Fundamental Concepts and Methods in Network Neuroscience

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Understanding brain connectivity is now a major focus of the human brain imaging community. The widespread use of data from the Human Connectome Project (HCP), combined with new releases from related projects, such as the developmental, lifespan, and disease-related HCPs, mean that researchers require training in sophisticated analytic techniques that are not typically part of standard training programs. Many of these approaches are not "off the shelf" and require deep understanding of their subtleties for valid application. Critically, connectivity analysis is no longer an exotic approach used only by expert practitioners; it is now a standard part of most brain imaging analyses. It is therefore critical to ensure that researchers completely understand the strengths and limitations of their analytic tools to promote rigorous and robust science.

This workshop will provide attendees with the unique opportunity to learn the pros, cons, and practical considerations of network neuroscience from experts in the field. As the field transitions to a post-HCP era in which connectivity analysis is the norm, the concepts and methods covered by this workshop will be an essential part of any neuroimager's training.

Objective

At the end of this workshop, attendees will understand:
- the strengths and weaknesses of different methods for parcellating the brain and defining network nodes;
- how to quantify and interpret different measures of structural and functional connectivity;
- how to define network communities and hubs, characterize communication processes on networks, and respect limitations of current analytic methods;
- appropriate techniques for statistical inference on networks;
- how to use both graph theoretic and biophysical models of brain network dynamics; and
- how to conduct multimodal analyses to gain greater insight into network organization

Target Audience

Our target audience includes neuroscientists trained in biological or psychological sciences who have had little prior exposure to graph theory, as well as individuals with a more quantitative background who have knowledge of the area and are interested in how graph theory can be applied to characterize neural networks. The breadth of topics covered in the workshop means that it is suitable for people with varying levels of experience.

Presentations

Basic concepts of network neuroscience

Nervous systems are complex, interconnected networks showing elaborate organization over multiple spatial and temporal scales. A diverse array of imaging techniques is available for interrogating different aspects of neural structure and dynamics at each scale. Integrating information from these diverse datasets and measurement techniques is a major challenge for modern neuroscience and is an essential step towards developing coherent models of brain function. Network neuroscience provides a unified, common language for making sense of such diverse data because it renders the measured system in its most abstract form: a network of nodes connected by edges. Nodes represent processing elements of the system, and could correspond to cells, cell populations, or macroscale brain regions. Edges represent some measure of structural or functional interaction between nodes, regardless of the spatial or temporal scale at which that interaction occurs. Abstracting the system in this way not only provides a common way of representing different nervous systems, but it also offers a rich repertoire of tools and measures from graph theory and network science that can be used to understand different aspects of network organization and dynamics. In this talk, I will explain some of the fundamental concepts of network neuroscience, discuss different approaches to building graph models of brain networks, and outline some of the key considerations that must be made to ensure valid interpretation of analysis results. An understanding of these issues provides a necessary foundation for the use of more advanced topics covered throughout the workshop.

Presenter

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Defining network nodes: how to best represent the brain?

At functional MRI measurement resolution, it is possible to apply network neuroscience methods to study functional connectivity patterns between every possible pair of voxels. However, the voxel unit is meaningless in relation to neuroanatomy, and the resulting 'dense connectomes' are computationally demanding and challenging to interpret. Therefore, it is common to study functional connectivity using a lower-rank representation of the brain as a set of functional nodes. A node consists of a group of voxels that can together be considered as one functionally homogeneous unit and represented by a single timeseries. Many different representational approaches for node definition are available, and the choice of method has important implications for network neuroscience results and interpretation that are rarely explicitly stated or even considered. This talk provides a critical overview of different node definition methods such as hard parcellations (functional vs anatomical atlases), weighted parcellations, and gradients. A key focus of this talk is to clearly lay out the challenges and trade-offs

involved in node definition. Considerations such as within-subject and between-subject variability, functional heterogeneity and multiplicity, representational ambiguity, and dimensionality will be discussed. OHBM's Audience Response System will be used to engage the audience in a discussion on how one should decide the best representation of the brain for a specific research question.

Presenter

Janine Bijsterbosch, Washington University in St Louis Saint Louis, MO
United States

Functional connectivity methods and measures

This lecture will introduce the concept of functional connectivity to describe coordinated activity in different brain areas. There are a number of ways that functional connectivity can be measured, and each has advantages and disadvantages for a given research question. Metrics such as Pearson correlation, partial correlation, independent component analysis, and coherence will be described and demonstrated. The lecture will begin by focusing on average functional connectivity measurements, then expand to consider methods that capture time-varying aspects of functional connectivity. An overview of the decisions that must be made for whole-brain analysis of functional connectivity (parcellation, overlapping of networks) will be presented as background for the remainder of this educational course. In addition to discussing the mechanics of measuring functional connectivity, this lecture will also examine its interpretation. The role of external inputs (whether residing within the brain or arising from physiological processes or environmental stimuli) will be demonstrated, and mitigation of nuisance variables will be briefly described. An overview of the lingering controversy over global signal regression will be given, highlighting both advantages and disadvantages of the practice. Finally, some considerations for measuring functional connectivity at different scales (from layers to networks) will be presented as an illustration of these concepts.

Presenter

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Quantifying structural connectivity

Estimation of the macroscopic structural connectome of the brain can be performed using diffusion MRI tractography[1]. While the fundamental principles of this technology are relatively simple, there is a wide array of technical limitations of which any researcher must be aware, and state-of-the-art developments for which uptake is strongly advocated. This session will present a breakdown of the requirements for the robust and quantitative reconstruction of brain structural connectomes in their most fundamental form. While attendees' attention will be drawn to relevant technologies, focus is placed on understanding of the complexities and challenges of structural

connectome construction, giving attendees the ability to critically assess the various technologies in the field and accurately contextualise them within the overall reconstruction and quantification framework. Firstly, the problem of structural connectome construction is decomposed to the challenge of quantifying some measure of white matter structural connectivity between two grey matter regions of interest; construction of the full structural connectome is simply the repetition of this process for all possible pairs of grey matter parcels. Following this, the four fundamental requirements for such measurement to be robust and meaningful are presented using the aptly-named acronym TRAQ: Trajectories; Reconstruction density; Attribution; Quantification (summary details below). Each of these presents an opportunity for audience engagement to assess knowledge of existing software tools / models / methods and to challenge pre-conceptions or heuristics. 1. The trajectories of estimated white matter connections must be faithful with respect to the underlying fibre bundles. Satisfying this requirement is typically broken into two parts: an appropriate mathematical model must be applied to the diffusion MRI signal in order to estimate local fibre orientations in each image voxel[2,3]; a tractography algorithm is responsible for reconstructing macroscale white matter fibre pathways based on these local fibre orientation estimates[4]. 2. The reconstruction density of the tractogram must be sufficient to adequately mitigate the intrinsic variance of the reconstruction process[5,6]. 3. The attribution of reconstructed trajectories to particular constituent parts of the network must be robust and reflective of the underlying biology. While oft overlooked, the algorithmic mechanism by which individual streamlines are assigned to those parcels constituting the nodes of the brain network can be ill-defined, and may have severe consequences for analyses if not performed in an appropriate manner[7]. This should be addressed both during tractography itself, by constraining the reconstruction according to the underlying biology[8], as well as during connectome construction[9]. 4. The quantitative value ascribed to each connection within the network must have some biological relevance. It is well known (and regularly wilfully overlooked) in the field of diffusion MRI that streamlines count cannot be used as a quantitative measure of end-to-end connection density[10]. To circumvent this, many instead sample the value of some quantitative measure within the spatial extent of each pathway; this however inherits the limitations of whichever underlying measure is used (e.g. the Fractional Anisotropy (FA) of the diffusion tensor model[2]). A new class of “semi-global” tractogram processing methods has emerged in recent years, which directly address the underlying source of the non-quantitative nature of classical streamlines tractography, thus providing quantitative estimates of connection density in a computationally feasible timeframe[11-14]. In some contexts it is also necessary to ensure that the derived quantitative metric be directly comparable between subjects, which in some instances requires explicit consideration[15]. Construction of brain networks using diffusion MRI tractography depends on a very large number of algorithmic processing steps, for almost none of which there is a consensus among experts in the field. This session will familiarise attendees with the demands of such analyses in their most fundamental, rudimentary form, thus improving awareness and enabling critical assessment of the software tools available. References [1] Hagmann, P.; Cammoun, L.; Gigandet, X.; Meuli, R.; Honey, C. J.; Wedeen, V. J. & Sporns, O. Mapping the Structural Core of Human Cerebral Cortex. PLoS Biology, Public Library of Science, 2008, 6, e159 [2] Tournier, J.-D.; Mori, S. & Leemans, A. Diffusion tensor imaging and beyond. Magnetic Resonance in Medicine, Wiley Subscription Services, Inc., A Wiley Company, 2011b, 65, 1532-1556 [3] Jeurissen, B.; Leemans, A.; Tournier, J.; Jones, D. K.; Sijbers, J. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Hum. Brain Mapp, 201

Presenter

Robert Smith, PhD, The Florey Institute of Neuroscience and Mental Health Melbourne, Victoria Australia

Connectome Thresholding, Inference and Null Networks

Once a brain network is mapped, before further analyses can be undertaken, researchers must make decisions about: how to perform network thresholding, if at all; what kind of methods to use for network inference tasks, such as testing for group differences; and, how to best benchmark graph-theoretic measures based on null networks. This session aims to provide attendees with knowledge to make informed decisions about these important methodological choices in connectome analysis. The session will begin with an introduction to network thresholding, primarily focussing on commonly used density and weight-based methodologies, but also introducing local thresholding methods, such as the disparity filter. Next, attendees will be introduced to the utility of null networks in determining whether a connectome's topological organization is more ordered than expected due to chance. The Maslov-Sneppen algorithm will be introduced and the important relationship between geometry and topology will be considered. The last topic of the session is connectome inference. Attendees will be introduced to various statistical tools for performing inference at the level of connections, nodes and whole connectomes. Time permitting, a live demonstration of one of these tools will be provided. At the completion of the session, attendees will have relevant knowledge, and know where to locate resources, to threshold, benchmark and perform statistical inference on connectomes

Presenter

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Spreading and influence in networks

A central question for connectomics is how the topology of brain networks supports neural signalling and inter-regional communication. The efficiency and integrative capacity of brain networks is commonly estimated in terms of shortest path length, which assumes that optimally short paths are exclusively selected for communication. In contrast to shortest paths, alternative models conceptualize neural signaling as a structurally-guided diffusive process. Altogether, these models can be thought of as forming a spectrum, depending on how much knowledge or information is imparted on the system. When neural elements have perfect knowledge of the global topology, they may take advantage of the shortest path architecture, while the absence of such information potentiates random diffusion of neural signals. Interposed between these extremes are a rich set of communicability models that take advantage of path ensembles and allow near-optimal alternative routes. Importantly, the centrality of individual nodes and their capacity to influence the rest of the network strongly depends on the spreading dynamics taking place on the network. By considering spreading dynamics, we create a rich taxonomy of hub types and roles that can be related to cognitive function and dysfunction. During this talk, I will present a conceptual framework for studying communication in structural and functional brain networks. I will focus on guided examples of how these measures should be implemented and interpreted. Each section of the talk will close with an audience quiz. Finally,

I will give an overview of how these models can be applied to study cognition, development and disease.

Presenter

Bratislav Misic, McGill University
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Modules in structural and functional brain networks

The human brain can be modeled as a network of nodes and edges that represent brain regions and structural/functional connections, respectively. Computational tools from network science and graph theory can then be used to analyze brain network data, offering insight into the brain's organization and function. While network analysis has helped characterize local and global patterns of brain connectivity, it has proven especially conducive to our study of the brain's meso-scale structure. Meso-scale structure refers to divisions of a network's nodes and edges into meaningful clusters. Clusters highlight a system's functional units, circuits, or pathways, and offer a coarse-grained view of its organization. While there are many types of meso-scale structure, the most widely studied variety is so-called modular structure, in which clusters correspond to internally dense sub-networks referred to as "modules." Within the field of network neuroscience, modular structure has taken on particular significance. Modules are thought to engender specialized brain function, to support cost-efficient wiring, and to confer robustness to perturbations. Recent studies have reported links between variation of the brain's modular structure and cognitive load, disease state, and development. Despite its potential, the study of modular structure in empirical brain networks has proven challenging, due largely to the fact that the brain's ground truth modules are unknown. Instead, modules are detected algorithmically, an approach that introduces arbitrary processing decisions, free parameters, and algorithmic biases. In this talk, I will review brain network meso-scale structure, in general, and modular structure, in particular. I will describe the present state of research in this area and I will survey current methodologies for the detection and characterization of modules in brain networks, focusing on the popular method "modularity maximization" and its application to both static and time-varying brain connectivity. I will discuss common pitfalls associated with the use of modularity maximization and offer strategies for successfully mitigating these factors. These sub-topics including guidelines on how to fix the values of free parameters, the compatibility of modularity maximization with signed and weighted networks, and appropriate null models for comparison.

Presenter

Richard Betzel, Indiana University, Bloomington Bloomington, IN
United States

Modeling the brain as a multilayer network

Brain networks are measured using multiple modalities, are often compared between individuals or groups, are task and state dependent, and evolve over time. Multilayer networks are therefore a natural choice to describe the evolution and interactions between network elements due to their ability to capture the complexity of multi-modal, multi-scale, spatiotemporal data sets. In this interactive talk, we will explore different methods for

constructing multilayer networks, and as a group, we will map different types of neuroimaging data onto the multilayer framework. Further, I will describe the types of network statistics that can be measured in multilayer networks and discuss the types of questions that neuroscientists can address using multilayer modeling. Finally, I will briefly present some recent examples of how multilayer network analysis has been used to gain insight into a multitude of different areas including learning, task performance, disease states, structure-function relationships, and brain network evolution. The lecture will close with a list of resources for participants to further explore the field of multilayer brain network modeling.

Presenter

Ann Sizemore, University of Pennsylvania

Multi-modal connectomics: combining micro- and macro- connectome data

The human brain comprises a complex network organized across several scales of organization: At the microscale level, the protein fingerprint of a region describes the local molecular architecture, with neurons and their axons, dendrites and synapses forming the fabric for local circuitry. In turn, at the macroscale level, these brain regions are interconnected by long-range white matter connections and functional interconnections forming large-scale anatomical and functional networks. Recent advances have made it possible to combine and integrate these different sources and scales of information at the connectome level. In this talk, we will discuss the field of 'multimodal connectomics', the multidisciplinary field that brings together data from different levels of nervous system organization together to form a better understanding of multi-scale relationships of brain structure, function, and behavior in health and disease. We will talk about the combination and integration of several fields of 'omics' with connectomics, discussing exemplary multiscale neuroscience studies that illustrate the importance of studying cross-scale interactions among the genetic, molecular, cellular, and macroscale levels of brain circuitry and connectivity and behavior. We will discuss in detail available multi-modal datasets and how to combine them with structural and functional MRI connectomics in practice. We will discuss the availability of these datasets, how to use them in the context of MRI, and discuss examples of online platforms to make a quick start in the field of multi-modal connectomics. We will discuss the practical challenges, current limitations and future directions of multimodal connectomics.

Presenter

Martijn van den Heuvel, VU Amsterdam Amsterdam
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The Virtual Brain simulation platform: Inferring principles of network interactions underlying cognition

The challenge in studying the brain as a complex adaptive system is that complexity arises from the interactions of

structure and function at different spatiotemporal scales (Deco et al. 2017). Modern neuroimaging can provide exquisite measures of structure and function separately, but misses the fact that the brain complexity emerges from the intersection of the two. Here is where computational modelling of brain networks can help. Models that simulate different combinations of subordinate features of behaviour of a complex system that often can only be measured invasively (e.g. local population dynamics and long-range interactions) identify the combination of features that most likely give rise to emergent behaviour that often is observable noninvasively (e.g. EEG, MEG, fMRI) - and importantly those that are less likely. We can exploit the power of large-scale network models to integrate disparate neuroimaging data sources and evaluate the potential underlying biophysical network mechanisms. This approach is now feasible because of the developments in a whole-brain simulation platform, TheVirtualBrain (TVB). TVB integrates empirical neuroimaging data from different modalities to construct biologically plausible computational models of brain network dynamics. TVB is a generative model wherein biophysical parameters for the level of cell population activity and anatomical connectivity are optimized/fitted so that they generate an individual's observed data in humans (Ritter et al 2013), macaques (Shen et al 2019) or rodents. The inferences about brain dynamics, complexity, and the relation to cognition are thus made at the level of the biophysical features (e.g., balance of excitation and inhibition in a cell population) that generated the observed data (Schirner 2018), rather than particular features of the data (e.g. FC). Through extended simulation, the TVB modeling platform allows for a complete exploration of dynamics that are consistent with a particular empirically-derived neural architecture. This exploration can span the dynamics that have been observed empirically and those that are not observed but are plausible potentials. This potentiality is directly related to complexity, in that complex systems will engender more options in the production of similar behavior, which also imparts more resilience (Tononi et al 1999). Potential configurations, or hidden repertoires (Ritter et al 2013), may also underlie broader concepts of "cognitive reserve" (Stern 2003), which has been used to describe the ability of some persons to maintain high levels of cognitive function in aging and also in the face of damage or disease. Deco G, Kringelbach ML, Jirsa VK, Ritter P (2017) The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. Sci Rep 7:3095 Ritter, P., M. Schirner, A. R. McIntosh and V. K. Jirsa (2013). "The virtual brain integrates computational modeling and multimodal neuroimaging." Brain Connect 3(2): 121-145. Schirner M, Rothmeier S, Jirsa VK, McIntosh AR, Ritter P (2015) An automated pipeline for constructing personalized virtual brains from multimodal neuroimaging data. Neuroimage 117:343-57 Schirner M, McIntosh AR, Jirsa V, Deco G, Ritter P (2018) Inferring multi-scale neural mechanisms with brain network modeling. eLife 7:e28927 Shen K, Bezgin G, Schirner M, Ritter P, Everling S, McIntosh AR (2019) A macaque connectome for large-scale network simulations in TheVirtualBrain Nature Scientific Data doi.org/10.1101/480905 Stern Y (2003) The concept of cognitive reserve: a catalyst for research. J Clin Exp Neuro 25:589-93 Tononi G, Sporns O, Edelman GM (1999) Measures of degeneracy and redundancy in biological networks. PNAS 96:3257-3262

Presenter

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