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Review

Comparing connectomes across subjects and populations at different scales

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ABSTRACT

Brain connectivity can be represented by a network that enables the comparison of the different patterns of structural and functional connectivity among individuals. In the literature, two levels of statistical analysis have been considered in comparing brain connectivity across groups and subjects: 1) the global comparison where a single measure that summarizes the information of each brain is used in a statistical test; 2) the local analysis where a single test is performed either for each node/connection which implies a multiplicity correction, or for each group of nodes/connections where each subset is summarized by one single test in order to reduce the number of tests to avoid a penalizing multiplicity correction. We comment on the different levels of analysis and present some methods that have been proposed at each scale. We highlight as well the possible factors that could influence the statistical results and the questions that have to be addressed in such an analysis.

Contents

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Introduction

The human brain, made up of more than 100 billion neurons that communicate through trillions of connections, is certainly the most complex organ in the human body. This ensemble of tissues, neurons, glial cells, axons and synapses produces our every thought, action, memory, feeling and experience (Philips, 2006). How the different components of the human brain interact is still unknown. Since Ramón y Cajal (1899) discovered that neurons are discrete unitary entities that conduct electrical signals in only one direction from dendrites (input) to the axon (output), neuroscientists have tried to shed light on the underlying substrate of the structurally integrated and functionally specialized regions of the human brain, with the final scope of understanding brain organization and function. Aware of these attempts, and of the challenge posed by formulating a comprehensive map of the anatomical and functional substrate of the human brain, Hagmann (2005) and Sporns et al. (2005) proposed a conceptual framework in which the entire brain structural connectivity was modeled as a network: the connectome.

Due to the innovations in medical imaging and image analysis, and in combination with the quickly developing fields of engineering and image processing, the determination of the interregional brain connectome became feasible. This helped to create a better understanding of the human brain, to quantify rates of variabilities, and to associate defined alterations in structural substrate with brain functional deficits and psychiatric diseases in a non-invasive manner. This relatively simple way of modeling the brain connectivity has been successfully used in the study of diseases such as schizophrenia (Bassett et al., 2008; Fornito et al., 2011; Liu et al., 2008), Alzheimer's disease (He et al., 2008), Parkinson's disease (Wu et al., 2009) and attention-deficit hyperactivity disorder (ADHD) (Sato et al., 2012; Wang et al., 2009b), among others.

Macroscopic brain connectivity can be derived either from morphological diffusion or functional neuroimaging data (e.g., Achard et al., 2006; Cammoun et al., 2012; Daducci et al., 2012; Friston, 2011; Hagmann et al., 2010a; Liu et al., 2008; van den Heuvel and Hulsoff-Pol, 2010). Sporns (2007) writes that "brain connectivity refers to a pattern of anatomical links (anatomical connectivity), of statistical dependencies (functional connectivity) or of causal interactions (effective connectivity) between distinct units within a nervous system." These pairwise relations can be represented either by a connection matrix A, where each cell a_{ij} of the matrix represents a certain measure of connectivity between two regions of interests (ROIs) i and j of the brain or, equivalently, by a network (in the graph theory sense). This is an abstract representation and a simplification of the complexity of the real brain network (Kaiser, 2011). The brain network is a weighted graph $G(V, E, W(E))$ with $|V|$ nodes that correspond to the ROIs, and $|E|$ connections (edges) between the nodes and a weight function that associate to each existing edge e in E, a univariate (or multivariate) weight.

Investigating differences between connectomes of different groups of individuals using connectivity matrices or networks is very attractive and challenging (van Wijk et al., 2010). It raises also a number of problems that investigators need tobe aware of. When summary measures like global clustering coefficient or global efficiency are used, little insight is gained on the details of potential pathological processes, and local phenomena are diluted in the global mean. Exploring in isolation specific connections on the other hand, requires a detailed understanding of the underlying phenomena. Such knowledge is rarely present in neuroscience and does not really require the connectome framework. Finally, exploring blindly all the connections of a network in order to identify potential connectivity differences is problematic since most of the time the number of tests to perform is high, which decreases the power of tests after the multiplicity correction.

The first level considered in brain connectivity studies and comparisons is the global level (Bassett and Bullmore, 2009). A single summary statistic is extracted for each subject and a t-test is usually performed to assess the between groups effect, afterremoving the influence of nuisance covariables. In such studies, several tests are usually performed on the same dataset using different network measures as summary statistics. Despite this multiplicity, no correction is applied in order to avoid theincrease of the rate of false discoveries.

The first attempt to address local statistical analysis in brain networks using a specially-dedicated method, is the method of Zalesky et al. (2010a) called the Network Based Statistic which proceeds by supra-thresholding to identify significantly differentiated connected components between groups. Other statistical methods have been proposed to asses local brain connectivity differences such as the Spatial Pairwise Clustering (Zalesky et al., 2012a), the statistical parametric network (Ginestet and Simmons, 2011) and the Sub-Network Based Analysis (Meskaldji et al., 2011a). These strategies have, however, some limitations as we will show in this review. In these approaches, the multiplicity correction cannot be avoided.

An alternative way to assess differences between groups through connectomes is to adopt a classification approach. The key idea is to extract discriminative features from a training dataset, in order to classify new subjects (Robinson et al., 2010). The classification approach has a completely different framework from the testing approach. Following the Neyman and Pearson formulation of testing, the first concern is to build tests or multiple testing procedures which make "not too many" false discoveries. In this review, we do not discuss the classification approach. However, we refer the reader to the following references: Robinson et al. (2010), Richiardi et al. (2011, in press).

This review is organized as follows. In the section Graph theory and brain networks, we review topological network measures and methods for comparing connectomes at the global level. In the section Local analysis, we review the statistical methods proposed in the literature at the local level with a short review of the most important aspects of multiple testing. We present as well in the Local analysis section, an adaptive method that exploits the positive dependence in brain networks, which control the rate of false discoveries at the level of connections/nodes. Finally, we discuss in the section Discussion: From raw data to brain graphs: what can influence the statistical inference?, the factors that could influence the statistical inference.

Graph theory and brain networks

Topological network measures

In recent years, modeling the human brain as a network has become popular as it is considered as a relatively simple way to characterize the complexity of the human brain connectivity and activity. The connectome and the graph theory frameworks have been increasingly used in the study of human neuroimaging data, especially in the case of neuropsychiatric disorders, as both are thought to formalize questions relative to possible alterations and evolution of the brain connectivity architecture. Indeed, freely available software packages have been introduced to analyze network topology (e.g. Brain Connectivity Toolbox (Rubinov and Sporns, 2010); eConnectome (He et al., 2011); NetworkX (http://networkx.lanl.gov/overview.html); GAT (Hosseini et al., 2012); igraph (http://igraph.sourceforge.net/) and Brainwaver (http://cran.r-project.org)). From this point of view, it seems therefore natural to compare groups of subjects, e.g. healthy versus pathological subjects, in terms of variation of quantitative measures which describe some brain network topological features. It has been shown, for example, that structural and functional brain networks share certain properties of complex networks such as small-world topology, highly connected hubs and modularity (Bullmore and Sporns, 2009).

A wide range of network measures is commonly used to characterize the global organizational principles and the local network properties of the large-scale brain networks. However, the link between graph properties and the brain's ability to segregate, integrate, modularize, process or transmit information is completely unknown.

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