





### **PhD** in Information Technology and Electrical Engineering Università degli Studi di Napoli Federico II

## **PhD Student: Michela Russo**

Cycle: XXXVII

### Artificial Intelligence & Gait Analysis for Neurological Diseases

Academic year: 2022/2023 - PhD Year: Second

Echelos Resso

**Tutor: prof. Maria Romano** 

Maria Romano

Date: 23 October, 2023

UniNA ITEE PhD Program

#### **1. Information:**

- > PhD student: Michela Russo
- > PhD Cycle: XXXVII
- > DR number: DR995854
- > Date of birth: 19/04/1995
- > Master Science degree: Biomedical Engineering
- > University: University of Naples FEDERICO II
- > Scholarship type: UNINA

2. Study and training activities:

Tutor: Maria Romano

#### Activity Type<sup>1</sup> Hours Credits Dates Organizer Certificate<sup>2</sup> Γ

Activity	Iype	Hours	Creatts	Dates	Organizer	Certificate
Complex network systems: introduction and open challenges	Seminar	2	0.4	17/11/2022	Pietro De Lellis	N
Cybercrime and information warfare: national and international actors	Seminar	2	0.4	18/11/2022	Dr. Pierluigi Paganini, Proff. S.P. Romano, R. Natella	N
Privacy and Data Protection	Seminar	2	0.4	22/11/2022	Dr. Stefano Mele, Proff. S.P. Romano, R. Natella	N
Durability of Fuel Cell Systems	Seminar	2	0.4	30/11/2022	Prof. Elodie Pahon	N
Muscle-based Human	Course	13	2.6	02/12/2022	Daniele Esposito	Y
Threat Hunting & Incident Response	Seminar	2	0.4	13/12/2022	Vladimir Kurdin, Proof. S.P. Romano, R.Natella	N
On the challenges and impact of Artificial Intelligence in the Insurance domain	Course	12	3	15/12/2022	Lorenzo Ricciardi Celsi	Y

# Training and Research Activities Report PhD in Information Technology and Electrical Engineering

Cycle: XXXVII

Author: Michela Russo

Study on validation of a ML model for	Research		6	1/11/2022		
predict cognitive				31/12/2022		
symptoms in PD						
patients using gait						
Study on wearable	Research		7	1/01/2023		
sensors for assessing	Research		/	-		
disease severity and				28/02/2023		
progression in PSP.						
Study on algorithms						
for detecting and						
extracting respiratory						
rate form ECG and						
Study on	Research		7	1/03/2023		
biomechanics of gait	ittistattii		· ·	-		
analysis.				30/04/2023		
Study on algorithms						
for detecting and						
extracting respiratory						
rate form ECG and						
Nanonauro: the newer	Sominor	1	0.2	3/05/2023	Dr Aitzol	V
of nanoscience to	Semma	1	0.2	5/05/2025	Garcia-	1
explore the frontiers of					Etxarri,	
neuroscience					Organizer	
					Prof. Carlo	
					Forestiere	
Using deep learning	Course	10	4	5/05/2023	PhD	Y
property					Andrea	
Models of human	Seminar	15	0.3	29/06/2023	Dr Hohn	N
motor coordination $-a$	Semma	1.5	0.5	27/00/2023	Hogan	1
critical assessment and					8	
some open problems						
Study on markerless	Research		7	1/05/2023		
system for human				-		
motion capture	D 1		7	30/06/2023		
Study on different	Research		/	1/0//2023		
analysis on gait				- 31/08/2023		
parameters				51/00/2023		
Beyond the Eve:	Seminar	1	0.2	15/09/2023	Proff Maria	Y
Vision and AI					Francesca	
Assistance in Surgery					Spadea,	
					Casella	
					Alessandro	

# Training and Research Activities Report PhD in Information Technology and Electrical Engineering

Cycle: XXXVII

**Author: Michela Russo** 

Incorporating Eikona Models for Advanced Cardiac Simulations	Seminar	1	0.2	18/09/2023	MsC Cristian Alberto Barrios Espinosa	Y
Computational Research Environment	Seminar	1.5	0.3	09/10/2023	MSc Lukas Baron	N
Literature discover & Management	Seminar	1	0.2	10/10/2023	MSc Lukas Baron	N
Sharing good practices and useful tools for efficient research software development	Seminar	1	0.2	11/10/2023	PhD Marie Houillon	Ν
Statistics for clinical studies and biomedical engineering	Seminar	1.5	0.3	11/10/2023	Prof. Maria Francesca Spadea	Y
OCT Angiography – What is seen and what we learn	Seminar	1	0.2	16/10/2023	MSc. Simon Hoffmann	Y
Learning 3D features descriptions for the registration in laparoscopic liver surgery	Seminar	1	0.2	19/10/2023	MSc Sara Schwab	Ν
Generating vectorcardiography heartbeat signal using an autoencoder	Seminar	1	0.2	19/10/2023	MsC Cristian Alberto Barrios Espinosa	N
Study on estimation pose technique to human motion capture	Research		7	1/09/2023 - 31/10/2023		
Assistant for the MSc course "Management delle strutture sanitarie"	Tutorship	14	0.56	1-12-2022 20-10-2023	Proff. Amato Francesco, Cesarelli Mario, Ponsiglione Alfonso Maria	
Assistant for the BSc course "Elaborazione di segnali e dati biomedici"	Tutorship	14	0.56	1-12-2022 - 20-10-2023	Proff. Amato Francesco, Romano Maria	

Courses, Seminar, Doctoral School, Research, Tutorship
 Choose: Y or N

	Courses	Seminars	Research	Tutorship	Total
Bimonth 1	5.6	2	6	0.08	13.68
Bimonth 2	0	0	7	0.16	7.16
Bimonth 3	0	0	7	0.16	7.16
Bimonth 4	4	0.5	7	0.16	11.66
Bimonth 5	0	0	7	0.32	7.32
Bimonth 6	0	2	7	0.24	9.24
Total	9.6	4.5	41	1.12	56.22
Expected	30 - 70	10 - 30	80 - 140	0-4.8	

#### 2.1. Study and training activities - credits earned.

#### 3. Research activity:

My research focuses on human mobility and postural control in individuals suffering from neurodegenerative disorders, including Parkinson's disease. Specifically, the integration of wearable and non-wearable sensors for gait measurement with artificial intelligence approaches enables the assistance of clinical decision making, differentiation of typical from atypical parkinsonism, and disease stage monitoring.

During my second year of Ph.D course, I have focused my interest in the following areas:

## • Identification of a Gait Pattern for Detecting Mild Cognitive Impairment in Parkinson's Disease

The aim of this study was to determine a gait pattern, i.e., a subset of spatial and temporal parameters, through a supervised machine learning (ML) approach, which could be used to reliably distinguish Parkinson's Disease (PD) patients with and without mild cognitive impairment (MCI).

A growing body of evidence suggests an association between cognitive decline and several gait and balance dysfunctions in PD [1], [2]. Gait analysis is a well-established tool for the systematic examination of gait changes [3]. ML strategies in the study of human movement have gained popularity as they offer an objective approach to identify or differentiate individuals with movement disorders [4]. Thus, 80 PD patients underwent gait analysis and spatial–temporal parameters were acquired in three different conditions (normal gait (GAIT), motor dual task (MOT) and cognitive dual task (COG)). Univariate statistical analysis was employed to assess the clinical features and spatial and temporal parameters of PD patients with and without MCI. IBM SPSS (v.27) was used to perform all the statistical analyses. Data normality and variance homogeneity were verified using the Kolmogorov-Smirnov test and the Levene's test, respectively. A t-test for independent samples was employed when both the previous assumptions were verified; a Mann-Whitney U test was otherwise employed. The level of significant was set at a p-value < 0.05 for all statistical analyses.

Afterward, a supervised learning analysis was performed through Knime analytics platform (v.4.4.2). Two analyses were carried out using spatial and temporal parameters of gait cycle: (1) supervised

algorithms were implemented on spatial and temporal parameters of each task; 2) a features selection method was implemented on the spatial and temporal parameters using as input all the three tasks to reduce the dimensionality of the dataset; both analyses were performed on one internal validation dataset, composed by 60 patients, and were tested on an external validation dataset, composed by 20 patients who were not considered in the implementation of the previous models, with the aim of evaluating the performance of such models (Figure 1).



Figure 1. Validation Methods into Two Types: Internal and External dataset.

Subsequently, a feature selection through a wrapper method was performed to find the best subset of features which maximized the classification accuracy for each ML algorithm.

Five ML algorithms and the wrapper method were implemented: Decision Tree (DT), Random Forest (RF), Naïve Bayes (NB), Support Vector Machine (SVM) and K-Nearest Neighbour (KNN). Specificity, sensitivity, precision, accuracy and area under the receiver operating characteristic curve were calculated. These findings confirmed that PD-MCI as compared with PD-NO MCI showed worse gait performance, reduced dynamic balance, especially under dual task condition, with subsequent increased risk of falling. In particular, compared with PD-NO MCI, PD-MCI patients displayed reduced step length, cycle length and velocity and increased double support phase and stance phase. Although, the PD-MCI versus PD-NO MCI patients showed significant differences in all three tasks, they displayed several dysfunctions during the COG task. These findings further support the tight connection between walking performance and cognitive dysfunction in PD, where the magnitude of the dual task interference on gait in PD appears to be directly related to the severity of the underlying cognitive dysfunction. Additionally, in line with previous research our ML algorithms detected PD-MCI with an accuracy over the 80.0%. In particular, SVM and RF showed the best performance and detected MCI with an accuracy of over 80.0%. The key features emerging from this study were stance phase, mean velocity, step length and cycle length; moreover, the major number of features selected by the wrapper belonged to the cognitive dual task, thus, supporting the close relationship between gait dysfunction and MCI in PD.

## • Wearable sensors for assessing disease severity and progression in Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is an atypical parkinsonism characterized by prominent gait and postural impairment. A profound alteration of the gait pattern presents early in the course of the disease and is spanned across all phenotypes [5]. The PSP rating scale (PSPrs) is a clinicianadministered tool to evaluate disease severity and progression [6]. More recently, digital technologies have been used to investigate gait parameters. Indeed, wearable sensors represent one of the most promising systems, displaying a satisfactory compromise between device complexity and the amount of acquired data [7], [8]. Therefore, object of this study was to implement a protocol using wearable sensors evaluating disease severity and progression in PSP. Patients were evaluated with the PSPrs as well as with three wearable sensors located on the feet and lumbar area. Each sensor features two accelerometers, one gyroscope and one magnetometer recording on three axes (vertical, mediolateral, anteroposterior) with a sample rate of 20–128 Hz. Three wearable sensors were used and placed with the provided straps as follows: one on each foot and one on the back in the lumbar area.

Spearman coefficient was used to assess the relationship between PSPrs and quantitative measurements. Correlations were deemed moderate with r between 0.3 and 0.59 and strong with  $r \ge 0.6$ . Furthermore, sensor parameters were included in a multiple linear regression model to assess their ability in predicting the PSPrs total score and sub-scores. The difference between baseline and a three-month follow-up for both PSPrs and wearable sensor variables was calculated using paired sample t-test or paired sample Wilcoxon test as needed. The statistical analysis was conducted using the Statistical Package for Social Science (SPSS, version 25). Alpha significance level was set to  $p \le 0.05$  for all statistical analysis.

Quantitative measurements showed multiple significant correlations with the PSPrs scores (r between 0.3 and 0.7; p < 0.05). Linear regression models confirmed the relationships. Several parameters extracted from our protocol showed a significant correlation with the PSPrs-TOT and sub-scores suggesting wearable sensors could be a marker of disease severity in PSP.

These findings suggest objective gait parameters may represent valid proxy of disease severity and reflect measures of activities of daily living. For these reasons, we propose wearable sensors can provide an objective, sensitive quantitative evaluation and immediate notification of gait changes in PSP. Our protocol can be easily introduced in outpatient and research settings as a complementary tool to clinical measures as well as an informative tool on disease severity and progression in PSP.

#### • A cluster analysis for Parkinson's Disease phenotyping with gait parameters

This study aimed to define whether a dataset of gait parameters acquired in patients with idiopathic Parkinson's disease (PD) can be used to identify homogeneous groups separated from each other and corresponding to different PD phenotypes. Gait impairment and postural instability can lead to dangerous conditions for PD patients [9]. In addition, the majority of PD patients reveal a variety of non-motor symptoms including cognitive, neuropsychiatric, sleep and sensory disorders [10]. However, the combination of these marks, which can lead to unsafe conditions for the patient and can have negative impact on quality of life, may differ significantly among patients. Indeed, PD is a highly heterogeneous disorder [11]. Generally, motor and non-motor impairments are determined by clinical experts by using specific evaluation scales [12]. These provide a qualitative analysis on how the staging of the functional disability or how movement and gait disturbances have been evolving in the

progression of the disease. Nevertheless, a quantitative gait analysis could potentially improve the actual practice that may support the diagnosis, symptom monitoring, rehabilitation and fall risk prevention in PD patients.

Gait Analysis combined with current machine learning (ML) techniques may help the clinicians to improve the prediction of an outcome or response to rehabilitation treatments. An optoelectronic motion analysis system was used to obtain spatial-temporal parameters of PD patients during a single walking task. An unsupervised ML technique, namely clustering, was employed on gait parameters extracted from gait analysis to find different motor-phenotypes in PD patients. The optimal number of data clusters was evaluated by using silhouette criterion, a value that estimates the goodness of clustering approach depending on how the data of the same cluster are similar each other and how groups are clearly distinguished. The value of the silhouette coefficient can range from -1 to 1. After defining the clustered data, a univariate statistical analysis was performed to find the differences between the clusters with IBM SPSS (v.28). Firstly, data preprocessing was carried out by identifying and properly removing of the outliers form each distribution using 'rmoutliers' function in MATLAB. Secondly, the Kolmogorov-Smirnov test and the Levene's test were employed to assess the normality distribution of the data and the homoscedasticity of variances between groups for normally distributed data, respectively. For the normally distribution data, a t-test for independent samples was employed; otherwise, a Mann-Whitney was performed. An  $\alpha$  significance level was set to p-value < 0.05. The clustering analysis was carried out with k = 2, given back by the silhouette criterion as the optimal result considering all the 16 spatial-temporal parameters. k-means algorithm clustered the data into

two groups: Cluster 1 and Cluster 2 with a sample size of 67 and 27, respectively (Figure 2). The two clusters were characterized by a specific gait-pattern. In particular, Cluster 2 was characterized by an increase of double support phase, stance phase and stance duration and a decrease of velocity, cadence, step and mean cycle length. These findings suggest that abnormalities in gait parameters may provide a data-driven PD phenotyping, which identify a worse motor and non-motor PD phenotype.



Figure 2. Cluster 1 vs Cluster 2 in 2D plot.

### • Biomechanics parameters of gait analysis to characterize Parkinson's disease: a systematic review.

Parkinson's disease (PD) is characterised by a slow, short-stepping, shuffling gait pattern caused by a combination of limitations in motor control due to a reduction in dopaminergic neurons. In fact, gait disorders are indicators of global health, cognitive status, and risk of falls, and increase with disease progression. Therefore, the use of quantitative information on the gait mechanisms of PD patients is one of the most promising discoveries, allowing early diagnosis, assessment of disease progression and therapeutic intervention. Over the years, a large number of studies have investigated the spatiotemporal parameters that are altered in the PD gait pattern, while kinematic and kinetic gait parameters are still in their early stages. Specially, kinematic parameters describe angular displacement based on the sagittal, coronal or transverse planes for various body regions and joints such as the ankle, knee, hip and pelvis area, while kinetic parameters refer to the forces and their effect on motion. Forces extrapolated by kinetic analysis are the sources of the motion in the kinematic movements. Commonly, these forces are represented by the ground reaction force (GRF) at the hip, knee and ankle joints calculated on the sagittal plane. By combining kinematic and kinetic parameters, it is possible to calculate the joint moments and powers. Thus, the combination of joint angles, moments and powers provides a detailed description of the mechanics of gait. I conduced a systematic review according to the PRISMA guidelines. The Scopus and PubMed databases were searched between 1999 and 2022. A total of 26 articles were included that reported gait changes in PD patients under different gait conditions: single free walking, sequential motor task and dual task. The results of our review showed that PD patients had alterations in the range of motion of the hip, knee and ankle joints, as well as a reduction in the power generated/absorbed and the extensor/flexor moment. These findings suggest that the PD gait pattern may be better understood using kinematic and kinetic parameters.

#### • Other research activities

During this year, I also conducted a study on algorithms for detecting and extracting the respiratory rate (RR) from the electrocardiography (ECG) and photoplethysmography signals. Continuous monitoring of respiration plays a key role in the detection and management of different conditions, such as stress, anxiety, and sleep disorders. For this study, signals from a publicly available database are used to develop and implement the proposed algorithms to process both ECG and PPG acquisitions and to predict RR waveforms based on accurate choice and extraction of different pertinent ECG and PPG characteristics. Results obtained with each selected feature are quantitatively compared in order to identify the most effective workflow to achieve reliable estimates of the breathing rate. The main findings of the study are promising, with the best error-metric values achieved with ECG-derived RR (EDR) rather than PCG-derived RR (PDR) signals (mean absolute errors equal to 1.04 and 1.64 breaths/min for EDR and PDR, respectively). The work suggests that the proposed approach could serve as a guide in the design and development of future cheap and non-invasive methods to monitor respiration activity.

#### 4. Research products

#### a. Scientific papers:

Title: Identification of a Gait Pattern for Detecting Mild Cognitive Impairment in Parkinson's Disease Authors: Russo, M.; Amboni, M.; Barone, P.; Pellecchia, M.T.; Romano, M.; Ricciardi, C.; Amato, F.. Journal: Sensors Year: 2023 Current Status: Published (<u>https://www.mdpi.com/1424-8220/23/4/1985</u>)

Title: Wearable sensors for assessing disease severity and progression in Progressive Supranuclear Palsy Authors: Abate, F; Russo, M; Ricciardi, C; Tepedino M.R.; Romano, M; Erro, R; Pellecchia, MT; Amboni M; Barone,P; Picillo, M. Journal: Parkinsonism and Related Disorders Year: 2023 Current status: Published (https://doi.org/10.1016/j.parkreldis.2023.105345.)

Title: Comparison of Techniques for Respiratory Rate Extraction from Electrocardiograms and Photoplethysmogram Authors: Ponsiglione, AM; Russo, M; Petrellese, MG; Tufano, V; Amato, F,; Romano, M. Journal: Physiological Measurement Year: 2023 Current status: Submitted

#### **b.** Conference paper

Title: A cluster analysis for Parkinson's Disease phenotyping with gait parameters
Authors: Russo, M.; Ricciardi C.; Amboni, M.; Volzone A.; Barone, P.; Romano, M.; Amato, F.
Journal: 2023 IEEE International Conference on Metrology for Extended Reality, Artificial Intelligence and Neural Engineering (MetroXRAINE)
Year: 2023
Current Status: Accepted

#### c. Review paper

Title: Biomechanics parameters of gait analysis to characterize Parkinson's disease: a systematic review Authors: Russo, M.; Amboni, M.; Pisani, N.; Calderone D.; Barone, P.; Amato, F.; Ricciardi, C.; Romano, M. Journal: Biocybernetics and Biomedical Engineering Year: 2023 Current Status: Submitted

#### 5. Conferences and seminars attended

### **IEEE International conference on Metrology for extended reality, artificial intelligence and neural engineering (2023IEEEMetroXRAINE); 25-27 October 2023, Milano.**

I will defence a conference paper: A cluster analysis for Parkinson's Disease phenotyping with gait parameters.

I will attend Youth Forum, a poster session where PhD students and young researchers will present their research themes and topics.

#### 6. Periods abroad and/or in international research institutions

During my second year of PhD, I'm carrying out study and research activity abroad, from 8<sup>th</sup> September to 16<sup>th</sup> December, at Institute of Biomedical Engineering, Karlsruhe Institute of technology, Germany, under the supervision of Prof. Maria Francesca Spadea ( <u>https://www.ibt.kit.edu/Spadea\_Francesca.php</u> ).

During the first two months (September and October), I investigated markerless techniques based on low-cost 2D video analysis in combination with computer vision techniques to overcome most of the limitations inherent to 3D marker-based motion capture system. The scope was to semplify the clinical routine of gait analysis, giving a quantitative information on gait-pattern during daily activities and supporting clinical decision making. Indeed, gait analysis in natural setting will allow to investigate specific motor-symptoms such as the freezing gait or the falls.

First of all, I started with a review of the literature to define the current state of research and the techniques used. This allowed me to define a suitable protocol for recording walking.

In particular, I acquired videos of the walk of volunteer subjects using a common smartphone, and investigated a markerless motion capture technique, using freely available approach to estimation pose technique such as MediaPose. I used this estimation pose technique to obtain the silhouette of the subjects from static images.

In the coming months I would like to extract the spatio-temporal of the gait cycle and the kinematic parameters of the lower limbs. Once the protocol and the image acquisition system have been optimised and standardised, as well as a comparison with the literature, taking advantage of the instrumentation available in Italy, I would like to apply this workflow to videos

of patients with Parkinson's disease and validate the results by carrying out an agreement study with commercial devices (e.g. OPAL(wearable sensors)) or with the same gold standard (optoelectronic systems) on videos.

Total months abroad : 3

#### 7. Tutorship

Assistant for the BSc course of "Elaborazione dei segnali e dati biomedici" (14h) held by Proff Amato Francesco & Romano Maria; assistant for the MBc course of "Managemente delle Strutture Sanitarie" (14h) held by Prof. Amato Francesco, Cesarelli Mario, Ponsiglione Alfonso Maria.

#### 8. Plan for year three

Next year I would like to focus on processing the gait signals and extracting the kinematic and kinetic parameters of the gait for a complete analysis of the gait. To this end, a larger cohort of subjects, possibly with other neurodegenerative diseases, will be considered.

In addition, I would like to carry out an agreement study between two systems for the measurement of spatio-temporal and kinematic gait parameters in patients with Parkinson's disease. The optoelectronic system from BTS Bioengineering will be used as a reference device to the wearable Opal system from APDM. Given the increasing importance of implementing wearable technologies in both clinical and research settings, the feasibility for non-specialist clinicians and the known sensitivity of the OPAL system, the present study could represent a further step forward in the implementation of quantitative assessment of gait in PD patients.

Finally, I will continue my collaboration with the Institute of Biomedical Engineering in Karlsruhe. I will carry out study on estimation pose techniques and computer vision for human motion capture.

#### Reference

- R. Morris, S. Lord, J. Bunce, D. Burn, e L. Rochester, «Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease», *Neurosci. Biobehav. Rev.*, vol. 64, pp. 326–345, mag. 2016, doi: 10.1016/j.neubiorev.2016.02.012.
- [2] M. Amboni, P. Barone, e J. M. Hausdorff, «Cognitive contributions to gait and falls: evidence and implications», *Mov. Disord. Off. J. Mov. Disord. Soc.*, vol. 28, fasc. 11, pp. 1520–1533, set. 2013, doi: 10.1002/mds.25674.
- [3] R. Baker, A. Esquenazi, M. G. Benedetti, e K. Desloovere, «Gait analysis: clinical facts», *Eur. J. Phys. Rehabil. Med.*, vol. 52, fasc. 4, pp. 560–574, ago. 2016.
- [4] A. Landolfi *et al.*, «Machine Learning Approaches in Parkinson's Disease», *Curr. Med. Chem.*, vol. 28, fasc. 32, pp. 6548–6568, 2021, doi: 10.2174/0929867328999210111211420.
- [5] G. U. Höglinger *et al.*, «Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria», *Mov. Disord. Off. J. Mov. Disord. Soc.*, vol. 32, fasc. 6, pp. 853–864, giu. 2017, doi: 10.1002/mds.26987.
- [6] L. I. Golbe e P. A. Ohman-Strickland, «A clinical rating scale for progressive supranuclear palsy», *Brain J. Neurol.*, vol. 130, fasc. Pt 6, pp. 1552–1565, giu. 2007, doi: 10.1093/brain/awm032.
- [7] M. Picillo *et al.*, «Gait Analysis in Progressive Supranuclear Palsy Phenotypes», *Front. Neurol.*, vol. 12, p. 674495, 2021, doi: 10.3389/fneur.2021.674495.
- [8] M. Amboni *et al.*, «Gait analysis may distinguish progressive supranuclear palsy and Parkinson disease since the earliest stages», *Sci. Rep.*, vol. 11, fasc. 1, Art. fasc. 1, apr. 2021, doi: 10.1038/s41598-021-88877-2.
- [9] A. Samii, J. G. Nutt, e B. R. Ransom, «Parkinson's disease», *The Lancet*, vol. 363, fasc. 9423, pp. 1783– 1793, mag. 2004, doi: 10.1016/S0140-6736(04)16305-8.
- [10] W. Poewe, «Non-motor symptoms in Parkinson's disease», Eur. J. Neurol., vol. 15, fasc. s1, pp. 14–20, 2008, doi: 10.1111/j.1468-1331.2008.02056.x.
- [11]J. C. Greenland, C. H. Williams-Gray, e R. A. Barker, «The clinical heterogeneity of Parkinson's disease and its therapeutic implications», *Eur. J. Neurosci.*, vol. 49, fasc. 3, pp. 328–338, 2019, doi: 10.1111/ejn.14094.
- [12] J. J. van Hilten, A. D. van der Zwan, A. H. Zwinderman, e R. a. C. Roos, «Rating impairment and disability in Parkinson's disease: Evaluation of the unified Parkinson's disease rating scale», *Mov. Disord.*, vol. 9, fasc. 1, pp. 84–88, 1994, doi: 10.1002/mds.870090113.