Exploring the Impact of Autism Spectrum Disorder on the Structural Connectome

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***Abstract*—Recent studies have begun to examine whether patients with neurological disorders show distinctive network properties in their connectomes. If so, the findings have the potential to lead to increased understanding of the underlying nature of the disorders, as well as more accurate diagnoses. In this paper I explore the structural connectomes of individuals with autism spectrum disorder (ASD), and compare them to a control set of individuals without the disorder. I attempt to determine whether there is a group difference for any network measures between the ASD set and the control set, and whether a classifier can be trained to identify whether a connectome is from an individual with ASD. I also investigate whether any network measure shows a correlation with the level of severity of ASD.**

I. Introduction

Network neuroscience involves the study of connectomes, which are matrix representations of brain networks encompassing the pairwise connections between the various regions of the brain. Overall the field attempts to understand how connectomes relate to the brain's capacity and function. In recent years a specific area of focus has been how diseases and disorders impact the connectome. Since the connectome represents the network of communication patterns between different brain elements, it provides a powerful tool to study the nature of neurological disorders which impact the way the brain operates.[2]

Autism spectrum disorder (ASD) is one such neurological disorder which has received this attention. ASD is a common disorder that affects close to one percent of the population, making it an obvious and important candidate for study.[3] Studies analyzing graph theory measures of the connectomes from subjects with ASD have shown that ASD connectomes exhibit some distinctive network properties. A 2015 study of structural connectomes found that subjects with ASD had decreased global efficiency, increased characteristic path length, and decreased strength of connections.[3] A 2021 study of functional connectomes found a higher mean modular variability in ASD subjects, suggesting more overall instability in global brain dynamics.[4]

In addition to network analysis, researchers have also used connectomes to investigate finding classifiers and biomarkers for ASD. A biomarker for ASD would be an objective empirical measure which can be shown to clearly predict whether an individual has the condition or not. A classifier is a machine learning model that takes input data, and uses features from the data (such as biomarkers) to predict which group the data belongs to. Research on ASD classifiers does not always involve connectomes. For example, Tunc et al.[1] used evaluation scores like MESL (Mullen Scales of Early Learning) and VABS (Vineland Adaptive Behavior Scales) as input data to a machine learning technique called a Support Vector Machine (SVM) to establish an ASD classifier. The classifier achieved high performance, with an accuracy of 84%.[1] Several studies searching for classifiers using functional connectomes have also been performed, with good results. One in particular showed that a functional connectome collected from a subject at the age of six months could be used to predict autism status at the age of 24 months.[5]

In this paper I will attempt to add to the previous work done on both network analysis and on finding a classifier for ASD. I will use a dataset with structural connectomes from both ASD subjects and healthy controls, compute graph theory measures on the connectomes, and attempt to determine if there is a significant statistical difference between any measure for the ASD set and the control set. I will then input the data into a Support Vector Machine and use it to generate a classification boundary which can be used to predict whether an individual has ASD or not. Finally, I will also analyze whether any of the computed measures correlate to the severity of ASD diagnosed in each subject.

II. Materials and Methods

A. Materials

My analysis will be performed on the CHARM dataset, provided by Penn Medicine. The CHARM dataset contains structural connectomes from 450 subjects. The data was collected from eleven different sites, and the subjects are a mix of patients with ASD and patients without ASD (healthy controls).

Even though 450 subjects were included in the study, only 313 subjects produced connectomes which passed a quality assessment review. I will only include the connectomes from these 313 in my analysis. Of these 313 subjects, 163 are diagnosed with ASD, while 150 are not diagnosed with ASD.

Each subject has only one brain image, but connectomes were generated using two different atlases, with the end result that there are two connectomes for each subject. The two atlases used are the Desikan atlas and the Schaefer atlas. The

Desikan atlas has 86 regions, and thus connectomes created using this atlas have 86 nodes in their network. The adjacency matrix from these connectomes is size 86 x 86 and has non-zero values in every position where there is a connection between regions. The edges are weighted, with greater values indicating a stronger connection between the two regions. The Schaefer atlas has 220 regions, and connectomes created using this atlas have 220 nodes. Edges are also weighted in these connectomes, and so adjacency matrices are similar as to what was described for the Desikan atlas connectomes, except they have size 220 x 220.

Each subject also has their sex, age, diagnosis (ASD or non-ASD), Autism Diagnostic Observation Schedule Calibrated Severity Score (ADOS_CSS), Social Communication Questionnaire (SCQ) score, and IQ recorded. I will use the diagnosis to distinguish between subjects with ASD and subjects without ASD. I will use the ADOS_CSS and SCQ score to interpret ASD severity. The ADOS_CSS score ranges from 1 to 10 with a higher score representing a more severe level of ASD.[1] The SCQ score can range from 0 to 39 with a higher score representing more social impairment.

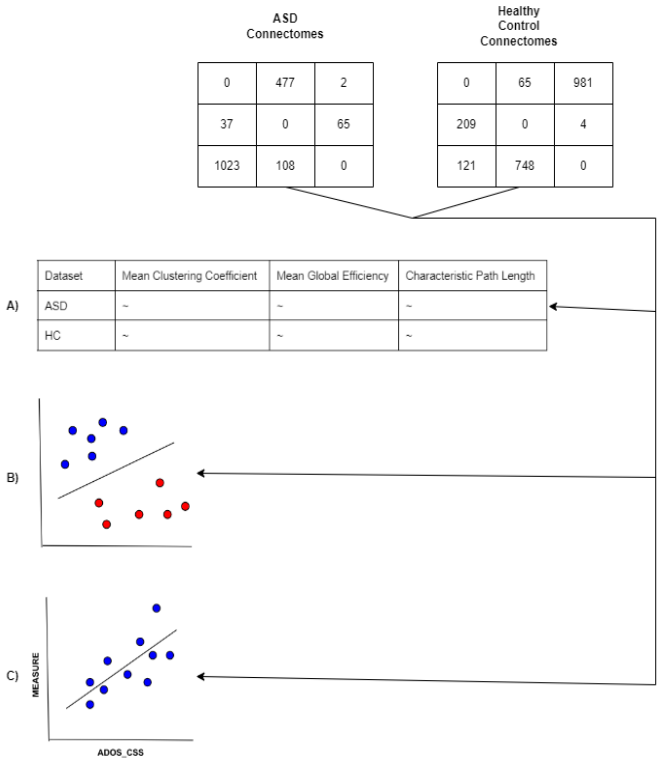

Fig. 1. Structural connectomes from both ASD subjects and Healthy Control subjects will be used A) to calculate and analyze graph theory measures B) as input into a Support Vector Machine, to determine a classifier for ASD C) to check for a correlation between graph theory measures and autism severity scores like ADOS_CSS

B. Methods

To calculate graph theory measures, I used code from the Brain Connectivity Toolbox (BCT).[6] I computed several key node level and network level measures we discussed in class that are supported by the BCT. Next, I attempted to determine whether there was a statistically significant group difference between the ASD set and healthy control set for several network measures. For this analysis, I chose to focus on measures which were identified in previous research as distinctive in connectomes from ASD subjects[3], as well as measures that highlight certain characteristics about the overall brain networks. This includes measures for degree, density, strength, clustering, centrality, path length, and assortativity.

I will use the Support Vector Machine machine learning technique to attempt to generate a classifier for ASD from the connectomes. Afterwards, I will use machine learning metrics like accuracy and precision to review the success of the resulting classifiers. I will use two different SVMs; one for the Desikan atlas connectomes and one for the Schaefer atlas connectomes. Once I have created a reasonably accurate classifier, I will work backwards to find which input features it is most reliant on to make its predictions, and hopefully use this information to identify a biomarker.

To test for links between specific graph theory measures and autism severity, I will use statistical correlation tests between the computed measures and the ADOS_CSS and SCQ scores. I will explore the best correlation tests to use, with Pearson correlation being a possible candidate.

III. Results

A. Group Difference

Desikan Atlas Group Difference		
Measure	Effect Size	P Value
degree avg	-0.29	0.047419
density	-0.29	0.047419
clustering coefficient	0.21	0.148264
characteristic path length	0.03	0.824202
global efficiency	0.13	0.383826
betweenness centrality	0.1	0.474474
eigenvector centrality	0.22	0.148264
global strength	0.05	0.709829
assortativity	-0.16	0.280886

TABLE I
GROUP DIFFERENCE CALCULATION ON NETWORK MEASURES USING THE DESIKAN ATLAS

Schaefer Atlas Group Difference		
Measure	Effect Size	P Value
degree avg	-0.17	0.360613
density	-0.17	0.360613
clustering coefficient	0.19	0.360613
characteristic path length	-0.14	0.427521
global efficiency	0.1	0.512949
eigenvector centrality	-0.08	0.571101
global strength	0.05	0.6318
assortativity	0.1	0.512949

TABLE II
GROUP DIFFERENCE CALCULATION ON NETWORK MEASURES USING THE SCHAEFER ATLAS

Results of group difference analysis on selected network measures from connectomes constructed using the Desikan

atlas are shown in Table I , and from connectomes constructed using the Schaefer atlas in Table II. As the set of data in each group comes from different subjects, and the data is parametric, the independent group t-test was used to calculate a P value for each measure. The P value represents whether there was a statistically significant difference between the groups for the measure. Calculated P values were corrected using the Benjamini-Hochberg procedure, in order to appropriately adjust for chance. Cohen's D was used to calculate the effect size for each measure, which represents the magnitude of the difference between the two groups.

The P value should be less than 0.05 in order for a result to be considered significant. The majority of my results do not meet this requirement. However, the group difference calculation for both the degree average and density measures have a P value less than 0.05 for connectomes constructed using the Desikan atlas. Each reports an effect size of -0.29, indicating that Desikan connectomes from the ASD group typically have a slightly less average degree and density than the healthy control group.

I am not sure why average degree and density show a significant difference when using the Desikan atlas but not when using the Schaefer atlas, but I plan to explore this question in my next report. In the background research I have done so far I have also not yet found another paper reporting this result (for any atlas), but I also plan to investigate that point further.

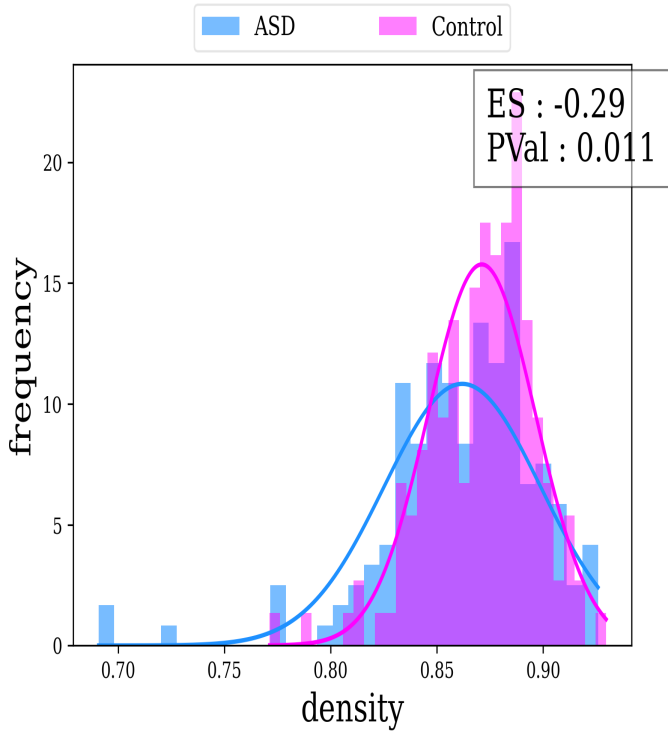

Fig. 2. A histogram showing the distribution of the density measure across the Desikan connectomes for both the ASD and healthy control groups. The groups are statistically different, with the ASD group exhibiting slightly lower density values.

My next report will also include details on my attempt to produce a machine learning classifier, and my attempt to correlate ASD severity scores with graph theory measures. I do not have results on those parts of my project to report right now.

References

[1] Tunç, B., Pandey, J., St. John, T., Meera, S.S., Maldarelli, J.E., Zwaigenbaum, L., Hazlett, H.C., Dager, S.R., Botteron, K.N., Girault, J.B. and McKinstry, R.C., 2021. Diagnostic shifts in autism spectrum disorder can be linked to the fuzzy nature of the diagnostic boundary: a data-driven approach. Journal of Child Psychology and Psychiatry, 62(10), pp.1236-1245.

[2] van den Heuvel, M.P. and Sporns, O., 2019. A cross-disorder connectome landscape of brain dysconnectivity. Nature reviews neuroscience, 20(7), pp.435-446.

[3] Roine, U., Roine, T., Salmi, J., Nieminen-von Wendt, T., Tani, P., Leppämäki, S., Rintahaka, P., Caeyenberghs, K., Leemans, A. and Sams, M., 2015. Abnormal wiring of the connectome in adults with high-functioning autism spectrum disorder. Molecular Autism, 6(1), pp.1-11.

[4] Xie, Y., Xu, Z., Xia, M., Liu, J., Shou, X., Cui, Z., Liao, X. and He, Y., 2022. Alterations in connectome dynamics in autism spectrum disorder: A harmonized mega-and meta-analysis study using the Autism Brain Imaging Data Exchange Dataset. Biological Psychiatry, 91(11), pp.945-955.

[5] Horien, C., Floris, D.L., Greene, A.S., Noble, S., Rolison, M., Tejavibulya, L., O'Connor, D., McPartland, J.C., Scheinost, D., Chawarska, K. and Lake, E.M., 2022. Functional connectome-based predictive modelling in autism. Biological Psychiatry.

[6] Rubinov, M. and Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage, 52(3), pp.1059-1069.