Dynamic Analysis of Resting State fMRI Data and Its Applications

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ABSTRACT

While most resting state connectivity studies assume that resting-state fMRI time series are stationary, there is growing evidence indicating that they are in fact dynamically evolving. This paper describes two pieces of our work related to the resting state dynamics. We assume the resting-state brain to be in quasi-static states with spontaneous switching between them. First, we apply a hidden Markov model to the resting state fMRI data and derive model parameters reflecting the states. With this approach, we identified 9 reproducible states, which resemble resting state networks described in the literature. The second piece of work is the dynamic parcellations of thalamus, leading the state specific parcellations and their merged results, both of which revealed new insights about the thalamic function and connectivity.

Index Terms— fMRI, functional connectivity, hidden Markov model, resting state fMRI, brain dynamics

1. INTRODUCTION

Resting state fMRI (rsfMRI) is becoming a widely used methodology for studying brain connectivity. While most of the studies to date have assumed the resting state to be stationary, such an assumption has been shown to be invalid. In fact, there is ample data indicating that the resting state fMRI data is nonstationary. However, there is a general consensus that such dynamics is not completely random but can be described by several quasi-state states and spontaneous switching between them. The work described in the present paper is based on this notion.

First, even though the resting state can be considered to consist of several quasistatic states, what these states are and when they appear are not trivial to determine. Several approaches have been introduced for ascertaining rsfMRI data. However, existing analysis approaches have limitations. Treating each time point as independent, techniques such as co-activation patterns (CAPs) [1, 2] and spatial independent component analysis (ICA) [3] have not fully exploited information contained in the temporal order of rsfMRI time series. On the other hand, while the sliding window approach [4] takes into account the sequential information in the data, the use of a fixed-length sliding window [5] may lead to the mixing of signal from multiple states in the same window, resulting in contamination and interference between states. Another dynamic approach, temporal ICA, can also be employed to investigate fMRI time series [6] but it is limited by the assumption of temporal independence [7].

One alternative approach is modeling with a hidden Markov models (HMM) which can describe the latent state switching process of the brain as a Markov chain with different transition probabilities between states. This dynamic model explicitly takes into account the temporal order of data and is not restricted by the aforementioned limitations. The HMM has been employed as a sequential modeling tool in studying the brain [8-11]. HMM was applied to electrophysiological data and detected 4 brain states of neuronal firing patterns in rodents subjected to different types of stimuli [8]. Applied to human data, the HMM was able to show changes in functional connectivity patterns in magnetoencephalography [9] and fMRI [10, 11]. On a related note, the hidden Markov random field, was applied in fMRI to detect binary state (on/ off) switching on voxel level [12-14]. The approach we propose here is significant different from existing fMRI work. In addition, we also introduce a method to determine the number of brain states based on the reproducibility of the algorithm.

Recently, rsfRMI connectivities have also been used as a basis to parcellate the brain. For example, whole brain parcellation was derived using a clustering technique [15] and thalamus was segmented using connections to different regions of the cortex [16]. With the understanding that the resting state brain can be described by a number of quasistatic states, it makes sense to parcellate the brain structures using a state-dependent approach. Thus, our second piece of work is to perform a state-specific parcellation of the thalamus based on its connections to the cortex and examine the state-specific parcellations and combined parcellation.

2. METHODS

2.1. Hidden Markov modelling

It has been shown that the brain is constantly switching from one metastable state to another [17]. In this work, the switching process of brain states was modeled as a Markov chain (GHMM), with the brain state represented by a multivariate Gaussian distribution. In order to derive the GHMM that best fits the fMRI observations, its parameter set $\tilde{\lambda}$ was estimated using the following objective function:

$$L = \arg \max_{\lambda} P(\boldsymbol{O}|\lambda), \qquad (1)$$

where λ is the parameter set for the GHMM, $\mathbf{O} = \{\mathbf{O}_t\}, t = 1, 2, ..., T$, are rsfMRI time series with T being the length of fMRI time series. The probability of the observations under a state is modeled as a multivariate Gaussian distribution with the mean vector representing the average activation pattern of each brain state.

The Baum-Welch algorithm [18] was employed to solve the optimization problem in equation (1). To initialize the algorithm, the fMRI time series, $\boldsymbol{0}$, were fed into a k-means clustering program to identify M cluster centers, and the resultant cluster centers were used to initialize the mean of the Gaussian distribution.

Different initializations of the Baum-Welch algorithm may converge to different local optima. While it is a common problem for approaches that require nonlinear optimization, it is turned around and used a means to determine the number of states. More specifically, we split our data of 100 subjects into 2 non-overlapping groups of subjects (50 subjects each), and trained the GHMM on each half of the dataset. The brain states, with a range of preset number, were extracted from both halves and compared to for their reproducibility. As shown in Fig. 1, the reproducibility was the highest when the number of states was set to 9. Therefore, our final results of GHMM analysis of resting state fMRI data were obtained with 9 states.



Fig. 1. The reproducibility of each brain state when total states' number is set to 9 (left) and 30 (right)

Upon the estimation of the parameters, the Viterbi algorithm [19] was used to decode the optimal brain state sequence, $\{q_t\}, t = 1, 2, ..., T$. We also calculated the posterior probability, $P(q_t|O, \tilde{\lambda}), t = 1, 2, ..., T$, of each brain state at all the time points.

2.2. Dynamic parcellation of thalamus

As previously used by Zhang *et al.* for thalamus parcellation with resting state connectionivity [16], our parcellation also focused on the connectivity of thalamic voxels with 5 cortical regions of interest (ROIs) in each hemisphere (10 total). These ROIs are prefrontal cortex (PFC), premotor

cortex (PMC) plus motor cortex (MC), somatosensory cortex (SC), parietal cortex (PC) plus occipital cortex (OC), and temporal cortex (TE). The thalamus was extracted using the Harvard-Oxford subcortical structural atlas (<u>http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases</u>) and voxels in ventricles or white matter regions were removed.

Preprocessing of the rsfMRI data included standard steps of rigid-body motion correction, cross-modal registration, spatial transformation, denoising with the ICAbased "fix" algorithm and regressing out nuisance signals [20, 21]. Further steps included band-pass filtering (0.009 Hz < f < 0.08 Hz) and spatial smoothing (FWHM = 6 mm)

This preprocessed data were fed into our analysis pipeline as follows. A sliding time window approach was applied to divide thalamus and cortex fMRI signals into windowed time series. Thalamo-cortical connectivity matrices were generated for each of these windows, temporally concatenated across subjects, and fed into a normalized spectral clustering algorithm to derive thalamocortical connectivity states at the group level, resulting in 9 states. Within each one of these states, fMRI time series from all subjects were temporally concatenated for deriving state-specific thalamo-cortical connectivity matrices.

For thalamus parcellation, the normalized spectral classifier was applied again for each state. Classifications of left and right thalamus were performed separately according to ipsilateral thalamocortical connectivity patterns. State-specific parcellations were examined individually and then combined to produce a merged parcellation by superimposing parcel boundaries from all states. In this merged result, different subunits were labeled according to their spatial overlap with subunits in a histology atlas [22]. For comparison purposes, static thalamus segmentation was also performed in a fashion similar to the dynamic analysis described in the subsequent section with the exception that the entire fMRI dataset was treated as a single state.

3. REULSTS

3.1. Hidden Markov modelling

Fig. 1 illustrates the reproducibility for two different of states: 9 and 30. It is evident that with 30 states, some of the states are not highly reproducible, possibly leading to unreliable results. When the number of states was reduced to 9, highly reproducible results were obtained. This result led us to set the number of states to 9.

The 9 reproducible states exhibit remarkable spatial contiguity, with clearly identifiable regions distributed over the brain. More interestingly, the spatial patterns of these states resemble those of resting state networks that have been derived based on stationary assumption of the fMRI time series. For example, the HMM states 2, 6, and 7 correspond to the attention network, as shown in Fig. 2. Furthermore, the spatial patterns of GHMM derived states exhibit similarities to those derived using an entirely different approach, co-activation patterns, which were

derived using an entirely different approach without the use of sequential information in the time series. An example of this similarity is also shown in Fig. 2.



Fig. 2. States with activation in attention network derived by HMM and the corresponding co-activation patterns.

With the results of temporal state probabilities, it is evident that the brain switches between different states from time to time. The dynamics of the switching is rather interesting, with an average dwell time on any given state on the order of 10 seconds or so. There occupancy time for different states ranged from 20% to 5% in this group of subjects.

3.2. Dynamic Parcellation of Thalamus

Fig. 3 illustrates 9 state-specific parcellations. For comparison, the static parcellation was also included. It is interesting to regions that appear in all 9 state-specific parcellations are also present in the static parcellation. On the other hand, some regions are state-specific and do not appear in the static parcellation. This observation suggests that a static approach may miss some connections that only appear in a small fraction of time and their corresponding thalamic substrate may not be identified.

Fig. 4 presents the result of merging all 9 state-specific parcellations. For comparison, we have included a histologic parcellation (spatially down sampled to match our rsfMRI resolution) and the static parcellation. There is remarkable agreement between the merged parcellation and the histological parcellation while there is much poorer agreement between the histology and the static parcellation. More specifically, small subregions of the thalamus shown in the histogy, including AV, VLa, VPLp, and PuA, are clearly visible in the merged parcellation but are absent in the static parcellation.



Fig. 3. State-dependent thalamo-cortical connections for the medial dorsal nucleus (MD). The dynamically derived segmentation of MD are compared with the Morel atlas in (A) and their cortical connectivity patterns are shown for all 9 dynamic states and the static state in (B). The connectivity patterns in (B) are derived from the overlapping regions across all the dynamic and static states (the white regions) with the highest cortical connections highlighted

4. DISCUSSIONS

While the dynamics of resting state brain has attracted a great deal of attention in the study of resting connectivity, existing methods for characterizing the dynamics are still problematic. The HMM approach we describe here is a potentially powerful approach because it provides a means to ascertain the number of states, the spatial patterns of the states, and the temporal characteristics of the states.

Our results showed that the approach is highly robust in identifying the states of the resting brain. In addition, the spatial resemblance of results with existing networks and/or patterns in the literature suggests that the approach leads to valid results, despite the use of an entirely different strategy. Furthermore, our approach provides the temporal characteristics of the states. Finally, compared with approaches utilizing a sliding window, our approach is not affected by temporal blurring and leads to more temporally accurate results. Our results to date indicate that the HMM warrants further investigation.

Functional connectivity based brain parcellation is also becoming widely accepted in the field. Statespecific parcellation has not been attempted before. The results of such parcellation reveal rich connectivity and dynamic insights of the thalamus and demonstrate a powerful parcellation tool that matches better with histology. The state-specific results also exhibit the phasic thalamocortical connectivity patterns that are consistent with thalamic function and its dynamic nature. Other applications of this approach are expected to provide more insights about brain connectivity.



Fig. 4. Atlas structures identified by the dynamic thalamus segmentation. These structures, including the anteroventral nucleus (AV), ventral lateral anterior nucleus (VLa), ventral posterior lateral posterior (VPLp), anterior pulvinar nucleus (PuA) can be seen in the merged dynamic parcels but not in the static parcels (A). The dynamic cortical connectivity patterns for each of these regions are shown (B). The strongest connections are marked with a solid bar.

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