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Connectivity-based parcellation of functional SubROIs in putamen using a sparse spatially regularized regression model

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ABSTRACT

In this paper, we present a novel framework for parcellation of a brain region into functional subROIs (Sub-Region-of-Interest) based on their connectivity patterns with other brain regions. By utilising previously established neuroanatomy information, the proposed method aims at finding spatially continuous, functionally consistent subROIs in a given brain region. The proposed framework relies on (1) a sparse spatially-regularized fused lasso regression model for encouraging spatially and functionally adjacent voxels to share similar regression coefficients; (2) an iterative merging and adaptive parameter tuning process; (3) a Graph-Cut optimization algorithm for assigning overlapped voxels into separate subROIs. Our simulation results demonstrate that the proposed method could reliably yield spatially continuous and functionally consistent subROIs. We applied the method to resting-state fMRI data obtained from normal subjects and explored connectivity to the putamen. Two distinct functional subROIs could be parcellated out in the putamen region in all subjects. This approach provides a way to extract functional subROIs that can then be investigated for alterations in connectivity in diseases of the basal ganglia, for example in Parkinson's disease.

1. Introduction

Functional magnetic resonance imaging (fMRI) is a functional neuroimaging technique that indirectly measures brain activity by detecting associated alterations in blood oxygenation (BOLD signal). In the past, most fMRI studies focused on detection of localized neural activities by modeling the relationship between fMRI signals and experiment stimulus, i.e., activity studies [1–3]. However, the human brain relies on efficient networks of interacting brain regions [4]. Hence, interests in studying the associations between brain regions have grown, i.e., connectivity studies [5–7]. Connectivity studies can be explored using task-related as well as resting state fMRI data, with the latter looking at spontaneous interactions between different brain regions without requiring active engagement from the subject. Resting state fMRI may therefore be more suitable for studies involving aging and diseased populations [8] who oftentimes suffer from sensory, motor and/or cognitive impairments rendering them incapable of performing challenging tasks.

Connectivity studies can be conducted at either the voxel or ROI (regions-of-interest) level. Voxel-based approaches usually involve a large number of variables, are computationally-inefficient, and must account for the massive amount of multiple comparisons. Such voxel-based approaches are typically done by spatially transforming all brain volumes to the same anatomical template. However, subtle misregistration can make the assumption that, after registration, a given voxel will represent the same functional region across all subjects tenuous. ROI-based connectivity analysis may reduce the number of multiple comparisons, and does not necessarily require spatial transformation, but requires careful consideration as to the definition of an ROI. Anatomical ROIs may be used to infer functional ROIs [9], but a single anatomical ROI, such as the putamen or amygdala, may in fact encompass distinct functional subROIs [10]. A number of attempts have been made to utilize data-driven approaches to subdivide a given ROIs into subROIs based on functional connectivity. One broad approach is based on cluster analysis [11] which first retrieves connectivity features of each voxel within an ROI using general linear regression models or Pearson's pairwise correlation coefficients, and then applies clustering according to the functional distances defined by the extracted features. Various clustering methods have been adopted in previous studies, such as the fuzzy clustering method [11],

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k-means clustering method [12], a self-organized mapping method [10] and maximum margin clustering method [13]. However, in order to acquire spatially continuous results, most clustering methods require meticulous denoising preprocessing methods as they are very sensitive to outliers in the data. Another popular category of data-driven approaches is based on graph theory, where each voxel represents one node in the graph, and methods such as the normalized cut approach [14] and modularity detection method [15] are used to separate the graph (and hence ROI) into distinct subROIs. Similar to clustering methods, graph theory methods do not take into account spatial information, and thus it is often difficult to obtain spatially continuous subROIs using graph theory methods. Furthermore, most graph theory methods are only concerned with the connectivity map between voxels within an ROI without incorporating connectivity from other ROIs, which might limit their usefulness.

In this paper, we propose a novel framework which defines subROIs in one ROI based on their functional connectivity to other ROIs. The proposed method employs a fused lasso regression model [16] with a spatial regularization penalty incorporated. The fused lasso approach encourages sparsity of the regression coefficients as well as sparsity of their successive differences between coefficients. We further introduce the normal lasso penalty for all voxels and the fused lasso penalty on spatially adjacent pairs of voxels.

Our framework differentiates from other approaches in the literature [11–15] in two main aspects. Firstly, in our proposed framework, we utilize the functional connectivity between voxels in the task ROI and the average time series of other related ROIs (where the task ROI and the related ROIs belong to one neural control loop). In the literature [11,14,15], people only consider the functional connectivity between voxels within the task ROI. Secondly, we incorporate spatial information that is often ignored in the literature [11,14,15] into our problem formulation. In addition, in order to limit the amount of bias that spatial constraint could introduce, we proposed a novel algorithm for adaptive, data-dependent parameter selection which allows us to only add spatial constraint when it is 'necessary'.

Functionally, in the basal ganglia–cortical loops in animals, the putamen is connected to several cortices with a clear topography [18]. We have chosen three reference brain regions namely the orbitofrontal (OF) cortex, cingulate gyrus (CG) and sensorimotor cortex (SMA) to assess connectivity to the ROI of interest, the putamen. Specifically, the DLS is more strongly connected to the SMA while the DMS has more reciprocal connections with the OF and CG [19] [18]. However, the spatial boundary between the DLS and the DMS is blurry and their exact locations are unknown due to overlapped connections; Some voxels of the DMS also have weak connections with the SMA while the DLS, too, may receive weak connections from the CG and OF. This scenario is illustrated in Fig. 1. In addition, as we observed in real fMRI data, due to the spatial signal noise, head movement and other possible artifacts, the data could be spatially corrupted with some outlier voxels. As a result, many current parcellation methods are not able to deal with such corrupted voxels to obtain a spatially continuous parcellation. Therefore, we plan to design an algorithm to parcellate the putamen region not only according to functional connectivity features from prior knowledge but also through integration of spatial information.

This pilot study aimed to investigate a novel technique to parcellate the putamen into two subregions with distinct functional and structural connections to the cortices of the brain. The putamen and caudate are two structurally distinct brain regions in the brainstem with the former lying more laterally and inferior to the latter. Due to the proximity of these two brain regions to each other and their shared neuronal connections, together, they are known as the striatum. Within the striatum (caudate and putamen), it has spatially segregated functional topography. The dorsolateral striatum (DLS) consists of the dorsal and lateral aspects of the caudate and putamen, and is associated with control of habitual, automatic movements. On the other hand, more medial areas within the caudate and putamen are known as the dorsomedial striatum (DMS) and this region is functionally related to learning and execution of goal-oriented movements. As an exploratory first step, in this paper, we chose to parcellate the putamen into the DLS and DMS subregions.

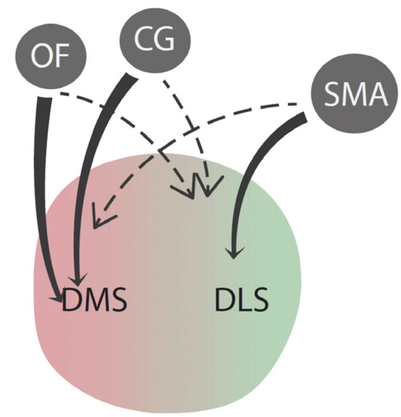

Fig. 1. Illustration of functional subROIs in the putamen brain region. The figure is made according to the graph shown in [18].

In the remainder of the paper, we will present the proposed method in Section 2. In Section 3.1, we investigated on a synthetic dataset to compare the results of the proposed method with those of clustering and graph theory methods. We tested the proposed method on real resting state fMRI dataset in Section 3.2. In Section 4, we presented a summary of our results with a conclusion.

2. Method

In this section, we will describe the proposed framework to separate a given ROI into functionally consistent and spatially continuous subROIs. We define the ROI to be separated as the task ROI and other ROIs used to estimate the connections with the task ROI as reference ROIs. We intended to find subsets of adjacent voxels (i.e., subROIs) in the task ROI that share similar connectivity patterns to other reference ROIs and iteratively merge them into groups. In the proposed algorithm, according to prior neuroanatomical knowledge, there are several reference ROIs that share similar connectivity patterns with one functional subROI in the task ROI (putamen in this paper) so that we can obtain the functional boundary between these subROIs.

The proposed framework can be summarized in Table 1. We will now elaborate on the individual components of the proposed framework in the following subsections. First, we start by describing the spatially regularized fused lasso model.

2.1. Spatially regularized fused lasso method

Let $X = [x_1, x_2, \ldots, x_n]$ be a $(T \times n)$-dimensional data matrix with n denoting the number of voxels and T denoting the length of time points. X represents the fMRI signals in the task ROI and x_i, $i = 1, 2, \ldots, n$ represents fMRI time course of voxel i. Y is a $(T \times 1)$ vector representing the signals of one reference ROI which is acquired by averaging time courses across all voxels contained in that reference ROI. Let β be a $(n \times 1)$ vector where each element in β represents