STATISTICAL MODELING OF PARKINSON'S DISEASE PHENOTYPES: COMPARATIVE AND PREDICTIVE APPROACHES

Introduction

Parkinson's Disease (PD) is a neurodegenerative disorder with a wide range of motor and non-motor symptoms. Clinically, patients are often categorized into subtypes based on dominant symptom profiles, most notably Tremor-Dominant (TD) and Postural Instability and Gait Difficulty (PIGD). In this report, we address two key objectives:

- **Aim 1:** To determine if patients can be accurately classified into TD and PIGD groups based on clinical, cognitive, and psychological variables.
- **Aim 2:** To evaluate whether a continuous phenotype ratio (tremor score / PIGD score) is associated with these same predictors, providing a more nuanced view of symptom severity along the TD–PIGD spectrum.

AIM 1: Classifying TD vs. PIGD Phenotypes

Methodology

TD and PIGD phenotypes often require different clinical management strategies. Knowing which group a patient belongs to can help personalize interventions. This analysis aims to determine whether existing cognitive and psychological measures are sufficient to statistically differentiate these two groups.

We filtered a sample of 58 PD participants to include only those with TD or PIGD phenotypes. After selecting 19 clinical, cognitive, psychological, and DT-related variables, we handled missing data via predictive mean matching (PMM) using the `mice` package. The dataset was split (80/20) into training and testing sets. Three classification models were applied:

- Logistic Regression
- Naive Bayes
- Random Forest

Model evaluation used confusion matrices and ROC curves.

Results

- **Logistic Regression** achieved high accuracy (85.7%) but produced convergence warnings and unstable probability estimates.
- **Naive Bayes** provided balanced sensitivity (66.7%) and specificity (75%) with accuracy of 71.4%.
- **Random Forest** performed poorly on test data (accuracy 42.8%, sensitivity 0%) but retained moderate specificity.

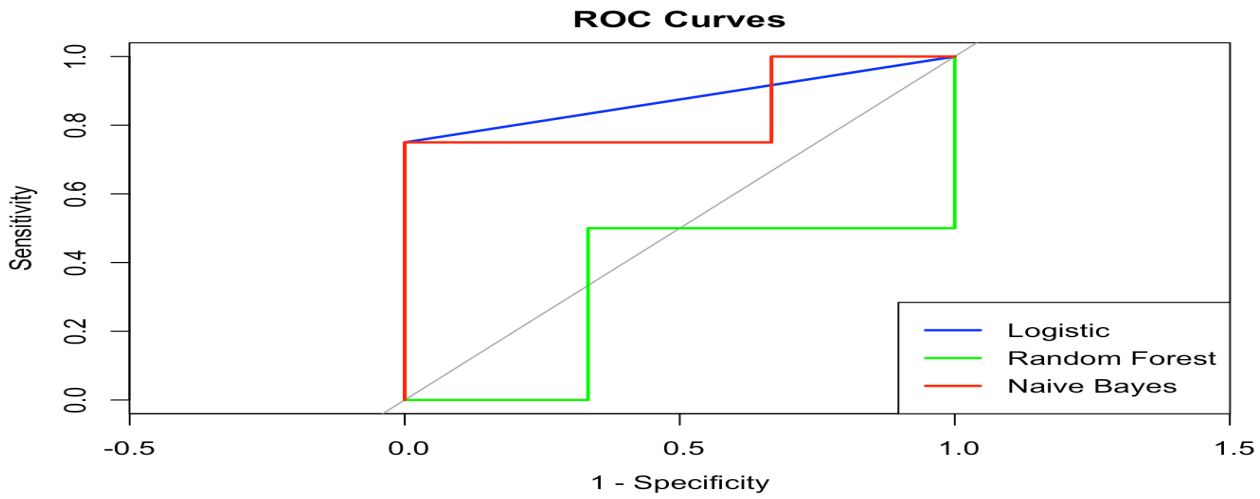
What We Learned (Statistically)

Naive Bayes showed the most stable performance, capable of differentiating TD from PIGD using psychological and clinical features. Logistic regression overfitted due to too many predictors relative to data size. Random Forest's failure indicated insufficient training data or poor generalization.

What This Means (Clinically)

This shows that simple, accessible psychological and motor assessments (e.g., anxiety, depression, Trails performance) can be used to classify PD patients into their respective subtypes. This supports using non-motor profiles to help guide treatment decisions.

Interpretation



Naive Bayes was the most stable and generalizable model. Logistic regression showed overfitting. Random Forest may require more data or feature refinement. The classification task aligns with Aim 1's goal of determining phenotype group membership.

This classification task helped us confirm that there are measurable, classifiable differences between the TD and PIGD phenotypes using cognitive, psychological, and DT-related metrics. This validates our methodological approach and supports future work that relies on phenotype separation in clinical and research settings.

AIM 2: Predicting Phenotype Ratio (Continuous Outcome)

While TD and PIGD classification is binary, real-world symptoms exist along a continuum. The phenotype ratio provides a way to quantify symptom dominance. This analysis aims to predict where a person lies along that spectrum using non-motor features.

Methodology

We modeled the continuous phenotype ratio using linear regression. Predictors included cognitive (MMSE, Trails, SDMT), psychological (ABC, GDS, PAS), DT measures (mdte, cogdt, cdte, maai), and covariates (age, sex, HY). Missing values were imputed using `mice`. The model was trained and evaluated using RMSE, MAE, and R-squared metrics.

Results

- **Adjusted R-squared**: 0.631
- **RMSE**: 1.29
- **MAE**: 1.09
- **F-statistic**: 6.43, $p < 0.001$

Significant predictors included:

- Persistent anxiety (PAS-A), depression (GDS), and balance discordance
- ABC confidence (negative effect)
- HY stage and Trails B completion time

What We Learned (Statistically)

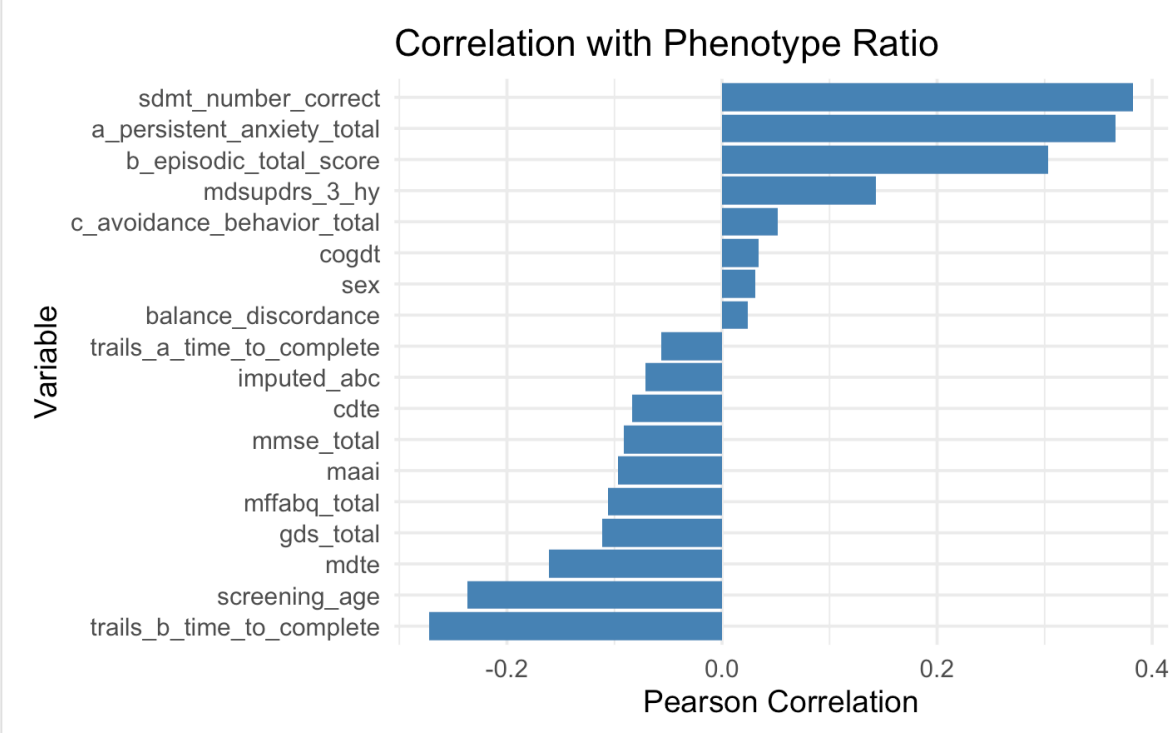
The model explains over 63% of the variability in the phenotype ratio. Non-motor variables such as anxiety and depression outperformed traditional cognitive measures in predicting severity.

What This Means (Clinically)

This implies that PD severity along the TD–PIGD continuum can be predicted using accessible psychological and DT measures. These tools may support continuous monitoring and early intervention strategies.

Interpretation

The regression model successfully explained 63% of the variance in phenotype severity. Key contributors were psychological and perceptual features. This completes Aim 2's objective to assess the linear relationship between phenotype ratio and non-motor variables.



This predictive modeling task allowed us to go beyond binary classification and quantify the spectrum of phenotype severity. It revealed that psychological distress and perceived balance ability are central indicators of where a patient lies on the tremor–PIGD continuum. Understanding these gradients enhances the potential for personalized symptom management and progression tracking.

Final Conclusion

This analysis fulfills both primary project aims:

- **Aim 1**: We successfully classified TD vs. PIGD phenotypes, with Naive Bayes yielding the most stable results.
- **Aim 2**: We demonstrated that cognitive, psychological, and DT-related variables significantly predict the phenotype ratio, with strong emphasis on anxiety, depression, balance confidence, and HY stage.

What We Set Out to Do

We aimed to answer two key questions:

1. Can we accurately classify TD vs. PIGD patients based on cognitive, psychological, and dual-task variables? (**Aim 1**)
2. Can we model where a patient falls on the tremor-PIGD continuum using the same features? (**Aim 2**)

What We Did

- We applied robust machine learning models to classify patients (Aim 1).
- We developed and validated a linear regression model to predict symptom severity using a continuous phenotype ratio (Aim 2).

What We Learned

- Naive Bayes was the best model for phenotype classification.
- Depression, anxiety, balance perception, and motor severity were the most powerful predictors of symptom dominance.

What It Means

Together, both aims show that **psychological and perceptual factors are not just symptoms, but potential drivers or indicators of PD phenotype expression**. This suggests that clinical evaluations of PD should prioritize non-motor symptom tracking for both classification and ongoing severity assessment.

This analysis meets the original objectives and lays the groundwork for future research, especially for modeling unclassified groups and creating predictive tools to enhance patient care.