC.

The discordance between structure and function is particularly pronounced at the mesoscopic scale. Intrinsic networks commonly observed in resting-state FC and meta-analytic coactivation cannot be recovered from structural networks [37,38] (Figure 1C). While intrinsic networks can be reproducibly defined using independent component analysis [19], community detection [39], or data-driven clustering [20,21], both in resting state recordings and in meta-analytic coactivation [24], application of comparable methods to diffusion-weighted SC or anatomical covariance networks yields networks that are more spatially contiguous [37,40]. For example, clustering or community detection methods typically fail to identify a default mode-like structural network, perhaps because not all parts of the network are anatomically inter-connected [26].

Structural and functional networks also show global organizational differences. For example, structural networks show evidence of extensive assortative mixing, whereby nodes with similar properties (e.g., degrees) are more likely to be connected, whereas the same is not true of functional networks [50]. At the mesoscopic scale, communities or modules recovered from structural networks are assortative, while communities recovered from functional networks are disassortative [38]. In other words, in functional networks there is a pronounced affinity among nodes with dissimilar attributes. As a result, tuning community detection algorithms to be sensitive to disassortative structures improves the match between structural and functional modules [38]. Altogether, a rich body of work demonstrates discordance between SC and FC that spans multiple scales, from the embedding of individual nodes and edges to their global arrangement.

Why the discrepancy between SC and FC? Functional interactions may arise via indirect structural connections, resulting in coherent time courses among regions that are two or more synapses removed from each other. In other words, the propensity of two regional time courses to correlate is driven not only by direct signaling between them, but also by the common inputs they receive from sensory organs and from the entire network [27,51]. A corollary is that functional interactions are much less distance-dependent than structural connections. Anatomical wiring is subject to material, spatial, and metabolic constraints [14]; these pressures manifest in reduced connection probability and connection weight with increasing spatial separation [15,16]. Although similar distance-dependence is observed for FC, its effect is weaker, ensuring systematic

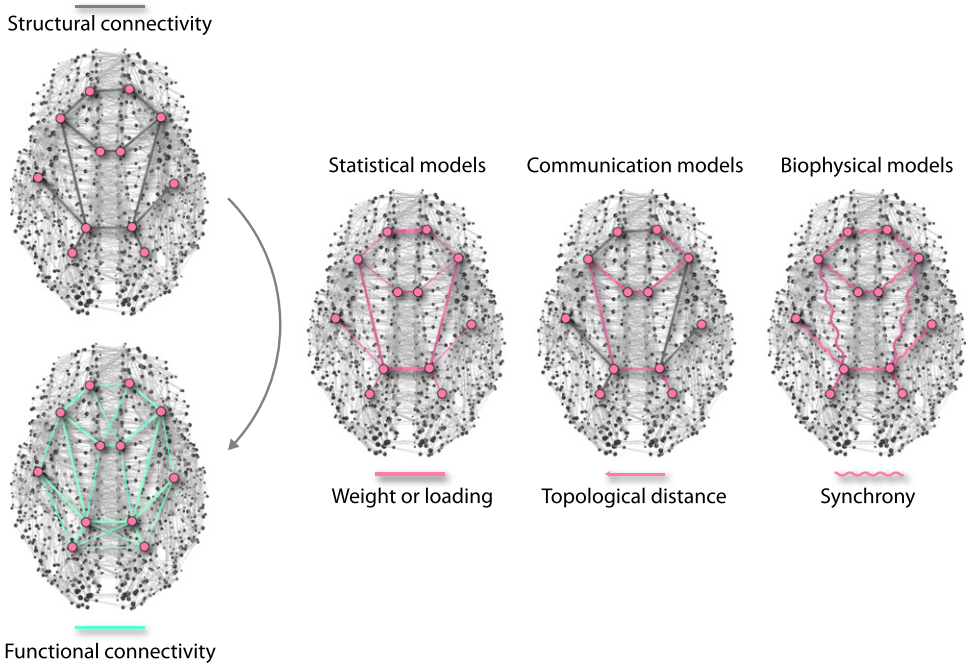

Figure 2. Models of Higher-Order Interactions. Due to the poor direct correspondence between structural and functional connectivity, multiple models of higher-order interactions have been proposed to translate structure to function. These models entail varying assumptions and complexity. Statistical models attempt to assign weights or loadings to structural, and in some cases, functional connections, to maximize correlations between network modalities [41,42]. Communication models embody one or more signaling mechanisms, ranging between those that are fully centralized (routing) or fully decentralized (diffusion) [37,43–45]. Biophysical models simulate patterns of synchrony among biologically realistic neuronal populations, thereby directly generating spontaneous or stimulation-induced activity [46–49].

differences between structural and functional configurations. In the next section we consider models that translate structure to function by conceptualizing function as an emergent property of multiple structural links.

Models of Higher-Order Interactions

As we have seen so far, there exists a nontrivial link between SC and FC, but the two are not perfectly aligned. A number of models have emerged that embody this link, including statistical models [41,42], communication models [37,43–45] and biophysical models [46–49]. Though different in their implementation and assumptions, the common idea is to emphasize collective, higher-order interactions among neural elements that transcends the strong local clustering and geometric dependence of dyadic structural relationships. Here we briefly review each of these analytic strategies, with a focus on their biological interpretation and predictive utility, and most importantly, what they teach us about the nature of the structure–function relationship in the brain.

Perhaps the simplest way to link structure and function is statistically. Varying forms of reduced rank regression have emerged as particularly useful, including canonical correlation [52] and partial least squares [41]. In these data-driven models the objective is to simultaneously identify weighted combinations of structural and functional connections that are maximally correlated across individuals [53] (Figure 2). An appealing feature of such models is that they embody multiple structure–function modes. In other words, a particular structural configuration or subnetwork

may give rise to distinct patterns of functional interactions [41]. Taking this idea further, artificial neural networks can be used to learn functional networks from structural networks. For example, a recent study used a variant of the word2vec algorithm to build a low-dimensional embedding representation of the connectome and used it to train a deep neural network to predict edge-wise FC [54]. Altogether, statistical models offer a data-driven way to associate combinations of structural and functional connections without assuming a specific mode of interaction among neuronal populations.

Communication models emerging from network science and telecommunication engineering conceptualize functional interactions as the superposition of elementary signaling events on the underlying anatomical network [43,55] (Figure 2). By explicitly formulating a model of inter-regional signaling, these models open two important questions, namely: how biologically realistic is the model, and how well does the model fit the attributes of the functional network? Early studies focused on centralized forms of communication, such as shortest path routing, whereby discrete signals travel via the shortest contiguous set of edges from a source node to a prespecified target node. More recently, attention has shifted to decentralized mechanisms where signals diffuse through the network [56,57], often broadcast on multiple fronts [37,51,58,59]. Others have considered mechanisms that are neither fully centralized nor decentralized, including communication via path ensembles [45,60] or **multiplexed** strategies involving multiple mechanisms [44,61–63]. An emerging consensus is that, given the strong relationship between geometric and topological proximity in the brain, it is possible for decentralized mechanisms to utilize the shortest path structure of the network, either by diffusion [44] or navigation [64]. A common methodological thread in these implementations is that pairwise FC is operationalized either as a transmission event [44] or as coactivation [37].

The most biologically detailed and well-studied models are biophysical dynamical systems [47,65,66]. Here the collective dynamics of a **neuronal ensemble** are assumed to be sufficiently low-dimensional such that they can be described by their mean firing rate. Ensembles are coupled by empirically determined anatomical connectivity into a spatially discretized network or into a spatially continuous sheet. Parameters such as conductances may be theoretically derived or empirically informed, and models may be extended to include stochastic fluctuations [67], time delays [65], and external stimulation [68]. Regional time courses are described by a system of coupled differential equations that capture both local fluctuations and influence from other connected regions, exhibiting a rich repertoire of oscillations, synchrony, and waves [69] (Figure 2). As a result, these models output realistic temporal waveforms [70,71], power spectra [72], and covariance patterns [28,49].

How can we compare these models and how well do they actually predict function from structure? A formal meta-analysis is challenging, as there is little consensus on important analytical choices. For instance, model fit may be reported as variance explained [28] or some form of squared error [42] and may be assessed in-sample [41] or out-of-sample [73]. Some studies focus on individual-participant estimates [28,74,75], while others focus on 'consensus' networks compiled from multiple individuals [37]. Among studies that focus on individuals, some report accuracies across participants (i.e., per edge) [76], while others report accuracies across edges (i.e., per participant) [75]. Due to inaccuracies in computational tractography, many studies report single-hemisphere predictions [44], while others report whole-brain predictions [63]. Finally, investigators utilize a range of parcellation schemes with differing numbers of nodes and edges (i.e., variables), making it challenging to directly compare model fits across studies. Lack of standardized reporting is not a problem specific to structure–function questions, but a more general concern in network neuroscience [77]. To our knowledge, out-of-sample predictions of FC are typically reported to be between $R = 0.3$ and $R = 0.5$, with the largest approximately $R = 0.6$ [54].

Individual Differences in Structure–Function Coupling

Although a consensus is emerging about the relationship between structural and functional networks at the group level, much less is known about the alignment between structural and functional configurations in individuals. *A priori*, strong alignment between structure and function appears desirable to ensure communication fidelity; a straightforward prediction would be that the correspondence between SC and FC should have behavioral consequences. Indeed, a recent study demonstrated that the extent of alignment between structure and function correlated with individual differences in cognitive flexibility [83]. Intriguingly, and reinforcing the idea of an imperfect match between structure and function, a recent study showed that SC and FC show distinct patterns of intersubject variance and therefore map onto cognitive function in distinct ways [84].

More broadly, individual differences in structure–function coupling provide a new opportunity to quantify the effects of manipulations and perturbations, such as cognitive tasks [83,85], development and aging [81,86,87], neurological and psychiatric diseases [70,88], and lesions [54,89,90]. An important question that can be answered with this approach is whether structure and function align to the same extent in domain-general versus domain-specific tasks, or in task versus rest. Given the prominent relationship between functional configurations in task and rest [25], it seems likely they would display a similar relationship with structure. Two recent studies support this notion, showing that regional differences in structure–function coupling observed in rest (discussed in more detail in the next section) can be recapitulated using task-based FC [81] and patterns of regional activation [85].

The challenge of studying individual differences in structure–function coupling may be compounded by individual variation in functional boundaries (see Outstanding Questions). Applying a uniform parcellation to all participants facilitates comparisons between individuals, but entails the assumption that areas can be mapped to identical spatial locations in every participant. Recent evidence from precision mapping studies using repeated measurements in single individuals suggests that functional boundaries can systematically vary across individuals [22,91–93], as well as within individuals but across sessions [94]. It is not difficult to imagine that structure–function relationships may not be perfectly captured if areas are misaligned across individuals. How to reconstruct networks while respecting individual differences in topographic organization remains a major question for future studies of structure–function relationships.

Regional Heterogeneity: Annotating Brain Graphs

Direct SC accounts for much of the variance observed in FC, while incorporating higher-order interactions and individual-subject variation bring the two even closer. And yet a sizable portion of variance in FC remains elusive. An emerging possibility is that macroscopic graph representations do not embody the requisite biological detail to completely predict function. The graph model deliberately abstracts away local attributes that we know to be important for neural activity and functional interactions, including transcription profiles, cytoarchitecture, receptor densities, laminar differentiation, and temporal dynamics. It is easy to envision how these attributes may influence how signals are generated, routed, transformed, and integrated by neuronal populations as they traverse the network, shaping the resulting functional connection patterns. In the following section we argue that the graph representation with uniform nodes leaves out important information, naturally limiting the extent to which FC can be predicted using only SC.

Multiple studies have related local molecular, microstructural, morphometric, and temporal measurements to macroscale network embedding. For example, transcriptional signatures

tend to covary more prominently among structurally and functionally connected regions [95–97], and prediction of function from structure is enhanced by information about gene coexpression [62]. Microstructural profile covariance is also correlated with FC, including morphometric similarity [98], intracortical myelination [99], and laminar differentiation [100]. Recent evidence from high-resolution MRI demonstrates that activity during cognitive tasks is layer-dependent [101], suggesting that structure–function relationships may also be layer-dependent. Likewise, neurotransmitter receptor distributions fundamentally shape the range and expression of functional interactions [102]. Finally, the intrinsic temporal dynamics of individual regions systematically vary across neocortex [103–106], promoting synchrony among some neuronal populations but also restricting synchrony among others. Altogether, how local properties relate to macroscale network connectivity remains an exciting open question [107,108]. Increasing focus on **annotated graphs**, in which nodes are labeled with additional metadata, may ultimately enrich our understanding of how local circuitry contributes to global functional patterns [109,110].

If global structure–function relationships depend on microscale properties, we are presented with an intriguing possibility: the relationship between structure and function may itself be heterogeneous across the brain (Figure 3). In other words, structure may be more tightly coupled to function in some areas compared with others. Indeed, several recent studies, independently conducted and using different methods, have found converging evidence that structure–function

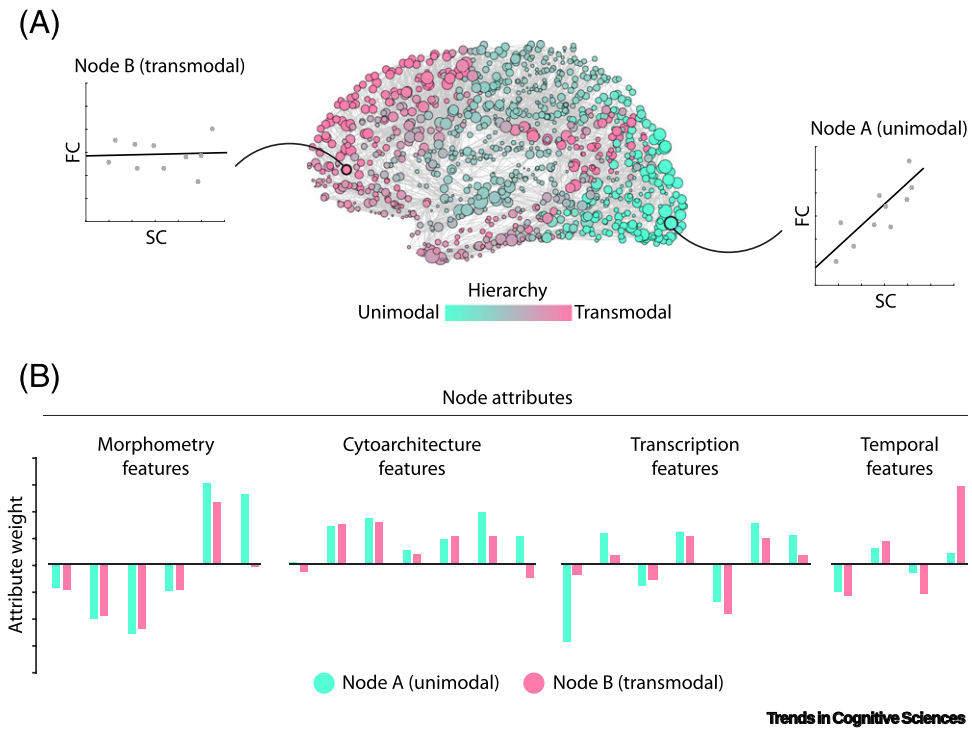

Figure 3. Regional Heterogeneity and Annotated Brain Graphs. The structure–function relationship may not be uniform across the brain and instead may be region-specific. (A) Nodes are colored by their position in a putative unimodal-transmodal hierarchy [78]. The structure–function relationship is stronger for nodes lower in the hierarchy than for nodes higher in the hierarchy [63,73,79–82] (B) The standard graph model of brain structure and function assumes all nodes are the same, but brain regions differ in multiple local attributes, including gene transcription, cytoarchitecture, receptor profiles, and temporal dynamics. Variation in local microscale attributes may influence how neuronal populations broadcast and integrate signal traffic, resulting in regional differences in macroscale structure–function coupling. Abbreviations: FC, functional connectivity; SC, structural connectivity.

relationships are organized around a hierarchical gradient spanning unimodal to transmodal cortex [78,111]. Specifically, structure and function appear to be tightly coupled in unimodal sensory areas, but systematically decouple towards transmodal cortex at the apex of the hierarchy [63,81,82,100]. This decoupling is observed over the course of normative development [81] and is observed not only for FC, but for task activation patterns as well [85]. A prominent account posits that rapid evolutionary expansion of association cortices effectively untethers polysensory regions from molecular signaling gradients and canonical sensory-motor activity cascades, resulting in fundamentally different structure–function relationships along the unimodal-transmodal hierarchy [79].

The gradual decoupling of structure and function may reflect systematic hierarchical variation in laminar differentiation [100] and cytoarchitecture [63]. Two recent computational modeling studies support this idea. In the first, microscale-related parameters of a biophysical model were allowed to differ between brain regions [73]. The best-fitting model was characterized by strong recurrent connections and excitatory subcortical input in sensorimotor regions; conversely, default network regions had weak recurrent connections and excitatory subcortical inputs [73]. A complementary study found that biophysical models could be fitted to FC significantly better if they were informed by hierarchical heterogeneity estimated from T1w/T2w ratios [80]. This regional heterogeneity may reflect spatial variation in cytoarchitecture; for instance, dendritic arborization patterns support distinct algorithmic transformations of converging inputs, including selecting, routing, and multiplexing information [112]. Altogether, multiple lines of evidence suggest that the present graph model with uniform nodes obscures important biological detail; an important question for future research is how to integrate node annotations in models of structure–function relationships [110].

Modulating Structure–Function Relationships

Perhaps the most important annotations missing from current macroscale wiring diagrams are the neurotransmitter receptor fingerprints of each node. Modulation via ascending projections from the brainstem and subcortical nuclei alters neuronal firing rate, making neurons more or less responsive to incoming signals. The resulting adjustments in neural gain fundamentally alter how signals are routed through the network, how they are transformed, and ultimately, how they are integrated [113,114].

Zooming out and considering the network as a whole, it is easy to see that **neuromodulation** provides a mechanism by which a static structural network can support distinct propagation patterns [113,114] (Figure 4). This phenomenon is observed across a variety of generic and real-world networked systems, where a single network can support distinct spatiotemporal propagation regimes depending on the interaction patterns unfolding on the network [115]. An intuitive example is road traffic: depending on conditions (time of day, day of the week, weather, construction), the same road network may feature distinct traffic loads and patterns. In an analogous manner, the system of ascending neuromodulatory projections confers the capacity to translate the static anatomical network into multiple functional configurations and flexibly switch between such configurations. Moreover, each receptor type has a specific distribution, affinity, and effect on neural gain, meaning that modulation can be either targeted or diffuse and can be exerted over a range of time scales.

Recent evidence from pharmacological modulation supports the notion that the ascending arousal system promotes distinct functional configurations [113,114,116]. Functional network reconfiguration has been associated with perturbations of noradrenergic [117,118], dopaminergic [104,119], and serotonergic signaling [120,121]. In computational models, due to the complex

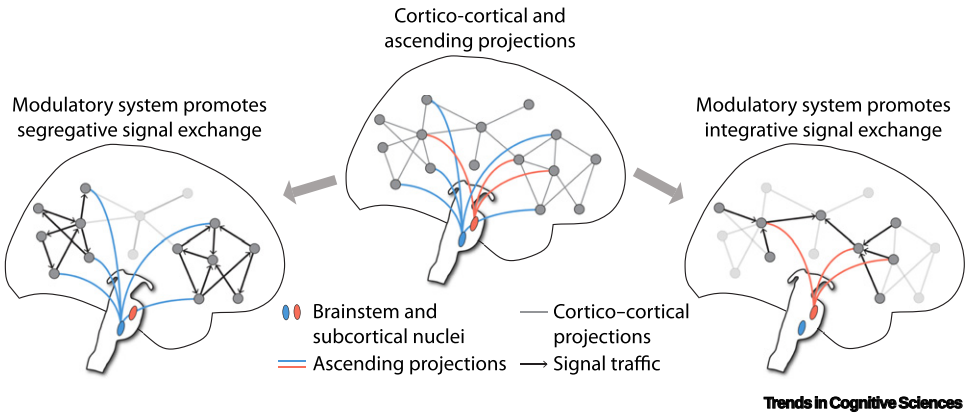

Figure 4. The Ascending Arousal System Modulates Structure–Function Relationships. Top: two putative arousal systems, originating from nuclei in the brainstem and subcortex and terminating at multiple cortical nodes, are shown in blue and orange. Left: modulation by the blue system promotes signal exchange within specialized, topologically segregated populations. Right: modulation by the orange system promotes signal exchange between neuronal populations. The ascending arousal system thus modulates functional interactions on the static structural network, facilitating fluid transitions among multiple functional configurations.

nonlinear dynamics playing out over the connectome, even small local modulation of the excitation-inhibition equilibrium can substantially change the organization of functional interactions, promoting dynamic switching between topologically integrated and segregated states [121,122]. Unfortunately, state-of-the-art computational models rarely take neuromodulation into account, while the brainstem and subcortex are often left out of network reconstructions due to challenges in fiber tracking and parcellating some nuclei. Understanding how neuromodulation fits into the structure–function relationship is a key frontier in the field (see Outstanding Questions).

Function or Property?

In the previous two sections we considered the possibility that network structure could be enriched by additional local information. Here we ask whether we are correctly defining network function in terms of FC. We begin by drawing the distinction between structure–function and structure–property relationships. In a complex system marked by a specific size, shape, arrangement, and orientation, a property may be any measurable feature, but this is different from their purpose or function. For instance, the mass and charge of a protein are features, but the function of the protein is to bind and interact with another molecule. Although resting correlation patterns display many intuitively appealing and methodologically convenient attributes, they are likely not the primary purpose of inter-regional signaling, but rather a manifestation of that process.

This idea has already gained a footing in the field, with multiple efforts under way to understand how the structural organization of the brain can influence properties other than resting state FC. One straightforward extension is to link structure and time-varying or dynamic FC [66,123]. Another is to operationalize higher-order interactions among pairwise functional connections, either by constructing hypergraphs that describe functional interactions among three or more nodes simultaneously [124] or temporal networks that capture interactions among nodes in successive time frames [125,126]. Given the degenerate nature of functional networks [127], there is also increasing effort to project functional dynamics to lower-dimensional spaces or manifolds that compactly summarize time-varying interactions [102].

Taking this notion further, we envision increasing focus on properties more directly linked to internal representations and behavior [128]. For example, SC may influence the participation of individual regions in intrinsic functional networks [129]. The anatomical connectional fingerprint or embedding of some areas may predispose them to frequently switch affiliation among large-scale cognitive systems, while others may display stable or invariant affiliation with one system [123]. Other approaches may focus directly on relating SC to task activation [85]. Particularly exciting are advances in artificial intelligence, such as reservoir computing, that make it possible to implement connectomes as artificial neural networks [130]. These 'neuromorphic' or 'biomimetic' networks, endowed with realistic connection patterns and biophysical dynamics, can process time-varying signals and be trained on a range of tasks, including speech recognition and spatial navigation, allowing researchers to directly assess the relation between anatomical connectivity and functional repertoire.

Concluding Remarks

Although the modern theory of structure–function relationships in the brain is still in its infancy, several of its intellectual arcs are now coming into focus. Structure leaves an indelible mark on function, but a rich literature supports the notion that the link between SC and FC is complex, precluding a simple one-to-one mapping. Emerging models emphasize higher-order interactions via anatomical links that transcend dyadic relationships, opening fundamentally new opportunities to ask how the wiring of the brain supports function. Structural network reconstructions enriched with cellular and molecular metadata, in concert with more nuanced representations of functions and properties, hold great potential for a refined and truly multiscale understanding of the structure–function relationship. Altogether, the confluence of technological, analytic, and theoretical advances opens fundamentally new opportunities to discover physical laws that translate structure to function in brain networks.

Acknowledgments

We thank Vincent Bazinet, Golia Shafiei, Bertha Vazquez-Rodriguez, Zhen-Qi Liu, and Justine Hansen for their valuable input. This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains for Healthy Lives initiative. B.M. acknowledges support from the Natural Sciences and Engineering Research Council of Canada (NSERC Discovery Grant RGPIN #017-04265), from the Canadian Institutes for Health Research (CIHR Project Grant PJT-155920), and from the Canada Research Chairs Program.

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Outstanding Questions

Do different regions and subnetworks utilize specialized signaling mechanisms or protocols? For instance, do unimodal regions send, receive, and transform signals in a fundamentally different way from transmodal regions?

How can we incorporate individualized parcellations to understand structure–function coupling? Could regional differences in structure–function coupling be due to greater interindividual variability of structural and functional organization in transmodal cortex compared with unimodal cortex?

Does the structure–function relationship vary across individuals? How is structure–function coupling related to individual differences in cognition and behavior, or to disease state?

Much of the literature on structure–function coupling focuses on resting-state recordings, but how does this relationship depend on external stimulation, cognitive engagement, and affective state? Do some tasks elicit more or less alignment between structural and functional connectivity?

The sequence of neurons and neuronal populations that a signal passes through presumably changes the nature of the signal and its downstream effect. How do local microscale properties (e.g., molecular, cytoarchitectonic, laminar, and receptor distributions) transform signals as they propagate through neuronal networks?

How does the ascending arousal system modulate the link between structure and function? Incorporating receptor profiles, as well as subcortical (e.g., striatal, thalamic) projections into statistical and computational models is a key challenge for future studies.

Much of the present review focuses on noninvasive, MRI-based measurements of structural and functional connectivity. Do the same findings hold for networks reconstructed at finer spatial scales, for instance, at the neuronal and laminar resolutions? Do the same findings hold for functional networks reconstructed using calcium imaging or electrophysiology?

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