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ANALYZING THE EFFECT OF RESOLUTION OF NETWORK NODES ON THE RESTING STATE FUNCTIONAL CONNECTIVITY MAPS OF SCHIZOPHRENIC HUMAN BRAINS

Pratik Jain, Anil K. Sao and *Atul S. Minhas, *Member, IEEE*

***Abstract*— Functional connectivity (FC) mapping from resting-state functional magnetic resonance imaging (rsfMRI) data is a widely used technique to characterize the brain abnormalities in mental health disorders. Using atlases for brain parcellation is an important intermediate step in calculation of FC maps. Atlases with varying resolution (number of nodes in an atlas) have been deployed by researchers to study the abnormal brain functions in Schizophrenia. In this work, we compared the variations in FC maps of Schizophrenic brains obtained from three different atlases: AAL atlas (2002), Dosenbach atlas (2010), and the Brainnetome atlas (2016). To evaluate the atlas-dependent variations in FC maps, we relied on the capability of the features of FC maps in accurately classifying a given data into healthy or Schizophrenia group. Our results indicate that the high-resolution Dosenbach and Brainnetome atlases perform better than AAL atlas in terms of the accuracy, sensitivity and specificity of the SVM classifier.**

I. INTRODUCTION

Schizophrenia is a mental health disorder where people do not interpret reality in a normal way. The common classical descriptors of its symptoms include hallucinations, delusions, disorganized speech or behaviour, reduced participation in daily activities and social isolation. Multiple neuroimaging techniques have been developed over the past two decades to reveal the cognitive impairments associated with these symptoms. A popular technique among them is the resting state functional magnetic resonance imaging (rsfMRI) which creates the functional connectivity (FC) maps of the brain. Researchers working in FC mapping have applied graph theory techniques to reveal multiple functional sub-networks of the brain, each specific to a certain brain function.

Unlike task-based fMRI, the participants undergoing rsfMRI are not presented with any stimulus (or task). Instead, they are asked to lie down inside MRI scanner with their eyes open or close and think of nothing in particular. The ease of performing rsfMRI has made it a popular choice over the task-based fMRI for Schizophrenic people who may not be able to satisfactorily perform the complex cognitive tasks required in task-based fMRI [1].

There are in general two widely used methods for generation of FC maps from rsfMRI data. First is a data-driven method that decomposes the fMRI data ($voxels \times timepoints$) into multiple maximally independent spatial maps and corresponding time courses, and select the meaningful components as the FC networks. The second method uses prior knowledge of brain structure to define a set of brain regions and limit the FC analyses to these regions. These predefined regions or regions of interest (ROI) are assembled in a three-dimensional labeled matrix called the brain atlas. The FC maps are then generated for the whole brain by finding a Pearson's Correlation between averaged time-series of each pair of ROIs [2], or by using frequency-domain methods such as Coherence [3] or wavelet decomposition [4].

A key requirement of the second method used for FC mapping is the brain atlas. The number of nodes (or ROIs) in atlas defines the resolution of atlas. Multiple atlases have been used in prior studies [5], [6], [7], but their effects on the features of FC maps has never been studied. This is significantly important for the machine learning based classification studies where features of FC maps are used to develop classifiers for classification of given data into either Schizophrenia or healthy group [5], [6], [7]. Notably, analyzing the FC maps of Schizophrenic brains has revealed the abnormal neural connectivity of a wide range of functional sub-networks of the brain. Therefore, choosing a proper resolution of atlas is highly important to track the widespread abnormal neural activities of Schizophrenic brains.

In this work, we have compared the effects of three widely used atlases for the FC mapping of Schizophrenic brains. For quantitative evaluation of these effects, we developed a support vector machine (SVM) based two-class classifier and compared the classification accuracy, specificity and sensitivity of the three classifiers based on the three atlases.

II. METHODS

A. Data acquisition

We downloaded two sets of data from two different publicly available databases. The first database was the OpenNeuro database from where we accessed the data available in the UCLA consortium for Neuropsychiatric Phenomics LA5c study [8] (accession number: ds000030). While there were other MRI data sets in this database, only the rsfMRI data of 121 healthy and 47 Schizophrenia subjects was used in this study. The detailed scan parameters for the T1-weighted structural scans and the EPI sequence for rsfMRI are described in [8] for this data set. During

*Corresponding author (e-mail: atul.minhas@mq.edu.au). Atul S. Minhas is with the School of Engineering, Macquarie University, Sydney, Australia. This work was supported by a startup grant to Dr Atul S. Minhas from School of Engineering, Macquarie University, Sydney, Australia.

Pratik Jain is with the School of Computing and Electrical Engineering, Indian Institute of Technology Mandi, Mandi, India.

Anil K. Sao is with the Department of Electrical Engineering and Computer Science, Indian Institute of Technology Bhilai, Bhilai, India.

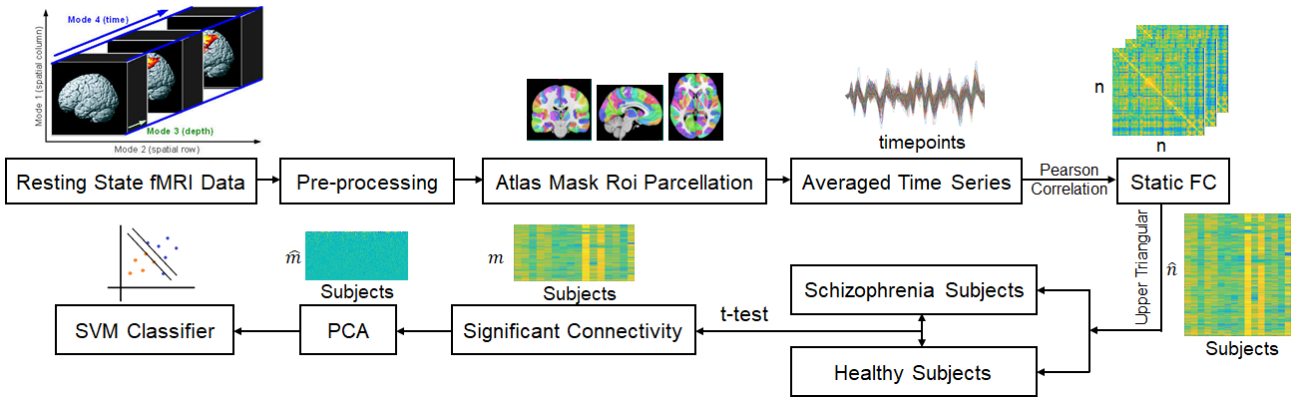

Fig. 1. Overview of data processing steps involved in developing the SVM based classifier.

the rsfMRI data collection, the participants were asked to remain relaxed and keep their eyes open for five minutes. The second database was the Centers of Biomedical Research Excellence (COBRE) [9] from where we took 73 healthy and 71 Schizophrenia subjects. The detailed scan parameters for the T1-weighted structural scans and the EPI sequence are shown in [9]. During data acquisition, all subjects were instructed to keep their eyes open and stare at fixation cross. We combined the data from the healthy and Schizophrenia subjects in these two data sets to create two groups with 194 healthy and and 118 Schizophrenia subjects. We calculated the temporal signal to noise ratio (tSNR) as per [10] and found it to be similar for the two groups of healthy (241±70) and Schizophrenia (216±63) subjects.

B. Data pre-processing

We pre-processed the raw rsfMRI data with the SPM12 toolbox (http://www.fil.ion.ucl.ac.uk/spm/). The data was available in NIfTI format and pre-processing included five operations: slice timing correction, realignment, co-registration, normalization, and smoothing. These operations transformed the raw rsfMRI data into a standard Montreal Neurological Institute (MNI) space, where the 3D brain volume data was mapped to the transformed space of size 91×109×91. The spatial resolution of each voxel was selected as 2 mm^3. Then, the time-series blood oxygen level dependent (BOLD) signal of each voxel was filtered in the frequency range of 0.01 to 0.1 Hz.

C. Generation of functional connectivity maps

After pre-processing, the 3D brain volume was parcellated using three different atlases: (1) Dosenbach 160 ROIs [11] combined with bilateral Amygdala and Parahippocampus [12], which makes it a 164 ROI atlas, (2) Brainnetome atlas with 246 ROIs [13], and (3) Automated Anatomical Labeling (AAL) atlas with 116 ROIs [14]. For a fair comparison of the resting state networks present in each of the three atlases, the Yeo 7 resting-state (RS) network atlas [15] was overlaid on each of these atlases, as described by [16], to obtain the 7 RS networks corresponding to the three atlases.

After parcellation, an averaged time-series was calculated for each region in each of the atlases. This resulted in a matrix $Y_i \in \mathbb{R}^{n\times 150}$, where n is the number of ROIs and 150 is the time-points for the i^{th} participant. Then, a $n \times n$ FC matrix was computed for each participant, whose elements correspond to the Pearson's correlation between each pair of the regions. Since FC matrices are symmetric, the upper triangular part of the matrix was arranged in an array of size $\tilde{n} = (n \times (n-1))/2$, representing the FC-vector for each of the i^{th} subject. The FC-vectors were mean-subtracted and normalized to make them comparable. For each of the three atlases, 194 and 118 FC-vectors were created for the healthy and Schizophrenia subjects, respectively.

D. Machine learning with Support Vector Machine

Every element of the FC-vector was considered as an independent variable with measurements from two groups: healthy controls (194 data points) and Schizophrenia (118 data points). Two-sample paired t-test was applied on these groups for each element of the FC-vector to find the elements with significant differences ($p \leq 0.01$) between the two groups. Applying such statistical filter reduced the dimension of the FC-vector of the i^{th} subject to $D_i \in \mathbb{R}^{m\times 1}$, where m is the number of connections with significant differences. This data was assembled in a $m \times p$ matrix, where p is the number of subjects used in training as: $D = [D_1, D_2, ..., D_p], D \in \mathbb{R}^{m\times p}$. The m dimensions of D_i were further reduced to $\tilde{m}$ ($\tilde{m} < m$) with $\tilde{m}$ covering 95% of the variance by applying Principle Component Analysis (PCA) to D. A two-class SVM based classifier was then trained to classify the data into healthy or Schizophrenia groups. A polynomial of degree 2 was used as the kernel function to create the SVM hyperplane. Leave-one-out cross-validation was applied to evaluate the classifiers with following metrics.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{1}$$

$$Specificity = \frac{TN}{FP + TN} \tag{2}$$

$$Sensitivity = \frac{TP}{TP + FN} \tag{3}$$

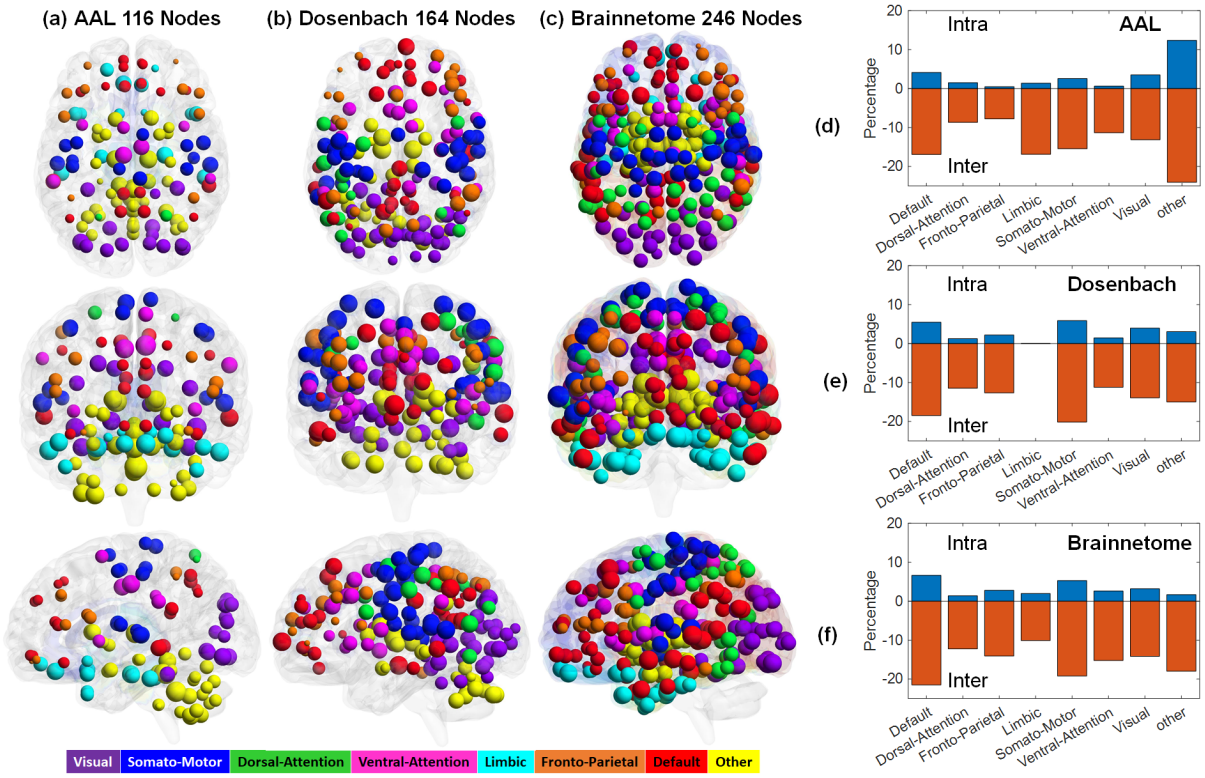

Fig. 2. (a-c) Visualization of nodes of the 3 atlases. The size (or diameter) of a given node indicates the total number of other nodes which are connected to this given node and with significantly different FC between healthy and Schizophrenia groups. Colour of the nodes indicates the resting state network they belong to. Maps created by Brain-Net viewer [17]. (d-f) Proportion of intra and inter connected significant nodes in each network.

Here, True Positive (TP) means the correctly diagnosed patients, False Positive (FP) means incorrectly identified patients, True Negative (TN) is correctly diagnosed controls and False Negative (FN) is incorrectly identified controls.

III. RESULTS

Fig 2 (a)-(c) show the seed voxels of each ROI in the three atlases. The size of a node indicates the number of nodes connected to this node with significant difference ($p < 0.01$) between the two groups: healthy and Schizophrenia. The color of a node indicates the resting state functional network to which the node belongs. We can notice the increase in density of the significant nodes in the same network from (a) to (c) with resolution of atlases varying from 116 to 246. The seed position is also different across the atlases which is an important factor that can affect the classification results.

Fig 2 (d)-(f) shows the percentage distribution of significant nodes within and across the different resting state functional networks. All the three atlases show about 20-25% of significant nodes belonging to the default mode and the somato-motor networks of which at most 8% belongs to the same network (intra-network connectivity). The other network shows the nodes which do not belong to any of the Yeo 7 networks [15]. The cross validation results from Table I indicate that the classifiers developed with FC maps from high-resolution Dosenbach and Brainnetome atlases have similar accuracy which is higher than the AAL atlas. Notably, the sensitivity and specificity are best for the Dosenbach and the Brainnetome atlas based classifiers, respectively. We also performed the permutation tests 1 and 2 as per [18] and found that the classification accuracy achieved was statistically different from chance level classification.

TABLE I
LEAVE ONE OUT CROSS VALIDATION RESULTS

Atlas	Accuracy [%]	Sensitivity [%]	Specificity [%]
AAL	73.40	53.39	84.54
Dosenbach	83.65	**72.88**	90.21
Brainnetome	**85.26**	72.03	**93.30**

IV. DISCUSSION

We presented the effect of resolution of atlases on the capability of SVM based classifier in classifying a given data into healthy controls or Schizophrenia groups. Choosing an atlas of certain resolution decides the number of ROIs and the number of voxels within an ROI. Some atlases cover the whole brain whereas some atlases only specify a seed point with a spherical region around the seed point chosen as the ROI. We have included both kinds of the atlases in our study.

Each mental health disorder affects the resting state functional networks of the human brain in a different way. Therefore, it becomes very important to choose an atlas with a proper resolution. While higher resolution atlases increase the computation time and demand larger memory for computations, our results indicate that they seem to

be necessary for analysis of FC maps in Schizophrenic brains. Prior studies indicate that there are impairments in the connectivity of the default mode network in Schizophrenic brains [19], [20]. We observed similar results in Fig 2 (d)-(f) with about 20-25% of the significantly different FC pairs belonging to the default mode network.

Noting from Fig 2 (a)-(c), the AAL and Dosenbach atlases have significant nodes in the cerebellum and sub-cortical regions. This indicates that these are important regions to observe in a Schizophrenic brain. However, since these regions are not present in any of the Yeo 7 networks, all the significant FC pairs belonging to these regions have become part of the other network in Fig 2 (d)-(f). Moreover, there are more ROIs in the cerebellum region of AAL atlas as compared to the Dosenbach atlas, but the Brainnetome atlas has no nodes in the cerebellum region. Also, there are few sub-cortical nodes in Dosenbach atlas. Noting from Fig 2 (d), we can observe around 12% of important nodes in the intra network connectivity of the other network, which indicates that connections within sub-cortical and the cerebellum regions are also impaired in schizophrenic brains. The Dosenbach atlas does not have any nodes in the limbic network. Therefore, no significant nodes appeared in Fig 2 (b, e). However, since significant inter- and intra-nodes are present in Fig 2 (d, f) in AAL and Brainnetome atlases in the limbic network, they seem important in Schizophrenia.

We also ran the SVM classifier 1000 times, each time with a random selection of healthy (=145) and Schizophrenia (=88) subjects for training and the rest for testing, making a 75-25% train-test split. This resulted in 1000 accuracy values. The Brainnetome Atlas performed the best with ($mean \pm std$) accuracy of 81.95 ± 4.15 compared to AAL with 71.37 ± 4.17 and Dosenbach with 80.34 ± 4.51.

It is worth noting that the AAL and the Brainnetome atlases cover the whole brain region, i.e on average the AAL atlas has 1598 voxels per region and Brainnetome atlas has an average of 571 voxels per region. On the other hand, Dosenbach atlas just considers a 5 mm sphere around the seed voxel and has on an average of 122 voxels per region. Despite the differences in Dosenbach and Brainnetome atlases, we still found them to be better than AAL atlas in terms of accuracy, sensitivity and specificity and attribute it to their high resolution compared to the AAL atlas.

V. CONCLUSION AND FUTURE WORK

We compared the effect of three different atlases and found the Brainnetome 246 atlas to be the best performing atlas in terms of the accuracy and specificity of classification. Future work should compare Brainnetome 246 atlas with other widely used atlases and test its classification accuracy with other classifiers before accepting it as the best performing atlas for Schizophrenia studies.

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