Sex Differences in the Human Connectome

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Abstract. The human brain and the neuronal networks comprising it are of immense interest to the scientific community. In this work, we focus on the structural connectivity of human brains, investigating sex differences across male and female connectomes (brain-graphs) for the knowledge discovery problem "*Which brain regions exert differences in connectivity across the two sexes?*". One of our main findings discloses the statistical difference at the pars orbitalis of the connectome between sexes, which has been shown to function in language production. Moreover, we use these discriminative regions for the related learning problem "*Can we classify a given human connectome to belong to one of the sexes just by analyzing its connectivity structure?*" . We show that we can learn decision tree as well as support vector machine classification models for this task. We show that our models achieve up to 79% prediction accuracy with only a handful of brain regions as discriminating factors. Importantly, our results are consistent across two data sets, collected at two different centers, with two different scanning sequences, and two different age groups (children and elderly). This is highly suggestive that we have discovered scientifically meaningful sex differences.

Keywords: human connectome, network science, network connectivity, graph measures, sex classification, pars orbitalis

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 how the brain functions, how vision is interpreted, how consciousness arises etc., all of which neuroscience deals with. 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 is that the brain can be thought to be composed of several simple elements that give rise to its complex patterns [19]. 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 immensely contributed to this phenomena [3,11,13].

One of the overarching ideas in today's 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. Several projects have recently been launched targeted at understanding human brain connectomes, including the Human Brain Project [1], the Human Connectome Project [2], the Brain Genome Superstruct Project [4], and the International Neuroimaging Data-Sharing Initiative [14].

It is to be noted that analyzing the human connectome is far more challenging in terms of scale (it has more than a billion times more connections than the letters in a genome) [5]. While the various human connectome projects are still ongoing, exciting initial results have been obtained by analyzing connectomes. Some important results include the small world property of brain networks [20], and the presence of a rich club of hubs [21]. Noting the larger goal outlined above, one of the research problems that seeks investigation is that of sex 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 the following:

1. *Knowledge discovery in connectomes across sexes:* What differences in the brain network (connectome structure) do the two sexes exhibit? What regions in the brain show discriminative characteristics?
2. *Learning to predict sex by the human connectome:* Would the connectivity structure of the brain admit classification of connectomes into sexes based solely on their connectivity characteristics?

Our study involves two independent groups of human subjects, both containing about 100 subjects, with about half male, half female. We found that there exist several regions in the brain that show statistically significant differences in their connectivity characteristics across the sexes. Among these regions, the *pars orbitalis* in the inferior frontal lobe of the brain stands out in particular. Learning classification models using only a handful of these several discriminative regions and their network properties, we achieve up to 79% prediction accuracy in classifying the human subjects into sexes 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.

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

2 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 [22]. 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 graph invariants (either global or local) and use standard machine learning techniques for classification. Duarte-Carvajalino et. al [6] analyzed connectome structure to help identify sex and kinship differences. They outlined structural differences in brain networks in terms of network invariants like communicability and edge betweenness centrality. This was done at a *global* (topological) scale with a set of 303 individuals.

Although the above two approaches are the only ones we are aware of that build classifiers to distinguish whether individuals differ across sex, a number of other studies conduct group-wise statistical analyses of MR-derived connectomes across sexes, using structural [12] and/or diffusion [9,15,7] data.

In this work, we investigate the 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 invariants can be used to classify connectomes with respect to sex.

3 Dataset Description

Our study involves two independent group of human subjects. More specifically, the first data set consists of connectome data for 114 individuals (50 females and 64 males, mean age: around 22 years). The second dataset consists of 79 connectomes (35 females and 44 males, mean age: around 78 years). Note that there are no cognitive impairments of subjects in our data sets. All connectomes were estimated using MRCAP [8]. Briefly, diffusion Magnetic Resonance data is collected for each subject. The pipeline automatically estimates tensors, performs deterministic tractography [16], and parcellation into the Desikan atlas [5] yielding a total of 70 nodes per graph. The undirected edge weight is the number of fibers that pass through any pair of nodes.

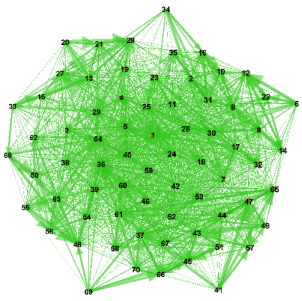

Fig. 1. Sample brain network of 70 regions.

Each sample or connectome in our datasets is assigned a class label (0 for males, 1 for females) thus identifying the sex of person with said connectome. 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). We normalize all edge weights per individual to lie between 0 and 1 to mitigate batches effects across individuals and scanning details [10]. Note that most previous investigations of MRI data restrict analysis to only a single dataset, and therefore do not face batch effects. Importantly, however, batch effects are notoriously larger than within sample variability, obfuscating the discovery of scientifically meaningful differences between populations.

The authors in [6] 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 properties).

We derived a new normalization scheme, extending their *Row Mean Normalization* scheme. 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. 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 Graph Invariants

Next we study the graph-centric properties of the human connectomes. In particular, we computed the following graph invariants[6] (also called "network measures") as described in [17], which we briefly summarize below:[7]

1. *Locally weighted clustering coefficient* is a measure of segregation and indicates the presence of clusters, as defined by the fraction of triangles around a given node. This has been generalized to weighted networks as well and represents the average intensity of triangles around a node.
2. *Weighted edge connectivity* represents the weight of the edge between pairs of nodes.

[6] We exploited the Brain Connectivity Toolbox to compute our graph invariants: `https://sites.google.com/site/bctnet/`

[7] The comprehensive list is available here: https://sites.google.com/site/bctnet/measures/list

3. *Edge betweenness centrality* is the fraction of all shortest paths in the network that contain a given edge. Edges with high values of betweenness centrality participate in a large number of shortest paths
4. *Node participation coefficient* is a measure of diversity of inter-modular connections of individual nodes.

For all the invariants, we compute the mean across all subjects of a class (i.e. males and females) and analyze the data for differences in the mean invariants across the two classes. We then proceed to analyze which differences are statistically significant. To determine whether a difference is statistically significant, we use a bootstrapping approach. This approach is suited very well for our work as we have a small sample size, and bootstrapping allows us to test our hypotheses by creating a large enough sample through repeated sampling. Moreover, it has the added advantage that no assumption on the sample distribution is made, other than independence between samples.

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:

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

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

5 Empirical Results

In this section, we first present statistical analysis of graph invariants across the sexes, and later proceed with our results on sex classification using the potentially discriminative invariants discovered through our analysis. We will show our analysis results mostly on our first dataset with 114 subjects (similar results hold for the second dataset).

5.1 Analysis of Graph Invariants

Analysis of the Mean Clustering Coefficient We analyzed the mean clustering coefficient of each node and present our findings (across the two sexes) in Fig. 2.

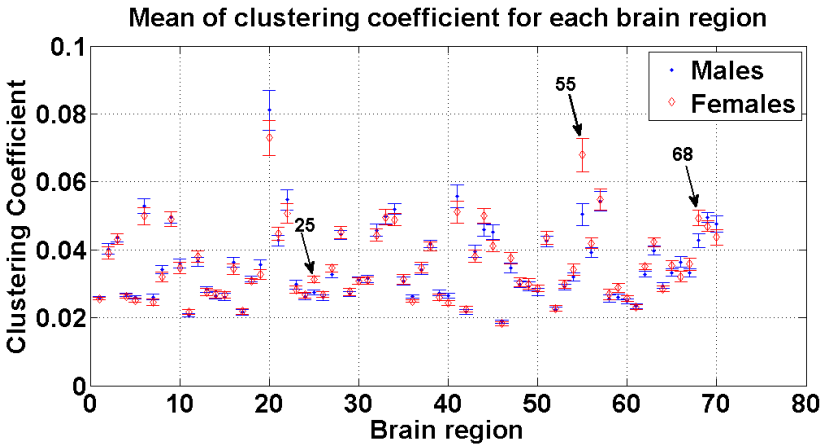

Fig. 2. Mean local clustering coefficient, for female (red) and male (blue).

We note that the mean clustering coefficient of Node 55 in females is higher than that of males. In order to rule out the effects of outliers (as the mean is influenced by outliers) we also looked at the median. We again noted that Node 55's clustering coefficient is higher in females than in males, bolstering our hypothesis that this difference could be discriminative.

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. 3. We observe that node 20 has high MCC in both sexes, while Node 55's MCC is visibly (and as we show later also significantly) higher for females. We find that Node 55 is the *pars orbitalis*, in the inferior frontal lobe of the brain[8]. Interestingly, Node 20 is its complementary matching region in the other hemisphere of the brain. It is known that pars orbitalis is involved in language production and participates in prefrontal associational integration (and probably hence the largest clustering coefficient).

The observed sample difference between Node 55's mean clustering coefficient across the sexes in our first dataset is noted as *0.0175*. To establish statistical significance of this difference, we used the bootstrapping procedure with a significance level of $\alpha = 0.05$ and $B = 3000$. We obtained a p-value of 0.0025 which is significant at 0.05 level (see 5.1 for more details).

The sample difference between Node 55's mean clustering coefficient in our second dataset is smaller, and is noted as 0.006023. The p-value obtained by running boot strapping for $B = 3000$ iterations is about $p \approx 0.1085$, which is

[8] `http://en.wikipedia.org/wiki/Orbital_part_of_inferior_frontal_gyrus`

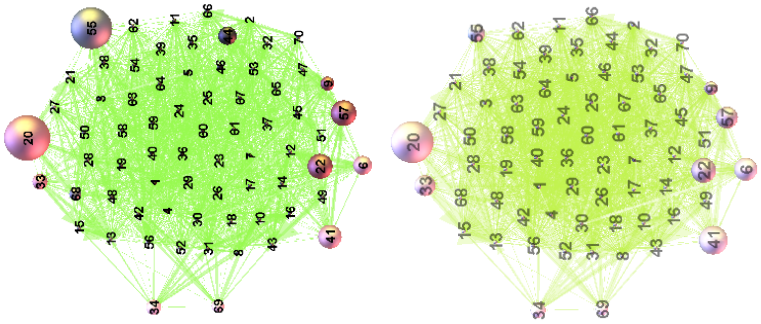

Fig. 3. Visualization of nodes (brain regions) ranked by Mean Clustering Coefficient (MCC) (the larger node size depicts larger MCC), (left) female, and (right) male.

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 are youths in their 20's, whereas 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 [18], while it remains for future work to investigate these effects.

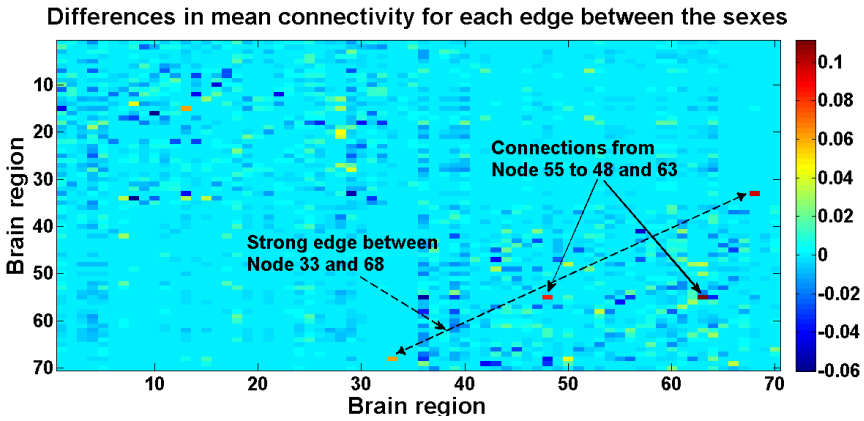

Fig. 4. Mean edge connectivity differences between female and male.

Analysis of the Mean Edge Connectivity We computed 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.4 shows the differences in the mean edge weights for each edge between female and male.

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

Analysis of the Edge Betweenness Centrality In the normalized 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 $70^2 = 4900$ edges (because edges are directed and there are no self-loops). 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.5 shows the mean edge betweenness centrality of each edge (for female and male) where certain edges stand out (note that we show only a small range instead of all 4900).

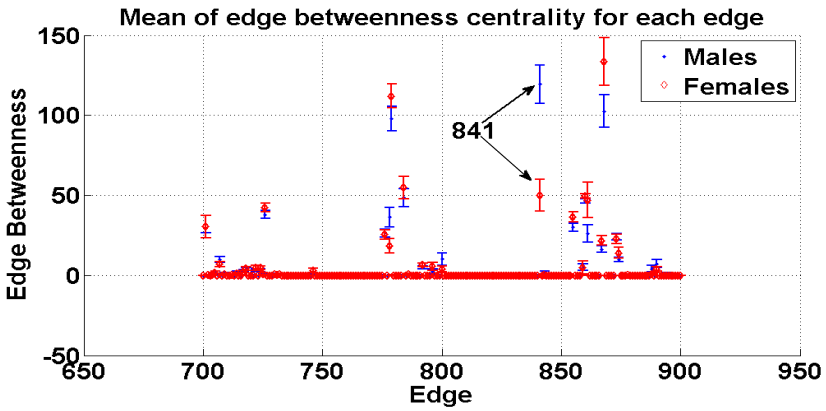

Fig. 5. Mean edge betweenness centrality for the network edges across sexes.

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 1 if its 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.

We investigated whether Node 55, which has been identified to be discriminative, is a hub. We note that although there is a difference in the participation coefficient in Node 55 among the sexes, we observe that there are other nodes having higher participation coefficients (see Fig.6). This indicates that Node 55 is unlikely to be a connector hub. In fact as we showed earlier Node 55 is locally well clustered (recall its high MCC). Therefore, while the clustering coefficient of Node 55 is higher in females than in males, the participation coefficient is lower in females than in males. This seems to indicate that the brain region corresponding to Node 55 connects closely with its neighbors (is densely clustered) within its own module mostly in one of the sexes (namely female).

Statistical Significance of Differences in Graph Invariants Finally, in order to establish the statistical significance of differences for all potential invariants we observed in this section, we employed the bootstrapping procedure with a significance level of $\alpha = 0.05$ and $B = 3000$. We show all the p-values

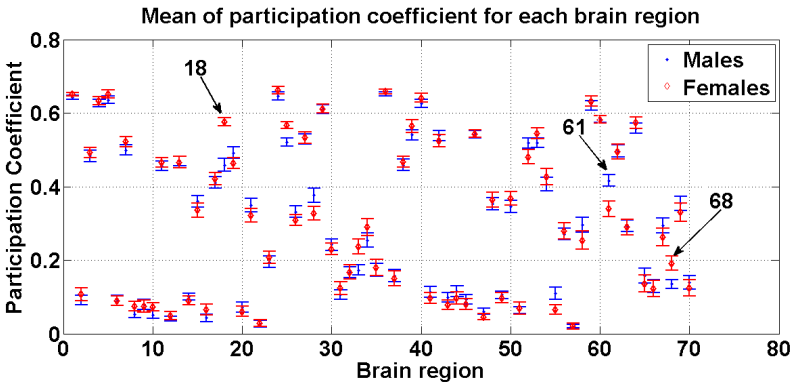

Fig. 6. Mean participation coefficient of each region across sexes.

obtained on our first data set in Table 3. We note that several of the differences are statistically significant at the 0.05 level (uncorrected for multiple hypothesis tests). It is left as future work to understand the clinical significance of these differences from a neuroscientific point of view.

Table 1. p-values obtained via boot-strapping

Network Measure	p-value
Clustering Coefficient Node 25	*0.00145*
Clustering Coefficient Node 55	*0.0025*
Clustering Coefficient Node 68	0.0287
Edge Between-ness Centrality Edge 841	< 0.001
Participation Coefficient Node 18	< 0.001
Participation Coefficient Node 61	*0.005*
Participation Coefficient Node 68	0.0146
Edge Weight between 33-68	< 0.001
Edge Weight between 68-33	*0.0912*

5.2 Learning Classification Models

Next we use the evidential graph invariants obtained from our analyses of network measures in the previous section and train classifiers using these invariants as features. In particular, we train a decision tree (DT) classifier, and a support vector machine (SVM) classifier with a non-linear radial basis kernel. We estimate the accuracy of our models using a Leave One Out Cross Validation (LOOCV) on both of our data sets.

For training our classifiers, we use specific features belonging to the same network measure as well as the combined set of features (see Table 2). Note that with only a few number of features, which we identified and selected through

our statistical analyses, we are able to achieve a classification accuracy of 79% on dataset 1 and 73% on dataset 2, using all the selected features.

Table 2. Accuracy of decision tree (DT) and support vector machine (SVM) classifiers on dataset 1 (DT1 and SVM1) and dataset 2 (DT2 and SVM2).

Network Measure	Feature Set	DT1	SVM1	DT2	SVM2
Clustering Coefficient	(Fig. 2) Nodes {25, 55, 68}	0.71	0.69	0.67	0.63
Edge Connectivity	(Fig. 4) Between Nodes 33–68	0.69	0.65	0.65	0.60
Edge Betweenness	(Fig. 5) Edge 841	0.67	0.69	0.73	0.73
Participation Coefficient	(Fig. 6) Nodes {18, 61, 68}	0.70	0.70	0.65	0.55
ALL	Combined feature set	0.73	0.79	0.73	0.64

We also evaluate the significance of the classification scores obtained. We use the standard technique of permutation tests, which permutes the class labels and repeats the classification procedure and computes the p-value thus indicating the significance of the classification accuracies. The p-values obtained by running the permutation test with 1000 permutations on data set 1 is shown in Table 3. We note that most of the classification scores are statistically significant at the 0.05 level (uncorrected for multiple hypothesis testing) which indicates that the classifiers indeed have discriminative power.

Table 3. p-values of classification accuracies for data set 1.

Network Measure	Feature Set	DT	SVM
Clustering Coefficient	(Fig. 2) Nodes {25, 55, 68}	0.002	0.004
Edge Connectivity	(Fig. 4) Between Nodes 33–68	0.008	0.011
Edge Betweenness Centrality	(Fig. 5) Edge 841	0.005	0.001
Participation Coefficient	(Fig. 6) Nodes {18, 61, 68}	0.006	0.001
ALL	Combined feature set	0.007	0.001

All in all, with only a handful of network measures we identified through our statistical observations and analyses, we were able to achieve up to 79% accuracy in sex classification. Moreover, we were able to explain and interpret the discriminative features in classifying human subjects into sexes based solely on their connectome structures.

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 sex classification. Our main contributions can be listed as follows.

- We have shown that there exists differences in network-centric measures in human connectomes across sexes, 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.

Importantly, we were able to show that these results persisted across two different data sets, collected at different institutions, using different scan parameters, and on populations with different ages. This is highly suggestive that our findings are not artifactual, rather, they represent legitimate scientific discoveries in human connectome analyses.

One of our main findings has been the statistical difference at the pars orbitalis of the connectome between the two sexes, which resides in the inferior frontal lobe of the brain and has been shown to function in language production.

Our study is a proof of principle that the connectome has some information about the brain. It remains as future work to use our techniques, as well as study other network measures of the connectome to identify additional evidential features, to learn new models for more (clinically) interesting covariates, such as classifying certain diseases like Alzheimer's.

We note that while high performance in such classification tasks is desired, the understanding of the findings is also crucial. For this reason, we used only those features that we were able to show statistical difference across sexes 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 (for instance, we believe it might be particularly interesting to study how the differences in these measures evolve with time by age).

Finally, we provide all of our data and code (specifically code for analytics, graph invariant mining, and classifiers)[9] for scientific reproducibility as well as for promoting further studies on related research topics.

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References

1. Human Brain Project - Home. *http://www.humanbrainproject.eu/.*
2. Human Connectome Project - Home. *http://www.humanconnectomeproject.org/.*
3. A. L. Barabási. *Linked: the new science of networks.* Perseus Pub., 2002.
4. R. L. Buckner. The Brain Genomics Superstruct Project. *http://sfari.org/funding/grants/abstracts/the-brain-genomics-superstruct-project.*

[9] All our code and both of our datasets are available at `https://bitbucket.org/jagatsastry/brain-analysis-for-gender-classification`

5. R. S. Desikan, F. Se, B. Fischl, B. T. Quinn, B. C. Dickerson, D. Blacker, R. L. Buckner, A. M. Dale, R. P. Maguire, B. T. Hyman, M. S. Albert, R. J. Killiany, and F. Ségonne. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31(3):968–980, July 2006.
6. J. M. Duarte-Carvajalino, N. Jahanshad, C. Lenglet, K. McMahon, G. I. de Zubicaray, N. G. Martin, M. J. Wright, P. M. Thompson, and G. Sapiro. Hierarchical topological network analysis of anatomical human brain connectivity and differences related to sex and kinship. *NeuroImage*, 59(4):3784–3804, 2012.
7. G. Gong, Y. He, and A. C. Evans. Brain Connectivity: Gender Makes a Difference. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, (April), Apr. 2011.
8. W. R. Gray, J. A. Bogovic, J. T. Vogelstein, B. A. Landman, J. L. Prince, and R. J. Vogelstein. Magnetic resonance connectome automated pipeline: an overview. *IEEE pulse*, 3(2):42–8, Mar. 2010.
9. R. J. Haier, R. E. Jung, R. a. Yeo, K. Head, and M. T. Alkire. The neuroanatomy of general intelligence: sex matters. *NeuroImage*, 25(1):320–327, Mar. 2005.
10. J. T. Leek, R. B. Scharpf, H. C. Bravo, D. Simcha, B. Langmead, W. E. Johnson, D. Geman, K. Baggerly, and R. A. Irizarry. Tackling the widespread and critical impact of batch effects in high-throughput data. *Nature reviews. Genetics*, 11(10):733–9, Oct. 2010.
11. J. Leskovec, J. Kleinberg, and C. Faloutsos. Graphs over time: densification laws, shrinking diameters and possible explanations. In *ACM SIGKDD*, 2005.
12. B. Lv, J. Li, H. He, M. Li, M. Zhao, L. Ai, F. Yan, J. Xian, and Z. Wang. Gender consistency and difference in healthy adults revealed by cortical thickness. *NeuroImage*, May 2010.
13. M. McGlohon, L. Akoglu, and C. Faloutsos. Weighted graphs and disconnected components: patterns and a generator. In *ACM SIGKDD*, 2008.
14. M. Mennes, B. B. Biswal, X. F. Castellanos, and M. P. Milham. Making data sharing work: The FCP/INDI experience. *NeuroImage*, null(null), Oct. 2012.
15. K. Menzler, M. Belke, E. Wehrmann, K. Krakow, U. Lengler, A. Jansen, H. M. Hamer, W. H. Oertel, F. Rosenow, and S. Knake. Men and women are different: Diffusion Tensor Imaging reveals sexual dimorphism in the microstructure of the thalamus, corpus callosum and cingulum. *NeuroImage*, Nov. 2010.
16. S. Mori and P. C. M. van Zijl. Fiber tracking: principles and strategies - a technical review. *NMR in biomedicine*, 15(7-8):468–480, 2002.
17. M. Rubinov and O. Sporns. Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, 52(3), 2010.
18. J. Song, A. S. Desphande, T. B. Meier, D. L. Tudorascu, S. Vergun, V. A. Nair, B. B. Biswal, M. E. Meyerand, R. M. Birn, P. Bellec, and V. Prabhakaran. Age-Related Differences in Test-Retest Reliability in Resting-State Brain Functional Connectivity. *PLoS ONE*, 7(12):e49847, Dec. 2012.
19. O. Sporns. *Networks of the Brain*. The MIT Press, 2010.
20. O. Sporns and J. D. Zwi. The small world of the cerebral cortex. *Neuroinformatics*, 2(2):145–162, Jan. 2004.
21. M. P. van den Heuvel and O. Sporns. Rich-club organization of the human connectome. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 31(44):15775–86, Nov. 2011.
22. J. T. Vogelstein, W. R. Gray, R. J. Vogelstein, and C. E. Priebe. Graph classification using signal subgraphs: Applications in statistical connectomics. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 99(PrePrints):1, 2012.