Gender Differences in the Human Connectome

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Abstract. The human brain and the neural networks underlying it are of immense interest to the scientific community. In this work, we focus on the functional connectivity of the human brain and investigate the gender differences across male and female connectomes. Our analysis methods reveal several regions in the brain that are statistically different among the two genders. We use these discriminative features for the related classification problem "*Can we classify a given human connectome to belong to one of the genders just by looking at its connectivity structure?*" and learn decision tree as well as support vector machine classification models for this task. One of our main findings disclose the statistical difference at the pars orbitalis of the connectome, which has been shown to involve in language production, between the genders.
***** Joshua, please rewrite in more neuroscientific terms? *****

Keywords: human connectome, network science, network connectivity, graph measures, gender classification

1 Introduction

The human brain has long been an object of great scientific interest. We revel at the immense capabilities that our highly evolved brains possess and wonder at how the brain functions, how vision is interpreted, how consciousness arises etc, all of which neuroscience deals with to a great extent. Recent advances in neuroscience and computer science have brought to the fore-front an exciting research area of Brain Networks. The fundamental idea giving rise to this area being that the brain can be thought of as composed of several simple elements that give rise to complex patterns like consciousness [2]. Thus the brain can be modeled as a network which admits the brain to network analysis. Over the years, network science has evolved to a great extent and is now in a position to analyze real world networks. Emergence of massive data, faster algorithms and the ubiquity of networks have contributed to this. ***** cite real networks *****

One of the overarching ideas currently in brain research is the idea that it is crucial to study the connections in the brain to gain deeper insight into the functioning of the brain. This is an exciting research area resulting from the confluence of neuroscience and network science which promises us great insight into the workings of the brain. Perhaps one of the most important projects,

analogous to the Human Genome Project in 2005, is the *Human Connectome Project* that was kicked off in 2009. The human connectome project which aims to map the brain's connectivity across regions can help understand diseases like schizophrenia and the Alzheimer's disease.

It is to be noted that analyzing the human connectome is far more challenging in terms of scale (it has more than a billion more connections than the letters in a genome)[3]. While the human connectome project is still an ongoing project , exciting initial results have been obtained by analyzing connectomes. Some important results include the small world property of brain networks, and the presence of a rich club of hubs. Noting the larger goal outlined above, one of the research problems that seeks investigation is that of gender differences in brain networks and what they imply in a biological setting. We investigate this problem in our work. The main questions we address are listed as the following:

1. What differences in the brain network (connectome structure) do the two genders exhibit?
2. Would these discriminative features admit to classification of connectomes into genders based solely on their brain structure?

Our study involves two independent group of human subjects. One group consists of 114 (50F/64M) subjects and another contains 79 (35F/44M) subjects. We find out that there exist several regions in the brain that show statistically significant difference across the genders. Among these regions, the *pars orbitalis* in the inferior frontal lobe of the brain stands out the most. Learning classification models using only a handful these several discriminative regions and their network properties as covariates, we achieve up to 73% classification accuracy in classifying the human subjects into genders by their connectome.

In the rest of the paper we survey related work, describe our datasets and research methods in detail, and present our experiments and findings. We conclude by interpreting our results and discussing future work.

2 Related Work

***** Joshua can you please elaborate on related work? *****

There are two main approaches to the above problem of identifying discriminative features of the connectome. The first approach would be to look for subgraph structures (also called signal sub-graphs) which are discriminative and build a classifier based on them. This approach has been described in detail by Vogelstein et.al [3]. This model has been shown to perform better than other standard graph classification techniques like graph k-NN based on nearest neighbors. The second approach is to identify discriminative network measures (either global or local) and use standard machine learning techniques for classification. Duarte-Carvajalino et. al [1] analyzed connectome structure to help identify sex

[3] `http://www.humanconnectomeproject.org/2012/03/mapping-out-a-new-era-in-brain-research-cnn-labs/`

and kinship differences. They confirmed the small node nature of brain networks, and also outlined structural differences in brain networks in terms of network measures like communicability, edge betweenness centrality which improved the classification rate to around 93% accuracy (based on gender for their data sets). This was done at a global scale (topological scale) with a set of 303 individuals.

In this work, we are investigating structural differences on two different data sets of human connectomes at a local scale, by studying the properties of local neighborhoods of brain regions. We then look at how these local discriminative network measures can be used to classify connectomes with respect to gender.

3 Dataset Description

Our study involves two independent group of human subjects, one consisting of 114 (50F/64M) subjects and another with 79 (35F/44M) subjects.

More specifically, the first data set consists of connectome data for 114 individuals (50 of them being of one sex and 64 of the other, mean age: around 21 years). Each sample is a brain network on 70 nodes (where each node represents a particular brain region, and each weighted edge represents density of fibers between those regions ***** Joshua I think waht student wrote here is incorrect, this is not structural connectivity right? ***** (strength of their connections). Each sample is represented as a weighted undirected graph and is thus represented as a sparse strictly upper triangular matrix.

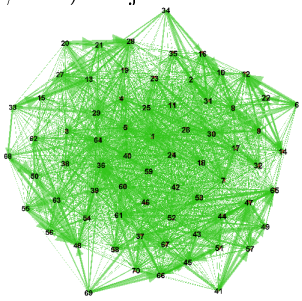

Fig. 1. Sample brain network

The second dataset consists of 79 connectomes (35 of them being of one sex and 44 of the other, mean age: around 70 years). ***** Joshua can you please add description on BLSA dataset, too? –how it is collected, built, etc.–probably also for the first dataset. *****

Each sample or connectome in our datasets is assigned a (class) label (0 or 1) thus identifying what sex the connectome belongs to. For all the experiments, we denote the sex with label 0 as *Sex 0* and the sex with label 1 as *Sex 1* respectively. A sample network is shown in Fig.1.

4 Connectome Network Analytics

4.1 Preprocessing the data sets

Each connectome is represented as a weighted undirected graph (that is symmetric and hence strictly upper triangular). Since each edge weight represents the connectivity strength between two regions, it is crucial that such connectome data be normalized between the range [0,1]. This is because these weights may vary from individual to individual. The authors in [1] also point out that there

exists an inherent bias in tractography for a given cortical region that depends on the volume of the region, number of fibre crossings etc. However they also point out that there is no unique way of normalizing this data. They do however outline different normalization schemes (based purely on topological measures) which we briefly highlight below as it is crucial to understand the interpretation of a normalization scheme:

***** Joshua could you please verify the normalizations below, I removed the 'fiber' words mostly as I think we have functional connectivity. *****

- *Global Normalization*: This essentially divides each edge weight by the total weight of all the edges in the connectome, effectively normalizing counts between each pair of regions by the total number, i.e. $w_{ij} = \frac{a_{ij}}{\sum_{ij} a_{ij}}$, where w_{ij} represents the normalized count (edge weight) and a_{ij} represents the raw edge weight between region i and region j. However this scheme leads to biased weights as it does not account for the fact that some regions are expected to have higher weights.
- *Geometric Mean Normalization*: This scheme divides the weight between each pair of edge by the geometric mean of the weights leaving region i or region j, i.e. $w_{ij} = \frac{a_{ij}}{\sqrt{\sum_i a_{ij} \sum_j a_{ij}}}$. This normalization is based on the assumption that each pair of brain regions has the same total weight., and is claimed to work correctly globally and on large sample sizes.
- *Row Mean Normalization*: This scheme divides each edge weight by the total weight incident on a node, i.e. $w_{ij} = \frac{a_{ij}}{\sum_j a_{ij}}$. It can be viewed as the probability of a connection between region i and region j given that $\sum_j a_{ij}$ weight emanates from region i. Note that this provides us valuable information regarding the differences in connectivity between cortical regions: even though a set of fibres leave a particular region i, only a subset of them are used for the connection to region j. This model also implies that $w_{ij} \neq w_{ji}$, thus making the resulting graph a weighted directed graph.

***** we can cut off from here if space needed–delete first two schemes *****

In our work we choose to use the *Row Mean Normalization* scheme, as it captures valuable information about the connectivity differences and models the brain more accurately. Moreover, in order to reduce the effect of mean brain size differences between males and females, we normalize the above by the maximum weight so that $max(w_{ij}) = 1$.

4.2 Network Measures

Next we study the graph-centric properties of the human connectomes. In particular, we compute the following network measures (we used the Brain Connectivity Toolbox[4] to obtain the measures below):

***** Vivek/Jagat: Should we briefly define each measure here? *****

[4] Brain Connectivity Toolbox: `https://sites.google.com/site/bctnet/`

1. Locally weighted clustering coefficient
2. Local efficiency
3. Degree distribution
4. Edge betweenness centrality
5. Participation coefficient of each node

For all the node-based measures, we compute the mean measure across all subjects of the class.

We next analyze the data for differences in the mean measures across classes (i.e. genders). To establish statistical significance of a difference, we use a bootstrapping approach. This approach is suited very well for our work as we have small sample size and bootstrapping allows us to test our hypotheses by creating a large enough sample through repeated sampling. Secondly it has the added advantage that no assumption on the sample distribution is made. We outline the bootstrapping algorithm in Algorithm 1.

Algorithm 1 Bootstrapping algorithm to establish statistical significance

Assume we have two independent sample sets (corresponding to samples of the sexes)
Observed Sample Set 1 is of size n :$\{x_{obs1}, x_{obs2}, x_{obs3} \dots x_{obsn}\}$ and has mean μ_{xobs}
Observed Sample Set 2 of size m : $\{y_{obs1}, y_{obs2}, y_{obs3} \dots y_{obsm}\}$ and has mean μ_{yobs}
Observed Difference in the sample mean is $t^*_{obs} = \mu_{xobs} - \mu_{yobs}$
We need to see if the above difference is statistically significant at a pre-determined level of significance α
Hypothesis:

- *Null Hypothesis (H_0)*: Samples are from the same population
- Alternative hypothesis (H_1): Samples are from different population and $\mu_x > \mu_y$

1. Merge the two sample sets into one sample set of size $(m + n)$
2. Draw a bootstrap sample, with replacement, of size $(m + n)$ from the merged set
3. Calculate the mean of the first n observations and set it to μ_{x*}
4. Calculate the mean of the remaining m observations and set it to μ_{y*}
5. Calculate the test statistic $t^* = \mu_{x*} - \mu_{y*}$
6. Repeat steps 2, 3, 4, 5 B times and obtain B values of the test statistic.
7. The p-value is then given by:

$$p - value = \frac{NumberOfTimes(t* > t_{obs}*)}{B} \tag{1}$$

8. Reject the null hypothesis if $p - value < \alpha$

5 Empirical Results

5.1 Analysis of the Mean Edge Connectivity

We found the average weight of each edge for each class (by averaging over all subjects belonging to a class) to identify any edge weight differences among

sexes. The heat map in Fig.2 shows the differences in the mean edge weights for each edge between Sex 0 and Sex 1. ***** Vivek/Jagat: Figure text too small, can you regenerate? *** *** Everyone: we need to decide how to present results on dataset 2. *****

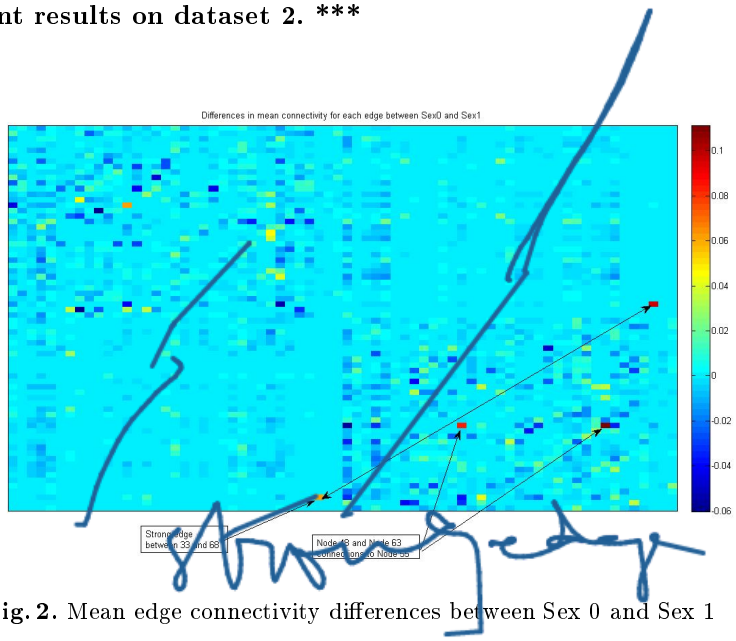

Fig. 2. Mean edge connectivity differences between Sex 0 and Sex 1

We note the following observations: (1) we find strong connections from Node 48 and Node 63 to Node 55, in one of the sexes; and (2) we also note a particularly dominant edge between Node 33 and Node 68 in one of the sexes.

While we do not have labelings for the brain regions represented by the nodes, we speculate that the particularly dominant edge is between the two hemispheres. This is based on the observation that the labelings given to connectome nodes (based on tractography) tend to be divided into two classes (based on hemisphere) where Nodes 1-35 and Nodes 36-70 belong to the left and right hemisphere, respectively. Thus we find that one of the sexes has a particularly dominant edge across hemispheres which could be discriminative.

We will elaborate more on Node 55's role as we present other measures in the following.

5.2 Analysis of the Mean Clustering Coefficient and Local Efficiency

We analyzed the mean clustering coefficient of each node and present our findings (across sexes) in Fig. 3. ***** Vivek/Jagat: blue is females, so let's replot for red being females. And again, increase font please. *****

We note that mean clustering coefficient of Node 55 in Sex 0 is higher than that in Sex 1. We hypothesize that this difference is statistically significant. In order to rule out the effects of outliers (as the mean is influenced by outliers) we

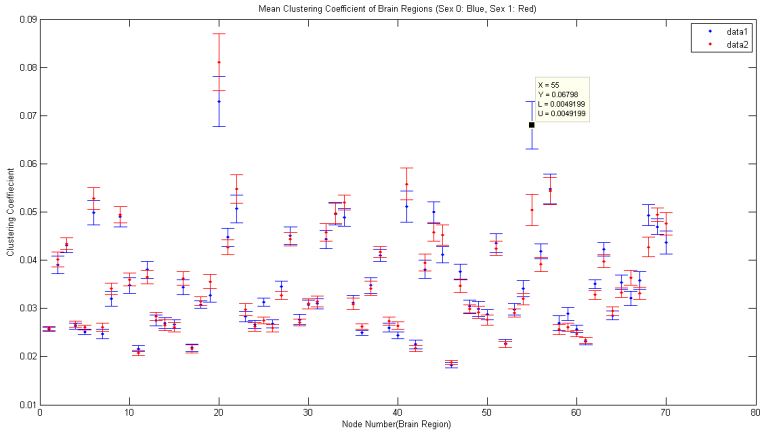

Fig. 3. Mean local clustering coefficient, for Sex 0 (blue, female) and Sex 1 (red, male)

also looked at the median. We again noted that Node 55's clustering coefficient is higher in Sex 0 than in Sex 1 bolstering our hypothesis.

To gain more insight, we ranked the brain regions according to their mean clustering coefficients (MCC) for both males and females, and we provide the corresponding network visualizations in Fig.4. We observe that the Node 20 has high MCC in both sexes, while Node 55's is visibly (and as we show below also significantly) higher for Sex 0. We find that Node 55 is the *pars orbitalis*, in the inferior frontal lobe of the brain. Interestingly, Node 20 is its complementary matching region in the other hemisphere. It is known that pars orbitalis is involved in language production and participates in prefrontal associational integration ***** please cite ***** (and probably hence the largest clustering coefficient). ***** Joshua: We want to beef up this paragraph or highlight it as a main finding. Also, what are the implications of this finding? *****

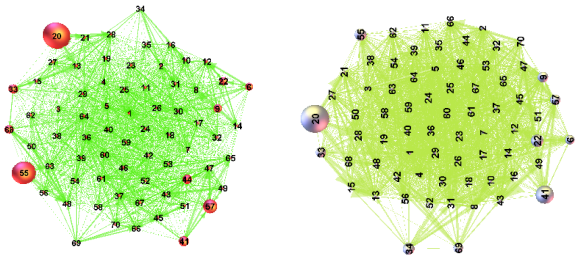

Fig. 4. Visualization nodes ranked by Mean Clustering Coefficient (MCC) (the larger node size depicts larger MCC), (left) Sex 0: female, and (right) Sex 1: male.

The observed sample difference between Node 55's mean clustering coefficient across the sexes in our first dataset is notes as *0.0175*. To establish statistical significance of this difference, we used the bootstrapping procedure with a significance level of $\alpha = 0.05$ and $B = 3000$. The histogram of the test statistic's values obtained on one run of the bootstrapping algorithm

obeyed a Normal distribution, which is inline with our intuition as we expect that the distribution of the differences in sample means to be normally distributed. More importantly, the number of times the test statistic was greater than the observed sample mean was very small, yielding a small p-value of $p = 0.0013$, which is significant at the $\alpha = 0.05$ level.

The sample difference between Node 55's mean clustering coefficient in our second dataset is smaller, and is notes as 0.006023. The p-value obtained by running boot strapping for $B = 3000$ iterations is about $p \approx 0.1087$, which is not statistically significant at the 0.05 level. However, this is not to conclude that there is no evidence of a difference, but simply that the evidence is not as strong as before. In the first data set, almost all the subjects were youths in their 20's, where as in the second data set, the mean age of the subjects is in the 70's. It is a possibility that the above difference may be influenced by the age factor, while it remains for future work to investigate these effects. ***** Joshua: how to say this properly? *****

***** How to integrate the results of dataset 2 here? *****

We also studied the Cumulative Distribution Function (CDF) of Node 55's clustering coefficient across sexes. The CDF showed that the clustering coefficients are in general lower in Sex 1 than in Sex 0. About 40% of the subjects in Sex 0 have a clustering coefficient less than 0.06 while about 70% of the subjects in Sex 1 have a clustering coefficient less than 0.06.

With respect to local efficiency, we found that Node 55 also shows higher efficiency in Sex 0 than in Sex 1 (see Fig.5). It is to be noted that there are other regions that also manifest differences although we highlighted only the largest ones. The efficiency is a measure of network integration. A high efficiency indicates that pairs of nodes on average have short communication distances and can be reached in a few steps. The local efficiency is then the efficiency calculated over the local neighborhood of a particular node.

5.3 Analysis of the Edge Betweenness Centrality

In the brain network of 70 nodes, we represent all the edges by an ID obtained by its position in the column major order of edges. Thus there are 4900 edges. Our analysis of edge betweenness centrality across different sexes indicates that there exists one edge (namely edge ID 841) which is discriminative across sexes. Fig.6 shows the mean edge betweenness centrality of each edge (for Sex 0 and Sex 1) where several edges stand out (note that we show only a small range instead of all 4900).

5.4 Analysis of the Participation Coefficient

The participation coefficient is a measure based on modularity. It represents the diversity of inter-modular connections of a given node. Intuitively the participation coefficient of a node is close to one if it's links are uniformly distributed across all modules and 0 if all its links are within its own module. A node with a high participation coefficient thus represents a connector hub in the brain.

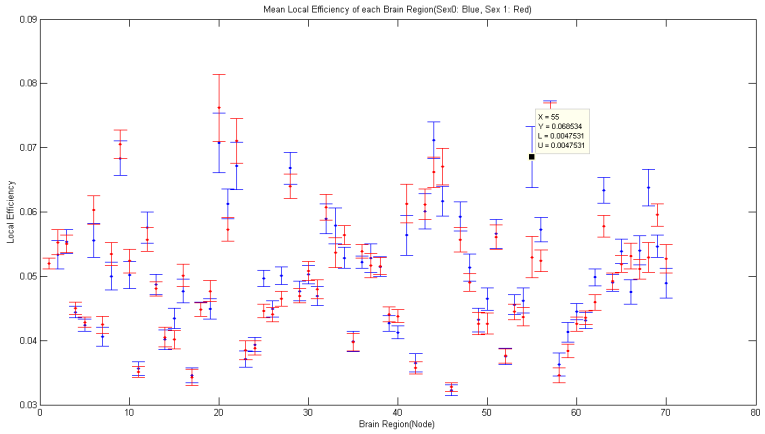

Fig. 5. Mean local efficiency, for Sex 0 (blue, female) and Sex 1 (red, male)

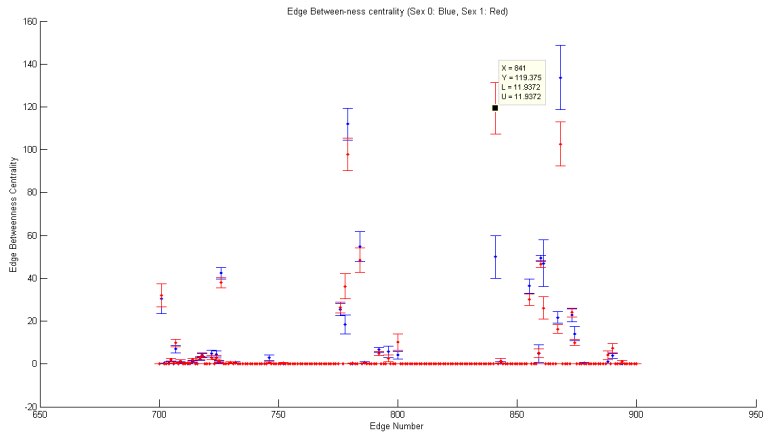

Fig. 6. Mean edge betweenness centrality for the network edges across genders.)

We investigated whether Node 55, which has been found to be discriminative, was a hub. We note that although there is a difference in the participation coefficient in Node 55 among the sexes, we see that there are other nodes having higher participation coefficients (see Fig.7). This indicates that Node 55 is unlikely to be a connector hub, in fact as we showed earlier Node 55 is locally well clustered. Therefore, while the clustering coefficient of Node 55 is higher in Sex 0 than in Sex 1, the participation coefficient is lower in Sex 0 than in Sex 1. This seems to indicate that the brain region corresponding to Node 55 connects closely with its neighbors (is densely clustered) with its own module mostly in one of the sexes (namely Sex 0).

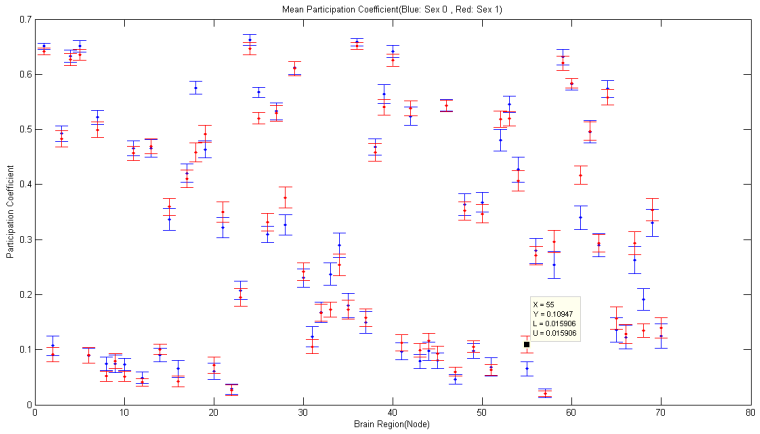

Fig. 7. Mean participation coefficient of each region across genders.)

5.5 Learning Classification Models

We used the evidential covariates obtained from our analyses of network measures and trained classifiers based on them; a decision tree classifier which helps us interpret the discriminative power of the measures, and a support vector machine classifier with a linear kernel. We estimated the accuracy of our models using a 10-fold cross-validation. We describe both of our models below separately.

Decision Tree Model We decided to investigate the best split obtained when using clustering coefficient of Node 55 alone as a feature. Based on the analysis of clustering coefficient, we would expect the decision tree to use a point at around 0.06. To avoid overfitting, we ensured the decision tree will always have a minimum of 10 elements in the leaf nodes. The decision tree as shown in Fig. 8 indeed reported the best split at around 0.0619.

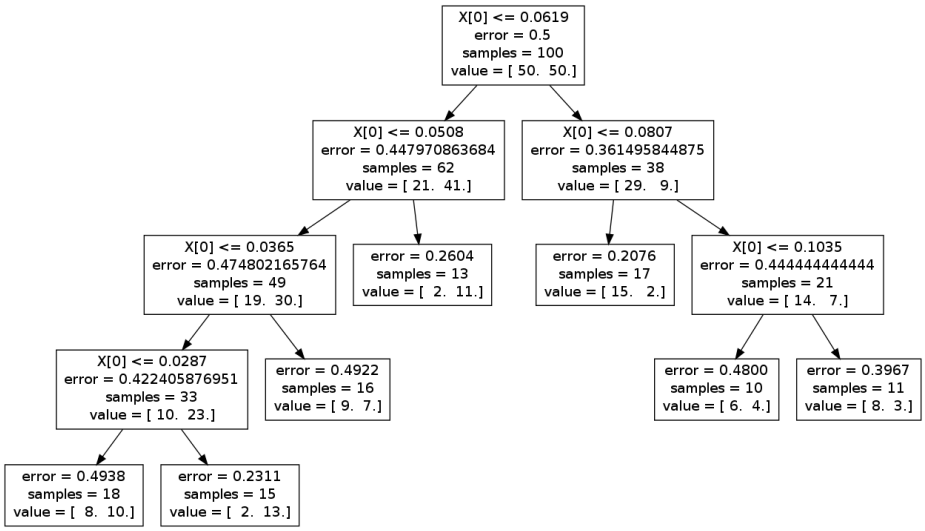

Fig. 8. Decision Tree based on Node 55's clustering coefficient alone.)

We tried various combinations of features to assess the best set of features which results in high classification accuracy. We outline them as the following.

Network Measure	Best Feature Set	Accuracy
Clustering Coefficient	Nodes {25, 55, 68}	0.68(±0.04)
Edge Between-ness Centrality	Edge 841	0.68(±0.06)
Participation Coefficient	Nodes {18, 61}	0.68(±0.10)

We note that with only a few number of features, which we identified from our statistical analyses given in the previous sections, we were able to achieve a classification accuracy of 0.68%.

Support Vector Machines Model We further studied how a support vector machine (with a linear kernel) performs on our classification task using our evidential features. We outline our results below.

Network Measure	Best Feature Set	Accuracy
Clustering Coefficient	Nodes {20, 55}	0.68(±0.05)
Edge Between-ness Centrality	Edge 841	0.58(±0.05)
Participation Coefficient	Nodes {18, 61, 68}	0.73(±0.05)

We note that both classifiers report comparable accuracies with our evidential network-centric features. It would be useful to evaluate the classifier on a larger data set to get better error margins on accuracy.

All in all, with only a handful of network measures we were able to achieve up to 0.73% accuracy, as well as were able to explain and interpret the discriminative features in classifying human subjects into genders based solely on their connectomes.

6 Conclusion

In this work, we studied the connectivity of the brain structure in human subjects, for the specific task of identifying regions that are significantly discriminative in gender classification. Our main contributions can be listed as follows.

- We have shown that there exists differences in network-centric measures in human connectomes across genders, such as clustering coefficients, edge betweenness centralities, and participation coefficients.
- We have shown that these differences can be exploited to learn classification models that perform considerably well where a few, handful of features is sufficient to boost the accuracy.

It remains as future work to study other network measures of the connectomes to identify other evidential features, and learn new models trained with higher number of features for our classification task. We note that while high performance in this task is desired, the understanding of the findings is also very crucial. For this reason, we used only those features that we were able to show statistical difference across genders for our learning task, rather than throwing in all the possible measures we obtained. We believe that this makes our study interpretable and opens new directions for further analyses.

***** Joshua please consider heavy rewriting here to make it stronger *****

Appendix

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References

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