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Review of Connectivity and Dynamics of Neural Information Processing

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ABSTRACT

Current literature on neural connectivity and dynamics, or equivalently, structure and function, is systemically reviewed in the current article. Based on fMRI data, I have specifically discussed how changes in the connectivity of a neural network affect the spatiotemporal network dynamics qualitatively. I have also considered local dynamics at the network nodes, which include fixed point dynamics, and oscillatory and chaotic dynamics. These properties are represented by the connectivity matrix such as its statistics, symmetry, and translational invariance. Since the connection topology changes when anatomical scales are traversed, the corresponding network dynamics also change. Consequently, different types of networks are encountered at different levels of neural organization. Neurostatistics contribute to elucidating neural connectivity.

Key words : Change-point, Connectivity, Covariance, fMRI data, Neural network, Neurostatistics

Introduction

Recent advances in non-invasive and cutting-edge neuroimaging have enabled the measurement of connections between distant regions in the living human brain, thus, establishing a new field of research, i.e., human connectomics. Different imaging modalities allow the mapping of structural connections (axonal fiber tracts), as well as functional connections (correlations in time series). Individual variations in these connections may be related to individual variations in behavior and cognition. Connectivity analysis has already led to several new insights about brain organization.

How far will the field be able to progress in deciphering long-distance connectivity patterns and in relating differences in connectivity to phenotypic characteristics in mentality, health, and disease?

In this review paper, I will discuss methods to study brain connectivity and its challenges, and excellent prospects for continuing improvements in data acquisition and analysis related to connectivity.

Preliminary functional magnetic resonance imaging (fMRI) studies were considered a success when any cortical activation was detected using full-field or hemifield visual stimulation [1,2]. Nevertheless, it was apparent from the outset that fMRI offered great potential for elucidating human brain function; developing it to the point of mapping the cortical areas.

Spontaneous fluctuations in the blood-oxygen-level dependent (BOLD) signal in fMRI were an early clue that this method might enable exploration of functional connectivity (FC). However, there was a lack of promising methods to explore long-distance connections in the human brain [3].

Two methods, i.e., diffusion-weighted MRI (dMRI) and resting-state fMRI (R-fMRI), can be used to make strong, albeit indirect, inferences about brain connectivity. The first,

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dMRI, estimates the orientation of fiber bundles in white matter, based on anisotropies in water diffusion. It provides inputs for tractography analyses that can be used to infer 'structural connectivity' (SC) between gray matter regions [4,5]. The second method, R-fMRI, uses temporal correlations in the slow fluctuations of the BOLD fMRI signal to infer FC. R-fMRI serves as an indirect, but nonetheless invaluable, indicator of gray-matter regions that interact strongly and, in many cases, are connected anatomically [6-11].

A growing number of studies have revealed important insights through systematic analyses of whole brain connectivity using fMRI. These include analyses of brain networks, modularity, and hubs, as well as the demonstration of connectivity-based parcellation [12-18].

Despite their promise and potential, the current methods for assessing structural and functional connectivity face serious technical limitations at multiple levels. Analyses of SC must cope with a high incidence of false positives and false negatives, combined with an inherent difficulty in making quantitative estimates of connection strength [5,19,20]. Analyses of FC are limited by the indirect nature of neurovascular coupling to neural activity and the presence of confounding long-range correlations of vascular origin [21]. In addition, functional correlations reflect more than direct anatomical connectivity [8], as common inputs and/or interactions can influence them, via serially connected areas. Both approaches also face limitations imposed by the difficulty of accurately parceling the brain into functionally distinct subdivisions (parcels) and in aligning data across subjects (inter-subject registration).

In this review, I survey the current state-of-the-art human connectomics method, including a comparison of techniques for mapping brain connectivity, the use of connectivity data to discern functionally specialized regions, the relation of structural to functional connections, and the use of network analysis measures to quantitatively characterize the architecture of the human connectome.

Neurobiological Considerations and Constraints

Human brain circuitry is extraordinarily complex by any measure. It is also probable that specific aspects of the brain's complexity may not yet be widely recognized. Behrens and Sporns [22] previously discussed human connectomics and some its properties was be listed as follows in [23,24]:

1. Scales of analysis

In vivo neuroimaging enables exploration of connectivity at a scale that is fine-grained, relative to overall brain dimensions; however, it is extremely coarse in relation to the brain's cellular components. At a cellular level, cerebral neocortex contains an average of approximately 90,000 neurons per mm^2 surface area, while white matter contains approximately 300,000 axons/mm^3. The density of synapses, however, is far greater ($310^8/mm^3$). Hence, even with the most optimistic scenarios for improved spatial resolution, a vast gulf will remain between the macro-connectome domain of in vivo neuroimaging and the microconnectome domain dealing with the 3D arrangement of neurons, axons, dendrites, synapses, and glia.

2. Brain parcellation

The human brain contains hundreds of distinct parcels that differ in their architecture, connectivity, and/or function, yet our understanding of their layout is incomplete. The analysis of dense connectomes will be a major thrust of human connectome studies. However, many analyses will capitalize on more compact representations provided by 'parcellated connectomes,' which describe average connectivity between different brain subregions (parcels). It is obviously important to have parcellation schemes that are as accurate as possible, so that connectivity patterns can be related to functionally meaningful parcels. The challenges in meeting this objective differ for each brain region.

3. Long-distance anatomical connectivity

Principles of long-distance connectivity determined in non-human primates have major and somewhat unexpected implications for understanding the human connectome. There is very little solid evidence on the detailed pattern of long-distance connections between gray-matter regions. For the cerebral cortex, quantitative analyses of cortico-cortical connections from retrograde tracer injections in the macaque are especially informative. It is of paramount importance to have in vivo imaging methods that can chart complex connectivity patterns quantitatively and with high spatial fidelity. This will require improvements in sensitivity, spatial resolution, acquisition time, and analysis methods.

4. Axonal trajectories

Information about the trajectories of fiber bundles and individual axons within white matter is critical for the analysis

and interpretation of SC using diffusion imaging, yet, surprisingly, little is known about these trajectories from animal studies.

5. Functional connectivity and neurovascular coupling

The complex nature of neurovascular coupling, including the spatial relationship between BOLD fMRI signals and underlying patterns of neuronal activity, has a major impact on the interpretation of FC studies.

6. Individual variability

Although the high degree of individual variability, especially of the convoluted cerebral cortex, poses major challenges for connectome analyses, it also offers a great opportunity for exploring the neural basis of individual differences over a wide range of behavioral phenotypes. The nature and magnitude of individual variability are markedly different for each major brain structure. Variability is greatest for the cerebral cortex, where it involves large differences in the pattern of cortical convolutions, in the location of cortical areas relative to these convolutions, in the size of each area, and presumably also in the patterns of long-distance connectivity.

The fidelity with which data are acquired and analyzed is one of the many differences between human brain macroconnectomics and genome sequencing. Genome sequencing is extremely accurate (99.99% or better), making it feasible to distinguish differences between individuals at the single nucleotide level. However, this is coupled with a very low level of nucleotide diversity across individuals (approximately 1 part in 1000). Although the accuracy with which human brain connectivity can be quantitatively assessed is vastly inferior to genome sequencing, the degree of individual variability in connectivity patterns is likely to be far greater. Each cortical area varies in surface area by two-fold or more across individuals and the strength of pathways between a pair of cortical areas can vary by one or two orders of magnitude [25].

The expected sensitivity and reliability in comparing connectomes across individuals and relating connectivity to behavioral phenotypes and genetic differences, however, is difficult to estimate. Nonetheless, despite these caveats, I am optimistic that major insights will emerge from mining of The Human Connectome Project (HCP) data, which will include the following: (i) a far more accurate charting of brain parcellations (particularly neocortical and cerebellar parcels), brain networks, and their dynamics; (ii) a quantitative characterization of network variability across individuals; and (iii) correlations between behavioral phenotypes and brain networks that provide a deeper understanding of the neural basis of individual variability. Such insights could be related to working memory, perceptual categorization, emotion, personality, or many other phenotypes that are available for data mining.

A Data Acquisition Perspective

Recent advances in neuroimaging have made it feasible to examine human brain connectivity systematically and across the whole brain in a large number of individuals. In a previous publication, Van Essen et al. [24] focused on data acquisition and analysis for further connectivity analysis.

A deeper understanding of human brain connectivity and its variability will provide valuable insights into what makes us uniquely human and accounts for the great diversity of behavioral capacities and repertoires in healthy adults. It will provide a critical baseline of knowledge for future studies of brain connectivity during development and aging and in a myriad neurodevelopmental, neuropsychiatric, and neurological disorders. Further, the data acquisition strategies and analysis methods developed under the auspices of the HCP will be freely shared and will benefit many other projects. Increasing both the commonality and sensitivity of methods used to characterize human brain connectivity across different studies will enhance our ability to detect subtle links between genetics, human brain connectivity patterns, and behavioral variation.

A key objective is to understand inter-individual variability of brain circuits, including its genetic bases and its relation to behavior, rather than merely aiming to determine the average, or typical connectivity in healthy adults.

Connectivity and Dynamics of Neural Information Processing

Jirsa [26] systematically reviewed the current literature on neural connectivity and dynamics, or equivalently, structure and function, with a focus on how changes in connectivity affect the spatiotemporal network dynamics qualitatively. To date, the three major criteria of comparison in previous studies have been the local dynamics at the network nodes, the presence of time delays, and properties of the connectivity

matrix. In the current review, I sketched existing knowledge, or more importantly, the limits thereof, for each type of network model.

Temporal dynamics and spatial distribution of neural activity is a function of the underlying cortical network connectivity. The connectivity has a major impact on the direction of information processing. Further, changes in brain connectivity can be used as a mechanism for learning. The effective geometry in which the dynamics of a system evolves is determined by its connectivity matrix, together with the boundary conditions of the system.

A rapidly evolving topic of research is the study of complex networks that focus on the statistical mechanics of network topology and the generation of such network topologies. Network topologies are characterized from the perspective of statistical mechanics by the number of nodes N and the number k of connections (or edges) to other nodes.

Current research in the field of synchronization of dynamic network systems primarily focuses on the two extremes of a range as follows: from networks of identical nodes with complex intrinsic dynamics and arbitrary connectivity, to networks of non-identical nodes with complex intrinsic dynamics with constrained connectivity. The interplay between connectivity and dynamics, or equivalently between structure and function, has been studied further to extend further knowledge.

This classification is important because neural information processing is not localized in one small area of the brain. Further, one class of network model cannot be used to describe it. Moreover, there is an anatomical hierarchy of connection topologies that require different network models on different levels of organization. For this reason, the study of neural information processing naturally led to the study of networks of networks, rather than to the study of a single network.

Functional Connectivity Based on Covariance Structure

Functional neuroimaging has experienced an explosive growth in recent years. Currently there several different imaging modalities that allow researchers to study physiological changes that accompany brain activation. Each of these techniques has advantages and disadvantages and each provides a unique perspective on brain function.

Since the mid-1990s, neuroscientists, statisticians, and computer scientists have increasingly used fMRI for FC studies, since it opened a novel method to explore the functional network of human brain with relatively high resolution. fMRI is a noninvasive technique for studying brain activity. During an fMRI experiment, a series of brain images are acquired while the participant performs a set of tasks. Changes in the measured signal between individual images are used to make inferences regarding task-related activations in the brain. fMRI has provided researchers with unprecedented access to the brain in action and, in the past decade, has provided countless new insights into the inner workings of the human brain. There are several common objectives in the analysis of fMRI data. These include localizing regions of the brain activated by a task, determining distributed networks that correspond to brain function and making predictions about psychological or disease states. Each of these objectives can be approached through the application of suitable statistical methods, and statisticians play an important role in the interdisciplinary teams that have been assembled to tackle these problems. This role can range from determining the appropriate statistical method to apply to a dataset, to the development of unique statistical methods geared specifically toward the analysis of fMRI data. Given the advent of more sophisticated experimental designs and imaging techniques, the role of statisticians promises to increase in the future.

Friston et al. [27,28] developed a time-series model for fMRI data. Goutte [29] proposed clustering methods to detect similarities in the activation between voxels in fMRI time-series datasets. Worsley et al. [30] proposed a method for the statistical analysis of fMRI data that seeks a compromise between efficiency, generality, validity, simplicity, and execution speed. Their method used simple bias reduction and regularization for voxel-wise autoregressive model parameters, with the combination of effects and their estimated standard deviations, across different runs/sessions/participants via a hierarchical random effects analysis using EM algorithm. Sophisticated time-series modeling was anticipated and further developed afterwards.

In this section, I will survey the covariance estimation research for FC. Examination of functional interactions through effective connectivity requires the determination of three distinct levels of information as follows [27,28]: (i) the regions involved in the process and forming the spatial support of the network, (ii) the presence or absence of interactions between each pair of regions, and (iii) the directionality of the existing interactions. The two main methods that were developed, i.e., structural equation modeling (SEM) and dynamical causal modeling (DCM), require precise prior information to be used.

Marrelec et al. [31] introduced partial correlation analysis to measure the statistical dependencies between two regions after removing the confounding effects of all other regions, and suggested a Bayesian analysis, which allows the estimation and testing of partial statistical dependencies between regions without prior model of the underlying functional interactions. Although partial correlation circumvents the challenge of prior selection of a structural model with SEM and DCM partial correlation still needs to be bridged to provide data-driven investigation of structural models i.e., interaction directionality.

Recent study of dynamic connectivity uses the covariance matrix and its function instead of correlations. Estimating the eigenvalues of a population covariance matrix from a sample covariance matrix is a problem of fundamental importance in multivariate statistics. The eigenvalues of covariance matrices play a key role in many widely used techniques, particularly principal component analysis (PCA). Friston et al. [32] utilized PCA for positron emission tomography data analysis. Independent component analysis was also popular for fMRI data analysis, mainly due to its potential to account for unknown, yet structured, spatiotemporal processes in neuroimaging data [33-35]. Further, probability independent component analysis could also efficiently and accurately extract signals of interest in the spatial, temporal, and subject/session domain [10]. In many modern data analysis problems, statisticians are faced with large datasets, where the sample size, n, is of the same order of magnitude as the number of variables, p. Random matrix theory predicts that in this context, the eigenvalues of the sample covariance matrix are not good estimators of the eigenvalues of the population covariance. The Marcenko-Pastur equation can be used to better estimate the eigenvalues of large dimensional covariance matrices [36]. For large dimensional case, Friedman et al. [37] solved the problem of estimating sparse graphs by a lasso penalty applied to the inverse covariance matrix using a coordinate descent procedure for the lasso. This covariance estimation can be used to describe the FC of the brain. Dynamic connectivity research, based on the covariance structure, is still an active ongoing project.

Intrinsic Brain Connectivity Using Functional Magnetic Resonance Imaging and Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is an extremely sensitive imaging method for detecting and characterizing differences in brain tissue microstructure and organization as a function of pathology, development and aging, and white matter plasticity. It may also be used to estimate trajectories of white matter pathways in the brain.

A recent trend in brain research can best be represented by the term 'brain connectome,' which describes the brain as a large complex network connected by local and inter-regional neurons. In vivo connectome research is mainly explored in terms of anatomical and functional connectivity defined by DTI and R-fMRI, respectively.

Statistical techniques combining fMRI and DTI data, such as anatomically weighted FC (awFC), which was developed by Bowman et al. [38], help describe the functional organization within the human brain. The awFC approach implements a hierarchical clustering algorithm that establishes neural processing networks using a new distance measure consisting of two components, i.e., a primary functional component that captures correlations between fMRI signals from different regions and a secondary anatomical weight reflecting SC probabilities. As DTI approaches continue to advance, they can be incorporated into the statistical analysis including fMRI and may yield higher accuracy.

Several studies show that DTI can produce MRI indices in specific white matter tracts that may be associated with clinical disability in multiple sclerosis, a disease that causes severe motor and cognitive deficits [39-43]. These studies provide important insights into the organization of the brain and the effect of brain disorders. The results of these studies may be used as a tool for the diagnosis and management of patient care, or as surrogate markers in future clinical trials, particularly if they are shown to be pharmacologically sensitive. Huang et al. [44] proposed a hierarchical Bayesian "scalar-on-image" regression procedure, which introduces a latent binary map estimating the locations of predictive voxels and penalizes the magnitude of effect sizes in these abnormal voxels, as an example of predicting clinical disability from DTI images.

Nonetheless, there are still important and unanswered questions and a need for tools that warrant further research in this exciting area of neuroimaging.

Concluding Remarks

Just like cartography of the earth's surface was the domain of intrepid explorers earlier this millennium, charting the structure, function, connectivity, and development of the

human brain (i.e., broadly, brain cartography) is one of the great challenges of the 21st century. There are interesting high-level similarities in the types of technological evolution for both types of cartography.

In a roughly analogous fashion, four major revolutions in cartography of the human brain can be discerned over the past century. The first period involved classical maps of brain architecture and functional organization, which were provided by Brodmann and other anatomists. The second period involved the production of brain atlases. The third period involved maps of brain structure and function, which were acquired using MR-based methods and visualization of brain volumes and surfaces. In the 21st century, neuroscience is entering a new realm in which human brain connectivity can be analyzed using the powerful tools discussed above and visualized using increasingly sophisticated navigational and informatics tools. The continued development of statistical methods that overcome the described challenges [45] are expected to enable discovery of connectivity functions and pathways that explain the brain structure with large parceled information.

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