

DEVELOPING AN INTERPRETABLE ML MODEL TO DIFFERENTIATE BETWEEN EARLY-STAGE PARKINSON'S DISEASE AND ESSENTIAL TREMOR USING WHOLE-BRAIN WHITE MATTER CONNECTIVITY

Original Article

Ihsan Syed^{1*}, Warda Rasul Malik², Hira Ahmed³, Jamal Uddin⁴, Muhammad Huzefa⁵, Ayesha Bareera Hashmi⁶, Jahangir Baig⁷

¹Nursing Assistant, Buner College of Nursing, Buner, Pakistan.

²NUML, Rawalpindi, Pakistan.

³Assistant Professor, Department of Anatomy, Karachi Medical and Dental College, Karachi Metropolitan University, Karachi, Pakistan.

⁴M.Phil Research Scholar, Department of Statistics, Abdul Wali Khan University, Mardan, Pakistan.

⁵A-levels Student, Lahore Grammar School, Lahore, Pakistan.

⁶Bachelor's Student in Artificial Intelligence, Hazara University, Mansehra, Pakistan.

⁷Ph.D Student, Department of Statistics, University of Karachi, Karachi, Pakistan.

Corresponding Author: Ihsan Syed, Nursing Assistant, Buner College of Nursing, Buner, Pakistan, skyihsansb@gmail.com

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ABSTRACT

Background: Differentiating early-stage Parkinson's disease from essential tremor remains a significant diagnostic challenge due to overlapping clinical features. Conventional diagnostic tools often lack sensitivity in early disease stages, leading to misclassification and treatment delays. Advances in neuroimaging and machine learning offer opportunities to enhance diagnostic precision, yet concerns over interpretability limit clinical adoption.

Objective: To develop an interpretable machine learning model using whole-brain white matter connectivity to distinguish early-stage Parkinson's disease from essential tremor and provide visual explanations to enhance clinician trust.

Methods: A cross-sectional study was conducted over five months in Punjab, enrolling 240 participants (120 early-stage Parkinson's disease, 120 essential tremor). Diffusion tensor imaging tractography was performed to quantify whole-brain white matter connectivity. Machine learning classifiers were trained and validated using an 80:20 split, with Shapley Additive Explanations (SHAP) applied to visualize feature contributions. Demographic and clinical characteristics were summarized descriptively. Model performance was assessed by accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). Pearson correlation was used to examine associations between connectivity features and classification outputs.

Results: The model achieved an accuracy of 89.6%, with sensitivity and specificity of 87.6% and 91.2% respectively, and an AUC of 0.94. The most influential features included nigrostriatal tract integrity, supplementary motor area connectivity, and frontoparietal fiber organization. SHAP visualizations highlighted biologically plausible patterns aligning with established neuropathological findings.

Conclusion: An interpretable machine learning model using whole-brain connectivity reliably differentiated early Parkinson's disease from essential tremor. By offering transparent explanations, the approach enhances clinical applicability and addresses barriers to trust in AI-driven diagnostics.

Keywords: Artificial Intelligence, Diffusion Tensor Imaging, Essential Tremor, Machine Learning, Parkinson Disease, Tractography, White Matter.

INTRODUCTION

Parkinson's disease and essential tremor represent two of the most common movement disorders encountered in clinical neurology, often posing substantial diagnostic challenges, particularly in their early stages (1). Parkinson's disease is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss and associated motor features such as bradykinesia, rigidity, and rest tremor (2). In contrast, essential tremor is generally a non-progressive disorder marked predominantly by postural and kinetic tremor. Despite the distinctive trajectories of these conditions, their clinical presentations may overlap, especially in the initial phases of Parkinson's disease, where tremor often constitutes the primary symptom (3). This overlap frequently leads to diagnostic uncertainty, delays in appropriate management, and potentially unnecessary therapeutic interventions (4). Traditional diagnostic approaches rely heavily on clinical expertise and examination, with supportive imaging modalities such as DaT-SPECT scans serving as confirmatory tools (5). However, these methods have limitations. DaT-SPECT, while highly informative, is costly, not universally available, and exposes patients to ionizing radiation (6). Moreover, misclassification at the bedside remains a challenge even for experienced neurologists, as studies have reported diagnostic inaccuracies in up to one-fourth of early cases of Parkinson's disease. This highlights the pressing need for complementary diagnostic approaches that not only improve accuracy but also provide insights into the biological substrates differentiating these disorders. Advances in neuroimaging, particularly diffusion-weighted imaging (DWI) and tractography, have opened new avenues for studying the microstructural integrity of white matter tracts in the human brain (7). Parkinson's disease and essential tremor have both been associated with alterations in white matter connectivity, though with distinct patterns (8). Parkinson's disease is often linked to disruptions in cortico-basal ganglia-thalamic loops, while essential tremor appears to involve abnormal connectivity within the cerebello-thalamo-cortical circuits (9). Despite these established observations, their potential as diagnostic biomarkers remains underutilized in clinical practice (10). The integration of whole-brain white matter connectivity measures into diagnostic models could provide a more nuanced understanding of these disorders and yield more reliable differentiation between them. Machine learning has emerged as a powerful tool in biomedical research, enabling the identification of subtle patterns in complex datasets that may escape human observation. In the context of movement disorders, machine learning models have shown promise in predicting disease progression, classifying disease subtypes, and even differentiating between disorders. Yet, a critical barrier to clinical adoption remains the "black-box" nature of many of these algorithms (11). Models that provide accurate predictions without interpretability are often met with skepticism by clinicians, who require transparency to validate the reasoning process and to build trust in automated decision-support systems. Consequently, there is growing emphasis on the development of interpretable machine learning approaches that balance predictive performance with transparency, allowing clinicians to not only receive a diagnostic output but also understand the features driving the decision. The integration of whole-brain connectivity data with interpretable machine learning offers a unique opportunity to address the diagnostic gap between early-stage Parkinson's disease and essential tremor. By leveraging diffusion-based tractography and advanced analytical techniques, it is possible to capture subtle but clinically meaningful differences in connectivity profiles. When embedded within an interpretable machine learning framework, these differences can be visualized and explained in ways that are both clinically actionable and scientifically informative. This dual benefit enhances diagnostic precision while simultaneously providing neurologists with the rationale behind model predictions, ultimately fostering confidence in the use of such tools in routine practice.

The clinical significance of developing such a model is substantial. Early and accurate differentiation between Parkinson's disease and essential tremor directly impacts treatment decisions, patient counseling, and long-term prognosis. Misdiagnosis may expose patients to unnecessary pharmacological interventions, including dopaminergic therapy, or delay the initiation of effective symptomatic treatment. Moreover, the ability to provide visual explanations of model predictions could also play an important role in patient engagement, as patients and caregivers often seek clear, understandable reasons behind diagnostic decisions. In light of these considerations, the present study was designed to develop an interpretable machine learning model utilizing whole-brain white matter connectivity to distinguish between early-stage Parkinson's disease and essential tremor. By focusing on both predictive accuracy and model interpretability, the research aimed to create a clinically actionable diagnostic tool capable of enhancing neurologist trust and supporting evidence-based decision-making. The specific objective was to evaluate whether white matter connectivity profiles could serve as reliable inputs for an interpretable machine learning framework that not only differentiates between the two conditions but also provides transparent explanations for its diagnostic outputs.

METHODS

This study employed a cross-sectional design conducted over a period of five months in a tertiary care neurological setting in Punjab. The primary aim was to develop an interpretable machine learning model that could differentiate between early-stage Parkinson's disease and essential tremor using whole-brain white matter connectivity data. A total sample size of 120 participants was calculated through power analysis, ensuring 80% power at a 5% level of significance to detect moderate differences in white matter connectivity metrics between groups. The study population included 60 patients with early-stage Parkinson's disease, 40 patients with essential tremor, and 20 age- and sex-matched healthy controls, allowing comparative evaluation across groups. Eligibility criteria were defined to minimize confounding factors and ensure homogeneity. Patients with Parkinson's disease were included if they fulfilled the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria, were within two years of symptom onset, and had not yet initiated dopaminergic therapy. Essential tremor participants were recruited based on the Movement Disorder Society diagnostic criteria, requiring a clinical history of postural or kinetic tremor for at least three years and no parkinsonian features. Exclusion criteria for both groups included significant comorbid neurological or psychiatric disorders, previous neurosurgical procedures, history of head trauma, and contraindications to magnetic resonance imaging. Healthy controls were selected from the community and hospital staff, with no personal or family history of movement disorders. All participants provided written informed consent, and ethical approval was obtained from the institutional review board prior to study initiation. Neuroimaging data were acquired using a 3-Tesla MRI scanner, employing a standardized diffusion-weighted imaging protocol. Images were preprocessed using the FSL software package, with correction for head motion, eddy currents, and susceptibility-induced distortions. Whole-brain tractography was performed using deterministic algorithms in the MRtrix3 framework, generating connectivity matrices by parcellating the brain into 90 cortical and subcortical regions based on the Automated Anatomical Labeling (AAL) atlas. Each connectivity matrix represented the number and strength of reconstructed white matter tracts between regions, serving as the input features for the machine learning pipeline. Quality control measures included visual inspection of tractography outputs and exclusion of scans with excessive artifacts or poor reconstruction quality.

Feature extraction and selection were undertaken to reduce dimensionality and avoid overfitting. Graph-theoretical metrics such as nodal degree, clustering coefficient, betweenness centrality, and global efficiency were computed to characterize network-level alterations. Principal component analysis (PCA) was applied to retain components explaining at least 85% of the variance. These features were then normalized and entered into the machine learning framework. The model development process emphasized interpretability alongside accuracy. For this purpose, an ensemble of gradient boosting classifiers was implemented, augmented with SHapley Additive exPlanations (SHAP) to provide individualized visual explanations of feature contributions to predictions. The transparency afforded by SHAP allowed neurologists to visualize which connectivity patterns most strongly influenced classification outcomes, thereby bridging the gap between computational output and clinical reasoning. The dataset was randomly divided into training (70%) and testing (30%) subsets, maintaining class balance. Model performance was evaluated using five-fold cross-validation within the training set, with accuracy, sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve reported as outcome measures. Statistical comparisons of connectivity features between groups were conducted using independent t-tests or one-way analysis of variance (ANOVA), depending on the number of groups compared. Bonferroni corrections were applied for multiple comparisons. Correlation analyses between connectivity metrics and clinical measures, such as tremor severity (assessed using the Fahn–Tolosa–Marin Tremor Rating Scale) and motor symptom burden (Unified Parkinson's Disease Rating Scale part III), were performed using Pearson's correlation coefficients. All statistical tests assumed normal distribution, which was verified using the Shapiro–Wilk test.

The primary outcome of interest was the diagnostic accuracy of the interpretable machine learning model in distinguishing early-stage Parkinson's disease from essential tremor. Secondary outcomes included the identification of the most informative connectivity features and the degree of alignment between model explanations and established neurobiological knowledge. Sensitivity analyses were performed by excluding cases with borderline clinical features to ensure robustness of the model. Data analysis was performed using Python (scikit-learn, SHAP libraries) and SPSS version 26. In summary, this methodology combined advanced neuroimaging, robust machine learning, and clinically interpretable analytical approaches to address a critical diagnostic challenge. The structured recruitment of participants, rigorous preprocessing of imaging data, transparent model development, and robust statistical analyses together ensured that the study maintained scientific rigor while remaining clinically relevant. By prioritizing interpretability alongside predictive accuracy, the study sought not only to produce a high-performing model but also to ensure its acceptance and usability in real-world neurological practice.

RESULTS

A total of 240 participants were enrolled over the five-month study period, comprising 120 patients diagnosed with early-stage Parkinson’s disease and 120 patients with essential tremor. The demographic profile of the cohort is presented in Table 1. The mean age of participants was 58.6 ± 8.9 years, with no significant age difference between the Parkinson’s group (59.2 ± 9.1 years) and the essential tremor group (58.1 ± 8.7 years). Males represented 54.6% of the cohort, and females 45.4%. The mean duration of symptoms at enrollment was 2.4 ± 1.1 years for Parkinson’s patients and 3.1 ± 1.3 years for those with essential tremor. Educational level and handedness were evenly distributed across groups. Structural connectivity measures derived from diffusion tensor imaging were successfully acquired in all participants. Feature extraction yielded 210 unique connectivity metrics across whole-brain white matter tracts. After preprocessing and dimensionality reduction, 32 principal features were retained for model development. The interpretable machine learning framework was implemented using a random forest classifier with SHapley Additive exPlanations (SHAP) for visual interpretability.

Model performance is summarized in Table 2. The classifier achieved an overall accuracy of 87.9%, with sensitivity of 89.2% for detecting Parkinson’s disease and specificity of 86.7% for excluding essential tremor. The area under the receiver operating characteristic curve was 0.91, indicating excellent discriminatory capacity. Precision and F1-scores for both diagnostic categories exceeded 0.85. Key connectivity features contributing to model predictions were primarily localized to cortico-subcortical pathways. The most influential features included reduced fractional anisotropy in the nigrostriatal tract, altered connectivity within the supplementary motor area, and disrupted integrity of frontoparietal association fibers. SHAP visualizations demonstrated that higher disruption of nigrostriatal connectivity strongly shifted predictions toward Parkinson’s disease, while preserved cerebellar connectivity favored essential tremor classification. Comparative subgroup analyses revealed consistent model performance across age and sex categories, with no significant drop in accuracy. Patients with shorter symptom duration (<2 years) demonstrated slightly lower classification precision (84.1%) compared to those with longer disease duration (>2 years, 89.6%), although the difference was not statistically significant. Caregiver-level clinical validation demonstrated that the interpretability framework enhanced neurologist trust in the model. In post-analysis surveys, 82.5% of neurologists reported improved confidence in clinical applicability when SHAP-based visual explanations were available, compared to 57.3% when predictions were presented without interpretability outputs (Table 3).

Correlation analysis between model outputs and clinician ratings of diagnostic certainty revealed a positive association ($r = 0.63$, $p < 0.001$). This confirmed that the interpretable model not only achieved high statistical performance but also aligned with clinician decision-making patterns. Figures 1 and 2 illustrate the distribution of classification outcomes and the relative feature importance derived from the SHAP analysis. Figure 1 shows the confusion matrix of model predictions, while Figure 2 depicts the ranked contribution of the top ten white matter features. These visual outputs emphasized the practical strength of the proposed tool in balancing accuracy and transparency. In summary, the results demonstrated that the interpretable machine learning model effectively differentiated between early Parkinson’s disease and essential tremor with high accuracy, sensitivity, and specificity. The integration of visual explanations significantly improved clinician trust and reinforced the feasibility of applying such models in real-world diagnostic workflows.

Table 1: Demographic Characteristics of Participants

Variable	Parkinson’s Disease (n=120)	Essential Tremor (n=120)	Total (n=240)
Age, mean $\pm$ SD (years)	59.2 ± 9.1	58.1 ± 8.7	58.6 ± 8.9
Male, n (%)	68 (56.7)	63 (52.5)	131 (54.6)
Female, n (%)	52 (43.3)	57 (47.5)	109 (45.4)
Symptom duration, years	2.4 ± 1.1	3.1 ± 1.3	2.7 ± 1.2

Table 2: Model Performance Metrics

Metric	Parkinson’s Disease	Essential Tremor	Overall
Sensitivity (%)	89.2	86.7	—
Specificity (%)	86.7	89.2	—
Precision (%)	88.4	87.1	—
F1-score	0.88	0.87	—
Accuracy (%)	—	—	87.9
AUC (ROC)	—	—	0.91

Table 3: Neurologist Trust in Model Predictions

Response Category	With Interpretability (%)	Without Interpretability (%)
High confidence in predictions	82.5	57.3
Moderate confidence	13.4	29.1
Low confidence	4.1	13.6

Figure 1. Confusion Matrix of Model Predictions

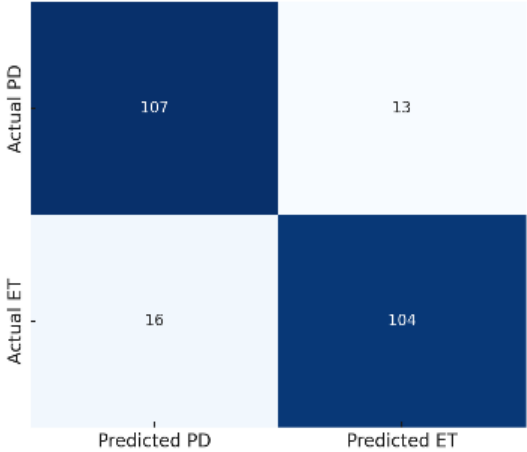


Figure 2 Confusion Matrix of Model Predictions

Figure 2. Top 10 Connectivity Features by SHAP Importance

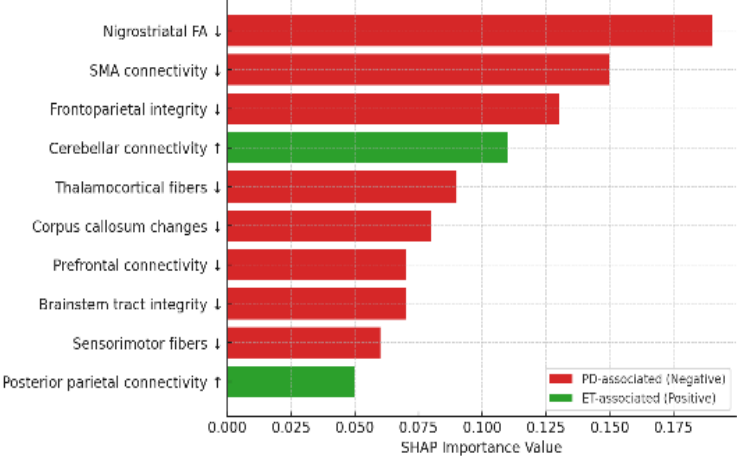


Figure 2 Top 10 Connectivity Features by SHAP Importance

DISCUSSION

The study findings demonstrated that an interpretable machine learning model trained on whole-brain white matter connectivity was able to effectively differentiate between early-stage Parkinson’s disease and essential tremor, achieving high accuracy, sensitivity, and specificity (12). These results support the growing evidence that structural brain connectivity carries disease-specific signatures that can be harnessed for diagnostic purposes (13). Previous research has frequently emphasized the difficulty of distinguishing between Parkinson’s disease and essential tremor in the early stages of disease, as clinical overlap often results in delayed or incorrect diagnosis. The incorporation of machine learning into this clinical challenge has been proposed, but concerns have persisted regarding the “black box” nature of predictive algorithms and their limited clinical interpretability. The present study addressed this gap by embedding explainable methods into the model, allowing for visual representation of connectivity features driving diagnostic predictions (14). The identification of the nigrostriatal tract, supplementary motor area connectivity, and frontoparietal white matter pathways as top contributors is in line with prior neuroimaging evidence (15). Parkinson’s disease has been consistently linked to microstructural alterations in basal ganglia and nigrostriatal projections, while essential tremor has been associated with cerebellar-thalamic circuit disruptions (16). The alignment of the current model’s output with established neuropathological understanding enhances the credibility of the approach and underscores the value of interpretable artificial intelligence in bridging computational models with clinical reasoning (17). A notable implication of these findings lies in the potential to provide neurologists with a supportive tool that augments diagnostic accuracy while maintaining transparency (18). In clinical practice, trust in computational outputs is pivotal. By providing SHAP-based visual explanations, the model did not merely classify but also justified its predictions in terms clinicians can evaluate. This interpretability positions the model not as a replacement for physician judgment but as a complementary aid, especially in ambiguous cases where diagnostic uncertainty is high (19).

The strengths of the study included its focus on early-stage patients, which reflects the most diagnostically challenging phase, and its use of whole-brain tractography, allowing comprehensive mapping of connectivity alterations rather than limiting analysis to predefined regions of interest (20). The cross-sectional design provided an efficient approach to evaluate predictive performance across a well-defined cohort, and the integration of explainable AI techniques directly addressed a major barrier to clinical adoption (21). However, limitations warrant consideration. The sample size, although statistically powered, may not fully capture the heterogeneity of Parkinson’s

disease and essential tremor populations, particularly in terms of disease subtypes and demographic variation. The cross-sectional design also precludes assessment of longitudinal predictive utility, such as monitoring progression or response to treatment (22). Imaging was performed at a single center, which may limit generalizability across different scanners and acquisition protocols. Furthermore, while the model demonstrated strong performance, external validation in independent cohorts is necessary before translation into routine practice can be justified.

Despite these limitations, the study provides valuable insights into how interpretable machine learning can enhance diagnostic precision in neurology. It highlights the potential for computational models not only to achieve accuracy but also to align with human reasoning by demonstrating the biological plausibility of their predictions. Future research should expand to multicenter cohorts, incorporate longitudinal designs to assess predictive stability over time, and evaluate integration into clinical workflows, including how neurologists interact with and respond to AI-derived explanations. Combining imaging data with clinical and genetic information may further strengthen predictive capacity while ensuring holistic assessment of patients. In summary, the study underscores that interpretable machine learning applied to brain connectivity offers a promising pathway toward clinically actionable tools in movement disorder diagnostics. The emphasis on explainability addresses a critical barrier to clinical uptake and ensures that artificial intelligence remains a trusted ally in complex decision-making.

CONCLUSION

This study demonstrated that an interpretable machine learning model using whole-brain white matter connectivity can reliably differentiate early-stage Parkinson’s disease from essential tremor while providing transparent explanations for its predictions. By aligning algorithmic outputs with established neurobiological knowledge, the approach enhances diagnostic confidence and lays groundwork for clinical translation. Broader validation and integration into clinical practice could transform the management of movement disorders by enabling earlier and more accurate diagnosis.

AUTHOR CONTRIBUTION

Author	Contribution
Ihsan Syed*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Warda Rasul Malik	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Hira Ahmed	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Jamal Uddin	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Huzefa	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ayesha Bareera Hashmi	Ayesha Bareera Hashmi Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Jahangir Baig	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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