Characterizing temporal variations of functional connectivity in resting-state

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TARGET AUDIENCE Neuroimaging scientists in the field of resting-state fMRI

PURPOSE The studies of temporal variation in functional connectivity (FC) using resting-state fMRI have been drawing increasing interest [1]. Mounting evidence has shown that resting-state FC exhibits substantial temporal variability, and such FC variability is physiologically and psychologically relevant [2, 3]. At present, sliding-window analysis is a dominant approach to characterize temporal dynamics of FC, but a remaining issue in sliding-window analysis is how to select the window size adaptively to cater for FC dynamics with different degrees of non-stationarity. Ideally, the window size should be selected to adapt to local variation in FC, so that transient information of FC will not be overlooked due to the use of a large window while spurious changes will not be incorrectly identified by using a too short window. In this study, we firstly introduce a data-driven variable window selection method for adaptively estimating time-varying correlation coefficient (TVCC) of multiple time-series data. Subsequently, we apply this method to investigate temporal variability of large-scale FC in a resting-state fMRI dataset.

METHODS We analyzed an open access resting-state fMRI dataset of 102 healthy participants (age range: 20-23 years) from the 1000 Functional Connectomes Project. Imaging was performed on a 3-T scanner. The resting-state scans were 7.2 min, TR was 1.8 second and each BOLD signal contained 240 time instances. Functional images were preprocessed using SPM8. Preprocessing included motion correction, realignment, and spatial normalization. fMRI time series were extracted from 164 ROIs in six networks: the cerebellum, cingulo-opercular, default mode, fronto-parietal, occipital and sensorimotor networks. Signals from head motion, white matter and cerebrospinal fluid were regressed out from the ROI time series using linear regression model. Then the time series were band-pass filtered between 0.01 to 0.1 Hz. For each subject, dynamic FC between ROIs was estimated by the proposed data-driven adaptive TVCC estimation method, resulting in a 164×164×240 array representing the temporal changes in FC as a function of time. The idea of the adaptive TVCC estimation method is to describe the dot product of two signals as a smooth function plus noise and to find the optimal window, which can minimize the mean square error of the smoothed dot product (time-varying covariance) at each time instance. The adaptive TVCC estimation method consists of the following steps: (1) to estimate the dot product of each pair of BOLD signals; (2) to determine the variable optimal window size which minimizes the mean integrated squared error at each time instance by using an iterative plug-in rule [4, 5]; (3) to estimate the time-varying covariance (smoothed dot products) using the variable optimal window size; (4) to estimate TVCC from time-varying covariance. More details about the TVCC estimation method can be referred to [6]. TVCCs were Fisher-transformed to z values prior to further analysis. The variances of TVCC time-courses were calculated to evaluate temporal variability of FCs between ROIs. The FC variability between two networks was calculated as the mean of variances of TVCCs between each node in one network and each node in the other network. A permutation test was employed to check whether there was significant difference between within-network FC variability and between-network FC variability. The variances of all TVCCs were categorized into two groups: between-network and within-network, and the difference between the means of these two groups were calculated. Then we mixed all the variances of TVCC and randomly divided it into two groups containing *Nw* and *Nb* elements, where *Nw* and *Nb* were the original numbers of elements in the within-network and between-network groups. The difference between the means of these new groups was calculated as a sample value. We repeated above steps 10000 times to generate 10000 samples of the difference of means of two groups, yielding the permutation distribution of the difference of means. Finally, the *p*-value of the true difference between the means of two groups was obtained by locating the observed value under the permutation distribution.

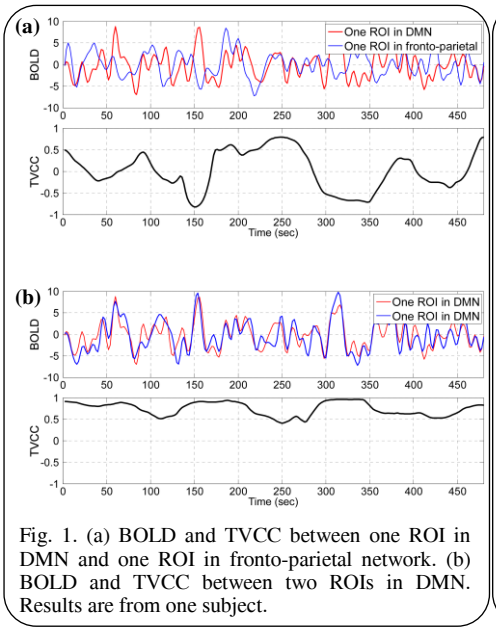

Fig. 1. (a) BOLD and TVCC between one ROI in DMN and one ROI in fronto-parietal network. (b) BOLD and TVCC between two ROIs in DMN. Results are from one subject.

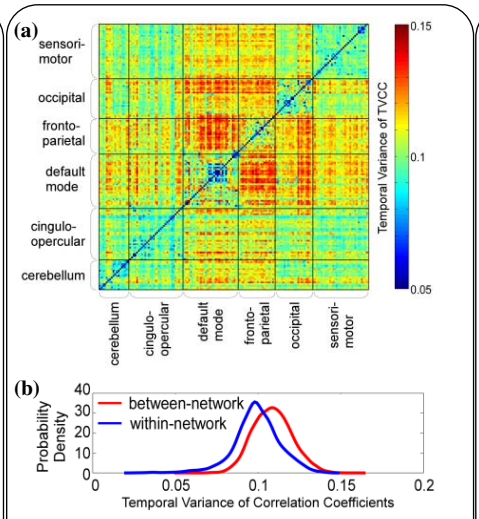

Fig. 2. (a) Temporal variances of TVCCs (group-averaged). (b) Probability densities of variance in FCs of all pairs of ROIs (within-network vs. between-network).

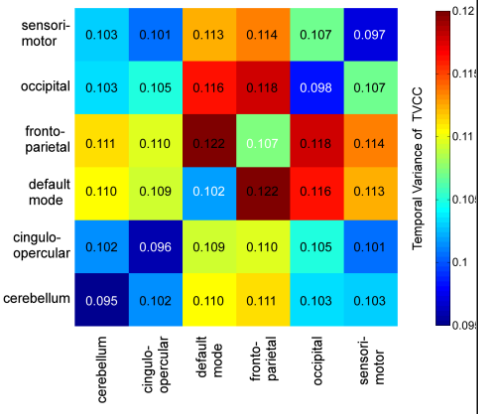

Fig. 3. FC variability between each pair of networks (calculated as the mean of temporal variance of TVCCs between each node in one network and each node in the other network).

RESULTS Fig. 1 shows that the FC between one ROI in the DMN and one ROI in the fronto-parietal network fluctuated remarkably, while the FC between two ROIs in the DMN was fairly stable. The group-averaged variances of TVCCs between each pair of ROIs are displayed in Fig. 2. It is shown that between-network FC variability was significantly larger than within-network FC variability (permutation test, $p = 3.6\times10^{-7}$). The FC variability between each pair of networks is further illustrated in Fig. 3. For each network, its within-network FC always had less variability than between-network FC. Particularly, the FC between the DMN and the fronto-parietal network exhibited markedly large temporal variability.

DISCUSSION AND CONCLUSION By employing a date-driven TVCC estimation method, we revealed that resting-state FCs show significantly dynamic patterns, and FCs between different ROIs as well as between different networks exhibit different degrees of variability. The results further demonstrated that between-network FC exhibits a significantly larger temporal variation than within-network FC, implying that the resting-network networks can also be characterized by the temporal variations of FC. The dynamic FCs with different variability in resting-state may convey important information about the integration and coordination of human brain network, and the relationship between such dynamic FC and behavior or physiological parameters warrant future studies.

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