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Bayesian exponential random graph modeling of whole-brain structural networks across lifespan

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ABSTRACT

Descriptive neural network analyses have provided important insights into the organization of structural and functional networks in the human brain. However, these analyses have limitations for inter-subject or between-group comparisons in which network sizes and edge densities may differ, such as in studies on neurodevelopment or brain diseases. Furthermore, descriptive neural network analyses lack an appropriate generic null model and a unifying framework. These issues may be solved with an alternative framework based on a Bayesian generative modeling approach, i.e. Bayesian exponential random graph modeling (ERGM), which explains an observed network by the joint contribution of local network structures or features (for which we chose neurobiologically meaningful constructs such as connectedness, local clustering or global efficiency). We aimed to identify how these local network structures (or features) are evolving across the life-span, and how sensitive these features are to random and targeted lesions. To that aim we applied Bayesian exponential random graph modeling on structural networks derived from whole-brain diffusion tensor imaging-based tractography of 382 healthy adult subjects (age range: 20.2–86.2 years), with and without lesion simulations. Networks were successfully generated from four local network structures that resulted in excellent goodness-of-fit, i.e. measures of connectedness, local clustering, global efficiency and intrahemispheric connectivity. We found that local structures (i.e. connectedness, local clustering and global efficiency), which give rise to the global network topology, were stable even after lesion simulations across the lifespan, in contrast to overall descriptive network changes – e.g. lower network density and higher clustering – during aging, and despite clear effects of hub damage on network topologies. Our study demonstrates the potential of Bayesian generative modeling to characterize the underlying network structures that drive the brain's global network topology at different developmental stages and/or under pathological conditions.

1. Introduction

Aging is a major risk factor of prevalent diseases in society, including neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Collier and Kordower, 2012; Niccoli and Partridge, 2012). During aging the human brain is subject to structural and functional changes that can cause behavioral problems and cognitive decline (e.g. reduced executive functioning or memory impairment). However, many elderly people do not suffer from behavioral and cognitive problems and are functioning well, despite structural and functional changes in brain networks. Therefore it is important to understand to what extent specific changes in brain connectivity across the lifespan contribute to increased risk and development of age-related neurological disorders, even in the absence of significant brain pathology (Burke and Barnes, 2006).

Graph analysis has proven to be an elegant tool to assess topological aspects of structural and functional connectivity in the brain (Bullmore and Sporns, 2009). Graph analysis describes the brain as a set of nodes, representing neural elements, linked by edges, representing some measure of structural, functional or causal interaction between the nodes. Many studies have successfully applied graph analysis to capture network topologies with either individual or aggregated node metrics (e.g. the average shortest path length, maximum betweenness centrality or overall clustering coefficient) (Bullmore and Sporns, 2009) and/or network properties such as small-worldness, rich club connectedness (Bullmore and Sporns, 2012; Cao et al., 2014) and modularity (Rubinov and Sporns, 2010). In the past decade, multiple studies have shown that normal aging is associated with substantial alterations in

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structural (Betzel et al., 2014; Dennis et al., 2013; Gong et al., 2009; Hagmann et al., 2010; Lim et al., 2015; Montembeault et al., 2012; Otte et al., 2015; Wu et al., 2012; Zhu et al., 2012) and functional (Achard and Bullmore, 2007; Andrews-Hanna et al., 2007; Betzel et al., 2014; Meier et al., 2012; Meunier et al., 2009; Nathan Spreng and Schacter, 2012; Wang et al., 2012) brain networks. Some of these studies focused on specific age categories: childhood to adulthood (Dennis et al., 2013; Hagmann et al., 2010) or young and older adults (e.g. (Meunier et al., 2009; Zhu et al., 2012)). From childhood to adulthood a decrease in path length and clustering, and increase in efficiency have been observed (Dennis et al., 2013; Hagmann et al., 2010) which may differ between the hemispheres (Dennis et al., 2013). Other studies have shown a higher local clustering and lower global efficiency in older adults compared to younger adults (Zhu et al., 2012), where modularity decreases across networks (Meunier et al., 2009). In line with these findings several studies have shown inverted-U shaped global efficiency across lifespan (Otte et al., 2015; Wu et al., 2012). Functional connectivity assessment has revealed increased integration and decreased randomness, whereas connectivity decreased significantly during adulthood (Smit et al., 2016). Despite these significant network changes, throughout development brain networks largely maintain small-world properties, modularity and stable hub-regions (Dennis et al., 2013; Gong et al., 2009; Hagmann et al., 2007). In general, the aging brain can be characterized by reduced centrality of hub regions with a decrease in global efficiency and an increase in local network clustering. Similar changes in hub regions and subsequent effects on global efficiency have also been characterized in various neurological disorders (Crossley et al., 2014; Stam, 2014).

Despite the popularity of descriptive graph analysis, it has non-trivial intrinsic limitations, particularly for intersubject or between-group comparisons where networks have different sizes, densities and degree distributions (Fornito et al., 2013; van Wijk et al., 2010). The most commonly used node metrics, like the clustering coefficient and path length, are highly dependent on the total number of connections and the average degree of a network (Stam et al., 2014; van Wijk et al., 2010). This hampers comparability of brain network topology across the human lifespan, as network densities substantially differ between ages (Dennis et al., 2013; Gong et al., 2009; Hagmann et al., 2010), which may be explained by changes in the integrity of connecting fibers or the cortical density of neurons (Salat, 2011; Westlye et al., 2010).

A second limitation is the lack of an appropriate generic null model to test the significance of a particular network measure against. A frequently used null model is a network with randomly shuffled edges that shares basic characteristics with the measured network, like degree distribution, size and density. Different network metrics require distinct null models if compared between networks (e.g., networks with asymmetric degree distributions cannot be explained by the Watts–Strogatz small-world network null model but require the Barabási–Albert scale-free model) (Fornito et al., 2013).

A third limitation of graph analysis is the type I error inflation if multiple network nodes are compared within the same brain, or if different network metrics are calculated from a single network.

Fourthly, graph analysis consists of univariable comparisons (i.e., network metrics are determined independent from each other) due to lack of a unifying framework (Telesford et al., 2011). However, many metrics are highly correlated and non-exclusive (Bounova and De Weck, 2012; Meghanathan, 2015).

A promising alternative analysis approach, which may in theory overcome the abovementioned limitations in descriptive graph analysis, is the framework of generative modeling (Fornito et al., 2013; Klimm et al., 2014), which aims to condense a complex network topology into a parsimonious description (i.e. mathematical equation). Growth models are a relatively well known class of generative models. They involve growing of artificial networks via addition of nodes and edges and rewiring of existing edges according to pre-specified mechanisms, and comparing topologies between these artificially grown and observed networks. Relatively simple growing mechanisms (i.e., the mathematical local structures) provide a generative model that allows growing of networks that closely resemble observed brain networks. A recent successful example is a growth model with two local structures: a combined distance penalty based on the cost of maintaining long-range connections and a topological term that favors links between regions sharing similar input (Vertes et al., 2012). Similar principles have been successfully applied by other recent studies on neural networks (Betzel et al., 2015; Goni et al., 2014). However, unambiguous determination of distances between non-connecting pairs of network nodes – required for distance penalties – is difficult.

Another recent and powerful class of generative models are the exponential random graph models. Their usefulness has been emphasized in social network studies (Robins et al., 2007b), but they may have equal potential for neuronal networks (Simpson et al., 2011). Until recently, exponential random graph models have been difficult to handle from a statistical point of view, due to the intractability of the normalizing constant and the problem of model degeneracy (Handcock, 2003), which has limited their applicability. The recent presentation of a Bayesian inference framework, using adaptive Markov chain Monte Carlo approaches to fit exponential random graph models, mitigated the issue of model degeneracy and significantly improved fitting performance (Caimo and Friel, 2011). Exponential random graph models are able to explore multiple local network features (e.g. connectedness, local clustering or global efficiency) simultaneously and assess how these local features give rise to the global network topology, thereby taking into account their mutual dependencies (note that the term 'local' is defined from a topological and not from a physical perspective, i.e. local clustering does not necessary imply physical proximity of involved nodes). In addition, exponential random graph models inherently account for bias due to density differences (van Wijk et al., 2010). More technically, the models capture the joint probability of a (global) network G, governed by $\boldsymbol{\vartheta}$, a set of network parameters (e.g. local clustering, edges) of a postulated generative process. If $\boldsymbol{\vartheta}$ is estimated well, synthetic networks – which are structurally similar to G – may be drawn from a probability distribution $P(G|\boldsymbol{\vartheta})$. Exponential random graph modeling may thus also be considered as a mathematical framework to condense the (global) topological information of a network into a limited set of parameters (i.e. the local network structures or features). This mathematical description theoretically provides: *i*) compression of the observed network data into a basic equation, *ii*) capturing of the most relevant patterns within the observed network, *iii*) generalization from the observed network to unobserved networks of the same type, i*v*) generalization across network sizes, and *v*) prediction of network topologies.

Exponential random graph models may provide unambiguous answers to fundamental questions related to brain-wide network organization and changes across lifespan, such as: how do local network features (i.e. neurobiologically meaningful constructs such as local clustering, connectedness and global efficiency) simultaneously give rise to (i.e. explain) the global network topology, and what is the relative significance (i.e. contribution) of those local structures during development and aging? Will there still be changes across lifespan in brain global efficiency or local clustering, if confounding effects such as correlations between metrics and decreased network density with increased age, are effectively taken into account? In fact, surprisingly little is known on how local network features simultaneously shape the global network characteristics so commonly reported in descriptive graph analysis studies. Furthermore, it is unknown to what extent local structures are affected by specific network damage in brain injuries and pathologies. For example, does damage to central hub regions result in distinct local features (such as brain network clustering or connectedness) as compared to diffuse network damage, and does this differ across the lifespan?