Network Methods to Characterize Brain Structure and Function

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Abstract

Network science provides tools that can be used to understand the structure and function of the human brain in novel ways using simple concepts and mathematical representations. Network neuroscience is a rapidly growing field with implications for systems neuroscience, cognitive neuroscience, and clinical medicine. In this chapter, we describe the methodology of network science as applied to neuroimaging data. We cover topics in constructing networks, probing network structure, generating network 'diagnostics', and experimental design. We discuss several current frontiers and the associated methodological challenges and considerations. We aim to provide a practical introduction to the field: we supplement the explanations and examples with pointers to resources for students or researchers interested in using these methods to address their own questions in empirical and theoretical neuroscience.

Why Network Neuroscience?

Each area of the human brain plays a unique role in processing information gleaned from the external world and in driving our responses to that external world via behavior. Mapping these roles has led to enormous insights into the complex and varied contributions of different brain regions to our mental function. However, the brain is far from a set of disconnected building blocks. Instead, at each moment throughout the day, parts of the brain communicate with one another in complex spatiotemporal patterns, like evolving dance partners in a multifarious choreography, which enable the formation of creative thoughts, the acquisition of new skills, and the adaptation of human behavior. Understanding this spatio-temporal complexity requires a paradigmatic shift in our conceptual approaches, empirical goals, and quantitative methods: in short, in the way that we design and interpret our models and experiments.

Systems neuroscience addresses this complexity by seeking to understand the structure and function of large-scale neural circuits and systems. How do individual brain areas interact with one another to enable cognitive function? How is cognition constrained by white matter pathways? How does the brain transition between functions like memory, attention, and movement? How do we control the interactions between different neural circuits in our brains?

To answer these questions, we can use tools from systems neuroscience to perform (i) data analysis to extract characteristic or predictive patterns in the data and (ii) forward modeling to build mathematical models of the system from first principles. The distinction here is important: *data analytical* approaches lead to descriptions of an observed process, e.g. "brain areas A and B tend to be alternately activated during a visual task". In contrast, *modeling* involves the creation of a set of mathematical descriptions (i.e. equations) which describe how components of the system behave, given certain inputs or conditions. For example, the activity in brain area A could be described by an equation that captures its behavior, including its dependency on the activity of brain area B, and *vice versa*. Crucially, the mathematical descriptions in a model can then be used to *predict* the behavior of the system given a different set of inputs, or in a different context. Naturally, models are much more difficult to create than descriptions.

In this chapter, we focus on newly developed tools for data analysis, which we refer to under the broad term *network neuroscience*, that we envision will dramatically inform the efforts in forward modeling in the coming years. Network neuroscience provides a simple and elegant systems approach to understanding how neural circuits function, how they constrain one another, and how they differ across individuals. A network representation of a biological system (e.g., a genome, proteome, or connectome) treats individual components (e.g., genes, proteins, brain regions) as network nodes and treats interactions between these components as network edges. Network science, an inter-disciplinary approach which spans biology, economics, sociology,

linguistics and computer science, provides a battery of quantitative diagnostics that enable us to describe the architecture of this network in a statistically principled manner. One can then study these properties of the network to gain insight into organizational principles and evolutionary drivers of complex cognitive phenomena.

As a basis for discussion throughout the chapter, we use data from a previously published experiment [1, 2] to illustrate how neuroimaging data can be transformed into a network, how these networks can be studied, and how they can be compared statistically with one another to address a neuroscientific question. It is important to keep in mind during this exposition that there is no generic 'correct' way to do a network analysis: to showcase some of the tools available, at each stage of our example analysis, we outline various alternative methodological choices available to the researcher.

A Few Foundational Concepts

In Figure 1, we illustrate the path from data to diagnostics commonly traversed in a network study. In a first step, data is collected from human subjects using one of the many neuroimaging modality currently in use: structural MRI, functional MRI, EEG, MEG, or diffusion imaging. Next, the data acquired from each subject is converted to network form. The construction of the network depends upon the researcher's choice in defining network *nodes* and network *edges*. Finally, the constructed networks are analyzed statistically to test hypotheses regarding the organization of the networks. Statistical diagnostics come in two forms: (i) previously defined network *diagnostics* that have proved useful in previous studies, or (ii) diagnostics created in an individual study to capture a pattern observed in the data.

In this section, we will describe this path in greater detail, illustrating choices that can be made at each stage of the analysis and the impact that these choices can have on the conclusions that can be drawn from the study.

Network Construction

Having decided to undertake a network analysis, you most likely have a neuroimaging data set in hand and are faced with the question of how to extract a network from it. To do that, we must define what a network actually is. A network can be defined in mathematical terms as a graph G composed of N nodes which represent brain regions and E edges between those nodes that represent region-to-region relationships. The use of the term *graph* here differs from the common usage depicting a visual representation of data on axes. Instead, in network science the term graph often refers to the join-the-dots pattern of connections (edges) between nodes.

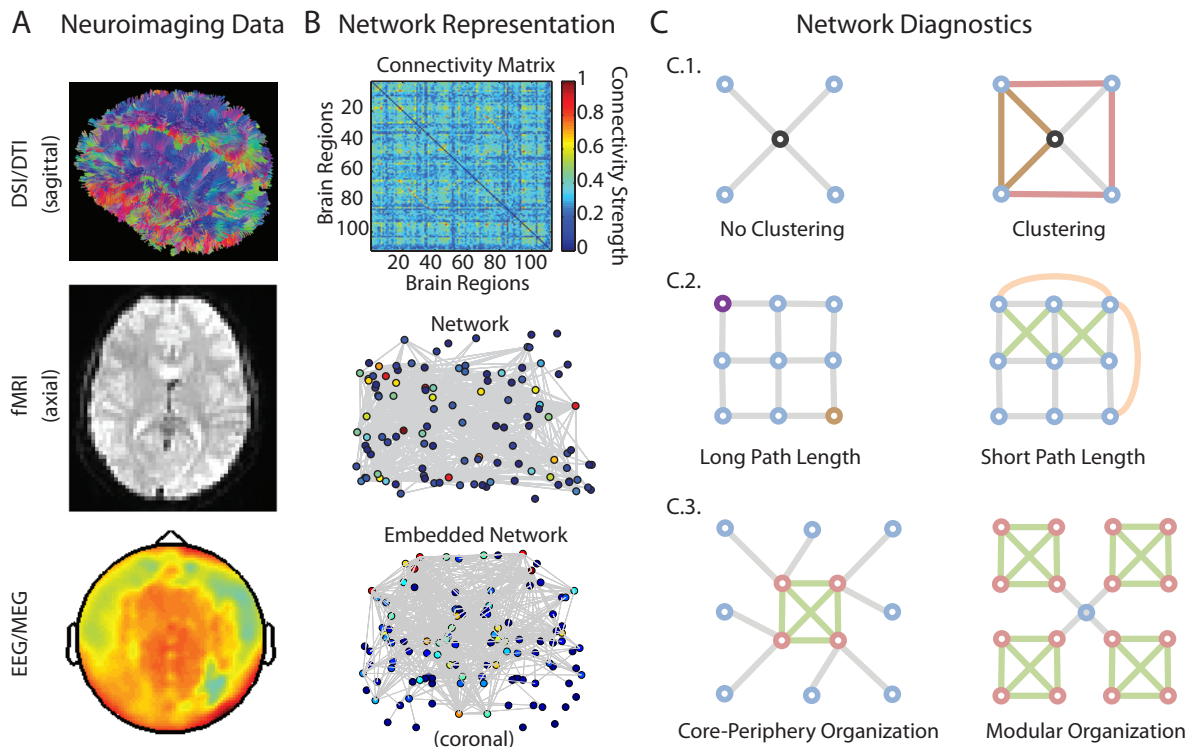

Figure 1: **From Data to Diagnostics: The Stages of a Network Study.** *(A)* Data Acquisition. Neuroimaging data can capture structural connectivity (e.g., diffusion spectrum imaging, DSI; diffusion tensor imaging, DTI) or functional connectivity (e.g., functional magnetic resonance imaging, fMRI; electroencephalography, EEG, or magnetoencephalography, MEG). *(B)* Representations of a Network. *(Top)* A connectivity matrix in which matrix elements (or pixel in the grid) represents one connection between two brain regions, and the color indicates the strength of that connection. *(Center)* A topographical network visualization in which brain regions that are strongly (weakly) connected to one another lie close to (far from) each other in the plane. *(Bottom)* An embedded network visualization in which nodes are placed in anatomically accurate locations. *(C)* Network Diagnostics. *(C.1)* The clustering coefficient is a diagnostic of local network structure. The left panel contains a network with zero connected triangles and therefore no clustering, while the right panel contains a network in which additional edges have been added to close the connected triples (i.e., 3 nodes connected by 2 edges; green) to form triangles (i.e., 3 nodes connected by 3 edges; brown), thereby leading to higher clustering. *(C.2)* The average shortest path length is a diagnostic of global network structure. The left panel contains a network with a relatively long average path length. For example, to move from the purple node (top left) to the orange node (bottom right) requires one to traverse at least 4 edges. The right panel contains a network in which addition edges have been added (green) to form triangles or to link distant nodes (peach), thereby leading to a shorter average path length by comparison. *(C.3)* Mesoscale network structure can take many forms. The left panel contains a network with a core of densely connected nodes (red circles; green edges) and a periphery of sparsely connected nodes (blue circles; gray edges). The right panel contains a network with 4 densely connected modules (red circles; green edges) and a connector hub (blue circle; gray edges) that links these modules to one another.

To construct a brain graph, we must choose how to subdivide the brain into network nodes (or brain regions) and how to define the edges (or interactions) between those nodes. The choice of nodes and edges in the extraction of brain networks from neuroimaging data varies widely and the question of whether a single most appropriate choice exists remains under debate [3, 4, 5, 6].

Types of Brain Networks In some cases, the choice of node and edge definition depends upon the type of network under study. In general, there are two types of brain networks. *Functional brain networks* are constructed from functional neuroimaging data (e.g., fMRI, EEG, or MEG) and network edges represent the functional or effective connectivity patterns between brain areas. *Structural brain networks* are constructed from diffusion-based neuroimaging data (e.g., diffusion tensor imaging or diffusion spectrum imaging) and network edges represent the 'hard-wired' white matter connectivity patterns between brain areas. Functional and structural brain networks each provide different types of information about brain organization and cognitive function. There is no simple relationship between a person's structural and functional networks: for example, areas that have no detectable white-matter connections can be functionally connected. The question of how these two types of networks relate to one another is a source of considerable scientific endeavor (e.g., [7, 8]).

Node Choice: Parcellation To create a network, we subdivide the system that we are studying into components and we represent these components as network nodes. The components of the brain are often thought of as regions of interest: primary visual cortex, dorsolateral prefrontal cortex, or fusiform gyrus. Each region can then be represented as a node in the brain network.

A map that segregates the many voxels of a neuroimaging data set into regions of interest or network nodes is referred to as a parcellation. There are two basic types of parcellations: (i) those based on neuroanatomy and cytoarchitectonics and (ii) those based on data-driven clustering methods. In applying a parcellation to neuroimaging data, our goal to choose areas of the brain that can be treated as separate units in the brain system [9], where "separate" can be defined in many different ways: functionally, structurally, or anatomically.

Neuroanatomical parcellations define brain regions based on the underlying neuroanatomy. The set of Brodmann areas is an example of a neuroanatomical parcellation, in which each brain region is comprised of tissue with a particular cytoarchitecture — that is, a particular arrangement and appearance of stained neuronal cell bodies, when slices of brain tissue are viewed under a microscope [10]. A network that uses Brodmann areas as network nodes can be used to probe the relationship between relatively large brain areas such as dorsolateral prefrontal cortex (Area 46), primary motor cortex (Area 4), and the fusiform gyrus (Area

37). Other parcellations that are similar in spirit include the Automated Anatomical Labeling atlas, the Harvard-Oxford atlas, and the LONI Probabilistic Brain Atlas. A key advantage of using neuroanatomical parcellations to define network nodes is that they enable neurobiological interpretation and simplify group-based interpretations and comparisons.

Connectivity-based parcellations define brain regions based on data-driven clustering methods that isolate sets of voxels with similar functional or structural properties. The functional parcellation of Power et al. [11] is an example of a connectivity-based parcellation in which each brain region is composed of voxels that show similar neurophysiological activity as measured by fMRI. The resultant network can be used to probe the interactions between functionally distinct areas in a given task, and these areas may or may not adhere to cytoarchitectonic boundaries. Connectivity-based parcellations have also been derived from diffusion imaging scans by clustering white matter tractography data (e.g., [12, 13, 14, 15]). In comparison to the neuroanatomical parcellations, the connectivity-based parcellations provide a unique window into individual differences in brain structure and function, which can empower the search for biological underpinnings of connectivity while somewhat complicating group comparisons.

After choosing a parcellation, we must choose how to apply that parcellation to the neuroimaging data set at hand. In the context of a functional imaging scan, we detect a time-varying signal (or 'time course') from each voxel (or 3 dimensional pixel) in the brain. The activity of all voxels within the region can be averaged together to create representative regional time courses [16]. However, it is possible that by averaging time series together, we lose important information about signal variability within a region. Alternative approaches include calculating the median regional activity or the first principal component of the activity — that is, a single representative signal that accounts for as much of the variability in the signals from all the included voxels as possible. In the context of a structural imaging scan, the white matter tracts terminating in a single region are treated identically, and so the 'strength' of a structural connection is simply proportional to the number of detected tracts which connect the two brain regions [17]. An alternative method, which avoids the difficulty and arbitrariness of making either-or decisions about whether tracts near boundaries end in one particular area or another, is to weight tracts according to their spatial placement. To quantify the connections to a given regions, tracts located close to the center of mass of tract termination points within that region could be more heavily weighted than tracts located farther away.

What is the effect of node choice on network studies? First, the definition of any particular node affects how one can interpret changes in that node's network properties. If we have defined a node to be the entire primary motor cortex, we must interpret changes in that node differently than if we had defined the node to be only hand motor cortex. Second, the choice of a parcellation scheme can alter the observed network structure. As a simple example, consider region size. When we use a parcellation scheme with relatively small nodes, we

will be probing the network structure of the brain at a higher resolution than if we used a parcellation scheme with relatively large nodes [18, 19, 20, 21]. While several studies have demonstrated that qualitative features of network organization are relatively immune to changes in parcellation scheme [19, 22, 23], quantitative properties of networks (to be discussed in the next section) and biological interpretations are necessarily altered.

Edge Choice: Structural and Functional Connectivity To characterize the relationships or *edges* between network nodes, we must define a type of interaction between brain areas. Two basic types of edges are commonly used: (i) those that estimate the 'hard-wired' anatomical connectivity between brain regions and (ii) those that estimate the functional coherence or real-time interactions between brain regions. The goal of these approaches is to define a single consistent type of interaction between brain regions from which to construct a single type of network [9]. Networks with multiple types of links are referred to as *multiplex* networks (e.g., [24, 25]), but these are rarely used in neuroimaging studies.

An anatomical edge can be defined by the existence of a white matter tract connecting brain region i to brain region j. This edge could either be given a binary value (e.g., 1 if a tract exists between region i and region j and 0 if a tract does not exit) or a continuous value (e.g., the number of tracts that exist between region i and region j). Alternatively, anatomical edges can be represented by the mean fractional anisotropy or magnetization transfer ratio (a proxy for myelination) along a tract or set of tracts between regions [17, 26]. Anatomical edges are used to represent the information transmission capabilities between large-scale brain regions [27].

A functional edge can be defined by coherent oscillatory activity in region i and region j, which can represent putative communication [28]. This edge could either be given a binary value (e.g., 1 if the coherence between region i and region j is statistically significant and 0 if it is not) or a continuous value (e.g., the magnitude of the coherence between region i and region j). Alternatively, functional edges can be defined based on any statistical relationship between regional time series [29, 30, 31, 32, 33]; examples include mutual information, synchronization likelihood, and partial correlation. A common choice in fMRI networks is the Pearson correlation [34]. If two brain areas have similar activity — however that is defined — network approaches assume that they are in some way functionally linked. These edges are taken to reflect functional interactions such as information transfer, coordination, or shared processing [3, 4, 6].

Probing Network Structure

After defining the nodes and edges of a network, we can begin to probe the organization of that network to better understand its structure and to some extent its function [35, 9]. Two key issues inform our next

steps: statistical noise in the data and the presence of multiple scales of interest in the network. In the recent literature, several methods have been proposed to address each of these factors and here we briefly review these approaches.

Statistical Noise. In empirical measurements of brain activity and anatomy, noise affects our confidence in the estimated strength of edges in both anatomical and functional brain networks. In a functional network, should we treat two regions as connected if their activity profiles are correlated with a Pearson's r of 0.01? Or in an anatomical network, should we treat two regions as being connected if they are linked by a single streamline as estimated by white matter tractography algorithms? Answers to these questions depend on our understanding of the noise present in the data. Noise in these data sets can stem from biological, measurement, or data-processing sources or a complicated combination of all three.

To maximize the power to detect neurophysiologically relevant connectivity patterns, two main solutions have been proposed. In one approach, we can test the statistical significance of each edge in the network, then remove statistically non-significant edges from the network by setting their value to 0. We then study the organization of the remaining (statistically significant) edges. This approach is often utilized in the context of functional networks. If edges are defined by statistical similarities in regional brain time series, the significance of the elements of the resulting connectivity matrix are affected by the large number of tests that have been performed, which significantly increases the chances of Type I (false positive) errors. Several multiple comparisons correction methods for these errors, such as Bonferroni and False Discovery Rate [36], have been proffered (e.g., [16, 1]), although some argue that these approaches are too stringent for network-based analyses [37]. A false positive correction in which edges are retained if their p-values are less than $1/N$ where N is the number of nodes in the network may be a suitable compromise (e.g., [38, 39]).

In a second approach, we do not perform any statistical thresholding on the edge weights. Instead, we study the entire network (inclusive of the noise), and then compare that network structure to null models that have been constructed to account for one or more sources of noise [2]. For example, we can construct a null model for functional brain networks by creating surrogate time series that maintain the mean, variance, and autocorrelation of the original signal. By comparing the real brain network to this null model, we can identify features of the network that cannot simply be accounted for linear properties of the time series. A critical area of ongoing research is the development of more sophisticated null models that seek to account for more complicated structure in biological networks such as growth and development, temporal dynamics, and physical embedding of the network inside of the skull [40, 41, 2].

Multiscale Structure. In studying many complex systems, we often try to isolate a single level of the system and study it intently in the hopes of gaining an intuition for how the system works. However, for most systems this is a simplification that often costs us understanding. Complex system often display multiscale structure, or non-trivial organization across different scales. The brain is no exception, having intricate architectures that exist and processes that occur across a range of spatial, temporal, and topological network scales [42].

The presence of multiscale structure in the brain constrains the types of methods that we can use to study brain networks. An important example of multiscale architecture lies in the spatial distribution of edges, which shows different organizational features depending on whether the edges are strong versus weak or short versus long, and on whether they connect regions that are within versus between hemispheres (e.g., [8, 43]). Simple binary networks (where edges are treated as either present or absent), and non-embedded networks (where edge locations in the brain are ignored) necessarily neglect this multiscale structure and in doing so dismiss potentially important biological signatures present in the data.

For simplicity, we will use the remainder of this subsection to discuss the role of edge strength in multiscale brain structure. To study the network topology (the arrangement of the elements in a network) and putative biological utility of edge strength, we can probe weighted networks (where edges maintain estimated strengths) using a variety of thresholding techniques. Cumulative thresholding is the procedure whereby a family of graphs is created from a single connectivity matrix; each graph in the family contains edges above a certain weight value or threshold (see Figure 2, top). The threshold for each graph in the family is unique, and specifies the density of edges in the graph: small values of the threshold produce dense graphs and large values of the threshold produce sparse graphs. Windowed thresholding is the procedure whereby a different family of graphs is created; each graph in the family contains edges whose weight values lie within a given weight range or window (see Figure 2, bottom; [44, 43]). The width of the weight range specifies the density of each graph in the family: small weight ranges produce sparse graphs and large weight ranges produce dense graphs.

Cumulative and windowed thresholding techniques can provide insight into the multiscale nature of a network's connectivity patterns, embedded in edge weights. The windowed thresholding approach has the advantage of isolating the network structure of strong versus weak edge weights. Strong edges can provide insight into the organization of energetically costly links in anatomical brain networks and of heavily utilized coordination links in functional brain networks. Weak edges — while technically less significant according to some statistical tests [16] — can imply strongly correlated network states [45] and can distinguish diseased network structures in schizophrenia [43]. Observed weak correlations between regional activity could be driven at least in part by the variability of neuronal activity signals, which plays an important role in

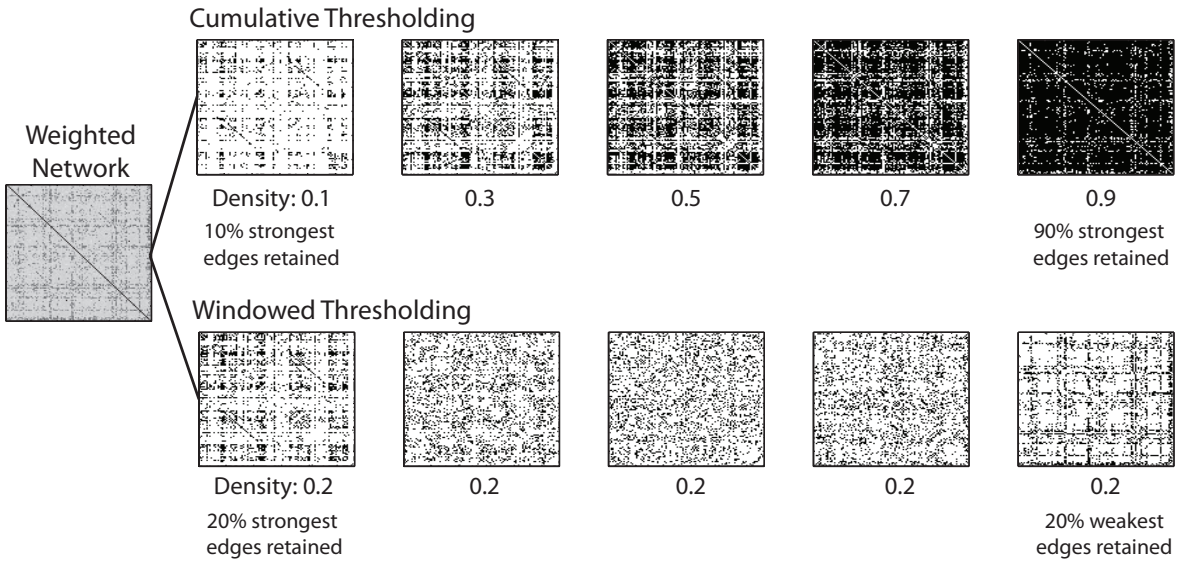

Figure 2: **Probing Multiscale Architecture in Network Edge Weights.** Multiscale structure in a weighted network (left) can be probed using thresholding techniques. *(A)* Cumulative thresholding is the procedure whereby a connectivity matrix is separated into a set of graphs that contain edges above a certain weight value or threshold. *(B)* Windowed thresholding is the procedure whereby a a connectivity matrix is separated into a set of graphs that contain edges whose weight values lie within a given weight range or window [44, 43].

cognitive function [46], development [47], and recovery from injury [48].

Generating Network Diagnostics

A network 'diagnostic' is simply a named measurement used to describe a network's properties. These properties can then be compared across different networks. For example, a patient's network diagnostics can be compared with those of a healthy participant; or a human brain network can be compared to a worm neuronal network to see whether the properties captured by that diagnostic are shared by neural systems in different species [20].

Network diagnostics are not quantities like mass, entropy, or replication rate that *a priori* have a clear physical meaning. Instead, they are mathematical definitions that formalize architectural concepts specific to network science [49]. As an outsider, this jargon can at times make the field seem impenetrable. However, upon closer inspection, many diagnostics captures an intuitive property of interconnected systems that can often be easily interpreted in the context of the brain [27, 50].

Local, Global, and Mesoscale Properties We can use network diagnostics to study the organization of anatomical and functional brain networks across spatial scales, from the neighborhood of the network

surrounding a single brain area (captured using *local* statistics) to the architecture of the entire network (captured using *global* statistics). A typical local diagnostic is the clustering coefficient C, which relates to the likelihood that a node's neighbors are connected to one another, forming triangles or loops (see Figure 1C1). The clustering coefficient can be calculated for each node separately, and then the values can be averaged across nodes to determine a mean clustering coefficient for the network. A brain-centric interpretation of the clustering coefficient is that it might quantify the amount of local information integration [27, 4].

A typical global diagnostic is the average shortest path length L. The shortest path between node i and node j is the smallest number of edges that must be traversed to get from node i to node j. The average shortest path is the mean shortest path over all possible pairs of nodes in the graph (see Figure 1C2). A brain-centric interpretation of the average shortest path length is that it might quantify the amount of global information segregation [27, 4]. A related concept — the network efficiency [51, 52] — is also calculated based on shortest paths through a graph. Networks with high efficiency have short path lengths and networks with low efficiency have long path lengths. Network efficiency has been interpreted in relation to the efficiency of information processing in the brain [53, 27].

Mesoscale diagnostics ("meso-" means "middle") capture intermediate-level properties of network organization. Rather than focusing on either the local neighborhood of a node or the global structure of the entire graph, mesoscale diagnostics characterize the organization of *groups* of nodes. For example, core-periphery diagnostics enable us to uncover a core of densely and mutually interconnected nodes and a periphery of sparsely connected nodes (see Figure 1C3, *left*; [54, 55]). Core-periphery organization might confer robustness to the brain's structural core [56] and enable a balance between stability and adaptivity in brain dynamics [57]. Modularity is another type of mesoscale property in which sets of nodes form densely connected subgroups (see Figure 1C3, *right*; [58, 59]). Modular organization provides a natural substrate for the combined integration and segregation of information processing arguably required for healthy brain function [4].

Despite the changing fashions for particular diagnostics (for example, small-worldness: a buzzword of the early 2000s which is now falling somewhat out of favor), no single diagnostic can capture all of the important organizational properties of networks [49]. The library of network diagnostics is continually growing as applied mathematicians, physicists, computer scientists, and others define new mathematical entities to capture previously unexplored patterns in network structure. While each diagnostic has a unique mathematical definition, it is possible for several diagnostics to produce values that are highly correlated with one another across network samples (e.g., across different brains). A current challenge is to determine the families of network diagnostics that provide complementary but not necessarily independent information about functional and anatomical brain organization [38].

Interpretational Caveats Network diagnostics can be intuitively interpreted in terms of information processing: high clustering can suggest that information is processed in local domains, while short path-length can suggest that information is being transmitted over longer distances within the network. However, the biological meaning of these interpretations requires a conceptual leap from topological to biological terms which are semantically equivalent, but not necessarily conceptually inter-changeable [60]. Biological efficiency, for example, has evolutionary implications which may not apply to network efficiency. More generally, such interpretations of network diagnostics require empirical validation demonstrating the relationship between quantifiable estimates of information processing or biological efficiency and network characteristics. Until then, a cautious interpretation of network diagnostics need not hamper the utility of these approaches in prediction, classification, diagnosis, and monitoring and in the study of system level dynamics underlying cognitive function.

Using Diagnostics to Probe Brain Network Structure We have shown how a variety of different networks could be produced from a single brain scan. The network diagnostics generated will vary considerably, depending on whether a weighted or binary network is used, whether we take a cumulative or windowed thresholding approach, and what range of connection densities we choose to consider. For example, we can see in Figure 3A that the value of the clustering coefficient tends to be small for sparse graphs and large for dense graphs, where neighbors of a node are more likely to also be connected to one another (see Figure 3A). The value of network efficiency shows the opposite effect: large values characterize sparse graphs and small values characterize dense graphs, where any pair of nodes is likely to be connected.

Given this variation, how do we choose which actual numbers should be used to represent a sample, when it is compared to another? The characteristic curves of diagnostic values as a function of graph density or mean edge weight provide useful signatures of brain networks in different states (e.g., health and disease, or various task states). We can collapse a curve extracted from a single participant into one number by calculating the area under the curve (AUC) [61]. The advantage of this procedure is that we can then determine group differences in this value by performing a simple t-test or permutation test. The disadvantage of this procedure is that we have necessarily lost information about the shape of the curve. Two groups might have identical AUC values but quite different curve shapes. An alternative approach is to use *functional data analysis*, a statistical technique developed for the principled study of curves, to determine whether the area between the curves is significantly different from zero [43, 62] (see Figure 3B).

While network diagnostic values and curves provide insight into the organization of the network, it is the mapping of these values back to brain regions that enables us to make fine-grained biological interpretations of our data. Different network diagnostics can display very different spatial distributions across the surface of

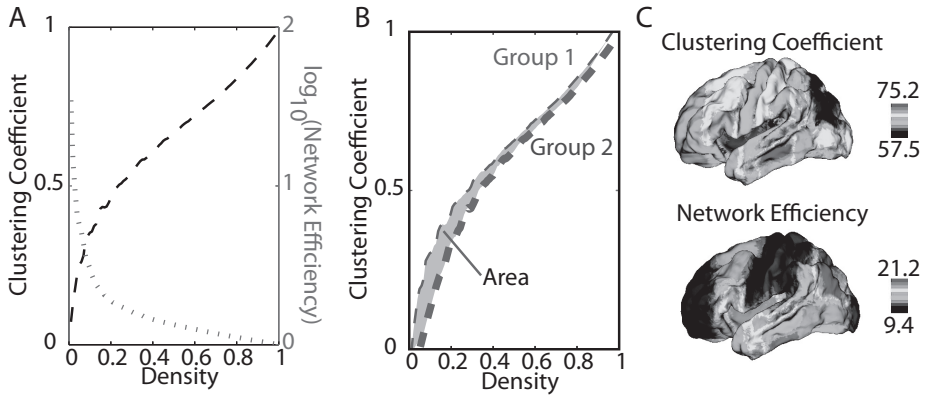

Figure 3: **Using Diagnostics to Probe Brain Network Structure.** *(A)* Clustering coefficient (left y-axis, black) and network efficiency (right y-axis, light gray) as a function of network density as estimated using cumulative thresholding techniques. *(B)* Schematic of mean clustering coefficient versus density curves for two sets of participants: Group 1 (thin, light gray dashed line) and Group 2 (thick, dark gray dashed line). Functional data analysis is a statistical framework that can be used to determine whether the area between the two curves is significant in comparison to a null model. *(C)* Area under the clustering coefficient versus density curve (top) and the network efficiency versus density curve (bottom) for 112 regions of the brain, defined according to the Harvard-Oxford atlas (see [1, 2] for additional details on this data set).

the brain (see Figure 3C). For example, in an early motor skill learning task [1, 2], the clustering coefficient is strong in the primary motor cortex and weak in visual association areas while the network efficiency displays the opposite trend. Such maps can be constructed for individual participants or for groups of participants and enable us to link our results to the large body of neuroimaging literature isolating functions of individual brain regions.

Experimental Design

Since its inception, network neuroscience has predominantly been exploratory in nature. In network-based studies of the brain, researchers are constantly fine-tuning methodological approaches and isolating empirical questions that are amenable to these approaches. Often these studies have included a re-analysis of previously published data, which had initially been examined from a more traditional perspective. The use of previously acquired data is unquestionably justified for many reasons, including but not limited to the use of taxpayer money for research studies, the time spent by subject participants in volunteering for the study, the difficulty in obtaining patient data, and the richness of data acquired by current neuroimaging techniques that cannot be mined completely using a single analytic approach. These studies have provided extensive early validation of network methods and their use in understanding the human brain.

However, the re-analysis of previously acquired data has its disadvantages. The most critical disadvantage is that these studies were often not conceived with network-based hypotheses in mind. New data acquired

using experimental paradigms specifically designed to test network hypotheses will open up entirely new fields of inquiry. The development of such paradigms and hypotheses is an important frontier in network neuroscience.

What Can Network Approaches Tell Us?

Is network neuroscience an enlightening new approach to cognitive science or is it simply an interesting intellectual exercise for the mathematically inclined? The empirical evidence to date strongly supports the former conclusion.

The first type of evidence comes from the fact that network neuroscience has provided diagnostics that display close relationships with more traditional measurements or known quantities. For example, people with a variety of psychiatric and neurological diseases have differently connected brains than people who are healthy [6]. When people perform different tasks, their brain regions interact differently, leading to alterations in network diagnostics (e.g., [63]). Over both long and short time scales (from years [64] to days and minutes [1]), your brain changes in how different regions interact with each other. As your behavior changes, so do your brain networks [65].

Together, these results provide important validation of the network approach to neuroscience. But not all of these results are surprising or ground-breaking. The results often grab the attention of the media instead because they directly address the perennial problem of cartesian dualism that pervades both lay and medical thinking: linking the mind to the brain. Indeed, studies demonstrating brain correlates of behaviors or psychiatric disease continually inform, and provoke new developments in, the philosophy of mind. In addition to their philosophical appeal, network methods can also display these results in a quantitative and visually appealing way. But do these results fundamentally advance our understanding of how the human brain works?

Network Neuroscience as Explanation

The growing consensus in the community is a resounding "Yes". Network science provides a fundamentally new level of explanation for cognitive function. And what do we mean by an "explanation"? Among other things, an explanation can (i) describe phenomena in terms of more fundamental and general principles, or (ii) provide a causal history of the phenomena [66]. Reductionist models of biological phenomena have traditionally provided explanations of the second form (providing causal histories) but in general have difficulty providing explanations of the first form (linking to fundamental principles). Network science, however, provides inherently new information about how the brain works in relation to general mathematical

and physical principles, and it is this new information that informs novel hypotheses, interpretations, and empirical studies.

Shifting Conceptual Paradigms Network science has supported a fundamental paradigm shift in the conceptual framework that we use for neuroscientific inquiry. By placing significant weight on the importance of interactions, network methods stand in contrast to other approaches focused primarily on the localization of cognitive functions to specific brain areas through the study of local brain activity. Instead, the principled investigation of time-dependent communication between brain regions, facilitated by network methods, has enabled the discovery and description of both intrinsic (the default mode network [67]) and extrinsic connectivity phenomena.

Revealing Organizational Principles Network science can be used to uncover organizational principles of complex systems. As an example, consider the use of network science in the identification of evolutionary and metabolic constraints on brain structure [20, 68]. By studying network architecture present in natural organisms, from human to worm, we can infer fundamental principles of brain organization, such as cost-efficiency in network organization [68], and posit their alteration in disease states [69]. Extracting these guiding principles is of critical importance in building an expanded theoretical neuroscience, and is a necessary complement to the accrual of increasingly detailed accounts of specific brain areas, pathways, and molecules.

Distilling Mechanisms of Disease In addition to uncovering organizational principles in the healthy brain, network neuroscience has provided new insights into the mechanisms of disease. In Alzheimer's disease, for example, regions of dense functional connectivity (also known as *network hubs*) correspond to areas of greatest plaque deposition [70]. In contrast to descriptions of plaque density from non-systems approaches, these results from network science suggest a disease mechanism: high metabolic function, information processing, and structural connectivity in brain network hubs might augment the pathological cascade in Alzheimer's disease. Network neuroscience methods have also played a primary role in our growing understanding of schizophrenia as a brain-wide pathology, characterized by extensive dysconnectivity rather than localized abnormal activity [71]. Even in the context of stroke, network methods have been used to show that communication pathways are altered far from the lesioned site [72], illustrating the wide-ranging possible uses of network methods in the study of both localized injury and distributed disease.

Network Neuroscience as a Young Field

Despite these exciting recent advances, network neuroscience is still a very young field and many challenges remain. Particularly salient frontiers evident in the recent literature include the following:

- Network Dynamics. The human brain is a dynamic system [73] underpinning the complexities of cognitive function. The extension of network methods to characterize the temporal changes in putative communication patterns in the brain is necessary to understand the constantly evolving nature of cognition [74, 1, 75, 76].

- Neurophysiological & Genetic Drivers of Network Organization. The brain networks that we observe are driven by lower level physiological processes (e.g., [43, 77]) and genetic phenomena (e.g., [78, 79]). Determining the role of molecular and cellular dynamics in large-scale network and systems neuroscience is critical for a mechanistic understanding of brain development and function.

- Network-Based Prediction. Network approaches provide novel possibilities for classification and prediction. Machine learning, mathematical modeling, and statistical analyses have shown promise in predicting brain state (e.g., [80]), disease progression (e.g., [81]), and potential receptivity to neurorehabilitation efforts [1, 57].

- Network Approaches to Behavior, Perception, and Evolution. Applications of network methods outside of neuroimaging could provide important insights into cognitive function. For example, the network concept of community structure has been used to capture the organization of human movements (e.g., [82]), the temporal relationships between concepts (e.g., [83]), and the genetic interactions underlying cellular machines impacting on neural function (e.g., [84]).

Together, these frontiers promise to provide important progress in our understanding of cognitive function, its neurophysiological and genetic underpinnings, and its relationship to behavior.

As with any young field, the scientific excitement of network neuroscience is paired with its growing pains. First, it is not always clear how to translate the findings of network neuroscience to the clinic, be that in the development of antipsychotic drugs or in the rehabilitation of injured patients. Progress in this area requires greater progress in clinical systems neuroscience. Second, sources of noise in specific subject populations (e.g., movement in adolescents or in people with schizophrenia) can produce network signatures, which if not adequately corrected for, can lead to the inaccurate identification of group differences in network structure. Indeed, the identification and understanding of individual differences in brain connectivity will be an important area of growth in the coming years. Third, some network diagnostics and concepts can appear to be fads: small-worldness and power-law degree distributions were of great interest until it was shown

that most real world networks are small-world and power-law degree distributions do not necessarily imply a specific underlying mechanism (e.g., criticality) [85]. Finally, simple network representations of complex systems like the brain necessarily abstract away many potentially important biological details: nodes are not all identical, but instead have different structural and functional properties (e.g., [8]). A critical effort in the coming years will be to extend network representations to take into account these inter-regional differences to create more biologically realistic models of this complex data. Despite these growing pains, network science is a vibrant, rapidly growing field that brings with it exceptional promise for both empirical and theoretical neuroscience.

Concluding Remarks

In this chapter, we have discussed why network methods provide an interesting approach to the study of neuroscientific problems in general. The promise, challenges, and controversies of network neuroscience make it an exciting area, ripe for rapid progress, and crying out for new minds. To encourage you to dive in, we have provided a list of reviews and resources to explore in Box 1 and a list of helpful toolboxes in Box 2. We hope that these tools will be of use to you as you walk the paths of methodological innovation and scientific discovery.

Box 1: Reviews and Resources

- Several reviews address the general techniques used in applying network science to neuroscience data [86, 87, 4, 88, 3, 89, 90, 91, 68, 92, 93, 92].
- A smaller number of reviews focus on network applications in disease [6, 94, 95, 71].
- "Networks: An Introduction" is an excellent network science textbook [49].
- "Networks of the Brain" is a wonderful book about the application of network science to neuroscience [27].

Box 2: Toolboxes & Helpful Code

- The Brain Connectivity Toolbox is a MATLAB toolbox for network characterization [50].
- The UCLA Multimodal Connectivity Package is a set of Python programs used to calculate connectivity metrics from a variety of neuroimaging modalities [96].
- Netwiki contains shared data and code for network analysis including methods for dynamic community detection [97].
- Statnet is a suite of packages for statistical network analysis, focusing especially on Exponential Random Graph Models (ERGMs), which test hypotheses about the processes which might have led to the generation of a particular network you have identified [98].
- NetworkX is a Python package with a large user-base focused on the creation, manipulation, and study of complex networks [99].
- Pajek is a Windows package which supports the decomposition, analysis and visualization of large networks [100].
- There are multiple options for visualizing static, dynamic (changing over time) and even interactive brain networks. These include Graphviz (or RGraphviz in R) [101], igraph [102], gephi [103], d3 [104], and helpful user contributions on matlab file-exchange [105].
- Sometimes there is no substitute for writing your own code.

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