



The human connectome: Origins and challenges

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ABSTRACT

The human connectome refers to a map of the brain's structural connections, rendered as a connection matrix or network. This article attempts to trace some of the historical origins of the connectome, in the process clarifying its definition and scope, as well as its putative role in illuminating brain function. Current efforts to map the connectome face a number of significant challenges, including the issue of capturing network connectivity across multiple spatial scales, accounting for individual variability and structural plasticity, as well as clarifying the role of the connectome in shaping brain dynamics. Throughout, the article argues that these challenges require the development of new approaches for the statistical analysis and computational modeling of brain network data, and greater collaboration across disciplinary boundaries, especially with researchers in complex systems and network science.

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Introduction

"In biology, if seeking to understand function, it is usually a good idea to study structure." (Crick and Koch, 2005; pg. 1276).

The human brain, sometimes referred to as the most complex object in the known universe, is a network of nerve cells, regions and systems whose interconnections remain largely unmapped. How this network is connected is critically important for how neural elements exchange signals and influence each other dynamically, how they encode statistical regularities present in the sensory environment, coordinate movement and behavior, retain traces of the past and predict future outcomes – in short, virtually all aspects of the human brain's integrative function (Sporns, 2011). The important role of network architecture as a structural substrate for the functioning of the brain constitutes the main rationale for the emerging field of connectomics, the comprehensive study of all aspects of brain connectivity (Sporns, 2012).

This brief review article has three parts. The first part sketches the historical origins of the idea that brain structure, particularly the pattern of structural connectivity comprising the connectome, is critically important for understanding brain function. The second part of the article aims to further explore the concept of the "connectome", by critically examining its status as an "ome" and by defining its scope and purpose. Finally, the article highlights some of the empirical and theoretical challenges that lie ahead.

History and origins

Tracing the connections of the human brain has been an important scientific goal for many decades, if not centuries (Schmahmann and Pandya, 2007). Early neuroanatomists were keenly aware of the inadequacy of their anatomical techniques given the brain's extraordinary intricacy and fragility. Steno's remarkably prescient 1665 lecture entitled "On the Anatomy of the Brain" spelled out the need for a research program aimed at creating detailed accounts of brain anatomy, and especially of the fibers coursing through the white matter. Motivating this program was the idea that the brain is a complicated machine and that "it is impossible to explain the movements of a machine if the contrivance of its parts is unknown", a stance summed up handily as "anatomy first, then physiology" (Steno, 1965; pg. 151). Steno's program was not materially advanced until the advent of a variety of new methods for staining and tracing neuronal connections which finally paved the way for detailed anatomical accounts of human brain connectivity. Paul Flechsig's and Joseph Jules Dejerine's landmark studies of the long-range fiber systems of the human brain, mainly carried out using myelin stains, were among the first to tackle the structural complexity of cerebral association pathways. Another pioneer, Carl Wernicke, who like Dejerine carried out anatomical studies in the context of clinical disorders, particularly related to language dysfunction, was among the first to associate clinical syndromes with specific disruptions of the brain's anatomical connections. Theodor Meynert's 1885 textbook of psychiatry developed a model of brain function that was firmly rooted in connectional anatomy, including the numerous cortical "association systems" whose disruption, he postulated, was a primary cause of psychiatric illness. Regarding the profuse connections comprising the cerebral white matter, he

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remarked that “the wealth of such fibers, and their variation in length, connecting as they do near and remote parts of the cortex, will suffice, without formulating an anatomical hypothesis, to unite any one part of the cortex to any other” (Meynert, 1885, pg. 150). Meynert's structural approach to the brain recognized the central role of fiber systems in functional integration. But an important ingredient was missing — a clear understanding of the nature of neural activity and the mechanisms by which neural elements exchange and transmit information. As a consequence, it was difficult at the time to mechanistically relate the paths of anatomical connections to the functioning of the brain as an integrated whole.

Nevertheless, the notion that circuit anatomy is critical for explaining function resurfaced numerous times over the past century, most notably with the compilation of the nearly complete cellular connection map of the nematode *Caenorhabditis elegans* by Sydney Brenner and colleagues (White et al., 1986). The key rationale for creating complete connectome maps is cogently expressed in the opening sentence of their seminal article: “The functional properties of a nervous system are largely determined by the characteristics of its component neurons and the patterns of synaptic connections between them” (White et al., 1986; pg. 2). While the *C. elegans* connection map has now been available for over 25 years its use for understanding physiology and behavior initially remained limited, partly because of the difficulty of obtaining physiological recordings needed to characterize component neurons and synapses. More recently, *C. elegans* connectomics is gathering new momentum with significant advances in elucidating principles of network organization (Sohn et al., 2011; Varshney et al., 2011) and in linking network features to physiological processes in specific behavioral domains (e.g. Jarrell et al., 2012). Intensive efforts to create comprehensive maps of neurons and connections in other invertebrate species, including *Drosophila* (Chiang et al., 2011), are currently underway.

In mammalian nervous system, anatomical and physiological studies carried out over several decades provided a significant body of evidence for the important role of structural connectivity in shaping physiological responses. Among the first to clearly express this idea was Semir Zeki, whose extensive studies of visual regions in the macaque cortex led to some of the first network diagrams of large-scale cortical systems. According to Zeki, anatomical connections were crucial for enabling two main aspects of the functional organization of cerebral cortex, the *segregation* of function into a mosaic of specialized brain regions and their *integration* in the course of perceptual processing. In his words, “patterns of anatomical connections in the visual cortex form the structural basis for segregating features of the visual image into separate cortical areas and for communication between these areas at all levels to produce a coherent percept” (Zeki and Shipp, 1988, pg. 311). Dan Felleman and David Van Essen's milestone analysis of regions and connections in the macaque visual cortex (Felleman and Van Essen, 1991) resulted in the first representation of cortical connections in the form of a “connection matrix”, a compact description of which regions were connected via structural inter-regional pathways. In addition to identifying hierarchical organization on the basis of connectivity patterns, the authors also remarked on the fact that each cortical area maintained a unique pattern of inputs and outputs and “in most cases, this pattern provides a characteristic ‘fingerprint’ that can uniquely distinguish one area from all others” (Felleman and Van Essen, 1991; pg. 9). The compilation of connection matrices for cortical and subcortical connection in several mammalian species laid the groundwork for quantitative statistical analyses of cortical connection patterns (Young, 1992, 1993). Later studies drew additional links between connectivity and function, including relations between structural attributes such as connectional fingerprints (Passingham et al., 2002) or clustering (Hilgetag and Kaiser, 2004; Hilgetag et al., 2000) and similarities in regional functional specialization.

As early network studies of cortico-cortical connections began to reveal key aspects of their network organization such as small-world attributes, and clustering or modularity (reviewed in Sporns et al., 2004), the lack of detailed connection maps for the human brain became a serious roadblock on the way towards understanding the structural basis of its functional organization. The need for a detailed anatomical map of the connections of the human brain had been bluntly stated by Francis Crick and Ted Jones, who wrote that “It is intolerable that we do not have this information [a connectome map] for the human brain. Without it there is little hope of understanding how our brains work except in the crudest way” (Crick and Jones, 1993; pg. 110). Perhaps it was Crick's background as a molecular biologist that led him towards a view of brain function that was critically informed by information about structure. In his last paper, published posthumously in 2005, Crick together with co-author Christof Koch examined the connectivity and physiology of the claustrum, an irregularly shaped sheet of gray matter that is not only centrally embedded within the cortical hemisphere (located underneath the insular cortex) but also very widely connected (Crick and Koch, 2005). Koch and Crick argued, largely on the basis of data on connectivity and cellular architecture, that the claustrum might be a crucial center for the confluence and integration of diverse neural information.

The importance of connectivity for explaining and predicting dynamic neuronal interactions is clearly demonstrated in the context of computational models. Beginning in the 1980's a number of researchers created computational models that combined data on anatomy (a set of structural connections, mathematically represented as a connection matrix) and physiology (a set of differential equations expressing basic biophysical processes related to excitation, inhibition and plasticity). As such models became dynamically active, either spontaneously or under the influence of external perturbations, they generated simulated time series data that could be related to recordings obtained from real neuronal systems. As the structural connectivity was varied, differences in the system's dynamic behavior, for example in emergent rhythmicity (e.g. Traub et al., 1989) or in synchronization among neural populations (e.g. Sporns et al., 1989), could be observed. Some computational models began to explore how connectivity data such as the connection matrices compiled for the macaque visual cortex can predict neuronal responses (Tononi et al., 1992), or shape global patterns of brain dynamics (Sporns et al., 2000; Tononi et al., 1994). It became clear that realistic brain dynamics depended on the presence of specific attributes and motifs in the underlying structural connectivity.

Crick and Jones had called for “the introduction of some radically new techniques” to allow progress in human brain anatomy, specifically designed to trace large-scale anatomical pathways connecting segregated brain regions. This goal finally came within reach a few years later, with the development of noninvasive diffusion imaging methods (reviewed in Le Bihan and Johansen-Berg, 2011). These methods and the associated computational techniques for inferring anatomical pathways are continually refined and validated, including in side-by-side comparison with classical anatomical techniques in animal models (e.g. Schmahmann et al., 2007). Validation studies are critical for establishing the capability and limitations of diffusion imaging and tractography applied to the human brain (Dell'Acqua and Catani, 2012), as well as for characterizing the neurobiological meaning of the parameters that are accessible with these imaging methods (Jbabdi and Johansen-Berg, 2011). The potential of diffusion imaging methods for mapping fiber anatomy has been demonstrated in numerous studies, for example in studies that explicitly compared connectivity profiles derived from structural and functional connectivity data (Johansen-Berg et al., 2004), as well as by improved techniques for mapping regions with complex fiber anatomy (Wedeen et al., 2005).

By 2005, the notion that brain function could be illuminated on the basis of structure was very much in the air, and so it is not surprising

that the central idea of creating a comprehensive map of the brain's structural connections arose nearly simultaneously in multiple places. The term “connectome” was first defined in a review article focusing on the structure of the human brain as “a comprehensive structural description of the network of elements and connections forming the human brain” (Sporns et al., 2005). The article laid out a detailed proposal for compiling the human connectome that was based on a combination of structural and functional mapping techniques, explicitly including structure–function relations as a key objective for future connectome projects. The proposal surveyed methods and prospects for creating connectome maps across micro-, meso- and macroscales, and concluded that, at least in regard to the human brain, the macro-scale of regions and inter-regional pathways seemed most promising as a near-term goal. The article went on to discuss a number of conceptual challenges, including individual variability, plasticity and development – challenges that for the most part remain in place today (see below). The paper concluded by suggesting an 8-step research strategy for compiling a first draft of the human connectome. These steps closely parallel most of the components stipulated by the U.S. National Institutes of Health as part of the Human Connectome Project which commenced in 2010 (van Essen et al., 2012; and other articles in this Special Issue).

Independently and in parallel, Patric Hagmann coined the term “connectomics”, defined as the study of the brain's set of structural connections (Hagmann, 2005). Researchers in cellular neuroscience also recognized the importance of connectivity and began to develop ideas aimed at mapping anatomical connectivity at the microscale. Kevin Briggman and Winfried Denk argued that “knowledge of all the pre- and postsynaptic synaptic connections of a cell is necessary to understand its role in a network.” (Briggman and Denk, 2006; pg. 562), and they proceeded to propose that neural connections should be mapped at the ultrastructural level with imaging and reconstruction methods specifically developed for electron microscopy. More recently, Denk and colleagues have referred to connectome mapping efforts as “structural neurobiology” (Denk et al., 2012). Light microscopic methods also offered important new avenues towards creating connectivity maps. In 2007, Jeff Lichtman and colleagues wrote about “connectomic maps” which they defined as “connectivity maps in which multiple, or even all, neuronal connections are rendered” (Livet et al., 2007, pg. 56). Their work introduced powerful new labeling and imaging approaches based on the combinatorial expression of multicolor markers by individual neurons.

Despite many differences in experimental methodologies for mapping anatomical connections at micro- and macroscales, when integrating over the motivations driving the connectome's multiple origins, there appears to be considerable agreement concerning the important role of structural connections for shaping dynamic or functional responses of neural elements. This principle holds across a wide range of systems and scales, from individual nerve cells to brain regions. What emerges, then, is a broad consensus regarding a preliminary definition of the connectome: The connectome is a comprehensive map of neural connections whose purpose is to illuminate brain function.

Defining the connectome

Before defining some of the central features of the connectome in more detail, it is worth considering the status of the connectome as an “ome” that can inform basic neuroscience. Following the genome, first defined in 1920, a number of “omes” have been introduced in recent years, particularly in the biological sciences. Most of these “omes” are inventories or lists of elementary components or their interrelations that jointly constitute a specific domain of biological knowledge. Importantly, an “ome” must be complete and represent what is being studied in its entirety. A number of “omes” record complete sets of molecular components. For example, the proteome and

the transcriptome specify the set of proteins and RNA species, respectively, expressed by a specific organism or cell type. Other “omes” record interactions that occur in networks, for example the interactome, defined as the complete set of physical interactions among proteins (see the recent review by Vidal et al., 2011). Not all “omes” end up being productive tools that achieve wide acceptance (witness the “cognome”, “functome”, and “unknome”). Which “omes” eventually survive is largely determined by their utility within their respective fields. In addition to their utility, successful “omes” share a number of attributes: universality (they apply to a broad range of systems and species), totality (they comprise a complete and finite set of data), and permanence (they remain valid and veridical as knowledge continues to grow).

These attributes must be kept in mind when critically examining the utility and power of the connectome. The connectome as a concept must have well-defined boundaries that express what it is about. In this context, there are two central aspects of the connectome that deserve closer scrutiny. First, as discussed above, the connectome is primarily grounded in brain structure, most importantly in various attributes of anatomical connectivity. Second, recording and representing the connectome require the formulation of network models that can be analyzed with the tools and methods of network science and that underpin mechanistic accounts of the brain's dynamic responses.

Brain connectivity can be characterized by a number of structural parameters. For example, connectivity can be summarized in an adjacency matrix whose structural links between pairs of elements are expressed as a binary number indicating whether a link is present (‘1’) or absent (‘0’). This extremely simple and compact description of connectivity was widely adopted in early data sets and analyses, but it only represents a very first step towards fully characterizing brain connectivity. Links that are recorded as present can be further characterized in a number of ways, including by recording the number or densities of more fine-grained connection elements (synapses, axonal fibers, reconstructed streamlines), their physiological strength, their spatial trajectories, caliber of projections and their metric lengths, conduction delays, and numerous biophysical attributes that define the links physiological effects and capacity for plastic change. All of these parameters are structural attributes of connections. As such, they are all part of the structural connectome, whose goal it is to describe all functionally relevant aspects of the neural architecture. As connectome mapping efforts progress, they should aim at including as many of these structural parameters as can be empirically measured. This point is particularly important in diffusion imaging and tractography since the appropriate characterization of white matter connectivity and microstructure requires careful application of methods and interpretation (Jones et al., 2013).

The emphasis on structure as the foundation of connectomics is important for several reasons. Perhaps most importantly, structure–function relationships are of significance across all areas of biology, from molecular to organismic scales. As discussed above, the pivotal role of structure for the functioning of the nervous system has been widely recognized. But there is another reason why the connectome fundamentally rests on a description of brain structure. Structure represents “ground truth”. Anatomical connections, whether they are individual synapses or inter-regional pathways, embody a large but finite set of relations among neural elements that (at least in principle) can be objectively verified and completely mapped. Anatomical connections either exist, or they don't, and different ways of measuring anatomy should ultimately converge and render a consistent map of their architecture. This stands in sharp contrast to “functional connections” that describe statistical dependencies derived from observations of neural time series (Friston, 2011). Most functional connections exhibit significant temporal fluctuations, may or may not disclose true causal relations between neural elements, and are highly dependent on measurement and analysis technique. This variability would make it difficult, if not impossible, to compile a finite “omic” catalog of functional (or effective) connections. Important exceptions

are so-called resting-state networks that have been shown to display relatively stable anatomical distributions and functional attributes, and that can be reliably extracted (Biswal et al., 2010). While some studies have demonstrated moderate to high test–retest reliability of resting-state functional connectivity measured with fMRI (Shehzad et al., 2009; Van Dijk et al., 2010), more recent work also suggests that reliability may depend on the specific functional connectivity measure employed in the analysis (Fiecas et al., 2013).

There is a natural affinity between connectomics and network science. While representing the connectome as a network or graphical model may at first seem rather abstract, appropriately chosen concepts of network science appear well suited to capture real neurobiological structures and processes. This parallels the proven utility of networks in other domains of biology (and beyond). The “omics” revolution that is still unfolding within the biological sciences is fueled by a paradigm shift away from reducing biological systems to individual parts (be they genes, proteins, neurons, or organisms) and towards considering all their parts and interactions at once. This paradigm shift requires the adoption of new models for representing, explaining and predicting complex biological functions, and these models draw heavily on the theoretical frameworks of system dynamics and network science. In a sense, connectomics is an extension of systems biology to neuroscience. The role of networks in systems biology is paralleled by the strong links that have formed, even at this early stage, between the emerging field of connectomics and the science of complex networks. These links are likely to grow even stronger in the future, and they will help in overcoming the many challenges connectomics currently faces.

Challenges

Scales

It has long been recognized that many complex systems exhibit multiscale organization (Simon, 1962). This mode of organization implies that the system can be partially decomposed into coherent functional components at different spatial scales. In the case of the brain these components may correspond to elements that are as small as individual neurons (or even subcellular compartments that are functionally specialized) and as large as brain regions and “functional networks” such as those revealed during resting brain dynamics. The challenge for connectomics is to capture this multiscale organization by charting network relations among elements across different spatial scales. For any given organism, descriptions of the connectome at individual scales differ radically. Consider, for example, a full description of the human cerebral cortex at cellular or system levels. Given current best estimates for the number of neurons and number of synaptic connections (on the order of 10^{10} – 10^{11} and 10^{14} – 10^{15} , respectively), the microscale connectome map would be extremely sparse: fewer than one in a million (less than one ten thousandth of a percent) of all possible synaptic connections actually exist. However, at system scale tracing and imaging studies of structural anatomy of regions and their projections suggest that around 20–40% of all interregional pathways (and possibly up to 60%; see Markov et al., *in press*) can be found. A possible model that unifies the different spatial scales encountered in brain network organization is that of a hierarchical or nested architecture, with larger network communities or modules at the system level that can be further subdivided into regions, neuronal populations and eventually individual circuits and neurons. Hierarchically modular organization not only promotes complexity, as discussed by Herbert Simon, but also may bring numerous benefits, including cost-efficiency of the physical arrangement of the brain's wiring (Bullmore and Sporns, 2012) and a propensity for richly structured sustained and evoked neural dynamics (Wang et al., 2011).

Differences in connection densities across scales will likely be associated with different organizational features of the network

architecture. This issue of scale closely relates to the problem of “node definition” which is fundamental for extracting networks from human imaging data derived from either diffusion or fMRI data. Node definition is a necessary first step for defining the network's basic elements, and several studies have shown that topological features of networks revealed by graph theory methods sensitively depend on how the brain is broken down or parcellated into elements (e.g. Zalesky et al., 2010). Parcellation can be performed on the basis of several different criteria, including cytoarchitectonics, gene expression patterns, regional myelination, temporal covariance in spontaneous or evoked responses, or similarity of anatomical and functional connections (reviewed in Sporns, *in press*; Wig et al., 2011). Detecting boundaries between coherent regions on the basis of any one, or multiple, of these criteria remains challenging. Recent work suggests that parcellation is most robust if performed according to multiple structural and functional criteria for the definition of regions and their boundaries (e.g. Nelson et al., 2010). Given the difficulty of parcellating the brain, it has been proposed that keeping track of the spatial and topographic arrangements of connections can give information that is complementary to discretizing the brain into nodes and edges (Jbabdi et al., *in press*). As it stands now, most extant studies side-step the parcellation problem by drawing upon atlas- or template-based regional definitions or by performing analyses on individual voxels or randomly aggregated voxel clusters. However, these approaches may be sub-optimal for capturing fine-grained aspects of network organization, especially features that exhibit significant variations across individual participants and thus are prone to mis-alignment. Objective data-driven parcellation (or alternative) methods applied to individual structural and/or functional data sets will become increasingly important as the next challenge for connectomics, assessing individual variability, comes into sharper focus.

Individual variability

Nervous systems of individuals from the same species often exhibit pronounced structural variability. Even in invertebrate species that are generally thought to possess fairly stereotypic brains, the morphology of specific single neurons can be highly variable across individuals. This structural variability includes attributes of connectivity such as the number, density and spatial placement of synaptic endings, as well as other structural features such as the branching pattern of dendritic and axonal compartments, or the molecular constituents responsible for neuronal responses and their plasticity. Despite this structural variability, there is a remarkable level of functional stability or homeostasis, resulting in globally consistent circuit dynamics despite abundant structural variation (Marder, 2011). The combination of structural variability and functional consistency suggests a high level of “degeneracy” (Tononi et al., 1999), the capacity to achieve a given neural function, for example rhythmic firing in central pattern generators, in a large number of possible circuits (Goaillard et al., 2009; Marder and Taylor, 2011). A high degree of degeneracy could make it difficult to detect consistent structure–function relations at the microscale – the “wiring diagram” of individual exemplars of neural circuits would not be sufficient for “reading out” or decoding how it functions (for further discussion of this issue see Parker, 2010). Instead, more reliable mappings between structure and function would require data from populations of circuits obtained from a large number of individuals.

Structural variability is also encountered at the macroscale, where brain mass and volume, the folding pattern of the cortical surface, and the absolute and relative sizes of brain regions and projections have all been shown to differ across individuals (e.g. Dougherty et al., 2003; Thompson et al., 1996). The extent to which these morphological variations impact variations in network connectivity remains largely unexplored. While between-subject variations in network topology are often seen in studies of human whole-brain structural

connectivity, a systematic assessment of how much of the observed variance is due to noisy acquisitions, registration errors, or instability in reconstruction algorithms has yet to be performed (see e.g. Bassett et al., 2010). The importance of understanding the nature of structural variations in brain anatomy and connectivity derives from its potential impact on behavioral and cognitive performance. A number of studies have shown that specific variations in structure are strongly associated with individual variations in sensory or motor processing (Kanai and Rees, 2011). For example, differences in cortical thickness and gray matter density in specific regions of parietal cortex can partially predict differences in the temporal dynamics of bistable perception (Kanai et al., 2010). In other studies, differences in gray matter volume in a select set of sensory regions are associated with differences in the ability to discriminate time intervals (Gilaie-Dotan et al., 2011), and individual variations in transcallosal connections are correlated with delays in traveling waves experienced during perceptual transitions among rivalrous stimuli (Genç et al., 2011).

Functional connectivity also exhibits significant variations across time, demonstrated for example in the course of learning (Lewis et al., 2009) as well as across individuals. A number of studies have shown relations between performance levels in specific tasks or task domains and resting or task-evoked functional connectivity among regions known to be involved (e.g. Hampson et al., 2006; Koyama et al., 2011; Seeley et al., 2007), as well as relations between complex personality traits such as impulsivity and resting-state network organization (Davis et al., in press). Interestingly, individual differences manifesting in the functional connectivity of the resting brain can also predict individual variations in future behavioral performance. Baldassare et al. (2012) examined resting-state functional connectivity among regions involved in perceptual processing and found that connectivity measures of individual subjects allowed forecasting the predisposition of the subject to perform a novel perceptual task. While numerous studies have shown that (resting-state) functional connectivity is related to underlying structural connectivity (see below), the extent to which behaviorally relevant differences in functional connectivity reflect underlying variations in structural connectivity (i.e. the connectome) is still largely unknown.

Individual variability poses several challenges for efforts to map the connectome. One challenge is the necessity to compile connectome maps across a large number of individuals, and to record and quantify patterns of variation in network architecture, a challenge that will be tackled in the Human Connectome Project (van Essen and Ugurbil, 2012). Comparing networks across individuals may become especially difficult if individual brains exhibit significant differences not only in the strength or density of connections, but also in the number and spatial distribution of network elements. Structural and functional imaging studies suggest that anatomical areas in parts of the human cerebral cortex can vary not only in areal size but even in the number of distinct subdivisions (e.g. Anwander et al., 2007; Bürgel et al., 2006). The extent to which these structural variations at the macroscale are correlated with individual differences in behavior and cognition, as well as whether they are heritable or experience-dependent, remains to be determined. It seems likely that structural variability will be a major area for future expansion in connectome studies.

Structural plasticity

All molecular and cellular components of the nervous system are continually remodeled, replaced and resynthesized – including all structural elements of the human connectome. Neuronal proteins such as channels, receptors, cytoskeletal elements, signaling molecules or enzymes are turned over on time scales of minutes to hours. The extreme fluidity of structural organization at molecular scales poses serious problems for the maintenance of long-term structural changes, possibly requiring self-replicating prion-like mechanisms to ensure the permanence of long-term memory (Shorter and

Lindquist, 2005). Even at the somewhat larger scales of cells and synapses, significant structural changes continually shape and mold patterns of brain connectivity. These structural changes are supported by a host of mechanisms, from synaptic modifications to neuronal growth and structural plasticity, operating not only during early development but throughout the lifespan. Numerous lines of evidence suggest that the structural arrangement of neuronal circuits, including their connection topology can undergo significant and rapid alterations in the adult brain (Holtmaat and Svoboda, 2009). These alterations involve both dendritic and axonal compartments. For example, sensory deprivation experiments have shown that changes in input are accompanied by changes in the density and pattern of dendritic spines on cortical neurons (Hofer et al., 2009). Similar changes are seen in somatosensory or motor cortex following experiential changes in sensory input or motor learning (Yang et al., 2009). While these changes are observed in conjunction with learning and experience, other changes in connectivity at the microscale appear to occur spontaneously, in the absence of any overt sensory or motor challenge. Changes in the branching patterns of axons and a significant turnover rate of synapses among neurons in adult macaque primary visual cortex was shown to occur on timescales of days and weeks, in the absence of any overt changes in sensory input or experience (Stettler et al., 2006). Spontaneous as well as experience-dependent dendritic spine dynamics are also observed in inhibitory interneurons of the cerebral cortex (Chen et al., 2012). These structural dynamics of cells and synaptic connections create serious problems for efforts to map the connectome at the microscale. Each map would only represent a snapshot of a dynamic process, and the lack of information about the rewiring kinetics of individual connections would further complicate the reliable inference of structure–function relations.

Even at the large scale, brain structure can be subject to significant changes due to experience, and these changes can be measured with modern neuroimaging methods that record properties of the brain's white and gray matter. For example, the acquisition of a new sensorimotor skill over a period of weeks to months results in changes in both gray matter volume and the structure of white matter pathways in regions of the brain that are known to be involved in sensorimotor coordination (Scholz et al., 2009). Such changes can be observed over remarkably short timescales. Sagi et al. (2012) detected structural plasticity in specific brain regions involved in spatial learning and memory in participants who had engaged in a single 2-hour session of playing a car racing video game. Because the nature of the signal measured in these experiments does not necessarily imply plasticity in axonal connections, further studies are needed to clarify if the observed change has an impact on structural connectivity.

We are left with a picture where not only the brain's microanatomy but also the large-scale structure of the connectome remains in flux and responsive to activity and experience throughout the lifespan. The challenge for connectome mapping studies then becomes one of tracing these patterns of plasticity and temporal variability (presumably by aggregating longitudinal observations from the same cohort of participants), and of expressing concomitant changes in network topology over time. Just as important as tracking the patterns of variability is the identification of topological invariants – metrics or indices of connectivity that remain largely constant in the face of persistent fluctuations, and that index individual characteristics that are stably expressed across time.

Structure–function relationship

As noted above, the primary target of connectomics is to create maps of the brain's physical (anatomical, structural) connections. Numerous empirical and computational studies suggest that such a “wiring diagram” would be tremendously useful as a fundamental resource for explaining and predicting aspects of brain function, from

the intrinsic dynamics arising in small-scale circuits and large-scale systems, to the flow of information resulting from extrinsically evoked brain activity. How does the connectome shape neural dynamics and behavior?

Several lines of research point to an important role of synaptic and interregional connectivity in generating statistical dependencies among neural elements, e.g. in generating neural information. At the microscale, an increasing number of studies have reported on the relation of synaptic connectivity in neuronal circuits and observed patterns in neural dynamics, especially the correlations observed in large neuronal populations (Cohen and Kohn, 2011; Feldt et al., 2011). For example, modeling studies have addressed the question how different connection topologies can induce pairwise correlations among spiking neurons (Pernice et al., 2011). Key findings include potentially strong effects of indirect structural couplings on the correlation structure (i.e. functional connectivity) of the network, and a role for highly connected hub neurons in inducing strong average correlations. In a similar vein, the relation between the connectivity architecture and the global pattern of correlations observed in large excitatory–inhibitory networks has been explored using linear response theory to predict pairwise correlations from structural paths (Trousdale et al., 2012). Drawing on concepts from graph theory, Vlachos et al. (2012) have argued that the “embeddedness” of a neuron, which can be assessed with a broad range of measures of centrality or influence, is crucially important for predicting its effective functional impact on the rest of the network. To assess this functional impact would require a graph model of structural connections. Recent empirical studies have also attempted to directly relate reconstructed neural circuits to specific functional properties of neurons, for example in the mouse retina (Briggman et al., 2011) and in mouse visual cortex (Bock et al., 2011). The latter study was able to trace the preferred orientation selectivity of individual neurons to their ultrastructurally mapped synaptic interconnections.

In parallel, a second line of evidence has revealed strong and robust relationships between large-scale patterns of long-distance connections between brain regions and their functional connectivity. This relationship has been intensively investigated in the area of human connectomics (reviewed in Honey et al., 2010). Hagmann et al. (2008) compared cortical structural networks derived from diffusion MRI and functional networks acquired during the resting-state, both acquired within the same set of participants and mapped onto the same random parcellation. Statistical analysis demonstrated that the presence and strength of a structural connection partially predicted the strength of a functional connection (Honey et al., 2009). However, the study also showed that many strong functional connections exist among structurally unconnected node pairs, thus rendering the inference of structural connections from functional connections impractical. Other studies (e.g. Greicius et al., 2009; Hagmann et al., 2010; Skudlarski et al., 2008; van den Heuvel et al., 2009), including some in nonhuman primates (Adachi et al., 2012), have confirmed a robust, albeit complex, relationship between structural connections and spontaneous dynamic (functional) couplings. It appears that much about the long-time average of resting brain functional connectivity can be explained by taking into account a mixture of direct and indirect network effects along structural connections and paths. The important role of structural connections for shaping resting brain signal fluctuations is further underscored by interventional studies (e.g. Johnston et al., 2008). In addition to predicting resting brain fluctuations, the connectional “fingerprint” of cortical regions can also accurately predict functional brain responses in individual participants, as shown for face-specific activation patterns in the fusiform gyrus (Saygin et al., 2011).

Resting brain dynamics can be computationally analyzed using neural mass models (Deco et al., 2008) combining data on structural connectivity and on biophysics of local interactions among cell populations. The success of such models in reproducing functional

connectivity patterns recorded during rest in both nonhuman primates (Adachi et al., 2012; Honey et al., 2007) and humans (Cabral et al., 2011; Honey et al., 2009) strengthens the hypothesis that resting brain fluctuations are shaped by the underlying anatomy. More recently, sophisticated dynamical models have not only focused on long-time averages in the network's correlation structure, but also revealed complex dynamic features that manifest on shorter time scales. First observed in a model of spontaneous dynamics in macaque cortex (Honey et al., 2007), rich temporal structure emerges in models of the resting human brain as well (Cabral et al., 2011; Deco et al., 2009; Ghosh et al., 2008). These studies have given rise to the idea that the resting brain resides in a regime that is close to instability which allows it to continually explore a dynamic repertoire of noisy brain states (Deco and Jirsa, 2012; Deco et al., 2011; Senden et al., 2012). This marginally stable dynamic regime ensures that system dynamics neither die out nor become completely random, giving rise to a series of patterns that are constrained and shaped by the connectome. In a sense the connectome serves as an anatomical skeleton that compresses the virtually infinite dynamic state space of the brain into a low-dimensional subspace or manifold.

The notion that the resting “state” is less a state than a set of dynamic recurrent patterns first arose in the context of theoretical models, and is now rapidly gathering momentum with a growing number of empirical demonstrations of fluctuations in functional connectivity in fMRI (Chang and Glover, 2010; Hutchison et al., 2012; Jones et al., 2012; Smith et al., 2012) as well as EEG/MEG recordings (de Pasquale et al., 2010). These fluctuations give rise to time series of functional networks, and capturing and tracking these networks are a major challenge (Sporns, in press). To adequately meet this challenge will require the development of new empirical as well as analytic methods. For example, new methods are needed that can assess the potential recurrence of network motifs or entire network configurations (e.g. Betzel et al., 2012), and that can determine if such recurrences occur at random or follow a specific “syntax” or sequence among network states.

Among all of the challenges currently facing connectomics, elucidating structure/function relations is perhaps the most urgent and at the same time least explored. It is important to address this challenge, not only to achieve a more complete mechanistic account of how the connectome shapes endogenous or resting brain dynamics, but also for a more comprehensive understanding of how structural connectivity underpins brain responses. More complete and accurate maps of structural connections may also serve as important priors for building improved models of effective connectivity (Stephan et al., 2009). A better understanding of structure/function relations is also important for identifying the structural basis of individual variations in behavioral and cognitive performance, as well as brain dysfunction associated with in a broad range of brain and mental disorders.

Outlook

This review has traced the origins of the connectome, and discussed some of the empirical and theoretical challenges it faces today. The rapid growth of connectome projects and related studies over recent years suggests that the connectome has already proven to be a fruitful conceptual advance for systems and cognitive neuroscience. Importantly, the connectome is far more than a large data set. It strongly implies the adoption of network models for brain function, including but not limited to the quantitative methods offered in abundance by network science. Network models are uniquely positioned to combine the aspects of segregation and integration, localized and distributed organization, and small-scale and large-scale perspectives on neural architectures. Network functions emerge from the collections of elementary units that are linked by connections and bound together dynamically. One can only hope that the connectome can facilitate new insights regarding the nature of integrative brain function.

However, limitations of connectomics exist and must be acknowledged, and if possible should be overcome. For example, some formulations of the connectomic research program seem to imply that all functionalities of neuronal circuits and systems can be derived or “read out” once the complete pattern of synaptic connections has been recorded. But circuit dynamics is not fully determined by the circuit's wiring diagram. For example, it can be powerfully altered and regulated by the action of neuromodulators. Circuit modulation cannot be adequately captured with standard circuit mapping tools, including those currently available at the microscale. The inability of connectome maps to capture modulatory processes has been cited as a major limitation of the structural approach inherent in all of connectomics (Bargmann, 2012; Brezina, 2010; Marder, 2012). One way to address this limitation is to complement discretized connectome maps with spatially embedded maps of neuromodulatory networks (Brezina, 2010). Additionally, connectome maps can be annotated with data on each connection's susceptibility to neuromodulation, as well as with data on the spatial arrangement of sources and targets of neuromodulators. Finally, it might be important to perform systematic comparisons between anatomical and physiological observations in order to capture each circuit's range of dynamic responses (see the proposal by Alivisatos et al., 2012). In a sense, the conundrum posed by circuit modulation is no more (and no less) severe than the realization that gene expression is modulated by powerful regulatory mechanisms operating in whole cells. Alas, connections, like genes, don't act autonomously, but only as part of integrated biological systems.

Looking to the future, despite numerous challenges and limitations, it seems likely that the connectome will change the way we view and study the brain. Some of these changes have already begun — a re-discovery of “network thinking” as a necessary counterweight to reductionist science, a resurgence of interest in recording individual differences across the human population, a number of new network approaches to brain injury and disorders, the growing synergy between empirical research and computational models, the “scaling up” of projects to achieve bold goals through teamwork and collaboration, the introduction of hypothesis-free discovery science, and the acceleration of efforts to publicly share research tools and data. It is hoped that the future of the connectome will avoid the excesses of passion and cynicism that have accompanied the rise of “omics” in other areas of biological science.

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Conflict of interest

The author declares that there is no conflict of interest.

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