Sex classification from resting state fMRI temporal complexity

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Abstract

Though the notion of sex-dimorphism in the brain has been largely discounted, the advent of large datasets like the Human Connectome Project has made it possible to build highly-accurate sex classification models with resting state fMRI data. To date, a host of signal features have been employed to build these models, and this study aims to determine the maximum performance of a model built on temporal complexity features, namely: sample entropy and frequency of low amplitude frequency fluctuations (fALFF). This study uses sample entropy (calculated at two different subseries lengths m=2 and m=5) and fALFF as input features to three different classification models (neural network with two hidden layers, support vector machine with a third-degree polynomial kernel, and logistic regression). Models were trained on a large set of resting data from the Human Connectome Project (n=392: 138 males, 254 females) and tested on 88 subjects (32 males, 56 females). Classification accuracies for all input features and models ranged from 67% to 84%, with the highest performing model and feature type combination being neural network and fALFF. Regional sex differences were also explored using average sex difference in temporal complexity measures, revealing regional patterns of sex-difference. While this study does indicate a link between regional temporal complexity and sex, the results do not imply a clear sex-dimorphism. Future work includes comparing the regional characteristic of the sex-difference identified in this paper with existing understandings of structural and functional sex differences.

Introduction

Sex difference in the brain

Biological sex can be described at the chromosomal, hormonal, and gonadal level, with the common understanding that chromosomes, specifically the presence or absence of the Y chromosome, influence the embryonic hormonal environment. The presence or absence of testosterone controls the fate of the Mullerian and Wolffian ducts, development of gonads, and—later in adolescence—development of secondary sex characteristics, which some attribute to sex-related difference in the brain (Rosenfeld 2017).

However, there are many environmental and genetic factors that complicate this "normal" or most common developmental pathway. For instance, a mutation in the androgen receptor gene can cause a condition called Androgen Insensitivity Syndrome (AIS), in which individuals with Y chromosomes are incapable of recognizing testosterone, leading them to develop external female genitalia and exhibit secondary sex characteristics of a female (Gottlieb, Trifero 2017). Additionally, the uterine hormonal environment of the mother is known to influence secondary sex characteristics of the offspring (Berenbaum et al., 2017).

Gender, on the other hand, is a social phenomenon and encompasses the behavior, expectations, and hierarchy structures of genders in a given culture (Maney 2016). Sex is widely regarded to be a binary, even with the existence of atypical sex chromosomes like in Turner's and Klinefelter Syndrome (Pienkowski et al. 2011), and gender is often thought of in the same way despite the existence of cultures with non-binary gender systems like those in Indigenous Pacific and Native American cultures (Ghoshal 2020). Though the concepts of sex and gender are often conflated, they are distinct and scientific examination of

differences between males and females should use the language of sex (Maney 2016).

Though sex chromosomes, and in turn, sex hormones, are known to influence brain organization to some degree, it is difficult to conclude that the male and female brains are distinct organs: that the brain is a sex-dimorphic organ in the same way that the external genitalia are. Early research into sex-differences in the brain have long focused on finding evidence of sex-dimorphism in the brain, mainly focusing on structural analyses of differences in the size of certain brain regions (Joel et al., 2016). Looking for evidence of dimorphism led to a suspected publishing bias in which the majority of published studies on sex difference in the brain report differences, sometimes with faulty methodology (Joel et al., 2016).

With little evidence of sex-dimorphism in the brain, a "mosaic model" of structural differences between male and female brains was proposed. The model notes that although male and female brains differ on average in a handful of regions, there are very few individuals who lie on the male or female end of the spectrum for every brain region in which a sex difference has been identified. Instead, the majority of people have a combination of male- and female- characteristic brain regions and brains are not easily separated (Joel et al. 2016).

Resting fMRI

In contrast with structural MRI, functional MRI (fMRI) takes subsequent blood-oxygen-level-dependent images of the brain. These images are generated at sampling frequencies of around 1 Hz, and although this is too low to detect instantaneous brain activity, the modality can still extract information from the hemodynamic response following neural activation. fMRI scans are conducted over a long period of time, with subjects either performing tasks or tests while in the scanner (task fMRI) or lying totally still (resting state fMRI).

Sex classification models

Recently, assisted by the advent of large neuroimaging datasets like the Human Connectome Project (HCP), multivariate classification models have sought to better separate sexes using a variety of classification algorithms and techniques. Models have been constructed with a variety of features from the resting state fMRI signal like parcel-wise connectivity (Weis et al. 2019), temporal characteristics of dynamic functional connectivity states (Fan et al. 2020), and the Hurst Exponent (Dhamala et al. 2020). These models are often complex and nonlinear and are difficult to extract meaningful neurological information from. A well-performing sex classification model is only able to identify a correlation between the features utilized and sex.

The dataset used in Weis et. al 2019, Fan et al. 2020, Dhamala et. al 2020 and other sex classification papers is the Young Human Connectome Project. This dataset collects functional and structural MRI data, cognitive testing scores, and other demographic data from a cohort of participants; a major aim of this dataset was to employ consistent imaging parameters, 3 and 7T MR images collected on the same machines, in order to improve the power of studies using the data by eliminating variation.

When it comes to sex, the Human Connectome Project collected information in survey form under a category labelled “gender.” As mentioned previously, the norm for neurological research is to write in terms of sex, which is why this paper and others does so. Since the responses to the gender item on the survey were either “male” or “female,” the dataset is binarized with respect to sex, making it simpler to employ classification algorithms. The size of the dataset, low variation in data collection parameters, and simple binarization of sex all make it simpler to employ classification algorithms to determine sex based on resting state fMRI signal features, which is

responsible for the proliferation of sex classification papers in this field.

Features in this study

This study aims to identify a link between temporal complexity and sex. Two features of interest include sample entropy—a calculation of temporal complexity which is based on the number of repeating patterns in a signal—and fractional amplitude of low frequency fluctuations (fALFF)— another measure of temporal complexity that focuses on low frequency components. A previous study determined that regional sample entropy distribution is highly related to individual differences, indicating it may be a good input feature for sex classification purposes (Zhang et al. 2021). fALFF has exhibited sex differences in some studies involving shyness (Yang et al., 2017) and conduct disorder, or CD (Cao et al., 2018).

Methods

Subject selection

We used the S500 release of the Human Connectome Project for this data, excluding subjects with missing files and those above a head movement threshold (Finn et al., 2015), resulting in a large data set (n=410; 170 males, 240 females).

Parcellation scheme, preprocessing, and feature extraction

The data was preprocessed using the FIX-denoising pipeline, which remove physiological and instrumental noise using a model trained on expert analyses of fMRI artifacts (Burgess et al. 2016); this pipeline was utilized as it does well to preserve sample entropy and high frequency characteristics compared to a custom-developed pipeline. A 90

region of interest (ROI) functional atlas developed by the Find Lab was employed for this study since it focuses on cortical regions where there is more likely to be variation in complexity.

The average of the preprocessed signal was averaged across each ROI, resulting in 90 regional signals for each subject. From the averaged regional signals, sample entropy was calculated using two different subseries lengths (m=2 and m=5), and fALFF was extracted at well. Three data types (sample entropy collected at two different subseries lengths and fALFF) were used as input features to multivariate models.

Modeling

The data set was randomly split into training and testing sets, 80% and 20% of whole dataset respectively, ten times. Since the data had more females than males, male instances were randomly oversampled to generate training and testing sets with equal numbers of males and females. Three models (neural network with two hidden layers, support vector machine with a third-degree polynomial kernel, and logistic regression) were trained on each of the three data types' training sets and tested on the corresponding test sets. Reported classification accuracies for each combination of model and data type are the averages of the ten random training and testing splits (10-fold cross-validation). Also reported were the area under curve (AUC) scores for each model and data type combination.

Visual representations of regional sex difference

In addition to model-building, visualizations of sex-difference in temporal complexity in the brain were generated by calculating the t-score of the differences in sample entropy in fALFF between males and females for each region of interest and across the whole 410-subject dataset.

Results

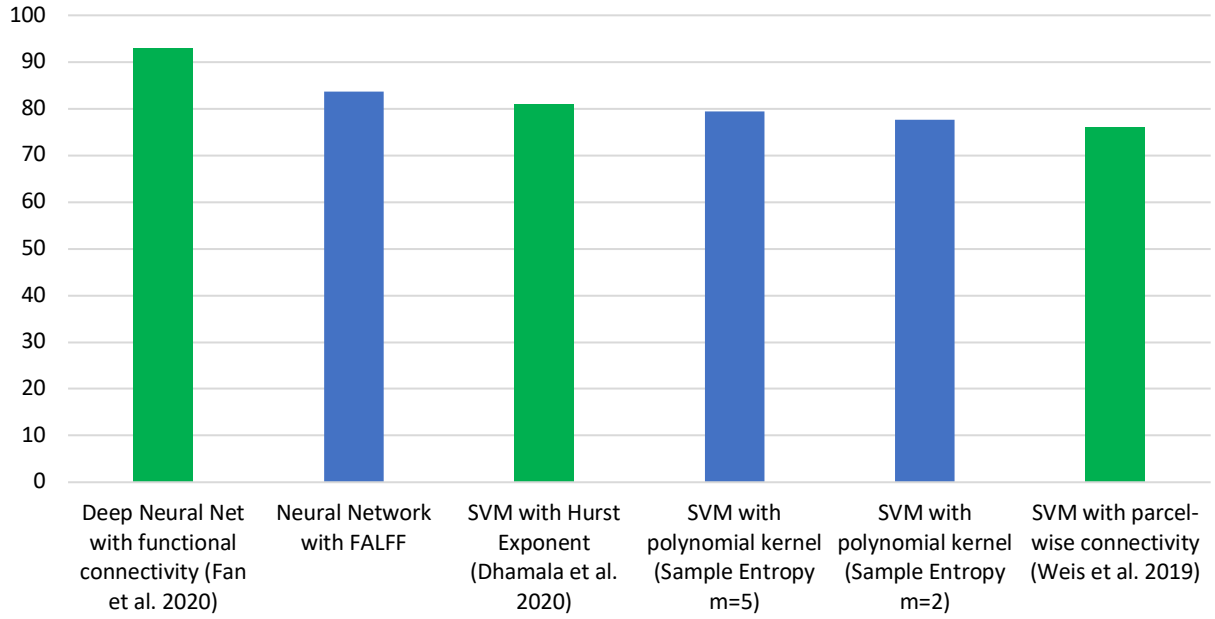

Figure 1: *Best classification accuracy from this study for each data type (blue) and classification accuracies from other studies (green) with their respective input features and model types listed.*

Classification accuracies ranged from 67% to 84% for each model and data type combination, which compares well with the model performance of previously published papers (Figure 1). The accuracies of other model and data type combinations are recorded in Table 1. The fact that the models were able to achieve some sort of success in separating males and females based on temporal

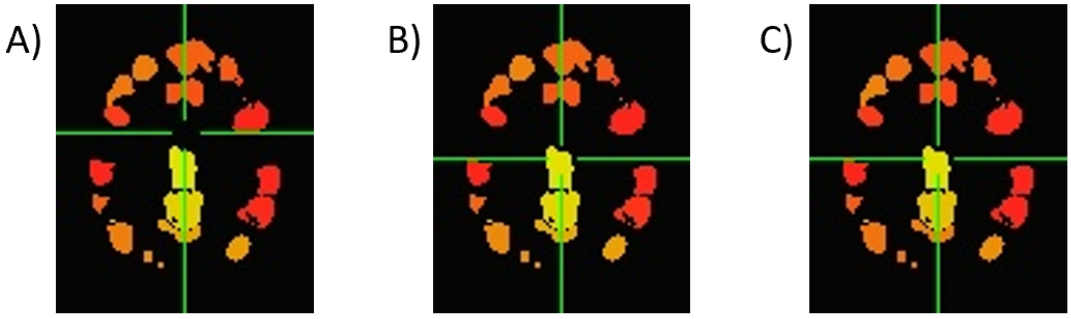

Figure 2: *One transverse slice of the Find atlas map with a color scale representing t-scores for sex difference in sample entropy, m=2 (A); sample entropy, m=5 (B); and fALFF (C). Areas in red exhibit higher absolute difference between sexes.*

complexity features indicates a link between this signal feature and sex, but any further conclusions would require different investigation into how these features differ between sexes.

parcellation schemes using atlases from the original analyses.

A heat map of the actual difference in features reveals that sample entropy is generally higher across every region of interest in males, while the opposite is true for fALFF with the same regional distribution (Figure 3).

Data	Model Type	Classification Accuracy	AUC Score
Sample Entropy(m=2)			
	Logistic Regression	0.7500	0.8647
	Support Vector Machine	0.7727	0.8714
	Neural Network	0.6723	0.7091
Sample Entropy(m=5)			
	Logistic Regression	0.7826	0.8280
	Support Vector Machine	0.7935	0.8256
	Neural Network	0.7508	0.7847
FALFF			
	Logistic Regression	0.7188	0.8941
	Support Vector Machine	0.7500	0.8869
	Neural Network	0.8374	0.8654

Table 1: *Classification accuracies and AUC scores for the generated sex classification models.*

Visualization of absolute sex difference in sample entropy and fALFF revealed that there is considerable overlap between the regional sex-difference distribution for each of these three data types (Figure 2). This common regional distribution needs to be further investigated and compared to existing literature concerning regional distribution of sex-differences in functional and structural analyses, which will require additional brain

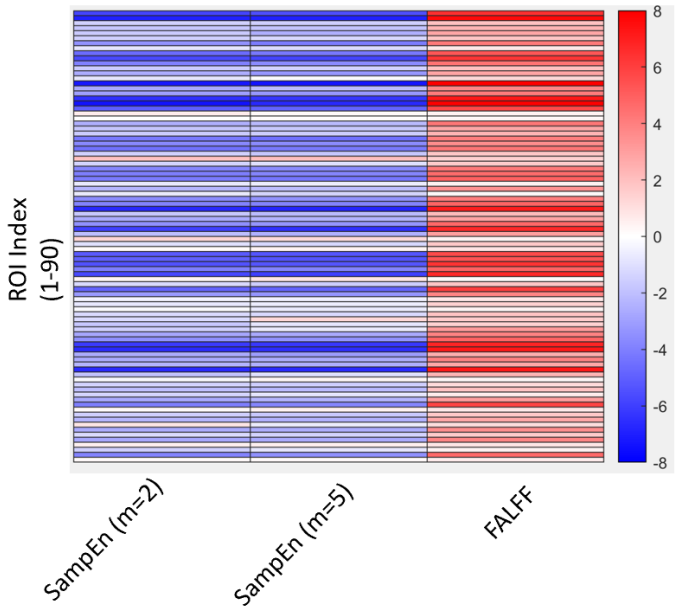

Figure 3: *Sex difference across regions of interest for two calculations of sample entropy (SampEn) and FALFF, with red representing the male end of the difference spectrum and blue representing the female end.*

Conclusion

In this study, we were able to identify a link between sex and temporal complexity by creating accurate sex classification models based on temporal complexity features. The model performance is in line with reported classification accuracies from previous sex classification papers using the same data set. Further comparison of this study with established literature on sex classification models would require a recreation of the subject selection and brain parcellation schemes employed in those studies. At this point, sex classification studies can only establish a link between sex and the input feature used to train models. Investigating the relative strength of relationships to different input features would involve comparing studies that control for preprocessing pipelines, subject pool, and model deployment. Future directions include comparing the regional distribution of sample entropy difference differences to understanding of structural and functional sex-differences in the brain to better contextualize

these findings and exploring parcellation

schemes used in other sex-classification papers.

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