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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.

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 connectional 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