Methylation of inflammatory and stress related genes associated with maternal depression and premature birth

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Motivation & Introduction

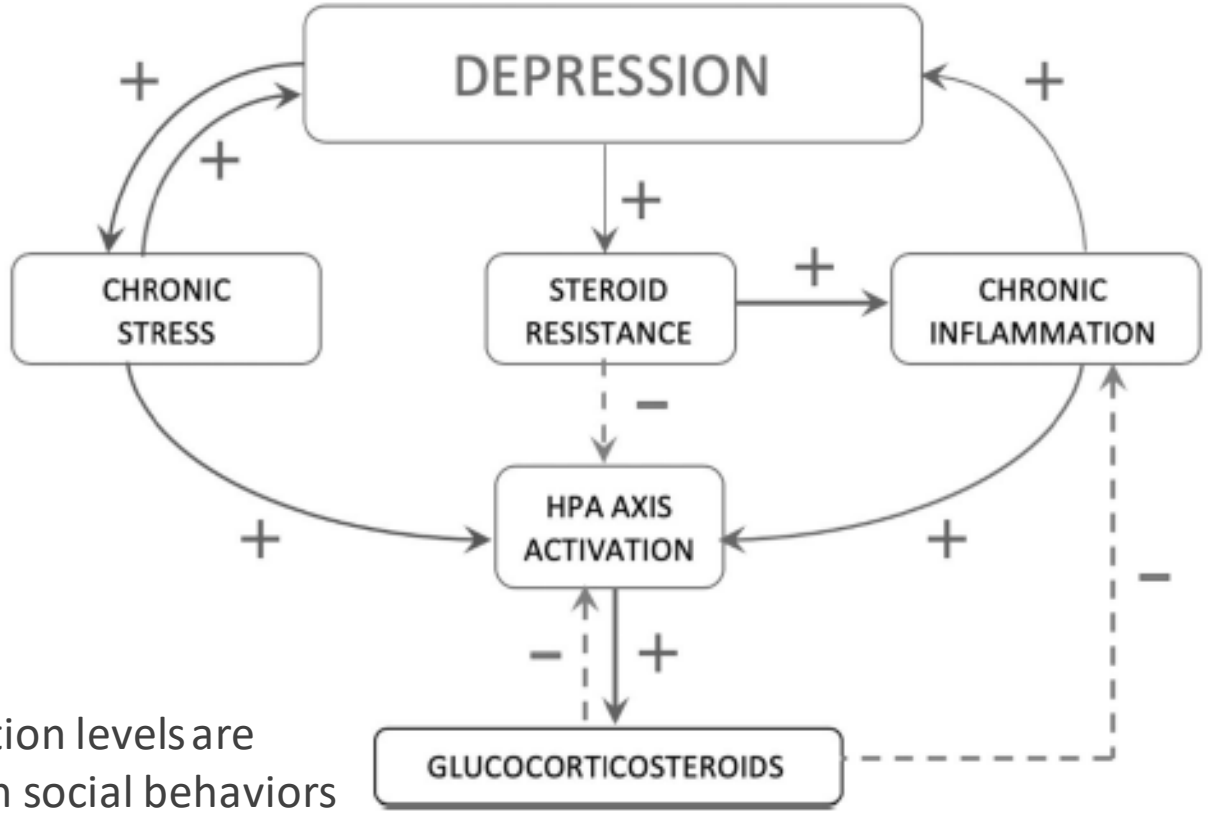
Background

- Latina women are uniquely stressed because of immigration status, racism, and sexism
- This population has
  - Largest rise in birthrate
  - Slowest decrease in premature births
  - Three to four times as likely to develop perinatal depression compared to the general population
- Studies have shown that maternal depression leads to higher risk of preterm birth

Age, years	
Mean (SD)	27.6 (6.35)
Marital status	
Married	34.7%
Not married but living with partner	39.5%
Single	25.8%
Education	
High school or less	85.0%
Some college	8.2%
Other	6.8%
Household income (Yearly)	
< $25,000	79.6%
$25,000 – 39,999	19.7%
> $40,000	0.7%
Nativity	
Non-US born	83.7%
US-born	16.3%
Years living in US	
Mean (SD)	12.0 (7.27)

Background

Experiencing discrimination is associated with increased methylation of stress-related genes such as BDNF

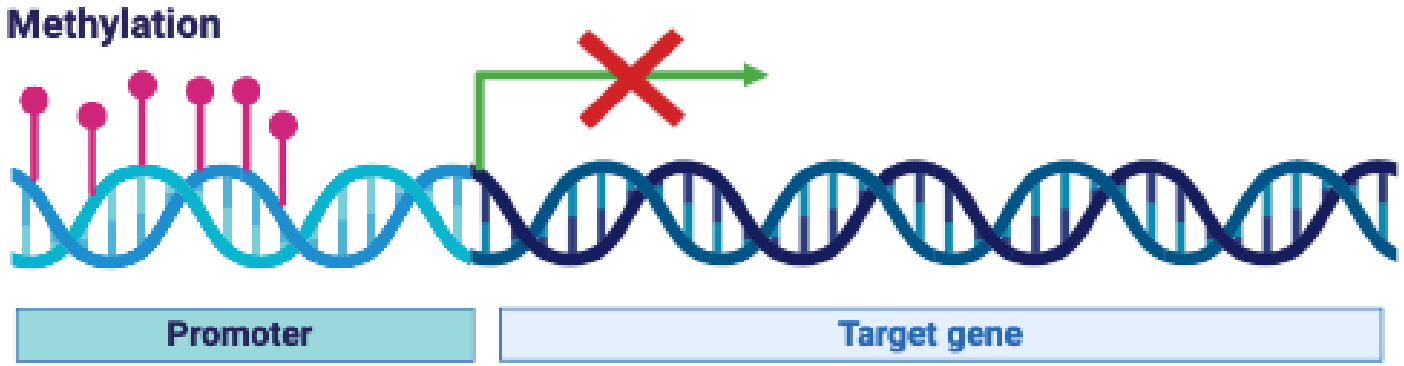


Increased expression of pro-inflammatory biomarkers such as TNFα are associated with preterm births

OXTR methylation levels are associated with social behaviors

Ł. P. Szałach, et. al. *Arch. Immunol. Ther. Exp. (Warsz).*, 2019.

Methylation



Methylation turns off gene expression

- Individual sites are binary: methylated or not
- Samples are measured in percent methylation per CpG site
- Use to calculate an average per gene

Motivation

Preceding studies look at one-to-one correlations between methylated genes and survey scores

Mainly focus on psychopathological effects on premature birth

Goal is **to provide results that enable the planning of interventions in at risk communities**

Methodology

Dataset Description

1. 151 entries for pregnant women of Hispanic Background
2. Blood Samples
   - Inflammatory Related Genes
   - Stress Related Genes
3. Psychological Assessments based on surveys (pre and postnatal)
   - Inventory of Depression and Anxiety Symptoms **(IDAS)**
   - General Anxiety Disorder **(GAD-7)**
   - Bi-dimensional Acculturation Scale **(BAS)**
   - Everyday Discrimination Scale **(EDS)**
   - Economic Hardship Measure **(EDM)**

Preprocessing

1st Dataset

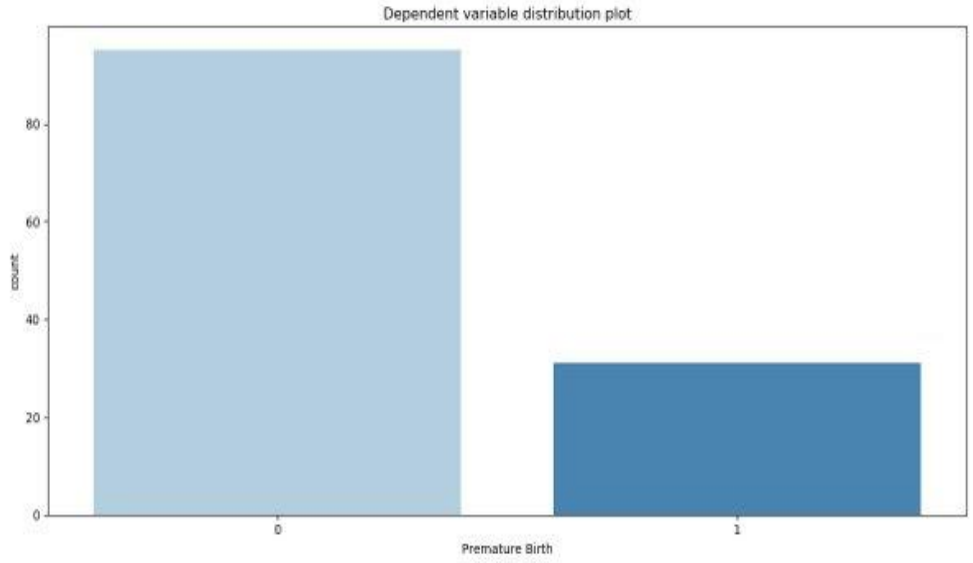
- 151 records and 714 features

2nd Dataset

- 152 records and 727 features

Calculated for premature birth and appended feature

- Due date and actual birth date

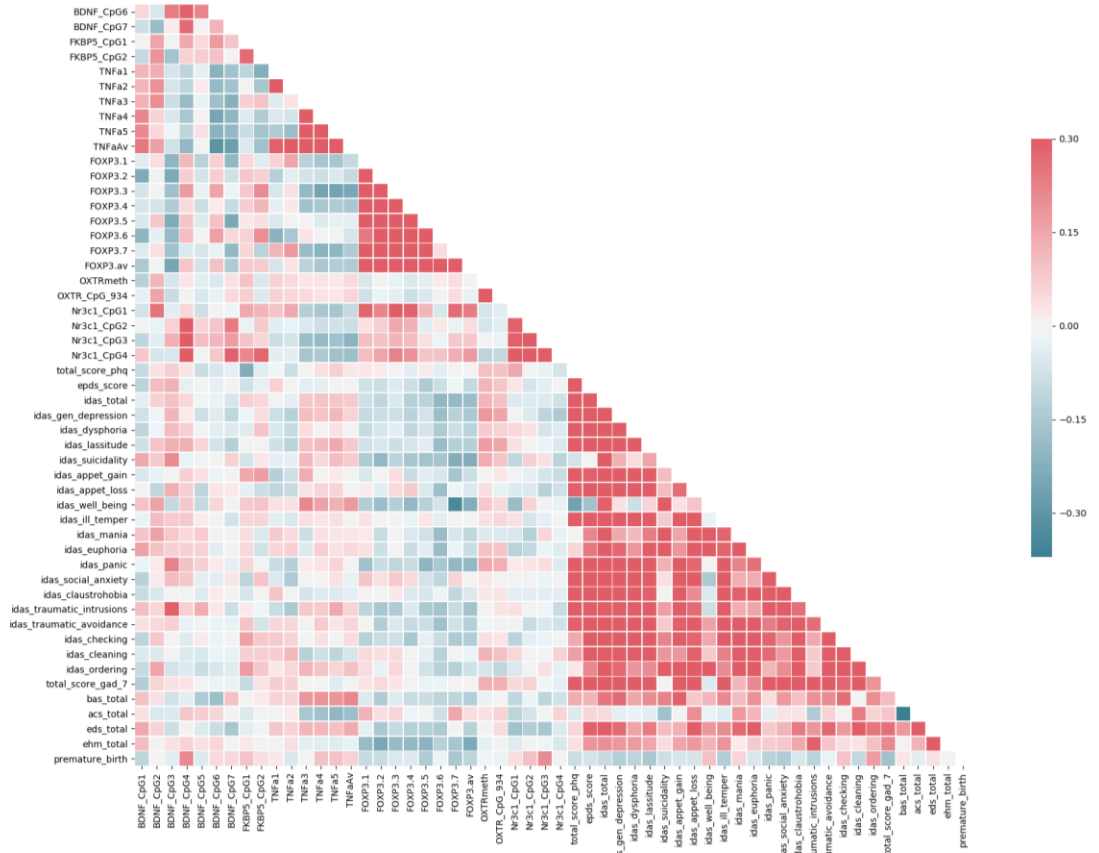


Data Exploration

Correlation between inflammatory related genes

Correlation between stress related genes

Correlation between Acculturative Stress and Acculturation with Stress Related Genes



Prediction

Read **into the model's feature importance and the permutation feature importance to predict depression**

Created **a similar model, to see how** our features **can help predict discrimination** score using the model's attributes

After **analyzing these relations, we** further looked into how our features **affect or correlate with premature birth**

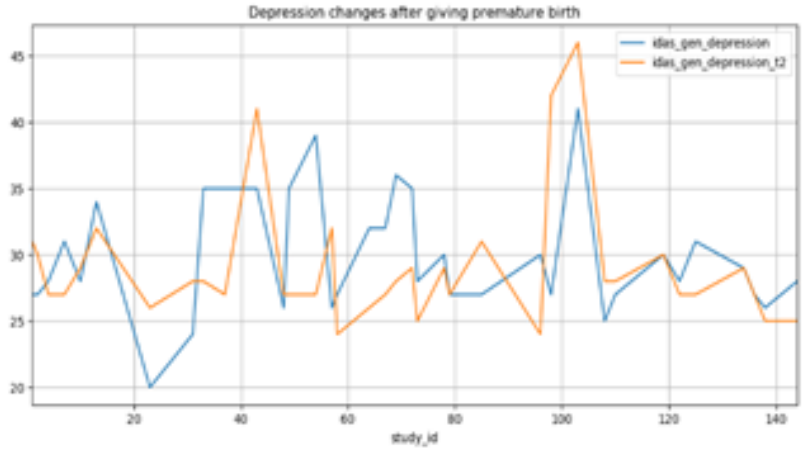
Classification

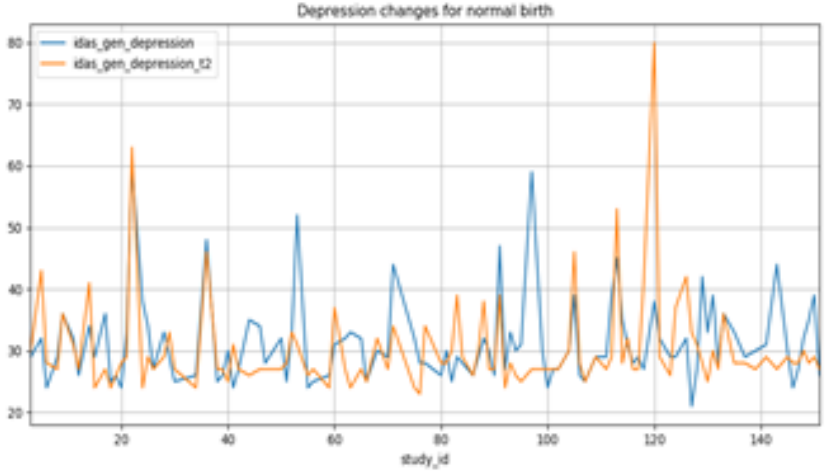
Experiments with Random Forest, SVM, Logistic Regression and Gradient Booster

Initially, results not as expected because of the bias in the data

Modified the class weights in Random Forest and got better results

Since it is a binary classifier, we used not only accuracy, but also precision, recall, and area under curve





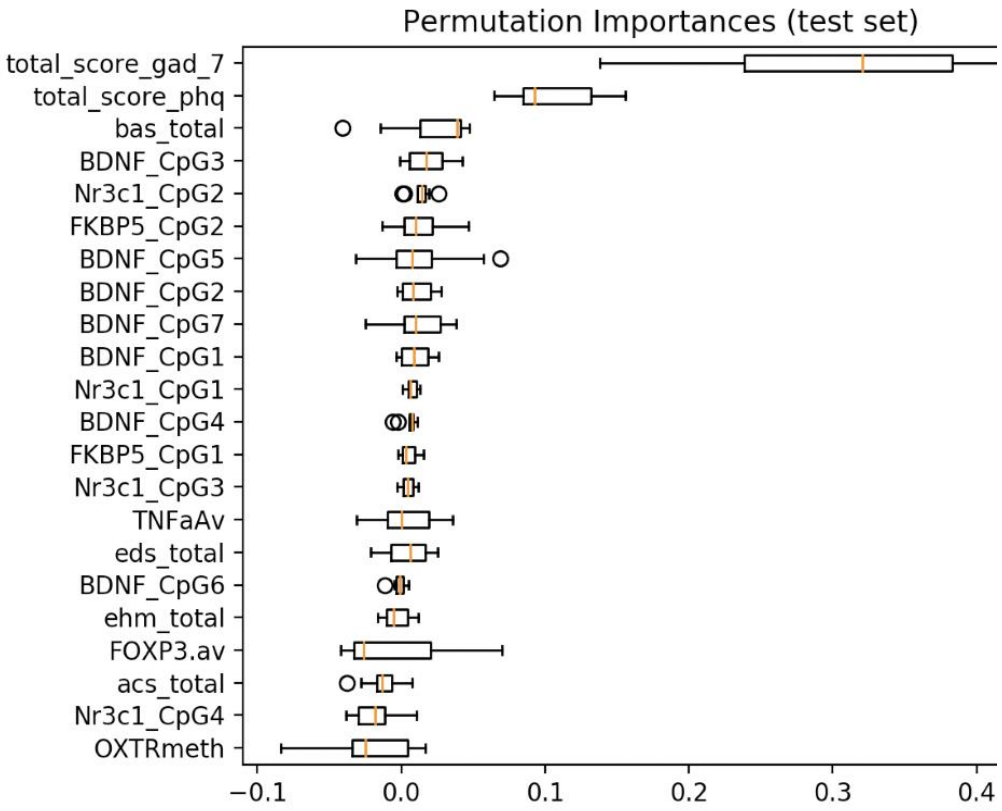
Regression

- Trained Random Forest and Gradient Booster Regressors to predict depression and discrimination scores
- Used mean squared error, mean absolute error, r squared error and variance score for evaluation
- For depression, both produced marginally close models, but not the best
- For discrimination, we didn't get great results

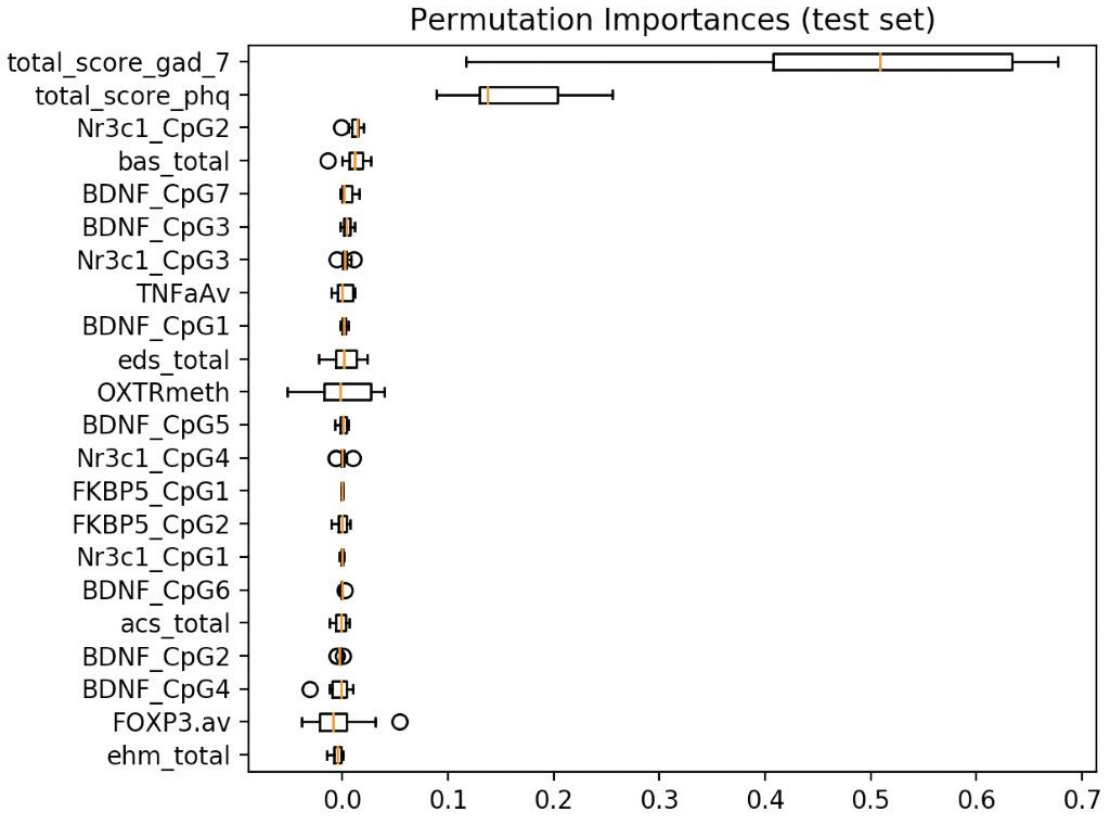
Results

Permutation Importance Plots For Predicting Depression

GRADIENT BOOSTING REGRESSOR:

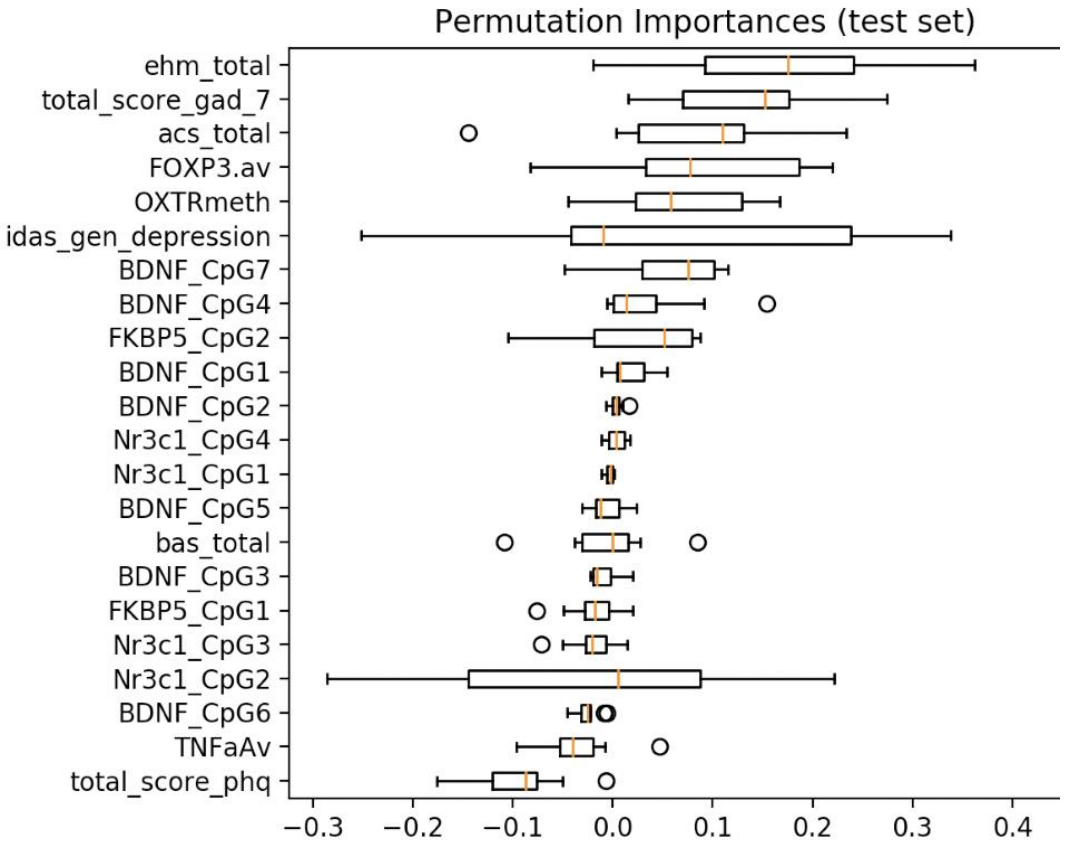


RANDOM FOREST REGRESSOR

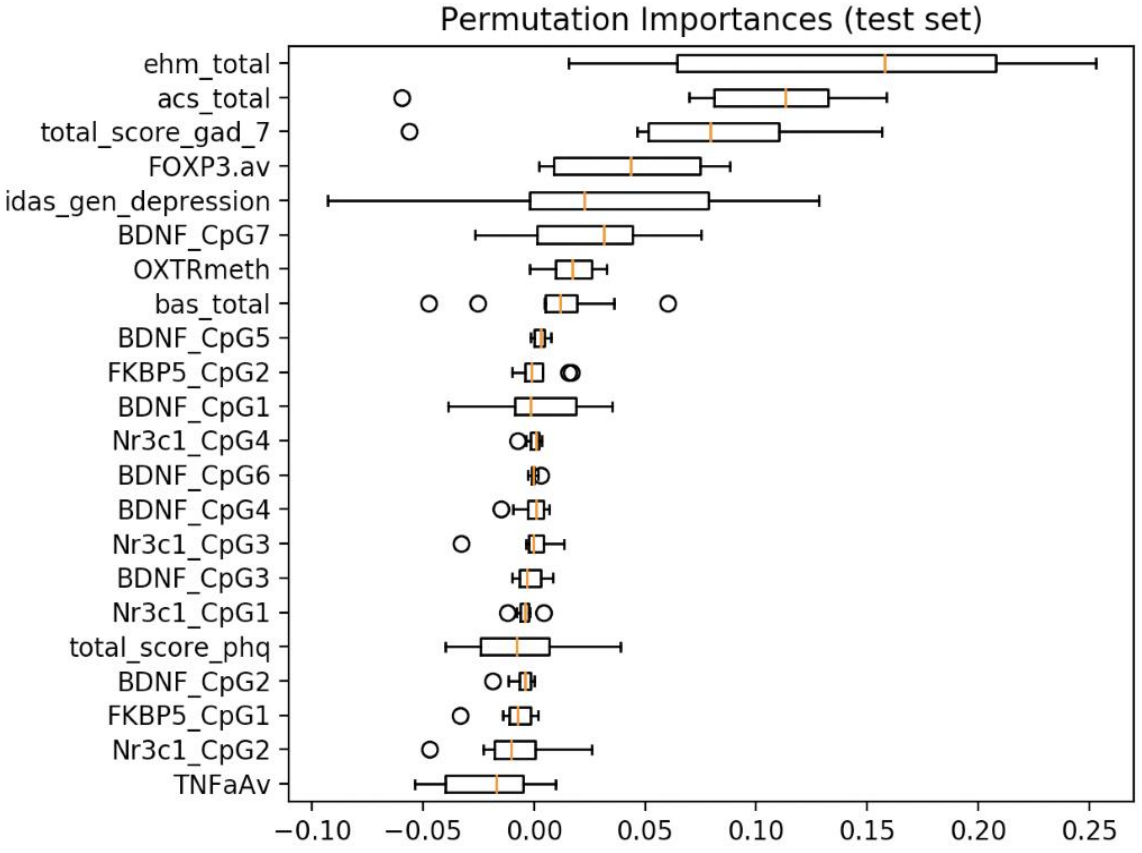


Permutation Importance Plots For Predicting Discrimination

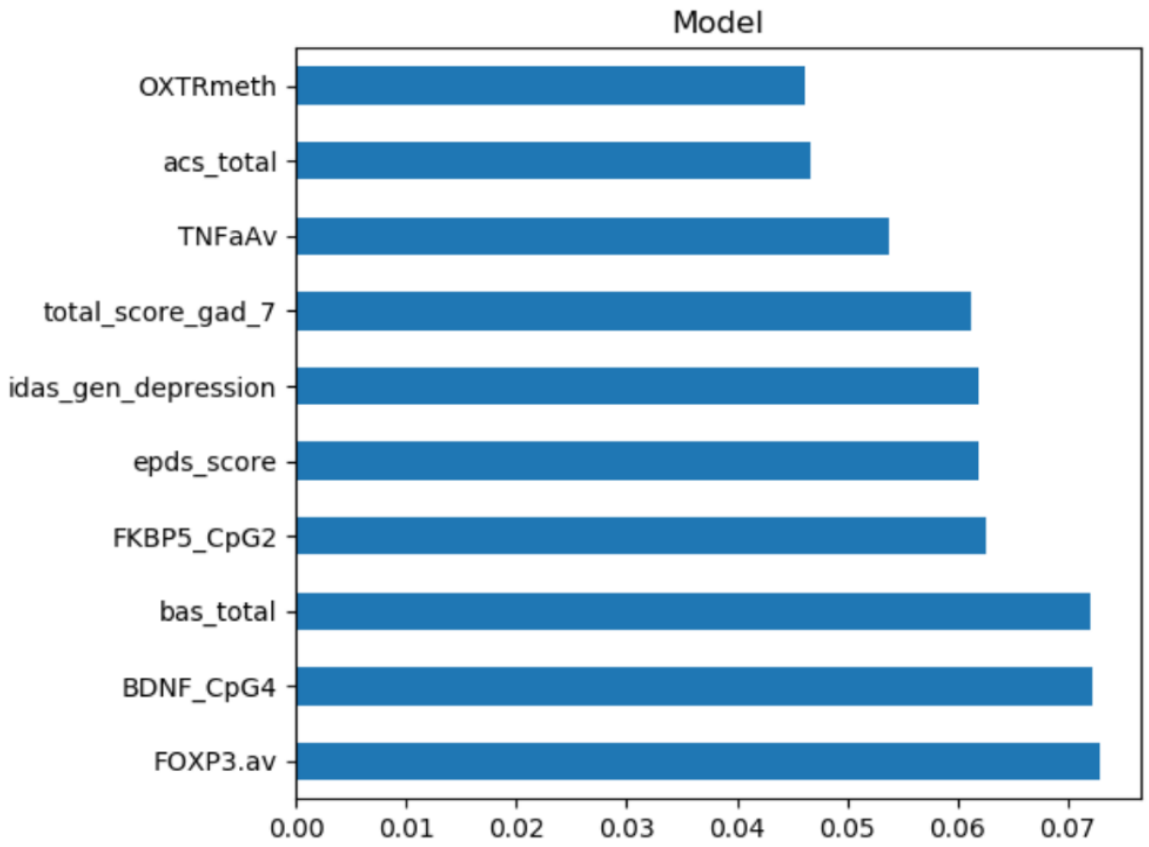
GRADIENT BOOSTING REGRESSOR:



RANDOM FOREST REGRESSOR



Feature Importance Plot For Preterm Birth



Evaluation Metrics For Regression Models

Regressor	Dependent Variable	Mean Squared Error	Mean Absolute Error	Variance	R-Score
Gradient Boosting	Depression	28.088	4.048	0.427	0.407
	Discrimination	9.978	2.397	0.291	0.073
Random Forest	Depression	23.280	3.712	0.514	0.508
	Discrimination	10.008	2.454	0.308	0.070

Evaluation Metrics For The Classification Model

Evaluation Parameters	Results
Accuracy Score	0.769
Precision for preterm birth	0.50
Recall for preterm birth	0.17
F1-Score for preterm birth	0.25
Support for preterm birth	6
ROC score	0.55833

Conclusions & Discussion

Extracted and interpreted correlations between the features responsible for depression and discrimination prediction.

Identified the significant features affecting the Preterm birth.

Determined significant associations between features and their importance in affecting depression and discrimination

Observed that the depression scores grow stronger after giving preterm birth

Limitations and Future Work

Limitations:

- Unbalanced distributions in our dataset
  - Depression scores were similarly distributed
  - Premature birth values were highly imbalanced

Future Work:

- Use the MScore of the epigenetic markers

- Categorize Depression/Discrimination scores

- Analyze specific IDAS subgroup scores with respect to depression and discrimination

- See specific APGAR score distribution for premature and normal birth

References

- N. K. Grote, J. A. Bridge, A. R. Gavin, J. L. Melville, S. Iyengar, and W. J. Katon, “A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction,” Arch. Gen. Psychiatry, vol. 67, no. 10, pp. 1012–1024, Oct. 2010.
- H. Santos, E. I. Fried, J. Asafu-Adjei, and R. Jeanne Ruiz, “Network structure of perinatal depressive symptoms in latinas: Relationship to stress and reproductive biomarkers,” Res. Nurs. Heal., vol. 40, no. 3, pp. 218–228, 2017.
- C. Mitchell, L. M. Schneper, and D. A. Notterman, “DNA methylation, early life environment, and health outcomes,” Pediatr. Res., vol. 79, no. 1–2, pp. 212–219, 2016.
- C. Maud, J. Ryan, J. E. McIntosh, and C. A. Olsson, “The role of oxytocin receptor gene (OXTR) DNA methylation (DNAm) in human social and emotional functioning: A systematic narrative review,” BMC Psychiatry, vol. 18, no. 1, pp. 1–13, 2018.
- S. M. Stasik-O’Brien et al., “Clinical Utility of the Inventory of Depression and Anxiety Symptoms (IDAS),” Assessment, vol. 26, no. 5, pp. 944–960, Jul. 2019.
- H. P. Santos et al., “Discrimination exposure and DNA methylation of stress-related genes in Latina mothers,” Psychoneuroendocrinology, vol. 98, no. August, pp. 131–138, 2018.

Questions?