Analysis of gait parameters and muscle activity in Parkinson's disease patients

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

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ABSTRACT

Parkinson's disease (PD) patients suffer gait disturbances, which are a major cause of disability, falls, reduced mobility, and quality of life. Gait assessment is important in the diagnosis and monitoring of the disease. Gait is one of the measures observed in the Unified Parkinson's disease rating scale part III (UPDRS III) and is scored by clinical observations to determine the severity of disease and efficacy of treatment. However, this is a subjective test and there is a need for quantifiable gait analysis to study the PD patients.

Walking patterns such as turning are affected in the early stages of the PD patients. The main consequence of turns in PD are falls or triggers freezing of gait (FOG), which can result in severe immobility and reduced quality of life. Thus, it is very important to evaluate the turning ability in PD and to investigate the effect of gait intervals across different turns. During the Unified Parkinson's disease rating scale (UPDRS) screening, neurologists observe their patients during the turn phase of their walks, but this is subjective and has not been quantified.

As the first objective, a series of experiments were performed on 72 participants: 24 with PD, 24 age-matched controls, and 24 young controls. The data recording was performed using a wireless inertial measurement unit (IMU), which can record acceleration, rotation, and surface electromyogram (sEMG) signals. The experimental protocol required the participants to walk in different turns and straight walking, designed in such a way that resembled the activities of daily living.

This research has investigated the effects of gait and muscle parameters based on the severity of disease and during turning. The study has proposed that variance and fraction of the gait sub-intervals can be used to estimate the severity of the disease. The study also shows that the variability of gait sub-interval, irrespective of the walking pattern, straight-line walking or turning, is suitable for the evaluation of PD patients, and differentiating from control. Finally, investigating the muscle characteristics of Tibialis anterior (TA) and Medial gastrocnemius muscle (MG), it was observed that there is an increase in co-activation, reduction in TA modulation, and increase in TA and MG lateral asymmetry among PD patients when compared to the control.

This research output has the potential to be used for the population-based screening for early diagnosis of disease while the patient performs simple walking and there is no need to perform the complicated task for evaluating PD. The research also highlights the importance of the sub-intervals of gait, which can be used for monitoring the progression of the disease and differentiating between PD and the control group. This method offers an alternative to the subjective measures used by clinicians. Additionally, the muscle characteristics can help clinicians better understand the neuromuscular activation underlying muscle contraction and altered muscle activation, resulting in gait impairment.

PUBLICATIONS

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Journal

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Chapter 1

1. Introduction

1.1 Introduction

Parkinson's disease (PD) is a progressive neurological condition that is caused by the degeneration of neurons in the part of the brain known as substantia nigra (Jankovic, 2008). These neurons play a significant role in controlling the movement and locomotion of the human body. Decline production of dopamine neurotransmitter in the substantia nigra leads to the excessive inhibition of the basal ganglia loop leading to the loss of habitual patterns associated with walking (Ringeval et al., 2015) and also causes rigid movement and decreased range of limb movement (Snijders et al., 2007).

PD patients have gait and postural impairment (Abraham et al., 2018; Marinus et al., 2018; Vetrano et al., 2018). Their gait and posture are one of the major symptoms and is used for diagnosis and monitoring of the disease (Borzi et al., 2019; Buckley et al., 2019; Heijmans et al., 2019). Expert neurologists monitor their patients by observing their gait to determine the progression of the disease and efficacy of the treatments, which requires a significant time of the experienced neurologist (Kerr et al., 2010; Adams and Leveson, 2012). Timely identification of gait and posture disorder symptoms and monitoring its progress in these patients can prevent falls and related injuries (Modarresi et al., 2018; Fernandez et al., 2019).

In PD patients, the magnitude of variability in gait is a significant parameter that helps in identifying the dynamic features (Frenkel et al., 2005; Olmo and Cudeiro, 2005). Gait in PD patients is characterized by reduced stride length, gait speed, swing interval and increased double support interval (Morris et al., 1998; Sofuwa et al., 2005; Combs et al., 2014). For straight walking, the stride interval, swing interval, and stance interval reported an increased inter-parameter variability for PD patients when compared to control (CO) (Crenna et al., 2007; Huxham et al., 2008).

Some walking-related activities such as turning in PD patients are even worse in the early stages of disease requiring more time to complete the turn (Crenna et al., 2007). Turning while walking is a common task performed by every individual in daily living. Turning is a complex task, that requires the central nervous system to coordinate body re-orientation towards a new direction while continuing with the on-going step cycle and maintaining postural stability in the medial-lateral plane (Mellone et al., 2016). Turn often triggers FOG events or falls in PD patients, which are termed as adverse events in case of PD. The dysfunctions in PD patients are linked to the loss of habit control systems in the basal ganglia, leading to greater dependence on voluntary control (Ringeval et al., 2015). Thus, it is very important to evaluate the turning ability in PD patients and to investigate the effect of gait sub-intervals across different turns. Currently, expert neurologist or clinicians commonly use UPDRS scale for monitoring and diagnosing the severity of disease. UPDRS scale consist of both motor and non-motor symptom assessment. Gait is one of the measures of UPDRS, which comprises of straight walking and turn. Neurologists observe their patients during the turn phase of their walks, but this is subjective and has not been quantified.

The study on muscle activity while walking can reveal clinical information on the gait deficits in PD patients (Bailey et al., 2018). Normally muscles stretch when they move and reflex when they are at rest. But for PD patients, muscles may not reflex, causing rigidity and difficulty walking (Busse et al., 2006). Surface electromyography (sEMG) analysis of muscle activity during gait is an efficient tool in differentiating PD patients from control and has applications for rehabilitation and detecting pathological gait conditions (Mariani et al., 2013). The transition from stance to walking is a result of a coordinated pattern of muscle activity (Lacquaniti et al., 1999). For CO, one of the muscle groups acts as an agonistic muscle and other as antagonistic muscle. Simultaneous activation of agonistic and antagonistic muscles results in joint stiffness and provides postural and movement instability (Latash, 2018), but

excessive coactivation can produce negative work, reduce the net torque at the joint and increase rigidity (Busse et al., 2006). Thus, there is a need to understand the muscle activation strategy in PD patients during different sub-intervals of gait, which can help the clinicians manifest the neuromuscular activation underlying the muscle contraction and altered muscle activation, resulting in gait impairment.

1.2 Problem statement

The walking style of PD patients, the Parkinsonian gait (PG), is characterized by small shuffling steps and hypokinesia. Deterioration of the gait of PD patients is a major cause of their falls and injuries (Allcock et al., 2009; Latt et al., 2009; Contreras and Grandas, 2012) and is an indicator of the progression of the disease (Bloem et al., 2001; Balash et al., 2005; Allcock et al., 2009). Many studies have quantified the differences in the gait of PD patients and control participants (Rios et al., 2001; Hausdorff et al., 2003; Hausdorff et al., 2007). While there are many studies on differentiating PD patients from control, the relationship between gait parameters, and the severity of the disease is not studied. This research focused on several key elements of the gait sub-interval: stride, swing, stance, and double-support interval.

Secondly, turning movements in PD patients have reported increased turning time, turn arc and number of steps to complete the turn (Crenna et al., 2007; Huxham et al., 2008; Spildooren et al., 2013). Turning is the most important trigger for FOG in PD patients. The main consequence of turns in PD patients is lateral falls, which can result in an eight-fold increase in hip fractures compared with falls during straight walking (Mellone et al., 2016; Johannesdottir et al., 2017). Thus, it is very important to evaluate the turning ability in PD patients and to investigate the effect of gait intervals across different turns, which has not yet been done. This research investigated the difference in the gait of patients with PD, age-matched controls, and young controls during three turning walking patterns.

Thirdly, a coordinated pattern of muscle activity is required during the transition from stance into walking. It has been observed that while CI increases for both, PD patients and the elderly, the mechanism appears to be very different. An increase in CI for the elderly is due to an increase in the muscle activation during mid-stance (Schmitz et al., 2009), in PD patients it is due to a reduction in the activity of lower limb muscle (Cioni et al., 1997). To better understand the muscle activation pattern in PD patients, it is essential to investigate the sub-phases of gait. The study with the elderly has revealed that there is a significant change to CI over the different sub-phases of the gait (Schmitz et al., 2009) when compared to young healthy. However, such a study has not yet been done for PD patients for straight-line walking on a level surface.

The thesis aims to address three of the gaps identified in the literature- to study the relationship between gait parameters and the severity of disease in PD patients, investigate the difference in the gait parameter during different walking pattern and understand on the muscle activation pattern of TA and MG muscle while walking in PD patients. The rationale for selecting TA and MG muscle for this study was due to its important role in helping to walk. These muscle groups activate concurrently resulting in transition from stance into walking and provide balance to human body (Neptune and McGowan, 2011). The changes in muscle activation patterns of TA and MG muscle reflect the impairment in motor control and movement, further resulting in limited control of limbs (Mitoma et al., 2000).

1.3 Research questions

This thesis aims to answer the following research questions-

Q1: How does the gait parameters vary with the severity of PD?

Q2: How does the gait parameters vary during straight line walking, U-turn, and turn around a point between PD patients and control?

Q3: How does Tibialis anterior (TA) and Medial gastrocnemius (MG) muscle activation vary between PD patients and control for different phases of gait?

1.4 Outline of the thesis

This thesis is divided into the following chapters:

Chapter 1 gives an introduction and research questions for this research study.

Chapter 2 introduces Parkinson's disease and its symptoms.

Chapter 3 presents an overview of the literature on gait analysis in Parkinson's disease patients. This chapter also explains the sensor and its validation performed for this study.

Chapter 4 provides a multidisciplinary review on IMU sensors used for gait analysis.

Chapter 5 reports the changes in the gait parameters based on the severity of Parkinson's disease and compared with control.

Chapter 6 discusses, the difference in gait parameters based on the walking pattern of Parkinson's disease patient, age-matched control, and young control.

Chapter 7 describes the difference in muscle activation strategies of Parkinson's disease patients, age-matched control, and young control.

Chapter 8 provides the conclusion of this research work and the future work related to this research is proposed.

Chapter 2

2. Parkinson's disease

2.1 Introduction

This chapter provides an overview of Parkinson's disease. It details the physiology and symptoms related to the disease. The currently used rating scale to evaluate the symptoms of PD is also described.

2.2 Parkinson's disease physiology

Parkinson's disease is a progressive neurological condition that affects the movement of the body. In Australia, approximately 80, 000 people are living with Parkinson's disease, the average age of diagnosis to be 60 years (Economics, 2015). PD is caused due to the declined production of dopamine in the brain. Dopamine is responsible for controlling the movement and locomotion of the human body. Many of the cells that produce dopamine are in the middle part of the brain, known as Basal ganglia. Figure 2.1 represents the neuron pathway in the middle part of the brain. There are two pathways -direct and indirect pathway, through which signals are transmitted to the cerebral cortex from the substantia nigra. From the cortex, the signals are transmitted to different muscles for performing a certain task.

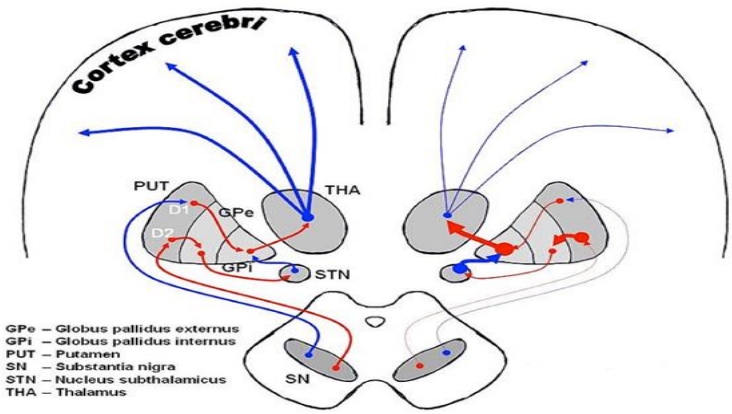


Figure 2.1: The schematic representation of the neuron pathway in the brain. The left side represents the healthy brain and the right side represents the PD brain neuron pathway (Borg, 2006).

In figure 2.1, D1 shows the direct pathway which helps in exciting the output from the thalamus to stimulate the actions, while D2 is the indirect pathway, which helps in suppressing the unwanted actions. The signals are transmitted by the dopamine neurotransmitter and hence any imbalance in the dopamine affects the balance of the pathway. In figure 2.1, the left side represents the healthy brain and right side represents the PD brain. The cause of decline of dopamine in the brain is unknown (Borg, 2006).

2.3 Parkinson's disease symptoms

2.3.1 Motor symptoms

The most common motor symptoms of PD are

- Resting tremor: Resting tremor is the shaking movements in lower and upper extremities when no action is performed or at rest. In the early stages of the disease, about 70 % of the PD people experience a slight tremor (Helmich et al., 2012). This tremor usually stops when the patient begins an action.
- Bradykinesia: It is the slowness in the movement. PD people with bradykinesia walk with short and shuffling steps (Politis et al., 2010). With the progression of the disease, PD patients have trouble in walking and limb co-ordination.
- Rigidity: Rigidity is the inflexibility and stiffness of the limbs, causing resistance to movement. For a healthy individual, muscles normally stretch when they move and relax when they are at rest. In PD patients, the muscles may not always relax and this caused a decreased range of motion (Dipiro et al., 2014).
- Postural instability: The most important sign of PD is postural instability, a tendency to be unstable when standing upright (Palakurthi and Burugupally, 2019). Some patients develop a tendency to sway either forward or backward while performing certain tasks such as rising from the chair, standing, or performing a turn (Kim et al., 2013). Postural instability along with FOG is the most common cause of falls and related injuries in PD patients (Jankovic, 2008).

2.3.2 Non-motor symptoms

The most common non-motor symptoms of PD are depression, emotional changes, dysphagia, cognitive dysfunction, and sleep problem. These symptoms can be treated with medication and therapy (Hauser, 2006).

2.4 Diagnosis of Parkinson's disease

There is no specific test to diagnose PD. Currently, PD is diagnosed by expert neurologists or clinicians based on clinical observation and self-reported symptoms. They evaluate the motor and non-motor symptoms of PD using a scale- UPDRS and Hoehn & Yahr scale (H&Y), (Goetz et al., 2004; Goetz et al., 2008) the intensity and disability scales using the Unified dyskinesia rating scale (UDysRS) (Goetz et al., 2008). In this research, we have used these scales to study the motor symptoms and measure the severity of the disease. Also, the cognitive impairment in the participant was assessed using the Montreal cognitive assessment (MoCA) (Nasreddine et al., 2005). For more details on the scales used, refer to Appendix I, II, III and IV.

H&Y scale was developed based on the concept that the severity of disease is related to the bilateral motor involvement and balance or gait impairment. The motor impairment was divided into different stages. Stage 1 are those with symptoms only on one side (Unilateral), stage 1.5 are those with unilateral symptom plus neck and spine involvement, stage 2 are those with symptoms on both side but no balance impairment, stage 2.5 are those with mild symptoms on both side with recovery on pull test, stage 3 are those with mild to moderate symptoms on both side with balance impairment and physically independent, stage 4 are those with severe disability but still able to walk or stand unassisted and stage 5 are those bedridden and need wheelchair for mobility.

H&Y scale can be used for the overall assessment of the severity of disease. The main limitation are – the scale focuses only on objective signs or disability of the patient and does not take into consideration many other clinical situations, a large variety of the impairment

are combined together to form stages and motor and non-motor impairments are not considered. To overcome these limitations, UPDRS was later introduced as primary outcome measure of treatment efficacy and H&Y scale as the descriptive categorical scale in PD (Goetz et al., 2004).

UPDRS is the clinical rating scale comprising of four parts- Part I assess the behavioral problem, Part II assesses activities of daily living, Part III assesses motor examination and Part IV covers complications of therapy. This study has used only UPDRS part III (UPDRS III) for evaluating motor symptoms in PD patients. Gait is one of the measures for the UPDRS III used to study the progression of the disease and is scored by visual observation of the walking pattern. The basic postural instability in PD patients is studied using the UPDRS - Postural Instability and Gait Disturbance (PIGD) which is calculated as the sum of sub-score of UPDRS III items: comprising of arising from a chair, posture, gait, postural stability, and body bradykinesia. However, there is a certain limitation- it is a subjective measure, may induce instructor bias, and has high inter-rater variability among experts who performs an examination on the same patient. Thus, there is a need for diagnosis method that is less subjective and more consistent.

UDysRS is used to evaluate the involuntary movements associated with long term treatment of dopaminergic medication PD. The focus of the scale is on the dyskinesia and disability in PD. Dyskinesia refers to the involuntary, erratic, or twisting movement present on different parts of the body-face, neck, hand, trunk and leg. Dyskinesia is divided into two- On-dyskinesia and off- dyskinesia. On- dyskinesia refers to the dystonic movement (mainly jerking or twisting movement) that occurs when the medication is working, while off-dyskinesia refers to the spasms or cramps that can be painful and occurs when the medication is not working or not taken. The disability scale focus on 4 tasks- communication, drinking from a cup, dressing, and ambulation. Each task are rated from 0-4 stage, varying from no dyskinesia to severe dyskinesia (Goetz et al., 2008).

MoCA is the screening assessment for detecting cognitive impairment in PD. These include different tasks- visuospatial/executive, naming, attention, language, abstraction, delayed recall and orientation. Visuospatial/executive are assessed for 5 points using a clock-drawing, drawing line starting from number to alphabet in ascending order and three-dimensional cube copy task. Naming is assessed for 3 points, with the task involving naming low-familiarity animals. Attention is assessed for 6 points involving target detection tapping, serial subtraction and digits forward and backward tasks. Language are assessed for 3 points using naming words beginning with letter F in one minute and repetition of two sentence. Abstraction are assessed for 2 points in identifying the similarity of objects. The delayed recall are assessed for 5 points that involves two learning trials of five words and recall after 5 minutes. Finally, orientation is evaluated for time and place in 6 points. The total score of MoCA test is 30 points, with a score above 26 considered as normal cognitive behavior (Nasreddine et al., 2005).

Chapter 3

3. Literature review on gait analysis

3.1 Introduction

Gait analysis is the study on human walking. Walking is a complex task that is a rhythmic alternating movement of two lower extremities that helps in forward, backward, and most often sidewise movement of the body (Ferrucci et al., 2000). To quantify and analyze the gait, the repeatable movements during the gait is defined as the gait-cycle, as shown in Figure 3.1.

3.2 Terminology in gait analysis

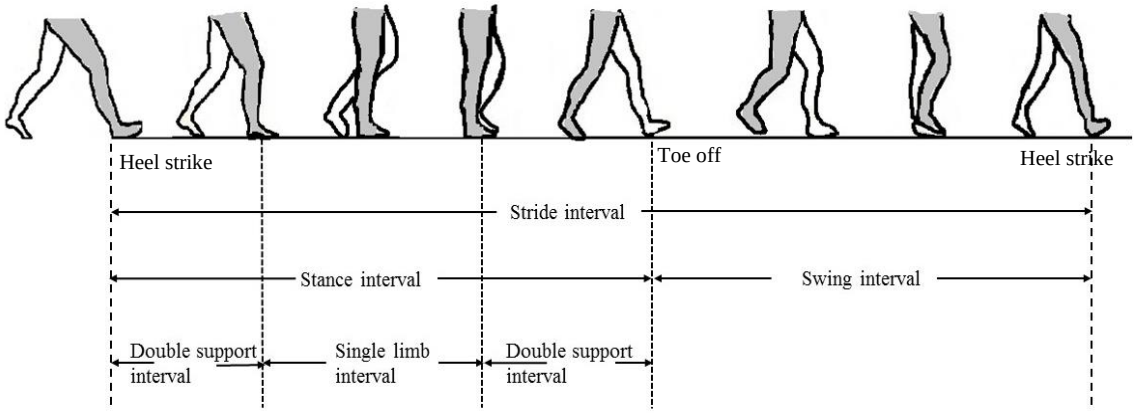


Figure 3.1: Diagram representing the intervals of gait

3.2.1 Gait-cycle

The gait-cycle is defined as the time from the first heel strike to the next heel strike of the same foot. A gait-cycle is also known as stride interval, as in Figure 3.1. The gait-cycle consists of two major phases: the stance phase and the swing phase. For a healthy individual, 60% of the gait-cycle forms the stance phase and the remaining 40% forms the swing phase (Wilhelm and Eduard, 1992; Umberger, 2010).

3.2.2 Stance phase

The stance phase is also known as the support phase as the body comes in direct contact with the ground. This phase begins with the heel of the foot striking the ground known as heel strike and ends when the toe of the same foot is taken off known as toe-off (Mochon and McMahon, 1980). The stance phase consists of a double support phase and a single-limb support phase.

3.2.3 Double support phase

The time of bilateral limb contact is defined as the double support phase. For a healthy individual, about 40% of the stance phase comprises of double support phase (Perry, 1992).

3.2.4 Single-limb support phase

This is the time in the stance phase, when only one limb encounters the ground. About 20% of the stance phase comprises of single-limb support phase (Lamoreux, 1971).

3.2.5 Swing phase

The swing phase is also known as the unsupported phase that is the foot is no longer in contact with the ground (Gottschall and Kram, 2005).

3.3 Gait characteristics of Parkinson's disease patients

3.3.1 Gait parameter

The spatial and temporal parameters of gait are recognized clinical assessment methods to identify the difference in gait patterns, motor pathologies, and impairments. The spatial parameters are step length, step width and temporal parameters are stride interval, swing interval, stance interval, and double support interval.

There is significant deterioration of gait of PD patients with progression of the disease (Bloem et al., 2001; Balash et al., 2005; Allcock et al., 2009) and this is a major cause of their falls and injuries (Allcock et al., 2009; Latt et al., 2009; Contreras and Grandas, 2012). In comparison with control, PD patients have reduced stride length (Morris et al., 1998; Sofuwa et al., 2005) and walking speed (Sofuwa et al., 2005; Combs et al., 2014) with increased double support duration (Morris et al., 1994; Morris et al., 2001; Ferrarin et al., 2002) during free ambulation on even surface. Neurologists monitor their patients by observing their gait to determine the progression of the disease and efficacy of treatments (Kerr et al., 2010; Matinolli et al., 2011; Adams and Leveson, 2012). This requires a significant time of experienced neurologists, and there is a need for quantifiable gait analysis that can be performed without the extensive infrastructure to monitor the severity of PD patients.

3.3.2 Gait variability

People with a normal gait, when walking on an even surface, have a long-range correlation between their strides, their inter-stride variability is insignificant, and the gait is rhythmic (Solomont et al., 2003). In comparison with control, PD patients walk slower with slower stride with reduced length (Morris et al., 1998), increased variability in the stride (Frenkel et al., 2005) and increased duration of double support phase of gait (Crenna et al., 2007; Huxham et al., 2008). These have been considered as an adaptive mechanism by the patient because of their fear of falls, slowed actions, and cognitive impairments.

There were many studies on the gait variability of PD patients, and it was found that the PD patients have high variability (Hausdorff et al., 1998; Hausdorff et al., 2003) and variable fractal properties of the inter-stride intervals (Blin et al., 1990; Frenkel et al., 2005). For more details on the literature that compares the gait variability of the spatio-temporal parameter in PD patients, refer to Chapter 4.

While there are many studies on differentiating PD patients from control, the relationship between gait parameters, and the severity of the disease has not been studied. This thesis focused on several key elements of the gait interval- stride, swing, stance, and double-support.

3.3.3 Turns events in PD patients

Many factors affect gait, i.e. age, gender, height, and weight of the person. Activities such as turning have also been found to significantly affect the gait of PD patients, even in the early stages of the disease (Carpinella et al., 2007). Turning is a complex task, that requires the central nervous system to coordinate body re-orientation towards a new direction while continuing with the on-going step cycle and maintaining postural stability in the medial-lateral plane. Turning is the most important trigger for FOG in PD patients. Turning movements in PD patients have reported increased turning time, turn arc (Crenna et al., 2007; Huxham et al., 2008; Spildooren et al., 2013) and the number of steps to complete the turn. The number of steps and peak speed during turning significantly differed among control, mild PD, and severe PD. The main consequence of turns in PD patients is lateral falls, which can result in an eight-fold increase in hip fractures compared with falls during straight walking. It is very important to evaluate the turning ability in PD patients and to investigate the effect of gait intervals across different turns, which has not yet been done. This thesis investigated the difference in the gait of patients with PD patients, age-matched controls, and young controls during three turning walking patterns.

3.4 Assessing gait in Parkinson's disease patients

Gait assessment is important in the diagnosis and monitoring of the disease. Gait is one of the measures for the UPDRS III and is scored by clinical observations to determine the severity of disease and efficacy of treatment. The limitation of such studies is that these are subjective measures, can have bias induced by the clinician or neurologist who performs the

test and can cause higher inter-rater variability and require excessive clinician time for the assessment. Hence, there is a need for quantifiable gait analysis to study PD patients (Yang et al., 2016).

Gait analysis is performed in gait laboratories which are equipped with multiple, high-speed cameras and pressure mats. In most cases, however, gait assessment is performed by trained neurologists, which requires the patients to visit their neurology clinics, and can result in their infrequent assessment (Morris and Dreher, 2018; Shipston et al., 2019). Timely identification of gait and posture disorder symptoms and monitoring its progress in these patients can prevent falls and related injuries (Modarresi et al., 2018; Fernandez et al., 2019).

Special purpose gait analysis laboratories require significant equipment, space, extensive software, and trained personnel. These are large and high-value facilities that are generally located in urban hospitals. These suffer from two major shortcomings: 1. the patient needs to visit the hospital and thus can only be examined in the clinic which may influence the gait. 2. the cost of these facilities is high and requires significant infrastructure (Ferrari et al., 2008; Godinho et al., 2016). This limits the regular access to PD patients.

3.5 Inertial measurement unit (IMU)

The growth of micro-electro-mechanical systems (MEMS) and wireless technologies have led to miniaturized, portable, wireless inertial measurement unit (IMU) devices which are relatively inexpensive (Ciuti et al., 2015; Mancini et al., 2016; Qiu et al., 2018; Brognara et al., 2019). One major application of MEMS IMUs is measuring human movement (Zihajehzadeh et al., 2014).

An Inertial measurement unit (IMU) consists of gyroscope and accelerometers which are used for the rotational and translational movement measurements. Due to the advancement in technologies and ease of measurement, IMUs are increasingly popular as a measurement tool for analyzing human locomotion (Weiss et al., 2011; Lowe and ÓLaighin,

2014; Weiss et al., 2014). IMUs can help in gait analysis by providing spatial and temporal parameters of gait, which are a recognized clinical assessment method to identify the difference in gait patterns (Johannes et al., 2017), the disease in PD patients (Baron et al., 2018) and enables the detection of gait deviation (Hobert et al., 2019; Keloth et al., 2019). However, there are number of errors associated with IMU sensors- the effect of gravity on the vertical axis, alignment of the axis and the effect of drift on the sensor. When performing the gait analysis, removal of these errors is challenging. A detailed list of literature on the IMU sensor used for gait analysis can be seen in Chapter 4.

3.6 Muscle activation during walking

Gait disturbance is a major cause of impairment in PD patients. In addition to the spatial and temporal parameters, the changes in the muscle activation pattern of lower limb muscles are used to examine the clinical information related to the gait disorder and also as a measure to differentiate PD patients from control (Bailey et al., 2018). A coordinated pattern of muscle activity results in the transition from stance into walking. Normally muscles stretch when they move and reflex when they are at rest. But for PD patients muscles may not reflex, causing rigidity and difficulty to walk. The changes in muscle characteristics have a functional implication on the motor control and movement, thereby limiting the control of foot and stride length (Mitoma et al., 2000). Thus, investigating the muscle activity of gait can reveal clinical information related to gait dysfunction in PD patients.

3.7 Surface electromyogram (sEMG)

The method of sEMG analysis is gaining its interest in research due to its non-invasive property of measurement. sEMG is the measure of the electrical activity of the muscle responsible for the movement. The muscle characteristics can provide information on the biomechanics and neuromuscular activity of walking. The analysis of sEMG of gait has

applications for rehabilitation and detecting pathological gait conditions (Amundsen et al., 2018; Smeets et al., 2019).

3.7.1 Anatomy and physiology of lower limb muscle

The nervous system is responsible for controlling the voluntary and involuntary actions of the body. The nervous system is divided into two-Central Nervous system (CNS) and Peripheral Nervous System (PNS). The Central nervous system (CNS) comprising of the brain and spinal cord, is responsible for the transmission of signals to and from the CNS and to different parts of the body, with the help of nerves in PNS (Benjamin et al., 1986). The two nerves of PNS are motor and sensory. The motor nerve provides information from CNS to the body, used to control muscle and glands, while sensory nerves provide information from the body to the CNS about the physical sensation. Muscle systems in the lower limb are responsible for providing balance and support and help in forwarding propulsion of the body. A coordinated pattern of muscle activity results in the transition from stance into walking (Hamner et al., 2010; Neptune and McGowan, 2011).

The main lower limb muscles that play an important role in controlling the locomotion and balance of the body are Tibialis anterior (TA) and Gastrocnemius muscle (GA) (Di Giulio et al., 2009). The gastrocnemius muscle is divided into

- Lateral gastrocnemius (LG) muscle – is the calf muscle, that connects the femur and Achilles tendon on the lateral side (towards the side).
- Medial gastrocnemius (MG) muscle - is the calf muscle, that connects the femur and Achilles tendon on the medial side (towards the center).

The comparison between MG and lateral gastrocnemius (LG) muscle for control shows that MG activity is more when compared to LG during the gait-cycle (Chisholm et al., 2015; Cibulka et al., 2017; Dick et al., 2017). Hence, in this thesis, the activity of TA and MG muscle is studied, as shown in Figure 3.2.

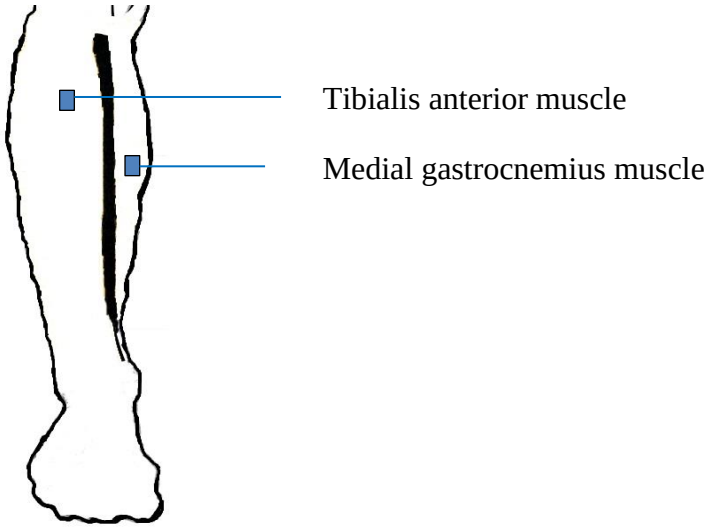


Figure 3.2: The tibialis anterior and medial gastrocnemius muscle location in the leg.

3.7.2 Tibialis anterior (TA) muscle

TA is the long, narrow muscle connecting tibia and metatarsal bones of the leg. The muscle functions as a dorsiflexor of the foot, resulting in lifting the toes off the ground. This is an important motion while walking and helps in maintaining body balance while transferring weight from one leg to the other.

3.7.3 Medial gastrocnemius (MG) muscle

MG is the large, muscular belly located on the medial side of the leg. It is connected between the femur and Achilles tendon-bone which descend to the heel of the leg. MG muscle functions as a plantar flexor of the foot, that helps in pushing the body forward while walking.

3.8 Muscle activity during gait in Parkinson's disease

The sEMG signal morphology of patients with PD is used as a differentiator from controls (Rissanen et al., 2007). The study on lower limb muscles of PD during walking shows that they have lower activation of gastrocnemius muscle during the stance phase of gait (Dietz et al., 1995), reduced ability to modulate their activation pattern (Milner et al., 1979). Their activity has reduced modulation and is not symmetrical (Bailey et al., 2018). It

has also been shown that PD has reduced TA during the stance phase of gait (Dietz et al., 1995) and reduced TA amplitude during late swing (Mazzetta et al., 2019). These changes in sEMG activity reflect the impairment in motor control and movement, further resulting in limited control of foot and stride length (Mitoma et al., 2000).

3.8.1 Co-activation index (CI)

Concurrent activation of agnostic- antagonistic muscles around the joints is referred to as co-activation. Co-activation of muscles stabilizes the joints and provides postural and movement stability (Latash, 2018), however, the excessive co-activation can produce negative work, reduce the net torque at the joint and increase rigidity (Busse et al., 2006). This is usually studied by analyzing the surface electromyogram (sEMG) that generates opposite torque during a task (Ervilha et al., 2012) and calculated as the Co-activation Index (CI). It has been observed that while CI increases for both, PD and the elderly, the mechanism appears to be very different. Increase in CI for the elderly due to increase in the muscle activation during mid stance (Schmitz et al., 2009), while in PD patients it is due to the reduction in the activity of lower limb muscle (Cioni et al., 1997). To better understand the co-activation in PD patients, it is essential to investigate the sub-phases of gait. The study with the elderly has revealed that there is a significant change to CI over the different sub-phases of the gait (Schmitz et al., 2009) when compared to young control. However, such a study has not yet been done for PD patients.

3.8.2 Asymmetry index (AI)

Control gait is largely bilaterally symmetrical, though people have a lateral preference, which can be attributed to anatomical and neurological differences, resulting in small bilateral asymmetry (Pirker and Katzenschlager, 2017). However, motor impairment can cause enhanced bilateral asymmetry which can reduce the rhythmicity of walking. It has been

found that PD patients have higher gait asymmetry (Park et al., 2016; Cole et al., 2017), while the associated change in muscle activation strategy has not been investigated.

Studies have observed that PD patients have higher asymmetry (Miller et al., 1996) compared to control while non-significant difference has been reported in other studies (Thaut et al., 1996). Both studies assessed had analyzed the gait asymmetry by considering the difference between right and left side mean value of the sEMG signal. These can result in incorrect analysis, as the difference between right and left leg may be due to a difference in leg dominance (Ankaralı et al., 2015). To overcome this, the Asymmetry index (AI) was introduced, where the higher to the lower side were compared and significant gait asymmetry was observed (Bailey et al., 2018). Nevertheless, these were not studied over different gait-cycles.

3.8.3 Modulation index (MI)

Human gait requires modulation of the muscle activity over a large range which conserves energy and provides stability (Toney and Chang, 2016) and this is measured using Modulation Index (MI) (Zehr and Chua, 2000). It has been shown that PD patients have reduced modulation while maintaining posture (Lang et al., 2019). However, no study has investigated the modulation during the sub-phases of gait, which would help understand the muscle activation within each sub-phase.

Chapter 4

4. IMU for gait analysis of Parkinson's disease patients: A multidisciplinary review

Brief outline of the chapter:

This chapter provided a multidisciplinary literature review on IMU sensors used for gait analysis. These are mainly divided into two parts- IMU sensor used for gait analysis and gait variability in PD patients. The effect of medication, rehabilitation and gait variability used for differentiating between PD and control are discussed.

4.1 Introduction

Parkinson's disease patients have gait and postural impairment (Abraham et al., 2018; Marinus et al., 2018; Vetrano et al., 2018; Raccagni et al., 2019), are one of the major symptoms that are used for diagnosis and monitoring of the disease (Borzi et al., 2019; Buckley et al., 2019; Heijmans et al., 2019). Timely identification of gait and posture disorder symptoms and subsequent monitoring of its progress in these patients can prevent falls and related injuries (Modarresi et al., 2018; Fernandez et al., 2019). Identifying gait impairments requires special purpose gait analysis laboratories equipment, space, extensive software, and trained personnel. These are large and high-value facilities that are generally located in urban hospitals, limiting regular access for many PD patients (Ferrari et al., 2008; Godinho et al., 2016). This limits regular access to these facilities for many PD patients due to economic and travel issues. To overcome this, it is necessary to have gait monitoring devices that are wireless and portable. The growth of micro-electro-mechanical systems (MEMS) and wireless technologies have led to miniaturized, portable, wireless inertial measurement unit (IMU) devices which are relatively inexpensive (Ciuti et al., 2015; Mancini et al., 2016; Qiu et al., 2018). One major application of MEMS IMUs is measuring human movement (Zihajehzadeh et al., 2014). Due to the small and portable nature of these devices, they can

easily be worn by the user while performing their regular activities (Weiss et al., 2011; Lowe and ÓLaighin, 2014; Weiss et al., 2014) and hence provide parameters of their natural gait impairment.

Gait is one of the measures for the UPDRS III (Goetz et al., 2008) and is scored by a neurologist when evaluating the patient (Kerr et al., 2010; Matinolli et al., 2011; Adams and Leveson, 2012). One limitation of this approach is the subjectivity and thus the clinician bias in the evaluation (Yang et al., 2016). Hence, there is a need for quantifiable and easy to use gait analysis techniques to study PD patients. Wearable sensors that can record the spatial and temporal parameters of gait can be useful for gait analysis of PD patients. In the selection of suitable sensors, it is essential to identify those that are suitable for monitoring the clinically relevant parameters. However, there appears to be a significant difference between the engineering knowledge of the sensors and the requirements of the clinicians. One of the aims of this review is to present a multidisciplinary review to help bridge the gap between the clinicians and engineers for the appropriate selection of equipment and establish their strengths and limitations.

This review has evaluated the papers that report the use of IMU for performing gait analysis of PD patients. This review also reports the works that have selected the appropriate choice of gait features and suitable measurement devices for characterizing gait in PD patients. The first step of this review was to identify the research that has been conducted to identify the suitable features that can distinguish between PD patients and control. The second step in this review was to identify the papers that report the use of IMU for gait analysis, with a focus on the work related to the identification of gait abnormalities of PD patients.

This is a thematic and multidisciplinary review, which will help the clinicians find the engineering solutions to their requirements. It will also help the engineers better understand the clinical requirements and identify possible research opportunities. We believe that the

major impact of this review would be that it will bring together the end-users with the engineers and facilitate the translation of the technology for real clinical outcomes that will benefit the PD patients.

4.2 Materials and methods

This review reports the outcome of the search for the development and use of IMU for gait analysis over the past 10 years. The terms and keywords used for the literature search in Pubmed were (“Parkinson” OR “Parkinson’s disease”) AND (“inertia” OR “wearable sensors” OR “body-fixed sensor” OR “accelerometer” OR “gyroscope” OR “gait” OR “walk”) located within the title and/or abstract. The review was conducted with a focus on the use of IMU for Parkinson's application. The exclusion criteria were: (1) case studies, books, book chapters, conference articles, editorials and letters (2) articles reporting results less than 10 participants due to the low level of reliability and statistical validity that can be obtained from such results. Six recent review papers on wearable sensors technology in PD patients have also been considered in this review.

The first section provides the summary table which briefly describes the aim and outcomes reported in each of these papers. This has been presented to facilitate the reader to make a high-level comparison between these papers. The next section provides an in-depth discussion of the papers reviewed, followed by identifying the needs and opportunities for future research. This section examines the key issues that have been highlighted by the referenced works, gaps in the research, and thus the potential for future research. Finally, a conclusion summarizes the key findings and the generic issues observed during the review.

4.3 Results

The results have been presented in two sub-sections- the comparison table and the review of the papers. The comparison Table 4.1 and Table 4.2 lists all the papers that have been reviewed, and has five columns:

- Serial number
- Reference
- Aim of the paper
- Gait parameter significantly different between PD patients and control
- Remarks of the paper

Table 4.1: Part I. Comparison of the publications on IMU sensors used for gait analysis in PD patients. Each paper has been briefly summarized in the previous section.

Sl. No	Reference	Aim of the paper	Gait parameter significantly different between PD patients and control	Remarks of the paper
1	(Palmerini et al., 2013)	Motor patterns of age-matched control and PD patients.	Temporal measures, jerk, and angular velocity.	Characterize PD motor impairment.
2	(Esser et al., 2013)	Phase plot variability of age-matched control and PD patients.	Angular velocity, the standard deviation of angular velocity.	Characterize PD motor impairment.
3	(Herman et al., 2014)	Gait and balance in PD subtype- Postural Instability Gait Disorder (PIGD), Tremor Dominant (TD)	Gait speed, shorter strides, increased stride variability.	PD subtype classification may be useful.
4	(Djurić-Jovicić et al., 2014)	IMU for studying the progress of the disease.	Stride classification on each segment of the leg.	IMU attached to shank was able to differentiate.
5	(Brodie et al., 2015)	IMU attached to the head.	Increased transverse plane head oscillations.	Characterize PD motor impairment.
6	(Trojaniello et al., 2015)	Gait temporal parameters in many diseases.	Decreased accuracy in pathological groups.	IMU attached to leg for highly impaired gait.
7	(Curtze et al., 2015)	Response to levodopa on six domains of balance and gait.	Arm swing and pace-related gait measures.	Neural circuits control balance and gait is different.
8	(Håkan et al., 2015)	Accelerometer cut points in PD patients.	Optimal cut-points were obtained.	Accelerometer cut points provided.
9	(Kleiner et al., 2015)	Automated Mechanical Peripheral Stimulation (AMPS) treatment in PD patients.	Stride length, gait velocity.	AMPS reduces motor impairment in PD patients.

10	(Del Din et al., 2016)	Gait characteristics in PD patients.	Variability of gait parameters.	Variability was able to differentiate.
11	(Ferrari et al., 2016)	Implementation of Kalman filter in IMU.	Root means square difference was 2.9%.	Method of accurate gait analysis.
12	(Elshehabi et al., 2016)	Effect of medication walking patterns.	Gait velocity, step duration, peak velocity	Dopaminergic medication affects PD.
13	(Horak et al., 2016)	Gait characteristics in OFF/ ON medication of PD patients.	Sway area, gait speed, and trunk motion	Different parameter changes between OFF to ON.
14	(Hatanaka et al., 2016)	Gait comparison in Progressive Supranuclear Palsy (PSP) and PD patients.	Similar hypokinetic gait in PSP and PD	Reduced vertical displacement in PSP patients.
15	(Curtze et al., 2016)	Balance and gait in PD patients and the effect of medication.	Turning speed, gait speed, and stride length.	Off-medication state is more related to disease severity
16	(Micó-Amigo et al., 2017)	Effect of walking distance in PD patients.	Gait parameter classification obtained.	Short distance gait assessment is useful.
17	(Warlop et al., 2017)	Nordic Walking (NW) walking in PD patients.	Variance, gait speed, and cadence.	NW improves gait parameters.
18	(Ginis et al., 2017)	Effect of cueing and prolonged walking in PD patients.	Less deviation in cadence.	Cueing improves gait impairment.
19	(de Souza Fortaleza et al., 2017)	Effects of a dual-task on the gait of patients with freezing of gait (FOG+) and without freezing of gait (FOG−).	FOG+ shorter stride length, slower stride velocity	Dual-tasking affects FOG+.
20	(Gougeon et al., 2017)	NW walking in PD patients.	Trunk frontal range of motion, peak velocity Cadence, gait speed and stride length	NW can improve postural stability.
21	(Kristina et al., 2017)	Association of kinematic gait parameters with quality of Life.	Use of assistive gait equipment	Quality of life improves using assistive devices.
22	(Montero-Odasso et al., 2017)	Motor-cognitive profiles in PD patients.	Gait speed and increased variability	Gait impairment related to cognitive decline.
23	(Johannes et al., 2017)	Gait characteristics in PD patient's disease progression.	Stride length, gait speed, foot clearance decreased, stride time, stance time, variability	Characterize PD motor impairment.
24	(Rovini et al., 2017)	Review on wearable sensors	Five main fields were studied	Overview of wearable sensors for studying PD patients.
25	(Raccagni et al., 2018)	Gait parameters study in many diseases.	Gait speed, stride length	Characterized PD, atypical parkinsonian disorders, progressive supranuclear palsy
26	(Bertoli et al., 2018)	Use of Trusted Events and Acceleration Direct and Reverse Integration (TEADRIP)	Stride length means absolute errors on average 2%.	Validated TEADRIP on 236 patients. large population.
27	(Zago et al., 2018)	Calibration of IMU in PD patients.	No difference in stride length, double support, step duration	IMU can be used for gait assessment.
28	(Creaby and Cole, 2018)	Review on walking biomechanics and falls	Spatiotemporal, kinematic and muscle activation pattern	Spatiotemporal and kinematic characterize fall in PD patients.

29	(Pau et al., 2018)	Laboratory and clinical gait assessment.	Laboratory setting affected speed and stride length	Gait assessment in the same environment reduces error.
30	(Caramia et al., 2018)	Classify between PD and control	Range of motion (RoM) variability	The best result from the knee range of motion.
31	(Felix et al., 2018)	IMU-based gait and balance assessment.	Gait speed	Gait speed related to PD patients.
32	(Aich et al., 2018)	Calibration of IMU in PD patients.	Classify between FOG+ and FOG -	IMU can assess FOG patients.
33	(Keloth et al., 2019)	Gait characteristics in PD patients walking pattern.	The variance of gait interval	IMU differentiate between PD and control.
34	(Raffegeau et al., 2019)	Review on the influence of dual-tasking	Single task and dual-task gait	Dual tasking severely affects PD patients.
35	(Brognara et al., 2019)	Review on application of wearable sensors	Gait parameters used for analysing PD patients	IMU can be used for gait assessment.
36	(Bailey et al., 2018)	Review of gait impairment in PD patients.	Gait quantification with multiple gait features	Gaps in gait impairment in PD patients.
37	(Sweeney et al., 2019)	Review on wearable cueing in PD patients.	Auditory, visual, somatosensory cueing	Effectiveness of cueing.

Table 4.2: Part II. Comparison of the publication on the gait variability of the spatiotemporal parameter in PD patients. Each paper has been briefly summarized in the previous section.

Sl. No	Reference	Aim of the paper	Gait parameter significantly different between PD patients and control	Remarks of the paper
1	(Olmo and Cudeiro, 2005)	Effect of cueing in PD patients	Step time variability	Cueing can improve gait performance in PD patients.
2	(Frenkel et al., 2005)	Treadmill walking on gait variability.	Stride and swing time variability	Treadmill enhance gait rhythmicity
3	(Baltadjieva et al., 2006)	Gait characteristics in de Novo PD patients.	Gait variability	Altered gait pattern in de Novo PD patients.
4	(Bartsch et al., 2007)	The long-term fluctuation of gait timing in PD patients.	Increased fluctuation in early PD, de Novo PD patients,	Fluctuation in gait timing affects PD patients.
5	(Henmi et al., 2009)	Evaluate stride-stride variability in PD patients.	Power spectrum	Spectral analysis may be used for studying PD gait.
6	(Hausdorff, 2009)	Gait characterize in PD patients	Stride length, gait variability	Gait variability characterizes ON/OFF state PD.
7	(Zampieri et al., 2010)	Differentiate the early-to-mid stage of PD patients.	Cadence	Variability was not able to differentiate.
8	(Krishnan and Wu, 2010)	Gait variability in PD patients.	Higher gait variability	Gait variability related to disease progression.

9	(Bryant et al., 2011)	Effect of levodopa and walking speed in PD patients.	Variability of step time, double support time, stride length, stride velocity	Levodopa decreased gait variability in PD patients.
10	(Roemmich et al., 2012)	Gait variability during the first two steps of gait initiation	Shorter steps, higher variability in step length, variability in swing time.	High gait initiation variability in PD patients.
11	(Hove et al., 2012)	Fractal scaling in PD patients.	Stride time fluctuation exponent	Reduced fractal scaling in PD patients.
12	(Galna et al., 2013)	Reliability of gait variability	More reliable during continuous walking.	Continuous walking and steps are not less than 30.
13	(Kirchner et al., 2014)	Fractal scaling under clinical conditions.	Fractal exponents by stitching short sequences	Stitching short sequences improved differentiating.
14	(Bello et al., 2014)	Gait during treadmill and overground walking.	Step length, step height, cadence, step width, and step width variability.	Gait characteristics improve during treadmill walking.
15	(Bryant et al., 2016)	Effects of levodopa on gait variability.	Variability of step time, swing time, stride length, stride velocity	Variability of double support time not affected by levodopa.
16	(Keloth et al., 2017)	Gait variability based on disease severity.	Stance, swing interval, self-similarity parameter	Less rhythmic gait for PD patients.
17	(Rennie et al., 2018)	Reliability of gait variability at slow and fast walking.	Step width variability	PD was reliable at normal and fast gait speeds.

The table is split into two parts: Part I examines “IMU sensors used for gait analysis”, and Part II reviews “Clinically relevant gait parameters for Parkinson’s disease”.

Table I summarizes the thematic review for the IMU applications for PD gait analysis. It lists 33 papers that describe original research related to IMU for PD gait analysis and 4 review papers. It highlights the clinical and engineering research on the use of IMU for PD gait. About half of the papers listed in this table (~17) report the clinical observations while 16 describe the sensors and analysis aspects of the research. Table II is a selection of 17 papers with the focus on gait variability of the spatiotemporal parameter in PD patients. This is a focused review of a very specific IMU features that have been highlighted in table I as being the most promising analysis method.

Earlier reviews on similar topics have focused either from engineering or viewpoint only. While such reviews have the strength of having focused audience and agenda, these tend to miss out on the relationship between the engineering outcomes and the clinical

requirements. This thematic review has brought together articles from the two disciplines and shows the available solutions and potential research opportunities.

Following the table, the next sub-section lists the highlights of each paper, and the gaps in the research reported in these papers. While this is a thematic review, in this section, the papers have largely been presented chronologically.

4.4 Review of the papers

4.4.1 Part I "IMU sensors used for gait analysis"

4.4.1.1 Validation of IMU sensor

IMU devices must be validated on PD patients to check the reliability, accuracy, and reproducibility of readings for gait analysis. (Esser et al., 2013; Palmerini et al., 2013) studied the reliability of IMU sensors to identify and quantify the gait of control and PD patients. (Palmerini et al., 2013) observed that the temporal measures and angular velocity can characterize PD from control using IMU sensors. However, the latter reference showed that spatial parameters cannot be used as a measure for the gait parameters to differentiate the two groups. The paper found a non-significant difference between the two groups for the gait features-cadence and stride length (Esser et al., 2013).

In the latter years, Mico et al (2017) performed a validation study on the short distance walking using the IMU sensor. They assessed 5-meter walks of PD patients with a single IMU sensor and observed that the gait parameters could be classified against the disease conditions. It was concluded that the short distance walking measurements are informative, thus helping the clinical evaluation of gait (Micó-Amigo et al., 2017). Johannes et al (2107) on the other hand, validated the use of wearable sensors on many patients in each group based on the Hoehn and Yahr (H & Y) scale for studying the disease progression. They observed that the gait parameters- stride length, gait speed, foot clearance decreased, stance time, and stride time, and its variability increased with disease progression. They concluded that

wearable sensors can be used effectively to measure the gait parameter and to monitor the disease progression in PD patients (Johannes et al., 2017).

Further, Pau et al (2018) studied the difference in the spatiotemporal parameters when walking was performed in a laboratory and clinical settings using the IMU sensor. They observed a decrease in gait speed and stride length (by 17% and 12% respectively) when passing from the clinical to the laboratory setting. They concluded that gait assessment should always be performed in the same conditions to avoid the error which could lead to inaccurate patient evaluation (Pau et al., 2018).

4.4.1.2 Gait impairment in sub-types of PD patients and comparison with different groups

IMU sensors have been used to investigate gait impairments in different patient groups and between subtypes of PD patients. The paper by Herman et al (2014), studied the changes to the gait parameter in PD subtypes- Postural Instability Gait Disorder (PIGD) and Tremor Dominant (TD). They observed that the gait parameters which were studied by them- gait speed, stride length, and stride variability, did not have a significant difference between Postural Instability and other groups. They also found that the gait of purely PIGD (p-PIGD) significantly differed from purely TD group (p-TD) with a reduction in gait speed, shorter strides, and increased stride variability. These findings suggest that the classification into p-PIGD and p-TD may be useful, which is based on the criteria that the PIGD or TD score <1 and no noticeable tremor in PIGD, and postural instability in TD groups (Herman et al., 2014). A similar study by Trojaniello et al (2015), found the suitable location of the IMU to capture the changes due to disease. They estimated the gait parameters in different groups of people- elderly, post-stroke patients, PD patients, and Huntington's disease patients using IMU positioned over the subject's trunk. The stride time and step time error increased (4% and 8% to reference value measured using gold standard instrumented mat) for pathological gait when compared to the elderly control. The paper shows that when highly impaired gait

is analyzed, a method employing one IMU placed on the leg is preferred (Trojaniello et al., 2015).

In 2016, Hatanaka et al (2016) conducted a comparative gait analysis between PSP and PD patients. Although PSP and PD patients showed similar hypokinetic gait, PSP patients showed characteristically reduced vertical displacement and a higher acceleration than PD patients at the same cadence (Del Din et al., 2016). Raccagni et al (2018) on the other hand studied gait impairment between PD patients and atypical Parkinsonian disorder patients. They found that gait of atypical Parkinsonian disorder patients was more severely impaired than PD patients, with a reduction in gait speed and stride length of the patients (Raccagni et al., 2018).

4.4.1.3 Effect of medication and different rehabilitation

Medication and other intervention techniques are used to help improve the quality of life of PD patients. However, due to the complex nature of the disease, it is important to evaluate the effectiveness of the patient for different symptoms. The paper by Curtze et al (2015) studied the effect of medication on six domains of gait and balance- postural sway, gait pace, dynamic stability, gait initiation, arm swing, and turning in people with mild and severe PD. They found that gait parameters varied differently in response to levodopa, thus suggesting multiple neural control circuits control the gait and balance in PD patients (Curtze et al., 2015).

The paper by Horak et al (2016) studied gait and balance parameters during ON/ OFF medication in PD patients and compared these with control patients. It was concluded that various balance and gait parameters are affected due to medication and there were significant differences between OFF to ON and between OFF and control patients (Horak et al., 2016). A similar study was conducted by Curtze et al (2016) which measured the relation between gait and balance to disease severity and the effect of the medication in PD patients (Curtze et al., 2016).

The different types of walking and relation to the effect of medication were studied using the IMU sensor. The paper by Elshehabi et al (2016) studied the effect of medication on straight walking and turning in a single task (ST) and dual-tasking (DT) using an IMU. They concluded that dopaminergic medication does not influence straight walking and turning in PD during DT. This shows that multitasking while walking has a limited effect from dopaminergic medication (Elshehabi et al., 2016).

4.4.1.4 IMU sensor-based gait variability study

Several studies that have used IMU sensors to measure the gait of PD patients have reported that variability in the gait parameters is an important feature and hence this is being considered as a separate topic in this review. The paper by Brodie et al (2015) observed an increase in stride-to-stride oscillation in PD, measured at the head using an IMU sensor. This shows that the uncontrolled head oscillation is linked to the gait impairment in PD (Brodie et al., 2015).

The effect of dual-tasking in patients with and without FOG while walking was studied by De Souza et al (2017) found that the effect of dual-tasking on the gait parameters was more in patients with FOG (FOG+) when compared to those without FOG (FOG-). They observed a decrease in stride length, stride velocity and increase in variability of these parameters while walking for FOG+ patients while performing a dual-task when compared to single-task walking (de Souza Fortaleza et al., 2017). The relation to motor and cognitive tasks was later analyzed by Montero et al (2017) and they observed that gait assessment with dual tasking can help extract the cognitive and motor contribution in PD. They concluded that the dual-tasking while walking decreases the cognitive and motor loading, progression to dementia syndrome and result in falls and mortality in patients (Montero-Odasso et al., 2017).

4.4.1.5 Recent review papers of the gait in PD patients

There have been a few recent review articles on the gait of PD patients. These review articles are highly focused and while extremely useful, do not cover the topic from a multidisciplinary viewpoint. Below is the summary of these in the context of technologies for gait analysis for PD.

The review paper by Rovini et al (2017) studied the use of wearable sensors in PD patients. The paper summarizes the use of wearable sensors in five main fields -early diagnosis of disease, tremor in PD patients, body movement analysis, motor fluctuation and long-term monitoring of PD patients. The paper demonstrates the need for monitoring the disease progression from beginning to the development of the disease, pharmacological therapy during disease progression and finally enhance the quality of life of PD patients (Rovini et al., 2017). The association between walking mechanism and related falls in PD patients is addressed in the review paper by Mark et al (2018). They found that those who have slower gait, walking speed, lower cadence, shorter strides, and more mediolateral head and pelvis motion have a higher risk of future falls. Thus, it was concluded that the spatiotemporal and kinematics parameters may have the potential to characterize falls in PD patients (Creaby and Cole, 2018).

A systemic review on the effect of dual tasking in the gait of PD patients was performed by Tiphanie et al (2019). They demonstrated that dual-tasking deteriorates walking speed regardless of the type of dual-task performed by the PD patients (Raffegeau et al., 2019). A review paper by Brognora et al (2019) studied the importance of wearable sensors for characterizing gait in PD patients. They concluded that wearable sensors are the low-cost and non-invasive device that can be used for analyzing gait in PD patients (Brognara et al., 2019). While there are many review papers on the gait analysis in PD patients, there was no review conducted on identifying the suitable gait features that can distinguish between PD patients and control and on the use of IMU sensors for gait analysis to the identify gait abnormalities

in PD patients. The review is also subdivided into- validation of IMU sensors, gait impairment in sub-types of PD patients and comparison with different groups, the effect of medication and different rehabilitation, IMU sensor-based gait variability study, the effect of rehabilitation on gait variability, the effect of medication on gait variability and gait variability used for differentiating between PD patients and control.

4.4.2 Part II "Gait variability in Parkinson disease patients"

4.4.2.1 Effect of rehabilitation on gait variability

Rhythmic Auditory Stimulation (RAS) and treadmill walking acts as a feedback circuit to the brain. The paper by Olmo and Cudeiro (2005) observed a significant difference in step time variability between PD and CO before and after rhythmic auditory stimulation. Thus, RAS can be suggested as a valuable method of improving the gait timing in PD patients (Olmo and Cudeiro, 2005). Similarly, the paper by Frenkel (2005) suggests that the treadmill may be used as an external cue to improve the gait characterize of PD patients. They observed a decrease in stride time variability when PD participants walk on a treadmill compared to overground walking. They concluded that the treadmill can be used as an external cue to improve the gait rhythm and thus reduce the gait variability (Frenkel et al., 2005). A similar observation was reported by Bello et al (2014) who studied the difference in spatiotemporal parameters during treadmill and overground walking and observed that the PD patients significantly increased their step-length and height and reduced their cadence, step-width and step-width variability on the treadmill (Bello et al., 2014).

4.4.2.2 Effect of medication on gait variability in

Levodopa or other dopamine medication have been found to affect the gait interval parameters in PD patients. PD patients with the active effect of medication are referred to as "ON state", while the ones without medication effect are "OFF state". The paper by Baltadjieva et al (2006) studied the gait interval of PD patients who were not treated with anti-Parkinson medication and compared these with the control. They found a significant

difference in double support and single limb support interval variability in PD patients with anti-Parkinson medication (Baltadjieva et al., 2006). A similar study by Bartsch et al (2007), analyzed the gait variability on PD patients who were not yet treated with medication and observed a significant difference in gait timing when compared to the control. These researchers have shown that there is a significant difference in the gait between the PD in OFF state and controls (Bartsch et al., 2007). Later, Bryant (2011) observed a decrease in step time, double support time, stride length and stride velocity variability after medication in PD patients. They also found that the variability of step-time and double support time is speed independent measures of gait (Bryant et al., 2011).

The paper by Elshehabi et al (2016) studied the effect of medication on straight-line walking and turning during dual-task and they found that only gait velocity was able to differentiate between ON and OFF state of medication (Elshehabi et al., 2016). On a different walking pattern- forwarding and backward walking, the paper by Bryant in (2016) studied the effect of levodopa on gait variability on these walking pattern in PD patients and they found that the variability of step-time, swing-time, stride-length, and stride-velocity decreased significantly with walking after medication while double-support-time variability remained unchanged after levodopa administration (Bryant et al., 2016). From the above, it appears that the effect of medication on the gait of PD patients needs further investigation.

4.4.2.3 Gait variability used for differentiating between case and control

The measure of the gait parameters has been shown to differentiate between PD patients and age-matched controls. The paper by Henmi et al (2009) studied the spectral properties of gait variability in young, elderly and PD patients and found that the power spectrum of PD was 4 times larger than the other two groups. Thus, the method of spectral analysis of stride-stride variability may be useful in differentiating PD patients from control (Henmi et al., 2009). A similar study by Zampieri et al (2010) analyzed the difference in the temporal gait parameters of PD patients and age-matched during walking. They found that the only

significant difference between PD patients and controls was based on the cadence (Zampieri et al., 2010). In the same year, Krishnan et al (2010) developed a statistical model to describe the higher gait variability in PD patients. The increase in the inter-stride variability has been proposed for the diagnosis of PD and monitoring the progression of the disease (Krishnan and Wu, 2010).

The paper by Del et al (2016) compared the gait characteristics in PD and control and found that there was a significant difference in gait variability while other gait features like step-velocity and swing-time were not able to differentiate between the two groups (Del Din et al., 2016). In contrast, Warlop et al (2017) observed a significant difference in gait speed, cadence and stride duration variability in PD ON state when compared to the control (Warlop et al., 2017). In the same year, Keloth et al (2017) studied the gait variability with different severity levels of PD and found greater variability and observed that the PD patients have less defined gait when compared to controls. They also found that among the stance and swing-phase of stride interval, the self-similarity was less for swing interval when compared to the stance interval of gait that decreased with the severity of PD. This suggests that PD has reduced periodicity and their gait is less rhythmic. It also showed that the patients seem to have a sense of urgency when in single-limb support and attempt to remain in the double support phase (Keloth et al., 2017).

4.5 Discussion and future research

The strength of this review is that it is multidisciplinary in nature, which has selected both, technical and clinical papers. This review has shown that there is number of researchers that have reported the investigation of IMU for the gait analysis and assessment of Parkinson's disease. However, most of the studies have not progressed for implementation in the clinical assessment of the PD patients. The work identified some of the reasons for this difference and identified methods that may facilitate the translation of this technology from research to the clinical applications.

Of the papers reviewed, 41% used foot sensitive sensors, 32% used an IMU sensor, and only a few used the expensive motion capture camera systems for performing gait analysis. Several gait parameters for analyzing gait variability have been reported. Stride time, also known as gait duration, was used in 78% of the studies. The sub-intervals of gait duration, mainly stance time, swing time and double support time was used in 45% of studies. Cadence, the ratio of the number of steps to the time taken, was only used 9% for analyzing the gait variability. The variability of spatial parameters was studied based on stride-length (27%) and step-length (7%). Only 14% of the total articles reported on limb asymmetry. In the majority (82%) of these studies, the gait parameters were derived from direct gait measurement in the lab. While such measurements have shown very valuable outcomes only 18% took the next step and used signal processing to filter the data and compute the gait parameters. This is surprising because the use of signal processing techniques can extract higher levels of valid signals from noise and improve the outcomes, identifying differences that would otherwise be invisible. The novel use of algorithms has the potential to be of clinical significance and to make any work more publishable. It may be possible to use existing data which has already been published and apply novel algorithms to obtain new or more robust outcomes.

In any area of human studies, confounding factors can affect measurements, and this can dilute or can lead to incorrect conclusions and ruin the outcomes of the study. For example, if patient medication is not recorded and considered during the analysis, then an effective measurement and analysis method may show no statistical difference, which may be due to the effect of the medication, and not the measurement method. Other confounding factors include the UPDRS level of the patients, the period since the onset of the disease, wearing-off time of the medication, cognitive impairment and loading, use of caffeine or alcohol prior to the tests, and other medical conditions. Other potential factors could be the gender, height, and race of the participants. Some of these factors can be controlled as part of the experimental design but others such as medication may split the patients into two or

more groups. This would lead to smaller groups which makes it more difficult to measure the statistical significance of the results. The basic demographic details of the participants such as age, height, and gender were specified in many of the articles (95%). Most of the studies (81% of the articles) have reported PD measurement based on H & Y scale details for studying the stages of PD patients while others have used UPDRS in addition to, or alternative to the measure of the severity of the disease (9 %). However, some studies did not report any one of these measures. Another limitation in many of these studies was that the medication history of the patients was only specified by 31% of the papers, and a large percentage of the articles failed to report this vital detail. Thus, a detailed comparison between many of these studies was not possible and it is difficult to make accurate conclusions.

There is scope for new research that reworks the existing research papers to fully report and investigate the effects due to the confounding factors. This may require a larger number of patients than the previous studies, but the results will be far more impactful, and useful to clinicians because the importance and effects of the different factors will become clearer. There is also the possibility of taking the same patients but adding confounding factors to see the effect on any measurements. While some of the confounding factors have been listed above, other possibilities include the non-motor symptoms of PD such as dementia, depression, anxiety and emotional problems, natural day-to-day variation, and the patient mindset at the start of a session such as happy, sad, or bored. Such information would be a valuable guide to other researchers and help better plan clinical observations. It may well be that in the future, journals need to be more demanding that confounding factors be stated and included in any analysis.

While reviewing the papers, we have noticed that there was a lack of consistency in the sensor specifications, the number of sensors, the placement of sensors, and the experimental protocol. The most common location of the sensor was on the feet and approximately 36%

of the papers used this location. Other common locations for the sensors included the shank (27%), and the chest and lower back position (18%). The articles used different experimental set-ups and methodologies for calculating the same spatiotemporal parameters and the variability of those parameters. It would be most valuable to survey these methods to identify the effectiveness and cost of each methodology and then propose one or more cost-effective strategies complete with the cost-benefits of each method. Such work is more likely to become useful in real clinical applications.

Another point of difference between the papers was the calibration of IMUs. While some of the papers have calibrated and validated IMU sensors or compared them with a gold standard such as motion capture camera (Esser et al., 2013; Palmerini et al., 2013; Zago et al., 2018), many others have not. Without such calibration, there can be significant estimation errors that can affect the accuracy of the measurements and the validity of any conclusions. In the future, all better papers should either undertake this calibration of IMU devices or use methodologies from other researchers who have done such calibration.

In some of the papers reviewed it was observed that gait variability was identified as an important gait measure that reflects the gait instability, rhythm and less motor control (Keloth et al., 2017; Keloth et al., 2019). It was also suggested that variability reduces with different interventions (Frenkel et al., 2005; Olmo and Cudeiro, 2005; Henmi et al., 2009). Other papers reported this variability to be insignificant (Zampieri et al., 2010; Elshehabi et al., 2016; Caramia et al., 2018). There is scope to study the clinical significance related to gait variability of PD subtypes and Parkinsonian disorders such as PIGD, TD, PSP during FOG and in relation to cognitive loading to prevent misdiagnosis.

The evidence from the literature is that gait analysis using IMU can be very effective in evaluating PD patients but this review and discussions with our clinical partners have shown that these methods are not routinely used by clinicians. Thus, there is significant

opportunity for the translation of this proven technology such that it is used by clinicians for monitoring their patients.

This chapter is based on the manuscript which is under review:

Keloth S, Arjunan S, Radcliffe P and Kumar D IMU for gait analysis of Parkinson's disease patients- A multidisciplinary review. *Sensors*.

Chapter 5

5. Changes in gait parameter with the severity of Parkinson's disease

Brief outline of the chapter:

This chapter reports the measure of the changes in gait parameter based on the severity of the disease and compares these with age matched control. The differences between PD and control, and based on the severity of PD had been reported in this chapter.

5.1 Introduction

In comparison with control, PD patients have reduced stride length (Morris et al., 1998; Sofuwa et al., 2005) and walking speed (Sofuwa et al., 2005; Combs et al., 2014) with increased double support duration (Morris et al., 1994; Vieregge et al., 1997; Morris et al., 2001; Ferrarin et al., 2002) during free ambulation on even surface. The increase in variability has been proposed for diagnostic and monitoring the progression of the disease. In this chapter, the variation in different gait intervals-stride interval, swing interval, stance interval, and double support interval is studied using two different method: a) using Detrending fluctuation analysis (DFA), which is a statistical method to find the self-similarity in patterns from a long-range correlated time series. b) using the Co-efficient of variation (CV). Both the methods detect the variation in the signal, with CV giving the amount of variability while DFA gives the structural complexity of the signal and the information on the correlation of signal at the instant to signal at any time. The long-range correlation in the signal is calculated using the self-similarity parameter (α).

The other important factor of gait that can be obtained from the heel-strike data is the lateral asymmetry. There is a natural asymmetrical gait pattern in humans due to limb dominance (Gabbard and Hart, 1996; Arevalo et al., 2018). During walking, the non-

dominant lower limb contributes more towards support and the dominant limb contribute more to propulsion (Hirokawa, 1989; Bracht-Schweizer et al., 2017). However, loss of limb coordination in producing rhythmic motion may cause pathological asymmetric gait (Sadeghi et al., 2001). This chapter reports the analysis of the four phases of the gait of PD and control, to identify which of these are most affected by disease and thus could be considered for diagnosing or monitoring the disease. This chapter also reports the lateral difference for the gait parameters for PD patients.

5.2 Materials and methods

5.2.1 Details of the dataset

The study has investigated the public dataset (Goldberger et al., 2000) of the gait data of 31 participants: 16 control referred to as CON, 6 with early stages referred to as PD1 and 9 with advanced stages of PD, referred to as PD2 (Moody et al., 2001). The severity of PD was based on the Hoehn and Yahr Scale (H&Y); PD1 corresponding to H&Y between 1 and 2.5, and PD2 with H & Y scale between 3 and 4. The anthropometric details of participants are listed in Table 5.1.

Table 5.1: Anthropometric details of participants

Anthropometric parameter	CON (n =16)	PD1 (n=6)	PD2 (n=9)
Age (Years)	45.66±9.14	66±14.3	67.33±8.7
Height (m)	1.83±0.085	1.88±0.12	1.85±0.17
Weight (kg)	68.935±10.75	81.33±14.3	70.88±17.66
Gender (male: female)	2:14	1:5	4:5

The data was recorded using bi-lateral insole force sensors placed at the ankle of the participant. The participants walked at their preferred speed (no recording on the gait speed) along a level ground 160 m long for 6 min without stopping. The output was sampled continuously at a rate of 300Hz and analyzed the start and end times of stride. The first 30 s of each subject's time series were removed to minimize any start-up effects.

5.2.2 Data analysis

The database consists of the four gait parameters: stride interval, swing interval, stance interval, and double support interval, shown in figure 3.1. The first step was the visualization of the data which was done by plotting the histogram of the four parameters for each side and each participant. The next step was computing the mean and coefficient of variance of the four parameters for each participant both, right and left side and compute the lateral difference; mean stride interval (μ_{st}), mean swing interval (μ_{sw}), mean stance interval (μ_{sta}), mean double support interval (μ_{ds}), variance stride interval (σ_{st}), variance swing interval (σ_{sw}), variance stance interval (σ_{sta}) and variance double support interval (σ_{ds}): σ_{ds} being common for left and right sides. The next step was to compute the self-similarity parameter using Detrending fluctuation analysis.

The details of the different methods are given below:

5.2.3 Histogram

The histogram is a graphical visualization of the data, that can help to understand the shape and spread of the data.

5.2.4 Coefficient of variance

The coefficient of variance (CV) is the statistical measure of the dispersion of the data points around the mean of the data. This helps to understand the amount of variability associated with the data. CV is defined as the ratio of the standard deviation to the mean of the data.

5.2.5 Detrending fluctuation analysis (DFA)

The self-similarity parameter of the data was computed using DFA (Beran, 1994; Hausdorff et al., 1996) which is robust for non- stationary signals (Hausdorff et al., 1997). It is a statistical method to find the self-similarity in patterns from a long-range correlated time series. The self- similarity parameter can estimate the behavior of the time series to be

periodic or non-periodic. Randomness associated with the gait pattern due to the severity of the PD was investigated using DFA.

The process of DFA is explained as follows:

Step 1: The time series with N samples were integrated to get the cumulated sum(y(k)).

Step 2: The series is divided into bins of size n (range 5 to 20). In each box, a least square straight line (also known as a trend, $y_n(k)$) is fit to the data.

Step 3: Next, the detrending is performed by subtracting the local trend from the integrated time series. The root mean square of detrended and integrated time series is calculated using the equation 1,

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k) - y_n(k)]^2} \qquad (1)$$

Step 4: The scaling parameter (also known as self-similarity parameter) is the slope of the log-log graph and represented by α which is in the range 0-1. If $0.5 < \alpha < 1$, the data has a long-range self-similarity while if $\alpha < 0.5$, the data is largely random. For a healthy individual the self-similarity parameter is in the range of $0.5 < \alpha < 1$ (Hausdorff et al., 1997). The hypothesis of the study is that the α value decreases with the severity of the disease.

5.2.6 Percentage of stance and swing

The stride interval was analyzed to determine the ratio of the stance and swing interval. This was performed to test whether there is a relative increase in the stance phase among the PD patients, and this increased with the severity of the disease.

5.3 Statistical analysis

The following statistical analysis test was conducted for this study

5.3.1 Normality test

Before performing the statistical test, the Shapiro-Wilk test was conducted to check for normal distribution of the raw data by considering all the gait parameters. Shapiro-Wilk test provides the highest power of distribution when compared to other tests like Kolmogorov-Smirnov test or Lilliefors correction (Ghasemi and Zahediasl, 2012).

5.3.2 Non-parametric tests

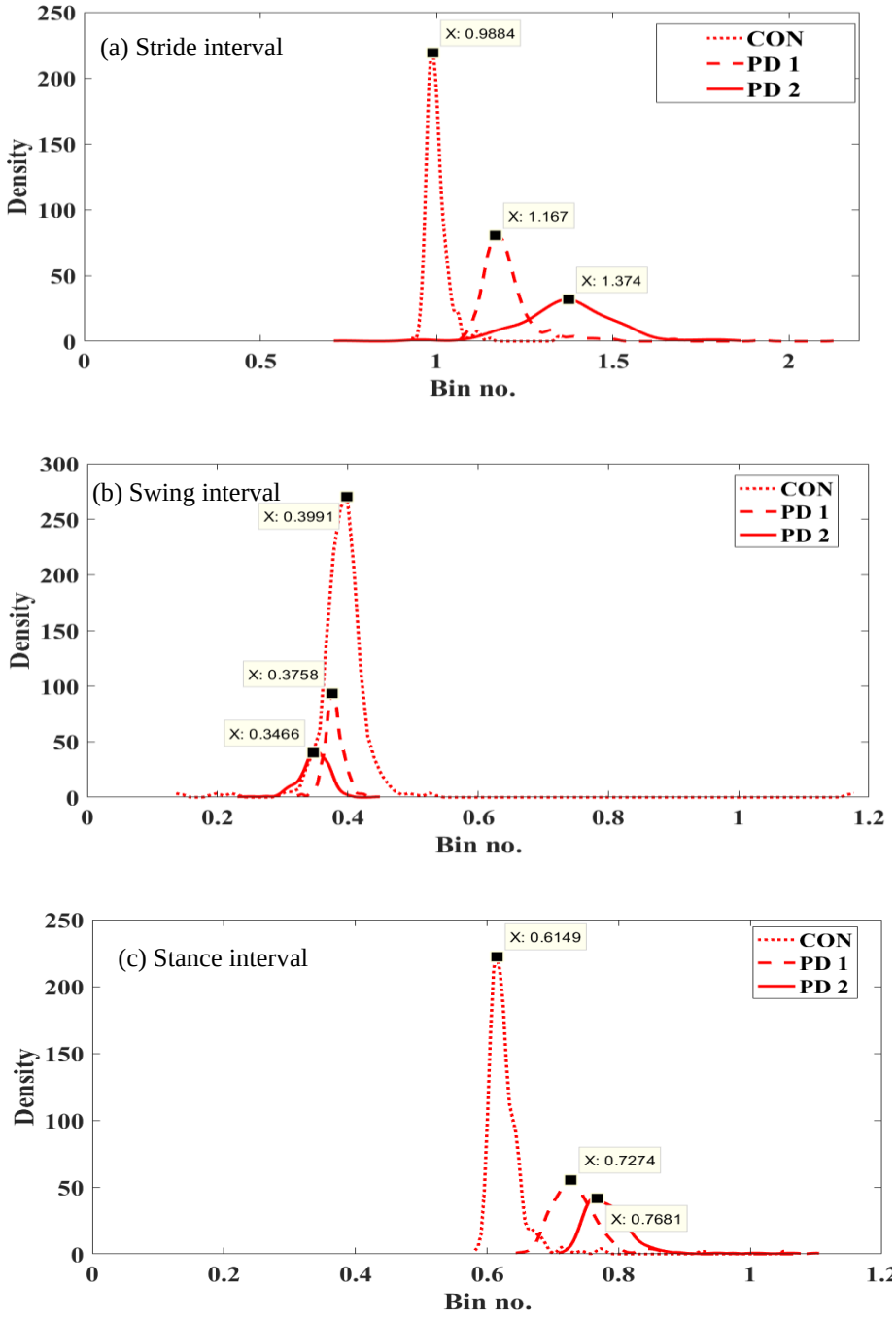
To test the significant difference between the groups, a non-parametric test Kruskal-Wallis test was performed (Siegel, 1988). The variance and mean of gait intervals: variance stride interval (σ_{st}) and variance swing interval (σ_{sw}), variance stance interval (σ_{sta}), variance double support interval (σ_{ds}), and mean stride interval (μ_{st}), mean swing interval (μ_{sw}), mean stance interval (μ_{sta}), mean double support interval (μ_{ds}) and the self-similarity parameter for a different group of participants were considered for checking the level of significance between the groups.

5.4 Results

5.4.1 Histogram

A histogram was used for the graphical visualization of the data to understand the difference in shape and spread of the data in each group (Arora et al., 2015). The group representative histograms of stride, swing, stance, and double support interval of right-leg of the three groups; CON, PD1, and PD2, a randomly selected participant from each group are shown in figure 5.1. The distributions are unimodal for all four parameters and the CON participants have narrow distributions. The distributions of PD1 are less constricted compared to CON and that of PD2 was the most spread. These also show that there is a noticeable increase in the mean stride, stance, and double support intervals from CON to PD1

and PD2. However, a decrease in mean swing interval is observed with PD2 when is compared to CON.



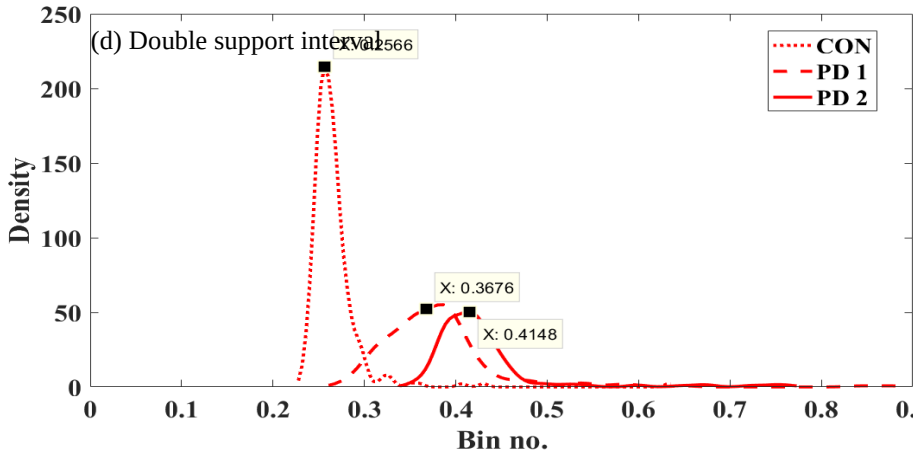


Figure 5.1: Histogram plot of participants randomly selected from each group (a) stride, (b) swing, (c) stance and (d) double support interval for CON, PD1 and PD2 participants respectively

5.4.2 Lateral differences

Table 5.2 shows the mean and variance of the left and right leg of gait parameters for CON, PD1, and PD2 participants. The subscript denoted by '*l*' and '*r*' denotes the left and right leg values of gait parameters. This shows that while there is a small difference between the left and right leg parameters for all participant groups, however, the statistical analysis did not show any statistically significant lateral difference ($p < 0.05$). Hence further analysis was performed only on the right-leg data.

Table 5.2: Comparison between left and right leg mean ±SD and variance ±SD of gait parameters for different groups

Gait intervals	Statistical parameter	CON	*p*-value	PD1	*p*-value	PD2	*p*-value
Stride interval	$\mu_{st,\,l}$	1.095 ± 0.093	0.462	1.215 ± 0.271	0.872	1.153 ± 0.123	0.894
	$\mu_{st,\,r}$	1.071 ± 0.047		1.122 ± 0.102		1.147 ± 0.119	
	$\sigma_{st,\,l}$	0.002 ± 0.003	0.497	0.005 ± 0.005	0.872	0.009 ± 0.010	0.964
	$\sigma_{st,\,r}$	0.001 ± 0.001		0.005 ± 0.004		0.007 ± 0.006	
Swing interval	$\mu_{sw,\,l}$	0.396 ± 0.039	0.282	0.389 ± 0.035	0.109	0.364 ± 0.063	0.757
	$\mu_{sw,\,r}$	0.381 ± 0.030		0.368 ± 0.037		0.361 ± 0.067	
	$\sigma_{sw,\,l}$	0.0004 ± 0.0002	0.763	0.0010 ±0.0005	1	0.002 ± 0.001	0.825
	$\sigma_{sw,\,r}$	0.0004 ± 0.0002		0.0009 ±0.0003		0.002 ± 0.001	
Stance interval	$\mu_{sta,\,l}$	0.682 ± 0.033	0.821	0.732 ± 0.078	0.336	0.791 ± 0.107	0.825
	$\mu_{sta,\,r}$	0.689 ± 0.032		0.753 ± 0.089		0.778 ± 0.104	
	$\sigma_{sta,\,l}$	0.002 ± 0.002	0.174	0.0042± 0.003	0.872	0.005 ± 0.004	0.658
	$\sigma_{sta,\,r}$	0.001 ± 0.001		0.004 ± 0.004		0.010 ± 0.017	

5.4.3 Features of stride, swing, stance, and double support interval

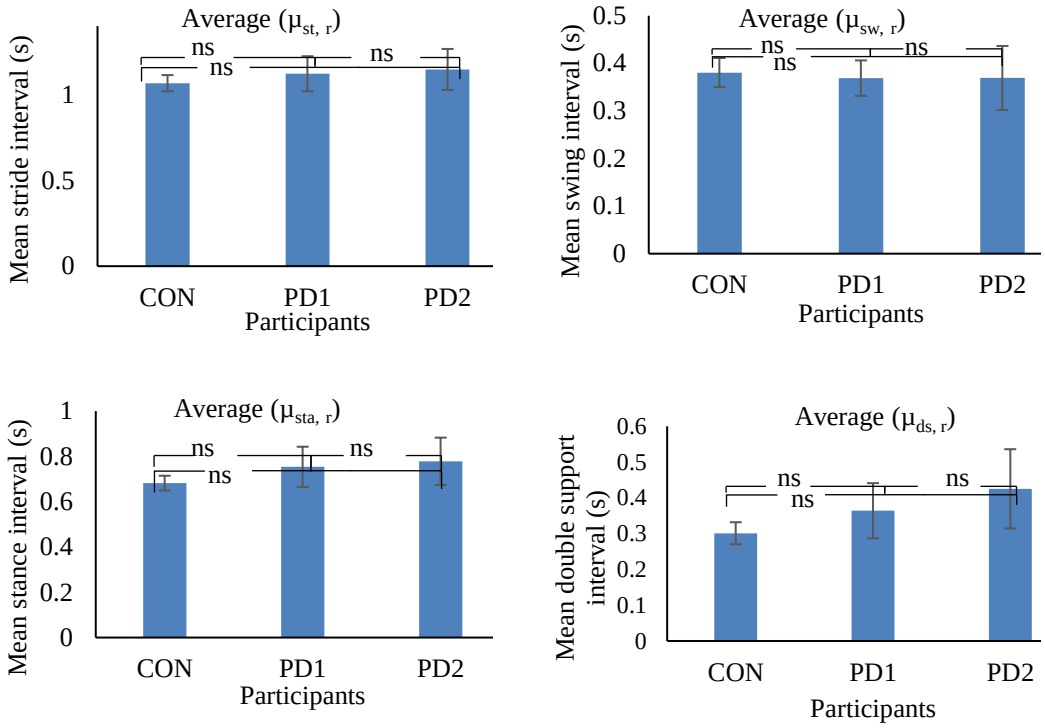
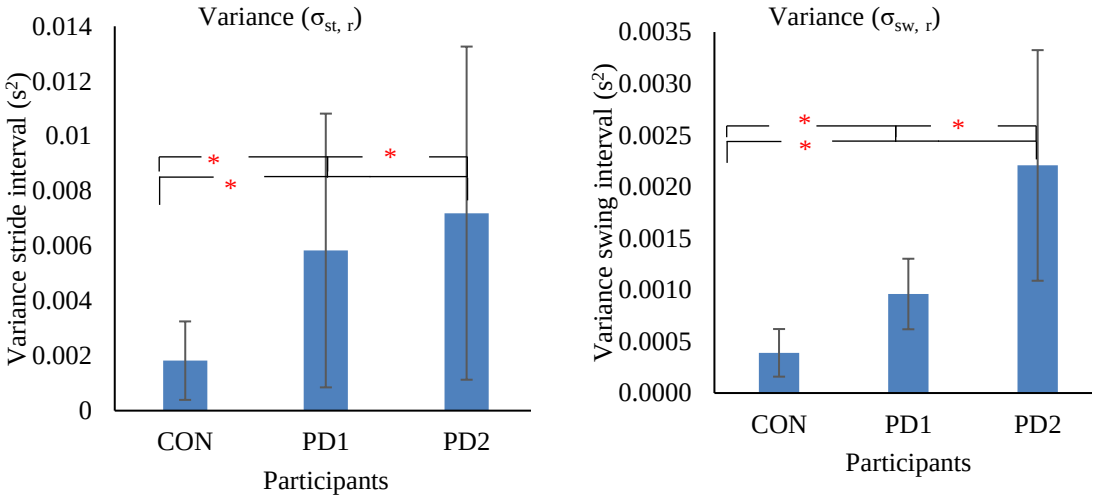


Figure 5.2: Bar chart showing mean stride, swing, stance, and double support interval for CON, PD1, and PD2 participants (Significance (p) =non-significant (ns)).



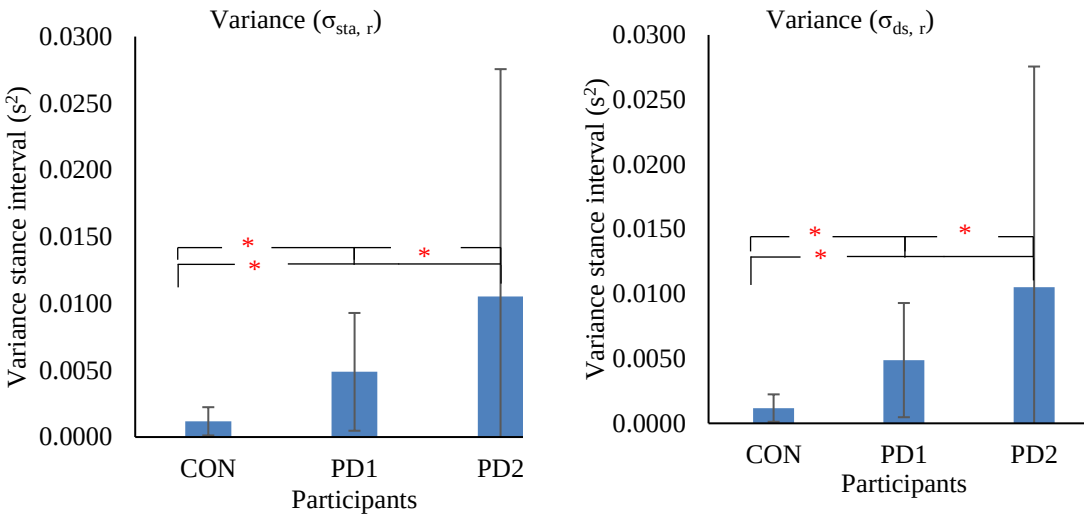


*Figure 5.3: Bar chart showing variance stride, swing, stance, and double support interval for CON, PD1, and PD2 participants respectively (*p (Significance) < 0.05, ns (non-significant).*

Figure 5.2 shows the unnormalized group-mean for the four parameters; stride, swing, stance, and double support interval for the three groups; CON, PD1, and PD2 participants. Figure 5.3 shows the variance of the four gait phases; stride, swing, stance, and double-support interval for CON, PD1, and PD2 participants, and the statistical significance results are shown in Table 5.3. From, figure 5.2, figure 5.3 and table 5.3, it is observed that,

- The mean of all the four gait parameters; stride-interval, swing interval, stance-interval and double-support interval are the least of CON, higher for PD1, and the maximum for PD2. However, the difference is not statistically significant.
- The variance of all the four gait parameters; stride-interval, swing interval, stance-interval and double-support interval are the least of CON, higher for PD1, and the maximum for PD2. The group-differences of all four parameters are statistically significant.

Table 5.3: Comparison between mean (±SD) and variance (±SD) of gait parameters when CON, PD1, and PD2 groups are compared

Gait intervals	Statistical parameter	CON	PD1	PD2	*p*-value
	$\mu_{st, r}$	1.071 ± 0.047	1.122± 0.102	1.147 ± 0.119	0.194

Stride interval	$\sigma_{st,\,r}$	0.001 ± 0.001	0.005 ± 0.004	0.007 ± 0.006	0.0005*
Swing interval	$\mu_{sw,\,r}$	0.381 ± 0.030	0.368 ± 0.037	0.361 ± 0.067	0.518
	$\sigma_{sw,\,r}$	0.0004 ± 0.0002	0.0009 ± 0.0003	0.002 ± 0.001	0.00003*
Stance interval	$\mu_{sta,\,r}$	0.689 ± 0.032	0.753 ± 0.089	0.778 ± 0.104	0.051
	$\sigma_{sta,\,r}$	0.001 ± 0.001	0.004 ± 0.004	0.010 ± 0.017	0.0004*
Double support	$\mu_{ds,\,r}$	0.301 ± 0.0308	0.363 ± 0.077	0.425 ± 0.1106	0.081
	$\sigma_{ds,\,r}$	0.0020 ± 0.003	0.00441 ± 0.003	0.0090 ± 0.0094	0.005*

5.4.4 Percentage stance and swing of stride interval

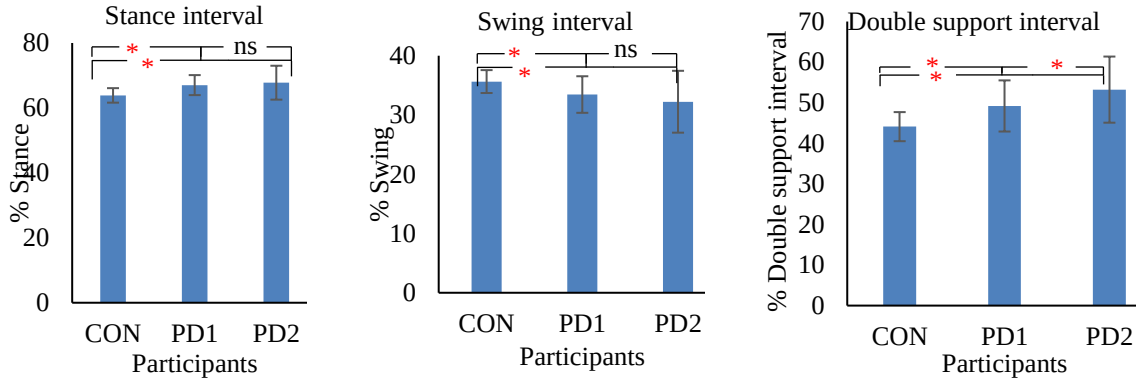


Figure 5.4: Bar chart showing the percentage of stance, swing, and double support interval for different groups

Figure 5.4 shows the percentage of stance, swing, and double support intervals for CON, PD1, and PD2 participants respectively, and the statistical significance is shown in Table 5.4.

Table 5.4: Percentage of stance, swing, and double support interval for different groups

Gait	CON (%)	PD1 (%)	PD2 (%)	*p*-value
Stance interval	63.85 ± 2.23	67.0 ± 3.08	67.76± 5.21	0.0295*
Swing interval	35.63 ± 1.73	33.04 ± 3.80	32.23 ± 5.2	0.0492*
Double support interval	44.10 ± 3.58	49.20 ± 6.3	53.22 ± 8.15	0.0021*

Figure 5.5 shows the bar chart representation of the mean self-similarity parameter with its standard deviation for control, PD1, and PD2. The self-similar properties of swing interval show the least value of α (in the range of 0.6) among the other phases of gait. The variations

in the self-similarity parameter are more significant in stride interval when compared with control and PD patients.

5.4.5 Self-similarity parameter

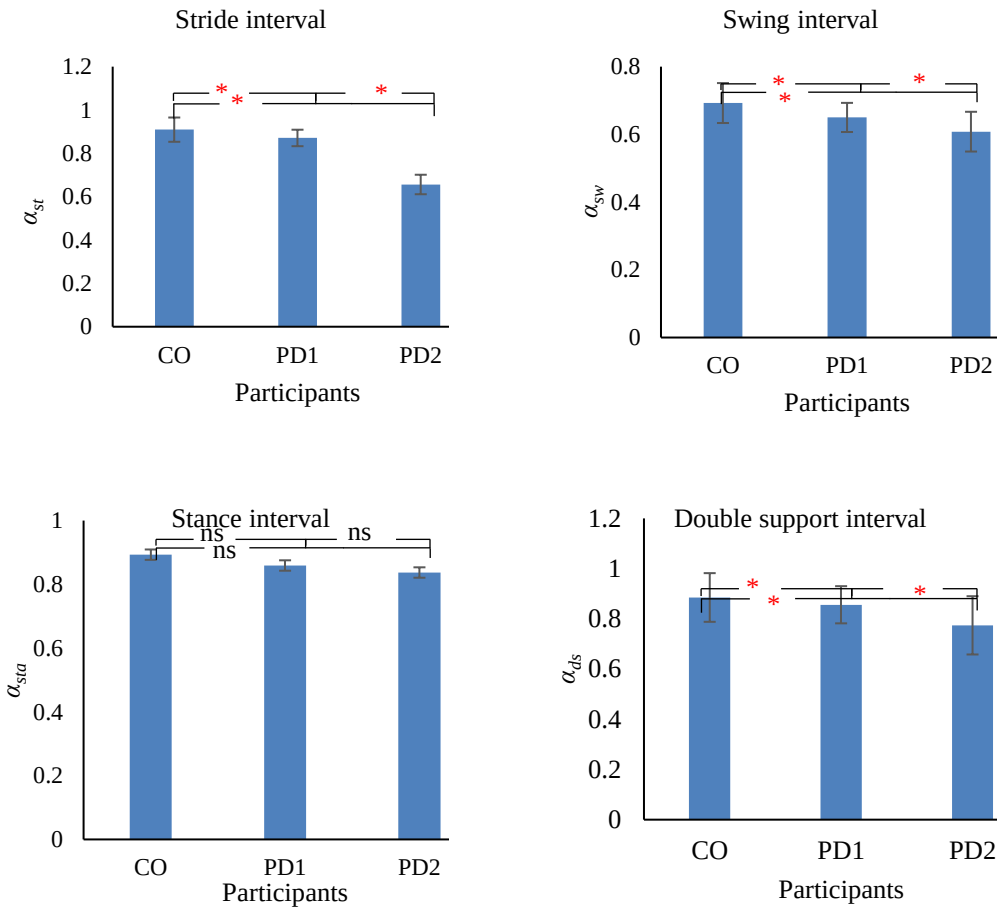


Figure 5.5: Mean (±SD) of the self-similarity parameter for CO, PD1, and PD2 during the stride, swing, stance, and double support intervals

Table 5.5: Self-similarity parameter using DFA mean ± SD for control, PD1, and PD2 respectively with significance (p-value).

Gait	CO	PD1	PD2	*p*-value
Stride interval (α_{st})	0.909±0.056	0.871±0.038	0.656±0.045	0.0001*
Swing interval (α_{sw})	0.692±0.059	0.650±0.043	0.608±0.058	0.0192*

Stance interval (α_{sta})	0.893±0.098	0.859±0.144	0.837±0.158	0.2860
Double support (α_{ds})	0.885±0.097	0.856±0.074	0.774±0.116	0.0430*

Table 5.5 lists the mean self -similarity parameter, α from the DFA of the three groups for the following gait intervals:

- α_{st} self-similarity parameter for stride interval,
- α_{sw} self-similarity parameter for swing interval,
- α_{sta} self-similarity parameter for stance interval,
- α_{ds} self-similarity parameter for double support interval.

The results show that for all the groups, $0.5 < \alpha < 1$ which indicates that the data could be chaotic and not random. It is also observed that α value for stance, swing, stride, and double support is lower in PD patients with advanced disease conditions. This indicates that PD patients have less defined gait and having less rhythmicity in their inter-stride, inter-swing intervals, inter-stance, and inter-double support interval. Thus, it is observed that rhythmicity decreases, with smaller α and hence high severity of PD.

Table 5.5 shows the Kruskal-Wallis test showed that the self-similarity parameter was significant ($p = 0.0001$) for stride interval, ($p = 0.0192$) for swing interval and double support interval ($p = 0.0430$). But stance interval was not showing any significance.

5.5 Discussion

5.5.1 Lateral difference

The mean and variance of gait parameters- stride, stance, and swing interval of left and right leg was compared for analyzing the lateral difference. The results show that there is no bi-lateral difference in the mean and variance of the four parameters for CON and PD participants. However, observation from the data indicates that while there is lateral

asymmetry, the difference is small and not statistically significant and hence only one side is sufficient for analysis.

5.5.2 Histogram method of visualization of data

This study has shown that there is a difference in the histograms of CON, PD1, and PD2 groups and the spread of the distribution is greater for patients with higher severity of the disease. The analysis of the gait data reveals that there was no significant difference in the mean values of the gait parameters; stride interval, swing interval, stance-interval and double-support interval with the severity of the disease, but the variance of these were significantly higher for PD compared with CON. It is also observed that the variance increased with the severity of the disease.

5.5.3 Analysis of mean and coefficient of variance of gait intervals

The analysis has shown that there is no significant difference in the mean value of inter-stride interval, there is a significant increase in its variance among the PD patients compared with the control, and the difference is greater for higher severity of the disease. This is in line with the observations of (Hausdorff et al., 1998; Hausdorff, 2005; Olmo and Cudeiro, 2005; Baltadjieva et al., 2006; Osamu et al., 2009; Krishnan and Wu, 2010; Ota et al., 2012; Keloth et al., 2017). The increased variability in stride-interval is associated with falls (Gray and Hildebrand, 2000; Hausdorff et al., 2003; Plotnik et al., 2011; Weaver et al., 2016; Johannes et al., 2017), and this finding shows that PD patients have a higher risk of falls.

While earlier studies have shown that there is an increase in the double-support duration in the PD patients (Mirek et al., 2007; Dipaola et al., 2016), our findings did not find this increase to be statistically significant. We have shown that the variability of stance-interval and double-stance interval is higher for PD patients and increases with the severity of the disease. This increase in the variability indicates poor coordination and loss of rhythmicity

and may be considered for quantifying the severity of disease and monitoring the progress of the patients.

This study has found that while there is no significant increase in the mean value of the stride intervals, there is a significant increase in the fraction of stance-interval compared with the swing-interval of PD patients, and this decreases with the severity of the disease. The percentage of stance-interval for PD2 patients increased by 3.91% while double-support interval by 9.12% and swing-interval decreased by 3.4% compared to CON participants. This may be attributed to a fear of falls and hence a sense of urgency for PD patients to remain in their double-support phase. The fraction may also be suitable for estimating the severity of the disease and monitoring the progress of the PD patients. The increase in the fraction of stance interval related to the increase in the severity of the disease. This can be done by measuring the fraction of stance interval or swing interval from the stride interval, in terms of percentage.

5.5.4 Self-similarity parameter of gait interval

For stride interval, the self-similarity is significantly higher for control (0.909±0.056) and decreases with the severity of PD patients, with PD1 (0.871±0.038) and PD2 (0.656±0.045). This shows that the stride interval of PD is less periodic when compared to control. Similarly, the self-similarity for swing interval is higher for control (0.692±0.059) and decreases with the severity of PD, with PD1 (0.650±0.043) and PD2 (0.608±0.058). This confirms the hypothesis reported (Hausdorff et al., 1998; Georg et al., 1999) and observations of (Frenkel et al., 2005) who also found an order of increase in variability among PD patients, with the greater increase being in patients with higher severity of the disease (Hausdorff, 2005; Baltadjieva et al., 2006; Osamu et al., 2009; Krishnan and Wu, 2010; Ota et al., 2012).

For stance interval, the self-similarity is higher for control (0.893±0.098) and decreases with the severity of PD patients, with PD1 (0.859±0.144) and PD2 (0.837±0.158). Since the stance interval was not significant between the groups, this study has also investigated the

self-similarity in the double support interval of gait. The double support interval of gait is more self-similar for control (0.885±0.097) and less for PD participants, with PD1 (0.856±0.074) and PD2 (0.774±0.116). Earlier studies (Mirek et al., 2007; Dipaola et al., 2016) have shown that PD patients show a longer time of double support when compared to control. Thus, this study has confirmed that the double support interval of gait gave less self-similarity for PD participants and decreases with the severity of the disease. This suggests there is a sense of urgency to remain in their support phase which could be due to the fear of fall.

The significance of this study is that there is a decrease in the self-similarity parameter, α obtained from DFA, as the severity of the disease increases. Earlier studies have shown that α of ECG is smaller for people with cardiac disease (Absil et al., 1999) and change in α of EEG for people with Alzheimer's disease (Stam et al., 2005). It has been reported that during walking at their own pace, the steps were similar irrespective of the time for control on a level surface (Hausdorff et al., 1996). This gives more self-similarity and the gait parameters for the control are well defined. The declined α in the gait of PD patients may be attributed to the impairment in the ability to generate more rhythmic movements (Schaafsma et al., 2003), and thereby resulting in a higher chance of falls. This decrease in the self-similarity indicates poor coordination and loss of rhythmicity and altered balance in PD patients. Falls in PD may lead to injuries, hip fracture, fear of falling and restriction of daily activities. This results in loss of independence and increase chance of mortality in PD.

5.6 Study limitations

This work has demonstrated that there is a significant PD severity group difference in the gait parameters recorded using insole sensors. Effective use of this technique for monitoring the progress of the PD will require further investigation of the effect of factors such as age, gender, and fatigue. It is also essential to develop the framework for the selection of the device and the measurement protocol to ensure the reproducibility of the recordings.

5.7 Summary

This chapter has investigated the gait interval difference between the PD and control, with the data taken from a public dataset (Goldberger et al., 2000). The results show that there is no bi-lateral difference in the gait parameters of PD patients when compared with the CON participant. It has found that the mean values of the four gait parameters are not statistically different for PD patients and CON; however, there is a significant increase in the variance of these gait parameters. The results have also shown that while the difference in the mean values of the gait parameters between the PD patients and CON is not significant, there is a significant increase in the fraction of the double-stance phase. The variance and fraction of the gait parameters can be used to measure the progress of the disease and estimate the severity of the disease.

Secondly, this chapter discusses the self-similar parameter of the gait interval, to study the long-range correlation of the signal. The analysis shows that the self-similarity parameter is less in participants with the severity of the disease. Among the stance and the swing phase of the stride interval, the inter-stance self-similarity is more when compared to inter-swing. It is also observed that the non-periodicity of the inter-stride, inter-swing, inter-stance, and inter-double support intervals is higher among PD patients and least among the control. This shows that PD patients have less rhythmic gait patterns when compared to control.

5.8 Clinical significance of the work in this chapter

There are two novelties of the study presented in this chapter that can be used by the clinician to monitor the progression of the disease. The first is that the variance of gait interval is significantly higher for PD patients and increases with the severity of the disease. This increase in the variability indicates poor coordination and loss of rhythmicity and may be considered for quantifying the severity of disease and monitoring the progress of the patients.

The second finding of the study is that the PD patients show decreased self-similar patterns in double support interval of gait, suggesting that there are less rhythmic gait intervals and a sense of urgency to remain in support phase of gait by the PD patients.

This chapter is based on the published papers:

Keloth S, Arjunan S and Kumar D (2017) Computing the variations in the self-similar properties of the various gait intervals in Parkinson Disease patients. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*: 2434-2437.

Keloth S, Arjunan S and Kumar D (2020) Variance of the gait parameters and fraction of double-support interval for determining the severity of Parkinson's disease. *Applied Sciences* 10: 577.

Chapter 6

6. Changes in gait parameter and walking patterns between Parkinson's disease and control

Brief outline of the chapter:

This chapter discuss the difference in gait parameters based on the walking pattern of Parkinson's disease patient, age-matched control, and young control. The method of pre-processing of gait signal, gait-cycle identification and gait feature extraction are explained in this chapter.

6.1 Introduction

Gait interval measurement has the advantage of being recorded by IMU, and these parameters have been considered for the diagnosis of PD patients (Blin et al., 1990; Frenkel et al., 2005; Hausdorff et al., 2007; Kirchner et al., 2014). However, these are influenced by several compounding factors, such as the height, weight, and age of the person (Hausdorff et al., 2008; Kim and Park, 2015; Hagovska and Olekszyova, 2016). The severity and duration of the disease can also influence the walking style of PD patients. The walking conditions and pattern of the path can also influence gait parameters (Seung et al., 2010; Emmanuel et al., 2018; Seung et al., 2018). While earlier studies have reported differences between PD and controls, numbers of these factors such as the walking pattern (Hausdorff, 2009; Almarwani et al., 2016) and its relation to an age-matched control (Haertner et al., 2018; Turcato et al., 2018) have not been considered.

Some walking patterns such as turning are affected even in the early stages of PD patients, with increased turning arcs (Bengevoord et al., 2016), time to complete the turn (Huxham et al., 2008; Spildooren et al., 2013) and a larger number of steps taken to complete the turn (Crenna et al., 2007). The number of steps and peak speed during turning

significantly differed among control, mild PD, and severe PD patients (King et al., 2012). It has been suggested that turning is more likely to cause functional impairment than straight walking since turning involves inter-limb coordination for the re-orientation of the body towards a new direction, balance relation between posture and gait and modification of walking patterns (Herman et al., 2011; Maidan et al., 2017). The main consequence of turns in PD patients is lateral falls, which can result in an eight-fold increase in hip fractures compared with falls during straight walking (Mellone et al., 2016; Johannesdottir et al., 2017). Thus, it is very important to evaluate the turning ability in PD patients and to investigate the effect of gait periods across different turns. During the UPDRS screening, neurologists observe their patients during the turn phase of their walks, but this is subjective and has not been quantified.

Researchers have proposed indices to quantify the variability in gait by an index, called variability index (Mileti et al., 2018). One of the main indexes used for this purpose is the Gait Phase Quality Index (GPQI), which shows how a PD patient's gait pattern deviates from the control (Guzik et al., 2018). It is the Euclidean distance, in a space of gait phase distribution, between the point determined by the gait phases percentage of the examined stride and the point determined by the average distribution of gait phases among control. A GPQI value close to 0% represents a gait pattern very similar to the control (Mileti et al., 2018).

This chapter investigated the effect of age, PD patients, and walking patterns on gait intervals to identify the walking pattern parameters that showed large differences between PD and the control. The mean and variance of the four parameters were considered: stride interval, swing interval, stance interval, and double support interval. Experiments were conducted where the participants performed three walking patterns: straight line, U-turn, and turning around a point during a single walking trail. The group differences of the gait

parameters between PD patients, age-matched controls, and young control participants for the three walking patterns were obtained.

6.2 Data recording

A wireless Trigno Inertial measurement unit (IMU) (Delysis, Boston, USA) system was used for the data recording of study participants. IMU device has three channels each for acceleration, rotation, and magnetic field and one for surface electromyogram (sEMG). The sEMG electrodes are active electrodes with an inter-electrode distance of 20mm and bandwidth of 20-450 Hz. The maximum wireless operating range of the sensor is 20m. The sampling rate of the sEMG signals is 2000 samples/second, of the accelerometer, and gyroscope signals are 148.14 samples/second, and of the magnetometer, signals are 74.07 samples/second.

6.2.1 IMU calibration

Before the start of the experiment, we have calibrated the IMU sensor to check for the accuracy of the sensor. IMU sensors have been reported for investigating the change of gait of PD patients (Sijobert et al., 2015). However, there was the number of potential inaccuracies that were not considered, the effect of gravity on the acceleration, and the drift correction on the rotational angle. The effect of gravity can be a significant issue when the accelerometer is attached to the shank and its angle is constantly changing over the gait-cycle. There can be several causes for the drift in the devices, such as noise, offset errors, or sensitivity to thermal changes. Even small amounts of noise, when integrated twice during the calculation of lateral displacement, can result in a significant error in the measurement. When performing gait analysis this error then becomes increasingly large when integrated over multiple gait-cycles. Another shortcoming of IMUs is that the accelerometer output has a gravitational component which is dependent on the angle of the sensor concerning the vertical. While IMUs can be calibrated to remove the gravitational component, such

calibrations assume that the direction of gravity concerning the sensor is steady, which however is not the case when the sensor is worn while people are walking. Thus, the standard approach of calibrating the IMU at the start of the experiment is necessary.

We have developed an algorithm to address the issue of gravity and drift error associated with the IMU sensor. First, we use gyroscope data to obtain the angle made by the foot during the heel strike and used this to form a generalized equation for gravity correction. The data is then detrended to remove the drift and the corrected for the acceleration. These steps are described below.

Step 1: Gravity Correction

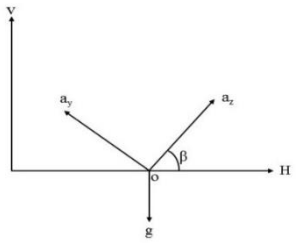


Figure 6.1: The angle, β, made by the foot during heel strike, with reference to the vertical, V, and horizontal, H, planes. The position of the accelerometer is represented by "o", ay and az represent the acceleration planes

The first step is to correct the horizontal and vertical acceleration for gravity. Based on the knowledge that the foot is plantarflexed and inclined at *β(t)* to the ground at heel strike (Figure 6.1) the reference planes of the accelerometer, *y*, and *z*, are inclined at this angle. Hence it is essential to correct the acceleration recording to get the true vertical and horizontal accelerations about the fixed vertical and horizontal reference frames, *V* and *H*. The generalized equations for horizontal and vertical acceleration aligned to the reference frame are given by

$$\beta(t)=\int_0^{t_{final}} \omega(t)\, dt \quad (1)$$

$$a_V(t) = - a_z(t) \sin(\beta(t)) + a_y(t) \cos(\beta(t)) - g \quad (2)$$

$$a_H(t)= a_z(t) \cos(\beta(t)) - a_y(t) \sin(\beta(t)) \quad (3)$$

where $\omega(t)$ is the angular velocity from the gyroscope in the sagittal plane from the time of initial contact ($t=0$) till the time of final contact (t_{final}), g is the acceleration due to gravity, a_z and a_y are the accelerations in the reference plane of the IMU, $a_V(t)$ and $a_H(t)$ are the corresponding accelerations in the true vertical and horizontal planes, which are gravity corrected signals.

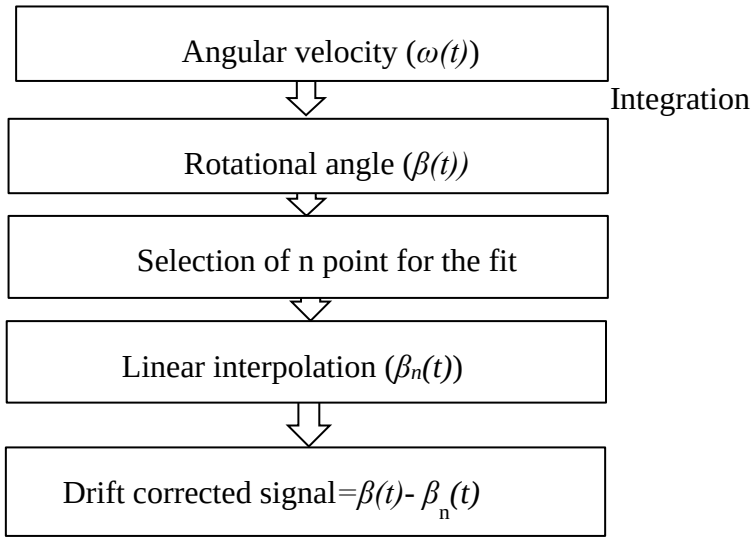


Figure 6.2: Flowchart showing the drift correction in the signal

Step 2: Drift Correction

The second main problem related to IMU sensor after gravity correction are error due to the drift in the signal. There are number of causes for the drift in the signal, such as noise, offset error and sensitivity to thermal changes. These error when integrated can result in significant errors along with the desired signal, contributing to misinterpretation. In the case of gait signals, stride length is computed based on the estimation of total distance covered while walking (Yang and Li, 2012) and based on the assumption of periodicity and regularity in the gait-cycle. However, this is not the case with pathological gait. The total distance covered while walking is obtained by double integration of acceleration signal, measured from the IMU sensor. So, any drift present in the IMU data which may lead to inaccurate estimates of the stride length. Several studies have proposed solution to address these shortcomings. It was shown that kalman filtering can be used to remove low frequency drift

from the IMU orientation data (Foxlin et al., 1998; Luinge and Veltink, 2005). The main drawback of this method is error in the vertical axis was not significantly reduced. An alternative approach is to use complimentary filters to remove frequencies from the selected range of the spectrum, but this system has proved to be inaccurate when changes in gait speed and cadence occur (Hyde et al., 2008; Mahony et al., 2008). The studies (Mathie, 2003; Bourke et al., 2011) have shown a method of gravity separation from linear and rotational acceleration components through filtering techniques. However, this system has not been validated in terms of changes in the magnitude and frequency of the acceleration. To overcome these issues, it is important to correct for the drift in the signal.

In this study,drift in the IMU data was corrected by performing linear interpolation, as shown in figure 6.2. Baseline fitting was performed to the computed rotational angle, $\beta(t)$. Baseline fitting is similar to detrend operation. The main difference between the baseline fitting method used in this study and the detrending operation is that, the technique uses manual interpolation of data. The manual interpolation of data is advantage for non-periodic and irregular signal, as in the case pathological gait signal.

As a first step, the noise from the accelerometer and gyrometer was corrected using a second-order bandpass Butterworth filter with a cut-off frequency of 0.01 Hz–20 Hz. To obtain the baseline-fit, requires the selection of the array on the rotational angle: $\beta(t)$, with n points required for the fit. The n point on the signal was taken as 20, which best describes the fit. A baseline is then linearly interpolated from these selected points. After linear fitting, the compensated output is obtained by subtracting the original signal $\beta(t)$ from the baseline fit. This compensated output has reduced drift and produces a more reliable estimate of the stride length.

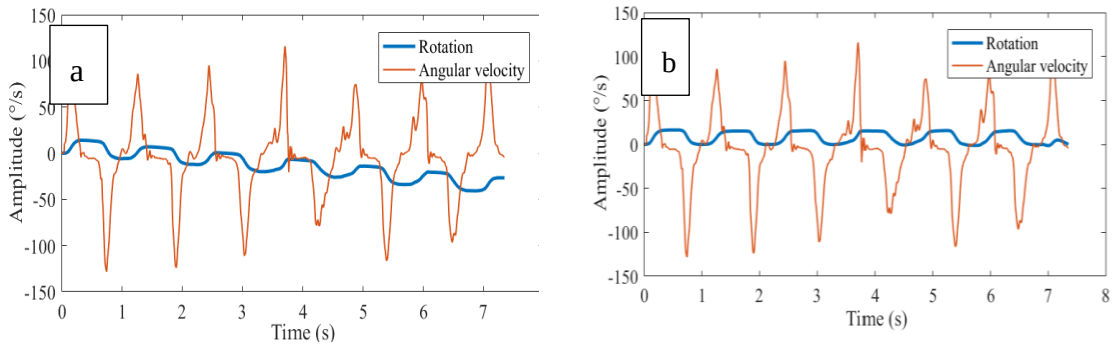


Figure 6.3: Angular velocity and angle of the foot concerning time using raw IMU data a) before drift correction and b) after drift correction.

Figure 6.3 represents the angular velocity and rotational angle of the foot signal (β(t)) concerning time. The left side of figure 6.3 shows the drifted rotational signal (represented in blue color) and the right side shows the drift corrected signal. It was observed from figure 6.3 that there is a cumulative error in the estimate of the maximum angle, and which gets corrected after drift correction.

6.3 Materials and methods

The experimental protocol was approved by the RMIT University Human Research Ethics Committee (BSEHAPP 22-15). Please refer Appendix V for the copy of letter of approval. The aim and experimental protocol were explained to the participants and their written informed consent was obtained before the start of the experiment. The study investigated the gait data of 72 participants: 24 with Parkinson's disease referred to as PD, 24 age-matched controls referred to as CO and 24 young controls referred to as YC. All PD patients were recruited from the PD outpatient clinic at Dandenong Neurology, Melbourne, Australia, while the CO participants were from multiple aged-care facilities and recreation facilities, and YC were recruited from RMIT University through appropriately located posters. The PD participants were excluded from the study if there were any clinically observed or self-reported skeletal injuries, neurological, musculoskeletal diseases other than

PD, and UPDRS III > 50. An individual's UPDRS III score >50 indicated that the patient had severe PD symptoms which were considered high-risk and unsuitable for the experiment by the human experiment's ethics committee. The CO participants were recruited to match the age distribution and gender of the PD patients approximately. The age-matched control (CO) participants were with no reported or observable PD symptoms. To confirm the suitability of the participants as controls, they were assessed according to the guidelines of the motor examination section of the UPDRS III, Hoehn, and Yahr (H & Y) scale and their self-assessment. They were excluded if there were any signs of PD, clinically observed or self-reported skeletal injuries, neurological, musculoskeletal diseases.

All PD patients were in their ON phase of the medication cycle. The number of participants in the experiment was based on the power calculation to achieve a statistical power of 80% (Nayak, 2010). The age group of participants considered for the study was 20–80 years. The participants in the CO and YC groups were chosen such that the gender ratio (male: female) was similar to that of the PD group .

Participant's demographic data, medical history, psychiatric history, current medication, and PD history (duration, symptoms, previous medication time, progression) were collected and de-identified for their privacy. They were assessed according to the guidelines of the motor examination section of the UPDRS III, the intensity and disability scales from the Unified dyskinesia rating scale (UDysRS), Hoehn and Yahr (H & Y) scale and the cognitive test from the Montreal cognitive assessment (MoCA). Table 6.1 shows the clinical characteristics of the three groups.

Table 6.1: The clinical characteristics in mean (± SD) of three group-PD, CO, YC.

	PD (n=24)	CO (n=24)	YC (n=24)	*p*-value
	Demographic variables			PD and CO
Age (Years)	71.91 ± 8.64	67.25 ± 3.77	27.91 ± 2.43	0.17
Gender (male/female)	17/7	17/7	18/6	
Height (cm)	169.26 ±8.89	166.54 ± 8.20	161.33 ± 4.26	0.23

Mass (kg)	81.25 ± 15.86	73.58 ± 12.46	60.29 ± 8.07	0.07
		Clinical variables		
Disease duration (Years)	4.27 ± 3.15	-	-	
UPDRS III	25.69 ± 10.95	0.41 ± 1.10	-	
UPDRS PIGD sub score	5.29 ± 3.07	-	-	
UDysRS	0.79 ± 1.35	-	-	
H &Y	2.27 ± 0.94	-	-	
Levodopa dosage (mg/day)	456.72±148.23	-	-	
Range of UPDRS III	9-48	0-5	-	
Range of H &Y	1-3	-	-	
Tremor at rest (lower limb)	0.125 ± 0.33	-	-	
Rigidity (lower limb)	1.16 ± 0.83	-	-	
Leg agility	1.27 ± 0.19	-	-	
Gait	1.08 ± 0.77	-	-	
Postural stability	1.41 ± 0.71	-	-	
Body bradykinesia	1.04 ± 0.75	-	-	
		Cognitive variables		
Total MoCA score	23.33 ± 5.30	27.33 ± 3.10	28.75 ± 1.35	
Visuospatial/ executive function	3.5 ± 1.74	4.41 ± 1.13	4.95 ± 0.20	
Attention	4.70 ± 1.33	6	6	
Delayed recall	2.41 ± 1.97	3.62 ± 1.55	4.16 ± 1.00	
Orientation	5.56 ± 0.57	5.95 ± 0.20	5.62 ± 0.71	

The IMUs were placed on the Medial gastrocnemius (MG) muscle and Tibialis anterior (TA) muscles of the left and right legs as shown in figure 3.2 and the positioning was based on the SENIAM recommendation (Siddiqi et al., 2015). The sensor placed in the TA muscle was used to compute the gait intervals, which was considered the best location to study gait events (Rueterbories et al., 2010). The acceleration and angular velocity curves in the Medio-Lateral (ML) axis of the IMU sensor placed in the TA muscle was further used for the calculation (Mitschke et al., 2018). The MG muscle data was used for the muscle parameter estimation. Please refer chapter 7.

6.3.1 Experimental protocol

The protocol consisited of many straight line walking followed by turns, that resembles a daily walking pattern of human being. The protocol required the participants to walk along a path marked on the floor with white markers and as shown in figure 6.4. A 600 mm diameter obstacle was placed at points 5 and 7 to guide the participants to perform a U-turn and turn around a point respectively. The length of the straight-line walking segments was suitable for minimum 2 bipedal gait-cycles for all the participants. The approximate length of the straight-line walking segments was 2m. The protocol required the participants to perform the walking twice. The walking path was a level concreted floor. The participants were asked to perform the task at their self-selected and comfortable walking speed. An assumption was made that the walking speed was constant throughout. All participants were encouraged to familiarize themselves with the path and equipment before starting the recording. Assessments were video-recorded and taken for reference.

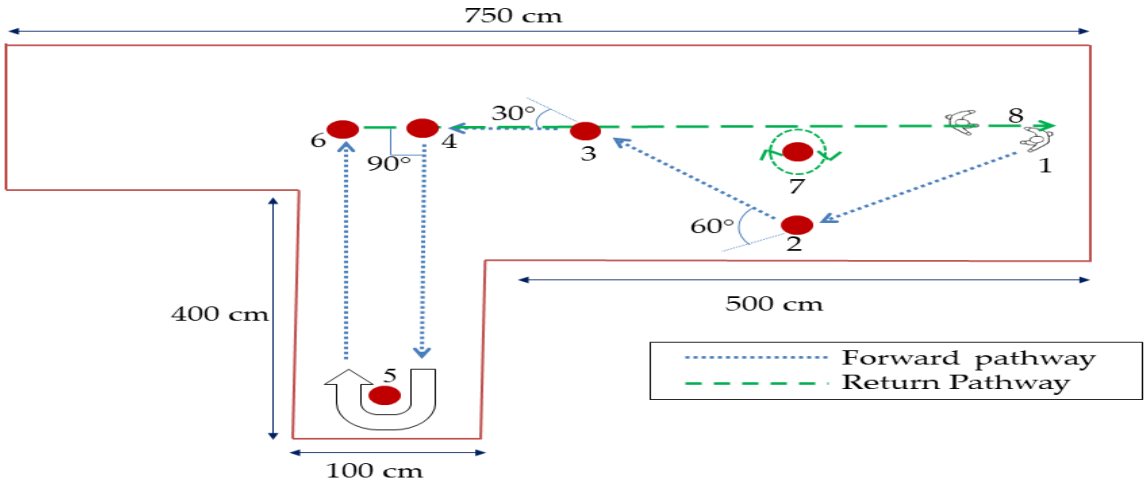


Figure 6.4: Walkway. 1. Start position, 2. 60° turn, 3. 30° turn, 4. 90° turn, 5. U-turn, 6. 90° turn, 7. Turn around a point, 8. Turn from the spot, 1. Start position.

6.3.2 Pre-processing of the signal

The IMU recordings were pre-processed to remove noise and offset. The offset in the recordings was removed using MATLAB. Secondly, the noise in the accelerometer and

gyrometer was corrected using a second-order bandpass Butterworth filter with a cut-off frequency of 0.01 Hz–20 Hz.

6.3.3 Turn identification

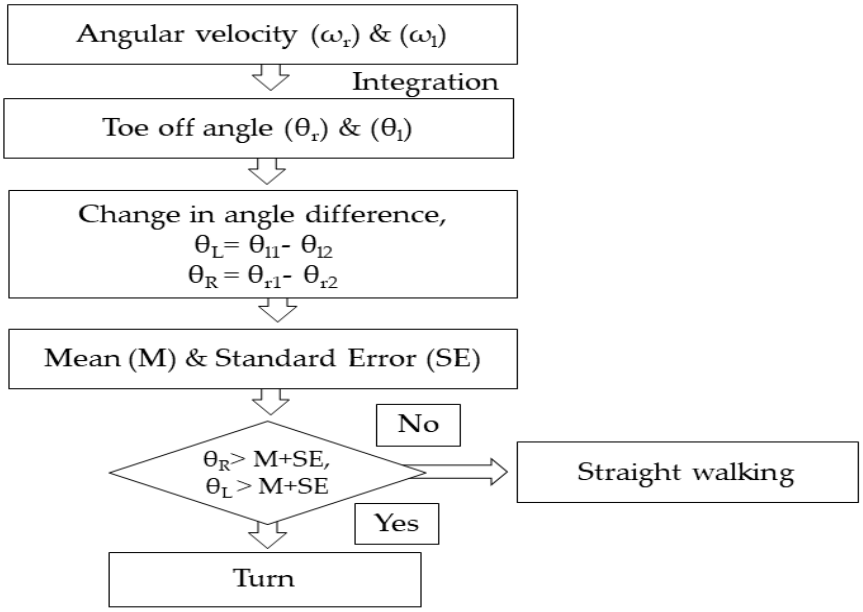


Figure 6.5: Flowchart to distinguish the turns from straight walking.

A change in the direction of walking is defined as a turn. To identify turns, the heel strike angular velocity in the Medio-Lateral (ML) axis of the IMU sensor placed in the TA muscle was considered for the study. The heel strike angle was calculated by the trapezoidal integration of the angular velocity curve of both the right and left limb. Finally, the change in the difference of the heel strike angle of the same limb was used to categorize straight walking and turns (England et al., 2015).

There was a small but statistically insignificant difference between the right and left side ($p > 0.05$) for all participant groups and for further analysis only the dominant right leg was considered. The selection of the dominant side was based on the questionnaire. Out of 24 PD and 24 YC, all were right dominant and for CO excluding one, all were right dominant. The flow chart describing the procedure to distinguish turns from straight walking is given in figure 6.5.

Figure 6.6 shows the absolute angle difference of one participant during walking. The turn was identified when the difference between the absolute angles of either right or left foot was greater than M + SE of the respective foot (England et al., 2015).

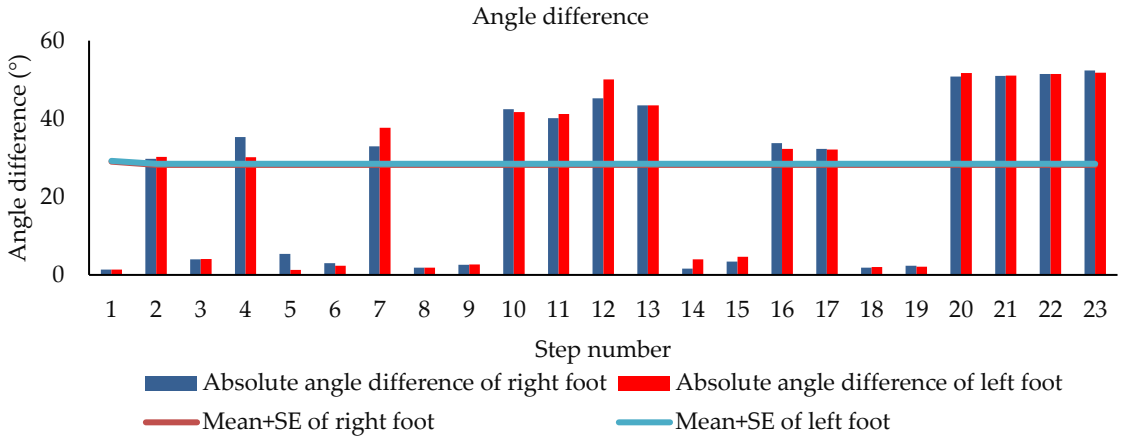
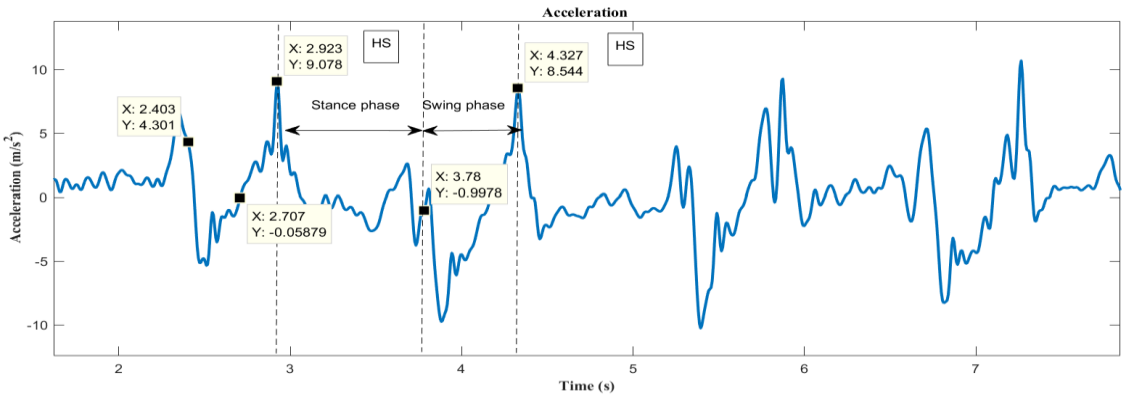


Figure 6.6: Angle difference of one participant during walking

6.3.4 Gait phase identification

A gait-cycle is defined as the difference between the times of two consecutive heel strikes of the same leg. The heel strike is the moment when the heel touches the ground and is identified by the highest peak in the acceleration curve (Grech et al., 2016). PD patients have smaller heel strike angles when compared to the control (Ginis et al., 2017), and the heel strike can be confused with the start of the swing phase. To avoid false heel strike detection, the gyroscope signal was also used to detect the end of the swing phase (mid-swing) represented as a peak in the gyroscope signal. The corresponding maximum peak in the accelerometer signal then represents the heel strike (Ferster et al., 2015).



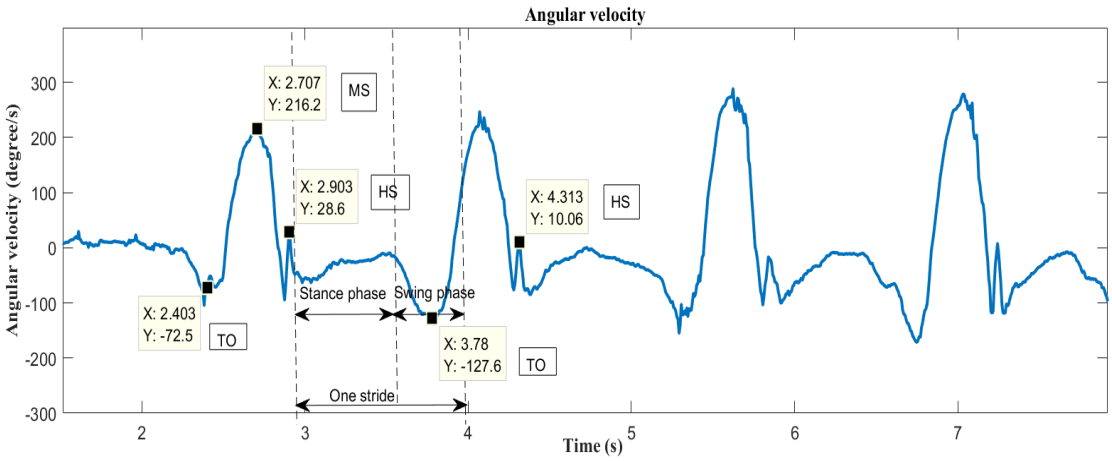


Figure 6.7: Acceleration and angular velocity curves showing HS, TO and MS of one stride.

Figure 6.7 shows the pre-processed acceleration and angular velocity curves in the mediolateral (ML) axis of the IMU sensor placed in the TA muscle, depicting the HS (heel strike), TO (toe-off) and MS (mid-swing) phases of gait.

6.3.5 Gait feature extraction

The study have considered the gait temperol parameters, as these are the considered to contribute more to the gait impariment in the early stages of the disease when compared to the spatial parameters of gait (Wahid et al., 2015). The following gait parameters were calculated from the right leg:

- Number of steps during the turn (steps).
- Total turn duration (s).
- Cadence = total number of steps/total turn duration (steps/min) for turns and straight walking the total turn duration was the total duration of straight walking.
- Stride duration– Time from HS to HS of the same foot (s).
- Stance duration–Time from HS to TO of the same foot (s).
- Swing duration–Time from TO to HS of the same foot (s).
- Double support duration–Time from right HS to left TO + Time from left HS to right TO (s)

- The variance of gait intervals was computed using the coefficient of variance (σ), as it was found to be the most common method in analysing the gait fluctuation (Chau et al., 2005). The σ for each gait interval was calculated as the ratio of the standard deviation of the gait parameter to the mean of the gait parameter. The variance of the stride interval, swing interval, stance interval, and double support interval was represented as σ_{st}, σ_{sw}, $\sigma_{sta,}$ and σ_{ds} respectively. Similarly, the mean of the stride interval, swing interval, stance interval, and double support interval was represented as μ_{st}, μ_{sw}, $\mu_{sta,}$ and μ_{ds}, respectively.
- Gait Phase Quality Index (GPQI) was calculated using the following formula (Mileti et al., 2018):

$$\text{GPQI} = \sqrt{\sum_{i=1}^{2}(FDS_{PD} - mFDS_{CO}) + (SS_{PD} - mSS_{CO}) + (SDS_{PD} - mSDS_{CO}) + (SW_{PD} - mSW_{CO})} \quad (1)$$

where FDS_{PD}, SS_{PD}, SDS_{PD}, SW_{PD} represented the percentage gait phase of PD, $mFDS_{PD}$, mSS_{PD}, $mSDS_{PD}$, mSW_{PD} represented the average value of percentage gait phase of CO. The GPQI calculation was computed for PD, to access the effect of gait phase distribution and represented by GPQIPDO and for CO computed as the gait phase distribution of CO, which differed from the CO average and represented by GPQICO. Similarly, a calculation was performed concerning the average value of the percentage gait phase of YC. The corresponding GPQI value for PD was represented by GPQIPDY and compared with GPQIYC. The GPQI was calculated for each participant and the average values were plotted.

6.3.6 Statistical analysis

The Shapiro–Wilk test was performed to check for normal distribution of the data, as it gave the highest power of distribution when compared to other similar tests (Ghasemi and Zahediasl, 2012). The data was not normally distributed and all the statistical significance of the group-based difference was obtained using the Kruskal–Wallis (KW) test which is a non-parametric test, recommended for comparing between multiple independent groups which have no normal distribution of data (Siegel, 1988). When significant differences were found,

a Bonferroni's test was performed (Mileti et al., 2018). Cadence, total turn duration, number of steps, σ_{st}, σ_{sw}, σ_{sta}, σ_{ds}, μ_{st}, μ_{sw}, μ_{sta}, and μ_{ds} were analyzed using the KW test when checking for group difference. The Wilcoxon test was performed to assess the difference within a group. The significance level (p) was set as 0.05 for all the statistical tests performed.

6.4 Results

Figure 6.8 shows that there was an age-associated trend of reduced cadence, an increased number of steps, and total duration for the turning task. It was also seen that there was a significant difference between these parameters among PD patients and age-matched controls. The cadence was statistically insignificant between the groups for straight walking and hence not reported.

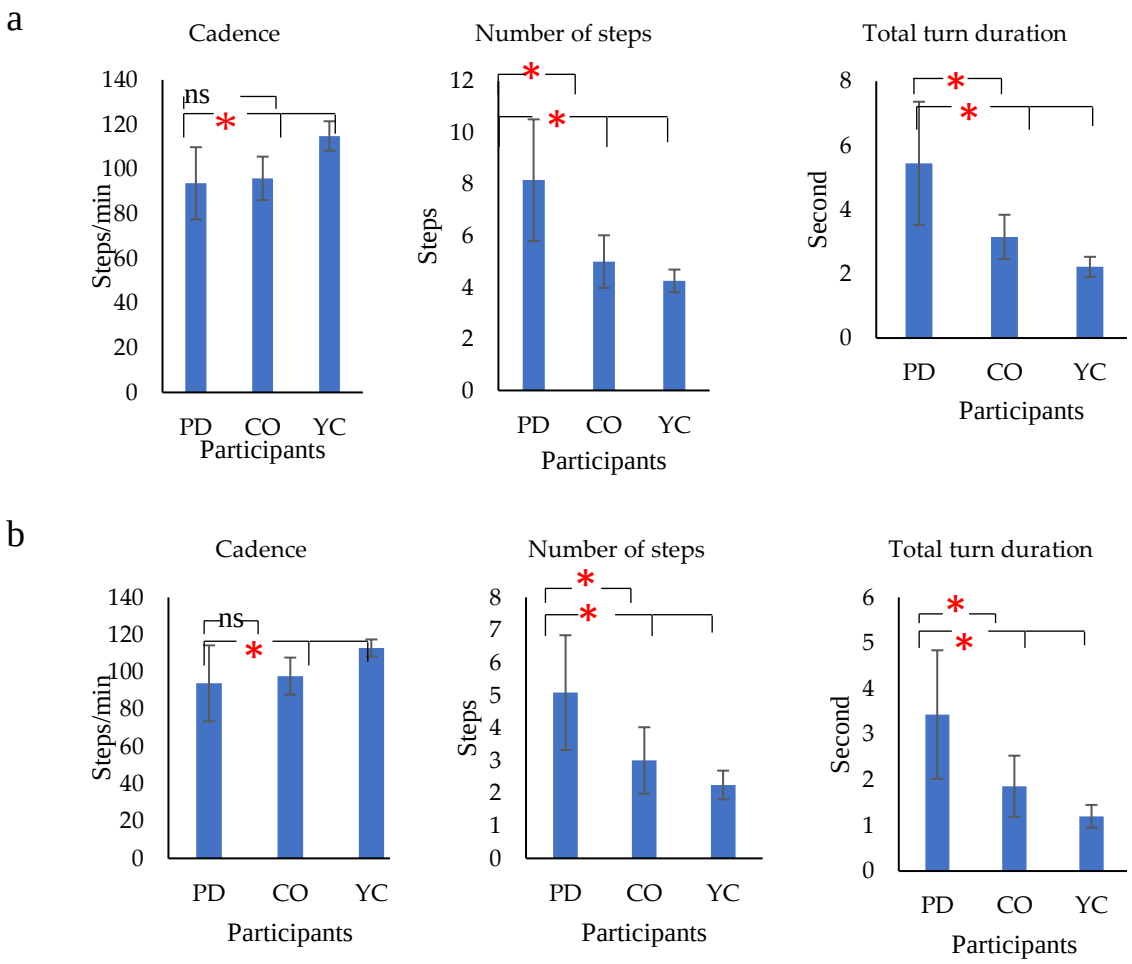


*Figure 6.8: Bar charts showing mean cadence, number of steps, and total turn duration for PD, CO, and YC participants for (a) U-turn and (b) Turn around a point (*p (Significance) < 0.05, ns (non-significant)).*

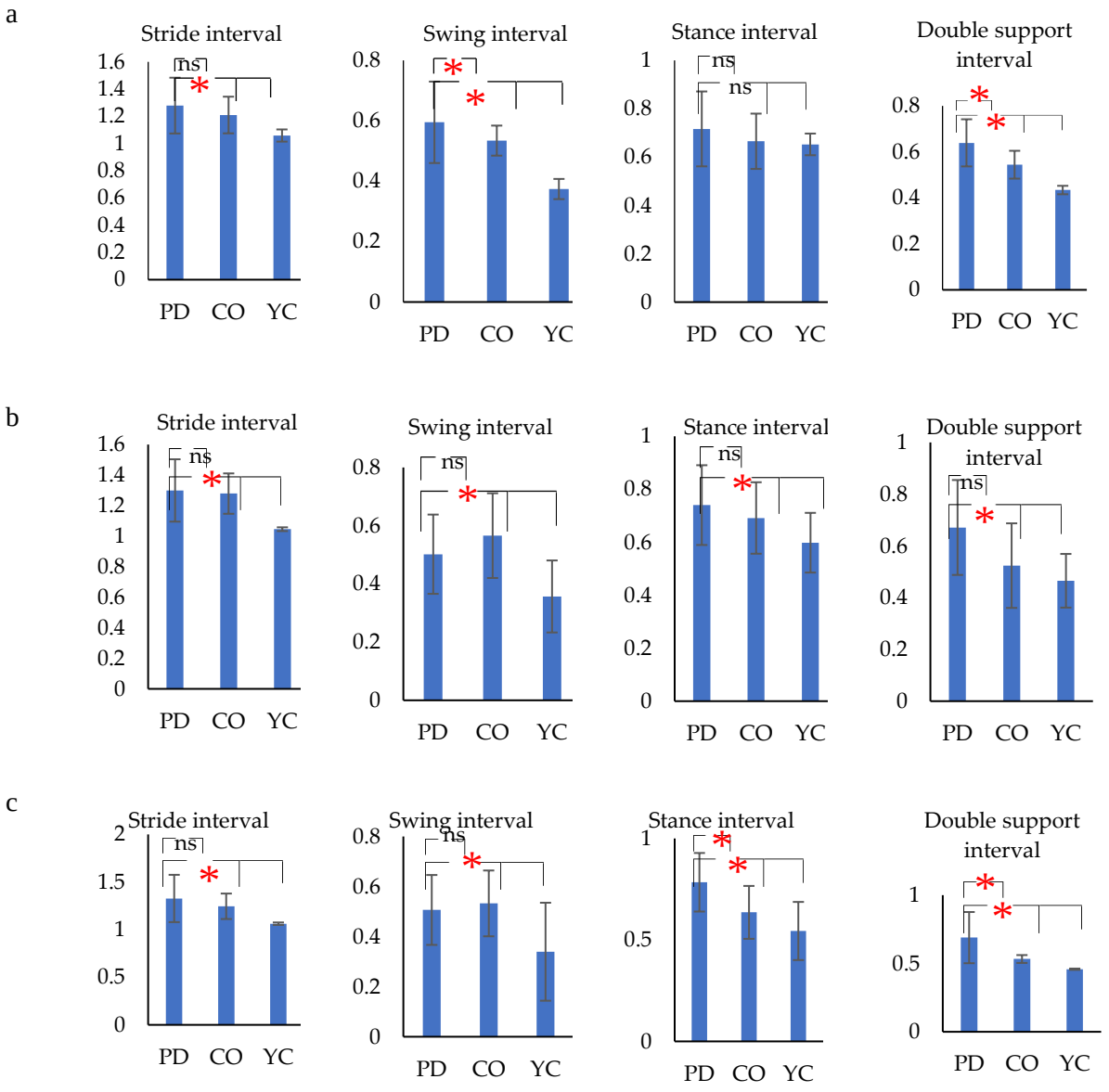


*Figure 6.9: Bar charts showing mean (SD) stride interval, swing interval, stance interval and double support interval for PD, CO and YC participants for (a) Straight walking (b) Turn around a point (c) U-turn (*p (Significance) < 0.05, ns (non-significant)).*

From figure 6.9, it can be seen that while some of the parameters did not show a significant difference between the groups, there was a significant difference for some of the gait intervals between PD, aged-matched control and young participants for the three patterns of walking– straight, turn around a point and U-turn. It was also observed that even when the group difference between the mean values was significant, this was of the order of 10 to 15%.

From figure 6.10 it is observed that there was a significant increase in the variability of all the gait interval parameters for all the three activities, and this was more pronounced when compared with the mean values (figure 6.9). From figure 6.10 and table 6.2, it is seen that the variance in all the four gait intervals, i.e., stride, swing, stance, and double support, showed the

highest difference between PD patients and control, irrespective of the control being age-matched or young, and this was the case for all the three gait tasks. This indicated that variance rather than the values of the gait interval parameters was suitable for differentiating between PD and control and may be suitable for the diagnosis of PD patients. It was also seen that the age-associated change in the variance was small when compared with the increase due to disease.

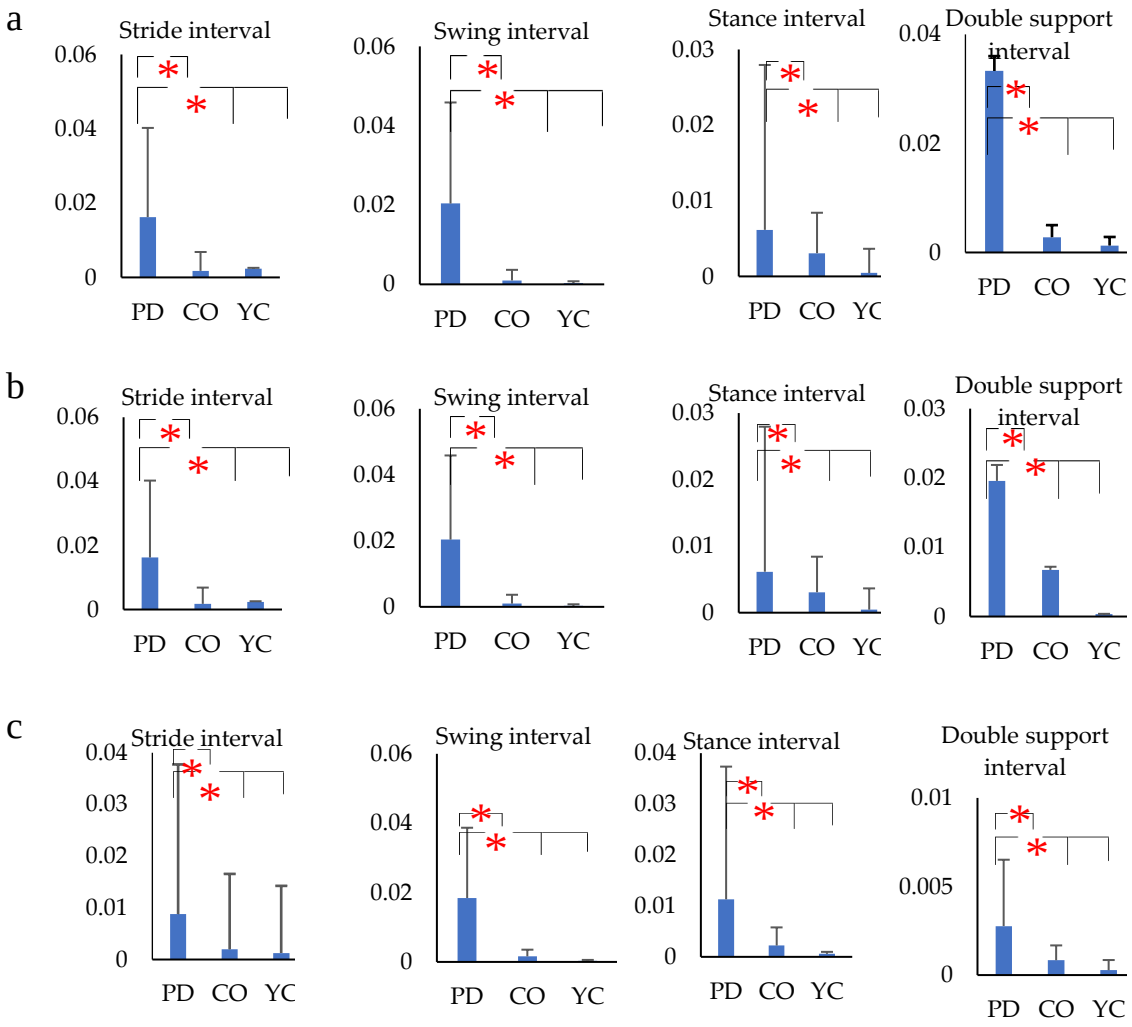


*Figure 6.10: Bar charts showing variance (SD) of stride interval, swing interval, stance interval and double support interval for PD, CO and YC participants for (a) Straight walking (b) Turn around a point (c) U-turn (*p (Significance) < 0.05).*

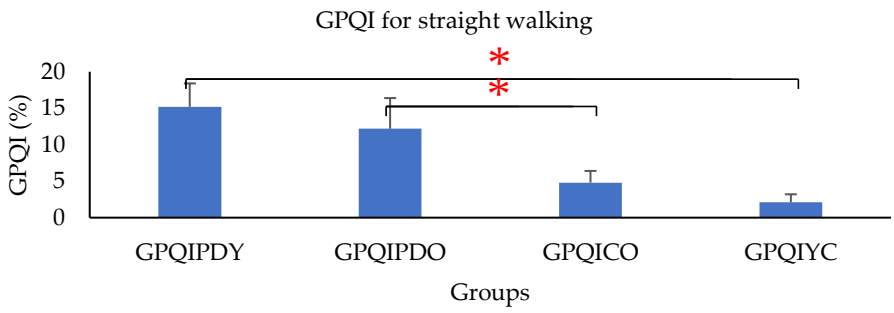
Table 6.2 shows the *p*-value obtained by comparing the mean and coefficient of variance of gait intervals for straight walking with U-turn and turn around a point separately. It was seen that the variance of gait intervals significantly differed for all the gait intervals for straight walking when compared to turns, except for the swing interval variance. It was also seen that the variance of all the gait interval significantly differed between PD and CO for U-turn and turn around a point walking (p <0.05). While, age-matched control (CO) participants didn't

show any significant difference in gait interval variance based on the walking pattern, except for double support interval variance. It was also seen that young control (YC), showed an insignificant difference in gait interval variance based on the walking pattern. Furthermore, the mean of the gait intervals was statistically insignificant based on the walking pattern, except for a few intervals as tabulated in table 6.2.

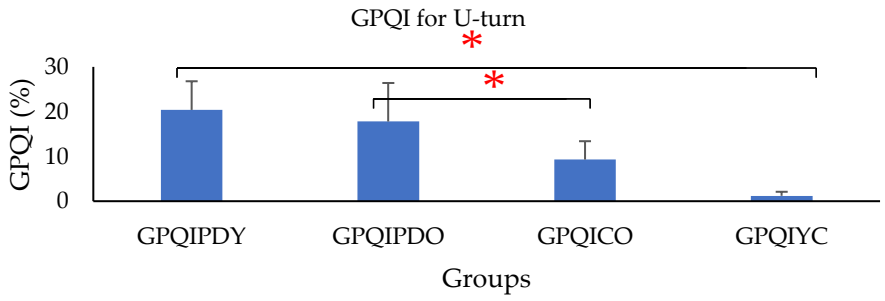
Table 6.2: The comparison of mean and coefficient of variance of gait intervals for straight with U-turn and turn around a point for each participant group. The p-value is tabulated below.

Participant	Walking pattern (straight walking compared with)	μ_{st}	μ_{sw}	μ_{sta}	μ_{ds}	σ_{st}	σ_{sw}	σ_{sta}	σ_{ds}
PD	U-turn	ns	ns	ns	ns	0.001*	ns	0.006*	0.000*
	Turn around a point	ns	ns	ns	ns	0.002*	ns	0.005*	0.005*
CO	U-turn	ns	ns	0.04*	ns	ns	ns	ns	0.021*
	Turn around a point	ns	0.045*	ns	ns	ns	ns	ns	0.031*
YC	U-turn	ns	ns	0.047*	ns	ns	ns	ns	ns
	Turn around a point	ns	ns	ns	ns	ns	ns	ns	ns

a



b



C

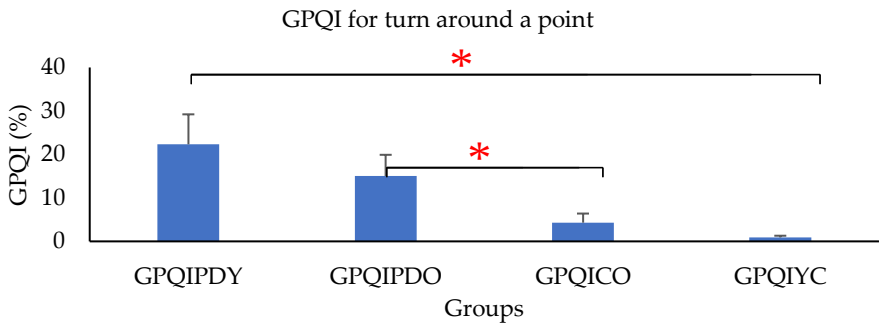


*Figure 6.11: Bar plot showing the mean (SD) GPQI for (a) straight walking, (b) U-turn, and (c) Turn around a point (*p (Significance) < 0.05).*

Figure 6.11 shows that there was a significant difference between GPQIPDO and GPQICO and similarly between GPQIPDY and GPQIYC for each of the walking patterns. The GPQI value was statistically insignificant based on the walking pattern and hence not reported.

6.5 Discussion

Gait variability can arise due to intrinsic and extrinsic causes (Schwartz et al., 2004). Variability in gait recordings may arise due to the type of walking surface, level of ambient light, or even due to instrumentation error (Menz et al., 2003; Richardson et al., 2004; Stacoff et al., 2005). Other causes are inherent to the person such as neurological, metabolic, and musculoskeletal health and injury.

This study investigated the group difference of gait parameters– cadence, number of steps, and total turn duration during U-turn and turn around a point. The results showed that for the turning task, the cadence decreased, and the number of steps and total turn duration increased with aging. The results showed that the gait of young control was rhythmic and variation in their gait parameters was small when compared with the older cohort, or PD patients. The decrease in cadence, increase in the number of steps and total turn duration in the age-matched control were in line with the literature (Griffin et al., 2000; Van Emmerik et al., 2016), where it has been reported that the variations in gait may be due to supraspinal and central pattern generators (Roberts et al., 2017) or the difference in time scale inputs arriving at the brain from visual, vestibular and mechanoreceptors in the feet (Yang et al., 2018). Aging is an internal variation that can cause changes in the natural bipedal locomotion (Owings and Grabiner, 2004; Romero et al., 2018). Our results showed that cadence did not show significant differences between PD (non-freezers) and CO, while the number of steps and total turn duration had a significant difference between the groups. While (Spildooren et al., 2013) has

shown that there was no significant difference between cadence of PD freezers, non-freezers and controls during a 180-degree turn but, (Spildooren et al., 2010; Spildooren et al., 2012) found that cadence increased significantly in freezers when compared to non-freezers and control during 180- and 360-degree turns. Both the studies above were performed in an OFF-period of medication while our study was with patients in their ON-state of medication. Literature (Morris et al., 1994; Chien et al., 2006) has shown the independence of cadence in PD ON and OFF period of medication when compared to the control. This study has confirmed that, cadence did not significantly differ between PD and CO, while the number of steps and total turn duration was statistically different between the PD and CO while performing a turn. Cadence also didn't have a statistically significant difference between the groups for straight walking and hence was not reported.

This study also investigated the group differences of gait intervals between PD, aged-matched control, and young control during straight walking, taking a U-turn and turn around a point. The results showed that there were significant differences between PD and age-matched control, and between the young and older cohort for most of the parameters. However, the largest difference between PD and control, irrespective of age, was seen in the variance measured as the coefficient of variance of the gait interval rather than the mean values of the parameters and was observed for all the three walking tasks that were investigated. This shows that while there are age-associated changes to the gait parameters the difference in variance between PD and control is significant, even without considering the age, and the difference was much greater than all other parameters. In the case of PD patients, irrespective of any of the three aforementioned walking tasks, there is a significant decrease in the ability to generate gait rhythm. This supports the works of Redgrave et al. (Redgrave et al., 2010) who found that PD patients lose their habit control systems in the basal ganglia which leads to a greater dependence on voluntary control of 'habitual' activities such as walking due to which there is greater variability. Literature (Roemmich et al., 2012; Ringeval et al., 2015; Lin et al., 2016) also show that the presence of neurological disorders such as in PD has major effects in increasing gait variability. The increase in stride variability in gait was a unique indicator of the inability to produce gait rhythm (Hausdorff, 2005; Brach et al., 2008) and risk of falls (Rios et al., 2001; Skjaeret et al., 2016). Loss of dopamine in the substantia nigra leading to the excessive inhibition of the basal ganglia loop leads to the loss of habitual patterns (Redgrave et al., 2010) associated with walking and also causes rigid movement and decreased range of limb movement (Snijders et al., 2007). One observation from this study was that while PD had

a complex set of symptoms and its measure required a battery of tests (Goetz et al., 2008), where gait was only one factor to be considered, the results showed that the gait variability alone appeared to be suitable for differentiating between case and control. However, this requires extensive investigation before it can be considered for diagnostic purposes.

Another important finding is based on the dependence of gait variability on the walking pattern for individual groups. The results showed that there was a significant increase in the stride interval, stance interval, and double support interval variance of gait for straight walking when compared to turns for PD patients. Literature (Earhart, 2013), shows that turning while walking is a challenging task that requires the control of balance. Significant differences in gait variability during turns can be related to FOG (Mancini et al., 2018) and as an early sign of the progression of disease in PD (Salarian et al., 2009; Spildooren et al., 2018). Age-matched control (CO) participants showed statistically insignificant differences in gait variance, except for double support interval based on the walking pattern. Thus, this study confirmed that gait in PD was disturbed based on the walking pattern.

This study investigated the GPQI for the groups, which could be used to show how PD gait pattern deviates from control. The results showed that there was a significant difference in the GPQI value between PD and control. The GPQI value matched with the values reported in (Mileti et al., 2018) for straight walking. Thus, these scores can be used by clinicians to classify the severity of a pathological gait pattern by quantifying the deviation from the control (Ancillao et al., 2017) and also to quantify the effect of a treatment or even to evaluate the natural improvement in gait patterns over time (Guzik et al., 2018). Thus, this study confirmed that there was a significant difference in gait patterns between the PD patients and the control group.

6.6 Limitations of this study

There were two limitations of the present study: Sample size in gender calculation and only the ON-state PD was tested. While 24 PD and 24 age-matched controls were a decent size based on literature, this was not sufficient for gender and body size matching, which are factors that contribute to gait parameters. The other factor is that literature shows (Schaafsma et al., 2003) that there is a significant effect caused by medication, where the difference may be even greater in the OFF state of medication.

6.7 Summary

This chapter has investigated the effect of gait parameters on different walking patterns-during straight walking, U-turn and turn around a point on 24 PD, 24 CO, and 24 YC participants. The study showed that the variance of any of the gait interval parameters obtained using an IMU during any of the walking patterns could be used to differentiate between the gait of PD and CO, PD, and YC. This can facilitate the quantitative assessment of the patients and can be considered for e-health applications.

6.8 Clinical significance of the study

There are two novelties of the study which have the potential to make a significant difference to the clinical assessment of PD patients. The first is that this study has shown that both, straight-line walking and turning are suitable for the evaluation of PD patients, and hence either could be used. Thus, the practice of making the patient perform complicated turns (Mellone et al., 2016; Miller Koop et al., 2018) is not required for such a study.

The second novelty is that this study has shown that by the use of IMU placed on the legs of the patients and measuring the gait period variance (On-Yee et al., 2017; Estep et al., 2018; Warlop et al., 2018), it is possible to identify PD patients while the patient performs simple walking. This has the potential to be used for population-based screening for early diagnosis of the disease.

Another important finding of this study is that it showed that the gait variance of these parameters only showed the difference between PD and controls, irrespective of their age. Thus, while there are significant differences in the gait parameters between young and old, the variability due to age was not significant.

This chapter is based on the published paper:

Keloth S, Viswanathan R, Jelfs B, Arjunan S, Raghav S and Kumar D (2019) Which gait parameters and walking patterns show the significant differences between Parkinson's disease and healthy participants? *Biosensors* 9(2).

Chapter 7

7. Differentiating Parkinson's disease using muscle activation strategies during walking

Brief outline of the chapter:

This chapter describes the difference in muscle activation of Parkinson's disease patients, age-matched control, and young control during walking. The different muscle parameters used for differentiating between the groups are studied in this chapter.

7.1 Introduction

PD is a neuromotor disorder with gait impairment and poor posture being common symptoms (Boonstra et al., 2008). PD patients are high-risk fallers and have an unsteady gait with shuffling, reduced strength, and increased rigidity (Hausdorff, 2009). Their gait has been found to have poor coordination, abnormal load distribution and difficulty to produce a normal "heel to toe" roll-over. There is a reduced pre-swing phase which is caused by decreased plantar forces at the forefoot, resulting in reduced leg acceleration during swing phase, stride length, and gait speed (Morris et al., 1998; Nieuwboer et al., 1999; Sofuwa et al., 2005). However, human gait is also influenced by the number of non-neurological factors such as orthopedics and it is possible to miss some of the gait impairment symptoms in the prodromal stage of the disease.

Surface electromyography analysis of the gait has applications for rehabilitation and diagnosis of neuromotor pathological gait conditions (Mariani et al., 2013). Investigation of the muscle activity during the sub-phase of gait can reveal subtle and clinically significant patterns during loading, flat-foot, and pre-swing phases (Mariani et al., 2013).

It is seen that PD patients have MG muscle activity during the stance phase of gait (Dietz et al., 1995) and reduced ability to modulate their activation pattern (Milner et al., 1979). Their activity has reduced modulation and is not symmetrical (Bailey et al., 2018). It has also been shown that PD patients have reduced TA activity during the stance phase (Dietz et al., 1995) and reduced TA amplitude during late swing (Mazzetta et al., 2019). The changes in sEMG of TA and MG muscle reflect the impairment in motor control and movement, further resulting in limited control of foot and stride length (Mitoma et al., 2000).

PD patients have higher concurrent activation of agonist- antagonist muscles around the ankle, which is referred to as co-activation (Dietz et al., 1995);(Lang et al., 2019). Co-activation stabilizes the joints and provides postural and movement stability (Latash, 2018), but excessive co-activation can produce negative work, reduce the net torque at the joint and increase rigidity (Busse et al., 2006). This is studied by analyzing the sEMG of the opposing muscles (Ervilha et al., 2012) and calculated as the Co-activation Index (CI). While CI increases for both, PD patients and the elderly, an increase in CI for the elderly is associated with an increase in the muscle activation during mid-stance (Schmitz et al., 2009), while in PD patients it is accompanied with a reduction in the overall muscle activity. There is a significant change to CI over the different sub-phases of the gait for the elderly when compared to young (Schmitz et al., 2009). However, such a study has not yet been done for PD patients for straight-line walking through the level ground.

PD patients have higher gait asymmetry (Park et al., 2016; Cole et al., 2017); (Bailey et al., 2018). which however had not been found earlier, based on the sEMG envelope of the lower limbs (Thaut et al., 1996). Earlier studies (Miller et al., 1996; Thaut et al., 1996) had analyzed the gait asymmetry by considering the difference between right and left side mean value of the sEMG signal. These can result in incorrect analysis, as the difference between right and left leg may be due to a difference in leg dominance (Ankaralı et al., 2015). To overcome this, Asymmetry Index (AI) was introduced, where the 'higher' vs 'lower' sides were compared, and using this, significant gait asymmetry was observed (Bailey et al., 2018). Nevertheless, this does not show how this asymmetry changes over the gait-cycle.

Symmetrical human gait requires modulation of muscle activity over a large range. This conserves energy and provides stability and is measured using the Modulation Index (MI). It has been shown that PD patients have reduced modulation while maintaining posture (Lang et al., 2019) but their MI during gait has not been reported.

The variability of the sEMG envelope is an indicator of the steadiness of the muscle activity and can be an indicator of the poor coordination and smoothness of the contraction. However, this has been rarely reported in the literature. The only studies that report the assessment of sEMG variability are based on the shape rather than the overall variation of the signal, and the results have been contradictory. While one study observed significantly higher sEMG shape variability for PD (Miller et al., 1996) when compared to age-matched control but other studies did not (Thaut et al., 1996). Recent work by the author assessed sEMG variability using a coefficient of variance and observed higher gastrocnemius activity

variability was related to higher motor dysfunction in PD (Bailey et al., 2018) as measured using UPDRS III. However, such a study on the variability of muscles was not analyzed for the sub-phases of gait for PD patients and during different walking patterns. Thus, the lack of separation of the two groups based on variability may be due to the gross nature of the analysis, where the gait was not sub-divided in the different phases.

The chapter has studied the muscle activation pattern of TA and MG muscle during different phases of gait in PD patients with early-stage Postural Instability and Gait Disturbance (PIGD) and controls, measured in a clinical setting using wearable sensors. Muscle activity of the agonist and antagonist muscles of the lower limb along with the gait data were recorded while the participants walked in a straight line inside the clinic. The muscle activation parameters that have been proposed in earlier studies- CI, AI, MI, and CV, were computed for the sub-phases of the gait: first double support (1DS), single support (SS) second double support phase (2DS) and swing (SW) phase.

7.2 Material and methods

The experimental protocol was approved by the RMIT University Human Research Ethics Committee (BSEHAPP 22-15). The details of the study and experimental protocol were explained to the participants and their written informed consent was obtained before the start of the experiment. The study has investigated the gait data of 72 participants: 24 with Parkinson's disease referred to as PD, 24 age-matched controls referred to as CO, and 24 young controls referred to as YC. The detailed description of the database is given in section 6.3.

7.2.1 Data recording

The muscle activation strategy during gait is dependent on the selection of the muscles being investigated. The comparison between MG and LG muscle for control shows that MG activity is more when compared to LG during the gait-cycle (Chisholm et al., 2015). The IMUs were placed on the MG and TA muscles of the left and right legs. The sensor placed in the TA muscle was used to compute the gait intervals, which was considered as the best location to study the gait events (Rueterbories et al., 2010).

7.2.2 Experiment protocol

The protocol required the participants to walk along a path marked on the level floor with white markers. While the protocol consisted of straight-line walking followed by turn events, only the straight-line walking was considered in this study. The approximate straight-line

walking distance was 2m. All participants were encouraged to familiarize themselves with the path and equipment before starting the recording. Assessments were video-recorded and taken for reference. A detailed description of the experiment protocol has been reported in our earlier paper (Keloth et al., 2019) or refer section 6.3.1.

7.2.3 Pre-processing of the signal

The IMU and sEMG recordings were pre-processed to remove noise. The noise in the accelerometer and gyrometer was corrected using a second-order bandpass Butterworth filter with cut-off frequency 0.01Hz- 20 Hz. The noise in the sEMG was corrected using 20-500 Hz 6th order Butterworth bandpass filter.

7.2.4 Gait and sEMG feature extraction

The computation of the gait parameter such as stride time, stance time, swing time, and double support time has been explained in detail in our earlier paper (Keloth et al., 2019). The following sEMG parameters were calculated as mentioned below:

A. Normalization of sEMG features

sEMG amplitude, frequency, and duration are affected by many factors such as electrode placements, subcutaneous fat thickness, muscle fiber type, and speed of the actions (Dreischarf et al., 2016). Normalization of sEMG signal reduces the inter-participant and inter- experiment differences and thus facilitates the comparison of sEMG between participants and across different muscles. Amplitude normalization of the muscle was done based on the peak root mean square (RMS) during the gait-cycle for each individual and each muscle separately (Halaki and Ginn, 2012). This method was found to be most efficient during walking (Yang and Winter, 1984). The data was then normalized in the time domain to make it possible to compare the different experiments and each gait-cycle corresponded to100 data points (Ghazwan et al., 2017).

B. Co-activation index (CI)

Simultaneous activation of the agonist-antagonist muscles around a joint is termed as co-activation. This provides additional stability to the joint but also causes rigidity, makes the actions less efficient, and often such movements are not smooth (Gribble et al., 2003). Co-activation index (CI) is the measure of co-activation, computed from the normalized sEMG of both TA and MG muscle. A larger value of CI denotes the simultaneous activation of TA-MG muscles around the joints, which can result in altered mechanical properties of the limb

(Gribble et al., 2003). A smaller value of CI denotes the alternate activation of TA and MG muscle across the joint to help in smooth locomotion, referred to as reciprocal inhibition (Iwamoto et al., 2017).

The TA-MG co-activation index (CI) was calculated by dividing the area of TA-MG overlap by the total area of TA-MG muscle as given in expression (1) (Unnithan et al., 1996).

$$CI = \frac{Overlapping\ area\ of\ TA\ and\ MG\ muscle}{Area\ of\ TA\ muscle + area\ of\ MG\ muscle} \quad (1)$$

CI was calculated for total gait-cycle (0-100%), stance, swing, and for the following sub-phases- 1DS, SS, 2DS, and SW. Even though the patient number were unsuitable for severity-based analysis, we divided PD patients according to their UPDRS III values to identify the possible trends. Table 7.1 shows the classification of groups based on the severity level.

Table 7.1: Group based on the severity level

Participant	Number of participants	UPDRS-III (Mean ± SD)	H & Y (Mean ± SD)
CO	24	-	-
PD 1	15	19.66 ± 6.65	1 to 2
PD 2	9	35.88 ± 8.22	2.5 to 3

C. Modulation index (MI)

The modulation index (MI) is the measure of the range of muscle activation. MI was calculated from expression 2

$$MI = \frac{sEMG_{max} - sEMG_{min}}{sEMG_{max}} * 100 \quad (2)$$

where $sEMG_{max}$ was the maximum RMS of sEMG activity and $sEMG_{min}$ was the minimum RMS of sEMG activity calculated for each TA and MG muscle, respectively. The larger value of MI denotes that the muscles produced a phasic burst of activity followed by relaxation and had a bigger range of activity during the movement. Smaller MI indicates that the muscle did not vary the activity significantly (Zehr and Chua, 2000).

D. Asymmetry index (AI)

Early-stage PD patients exhibit lateral asymmetry and based on this, we hypothesized asymmetrical muscle activity during their regular walking. The tendency of the person to use one side of the body involuntary motor task is called lateral preference (Carpes et al., 2010). Bilateral muscle asymmetry was calculated using the Asymmetry index (AI) as the absolute value from expression (3). AI was calculated using the sEMG RMS values of both right and left leg for the consistency with the state-of-the-art (Bailey et al., 2018). As a first step, the

sEMG-RMS of both TA and MG muscles for both, right and left leg was calculated separately. Secondly, the AI was calculated separately for TA and MG muscle by substituting the value of sEMG RMS in the expression (3), where leg 1 corresponds to the higher value of sEMG RMS and leg 2 corresponds to the lower value of sEMG RMS.

$$AI = 100 - (\frac{leg\ 1}{leg\ 2} * 100) \qquad (3)$$

E. Coefficient of variance (CV)

CV was calculated for both TA and MG muscle. Firstly, the RMS amplitude was calculated for each window, and then the mean CV across all windows was calculated for each phase of gait (Guidetti et al., 1996). CV was measured as the ratio of the standard deviation to the mean sEMG RMS, as in the expression (4).

$$CV\ \% = \frac{Standard\ deviation}{Mean\ RMS} * 100 \qquad (4)$$

7.2.5 Statistical analysis

The Shapiro-Wilk test was performed to check the null hypothesis 'data is normally distributed' and this is accepted with $p > \alpha$, $\alpha = 0.05$. The analysis showed that $p < 0.02$, and thus the data was found to be not normal. The statistical significance of the demographic variables was performed using the non-parametric Mann-Whitney U test. Mann-Whitney U test was conducted to determine the difference in the demographic variables between PD and CO. The Mann-Whitney U test was performed to check the null hypothesis 'the difference in demographic variables are equal' between PD patients and CO. The statistical analysis results using Mann-Whitney U test shows non statistical significance difference for each demographic variable: age ($p = 0.09$), height ($p = 0.13$), weight ($p = 0.09$). The statistical significance of the group-based difference was obtained using the Kruskal-Wallis test which is a non-parametric test, recommended for comparing between multiple independent groups (Siegel, 1988). The spearman correlation study was performed to study the relation between sEMG features and clinical features. The criteria used to evaluate Spearman correlation coefficients were weak (values of 0.25 - 0.50), moderate (values of 0.50 - 0.75), and strong (values of 0.75 and above).

7.3 Results

Figure 7.1 shows the sEMG profile of TA muscle for PD patients, CO, and YC groups. TA muscle is more active in PD patients during the SW phase of gait when compared to age-

matched controls and young control groups. TA was also found to be more active among the YC for all phases except the SS phase of gait.

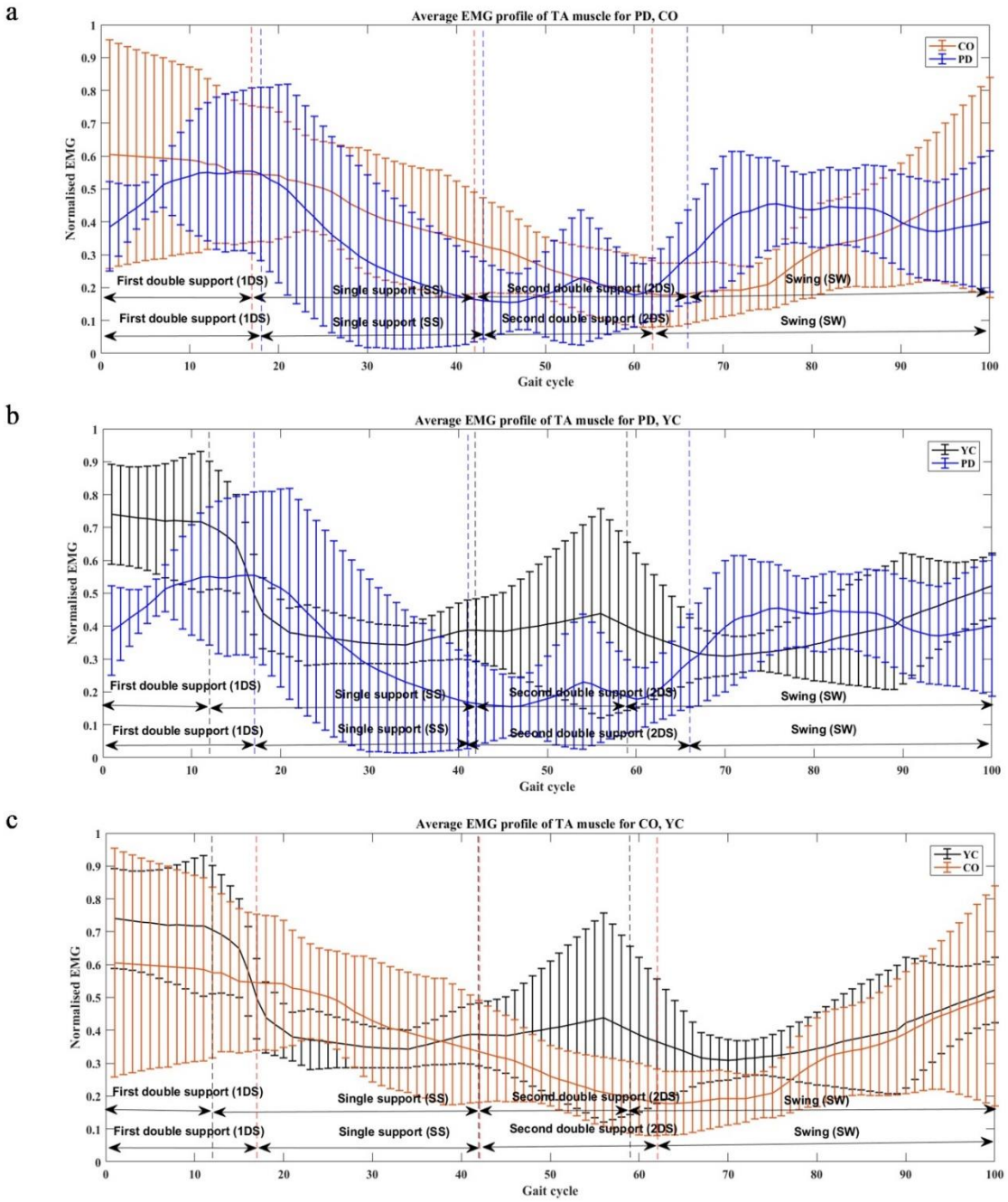


Figure 7.1: Plot showing the average sEMG profiles of TA muscle between a) PD and CO participants b) PD and YC participants c) CO and YC participants for sub-phases of the gait-cycle (first double support (1DS), single support (SS), second double support phase (2DS) and swing (SW) phase).

Figure 7.2 shows the sEMG profile of MG muscle for PD, CO, and YC groups. It is observed that for PD patients, the MG muscle is less active compared to the other groups during all phases of gait. The decreased activation of MG muscle of PD patients shows their reduced

ability to modulate the activation pattern compared to healthy control. These changes in the MG muscle reflect the impariment in the motor control and movement. The physiology of walking shows that MG muscle functions as a plantar flexor of the foot, that helps in pushing the body forward while walking. The reduced activation of MG muscle can leads to the increased risk of falls in PD.

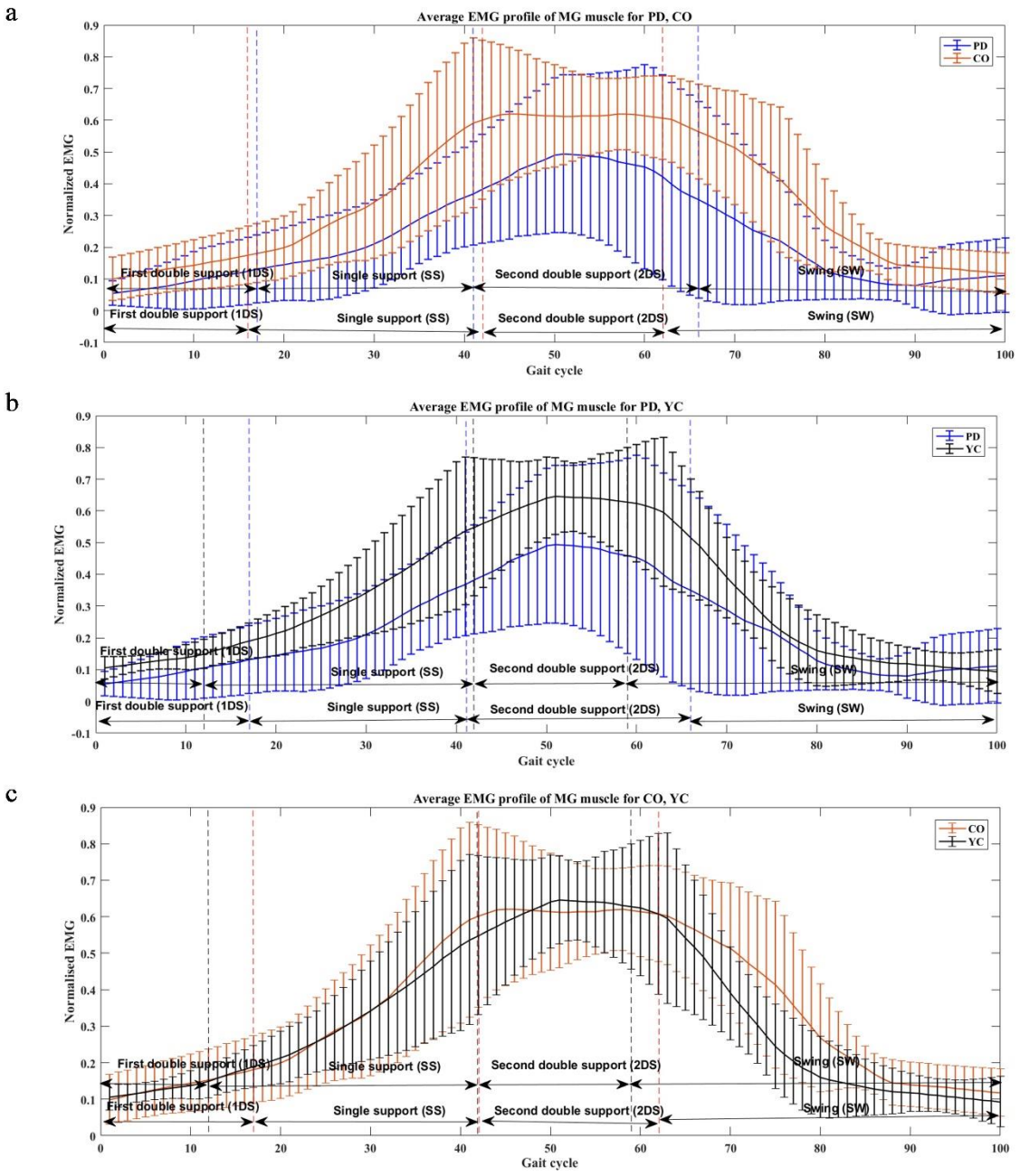
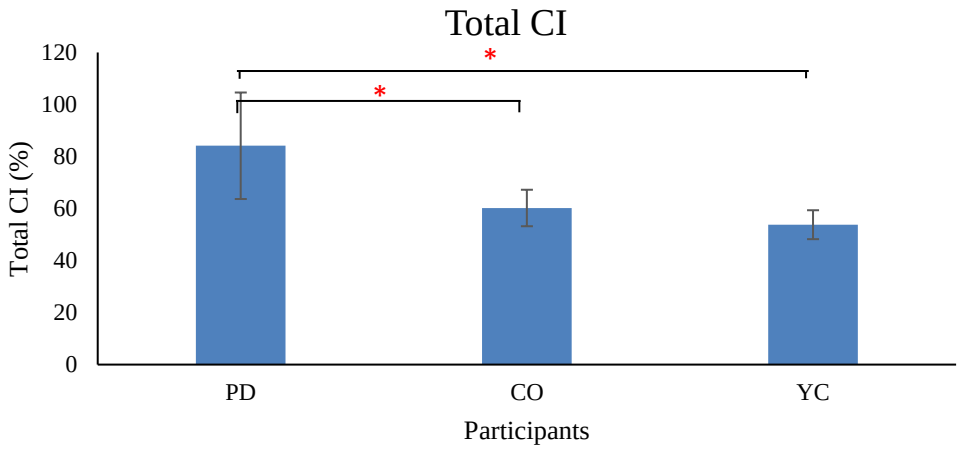


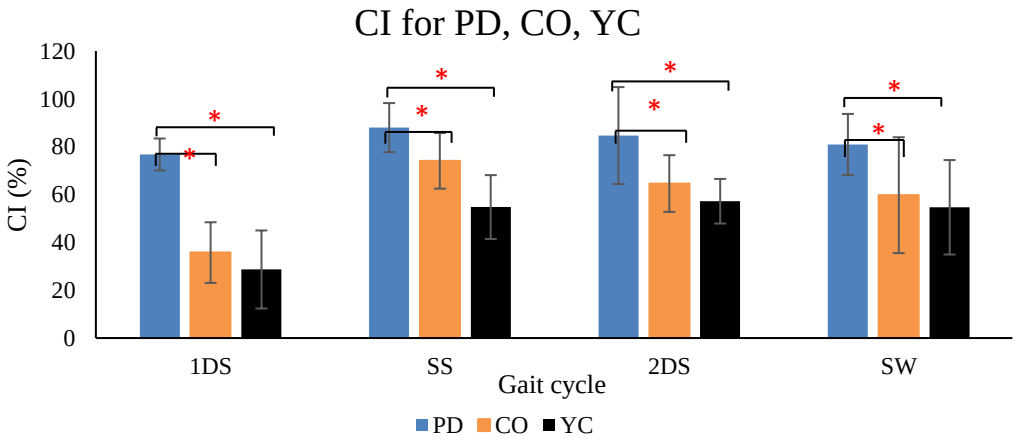
Figure 7.2: Plot showing the average sEMG profiles of MG muscle between a) PD and CO participants b) PD and YC participants c) CO and YC participants for sub-phases of the gait-cycle (first double support (1DS), single support (SS), second double support phase (2DS) and swing (SW) phase)

The CI values were calculated for both the legs, however, the statistical test showed that there was no significant difference, thus only one side has been reported. From Figure 7.3 a) and b), it is seen that the average CI was significantly higher for PD patients when compared to the control group (CO and YC) for the total percentage of gait and during different gait phases - 1DS, SS, 2DS and SW. Figure 7.3 c) shows that the average CI was significantly higher for different levels of severity- PD1, PD2 when compared to the age-matched control (CO).

a



b



c

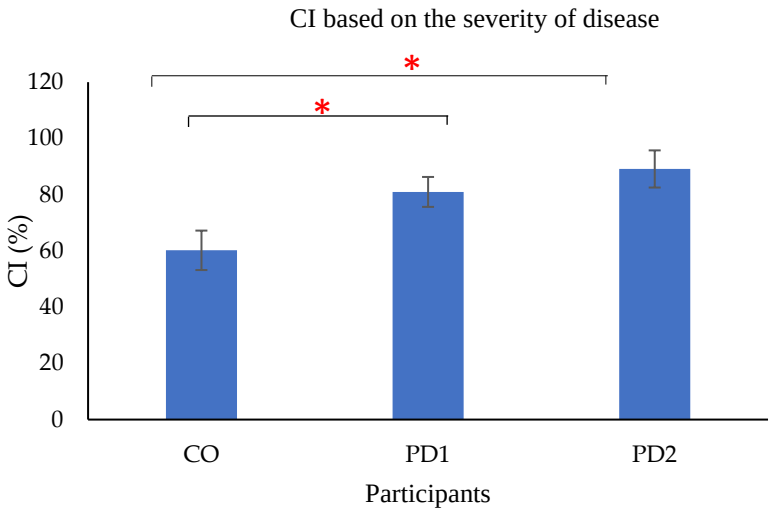
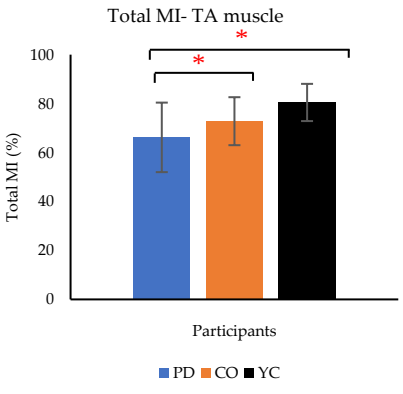


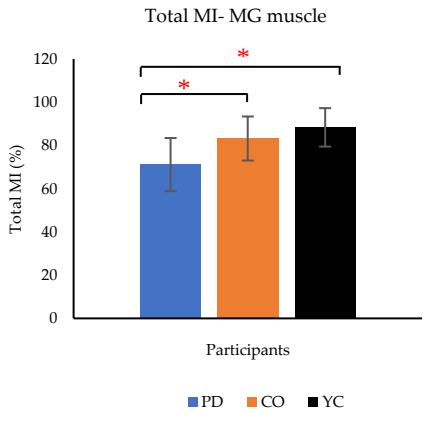
Figure 7.3: Bar plot showing average CI changes for a) total percentage of gait-cycle b) for sub-phases of the gait-cycle for PD, CO, and YC participant c) based on the severity of PD respectively

For total gait-cycle (0-100%), the average MI for TA muscle was 66.19 ± 12.3, 72.81± 10.21, and 80.45± 8.91 for PD patients, CO, and YC participants respectively, while that for MG muscle was 71.13 ± 14.3, 83.20 ± 9.81, and 88.37 ±7.64 for PD patients, CO and YC participants, as shown in Figure 7.4a and Figure 7.4b. Figure 7.4c and Figure 7.4d shows the average MI of both TA and MG for the 4 sub-phases of gait. The between-group differences for both were significant with $p<0.05$. When considering the four sub-phases of the gait, MI of PD patients for TA muscle was lower for 3 sub-phases of gait (SS, 2DS, SW) and higher for 1DS. For MG muscle, the MI value was lower for all 4 sub-phases of gait (1DS, SS, 2DS, and SW).

a



b



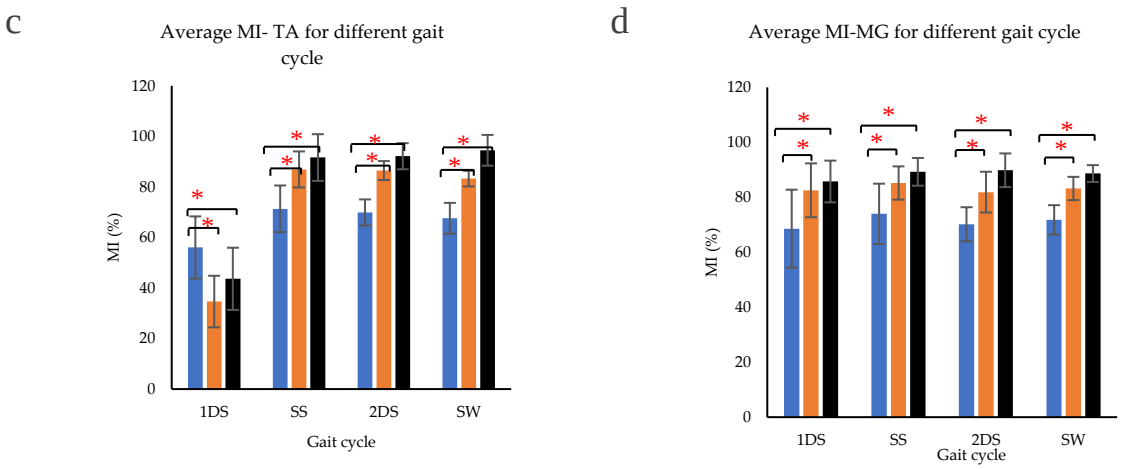


*Figure 7.4: Average MI values of TA and MG muscle for the total percentage of the gait-cycle (a, b) different gait-cycle (c, d) respectively, (*p (Significance) < 0.05).*

Table 7.2: Correlation study on sEMG features and clinical features

Clinical variables	Total CI	Total MI-TA muscle
Postural stability	0.612 (0.054)	0.658(0.023)
Rigidity (lower limb)	0.682 (0.011)	0.881 (0.033)
Gait	0.870 (0.002)	0.794 (0.002)
Body bradykinesia	0.880 (0.006)	0.612(0.015)
UPDRS PIGD	0.852 (0.018)	0.784(0.012)
Year of disease	0.565 (0.003)	0.683 (0.07)
H & Y Scale	0.322 (0.241)	0.569 (0.061)
UPDRS III	0.385 (0.157)	0.722 (0.017)

The r (*p*-value)- Spearman correlation coefficients(r) are indicated with the level of significance (*p*).

Table 7.2 shows the correlation study between sEMG features (mainly total CI and MI) and clinical features. The correlation coefficient and statistical significance values are reported. Total CI values showed a strong significant correlation with the clinical features- gait, bradykinesia, and UPDRS PIGD, while total MI of TA muscle was related to rigidity, gait, and UPDRS PIGD. The MI of MG muscle and AI of both TA and MG muscle was not significantly correlated with clinical features and hence not reported.

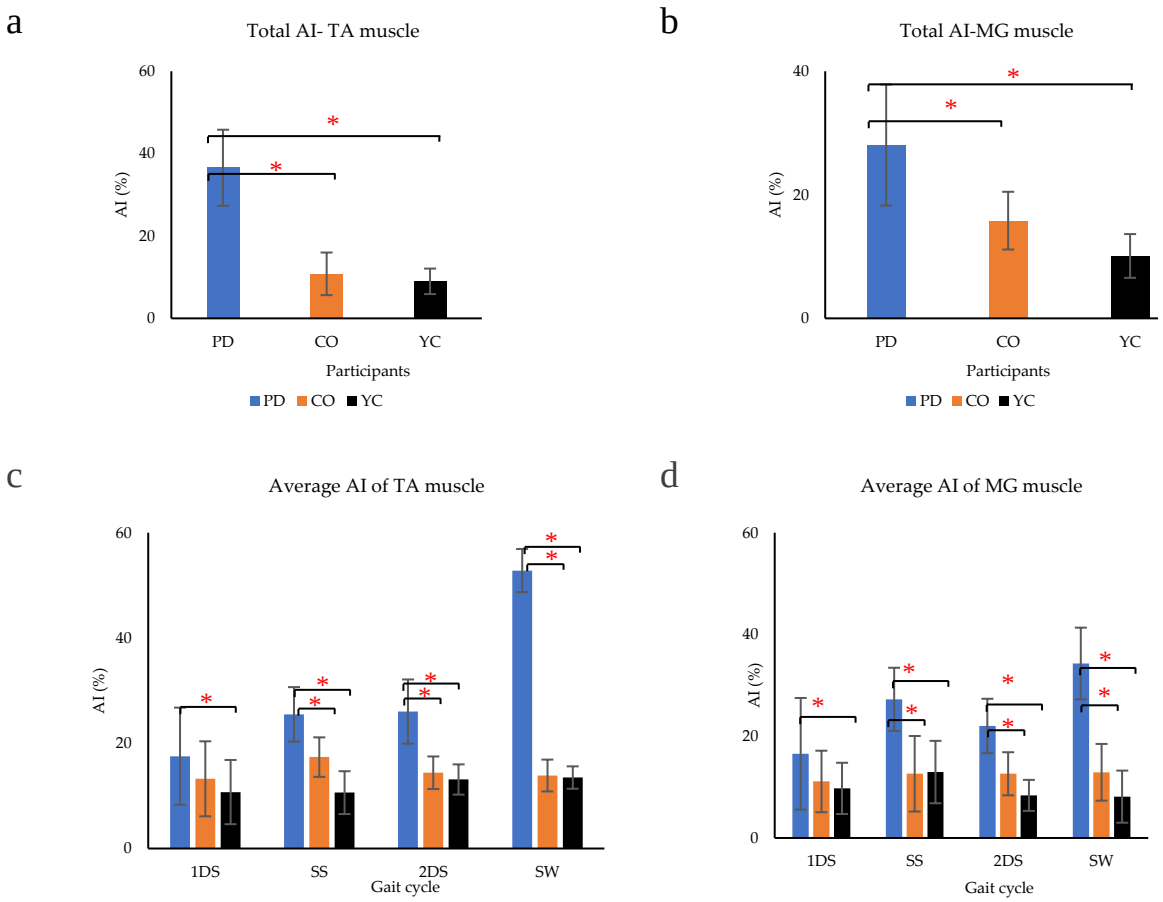


Figure 7.5: Average AI of TA and MG muscle for different gait-cycle based on RMS value (a, b) respectively

Figure 7.5 shows the average AI values for the total percentage of the gait-cycle (a, b) and different phases of gait (c, d) of TA and MG muscle for PD, CO, and YC groups. It was observed that 17 PD patients (17 out of 24), 12 CO (12 out of 24), and 4 YC (4 out of 24) had left side higher than the right, even though all were right-side dominant. Thus, AI was calculated using RMS values of sEMG for consistency with the references on the field. It was seen that PD patients had significantly higher AI when compared to the control for total gait-cycle (0-100%), as shown in Figure 7.5a and Figure 7.5b. We also observed a significant difference in AI for all sub-phases of gait between the PD patients and control (p<0.05), except during the 1DS, as shown in Figure 7.5c and Figure 7.5d. For PD patients, the highest asymmetry among the different sub-phases of gait was observed during the swing phase of gait. We noticed a higher value of sEMG RMS in left side for PD (17 patients out of 24), CO (12 out of 24) and YC (4 out of 24).

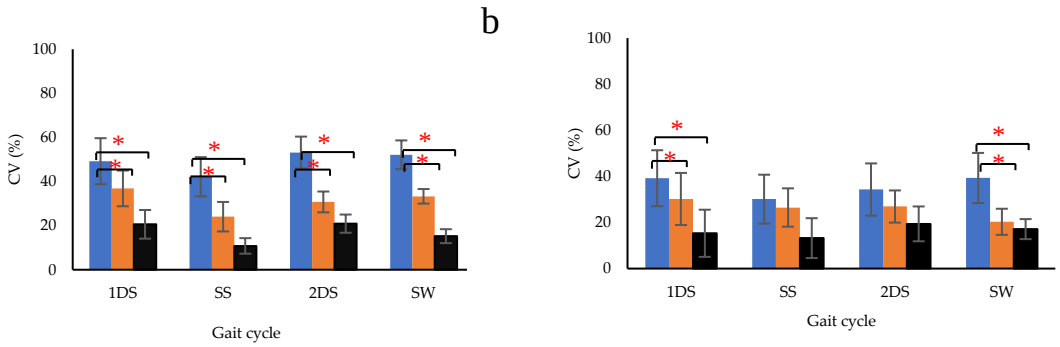


Figure 7.6: Variability in the muscle activation of a) TA and b) MG muscle compared between PD and control for different gait-cycle.

Figure 7.6 shows the variability of muscle pattern of TA and MG muscle compared between PD and CO, PD and YC for different gait-cycles. Results show that the muscle variability of TA is significantly different between PD and CO, PD and YC for all the percentage of the gait-cycle (1DS, SS, 2DS, SW). It also shows that TA variability is highest for PD patients when compared to control. Results of MG muscle shows that the variability of muscle pattern significantly differed between PD and CO, PD, and YC for all the percentage of the gait-cycle (1DS, SS, 2DS, SW), except at SS and 2DS phase of the gait-cycle. It also shows that MG variability is highest for PD patients when compared to controls.

Table 7.3: The table showing the statistical significance (p) between PD and CO, PD and YC for different sEMG features.

sEMG features	Gait-cycle	*p*-value	*p*-value
		PD and CO	PD and YC
CI	1DS	0.000	0.000
	SS	0.042	0.015
	2DS	0.030	0.024
	SW	0.033	0.024
AI-TA muscle	1DS	0.057	0.049
	SS	0.048	0.042
	2DS	0.045	0.045
	SW	0.003	0.002
AI-MG muscle	1DS	0.052	0.049
	SS	0.042	0.042
	2DS	0.048	0.042

	SW	0.03	0.024
MI- TA muscle	1DS	0.030	0.045
	SS	0.042	0.033
	2DS	0.036	0.027
	SW	0.039	0.021
MI-MG muscle	1DS	0.042	0.036
	SS	0.045	0.039
	2DS	0.048	0.033
	SW	0.045	0.035

The co-activation index (CI), Asymmetry index (AI) and Modulation index (MI) for both Tibialis anterior (TA) and Medial gastrocnemius (MG) muscles for sub-phases of gait-cycle -first double support (1DS), single support (SS), second double support phase (2DS) and swing (SW) phase are represented below.

Table 7.3 shows the statistical significance value between PD and CO, PD, and YC group for different sEMG features.

7.4 Discussion

It is common for Parkinson's disease patients to suffer lateral asymmetry and gait impairment in the early stage of the disease. The decline of posture instability and gait quality (PIGD) is one of the important parameters for monitoring the progression of the disease. PD gait is characterized by an abnormal loading response (Hughes et al., 1990), reduction of pre-swing phase, worsening stride length and gait speed (Nieuwboer et al., 1999), but many of these symptoms are not visually noticeable in the early stage of the disease. The investigation of these indices requires the analysis of their sub-phases of gait which has been shown in other disease conditions (Shimada et al., 2005; Chow et al., 2012) to be useful in identifying subtle changes and useful for detecting people who may be at risk of falls (Cole et al., 2017) and pathological changes (Mariani et al., 2013).

Changes to the gait may have a number of factors, many of which are not neurological, and hence gait analysis has its limitations. To overcome this limitation, earlier studies have the neuromuscular strategies of PD patients. These studies investigated the neuromuscular over the gait-cycle (Cioni et al., 1997; Bello et al., 2019) and observed changes to the amplitude and timing of muscle activation strategies between PD and control, and due to levodopa. Bailey et al (Bailey et al., 2018) found changes to the symmetry and modulation of the activation

averaged over the complete gait-cycle. Bello et al found differences in the co-activation for the sub-phases of gait between PD and controls (Cioni et al., 1997; Bello et al., 2019).

This study has combined the strengths of the earlier studies and investigated all the parameters proposed in the earlier studies to measure the differences between PD patients with low PIGD (average 5.29), age-matched controls, and young controls for the different sub-phases of the gait-cycle. Relative muscle activity, co-activation index, sEMG modulation, and gait asymmetry for the sub-phases of gait were computed for the three groups. To ensure that the works were easy to translate and introduced for clinical practice, the recordings were performed while the patients walked on the level floor of a medium-size clinic using wearable sensors. The observations are discussed below in 4 sections.

7.4.1 Muscle activity profile of TA and MG muscle

In line with the state of art, the age-matched controls exhibit greater activation of TA during midstance (Schmitz et al., 2009) while PD patients have reduced activation of TA during stance (Dietz et al., 1995). Only one notable observation in this study was derived from the muscle activity profile; there was the hyperactivity of TA during the early and mid-swing phases of gait for PD patients when compared to the control. Another observation was that the RMS of MG was less for PD during all gait phases when compared to the control.

7.4.2 Co-activation of TA and MG muscle

Our results are in line with the state of the art where it was reported that the PD patients exhibit increased co-activation (Dietz et al., 1995) compared to controls, and older controls have higher CI compared to young controls (Mazzetta et al., 2019). Increased co-activation is reported as a neuromotor strategy when postural stability is challenged (Lamontagne et al., 2000).

The investigation of CI during the 4 sub-phases show that for all groups, the 1DS had the lowest CI, and highest CI was during SS, which may be explained in terms of the need for stabilization of the muscles during that phase of gait (Lamontagne et al., 2000). It was also observed that the CI was significantly higher for all sub-phases of gait with the greatest difference being during the 1DS ($p<0.001$) while CI of controls (irrespective of age) modulated over the cycle. This can be interpreted that PD patients appear to need extra ankle joint support all the time, while controls need that only during the SS phase.

The investigation of CI based on the severity of disease shows that there was a significant difference between CO and PD1, CO and PD2 ($p<0.05$). Excessive co-activation of the ankle

muscle may be the cause of gait impairment, and maybe the precursor to observable symptoms. The significant difference between PD in stage 1 and controls shows that there is the potential of using CI of the TA and MG muscle to detect the disease conditions before it is manifested as a clinically observable symptom.

Increased co-activation of agonist-antagonist muscles results in the stiffening of legs and impaired gait in PD patients (Dietz et al., 1995). Our results also show that the increase in co-activation strongly correlated with the clinical features - bradykinesia, gait, and UPDRS PIGD. UPDRS PIGD item can be considered as a simple clinical measure of assessing balance and gait (Kelly et al., 2015). Thus, excessive co-activation of ankle muscle may cause gait impairment and increase the risk of falls, leading to loss of independence in PD patients. The results show that there is the potential of using CI for monitoring the progression of the disease, but longitudinal studies need to be conducted to validate this.

7.4.3 sEMG modulation of TA and MG muscle

Modulation index (MI) describes the ability to activate and inhibit the muscle as required for the movement, the higher value indicates the greater neuromuscular control (Lang et al., 2019). The investigation in the sub-phases of the gait reveals that in the 1DS phase, MI for TA muscle is significantly higher for PD patients when compared to control. These show that TA muscle activity was largely modulated at the 1DS phase of gait and these abnormal modulations of TA muscle would have inhibited the step-step transition in walking. The MI for MG muscle was lower for PD patients during all sub-phase of gait. The reduced ability to regulate muscle activation may be linked to the impairment in the proprioceptive system (Kurz et al., 2018), resulting in poor modulation of muscle (Miranda et al., 2019).

Another finding was that the MI-TA muscle strongly correlated with the clinical features-rigidity, gait, and UPDRS PIGD score. Lack of modulation of the muscle activity indicates that the muscle does not relax properly, leading to increase work-done, and manifesting as rigidity.

7.4.4 Gait lateral asymmetry of TA and MG muscle

In the state of art, it has been shown that PD patients have higher bilateral asymmetry of gait (Park et al., 2016), and have an increased AI averaged over the gait-cycle (Debaere et al., 2004). Ours is the first study where the AI of the sub-phases of gait has been investigated. The results confirm that the AI value of PD patients is higher than controls. It also shows that for control participants, the AI value was approximately the same for all the sub-phases. While for

PD patients, AI value was significantly higher during the SW phase for TA muscle and during SS and SW phase for MG muscle.

This shows that for PD patients, the unsupported phase of gait is highly asymmetrical. Increased asymmetry and reduced modulation of muscle could be based on the reduced ability of basal ganglia to generate repetitive and habitual movements (Debaere et al., 2004).

7.4.5 Variability of TA and MG muscle

In PD patients, the magnitude of variability in gait is a significant parameter that helps in identifying the dynamic features. We have seen a significant difference in the variability of TA muscle for all phases of gait. The highest variability of muscle pattern was observed for PD patients when compared to control both for TA and MG muscles. Signals with a high CV reflect a greater amount of fluctuations or adjustments of the neuromuscular system (Hunter et al., 2016). Muscle activity with increased variation over the gait-cycle may also suggest an inefficient gait and suggesting PD patients could have higher energy usage for similar work.

7.5 Summary

This chapter has reported the sEMG characteristics of TA and MG muscle of 24 PD, 24 CO, and 24 YC participants. This study has found that there is a significant higher co-activation of the TA and MG muscles, reduced modulation, and increased in asymmetry in PD patients compared with age-matched controls of the sub-phases of the gait-cycle. It has also found that there was no significant difference in these parameters due to age among controls, i.e. age-matched controls and young controls which indicates that these changes are not age-related. While many of the PD patients had low posture and gait difficulty scores (5.29 ± 3.07), the difference in the sEMG was very significant. The difference was also observed for both, stage 1 and stage 2 PD patients and this indicates that there is the potential to use sEMG of the TA and MG muscles for prodromal detection of gait abnormalities in PD patients, for early diagnosis of PD, and also for monitoring the progression of PD. This has the advantage over observing the gait parameter which may have the number of confounding factors. Another advantage of this method is that this can be investigated during the level, straight-line short distance walking inside an office using wearable sensors.

7.6 Limitation of the study

There are three limitations of the present study: reduced walking distance, only PD-ON state patients were tested, and postural instability was assessed only using the UPDRS PIGD score. Even though, we found a significant difference in the muscle characteristics of PD patients when compared to control, the walking distance considered for the study may be insufficient to address the walking style in PD patients. Medication can also significantly affect the tonic state of muscle, where the difference may be even greater in the OFF state of medication. Secondly, UPDRS PIGD scores are simple clinical assessment measures for postural instability.

7.7 Novelty and clinical significance of the study

There are two novelties of the present study which show the importance of monitoring sEMG of gait. The first is that there was a significant difference in the CI of age-matched control between stage 1 and stage 2 of PD patients. This indicates that there is a potential for sEMG to be used for detecting and monitoring the disease.

The second novelty of the study is that the asymmetrical activation of muscle is observed in both the TA and MG muscle, which is more pronounced in the swing phase of gait. This shows the reduced ability of PD patients to generate repetitive movements during the unsupported phase of gait. These findings on asymmetry can be used as a marker for analyzing the improvement by pharmacological treatment and rehabilitation of PD patients.

This chapter is based on the manuscript which is under review and conference paper accepted for publication:

Keloth S, Arjunan S, Raghav S and Kumar D Detection of Parkinson's disease using muscle activation strategies during walking. *IEEE TNSRE* .

Keloth S, Arjunan S, Raghav S, Radcliffe P and Kumar D (2020) Differenciating between Parkinson's disease patient and controls using varability in muscle activation during walking *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*.

Chapter 8

8. Conclusion

Brief outline of the chapter:

This chapter provides the conclusion of the research work and the future work related to this research is proposed.

8.1 Introduction

PD is a movement disorder that causes difficulty in movement, postural instability, muscle rigidity, and reduced gait speed. These are the major cause of disability, falls and reduced quality of life. Gait assessment is important in diagnosing and monitoring the disease. Gait is one of the measures for the UPDRS III (Goetz et al., 2004; Goetz et al., 2008) and is scored by clinical observations to determine the severity of disease and efficacy of treatment. However, this is a subjective test and requires extensive time effort, and there is a need for quantifiable gait analysis to study PD patients.

8.2 Main contribution

This thesis has addressed the following research questions:

Q1. How does the gait parameters vary with the severity of PD?

Studies have quantified the difference in the gait parameter of PD and control (Hausdorff et al., 1998; Rios et al., 2001; Hausdorff et al., 2003; Hausdorff et al., 2007), while the relationship between gait parameters and the severity of the disease is not studied (Investigated in Chapter 5).

The main contribution from chapter 5 is listed below:

There are two novelties of the study that can be used by the clinician to monitor the progression of the disease.

- The first is that the variance of gait interval is significantly higher for PD patients and increases with the severity of the disease. This increase in the variability indicates poor coordination and loss of rhythmicity and may be considered for quantifying the severity of disease and monitoring the progress of the patients.

- The second finding of the study is that the PD patients show decreased self-similar patterns in double support interval of gait, suggesting that there are less rhythmic gait intervals and a sense of urgency to remain in support phase of gait by the PD patients.

Q2. How does the gait parameter vary during straight walking, U-turn, and turn around a point between PD patients and control?

Turning movements in PD have reported increased turning time, turn arc (Crenna et al., 2007; Huxham et al., 2008; Spildooren et al., 2013) and the number of steps to complete the turn. The main consequence of turns in PD is lateral falls, which can result in an eight-fold increase in hip fractures compared with falls during straight walking. It is very important to evaluate the turning ability in PD and to investigate the effect of gait intervals across different turns, which has not yet been done (Investigated in Chapter 6).

The main contribution of Chapter 6 is:

There are two novelties of the study which have the potential to make a significant difference to the clinical assessment of PD patients.

- The first is that this study has shown that both, straight-line walking and turning are suitable for the evaluation of PD patients, and hence either could be used. Thus, the practice of making the patient perform complicated turns (Mellone et al., 2016; Mancini et al., 2018) is not required for such a study.

- The second novelty is that this study has shown that by the use of IMU placed on the legs of the patients and measuring the gait period variance (On-Yee et al., 2017; Estep et al., 2018; Warlop et al., 2018), it is possible to identify PD patients while the patient performs simple walking. This has the potential to be used for population-based screening for early diagnosis of the disease. Another important finding of this study is that it showed that the gait variance of these parameters only showed the difference between PD and controls, irrespective of their age. Thus, while there are significant differences in the gait parameters between young and old, the variability due to age was not significant.

Q3. How does Tibialis anterior (TA) and Medial gastrocnemius (MG) muscle activation vary between PD and control for different phases of gait?

A coordinated pattern of muscle activity results in the transition from stance into walking. The co-activation studies of muscles will help to understand the stiffness and rigidity across

the joints. Normally muscles stretch when they move and reflex when they are at rest. But for PD muscles may not reflex, causing rigidity and difficulty to walk (Busse et al., 2006). To better understand the muscle activation pattern in PD patients, it is essential to investigate the muscle features during gait events (Investigated in Chapter 7).

The main contribution of Chapter 7 is:

There are two novelties of the present study which show the importance of monitoring the sEMG of gait.

- The first is that there was a significant difference in the CI of age-matched control between stage 1 and stage 2 of PD patients. This indicates that there is a potential for sEMG to be used for detecting and monitoring the disease.
- The second novelty of the study is that the asymmetrical activation of muscle is observed in both the TA and MG muscle, which is more pronounced in the swing phase of gait. This shows the reduced ability of PD patients to generate repetitive movements during the unsupported phase of gait. These findings on asymmetry can be used as a marker for analyzing the improvement by pharmacological treatment and rehabilitation of PD patients.

8.3 Limitation and future work

The study has found that the gait and muscle parameters can be used for quantitative gait analysis in Parkinson's disease patients. There were a few limitations of the present study: Sample size in gender calculation and only the ON-state PD was tested. While 24 PD and 24 age-matched controls were a decent size based on literature, this was not sufficient for gender and body size matching, which are factors that contribute to gait parameters. The other factor is that literature shows (Schaafsma et al., 2003) that there is a significant effect caused by medication, where the difference may be even greater in the OFF state of medication. The future work can consider the effect of medication on the gait parameters while performing different turning task.

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Appendices

I. Rating scale-UPDRS III

	Rating Scale 0	**Rating Scale 1**	**Rating Scale 2**	**Rating Scale 3**	**Rating Scale 4**
Speech	Normal	Slight loss of expression, diction and/or volume	Monotone, slurred but understandable; moderately impaired	Marked impairment, difficult to understand	Unintelligible
Facial Expression	Normal	Minimal hypomimia, could be normal “poker face”	Slight but definitely abnormal diminution of facial expression	Moderate hypomimia, lips parted some of the time	Masked or fixed facies with severe or complete loss of facial expression; lips parted ¼ inch or more
Tremor at rest (Right upper limb)	Absent	Slight and infrequently present	Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present	Moderate in amplitude and present most of the time	Marked in amplitude and present most of the time
Tremor at rest (Left upper limb)	Absent	Slight and infrequently present	Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present	Moderate in amplitude and present most of the time	Marked in amplitude and present most of the time
Tremor at rest (Right lower limb)	Absent	Slight and infrequently present	Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present	Moderate in amplitude and present most of the time	Marked in amplitude and present most of the time
Tremor at rest (Left lower limb)	Absent	Slight and infrequently present	Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present	Moderate in amplitude and present most of the time	Marked in amplitude and present most of the time

Action or postural tremor of hands (Right upper limb)	Absent	Slight present with action	Moderate in amplitude, present with action	Moderate in amplitude with posture holding as well as action	Marked in amplitude; interferes with feeding
Action or postural tremor of hands (Left upper limb)	Absent	Slight present with action	Moderate in amplitude, present with action	Moderate in amplitude with posture holding as well as action	Marked in amplitude; interferes with feeding
Rigidity (Judged on passive movement or major joints with patient relaxed in sitting position. Cogwheeling to be ignored) (Neck)	Absent	Slight or detectable only when activated by mirror or other movements	Mild to moderate	Marked, but full range of motion easily achieved	Severe, range of motion achieved with difficult
Rigidity (Judged on passive movement or major joints with patient relaxed in sitting position. Cogwheeling to be ignored) (Right upper limb)	Absent	Slight or detectable only when activated by mirror or other movements	Mild to moderate	Marked, but full range of motion easily achieved	Severe, range of motion achieved with difficult
Rigidity (Judged on passive movement or major joints with patient relaxed in sitting position. Cogwheeling to be ignored) (Left upper limb)	Absent	Slight or detectable only when activated by mirror or other movements	Mild to moderate	Marked, but full range of motion easily achieved	Severe, range of motion achieved with difficult
Rigidity (Judged on passive movement or major joints with patient relaxed in sitting position. Cogwheeling to be ignored) (Right lower limb)	Absent	Slight or detectable only when activated by mirror or other movements	Mild to moderate	Marked, but full range of motion easily achieved	Severe, range of motion achieved with difficult

Rigidity (Judged on passive movement or major joints with patient relaxed in sitting position. Cogwheeling to be ignored) (Left lower limb)	Absent	Slight or detectable only when activated by mirror or other movements	Mild to moderate	Marked, but full range of motion easily achieved	Severe, range of motion achieved with difficult
Finger taps (Patient taps thumb with index finger in rapid succession) (Right Side)	Normal	Mild slowing and/or reduction in amplitude	Moderate impaired. Definite and early fatiguing. May have occasional arrests in movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task
Finger taps (Patient taps thumb with index finger in rapid succession) (Left Side)	Normal	Mild slowing and/or reduction in amplitude	Moderate impaired. Definite and early fatiguing. May have occasional arrests in movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task
Hand movements (Patient opens and closes hands in rapid succession) (Right Side)	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in ongoing movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task
Hand movements (Patient opens and closes hands in rapid succession) (Left Side)	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in ongoing movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task
Rapid alternating movements of hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously) (Right Side)	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task

Rapid alternating movements of hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously) (Left Side)	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task
Leg agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches) (Right Side)	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task
Leg agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches) (Left Side)	Normal	Mild slowing and/or reduction in amplitude	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement	Can barely perform the task
Arising from chair (Patient attempts to rise from a straight backed chair, with arms folded across chest)	Normal	Slow; or may need more than one attempt	Pushes self-up from arms of seat	Tends to fall back and may have to try more than on time, but can get up without help	Unable to arise without help
Posture	Normal erect	Not quite erect, slightly stooped posture; could be normal for older person	Moderately stooped posture with kyphosis; can be moderately leaning to one side	Severely stooped posture with kyphosis; can be moderately leaning to one side	Marked flexion with extreme abnormality of posture

Gait	Normal	Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion	Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion	Severe disturbance of gait, requiring assistance	Cannot walk at all, even with assistance

II. Rating scale- Modified Hoehn and Yahr staging (H & Y)

Stages	Signs
Stage 0	No signs of disease
Stage 1	Unilateral disease
Stage 1.5	Unilateral plus axial involvement
Stage 2	Bilateral disease, without impairment of balance
Stage 2.5	Mild bilateral disease, with recovery on pull test
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severe disability but still able to walk or stand unassisted
Stage 5	Bedridden and need wheelchair for mobility

III. Rating scale-Unified dyskinesia rating scale (UDysRS)

0=No dyskinesia

1=Questionable or mild dyskinesia

2=Moderate dyskinesia with movements which are not intrusive nor distort voluntary movements

3=Severe dyskinesia which disturbs but does not prohibit posture or voluntary movements

4=Incapacitating dyskinesia which prohibits some postures and voluntary movements

Impairment Score	Communication	Drinking	Dressing	Ambulation	Highest Score
Face					(16)
Neck					(17)
R Arm/ Shoulder					(18)
L Arm/ Shoulder					(19)
Trunk					(20)
R Leg/ Hip					(21)

L Arm/ Hip					(22)

DISABILITY SCALE

Communication

0=No dyskinesia

1=Dyskinesia present but does not impair communication

2=Dyskinesia impairs communication but patient is fully understandable

3=Dyskinesia interferes with communication such that parts of communication cannot be understood but overall content is understandable

(23) _____

4=Dyskinesia interferes with comprehension of overall communication

Drinking from a cup

0=No dyskinesia observed

1=Dyskinesia present but it does not affect performance of the task

2=Dyskinesia affect the smooth performance but causes no splashing or spilling

3=Dyskinesia affects performance such that patient spills a few drops of water

4=Dyskinesia affects performance such that patient spills more than a few drops or dyskinesia cause coughing

or choking. (24) _____

Dressing

0=No dyskinesia observed

1=Dyskinesia present but does not interfere with or slow dressing

2=Dyskinesia affects smooth performance of task but the performance is at most minimally slowed

3=Dyskinesia interferes and slows performance but it is completed within 60 seconds (25) _____

4=Dyskinesia precludes completing the task within 60 second

Ambulation

0=No dyskinesia observed

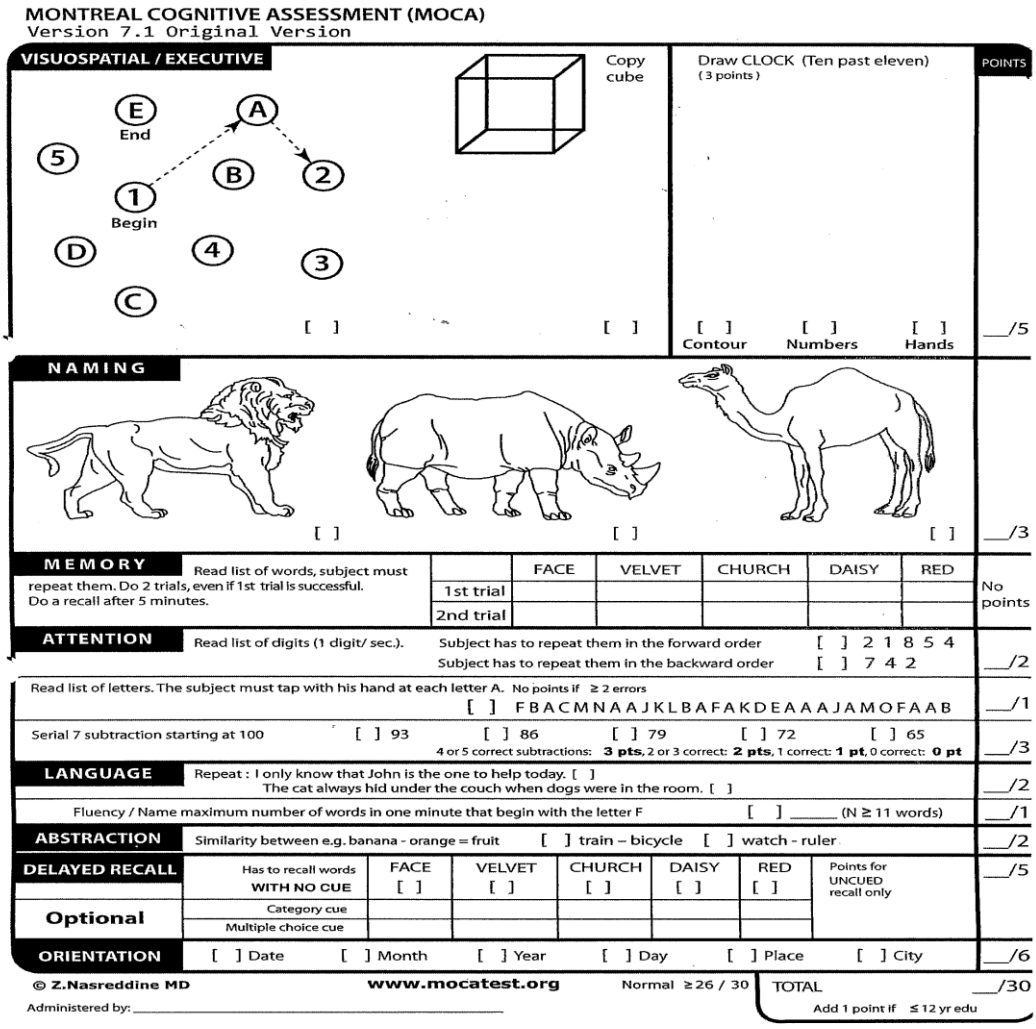
1=Mild dyskinesia present but does not alter normal synchrony or cadence

2=Dyskinesia is present which alters the normal cadence of rising, sitting or walking but does not slow overall performance.

3=Dyskinesia is present which disrupts or distorts arising, sitting or walking. Performance is slowed. Patient is able to rise and walk without imminent danger of falling. (26) _____

4=Dyskinesia prohibits walking safely without assistance

IV. Montreal cognitive assessment (MoCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] Contour [ ] Numbers [ ] Hands ___/5

NAMING ___/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) ___/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL ___/5

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30 TOTAL ___/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

V. Letter of approval

RMIT UNIVERSITY

18 August 2017

Professor Dinesh Kant Kumar
School of Engineering
REMIT University

Dear Prof Kumar

BSEHAPP 22-15 KUMAR Analysis of handwriting and gait in Parkinson's and multiple sclerosis

Thank you for requesting an amendment to your Human Research Ethics project titled: **Analysis of handwriting and gait in Parkinson's and multiple sclerosis**, which was originally approved by Science Engineering and Health CHEAN in 2015 for a period of **2 years**.
I am pleased to inform you that the CHEAN has **approved** your amendment as outlined in your request and the title will now be changed to "**Understanding health behaviours in people diagnosed with diabetes."**

The CHEAN notes and thanks you for providing all documentation that incorporates these amendments. This documentation will be appended to your file for future reference and your research may now continue.

The committee would like to remind you that:
All data should be stored on University Network systems. These systems provide high levels of manageable security and data integrity, can provide secure remote access, are backed up on a regular basis and can provide Disaster Recover processes should a large scale incident occur. The use of portable devices such as CDs and memory sticks is valid for archiving; data transport where necessary and for some works in progress; The authoritative copy of all current data should reside on appropriate network systems; and the Principal Investigator is responsible for the retention and storage of the original data pertaining to the project for a minimum period of five years.
Final reports are due within six months of the project expiring or as soon as possible after your research project has concluded.

The annual/final reports forms can be found at:
www.rmit.edu.au/staff/research/human-research-ethics

Yours faithfully,

Associate Professor Barbara Polus
Chair, Science Engineering & Health
College Human Ethics Advisory Network