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Universidade do Minho
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Cristina Manuela Peixoto dos Santos

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DIREITOS DE AUTOR E CONDIÇÕES DE UTILIZAÇÃO DO TRABALHO POR TERCEIROS

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

ABSTRACT

This dissertation presents the work done during the fifth year of the course Integrated Master's in Biomedical Engineering, in Medical Electronics. This work was carried out in the Biomedical & Bioinspired Robotic Devices Lab (BiRD Lab) at the MicroElectroMechanics Center (CMEMS) established at the University of Minho. For validation purposes and data acquisition, it was developed a collaboration with the Clinical Academic Center (2CA), located at Braga Hospital.

The knowledge acquired in the development of this master thesis is linked to the motor rehabilitation and assistance of abnormal gait caused by a neurological disease. Indeed, this dissertation has two main goals: (1) validate a wearable biofeedback system (WBS) used for Parkinson's disease patients (PD); and (2) develop a digital biomarker of PD based on kinematic-driven data acquired with the WBS. The first goal aims to study the effects of vibrotactile biofeedback to play an augmentative role to help PD patients mitigate gait-associated impairments, while the second goal seeks to bring a step advance in the use of front-end algorithms to develop a biomarker of PD based on inertial data acquired with wearable devices. Indeed, a WBS is intended to provide motor rehabilitation & assistance, but also to be used as a clinical decision support tool for the classification of the motor disability level. This system provides vibrotactile feedback to PD patients, so that they can integrate it into their normal physiological gait system, allowing them to overcome their gait difficulties related to the level/degree of the disease. The system is based on a user- centered design, considering the end-user driven, multitasking and less cognitive effort concepts.

This manuscript presents all steps taken along this dissertation regarding: the literature review and respective critical analysis; implemented tech-based procedures; validation outcomes complemented with results discussion; and main conclusions and future challenges.

Keywords: Parkinson's disease; **biomarker; Wearable Biofeedback Systems; vibrotactile biofeedback; rehabilitation & assistance; clinical decision support tool;**

RESUMO

Esta dissertação apresenta o trabalho realizado durante o quinto ano do curso Mestrado Integrado em Engenharia Biomédica, em Eletrónica Médica. Este trabalho foi realizado no Biomedical & Bioinspired Robotic Devices Lab (BiRD Lab) no MicroElectroMechanics Center (CMEMS) estabelecido na Universidade do Minho. Para efeitos de validação e aquisição de dados, foi desenvolvida uma colaboração com Clinical Academic Center (2CA), localizado no Hospital de Braga.

Os conhecimentos adquiridos no desenvolvimento desta tese de mestrado estão ligados à reabilitação motora e assistência de marcha anormal causada por uma doença neurológica. De facto, esta dissertação tem dois objetivos principais: (1) validar um sistema de biofeedback vestível (WBS) utilizado por doentes com doença de Parkinson (DP); e (2) desenvolver um biomarcador digital de PD baseado em dados cinemáticos adquiridos com o WBS. O primeiro objetivo visa o estudo dos efeitos do biofeedback vibrotáctil para desempenhar um papel de reforço para ajudar os pacientes com PD a mitigar as deficiências associadas à marcha, enquanto o segundo objetivo procura trazer um avanço na utilização de algoritmos front-end para biomarcar PD baseado em dados inerciais adquiridos com o dispositivos vestível. De facto, a partir de um WBS pretende-se fornecer reabilitação motora e assistência, mas também utilizá-lo como ferramenta de apoio à decisão clínica para a classificação do nível de deficiência motora. Este sistema fornece feedback vibrotáctil aos pacientes com PD, para que possam integrá-lo no seu sistema de marcha fisiológica normal, permitindo-lhes ultrapassar as suas dificuldades de marcha relacionadas com o nível/grau da doença. O sistema baseia-se numa conceção centrada no utilizador, considerando o utilizador final, multitarefas e conceitos de esforço menos cognitivo.

Portanto, este manuscrito apresenta todos os passos dados ao longo desta dissertação relativamente a: revisão da literatura e respetiva análise crítica; procedimentos de base tecnológica implementados; resultados de validação complementados com discussão de resultados; e principais conclusões e desafios futuros.

Palavras-Chave: Doença de Parkinson; biomarcador; Wearable Biofeedback Systems; biofeedback vibrotáctil; reabilitação & assistência; ferramenta de apoio à decisão clínica;

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List of Abbreviations and acronyms

A

AI	Artificial intelligence
A/P	Anterior-posterior
ABC	Activities-specific Balance Confidence scale
AS	Asymmetry
ACC	Accuracy

B

BBS	Berg Balance scale
BCG	Biofeedback continuous group
BEG	Biofeedback event-driven group

C

CoA	Cue-oriented assistance
COP	Center of pressure displacement
CNN	Convolutional neural network
CG	Control group

D

DL	Deep Learning

F

FC	Final contact

H

H&Y	Hoehn and Yahr scale
HR	Heuristic rules

I

IMUs	Inertial Measurement Units
ICC	Intraclass correlation coefficient
IC	Initial contact

K

KNN	K-nearest neighbors

L

LOS Limits of stability

LDA Linear Discriminant Analysis

LSTM Long short-term memory

M

MMSE Mini-Mental State Examination

MoCA Montreal Cognitive Assessment

ML Machine Learning

M/L Medial lateral

mRMR Minimum Redundancy - Maximum Relevance

MG Mixed Group

MCC Matthews Correlation Coefficient

N

NI Not identifiable

P

PD Parkinson's Disease

PIGD Postural Instability and Gait Disorder

PDQ-39 The Parkinson's Disease Questionnaire

PCA Principal Component Analysis

Q

QoL Quality of Life

R

RF Random forests

RBF Radial basis function

S

SVM Support vector machine

SD Standard deviation

SENS Sensitivity

T

TUG Timed Up and Go test

U

UPDRS Unified Parkinson's Disease Rating Scale

UPSRS-III Unified Parkinson's Disease Rating Scale part III

W

WBS Wearable biofeedback system

WBD Wearable biofeedback devices

1 Introduction

1.1 MOTIVATION

Parkinson's disease (PD) is a chronic progressive neurodegenerative movement disorder characterized by a profound and selective loss of nigrostriatal dopaminergic neurons [1]. PD is the second most common neurodegenerative disorder and is expected to impose an increasing social and economic burden on societies as populations age [2].

This disease presents symptoms as akinesia, bradykinesia, rigidity of movements, tremors, postural instability, and gait disturbances [3], as episodes of blockage known as freezing of gait (FOG). In addition to the motor symptoms, mental disorders like depression or psychosis, and autonomic and gastrointestinal dysfunction may occur; all these disorders considerably impair the quality of life (QoL) of PD patients [3].

Pharmacological therapies are usually followed to treat motor symptoms. They depend on the stage of the disease and the patients' initial response to treatment. With the disease progression, there is a loss of medication efficacy, so the patients need higher doses of medication in shorter periods of time [4]. Further, surgical interventions (e.g., deep brain stimulation) are usually followed to treat early and late complications of PD [5], but likewise medication, in long term, does not alter the course of motor symptoms. Medication and surgical treatments have shown to suppress the symptoms of tremor, bradykinesia, and muscle rigidity, but do not prevent the progression of other motor complications. The treatments are not as effective in treating gait-associated disabilities and postural instabilities, which increase the loss of balance and risk of falling, restricting motor performance and limiting the level of independence in daily activities [6]. This pharmacologic/surgical barrier encouraged new investigations to find new methods/solutions than can help patients with PD to improve their motor symptoms.

Indeed, new technological-based solutions, namely wearable biofeedback devices (WBD) have shown an innovative and enthusiastic perspective. These solutions have proven to be efficient in ensuring continuous improvement of motor symptoms, contributing to patient's greater autonomy [5], [6]. These new wearable technologies integrate sensors that can detect alterations on users' motor performance and deliver proprioceptive cues (bio-feedback) [4], [6].

Cueing can be defined as using external stimuli which provides temporal (related to time) or spatial (related to space) information to facilitate movement (gait) initiation and continuation [7]. Patients may use sensory cueing as an artificial means to stimulate the proprioceptive inputs, being the proprioception the sense of self-movement and body position [8]. Improving proprioceptive feedback could enhance sensory processing deficits, ameliorating gait performance and increase the outcomes of PD-rehabilitation/assistance [8], [9].

Visual, auditory and vibrotactile cues have been used to aid function in persons with PD. Sometimes these cues are provided simultaneously (e.g., vibrotactile-visual cueing) [10]. In these individuals, the spatial and temporal characteristics of on-going gait (velocity, stride length and cadence) have been improved [11]. Furthermore, sensory cueing can produce changes in postural control, stepping pattern, unfreezing gait-blocks, prevent falls, and, consequently, lead to less gait variability. Overall, sensory cueing can be used in the daily living of the subjects, improving their performance.

Although scientific community has continuously developed and improved WBD, as pointed in [12], current solutions require (i) integration of all tech-subsystems into a single device, in order to overcome wearability issues (ii); ability to be used in patients' daily lives, considering ergonomic and comfort requirements; (iii) personalized biofeedback strategies according to user motor disability level; and (iv) include more clinical evidence and usability,

Also, for the more traditional methods (pharmacological therapies), there is a need to monitor the motor manifestations and clinicians usually use scales (e.g. UPDRS). These categorical scales are susceptible of subjectivity and noncommon analysis between clinical community [13]. Clinicians are limited to the information observed during the medical appointments which can be affected by patients' mood and motivation or medication phase [13]–[16]. Besides, motor symptoms' assessments during routine consultations are strongly dependent of patients' memory to describe their last motor episodes [15]. These facts highlight a remaining challenge among the scientific community: to develop technological solutions that enable to monitor motor symptoms in patients' home-settings providing continuous and more objective data [14].From sensory acquisitions, WBD can provide relevant motor metrics that are useful for a continuous and objective monitoring of PD motor symptoms. However, current WBD do not explore the estimation of these motor metrics as a clinical decision support tool for the classification of the disease degree.

1.2 PROBLEM STATEMENT

This thesis intends to take a systematic approach to address the state-of-the-art limitations of WBD, aiming to (i) study the effects of vibrotactile cueing with end-users (patients with PD) and (ii) evolve the digital biomarkers field on PD based on kinematic data. Following a user-centred approach, firstly it was required to identify which gait-related metrics could translate the effects of biofeedback. These gait-related metrics should be estimated based on sensory acquisitions from WBD aiming to use a unique device able to provide sensory cueing, but also measure relevant motor metrics. Also, to validate the biofeedback strategy, the clinical protocol should include motor daily activities, a carefully delineation of group studies

and include usability tests to access the acceptability of the proposed cueing-based strategy and WBD. Sensory kinematic-driven data recorded, and consequent gait-related metrics estimated, besides to allow to study the biofeedback effects, have potential to be applied to statistical and artificial intelligence (AI) methodologies to biomarker PD. Indeed, AI models will allow to be integrated on clinical APP to automatically complement traditional examinations during routine consultations. On a hypothetical scenario, patients could use the WBD in their homes or during a required moment in consultation, to acquire kinematic data & gait-associated spatiotemporal parameters to be applied on the AI-models integrated on the desktop clinical APP. The clinical APP will complement the traditional motor examination based on UPDRS scale by digitally biomarking the classified score level.

1.3 GOALS AND RESEARCH QUESTIONS

This dissertation has two main goals. The first one aims to validate a WBD to study the effects of vibrotactile biofeedback to play an augmentative role to help PD patients mitigate gait-associated impairments. The second key-goal envisions the development of a digital biomarker of PD based on kinematic-driven data acquired with the WBS to bring a step advance in the use of front-end algorithms to biomarker PD. From an unique device, a WBD, it is intended to provide motor rehabilitation & assistance, but also to be used as a clinical decision support tool for biomarker mobility on PD. The system will be validated with PD patients, in a hospital context, through the definition of inclusion and exclusion criteria as well as clinical protocols, to enable a user-driven design.

To achieve these main goals, it is necessary to gather a body of knowledge about current state-of-the-art of WBD in PD, both technological and clinical validation points-of view. It is required a critical analysis on the achievements and limitations of WBD already validated with PD patients, but also on the studies about the use of inertial data to determine the disease level or mobility degree stratified by related disease -associated scales. This analysis provides the required scientific knowledge to overcome the identified tech & end-user driven requirements of this dissertation. Thus, these main aims can be divided into several goals, to represent all the methodological steps established to attain the ultimate goal, as follows:

- Goal 1: do a literature review about WBD used in PD to improve motor performance. It is expected to summarize the investigations about WBD in PD, their achievements and identify their gaps.
- Goal 2: to cover a critical review on the literature to understand how wearable sensors can support PD monitoring using AI & statistical analysis.

- Goal 3: validate a WBD, an instrumented waistband, with end-users. It is expected the acquisition and analysis of motor metrics that allow to study the effects of vibrotactile biofeedback.
- Goal 4: the fourth goal aims to enhance a gait analysis tool (desktop APP) able to segment a gait cycle and estimate gait-associated metrics (from different locomotion domains, as pace, rhythm, variability and asymmetry) based on sensory information (kinematic data) acquired by WBD.
- Goal 5: accomplish a statistical study about the gait-associated metrics aiming to study the ability of a wearable motion LAB to serve as a biomarker of PD motor stages and an indicator of patients' QoL.
- Goal 6: the implementation of an AI-based model to classify the mobility level of PD based on kinematic-driven data and gait-related metrics. It is expected with this tool to complement traditional clinical motor examination by classifying the UPDRS score. The application of these models should lead to an accuracy of at least 95% in the classification of the mobility level.

In this dissertation we intend to answer several research questions:

- RQ.1 "How have the WBD been implemented, applied and clinically validated in PD to mitigate gait associated impairments?"; This research question is associated with Goal 1 and is answered in Chapter 2.2.
- RQ.2 "How have the AI-based and statistical methods been used for PD monitoring?"; This research question is associated with Goal 2 and is answered in Chapter 2.3.
- RQ.3 "Can gait event-driven biofeedback loop integrated on a WBD help PD patients to mitigate gait-associated disabilities?"; This research question is associated with Goal 3 and is answered in Chapter 4.
- RQ.4 "Can the wearable motion LAB outcomes contribute as a biomarker of motor stage and quality of life in PD supported by a statistical analysis?"; This research question is associated with Goal 5 and is answered in Chapter 5.2.2.
- RQ.5 "Which AI model based on wearable motion LAB produces best results as a biomarker of motor stages (UPDRS-III score) in PD?"; This research question is associated with Goal 6 and is answered in Chapter 5.2.3.

1.4 MAIN CONTRIBUTIONS

A WBD was validated where positive effects were found regarding the application of vibrotactile biofeedback to play an augmentative role to help PD patients mitigate gait-associated impairments. Also,

from the same device, it was accomplished a statistical and AI-based analysis to study the ability of a wearable motion to serve as a biomarker of PD. In particular, the main contributions of this work are:

- Validation of a WBD, an instrumented waistband, able to provide closed loop vibrotactile cueing to help PD patients mitigate gait impairments: clinical protocol, contact with end-users and statistical analysis about the effects of the proposed biofeedback and device usability acceptance.
- Gait analysis tool (desktop APP) able to segment a gait cycle into initial and final contact and estimate spatiotemporal gait parameters from different domains (as pace, rhythm, variability and asymmetry).
- Statical study about how wearable sensory acquisitions could be applied to biomarker PD motor stages and QoL.
- Implementation and comparation of different AI-based models able to stratify PD motor disability level.

1.5 DISSERTATION STRUCTURE

This manuscript is organized as follows.

Chapter 2 presents the state-of-the-art analysis. After, a contextualization about PD and benefits of sensory cueing, it presents a review about WBD used on PD to identify what technologies have been applied on WBD and how biofeedback can be provided to these patients. Furthermore, in a second part, it is identified on the literature how the wearable sensors have been applied to support PD motor monitoring using AI & statistical approaches.

Chapter 3 presents +sense project and its main modules, with the main focus on the WBD. It presents the +sBiofeedback and +sMotion modules, responsible to provide biofeedback and analyze users' gait.

In Chapter 4, a statistical analysis is demonstrated to prove that +sMotion can provide biofeedback capable of improving the gait of Parkinson patients. Furthermore, it is intended to show how best to provide this biofeedback to the patient.

In Chapter 5, it is demonstrated statistically that there are specific gait patterns in patients with different levels of disease progression and stage. These different levels may be due to motor differences in the patients' gait or psychological differences in the patients' quality of life. Various AI methods are also introduced in order to distinguish patients by their motor deficits.

Finally, all the conclusions drawn from this extensive work are described. In addition, further improvements that can be developed in the future in order to improve this work are also described.

1.6 PUBLICATIONS AND ORAL PRESENTATIONS

The accomplished work allowed the publication and oral presentation of a conference paper:

André Branquinho, H. Gonçalves, Joana F. Pinto, Ana M. Rodrigues, Cristina P. Santos. "Wearable gait Analysis LAB as a biomarker of Parkinson's disease motor stages and Quality of life: a preliminary study", 21st IEEE International Conference on Autonomous Robot Systems and Competitions (ICARSC2021), 2021.

2 Literature Review

2.1 INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is expected to impose an increasing social and economic burden on societies as populations age [17]. PD motor symptoms includes akinesia, bradykinesia, rigidity of movements, tremors, postural instability and gait disturbances [2], as episodes of blockage known as freezing of gait (FOG).

Pharmacological therapies are usually followed to treat motor symptoms, being prescribed concerning the stage of the disease and the patients' initial response to treatment. With the disease progression, there is a loss of medication efficacy, so the patients need larger doses of medication in shorter periods of time [4]. Further, surgical interventions (e.g., deep brain stimulation) are usually followed to treat early and late complications of PD [2], but likewise medication, in long term, does not alter the course of motor symptoms. Medication and surgical treatments have been shown to suppress the symptoms of tremor, bradykinesia, and muscle rigidity, but does not prevent the progression of other motor complications, such as gait-associated disabilities and postural instabilities, which increases the loss of balance and risk of falling, restricting motor performance and limiting the level of independence in daily activities with aging [10]. This pharmacologic/surgical barrier encouraged to new innovative and enthusiastic methods, which proven to be efficient in ensuring continuous treatment and management of motor symptoms [5], [6].

2.1.1 SENSORY CUEING THERAPY AS A NON-PHARMACOLOGICAL/SURGICAL INTERVENTION IN PD MOTOR TREATMENTS

Non-pharmacological/surgical approaches can be represented by two categories, considering the timing and durability of the treatment effect, as depicted in Figure 1: (1) transient effect, and (2) long-lasting effect [18].

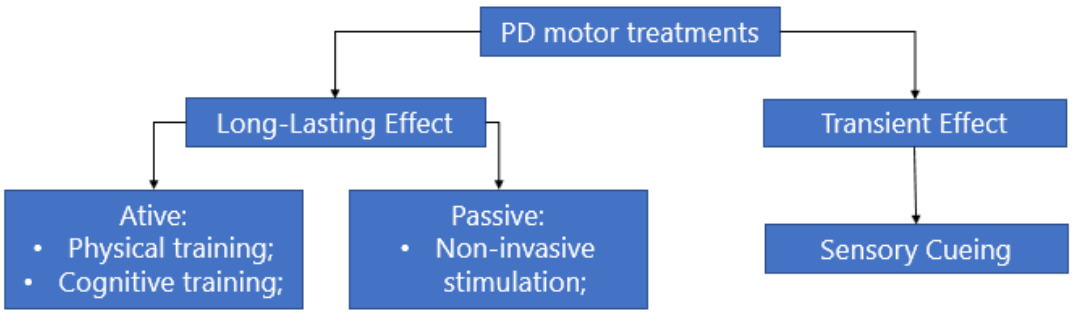

Figure 1. Representation of the two approaches followed by clinicians in PD: Transient effect and Long-lasting effect therapies.

Long-lasting effect therapies includes two potential action mechanisms considering the intervention method: active or passive. The active mechanism is based on physical training (such as, exercise, aquatic therapy, slackline training, curved-walking training and robot-assisted training) and cognitive training (e.g., motor learning, action observation and computerized training). Passive mechanism comprises non-invasive-stimulation as transcranial direct current stimulation, repetitive transcranial magnetic stimulation and automated mechanical peripheral stimulation. The effects produced by long-term therapies are the result of long-term modulation of the cortico-striatal and thalamo-cortical circuits[18].

As to the transient effect therapies, they are based on the use of sensory cues: visual, proprioceptive stimuli/vibrotactile, auditory and multiple modalities [18]. Cueing can be defined as using external stimuli which provides temporal (related to time) or spatial (related to space) information to facilitate movement (gait) initiation and continuation [7]. Patients may use sensory cueing as an artificial means to stimulate the proprioceptive inputs, being the proprioception the sense of self-movement and body position [8]. Improving proprioceptive feedback could enhance sensory processing deficits, ameliorating gait performance and increase the outcomes of PD-rehabilitation/assistance [8], [9].

Visual, auditory and vibrotactile cues have been determined to aid function in persons with PD. Sometimes these cues are provided simultaneously (e.g., vibrotactile-visual cueing) [10]. In these individuals, the spatial and temporal characteristics of on-going gait (velocity, stride length and cadence) have been improved [11]. Furthermore, sensory cueing can produce changes in postural control, stepping pattern, unfreezing gait-blocks, prevent falls, and, consequently less gait variability. Overall, sensory cueing can be used in the daily living of the subjects, improving their performance, and it is possible to affirm that the sensory vibrotactile cue allows high improvements in the patients' gait, specifically, in the FOG events [19].

The effects produced by the transient therapies are the result of shift to spared motor pathways (anterior putamen brain area) [18], based on the biological model of Lewis and Barker, normal gait is dependent on processing within both cortical (PPN and GPi/SNr) and sub-cortical (spinal cord) regions and the evidence presented suggests a critical role for the PPN (pedunculopontine nucleus) in regulating the outflow of these processes in human locomotion. Furthermore, any insult to the integrity of this structure would provide a non-dopaminergic mechanism to explain disturbances in gait [20]. Disturbances on the output of the GPi/SNr circuitry have a profound effect on determining the level of activation within the PPN and in combination this will clinically manifest as a parkinsonian gait [20]. Thus, the literature

suggests the use of sensory cueing therapies shifts to spared neural motor pathways, and this way, improve the quality of live for the people with parkinsonian gait.

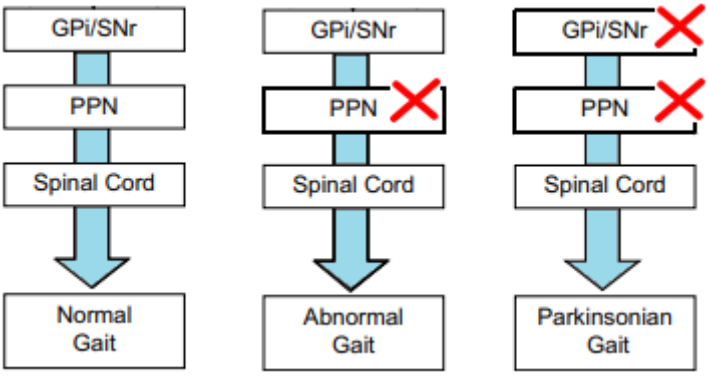

Figure 2. Different neural motor pathways.

2.1.2 Neural mechanisms of gait when applying sensory cueing

Motor symptoms in PD result from a degeneration of dopaminergic (DA) neurons in the substantia nigra, leading to a DA deficiency in the basal ganglia (BG) [10], [21]–[23]. The basal ganglia play significant roles in the production and control of automatic and well-learned motor movements [24].The internal timing depends on striatal dopaminergic levels [22], with unusual levels come timing problems, and these problems could be a potential marker for frontal and striatal dysfunctions in PD, causing the gait impairments. This is supported by the finding that DA replacement therapy reduces the timing deficits in PD, and that timing deficits are induced by changes in the expression levels of dopamine receptors (striatal D2 receptors) [22].

There are two fundamental modes of timing, which present distinct underlying neural networks, the implicit and explicit timing [25]. Explicit timing is required to make deliberate estimates of duration and relies on internal sense of time. Implicit timing utilizes external cues and relies less on conscious time-based judgments, engaging automatic timing systems. An example of an implicit timing task is the serial prediction task, which requires the subject to use a regularly timed stimulus to make temporal predictions about future stimuli [22].

Between these two timings, the patients with PD have greater difficulty with explicit timing. More specifically, PD patients have problems with explicit temporal discrimination tasks involving tactile, visual, and auditory stimuli. Also, the performance of explicit timing decreases as disease severity increases. While implicit timing mainly recruits the cerebellum and is less dependent on the BG and the supplementary motor area (SMA), explicit timing recruits the BG, the SMA, the mid-premotor cortex (PMC), and the cerebellum [22].

The BG–SMA–PMC network is directly involved in rhythm perception in the presence or absence of motor actions. In this network, the dorsal striatum (caudate and putamen) of the BG serves the most crucial role since it generates the internal pacing required for time estimation [22]. Thus, the BG is directly involved in perceptual and motor timing. The D2 receptors in the striatum mediate the DA signaling that controls the speed of this internal pacing. The lack of DA innervation to the BG in PD causes slower internal pacing, which leads to problems in motor and perceptual timing abilities [22]. However, although patients with PD have impairments with external timing due to internal pacing dysfunction, they still can make temporal predictions through implicit timing. There implicit timing is still mostly intact, so they compensate the disruption in the BG-SMA-PMC (explicit timing) by recruiting the cerebellum (essential for implicit timing) [22], [25]. So, patients can still use external cues to inform decisions based on time, for example when the next step should occur. Therefore, biofeedback systems apply sensory cueing for patients use their implicit timing abilities still present to recalibrate their internal clock with external cues [25].

The schema in the next figure summarizes the basic neural pathways involved in gait with the application of sensory cues. In the absence of external cueing, internal cueing signals generated by the BG–SMA–PMC circuit feed into the motor programs, which are carried out in the medial motor areas comprised of the SMA and the cingulate motor area [22]. During locomotion, the somatosensory information, such as proprioception, is carried by the spinocerebellar, the spinothalamic, the spinoreticular, and the spinohypothalamic tracts back to the brain. The information carried by the somatosensory feedback modulates the internal clock of explicit timing in the BG–SMA–PMC circuit and helps plan and predict future cued motor tasks. The external cues can overtake the damaged BG and, by inducing motor–sensory feedback signals that recalibrate internal pacing, help the patients improve their gait. After the correct temporal scheme is re-established and potentiated through the BG–SMA–PMC circuit, patients can sustain improved locomotion for a period in the absence of external cueing [22].

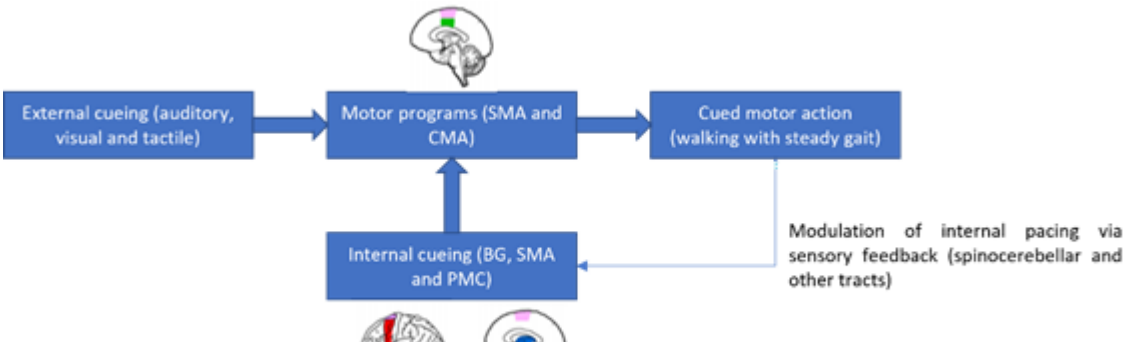

Figure 3. The basic neural pathways involved in gait with the application of sensory cues.

2.1.3 WEARABLE BIOFEEDBACK DEVICES: THE POTENTIAL TO PROVIDE MOTOR ASSISTANCE & MONITORING

The technological evolution and application of miniaturized and portable assistance/rehabilitation devices has allowed the use of sensory cues through WBD. They are equipped with sensors that enable sensory acquisition and can trigger a cue-information. The sensors may detect alterations on gait or balance, and through the detection of such motor anomalies deliver proprioceptive cues [4], [6]. Most of the reviews have positive findings in favour of the use of sensory cueing and they conclude that the effect of external sensory cued therapy on activities for daily living of patients with PD is helpful.

Parkinson's disease (PD) can cause various symptoms, and its severity will depend on the stage of the disease. Diagnosing this disease in its early stages is very difficult, since the early symptoms of this disease can be confused with symptoms of other neurological diseases. Accurately diagnosing PD is important so that patients can receive the proper treatment and advice regarding care. In addition, diagnosing PD early is important because treatments such as levodopa are more effective when administered early in the disease. Non-pharmacologic treatments, such as increased exercise, are also easier to perform in the early stages of PD and may help slow down disease progression [1].

For optimal treatment of this disease, it is important to know the state of its progression, since motor manifestations, ability to perform daily functional activities and symptomatic response to medication may differ depending on the level of disease progression. For rating the severity of disease clinical scales are used, of which the most common are the Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr [26] staging and PDQ-39.

The UPDRS scale is the most accepted tool for evaluation of interventions and as a clinical tool to follow patients. The current UPDRS includes four subscales. Subscale 1 covers mentation, behavior and mood. Subscale 2 rates activities of daily living. Subscale 3 is a clinician rating of the motor manifestations of PD. Subscale 4 covers complications of therapy. Data for subscales 1, 2, and 4 are elicited from patients and caregivers, whereas data for subscale 3 is examination-based [26].

The Hoehn and Yahr staging is probably one of the most widely known evaluation of people with PD and was first described in 1967. It is really a simple staging from 0 to 5 of the motor manifestations of PD, intended to reflect the degree of progression, and combines features of motor impairment and disability [26].

The PDQ-39 is a 39-item self-report questionnaire that assesses the health-related quality of Parkinson's disease over the past month, how often patients experience difficulties on the 8 dimensions of quality of life, and the impact of the disease on specific dimensions of functioning and well-being [27].

These categorical scales are susceptible of subjectivity and noncommon analysis between clinical community [13]. Clinicians are limited to the information observed during the visitors which can be affected by patients' mood or medication phase [13]–[16]. Besides, motor symptoms assessments during routine consultations are strongly dependent of patients' memory to describe their last motor episodes [15]. These facts highlight a remaining challenge between the scientific community to develop technological solutions that enable to monitor motor symptoms in patients' home-settings providing continuous and more objective data [14], [28].

2.2 How wearable biofeedback devices can improve motor performance in Parkinson's disease: a review

2.2.1 Introductory insights

Some studies have already been developed and with positive findings with the use of sensory cues through WBD. However, for future research in WBD, it is important to understand what has already been achieved and what limitations are yet to overcome.

The literature biofeedback systems employed different sensory cues (visual, auditory and tactile), in open or closed loop and to different purposes to improve the motor symptoms in PD patients: FOG [29]–[34], balance [10], [35]–[39] and reducing the risk of fall [40], [41]. The sensory cues are applied to produce changes in postural control [40], [42], stepping pattern [32], unfreezing gait-blocks [29], prevent falls [40], [41], and, consequently less gait variability. Other reviews [14], [43], [44], usually, have some of the follow gaps: portray only one problem, like FOG for example, do not include studies that improve other problems associated with PD; use only patients with a specific stage of disease; do not describe the location of the sensors and actuators; do not depict the algorithms used and the processors used; do not refer the wearability of the biofeedback system; they do not describe how the articles validate the WBD; sometimes, they only use articles that have one specific outcome; and they don't feature the biofeedback strategies employed in the articles. This review aims to cover the identified gaps.

The purpose of this review is to find out how the technologies were integrated into the WBD; how the biofeedback strategies were applied; and how the devices were validated (study population, protocols, criteria study metrics and WBD effects).

This review objective is to determine what type of WBD have been assessed in PD, in the last ten years, and with which goals and effectiveness. For this purpose, it was summarized and assessed the quality of the current evidence. The following questions were investigated and answered:

- RQ1 “Which technologies were integrated WBD, what are their setting parameters and where were they placed?
- RQ 2 “How have the biofeedback loops been applied in PD to mitigate gait-associated impairments?”
- RQ.3 “How the WBD have been clinically validated?”

2.2.2 Methods: Data Sources, Search Strategy and Studies Selection

An electronic systematically search was carried out on databases as Google Scholar, PubMed and Web of Science, looking for research papers that based on sensory cueing biofeedback technologies for improving PD gait-associated disabilities. The literature search was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), as depicted on Figure 4. The keywords used on the databases were: [“Biofeedback AND Parkinson's Disease”]; [“Freezing of gait AND Parkinson's Disease”]; [“Freezing of gait AND Medical Devices”]; [“Sensory Cues AND Parkinson’s Disease”]; [“Rehabilitation AND Parkinson’s Disease”]; [“Vibrotactile AND Parkinson's Disease”]; and [“Parkinson's Disease AND Assistance”].

Studies were included in the review if they fulfilled the following inclusion criteria: (i) studies of idiopathic PD; (ii) cueing systems were used as part of rehabilitation or assistance strategies; (iii) wearable technology was integrated; and (iv) results were published in the English language and within the past 10 years. The exclusion criteria were: (i) studies not validated with patients with PD; (ii) studies that used invasive therapies; and (iii) studies that do not present technological resources.

2.2.3 Results

2.2.3.1 General Results

A total of 97 articles were identified: Google Scholar (n=31), PubMed (n=42), and Web of Science (n=23) databases. Duplicates were removed (n=61). Articles were excluded if the titles (n=6) and abstracts (n=9) did not correspond to the inclusion and exclusion criteria. If the abstract of an article did not provide enough information to determine its eligibility, the full article was reviewed. After the full-text papers were reviewed, fifteen articles met the eligibility criteria and were included in this scoping review. Figure 4 depicts this approach. Fifteen original studies were identified [10], [29], [38]–[42], [30]–[37] and were grouped and discussed according to their application goal, if they were used to mitigate FOG, to improve balance or to reducing the risk of falls.

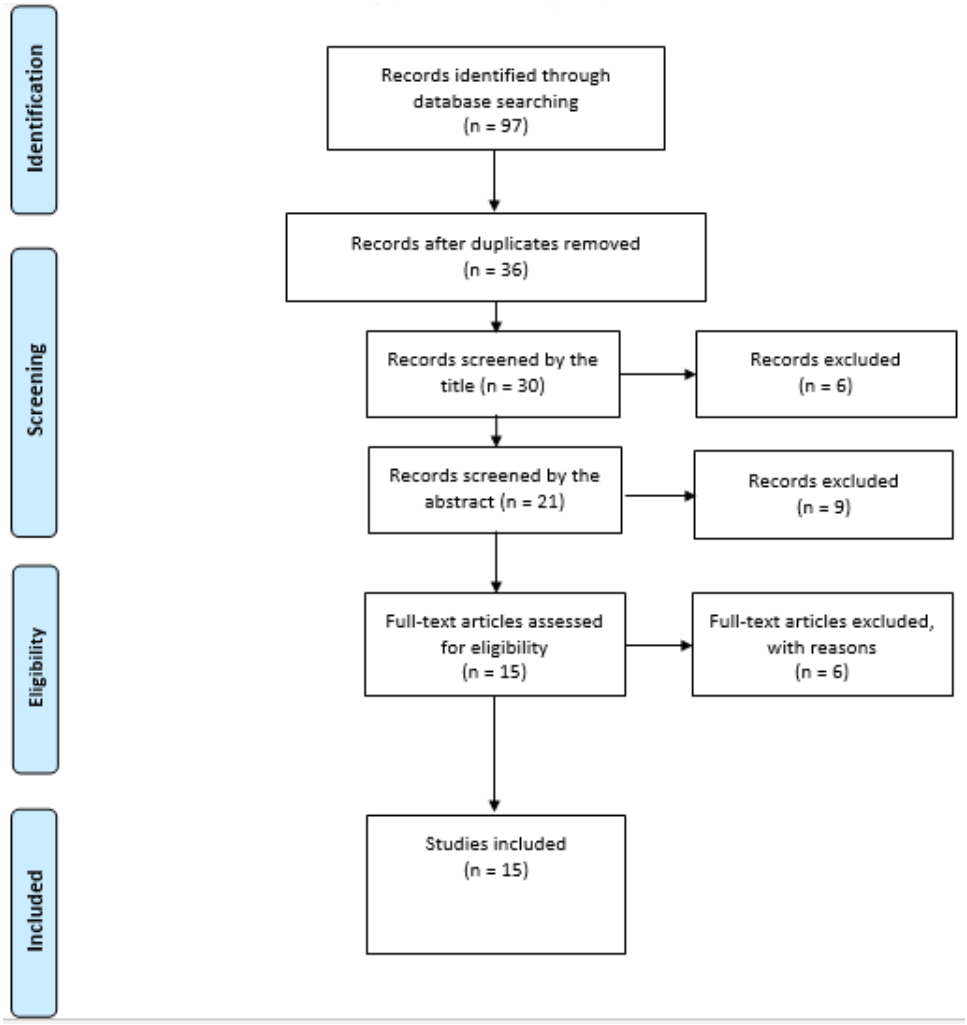

Figure 4. PRISMA Flow Chart.

2.2.3.2 TECHNOLOGY SUPPORTING WBD

WBD are constituted by a cueing system or actuation system that is responsible for providing the cues, and a sensory system that is responsible for acquire physiological measurements.

WBD developed to mitigate PD gait-associated disabilities employed the three types of sensory cueing. Eleven studies applied vibrotactile cueing, while four studies used visual cueing and three investigations utilized auditory cueing. The systems that used vibrotactile cueing are based on linear [10], [29], [34], [35] and rotary electromagnetic actuators [30]–[33], [36], [37], [41]. The vibratory frequencies applied varied from a range of 200-300Hz. Regarding on-body vibratory motors location, different zones were used, being a higher concentration of studies which integrated motors in upper trunk, namely in waist level [25], [29], [35], [37], [41] and torso [10]. Less frequently, some studies placed the vibrotactile actuation system on the head [36], ankle [30], legs [16], [31]–[33] and wrist [34].

For the visual cueing, the information was provided using monitors [10], [38], [39] or semi-immersive binocular head-mounted displays [40].

For the auditory cueing, the information was provided using headphones [42] and earphones [30].

Regarding the sensory acquisition system, Inertial Measurement Units (IMUs) [10], [29]–[35], [40] were frequently integrated into the WBD. Advantageously IMUs have built-in tri-axial accelerometers, gyroscopes and/or magnetometers on a single miniaturized chip, such as SwayStar [36], e Sensaction-AAL [42], TMA [38], Xsens [39] and VertiGuard [41]. Thirteen studies [10], [29], [39], [40], [42], [30]–[36], [38] used acceleration and angular velocity as input of control biofeedback strategies. Only [38] used the magnetometer output signals. Force sensor resistive (FSRs) were also employed in sensory acquisition systems [32], [37], [39], being integrated on shoe insoles [32]. Conversely to these wearable sensors, IMUs and FSRs, [37] and [39] used force plates to provide the sensory information regarding patients' gait and balance.

In terms of total wearability, only five studies from the total of fifteen studies did not integrate the actuation and sensory system on a unique device.

Table I. Information about the Gait-associated disabilities, Sensory cueing system, Sensory acquisition system and Single one wearable system

Articles/Year	**Gait-associated disabilities**	**Sensory cueing system**				**Sensory acquisition system**			**Single one wearable system**
		Cue	Device	Number	Location	Device	Location	Number	
[35]/2018	Balance	Vibrotactile	C2 tactors (LRA)	4	Waist	IMU	Lower back	1	Yes
[36]/2012	Balance	Vibrotactile	ERM	8	Head	SwayStar	Lower back	2	Yes
[37]/2018	Balance	Vibrotactile	Sensory Kinetics System ERM	8	Waist	Force plate	Feet	1	No
[10]/2015	Balance	Vibrotactile or visual, or both	C2 tractors (LRA)/ one monitor	4	Torso	IMU	Lower back	1	No
[38]/2017	Balance	Visual and auditory	Moving avatar displayed on the monitor and/or auditory feedback about his/her motion	2	Eyes	Wearable inertial sensors (TMA)	Upper trunk, lower trunk, and lower limbs	8	No
[39]/2013	Balance	Visual	42" flat-panel LCD monitor	1	Eyes	Inertial sensors (Xsens) and a force plate	Feets, upper leg and chest	3	No
[42]/2011	Posture	Auditory	System with headphones	1	Ears	Sensaction-AAL	Lower Back	1	Yes
[40]/2014	Falls	Visual	Semi-immersive binocular head-mounted display	1	Eyes	IMU	Cranial vertex and at the level of the spine	2	Yes
[41]/2012	Falls	Vibrotactile	Vibration stimulator ERM	4	Waist	Vertiguard	Belt	1	Yes
[29]/2018	FOG	open-loop cueing (auditory), close-loop (vibrotactile)	VibroGait (LRA)/ metronome	1	Waist	wireless, synchronized inertial sensors (IMU)	both shins, feets, wrists, sternum and on the posterior trunk	8	No
[30]/2019	FOG	Auditory and Vibrotactile	Vibration motor (ERM) and BLE capable earphones	2	Ankle	IMU	Ankle	2	Yes
[31]/2017	FOG	Vibrotactile	Vibratory motor ERM	2	Leg	MPU 6050/IMU	Right leg	1	Yes
[32]/2016	FOG	Vibrotactile	Vibratory motor ERM	1	Left sole	IMU/pressure sensor embedded into a shoe insole	Right ankle/foot	1/1	Yes
[33]/2017	FOG	Vibrotactile	Micro Vibrating motors DC ERM	2	Both legs	IMU	Right limb (ankle)	1	Yes
[34]/2016	FOG	Vibrotactile	C-2 tactor (LRA)	1	Wrist	IMU	Shins	2	Yes

2.2.3.3 BIOFEEDBACK STRATEGIES

Table II summarizes the identified manuscripts regarding the adopted biofeedback strategies. Studies were grouped regarding the type of biofeedback strategy, sensory acquired response, sensory cueing provided and implemented algorithm. Regarding, the biofeedback strategy it was used a categorization described in [12] which subdivide biofeedback strategies in three types: 1) rescue strategies; 2) phase-dependent; 3) on-going;.

When applied rescue biofeedback strategies, technological devices delivered sensory cueing after a gait-associated disability occur (e.g., when FOG is detected, or patient sway overcomes a pre-defined threshold) as verified on [30]–[33], [35]–[38], [41], [42]. Phase-dependent strategies deliver sensory cueing concerning a identified sensory state (e.g., during the gait stance phase) as applied by [29], [34]. On-going biofeedback strategies provided sensory cueing during the time that a certain exercise is done as employed in [39], [40]. Preferably, the identified studies provided rescue strategies [30], [31], [42], [32]–[38], [41], while [29] adopted a phase-dependent biofeedback strategy and [39], [40] provided going biofeedback. [9] combined rescue and on-going strategy.

Eleven studies used real time algorithms based on heuristic rules [10], [29], [42], [34]–[41]. [30] used a machine learning algorithm to detect FOG. Discrete Transformed Wavelet and Fast Fourier Transform with heuristic rules were also applied by [33] and [32], respectively, to process sensory Information and delivery cues.

WBD requires a central processing unit responsible to read the sensory information, filter, interpret and process the acquired information and send the commands to the actuation systems, when required. Six studies used computers [10], [32], [37]–[40], while [42] used a Personal digital assistant Other electronic boards were applied, as a FPGA on [30] and ATmegas' on [29], [34], [41]. Further, a smartphone was also used by [33] and combined with an ATmega board in [31]

Table II. Information about the different biofeedback strategies, sensory acquired response, sensory cueing provided and algorithm used.

Study	Gait-associated disabilities	Biofeedback strategy type	Sensory acquired response	Sensory cueing provided	Algorithm	
					Approach	Processor
[35]	Balance	Rescue	Angular displacements and velocities in the A/P and M/L directions	Vibrotactile	HR	NI
[36]	Balance	Rescue	Trunk sway (angular velocity)	Vibrotactile	HR	NI
[37]	Balance	Rescue	Center of pressure path length, velocity, and sway area	Vibrotactile	HR	Computer
[10]	Balance	Rescue and on-going	Angular displacements and velocities in the A/P and M/L directions	Vibrotactile or visual, or both	HR	Computer
[29]	FOG	Phase-dependent	3-D linear accelerations and 3-D angular velocities	Open-loop cueing (auditory), close-loop (vibrotactile)	HR	ATmega328
[42]	Posture	Rescue	Trunk inclination and local accelerations	Auditory	HR	Personal digital assistant (PDA)
[40]	Falls	On-going	Angular measures, angular velocity and acceleration	Visual	HR	Computer
[30]	FOG	Rescue	Accelerations and angular velocities	Auditory and Vibrotactile	ML	FPGA
[38]	Balance	Rescue	Acceleration, angular velocities, 3-d magnetometer measures and the sensor's orientation in space (Euler angles)	visual and auditory	HR	Computer
[39]	Balance	On-going	Acceleration and rotation of the upper body; center-of-pressure displacements (COP)	Visual	HR	Computer
[31]	FOG	Rescue	Acceleration data of the lower extremity	Vibrotactile	wavelet transform-based algorithm	ATmega328/smartphone
[32]	FOG	Rescue	Acceleration (vertical linear acceleration) and gyroscope information; Pression on the left sole	Vibrotactile	FFT + HR	Computer
[33]	FOG	Rescue	Acceleration	Vibrotactile	DWT	Smartphone
[34]	FOG	Phase-dependent	3D accelerations and 3D angular velocities	Vibrotactile	HR	ATmega328

[41]	Falls	Rescue	Body sway analysis, gyroscopic information	Vibrotactile	HR	ATMega168

HR – Heuristic rules; ML – Machine Learning; FFT – Fast Fourier Transform; DWT – Discrete Transformed Wavelet; NI – Not Identified;

The adopted biofeedback strategies were analysed on the following sub-chapters, considering the type of biofeedback.

- Rescue biofeedback strategies:

Beom-Chan Lee et al. [35] explored the effects of two coding schemes (binary versus continuous) for vibrotactile biofeedback during dynamic weight-shifting exercises that are common physical therapists' recommended balance exercises used in clinical settings. The proposed biofeedback system consisted on the acquisition of the angular and velocity displacement to adopt a heuristic rule algorithm to identify the motion error and, when detected, supply a vibrotactile cueing. It was used a custom software to generate a target motion based on 90% of the patients' measured limits of stability (LOS) in each four movement directions (i.e., anterior-posterior (A/P) and medial-latera (M/L) direction). LOS in each A/P and M/L direction were obtained from body sway in degrees which corresponded to the furthest deviations of body sway from a neutral starting point with respect to the ankle joint. A proportional plus derivative control scheme based on differences in both body sway angle and angular velocity between the target and participant's motions was used to determine the motion error. The custom software activated the vibrotactile motor with the maximum peak-to-peak amplitude when the absolute motion error exceeded 1 degree, while all motors were deactivated when the absolute motion error dropped below 1 degree. Another control scheme was used based on a continuous coding scheme, where the intensity of the vibrations was continuously modulated as a function of the magnitude of the absolute motion error between 0 and 1 degree.

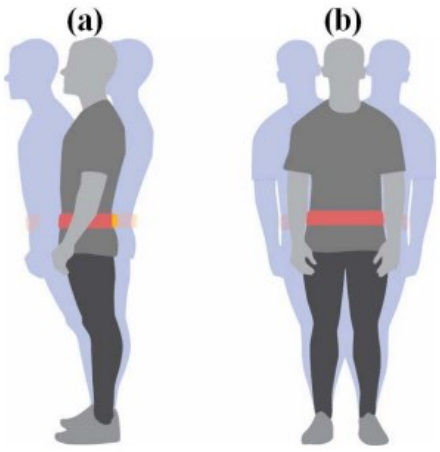

Figure 5.Illustration of the dynamic weight-shifting balance exercises in the A/P (a) and M/L (b) direction. Based on REF. Taken from [35].

In [36], it was investigated whether balance in PD can improve by offering patients feedback about their own trunk sway as a supplement to natural sensory inputs. The system consisted of: two angular velocity sensors worn on the back which measured A/P and M/L movements of the trunk; and a headband with eight vibrotactile motors equally spaced, which delivered 250Hz vibratory cueing. When the trunk sway exceeded the A/P or M/L sway threshold, the headband provided vibrotactile cueing activating the motors in the corresponding direction of the movement, aiming to help patients to correct their posture. Once the patient body sway crossed the trunk sway threshold, the vibrotactile at the corresponding site remained active as long as the threshold was exceeded.

Carleigh et al. [37] investigated the postural control response to vibrotactile feedback provided at

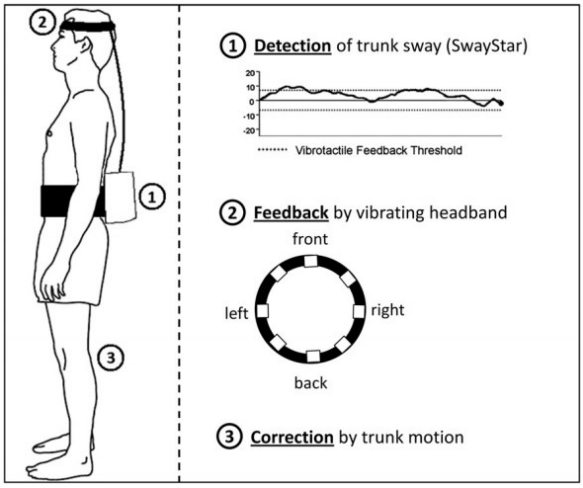

Figure 6. Schematic illustration of the biofeedback system. Taken from [36].

the trunk during challenging stance conditions. The system used a force plate to provide the sensory information, namely the patient centre of pressure (CoP). Vibrotactile feedback was provided when patients' CoP overcomes 10% of the CoP estimated on the baseline session. To provide the vibrotactile information, it was used a belt with eight embedded sensors around the participant's waist at the level of the umbilicus.

Figure 7. Participant wearing vibrotactile belt at the waist level and standing on the force platform. Taken from [37].

Anat Mirelman et al. [42], tested the feasibility and effects of training with auditory biofeedback in patients with vestibular dysfunction. This audio-biofeedback system uses the information of trunk inclination and local accelerations, measured by Sensaction-AAL, to provide auditory biofeedback via headphones. This auditory feedback was modulated in frequency and amplitude by the participants movement and change of body orientation in both the M/L and A/P directions. The modulation of the sound was tied to one or more target zones which were adaptively estimated during a short initial calibration phase in the beginning of each training session. Two different types of feedback were used: negative feedback, a sound outside of the target zone, for example, posture correction during standing; in the form of a higher pitch sound was provided if the subject returned to a mal aligned posture from the desired erect position; positive feedback, a sound inside the target zone, in which the device was silent

Figure 8. The ABF device used in this study. Taken from [42].

when the movement was correct.

Val Mikos et al. [30] studied a biofeedback system that provided vibrotactile cueing in the ankle, when an episode of FOG was detected. FOG episodes were detected by processing the acceleration and angular velocities acquired by an IMU placed on the patient's right ankle. The algorithm used Neural

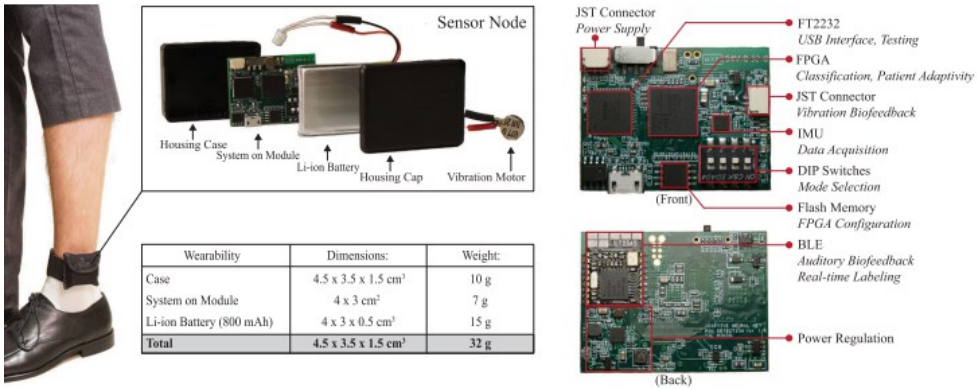

Figure 9. Biofeedback system. Taken from [30].

Networks, for FOG-detection in real-time and adaptability.

Ilaria Carpinella et al. [38] aimed to analyse the feasibility and efficacy of a novel system (Gamepad) for balance and gait biofeedback rehabilitation in PD. The Gamepad consisted of 6 wearable inertial sensors (TMA), a personal computer with a display screen and customized software, for real-time data acquisition/processing and feedback generation, as depicted in Figure 10. The monitor displayed an avatar that replicates the motion of the subject and if the avatar exceeded the target area (within the black bars) its head become red and an alarm sound is provided.

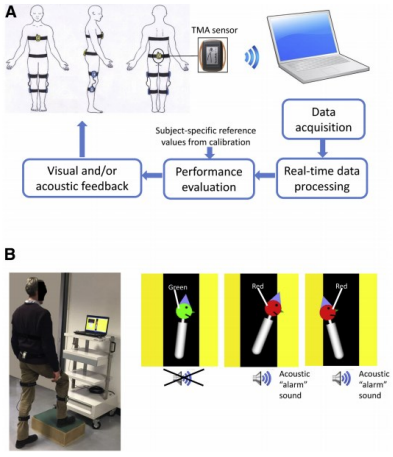

Figure 10. (A) Schematic representation of the Gamepad system. (B) Example of a subject controlling the AP inclination of his trunk while placing a foot on a step (left panel). The patient performs the task by looking at an avatar replicating the motion of his trunk on the PC screen (right panels). If the avatar is not maintained within the black bar (tailored reference target area), its head becomes red and an alarm sound is provided. Taken from [38].

Catalina Punin et al. [31] described a low-cost wearable system for non-invasive gait monitoring and external delivery of superficial vibratory stimulation to the lower extremities triggered by FOG episodes. The proposed device, acquired inertial data from right and executes vibratory feedback on the left leg, as

depicted in Figure 11. A discrete wavelet transformation was used to proceed acquired acceleration data to detect FOG, which had a specificity of 86.66% and a sensitivity of 60.61% in the FOG detection.

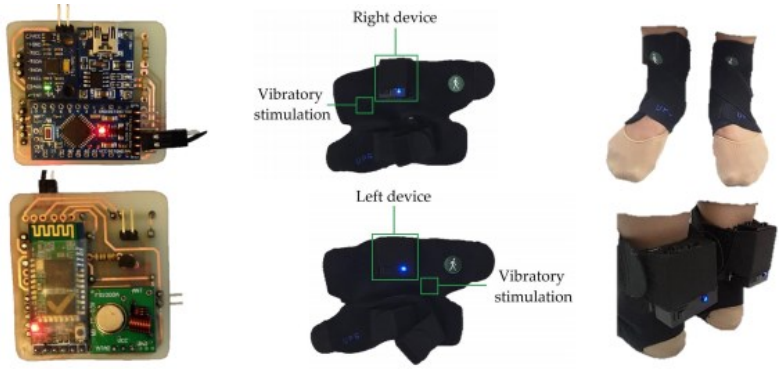

Figure 11. Device placed in patient. Taken from [31].

Alvarado Cando et al. [32] presented a low-cost stimulus system to support patient response to a FOG episode by using a vibratory cueing. Freezing episodes were automatically detected by using a FFT analysis on inertial data from an IMU placed patients' right ankle. A pressure sensor embedded into a shoe insole is also used to reduce false-positive episodes, as depicted in Figure 12. This data is transmitted using Bluetooth technology to a PC and once a freezing event is detected, vibratory feedback

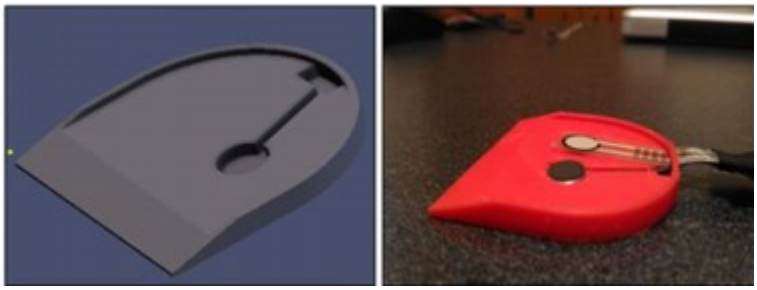

Figure 12. Right shoe insole: design (left) and construction (right). Taken from [32].

was produced on the left insole by triggering a micromotor at 275 Hz, when a FOG event was identified.

Figure 13. Vibratory stimulus embedded system. Taken from [32].

In research [33], it was developed a hardware-based wireless system to detect FOG and deliver sensory cues to stimulate walking progression, prevent falls, and improve patients' lifestyles. The actuation system was placed near the posterior tibial nerve of the lower extremities and patients' gait was

automatically detected by a three-axis accelerometer coupled to an IMU. A smartphone was used to process the acquired inertial, by applying the DWT and detect the FOG episodes. When FOG was detected, the vibrotactile actuation system was activated on both legs.

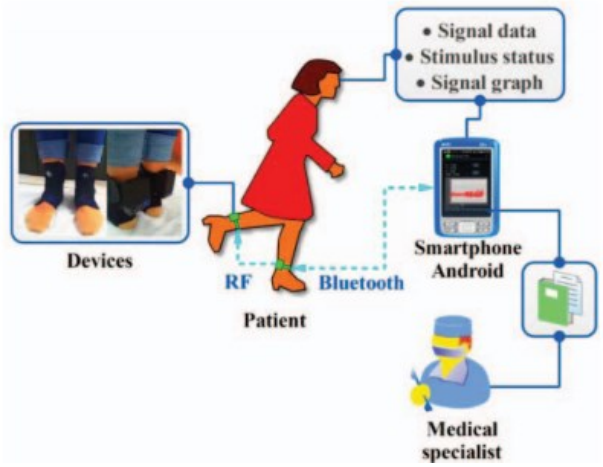

Figure 14. Device and biofeedback system. Taken from [33].

[41] aimed to assess the effectiveness of a balance training with a vibrotactile neurofeedback system, named Vertiguard-RT. Vertiguard-RT is a commercial body-worn device fixed on a belt, which records body sway in the roll (lateral) and pitch (antero-posterior) planes at the centre of body mass as depicted in Figure 15. Trunk sway was measured by built-in gyroscopes at the hip while the subjects were asked to carry out the standard balance deficit test (SBDT). Pitch and roll angles were continuously measured and compared with individual predefined thresholds to provide vibrotactile sensory cueing in specific directions. If patients' trunk pitch/roll angles exceeded the threshold, the vibrations started and were stronger when sway increased. If the patients sway was below the thresholds, no vibrotactile cueing was applied.

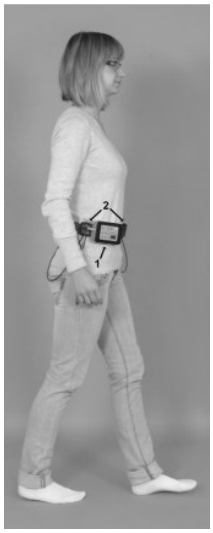

Figure 15. Vertiguard1-RT vibrotactile neurofeedback system with a main unit (1) and vibration pads (2). Taken from [41].

- Phase-dependent biofeedback strategies:

Martina Mancini et al. [29] investigated the immediate effectiveness of open- and closed-loop cueing in improving walking turning characteristics, given turning can be a trigger-factor for freezing events. Vibrotactile biofeedback was applied during the gait stance phase and an open-loop feedback strategy was also explored by delivering a metronome beat. For the closed-loop vibrotactile biofeedback strategy, data provided by IMUs, placed on both shins, feet, wrists, sternum and posterior trunk, where used to detect patients gait stance phase and, during this gait phase-dependent, vibrotactile was provided.

Will Harrington et al. [33] also designed and tested a phase-dependent vibrotactile biofeedback system. The system used accelerometers and gyroscopes on both foots, as depicted in Figure 16, to detect when the users were in the stance phase of gait and delivers vibrotactile cueing.

- On-going biofeedback strategies:

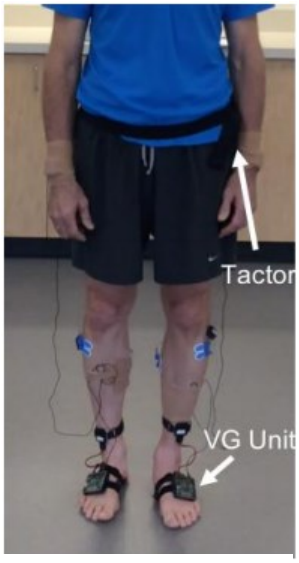

Figure 16. Experimental Setup. Taken from [33].

The study [40] aimed to evaluate if a visual biofeedback was able to improve patients' postural control in response to a postural disturbance, by providing a visualization of a self-avatar through a head-mounted display.

In order to evaluate the effect of the visualization in real time of the body's geometry on postural orientation and stabilization, a visual biofeedback device was developed. The investigators used IMU sensors. Two sensors were placed in the cranial and at the level of the spine processes of the 7th–8th

thoracic vertebras. The visual feedback was provided by a semi-immersive binocular head-mounted display which simulated the viewing of the image (a graphic representation of the body's geometry of the

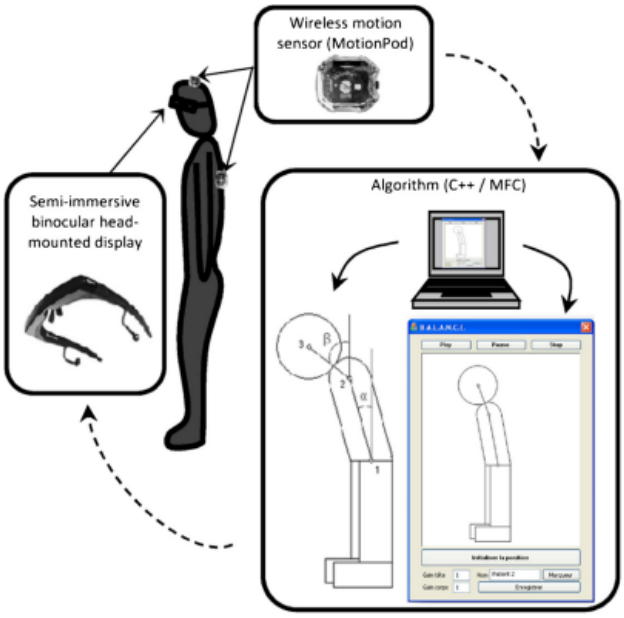

Figure 17. Architecture of the visual biofeedback device used in this study. Taken from [40].

participant) at a distance of 1 meter.

Maarten RC van den Heuvel et al. [39] aimed to investigate whether a training program capitalizing on virtual-reality-based visual feedback is more effective than an equally-dosed conventional training in improving standing balance performance. Movement registration was accomplished using inertial sensors (Xsens) and a force plate, while visual feedback was given using three workstations set up in a gym. A computer was used to map body motion to move an object (avatar) on the monitor, by interactions with balance games that were running on the workstations. Figure 18 illustrates the key features of these workstations.

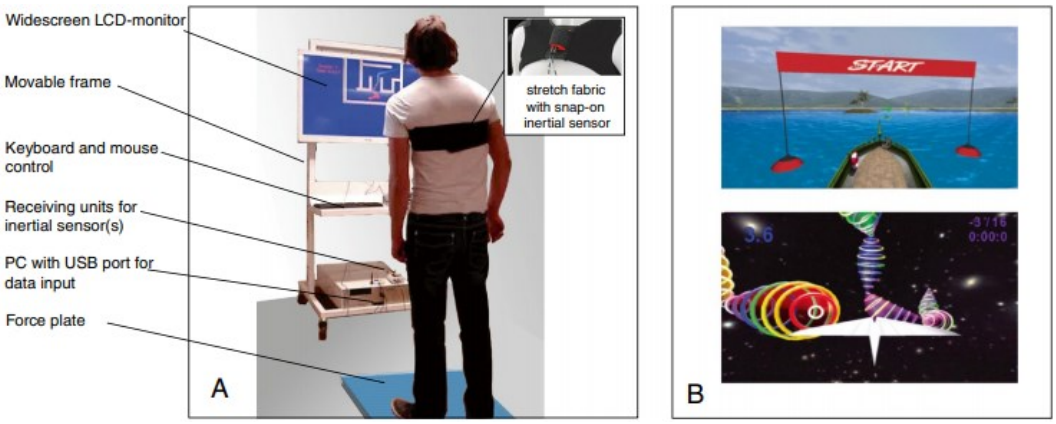

Figure 18. Illustration of the intervention of the experimental group. A: Setup of mobile workstation with force plate and/or inertial sensor. B: Screenshots of examples of balance games. See text for further details. Taken from [39].

- Combination of rescue and on-going biofeedback strategies:

Research described in [10] purposed to evaluate the effects of guidance modalities during common dynamic weight-shifting exercises used in clinical settings. A motion guidance system providing visual biofeedback, vibrotactile biofeedback, or both, was used during weight-shifting exercises. An IMU was used to measured angular displacements and velocities of body tilt in A/P and M/L directions. A custom software was used to generate target movement trajectories in degrees by measuring the participant's 90 % of LOS in A/P and M/L directions. This software provided command signals to activate tactors when the absolute value of the error signal exceeded the tactor activation threshold set at 1.0°. Vibrotactile biofeedback was deactivated when the error signal dropped below 1.0°, and thus the tactor activation

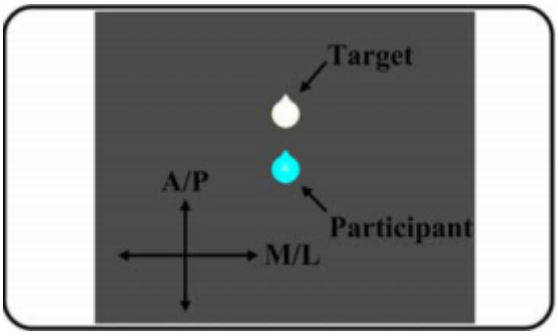

Figure 19. Visual biofeedback. A white and light blue object depicts the target and participant's movements in A/P and M/L directions. Taken from [10].

was binary in nature. Similar to a computerized visual display of body sway, two virtual objects were displayed in a virtual environment in order to indicate target and participant's movements, as illustrated in the Figure 19.

2.2.3.4 Clinical Highlights: Participants, criteria study, metrics and WBS effects

Table 3 summarizes the clinical highlights of the studies. It shows the study design, the number of PD patients used, the control group, the criteria of the study (inclusion and exclusion) to select the patients, the protocol and metrics followed in the trials and the effects of the WBS.

In [35], there were used three metrics: LOS, PE and XCOR. The participants LOS in each A/P and M/L direction were obtained from body sway in degrees that corresponded to the furthest deviations of their body sway from a neutral starting point with respect to the ankle joint. Also, to characterize participants' ability to perform dynamic weight-shifting balance exercises as a function of the coding scheme and movement direction, two metrics were computed for each trial: cross-correlation (XCOR) and position error (PE). XCOR quantitatively measures similarities of two time-series signals as a function of

the angular displacement of the participant relative to the angular displacement of the target. PE is computed as an average absolute difference between the target and participant's movements in degrees. This study shows that both groups had greater XCOR and less PE with the continuous coding scheme than with the binary coding scheme. This study also revealed that both groups of participants significantly improved LOS in both A/P and M/L directions.

In [36], the outcome measures included duration until completion of the task (only for the walking tasks), the 90% range of pitch and roll sway angle and the 90% range of pitch and roll sway angular velocity. Since roll sway angle, roll sway angular velocity, and pitch sway angular velocity were decreased in the biofeedback group compared to controls, it is believed that WBS can improve balance in PD.

In [37], it was used the CoP raw data to find the total path length, mean velocity and 95% elliptical sway area. The investigators proved the effectiveness of the vibrotactile biofeedback during challenging stance conditions. They measured a decrease on the distance travelled by CoP, a decrease on the mean velocity, an increase on the sway area and an increase on the α value (sway fluctuations occur in few time scales).

Table III. Information about the clinical highlights of the studies.

Study	Study Design	Participants		Criteria study		Randomized	Protocol	Metrics	WBD Effect
		PD	Control	Inclusion	Exclusion				
[35]	Case-control Study	9	NI	Bilateral symptoms with impaired postural stability;	1) cognitive score less than 24; 2) were not ready for physical activity; 3) dyskinesia; 4) severe distal sensory loss; 5) were medically unstable; and 6) any peripheral, neurological or musculoskeletal conditions.	No	Dynamic weight-shifting balance exercises	LOS; Position error; XCOR;	Better LOS and less position error; Improvement of XCOR;
[36]	Case-control Study	20	10 PD	All participants were tested while on medication;	Causes of balance impairment other than PD; inability to walk without walking aids; cognitive or psychiatric disturbances; severe co-morbidity;	Yes	Pre-training: two sets of six gait and six stance tasks; Training: six balance exercises five times; Pos-training: repeated all twelve tasks;	Sway angle and sway angular velocity in the roll and pitch plane; task duration;	Decrease: sway angle and sway angular velocity in the roll and pitch plane;
[37]	Case-control Study	9	10 healthy older adults	High fall risk;	NI	No	30 seconds standing barefoot in different conditions : feet together, eyes open on firm surface, feet together, eyes closed on firm surface,3) feet together, eyes open on foam surface, 4) feet together, eyes closed on foam surface, 5) tandem stance with eyes open on firm surface.	COP (Path length and velocity); Sway area;	Decrease: COP Path length and velocity; Increase: Sway area;
[10]	Case-control Study	11	9 healthy elderly	Bilateral symptoms with impaired postural stability (a score of 3 or 4 on the Hoehn and Yahr scale); taking medication to alleviate tremor, bradykinesia, and muscle rigidity;	1) not read and comprehend English; 2) difficulty standing for prolonged periods; 3) unable to stand for 1 min with their eyes open and closed; 4) severe distal sensory loss as	No	-12 familiarization trials; -5 min seated rest; -weight-shifting balance exercises as a function of the modality and direction with 5 repetitions for a total of 30 trials,	SOT; LOS; Position error;	Improve LOS; Decrease position errors;

					demonstrated by a 5.07 g monofilament test; 5) limited ankle range of motion; 6) reported lower extremity fracture/ sprain in the past six months or previous lower extremity total joint replacement; 7) medically unstable; 8) active motionprovoked vertigo or a diagnosed vestibular deficit; 9) cognitive level less than 24 determined by MMSE.		the order of trials was randomized for each participant;		
[29]	**Case-control Study**	43	NI	Diagnosis of idiopathic Parkinson's disease with sensitivity to levodopa and of-medication; Hoehn & Yahr scores of II-IV;	Other factors afecting gait; inability to stand; inability to walk for 2 minutes at a time; Inability to safely walk 20 feet without walking aids; any musculoskeletal or vestibular disorder; dementia;	No	One minute under single- and dual-task for 3 randomized conditions: (i) Baseline; (ii) Turning to the beat of a metronome (open-loop); and (iii) Turning with phase-dependent tactile biofeedback (closed-loop).	FOG ratio; %freezing time; N° of turns; Average of velocity; Average of jerkiness of turnings;	Decrease: FOG ratio; %freezing time; N° of turns; Average of velocity; Average of jerkiness of turnings;
[42]	Longitudinal Case Report	7	NI	Idiopathic PD (at least 2 years); ability to walk independently without a walking aid; e absence of serious co-morbidities that could impact gait or balance;	Suffered from major depression; score <24 on MMSE; clinically significant hearing problems which may hinder their ability to hear the feedback sound provided; medically unstable;	No	1 week of baseline training; 6 weeks of individualized training (3 per week) with posture control, transfer training, sway, reaching and stepping; 1 week of post training testing; 1 mouth later the follow up;	BBS; TUG; 5CR; PDQ-39; UPDRS; ABC; GDS-15;	Improve posture, static and dynamic balance and activities of daily living (ADLs);
[40]	**Cross-sectional study**	17	NI	ON-state of dopamine treatment;	NI	No	Sequences of pull-tests, either with eyes open, eyes closed or visual biofeedback, crossed with the verbal instruction to focus either on the stabilization or on the vertical body orientation.	N° of falls; the stability performance; trunk orientation; trunk inclination;	Improved postural control (stabilization and orientation); less falls;

[30]	NA	63	NI	NI	NI	NI	7-meter timed up-and-go exercises and random walks	Specificity and sensitivity in the detection FOG	NI
[38]	Randomized controlled trial	42	Physiotherapy group N=20	Hoehn and Yahr stage 2 to 4; ability to stand up >10 seconds; inability to stand on 1 foot >10 seconds; ability to walk for at least 6m; stable drug usage;	Implanted deep brain stimulator; MMSE score <24;	Yes	Both groups underwent 20 sessions of training for balance and gait. The experimental group performed tailored functional tasks using Gamepad and the physiotherapy group underwent individually structured physiotherapy without feedback.	BBS; 10MWT; UPDRS; TUG; Freezing of Gait Questionnaire; PDQ-39; Prokin-PK252; CoP;	Improving Balance performances; Decrease sway/COP; Increase BBS;
[39]	Randomized controlled trial	36	Yes	ON-phase of levodopa medication; idiopathic PD, mild to moderate stage (i.e. Hoehn & Yahr stages II and III); able to participate in either of the training programs and written and verbal informed consent;	Presence of neurological, orthopedic, or cardiopulmonary problems that can impair participation; insufficient cognitive function (MMSE < 24); an unstable medication regime; any condition that renders the patient unable to understand or adhere to the protocol such as cognitive, visual, and/or language problems.	Yes	Patients are allocated to either a five-week training program with balance exercises containing augmented VF (experimental group), or a five-week balance training program that follows existing guidelines (control group)	COP; FRT; BBS; 10 MWT; UPDRS; Falls Efficacy Scale; PDQ-39; EEG-related outcomes;	Improvements in standing balance;
[31]	**Cross-sectional study**	7	1 healthy for control	Between 60 and 84 years of age;	NI	No	During testing, patients made some activities to stimulate FOG occurrence: • Walk in straight line, • 180 degree turns on the walk, • Climb steps	Specificity and sensitivity in the detection FOG; Acceleration and energy levels;	Decrease of FOG duration;
[32]	Case Report	5	1 healthy patient	NI	NI	No	Starting from a stand position (1); the participant will walk in a straight line (2); turn to left side (3); walk along a carpet of 2 meters (4); turn to left side again (5); and	Performance time; freezing duration; N° of FOG episodes;	Decrease: Performance time; freezing duration;

							finally walk around a chair and sit on it (6).		N° of FOG episodes;
[33]	**NA**	7 PD	1 healthy patient	NI	NI	No	Walk in a straight line, turns 180 degrees in the walk and climb stairs	Specificity and sensitivity in the detection FOG	NI
[34]	Cross-sectional study	8	NI	Idiopathic PD with FOG; be able to walk independently; tested OFF their antiparkinson medication in the morning;	Neurological disorders other than PD; orthopedic disorders; other impairments that could interfere with gait;	No	Turning was compared across 3 randomized conditions: i) turning without any external cue (baseline condition), ii) turning to the beat of a metronome (control condition), and iii) turning with phase-dependent tactile biofeedback via light vibration to the wrists every time the ipsilateral foot was in stance phase (biofeedback condition).	% time spent freezing; average turn peak velocity and jerkiness; FOG ratio;	Decrease: % time spent freezing; average turn peak velocity and jerkiness; FOG ratio;
[41]	**Cross-sectional study**	10	NI	Had suffered at least one fall over the past three months; using the usual medication;	Used a wheelchair; additional neurological deficits; a history of peripheral vestibular disease; otoneurological examination was normal; dementia and the score in the Mini-mental test was 25 points or greater;	No	Computer-controlled platform training: -Baseline condition: no cue; -Randomized backward/forward translations: w/ feedback; SBDT tasks: -Baseline condition: no cue; -W/ biofeedback;	SBDT; SOT; DHI; ABC; N° of falls in the last three months; Average body sway;	Decrease: DHI; N° of falls; Body sway;
NI- not identifiable									

Study [10] used the SOT, which is commonly used to quantitatively assess the sensory and voluntary motor control of balance during standing, the LOS in both A/P and M/L direction and position error. The investigators concluded that both groups had the smallest position error between the target and participant movements when performing weight-shifting balance exercises accompanied by simultaneous delivery of visual and vibrotactile biofeedback regardless of A/P and M/L directions. They also find a LOS increase and no significant differences of the SOT scores between the two groups were observed in the evaluation of baseline balance performance.

In [29] it was estimated the FOG ratio as an index of freezing severity, the percentage of freezing time (time for which FOG ratio was higher than 1), the number of turns and the average turns peak velocity. It was also estimated the average jerkiness of the turns, quantifying the fluidity of turning. This study showed a marked improvement in certain measures of turning quality, freezing and smoothness, and decreased speed of turning while using either open-loop (metronome) or closed-loop (tactile biofeedback) cueing in people with PD. The investigators demonstrated a marked reduction of FOG severity and percentage time spent freezing during turning on objective measures of FOG indicating that both open-loop and closed-loop cues were similarly effective in reducing freezing. They also proved that cueing reduced the number of turns, and the average velocity of turning, but it significantly improved turning smoothness.

In [42], it was used: the Berg-Balance Scale (BBS), which consists of 14 different balance tasks such as standing, reaching, bending, and transferring abilities; The Timed Up-and-Go (TUG) test was used to assess the ability to perform sequence movements of functional mobility; the 5 chair rise (5CR) test was used to assess the ability to perform sit-to-stand and stand-to-sit transfers; The scores of the sub items and the total score of the Parkinson's disease questionnaire (PDQ-39) were used to determine health-related quality of life. To quantify extra-pyramidal signs and disease severity, the Unified Parkinson's Disease Rating Scale (UPDRS) was used and to assess the confidence in daily activities and the level of fear of falling, it was used the Activities-specific Balance Confidence (ABC) scale. Finally, the Geriatric Depression Scale short form (GDS-15) was used for the assessment of emotional wellbeing and depressive mood.

This study demonstrated some potential therapeutic effects on postural control and psychosocial aspects of the disease. Small, but positive changes were observed in the BBS, 5 chair rise test, TUG and the pull test of the UPDRS rating scale.

In [40], it was used as results metrics, the percentage of falls and instability during the trials, trunk orientation and trunk inclination. The investigators conclude that both components of postural control, i.e., stabilization and orientation, improved with the visual biofeedback, in comparison with the

eyes open and eyes closed conditions. Also, improving postural orientation, by extracting the body geometry information from the biofeedback to orient accurately the axial segments in the space, could have improved consecutively balance control. They observed that the occurrence of falls was significantly reduced by the visual biofeedback.

The paper [30] concluded that the proposed FOG detection system was successfully integrated into a sensor node that allows for patient adaptivity in real-time. The classification accuracy is comparable to recent software implemented ML based FOG classifiers and exceeds other FOG detection systems when evaluated on an unseen test set. Specifically, the system achieves 92.9% in average of sensitivity and specificity when exploiting its patient adaptive learning capability.

[38] measured balance and self-selected gait speed from BBS and 10-m walk test, respectively. Secondary outcomes included the following: disease-specific impairments (UPDRS-III), basic mobility function (timed Up and Go test), perceived confidence during activities of daily living (ABC), freezing severity (Freezing of Gait Questionnaire), perceived quality of life (PDQ-39), and a stabilometric assessment using a force platform (Prokin-PK252). Cop sway in AP and ML was also used. The investigators concluded that the experimental group had significant higher scores on the BBS than the physiotherapy without biofeedback group. Also, the findings about the BBS and ML body sway seemed to support the hypothesis that Gamepad-based training is superior to physiotherapy without feedback in improving balance in PD and increasing retention of some beneficial effects in the short term. The amplitude of CoP ML sway at post training was lower in the experimental group than the physiotherapy without biofeedback group, with a statistically significant large effect size favouring the experimental group. This finding is particularly notable because ML sway amplitude was found to be the best stabilometric parameter predicting future falls.

The study [39], used as primary outcomes the Functional Reach Test (FRT). The secondary outcomes included BBS and gait metrics, UPDRS, Falls Efficacy Scale, PDQ-39, COP as a postural outcome and, finally, EEG-related outcomes. The results indicated that balance therapy that incorporates some computer-based exercises can be at least as effective as conventional therapy. Such visual feedback-assisted balance training could be a cheap alternative to supervised one-on-one therapy, feasible to carry out at home and offering patients extra incentives for training as the exercises incorporate elements of gaming and competition by means of scores.

[31] obtained results of acceleration and energy. The acceleration data provided characteristics of the walk and allow for differentiating and extracting characteristics of the episodes of FOG, while the energy levels establish the beginning, duration and end of the episodes, permitting the activation of the

vibratory stimulation until the resumption of the gait. The technique used in this paper had a specificity of 86.66% and a sensitivity of 60.61% in the FOG detection. Also, highlights an improvement in the time reduction of the FOG episodes of each patient using vibrational stimulation versus measurements without any stimulation, approximately 27% reduction in the duration of FOG episodes.

In [32], time of the performance, duration of FOG and the number of FOG events are recorded. The results obtained from the participants shows that a vibratory stimulus generates a reduction on the freezing duration of 50.94%, also the time to complete the trial reduces showing an improvement of 34.25%.

[33] used DWT energy to obtain a WBD with a specificity of 86.66% and a sensitivity of 60.61% in the detection FOG, while the effectiveness for the resumption of the march after being detected a FOG is of 80%.

[34] extracted the FOG ratio as index of freezing severity, the percentage of time spent freezing during the task, average turn peak velocity and average turn jerkiness. It was obtained a reduction of FOG ratio from 2.5 to 1, a reduction of the % time freezing from 48% to 19%, a reduction of the peak velocity in turning from 95.2°/s to 84.2°/s and a reduction of the average of jerkiness on turnings from 0.54 m^2/s^5 to 0.41 m^2/s^5.

[41] used as outcomes the mean value of body sway in roll and pitch plane of SBDT/gSBDT, the SBDT composite score (Risk-of-Falling indicator), the SOT, the dizziness handicap inventory (DHI), the ABC and the number of falls in the last three months. The investigators conclude that there was a statistically significant improvement in body sway, number of falls, scores of SOT and ABC.

Regarding the study design, according to [45]:the articles [10], [29], [35], [37], [42] were Case-Control Studies; [31], [34], [40], [41] used a Cross-Sectional Study; the articles [38], [39] were Randomized-Controlled Trials; [42] was a Longitudinal Case Report; and [32] presented Case Report.

The study inclusion criteria for the participants selection was diagnosis of PD [29], [34], [35], [39], [42], having bilateral symptoms with impaired postural stability [10], [35], on medication [10], [36], [38]–[41], high risk of fall [37], [41], a Hoehn & Yahr scores of II-IV [10], [29], [38], [39], off-medication [29], [34], age between 60 and 84 years [31], ability to walk independently (ability to do the training) and do not present serious co-morbidities that could impact gait or balance [34], [38], [39], [42]. Regarding the study exclusion criteria, the participants were excluded if they had cognitive level less than 24 determined by MMSE [10], [35], [38], [39], [41], [42], were physically disabled for some reason [10], [29], [34]–[36], [41], they had severe distal sensory lost [10], [35], sensory loss [39], [42], dementia [29], [41], orthopaedic problems [34], [39], medically instable [10], [35], musculoskeletal or vestibular

disorder [29], [35], implanted deep brain stimulator [38] and neurological disorders other than PD [34]–[36], [41]. The participants selection had a clinical, cognitive and motor/sensory assessment. Further, factors that can influence the tests or the results must be eliminated.

Regarding scales used the Hoehn and Yahr (H&Y) scale and Unified Parkinson's Disease Rating Scale (UPDRS) were the most common scales, and they were used in [10], [29], [34], [36], [38]–[42]. Other scale, PDQ-39, was used to evaluate the patient's quality of life in the studies [38], [39], [42]. The Activities-specific Balance Confidence (ABC) was used in the studies [40], [41] to assess the balance sheet comprehensively. For having information about patients cognitive and mental stage was used the Mini Mental State Examination (MMSE) in the studies [10], [35], [38], [39], [41], [42] and the Montreal Cognitive Assessment (MoCA) [29], [42]. It was also used a FOG-questionnaire in the studies [38]. This scales approached can be distinguish in three groups: used for clinical assessment (UPDRS; H&Y); used for cognitive assessment (MoCA; MMSE); and motor/sensory assessment (ABC);.

In term of metrics used for evaluating patients using biofeedback strategies, they depend of the gait-associated disability of the paper. When the paper pretended to ameliorate FOG, metrics like FOG ratio [29], [34], %freezing time/freezing duration [29], [32], [34] and N° of FOG episodes [32] are used to evaluate the WBD. For balance proposes the metrics used were LOS [10], [35], position error [10], [35], path length [37], center of position (COP) [37], [39], sway area [37], roll/pitch [36], sway angle and angular velocity [36] XCOR [35] and SOT [10]. If the WBD was used to reduce falls the metrics used were the N° of falls [40], [41], body sway [41], ABC [41] and SBDT [41]. Other metrics were used when the studies had specific goals: validate the FOG detection system (Specificity and sensitivity) [30], [31], [33]; the TUG was used to posture purposes[42]; the 10MWT [38], [39]; time to perform a circuit [32]; metrics related to cognitive assessments and sensory perception like DHI [41] and SOT [10], [41]; studies that the tests involved turning had velocity during turns, number of turns, average turn peak velocity and jerkiness [29], [34].

2.2.4 Discussion

- RQ1 "Which technologies were integrated in the WBD, what are their setting parameters and where were they placed?"

WBD make use of technology to provide the user additional sensory information, beyond the one naturally available to him. This review showed how these devices provide sensory information to patients with PD. To do this, WBDs integrate sensors to measure motor information from patients and through an

actuation system provide sensory cues. Central processing system is responsible to process the acquired data and provide the commands to activate the actuation system.

The actuation systems included vibrotactile, visual and auditory sensory cueing. Vibrotactile cueing were delivered using miniaturized vibratory motors, which advantageously are small, being easily integrated on wearable devices

Concerning the vibratory frequencies adopted, it was observed that varied between a range of 200 to 300 Hz, which belongs to the human range of vibratory perception [25], so for the WBS the best is to use these frequencies.

Head, waist, torso ankles, legs, insole and wrist were the body zones selected to place the actuators. Even so, it was observed that the location and number of actuators could be related with the specific purpose of the device. For FOG purposes, it was typically used one actuator in one leg [29], [30], [32], [34] or one in each leg/foot [31], [33]. This could be explained since FOG are described as the feeling of have the feet glued to the ground, being suggestive to provide the sensory information also on the lower limbs, required only one motor. For fall/balance purposes, actuators were mainly placed on the trunk, being used frequently four actuators to cover A/P and M/L planes.

For the visual cueing, the information was provided using monitors [10], [38], [39] or semi-immersive binocular head-mounted displays [40]. The monitors were used to display figures or images giving to the patient visual information usually about is body position or about the task he must do. These monitors have the advantage of being common in our daily lives (e.g., monitor of the pc, television, etc.) and portable, but in other hand they are no wearable. Indeed, this is the higher disadvantage of this WBD based on visual cueing, since limits the use on rehabilitation sessions with more complex configurations, not being used during daily routine of patients. The semi-immersive binocular head-mounted display is a small display or projection technology integrated into eyeglasses. This device does not block the user's vision but superimposes the image on the user's view of the real world. So, this device can display the same information that monitors can and much more, being able to immerse the patient in an augmented reality. This device is fully wearable but has the disadvantage of being expensive. Also, when applied on daily basis scenarios could require some patients' cognitive efforts to focus on visual cueing.

For the auditory cueing, the information was provided using headphones and earphones. These two devices are totally wearable and economic. The headphones present some advantages when compared to earphones, since they can provide more comfort to the patient and they have better noise cancellation, giving the patient the ability to be more focused and immersed. However, this immersive

ability could be a disadvantage for WBD applied on home scenarios, since patients could not listen the other sounds.

To acquire inertial information, it was used two types of devices: IMUs and FSRs.

IMUSs acquire inertial data about the part of the body where is placed, being the most frequently sensors integrated on the sensory systems of the WBD. IMUs presents low-power consumption, are portable and easily integrated on wearable devices once they make use of front-end miniaturized technology [45]. In addition to these advantages, IMUs can be used for all purposes, balance, falls, posture and FOG.IMUs location usually depends on the WBD purpose. For FOG purposes, information about patients' gait is usually needed, so the sensor was usually placed on leg areas (ankle, foot and shins). For balance, posture and falls, sensors were usually placed on the lower back [10], [35], [36], [38], [41], [42], but also on chest, head and upper torso [38]–[40]. This body placement allows to obtain information about patients' sway, trunk inclination and changes in their posture.

The number of IMUs used also changes by means of the objective. When the WBD was applied to overcome FOG, one IMU was placed on the leg to obtain user gait information [31]–[33]. However, if it was required an analysis about the gait cycle of both legs, one IMU was placed on each leg [29], [30], [34] which difficult the wearability and the comfort issues. For balance, posture and falls, it can be used only one in the lower back [10], [35], [36], [38], [41], [42], since this alone, can give us a lot of information about sway, inclination and variations in the patient's posture. But, some studies, apply more than one, so they can have more information, normally, information about all upper body of the patient [38]–[40].

Besides IMUs, FSRs were also employed, which were placed on shoe insoles providing information about user foot contact [32], [37], [39]. Advantageously, these devices based on instrumented shoes integrates the actuation and sensory system on an unique device. However, this could limit the user footwear.

Regarding wearability issues, although most of the identified studies used fully wearable devices [30]–[36], [40]–[42], while 30% of the studies sacrifice wearability to get additional information (use of force plates) or provide additional cueing (auditory/visual cueing without wearable devices) or even have more computational power [10], [29], [37]–[39].

- RQ 2 “How have the biofeedback loops been applied in PD to mitigate gait-associated impairments?”;

Most of the studies implemented biofeedback loops that provide rescue strategies to help patients overcome some gait-associated disability: "when body sway exceeds a pre-defined threshold" [10], [35], [36], [41], “when participants swayed > 10% over the center of their base of support” [37], "when the patients where outside or inside of the target zone/area" [38], [42] and when the FOG occur [30]–[33]. In other words, if one of these events occur the biofeedback was activated. This type of biofeedback loop was used for all the four purposes: FOG, balance, posture and falls.

Typically, when WBD were applied to help patients with their balance or prevent falls, on-going biofeedback strategies were adopted, being usually used visual cues. Sensory cueing delivers information about users' position/orientation and target position/orientation during weight-shifting exercises; about users' orientation using virtual objects and avatars [10], [39], [40].

Another type of biofeedback strategy can be considered. In [29] and [34] it was applied phase-dependent biofeedback. This biofeedback is always provided in determinate event (e.g., during appropriate phases of gait cycle). This strategy was only used for FOG purposes.

Despite a wide spectrum of biofeedback strategies, all strategies presented positive results in help PD patients to overcome their gait-associated impairments. However, no one of the identified studies personalized the biofeedback strategy to the disease degree.

RQ.3 “How the WBD have been clinically validated?”;

To clinically validate this biofeedback systems the identified studies, usually included a baseline session, without providing biofeedback, and another session with biofeedback, providing the cue.

Particularly, [29], [34] used closed-loop cueing and open-loop cueing session to compare both approaches. For the open-loop condition they used a metronome and for the close-loop condition the investigators provided a phase-dependent vibrotactile biofeedback.

Most of the studies linked the protocol used with the target WBD application regarding the PD gait-associated disabilities. For example, the studies which addressed FOG mitigation, the clinical protocol included gait tasks like walking in straight line [30]–[33], turning [29], [31]–[33], [41] and climbing stairs [31], [33]. Balance, posture and falls problematics, clinical protocol included balance exercises can be distinguished by the tasks that the patients performed. Concerning the WBD developed to address balance, posture and falls, the validation trials included balance exercises [10], [35]–[42]. Further, multitasking condition were also evaluated by [29], [36], [38], [39] where participants performed the same gait tasks with and without concurrent cognitive tasks (dual-task condition). This dual-task condition revealed whether performing more than one task can affect the perception of the provided cues and

addresses everyday multitasking situations, situations than can produce FOG occurrences, trigger unbalance moments and consequently falls.

Only one of the identified studies [40] was validated on home-based condition to explore the possibility for future independent home training with the biofeedback system. The study verified that home-environment can influence patients' motor performance, being required more validation on home or near-home scenarios. Also, only this study performed a follow-up assessment to compare the results with the baseline, which enabled to evaluate the retaining effects of biofeedback training. It is required to standardize a protocol to achieve an objective and common procedure able to validate the biofeedback strategies regarding the clinical purpose, device acceptability, retaining effect, multitasking condition and include daily motor tasks and home/near-home scenarios.

Regarding the study design, according to [45]:the articles [10], [29], [35], [37], [42] were Case-Control Studies; [31], [34], [40], [41] used a Cross-Sectional Study; the articles [38], [39] were Randomized-Controlled Trials; [42] was a Longitudinal Case Report; and [32] presented Case Report. The inclusion of randomized groups brings bias and variability to the clinical study, which can be important to address different patients' symptomatology. However, when comparing a strategy, it could be benefit include a well-known case control group study.

Evaluating the control groups, it can be observed that some of them are not enough to obtain the best results, they can introduce bias to the study. Some of these groups are too small to reach the best conclusion, for example the control group of the article [31], [32], [34] is only one healthy subject.

Regarding scales to evaluate the patients, they were a means of assessing the symptoms of the condition. They provided information on the course of the condition and/or assess quality of life. They may also helped to evaluate treatment and management strategies, which can be useful to researchers as well as to people with Parkinson's, their carers and medical team.

The use of WBD had led to an overall improvement in the patients' performance. In terms of balance, the patients had better LOS, less PE and improved in terms of sway. For posture, the patients had improved posture, static and dynamic balance. In the field of falls, the patients decrease the number of falls, decreased the body sway and improved postural control. In FOG domain, there were a decrease in the number of FOG episodes, in the FOG duration and a general decrease of overall jerkiness.

2.2.5 Conclusions and Future directions

All in all, the presented WBD showed innovative and confident results. They have been successfully used to improve patients' balance and posture, as well as reduce the number of falls, the number of FOG episodes and the time PD patients are in FOG.

In general, all systems tend to choose their sensors and actuators so that they are easy to use. However, there is still a great difficulty in creating small, easy-to-wear and fully wearable devices.

There are several biofeedback strategies, rescue, phase-dependent and on-going. To provide these sensory cues the most common method has been the use of heuristic methods. Despite all this information, evidence is still lacking as to which is the best strategy.

For system validation, several different protocols and several different metrics were used to understand the effect of the system. However, to improve this validation, activities such as walking should be considered more, since it is the most common and functional human activity. Also, to understand the effect of the WBDs a larger number of metrics should be used.

Table IV. Limitations identified in the review, end users' requirements and guidelines.

Limitations	End-users' requirements	Guidelines
Sensors and actuators with different configurations, in terms of body location and number	Small, fully wearable and comfortable	Decrease the number of actuators and sensors, so that they can be integrated into a single, fully wearable and comfortable system.
Lack of evidence on how best to provide biofeedback	Optimize patients' performance	Conduct studies comparing improvements of different biofeedback strategies in patients
Need to know the spectrum of effects of WBD on patients	Improve patients' gait-associated disabilities	Conduct studies where more patient metrics are used to validate WBDs

2.3 How wearable sensors can support Parkinson's disease monitoring using artificial intelligence & statistical analysis: a review

2.3.1 Introductory insights

Technological developments have allowed the creation and development of small devices, which, being wearable, when used on patients, allow data to be obtained, e.g., IMUs'. This data provides important and unique information about the patient, whether this data is raw or processed to obtain

metrics. This date obtained, can be used for continuous and objective monitoring of patients, and in turn serve as a biomarker for PD disease. Statistical [9-15][17][18] and artificial intelligence [19][21-26][28] methods have now been developed that can use this patient information to provide insight into the patient's health status. This creates enormous potential, and the evaluation of PD patients could become less subjective.

Recent papers [9-28] have proven that through the use of both statistical methods and artificial intelligence it is possible to distinguish healthy individuals from sick ones [9-14][17-19][22-26][28], and to distinguish the various degrees of progressive diseases among patients [14-15][18][21].

The studies searched proved that these methods are relevant and appealing. However, for future research in statistical and AI algorithms, it is important to understand what has already been achieved and what limitations are yet to overcome.

The purpose of this review is to find out how the data obtained from the wearable devices was applied and with what purpose; what type of data was used in the AI and statistical methods; and which AI and statistical methods were used for PD diagnostic and management.

This review objective is to determine what type of AI and statistical methods have been used in PD diagnostic and management, in the last ten years, and with which goals and effectiveness. The following questions were investigated and answered:

- RQ1 “For what purpose have the wearable sensors data combined with AI-based and statistical methods been applied to PD monitoring?”
- RQ 2 “Which type of data was acquired and supplied AI-based and statistical methods for PD monitoring? “
- RQ.3 “Which AI-based and statistical methods models and how they have been implemented for PD monitoring?”

2.3.2 Methods

An electronic systematically search was carried out on databases as Google Scholar, PubMed and Web of Science, looking for research papers that based on artificial intelligence & statistical analysis helped to improve PD monitoring and classification. The literature search was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), as depicted on Figure 20. The keywords used on the databases were: [“Statistical Analysis AND Parkinson's Disease”]; [“Statistical Differences AND Parkinson's Disease”]; [“Statistical Differences AND UPDRS”]; [“Statistical Differences AND PDQ-39”]; [“Statistical Analysis AND Motor Metrics AND Parkinson's

Disease"]; ["Statistical Analysis AND Wearable Device AND Parkinson's Disease"]; ["Statistical Analysis AND Clinical Scales AND Parkinson's Disease"]; ["Artificial Intelligence AND Parkinson's Disease"]; ["Machine Learning AND Parkinson's Disease"]; ["Machine Learning AND UPDRS"]; ["Machine Learning AND PDQ-39"]; ["Deep Learning AND Parkinson's Disease"]; and ["Artificial Intelligence AND Motor Metrics AND Parkinson's Disease"]; ["Artificial Intelligence AND Wearable Devices AND Parkinson's Disease"]; ["Artificial Intelligence AND Clinical Scales AND Parkinson's Disease"];.

Studies were included in the review if they fulfilled the following inclusion criteria: (i) studies of idiopathic PD; (ii) artificial intelligence & statistical analysis were used to PD management/monitoring and/or classification; (iii) wearable technology was integrated; and (iv) results were published in the English language and within the past 10 years. The exclusion criteria were: (i) studies not validated with patients with PD; (ii) studies that do not present technological resources.

2.3.3 Results

2.3.3.1 General Results

A total of 150 articles were identified: Google Scholar (n=43), PubMed (n=87), and Web of Science (n=20) databases. Duplicates were removed (n=73). Articles were excluded if the titles (n=26) and abstracts (n=16) did not correspond to the inclusion and exclusion criteria. If the abstract of an article did not provide enough information to determine its eligibility, the full article was reviewed. After the full-text papers were reviewed, seventeen articles met the eligibility criteria and were included in this scoping review. Figure 20 depicts this approach. Seventeen original studies were identified [13], [15], [54]–[60], [46]–[53] and were grouped and discussed according to their application goal, if they were used to distinguish PD from the control or to stage the progression of the disease.

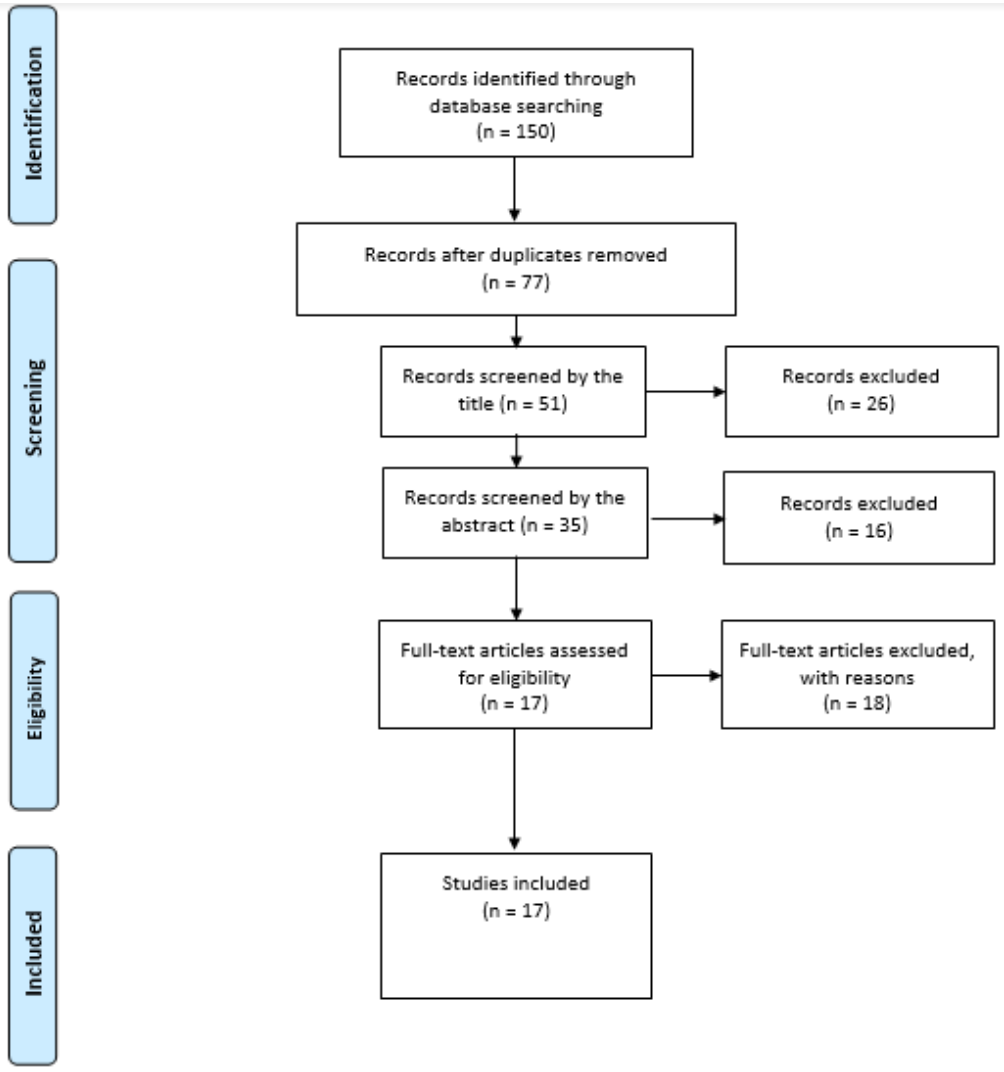

Figure 20. PRISMA Flow Chart.

2.3.3.2 PURPOSE

The Table V highlights the purpose of the articles reviewed. These studies were grouped in three different categories, (i) those that distinguished PD from healthy subjects (Disease classification) [53], [55], [56], [58]–[60], (ii) those that distinguished different stages among PD patients (Disease level classification) [50] and (iii) those that purpose to do both [15], [46]–[49], [51], [54], [57]. This table also illustrates the scales used to make the division between the levels of PD and their stratification into groups.

Table V. Purpose and scales used.

Paper	Method	Stratification (Purpose)	Clinical Scale
[46]	Statistical Method	PD vs Healthy MDS-UPDRS part II-III PIGD subscore	UPDRS, PIGD, PDQ-39 and H&Y

		PDQ-39 mobility subscale H&Y stage	
[47]	Statistical Method	PD vs Healthy, H&Y stage, UPDRS-III and WOQ-19 score	H&Y, UPDRS-III and WOQ-19
[48]	Statistical Method	PD vs Healthy, UPDRS and PIGD scores	UPDRS and PIGD
[13]	Statistical Method	PD vs Healthy, UPDRS and H&Y score	H&Y and UPDRS
[15]	Statistical Method	PD vs Healthy, UPDRS, H&Y, SF-12 and Short Fes-I scores	UPDRS, H&Y, SF-12 and Short FES-I
[49]	Statistical Method	PD vs Healthy, PD UPDRS item 30 = 0 vs PD UPDRS item 30 ≥ 1 vs Healthy and UPDRS score	UPDRS
[50]	Statistical Method	UPDRS-III, ABC and PDQ-39 scores	UPDRS-III, ABC and PDQ-39
[51]	Statistical Method	PD vs Healthy, UPDRS-III, Berg Balance scale, TUG and H&Y scores	UPDRS-III, Berg Balance scale, TUG and H&Y
[52]	Statistical Method	Mild PD vs Severe PD vs Healthy	H&Y
[53]	AI	PD vs Healthy	-
[54]	AI	PD Mild vs PD Moderate vs PD Severe vs Healthy	UPDRS and H&Y
[55]	AI	PD vs Healthy	-
[56]	Statistical Method AI	PD vs Healthy	-
[57]	AI	PD stage I vs PD stage II vs PD stage III vs Healthy	H&Y
[58]	AI	PD vs Healthy	-
[59]	AI	Mild PD vs Geriatrics vs Healthy	-
[60]	AI	PD vs Healthy	-

D. Campbell et al. [46] purposed to assess the suitability of an gait and balance device for diagnosis and estimation of PD severity. Statistical methods were used to compare the PD patients with the control group and, in addition, to group the patients into different groups depending on the

performance of each patient. PD subjects were stratified by MDS-UPDRS part II score, MDS-UPDRS part III scores, PIGD subscore, PDQ-39 mobility subscale and H&Y stage.

Michele Pistacchi et al. [47] aimed to quantify and identify spatiotemporal and kinematic gait parameters in order to investigate whether early PD patients could present an abnormal gait pattern when compared to healthy controls. Statistical methods were used to compare the PD with the control group, but also to investigate a relationship between the parameters obtained from the PD with the H&Y, UPDRS-III and WOQ-19 scales.

Florian Lipsmeier et al. [48] assessed the feasibility, reliability and validity of smartphone-based digital biomarkers of PD in a clinical trial setting. It was proved statistically significant differences between PD and the control group but, also, a relation of the PD features with UPDRS and PIGD scales demonstrating the feasibility of a digital biomarker for this disease.

Johannes C. M. Schlachetzk et al. [13] developed a wearable sensor-based gait analysis system as diagnostic tool that objectively assesses gait parameter in Parkinson's disease without the need of having a specialized gait laboratory. This study showed that PD and the healthy control group had significant differences in the almost all gait parameters. It has also been proven that there are statistically significant differences in gait parameters between different stages of PD disease, as indicated by the H&Y and UPDRS scales.

Nima Toosizadeh et al. [15] aimed to assess statistical differences between in-clinic and in-home gait speed, and sit-to-stand and stand-to-sit duration in PD patients, in comparison with healthy controls, and determine the objective physical activity measures, including gait, postural balance, instrumented Timed-up-and-go (iTUG), and in-home spontaneous physical activity (SPA), with the highest correlation with subjective/semi-objective measures, including health survey (SF-12), short FES-I, UPDRS scale and H&Y stage.

Gilad Yahalom et al. [49] aimed to test the feasibility of smartphones to detect PD during the Timed Up and Go (TUG) test. This work made a statistical analysis that permitted to distinguish PD patients from healthy controls and distinguish between two PD levels too, within the PD patients a division was made according to the score of item 30 of the UPDRS, the patients with the score=0 and the patients with a score≥1. Also was found a significant correlation between the gait parameters and the 4-axial motor UPDRS item score in all PD patients.

Carolin Curtze et al. [50] purpose a study where the main goal was to determine which objective measures of balance and gait are most related to patient perception of mobility disability and disease severity in people with PD and to examine the effect of levodopa therapy on these correlates. Patient

perception of mobility disability was assessed with the Activities-specific Balance Confidence (ABC) scale and the mobility subscale of the Parkinson's Disease Questionnaire (PDQ-39). Disease severity was assessed with the Unified Parkinson's Disease Rating Scale, part III.

Roberta de Melo Roiz et al. [51] compared the spatiotemporal and kinematic parameters of Parkinsonian gait with the healthy elder subjects' group and measure the relation between these parameters and clinical instruments: UPDRS-III, Berg Balance scale, TUG and H&Y. So, in this study is done a comparison between PD and healthy and a correlation between PD parameters with different levels of disease progress, different scores on the referred scales.

Laurie A. King et al. [52] purposed to determine whether the common clinical assessment instruments reflect turning deficits in persons with PD compared with an instrumented measure. In this study, the PD participants were divided into a mild group and a severe group, as determined by the H&Y, with mild defined as scores of 1 to 2 and severe defined as scores of 3 to 4. So, there were a comparation of instrumented turning measures (e.g., turning duration, number of steps and peak speed) and clinical measures (e.g., ABC, Berg Balance Scale and Tinetti) between the three groups (Healthy vs PD Milde vs PD Severe), that is, for disease classification and disease level classification.

Satyabrata Aich et al. [53] proposed a method for measuring gait parameters using wearable sensors and identified PD patients automatically based on machine learning techniques. So, this study can distinguish PD patients from healthy controls through machine learning algorithms.

Qi Wei Oung et al. [54] proposed a multiclass classification with three classes of PD severity level (mild, moderate and severe) and healthy control. Each subject was rated by a neurologist based on the UPDRS scale together with H&Y severity scale. The scales ranged from 0 to 4 where '0' represents healthy, '1' represents mild stage, '2' represents moderate stage, '3' represents severe stage and '4' represent bedridden/wheelchair stage. So, using AI was achieved a way to distinguish between PD and healthy and between PD in different stages of the disease progression.

Hany Hazfiza Manap et al. [55] aimed to investigate the parameters that could be used to identify abnormal gait pattern in Parkinson's disease subjects during normal walking. With Artificial Neural Network and with these parameters they found a way to distinguish PD form healthy subjects.

Ferdous Wahid et al. [56] aimed firstly, to use a multiple regression normalization strategy that accounts for subject age, height, body mass, gender, and self-selected walking speed to identify differences in spatiotemporal gait features between PD patients and controls; and secondly, to evaluate the effectiveness of machine learning strategies in classifying PD gait after gait normalization. This study, distinguished PD and controls through statistical analysis and machine learning techniques.

Carlotta Caramia et al. [57] aimed to use machine learning to distinguish different levels of PD symptoms severity and an equal number of age-matched health. For this purpose, the PD patients were ranked using stage I, II or III of the H&Y motor scale. In this way, a distinction was achieved between different levels of disease and between the PD and the healthy.

Enas Abdulhay et al. [58] proposed to diagnose PD using the gait analysis, that consists of the gait cycle, which can be broken down into various phases and periods to determine normative and abnormal gait, distinguishing PD from healthy.

Elham Rastegari et al. [59] aimed to investigate the potential benefit of accelerometers as an objective tool for diagnostic purposes in PD. For this purpose, the study used patients with mild PD, healthy individuals and geriatrics who present similar gait deficiencies.

Lina Tong et al. [60] proposed a convolutional neural network (CNN)-based PD hand tremor detection method, using the acceleration information of both PD patients with hand tremor and healthy subjects.

2.3.3.3 DATA INPUT

Table VI presents the characterization of the wearable sensors-based systems according to the technology used, regarding the type, number and location of devices included. Also, it is highlighted the data acquisition process regarding the participants, the protocols used and the information about the dataset obtained.

Table VI. Characterization of the wearable sensors-based systems

Paper	Sensors			Data acquisition		Dataset	
	Type	**Number**	**Location**	**Participants**	**Protocol**	**Public (P) /Authors (A)**	**Preparation**
[46]	PDM®Mobility Lab (Opals)	6	One on each ankle, wrist, the lower back, and the upper chest	135 PD subjects and 66 age-matched controls	Each subject performed the instrumented Timed-Up-and-Go (iTUG) and the instrumented Sway (iSway) tests	A	Gait parameter estimation
[47]	Infrared cameras/ dynamometric platform	6/1	C7 apophysis, acromion-clavicular joint, S2 apophysis, anterior superior iliac spine, greater femoral trochanter, femoral lateral epicondyle, peroneal head, medial malleolus and heel (only for standing), fifth metatarsal head, middle third of the thigh (bar shaped marker), middle third of the calf (bar shaped marker).	44 PD and 44 age and sex-matched controls	Stand up and walk back and forth 10 meters, reversing direction 6 times	A	Gait parameter estimation
[48]	Smartphone	1	Depending on the exercise	44 PD and 35 age-matched controls	45 days doing six daily motor active tests (sustained pho-nation, rest tremor, postural tremor, finger-tapping, balance, and gait), then carried the	A	Gait parameter estimation, feature extraction and use of AI to gait event detection

					smartphone during the day (passive monitoring)		
[13]	Tri-axial accelerometer/ gyroscope	2	Lateral side of each shoe	190 PD and 101 age-matched controls	4x10 meter walk	A	Gait events detection and gait parameters estimation
[15]	Tri-axial accelerometer/ gyroscope	5	Shanks, thighs and the trunk	15 PD and 35 age-matched controls	Participants performed two tests of normal gait (<25 steps), four 30-second trials of balance assessment, iTUG and SPA	A	Gait and other parameters estimation
[49]	Smartphone	1	Chest	44 PD (21 PD with UPDRS item 30 =0 and 22 with item 30 >1)	2 trials, 3- and 10-meters TUG	A	Gait and other parameters estimation
[50]	Xsens	6	Ankles, wrists, sternum, and lumbar region	104 PD	Participants performed 3 trials of the ISAW, consisting of standing quietly for 30 seconds, initiating gait with the most affected leg (participant specified), walking 7 m, turning 180 degrees, and walking back 7 m.	A	Gait and Balance parameters estimation
[51]	Infrared cameras and reflective markers	6/18	Acromion on shoulder, thoracic vertebra 12th, anterior superior iliac spine, sacrum, central line of patella, the knee lateral joint line, tuberosity of tibia, 3 cm of lateral malleolus, posterior	12 PD and 15 healthy elders	Instructed to walk naturally on a walkway, with bare feet. The walkway was 10 meters long.	A	Gait parameters estimation

			to the calcaneus, between the 2nd and 3rd metatarsal, 1.0-1.5 cm proximal to the upper metatarsals head.				
[52]	Xsens	6	The posterior trunk, one on the anterior shank of each leg, one on the dorsum side of each arm and the sternum	46 PD (23 with mild PD and 23 with severe PD) and 40 healthy controls	Calculation of the scores of several scales and 3 trials of iTUG	A	Gait parameters estimation
[53]	Tri-axial accelerometer/ gyroscope	4	Knees and ankles	40 PD and 40 healthy controls	NI	A	Gait parameters estimation
[54]	IMU	4	Both wrist and limbs	15 Healthy, 20 PD Mild, 20 PD Moderate and 15 PD Severe	Standardized series of activities, for instance arising from chair, supination and pronation hand movements, hand movements, finger tapping, toe tapping and leg movements. Enquired to sustain vowels “Bah” phonations for as long as possible	A	Raw data for feature extraction
[55]	Reflective markers /and infrared cameras / embedded force plate	32/6/2	NI	12 PD and 20 Healthy	Walk freely at their comfortable speed	A	Gait event detection and gait parameters estimation

[56]	Reflective markers/instrumented force platforms	15/2	Helen Hayes marker set	23 PD patients and 26 aged-matched healthy	Subjects walked at their preferred walking speed ten times across an 8 m walkway.	A	Gait parameters estimation
[57]	IMUs	8	One sensor was placed on each foot dorsum, one on each shank, one on each thigh, one on the chest and one in the back side on the lumbar zone	25 patients with idiopathic PD at different stages of the H&Y motor scale and 25 healthy. 8 subjects belonging to stage I, 9 to stage II, and 8 to stage III of H&Y	NI	A	Gait event detection and gait parameters estimation
[58]	Force sensors	16	8 each foot	93 PD and 73 Healthy	Walked at their usual, self-selected pace for approximately 2 min on level ground	P	Raw data, Gait event detection and gait parameters estimation
[59]	SHIMMER	2	Right and left ankle	10 PD, 10 geriatrics and 10 Healthy	40-meter walk protocol	P	Raw data and Gait parameters estimation
[60]	MEMS inertial sensor	1	Wrist	5 PD and 5 Healthy	Walking 10 m forward, standing still for 2 s, turn back, standing still for 2 s, walking backward for 10 m, standing still for 2 s, and turn back. The process was repeated four times.	A	Raw data

For the sensory acquisition systems, tri-axial accelerometer and gyroscope [13], [15], [53] were commonly integrated. They can be found as IMU's [54], [57] or by other names as Opals [46], Xsens [50], [52], MEMS inertial sensor [60] and SHIMMER [59]. It is also possible to acquire tri-axial data using smartphones [48], [49].

Other studies [47], [51], [55], [56], to obtain data from patients' gait, used reflective markers and infrared cameras. These infrared cameras were able to detect signals reflected by the passive markers positioned in the patient's body, obtaining the information of each body part. To complement this information, some studies [47], [55], [56] used at same time platforms, that enable to analyze force components, pressure coordinates and twisting movements.

In the study [58] wearable force sensors were used under each foot, obtaining the vertical ground reaction force.

Regarding the number of sensors, it depends on the location of the body that you want inertial information from. It is common, that the number of sensors used in studies with reflective markers or force sensors, being larger. Michele Pistacchi et al. [47] used six reflective markers and one dynamometric platform, Roberta de Melo Roiz et al. [51] used eighteen reflective markers, Hany Hazfiza Manap et al. [55] used thirty-two reflective markers and two force plates, Ferdous Wahid et al. [56] used fifteen reflective markers and two force platforms and Enas Abdulhay et al. [58] used 16 force sensors, 8 on each foot. The location of the reflective markers it is very specific, normally following the Helen Hayes marker set [56], and including positions such as C7 apophysis, acromion-clavicular joint, S2 apophysis, anterior superior iliac spine, greater femoral trochanter, femoral lateral epicondyle, peroneal head, medial malleolus and heel, fifth metatarsal head, middle third of the thigh and middle third of the calf [47], acromion on shoulder, thoracic vertebra 12th, sacrum, central line of patella, the knee lateral joint line, tuberosity of tibia, 3 cm of lateral malleolus, posterior to the calcaneus, between the 2nd and 3rd metatarsal and 1.0-1.5 cm proximal to the upper metatarsals head [51].

For the tri-axial inertial sensors, D. Campbell Deweya et al. [46] used six sensors, one on each ankle and wrist, one on the lower back and one on the upper chest. Florian Lipsmeie et al. [48] one smartphone and his location was mainly in the pocket or in the hands of the subjects. Johannes C. M et al. [13] two sensors, one on the lateral side of each shoe. Nima Toosizadeh et al. [15] five sensors, one on each shank, one on each thigh and one on the trunk. Gilad Yahalom et al. [49] one smartphone strapped to the chest. Carolin Curtze et al, [50] six sensors, one on both ankles and wrists, one on sternum and one on the lumbar region. Roberta de Melo Roiz et al. [51] six sensors, one on the posterior trunk, one on the anterior shank of each leg, one on the dorsum side of each arm and one on the sternum.

Satyabrata Aich et al. [53] four sensors, one on each knee and each ankle. Qi Wei Oung et al. [54] four IMU's one on each wrist and each limb. Carlotta Caramia et al. [57] eight IMU's, one on each foot, one on each shank, one on each thigh, one on the chest and one in the back side on the lumbar zone. Elham Rastegari et al. [59] two sensors, one on each ankle. And Lina Tong et al. [60] one inertial sensor on the wrist.

When it comes to the dataset, most articles collect their own subjects information [13], [15], [54]–[57], [60], [46]–[53], except for two studies. Enas Abdulhay et al. [58] used a public dataset maintained by Physionet and Elham Rastegari et al. [59] used data from a publicly available data set collected by Barth and colleagues.

With the information collected by the sensors, some articles used the raw data [54], [58]–[60], some estimated gait parameters or other parameters (e.g Balance, tremor parameters, etc.) from the patients [15], [46], [57]–[59], [47]–[49], [51]–[53], [55], [56] and some processed the data to obtain gait event detection [13], [48], [55], [57], [58].

Regarding the data acquisition, the articles differ in the number and type of patients used and in the protocol adopted. D. Campbell Deweya et al. recruited 135 PD subjects and 66 age-matched controls, and they performed the iTUG and the iSway tests. Michele Pistacchi et al. [47] made 44 PD and 44 age and sex-matched controls stand up and walk back and forth 10 meters, reversing direction 6 times. Florian Lipsmeie et al. [48] made 44 PD and 35 age-matched controls doing six daily motor active tests for 45 days (sustained phonation, rest tremor, postural tremor, finger-tapping, balance, and gait), carrying the smartphone during the day. Johannes C. M. Schlachetzk et al. [13] made 190 PD and 101 age-matched controls do a 4x10 meter walk task. Nima Toosizadeh et al. [15] used 15 PD and 35 age-matched controls to perform two tests of normal gait, four 30-second trials of balance assessment, iTUG and SPA. Gilad Yahalom et al. [49] made 44 PD, 21 PD with UPDRS item 30 =0 and 22 with item 30 >1, do two trials, one 3- and one 10-meters TUG. Carolin Curtze et al. [50] used 104 PD to perform 3 trials of the ISAW, consisting of standing quietly for 30 seconds, initiating gait with the most affected leg, walking 7 m, turning 180 degrees, and walking back 7 m. Roberta de Melo Roiz et al. [51] made 12 PD and 15 healthy elders walk naturally 10 meters on a walkway. Laurie A. King et al. [52] made 46 PD, 23 with mild PD and 23 with severe PD, and 40 healthy controls do three trials of iTUG. Satyabrata Aich et al. [53] used 40 PD and 40 healthy controls but there is no information about the protocol used. Qi Wei Oung et al. [54] made 15 Healthy, 20 PD Mild, 20 PD Moderate and 15 PD Severe perform a standardized series of activities, arising from a chair, supination and pronation hand movements, hand movements, finger tapping, toe tapping and leg movements. They were also enquired to sustain vowels "Bah"

phonations for as long as possible. Hany Hazfiza Manap et al. [55] used 12 PD and 20 Healthy to walk freely at their comfortable speed. Ferdous Wahid et al [56] made, 23 PD patients and 26 aged-matched healthy, walk at their preferred walking speed ten times across an 8 m walkway. Carlotta Caramia et al. [57] used 25 PD at different stages of the H&Y motor scale and 25 healthy, 8 subjects belonging to stage I, 9 to stage II, and 8 to stage III of H&Y, but there is no information about the protocol used. Enas Abdulhay et al. [58] used a dataset were 93 PD and 73 healthy walked at their usual self-selected pace for approximately 2 min on level ground. Elham Rastegari et al. [59] made 10 PD, 10 geriatrics and 10 healthy perform a 40-meter walk. Lina Tong et al. [60] used 5 PD and 5 Healthy to walk 10 m forward, stand still for 2 s, turn back, stand still for 2 s, walk backward for 10 m, stand still for 2 s, and turn back. The process was repeated four times.

2.3.3.4 Methods & Performance

Table VII highlights the methods used and their performance. [13], [15], [46]–[52] applied statistical methodologies, while [53], [57]–[60] implemented AI algorithms. In [54]–[56], it was firstly performed a statical analysis following AI-based procedures.

Table VII. Methods used and their performance.

		Statistical		**AI**				
Paper	Sample	Method	Performance	Model	Features	Features selection/extraction	Programming Language	Performance
[46]		Multiple linear and logistic regressions, ROC analyses, and t-tests	TUG and iSway variables correlate highly with diagnosis and disease severity					
[47]		T-test	All spatial and temporal parameters were significantly different between PD and healthy. The motor impairment scales (H&Y and UPDRS-III) and non-motor impairment scale (WOQ-19) were statistically correlated directly with age, disease duration, mean speed, cadence, and levodopa therapy					
[48]		Intraclass correlation coefficient (ICC) and Mann–Whitney U tests	All active test and passive monitoring features significantly discriminated PD from controls, all active test features, with the					

			exception of sustained phonation, were significantly related to their corresponding MDS-UDPRS scores and for the passive monitoring features, only turn speed was significantly related to average PIGD scores					
[13]		T-test, one-way ANOVA followed by Bonferroni's post-hoc test	Significant differences between both groups in all sensor-measured spatiotemporal gait parameters, As the disease progresses, gait impairment become more prevalent					
[15]		Linear regression-analysis of variance models and Pearson correlations, ANOVA, t-test and Cohen's Effect size	Better correlation between supervised and unsupervised motor function assessments in healthy controls compared to PD group. In the PD group, parameters related to velocity and range-of-motion of lower extremity within gait assessment, and turning duration and velocity within iTUG test demonstrated					

			strong correlations with PD stage					
[49]		One-way ANOVA, post-hoc Tukey analysis, Chi-square and Pearson correlation	It was found statistically differences between the 3 groups (PD with UPDRS item 30=0, PD with UPDRS item 30 >1 and Healthy controls)					
[50]		Spearman correlations	Off-medication state is more related to disease severity and patient perception of mobility disability. turning, gait speed and stride length are the measurements that best reflect patients' quality of life and balance confidence.					
[51]		Mann-Whitney nonparametric test and Spearman correlation	Clinical instruments used did not present proper psychometric parameters to measure the PD patient's gait, while the 3D system characterized it better.					
[52]		Kruskal-Wallis test and Spearman correlation	Turning is impaired, even in mildly impaired participants with PD and that this deficit is not obviously reflected in common clinical scales of					

			balance such as the Berg or Tinetti. It may be more useful for a clinician to examine particular items within the Berg or the turning component of the TUG if turning difficulty is suspected					
[53]				Recursive partitioning and regression trees (RPART), C4.5, pruning rule-based classification tree (PART), bagging classification and regression tree, Random Forest and Boosted C5.0with the Naïve Bayes method as the probabilistic classifier, and LDA with the SVM and radial basis	12 spatiotemporal parameters such as cadence, stride time, opposite foot off, opposite foot contact, step time, single support, double support, foot off, stride length, step length, walking speed, step width	Random feature elimination and PCA	NI	Maximum accuracy of 88.89% using a support vector machine with a radial basis function combined with a random feature elimination set

				function (RBF) as linear classifiers				
[54]		ANOVA	These features show low p-value ($p<0.0001$), implying that these features are clinically significant	K-nearest neighbor (KNN), probabilistic neural network (PNN) and extreme learning machine (ELM)	Wavelet Energy, Shannon Wavelet Entropy, Renyi Wavelet Entropy, Tsallis Wavelet Entropy, Permutation Entropy and Fuzzy Entropy	Signal Decomposition using EWPT. Instantaneous amplitudes and frequencies from Hilbert Transform. Wavelet Energy and Entropy Based Feature Extraction.	NI	Classification accuracies of more than 90% using EWT/EWPT-ELM based on signals from motion and audio sensors respectively. Additionally, classification accuracy of more than 95% was achieved when EWT/EWPT-ELM is applied to signals from integration of both signal's information.
[55]		t-test and Pearson correlation	Based on the statistical analysis results, it was found that step length, walking speed, knee angle as well as vertical parameter of ground reaction force are the four significant features as indicators for classification of subject with Parkinson's disease	Artificial neural network (ANN) with multilayer perceptron (MLP) algorithm	Basic • Time cycle (s) • Cadence (steps per minutes) • Step length (m) • Walking speed (m/sec) Kinetic: • Maximum vertical heel contact • Vertical minimum mid-stance force • Maximum vertical push off force • Maximum horizontal	Different sets of features were used: Basic; Kinetic; Kinematic; Basic & kinetic; Basic & kinematic; Kinetic & kinematic; Basic, kinetic & kinematic; Four significant features selection via Statistical Analysis;	-	Best performance was obtained using the dataset with only the Four significant features selection via Statistical Analysis =95.63% accuracy

					heel strike force during braking phase • Maximum horizontal push-off force Kinematic: • Ankle angle at heel strike and toe off • Knee angle at heel strike and toe off • Hip angle at heel strike and toe off • Maximum extension and flexion of ankle angle • Maximum extension and flexion of knee angle • Maximum extension and flexion of hip angle			
[56]		Coefficient of variation (CV) and Spearman's rank order correlation coefficient (ρ)	Using raw data (i.e., before normalization), the only significant differences in spatiotemporal gait features between the PD patients and controls were stride length and double support time. When the raw data were normalized using the DS equations, significant	Five machine learning strategies were employed to classify PD gait: kernel Fisher discriminant (KFD), naıve Bayesian approach (BA),k-nearest neighbor	Spatiotemporal gait features including stride length, step length, step width, cadence, double support time, stance time, swing time, step time, and stride time	A multiple regression normalization strategy that accounts for subject age, height, body mass, gender, and self-selected walking speed. Use of dimension equations or use of multiple regression (MR) normalization strategy	-	Accuracy of 92.6%after normalizing gait data using the multiple regression approach, compared to 80.4% (support vector machine) and 86.2% (kernel Fisher discriminant) using raw data and data normalized using dimensionless equations, respectively

			differences between the PD patients and controls were observed in stride length, step length and double support time. After normalizing using the MR approach, stride length, stance time, cadence and double support time	(kNN), SVM ,and Random Forest (RF)				
[57]				Naive Bayes (NB), LDA, k-NN, Decision Tree (DT), and SVM with both linear and non-linear kernel (rbf) bases.	Two categories of parameters were extracted from raw data: range of motions (RoMs) and spatiotemporal parameters. RoMs are calculated for ankle, knee, hip and chest. The spatiotemporal parameters are the step length, step time, stride time and stride speed	Different sets of features. PCA.	Machine Learning toolbox of Matlab R2017a to define and cross-validate all the classifiers	Average classification accuracy ranged between 63% and 80% among classifiers and increased up to 96% for one meta-classifier configuration
[58]				The Medium Gaussian SVM and Medium Tree	Stance time, swing time, stride time, foot strike profile, Frequency domain analysis, Power spectral density, Tremor analysis, Fast Fourier	FFT and power spectral density	NI	An average accuracy of 92.7% is achieved for the diagnosis of PD from gait analysis and tremor analysis is used for knowing the severity of PD

					Transform and Power Spectral Density			
[59]				Support Vector Machine, Random Forest, AdaBoost, Bagging, Naïve Bayes and Similarity Network.	Average stride time, RMS of Acceleration/Body Oscillation, Maximum and Minimum Acceleration, Variability of Signal per Stride, Signal Vector Magnitude, Symmetry, Stride to stride variability, velocity and Signal Smoothness	Maximum Information Gain Minimum Correlation to select an appropriate feature se (MIGMC).	NI	Some methods had 100% of accuracy
[60]				CNN, support vector machine and back propagation neural network.	Root mean square, Variance, Absolute Mean, Mean power frequency and peak power	-	NI	It is proved that this method (CNN) can detect PD hand tremor symptoms effectively and has better performance than typical machine learning methods.

- Statistical analysis: Statistical procedures included unpaired and paired significance tests, variables correlation and application of regressions models.

[46] used multiple linear and logistic regressions, ROC analyses and significance test to show that TUG and iSway variables correlate highly with PD diagnosis and PD severity.

Michele Pistacchi et al. [47] used significance tests to prove that all spatial and temporal parameters were significantly different between PD and healthy subjects and, also, the H&Y, UPDRS-III and WOQ-19 were statistically correlated directly with age, disease duration, mean speed, cadence, and levodopa therapy..

[48] used intraclass correlation coefficient (ICC) and Mann–Whitney U tests (unpaired significance tests) and showed that all active test and passive monitoring features significantly discriminated PD from controls, all active test features, except for sustained phonation, were significantly related to their corresponding MDS-UDPRS scores and for the passive monitoring features, only turn speed was significantly related to average PIGD scores.

Johannes C. M. Schlachetzk et al. [13] performed a significance tests and a one-way ANOVA followed by Bonferroni's post-hoc test to prove that exists significant differences between PD and healthy in all sensor-measured spatiotemporal gait parameters and, as the disease progresses, gait impairment become more prevalent.

[15] accomplished Pearson correlations, ANOVA, t-test and Cohen's Effect size to show that exists better correlation between supervised and unsupervised motor function assessments in healthy controls compared to PD group. Also, in the PD group, parameters related to velocity and range-of-motion of lower extremity within gait assessment and turning duration and velocity within iTUG test demonstrated strong correlations with PD stage.

Gilad Yahalom et al. [49] used one-way ANOVA, post-hoc Tukey analysis, Chi-square and Pearson correlation and found statistically differences between the 3 groups (PD with UPDRS item 30=0, PD with UPDRS item 30 >1 and Healthy controls).

[50] with Spearman correlations proved that the off-medication state is more related to disease severity and patient perception of mobility disability. Also, turning, gait speed, and stride length are the measurements that best reflect patients' quality of life and balance confidence.

Roberta de Melo Roiz et al. [51] used Mann-Whitney test and Spearman correlation to show that clinical instruments used did not present proper psychometric parameters to measure the PD patient's gait, while the 3D system used characterized it better.

Laurie A. King et al. [52] proved with Kruskal-Wallis test and Spearman correlation that turning is impaired, even in mildly impaired participants with PD and that this deficit is not obviously reflected in common clinical scales of balance such as the Berg or Tinetti. It may be more useful for a clinician to examine particular items within the Berg or the turning component of the TUG if turning difficulty is suspected.

- AI-based analysis: For the AI methods it was identified the models, features, features selection/extraction methods and programming language used, as well as the performance recorded.

  axz

Satyabrata Aich et al. [53] used twelve spatiotemporal parameters such as cadence, stride time, opposite foot off, opposite foot contact, step time, single support, double support, foot off, stride length, step length, walking speed, step width and applied two feature selection methods Random feature elimination (RFE) and PCA. Then it was used several ML methods to obtain the classification performance, recursive partitioning, and regression trees, C4.5, pruning rule-based classification tree, bagging classification and regression tree, Random Forest and Boosted C5.0 with the Naïve Bayes method as the probabilistic classifier, and LDA with the SVM and radial basis function (RBF) as linear classifiers. The best performance was an accuracy of 88.89% using a support vector machine with a radial basis function combined with a random feature elimination set.

Qi Wei Oung et al. [54] showed using the ANOVA that all the features, Wavelet Energy, Shannon Wavelet Entropy, Renyi Wavelet Entropy, Tsallis Wavelet Entropy, Permutation Entropy and Fuzzy Entropy, were clinically significant and were suitable for the classification of PD severity. For the feature extraction process, signal decomposition using EWPT, instantaneous amplitudes and frequencies from Hilbert Transform and wavelet energy and entropy based feature extraction were used. The methods applied were K-nearest neighbor, probabilistic neural network and extreme learning machine and the best performance achieved was an accuracy of more than 95%.

Hany Hazfiza Manap et al. [55] calculated different sets of features (Basic, Kinetic and Kinmatic). T-test and Pearson correlation were used to prove that step length, walking speed, knee angle as well as vertical parameter of ground reaction force are the four significant features as indicators for classification of subject with Parkinson's disease. Applying an Artificial neural network (ANN) with multilayer perceptron (MLP) algorithm, the best performance was obtained using the dataset with only the four significant features selection via Statistical Analysis, 95.63% accuracy.

Ferdous Wahid et al. [56] calculated spatiotemporal gait features including stride length, step length, step width, cadence, double support time, stance time, swing time, step time and stride time. Ferdous used two strategies, a multiple regression normalization strategy that accounts for subject age, height, body mass, gender, and self-selected walking speed and dimension (DS) equations or use of multiple regression (MR) normalization strategy. It was used a coefficient of variation and Spearman's rank order correlation coefficient to prove that using raw data, the only significant differences in spatiotemporal gait features between the PD patients and controls were stride length and double support time. When the raw data were normalized using the DS equations, significant differences between the PD patients and controls were observed in stride length, step length and double support time. After normalizing using the MR approach significant difference were found in stride length, stance time, cadence and double support time. With the use of five machine learning, kernel Fisher discriminant, naïve Bayesian approach, k-nearest neighbor, SVM and Random Forest, the best performance found was an accuracy of 92.6% after normalizing gait data using the multiple regression approach.

Carlotta Caramia et al. [57] used two categories of parameters, extracted from raw data, range of motions and spatiotemporal parameters. Range of motions were calculated for ankle, knee, hip and chest. The spatiotemporal parameters calculated were the step length, step time, stride time and stride speed. It was used different sets of features and PCA for feature selection. Applying naive bayes, LDA, K-nearest neighbor, Decision Tree, and SVM with both linear and non-linear kernel base, an average classification accuracy ranged between 63% and 80% among classifiers and increased up to 96% for one meta-classifier configuration.

Enas Abdulhay et al. [58] utilized these features, stance time, swing time, stride time, foot strike profile, frequency domain analysis, power spectral density, tremor analysis, FFT and Power Spectral Density. With Medium Gaussian SVM and Medium Tree it was obtained an average accuracy of 92.7% for the diagnosis of PD from gait analysis.

Elham Rastegari et al. [59] used average stride time, RMS of Acceleration/Body Oscillation, Maximum and Minimum Acceleration, Variability of Signal per Stride, Signal Vector Magnitude, Symmetry, Stride to stride variability, velocity and Signal Smoothness as features. A Maximum Information Gain Minimum Correlation was applied to select appropriate features. Support Vector Machine, Random Forest, AdaBoost, Bagging, Naïve Bayes and Similarity Network were applied and some methods had 100% of accuracy.

Lina Tong et al. [60] extracted the root mean square, variance, absolute mean, mean power frequency and peak power from the raw data and using CNN, support vector machine and back

propagation neural network proved that CNN can detect PD hand tremor symptoms effectively and has better performance than typical machine learning methods.

2.3.4 Discussion

- *RQ1: For what purpose have the wearable sensors data combined with AI-based and statistical methods been applied to PD monitoring?*

Most of the identified studies used statistical and AI-based methods to stratify and classify the PD [13], [15], [46]–[49], [51], [52], [54], [57]. For that, the studies compared PD vs healthy groups and then use clinical scales to distinguished the different levels of PD [13], [15], [46]–[48], [51]. Further, H&Y and UPDRS were the most common scales used to distinguish between disease level [13], [15], [57], [46]–[52], [54], since are the two scales clinically most accepted for PD evaluation and evolution through the time. In addition, these are the scales usually easily examined by the clinicians during consultations.

For the studies that used statistical methods the most common purpose was disease level stratification and disease classification [13], [15], [46]–[52].

Concerning the studies that applied AI-based methods [53]–[60], the most common purpose was disease classification, being observed on all studies of AI. Usually, the algorithm classified two labels, PD or healthy, although in [59] the method stratified into three labels (a mild PD group, a geriatrics healthy group and a healthy group without geriatrics). AI-based studies that done disease level classification used the H&Y and/or UPDRS to group the PD in different severity groups [54], [57].

Aiming to achieve a complete assessment, on the literature, it remains the challenge of extend these analyses to different domains of health and well-being. PD causes motor and non-motor symptoms, and their clinical examination benefit from a complementary examination based in these technological methods. For example, wearable sensors measure patients' motion that could translate poor mobility which can affect daily motor tasks performance, well-being emotional, physical discomfort and consequently less quality of life. Thus, the sensory information when applied to statistical and AI-based methodologies and correlated with other scales responsible for this type of assessments (as, PDQ39) will provide a complementary stratification of patients for different and complementary domains.

- *RQ2: Which type of data was acquired and supplied AI-based and statistical methods for PD monitoring?*

Along the last years, with the growing technological evolution, wearable sensors have proven their high potential for motion monitoring.

The majority of the studies used gait or other related parameters (gait cycle events/phases) to apply statistical or AI methodologies. [13], [15], [55]–[59], [46]–[53], [15], [49], [50].

In terms of data acquisition, most studies collected their own data [13], [15], [54]–[57], [60], [46]–[53]. Two studies of AI-based methods used data previously collected and present in public databases [58], [59].

For the sensory acquisition systems, the most common sensors were tri-axial accelerometer and gyroscope integrated on IMUs boards [13], [15], [53], as Xsens [50], [52] and SHIMMER [59]. This inertial data was also acquired using smartphones [48], [49]. IMUs have the advantage of being totally wearable and easy to be worn, given its small dimensions. Also, inertial sensors can collect a lot of kinematic-driven information about the part of the body where were placed, being easily used in home-settings and with the user performing varied activities (e.g walking, sitting, getting up, climbing stairs, etc).

By other side [47], [51], [55], [56], used input data from reflective markers and infrared cameras. When comparing these systems with IMUs, these systems presents disadvantages, they are more complex, expensive, require carefully placement of markers on specific body segments, being required more sensors and more computational time/power-consuming.

Particularly, [47], [55], [56] used force platforms, that enable to analyze force components, pressure coordinates and twisting movements. They have the advantage of collecting different and more specific type of data than the previous sensors, however, these sensors are not wearable, and their portability and installation can be more time consuming and complex. By other side, [58] used force sensors under each foot, obtaining the vertical ground reaction force, thus presenting the advantage of being wearable when compared to platforms.

From the literature review, it is observed the potential of wearable sensors to record meaningful information to be applied on statistical and AI-based analysis, but it is still not clear the best configuration to place the body sensors. Given the potential of applicability of these sensors on home scenarios, the monitoring device should integrate a number of sensors that represents a trade-off between the required sensory information and the computational requirements and patients' comfort. For example, since most of the metrics are related with patients' gait, lower trunk inertial data has the potential to measure a complete gait cycle, while when placing the sensors on lower limbs, it is required one sensor for each limb to obtain the same information.

Although the most recent studies already included data inputs recorded from higher numbers of participants, it Is observed a need for inclusion of more participants, specifically assessed different scales. Further, regarding the protocol for data acquisition, most studies subjects performed simple activities, such as walking [13], [15], [56], [58]–[60], [46]–[52], [55], turning [46], [47], [49], [50], [60], standing up [46], [49], [52], [54], and standing up [46], [48], [50], [54], [60]. These simple walking activities allowed the acquisition of several information about patients' gait and balance. Some articles applied pre-defined protocols, such as iTUG [15], [46], [49], [52], iSway [46], iSAW [50] and SPA [15], presenting the advantage of using already pre-defined and validated methods. However, besides walking conditions, the data input should include sensory data from routine motor tasks on home scenarios, allowing to achieve more feasible data about the patients' real motor state. This will enable to monitor the patients in real life situations.

- *RQ3: Which AI-based and statistical methods models and how they have been implemented for PD monitoring?*

Statistical methos were frequently applied to distinguish PD from control groups or stratify disease level. To distinguish between PD subjects from healthy subjects , typically significance tests were used to compare two groups, such as unpaired t-test [13], [15], [46], [47], [55], Mann-Whitney test [48], [51], one-way ANOVA [13], [15], [49], [54] and Kruskal-Wallis [52]. By other side, when the goal is to relate the measurements from wearable sensors with disease severity/clinical scales, it is most common use correlations (Pearson[15], [49], [55] and Spearman factor [50]–[52], [56]).

In terms of AI, the most common features calculated using raw data [54], [58]–[60] were root mean square, variance and absolute mean of the signal, RMS of acceleration/body oscillation, maximum and minimum acceleration, variability of signal per stride, signal vector magnitude, signal smoothness, frequency domain analysis, power spectral density, tremor analysis, fast Fourier transform, power spectral density, wavelet energy, Shannon wavelet entropy, Renyi wavelet entropy, Tsallis wavelet entropy, permutation entropy and fuzzy entropy. These features were obtained through simple operations performed on the raw data.

Further, gait spatiotemporal parameters or kinematic metrics were also estimated when considering features related with user walking, such as stride length, step length, step width, cadence, double support time, stance time, swing time, step time, stride time, stride and step speed, time cycle, range of motion of the ankle, knee, hip and chest, ankle angle at heel strike and toe off, knee angle at heel strike and toe off, hip angle at heel strike and toe off, maximum extension and flexion of ankle angle, maximum extension

and flexion of knee angle and maximum extension and flexion of hip angle [53], [55]–[58]. Advantageously, these features can be easily estimated using signals from wearable tri-axial accelerometers and gyroscopes.

To select the best features for the AI models, the studies, usually, used different sets of features combinations [55], [57] and PCA [53], [57].

The AI-based methods depend on whether machine learning or deep learning was used. The most common machine learning techniques implemented were Random Forest [53], [56], [59], LDA [53], [57], SVM [53], [56]–[59], K-nearest neighbor [54], [56], [57] and naïve Bayesian approach [53], [56], [57], [59]. For deep learning methods, the most commons were MLP [55] and CNN's [60]. Normally, machine learning is powered with gait and other parameters, and, deep learning most relevant method, CNN, is powered with raw data/raw data features.

In terms of performance, statistical methods were used to find significant differences in mobility between the groups (e.g PD vs control) or provide information about the correlation between some motion feature with the disease progression/severity, while AI-based methods were used to show with what accuracy the groups from each scale can be classified.

Regarding programming language, it was only identified the use of the Machine Learning toolbox of Matlab R2017a [57].

2.3.5 Conclusions and Future directions

All identified studies presented promising results in the use of AI and statistics methods in PD.

It was observed that by combining the outcomes form wearable sensors with AI and statistically methods, a very useful tool can be obtained to help in diagnosis and stratification of disease degree, either by assigning different grades on the scales associated with PD, or by distinguishing between healthy and patients.

As for the type of data used, the most common is information about the subjects' gait, either through gait metrics or raw data from inertial sensors, which are the most practical and lower-cost sensors. However, most of the studies used more than one sensor, making the system more intrusive and difficult to wear. So, there is a need to get the data from a simpler device that is able to get the patient information from a single sensor.

Raw data tended to be used more in AI, while statistic methods used more estimation of gait parameters. To acquire the data input, subjects typically performed simple motor tasks, such as walking and turning. However, there is a lack of data from activities performed in other environments, such as day-to-day activities in a comfortable setting for the patient, such as at home.

In terms of statistics, the methods used depend on the type of data and its normality. For establishing correlations between metrics and between metrics and scales the Pearson correlation is most often used. As for AI the most used machine learning methods are RF and KNN, and for deep learning CNN. Since PD is a disease that also affects patients psychologically, it is necessary to further apply these methods to clinical scales that translate patients' quality of life.

Table VIII. Limitations identified in the review, end users' requirements and guidelines.

Limitations	**End-users' requirements**	**Guidelines**
Sensors with different configurations, in terms of body location and number	Small, fully wearable and comfortable	Decrease the number of sensors, so that they can be integrated into a single, fully wearable and comfortable system.
Lack of data from activities performed in other environments	Optimize the date obtained	Conduct studies in home-based scenarios
Little use of quality-of-life scales	Full knowledge of the patient's condition	Conducting studies, which use these AI and statistical methods in quality-of-life scales, such as the PDQ-39

3 Problem description

3.1 INTRODUCTION

This chapter is about demonstrating what problems still exist in terms of WBD, and how they are intended to be solved. First, it is demonstrated how the problem of biofeedback validation will be solved and how best to provide biofeedback, through +sBiofeedback. Second, the problem of technological complexity is solved by introducing the +sMotion device. Third, the problem of the small number of metrics used in studies is solved, by calculating increasingly varied metrics from different fields. Fourth, an application is shown that illustrates how the misclassification of gait events is solved. And lastly, +sC-support is shown, which aims to use AI to classify PD or even stratify its levels, solving the problem of lack of devices capable of complementing doctors in assessing patients.

3.2 +SENSE

This thesis is integrated into the +sense project. +sense presents front-end high-tech solutions based on wearable biofeedback devices which rely on acquisition, interpretation and feedback of patients' sensorimotor information. The project envisions to improve patients' quality of lite, being less dependent on third parties by promoting their motor autonomy. There are four +sense modules, as shown in the next image: (1) +sBiofeedback; (2) +sMotion; (3) +sC-support and (4) +sImmersive. This dissertation contributed and used the first three modules.

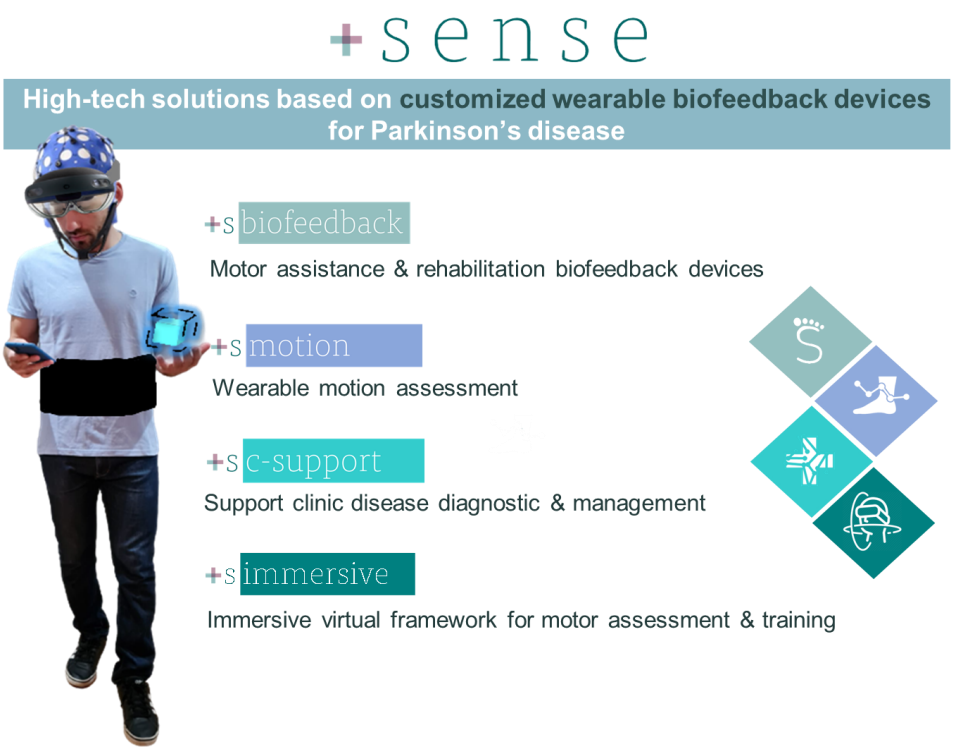

Figure 21. +sense modules.

3.3 +SBIOFEEDBACK: A WEARABLE BIOFEEDBACK DEVICE

+sBiofeedback module was the first sub-system developed in this project. It comprises an instrumented waistband, adaptable to different users' physiognomies, which integrates a sensory, an actuation and central-processing system, as described in Figure 22. These hardware components were fully integrated on a 3D printing box, which is attached to a waistband. An IMU is integrated to provide lower trunk inertial data (advantageously, one sensor can measure a complete gait cycle and postural metrics). From a real-time processing of the acquired sensory data, it is delivered vibrotactile information through actuators (vibratory motor) integrated in the waistband. An OTG USB driver was used to storage the inertial data captured during the device utilization. Further, the system contains a mobile APP to, via Bluetooth, access the device.

Figure 22. +sBiofeedback module.

The WBD integrates a closed-loop vibrotactile cueing strategy (biofeedback) and an open-loop vibrotactile cueing strategy (feedback). On closed-loop strategy, the vibrotactile cueing are delivered in a specific event of gait cycle, the final contact (toe-off). Since patients typically felt their foot glued to the ground in freezing episodes or cannot maintain a regular cadence, this gait event can be neurological correlated to overcome PD gait impairments. It is expected that patients reintegrate the pattern of walking into their neural motor system, aiming to bypass the nervous messages which could be in fault during gait disabilities. The open-loop strategy provides vibrotactile cueing 2 in 2 seconds according to [61]. The assistive and rehabilitative medical device was developed to help patients to maintain a regular, fluid gait cadence, avoiding episodes of freezing and promoting the management of balance. This dissertation aims to validate this device with end-users with a well-delineated protocol.

3.4 +sMotion: A WEARABLE GAIT ANALYSIS LAB

+sMotion module is responsible to acquire and monitor lower trunk inertial signal, provide real-time gait segmentation, post-processing gait analysis and gait-associated metrics estimation. This module is linked with +sBiofeedback, since also comprises the same instrumented waistband, the WBD. Thus, +sMotion includes a wearable gait analysis LAB which is a part of a WBD, comprising the 1) Sensory Acquisition Unit; 2) Processing Unit; 3) Data Storage Unit; 4) Mobile APP; and 5) +S Desktop GUI, as depicted in Figure 23.

Figure 23. +sMotion overview.

Sensory acquisition relies on the use of the MPU-6050 Inertial Measurement Unit to acquire acceleration and angular velocity data. The Processing unit comprises a STM32F4-Discovery to receive the acquired data from the sensory acquisition unit and run in real-time a gait event detection algorithm based on heuristic rules with adaptive thresholds and ranges to segment a gait cycle from both legs into: initial contact (IC)/Heel-strike (HS), foot-flat (FF), mid-stance (MSt), final contact (FC)/toe-off (TO) and heel-off (HO). Acquired inertial data and identified events are saved in the Data Storage Unit, a OTG USB driver. The Mobile APP is an Android APP that wirelessly communicates with the processing unit, via Bluetooth, enabling to start/stop data acquisition, control operability settings and plotting the acquired data. +S Desktop GUI is an interface developed in MATLAB® able to read the data saved on the USB driver and estimate the gait-associated metrics. This dissertation addressed the development of the +S Desktop GUI able to load, reprocess data and estimate several gait-associated metrics.

3.4.1 GAIT SEGMENTATION

The proposed gait segmentation algorithm detects events HS (IC), FF, MSt, TO (FC) and HO for each leg. The method consists of seven stages: (1) calibration, (2) motion compensation, (3) filtering, (4) 1st derivative computation, (5) finite state machine, (6) event-to-leg assigning and (7) thresholds and events range duration calculation. The algorithm used is based on the study [62], and can be seen in Figure 24. For this dissection, only the calculation of the ICs' and FCs' is required.

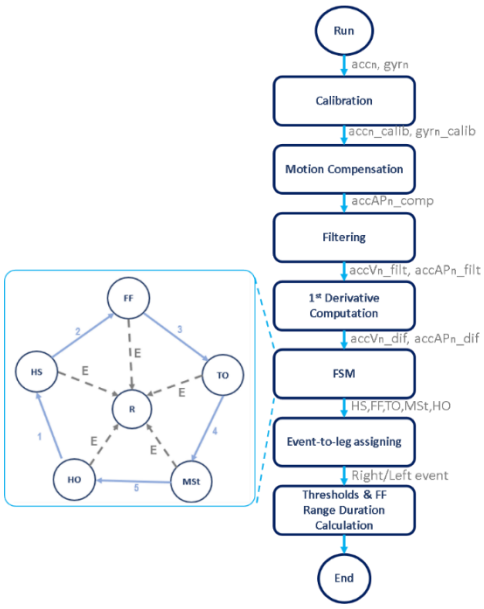

Figure 24. Computational method for the real-time gait segmentation adapted to patients with PD: flowchart of the proposed gait monitoring system adapted to patients with PD.

3.4.2 GAIT-ASSOCIATED FEATURES ESTIMATION

ICs (HS) and FCs (TO) detection enable the estimation of several gait-associated metrics, from different fields, such as **pace, rhythm, variability and asymmetry.**

For the **rhythm**, it was calculated the **step time**, which is the time spend doing a step, the **stride time**, which is the time of a patients stride, the **stance time**, which is the time that the foot is in contact with the ground, the **swing time**, follows the **stance time** and is the time during which the same foot is in the air, the **double support time**, which is the time that both feet are in contact with the ground, the **stance phase**, which is the percentage of time during a stride that is spent with the foot in contact with the ground, the **swing phase**, which is the percentage of time during a stride that is spent with the same foot in the air and the **double support phase**, which is the percentage of time during a stride that is spent with both feet in contact with the ground.

For the **pace**, it was calculated the **step length**, which is the distance between the point of initial contact of one foot and the point of initial contact of the opposite foot, the **stride length**, which is the

distance between two consecutive steps, the **step velocity**, which is the velocity of the step and **cadence**, which is the number of steps per minute.

For the **variability**, it was calculated the **standard deviation** of all metrics in the pace and rhythm domain.

For the **asymmetry**, it was calculated the **difference of some metrics**, step length, step time, step velocity, swing time and stance time, **between the right and the left leg**.

The equations for calculating the metrics of the above-mentioned domains are illustrated in Table IX.

Table IX. Metrics used and the method of obtaining them.

Domain	Metric	Method
Pace	Step Length*	2√(2Lh-h^2)
	Stride Length	〖Step Length〗_i + 〖Step Length〗_(i+1)
	Velocity	〖Step Length〗_i/ 〖Step Time〗_i
	Cadence	〖Velocity〗_i·60/ 〖Step Length〗_i
Rhythm	Step Time	〖IC〗_(i+1)- 〖IC〗_i
	Stride Time	〖IC〗_(i+2)- 〖IC〗_i
	Stance Time	〖FC〗_(i+1)- 〖IC〗_i
	Swing Time	〖StanceTime〗_i + 〖StrideTime〗_(i+1)
	Double Support Time	〖IC〗_(i+1)- 〖FC〗_i
	Stance Phase	Stance Time·100/Stride Time
	Swing Phase	Swing Time ·100/Stride Time
	Double Support Phase	Double S. Time·100/Stride Time
Variability	Step length SD	Standard deviaton of Step Length
	Step Time SD	Standard deviaton of Step Time
	Velocity SD	Standard deviaton of Velocity
	Swing Time SD	Standard deviaton of Swing Time
	Swing Phase SD	Standard deviaton of Swing Phase
	Stance Time SD	Standard deviaton of Stance Time
	Stance Phase SD	Standard deviaton of Stance Phase
	Double Support Time SD	Standard deviaton of Double Support Time
	Double Support Phase SD	Standard deviaton of Double Support Phase
	Stride Time SD	Standard deviaton of Stride Time
	Stride Length SD	Standard deviaton of Stride Length
	Cadence SD	Standard deviaton of Cadence
Asymmetry	Step Length AS	〖Step Length〗_i- 〖Step Length〗_(i+1)
	Step Time AS	〖Step Time〗_i- 〖Step Time〗_(i+1)
	Velocity AS	〖Velocity〗_i- 〖Velocity〗_(i+1)
	Swing Time AS	〖Swing Time〗_i- 〖Swing Time〗_(i+1)
	Stance Time AS	〖Stance Time〗_i- 〖Stance Time〗_(i+1)

***Based on Inverted Pendulum method: where L corresponds to the pendulum height, experimentally measured from the floor to the place where the sensor is placed in user body and h refers to the double integration of vertical acceleration between two consecutive steps (from IC_i to the following IC_{i+1}); i: current moment from sequential users' steps.**

3.4.3 +S APP DESKTOP GUI

The gait event detection algorithm is not 100% effective; it has some miss detection. To calculate fully correct and reliable metrics/features through well-estimated gait events, an application was developed to reprocess the miscalculations in the heel strike and toe off events, IC and FC events. This application was implemented in MATLAB® Graphical user interfaces (GUIs), using the Matlab2021a, being presented in Figure 25.

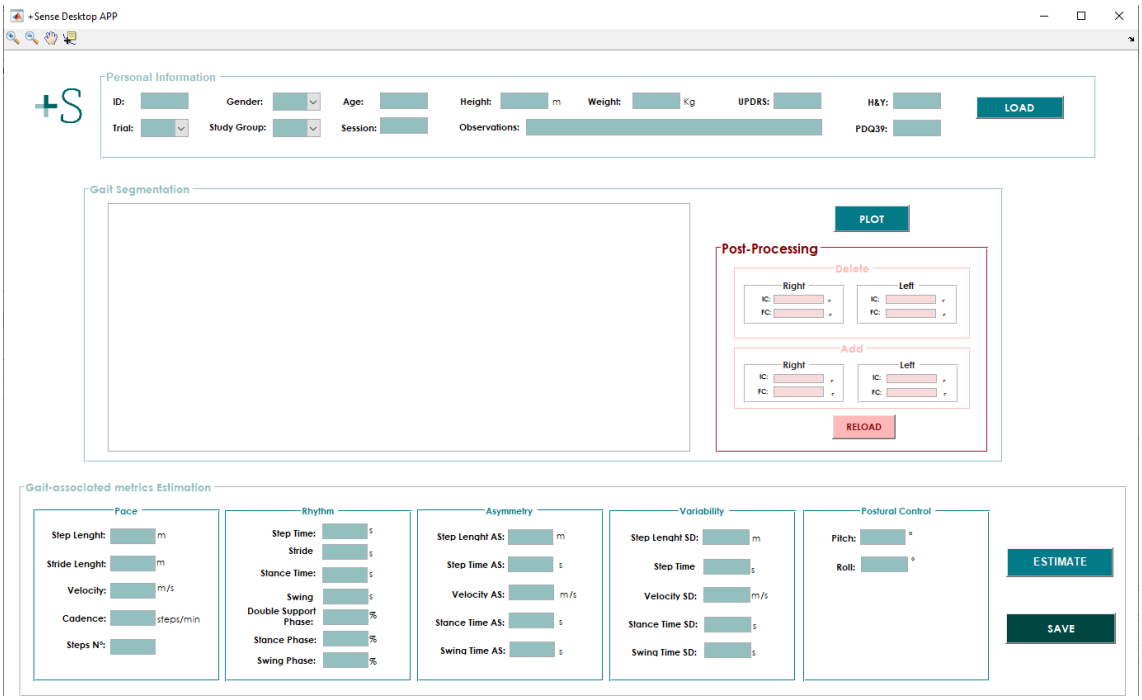

Figure 25. +Sense APP

+S APP is divided into three sections: personal information, gait segmentation and gait parameters estimation. The gait segmentation section includes a post-processing area. The first section includes a field, Personal Information, where is inserted patient data, an example of its completion is showed in Figure 26. This data consists of ID, trial type, gender, study group, age, height, weight, UPDRS, PDQ-39 and H&Y values and the session number. This field also has a "Load" button, this is for reading the data files acquired through patient trials.

Next, a section dedicated to gait segmentation. In this section, it is possible to plot the read data using the "Plot" button, the plot will come with the IC and FC events calculated. Sometimes the data comes with errors in the classification of the ICs or FCs, as can be seen in Figure 26. To correct these errors, the post-processing area was created.

Figure 26. Personal Information and a plot with event detection error.

In the post-processing area, it is possible to eliminate the points, IC or FC, that are placed in the wrong position, and add these same points in the correct position using the “Reload” button. Figure 27 shows the correction made in the point miscalculated showed in Figure 26.

Figure 27. Correction of the Plot.

The last area of the application is called Gait Parameters Estimation. In this area, if the "Estimate" button is pressed, the metrics/features associated with the gait will be calculated, and the ones, shown in the Figure 28, will be displayed in the APP.

Figure 28. Calculation and display of the metrics.

In this last area there is also the "Save" button. This is for saving the metrics and patient information in an excel file.

3.4.4 +sC-support

+sC-support uses the outcomes measured with +sMotion to apply AI models able to accomplish PD management.

In this way, through a single sensor, on the patient's waist, it is possible to estimate a set of metrics, which when applied in AI are able to diagnose PD disease or even stratify its levels. In this way, +sC-support is able to complement physicians in the evaluation of patients.

This dissertation has an impact contribution to this module. An extensive statistical study was conducted to verify if gait metrics vary between patients and non-patients, and between different levels of UPDRS-III and PDQ-39. Next, various AI methods were applied in order to be able to obtain good results in distinguishing healthy from sick and the various levels of the UPDRS-III.

3.4.5 Conclusion

This thesis was developed aiming to contribute to the +sense project. Specifically, it contributed to +sBiofeedback, +sMotion and to +sC-support.

For the +sBiofeedback module, a validation was performed with end-users and with a well-defined protocol. The objective was to verify the best way to apply biofeedback to patients and its effects on them.

For the +sMotion module, this dissertation contributed with an APP capable of correcting miss detections in the gait segmentation, and also with the calculation of metrics capable of describing the end-users' gait characteristics.

For the +sC-support module, this dissertation contributed an extensive statistical and IA study to stratify and diagnose PD, using clinical scales such as UPDRS-III and PDQ-39.

4 A WEARABLE BIOFEEDBACK DEVICE TO IMPROVE MOTOR SYMPTOMS IN PARKINSON'S DISEASE

4.1 INTRODUCTION

This chapter describes how +sBiofeedback module, which includes the WBD, can be used to improve motor symptoms in PD patients. It is presented the design study, protocol and metrics of evaluation. An extensive statistical study was conducted to verify and show the improvements of PD symptoms in patients who received biofeedback.

4.1.1 HYPOTHESIS, RESEARCH QUESTIONS &STUDY DESIGN

The research question that was intended to be answered with the WBD validations was "Does the vibrotactile biofeedback succeed in improving gait performance of patients with Parkinson's disease?". It was also intended to test the hypothesis that the vibrotactile sensory cueing associated to a particular gait event (toe-off/final foot contact/FC) can help patients with PD to reorganize their natural motor patterns and overcome gait impairments. So, it was accomplished a randomized controlled trial.

4.2 METHODOLOGY

4.2.1 EXPERIMENTAL SETUP & PARTICIPANTS

Forty patients diagnosed with PD were recruited during their regular visit in Neurology Service in Hospital of Braga (PD-Group). Demographic data, such as gender, age, height, and weight were recorded for all subjects. All patients gave informed consent and the study granted ethical approval by the Hospital of Braga Ethical Commission 36/2018, following the principles of the Declaration of Helsinki and the Oviedo Convention. Patients were recruited if they present H&Y≤3, age between 50-85 years old, did not have cognitive impairment, presented autonomous gait, and were evaluated by the same neurologist. All patients when performed the experimental protocols were in the ON phase. Clinically, they were evaluated regarding Hoen and Yahr scale (H&Y), UPDRS-III and New Freezing of Gait Questionnaire (nFOGQ). Further, all patients answered to the PDQ-39.

Table X. Patients' characteristics.

Characteristics		Participants (N=40)
Age [years] (mean±SD)		66.83±9.52
Height [cm] (mean±SD)		163.92±7.89
Weight [Kg] (mean±SD)		71.53±14.04
Gender	female	N=19
	male	N=21
H&Y	(mean±SD)	1.83±0.87
	1	N=16

	2	N=15
	3	N=9
UPDRS-III	(mean±SD)	22.08±11.40
	Low (1-12)	N=11
	Middle (13-22)	N=15
	High (≥23)	N=14
NFOG-Q	**(**mean±SD)	11.03±10.46
PDQ-39	(mean ± SD)	37.34±22.55
	High (1-33)	N=16
	Middle (34 -66)	N=14
	Low (67-100)	N=10

These forty patients were randomly assigned to four groups, each with 10 participants. The four groups were:

- Control group (CG): Participants did not receive vibrotactile sensory cueing. They executed three trials without biofeedback (N);
- Mixed group (MG): Participants received gait event-driven and continuous vibrotactile sensory cueing (closed-loop and open-loop cueing, respectively). They executed three trials, one trial with gait-event driven biofeedback (B), one trial with continuous biofeedback (C) and one trial without biofeedback (N);
- Biofeedback event-driven group (BEG): Participants received gait event-driven vibrotactile sensory cueing (closed-loop cueing). They executed two trials with gait-event driven biofeedback (B) and one trial without biofeedback (N);
- Biofeedback continuous group (BCG): Participants received continuous vibrotactile sensory cueing (open-loop cueing). They executed two trials with continuous biofeedback (C) and one trial without biofeedback (N).

The continuous biofeedback trial consists of a vibrotactile stimulus activated every two seconds, while the gait-event driven biofeedback consists of the same stimulus but was only provided when the patient is in right leg FC gait event.

Regarding the protocol, a complex circuit was used, and in this circuit the patients received the vibrotactile sensory cues considering their study group and dedicated trials. This circuit follows the following task pattern: walking forward thirty meters, turning right when they reach the corner, walking forward two meters, turning around when they reach a cone, walking forward two meters, turning left when they reach the other corner, walking forward thirty-two meters, reversing the walk when they reach another cone, walking forward two meters, and stopping when they reach the starting point. This circuit was performed at 2CA Braga, Academic Clinical Center of Braga Hospital, the path is illustrated in Figure 29.

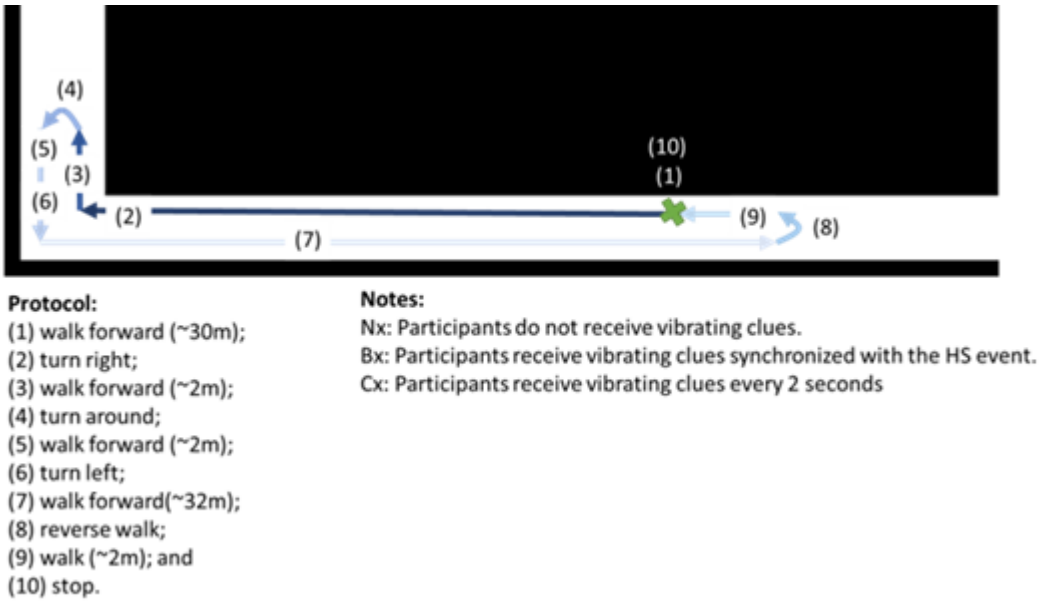

Figure 29. Second part of the protocol, a more complex circuit.

4.2.2 Data collection methods and study variables

Data will be collected using the methods described in the following table. +sMotion was used to calculate the gait parameters of the patients.

Table XI. Variables to be measured and collection method for the present study.

Variables		Method
Motor	UPDRS Scale	UPDRS
	H&Y Scale	H&Y
	NFOG-Q	NFGOQ
	Spatiotemporal gait parameters	+sMotion
	Gait Cycle Segmentation	
QoL	Daily Living Activities Questionnaire	ADL Checklist
	PDQ-39 Questionnaire	PDQ39
Sociodemographic Data		Interview
Usability Questionnaire		System Usability Questionnaire

4.2.3 Data analysis

All processes subject to statistical analysis will be depicted. These were performed using SPSS2019 and the metrics used were those most commonly used in the literature described in Chapter 2.

To verify if vibrotactile biofeedback can help the gait of PD patients and to note which strategy is best, first these three groups gait metrics were compared: control group (CG), biofeedback event-driven group (BEG) and biofeedback continuous group (BCG). At the beginning of this process, all descriptive statistics were calculated for the metrics of the respective groups, to obtain mainly information about their mean, maximum, minimum and standard deviation (inter-subject assessment). Afterwards, two normality tests, Kolmogorov-Smirnov and Shapiro-Wilk, were performed on the metrics of each group. Verifying that the data distributions were non-parametric, the Kruskal-Walli's test was performed in order to observe the significant differences between the groups. The null hypothesis (HO) used in this study was "There are not statically differences between variables means of CG, BEG and BCG". Finally, to draw conclusions about the relationships between the metrics and the group type, a Spearman correlation was performed.

Later, a similar process was performed to study the mixed group (MG). Was started by separating the three tests performed on the patients in this group, the control test (N), the test using event-driven biofeedback (B), and the test using continuous biofeedback (C) (intra-subject assessment). For each of the metrics of each test mentioned, normality was studied using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since the data distributions were normal, a one-way ANOVA was performed to compare the three tests in this group. The null hypothesis used in this study was "There are not statically differences between variables means of N, B and C". To draw conclusions about the relationships between the metrics and the trial type, a Spearman correlation was performed.

A study of the system's acceptability was also performed, in order to verify whether the system is comfortable and easy to use.

4.3 **RESULTS**

The Table XII shows the comparison between the gait performance of the various groups, inter-subject assessment. Furthermore, were quantified variables of gait performance with strategy.

Table XIII. Inter-subject assessment. ρ: significance level at 10% with H0="There are not statically differences between variables means of CG, BEG and BCG"; significant correlation at 5% n * and at 1% in **; (+)(-): prototypical parkinsonian motor signals.

Inter-subject assessment

Domain	Variables	CG (N)	BEG (B)	BCG (C)	ρ (Kruskal Wallis test)	Pearson rho (ρ-value)
		Mean ± SD	Mean ± SD	Mean ± SD		

Rhythm	(+) Step time (s)	0,580±0,014	0,550±0,010	0,566±,0215	0,526	-0,124 (0,307)
	(+) Stance phase (%)	65,903±0,826	62,394±1,415	63,8546±1,931	**0,035***	**-0,181 (0,134)**
	(-) Swing phase (%)	33,461±0,813	37,545±1,481	37,321±1,946	**0,039***	**0,254* (0,034)**
Pace	(-) Step length (m)	0,547±0,017	0,587±0,033	0,515±0,0176	0,126	-0,098 (0,419)
	(-) Velocity (m/s)	0,967±0,034	1,079±0,034	0,955±0,038	0,114	0,030 (0805)
	(-) Cadence (steps/min)	107,050±2,351	112,480±2,313	111,591±2,896	0,467	0,138 (0,256)
Variability	(+) SD Step time	0,085±0,005	0,083±0,011	0,127±0,030	0,402	-0,057 (0,641)
	(+) SD Step length	0,123±0,005	0,110±0,004	0,13436±0,010	**0,080***	**0,046 (0,704)**
	(+) SD Velocity	0,226±0,010	0,233±0,007	0,282±0,0165	**0,015***	**0,327** (0,006)**
Asymmetry	(+) AS Step time	0,025±0,005	0,059±0,015	0,036±0,006	**0,043**	**0,273* (0,022)**
	(+) AS Step length	0,113±0,015	0,113±0,013	0,136±0,022	0,640	0,111 (0360)
	(+) AS Velocity	0,209±0,027	0,232±0,026	0,309±0,045	0,168	0,227 (0,058)

There was an improvement in the rhythm, pace and variability domains in the BEG when compared to the control group. For the BCG group, an improvement in the rhythm and pace domains was found.

Table XIII shows the same study, inter-subject assessment, but only comparing the control group with the event-driven biofeedback group.

Table XIV. Inter-subject assessment. ρ: significance level at 10% with H0="There are not statically differences between variables means of CG and BEG "; significant correlation at 5% n * and at 1% in **; (+)(-): prototypical parkinsonian motor signals.

Inter-subject assessment

Domain	Variables	CG (N)	BEG (B)	ρ (Kruskal Wallis test)	Pearson rho (ρ-value)
		Mean ± SD	Mean ± SD		
Rhythm	(+) Step time (s)	0,580±0,014	0,550±0,010	0,332	-0.139 (0,337)
	(+) Stance phase (%)	65,903±0,826	62,394±1,415	**0,009***	**-3,71** (0,008)**

	(-) Swing phase (%)	33,461±0,813	37,545±1,481	**0,021***	**0,331* (0,019)**
Pace	(-) Step length (m)	0,547±0,017	0,587±0,033	0,205	0,181 (0,208)
	(-) Velocity (m/s)	0,967±0,034	1,079±0,034	**0,063***	**0,266 (0,062)**
	(-) Cadence (steps/min)	107,050±2,351	112,480±2,313	0,294	0,150 (0,299)
Variability	(+) SD Step time	0,085±0,005	0,083±0,011	0,227	-0,173 (0,231)
	(+) SD Step length	0,123±0,005	0,110±0,004	**0,066***	**-0,263 (0,065)**
	(+) SD Velocity	0,226±0,010	0,233±0,007	0,417	0,116 (0,422)
Asymmetry	(+) AS Step time	0,025±0,005	0,059±0,015	0,513	0,294* (0,038)
	(+) AS Step length	0,113±0,015	0,113±0,013	**0,039***	**0,96 (0,519)**
	(+) AS Velocity	0,209±0,027	0,232±0,026	0,276	0,156 (0,281)

Next, an intra-subject assessment is presented, showing a comparison between trials in the mixed group.

Table XV. Intra-subject assessment. ρ: significance level at 10% with H0="There are not statically differences between variables means of N, B and C"; (+)(-): prototypical parkinsonian motor signals.

Intra-subject assessment

Domain	Variables	MG (N)	MG (B)	MG (C)	ρ (Repeated measures ANOVA)
		Mean ± SD	Mean ± SD	Mean ± SD	
Rhythm	(+) Step time (s)	0,580±0,014	0,535±0,061	0,546±,080	0,374
	(+) Stance phase (%)	63,539±2,179	65,027±5,202	63,576±2,989	0,285
	(-) Swing phase (%)	35,980±2,483	34,714±5,389	36,991±3,360	0,176
Pace	(-) Step length (m)	0,552±0,110	0,543±0,112	0,540±0,102	0,559
	(-) Velocity (m/s)	1,036±0,198	1,031±0,206	1,00±0,171	0,279
	(-) Cadence (steps/min)	113,121±9,925	114,202±11,388	112,824±14,757	0,471

Variability	(+) SD Step time	0,056±0,021	0,054±0,023	0,064±0,022	0,242
	(+) SD Step length	0,115±0,047	0,117±0,035	0,120±0,035	0,235
	(+) SD Velocity	0, 213±0,071	0,238±0,072	0,219±0,069	0,376
Asymmetry	(+) AS Step time	0,019±0,016	0,038±0,041	0,023±0,013	0,728
	(+) AS Step length	0,102±0,065	0,106±0,086	0,119±0,098	0,194
	(+) AS Velocity	0,172±0,127	0,226±0,151	0,219±0,168	0,531

The next tables show the results of the system acceptability, that is, the results of the system usability questionnaire. In this questionnaire there are several statements and each one of the forty patients select from 1 to 5 how much they agree with these statements. In the table, it is represented the number of patients who answered the question with the number 1, 2, 3, 4, and 5.

Table XVI. System Usability Questionnaire

	1	**2**	**3**	**4**	**5**	**Mean**
1 - I think I would like to use this system frequently.	3	1	10	11	15	3,85
2 - I found the system unnecessarily complex.	27	8	4	1		1,48
3 - I found this system easy to use.			1	13	26	4,63
4 - I think I would need the support of a technical person to be able to use this system.	20	9	3	4	4	2,08
5 - I think the various functions of the system are very well integrated.	1		7	16	16	4,15
6 - I think the system is very inconsistent.	25	7	6		2	1,68
7 - I imagine that most people would learn to use this system very quickly.	3	3	2	11	21	4,10
8 - I found the system very complicated to use.	27	10	1	1	1	1,48

9 - I feel confident using the system.		1	7	17	15	4,15
10 - I needed to learn many things before starting this system	24	7	6	2	1	1,73
11- I found the system comfortable.			2	6	32	4,75

4.4 DISCUSSION

For the inter-subject assessment, Table XII and XIII, can be seen an improvement in the rhythm variables. In step time, there was a decrease in the average time in the BEG and BCG when compared to the CG, thus improving the parkinsonian gait, which is characterized by steps that take longer. As for the stance phase, there is a decrease in this variable in BEG and BCG when compared to CG, approaching 60%. This decrease shows an improvement in the parkinsonian characteristics of the patients since a healthy gait tends to have a stance phase close to 60%. For the swing phase, there is an increase in the mean values in the BEG and BCG groups when compared to the CG, approaching 40%. These results show an improvement in the parkinsonian gait, since healthy gait has swing phase values close to 40%. In these rhythm variables, only the stance phase (ρ=0,035) and the swing phase (ρ=0,039) showed statistically significant differences between the groups.

In the Pace variables, there were no statistically significant changes between the groups, but there were conclusive differences in the means of these variables. In step length, there was an improvement in this characteristic in the BEG group when compared to the control group, since there was an increase in the average step length, and parkinsonian gait is characterized by shorter steps. In the BCG group, the opposite was observed, a decrease in the average when compared to the CG group. In terms of velocity, it was found that there is an improvement in the mean value of the BEG group compared to the CG, because parkinsonian gait is characterized by being slower. The opposite was verified for the BCG group, since there was a decrease in the average when compared to the CG. As for cadence, there was an improvement in this characteristic in the BEG and BCG groups when compared to the CG. Both presented an increase in this characteristic, thus translating into an improvement of the parkinsonian characteristics of the patients, since the parkinsonian gait tends to have a decrease in cadence.

In the variability characteristics, the goal would be to decrease the mean values of the BEG and BCG groups when compared to the CG, since parkinsonian gait presents more variability than healthy gait. This was only verified for the metrics SD step time and SD step length in the BEG group. All others

increased when compared to the CG. There were statistically significant differences for the variables SD step length (ρ=0,080) and SD velocity (ρ=0,015).

In terms of the Asymmetry metrics, it would be expected that in the BEG and BCG groups there would be a decrease in the mean values of the metrics when compared to the CG, since parkinsonian gait presents more asymmetries than healthy gait. This did not happen for any of the metrics, there was only an equality between the mean AS step length in the BEG group, with a decrease in its standard deviation, when compared to the CG, which may mean a lower dispersion of values, meaning an improvement in the asymmetry of this variable. There were statistically significant differences for the variable AS step time (ρ=0,043).

Overall, it is concluded that BEG has achieved many improvements in metrics when compared to CG, some of them quite significant. While BCG, obtained only a few of these improvements, few compared to BEG. Thus, it can be concluded that **the best method for improving Parkinsonian gait is event-driven biofeedback, biofeedback provided at the specific event, FC of the right leg. This evidence proves that vibrotactile biofeedback can improve the gait performance of patients with Parkinson's disease, and that the vibrotactile sensory cue associated with a given gait event can help patients with PD reorganize their natural motor patterns and overcome gait impairments.**

Comparing only BEG with CG, new statistically significant differences were found. There were significant differences in stance phase (ρ=0,009)**, swing phase** (ρ=0,021)**, velocity** (ρ=0,063)**, SD step length** (ρ=0,066) **and AS step length** (ρ=0,039)**, translating into a more significant improvement of these variables in the BEG.**

As for the Pearson correlation, it was found that the metrics that correlated best with the groups, CG, BEG and BCG, were stance phase, swing phase, SD step length, SD velocity, and AS step time, when comparing the three trial types. When only comparing CG to BEG the metrics that best related to the group were stance phase, swing phase, velocity, SD step length and AS step length.

For the mixed group, one would expect the metrics resulting from event-driven biofeedback to have an improvement over the metrics resulting from the trial without biofeedback. The same should be true for the metrics from the continuous biofeedback, these should improve over the trial without biofeedback but should improve less than those from the event-driven biofeedback. However, this only happens for step time. This may be due to the execution of the trials all in a row in a short period of time and to the small sample size. As for the ANOVA results, there were no statistically significant differences between the trials in the mixed group.

In terms of usability, positive responses were obtained. Most patients found the system comfortable, easy to use, and would not mind using it independently.

4.5 Conclusion

With this study, it was possible to conclude which method of providing vibrotactile biofeedback to patients was best. Closed-loop cueing, i.e. BEG, had the best results, since most of the gait metrics improved in the patients with PD, and this improvement was very significant. BEG showed better results when compared to open-loop cueing, i.e. BCG, and was therefore the better of the two methods. **This evidence proves that vibrotactile biofeedback can improve the gait performance of patients with Parkinson's disease, and that the vibrotactile sensory cue associated with a given gait event can help patients with PD reorganize their natural motor patterns and overcome gait impairments.**

The study of the mixed group did not allow to conclude anything about the aforementioned hypothesis, the best results were not obtained. In the future it is intended to repeat this study with more patients and with a more spaced trial repetition.

As for the acceptability of the system, it can be concluded that it is quite easy and intuitive to use. Most patients accepted the use of the system and would not mind using it more often.

5 +sMotion as a biomarker of Parkinson's disease motor stages and quality of life

5.1 INTRODUCTION

This chapter describes the whole process of making +sMotion a tool to support the diagnosis of motor phases of PD, through the implementation of artificial intelligence. (+sC-support). The hypotheses, research questions, study design, and the entire elaboration of the developed study will be discussed.

5.1.1 STUDY PURPOSE

The first goal of this chapter, was to develop a statistical study aiming to verify if +sMotion has the ability to distinguish healthy from PD patients and to distinguish PD patients from each other according to their stage of progression and evolution of their disease, using the scales normally used for this, PDQ-39 and UPDRS-III.

Secondly, it was intended to develop several AI models and verify which ones are best suited for diagnosing motor disability in PD (given by the UPDRS-III scale), distinguish between patient and non-patient impaired gait and biomark/stratify motor disabilities levels. To do this, we acquired data from the patients, either healthy or with different levels of disability given by the UPDRS-III scale. These data was then used in different methods until it was reached the best results, according to the specified metrics. It was used two different datasets, several machine learning and deep learning methods, several functions for data preprocessing and several feature selection methods. These previous processes were studied to finally obtain the model with the best combinations and best results.

5.2 METHODOLOGY

5.2.1 HYPOTHESIS, RESEARCH QUESTIONS & STUDY DESIGN

In this chapter, we intend to answer to the research questions “Can the +sMotion be a biomarker of motor impairments in Parkinson’s disease?” and ”Can the +sMotion be a biomarker of quality of life in Parkinson’s disease measured by patients’ motor impairments?”, through a statistical analysis. The research questions "Is +sMotion able to distinguish between patient and non-patient impaired gait?" and “Is +sMotion able to biomark/stratify motor disabilities levels?” are answered through an AI-based analysis. The underlying hypothesis was that the +sMotion can be a biomarker of motor impairments in PD and a biomarker of quality of life in PD measured by patients’ motor impairments. In order to verify the hypothesis, it was conducted a cross-sectional study.

5.2.1.1 EXPERIMENTAL SETUP & PARTICIPANTS

For the study, forty patients were assigned to three groups, according to the scale used. To verify that +sMotion can be a biomarker of motor impairments in PD, three groups of PD, plus a control group of healthy, were used:

- UPDRS III Low (L): 11 participants who had a score of UPDRS-III between 1 and 12;
- UPDRS III Middle (M): 15 participants who had a score of UPDRS-III between 13 and 23;
- UPDRS III High (H): 14 participants who had a score of UPDRS-III higher than 23;
- Control Group: 10 age-matched healthy subjects;

The sociodemographic characteristics of the PD patients are described in Table X in Chapter 4. In Table XVII are the socio-demographic characteristics of the healthy people used in the control group, values presented as mean(standard deviation).

Table XVII. Control group characteristics.

Characteristics	**H-Group**
Gender	Female: N=6
	Male: N=7
Age [years]	52.92(10.47)
Height [cm]	166.69(8.41)
Weight [Kg]	72.92(15.41)

Table XVIII. Groups used for statistical and AI methods.

Group	**Number of patients**
UPDRS III Low	11
UPDRS III Middle	15
UPDRS III High	14
Healthy Control Group	10

To verify that +sMotion can be a biomarker of quality of life in PD, three groups were used:

- PDQ39 Never have (ND) difficulties in performing daily activities: 16 participants who had a score of PDQ-39 between 0 and 33;
- PDQ39 Sometimes have (SD) difficulties in performing daily activities: 14 participants who had a score of PDQ-39 between 34 and 66;
- PDQ39 Always have (AD) difficulties in performing daily activities (66-100): 10 participants who had a score of PDQ-39 between 66 and 100;

The sociodemographic characteristics of the PD patients are described in Table X in Chapter 4.

Group	Number of patietns
PDQ39 ND	16
PDQ39 SD	14
PDQ39 AD	10

Regarding the trials protocol, all patients walked forward in a straight line over 10 meters (two/three times) without biofeedback. The circuit used is at 2CA Braga, Academic Clinical Center of Braga Hospital, and the path is illustrated in Figure 30.

Table XIX. Groups used for statistical methods.

Figure 30. Protocol, walking forward in a straight line over 10 meters.

This circuit was made using +sMotion in order to obtain metrics from the domains of rhythm, pace, variability and asymmetry.

5.2.2 METHOD 1: HOW STATISTICAL ANALYSIS SUPPORTS DIAGNOSTIC ASSESSMENT OF MOTOR PHASES OF PARKINSON'S DISEASE AND QUALITY OF LIFE MONITORING

5.2.2.1 DATA ANALYSIS

To test whether +sMotion can be a biomarker of motor impairments and quality of life in PD, several statistical studies were conducted to compare the metrics of rhythm, pace, variability and asymmetry domains with the evolution on the respective scales, PDQ-39 and UPDRS-III. To this end, a comparison was first made between the healthy group and the group of patients with PD. It was performed a descriptive statistical analysis of the metrics of both groups to verify, mainly, the differences between the means and the standard deviations. Then, normality tests were performed for each of the metrics in each group, and, since they were essentially non-normally distributed, a Mann-Whitney test was performed to check for significant differences between the metrics in the healthy group and the group with PD.

Subsequently, a comparison was made between the metrics of the different UPDRS-III groups, Low, Middle and High group. A descriptive statistic was performed to check the differences between the metrics of both groups, mainly differences in the means. The study of the normality of the metrics for each group was applied, and, finding that most show a non-normal distribution, a Kruskal-Walli's test was performed to find the significant differences in the metrics of the different UPDRS-III groups. A Spearman correlation was performed to quantify the associations between the metrics and between the metrics and the scales used in the study, as shown in Appendix's.

For the PDQ-39 scale, the process performed was the same as for the UPDRS-III, only there was a difference in the groups that were distributed by the ND, SD, and AD groups.

5.2.2.2 RESULTS

The next tables refer to the difference of the metrics between PD and healthy people and between the different levels of motor impairment of Parkinson's, UPDRS-III Low, Middle and High. Table XXI shows the comparison between PD and healthy people.

Table XXI. Significance test between PD vs Healthy. ρ: significance level at 5% with H0="There are not statically differences between variables means of PD and Healthy"; (+)(-): prototypical parkinsonian motor signals.

Significance test between PD vs Healthy

Domain	Variables	PD	HEALTHY	ρ

		Mean	±SD	Mean	±SD	(Mann-Whitney test)
Rhythm	(+) Step time (s)	0,562	0,085	0,542	0,030	0,776
	(+) Stance phase (%)	64,458	3,008	61,444	2,616	**0,000**
	(-) Swing phase (%)	33,974	4,640	36,455	3,052	**0,003**
Pace	(-) Step length (m)	0,547	0,116	0,549	0,098	0,864
	(-) Velocity (m/s)	0,991	0,205	1,012	0,153	0,816
	(-) Cadence (steps/min)	110,528	16,495	111,902	7,143	0,831
Variability	(+) SD Step time	0,104	0,044	0,063	0,019	**0,000**
	(+) SD Step length	0,064	0,029	0,043	0,022	**0,000**
	(+) SD Velocity	0,186	0,071	0,117	0,036	**0,000**
Asymmetry	(+) AS Step time	0,117	0,093	0,050	0,033	**0,000**
	(+) AS Step length	0,051	0,039	0,028	0,034	**0,000**
	(+) AS Velocity	0,196	0,160	0,080	0,058	**0,000**

Table XXIII shows the relationship between the metrics in the different degrees of disease disability.

Table XXIII. Significance test between UPDRS-III groups. ρ: significance level at 5% with H0="There are not statically differences between variables means of UPDRS-III Low (L), Middle (M) and High (H)"; (+)(-): prototypical parkinsonian motor signals.

Domain	Variable	UPDRS	Mean	±std	ρ	ρ	Group combination
Rhythm	Step time (s)	L	0,529	0,051	**0,011**	**0,06**	L – M
		M	0,573	0,087		**0,010**	L – H
		H	0,581	0,090		0,747	M – H
	Stance phase (%)	L	63,365	2,931	0,438	0,549	L – M
		M	64,406	2,853		0,448	L – H
		H	65,148	2,786		0,979	M – H
	Swing phase (%)	L	36,329	3,386	**0,0411**	0,303	L – M
		M	34,872	3,128		**0,031**	L – H
		H	31,979	4,629		0,474	M – H
Pace	Step length (m)	L	0,588	0,082	**0,0128**	0,247	L – M
		M	0,559	0,119		**0,008**	L – H
		H	0,516	0,109		0,280	M – H
	Velocity (m/s)	L	1,119	0,113	**0,000**	**0,005**	L – M
		M	0,992	0,211		0,000	L – H

		H	0,911	0,201		**0,295**	M - H
	Cadence(steps/min)	L	115,419	9,807	**0,0135**	**0,055**	L – M
		M	107,662	15,259		**0,014**	L – H
		H	107,650	17,471		0,835	M – H
Variability	SD step length	L	0,0926	0,041	0,220	0,594	L – M
		M	0,102	0,041		0,191	L – H
		H	0,111	0,047		0,674	M – H
	SD step time	L	0,055	0,026	**0,032**	0,665	L – M
		M	0,059	0,024		**0,030**	L – H
		H	0,0730	0,029		0,161	M – H
	SD velocity	L	0,183	0,073	0,192	0,896	L – M
		M	0,169	0,055		0,456	L – H
		H	0,201	0,0768		0,178	M – H
Asymmetry	AS step length	L	0,105	0,072	0,555	0,687	L – M
		M	0,115	0,085		0,5460	L – H
		H	0,134	0,112		0,965	M – H
	AS step time	L	0,047	0,036	**0,036**	0,806	L – M
		M	0,047	0,046		0,206	L – H
		H	0,056	0,030		**0,0325**	M – H
	AS velocity	L	0,187	0,160	0,170	0,933	L – M
		M	0,171	0,134		0,384	L – H
		H	0,239	0,1787		0,166	M – H

To better verify the evolution of the averages of the metrics with the progression of disability, portrayed by the UPDRS-III scale, polar plots were produced.

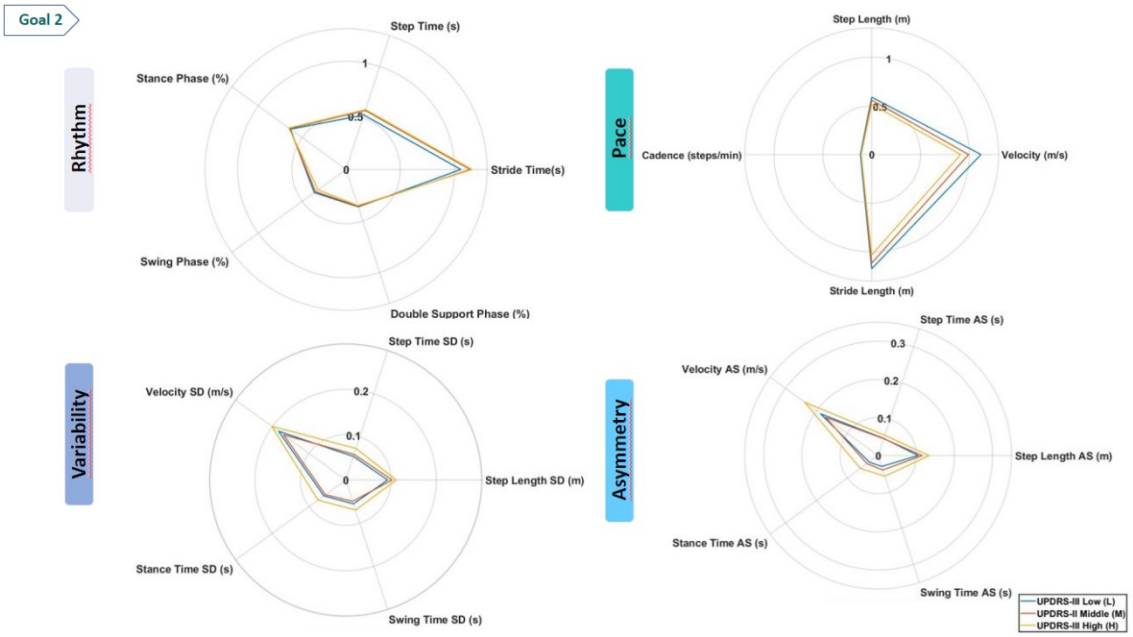

Figure 31. UPDRS-III Polar Plots.

To quantify the association between gait-related metrics and the UPDRS, the correlation matrix resulting from a Spearman's correlation, is presented in Appendix I.

Table XXIV depicts the differences of the metrics with the evolution of the PDQ-39 scale, that is, the relationship between the metrics and the level of quality of life.

Table XXIV. Significance test between PDQ-39 groups. ρ: significance level at 5% with H0="There are not statically differences between variables means of PDQ-39 ND, SD and AD"; (+)(-): prototypical parkinsonian motor signals.

Domain	Variable	PDQ39	Mean	±std	p	p	Group combination
Rhythm	Step time (s)	ND	0,528	0,045	**0,001**	**0,003**	ND– SD
		SD	0,580	0,070		**0,013**	ND – AD
		AD	0,596	0,115		0,991	SD – AD
	Stance phase (%)	ND	1,055	0,090	**0,002**	**0,003**	ND– SD
		SD	1,160	0,141		**0,016**	ND – AD
		AD	1,188	0,231		0,981	SD – AD
	Swing phase (%)	ND	63,192	2,804	0,080	0,073	ND– SD
		SD	64,856	1,934		0,347	ND – AD
		AD	65,612	2,531		0,830	SD – AD
Pace	Step length (m)	ND	36,258	2,885	**0,000**	**0,003**	ND– SD
		SD	34,677	2,554		**0,000**	ND – AD
		AD	30,480	4,178		0,658	SD – AD
	Velocity (m/s)	ND	0,571	0,088	0,064	0,919	ND– SD
		SD	0,565	0,121		0,061	ND – AD
		AD	0,504	0,104		0,151	SD – AD
	Cadence(steps/min)	ND	1,138	0,177	0,065	0,938	ND– SD
		SD	1,130	0,241		0,064	ND – AD
		AD	1,008	0,206		0,144	SD – AD

Variability	SD step length	ND	1,079	0,103	**0,000**	0,250	ND– SD
		SD	0,998	0,243		**0,000**	ND – AD
		AD	0,872	0,191		**0,011**	SD – AD
	SD step time	ND	114,968	9,025	**0,004**	**0,008**	ND– SD
		SD	106,019	12,945		**0,028**	ND – AD
		AD	106,790	21,734		0,990	SD – AD
	SD velocity	ND	0,087	0,041	**0,000**	**0,071**	ND– SD
		SD	0,105	0,041		**0,000**	ND – AD
		AD	0,126	0,046		0,114	SD – AD
Asymmetry	AS step length	ND	0,049	0,024	**0,000**	**0,008**	ND– SD
		SD	0,066	0,020		**0,000**	ND – AD
		AD	0,080	0,030		0,190	SD – AD
	AS step time	ND	0,155	0,060	**0,000**	**0,010**	ND– SD
		SD	0,194	0,063		**0,000**	ND – AD
		AD	0,218	0,074		0,382	SD – AD
	AS velocity	ND	0,112	0,094	0,656	0,629	ND– SD
		SD	0,200	0,175		0,303	ND – AD
		AD	0,239	0,181		0,460	SD – AD

To better verify the evolution of the averages of the metrics with the progression of the quality of life, portrayed by the PDQ-39 scale, polar plots were produced.

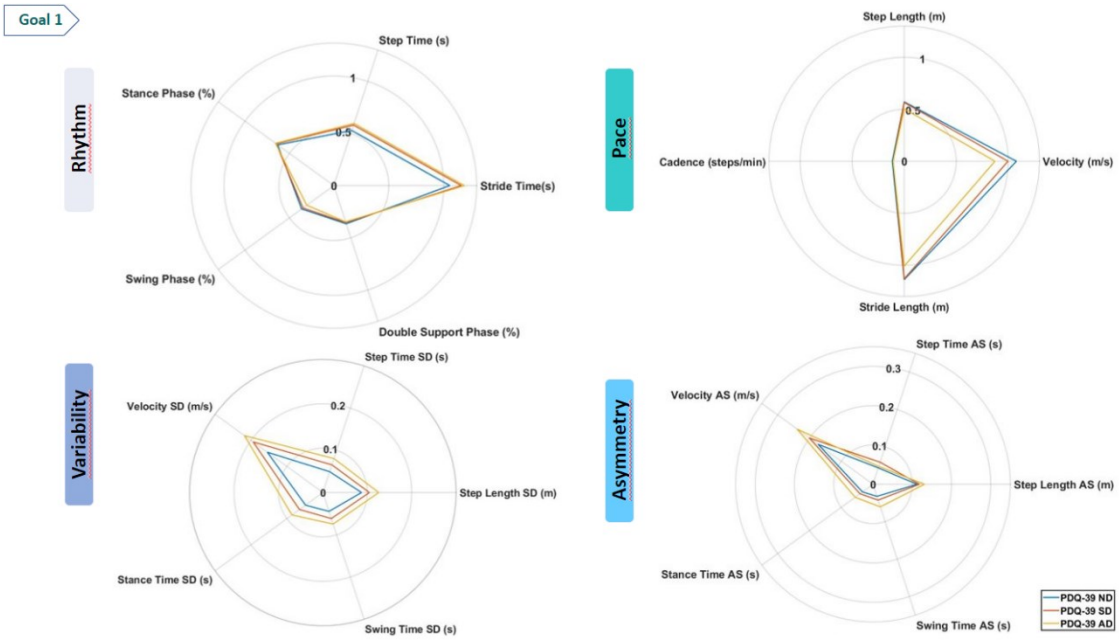

Figure 32. PDQ-39 Polar Plots.

To quantify the association between gait-related metrics, the PDQ-39 and UPDRS-III, the correlation matrix resulting from a Spearman's correlation, is presented in Appendix II.

5.2.2.3 DISCUSSION

To verify whether +sMotion **can be a biomarker of motor impairments**, first were checked the differences obtained between the PD patients and the healthy control group. All the variables, in all the domains (rhythm, pace, variability and asymmetry), obtained average values similar to those found in the literature [13], [15], [46], [47], [50], [51]. For rhythm, step time is lower in healthy patients than in PD patients, stance phase is closer to 60% in healthy patients than in PD patients, and swing phase is closer to 40% in healthy patients than in PD patients. For the Pace, the step length of PD patients is slightly lower than that of healthy patients, the speed of PD patients is lower than that of healthy patients, and the average cadence value is also lower when compared to healthy patients. Considering variability, the expected results were also verified. All metrics presented a mean higher in PD patients compared to the healthy control group, since they tend to have a gait with higher variability. The same was verified for the asymmetry, since the patients with PD present average asymmetry values higher than the values of the healthy group. These results prove that +sMotion can distinguish between patients with PD and healthy individuals.

Statistically significant differences between groups were obtained in the metrics stance phase (p=0.000), swing phase (p=0.003), SD step time (p=0.000), SD step length (p=0.000), SD Velocity (p=0.000), AS step time (p=0.000), AS step length (p=0.000) and AS velocity (p=0.000). This proves that **+sMotion can distinguish PD patients from healthy ones**.

Comparing only PD patients, **with different levels of disability given by the UPDRS-III scale**, it was found that the metrics have a pattern of evolution with the progression of disease disability, as in the literature [13]. Step time increases as the respective scale increases, which is as expected, since patients with more difficulty tend to take longer to perform the gait. As for the stance phase, there is an increase with the progression of the scale, this is to be expected since the worse the ability to perform the gait, the further away from the normal 60%. The swing phase tends to decrease as expected, since the worse the degree of disability, the further away from the normal 40% will be. For step length, there is a decrease with disease progression, as expected, since with increasing PD characteristics the shorter the steps will be. The speed tends to decrease with the progression of the disease, the more advanced the disability caused by PD, the slower the patients tend to become. For cadence, a decrease was observed as the scale increased, which is expected, since the larger the scale, the greater the disability, and therefore the slower the movements of the patients, steps that take longer, leading to fewer steps per minute. For the variability and asymmetry metrics, there is a general increase with disease progression, that is, the higher the scale, the greater the asymmetry and variability of the patients' metrics.

This was not true only for SD velocity and AS velocity, which decreased from L to M and then increased from M to H, which could be related to the small sample size, giving some randomness in the results. All the evolutions of the metrics described can be better observed with the help of the polar plots, which allow us to verify these patterns of increase or decrease as the UPDRS-III scale progresses. There are statistically significant differences in step time (p=0.011), swing phase (p=0.041), step length (p=0.013), velocity (p=0.000), cadence (p=0.014), SD step time (p=0.032) and AS step time (p=0.036). Proving that **+sMotion can be a biomarker of motor impairments**.

To verify if the **+sMotion can be a biomarker of quality of life in PD**, it was done the same study but for the PDQ-39 scale. It was found that the metrics show a pattern according to the progression of the scale. For step time, there is an increase, which was expected since when this metric tends to worsen according to the typical evolution of Parkinson's, quality of life tends to decrease. For the stance phase, there was an increase with the progression of the scale, that is, a departure from the normal 60% with the degradation of quality of life, which was expected since the more aggravated the parkinsonism, the farther the stance phase will be from normal and consequently the worse the quality of life of the patient. As for the swing phase, there is a decrease, a departure from the normal 40%, with the progression of the scale, which was expected, since the more aggravated the parkinsonism, the worse the swing phase and consequently the worse the patient's quality of life. For step length, a decrease was observed with the evolution of the scale, since the more aggravated the parkinsonism is, the smaller the step length will be, making the quality of life of the patients more and more difficult. The same is true for speed and cadence, these have a decrease with increasing scale, noting that the slower the steps are and the fewer steps patients take per minute, the worse their quality of life. For variability and asymmetry, an increase is generally observed with the progression of the scale, because with the progression of Parkinson's, patients tend to have a more variable and asymmetric gait, causing their quality of life to worsen.

All the metric patterns described above can be best observed in the polar plots.

In this PDQ-39 scale, some metrics were found to have statistically significant differences in relation to the progression of the scale, these were step time (p=0.001), stance phase (p=0.002), step length (p=0.000), all the metrics in the variability domain (p=0.000), AS step time (p=0.000) and AS step length (p=0.000). Proving that **+sMotion can be a biomarker of quality of life in PD**.

This evidence points to the possibility of using these metrics in AI, since statistically significant differences were found. These patterns in the evolution of metrics depending on whether you are sick or not, or the degradation of metrics as the scales increase, allow to use AI to distinguish patients.

5.2.3 Method 2: Artificial intelligence-based approach to support diagnostic assessment of motor phases of Parkinson's disease

5.2.3.1 Dataset preparation, pre-processing and feature selection

Two different types of datasets were prepared, one with the calculated metrics associated with the subjects' gait (non-sequential features), mainly for machine learning, and another for deep learning methods, the latter's data being extracted directly from the patients' inertial signals (sequential features).

In order to support diagnostic assessment of motor phases of PD, the UPDRS-III scale was used for this purpose, making the output labels of the AI methods the respective value of this scale, Low, Middle, High or zero in case it is healthy.

For this purpose, a script was made, whose flowchart is shown in Figure 33, whose final result gives rise to two types of datasets, the one for the simpler methods, the dataset with non-sequential features, and the dataset for the more complex methods, the dataset with sequential features.

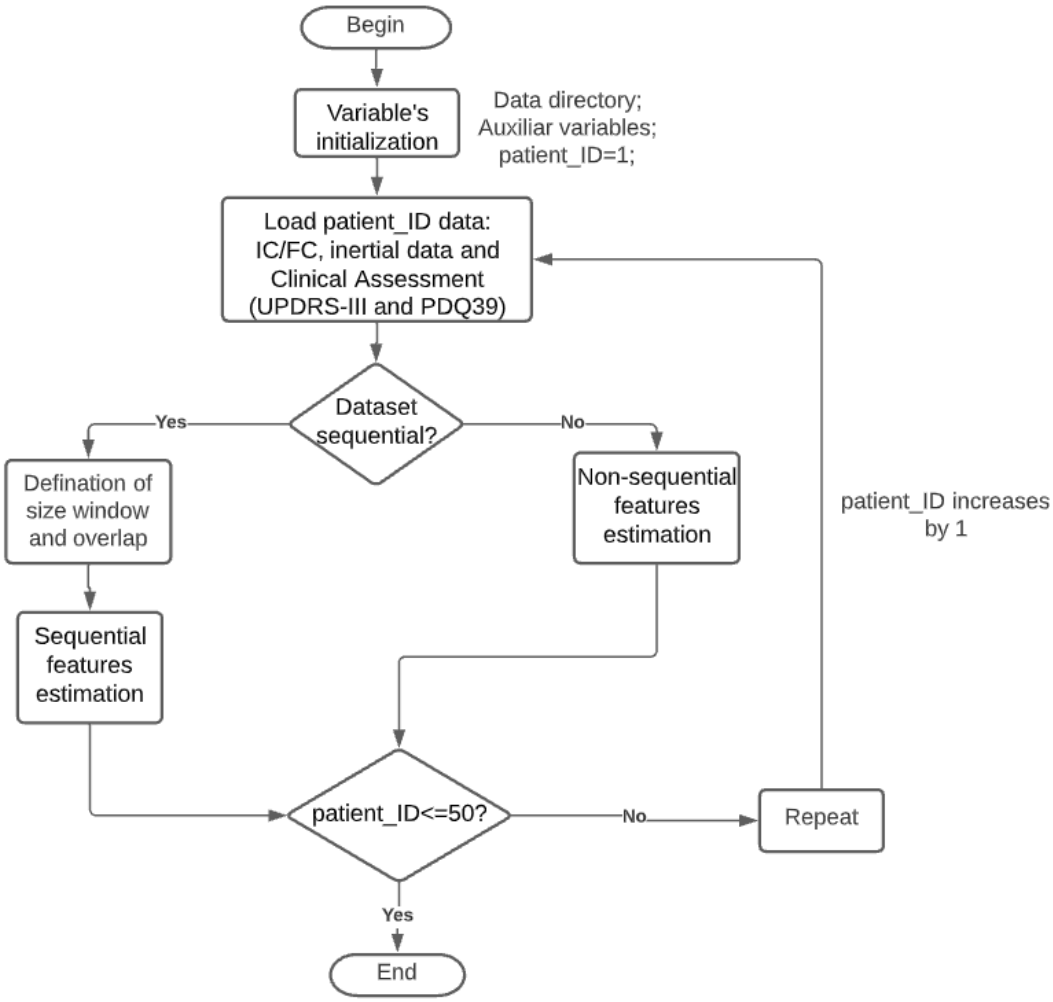

Figure 33. Flowchart of the script for creating datasets.

This script starts by creating the variables that will store the datasets and insert the directories for the inertial data and the corresponding patient ICs and FCs. This code will then load the date of the first patient, their ICs and FCs and their disease information, UPDRS-III and PDQ-39 scales. If the dataset wanted is sequential, it calculates the sequential features and puts them into temporal windows with the desired size and overlap and then add them to the dataset storage variable. If sequential features were not wanted, the code calculates the non-sequential metrics that depend on the gait of the patients and add them to the dataset storage variable. Finally, it repeats this process for all patients, until the data for all patients is part of the final dataset.

This script was performed in Matlab2020a and examples of the outputs can be seen in Figure 34 and 35.

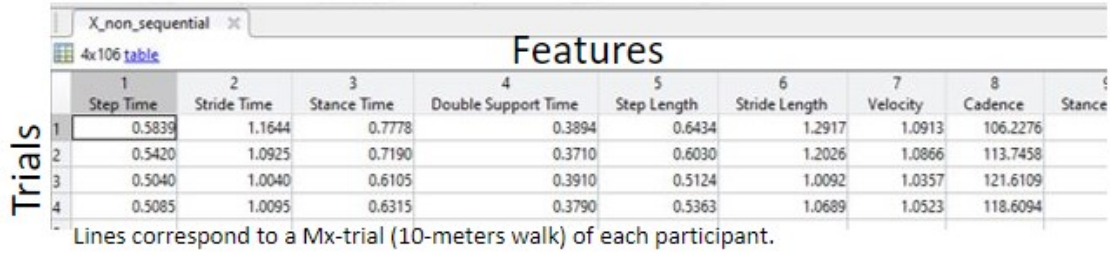

Figure 34. Example of the non-sequential dataset.

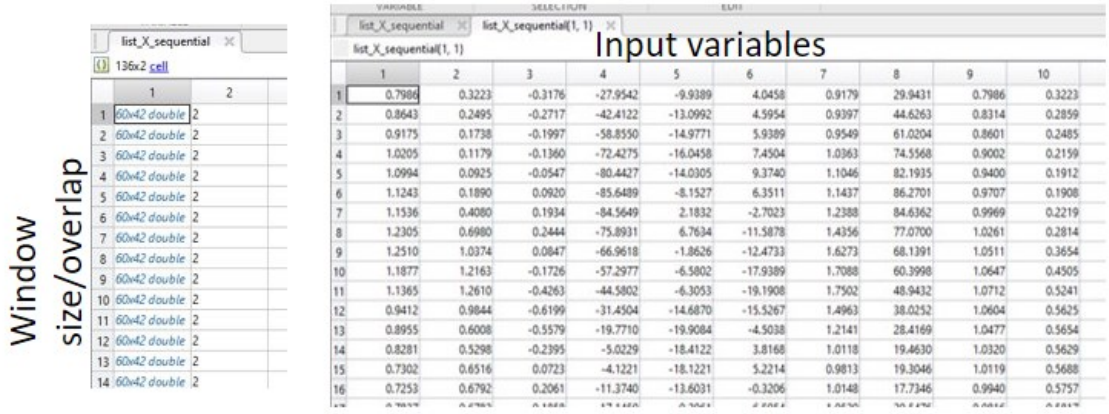

Figure 35.Example of the sequential dataset.

As can be seen, in the non-sequential dataset each row corresponds to a trial, and each column corresponds to the non-sequential metric/feature. Thus, each value is the average of that metric obtained in that trial. The last column corresponds to the label, each patient's UPDRS-III value, being zero for the healthy ones, 1 for Low, 2 for Middle and 3 for High. This type of dataset was used in the SVM, KNN and RF models and the non-sequential features used are displayed in Figure 36.

Features for non-sequential dataset (N=105): Step Time, Stride Time, Stance Time, Double Support Time, Step Length, Stride Length, Velocity, Cadence, Stance Phase, Double Support Phase, Swing Phase, Swing Time, SD Step Length, SD Step Time, SD Velocity, SD Stance Time, SD Swing Time, SD Double Support Time, SD Stride Time, SD Stride Length, SD Cadence, SD Double Support Phase, SD Swing Phase, SD Stance Phase, Max Step Length, Max Step Time, Max Velocity, Max Stance Time, Max Swing Time, Max Double Support Time, Max Stride Time, Max Stride Length, Max Cadence, Max Double Support Phase, Max Swing Phase, Max Stance Phase, Min Step Length, Min Step Time, Min Velocity, Min Stance Time, Min Swing Time, Min Double Support Time, Min Stride Time, Min Stride Length, Min Cadence, Min Double Support Phase, Min Swing Phase, Min Stance Phase, Asy Step Length, Asy Step Time, Asy Velocity, Asy Stance Time, Asy Swing Time, RMS Pitch, Mean Pitch, Max Pitch, Min Pitch, SD Pitch, RMS Roll, Mean Roll, Max Roll, Min Roll, SD Roll, Mean Accx, Mean Accy, Mean Accz, Mean Gyrx, Mean Gyry, Mean Gyrz, SD Accx, SD Accy, SD Accz, SD Gyrx, SD Gyry, SD Gyrz, Max Accx, Max Accy, Max Accz, Max Gyrx, Max Gyry, Max Gyrz, Min Accx, Min Accy, Min Accz, Min Gyrx, Min Gyry, Min Gyrz, RoM Accx, RoM Accy, RoM Accz, RoM Gyrx, RoM Gyry, RoM Gyrz, RMS Accx, RMS Accy, RMS Accz, RMS Gyrx, RMS Gyry, RMS Gyrz, Max Freq Accx, Max Freq Accy, Max Freq Accz, Max Freq Gyrx, Max Freq Gyry and Max Freq Gyrz;

Figure 36. Non-sequential features.

For the sequential dataset, the first column corresponds to the values depending on the size of the time window and the overlap, and the second column corresponds to the patients' label, UPDRS-III value of the patient in question, being zero for the healthy ones, 1 for Low, 2 for Middle and 3 for High. For each time window, is obtained a matrix where the number of rows corresponds to the size of the time window and the number of columns is the number of calculated sequenced features. The calculated

sequential features are shown in Figure 37. This type of dataset will be used for the LSTM and CNN models.

Input variables for sequential dataset (N=46): ACC X, ACC Y, ACC Z, GYR X, GYR Y, GYR Z, SVMAcc, SVMGyr, meanAccX, meanAccY, meanAccZ, meanGyrX, meanGyrY, meanGyrZ, stdAccX, stdAccY, stdAccZ, stdGyrX, stdGyrY, stdGyrZ, rmsAccX, rmsAccY, rmsAccZ, rmsGyrX, rmsGyrY, rmsGyrZ, IndexAccX, IndexAccY, IndexAccZ, IndexGyrX, IndexGyrY, IndexGyrZ, SlopeAcc, SlopeGyr, AccSagital, AccAxial, AccCoronal, GyrSagital, GyrAxial, GyrCoronal, DeltaAcc and DeltaGyr;

Figure 37. Sequential features.

For preprocessing it was done data normalization using two methods. The first is min-max, for every feature, the minimum value of that feature gets transformed into a 0, the maximum value gets transformed into a 1, and every other value gets transformed into a decimal between 0 and 1. The second method used was the z-score, process of normalizing every value in a dataset such that the mean of all of the values is 0 and the standard deviation is 1.

For feature selection, either all features were used or two different feature selection methods were used. The first method used was PCA [63], that is a popular linear feature extractor used for unsupervised feature selection based on eigenvectors analysis to identify critical original features for principal component. In a nutshell, PCA aims to find the directions of maximum variance in high-dimensional data and projects it onto a new subspace with equal or fewer dimensions than the original one. The second method used was mRMR, that is a feature selection approach that tends to select features with a high correlation with the class (output) and a low correlation between themselves [64].

5.2.3.2 Training models pipeline configuration

Next, the pipeline of the model training/testing process will be schematized. Figure 38 shows a flowchart with this schematization.

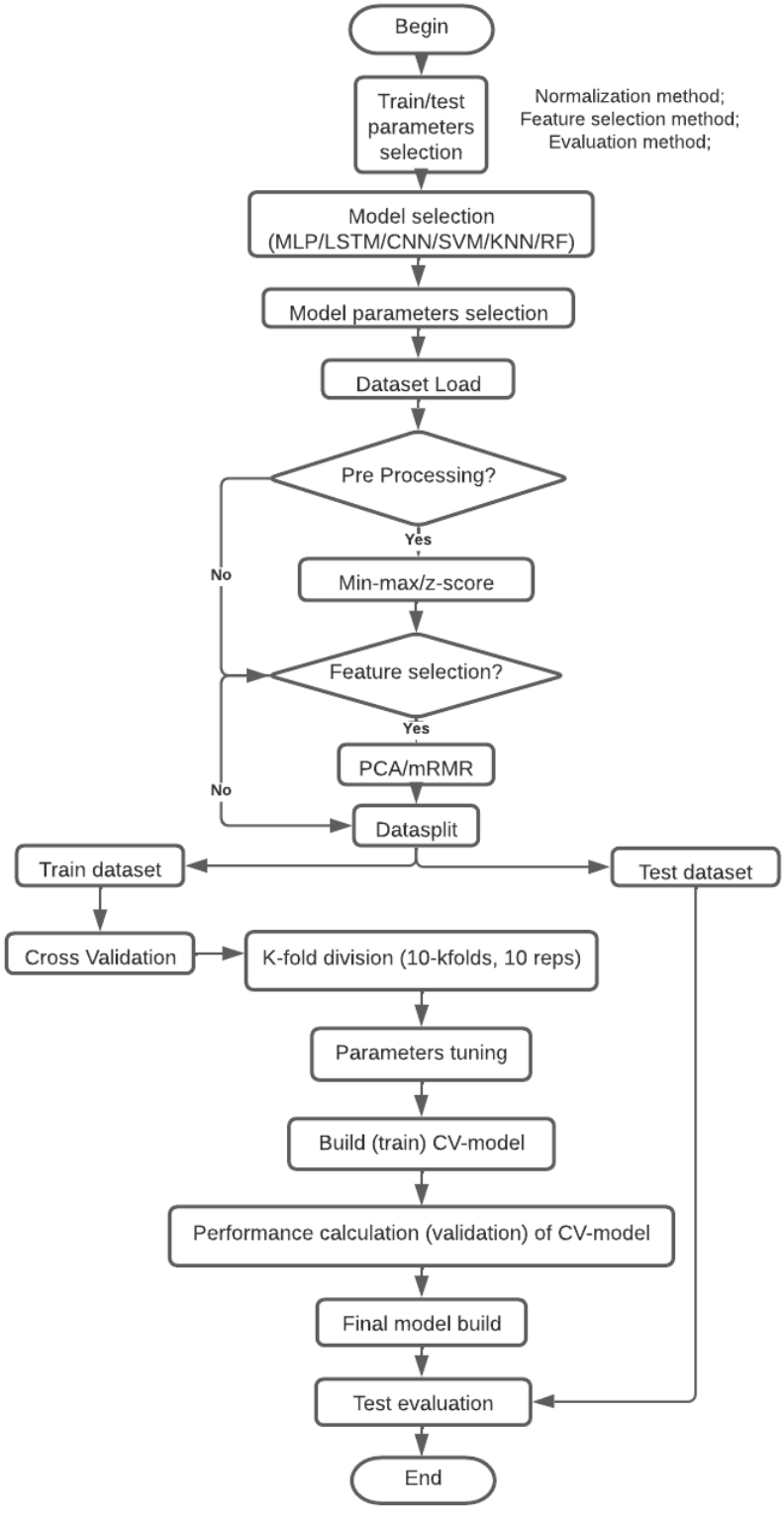

Figure 38.Schematic of the code created for training and testing the models.

The code used belongs to a framework that was created by the BiRD Lab. In this framework the necessary changes were made for the implementation of this work. The grid-search function was

improved, the methods were changed in order to work for four labels and the whole process of testing the models was created.

The code used, implemented in Matlab 2020a, allows to initially select the parameters to create the models, that is, it allows to choose which normalization method, feature selection and evaluation method are wanted. Next it can be chosen the AI method: LSTM, CNN, SVM, KNN and RF. With the model chosen, it can be selected its parameters or choose to grid search them. With all this information, the code can then perform the task of training the model. Initially, the dataset is loaded, which can be sequential or non-sequential, depending on the method chosen. This dataset undergoes the selected changes in terms of normalization and feature selection or not, and, finally, it undergoes a datasplit that separates the dataset in two, 70% for training and 30% for testing [65]. The training dataset will then be used for cross-validation, which in the case of this study is a 10 k-folds division with 10 repetitions [66]. During this process, if grid search was selected, tuning of the model's hyperparameters will occur, to obtain the best possible accuracy results for the model. The 10 models were then created and their average performance is calculated, thus giving the CV-model performance. At the end of this process, a final model is created with the complete training dataset and consecutively tested, to get the total performance of this final model.

5.2.3.3 Performance evaluation

To compare the models and find out which are the best, several performance metrics were calculated, the Matthews Correlation Coefficient (MCC), accuracy (ACC), sensitivity (SENS), and F1 score. All of these were calculated using the confusion matrices, both the one resulting from training and testing. All these metrics can be calculated through True Positives (TP), True Negatives (TN), False Positives (FP) and False Negatives (FN), obtained from the confusion matrices. Next, it is demonstrated the formulas used for this calculation. Note that our confusion matrix will be a 4x4 matrix, since it was used four labels, 0 in case of being healthy, 1 for the mildest stage of PD disability given by the UPDRS-III scale, 2 for the intermediate state and 3 for the highest state.

For the MCC, F1 score, ACC and SENS the formulas used were:

$$\mathrm{MCC} = \frac{TP \times TN - FP \times FN}{\sqrt{(TP+FP)(TP+FN)(TN+FP)(TN+FN)}}$$

Figure 39. Formula for calculating the MCC.

$$F_1 \text{ score} = \frac{2PPV \times TPR}{PPV + TPR} = \frac{2TP}{2TP + FP + FN}$$

Figure 40. Formula for calculating the MCC. PPV-precision TPR- sensitivity.

$$Accuracy = \frac{TP + TN}{TP + FP + FN + TN}$$

Figure 41. Formula for calculating the Acc.

$$Sensitivity = \frac{TP}{TP + FN}$$

Figure 42. Formula for calculating the Sens.

5.2.3.4 RESULTS: TRAINING PERFORMANCE AND TESTING RESULTS

This section shows the performance, both training and testing, of the various models and possible combinations of preprocessing and feature selection. Due to the large number of combinations, only the best results of hyperparameters tunning of each model are shown in the next table. All results are displayed in the Appendices.

Table XXV. AI results, training and test.

Model	Dataset	Norm.	Feature selection	Model parameters	Cross-validation	Results							
						Train				Test			
						MCC	SENS	F1	ACC	MCC	SENS	F1	ACC
SVM	No sequential	Min-Max	PCA	Polynomial 3	10 k-fold	0.88	91.50%	0.91	95.24%	0.83	87.26%	0.86	92.88%
KNN	No sequential	Min-Max	All	Weighted		0.92	93.85%	0.94	96.77%	0.88	91.40%	0.91	95.42%
RF	No sequential	Z-score	mRMR	Linear		0.51	63.79%	0.63	77.57%	0.68	75.59%	0.76	86.20%
LSTM	Sequential	-	-	step time; hidden layers=150; batch size=64; optimizer=adam; layers=3: lstm + layers 1 input + 1 fullyconected softmax;		0.97	98.03%	0.98	98.22%	0.99	99.34%	0.99	99.42%
CNN	Sequential	-	-	stride time; hidden layers= 150; batch size=64; optimizer=adam; layers=3: conv+ layers 1 input + 1 fullyconected softmax;		0.97	97.90%	0.98	98.13%	0.98	98.77%	0.99	98.93%

5.2.3.5 Discussion

With this study of AI, it can be proven through the best results, that deep learning methods show better results, both in training and testing. This may be due to the fact that deep learning uses the sequential datasets that comprise the raw data. In the non-sequential datasets, were used non-sequential data that present parameters calculated through the patient's gait, sometimes these metrics can be more similar between patients of different states in the PD scales. Also, the healthy and the PD patients in the first state tend to show more subtle differences in these parameters. When it comes to raw data, you can detect more differences in the patients' signals, hence deep learning shows better results.

As for the non-sequential methods, the best method appears to be KNN (ACC=96.77%), followed by SVM (ACC=95,24%) and lastly RF (ACC=77.57%). For the SVM method, one notices a marked improvement using polynomial and Gaussian functions, this is due to the fact that four different label types were being classified, making a linear function not sufficient.

Classification was always better using normalization and tended to be better using min-max, only in RF was z-score noted to be more effective than min-max. As for the feature selection methods, it is not possible to say which is the best, since this depends on the machine learning method used.

As for the deep learning methods, both CNN (ACC=98.13%) and LSTM (ACC=98.22%) show similar results, however CNN required much more computational effort in training.

In order to improve performance, relative to the datasets, more data would be needed from both PD and healthy patients. Another factor that could influence performance would be to use more balanced data, that is, to use the same number of subjects and the same amount of data for each label, thus having a more balanced representativeness.

Another important factor to improve performance would be to test more architectures in the models, test more parameter combinations, vary the number and type of layers or even test new IA models.

5.3 Conclusions

Through the statistical study, it was proven that +sMotion was able to distinguish PD from healthy people. Furthermore, it was verified that the metrics of the patients suffer a specific evolution with the evolution of the UPDRS-III and PDQ-39 scales, that is, with the progression of the disease, the metrics have a specific evolution that can be detected by +sMotion. Thus, +sMotion can biomark the motor impairments and the quality of life of patients, thus proving that the metrics obtained can be used in AI methods to classify and stratify patients in the scales. In the AI methods obtained, it has been proven that it is possible for these to be used to classify patients. Better results were obtained for deep learning

methods when compared to machine learning methods, and the best method can be considered LSTM, since it has less computational effort.

6 Conclusions and future directions

In this thesis the intended and planned objectives were achieved.

RQ.1 "How have the WBD been implemented, applied and clinically validated in PD to mitigate gait associated impairments?"

An extensive literature review was conducted to understand how WBDs were being implemented, applied, and clinically validated. In this review, several limitations were identified and how they could be addressed. Firstly, it was found that the arrangement of sensors and actuators is very elaborate and needs to be simplified by using only one sensor and actuators in the area where the sensor is placed, so that the system is comfortable and fully wearable. It was found that there is still little scientific evidence on which is the best strategy to provide biofeedback, so a study is needed to analyze the performance of patients using different biofeedback strategies to verify the best way to provide it. There is also a need to verify the extent that biofeedback has on patient performance, that is, we need to increase the study of the effects of biofeedback to see the effect it has on more metrics.

RQ.2 "How have the AI-based and statistical methods been used for PD monitoring?"

An extensive literature review was conducted to understand how statistical and IA methods have been used to monitor PD. In this review, several limitations and ways to improve them were identified. It was found that in data collection, multiple sensors are used and their configurations are elaborate. This can cause discomfort to the patient and make the data collection less than ideal, so data collection systems need to be optimized so that it features only one sensor and is comfortable and fully wearable. In addition, data collection protocols tend not to contemplate day-to-day activities in home settings. This would be improved by having studies performed by patients at home in their comfort space, thus improving the quality of the data obtained. Another limitation of the studies conducted is the lack of the use of statisticians and IA with QoL scales. As we know, PD has profound effects on the quality of life of patients, so it is necessary to develop further studies to verify the consequences of the evolution of PD on the QoL of patients, using specific scales for this purpose (PDQ-39).

RQ.3 "Can gait event-driven biofeedback loop integrated on a WBD help PD patients to mitigate gait-associated disabilities?"

In order to further improve +sMotion to assist people with PD, statistical studies have been done in order to understand what effects biofeedback has on patients. Good results were obtained, since it was concluded that feedback can improve the gait parameters of patients, with event-driven biofeedback being better than continued biofeedback. However, there were no positive conclusions to be drawn from the study of the statistic in the mixed group.

RQ.4 "Can the wearable motion LAB outcomes contribute as a biomarker of motor stage and quality of life in PD supported by a statistical analysis?"

A validation of +sMotion was performed with end users, i.e. by using it on healthy patients and on patients with different levels of PD scales, it was obtained several metrics of their gait. Through the statistical study of these same metrics, it was proven that +sMotion can be used as a tool for gait monitoring. The results were very positive, since statistically, the metrics calculated by +sMotion were sufficient to distinguish PD from healthy individuals, and, in addition, to distinguish patients at different levels of the UPDRS-III and PDQ-39 scales, and thus be able to serve as a biomarker of motor stage and quality of life in PD.

RQ.5 "Which AI model based on wearable motion LAB produces best results as a biomarker of motor stages (UPDRS-III score) in PD?"

For the AI application, +sMotion was able to serve as a tool to classify the level of PD based on the patients' gait, aiming to contribute to +sC-support module. The +sMotion was able to use machine learning and deep learning methods to classify the patients' disease level based on the parameters measured. In this context it can be concluded that the deep learning methods worked better than the machine learning methods, this factor may be due to the method itself but also the features used in both. In terms of methods LSTM would be the best due to its reduced computational effort compared to CNN.

Future work

In future work, the mixed group, on the vibrotactile biofeedback study, must be improved, by reducing outliers, using more parameters, and through a re-testing and follow-up.

For the IA, it is planned to use more feature selection and normalization methods, introduce MLP and LDA, and try to use AI to detect gait events. Furthermore, a more exhaustive DL study needs to be introduced, using more combinations of architectures and parameters, in order to improve the results.

Overall, the use of more data from both PD and healthy patients will be necessary in order to improve the results and draw better conclusions.

7 References

[1] S. Brauer, “Parkinson ’ s disease Acute pain,” *Aust. J. Physiother.*, vol. 53, no. June 2004, p. 2007, 2009, doi: 10.1016/S0004-9514(07)70017-X.

[2] S. Y. Chen and S. T. Tsai, “The epidemiology of Parkinson’s disease,” *Tzu Chi Med. J.*, vol. 22, no. 2, pp. 73–81, 2010, doi: 10.1016/S1016-3190(10)60044-4.

[3] S. Von Campenhausen *et al.*, “Prevalence and incidence of Parkinson’s disease in Europe,” *Eur. Neuropsychopharmacol.*, vol. 15, no. 4, pp. 473–490, 2005, doi: 10.1016/j.euroneuro.2005.04.007.

[4] E. Heremans, A. Nieuwboer, and S. Vercruysse, “Freezing of gait in Parkinson’s disease: Where are we now? Topical collection on movement disorders,” *Curr. Neurol. Neurosci. Rep.*, vol. 13, no. 6, 2013, doi: 10.1007/s11910-013-0350-7.

[5] D. Bega, P. Gonzalez-Latapi, C. Zadikoff, and T. Simuni, “A Review of the Clinical Evidence for Complementary and Alternative Therapies in Parkinson’s Disease,” *Curr. Treat. Options Neurol.*, vol. 16, no. 10, 2014, doi: 10.1007/s11940-014-0314-5.

[6] A. Nieuwboer, “Cueing for freezing of gait in patients with Parkinson’s disease: A rehabilitation perspective,” *Mov. Disord.*, vol. 23, no. SUPPL. 2, 2008, doi: 10.1002/mds.21978.

[7] D. Sweeney, L. R. Quinlan, P. Browne, M. Richardson, P. Meskell, and G. Ólaighin, “A technological review of wearable cueing devices addressing freezing of gait in Parkinson’s disease,” *Sensors (Switzerland)*, vol. 19, no. 6, 2019, doi: 10.3390/s19061277.

[8] T. Tan, Q. J. Almeida, and F. Rahimi, “Proprioceptive deficits in Parkinson’s disease patients with freezing of gait,” *Neuroscience*, vol. 192, pp. 746–752, 2011, doi: 10.1016/j.neuroscience.2011.06.071.

[9] K. A. Ehgoetz Martens, F. Pieruccini-Faria, and Q. J. Almeida, “Could Sensory Mechanisms Be a Core Factor That Underlies Freezing of Gait in Parkinson’s Disease?,” *PLoS One*, vol. 8, no. 5, 2013, doi: 10.1371/journal.pone.0062602.

[10] B. C. Lee, T. A. Thrasher, S. P. Fisher, and C. S. Layne, “The effects of different sensory augmentation on weight-shifting balance exercises in Parkinson’s disease and healthy elderly people: A proof-of-concept study,” *J. Neuroeng. Rehabil.*, vol. 12, no. 1, pp. 1–10, 2015, doi: 10.1186/s12984-015-0064-y.

[11] L. E. Dibble, D. E. Nicholson, B. Shultz, B. A. MacWilliams, R. L. Marcus, and C. Moncur, “Sensory cueing effects on maximal speed gait initiation in persons with Parkinson’s disease and healthy elders,” *Gait Posture*, vol. 19, no. 3, pp. 215–225, 2004, doi: 10.1016/S0966-6362(03)00065-1.

[12] H. R. Gonçalves, A. M. Rodrigues, and C. P. Santos, "Vibrotactile biofeedback devices in Parkinson's disease: a narrative review," *Med. Biol. Eng. Comput.*, vol. 59, no. 6, pp. 1185–1199, 2021, doi: 10.1007/s11517-021-02365-3.

[13] J. C. M. Schlachetzki *et al.*, "Wearable sensors objectively measure gait parameters in Parkinson's disease," *PLoS One*, vol. 12, no. 10, pp. 1–18, 2017, doi: 10.1371/journal.pone.0183989.

[14] E. Rovini, C. Maremmani, and F. Cavallo, "How wearable sensors can support parkinson's disease diagnosis and treatment: A systematic review," *Front. Neurosci.*, vol. 11, no. OCT, 2017, doi: 10.3389/fnins.2017.00555.

[15] N. Toosizadeh, J. Mohler, H. Lei, S. Parvaneh, S. Sherman, and B. Najafi, "Motor performance assessment in Parkinson's disease: Association between objective in-clinic, objective in-home, and subjective/semi-objective measures," *PLoS One*, vol. 10, no. 4, pp. 1–15, 2015, doi: 10.1371/journal.pone.0124763.

[16] C. Buckley, B. Galna, L. Rochester, and C. Mazzà, "Upper body accelerations as a biomarker of gait impairment in the early stages of Parkinson's disease," *Gait Posture*, vol. 71, no. October 2017, pp. 289–295, 2019, doi: 10.1016/j.gaitpost.2018.06.166.

[17] B. N. Dugger and D. W. Dickson, "cshperspect-PRI-a028035.pdf," pp. 1–22, 2017.

[18] M. Delgado-Alvarado, M. Marano, A. Santurtún, A. Urtiaga-Gallano, D. Tordesillas-Gutierrez, and J. Infante, "Nonpharmacological, nonsurgical treatments for freezing of gait in Parkinson's disease: A systematic review," *Mov. Disord.*, vol. 35, no. 2, pp. 204–214, 2020, doi: 10.1002/mds.27913.

[19] R. Velik, "Effect of On-Demand Cueing on Freezing of Gait in Parkinson' s Patients," *Int. J. Medical, Pharm. Sci. Eng.*, vol. 6, no. 6, pp. 10–15, 2012, [Online]. Available: http://www.researchgate.net/publication/257846272_Effect_of_On-Demand_Cueing_on_Freezing_of_Gait_in_Parkinsons_Patients%0Ahttp://xueshu.baidu.com/s?wd=paperuri%3A%28c244e5319d871615c55319fdddc5827b%29&filter=sc_long_sign&sc_ks_para=q%3DEffect of On-Demand.

[20] S. J. G. Lewis and R. A. Barker, "A pathophysiological model of freezing of gait in Parkinson's disease," *Park. Relat. Disord.*, vol. 15, no. 5, pp. 333–338, 2009, doi: 10.1016/j.parkreldis.2008.08.006.

[21] J. A. Opara, A. Małecki, E. Małecka, and T. Socha, "Motor assessment in parkinson's disease," *Ann. Agric. Environ. Med.*, vol. 24, no. 3, pp. 411–415, 2017, doi: 10.5604/12321966.1232774.

[22] A. Ashoori, D. M. Eagleman, and J. Jankovic, "Effects of auditory rhythm and music on gait disturbances in Parkinson's disease," *Front. Neurol.*, vol. 6, no. NOV, 2015, doi: 10.3389/fneur.2015.00234.

[23] C. A. Davie, "A review of Parkinson's disease," *Br. Med. Bull.*, vol. 86, no. 1, pp. 109–127, 2008, doi: 10.1093/bmb/ldn013.

[24] N. Muthukrishnan, J. J. Abbas, H. A. Shill, and N. Krishnamurthi, "Cueing paradigms to improve gait and posture in parkinson's disease: A narrative review," *Sensors (Switzerland)*, vol. 19, no. 24, pp. 1–16, 2019, doi: 10.3390/s19245468.

[25] H. Gonçalves, R. Moreira, A. Rodrigues, and C. Santos, "Finding Parameters around the Abdomen for a Vibrotactile System: Healthy and Patients with Parkinson's Disease," *J. Med. Syst.*, vol. 42, no. 11, 2018, doi: 10.1007/s10916-018-1087-2.

[26] J. S. Perlmutter, "Assessment of parkinson disease manifestations," *Curr. Protoc. Neurosci.*, no. SUPPL.49, pp. 1–16, 2009, doi: 10.1002/0471142301.ns1001s49.

[27] P. Hagell and C. Nygren, "The 39 item Parkinson's disease questionnaire (PDQ-39) revisited: Implications for evidence based medicine," *J. Neurol. Neurosurg. Psychiatry*, vol. 78, no. 11, pp. 1191–1198, 2007, doi: 10.1136/jnnp.2006.111161.

[28] A. Branquinho, H. R. Goncalves, J. F. Pinto, A. M. Rodrigues, and C. P. Santos, "Wearable gait Analysis LAB as a biomarker of Parkinson's disease motor stages and Quality of life: A preliminary study," *2021 IEEE Int. Conf. Auton. Robot Syst. Compet. ICARSC 2021*, no. i, pp. 234–239, 2021, doi: 10.1109/ICARSC52212.2021.9429770.

[29] M. Mancini, K. Smulders, G. Harker, S. Stuart, and J. G. Nutt, "Assessment of the ability of open- and closed-loop cueing to improve turning and freezing in people with Parkinson's disease," *Sci. Rep.*, vol. 8, no. 1, pp. 1–9, 2018, doi: 10.1038/s41598-018-31156-4.

[30] V. Mikos *et al.*, "A Wearable, Patient-Adaptive Freezing of Gait Detection System for Biofeedback Cueing in Parkinson's Disease," *IEEE Trans. Biomed. Circuits Syst.*, vol. 13, no. 3, pp. 503–515, 2019, doi: 10.1109/TBCAS.2019.2914253.

[31] C. Punin *et al.*, "A non-invasive medical device for parkinson's patients with episodes of freezing of gait," *Sensors (Switzerland)*, vol. 19, no. 3, 2019, doi: 10.3390/s19030737.

[32] O. A. Cando, K. R. Hidalgo, and B. C. Palacios, "A low-cost vibratory stimulus system to mitigate freezing of gait in Parkinson's disease," *Proc. 2016 IEEE ANDESCON, ANDESCON 2016*, pp. 0–3, 2017, doi: 10.1109/ANDESCON.2016.7836267.

[33] C. Punin, B. Barzallo, M. Huerta, A. Bermeo, M. Bravo, and C. Llumiguano, "Wireless devices to

restart walking during an episode of FOG on patients with Parkinson's disease," *2017 IEEE 2nd Ecuador Tech. Chapters Meet. ETCM 2017*, vol. 2017-Janua, pp. 1–6, 2018, doi: 10.1109/ETCM.2017.8247520.

[34] W. Harrington *et al.*, "Alleviating freezing of gait using phase-dependent tactile biofeedback," *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS*, vol. 2016-Octob, pp. 5841–5844, 2016, doi: 10.1109/EMBC.2016.7592056.

[35] B. C. Lee, A. Fung, and T. A. Thrasher, "The Effects of Coding Schemes on Vibrotactile Biofeedback for Dynamic Balance Training in Parkinson's Disease and Healthy Elderly Individuals," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 26, no. 1, pp. 153–160, 2018, doi: 10.1109/TNSRE.2017.2762239.

[36] W. Nanhoe-Mahabier, J. H. Allum, E. P. Pasman, S. Overeem, and B. R. Bloem, "The effects of vibrotactile biofeedback training on trunk sway in Parkinson's disease patients," *Park. Relat. Disord.*, vol. 18, no. 9, pp. 1017–1021, 2012, doi: 10.1016/j.parkreldis.2012.05.018.

[37] C. M. High, H. F. McHugh, S. C. Mills, S. Amano, J. E. Freund, and S. Vallabhajosula, "Vibrotactile Feedback Alters Dynamics Of Static Postural Control In Persons With Parkinson's Disease But Not Older Adults At High Fall Risk," *Gait Posture*, vol. 63, no. May, pp. 202–207, 2018, doi: 10.1016/j.gaitpost.2018.05.010.

[38] I. Carpinella *et al.*, "Wearable Sensor-Based Biofeedback Training for Balance and Gait in Parkinson Disease: A Pilot Randomized Controlled Trial," *Arch. Phys. Med. Rehabil.*, vol. 98, no. 4, pp. 622-630.e3, 2017, doi: 10.1016/j.apmr.2016.11.003.

[39] M. R. C. van den Heuvel, G. Kwakkel, P. J. Beek, H. W. Berendse, A. Daffertshofer, and E. E. H. van Wegen, "Effects of augmented visual feedback during balance training in Parkinson's disease: A pilot randomized clinical trial," *Park. Relat. Disord.*, vol. 20, no. 12, pp. 1352–1358, 2014, doi: 10.1016/j.parkreldis.2014.09.022.

[40] S. Caudron, M. Guerraz, A. Eusebio, J. P. Gros, J. P. Azulay, and M. Vaugoyeau, "Evaluation of a visual biofeedback on the postural control in Parkinson's disease," *Neurophysiol. Clin.*, vol. 44, no. 1, pp. 77–86, 2014, doi: 10.1016/j.neucli.2013.10.134.

[41] M. Rossi-Izquierdo *et al.*, "Vibrotactile neurofeedback balance training in patients with Parkinson's disease: Reducing the number of falls," *Gait Posture*, vol. 37, no. 2, pp. 195–200, 2013, doi: 10.1016/j.gaitpost.2012.07.002.

[42] A. Mirelman *et al.*, "Audio-biofeedback training for posture and balance in patients with Parkinson's disease," *J. Neuroeng. Rehabil.*, vol. 8, no. 1, pp. 1–7, 2011, doi: 10.1186/1743-

0003-8-35.

[43] A. Channa, N. Popescu, and V. Ciobanu, "Wearable solutions for patients with parkinson's disease and neurocognitive disorder: A systematic review," *Sensors (Switzerland)*, vol. 20, no. 9, 2020, doi: 10.3390/s20092713.

[44] C. Z. H. Ma, D. W. C. Wong, W. K. Lam, A. H. P. Wan, and W. C. C. Lee, "Balance improvement effects of biofeedback systems with state-of-the-art wearable sensors: A systematic review," *Sensors (Switzerland)*, vol. 16, no. 4, 2016, doi: 10.3390/s16040434.

[45] N. Ahmad, R. A. R. Ghazilla, N. M. Khairi, and V. Kasi, "Reviews on Various Inertial Measurement Unit (IMU) Sensor Applications," *Int. J. Signal Process. Syst.*, vol. 1, no. 2, pp. 256–262, 2013, doi: 10.12720/ijsps.1.2.256-262.

[46] D. C. Dewey *et al.*, "Automated gait and balance parameters diagnose and correlate with severity in Parkinson disease," *J. Neurol. Sci.*, vol. 345, no. 1, pp. 131–138, 2014, doi: 10.1016/j.jns.2014.07.026.

[47] M. Pistacchi *et al.*, "Gait analysis and clinical correlations in early Parkinson's disease," *Funct. Neurol.*, vol. 32, no. 1, pp. 28–34, 2017, doi: 10.11138/FNeur/2017.32.1.028.

[48] F. Lipsmeier *et al.*, "Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial," *Mov. Disord.*, vol. 33, no. 8, pp. 1287–1297, 2018, doi: 10.1002/mds.27376.

[49] Y. G. *et al.*, "Smartphone-based timed up and go test can identify postural instability in Parkinson's disease," *Israel Medical Association Journal*, vol. 22, no. 1. pp. 37–42, 2020, [Online]. Available: https://www.ima.org.il/FilesUploadPublic/IMAJ/0/400/200446.pdf%0Ahttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=2004966856.

[50] C. Curtze, J. G. Nutt, P. Carlson-Kuhta, M. Mancini, and F. B. Horak, "Objective gait and balance impairments relate to balance confidence and perceived mobility in people with parkinson disease," *Phys. Ther.*, vol. 96, no. 11, pp. 1734–1743, 2016, doi: 10.2522/ptj.20150662.

[51] R. de M. Roiz, E. W. A. Cacho, M. M. Pazinatto, J. G. Reis, A. Cliquet, and E. M. A. Barasnevicius-Quagliato, "Gait analysis comparing Parkinson's disease with healthy elderly subjects," *Arq. Neuropsiquiatr.*, vol. 68, no. 1, pp. 81–86, 2010, doi: 10.1590/S0004-282X2010000100018.

[52] L. A. King, M. Mancini, K. Priest, A. Salarian, F. Rodrigues-De-Paula, and F. Horak, "Do clinical scales of balance reflect turning abnormalities in people With Parkinson's disease?," *J. Neurol. Phys. Ther.*, vol. 36, no. 1, pp. 25–31, 2012, doi: 10.1097/NPT.0b013e31824620d1.

[53] S. Aich and H.-C. Kim, "Auto Detection of Parkinson's Disease based on Objective Measurement

of Gait Parameters using Wearable Sensors," *Int. J. Adv. Sci. Technol.*, vol. 117, no. August, pp. 103–112, 2018, doi: 10.14257/ijast.2018.117.09.

[54] Q. W. Oung, H. Muthusamy, S. N. Basah, H. Lee, and V. Vijean, "Empirical Wavelet Transform Based Features for Classification of Parkinson's Disease Severity," *J. Med. Syst.*, vol. 42, no. 2, 2018, doi: 10.1007/s10916-017-0877-2.

[55] H. H. Manap, N. Md Tahir, and A. I. M. Yassin, "Statistical analysis of Parkinson disease gait classification using artificial neural network," *IEEE Int. Symp. Signal Process. Inf. Technol. ISSPIT 2011*, pp. 060–065, 2011, doi: 10.1109/ISSPIT.2011.6151536.

[56] F. Wahid, R. K. Begg, C. J. Hass, S. Halgamuge, and D. C. Ackland, "Classification of Parkinson's disease gait using spatial-temporal gait features," *IEEE J. Biomed. Heal. Informatics*, vol. 19, no. 6, pp. 1794–1802, 2015, doi: 10.1109/JBHI.2015.2450232.

[57] C. Caramia *et al.*, "IMU-Based Classification of Parkinson's Disease from Gait: A Sensitivity Analysis on Sensor Location and Feature Selection," *IEEE J. Biomed. Heal. Informatics*, vol. 22, no. 6, pp. 1765–1774, 2018, doi: 10.1109/JBHI.2018.2865218.

[58] E. Abdulhay, N. Arunkumar, K. Narasimhan, E. Vellaiappan, and V. Venkatraman, "Gait and tremor investigation using machine learning techniques for the diagnosis of Parkinson disease," *Futur. Gener. Comput. Syst.*, vol. 83, pp. 366–373, 2018, doi: 10.1016/j.future.2018.02.009.

[59] E. Rastegari, S. Azizian, and H. Ali, "Machine learning and similarity network approaches to support automatic classification of Parkinson's diseases using accelerometer-based gait analysis," *Proc. Annu. Hawaii Int. Conf. Syst. Sci.*, vol. 2019-Janua, pp. 4231–4242, 2019, doi: 10.24251/hicss.2019.511.

[60] L. Tong, J. He, and L. Peng, "CNN-Based PD Hand Tremor Detection Using Inertial Sensors," *IEEE Sensors Lett.*, vol. 5, no. 7, pp. 5–8, 2021, doi: 10.1109/LSENS.2021.3074958.

[61] H. Kingma *et al.*, "Vibrotactile feedback improves balance and mobility in patients with severe bilateral vestibular loss," *J. Neurol.*, vol. 266, no. 1, pp. 19–26, 2019, doi: 10.1007/s00415-018-9133-z.

[62] H. R. Gonçalves, R. Moreira, A. Rodrigues, G. Minas, L. P. Reis, and C. P. Santos, "Real-time tool for human gait detection from lower trunk acceleration," *Adv. Intell. Syst. Comput.*, vol. 747, pp. 9–18, 2018, doi: 10.1007/978-3-319-77700-9_2.

[63] A. Malhi and R. X. Gao, "PCA-based feature selection scheme for machine defect classification," *IEEE Trans. Instrum. Meas.*, vol. 53, no. 6, pp. 1517–1525, 2004, doi: 10.1109/TIM.2004.834070.

[64] B. Q. Li, L. Le Hu, L. Chen, K. Y. Feng, Y. D. Cai, and K. C. Chou, "Prediction of protein domain with mRMR feature selection and analysis," *PLoS One*, vol. 7, no. 6, 2012, doi: 10.1371/journal.pone.0039308.

[65] A. Gholamy, V. Kreinovich, and O. Kosheleva, "Why 70/30 or 80/20 Relation Between Training and Testing Sets : A Pedagogical Explanation," *Dep. Tech. Reports*, pp. 1–6, 2018.

[66] R. T. Gareth James, Daniela Witten, Trevor Hastie, *An Introduction to Statistical Learning: with Applications in R (Springer Texts in Statistics) 1st ed.* 2013.

8 APPENDICES

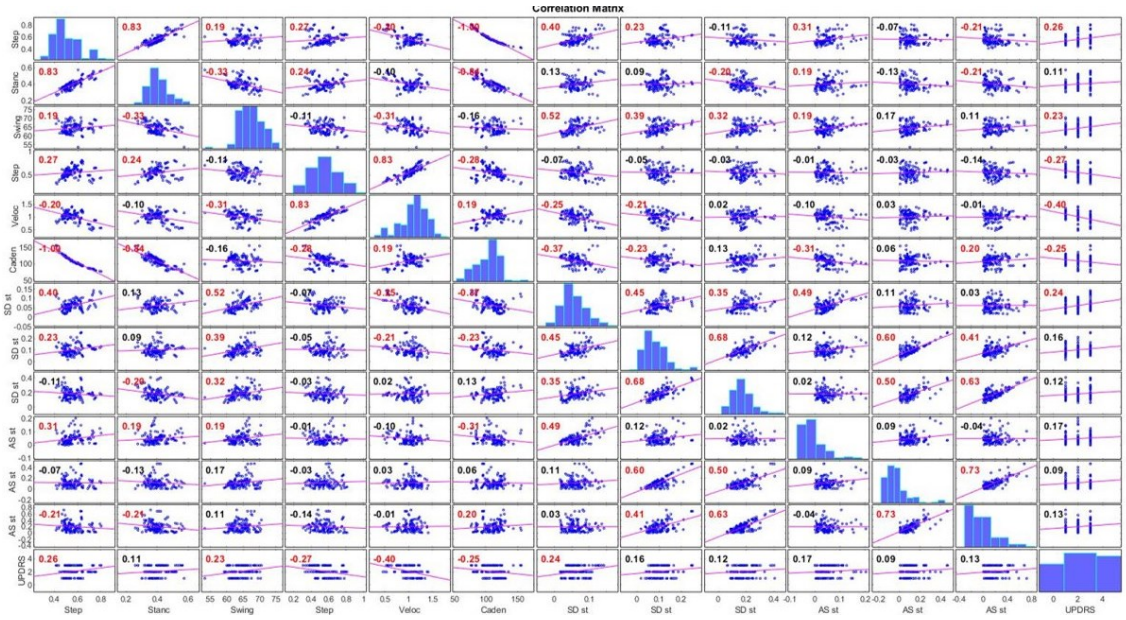

Figure 43. Appendix I. Spearmans correlation – UPDRS-III.

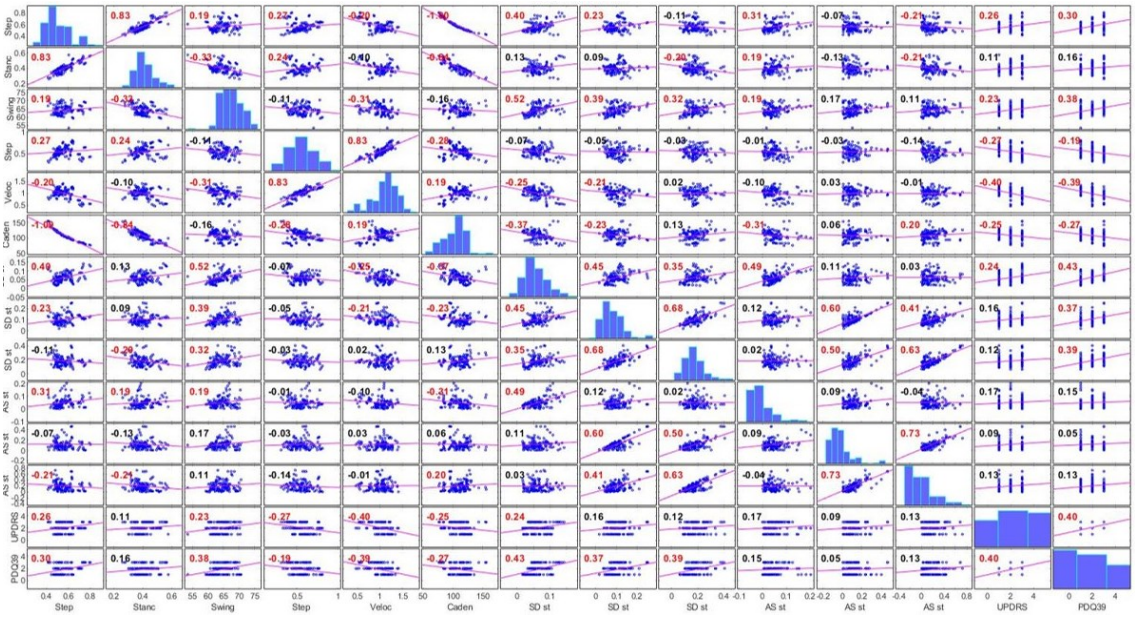

Figure 44. Appendix II. Spearmans correlation - UPDRS-III and PDQ-39.

Table XXVI. SVM results.

Model	Normalization	Feature Selection	Model Parameters	Cross-Validation	Grid Search	Train			Test		
						ACC	SENS	MCC	ACC	SENS	MCC
SVM	Min-Max	All	Linear	10 k-fold with 10 repetitions	ON	86.86%	76.93%	0.69	93.05%	88.27%	0.84
			Polynomial 2			93.58%	88.83%	0.84	92.88%	87.60%	0.83
			Polynomial 3			94.13%	89.83%	0.85	94.26%	90.93%	0.87
			Gaussian			94.61%	90.61%	0.86	96.62%	94.40%	0.92
	Z-score		Linear			84.88%	74.28%	0.65	93.05%	88.27%	0.84
			Polynomial 2			92.64%	87.37%	0.82	94.24%	90.38%	0.87
			Polynomial 3			92.82%	87.94%	0.83	93.05%	88.88%	0.84
			Gaussian			93.33%	88.52%	0.83	96.62%	94.39%	0,92
	Min-Max	PCA	Linear			84.57%	74.16%	0.64	82.62%	71.63%	0.61
			Polynomial 2			94.42%	89.96%	0.86	90.38%	84.58%	0.78
			Polynomial 3			95.24%	91.50%	0.88	92.88%	87.26%	0.83
			Gaussian			94.20%	89.56%	0.85	95.40%	93.04%	0.89
	Z-score		Linear			84.04%	74.20%	0.64	85.46%	77.50%	0.68
			Polynomial 2			92.10%	86.41%	0.81	94.26%	90.83%	0.87
			Polynomial 3			94.19%	89.91%	0.86	94.26%	90.83%	0.87
			Gaussian			93.66%	88.93%	0.84	94.26%	90.83%	0.87
	Min-Max	mRMR	Linear			78.47%	65.49%	0. 53	89.36%	82.11%	0.75
			Polynomial 2			72.71%	61.92%	0.43	93.04%	88.49%	0,84
			Polynomial 3			76.72%	64.90%	0.50	91.85%	85.96%	0.81
			Gaussian			94.91%	91.31%	0.87	94.34%	91.84%	0.87
	Z-score		Linear			81.05%	68.73%	0.58	89.23%	83.97%	0.76

			Polynomial 2			86.76%	79.43%	0.70	86.42%	82.81%	0.71
			Polynomial 3			79.15%	70.71%	0.55	80.39%	79.17%	0.60
			Gaussian			89.43%	81.21%	0.74	87.75%	80.87%	0.72

Table XXVII. KNN results.

Model	Normalization	Feature Selection	Model Parameters	Cross-Validation	Grid Search	Train			Test		
						ACC	SENS	MCC	ACC	SENS	MCC
KNN	Min-Max	All	Weighted	10 k-fold with 10 repetitions	ON	96.77%	93.85%	0.92	95.42%	91.40%	0.88
			Equal			96.77%	93.85%	0.92	95.42%	91.40%	0.88
	Z-score		Weighted			94.58%	90.18%	0.87	97.78%	95.45%	0.94
			Equal			94.68%	90.40%	0.87	97.80%	95.50%	0.94
	Min-Max	PCA	Weighted			96.45%	93.04%	0.91	96.62%	93.21%	0.91
			Equal			96.45%	93.04%	0.91	96.62%	93.21%	0.91
	Z-score		Weighted			93.37%	87.87%	0.83	96.67%	95.31%	0,92
			Equal			93.81%	88.47%	0.85	96.62%	93.67%	0,92
	Min-Max	mRMR	Weighted			94.28%	89.01%	0.86	94.29%	90.77%	0.87
			Equal			94.50%	89.44%	0.86	94.29%	90.77%	0.87
	Z-score		Weighted			93.53%	87.80%	0.84	95.45%	92.12%	0.89
			Equal			93.71%	88.01%	0.84	95.45%	92.12%	0.89

Table XXVIII. RF results.

Model	Normalization	Train	Test

		Feature Selection	Model Parameters	Cross-Validation	Grid Search	ACC	SENS	MCC	ACC	SENS	MCC
RF	Min-Max	All	Linear	10 k-fold with 10 repetitions	ON	72.89%	58.24%	0.43	69.99%	54.78%	0.38
			Quadratic			73.27%	59.40%	0.44	71.46%	54.27%	0.39
	Z-score		Linear			72.77%	58.05%	0.43	73.25%	57.36%	0.42
			Quadratic			74.15%	59.72%	0.45	77.46%	64.76%	0.50
	Min-Max	PCA	Linear			73.15%	58.24%	0.43	70.47%	58.08%	0.40
			Quadratic			72.30%	57.11%	0.42	79.38%	68.75%	0.55
	Z-score		Linear			76.04%	61.68%	0.48	79.57%	67.51%	0.55
			Quadratic			76.06%	61.96%	0.48	80.26%	68.44%	0.56
	Min-Max	mRMR	Linear			75.88%	61.03%	0.46	70.16%	55.00%	0.38
			Quadratic			74.72%	59.89%	0.46	78.67%	68.72%	0.55
	Z-score		Linear			77.57%	63.79%	0.51	86.20%	75.59%	0.68
			Quadratic			74.78%	59.88%	0.46	87.58%	79.74%	0.72

Table XXIX. LSTM results.

Model	Size Window	Hidden Layers	Layers	Batch Size	Cross-Validation	Optimizer	Train			Test		
							ACC	SENS	MCC	ACC	SENS	MCC

LSTM	Mean step time	150	sequenceInputLayer lstmLayer lstmLayer lstmLayer fullyConnectedLayer softmaxLayer classificationLayer	64	10 k-fold with 10 repetitions	adam	98.22%	98.03%	0.97	99.42%	99.34%	0.99
	Mean stride time		sequenceInputLayer lstmLayer lstmLayer lstmLayer fullyConnectedLayer softmaxLayer classificationLayer				98.25%	97.99%	0.97	98.53%	98.51%	0.98

Table XXX. CNN results.

Model	**Size Window**	**Hidden Layers**	**Layers**	**Batch Size**	**Cross-Validation**	**Optimizer**	**Train**			**Test**		
							ACC	SENS	MCC	ACC	SENS	MCC

CNN	Mean step time	150	imageInputLayer convolution2dLayer reluLayer maxPooling2dLayer convolution2dLayer reluLayer maxPooling2dLayer convolution2dLayer reluLayer maxPooling2dLayer fullyConnectedLayer softmaxLayer classificationLayer	64	10 k-fold with 10 repetitions	adam	98.11%	97.85%	0.97	98.79%	99.60%	0.98
	Mean stride time		imageInputLayer convolution2dLayer reluLayer maxPooling2dLayer convolution2dLayer reluLayer maxPooling2dLayer convolution2dLayer reluLayer maxPooling2dLayer fullyConnectedLayer				98.13%	97.90%	0.97	98.93%	98.77%	0.98


softmaxLayer
classificationLayer