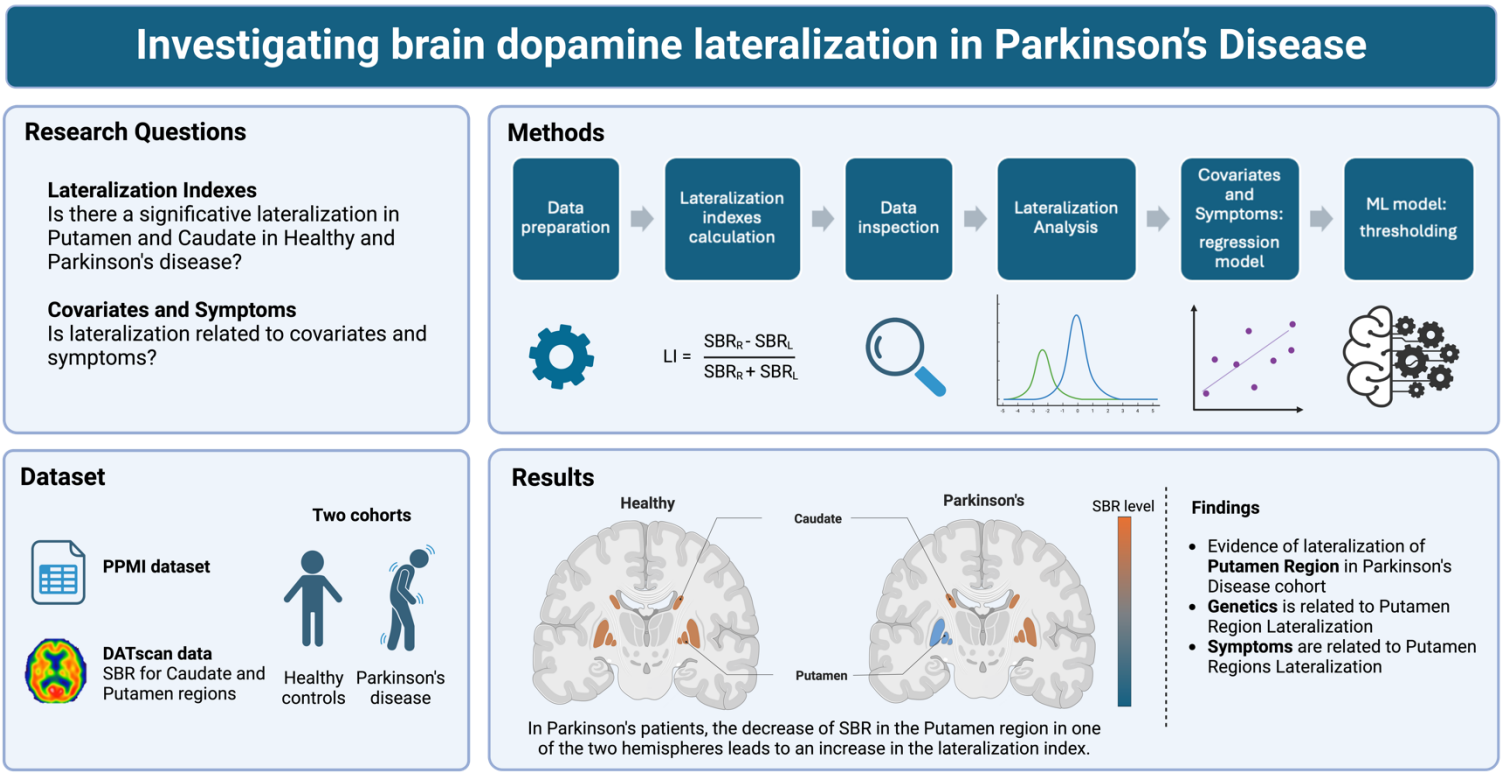
UNIVERSITÀ DEGLI STUDI DI PADOVA

DIPARTIMENTO DI INGEGNERIA DELL'INFORMAZIONE

Investigating brain dopamine lateralization in Parkinson's Disease

Ghiotto A., Longhini M., Palmarini C., Ruzzante P.

University of Padua, Department of Information Engineering (DEI).
Biomarkers, Precision Medicine and Drug Development, Prof. M. Veronese, AY. 2023-24



ABSTRACT

Parkinson's disease (PD) diagnosis and monitoring often use dopamine transporter (DAT) imaging with single-photon emission computed tomography (SPECT). This study investigated the lateralization of brain dopamine function and the potential of DATSCAN as a reliable biomarker for PD diagnosis. Utilizing data from the Parkinson's Progression Markers Initiative (PPMI), the Striatal Binding Ratio (SBR) values in the Caudate and Putamen regions of both Healthy Controls (HC) and PD patients were analyzed to extract a Lateralization Index metric. Significant lateralization was observed in the Putamen region of PD patients, indicating asymmetric dopaminergic degeneration. Genetics was identified as a significant factor influencing lateralization in the Putamen region of PD patients. Symptom-related variables also appear to be correlated with the Lateralization Index. A machine learning model was developed, successfully predicting PD diagnosis based on the Putamen's Lateralization Index, confirming both the literature results and the findings of this study and demonstrating the potential of this metric as a diagnostic tool. These findings highlight the importance of understanding dopaminergic asymmetry in PD progression and the potential application of DATSCAN in clinical diagnostics as an asymmetry biomarker. Future research should focus on validating these results in more heterogeneous cohorts and exploring the mechanisms behind lateralization to enhance early diagnosis.

BACKGROUND

Introduction to Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects movement control. Characterized by the loss of dopamine-producing neurons in the substantia nigra, a region of the brain integral to regulating movement, PD manifests through a variety of motor and non-motor symptoms.

Motor symptoms of Parkinson's disease include slowness of movement, rigidity, tremor, and postural instability. These symptoms typically begin asymmetrically and gradually progress to involve both sides of the body. Non-motor symptoms, which can precede motor symptoms by several years, include autonomic dysfunction, cognitive impairment, mood disorders, and sleep disturbances [1].

The exact cause of Parkinson's disease remains unknown, though it is believed to result from a combination of genetic and environmental factors [2]. Diagnosing Parkinson's disease typically involves a combination of medical history, physical examination, neurological and laboratory tests, and it is challenging to make an accurate diagnosis of PD in the early stages [3].

Current treatment strategies for PD are primarily symptomatic, aiming to improve quality of life by managing motor and non-motor symptoms. Despite these treatments, there is no cure for PD, and disease progression cannot be halted.

Ongoing research is focused on understanding the molecular and cellular mechanisms underlying PD, identifying biomarkers for early diagnosis, and developing neuroprotective therapies. Advances in genetics, neuroimaging, and neurophysiology hold promise for unravelling the complexities of Parkinson's Disease and improving outcomes for those affected by this challenging condition.

DAT SPECT

Single Photon Emission Computed Tomography (SPECT) is a sophisticated imaging technique that enables the visualization and quantification of cerebral blood flow and metabolic processes. Utilizing gamma-emitting radioisotopes, SPECT provides three-dimensional images of functional activity within the brain by detecting the photons emitted from the injected radiotracers [4].

In the context of Parkinson's Disease, SPECT is primarily employed to evaluate the integrity of the dopaminergic system [4].

Asymmetric hemispheric loss of dopaminergic neurons is one of the characteristic features of Parkinson's Disease. This loss leads to reduced dopamine levels in the brain, affecting both motor and cognitive functions. The dopamine transporter (DAT) is a protein responsible for the reuptake of dopamine from the synapse back into neurons, and its loss is a marker of dopaminergic neuron degeneration [5].

In PD, the degeneration of dopaminergic neurons often occurs asymmetrically, meaning that one side of the brain is more affected than the other [5]. This asymmetry can be measured using imaging techniques such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) that highlight DAT availability [4]. Patients with predominant right hemisphere dopaminergic loss experience greater motor impairment, while those with more pronounced left hemisphere loss exhibit significant cognitive decline. This asymmetry influences both the initial presentation of symptoms and their progression over time. Together, these findings underscore the importance of DAT-SPECT as both a diagnostic and prognostic biomarker in PD. By providing a clearer picture of the underlying neuronal loss, DAT-SPECT aids in the early and accurate diagnosis of PD, helps monitor disease progression, and could potentially guide tailored therapeutic interventions [4].

Lateralization in Parkinson Disease

Parkinson's disease is an asymmetric condition compared to other degenerative parkinsonism, and a certain degree of the asymmetry is typically maintained throughout the course of the disease [6].

The underlying motor symptoms are primarily related to the loss of dopamine in the basal ganglia, which occurs bilaterally, but only a small percentage of PD patients (around 16.4%) shows symmetric motor symptoms, compared to other parkinsonism. In a large clinical series of 1277 individuals diagnosed with PD, 46% met criteria for asymmetric disease, associated with a shorter disease duration, younger age at symptomatic onset, asymmetrical initial symptom onset, hand dominance and a positive self-reported family history of "other" neurodegenerative disorders. Hand dominance is related to the side of asymmetric

disease such that left-handed individuals tend to have more severe disease on the left side of the body [6].
Asymmetry of clinical features is a common finding in PD and many patients have not only unilateral motor symptoms but also non-motor deficits at the time of onset, while asymmetry may become less prominent over the course of the disease.
In early PD, the lateralization of brain activity during unilateral movement is significantly reduced, the disruption of the lateralized brain activity pattern may be a reason underlying some motor deficits, like mirror movements or impaired bilateral motor coordination.
The motor asymmetry observed in PD may serve as a clinical parameter to differentiate PD from other parkinsonian syndromes. Indeed, clinical asymmetry in PD can be even found at later stages of the disease, with more marked extrapyramidal involvement on the body side first affected.
In the literature, numerous studies based on different imaging techniques have investigated the issue of lateralization in patients with PD [6].
Various imaging techniques such as SPECT and PET studies using fluorine-18-labelled fluorodopa (18F-DOPA) have revealed reduced tracer uptake in the posterior putamen contralateral to the predominantly affected side in Parkinson's disease (PD). Shape analysis suggests a progressive medial-to-lateral involvement of the putamen, correlating with the distribution of dopamine transporter (DAT) depletion. PET studies in PD cases have shown lateralization of dopaminergic function, with different regions of the brain correlating with specific cognitive tasks [6].
Functional MRI investigations have demonstrated weakened lateralization of brain activity during movement in PD patients, suggesting compensatory efforts from cortical motor regions and the cerebellum.
Additionally, MRI studies have revealed significant differences in brain structures and iron deposition asymmetry between symptomatic and non-symptomatic hemispheres in PD patients. Proton MRI spectroscopy has shown metabolic differences between the ipsi- and contralateral substantia nigra (SN) of affected extremities [6].
Levodopa treatment has been found to provide additional dopaminergic input, improving movements for the more severely affected side, indicating asymmetry in the impact of reduced dopamine in the cortico-striatal system. Cortical degeneration in PD differs between cerebral hemispheres, with patterns of atrophy suggesting early susceptibility of the left hemisphere. Recent magnetoencephalographic studies have shown a direct relationship between symptom asymmetry and neuronal activity during movement in PD patients.
Overall, imaging studies provide insights into the asymmetrical nature of PD, influencing diagnosis, treatment, and understanding of disease progression [6].

Research questions

Starting from a dataset derived from the PPMI study, as described in the following section of this report, the objective of this work was to investigate dopamine brain lateralization and its relationship with demographical covariates and symptoms. Thus, the study has been divided into 2 phases. In the first step, the study focused on analyzing dopamine lateralization between the two hemispheres for both PD and HC cohorts, while the second phase considered cohorts' covariates and symptoms, to assess their relationship with lateralization.
The first phase of the study analyzed the asymmetry of brain hemispheres for HC and PD cohorts through the DATSCAN measures of DAT binding in the Caudate and Putamen, the brain regions involved in learning and in the regulation of voluntary movements. DATSCAN measures have been used for calculating Lateralization Indexes of the brain regions, to give a standardized measure of the asymmetry.
The second part of the research focused on the covariates and symptoms variables, aiming to investigate if and how dopamine function lateralization is linked to these variables in both cohorts. To address this question, analyses were conducted on the selected variables, using a regression model. Covariates included demographical variables and other parameters related to DATSCAN imaging technique. Symptoms variables - only evaluated on PD cohort - included metrics which evaluate PD symptoms, described by numerical scores based on the severity of the patient's condition. Some of these scores are grouped into multiple "Total Scores", such as NP1PTOT, NP2PTOT, and NP3TOT, which aggregate severity values for certain symptoms for each patient. These values were analyzed to investigate the association between PD symptoms and lateralization, as described in the following sections of the report.

METHODS

Statistical pipeline

From a practical standpoint, statistical analysis of this study – completely performed on MATLAB - began with the inspection and manipulation of the dataset, followed by inferential statistics, covariate analysis, and finally, a machine learning model was developed to confirm the results obtained and suggest a practical application of the findings.

The initial dataset was first reduced to only the variables of interest - including their categorization - and divided into the two cohorts of interest: Healthy Controls (HC) and Parkinson's disease (PD). The study then continued with the cleaning of NaN values and outliers' removal, followed by the calculation of lateralization indices. Subsequently, the study focused on verifying the lateralization hypothesis for healthy and Parkinson's patients using the Wilcoxon signed-rank test. The statistical characterization of the dataset finally verified standard analysis metrics and evaluated the correlation between variables. The study then focused, using a regression model, on analyzing the covariates and symptoms significantly related to lateralization indices. Finally, a machine learning model helped confirm the results and identify the best threshold for dividing the cohorts.

PPMI dataset

The dataset analyzed in this study originates from the PPMI study, an initiative launched by the Michael J. Fox Foundation in collaboration with a core group of academic scientists and industry partners. The aim of this project is to address the lack of biomarkers capable of predicting the diagnosis and progression of Parkinson's disease by building a publicly available dataset [7] for studies and publications. The full dataset is composed of 1556 patients and 158 features. The features cover a wide range of information about the patient's condition and symptoms evaluation (some of those both for PD and HC): demographics (such as age, sex, ethnicity), genetics (e.g.: family history of Parkinson's Disease or presence of a particular mutation), symptoms (MDS-UPDRS Scores, Hoehn-Yahr Stage, MoCA total score, etc.), binding ratios for interested brain areas with different biomarkers.

Data preparation

Out of all 158 variables, only a subset was selected for analysis in this study. The selection process retained only those variables considered relevant for the evaluation of lateralization, based on scientific literature [6]. All demographic and genetic variables were included to determine their significance in the covariate analysis. For symptoms' variables, only the most general and summary ones are kept, to avoid redundance. For imaging features, all MRI-related variables were excluded (as MRI was not considered in this study), keeping only SPECT-related variables. Specifically, the Striatal Binding Ratio values pertinent to the regions of interest for lateralization analysis (Caudate and Putamen) were included, as they are used to calculate the lateralization index. Additionally, features related to the quality and completeness of the acquisition were maintained to ensure the selection of the most informative patients. Subsequently, the categorical variables were categorized, and a new variable was calculated to describe the age of symptoms onset (SXAGE).

The patient selection process involved several exclusion criteria: patients from cohorts labelled as SWEDD and Prodromal are removed due to their small number, leaving only those classified under Parkinson's Disease (PD) and Healthy Controls (HC). Further exclusions regarded patients with a low DATSCAN quality rating (with lowest of quality considered inadequate for drawing reliable conclusions), those with incomplete DATSCAN data, and those who are left-handed or mixed handed; only right-handed individuals were retained to maintain homogeneity in handedness.

After this selection step, the dataset was split into 2 sub-datasets, separating the two remaining cohorts: Healthy Controls and Parkinson's Disease.

To address missing data, the percentage of NaN (Not a Number) values has been calculated for each variable. Variables with more than 40% NaN values, specifically NP4TOT (MDS-UPDRS Part IV Total Score) and LEDD (Levodopa Equivalent Daily Dose) for both PD and HC patients, were excluded from further analysis. Outliers' analysis has been conducted with the IQR method, removing patients with values out of the boundaries.

Next, lateralization indexes [8] were calculated to assess brain dopamine distribution asymmetries through the Striatal Binding Ratios: these indexes enclose the information of the dopamine disparity between the hemispheres and cover a range from -1

(left hemisphere completely dominant) to +1 (right hemisphere completely dominant). A value of 0 represents the perfect symmetry between the hemispheres, with no relevant dominance. For both the Caudate and Putamen regions, Lateralization Indexes were derived by taking the difference between the right and left values of Striatal Binding Ratio and dividing it by their sum [8].
Thus, the lateralization index for both regions was calculated as:

$$LI = \frac{SBR_R - SBR_L}{SBR_R + SBR_L}$$

Where SBR_R and SBR_L are the Striatal Binding Ratios for right and left hemisphere.
Descriptive statistics were then calculated for the lateralization indexes, to provide a preliminary overview about the characteristic and the distributions. Results has been reported in **Errore.**

Cohort	Lat.Idx.	Median	SD	Skewness
HC	LAT_IDX_CAUDATE	-0.01	0.05	-0.0126
	LAT_IDX_PUTAMEN	0.00	0.07	-0.1925
PD	LAT_IDX_CAUDATE	0.00	0.11	-0.1484
	LAT_IDX_PUTAMEN	0.04	0.20	-0.1022

Table 1: Main statistical parameters for Lateralization Indexes.

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Lateralization Analysis

After calculating the descriptive statistics and the initial inspection of the nature of the variables, the study proceeded with the core analysis: examining the lateralization indexes to evaluate any possible lateralization in the Putamen or Caudate regions, measured using the Striatal Binding Ratio.
This part of the analysis started from a Normality test: specifically, the Lilliefors test (*lillietest in MATLAB*) was performed on the four Lateralization Indexes (Caudate and Putamen, both for HC and PD) to examine their distributions. The Gaussianity test revealed that only one of the four lateralization indexes had a normal distribution. Therefore, to continue the inferential analysis and determine if there were statistically significant differences between the lateralization indexes, a non-parametric test (which does not require the assumption of Gaussianity) was necessary. As previously reported, the Lateralization Index can vary between -1 and +1: a value close to zero represents an absence of lateralization, whereas a lateralization index significantly different from zero indicates that the corresponding brain area shows lateralization. The study thus applied the One-Sample Sign test to verify whether the medians of lateralization indexes were significantly different from zero. For assessing these hypotheses in MATLAB, *signrank(x)* function has been used: this test proves the hypothesis that the data in the vector *x* come from a distribution whose median is zero and returns the p-value from the test. The symmetry hypothesis required for this text had been previously verified. The test revealed a significant difference in the median of the Lateralization Index for the Putamen for PD cohort (*p-value<0.05*), indicating that the lateralization index median is significantly different from zero in this group. Conversely, no significant difference between the SBR of the right and left hemispheres was found in healthy subjects, nor for the Caudate region in the Parkinson's disease cohort. The results for PD cohort confirm the expectations regarding the Caudate and Putamen regions [9].

Demographical Covariates and Symptoms Analysis

To explore patients' covariates and symptoms, a multicollinearity analysis was initially conducted using correlation plot and Variance Inflation Factor (VIF) analysis.
From a visual inspection, the correlation map of both PD and HC showed obvious signs of correlation between covariates such as sex, height and body weight. For PD patients, a high correlation was visible between SXAGE and ENROLL_AGE (age at enrolment). However, none of the two was removed since VIF analysis did not produce a value above the threshold for which variables can be considered highly correlated [10] due to the presence of patients for which the time of disease onset and the start of study participation differs. A visible difference in the maps of the two cohorts is the correlation between the Lateralization Indexes of Caudate and Putamen, which is absent for HC and high for PD (Figure 1).
The study of covariates influencing lateralization indexes was conducted using linear regression [10] analysis (*fitlm* in MATLAB) (Table 5). From the results obtained, only those with an F-statistic p-value less than 0.05 and regression coefficients p-values less than or nearly 0.05 were considered significant.
The findings indicated that no demographic covariate can be deemed significant for healthy controls. However, for PD patients, GENETICS (disease mutation) was the only significant covariate for the Lateralization Index of the Putamen.
Regarding Parkinson's symptoms, only NP3TOT is significant for the Lateralization Index of the Caudate.

For the Putamen, many models satisfied exclusion criteria. Among these, the one with the highest R-squared value is the combination of NP1PTOT, NP2PTOT, and NP3TOT (respectively, MDS-UPDRS Part I - Patient Questionnaire - Total Score, MDS-UPDRS Part II Total Score, MDS-UPDRS Part III Total Score).

	PD	HC
Age at enrolment	63.14 ± 9.36	62.10 ± 11.75
Education years	15.89 ± 3.46	16.25 ± 3.17
Age at symptoms onset	60.10 ± 9.94	

Table 22: Continuous demographical covariates.

		PD	HC
Sex	Female	208	61
	Male	357	108
Ethnicity	Asian	8	5
	Black	4	6
	Indals	1	1
	Unknown	7	1
	White	538	154
	Not Specified	7	2
Genetics	PARKIN	7	
	SRDC	415	
	LRRK2	94	
	SNCA	10	
	GBA	39	

Table 33: Categorical demographical covariates.

	PD
NP1PTOT	4.76 ± 3.61
NP1RTOT	1.53 ± 2.03
NP2PTOT	6.33 ± 4.77
NP3TOT	21.96 ± 10.01
MCATOT	26.62 ± 2.65
NHY	1.68 ± 0.50

Table 44: Symptoms for PD patients.

Machine Learning Model

After the statistical analysis, the study concluded with the implementation of a machine learning model, with just one input features: the Lateralization Index of Putamen. The model has been used to confirm the results obtained from inferential statistics and determine the optimal threshold for group division (comparing it with the 0.2 literature value [11][12]). Additionally, the study aimed to demonstrate a potential practical application of using the Lateralization Index.

ML models have proven to be valuable tools in enhancing diagnostic accuracy for PD diagnosis [13]. Various ML algorithms such as support vector machines (SVMs), decision trees, and neural networks have been applied to clinical and imaging data to differentiate PD patients from healthy controls, through several different data modalities (voice, EMG, MRI, SPECT, PET, etc.) [13].

Due to the imbalance of dataset in favor of the Parkinson's disease class, the whole imbalanced dataset (with a ratio of HC to PD equal to 1:3) has been under sampled, reducing the PD cohort, to guarantee

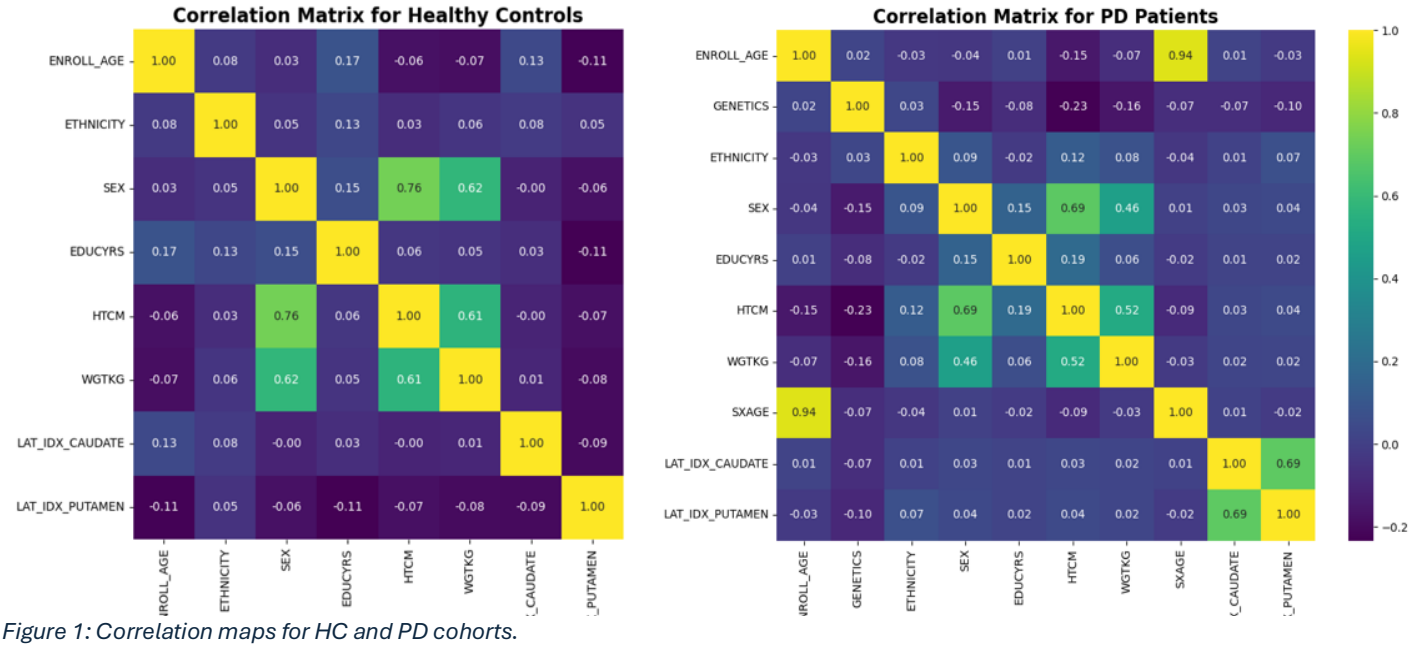

Figure 1: Correlation maps for HC and PD cohorts.

a more reliable model training [14]. In this way, the total dataset was composed of 339 patients: 169 for HC and 170 for PD cohorts.

To identify the most effective model for this study, several classifier models were initially trained, including K-Nearest Neighbors (KNN), decision trees, Random Forest, SVMs, and Neural Networks, using the *fitcauto* function, which can optimize hyperparameters automatically. A cross-validation partition (*cvpartition*) with 5 folds ensured robust training despite the small dataset.

Each model was evaluated based on its performance, taking into consideration all the main metrics. The *fitcauto* indicated the Random Forest classifier as the best-performing model, demonstrating superior accuracy and generalization capabilities compared to the other classifiers.

After training, the model's predictions on the test set were evaluated using standard performance metrics. The model achieved a test accuracy of 82.35%, indicating its overall correctness in predicting both Parkinson's disease cases and healthy controls. The precision of 88% highlighted an excellent proportion of correctly predicted positive cases among all predicted positive outcomes. Sensitivity, measuring the model's ability to correctly identify patients with Parkinson's disease, stood at 70.97%, while specificity reached 91.89%.

To determine the optimal threshold for classifying the groups, the Receiver Operating Characteristic (ROC) curve was analyzed using the *perfcurve* function. Youden's J statistic was used to identify the optimal threshold. Youden's index (J) [15] is defined as:

$$J = sensitivity + (specificity - 1)$$

and the optimal threshold is the point that maximizes J. The Area Under the Curve (AUC) [16] was found to be 0.95, indicating excellent model performance. The optimal threshold value for Lateralization Index, determined using Youden's J statistic, was identified and found to be 0.27.

The result confirms the literature threshold values, which sets the range between 0.2-0.3 [11] as the optimal threshold for considering significant lateralization. However, the limited data availability and the performance evaluation for sensitivity suggest areas for improvement in the model's performance, to increase the capacity of the model to detect patients affected by Parkinson's disease and reduce the number of false negative misclassifications.

RESULTS

The study aimed to investigate the lateralization of dopamine function in the brain and its relationship with Parkinson's Disease (PD). Using a comprehensive dataset from the Parkinson's Progression Markers Initiative (PPMI), a detailed analysis of dopamine lateralization in both healthy controls and PD patients was conducted, focusing on the Striatal Binding Ratio (SBR) values in the Caudate and Putamen regions.

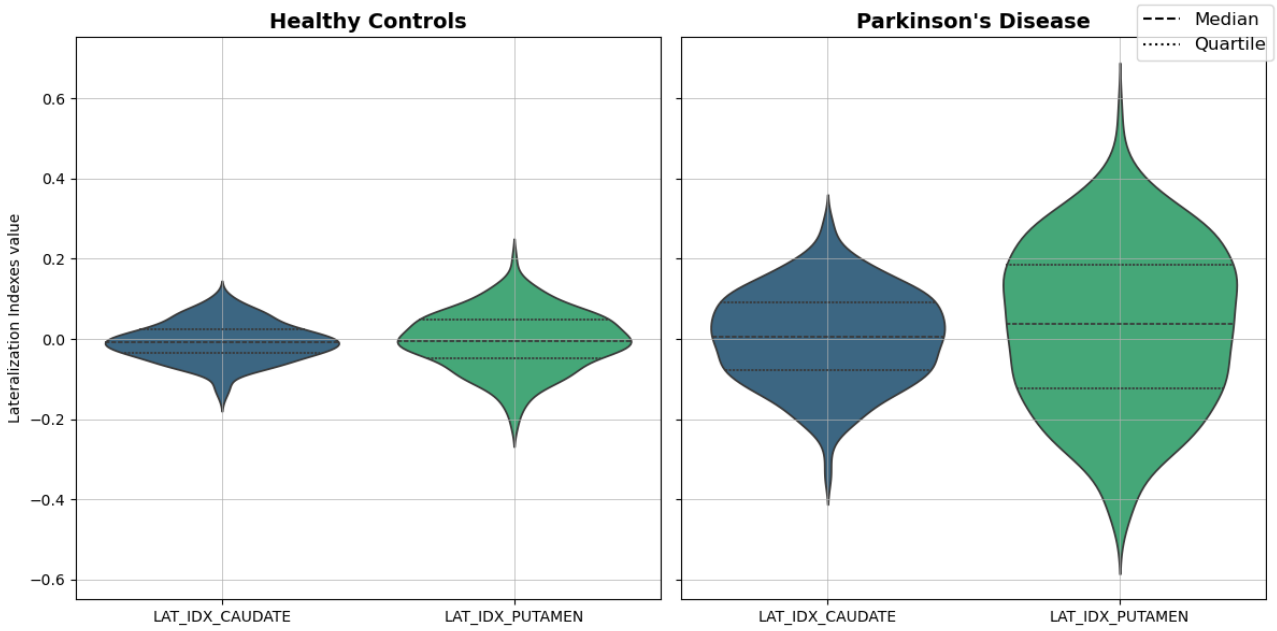

Figure 2: Lateralization Indexes distributions for Healthy Controls and Parkinson's Disease.

The analysis revealed significant lateralization in the Putamen region among PD patients compared to healthy controls. This finding underscores the asymmetrical nature of dopaminergic degeneration in PD, consistent with previous literature indicating a more pronounced loss of dopamine transporters in one hemisphere. The study also examined the effects of various covariates and symptom-related factors on lateralization, identifying genetics as a significant variable. Symptoms were also found to be correlated with the lateralization index.
The study concluded with a practical example of applying these findings through a machine learning model. The model confirmed the statistical results and demonstrated the potential use of the lateralization index of the Putamen region in diagnosing Parkinson's disease, achieving performances comparable to current diagnostic techniques. The ROC curve analysis suggested a threshold of 0.27 as the best threshold for separating the cohorts.

	Variable	Covariates	Coefficients p-values	F-statistic (p-value)	R^2
Demographical	LAT_IDX_PUTAMEN	GENETICS	0.0005, 0.0202	5.4169 (0.0203)	0.0095
Symptoms	LAT_IDX_CAUDATE	NP3TOT	0.0304, 0.0422	4.1452 (0.0422)	0.0073
	LAT_IDX_PUTAMEN	NP1PTOT	0.0005, 0.0138	6.1039 (0.0138)	0.0107
	LAT_IDX_PUTAMEN	NP1PTOT, NP2PTOT	0.0037 0.0016, 0.0461	5.0660 (0.0066)	0.0177
	LAT_IDX_PUTAMEN	NP1PTOT NP2PTOT NP3TOT	0.0004, 0.0019, 0.0111, 0.0413	4.7915 (0.0026)	0.0250

Table 5: Demographical covariates and symptoms analysis, linear regression results.

DISCUSSION

This study provides significant insights into the lateralization of dopamine function in the brain and its implications for Parkinson's Disease (PD). The findings highlight the asymmetric nature of dopaminergic degeneration, particularly in the Putamen region, among PD patients. This asymmetry aligns with previous research, which has consistently reported greater dopaminergic loss in one hemisphere.
Several key factors were identified as influencing dopamine lateralization, with genetics being a significant variable. This suggests a complex interplay of genetic factors in the progression of PD. Additionally, symptom-related factors were identified also as correlated with the lateralization index, indicating that the severity and type of symptoms may be influenced by the degree of dopaminergic asymmetry.
The practical implications of these findings are underscored by the application of a machine learning model to predict PD diagnosis based on the Lateralization Index of the Putamen region. This model confirmed the statistical results, demonstrating the potential of using Lateralization Indexes as a diagnostic tool. Such an approach could complement existing diagnostic methods, offering a non-invasive and cost-effective alternative. However, further investigations and additional models are needed to thoroughly assess the classification capability.
Future research should aim to validate these findings in larger, more heterogeneous cohorts and explore the underlying mechanisms driving dopaminergic lateralization. Additionally, longitudinal studies could provide valuable insights into how lateralization progresses over time and its relationship with disease severity and treatment response. Understanding these dynamics could enhance early diagnosis and lead to more personalized therapeutic strategies for PD patients.

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