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Author manuscript *Neuroimage*. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Neuroimage. 2015 June ; 113: 310-319. doi:10.1016/j.neuroimage.2015.03.021.

## 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.

### Keywords

Graph Theory; Connectivity; fMRI; Small-World; Network Model; Mixed Model

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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; Cao et al., 2014; and others) and/or weak connections in the continuous case. A schematic exhibiting this network generation process is presented in Figure 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 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

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

we want the ability to model the probability density function of the network given the covariates  $P(Y_i|X_i, \theta_i)$ , where  $\theta_i$  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 et al. 2009). The study has two age groups, healthy young adults aged 27 + 5.8 years old (n=20) and healthy older adults aged 73 + 6.6 years old (n=19). Three separate conditions of fMRI scans were used, resting, visual (viewing of a silent movie), and multisensory (MS) (visual and auditory - movie with sound), each lasting 5.6 minutes. Further details about these conditions along with additional network analyses can be found in a previous publication (Moussa et al., 2011). For each fMRI scan, blood-oxygen-level dependence (BOLD) contrast was measured using a 1.5T MRI scanner and a whole-brain gradient echo- planar imaging (EPI) sequence with the following parameters:

To process the data, functional scans were normalized to standard brain space with a  $4 \times 4 \times 5$  mm voxel size. Data were band pass filtered (0.00765-0.068 Hz), and motion parameters, global signal, and mean white matter (WM) and cerebral spinal fluid (CSF) signals were regressed from the imaging data. Brain networks for each participant were then constructed by calculating Pearson correlation coefficients between the time courses of all node pairs adjusted for motion and physiological noises (see Hayasaka and Laurienti, 2010 for further details). These node time courses were obtained by averaging the voxel time courses in the 90 distinct anatomical regions (90 ROIs-Regions of Interest) defined by the Automated Anatomical Labeling atlas (AAL; Tzourio-Mazoyer et al., 2002). Refer to the Introduction and Figure 1 for further discussion on brain network generation.

It is important to note that our modeling framework is independent of the method used to generate (estimate) the network (e.g., full correlation, partial correlation, mutual information, generalized synchronization, etc.). We use full correlation here as has been standard in network analyses. Partial correlation better distinguishes direct from indirect connections, and improving and employing partial correlation methodology may ultimately be the best approach. However, when calculating connectivity for a large number of region pairs, partial correlation may underperform full correlation due to the small fraction of indirect connections and the overremoval of signal resulting from the large number of regressors (Smith et al., 2011). Moreover, the estimation of partial correlation via computation of the inverse of the covariance matrix becomes unstable as the number of regions approaches the number of time points, and the covariance matrix becomes noninvertible when the number of regions surpasses the number of time points. Regularization and other methods have been proposed to attempt to address this computational issue, but have still been limited to fairly coarse networks (Ryali et al., 2012, Chen et al., 2013, Seghouane and Khalid 2012). We speculate that the quantitative results (magnitude of parameter estimates) of our modeling approach would vary some as a function of the network estimation method used, but that the qualitative findings (inferential conclusions) would remain the same. Future work will examine this speculation.

#### Two-part mixed modeling framework for weighted brain networks

**Definition**—Given that we have positively weighted networks, with negative weights set to 0/no connection (for reasons noted in Telesford et al., 2011; Cao et al., 2014; and others), a two-part mixed-effects model will be employed in order to be able to model both the probability of a connection (presence/absence) and the strength of a connection if it exists. Several two-part models have been proposed in the literature for a variety of applications (Liu et al., 2008; Albert and Shen, 2005; Tooze et al., 2002). However, they have yet to be developed for networks in general or, more specifically, for brain networks.

Let  $Y_{ijk}$  represent the *strength* of the connection (quantified as the correlation in our case) and  $R_{ijk}$  indicate whether a connection is present (*presence* variable) between node *j* and node *k* for the *i*<sup>th</sup> subject. Thus,  $R_{ijk} = 0$  if  $Y_{ijk} = 0$ , and  $R_{ijk} = 1$  if  $Y_{ijk} > 0$  with conditional probabilities

$$P\left(R_{ijk}=r_{ijk}|\boldsymbol{\beta}_{r};\boldsymbol{b}_{ri}\right) = \begin{cases} 1-p_{ijk}\left(\boldsymbol{\beta}_{r};\boldsymbol{b}_{ri}\right) & if \quad r_{ijk}=0\\ p_{ijk}\left(\boldsymbol{\beta}_{r};\boldsymbol{b}_{ri}\right) & if \quad r_{ijk}=1 \end{cases}, \quad (1)$$

where  $\beta_r$  is a vector of population parameters (fixed effects) that relate the probability of a connection to a set of covariates  $(X_{ijk})$  for each subject and nodal pair (dyad), and  $b_{ri}$  is a vector of subject- and node-specific parameters (random effects) that capture how this relationship varies about the population average  $(\beta_r)$  by subject and node  $(Z_{ijk})$ . Here  $Z_{ijk}$  is the design matrix for subject *i* that contains the covariate values corresponding to the respective random effects  $b_{ri}$  (i.e., it is analogous to  $X_{ijk}$  for the fixed effects  $\beta_r$ ). Hence,  $p_{ijk}(\beta_r; b_{ri})$  is the probability of a connection between nodes *j* and *k* for subject *i*. We then have the following logistic mixed model (part I model) for the probability of this connection:

$$logit(p_{ijk}(\boldsymbol{\beta}_r; \boldsymbol{b}_{ri})) = \boldsymbol{X}_{ijk} \boldsymbol{\beta}_r + \boldsymbol{Z}_{ijk} \boldsymbol{b}_{ri}.$$
 (2)

This transition from the assumptions in Equation 1 to Equation 2 is classical in statistics given that logistic regression models are used to predict binary responses from covariate information. That is, they model the probability of a binary outcome as a function of variables of interest. Thus, Equation 2 provides a standard framework for estimating the probabilities in Equation 1. For the part II model, which aims to model the strength of a connection given that there is one, we let  $S_{ijk} = [Y_{ijk}|R_{ijk} = 1]$ . In our case, the  $S_{ijk}$  will be the values of the correlation coefficients between nodes *j* and *k* for subject *i*. We can then use Fisher's Z-transform, denoted as *FZT*, and assume normality (we have empirically observed normality in strength distributions and the modeling assumption of normality given the covariates was assessed and met for our data) for the following mixed model (part II model)

$$FZT\left(S_{ijk}\left(\boldsymbol{\beta}_{s};\boldsymbol{b}_{si}\right)\right) = \boldsymbol{X}_{ijk}^{'}\boldsymbol{\beta}_{s} + \boldsymbol{Z}_{ijk}^{'}\boldsymbol{b}_{si} + e_{ijk}, \quad (3)$$

where  $\beta_s$  is a vector of population parameters that relate the strength of a connection to the same set of covariates  $(X_{ijk})$  for each subject and nodal pair (dyad),  $b_{si}$  is a vector of subjectand node-specific parameters that capture how this relationship varies about the population average  $(\beta_s)$  by subject and node  $(Z_{ijk})$ , and  $e_{ijk}$  accounts for the random noise in the connection strength of nodes *j* and *k* for subject *i*. Again  $Z_{ijk}$  is the design matrix for subject *i* that contains the covariate values corresponding to the respective random effects  $b_{si}$ .

The covariates ( $X_{ijk}$ ) used to explain and predict both the presence and strength of connection are 1) *Net*: the average of the following network measures (categorized in Table 1 and further detailed in Simpson et al., 2013a and Rubinov and Sporns, 2010) in each dyad: Clustering (*C*), Global Efficiency (*Eglob*), Degree (*k*) (difference instead of average to capture "assortativity"), Modularity (*Q*), and Leverage Centrality (*l*); 2) *COI*: Covariate of Interest (Age Group in our case); 3) *Int*: Interactions of the Covariate of Interest with the metrics in 1) and Sex; and 4) *Con*: Confounders (Sex, Years of Education, Spatial Distance (between nodes) [importance of geometric distance noted by Friedman et al., 2014], and the square of Spatial Distance in our case). Thus, we can decompose  $\beta_r$  and  $\beta_s$  into  $\beta_r = [\beta_{r,0} \beta_{r,net} \beta_{r,coi} \beta_{r,int} \beta_{r,con}]'$  and  $\beta_s = [\beta_{s,0} \beta_{s,net} \beta_{s,coi} \beta_{s,int} \beta_{s,con}]'$  to correspond with the

population intercepts and these covariates. For the random-effects vectors we have that  $b_{ri}$  =  $[b_{ri,0} \mathbf{b}_{ri,net} \mathbf{b}_{ri,dist} \delta_{ri,j} \delta_{ri,k}]'$  and  $\mathbf{b}_{si} = [b_{si,0} \mathbf{b}_{si,net} \mathbf{b}_{si,dist} \delta_{si,j} \delta_{si,k}]'$ , where  $b_{ri,0}$  and  $b_{si,0}$ quantify the deviation of subject-specific intercepts from the population intercepts ( $\beta_{r,0}$  and  $\beta_{s,0}$ ),  $b_{ri,net}$  and  $b_{si,net}$  contain the subject-specific parameters that capture how much the relationships between the network measures in 1) and the presence and strength of a connection vary about the population relationships ( $\beta_{r,net}$  and  $\beta_{s,net}$  respectively,  $b_{ri,dist}$  and  $b_{si,net}$  contain the subject-specific parameters that capture how much the relationship between spatial distance and the *presence* and *strength* of a connection vary about the population relationships respectively,  $\delta_{ri,j}$  and  $\delta_{si,j}$  contain nodal-specific parameters that represent the propensity for node j (of the given dyad) to be connected and the magnitude of its connections respectively, and  $\delta_{ri,k}$  and  $\delta_{si,k}$  contain nodal-specific parameters that represent the propensity for node k (of the given dyad) to be connected and the magnitude of its connections respectively. In general, additional covariates can also be incorporated as guided by the biological context. For example, if interested in which individual connections are responsible for a found topological difference between groups, and if the connections responsible are consistent across subjects within a group, indicator variables for those dyads along with the relevant interactions of those dyadic indicator variables with network metric covariates and grouping variable of interest can be added to the model. To illustrate, consider the result we found (see Results section) that dyads with higher clustering (C) tend to have stronger connections in older adults than young adults. The parameter estimate for an interaction between a specific dyad, age group, and C would indicate whether that specific pair of brain areas is consistent with (responsible for) higher strength in older adults when C is higher. A zero or positive estimate would indicate that the brain areas play a role in the noted difference. A negative estimate would indicate that the brain areas play less of a role or may even counter the noted difference depending on its magnitude. However, since system level topological differences may differ greatly in their locations across subjects within groups, it is possible that no unique brain region pairs are responsible for the differences. These differences point to organizational but not necessarily location differences between groups. A step-down inspection of which brain area pairs in a given *individual* within a group contribute to the results could be conducted by examining the average C of the brain region pairs, for instance, and the strength of the given connections.

We assume that  $\boldsymbol{b}_{ri}, \boldsymbol{b}_{si}$ , and  $\boldsymbol{e}_i = \{e_{ijk}\}$  are normally distributed and mutually independent, with variance component covariance structures for  $\boldsymbol{b}_{ri}$  and  $\boldsymbol{b}_{si}$ , and the standard conditional independence structure for  $\boldsymbol{e}_i$ . That is,  $\boldsymbol{b}_{ri} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_{ri} (\boldsymbol{\tau}_r) = \mathbf{diag} (\boldsymbol{\tau}_r))$  where

$$\boldsymbol{\tau}_{r} = \left(\sigma_{r,0}^{2}, \boldsymbol{\sigma}_{r,net}^{2}, \boldsymbol{\sigma}_{r,dist}^{2}, \sigma_{r,node1}^{2}, \sigma_{r,node2}^{2}, \dots, \sigma_{r,node90}^{2}\right) \text{ and}$$
  

$$\boldsymbol{b}_{si} \sim N\left(\boldsymbol{0}, \boldsymbol{\Sigma_{si}}\left(\boldsymbol{\tau_{s}}\right) = \operatorname{diag}\left(\boldsymbol{\tau_{s}}\right)\right) \text{ where}$$
  

$$\boldsymbol{\tau}_{r} = \left(\sigma_{s,0}^{2}, \boldsymbol{\sigma}_{s,net}^{2}, \boldsymbol{\sigma}_{s,dist}^{2}, \sigma_{s,node1}^{2}, \sigma_{s,node2}^{2}, \dots, \sigma_{s,node90}^{2}\right)^{'} \text{ are the } q(=98) \times 1 \text{ vectors of}$$

variances for each element of the random effects vectors, and  $e_i \sim N(0, \Sigma_{ei} = \sigma^2 I)$ . Thus, each nodal variance component contributes equally to the connections of the given node. We believe that this is a reasonable assumption as the variance component serves as the average (latent) propensity of a node to be connected (and the magnitude of its connections) above and beyond other factors in the model that contribute to its connectivity. Having one

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component per node allows capturing this additional variability while maintaining parsimony so as not to overfit the model or make it computationally infeasible. We considered more parameterized models (e.g., a variance component for all 4005 nodal pairs), but they failed to converge regardless of the optimization approaches employed. Here parameter estimation is conducted via restricted pseudo-likelihood (Wolfinger and O'Connell, 1993) with the residual approximation of the *F*-test for a Wald statistic employed for inference. However, the model can also be imbedded within other appropriate estimation and inferential approaches.

It is important to note that the explanatory network metric covariates (Table 1) are computed on (functions of) the networks for each individual. In the network literature these are referred to as endogenous covariates because they are inherent features of the outcome variable (observed networks), as opposed to the other exogenous variables (demographics, etc.) which are not. There is a long history of modeling a network as a function of endogenous network metrics to identify how nodal properties are related to the probability (and strength) of connections (O'Malley, 2013; Simpson et al., 2011, 2012; Robins et al., 2007). Part of the motivation for our modeling framework was the desire to port this approach into the multiple-network context and blend it with the more standard exogenous covariate approach to create a hybrid method that allows examining and accounting for both an individual's endogenous network structure and exogenous phenotypic characteristics in a manner suitable for brain network analyses. The network metric covariates allow examining how nodal properties influence the connection between two brain areas. More specifically, the parameter estimates associated with the metrics indicate the expected change in the log odds of an edge existing and change in the strength of an existing edge for each unit increase in the corresponding network metric (see Appendix for further details).

In general, two-part models allow the modeling of semicontinuous outcomes in which a large portion of responses equal 0 (non-connections in our case) and the remaining responses come from a continuous distribution (strength values in our case). Distributional assumptions preclude modeling the data in a standard single-model fashion (Albert and Shen, 2005; Liu et al., 2008). The two model parts can be estimated separately or jointly. Current joint modeling approaches have been computationally limited to estimating an additional parametric function representing the correlation between one random effect in the part I model and one in the part II model. Given that we have 98 random effects in each part of our model, and that preliminary analyses found no correlation between subject-specific random intercepts in the two parts, we estimated the two parts separately via the approach noted in the previous paragraph. One could just employ the part I model by binarizing all values if only interested in edge presence, but that would provide a much less powerful and informative analysis given that the information on strength is ignored. Similarly, one could just model the positive values using the part II model, but that omits around half of the data (that are equal to 0) and ignores the fact the relationship between covariates and edge presence is different than the relationship between those covariates and edge strength (as evidenced by the different parameter estimates for the two model parts in our Results section). Thus, the two model parts provide different, but complementary information.

As alluded to in the Introduction, and detailed in the next section, our modeling framework allows *explaining* the relationship between covariates and network connectivity, *comparing* network connectivity among groups, *predicting* network connectivity based on participant and nodal characteristics, *simulating* networks as a means of assessing goodness-of-fit (GOF) and gaining a better understanding of network topological variability, and *thresholding* networks leveraging group information. For explaining, comparing, and thresholding, we remove random effects with estimated variance components equal to zero from the model detailed above in order to preserve power and control test size (Littell, 2006). For predicting and simulating networks we employ the full model as our GOF assessments have shown that it better captures network topology.

#### Framework Utility

**1. Explain:** Our framework allows explaining (quantifying) the relationship between endogenous network features and the probability and strength of a connection between nodes (brain areas) via estimation of  $\beta_{r,net}$  and  $\beta_{s,net}$ , the relationship between exogenous covariate(s) of interest and confounders and the probability and strength of connections via estimation of  $\beta_{r,coi}$ ,  $\beta_{r,con}$ ,  $\beta_{s,coi}$  and  $\beta_{s,con}$ , and if (and how) the relationships between network features and the probability and strength of connections varies for different values of the covariate(s) of interest (between young and older adults in our case) via estimation of  $\beta_{r,int}$  and  $\beta_{s,int}$ . Specific interpretations of fixed effect parameters (after centering continuous covariates) for our data context are given in the Appendix.

**2. Compare:** In addition to simply quantifying the relationship between covariates and the presence and strength of connections while reducing spurious correlations through inclusion of confounding covariates, this framework also allows making formal statistical comparisons about connectivity, network structure, and edge properties between groups (e.g., young vs. old, healthy vs. diseased, etc.). The Appendix contains illustrative interpretations of possible combinations of significant and non-significant parameters for our comparison of young and older adults.

**<u>3. Predict:</u>** Our approach enables making predictions about brain function in several ways:

- 1) Predictions about the *presence* and *strength* of connections between brain regions based on a disease or behavioral outcome of a participant can be made by "learning" the model parameters (estimating the  $\beta$ s) and then using this estimated model for predictions based on new data, thus providing a quantitative means to improve diagnoses, prognoses, and treatment planning;
- 2) Predictions about the topological relationships between network metrics and the *presence* and *strength* of connections based on participant characteristics;
- **3**) Predictions about network structure and its variability via simulations of networks based on model fits (see next subsection).

Given our research interest for the aging data, we focus on the latter two. In the Results/ *Predict* subsection we focus on 2) for the example data, with a discussion of making

predictions about network structure and its variability reserved for the following subsection and Results/*Simulate* subsection.

**4. Simulate:** The two-part mixed modeling framework can also be used to simulate random realizations of networks that retain constitutive characteristics of the original networks. The fitted model yields both a probability mass function for the likelihood of network connections (Equation 2) and probability density function for the strength distribution of network connections (Equation 3) given the covariates. Consequently, group- and individual-level networks can be simulated from this joint distribution, by following the approach of Song et al. (2013) for example, providing a number of benefits delineated below.

- Model goodness-of-fit (GOF) assessment(s) aligned with the research question(s) of interest: Simulations allow assessing many facets of model fit by comparing a set of descriptive metrics (means, medians, distributions, etc.) from the simulated networks with those of the observed networks. For good fitting models, the metrics of interest should closely match (Simpson et al., 2011).
- 2) Representative group-based network creation with anatomical (dyadic) information incorporated: This simulation framework fits all networks simultaneously and thus it does not become more labor intensive to create representative networks with an increasing sample size as is the case with the ERGM based approach (Simpson et al., 2012). Also unlike the ERGM approach, it enables refining the process through the inclusion of additional biologically relevant variables and anatomical information.
- 3) Network variability assessment: Insight into biological variability can be gleaned via the distribution of possible brain networks produced from the simulations. These analyses can aid in elucidating network level features that play a role in various brain disorders. For instance, our aging study analyses showed that young subjects have more degree assortative networks during the visual and multisensory tasks. We can empirically examine how this difference affects the variability of simulated networks, thus helping to illuminate neurological mechanisms that lead to age-related cognitive decline (e.g., lack of interconnectivity among high degree brain areas leads to less stability in neuronal communication in the brains of older adults).

The validity of the results from 2) and 3) (as well as most other subsequent analyses) require a good fitting model, thus we focus on 1) here.

**5. Threshold:** As noted in previously, additional covariates can be included as guided by the questions of interest. As a consequence, this framework provides a powerful approach to network thresholding via inclusion of dyadic indicator variables. Given the sensitivity of network topology (and subsequent network analyses) to the thresholding process, approaches that refine this process are paramount (Simpson et al., 2013a; van Wijk et al., 2010). As opposed to most approaches which just use individual participant-level data to threshold a network (Telesford et al., 2011), our framework allows leveraging group-level

data for this purpose. Better distinguishing between "true" weak connections and those resulting from noise may mitigate some of the challenges associated with weighted network analysis and provide more confidence in resulting conclusions (Simpson et al., 2013a).

### Results

We analyzed the aging study data with the two-part mixed-effects modeling framework. All standard modeling assumptions and diagnostics were checked (Muller and Fetterman, 2002; Cheng et al., 2009). With the appropriate choice of estimation and inferential algorithms, model fitting is quite fast. On a Windows computer with 16GB of RAM and 3.40GHz processor, the fit (with the estimation and inferential algorithms noted in the model definition section) for each condition took approximately four minutes (not counting the time it takes to calculate the network metric covariates that go into the model) in SAS v9.3. Contrastingly, for example, fitting takes over four days when employing the Satterthwaite (as opposed to residual) approximation of the *F*-test for a Wald statistic for inference. In this case, the two approximations yielded virtually identical results. Here we illustrate the framework's ability to explain, compare, predict, and simulate. We provide the essential SAS macros employed in these illustrations in Supplementary Appendices S1-S3 (portions of the code were modified from Song et al., 2013). Future work will provide a thorough examination of its thresholding capabilities as this will require a paper in itself.

#### 1. Explain

The resulting parameter estimates, along with the standard errors and p-values (based on the residual approximation of the F-test for a Wald statistic), associated with each of the fixed effect covariates for each scan condition are presented in Table 2. These estimates quantify (explain) the relationship between the endogenous network features and the probability and strength of a connection between nodes (brain areas), the relationship between age and the confounders (sex, years of education, spatial distance between regions, and the square of spatial distance) and the probability and strength of connections, and if (and how) the relationships between network features and the probability and strength of connections varies between young and older adults (see the Appendix for detailed interpretations of each parameter).

As evidenced by the magnitude of the estimates in the table relative to their standard errors, global efficiency (Functional Integration) and leverage centrality (Information Flow) play an important role in explaining the presence of connections between two brain regions across task conditions, while clustering (Functional Segregation) serves as a relatively important factor in the strength of these connections. Clustering also proves important in brain connectivity for young adults, but not older adults, during the visual and multisensory tasks. Spatial distance well predicts connection probability and strength across task conditions.

#### 2. Compare

Below is a summary of the important inferential results from the analysis of the aging data gleaned from Table 2 (bolded p-values).

#### Rest: Presence - No Age Differences

Strength – Old: - Same as Young when C, Eglob, l, and Q are equal to their averages

- Increases and higher than Young when C, Eglob, and l increase
- Decreases and lower than Young when Q increases

<u>Conclusion</u>: There are no age-related differences in the overall number of connections. The age-related differences in the overall strength of connections vary by dyadic clustering, global efficiency, and leverage centrality, and overall modularity. More specifically, older adults have stronger connections between nodes with higher clustering, global efficiency, and leverage centrality values, and weaker overall connection strength with higher overall modularity than young adults.

Visual: Presence – Old: - Same as Young when C, Eglob, I, and k difference are equal to their averages

- Increases and higher than Young when k difference increases
- Decreases and lower than Young when C, Eglob, and l increase

*Strength* — **Old:** - Same as Young when *l* is equal to its average

- Increases and higher than Young when l increases

<u>Conclusion</u>: The age-related differences in the overall number of connections vary by dyadic clustering, global efficiency, leverage centrality, and degree difference. More specifically, older adults are less likely to have connections between nodes with higher clustering, global efficiency, and leverage centrality values, and more likely to have connections between nodes with a greater degree difference (less assortative) than younger adults. The age-related differences in the overall strength of connections vary by dyadic leverage centrality. More specifically, older adults have stronger connections between nodes with higher leverage centrality and the stronger connections between nodes with higher leverage centrality.

Multi: Presence - Old: - Same as Young when C and k difference are equal to their averages

- Increases and higher than Young when k difference increases

- Decreases and lower than Young when C increases

Strength - Old: - Lower for Old Males when Eglob and l are equal to their averages

- Same as Young for Old Females when Eglob and l are equal to their averages

- Increases faster for Old than Young when Eglob and l increase

<u>Conclusion</u>: The age related differences in the overall number of connections vary by dyadic clustering and degree difference. More specifically, older adults are less likely to have connections between nodes with higher clustering, and more likely to have connections between nodes with a greater degree difference (less assortative) than young adults. The age-related differences in the overall strength of connections vary by dyadic global efficiency and leverage centrality. More specifically, connection strengths increase faster for older adults between nodes as dyadic global efficiency and leverage centrality values increase. Additionally, older women have more overall connection strength than older men.

These comparison results provide a fairly comprehensive appraisal of structural differences between young and older adults. While plausible biological interpretations would be quite speculative at this point, the less degree assortative network structure in older adults during the visual and multisensory tasks provides a more explicable finding. Degree assortativity implies the existence of a resilient core of interconnected high-degree hubs (highly connected brain regions). During the performance of a task, the high degree nodes are those that belong to task-relevant networks (Moussa et al., 2011; Rzucidlo et al., 2013; Ma et al., 2012; Cao et al., 2014). The loss of assortativity in the older adults during the tasks suggests that there is reduced connectivity within the task-relevant networks and greater connectivity

to other network nodes. This finding is consistent with cognitive studies showing that older adults are more vulnerable to distraction when performing tasks (Alain and Woods, 1999; Darowski et al., 2008; Grady et al., 2006).

#### 3. Predict

Here we illustrate the utility of the modeling framework for prediction with the aging study data by focusing on degree (k) difference. Predictions based on other network metrics can be done similarly. Figure 2 shows the 95% prediction intervals for connection probability and strength as a function of degree difference in young and older participants at rest, during the visual task, and during the multisensory task. The 95% prediction interval provides a modelbased definition of normal range for both groups. In contrast to confidence intervals which yield an (narrower) interval estimate for an average of participants, the prediction interval gives an interval estimate for a single participant. As can be seen from the figure, older adults have a higher predicted connection probability when two nodes have the same degree; however, this probability drops off at a slightly faster rate than for the young as the disparity between the degrees of two nodes increases at rest and during a visual task. That is, older adults are predicted to have brain networks that are more degree assortative than young adults at rest. Contrastingly, younger adults are predicted to have more degree assortative networks during visual and multisensory tasks given the faster decay of their connection probabilities. As noted in the previous section, this finding is consistent with the hypothesis that older adults tend to be more distractable, or be more cognitively vulnerable, while engaged in a task. Also as evidenced by Figure 2, older adults have a lower predicted connection strength that parallels the decay of the young adults as the disparity between the degrees of two nodes increases at rest, during a visual task, and during a multisensory task. That is, an older adult is likely to have weaker coupling between brain region pairs than a young adult regardless of the regional connectivity patterns.

#### 4. Simulate

To assess the goodness-of-fit of our model to the aging study data, and to illustrate the utility of our framework for simulating realistic brain networks, we simulated 100 networks based on the fitted models to the data at rest, during the visual task, and during the multisensory task. We then calculated several (weighted) descriptive metrics commonly used in the neuroimaging literature for the observed and simulated networks. Table 3 displays the results for clustering coefficient (C), global efficiency (*Eglob*), characteristic path length (L), mean nodal degree (K), leverage centrality (l), and modularity (Q). As evidenced by the results, the simulated networks are very similar to the observed networks in terms of clustering, path length, and global efficiency, and relatively similar for leverage centrality and degree across task conditions. While the simulated networks are not as similar for modularity, our method provides a huge step forward methodologically given that, to our knowledge, it is the only approach that allows the simulation of weighted networks that capture several important topological properties simultaneously. Moreover, the framework serves as a foundation upon which future work can further refine network simulation accuracy.

#### 5. Threshold

Implementing the group-level thresholding approach requires adding indicator variables for the dyads of interest to the strength model defined in Equation 3 and then appropriately assessing the significance of the associated parameter. Adding interactions of the grouping variable (e.g., age group in our case) and the dyads of interest allows leveraging the data in a particular group, as opposed to all groups, in assessing the significance of a dyad. Nonsignificant dyads can be considered candidates for removal from the networks of participants with weak connections in those areas. As noted earlier, future work will examine this thresholding capability and assess its performance in the brain network context as it necessitates a paper in itself.

### Discussion

The recent explosion of brain network analyses has led to a paradigm shift in neuroscience; however, the statistical methods needed to draw deeper biological insights from these analyses have lagged behind. Our two-part mixed-effects modeling framework fills this void and provides a comprehensive approach to studying system level brain properties to further our understanding of normal and abnormal brain function as illustrated by our analysis of the aging study data. As detailed in Materials and methods, the approach allows *explaining* the relationship between covariates and network connectivity, *comparing* network connectivity among groups, *predicting* network connectivity based on participant and nodal characteristics, *simulating* networks as a means of assessing goodness-of-fit (GOF) and gaining a better understanding of network topological variability, and *thresholding* networks leveraging group information.

Future work within this framework will focus on further demonstrating its simulation capabilities and thoroughly assessing its utility as a network thresholding aid as previously discussed. Generating accurate and informative representative group-based networks via simulation provides one avenue for inquiry that has been underexplored in the literature (Simpson et al., 2012). Additionally, creating signature networks via individual and group-level simulations and examining the subsequent distributions of these generated networks may prove useful in disease prediction. For example, we plan to apply our approach to data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to determine if simulated networks and their distributions at baseline are predictive of cognitive decline at follow up.

Modifications and extensions to our framework also provide opportunities for future research. The movement of the field toward more resolved network atlases (hundreds or thousands of nodes) will likely necessitate the development of dimension reduction methods that can be appropriately overlaid on our approach. Even with 90 nodes there are 4005 dependent variables (possible connections) per participant, requiring careful choice of the estimation and optimization algorithms, as well as the denominator degrees of freedom approximation (used for inference) for convergence (Kiernan et al., 2012). With 1000 nodes the number of dependent variables for each participant's network jumps to 499,500. Longitudinal (or multitask) brain network modeling remains an untapped area in need of development (Simpson et al., 2013a). Extending our static modeling approach to this domain via incorporation of time-dependent random effects or Kronecker product covariance

modeling (Galecki, 1994; Naik and Rao, 2001; Simpson, 2010; Simpson et al., 2014a; Simpson et al., 2014b) provides a potential solution. For the latter, following the notation in equations 2 and 3, we could assume that the random error is distributed

 $e_i \sim N\left(0, \Sigma_{ei} = \sigma^2 (task) [\Gamma \otimes \Omega]\right)$ , where  $\sigma^2(task)$  is the variability of connections strengths across the network dyads and varies by task,  $\Gamma$  contains the correlations between tasks, and  $\Omega$  contains the correlations between connection strengths of dyads which may be modeled explicitly or assumed to have the standard conditional independence structure (i.e.,  $\Omega = \sigma^2 I$ ). Specification of the structure for ! should be informed by the study design and examination of observed correlations (Simpson et al., 2013a). Incorporating negative connections (i.e., negatively correlated nodes/brain regions) into static or longitudinal brain network analyses will also prove important. The lack of metrics for quantifying functional segregation and integration (e.g., *C* and *Eglob*) with negatively weighted edges remains the current limiting factor.

Our framework is situated at the interface of statistical, network, and brain science, providing a synergistic analytic foundation for whole-brain network data. As mentioned above, this flexible approach can be modified and extended to refine its utility. It provides a step toward filling the methodological needs of the emerging area of brain network analysis and will engender deeper insights into the complex neurobiological interactions and changes that occur in many brain diseases and disorders.

#### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

#### Acknowledgements

This work was supported by NIBIB K25 EB012236-01A1 (Simpson), and Wake Forest Older Americans Independence Center (P30 21332) and the Sticht Center on Aging (Laurienti). The authors thank F. DuBois Bowman from the Department of Biostatistics at Columbia University for his insightful conversations and guidance. An earlier version of this manuscript can be found at arxiv.org (Simpson et al., arXiv:1409.7086 [stat.AP]).

#### Appendix: Parameter interpretations

Specific interpretations of fixed effect parameters (after centering continuous covariates) for our data context are given below.

### $\beta_{r,0}$ and $\beta_{s,0}$

The log odds of an edge existing and the average strength of that connection for dyads with average values for the network metrics and spatial distance from the network of a young male with the average educational attainment.

### $\beta_{r,net}$ and $\beta_{s,net}$

The change in the log odds of an edge existing and the average strength of that connection for a dyad with each unit increase in the given network metric from the networks of young adults.

### $\beta_{r,age}$ and $\beta_{s,age}$

The change in the log odds of an edge existing and the average strength of that connection for dyads from the networks of older males with average values for the network metrics.

### $\beta_{r,sex}$ and $\beta_{s,sex}$

The change in the log odds of an edge existing and the average strength of that connection for dyads from the networks of younger females.

### $\beta_{r,educ}$ and $\beta_{s,educ}$

The change in the log odds of edges existing and the average strength of those connections with each year increase in educational attainment.

### $\beta_{r,dist}/\beta_{r,dist}^2$ and $\beta_{s,dist}/\beta_{s,dist}^2$

The quadratic change in the log odds of an edge existing and the average strength of that connection with each mm (scaled to dm for model fit) increase in spatial distance between the two nodes of a given dyad.

### $\beta_{r,age \times net}$ and $\beta_{s,age \times net}$

The additional change (relative to  $\beta_{r,net}$  and  $\beta_{s,net}$ ) in the log odds of an edge existing and the average strength of that connection for a dyad with each unit increase in the given network metric from the networks of older adults.

### $\beta_{r,age \times sex}$ and $\beta_{s,age \times sex}$

The additional change (relative to  $\beta_{r,sex}$  and  $\beta_{s,sex}$ ) in the log odds of an edge existing and the average strength of that connection for dyads from the networks of older females.

For illustrative purposes, below are interpretations of possible combinations of significant and non-significant parameters for our comparison of young and older adults (NS-not significant, S-significant).

## $\beta_{r/s,age}(NS), \beta_{r/s,age \times sex}(NS), \beta_{r/s,age \times net}(NS)$

No overall connectivity differences (proportion and strength of edges) or topological differences (relationship between dyad characteristics and probability and strength of edges; i.e., connectivity differences that vary as a function of the value of the network metrics)

between young and older adults. May still have differences in specific edges that can be assessed by including edge (dyadic) indicator variables in the model as desired.

### $\beta_{r/s,age}(NS), \beta_{r/s,age \times sex}(NS), \beta_{r/s,age \times net}(S)$

Connectivity differences between young and older adults vary (potentially compensatorily) by the values of the network metrics (are functions of the network metrics).

### $\beta_{r/s,age}(S), \beta_{r/s,age \times sex}(NS), \beta_{r/s,age \times net}(NS)$

Overall connectivity differences, but no topological differences between young and older adults.

### $\beta_{r/s,age}(S), \beta_{r/s,age \times sex}(NS), \beta_{r/s,age \times net}(S)$

Connectivity differences between young and older adults vary (potentially compensatorily) by the values of the network metrics (are functions of the network metrics).

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### Highlights

• We develop an analytical foundation for whole-brain network data analysis.

- Framework situated at the interface of statistical, network, and brain science.
- Allows modeling the probability and strength of network connections.
- Captures dependence structure & important topological properties of brain networks.
- Allows describing, comparing, predicting, simulating, and thresholding networks.



### Figure 1.

Schematic for generating brain networks from fMRI time series data (partially recreated from Simpson et al., 2013a and 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.



#### Figure 2.

Prediction intervals for connection probability and strength as a function of degree difference in young and older participants at rest, during a visual task, and during a multisensory task.

#### Table 1

#### Explanatory network metrics by category

Category	Metric(s)
1) Functional Segregation	Clustering Coefficient
2) Functional Integration	Global Efficiency
3) Resilience	Degree Difference
4) Centrality and Information Flow	Leverage Centrality
5) Community Structure	Modularity

#### Table 2

Aging Data: Estimates, Standard Errors (SE), and P-values

	Rest			Visual		Multisensory			
Parameter	Estimate	SE	* P-value	Estimate	SE	* P-value	Estimate	SE	* P-value
$\beta_{r,0}$	-0.3141	0.0569	< 0.0001	-0.2905	0.0534	< 0.0001	-0.0585	0.0634	0.3556
$\beta_{r,C}$	0.7807	0.3424	0.0355	6.7083	0.8969	< 0.0001	13.3638	1.6908	< 0.0001
$\beta_{r,Eglob}$	32.6231	2.3322	< 0.0001	34.7897	2.3725	< 0.0001	32.8996	1.9054	< 0.0001
$\beta_{r,k}$	-1.4442	0.1522	< 0.0001	-1.7862	0.1410	< 0.0001	-2.0598	0.1361	< 0.0001
$\beta_{r,Q}$	-0.7345	1.1361	0.5179	-0.8004	1.2082	0.5077	-3.1672	1.5257	0.0379
$\beta_{r,l}$	1.1598	0.0785	< 0.0001	1.4156	0.0792	< 0.0001	1.5381	0.0919	< 0.0001
$\beta_{r,age}$	-0.0438	0.07733	0.5709	0.0884	0.0733	0.2279	-0.0200	0.0866	0.8171
$\beta_{r,sex}$	-0.0085	0.0825	0.9178	0.0413	0.0725	0.5690	-0.0479	0.0984	0.6265
$\beta_{r,educ}$	0.0027	0.0103	0.7954	-0.0007	0.0097	0.9467	0.0159	0.0130	0.2212
$\beta_{r,dist}$	-1.4266	0.0572	< 0.0001	-1.4593	0.0694	< 0.0001	-1.4419	0.0689	< 0.0001
$\beta_{r,dist}^2$	2.6558	0.1417	< 0.0001	2.6648	0.1364	< 0.0001	3.0032	0.2079	< 0.0001
$\beta_{r,age \times C}$	1.1249	0.7986	0.1943	-6.3557	0.9239	< 0.0001	-10.2034	2.3529	< 0.0001
$\beta_{\textit{r,age} \times \textit{Eglob}}$	-1.7255	3.3478	0.6063	-7.8023	3.3969	0.0216	-2.3070	2.7258	0.3974
$\beta_{r,age  imes k}$	0.2455	0.2185	0.2873	0.5473	0.2013	0.0066	0.7766	0.1943	< 0.0001
$\beta_{r,age  imes Q}$	1.5858	1.5753	0.3141	2.1234	1.7684	0.2298	3.1948	1.9126	0.0948
$\beta_{r,age  imes l}$	0.0638	0.1154	0.5803	-0.3755	0.1086	0.0005	-0.2247	0.1324	0.0896
$\beta_{r,age \times sex}$	0.1914	0.1145	0.1301	-0.0544	0.1093	0.6187	0.1490	0.1353	0.2706
$\beta_{s,0}$	0.2290	0.0091	< 0.0001	0.2173	0.0133	< 0.0001	0.2380	0.0130	< 0.0001
$\beta_{s,C}$	2.2940	0.2428	< 0.0001	2.4104	0.3409	< 0.0001	2.1541	0.2161	< 0.0001
$\beta_{s,Eglob}$	0.9534	0.1823	< 0.0001	1.3179	0.1841	< 0.0001	0.9801	0.2003	< 0.0001
$\beta_{s,k}$	-0.2524	0.0153	< 0.0001	-0.0016	0.0244	0.9468	-0.2523	0.0177	< 0.0001
$\beta_{s,Q}$	-0.0373	0.1723	0.8285	-0.4926	0.3018	0.1540	-0.6634	0.3120	0.0335
$\beta_{s,l}$	-0.0036	0.0109	0.7426	0.0032	0.0147	0.8274	-0.0164	0.0126	0.1948
$\beta_{s,age}$	-0.0106	0.0124	0.4262	-0.0012	0.0180	0.9448	-0.0429	0.0178	0.0157
$\beta_{s,sex}$	-0.0046	0.0132	0.7263	0.0209	0.0181	0.2995	-0.0341	0.0202	0.0903
$\beta_{s,educ}$	-0.0009	0.0017	0.5814	-0.0014	0.0024	0.5703	0.0028	0.0027	0.2922
$\beta_{s,dist}$	-0.1718	0.0054	< 0.0001	-0.1769	0.0055	< 0.0001	-0.1723	0.0054	< 0.0001
$\beta_{s,dist}^2$	0.3910	0.0118	< 0.0001	0.3838	0.0141	< 0.0001	0.3902	0.0148	< 0.0001
$\beta_{s,age \times C}$	0.7214	0.3494	0.0467	0.4342	0.4808	0.3998	0.1812	0.3009	0.5470
$\beta_{s,age  imes Eglob}$	0.7042	0.2623	0.0097	0.1866	0.2640	0.4797	0.6309	0.2864	0.0276
$\beta_{s,age  imes k}$	0.0009	0.0220	0.9662	-0.0016	0.0244	0.9468	0.0024	0.0253	0.9234
$\beta_{s,age  imes Q}$	-0.6957	0.2464	0.0071	0.2925	0.3990	0.4635	-0.1478	0.3896	0.7044
$\beta_{s,age  imes l}$	0.0556	0.0157	0.0007	0.0464	0.0209	0.0455	0.0349	0.0183	0.0560
$\beta_{s,age \times sex}$	0.0001	0.0184	0.9952	-0.0312	0.0269	0.2995	0.0513	0.0276	0.0632

Bold values indicate important age-related inferential results used to draw conclusions in next subsection.

\* Adjusted using the adaptive FDR procedure detailed in Benjamini and Hochberg (2000).

#### Table 3

Weighted network metrics of observed and simulated networks from the aging study data at rest.

		Observed (N=39)	Simulated (N=100)
Condition	Metric	Mean (SE)	Mean (SE)
Rest	Clustering coefficient (C)	0.149 (0.001)	0.155 (0.000)
	Global Efficiency (Eglob)	0.231 (0.001)	0.214 (0.000)
	Characteristic path length (L)	4.677 (0.109)	4.720 (0.004)
	Mean Nodal Degree (K)	10.649 (0.055)	12.747 (0.016)
	Leverage Centrality (1)	2.678 (0.015)	1.945 (0.003)
	Modularity $(Q)$	0.342 (0.001)	0.136 (0.000)
Visual	Clustering coefficient (C)	0.150 (0.001)	0.150 (0.000)
	Global Efficiency (Eglob)	0.232 (0.001)	0.205 (0.000)
	Characteristic path length (L)	4.553 (0.073)	4.992 (0.008)
	Mean Nodal Degree (K)	10.656 (0.056)	12.379 (0.025)
	Leverage Centrality (1)	2.671 (0.015)	2.155 (0.010)
	Modularity $(Q)$	0.348 (0.001)	0.136 (0.000)
Multisensory	Clustering coefficient (C)	0.140 (0.001)	0.165 (0.000)
	Global Efficiency (Eglob)	0.230 (0.001)	0.218 (0.000)
	Characteristic path length (L)	4.431 (0.011)	4.700 (0.008)
	Mean Nodal Degree (K)	10.547 (0.052)	13.830 (0.027)
	Leverage Centrality (1)	2.862 (0.014)	2.054 (0.006)
	Modularity (Q)	0.327 (0.001)	0.123 (0.000)