Brainstem Functional Parcellation Based on Spatial Connectivity Features Using Functional Magnetic Resonance Imaging

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Abstract. The brainstem controls almost all normal functions in the life, such as breathing, memory, movement, and is closely related to many neurological diseases. Despite the importance of the brainstem, the delineation of its functional sub-regions remains largely unexplored. In this study, we aim to explore functional parcellation of the brainstem using functional magnetic resonance imaging (fMRI), and propose a novel framework by combining spatial functional connectivity features of the brainstem and NCut spectral clustering. Firstly, functional connectivity between the brainstem and other cortical and sub-cortical brain regions is estimated using fMRI data. Secondly, the estimated spatial functional connectivity features are used to detect functional sub-regions of the brainstem using NCut spectral clustering. Finally, the Dice coefficient was used to evaluate the reproducibility of brainstem functional parcellation. The results show that the Dice coefficient obtained by the proposed method was 0.74, which is higher than that of the parcellation using temporal features of the brainstem (Dice coefficient of 0.32). In addition, NCut spectral clustering outperformed other clustering methods regarding the reproducibility of brainstem functional parcellation. The proposed method explores the potentials of spatial functional connectivity features for brainstem functional parcellation. It may serve as a promising tool for studying the functions and dysfunctions of the brainstem.

Keywords: functional parcellation · functional magnetic resonance imaging · functional connectivity · brainstem

1 Introduction

The brainstem, as an indispensable component of the central nervous system, plays a crucial role in maintaining vital functions in individuals. Many critical physiological functions, including but not limited to heartbeat, respiration, and digestion, are closely associated with the brainstem [1]. In the human body, it can be regarded as one of the most crucial organs. Current research indicates that many neurological disorders are related to brainstem dysfunctions [2]. For instance, the neuropathological changes associated with

Parkinson's disease primarily occur in the brainstem [3]. The delineation of functional sub-regions of the brainstem contributes to the understanding of functional organizations of the brainstem and its relationship with brain diseases.

While there is a collection of functional parcellation studies for the cortex and sub-cortex of the brain, functional parcellation of the brainstem remains largely unexplored, in spite of its importance in the understanding of brain functions and dysfunctions [4]. Currently, the sub-regions of the brainstem are mostly delineated by using anatomical principles [5, 6]. These methods rely on the morphological features and spatial information of different sub-structures [7]. One study conducted in vivo segmentation of the brainstem by using a semi-supervised approach, resulting in eleven sub-regions of the brainstem [8]. In another study, a data-driven approach was utilized to extract functional parcellations of the brainstem [9]. This approach adopted a modularity-based criterion to generate functional sub-regions of the brainstem using temporal brainstem voxel signals. While the brainstem voxel signals provide important information regarding the temporal features of the brainstem, the spatial connectivity pattern between the brainstem and other cortical and sub-cortical brain regions is another key feature to characterize the brainstem. However, such spatial features have not been taken into account for functional parcellation of the brainstem.

In this study, a novel framework was proposed for brainstem functional parcellation using fMRI, which incorporates spatial functional connectivity features. The proposed method combines the spatial functional connectivity features of the brainstem with NCut spectral clustering [10]. The functional connectivity patterns between the brainstem and other cortical and subcortical regions of the brain characterize the spatial features of the brainstem. NCut spectral clustering is used to partition the brainstem into functional sub-regions based on the similarity between spatial patterns of brainstem voxels. To the best of our knowledge, this study is the first to utilize spatial functional connectivity features for the functional parcellation of the brainstem.

2 Materials and Methods

This study proposes a new framework for brainstem functional parcellation by combining spatial functional connectivity features of the brainstem and NCut spectral clustering. Figure 1 shows the overall workflow of the proposed method. Firstly, using fMRI data, the functional connectivity between brainstem voxels and cortical as well as subcortical brain regions is estimated, thereby capturing the spatial features of the brainstem. Secondly, the correlation between spatial functional connectivity features of brainstem voxels is calculated to generate a similarity matrix between brainstem voxels. Lastly, NCut spectral clustering [10], an unsupervised machine learning algorithm, is employed to partition brainstem voxels into functional sub-regions based on the generated similarity matrix. To assess the efficacy of the proposed method, the reproducibility of functional sub-region delineation is evaluated using the Dice coefficient [11].

2.1 fMRI Dataset and Preprocessing

The data for this study was obtained from the publicly available Human Connectome Project (HCP) dataset [12]. The participants with substantial head motion parameters and
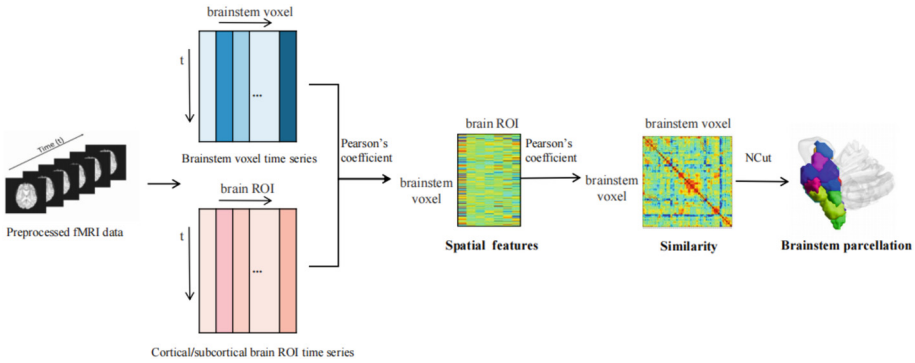
Fig. 1. The overall workflow of the proposed method for brainstem functional parcellation.

those who did not undergo repeated scanning sessions were excluded from the analysis due to concerns regarding data quality and reliability. As a result, the resting-state fMRI data from 170 healthy adult participants were included in this study.

The fMRI data was collected using a 3T magnetic field strength and a gradient-echo EPI sequence. The scanning parameters included a repetition time (TR) of 720ms, an echo time (TE) of 33.1ms, a flip angle (FA) of 52°, a field of view (FOV) of 208 × 180mm (RO × PE), a matrix size of 64 × 64, a slice thickness of 2.0mm, 72 slices, and an isotropic voxel size of 2.0mm. The data was acquired with a multiband factor of 8, an echo spacing of 0.58ms, and a bandwidth (BW) of 2290Hz/Px. Each participant underwent two fMRI scans, with each scan consisting of 1200 volumes. The total scan time for each participant was approximately 14 min [13]. In this study, the two scans are referred to as REST1 and REST2, respectively.

The preprocessing pipeline for HCP data consists of spatial and temporal processing procedures. Spatial preprocessing involves a series of steps, including spatial artifact removal, surface generation, cross-modal registration, and alignment to a standard space. On the other hand, temporal preprocessing involves the application of MELODIC ICA, where artifact and motion-related time courses are regressed out from both volumetric and grayordinate data [12]. Moreover, this approach also acts as a noise reduction technique for the signals originating from the brainstem region.

A template derived based on multimodal data [14] was used to define the regions of interest (ROIs), including both brainstem and brain cortex/subcortex. The average time series within each cortical and subcortical ROIs, as well as the voxel time series within the brainstem, were extracted for the subsequent analyses.

2.2 Spatial Functional Connectivity Features of Brainstem Voxels

In this study, we evaluated the similarity between voxels of the brainstem using their spatial features (i.e., functional connectivity patterns), rather than commonly used temporal features (i.e., original fMRI time series) [9]. Specifically, spatial functional connectivity features were assessed by correlating the signals from brainstem voxels with those from brain cortical/subcortical ROIs. These functional connectivity features captured the

spatial patterns of interaction between the brainstem and other cortical and subcortical brain regions. Subsequently, the similarity matrix between the voxels of the brainstem was constructed by computing the correlation between spatial functional connectivity features of brainstem voxels.

2.3 NCut Spectral Clustering for Brainstem Functional Parcellation

2.3.1 Clustering Methods

To extract functional sub-regions of the brainstem from the similarity matrix obtained from brainstem spatial functional connectivity features, we employed NCut spectral clustering method [15]. Spectral clustering projects the data into a lower-dimensional space and then applies a clustering algorithm, such as K-means, to group the data points. By leveraging the spectral properties of the similarity matrix, this method can effectively capture the underlying structure and identify functional sub-regions of the brainstem [16].

Given an input sample set $D = (x_1, x_2, \ldots, x_n)$, the similarity matrix generation method, and the number of clusters k, the similarity matrix S is constructed based on the provided similarity matrix generation method. Subsequently, the similarity matrix undergoes an absolute value transformation. Furthermore, only the similarity values corresponding to adjacent voxels are retained, while those values between non-adjacent voxels is set to zero. This leads to the construction of the adjacency matrix W and the degree matrix D. Subsequently, the Laplacian matrix L is computed. The graph partitioning requires constructing a normalized Laplacian matrix $L_n = D^{-\frac{1}{2}} L D^{-\frac{1}{2}}$. Eigenvalues of L_n are calculated. The computed eigenvalues are arranged in ascending order, with the first k eigenvalues being selected to construct the eigenvector f. The eigenvector f is then normalized to form the $n * k$ dimensional feature matrix H. Each row in H is treated as a k-dimensional sample, yielding a total of n samples. A clustering method is then applied, typically utilizing the K-means clustering algorithm. The final outcome of this process is the cluster partition $C = (c_1, c_2, \ldots, c_k)$ [17].

2.3.2 Group-Level Analysis

After obtaining individual-level brainstem functional parcellations using NCut spectral clustering, group-level analysis is performed to derive a population-level brainstem template. Group-level analysis is a method that combines individual brainstem functional parcellations to obtain a representative brainstem template that captures shared characteristics of the group.

We employed a two-level analysis to obtain the group-level parcellation [18]. It is accomplished by constructing an adjacency matrix A of size $N * N$, where N represents the number of vertices in the brainstem. The edges in the stability graph are weighted based on the frequency of occurrence of the same parcel assignments for two vertices, v_i and v_j, across all individual subject parcellations. Once the stability graph is constructed, it is further subdivided into different regions using a graph partitioning algorithm, such as spectral clustering with normalized cuts [19], resulting in a group-level parcellation.

2.3.3   Optimal Parcellations

Determining the optimal number of functional sub-regions is an important issue. Eigenmap is one of the methods that can be used for estimating the number of clusters [21]. Eigengap is computed by analyzing the eigenvalues obtained from the spectral decomposition of a given matrix. Specifically, the eigengap is computed by calculating the absolute difference between consecutive eigenvalues. Larger eigengap typically indicates significant differences between distinct clusters and serves as a basis for selecting the appropriate number of clusters. A common approach is to identify the peaks in the eigenvalue gaps as the optimal number of clusters [22].

2.3.4   Commonly used Clustering Methods

To evaluate the performance of the proposed framework, we compared the performance of NCut spectral clustering with other commonly clustering methods, including K-means clustering, modularity and RatioCut spectral clustering. K-means is a widely used clustering algorithm that aims to partition data into k clusters by minimizing the within-cluster sum of squares [18, 23]. Modularity is a popular community detection method, which measures the density of connections within communities and compares it to a random network, aiming to maximize a modularity quality function [24]. RatioCut can be regarded as a simplification of the NCut clustering method. It disregards considerations of node degrees and connectivity and instead focuses on minimizing the number of cut edges [25].

2.4   Reproducibility of Brainstem Functional Parcellation

The Dice coefficient was employed to assess the reproducibility of brainstem functional parcellation [26, 27].

The Dice coefficient measures the overlap between two parcellation results, where a higher value indicates a greater similarity between the parcellations [28]. The calculation of the Dice coefficient is as follows:

$$Dice(A, B) = \frac{2|A \cap B|}{|A| + |B|}$$

The numerator of the Dice coefficient is twice the intersection of sets A and B, and the denominator is the sum of the lengths of sets A and B. Therefore, the Dice coefficient ranges from 0 to 1, where a higher value indicates a greater overlap and similarity between two parcellation results.

3   Experiments

We utilized this framework to extract functional subregions of the brainstem from 170 healthy subjects. Firstly, we built an individual similarity matrix for each subject using spatial functional connectivity features of the brainstem. Subsequently, NCut spectral clustering was applied to the matrix of each subject, resulting in an individual brainstem functional parcellation for each participant. Finally, a two-level group analysis method

was employed to derive the group-level parcellation by integrating the individual brainstem functional parcellation results. The eigengap method was used to select the optimal number of clusters, and the range of the number of clusters was set to 15–25 by referring to the previous literature [20]. To evaluate the proposed method, we used the Dice coefficient between the two scans, REST1 and REST2, to measure the reproducibility of brainstem functional parcellation. Higher reproducibility indicates better parcellation performance.

4 Results

We computed the eigen-gap values within the range of 15 to 25 subregions. The eigen-gap indicates significant transitions in the eigenvalues. As shown in Fig. 2, there is a substantial jump at 21 clusters, leading to the selection of 21 sub-regions as the optimal division for functional parcellation of the brainstem.
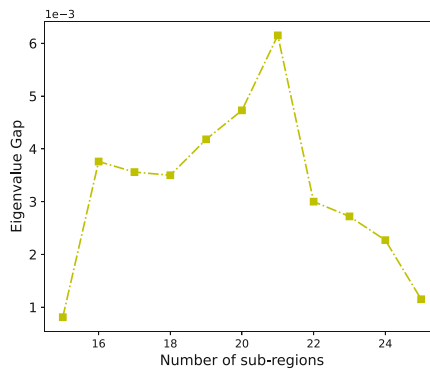

Fig. 2. Eigen-gap analysis for functional parcellation of the brainstem.

To validate the proposed method, we compared different clustering methods and features with the number of clusters ranging from 15 to 25. Specifically, we first compared the reproducibility between the proposed spatial functional connectivity features and traditional temporal features, and then compared different clustering methods, including NCut, RatioCut, K-means and modularity.

Figure 3 shows the Dice coefficient of brainstem functional parcellation using the proposed method with spatial functional connectivity features, compared to that using temporal fMRI time series features. The boxplot was drawn based on the Dice coefficients across different number of clusters. It can be seen that the brainstem parcellation based on spatial connectivity features outperformed that based on temporal features in terms of the Dice coefficient. This trend was consistent throughout the number of clusters ranging from 15 to 25.

For the optimal parcellation with 21 brainstem subregions, the Dice coefficient using the proposed method with spatial functional connectivity features was 0.74. Such performance was higher than that obtained using the fMRI temporal time series features, which yielded a Dice coefficient of 0.32.
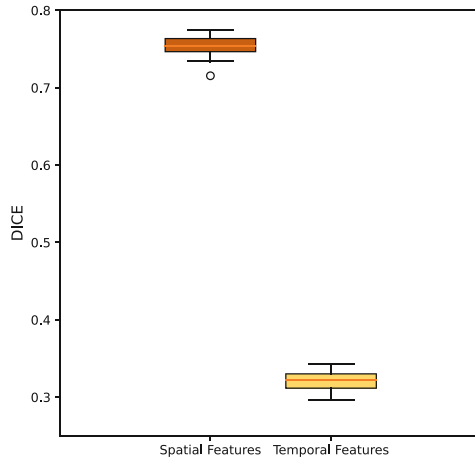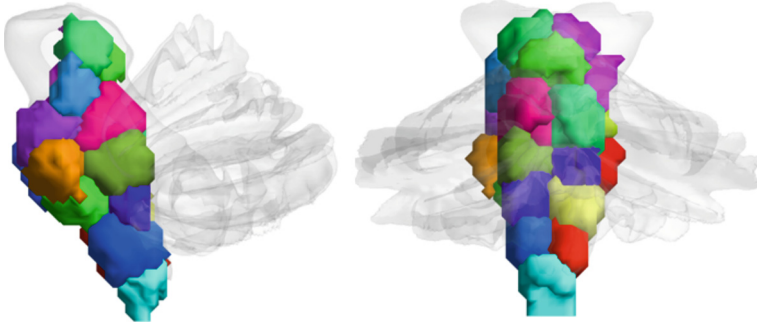
Fig. 3. Comparisons of the reproducibility of brainstem functional parcellation using spatial functional connectivity features and temporal fMRI time series features. The boxplot was drawn based on the Dice coefficients across different numbers of clusters.
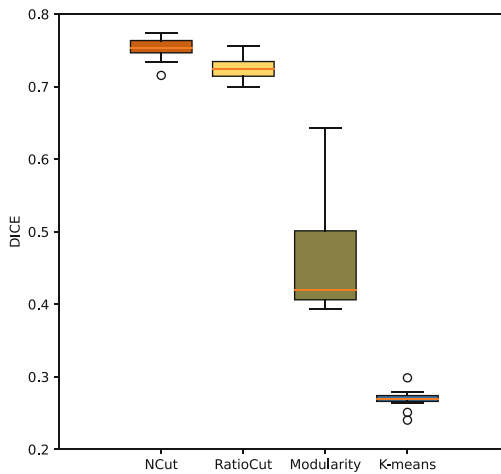
Fig. 4. Comparisons of the reproducibility of brainstem functional parcellation using different clustering methods. The boxplot was drawn based on the Dice coefficients across different numbers of clusters.

The reproducibility of different clustering methods using spatial functional connectivity features of the brainstem were compared in Fig. 4. The boxplot was drawn based on the Dice coefficients across different numbers of clusters. The results showed that the NCut method achieved higher Dice coefficients compared to other methods. The consistent trend was observed across different numbers of clusters ranging from 15 to 25.

When the brainstem was divided into 21 subregions, the results showed that NCut spectral clustering exhibited the best reproducibility with a Dice coefficient of 0.74, outperforming that of RatioCut (a Dice coefficient of 0.69), modularity (a Dice coefficient of 0.40), and K-means (a Dice coefficient of 0.27).

Fig. 5. Visualization of functional sub-regions of the brainstem obtained using the proposed method.

Finally, the group-level brainstem functional parcellation obtained using the proposed method is shown in Fig. 5. The brainstem is partitioned into 21 functional sub-regions.

5 Conclusions

This study proposed a novel framework for brainstem functional parcellation by combining the spatial functional connectivity features of the brainstem and NCut spectral clustering. The proposed method exhibited the best reproducibility in terms of Dice coefficient, outperforming that achieved by using temporal fMRI time series features and other clustering methods. The results demonstrated the advantage of spatial functional connectivity features of the brainstem over temporal fMRI time series features and the superiority of NCut spectral clustering. The current study provides the delineation of functional sub-regions of the brainstem, benefiting the exploration of functional organizations of the brainstem and brainstem pathology of brain diseases.

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