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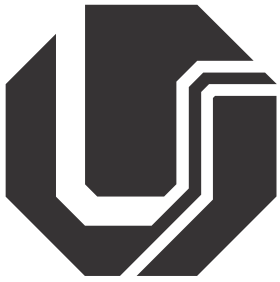

LÍGIA REIS NÓBREGA

A method to assess freezing of gait in Parkinson's disease with inertial sensors

UBERLÂNDIA, MG

2023

LÍGIA REIS NÓBREGA

A method to assess freezing of gait in Parkinson's disease with inertial sensors

Doctoral thesis submitted to the Post-Graduate Program in Electrical Engineering at the Federal University of Uberlândia in partial fulfillment of the requirements for the degree of Doctor of Sciences.

Line of research: Digital Signal Processing and Computer Networks.

Supervisor: Prof. Dr. Adriano de Oliveira Andrade

Co-supervisor: Prof. Dr. Adriano Alves Pereira

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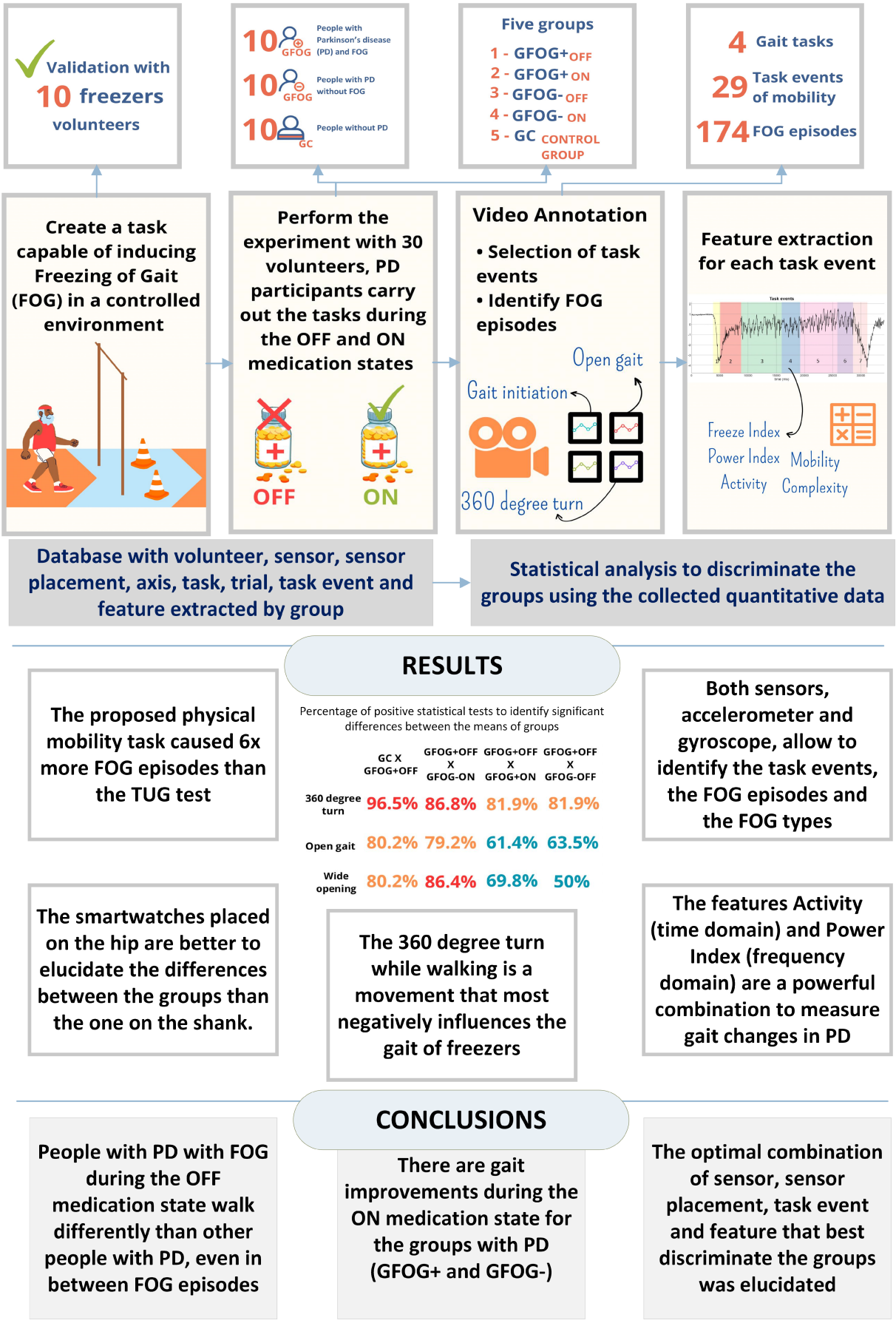
"A alegria não chega apenas no encontro do achado, mas faz parte do processo da busca. E ensinar e aprender não pode dar-se fora da procura, fora da boniteza e da alegria." Paulo Freire

ABSTRACT

Parkinson's disease (PD) is a chronic and degenerative condition of the central nervous system that causes progressive loss of dopamine-producing neurons. Freezing of gait (FOG) is a particular proximal symptom of Parkinson's disease, characterized by a brief motor block defined as an episodic inability to generate effective stepping. This very distressing gait disorder leads to a high risk of falls, decreases independence, causes embarrassment, and limits social interactions. Evaluation of the clinical effects of PD treatment would benefit from objective and standardized FOG measures, and an accurate treatment and rehabilitation of FOG can reduce accidents and improve the quality of life of people with PD who suffer from this sign. The purpose of this study was to develop and validate a physical mobility task able to induce FOG in a controlled environment, employing known triggers of FOG episodes. Then, to extend the approach to FOG assessment, different gait parameters were analyzed in order to develop a more useful system to monitor freezers in PD. The signals of three inertial sensors with a 3D gyroscope and accelerometer were used to compare the walk pattern between people with PD who have the symptom of FOG (GFOG+ group), people with PD who do not have the symptom of FOG (GFOG- group), and healthy age-matched individuals (GC group). The total number of FOG occurrences during data collection was 174. The proposed tasks were able to trigger 120 FOG episodes, while the TUG test caused 24 and the voluntary stop caused 30. The accelerometer and gyroscope could not only detect FOG episodes but also allow for the visualization of the three types of FOG: akinesia, festination, and trembling in place. The comparison results showed that the variable that best represents the differences between the groups is Activity followed by the Power Index. The 360-degree turn event is the moment of the task in which the proposed method better discriminates the data between the groups. There was a consistent pattern: the number of statistically significant pairwise comparisons was highest for the second 360-degree turn, followed by the third and first 360-degree turns. The second 360-degree turn is also the task event most able to trigger FOG episodes. Gait changes, represented by gait variability and the amount of movement during gait execution, also appear while walking in a straight line, proving that people with FOG walk differently than people who do not have FOG, even in between the FOG episodes.

Keywords: Parkinson's disease; Freezing of gait; gait changes; Inertial sensors; Objective assessment.



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List of Abbreviations

APA Anticipatory Postural Adjustments

APT *Associação Parkinson Triângulo*

BEST Balance Evaluation Systems Test

CAR Centre for Automation and Robotics

CNS Central Nervous System

CSIC Higher Council of Scientific Research

DMT Digit Monitoring Task

DT Dual task

ECG Eletrocardiology

EEG Eletroencephalography

EOG Electrooculogram

FES-I Fall Efficacy Scale – International

FI Freeze Index

FIK Freeze Index using Koopman operator for spectral analysis

FOG Freezing of Gait

FOG-Q Freezing of Gait Questionnaire

FTH Freeze Index Threshold

GC Control Group

GFOG+ Parkinson's disease patients with history of Freezing of Gait

GFOG- Parkinson's disease patients with no history of Freezing of Gait

HAP Human Activity Profile

IMU Inertial Measurement Unit

M-EDL Motor Experiences of Daily Life

MDS Movement Disorder Society

MDS-UPDRS Movement Disorder Society - Unified Parkinson's Disease Rating Scale

MMSE Mini Mental State Examination

MT Motor task

NIATS Centre for Innovation and Technology Assessment in Health

PD Parkinson's disease

PI Power Index

PIGD Postural Instability and Gait Difficulty

PTH Power Index Threshold

RA Rigid Akinetic

RAS Rhythmic Auditory Stimulation

RGB-D Red Green Blue-Depth

RNN Recurrent Neural Network

SIP Stepping in-place

STMP Short-term motor patterns

TD Tremor Dominant

TF time in seconds that the volunteer spent frozen

TUG Timed Up and Go

UFU Federal University of Uberlândia

UPDRS Unified Parkinson's Disease Rating Scale

UPM Polytechnic University of Madrid

VR Virtual Reality

VS Voluntary Stop

WHO World Health Organization

WSN Wireless Sensor Network

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1

Introduction

1.1 Problem formulation

This thesis focuses on the problem of assessment of Parkinson's disease (PD) motor sign Freezing of Gait (FOG). The fact that there is still no cure for PD defies science; however, this is not the only issue. Another is the lack of appropriate treatment and follow-up techniques on the course of the disease.

Over the years, numerous researchers have concentrated on the identification of both motor and non-motor PD symptoms (119, 15). Some behaviors are notable during the movement execution in PD, such as decreased regular rhythm, moderate slowness or interruption of the task, and decreased range of motion (34). The motor signs of PD patients fluctuate from day to day or even from hour to hour, with fatigue and the influence of medication schedules (45).

Freezing of gait (FOG) is one of the most disabling symptoms of Parkinson's disease, which is a brief episodic absence or marked reduction in stride progression, despite the intention to walk (83). This sudden inability to begin or continue movement can affect performance in daily activities and subject the individual to frequent falls (71).

Patients with FOG walk differently than patients who do not have FOG (16). It has been reported that FOG is associated with a heightened risk of recurrent falls (4). Recurrent falls occur when an individual falls more than once in one year (4). Literature shows that the risk factors for a single fall may differ from the risk factors for recurrent falls (62). Besides that, fear of falling and reduced mobility are increased in recurrent fallers when compared to single fallers (4). Once recurrent falls are evident, the average survival time is lowered to around 7 years (16).

A progressive disorder influences the decision-making process (45), patients with PD state that gait problems, falls, reduced mobility, and a decrease in social activities are the main factors that have a negative impact on their quality of life. To explore how perceptions of fall risk influence the decisions of PD patients and their care partners, a qualitative study (45) with several interviews elucidated the complex interaction between

perceptions of fall risk and behavior. According to the interviews, the desire to lead a "normal life", which means a life as similar as possible to that of healthy individuals, influences how people with PD weigh up the risks and benefits of executing daily living activities. Results found a tension between the fear of falling and the desire to have a socially active life, suggesting that people with PD weigh up the benefits and costs of risky behavior versus safe behavior, aiming for a target level of risk that is acceptable to them. It is important to highlight that there is no "one size fits all" approach to fall prevention management in PD, but it is certain that the lives of patients with PD who suffer from FOG are more severely affected by the fear of falling. The risk of fall increases because the most frequent presentation of FOG is not the akinetic type in which there is no movement at all. Video studies did, in fact, show that FOG is commonly associated with an effort to overcome the block, the trembling in place or festination types of FOG. Akinetic freezers who accept the block and wait for spontaneous resolution may be less prone to fall (16).

In the clinical assessment, asking about "freezing" in relation to FOG is typically insufficient because not all patients will understand this topic correctly. It often proves difficult to clarify the precise FOG circumstances, yet this is critical for the implementation of FOG prevention strategies. Useful information may be obtained by consulting the spouse, caregiver, or using a FOG diary (16). The current approaches for assessing FOG include a few elements of the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), a questionnaire to quantify FOG, the New FOG-Q, and the manual analysis of videos with mobility tasks.

These methods are subjective, and their disadvantages are mostly observed when they are replicated in real-life situations compared to controlled laboratory conditions. The MDS-UPDRS has poor agreement between inexperienced raters (58). It has been reported that people with PD who score high on the New FOG-Q in their daily routine are not necessarily those most predisposed to experience FOG during clinical trial protocols (114). And the reliability of video analyses is not robust when employed alone, also with low agreement between raters (91).

In addition, there is a real difficulty in provoking FOG during a routine clinical examination (91). The challenge of causing FOG in a controlled environment without the use of complex technologies and respecting the frailty and limitations of the PD patient arose due to its convenience. Laboratory testing of gait motor skills on swaying platforms or treadmills is impractical in most clinical settings due to their length and complexity, and it is not wise to use them on frail patients (92). Therefore, an objective method capable of detecting abnormal gait patterns and, consequently, FOG, in the clinical practice, is desirable.

In order to solve these problems, a series of experiments were conducted to shed light on the investigation of FOG. It was expected that by means of the use of inertial sensors

and camera, along with the employment of different provoking strategies to trigger FOG, it is possible to quantify the FOG symptom and improve the understanding of how to assess freezers in PD.

1.2 Relevance of the thesis

Parkinson's disease (PD) is a chronic and degenerative disease that compromises a person's motor and non-motor functions (115). It affects individuals of different ages, and epidemiological studies highlight an incidence of 17 cases per 100,000 people per year, with a higher incidence in men (42). Parkinson's disease is the second-most prevalent neurological disorder and it is estimated that by 2040, more than 12 million people will be diagnosed with PD. (26).

In Brazil, an approximation of the prevalence of Parkinson's disease estimated that there were 220.000 people suffering from PD in 2016, and that number will more than quadruple by 2030. Nevertheless, if it were considered that the nation had 21 million or more people over the age of 60 in 2009, Parkinson's patients made up 3.3% of the over-60 population in the state of Minas Gerais (17).

According to Bartels et al. (12), the prevalence of freezers, who are people diagnosed with PD in whom the FOG symptom manifests, ranges from 7% in the early stages to 60% in the severe stages. Rawson et al. (102) stated that between 20 and 60% of people living with PD will eventually experience the FOG symptom, and Saad et al. (105) considered that more than half of patients with PD could develop FOG in the course of the disease. Morris et al. (72) reported that progressively more people who experience FOG restrict walking and reduce their level of physical activity to avoid triggering the motor disorder.

The study by Moreira (71) considered FOG, along with excess saliva, the need for assistance with personal hygiene, and high-intensity tremor at rest, as the factors that most interfere with the quality of life of people with Parkinson's disease. These factors cause a decrease in independence and difficulty in performing daily tasks, which causes embarrassment and limits social interactions. These markers of worsening quality of life in moderate stages of PD are related to stigma, cognitive impairment, and greater mobility difficulties (71). In the domain of mobility, the difficulty in performing common actions, the need to hide the symptoms of the disease, such as FOG, and insecurity in the presence of new people, fear of falling, sadness, and irritability are factors that negatively affect the quality of life (71).

A permanent and guaranteed cure of FOG is not yet available, but a sufficiently precise and accurate FOG monitoring system can be useful for increasing information about the patient during the clinical visit to help the physician's evaluation (115). A gold standard for the detection and evaluation of the FOG phenomenon using quantitative assessment is also not currently available (83, 102, 105, 46). The importance of this work

arises because the assessment of freezers in PD with accurate detection and rating of the severity and impact of FOG are crucial for appropriate treatment and follow-up (102, 105). Furthermore, determining methods to assess physical mobility in PD could prevent falls, and reduce or overcome FOG episodes (102, 105).

The wide adoption of accelerometers and gyroscopes observed in the literature demonstrates the maturity of this type of sensor and the viability of its application in real systems. In this context, the use of sensor-based systems provides accurate and objective information to monitor symptom evolution and optimize FOG assessment (113).

1.3 The object of the research

The research object of this doctoral thesis is the physical mobility motor task developed to trigger FOG in a controlled environment in people with Parkinson's disease with FOG history. Also, the quantitative parameters obtained using an accelerometer and gyroscope from people with PD with FOG, people with PD without FOG, and people without PD. The obtained parameters were analyzed to quantify motor patterns and applied to discriminate between the groups.

1.4 The aim of the thesis

The aim of the thesis is extend the approach of FOG assessment by observing different gait parameters to elucidate the optimal combination of sensor, sensor placement, task and feature to be extracted to identify gait changes in Parkinson's disease. In addition, to determine which FOG-provoking strategy most significantly influences the gait of freezers and results in more FOG episodes. The method is validated using Inertial Measurement Unit (IMU) with accelerometer and gyroscope, and video recordings.

1.5 The objective of the thesis

In order to solve the stated problem and reach the aim of the thesis, the objective of this work is to elucidate the optimal combination of sensor, sensor placement, task, and feature to be extracted to identify gait changes in Parkinson's disease and to determine which FOG-provoking strategy most significantly influences the gait of freezers, using the IMU information of data acquisition and applying two approaches: the Moore-Bachlin algorithm and Hjorth's parameters. The Moore-Bachlin algorithm is the Freeze Index and the Power Index, both features in the frequency domain. The Hjorth's parameters are Activity, Mobility, and Complexity. They are features in the time domain related to amplitude, frequency and entropy, respectively.

To complete the challenge, the following specific objectives were formulated:

1. To induce FOG events with a simple physical mobility task in a controlled environment.

2. To investigate which task is best able to trigger FOG events: the voluntary stop, the Timed Up and Go (TUG) test, the motor task, or the dual task.

3. To differentiate the FOG types by interpreting the signals of the inertial sensors.

4. To elucidate the percentage of FOG events in each FOG-provoking strategy included in the mobility tasks.

5. To investigate if data acquired with the NetMD system, the technology chosen to be used with three smartwatches and one smartphone that collect motion data, allows discrimination between subjects with PD with a history of FOG, subjects with PD with no history of FOG, and people without PD.

6. To propose features able discriminate between the groups, the classic Moore-Bachlin algorithm or Hjorth's parameters and to elucidate which group of features or feature combination is better suited to detect gait changes during the execution of the proposed mobility tasks.

7. To investigate if there are gait improvements during the ON medication state compared with the OFF medication state of the groups with PD (GFOG+ and GFOG-) according to the features extracted from the data analysis.

8. To perform statistical tests and identify the number of positive tests for the differences between the groups considering the smartwatches, the sensors, the axes, the features, the tasks, and the task events.

9. To generate an open access database that researchers can access and contribute to the development of new technologies to improve the quality of life of individuals with Parkinson's disease.

1.6 Research methodology

The investigation in this thesis is divided into three parts. In the first part, a study of the literature is conducted to comprehend Parkinson's disease and the freezing of gait (FOG). Then, to acquire experience, the review was followed by a semester internship in a center that welcomes and offers activities for individuals with PD in the city of Uberlândia (Brazil), providing direct contact with individuals with Parkinson's disease. This coexistence helps in a better understanding of the disease.

In the second part of the investigation, two physical mobility motor tasks were developed to trigger FOG in a controlled environment: a simple motor task and a dual task.

These tasks were included in an experimental protocol, and they were validated using inertial sensors. The experiment was performed by 10 people with PD who have the FOG sign (GFOG+), 10 people with PD with no history of FOG (GFOG-), and 10 healthy individuals, the control group (GC). The subjects from each group were paired in terms of age and sex, and subjects with PD were evaluated using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Inertial signals from the Net MD system, gyroscope, and accelerometer were collected during the execution of four gait tasks. People with PD executed the gait tasks during the OFF and ON medication states.

The third part of the investigation comprises data organization and annotation using video recordings. A data analysis was performed (i) to elucidate which task is best able to trigger FOG events, (ii) the percentage of FOG events in each FOG-provoking strategy included in the mobility tasks, (iii) to differentiate the FOG types by interpreting the signals of the inertial sensors, (iv) for the discrimination of motor patterns from the three groups of subjects, and (v) to elucidate which group of features or single feature is better suited to detect gait changes during the execution of the proposed mobility tasks.

Figure 1.1 represents the flow diagram of the fundamental stages of the thesis. Step 1 illustrates the development and testing of the tasks and technology applied to the experimental protocol. Step 2 illustrates data collection and data management, storage, annotation, preprocessing, processing, and statistical analysis.

1.7 Scientific novelty of the thesis

The novelties of the proposed study are:

1. Design, development, employment, and validation of a system to assess FOG in PD in a controlled environment in a simple, safe way and using little space.

2. Innovation in the way of evaluating the gait of freezers and other Parkinson's disease-related changes in gait using wireless inertial sensors, in addition to performing FOG detection using the inertial data along with the video annotation.

3. Delineate the optimal combination of sensor, sensor placement, task and feature to be extracted to identify gait differences in Parkinson's disease. In addition, to determine which FOG-provoking strategy most significantly influences the gait of freezers and results in more FOG episodes.

1.8 Practical value of the research findings

The intractable nature of FOG may be related, in part, to difficulty in assessing its characteristics and incidence (70). A treatment in PD without objective feedback on the

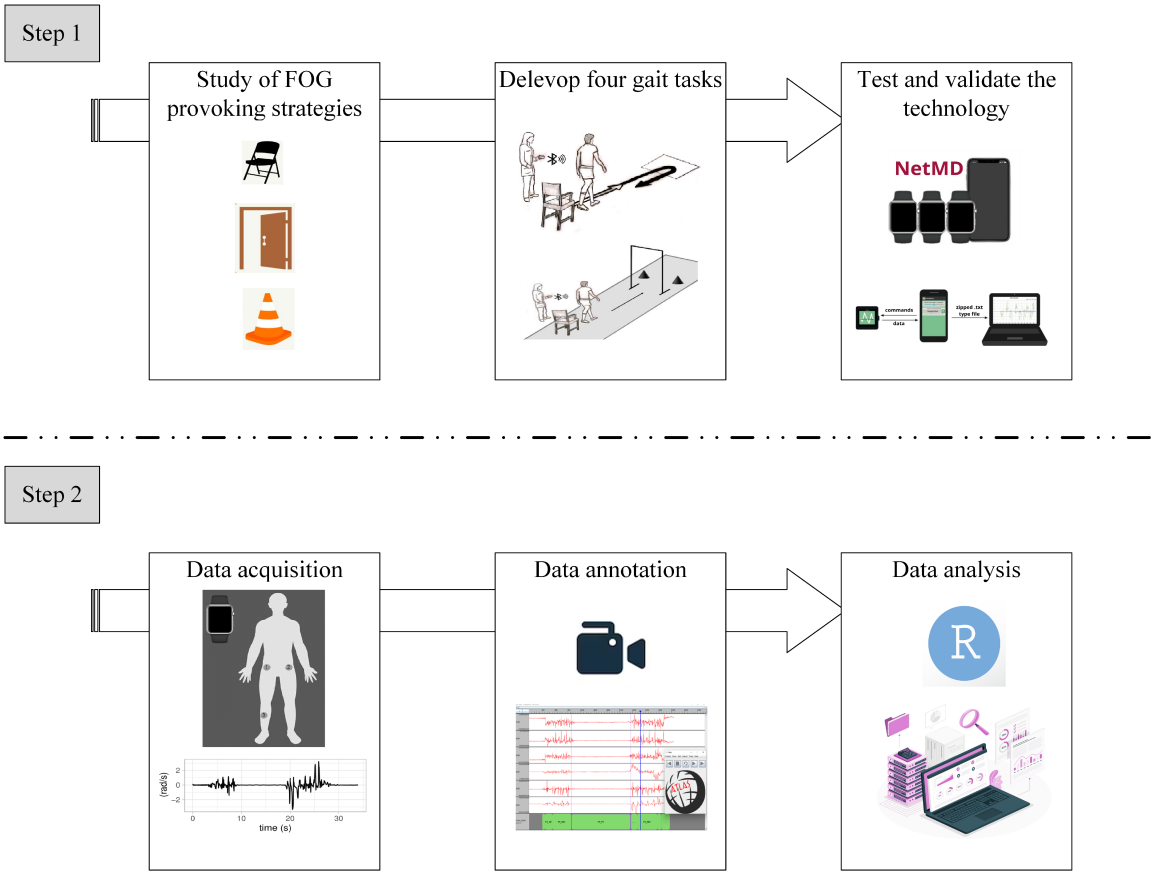

Figure 1.1 – Flow diagram of the fundamental stages of the thesis. Step 1 illustrates the development and testing of the tasks and technology applied to the experimental protocol. Step 2 illustrates data collection related to gait, storage, annotation, processing, and statistical analysis.

influence of therapy on FOG is likely to be ineffective. The possibility of monitoring FOG with a reliable system that can provide objective feedback to treatment could improve management of FOG in PD. Therefore, a system is proposed for helping specialists with the assessment of FOG for PD patients and provide efficient and on time treatment.

The results of the research are to be used for the development of systems for human motion quantification. Features extracted from the signals and data annotation of gait movements can be used for the characterization and discrimination of gait motor patterns.

The major limitations of clinical assessments of FOG are cost, complexity, and specific space requirements. Therefore, a simple physical mobility task that can induce FOG in a controlled environment is of great interest for FOG treatment and rehabilitation.

The investigated tools for data annotation and visualization can be used for the development of computer-aided diagnosis systems to allow the diagnosis and follow-up of people with PD who have the FOG symptom. The inertial signals enhanced the visual discrimination of different features that may represent the volunteers. By using these visualization tools, a control zone can be estimated and used as a reference for the many exams that a person with PD goes throughout their life.

The measurement of the FOG condition by creating a FOG status may help specialists determine the appropriate treatment. The FOG status includes the number of FOG episodes, the duration of each FOG, the time each FOG occurred, and the results of features extracted from wearable inertial sensors. The possibility of continuous evaluation of the patient by physicians by means of feature extraction results in the best evaluation focused on the patient, and an appropriate treatment can control FOG and eventually prevent falls caused by the sudden phenomenon.

There is limited, yet growing, evidence relating to rehabilitation in the follow-up of FOG. The protocol for rehabilitation suggests that movement strategies may allow people with PD to use the intact frontal cortex in order to move faster, more easily, and safely using cognitive control. Movement strategy training consists of using mindfulness, partial practice, mental rehearsal, and visual or auditory cues to normalize initiation, execution, termination, speed, and range of motion (72).

In this research, an offline FOG assessment system was developed to generate objective information about the gait of three groups during different task executions and evaluate gait changes comparing people with PD with the symptom of FOG, people with PD with no history of FOG, and age-matched controls. This method to assess freezing of gait and gait changes could be used by health professionals to obtain more information about the FOG condition and symptom characteristics of the freezers PD patients and also to classify a patient according to his gait patterns. For example, it is possible to verify how close or distant the gait patterns are from normal, i.e. healthy individuals results.

Figure 1.2 illustrates the conceptual idea of the proposed system. During the exam the patient will execute the proposed physical mobility motor tasks using smartwatches positioned in strategic places of the body in a controlled environment while the health professional accompanies the trajectory and collect data via bluetooth with a cellphone. This data is transferred for a computer and the health professional will be able to view the results of the exam on the computer screen. The proposed system with the use of smart sensors and a physical mobility motor task developed to trigger FOG can be used to record changes in gait over time, as well as changes in the duration and number of FOG events. A specific improvement by reducing the time in seconds of FOG and the number of FOG episodes for freezers is of particular interest.

The conceptual idea presented in Figure 1.2 shows that the health professional is able to classify the patient by interpreting the results of the boxplot in the safety region, the region of attention or the risk region. The safety region is where the results of the mathematical equations applied on data collected of one individual are similar to the results obtained for the gait analysis of healthy individuals. The region of attention is in between the safety and the risk regions, it means that the patient does not have the results similar to healthy individuals, however the results are close in region with them, in this case the health professional should recommend a clinical evaluation to have more

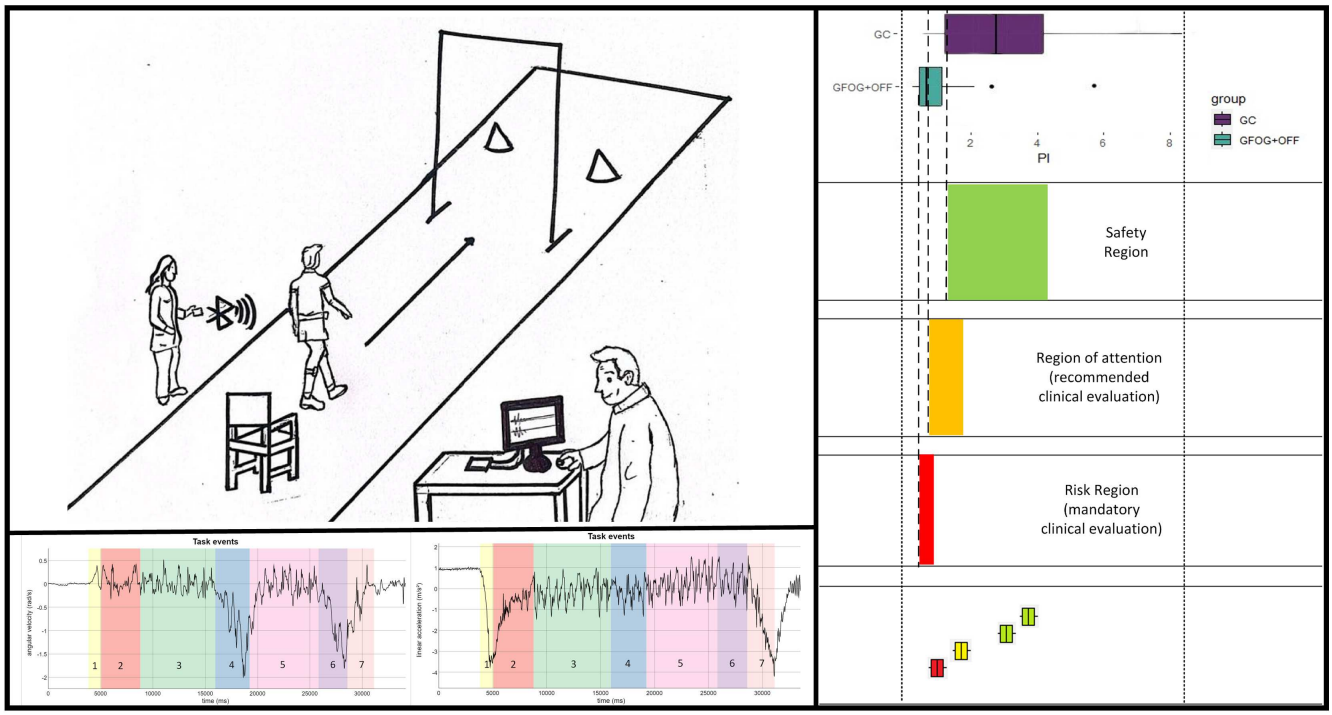

Figure 1.2 – Conceptual idea of the proposed system. During the exam, the patient will execute specific physical mobility motor tasks, while the health professional will be able to view the results of the exam on the computer screen. The boxplots represent the results of the power index (PI) obtained from two groups: in purple, the GC is for the control group, the healthy individuals; in cyan, the GFOG+OFF is for the group of people with Parkinson's disease with the FOG sign during the OFF medication state. The power index measures the amount of movement in a windowed signal. The safety region is where the results of the PI of one individual are similar to the results obtained for the gait analysis of healthy individuals. The risk region is where the results applied to the data collected by one individual are similar to the results obtained from the gait analysis of freezers without medication. The region of attention is in between the safety and the risk regions. The four boxplots (red, yellow, and green) under the figure show examples of results with four possible scenarios.

information about the patient. The risk region is where the results applied on data collected of one individual are similar to the results obtained from the gait analysis of freezers without medication, which means the worst case scenario. In the risk region, the clinical evaluation is mandatory.

1.9 Approval of the research findings

The results of the research were published in nine scientific publications: three in peer-reviewed scientific journals and six in conference proceedings.

1.9.1 Papers in reviewed scientific journals

1. Nóbrega LR, Cabral AM, Oliveira FHM, de Oliveira Andrade A, Krishnan S, Pereira AA. Wrist Movement Variability Assessment in Individuals with Parkinson's Disease. Healthcare (Basel). 2022 Aug 30;10(9):1656. doi: 10.3390/healthcare10091656. PMID: 36141268; PMCID: PMC9498573.

2. Nóbrega LR, Rocon E, Pereira AA, Andrade AO. A Novel Physical Mobility Task to Assess Freezers in Parkinson's Disease. Healthcare (Basel). 2023 Jan 31;11(3):409. doi: 10.3390/healthcare11030409. PMID: 36766984; PMCID: PMC9914147.

3. Beigi OM, Nóbrega LR, Houghten S, Pereira AA, Andrade AO. Freezing of gait in Parkinson's disease: Classification using computational intelligence. Biosystems. 2023 Aug 25; 232:105006. doi: 10.1016/j.biosystems.2023.105006.

1.9.2 Conference Papers

1. Nóbrega LR, Silva GL, Pereira AA, Andrade AO. "Uma revisão na literatura sobre o congelamento da marcha em pacientes com Doença de Parkinson". In XII Simpósio de Engenharia Biomédica – IX Simpósio de Instrumentação e Imagens Médicas, 2019. Zenodo. https://doi.org/10.5281/zenodo.3469963.

2. Nóbrega LR, Pereira AA, Andrade AO. "On the use of wrist flexion and extension for the evaluation of motor signs in Parkinson's Disease". In XXVII CBEB – Congresso Brasileiro de Engenharia Biomédica, 2020. DOI: 10.1007/978-3-030-70601-2-61

3. Nóbrega LR, Pereira AA, Andrade AO. "Task event annotation using software ATLAS". In XIV Simpósio de Engenharia Biomédica (ISSN: 2358-3568), 2022. DOI: 10.5281/zenodo.7491876

4. Nóbrega LR, Luiz LMD, Andrade AO, Pereira AA. "Identification of Relevant Features to Assess Bradykinesia and Gait Disorders in PD Using Inertial Sensors – a Narrative Review". In IX Latin American Congress on Biomedical Engineering XXVIII Brazilian Congress on Biomedical Engineering, 2022.

5. Morais CR, Nóbrega LR, Andrade AO, Pereira AA. "Protocolo para avaliação do congelamento da marcha na doença de Parkinson". In XII Simpósio de Engenharia Biomédica (ISBN: 978-65-5379-009-4), 2021. DOI: 10.47573/XIIISEB

6. Beigi OM, Nóbrega LR, Houghten S, Andrade AO, Pereira AA. "Classification of Parkinson's Disease Patients and Effectiveness of Medication for Freezing of Gait". In IEEE Conference on Computational Intelligence in Bioinformatics and Computational Biology (CIBCB), Ottawa, ON, Canada, 2022, pp. 1-8. DOI: 10.1109/CIBCB55180.2022.9863050.

1.10 Structure of the thesis

The thesis consists of an introduction, five chapters and general conclusions. The volume of the document is 134 pages, in which are given 51 figures and 25 tables.

2

A study of gait dysfunctions and the FOG symptom in Parkinson's disease

In this chapter, the definition and prevalence of Parkinson's disease is presented, as well as the motor clinical manifestations, phenotypes, clinical evaluation, and the most used medication treatment. This chapter also addresses gait disorders in Parkinson's disease and introduces the object of study, the freezing of gait (FOG). Regarding FOG, the chapter presents its definition, prevalence, environments, and situations that can cause the episode. Besides that, the non-exclusive hypotheses that try to explain the behavior are explored, as well as the compensation strategies to mitigate the event, and the evaluation methods available according to the literature.

2.1 Parkinson's disease

Parkinson's disease (PD) is a condition of the Central Nervous System (CNS), more specifically in the substantia nigra of the midbrain, that causes progressive loss of dopamine-producing neurons. The death of dopaminergic neurons and the atrophy and degeneration of the basal ganglia compromise the dopaminergic pathway and complicate communication between the substantia nigra and the striatum, the synapse that results in the release of dopamine. This decrease in dopamine reduces the activity of the motor areas of the cerebral cortex, which causes symptomatic changes and influences motor function and movement (30).

Parkinson's disease affects individuals of different ages, and epidemiological studies highlight an incidence of 17 cases per 100,000 people per year, with a higher incidence in men (42). PD is potentially devastating and multifactorial; both genetic and environmental factors are implicated in the development of the disease (89).

In 1817, James Parkinson, an English physician, published in London an essay entitled "An Essay on the Shaking Palsy" (49, 90), which is the world's first well-defined description of Parkinson's disease (123). Parkinson's disease became known as a "disease characterized by the presence of involuntary trembling movements, a decrease in muscle

strength, a tendency to lean the trunk forward, and changes in gait" (88). The first definition of Parkinson's disease by James Parkinson over 200 years ago was precise and revolutionary.

Later, some aspects were contested by Jean-Martin Charcot, considered the first professor of nervous system diseases in the world (123). For example, the presence of muscle weakness was defined as muscle rigidity, and the original description regarding the preservation of higher cortical functions was also updated (123), considering that Parkinson's disease can affect an individual's cognitive functions (93). Furthermore, Charcot suggested changing the name of "shaking paralysis" to "Parkinson's disease" and introduced the concept of bradykinesia (123), which is slowness in performing tasks.

2.2 Clinical and motor manifestations of Parkinson's disease

Clinically, Parkinson's disease is characterized by motor dysfunctions such as tremor, rigidity, slowness of movement, and changes in posture, balance, and gait (116). These deficiencies cause the cardinal signs of PD: bradykinesia, muscle rigidity, resting tremor, and postural instability (116, 118).

Bradykinesia is characterized by slowness in performing movements; the main signs are increased reaction time, prolonged time to change a motor pattern, weakness, and rapid fatigue when performing prolonged tasks (37). The parkinsonian tremor has a frequency between 4 and 6 Hz and has a unilateral onset; it manifests itself in the distal extremities and may affect the lips, chin, mandible, and lower limbs (48). Muscle stiffness is characterized by muscle hardening at rest, causing limb and joint inflexibility (41). Muscle rigidity potentially contributes to bradykinesia when it is antagonistic to movement. Finally, postural instability is the difficulty or inability to keep the body in balance and is related to gait disorders in PD (63).

The diagnosis of PD requires the presence of bradykinesia in addition to at least one of the other cardinal motor signs: tremor, muscle rigidity, or postural instability. The diagnosis is basically made clinically, considering some evaluation criteria in addition to a good response to drug therapy (96). They may also include imaging tests or laboratory tests, which are uncommon in clinical practice (93).

The sum of the primary signs in PD causes secondary complications, such as hypokinesia, micrographs, masking of the face, contractures, and fatigue. In addition, the accuracy of reaching movements, fine motor coordination, and spontaneous movements and gestures may also be affected (48, 3, 27, 85). The main and secondary signs of PD interfere with daily functional skills and generate physical dependence, which can lead to depression and loneliness. Although PD is considered a movement disorder, non-motor manifestations further burden parkinsonian disorders and affect daily activities

(109). These dysfunctions are usually sleep disturbances, cognitive alterations, constipation, postural hypotension, sexual dysfunction, and urinary dysfunction, in addition to depression, daytime sleepiness, fatigue, and hyposmia (115, 93). Mood swings, apathy, sensory symptoms such as pain and paresthesia, and problems with weight loss may also occur (123, 115, 93).

It is important to highlight that the set of symptoms present in Parkinson's disease is called symptoms of Parkinsonism. Parkinsonism is the cell death of the basal ganglia, and the symptoms are similar to PD but appear more aggressively (123).

Furthermore, drug treatment for PD is not effective in treating Parkinsonism (124). Although most people with Parkinsonism have PD, not all Parkinsonism is due to the disease. Parkinsonism can be caused by several factors, such as Secondary Parkinsonism, which is caused by a previous disease, such as a stroke, and Medication Parkinsonism, which is caused by medications used for a long time, such as some specific remedies for nausea, labyrinthitis, high blood pressure, antipsychotic drugs, and mood regulation (124).

The manifestations of Parkinson's disease are diverse and occur in a heterogeneous way; commonly, the most known complications are motor dysfunctions, despite the recurrence of non-motor dysfunctions. The motor symptoms happen unilaterally initially, and one of the hemibodies remains more affected throughout the disease (93). Factors that complicate PD are the variation in the size of the steps, postural instability, and gait difficulties that negatively reflect on the movements of sitting down and standing up, forcing patients to walk with shorter steps and without the movement of standing. pendulum in the arms and cause freezing of gait.

All these motor problems can result in a fall, which is very harmful for the patient [4, 8]. There are considerable risk factors known to be associated with falls in people with PD, such as the FOG, leg muscle weakness, and postural instability (4).

Studies show that more than 60% of people with Parkinson's disease have fallen at least once, of which 39% have recurrent episodes of falling (4). The fear of falling is more evident for PD patients when compared with healthy age-matched individuals, and it severely affects the quality of life (1).

2.3 Phenotypes of Parkinson's disease

According to the predominant motor symptoms, it is possible to classify the person with PD according to their phenotype; that is, there are subgroups in Parkinson's disease.

It is well established in the literature that different subgroups of PD have different courses and clinical outcomes (132). The main clinical subgroups in PD are Tremor Dominant (TD), Rigid Akinetic (RA), and Postural Instability and Gait Difficulty (PIGD) (44). Some patients compose a mixed group (131).

There is evidence that the neural pathology between these subtypes differs (36), but it is still not fully understood why these manifestations differ among patients with PD. To classify the phenotype of a person with PD, it is necessary to perform one or more clinical assessments, considering the predominant motor signs and the initial description of the patient (131). The Tremor Dominant type (PD-TD) is characterized by tremor of one or more limbs with a relative lack of severe bradykinesia and rigidity; it is the subgroup that presents resting tremor, typically unilateral and with progressive worsening. People in the PD-TD subgroup tend to have slower disease progression, fewer non-motor symptoms, more chances of improvement with levodopa, and a higher survival rate when compared to PD-PIGD (53).

The Rigid Akinetic type (DP-RA) is the type characterized by problems due to slowness in the onset of movement, rigidity followed by abnormal stiffening of the muscle, slowness to perform everyday tasks, and increasing impairment of movement (131). Visual motor memory, defined as the ability to generate motor commands that create movement and a graphic representation of memorized visual patterns, is also more affected in PD-RA patients (131). It is responsible, for example, for the efficiency of writing and calligraphy because, to recreate the tracing of the letters, it is necessary to memorize motor movements. Patients with PD-RA show a more rapid progression of motor symptoms and have a higher risk of developing dementia and moderate cognitive deficits when compared to patients with PD-TD (132, 36). Compared to DP-TD, DP-RA also has more difficulties in the learning process and in the perception and speed of the visual and peripheral processes. Therefore, regarding neurophysiological impairments, the PD-TD type is favorable to the PD-RA type (131).

Individuals with postural instability and gait difficulty (PD-PIGD) have a faster progression of the disease than PD-TD and a higher risk of developing the freezing of gait symptom (70). The classification of the different phenotypes of the disease represents a difference in the prognosis of the patient; it is reported that PD-TD patients have a better initial prognosis and less motor impairment, with possibilities of better maintenance of the quality of life (68). The PD-PIGD classification, with characteristics of dysfunctions in instability and gait, has a worse prognosis and a close relationship with cognitive impairments with the evolution of the disease (7). Therefore, detecting and evaluating the subtype of Parkinson's disease is indispensable (131).

2.4 Clinical assessment in Parkinson's disease

Assessments in Parkinson's disease are made specifically and they aim to analyze motor and non-motor signs. There are several collection instruments for a qualitative assessment, that is, tools that corroborate the clinical assessment of the patient; the most commonly used is the MDS-UPDRS (Movement Disorder Society-Unified Parkinson's

Disease Rating Scale).

The need for a common and consistent method for the assessment of PD led to the creation of the Development Committee of the Unified Parkinson's Disease Rating Scale (UPDRS) in 1984 (34). The UPDRS was published by Fahn and Elton in 1987 and introduced as a general assessment method, including assessment of self-reported impairment (activities of daily living, ADL) and clinical assessment by a physician (motor examination, MS) (125).

In 2008, the scale was revised and updated by the International Parkinson and Movement Disorder Society (MSD) and has since been designated the MDS-UPDRS (34, 101). The MDS-UPDRS is described as the gold standard (34) and has been the most widely used clinical scale for monitoring and diagnosing PD (66). The scale has four parts. Part I covers non-motor aspects of daily life experiences, such as drowsiness, anxiety, and apathy, and is answered by the evaluator and the patient. Part II assesses everyday motor aspects, such as dressing, eating, and walking, and is answered only by the patient. Part III represents a motor assessment with instructions for the assessor to provide or demonstrate for the patient to perform, and Part IV comprises motor complications such as dyskinesia, dystonia, and motor fluctuation. Parts III and IV of the MDS-UPDRS are completed only by the assessor. Each item receives a score from 0 (normal) to 4 (severe) (34).

2.5 Medication treatment of Parkinson's disease

The common drug treatment for Parkinson's disease is comprised of dopamine precursor drugs, dopamine agonist drugs, and non-dopaminergic drug classes. Among these, levodopa stands out, which is one of the most commonly used drugs, as it has forms of release that depend on the composition and the patient's needs (93). Levodopa, a metabolic precursor of dopamine, is commonly used to manage the motor symptoms of PD by replenishing endogenous dopamine in the striatum and is the main medication used in the treatment of Parkinson's disease (70). It is understood that if the patient takes the medication regularly and at the correct dose, fluctuations in the disease's symptoms are minimized; however, as the disease progresses, levodopa ceases to work with total effectiveness and leads the patient to experience a greater medication OFF period.

The medication OFF period occurs before the scheduled time for the next dose of the medication, in which the patient feels that the effect of the medication has ended. When the patient is under the effect of medication and feeling better, the period is classified as ON. However, as a side effect, the patient may present with motor complications such as dyskinesia during the ON period of the medication (93).

2.6 Gait changes in Parkinson's disease

Gait deterioration in Parkinson's disease is a growing concern as it affects the patient's quality of life (40, 120). Gait changes appear in the early stages of the disease (11). Gait disturbances in PD can be continuous or episodic.

Continuous disorders appear in most patients; they acquire a flexed posture, have difficulties in axial rotation of the upper body, have reduced arm swing, and have difficulty getting up from a chair (48). Continuous gait disturbances are more pronounced in patients of the akinetic-rigid type (DP-RA) and in patients with postural instability and gait difficulties (DP-PIGD) and include asymmetric attenuation or absence of arm swing, stooped posture and variation, a decrease in stride length, and difficulty turning in block. In addition, gait becomes increasingly slower with the progression of PD.

Episodic disorders occur in a portion of the PD population, such as festination gait and freezing of gait. Festinations are rapid steps that decrease in size and become shorter and shorter (70). The propensity that the patient with PD has to lean forward during gait forces him to step with the forefoot, and inevitably, he begins to take faster and shorter steps, thus adopting, even if involuntarily, an accelerated pace (83). Freezing of gait is characterized by difficulty in walking forward because, despite the desire to perform the movement, the individual feels unable to lift the foot off the ground (84). This episodic disorder is a unique disorder that causes a block in walking, and the individual cannot continue or initiate the movement of walking.

When the person with PD is in the OFF period of the medication, the continuous gait disturbances are more accentuated, and the gait is characterized by slowness, reduction or absence of arm swinging, reduced trunk rotation, reduced range of motion of the hip, knee, and ankle, forward leaning, reduction in the amplitude of the steps, and decrease in the height of the foot displacement during the swing phase. Another aspect noted is the increase in the contact time of the foot with the ground, called the double support phase.

When walking during the ON period of the medication, the person with PD still has reduced speed, but the slowness is attenuated. In a controlled study (72), peak gait speed and stride length were sensitive to levodopa medication, whereas temporal variables such as cadence and duration of swing and stance phases were drug-resistant. Gait disturbances in PD are difficult to treat with levodopa; however, many PD patients experience reduced freezing of gait during the ON state of the medication (23).

2.7 Freezing of gait (FOG)

Freezing of gait, or FOG, is more common in advanced PD (72, 129, 13, 127). However, it can also appear in the early stages of the disease, with milder and shorter episodes, especially in patients without adequate treatment (83). The prevalence of FOG ranges

from 7% in the early stages of the disease to 60% in the more advanced stages (12). Rawson et al. (102) state that between 20 and 60% of people living with PD will develop this symptom, and Saad et al. (105) consider that more than half of patients with PD could develop FOG in the course of the disease. Morris et al. (72) report that progressively more people who experience FOG restrict walking and reduce the level of physical activity to avoid triggering the motor disorder.

The definition of FOG was established in 2010 as "a brief episodic absence or marked reduction in stride progression, despite the intention to walk" (83). Ricciardi (103) defined FOG as "an episode of inability to generate an effective stride with no known cause other than parkinsonism or high levels of motor disorder". Bartels (12) defined FOG as a hesitation at the onset of movement that lasts longer than a second, a significant stop in locomotion for no reason, or if it appears that the individual is trying to initiate or continue movement without success. The episode is commonly accompanied by a tremor in the legs as an effort to overcome the block associated with high-frequency components (2–6 Hz) (70, 60, 108).

In 1995, Thompson and Marseden (16, 83, 94, 60) defined three types of FOG: (I) Blocked gait, when the feet seem to be glued to the ground, without movement in the trunk and limbs, like complete or partial akinesia; (II) Festination, when the normal gait rhythm changes to a shuffling gait, with faster and shorter steps until the stop; and (III) Local tremor, when the lower limbs may show signs of tremor while fixed to the ground, with quick and alternating knee movements.

FOG can be provoked or accentuated by environments and tasks. The study by Okuma (84) points out some factors and moments of gait that can trigger FOG, citing the movements of passing through narrow spaces, immediately before reaching a destination, starting to walk, and turning during walking. Most PD patients have a preferred side to turn, but there is a complex relationship between the direction of turning and the dominant side of the disease.

The environments most known to trigger FOG are doorways, narrow hallways, and small, messy spaces (72, 110, 13). Narrow passages created by outdoor furniture and plants can also block gait. The patient may have enough confidence, physical capacity, and motor planning ability to walk without restraint in a clinical setting but still report limitations in walking around the house for exercise.

Situations in which the individual walks and simultaneously performs cognitive processing or motor activity are known as dual tasking. In practice, dual-tasking associates secondary tasks with the gait route, such as carrying a tray (a motor task) or saying the months of the year in descending order (a cognitive task) (110). The literature shows that dual-tasking compromises the gait of people with PD (72) and it can be a trigger for FOG (96, 68, 7, 13).

External or internal pressure to perform a task or a sudden demand increases the

propensity for FOG. Anxiety and stress situations are also determinants of the presence and intensity of the episode. Examples such as using public transport, crossing a busy street before the traffic light, using the elevator, answering the doorbell, or the telephone ringing are situations that can trigger FOG (72, 84). Moreover, factors such as commuting, attention, visuospatial processing, sensory integration, and emotions contribute to the freezing of gait (96, 110, 108).

Although FOG is a common gait disorder (61), it does not affect all patients equally, suggesting that comparing people with PD with a history of FOG and people with PD who do not experience FOG may aid in the search for neurobehavioral markers of the symptom.

FOG research has been driven by important approaches (61), one of which is the attempt to reduce falling events among people with Parkinson's disease (55). People who experience FOG report that they lose control over their gait for a few seconds (115), and when the episode happens, the feet stop moving but the center of gravity continues to move forward. This causes an imbalance that cannot be compensated for by protective steps due to movement being blocked and increases the chances of the patient suffering a fall (84).

Falls in PD are a complex health problem; the direct consequences are fractures, head trauma, contusions, and other injuries, increasing the chances of hospitalization and institutionalization. Indirect consequences include fear of further falls, limitations in activities of daily living, and death (55). FOG and falls pose serious risks to the health of people with PD. In addition to the immediate clinical effects on those who are affected, there are also the rising costs of healthcare for society (16).

The study by Lopes (55) tried to identify fall predictors in individuals with PD and compare people with Parkinson's disease who suffer recurrent falls with people with Parkinson's disease who do not fall, considering sociodemographic, anthropometric, clinical characteristics and functional status, such as age, gender, body mass, PD progression, levodopa dose, MDS-UPDRS part II and III scores, New Freezing of Gait Questionnaire (FOG-Q) score, Human Activity Profile (HAP) score, fear of falling measured by the Fall Efficacy Scale – International (FES-I) scale, gait speed, functional strength of the lower limbs, balance using the Mini Balance Evaluation Systems Test (BEST) scale, mobility through the TUG test and dual task , which is the dual-task TUG test. The group of people with Parkinson's disease who suffer recurrent falls showed the worst performance in the values of MDS-UPDRS, New FOG-Q, HAP, FES-I, Mini BEST test, TUG, and TUG with dual task. Therefore, factors associated with a high risk of falling in PD are disease progression, severity of the FOG symptom, levodopa dose, severe motor difficulties, motor fluctuations, loss of upper limb sway, and dyskinesia.

The most dangerous outcome of falls is probably hip fractures, which are linked to high rates of morbidity and mortality in Parkinson's disease and frequently result in nursing

home admission. About 25% of patients will have a hip fracture within ten years of their diagnosis, and smaller wounds such as joint dislocations, bruising, or skin lacerations are quite frequent and a substantial source of pain and discomfort for patients. A retrospective cohort study reviewed the records of PD patients compared with age and sex-matched healthy individuals, and the results show the risk of fracture is significantly higher in those with PD (31).

Personal and environmental factors can influence the functionality of an individual with PD in a positive or negative way. Deficiencies in body functions can induce social isolation, as the patient is embarrassed or afraid of falling. Thus, patients with gait dysfunction have difficulty participating in social activities and prefer to limit or avoid them. PD individuals with fear of falling have lower mobility, decreased capacity to execute activities of daily living, and a lower quality of life (16).

Freezing of gait usually happens during the OFF period (83), and therefore several studies that aim to evaluate the FOG perform the experiments in the OFF state of the medication. However, an editorial note (23) showed that there are many unanswered questions about ON state FOG; the text says that the true incidence and prevalence of this condition are not well known and are likely to be underreported. In the study by Schaafsma (108), nineteen volunteers with PD and a history of FOG were recorded while performing a physical mobility task. The experiment was carried out in the ON and OFF states of the medication so that the data could be later analyzed and the researchers could evaluate the effect of levodopa on participants' gait. The results suggest that levodopa raises the threshold for FOG to occur but does not cure the episode. In addition, other studies performed experiments with patients in both medication states (12, 40, 77). There is a consensus among authors that further studies are needed to characterize the FOG phenomenon and the types of patients in whom it occurs (23).

2.8 Hypothesis of freezing of gait

The contribution of the environment, factors related to tasks, attention, mental state, and prolonged use of medication can contribute to the occurrence of FOG (72). There are some hypotheses presented in the literature about the freezing of gait related to automaticity, rhythmic control, the generation of abnormal patterns, and anticipatory postural adjustments.

Automaticity is impaired in advanced PD, and this increases stress on voluntary and cognitive mechanisms (81). Walking is an automatic motor task that requires a low level of cognitive function since it represents a spontaneously acquired practical movement (83). However, evidence suggests a complex interaction between gait impairment and cognition (103), hypothesizing that individuals with Parkinson's disease who experience gait impairment are unable to properly recruit specific cortical and subcortical neural

regions within the network of cognitive control during the simultaneous performance of motor and cognitive functions (110). Therefore, PD patients who do not experience episodes of freezing of gait can counteract the negative effects of automaticity deficits by increasing cognitive control, whereas people who have FOG do not have this control. Impaired automation may explain why FOG often occurs during walking and challenges dynamic cognitive-motor control due to the performance of a secondary activity (84, 110).

Another hypothesis is that FOG is associated with a central deficit in rhythmic gait control. Readiness potential refers to the preparation of cortical motor neurons in a state of readiness to perform a sequence of movements. During the performance of a sequence of previously learned movements, the basal ganglia define and maintain a plan of cortically selected movements; the parameter of the movement sequence (fast or slow; walking or running) is selected with specific amplitude and speed and discards the need for conscious attention (72). Therefore, when the basal ganglia are functioning normally, an individual may divert attention to a secondary task while they automatically maintain a set of rhythmic movements. The physiological malfunction in PD causes a mismatch between the cortically selected step size and the step size reported by the basal ganglia (22). The muscle receives conflicting information since the motor cortex, unaffected by PD, sends an automatic gait with a certain step size that has been learned over time, while the basal ganglia, affected by PD, send faulty information. This dysfunction between the basal ganglia and motor cortical areas generates information incompatibility and results in a set of motor disorders that cause hypokinesia, reduced movement size and gait speed, a short step pattern with reduced amplitude, and a value of strength insufficient to start or continue the step.

The next hypothesis is that FOG is associated with the generation of abnormal gait patterns. Nieuwboer et al. (77) concluded that freezing of gait is caused by a combination of increasing inability to generate a standard stride length. The hypothesis of the generation of abnormal gait patterns considers the abnormalities in the space-time characteristics of the gait just before the FOG episode (78). Studies analyzed the steps that precede the FOG and showed that there is a cumulative loss of range of motion in addition to changes in cadence and abnormal activation of the tibialis anterior and gastrocnemius muscles (70, 127, 78, 77).

Anticipatory Postural Adjustments (APA) are related to the activation of postural muscles before the disturbance occurs and are triggered in order to minimize the effects of a predicted disturbance (107). Therefore, another FOG hypothesis is that the postural adjustment system of patients with PD is impaired because, with the variability of the steps, the muscles receive contradictory information before the stride. Jacobs et al. (47) showed that multiple anticipatory postural adjustments (APAs) produce knee tremors and cause difficulty in movement planning, and that FOG associated with a subsequent loss of balance may be caused by the inability to couple normal anticipatory postural

adjustments during walking.

FOG is more likely to occur when the person with PD performs more complex or lengthy motor skills than simple, isolated movements, such as repeatedly lifting one leg (72). Multiple hypotheses have been raised to explain the mechanism of the FOG symptom in PD, but the authors have not found a consensus, and there is no model that universally explains the occurrence of the episode (13).

2.9 Qualitative assessment of freezing of gait

Freezing of gait is still a poorly understood phenomenon (94), and its pathophysiology is still not clear enough (12). For the clinical assessment of FOG, three methods are frequently reported in the literature and used in clinical practice. The evaluation applies the MDS-UPDRS Part III, the TUG test (Timed Up and Go), which is a specific test for gait, and the questionnaire to assess freezing of gait, the New FOG-Q.

The clinical assessment of FOG is included in the MDS-UPDRS, the most widely used clinical scale to assess PD (34). In item 2.13 of Part II of the MDS-UPDRS, from Motor Experiences of Daily Life (M-EDL), the evaluator asks the patient if during the last week, on a normal day, there has been a blockage or sudden stop during walking, such as if the foot was glued to the floor. The response is a score from 0 ("No") to 4 ("Due to the FOG episodes, I need help walking"). In item 3.11 of Part III of the MDS-UPDRS, the motor examination, the gait assessment is performed while the patient walks away from and approaches the examiner, so that both sides of the body are observed simultaneously. The patient should walk at least 10 meters, then turn and return to the evaluator. The evaluator looks for hesitations at the beginning and hesitations in the movements, mainly when turning around and reaching the end of the task. The rater scores the patient's gait from 0 (no block) to 4 (patient freezes several times while walking in a straight line).

It is important to note that Part II of the MDS-UPDRS has 13 items and Part III has 18 items in total, so there are 2 specific items for the FOG assessment out of 31. The MDS-UPDRS has the advantage of being available for the majority of physicians; However, it requires experience and may not reveal FOG even for cases confirmed by medical history (94). The FOG assessment in the MDS-UPDRS is not an accurate representation, and this is a consequence of the FOG being often difficult to observe during a clinical visit (64).

The TUG test (Timed Up and Go) is a clinical evaluation that was created in 1991 (92) and consists of recording the time required for the volunteer to stand up from a chair, walk three meters, turn around with a U-turn, return the same way, and sit down (114).

The New Freezing of Gait Questionnaire (New FOG-Q) was developed by Nieuwboer (77) in a study that updated the first Freezing of Gait Questionnaire (FOG-Q) by Giladi (32, 33). In Brazil, the questionnaire was validated by Baggio (87) and is suggested

in the Brazilian Version of the European Physical Therapy Guideline for Parkinson's disease. The New FOG-Q is divided into three parts. The first part distinguishes between individuals with and without gait freezing with just one question: "Have you had episodes of gait freezing in the last month?". The second part has five items that assess the severity of frozen gait with scores ranging from 0 to 4. The last part has three questions that consider the impact of frozen gait on daily life, with scores ranging from 0 to 3.

The disadvantages of these methods are mostly observed when they are replicated in real-life situations compared to controlled laboratory conditions. For example, people with PD who score high on the New FOG-Q in their daily routine are not necessarily those most predisposed to experience FOG during clinical trial protocols (114). Therefore, researchers have made attempts to find a suitable method to evaluate and monitor FOG objectively rather than using only the subjective testing methods of clinical evaluations (2).

Close supervision is important to monitor the progression of PD, so people with PD should visit the neurologist every few months. During the visit, the physician assesses the patient by asking him to perform a set of specific MDS-UPDRS activities. The information gathered by the specialist is subjective as it is limited to one session every few months; in addition, the physician's assessment may be influenced by the patient's mood or atypical behaviors that day. As with other symptoms, FOG should be monitored to assess disease progression. Tools to measure FOG in PD during a clinical visit can generate objective data to improve clinician assessments (106).

2.10 Quantitative assessment of freezing of gait

Objective evaluations provide more complete data as a means of supporting medical decisions (21). Quantitative assessments can measure treatment strategies and characterize a movement and should be used in parallel with clinical assessments. Mechanisms of a disease that are affected by a given drug, such as FOG in PD that is affected by levodopa, must be recognized by means of an appropriate biomarker in order to increase the chances of successful treatment (52). Furthermore, there must be a way to measure the efficiency of the compensation strategies addressed in movement rehabilitation (82).

Advances and improvements in the computational power of small devices allow smart sensors to be widely used to assess movement disorders. Wearable sensors are a tool to assess motor symptoms such as FOG in PD (115). The advantage of using wearable sensors to collect movement data is the possibility of application in real-life environments (115). Although several studies have used wearable sensors to detect gait disorders, such as FOG, there is no agreement on the most effective system design, i.e., sensor type, number of sensors, sensor placement on the body, and algorithm used in signal processing to detect FOG (115).

In recent years, wearable devices have received a lot of attention because they are based on detection activities and are able to differentiate individuals with Parkinson's disease from individuals with other neurological disorders, as well as from healthy elderly people. The popularity of wearable devices is due to their usability and low cost (115). The literature proves the possibility of monitoring wearable devices outside the clinical environment. The problem with people using wearable devices on their own is that use by PD patients and FOG is unreliable, and PD patients can experience memory loss and dementia (115). To use wearable sensors outside the controlled clinical environment, users must place the sensors in the correct position. The flexibility of using this technology on its own can cause variations in data capture and impact the quality of the gait assessment. The main sources of variation in the collected data are the sensors, the mounting location, the mounting side, and the speed of executing movements (115). There are many factors that affect data capture by wearable sensors outside the controlled clinical environment; Some studies use Kinect to analyze the gait and detect FOG of people with PD at home, they show positive feedback for domestic usability, but with limitations in outdoor use (29, 8).

In the field of FOG detection, the variable Freeze Index (FI) extracted from the vertical linear acceleration of the leg stands out. Moore et al. (70) have proposed a technique to identify FOG episodes using power spectrum analysis of the vertical linear acceleration of the shank, the Freeze Index (FI). FI is defined as the ratio between the power in the freeze band (3–8 Hz) and the power in the locomotor band (0.5–3 Hz). Thus, the Freeze Index can be found by dividing the frequency range of the wave during FOG by the frequency range of normal walking, in other words it is possible to find FI, which informs the severity of the FOG episode, when performing a transform from the time domain to the frequency domain and calculating the spectral density of the signal. The literature shows that the frequency band during FOG is 3-8 Hz and the normal walk is 0.5-3Hz. Bachlin et al. (11) updated Moore's FOG detection algorithm, proposing a lighter architecture in which acceleration data from three sensors attached to the body were transmitted to a wearable computer through wireless Bluetooth and introducing a new term called Power Index (PI), which is the sum of the freeze band and locomotor band; PI indicates the amount of movement during walk (74). FOG episodes in predictions systems are then determined using two thresholds, the Freeze Index Threshold (FTH) and the Power Index Threshold (PTH).

FI was compared with several other features as show the literature (91, 24, 20). This includes cadence algorithms (24, 20), features in time domain as mean, standard deviation, entropy, variance, harmonicity and predictability (74, 91, 106). Nevertheless, FI is a reliable parameter to detect FOG and it could be associated to different methods in order to detect walk patterns modification.

Coste (24) compared two algorithms to detect FOG, one is the Moore-Bachlin algo-

rithm and the other is FOG criterium algorithm, based on cadence. The authors showed that the FI is capable of detecting FOG monitoring changes in the signal power spectra. A similar work was conducted by Capecci (20), in which the authors aimed to compare the cadence obtained from the second harmonic of power spectrum density with FI and PI. The results showed that these features are capable of detecting FOG with more sensibility and specificity than the cadence algorithm. Cadence is important to analyze for gait changes detection, for example to characterize FOG and festination gait.

Pham (91) compared the Freeze Index (FI) with an alternative FI analysis, the Freeze Index using Koopman operator for spectral analysis (FIK) and with a set of 244 features, including mean, standard deviation, entropy, energy and others. Results showed that the common FI is one of the best features in saliency, clusterability and robustness. Further conclusion is that multiple channels increase the reliability in FOG detection and the vertical acceleration of the hip sensor was the best choice for better detection performance in the study.

San-Segundo (106) extracted four feature sets and used classification algorithm to elucidate the best combination for a better FOG detection performance. The first set included mean, standard deviation, variance, entropy, power in the freeze and locomotor band, Power Index and Freeze Index. The second feature set gathered 90 features on time and frequency domain. The third set was the Mel Frequency Cepstral Coefficients. The fourth set was harmonicity and predictability on time and frequency domains and spectral flux. They got the best results using random forest classification algorithm for the first data set.

In this context, quantitative evaluation studies that propose the use of different types of sensors, generate objective parameters with data acquisition, and combine the parameters in order to obtain a more accurate data when analysing the gait corroborate with the creation of biomarkers to assess gait and FOG in PD (99).

2.11 Solutions for freezing of gait

There is limited but growing evidence on movement rehabilitation in the management of freezing of gait (72). Nonnekes et al. (82) presented an overview and classification of the many available compensation strategies to contribute to the understanding of the underlying mechanisms for treating freezing of gait and to aid in the development of focused rehabilitation techniques. In all, seven main categories were highlighted: inside track, outside track, changing mental state, changing balance condition, adapting a new locomotion pattern, using alternative ways to walk, and using legs in other ways to move forward.

Internal cues suggest that people with PD use cognitive control to walk, using strategies such as mindfulness and mental rehearsal (72). External cues such as auditory and

visual cues temporarily reduce FOG (72). Through the study by Sijobert (114), the feasibility of using a method such as electrical stimulation as a somatosensory cue to improve gait was proven. The aim of the study was to investigate the ability of this feedback model to prevent or reduce FOG events and improve gait performance. Another solution presented to try to reduce the occurrence and duration of freezing of gait in people with PD is the use of a Rhythmic Auditory Stimulation (RAS) (115). A RAS device can generate a continuous rhythmic sound, which interferes with the force to perform the movement and improves motor perception and stride timing, or a punctual stimulus, which produces a rhythmic sound as an auditory cue to help the patient maintain or resume normal driving when FOG is detected.

For safety reasons, patients with FOG episodes are not advised to use a standard walker (25), but there are walkers that project a laser line on the floor that works as a visual cue to help with walking. There are simpler visual cues, as a white tape glued to the floor to represent lines and help the patient to walk (72). Auditory cues are more effective than visual cues. However, there is no gold standard for assessing the effect of different FOG interventions, which considerably limits comparative studies (72). In addition, most patients do not adhere to these more elaborate technologies that can attract attention.

Altering the state of mind is about increasing motivation and trying to recognize and manage anxiety and fear of falling. A strategy to alter the balance condition is to make wider turns when turning while walking (82). And to adapt a new pattern of locomotion, PD patients can use a variety of strategies to compensate for gait deficits, such as walking while bouncing a ball or crossing legs while walking (82).

Another category of compensation strategies is adapting an alternative way to get around, such as raising the knee a little higher than usual, shuffling like roller blading, or jogging (82). Some patients report that they cannot walk forward, but they can walk backward or sideways. Other ways of using the legs to move forward include riding a bicycle or scooter, for example (82).

Learning compensation strategies can help patients find an alternative that best matches their individual needs, preferences, and health care and include these in their therapeutic arsenal. Compensation strategies do not have the same effect in each patient and can sometimes worsen gait performance. This suggests that each supraspinal structure involved in the locomotor network is not affected to the same extent in all individuals and that neural reduction reserved for patients with gait problems creates a fine line between the induced compensation and its benefits (82).

A FOG diary is an interesting alternative to clarify the precise FOG circumstances of an individual. Similar to a fall diary, in which the patients write down every time they fall, a FOG diary should be encouraged by the therapists. The fall diary is the preferred method of fall monitoring (4); therefore, a FOG diary should be advantageous as well.

Translated into clinical practice, this implies that all PD patients should be educated

and informed about available compensation strategies and that, in conjunction with an experienced therapist, the optimal compensation strategy for that specific individual should be identified. These evaluations should not be limited to one occasion and should be repeated if the strategy loses effect over time (82).

2.12 Conclusion

This chapter presents an overview of Parkinson's disease and its manifestations and focuses on the gait disfunctions in PD, such as the Freezing of Gait.

The aim of the thesis is to extend the approach of FOG assessment by observing different gait parameters and determining which FOG-provoking strategy most significantly influences the gait of freezers and results in more FOG episodes. Therefore, previous concepts about the FOG hypothesis, FOG triggers, FOG qualitative and quantitative assessment, and solutions were needed.

The next chapter will present the experimental protocol and data acquisition process to complete the challenge to assess freezers in a controlled environment and elucidate the optimal combination of sensor, sensor placement, task, and feature to be extracted to identify gait changes in Parkinson's disease.

3

Experimental protocol and data acquisition

This chapter aims to elucidate the data acquisition process of this research by presenting the subjects, the clinical assessment, the four tasks, and the technology applied for data collection. The detailed experimental protocol is also presented in this chapter.

The purpose of data collection is to generate objective measures that are generalizable to a larger population. There was a time when data collection took place through questionnaires with predetermined response categories, medical records, or medical documents (56). Nowadays, several technological advancements have occurred to aid in obtaining more precise information from individuals, including the addition of quantitative measures for biological systems using various types of signal processing methods and sensors. There are significant opportunities for using data to improve medical practice, characterize the individual's features using a model centered on the patient, produce more efficient information and services, generate new knowledge, and drive innovation.

In this sense, data collection tools help to get a clearer picture of a patient's health, manage information quickly, and share it with other researchers.

3.1 Introduction

The study was conducted according to the guidelines of the Declaration of Helsinki, and all protocols were approved by the Ethics Committee (CAAE: 38885720.3.0000.5152) of the Federal University of Uberlândia, Brazil. Informed consent was obtained from all subjects involved in the study. The experiment was performed in a place destined for the clinical care of Parkinson's disease patients.

This work presents a method based on wearable sensors and the analysis of inertial sensors, three triaxial accelerometers, and three triaxial gyroscopes, to characterize the gait of individuals with PD who have the FOG symptom, individuals with PD who do not have the FOG symptom, and healthy individuals without PD.

Four mobility tasks were performed by the participants, and the data were annotated by an expert in gait disorders in Parkinson's disease using video recordings synchronized

with the signals from the inertial sensors.

Data collection was carried out at *Associação Parkinson Triângulo* (APT), an institution that offers free activities for individuals with PD in the city of Uberlândia. The APT environment is welcoming for volunteers who already participate in weekly activities there and has ideal environments to carry out the clinical evaluation and the data collection.

Participants with PD were selected using convenience sampling. The invitation to the research was made personally during a momentary activity break during the hours of physiotherapy at the APT facilities. After the individual agreed to participate, the researchers scheduled a specific day and time for data collection according to the availability of the volunteer and the research group.

Participants with PD were informed in advance that, to participate in the experiment, they should not take the first levodopa medication of the day and arrive at the APT during the OFF-medication state, which means more than 12 hours without taking levodopa. One day before data collection, researchers reminded the volunteers about their need to be in an OFF-medication state.

3.2 Subjects

Thirty subjects were enrolled if they met the eligibility criteria and signed informed consent prior to the study. They were divided into ten PD patients with a history of FOG Parkinson's disease patients with history of Freezing of Gait (GFOG+), ten PD patients age-matched with no history of FOG Parkinson's disease patients with no history of Freezing of Gait (GFOG-), and ten age-matched controls Control Group (GC). There are six female and four male participants in each group. The PD participants had idiopathic PD and were able to walk unassisted during the OFF-medication state.

The number of participants, ten volunteers in each group, was defined according to previous studies related to the FOG analysis (70, 74, 91, 10). The criteria for inclusion in the GFOG+ group are: (1) participants who were diagnosed with PD clinically; (2) Hoehn and Yahr Stages 2 or 3; (3) PD patients who showed gait disturbances of FOG; and (4) Age between 50 and 76 years old. The inclusion criterion for the GFOG- group is the same as for the GFOG+ group, except for the existence of the gait disturbance of FOG. The inclusion criterion for the GC group was age because the healthy participants needed to be age-matched with the PD groups. The criteria for exclusion for the three groups are as follows: (1) presence of severe visual and auditory impairments; (2) presence of other associated musculoskeletal or neurodegenerative diseases; (3) use of medication that can cause vertigo or imbalance; (4) Mini Mental State Examination (MMSE) showing evidence of cognitive impairments (102, 12).

The evidence of cognitive impairment is a Mini Mental Status Examination (MMSE) score less than nine (12, 102). A total score of 30 on Mini Mental indicates no cognitive

impairment, and scores between 26 and 30 are considered normal. People who score between 25 and 20 have mild cognitive impairment; those scoring between 20 and 10 have moderate cognitive impairment; and scores between 9 and 0 denote severe cognitive impairment, indicating problems with all basic activities.

3.3 Research Group

The execution team for data acquisition had five researchers, one physiotherapist to perform the clinical assessment on the participants; one researcher was responsible for explaining and obtaining the informed consent form from the participant, organizing the environments in which data collection was carried out; charging the devices necessary to perform data collection; controlling the sensors and light during data collection; transferring the data to the computer; and confirming that the inertial signals are coherent. Another physiotherapist accompanied the participants during the physical mobility tasks to prevent falls and increase safety. This professional did not interfere in the performance of the tasks but provided support to the patient if necessary. The fourth researcher was placed close to the existing wide-opening in tasks 3 and 4 to increase safety and avoid an adverse event in case the volunteer lost balance and bumped into the wide-opening. This person was also responsible for playing the audio track and annotating the drawn number for task 4. The fifth researcher was responsible for filming the tasks performances.

3.4 Clinical Assessment

An experienced physiotherapist confirmed the OFF-medication state of the participant with PD before the clinical examination. Then, the subjects completed several questionnaires to measure their clinical characteristics. The mini mental state examination MMSE assessed cognitive functioning; the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) measured daily living activities (Part II) and the severity of motor symptoms in PD (Part III) [51], and the New Freezing of Gait Questionnaire (New FOG-Q) was used as a subjective measure of freezing of gait severity [81, 95]. Those are methods frequently reported in the literature and used in clinical practice.

The New FOG-Q was applied only to the GFOG+ group because the participants in the GFOG+ group had a FOG history with different severity and frequency [96]. The New FOG-Q score informs the subjective perception of the severity and impact of FOG on gait performance (55). Therefore, the FOG history of the GFOG+ participants was investigated and its severity was rated using the New Freezing of Gait Questionnaire (new FOG-Q) (102, 64, 14, 77, 130).

The GC group, people without PD, completed only the MMSE before data collection.

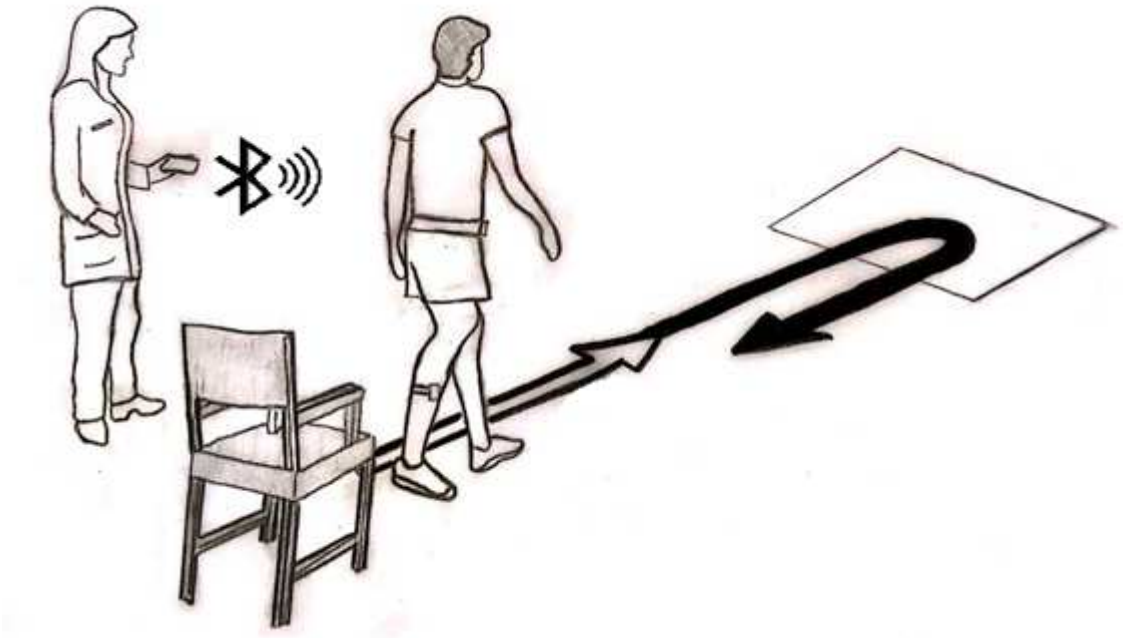

Figure 3.1 – Representation of the TUG test. The individual stands up from the chair, walks three meters, executes a 180 degree turn in the center of a squared tape on the floor, returns to the chair and sits

3.5 Mobility tasks for data acquisition

Patients were asked to perform four different physical mobility tasks: task 1 is the voluntary stop, task 2 is the TUG test, task 3 is a physical mobility motor task, and task 4 is a physical mobility dual task. Figure 3.5 presents the study design.

3.5.1 Voluntary Stop

In the voluntary stop, task 1, the subject [1] stands up from a chair, [2] walks three meters, [3] stays standing for 10 seconds, [4] executes a 180-degree turn, [5] returns to the chair, [6] completes another 180-degree turn, and [7] sits down; The voluntary stop is a modified version of the Timed Up and Go test in which a 10 second standing position is added to compare the voluntary stop with the involuntary stop (FOG event) (72).

3.5.2 TUG test

Task 2 is the Timed Up and Go test (TUG), the golden standard physical mobility task for gait analysis in PD. This test has been applied in several studies that address the FOG symptom (5, 80, 133, 114).

To complete the TUG test, the subject [1] stands up from a chair, [2] walks three meters, [3] executes a 180-degree turn, [4] returns to the chair, [5] completes another

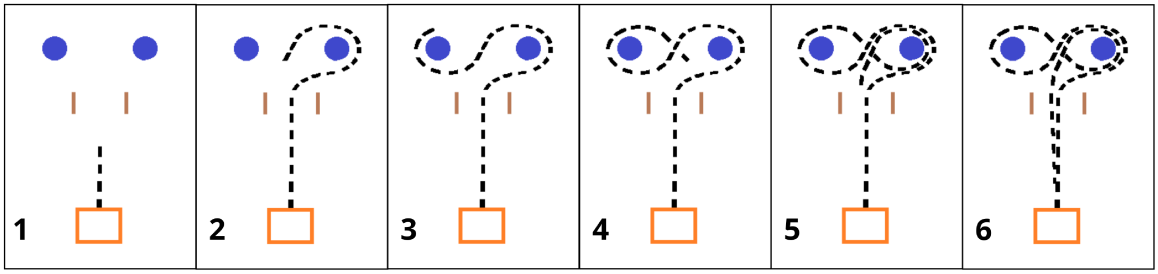

Figure 3.2 – Movement execution for the physical mobility motor task

180-degree turn, and [6] sits down. As shown in Figure 3.1.

Figure A.1 shows the environment in which tasks 1 and 2 happened in the APT facilities: the voluntary stop and the TUG test, respectively.

3.5.3 Physical mobility motor task

In the physical mobility motor task, task 3, subject [1] stands up from the chair, [2] walks three meters, [3] passes through a wide opening of 67.5 cm, and [4] moves 1.3 meters to contour two obstacles, forming a path in the shape of infinite. [5] Initially, the subject performs a 360 degree turn to avoid the obstacle located on the same side as the most affected body part, as determined by the physical therapist during the clinical evaluation; [6] the volunteer then moves toward the second obstacle and performs a complete 360 degree turn to avoid it; [7] he moves in the direction of the first obstacle and executes a second 360 degree turn to avoid it; [8] He returns to the direction of the wide opening again; [9] walks on the way to the chair; [10] completes another 180-degree turn, and [11] sits down. Figure 3.2 shows the movement execution for the physical mobility motor task. The task is complete once the subject is seated in the chair (81).

Task 3 was presented to the volunteer before data collection for familiarization. The volunteer, with the help of a physiotherapist, went through the path of the motor task once before data collection with the inertial sensors. Figure 3.3 presents the physical mobility motor task environment.

3.5.4 Physical mobility dual task

Task 4, the physical mobility dual task, is to execute the same sequence of movements showed in Figure 3.2; the patients perform the same motor task described in task 3 while performing the Digit Monitoring Task (DMT) (13), in which a random integer number (from 1 to 9) is assigned to each volunteer and the researcher instructs the volunteer to silently count, without using fingers, the number of times the digit is announced over a loudspeaker (81, 13).

The audio track (Figure 3.4) was identical for all participants, and it was transcribed so that the researcher had access to the correct digit. For each trial, a digit from the set

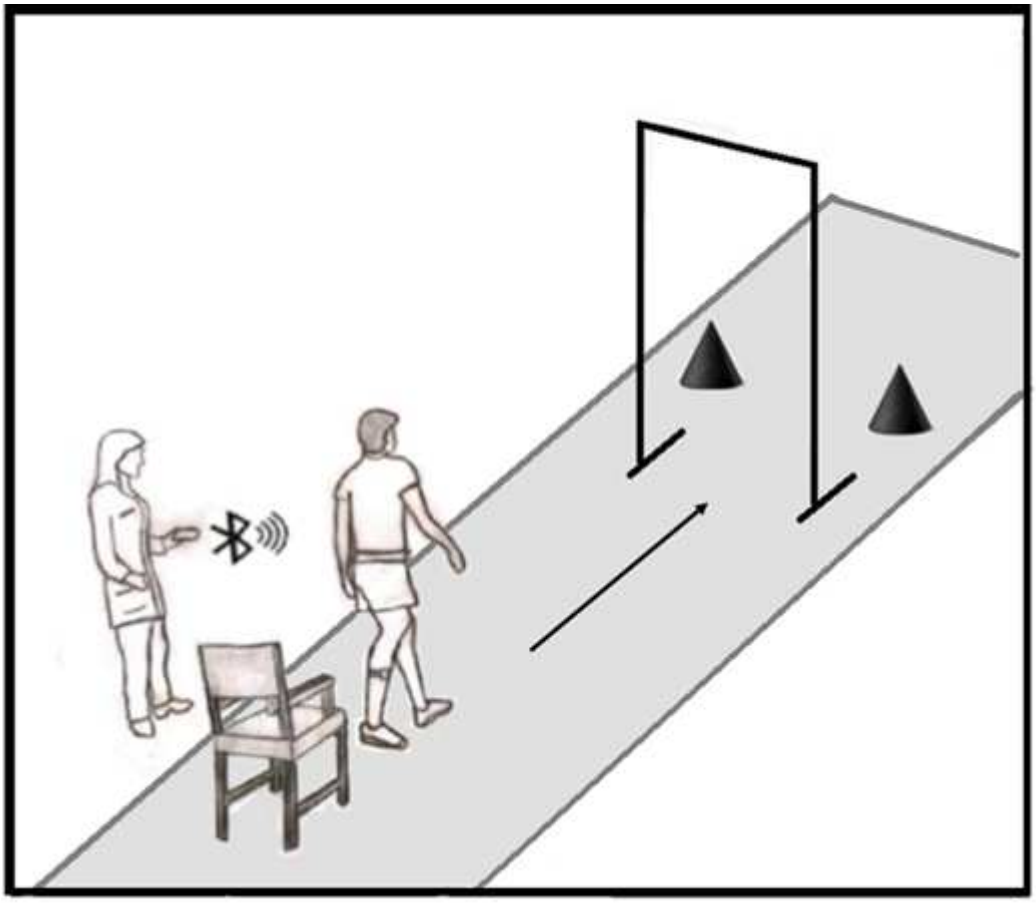

Figure 3.3 – Representation of the simple physical motor task that induces FOG in a controlled environment

of 1 to 9 was drawn without replacement.

At the end of the experiment, the researcher asks the participant how many times he heard the drawn digit. The entire data collection is recorded for later verification of the results, to check the volunteers' responses and compare them with the actual number of times the digit appeared in the audio.

To prevent gait synchronization with the audio track, the interval between auditory stimuli ranged from 100 to 1000 milliseconds (13). The duration of the audio was sixty seconds, which is the average time required to complete the proposed physical mobility motor task. Participants were instructed to continue counting the digit even if they completed the motor task prior to the conclusion of the audio.

The DTM cognitive task was presented once to the volunteer before data collection; the objective was to teach the volunteer how to successfully complete the cognitive task. Figures A.2, A.3, and A.4 show the environment in which tasks 3 and 4 took place.

Tasks 3 and 4, the physical mobility motor task and dual task, can induce FOG in freezers using known triggers of FOG episodes in a controlled environment (81). The development of these tasks is further explained in Chapter 5.

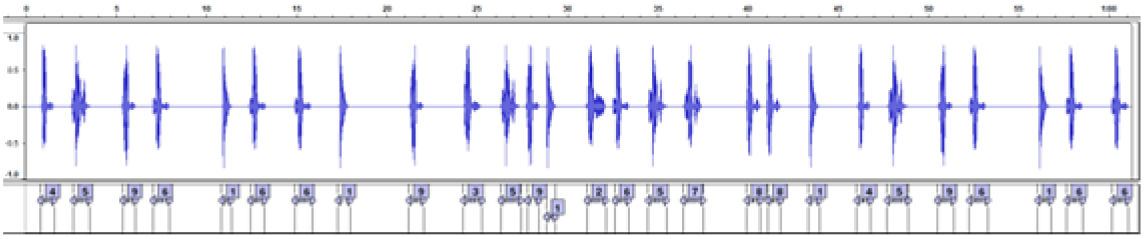

Figure 3.4 – Screenshot of Audacity. The audio track is shown (top) together with the digits (bottom). This audio track was used for all dual-task trials. The duration of the track is sixty seconds

3.6 Technology used in data acquisition

Inertial sensors are the gold standard in the literature for motion studies (88, 14, 21, 19). According to Bertoli (14), inertial sensors represent a powerful tool to perform movement analysis and allow researchers to investigate complex locomotor patterns, with which they are able to gather additional insights about motor control. The proposal for a quantitative evaluation is related to the quality of the evaluations, considering the meticulous and imperceptible changes in the qualitative evaluation and the promising results they can offer.

The movement disorder Monitoring System (NetMD) (57) allows for the analysis and monitoring of movement disturbances remotely and continuously through inertial signals. It was used to acquire motion data from participants while they performed the four tasks of the experimental protocol. NetMD is based on the combined action of an Android mobile phone with three smartwatches (Smartwatch 3 SWR50 model, from Sony), with communication established via Bluetooth, as presented in Figure 3.6.

Through this system, it is possible to acquire inertial signals from the 3D accelerometer and 3D gyroscope coupled in each smartwatch with a sampling frequency of 50 Hz and a temporal resolution of 20 milliseconds. These sensors are sensitive to acceleration and angular velocity, allowing for monitoring of almost all human physical activity in three dimensions (x, y, and z). The x axis is the horizontal axis (side-to-side axis), the y axis is the vertical axis (longitudinal axis), and the z axis is the depth axis (anterior-posterior axis).

The resulting files with data of linear acceleration and angular velocity are stored in txt files on the Android mobile phone and are available for copying to the computer so that it is possible to process them in RStudio (122).

Distractions can significantly increase gait variability in PD (70); however, the smartwatches used to monitor walking are unobtrusive, small, and lightweight (5 cm x 2.7 cm x 1 cm and 38,65 g), so they did not interfere with locomotion. Figure 3.7 shows the three smartwatches and the smartphone with the NetMD app running.

NetMD was developed by a group of researchers from the Centre for Automation and Robotics (CAR) of the Higher Council of Scientific Research of the Polytechnic University

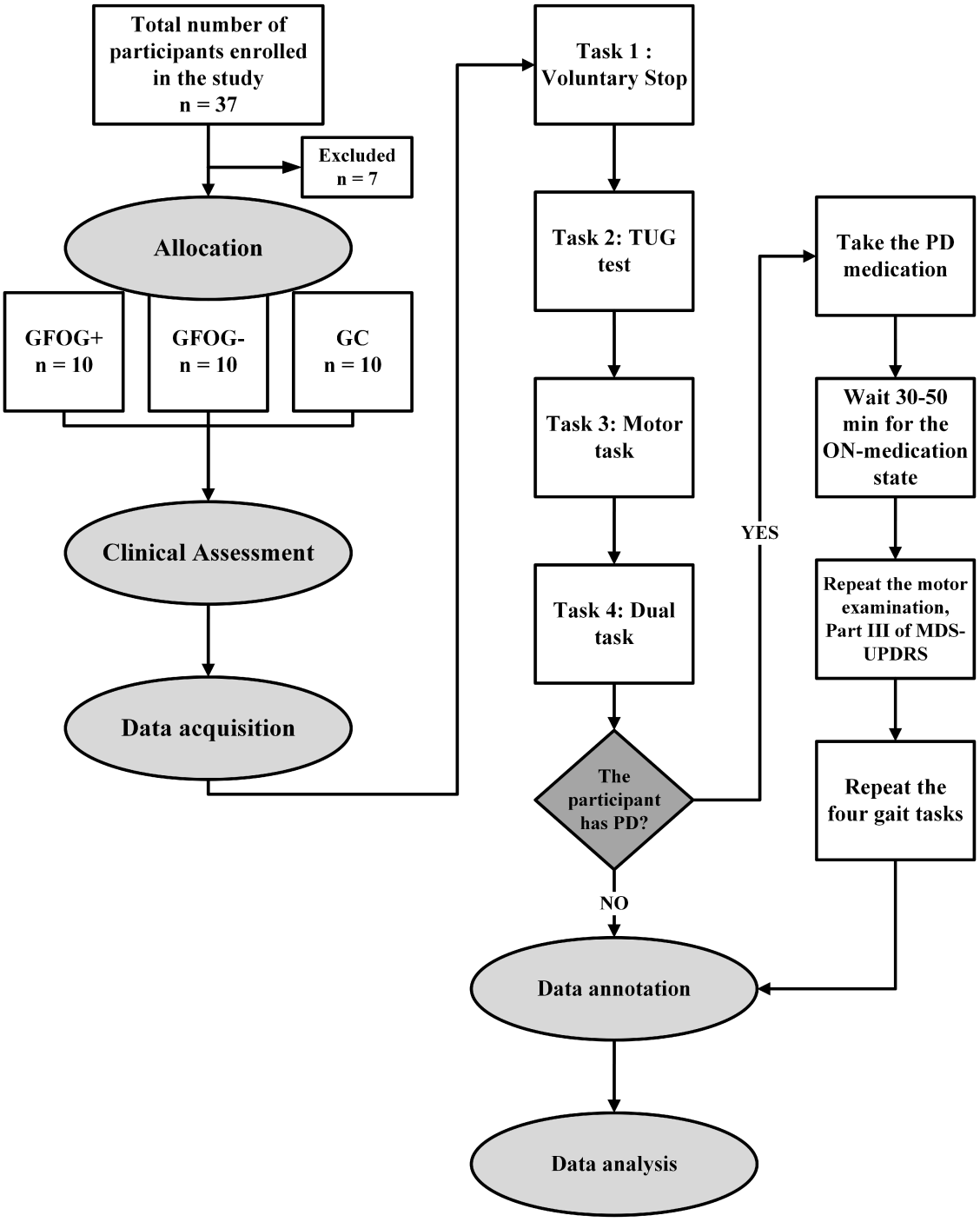

Figure 3.5 – Study design showing the total number of participants and their allocation. The experimental protocol consists of the clinical assessment and the data acquisition using camera and inertial sensors while the subjects execute four gait tasks. The collected data were stored, annotated, and processed for data analysis

of Madrid (CSIC-UPM) and it is not a system for sale. This technology was used to stablish the partnership and collaborative research between the developers and the Centre for Innovation and Technology Assessment in Health (NIATS) of the Federal University of Uberlândia (UFU).

Three smartwatches with wireless inertial sensors were used, each smartwatch goes

Figure 3.6 – Representation of NetMD system with three smartwatches and one cell phone, the technology used to collect data

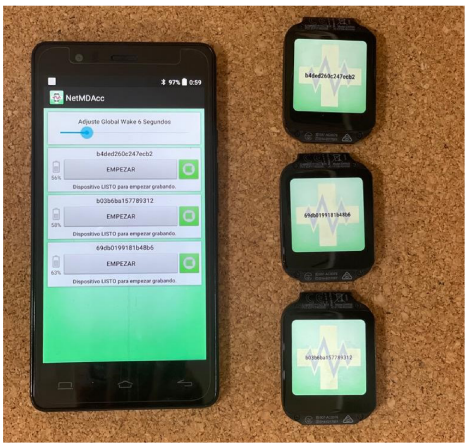

Figure 3.7 – NetMD application running in the three smartwatches that have the inertial sensor coupled and the cellphone that controls the smartwatches

Figure 3.8 – The two belts with the smartwatches cases for the hip and shank.

inside a case. The cases were attached to two adjustable belts. One belt is attached to the participant's hip, positioning the smartwatches over the iliac crests: smartwatch 1 goes over the right iliac crest, and smartwatch 2 goes over the left iliac crest. The other belt goes on the shank, and the smartwatch 3 goes on the leg under the knee, on the side most affected by PD, as identified during the clinical examination.

Figure 3.8 shows the belts and the case built specifically for the smartwatches and printed with a 3D printer, and Figure 3.9 shows the position of each smartwatch. Figure 3.10 shows the front and back views of one smartwatch that composes the NetMD system.

Figure 3.11 shows an overview of the technology and materials used for the data

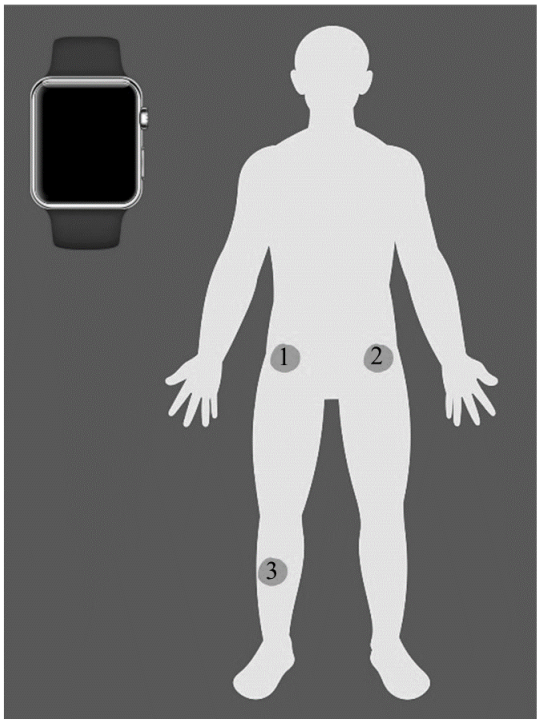

Figure 3.9 – Location of the smartwatches attached on the participant's body. Two IMU positioned on the iliac crest and one on the shank.

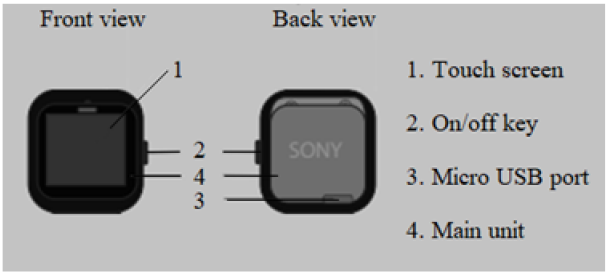

Figure 3.10 – Representation of front and back view of one smartwatch of NetMD system.

collection. The cellphone is used to control the smartwatches and store data from the inertial sensors coupled to each smartwatch.

A smartphone camera was used as an environmental sensor because several studies have proven that videotape data acquisition is very useful for movement analysis and assessment (21, 20). Therefore, the environment in which the experimental protocol was conducted had a camera positioned to capture all the pathways. Each video presents a complete task starting and ending in a sitting position (20). The video recordings were synchronized with the inertial sensors, so the task events and FOG episodes could be manually annotated using the software ATLAS (67).

Figure 3.11 – Smartwatches, belts, and cellphone for data collection

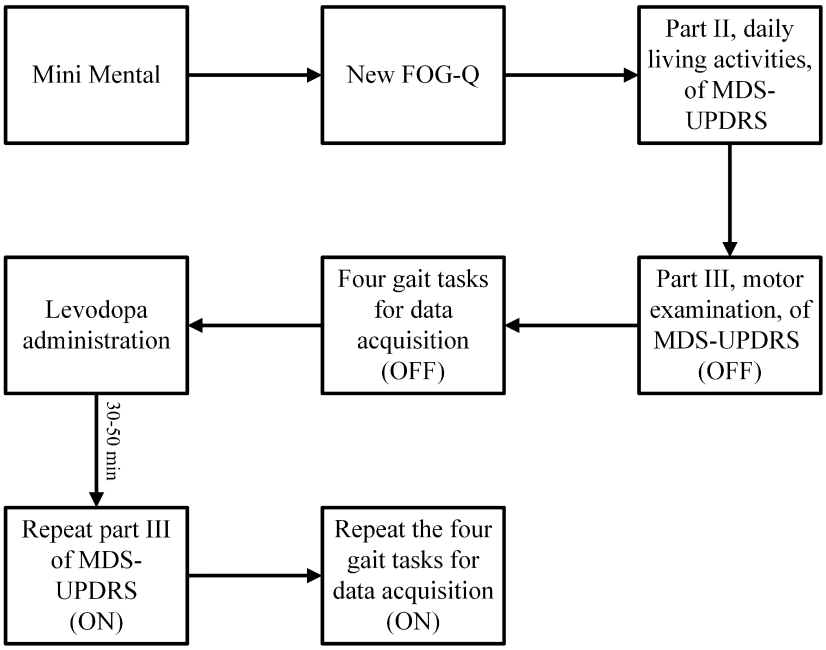

Figure 3.12 – Experimental protocol for the GFOG+ group, people with PD with FOG.

3.7 Data acquisition during the ON-medication state

The experimental protocol was performed during the OFF and ON medication states (12, 40, 77, 117) which was determined by patient feedback and the clinical assessment of the physiotherapist familiar with the volunteers with PD. The individuals with PD were in the OFF-medication state before levodopa administration and reached the ON-medication state 30–50 minutes after taking the medicine (70, 60).

The physiotherapist then repeats Part III of the MDS-UPDRS, and the PD participants repeat the four tasks for data collection. Figures 3.12, 3.13 and 3.14 show the experimental protocol for the three groups.

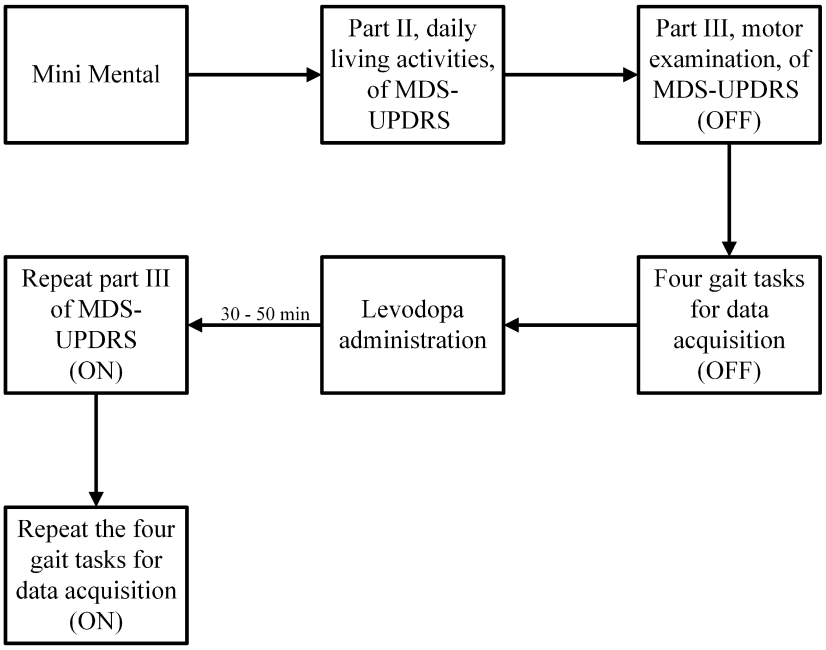

Figure 3.13 – Experimental protocol for the GFOG- group, people with PD without FOG.

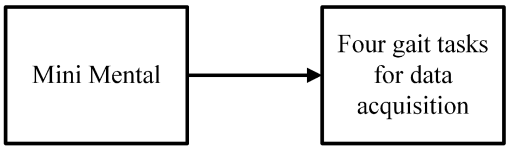

Figure 3.14 – Experimental protocol for the GC group, people without PD.

3.8 Results of clinical assessment

Tables 3.1, 3.2, 3.3 and 3.4 display the clinical characteristics of the volunteers. Table 3.1 displays the clinical characteristics of the GFOG+ group: sex, age, TD is the time of PD diagnosis in years, FOGQ is the New FOG Questionnaire (New FOG-Q) score, the Mini Mental Status Examination (MMSE) score, and the duration of the OFF-medication state in hours. Table 3.2 also shows information about the GFOG+ group with the MDS-UPDRS data, Part II is the MDS-UPDRS Part II score, the score of item 2.13 of MDS-UPDRS Part II, Part III OFF and ON are the MDS-UPDRS Part III score during the OFF and ON states of medication, and the total scores of MDS-UPDRS.

Table 3.3 displays the clinical characteristics and MDS-UPDRS results of the GFOG- group: sex, age, the time of diagnosis in years, the Mini Mental Status Examination (MMSE) score, the duration of the OFF-medication state in hours, the MDS-UPDRS Part II score, the MDS-UPDRS Part III score during the OFF and ON states of medication, and the total scores of MDS-UPDRS.

Table 3.4 displays the information about the GC group, sex, age, and the Mini Mental Status Examination (MMSE) score.

The GFOG+ participants (60.8 $\pm$ 7.48 years old) have been diagnosed with PD for

12.5 ± 5.75 years; their MDS-UPDRS Part II score is 17.1 ± 10.78, with a mean of 1.5 for item 13, "Freezing of gait". The MDS-UPDRS Part III score in the OFF-medication state is 57.5 ± 27.66, and the MDS-UPDRS Part III score in the ON-medication state is 41.7 ± 24.47. The new FOG Questionnaire (NFOGQ) is 19.2 ± 4.7, and the MMSE score is 25.5 ± 3.92. The GFOG- participants (65.1 ± 4.38 years old) have been diagnosed with PD for 6.9 ± 4.58 years; the MDS-UPDRS Part II score is 9.9 ± 3.75; the MDS-UPDRS Part III score in the OFF-medication state is 41.2 ± 15.51; and the MDS-UPDRS Part III score in the ON-medication state is 29.7 ± 14.27. The MMSE score is 26.6 ± 2.27.

Table 3.1 – Clinical characteristics of the GFOG+ volunteers, ten PD patients with a history of FOG. Information about the sex and age of the volunteers. TD is the time of diagnosis in years, FOGQ is the score of the new FOG questionnaire, MMSE is the Mini Metal score and Time OFF is the time in hours that the volunteer is without levodopa medication for the first part of data collection.

V	Sex	Age	TD	FOGQ	MMSE	Time OFF
1	M	50	15	14	27	12h
2	F	51	7	23	28	13h
3	M	57	15	19	15	13h
4	F	59	12	21	27	13h
5	F	63	10	23	26	13h
6	F	65	14	16	28	10h
7	F	66	25	15	24	13h
8	M	68	6	23	28	13h
9	M	73	6	26	27	12h30
10	F	56	15	12	25	13h30

Table 3.2 – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) results of the GFOG+ volunteers, ten PD patients with a history of FOG. Part II of the MDS-UPDRS is the daily life activities questionnaire and Part III is the motor examination. Item 2.13 refers to the FOG sign.

V	Part II	Item 2.13	Part III OFF	Part III ON	Total OFF	Total ON
1	18	2	62	50	80	68
2	16	2	49	39	65	55
3	21	1	51	26	72	47
4	10	1	20	7	30	17
5	12	1	53	32	65	44
6	6	1	35	37	41	43
7	22	2	94	57	116	79
8	9	1	49	37	58	46
9	44	3	115	100	159	144
10	13	1	47	32	60	45

The GC participants (64.7 ± 6.76 years old) completed only the MMSE (26.7 ± 2.21) test before the experiment.

Using the Shapiro-Wilk normality test, the distributions of the participants ages are not significantly different from the normal distribution; from the output (p-value > 0.05) of GFOG+ (p-value = 0.8674), GFOG- (p-value = 0.3105), and GC (p-value = 0.3998), we can assume their normality.

Table 3.3 – Clinical characteristics and MDS-UPDRS results of the GFOG- volunteers, ten PD patients with no history of FOG. Information about sex and age of the volunteers. TD is the time of diagnosis in years. MMSE is the Mini Mental score and Time OFF is the time in hours that the subject is without take the levodopa medication. Part II and Part III of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) represent the daily life activity questionnaire and the motor examination, respectively.

V	Sex	Age	TD	MMSE	Time OFF	Part II	Part III OFF	Part III ON	Total OFF	Total ON
1	M	59	8	26	13h	13	55	36	68	49
2	F	60	3	29	16h	9	21	7	30	16
3	F	62	3	27	18h	11	38	20	49	31
4	F	62	6	26	14h	4	24	24	28	28
5	M	63	15	23	11h30	14	66	56	80	70
6	M	67	14	23	14h	16	53	44	69	60
7	F	68	2	29	18h	5	31	25	36	30
8	F	69	8	26	12h30	9	54	35	63	44
9	M	70	7	29	12h	9	44	34	53	43
10	F	71	3	28	12h	9	26	16	35	25

Table 3.4 – Clinical characteristics of the GC volunteers, the Control Group. Information about the sex and age of the subjects. The Mini Mental score is the cognitive test used as eligibility criteria.

V	Sex	Age	MMSE
1	F	56	25
2	M	59	27
3	F	59	30
4	M	59	24
5	F	63	30
6	F	65	25
7	F	68	27
8	M	68	27
9	M	74	24
10	F	76	28

3.9 Conclusion

This chapter presents the experimental protocol for data acquisition to generate an open access database that could contribute to the development of new methods to assess individuals with Parkinson's disease with FOG history.

Information about the subjects, the research group, the clinical assessment, the mobility tasks, and the technology used for data acquisition is presented. As well as the results of the clinical assessment. These data are referenced in the studies that will be presented in chapters 5 and 6. The chosen method involves video annotation, and the amount of data arising from data collection is large and requires detailed and careful organization. Video annotation and the organization of the data will be presented in Chapter 4.

4

Data organization and data annotation

Data is a valuable resource that may be re-used ans combined indefinitely for a variety of purposes in healthcare. Collecting data and effectively managing information can be keys to patient engagement and care. Advances in data science mean that there are more ways to collect, manage, link, and analyze health and biological data in order to generate information for research.

The aim of this chapter is to elucidate the steps to complete the task event annotation process using the software ATLAS. The task events were manually annotated, and the inertial signal for each task event was labeled with the initial and final time.

The presentation, visualization, statistical tests, and data analysis were conducted using RStudio, a software that generates good visualization graphs and allows for the understanding of the signals. RStudio provides free and open-source tools for R and professional software ready for development work at scale (122).

The experiments presented in this study were recorded with a cell phone camera, and the ground truth was generated when the FOG episodes and task events were annotated by a researcher specialist in FOG using the videos and interpreting the inertial sensor signals (70, 60, 106). The responsible researcher watched and studied the videos and marked the beginning and end of each event that occurred during the experiment (20).

Figure 4.1 presents the possibilities that can happen in each task event during the mobility tasks, while the participant is performing a task event, the results can show the gait as (1) a normal gait, when the subject walks without interruptions; (2) a gait with continuous disorders, when the subject presents slow steps or gait variability; or (3) a gait with FOG events, when the subject freezes during the execution of the task event.

4.1 Data organization

Figure 4.2 shows the study design for the three groups and how the data acquired was stored in folders for later analysis. The groups GFOG+ and GFOG- carried out the experimental protocol during the OFF and ON medication states, while the group GC

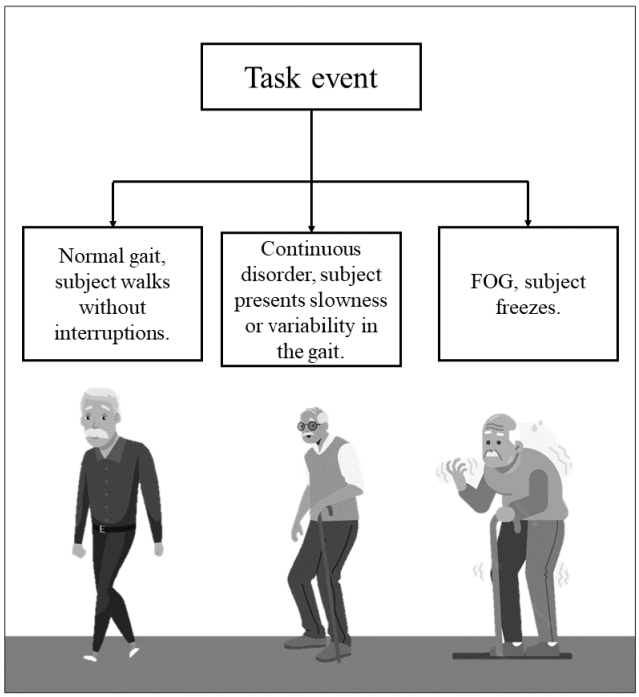

Figure 4.1 – The possible scenarios of patterns presented in each task event while the volunteers carry out the proposed activities.

performed the four tasks once. In the figure 4.2, Voluntary Stop (VS) represents task 1; TUG represents task 2, the TUG test; MT represents task 3, the physical mobility motor task; and DT is task 4, the physical mobility dual task. Figure 4.2 shows three trials for each task, which means that the task was performed three times so that the researchers could obtain a greater number of variables to guarantee a more robust statistical value to the research. S1, S2, and S3 represent the smartwatches; they were attached to the right iliac crest, the left iliac crest, and the shank of the side most affected by the disease, respectively. Each smartwatch gives information about the accelerometer and gyroscope on axes x, y, and z. Therefore, AX means accelerometer on the x axis, AY is the accelerometer on the y axis, AZ is the accelerometer on the z axis, GX is the gyroscope on the x axis, GY is the gyroscope on the y axis, and GZ is the gyroscope on the z axis.

To increase the signal resolution, the acquired inertial signals were interpolated using splines, increasing the sampling frequency to 100 Hz and the temporal resolution to 10 milliseconds. Figure 4.3 shows the time series for the z axis of the gyroscope located on the shank most affected by the PD. GFOG+ represents a volunteer with Parkinson's disease who has the FOG symptom; GFOG- represents a volunteer with Parkinson's disease who does not have the FOG symptom; and GC represents an age-matched healthy volunteer. Each task was completed during the OFF period (12 hours without PD medication) and the ON period (with PD medication). The graphs depict the angular velocity (rad/s) in the z axis for four tasks: task 1, the voluntary stop; task 2, the TUG test; task 3, the physical mobility motor task; and task 4, the physical mobility dual task.

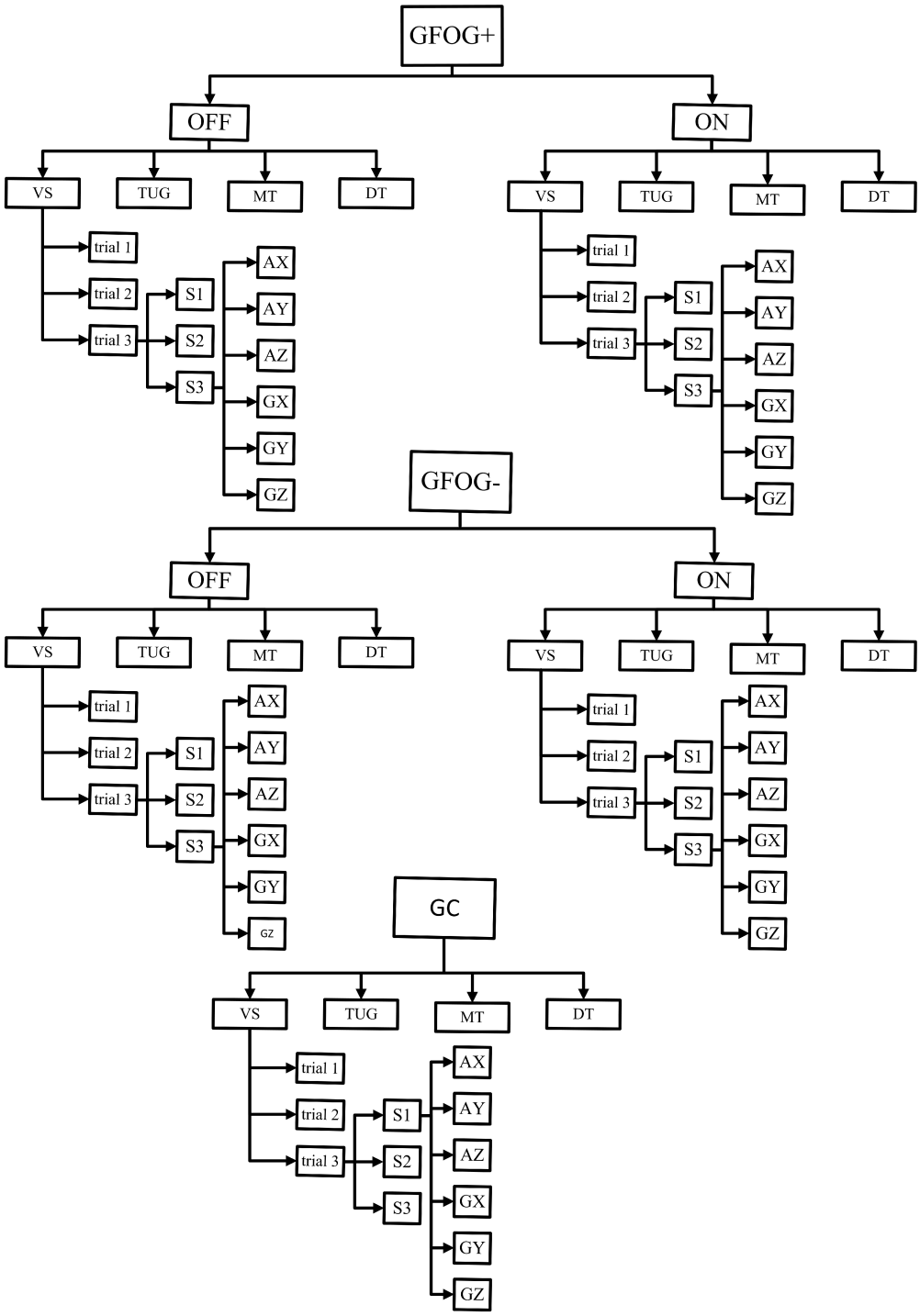

Figure 4.2 – The study design for the three groups, GFOG+, GOFG-, and GC. This figure also shows how the data acquired was stored in folders for later analysis.

4.2 Data annotation

Four gait tasks were performed by the participants, and the data were annotated by the researcher using the video recordings synchronized with the signals from inertial sensors.

The first step in any signal processing process is to understand the biological system

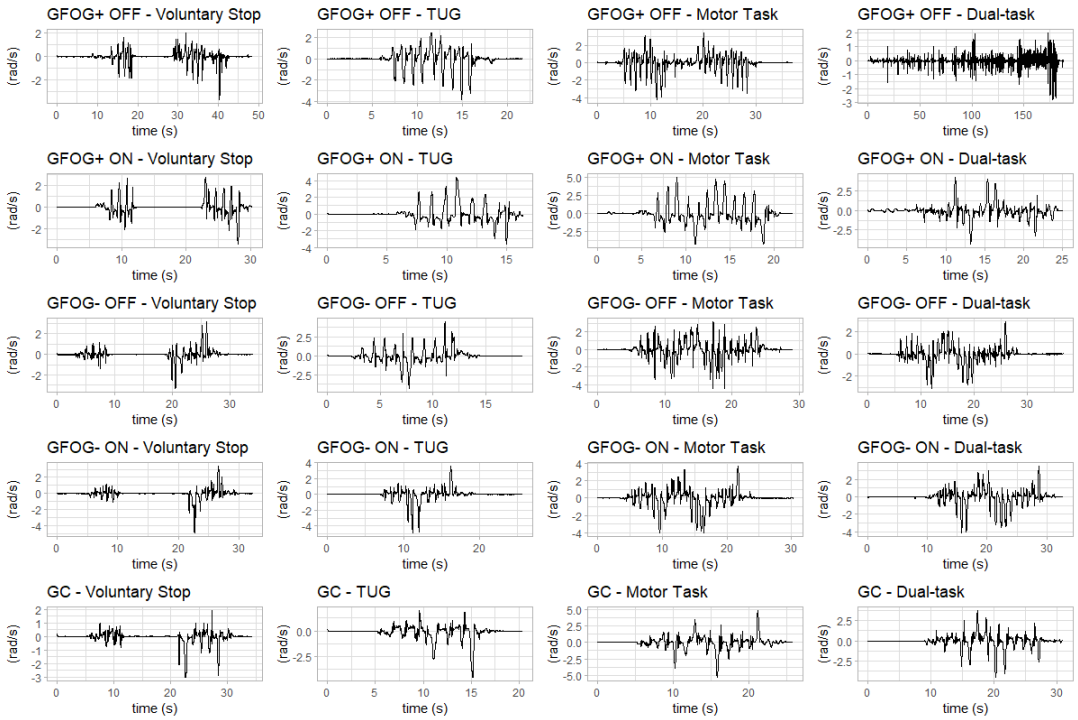

Figure 4.3 – Time series of the z axis gyroscope of the shank. An example from each group (GFOG+, GFOG-, and GC) of the four tasks that compose the experimental protocol, OFF and ON medication states are also presented.

responsible for generating the signals. Without this, it will not be possible to properly interpret the results and understand possible inconsistencies that may arise during the data analysis process (76). Biological systems are responsible for producing biomedical signals that reflect the state of the system; therefore, using inertial sensors while carrying out gait tasks as proposed by this study can show the state of gait performance in PD individuals with a history of FOG, PD individuals with no history of FOG, and individuals without PD, as shown in Figure 4.3.

Data annotation is the process of labeling data using human activity to tag the content in various formats such as video, images, audio, or text (35). The present study focuses on video annotation. Video annotation uses techniques such as bounding boxes to recognize motion frame-by-frame or using a video annotation tool, which is the method chosen for this work (35). The video annotation tool used is the Software ATLAS (67). ATLAS is a graphical tool for annotating multimodal data flows.

In a human-machine interaction scenario, in addition to multichannel audio and video inputs, various biophysiological data can be recorded. This allows viewing on the same screen one or more videos together with the collected signal (biomedical signal) in a synchronized way, showing a marker that slides through the signal simultaneously with the video display, as shown in Figure 4.4. So that the synchronization of the video with the collected signal can happen (67). Figure 4.4 shows the ATLAS software interface with one video of the voluntary stop, the signals of S1AX (accelerometer of smartwatch 1 on x axis),

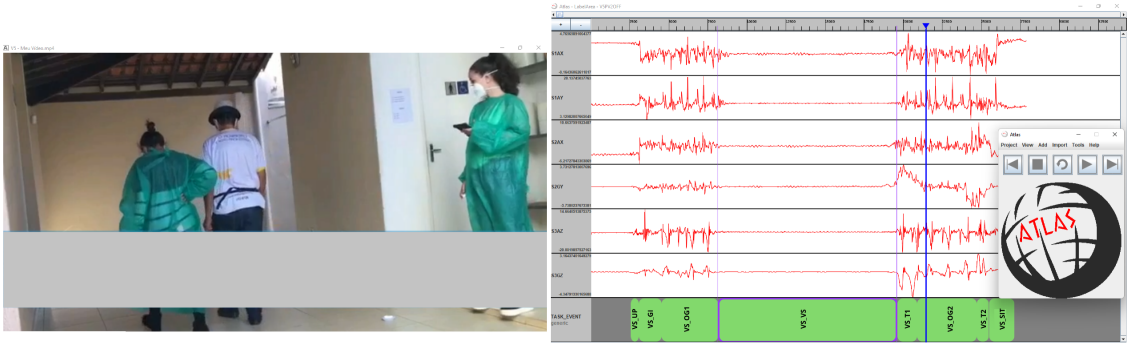

Figure 4.4 – ATLAS software interface showing one video of the voluntary stop and the signals of S1AX, S1AY, S2AX, S2GY, S3AZ, S3GZ. In the labels, VS_UP means the event to stand up from the chair, VS_GI is the gait initiation, VS_OG1 is the first open gait, VS_VS is the voluntary stop of 10 seconds, VS_T1 is the first turn of 180 degree, VS_OG2 is the second open gait, VS_T2 is the second turn of 180 degree, the turn to sit, and VS_SIT means the event to sit down.

S1AY (accelerometer of smartwatch 1 on y axis), S2AX (accelerometer of smartwatch 2 on x axis), S2GY (gyroscope of smartwatch 2 on y axis), S3AZ (accelerometer of smartwatch 3 on z axis), and S3GZ (gyroscope of smartwatch 3 on z axis); and the label for video annotation.

Task events of the gait that were annotated and their respective descriptions. Tables 4.1, 4.2 and 4.3 are related to the task events of each task of the experimental protocol.

The task events were manually annotated on ATLAS, and the inertial signal (accelerometer and gyroscope in x, y, and z axes) for each task event was labeled with initial and final time. This was possible because the researcher watched the video recordings

Table 4.1 – Task events of task 1, the voluntary stop.

Task events	Description
Stand up	The subject stands up from a chair.
Gait initiation	The subject completes the first step, which is the first two contacts of the foot with the floor after standing up.
First open gait	The subject walks three meters between the chair and square of tape on the floor.
Standing for 10 seconds	The subject stops and stays standing for ten seconds, the subject is advised when to turn by the researcher who is filming.
180-degree turn	The subject completes a 180-degree turn in place.
Second open gait	The subject walks three meters between the tape square on the floor and the chair.
Second 180-degree turn	The subject turns in place to be at the position able to sit in the chair.
Sit	The subject sits on the chair

and the inertial signal in synchronized form using the software ATLAS.

Figure 4.5 shows an example of a labeled signal for task 1, the voluntary stop. It is possible to see that the task has eight task events, according to Table 4.1 stand up, gait initiation, first open gait, ten seconds standing, 180-degree turn, second open gait, second

Table 4.2 – Task events of task 2, the TUG test.

Task events	Description
Stand up	The subject stands up from a chair.
Gait initiation	The subject completes the first step, which is the first two contacts of the foot with the floor after standing up.
First open gait	The subject walks three meters between the chair and square of tape on the floor.
180-degree turn	The subject completes a 180-degree turn in place.
Second open gait	The subject walks three meters between the tape square on the floor and the chair.
Second 180-degree turn	The subject turns in place to be at the position able to sit in the chair.
Sit	The subject sits on the chair

Table 4.3 – Task events of tasks 3 and 4, the physical mobility motor task and dual task.

Task events	Description
Stand up	The subject stands up from a chair.
Gait initiation	The subject completes the first step, which is the first two contacts of the foot with the floor after standing up.
First open gait	The subject walks three meters between the chair and the wide opening.
First pass through a narrow door	The subject walks through the door, which is approximately 40 cm before and 40 cm after the wide opening.
First turn	The subject contours the first obstacle with a 360-degree turn.
Second turn	The subject contours the second obstacle with a 360-degree turn.
Third turn	The subject contours the first obstacle again with a 360-degree turn.
Second pass through a narrow door	The subject walks through the wide opening for the second time.
Second open gait	The subject walks three meters between the wide opening and the chair.
Fourth turn	The subject turns in place to be at the position able to sit in the chair.
Sit	The subject sits on the chair

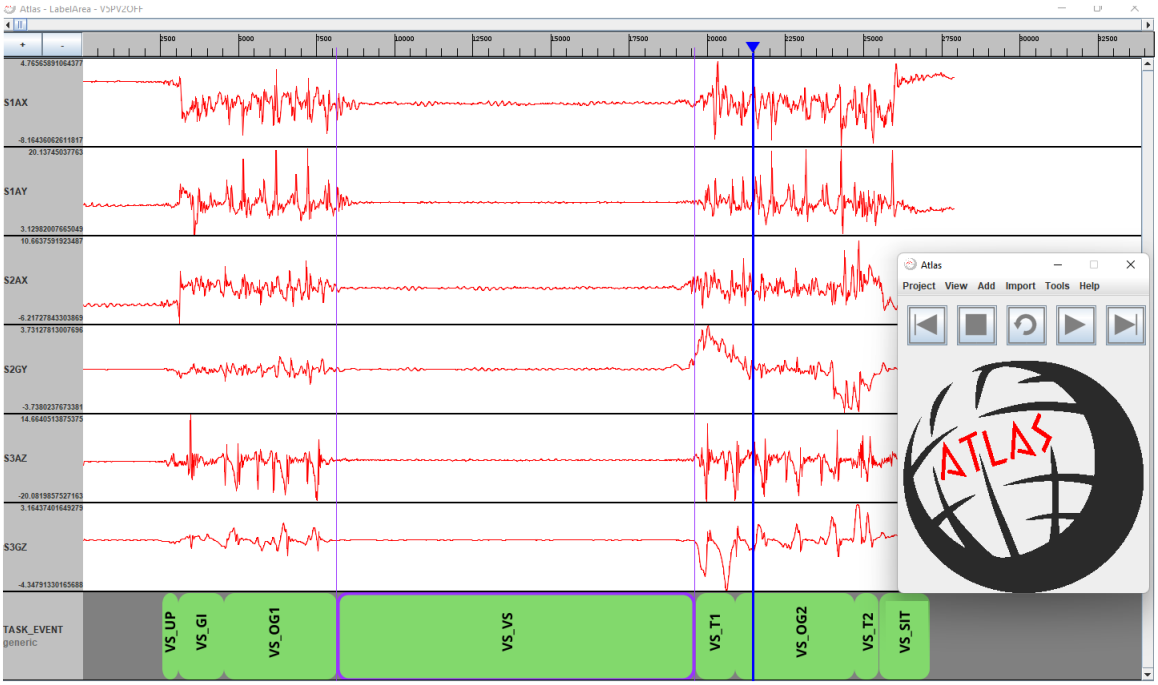

Figure 4.5 – ATLAS software interface with the signals of accelerometers and gyroscopes during the voluntary stop divided into eight events.

180-degree turn, and sit down.

To help the synchronization process, there was a pulse in the video recording, a LED tap light that is captured on the video turns on when the data collection with the inertial sensor starts. This LED tap light was controlled by a wireless remote. So, by pressing the remote button that manages the light simultaneously with the NetMD application button to control the smartwatches, we could create a marker to facilitate and guarantee the synchronization of the video and the inertial signals. The video needed to be cut according to the trials collected using the inertial sensors. The process of cutting the video was conducted using the software Wondershare Filmora. Wondershare Filmora provides free tools to create and edit videos with advanced features like keyframing and motion tracking.

Figures 4.6 and 4.7 show the ATLAS software screen with the video synchronized with the accelerometer and gyroscope in the x axis for the sensor placed on the left end of the iliac crest (S2AX and S2GX) and the label of the task events (TASK EVENT) with eleven labeled tasks, the eleven tasks shown in Table 4.3. In Figure 4.7, the subject is performing the open gait task event, walking three meters between the chair and the wide opening for the first time.

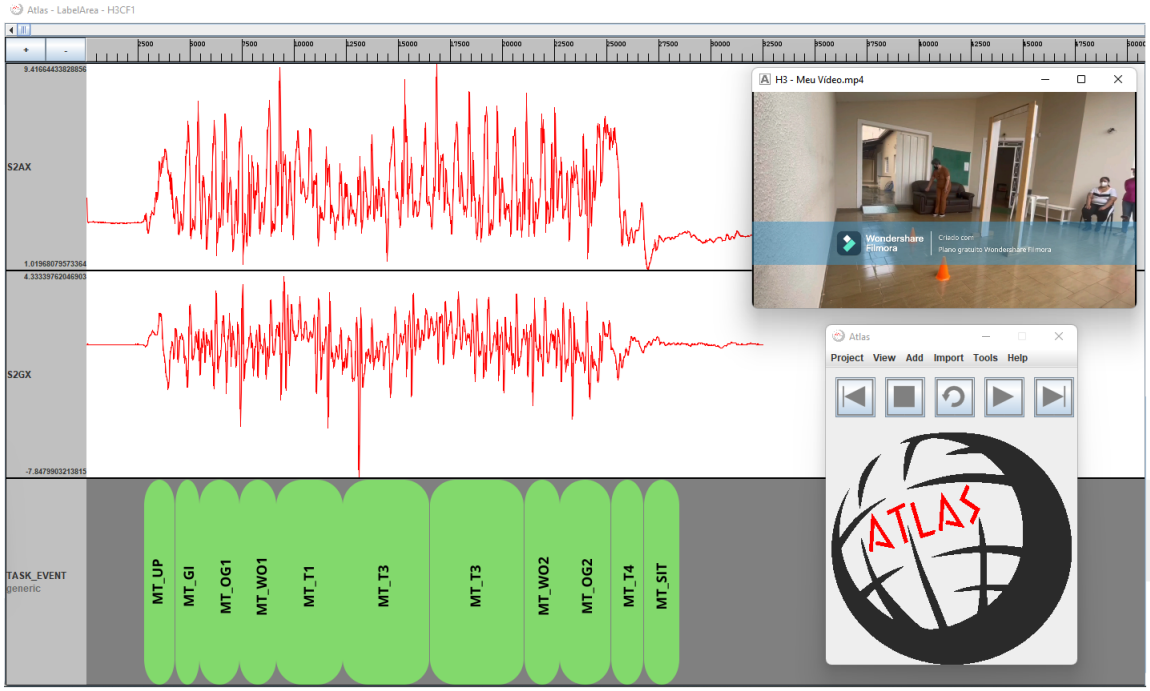

Figure 4.6 – ATLAS screen with the video synchronized of the motor task with the accelerometer and gyroscope in x axis for the sensor placed on the left end of the iliac spine (S2AX and S2GX) and the label of the task events (TASK_EVENT). In the labels, MT_UP means the event to stand up from the chair, MT_GI is the gait initiation, MT_OG1 is the first open gait, MT_WO1 represents to pass through the wide opening for the first time, MT_T1 is the first turn of 360 degree, MT_T2 is the second turn of 360 degree, MT_T3 is the third turn of 360 degree, MT_WO2 represents to pass through the wide opening for the second time, MT_OG2 is the second open gait, MT_T4 is the 180 degree turn, the turn to sit, and MT_SIT means the event to sit down.

4.3 Protocol for data annotation

Figures 4.8 to 4.14 represent the flow diagrams of the seven steps to complete the task event annotation process using the software ATLAS.

Figure 4.8 shows step 1: compress videos and organize sensor files for each trial. Video compression is important because, depending on the volume of information, processing may be slower, so it is advantageous to compress the video before inserting it into the program. It is possible to download a video compressor app for Android and iOS.

Figure 4.9 presents step 2, to separate video by trial using Wondershare Filmora software. The pulse as a LED tap light that is captured on the video turns on when the data collection with the inertial sensor starts was very helpful to complete this step.

Figure 4.10 shows the diagram flow of step 3, the creation of a project on ATLAS and filling the data track folder. In this step, it is important to plot the signal on RStudio and annotate the time for the initial movement, to stand up from a chair, for the three sensors (two on the end of the iliac spine and one on the leg) and highlight the shortest time, which is the sensor that was pressed first. This will be the inertial signal to be synchronized

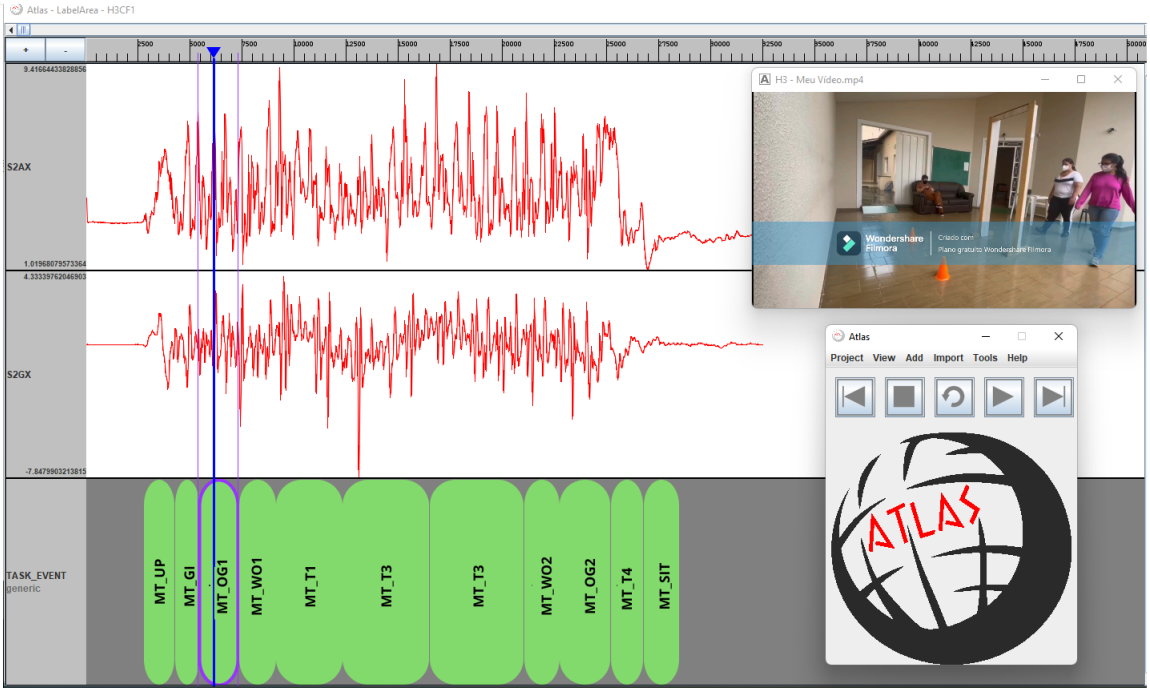

Figure 4.7 – ATLAS screen shows the blue cursor on the third task event, which means the first open gait, on the video the volunteer is walking from the chair to the wide opening.

initially with the video on ATLAS. The steps from 1 to 4 are very important to prepare the data for the analysis on ATLAS.

Figure 4.11 presents step 4: adding biomedical signals and video recording to data collection. This step shows how to add the biomedical signal and the video to the ATLAS project. It is important for the researcher to verify if the synchronism of both signal and video is correct; otherwise, changes can be made using the edit video software.

Figure 4.12 shows step 5, to add annotation labels with the name of each task event on ATLAS. This step shows where to press in ATLAS software to add a label and start the annotation data process. It is important to rename the labels with the respective task event. Figure 4.13 represents step 6, to annotate the initial and final tasks for each task event on ATLAS by simply clicking and dragging the label to the events' initial and final times.

Three sensors were used in the data collection, the last step, to cut the sensor signal, represents the effort to make the three sensor signals have the same initial movement time, to stand up from the chair.

Results show that the gait task used as a physical mobility task was capable of creating waveforms that could be discriminated. The task events for the four tasks could be manually annotated as follows: Task 1, the voluntary stop: (1) stand up; (2) gait initiation; (3) first open gait; (4) stop and stay standing for 10 seconds; (5) 180-degree turn; (6) second open gait; (7) second 180-degree; and (8) sit down. Task 2, the TUG test: (1) stand up; (2) gait initiation; (3) first open gait; (4) 180-degree turn; (5) second open gait; (6) second 180-degree; and (7) sit down. Tasks 3 and 4, the physical mobility

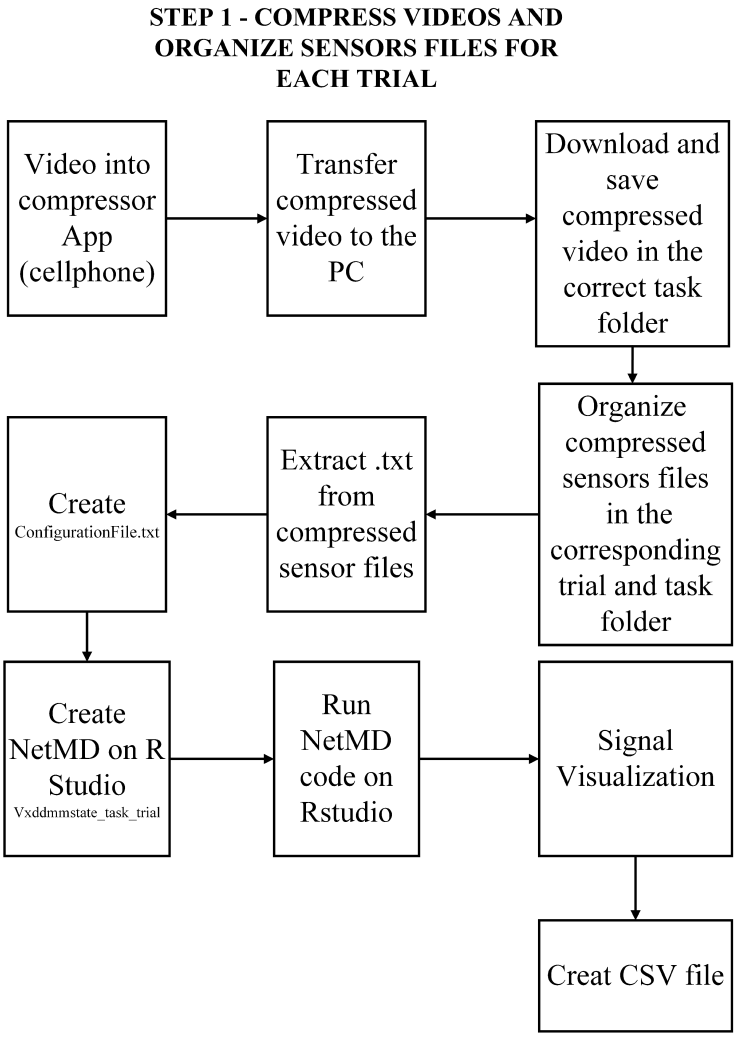

Figure 4.8 – Flow diagram presenting the Step 1, to compress videos and organize sensors files for each trial.

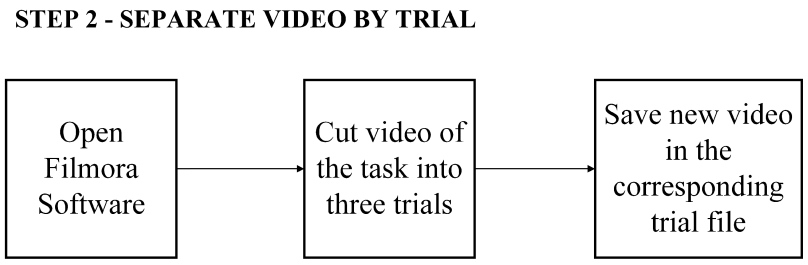

Figure 4.9 – Flow diagram presenting the Step 2, to separate video by trial using Wondershare Filmora software.

task, and the dual task: (1) stand up; (2) gait initiation; (3) first open gait; (4) first pass through a narrow door; (5) first turn; (6) second turn; (7) third turn; (8) second pass through a narrow door; (9) second open gait; (10) fourth turn; and (11) sit down. The difference between the physical mobility motor task and the physical mobility dual task is that, during the dual task, the participant performs the same motor task described in task 3 while performing a cognitive task; this is the reason the task events for both tasks

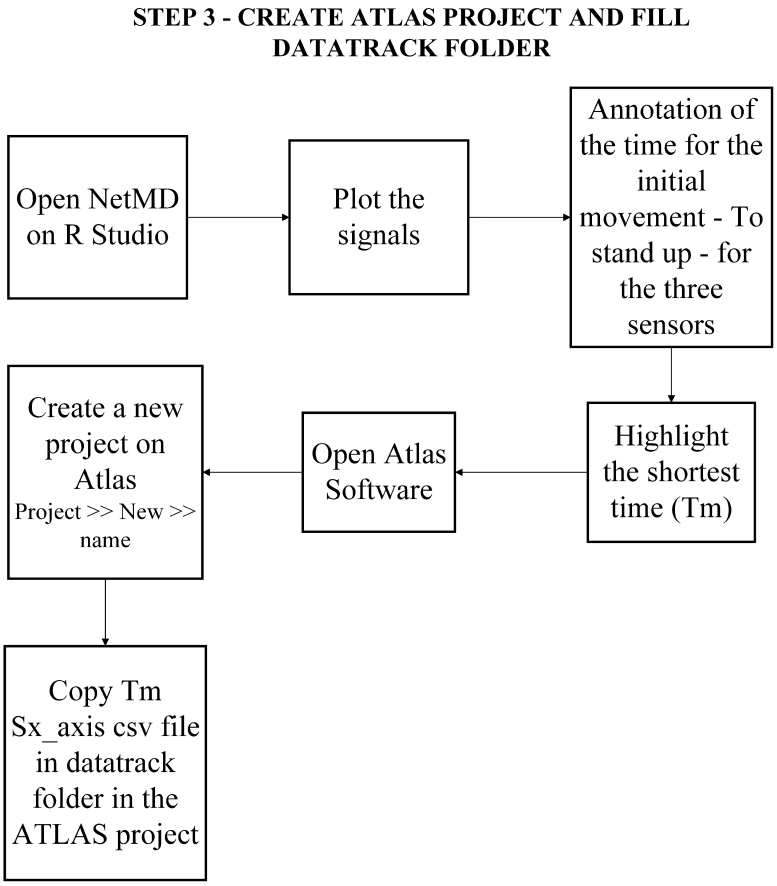

Figure 4.10 – Flow diagram presenting the Step 3, to create a project on ATLAS and fill datatrack folder.

are equal. This experiment shows that it is possible to annotate the task events of a data collection using synchronized video and signal tracks. The authors were able to elucidate the steps to complete the task event annotation process using the software ATLAS.

Figure 4.14 shows step 7: cutting the sensor signals using RStudio, the step that allows the annotation of each task event to be used in all collected signals.

The purposes, procedures, and benefits of quantitative evaluation of biological systems are well known and accepted by the academic community (56). Data video annotation as proposed here could be used as a tool to properly interpret the results, understand possible inconsistencies that may arise during the data analysis process, and understand the biological system responsible for generating the signals. The inertial signals and the video recording with a smartphone camera were used as input for the video annotation software presented in this study. This allowed the researchers to annotate the tasks and events of a data collection. As a result, the authors were able to elucidate the seven steps to complete the task event annotation process using the software ATLAS.

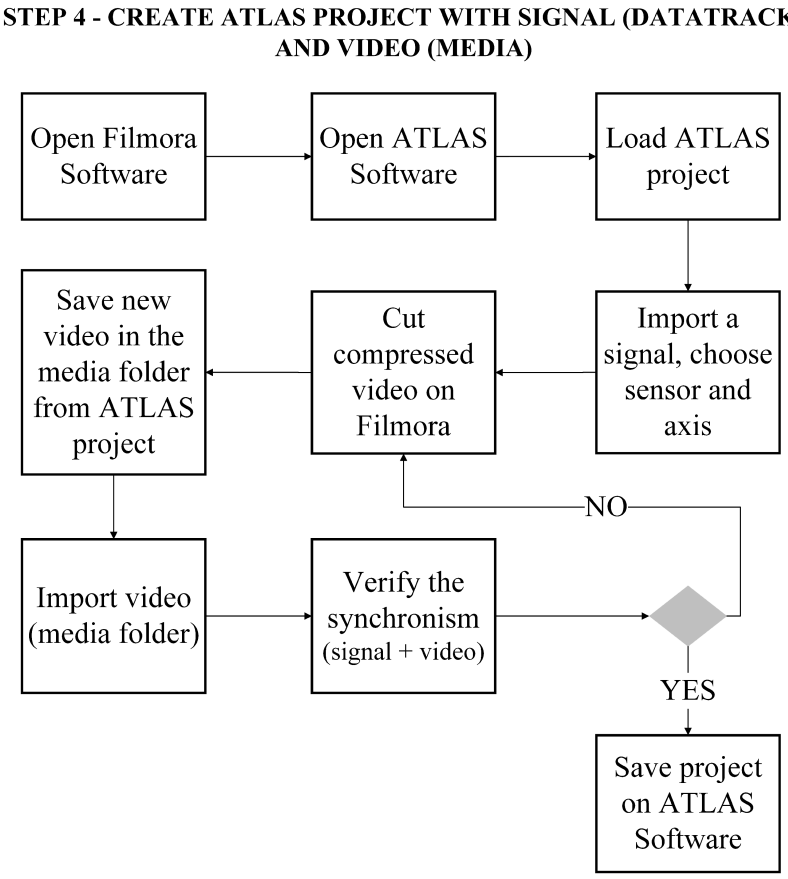

Figure 4.11 – Flow diagram presenting the Step 4, to add the biomedical signals and the video recording of data collection.

4.4 The topic of data annotation is discussed

Schaafsma et al. (108) also videotaped a gait task, and the video analysis was made by three observers who independently watched the task videotapes and elucidated the number of gait disturbance episodes called freezing of gait. The researchers clarify that using exclusively the video rating method, they might have missed the annotation for very brief gait-specific episodes (12). In the study of Popovic et al. (94), the gait analysis was carried out from three sources: videotapes, ground reaction forces, and accelerations.

The conclusion is that for efficient data collection, the correct methods of organization, processing, storage, and analysis are crucial. The first and most important stage of research is to choose methods that meet the needs and aims of the work, considering which information should be collected and the instruments needed.

There are a lot of opportunities for data use, as there has become a strong public interest in the responsible use of data to support the development of knowledge and innovation through scientific research concerning healthcare. These innovations aim to improve the well being of all through improved health advice, treatment, and care. The convenience offered by data annotation from biomedical signals includes getting a clearer picture of a patient's health, managing information quickly, sharing it with other researchers, under-

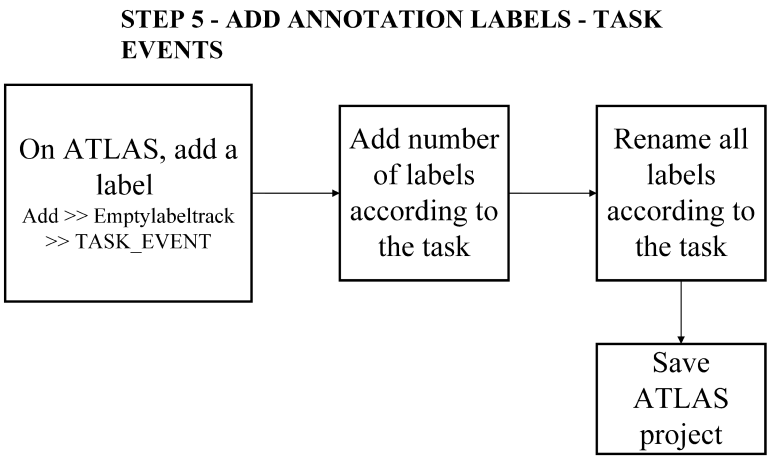

Figure 4.12 – Flow diagram presenting the Step 5, add annotation labels with the name of each task event on ATLAS.

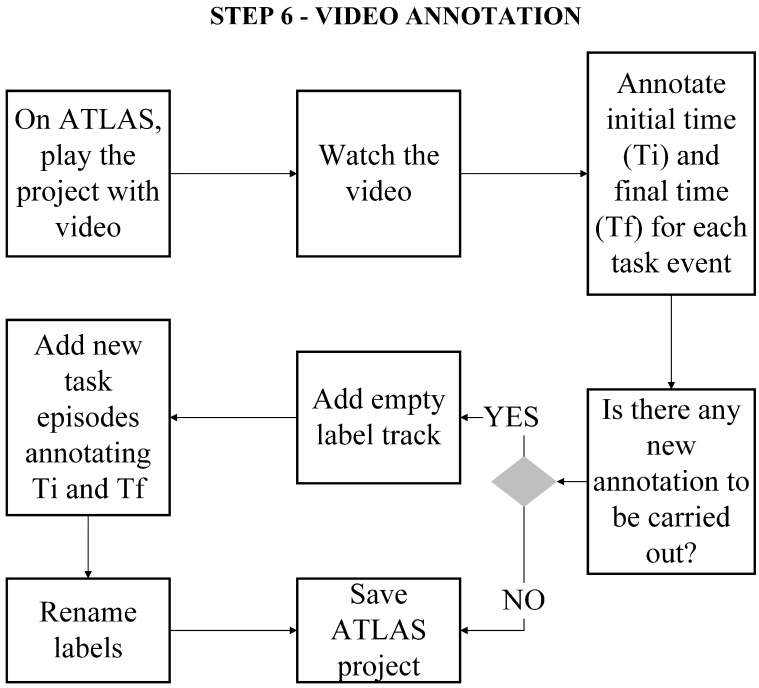

Figure 4.13 – Flow diagram presenting the Step 6, annotate initial and final time for each task event.

standing the biological system responsible for generating the signals, and interpreting the results during the data analysis process. This builds a stronger evidence base to predict, prevent, and treat disease, helping the development of new treatments or personalized treatments and care according to the individual's needs.

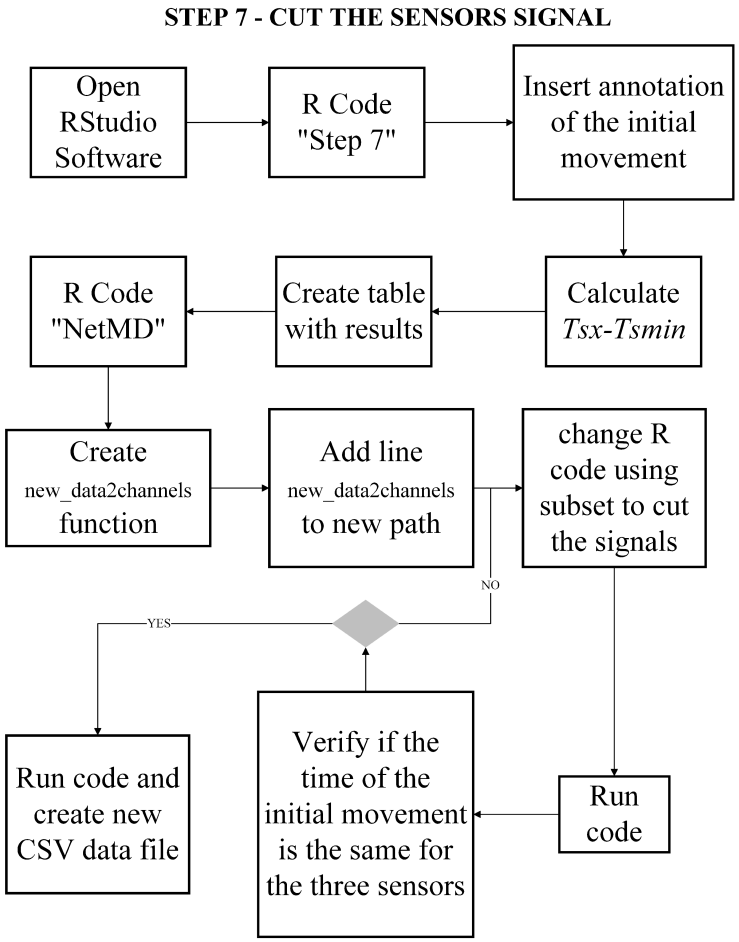

Figure 4.14 – Flow diagram presenting the Step 7, to cut the sensor signals using RStudio.

4.5 Conclusion

The system presented in this chapter has shown satisfactory results. The limitation of the study is the time spent carrying out the seven steps of a large data collection. As a conclusion, ATLAS software proved to be an efficient tool to help with signal visualization and comprehension. Results show that is is possible to annotate the task events of a data collection by accessing videos and the signals collected using inertial sensors in a synchronized way on ATLAS. The seven steps carried out to complete the task event annotation process were elucidated.

The conclusion of this phase of the work allowed to validate the proposed physical mobility task to assess freezers in Parkinson's disease, presented on Chapter 5, and to create a strategy for evaluating Parkinson's disease-related changes in gait, presented on Chapter 6.

It is important to highlight that data video annotation is a tool to properly interpret the results, understand possible inconsistencies that may arise during the data analysis process, and understand the biological system responsible for generating the signals. Video annotation was used to identify FOG episodes and the events of the gait tasks.

5

A novel physical mobility task to assess freezers in Parkinson's disease

The purpose of this chapter is to describe the development and validation of a physical mobility task that induces freezing of gait in a controlled environment, employing known triggers of FOG episodes according to the literature. To validate the physical mobility tasks, we recruited 10 freezers PD volunteers (60,6±7,29 years-old) with New FOG-Q ranging from 12 to 26. The validation of the proposed method was carried out using inertial sensors and video recordings. All subjects were assessed during the OFF and ON medication states. The total number of FOG occurrence during data collection is elucidated. The Inertial Measurement Unit (IMU) with accelerometer and gyroscope could not only detect FOG episodes but also allowed to visualize the three types of FOG: akinesia, festination and trembling in place.

5.1 Introduction

The need to assess physical mobility in clinical practice was raised by Podsiadlo and Richardson (92) in 1991, when the Timed-Up and Go (TUG) test using a time score in seconds was proposed to assess risk of fall in elderly populations. Similarly, our hypothesis is that it is possible to assess FOG episodes in freezers with a simple and short test, using limited space. Laboratory testing of gait motor abilities on sway platforms or treadmills are impractical in most clinical settings, due to their length and the complexity, furthermore, it is not profitable to use them in frail patients (92). The challenge to cause FOG in a controlled environment without the use of complex technologies and respecting the fragility and limitation of the PD patient came about because of its convenience. The objective of the current study is to develop a simple physical mobility task that induces FOG in a controlled environment using known triggers of FOG episodes as described in the literature in order to evaluate freezers in PD. Using Inertial Measurement Unit (IMU) with accelerometer and gyroscope and video recordings, the proposed method was validated.

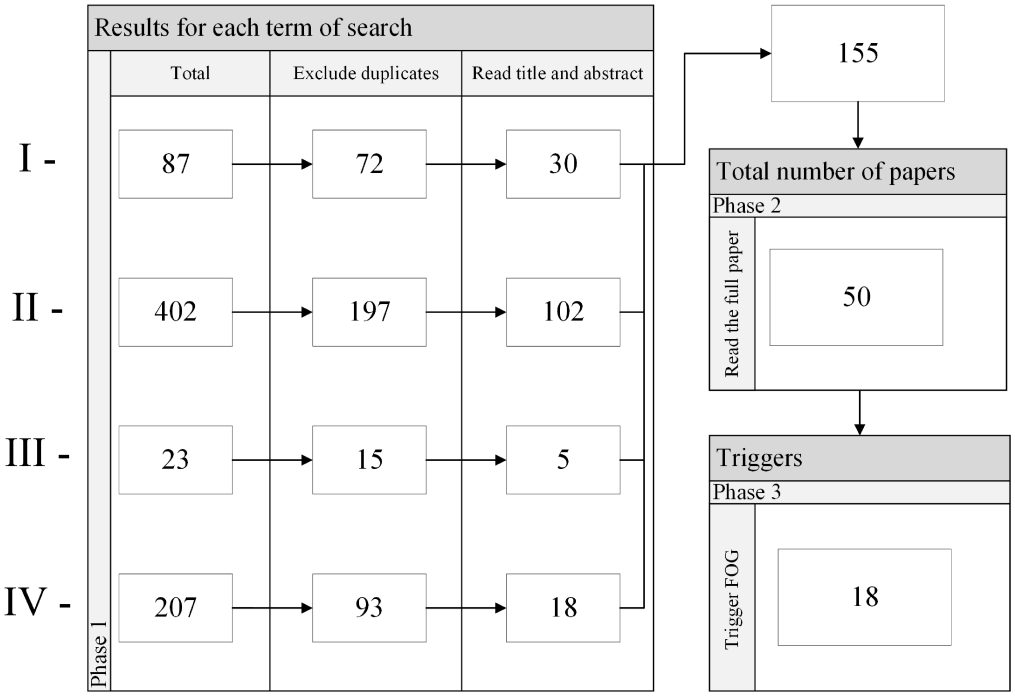

Figure 5.1 – Flow diagram depicting the strategy adopted for literature review. The search terms are identified by I, II, III and IV.

5.2 Methods

5.2.1 Literature review

The current study included a review of the literature on the assessment of FOG in Parkinson's disease. Our review was conducted to bring together the various methods used in related studies to cause FOG. The main databases used in our review were IEEE, Pubmed, Lilacs, and Medline. The following combinations of terms were used to maximize the scope and type of material referred in the search: (I) Parkinson (and) Freezing (and) Trigger (and) (clinic (or) clinical) (and) (pattern (or) standard); (II) Parkinson (and) Freezing (and) (clinic (or) clinical) (and) (behavior (or) conduct); (III) Parkinson (and) Freezing (and) Trigger (and) hypothesis; and (IV) Parkinson (and) Freezing (and) (different (or) distinct) (and) (clinic (or) clinical) (and) Cues. The search was carried in English.

5.2.2 Result of the literature review

Figure 5.1 depicts the flow diagram of the literature review. In Phase 1, the first column shows the total number of articles for each search term (i.e., I, II, III, and IV), the second column is the number of articles after excluding duplicates, and the third column is the number of articles left after reading the title and abstract. A total of 155 papers were fully read, and 50 studies were left to compose the literature review. Tasks

that could trigger FOG in a controlled environment are presented in 18 papers, from which all the motor triggers mentioned were included in the present study.

FOG is usually triggered by postural transitions (14); the triggers considered as possible ways to cause FOG according to the literature review are to sit and stand up from a chair, walk through a doorway, reach a destination, turn 180 degree and 360 degree, and carry out a dual task. The triggers considered in each study included in the literature review are shown in Table 5.1, column chair represents to sit and stand from a chair, column narrow doorway stands for walk through a doorway or a wide opening, RN is an acronym for reach a destination.

Table 5.1 shows 17 studies; it does not include the study of Saad et al. (105) because freezer volunteers were not recruited. For the experiment, healthy researchers simulated FOG during a walk. The following paragraphs describe the studies included in the literature review.

Velik et al. (126) and Alvarez et al. (6) aimed to continuously monitor the patient in daily life instead of triggering FOG in a controlled environment, and Muralidharan et al. (75), Shine et al. (111), Killane et al. (51), and Waechter et al. (128) used Virtual Reality (VR) to induce FOG episodes. The VR experiments that explain the effect of sensory and cognitive processes on FOG are usually setups in which the patient navigates through a series of doorways while simultaneously responding to a cognitive task (51, 75, 121, 128). The virtual reality results are generally shown in motor arrests, defined as an instance where the step latency is twice as long as the normal latency. This measure has a good correlation with the number of FOG episodes during the classic TUG test (75, 105). Although there is a real need to compare the behavior obtained by VR models with actual walking tasks, VR proved to be a reliable method to elicit FOG episodes in a controlled clinical test environment (51, 75, 112, 128). On the other hand, VR is an expensive technology, with previous training needed, and they compare results based on the behavior presented during the VR tasks, which simulate the effect of locomotion (75).

The literature review showed some studies (126, 6) that were carried out in a more spacious and wider environment with the aim of capturing and recording daily life motion and detecting FOG. In Velik et al. (126), researchers carried out an experiment where the subject executed a motor dual task by going to different rooms in a house carrying objects, such as hanging clothes in the laundry. The objective of the experiment was to quantify how sensory cues affect the duration of FOG episodes. To allow cueing, subjects wore a backpack with a small and lightweight laptop, which was remote controlled from another computer via Wi-Fi (126). FOG detection in Velik et al. (126) was made by an assistant experienced in the recognition of FOG episodes. This person would observe the volunteer performing the course and trigger a cue (auditory, visual, or vibratory) always two seconds after a FOG episode occurred. To detect FOG episodes, Alvarez et al. (6) used a Recurrent Neural Network (RNN). They extracted information from the trajec-

tories of a 360-degree panoramic camera (Zenith), an Red Green Blue-Depth (RGB-D) camera (Kinect), Wireless Sensor Network (WSN) sensors, inertial sensors (accelerometer, gyroscope, and magnetometer), and binary sensors placed on doors and drawers to detect when they are opened or closed (6).

To assess dual tasks abilities in patients with early stage PD, Zirek et al. (133) applied

Table 5.1 – Studies included in the literature review with triggers able to cause FOG episodes.

Paper	Chair	Narrow doorway	RD	180 degree turn	360 degree turn	Dual task
Schaafsma (2003)	X	X	X	X	X	
Bartels (2003)	X	X			X	
Jovanov (2009)	X			X		
Spildoren (2010)				X	X	X
Popovic (2010)	X	X		X		
Velik (2012)	X	X	X	X	X	X
Shine (2013)						X
Beck (2015)		X				X
Handojoseno (2015)	X			X		
Killane (2015)		X				X
Waetcher (2015)		X				X
Cando (2016)	X		X	X	X	
Tard (2016)						X
Bertoli (2017)				X	X	
Muralidharan (2017)		X				X
Alvarez (2018)	X	X	X	X	X	
Wang (2020)				X		
Present study	X	X	X	X	X	X

the TUG test under single and dual task conditions. The findings show that tasks that increase the demand for complex attention are more sensitive to showing impaired dual task ability. However, the referred study did not focus on freezers, in fact, one of the inclusion criteria was having a score of 3 or less in the New FOG-Q. Therefore, no FOG analysis was considered.

Beck et al. (13) aimed to explore how the interaction between cognitive and sensorial perception influences FOG. The results advise that although increasing demand on attention does substantially deteriorate gait in freezers, an increase in cognitive demand is not exclusively responsible for FOG once visual cues are able to overcome any interference evoked by the dual task (13).

Spildooren et al. (117) elucidated in their study that 360-degree turns in combination with a cognitive dual task are the most important triggers to cause FOG. Seven from fourteen participants froze during his protocol, but the number of FOG episodes is not presented in the results section.

In the work of Schaafsma (108), to assess the effect of dopaminergic medication on distinct FOG subtypes in the OFF state, nineteen participants were videotaped while walking 130m during the OFF and ON medication states. Three different observers characterized the type, duration, and clinical manifestations of FOG and quantified FOG by analyzing the videotapes. During the OFF state, FOG was elicited by turning (63 percent), starting (23 percent), walking through a narrow doorway (12 percent), and reaching a destination (9 percent) (108).

Schaafsma et al. (108) analyzed FOG not only considering the type of FOG (leg movement observed) but also the FOG subtypes related to the trigger to respond if levodopa improves FOG. The gait task was videotaped, and the video analysis was made by three observers. The number of FOG episodes in Schaafsma et al. (108) is undisclosed; results only show the percentage of FOG occurrence according to the triggers used.

In the study of Bartels et al. (12), patients were asked to stand up from a chair, walk 20 meters, make a 360-degree turn to the right and a 540-degree turn to the left, and walk the same route back, ending with a turn to sit back in the chair. At the 10 meter mark, the participants walk between two chairs, which create a narrow path 50 cm apart. For the second task, patients walk an additional 50 meters, passing through two doorways (12). Some patients could not walk two laps during the OFF state and were excluded from the study (12); the final number of volunteers was not presented in the paper.

A simple method was presented by Popovic et al. (94) for triggering and detecting FOG episodes using a series of stride force profiles recorded with force sensitive resistors. Data from nine participants was collected, and 24 FOG episodes were considered. Patients were asked to stand up from the chair, walk toward the room, walk through a doorway, reach the 13-meter marker, make a 180-degree turn to the left, and walk the route back. Findings showed that FOG most often occurs during turns and gait initiations.

In the study of Popovic et al. (94), the periods of FOG episodes were studied from three sources: videotapes, ground reaction forces, and acceleration. Similar to the present work, video recordings were used for method validation. The method proposed by Popovic (94) was indeed simple but not as effective as the method proposed in the present study in relation to the number of FOG episodes triggered.

Handojoseno et al. (38) demonstrated the potential of Eletroencephalography (EEG) feature extraction and could give insights into the pathophysiology of FOG in PD. It was found that both power spectral density and wavelet energy could potentially act as biomarkers during FOG episodes. The dimension of data collection is 5 hours and 30 minutes of TUG tests, and 404 FOG episodes, ranging from 1 to 220 seconds, were labeled by two clinicians specializing in movement disorders (38). Popovic et al. (94) and Handojoseno et al. (38) highlight the importance of further exploration regarding a reliable method to provide quantitative measures in the assessment of FOG in PD.

A study from Wang et al. (130) applied an in-place movement experiment for PD patients to provoke FOG and acquire a multimodal physiological signal, using IMU, EEG, Electrooculogram (EOG), and Eletrocardiology (ECG) sensors. Over 700 FOG episodes were provoked from 15 subjects, and most of them were provoked by the rapid turn condition. The subjects were examined in OFF medication state. There were five sessions of three conditions: (i) Stepping in-place (SIP); (ii) half turning at a self-selected speed for 2 minutes; and (iii) half turning at a rapid speed for 2 minutes. Each session lasted about six minutes, for a total of 30 minutes of data collection (130). Common sense leads us to conclude that performing half turns at a rapid speed in place for several minutes, even at a self-selected speed, can cause dizziness, vertigo, malaise, discomfort, and a high risk of falling. The experiment setup proposed by Wang et al. (130) is efficient in triggering FOG episodes, but it is not practical for clinical care and could not be applied to frail patients.

5.2.3 Creating the physical mobility task to trigger FOG

The motor task consists of routine actions such as sitting and standing from a chair, walking in a straight line, passing through a doorway, and turning right and left. The selection of the opening width (67,5 cm) was based on a study conducted by Almeida et al. (5), who suggested a modified TUG test in which the volunteer walks through a door while performing the TUG test. The experiment was conducted with three different opening sizes: spacious (1.8 m), normal (0.9 m), and narrow (0.675 m), and the results demonstrated that the narrowest passageway had the greatest impact on the gait of the freezers. Table 5.1 shows the main provoking strategies to trigger FOG according to the literature, they are: pass through a narrow wide opening, reach a destination, 180-degree turn, and 360-degree turn. These were included in the physical mobility motor task, besides the open gait, which is to walk 3 meters in straight line. Table 5.1 also shows that

the dual task is used in 8 of the 17 studies, so we created two physical mobility tasks, one with a simple motor task and the other with a dual task, in which the participant performed the same simple motor task while also performing a cognitive task. These tasks are detailed presented in Chapter 3.

5.2.4 Testing the physical mobility motor task

The study was conducted according to the guidelines of the Declaration of Helsinki, and all protocols were approved by the Ethics Committee. Informed consent was obtained from all subjects involved in the study. The experiment was performed in a place destined for the clinical care of Parkinson's disease patients. Before carrying out the proposed physical mobility tasks, the motor task, and the cognitive-motor dual task, participants performed the TUG test, a physical mobility task for gait analysis in Parkinson's disease, and a voluntary stop, which is a modified version of the TUG test in which the participants stay standing for ten seconds before turning in 'u'.

5.2.5 Subjects

We included 10 volunteers with PD (94, 102) between the ages of 50 and 73 years old (mean: 60.6 years old; standard deviation: 7.29 years old) who suffer from FOG symptom. Tables 4.1 and 4.2 display the clinical characteristics and MDS-UPDRS information of the volunteers, six of whom are female and four of whom are male. For this chapter we used the data from the GFOG+ group.

The volunteers were able to walk independently for 10 meters and reported experiencing FOG in the prior month. FOG severity was rated using the New Freezing of Gait Questionnaire (new FOG-Q) (14, 64, 77, 79, 102, 130). All the participants included in this study had a FOG history with different severity and frequency (38). All subjects were assessed first in the morning in the OFF-medication state, which is at least 12 hours since the last intake of dopaminergic medication, then after data collection, they took their first dose of dopaminergic medication of the day and the experiment was repeated after 30-50 minutes (70, 60), at the ON-medication stage (12, 79, 117, 130).

Clinical data to rate severity of PD, as the MDS-UPDRS and the Hoehn Yahr Scale, were collected during the OFF and ON states (12, 64, 79). The subjects wore their regular footwear and no walking aid (cane or walker) (92, 126). A physiotherapist followed the subject during data collection to monitor possible loss of balance and prevent falls, but no physical assistance was given (79, 126).

5.2.6 Data analysis

To detect FOG and characterize its occurrence, we considered the definition of Bartels (12): FOG can appear as a hesitation in the beginning of the movement that lasts more

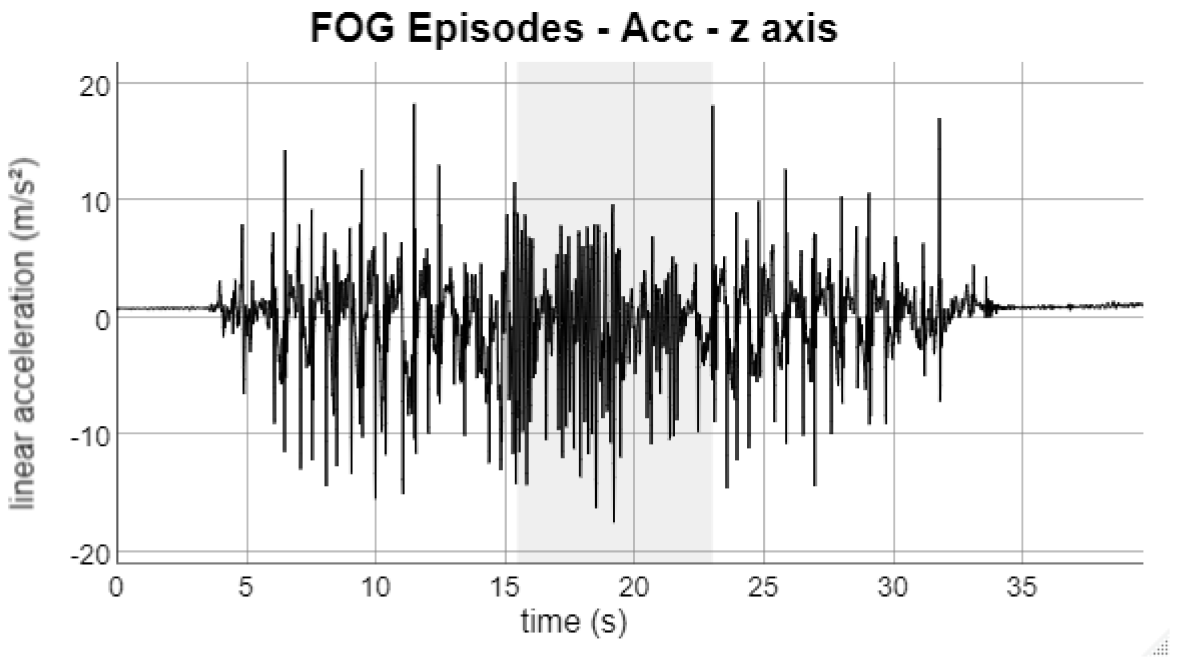

Figure 5.2 – Example of a FOG episode shadowed in gray detected by the sensor placed on the volunteer most affected leg. FOG episodes are highlighted in gray.

than one second; as a significant hesitation in the locomotion without an apparent reason; or when it looks like the volunteer fails when he tries to begin or continue the movement.

The detection of FOG was carried out by an experienced researcher. Figures 5.2 and 5.3 show a typical example of a recorded signal. The FOG episode is shadowed in gray. Figure 5.2 is the z axis of the accelerometer, and Figure 5.3 is the y axis of the gyroscope, both from the sensor placed on the shank most affected by PD.

As shown in Figures 5.2 and 5.3, FOG can be detected using only the analysis of the accelerometer signal (6). When a FOG episode occurs, the frequency of the accelerometer increases and the amplitude of the gyroscope decreases (19). In addition to the signals of the three inertial sensors attached to the body of the volunteer, all FOG episodes were manually annotated by evaluating the video recordings (50) in conjunction with the inertial signals using ATLAS (67).

5.3 Results

The results are presented to validate the proposed physical mobility tasks. Table 5.2 shows the number of FOG episodes during the voluntary stop (VS), the total number of FOG episodes is 21 during OFF state and 9 during ON state. Table 5.3 shows the number of FOG episodes during the TUG test, the total number of FOG episodes is 18 during OFF state and 6 during ON state. Table 5.4 shows the number of FOG episodes during the proposed physical mobility motor task (MT), the total number of FOG episodes is 53 during OFF state and 7 during ON state. Table 5.5 shows the number of FOG episodes

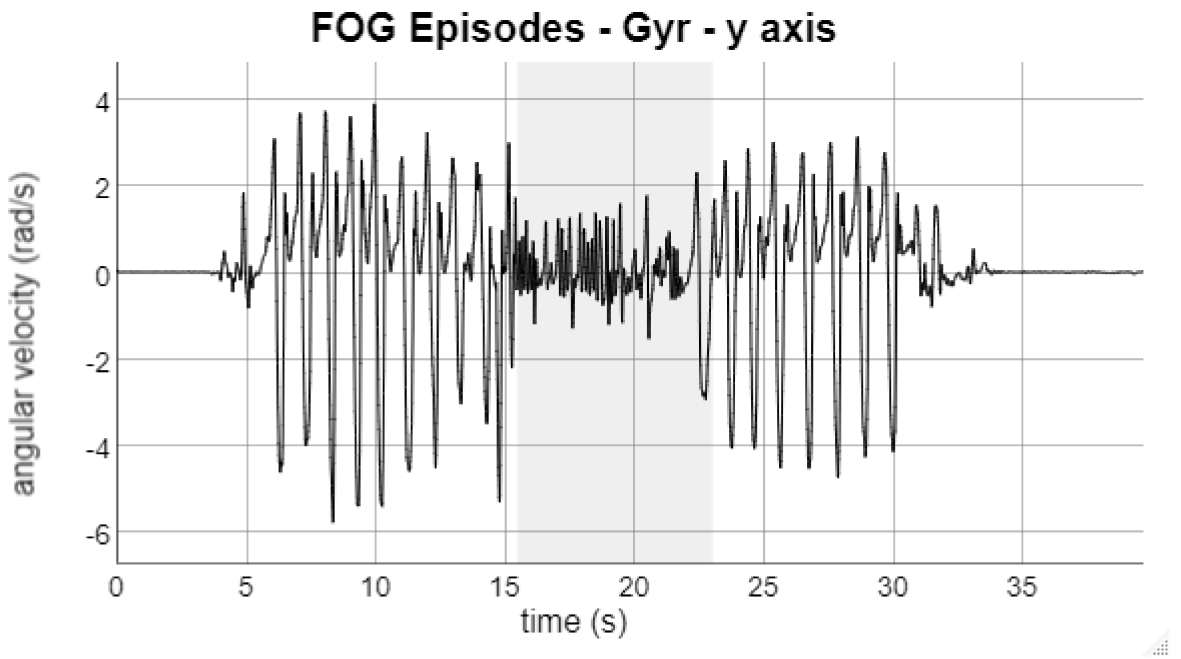

Figure 5.3 – Example of a FOG episode shadowed in gray detected by the sensor placed on the volunteer most affected leg. FOG episodes are highlighted in gray.

during the dual task (DT), the total number of FOG episodes is 54 during OFF state and 6 during ON state. Three trials were conducted in each medication state (ON or OFF) to increase the number of observations, thereby contributing to a more reliable result.

Results show that the voluntary stop was capable of causing 30 FOG events, the TUG test induced 24 FOG events, the physical mobility motor task caused 60 FOG events, and the dual task caused 60 FOG events.

Table 5.6 shows the information about the score of the New FOG Questionnaire (New FOG-Q) and the total number of FOG episodes for each volunteer during OFF and ON

Table 5.2 – Number of FOG episode for each volunteer and the total number of FOG episodes during the OFF and ON medication states for the voluntary stop (VS).

V	VS1 OFF	VS2 OFF	VS3 OFF	TOTAL OFF	VS1 ON	VS2 ON	VS3 ON	TOTAL ON
1	0	1	0	1	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	2	1	0	3	0	0	0	0
6	0	1	1	2	0	0	0	0
7	0	2	3	5	0	0	0	0
8	3	1	0	4	0	0	0	0
9	2	2	2	6	3	3	3	9
10	0	0	0	0	0	0	0	0

medication states while performing the proposed physical mobility tasks, the motor task, and the cognitive-motor dual task. Table 5.6 also shows the time in seconds that the volunteer spent frozen (TF).

Table 5.6 displays the total duration time of FOG episodes, TF, as employed in several studies (13, 75, 130, 19, 50), which represents the sum, in seconds, of the time difference between the beginning and end of each FOG episode. The results depict the number of FOG occurrences and total duration of FOG episodes for each participant during the OFF and ON medication states.

Table 5.7 compares the results of the present study with the results of the studies included in the literature review that could trigger and detect FOG episodes during data collection. Table 5.7 shows the author and year of the paper (see also Table 5.1), the sample size N, which is the number of participants who took part in the study, the

Table 5.3 – Number of FOG episodes per volunteer and the total number of FOG episodes during the OFF and ON medication states for the TUG test (TUG).

V	TUG1 OFF	TUG2 OFF	TUG3 OFF	TOTAL OFF	TUG1 ON	TUG2 ON	TUG3 ON	TOTAL ON
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	2	1	0	3	0	0	1	1
6	0	0	0	0	0	0	0	0
7	1	0	0	1	0	0	0	0
8	0	3	4	7	0	0	0	0
9	2	3	2	7	1	2	2	5
10	0	0	0	0	0	0	0	0

Table 5.4 – Number of FOG episodes per volunteer and the total number of FOG episodes during the OFF and ON medication states for the physical mobility motor task (MT).

V	MT1 OFF	MT2 OFF	MT3 OFF	TOTAL OFF	MT1 ON	MT2 ON	MT3 ON	TOTAL ON
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	7	9	7	23	0	0	0	0
4	2	3	3	8	0	0	0	0
5	2	3	1	6	1	0	0	1
6	1	0	0	1	0	0	0	0
7	1	2	0	3	0	0	0	0
8	2	1	1	4	0	0	0	0
9	1	5	1	7	2	2	2	6
10	0	0	1	1	0	0	0	0

number of freezers, which represents the number of participants who froze during the experiment, the number of FOG events, the recording time, and the number of trials.

Not all papers disclosed the duration of the trials, so recording time was not indicated in lines 1, 2, 3, and 5 of Table 5.7. The authors conclude that, analogous to what happened in our work, not all trials have a specific time to be completed, so we chose to analyze the number of trials that are informed in the methods of the studies, except in Handojoseno et al. (38), to compare with the number of FOG events that occurred during the proposed physical mobility tasks, the motor task, and the dual task, during the OFF medication state.

The three types of FOG according to the literature (70, 84, 94, 108) are presented in Figures 5.4, 5.5, and 5.6. The figures show data from the accelerometer and gyroscope

Table 5.5 – Number of FOG episodes per volunteer and the total number of FOG episodes during the OFF and ON medication states for the physical mobility dual task (DT).

V	DT1 OFF	DT2 OFF	DT3 OFF	TOTAL OFF	DT1 ON	DT2 ON	DT3 ON	TOTAL ON
1	0	0	0	0	0	0	0	0
2	2	0	1	3	0	0	0	0
3	3	6	7	16	0	0	0	0
4	5	5	3	13	0	0	0	0
5	2	1	0	3	0	0	2	2
6	1	0	0	1	0	0	0	0
7	0	2	0	2	0	0	0	0
8	4	4	2	10	0	0	0	0
9	1	2	3	6	1	2	1	4
10	0	0	0	0	0	0	0	0

Table 5.6 – Information about the score of New FOG-Q and the total number of FOG episodes for the physical mobility tasks considering the sum of events in the motor task and the dual task.

V	New FOG-Q	Number of FOG OFF	TF(s) OFF	Number of FOG ON	TF(s) ON
1	14	0	0	0	0
2	23	3	4.498	0	0
3	19	39	179.735	0	0
4	21	21	691.521	0	0
5	23	9	27.448	3	4.922
6	16	2	6.273	0	0
7	15	5	12.918	0	0
8	23	14	571.886	0	0
9	26	13	88.480	10	64.821
10	12	1	1.769	0	0
Total		107	1,584.528	13	69.743

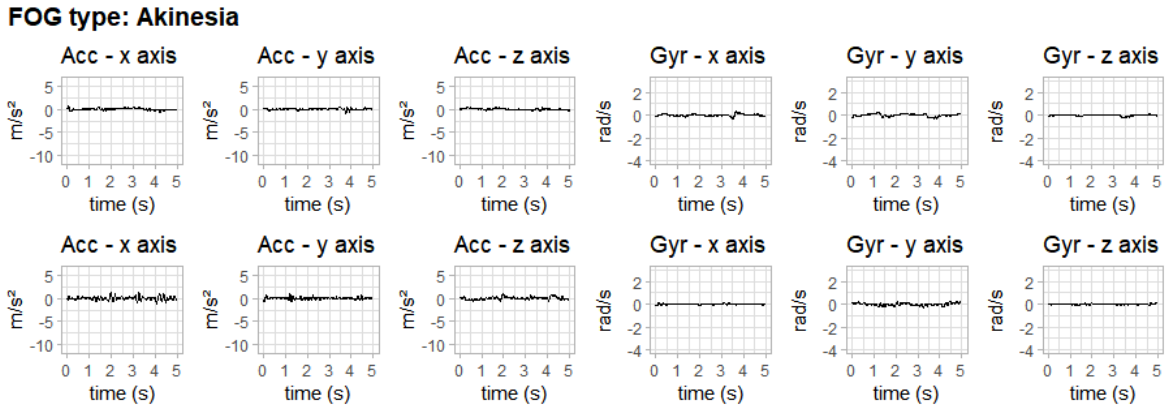

Figure 5.4 – Typical waveforms of inertial signals during akinesia.

on the x, y, and z axes placed on the right iliac spine. The waveforms shown in Figures 5.4, 5.5, and 5.6 are typical signals occurring during akinesia, shuffling, and trembling in place.

Figure 5.4 shows one type of freezing, the akinesia of two volunteers, lines 1 and 2, respectively. This FOG type can manifest as complete akinesia, in which the entire body is frozen, or partial akinesia, in which only the lower body is frozen. Figure 5.5 shows the second type of freezing, festination, or shuffling of two volunteers, lines 1 and 2, respectively. This FOG type is characterized by a change in normal gait rhythm. Finally, Figure 5.6 shows the third type of freezing and trembling in place of two volunteers, lines 1 and 2, respectively. This FOG type happens when the lower extremities show signs of shaking while glued to the ground.

Table 5.8, based on the work of Podsiadlo and Richardson (92), illustrates how the proposed physical mobility motor task can be used to record changes in the duration and

Table 5.7 – Number of FOG episodes triggered by each experiment included in the literature review.

Author	N	Number of freezers	Number of FOG events	Recording time	Number of trials
Bartels 2003	19	—	237	—	57
Popovic 2010	9	—	24	—	18
Beck 2015	20	4	23	—	240
Handojoseno 2015	16	—	404	5h30min	—
Cando 2016	5	4	11	—	10
Alvarez 2018	18	—	200	8h20min	700
Wang 2020	15	15	700	22h30min	225
Present study	10	9	107	—	60

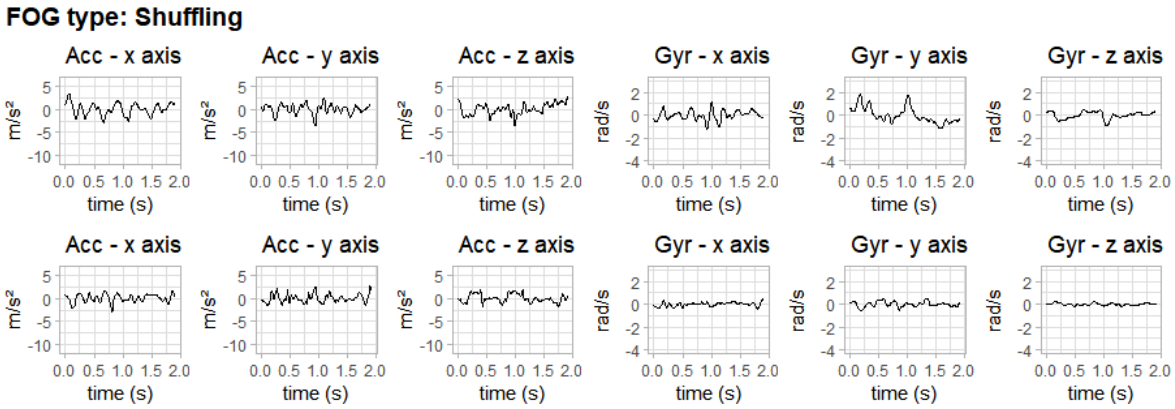

Figure 5.5 – Typical waveforms of inertial signals during festination.

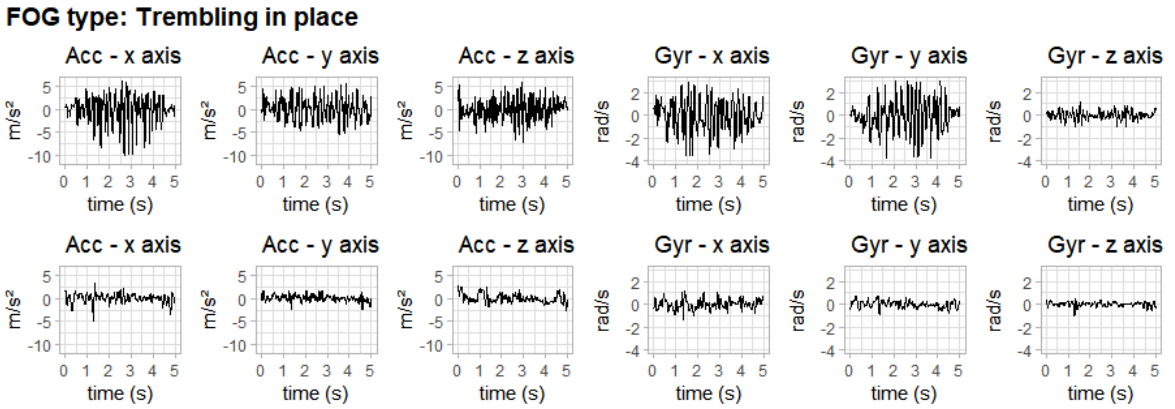

Figure 5.6 – Typical waveforms of inertial signals during trembling in place.

number of FOG events over time. A specific improvement by reducing the time in seconds of FOG and the number of FOG episodes for freezers is of particular interest.

5.4 Discussion

The results of this study support our hypothesis that it is possible to cause FOG in a controlled environment with a short and simple physical mobility motor task, using limited space, without the use of complex technologies such as force platforms and treadmills, and respecting the fragility and limitations of a Parkinson's disease patient. Besides that, the findings show that it was possible to detect FOG and distinct FOG types, i.e., freezing, shuffling, and trembling in place, by means of inertial sensors placed on the hips and shank. In our population of Parkinson's disease patients, the proposed physical mobility tasks to assess FOG, both motor and dual tasks, were practical and reliable.

The time in seconds to complete TUG provides a score that is an objective mean of following the functional changes of an individual over time (92). In the same sense, the proposed physical mobility motor task to assess FOG can be used either as a screening test or a descriptive tool, as shown in Tables 5.7 and 5.8.

The New FOG-Q is reliable (79) and it has been used in several experiments (14, 64, 102). Therefore, it is considered an important measurement to elucidate FOG severity during the assessment of freezers in Parkinson's disease. Table 5.6 shows that the highest score of the New FOG-Q belongs to volunteer 9, a subject that experienced several FOG episodes during OFF and ON medication states. Volunteer 8 has the second highest score for the New FOG-Q, with 14 FOG events and nine minutes and three seconds spent in FOG condition during data collection (See Table 5.6). Volunteer 5 has the third highest score of the New FOG-Q and freezes during OFF and ON medication states. Only volunteers 5 and 9 froze under both medication conditions. Volunteer 2 had a significantly high New FOG-Q score; however, the subject froze only three times.

Volunteers 3 and 4 have the highest number of FOG events and time spent frozen; both have a New FOG-Q score greater than 19. For the volunteers with a New FOG-Q score lower than 14 (volunteers 1 and 10), the number of FOG events was 1 or 0, and the time spent frozen was less than 2 seconds. Only one volunteer did not freeze during the experiment.

Motor performance among PD patients generally shows large variability. This was also the case among the group of patients who participated in this study. For example, during nonfreezing episodes, some patients maintained a regular gait that could hardly be distinguished from that of healthy elderly people, while others had a slow and unstable gait (11).

Bachlin (11) stated that a limitation in FOG studies is that the controlled environment and the presence of the physiotherapist may reduce the likelihood of FOG in the patients

Table 5.8 – An example of how the proposed physical mobility motor task can be used to record changes in the duration and number of FOG events over time.

Patient	Age	Date	Walking aid	New FOG-Q	Sate	TFOG	Number of FOG events
		March 1	—	12	OFF	6s	2
					ON	0s	0
1	57	May 1	—	12	OFF	30s	6
					ON	0s	0
		July 1	—	13	OFF	8s	3
				13	ON	0s	0
		April 10	cane	19	OFF	27s	4
					ON	2s	1
2	63	July 10	cane	20	OFF	32s	6
					ON	0s	0
		October 10	cane	20	OFF	30s	8
					ON	0s	0

that do not experience any FOG events during data collection, and the authors could not explain why two volunteers did not have any FOG during their study. The physical mobility motor test presented here addresses the problem of triggering FOG in a controlled environment. It was imposed that the presence of a physiotherapist is required to prevent falls during data collection and to ensure the patients' safety, even though it could affect the likelihood of FOG episodes happening. During the present study, one volunteer did not have any FOG during data collection. The video recordings of our data collection show that volunteer 1 used strategies for overcoming FOG episodes, such as adapting a rhythm faster than usual and lifting the leg higher than usual to walk (102).

Table 5.6 shows that the time spent frozen is not directly correlated with the number of FOG events. For example, volunteer 3 had 39 FOG events during the OFF medication state while performing the motor task and the dual task, but the time he spent frozen was less than 3 minutes, while volunteer 8 had 14 FOG events while performing the same tasks, but he spent more than 9 minutes in a FOG condition while performing the proposed tasks. The same happens with volunteer 4, who had 21 FOG events and spent more than 11 minutes in a FOG condition. Volunteer 9 is the oldest volunteer (73 years old) and he has the highest NFOG-Q (score 26), this is worth to be mentioned because his results of the number of FOG episodes do not change significantly during OFF and ON medication states.

Velik et al. (126) and Alvarez et al. (6) recorded daily life motion to detect specific motor patterns of the limbs since it is often difficult to observe them during clinical visits (64). However, to achieve this feat, expensive technology, large available space, and previous training of staff to operate the cameras and sensors were needed. Not to mention the storage capacity needed so that all recordings are saved and can be later watched by experienced evaluators for the detection of FOG. Meanwhile, the present work raises the possibility that FOG assessment can be carried out, supported by health professionals, in a limited space by performing a physical mobility task designed to trigger FOG events. Furthermore, the detection of FOG events for posterior analysis can be executed with the use of inertial sensors and video recordings from a cell phone camera.

The proposed method to assess FOG allows for triggering and detecting FOG episodes in a controlled environment using a physical mobility task combined with three smartwatches with inertial sensors and a mobile phone. We were able to create an accurate representation of daily life situations that cause FOG by developing a task that includes all the movements highlighted in the literature as potential triggers to FOG episodes, for instance, to initiate gait, walk through a narrow doorway, make left and right 360-degree turns, and reach a destination.

It was possible to detect FOG using inertial sensors placed on the hips and shank of the subjects while they performed the proposed physical mobility tasks, the Motor task (MT) and the Dual task (DT). Table 5.6 shows the number of FOG episodes and the

total time in seconds of FOG duration. Tables 5.4 and 5.5 show the total number of FOG episodes for each trial of the motor task and the dual task per volunteer. This number is considered high when compared to the work of Popovic et al. (94), Beck et al. (13) and Cando et al. (19) presented in Table 5.7, and when compared to the number of FOG events caused by the TUG test, displayed in Table 5.3.

Dopaminergic medication has a significant effect on the occurrence of FOG (12, 108). Clinical experience suggests that most patients who experience FOG improve with dopaminergic medication; however, FOG persists in a milder form (12). The results of Schaafsma (108) suggest the medication increases the threshold of FOG occurrence but does not cure the symptom. Tables 5.2, 5.3, 5.4, and 5.5 show the difference in the number of FOGs comparing OFF and ON medication states while performing the proposed motor tasks. They show that 125 FOG episodes occurred in the OFF state and 19 FOG episodes occurred in the ON state. Therefore, the proposed method is able to detect the reduction in FOG events when patients are using dopamine.

In Tables 5.4 and 5.5, the important information is the number of FOG events triggered by the motor task (MT) and the dual task (DT). The simple motor task caused 53 FOG episodes, while the dual task caused 54 during the OFF-medication state. The TUG test, which is widely used in the clinical evaluation of PD patients, triggered 18 FOG episodes during OFF-medication state. During the ON-medication state, there were 7 FOG episodes for MT, 6 for DT, and 6 for the TUG test. The close results between the proposed tasks may indicate that the dual task is not crucial to trigger FOG, once both simple motor tasks and the dual task caused 60 FOG episodes each. Furthermore, the results also show the effectiveness in triggering FOG of the novel physical mobility task to assess freezers in Parkinson's disease because it was able to cause three times more FOG episodes during the OFF-medication state than the TUG test.

Studies that investigated dual task (13, 51, 117, 133) have evidence that cognitive load has a negative effect on the gait in patients with PD; however, when it comes to FOG-provoking strategies, the dual task is non-essential according to our findings. Considering the equipment and resources needed to complete the dual task, e.g., the device to play the audio track with the numbers for the Digit Monitoring Task, the speaker, and the number draw, and the complexity of the dual task, not only for the person who is performing the dual task but also for the researcher group, one can conclude that, when the physical mobility motor task is specially designed to cause FOG episodes with triggers of movement and environmental constraints, the dual task is not fundamental.

As Appendix B illustrates, the GFOG+ group's mental load for the DMT was regular. The average percentage of volunteers who made a mistake was fewer than 50%. Maybe a more complex second task would have a different effect.

Figures 5.4, 5.5, and 5.6 show, respectively, the distinct FOG types of freezing, festination, and trembling in place, as defined by Thompson and Marseden (16, 83, 94, 60). In

the work of Schaafsma (108), three different observers characterized the type, duration, and clinical manifestations of FOG and quantified FOG by analyzing the videotapes. In the study of Bartels et al. (12), three observers independently watched the task videotapes and elucidated the number of FOG episodes. A FOG episode was considered to have taken place if a patient hesitated for one second or more (12). The researchers clarify that using exclusively the video rating method, they might have missed very brief FOG episodes (12). To analyze FOG episodes using only video recordings represents a subjective assessment of the patient because it depends on the observer's experience and expertise, the shooting angle, and the quality of the video. It has been proven by several studies (94, 38, 130) that the use of sensors optimizes data collection.

The literature review showed that 11 studies were able to trigger FOG in a controlled environment. Table 14 shows the papers over time that disclose the number of FOG episodes during the experiment. Table 13 displays the total number of volunteers included in the research; column freezers are the actual number of volunteers who froze during data collection (13, 130, 19).

The difficulty of accessing the FOG and causing it in a controlled environment is also disclosed in the studies of Saad et al. (105) and Jovanov et al. (50) in which, to test new equipment, the researchers had to simulate FOG episodes themselves.

Table 5.8 is an example of how the proposed physical mobility motor task can be used to record changes in the duration and number of FOG events over time in a setting where freezers perform the task shown in Figure 3.3 regularly, which allows the examiner to assess the FOG symptom during a clinical visit.

An intervention designed by Rawson (102) to reduce FOG in PD was tested in seven patients. The participants completed what the authors called a 'FOG boot Camp', a 6-week program with one and a half hour classes each week designed and taught by two specialists in neurological and geriatric physiotherapy, respectively (102). The classes had education and group discussions on strategies for overcoming the FOG episode. It was followed by a practice of the strategies in environments designed to trigger FOG, such as sharp turns, walking through a narrow path, walking through a doorway, and turning to sit in a chair (102).

The applied strategies were based on existing literature and included sensorial cues (auditory, visual, and vibratory) and self-initiated strategies that required executive functioning and attentional processes, such as lifting one leg higher, walking in sideways, moving one foot backward before walking, making wider turns, shifting leg weight, and imagining a clock on the ground to help with turning (84, 102). The main objective of Rawson et al. (102) was to determine the feasibility, safety, and acceptability of a once-weekly community-based group intervention. Participants had favorable feedback and showed reduced FOG.

External rhythmic cues have been found effective in overcoming FOG (126, 19, 104).

However, the continuous presence of an auditory, visual, or vibratory cue may reduce effectiveness and disturb normal social activity (130). Therefore, taking the dopaminergic medication correctly and learning self-initiated strategies to reduce or overcome FOG episodes is the best current alternative for freezers.

The proposed physical mobility motor task could be used as a tool to measure functional changes, record changes in the duration and number of FOG events over time, assess the impact on gait of a medication dosage change, and test the acknowledgement and effectiveness of learned self-strategies to overcome FOG. The improvement of gait mobility and the decrease in frequency of FOG events are the goals when assessing gait in freezers (102).

5.5 Conclusion

To design the proposed physical mobility tasks, we carried out a literature review, and it was possible to set up a practical motor task to assess freezers in Parkinson's disease. This paper presents the development of a simple physical mobility task capable of causing FOG in a controlled environment using known triggers. A group of 10 volunteers who experience FOG in daily life participated in the validation of the proposed method, which was carried out using inertial sensors and video recordings. Accelerometers and gyroscopes were able not only to detect FOG episodes but also to show the different types of FOG that depend on leg movement (akinesia, shuffling, and trembling). The proposed tasks caused 120 FOG episodes. Volunteers froze more during the OFF-medication state compared to the ON state, and the number of FOG episodes was higher while performing the proposed physical mobility tasks than the voluntary stop and the TUG test. The proposed method may be used to complement clinical examinations in the assessment of freezers.

6

A novel strategy for evaluating Parkinson's disease-related changes in gait

This chapter aims to extend the approach to FOG detection by analyzing different gait parameters and comparing the results from the Moore-Bachlin algorithm and Hjorth's parameters in order to develop a more useful system to monitor and assess freezers in PD. The signals of three IMU sensors with 3D gyroscope and accelerometer are used to compare the walk pattern between people with Parkinson's disease who have the symptom of FOG, people with Parkinson's disease who do not have the symptom of FOG and healthy age-matched individuals, using the known Moore-Bachlin algorithm and Hjorth's parameters as an alternative approach.

The results show the optimal combination of sensor, sensor placement, task, task event, and feature to collect gait information and identify gait differences in PD.

6.1 Introduction

Parkinson's disease (PD) is a common neurologic disorder caused by a progressive loss of nerve cells or dopaminergic and other subcortical neurons in the substantia nigra area of the basal ganglia (70, 18, 11) that results in decreased control of body movement (74). Due to progressive disability, PD can lead to gait disturbances. In PD, individuals experience continuous disorders including a flexed posture, difficulties in axial rotation of the trunk, reduced arm swing and difficulty getting up from a chair (48) . Besides that, freezing of gait is a common negative effect of PD that affects gait performance (11), considerably hindering the independence of the person with Parkinson.

Freezing of gait (FOG) is a particular proximal symptom, a very brief motor block defined as an episodic inability to generate effective stepping (24, 79). Most FOG episodes last less than 10 seconds, and only a few last more than 30 seconds (108). FOG might be associated with a specific pathology that not all individuals with PD have (16). In fact, FOG has only ever been mentioned in connection with extrapyramidal, hypokinetic

movement disorders; it is not confined solely to Parkinson's disease. All parkinsonian disorders, including progressive supranuclear palsy, can manifest FOG (16).

This very distressing gait disorder leads to a high risk of falls (24, 20). Because a sudden FOG is likely to disturb balance and thereby represent a common cause of falls in PD (16). Falls in PD are a complex health problem. On the one hand, the direct consequences are fractures, head trauma, bruises, and other injuries that increase the chances of hospitalization and institutionalization. On the other hand, the indirect consequences include fear of further falls and impose limitations in activities of daily living (55). The resultant loss of independence and the treatment cost of injuries add considerably to the healthcare expenditures associated with PD (16).

Individuals with PD accept some limitations, but they report feeling frustrated and discouraged by the need to stop or modify activities. Furthermore, the apprehension of falling in public and the subsequent embarrassment that it would bring often lead to less engagement in daily living activities (45). Restriction of activity results in physical deconditioning and decline in muscle strength, which may increase risk of falls (4). The study of Franchignoni et al. (28) confirms that individuals with PD who experience a fear of falling tend to exhibit poor performance on tests related to balance, posture, and mobility.

Increased fear of falling has been associated with recurrent falls (4), this is an important issue in PD because it is known that PD people have postural disabilities (1), especially for PD freezers (4). Due to their diminished mobility, some patients become largely socially isolated and lose their independence, whereas others lose their social contacts. Not surprising, falls in PD are often associated with depression. Prolonged immobility eventually contributes to the development of osteoporosis, heightening the risk of future fractures, as well as cardiovascular morbidity or mortality, and pneumonia. Additionally, constipation, pressure sores, and compromised sleep quality are connected to immobility. Finally, people with balance or gait disorders are more susceptible to experience fatal injuries (16).

Clinical assessment of FOG is based on subjective patient reports, such as the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (34) and the New Freezing of Gait Questionnaire (New FOG-Q) (79). Clinical evaluation of video recordings of patients by one to three observers is the gold standard for identifying FOG events (69, 24).

A few wearable sensors have been proposed for providing quantitative assessment of FOG (130, 20). Evaluation of the clinical effects of the treatment would benefit from objective, standardized FOG measures (24), and an accurate treatment and rehabilitation of FOG can reduce accidents and thus improve the quality of life of people with PD who suffer from this symptom.

Current methods for assessing FOG using smart sensors can be categorized based on

the sensor types, sensor placements, extracted features, and analytics methods (74). The detection of FOG requires the application of specific signal processing and classification methods adapted to this type of phenomenon (106). Many studies used three dimensional (3D) gyroscopes or accelerometers to describe body motion and detect clinical characteristics of PD patients (130).

Moore et al. (70) have proposed a technique to identify FOG episodes using power spectrum analysis of the vertical linear acceleration of the shank, the Freeze Index (FI). FI is defined as the ratio between the power in the freeze band (3–8 Hz) and the power in the locomotor band (0.5–3 Hz). Bachlin et al. (11) updated Moore's FOG detection algorithm, proposing a lighter architecture in which acceleration data from three sensors attached to the body were transmitted to a wearable computer through wireless Bluetooth and introducing a new term called Power Index (PI), which is the sum of the freeze band and locomotor band; PI indicates the amount of movement during walk (74). Furthermore, the Moore-Bachlin algorithm that applies freeze and Power Index to detect FOG and indicate the amount of movement was used in several experiments (105, 20, 24, 91, 74, 130, 106). The Moore-Bachlin algorithm could be associated with different methods based on gait parameters in order to detect walk pattern modifications. IMU data allow going further in the analysis of gait by estimating various parameters (24).

Hjorth's parameters are statistical parameters in the time domain introduced by Bo Hjorth (43) and used in signal processing. These parameters are Activity, Mobility, and Complexity. They are commonly used in the analysis of electroencephalography signals for feature extraction (95, 39). Recently, they were used to identify and characterize Short-term motor patterns (STMP) in rest tremor in individuals with Parkinson's disease using the inertial sensor gyroscope (98).

Activity, Mobility, and Complexity can together characterize the signal patterns in terms of amplitude, time scale, and complexity. The statistically sound nature of Hjorth's parameters guarantees that they also have meaning in the description of the power spectrum associated with the time domain pattern (43). Thus, Hjorth's parameters offer a way to measure basic signal properties by means of a time-domain-based calculation, requiring less complex processing data compared to Moore-Bachlin frequency analysis.

This study aims to extend the approach to FOG detection by observing different gait parameters and comparing the results from the Moore-Bachlin algorithm and Hjorth's parameters in order to develop a more useful system to monitor and assess freezers in PD. The signals of three IMU sensors with 3D gyroscope and accelerometer were used to compare the walk pattern between individuals with Parkinson's disease who have the symptom of FOG, individuals with Parkinson's disease who do not have the symptom of FOG and healthy age-matched individuals, using the known Moore-Bachlin algorithm and Hjorth's parameters as an alternative approach. The hypothesis is that both methods, the Moore-Bachlin algorithm and Hjorth's parameters, are capable of detecting changes

in motion during gait that can discriminate the three groups.

The difficulties in determining FOG's characteristics and incidence may contribute to its intractable nature (70). Without unbiased information on the impact of therapy on FOG, an adequate treatment and consistent PD follow-up are likely to be ineffectual. Additionally, it is important to regularly check the gait of PD patients to detect FOG risk and undertake a FOG assessment as indicated. Therefore, the possibility of monitoring gait changes of freezers and PD patients periodically with a reliable system that can provide objective feedback to treatment could improve the management of FOG in PD.

6.2 Materials and Method

This is a cross-sectional study to investigate FOG detection and changes in motion during gait using inertial sensor analysis. The study was conducted according to the guidelines of the Declaration of Helsinki, and all protocols were approved by the Ethics Committee. In addition, informed consent was obtained from all subjects involved in the study. The study had four phases: (1) the acquisition of motion and clinical data via experiments; (2) data preprocessing; (3) feature extraction; (4) and statistical analysis. During the experiment, accelerometer and gyroscope signals were collected. In the data preprocessing phase, preprocessing the inertial signals is a step to prepare the signal for feature extraction that is Freeze Index (FI), Power Index (PI), Activity, Mobility, and Complexity. The data analysis starts with the manual video annotation, which is the golden standard for FOG detection and will be the ground truth of the work, followed by feature extraction and statistical analysis to complete the gait assessment. The proposed method to detect gait changes in motion is based on two methods, the Moore-Bachlin algorithm and Hjorth's parameters, applied to the signals acquired with the inertial sensors. The objective is to extract features capable of distinguishing the gait of PD freezers from the gait of PD people who do not freeze, and normal gait. According to the literature, the features chosen to be extracted can detect FOG events (FI), measure the severity of FOG (FI), calculate the amount of movement and changes in motion (PI), elucidate the variability of data (Activity), identify the mean power and mean frequency (Mobility), and calculate the deviation from the sine shape as an increase in unity (Complexity). These features have low computational costs and good performance (115).

6.2.1 Experimental Protocol

Thirty subjects were enrolled if they met the eligibility criteria. They were divided into ten PD patients with a history of FOG (GFOG+), ten PD patients age-matched with no history of FOG (GFOG-), and ten age-matched controls (GC). The subjects completed

several questionnaires to measure their clinical characteristics. Table 6.1 shows the clinical information about the subjects.

Patients were asked to perform four different physical mobility tasks: task 1 is the voluntary stop; Task 2 is the Timed Up and Go test (TUG); Task 3 is a physical mobility motor task to assess freezers in PD; and Task 4 is a physical mobility dual task. The motor task and the dual task can induce FOG in freezers using known triggers of FOG episodes in a controlled environment (81).

6.2.2 Description of apparatus and sensor positioning

The Movement Disorder Monitoring System (NetMD) (57) that allows to analyze and monitor movement disturbances remotely and continuously through inertial signals was used to acquire motion data from participants while they performed the four tasks of the experimental protocol.

Three smartwatches with wireless inertial sensors were used, two of which were attached over the two ends of the iliac spine, and one on the shank. The triaxial accelerometer and gyroscope measured body movements in all directions, including the anterior-posterior, medio-lateral, and vertical axes.

6.2.3 The architecture and data processing

Figure 6.1 shows the flow diagram of data analysis. The development of the experiment depended on data acquisition, data visualization, data annotation, data preprocessing, and feature extraction for data analysis.

6.2.4 Signal annotation and description of gait events

To achieve more objective recognition of gait events, in addition to capturing inertial signals during task performance by each participant, the entire route undertaken was

Table 6.1 – Clinical Information about the subjects.

Characteristics		GFOG+	GFOG-	GC
Age (years old)		60.8 ± 7.48	65.1 ± 4.38	64.7 ± 6.76
Time of diagnosis (years)		12.5 ± 5.75	6.9 ± 4.58	
MDS-UPDRS Part II		17.1 ± 10.78	9.9 ± 3.75	
MDS-UPDRS	OFF	57.5 ± 27.66	41.2 ± 15.51	
Part III	ON	41.7 ± 24.47	29.7 ± 14.27	
New FOG-Q		19.2 ± 4.7		
MMSE		25.5 ± 3.92	26.6 ± 2.27	26.7 ± 2.21

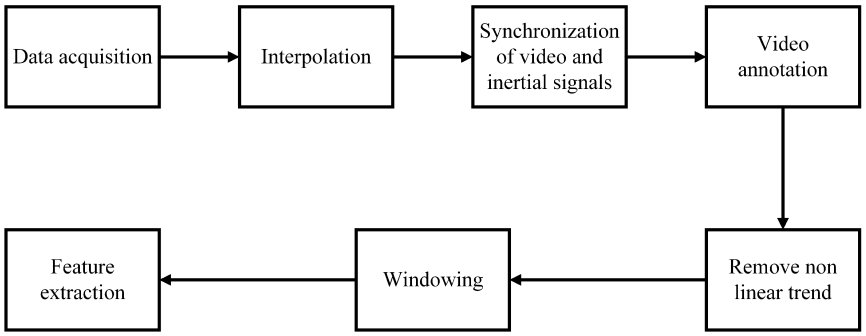

Figure 6.1 – Flow diagram of data analysis.

recorded using a camera situated within the environment where the protocol was performed. Thus, a smartphone camera was used as an environmental sensor to enable a more comprehensive gait analysis in subsequent stages.

Synchronizing the video recordings with the inertial signals that capture the entire route is a crucial stage in the analysis, as it facilitates a more comprehensive interpretation of gait events through the inertial signals. For this purpose, each collected signal was resampled at a frequency of 100 Hz using spline interpolation. This step was executed in R (122) to improve the temporal resolution of the signals and match the timing of the signals to the timing of the videos, allowing for perfect synchronization.

The video recordings were synchronized with the inertial sensors, and the task events and FOG episodes were manually annotated, using ATLAS, a graphical tool for annotating multimodal data flows (67). Data annotation involved the process of labeling data using human ability to tag the content; besides the FOG annotation, it was carried out a task event annotation, in which each event of the task was annotated with initial and final time (65).

Each task that composed the study has a different number of task events. For instance, the voluntary stop has eight task events, the TUG test has seven task events, and the physical mobility motor task and dual task have eleven task events each. Figures 6.2 and 6.3 show typical signals detected during the TUG test. The task had seven events addressed in different colors.

The task events from each task that compose the study were identified as follows:

1. Task 1: voluntary stop: (1) stand up; (2) start walking; (3) first open gait; (4) ten seconds standing; (5) 180-degree turn; (6) second open gait; (7) 180-degree turn; and (8) sit down.

2. Task 2: TUG test: (1) stand up; (2) start walking; (3) first open gait; (4) 180-degree turn; (5) second open gait; (6) 180-degree turn; and (7) sit down.

3. Task 3: Mobility motor task: (1) stand up; (2) start walking; (3) first open gait; (4) pass through a narrow passage; (5) contour the first obstacle with a 360-degree

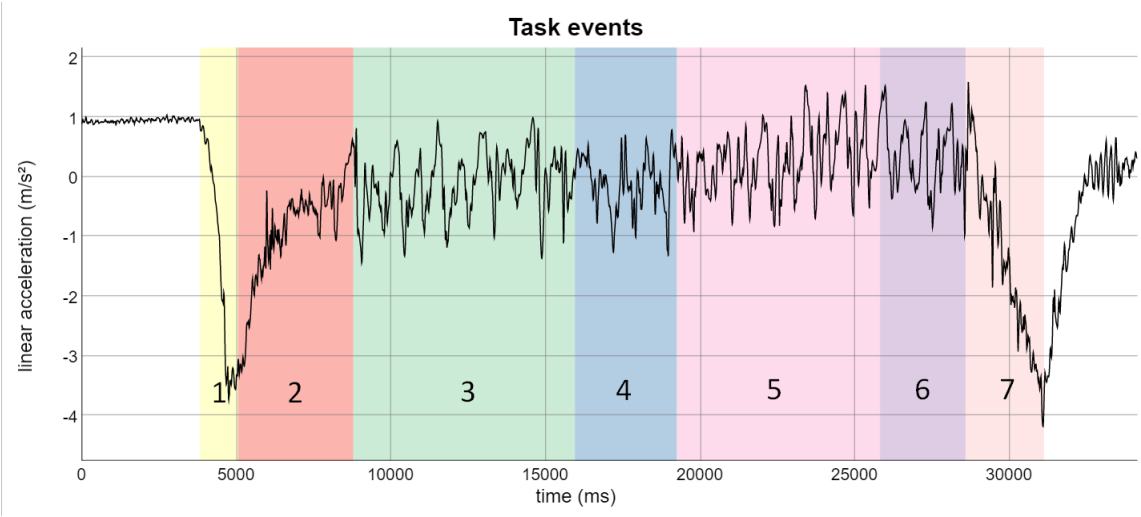

Figure 6.2 – Events annotated during the TUG test of a volunteer from the group GFOG+. This figure represents the signal of the accelerometer on X axis.

turn; (6) contour the second obstacle with a 360-degree turn; (7) contour the first obstacle again; (8) pass through the wide opening going to the direction of the chair; (9) second open gait; (10) 180-degree turn; and (11) sit down.

4. Task 4: Dual Task: Same as Task 3, but with a cognitive task simultaneously.

The annotation process allowed to understand the inertial signal pattern and how the waveforms behave in each task event. For example, it was possible to visualize the vertical acceleration signal from the shank behavior during the 360-degree turn and when the participant is passing through the wide opening. Besides that, it was possible to detect and annotate the FOG events that occurred during the experiment. A FOG event tag started when the gait pattern was arrested and ended when the pattern was resumed. In this case, another label could be added to the ATLAS project with the initial and final times of the FOG episodes.

6.2.5 Signal preprocessing

After identifying and annotating the events, the signals were processed using the R programming language and the integrated development environment RStudio (122). Initially, trends not relevant to the investigated phenomenon and present in the signals (e.g., the DC component of gravity and movements of other regions of the body (86) were removed. For this, trends were first modeled by estimating the mean for rectangular windows of 250 ms with 50% overlap. Then, the estimated values of mean were interpolated using splines so that they would have the same number of samples as the original inertial signal. Finally, the estimated trends were subtracted from the original signal, resulting in the signal without nonlinear trends. Figure 6.4 shows the original signal of the gyroscope on the X axis of the sensor on the shank and the detrend signal using the mean vector,

Figure 6.3 – Events annotated during the TUG test of a volunteer from the group GFOG+. This figure represents the signal of the gyroscope on Y axis.

which shows that the trend has been effectively removed and the behavior of the original signal is maintained.

6.2.6 Signal windowing

This study aims to observe different gait parameters and compare the results from the Moore-Bachlin algorithm and Hjorth's parameters from data acquired from subjects while they performed four gait tasks. Therefore, data analysis is focused on the gait and mobility of the subjects. The signal of interest starts from the beginning of the walk and goes up to the last 180-degree turn before sitting down. The signal of interest without the nonlinear trend is windowed using the annotation from the task events (74, 24, 11, 106), considering rectangular windows of the size of each task event. From each window, features from the time and frequency domains were extracted in order to identify walk pattern modifications.

6.2.7 Feature extraction

The first approach is the Moore-Bachlin algorithm (70, 11, 91). The Freeze Index (FI) is defined in Equation 6.1, using power spectrum analysis of the linear acceleration and the angular velocity on axes X, Y, and Z of the three sensors. The Power Index (PI) is defined in Equation 6.2. The freeze band is between 3 and 8 Hz, and the locomotor band is between 0.5 and 3 Hz.

$$FI = \frac{P_{FB}}{P_{LOC}} \tag{6.1}$$

$$P = P_{FB} + P_{LOC} \tag{6.2}$$

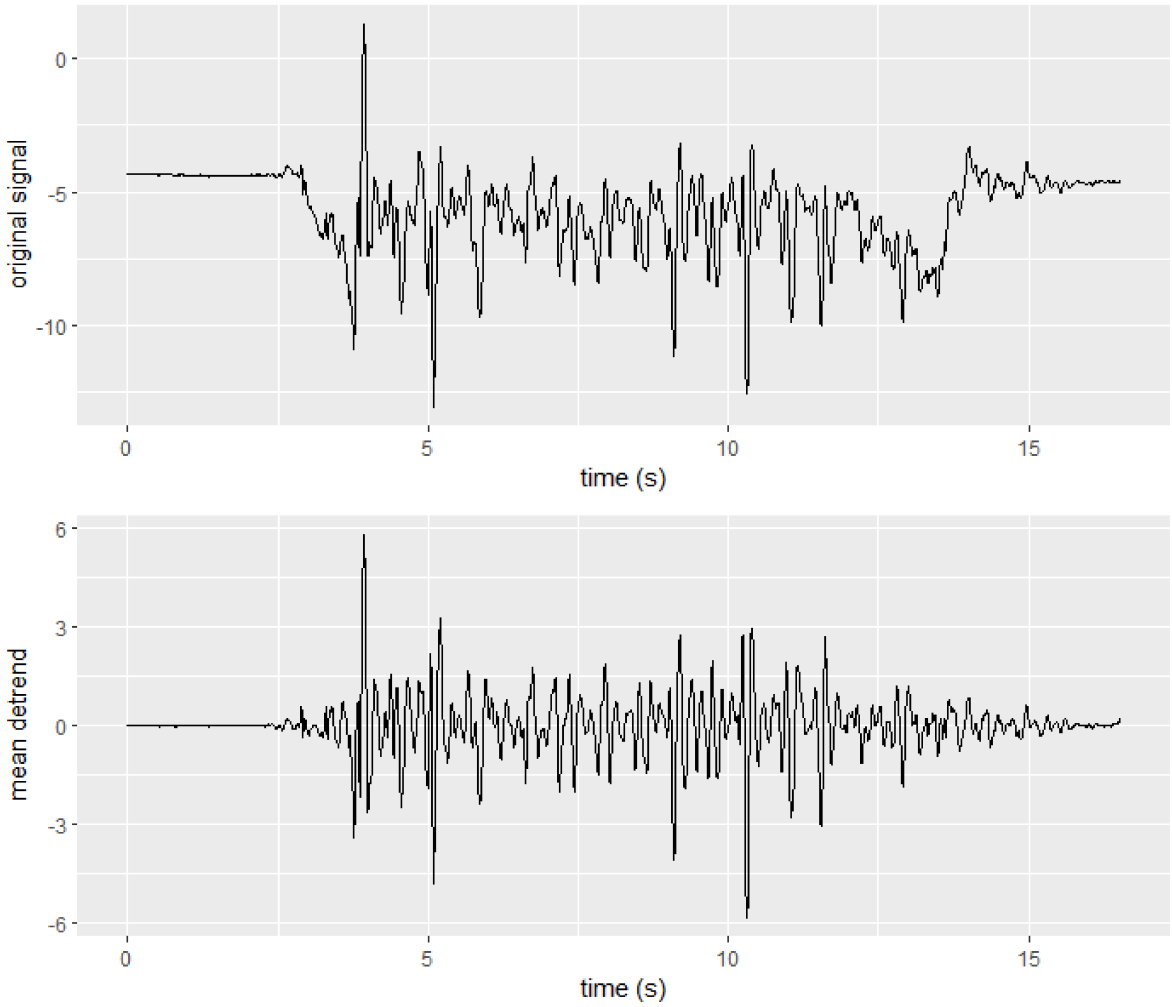

Figure 6.4 – Gyroscope signal on the X axis during the TUG test. Figure shows the original signal and the signal without nonlinear trends.

Where P_{FB} is the power in the freeze band and P_{LOC} is the power in the locomotor band.

To estimate these two features, the signal is decomposed into two bands, one in the freeze band (3–8 Hz) and the other in the locomotor band (0.5–3 Hz). The next step was to generate the power spectral density (PSD), as shown in Figure 6.5. The area under the curve of the power spectral density graph in the freeze band is the power of the freeze band (P_{FB}), and the area under the curve of the power spectral density graph in the locomotor band is the power of the locomotor band (P_{LOC}). The second set of features is Hjorth's parameters, which comprises the Activity (Equation 6.3), Mobility (Equation 6.4) and Complexity (Equation 6.5).

$$Activity = \sigma(x)^2 \tag{6.3}$$

Where σ is the standard deviation of a signal x.

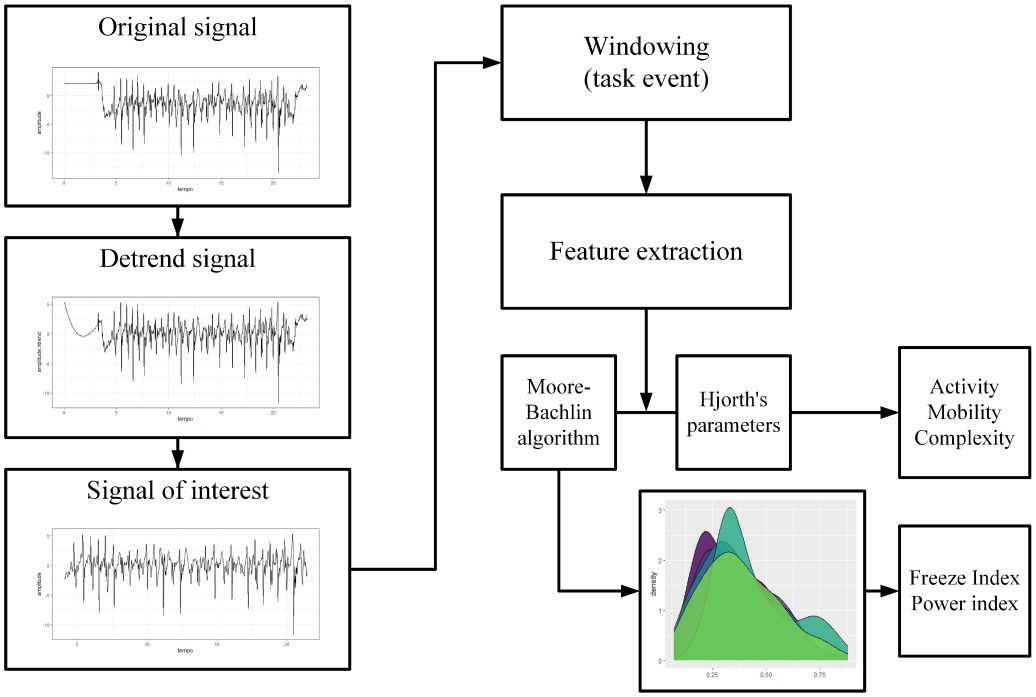

Figure 6.5 – Data processing to extract features using the method Moore-Bachlin (Freeze Index and Power Index) and Hjorth's parameters (Activity, Mobility, and Complexity).

$$Mobility = \sqrt{\frac{Activity(\dot{x})}{Activity}} \tag{6.4}$$

$$Complexity = \sqrt{\frac{Mobility(\dot{x})}{Mobility}} \tag{6.5}$$

Where $\dot{x}$ is the first discrete derivative of x, i.e., $\dot{x} = \frac{x_i - x_{i-1}}{\Delta t}$ and i is the i-th discrete time instant.

Activity is the squared standard deviation of the amplitude, understood as the variance or mean power. Mobility is the standard deviation of the slope with reference to the standard deviation of the amplitude. It is expressed as a ratio per time unit and may also be interpreted as a mean frequency. Complexity is a measure of excessive details with reference to the sine wave corresponding to unity (43).

A study made with synthetic signals in sine waves to assess Hjorth's parameters discovered that Activity is related to amplitude, Mobility is related to frequency, and Complexity is related to entropy (97). The tests were made by changing the amplitude, the frequency, and the entropy of the synthetic signal. For example, when increasing amplitude, the features Mobility and Complexity remain constant, but the feature Activity increases. When increasing the frequency, the features Activity and Complexity remain constant, but the feature Mobility increases. Complexity is more elaborate data; it is expressed as the number of standard slopes generated during the average time required for the generation of one standard amplitude, as given by Mobility. Due to the nonlinear

calculation of standard deviation, this parameter quantifies any deviation from the sine shape as an increase in unity (43). That can be interpreted as a change related to entropy (97).

After signal processing, FI, PI, Activity, Mobility, and Complexity values were estimated from each signal window. Furthermore, it is known which task event the windowed signal represents and whether it happened FOG or not. This allowed us to identify which feature has the most significant statistical results, the variables aim to detect FOG events (FI), measure the severity of FOG (FI), calculate the amount of movement and changes in motion (PI), elucidate the variability of data (Activity), identify the mean power and mean frequency (Mobility), and calculate the deviation from the sine shape as an increase in unity (Complexity).

6.2.8 Data analysis

For the statistical analysis, the data were organized into 17 variables:

1. Group: There are five possible groups: GC, GFOG+OFF, GFOG+ON, GFOG-OFF, GFOG-ON. They are the control group (GC) formed by healthy individuals, the GFOG+ group, which is the group of people who have PD and have a history of FOG, during OFF (GFOG+OFF) and ON medication state (GFOG+ON), and GFOG-group, which is the group of people who have PD but do not have the FOG symptom also during OFF (GFOG-OFF) and ON medication state (GFOG-ON).
2. Subject: varies from 1 to 10.
3. State: OFF, ON or NA (for the control group).
4. Task: task 1 (voluntary stop), task 2 (TUG test), task 3 (the motor task) and task 4 (the dual task).
5. Trial: 1, 2 or 3.
6. IMU ID: the smartwatch used, 1) right side of the iliac spine, 2) left side of the iliac spine or 3) leg, over the tibia.
7. Sensor: A (accelerometer) or G (gyroscope).
8. Axis: X, Y, or Z.
9. Fog: logical value, which indicates the FOG events imported from ATLAS software.
10. Event: 37 events, the voluntary stop has eight events, the TUG test has seven events and the motor and dual task have eleven events each.
11. Wnd: initial and final time of the event.

12. qq: 0 or 1, this logical value indicates if a FOG episode happened in this task event (qq = 1) or not (qq = 0).

13. Activity: first Hjorth's parameter, feature extracted from the windowed signal representing Activity.

14. Mobility: second Hjorth's parameter, feature extracted from the windowed signal representing Mobility.

15. Complexity: third Hjorth's parameter, feature extracted from the windowed signal representing Complexity.

16. Freeze Index: first Moore-Bachlin parameter, feature extracted from the windowed signal representing the Freeze-index

17. Power Index: second Moore-Bachlin parameter, feature extracted from the windowed signal representing the Power-index.

Task events that do not represent mobility, such as UP and SIT tasks ("VS_UP", "VS_SIT", "TUG_UP", "TUG_SIT", "MT_UP", "MT_SIT", "DT_UP", "DT_SIT") were not considered in data analysis. The data analysis was completed in two stages. In the first stage, the FOG events were observed. The organization and annotation of data allowed to elucidate the provoking strategies that most caused the FOG event for the GFOG+ group. The second stage involved the statistical analysis with the stats-type set to zero, which represents the GFOG+ gait without considering the FOG events, excluding data with the logical number that indicates if a FOG event is equal to zero, and the GFOG- and GC gait, for comparison. The Kruskal-Wallis test, a non-parametric alternative when the assumptions of the one-way ANOVA test are not met, was used for statistical analysis. Post hoc is the statistical test carried out to identify significant differences between the means of groups. The post hoc test of Kruskal-Wallis is the Wilcox rank test. The paired-sample Wilcox test is a non-parametric alternative because the data are not normally distributed. There are ten comparisons between groups:

1. GFOG+OFF vs. GC

2. GFOG+OFF vs. GFOG-OFF

3. GFOG+OFF vs. GFOG-ON

4. GFOG+OFF vs. GFOG+ON

5. GFOG-OFF vs. GC

6. GFOG-OFF vs. GFOG+ON

7. GFOG-OFF vs. GFOG-ON
8. GFOG-ON vs. GC
9. GFOG+ON vs. GC
10. GFOG+ON vs. GFOG-ON

It is possible to identify how many tests are positive for differences for each smartwatch (S1, S2, or S3), where S1 (b4ded260c247ecb2) is on the right side of the iliac spine, S2 (69db0199181b48b6) is on the left side of the iliac spine, and S3 (b03b6ba157789312) is on the leg, over the tibia. Additionally, it is possible to identify how many tests are positive for differences for each sensor (accelerometer and gyroscope), axis (X, Y, and Z), and feature (Freeze Index, Power Index, Activity, Mobility, and Complexity).

6.3 Results

Thirty participants were enrolled in this study, ten in the GFOG+ group, the group composed by individuals with PD and FOG, ten in the GFOG- group, the group composed by individuals with PD without FOG and ten in the GC, the control group. Three wearable triaxial accelerometers and gyroscopes were used. All participants wore IMU sensors on both ends of the iliac spine and on one leg, on the shank. Four mobility tasks were completed by the volunteers. Individuals with Parkinson's disease did the experiment twice, the first experiment during the OFF-medication state, 12 hours without taking the levodopa medicine; and the second during the ON-medication state, 30-50 minutes after taking levodopa. A total of six hundred trials of data were collected. Nine participants from the GFOG+ group had FOG episodes during the experiment, and one did not. A total of 160 FOG events (0–39 per subject) were recognized using video analysis by one observer. Figure 6.6 shows the task events ranked according to the total number of FOG episodes. It exhibits the percentage of FOG episodes for each FOG provoking-strategies. This figure shows only the information about the GFOG+ group and it is separated in two states, OFF and ON medication state. The task names are indicated on the X axis of the figure, as described below:

Tasks VS – voluntary stop; TUG – TUG test; MT – motor task; DT – dual task.

Task events GI – gait initiation, OG – open gait; T – turns; WO – pass through wide opening; VS – voluntary stop.

In Figure 6.6, 27 task events are presented in the top of the graph, the total number of task events is 29. The events MT_OG1 and MT_WO2, that are the first open gait of the motor task and the second passage through a wide opening do not appear, therefore, one can conclude that there is no FOG episode during these events.

Table 6.2 – Acronym of the task event and its description.

Task events	Description
MT_T3	the third 360 degree turn of the motor task
MT_T2 *	the second 360 degree turn of the motor task
DT_GI *	the gait initiation of the dual task
DT_T3 *	the third 360 degree turn of the dual task
DT_T2	the second 360 degree turn of the dual task
VS_T1 *	the first 180 degree turn of the voluntary stop
MT_T1	the first 360 degree turn of the motor task
DT_T1	the first 360 degree turn of the dual task
VS_T2 *	the second 180 degree turn of the voluntary stop, turn to sit
TUG_GI	the gait initiation of the TUG test
TUG_T1 *	the first 180 degree turn of the TUG test
DT_WO1	the first narrow passage of the dual task
VS_GI	the gait initiation of the voluntary stop
TUG_T2 *	the second 180 degree turn of the TUG test, turn to sit
MT_GI *	the gait initiation of the motor task
MT_T4 *	the first 180 degree turn of the motor task, turn to sit
DT_WO2	the second narrow passage of the dual task
DT_T4 *	the first 180 degree turn of the dual task, turn to sit
VS_OG2	the second open gait of the voluntary stop
TUG_OG2	the second open gait of the TUG test
MT_OG2	the second open gait of the motor task
MT_WO1	the first narrow passage of the motor task
DT_OG1	the first open gait of the dual task
VS_VS *	the voluntary stop of the voluntary stop
DT_OG2	the second open gait of the dual task
VS_OG1	the first open gait of the voluntary stop
TUG_OG1 *	the first open gait of the TUG test

Table 6.3 – The number of statistical tests with p-value < 0.05 for each smartwatch.

Smartwatch	IMU ID	position	n
S1	b4ded260c247ecb2	Right side of iliac spine	505
S2	69db0199181b48b6	Left side of the iliac spine	475
S3	b03b6ba157789312	Shank	369

The events are repeated throughout the tasks. For instance, the GI event is used to start each task. This event shows the volunteer's position as he prepares to walk until he makes two contacts with the ground and completes a step. The number of FOG episodes is represented in 'n' and the 'perct' represents the percentage of FOG triggered by this event in particular.

To better understand the labels, Table 6.2 shows the acronym and its definition. Table 6.2 is ordered by the events presented in Figure 6.6. The asterisk in Table 6.2 represents the task events in which the FOG episode happened during the ON-medication state.

Figure 6.7 shows the events presented in Table 6.2 in alphabetical order, where n is the number of FOG episodes and perct is the percentage of FOG triggered by the provoking strategy. This figure shows only the information about the GFOG+ group and it is separated in two states, OFF and ON medication state.

The statistical analysis with the stats type equal to zero represents the GFOG+ gait without considering the FOG events. That means that we could evaluate the gait changes of the groups considering their regular gait, without the episodic disorder FOG. For the smartwatches, the results show that the sensors positioned at both ends of the volunteer's iliac spine are better at differentiating the groups when compared to the sensor on the shank. However, all three smartwatches can identify differences between groups (Table 6.3).

For the sensors, the results show that both sensors (i.e., the accelerometer and gyroscope) yield similar results, and they allow for the identification of differences between groups. The number of statistical tests with p-value < 0.05 for the accelerometer was 686 and for the gyroscope was 663. In terms of the axis, the results show that there is no difference between the axes analyzed since they all yield similar results, as shown in

Table 6.4 – The number of statistical tests, n, with p-value < 0.05 for each axis (X, Y, Z).

Axis	n
X	480
Y	465
Z	404

Table 6.5 – The number of statistical tests, n, with p-value < 0.05 for each extracted feature. MB is Moore-Bachlin algorithm and HP is Hjorth's parameters.

Method	Feature	n	percent
HP	Activity	411	30.46
MB	Power Index	357	26.46
HP	Complexity	213	15.78
MB	Freeze Index	199	14.75
HP	Mobility	169	12.52

Table 6.6 – The number of statistical tests that identified the difference between the groups for the 360-degree turn.

Prov. Strategy	Task event	Feature	GC vs. GFOG+ OFF	GFOG+ OFF vs. GFOG+ ON	GFOG+ OFF vs. GFOG- OFF	GFOG+ OFF vs. GFOG- ON	GC vs. GFOG- OFF
360 degree turn	MT_T1	ACT	12	9	10	11	6
		PI	12	9	10	11	5
	MT_T2	ACT	11	10	11	11	9
		PI	12	11	11	10	8
	MT_T3	ACT	12	7	7	6	12
		PI	12	7	10	8	12
	DT_T1	ACT	12	11	12	12	9
		PI	10	10	10	11	10
	DT_T2	ACT	12	11	10	12	9
		PI	12	11	9	12	9
	DT_T3	ACT	11	11	9	10	10
		PI	11	11	9	11	10

Table 6.7 – The number of statistical tests that identified the difference between the groups for the open gait.

Prov. Strategy	Task event	Feature	GC vs. GFOG+ OFF	GFOG+ OFF vs. GFOG+ ON	GFOG+ OFF vs. GFOG- OFF	GFOG+ OFF vs. GFOG- ON	GC vs. GFOG- OFF
open gait	VS_OG1	ACT	8	9	8	10	1
		PI	10	8	7	10	0
	VS_OG2	ACT	9	9	9	9	0
		PI	9	7	9	8	1
	TUG_OG1	ACT	9	6	7	10	2
		PI	9	7	7	9	2
	TUG_OG2	ACT	10	6	9	10	0
		PI	10	6	8	8	0
	MT_OG1	ACT	9	4	2	10	5
		PI	7	2	1	5	3
	MT_OG2	ACT	12	11	11	12	5
		PI	12	10	10	11	4
	DT_OG1	ACT	11	9	11	11	1
		PI	8	7	5	8	2
	DT_OG2	ACT	11	10	9	11	2
		PI	10	7	9	10	2

Table 6.8 – The number of statistical tests that identified the difference between the groups for walking through the wide opening.

Prov. Strategy	Task event	Feature	GC vs. GFOG+ OFF	GFOG+ OFF vs. GFOG+ ON	GFOG+ OFF vs. GFOG- OFF	GFOG+ OFF vs. GFOG- ON	GC vs. GFOG- OFF
pass through a wide opening	MT_WO1	ACT	11	9	8	12	6
		PI	9	6	3	8	2
	MT_WO2	ACT	11	11	8	12	3
		PI	10	8	3	11	3
	DT_WO1	ACT	11	10	10	12	3
		PI	8	7	6	8	0
	DT_WO2	ACT	10	9	9	12	2
		PI	7	7	1	8	3

Table 6.9 – The number of statistical tests that identified the difference between the groups for the gait initiation.

Prov. Strategy	Task event	Feature	GC vs. GFOG+ OFF	GFOG+ OFF vs. GFOG+ ON	GFOG+ OFF vs. GFOG- OFF	GFOG+ OFF vs. GFOG- ON	GC vs. GFOG- OFF
gait initial- ization	VS_GI	ACT	11	10	6	10	3
		PI	10	7	3	7	7
	TUG_GI	ACT	7	2	0	4	6
		PI	6	0	0	1	7
	MT_GI	ACT	10	2	5	6	7
		PI	6	0	0	2	6
	DT_GI	ACT	8	3	6	7	0
		PI	3	0	2	2	0

Table 6.10 – The number of statistical tests that identified the difference between the groups for the 180-degree turn.

Prov. Strategy	Task event	Feature	GC vs. GFOG+ OFF	GFOG+ OFF vs. GFOG+ ON	GFOG+ OFF vs. GFOG- OFF	GFOG+ OFF vs. GFOG- ON	GC vs. GFOG- OFF
180 degree turn	VS_T1	ACT	9	6	3	6	2
		PI	3	0	1	3	0
	VS_T2	ACT	9	7	3	4	4
		PI	6	6	1	6	1
	TUG_T1	ACT	6	1	1	4	3
		PI	2	0	1	1	1
	TUG_T2	ACT	9	3	2	2	4
		PI	5	0	1	1	2
	MT_T4	ACT	11	8	7	8	5
		PI	7	10	7	9	0
	DT_T4	ACT	11	10	6	10	6
		PI	11	9	3	8	6

Table 6.4. The X-axis is the horizontal axis (side-to-side axis), the Y-axis is the vertical axis (longitudinal axis), and the Z-axis is the depth axis (anterior-posterior axis).

The results show that the variable that best represents the differences between groups is Activity (>30%), followed by Power Index (>26%). These two features account for over half of the total observations, as depicted in Table 6.5.

Among the ten possible comparisons between the five groups (GC, GFOG+OFF, GFOG+ON, GFOG-OFF, GFOG-ON), five were promising for the Activity and Power Index features. In these cases, multiple pairwise comparisons were statistically significant (p-value < 0.05), that is, suggesting a difference between the referred groups. These comparison pairs were:

1. GFOG+OFF vs. GC
2. GFOG+OFF vs. GFOG-OFF
3. GFOG+OFF vs. GFOG-ON
4. GFOG+OFF vs. GFOG+ON
5. GFOG-OFF vs. GC

Figure 6.8 shows the results with statistical significance per task event; n represents the number of pairwise-comparisons that have a p-value < 0.05. The events are arranged in alphabetical order and the graphic also shows the abbreviation of the event next to point.

In Figure 6.8, the FOG-provoking strategies were separated into the following groups: the color red stands for 360-degree turns, orange denotes open gait, blue for passing through a door, purple for starting to walk, and green for 180-degree turns.

It is possible to notice that in the interval between n = 200 and n = 250, only the 360-degree turn event appears (points in red), so this is the moment of the task in which the proposed method better discriminates the data between the groups. Interestingly, there was a consistent behavior observed during both the motor task and the dual task. For these tasks, the number of statistically significant pairwise-comparisons was highest for the second 360-degree turn, followed by the third and first 360-degree turns.

From n = 150 and n = 200, it shows the open gait and the passage through a wide opening, which indicate that the person is walking in a straight line. Between n = 100 and n = 150 the open gait and pass through a wide opening are mixed with the gait initiation and the 180-degree turn. Between n = 50 and n = 100 only the 180-degree turn, and gait initiation appear.

In Tables 6.6 to 6.10, the number of statistical tests that identified the difference between the groups is presented for the sensors on the belt, which has two smartwatches with a triaxial accelerometer and gyroscope. The maximum limit for axes in Tables 6.6 to 6.10 is 12 (S1AX, S1AY, S1AZ, S1GX, S1GY, S1GZ, S2AX, S2AY, S2AZ, S2GX, S2GY, S2GZ). The tables show the groups being compared considering the features Activity and Power Index.

For the table to be intuitive, a color legend was used. Cells with values from 0 to 3 are in red, 4 to 6 in orange, 7 to 9 in blue, and 10 to 12 in green. The red color represents a bad result, the orange color represents a regular result, the blue color represents a good result, and the green color represents an excellent result.

The method differentiates the GFOG-OFF from the GC group only during the 360-degree turn. The method differentiates GFOG+OFF from GFOG-OFF, GFOG+ON, and GFOG-ON during the 360-degree turn and while the person is walking in a straight line, as in the open gait (MA) or passing through a wide opening (PP). The ranking of combinations that the method is able to identify with the GFOG+OFF group is presented below.

(1^{o}) GFOG+OFF vs. GC
(2^{o}) GFOG+OFF vs. GFOG-ON
(3^{o}) GFOG+OFF vs. GFOG+ON
(4^{o}) GFOG+OFF vs. GFOG-OFF

The 180-degree turn and gait initiation do not allow the method to identify the difference between GFOG+OFF from GFOG-OFF, GFOG+ON, and GFOG-ON; however, the movement from turning to sitting in the motor task and dual task seems to be able to elucidate this difference. The Activity variable stands out over the Power Index, even though the two variables are positively correlated (COR $>$ 0.9), as shown in the autoplots of Figures 6.9 and 6.10.

The autoplot function in ggplot2 was used to generate various types of plots. It is a powerful generic function to visualize various data objects with better default graphs. The function returns a figure that gives information about the number of samples in each group and shows the boxplot, the density plot, the scatter plot, the histogram, and the correlation between the variables.

Observe two examples of autoplots in Figures 6.9 and 6.10. These autoplots show the number of samples in each group, the boxplot, the density plot, the scatter plot, the histogram, and the correlation between the features, i.e., Freeze Index, Power Index, Activity, Mobility, and Complexity. Correlation between Activity and Power Index is 0.963 in Figure 6.9 and 0.961 in Figure 6.10.

The boxplots from Figure 6.9 and 6.10 with a better visualization are presented in Figure 6.11, it shows the results for Activity and Power Index variables. First line represents the boxplots for the second 360-degree turn during the physical mobility motor task and the second line represents the boxplots for the second 360-degree turn during the physical mobility dual task.

The statistical test allowed us to determine where the real differences between the groups are located and to discover the best approach or quantifying gait alterations in PD.

6.4 Discussion

This study aims to explore new combinations of inputs and features extraction changes for assessing gait in PD. We investigated the provoking strategies used to trigger FOG in PD and proposed a new method to detect changes in gait patterns, calculating the Freeze Index (FI) and Power Index (PI) with the Moore-Bachlin algorithm and the Activity, Mobility, and Complexity, the Hjorth's parameters.

The results presented in this study can be used to assess freezers in PD and to evaluate Parkinson's disease patients. Some participants exhibited dyskinesia after taking medication to perform the experiment in the ON state; Dyskinesia typically occurs more than 60 minutes after administering the levodopa dose and initially affects the upper body, mainly the face and neck, however, the low natural frequency of dyskinesia, less than 3 Hz, suggests that it is unlikely to interfere with the identification of FOG (70). None of the participants reported uncomfortable sensations using the sensors. Some expressed

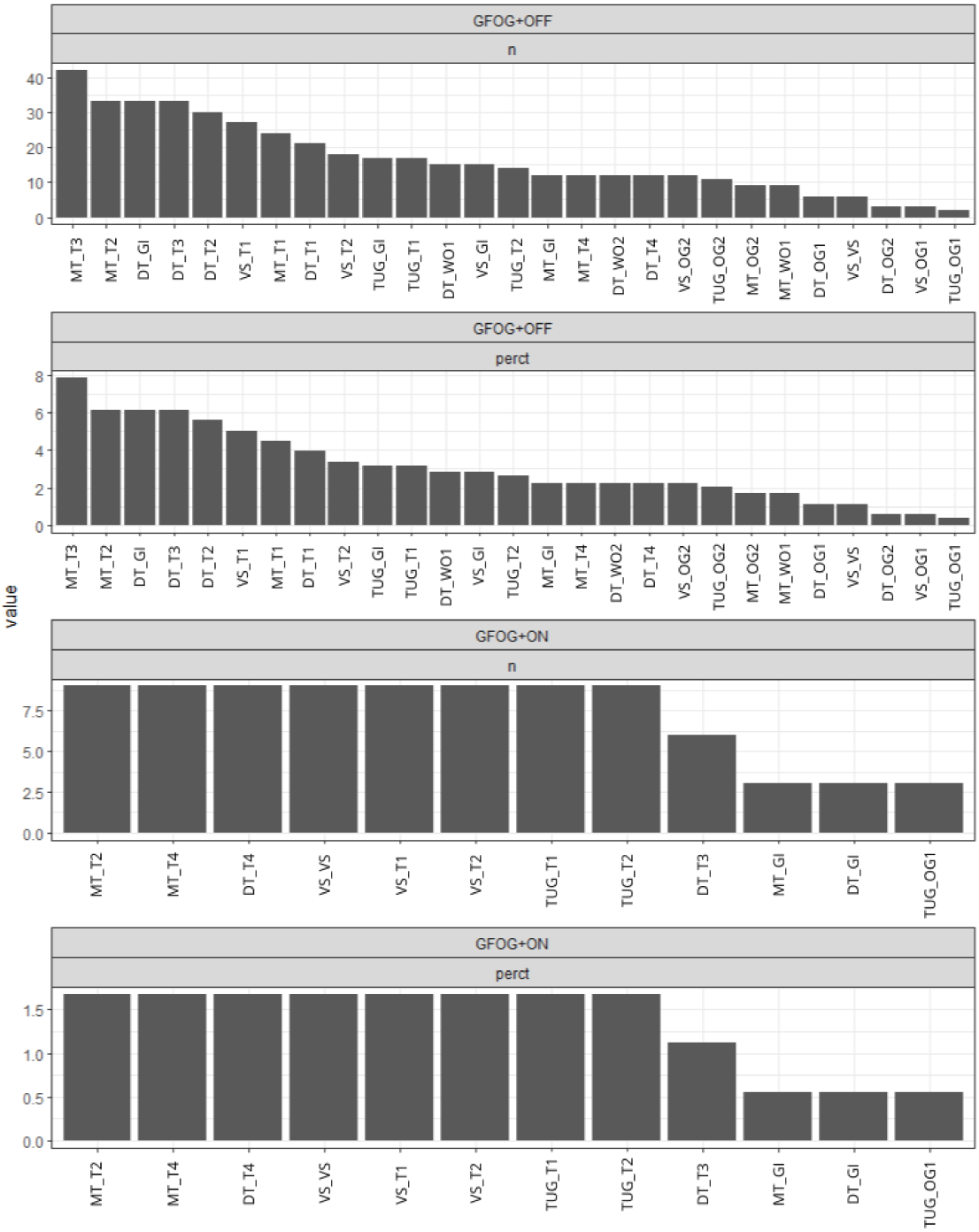

Figure 6.6 – Task events ranked according to the total number of FOG episodes, where n is the number of FOG episodes and perct is the percentage. Data is presented for the GFOG+OFF and GFOG+ON group.

interest in the possibility of being helped with the walking task and seemed to accept the use of wearable technology well.

Figure 6.6 shows that the developed motor task to trigger FOG is the task that leads the ranking of FOG episodes during the OFF and ON states, followed by the dual task. The 360-degree turn, followed by the 180-degree turn are the task events that most trigger FOG episodes. The gait initiation seems to be an important event, once it appears several

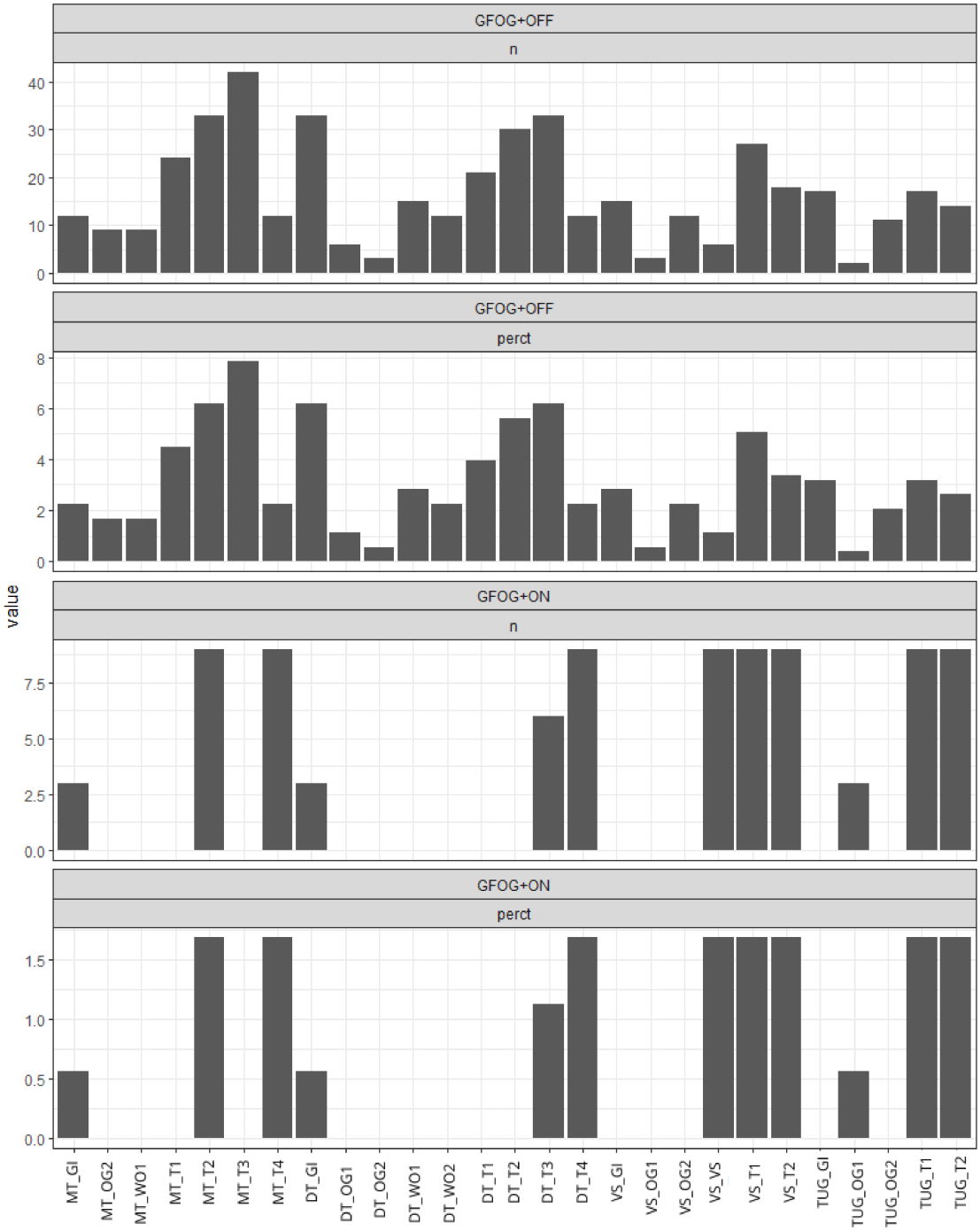

Figure 6.7 – The events presented in Table 6.2 in alphabetical order, where n is the number of FOG episodes and perct is the percentage of FOG triggered by the provoking strategy.

times between the 8th and 18th position of Table 6.2. The open gait appears as the least likely event to cause FOG. The event to pass through a narrow wide opening appears in the 12th, 17th and 22nd positions.

Gait initiation, which represents the transition from a standing posture to cyclic walking, is altered in PD (108, 81). In general, patients with PD start walking with significantly shorter steps and with high variability in step length compared to healthy individuals, they also have greater variability in step duration.

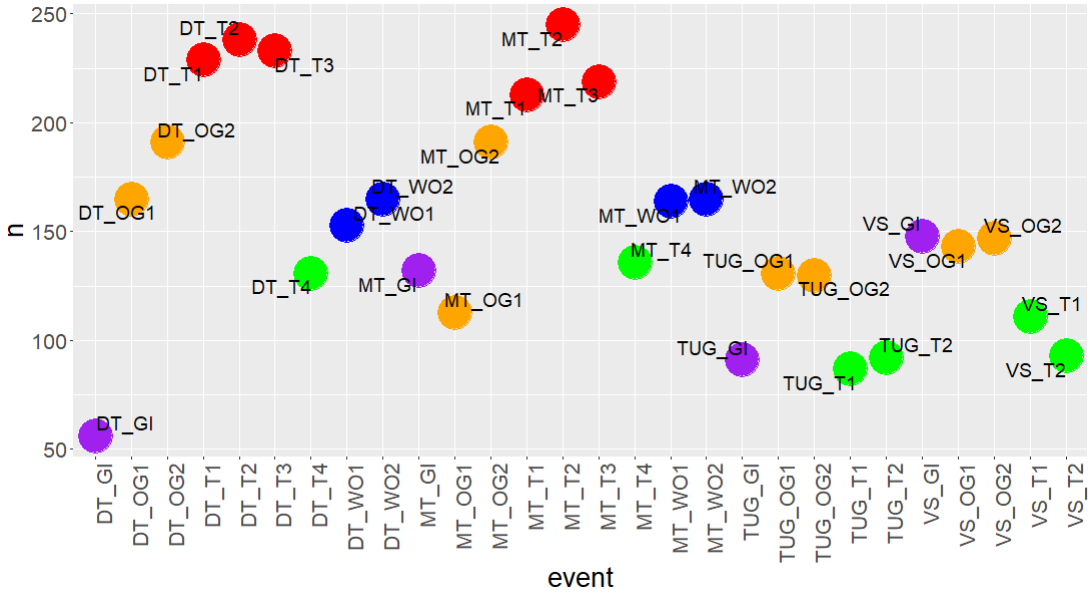

Figure 6.8 – Number of pairwise-comparisons, n, with significant statistical differences.

Only twelve task events could cause FOG in the GFOG+ group following the morning dosage of medicine, according to the graphs for this group in Figure 6.6. In Table 6.2, they are indicated by an asterisk. Most of these actions involved gait initiation, 180-degree turns, and 360-degree turns. The volunteer's voluntary stop, the ten seconds during which they remain standing while data is being collected, could also cause FOG in both the ON and OFF medication phases.

Figure 6.7 expand the information of Figure 6.6. It shows that the highest percentage of FOG episodes triggered belongs to the 360 degree turn of the motor task (MT_T2 and MT_T3) the gait initiation for the dual task (DT_GI), and the 360 degree turn of the dual task (DT_T2 and DT_T3).

In this visualization mode of Figure 6.7, it is possible to see that the tasks that cause FOG episodes during the ON medication are the 180 degree turn (MT_T4, DT_T4, VS_T2, TUG_T2, VS_T1, TUG_T1) with attention that four from six events are the 180 degree turn to sit movement, the 360 degree turn (MT_T2 and DT_T3), the gait initiation for the motor and dual task and the voluntary stop (VS_VS). Furthermore, it is possible to visualize the importance of the four tasks to trigger the event in the ON medication state.

In Figure 6.7, it is possible that some events caused FOG episodes during the OFF medication state and that did not triggered FOG during the ON medication state. Literature shows that most FOG episodes occur while patients attempt to initiate walking and during turning movements (16). The occurrence of FOG is four times more frequent during turning events than walking in a straight line (114).

In the study by Spildooren (117), the researchers asked the participants not to take the first dose of the levodopa medication to carry out the experiment, in which the patients

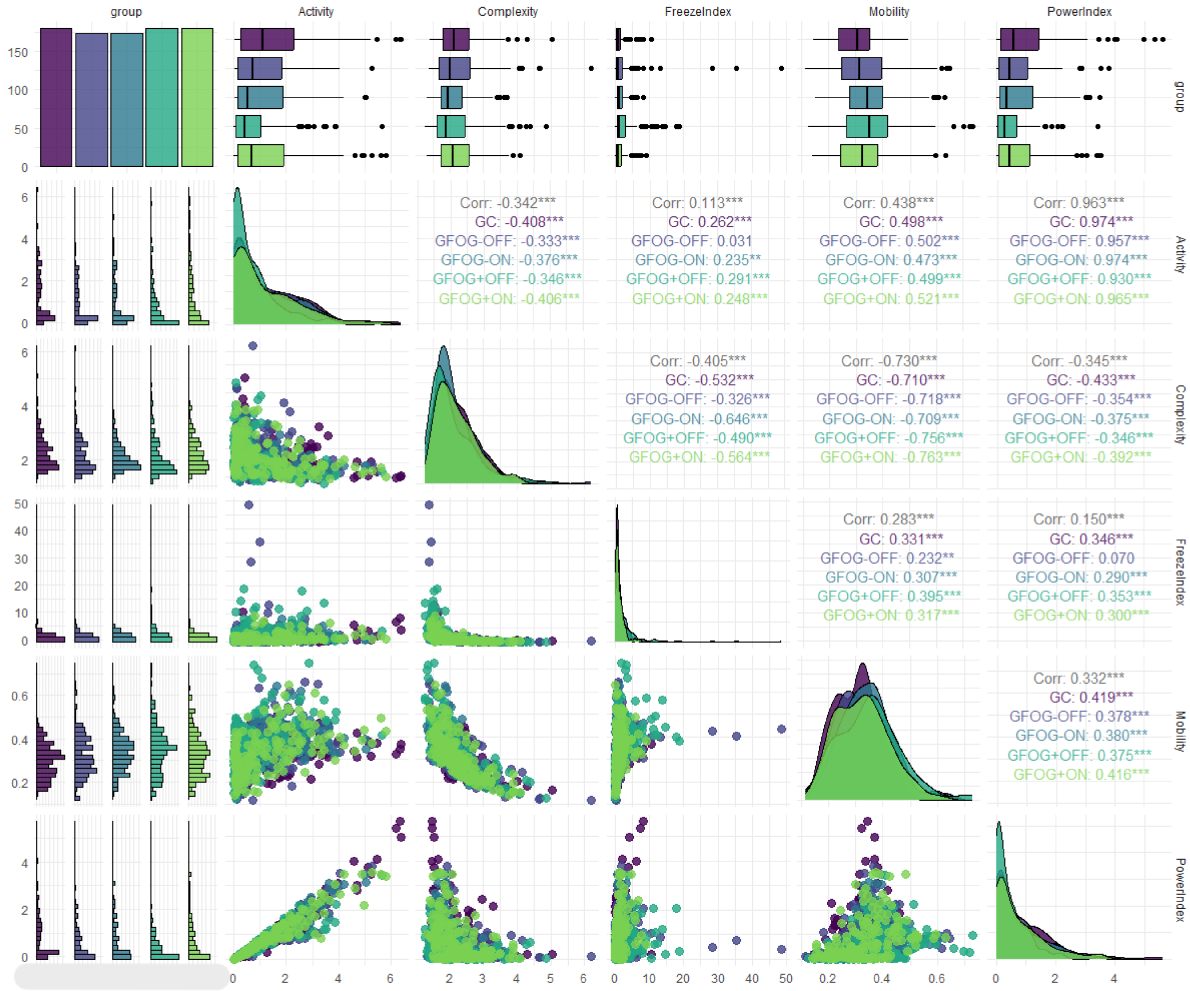

Figure 6.9 – Autoplot for the second 360-degree turn during the physical mobility motor task.

walked for five meters and turned left or right, going around a marker on the floor. In that study, it was found that the trigger that most caused the episode of FOG was turning 360 degrees while performing a dual task. During the turn, the volunteers with PD who have a history of FOG increased the cadence, while the other volunteers, the control group, and the group with PD without a history of FOG decreased the cadence at that moment of the walk.

The movement of turning is related to falls, because numerous falls are caused by sudden shifts in posture, particularly turning movements of the trunk, or by attempts to accomplish multiple tasks while walking or balancing. The more difficult the tasks are, the worse the performance becomes. It seems that PD patients have special difficulty prioritizing what is most crucial, maintaining a safe walk and an upright posture, under challenging circumstances. Patients often execute all tasks equally well. However, they tend to suffer from poor balance or gait. Falls frequently occur during transfers, such as standing up from a chair or bed. Trips and slip-related falls are relatively uncommon (16).

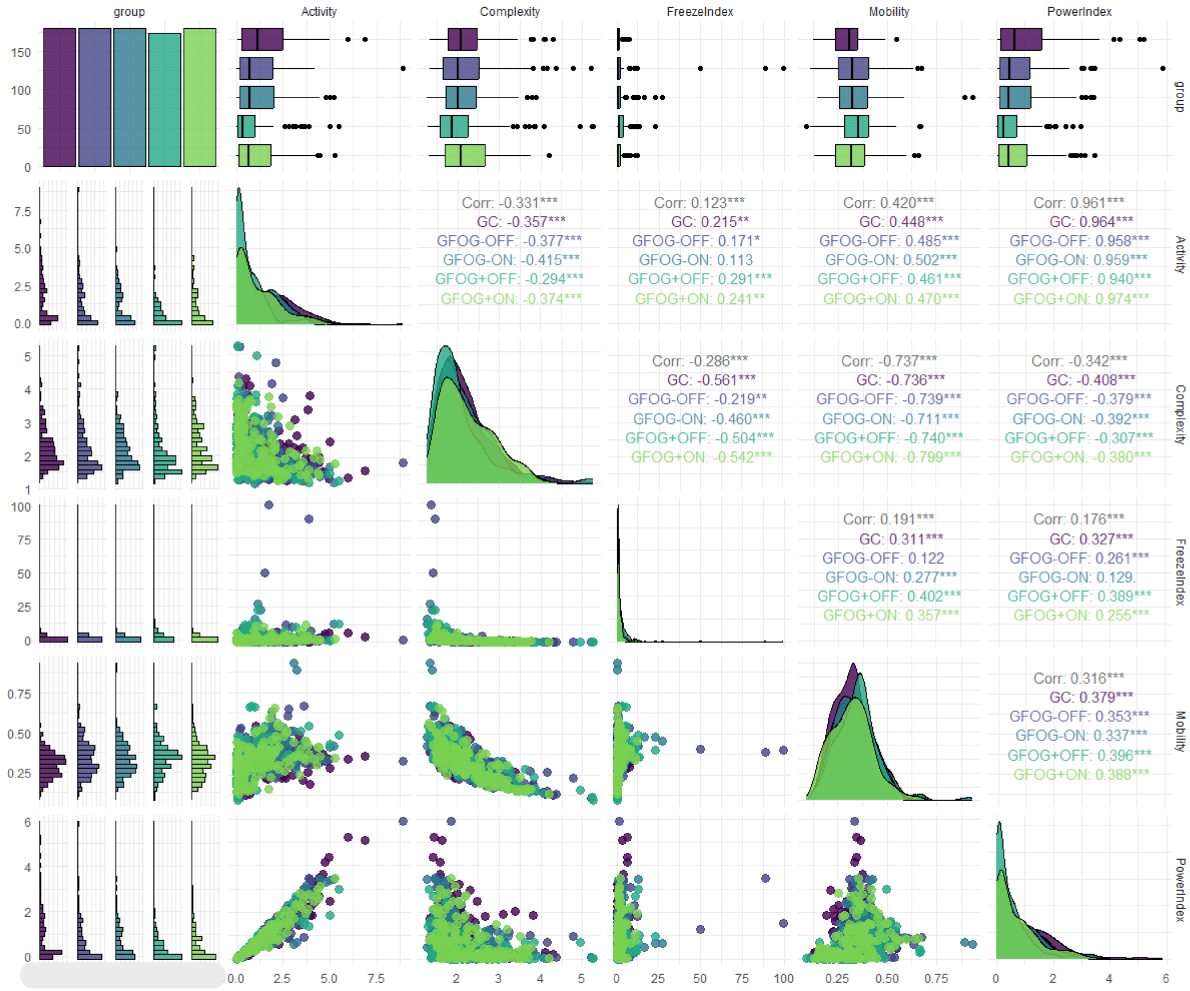

Figure 6.10 – Autoplot for the second 360-degree turn during the physical mobility dual task.

Statistical results show that the sensors on the iliac spine are better at differentiating the groups when compared to the sensor on the shank. However, all three placements of the smartwatches can identify differences between groups. The importance of the sensors positioned on the iliac spine is explained because during the stance and swing phases, the pelvis, respectively, depicts rotational motions in the horizontal plane that occur externally and internally. The movement alternates between each side since the pelvis is a solid structure. Less hip flexion and extension movements are implied by this rotational action, as well as less vertical center of gravity oscillation. As the pelvis shifts to the side of the swinging limb, opposing the elevation brought on by the contralateral limb during medium support, the movement of the pelvic inclination in the frontal plane also contributes to the lower vertical oscillation of the center of gravity. The pelvis lateralizes over the supporting limb with each step. Each step results in a 4–5 cm lateral displacement of the pelvis. If the step width widens while the person is walking, the displacement is higher.

The features Activity and Power Index represent more than half of the total observa-

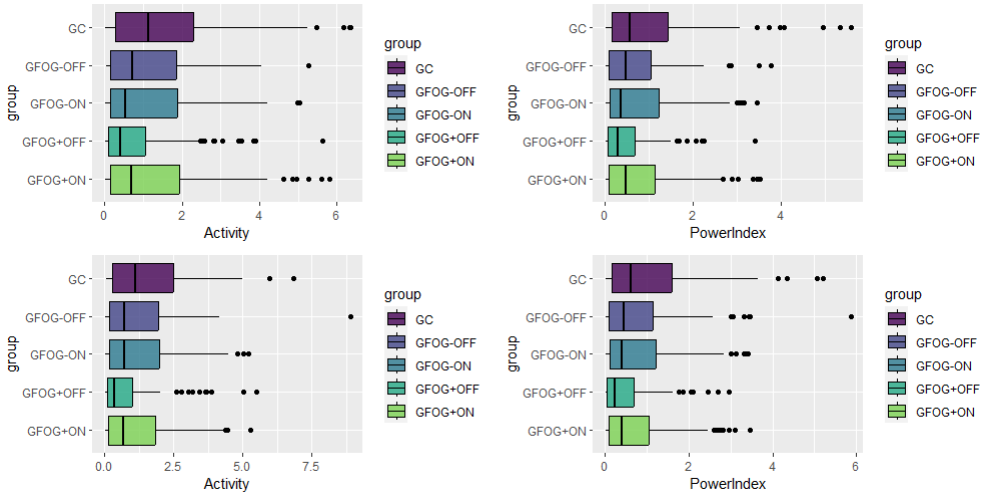

Figure 6.11 – Boxplot for the second 360-degree turn during the physical mobility dual task.

tions of statistical test with significant difference between groups. Activity is the most important feature, followed by Power Index, these features are positively correlated (Figures 6.9 and 6.10).

The discovery of Activity and Power Index as a powerful combination to measure gait changes in PD is important for FOG study. The literature shows that Freeze Index (FI) and Power Index (PI) are important features to be extracted from linear acceleration signals to detect FOG, measure the severity of the FOG episode, and calculate the amount of movement in the windowed signal (70, 11, 24, 91, 20, 106, 105, 74).

Freeze Index (FI) is used for FOG detection and to measure FOG severity. The results of FI for the present study did not stand out; this was expected because we excluded the windows of signal with FOG episodes. When the stats-type was set to zero to carry out the statistical analysis, this meant that the analysis would include the GFOG+ gait without considering the FOG episodes, excluding data with a logical number equal to one. This was the way we found to compare GFOG+, GFOG-, and GC gait equally.

As a future work, it is valuable that we elucidate the FI from data set including the FOG episodes signals, because knowing this information can be useful in clinical trials to evaluate new therapies or to assess the effect of rehabilitation intervention for FOG.

Wang (130) proposed an analysis of the FI on electroencephalography (EEG) sensors and accelerometers sensors placed on the ankle and concluded that the multimodal signal model is better than the single one, comparing only the EEG and accelerometer sensors. Mostafa (74) proposed a frequency analysis with deep learning techniques to detect FOG and trigger a rhythmic auditorium stimuli with minimum latency based on the Moore-Bachlin algorithm. The Hjorth's parameters, commonly used in the analysis of EEG signals for feature extraction (95, 39), was applied in this study as an approach to measure changes in gait. Recently, these parameters were used to identify and characterize short-term motor patterns in rest tremor in individuals with Parkinson's disease (98) and the

results were satisfying.

In the present study, for each moving window, five features related to the time and frequency domain were extracted, Freeze Index, Power Index, Activity, Mobility, and Complexity. The method proposed by this study shows that Activity and Power Index are important features to be extracted from triaxial accelerometers and gyroscopes positioned on the two iliac spines to measure the variability and the amount of movement during mobility tasks.

Figure 6.8 shows that the 360 degree turn event is the moment of the task in which the proposed method better discriminates the data between the groups. It is followed by the open gait and the passage through a wide opening, which indicate that the person is walking in a straight line. This information proves that people from the GFOG+OFF group walks differently from the other groups, even if they are not frozen, their gait without medicine is more affected than the GFOG-OFF group.

The task events that showed the least statistical differences were the 180 degree turn and gait initiation. These provoking strategies seems to be important to trigger FOG, however during the regular walk of a freezer they do not differentiate the groups as much as the other task events. Thus, this suggests that factors inducing freezing of gait might not exhibit abnormalities in the gait pattern but could disrupt the subsequent walking pattern.

In addition, the results presented in Figure 6.8 indicate that a higher number of statistical differences among the gait patterns of the distinct groups were associated with the second 360 degree turn. This highlights two interesting aspects. Firstly, the fact that individuals with gait freezing perform a first turn along the route may trigger freezing episodes and introduce heightened walking challenges, potentially rendering a second 360 degree turn more difficult. Secondly, subsequent 360 degree turns (T2) appear to be more difficulty for freezers compared to non-sequential turns that are associated to gait-concluding, such as the act of turning to sit in a chair (T3).

One can conclude that the 360-degree turn affects the gait of the GFOG+ group volunteers because it is a more complex task that can cause insecurity while performing the movement. There is training to make the person safer to perform this movement, such as progressive resistance training (9, 54).

Practically, this insight could prove valuable in mitigating severe freezing episodes in freezers, thus promoting more comfortable indoor walking and engagement in daily activities. On the other hand, healthcare professionals can also use this strategy of consecutive turns to assess gait impairment in these patients without the need for very complex tasks or subjecting patients to states of discomfort, allowing for a more humanized gait assessment and rehabilitation.

Figure 6.11 shows that the boxplot from the GFOG+OFF group is shifted to the left on the four graphs represented. The boxplot of the GC group is larger, and it is

similar to the GFOG-OFF, GFOG-ON, and GFOG+ON; otherwise, the boxplot of the GFOG+OFF is always smaller, representing less variability of data.

One can conclude that the Activity and Power Index are lower for the freezers during the OFF state of medication. Activity is understood as the variance of data, and it shows the variability. The Power Index calculates the amount of movement in the windowed signal.

This result is in accordance with the literature because the PD symptoms such as rigidity, bradykinesia, and postural instability combined result in a flexed posture while walking, with decreased axial rotation of the trunk, reduced arm swing, and a lower gait (48). Therefore, it is expected that people with PD and severe gait problems have less motor activity, which means less variability in the movement of walking, and a lower Power Index, which means that the quantity of movement presented in the windowed signal during the mobility task execution is smaller than that of a healthy individual with sufficient capacity for movement or an individual with PD who has taken levodopa.

Observing the statistical results, at an initial moment, it is possible to identify that the GFOG+OFF group differs from all other groups; that is, the analysis of the data shows that the GFOG+OFF group (individuals with PD and the symptom of FOG during the OFF state of the medication) performs the walking movement differently from the group of people with PD under the effect of levodopa (ON) and without medication (OFF) and from the group without Parkinson's during mobility tasks.

Furthermore, the results show that there is a statistically significant difference between the GFOG+OFF and GFOG+ON groups; that is, the volunteers with PD who have the FOG symptom walk differently under the effect of medication. The same observation could not be made for the GFOG-OFF and GFOG-ON groups. Participants with PD without the symptom of FOG do not differentiate between the OFF and ON states.

Considering the parameters presented in this experiment, the results show that the GFOG-OFF group can be differentiated from the control group using the Activity and Power Index variables extracted from the signal while performing the 360 degree turn. Five comparisons were not included in the analysis due to a lack of significant statistical differences.

It is also concluded that during the ON state of the medication, the person with PD with or without the symptom of FOG (GFOG-ON and GFOG+ON) cannot be differentiated from the control group, suggesting that the medication led to an enhancement in mobility of the participants with PD and FOG. In addition, no relevant difference was identified between the GFOG+ON groups and the GFOG-OFF and GFOG-ON groups, supporting this hypothesis.

FOG is relatively common and disabling in people with PD. It can be heightened by stress, anxiety, and negative emotions such as anger, fear, or despair. It can also be triggered by environmental constraints (73) and specific movements, like turning, initiate

gait and pass through narrow passages. These movements that are FOG provoking were reunited to create the tasks presented in this study and the most often occurs when the participant with PD is in the OFF medication state.

Quantitative assessments provide more complete data but should be used in parallel with the clinical assessment (21). Collaborative problem solving and goal settings help therapists and their patients to co-design interventions based on the patient's needs, thereby modeling the formulation of effective and acceptable prevention and management FOG plans. PD medication, physiotherapy and relaxation techniques arguably provide the best combination of therapies to manage their debilitating neurological disorder. This can be seen as the management of fall risk through constructive and pro-active health behavior (45). Physiotherapists might focus on posture, balance, gait, and transfers that can be targeted. Cueing that helps de-FOG, teaching alternate motor methods to make safer transfers, gait training, and exercises to improve stability, flexibility, and general fitness are a few examples of potentially helpful interventions (16). Furthermore, therapists should explore any FOG prevention behaviors that have been adopted by a freezer PD patient and can use tools such as the method presented by this thesis to explore and develop safe movement habits.

The experiment simplifies the assessment of freezers in PD because it clarifies the task events that most trigger FOG episodes and the task events that better explain the changes in gait between the groups, the 360 degree turn. Besides that, results show that the end of iliac spine is the best sensor location to identify the differences between the groups and the features Activity and Power Index are more suitable to discriminate the groups. The possibility of monitoring gait changes of freezers and PD patients periodically with a reliable system that can provide objective feedback to treatment could improve the management of FOG in PD.

6.5 Conclusion

In this chapter, we presented a method for gait analysis using a triaxial linear waist-mounted accelerometer and gyroscope. Experiments include four tasks: voluntary stop, TUG test, physical mobility motor task, and physical mobility dual task, conducted on thirty participants, ten in the GFOG+ group, ten in the GFOG- group, and ten in the GC group. An expert observer identified the FOG episodes using offline video analysis and annotation. The organization of data allowed to identify that 360-degree turn, followed by the 180-degree turn and gait initiation are task events most able to trigger FOG episodes. Furthermore, statistical results show that the 360-degree turn is also the task event most capable of discriminating the groups using Activity and Power Index features. Gait changes, represented as gait variability and the amount of movement during gait execution, also appear while walking in straight line, proving that people with FOG walk

differently than people who do not have FOG, even in between the freezing episodes.

7

General Conclusions

The ability to move around is vital in our daily lives. However, Parkinson's disease can limit the human capacity for movement. To have a neurodegenerative disease like PD that progresses over time may lead an individual to a sense of loss and disappointment because life will not play out as the person planned and the limitations are an overarching factor that influences decisions about what activities to undertake and how to undertake them (45).

The evaluation of PD is based on the findings of the clinical assessment because there is no test available to provide a conclusive diagnosis of PD or to asses treatment efficiency during the course of the disease. With repeated testing over time, diagnostic precision increases (100). Since the diagnosis is mostly dependent on the patient's history, clinical signs and symptoms, and response to treatments, the clinician's and physiotherapist's knowledge and expertise are crucial (59).

One of the potential trends is the use of sensor devices, which are inexpensive, low-power, unobtrusive, and accurate in their readings, for managing and monitoring the pathology in order to reduce this issue. The capture of previously inaccessible phenomena in PD is made possible by the accessibility of technologies.

The importance of this work arises because accurate detection and rating of the severity and the impact of FOG is crucial for appropriate treatment and follow-up (102, 105). Furthermore, determining methods to assess the physical mobility of freezers during clinical practice and considering the FOG analysis for adequate treatment and follow-up could prevent falls, reduce or overcome FOG episodes, and increase the quality of life of individuals affected by FOG (102, 105).

FOG manifests itself differently between patients and is strongly context-dependent, but in terms of inertial sensors and their spectral information, some common features associated with FOG can be used for gait analysis (113). Individuals with advanced PD are generally subject to altered gait patterns, which makes it difficult to reliably identify and detect gait events or compute gait parameters (114). To fully assess the range of balance and gait disorders in Parkinson's disease, the assessment should therefore include

a battery of functional tests, such as the ones presented in this thesis. According to Bloem (16), it is crucial to evaluate the safety of turning movements, transfers, and gait in PD.

The experiments presented in this thesis made the following contributions to the field:

1. To induce FOG events with a simple physical mobility task in a controlled environment.

2. To investigate which task is best able to trigger FOG events: the voluntary stop, the TUG test, the motor task, or the dual task.

3. To differentiate the FOG types by interpreting the signals of the inertial sensors.

4. To elucidate the percentage of FOG events in each FOG-provoking strategy included in the mobility tasks.

5. To investigate if data acquired with the Net MD system allows discrimination between subjects with PD with a history of FOG, subjects with PD with no history of FOG, and people without PD.

6. To propose features able discriminate between the groups, the classic Moore-Bachlin algorithm or Hjorth's parameters and to elucidate which group of features or feature combination is better suited to detect gait changes during the execution of the proposed mobility tasks.

7. To investigate if there are gait improvements during the ON medication state compared with the OFF medication state of the groups with PD (GFOG+ and GFOG-) according to the features extracted from the data analysis.

8. To perform statistical tests and identify the number of positive tests for the differences between the groups considering the smartwatches, the sensors, the axes, the features, the tasks, and the task events.

9. To generate an open access database that researchers can access and contribute to the development of new technologies to improve the quality of life of individuals with Parkinson's disease.

At the end of the study, it was possible to extend the approach of FOG assessment by observing different gait parameters and elucidate the optimal combination of sensor, sensor placement, task and feature to be extracted to identify gait changes in Parkinson's disease. Furthermore, the study could determine which FOG-provoking strategy most significantly influences the gait of freezers and results in more FOG episodes. The method was validated using Inertial Measurement Unit (IMU) with accelerometer and gyroscope, and video recordings.

The results of this thesis provide a new way to quantify and assess the freezing of gait and suggest a pipeline to improve data visualization. The visual representation presented in our research could be used as a visualization tool for follow-up treatments of FOG in PD. A careful clinical approach combined with the method proposed in this thesis may lead to an individually tailored treatment that can offer at least partial relief for many affected PD patients.

By the end, future studies can focus on the improvement of feature analysis by training a model of machine learning to determine good and reliable values for all the weights and the bias from labeled examples. It is also suggested to increase the number of participants in order to acquire more robust information related to gait patterns and allow the analysis of more complex movements. For example, a study with freezers divided by their FOG types.

References

1 ADKIN, Allan; FRANK, James; JOG, Mandar; LABORATORY, Posture. Fear of Falling and Postural Control in Parkinson's Disease. **Movement Disorders**, v. 5, n. 18, p. 496–502, Apr. 2003. DOI: https://doi.org/10.1002/mds.10396.

2 AICH, Satyabrata; PRADHAN, Pyari; PARK, Jinse; SETHI, Nitin; VATHSA, Vemula; KIM, Hee-Cheol. A Validation Study of Freezing of Gait (FoG) Detection and Machine-Learning-Based FoG Prediction Using Estimated Gait Characteristics with a Wearable Accelerometer. **Sensors**, MDPI AG, v. 18, n. 10, 30 Sept. 2018. DOI: 10.3390/s18103287.

3 ALBERTS, Jay L.; SALING, Marian; ADLER, Charles H.; STELMACH, George E. Disruptions in the reach-to-grasp actions of Parkinson's patients. **Experimental Brain Research**, Springer Science and Business Media LLC, v. 134, n. 3, p. 353–362, 15 July 2000. DOI: 10.1007/s002210000468.

4 ALLEN, Natalie E.; SCHWARZEL, Allison K.; CANNING, Colleen G. Recurrent Falls and in Parkinson's and Disease: A Systematic Review. **Hindawi**, 2013. DOI: https://doi.org/10.1155/2013/906274.

5 ALMEIDA, Maria Fernanda S.; CAVALHEIRO, Guilherme L.; PEREIRA, Adriano A.; ANDRADE, Adriano O. Investigation of Age-Related Changes in Physiological Kinetic Tremor. **Annals of Biomedical Engineering**, Springer Science and Business Media LLC, v. 38, n. 11, p. 3423–3439, June 2010. DOI: 10.1007/s10439-010-0098-z.

6 ALVAREZ, Federico; POPA, Mirela; SOLACHIDIS, Vassilios; HERNÁNDEZ-PENALOZA, Gustavo; BELMONTE-HERNÁNDEZ, Alberto; ASTERIADIS, Stylianos; VRETOS, Nicholas; QUINTANA, Marcos; THEODORIDIS, Thomas; DOTTI, Dario; DARAS, Petros. Behavior Analysis through Multimodal Sensing for Care of Parkinson's and Alzheimer's Patients. **IEEE MultiMedia**, IEEE, v. 25, n. 1, p. 14–25, Apr. 2018. DOI: 10.1109/MMUL.2018.011921232.

7 ALVES, Guido; LARSEN, Jan Petter; EMRE, Murat; WENTZEL-LARSEN, Tore; AARSLAND, Dag. Changes in motor subtype and risk for incident dementia in Parkinson's disease. **Movement Disorders**, Wiley, v. 21, n. 8, p. 1123–1130, 24 Apr. 2006. DOI: 10.1002/mds.20897.

8 AMINI, Amin; BANITSAS, Konstantinos; YOUNG, William R. Kinect4FOG: monitoring and improving mobility in people with Parkinson's using a novel system incorporating the Microsoft Kinect v2. **Disability and Rehabilitation: Assistive Technology**, Informa UK Limited, v. 14, n. 6, p. 566–573, May 2018. DOI: 10.1080/17483107.2018.1467975.

9 AUBE, Daniel; WADHI, Tanuj; RAUCH, Jacob; ANAND, Ashmeet; BARAKAT, Christopher; PEARSON, Jeremy; BRADSHAW, Joshua; ZAZZO, Spencer; UGRINOWITSCH, Carlos; DE SOUZA, Eduardo O. Progressive Resistance Training Volume: Effects on Muscle Thickness, Mass, and Strength Adaptations in Resistance-Trained Individuals. **Journal of Strength and Conditioning Research**, Ovid Technologies (Wolters Kluwer Health), v. 36, n. 3, p. 600–607, Feb. 2020. ISSN 1064-8011. DOI: 10.1519/jsc.0000000000003524.

10 BACHLIN, Marc; PLOTNIK, Meir; ROGGEN, Daniel; INBAR, Noit; GILADI, Nir; HAUSDORFF, Jeffrey; TROSTER, Gerhard. Parkinson's disease patients' perspective on context aware wearable technology for auditive assistance. In: 2009 3rd International Conference on Pervasive Computing Technologies for Healthcare. IEEE, Aug. 2009. DOI: 10.4108/icst.pervasivehealth2009.6001.

11 BACHLIN, Marc; PLOTNIK, Meir; ROGGEN, Daniel; MAIDAN, Inbal; HAUSDORFF, Jeffrey; GILADI, Nir; TROSTER, Gerhard. Wearable Assistant for Parkinson's Disease Patients With the Freezing of Gait Symptom. **IEEE Transactions on Information Technology in Biomedicine**, Institute of Electrical and Electronics Engineers IEEE, v. 14, n. 2, p. 436–446, 10 Nov. 2009. DOI: 10.1109/titb.2009.2036165.

12 BARTELS, Anna L; BALASH, Yacov; GUREVICH, Tanya; SCHAAFSMA, Joanna D; HAUSDORFF, Jeffrey M; GILADI, Nir. Relationship between freezing of gait (FOG) and other features of Parkinson's: FOG is not correlated with bradykinesia. **Journal of Clinical Neuroscience**, Elsevier BV, v. 10, n. 5, p. 584–588, Sept. 2003. DOI: 10.1016/s0967-5868(03)00192-9.

13 BECK, Eric N.; MARTENS, Kaylena A. Ehgoetz; ALMEIDA, Quincy J. Freezing of Gait in Parkinson's Disease An Overload Problem? Ed. by Ramesh Balasubramaniam. **PLOS ONE**, Public Library of Science (PLoS), v. 10, n. 12, 17 Dec. 2015. DOI: 10.1371/journal.pone.0144986.

14 BERTOLI, Matilde; CEREATTI, Andrea; DELLA CROCE, Ugo; MANCINI, Martina. An Objective Assessment to Investigate the Impact of Turning Angle on Freezing of Gait in Parkinson's Disease. In: IEEE Biomedical Circuits and Systems BIOCAS. IEEE, 2017. DOI: 10.1109/BIOCAS.2017.8325122.

15 BIASE, Lazzaro di; SUMMA, Susanna; TOSI, Jacopo; TAFFONI, Fabrizio; MARANO, Massimo; RIZZO, Angelo Cascio; VECCHIO, Fabrizio; FORMICA, Domenico; LAZZARO, Vincenzo Di; PINO, Giovanni Di; TOMBINI, Mario. Quantitative Analysis of Bradykinesia and Rigidity in Parkinson's Disease. **Frontiers in Neurology**, Frontiers Media SA, v. 9, Mar. 2018. DOI: 10.3389/fneur.2018.00121.

16 BLOEM, Bastiaan; HAUSDORFF, Jeffrey; VISSER, Jasper; GILADI, Nir. Falls and freezing of gait in Parkinson's disease: A review of two interconnected, episodic phenomena. **Movement Disorders**, Wiley, v. 19, n. 8, p. 871–884, 21 Apr. 2004. DOI: 10.1002/mds.20115.

17 BOVOLENTA, Tânia Maria; FELÍCIO, André Carvalho. Parkinson's patients in the Brazilian Public Health Policy context. **Einstein (São Paulo)**, FapUNIFESP (SciELO), v. 14, n. 3, p. 7–9, Sept. 2016. DOI: 10.1590/s1679-45082016ed3780.

18 BRAAK, Heiko; GHEBREMEDHIN, Estifanos; RUB, Udo; BRATZKE, Hansjurgen; TREDICI, Kelly Del. Stages in the development of Parkinson's disease-related pathology. **Cell and Tissue Research**, Springer Science and Business Media LLC, v. 318, n. 1, p. 121–134, Aug. 2004. DOI: 10.1007/s00441-004-0956-9.

19 CANDO, O. Alvarado; HIDALGO, K. Robles; PALACIOS, B. Chacón. A Low-Cost Vibratory Stimulus System to Mitigate Freezing of Gait in Parkinson's disease. In: 2016 IEEE ANDESCON. IEEE, 2016. DOI: 10.1109/ANDESCON.2016.7836267.

20 CAPECCI, Marianna; PEPA, Lucia; VERDINI, Federica; CERAVOLO, Maria Gabriella. A smartphone-based architecture to detect and quantify freezing of gait in Parkinson's disease. **Gait and Posture**, Elsevier BV, v. 50, p. 28–33, Oct. 2016. DOI: 10.1016/j.gaitpost.2016.08.018.

21 CARMO VILAS-BOAS, Maria do; CUNHA, Joao Paulo Silva. Movement Quantification in Neurological Diseases Methods and Applications. **IEEE Reviews in Biomedical Engineering**, Institute of Electrical and Electronics Engineers (IEEE), v. 9, p. 15–31, 2016. DOI: 10.1109/rbme.2016.2543683.

22 CHEE, Rachel; MURPHY, Anna; DANOUDIS, Mary; GEORGIOU-KARISTIANIS, Nelly; IANSEK, Robert. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. **Brain**, Oxford University Press OUP, v. 132, n. 8, p. 2151–2160, May 2009. DOI: 10.1093/brain/awp053.

23 CHEN, Robert. Paradoxical worsening of gait with levodopa in Parkinson disease. **Neurology**, v. 7, n. 78, Feb. 2012. DOI: https://doi.org/10.1212/WNL.0b013e318246d6fa.

24 COSTE, Christine Azevedo; SIJOBERT, Benoît; PISSARD-GIBOLLET, Roger; PASQUIER, Maud; ESPIAU, Bernard; GENY, Christian. Detection of Freezing of Gait in Parkinson Disease: Preliminary Results. **Sensors**, MDPI AG, v. 14, n. 4, p. 6819–6827, Apr. 2014. DOI: 10.3390/s140406819.

25 CUBO, Esther; MOORE, Charity G; LEURGANS, Sue; GOETZ, Christopher G. Wheeled and standard walkers in Parkinson's disease patients with gait freezing. **Parkinsonism and Related Disorders**, Elsevier BV, v. 10, n. 1, p. 9–14, Oct. 2003. DOI: 10.1016/s1353-8020(03)00060-9.

26 DORSEY, E. Ray; SHERER, Todd; OKUN, Michael S.; BLOEM, Bastiaan R. The Emerging Evidence of the Parkinson Pandemic. Ed. by Patrik Brundin, J. William Langston and Bastiaan R. Bloem. **Journal of Parkinson's Disease**, IOS Press, v. 8, s1, s3–s8, Dec. 2018. DOI: 10.3233/jpd-181474.

27 ERRO, Roberto; STAMELOU, Maria. The Motor Syndrome of Parkinson's Disease. In: INTERNATIONAL Review of Neurobiology. Elsevier, 2017. P. 25–32. DOI: 10.1016/bs.irn.2017.01.004.

28 FRANCHIGNONI, Franco; MARTIGNONI, Emilia; FERRIERO, Giovanni; PASETTI, Carlo. Balance and fear of falling in Parkinson's disease. **Parkinsonism and Related Disorders**, Elsevier BV, v. 11, n. 7, p. 427–433, Nov. 2005. DOI: 10.1016/j.parkreldis.2005.05.005.

29 GALNA, Brook; BARRY, Gillian; JACKSON, Dan; MHIRIPIRI, Dadirayi; OLIVIER, Patrick; ROCHESTER, Lynn. Accuracy of the Microsoft Kinect sensor for measuring movement in people with Parkinson's disease. **Gait and Posture**, Elsevier BV, v. 39, n. 4, p. 1062–1068, Apr. 2014. DOI: 10.1016/j.gaitpost.2014.01.008.

30 GALVAN, Adriana; WICHMANN, Thomas. Pathophysiology of Parkinsonism. **Clinical Neurophysiology**, Elsevier BV, v. 119, n. 7, p. 1459–1474, 7 May 2008. DOI: 10.1016/j.clinph.2008.03.017.

31 GENEVER, Richard W.; DOWNES, Thomas W.; MEDCALF, Pippa. Fracture rates in Parkinson's disease compared with age- and gender-matched controls: a retrospective cohort study. **Age and Ageing**, British Geriatrics Society, v. 34, n. 1, p. 21–24, Oct. 2005. DOI: 10.1093/ageing/afh203.

32 GILADI, Nir; MCDERMOTT, Michael P; FAHN, Stanley; PRZEDBORSKI, Serge; JANKOVIC, Joseph; STERN, Matthew; TANNER, Caroline. Freezing of gait in PD Prospective assessment in the DATATOP cohort. **Neurology**, NCBI, v. 53, p. 1712–1721, June 2001. DOI: 10.1212/WNL.56.12.1712.

33 GILADI, Nir; TAL, Joseph; AZULAY, Tali; RASCOL, Oliver; BROOKS, David J.; MELAMED, Eldad; OERTEL, Wolfgang; POEWE, Werner H.; STOCCHI, Fabrizio; TOLOSA, Eduardo. Validation of the freezing of gait questionnaire in patients with Parkinson's disease. **Movement Disorders**, Wiley, v. 24, n. 5, p. 655–661, Jan. 2009. DOI: 10.1002/mds.21745.

34 GOETZ, Christopher G.; TILLEY, Barbara C.; SHAFTMAN, Stephanie R.; STEBBINS, Glenn T.; FAHN, Stanley; MARTINEZ-MARTIN, Pablo; POEWE, Werner; SAMPAIO, Cristina; STERN, Matthew B.; DODEL, Richard; DUBOIS, Bruno; HOLLOWAY, Robert; JANKOVIC, Joseph; KULISEVSKY, Jaime; LANG, Anthony E.; LEES, Andrew; LEURGANS, Sue; LEWITT, Peter A.; NYENHUIS, David; OLANOW, C. Warren; RASCOL, Olivier; SCHRAG, Anette; TERESI, Jeanne A.; HILTEN, Jacobus J. van; LAPELLE, Nancy. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. **Movement Disorders**, Wiley, v. 23, n. 15, p. 2129–2170, 20 Nov. 2008. DOI: 10.1002/mds.22340.

35 GREWE, Jan; WACHTLER, Thomas; BENDA, Jan. A Bottom-up Approach to Data Annotation in Neurophysiology. Ed. by Friedrich T. Sommer. **Frontiers in Neuroinformatics**, Frontiers Media SA, v. 5, 30 Aug. 2011. DOI: 10.3389/fninf.2011.00016.

36 GUAN, Xiaojun; ZENG, Qiaoling; GUO, Tao; WANG, Jiaqiu; XUAN, Min; GU, Quanquan; WANG, Tao; HUANG, Peiyu; XU, Xiaojun; ZHANG, Minming. Disrupted Functional Connectivity of Basal Ganglia across Tremor-Dominant and Akinetic/Rigid-Dominant Parkinson's Disease. Ed. by Changiz Geula and Mariana Leriche. **Frontiers in Aging Neuroscience**, Frontiers Media SA, v. 9, 2 Nov. 2017. DOI: 10.3389/fnagi.2017.00360.

37 HALLETT, Mark; KHOSHBIN, Shahram. A physiological mechanism of bradykinesia. **Brain**, v. 103, n. 2, p. 301–314, June 1980. DOI: 10.1093/brain/103.2.301.

38 HANDOJOSENO, Ardi; SHINE, James; NGUYEN, Tuan; TRAN, Yvonne; LEWIS, Simon; NGUYEN, Hung. Analysis and Prediction of the Freezing of Gait using EEG Brain Dynamics. **IEEE Trans Neural Syst Rehabil Eng**, IEEE, v. 23, n. 5, p. 887–897, Dec. 2014. DOI: 10.1109/TNSRE.2014.2381254.

39 HASAN, S. M. Shafiul; SIDDIQUEE, Masudur R.; ATRI, Roozbeh; RAMON, Rodrigo; MARQUEZ, J. Sebastian; BAI, Ou. Prediction of gait intention from pre-movement EEG signals: a feasibility study. **Journal of NeuroEngineering and Rehabilitation**, Springer Science and Business Media LLC, v. 17, n. 1, Apr. 2020. DOI: 10.1186/s12984-020-00675-5.

40 HAUSDORFF, Jeffrey M.; SCHAAFSMA, Joanna D.; BALASH, Yacov; BARTELS, Anna L.; GUREVICH, Tanya; GILADI, Nir. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. **Experimental Brain Research**, Springer Science and Business Media, v. 149, n. 2, p. 187–194, 22 Jan. 2003. DOI: 10.1007/s00221-002-1354-8.

41 HELDMAN, Dustin A.; GIUFFRIDA, Joseph P.; CHEN, Robert; PAYNE, Megan; MAZZELLA, Filomena; DUKER, Andrew P.; SAHAY, Alok; KIM, Sang Jin; REVILLA, Fredy J.; ESPAY, Alberto J. The modified bradykinesia rating scale for Parkinson's disease: Reliability and comparison with kinematic measures. **Movement Disorders**, Wiley, v. 26, n. 10, p. 1859–1863, Apr. 2011. DOI: 10.1002/mds.23740.

42 HIRSCH, Lauren; JETTE, Nathalie; FROLKIS, Alexandra; STEEVES, Thomas; PRINGSHEIM, Tamara. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. **Neuroepidemiology**, S. Karger AG, v. 46, n. 4, p. 292–300, 23 Apr. 2016. DOI: 10.1159/000445751.

43 HJORTH, Bo. EEG Analysis Based on Time Domain Properties. **Electroencephalogr. Clin. Neurophysiol.**, p. 306–310, 1970. DOI: https://doi.org/10.1016/0013-4694(70)90143-4.

44 HOEK, Take van der; BUS, Boudewijn; MATUI, Patricia; MARCK, Marjolein van der; ESSELINK, Rianne; TENDOLKAR, Indira. Prevalence of depression in Parkinson's disease: Effects of disease stage, motor subtype and gender. **Journal of the Neurological Sciences**, Elsevier BV, v. 310, n. 1, p. 220–224, 29 July 2011. DOI: 10.1016/j.jns.2011.07.007.

45 HUANG, Yingli; CANNING, Colleen G.; SONG, Jooeun; CLEMSON, Lindy; ALLEN, Natalie E. How does perceived fall risk influence decisions about whether to undertake activities in people with Parkinson's disease and their care partners? A qualitative study. **Disability and Rehabilitation**, Informa UK Limited, v. 44, n. 20, p. 6000–6008, July 2021. DOI: 10.1080/09638288.2021.1955983.

46 HUERTA, Mónica; BARZALLO, Boris; PUNIN, Catalina; GARCIA-CEDEÑO, Andrea; CLOTET, Roger. Review of Active Extracorporeal Medical Devices to Counteract Freezing of Gait in Patients with Parkinson Disease. Ed. by Amar Kanekar. **Healthcare**, MDPI AG, v. 10, n. 6, p. 976, 24 May 2022. DOI: 10.3390/healthcare10060976.

47 JACOBS, Jesse V.; LOU, Jau-Shin; KRAAKEVIK, Jeff A.; HORAK, Fay B. The supplementary motor area contributes to the timing of the anticipatory postural adjustment during step initiation in participants with and without Parkinson's disease. **Neuroscience**, Elsevier BV, v. 164, n. 2, p. 877–885, Dec. 2009. DOI: 10.1016/j.neuroscience.2009.08.002.

48 JANKOVIC, Joseph. Parkinson's disease: clinical features and diagnosis. **Journal of Neurology, Neurosurgery and Psychiatry**, BMJ, v. 79, n. 4, p. 368–376, Apr. 2008. DOI: 10.1136/jnnp.2007.131045.

49 JOST, Wolfgang H.; REICHMANN, Heinz. "An essay on the shaking palsy" 200 years old. **Journal of Neural Transmission**, Springer Science and Business Media LLC, v. 124, n. 8, p. 899–900, Feb. 2017. DOI: 10.1007/s00702-017-1684-0.

50 JOVANOV, Emil; WANG, Emily; VERHAGEN, Leonard; FREDRICKSON, Metman; FRATANGELO, Robert. deFOG–A real time system for detection and unfreezing of gait of Parkinson's patients. In: 2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE, 2009. DOI: 10.1109/IEMBS.2009.5334257.

51 KILLANE, Isabelle; FEARON, Conor; NEWMAN, Louise; MCDONNELL, Conor; WAECHTER, Saskia M.; SONS, Kristian; LYNCH, Timothy; REILLY, Richard B. Dual Motor-Cognitive Virtual Reality Training Impacts Dual-Task Performance in Freezing of Gait. **IEEE Journal of Biomedical and Health Informatics**, Institute of Electrical and Electronics Engineers (IEEE), v. 19, n. 6, p. 1855–1861, Nov. 2015. DOI: 10.1109/jbhi.2015.2479625.

52 LANG, Anthony E.; ESPAY, Alberto J. Disease Modification in Parkinson's Disease: Current Approaches, Challenges, and Future Considerations. **Movement Disorders**, Wiley, v. 33, n. 5, p. 660–677, Apr. 2018. DOI: 10.1002/mds.27360.

53 LIAN, Teng-Hong; GUO, Peng; ZUO, Li-Jun; HU, Yang; YU, Shu-Yang; YU, Qiu-Jin; JIN, Zhao; WANG, Rui-Dan; LI, Li-Xia; ZHANG, Wei. Tremor-Dominant in Parkinson Disease: The Relevance to Iron Metabolism and Inflammation. Ed. by Isabella Zanella. **Frontiers in Neuroscience**, Frontiers Media SA, v. 13, 27 Mar. 2019. DOI: 10.3389/fnins.2019.00255.

54 LIU, Chiung-ju; LATHAM, Nancy K. Progressive resistance strength training for improving physical function in older adults. **Cochrane Database of Systematic Reviews**, Wiley, July 2009. ISSN 1465-1858. DOI: 10.1002/14651858.cd002759.pub2.

55 LOPES, Larissa Karlla Rodrigues; SCIANNI, Aline Alvim; LIMA, Lidiane Oliveira; CARVALHO LANA, Raquel de; RODRIGUES-DE-PAULA, Fátima. The Mini-BESTest is an independent predictor of falls in Parkinson Disease. **Brazilian Journal of Physical Therapy**, Elsevier BV, v. 24, n. 5, p. 433–440, Sept. 2020. DOI: 10.1016/j.bjpt.2019.07.006.

56 LOPETEGUI, Marcelo; YEN, Po-Yin; LAI, Albert; JEFFRIES, Joseph; EMBI, Peter; PAYNE, Philip. Time motion studies in healthcare: What are we talking

about? **Journal of Biomedical Informatics**, Elsevier BV, v. 49, p. 292–299, June 2014. DOI: 10.1016/j.jbi.2014.02.017.

57 LÓPEZ-BLANCO, Roberto; VELASCO, Miguel A.; MÉNDEZ-GUERRERO, Antonio; ROMERO, Juan Pablo; CASTILLO, María Dolores del; SERRANO, J. Ignacio; BENITO-LEÓN, Julián; BERMEJO-PAREJA, Félix; ROCON, Eduardo. Essential tremor quantification based on the combined use of a smartphone and a smartwatch: The NetMD study. **Journal of Neuroscience Methods**, Elsevier BV, v. 303, p. 95–102, June 2018. DOI: 10.1016/j.jneumeth.2018.02.015.

58 LUIZ, Luiza Maire David; MARQUES, Isabela Alves; FOLADOR, João Paulo; OLIVEIRA ANDRADE, Adriano de. Intra and inter-rater remote assessment of bradykinesia in Parkinson's disease. **Neurología**, Elsevier BV, Sept. 2021. DOI: 10.1016/j.nrl.2021.08.005.

59 LYONS, Kelly; PAHWA, Rajesh. Diagnosis and Initiation of Treatment in Parkinson's Disease. **International Journal of Neuroscience**, Informa UK Limited, v. 121, n. 2, p. 27–36, Sept. 2011. DOI: 10.3109/00207454.2011.620197.

60 MACDOUGALL, Hamish; MOORE, Steven. Marching to the beat of the same drummer: the spontaneous tempo of human locomotion. **Journal of Applied Physiology**, v. 99, n. 3, p. 1164–1173, Sept. 2005. DOI: 10.1152/japplphysiol.00138.2005.

61 MACHT, Michael; KAUSSNER, Yvonne; MÖLLER, Jens Carsten; STIASNY-KOLSTER, Karin; EGGERT, Karla Maria; KRÜGER, Hans-Peter; ELLGRING, Heiner. Predictors of freezing in Parkinson's disease: A survey of 6,620 patients. **Movement Disorders**, Wiley, v. 22, n. 7, p. 953–956, 20 Mar. 2007. DOI: 10.1002/mds.21458.

62 MAK, Margaret K. Y.; PANG, Marco Y. C. Parkinsonian single fallers versus recurrent fallers: different fall characteristics and clinical features. **Journal of Neurology**, Springer Science and Business Media LLC, v. 257, n. 9, p. 1543–1551, May 2010. DOI: 10.1007/s00415-010-5573-9.

63 MANCINI, Martina; PRIEST, Kelsey C; NUTT, John G.; HORAK, Fay B. Quantifying freezing of gait in Parkinson's disease during the instrumented timed up and go test. In: 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE, 21 Aug. 2012. DOI: 10.1109/embc.2012.6346151.

64 MANCINI, Martina; SMULDERS, Katrijn; COHEN, Rajal G.; HORAK, Fay B.; GILADI, Nir; NUTT, John G. The clinical significance of freezing while turning in Parkinson's disease. Ed. by OP32 3181 S.W. Sam Jackson Park Rd. **Neuroscience**, Elsevier BV, v. 343, p. 222–228, Feb. 2017. DOI: 10.1016/j.neuroscience.2016.11.045.

65 MANUAL ATLAS. https://zenodo.org/record/7091122. Accessed: 2023-08-22. DOI: 10.5281/zenodo.7091122.

66 METMAN, Leo Verhagen; MYRE, Brian; VERWEY, Niek; HASSIN-BAER, Sharon; ARZBAECHER, Jean; SIERENS, Diane; BAKAY, Roy. Test-retest reliability of UPDRS-III, dyskinesia scales, and timed motor tests in patients with advanced Parkinson's disease: An argument against multiple baseline assessments. **Movement Disorders**, Wiley, v. 19, n. 9, p. 1079–1084, 16 Sept. 2004. DOI: 10.1002/mds.20101.

67 MEUDT, Sascha; BIGALKE, Lutz; SCHWENKER, Friedhelm. ATLAS Annotation tool using partially supervised learning and multi-view co-learning in human-computer-interaction scenarios. In: THE 11th International Conference on Information Sciences, Signal Processing and their Applications: Special Sessions. IEEE, Sept. 2012. DOI: 10.1109/ISSPA.2012.6310495.

68 MOCCIA, Marcello; TEDESCHI, Enrico; UGGA, Lorenzo; ERRO, Roberto; PICILLO, Marina; CARANCI, Ferdinando; BARONE, Paolo; BRUNETTI, Arturo. White matter changes and the development of motor phenotypes in de novo Parkinson's Disease. **Journal of the Neurological Sciences**, Elsevier BV, v. 367, p. 215–219, 8 June 2016. DOI: 10.1016/j.jns.2016.06.015.

69 MOORE, Steven T; YUNGHER, Don A; MORRIS, Tiffany R; DILDA, Valentina; MACDOUGALL, Hamish G; SHINE, James M; NAISMITH, Sharon L; LEWIS, Simon JG. Autonomous identification of freezing of gait in Parkinson's disease from lower-body segmental accelerometry. **Journal of NeuroEngineering and Rehabilitation**, Springer Science and Business Media LLC, v. 10, n. 1, p. 19, 2013. DOI: 10.1186/1743-0003-10-19.

70 MOORE, Steven T.; MACDOUGALL, Hamish G.; ONDOC, William G. Ambulatory monitoring of freezing of gait in Parkinson's disease. **Journal of Neuroscience Methods**, 2008. DOI: 10.1016/j.jneumeth.2007.08.023.

71 MOREIRA, Raissa Carla; ZONTA, Marise Bueno; ARAUJO, Ana Paula Serra de; ISRAEL, Vera Lucia; TEIVE, Helio A. G. Quality of life in Parkinson's disease patients:progression markers of mild to moderate stages. **Arquivos de Neuro-Psiquiatria**, 2017. DOI: 10.1590/0004-282X20170091.

72 MORRIS, Meg; HUXHAM, Frances; MCGINLEY, Jennifer; DODD, Karen; IANSEK, Robert. The biomechanics and motor control of gait in Parkinson disease. In: 6. v. 16, p. 459–470. DOI: 10.1016/s0268-0033(01)00035-3.

73 MORRIS, Meg E.; IANSEK, Robert; GALNA, Brook. Gait festination and freezing in Parkinson's disease: Pathogenesis and rehabilitation. **Movement Disorders**, Wiley, v. 23, S2, s451–s460, July 2008. DOI: 10.1002/mds.21974.

74 MOSTAFA, Tahjid Ashfaque; SOLTANINEJAD, Sara; MCISAAC, Tara L.; CHENG, Irene. A Comparative Study of Time Frequency Representation Techniques for Freeze of Gait Detection and Prediction. **Sensors**, MDPI AG, v. 21, n. 19, 27 Sept. 2021. DOI: 10.3390/s21196446.

75 MURALIDHARAN, Vignesh; BALASUBRAMANI, Pragathi; CHAKRAVARTHY, Srinivasa; GILAT, Moran; LEWIS, Simon; MOUSTAFA, Ahmed. A Neurocomputational Model of the Effect of Cognitive Load on Freezing of Gait in Parkinson's Disease. Ed. by Florida Atlantic University. **Frontiers in Human Neuroscience**, Frontiers Media SA, v. 10, 9 Jan. 2017. DOI: 10.3389/fnhum.2016.00649.

76 NELSON, Eugene C.; SPLAINE, Mark E.; GODFREY, Marjorie M.; KAHN, Victoria; HESS, AnnMarie; BATALDEN, Paul; PLUME, Stephen K. Using Data to Improve Medical Practice by Measuring Processes and Outcomes of Care. **The Joint Commission Journal on Quality Improvement**, Elsevier BV, v. 26, n. 12, p. 667–685, Dec. 2000. DOI: 10.1016/s1070-3241(00)26057-4.

77 NIEUWBOER, Alice; DOM, Rene; WEERDT, Willy De; DESLOOVERE, Kaat; FIEUWS, Steffen; BROENS-KAUCSIK, Eva. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. **Movement Disorders**, Wiley, v. 16, n. 6, p. 1066–1075, 2 Nov. 2001. DOI: 10.1002/mds.1206.

78 NIEUWBOER, Alice; DOM, Rene; WEERDT, Willy De; DESLOOVERE, Kaat; JANSSENS, Luc; STIJN, Vangheluwe. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. **Brain**, Oxford University Press (OUP), v. 127, n. 7, p. 1650–1660, 21 May 2004. DOI: 10.1093/brain/awh189.

79 NIEUWBOER, Alice; ROCHESTER, Lynn; HERMAN, Talia; VANDENBERGHE, Wim; EMIL, George Ehab; THOMAES, Tom; GILADI, Nir. Reliability of the new freezing of gait questionnaire: Agreement between patients with Parkinson's disease and their carers. **Gait and Posture**, Elsevier BV, v. 30, n. 4, p. 459–463, Nov. 2009. DOI: 10.1016/j.gaitpost.2009.07.108.

80 NILSSON, Maria H.; HAGELL, Peter. Freezing of Gait Questionnaire: validity and reliability of the Swedish version. **Acta Neurologica Scandinavica**, Hindawi Limited, v. 120, n. 5, p. 331–334, Nov. 2009. DOI: 10.1111/j.1600-0404.2009.01175.x.

81 NÓBREGA, Lígia Reis; ROCON, Eduardo; PEREIRA, Adriano Alves; OLIVEIRA ANDRADE, Adriano de. A Novel Physical Mobility Task to Assess Freezers in Parkinson's Disease. Ed. by Daniele Giansanti. **Healthcare**, MDPI AG, v. 11, n. 3, p. 409, 31 Jan. 2023. DOI: 10.3390/healthcare11030409.

82 NONNEKES, Jorik; RUŽICKA, Evžen; NIEUWBOER, Alice; HALLETT, Mark; FASANO, Alfonso; BLOEM, Bastiaan R. Compensation Strategies for Gait Impairments in Parkinson Disease. **JAMA Neurology**, American Medical Association (AMA), v. 76, n. 6, p. 718, 25 Mar. 2019. DOI: 10.1001/jamaneurol.2019.0033.

83 OKUMA, Yasuyuki. Freezing of Gait and Falls in Parkinson's Disease. **Journal of Parkinson's Disease**, IOS Press, v. 4, n. 2, p. 255–260, 2014. DOI: 10.3233/jpd-130282.

84 OKUMA, Yasuyuki. Practical approach to freezing of gait in Parkinson's disease. **Practical Neurology**, BMJ, v. 14, n. 4, p. 222–230, Feb. 2014. DOI: 10.1136/practneurol-2013-000743.

85 OLIVEIRA, Fábio Henrique Monteiro; CUNHA, Daniel Fernandes da; RABELO, Amanda Gomes; LUIZ, Luiza Maire David; VIEIRA, Marcus Fraga; PEREIRA, Adriano Alves; OLIVEIRA ANDRADE, Adriano de. A non-contact system for the assessment of hand motor tasks in people with Parkinson's disease. **SN Applied Sciences**, Springer Science and Business Media LLC, v. 3, n. 1, 6 Jan. 2021. DOI: 10.1007/s42452-020-04001-5.

86 OLIVEIRA ANDRADE, Adriano de; PAIXÃO, Ana Paula Sousa; CABRAL, Ariana Moura; RABELO, Amanda Gomes; LUIZ, Luiza Maire David; DIONÍSIO, Valdeci Carlos; VIEIRA, Marcus Fraga; PEREIRA, Janser Moura; RUEDA, Alice; KRISHNAN, Sridhar; PEREIRA, Adriano Alves. Task-Specific Tremor Quantification in a Clinical Setting for Parkinson's Disease. **Journal of Medical and Biological Engineering**, Springer Science and Business Media LLC, v. 40, n. 6, p. 821–850, Oct. 2020. DOI: 10.1007/s40846-020-00576-x.

87 OLIVEIRA BAGGIO, Jussara; CURTARELLI, Mônica; RODRIGUES, Guilherme; TUMAS, Vitor. Validity of the Brazilian version of the freezing of gait questionnaire Validação da versão brasileira da escala de congelamento da marcha. **Arq Neuropsiquiatr**, Scielo, v. 70, n. 8, p. 599–603, Apr. 2012. DOI: 10.1590/S0004-282X2012000800008.

88 PALACIOS-SÁNCHEZ, Leonardo; NUPAN, Martha Torres; BOTERO-MENESES, Juan Sebastián. James Parkinson and his essay on "shaking palsy", two hundred years later. **Arquivos de Neuro-Psiquiatria**, FapUNIFESP (SciELO), v. 75, n. 9, p. 671–672, Sept. 2017. DOI: 10.1590/0004-282x20170108.

89 PAPAPETROPOULOS, Spiridon; ADI, Nikhil; ELLUL, John; ARGYRIOU, Andreas; CHRONI, Elisabeth. A Prospective Study of Familial versus Sporadic Parkinson's Disease. **Neurodegenerative Dis**, Karger, v. 4, p. 424–427, Oct. 2007. DOI: 10.1159/000107702.

90 PARKINSON, James. An Essay on the Shaking Palsy. **J Neuropsychiatry Clin Neurosci.**, American Psychiatric Association, v. 14, n. 2, p. 223–236, 1 May 2002. DOI: 10.1176/jnp.14.2.223.

91 PHAM, T.; NGUYEN, D.; DUTKIEWICZ, E.; LEONG, P. Wearable Healthcare Systems: A Single Channel Accelerometer Based Anomaly Detector for Studies of Gait Freezing in Parkinson's Disease. In: INTERNATIONAL Conference on Communications IEEE. IEEE, July 2017. DOI: 10.1109/ICC.2017.7997415.

92 PODSIADLO, Diane; RICHARDSON, Sandra. The Timed Up and Go: A Test of Basic Functional Mobilitv for Frail Elderly Persons. **J Am Geriatr Soc**, 1991. DOI: 10.1111/j.1532-5415.1991.tb01616.x.

93 POEWE, Werner; SEPPI, Klaus; TANNER, Caroline; HALLIDAY, Glenda; BRUNDIN, Patrik; VOLKMANN, Jens; SCHRAG, Anette-Eleonore; LANG, Anthony. Parkinson disease. **Nature Reviews Disease Primers**, Springer Science and Business Media LLC, v. 3, n. 1, 23 Mar. 2017. DOI: 10.1038/nrdp.2017.13.

94 POPOVIC, Mirjana B.; DJURIC-JOVICIC, Milica; RADOVANOVIC, Sasa; PETROVIC, Igor; KOSTIC, Vladimir. A simple method to assess freezing of gait in Parkinson's disease patients. **Brazilian Journal of Medical and Biological Research**, FapUNIFESP SciELO, v. 43, n. 9, p. 883–889, 16 Sept. 2010. DOI: 10.1590/s0100-879x2010007500077.

95 PORTNOVA, Galina V.; ATANOV, Michael S. Nonlinear EEG parameters of emotional perception in patients with moderate traumatic brain injury, coma, stroke and schizophrenia. **AIMS Neuroscience**, American Institute of Mathematical Sciences (AIMS), v. 5, n. 4, p. 221–235, 2018. DOI: 10.3934/neuroscience.2018.4.221.

96 POSTUMA, Ronald B.; BERG, Daniela. The New Diagnostic Criteria for Parkinson's Disease. In: INTERNATIONAL Review of Neurobiology. Elsevier, 2017. P. 55–78. DOI: 10.1016/bs.irn.2017.01.008.

97 RABELO, Amanda. **Identification and characterization of short-term motor patterns in rest tremor of individuals with Parkinson's disease**. PhD thesis – EDUFU - Editora da Universidade Federal de Uberlandia. DOI: 10.14393/ufu.te.2023.515.

98 RABELO, Amanda; FOLADOR, João Paulo; CABRAL, Ariana Moura; LIMA, Viviane; ARANTES, Ana Paula; SANDE, Luciane; VIEIRA, Marcus Fraga; ALMEIDA, Rodrigo Maximiano Antunes de; OLIVEIRA ANDRADE, Adriano de. Identification and Characterization of Short-Term Motor Patterns in Rest Tremor of Individuals with Parkinson's Disease. **Healthcare**, MDPI AG, v. 10, n. 12, p. 2536, Dec. 2022. DOI: 10.3390/healthcare10122536.

99 RABELO, Amanda Gomes. Objective Assessment of Bradykinesia Estimated from the Wrist Extension in Older Adults and Patients with Parkinson's Disease. In. DOI: 10.1007/s10439-017-1908-3.

100 RAJPUT, Ali H.; ROZDILSKY, Bohdan; RAJPUT, Alex. Accuracy of Clinical Diagnosis in Parkinsonism — A Prospective Study. **Canadian Journal of Neurological Sciences**, Cambridge University Press (CUP), v. 18, n. 3, p. 275–278, Aug. 1991. DOI: 10.1017/s0317167100031814.

101 RAMAKER, Claudia; MARINUS, Johan; STIGGELBOUT, Anne Margarethe; HILTEN, Bob Johannes van. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. **Movement Disorders**, Wiley, v. 17, n. 5, p. 867–876, 6 Sept. 2002. DOI: 10.1002/mds.10248.

102 RAWSON, Kerri S; CREEL, Patricia; TEMPLIN, Lizbeth; HORIN, Adam P; DUNCAN, Ryan P; EARHART, Gammon M. Freezing of Gait Boot Camp: feasibility, safety and preliminary efficacy of a community-based group intervention. **Neurodegenerative Disease Management**, Future Medicine Ltd, v. 8, n. 5, p. 307–314, 18 Oct. 2018. DOI: 10.2217/nmt-2018-0022.

103 RICCIARDI, Lucia; BLOEM, Bastiaan R.; SNIJDERS, Anke H.; DANIELE, Antonio; QUARANTA, Davide; BENTIVOGLIO, Anna Rita; FASANO, Alfonso. Freezing of gait in Parkinson's disease: The paradoxical interplay between gait and cognition. **Parkinsonism and Related Disorders**, Elsevier BV, v. 20, n. 8, p. 824–829, Aug. 2014. DOI: 10.1016/j.parkreldis.2014.04.009.

104 ROCHA, Priscila A; PORFIRIO, Gustavo M; FERRAZ, Henrique B; TREVISANI, Virginia F M. Effects of external cues on gait parameters of Parkinson's diseasepatients: A systematic review. **Clinical Neurology and Neurosurgery**, Elsevier, v. 124, p. 127–134, July 2014. DOI: 10.1016/j.clineuro.2014.06.026.

105 SAAD, Ali; GUERIN, Franyois; AYACHE, Mohammad; LEFEBVRE, Dimitri. Sensoring and Features Extraction for the Detection of Freeze of Gait in Parkinson Disease. In: IEEE-SSD. IEEE, 2014. DOI: 10.1109/SSD.2014.6808786.

106 SAN-SEGUNDO, Rubén; TORRES-SÁNCHEZ, Roque; HODGINS, Jessica; TORRE, Fernando De la. Increasing Robustness in the Detection of Freezing of Gait in Parkinson's Disease. **Electronics**, MDPI AG, v. 8, n. 2, p. 119, 22 Jan. 2019. DOI: 10.3390/electronics8020119.

107 SCARIOT, Vanessa; CLAUDINO, Renato; SANTOS, Eloa Cristhina dos; RIOS, Jaqueline Lourdes; SANTOS, Marcio J dos. Anticipatory and compensatory postural adjustments during catching a ball in condition of postural instability and stability. **Fisioter Pesqui**, Scielo, v. 19, n. 3, p. 228–235, Sept. 2012. DOI: 10.1590/S1809-29502012000300007.

108 SCHAAFSMA, Joanna; BALASH, Yacov; GUREVICH, Tanya; BARTELS, Anna; HAUSDORFF, Jeffrey; GILADI, Nir. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. **European Journal of Neurology**, Wiley, v. 10, n. 4, p. 391–398, July 2003. DOI: 10.1046/j.1468-1331.2003.00611.x.

109 SEPPI, Klaus; WEINTRAUB, Daniel; COELHO, Miguel; PEREZ-LLORET, Santiago; FOX, Susan H.; KATZENSCHLAGER, Regina; HAMETNER, Eva-Maria; POEWE, Werner; RASCOL, Olivier; GOETZ, Christopher G.; SAMPAIO, Cristina. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. **Movement Disorders**, Wiley, v. 26, S3, s42–s80, Oct. 2011. DOI: 10.1002/mds.23884.

110 SHINE, James; MATAR, Elie; WARD, Philip; BOLITHO, Samuel; PEARSON, Mark; NAISMITH, Sharon; LEWIS, Simon. Differential Neural Activation Patterns in Patients with Parkinson's Disease and Freezing of Gait in Response to Concurrent Cognitive and Motor Load. Ed. by Robert Chen. **PLoS ONE**, Public Library of Science PLoS, v. 8, n. 1, 30 Jan. 2013. DOI: 10.1371/journal.pone.0052602.

111 SHINE, James; MOUSTAFA, Ahmed; MATAR, Elie; FRANK, Michael; LEWIS, Simon. The role of frontostriatal impairment in freezing of gait in Parkinson's disease. Ed. by Alessandro Stefani. **Frontiers in Systems Neuroscience**, Frontiers Media SA, v. 7, 4 Oct. 2013. DOI: 10.3389/fnsys.2013.00061.

112 SHINE, James M.; MATAR, Elie; WARD, Philip B.; FRANK, Michael J.; MOUSTAFA, Ahmed A.; PEARSON, Mark; NAISMITH, Sharon L.; LEWIS, Simon J. G. Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia. **Brain**, Oxford University Press (OUP), v. 136, n. 12, p. 3671–3681, 19 Nov. 2013. DOI: 10.1093/brain/awt272.

113 SIGCHA, Luis; COSTA, Nélson; PAVÓN, Ignacio; COSTA, Susana; AREZES, Pedro; LÓPEZ, Juan Manuel; ARCAS, Guillermo De. Deep Learning Approaches for Detecting Freezing of Gait in Parkinson's Disease Patients through On-Body Acceleration Sensors. **Sensors**, MDPI AG, v. 20, n. 7, p. 1895, 29 Mar. 2020. DOI: 10.3390/s20071895.

114 SIJOBERT, Benoit; AZEVEDO, Christine; ANDREU, David; VERNA, Claudia; GENY, Christian. Effects of Sensitive Electrical Stimulation-Based Somatosensory Cueing in Parkinson's Disease Gait and Freezing of Gait Assessment. **Artificial Organs**, Wiley, v. 41, n. 11, p. 222–232, Nov. 2017. DOI: 10.1111/aor.13059.

115 SOLTANINEJAD, Sara; CHENG, Irene; BASU, Anup. Kin-FOG: Automatic Simulated Freezing of Gait Assessment System for Parkinsons Disease. **Sensors**, MDPI AG, v. 19, n. 10, p. 2416–2438, 27 May 2019. DOI: 10.3390/s19102416.

116 SOUZA, Cheylla Fabricia; ALMEIDA, Helayne Carolyne; SOUSA, Jomario Batista; COSTA, Pedro Henrique; SILVEIRA, Yonara Sonaly; BEZERRA, João Carlos. Parkinson's disease and the Process of Aging Motor: Literature Review. **Revista Neurociências**, 2011. DOI: https://doi.org/10.34024/rnc.2011.v19.8330.

117 SPILDOOREN, Joke; VERCRUYSSE, Sarah; DESLOOVERE, Kaat; VANDENBERGHE, Wim; NIEUWBOER, Eric Kerckhofsand Alice. Freezing of Gait in Parkinson's Disease: The Impact of Dual-Tasking and Turning. **Movement Disorders**, Wiley, v. 25, n. 15, p. 2563–2570, July 2010. DOI: 10.1002/mds.23327.

118 SPRENGER, Fabienne; POEWE, Werner. Management of Motor and Non-Motor Symptoms in Parkinson's Disease. **CNS Drugs**, Springer Science and Business Media LLC, v. 27, n. 4, p. 259–272, Mar. 2013. DOI: 10.1007/s40263-013-0053-2.

119 SUMMA, Susanna; TOSI, Jacopo; TAFFONI, Fabrizio; DI BIASE, Lazzaro; MARANO, Massimo; RIZZO, Angelo Cascio; TOMBINI, Mario; DI PINO, Giovanni; FORMICA, Domenico. Assessing bradykinesia in Parkinson's disease using gyroscope signals. In: 2017 International Conference on Rehabilitation Robotics (ICORR). IEEE, July 2017. P. 1556–1561. DOI: 10.1109/ICORR.2017.8009469.

120 SVEINBJORNSDOTTIR, Sigurlaug. The clinical symptoms of Parkinson's disease. **Journal of Neurochemistry**, Wiley, v. 139, p. 318–324, July 2016. DOI: 10.1111/jnc.13691.

121 TARD, Céline; DUJARDIN, Kathy; BOURRIEZ, Jean-Louis; MOLAEE-ARDEKANI, Behnam; DERAMBURE, Philippe; DEFEBVRE, Luc; DELVAL, Arnaud. Attention modulation during motor preparation in Parkinsonian freezers: A time–frequency EEG study. **Clinical Neurophysiology**, Elsevier BV, v. 127, n. 12, p. 3506–3515, 6 Sept. 2016. DOI: 10.1016/j.clinph.2016.09.014.

122 TEAM, RStudio. **RStudio: Integrated Development for R.** Boston, MA, 2020. Available from: <http://www.rstudio.com/>.

123 TEIVE, Hélio. O PAPEL DE CHARCOT NA DOENÇA DE PARKINSON. **Arq. Neuro-Psiquiatr**, v. 1, n. 56, p. 1895, Mar. 1998. DOI: 10.1590/S0004-282X1998000100026.

124 TEIVE, Hélio AG. Etiopathogenesis of Parkinson Disease. **Neurociências**, v. 13, n. 4, p. 201–214, Dec. 2005. DOI: https://doi.org/10.34024/rnc.2005.v13.8794.

125 VAN HILTEN, Jacobus; VAN DER ZWAN, Albert; ZWINDERMAN, Aeilko; ROOS, Raymond. Rating Impairment and Disability in Parkinson's Disease: Evaluation of the Unified Parkinson's Disease Rating Scale. **Movement Disorder**, v. 9, n. 1, p. 84–88, 1994. DOI: https://doi.org/10.1002/mds.870090113.

126 VELIK, Rosemarie. Effect of On-Demand Cueing on Freezing of Gait in Parkinson's Patients. **International Journal of Biomedical Engineering**, SJR, v. 6, n. 6, p. 1247–1252, Jan. 2012. DOI: 10.5281/zenodo.1088086.

127 VERCRUYSSE, Sarah; GILAT, Moran; SHINE, James M.; HEREMANS, Elke; LEWIS, Simon; NIEUWBOER, Alice. Freezing beyond gait in Parkinson's disease: A review of current neurobehavioral evidence. **Neuroscience and Biobehavioral Reviews**, Elsevier BV, v. 43, p. 213–227, June 2014. DOI: https://doi.org/10.1016/j.neubiorev.2014.04.010.

128 WAECHTER, Saskia M.; FEARON, Conor; MCDONNELL, Conor; GALLEGO, Juan; QUINLIVAN, Brendan; KILLANE, Isabelle; BUTLER, John; LYNCH, Tim; REILLY, Richard. The impact of dual tasking on cognitive performance in a Parkinson's disease cohort with and without freezing of gait: an EEG and behavioral based approach. In: 7TH Annual International IEEE EMBS Conference on Neural Engineering Montpellier. IEEE, 2015. DOI: 10.1109/NER.2015.7146813.

129 WALTON, Courtney C.; O'CALLAGHAN, Claire; HALL, Julie M.; GILAT, Moran; MOWSZOWSKI, Loren; NAISMITH, Sharon L.; BURRELL, James R.; SHINE, James M.; LEWIS, Simon J. G. Antisaccade errors reveal cognitive control deficits in Parkinson's disease with freezing of gait. **Journal of Neurology**, Springer Science and Business Media, v. 262, n. 12, p. 2745–2754, Oct. 2015. DOI: 10.1007/s00415-015-7910-5.

130 WANG, Ying; BEUVING, Floris; NONNEKES, Jorik; COHEN, Mike X; LONG, Xi; AARTS, Ronald; WEZEL, Richard van. Freezing of gait detection in Parkinson's disease via multimodal analysis of EEG and accelerometer signals. In: ANNU Int Conf IEEE Eng Med Biol Soc. Pubmed, 2020. DOI: 10.1109/EMBC44109.2020.9175288.

131 ZEČEVIĆ, Ivan; VASELIĆ, Nada. Visuomotor characteristics and differences between the tremor-dominant and akinetic-rigid type of Parkinson's disease. **Applied Neuropsychology: Adult**, Informa UK Limited, v. 28, n. 6, p. 745–751, Dec. 2019. DOI: 10.1080/23279095.2019.1699097.

132 ZHANG, Jiuquan; WEI, Luqing; HU, Xiaofei; XIE, Bing; ZHANG, Yanling; WU, Guo-Rong; WANG, Jian. Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of intrinsic brain activity. **Parkinsonism and Related Disorders**, Elsevier BV, v. 21, n. 1, p. 23–30, Jan. 2015. DOI: 10.1016/j.parkreldis.2014.10.017.

133 ZIREK, Emrah; HUSEYINSINOGLU, Burcu Ersoz; TUFEKCIOGLU, Zeynep; BILGIC, Basar; HANAGASI, Hasmet. Which cognitive dual-task walking causes most interference on the Timed Up and Go test in Parkinson's disease: a controlled study.

Neurological Sciences, Springer Science and Business Media LLC, v. 39, n. 12, p. 2151–2157, Sept. 2018. DOI: 10.1007/s10072-018-3564-2.

Glossary

Android Mobile Phone

Smart phone that runs on the Android operating system developed by Google and is used by a variety of mobile phone manufacturers.

CNS

Central Nervous System is the brain and spinal cord, responsible for receiving, processing, and responding to sensory information.

Dopamine

A compound present in the body as a neurotransmitter that is produced in the substantia nigra, ventral tegmental area, and hypothalamus of the brain.

Dyskinesia

Abnormality or impairment of voluntary movement.Dyskinesias are erratic, writhing movements of the face, arms, legs or trunk. They are often fluid and dance-like. They are not a symptom of Parkinson's disease (PD) itself. Rather, they are a complication from some Parkinson's medications.

ECG

Electrocardiology determines heart activity.

EEG

Electroencephalography monitors brain activity.

EOG

Electrooculography determines eye movement.

Freezers

People with Parkinson's disease who have the symptom of Freezing of Gait.

Hoehn and Yahr scale

A scale for assessing the disability of individuals with PD capable of indicating their general condition in a quick and practical way.

Wearable sensors

An electronic device that can be attached to the body or embedded in a clothing garment and is able to record information about the user's body movements.

A

Appendix 1

A.1 Environment for data collection

This appendix shows photos of data collection environment in the Parkinson Triângulo Association. Figure A.1 shows the environment in which the Voluntary Stop and Timed-up and Go (TUG) test were carried out. Figures A.2, A.3, and A.4 show the physical mobility tasks environment.

For the motor and dual tasks, the distance between the chair and the wide opening is 3 meters, the distance between the wide opening and the obstacles is 1.3 meters, and the distance between the obstacles is 0.95 meters. The width of the wide opening is 67.5 centimeters.

Data collection was carried out at APT and it followed the recommendations of the World Health Organization (WHO) regarding the prevention of COVID-19. The researchers, volunteers, and companions wore masks protecting their noses and mouths throughout the contact; alcohol gel bottles were always available; and the body temperature of the people involved in the experiment was measured upon arrival.

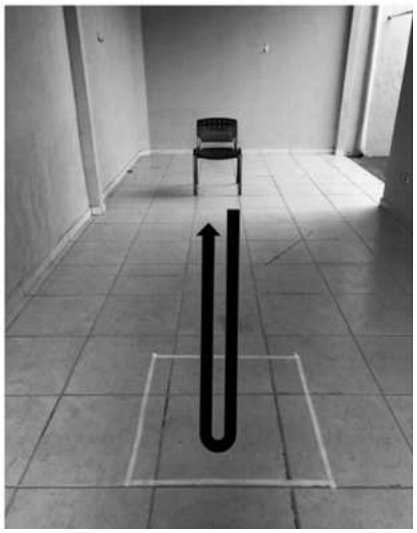

Figure A.1 – Environment in which the Voluntary Stop and TUG test were carried out.

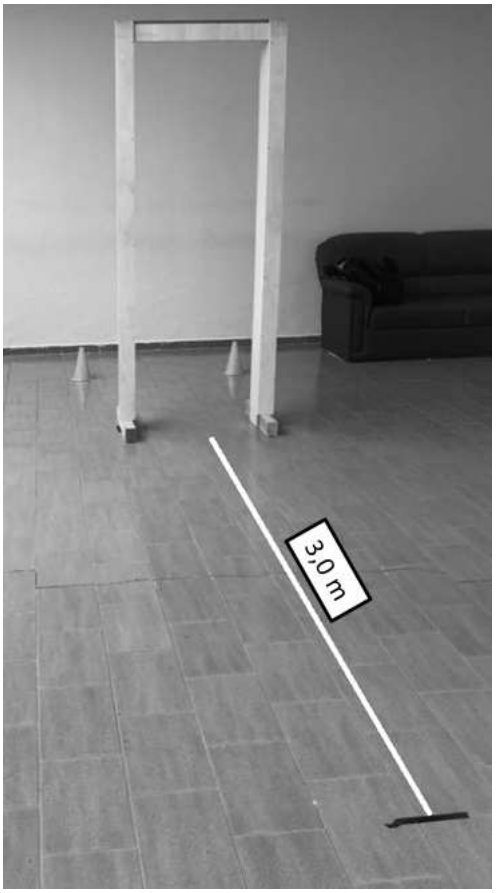

Figure A.2 – Physical Mobility tasks environment, this figure shows the distance of three meter between the chair and the wide opening.

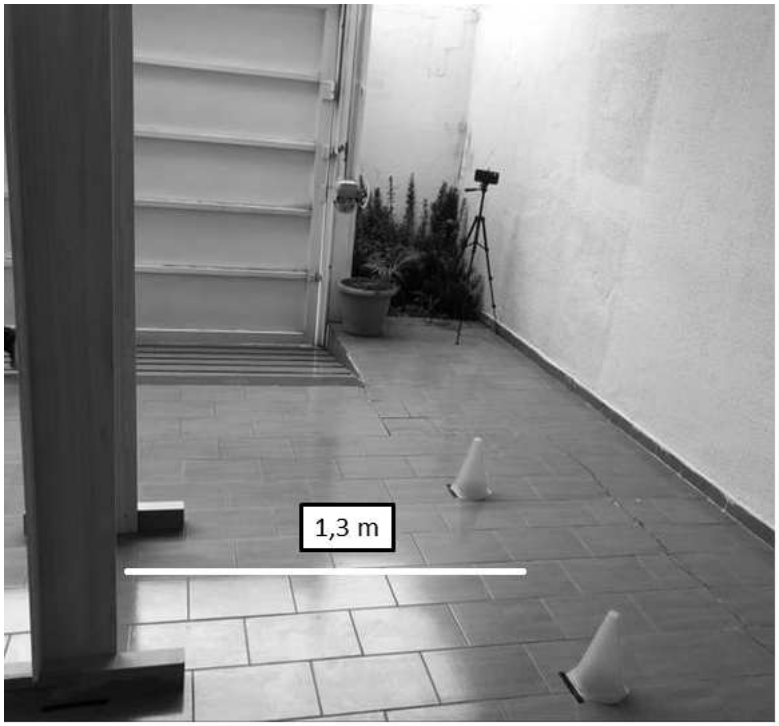

Figure A.3 – Physical Mobility tasks environment, this figure shows the distance of 1,3 meters the wide opening and the obstacles to contour.

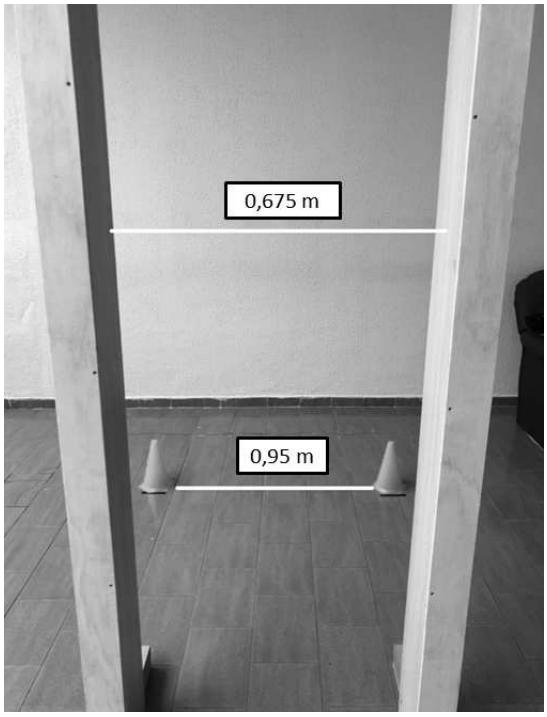

Figure A.4 – Physical Mobility tasks environment, this figure shows the distance of 0,95 meters between the obstacles to contour and the width of the wide opening 67,5 centimeters.

B

Appendix 2

B.1 Results of the cognitive task applied for the dual task

This appendix presents the results of the Digit Monitoring Task (DMT) for each group, GFOG+, GFOG- and GC. The DMT was used as the cognitive task applied for the dual task.

Table B.1 presents how many times each number was mentioned in the audio track. For each trial, a digit from the set of 1 to 9 was drawn without replacement.

Audio transcript: 459616619359126578814596166

Tables B.2, B.3 and B.4 show the volunteer's answer during the DMT for each trial of the dual task. The table is colored in green and red to show the right (green) and wrong (red) answers given by the volunteers. The second column shows the percentage of mistakes per volunteer. The percentage mean of the volunteers mistakes is 45.65% for the GFOG+ group, 25,01% for the GFOG- group and 8,35% fog the GC group.

Table B.1 – The number of times each digit from 1 to 9 is mentioned in the audio track.

Digit 1	Digit 2	Digit 3	Digit 4	Digit 5	Digit 6	Digit 7	Digit 8	Digit 9
5 times	once	once	twice	5 times	7 times	once	twice	4 times

Table B.2 – Answers of the volunteers from the GFOG+ group during the Digit Monitoring Task (DMT) for each trial of the dual task. N stands for number drawn and R for result, the number of times each digit is mentioned in the audio track. Correct answers in green and wrong answers in red.

GFOG+	% OF MIS-TAKES	OFF						ON					
V		N1	R1	N2	R2	N3	R3	N1	R1	N2	R2	N3	R3
1	50%	3	1	6	7	8	3	9	4	4	1	5	4
2	0%	6	7	8	2	7	1	1	5	4	2	3	1
3	83,3%	5	3	2	2	4	1	7	1	3	2	6	6
4	33,3%	7	0	9	4	6	5	3	1	2	1	8	2
5	50%	1	4	7	1	8	1	4	2	9	2	2	1
6	33,3%	2	0	9	4	1	5	6	7	7	1	5	4
7	50%	4	2	3	2	6	6	5	4	9	4	2	1
8	50%	9	4	7	1	3	0	2	1	6	3	5	4
9	33,3%	2	1	4	2	9	4	5	4	3	2	8	2
10	83,3%	2	4	1	7	8	7	4	2	3	2	6	6

Table B.3 – Answers of the volunteers from the GFOG- group during the DMT for each trial of the dual task.

GFOG-	% OF MIS-TAKES	OFF						ON					
V		N1	R1	N2	R2	N3	R3	N1	R1	N2	R2	N3	R3
1	50%	1	5	3	2	7	1	9	4	5	4	4	3
2	16,7%	1	5	5	4	6	7	7	1	4	2	8	2
3	50%	7	1	4	2	1	4	9	3	8	3	3	1
4	33,3%	1	5	3	1	6	6	2	1	5	4	7	1
5	16,7%	2	1	3	1	8	2	7	1	5	4	4	2
6	33,3%	2	2	8	2	4	2	6	8	7	1	3	1
7	16,7%	9	4	4	2	7	1	3	1	8	2	1	4
8	0%	4	2	2	1	7	1	6	7	5	5	8	2
9	16,7%	4	2	1	5	6	7	5	4	3	1	9	4
10	16,7%	1	5	3	1	4	2	7	1	6	6	9	4

Table B.4 – Answers of the volunteers from the GC group during the DMT for each trial of the dual task.

GC V	% OF MISTAKES	N1	R1	N2	R2	N3	R3
1	0%	8	2	4	2	6	7
2	0%	4	2	7	1	1	5
3	16,7%	8	2	5	4	6	7
4	0%	1	5	8	2	2	1
5	0%	9	4	1	5	7	1
6	16,7%	2	1	1	4	8	2
7	16,7%	9	4	6	8	5	4
8	0%	8	2	9	4	1	5
9	16,7%	9	4	3	1	1	4
10	16,7%	6	7	3	1	5	4

C

Appendix 3

C.1 Supplementary Material

This appendix aggregates the supplementary materials produced during the development of this dissertation.

C.1.1 Manual of ATLAS software

The following link contains a supplementary material file that includes a manual of ATLAS software teaching the installation and use, two video files with examples of how the smartwatches work with the software ATLAS, the code and examples of files XML.

- https://zenodo.org/record/7091122

C.1.2 Information about the cognitive task applied for the dual task

The following link contains a supplementary material file that includes the audio track with 60 seconds used in the data collection for the dual task and the results of the Digit Monitoring Task for each group, GFOG+, GFOG- and GC.

- https://zenodo.org/record/8421342

C.1.3 Ethics committee approval

This subsection presents information on approval by the ethics committee of Federal University of Uberlândia, Brazil.

Research Title: Avaliação quantitativa dos sinais motores de indivíduos com a doença de Parkinson

Proposing Institution: Faculty of Electrical Engineering

CAAE: 38885720.3.0000.5152

C.1.4 Open access database

Researchers can use the open-access database found at the DOI that follows to help create novel innovations that will enhance the quality of life for people with Parkinson's disease. They can also contribute further with the Centre for Innovation and Technology Assessment in Health (NIATS) researches. Restricted download access to the data reported in this study is provided by Zenodo. A request must be made in Zenodo in order to access the database, and the request's justifiedness will determine how it is reviewed.

- DOI = 10.5281/zenodo.10498983