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A two-part mixed-effects modeling framework for analyzing whole-brain network data

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ABSTRACT

Whole-brain network analyses remain the vanguard in neuroimaging research, coming to prominence within the last decade. Network science approaches have facilitated these analyses and allowed examining the brain as an integrated system. However, statistical methods for modeling and comparing groups of networks have lagged behind. Fusing multivariate statistical approaches with network science presents the best path to develop these methods. Toward this end, we propose a two-part mixed-effects modeling framework that allows modeling both the probability of a connection (presence/absence of an edge) and the strength of a connection if it exists. Models within this framework enable quantifying the relationship between an outcome (e.g., disease status) and connectivity patterns in the brain while reducing spurious correlations through inclusion of confounding covariates. They also enable prediction about an outcome based on connectivity structure and vice versa, simulating networks to gain a better understanding of normal ranges of topological variability, and thresholding networks leveraging group information. Thus, they provide a comprehensive approach to studying system level brain properties to further our understanding of normal and abnormal brain function.

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Introduction

Whole-brain functional magnetic resonance imaging (fMRI) network analyses have moved to the forefront of neuroimaging research over the last decade. fMRI measures localized brain activity by capturing changes in blood flow and oxygenation via the blood oxygen level-dependent (BOLD) contrast (Ogawa et al., 1990). These measurements are recorded from cubic subdivisions of the brain roughly a few millimeters in size called voxels. Averaging the BOLD signal time series across voxels within specified regions provides coarser representations. Functional connectivity analysis (FC) examines functional similarities between time series pairs in specified voxels or regions (Sporns, 2010; Biswal et al., 1995; Friston, 1994). Functional brain network analysis serves as a distinct subfield of connectivity analysis in which functional associations are quantified for all n time series pairs to create an interconnected representation of the brain (a brain network). The resulting $n \times n$ connection matrix is generally thresholded to create a binary adjacency matrix that retains "significant" connections while removing weaker ones. Weighted (continuous) network analyses, which we focus on here, have gained traction but still lag behind due to computational and methodological challenges they pose (Telesford et al., 2011; Rubinov and Sporns, 2011; Ginestet et al., 2011). The connection matrix is still often thresholded to remove negative connections (for reasons noted in Telesford et al., 2011; M. Cao et al., 2014; and others) and/or weak connections in the continuous case. A schematic exhibiting this network generation process is presented in Fig. 1.

This emerging area of fMRI brain network analysis allows studying the brain as a system, providing profound clinical insight into the link between system level properties and behavioral and health outcomes (Biswal et al., 2010; Sporns, 2010; Bullmore and Sporns, 2009; Bassett and Bullmore, 2009). The application of network science (an interdisciplinary offshoot of graph theory) has facilitated these analyses and our understanding of how the brain is structurally and functionally organized. Both binary and weighted versions of graph metrics such as degree, clustering coefficient, path length, efficiency, centrality, and modularity serve as common descriptive topological properties of interest. While network science has catalyzed a paradigmatic shift in neuroscience, methods for statistically modeling and comparing groups of networks have lagged behind (Simpson et al., 2013a). These comparisons have great appeal for researchers interested in gaining further insight into complex brain function and how it changes across different mental states and disease conditions. Most current approaches to modeling and comparing brain networks either rely on a specific extracted summary metric (e.g., clustering coefficient) which may lack clinical use due to low sensitivity and specificity, or on mass-univariate nodal or edge-based comparisons that ignore the inherent topological

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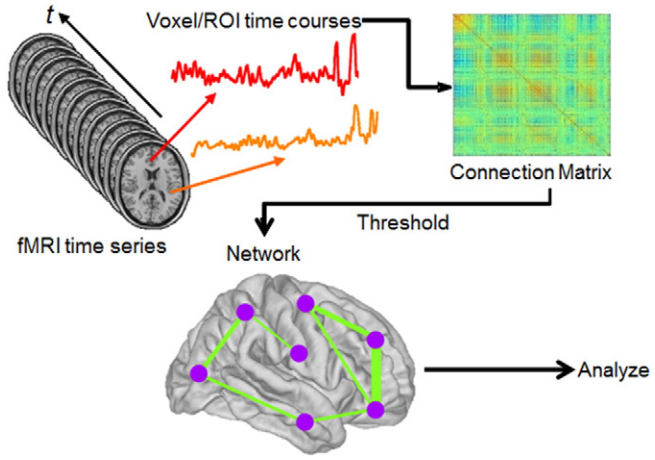

Fig. 1. Schematic for generating brain networks from fMRI time series data (partially recreated from Simpson et al., 2013a; Fornito et al., 2012). Functional connectivity between brain areas is estimated based on time series pairs to produce a connection matrix. A threshold is commonly applied to the matrix to remove negative and/or "weak" connections.

properties of the network while also yielding little power to determine significance (Zalesky et al., 2010; Ginestet et al., 2014). While some univariate approaches like the network-based statistic (NBS) (Zalesky et al., 2010) have proven useful, gleaning deeper insights into normal and abnormal changes in complex functional organization demands methods that leverage the wealth of data present in an entire brain network. This systemic organization confers much of our brains' functional abilities as functional connections may be lost due to an adverse health condition but compensatory connections may develop as a result in order to maintain organizational consistency and functional performance. Consequently, brain network analysis necessitate a multivariate modeling framework that allows assessing the effects of multiple variables of interest and topological network features (e.g., demographics, disease status, nodal clustering, nodal centrality, etc.) on the overall network structure. That is, if we have

$$\text{Data}\begin{cases} \boldsymbol{Y}_i : \text{network of participant } i \\ \boldsymbol{X}_i : \text{covariate information (metrics, demographics, etc.)} \end{cases}$$

we want the ability to model the probability density function of the network given the covariates $P(\boldsymbol{Y}_i|\boldsymbol{X}_i, \boldsymbol{\theta}_i)$, where $\boldsymbol{\theta}_i$ are the parameters that relate the covariates to the network structure.

More recent brain network comparison methods that attempt to better exploit the topological features of network data include the exponential random graph modeling framework (ERGM) (Simpson et al., 2011, 2012), the permutation network framework (PNF) (Simpson et al., 2013b), and the multivariate distance matrix regression (MDMR) framework (Shehzad et al., 2014). While all show promise, they lack the flexibility of the modeling and inferential tools developed for fMRI activation data. The ERGM framework allows efficiently representing complex network data and inherently accounts for higher order dependence/topological properties, but multiple-subject comparisons can pose problems given that these models were originally developed for the modeling of one network at a time (Simpson et al., 2011). Moreover, the amount of programming work increases linearly with the number of subjects since ERGMs must be fitted and assessed for each subject individually (Simpson et al., 2012). Incorporating novel metrics (perhaps more rooted in brain biology) may be difficult due to degeneracy issues that may arise (Handcock, 2002; Rinaldo et al., 2009; O'Malley, 2013). While well-suited for substructural assessments, edge-level examinations remain difficult with these models. Additionally, most ERGM developments have been for binary networks; approaches for weighted networks have been proposed but remain in their infancy (Krivitsky, 2012; Desmarais and Cranmer, 2012). The PNF approach enables comparing groups of brain networks by assessing the topological consistency of key node sets within and between groups. However, it is a strictly inferential (and not modeling) approach, and thus precludes quantifying and predicting relationships between disease outcomes and network structure, and simulating network structure. Unlike the PNF, the MDMR framework allows controlling for confounding covariates in group comparisons via a "psuedo-F" statistic; however, it too lacks the ability to simulate networks or make predictions. It also fails to account for the dependence in connectivity patterns across voxels.

To address the limitations of the current methods, we propose a two-part mixed-effects modeling framework that allows modeling both the probability of a connection (presence/absence of an edge) and the strength of a connection if it exists. Models within this framework enable quantifying the relationship between an outcome (e.g., disease status) and connectivity patterns in the brain while reducing spurious correlations through inclusion of confounding covariates. The models provide a means to test for overall group differences in the strength and probability of network connections, group differences in network topology, and individual edge differences (edge covariates can be easily implemented in the model) while accounting for the complex dependence structures of the networks. They also enable prediction about an outcome based on connectivity structure and vice versa, simulating networks to gain a better understanding of normal ranges of topological variability, and thresholding networks leveraging group information. In short, this multivariate statistical and network scientific fusion approach allows going beyond just reporting an omnibus group comparison p-value and enables a more thorough examination of system level properties.

Moreover, our framework provides the first baseline multivariate brain network modeling approach, from which incremental modifications can be made going forward. As noted, current statistical methods in brain network analysis focus on direct inference, comparing some characteristic of two groups of networks. However, to our knowledge, there is no framework that allows multivariately modeling the probability distribution of (weighted) networks as a function of endogenous (network metrics) and exogenous (demographics, etc.) covariates (i.e., a multivariate multiple regression approach). Thus, no comparable alternatives currently exist. This lack of a baseline modeling framework served as the impetus for our work. In addition to providing more appropriate group comparisons by accounting for the dependence structure of the network and allowing the inclusion of confounding covariates, the power of our approach is that in modeling network distributions, it is the only approach that allows exploring the relationship between covariates and all network connections simultaneously, predicting networks based on participant characteristics, and simulating networks from the modeled distributions. Thus our approach can be seen as providing a needed analytic foundation and a complementary statistical tool to those that have been developed thus far.

For the following discussion of the two-part mixed-effects modeling framework, we describe the motivating data concerning age-related cognitive decline in the next section. We then detail our modeling approach and its utility and use the aging data to illustrate the use of the proposed framework. We conclude with a summary discussion including planned future research.

Materials and methods

Motivating example

Our data come from a prior study that aimed to assess the neurological underpinnings of age-related cognitive decline by examining the effects of aging on the integration of sensory information (Hugenschmidt

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