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Discrimination of idiopathic Parkinson's disease and vascular parkinsonism based on gait time series and the levodopa effect

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ABSTRACT

Idiopathic Parkinson's disease (IPD) and vascular parkinsonism (VaP) present highly overlapping phenotypes, making it challenging to distinguish between these two parkinsonian syndromes. Recent evidence suggests that gait assessment and response to levodopa medication may assist in the objective evaluation of clinical differences. In this paper, we propose a new approach for gait pattern differentiation that uses convolutional neural networks (CNNs) based on gait time series with and without the influence of levodopa medication. Wearable sensors positioned on both feet were used to acquire gait data from 14 VaP patients, 15 IPD patients, and 34 healthy subjects. An individual's gait features are affected by physical characteristics, including age, height, weight, sex, and walking speed or stride length. Therefore, to reduce bias due to intersubject variations, a multiple regression normalization approach was used to obtain gait data. Recursive feature elimination using the linear support vector machine, lasso, and random forest were applied to infer the optimal feature subset that led to the best results. CNNs were implemented by means of various hyperparameters and feature subsets. The best CNN classifiers achieved accuracies of 79.33%±6.46, 82.33%±10.62, and 86.00%±7.12 without (off state), with (on state), and with the simultaneous consideration of the effect of levodopa medication (off/on state), respectively. The response to levodopa medication improved classification performance. Based on gait time series and response to medication, the proposed approach differentiates between IPD and VaP gait patterns and reveals a high accuracy rate, which might prove useful when distinguishing other diseases related to movement disorders.

1. Introduction

Gait impairment is a common characteristic of patients with neurodegenerative parkinsonian syndromes, and it appears in the prodromal stages, with progressive evolution over time (Lord et al., 2013; Kubota et al., 2016; Ferreira et al., 2019; Rehman et al., 2019; Mirelman et al., 2019). Evidence suggests that gait assessment can be a useful tool to support the diagnosis of idiopathic Parkinson's disease (IPD) at an early stage (Rehman et al., 2019; Mirelman et al., 2019), along with the possibility of differential diagnosis of parkinsonian syndromes, such as IPD versus vascular parkinsonism (VaP) (Ferreira et al., 2019; Fernandes et al., 2018). However, the differential diagnosis between IPD and VaP is difficult to achieve, especially in the early stages, since these two diseases present highly overlapping phenotypes (Zijlmans et al., 2004; Lehosit, 2015). Both diseases are characterized by bradykinesia, rigidity, gait impairment, and postural instability. IPD is the most common parkinsonian syndrome, with a high prevalence of over 180/100000 inhabitants (Ferreira et al., 2017), while VaP is less frequent (3% to 5% of patients with parkinsonism) (Zijlmans et al., 2004). Compared to IPD patients, VaP patients often present less tremor but show frequent pyramidal tract signs and dementia. VaP patients also experience considerable gait difficulty when walking, with more extended legs, hips, and

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trunk and a prominent dragging of the feet, and a poorer response to levodopa medication (Zijlmans et al., 2004; Gupta and Kuruvilla, 2011; Ferreira et al., 2019).

To investigate the potential of gait data to discriminate between VaP and IPD, a previous study (Fernandes et al., 2018) evaluated the effectiveness of machine learning strategies, particularly multiple layer perceptrons (MLPs) and deep belief networks (DBNs), based on the different gait measures (per gait cycle) acquired through wearable sensors. Similar to previous studies (Tahir and Manap, 2012; Manap et al., 2011), the above approach achieved good classification performance (classification accuracy between 91.1% and 93.3%) in the ability to discriminate between normal and parkinsonian gait. However, when attempting to distinguish between VaP and IPD gait patterns, the performance of the classifiers decreased (with classification accuracy between 50% and 63.3%). Therefore, there is a need to develop new approaches when evaluating the potential of gait data as a tool to support the differential diagnosis between VaP and IPD. Traditional mean and standard deviation values of gait time series are used in the classification of different pathological gaits (Tahir and Manap, 2012; Manap et al., 2011; Wahid et al., 2015; Fernandes et al., 2018; Rehman et al., 2019). In a recent study (El Maachi et al., 2020), gait time series were used as input signals for automated IPD gait recognition. An accuracy of 98.7% was achieved using a convolution neural network-based approach. In contrast to most conventional methods, such as support vector machines (SVMs), random forest (RF), multiple layer perceptrons (MLPs), and deep belief networks (DBNs), convolutional neural networks (CNNs) are capable of automatic feature extraction from time/space series, eventually detecting superior features and eliminating the need for handcrafted feature engineering (Wang et al., 2019). This study introduced gait time series as input for the proposed approach based on CNNs. Furthermore, since the response to levodopa is considered a good biomarker for the diagnosis of VaP (Rektor et al., 2018)), the signals obtained in two different states—with and without the effect of levodopa–were considered.

Different factors, including age, sex, height, weight, and walking speed, can affect a subject's gait characteristics (Wahid et al., 2015; Wahid et al., 2016). The studies of Wahid et al. and Mikos et al. (Wahid et al., 2015; Wahid et al., 2016; Mikos et al., 2018) employed a multiple regression (MR) normalization method on gait data to minimize the effect of intersubject physical differences and self-selected speed. MR normalization was implemented in this study since, compared to other methods such as dimensionless equations and detrending methods, MR normalization achieved better results in reducing the interference of subject-specific physical properties and gait variables, thereby improving parkinsonian gait classification accuracy using machine-learning methods (Wahid et al., 2015). It has been shown that the accuracy of IPD diagnosis through SVM and RF approaches improves from 81% to 89% and 75% to 93%, respectively, when gait data are normalized using the MR approach (Wahid et al., 2015). As in (Wahid et al., 2015; Wahid et al., 2016; Mikos et al., 2018), here, age, height, weight, sex, and self-selected walking speed were used as independent variables. Additionally, this study included the subjects' stride length as an independent variable, since this variable has been shown to significantly affect foot clearance gait features (Alcock et al., 2018; Ferreira et al., 2019).

In this paper, we propose a new approach to gait pattern differentiation using CNNs based on time series gait data, which considers the effect of physical properties and response to levodopa medication. To the best of our knowledge, this is the first study that uses gait time series data and levodopa response in the prediction of IPD and VaP. The paper is organized as follows. Our experimental design and proposed approach are described in Section 2. The experimental results are presented in Section 3. A discussion based on the experimental results is presented in Section 4. Conclusions and future directions are described in Section 5.

2. Materials and Methods

2.1. Participants

VaP and IPD patients were consecutively selected from Movement Disorder outpatient consultations. In compliance with published clinical criteria (Zijlmans et al., 2004), the diagnosis was supported by retrospective clinical history, with a longitudinal reassessment of clinical diagnosis. The exclusion criteria for all patients were the presence of resting tremor, moderate-severe dementia (CDR>2), musculoskeletal disease, and overt clinical progression since diagnosis (Hoehn-Yahr>3). The number of VaP patients was generally low (compared to that of IPD patients), and the exclusion criteria further reduced the number of VaP patients who could be included in the study. To obtain a balanced dataset, the number of IPD and VaP patients should be approximately the same. At the end of the recruitment phase, gait data from 14 VaP patients and 15 IPD patients were collected (Table 1). Thirty-six healthy adults of different ages and sexes were also recruited for the collection of gait data for use in the data normalization process (Table 1). The local hospital ethics committee approved the study protocol, submitted by ICVS/UM and Center Algoritmi/UM. Written consent was obtained from all subjects or their guardians.

2.2. Gait data acquisition

Two Physilog® sensors (Gait Up®, Switzerland) were used to collect gait data. The sensors were attached to the dorsum of each shoe using two elastic bands. The sensors did not require any alignment or calibration before the measurement. The participants were asked to walk a 60-m continuous course (a 30-m corridor with one turn) at a self-selected walking speed. Patients were assessed twice: in the "off state", after 12 h without any medication; and in the "on state", 60 min after taking suprathreshold levodopa medication (150% of their usual morning dose). As in other studies (Thomas et al., 2017; Senek et al., 2017), a suprathreshold 50% increase in the morning levodopa dose was administered to assess the magnitude of change from the off to the on states, thus supporting clinical diagnosis (Albanese et al., 2001). An additional objective was the rapid achievement of the best possible simulation of dopaminergic transmission (Albanese et al., 2001), as some gait impairments may be refractive under low doses of levodopa (McKay et al., 2019). The data recorded by the two sensors were converted to the left and right gait time series per gait variable using gait analysis software (Gait Up®, Switzerland). The dedicated algorithms have been described elsewhere (Mariani et al., 2010; Mariani et al., 2012; Dadashi et al., 2014).

The collected spatial, temporal, and foot clearance gait variables used in this study were as follows: speed (velocity of one stride), cycle duration (duration of one stride), cadence (number of strides per minute), stride length (distance between successive initial ground contacts using the same foot), stance (percentage of stride that the foot is on the ground), swing (percentage of stride that the foot is in the air), loading (percentage of stance between the heel strike and the foot placed fully on the ground), foot flat (percentage of stance where the foot is fully on the ground), pushing (percentage of stance between the foot fully positioned on the ground and the toe leaving the ground), double support (percentage of stride that both feet touch the ground), peak swing

Table 1
Anthropometric data of healthy controls and parkinsonism study groups.

	Controls	IPD Patients	VaP Patients
Age (years)	52.76 ± 22.91	76.60 ± 4.29	80.53 ± 4.63
Weight (kg)	68.84 ± 10.28	73.24 ± 12.53	66.17 ± 10.38
Height (m)	1.68 ± 0.090	1.67 ± 0.082	1.61 ± 0.085
Sex (Female/Male)	23/13	4/11	6/8

(maximum angular velocity during swing), strike angle (angle between the foot and the ground when the heel hits the ground), lift-off angle (angle between the foot and the ground when the toes are leaving the ground), maximum heel (maximum height above the ground reached by the heel), maximum toe clearance 1 (maximum height above the ground reached by the toes after maximum heel strike), minimum toe clearance (minimum height of the toes during the swing phase) and maximum toe clearance 2 (maximum height above the ground reached by the toes just before heel strike).

2.3. Framework for classification modeling

The proposed framework for the classification of gait patterns uses convolutional neural networks (CNNs) (LeCun et al., 1989) based on gait time series and the effect of medication (Fig. 1). When the latter is eliminated, the proposed framework is simplified to perform classification modeling based only on off-state gait time series. In both cases, the gait time series data are preprocessed by using multiple regression normalization and feature selection approaches as a base before applying the CNN classifiers.

2.3.1. Multiple Regression Normalization

Each gait time series value was normalized using the following multiple regression model (Wahid et al., 2015):

$$\hat{y}_i = \beta_0 + \sum_{j=1}^{p} \beta_j x_{ij} + \varepsilon_i \quad (1)$$

where $\hat{y}_i$ represents the prediction for the dependent gait variable for the ith observation, x_{ij} represents the jth independent variable, β_0 represents the intercept term, β_j represents the coefficient for the jth physical property, and ε_i represents the residual error for the ith observation.

Previous studies have indicated that gait data are significantly affected by the subject's height, weight, age, sex (Senden et al., 2012; Dadashi et al., 2014; Wahid et al., 2016; Mikos et al., 2018), walking speed (Kirtley et al., 1985; Wahid et al., 2016; Mikos et al., 2018) and stride length (Alcock et al., 2018; Ferreira et al., 2019). Therefore, age, height, weight, sex, speed, and stride length were considered independent variables. The model's coefficients were estimated by using data on the mean values of the physical properties and gait features obtained from healthy adults. First, Pearson's correlation coefficients and scatter plots among all variables were generated to examine the associations between the variables. Regression models were computed for all combinations of independent variables that presented a linear relationship with the dependent variable. Variance inflation factors (VIFs) were calculated to check the presence of multicollinearity. All models with a VIF value greater than 3.3 (Kock et al., 2012) were excluded. Akaike's information criterion (AIC) and adjusted R^2 metrics were used to select the best-fit model. For each regression model, a normal quantile–quantile ($Q-Q$) plot of the residuals and a residual plot were generated to ensure the assumptions of normality of regression residuals and homoscedasticity, respectively. To identify influential outliers, standardized residual values were assessed (Tabachnick et al., 2007). In each subject group, the best-fit regression models were then used to normalize each gait variable by dividing the value of the original dependent gait variable, y_i, by the predicted gait variable from (1), $\hat{y}_i$, by:

$$y_i^n = \frac{y_i}{\hat{y}_i} \quad (2)$$

where y_i^n represents the normalized gait variable for the ith observation.

2.3.2. Feature selection

Gait data are characterized by the high correlation between features (Rehman et al., 2019; Fernandes et al., 2018). To prevent redundancy and overfitting, feature selection was performed based on the mean values of the gait characteristics in the off state (Fig. 1) to find the optimal combination of features for the CNN classifiers. The mean values were scaled to have zero mean and unit variance. Feature selection was conducted by using recursive feature elimination (RFE) through RF, linear kernel SVM (L-SVM), and Lasso. During each step, the optimal number of features was selected based on their contribution to the classification accuracy obtained through stratified 5-fold cross-validation (Granitto et al., 2006). The general algorithm for RFE can be described as follows: the first step consists of selecting an initial set of features and an assessment of the importance of each; subsequently, the least important feature is removed from the current set of features. This procedure is iterated on the pruned set until the desired number of features is obtained or when there is only one feature left.

2.3.3. Classification

CNN classifiers were trained through three different datasets: off state, on state, and off/on state. The CNN classifiers were implemented using two convolutional layers; the final feed-forward neural network was also present in two deeper hidden layers. Different configurations of hyperparameters were evaluated for the classification of IPD and VaP patients. Multiple combinations between the number of filters, convolution window size, stride length of the convolution operation, learning rates, dropout rates, and epochs were evaluated. In the case of multiple off/on state input data (Fig. 1), the CNN models shared the same hyperparameters. At each feature selection step, multiple configurations of CNN classifiers were implemented, and the classification performance was assessed. Finally, the optimal feature set was the one that achieved the best classification performance. The TensorFlow (Abadi et al., 2016), Keras (Chollet et al., 2015), and scikit-learn (Pedregosa et al., 2011) libraries within the Python programming language were used to develop and implement the classifiers.

To evaluate the performance of the different classifiers, the accuracy, specificity, sensitivity, precision, and F1 score metrics were computed (Hossin et al., 2015). In this case, a false negative indicated that the classifier incorrectly predicted an IPD patient as a VaP patient.

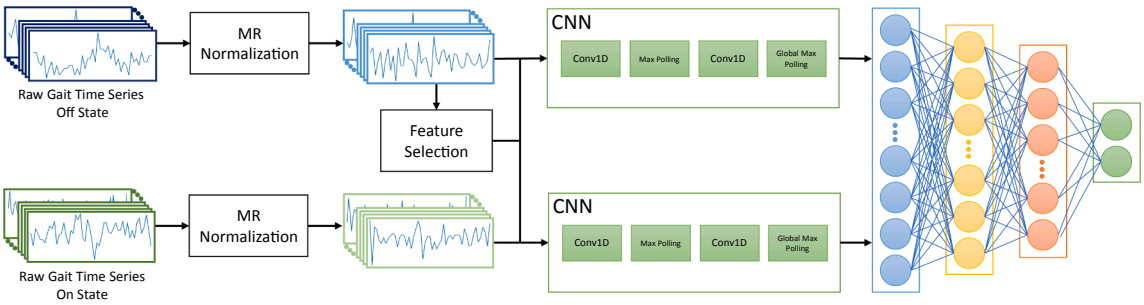

Fig. 1. The proposed framework for classification modeling using Convolutional Neural Networks (CNNs).

3. Results

3.1. Multiple linear regression models

The best multiple regression models of spatial and temporal gait variables include speed as an independent variable. In this study, stride length was included as an independent variable in the regression models of the strike angle, lift-off angle, and maximum toe clearance 2 (Table 2). With the exceptions of swing/stance (adjusted $R^2 = 0.227$), double support (adjusted $R^2 = 0.277$), and maximum toe clearance 1 (adjusted $R^2 = 0.006$), all the other models had adjusted $R^2 > 0.350$ (see Table 3). The best-fit models had one, two, or three explanatory variables, and all six independent variables were included more than once. No influential outliers were identified in any of these models.

3.2. Feature selection and classification

By resorting to RFE using RF, optimal performance was achieved with four gait variables (Fig. 2). When employing both Lasso and L-SVM, optimal performance was obtained with four and five gait variables, respectively (Fig. 2). Based on the importance of the features obtained through each of the three methods illustrated in Fig. 2, the results showed that strike angle, maximum toe clearance 2, maximum heel clearance, peak swing, and cadence were the five common gait variables among the top eight variables in each method. The best performances were achieved by the RF-CNN classifier with accuracies of 79.33%, 82.33%, and 86.00% without (off state), with (on state), and with the simultaneous consideration of the effect of levodopa medication (off/on state), respectively (Table 3).

4. Discussion

In this study, we developed a new approach using CNNs based on multiple regression-normalized gait data acquired through wearable sensors and the response to levodopa medication to classify and discriminate IPD and VaP gait profiles.

Following the normalization analysis, walking speed emerged as the final result of several spatial and temporal gait variables, thus justifying the use of speed in our MR models to predict other spatial and temporal variables (see Table 2). Indeed, previous studies have demonstrated that speed is correlated with most spatial and temporal gait variables (Bejek et al., 2006; Wahid et al., 2015; Wahid et al., 2016; Mikos et al., 2018), and differences between groups (healthy subjects versus osteoarthritis patients (Zeni and Higginson, 2009)) may even be significantly diluted after speed is taken into account. Overall, this supports the opinion that the definition of normality ranges for all gait variables should always be defined with reference to walking speed (Kirtley et al., 1985). Additionally, stride length was included as an independent variable for the development of the MR models. Stride length has been shown to affect some gait variables, more specifically foot clearance (Alcock et al., 2018; Ferreira et al., 2019). Our results corroborate this hypothesis, since the selected MR models for strike angle, lift-off angle, and maximum toe clearance 2 include stride length as an independent variable (Table 2). Furthermore, the MR models that best predicted foot clearance patterns included stride length as an independent variable. As such, future work addressing foot clearance should always take stride length into account.

The feature importance revealed by RF showed some similarities with the Lasso and L-SVM findings, although substantial differences were also present. These results might be explained by the fact that RF uses bootstrapping (sampling with replacement) to select the samples that are used to generate each decision tree. Furthermore, when generating each decision tree, only a subset of features is considered at each node when searching for the best node split (in the case of this study, only four features were considered at each node split). Another possible reason for the difference in results might lie in that RF is a nonlinear technique, while Lasso and L-SVM are both linear techniques. Given these results, if one is to gain sound knowledge of gait features and the habits of IPD and VaP populations, one should focus on the features that are consistently important across the feature selection techniques used: maximum toe clearance 2, cadence, strike angle, peak swing, and maximum heel clearance. However, since the gait features are highly correlated, it cannot be stated that these five are the only important gait features. When analyzing Pearson's correlation between gait features, one can conclude that some features, such as cadence and ground cycle duration, are highly correlated; therefore, if cadence is considered an important feature, then ground cycle duration should also be an important feature.

CNN classifiers showed higher performance on the off/on state than on the off state. These findings are consistent with the common clinical observation that VaP patients are less responsive or nonresponsive to

Table 2
Resulting multiple linear regression models for the gait variables. The adjusted R^2 and Akaike information criterion (AIC) are shown. The independent variables are age (A), height (H), speed/velocity (V), sex (S), weight (W) and stride length (SL).

Gait variable	Multiple Linear Regression Model							AIC	Ajusted R^2
Temporal Variables									
Cycle Duration	$= +0.84$	$-0.0011 \cdot A$	$+0.372 \cdot H$	$-0.286 \cdot V$				−143.71	0.771
Cadence	$= +137.86$	$+0.128 \cdot A$	$-42.44 \cdot H$	$+33.41 \cdot V$				197.76	0.776
Stance	$= +67.71$			$-5.933 \cdot V$				146.57	0.227
Swing	$= +32.28$			$5.933 \cdot V$				146.57	0.227
Loading	$= +16.72$			$+2.68 \cdot V$	$+2.41 \cdot S$	$-0.129 \cdot W$		154.30	0.363
Foot Flat	$= +63.20$	$+0.079 \cdot A$		$-17.73 \cdot V$		$+0.162 \cdot W$		190.02	0.662
Pushing	$= +21.81$	$-0.067 \cdot A$		$+14.88 \cdot V$		$-0.076 \cdot W$		181.53	0.600
Double Support	$= +35.78$			$-11.89 \cdot V$				187.90	0.277
Spatial Variables									
Stride Length	$= -0.23$	$-0.0014 \cdot A$	$+0.502 \cdot H$	$+0.611 \cdot V$				−126.29	0.928
Peak Swing	$= +154.26$			$+178.691 \cdot V$				340.04	0.570
Foot Clearance Variables									
Strike Angle	$= +16.14$		$-13.82 \cdot H$		$+3.83 \cdot S$		$+22.86 \cdot SL$	195.22	0.515
Lift-Off Angle	$= -28.99$	$+0.178 \cdot A$					$-35.40 \cdot SL$	214.51	0.767
MaxHC	$= +0.137$	$-0.00065 \cdot A$	$+0.085 \cdot H$		$+0.030 \cdot S$			−147.28	0.449
MaxTC1	$= +0.105$						$-0.027 \cdot SL$	−170.17	0.006
MinTC	$= +0.013$	$+0.0003 \cdot A$						−244.59	0.427
MaxTC2	$= +0.023$	$-0.00057 \cdot A$			$+0.024 \cdot S$		$+0.115 \cdot SL$	−181.17	0.736

MaxHC: Maximum Heel Clearance; MaxTC1: Maximum Toe Clearance 1; MinTC: Minimum Toe Clearance; MaxTC2: Maximum Toe Clearance 2.

Table 3
Performance measures obtained with each classifier trained based on the gait variables selected by the recursive feature elimination approach. All performance results are in percentage

Best Model	Accuracy	Sensitivity	Specificity	Precision	F1 Score
Off State					
Random Forest - CNN	79.33 ± 6.46	80.00 ± 16.33	76.67 ± 20.00	83.33 ± 13.94	78.29 ± 6.36
Lasso - CNN	78.67 ± 9.33	86.67 ± 16.33	70.00 ± 16.33	78.33 ± 11.30	77.95 ± 9.81
Linear SVM - CNN	75.33 ± 10.02	66.67 ± 0.00	83.33 ± 21.08	86.67 ± 16.33	74.71 ± 10.32
On State					
Random Forest - CNN	82.67 ± 10.62	86.67 ± 16.33	76.67 ± 20.00	83.33 ± 13.94	81.71 ± 10.90
Lasso - CNN	78.67 ± 9.33	86.67 ± 16.33	70.00 ± 16.33	78.33 ± 11.30	77.95 ± 9.81
Linear SVM - CNN	75.33 ± 10.02	80.0 ± 16.33	70.0 ± 16.33	76.67 ± 12.25	74.71 ± 10.32
Off/On State					
Random Forest - CNN	86.00 ± 7.12	80.00 ± 16.33	90.00 ± 20.00	95.00 ± 10.00	84.95 ± 7.95
Lasso - CNN	82.67 ± 10.62	86.67 ± 16.33	80.00 ± 16.33	83.33 ± 13.94	82.48 ± 10.62
Linear SVM - CNN	82.67 ± 10.62	86.67 ± 16.33	80.00 ± 16.33	83.33 ± 13.94	82.48 ± 10.62

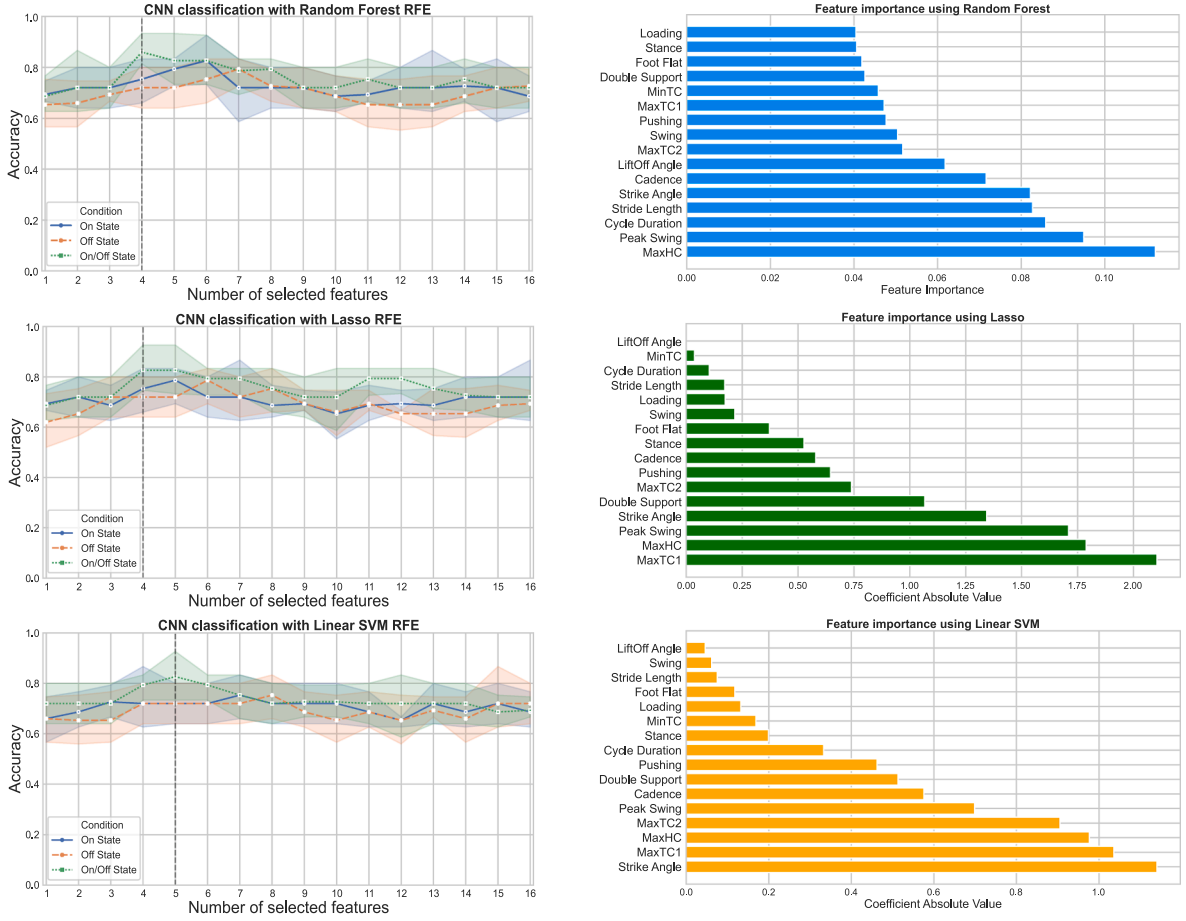

Fig. 2. Selection of optimal number of gait features (left) and feature importance results (right) obtained based on Random Forest feature importance, Least absolute shrinkage and selection operator (Lasso) coefficients and Support Vector Machine Linear Kernel coefficients.

levodopa medication (Thanvi et al., 2005; Lehosit, 2015), thus improving on the differences observed in patients with IPD. In a recent study (Fernandes et al., 2018), multiple layer perceptrons (MLPs) and deep belief networks (DBNs) were used for the classification of IPD and VaP patients based on gait characteristics (e.g., mean stride length), achieving accuracies of 63.88% and 72.81%, respectively. The superior classification performance reached in the models presented here may be explained by the fact that time series are better able to capture the underlying gait pattern differences between VaP and IPD patients. We hypothesize that this may also be explained by the high variability of walking events observed in IPD and VaP patients (Ferreira et al., 2019), indicative of the increased added value of using time series classifiers. In this study, the best CNN classifier was based on five gait features on the on/off state selected by the RF-RFE approach, with 86.00% ± 7.12 accuracy, 80.00% ± 16.33 sensitivity, and 90.00%±20.00 specificity. To the best of our knowledge, these results achieved by the CNN classifiers constitute the best classification performances obtained for the differentiation of IPD and VaP based on gait data. The five gait features differentiating VaP from IPD patients were stride length, maximum toe clearance 1, lift-off angle, strike angle, and loading. Our observation is consistent with previous work, showing that, characteristically, VaP patients have a shorter stride length, as well as a shuffling gait, which

causes foot clearance impairments; in contrast, IPD patients display higher stride length, speed, and foot clearance measures (Thompson and Jankovic, 1999; Lehosit, 2015; Ferreira et al., 2019).

Our work has some limitations that should be addressed. First, the regression models were based on a small control dataset, and only the independent variables presenting a linear correlation with each gait characteristic were considered. However, we noted that the same linear correlations were observed in the patient group, albeit with lower strength. Improved predictability of the regression models may be obtained with a larger number of control subjects. An additional limitation is that the present findings show good classification performance using the proposed approach only in the context of moderate stages of Parkinson's disease (Hoehn-Yahr < 3). Parkinson's disease is a progressive neurodegenerative disease that develops over several years and, on average, for more than a decade (Poewe et al., 2017). Typically, in early Parkinson's disease phases, patients present mild unilateral parkinsonian symptoms (e.g., bradykinesia, tremor and rigidity). Only after several years, in its moderate stages, do patients begin to present postural and gait impairments, although independent mobility is still preserved. In the absence of biological and imaging biomarkers, this clinical picture of a slowly progressive disorder is still the milestone of the differential diagnosis of Parkinson's disease and atypical parkinsonian disorders, such as VaP. In routine daily practice, it is still not uncommon for patients to seek medical assistance only during the moderate stages of Parkinson's disease, which, compounded by a lack of background history and future uncertainty, highlights the critical importance of clinical diagnosis. Moreover, since cerebrovascular disease is such a common medical phenomenon in the general population, there is growing evidence that patients may present mixed pathology (e.g., neurodegeneration caused by Parkinson's disease aggravated by vascular pathology (Rektor et al., 2018)). As such, even though the proposed approach may lack reproducibility in the early and late stages of Parkinson's disease, it is worthy of consideration for the moderate stages of Parkinson's disease, a phase during which a differential diagnosis of atypical parkinsonian disease will prove to be very important.

5. Conclusion

We have shown that the proposed framework using CNN classifiers based on gait variables and the response to levodopa can support the differential diagnosis between VaP and IPD with high accuracy. In this respect, time series gait analysis may better reflect stride inconsistency and variability related to cognitive dysfunction and/or the loss of automaticity, which is subjacent to different parkinsonism syndromes. Further studies using larger datasets of IPD and VaP patients are necessary to better corroborate the results regarding the set of gait variables that would best constitute potential biomarkers and their intercorrelation with higher-order cognitive dysfunction. Moreover, the results show that the proposed approach can discriminate the two overlapping pathologies with great accuracy, which justifies its application and evaluation in the discrimination of other movement disorders.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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