Inferring Group-Wise Consistent Multimodal Brain Networks via Multi-view Spectral Clustering

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Abstract. Quantitative modeling and analysis of structural and functional brain networks based on diffusion tensor imaging (DTI)/functional MRI (fMRI) data has received extensive interest recently. However, the regularity of these structural or functional brain networks across multiple neuroimaging modalities and across individuals is largely unknown. This paper presents a novel approach to infer group-wise consistent brain sub-networks from multimodal DTI/fMRI datasets via multi-view spectral clustering of cortical networks, which were constructed on our recently developed and extensively validated large-scale cortical landmarks. We applied the proposed algorithm on 80 multimodal structural and functional brain networks of 40 healthy subjects, and obtained consistent multimodal brain sub-networks within the group. Our experiments demonstrated that the derived brain sub-networks have improved inter-modality and inter-subject consistency.

Keywords: DTI, fMRI, multimodal brain connectivity, multi-view clustering.

1 Introduction

Studying structural/functional brain networks via DTI/fMRI has attracted increasing interest recently due to its potential in elucidating fundamental architectures and principles of the brain [1]. E.g., in [2], Beckmann applied PICA to analysis fMRI; in [3], the functional connectivity in resting brain is studied to infer default mode network. In many previous studies, structural and functional brain networks are typically examined separately, leaving their relationship largely unknown. In addition, the regularity of the structural or functional brain networks across multiple neuroimaging modalities and across different brains has rarely been investigated. Essentially, better quantitative characterization of the relationship between multimodal brain networks and its consistency across individuals could significantly advance our understanding of the human brain architectures [4].

In response to this issue, this paper presents a novel approach to infer group-wise consistent brain networks from multimodal DTI/fMRI datasets via multi-view spectral clustering of large-scale cortical landmarks and their connectivities. Based on our

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recently developed and validated large-scale connectivity-based cortical landmarks [5] as network nodes, we constructed both structural and functional brain networks from multimodal DTI/fMRI data of 40 healthy brains. Then, we applied an effective multi-view spectral clustering algorithm [6] on these 80 multimodal structural and functional brain networks to derive consistent multimodal brain sub-networks.

The prominent advantage of multi-view spectral clustering methodology is that it can effectively deal with heterogeneous features by maximization of the mutual agreement across multimodal clusters in different views [6]. In this work, we considered each structural or functional network in a subject as a separate view of the studied large-scale network. We modeled the clustering of group-wise consistent multimodal brain sub-networks in a unified multi-view clustering framework, by which the substantial variability of large-scale brain networks across modalities (DTI and R-fMRI) and different individuals (40 subjects) is modeled and handled by the powerful multi-view spectral clustering method. This is the major methodological novelty and contribution of this paper.

Our experimental results have shown that the derived brain sub-networks via the multi-view spectral clustering method have improved inter-modality predictability and consistency in comparison with clustering results by single modality, and have improved inter-subject consistency. More importantly, they are consistent with current neuroscience knowledge and better explain the relationship between brain structure and function. Our study provides novel insights on inferring reliable and reproducible multimodal networks and network-based signatures for the elucidation of brain function and dysfunction in the future.

2 Methods

Our computational pipeline is summarized in Fig. 1. Both structural and functional brain networks (Fig. 1a-b) were constructed from DTI and resting state fMRI (R-fMIR) data of the same group of subjects based on our recently validated 358 cortical landmarks [5]. The joint connectivity matrix (Fig. 1c) is then computed via multi-view spectral clustering algorithm. Then, the clustering procedure generates group-wise consistent multimodal sub-networks (Fig. 1d), which are then projected back to the original 358 cortical landmark space for visualization and validation (Fig. 1e). Finally, we quantitatively compared different schemes in clustering brain network.

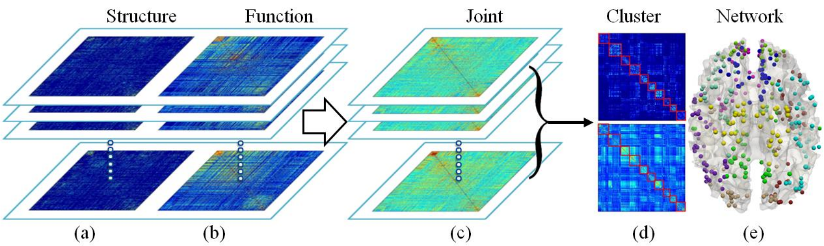

Fig. 1. The computational pipeline of proposed approach. (a) Structural connectivity matrix. (b) Functional connectivity matrix. (c) Joint connectivity matrix obtained via multi-view clustering algorithm. (d) Group-wise clustering. (e) Cluster sub-network.

2.1 Multimodal Brain Network Construction

A prerequisite to perform multi-view clustering of structural and functional networks is that the network nodes should possess correspondences across different modalities and individual brains. Recently we created and validated 358 cortical landmarks that have intrinsically established structural and functional correspondences in different brains [5], providing natural and ideal nodes for brain network construction. In brief, each of the 358 cortical landmarks was optimized to possess group-wise consistent white matter fiber connection patterns, which have been demonstrated to be predictive of functional localizations in the brain [5, 7]. The neuroscience basis is that each brain's cytoarchitectonic region has a unique set of intrinsic axonal inputs and outputs, called the "connectional fingerprint" [8], which largely determines the functions that brain area can perform. In particular, the functional correspondences of these 358 cortical landmarks were extensively validated by functional brain networks derived from both task-based fMRI data and R-fMRI data [5].

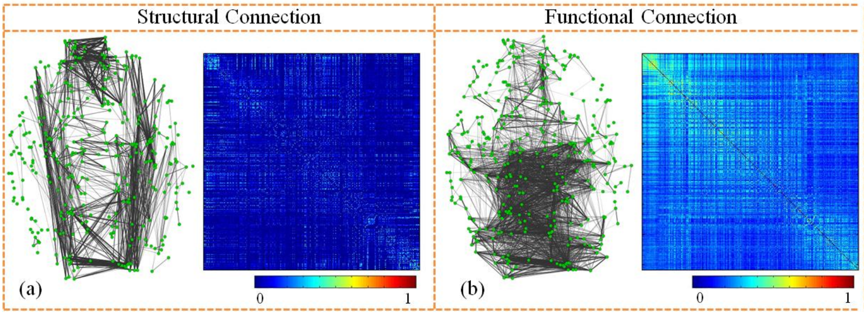

Fig. 2. An example of the constructed structural (a) and functional (b) networks. Both networks used the same set of 358 cortical ROIs as nodes. Each sub-figure shows a joint view of ROIs (green dot) and their connections (gray line) with corresponding connectivity matrix on right.

Based on these 358 cortical landmarks/ROIs (Fig. 2), we constructed both structural (Fig. 2a) and functional (Fig. 2b) networks for 40 healthy brains with multimodal DTI/R-fMRI data. We adopted R-fMRI data to construct the connectivity matrix of functional networks as follows. First, we performed brain tissue segmentation directly on DTI data [9], and used the gray matter segmentation map as a constraint for R-fMRI BOLD signal extraction. A principal component analysis was then conducted for the R-fMRI time series of all gray matter voxels within a ROI, and the first principal component was adopted as its representative R-fMRI BOLD signal. Then, the functional connection strength between ROIs is defined as the Pearson correlation of their R-fMRI BOLD signals.For the structural connectivity matrix, it was constructed from DTI data. Briefly, for each pair of ROIs, their connection strength is defined as the average FA (fractional anisotropy) value along the fiber bundle connecting the two ROIs. If there is no connecting fiber bundle between two ROIs, the connection strength is set to 0. An example of the constructed structural and functional networks is shown in Fig. 2.

2.2 Spectral Clustering

We used the spectral clustering to cluster the brain networks based on the connectivity matrix described above. In brief, spectral clustering is a technique that takes the advantage of the property of Laplacian of graph to reduce feature dimension for clustering. Specifically, k-means algorithm is used to cluster nodes on the first k eigenvectors of graph Laplacian with the smallest eigenvalue. The outline of the algorithm applied on our data is listed below. More details of the algorithm can be found in [10].

Input: Connectivity matrix S with size $n \times n$, where S_{ij} is the connection strength between nodes i and j. Number k of clusters to construct.
Output: Clusters of nodes.

1. Compute the normalized Laplacian $L = I - D^{-1/2} S D^{-1/2}$, where $D_{ii} = \sum_j S_{ij}$ is a diagonal matrix with graph degree on diagonal and 0 for the rest.
2. Compute the first k eigenvectors $u_1, ..., u_k$ of L with smallest eigenvalue.
3. Let U denotes a $n \times k$ matrix containing $u_1, ..., u_k$ that U_{ij} is the i^{th} value of u_j. Normalize each row of U to obtain V.
4. i^{th} row in V corresponds to the i^{th} node in S. Cluster nodes using each row of V as the feature vector via the k-means algorithm.

2.3 Co-training Approach for Multi-view Clustering

In our research problem, we have both structural connectivity and functional connectivity for large-scale brain network clustering. To find a common brain sub-networks across different modalities, the most intuitive way is to assign a weight to each view or modality. However, it is difficult to define optimal weights, especially when ROIs are unlabeled and there exists significant variability across modalities as shown in Figs. 2a and 2b. Thus, how to fuse these multimodal networks to achieve relatively consistent sub-networks becomes an important issue. Recently, a clustering method dubbed *multi-view clustering* has been developed to solve this type of problem [6, 11]. In this paper, we adopted a co-training approach based on spectral clustering [6] to maximize the agreement between structural network and functional network to find the consistent multimodal sub-networks of the human brain.

In spectral clustering, the reason why the first k eigenvectors can be used for clustering is that they contain the most discriminative information that can differentiate each cluster. By projecting the connectivity matrix to the space of the first k eigenvectors, the inner cluster details will be discarded and only essential information required for clustering retains. Thus, we can project the functional connectivity matrix to the space of the first k eigenvector of the Laplacian of structural connectivity matrix and then project it back and vice versa for structural connectivity matrix. By doing this iteratively, we can keep the common network between different modalities and discard the inconsistent information. Then, we combined feature vectors of both views and computed the Gaussian similarity between each ROI to obtain the joint connectivity matrix (Fig. 1c). The detailed algorithm is as follows [6].

Input: Connectivity matrix of two views S_1^0, S_2^0, number k of clusters to construct.

Output: Joint connectivity matrix S^*.

1. Compute the initial normalized Laplacian L_1^0, L_2^0 of each connectivity matrix, and the first k eigenvectors U_1^0, U_2^0 with smallest eigenvalue of L_1^0, L_2^0.
2. **for** i = 1 to *iter*
3. $S_1^i = [U_2^{i-1} U_2^{i-1^T} S_1^{i-1} + (U_2^{i-1} U_2^{i-1^T} S_1^{i-1})^T]/2$
4. $S_2^i = [U_1^{i-1} U_1^{i-1^T} S_2^{i-1} + (U_1^{i-1} U_1^{i-1^T} S_2^{i-1})^T]/2$
5. Compute Laplacian and corresponding first k eigenvectors U_1^i, U_2^i of S_1^i, S_2^i.
6. Normalize each row of U_1^i, U_2^i. Then combined normalized matrix to form a $n \times 2k$ matrix V.
7. i^{th} row in V correspond to the i^{th} node in S_1, S_2.
8. Compute the Gaussian similarity $e^{\frac{-\|V(i)-V(j)\|_2^2}{\sigma}}$ between each row to obtain the joint connectivity matrix S^*.

3 Experimental Results

3.1 Data Acquisition, Preprocessing and Experiment Setup

Our experiment was performed on 40 healthy adults. Both DTI and R-fMRI were acquired for each subject. The parameters are as follows: R-fMRI: 64×64 matrix, 4 mm slice thickness, 220 mm FOV, 30 slices, TR = 2s; DTI: 256×256 matrix, 3 mm slice thickness, 240 mm FOV, 50 slices, 15 DWI volumes. Preprocessing including tissue segmentation, surface reconstruction and fiber tracking was performed with the same method in [5]. Then a set of large-scale, group-wise consistent ROIs were obtained on the cerebral cortex of each subject using method in [5]. The structural and functional connectivity matrices are then computed using method described in section 2.1. Examples of ROIs and connectivity matrices are shown in Fig. 2.

For comparison, the clustering has also been performed on structure connectivity matrix, function connectivity matrix and the mean of these two modalities. When only the structural connectivity matrix is used, the clustering only considers structural networks and thus the clustering of functional networks will be determined by the clustering result of the structural networks. Similarly, when the functional connectivity matrix is used, the clustering results of functional network will determine the grouping of structural networks. In the third scenario of using averaged structural and functional networks, we assigned equal weight to each view to obtain an average connectivity matrix. Then, the result sub-network will be based on both networks.

3.2 Clustering Results

The clustering results when the cluster number *k* is 10 are shown in Fig. 3. Each cluster is highlighted by a red box. By visualization, it is evident that the proposed multi-view clustering method generates more consistent sub-networks across modalities. When only structure network is used for clustering, the ROIs that have strong fiber connections are clustered together. However, the functional networks obtained have weaker connections between ROIs within each sub-network (Fig. 3c). Similarly, the clusters obtained by clustering functional network only tend to have weaker structural connections within each clustered sub-network (Fig. 3d). In contrast, the clusters by multi-view clustering and mean connectivity matrix considered both aspects (Fig. 3a-b). Importantly, our further quantitative analysis in section 3.3 will demonstrate that the clusters by multi-view clustering are more mutually consistent and predictable across different modalities and subjects.

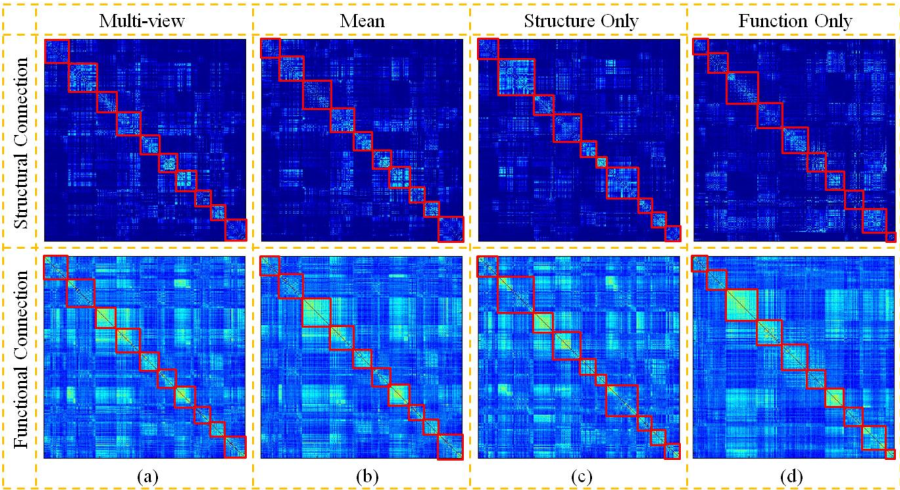

Fig. 3. Clustering results when *k* is 10. Each cluster of sub-network is highlighted by a red box. For each subfigure, the ID of the cluster from left to right is 1 to 10 respectively. (a)-(d) are results of clustering using multi-view, mean, structure only, and function only accordingly.

The clustered sub-networks by four schemes when k is ten are visualized in Fig. 4. Overall, there are certain similarities in the global patterns of clustered sub-networks by these four schemes (e.g. sub-network #3, #4, and #5 in Fig. 4). However, detailed examination of these sub-networks suggests that the multi-view clustering result has better agreement across modalities. For instance, according to the functional meta-analysis [5], both of the two ROIs highlighted by red box in Fig. 4 are involved in auditory perception and cognitive attention networks and should be clustered into the same network. But the clustering results based on structural connectivity matrix (Fig. 4c) and mean connectivity matrix (Fig. 4b) both failed in clustering these two ROIs into the same network.

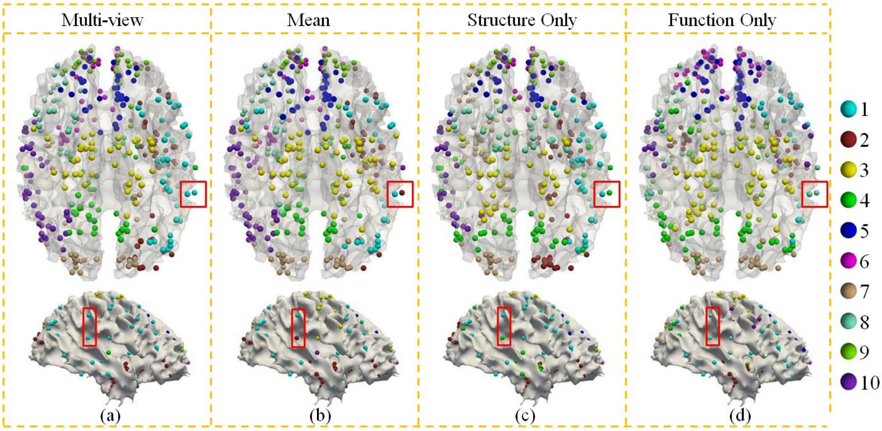

Fig. 4. Visualization of clustered brain sub-networks when k is 10. Each clustered sub-network is color-coded by a different color. The color scheme is on the right. The ID of each sub-network is the same with Fig. 3. (a)-(d) are results of clustering using multi-view, mean, structure only, and function only accordingly.

3.3 Quantitative Comparisons

In order to examine the clustering methods' sensitivity to cluster numbers and quantitatively compare these four schemes, we varied the cluster number k from 8 to 15 and measured the consistency between structural and functional sub-networks within each cluster. We used a linear regression model to predict functional network by structural network using the methods similar to that in [12]. Then, the regression residual is considered as the metric to assess how structural network is predictive and compatible with the functional network [12]. As shown in Fig. 5a, our results demonstrate that the regression residual by the proposed multi-view spectral clustering method is substantially smaller than other approaches, which indicates that the simultaneously clustered structural and functional brain sub-networks have improved predictability and consistency across modalities.

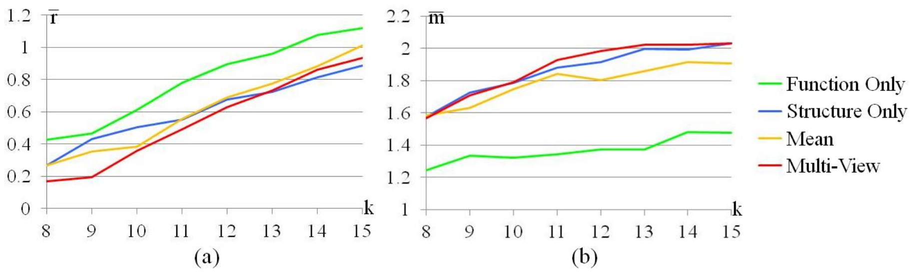

Fig. 5. Measurement of consistency between structural and functional networks of each clustered sub-network obtained by four different schemes. The horizontal axis is the number of clusters k, and the vertical axis is the consistency measurement. (a) Average residuals after linear regression from structural network to functional network within each cluster. (b) Average mutual information between each structural network and functional network within each cluster.

Furthermore, the mutual information between the structural and functional connectivity matrix within each clustered sub-network is computed and averaged across different brains. As mutual information is a quantitative measurement of the mutual dependence of two matrices, the relatively higher average mutual information within sub-networks by the proposed multi-view clustering result shown in Fig. 5b further indicates that this approach can generate more consistent multimodal brain networks across individuals compared with other three schemes.

4 Discussion and Conclusion

This paper presents a novel framework of clustering group-wise consistent multimodal brain networks based on DTI/R-fMRI datasets. The major methodological contribution of this work is modeling the inter-subject and inter-modality variations of brain networks by the multi-view spectral clustering algorithm. Experimental results demonstrated that the proposed multi-view clustering approach performs better than other schemes, and offered novel insights into the regularity of brain networks across modalities and individual brains. The effort in this paper can help construct both structurally and functionally meaningful and consistent brain networks in the future, which would have significant implications in basic and clinical neurosciences.

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