PATTERN RECOGNITION OF FUNCTIONAL BRAIN NETWORKS

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ABSTRACT

Functional brain network analysis has been a powerful tool for measuring brain function in normal and pathologic states based on resting state fMRI (rsfMRI) data. Recent advances in pattern recognition and sparse modeling have enabled us to characterize subject-specific functional brain networks and derive clinically useful biomarkers. In this paper, we briefly introduce our recent work in the development of functional brain network analytic techniques, including functional brain network modeling, pattern recognition of functional brain networks, as well as modeling heterogeneous patterns of functional connectivity. Finally, we discuss some current challenges that have received and are likely to receive more attention in the near future.

Index Terms— functional brain network, pattern recognition, sparse modeling, brain parcellation, brain decomposition

1. INTRODUCTION

Resting state fMRI (rsfMRI) provides reproducible, task-independent biomarkers of coherent functional activity linking different brain regions [1]. Functional brain network analysis of the rsfMRI data has revolutionized our ability to measure brain function in normal and pathologic states by modeling the brain as a network, consisting of a set of nodes and a connectivity matrix measuring functional coherence between the nodes [2-5]. A variety of quantitative measures of the brain network nodes and connectivity can be derived from the rsfMRI data and have been investigated at the group level as well as on an individual basis. Recent advances in pattern recognition and sparse modeling of rsfMRI data have enabled us to characterize subject-specific functional connectivity (FC) and derive clinically useful biomarkers, and many pattern classification studies of brain networks have demonstrated promising performance for predicting brain maturity and distinguishing diseased from normal brain states [6-11].

In order to characterize subject-specific functional brain networks and provide individualized biomarkers based on rsfMRI data, we have developed functional brain network modeling and pattern recognition methods [8-17]. We first introduce subject-specific functional network modeling methods to capture inter-subject variations in FC based on rsfMRI data [12-15, 17]. Our methods either parcellate the functional brain into local functional units [12, 14] or decompose the functional brain into spatial intrinsic connectivity networks (ICNs) with group constraints [13, 15, 17]. Both the local functional units and ICNs can be used as brain network nodes for constructing subject specific functional brain networks based on rsfMRI data of individual subjects without sacrificing correspondence across subjects. Second, we introduce pattern recognition methods of functional brain networks for establishing clinically useful biomarkers with better sensitivity and specificity in prediction and classification, including a sparse dictionary learning method to represent FC measures that provide improved robustness and interpretability for use in pattern recognition [9], a manifold learning method for identifying discriminative ICNs and constructing effective pattern classifiers [11], and a pattern recognition method for capturing heterogeneous patterns of functional connectivity [8]. Finally, we conclude this paper with a discussion of current challenges in pattern recognition of functional brain networks.

2. FUNCTIONAL BRAIN NETWORK MODELING

Functional brain network analyses model the brain as a network consisting of a set of nodes, e.g., spatial regions of interest (ROIs) or spatial ICNs, and a connectivity matrix measuring functional coherence between the nodes based on their associated time courses [2-5]. Since the brain network node definition can have a major impact on the network construction and analysis [18], many methods have been developed to define functionally meaningful network nodes, including brain parcellation [12, 19-24] and brain decomposition methods [4, 5, 15, 25-29].

2.1. Functional brain parcellation

As the precise functional organization of the brain remains unclear, no widely accepted means are available for defining nodes for brain network analysis. Anatomical atlases, such as the AAL atlas [30], have been adopted to define brain network nodes in many studies. However, anatomically

defined ROIs often do not possess the desired functional properties, such as intra-region functional homogeneity, inter-region functional distinctiveness, and inter-subject functional consistency of the same region, because the functional units do not locate relative to anatomical structures consistently across subjects [31-34].

To define functionally meaningful network nodes, many methods have been developed to partition the brain space into functionally coherent, spatially disjoint regions using clustering algorithms, such as region growing [19], hierarchical clustering [20], graphical models [21, 22], and normalized cuts [23, 24]. However, these parcellation methods are limited in requiring a good initialization step [19], generating parcels that are too isotropic [23, 24], relying on complex models [21, 22], or relying on iterative heuristics that could accumulate errors [20]. In order to overcome these limitations, at least partially, we have proposed a novel method, GRASP: geodesic Graph-based Segmentation with Shape Priors for the functional parcellation of the cortex [12], based on discrete graphical models, which depends on only one parameter that regularizes the number of parcels to be obtained, adopts a geodesic star shape prior to enforce each parcel's spatial connectedness, relies on an optimization strategy that can recover from errors, can produce very anisotropic parcels, and can be solved using efficient solvers [35]. Our method has been validated with 859 subjects from the PNC database [36] and achieved higher reproducibility than normalized cuts and hierarchical clustering for similar fit of the parcellation to the rsfMRI data [12]. Fig.1 shows representative brain parcellation results obtained using GRASP at different spatial scales. The method has been extended for deriving personalized brain parcellation results [17].

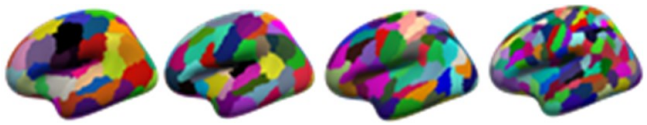

Fig. 1. Functionally coherent cortical regions determined by GRASP at different spatial scales. Data were obtained from [12].

2.2. Functional brain decomposition

Decomposing the brain into spatially overlapping components is an appealing method for modeling many-to-many mapping between brain regions and functions in rsfMRI data analysis. The brain decomposition methods typically build upon matrix factorization methods to decompose the functional imaging data into a set of spatial components, often referred to as ICNs, such as Default Mode Network (DMN). The most commonly used brain decomposition methods are built upon spatial or temporal independent component analysis (ICA) [4, 5]. More recently, a few methods have been proposed to discover ICNs from fMRI data with non-independence assumptions [13, 25-27, 29].

Most of the extant brain decomposition methods, except those with nonnegative constraints, tend to produce highly dispersed ICNs with both positive and negative loadings that are typically corresponding to anti-correlated signals. Since time courses associated with ICNs are projection results of the original fMRI time series onto the ICNs, it is not an easy task to interpret biological meaning of time courses of an ICN with both positive and negative loadings. To overcome these challenges, we propose a collaborative, sparse, nonnegative matrix decomposition framework, tailored to handle individual subject data for identifying a set of subject specific ICNs [13]. In particular, our framework is built on sparse non-negative matrix factorization methodology. Our method adopts several regularization terms to enhance its performance, including an inter-subject consensus prior to regularize the common structure of ICNs across subjects, intra-subject priors to obtain ICNs with spatial and functional coherence, and an intra-subject parsimonious prior in the temporal domain to encourage compact decomposition in a data-driven way. Our method has been validated based on both simulated and real rsfMRI datasets, and the experiment results have demonstrated that our method could obtain sparse, reproducible ICNs with better functional coherence and subject specific functional information [13].

3. PATTERN RECOGNTION OF FUNCITONAL BRAIN NETOWRKS

From functional brain networks, one can compute a variety of complementary measures to characterize functional network nodes and FC patterns. Such measures have been used as features in pattern recognition studies of rsfMRI data with promising performance for predicting brain maturity and distinguishing diseased from normal brain states [6-11].

3.1. Pattern recognition of FC measures

FC measures can be directly used as features in pattern recognition studies [6]. However, the FC measures are inherently correlated and reside in a non-Euclidean space. Prediction models that do not take into consideration the inherent correlations among network measures may fail to detect subtle and complex/multivariate FC patterns, as classification with correlated features typically has unreliable performance [37].

To characterize functional brain networks with improved robustness and interpretability, our group recently proposed sparse connectivity pattern (SCP) learning, leveraging the effective non-linearity of sparse dictionary learning as a means for describing the functional connectivity patterns of brain networks [9, 10]. The SCP learning algorithm could obtain a parsimonious

representation of whole-brain functional connectivity, consisting of a set of sparse, overlapping networks, referred to as SCPs. Due to the use of L1 norm minimization and the associated ability to select only a few of all possible SCPs for a decomposition of the brain connectivity measures, sparse decompositions have the ability to use different SCPs to represent data of different individuals. Furthermore, the sparsity constraint regularizes the data fitting and increases robustness to noise by balancing data fitting and model sparsity. As a consequence, the obtained SCPs are able to effectively represent clustered imaging data from heterogeneous populations, by using different SCPs for different subpopulations.

The resulting SCPs tend to be both more accurate in simulated data and more reproducible in split sample experiments [9, 10]. Furthermore, SCPs tend to be more interpretable than components obtained by other multivariate methods, such as ICA, as these other methods tend to form complex weighting of the data throughout the entire brain, rendering them difficult to interpret without proper thresholding. Finally, our methods also minimize the negative impact of correlated features on the robustness of prediction models by transforming the original correlated FC measures to a new coordinate system spanned by the SCP basis functions identified by the sparse coding. Our method has been validated based on several publicly available datasets, including PNC database [36]. Fig. 2 shows representative results obtained using our SCP learning method [9].

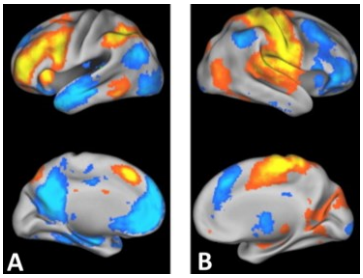

Fig.2. Two representative SCPs identified. A: DMN anti-correlated with fronto-parietal network; B: Sensorimotor regions anti-correlated with fronto-parietal network. Data were obtained from [9].

3.2. Pattern recognition of Spatial ICNs

Beside the FC measures, the subject specific spatial ICNs can also be treated as imaging features for statistical analysis and pattern recognition. For example, spatial independent components have been used as features in group comparison and pattern classification studies [7, 11]. Particularly, voxelwise values of spatial independent components were directly used as features for building classifiers [7]. However, due to high dimensionality of voxelwise measures of the spatial independent components, feature selection or feature transformation techniques have to be applied for reducing the feature dimensionality [7], which makes the interpretation of classification models difficult since they are built on part of the original components if feature selection is used or certain combinations of the original components if feature transformation is used. Moreover, a priori knowledge is often needed to select components and no systematic component selection method is available.

We have proposed a novel discriminant analysis algorithm, capable of automatically identifying discriminative spatial ICNs and combining them for classification [11]. The key techniques used in our method include 1) representing the independent components of each individual subject as a linear subspace, referred to as functional connectivity pattern (FCP), 2) adopting a Grassmann manifold distance metric to measure distance between FCPs of different subjects, and 3) using a component selection method to choose ICNs (selecting or removing whole ICNs) in conjunction with support vector machine (SVM) classifiers for optimizing the classification performance [11]. Our method also overcomes the scaling ambiguity problem associated with matrix factorization methods due to the use of the Grassmann manifold distance metric. Fig. 3 shows discriminative ICNs selected in a schizophrenia study [11].

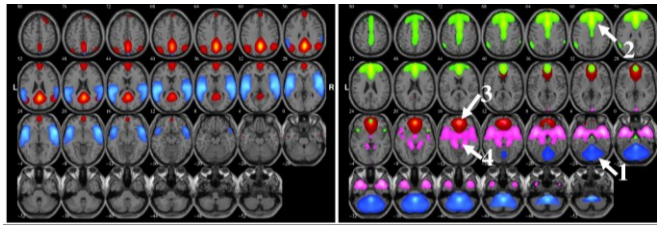

Fig. 3. Discriminative ICNs identified in a schizophrenia study (the numbers indicates the order of the ICNs were selected) using our Grassmann manifold learning based classification method. Data were obtained from [11].

3.3. Characterization of heterogeneous FC patterns

When comparing two groups, such as patients versus controls, a common assumption in both mass-univariate and multivariate pattern analysis methods is that there is a single underlying pattern capturing the group difference. Therefore, existing methods are often designed to seek a single pattern distinguishing between two groups. If only a subgroup of individuals displays a particular pathologic pattern, all these methods fall short of capturing the relevant differences, and at best find the “common denominator” among all individuals within a group. Such within-group heterogeneity calls for methods that characterize group differences using multiple patterns, corresponding to different sub-clusters or sub-populations.

To overcome this limitation, our group recently proposed pattern recognition methods to capture heterogeneity patterns that differentiate between two

populations [8, 38, 39], rather than a single common denominator pattern. Particularly, we proposed a method to explicitly model and capture heterogeneous FC patterns in a Mixture-of-Experts framework [8]. By combining unsupervised modeling of mixtures of distributions with supervised learning of classifiers, our method is capable of approximating non-linear boundary between two different groups with a piece-wise linear boundary, thus allowing discovery of multiple patterns of group differences. Our method has achieved promising pattern classification performance and identified discriminative subgroup patterns in validation experiments based on both simulated data and rsfMRI data from the Baltimore Longitudinal Study of Aging. Particularly, in the investigation of heterogeneous effects of aging on brain function in cognitively normal older adults (>85years) relative to a reference group of normal young to middle-aged adults (<60years), we found strong evidence for the presence of two subgroups of older adults, with similar age distributions in each subgroup, but different FC patterns associated with aging. As shown in Fig.4, while both older subgroups showed reduced FC in the DMN, they displayed different FC patterns [8].

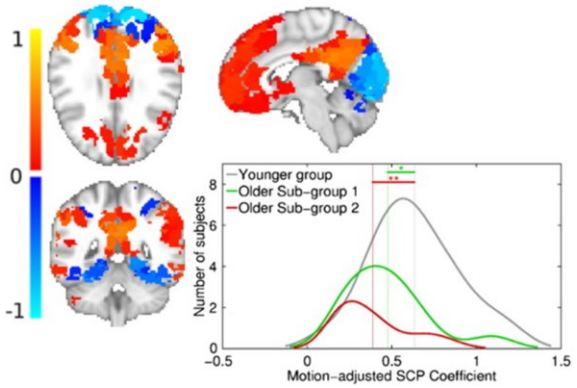

Fig. 4. A SCP whose average FC is reduced in both older subgroups, including the DMN regions (red–yellow) and their anti-correlation with the medial visual areas (blue–light blue). The distribution fit of the underlying SCP coefficient histograms is also shown for each subgroup. Significance levels are indicated as follows: '**' for p-value < 0.01 and '*' for p-value < 0.05. Data were obtained from [8].

4. CURRENT AND FUTURE CHALLENGES AND DIRECTIONS

Recent years have witnessed impressive progress in both functional brain network modeling and pattern recognition of functional brain networks. We briefly review some current challenges that have received and are likely to receive more attention in the near future.

Personalized brain network modeling has received increasing attention. Since brain network nodes play important roles in brain network modeling, effort has been devoted to the development of personalized brain parcellation [14, 17, 40, 41] and brain decomposition methods [15, 26, 28, 42]. It is essentially a multi-objective optimization problem to achieve a group-consistent, subject-specific functional parcellation or decomposition of the brain, and often a trade-off between group-consistency and subject-specificity has to be made. The existing studies often adopt heuristic strategies to compute a personalized brain parcellation or decomposition without losing comparability across subjects, such as initializing personalized computation with a group level result or regularizing the personalized results with a group similarity constraint. Although such strategies have been successful in many studies, mathematically principled ways are needed. As complementary methods, the brain parcellation and the brain decomposition methods have been developed in parallel. A unified framework of the parcellation and the decomposition may provide better modeling of the functional brain networks.

Many pattern recognition studies of brain networks have demonstrated promising performance for predicting brain maturity and distinguishing diseased from normal brain states [6-11]. In these studies, pattern recognition models are typically built upon either FC measures or measures of brain network nodes, particularly spatial ICNs. It is expected that an effective combination of both FC measures and measures of brain network nodes in pattern recognition could achieve better performance than pattern recognition models built upon either FC measures or measures of network nodes alone.

Our studies have also demonstrated that modeling heterogeneous imaging patterns explicitly in pattern recognition is capable of improving both pattern recognition performance and interpretability of the identified patterns [8, 38, 39]. Such a strategy might be also useful in the brain network modeling to define personalized brain network nodes by taking into consideration heterogeneous subgroup effects.

5. ACKNOWLEDGEMENTS

This study is partially supported by NIH grant EB022573.

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