SAPIENZA
UNIVERSITÀ DI ROMA

GAIT CHARACTERIZATION USING WEARABLE INERTIAL SENSORS IN HEALTHY AND PATHOLOGICAL POPULATIONS

Research Doctorate in Automatic Control, Bioengineering and Operation Research (ABRO)
Curriculum: Bioengineering (ING-INF/06) – XXXI Cycle

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Summary

Gait analysis is emerging as an effective tool to detect an incipient neurodegenerative disease or to monitor its progression. It has been shown that gait disturbances are an early indicator for cognitive impairments and can predict progression to neurodegenerative diseases. Furthermore, gait performance is a predictor of fall status, morbidity and mortality.

Instrumented gait analysis provides quantitative measures to support the investigation of gait pathologies and the definition of targeted rehabilitation programs. In this framework, technologies such as inertial sensors are well accepted, and increasingly employed, as tools to characterize locomotion patterns and their variability in research settings. The general aim of this thesis is the evaluation, comparison and refinement of methods for gait characterization using magneto-inertial measurement units (MIMUs), in order to contribute to the migration of instrumented gait analysis from state of the art to state of the science (i.e.: from research towards its application in standard clinical practice).

At first, methods for the estimation of spatio-temporal parameters during straight gait were investigated. Such parameters are in fact generally recognized as key metrics for an objective evaluation of gait and a quantitative assessment of clinical outcomes. Although several methods for their estimate have been proposed, few provided a thorough validation. Therefore an error analysis across different pathologies, multiple clinical centers and large sample size was conducted to further validate a previously presented method (TEADRIP). Results confirmed the applicability and robustness of

the TEADRIP method. The combination of good performance, reliability and range of usage indicate that the TEADRIP method can be effectively adopted for gait spatio-temporal parameter estimation in the routine clinical practice.

However, while traditionally gait analysis is applied to straight walking, several clinical motor tests include turns between straight gait segments. Furthermore, turning is used to evaluate subjects' motor ability in more challenging circumstances. The second part of the research therefore headed towards the application of gait analysis on turning, both to segment it (i.e.: distinguish turns and straight walking bouts) and to specifically characterize it. Methods for turn identification based on a single MIMU attached to the trunk were implemented and their performance across pathological populations was evaluated. Focusing on Parkinson's Disease (PD) subjects, turn characterization was also addressed in terms of onset and duration, using MIMUs positioned both on the trunk and on the ankles. Results showed that in PD population turn characterization with the sensors at the ankles lacks of precision, but that a single MIMU positioned on the low back is functional for turn identification.

The development and validation of the methods considered in these works allowed for their application to clinical studies, in particular supporting the spatio-temporal parameters analysis in a PD treatment assessment and the investigation of turning characteristic in PD subjects with Freezing of Gait. In the first application, comparing the pre and post parameters it was possible to objectively determine the effectiveness of a rehabilitation treatment. In the second application, quantitative measures confirmed that in PD subjects with Freezing of Gait turning 360° in place is further compromised (and requires additional cognitive effort) compared to turning 180° while walking.

Keywords: Clinical gait analysis; Spatio-temporal parameters; Turn; Inertial sensors; Wearable sensors; MIMU; Elderly; Parkinson's disease; TUG; Biomechanics; Freezing; FoG; Validation; Multicentric study; Rehabilitation.

Acknowledgements

My sincere gratitude goes to all the people who allowed me to undertake this PhD, and to all who helped me getting through it.

I would like to thank my supervisor Prof. Ugo Della Croce and my co-supervisor Andrea Cereatti for all teachings, invaluable support and criticism during my PhD experience.

I am deeply grateful to Martina Mancini for the chance to work in the Balance Disorder Laboratory at OHSU.

I should also thank my parents for bearing with me and taking care of me, especially before submission deadlines.

I also thank my lab mates and my friends in Sassari and Turin, and those in GPEM, for their advices and support.

Lastly, I would like to thank all the people who contributed with their advices, their collaboration and their support to the development of this thesis.

List of publications

Submitted

M. Bertoli, U. Della Croce, A. Cereatti, M. Mancini, "Objective Measures to Investigate Turning Impairments and Freezing of Gait in people with Parkinson's disease" – Gait&Posture (*under review*)

International Peer-Reviewed Journals

M. Bertoli, A. Cereatti, D. Trojaniello, L. Avanzino, E. Pelosin, S. Del Din, L. Rochester, P. Ginis, E. M. J. Bekkers, A. Mirelman, J. M. Hausdorff, and U. Della Croce, "Estimation of spatio-temporal parameters of gait from magneto-inertial measurement units: multicenter validation among Parkinson, mildly cognitively impaired and healthy older adults," BioMedical Engineering OnLine, vol. 17, no. 1, pp. 58, 2018. DOI:10.1186/s12938-018-0488-2.

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National Conference Proceedings

M. Bertoli, A. Cereatti, and U. Della Croce, Identification of multiple U-turns using gyroscopes : comparative assessment of two methods, 2016 *(V GNB)*.

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Glossary

MIMU: Magneto-Inertial Measurement Unit

PD: Parkinson's Disease

MCI: Mild Cognitive Impairment

ELD: Elderly (older adults)

GE: Gait Events

IC/FC: Initial/Final Contact

LCS/GCS: Local/Global Coordinate System

NW/FW: Normally/Fast paced Walk

UNIGE: University of Genova

KULEU: KU Leuven

TASMC: Tel Aviv Sourasky Medical Center

NEWCA: Newcastle University

OHSU: Oregon Health and Science University

OFDRI: Optimally Filtered and Direct and Reverse Integration

TEADRIP: Trusted Events and Acceleration Direct and Reverse Integration along the direction of Progression (spatio-temporal parameters estimation method)

BS: Sardinian folk dance

FoG: Freezing of gait

PD+FoG/PD-FoG: PD subject showing/not showing FoG

U-turn: 180° turn while walking

ANOVA: analysis of variance statistical test

Chapter 1

Introduction

1.1 General introduction

Gait analysis aims at gathering quantitative information about the biomechanics of the locomotor system during walking [*Cappozzo* 1984]. The methods for evaluating gait are numerous, depending mainly on the instrumentation used, and are constantly evolving [*Tao* 2012; *Cappozzo* 2014; *Horak* 2015; *Iosa* 2016]. Nowadays, instrumented gait analysis is a crucial tool for determining gait related impairments and relevant treatments [*Benedetti* 2017]. Technological progress has promoted the development of innovative measurement systems that allow investigating the locomotor tasks in different conditions and with a high descriptive level. In particular inertial sensors, wearable and relatively low cost, are an appealing solution and are gaining great interest in this field [*Cuesta-Vargas* 2010]. In fact, thanks to their versatility, gait (but more in general movement) analysis by means of inertial sensors has begun to spread outside of the research context into the clinical practice and the everyday life. However, if inertial sensors-based gait analysis on healthy subjects in controlled conditions is largely used and validated, the same cannot be said about impaired populations or unconstrained walking. In fact, pathological gait patterns differ from the physiological ones in unpredictable ways (often due to impairments and consequent compensatory strategies) and with large variability, and therefore their analysis requires great fine tuning efforts for clinical applications. Similarly, walking in unrestricted conditions (e.g.: climbing stairs, turning, passing obstacles, ...) generates heterogeneous gait patterns that, to be analyzed properly, needs to be correctly identified and classified. Currently there is no acclaimed method for such evaluation in a robust way, even though several solutions have been proposed [*Preece* 2009; *Rueterbories* 2010; *Storm* 2016]. Since portability is one of the best inertial sensors features, allowing for the measurement of the human motion during daily life activities, being able to reliably evaluate gait outside of dedicated settings is of

paramount importance. Thus, the validity of clinically suitable gait analysis in ecological conditions by means of inertial sensors is still an open issue.

1.1.1 Clinical gait analysis

Clinical gait analysis focuses on the monitoring and evaluation of individuals with conditions affecting their ability to walk, with the goal of providing answers to specific clinical questions, assessing the effect of an intervention, limiting motor impairments or rehabilitating from traumatic events [*Cappozzo* 1984; *Baker* 2006]. Traditionally, the measurement systems used in laboratories are stereophotogrammetry, force platforms and electromyography (EMG) [*Benedetti* 2017]. These instrumentations are required in order to acquire the kinematic, kinetic and EMG data needed for a comprehensive gait analysis.

Stereophotogrammetric systems provide the kinematic data: by means of passive or active markers they can track the movement (i.e.: positions in time) of the subject. The markers are attached to specific locations on the subject's body (usually on bony landmarks) and, in order to be able to reconstruct the kinematics of a body segment (usually pelvis, thighs, shanks and feet, all considered as rigid bodies), they must be at least 3 for each segment. Furthermore, in order to exploit the photogrammetric principle, markers must be located in a calibrated measuring volume and captured by at least two cameras simultaneously. If these requirements are followed, it is possible to accurately reconstruct the instantaneous 3D positions of markers (and therefore subject) with respect to a reference coordinate system.

Force platforms (in union with stereophotogrammetric systems) provide the kinetic data: they determine ground reaction forces. They consist of load cells that measure the 3D components of forces and torques acting on them. Thus, having knowledge of the motion of the limbs and external forces, through inverse dynamics it is possible to

estimate the internal moments and forces acting within at the joints connecting the body segments.

EMG systems provide the EMG data: they measure the electrical activity of the muscles. Depending on how selective (and invasive) a recording needs to be, fine-wire or surface EMG can be used. The latter is commonly used for research purposes, with either bipolar electrodes or high-density matrices. From surface EMG, given at least two electrodes attached to the subject' skin (and an acquisition system), the activation times and magnitude of the underlying muscles can be estimated.

This entire set of system though is not necessarily required for an effective gait analysis: even if the best results are obtained merging kinematics, kinetics and EMG together, their individual analysis can still be used to diagnose specific pathologies, predict the outcome of treatments, or determine the effectiveness of rehabilitation programs. Gait kinematics especially is frequently studied on its own with productive results. In particular, inside this field several research studies are focusing on the use of spatio-temporal parameters, which are used to characterize the subject's walking pattern. For a visual explanation on how these parameters are defined a representative scheme can be seen in Figure 1-1. For each gait cycle (i.e.: the interval between one foot-ground contact and the subsequent one from the same side, also 'stride') standard phases are defined: stance and swing (for the same side) and single support and double support (when both sides are considered). These intervals are the primary temporal parameters. Other temporal parameters, such as the cadence, can be easily computed from them. Spatial parameters such as the stride length and step length are determined at foot-ground contact from the distances covered for each gait cycle. Gait speed can then be calculated as the ratio of stride length over stride time. Except from stereophotogrammetric systems, which are considered the gold standard for gait analysis, spatio-temporal parameters can also be determined from a (ever increasing) number of other technologies. In the next paragraphs, two of them (the most popular

among the portable ones) will be described since directly used in this thesis: the instrumented mat and the inertial sensors.

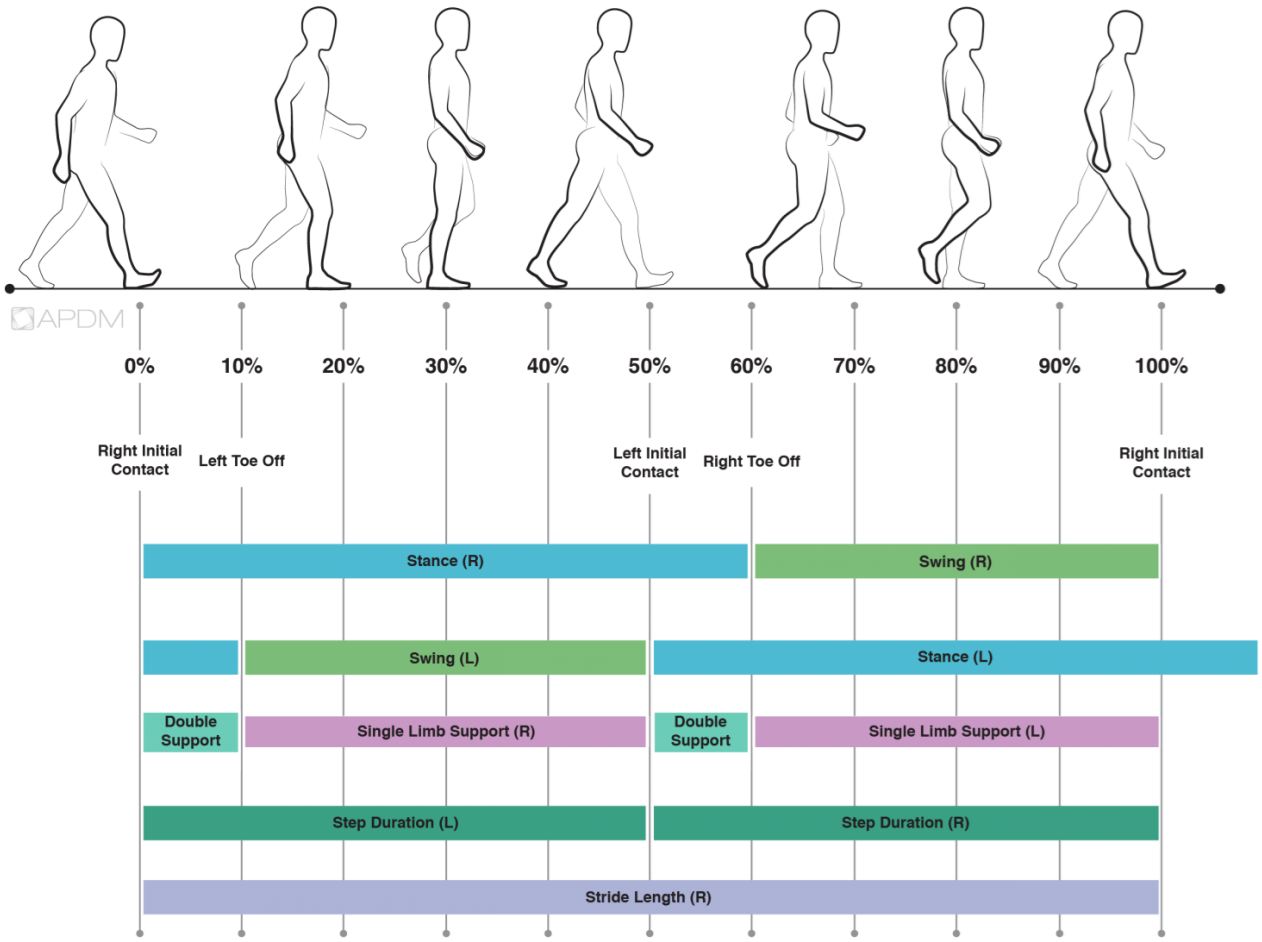

Figure 1-1 Gait cycle and spatio-temporal parameters representative scheme

1.1.1.1 Instrumented mat

The instrumented mat consists of a 'carpet' walkway with pressure sensors embedded within its length, capable of record and quantify the footstep patterns. Each sensor, associated with its own spatial coordinate, provides a value in proportion to the pressure detected. Irrespectively of the source of the pressure, sensors are activated for every external contact. In the majority of these systems, data from the activated sensors are collected by a series of on-board processors and transferred via cable in real-time

to the acquiring computer. Proper spatio-temporal parameters can then be computed in post-processing, usually by a dedicated software in a semi-automatic way. The acquisition frequency can be up to hundreds of Hertz; a typical value being 120Hz, sufficient for most clinical applications. Temporal resolution is therefore in the order of magnitude of few milliseconds, while spatial resolution ranges from 10mm to 1cm. Walkway dimension usually do not exceed a one-meter width and a 7-meter length.

The advantages of this system are definitely multiple: high accuracy and repeatability of measurements, reduced costs, and fast (or no) preparation of the subject to the measure (no markers placement). But most importantly, it is a portable tool that, with a quick set-up, can be positioned on every flat surface, either inside a laboratory or outside. Furthermore, it is not affected by electromagnetic disturbances (like inertial sensors) or sensing artifacts and occlusions (like stereophotogrammetric systems). Subjects can freely walk over the carpet without the encumbrance of wires or markers and data can be quickly obtained for each step within the passage. In the last decade, instrumented mats usage has highly increased, not only for research [*Lebold* 2010; *Almeida* 2010; *Tseng* 2012], but also for clinical purposes.

A major limitation though, is that only steps that fall within the walkway are recorded, and therefore only straight gait on a restricted path can be analyzed; no turnings or obstacle negotiation tasks can be directly studied with these systems. Furthermore, they can be relatively expensive (tens of thousands of euros).

As an example, three representative models, among the several types available on the market, are illustrated in Figure 1-2. The GAITRite (CIR Systems, Inc.) and Zeno (Protokinetics) are two commonly used mats, both featuring accepted validity and reliability of the spatio-temporal parameters measured in normal and pathological gait[*Bilney* 2003; *Beijer* 2013]. The Strideway System (Tekscan), also validated from the literature [*Zammit* 2010; *Coda* 2014], instead is an example of baropodometric platform

Figure 1-2 Instrumented mats

(of which instrumented mats can be considered a sub-category) which, on top of spatio-temporal parameters, returns also the foot plantar pressure distributions.

It also worth to mention that another technology, based on optical sensors but similar in principle and with analogous advantages and disadvantages, was recently proposed (OptoGait). This system measures the same parameters as the instrumented mat, but with a different detection approach. The OptoGait is made by a transmitting and a receiving infrared LED bar, within which the subject walks. It detects the interruptions of the communication between the bars and calculates the duration and position with an accuracy of 1 ms in time and 1 cm in space.

1.1.1.2 Magneto-inertial sensors

Magneto-inertial sensors, or -in this thesis- magneto inertial measurement units (MIMUs), use the principle of inertia of a mass to measure linear acceleration and angular velocity, and the magnetoresistive effect to determine local magnetic field. MIMUs therefore embody the integration of multiple sensors: accelerometers, gyroscopes and magnetometers. Since the measures are attainable along a single

sensing axis, typically each sensor is mounted in a three-axial configuration (orthogonally arranged) in order to form a proper 3D sensor. Measures are therefore provided with respect to the reference frame of the sensor, which is not fixed, but typically corresponds to the axes of a Cartesian coordinate system aligned with the unit [*Cereatti* 2015].

The most interesting solution that MIMUs can offer though is the estimation of their orientation in the 3D space with respect to a global reference system. In static conditions, in order to obtain the sensor orientation, the accelerometer can be used as an inclinometer: since it senses only the acceleration due to gravity (which is proportional to the inclination with respect to gravity direction), it can determine the deviation of its sensitive axis from the vertical direction (for each of the three axis) and by simple trigonometry orientation can directly be calculated [*Luczak* 2006]. While a three-axial accelerometer is sufficient in static conditions, in dynamic conditions MIMU orientation estimate is not straightforward. A basic approach consist in using the gyroscope to directly measure the angular velocity and, by computing its numerical integration, given an initial reference, obtain an estimation of the rotated angle and actual orientation. This approach though is prone to errors due to gyroscope bias drifts that grow unbounded over time (the signals measured by the inertial sensors are characterized by an unpredictable low-frequency red noise) and furtherly propagates in the numerical integration process [*Sabatini* 2011; *Picerno* 2017]. A more comprehensive approach consist in achieving orientation estimates by sensor fusion algorithms, which combine the complementary characteristics of the integrated sensors [*Bergamini* 2014]. The orientation computed from the angular velocity integration can be adjusted by means of the accelerometers, but the correction applies only with respect to the vertical (obtaining corrected pitch and roll angles, or, jointly, attitude or inclination). Reference information about the sensor's orientation in the horizontal plane are then needed to correct the orientation estimate about the vertical

direction (yaw angle or heading). To this purpose, readings from the magnetometer (which senses the local magnetic north as absolute reference) can be used, so that a full 3D orientation of the sensor in space can be obtained. Since the global coordinate system definition is based only on gravity and local magnetic north, its origin results undefined. Therefore only MIMU's pose, but not position, can be estimated in the 3D space. Given an initial position though, its movement over time can be tracked [*Zhou* 2008].

MIMUs are gaining popularity among the several other technologies for motion tracking thanks to their advantages of being small, portable, and with limited power consumption, thus allowing for unconstrained motion monitoring [*Rueterbories* 2010; *Tao* 2012; *Bergamini* 2014]. As illustrated in Figure 1-3, MIMUs are small sized (few centimeters) and neither cumbersome nor heavy (weight of few tens of grams). The acquisition frequency mostly ranges between 100 and 500 Hertz, and they are appropriate for real-time applications. MIMUs are generally embedded with Bluetooth/wireless modules or SD cards for data streaming or on-board logging, respectively. They can be used either as a stand-alone device, or, in a combination of

Figure 1-3 Magneto inertial measurements units

synchronized units, as a wearable system. Often sensor fusion algorithms are already implemented in commercially available MIMUs, and various manufacturers also offer software suites for the gait spatio-temporal parameters estimation. Furthermore, MIMUs are completely self-contained, since they don't require an external source to measure the physical quantities related to their motion (and therefore the motion of the objects to which the sensors are fixed)[*Sabatini* 2011]. In addition, thanks to recent technological advances and high market demands (these sensors are in fact largely used in the consumer electronics), their cost drops while their performance improves.

However, some limitations are yet to be overcome in orientation estimate accuracy. An open problem is the so called "gravity removal": the difficulty of correctly determining, in the acceleration signals, the component due to the gravity from the component related to the motion of the sensor [*Rampp* 2015]. As a consequence, the vertical reference can be considered reliable only for static or constant velocity conditions [*Veltink* 1996]. Most importantly, the local magnetic north (and therefore the horizontal reference) can be distorted by nearby ferromagnetic materials or electrical appliances, which critically disturbs the signals sensed by the magnetometer [*Bachmann* 2004]. This problem becomes especially apparent within man-made indoor environments and justifies the fact that the estimation of the heading is often regarded as more critical than that of the attitude [*Roetenberg* 2005].

1.1.2 Gait segmentation

As explained in the previous section, the main advantage of inertial sensors is that they enable performing gait analysis in daily-living conditions, where the subject walks casually. In fact, moving from laboratory settings to more ecological conditions allows to reduce the influence exercised by the environment (i.e. the lab) and by the presence of the healthcare professionals and to collect realistic data continuously over an

extended period of time and long distances. However, while protocols and definitions for the estimate of gait spatio-temporal parameters are well delineated and validated on straight bouts, they lack of standardization in some variants of gait encountered in real life, such as stairs and/or turns [*Huxham* 2006]. Gait analysis in unsupervised settings is therefore appealing but challenging.

An intuitive approach to solve the problem is to identify the straight walking bouts in such variants of gait and estimate the traditional spatio-temporal parameters on those intervals only. To do so, a valuable help comes from body of literature focusing on 'activity recognition' [*Preece* 2009; *Mannini* 2013; *Wullems* 2017]. Being aware of what kind of gait is being analyzed (i.e.: classifying it) is of paramount importance for two reasons: first, trivially, it allows to avoid errors due to a misrepresented movement and second, it allows to select the most appropriate and explicative measures that describe the specific gesture. An example of the need for this classification comes from the turn analysis. Considering the first reason (avoiding errors), a problematic topic is the stride detection during turning. Several spatio-temporal parameters estimation methods detect a gait cycle by detecting the swing of the leg from the mediolateral angular velocity [*Salarian* 2004; *Sabatini* 2005; *Catalfamo* 2010; *Greene* 2010; *Mannini* 2012]. While this is correct in straight gait, it may not be applicable during turning where, in the swing phase, angular velocity mediolateral component is reduced and there is a greater vertical component. This would lead to a stride missed detection during turning not because of a failure of the method, but because of its improper application on another motor gesture. Considering the second reason (appropriate measure), an example is the usage of the symmetry index. The symmetry index is derived from right and left spatio-temporal parameters to quantify gait symmetry and it is used to evaluate gait functionality. During turning the measure itself can be computed, but since turning is an intrinsic asymmetric gesture its analysis would not

lead to meaningful results. Instead, other measures specific for the turning task are to be considered.

1.2 Thesis objectives

An overview of the research project is reported in Figure 1-4. The three main research questions to which this work tries to answer are reported in bold.

The broad scope of the research conducted and reported in this PhD thesis regards the development, application and testing of MIMU based methods for assessing gait quantitative measures across straight walking bouts and turnings in clinical contexts.

Specifically, as illustrated in Figure 1-4, the aim of this thesis is twofold: characterization of straight gait by means of traditional spatio-temporal parameters (straight gait analysis) and characterization of gait during turning (turn analysis).

The first part of the research project focused on the fine tuning of a proposed method to estimate gait spatio-temporal parameters using two MIMUs positioned on the ankles. This operation was done so that the method could be applied on a large cohort of healthy and pathological subjects acquired in different clinical centers. The estimates obtained were then validated against the spatio-temporal parameters acquired by an instrumented mat. Such a validation is in fact required to answer the question "can parameters be estimated ubiquitously?" and allows to declare the method robust across facilities and therefore usable in different context.

A preliminary step for the method application required the automatic segmentation of the gait data acquired into straight bouts and turns. This posed a research question on which turn identification method was to be used, and lead to the turn studies that were performed in parallel to the straight gait analysis. First, methods for turn identification based on a single MIMU positioned on the trunk were compared among each other

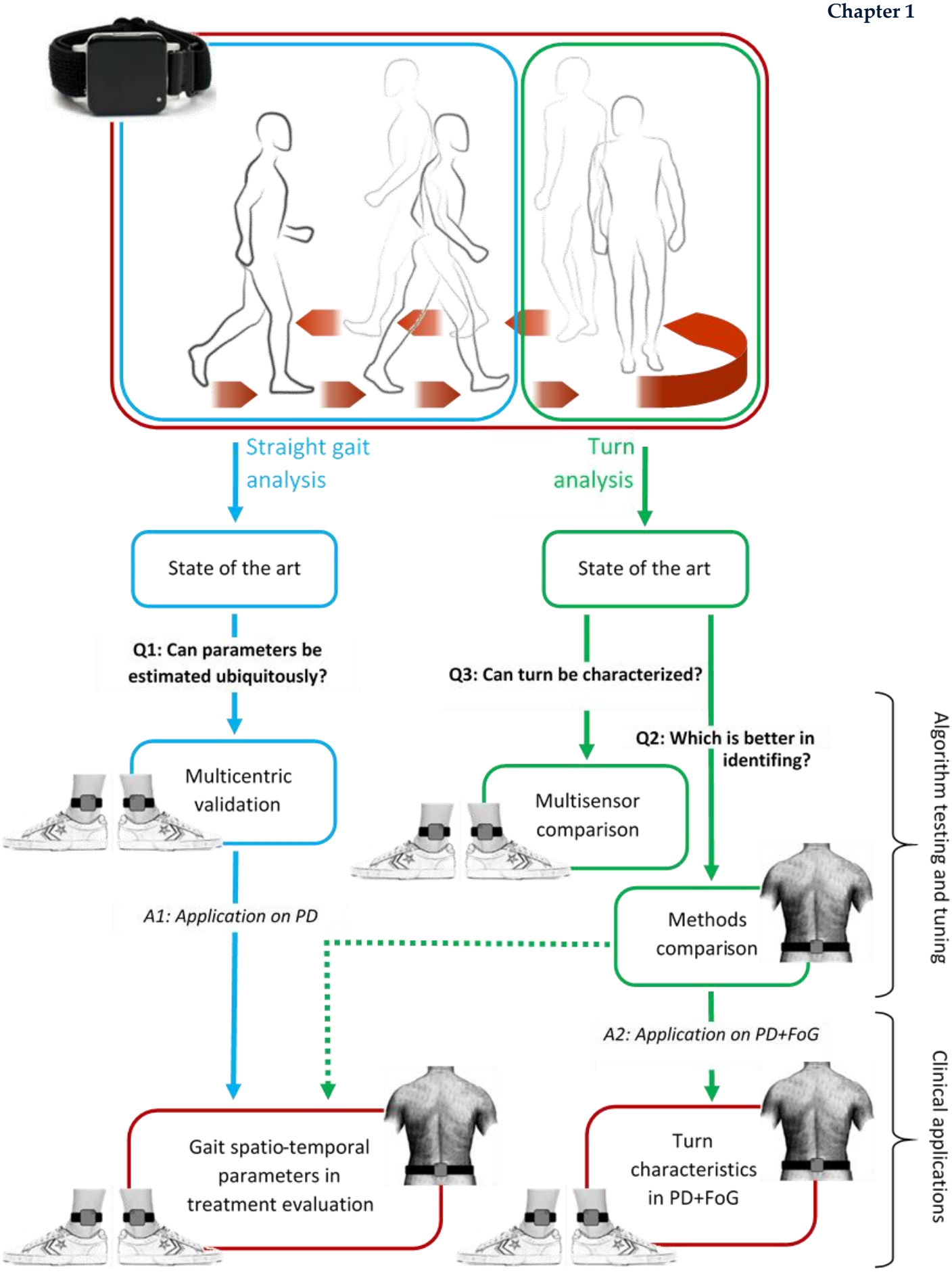

Figure 1-4 Overview of the thesis project

and to reference data provided by the instrumented mat and their performance was evaluated ("which is better in identifying turns?"). Then, their capability of determining the beginning and ending instants of turns was investigated. Finally, a novel method to determine such instants based on two MIMUs on the ankles was proposed ("can turn be characterized?"). The reason for applying the method at the ankles (where traditional spatio-temporal parameters are better estimated) comes from the wish of using the most unobtrusive instrumental setup.

The results of these works allowed to migrate the acquired knowledge to applications in clinical studies. Spatio-temporal parameters were analyzed in a pre-post Parkinson's Disease (PD) treatment assessment to determine its validity, and turning characteristics in PD subjects with Freezing of Gait were analyzed to investigate their specific motor deficit.

1.3 Outline of the thesis

The thesis is organized as follows.

Chapter 1 (current chapter) introduces the topic of this thesis through the presentation of characteristics of clinical gait analysis. The technologies commonly employed to determine gait quantitative measures are briefly introduced. The motivations of the research work, as well as the methodology applied, are presented together with the objectives and outline of the thesis.

Chapter 2 elaborates on gait spatio-temporal parameters and, for reference context, glides on parameters estimation using MIMUs. An estimation method using shank worn MIMUs is validated on a large cohort of pathological subjects. Results of the technical validation of the proposed method are reported against a gold standard for two walking speed and across four clinical centers that provided the gait data.

Chapter 3 illustrates why 180° turns are important in clinics and presents a comparative evaluation of different methods for turn identification using a single MIMU unit attached to the trunk on healthy and pathological subjects. A further study concerning ankle based methods is presented extending the previous results.

Chapter 4 explains how the methods presented in chapter 2 and 3 can be applied in a clinical gait analysis. In this study gait spatio-temporal parameters are analyzed along clinical outcome measures to assess the effects of a dance treatment on functional performance in individuals with Parkinson's Disease (PD).

Chapter 5 describes a study that exploit quantitative measures computed during turnings to investigate differences in PD subjects with and without freezing of gait.

Chapter 6 discusses the achievements of the research performed during the PhD program and an outlook for future research.

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Chapter 2

Gait spatio-temporal parameters estimation in straight walking*

* This chapter is based on **M. Bertoli**, A. Cereatti, D. Trojaniello, L. Avanzino, E. Pelosin, S. Del Din, L. Rochester, P. Ginis, E. M. J. Bekkers, A. Mirelman, J. M. Hausdorff, and U. Della Croce, "**Estimation of spatio-temporal parameters of gait from magneto-inertial measurement units: multicenter validation among Parkinson, mildly cognitively impaired and healthy older adults**," *BioMedical Engineering OnLine*.

2.1 Inertial sensors instrumented gait: State of the art

Since walking is the most efficient form of locomotion on level terrain, most humans have a very similar gait pattern, constituted by repetitive sequential gait cycles. Key element for spatio-temporal parameters estimation is therefore the segmentation of inertial sensors derived gait data into gait cycles, usually by the identification of the initial contact (IC) of the foot with the ground. Thanks to their huge repeatability, distinctive traits can be recognized in acceleration and angular velocity data to identify ICs. However, depending on MIMU positioning on the human body, a high variability in magnitude and frequency of raw inertial data have been extensively reported. As a consequence, a multitude of different methods for gait cycle extraction have been proposed [*Aminian* 2002; *Zijlstra* 2003; *Salarian* 2004; *Sabatini* 2005; *Jasiewicz* 2006; *Greene* 2010; *Catalfamo* 2010; *Mariani* 2010; *González* 2010; *McCamley* 2012; *Pham* 2017]. Among these, two main approaches in sensor configurations can be outlined: single, with the sensor usually attached to the trunk, and bilateral, with sensors attached to either feet or shanks. Indeed, MIMU positioning plays a primary role in the robustness and accuracy of the ICs detection. An attractive solution is to attach only one MIMU at the waist level so that ICs of both feet can be detected, while minimally conditioning the subject. On the other hand, as a general rule, the closer the sensor to the ground (point of contact), the better the possibility of precisely detecting the IC. Therefore, single MIMU approach methods present an increased difficulty in robust and accurate IC detection and, consequently, gait temporal parameters estimation [*Trojaniello* 2014a; *Trojaniello* 2015]. In bilateral MIMU approach, attaching the MIMUs to the shanks may offer some advantages over the feet, since it provides a more rigid positioning. In fact, throughout the gait cycle the foot undergoes large deformations. Moreover, inertial data were found to be less variable between subjects for shank-attached MIMUs than from foot-attached MIMUs [*Trojaniello* 2014b].

Table 2-1 Algorithms for gait timing estimation from MIMU measurements

Algorithms	Sensor position	Target Variable	Computational Approach	Analysed subjects
Bugané 2012	Trunk	Acceleration	'peak identification' (IIR)	Healthy
Lee 2010	Trunk	Acceleration	'peak identification' (FIR)	Healthy, Hemiplegic after stroke
McCamley 2012	Trunk	Acceleration	'peak identification' (WT)	Healthy
Gonzaléz 2010	Trunk	Acceleration	'zero crossing' (FIR)	Healthy
Shin 2011	Trunk	Acceleration	'zero crossing' (Raw)	Healthy
Zijlstra 2003	Trunk	Acceleration	'zero crossing' (IIR)	Healthy
Lee 2010	Shank	Acceleration	'peak identification' (IIR)	Healthy
Trojaniello 2014	Shank	Acceleration	'peak identification' (Raw)	Healthy, Choreic, Hemiparetic, PD
Khandelwal 2014	Shank	Acceleration	'peak identification' (WT)	Healthy
Catalfamo 2010	Shank	Angular velocity	'peak identification' (IIR)	Healthy
Greene 2010	Shank	Angular velocity	'peak identification' (Raw)	Healthy
Salarian 2004	Shank	Angular velocity	'peak identification' (Raw)	Healthy Parkinson's disease
Aminian 2002	Shank	Angular velocity	'peak identification' (WT)	Healthy
Jasiewicz 2006	Foot	Acceleration	'peak identification' (Raw)	Healthy Spinal-cord injured
Sabatini 2005	Foot	Angular velocity	'peak identification' (IIR)	Healthy
Ferrari 2016	Foot	Angular velocity	'peak identification' (Raw)	Healthy Parkinson's disease
Mariani 2013	Foot	Angular velocity	'zero crossing' (IIR)	Healthy Parkinson's disease

Regardless of MIMUs configuration, methods for IC, as well as final contacts (FC), identification often exploit a signal analysis based approach: fixed or adaptive thresholds and peaks detection in both the time and/or frequency domain. However, standard methods are negatively influenced by inter-subject variability. Interestingly,

machine learning methods based on Markov models showed to have less dependence on inter subject variability [*Mannini* 2012].

A systematic review of the most relevant solutions for gait events (GE: ICs and FCs) identification in terms of experimental protocol adopted, computational approach and performance can be found in [*Pacini Panebianco* 2018] and summarized in Table 2-1.

While methods for GE detection provide sufficient information for computing temporal parameters, for the spatial parameters anthropometric data or an estimate of the sensor position are needed in addition. To determine spatial parameters using MIMUs, three main approaches can be applied: human gait models, machine learning methods or direct integration [*Yang* 2012]. However, all of these methods present some limitations. Human gait models, for instance those exploiting the inverted pendulum [*Allseits* 2017], have been developed based on healthy gait, and thus their application to pathological gait patterns could be problematic. Thanks to advances in deep learning and dataset availability, machine learning methods are recently gaining popularity [*Hannink* 2017a], but often require some level of customization, and the performance of such methods depends on the completeness and homogeneity of the training data set used to build them. Direct integration (i.e.: gravity-free linear acceleration double integration) main setbacks, as anticipated in the previous chapter, are the drift in MIMU signals and the need for an initial velocity estimate, but several technical measures to overcome them have been devised [*Cereatti* 2015; *Picerno* 2017]. Among those, a great aid comes from the cyclical nature of gait: drift introduced errors can in fact be reduced by restricting the time interval of integration to a single gait cycle [*Skog* 2010]. It is then still required to identify an instant of known velocity to be used as initial condition value for the acceleration integration. To this purpose, for sensors positioned on the foot Peruzzi and co-workers [*Peruzzi* 2011] suggested to apply the Zero Velocity Update (ZUPT) in correspondence of the foot flat phase. For sensors positioned on the shanks instead, an expedient consist in estimating the sensor initial velocity using the inverted pendulum model [*Yang* 2012]. Alternatively, for drift

compensation advanced filtering integration techniques [*Köse* 2012b] or de-drifting functions can be used [*Veltink* 2003; *Sabatini* 2005; *Mariani* 2010; *Chang* 2016]. Yet, it is important to remember that the accuracy in GE detection plays a fundamental part since errors in determining the gait cycle or the known velocity instants propagate in spatial parameters estimation.

In conclusion, spatio-temporal parameters estimation methods achieve an acceptable level of accuracy when applied to healthy gait, while in severe pathological gait conditions there is still room for improvement. In the next section a thorough error analysis across different pathologies, multiple clinical centers and on large sample size is presented. A previously presented method [*Trojaniello* 2014b] for the estimate of spatio-temporal parameters, named Trusted Events and Acceleration Direct and Reverse Integration along the direction of Progression (TEADRIP), was applied on a large cohort (236 patients) including Parkinson, mildly cognitively impaired and healthy older adults collected in four clinical centers. Data were collected during straight-line gait, at normal and fast walking speed, by attaching two MIMUs on the shanks. The parameters stride, step, stance and swing durations, as well as stride length and gait velocity, were estimated for each gait cycle. The TEADRIP performance was validated against data from an instrumented mat.

2.2 Estimation of spatio-temporal parameters of gait from magneto-inertial measurement units: multicenter validation among Parkinson, mildly cognitively impaired and healthy older adults

2.2.1 Introduction

Objective measures of the temporal and spatial parameters of gait allow to define the level of impairment and to characterize functional gait performance, which can serve as a biomarker of mobility [*Mirelman* 2011; *Horak* 2015; *Della Croce* 2017]. Magneto-

inertial measurement units (MIMUs) have been frequently presented as an affordable solution to assess gait parameters in a variety of environments [*Horak* 2015; *Iosa* 2016; *Chen* 2016; *Della Croce* 2017]. However, the accuracy of the gait spatio-temporal parameters obtained using MIMUs can vary remarkably depending on the algorithms used to detect ICs and FCs and estimate distances [*Cereatti* 2015]. Moreover, methods developed and validated on healthy gait are not guaranteed to be effective in assessing parameters for specific pathological gaits [*Trojaniello* 2014b]. So far, no study addressed the robustness of the detection algorithm across data coming from multiple clinical centers, despite its value for further supporting clinical use. Finally, and probably most importantly, the majority of the studies in the literature validated MIMU-based methods for the estimation of the gait spatio-temporal parameters only on limited sample sizes [*Salarian* 2004; *Trojaniello* 2014b; *Chang* 2016; *Bötzel* 2016; *Visi* 2017; *Pham* 2017].

A promising method for the automatic GEs detection and spatio-temporal parameters was presented by Trojaniello et al. [*Trojaniello* 2014b] and tested in real life settings in successive work by Storm et al. [*Storm* 2016]. The method, here named TEADRIP (Trusted Events and Acceleration Direct and Reverse Integration along the direction of Progression), was validated on four different gait conditions (i.e. healthy elderly, hemiparetic, Parkinson and choreic gait) and two different walking speeds, and it was shown that its performance was comparable or better than other methods proposed [*Storm* 2016; *Hannink* 2016].

The aim of the present study was to further extend TEADRIP validation for the spatio-temporal parameters estimation to gait inertial data recorded in a multicenter trial (four clinical centers) on a very large sample size of participants (two-hundred-thirty-six) including patients with Parkinson's Disease (PD), mild cognitive impairment (MCI) and healthy older adults.

2.2.2 Materials and Methods

2.2.2.1 Subjects

Two-hundred-thirty-six community-living older adults who self-reported two or more falls within the previous six months were enrolled in the study across four clinical centers in four countries (Belgium, Israel, Italy, and the UK). The subjects were part of the randomized controlled trial performed within the EU funded V-Time project and the study was approved by the medical ethics review committee at each site [*Mirelman* 2013]. Eligible individuals were enrolled if they were aged 60–90 years, on stable medication for the past month and able to walk for at least five minutes unassisted (refer to Mirelman et al. [*Mirelman* 2016] for additional eligibility criteria). Individuals who agreed to participate in the study were asked to sign informed written consent. Participants were divided into three groups: older adults with no cognitive impairment (ELD), older adults with mild cognitive impairment (MCI) and people with Parkinson's disease (PD). Population characteristics for each clinical center are detailed in Table 2-2.

Table 2-2 Subject characteristics for clinical centers.

Clinical Center	N	Females	Males	Age mean±sd [years]	ELD	PD	MCI
UNIGE	52	35	17	73±5	16	28	8
KULEU	58	40	18	74±7	27	14	17
TASMC	75	37	38	73±7	20	53	2
NEWCA	51	26	25	74±8	17	30	4
Total	236	138	98	74±7	80	125	31

N: total number, ELD: healthy older adults, PD: Parkinson's disease subjects, MCI: mild cognitive impaired subjects.
(Subjects between centers were age matched)

2.2.2.2 Instrumentation

Two synchronized MIMUs (Opal, APDM Inc), featuring a tri-axial accelerometer, gyroscope and magnetometer (unit mass 22 g, unit size 48.5 mm × 36.5 mm × 13.5 mm)

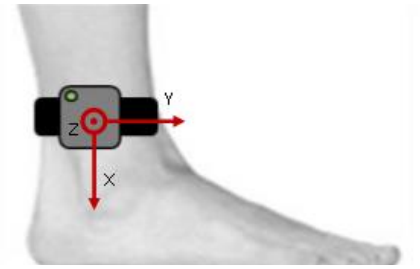

Figure 2-1 Sensor placement (R-MIMU) and its Local Coordinate System axes

were used. Inertial data were streamed wirelessly to a laptop ("robust synchronized streaming mode") and stored for offline analysis. Sampling frequency was set at 128 Hz and the accelerometer range at ±6 g. The MIMUs were attached with velcro straps to the subject ankles, laterally, about 30 mm above the malleoli. The sensors were aligned approximately along the three anatomical directions with X, Y and Z axes pointing downward, forward and to the right, respectively, for the MIMU on the right ankle (R-MIMU), and downward, backward and to the left for the MIMU on the left ankle (L-MIMU) (Figure 2-1).

An estimate of the MIMUs local coordinate system (LCS) orientation with respect to the global coordinate system (GCS) was provided by the manufacturer's proprietary software. A spot check of the MIMU performance was performed according to the guidelines proposed previously [*Picerno* 2011]. The GEs and spatio-temporal parameters resulting from the processing of the recordings of an instrumented 7-meter instrumented mat acquiring data at 120 Hz (Zeno Walkway, ProtoKinetics LLC) and analyzed with a dedicated software (PKMAS, ProtoKinetics LLC) were used for validation purposes. The instrumented mat measurements had a temporal accuracy of ±1 sample (about 8 ms) and spatial resolution accuracy of ±12.7 mm. The MIMU and the instrumented mat were synchronized via hardware (~8 ms). A custom-made cable was used to apply an external trigger generated by the instrumented mat to the access point controlling the MIMUs.

2.2.2.3 Experimental protocol

The data acquisition took place in the following laboratories: the Center for the Study of Movement, Cognition, and Mobility, Tel Aviv Sourasky Medical Centre, Israel (TASMC); the Neuromotor Rehabilitation Research Group, KU Leuven, Belgium (KULEU); the Clinical Ageing Research Unit, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust, UK (NEWCA); the laboratory of the Department of Neurosciences, University of Genoa, Italy (UNIGE).

Recordings started with subjects standing still for a few seconds at three meters from the instrumented mat and then walking back and forth for about one minute at a comfortable speed (normally paced walk, NW) along a 12-meter walkway which included the instrumented mat in its central portion. The same protocol was repeated at a higher walking speed (fast paced walk, FW). Subjects wore their own shoes and they could rest in between acquisitions if needed. Walking aids such as canes or tripods were allowed if used in daily life.

2.2.2.4 Gait events identification and gait temporal and spatial parameters estimation

A preliminary analysis was performed to eliminate operator-dependent swap between right and left MIMUs.

A first approximate segmentation of MIMU signals into gait cycles was performed by detecting the peaks in the medio-lateral (Z) component of the angular velocity. These peaks usually occur during the leg swing motion. Gait cycles not detected or erroneously detected in this processing phase lead to missed or extra GEs, respectively.

Both ICs and FCs were then identified as in [*Trojaniello* 2014b], although the FC search interval was made to begin at the minimum Z angular velocity rather than the maximum Y acceleration, being the former easier to identify. An example of IC and FC identification during a passage on the instrumented mat is depicted in Figure 2-2 and

Figure 2-3. Once the ICs and FCs were identified from both R-MIMU and L-MIMU signals, the following gait temporal parameters were calculated per gait cycle for both sides: Stride Time, Step Time, Swing Time and Stance Time.

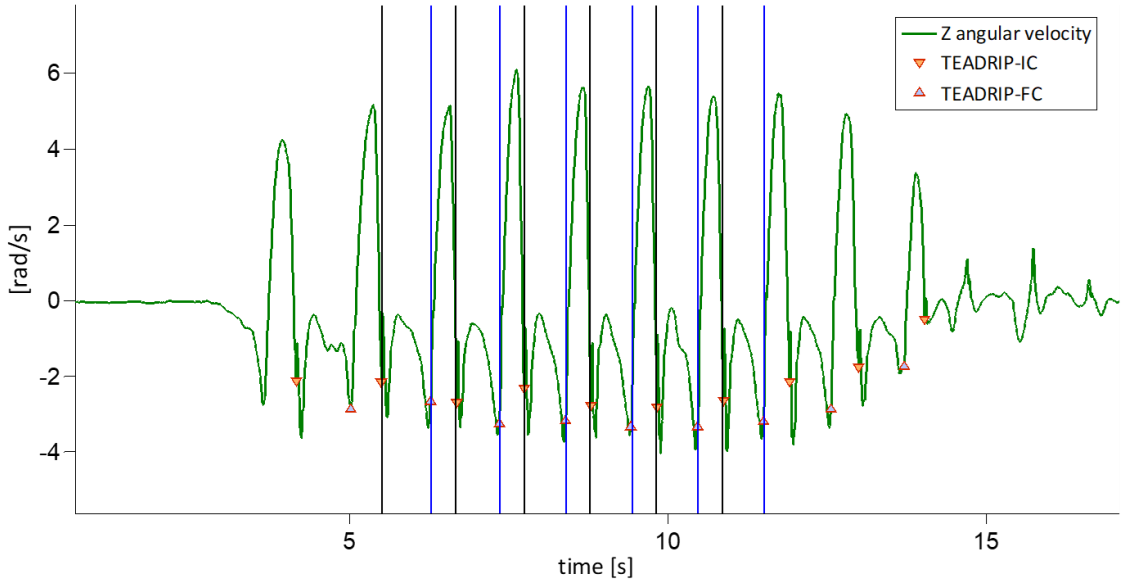

Figure 2-3 TEADRIP and instrumented mat gait events representation for the first passage over the mat (right side only). GEs identified by the TEADRIP method are depicted as red triangles, while GEs identified from the instrumented mat are depicted as vertical line

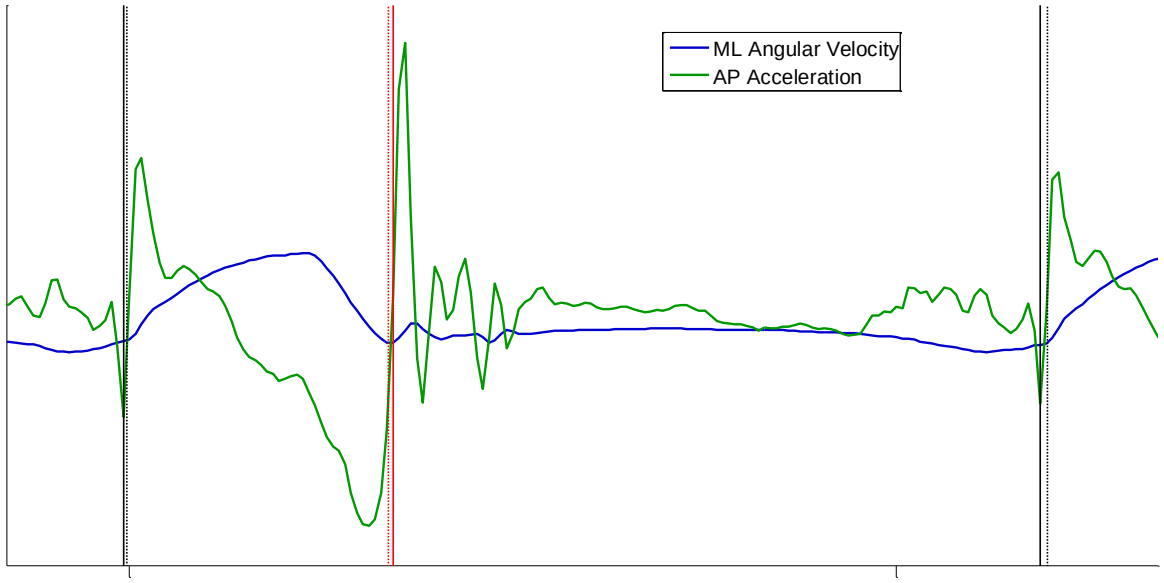

Figure 2-2 TEADRIP and instrumented mat gait events enlargement (left side only). 1 div.= 1s. IC identified by the TEADRIP method is depicted as red solid vertical line, while IC identified from the instrumented mat is depicted as red dotted vertical line. Black vertical lines represents the IC (solid from TEADRIP, dotted from the mat).

The stride length was also estimated as described by Trojaniello et al. [*Trojaniello* 2014b]. For each stride, ankle acceleration components were expressed in the GCS and, after gravity removal, optimally filtered and direct and reverse integrated (OFDRI technique [*Köse* 2012a]). The direction of progression was found by rotating the axes on the horizontal plane until one component of the velocity resulting from the above-mentioned integration was maximized. The MIMU acceleration was reoriented accordingly. The acceleration component along the direction of progression was integrated by means of the OFDRI, using as initial integration value the MIMU estimated forward linear velocity, given by the product of the Z angular velocity at mid-stance and the MIMU distance from the malleolus [*Peruzzi* 2011]. A further simple integration provided the forward displacement during a stride cycle (Stride Length). Gait Velocity was calculated for each cycle as Stride Length divided by Stride Time.

Temporal and spatial parameters resulting from TEADRIP were discarded when a stride was not fully included in the instrumented mat. Spatial parameters were discarded when the estimate of the MIMU GCS orientation as provided by the manufacturer's software failed. In case of freezing of gait for the PD subjects, the relevant portion of the trial was excluded from the analysis.

2.2.2.5 Errors associated to the gait events identification and spatio-temporal parameters estimation

To estimate the accuracy of the TEADRIP method, only gait data recorded while the participant walked on the instrumented mat (straight walking without turns) were considered. This gait data selection was made by excluding, for each passage over the mat, MIMU data recorded before the first IC and after the last FC as identified by the instrumented mat.

A GEs matching procedure was implemented to ensure that an unexpected additional time delay between MIMUs and instrumented mat would not compromise the

comparison of their outputs. To match a TEADRIP estimated IC with the corresponding IC measured with the instrumented mat, a search interval around the latter was defined, which spanned from the FC preceding the IC to the FC following the IC. The TEADRIP estimated IC that fell in the interval was selected as the matching IC. If more than one TEADRIP estimated IC was found in the search interval, the farthest from the IC measured by the instrumented mat was counted as an extra IC, while if none fell in the interval a missed IC was counted. If an extra TEADRIP estimated IC was found between two subsequent mat-measured FCs further apart than 1.3s (which is approximately the average higher limit for PD stride duration, [*Hass* 2012]), then the entire gait cycle was discarded (mat measure failure). The same procedure was applied to match TEADRIP estimated FCs to the corresponding FCs measured by the instrumented mat.

For each gait cycle, the stride-by-stride errors affecting the TEADRIP estimations of the GEs and the spatio-temporal parameters were computed as differences with respect to the relevant measurements obtained from the instrumented mat. Difference plots (Bland-Altman) were used to visually check the distributions of the spatio-temporal parameters errors between the two measurement systems.

For each subject, the mean error (*me*) and mean absolute error (*mae*) values for the estimated GEs and gait spatio-temporal parameters were calculated by averaging stride-by-stride errors computed over the entire gait trial (left and right sides were not differentiated). The standard deviation of the stride-by-stride error (*sde*) was also determined for each recorded trial. The TEADRIP estimations of the gait temporal and spatial parameters were also evaluated using the ratio between the *mae* and the mean value of the parameter as measured by the instrumented mat (*%mae*).

A three-way repeated measures analysis of variance (ANOVA) was performed on the *mae* for both GEs and spatio-temporal parameters to investigate the difference in the errors between subject groups (ELD, MCI, PD), between clinical centers (UNIGE, KULEU, TASMC, NEWCA) and within imposed walking speed (NW, FW). Since GEs

mae were found not to be normally distributed (as resulted from a Shapiro-Wilk test), they were transformed to a logarithmic scale in order to ensure a normal distribution before undergoing ANOVA. Where a significant difference was found, post hoc tests for subject groups and clinical centers were performed with Bonferroni correction. All data were analyzed using SPSS v.24 (IBM Corporation) at a 5% level of significance.

2.2.3 Results

Over 15,000 gait cycles (see Table 2-3) were selected from the instrumented mat and compared to those identified using the TEADRIP.

Table 2-3 Number of initial contacs and strides analyzed in each clinical center.

Clinical Center	Initial Contacts	Stride Time Estimates	Stride Length Estimates
UNIGE	5818	3512	3387
KULEU	5405	4156	4072
TASMC	7168	5824	5759
NEWCA	3632	2636	2585
Total	22068	16167	15840

(note that the number of Stride Length estimates differs from that of Stride Time since Stride Length values were not computed for those trials in which the estimate of the MIMU GCS orientation failed).

The mean and standard deviation values of the mean trial values of the spatio-temporal parameters as determined by the instrumented mat in each clinical center at the two gait speeds are reported in Table 2-4.

Table 2-4 Gait spatio-temporal parameters mean values (sd) across subjects for clinical centers and walking speeds.

Clinical Center	Stride Time [s]		Stance Time [s]		Swing Time [s]		Step Time [s]		Stride Length [m]		Gait velocity [m/s]	
	NW	FW	NW	FW	NW	FW	NW	FW	NW	FW	NW	FW
UNIGE	1.09 (0.09)	0.99 (0.09)	0.72 (0.07)	0.64 (0.07)	0.38 (0.03)	0.36 (0.03)	0.55 (0.04)	0.50 (0.05)	1.11 (0.16)	1.21 (0.16)	1.02 (0.17)	1.23 (0.21)
KULEU	1.13 (0.20)	1.02 (0.16)	0.73 (0.18)	0.64 (0.14)	0.40 (0.04)	0.38 (0.03)	0.57 (0.10)	0.51 (0.08)	1.19 (0.21)	1.31 (0.24)	1.09 (0.29)	1.33 (0.33)
TASMC	1.13 (0.14)	1.00 (0.13)	0.74 (0.11)	0.64 (0.10)	0.40 (0.07)	0.36 (0.04)	0.56 (0.07)	0.50 (0.07)	1.12 (0.25)	1.25 (0.23)	1.01 (0.26)	1.27 (0.29)
NEWCA	1.09 (0.08)	0.98 (0.10)	0.71 (0.07)	0.63 (0.08)	0.38 (0.03)	0.35 (0.03)	0.54 (0.04)	0.49 (0.05)	1.16 (0.19)	1.26 (0.23)	1.07 (0.20)	1.30 (0.29)

Values averaged across subjects of the measures from the instrumented mat. NW normal paced trials, FW fast paced trials

2.2.3.1 Gait event identification and spatio-temporal parameters estimation errors

The Difference plots of Stride, Stance and Step Time and Stride Length are reported in Figure 2-4. The estimated limits of agreement were 27 ms (2.6%) for Stride Time, 56 ms (8.5%) for Stance Time, 31 ms (5.8%) for Step Time and 60 mm (5.3%) for Stride Length.

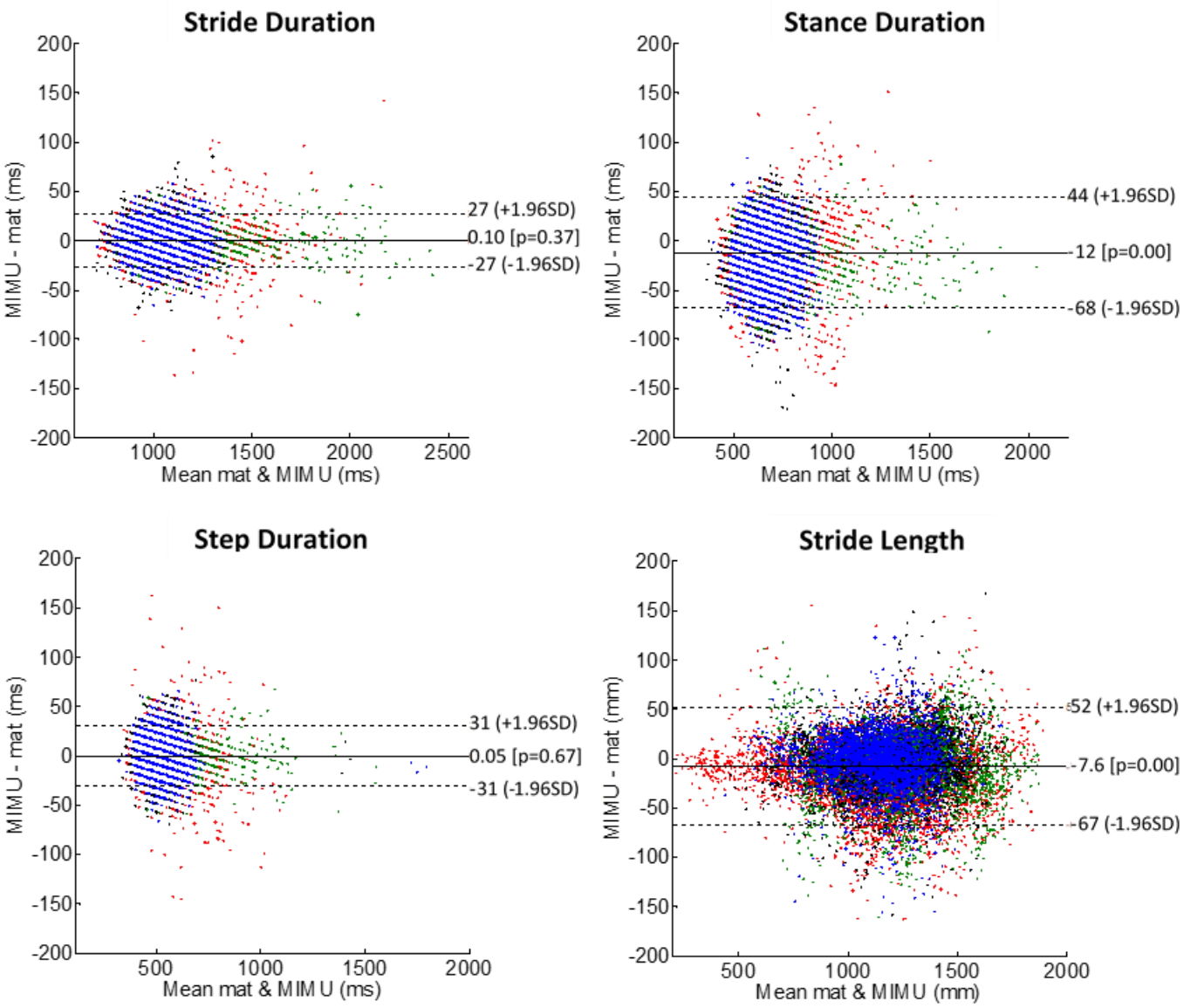

Figure 2-4 Difference (Bland-Altman) plots for stride, stance and step durations and for stride length. Limits of agreement are, respectively, 27 ms, 56 ms, 31 ms and 60 mm. Red: TASMC; green: KULEU; black: NEWCA; blue: UNIGE

The values of the $\overline{me}$, $\overline{sde}$, $\overline{mae}$ for IC and FC, averaged across the subjects of each clinical center, are reported for both for NW and FW trials in Table 2-5. The GEs errors for the participants from Newcastle could not be assessed due to a non-constant delay between MIMUs and instrumented mat signals across data acquisition sessions. However, being the delay constant within any acquisition session, this did not affect the estimation of the errors related to temporal parameters. The same descriptive statistics in addition to the $\overline{\%mae}$ are presented in Table 2-6 for each clinical center (both for NW and FW trials) for Stride Time, Stance Time, Swing Time, Step Time, Stride Length and Gait Velocity. Table 2-7 reports the subjects *mae* averaged across each group for both NW and FW trials.

Table 2-5 Subject mean error, standard deviation and mean absolute error averaged across clinical centers for both walking speeds (gait events).

Parameter	Clinical Center	$\overline{me}$		$\overline{sde}$		$\overline{mae}$	
		NW	FW	NW	FW	NW	FW
Initial Contact [ms]	UNIGE	9	9	10	11	15	14
	KULEU	3	4	9	9	11	10
	TASMC	5	8	10	11	12	13
	NEWCA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Final Contact [ms]	UNIGE	-9	-9	13	13	20	20
	KULEU	-8	-7	12	14	21	19
	TASMC	-3	-2	12	14	19	17
	NEWCA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

$\overline{me}$: subject mean error averaged across centers; $\overline{sde}$: subject error standard deviation averaged across centers; $\overline{mae}$: subject mean absolute error averaged across centers.

Table 2-6 Subject mean error, standard deviation, mean absolute error and its relative percentage averaged across clinical centers for both walking speeds (spatio-temporal parameters).

Parameter	Clinical Center	$\overline{me}$		$\overline{sde}$		$\overline{mae}$		$\overline{mae\ \%}$	
		NW	FW	NW	FW	NW	FW	NW	FW
Stride Time [ms]	UNIGE	<1	<1	15	14	12	11	1	1
	KULEU	<1	<1	12	11	9	9	1	1
	TASMC	<1	<1	14	13	10	10	1	1
	NEWCA	-1	<1	15	15	12	11	1	1
Stance Time [ms]	UNIGE	-20	-18	17	17	29	27	3	3
	KULEU	-11	-11	17	15	25	22	2	2
	TASMC	-8	-10	17	16	24	23	2	2
	NEWCA	-11	-12	17	15	24	23	3	4
Swing Time [ms]	UNIGE	20	18	17	17	29	27	3	3
	KULEU	11	11	17	16	25	23	2	2
	TASMC	8	10	18	16	24	23	2	2
	NEWCA	12	13	17	15	25	23	2	3
Step Time [ms]	UNIGE	<1	<1	16	15	13	12	1	1
	KULEU	<1	<1	14	13	11	11	1	1
	TASMC	<1	<1	16	15	12	12	1	1
	NEWCA	<1	<1	15	14	13	12	2	2
Stride Length [mm]	UNIGE	-1	-3	22	27	21	22	2	2
	KULEU	-8	-5	19	21	22	25	2	2
	TASMC	-14	-15	19	22	26	28	2	2
	NEWCA	-4	-6	19	30	19	27	2	2
Gait Velocity [mm/s]	UNIGE	-2	-4	23	30	21	24	2	2
	KULEU	-7	-5	20	25	21	27	2	2
	TASMC	-13	-16	20	25	25	30	3	2
	NEWCA	-4	-5	18	36	19	31	2	2

$\overline{me}$: subject mean error averaged across centers; $\overline{sde}$: subject error standard deviation averaged across centers; $\overline{mae}$: subject mean absolute error averaged across centers; $\overline{\%mae}$: mean absolute error referred to parameter estimate averaged across centers.

Table 2-7 Group average of the subjects mean absolute errors for the gait events and spatio-temporal parameters for both walking speeds.

Parameter	ELD		MCI		PD	
	NW	FW	NW	FW	NW	FW
Initial Contact [ms]	10	11	10	10	14	14
Final Contact [ms]	21	20	20	19	20	18
Stride Time [ms]	10	9	10	10	11	11
Stance Time [ms]	24	23	23	23	26	24
Swing Time [ms]	24	23	23	23	27	25
Step Time [ms]	11	10	11	10	13	12
Stride Length [mm]	21	25	19	23	23	25
Gait Velocity [mm/s]	21	29	18	25	22	28

ELD: healthy older adults, PD: Parkinson's disease subjects, MCI: mild cognitive impaired subjects.

Table 2-8 summarizes the ANOVA results; significant differences are indicated in bold. The analysis across clinical centers for the GE errors were performed only between UNIGE, TASMC and KULEU since NEWCA GE errors were not available.

Table 2-8 ANOVA results for the errors in determining the gait events and the gait spatio-temporal parameters.

		Initial Contact	Final Contact	Stride Time	Stance Time	Swing Time	Step Time	Stride Length	Gait Velocity
Walking Speed	F-value	0.12	3.30	0.10	1.78	1.59	2.93	4.78	27.32
	p-value	0.73	0.07	0.76	0.18	0.21	0.09	***0.03***	***0.00***
Clinical Center	F-value	1.97	0.56	2.40	0.60	0.50	0.53	1.66	1.59
	p-value	0.14	0.57	0.07	0.61	0.68	0.66	0.18	0.19
Subject Group	F-value	5.21	0.64	3.61	0.81	1.02	4.61	0.01	0.13
	p-value	***0.01***[a]	0.53	***0.03***[b]	0.45	0.36	***0.01***[c]	0.99	0.88

Significant post hoc results: a) ELD-PD (p=0.01); b) ELD-PD (p=0.01); c) ELD-PD (p=0.01). Underlined results are from the comparison of UNIGE,TASMC and KULEU only.

A significant group main effect was found for IC identification. Post hoc analyses revealed that for IC errors there was a significant difference between ELD and PD (p=0.01), with larger errors for the PD group.

While no temporal parameter error showed any center effect, Stride Time and Step Time errors were significantly different across groups. Post hoc analyses revealed that there was a significant difference for errors between ELD and PD (p=0.01 for Stride Time and p=0.01 for Step Time), with larger errors for the PD group.

Group did not have a significant effect on the error of spatial parameters, while there was a significant effect for walking speed.

2.2.4 Discussion

The tested method was successfully applied on a total of more than 20,000 ICs and FCs collected on 236 older adults (healthy, Parkinsonian and MCI participants). In performing the validation, additional care had to be taken to deal with limitations of the instrumented mat measurements used as reference values for the TEADRIP estimations of the gait parameters, such as steps outside the instrumented surface and unexpected failures.

The average values of the spatio-temporal parameters estimated by the instrumented mat showed a homogeneity across the clinical centers and values consistent with the literature.

The IC $\overline{me}$ showed, in all centers and at both walking speeds, an average delay of up to 10 ms as identified by TEADRIP with respect to that identified by the instrumented mat, while the opposite holds for the FC. The amplitude of the subjects $\overline{sde}$ was slightly higher for the FC confirming the higher uncertainty in detecting FCs as opposed to ICs encountered in most validation studies. Similar conclusions can be drawn by looking just at the $\overline{mae}$ values. The opposite delays for IC and FC TEADRIP estimates reflected in a slight underestimation of the stance phase and an overestimation of the swing phase, but did not have any detrimental effect on the estimation of either Stride Time or Step Time, which showed extremely low $\overline{me}$ values. All temporal parameters exhibited a $\overline{sde}$ for each clinical center between 10 and 20 ms,

confirming a limited variability of the errors within the trials at both walking speeds and in all clinical centers. The spatial parameters $\overline{me}$ in all clinical centers and for both walking speeds showed a global slight underestimation performed by TEADRIP. Overall, the $\overline{\%mae}$ of both temporal and spatial parameters was often below and, except NEWCA Stance Time at FW, never over 3% which is an excellent result, although a thorough comparison with the results obtained in studies proposing other methods is not straightforward [*Salarian* 2004; *Sabatini* 2015; *Sijobert* 2015; *Zhuang* 2016; *Chang* 2016; *Ferrari* 2016; *Kong* 2016; *Hannink* 2017a; *Agostini* 2017; *Visi* 2017; *Song* 2017]. Regarding the estimation of the spatial parameters, it has been shown in the study conducted by Hannink et al. [*Hannink* 2017b], that the OFDRI technique was the best performing among the double integration methods for mobile gait analysis tested in their study.

Even more importantly, all results of TEADRIP estimations were extremely consistent across all clinical centers and with the previous results obtained in a single center on much smaller population samples [*Trojaniello* 2014b]. Since the *mae*, as opposed to the *me*, is not affected by a potential cancellation due to cycle-differences of opposite signs, it was chosen as the quantity to investigate with the ANOVA, which showed minimal statistical difference in the performance of the TEADRIP across subject groups, clinical centers and gait speeds. In particular, only spatial parameters errors were significantly different between walking speeds. The difference is probably the result of a more difficult estimation of a correct initial constant value needed to estimate velocity from acceleration when the task is performed at higher speed.

Consistently with the results of the previous study employing TEADRIP [*Trojaniello* 2014b], estimates of ICs for PD subjects were affected by errors significantly different from those obtained in the ELD subject group. In partial disagreement with the results of the previous study, a different error between ELD and PD was also found for Stride Time and Step Time estimations. However, this difference may be a consequence of the above mentioned difference between IC timing errors. These results therefore

provide a clear insight of the margin of tolerance associated to the estimation of the different temporal parameters for different populations. For instance, when estimating the IC, an average uncertainty error of 10 ms is expected for ELD and MCI subjects, while slightly higher errors (14 ms) should be considered when analyzing PD subjects.

Overall, the results obtained in this study extend the validity of the TEADRIP method, originally employed in [*Trojaniello* 2014b] on four smaller subject groups, and combined with the findings of the work of Storm et al. [*Storm* 2016], who applied the same gait parameter estimation method to free-living gait, make TEADRIP a well-validated gait parameter estimation method.

2.2.5 Conclusions

TEADRIP, the gait parameter estimation method employed in this study, was effectively validated on a large number of subjects recorded in four different clinical centers. Not only was the performance comparable to that of the instrumented mat used as a reference, but it was also characterized by a greater amount of recorded data (longer and more diversified walks can be instrumented). Furthermore, as demonstrated in earlier work [*Storm* 2016], these results hold also for outdoor straight line walking. The TEADRIP is therefore a valuable candidate for becoming a standard for the estimation of gait spatio-temporal parameters with MIMUs placed on the ankles.

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Chapter 3

*Turn identification in gait**

* This chapter is based on **M. Bertoli**, A. Cereatti, D. Trojaniello, A. Ravaschio, and U. Della Croce, "**The identification of multiple U-turns in gait: comparison of four trunk IMU-based methods**," *Proc. 11th Int. Conf. Body Area Networks* (2017) and on **M. Bertoli**, A. Cereatti, U. Della Croce, A. Pica, and F. Bini, "**Can MIMUs positioned on the ankles provide a reliable detection and characterization of U-turns in gait?**," *IEEE Int. Symp. Med. Meas. Appl.* (2018)

3.1 U-turns in clinical evaluations

In clinical evaluations, to perform an effective gait analysis a large number of steps is usually required in order to be able to analyze not only the spatio-temporal parameters mean values, but also their variability [*Hausdorff* 2005]. Typically though, a long enough hallway where to test the subjects without traffic or distractions is not available. Therefore a "walk back and forth" approach is commonly used, where the subject is asked to walk straight, reverse direction with a U-turn (i.e.: 180° turn) and walk back. One of the most standardized among these procedures is the 2 minutes walking test (2MWT) (or its longer version, the 6 minutes walking test), where the subject continuously walk back and forth on a 7 m straight walkway for 2 minutes [*Katzel* 2012; *Fang* 2018]. Considering a walking speed of 1 m/s, that implies at least 10 turns per trial. It is therefore evident that if only straight gait data needs to be analyzed, the turns must be identified and removed. Instead, if the entire trial is being evaluated, it needs to be segmented in straight bouts and turns, in order to analyze them separately. In fact, recently also the analysis of the turning phase itself has gained attention, also thanks to the widespread use of the timed up and go test (TUG) [*Podsiadlo* 1991; *Shumway-Cook* 2000; *Whitney* 2004; *Stegemöller* 2014]. The TUG is a simple technique for evaluating competence in its sub phases: get up from a chair, walk straight (3 m), turn around (180°), walk back, turn around again and sit down. A shortcoming of the traditional TUG test is that it relies only on one measure (i.e.: time) to evaluate the overall performance of a sequence of motor tasks. Several studies therefore suggested to augment the TUG by using inertial sensors to obtain quantitative measures specific to each task [*Giansanti* 2006; *Higashi* 2008; *Salarian* 2010]. An extensive review ([*Sprint* 2015]) summarizes the benefits and limitations of technologies utilized for TUG instrumentation, and the main findings using each approach. Benefits from the instrumented TUG include additional performance parameters, generated reports, and more importantly the ability to be self-

administered in the home, designating it a valid tool for the future of automating clinical assessments.

Thanks to their low invasiveness, inertial sensors have been extensively employed for instrumenting the TUG test, and increasing evidence shows that quantitative measures from the TUG (in particular for the turning phase) provide additional information relevant for clinical assessments. In fact, the instrumented TUG is frequently used in longitudinal assessment of older people as a screening tool to identify aging effects ([*Vervoort* 2016; *Smith* 2016]) and cognitive decline ([*Greene* 2012]). Moreover, it is widely used in fall risks assessments ([*Weiss* 2011]) and in mobility assessments in Parkinson's Disease ([*Zampieri* 2011; *Reinfelder* 2015; *Van Uem* 2016]).

In conclusion, 180 degrees is a common amplitude for turns in clinics and, either to remove it from straight gait data or to focus on its analysis, a robust method for its identification is needed. In the next paragraphs a comparative evaluation of such methods in walking tasks with multiple 180° turns is presented. Methods robustness was evaluated by recording MIMU data on healthy and pathological subjects (healthy elderly, stroke survivors, patients with Parkinson's Disease and choreic patients) walking at two different speeds.

3.2 The identification of multiple U-turns in gait: comparison of four trunk MIMU-based methods

3.2.1 Introduction

Numerous clinical motor tests may include one or more turns between straight gait segments, either due to space constraints or to analyze the subject's motor ability under more challenging tasks. In fact, it has been observed that in pathologic subjects turning can pose more difficulties in goal-directed locomotion. For instance, functional turning is a common problem in people with Parkinson's disease (PD), who take more steps to

turn than those without PD [*Morris* 2001]. Similarly, hemiparetic post-stroke subjects tend to struggle with sensory and neuromotor organization and so with controlling movement: it has been demonstrated a relationships between physical impairments, locomotor capacities and frontal plane gait parameters [*De Bujanda* 2003].

Such difficulties can be revealed by a widely used clinical test: the Time-Up-and-Go (TUG), where a 180 degrees turn (U-turn) is expected approximately in the middle of the trial followed by a second one toward the end. U-turns were therefore chosen to be studied in this work, since they are commonly employed in such clinical examinations [*Higashi* 2008; *Salarian* 2010; *Weiss* 2011; *Coulthard* 2015; *Smith* 2016].

The correct U-turn identification is the primary step to segment a walking trial. The gait bout can thus be segmented into straight walks and turns, so that the standard gait parameters can be computed from the isolated portions of straight walk, and peculiar traits of the U-turns can be described.

Identifying turns during walking is of great interest also in remote monitoring applications aiming at describing activities during daily life, including straight walking and turns.

In the literature, two main approaches have been employed to identify and analyze turns in gait. One consists in segmenting the gait into steps, defining a direction of progression (DoP) for each step, and identifying as turns those steps whose DoP shows an angle with the previous one [*Mariani* 2010]. This methodology is mostly used in pedestrian navigation applications [*Bebek* 2010; *Alvarez* 2012]. The second approach identifies a turn from the analysis of the MIMU signals characteristics, and works independently from step detection [*Fleury* 2007; *El-Gohary* 2013; *Novak* 2014; *Nguyen* 2015].

The objective of the present study is to perform a comparative evaluation of four automated methods to be used in a clinical context during a walking trial to identify U-turns. The algorithms were designed to segment a gait bout into straights and turns

without the preliminary determination of the gait cycles. Furthermore, the selected methods distinguish multiple U-turns without the a-priori knowledge of their number and timing in the walking bout, contrary to others [*Salarian* 2009; *Weiss* 2011; *Fino* 2015].

The selected methods have shown satisfactory performance when applied to the specific pathological populations, however their applicability over a variety of different pathological gait conditions or different gait speeds has not been systematically explored.

3.2.2 Materials and methods

3.2.2.1 Instrumentation

Data were recorded by an MIMU (Opal™, APDM, Inc,) positioned on the low back between L4 and S2 [*Trojaniello* 2014a]. The performance of the MIMU was tested according to the guidelines proposed by [*Picerno* 2011]. The MIMU recorded linear accelerations, angular velocities and local magnetic field with respect to the axes of a local frame (LF: xyz, z pointing upwards) aligned to the edges of the unit housing. The MIMU was positioned so that its reference axes were oriented approximately along the three anatomical directions. An estimate of the LF orientation with respect to the global frame (GF: XYZ, Z coinciding with the gravity direction) was provided by an on-board Kalman filter. The signals from the MIMU were recorded at 128 Hz, streamed wirelessly to a laptop and stored for offline analysis. A gait pressure mat (GAITRite Electronic Walkway, CIR System Inc) acquiring at 120 Hz was used for validation purposes. The instrumented mat returned the timing of all foot contacts, in particular initial and final ones for every passage on it. The MIMU and the instrumented mat were synchronized (±1 sample).

3.2.2.2 Subjects

Ten healthy elderly (ELD), ten PD subjects, ten stroke survivors (ST) and ten subjects with a choreic movement disorder (COR) were enrolled. Their sex and range age were 6F(4M), 61÷79 ELD; 5F(4M), 68÷79 PD; 2F(8M), 38÷76 ST; 5F(5M), 29÷79 COR. The ST group was equally divided into subjects with left or right most affected side. The Declaration of Helsinki was respected, all subjects provided informed written consent, and local ethic committee approval was obtained.

3.2.2.3 Data acquisition Protocol

Subjects were asked to walk along a pre-designed loop made of two U-turns, as depicted in Figure 3-1. At the beginning of each acquisition, subjects were asked to stand still for a few seconds. Subjects wore their own shoes, and walking aids such as canes or tripods were allowed if used routinely. Subjects could rest in between acquisitions if requested.

Two gait conditions were recorded for each subject: self-selected, comfortable velocity (Normal Walk, NW) and higher velocity (Fast Walk, FW). Each data acquisition lasted about one minute. The total number of U-turns performed for each group for both walking speeds is reported in Table 3-1.

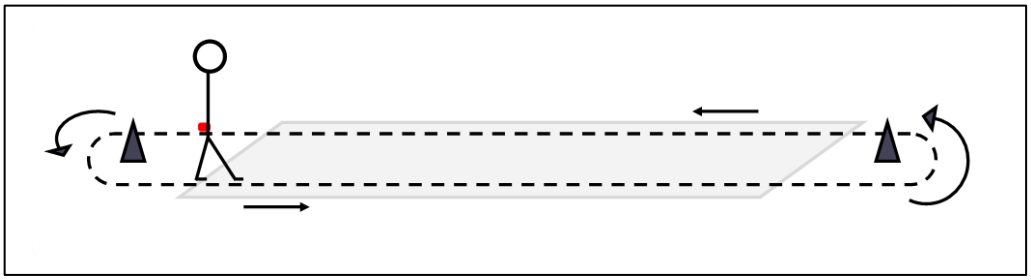

Figure 3-1 Experimental setup

Table 3-1 Total number of actual U-turns analyzed

	ELD	***PD***	***ST***	***COR***
NW	48	41	30	47
FW	63	49	38	72

3.2.2.4 Methods Description

Method A

In the work of El-Gohary and colleagues, data were collected by an MIMU positioned on the lumbar spine of 19 healthy subjects and 21 patients with PD [*El-Gohary* 2013]. As a first step, exploiting orientation estimates in the quaternion form, body frame sensor measurements were expressed in the GF. Angular velocity vertical component ω_z was extracted and low pass filtered (Butterworth, 1.5 Hz cutoff frequency). Candidate turns were isolated for each ω_z maximum higher than 15°/s, and their duration was set based on 5°/s threshold. Additional controls were performed to reduce false positives. First of all, candidate turns in the same direction separated by less than 50ms were merged. Then, turns lasting less than 0.5s or more than 10s were discarded.

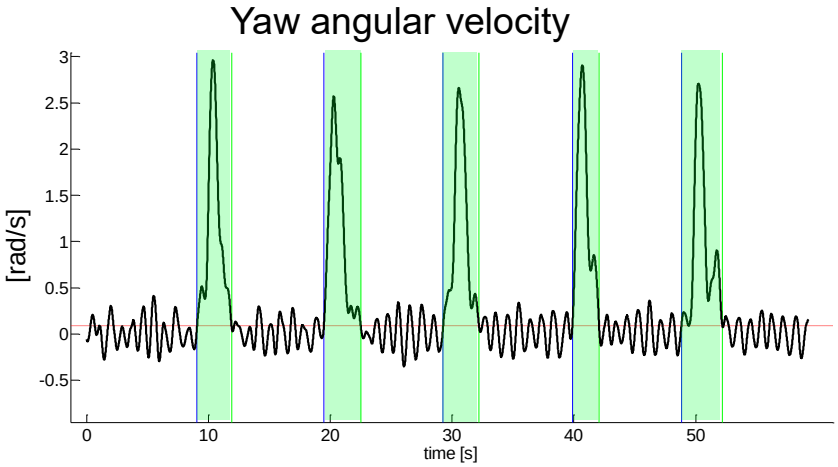

Figure 3-2 Turns as identified by method A

Finally, the relative turn angle was computed integrating ω_z over the turn duration and, when resulting less than 45°, lead to the turn elimination. The remaining ones were detected as U-turns. The method is illustrated in Figure 3-2.

Method B

In the work of Nguyen and colleagues, data were collected from 16 ELD by MIMUs mounted on a motion capture suit [*Nguyen* 2015]. Among other sensors locations, they determined that the MIMU on the back was the best suited for identifying turns. A band pass filter was first applied to the raw z-component of the angular velocity (zero-phase, second-order Butterworth filter, low and high cut off frequencies set at 0.0025 Hz and 0.7 Hz, respectively). The filtered signal was then de-trended and normalized for uniformity across subjects. A U-turn was detected for each peak higher than 0.6 (absolute value). In addition, in our implementation when the time distance between two or more peaks was less than four seconds, they were associated to a single turn. The method is illustrated in Figure 3-3.

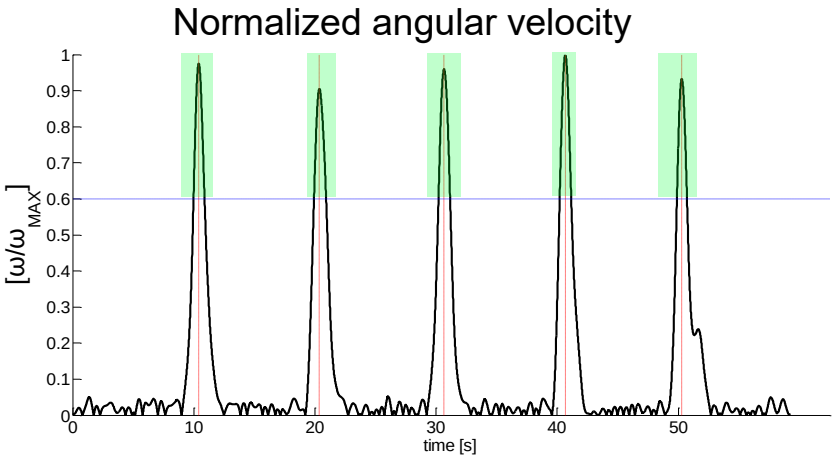

Figure 3-3 Turns as identified by method B

Method C

In the work of Novak and colleagues, data were collected by nine MIMUs placed on the entire body of ten healthy subjects and one above-knee amputee [*Novak* 2014].

Comparing different sensor locations, they found that using a sensor on the back yields the best results. Their work is based upon previous research by Mariani et al. and El-Gohary et al. ([*Mariani* 2010; *El-Gohary* 2013]), and it combines the analysis of the orientation around the Z axis (Kalman filter output, angular displacement) and of the angular velocity (raw gyroscope output, ω_z). The U-turn is detected by optimizing parameters of empirically-defined rules. Orientation angles were derived directly from the quaternions (estimated by the sensor through the Kalman filter). In our implementation, the Z-angular displacement was then filtered (zero-phase, second-order Butterworth filter with high cut-off frequency set at 1 Hz) and smoothed by means of mobile average windows two seconds long. The ω_z was also filtered (zero-phase, second-order Butterworth filter, 1.5 Hz high cut-off frequency). A U-turn is detected when a heuristically determined threshold is exceeded in the Z-angular displacement (90° in 3 s), or in the ω_z (45°/s). The method is illustrated in Figure 3-4.

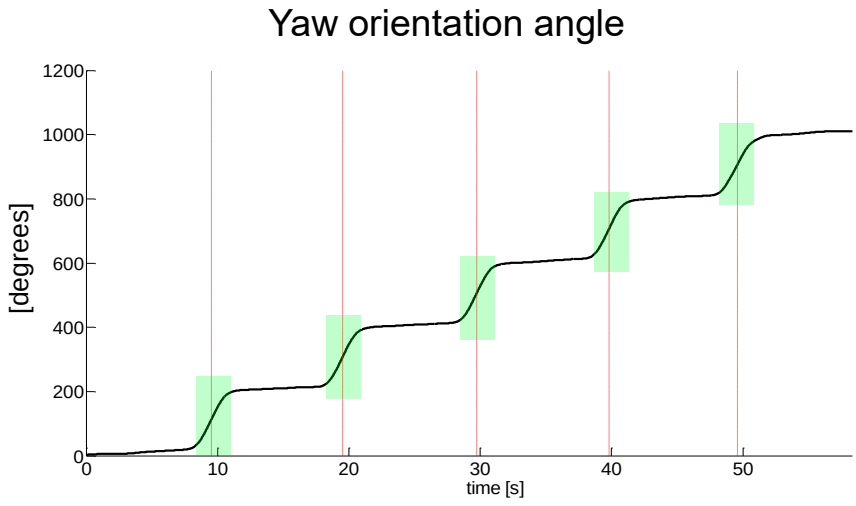

Figure 3-4 Turns as identified by method C

Method D

In the work of Fleury and colleagues, data were collected by a tri-axial magnetometer located on the upper trunk of eight healthy subjects [*Fleury* 2007]. They pre-processed the raw signal filtering in the bandwidth [0.5Hz; 2Hz] with a three order bandstop digital filter, and then low-pass filtering with a 4Hz cutoff frequency. "Activity windows" were then defined using the standard deviation computed on 2s windows. The turn was identified by measuring the change of the local magnetic field as measured in the magnetometer LF (plane xy). The Euclidean norm of the difference of the local magnetic field vector measured in two instants (2s apart) of the gait trial was computed over the entire signal. A U-turn is detected for each peak in the norm higher than empirically-fixed threshold. The method is illustrated in Figure 3-5.

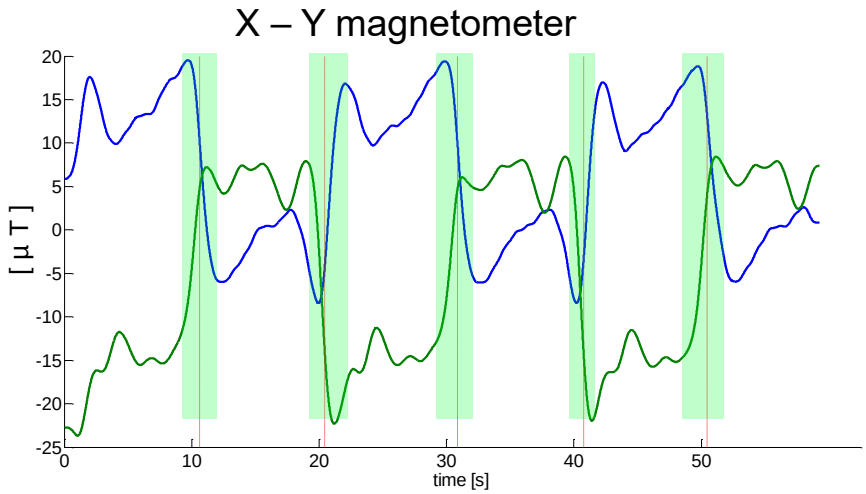

Figure 3-5 Turns as identified by method D

3.2.2.5 Data Analysis

To facilitate the comparison between methods and avoid misinterpretation, those gait trials ending while the subject was performing a turn were truncated in order to eliminate the last turn.

Number of Missed and Extra U-turns

The number of actual U-turns was provided by the mat. The number of U-turns detected was determined for each tested method. From actual and detected U-turns, missed U-turns and extra U-turns could be determined for each tested method, group and walking speed [*Trojaniello* 2015].

3.2.3 Results

All four methods showed neither extra nor missed U-turns in the ELD and PD groups at both speeds.

Method A was the only method to detect two extra U-turns in the NW trials of the COR group, and one in the FW.

Method B showed no missed U-turns in the NW trials for all groups. For the FW trials, one and two missed U-turns were observed in the ST and COR groups, respectively.

Method C missed only a single U-turn in the NW trials of ST group.

Method D showed neither extra nor missed U-turns.

3.2.4 Discussion

The aim of the present study was to test different methods for the identification of U-turns on various pathological groups walking at different speeds. In the original works, all the tested methods, except for method A, were applied and tested on the gait of healthy subjects.

When applied to the ELD group, none of the methods missed any U-turns or detected any extra ones, thus confirming their adequacy as long as physiological gait is analyzed. Interestingly, the same consideration applies to the PD group.

The results obtained indicate that the tested methods are more likely to fail when applied to the gait of stroke survivors and the choreic subjects, which is characterized by irregular walking patterns.

Method A only failed when applied to the gait of choreic subjects (three extra U-turns out of 109 total actual U-turns), probably due to the increased variability of the gyroscopic signals associated to the jerky nature of choreic motion.

Method B missed a few U-turns at fast walking speed, probably because the thresholds, defined on the normalized signal recorded at comfortable speed, resulted to be too high (scaled peaks below threshold were missed).

Methods C and D were the best performing on our dataset. Method C may take advantage of the combined analysis of the angular velocity and orientation angle, possibly reducing the probability of detecting extra U-turns.

Method D is the only one based on magnetometer signals, and it appeared to be extremely robust with respect to the location of the MIMU. In fact, while its original version requires the MIMU to be placed on the upper chest, we obtained excellent results from signals recorded by an MIMU placed on the lower back. A limitation of this method though is the intrinsic low reliability of the magnetometer due to possible ferromagnetic disturbances.

Additional work will be necessary to test methods that identify and characterize turns other than 180 degrees. In fact, the use of the magnetometer might not be as successful as it was shown for U-turns identification.

In this study, we have shown that a single MIMU located on the low back can better identify U-turns. However, as shown by [*Trojaniello* 2014b], gait events and all the derived spatio-temporal parameters can be best detected with MIMUs attached to the lower limbs. As a consequence, three MIMU configuration (two MIMUs on the lower limbs and one on the lower back) may effectively describe crucial features of both straights and turns in both healthy and pathological gait at different walking speeds.

3.3 Can MIMUs positioned on the ankles provide a reliable detection and characterization of U-turns in gait?

3.3.1 Introduction

Several methods have been proposed to identify and/or characterize turns during locomotion using MIMUs ([*Salarian* 2009; *Mariani* 2010; *El-Gohary* 2013; *Fino* 2015; *Bertoli* 2016]). They vary in terms of MIMUs number and location, types of signals analyzed and most importantly on the definition of "turn" during gait.

In general, two different approaches may be used to identify and characterize turns: a) by defining a direction of progression (DoP) on a step-by-step basis and determining its changes ([*Mariani* 2010; *Barrois* 2017]) or b) by computing the rotational displacement about a vertical axis within a given interval of time ([*Higashi* 2008; *Salarian* 2010; *Weiss* 2013; *Nguyen* 2015; *Beyea* 2017]). The first approach is convenient if MIMUs are located distally (feet or ankles), which is often the case when analyzing gait parameters [*Trojaniello* 2014b]. This approach requires a preliminary determination of the steps during the turns, which in some cases could be critical. The second approach is particularly advantageous when the MIMUs are located more proximally (pelvis, low back or trunk) and it does not rely on the identification of steps to characterize turns. However, such MIMU location may not be optimal for the estimation of the gait parameters [*Trojaniello* 2014a].

In this study we wanted to investigate the possibility of detecting and characterizing turns during walking with the purpose of segmenting the walking trials into straight walking bouts and turns. Specifically, the objective of this study was twofold: a) to determine if, in analyzing the gait of healthy elderly (ELD) and individuals with Parkinson Disease (PD), a popular method for turn detection and characterization based on gyroscopic signals recorded at the low back could be successfully applied to signals recorded by MIMUs located near the ankles, and b) if unsuccessful, to revise it

so that turns could be characterized regardless of the proximal or distal location of the MIMUs.

3.3.2 Materials and methods

3.3.2.1 Experimental setup

The study included 10 ELD and 10 PD. The Declaration of Helsinki was respected, all subjects provided informed written consent, and local ethic committee approval was obtained

Two MIMUs (Opal™, APDM, Inc.) were attached just above the malleoli (ank-MIMUs) and a third one to the low back between L4 and S2 (lb-MIMU), as depicted in Figure 3-6 [*Trojaniello* 2014b]. The MIMUs were positioned so that their reference axes were oriented approximately along the three anatomical directions during upright posture. The performance of the MIMUs was tested according to the guidelines proposed in [*Picerno* 2011]. The MIMUs recorded linear accelerations, angular velocities and local magnetic field with respect to the axes of a local frame aligned to the edges of the unit housing. The signals from the MIMUs were recorded at 128 Hz, streamed wirelessly to a laptop and stored for offline analysis.

Subjects walked back and forth for one minute along a 12-m walkway starting from a still standing position, and performing a U-turn at each end of the walkway. For each subject, two gait conditions were tested: normal walk (NW – self-selected, comfortable

Figure 3-6 MIMU positioning

speed) and fast walk (FW – walking as fast as possible). The turn direction was not imposed. The total number of turns recorded during the one minute acquisition varied.

3.3.2.2 Turn detection and characterization

Turns were detected and characterized using the method proposed by El-Gohary and colleagues [*El-Gohary* 2013] from lb-MIMU signals (EG). The EG method was chosen being probably the most widely used method to be applied to lb-MIMU signals. The method can be applied to a walking trial with multiple turns, without the need of a-priori knowledge of neither the number nor the direction of turns. It provides turn onsets and durations. Candidate turns were detected from the peaks of the recorded vertical component of the angular velocity higher than 15°/s. The 5°/s threshold crossing preceding and that following each peak were set as instants of turn onset and ending. Candidate turns in the same direction separated by less than 500 ms were merged, and candidate turns lasting less than 0.3s or more than 10s were discarded. Finally, the relative turn angle was computed integrating the vertical angular velocity over the turn duration and, if it resulted less than 45°, the candidate turn was discarded.

Since the amplitude of the above mentioned peaks measured with ank-MIMUs was about twice as large as those measured at the low back, the EG method was modified by setting a higher angular velocity threshold. Candidate turns were detected for each peak in the vertical component of the angular velocity higher than 30°/s. Two candidate turns were merged if closer than 100 ms, and the minimum turn angle amplitude to discard a candidate turn was set to 30°. A turn onset value and a turn ending value resulted from the EG method applied to each ank-MIMU. The smallest of the two onset values was selected as turn onset and the largest of the two ending values was set as turn ending. An example of the results obtained from an ELD NW trial is represented in Figure 3-7.

An original method based on the estimation of the angular displacement (AD) was introduced in this work to investigate the possibility of limiting the potential downsides of forcing the application of the EG method to MIMU signals originated from a body location different form that it was designed for. After de-trending the gyroscopic output and removing the offset, the vertical angular velocity component was integrated (to obtain an estimate of the angular displacement) and filtered (zero-phase, second-order Butterworth filter with high cut-off frequency set at 0.5 Hz). A two seconds sliding window was applied (moving one sample per step). For each window, the initial value of the angular displacement was subtracted from all values in the window and then the average value over the window was computed. U-turns were detected for each peak larger than 45° (threshold value empirically set) of the resulting curve. The timings of the crossings of a 10° threshold before and after each peak were recorded for both sides. Turn onsets were identified as the average value between left and right threshold crossing timings before the peak, while turn endings were identified as the average between left and right crossing timings after the peak. An example of the method applied to an ELD NW trial is depicted in Figure 3-8.

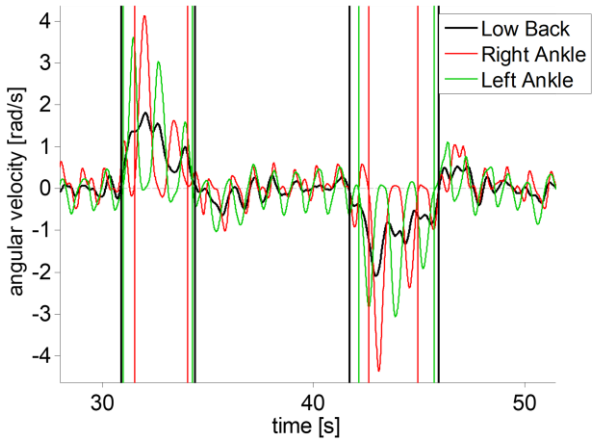

Figure 3-7 Vertical component of the angular velocity as obtained from the lb-MIMU and ank-MIMUs. The vertical lines represent the turn onsets and endings as determined by applying the EG method to the relative angular velocities.

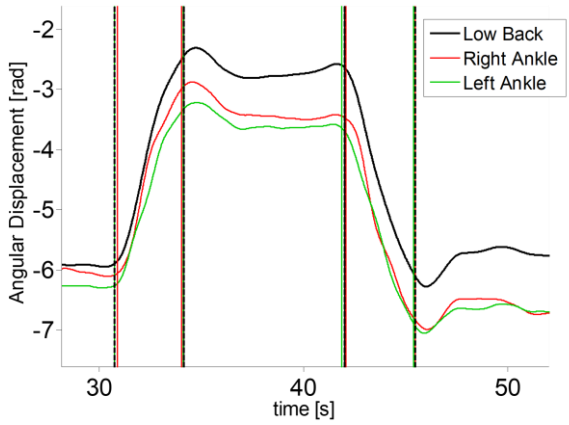

Figure 3-8 Angular displacement in the horizontal plane as obtained from the lb-MIMU and ank-MIMUs. The vertical lines represent the turn onsets and endings as determined by applying the AD methods to the relative angular displacement.

3.3.2.3 Data analysis

First, turns were detected and relevant onset timing and duration values determined using the EG method applied to the ank-MIMU signals, and their difference from the values obtained by applying the EG method to the lb-MIMU signals on the ank-MIMU signals was calculated. Next, the difference of the turns onset timing and duration as determined using the AD method applied to the ank-MIMUs and those obtained with the EG method applied to the lb-MIMU signals were calculated. Finally, to assess the AD method robustness with respect to the MIMU location the difference of the turns onset and duration values obtained by applying the AD method to ank-MIMU signals and those obtained by applying the AD method to lb-MIMU signals was calculated.

All above mentioned differences were averaged across each trial to obtain 'mean difference' and 'mean absolute difference' values.

3.3.3 Results

The descriptive statistics of the turn duration values, as estimated by the EG method from the lb-MIMU, are represented in the five-number summary plots in Figure 3-9. Mean turn duration was 354 ms for ELD NW, 327 ms for ELD FW, 416 ms for PD NW and 394 ms for PD FW.

The number of U-turns detected by the EG method applied to the ank-MIMU signals was equal to that resulting from the EG method applied to the lb-MIMU signals (48 ELD NW, 63 ELD FW, 41 PD NW, 49 PD FW).

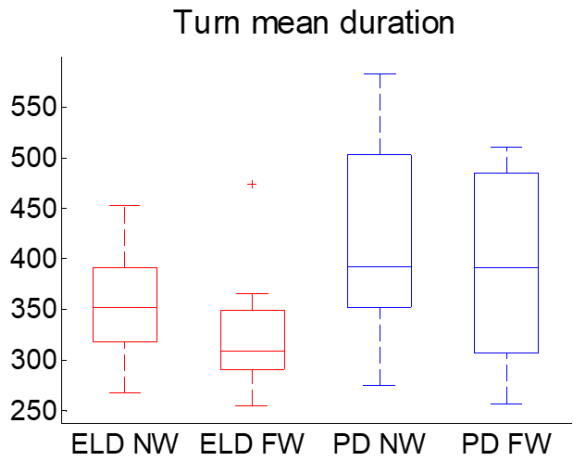

Figure 3-9 Turn mean duration values, as estimated by the EG method applied to the signals recorded by the MIMU on the low back, for both groups (red=ELD, blue= PD) and walking speeds.

Figure 3-10 shows the five-number summary plots for turn onset mean difference between the values obtained from the EG method applied to ank-MIMU signals and those obtained from the original EG method applied to lb-MIMU signals and between the values obtained from the AD method applied to ank-MIMU signals and those obtained from the original EG method applied to lb-MIMU signals for both walking speeds and both groups. The turn onsets estimated using the EG method applied to the ank-MIMU signals were on average 130 ms delayed (200 ms mean absolute difference) for the ELD group and 160 ms (340 ms mean absolute difference) for the PD group. From the comparison of the AD method applied to the ank-MIMU signals and the original EG method on lb-MIMU signals, on average the turn onset mean difference and mean absolute difference were respectively -20 ms and 210 ms for the ELD group and 60 ms and 280 ms for the PD group.

The mean difference between turn duration values obtained from the EG method applied to ank-MIMU signals and those obtained using the original EG method applied to lb-MIMU signals and between the turn duration values obtained from the AD method applied to ank-MIMU signals and the original EG method applied to lb-MIMU signals were computed for both walking speeds and both groups and the relevant five-number summary plots reported in Figure 3-11. The turn durations

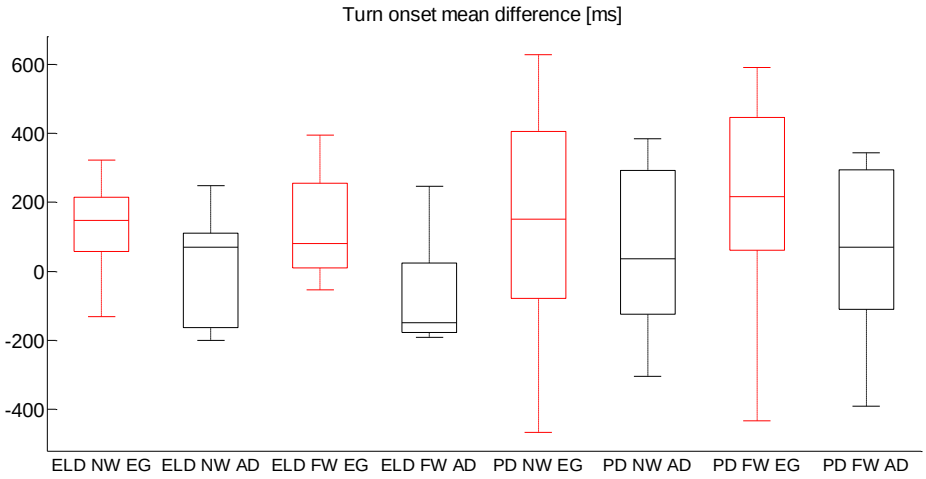

Figure 3-10 Minimum, first quartile, median, third quartile and maximum values for turn onset timing mean difference for both groups and walking speeds. In black results from the difference between turn onset timing values obtained from the EG method applied to the ank-MIMU signals and those obtained from the EG method applied to the lb-MIMU signals, in red results from the difference between turn onset timing values obtained from the AD method applied to the ank-MIMU signals and those obtained from the EG method applied to the lb-MIMU signals.

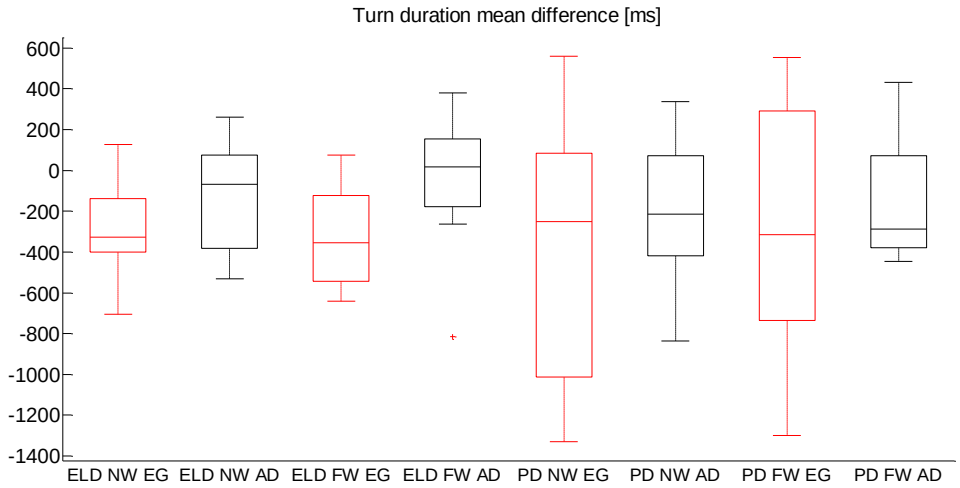

Figure 3-11 Minimum, first quartile, median, third quartile and maximum values for turn duration mean difference for both groups and walking speeds. In black results from the difference between turn duration values obtained from the EG method applied to the ank-MIMU signals and those obtained from the EG method applied to the lb-MIMU signals, in red results from the difference between turn duration values obtained from the AD method applied to the ank-MIMU signals and those obtained from the EG method applied to the lb-MIMU signals.

The ELD FW AD outlier observed appears in the corresponding mean turn duration (Figure 3-9) and it is due a longer turn duration estimated by the EG method.

estimated using the EG method applied to the ank-MIMU signals were on average 300 ms shorter for both ELD and PD groups (mean absolute difference equal to 390 ms and 580 ms, respectively). Similarly, the turn durations estimated using the AD method applied to the ank-MIMU signals were on average 90 ms shorter (mean absolute difference equal to 310 ms) for the ELD group and 180 ms shorter (mean absolute difference equal to 390 ms) for the PD group.

The five-number summary plots for turn onset and duration mean difference between values obtained from the AD method applied to ank-MIMUs signals and to lb-MIMU signals are reported in Figure 3-12 for both walking speeds and both groups. On average, the turn onset mean absolute difference was 30 ms for the ELD group and 60 ms for the PD group. On average, the turn duration mean absolute difference was 70 ms for the ELD group and 110 ms for the PD group.

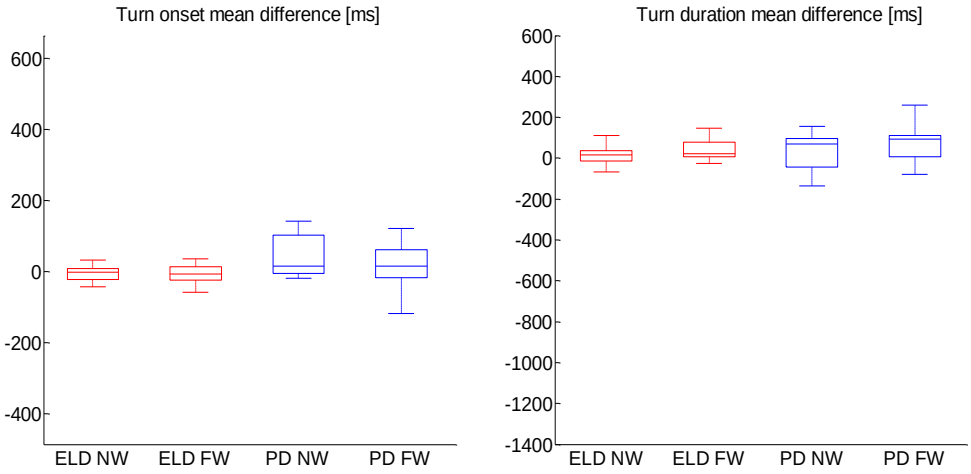

Figure 3-12 Minimum, first quartile, median, third quartile and maximum values of the mean difference between turn onset timing (left) and duration (right) values obtained from the AD method applied to the ank-MIMU signals and those obtained from the AD method applied to the ank-MIMU signals and those obtained from the AD method applied to the lb-MIMU signals, for both groups (red=ELD, blue= PD) and walking speeds.

3.3.4 Discussion

In this study we evaluated if the use of a common algorithm for the detection and characterization of U-turns from data normally recorded with a MIMU located in the

lower back (EG method) [*El-Gohary* 2013] could be extended to the recordings of MIMUs located just above the ankles. In addition, to limit the potential downsides of such use of the algorithm, we introduced a method that could be applied either to signals of a MIMU applied on the low back or to signals of MIMUs located just above the ankles. Two groups of subjects and two gait speeds were included in the comparison to evaluate the robustness of the various methods implementations. None of the methods missed a U-turn nor detected an extra one.

On average, only for the PD group at both walking speed the turn onset timings estimated by the EG method applied to the ank-MIMUs were delayed, with respect to those estimated by the original EG method, more than those estimated by the AD method applied to the ank-MIMUs signals. Therefore, the AD method provided a limited improvement in assessing the turn onsets.

Conversely, in estimating the time duration for the ELD group, the AD method showed lower differences from the estimates obtained with the original EG method than the EG method applied to the ank-MIMUs signals, while for the PD group only a smaller variability of such differences is observed. These results imply that the AD method provided a limited improvement also in estimating the turn duration. Therefore, the AD method reduced the downsides of the EG method applied to the ank-MIMUs, although only partially and at different levels depending on the group and walking speed.

On the other hand, the AD method showed a much higher robustness to MIMU location choice than the GE method. This circumstance highlights that the approach used in the AD method is promising. However, more work needs to be done to further reduce the differences with respect to the turn characterization provided by the original GE method. Specifically, more robust criteria to set the parameters of the AD method than the heuristic settings used in this study may improve its performance further.

Some of the delay observed in determining the turn onset when both methods were applied to the ank-MIMU signals can be associated to the findings of several studies ([*Patla* 1999; *Fuller* 2007; *Lamontagne* 2009; *Hollands* 2010]) that demonstrated that the sequencing of body segment reorientation in turning starts from the head and propagates down. The temporal sequence of axial segment reorientation could therefore explain why turn onsets are identified first on the low back.

Our results are confirmed by the results presented in [*Novak* 2014] in which the authors tested a method to detect the turn onset on various MIMU positions (foot, shank, thigh, lower and upper back and head). Their method combined the analysis of the orientation around the vertical axis (angular displacement) and of the yaw angular velocity (raw gyroscope output). The MIMUs on the legs compared to those on the trunk consistently produced worse onset detection with respect to reference turn onsets as determined by a stereo-photogrammetric systems.

However, the goal of our work was not to describe the way people turn while walking but rather detect and characterize turns in terms of turn onset and duration with the sole purpose of segmenting walking trials into straight walking bouts and turns. In this context we attempted to identify a method applicable to MIMU signals recorded either at the low back or at the ankles and able to determine turn onsets and durations similarly to an established method applicable only to low back MIMU recordings. In this respect, the method introduced can be used as a starting point for a robust characterization of turns during gait.

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Chapter 4

Gait spatio-temporal parameters for treatment evaluation[*]

[*] This chapter is based on P. Solla, L. Cugusi, **M. Bertoli**, A. Cereatti, U. Della Croce, D. Pani, L. Fadda, A. Cannas, F. Marrosu, G. Defazio, G. Mercuro, "**Sardinian Folk Dance for Individuals with Parkinson's Disease: a Randomized Controlled Pilot Trial**" - Journal of Alternative and Complementary Medicine

4.1 Clinical gait analysis in Parkinson's disease

Walking may seem an effortless ability, but actually being able to adapt one's gait to a range of different environments is a highly developed motor skill, easily disrupted by motor impairments [*Morris* 2001a]. Among the most common movement disorders there is Parkinson's Disease (PD), which is also the second most frequent degenerative disease of the central nervous system [*Tysnes* 2017]. A recent review by Hirsch and colleagues estimated PD overall prevalence as 38 per 100,000 person-years in females and 61 in males [*Hirsch* 2016]. Their analysis underlines these numbers increase with aging: annual incidence in people over 80 years is reported as 103 for females and 258 in males. Converted to gender-specific incidence proportions, they report 37 in females and 44 in males, with an increase to 66 in females and 110 in males at age 80+, confirming the higher prevalence in men than in women. Generalizing, a commonly accepted occurrence is approximately in 1-2 % of the population over 65 years, with an increase to 3 % to 5 % in people 85 years and older [*Alves* 2008].

Characteristic features of Parkinson disease include neuronal loss in specific areas of the substantia nigra and widespread intracellular protein (α-synuclein) accumulation [*Poewe* 2017]. Loss of dopaminergic neurons in the pars compacta of the substantia nigra leads to reduced facilitation of voluntary movements [*Tysnes* 2017]. PD is therefore most commonly associated with motor symptoms, such as rest tremor, rigidity, and gait disorders, even though there are numerous non-motor symptoms such as cognitive impairment (including frontal executive dysfunction, memory retrieval deficits and dementia), hyposmia, anxiety, and depression [*Kadastik-Eerme* 2015]. Motor deficits reflected in gait are hypokinesia (or bradykinesia), diskinesia and akinesia. Hypokinesia, the most common movement disorder in PD, refers to reduced movement speed and size [*Morris* 1994]. Akinesia (absent movement) [*Giladi* 1992; *Burleigh-Jacobs* 1997] and dyskinesia (involuntary choreiform movements) [*Hagell* 1999; *Morris* 2000] are less common causes of gait disturbance.

To assess motor impairment and its progression, clinically the most commonly used score is the Unified Parkinson's Disease Rating Scale (UPDRS) (and the MDS-UPDRS, its revised form) [*Goetz* 2008]. In research settings, a steadily increasing number of studies is exploiting quantitative gait analysis to evaluate spatio-temporal parameters in PD [*Salarian* 2004; *Moore* 2007; *Hass* 2012a; *Horak* 2015; *El-Gohary* 2016; *Del Din* 2016; *Schlachetzki* 2017]. In fact, individuals with PD progressively lose flexibility and adaptability in their locomotor responses and typically walk with a short stepped shuffling gait. Short steps, and a higher double support time, have been hypothesized to be a strategy to control faulty balance on one leg during a long step [*Morris* 1994]. In fact, postural instability is also associated to PD. In walking, this is reflected by larger step-to-step variability compared to healthy subjects: steps duration, length, and width over multiple gait cycles vary more in PD subjects compared to healthy controls [*Hausdorff* 2005].

Although pharmacological treatment is the primary therapy for PD, non-pharmacological interventions have become increasingly recognized in the management of PD [*Smulders* 2016]. A growing body of evidence documents the beneficial effects of physical activity on both motor and non motor symptoms [*Alves da Rocha* 2015]. The usefulness of various exercise-based strategies is supported in terms of classic motor outcomes (such as the UPDRS), specific parameters (such as gait speed, balance control and muscle strength) or global measures (e.g.: Quality of Life) [*Bergen* 2002; *Keus* 2009; *Seppi* 2011; *Bloem* 2015]. These findings are flanked by the potential role of physical activity in promoting neuroplasticity and repair in Parkinson's disease (PD) [*Xu* 2010; *Petzinger* 2013].

In conclusion, Parkinson disease mainly affects older people, leading to difficulty in the performance of skilled motor tasks such as walking. Given the rapid population ageing, the biomechanics and motor control of gait in PD subjects is a topic of growing interest for researchers and clinicians. Furthermore, beyond motor and cognitive impairments, quality of life in PD also deteriorated significantly with increasing

disease severity particularly in those aspects related to physical and social functioning [*Schrag* 2000] In order to evaluate the role of physical activity as treatment for both motor and non-motor aspects of PD, further studies should address its enhanced therapeutic potential.

4.2 Sardinian Folk Dance for Individuals with Parkinson's Disease

Among different exercise models proposed for individuals with Parkinson's Disease (IwPD), the popularity of traditional forms of dance is increasing. The aim of the study presented in this chapter was to evaluate the effects of Sardinian folk dance (*Ballu Sardu*, BS) on functional performance and motor and non-motor symptoms in IwPD.

Twenty IwPD (13M, 7F; 67.4±6.1 years) were randomly assigned to BS (n=10) or usual care (n=10). The dance program consisted of two sessions/week, 90-minutes/class, for 12-weeks.

Motor and non-motor symptoms, as well as functional performance, were evaluated using different questionnaires and tests such as the Unified Parkinson's Disease Rating Scale Part–III (UPDRS-III), Six-Minute Walking Test (6MWT), Berg Balance Scale (BBS), Timed Up-and-Go Test (TUG), Five Times Sit-to-Stand Test (FTSST), Back Scratch Test (BST), Sit and Reach Test (SRT), instrumented gait analysis, Parkinson's Disease Fatigue Scale (PFS-16), Beck Depression Inventory (BDI-II), Starkstein Apathy Scale (SAS), and Montreal Cognitive Assessment Scale (MOCA).

Repeated-measures ANOVA revealed significant Time*Group interactions for UPDRS-III and functional variables such as the 6MWT, BBS, FTSST, TUG (all, p<0.001), BST (p=0.04), and gait analysis parameters (Stride length, p=0.031; Gait speed, p=0.049 and gait fatigue index (GFI), p=0.005). For non-motor symptoms, significant

Time*Group interactions for depression (p<0.001), apathy (p=0.016), and MOCA scores (p=0.012), were observed.

BS is an enjoyable activity which has been proved to be superior to usual care alone in inducing changes in different motor and non-motor symptoms associated with PD. Results show that BS can be considered a safe tool for contrasting impairments observed in IwPD due to the intrinsic nature of the neurodegenerative disease.

4.2.1 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition comprising a spectrum of functional, motor and non-motor symptoms [*Hughes* 1992; *Chaudhuri* 2006]. Treatment for PD has traditionally been based on the use of dopaminergic medications, even though non-pharmacological approaches such as exercise-based activities are gaining attention for managing its complex symptomatology [*Goodwin* 2008; *Tomlinson* 2014]. In this regard, there is evidence that conventional physical activities such as treadmill training [*Fisher* 2008; *Kurtais* 2008; *Goetz* 2008], resistance exercise [*Dibble* 2009; *Hass* 2012b; *Corcos* 2013] and adapted physical activity programs can have positive effects in improving functional mobility [*Cugusi* 2014], static and dynamic balance, as well as non-motor disturbances in individuals with PD (IwPD).

Recently, several non-conventional physical activities have been proposed for IwPD to improve functional mobility and enhance well-being, social inclusion and quality of life (QOL) [*Alves da Rocha* 2015; *Kwok* 2016]. Among these, Tai Chi [*Corcos* 2012; *Li* 2012], boxing [*Combs* 2011], Nordic walking [*Cugusi* 2015b; *Bang* 2016; *Cugusi* 2017], aquatic-based exercise programs [*Volpe* 2014; *Carroll* 2017] and dance-based approaches have been investigated thoroughly[*Hackney* 2009b; *Duncan* 2011a; *Delextrat* 2016; *Shanahan* 2017; *dos Santos Delabary* 2017].

In particular, the use of different forms of dance as a strategy to manage PD-induced disability is gaining popularity among IwPD, for whom social relations and

participation in group activities have been reported to play a key role in the achievement of health goals [*Kiepe* 2012].

Dance activity is an accessible and appealing form of fitness workout. The supportive, social nature of dance classes and the guide of a dance teacher are important features that may help IwPD to overcome psychological barriers, which often prevent them from participating in exercise programs [*Ellis* 2013; *Baig* 2015]. Dance allows a multisensory experience and is therefore more than a set of single movements driven by music, because it not only involves physical domains but also emotional, cognitive, cultural and socio-ethnocoreutic aspects. Indeed, the traditional folk dance has been described as a form of dance that *"may stimulate selective, deep limbic neuronal circuits and cause an emotional involvement, binding the subjective experience of individuals with a dynamic, objective reality of the community, also involving the motor side in the dance rhythm, in what could be construed as a symbolic and therapeutic function"* [*Sironi* 2015]. Previous experiences have demonstrated that social and community forms of cultural dance, such as Irish dance or Argentine tango, can improve functional mobility and increase socialization, also promoting the adherence to exercise programs in IwPD [*Volpe* 2013; *Foster* 2013; *Shanahan* 2015; *Rios Romenets* 2015; *McNeely* 2015; *Shanahan* 2016; *Shanahan* 2017; *dos Santos Delabary* 2017].

One of the most ancient Mediterranean dances is Sardinian folk dance, commonly referred to as *Ballu Sardu* (BS). This traditional form of dance is still very popular in Sardinia, embodying not only an enjoyable social moment but also the cultural expression of the community [*Carta Mantiglia* 1999; *Cugusi* 2015a]. BS is typically danced in a closed or open circle by couples who are holding hands, *palm-to-palm*. The movements of the dancers change with the music's rhythms, generally characterized by a first component, which is slow and quiet, and a second more lively and rhythmic component which includes steps and jumps. Due to its natural characteristics which address both motor and cognitive functions (*i.e.*, coordination, balance, cardiovascular endurance, visual memory, mobility and posture) and social aspects such as group

activities, emotional response to the music, historical re-enactment, and physical contact [*Cugusi* 2015a], BS dance may be a valuable and feasible therapeutic approach for managing several movement disorders, including PD.

Therefore, the purpose of the present study was to evaluate the effects of participation in a BS dance program on functional and gait performance, motor symptoms, and on specific cognitive and affective non-motor symptoms in IwPD with mild to moderate disability.

4.2.2 Materials and Methods

4.2.2.1 Study design and participants

The study is a single-blind, randomized controlled pilot trial. Consecutive subjects with a definite diagnosis of PD were recruited from patients attending the outpatient Movement Disorders Clinic of the University of Cagliari. Inclusion criteria for the study included a clinical diagnosis of PD according to Gelb's criteria [*Gelb* 1999], a score ≤ 3 on the Hoehn and Yahr (H&Y) scale [*Hoehn* 1967], ability to walk without walking aids, stable medication regimen in the four weeks prior to the study, and a score ≥ 24 on the Mini-Mental State Examination [*Folstein* 1975]. Exclusion criteria for the study were: H&Y stage > 3, diagnosis of dementia according to DSM-5 criteria, atypical parkinsonism, pharmacological treatment with drugs not approved for PD, the presence of any complementary disability or autonomic problems that precluded the training program, or any specific health condition for which exercise was contraindicated. A history of falls in the previous three-month period, as well as the presence of dyskinesias, freezing, and static-dynamic postural instability, was also verified prior to enrollment.

As reported in Figure 4-2, twenty patients meeting eligibility criteria (13M, 7F; mean age 67.4 ± 6.1 years) were randomly allocated into two groups using a random number program generator (Research Randomizer 4.0 software).

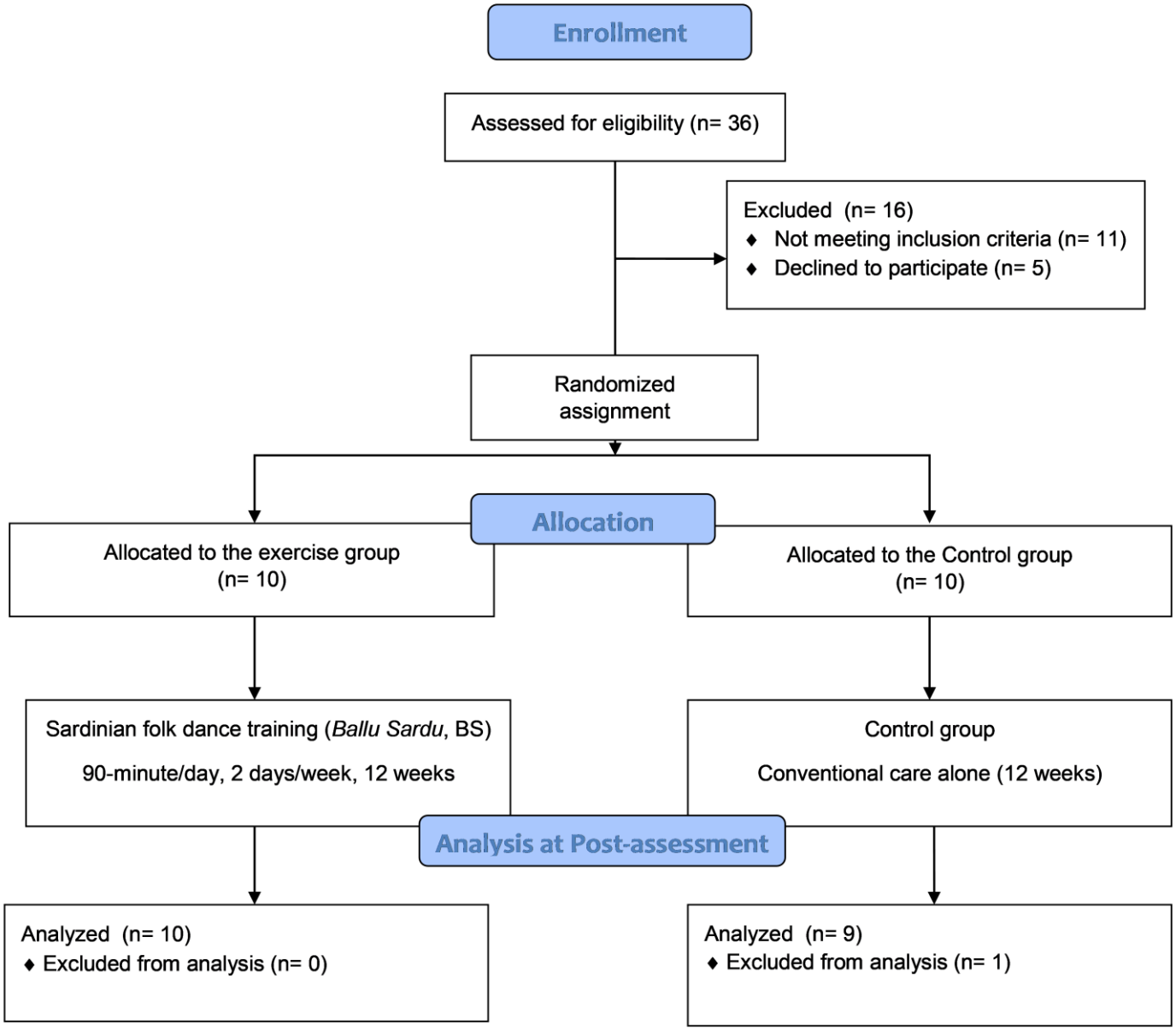

Figure 4-1 CONSORT flow chart for the study design

The exercise group received usual care (medical therapy) *plus* a 12-week BS dance program, while individuals in the control group did not perform any type of specific exercise program, maintained their habitual activities, and continued their usual care involving medical therapy alone. All participants were informed on the aims of the study and its procedures prior to enrolment and written informed consent was obtained from all subjects. The study was approved by the Institutional Review Board

at the University of Cagliari (Registration number: NP/3339) and was performed in accordance with the Declaration of Helsinki.

4.2.2.2 Experimental procedures

Participants in both groups were instructed to continue with their usual care and advised not to change their daily activities during the trial. Assessments were performed by three experienced evaluators (a neurologist for PD motor and non-motor symptoms, a physiotherapist for functional outcomes, and a bioengineer for gait analysis). Evaluators were blinded to group allocation and not involved in routine clinical follow-up. All outcomes in both groups were assessed at baseline (within two weeks prior to starting the dance program) and after the completion of the 12-week intervention (at week 13). Assessments were carried out when participants were in the *"on"* phase (*i.e.,* when medications were working and symptoms were controlled). Participants' anti-parkinsonian medications were monitored by using a self-report measure.

4.2.2.3 Motor symptoms and functional outcomes

All participants received a structured clinical evaluation which included evaluation of their clinical history, the presence and severity of any motor complications related to use of dopaminergic treatment (both motor fluctuations and dyskinesias), and the presence of non-motor disturbances.

Motor disability was assessed using the motor component of Unified Parkinson's Disease Rating Scale (UPDRS-III) [*Fahn* 1987], and the modified H&Y scale [*Hoehn* 1967]. Functional performance was evaluated using a set of standardized tests, including the Six-Minute Walking Test (6MWT) to evaluate cardiovascular fitness [*Garber* 2003] and the Five Times Sit-to-Stand Test (FTSST) to estimate dynamic strength in the lower limbs [*Duncan* 2011b]. Neuromotor performance was assessed

using the Timed Up-and-Go Test (TUG) for functional mobility [*Morris* 2001b] and using the Berg Balance Scale (BBS) to evaluate static balance [*Qutubuddin* 2005]. Participants' lower body joint mobility was assessed by the Sit-and-Reach Test (SRT) [*Bozic* 2010] and the Back Scratch Test (BST) was used to assess the upper body joint mobility [*Rikli* 1999].

4.2.2.4 Gait analysis

During the assessments, each subject was instrumented with a wearable gait analysis system composed of three synchronized magneto-inertial measurement units (MIMUs) (Opal, APDM, sample frequency=128 Hz). As illustrated in Figure 4-2, two MIMUs were attached to the participant's ankles (2 cm above the left and right malleolus) and one on the back approximately at the level of the fifth lumbar vertebrae (L5). Participants were instructed to perform a 2-Minute Walking Test (2MWT) at a self-selected speed, walking back and forth in a loop composed by a 7-meter straight path and two 180° turns.

Inertial data from the 2MWT were segmented and turnings were discarded [*Bertoli* 2017]. For each remaining gait cycle, spatio-temporal parameters such as stride length (*m*), gait speed (*m*/*s*), cadence (*steps*/*min*), number of straight walks, and straight walking time (*s*) were estimated [*Trojaniello* 2014; *Bertoli* 2018]. In addition, during the 2MWT a gait fatigue index (GFI) (***Eq.1***) based on any decrease in gait speed observed during the test, adapting the equations used previously in repeated-sprint studies [*Oliver* 2009], was calculated, as follows:

$$\textbf{GFI \%:}\ \frac{MGS_B - MGS_A}{MGS_A} \times 100 \qquad \textbf{(1)}$$

where MGS_B = gait speed over a straight path from the second to the last lap, and MGS_A = gait speed over straight paths of the second lap (negative values indicated the presence of fatigue: -50% indicated a one third reduction in participant's initial speed, while a value of -100% indicated participant's initial speed had reduced by half). Data obtained from the gait examination were exported to SPSS, Version 18 (SPSS, Chicago, USA) for further analyses.

Figure 4-2 Individual with PD wearing the MIMUs on the left; MIMU positionings above the ankles and at L5 level on the right

4.2.2.5 Non-motor symptoms

The Parkinson's Disease Fatigue Scale (PFS-16) was used to evaluate fatigue. The PFS is a 16-item scale which asks subjects to assess physical aspects of fatigue and its influence on their daily functioning. Items on the PFS-16 are rated on a scale from 1 to 5. Total PFS-16 scores are the average of item scores across the 16 items, with higher scores representing more fatigue [*Brown* 2005]. The Beck Depression Inventory (BDI-II) was used to estimate depressive symptoms. This questionnaire contains 21 items

evaluating the presence and severity of depressive symptoms at the time of completion and during the previous two weeks, with higher total scores indicating more severe depressive symptoms [*Beck* 1996]. Analysis of apathy symptoms was performed using the short version of the Starkstein Apathy Scale (SAS). The scale consists of 14 items, with lower total scores indicating less severe apathy levels [*Pedersen* 2012]. The Montreal Cognitive Assessment Scale (MOCA) [*Kletzel* 2017] was used to evaluate cognitive deficits. The MOCA scale allows users to identify cognitive impairments in domains such as attention, concentration, executive functions, memory, visual-spatial skills, calculation, and orientation. Total scores on the MOCA range from 0 to 30, with scores above 26 being considered to be in normal range.

4.2.2.6 Sardinian folk dance intervention

The ten participants assigned to the BS group underwent a Sardinian folk dance program based on an adapted form of BS. The training program consisted of 24, 90-minute class sessions, performed twice per week for twelve weeks. Adherence to the training sessions, including attendance at classes and any adverse effects, were recorded. The exercise protocol was performed in close collaboration with the Adapted Physical Activity (APA) Master's Degree Course of the University of Cagliari and with a sports association that promotes exercise therapy (*Team Kayak Sardegna*).

Each 90-minute BS session involved three phases. During the initial 30 minutes, warm-up exercises, balance training, coordination, mobilization, ankle control exercises, proprioception and breathing exercises were performed. During the following 50 minutes, a Sardinian folk dance teacher conducted the dance supported by traditional records (based on *launeddas* rhythms). The BS sessions comprised different forms of Sardinian folk dance beginning with the mono-structured forms and progressing to the bi-structured ones. Mono-structured forms combine rhythmic and homogeneous movements which are more suitable to the needs of BS beginners with PD. The mono-

structured and bi-structured BS forms are differentiated by the use of two alternating rhythms, slow and fast (in Sardinian language: *seriu* and *alligru,* respectively). During the BS sessions, subjects held hands or arms to form a circle that rotated clockwise. The dynamics of BS include steps and small jumps, with stop on the right foot. In BS dancing, movements of the legs are performed from predominantly the mid-thigh down. During the dance, the knees were kept slightly bent to ensure a uniform springing of the forefoot. The different types of mono-structured dances (characterized by slow and gentle rhythms) and bi-structured dances (characterized by a slow and a more lively rhythmic music component) employed in our study included the *Ballu Seriu* (The Slow Dance), the *Passu Torrau* (The Returned Step), and the *Ballu Tundu* (The Circle Dance) [*Carta Mantiglia* 1999; *Cugusi* 2015a]. The final 10 minutes of the 90-minute session consisted of deep breathing and static stretching exercises. All 24 training sessions were entirely supervised by a physiotherapist assisted by two APA specialists. Other subjects (relatives, friends and caregivers) were also allowed to participate in BS sessions not only to support their relatives but also to create an opportunity for them to enjoy the dance with subjects as well.

4.2.2.7 Statistical Analysis

Data were analyzed using Statistical Software for the Social Sciences (SPSS Inc., Version 18, Chicago, IL, USA). Descriptive statistics were calculated for all the variables considered. For our sample size calculations, we considered previous studies that employed other forms of non-conventional exercise-based activities for IwPD that reported large effect sizes (ESs) for UPDRS-III scores ranging from 1.38 ([*Bang* 2016]) to 1.46 ([*Carroll* 2017]). In addition, during our calculations, we considered studies that specifically focused on the effects of dance-based therapy in this population in which moderate ESs were observed (0.65 in [*Hackney* 2009a] and 0.68 in [*Duncan* 2011a]). We then carried out an *a priori* power analysis (G*Power 3.1 software, Germany) assuming a moderate ES (Cohen's d =0.7) and an alpha level of 0.05; based on these assumptions,

the software indicated that we would need 10 subjects per group to achieve at least 80% statistical power. Equality of variance was analyzed using Levene's test. Data sphericity was evaluated using Mauchly's test. In the case of non-spherical data, a Greenhouse-Geisser correction was applied. Kolmogorov-Smirnov and the Shapiro-Wilks tests were used to test the normality of distributions. Main effects (Time, Group) and two-way interactions (Time*Group) were analyzed using repeated measures analysis of variance (RM-ANOVA). In case of significant differences, Bonferroni-adjusted pairwise comparisons were used to identify differences. Statistical significance for all tests was set at $p < 0.05$. The clinical relevance of the intervention-induced changes was estimated by calculating ES using Cohen's d (small ES ≤ 0.5; moderate ES = 0.51-0.79; large ES ≥ 0.8) [*Cohen* 1988], according to the formula by Hedges and Olkin, which corrects for bias arising from the use of pooled standard deviations [*Hedges* 1985; *Lakens* 2013].

4.2.3 Results

At baseline, no significant differences were identified between the groups for any of the demographic and clinical characteristics reported in Table 1**.** In addition, the two groups showed no significant differences in any of the variables analyzed. No changes in medication administration or loading doses occurred during the 12 weeks of BS training, and no adverse effects were recorded during the protocol. Participant attendance at the dance classes during the program was 92.9%. Reasons for lack of attendance at dance classes included concomitant illness and individual conditions unrelated to PD. Data from one participant in the control group were discarded after initial review as severe dyskinesia and freezing significantly altered the registration of gait patterns during analyses.

Table 4-1 Demographic and clinical features of PD patients

Sample characteristics	BS group	Control group	*p* Value
Age (years)	67.8±5.9	67.1±6.3	*p=0.80*
Males (%)	6/10 (60)	7/10 (70)	*p=0.66*
PD duration (years)	4.4±4.5	5±2.9	*p=0.73*
Hoehn & Yahr	2.1±0.6	2.3±0.4	*p=0.39*
LEDD (mg/day)	481.1±213.1	487.5±198.5	*p=0.95*
Weight (Kg)	67.7±9.4	69.6±10.7	*p=0.68*
Height (m)	1.6±0.07	1.6±0.09	*p=1*
BMI (Kg/m^2)	26.0±3.4	25.9±4.6	*p=0.96*

Note. Values are Mean ± SD and percentage (%)
Abbreviations. BS, Ballu Sardu; PD, Parkinson's Disease; LEDD, Levodopa Equivalent Daily Dose; BMI, Body Mass Index.

4.2.3.1 Motor symptoms and functional performance

Analysis of UPDRS-III scores revealed that tremor at rest, tremor during action, and postural instability were the most common issues reported by participants. RM-ANOVA showed a significant main effect of Time (F=11.273; p=0.004) on UPDRS-III scores, and a significant Time*Group interaction (F=22.191; p<0.001, ES 2.19). Post-hoc testing with Bonferroni-corrected pairwise comparisons revealed that following the intervention, UPDRS-III scores decreased significantly in the BS group only. Post-hoc testing also revealed a statistically-significant 72.4% increase in the distance participants in the BS group were able to cover during the 6MWT, with a large between-group ES (F=41.124; p<0.001; ES 2.98).

Analysis of static balance scores from the BBS using RM-ANOVA revealed a significant main effect of Time (F=32.184; p<0.001) on BBS scores, and a significant Time*Group interaction (F=49.834; p<0.001). Pairwise comparisons revealed significant increases in BBS scores in the BS group only, with a large between-group ES (3.51). Following the intervention, both groups displayed significant reductions in the

amount of time needed to complete the TUG test (BS group: -26.4%; $p<0.001$; control group: -6.5%; $p=0.022$). Participants in the BS group performed significantly better on the TUG test, with a large between-group ES ($F=26.014$; $p<0.001$; ES 2.37).

In our analysis of dynamic strength scores for the lower limbs using the FTSST, pairwise comparisons revealed that the amount of time needed by the participants to complete the test reduced only in the BS group (-31.6%), while that needed by the control group increased significantly (+5.6%; $p=0.04$), showing a large between-group ES ($F=95.685$; $p<0.001$; ES 4.54).

RM-ANOVA testing identified a significant main effect for Time (F=9.130; $p=0.01$) and a significant Time*Group interaction (F=5.152; $p=0.04$) for the BST. Improved upper-body flexibility was only observed in individuals in the BS group during the study (BS group: +37.2%; $p=0.005$; control group: +5.4%; $p=0.56$), resulting in a large ES (1.21). Analysis of SRT test data using RM-ANOVA identified no significant differences within groups, and no significant Time*Group interactions ($p=0.42$).

4.2.3.2 Gait analysis

Analysis of stride length data from the study using RM-ANOVA found a significant Time*Group interaction (F=5.608; $p=0.03$); post-hoc testing using pairwise comparisons identified significant improvements in stride length for participants in the BS group (+4.7%; $p=0.023$), with a large between-group ES (1.13). By contrast, in the control group, stride length decreased slightly during the study (-1.5%), although these changes were not statistically significant ($p=0.364$).

Analysis of walking speed using pairwise comparisons found that only participants in BS group displayed a statistically significant increase in this variable during the study (BS group: +8.1%; $p=0.002$; control group: +0.8%; $p=0.652$), with a large between-group ES ($F=4.524$; $p=0.049$; ES 1.02).

Table 4-2 PRE to POST changes in motor symptoms and functional performance within- and between-subjects

Motor symptoms and functional performance	**BS group**			**CONTROL group**			**BS *vs* CONTROLS**
	PRE	**POST**	**PRE-POST** ***Within-subjects***	**PRE**	**POST**	**PRE-POST** ***Within-subjects***	**Time*Group Interaction**
UPDRS-III *95% CI*	13.00±7.23 *(8.24 – 17.76)*	7.70±6.70 *(3.37 – 12.03)*	-40.8% p<0.001§	14.67±7.02 *(9.65 – 19.68)*	15.55±6.25 *(10.99 – 20.12)*	+6% *p*=0.364	F=22.191 *p*<0.001§ ES=2.19
6MWT *(m)* *95% CI*	330.7±120.48 *(250.44 – 410.96)*	570.20±76.59 *(511.19 – 629.21)*	+72.4% *p*<0.001§	333.28±120.07 *(248.68 – 417.87)*	331.44±100.12 *(269.24 – 393.65)*	-0.5% *p*=0.947	F=41.124 *p*<0.001§ ES=2.98
BBS *95% CI*	40.0±3.5 *(36.9 – 43.1)*	46.9±3.6 *(43.4 – 50.4)*	+17.2% *p*<0.001§	37.3±5.2 *(34.0 – 40.6)*	36.6±6.0 *(32.9 – 40.3)*	-1.9% *p*=0.36	F=49.834 *p*<0.001§ ES=3.51
TUG *(s)* *95% CI*	6.9±1.04 *(6.16 – 7.64)*	5.08±0.78 *(4.41 – 5.74)*	-26.4% *p*<0.001§	7.43±1.18 *(6.65 – 8.21)*	6.95±1.19 *(6.25 – 7.65)*	-6.5% *p*=0.022*	F=26.014 *p*<0.001§ ES=2.37
FTSST *(s)* *95% CI*	9.69±0.55 *(8.64 – 10.74)*	6.63±0.60 *(5.48 – 7.78)*	-31.6% *p*<0.001§	10.88±2.22 *(9.78 – 11.99)*	11.49±2.43 *(10.28 – 12.70)*	+5.6% *p*=0.040*	F=95.685 *p*<0.001§ ES=4.54
BST *(cm)* *95% CI*	-13.7±9.4 *(-22.9 – -4.4)*	-8.6±8.5 *(-16.8 – 0.4)*	+37.2% *p*=0.005#	-14.7±11.1 *(-22.2 – -7.1)*	-13.9±9.7 *(-20.6 – -7.2)*	+5.4% *p*=0.56	F=5.152 *p*=0.04* ES=1.21
SRT *(cm)* *95% CI*	-5.0±9.4 *(-11.8 – 1.8)*	-1.3±11.1 *(-8.3 – 5.6)*	+74% *p*=0.06	-7.6±6.1 *(-13.5 – -1.7)*	-5.9±4.1 *(-11.9 – 0.1)*	+22.4% *p*=0.27	F=0.695 *p*=0.42 ES=0.46

Note. Values are mean ± SD and percentage (%); * Significant for $p<0.05$; # Significant for $p<0.01$; § Significant for $p<0.001$

Abbreviations. BS, *Ballu Sardu*; CI, Confidence Interval; ES: Effect Size (calculated by the Hedges *g*; small <0.5; moderate 0.51–0.79; large >0.8) (58); UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; 6MWT: Six-Minute Walking Test; BBS, Berg Balance Scale; TUG, Timed Up-and-Go Test; FTSST, Five Times Sit-to-Stand Test; BST, Back Scratch Test; SRT, Sit and Reach Test.

Table 4-3 PRE to POST changes in gait analysis parameters within- and between-subjects

Gait analysis	BS group			CONTROL group			BS *vs* CONTROLS
	PRE	POST	PRE-POST *Within-subjects*	PRE	POST	PRE-POST *Within-subjects*	Time*Group Interaction
Stride length *(m)* *95% CI*	1.27±0.08 *(1.18 – 1.36)*	1.33±0.10 *(1.23 – 1.43)*	+4.7% p=0.023*	1.29±0.18 *(1.19 – 1.39)*	1.27±0.19 *(1.16 – 1.38)*	-1.5% p=0.364	F=5.608 p=0.031* ES=1.13
Gait speed *(m/s)* *95% CI*	1.24±0.13 *(1.11 – 1.36)*	1.34±0.09 *(1.24 – 1.44)*	+8.1% p=0.002$^{\#}$	1.19±0.23 *(1.05 – 1.33)*	1.20 ± 0.20 *(1.09 – 1.31)*	+0.8% p=0.652	F=4.524 p=0.049* ES=1.02
Cadence *(step/min)* *95% CI*	133.71±12.21 *(125.40 – 142.03)*	140.60±9.00 *(135.21 – 145.99)*	+5.1% p=0.010$^{\#}$	123.89±12.64 *(114.59 – 133.18)*	129.56±6.59 *(123.54 - 135.59)*	+4.6% p=0.046*	F=0.117 p=0.736 ES=0.16
Number of straight walks *95% CI*	17.10±1.85 *(15.46 – 18.74)*	18.90±1.29 *(17.53 – 20.26)*	+10.5% p<0.001§	16.12±3.04 *(14.29 – 17.96)*	16.75±2.71 *(15.22 – 18.28)*	+3.9% p=0.147	F=4.572 p=0.048* ES=1.02
Straight walking time *(s)* *95% CI*	62.93±4.77 *(58.39 – 67.48)*	61.64±4.06 *(57.59 – 65.69)*	-2% p=0.398	68.93±8.70 *(63.85 – 74.01)*	67.13±7.88 *(62.61 –71.66)*	-2.6% p=0.298	F=0.050 p=0.827 ES=0.11
Gait fatigue index *(%)* *95% CI*	-7.24±3.88 *(-10.40 – -4.09)*	-3.83±6.08 *(-8.56 – 0.90)*	+47.1% p=0.085	-5.70±5.06 *(-9.23 – -2.17)*	-11.46±8.14 *(-16.75 – -6.17)*	-101.05% p=0.014*	F=10.797 p=0.005$^{\#}$ ES=7.72

Note. Values are mean ± SD and percentage (%); * Significant for p<0.05; $^{\#}$ Significant for p<0.01; § Significant for p<0.001

Abbreviations. BS, Ballu Sardu; CI, Confidence Interval; ES: Effect Size (calculated by the Hedges *g*; small <0.5; moderate 0.51–0.79; large >0.8) (58).

Analysis of walking cadence data from the study showed that walking cadence increased for both groups (BS group: +5.1%; p=0.01; control group: +4.6%; p=0.046), but no Time*Group interaction was observed, and the between-group ES was very small (0.16). However, pairwise comparisons revealed a statistically significant increase in the number of straight walks participants in the BS group were able to perform (+10.5%; p<0.001), while participants in control group showed a non-significant, +3.9% increase. A large between-group ES was observed (F=4.572; p=0.048; ES 1.02).

Analysis of gait-fatigue data (GFI) revealed a significant Time*Group interaction (F=10.797; p=0.005). Pairwise comparisons revealed a significant worsening of gait-fatigue for the control group, while participants in the BS group showed a trend towards improvement, although the trend failed to reach statistical significance (p=0.085). A very large ES was calculated between the groups (F=10.797; p=0.005; ES 7.72).

4.2.3.3 Non-motor symptoms

Following the intervention, no differences were found in perceived fatigue (PFS-16) between the two groups, while a main effect of Time (F=44.788; p<0.001) and a Time*Group interaction (F=47.957; p<0.001) were detected for the depressive symptoms, as assessed by the BDI-II. BDI-II score improved only in the BS group, displaying a large between-group ES (3.22). A significant Time*Group interaction with a large between-group ES (F=7.106; p=0.016; ES 1.24) was detected for apathy symptoms, which remained unchanged in the BS group (p=0.276), while SAS scores worsened significantly in the control group (p=0.018).

Table 4-4 PRE to POST changes in non-motor symptoms within- and between-subjects

Non-motor symptoms	BS group			CONTROL group			BS *vs* CONTROLS
	PRE	POST	PRE-POST *Within-subjects*	PRE	POST	PRE-POST *Within-subjects*	Time*Group Interaction
PFS-16 *95% CI*	33.10±12.74 *(23.52 – 42.68)*	33.30±14.69 *(23.95 – 42.65)*	+0.6% p=0.917	34.11±15.98 *(24.01 – 44.21)*	37.67±13.23 *(27.81 – 47.53)*	+10.4% p=0.093	F=1.487 p=0.239 ES=0.57
BDI-II *95% CI*	14.10±3.45 *(11.46 – 16.74)*	7.60±2.06 *(5.42 – 9.78)*	-46.1% p<0.001§	13.67±4.47 *(10.88 – 16.45)*	13.78±4.24 *(11.48 – 16.08)*	+0.8% p=0.874	F=47.957 p<0.001§ ES=3.22
SAS *95% CI*	9.20±3.46 *(6.33 – 12.07)*	7.70±1.89 *(5.23 – 10.17)*	-16.3% p=0.276	10.11±5.08 *(7.09 – 13.14)*	13.78±5.02 *(11.17 – 16.38)*	+36.3% p=0.018*	F=7.106 p=0.016* ES=1.24
MOCA *95% CI*	25.00±3.97 *(22.68 – 27.32)*	26.40±3.47 *(24.31 – 28.48)*	+5.6% p=0.006#	25.67±2.83 *(23.22 – 28.11)*	25.22±2.68 *(23.02 - 27.42)*	-1.7% p=0.363	F=7.913 p=0.012* ES=1.31

Note. Values are mean ± SD and percentage (%); * Significant for p<0.05; # Significant for p<0.01; § Significant for p<0.001

Abbreviations. BS, Ballu Sardu; CI, Confidence Interval; ES: Effect Size (calculated by the Hedges *g*; small <0.5; moderate 0.51–0.79; large >0.8) (58); PFS-16, Parkinson's Disease Fatigue Scale; BDI-II, Beck Depression Inventory; SAS, Starkstein Apathy Scale; MOCA, Montreal Cognitive Assessment Scale.

For cognitive impairments (MOCA), a significant Time*Group interaction with a large between-group ES was observed (F=7.913; *p*=0.012; ES 1.31). Pairwise comparisons revealed a significant improvement in cognitive impairment scores for participants in the BS group only, while cognitive impairment scores for the control group showed a slight, non-significant worsening (*p*=0.363).

4.2.4 Discussion

Previous research has shown that the use of dance-based therapies is associated with improved motor function and balance capacity in IwPD [*dos Santos Delabary* 2017], particularly Argentine tango [*Foster* 2013; *Rios Romenets* 2015; *McNeely* 2015], and Irish set dancing [*Volpe* 2013; *Shanahan* 2015; *Shanahan* 2016; *Shanahan* 2017]. These studies focused on motor performance, with only a limited number of investigations [*Hackney* 2009c; *McKee* 2013; *Hashimoto* 2015; *de Natale* 2017] also appraising the effects of dance-based activities on non-motor symptoms such as affective or cognitive impairments.

Results of our study indicate BS as a safe and feasible form of physical exercise that is likely to have positive effects on functioning and non-motor symptoms in IwPD. Indeed, in line with previous reports which have focused on other types of dance-based activities [*Shanahan* 2017], overall attendance at BS classes in our study was excellent, and no safety issues or adverse effects were reported.

However, given the design of the present study, which compared participants undergoing dance-based therapy to a non-active control group, the interpretation of these findings need to take the neurodegenerative nature of PD into proper consideration. In fact, if left untreated, IwPD tend to display a worsening of motor- and non-motor symptoms [*Poewe* 2010], which was the case for our control group, where a significant decline was observed in 3 out of 17 outcome measures (FTSST, GFI, SAS) we evaluated. In this context, non-active controls may not prove to be a stable reference for evaluating the effectiveness of exercise-based interventions and may

require a comprehensive appraisal of not only between-group, but also within-group results to quantify the net changes obtained after the BS program.

Analysis of UPDRS-III scores showed a significant improvement in PD motor symptoms following participation in the BS program. UPDRS-III scores decreased by 5.3 points for participants in the BS group, which is likely to be clinically relevant since it exceeds the threshold for a clinically-important difference (CID) for IwPD, which has previously been defined as a change in UPDRS–III scores between 2.5 and 5.2 points [*Shulman* 2010]. These findings are comparable to those of previous studies on dance-based activities where the dance group exhibited a reduction in the UPDRS-III that exceeded the abovementioned CID [*Sharp* 2014].

Following the intervention, significant improvements in cardiovascular fitness were observed in the BS group. The distance that participants in the BS groups could cover during the 6MWT increased by 239.5 meters, greatly exceeding the cut-off for a minimal detectable change (MDC) for this outcome, which has been previously established as a change of at least 82 meters [*Steffen* 2008]. Improved fitness and aerobic capacity are expected findings when reconditioning protocols such as treadmill training [*Mehrholz* 2015; *Bryant* 2016] or Nordic walking programs [*van Eijkeren* 2008] are employed, but improvements in fitness and aerobic capacity were a novel finding following a dance protocol. Significant improvements in postural stability (+6.9 points on the BBS score) which surpassed the MDC for IwPD (+5.9 points) [*Steffen* 2008] were also observed in the BS group. This finding is in line with results from a previous study depicting a close relationship between increased walking distance and decreased risk of falls [*Falvo* 2009].

Spatio-temporal dimensions of gait such as gait speed, stride length, and cadence improved following participation in the BS intervention. In particular, walking speed (which is regarding by many experts as the best predictor of disability severity and functional decline in PD [*Middleton* 2015]), increased significantly during the dance intervention. Clinically, the degree to which walking speed changed during the

intervention (+0.10 m/s) can be interpreted as a small- to moderate-change according to cut-points outlined by Hass *et al.* (small= +0.06 m/s; moderate= +0.14 m/s; large= +0.22 m/s) [*Hass* 2014]. Analysis of gait in our study also included an assessment of gait fatigue index (GFI), which is widely recognized as an integral part of the spectrum of motor impairments associated with PD, reflecting both central and peripheral impairments, along with the functional deterioration induced by the disease [*Chaudhuri* 2004]. Accordingly, while GFI worsened in the control group, GFI showed a trend towards improvement following the BS training. However, given that the differences in GFI were only statistically significant in the control group (who worsened), the role that dance-based activities may have had in countering the neuromuscular fatigue observed in IwPD warrants careful interpretation.

Results of the study found that dynamic strength in the lower limbs increased significantly following participation in the BS dance program, while the control group, which was not given the dance-based intervention, exhibited significant worsening, reflecting the neurodegenerative nature of PD [*Poewe* 2010], which impacts muscle strength as well [*Yazar* 2018]. In addition, participants in the BS group showed significant improvements in mobility in the upper body (assessed by BST), displaying a significant Time*Group interaction, while no difference was detected in participant's lower body flexibility (assessed by SRT). This finding likely suggests the need to integrate additional phases of stretching for the lower body into the BS dance intervention, which are targeted specifically by this form of dance. Walking ability and functional mobility also improved following BS, with potential practical implications in reducing falls, although results of the TUG test did not reach the MDC recognized for this outcome (-1.82 s against a MDC of -4.85 s) [*Dal Bello-Haas* 2011]. Several studies have highlighted how physical activity and structured exercise programs can improve non-motor symptoms [*Nocera* 2013; *Cusso* 2016] , as we also previously observed following Nordic walking and adapted physical activity programs [*Cugusi* 2015b; *Cugusi* 2017]. In this line and in addition to our previous research, this study revealed

a significant reduction of depressive symptoms at large ESs, suggesting a possible clinical relevance. With regards to apathy score (which we assessed using the SAS), we only observed a trend towards improvement in participants who took part in the BS program, while apathy scores in the control group worsened significantly. This, in turn, resulted in significant between-group differences which likely inflated our findings and require cautious interpretation.

Finally, findings from this study are in line with previous evidence showing how practicing non-conventional forms of dance-based activity may lead to enhanced cognitive performance [*Hashimoto* 2015; *de Natale* 2017]. Indeed, in the study by De Natale *et al.* [*de Natale* 2017] found that a 10-week program of Argentine tango had a positive impact on cognitive domains and improved executive function (assessed by the Trail Making Test), while Hashimoto *et al.* [*Hashimoto* 2015] found that after 12 weeks of dance-based exercise, participants displayed significant improvements in task switching and mental flexibility (assessed by the Frontal Assessment Battery and the Mental Rotation Task response time), supporting the concept that non-conventional dance-based activities may influence higher cortical functions as well.

Taken together, all these factors may help explain the global effects that the physical workout of BS exerted on our cohort of IwPD.

4.2.4.1 Study limitations and future perspectives

Considering the exploratory nature of this pilot trial, the findings presented here should be interpreted carefully, especially in relation to the type of control group that was utilized here. Indeed, our controls did not perform any specific type of exercise program and maintained their usual medical therapy and habitual activity during the entire intervention protocol.

In future studies, BS dance may be compared to already established exercise training programs and other dance-based activities such as the Argentine tango, for which a

considerable body of knowledge is available regarding its effects on disability, independence, and QOL for IwPD. In addition, these results open the door for new comparisons between different exercise-based programs and innovative social-engagement activities, which would be intriguing to pursue.

4.2.5 Conclusions

Results of our study showed that IwPD who participated in a dance-based BS program displayed significant improvements in a variety of domains, ranging from clinical and functional performance to gait and non-motor symptoms. Incorporating socially-engaging forms of exercise into the clinical management of PD may improve participation and compliance with exercise-based interventions among IwPD, benefiting their overall functioning and, subsequently, QOL. In addition, since in our study, the control group experienced significant changes (worsening in the majority of cases) due to the natural progression of PD, the BS intervention may be also viewed as an enjoyable and safe tool for contrasting the impairments observed in the PD population due to the intrinsic neurodegenerative nature of the disease.

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Chapter 5

Objective measures to investigate turning impairments and freezing of gait in people with Parkinson's disease[*]

[*] This chapter is based on **M. Bertoli**, A. Cereatti, U. Della Croce, and M. Mancini, "**An objective assessment to investigate the impact of turning angle on freezing of gait in Parkinson's disease**," *IEEE Biomed. Circuits Syst. Conf.* (2017) and on **M. Bertoli**, U. Della Croce, A. Cereatti, M. Mancini, "**Objective Measures to Investigate Turning Impairments and Freezing of Gait in People with Parkinson's Disease**" – *Gait&Posture*.

Abstract

Turning is impaired in Parkinson's Disease subjects (PD) and it is a common trigger for freezing of gait (FoG). FoG is often described as a sudden inability to continue the forward walking progression. Recent evidence suggests that PD subjects who freeze, i.e. freezers (PD+FoG), have worse turning performance than non-freezers (PD-FoG), and this is exacerbated by increasing the turn angular amplitude.

We therefore investigated the difference in objective measures for turning 180 degrees while walking (U-turn) versus turning 360 degrees in place in PD+FoG compared to PD-FoG, and how this difference was affected by a dual task. Quantitative turning measures and their dual task cost were computed, and differences were investigated between groups (PD+FoG/PD-FoG) and within turning tasks (180° while walking/360° in place) using ANOVA. Objective measures in PD+FoG were compared across turns with actual FoG episodes and those without. Associations between turn measures and clinical scales were examined with Spearman correlations.

Turn duration and number of steps were greater, and peak angular velocity slower, in freezers compared to non-freezers ($p<0.001$). Turn duration, number of steps and jerk were greater, and anteroposterior range smaller, in the 360° turn in place compared to the 180° turn while walking in both groups. Turn duration and number of steps showed significant interaction ($p<0.01$). Dual task costs were similar across groups, but turn duration showed significant interaction ($p=0.03$). Turning characteristics in trials with observed FoG were similar to trials with no FoG when turning while walking, but not for turning in place. PIGD subscore in non-freezers was correlated with all turn measures; whereas in freezers PIGD was correlated with turn measures in turning while walking but only with turn duration for turning in place. UPDRS III in non-freezers was correlated with turn duration and number of steps in turning in place, while in freezers it was correlated with turn duration, peak velocity and jerk in turning while walking.

Turn measures (duration and number of steps) revealed quantitative differences for freezers, who, with respect to non-freezers, showed more impairments in 360 degrees turning in place but not in 180 degrees turning while walking. However, as the turning challenges were increased by adding a dual-task, results from freezers were similar to those from non-freezers.

Significant differences between the two groups across the two turning tasks validated the hypothesis that sharper turns might cause higher instability in freezers compared to non-freezers.

5.1 Introduction

Freezing of gait (FoG), a sudden and transient failure to initiate or maintain locomotion [*Nutt* 2011], is one of the most disabling features in Parkinson's Disease (PD). FoG can be described as the "absence or marked reduction of the forward progression of the feet, despite the intention to walk" [*Nutt* 2011]. It is associated with increased risk of falls, it interferes with daily activities and it substantially affects quality of life [*Moore* 2007]. FoG is an episodic phenomenon of still controversial pathophysiology, and the episodes are usually triggered by specific situations, for example turning, walking through narrow passages, crossing busy streets, initiating walking, approaching a destination [*Giladi* 2008; *Snijders* 2012]. In particular, it has been shown that turning may be the most effective task in provoking FoG [*Snijders* 2008]. In fact, turning is a challenging motor task, requiring a coupling between anticipatory postural adjustments and scaling of walking [*Nutt* 2011].

Besides specific motor tasks, another common trigger for FoG is the presence of a concurrent cognitive task while walking or turning, often referred as dual-tasking (DT). In fact, the addition of a concurrent cognitive task has been found to further impair the motor performance in PD subjects with FoG (PD+FoG) compared to PD subjects who do not experience FoG (PD-FoG) [*Morris* 2001]. In this respect, recent

studies showed that the DT cost for stride length, cadence and gait speed during straight walking was significantly increased in PD+FoG compared to PD-FoG. [*Camicioli* 1998; *Spildooren* 2010; *Earhart* 2013; *Peterson* 2016; *de Souza Fortaleza* 2017]. However, the impact of DT on turning in PD+FoG is still controversial.

Spildooren et al. [*Spildooren* 2010] found a significant effect of DT on the number of FoG episodes only in PD+FoG during a 360 degrees turning task, while DeSouza et al. [*de Souza Fortaleza* 2017] did not find any significant interaction between condition (ST/DT) and group (PD+FoG/PD-FoG) for duration and peak speed during a 180 degrees turn.

Since in laboratory settings FoG episodes occur more rarely [*Jankovic* 2008; *Nutt* 2011; *Snijders* 2012], motor tasks including turning while walking or turning in place are often used in the clinic to elicit FoG episodes. Specifically, it has been described that while walking sharper turns characterized by smaller turning radii and greater angular amplitude tend to elicit more freezing episodes compared to turns at smaller angles [*Spildooren* 2010; *Bhatt* 2013]. Specifically, Snijders and colleagues, and Mancini and colleagues, showed that repeated 360 degrees turns in place were more effective in eliciting FoG compared to 180 degrees turns during walking [*Snijders* 2012; *Mancini* 2017]. A recent systematic review focusing on the differences in turning between PD+FoG and PD-FoG highlighted that PD+FoG in general tend to turn with longer turn duration, slower turn peak velocity, increased number of steps and higher cadence compared to PD-FoG [*Spildooren* 2018]. In addition, the review also highlighted that differences in turning between PD+FoG and PD-FoG are exacerbated by increasing the turning angular amplitude [*Spildooren* 2018]. However, due to differences in set-up among studies, it is still unclear whether a 360° turn in place would increase FoG occurrences compared to a 180° turn while walking. Furthermore, small evidence exists on which characteristics of turning and which kind of turn would differ the most among PD+FoG and PD-FoG.

Wearable inertial sensors have increasingly been used for instrumented clinical evaluations to gather additional insights on motor control. In this context, the assessment of turning tasks by means of inertial sensors allows obtaining quantitative outcomes and investigating complex locomotor patterns [*Della Croce* 2017].

Several studies ([*Visser* 2007; *Zampieri* 2010; *Bhatt* 2013; *Bengevoord* 2016; *Mancini* 2017]) demonstrated that objective measures from a turning task can differentiate between PD patients and healthy controls, and highlighted the need for further research to focus on the clinical relevance of such measures. In particular, as also suggested in Visser et al., it would be interesting to correlate yaw angular velocity during turning to clinical measures as those for FoG, as this approach might be useful to evaluate the outcome of intervention studies aimed at improving FoG [*Visser* 2007]. Furthermore, investigating the underlying mechanism of FoG is important to advice an effective rehabilitation intervention.

To this purpose, we developed and applied a method, based on the use of inertial sensors, to perform a quantitative gait analysis in presence of 180° and 360° turns in PD+FoG and PD-FoG, and compared the outcome across turning task and populations.

As turning is thought to require more coupling of posture and stepping, and more cognitive control compared to straight ahead gait [*Herman* 2011; *King* 2012; *Peterson* 2016], we hypothesize that turning in place at a large angular amplitude with a cognitive challenge would be more difficult for PD+FoG than for PD-FoG, and in the PD+FoG group it would elicit more FoG. Therefore, our aims were: 1) to quantify how turning characteristics change between 180° turning while walking and 360° turning in place in PD+FOG and PD-FOG, 2) to determine whether a concurrent dual task similarly impacts the two different turning tasks in PD+FoG and PD-FoG.

5.2 Material and Methods

5.2.1 Participants

Forty-two subjects with PD and 43 healthy elderly controls were recruited through the Parkinson's Center of Oregon clinic at Oregon Health & Science University (OHSU). Based on the first question of the New FoG Questionnaire (NFOG-Q) [*Nieuwboer* 2009] -"Have you experienced FoG in the past month?"- PD subjects were divided in two groups. Twenty-four (19M, 5F) answered 'yes' and were classified as freezers (PD+FoG), while eighteen (14M, 4F) answered no, and were assigned to the non-freezers (PD-FoG) group. Subjects' characteristics and clinical scores are reported in Table 5-1.

Table 5-1 Subjects characteristics in Parkinson's disease freezers (PD+FoG) and non-freezers (PD-FoG) and healthy controls (Mean±STD)

	Controls	PD-FOG	PD+FOG
Age (years)	68.8±6.2	70.3±6.8	69.2±7.1
Gender	33M 10F	14M 4F	19M 5F
NFoG - Q (score)		-	16.5±6.0
Disease Duration (years)		7.7±4.3	8.7±6.2
MDS-UPDRS III		43.6±11.3	45.8±12.1
PIGD subscore		3.8±2.5	7.6±3.7
MoCA		26.2±3.3	24.9±4.9

Inclusion criteria were: diagnosis of idiopathic PD with sensitivity to levodopa and off-medication Hoehn & Yahr scores of II-IV. Exclusion criteria: Other factors affecting gait (hip replacement, musculoskeletal disorder, uncorrected vision or vestibular problem), or an inability to stand or walk for 2 minutes at a time. Individuals were also excluded if they could not safely walk 20 feet without walking aids, or if they had dementia, severe tremor, or metal in their bodies (another aspect of this study included neuroimaging).

All participants provided informed written consent to a protocol approved by OHSU's Institutional Review Board.

5.2.2 Experimental Setup

All the participants with PD were tested in the practically defined OFF state (after withdrawing their antiparkinsonian medication for at least 12 hours). A trained examiner administered the motor section (III) of the MDS-UPDRS [*Goetz* 2008] to rate disease severity. The Posture Instability and Gait Disability (PIGD) subscore was also calculated from the MDS-UPDRS Part III [*Stebbins* 2013]. The Montreal Cognitive Assessment (MoCA) was used to assess general cognition [*Nasreddine* 2005], and the perceived severity of FoG was recorded by means of the NFOG-Q [*Nieuwboer* 2009].

Participants performed a series of motor tasks while wearing three inertial sensors (Opals - APDM, Inc.) positioned on both feet (dorsally) and on the back (approximately at the level of L5). Each individual was asked to perform the following two motor tasks:

- 180° turning while walking (U-turn), as part of a two minutes long walk. The subjects walked straight for 7 meters at a comfortable speed, turned back and kept walking in the opposite direction. No indications were given about direction of turning or strategy.

- 360° turning in place. Starting from a standing position, subjects turned 360° clockwise, and then 360° counter-clockwise, repeating this sequence for one minute.

The two turning tasks were then repeated in a dual task (DT) condition, i.e.: with an added concurrent cognitive task. The concurrent dual task consisted in repeating the alphabet skipping one letter (A, C, E, etc.) during the turning while walking, and in serial subtractions by 3 s for the turning in place. In the DT condition, no instructions were given on whether to pay more attention to the motor or cognitive task.

The reference frame of the inertial sensor was oriented approximately along the three human body anatomical directions. An estimate of its orientation with respect to the global frame was provided by an on-board Kalman filter. The signals from the Opal

sensors were recorded at 128 Hz, streamed wirelessly to a laptop and stored for subsequent offline analysis with Matlab (MathWorks. R2016a).

5.2.2.1 Data Analysis

Inertial sensor data were automatically segmented to detect turns. To this purpose, two different algorithms were implemented to identify the 180° and 360° turns.

For the 180° turns, the algorithm was based on previous work from [*El-Gohary* 2013]. The angular velocity was expressed in the global coordinate system and its vertical component low pass filtered (Butterworth, 1.5 Hz cutoff frequency). The offset was then removed (by subtracting the mean of the signal during the first 3 seconds, during which the subject was standing still). Candidate turns were detected as vertical angular velocity peaks higher than 15°/s, and for each peak the preceding and following 5°/s threshold crossing were set as instants of turn beginning and ending. Additional checks were performed on the candidate turns in order to isolate the 180° turn. First of all, turns in the same direction separated by less than 0.1 s were merged. Then, turns lasting less than 0.5 s or more than 10 s were discarded. Finally, the relative turn angle was computed integrating the vertical angular velocity over the turn duration and, when resulting less than 45°, lead to the turn elimination.

For the 360° turns, a novel algorithm was implemented based on an approach exploiting local magnetic field inversion and angular velocity [*Bertoli* 2016]. The two planar components (AP and ML) of the magnetometer signals were low pass filtered (Butterworth, 1 Hz cutoff frequency), and their sum was computed. The mean value computed during the first 3 s from this composed signal was removed, and a moving average (windows length 0.5 s) was used for smoothing. Prototype turns were detected as peaks higher than 70% of the signal max value and further apart than 3 s, and for each peak the preceding and following 20% threshold crossing were used to isolate the turn. For each prototype turn, the zero-crossings of the filtered, offset-free vertical

angular velocity were used as turn beginning and ending instants. An additional control was performed in case of an incorrect merging of two consecutive turns: the turning angle was computed integrating the vertical angular velocity absolute value over the turn duration and, when resulting greater than 400°, lead to the turn division.

For the first turn in each trial (see example in Figure 5-1), the following quantitative measures were computed: Turn Duration, Peak angular Velocity, Number of Steps, Jerk and Range of Acceleration. Specifically, turn duration (s) was measured as the time interval from the beginning to the ending of the turn. Turn peak velocity (°/s) was defined as the vertical angular velocity maximum peak amplitude. Number of steps was computed from peaks in the vertical acceleration recorded at the feet. Turn jerk (integrated squared jerk, m^2/ s^5), integral of the squared time derivative of the linear acceleration, was used to quantify fluidity of turning in both anteroposterior (AP) and mediolateral (ML) directions. Turn range (m/s^2) was also computed for both ML and AP accelerations.

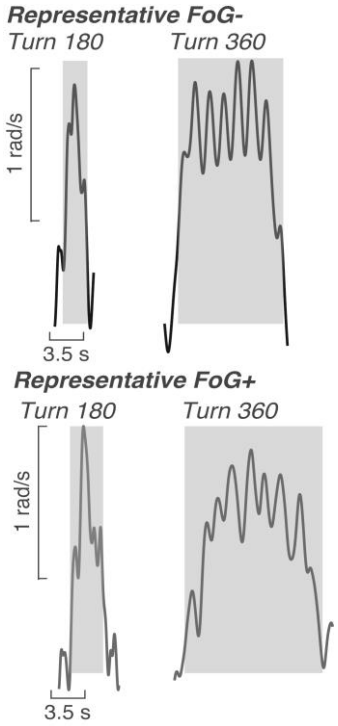

Figure 5-1 Time series of trunk angular velocity profiles during the 180 and 360 turning tasks in a PD-FoG (upper panel) and a PD+FoG (lower panel). In PD+FoG the time needed to complete the turns is longer than in PD-FoG.

The dual-task cost (DT cost) was calculated as DT cost [%] = 100* (DT turning measure – ST turning measure)/ST turning measure.

The video recordings of the trials were reviewed by an expert examiner to determine the occurrence of freezing episodes during turning.

The data from the 43 healthy controls were used as reference and not statistically compared with the two PD groups.

A two-way (groups×turn) repeated measures analysis of variance (ANOVA) was used to investigate the difference in the measures between groups (PD+FoG/PD-FoG) and within turning tasks (180° while walking/360° in place). Since turn jerk, turn duration and step number distributions were not normal, for the ANOVA analysis they were transformed into logarithmic scale. Similarly, a two-way ANOVA was used to investigate the difference in the measures DT cost between groups (PD+FoG/PD-FoG) and within turn tasks (180° while walking/360° in place). In addition, turning measures obtained in trials with observed FoG were compared to those obtained in trials without FoG episodes by means of a t-test (for all turning tasks except for 360° in place dual task condition, due to unbalanced distributions).

Non-parametric (Spearman) correlations were performed to investigate the associations between objective measures of turning and clinical scales. Statistical significance was set at $p<0.05$. SPSS (IBM V.23) was used to run statistical analyses.

5.3 Results

Figure 5-2 and Figure 5-3 represent the mean and SEM of the objective measures in the single task condition and of their dual task cost.

Table 5-2 and Table 5-3 summarizes the ANOVA results for the turn measures, significant differences ($p<0.05$) are indicated in bold.

The increase in turn duration and number of steps for turning in place compared to turning while walking was significantly larger in freezers compared to non-freezers.

Turn duration was longer for the 360° turning in place compared to the 180° turning while walking in both PD+FoG and PD-FoG (significant turn effect: F=159.22, p<0.001). PD+FoG took a longer time to complete both the turnings compared to PD-FoG (group effect: F=18.62, p<0.001). In addition, the turn duration increase from turning while walking to turning in place was larger for PD+FoG compared to PD-FoG with a significant interaction effect (F=6.68, p=0.01).

The number of steps showed similar significant results: - there was a significant difference between groups (F=19.38, p<0.001) with PD+FoG taking more steps compared to PD-FoG; - a significant difference in turning task (F=159.23, p<0.001), with the turning in place requiring more steps than that while walking; and – an interaction effect (F=9.37, p<0.001), PD+FoG required significantly more steps in the 360° turning in place than that while walking compared to PD-FoG.

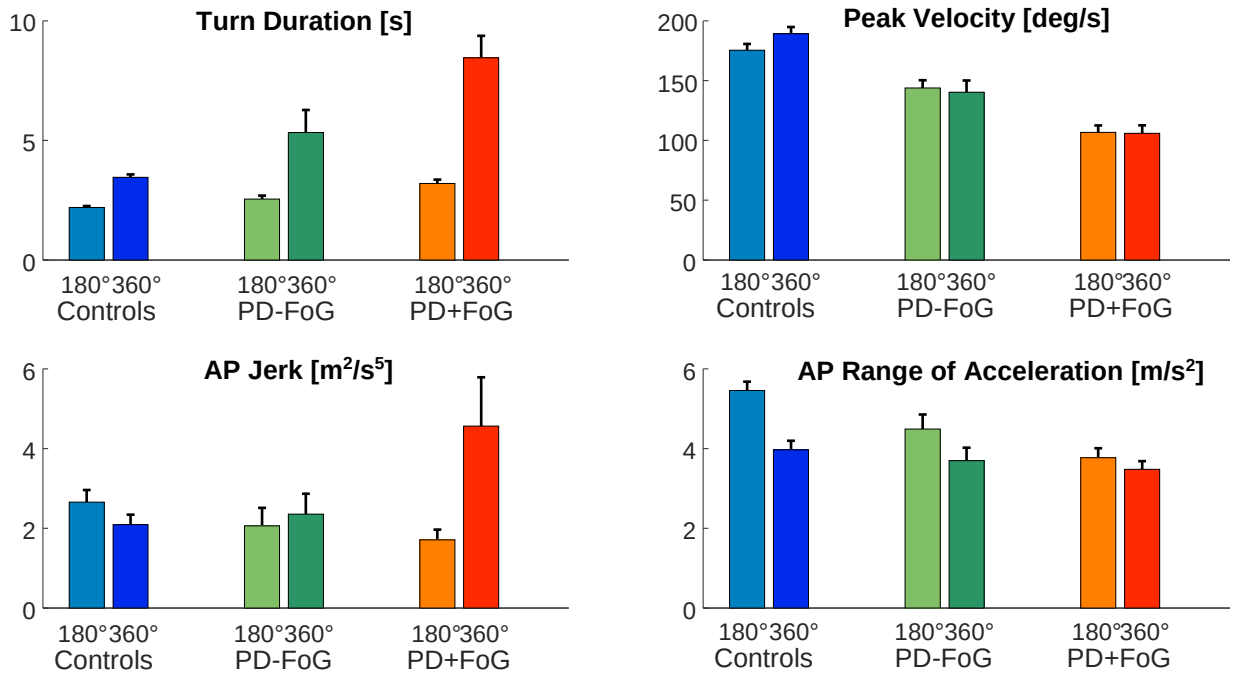

Figure 5-2 Mean and SEM of the objective measures in the single task condition for healthy controls, non-freezers (PD-FoG) and freezers (PD+FoG)

Turn peak velocity was similar for the turning in place compared to the turning while walking, however it was significantly slower in freezers compared to non-freezers.

In general, turn peak velocity was higher for controls and lower for PD+FoG. PD+FoG used a lower peak velocity to perform both the turnings compared to PD-FoG (group effect: $F=14.67$, $p<0.001$).

The range of acceleration while turning showed difference on the type of turn, but not between groups.

The anteroposterior range of acceleration while turning was similar in PD-FoG and PD+FoG ($F=2.69$, $p=0.11$), however it was significantly lower for the turning in place compared to that while walking ($F=7.87$, $p=0.01$). Similarly, the mediolateral range of acceleration while turning was similar in PD-FoG and PD+FoG and, even if for PD+FoG it was larger in turning in place than while walking, there was no statistically significant interaction ($F=0.30$, $p=0.59$).

Turn jerk was higher for turning in place compared to turning while walking, but was similar among freezers and non-freezers.

Turn jerk was similar across groups, but increased from turning 180° while walking to turning 360° in place both in anteroposterior ($F=5.08$, $p=0.03$) and mediolateral direction ($F=29.12$, $p<0.001$). A greater increase from turning while walking to turning in place in PD+FoG compared to PD-Fog almost reaches statistical significance for anteroposterior ($F=3.62$, $p=0.07$) jerk, but not for mediolateral ($F=1.17$, $p=0.29$) jerk.

Table 5-2 Turn objective measures in Parkinson's Disease subjects with (PD+FoG) and without (PD-FoG) freezing of gait during single task condition.

		180° turn while walking	***360° turn in place***	**Group**		**Turn**		**Interaction**	
		Mean±sd	Mean±sd	F-value	p-value	F-value	p-value	F-value	p-value
Turn Duration (s)	PD-FOG	2.55±0.58	5.33±3.88	18.62	***0.00***	159.22	***0.00***	6.68	***0.01***
	PD+FOG	3.20±0.75	8.45±4.22						
Number of Steps (N)	PD-FOG	5.24±1.18	9.92±3.40	19.38	***0.00***	159.23	***0.00***	9.37	***0.00***
	PD+FOG	6.41±1.31	19.48±10.00						
Peak Velocity (degrees/s)	PD-FOG	143.87±26.18	140.30±40.87	14.67	***0.00***	0.01	0.91	0.28	0.60
	PD+FOG	106.77±26.61	106.03±30.62						
ML Range (m/s^2)	PD-FOG	5.31±1.64	5.09±1.81	0.01	0.94	0.01	0.94	0.30	0.59
	PD+FOG	5.14±1.52	5.45±1.78						
AP Range (m/s^2)	PD-FOG	4.49±1.46	3.70±1.34	2.69	0.11	7.87	***0.01***	0.41	0.52
	PD+FOG	3.77±1.09	3.48±0.94						
ML Jerk (m^2/s^5)	PD-FOG	3.43±2.72	6.05±5.90	0.80	0.38	29.12	***0.00***	1.17	0.29
	PD+FOG	4.01±3.74	9.58±9.36						
AP Jerk (m^2/s^5)	PD-FOG	2.06±1.80	2.36±2.12	0.34	0.56	5.08	***0.03***	3.62	0.07
	PD+FOG	1.71±1.17	4.57±5.60						

Table 5-3 Turn objective measures' dual task cost in Parkinson's Disease subjects with (PD+FoG) and without (PD-FoG) freezing of gait.

		180° turn while walking	***360° turn in place***	**Group**		**Turn**		**Interaction**	
		Mean±sd	Mean±sd	F-value	p-value	F-value	p-value	F-value	p-value
Turn Duration (s)	PD-FOG	13.76±22.03	23.69±22.96	0.85	0.36	16.97	***0.00***	4.97	***0.03***
	PD+FOG	8.01±19.06	53.86±70.00						
Number of Steps (N)	PD-FOG	3.84±15.94	20.78±28.71	0.06	0.81	8.76	***0.01***	0.47	0.50
	PD+FOG	4.00±27.10	26.24±35.60						
Peak Velocity (degrees/s)	PD-FOG	-6.78±13.29	-14.01±11.65	0.68	0.42	12.19	***0.00***	3.43	0.07
	PD+FOG	-4.42±19.67	-21.84±20.30						
ML Range (m/s^2)	PD-FOG	-6.47±16.96	-8.71±11.64	0.41	0.53	2.83	0.10	0.74	0.40
	PD+FOG	-8.31±17.65	-14.14±26.55						
AP Range (m/s^2)	PD-FOG	-6.87±24.47	-8.89±16.74	0.40	0.53	0.49	0.49	0.20	0.66
	PD+FOG	-7.88±36.65	-15.24±18.81						
ML Jerk (m^2/s^5)	PD-FOG	-0.54±33.45	5.56±52.92	0.07	0.80	0.01	0.91	0.08	0.77
	PD+FOG	1.73±56.30	3.36±56.60						
AP Jerk (m^2/s^5)	PD-FOG	-19.54±27.06	5.44±46.87	0.24	0.63	2.13	0.15	0.01	0.92
	PD+FOG	-1.14±92.93	6.62±58.06						

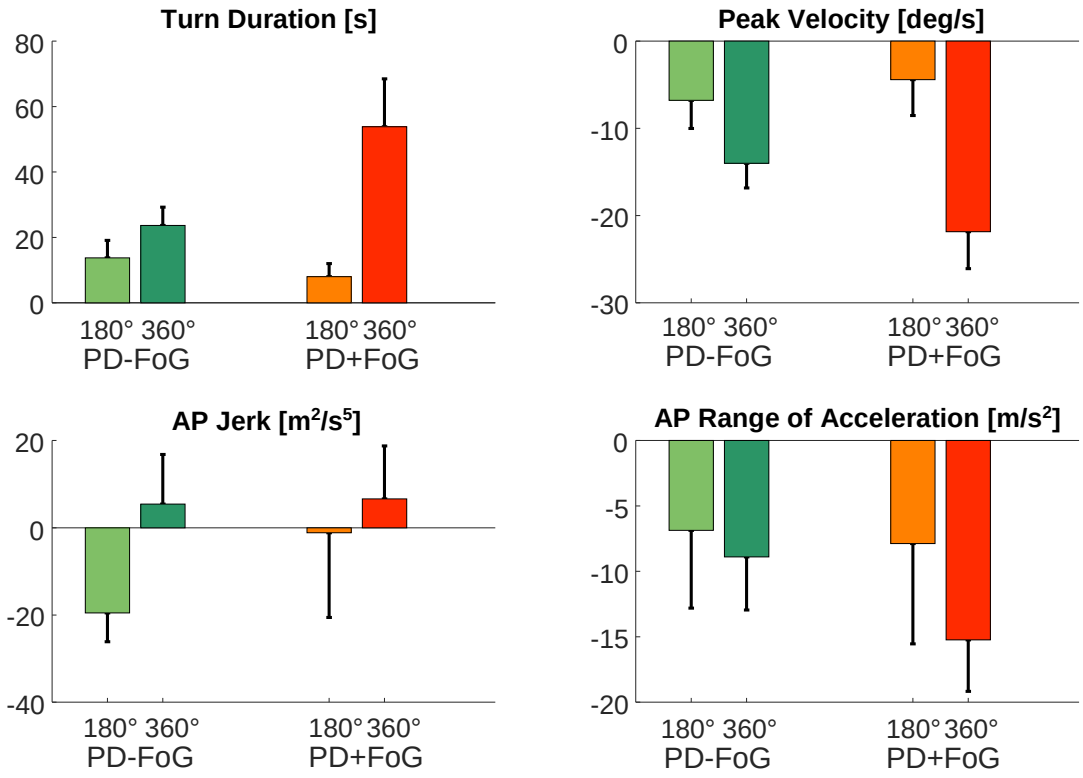

Figure 5-3 Mean and SEM of the objective measures' dual task cost for non-freezers (PD-FoG) and freezers (PD+FoG)

DT cost was similar in freezers compared to non-freezers.

The DT cost of turning duration, steps number, and turning peak velocity showed a significant condition effect: both PD+FoG and PD-FoG took longer time, a higher number of steps, and slower peak velocity for 360° turning in place compared to 180° turning while walking (Table 5-3). In addition, only the DT cost of turn duration revealed a significant interaction effect ($F=4.97$, $p=0.03$), meaning that the increase in DT cost from turning while walking to turning in place was larger in PD+FoG compared to PD-FoG.

Disease severity, characterized by the MDS-UPDRS III, showed limited associations with the objective measure of turning, while the PIGD subscore was strongly associated with the majority of turning measures.

Figure 5-4, Figure 5-5 and Figure 5-6 summarize the correlation results.

In the PD-FoG group, the MDS-UPDRS III was not correlated to any measure for the turning while walking task; while a higher (worse) MDS-UPDRS III was associated with longer turn duration and greater number of steps for the turning in place in place task ($r>0.55$, $p<0.02$). In the PD+FoG group, a higher (worse) MDS-UPDRS III was associated with lower turn peak velocity, higher turn duration, lower mediolateral and anteroposterior jerk and smaller mediolateral range of acceleration for turning while walking ($r>0.44$, $p<0.04$); while it was not correlated to any measure in the turning in place task.

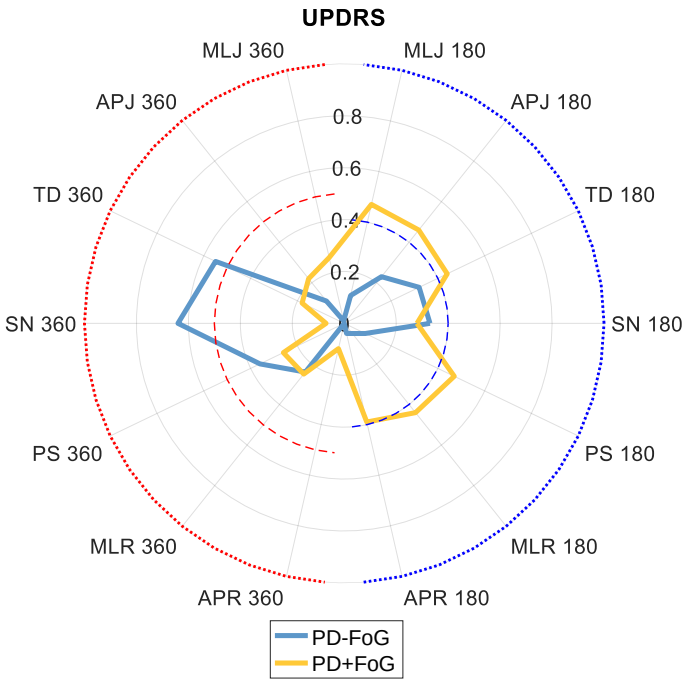

Figure 5-4 Spearman correlations (ρ in absolute value) of UPDRS with the turning measures during 180° turn while walking (blue, on the right) and 360° turn in place (red, on the left) for PD-FoG and PD+FoG. Dashed semi-circle delimit significance ($p<0.05$). MLJ, APJ: ML, AP Jerk. TD: Turn Duration. SN: Number of Steps. PS: Peak Velocity. MLR, APR: ML, AP Range of Acceleration.

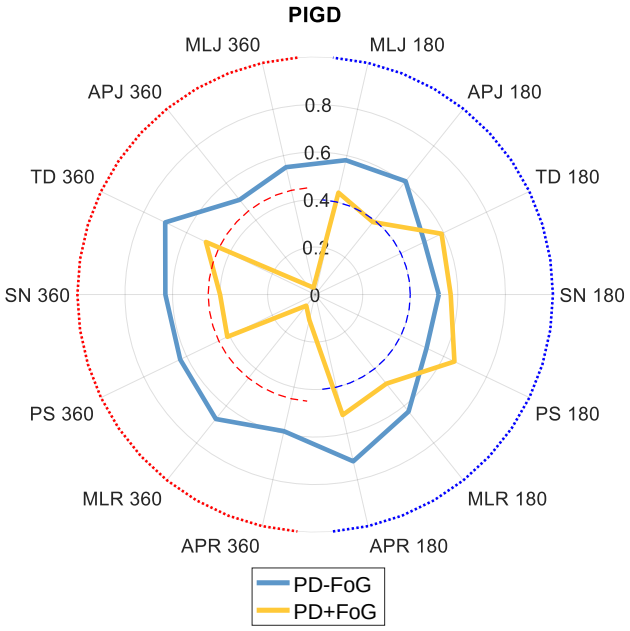

Figure 5-6 Spearman correlations (ρ in absolute value) of PIGD with the turning measures during 180° turn while walking (blue, on the right) and 360° turn in place (red, on the left) for PD-FoG and PD+FoG. Dashed semi-circle delimit significance (p<0.05). MLJ, APJ: ML, AP Jerk. TD: Turn Duration. SN: Number of Steps. PS: Peak Velocity. MLR, APR: ML, AP Range of Acceleration.

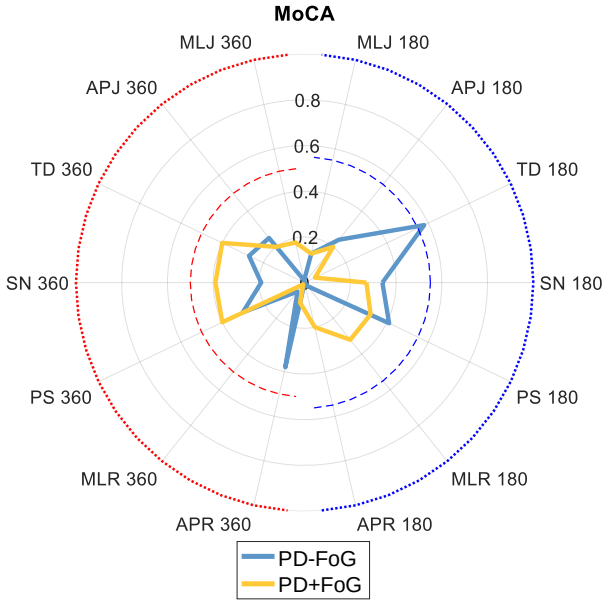

Figure 5-5 Spearman correlations (ρ in absolute value) of MoCA with the turning measures during 180° turn while walking (blue, on the right) and 360° turn in place (red, on the left) for PD-FoG and PD+FoG. Dashed semi-circle delimit significance (p<0.05). MLJ, APJ: ML, AP Jerk. TD: Turn Duration. SN: Number of Steps. PS: Peak Velocity. MLR, APR: ML, AP Range of Acceleration.

In the PD-FoG group, the PIGD subscore was correlated to all the turning measures ($r>0.51$, $p<0.04$) for both the turning tasks; specifically, a higher PIGD subscore was associated with longer turn duration, greater number of steps, and lower turn peak velocity, jerk and range of acceleration. Instead, in the PD+FoG group, a higher PIGD subscore was significantly associated to longer turn duration, greater number of steps, lower turn peak velocity, smaller range of anteroposterior and mediolateral acceleration and lower mediolateral jerk in the turning while walking task ($r>0.44$, $p<0.04$); while it was associated with turn duration only for the turning in place ($r=0.51$, $p=0.02$).

Finally, in the PD-FoG group, a higher MoCA score was significantly associated with a longer turn duration for the turning while walking task ($r=0.58$, $p=0.02$); while it was not correlated to any measure in the turning in place task.

The disease duration was not associated to any turning measure.

Turning characteristics in trials with observed FoG were similar to trials with no FoG when turning while walking, but not for turning in place.

Table 5-4 summarizes the t-test results for the turn measures in PD+FoG with and without observed FoG, significant differences ($p<0.05$) are indicated in bold.

During the turning while walking task, 6 out of 23 individuals in the PD+FoG group showed freezing in the single-task condition and 8 out of 23 showed freezing in the dual-task condition. One participant did not allow video recordings, therefore videos from that participant were missing.

The turning measures were similar in the trials with and without observed FoG.

During turning in place, freezing was observed in 15 PD+FoG in the single-task conditions and in 19 for the dual-task. For the single task turning in place, the number of steps, but not the turn duration, was significantly larger in trials with observed FoG than in trials without FoG episodes ($p=0.01$). Also the mediolateral range of

acceleration (p=0.02) and the mediolateral and anteroposterior jerk (p=0.02 and p=0.04, respectively) were greater for trials with observed FoG.

Table 5-4 Turn objective measures in Parkinson's Disease subjects with freezing of gait: comparison across trial with and without actual freezing episode

		180° turn while walking Single Task			*180° turn while walking Dual Task*			*360° turn in place Single Task*		
	Freez episode	Mean±sd	t	p	Mean±sd	t	p	Mean±sd	t	p
Turn Duration (s)	yes	3.41±1.09	0.52	0.62	3.51±0.47	0.48	0.64	10.05±4.89	1.92	0.07
	no	3.14±0.67			3.36±0.90			6.68±2.95		
Number of Steps (N)	yes	7.50±1.58	1.74	0.14	7.75±2.52	1.39	0.21	24.71±10.82	3.17	***0.01***
	no	6.20±0.94			6.18±1.72			13.25±5.18		
Peak Velocity (degrees/s)	yes	99.58±17.24	-0.89	0.39	87.49±12.59	-1.83	0.08	100.35±35.96	-0.80	0.43
	no	109.43±30.86			105.08±30.35			111.85±28.04		
ML Range (m/s^2)	yes	5.07±0.85	0.12	0.91	4.34±1.07	-0.24	0.82	6.05±2.00	2.50	***0.02***
	no	5.00±1.79			4.48±1.48			4.33±1.07		
AP Range (m/s^2)	yes	2.96±0.81	-1.97	0.08	2.88±0.94	-1.10	0.29	3.74±1.02	1.98	0.06
	no	3.86±1.05			3.42±1.16			2.95±0.77		
ML Jerk (m^2/s^5)	yes	3.80±0.70	-0.10	0.92	4.13±3.21	0.83	0.43	13.53±11.07	2.63	***0.02***
	no	3.92±4.65			2.89±2.55			4.12±4.53		
AP Jerk (m^2/s^5)	yes	1.45±0.58	-0.73	0.47	1.66±2.13	0.31	0.77	6.67±6.97	2.26	***0.04***
	no	1.77±1.41			1.39±0.84			1.79±2.24		

5.4 Discussion

The aim of this study was to quantitatively characterize, by means of wearable inertial sensors, 180° turning while walking and 360° turning in place in subjects with PD to investigate the impact of turning on FoG. Also, we investigated the changes in turning performance with the addition of a concurrent dual task while turning.

In both groups, as expected, turning 360° in place required longer time and a higher number of steps than turning 180° while walking, but interestingly similar peak velocity. The range of acceleration was similar in both turning tasks in the mediolateral direction, but greater for turning while walking in the anteroposterior direction compared to turning in place. In addition, turning jerk was greater during turning in

place compared to turning while walking in both the anteroposterior and mediolateral direction. While some of these differences were similar in PD-FoG and PD+FoG, turn duration and number of steps showed a significant interaction effect, demonstrating that PD+FoG showed further impairments when turning in place compared to turning while walking with respect to PD-FoG.

We also found that turning in place may require a greater cognitive effort compared to turning while walking, as indicated by the greater dual task cost for turn duration, number of steps and peak velocity performing the turning in place compared to turning while walking in both groups. Additionally, the increase in dual-task cost of turn duration (and almost in peak velocity) from turning while walking to turning in place was greater in PD+FoG compared to PD-FoG (interaction effects).

When summarizing differences between PD+FoG and PD-FoG we found that PD+FoG took generally longer time to turn, turned at slower peak velocity and needed more steps to complete a turn, but showed similar range of acceleration during turning and a tendency for higher jerk during turning compared to PD-FoG.

These findings are in keeping with other studies showing that PD+FoG have more difficulties during turning in place compared to turning while walking [*Spildooren* 2018]. Also, the greater increase in turning duration and number of steps from turning 180° while walking to turning 360° in place in freezers is consistent with previous findings [*Spildooren* 2010]. Such result may be due to the fact that the PD+FoG group showed more freezing episodes in the turning in place with respect to turning while walking, resulting in an increased turn duration and number of steps needed to complete the task. Turn duration also showed an interaction effect in the dual task cost condition, meaning that not only PD+FoG showed a significantly longer turn duration for the 360° turn in place compared to the 180° turn while walking compared to PD-FoG, but this trend was further confirmed when adding a cognitive task. This result supports our hypothesis that turning in place with a cognitive challenge would be more difficult in PD+FoG compared to PD-FoG.. In line with [*de Souza Fortaleza* 2017],

where for turn duration no interaction was found in turning 180° while walking between PD+FoG/PD-FoG groups and within single task/dual task conditions, in our results the dual task cost alone did not show a group effect.

As previously reported by De Souza et al [*de Souza Fortaleza* 2017], the peak velocity in 180° turn while walking was significantly lower in PD+FoG compared to PD-FoG. Also in 360° turn in place peak velocity was lower in PD+FoG compared to PD-FoG, in partial disagreement with [*Mancini* 2017], where this decrement did not reach significance, even though a trend can be observed. In contrast to our hypothesis, in the single task condition we did not find any interaction between group and turning task for peak velocity. This was rather unexpected, considering a lower turn mean velocity due to the longer turn duration, but we did not actually control for actual turn amplitude. However, also in [*Mancini* 2018] there was no significant interaction in peak velocity between PD+FoG/PD-FoG and within small-medium (40°-120°)/medium-large (120°-260°) turning angle amplitudes. Interestingly, we observed a greater decrease in turning peak velocity from turning 180° while walking to 360° in place in the DT condition in the PD+FoG group compared to the PD-FoG group, almost approaching significance for interaction effects ($p=0.07$). As for turn duration, also for peak velocity we did not find a group effect in the dual task cost, similar to [*de Souza Fortaleza* 2017] (no interaction between PD+FoG/PD-FoG and within ST/DT conditions).

Comparing the turning tasks, anteroposterior range of acceleration was greater in turning 180° while walking with respect to 360° in place for both groups. This could be due the intrinsic characteristics of the turn task, since in the turning while walking subjects may be preparing to walk forward exiting from the turn. The range of acceleration while turning were similar in the two groups for turning while walking and turning in place, as previously found by [*Mancini* 2018] for ML range. Similarly, [*Bengevoord* 2016] found that during a turning 180° while walking, neither the anterior nor the medial center of mass position were different between freezers and non-

freezers, probably meaning that the overall trajectory is the same in both groups. In addition, turning jerk was higher for the turning in place compared to the turning while walking task. No group effects were observed, even though, in the mediolateral direction, PD+FoG generally showed a higher jerk compared to PD-FoG. Mancini et al. [*Mancini* 2017] obtained a similar result considering the average turn jerk for a continuous two minutes turning in place. In [*Mancini* 2018], where turning in daily life was examined, jerk and range of acceleration also did not show any significant group x turn amplitude interaction, but an interaction effect emerged when analyzing the coefficients of variation. In the present study, we only analyzed the first turn to be more consistent across turning tasks, therefore we could not compute the coefficient of variation, which could provide further insights.

Subjects turning in place showed higher jerk compared to turning while walking, with a higher jerk in the mediolateral direction with respect to the anteroposterior one. A trend for greater increase in freezers from turning 180° while walking to 360° in place can be observed, suggesting that particularly freezer needs more adjustments in turning in place, having less control of the turn smoothness.

It has to be pointed out that, while in general dual task cost seems to be greater in freezers compared to non-freezers, for turn duration and peak velocity in turning 180° while walking it is lower. The lack of significant differences between groups could be because non freezers executed both motor and cognitive task with the same attention, while freezers instead prioritized the motor task and did worse in the cognitive one (not actively dual tasking in turning while walking).

Results from associations with clinical outcomes highlight that the PIGD – subscore that specifically describes the motor performance of gait (and posture) – was correlated to the turning measures for the PD-FoG group, but not as much for the PD+FoG one, especially in the turning in place task. This may suggest that while turning deficits are related to disease progression in PD-FoG, freezing is adding a different component to turning deficits not necessarily associated to disease progression.

The turning measures for the turning while walking were similar across trials with and without freezing episodes. Instead, we would have expected some difference, especially for the turn duration that we expected to be longer in those trials where freezing was observed. Adding the dual task lead to the same result. Only in the turning in place, which as in previous studies [*Snijders* 2012; *Mancini* 2017] results more provocative for FoG episodes, a difference in the turning measures emerges, suggesting that turning in place poses additional difficulties to turning while walking, specifically in those people who experience FoG.

A limitation to the present study is that, since we focused the analysis only on the first turn, we couldn't calculate a cognitive dual task cost for that limited time interval. Furthermore, the dual task paradigm employed in the two turning tasks was different, and may therefore have engaged subject's attention to a different extent.

5.5 Conclusion

Freezing of gait is a challenge to our understanding of the pathogenesis of gait disorders in PD patients. Recent evidence showed that freezing related turning deficits have both spatiotemporal and rotational motor control components, indicating a possible involvement of the vestibular system in freezing of gait. Objective measures are critical for investigating how turn performance differs across freezers and non-freezers, especially because the increasing number of MIMU-instrumented assessments of turning, both in the clinic and at home, is gaining attention, allowing for the study of complex locomotor patterns and the gathering of additional insights on motor control. Results from our study indicated interesting trends across freezers for turn measures, confirming their managing of the scaling from U-turn to 360 turn is impaired compared to non-freezers in terms of duration and steps utilized. However, contrarily to freezers attention disruption hypothesis, the higher motor cost due to an added cognitive task while turning was not exacerbated in freezers compared to non-

freezers. Further research should be undertaken on the dual task effect on postural transition, which from our data resulted similar for freezers and non-freezers.

By comparing the response of freezers and non-freezers in increasingly challenging motor task as turns at different angles, different approaches can be highlighted. These results emphasize the importance of investigating challenging motor conditions as turns in PD subjects suffering of freezing of gait for the study of its underlying mechanism.

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Chapter 6

Conclusion and future directions

MIMU technology has the potential to measure human gait with a level of accuracy and repeatability comparable to instrumented mats, with the added advantage of being wearable, with a very low impact on the patient, and capable of long time recordings. MIMUs are therefore suitable for continuous monitoring during daily life: in fact, advances in technology, along with appropriate methodologies, enable performing pervasive and ubiquitous gait data collection. Being an essential part of mobility in daily life constituted of straight and turn walking bouts, in this thesis we focused on the importance of segmenting and characterizing straight gait and turns.

In this context, the work reported in this thesis aimed at the development, application and testing of MIMU based methods for assessing gait quantitative measures across straight locomotion and turnings. Previously proposed methods and their applications were analyzed in clinical settings and new methods for gait measures quantification were proposed.

The spatio-temporal parameters estimation method employed in this thesis was successfully applied to the straight gait of healthy and pathological older adults (Parkinson's disease and mildly cognitively impaired individuals). Its use was effectively validated on a large cohort of subjects walking at different velocities (normal and fast) in four different clinical centers. In this work, a strong effort was done to implement the method so that it could be applied smoothly on such different data. Results showed that the spatio-temporal parameters estimation errors were consistent with those found in previous single-center studies with smaller population samples. Furthermore, an external work demonstrated that these results hold also for outdoor straight line walking. The combination of robustness and range of applicability of this ankle-MIMU based method connotes its use for the estimation of gait spatio-temporal parameters as suitable in the routine clinical practice. Moreover, the parameters estimated from the MIMUs were as accurate as those obtained from the instrumented mat used as a reference (limits of agreements were − 27 to 27 ms for stride duration, − 68 to 44 ms for stance duration, − 31 to 31 ms for step duration and −

67 to 52 mm for stride length), and, in addition, they could be computed for longer bouts (extended and diversified walks can be instrumented).

Addressing the identification of U-turns (180°), the literature was reviewed and trunk-MIMU based methods were selected. In this part of the work, while consolidating the existing state-of-the-art knowledge, an attempt was done to single out a universal method to robustly detect U-turns while walking, but a satisfactory solution was not found. Four methods were implemented and tested on different pathological groups walking at different speeds. The performance of such methods was evaluated in order to determine the best one available for straight/turn segmentation. Results showed that these methods were more likely to fail when used on stroke survivors and choreic subjects, whose gait is characterized by irregular walking patterns. Yet, it was demonstrated that a single MIMU positioned on the low back could acceptably identify U-turns in Parkinson's Disease (PD) subjects. However, gait events (and the derived spatio-temporal parameters) can be better estimated with MIMUs attached to the lower limbs. Therefore, while looking for the least obtrusive solution, the use of one of the previously tested methods for U-turns detection with MIMUs positioned on the shanks was evaluated. In addition, it was introduced a new method suited to be applied either to signals recorded at the low back or at the shanks (just above the ankles). Results confirmed that turn characterization with the sensors at the shanks is problematic: compared to MIMU on the trunk, those on the lower limbs generated a hundred millisecond difference in onset detection. Nevertheless, MIMUs can be successfully positioned on the shanks when the goal is characterizing turns in terms of onset and duration with the sole purpose of segmenting walking trials into straight bouts and turns. In this respect, the method introduced can be used as a starting point for a robust characterization of turns during gait.

Results from these studies were then transferred in clinical applications and practically used for PD subjects assessments.

In the study with our clinical partner at University of Cagliari, MIMU instrumented gait analysis was used to support the assessment of Sardinian folk dance (BS) as non-conventional treatment in individuals with Parkinson's disease. The objective spatio-temporal parameters were used, in combination with clinical scores, to evaluate BS effects on functional performance and motor and non-motor symptoms. The main contribution of this work is the actual adoption of measures obtained from inertial sensors: the objective measures collected in the BS dance exercise group were compared against those collected in a control group before and after the BS treatment. Results showed that individuals with PD who participated in the BS therapy program obtained significant improvements in a variety of domains ranging from the clinical and functional performance to gait and non-motor symptoms (both UPDRS-III and gait speed significantly decreased and increased, respectively). The use of instrumented gait analysis, providing quantitative measures, in this context therefore allowed to objectively evaluate the outcome of a novel rehabilitation treatment.

In the study in collaboration with Portland Health and Science University, the turn characterization methods were extended and applied to 180° and 360° turns to investigate Freezing of Gait in PD population. This quantitative gait analysis allowed to directly compare, using the same set-up, freezers and non-freezers performing a 180° turn while walking and a 360° turn in place to determine differences in the FoG occurrences. Results showed that measure such as turn duration and number of steps employed to turn, as well as peak angular velocity, were able to differentiate freezers from non-freezers. In the freezer population, out of 23 subjects, 6 showed an actual FoG episode in the 180° turn while walking and 15 in the 360° turn in place, confirming that 360° turn in place is more effective in triggering FoG. When a concurrent dual task was added, FoG episodes were observed in 8 freezers during the 180° turn while walking and in 19 freezers during the 360° turn in place, implying that an added dual task increases FoG manifestation, but turning type is of greater consequence for FoG occurrences. A MIMU instrumented gait analysis including 360° turns is therefore a

promising solution for investigating freezing of gait mechanism in PD population. Furthermore, the measures obtained can be useful to develop algorithms for generating a biofeedback aimed at alleviating or preventing freezing of gait prior challenging motor tasks. The findings reported can also be relevant to evaluate the outcome of interventions aiming at reducing freezing of gait, or to devise optimal and more effective rehabilitation treatments.

However, at the state of the art and in conclusion of the presented research, the methods for gait characterization have been mainly validated during straight walking and 180° turn in the confined environment of gait laboratories, and their performance in the real-world is still an open issue. In order to improve and overcome these limitations, a look to the future challenges should be addressed. The most important current need is the consolidation of identifying gait events and turns in ecological conditions not only in healthy subjects, but especially in populations with movement disorders. The work in this thesis addressed at first the consolidation of gait events identification and spatio-temporal parameters estimation and tried to give a significant contribution with a multi-centric validation study. It then also contributed to the turn identification body of literature, but with a major limitation: only 180° turns were analyzed. The focus was on 180° turns mainly for two reason: i) it is a most common type of turn employed in clinical contexts, and ii) its definition is quite specific. In fact, one of the issues in analyzing turns is the lack of an exact definition [*Pham* 2017]. The same angle can be turned with a larger or smaller curvature, therefore with more or less steps. If, for instance, a subject walking straight wants to turn 45° to the right, (s)he could do it in a single step or in three consecutive steps, each changing the direction of progression by 15° with respect to the previous one. The characterization of turns at angles lower than 180° is therefore more delicate and remains an open issue, while the notion of reversing the direction of progression in 180° turns helps in their definition. Furthermore, a precise definition of turn onset is fleeting also in 180° turns, because it heavily depends on which segment of the body

is under analysis. In fact, it has been shown that a cranio-caudal strategy is adopted for body reorientation, meaning that the head will start turning before the feet [*Lebel* 2017].

Another topic that will need further attention toward a more effective gait characterization is the MIMU-based clearance estimation [*McGrath* 2011; *Trojaniello* 2015]. Foot clearance is the vertical distance of the foot from the ground, or any underneath obstacle. Its analysis has recently gained attention since it has been associated with fall risk in older population and it is a primary indicator to study obstacle negotiation. However, it is a parameter that measuring instruments such as the instrumented mat cannot assess. It is therefore important, in order to investigate a full 3D foot trajectory, to validate a robust method for the MIMU-based clearance estimation.

In conclusion, MIMU-instrumented gait analysis has the potential to detect locomotor deficits not yet visible to the clinical eye, and therefore it has an important impact for treatment and prevention strategies. Hence, gait analysis under controlled environment is a useful tool, but does not reveal functional subject variability in everyday activity patterns. This thesis made an effort to illustrate means of performing such analyses. One of the currently open issues in clinical gait analysis is in fact the possibility to effectively perform ecological assessments in patients with movement disorders. The work in this Ph.D. thesis led to promising results and, together with numerous studies currently published in the literature about real-world gait analysis evaluations, provides evidence to support the development of ecological solutions by means of inertial sensors, thus allowing not only the measurement of the gait impairment actual extent, but also a close monitoring of rehabilitation programs effectiveness.

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