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Evaluation of sliding window correlation performance for characterizing dynamic functional connectivity and brain states

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ABSTRACT

A promising recent development in the study of brain function is the dynamic analysis of resting-state functional MRI scans, which can enhance understanding of normal cognition and alterations that result from brain disorders. One widely used method of capturing the dynamics of functional connectivity is sliding window correlation (SWC). However, in the absence of a "gold standard" for comparison, evaluating the performance of the SWC in typical resting-state data is challenging. This study uses simulated networks (SNs) with known transitions to examine the effects of parameters such as window length, window offset, window type, noise, filtering, and sampling rate on the SWC performance. The SWC time course was calculated for all node pairs of each SN and then clustered using the k-means algorithm to determine how resulting *brain states* match known configurations and transitions in the SNs. The outcomes show that the detection of state transitions and durations in the SWC is most strongly influenced by the window length and offset, followed by noise and filtering parameters. The effect of the image sampling rate was relatively insignificant. Tapered windows provide less sensitivity to state transitions than rectangular windows, which could be the result of the sharp transitions in the SNs. Overall, the SWC gave poor estimates of correlation for each brain state. Clustering based on the SWC time course did not reliably reflect the underlying state transitions unless the window length was comparable to the state duration, highlighting the need for new adaptive window analysis techniques.

Introduction

Resting-state functional MRI (rsfMRI) has had much success as a tool for the study of normal and disordered brain function (Rombouts et al., 2005; Sorg et al., 2007; Zang et al., 2007; Xia et al., 2013). Initially, rsfMRI analysis assumed networks in the resting-brain were stationary over the whole scan length (typically ranging from six to ten minutes), but more recently methods that examine the network connectivity as a function of time have been applied. Several studies have reported that the connectivity of these networks changes over the course of the scan (within a few seconds) and reveal a number of functional connectivity (FC) states in the brain, which can be sensitive to changes related to neurological disorders (Sakoğlu et al., 2010; Leonardi et al., 2013a, 2013b; Damaraju et al., 2014; Li et al., 2014; Ou et al., 2015). These dynamics are also linked to changes in human behavior (Kucyi et al., 2013; Thompson et al., 2013a, 2013b; Jia et al., 2014; Sadaghiani et al., 2015).

Sliding window correlation (SWC) is the simplest and most commonly used method for dynamic FC analysis and most of the dynamic FC studies use it at some point (Schulz and Huston, 2002; Chang and Glover, 2010; Kiviniemi et al., 2011; Handwerker et al., 2012; Chang et al., 2013; Hutchison et al., 2013a, 2013b; Keilholz et al., 2013; Thompson et al., 2013a, 2013b; Wilson et al., 2015). It should be noted that in this study dynamic FC refers to the dynamics of resting-state networks only and not the dynamics because of any environmental input or task. In the SWC, a temporal window of a certain size and shape is selected, and the correlation coefficient between two signals of interest within that window is computed. Afterwards the window is shifted (slided) by some offset, and the process is repeated for the entire scan length. Despite the popularity of the SWC, results are strongly dependent on window length (Sakoğlu et al., 2010; Hutchison et al., 2013a, 2013b; Keilholz et al., 2013; Wilson et al., 2015) and the ideal values for this and other parameters for the dynamic FC analysis remain unknown. A nice but simplified examination of the relationship between the minimum window length and the frequency components of the signals has been presented (Leonardi and Van De Ville, 2015). Another study used windows of different sizes on resting state and sleep data

Abbreviations: rsfMRI, resting-state functional magnetic resonance imaging; FC, functional connectivity; SWC, sliding window correlation; SN, simulated network; GT, ground truth.

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and reported that short epochs can be used effectively for dynamic FC analysis (Wilson et al., 2015). However, no study has convincingly identified the best window length for dynamic FC analysis. Furthermore, since these brain networks change states at random times, using the same window over the entire rsfMRI scan may not be the optimum method to capture the true dynamic configurations of these networks. The effect of window length, offset, and other parameters has not been systematically examined in realistic data, and a recent study that looked at the effect of window length on the correlation between the BOLD signal and simultaneously-acquired local field potentials found that the optimal window length is somewhat ambiguous (Thompson et al., 2013a, 2013b).

After the SWC is performed pairwise for the brain areas of interest, clustering is often used to find the number of 'states' that occur over the length of the scan, and the times at which transitions occur (Hutchison et al., 2013a, 2013b; Allen et al., 2014; Damaraju et al., 2014; Shakil et al., 2014). The most commonly used method for clustering SWC results is based on the k-means algorithm (Hutchison et al., 2013a, 2013b; Allen et al., 2014; Damaraju et al., 2014; Shakil et al., 2014). The accuracy of the clustering depends on the clustering algorithm and the ability of the SWC to resolve transitions of interest, emphasizing the need to evaluate the SWC parameters.

The biggest obstacle in identifying the best approach to the SWC and clustering for dynamic FC analysis is that there is no 'ground truth (GT)' in standard rsfMRI data, since the actual network dynamics, number of states, and state transitions are all unknown. This study circumvents this problem by using simulated networks (SNs) with known transition points created from real rsfMRI data. We evaluate the SWC algorithm and the effects of window size, window shift, window type, noise, filtering, and sampling or repetition time (TR) on the SWC results, and on the correct identification of state transitions and durations obtained from these results using k-means clustering. As expected, window size and offset had a substantial impact on the accuracy of the results, followed by the impact of noise and filtering, while TR had a very small impact. Tapered windows resulted in poorer state identification than rectangular windows due to the abrupt sharp state transitions present in the SNs. These findings motivate further work on methods that can dynamically adapt the length of the window during the analysis or the formulation of an algorithm which can more accurately detect the state transition points.

Material and methods

Data and preprocessing

We used rsfMRI scans of nine healthy human subjects (four females, ages: 21–57 years, downloaded from Nathan Klein Institute's Enhanced Rockland dataset of 1000 Functional Conectome Project (http://www.nitrc.org/projects/fcon_1000/). The scans were done on SIEMENS MAGNETOM TrioTim syngo MR B17 scanner. The scanning parameters were: TR = 645 ms, voxel size = 3 mm isotropic, duration = 10 min, TE = 30 ms, slices = 40, multi-band accel, factor = 4, and time points = 900. Each scan contained 900 volumes and the initial 10 volumes of each scan were discarded to compensate for transient scanner instability. All preprocessing was done in statistical parametric mapping (SPM 12, http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included motion correction, coregistration of the functional images with the anatomical image, segmentation, normalization, and smoothing. Default parameter values from SPM12 were used during preprocessing but smoothing was done using a Gaussian kernel of size 8 and for normalization a voxel size of $3 \times 3 \times 3$ was chosen. The images were coregistered to the AAL atlas (Tzourio-Mazoyer et al., 2002) using nearest neighbor interpolation without any warping.

After preprocessing, five functional networks (dorsal DMN, ventral DMN, anterior-salience, visuospatial, and sensorimotor) were extracted using the masks from the Stanford FIND (http://findlab.stanford.edu/home.html) lab (Shirer et al., 2012) for all subjects.

Region-of-interest (ROI) time series

For each subject, seven, non-overlapping, three-dimensional, regions-of-interest (ROIs) consisting of $3 \times 3 \times 3$ voxels were chosen from each of the abovementioned five networks (dorsal DMN, ventral DMN, anterior-salience, visuospatial, and sensorimotor). The anatomical location of the ROIs in the five networks (taken from Supplementary data of Shirer et al. (2012)) is given in Supplementary Fig. 1. Maps of the five functional networks (taken from Supplementary data of Shirer et al. (2012)) along with the locations of the ROIs selected for the current study (arrows) are given in Supplementary Fig. 2. Each ROI time series was formed by extracting the intensities of the voxels in the ROI and then computing their mean at each time point. In order to observe the dependency of the analysis on the location of ROIs, we later performed the analysis on a second, entirely different sets of ROIs (shown in Supplementary Fig. 3). These ROIs were used to create simulated networks (SNs) as described in the next section. The averaged time series of each ROI was extracted and bandpass filtered (0.016–0.08 Hz, order 20 FIR) before the formation of the SNs. As expected, the ROIs that came from the same network were highly correlated, which was confirmed by computing the pairwise stationary correlations (Supplementary Fig. 4).

Sliding window correlation of actual resting-state networks

The main goal of this study was to analyze the performance of the SWC with variable parameters using SNs with known timing formed from real rsfMRI data. However, before starting this analysis we computed the pairwise SWC of the time series of the five actual networks (dorsal DMN, ventral DMN, anterior-salience, visuospatial, and sensorimotor) using the same window sizes as the ones used for the SNs (discussed in detail in the Simulated networks and sliding window correlation section). The purpose was to compare the SWC of the actual data with the results of previous studies (Hutchison et al., 2013a, 2013b; Keilholz et al., 2013; Wilson et al., 2015), and to determine how the abrupt intensity changes (outliers) introduced in our SNs due to state transitions (explained in the Simulated networks and sliding window correlation section) might influence results of the SWC.

Simulated networks and sliding window correlation

To form a SN, seven ROIs from one of the abovementioned rsfMRI networks were used. A portion of the time courses for these ROIs was taken and used as the time courses for the seven nodes of the SN until the first state transition point t_1. At t_1, a portion of the time courses from the seven ROIs of a different network was added to the SN to create a new state lasting from t_1 to t_2. This process was repeated until the desired length of 890 time points was obtained. For example, if we chose the nodes from ventral DMN from t_1 to t_2, then the nodes from t_2 to t_3 were from another network e.g. sensorimotor network of the same subject, and this process continued till we reached the last interval from t_{n-1} to t_n. Formation of the SNs in such a manner incorporated real rsfMRI data but gave us control over the time at which the SNs changed states (switched from one resting-state functional network to another) since we chose the transition times t_1 to t_n. It should be noted here that our SNs were formed from five resting-state networks but some of them had more than five transitions which means the data from the same resting-state network would be taken more than once in formation of these SNs. However, apart from one SN (QPeriodicSN explained later in this section) there is no repetition of data. For example, if the data from ventral DMN is taken for the durations t_{x-1} to t_x and t_{y-1} to t_y (x and y are integers) for a SN then it would be from two entirely different non-overlapping intervals of the ventral DMN. This step insured that

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