Time-dependence of graph theory metrics in functional connectivity analysis

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ABSTRACT

Brain graphs provide a useful way to computationally model the network structure of the connectome, and this has led to increasing interest in the use of graph theory to quantitate and investigate the topological characteristics of the healthy brain and brain disorders on the network level. The majority of graph theory investigations of functional connectivity have relied on the assumption of temporal stationarity. However, recent evidence increasingly suggests that functional connectivity fluctuates over the length of the scan. In this study, we investigate the stationarity of brain network topology using a Bayesian hidden Markov model (HMM) approach that estimates the dynamic structure of graph theoretical measures of whole-brain functional connectivity. In addition to extracting the stationary distribution and transition probabilities of commonly employed graph theory measures, we propose two estimators of temporal stationarity: the *S*-index and *N*-index. These indexes can be used to quantify different aspects of the temporal stationarity of graph theory measures. We apply the method and proposed estimators to resting-state functional MRI data from healthy controls and patients with temporal lobe epilepsy. Our analysis shows that several graph theory measures, including small-world index, global integration measures, and betweenness centrality, may exhibit greater stationarity over time and therefore be more robust. Additionally, we demonstrate that accounting for subject-level differences in the level of temporal stationarity of network topology may increase discriminatory power in discriminating between disease states. Our results confirm and extend findings from other studies regarding the dynamic nature of functional connectivity, and suggest that using statistical models which explicitly account for the dynamic nature of functional connectivity in graph theory analyses may improve the sensitivity of investigations and consistency across investigations.

Introduction

Connectomic analysis using graph theoretical methods is increasingly found to be a powerful quantitative method for investigating complex brain networks on the whole-brain level. Through the computation of neurobiologically interpretable network measures, graph theory provides a mathematical framework through which topological properties of the network may be studied, including aspects related to clustering, efficiency, modularity, long-range connectivity, and small-worldness (Rubinov and Sporns, 2010; Bullmore and Bassett, 2011). Its application to functional data on resting state networks from functional MRI, magnetoencephalography, and electroencephalography has provided

novel insights into various neurological and psychiatric diseases (Stam and Reijneveld, 2007; Ponten et al., 2009; Vlooswijk et al., 2011; Chiang and Haneef, 2014). Increasingly, studies are demonstrating the utility of graph theory measures of functional connectivity for identifying abnormalities in network connectivity and serving as clinical diagnostic markers and as markers of disease severity (Wilke et al., 2011; Vlooswijk et al., 2010; Micheloyannis et al., 2006; Supekar et al., 2008).

Despite the large number of analyses of resting-state network connectivity that use graph theory to explore network connectivity, the majority rely on the assumption of temporal stationarity. In most cases, the strength of inter-regional signal associations is calculated using some measure of linear dependence, such as the synchronization likelihood or a measure of correlation, over the entire scanning session. The strength of these associations is then either analyzed as weighted graphs or binarized into unweighted graphs (Bullmore and Bassett,

2011). However, recent evidence increasingly shows that inter-regional signal associations are dynamic over time, and are highly modulated by attention, medications, and cognitive state (Chang and Glover, 2010). In addition, (Honey et al., 2009) have found that resting state functional connectivity exhibits a large degree of variability both within and across scanning sessions. (Ma et al., 2014) have also demonstrated that functional connectivity fluctuates over time within scans, furthermore finding that first-order temporal dynamics may approximate these dynamics. Although the reasoning behind the dynamic nature of resting-state brain topology is a relatively new concept and under investigation, it is thought to reflect the configuration of functional networks around a stable anatomical skeleton (Deco et al., 2011). Computational modeling and empirical work have demonstrated that, at shorter time scales, these various functional network configurations may be spontaneously visited around the same anatomical skeleton in the presence of local cell dynamics (Deco et al., 2011). While some aspects of brain topology, such as the level of small-worldness, may exhibit greater temporal stationarity in order to maintain a relatively constant optimum network configuration, others, such as local measures, may be more susceptible to local cell dynamics and more likely to traverse multiple configurations. Various functional configurations may also exist in order to allow flexibility to support different cognitive functions (Fair et al., 2009).

Recently, studies have noted that conflicting results have arisen in graph theory investigations of functional connectivity. Investigations of clustering coefficient and characteristic path length, for example, have variably found evidence of increase, decrease, or no change in patients with epilepsy compared to controls (Chiang and Haneef, 2014; van Diessen et al., 2014). One contributing factor to current inconsistencies in the literature may be small sample sizes and moderate effect sizes (van Diessen et al., 2014). In light of recent evidence that resting-state functional connectivity is in fact non-stationary, however, another major factor may be greater temporal instability in some topological characteristics than others, leading some investigations to capture the topology of particular functional network configurations while other investigations may capture other topological configurations. Understanding of temporal dynamics of graph measures of network topology may help address these previous literature inconsistencies.

The aim of this study is to identify which aspects of network topology exhibit less within-scan temporal variability in resting state networks, with the objective of evaluating which graph theory metrics may be robustly estimated using static functional connectivity analyses. To the best of our knowledge, this is the first attempt of quantifying the relative temporal stationarity of graph theory metrics of brain network topology in functional connectivity analysis. In particular, we use a Bayesian hidden Markov model to estimate the transition probabilities of various graph theoretical network measures using resting-state fMRI (rs-fMRI) data. We propose two estimators of temporal stationarity, which can be used to quantitate different aspects of the temporal stationarity of functional networks: the N-index, which is a deterministically-based estimator of the number of change-points, and the S-index, which is a probabilistically-based estimator that takes into account stochastic variation in the estimated states. Based on the estimated stationarity distribution and transition probabilities, we evaluate the relative levels of temporal stationarity among various commonly investigated measures of brain network topology. Additionally, we point to possible hierarchical extensions of our model which may be used to aid in disease prediction, by showing that incorporating temporal dynamics into investigations of brain connectivity may increase discriminatory power of graph theory metrics.

Materials and methods

In order to determine which aspects of network topology are robust under static functional connectivity analysis, we investigate commonly

employed graph theoretic measures in current literature using a Bayesian hidden Markov model. We apply our proposed estimators to the healthy control and temporal lobe epilepsy populations, and illustrate that differences in temporal dynamics between epileptic and healthy brain networks may be quantitated and may provide a potential diagnostic marker.

Participants

Participants consisted of 24 healthy controls (HC; average age, 32.50 ± 1.88 SE (y); age range/Q_1/Q_3, 19–64/27/35 (y); 8 females) and 32 patients with temporal lobe epilepsy (TLE; average age, 37.56 ± 1.86 SE (y); age range/Q_1/Q_3, 20–63/32/45 (y); 16 females; average epilepsy duration, 18.79 ± 2.25 SE (y); epilepsy duration range/Q_1/Q_3, 2–45/6/31 (y)). Healthy control subjects had normal structural MRIs and no history of neurologic illness or were taking neurologic medications. TLE patients were recruited from the University of California, Los Angeles (UCLA) Seizure Disorder Center. Diagnostic evaluation for all subjects included video-EEG monitoring, high-resolution MRI, FDG-PET scanning, and neuropsychological testing. Written informed consent was obtained prior to scanning for all subjects in accordance with guidelines from the UCLA Institutional Review Board. A two-sample t-test with unequal variances and Fisher exact test showed no significant difference in age or gender, respectively at the $\alpha = 0.05$ level of significance.

Image acquisition and pre-processing

Imaging was performed with a 3 T MRI system (Siemens Trio, Erlangen, Germany). Functional imaging was performed with the following parameters: TR = 2000 ms, TE = 30 ms, FOV = 210 mm, matrix = 64×64, slice thickness 4 mm, 34 slices. Subjects were instructed to relax with eyes closed during imaging. No auditory stimulus was present except for the acoustic noise from imaging. High-resolution structural images were obtained during the same imaging study with the parameters: TR = 20 ms, TE = 3 ms, FOV = 256 mm, matrix = 256×256, slice thickness 1 mm, 160 slices. The images were acquired in the axial plane using a spoiled gradient recalled (SPGR) sequence for the anatomical images and an echo planar imaging (EPI) sequence for the functional images. The imaging sessions included multiple simultaneous EEG and fMRI recordings, each lasting 5 to 15 min. For resting state fMRI analysis, 20 min of BOLD fMRI data was used for each subject. To limit the influences of motion, subjects were checked to ensure that no subjects had a maximum translation of >1.5 mm (HC, 0.24 ± 0.04 mm; TLE, 0.37 ± 0.04 mm). Resting-state fMRI was performed for TLE patients after the comprehensive epilepsy surgery evaluation and prior to epilepsy surgery. Patients remained on their regular medications during the fMRI. None of the patients had a seizure in the 24 h preceding the imaging. None of the patients had seizures during the study as confirmed by the simultaneous EEG obtained during fMRI. The EEG results were not included in the data analysis other than to exclude seizures. Details of the simultaneous EEG methods have been described previously (Stern et al., 2011). Neuroimaging and fMRI pre-processing steps are similar to that described previously (Haneef et al., 2014). Preprocessing was performed using FSL (fMRIB Software Library) version 5.0.7 (Oxford, United Kingdom, www.fmrib.ox.ac.uk/fsl) (Woolrich et al., 2001; Forman et al., 1995) and included head movement artifact correction (Jenkinson et al., 2002), nonbrain tissue elimination (Smith, 2002), high-pass filtering (100 s), spatial smoothing at 5 mm full-width half-maximum, and mean-based intensity normalization as described previously for resting-state fMRI analyses (Fox et al., 2005; Uddin et al., 2009). Excessive head movement was corrected using motion scrubbing through nuisance regression (Power et al., 2012). We used the tool fsl_motion_outliers within FSL to identify TRs that showed instantaneous changes in blood oxygen level-dependent (BOLD) intensity that exceeded threshold (75th percentile + 1.5× interquartile range). The average number of