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Interplay between gait and neuropsychiatric symptoms in Parkinson's Disease

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Abstract

Parkinson's Disease (PD) is a neurodegenerative disease which involves both motor and non-motor symptoms. Non-motor mental symptoms are very common among patients with PD since the earliest stage. In this context, gait analysis allows to detect quantitative gait variables to distinguish patients affected by non-motor mental symptoms from patients without these symptoms. A cohort of 68 PD subjects (divided in two groups) was acquired through gait analysis (single and double task) and spatial temporal parameters were analysed; first with a statistical analysis and then with a machine learning (ML) approach. Single-task variables showed that 9 out of 16 spatial temporal features were statistically significant for the univariate statistical analysis (p-value< 0.05). Indeed, a statistically significant difference was found in stance phase (p-value=0.032), swing phase (p-value=0.042) and cycle length (p-value=0.03) of the dual task. The ML results confirmed the statistical analysis, in particular, the Decision Tree classifier showed the highest accuracy (80.9%) and also the highest scores in terms of specificity and precision. Our findings indicate that patients with non-motor mental symptoms display a worse gait pattern, mainly dominated by increased slowness and dynamic instability.

Key Words: Gait Analysis; Machine Learning; Parkinson's disease; Rehabilitation engineering.

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Parkinson's Disease (PD) is a progressive, disabling disorder and the second most common neurodegenerative disease after Alzheimer disease. PD clinical picture is characterized by a combination of motor (bradykinesia, resting tremor, rigidity, and stability impairment) and non-motor symptoms (cognitive decline, psychosis, autonomic symptoms, etc.) that worsen as the disease progresses. Among non-motor symptoms, neuropsychiatric symptoms, including cognitive impairment, depression, psychosis, apathy, are associated with worse quality of life, can significantly contribute to patient disability and even increase mortality.[1-3] Neuropsychiatric non-motor symptoms and gait in PD appear being closely related in a complex pattern. Gait is no longer considered as an automatic task, but an activity requiring multiple cognitive skills,[4] as a consequence, gait has been considered a reliable surrogate biomarker of cognitive decline in PD.[5] In addition, affective symptoms, like depression and anxiety and psychotic symptoms,[6-7] have been associated with gait dysfunction and instability in PD. Indeed, the relationship between neuropsychiatric symptoms and gait is quite complex, thus reflecting, at least to some extent, the progression of the neurodegenerative process involving non-dopaminergic networks and posterior cortical areas.[8-9] Gait analysis has been used for years to measure, describe and assess the human movement in a three-dimensional,

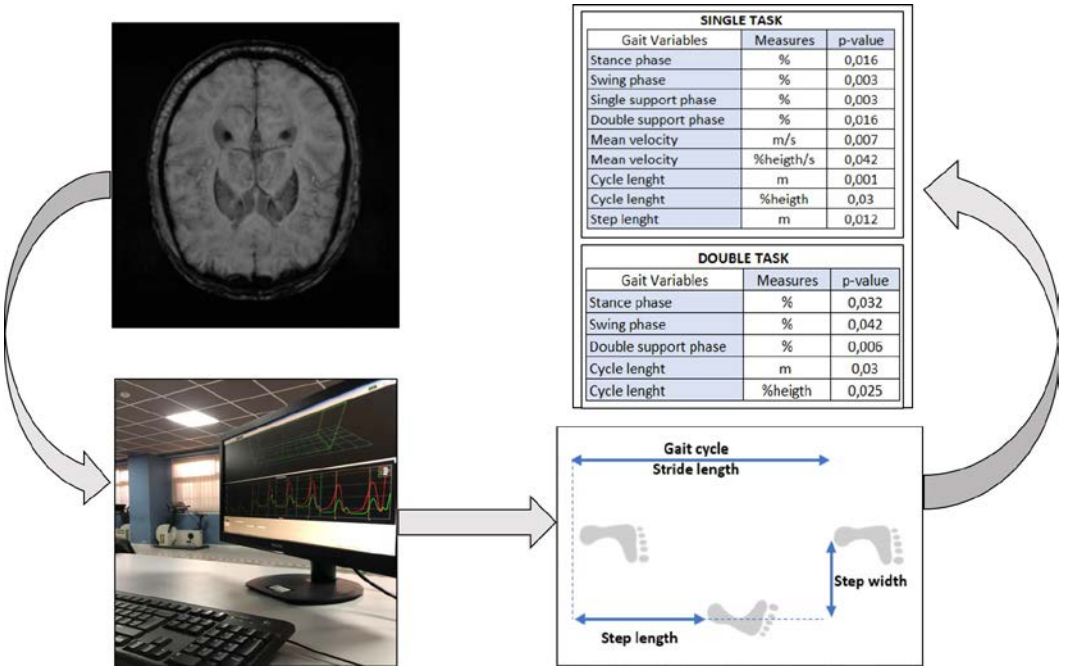

Fig 1. *Workflow of the research study*

computerized and non-invasive way. It has been used in literature to study neurodegenerative disease such as: Parkinsonism, Multiple Sclerosis, a progressive and demyelinating disease of the central nervous system, Progressive Supranuclear Palsy.[10-11] Similarly, machine learning (ML) has been employed for similar purposes; there are many combined uses of ML and gait analysis: some researchers tried to make an automatic diagnosis of PD, others focused on the classification of different Parkinsonism or the stages of PD through gait analysis features.[12-13] Others have explored the possibility to predict the presence of non-motor symptoms: Ricciardi et al. employed spatial and temporal features obtained through gait analysis to differentiate PD patients with and without mild cognitive impairment, implementing ML algorithms.[14]

The aim of this study is to employ spatial and temporal features obtained through gait analysis to find differences in patients with and without non-motor mental symptoms through a univariate statistical analysis and then implementing ML algorithms and help the clinicians into investigating the interplay between gait and neuropsychiatric symptoms in PD (Figure 1).

Materials and Methods

The dataset

The population of the present study was composed by 68 subjects, affected by PD according to the diagnostic criteria for PD established by the United Kingdom Parkinson's Disease Society Brain Bank.[15] Patients were consecutively enrolled among those referring to the Center for Neurodegenerative Diseases of the University of Salerno.

The study was performed in accordance with the 1964 Declaration of Helsinki and was approved by Campania Sud reference ethics committee of the Center for Neurodegenerative Diseases of the University of Salerno (04/12/2020, protocol number: 177). Written informed consent was obtained from all participants.

Inclusion and exclusion criteria are reported elsewhere.[16]

Motor and non-motor symptoms of PD were evaluated by means of Unified Parkinson Disease Rating Scale (UPDRS) and Hoehn and Yahr Scale (H&Y). The UPDRS is the most common clinical rating scale to define the severity of PD, which consists in the following parts: clinical assessment of mentation, behaviour and mood (UPDRS-Part I), auto-assessment of activities of daily living (UPDRS-Part II), motor examination (UPDRS-Part III) and the complications of therapy (UPDRS-Part IV).

Non-motor mental symptoms were recognized by the use of UPDRS-Part I. This is composed of two parts:

Part IA focuses on complex behaviours and includes six items, namely cognitive impairment, hallucinations and psychosis, depression, anxiety, apathy and impulse control disorders while Part IB is a component of the self-administered patient questionnaire that covers questions on non-motor experiences of daily living. In this study, the dataset was created by summing the scores concerning the first six items of the UPDRS part IA. Each item of the UPDRS Part IA may range from 0 (the symptom is absent) to 4 (the symptom is severe).

Thus, based on the clinical opinion of the relevance of non-motor mental symptoms, the patients were classified as follow, according to an arbitrary cut-off:

- Sum of the first six elements of UPDRS part IA ≥ 3 implied presence of clinically significant non-motor mental symptoms.
- Sum of the first six elements of UPDRS part IA < 3 implied absence of clinically significant non-motor mental symptoms.

Gait Analysis

Gait analysis was acquired for each patient through a BTS SMART DX System; it included six infrared cameras, two video cameras, two force plates, a set of passive markers and a data acquisition software (Smart Clinic). The Davis protocol was applied for all the acquisitions;[17] it consists of four phases:

1. Anthropometric measures, such as height and weight of the patient as well as the length of the leg, the diameters of the ankle and the knee and many others.
2. Positioning of 22 reflective markers on specific points along the body of the patients.
3. Standing phase.
4. Walking phase on a path of 10 meters at least 4 times for each patient for a total of 40 meters.

Patients' gait was assessed during 3 experimental conditions, in order to investigate the effect of the dual-tasks, as explained elsewhere:[3,18]

a. single task, GAIT (normal walking)
b. motor dual-task, MOT (walking while carrying a tray with 2 glasses filled with water)
c. cognitive dual-task, COG (walking while serially subtracting the number 7 starting from 100)

The variables acquired were 16 for each one of 3 tasks (GAIT, MOT, COG); these variables are extracted from both right side and left side, the mean of two sides is computed in order to obtain only 16 parameters for each trial. The final dataset is composed of 48 features (16 features x 3 tasks).

Tools, Techniques and Evaluation Metrics

First, the personal and clinical features of PD patients with and without non-motor mental symptoms were compared through a traditional statistical analysis: the U-test of Mann-Whitney was used to compare numerical variables, while the differences in the distribution of categorical variables were assessed by

Table 1. *Statistical analysis performed on the spatial and temporal features.*

Variables	Group with Non-motor mental symptoms (N=26)	Group without Non-motor mental symptoms (N=42)	p-value
Age	62.40 ± 8,36	64.39 ± 8,45	0.331
BMI	28.75 ± 4.02	27.19 ± 2.99	0.099
Gender (M/F)	13/13	33/9	**0,014**
Disease Duration	4.76 ± 2.78	4.95 ± 2.47	0.736
LEDD	600.44 ± 467.23	511.49 ± 349.06	0.649
Hoehn &Yahr	1.94 ± 0.36	1.77 ± 0.37	**0.045**
UPDRS –Part I	13.04 ± 5.86	4.40 ± 2.55	**0.000**
UPDRS-Part IA	5.70 ± 3.32	0.67 ± 0.754	**0.000**
UPDRS-Part IB	7.35 ± 3.49	3.74 ± 2.39	**0.000**
UPDRS –Part II	10.5 ± 6.87	5.76 ± 3.82	**0.003**
UPDRS –Part III	25.00 ± 10.08	21.31 ± 7.02	0.213
UPDRS –Part IV	1.96 ± 3.44	1.52 ± 2.59	0.787

In bold the significant statistical values with p < 0.05.

the chi-square test. The statistical significance was set at p-value < 0.05. The computation was supported by the Statistical Package for the Social Sciences (IBM SPSS v. 26). Then, a ML evaluation was performed through MATLAB (R2020b).[19-21] ML evaluation was carried out through the application of supervised learning algorithms on our dataset: Decision Tree (DT), K-Nearest Neighbour (KNN), Naïve-Bayes (NB), Support Vector Machine (SVM), Discriminant Analysis (DA), Random Forest (RF) and Boosted Tree (BT). For each algorithm, the performances have been evaluated through the "Leave-One-Out" cross-validation. It is a special cross-validation where the number of folds is equal to the number of records in the dataset. Therefore, all the data were used to train the dataset excluding one that is left out for the test; the procedure is repeated as many times as the number of patients. The Wrapper features selection method was applied on the whole dataset; this method allows to reduce the dimensionality of the dataset, composed by 48 features, in order to identify the main features for maximizing the accuracy of the classification. The evaluation metrics employed

Table 2. *Statistical analysis on clinical and personal data*

Features [u.m.]	**Mean values*** **p-value**		
	GAIT	**MOT**	**COG**
Cycle Duration [s]	1.10 ± 0.09 / 1.10 ± 0.11 0.724	1.09 ±0.07 /1.08 ±0.12 0.905	1.19±0.15/1.15±0.14 0.367
Stance Duration [s]	0.68 ± 0.07 /0.66 ± 0.07 0.283	0.66 ± 0.06 /0.66 ± 0.08 0.423	0.74±0.10/0.71±0.09 0.154
Swing duration [s]	0.43 ± 0.03 / 0.44 ± 0.04 0.053	0.46 ± 0.21 / 0.43 ± 0.05 0.709	0.29±0.10/0.27±0.10 0.545
Swing Duration Variability [s]	0.05 ± 0.07 / 0.03 ± 0.02 0.677	0.04 ± 0.02 /0.03 ± 0.02 0.256	0.12±0.06/0.11±0.04 0.316
Stance Phase [%]	60.81±2.79/60.20 ± 1.36 **0.016**	61.13 ±2.06/60.46± 1.85 0.143	62.652.28±/61.57±1.94 **0.032**
Swing Phase [%]	38.55±1.87/39.82 ± 1.36 **0.003**	38.87±2.06/39.61 ± 1.75 0.106	37.57±2.27/39.19±4.47 **0.042**
Single Support Phase [%]	38.29±2.86/39.84 ± 1.36 **0.003**	38.88 ±2.05/39.65± 1.85 0.124	37.69±2.40/38.17±2.62 0.169
Double Support Phase [%]	11.07±1.94/10.55 ± 2.90 **0.016**	12.15±2.79/11.41 ± 3.11 0.100	14.09±4.11/12.01±2.21 **0.006**
Mean velocity [m/s]	0.95 ± 0.16 / 1.07 ± 0.14 **0.007**	0.95 ± 0.19 /1.05 ± 0.16 0.065	0.83±0.19/0.91±0.17 0.152
Mean velocity [%height/s]	58.58±11.51/63.05±7.64 **0.042**	58.98±10.83/61.61±8.81 0.600	52.01±12.68/53.98±9.70 0.405
Cadence [steps/min]	107.31±11.09/110.46±11.46 0.408	111.15±7.48/112.14±12.62 0.910	103.40±12.78/106.06±13.12 0.412
Cycle Length [m]	1.05 ± 0.14 / 1.16 ± 0.13 **0.001**	1.03± 0.17/1.12±0.14 **0.030**	0.97±0.16/1.04±0.18 0.071
Cycle Length [%height]	65.02 ± 11.17/68.66±6.78 **0.030**	63.79± 11.46/66.10±7.90 0.226	60.34±12.65/61.33±9.94 0.357
Step Length [m]	0.49 ± 0.10 /0.54 ± 0.13 **0.012**	0.48±0.11/0.54±0.10 **0.025**	0.38±0.13/0.33±0.12 0.061
Step Length Variability [m]	0.22 ± 0.47 / 0.24 ± 0.47 0.553	0.22±0.59/0.11±0.21 0.119	0.30±0.30/0.17±0.12 0.226
Step Width [m]	0.39 ± 1.55 / 0.31 ± 1.37 0.589	0.40±1.55/0.10±0.04 0.819	0.14±0.15/0.10±0.05 0.603

u.m. = unit of measure

**Mean ± std.dev. of the group with and without non-motor mental symptoms, respectively*

In bold the significant statistical values with p < 0.05.

in this study were: accuracy, that is the most general one to indicate how many correct classifications are achieved; specificity and sensitivity, that are specific of the medical field; precision, that is a measure of the positive patterns correctly predicted from the total predicted patterns in a positive class; Area Under the Receiver Operating Characteristic (AUCROC), that is a qualitative indicator for binary classification ranging from 0 to 1 where 1 is the best result.

Results and Discussion

Among the 68 PD patients, 26 were classified as subjects with clinically significant non-motor mental symptoms and 42 as subjects without clinically significant non-motor mental symptoms, according to the above-mentioned criteria. The two groups were compared on personal data (Body Mass Index (BMI), age and disease duration), clinical data (Levodopa Equivalent Daily Dose (LEDD), H&Y scale, UPDRS scale) and spatial and temporal gait parameters for each task. Table 1 shows personal and clinical features of the two groups. The two groups did not differ in age (p-value=0,331), BMI (p-value=0,099), disease duration (p-value=0,736), antiparkinsonian treatment (p-value=0,649), UPDRS III and IV scores (p-value=0,213 and p-value =0,787,respectively). As expected, the UPDRS I and II scores (p-value=0,000 and p-value =0,003,respectively), which contains several items related to mental status and disability, were significantly increased in the non-motor mental symptoms group that also displayed more advanced stage as indicated by higher H&Y scale (p-value=0,045) in line with the findings that neuropsychiatric symptoms are associated with worse disase progression. Comparing gender distribution, the two groups significantly differed, with female gender being less frequent in the group without non-motor mental symptoms. This finding is consistent with the observation that female sex is associated with worse outcomes for hallucinations and depression.[22]
Accordingly, we speculate that such differences are not confounding factors but features associated with the categorization. Our findings indicate that patients with non-motor mental symptoms display a worse gait pattern, mainly dominated by increased slowness and dynamic instability. It is worth noting that the two groups mostly differed on gait parameters during the single task, maybe suggesting a general disease-related effect of the dual task overcoming the possible difference between the two groups. Interestingly, when analysing the effect of the secondary tasks, our findings suggest that the two dual-tasks seem exert quite different effects on gait. In particular, the MOT task mostly affected the pace domain, whereas the COG task primarily impaired dynamic stability. One potential explanation of these results could be related to the different resources required to perform the secondary task.[18]
The results of the analysis regarding the spatial and temporal features are shown in Table 2. During GAIT task the group with non-motor mental symptoms as compared with the group without showed increased stance phase with consequent reduced swing phase, augmented double support phase counterbalanced by reduced single support phase, reduced velocity and reduced pace-related spatial variables and step length. In the MOT task, only spatial features, namely cycle and step length, continued to result significantly different between the two groups; whereas in the COG task, only temporal variables, i.e., stance phase, swing phase and double support phase, remained different between the two groups (Table 2).
As regards the ML analysis, Table 3 shows the results obtained through the analysis performed through the WRAPPER features selection method. The best

Table 3. *Evaluation metrics obtained in the ML analysis per each algorithm.*

Classifier	Accuracy [%]	Sensitivity [%]	Specificity [%]	Precision [%]	AUCROC
DT	80.9	88.1	69.2	82.2	0.737
KNN	72.1	97.6	30.8	69.5	0.586
NB	70.6	80.9	53.8	73.9	0.674
SVM	75.0	90.5	50.0	74.5	0.683
DA	70.6	80.9	53.8	73.9	0.680
RF	77.9	90.5	57.7	77.5	0.727
BT	70.6	78.6	57.7	75.0	0.794

accuracy was obtained by employing the DT algorithms (80.9%), which also showed the highest scores in terms of specificity and precision. The sensitivity was particularly high in the KNN algorithm (97.6%), but it showed the lowest specificity (30.8%), AUCROC (0.586) and precision (69.5%) if compared with the other classifiers. Similarly, the SVM showed a high sensitivity (90.5%) and a low specificity (50.0%). The NB and the DA classifiers obtained the same scores in each metric, except for the AUCROC (0.674 and 0.680, respectively). The BT showed the highest AUCROC score (0.794).

Moreover, the Wrapper identified for each classifier the best spatial temporal features, which allowed to define the gait pattern of patients with non-motor mental symptoms. In particular, 15 spatial temporal variables have been selected among the three different tasks, the common features belonged to GAIT task and are the following:

- Stance Phase (%),
- Swing Phase (%),
- Swing Duration Variability (s),
- Mean Velocity (s),
- Double Support Phase (%),
- Step Length (m).

Overall, by comparing the previous list with the results of Table 2, it is worth noting that these variables matched the most of the significant variables (p-value<0.05) of the statistical analysis, but ML selected also the "Swing Duration Variability", which confirmed the potentiality of ML in pointing out the most important spatial temporal features. In addition, analysing the frequencies of the variables from all the algorithms, "Mean Velocity" and "Swing Duration Variability" were the most selected, indicating that a raw measure of slowness (Table 2), i.e., velocity, coupled with an indicator of instability, and swing duration variability,[23] are the features better distinguishing PD patients with and without non-motor neuropsychiatric symptoms. Previously, Ricciardi et al. identified cognitive impairment in PD patients using quantitative gait variables during different tasks and throught three ML algorithms (DT with an accuracy of 86,8%, RF with 82,4% and KNN with 83.8%).[12] The present study shows that using spatial and temporal variables as input of ML algorithms allowed to display good accuracy, sensitivity and precision (greater than 80%) in distinguishing the patients with and without non-motor mental symptoms.

In conclusion, this study aimed to employ univariate statistical analysis and ML algorithms using spatial - temporal variables for the recognition of gait pattern associated to non-motor mental symptoms in PD. The statistical analysis results were mostly confirmed by the ML analysis (matching between significant variables and features chosen by ML) and indicated that PD patients with non-motor mental symptoms as compared with PD patients without display a worse gait pattern, mainly characterized by increased slowness and dynamic instability. These findings further support the idea that peculiar gait dysfunction and neuropsychiatric symptoms in PD mirror the progression of the neurodegenerative process toward non-dopaminergic networks and widespread cortical areas. A limitation of the present study includes in the same group different mental symptoms that might have distinct associations with gait parameters; therefore, a possible future development could be analysing larger samples stratified for symptoms, i.e., cognitive impairment, affective symptoms, psychotic disorders, impulse control disorders. Finally, the present results may corroborate the use of integrated therapeutic approaches in rehabilitation, like cognitive training interventions or/and utilization of pharmacological therapy enhancing cognitiver skills for improving walking performance.

List of acronyms

AUCROC - Area Under the Receiver Operating Characteristic
BMI - Body Mass Index
BT - Boosted Tree
COG- Cognitive Dual-Task
DA - Discriminant Analysis
DT - Decision Tree
GAIT – Single Task
H&Y- Hoehn & Yahr Scale
KNN- K-Nearest Neighbour
LEDD - Levodopa Equivalent Daily Dose
ML – Machine Learning
MOT- Motor Dual-Task
NB – Naïve Bayes
PD – Parkinson's Disease
RF - Random Forest
UPDRS - Unified Parkinson Disease Rating Scale

Contributions of Authors

MR, GC, AMP, MR and CR performed the statistical analysis. MA, AV, GR and PB checked the data quality. MR, MA, AV, GR and CR collected the data. MR, MA and CR wrote the manuscript. All the authors reviewed the manuscript and all the authors have approved the edited final typescript.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are not publicly available due to privacy policy.

Ethical Publication Statements

We confirm that we have read the journal's position on ethical issues involved in publication and affirm that this report is consistent with those guidelines.

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