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Comparing test-retest reliability of dynamic functional connectivity methods

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A B S T R A C T

Due to the dynamic, condition-dependent nature of brain activity, interest in estimating rapid functional connectivity (FC) changes that occur during resting-state functional magnetic resonance imaging (rs-fMRI) has recently soared. However, studying dynamic FC is methodologically challenging, due to the low signal-to-noise ratio of the blood oxygen level dependent (BOLD) signal in fMRI and the massive number of data points generated during the analysis. Thus, it is important to establish methods and summary measures that maximize reliability and the utility of dynamic FC to provide insight into brain function. In this study, we investigated the reliability of dynamic FC summary measures derived using three commonly used estimation methods - sliding window (SW), tapered sliding window (TSW), and dynamic conditional correlations (DCC) methods. We applied each of these techniques to two publicly available rs-fMRI test-retest data sets - the Multi-Modal MRI Reproducibility Resource (Kirby Data) and the Human Connectome Project (HCP Data). The reliability of two categories of dynamic FC summary measures were assessed, specifically basic summary statistics of the dynamic correlations and summary measures derived from recurring whole-brain patterns of FC ("brain states"). The results provide evidence that dynamic correlations are reliably detected in both test-retest data sets, and the DCC method outperforms SW methods in terms of the reliability of summary statistics. However, across all estimation methods, reliability of the brain state-derived measures was low. Notably, the results also show that the DCC-derived dynamic correlation variances are significantly more reliable than those derived using the non-parametric estimation methods. This is important, as the fluctuations of dynamic FC (i.e., its variance) has a strong potential to provide summary measures that can be used to find meaningful individual differences in dynamic FC. We therefore conclude that utilizing the variance of the dynamic connectivity is an important component in any dynamic FC-derived summary measure.

1. Introduction

The functional organization of the brain has a rich spatio-temporal structure that can be probed using functional connectivity (FC) measures. Defined as the undirected association between functional magnetic resonance imaging (fMRI) time series from two or more brain regions, FC has been shown to change with age (Betzel et al., 2014; Gu et al., 2015), training (Bassett et al., 2015, 2011), levels of consciousness (Hudson et al., 2014), and across various stages of sleep (Tagliazucchi and Laufs, 2014). Traditionally, FC has been assumed to be constant across a given experimental run. However, recent studies have begun to probe the temporal dynamics of FC on shorter timescales (i.e., seconds instead of entire runs lasting many minutes) (Hutchison et al., 2013a; Preti et al., 2016). Such rapid alterations in FC are thought to allow the brain to continuously sample various configurations of its functional repertoire (Sadaghiani et al., 2015; Preti et al., 2016). These studies of dynamic FC have also enabled the classification of whole-brain dynamic FC profiles into distinct "brain states", defined as recurring whole-brain connectivity profiles that are reliably observed across subjects throughout the course of a resting state run (Calhoun et al., 2014). A common approach to determining the presence of such coherent brain states across subjects is to perform k-means clustering on the correlation matrices across time. Brain states can then be summarized as the patterns of connectivity at each centroid, and additional summary metrics such as the amount of time each subject spends in a given state can be computed. Using this definition of brain state, it has been shown that the patterns of

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connectivity describing each state are reliably observed across groups and individuals (Yang et al., 2014), while other characteristics such as the amount of time spent in specific states and the number of transitions between states vary with meaningful individual differences such as age (Hutchison and Morton, 2015; Marusak et al., 2017) or disease status (Damaraju et al., 2014; Rashid et al., 2014). However, this approach towards understanding what has recently been termed the "chronnectome" is still in its infancy (Calhoun et al., 2014).

A number of methodological issues have limited the interpretability of existing studies using dynamic connectivity. For instance, detecting reliable and neurally-relevant dynamics in FC is challenging when there are no external stimuli to model. Dynamic FC research generally relies upon the use of resting state fMRI (rs-fMRI) data and therefore, it is unclear whether the states that are identified accurately reflect underlying cognitive states. Another issue is that dynamic FC methods substantially increase the number of data points to consider initially (e.g., a $T \times d$ (time-by-region) input matrix becomes a $d \times d \times T$ array). This is in contrast to statistical methods that reduce the dimensionality of the data. Also, the signal-to-noise ratio of the blood oxygen level dependent (BOLD) signal in rs-fMRI is low, and it is often unclear whether observed fluctuations in the temporal correlation between brain regions should be attributed to dynamic neural activity, non-neural biological signals (such as respiration or cardiac pulsation), or noise (Handwerker et al., 2012; Hlinka and Hadrava, 2015). Due to these methodological challenges, metrics of dynamic FC are sensitive to the method used to estimate them (Lindquist et al., 2014; Hlinka and Hadrava, 2015; Leonardi and Van De Ville, 2015), and uncertainty remains regarding the appropriate estimation method to use. An important concern moving forward is to establish methods that maximize the reliability of dynamic FC metrics, which in turn will enhance our ability to use individual variability in dynamic FC metrics to understand individual variability in behavior and cognitive function.

The most widely used method for detecting dynamic FC is the sliding window (SW) method, in which correlation matrices are computed over fixed-length, windowed segments of the fMRI time series. These time segments can be derived from individual voxels (Handwerker et al., 2012; Hutchison et al., 2013b; Leonardi and Van De Ville, 2015), averaged over pre-specified regions of interest (Chang and Glover, 2010), or estimated using data-driven methods such as independent component analysis (Allen et al., 2012a; Yaesoubi et al., 2015). Observations within the fixed-length window can be given equal weight as in the conventional SW method, or allowed to gradually enter and exit the window as it is shifted across time, a strategy that is used by the tapered sliding window (TSW) method (Allen et al., 2012a). Potential pitfalls of the family of SW methods include the use of arbitrarily chosen fixed-length windows, disregard of values outside of the windows, and an inability to handle abrupt changes in connectivity patterns.

Model-based multivariate volatility methods attempt to address these shortcomings through flexible modeling of dynamic correlations and variances. Widely used to forecast time-varying conditional correlations in financial time series, model-based multivariate volatility methods have consistently been shown to outperform SW methods (Hansen and Lunde, 2005). The dynamic conditional correlations (DCC) method is an example of a model-based multivariate volatility method that has recently been introduced to the neuroimaging field (Lindquist et al., 2014). Considered as one of the best multivariate generalized autoregressive conditional heteroscedastic (GARCH) models (Engle, 2002), the DCC method effectively estimates all model parameters through quasi-maximum likelihood methods. Additionally, the asymptotic theory of the DCC model provides a mechanism for statistical inference that is not readily available when using other techniques for estimating dynamic correlations, though such mechanisms are currently under development (Kudela et al., 2017). In a previous study, simulations and analyses of experimental rs-fMRI data suggested that the DCC method achieved the best overall balance between sensitivity and specificity in detecting temporal changes in FC (Lindquist et al., 2014). Specifically, it was shown that the DCC method was less susceptible to noise-induced temporal variability in correlations compared to the SW method and other multivariate volatility methods.

The goal of this study was to identify estimation methods that provide accurate and reliable measures of various dynamic FC metrics. In particular, we compared the reliability of summary measures estimated using a family of SW methods (that represent the most commonly used dynamic FC estimation methods) and those estimated using the DCC method (that represents a more advanced model-based multivariate volatility method). We assessed the reliability of two types of dynamic FC summary measures: 1) basic summary statistics, specifically the mean and variance of dynamic FC across time, and 2) statistics derived from brain states, specifically the dwell time and number of change points between states. We compared the reliability of these methods using two publicly available rs-fMRI test-retest data sets: 1) the Multi-Modal MRI Reproducibility Resource (Kirby) data set (Landman et al., 2011), which used a well-established echo planar imaging (EPI) sequence with a repetition time (TR) of 2000 ms, and 2) the Human Connectome Project 500 Subjects Data Release (HCP) data set (Van Essen et al., 2013), which used a simultaneous multi-slice EPI sequence with a TR of 720 ms. These two data sets differ in terms of the acquisition parameters used and in the preprocessing steps performed to clean the data, with acquisition and processing parameters for the former representing well-established procedures used by many rs-fMRI researchers, and those for the latter representing cutting-edge procedures designed to optimize data quality. We hypothesized that the DCC-estimated dynamic FC summary measures would be more reliable than those estimated using the conventional SW and TSW methods, and that dynamic FC summary measures obtained using the HCP data would be more reliable than those obtained using the Kirby data.

2. Methods

2.1. Image acquisition

2.1.1. Kirby data

We used the Multi-Modal MRI Reproducibility Resource (Kirby) from the F.M. Kirby Research Center to evaluate the reliability of dynamic FC summary measures obtained using a typical-length, standard EPI sequence, which were cleaned using established preprocessing procedures. This resource is publicly available at http://www.nitrc.org/projects/multimodal. Please see Landman et al. (2011) for a detailed explanation of the entire acquisition protocol. Briefly, this resource includes data from 21 healthy adult participants who were scanned on a 3T Philips Achieva scanner. The scanner is designed to achieve 80 mT/m maximum gradient strength with body coil excitation and an eight channel phased array SENSitivity Encoding (SENSE) (Pruessmann et al., 1999) head-coil for reception. Participants completed two scanning sessions on the same day, between which participants briefly exited the scan room and a full repositioning of the participant, coils, blankets, and pads occurred prior to the second session. A T1-weighted (T1w) Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) structural run was acquired during both sessions (acquisition time = 6 min, TR/TE/TI = 6.7/3.1/842 ms, resolution = $1 \times 1 \times 1.2$ mm^3, SENSE factor = 2, flip angle = 8°). A multi-slice SENSE-EPI pulse sequence (Stehling et al., 1991; Pruessmann et al., 1999) was used to acquire one rs-fMRI run during each session, where each run consisted of 210 vol sampled every 2 s at 3-mm isotropic spatial resolution (acquisition time: 7 min, TE = 30 ms, SENSE acceleration factor = 2, flip angle = 75°, 37 axial slices collected sequentially with a 1-mm gap). Participants were instructed to rest comfortably while remaining as still as possible, and no other instruction was provided. We will refer to the first rs-fMRI run collected as session 1 and the second as session 2. One participant was excluded from data analyses due to excessive motion.

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