Convolutional Neural Networks for the Prediction of ASD and Biomarker Identification

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I. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is characterized by social and communicationdeficits as well as restricted, repetitive behaviors. Early diagnosis and intervention are critical for improvinglong-term outcomes; however, the current gold standard assessment tools are limited in their ability to accurately and efficiently diagnose ASD, particularly in young children. Typically, ASD diagnoses are based on behavioral criteria, but there is growing interest in the identification of objective biomarkers to aid in the diagnoses [14]. Biomarkers are measurable characteristics that can be used to indicate the presence or severity of a disease. In the case of ASD, biomarkers could be used to improve and validate diagnoses, especially in young children, and potentially before the emergence of symptoms.

Due to advancements in multimodal neuroimaging in recent years, neuroscience has gained unprecedented opportunities to interrogate the living human brain at multiple scales in both health and disease [4], and these advancements have been especially useful in the study of neurodevelopmental disorders [7]. The field of network neuroscience aims to investigate such disorders by leveraging magnetic resonance imaging (MRI) and and various tractography algorithms to construct 'brain graphs' or 'connectomes' which are matrix representations of the structural and/or functional connections between various regions of the brain.

Several studies have been conducted to examine changes in functional connectivity in individuals with ASD relative to typically developing controls [6], [18]. However, less is known about changes in structural connectivity in individuals with ASD. By capitalizing on diffusion-weighted magnetic resonance imaging (dMRI), previous studies were able to identify abnormalities in the connectivity strength of several inter-regional fiber pathways in individuals with ASD [2]. Despite the identification of these abnormalities, the diagnosis of ASD based on brain imaging remains a challenge. One reason for this challenge is that the abnormalities associated with ASD are often subtle and are often difficult to detect. This calls for the application of sophisticated computational methods to aid in the diagnoses.

In recent years, there has been an explosion of interest in the potential of machine learning to revolutionize different aspects of neuroscience [1], [16]. However, given the complex and high-dimensional nature of connectomes, traditional machine learning approaches are not well-suited for connectome classification problems. Recent advances in deep learning, specifically Convolutional Neural Networks (CNNs), have shown promise in the prediction of clinical neurodevelopmental outcomes from brain networks (connectomes). For example, *BrainNetCNN* was developed for the prediction of cognitive and motor scores from the connectomes of infants born preterm [5].

In this study, we propose a novel convolutional neural network (CNN) architecture capable of distinguishing between connectomes of autistic and typically developing children. We will also attempt to identify biomarkers that better identify ASD in children. We will utilize graph theory measures as the features for our model. Additionally, we will analyze the relationships between the potential biomarker(s) and autism severity, social communication, and intellegence as assessed by the Autism Diagnostic Observation Schedule Clinical Severity Score (ADOS-CSS), Social Communication Questionaire (SCQ) score, and Intelligence Quotient (IQ) respectively.

II. Materials and Methods

Fig. 1 provides an overview of the proposed approach for the development of a CNN-based classifier for ASD. In this section, we first describe the dataset used and the methodology involved in the generation of the structural connectomes from the raw MRI image data. We then describe the calculation of graph-therory measures which will serve as features for the classifier. We also describe the exploratory analysis performed as well as the application of various feature selection techniques in an attempt to identify potential biomarkers for ASD and reduce the feature space for the classifier.

Dataset. This study was conducted data provided by our collaborators at Penn Medicine. dMRI scans were collected from a cohort of 313 children between 6 and 19 years old, including children with ASD ($n = 163$; age $= 12.10 \pm 2.76$; 133 males; 30 females) as well as typically developing controls ($n = 160$; age $= 11.87 \pm 2.82$; 115 males; 35 females). For each subject, only a single dMRI scan was performed. The age, sex, Social Communication Questionnaire (SCQ) score, and IQ were recorded for all subjects in the cohort. The SCQ score is considered the gold standard measure of communication

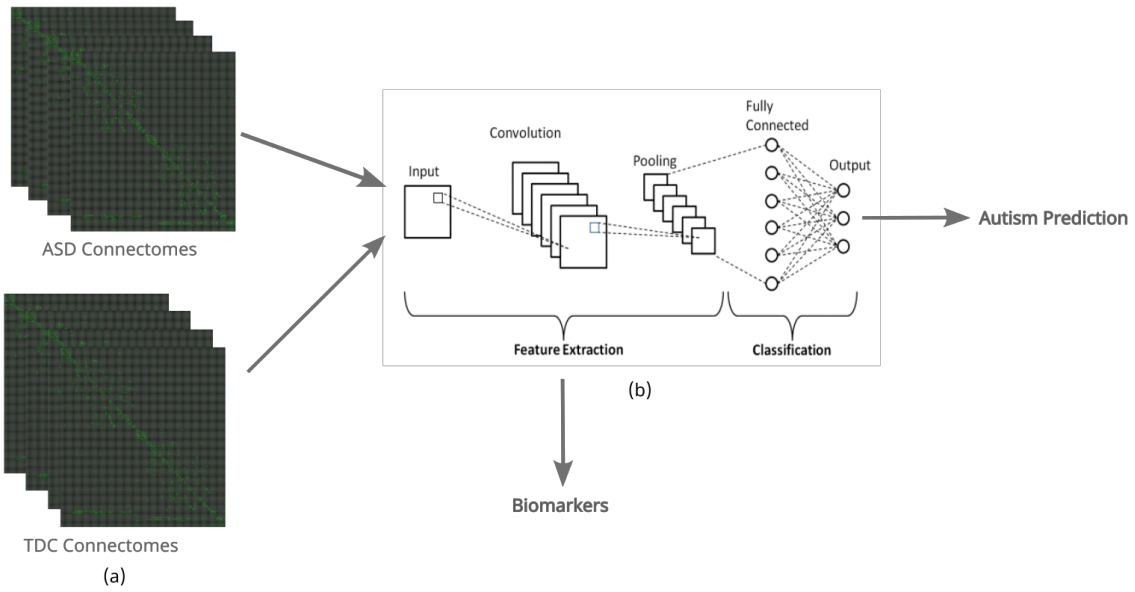

Fig. 1. Overview of autism prediction and biomarker identification using a Convolutional Neural Network based classifier. (a) (top) Structural connectomes of patients with Autism Spectrum Disorder. (bottom) Structural connectomes of Typically Developing Controls. (b) Schematic diagram for convolutional neural network.

skills, and ranges from 0 to 39; a score of 15 or higher is considered to be indicative of ASD, whereas a score of 14 or below is within the range of typical development. For subjects with ASD, the Autism Diagnostic Observation Schedule Calibrated Severity Score (ADOS-CSS) was also recorded. The ADOS Clinical Severity Score is a semi-structured, play-based assessment administered by a trained professional; iit is the gold-standard measure for autism severity and ranges from 1 to 10, with higher scores indicating greater severity of autism.

Connectomes. Two connectomes were obtained from each dMRI scan; the first set of structural connectomes were construced using the Desikan atlas to define nodes, while the second set of connectomes were constructed using nodes defined by the Schaefer atlas. The Desikan atals parcellates the brain into 86 distinct regions while the Schaefer atlas parcellates the brain into 220 regions. The adjacency matrices for the Desikan connectomes were 86 x 86 in size. Whereas, the adjacency matrices for the Schaefer connectomes were 220 x 220 in size. The edges for both sets of connectomes were generated using tractographic tools.

Graph Theory Measures. Several graph theory measures were computed for each set of connectomes. The 'bctpy' package – a python-based implementation of the Brain Connectivity Toolbox – was used to compute graph theory measures [12]. Both node-level and network-level measures were computed and compared using the two-sample t-test with variances assumed to be unequal; the Cohen's d effect sizes were also calculated for each comparison.

Exploratory Analysis. In order to identify potential biomarkers from the computed graph theory measures, an exploratory analysis was performed. The association between the graph theory measures and autism severity was assessed by fitting the data to linear fixed-effects models to account for the effects of any covariates. The exploratory analysis was performed in the R [11] and figures were generated using the 'ggplot2' and 'ggstatsplot' packages [10], [17].

Biomarker Discovery. Multiple feature selection techniques were evaluated in an attempt to identify potential biomarkers from the graph theory measures. The 'scikit-learn' package was used to perform feature selection in python [9]. Univariate feature selection was performed using the 'SelectKBest' function, and statistical significance was assessed using the ANOVA F-scores for each measure. Additionally, the data were fit to a Random Forest Classifier to distinguish between ASD and TDC connectomes. A 70/30 split was used for training and testing the model. The 'SelectFromModel' function was then used to identify potential biomarkers from the Random Forest Classifier; features were selected based on the 'importance' scores computed when the model was trained. Both sets of features were then compared and only features present in both were ultimately selected as potential biomarkers.

III. Results

A. Comparison of Global Graph Theory Measures.

We began by comparing the computed graph theory measures between the ASD and TDC groups. Group differences were calculated for each of the measures using the student's t-test. Measures with p-values below 0.05 were considered significant. Of the 37 global graph theory measures calculated, only the following six were significant: Average degree, degree between modules, degree within modules, inter-hemispheric degree, density and eigenvector centrality. Fig. 2 shows boxplots comparing the six significantly different measures. The

TABLE I
GROUP DIFFERENCES BETWEEN ASD AND TDC FOR GLOBAL GRAPH THEORY MEASURES.

Measure	p	Cohens_d
Average Degree Within Module	1.89e-05	-0.4886968
Average InterHemispheric Degree	5.46e-03	-0.3147607
Average Degree	1.05e-02	-0.2891104
Density	1.05e-02	-0.2891106
Average Degree Between Modules	1.83e-02	-0.2665902
Average Eigenvector Centrality	4.98e-02	0.2225106

Cohen's d effect sizes and p-values for each of the 6 global graph theory measures are shown in Table I.

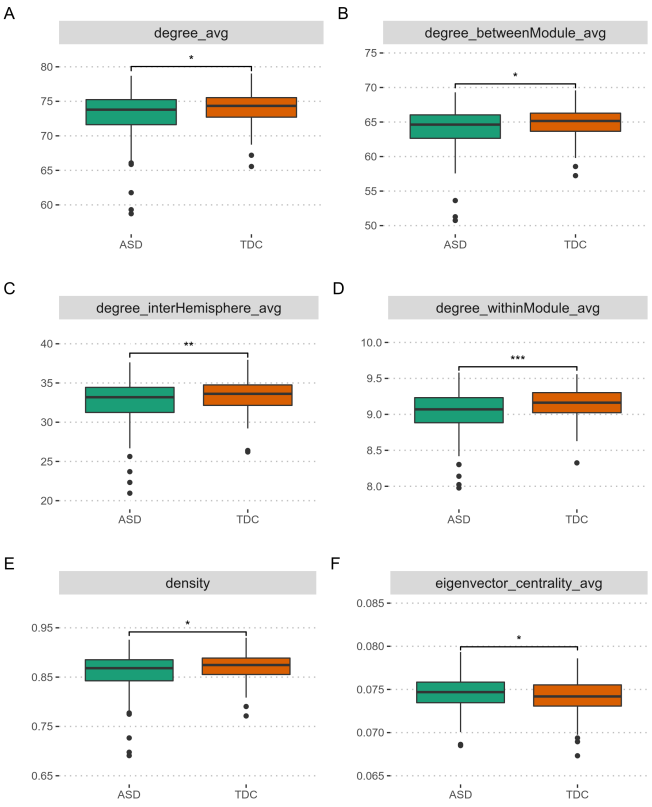

Fig. 2. Significant Group differences between ASD and TDC connectomes for six graph theory measures. The significance is indicated by the starts '*' above the braces in each sub-plot. (A) Average Degree (B) Average Degree Between Modules (C) Average Inter-Hemispheric Degree (D) Average Degree Within Modules (E) Network Density (F) Average Eigenvector Centrality

The global graph theory measures were then correlated with IQ, ADOS-CS, and SCQ scores. No significant correlations were observed between with SCR or ADOS-CS scores. The average inter-hemispheric degree and average degree within modules were found to exhibit significant, weak correlations with IQ scores among autistic children. Fig. 3 shows linear regression lines fitted to the data; the scatter plots are annotated with the correlation coefficient (R) and p-value for each case.

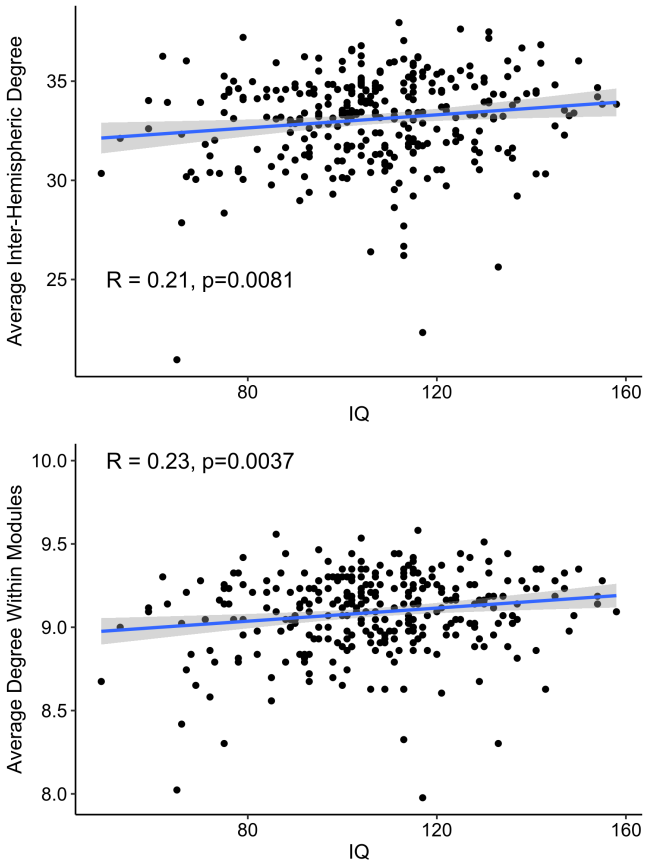

Fig. 3. Scatterplots with fitted linear regression lines for global graph theory measures significantly correlated with IQ. (Top) Average Inter-Hemispheric Degree (Bottom) Average Degree Within Modules

B. Feature Selection for Biomarker Discovery.

In order to improve the quality of data provided to the machine learning model, we excluded low-variance measures (features) from the dataset; of the 37 graph theory measures, 11 were excluded. First, the ANOVA F-statistics (scores) and corresponding p-values were computed for each measure, and features with the top 10 highest scores were selected. Of the top 10 features, only 5 had p-values less than 0.05 including: Average Degree Within Modules, Average Interhemispheric Degree, Density, Average Degree and Average Degree Between Modules. Next, we fit the data to a Random Forest Classifier; we observed 62.77% prediction accuracy with the model. Important features were then extracted from the fit classifier; 11 features were selected via this method including: Average Degree Within Modules, Average Intrahemispheric Degree, Average Participation Coefficient, Average Eigenvector Centrality, Global Interhemispheric Stength, Average Betweeness Centrality, Characteristic Path Length, Global Modularity, Assortativity and Average Interhemispheric Degree. The f-scores and importance scores for both sets of features are shown in Fig. 4. Only the average degree within modules and average interhemispheric degree were present in both sets of

features.

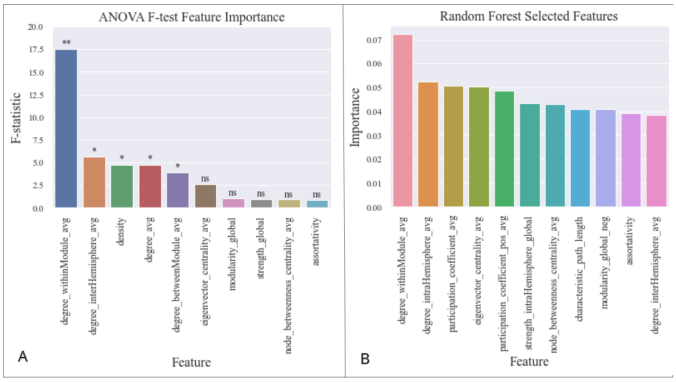

Fig. 4. (A) ANOVA F-scores for the top 10 features overlayed with corresponding significance levels. (B) Feature importance scores from the Random Forest Classifier.

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