

Automatic Classification and Prediction Models for Early Parkinson's Disease Diagnosis from SPECT Imaging

R. Prashanth^{a,1}, Sumantra Dutta Roy^a, Pravat K. Mandal^{b,c}, and Shantanu Ghosh^d

^aDepartment of Electrical Engineering, Indian Institute of Technology Delhi, India

^bNeurospectroscopy and Neuroimaging Laboratory, National Brain Research Centre, India

^cDepartment of Radiology, Johns Hopkins Medicine, Maryland, USA

^dMartinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Massachusetts, USA

Abstract

Early diagnosis of Parkinson's Disease (PD) is crucial for effective neuroprotection and early management. Recent neuroimaging techniques such as dopaminergic imaging using Single Photon Emission Computed Tomography (SPECT) with ¹²³I-Ioflupane (DaTSCAN) have shown to detect even early stages of the disease. In this paper, we use the Striatal Binding Ratio (SBR) values that are calculated from the ¹²³I-Ioflupane SPECT scans (as obtained from the Parkinson's Progression Markers Initiative (PPMI) database) for developing automatic classification and prediction/prognostic models for Early PD. We used support vector machine (SVM) and logistic regression in the model building process. We observe that the SVM classifier with RBF kernel produced a high accuracy of more than 96 % in classifying subjects into Early PD and healthy Normal; and the logistic model for estimating the risk of PD also produced high degree of fitting with statistical significance indicating its usefulness in PD risk estimation. Hence, we infer that such models have the potential to aid the clinicians in the PD diagnostic process.

Keywords: Computer aided Early Diagnosis, Parkinson's Disease, Risk Prediction, Pattern Analysis, Support Vector Machine, Logistic Regression

1. Introduction

Parkinson's disease (PD) is a severe progressive neurodegenerative disorder which is neuropathologically characterized by the loss of dopaminergic neurons in the substantia nigra which result in substantial reduction of dopamine content in the striatum (which is composed of caudate nucleus and putamen, and is the main output region of the substantia nigra), and a corresponding loss of dopamine transporters (DATs) (Booij, et al., 1997). Currently, there are no definitive tests for the diagnosis of PD, and the clinical diagnosis is based on the presence

¹ Corresponding author: Email: eez108051@ee.iitd.ac.in, Ph: +91-9891279885

Abbreviations: PD– Parkinson's disease, PPMI– Parkinson's Progression Markers Initiative, SPECT– Single Photon Emission Computed Tomography, SVM– Support Vector Machine, SBR– Striatal Binding Ratio

of cardinal symptoms (tremor at rest, rigidity, bradykinesia, postural instability) and the response of the subject to PD medications (mainly levodopa).

The clinical diagnosis is clear-cut in the advanced stage of the disease when the symptoms are full-blown. However, in the early stages of the disease, when the symptoms are mild/incomplete or subtle, an accurate diagnosis becomes difficult (Booij & Knol, 2007; Cummings, et al., 2011; Sixel-Doring, Liepe, Mollenhauer, Trautmann, & Trenkwalder, 2011; Tolosa, Borgh, Moreno, & Da, 2007). For instance, the Parkinson's Progression Markers Initiative (PPMI), which is the first large-scale study to explore and identify PD progression markers, points out that early diagnosis of *de novo* PD subjects, like those being recruited for PPMI, is difficult because characteristic signs and symptoms have not yet fully emerged and patients may present atypical signs and symptoms (PPMI Study Protocol, <http://www.ppmi-info.org/wp-content/uploads/2013/09/Attachment-4-PPMI-Protocol-AM6-V7-FINAL-Final.pdf>).

Early and accurate diagnosis of PD is crucial for several reasons: early management, avoidance of unnecessary medical examinations and therapies and their associated financial costs, side-effects and safety risks (Cummings, et al., 2011). Correct diagnosis is also critical for patients being recruited for clinical trials like the PPMI study. Single Photon Emission Computed Tomography (SPECT) with ^{123}I -Ioflupane (DaTSCANTM, GE Healthcare; also known as [123I]FP-CIT) has shown the potential to discriminate PD patients from healthy controls by depicting the presynaptic dopaminergic deficits in the caudate and putamen, even in the early stages of the disease and are becoming a valuable tool for the clinician (Bairactaris, et al., 2009; Benamer, et al., 2000; Booij, et al., 1997; Seifert & Wiener, 2013; Tolosa, et al., 2007; Winogrodzka, et al., 2001).

Diagnostic tools based on machine learning techniques such as the support vector machine (SVM) and multivariate logistic regression (MLR), are important as they could assist the clinician in the early diagnosis, treatment planning and monitoring of disease progression (Orru, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012). Both SVM as well as the MLR are increasingly used in neuroimaging studies due to the following advantages: they allow characterization at the individual level, rather than at group level, therefore yielding results with a potentially high level of clinical translation; and they are multivariate and supervised techniques which take into account characteristics of different distributed populations encoded in complex high-dimensional feature space and use them to train the model and then, categorize the data. SVM aims to find a hyperplane that classifies subjects into Early PD or Normal Control. On the other hand, MLR determines the probability of subject having PD that might be useful to classify subjects into different risk categories as studies suggest that the SPECT imaging using ^{123}I -Ioflupane can also depict the progression of dopaminergic degeneration in PD (Winogrodzka, et al., 2001).

Closely related work are that of Segovia et al. 2012, Illán et al. 2012, Rojas et al. 2013 and Towey, Bain & Nijran 2011. Segovia et al. 2012 extracted out the voxels corresponding to the striatum and then performed data decomposition using partial least squares followed by

classification into controls and Parkinsonian syndrome (PS) by means of an SVM classifier. Illán et al. 2012 also extracted the voxels corresponding to the striatum and then performed classification into controls and PS by using a SVM classifier with linear kernel. Rojas et al. 2013 also selected the voxels corresponding to the striatum and then carried out three experiments. One using all features followed by classification using SVM classifier. Two using reduced number of features through independent component analysis (ICA) followed by classification using SVM. Third using reduced number of features through principal component analysis (PCA) followed by classification using SVM. They observed that they obtained the highest accuracy with PCA. Towey, Bain & Nijran 2011 used information from all voxels to a feature extraction process through singular value decomposition followed by classification into PS or non-PS (this study did not include controls). These studies had the following three limitations: they used huge number of features which required effective feature reduction techniques and such techniques may cause loss of information which may affect in the decision making process; their data set was of limited size; and none of the studies concentrated on prognostic or prediction models for estimating the probability of PD in subjects that might be useful in categorizing subjects into different risk categories.

The contributions of the paper are as follows:

1. We use only four features which are the striatal binding ratio (SBR) values for each of the four striatal regions (left and right caudate, the left and right putamen) computed using either semi-automatic or highly accurate automated algorithms (Zubal, Wisniewski, Marek, & Seibyl, 2011), obtained from the PPMI (Kenneth Marek, et al., 2011) database, which is the first large-scale landmark study to identify progression biomarkers in PD, to develop automated classification and prediction/prognostic models which may aid the clinician in early diagnosis of the disease. We observe that the performance of SVM classifier using RBF kernel produced an accuracy which is higher than that obtained for the closely related works (Illan, et al., 2012; Rojas, et al., 2013; Segovia, et al., 2012; Towey, Bain, & Nijran, 2011).
2. The sample size used for the experiments is also the highest as compared to the related works (Illan, et al., 2012; Rojas, et al., 2013; Segovia, et al., 2012; Towey, Bain, & Nijran, 2011) and the PPMI database which we have used is an multi-centre international study involving subjects from different countries adding diversity in the database which was not there in related works, thereby making the models robust.
3. This is also first time that prediction/prognostic models based on SBR features for estimating the risk of PD is attempted using MLR and we observe the logistic model showed high performance with statistical significance indicating its usefulness in PD risk estimation.

The paper is organized as follows. Section 2 contains the flowchart of the analysis carried out and describes about the PPMI database, study cohort, SBR values, statistical analysis of features, classification and prediction/prognostic model design. Section 3 provides the results and discussion as observed from the experiments carried out. And finally we provide the conclusion of the work carried out.

2. Materials and Methods

A flow chart of the analysis that is carried out in the paper is shown in Fig. 1. We use the SBR values from the four striatal regions (left and right caudate, and left and right putamen) as obtained from the PPMI database for the experiments. All the four features are tested for statistical significance before performing classification and PD risk estimation.

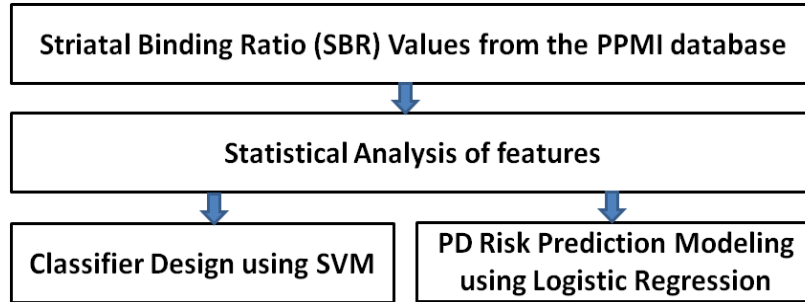


Fig. 1. Flowchart of the analysis carried out

2.1 Database and Study Cohort and details

Data used in the preparation of this article were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, please visit www.ppmi-info.org. The PPMI (Kenneth Marek, et al., 2011) is a landmark and first large-scale, comprehensive, observational, international, multi-center study to identify PD progression biomarkers to improve understanding of the disease etiology as well as effectiveness of disease modifying therapeutic trials. For our experiments, we used the Striatal Binding Ratio (SBR) values of the four striatal regions (left and right caudate, the left and right putamen) that were computed from DaTSCAN SPECT images and were available from the PPMI database.

The database was downloaded on 18th March 2013. As per this date, the database contained SBR values from 179 normal (total of 181 observations as two of the subjects were scanned at 12 months along with the scan at screening visit) and 369 early PD (a total of 493 observations) subjects (Table 1). As PPMI is a longitudinal study, the subjects are evaluated longitudinally, i.e., evaluations occur at screening/baseline and at 3 month intervals during the first year of participation and then every 6 months thereafter.

Table 1.

SBR values (mean \pm standard deviation) corresponding to right caudate, left caudate, right putamen and left putamen, for Normal and Early PD population. For the Early PD group, all the subjects were in their early stage of the disease (Hoehn and Yahr (HY) stage I and II) and the mean \pm standard deviation of the HY for the Early PD population is 1.58 ± 0.49 .

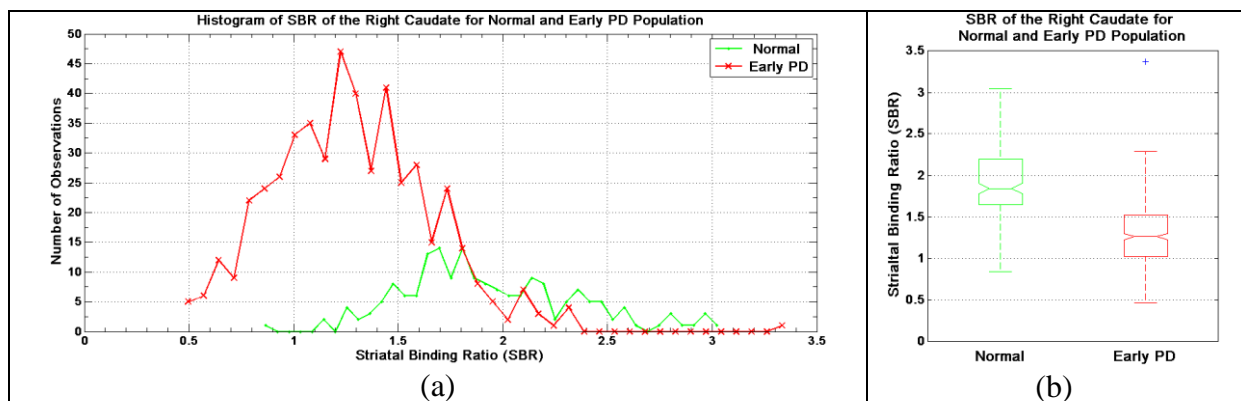
<i>Case</i>	<i>No. of Observations</i>	<i>right caudate</i>	<i>left caudate</i>	<i>right putamen</i>	<i>left putamen</i>
Normal	181	1.93 ± 0.42	1.91 ± 0.42	1.29 ± 0.40	1.33 ± 0.40
Early PD	493	1.28 ± 0.38	1.26 ± 0.36	0.63 ± 0.24	0.63 ± 0.25

The details of PPMI subject selection criteria, protocols in DaTSCAN imaging and the steps used by the Imaging Core (<http://www.ppmi-info.org/about-ppmi/who-we-are/study-cores/>) of the PPMI for calculating the SBR is provided in Appendices A, B and C respectively. The PPMI Central SPECT Core Lab reconstructed, attenuation corrected, and analyzed the data with a standardized region of interest template for the extraction of regional count densities in the left and right caudate and putamen. The SBR values are calculated for the right caudate, left caudate, right putamen and left putamen using occipital lobe region as the reference.

2.2 Statistical significance of SBR-based features

To assess the statistical significance of each of the SBR-based features (predictors), univariate logistic regression analysis (Bewick, Cheek, & Ball, 2005) was used. All statistical analysis was carried out using SPSS 21 software (SPSS Inc., Chicago, IL). The threshold of significance was defined as a value of $p < 0.05$.

Along with it, we also plot the histograms and notched box plots for each SBR feature to visualize distribution of a feature between Normal and Early PD population (Fig. 2). The notched box plots (Fig. 2 (b, d, f, h)) shows that notches of the two boxes corresponding to Normal and Early PD, are fairly separated indicating the significance of these features. The histogram plots (Fig. 2 (a, c, e, f)) show that amount of overlap of distribution between the normal and early PD groups. The overlap is relatively higher for the SBRs of the right and left caudate as compared to the SBRs of right and left putamen. The amount of overlap of the distribution of SBR measures determines the difficulty of the classification problem. Higher the overlap, the more difficult is the classification. The application of diagnostic tools comes into play here as they are capable of incorporating characteristics of these different distributed populations encoded in complex high-dimensional feature space, and using them to train the model and categorize the data.



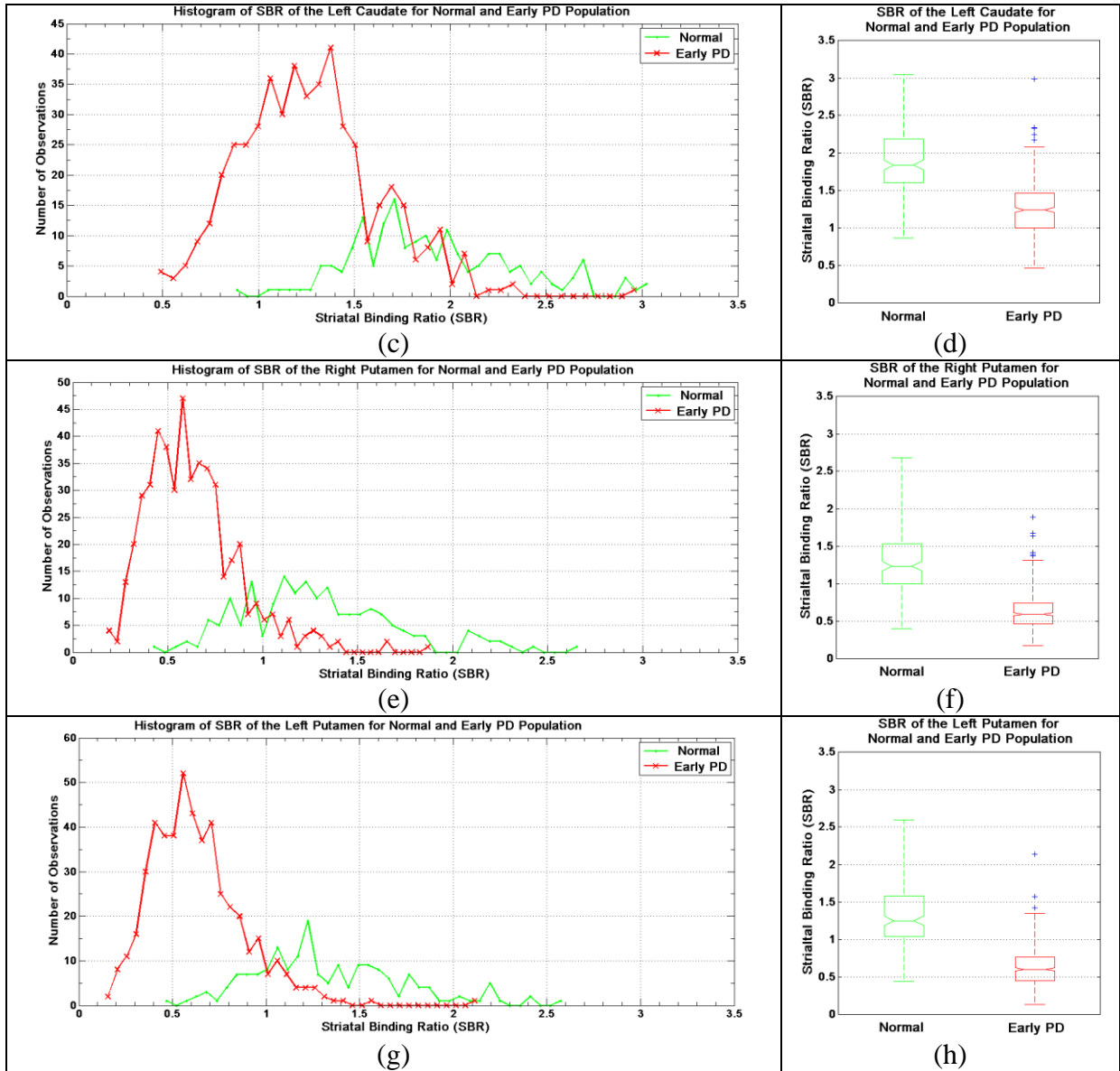


Fig. 2. Histogram plots and notched box plots² of the Striatal Binding Ratio (SBR) values for (a, b) right caudate (c, d) left caudate (e, f) right putamen (g, h) left putamen for Normal and Early PD population

2.3 SBR-based classification and prediction/prognostic modeling to distinguish Early PD from Healthy Controls

Among the techniques for model building, Support Vector Machine (SVM) and logistic regression are widely used in biomedicine (Dreiseitl & Ohno-Machado, 2002). SVMs are hard classifiers which directly target on the classification decision boundary without producing the probability estimation (Boser, Guyon, & Vapnik, 1992). On the other hand, logistic regression is a soft classifier which explicitly estimate the class conditional

² On each box of the notched box plot, the central mark is the median (q_2), the edges of the box are the 25th (q_1) and 75th (q_3) percentiles, the whiskers extend to the most extreme data points not considered outliers, and outliers are plotted individually. The extremes of the notches or the centers of the triangular markers correspond to $q_2 \pm 1.57(q_3 - q_1) / \sqrt{n}$ where n ($n=674$) is the number of observations.

probabilities and then perform classification based on estimated probabilities. The advantage with soft classifier techniques like the logistic regression is that, it produces output in the form of probabilities which enable us to categorize the subject into clinically-important categories based on the predicted probability. However, the classification accuracy with logistic regression can be lower because of their linearity as compared to SVM (as we see in Sections 3.2 and 3.3) as SVMs can nonlinearly map samples into a higher dimensional space, so it is able to handle the case when the relation between the class label and features is nonlinear. We used LIBSVM (Chang & Lin, 2011) for building the SVM classifier and SPSS 21 software (SPSS Inc., Chicago, IL) for developing the logistic model.

2.3.1 Automatic SVM-based Classification to classify Early PD from healthy controls

Support vector machines (SVMs) are supervised techniques for classification which finds a linear hyperplane (decision boundary) with the largest margin by mapping the input features to a higher dimension through either linear or non-linear kernel functions (Boser, et al., 1992).

Given training vectors (which are the observations) $\mathbf{x}_i \in R^d; i = 1, \dots, n$, where n is the number of observations which is 674 and d is the number of features which is 4), in two classes (Normal and Early PD) and the class label $\mathbf{y} \in R^n$ for each observation such that $\mathbf{y}_i \in \{\text{Early PD} = 1, \text{Normal} = 0\}$. In our case as the data is unbalanced for both the classes (different proportion of both classes: Normal, $n_1 = 181$ (26.85%) and Early PD, $n_2=493$ (73.15%)), we use the SVM formulation incorporating different penalty parameters for positive (Early PD) and negative (Normal) classes as described in (Chang & Lin, 2011; Osuna, Freund, & Girosi, 1997) as shown below

$$\min_{\mathbf{w}, b, \xi} \frac{1}{2} \mathbf{w}^T \mathbf{w} + C^+ \sum_{y_i=1} \xi_i + C^- \sum_{y_i=0} \xi_i \quad (1)$$

subject to

$$y_i(\mathbf{w}^T \phi(\mathbf{x}_i) + b) \geq 1 - \xi_i \quad ; \quad \xi_i > 0, i = 1, \dots, n \quad (2)$$

where C^+ and C^- are regularization parameters for positive and negative classes, respectively, ξ_i is called the slack variable, $\phi(\mathbf{x}_i)$ is a function that maps \mathbf{x}_i into a higher dimension feature space. The optimal \mathbf{w} obtained after solving, satisfies

$$\mathbf{w} = \sum_{i=1}^n y_i \alpha_i \phi(\mathbf{x}_i) \quad (3)$$

and the decision function is given by

$$\text{sgn}(\mathbf{w}^T \phi(\mathbf{x}_i) + b) = \text{sgn}\left(\sum_{i=1}^n y_i \alpha_i K(\mathbf{x}, \mathbf{x}_i) + b\right) \quad (4)$$

where $K(\mathbf{x}, \mathbf{x}_i)$ is the kernel function defined by $K(\mathbf{x}, \mathbf{x}_i) = \phi(\mathbf{x})^T \phi(\mathbf{x}_i)$ and α_i 's are the Lagrange multipliers used.

By using different kernel functions, varying degrees of nonlinearity and flexibility can be included in the model. For our experiments, we used the linear kernel defined by $K(\mathbf{x}, \mathbf{x}_i) = \mathbf{x}^T \mathbf{x}_i$, and the non-linear kernel of Radial Basis Function (RBF) defined by $K(\mathbf{x}, \mathbf{x}_i) = \exp(-\gamma \|\mathbf{x} - \mathbf{x}_i\|^2)$; $\gamma > 0$ for the SVM classifier. The classifier was evaluated using 10-fold cross validation.

2.3.2 Prediction/Prognostic modeling for Early PD using multivariate logistic regression

In this work, multivariate binomial logistic regression technique (Bewick, et al., 2005; Dreiseitl & Ohno-Machado, 2002; Kerr, et al., 2010) was used for developing prediction/prognostic models for the purpose of risk prediction in PD. Binomial logistic regression basically models the probability of occurrence of one (Early PD group) of the two classes of a dichotomous criterion.

A linear combination of predictors (features) is used to fit a logit transformation of the probability of Early PD for each observation (n_i) as

$$\text{logit}(\pi_i) = \ln\left(\frac{\pi_i}{1 - \pi_i}\right) = \alpha + \beta_1 x_{1i} + \dots + \beta_k x_{ki} \quad (5)$$

where π_i is the likelihood of subject outcome to be PD, for each subject (n_i), which is given by $\pi_i = P(y_i = 1 | \mathbf{x}_i, \boldsymbol{\beta}, \alpha)$; α is the intercept in the model which a constant and $\boldsymbol{\beta} = \{\beta_1, \dots, \beta_k\}$ are the regression coefficients and $\mathbf{x}_i = \{x_{1i}, \dots, x_{ki}\}$ are the features in the logistic model (can be interaction term also). The regression coefficients are estimated using maximum likelihood estimation, and then solving the logit in order to n_i , the probability of having PD for each subject, which is the risk predictor, is given by

$$\pi_i = \frac{1}{1 + \exp -(\alpha + \boldsymbol{\beta} \cdot \mathbf{x}_i)} \quad (6)$$

3. Results and Discussion

3.1 Statistical significance of SBR-based features

Table 2 shows the results of univariate logistic regression analysis performed on the four SBR features (right caudate, left caudate, right putamen and left putamen). It is observed that all of them are statistically significant with $p < 0.05$. Table 2 also shows the Nagelkerke R^2 values (Nagelkerke, 1991), which is a variation of index R^2 that is used in ordinary least squares (OLS) regression. It is observed that higher Nagelkerke R^2 values are obtained for putamenal SBR (both right and left) as compared to the caudate SBR indicating that putamenal SBR is more useful in discriminating healthy Normal and Early PD. This is also evident from the histogram plots where we observed lower overlaps for putamenal SBR (as shown in Fig.2 (e, g)) than for caudate SBR (as shown in Fig.2 (a, c)). We observe that this

finding goes with the findings from following studies (Kish, Shannak, & Hornykiewicz, 1988; Piggott, et al., 1999) which did post-mortem studies to demonstrate severe reductions in the dopamine concentration in the striatum of PD patients, with greater reduction in the putamen than the caudate.

Table 2

Result of statistical testing of each feature through univariate logistic regression using SPSS

<i>Predictor</i>	β	SE_{β}	<i>Wald</i>	<i>df</i>	<i>p-value</i>	<i>Nagelkerke R²</i>
right caudate	-4.137	.346	142.689	1	.0000	0.492
left caudate	-4.243	.351	146.220	1	.0000	0.499
right putamen	-6.367	.502	160.937	1	.0000	0.638
left putamen	-7.015	.568	152.625	1	.0000	0.682

Each feature was tested for statistical significance using univariate logistic regression analysis. The table does not show the constants (α 's) for each model. β is the value of the regression coefficient in the univariate model, SE is its standard error, Wald is the Wald test statistic, *df* is the degree of freedom, *p-value* is the significance of each regression coefficient, Nagelkerke R^2 is the pseudo- R^2 measure that is a variation of R^2 used in ordinary least squares (OLS) regression.

3.2 Automatic Classification and prediction/prognostic modeling for Early PD

We use SVM and multivariate logistic regression to develop models for distinguishing Early PD from healthy Normal. SVMs performed hard classification, where as MLR performed soft classification enabling us to develop prediction/prognostic model for PD risk estimation. We used SVM with RBF kernel and compared it with the SVM classifier with the linear kernel. Subsections below shows the performance measures obtained for the SVM classifiers and logistic model.

The highlights of the present study are that: We observe that the performance measure obtained by the SVM classifier using RBF kernel is highest among all the closely related works (Illan, et al., 2012; Rojas, et al., 2013; Segovia, et al., 2012; Towey, Bain, & Nijran, 2011). We used only four features without needing any feature selection techniques preventing any loss of information from the features. The sample size used for the experiments is also the highest as compared to the related works and the PPMI database which we have used is an multi-centre international study involving subjects from different countries adding diversity in the database which was not there in related works. This is also first time that prediction/prognostic models based on SBR features for estimating the risk of PD is attempted using MLR and we observe high performance from these models also.

3.2.1 SVM-based automatic classification to distinguish Early PD from Healthy controls

Table 3 shows the accuracies obtained during the 10-fold cross validation for the SVM classifier using RBF and linear kernels. Table 4 shows the confusion matrices for the SVM classifier with the RBF and linear kernel respectively. It is observed that the SVM classifier with RBF kernel (Accuracy = 96.14%, Sensitivity = 96.55% and Specificity = 95.03%) performs better than the linear one (Accuracy = 92.28%, Sensitivity = 95.33%, Specificity = 83.98%). This is because RBF kernel can nonlinearly map samples into a higher dimensional

space, so it is able to handle the case when the relation between the class label and features is nonlinear. Fig. 3 shows the box plot of SBRs for misclassified cases for the SVM classifier using RBF kernel which shows the cases misdiagnosed as PD had higher values of SBR than usual and cases misdiagnosed as healthy normal had lower values of SBR than usual.

Table 3

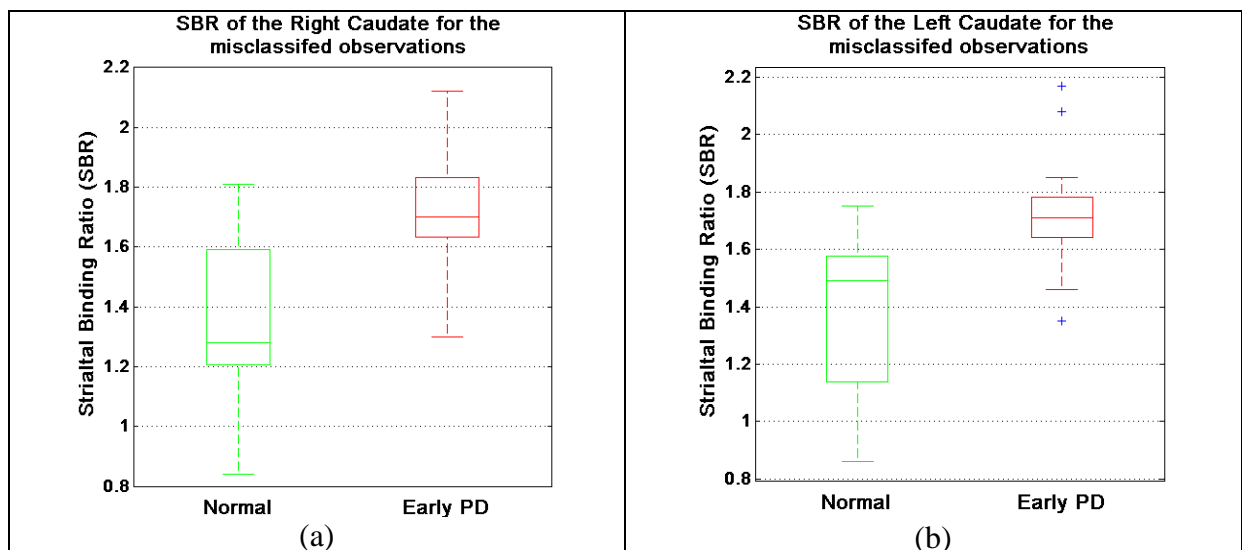
Accuracies (in %) obtained for the SVM classifier using RBF and linear kernel, for each fold during 10-fold cross-validation

<i>Fold No.</i>	<i>Accuracy(%)</i>	
	<i>RBF</i>	<i>Linear</i>
1	97.01	94.03
2	97.06	92.65
3	95.59	92.65
4	97.06	92.65
5	95.59	94.12
6	94.03	92.54
7	98.51	95.52
8	92.54	89.55
9	95.52	92.54
10	98.51	86.57
Mean Accuracy	96.14	92.28

Table 4

Confusion matrix components and performance measures for the SVM classifier with RBF kernel (SVM_{RBF}) and SVM classifier with Linear kernel (SVM_{Linear})

Classifiers	True Positive	False Negative	False Positive	True Negative	Accuracy (%)	Sensitivity (%)	Specificity (%)
SVM_{RBF}	476	17	9	172	96.14	96.55	95.03
SVM_{Linear}	470	23	29	152	92.28	95.33	83.98



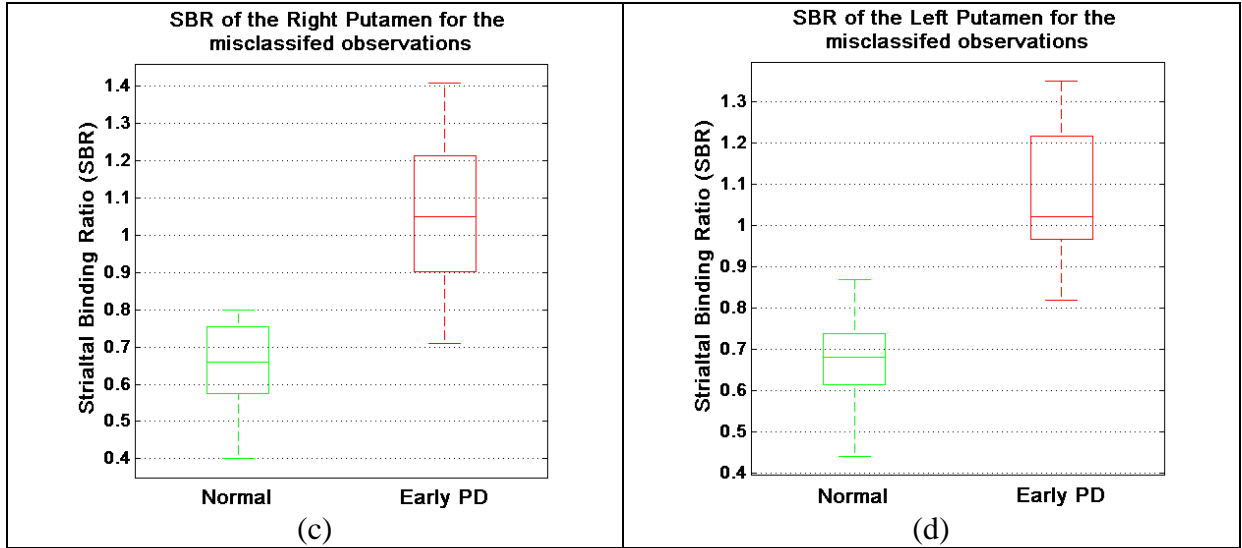


Fig. 3. Box plot of Striatal Binding Ratio (SBR) of (a) right caudate (b) left caudate (c) right putamen (d) left putamen for the misclassified samples from SVM classifier with RBF kernel.

3.2.2 Prediction/Prognostic modeling for Early PD using multivariate logistic regression

Prediction/prognostic modeling for PD risk estimation is carried out by using multivariate logistic regression analysis. A four-predictor (using all the 4 features) logistic model was initially fitted to the data. Table 5 shows the result of model and it is observed that two features (right caudate and left caudate) were not contributing to the model as per the p -value ($p > 0.05$), although they contain significant information to distinguish between Early PD and Normal as discussed in Section 3.1.

Table 5

Four-predictor logistic model developed using predictors of left putamen, right putamen, left caudate and right caudate SBR values

Predictors	β 's	SE_{β}	Wald	df	p-value	$exp(\beta)$ (odds ratio)	95% C.I. for $exp(\beta)$	
							Lower	Upper
Left putamen	-5.6938	0.92	38.12	1	0.0000	0.0034	0.00	0.02
Right putamen	-3.7380	0.83	20.36	1	0.0000	0.0238	0.00	0.12
Left caudate	0.5071	0.81	0.39	1	0.5337	1.6605	0.34	8.20
Right caudate	0.7960	0.82	0.94	1	0.3330	2.2167	0.44	11.11
Constant	7.4655	0.74	100.95	1	0.0000	1746.7824		

β is the value of the regression coefficient, SE_{β} is its standard error, Wald is the Wald test statistic, df is the degree of freedom, p -value shows the significance of each regression coefficient in the multivariate model.

To tackle this issue, instead of using these two features, we included the interaction term, which is the product of the two (right caudate*left caudate), and then fitted the model, which is now a three-predictor model. Table 6 show the results of this model fitting and it is observed that in this model all the three predictors (left caudate, right caudate and (right

caudate*left caudate)) were significantly contributing to the model ($p < 0.05$). The model, thus obtained was

$$\text{logit}(\pi_i) = 8.5132 - 5.8881 * \text{left putamen} - 3.7033 * \text{right putamen} + 0.4504 * (\text{left caudate} * \text{right caudate}) \quad (7)$$

According to the model, the log of the odds of the subject being Early PD was negatively related to both left and right putamen and positively to the interaction term (left caudate*right caudate). In other words, higher the SBR in the right and left putamen, the less likely that the subject has PD. Table 6 also shows that among the three predictors, the SBR corresponding to the left and right putamen had higher significance than the interaction term.

Table 6

Three-predictor logistic model through logistic regression using the predictors left putamen, right putamen and the interaction term which is the product of left and right caudate (left caudate*right caudate) SBR values.

<i>Predictors</i>	β 's	SE_{β}	<i>Wald</i>	<i>df</i>	<i>p-value</i>	$exp(\beta)$ (odds ratio)	95% C.I. for $exp(\beta)$	
							<i>Lower</i>	<i>Upper</i>
Left putamen	-5.8881	0.83	50.11	1	0.0000	0.0028	0.00	0.01
Right putamen	-3.7033	0.70	27.83	1	0.0000	0.0246	0.01	0.10
(Left caudate * right caudate)	0.4504	0.20	5.17	1	0.0230	1.5689	1.06	2.31
Constant	8.5132	0.66	167.41	1	0.0000	4980.0569		

β is the value of the regression coefficient, SE_{β} is its standard error, Wald is the Wald test statistic, df is the degree of freedom, p -value shows the significance of each regression coefficient in the multivariate model.

3.2.2.1 Evaluation of the logistic regression model

The evaluation of the model is carried out as given in (Peng, Lee, & Ingersoll, 2002)

(i) Overall Model Evaluation

Table 7 gives the overall test for the three-predictor logistic model. The Chi-square value of 455.985 with a $p < 0.05$ indicates that this model as a whole fits significantly better than a null model (model with no predictors).

Table 7

Omnibus Tests of Model Coefficients

	<i>Chi-square</i>	<i>df</i>	<i>p-value</i>
Step	455.9850	3	.0000
Block	455.9850	3	.0000
Model	455.9850	3	.0000

(ii) Statistical tests of individual parameters in the multivariate logistic model

The statistical significance of regression coefficients corresponding to each predictor is tested using the Wald chi-square statistic. As observed in Table 6, all the three predictors along with the constant, which is the intercept, are all significant ($p < 0.05$).

(iii) Goodness-of-fit statistics

The Goodness-of-fit statistics, through Hosmer and Lemeshow test (Hosmer & Lemeshow, 2000) and R^2 indices, assess the fit of a logistic model against actual outcomes. The Hosmer and Lemeshow test is a statistical test for goodness of fit for logistic regression models. In Hosmer and Lemeshow test, the data are divided into approximately ten groups and then chi-square statistics is calculated using the observed and expected number of cases in each group defined by increasing order of estimated risk. Table 8 shows the result of the Hosmer and Lemeshow test. It gave a small chi-square of 2.916 (with larger p -value closer to 1) with 8 degrees of freedom indicating that the actual outcome (Early PD or Normal) is not significantly different from those predicted risk and therefore, the overall model was well fit to the data. Table 8 also shows R^2 indices, defined by Cox and Snell (Cox & Snell, 1989), and Nagelkerke (Nagelkerke, 1991). These indices are variations of the R^2 that is defined for the ordinary least squares (OLS) regression model. Cox and Snell R^2 of 0.4916 and Nagelkerke R^2 of 0.713 indicates that the model is useful in risk prediction.

Table 8
Goodness-of-fit tests

1. Hosmer and Lemeshow Test

<i>Chi-square</i>	<i>df</i>	<i>p-value</i>
2.9162	8	.9395

2. Cox & Snell R Square = 0.4916

3. Nagelkerke R Square = 0.7149

(iv) Validation of the predicted probabilities

Logistic regression predicts the logit of an event outcome (Early PD or Normal) from a set of predictors. The predicted probabilities, which are obtained from the logit, can then be revalidated with the actual outcome to determine if high probabilities are indeed associated with higher risk of PD and low probabilities with lower risk of PD. The degree to which predicted probabilities agree with actual outcome is shown through a classification table as shown in Table 9. The overall classification accuracy was as high as 90.8 (with cutoff set as 0.5) indicating that the model with 3 predictors performs well in predicting the subject outcome. It is observed that the classification accuracy is not as high as that we obtained using SVM classifier with RBF kernel. This is because logistic regression models are discriminative models for classification that produces linear decision boundaries, and are not that flexible as the non-linear SVMs.

Table 9
Classification Table^a

Observed	Predicted		% Correct
	Normal	Early PD	
Normal	140	41	77.35
Early PD	21	472	95.74
Overall %			90.80

^acutoff value is 0.5.

Sensitivity = 95.74% , Specificity = 77.35%

To provide a visual demonstration of the correct and incorrect predictions, a histogram of the predicted risk probabilities is plotted (Fig. 4). It is observed that a U-shaped distribution with cases clustered at each end showing correct classification, indicating that the predictions are well-differentiated. Along with it, we also plotted these probabilities with the lowest putamenal SBR (Fig. 5). It is observed that all the observations now fit a logistic sigmoid. It is to be noted that as the logistic model is multivariate, the subject outcome (Early PD or Normal) is determined by all the three predictors used in the model. Fig. 5 is mainly for the purpose of visualizing the predicted probability and putamenal SBR was chosen in x-axis as it was more significant in risk prediction (as per Table 6).

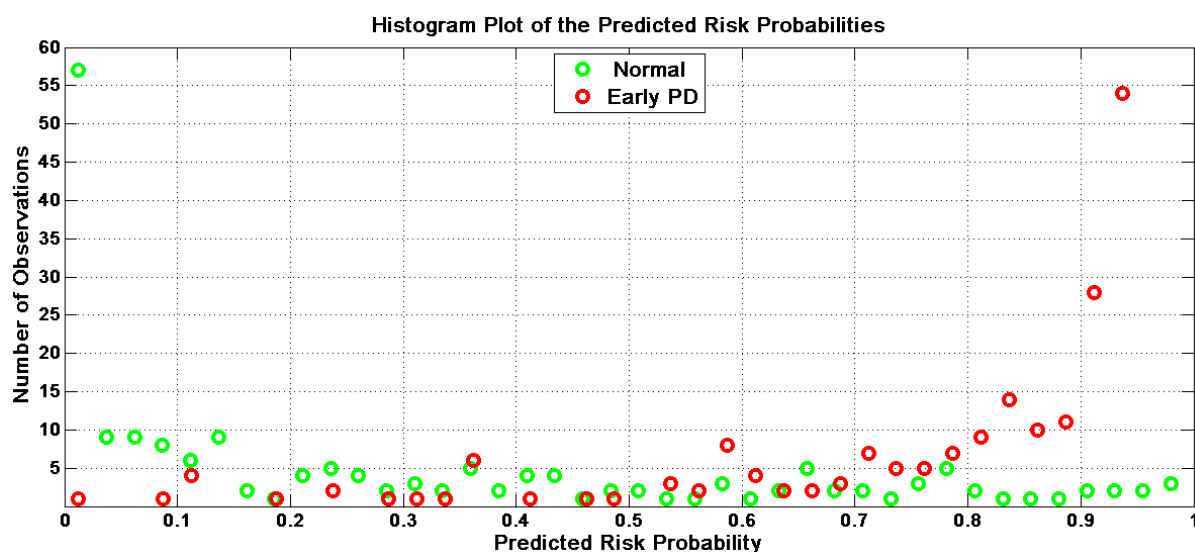


Fig. 4. Histogram of the predicted risk probabilities (plotted with 40 bins). The maximum limit of the y-axis was reduced to 60 for better visualization. The number of Early PD observations with the risk probability of 0.9615 (80 observations) and 0.9865 (218 observations) are not shown here. 0.9615 and 0.9865 are bin centers.

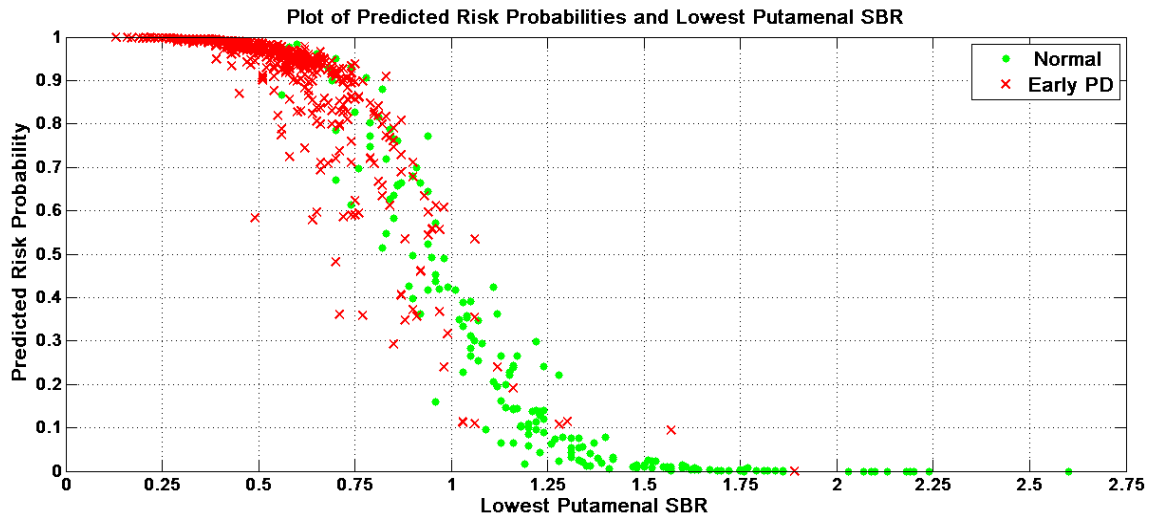


Fig. 5. Plot of the predicted risk probabilities against the lowest putamenal Striatal Binding Ratio (SBR)

3.3 Future Work

There are few other conditions other than PD, which show the similar clinical symptoms as in PD, such as Scans Without Evidence of Dopaminergic Deficit (SWEDD) and Essential Tremor (ET). Proper diagnosis of these conditions is very crucial as misdiagnosis as PD may lead to unnecessary medical examinations and therapies and associated side-effects. Other than the classification of Early PD patients from healthy Normal, these models may also find useful in the detection of SWEDD subjects and subjects with ET as they are likely to have normal SPECT scans as explained in the below subsections. The validity of these models in distinguishing Early PD from SWEDD or ET is to be carried out as our future work.

3.3.1 Application in distinguishing SWEDD subjects from Early PD

Dopaminergic studies have shown that approximately 10% of subjects thought clinically to have PD have normal dopaminergic functional imaging scans. These subjects are referred to as SWEDDs (Scans Without Evidence of Dopaminergic Deficit) (Schwingschuh, et al., 2010). There is substantial evidence which suggest that these subjects, most likely, do not have PD as long term follow-up of these subjects indicated poor response to PD medications (levodopa) (K. Marek, Jennings, & Seibyl, 2005) and lack of progression on sequential dopaminergic imaging (Schneider, et al., 2007). The SBR values for SWEDD are similar to healthy controls and cross-sectional data across an age range show a similar age-associated reduction as healthy controls (<http://www.ppmi-info.org/wp-content/uploads/2012/06/Seibyl-PPMI-MDS-2012.pdf>). The results of these studies indicate that abnormal dopamine transporter imaging (like DaTSCAN imaging using SPECT), at least in cases in which there is diagnostic uncertainty, is strongly supportive of a diagnosis of parkinsonism (Cummings, et al., 2011; Schwingschuh, et al., 2010). Distinguishing SWEDD subjects from PD is important as most of the subject receive unnecessary and inappropriate treatment for many years (Schwingschuh, et al., 2010). As the proposed classifier is able to distinguish a

abnormal scan (PD) from a normal scan with a high accuracy, such system may be useful in differentiating SWEDD from PD and act as an adjunct to other diagnostic evaluations.

3.3.2 Application in distinguishing Essential Tremor (ET) subjects from Early PD

Although distinguishing PD from essential tremor (ET) on a clinical basis is straightforward, ET is increasingly recognized as a heterogeneous disorder that can encompass features such as rest tremor which can challenge accurate diagnosis (Cohen, Pullman, Jurewicz, Watner, & Louis, 2003; Louis, 2009). In a study with 71 patients with ET, it was observed that about 1 in 3 patients with tremor was misdiagnosed as having ET, with most frequent false diagnosis being PD and dystonia (Jain, Lo, & Louis, 2006). A series of studies, cross-sectional and longitudinal, have shown a decrease in dopamine transporter density in PD patients compared to ET and no differences between ET and healthy controls (Benamer, et al., 2000; Doepp, et al., 2008; Isaias, et al., 2010). As the ET patients have scans in the normal range, the proposed classifier system may aid in distinguishing ET from PD and act as an adjunct to other diagnostic evaluations.

Conclusion

Early diagnosis of Parkinson's disease is of at most importance for early management and treatment planning as clinical symptoms in PD arise only when there is more than 60% loss of dopaminergic neurons. There are no laboratory tests for the diagnosis of PD causing a high rate of misdiagnosis especially when the disease is in the early stages and when the diagnosis is made by a non-specialist. Hence, diagnostic tools based on machine learning techniques are important as they can aid the clinician in the diagnosis process. Recent neuroimaging studies with SPECT using ^{123}I -Ioflupane (DaTSCAN) as radiotracer have shown to be a sensitive marker even in the early stages of the disease. In this work, we developed diagnostic models using machine learning techniques for classification into Early PD and healthy Normal as well as prediction/prognostication of PD. We use the striatal binding ratio (SBR) values for the four striatal regions (left and right caudate, and left and right putamen) obtained from the Parkinson's Progression Marker's Initiative (PPMI) database which is a landmark and first large-scale longitudinal study of PD to explore progression biomarkers. We observe that the SVM classifier using RBF kernel produced a high accuracy in classifying Early PD from Normal, and the prediction/prognostic model based using multivariate logistic regression also gave high performance along with statistical significance indicating the usefulness of the model in PD risk estimation. The contributions of the present study are 1) We obtained high classification performance using only four features without needing any feature selection techniques making the system simple. 2) The sample size used for the experiments is very high and the PPMI database which we have used is an multi-centre international study involving subjects from different countries adding diversity in the database and thereby making the models more robust 3) This is also first time that prediction/prognostic models based on SBR features for estimating the risk of PD is attempted using MLR and we observe high performance from these models also. Other than classifying Early PD from Normal, these models can also find useful in detecting Early PD from SWEDD subjects and subjects with Essential Tremor as these subjects are likely to have normal SPECT scans. Hence, we

infer from the study that these models have the potential to distinguish abnormal scans from Early PD from normal scans from healthy Normal or SWEDD subjects or subjects with Essential Tremor. Application of these models needs to be validated for SWEDD and ET conditions which we propose to carry out as the future work.

Author's Contributions

RP has setup the conceptual research design, did most of the data analysis and interpretation and wrote the first draft of the manuscript. SDR and SG collaborated on data analysis and in the writing and revision of the manuscript. PKM collaborated on the conceptual design of the research and in the critical revision of the manuscript for important intellectual content. PPMI provided the necessary data for analysis. All authors read and approved the final manuscript.

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Appendices

A. Subject Selection Criteria

The PPMI mainly concentrates in recruiting early-untreated PD subjects and age-matched healthy controls for the study. As per the PPMI subject selection criteria (Kenneth Marek, et al., 2011), PD subjects are recruited at disease threshold, i.e., they are required to have an asymmetric resting tremor or asymmetric bradykinesia or two of bradykinesia, resting tremor and rigidity with diagnosis within two years and to be untreated for PD (Kenneth Marek, et al., 2011). All subjects in the PPMI study undergo dopamine transporter (DAT) imaging and

DAT deficit was required for enrollment into PD category. Healthy subjects have no significant neurologic dysfunction, no first degree family member with PD and have Montreal Cognitive Assessment > 26 (Kenneth Marek, et al., 2011).

B. DaTSCAN Imaging

As per the PPMI Imaging Protocol (Schedule of Activities) (<http://www.ppmi-info.org/wp-content/uploads/2010/07/Imaging-Manual.pdf>), subjects with PD have DaTSCAN imaging at screening and at months 12 (Visit 4), 24 (Visit 6), and 48 (Visit 10) or at premature withdrawal (if a scan has not been completed in the last 12 months). Healthy control subjects have DaTSCAN imaging at screening. Prior to DaTSCAN injection, subjects are pretreated with saturated iodine solution (10 drops in water) or perchlorate (1000 mg.). The target dose for subjects is 185 MBq or 5.0 mCi of DaTSCAN. The dose range for injection is 111 to 185 MBq or 3.0 to 5.0 mCi of DaTSCAN. Subjects are imaged 4 ± 0.5 hours later.

Reconstructed SPECT scans from the PPMI Imaging sites are sent to the Imaging Core at Institute for Neurodegenerative Disorders (IND) in New Haven, CT for visual assessment to check for the evidence of dopamine transporter deficit. Two qualified readers assess each scan and their assessment must be in agreement. If the reader's assessments differ, the scan will be adjudicated and the agreed interpretation will be sent to the site. The imaging interpretation will serve as final criteria for enrolment into the study (<http://www.ppmi-info.org/wp-content/uploads/2013/02/PPMI-Protocol-AM5-Final-27Nov2012v6-2.pdf>). For each subject, the Imaging Core calculates Striatal Binding Ratios (SBR) values, which is the DaTSCAN uptake in the striata, relative to the DaTSCAN uptake in the occipital area and this ratio is the primary outcome that is used for quantitating dopamine transporters in suspected parkinsonian syndromes.

C. Striatal binding ratio calculation

For calculating the striatal binding ratio (SBR) from a specific region, the Imaging Core of the PPMI carried out following steps (http://www.ppmi-info.org/wp-content/uploads/2013/06/Seibyl-PPMI-MDS-2013-Sydney__sjl.pdf):

1. Central SPECT Core lab iteratively (HOSEM) reconstructs the data from raw projection data using HERMES (Hermes Medical Solutions, Skeppsbron 44, 111 30 Stockholm, Sweden) system.
2. The HOSEM reconstructed files were then transferred to the PMOD (PMOD Technologies, Zurich, Switzerland) for subsequent processing including attenuation correction based on phantoms acquired during the site visit.
3. Spatial normalization of image is carried out next to standard Montreal Neurologic Institute (MNI)space to create consistent orientation.
4. Next the transaxial slice with the highest striatal uptake was identified and the 8 hottest striatal slices around it were averaged in to generate a single slice image.
5. Apply standard region of interest template on the four striatal regions (left and right caudate, and left and right putamen), and the occipital cortex (reference region).

6. Extract count densities and calculate Striatal Binding Ratios (SBR) for each of the four striatal regions using:

Striatal Binding Ratios (SBR) = Specific striatal binding/occipital reference region
= (Total striatal count density – occipital count density)/ occipital reference count density