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1 Introduction

How does the brain change over time? While researchers are beginning to understand more about how the set of connections between neurons and regions, the connectome, is organized, this book describes how such an organization arises during development and evolution, how it changes in health and disease, and how external interventions can alter its architecture. For this aim, we describe mechanistic insights, based on computational models and experimental studies, that can link the changes at the local level of individual neurons to the observed large-scale alterations in connectivity between brain regions.

Over the past several years, connectome information about large cohorts of human subjects and patients at different stages of brain development or disease progression has become available. There are continuing efforts to increase data quality, to enable data sharing, and to analyze brain network architecture. There is increasing availability of longitudinal data, measuring the same subjects at multiple time points. Along with connectome data of the early stages, before and shortly after birth, this allows us for the first time to observe the development of connectomes.

Given the availability of both data on brain networks and tools to describe the organization and behavior of these networks, the field of network neuroscience can inform how we look at connectome changes. There are different approaches that one can take to analyze connectome changes. First, one may look at changes in the network organization at different time points using network science approaches. This analysis of network features gives a first insight into which network functions—for example, integration and segregation of information flows—might be altered. Second, one may simulate neural activity within the network to understand how changes in network structure influence network behavior. Finally, one may use computational models to evaluate the mechanisms that lead to the observed changes in network structure. Such approaches can help us to understand how connectome changes arise and change

brain function, and they could suggest hypotheses that can be tested experimentally in the future.

There are also more direct applications of network neuroscience in understanding connectome changes. As will be described, there are distinct network changes for brain disorders. Computer models will be essential to inform diagnosis and treatment of individual patients. As each case is different, it is impossible to have an experimental animal or clinical human study with exactly the same condition as found in an individual. In addition, given dozens of variables that play a role, and with interactions between variables influencing each other, it will be impossible to provide mathematical equations that describe the relationships between all variables. The only solution for better diagnosis and treatment of individual patients is a personalized computational representation, based on connectome, physiome, genome, and other available data. With such a system, the plausibility of different disease origins and the outcomes of different interventions can be tested in silico to find the most suitable option for an individual patient.

The study of mechanisms of network changes can also be helpful for designing experimental studies, for understanding the link between brain network structure and performance, and for improving the design and development of artificial neural networks. The range of applications that can benefit from an understanding of connectome changes includes, for example, the following:

- The design of artificial neural networks—for example, for deep learning—includes features of connectomes such as layers but only includes a small subset of mechanisms for network growth and development. This particularly limits the ability of such systems to provide more complex behavior such as multimodal integration, adaptivity to new environments, and learning from small training data sets. Building networks that grow based on mechanisms identified in biological neural networks might provide new breakthroughs in this field.
- Knowing about the link between connectome structure and function will help us to understand why network features arise during individual brain development and during the evolution of neural systems. Not all network features might have a direct or strong link to cognitive processing.
- Knowing the developmental origin of brain diseases provides another biomarker that can be used to help with diagnosis, the stratification of the patient cohort, and treatment planning. Understanding the developmental pathways of network changes could, given the current brain network of a patient, help to predict which factors played a role in the genesis of these connectome changes.

- Understanding the mechanisms that lead to network changes can help to improve brain function following brain injury by facilitating the design of rehabilitation interventions that increase positive network changes while trying to prevent network changes that have a negative effect on brain function.
- For brain stimulation, while there are some models about immediate stimulation effects, during and shortly after stimulation, it will be crucial to understand long-term effects in order to predict effects and minimize negative side effects.

In part I, before we can look at connectome changes, we first need to describe how brain networks can be measured and how we can analyze their features. Chapter 2 provides an overview of network reconstruction and of the analysis of topological and spatial features. Furthermore, I show how activity in these networks can be modeled by giving a brief overview of dynamic features of brain networks. Chapter 3 shows how topological features arise during brain evolution, starting with simple nerve nets and moving on to modular and hierarchical networks. Chapter 4 gives an overview of the architecture of brain networks for the organisms for which we already have full or partial information about their connectomes: *Caenorhabditis elegans*, fruit fly, pigeon, mouse, rat, ferret, cat, rhesus monkey, marmoset monkey, and human. Part II discusses the maturation of network features during individual brain development. Chapter 5 shows how regional patterns such as cortical maps can be formed and how genetic factors, competition, and homeostasis can induce these patterns. Chapter 6 shows how layers can form; it includes experimental and computational results indicating the roles of cell growth, cell migration, and cell death. Chapter 7 looks at axon growth and the formation of synaptic connections determining principles of initial connection establishment. Chapter 8 looks at network hubs, outlining different hub types and different mechanisms that can generate hubs during brain development. Chapter 9 describes how modules, enabling segregated information processing, can arise due to developmental time windows and genetic factors. Chapter 10 describes how cortical folding changes during development and what principles and mechanisms might cause these changes. Part III looks at how connectomes change during the life span in health and disease and how interventions can interfere with these processes. Chapter 11 is about healthy brain development, outlining changes until adulthood. Chapter 12 talks about changes due to neurodevelopmental disorders such as schizophrenia, autism spectrum disorders, major depression, epilepsy, and Tourette's syndrome as well as about underlying mechanisms for these changes. Chapter 13 deals with age-related disorders such as Alzheimer's disease, Lewy body dementia, and Parkinson's disease as well as with models of disease progression. Chapter 14 describes how connectomes

react to lesions, caused by stroke, traumatic brain injury, or loss of peripheral input, and how computational models can be used to test underlying mechanisms for these changes. Chapter 15 highlights the emerging role of brain stimulation, being used on patients but also on healthy subjects, in altering the dynamics but also the topology of brain networks.

How can we determine brain connectivity and how can we analyze brain networks? The next chapter will show how structural and functional connectivity can be determined and how topological, spatial, and dynamic characteristics of the network can be analyzed.

2 Features of Complex Networks

The set of connections in neural systems, now called the connectome (Sporns et al., 2005), has been the focus of neuroanatomy for more than a hundred years (Ramón y Cajal, 1892; His, 1888). However, it has attracted recent interest due to the increasing availability of network information at the global (Felleman and Van Essen, 1991; Scannell et al., 1995; Burns and Young, 2000; Tuch et al., 2003) and local levels (White et al., 1986; Denk and Horstmann, 2004; Lichtman et al., 2008; Seung, 2009) as well as the availability of network analysis tools that can elucidate the link between structure and function of neural systems. Within the neuroanatomical network (structural connectivity), the nonlinear dynamics of neurons and neuronal populations result in patterns of statistical dependencies (functional connectivity) and causal interactions (effective connectivity), defining three major modalities of complex neural systems (Sporns et al., 2004). How is the network structure related to its function, and what effect does changing network components have (Kaiser, 2007)? Since 1992 (Achacoso and Yamamoto, 1992; Young, 1992), tools from network analysis (Costa, Rodrigues, et al., 2007) have been applied to study these questions in neural systems.

What are the benefits of using network analysis in neuroimaging research? First, networks provide an abstraction that can reduce the complexity when dealing with neural networks. Human brains show a large variability in size and surface shape (Van Essen and Drury, 1997). Network analysis, by hiding these features, can help to identify similarities and differences in the organization of neural networks. Second, the overall organization of brain networks has been proven reliable in that features such as small worldness and modularity, present but varying to some degree, are found in all human brain networks (and those of other species, too). Third, using the same frame of reference, given by the identity of network nodes as representing brain regions, both comparisons between subjects as well as comparisons of different kinds of networks (e.g., structural vs. functional) are feasible (Rubinov and Sporns, 2010).

3 Evolution of Neural Systems

While organisms adapt to their environment, their solutions are constrained by previous solutions that were found during evolution. For example, the extracellular concentration of salt in humans is the same as in the oceans, despite humans living on land. In addition, for the same problem, solutions may differ. The eyes of mammals and the octopus, while using the same laws of optics for seeing light, have a different anatomical organization. As for other aspects of biology, it is useful to look at brain networks in terms of their evolution (Striedter, 2005). Within the last three decades, we have started to develop pictures of the global connectivity, at varying resolution, of the nervous systems of a number of phylogenetically disparate species. The archetypal "connectome" to be elucidated was that of the hermaphrodite form of the roundworm *Caenorhabditis elegans* (White et al., 1986; Durbin, 1987; Cook et al., 2019), which has a relatively small nervous system allowing for elucidation of a complete wiring diagram. Since then, we have started to discover mesoscale connectomes of the much more complex brains of the pigeon (Shanahan et al., 2013), rat (Burns and Young, 2000), mouse (Oh et al., 2014), cat (Scannell et al., 1995), and rhesus monkey (Felleman and Van Essen, 1991). These species live in different habitats, on water, on land, or airborne, but is this also reflected in a specialized organization of brain connectivity? Even if the functional requirements were similar, did evolution come up with different solutions, as it did for the anatomy of the eye in cephalopods (such as the octopus) and vertebrates?

3.1 Nerve Nets—Cnidaria

There are controversies over which metazoans are the most basal, but according to the conventional view of animal phylogeny, the most ancient metazoans that show neural networks are Cnidaria (such as jellyfish). These animals show a diffuse two-dimensional

12 Neurodevelopmental Disorders

12.1 Overview

During normal brain development, long-distance connections, hubs, and small-world and modular features are preserved to yield a balance of integrated and separated information processing. Consequently, any changes in these crucial features might be linked to the cognitive deficits that we observe for developmental brain disorders. There is a growing literature on changes in both global features and individual connections in brain disorders, with *pathoconnectomics* (Rubinov and Bullmore, 2013) being one term to describe the network neuroscience of these conditions. Within this chapter, we look at neurodevelopmental conditions where behavioral symptoms arise within the first 40 years of life.

Studies in both structural and functional connectivity reported aberrant connectivity possibly caused by imperfect maturation of a brain network in neurodevelopmental disorders such as schizophrenia, the autistic spectrum, and epilepsy. It is important to note that altered features could either be linked to cognitive deficits observed in these diseases or, in contrast, be beneficial alterations that compensate for disruptive changes elsewhere in the network.

Recent efforts to understand brain network changes have focused on deviations of global network features from healthy controls. For functional connectivity, a deviation from a small-world architecture, moving either toward a more random or a more regular (lattice) organization, was proposed to be linked to cognitive and psychiatric disturbances (Reijneveld et al., 2007). Related to global information flow, it was proposed that reductions in brain connectivity can lead to more information being routed through hubs. In turn, this could lead to an "overload" and, as a consequence, a failure of hub nodes leading to the observed deficits in brain function (Stam, 2014).

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