BRAIN STATE CHANGE DETECTION VIA FIBER-CENTERED FUNCTIONAL CONNECTIVITY ANALYSIS

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ABSTRACT

Structural and functional brain connectivity has been extensively studied via diffusion tensor imaging (DTI) and functional MRI (fMRI) in recent years. An important aspect that has not been adequately addressed before is the connectivity state change in structurally-connected brain regions. In this paper, we present an intuitive approach that extracts feature vectors describing the functional connectivity state of the brain with the guidance of DTI data. The general idea is that the functional connectivity patterns of all of the fiber-connected voxels within the brain are concatenated into a feature vector to represent the brain's state, and brain state change points are determined by the abrupt changes of the vector patterns calculated by the sliding window approach. Our results show that we can detect meaningful critical brain state change time points in task-based fMRI and natural stimulus fMRI data. In particular, the detected brain state change points in task-based fMRI data well corresponded to the stimulus task paradigm given to the subjects, providing validation to the proposed brain state change detection approach.

Index Terms - fMRI, DTI, functional connectivity, brain state

1. INTRODUCTION

Recent neuroscience research suggests that the function of any area of the cerebral cortex, including that of primary visual cortex, is subject to top-down influences of attention, expectation, and perceptual task [1]. For instance, the function of any cortical area is not fixed, and each cortical area runs different ''programs'' according to context and to the current perceptual requirements [1]. Therefore, dynamic interactions between connections from higher- to lower-order cortical areas and intrinsic cortical circuits mediate the moment-by-moment functional switching in brain [1], and thus providing the neuroscience basis of brain state change.

In this paper, we present a brain state change detection approach based on the functional connectivity patterns of DTI-derived white matter fibers. Our basic premise is that axonal fibers obtained from DTI data are the structural substrates of functional connectivity between brain regions, and thus provide a natural anatomical localization for inference of functional connectivity. Therefore, we measure the correlation of fMRI time series of two ends of a fiber [2] to define the functional connectivity between the voxels it connects. The functional connectivity patterns of all of the white matter fibers within the whole brain are concatenated into a feature vector to represent the brain's state, called Connectivity State Vector (CSV), and the brain state change points can be determined by the abrupt changes of the CSV patterns calculated by the sliding window approach in the time series.

2. RELATED LITERATURE

There have been a variety of studies in the literature that tackled the problem of brain state change detection. For instance, statistical methods such as HEWMA has been applied on fMRI signals to detect BOLD signal state change in response to stimulus [5] [6], and the results have been related to brain state change. Brain networks have been reported to form and disappear during certain tasks, and the Temporal Clustering Analysis (TCA) approach was developed to detect the dynamic behavior of brain state changes [7], [8]. Also, brain state change has been discussed from a sensory processing perspective, and the brain will go through a succession of states when performing a task, with each state serving as the source of top-down influences for the subsequent states [1].

In our study, brain state is defined as the specific organization of brain's functional connectivity [9], in order to perform the corresponding task. Brain state changes are the brain's dynamics in response to external stimulus and/or previous brain states. For instance, in cognitive binding process, different regions in the inferior temporal cortex may dynamically synchronize to finish a task of object recognition [1]. Quantitative characterization and visualization of these time-dependent dynamics of functional networks can possibly elucidate important temporal attributes of functional connections that cannot be revealed by static brain network connectivity analysis. Hence, in this paper, we adopt a network-based approach [11] and utilize the whole brain functional connectivity pattern to represent brain state.

3. METHODOLOGY

3.1. Overview

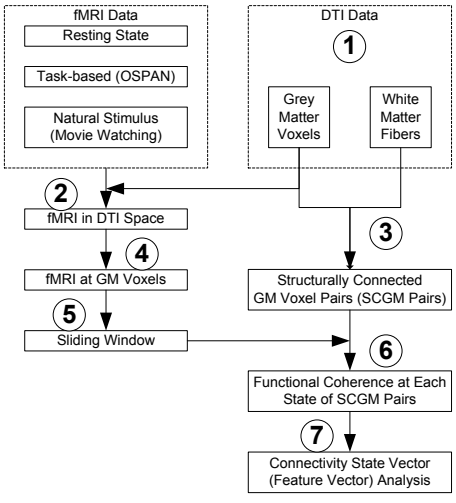

Fig.1 Demonstration of the algorithmic pipeline. The steps are as follows: (1) brain tissue segmentation (gray matter (GM) and white matter (WM)) and fiber tractography using DTI data; (2) fMRI to DTI space registration; (3) structurally-connected GM (SCGM) voxel pairs identification; (4) fMRI signal extraction at each GM voxel in SCGM; (5) applying sliding window to fMRI signals; (6) functional connectivity calculation within each sliding window; (7) feature vector construction for each sliding window.

The algorithmic pipeline is composed of seven steps and is summarized in Fig. 1. The identification of dynamical brain state change is based on two key techniques: 1) We used white matter fibers to guide the identification of meaningful functional connectivity of gray matter voxels, and only functional connectivity of gray matter voxel pairs (Step 3 in Fig. 1) that are connected by white matter fibers are considered to be elements of the CSV vector. This constraint greatly reduces the vector size from $O(n^2)$, n being the total number of gray matter voxels to $O(m)$, m being the total number of fibers. 2) We use dynamic sliding window (Step 5 in Fig. 1) to obtain transitions between time points by using the sliding window, rather than analyzing the single correlation between whole time series of two voxels [12]. As a result, the dynamic nature of brain networks can be captured. Additionally, we compare the similarities between the CSV vectors obtained from different time ranges to detect the critical brain state change points. The details of the 7 steps are in the below sections.

3.2. Data acquisition and preprocessing

Three types of fMRI data were analyzed in this study: OSPAN working memory tasked-based fMRI data [13], resting-state fMRI data [12] and natural-stimulus fMRI data [13]. In the OSPAN working memory tasked-based scan [13] [14], five subjects were scanned and fMRI images were acquired on a 3T GE Signa scanner. Acquisition parameters were as follows : fMRI: 64x64 matrix, 4mm slice thickness, 220mm FOV, 30 slices, TR=1.5s, TE=25ms, ASSET=2. Each participant performed a modified version of the OSPAN task (3 block types: OSPAN, Arithmetic, and Baseline) while fMRI data was acquired. In the natural stimulus fMRI scan [13], we randomly selected video shots from the TRECVID 2005 database [18], which were presented to the subjects during their scans. The acquisition parameters were as follows: dimensionality 128*128*60*240, spatial resolution 2mm*2mm*2mm, TR 5s, TE 25ms, and flip angle 90. In the resting state fMRI scan [12], nine volunteers were scanned in a 3T GE MRI system. Resting state fMRI data were acquired with dimensionality 128*128*60*100, spatial resolution 2mm*2mm*2mm, TR 5s, TE 25ms, and flip angle 90 degrees. DTI data were acquired using the same spatial resolution as the resting state fMRI data; parameters were TR 15.5s and TE 89.5ms, with 30 DWI gradient directions and 3 B0 volumes acquired. Preprocessing steps are referred to [12, 13, 15].

3.3. Functional connectivity measurement based on structurally connected gray matter voxels (SCGM pairs)

We define the structural connectivity based on the tracked white matter fibers from DTI images and mapped fMRI signals onto the gray matter volume using the similar methods in [12]. Denote the set of all gray matter voxels as V, $v_i \in V$, then the structural connectivity (*sc*) is defined as:

$$sc(v_g, v_h) = \begin{cases} 1, & if\ there\ is\ a\ fiber\ connecting\ v_g, v_h \\ 0, & otherwise \end{cases} \quad (1)$$

Examples of gray matter voxel pairs which are connected by fiber are displayed in Fig. 2(a). Since fMRI time series data has been transformed into the DTI space, we extract fMRI time series signal in each GM voxel and thus we can compute functional connectivity for any pair of GM voxels (Fig. 2(b)).

To capture the dynamic functional connectivity strength in the temporal domain, we defined the functional connectivity in each specific time interval from t_i to t_j in Eq. (2):

$$fc(v_g, v_h, t_i, t_j) = Pearson\ correlation\ between\ fMRI\ signals\ of\ v_g, v_h\ from\ t_i \text{ to } t_j \quad (2)$$

Assume that there are totally l time points, with time window size as *S,* and apply a sliding time window t_i to t_{i+s} $where\ 1 \le i \le l - S$. Denote the set of fiber-connected gray matter pairs as $\text{SCGM} = \{(v_g, v_h) | sc(v_g, v_h) = 1\}$ and the size as $\text{m} = |\text{SCGM}|$. The order of elements in SCGM was maintained by indexing all (v_g, v_h) in the set SCGM. As demonstrated in Fig. 2(b) and 2(c), different states (time window) have different functional connectivities. Our extensive observation from the data is that this strength is very dynamical along the time axis (e.g., in Fig. 3). To capture the connectivity state at each specific time window, we generated the CSV connectivity state feature vector $F_{i,s}$ defined at t_i to t_{i+s}, consisting of m (m is the total number of fibers in the whole brain) element with $fc(v_g, v_h, t_i, t_j), for\ \forall (v_g, v_h) \in SCGM$, which is similar to the idea used in [16]. This $F_{i,s}$ feature vector contains all connectivity strength measurements in a time window t_i to t_{i+s} for all fiber-connected GM voxel pairs.

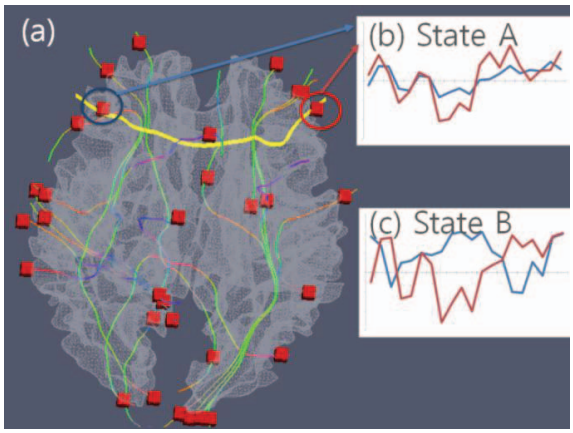

Fig.2 (a) A few SCGM pairs (gray matter voxel pairs connected by fiber) are displayed. Red boxes are gray matter voxels, and curves are fibers that connect pairs of GM voxels. Only 23 randomly selected SCGM pairs and 23 fibers connecting them are displayed for visualization purpose. Two circled voxels are structurally connected and has high functional connectivity at state A (Fig. 2(b)) and low functional connectivity at B (Fig. 2(c)); the yellow curve is the fiber connecting these two GM voxels. (b) Highly correlated fMRI time series from two circled voxels in state A. (c) fMRI time series from same voxels in state B which has low connectivity.

By applying threshold T_1 to all elements in $F_{i,s}$ and fill with 0 if $F_{i,s}(k) < T_1$ and 1 if $F_{i,s}(k) \ge T_1$, we constructed another state feature vector $E_{i,s}$. With a sliding window, we obtained $l - S$ state

vectors for both $F_{i,s}$ *and* $E_{i,s}$ *where* $1 \le i \le l - S$. $E_{i,s}$ can be viewed as a set of unweighted edges in state i of the functional networks. Both vectors are very useful for capturing the brain state change behavior. In Fig. 3, 253 (corresponds to time point) state feature vectors, with vector length of 91509 (corresponds to fiber number) are displayed, where we can observe clear state change points, suggesting the effectiveness of our CSV model for representation of brain state.

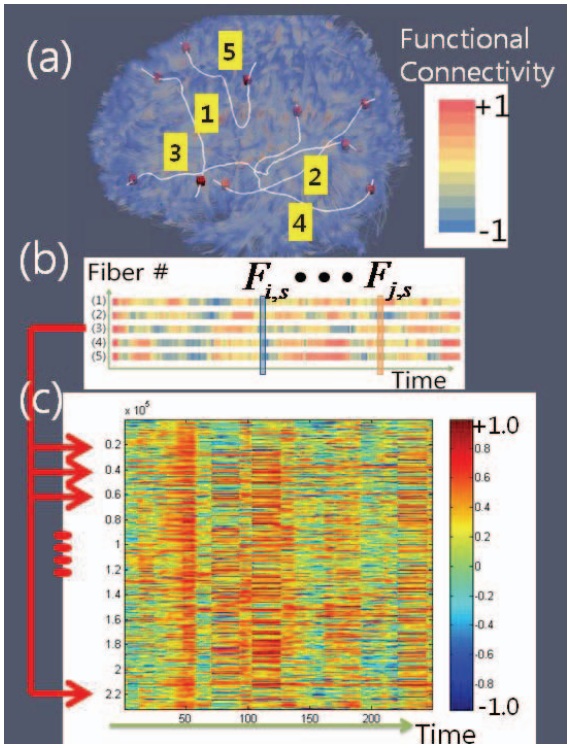

Fig.3 (a) DTI fibers. Five connections are highlighted. (b) Functional connectivities of five SCGM pairs changing along the time axis. The range is -1.0 to 1.0. (c) Combined CSV vectors $F_{i,s}$ from applying a sliding window. Matrix is $m\ by\ l - S$ $(91509\ by\ 253)$ having each CSV state vector as a column.

3.4. Constructing similarity matrix between CSV feature vectors for brain state change detection

We propose to detect brain state change by examining the temporal change of CSV vectors. To compare CSV vector similarity between connectivity states from t_i to t_{i+s} and from t_j to t_{j+s}, we compare similarity between $F_{i,s}$ and $F_{j,s}$ (or between $E_{i,s}$ and $E_{j,s}$). To measure the similarity between $F_{i,s}$ and $F_{j,s}$, the Pearson correlation coefficient of two CSV vectors is used. Figure 4 shows the symmetric matrix having similarity measurements of all (i, j) pairs of CSV vectors. To measure similarity between $E_{i,s}$ and $E_{j,s}$, we used L_1 norm for distance measure. So similarity is defined as $\frac{1}{m}\sum_{k=1}^{m}(1 - |E_{i,s}(k) - E_{j,s}(k)|)$. Fig. 4 shows an example of the similarity matrix for (i, j) pairs of CSV vectors. (point i represent $[t_i, t_{i+s}]$, and point j represent $[t_j, t_{j+s}]$).

If the brain state within a time period is stable, we will have high similarity between $F_{i,s}$ and $F_{j,s}$ when $j - i < S$, meaning that there is overlap between time window $(t_i\ to\ t_{i+s})$ and $(t_j\ to\ t_{j+s})$. On the other hand, if the brain state is not stable, there should be low similarity between $F_{i,s}$ and $F_{j,s}$ when $j - i > S$. Hence, if there is brain state change, we can detect the critical point having low similarity with overlapping window and high similarity with less or non-overlapping window (Fig. 4). That is, the brain state change could be identified as the abrupt change in the similarity matrix. It should be noted that the CSV represents all of the fibers in the whole brain, and thus the brain state change shown in Fig. 4 reflects the global functional connectivity change in the brain.

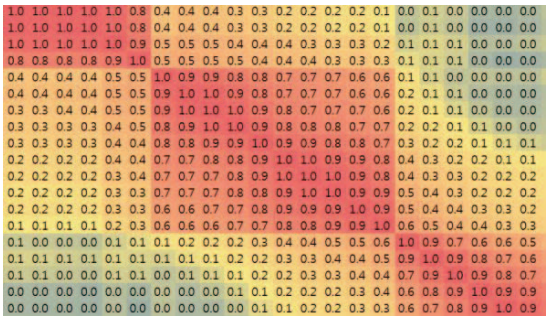

Fig.4 Similarity matrix between CSV feature vectors, showing clear boundaries that represent brain state changes.

4. EXPERIMENTAL RESULTS

In this section, we applied the approaches in section 3 on three datasets to evaluate and validate the proposed framework. The first experiment used task-based fMRI data to validate the brain state change detection results as there are benchmark block-based stimuli in task-based paradigm. In the second experiment, we used the proposed framework to investigate brain state changes in resting state and under natural stimulus. The third experiment compared our approach with the TCA method in [7].

4.1. Results on task-based fMRI data

We applied the approaches in section 3 on the working memory task-based fMRI data [13] [14]. We have tried window size from 11 to 35 time points and only two window sizes 11 and 23 are chosen for display purpose in this paper. Using window size 23, there were totally 248 overlapping windows and corresponding CSV vectors obtained from the task-based fMRI data. The CSV vectors of one randomly selected subject are shown in Fig. 5.

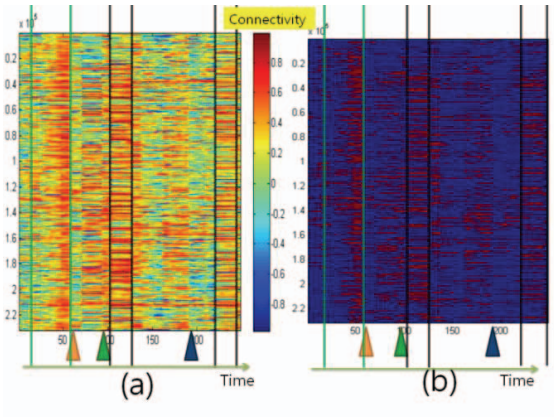

Fig.5 CSV vector visualization over time. (a) Matrix with $F_{i,s}$ as columns. (b) Matrix with $E_{i,s}$ as columns.

From Fig. 5, we can see abrupt changes (marked by colored lines) between CSV feature vectors, which corresponds to our premise that the human brain goes through a series of state changes when performing different tasks. Such trend can be more clearly seen in the similarity map in Fig. 6, where each cell corresponds to the similarity between each pair of CSV feature vectors (the diagonal line is the correlation of a feature vector with itself) and the color of each cell represents the value of correlation. From the correlation map, boundaries of CSV feature vector changes, represented by blue columns in Fig. 6, can be clearly identified. Intuitively, the difference between the CSV feature vectors is caused by the change of global brain connectivity at a specific time, which is just the brain state change according to our definition. Also, there are several boxes with relatively high correlation in Fig. 6, indicating that functional connectivity will remains relatively constant for a period of time, until another stimulus comes.

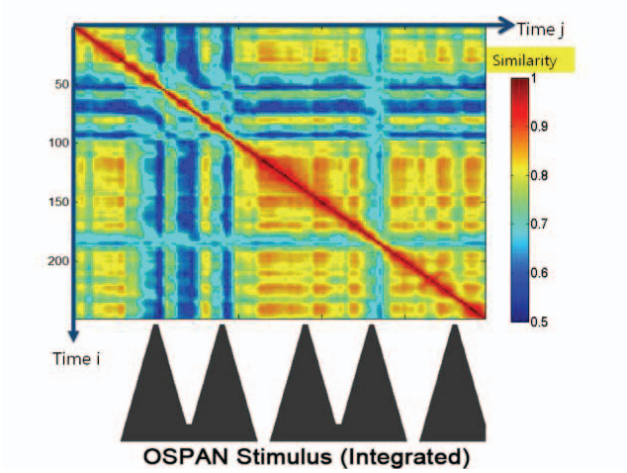

Fig.6 Alignment between CSV feature vector similarity map and the integrated OSPAN stimulus function. Blue areas correspond to brain state changes.

We averaged all of the elements in the CSV vector into a global value by equal weights, and represented the dynamics of global CSV value as a brain state curve. In Fig. 7, the global CSV value curve is displayed along with the OSPAN task stimulus curve. We can see that the global CSV value curve, which indicates the functional synchronization level of the whole brain, is in quite close correspondence with the stimulus curve. We integrated the sliding window stimulus function $S(t)$ (Fig. 7(a)) to obtain $\int_t^{t+s} S(t)dt$ for each CSV vector (Fig. 7(b)). Whenever the brain was under steady stimulus state or baseline state, the global CSV state curve reaches the peak (they are highlighted in yellow and green bubbles in Fig. 7 respectively). When in transitional state, the overall functional connectivity magnitude changes dramatically. In addition, we generated m (total number of fibers in the brain) random connections between any GM voxel pairs and measured their CSV curves (green curve in Fig. 7(b)). And the randomly connected GM voxels have significant lower functional connectivities than the fiber-centered SCGM, suggesting that the fiber-centered functional connectivity approach has much better sensitivity in detecting brain state changes.

The results in Fig. 5 – Fig. 7 are consistently reproducible in all of the four subjects we scanned in this study. Hence, we conclude that the proposed CSV model and global CSV value can effectively represent the overall functional connectivity in the brain, and thus their abrupt changes along the time axis can reasonably identify brain state change. Given that the global CSV change points correlated well with the stimulus curve in the task-based fMRI paradigm, we consider this result as a validation of our method for brain state change detection.

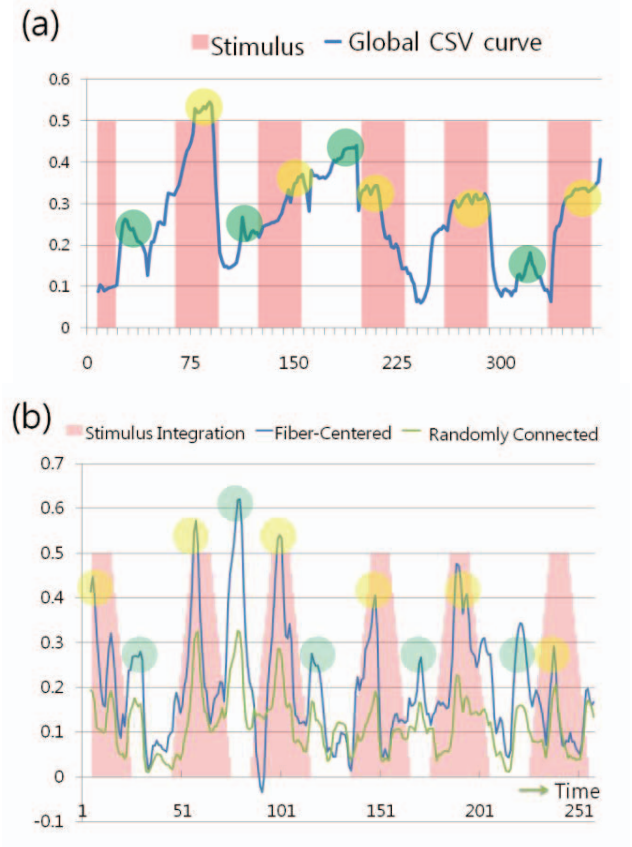

Fig.7 Alignments of stimulus curve and global CSV value curve. (a) Average of CSV feature vectors (global CSV value) vs. stimulus curve; (b) Global CSV value curves for fiber-centered and randomly connected voxels respectively, and the integrated stimulus curve; Points with peak connectivity in the stimulus periods are highlighted by yellow circles. Points with peak connectivity in baseline periods are highlighted by green circles.

In order to analyze the spatial distribution of brain connectivity patterns, we applied the HAMMER registration toolkit [17] to label each SCGM pair by a Montreal Neurological Institute (MNI) atlas region (thus each pair would belong to one or two MNI regions). After that, we picked 26 MNI atlas regions and computed the connectivity edge degree of each region at four different time windows. Then we obtained the regions with higher connectivity edge degree by thresholding, and visualized them in Fig. 8(a). The four time windows were marked by (1) to (4), with time window (1) and (3) were in baseline periods, (2) and (4) in (a) were in stimulus periods, as shown in Fig. 8(b). Also, in Fig. 8(c), the maps of connectivity edge degree of 26 regions were visualized. In each brain state from (1) to (4), the colored bar in Fig. 8(c) corresponds to a region visualized in Fig. 8(a) with the same color.

In Fig. 8(c), the length of each color bar is proportional to the connectivity edge degree of that region. From Fig. 8, it can be seen that, the activated brain regions formed different patterns in baseline periods and stimulus periods. In baseline periods, there are much less activated brain regions; while in stimulus periods, activated regions are distributed all over the brain.

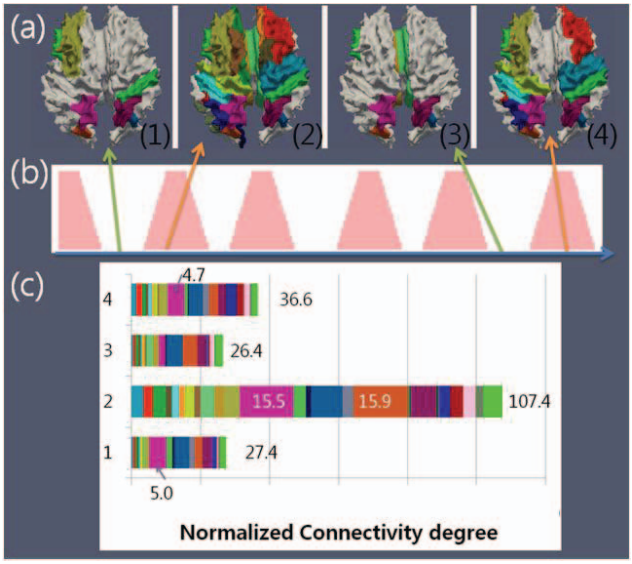

Fig.8 Relative activation levels of MNI atlas regions. (a) Regions having high connectivity are highlighted with their colors on cortical surface, during four separate brain states ((1)-(4)). (b) Integrated stimulus curve. (c) Proportional connectivity levels of 26 regions in state (1)-(4), some connectivity edge degrees are shown above the color bar. And the total connectivity edge degrees of each time window are shown at the right of the bar.

4.2. Results on resting state fMRI and natural stimulus fMRI data

We applied the approaches in section 3 on resting state fMRI data and natural stimulus fMRI data to detect brain state changes. As shown in Fig. 9(a), there is no abrupt state change in resting state, which indicates that the whole-brain functional connectivity is relatively stable during resting state. This can also be confirmed by the visualized CSV feature vectors in Fig. 9(c). This result is reproducible in all of the nine subjects' brains, indicating that the CSV model is reasonable for the representation of brain state under rest.

When the approaches in section 3 were applied on natural stimulus fMRI data under movie watching [13], there are significant brain state changes, as shown in Fig. 9(b), which can also be observed by the visualized CSV vectors in Fig. 9(d). Due to the lack of quantitative measurements of natural stimulus of multimedia movie, at current stage, we only perform this qualitative studies and further quantitative analysis of the CSV vectors and natural stimulus curves are left to our future work. It should be emphasized that our CSV model and brain change detection method can clearly reveal the brain dynamics during natural stimulus of movie watching.

4.3. Comparison with TCA

Temporal clustering analysis (TCA) is a method that uses the fMRI BOLD signal to detect the occurrence of maximal signal response in the brain [7]. TCA is performed by creating a histogram of the voxels that reach their maximum signal at each time point in the time axis, and then the global signal peaks can be selected [7]. For the purpose of comparison, the TCA method was applied on the same dataset in section 4.1, and the result is shown in Fig. 10.

It can be seen in Fig. 10 that certain brain responses to the stimulus can be detected by TCA, and they are in correspondence with our results (highlighted by yellow circles). However, the number of brain state changes that can be successfully identified by our method is much more (green circles), meaning that our method is more sensitive to brain state changes. The above results are reproducible in all of the subjects we scanned. This result suggests the superiority of our CSV-based method over the TCA method. Our interpretation of the difference between our method and the TCA method is: TCA is performed on the raw fMRI signals, which might suffer from the low signal-to-noise ratio; while our CSV model is based on the temporal correlation curve between SCGM pairs, which reflects the dynamics of functional connectivity and might be more robust to noises [2].

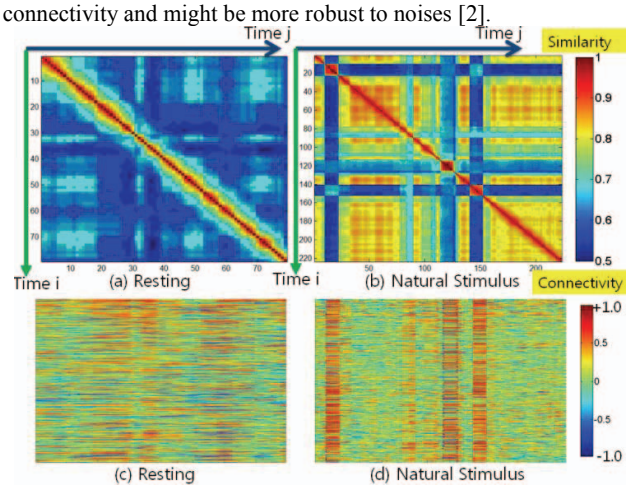

Fig.9 CSV feature vectors and similarity matrices in resting state and under natural stimulus. (a) Similarity matrix for resting state fMRI data. (b) Similarity matrix for natural stimulus fMRI data. (c) CSV feature vectors for resting state. (d) CSV feature vector for natural stimulus.

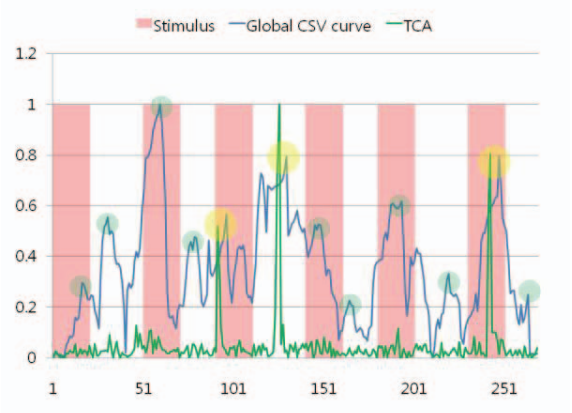

Fig.10 Result comparison with TCA. The blue curve is the global SCV curve obtained by our method, and the green line is the clustering result obtained by TCA. Regions detected in both

methods are highlighted by yellow circles. Regions detected by our method only are highlighted by blue circles.

5. CONCLUSION

In this study, we investigated the concept of brain state change from the global functional connectivity perspective, and developed a fiber-centered CSV model that can model and detect brain state change based on data-driven approaches. The CSV model represents brain connectivity state through temporal correlations of fMRI time series signals between structurally-connected grey matter voxels in sliding windows. The brain state change detection results obtained by our model on task-based fMRI data well correspond to the stimulus paradigm, and are better than the results obtained by the TCA method. Our CSV model is also applied to resting state fMRI and natural stimulus fMRI data and reasonable results are obtained, further indicating the effectiveness of our approaches.

In the future, we plan to improve the CSV model by integrating more information from functionally-specialized brain sub-networks such as the attention, emotion, vision, and language systems for better characterization of brain dynamics, and further evaluate and validate the approaches via synthesized and real fMRI data. Also, the CSV model and brain state change approach will be applied to study brain diseases that might be associated with abnormal brain dynamics.

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