FIBER CLUSTERING BASED WHITE MATTER CONNECTIVITY ANALYSIS FOR PREDICTION OF AUTISM SPECTRUM DISORDER USING DIFFUSION TENSOR IMAGING

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ABSTRACT

Autism Spectrum Disorder (ASD) has been suggested to associate with alterations in brain connectivity. In this study, we focus on a fiber clustering tractography segmentation strategy to observe white matter connectivity alterations in ASD. Compared to another popular parcellation-based approach for tractography segmentation based on cortical regions, we hypothesized that the clustering-based method could provide a more anatomically correspondent division of white matter. We applied this strategy to conduct a population-based group statistical analysis for the automated prediction of ASD. We obtained a maximum classification accuracy of 81.33% between ASDs and controls, compared to the results of 78.00% from the parcellation-based method.

Index Terms— ASD, Fiber clustering, Parcellation

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder characterized by core impairments in social interaction, communication, behaviors and interests [1]. While the presentation of ASD is highly heterogeneous in terms of clinical severity, comorbid language, intellectual ability, etc., altered brain connectivity has been hypothesized to explain the socio-emotional deficits across the autism spectrum. Diffusion tensor imaging (DTI), which can infer the underlying tissue structure of brain white matter *in vivo*, has been recently used to investigate the association between the ASD symptoms and the altered brain connectivity in a non-invasive way. For example, the altered structures within long-range white matter tracts linking socio-emotional processing regions may be important pathogenic factors contributing to the social impairments in ASD [1].

While the current diagnosis of ASD is mainly based on observation of behavior, it is of interest to investigate the population-based statistics of brain connectivity for automated diagnosis. There have been studies carried out on DTI to elucidate the group differences between ASD and typically developing controls (TDC). Traditional approaches, e.g., voxel-based morphometry (VBM), rely on a group-level, voxel-wise comparison [2], but can be significantly biased toward local group differences [3]. There are also methods focusing on certain preselected regions of interest (ROIs), e.g., anterior cingulate [4], but they require a priori knowledge of affected regions specific to pathology. In addition, these methods only emphasize local group differences, regardless of global changes, making them potentially less effective for the non-focal psychiatric disease of ASD [5] .

Although local statistics have provided support for the behavioural correlates of white matter tracts in ASD, a method that can infer the global white matter connections could potentially provide more sensitive and specific diagnostic decision among populations. Parcellation-based methods, which divide the white matter according to a cortical parcellation, are often used for studying connectivity and have been applied to ASD prediction. For example, Caspar et al. [6] computed a white matter connectome matrix for each subject based on the number of fibers connecting different cortical regions. Connectome features, e.g., number of connected components of the matrices, were extracted to perform ASD classification. Instead of using the features from the connectivity matrix, Mostapha et al. [7] extracted anisotropy and diffusivity measures of the fiber bundles that connect different brain regions as white matter connectivity features (shape features of brain cortex were also used) for ASD prediction.

The fiber clustering approach is another widely used strategy for modeling the connections of white matter. Unlike the parcellation-based segmentation according to the cortical region atlas, clustering-based methods organize fibers into fiber tracts or bundles, in which all fibers follow similar trajectories [8]. In this study, we focus on clustering-based segmentation to observe brain connectivity for ASD prediction. Due to the trajectory-similar characteristics, the clustering-based segmentation may be more corresponding to the traditional anatomical divisions of white matter when compared to the parcellation-based method [9]. We hypothesized that such

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correspondence could be helpful for measuring the properties of the anatomy of the fiber tracts and thus could be more discriminative on differentiating between ASD and TDC.

2. METHODS

2.1. Data Acquisition and Tractography

The evaluation dataset included diffusion weighted imaging (DWI) from 150 male subjects (70 ASD and 80 TDC), with similar age distributions (ASD: 11.11 $\pm$ 2.45 v.s. TDC: 11.04 $\pm$ 2.43). DWI data were acquired using a Siemens 3T Verio^{TM} scanner with a 32 channel head coil. A monopolar Stejskal-Tanner diffusion weighted spin-echo was used to perform HARDI acquisition (TR/TE = 14.8s/110ms, b = 3000s/mm^2, 2mm isotropic resolution, and 64 gradient directions). 3D Slicer [10] was used to perform DTI estimation (with weighted least squares) and whole-brain tractography using the second-order Runge-Kutta method.

2.2. Fiber Clustering

Fiber clustering was conducted based on our previous work [8], including: 1) a study-specific automated cluster atlas generation for a high-dimensional model of white matter structure, and 2) an automated segmentation for the tract correspondence across subjects[1]. The method works in a data-driven way across multiple subjects, without utilizing the additional information of cortical parcellation. Fig. 1 illustrates the workflow of the fiber clustering process.

1) The atlas generation was conducted on a subset of 20 randomly selected subjects (10 from ASD and 10 from TDC). We first conducted an unbiased multi-subject registration of whole brain tractography so that the tractography was in a common space [11]. We further incorporated the B-spline model into the registration to enable non-rigid deformations. After group registration (Fig. 1(c)), each fiber was converted to a point in a spectral embedding space and the clustering was then performed. Similar fibers from all or most subjects were thus grouped into the same population white matter cluster, leading to the cluster atlas (Fig. 1(d)).

2) The fibers of all subjects in the dataset were then labeled according to the atlas. All tractography was first aligned to the group registration to have the same space with the atlas. The registered fibers were then converted into the atlas embedding space and labeled according to the nearest atlas cluster centroid (Figs. (e) and (g)).

2.3. Feature Extraction, Selection and ASD Prediction

Feature extraction was conducted after fiber clustering to quantitatively describe the fiber tracts. Fractional anisotropy (FA) and mean diffusivity (MD) measures, which may be more discriminative between ASD and TDC [12], were applied in this study. For each fiber tract, statistics of the two measures were computed, including: mean, maximum, minimum, and percentiles (p10, p25, p50, p75 and p90 in ascending order). For any empty cluster (due to anatomical or tractography variability), each measure was set to the mean from the non-empty corresponding clusters across all subjects. These features were used separately in our experiments to inspect their individual discriminative ability (Fig.2).

Feature selection was then performed to identify highly descriptive fiber tracts that largely contributed to the classification of ASD/TDC. Specifically, given a clustering with K clusters and a certain feature f (e.g., maximum of FA), each subject was represented as $S = \{f_k | k \in [1, K]\}$. We employed the signal-to-noise (s2n) ratio coefficient for feature filtering, which has been demonstrated to be effective for ASD classification [5]. s2n ranks each dimension of the feature (i.e., cluster) based on the ratio of the absolute difference of the class means over the average class standard deviation.

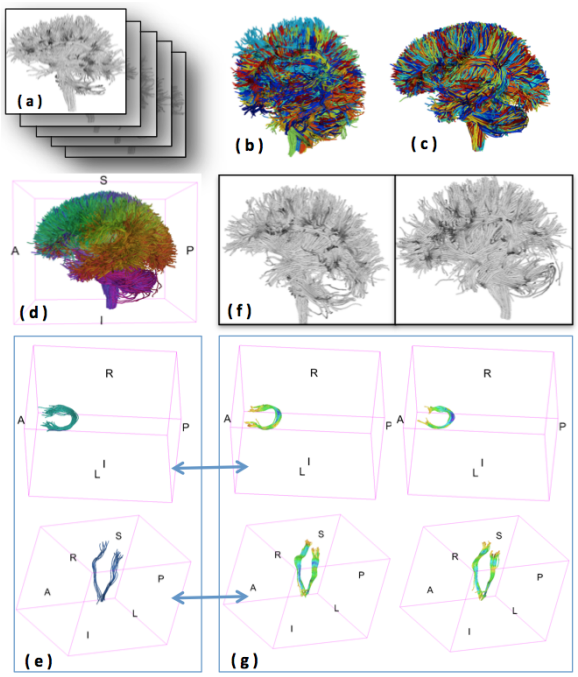

Fig. 1. Outline of the fiber clustering process: (a) is the tractography of multiple subjects for atlas generation. (b) and (c) show the comparisons before and after the group tractography registration. To facilitate visual observation, fibers from different subjects are colored differently. (d) is the obtained clustering atlas, with the different colors representing the different clusters. Sample clusters are displayed in (e). (f) is the tractography from two different subjects. After the alignment according to the group registration, all fibers are labeled based on the clusters within the atlas. (g) gives the labeling results, corresponding to the clusters in (e).

[1] Source codes are available at https://github.com/ljod/whitematteranalysis

Table 1. Prediction accuracies using the parcellation- and our clustering-based approaches.

K	200	400	600	800	avg
Parcellation	68.67	69.33	76.67	78.00	73.17
Clustering	76.00	79.33	80.00	81.33	79.12

The ranking scores were computed on a set of training subjects annotated with ASD or TDC (see Section 3 for the validation process) and the top R ranked clusters were kept for the new feature representation $S' = \{f_{k'}|k' \in [1, R]\}$.

We used support vector machine (SVM) to conduct the ASD prediction. SVM is one of the most widely used classifiers for high dimensional features and is effective for capturing the multivariate relationships among anatomical regions in ASD [13]. In our experiments, we used the *nu-SVC* SVM with polynomial kernel and default parameters from LIBSVM[2]. We conducted leave-one-subject-out cross-validation for performance evaluation. Given a certain feature (e.g., maximum of FA), feature selection and the SVM model were trained on the training set and the average accuracy of all runs was reported as the prediction accuracy.

We compared our method with the parcellation-based approach, in which Freesurfer [14] was used to segment gray matter into 87 regions and the fibers connecting all pairs of gray matter regions were extracted to parcellate the white matter [15]. To make a fair comparison, we used the K (same as the number of clusters) parcellation-based fiber bundles that contained the most fibers across all subjects. The same feature extraction and selection process were then applied for accuracy computation. We conducted the experiments in high performance computing clusters (HPC). It took about 8 hours for cluster atlas generation (10 cores) and 2 hours for fiber labeling of each subject (2 cores). Freesurfer took approximately overnight for each parcellation[3].

3. RESULTS

Table 1 displays the overall classification accuracy comparison between the parcellation- and our clustering-based methods. For each K, the highest accuracy among all features (as introduced in Section 2.3) was reported. The clustering-based method obtained higher prediction accuracy than the parcellation-based approach for every K under study. A maximum accuracy of 81.33% was obtained using our strategy, compared to the performance of 78.00% from the parcellation-based approach. This may be because the clustering-based method grouped the fibers following similar trajectories, which more likely belong to the same anatomical structure. In this way, the obtained tractography segmentation could be more representative of the anatomical division of white matter when compared to the segmentation according to the gray matter regions. In general, a larger number of clusters tended to provide better performance.

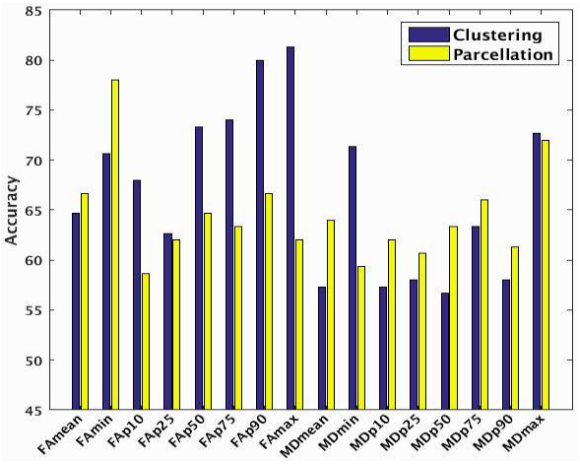

Fig. 2. Prediction accuracies using different features.

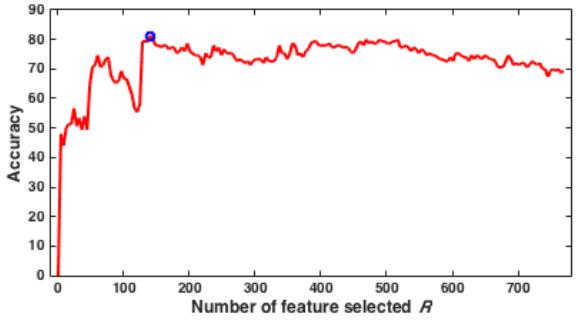

Fig. 3. Average prediction accuracy given the number of selected features R, with maximum FA and K=800.

Fig. 2 shows the effects of different features. The accuracies are from the experiments where the two methods obtained the best performance (K=800). Overall, FA gave better results compared to the MD features, suggesting that the anisotropy measure might be more discriminative for predicting ASD than the diffusivity feature. Across the FA features, we can observe that the parcellation-based approach had better results given minimum FA and the clustering-based method performed better with the maximum and p90 of FAs. For the MD features, we obtained higher accuracies using the maximum and minimum values with fiber clustering. These observations indicate that the extreme fiber statistics may be more effective in identifying the differences between ASD and TDC.

Fig. 3 shows the curve of average accuracy given the number of selected features R in our clustering-based method. The curve is from the experiment when the best result was obtained across all features (f=FAmax, K=800). The blue circle indicates the highest accuracy from R_{peak}=141. The pre-

[2]The package was downloaded at https://www.csie.ntu.edu.tw/ cjlin/libsvm/
[3]https://surfer.nmr.mgh.harvard.edu/fswiki/ReconAllRunTimes

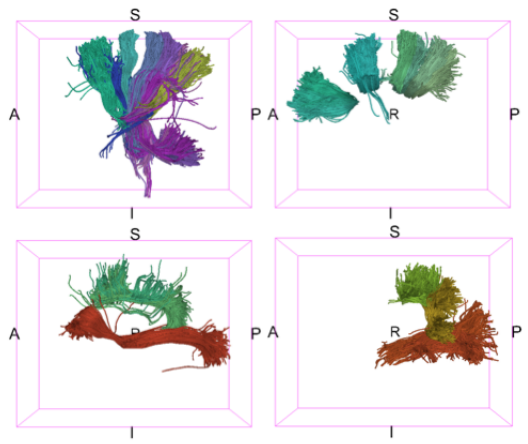

Fig. 4. Visual presentation of the selected clusters with robustly discriminative FAmax (top left: corona radiata and cortico cerebellar, top right: corpus callosum, bottom left: cingulum and inferior fronto-occipital fasciculus, bottom right: arcuate fasciculus (indirect segment) and inferior longitudinal fasciculus).

diction performance was improved significantly before this point and became stable after arriving at the peak.

We assessed which anatomical regions had features that were robustly selected during the cross-validation in our most successful trial (R_{peak}=141, f=FAmax, K=800). First, to determine candidate regions, for each fiber cluster, we conducted a t-test on maximum FA using the whole dataset. 40 fiber clusters were identified with p-value < 0.05. Of these selected clusters, 36 of the 40 were retained as selected features across all validation runs. Fig. 4 gives a visual illustration of these 36 selected clusters. Some of these fibers connect the socio-emotional processing regions, such as those from the cingulum, inferior fronto-occipital fasciculus and arcuate fasciculus, which have been implicated in ASD [1].

4. CONCLUSION

We have proposed a method for population-based analysis of brain connectivity alterations to elucidate group differences for ASD prediction. Our method was based on fiber clustering tractography segmentation that can reconstruct anatomically-defined white matter tracts. Compared to the parcellation-based approach, we obtained a higher prediction accuracy without using the additional information from cortical parcellation.

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