Stride length-cadence relationship in parkinsonian gait

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Doctoral Thesis UDC / 2019

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UNIVERSIDADE DA CORUÑA

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Submitted: 15.10.2019

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DECLARE:

That the Master in Teacher of Physical Education and Teacher of Italian language and culture Míra Ambrus, has developed under their supervision the work called "Stride length-cadence relationship in parkinsonian gait". This work satisfies all the requirements for a dissertation to aim for the International PhD in the University of A Coruña.

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For my family

ACKNOWLEDGEMENTS

I would like to say thank you to everyone who has supported me during the completion of my doctoral thesis.

First of all, I would like to say thank you to my supervisors. I have appreciated your help and kindness.

Dr. Miguel Fernández del Olmo, thank you for welcoming me to start off my PhD in A Coruna as an international PhD student. I appreciate your help from the beggining, from the many translations from Spanish or Gallician to English to the administrative matters. Thank you for your scientific advice and support.

Dr. José Andrés Sánchez, thank you so much for all your help with the biomechanics devices, especially for teaching me how to use Optogait. Thank you for motivating and supporting me, as well as teaching me Spanish. I enjoyed working with you during the measurements, and I will never forget your funny, radiant, and positive attitude.

To my research group colleague, better say friend, Helena, many thanks for always listening me, giving me advice, and helping me with everything from the language to accomodation, and even opening your home to me! It was a pleasure to know you and your family. You are always welcome in my home. Gracias amiga!

To Noa and my colleague Catherine from the University of Bern, I have appreciated your help proofreading my English writing.

To the participants who took part in my projects, thank you for your time and kindness. I learned so much from you about Parkinson's disease and what it means to live your lives with this incredibly hard disease. I apprecite your stories and the times you shared with me. Never give up!

To my grandmother, Márta, for always listening me and supporting me with her love, care and cakes when I was visiting home! To Csabi, who supported and motivated me throughout my Phd. Thank you for your words and being with me during the challenging times.

To my lovely, best parents in the word, thank you for supporting me every time I needed it. My mother, Márta, and my father, László, thank you so much for your time, effort, love, patience, and care! For listening me, giving me advice, helping me and also supporting me economically. I am very happy to have you besides me! Thank you for letting me go far from home and spend two years very far from you. This work would not have been possible without you! Nagyon szépen köszönöm! Szeretlek titeket nagyon!

"With Parkinson's, exercise is better than taking a bottle of pills. If you don't do anything you'll just stagnate."

BRIAN LAMBERT,

"Parkinson's is no barrier to cycling", New Zealand Herald, January 22, 2016

SUMMARY

Parkinson's disease (PD) is a neurodegenerative disorder which modulates motor function from speech to gait. Gait disorders are the most disabling motor impairments in PD patients, as they affect their quality of life.

The regulation of the stride length represents one of the main goals in rehabilitation interventions in PD subjects. However, the effects of physical therapy interventions on the stride length-cadence relationship (SLCrel) in PD subjects have not been examined due to the lack of a gait evaluation that explores that relationship.

Furthermore, the use of treadmills in gait rehabilitation in PD patients has been proven to improve gait performance. Understanding the mechanisms underlying these improvements will ameliorate the efficacy of physical therapy in PD. However, it remains unclear whether walking on the treadmill changes the SLCrel in PD.

The presented work consists of two studies. The first explores the reliability of the SLCrel in a group of PD subjects. The second investigates the SLCrel in PD subjects walking on a treadmill vs. overground, and compare with age-matched healthy subjects.

The results of this thesis confirm that SLCrel in parkinsonian gait is a reproducible measure across a period of three months, and may be a useful tool to explore the specificity of gait rehabilitation interventions in PD subjects. Furthermore, support the potential therapeutic effects of treadmill walking for gait rehabilitation in PD.

RESUMEN

La enfermedad de Parkinson (EP) es un trastorno neurodegenerativo que modula la función motora desde el habla hasta la marcha. Los trastornos de la marcha son las discapacidades motoras más incapacitantes en los pacientes con EP, ya que afectan su calidad de vida.

La regulación de la longitud del paso representa uno de los objetivos principales en las intervenciones de rehabilitación en sujetos con EP; sin embargo, no se ha examinado el efecto de la intervención fisioterapéutica en la relación longitud-cadencia de zancada (SLCrel) en sujetos con EP debido a la ausencia de una evaluación de la marcha que explore la vinculación entre dichos parámetros.

Además, se ha demostrado que el uso de la cinta rodante en la rehabilitación de la marcha en pacientes con EP mejora su rendimiento. Comprender los mecanismos que subyacen a estas mejoras permitiría mejorar la intervención de la terapia física en la EP. Sin embargo, no se han encontrado evidencias contundentes de que caminar en cinta rodante modifique la SLCrel en la EP.

El trabajo presentado contiene dos estudios. El primero explora la confiabilidad de la SLCrel en un grupo de sujetos con EP. El segundo investiga la SLCrel en sujetos con EP que caminan en una cinta rodante frente a la marcha en pasillo, siendo los resultados comparados con los obtenidos con sujetos sanos con una edad equiparable.

Los resultados de esta tesis confirman que la SLCrel en la marcha parkinsoniana es una medida reproducible hasta un período de tres meses, y que puede resultar una herramienta útil para explorar la especificidad de las intervenciones de rehabilitación de la marcha en sujetos con EP. Además, los resultados respaldan los efectos terapéuticos potenciales de caminar en cinta rodante para la rehabilitación de la marcha en la EP.

RESUMO

A enfermidade de Parkinson (EP) é un trastorno neurodegenerativo que modula a función motriz desde o fala ata a marcha. Os trastornos da marcha son as discapacidades motoras máis incapacitantes nos pacientes con EP, xa que afectan a súa calidade de vida.

A regulación da lonxitude do paso representa un dos obxectivos principais nas intervencións de rehabilitación en suxeitos con EP; con todo, non se examinou o efecto da intervención fisioterapéutica na relación lonxitude-cadencia dezancada (SLCrel) en suxeitos con EP debido á ausencia dunha avaliación da marcha que explore a vinculación entre os devanditos parámetros.

Ademais, demostrouse que o uso da cinta rodante na rehabilitación da marcha en pacientes con EP mellora o seu rendemento. Comprender os mecanismos que subxacen a estas melloras permitiría mellorar a intervención da terapia física na EP. Con todo, non se atoparon evidencias contundentes de que camiñar en cinta rodante modifique a SLCrel na EP.

O traballo presentado contén dous estudos. O primeiro explora a confiabilidad da SLCrel nun grupo de suxeitos con EP. O segundo investiga a SLCrel en suxeitos con EP que camiñan nunha cinta rodante fronte á marcha en corredor, sendo os resultados comparados cos obtidos con suxeitos sans cunha idade equiparable.

Os resultados desta tese confirman que a SLCrel na marcha parkinsoniana é unha medida reproducible ata un período de tres meses, e que pode resultar unha ferramenta útil para explorar a especificidade das intervencións de rehabilitación da marcha en suxeitos con EP. Ademais, os resultados apoian os efectos terapéuticos potenciais de camiñar en cinta rodante para a rehabilitación da marcha na EP.

PREFACE

The present work, the thesis titled “Stride length-cadence relationship in parkinsonian gait” includes experimental work performed between 2016 and 2017 at the Faculty of Sports Science and Physical Education of University of A Coruña, Department of Sports Science.

The thesis contains two original experimental studies. Both studies have already been published in an international peer review journal Gait and Posture.

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ABBREVIATIONS

ANOVA	Repeated-measures analysis of variance
BG	Basal ganglia
Cad	Cadence
CI	Confidence interval
CV	Coefficient of variation
fMRI	Functional magnetic resonance imaging
GPe	Globus pallidus pars externa
H&Y	Hoehn and Yahr scale
ICC	Intra-class correlation coefficient
MID	Minimal important difference
MMSE	Mini-mental state examination
MPTP	1-methyl-4-phenyl-1,2,3,6,tetrahydropyridine
MSNs	Medium spiny neurons
PD	Parkinson's disease
SEM	Standard error of mean
SL	Stride length
SLCrel	Stride length-cadence relationship
SMA	Supplementary motor area
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SPECT	Single photon emission computed tomography
STN	Subthalamic nucleus
T1	Test 1
T2	Test 2
UPDRS	Unified Parkinson´s Disease Rating Scale
UPDRS-III	Unified Parkinson´s Disease Rating Scale Part III

LIST OF PUBLICATIONS INCLUDED IN THE THESIS

STUDY 1

Ambrus, M. Sanchez, J.A. Fernandez-del-Olmo, M., 2019. Test-retest reliability of stride length-cadence gait relationship in Parkinson's disease. Gait & Posture 71, 177-180.

STUDY 2

Ambrus, M. Sanchez, J.A. Fernandez-del-Olmo, M., 2019. Walking on a treadmill improves the stride length-cadence relationship in individuals with Parkinson's disease. Gait & Posture 68, 136–140.

OTHER SCIENTIFIC CONTRIBUTIONS

The author contributed with oral presentation and she was also a moderator of the following international congress:

M. Ambrus, J.A. Sanchez, M. Fernandez-del-Olmo. "Relationship between the stride length and cadence in patients with Parkinson’s disease". 3rd Intentional Conference on Parkinson's Disease and Movement Disorders (USA, Chicago, September 2017).

Míra Ambrus, J Alzheimers Dis Parkinsonism 2017, 7:5 (Suppl) DOI: 10.4172/2161-0460-C1-030

The author has spent 5 months internship at the University of Bern, Institute of Sport Science in Switzerland, between January 2018 until June 2018. The author during her stay in Switzerland conducted an experimental study on effects of clothing on kinematic parameters of posture and gait, as well as she became a supervisor of a master student with a topic of Parkinson’s disease and dance, who finished her thesis with a very good result.

CHAPTER I.
INTRODUCTION

1.1 PARKINSON'S DISEASE

This chapter gives a comprehensive overview of Parkinson's disease, including epidemiology, etiology, brain of PD patients, symptomatology, diagnosis-, and evaluation of PD and the treatment of the disease.

1.1.1 General overview and the epidemiology of Parkinson's disease

Parkinson's disease (PD) is considered to be the second most common neurodegenerative disorder after Alzheimer's disease (Twelves, Perkins, Uk, & Counsell, 2003), and affects the 1% of the population over the age of fifty (Kirtley, 2006). The disease has been described in 1817 by James Parkinson in the classic "Essay on the Shaking Palsy" (Parkinson, 2002). The causes of PD remains unknown and no cure for the disease has been found (Morris, Iansek, Matyas, & Summers, 1994b).

PD modulates motor function from speech to gait and the most common symptoms are akinesia, rigidity, tremor and postural instability (Hoehn & Yahr, 1967). Moreover, PD is a chronic, progressive disorder which normally affects elderly people. Incidence and prevalence are higher in men than in women (Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011), and there is 1% chance over the age of 65 year (Jahanshahi & Marsden, 2000; Schoenberg, 1987). Nevertheless, PD is associated with a loss of independence (Schoenberg, 1987), and the risk of falls are also higher (Koller, Glatt, Vetere-Overfield, & Hassanein, 1989).

Furthermore, PD has motor and non-motor symptoms. The signs of motor functions are the tremor of the hands, arms, legs, jaw and face; the bradykinesia or slowness of movement; rigidity or stiffness of the limb and trunk and the postural instability or impaired balance and coordination. The secondary signs are freezing, PD patients become unable to start movements or continue to move forward (Hausdorff, 2007); unwanted acceleration, when people talk very fast and hard to understand; also their face expression become less expressive. There are non-motor symptoms as well, as loss of sense of smell, sleep disturbances, mood disorders, depression, cognitive problem etc. The non-motor symptoms may precede motor symptoms (Tibar et al., 2018).

The level of severity of motor signs associated with PD can be measured using the Unified Parkinson's Disease Rating Scale Part-III (UPDRS-III) (Hughes, Daniel, &

Kilford, 1992) and Hoehn and Yahr scale (H&Y) (Hoehn and Yahr, 1967). The UPRDS is a rating scale made up of numerous sections including mentation, behaviour, activities of daily life, and motor evaluation. Meanwhile, the H&Y scale describes the progress of the PD symptoms. Originally H&Y scale included stages 1 through 5, however stage 0, 1.5 and 2.5 have been added. This modified H&Y allocates states from 0 to 5 to indicate the relative level of disability in PD patients (Fahn & Elton, 1987).

The main pathological finding associated with the motor deficits of PD is the degeneration of the dopaminergic neurons of the substantia nigra pars compacta (Halliday, Lees, & Stern, 2011). The motor symptoms appear when at least 60% of dopaminergic neurons are lost and 80–85% of dopamine content in the striatum is depleted (Jankovic, 2008).

1.1.2 Etiology

The cause of PD is still unknown, but risk of developing PD is no longer viewed as primarily due to environmental factors (Kalia & Lang, 2015). However, it seems that the environmental and genetic factors contribute to the onset of PD (Schapira & Jenner, 2011) (Figure1). The 1-methyl-4-phenyl-1, 2, 3, 6,tetrahydropyridine (MPTP), a substance structurally similar to the herbicide paraquat, that could demolish dopaminergic neurons causing chronic parkinsonism, was discovered in 1980s (Langston, Langston & Irwin, 1984). The finding of MPTP was stimulated studies focus on environmental factors, and most important, created new experimental models of PD.

Environmental factors

The occurrence of PD is from the general - in terms of a potential role for industrialization, rural environment, well water, plant-derived toxins, and bacterial and viral infection - to the specific, as occurs with exposure to organic solvents, carbon monoxide, and carbon disulfide (Schapira & Jenner, 2011).

Even though the broad literature, the evidences of environmental factors, as pesticides, metals or magnetic fields are less (Richardson et al., 2009; Kieburtz & Wunderle, 2013). Some of the factors, such as, smoking a cigarett and caffeine intake appears protective, however the appearance of many factors are still not clear, for example, exercise, anti-inflammatories, antihypertensive and antilipidaemics (Chin-Chan, Navarro-Yepes, & Quintanilla-Vega, 2015; Kalinderi, Bostantjopoulou, & Fidani, 2016).

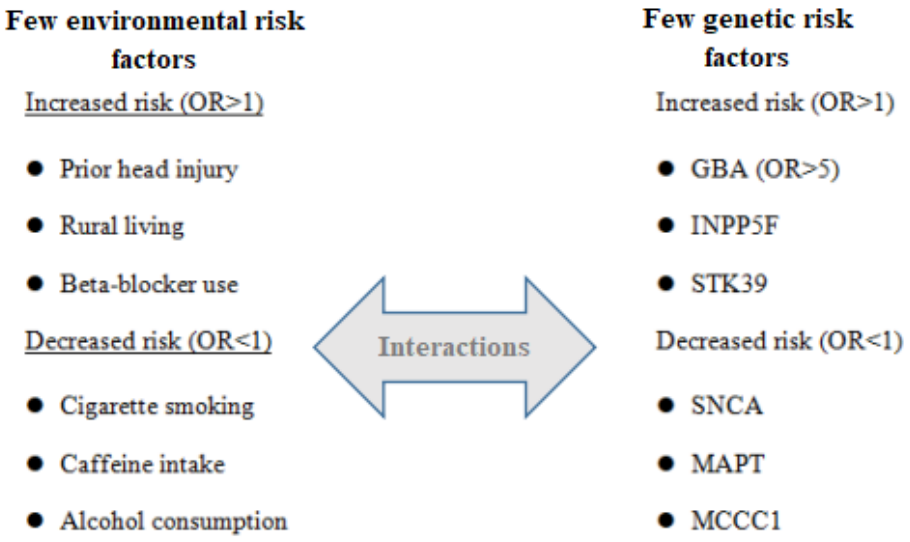

Figure 1. Risk factors of the development of Parkinson's disease

There are various environmental exposures that increase (OR >1) or decrease (OR <1) the risk of developing Parkinson's disease (left), and also genetic risk factors, which are polymorphisms within certain genes that influence risk for developing Parkinson's disease (right). The interplay between environmental and genetic risk factors is under investigation. OR=odds ratio. (Adapted from Kalia & Lang, 2015)

Genetic factors

In turn, the last years has been characterized by a remarkable acceleration in the identification of genes that appear to cause an illness very similar to PD or PD itself (Wirdefeldt et al., 2011). Up to now, 18 mutations in genes / loci have been identified, that include autosomal dominant forms, recessive autosomal forms, locus and mutations of genes associated with PARK10-16. However, only 10 to 15% of patients with the disease present a familiar form, pointing that more PD genes and loci remain to be identified. The increasing knowledge about genetics of PD has provided clues about the molecular mechanisms involved in its pathogenesis. For instance, PARK1 and PARK4 are α-synuclein genes located on chromosome 1 and 4, respectively which carries the genetic code for the production of α-synuclein protein present in Lewy bodies (Fujioka & Wszolek, 2014).

1.1.3 The basal ganglia in PD

The basal ganglia (BG) are subcortical structures composed of several interconnected nuclei. They form a highly organized network involved in the control of movement, as well as associative learning, planning, working memory and emotion (Obeso et al.,

2008b). These sets of nuclei include the striatum (caudate and putamen), the globus pallidus pars external (GPe) and the internal pars (GPi), the subthalamic nucleus (STN) and the substantia nigra pars compacta (SNc), and pars reticulata (SNr). The organization of the connectional relationships of the BG has had a large influence on the insight into the pathophysiology of PD (DeLong & Wichmann, 2010).

The projections of the BG have an ascending and a descending component. The ascending component called basal ganglia-thalamo-cortical loops, projects to the cortical areas. The BG loops are divided in different parts, as motor, oculomotor, associative, limbic, and orbitofrontal (DeLong, 1990). This layout explains the influence of BG on sensorimotor, cognitive/executive and emotional-motivational functions. Meanwhile, the descending component consists of the BG projections to the mesencephalic structures and, on the other hand, to motor output structures in the lower brainstem and spinal cord. The BG has an impact on posture and balance, as well as on muscle tone..

In the late 1980s, the classical model of BG organization was developed and it was concentrated on motor control (Albin, Young, & Penney, 1989; DeLong, 1990). The mentioned model was based on the sequent findings:

- First, the cortical motor areas and the primary somatosensory cortex project to the striatum in a somatotopical manner.
- Second, the striatal efferent neurons are GABAergic medium spiny neurons (MSNs) that project to BG output, i.e., GPi and SNr, through “direct” and “indirect” pathways. MSNs of the “direct” monosynaptic pathway include dopamine D-1 receptors, co-express the peptides substance-P and dynorphin, and project directly from putamen to GPi/SNr. Meanwhile MSNs of the “indirect” polysynaptic pathway contain dopamine D-2 receptors and co-express enkephalin, and pass to the GPe and from there to both output nuclei (GPi and SNr), either directly or trough the intercalated STN.
- Third, dopamine modulates glutamatergic effects of corticostriatal inputs by exerting a double effect on striatal neurons, exciting D1 neurons in the direct pathway and inhibiting D2 neurons in the indirect circuit (Gerfen & Surmeier, 2011), which in turn exert a tonic inhibition of the thalamus. Lastly, reduced BG output leads to movement facilitation and increased BG activity to movement inhibition.

According to the model above, in PD condition the dopamine deficiency causes a hyperactivity of the indirect pathway and hypoactivity of the direct pathway, advocating increased activity in the STN and GPi/ SNr, which causes greater thalamic inhibition and a decrease in the excitation of the cortical motor systems and the brainstem (Obeso et al., 2000). Therefore, the balance of BG activity moves toward the "indirect" circuit, where the GPe-STN-GPi microcircuit plays a dominant role (Figure 2).

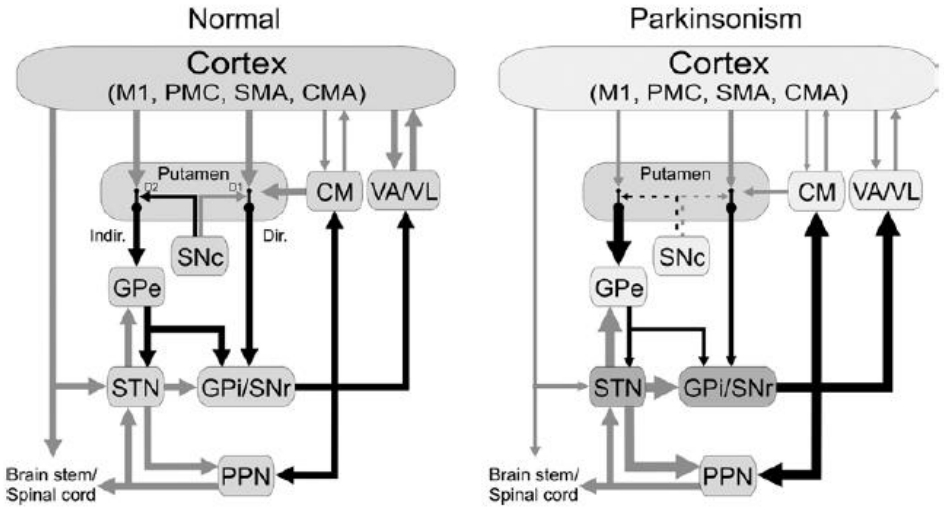

Figure 2. Parkinsonism-related changes in overall activity ("rate model") in the basal ganglia-thalamocortical motor circuit

Black arrows indicate inhibitory connections; gray arrows indicate excitatory connections. Abbreviations: CM, centromedian nucleus of thalamus; CMA, cingulate motor area; Dir., direct pathway; D1, D2, dopamine receptor subtypes; Indir., indirect pathway; M1, primary motor cortex; Pf, parafascicular nucleus of the thalamus; PMC, premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; VA, ventral anterior nucleus of thalamus; VL, ventrolateral nucleus of thalamus. (Adapted from Wichmann, Delong, Guridi & Obeso, 2011)

The classical model may explain the origin of akinetic features of PD, for example movement initiation, and the response to drugs and surgery. Likewise, the reduced blinking rate, a positive Meyerson's sign, and decreased arm swing areprobably mediated by brainstem mechanisms, which are also functionally impaired by exaggerated BG inhibitory outputs. Nevertheless, the BG models can not provide an eventual explanation for rigidity and tremor, as well as gait dysfunction, attention and learning deficits, emotional disturbances, and cognitive disorders, all of which have now been acknowledged to form part of the global clinical picture of PD (Marsden & Obeso, 1994; Obeso et al., 2008a,b).

1.1.4 Symptomatology

The symptomatology of PD is now recognized as heterogeneous, with clinically significant non-motor features (Kalia & Lang, 2015). The complexity of PD is accompanied by clinical challenges. To make a definitive diagnosis at the earliest stages of the disease is very complicated, and the management of symptoms at later stages is also challenging (Kalia & Lang, 2015).

Motor symptoms

The lack of dopamine within the basal ganglia leads to a movement disorder characterized by classical parkinsonian motor symptoms. Since James Parkinson's initial description, the classical motor symptoms of PD have been recognized as dominant components of the disease (Goetz, 2011). These symptoms include bradykinesia, muscular rigidity, rest tremor, and postural-, gait impairment.

- **Bradykinesia**

  Bradykinesia is frequently used synonymously with akinesia and hypokinesia (Berardelli et al., 2001). Bradykinesia refers to slowness of a performed movement, whereas akinesia refers to poverty of spontaneous movement or associated movement. The term hypokinesia, in addition to being slow, means smaller amplitude of movement. These symptoms are related. However, the term bradykinesia in the literature tends to group these motor features within the same construct. Bradykinesia is the motor sign that appears to correlate best with a degree of dopamine loss (Rodríguez-Oroz, 2009).

- **Rigidity**

  Rigidity is an increase in resistance to passive movement. Different authors mentioned that rigidity should be coherent to an enhancement of stretch reflex excitability (Cantello et al., 1991; Moreau et al., 2002). Rigid patients show an increased cortical excitability, linked with dopamine depletion and increased BG output (Rodríguez-Oroz, 2009). In turn, it is not clear how BG changes associated with dopamine depletion alter the excitability of stretch reflex mechanisms.

- **Tremor**

  The most common and easily recognized symptom of PD is tremor. Tremor can slow the initiation of any movements. It is typified by a low frequency rhythmic oscillation within a bandwidth of 4 or 6 Hz at rest (Shahed & Jankovic, 2007). Normally the tremor starts as unilateral, but with the progress of the disease can become bilateral. It can be located on a finger or in a hand, or can affect many parts of the body. Another important feature is that is completely variable; it might change according to personal circumstances. Moreover, tremor disappears during sleep phases and decreases during rest period. Instead, with anxiety, tension and intense concentration the tremor increases (Jahanshahi & Marsden, 2000).

  Although the physio-pathological base is unknown (Carr, 2002), in some cases, this tremor seems to be the result of the loss of particular subgroups of dopaminergic neurons (Hirsch et al., 1992). Bergman et al. (1998) associate this tremor with rhythmic and synchronous neuronal discharges in several nuclei of the basal ganglia and the thalamus. It is clear now that classical tremor in PD is mediated by an abnormal oscillatory activity in an extensive motor network that involves the basal ganglia, cerebellum, thalamus, and motor cortex (Hallett, 2014).

- **Postural stability and gait disorders**

  PD patients have difficulties in balance, sitting, standing, walking and also in turning. When PD patients stand, they have a flexed posture with the body inclined slightly forward, with flexed knees and arms in front of the body (Kim, Allen, Canning, & Fung, 2013). The gait of PD patients is typically slow, with short, shuffling steps, swinging arms and a flexed posture. The cause of the postural instability and gait problems is complex, and is the result of a combination that includes changes in postural reflexes, rigidity and akinesia (Hanakawa et al., 1999a).

Non-motor symptoms

PD is also associated with several non-motor symptoms (Kalia & Lang, 2015). Non-motor features are olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue (Table 1), as well as complex behavioral disorders. These symptoms are common in early PD (Khoo et al., 2013), and also often present before the classical motor symptoms, most notably depression, hyposmia or rapid eye movement sleep behaviour disorder (Postuma et al., 2012; Poewe, 2008). Cognitive dysfunction also may be present from the early stages of PD and might involve a more extensive cognitive dysfunction in the future stages.

Table 1. *Non-motor features of Parkinson's disease*

Neuropsychiatric dysfunction	**Sleep disorders**
● Mood disorders	● Sleep fragmentation and insomnia
● Apathy and anhedonia	● Rapid eye movement sleep behaviour disorder
● Frontal executive dysfunction	
● Dementia and psychosis	● Excessive daytime somnolence
Autonomic dysfunction	**Sensory symptoms and pain**
● Orthostatic hypotension	● Olfactory dysfunction
● Urogenital dysfunction	● Abnormal sensations
● Constipation	● Pain

(Adapted from Poewe, 2008)

1.1.5 Diagnosis of PD

The diagnosis of PD is commonly considered simple; however, there is no definitive test for diagnosis. In the reality, only 75% of the clinical diagnoses are confirmed by anatomo-pathological studies in the autopsy of patients who received this diagnosis (Hughes et al., 1992; Jankovic, 2008). This diagnosis is still essentially clinical; the performance of brain computed tomography or brain magnetic resonance should be considered as a routine investigation, in order to exclude possible secondary causes (Tapia-Nuñez & Chana-Cuevas, 2004).

Gelb, Oliver, & Gilman, (1999) have proposed several combinations of clinical parameters in order to identify different levels of diagnosis:

- Possible: Presence of at least two of the four cardinal signs: tremor of rest, rigidity, bradykinesia and asymmetric beginning (of which one must be tremor or bradykinesia). Absence of atypical symptoms and response to the use of levodopa or dopaminergics (or absence of an adequate treatment with levodopa or dopaminergics).
- Probable: Presence of at least three of the four cardinal signs. Absence of atypical symptoms for at least 3 years. Response to the use of levodopa or dopaminergics.
- Definitive: Presence of all possible criteria for the diagnosis of PD. Confirmation with the autopsy.

1.1.6 Evaluation of PD

The evolution of the treated PD can be divided into the following stages (Obeso, Rodriguez-Oroz, & Lera, 1999):

- Initial stage: corresponds to the first 3-5 years after the diagnosis and introduction of levodopa treatment. Symptoms and motor signs are mild, often asymmetrical, affecting mainly one limb.
- Intermediate stage: corresponds to the period between 5 and 10 years after diagnosis and the onset of the disease. It is characterized mainly because the symptoms and signs are bilateral, although still asymmetric, and because at least 50%-70% of patients develop motor complications and around 25% psychiatric complications.
- Late or advanced stage: corresponds to patients who have an evolution greater than 10-12 years. There is a combination of motor and psychiatric complications, with signs that correspond less to treatment with levodopa and other drugs with dopaminergic agonist action. A considerable proportion of patients, at least 30%, also show signs of cognitive deterioration.

The age of onset of the disease is a fundamental factor in the evolution. Patients with early onset of the disease (under 45 years of age) develop motor and psychiatric complications faster than those who have started at advanced ages; but the incidence of cognitive impairment and motor signs with a poor response to dopaminergic drugs is much lower, so that the patient's general situation may be better.

1.1.7 Treatment

The therapies available for PD only treat symptoms of the disease. Nowadays, treatment approaches in PD are focused on the development of disease-modifying drugs that slow or stop the progress of the disease. The main intervention for PD patients is medical treatment, including pharmacology and surgical options (Kakkar & Dahiya, 2015). However, a single agent could not be capable of achieving to stop or slow the progress of the disease. The most effective strategy might be to target selected dysfunctional molecular pathways in specific patients and to target several molecular pathways with several drugs (Kalia & Lang, 2015).

In the past few years, there has been significant progress in the knowledge of the etiology and pathophysiology of PD, which helps the development of new treatments. However, current treatments for PD have some limitations, such as medication-related complications and surgical risks. These facts show that the current treatments should be improved, and also should investigate adjunctive therapies.

Pharmacological therapy

Potential pharmacological aims for disease modification in PD include neuroinflammation, mitochondrial dysfunction and oxidative stress, calcium channel activity, LRRK2 kinase activity, as well as α-synuclein accumulation, aggregation, and cell-to-cell transmission (including immunotherapy techniques) (AlDakheel, Kalia, & Lang, 2014; Tran et al., 2014).

The main support of treatment for motor symptoms is drugs that increase intracerebral dopamine concentrations or stimulate dopamine receptors (Kalia & Lang, 2015). These drugs encompass levodopa, dopamine agonists, monoamine oxidase type B inhibitors, and, less commonly, amantadine (Connolly & Lang, 2014).

Treatment should be started when symptoms cause the patient disability or discomfort. The goal is improving function and quality of life of people with PD. Bradykinesia and rigidity reliably react to dopaminergic treatments early in the disease. Monoamine oxidase type B inhibitors are at best only moderately beneficial. Dopamine agonists or levodopa are needed for more rigorous symptoms and progressive disability. Meanwhile levodopa provides an excellent symptomatic benefit; the long-term use is linked with motor complications, as dyskinesia and motor fluctuations (Kalia & Lang, 2015). In

contrast to bradykinesia and rigidity, tremor is inconsistently responsive to dopamine replacement therapy, especially in lower doses. Meanwhile for the treatment of tremor anticholinergic drugs, such as trihexyphenidyl, or clozapine can be effective (Kalia & Lang, 2015).

Surgical treatment

The surgical treatment in PD started at the beginning of the 20th century. Potential surgical treatments include targeted gene therapy, cell transplantation, and deep brain stimulation of subthalamic nuclei (Kordower & Bjorklund, 2013; Lindvall, 2013; Charles et al., 2014). A well established treatment for the motor symptoms of PD is the deep brain stimulation. Several findings showed that deep brain stimulation of either the subthalamic nucleus or globus pallidus internus is effective in moderate-to-severe PD (Kalia, Sankar, & Lozano, 2013). Furthermore, thalamic deep brain stimulation could be an option for treatment of tremor. When the parkinsonian motor features persist to respond to levodopa but motor fluctuations and dyskinesia become disabling, the surgical treatment could be an option. Moreover, non-motor symtoms, including non-motor fluctuations, sleep-related symptoms, and behavioural abnormalities, can improve with deep brain stimulation.

The average time to surgical treatment is about 10-13 years after diagnosing PD. Findings have been shown that deep brain stimulation of the subthalamic nucleus early in the disease course improved the quality of life of PD patients (Schuepbach et al., 2013).

Multispecialty care

Next to medical treatment, most of the PD patients continue to have motor and non-motor symptoms. Order to improve quality of life, motor functioning, the multispecialty approach seems to be better than a single-clinician approach. The work of medical specialists, specialized nurses, and health-care professionals (such as physical therapists, occupational therapists, speech-language therapists, dieticians, social workers, sexologists and neuropsychologists) is important for PD care (Van der Marck & Bloem, 2014).

1.2 GAIT IN PARKINSON'S DISEASE

This chapter summarizes the neurophysiology of gait in PD. Moreover expresses the importance of the stride length- cadence relationship (SLCrel) and gait measurements in PD.

1.2.1 Neurophysiology of gait in PD

Human walking is very complex and dynamic process, including coordination of lower limb bones and joints such as pelvis, hip, knee, ankle and foot. Even simple movements need complex interactions between the central- and peripheral nervous systems and skeletal muscle system to achieve proper movements which involves activation of spinal and supraspinal neuronal circuits. The supraspinal motor neuronal network is formed by the cortical area (cortex) and subcortical areas in brain (BG, thalamus, brain stem). Proper interactions result in stable gait mechanism. However, the gait mechanism of PD patients do not work properly. The cortico-frontal regions are contributed in the physio-pathology of PD gait. The interaction between BG and SMA is disrupted during hypokinesia in PD patients. The SMA and frontal lobe are associated with gait dysfunction, bradykinesia, and cause problem in gait initiation, speed control and movement planning (Matsui et al., 2005; Mito et al., 2006, Della Sala et al., 2002).

Gait deficits in PD

Gait disturbances and falls are principal and the most significant motor complaints in PD leading to decline in quality of life of the patients and are one of the hallmarks of the advanced stages of PD (Ebersbach, Moreau, Gandor, Defebvre, & Devos, 2013). The gait of PD patients is defined by slowness, reduced SL, reduced gait speed, small shuffling steps, flexed posture, reduced arm swing and problem in gait initiation (Ebersbach, Sojer, Valldeoriola, Wissel, Müller, Tolosa, & Poewe, 1999; Morris et al. 1994b; Morris, Iansek, Matyas, & Summers, 1996). Morris et al. (1994b, 1996) suggested that the bradykinetic manifestations of PD cause the reduced SL and gait speed, which are the key of the gait changes in PD. The reduced average SL has an important role in the gait disturbances of PD, moreover the decline in the ability to produce normal gait rhythm is also a critical characteristic of PD gait. Patients with PD walk with increased stride-to-stride variability, which is associated with the alterations in rhythm generation and motor programming (Hausdorff et al., 2007). The stride-to-stride gait variability is an

important predictor for the prognosis of the disease and it is associated with the risk of falls. The stride-to-stride variation is mostly estimated from the gait cycle time and the increased stride-to-stride variability may reflect an unsteady gait (Hausdorff, 2007). More complex gait disturbances may appear, such as freezing of gait, motor blocks, festination and disequilibrium in the advanced stages of PD. The gait features above cause significant disabilities resulting from falls, immobility, and loss of independence (Bloem et al., 2016).

Gait dysfunction, such as gait slowness, increased step variability, poor postural control in PD patients are due to altered activity in the structures of supraspinal locomotor network including the cortex, cerebellum, BG, and brain stem (Peterson & Horak, 2016). Figure 3 shows the structure of supraspinal control of locomotion in PD patients. There is an increased inhibition of globus pallidus external segment and reduced inhibition of globus pallidus internal segment which cause inhibition of the thalamus and pedunculopontine nucleus (PNN). Thus, the connection between BG and SMA is weaker in PD while performing self-initiated movement. However, most probably the altered BG could be compensated by the increased activity in the cerebellum, orbitofrontal cortex and caudate nucleus (Wu & Hallett, 2013; Hanakawa et al., 1999; Ouchi et al., 2001). Moreover, it was suggested, that during external cues PD patients use their lateral premotor area for visually generated gait improvements (Shibasaki, Fukuyama, & Hanakawa, 2004). Furthermore, PD patients can increase their movement size and speed by using frontal cortical areas of the brain to bypass the defective BG (Morris, Huxham, McGinley, & Iansek, 2001).

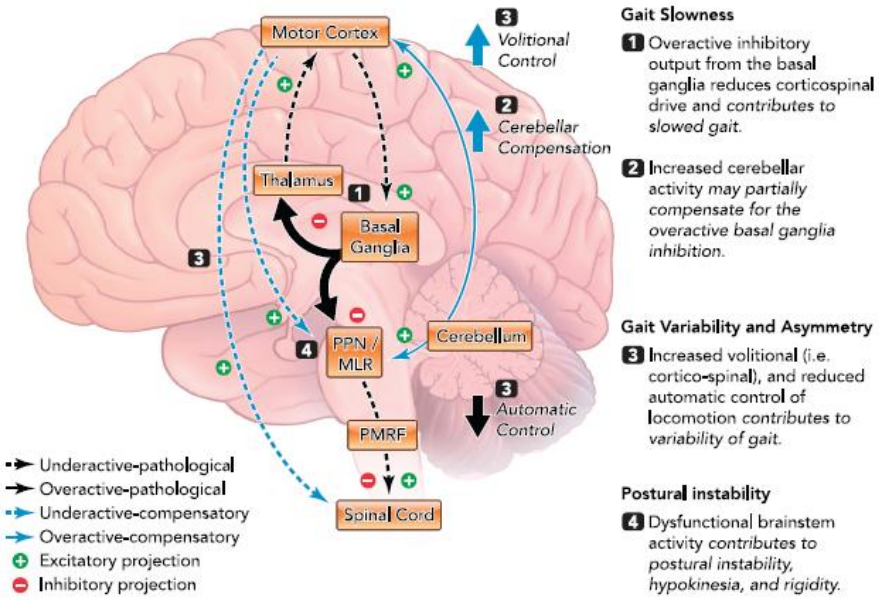

Figure 3. Structure of supraspinal control of locomotion in PD patients

Alterations in activity of the basal ganglia (*1*) and brain stem (*4*) contribute to gait slowness and increased postural instability, respectively, and increased cerebellar activity may partially compensate for these alterations (*2*). Increased volitional control (i.e., cortico-spinal) and reduced automatic control (*3*) may contribute to increased gait variability and asymmetry. See text above for more information. PPN, pedunculopontine nucleus; MLR, mesencelphalic locomotor region; PMRF, pontomedulary reticular formation; SMA, supplementary motor area. (From: Peterson and Horak, 2016.)

It is difficult to explore the neurophysiology mechanism of gait in PD, however can be studied by different techniques, as positron emission tomography, functional magnetic resonance imaging (fMRI), single emission computed tomography (SPECT) and EEGs, EMGs (Shibasaki et al., 2004). SPECT has been used to investigate the mechanisms underlying the improvement of gait in PD patients when exposed to visual stimuli. In these conditions, it seems that PD patients can compensate for the impaired SMA function by the activation in the lateral premotor cortex (Hanakawa et al., 1999a). In 2015, using fMRI technique, Wu et al.(2015), had shown that in PD population during automatic movements such as walking, the activity of posterior putamen is decreased (sensorimotor area), meanwhile the activation in the anterior putamen is increased (association area). The connectivity from anterior putamen to primary motor cortex is strengthened during automatic processing (Wu et al., 2015). This might be an indication of using attentional control to overcome damaged automatic control in PD (Redgrave et al., 2010). Furthermore, greater activity was observed in several brain regions of PD

patients (dorsolateral prefrontal cortex, premotor cortex, parietal cortex and cerebellum) and less effective connectivity between motor areas compared to normal subjects while performing automatic movements (Wu & Hallett, 2005).

To summarize, the physiopathology of PD gait is very complex, and the neurophysiology of gait has not been thoroughly studied in PD patients, which hinders the targeting of successful treatment strategies. In PD patients, the cortico-frontal regions are altered which leads to the physiopathology of gait.

1.2.2 Stride length, gait speed and cadence

Stride length (SL)

There is a correlation between disease severity in PD and SL (Morris, Iansek, Matyas, & Summers, 1998; Shoushatari et al., 2011). SL is already disturbed in the early stage of the disease. The reduced SL is a hypokinetic feature of parkinsonian gait. The SL reduction in PD patients in combination with gait initiation difficulties is caused by cortical disturbances, especially in the primary motor cortex (Shoushtarian, Murphy, & Iansek, 2011). The SL is regulated by the corticospinal tract. The cortex receives non-appropriate signals from the BG which alter the SL.

Gait speed

Next to SL, the gait speed control is also associated with the cortex, which is altered in PD, Gait speed and SL are strongly correlated (Hausdorff, 2009) and the reduced size of steps are related with the slowed gait in PD (Morris, Iansek, Matyas, & Summers, 1994a). The reduced ankle plantar flexion in PD cause reduced gait velocity (Skinner et al., 2015). When PD patients have reduced SL and slowed gait speed it can help to avoid falls.

Cadence

Cadence is controlled by the brainstem connections (Snijders et al., 2011). Tudor-Locke et al. (2018) found that the lower cadence is associated with various health markers. Morris et al. (1994b) and Bayle et al. (2016) stated that cadence remain intact in PD. To regulate the rhythm is related with the spinal cord, which is not damaged in PD, probably that is why the number of steps remains intact. Moreover, PD patients have an increased

number of steps during walking compared to healthy control subjects (Morris et al., 1996).

1.2.3 Stride length- cadence relationship

The SLCrel had been used to examine central gait control mechanisms in healthy adults and in subjects having pathological gait disturbances (Ziljstra et al., 1995; Morris et. al, 1998; Egerton, Danoudis, Huxham, & Iansek, 2011; Egerton, Williams, & Iansek, 2012; Howard, Wallace & Stokic, 2013). The analysis of the SLCrel supports the view of a duality of gait control utilizing automatic and/or attentional pathways (Egerton et al., 2011).

Several studies investigated the changes of SL, gait speed and cadence parameters in PD, however the SLCrel is less known. Morris et al. (1998) stated that the SLCrel has been used to investigate the gait changes in PD. Egerton et al. (2011) hypothesized that self-selected speed would use minimal attention to gait parameters. In contrast, forced SL or cadence would require the use of attentional pathway. A linear relationship between SL and cadence would indicate automatic control. Danoudis & Iansek (2014) suggested that, BG through connections to frontal cortical regions are responsible for maintaining the stable relationship between SL and cadence and it allows the running of self-selected speed automatically. Egerton et al. (2012) and Zijlstra, Rutgers, Hof, & Van Weerden (1995) found that, when healthy adults change their self-selected walking speed, they increase or decrease their SL and cadence in a relatively constant linear relationship. In contrast, in PD patients Morris et al. (1996, 1998) and Danoudis & Iansek (2014) found that, the slope of the SLCrel remains insensitive, while the intercept of the SLCrel is smaller than in healthy subjects, which means a smaller SL associated with a higher cadence. Intercept would correspond to the base of SL for a certain cadence, while slope would represent the value of the increase or reduction of the SL as the cadence increases.

The findings are divisive, for example in the study of Wall & Turnbull (1992), PD patients had shorter SL and decreased cadence than elderly people. In contrast, Stern, Franklyn, Imms, & Prestidge (1983) and Blin, Ferrandez, & Serratrice, (1990) found that the normal relationship between velocity, SL and cadence are preserved in PD. Blin et al. (1990) recorded SL and cadence values during preferred speed walking and compared with age-matched control subjects, linear models were found between SL versus velocity and cadence versus velocity. However, this study measured the regression in the overall

sample, not for each individual. From this finding, it was concluded that the relationships between velocity, SL and cadence in PD were not significantly different from normal. Differences in methodology, as in the previous research, could lead to some of the variance in findings.

Other studies demonstrated that SL and cadence are the key determination of gait speed (Morris et al., 1998; Zijlstra et al., 1995; Perry & Burnfield, 2010). Therefore, it is important to understand the relation between SL and cadence in PD. It is clear already, that in PD patients the slope of the SLCrel remains unaffected but accompanied with lower interception than it is in healthy people (Egerton et al., 2012; Danoudis et al., 2014), as previously was mentioned. Thus, smaller SL is associated with a higher cadence. Hence, the difficulty in the regulation of SL can be normalized by using attentional strategies, like external cues or taking levodopa medication (Morris et al., 1996, 1998), it suggest that the ability to generate a normal SLCrel is not lost in PD subjects (Morris et al., 1996).

The regulation of the SL is very important in PD rehabilitation, although the effects of physical therapy interventions on the SLCrel have not been examined. Most of the studies, which are related to the evaluation of the efficacy of the rehabilitation and exercise interventions, use independently, changes in SL, cadence or speed (Kwakkel, de Goede, & van Wegen, 2007). Thus, although, increases in gait speed may reflect a functional improvement, these do not necessarily reflect an amelioration of PD symptomatology (Kwakkel et al., 2007). Even if gait speed do not increase after intervention, it may be effective at improving gait automaticity, and may lead to an improvement in mobility, even without gait speed changes, likewise, increase in walking speed may not necessarily improve gait automaticity (Clark, 2015). In addition, with ageing, the physical function is getting worst and it is difficult to demonstrate whether the rehabilitation program has a specific impact in PD or rather a generalized benefit from the exercise (Bello et al., 2013). The highlight of the SLCrel is that, it may help to provide the specific therapeutic effect of rehabilitation programs and optimize the rehabilitation strategy. However, the reliability of SLCrel in PD subjects has not been investigated, and it is important since most of the measures in physical therapy suffer from the deficiency of reliability (Kwakkel et al., 2007).

1.2.4 Gait measurements in PD

Now-days, gait measurements have an important role to identify signs of neurodegenerative disorders and measure the effectiveness of interventions (Lord et al., 2013). Gait measurements are useful to explore the disease progression of PD. Several equipments allow us to analyse gait, for instance, foot switches, electronic walkways, body-worn sensors, electromyography, and 3-dimensional motion analysis (Lord et al., 2013). By using the technologies described above, it is possible to measure the spatiotemporal and dynamic characteristics of gait. The reliability and validity of the measurements are important, in order to have an accurate, useful result. Bohannon, Andrews, Thomas (1996) and Lim at al. (2005) stated that the reliability and validity of spatiotemporal characteristics for healthy controls and for some neurodegenerative diseases is good. However, needs to develop the reliability and validity of dynamic gait characteristics.

Measuring gait speed in PD is used in both clinic and home environments. To measure gait speed is useful as a global characteristic of performance, but does not reveal the underlying impairments nor the nature of pathology (Lord, Galna, & Rochester, 2013). Previous studies mentioned that fast gait speed should be use rather than preferred gait speed, because fast speed may be more sensitive measure of pathology (Mirelman et al., 2011; Verghese, Holtzer, Lipton, & Wang, 2012).

PD gait characteristics, as reduced SL, slowed walking speed, increased variability of SL and stride time can be the manifestation of the disease. However, other disorders as normal pressure hydrocephalus have similar features with PD, which causes difficulties with the diagnosis (Nutt, Marsden, & Thompson, 1993; Stolze et al., 2001). To be able to detect early pathology, it is important to understand the sensitivity of gait characteristic (Lord et al., 2013).

Gait speed has an excellent utility as gait characteristic (Wade, 1992), however to be able to detect important gait changes, a more selective approach is warranted (Lord et al., 2013).

Gait measurements are useful tools to understand better gait changes due to rehabilitation programs, and as it was mentioned before using the SLCrel as a tool to measure gait

changes in PD, could help to understand better the changes and explore the specific effects of gait interventions.

1.3 GAIT REHABILITATION IN PD AND THE TREADMILL

This section summarize the possibilities to rehabilitate PD patients. Furthermore, includes from general to specific effects of exercise in PD. On the other hand, talks about the treadmill as a tool in gait research, a tool of rehabilitation and a possibility to improve gait in PD by treadmill. Moreover, discuss the possible mechanism implicated in treadmill gait advantages in PD.

1.3.1 Gait rehabilitation in PD

Though pharmacological therapies many symptoms of PD improves, mostly in the early stages of the disease, as the disease progresses the effectiveness of pharmacological therapy is reduced, leading to the worsening of gait disorders and the appearance of more complex gait symptoms. Even after surgical treatment, some of the PD symptoms, such as freezing of gait and postural instability remains or worsen (Pötter-Nerger & Volkmann, 2013). However, nowadays physical activity became more important component in the rehabilitation of PD, as current pharmacological and surgical treatment approaches do not fully address many aspects of the disease. In turn, the specific benefits of physical activities are not yet clearly identified (Lauzé, Daneault, & Duval, 2016). Nevertheless, there are many possibilities to use various exercise approaches, that should focus on to maximize exercise tolerance, improve the gait pattern, maintain or increase independence regarding mobility, and reduce the risk of falls (Keus, Munneke, Nijkrake, Kwakkel, & Bloem, 2009; van der Eijk, Faber, Al Shamma, Munneke, & Bloem, 2011). Furthermore, Clark (2015) suggested that, gait rehabilitation should focus on the recovery of automaticity.

Physical therapy is the most widely used non-pharmacological therapy for gait rehabilitation of PD. The aim of the traditional rehabilitation program is muscle stretching, motor coordination, balance, and gait training (van der Kolk & King, 2013). Furthermore, Morris (2000) and Goodwin, Richards, Taylor, Taylor, & Campbell, (2008) supported the use of physical therapy in PD, as improving the performance of functional motor tasks, especially on gait, postural instability and prevention of falls. Moreover, in order to activate alternative pathways in the brain bypassing the defective BG circuits of PD patients, the use of external cues (visual, auditory, or proprioceptive cues) and cognitive strategies became important in PD rehabilitation (Morris et al., 1996;

Nieuwboer et al., 2007). For instance, Rochester et al. (2010) showed that using visual, auditory and somatosensory cues during gait rehabilitation in PD patients increased the automaticity of walking. Several studies showed that, general physical therapy, stretching, muscle strengthening, balance, treadmill training, cuing, dance and martial arts (boxing, tai-chi) improve PD gait and their quality of life.

Numerous studies proved that dance improve gait in PD. Furthermore, combining music with exercise in dance can therefore increase accessibility, enjoyability, and motivation, as well as improving mood and stimulating cognition (Rios Romenets, Anang, Fereshtehnejad, Pelletier, & Postuma 2015). Argentine tango may be particularly helpful for improving balance and functional mobility in patients with PD (Hackney, Kantorovich, Levin, & Earhart, 2007). Tango may be especially useful for freezing of gait, and prevention of falls, because of the specific steps that rhythmically entrain forwards/backwards walking (Hackney et al., 2009). Likewise, after boxing training PD patients demonstrated significant improvements in gait velocity and endurance, also improved balance, mobility, and quality of life (Combs et al., 2013). Moreover, tai-chi has improved balance, postural stability and lowered the incidence of falls of PD patients. The effects of tai-chi training maintained for three months after the intervention (Li et al., 2012).

Despite, there are various exercise approaches, there is still no consensus about the optimal approach. Innovative techniques have been recently proposed: virtual reality, motor imagery and action observation, robot-assisted physiotherapy (Abbruzzese, Marchese, Avanzino, & Pelosin, 2016; Melo et al., 2018). Moreover, the findings of Tramontano et al. (2016) support the usage of complementary rehabilitative strategies based on sensorymotor stimulation in PD rehabilitation program, by helping to improve gait in shorter time. Furthermore, Lefaivre & Almeida (2015) also found that training which improves sensorial input could improve balance and gait in PD patient. In turn, the rehabilitation programs for PD patients should be target oriented and individual based.

Lauzé et al. (2016) reported that physical activity interventions have positive impact on physical and functional capacities, and the positive effect is visible specifically on gait, mobility, posture and balance. However the impact on the symptoms of the disease are moderated.

1.3.2 General vs specific effects of exercise in PD

The regulation of the SL is a main goal in the rehabilitation of PD patients, thus intervention programs should focus on the recovery of this parameter. However, evaluating the efficacy of rehabilitation using independently, changes in SL, cadence or speed may reflect a functional improvement (Kwakkel et al., 2007) from the benefits of exercise, and do not necessarily show an amelioration of PD symptomatology. Nevertheless, measuring the SLCrel may help to understand if the intervention has a specific therapeutic effect or not, which would help to develop rehabilitation strategies. Moreover, measuring the SLCrel on treadmill may help to evince the specific effect of the treadmill rehabilitation of PD.

1.3.3 Walking on treadmill in healthy population

The treadmill is a machine used for walking or running while staying in the same place. In the middle of the 20th century, the motorized treadmill began to be employed in the medical field for ergometry studies (Yu, Bruce, Lovejoy, & McDowell, 1951; Bruce, 1956). Currently, treadmill is a popular instrument in gyms, hospitals and research centers.

Many advantages are associated with treadmills, for this reason treadmills are often used for gait research. Treadmills are relatively cheap and easy to obtain. Allow researchers to collect data on locomotion over large distance within a small area. Many studies have been investigated the differences in kinematics between treadmill and overground gaits. Nevertheless, no study to date has explored the SLCrel walking on a treadmill. Most of the studies have included walking, jogging, sprinting and running with different subjects. However, when comparing spatiotemporal parameters on treadmill to overground, the results are variable and the differences are still not very clear.

People walk differently on treadmills than overground, overground walking is more natural than walking on treadmill (Parvataneni, Ploeg, Olney, & Brouwer, 2009). When walking on treadmill the foot is pulled back automatically as soon as it reach the belt (Warabi, Kato, Kiriyama, Yoshida, & Kobayashi, 2005) and stimulation of sensory receptors may change the movement pattern (Kalantari, Baxendale, & Rezasoltani, 2011). Thus, gait on treadmill changes from normal walking. Warabi et al. (2005) comparing the differences between gait at overground and gait in treadmill in healthy

subjects, found that on the treadmill the contact time was reduced, cadence increased and the coefficient of variation of contact time decreased. Similar results had already been observed by other authors (Stolze et al., 1997; Alton, Baldey, Caplan, & Morrissey, 1998). However, other studies argue that there are no clear differences between walking on the treadmill and on the ground (Murray, Spurr, Sepic, Gardner & Mollinger, 1985, Greig, Butler, Skelton, & Mahmud, 1993, Hollman et al., 2016). Alton et al. (1998) stated greater SL on treadmill, however did not find any significant differences. Significant difference has been found only in men subjects, where cadence was higher (Alton et al., 1998). In adults cadence increase by 7% on treadmill compared to overground walking and SL was significantly smaller on treadmill (Stolze et al., 1997). Murray et al. (1985) and Strathy et al. (1983) did not refer marked differences between the gait on treadmill and on overground; although they did find some statistically significant differences, such as a higher cadence and a shorter step length in treadmill walking. The increased step frequency is correlated to an urgency to place the foot of the swing limb onto the treadmill (Alton et al., 1998). Contrary, other research showed increased SL and decreased step frequency (Wall & Charteries, 1981). The mentioned study explained the increased step length by the increase in hip range of motion during swing phase, however Stoquart et al. (2008) did not find hip motion differences during treadmill walking.

Dingwell, Cusumano, Cavanagh, & Sternad, (2001) found a decrease in the variability of the accelerations of the limbs, as well as a tendency towards the decrease of the step length in walking on the treadmill compared to overground.

Frenkel-Toledo et al. (2005) observed that healthy controls walking on treadmill by grabbing the handrail, reduced the temporal variability of the stride and the temporal variability of the swing phase compared to walking overground with a walker. No changes were found in the SL or in the average stride time.

Hollman et al. (2016) showed that, the mean values for spatiotemporal gait parameters were statistically equivalent between treadmill and overground walking The short and long-term variability were considerably reduced on treadmill as compared to overground walking. The fact demonstrates the importance of consideration of gait variability when using treadmills for research or clinical purposes. Treadmill training may cause invariant gait patterns, which bring difficulty to compare locomotor skills gained on a treadmill to overground walking conditions. Meanwhile Fellin, Seay, Gregorczyk, & Hasselquist

(2016) showed that, variability was not systematically lower during treadmill walking compared to overground walking.

Alton et al. (1998) found a greater range of hip movement and a greater hip flexion angle during walking on the treadmill compared to walking on the overground. By contrast, Riley, Paolini, Della Croce, Paylo, Kerrigan (2007) found a decrease in the hip and knee angles on the treadmill. Although the differences were significant, the authors considered them as small and unimportant differences. Riley et al. (2007) and Lee & Hidler (2008) reported a kinematics of walking between the treadmill and overground, where the range of motion of the knee was lower on the treadmill, although the difference was significant, it was small.

There is not an overall agreement on the differences between the treadmill and the overground regarding to the dynamics of the walking. Several studies indicate that the reaction forces at overground do not differ much between the two walking situations (Kram, Griffin, Maxwell Donelan, & Hui Chang. 1998, Riley et al., 2007, Lee & Hidler, 2008). White, Yack, Tucker, & Lin (1998) found that reaction forces at overground were higher on the treadmill during medium support and lower on late support. Meanwhile, Lee & Hidler (2008), found no differences in reaction forces. The authors pointed out that the small differences found by White et al. (1998) may be due to the fact that they used different systems to evaluate the two situations. In the study by Lee & Hidler (2008), there were also moments of minor force in the dorsiflexion of the ankle and extension of the knee; and major in the extension of hip, when subjects walked on treadmill compared to walking at overground. As well as a different muscular activation in the two situations (a lower activation of the tibialis anterior in the support phase and a greater activation of the gastrocnemius at the end of the oscillation phase, among others) (Lee & Hidler, 2008). Treadmill walking probably places greater on muscle forces, compared with overground walking with the same speed (Alton et al., 1998; Perry & Burnfield, 2010). Khademi-Kalantari, Rahimi, Hosseini, Baghban, & Jaberzadeh, (2017) stated that muscle activity magnitude of walking on treadmill is higher than during overground walking, in their study, during treadmill walking the magnitude had a greater slope compared to overground, as the speed increased from slow to fast. Thus, the highest magnitude of lower limb muscle activity was found during the fast treadmill walk. Contrary, the lowest magnitude was related to slow overground walk.

Lee & Hidler (2008) mentioned that, the differences in most of the mentioned studies could be in the use of different measuring devices. Another explanation can be that the measurements have been taken without sufficient period of practice, since Matsas, Taylor, & McBurney (2000) stated that the differences in the kinematic parameters of the knee and various temporal and spatial measures between the overground and treadmill walking, disappear after six minutes. Other studies found that small variations in the speed of the treadmill band could alter the mechanics of walking, which should be considered when evaluating the dynamics of walking on the treadmill (Savelberg, Vorstenbosch, Kamman, Van De Weijer, & Schambardt, 1998). Therefore, the use of treadmills with low power could lead to small fluctuations in speed during the running cycle. However, it seems that there are no indications that the same happens during walking.

To conclude, there is no greater or clear agreement about the differences for spatiotemporal variables between treadmill and overground walking in healthy subjects.

1.3.4 Walking on treadmill in PD

The use of treadmill has been introduced for gait rehabilitation in neurological pathologies such as PD. Miyai, Fujimoto, Ueda, Yamamoto, & Nozaki, 2000; Miyai et al., 2002) conducted two initial projects to investigate treadmill training with supported body weight in people with PD, and found improvements in UPDRS, ambulation speed and number of steps. Afterwards, their findings were repeated and extended. Furthermore, recent studies suggested that treadmill training may improve gait speed and SL (Mehrholz et al., 2015). Lately, PD patients after treadmill gait training presented mobility improvements in comparison to traditional physiotherapeutic training (Melo et al., 2018).

The quality of life, motor UPDRS, gait speed improved significantly after six weeks of intensive treadmill training without body weight support; however, stride time variability and swing time variability did not change significantly (Herman, Giladi, Gruendlinger, & Hausdorff, 2007). Kurtais, Kutlay, Tur, Gok, & Akbostanci (2008) using the same training conditions found reduced variability of swing time improvements in overground walking, and also obtained longer SL, increased speed, decreased double support time. Mehrholz et al. (2015) provided evidence of the use of treadmill training in patients with PD in order to improve gait parameters that included speed and SL,

contrary walking distance and cadence did not improved. Besides, eight weeks of high intensity treadmill training with 10% of body weight support increased gait speed, step and SL, hip and ankle joint excursion and improved weight distribution during sit-to-stand in PD patients (Fisher et al., 2008). In the study of Smith, Jackson, Edginton-Bigelow, & Laubach (2015) has been stated that after eight weeks of treadmill training PD patients improved in gait speed, 6-minute walk test, instrumented Timed Up and Go, and in different balance tests. Furthermore, in the study of Shulman et al. (2013), three months of lower-intensity treadmill training showed greatest improvement in gait speed, but both the higher- and lower-intensity treadmill exercises improved cardiovascular fitness. However, only the stretching and resistance exercises improved muscle strength. Therefore, treadmill can improve gait speed and fitness for PD patients, but the combination of treadmill and resistance exercises may give a better benefit of PD rehabilitation.

Differences between treadmill and overground walking in PD

In order to find the effect of the treadmill in gait rehabilitation in PD, it is necessary to determine the differences between treadmill walking and overground walking. Frenkel-Toledo et al. (2005) found that, walking overground PD patients have smaller SL and slower gait speed compared to controls, however walking with a walking aid gait speed improved. Their study also showed that during treadmill walking, PD patients walked less variable and more stable, which support the idea that treadmill can be used as an external pacemaker (Frenkel-Toledo et al., 2005; Bello & Fernandez-Del-Olmo, 2012). Furthermore, ten minutes after a treadmill gait session improvements in gait speed were also found, where advanced PD patients increased their gait speed as a result of an improvement in SL in comparison with overground walking (Bello, Sanchez, & Fernandez-del-Olmo, 2008). Moreover, PD patients increased their step length, but no other gait parameters, after treadmill training in comparison with overground training (Bello et al., 2013).

Warlop, Detrembleur, Stoquart, Lejeune, & Jeanjean (2018) investigated the immediate influence of treadmill walking compared to overground walking on gait variability and spatiotemporal gait variables in PD and healthy controls. The study demonstrated a more regular and temporally organized gait pattern in PD patients, while healthy controls remained unaffected. During treadmill walking the more complex and regular gait in PD could be explained by a greater dependence on environmental conditions.

Furthermore, they found reduced gait speed and an accompanying decreased step length, which suggest a cautious gait pattern adopted by PD participants walking on a treadmill. The present findings highlight that gait analysis using treadmill should be warily considered in PD and especially for gait variability assessment, however it should be mentioned that participants walked on the treadmill without holding the handrails, which could explain the cautious gait pattern.

The effect of the treadmill seems to be different depending on the degree of the disease. Bello et al. (2008) found that advanced PD subjects significantly decreased their cadence and increased SL during treadmill training. Meanwhile over the treadmill moderate PD and control subjects increased their cadence and maintain similar step length as in overground. These findings were reported previously in the study of Frenkel-Toledo (2005). Warlop et al. (2018) found that gait automaticity decrease with disease progression, so more advanced PD patients could benefit the most from treadmill. The previous study also stated that, walking on treadmill does not seem to require more involvement of attentional resources in healthy and PD populations. In order to determine whether the treadmill has a specific therapeutic effect in PD, the immediate effects of one treadmill session in comparison with one session of overground walking have to be investigated and also the SLCrel has to be explored.

Long lasting effects of treadmill training

The main goal of all rehabilitation program is that it should be effective even after the end of the intervention. An important feature of treadmill training programs is the reported long-lasting effects (Miyai et al., 2002; Toole, Maitland, Warren, Hubmann, & Panton,, 2005; Herman et al., 2007; Bello, 2013; Nadeau, Pourcher, & Corbeil, 2014). Improvements in balance, gait, range of motion and motor UPDRS were maintained for one month, after four weeks of treadmill training (Toole et al., 2005). Lately, improvements in speed, cadence and SL have been stated that sustained until six months after the treadmill training (Nadeau et al., 2014). Noteworthy, a recent study (Pelosin et al., 2017) showed that the use of three different frequencies during the treadmill training program (low, intermediate and high) influences short and long-lasting effects improving gait disturbances and reducing falls risk in PD patients. It is possible that these results are specifically affected by the frequency of training and may be related to learning mechanisms and fatigue.

Immediate effects of treadmill training

Next to the long-term effects, have also been examined the immediate effects of one treadmill session. Gait speed, SL and double stance improved immediately after one session of treadmill walking (Miyai et al., 2000). Ten minutes after a treadmill gait session improvements in gait speed were also found, where advanced PD patients increased their gait speed as a result of an improvement in SL (Bello et al., 2008). The study of Pohl, Rockstroh, Ruckriem, Mrass, & Mehrholz (2003) used three different interventions as, structured speed-dependent treadmill training, limited progressive treadmill training and conventional gait training. Findings showed that speed and SL, can be improved through a single intervention of structured speed-dependent treadmill training or limited progressive treadmill training, but not through conventional gait training.

The positive effects of treadmill walking on PD subjects can be expressed through improvements in the following aspects:

-quality of life
-UPDRS score
-number of steps
-gait speed
-SL
-double stance
-mobility
-hip and ankle joint excursion
-weight distribution during sit-to-stand
-balance
-cardiorespiratory system
-time up and go test

To conclude, the study of Bello et al. (2008) suggested that treadmill training could be used for the rehabilitation of gait in PD patients. Moreover, the use of the treadmill is effective in PD patients, increase step length and improve the main gait impairment in PD. Contrary, Warlop et al. (2018) stated that treadmill can misrepresent the gait as more healthy than it is, so gait analysis using treadmill should be guardedly considered in PD, especially for gait variability evaluation in gait lab. Several studies reported positive results, but the real therapeutic potential of treadmill training and the

mechanisms underlying the benefits are still unclear. However, previous results where PD patients increased their SL during treadmill training, could suggest that the treadmill could help to normalize gait pattern in PD subjects (Fernández-Del-Olmo, 2016). These findings together could suggest that treadmill could help to normalize the SLCrel in PD subjects. The SLCrel modulation when walking on the treadmill could illuminate the benefits of treadmill training programs in PD patients. Despite, no study to date has explored the SLCrel in neither PD nor healthy subjects walking on a treadmill. Nevertheless, analyzing the SLCrel walking on treadmill could extend previous findings and confirm the potential therapeutic effects of treadmill walking for gait rehabilitation in PD.

1.3.5 Mechanisms implicated in treadmill gait advantages in PD

The greater improvements by treadmill rehabilitation than traditional therapies in PD patients (Miyai et al. 2000, 2002; Pohl et al. 2003) suggest that there are mechanisms that are specific to the treadmill. The mechanisms can be related with the features of the treadmill, such as constant speed or the use of handrails or with the different context in which the walking is achieved, such as the external cues provided by the treadmill and the attentional strategies used by PD patients.

The changes in gait on treadmill are more likely the results of the alterations in the pacing mechanism (Hausdorff, 2007). Bello et al. (2008) suggested that the adaptation to the treadmill is related to sensory cues, because is possible that PD patients on treadmill use the proprioceptive cues of the belt as a pacemaker. Furthermore, an explanation for the changes on the treadmill could be also that during treadmill gait, the belt forces stepping, probably through stretch facilitation of hip flexors and ankle plantar flexors at the end of the stance phase (Shepherd & Carr, 1999). Moreover, Olalla et al (2018) found that, in PD subjects the co-activation of the thigh muscles was significantly decreased during treadmill walking in comparison with overground walking, which may be related to the belt movement, as during walking with the treadmill simulator no changes has been reported. Likely, PD patients could also use the distance from the front of the treadmill, as a visual cue. When the treadmill training is combined with visual cues, PD subjects can improve their gait parameters even more (Schlick et al., 2015).

The visual cues and the support of the handrail are two of the possible explanations that have already been rejected. Bello, Marquez, Camblor, & Fernandez-Del-Olmo, (2010) used a treadmill simulator built by extracting the belt, the study showed that during treadmill walking visual feedback was not the main mechanism involved in the step length increase in PD patients. Additionally, when patients were holding the handrail of the treadmill, they could improve their balance and may account for the adaptation of the step length observed over the treadmill (Bateni & Maki, 2005). However, two studies have shown that PD patients reduce their speed and SL by walking with a wheeled walker in comparison to normal gait (Frenkel-Toledo et al., 2005; Bello et al., 2010). Hence, the support of the handrail is also rejected.

Nevertheless, the most reasonable explanations for the changes in gait on treadmill is related to belt movement and proprioceptive signals. It is already known that PD patients can generate a normal gait pattern in the presence of adequate regulatory sensory stimulation. Signs on the floor at the desired step length, may help to initiate and execute gait in PD. Using transverse and longitudinal lines on the treadmill would bypass the defective internal pallidocortical projections in PD, activating compensatory cortical pathways, possibly through the right lateral premotor cortex, which controls externally guided movements (Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999b). Frenkel-Toledo et al. (2005) suggested that the treadmill provides external cues to reduce gait variability and the study of Bello et al. (2010) confirmed that improvements in SL in PD are due to the belt movement itself, probably by the proprioceptive afferents generated by belt displacement. Hence, treadmill walking can supply proprioceptive signals that could bypass the defective pallidocortical circuit in PD.

Thus, the proprioceptive afferents generated by the belt movement could provide suitable sensory inputs for the stimulation of the central pattern generators, that is the spinal locomotor circuitry (Protas et al., 2005; Herman et al., 2007; Fisher, 2008). Studies found positive effect of the treadmill in humans with a spinal lesion and it has been attributed to the activation of the central pattern generators (Dietz, 2003; Shepherd & Carr, 1999). Therefore, the spinal locomotor circuitry in PD would be imitated by treadmill walking.

Furthermore the treadmill improvements could be related to the assumption that treadmill gait can induce motor learning in PD (Protas et al., 2005; Herman et al., 2007; Fisher, 2008). This could elucidate why the improvement in gait is yet persistent several months

after, once the treadmill training is done (Herman et al., 2007). The motor learning induced by treadmill training can also be mediated by the central pattern generators, since in PD learning take place at the spinal level. While it is also possible, that the neural changes may occur at cortical level, since Fisher et al. (2008) reported normalization of corticomotor excitability after treadmill walking exercise at high-intensity, likewise gait improvements in the early stage of PD.

Attentional resources have also been proposed as a mechanism involved in the gait improvements associated with treadmill use in PD next to the belt movement and proprioceptive signals (Bello & Fernández-Del-Olmo, 2012). While the regulation of gait pattern does not require attention in healthy adults, because it is an automatic process, people with PD are able to improve their gait when focusing their attention to their walking movement. This fact suggests an impairment in the automatic control of their gait (Morris et al., 1996). Hence, it is likely that the constant environment and without distractions associated with walking over the treadmill could allow PD patients to focus to their gait in comparison with an overground walking condition, and consequently, bypass the defective pallidocortical circuit in PD. Nevertheless, the study of Fernández-Lago et al. (2015) showed that PD subjects walking on a treadmill while performing a cognitive task, are able to maintain the reduction of their gait variability. Furthermore, their cognitive execution was similar during treadmill and overground walking. Thus, it suggests that attentional resources in PD subjects are not involved in gait improvements on treadmill. In agreement with the previous finding, Warlop et al. (2018) also reported that walking on treadmill does not seem to require more attentional resources in PD populations (Warlop et al., 2018).

Therefore, there are several mechanisms that explain the benefits of treadmill in PD gait, however, there are also arguments that question them (Table 2).

Table 2. *The main mechanisms implicated in treadmill gait benefits in PD*

Mechanism	Arguments to support the mechanism	Arguments to question the mechanism
Central Pattern Generator	Treadmill training could provide adequate sensory inputs, which may stimulate the spinal locomotor circuitry	It is undetermined whether central pattern generator is relevant in the gait improvement of PD patients
External sensory cues	Treadmill walking provides propioceptive signals that may be used by PD patients, triggering intact circuits and by- passing the defective pallidocortical circuit, in order to control movement	Changes in regional flow evaluated with SPECT during treadmill walking, showed absence of the lateral premotor cortex-parietal over activation that seems to accompany externally triggered movements in PD patients, indicating that treadmill walking has an internally driven mechanism
Visual feedback	Modifications in the optical flow lead to modification in the gait pattern. Absence of visual flow may force the subject to look for another source of visual information, as an anchor for maintaining a stable position	Only the absence of visual flow do not increase the step length in PD patients
Attentional strategies	PD patients can use attentional strategies and compensate for the damaged automaticity	
Imposed and constant gait speed	The constant speed of the treadmill could reduce the degrees of freedom and help to minimize stride-to-stride variations in gait timing	
Hand support	Walking aids that have hand support, can improve balance and mobility in older adults and people with other clinical conditions	PD patients reduce their speed and SL when they walk with a wheeled walker in comparison with normal gait
Motor learning	Improvement in gait is sustained several months after the treadmill training is completed	

(Adapted from Bello et al., 2012)

CHAPTER II.

QUESTIONS OF RELEVANCE

After the introduction of this thesis, some questions of interest remain unresolved:

1) Is the SLCrel a reliable measure to evaluate gait in PD subjects?

2) Does treadmill has similar effects in PD patients and age-matched healthy controls?

3) Does the intercept of the SLCrel is lower in PD patients than controls?

4) Does the intercept of the SLCrel increases on the treadmill in PD subjects?

The two studies of this thesis attempt to answer these questions. Question 1 will be addressed in the first study. Questions 2, 3 and 4 will be addressed in the second study.

CHAPTER III. HYPOTHESIS AND MAIN AIMS OF THE STUDIES

3.1 STUDY I: TEST-RETEST RELIABILITY OF STRIDE LENGTH-CADENCE RELATIONSHIP IN PARKINSON'S DISEASE

3.1.1 Hypothesis

The SLCrel is a reliable measure in Parkinsonian gait.

3.1.2 Aims

- To explore the SLCrel in two sessions in PD patients, separated by a period of three months.
- To evaluate the reliability of the SLCrel in a group of PD subjects.

3.2 STUDY II: WALKING ON A TREADMILL IMPROVES THE STRIDE LENGTH-CADENCE RELATIONSHIP IN INDIVIDUALS WITH PARKINSON'S DISEASE

3.2.1 Hypothesis

- The intercept of the SLCrel is lower in PD group than controls.
- The intercept of the SLCrel increases on the treadmill in PD subjects.

3.2.2 Aims

- To compare the SLCrel in PD subjects walking on a treadmill vs. overground.

To evaluate, whether the treadmill has similar effects in PD groups and age-matched healthy controls.

CHAPTER IV.

STUDIES

4.1 STUDY I TEST-RETEST RELIABILITY OF STRIDE LENGTH-CADENCE RELATIONSHIP IN PARKINSON'S DISEASE

4.1.1 Abstract

Introduction

The gait pattern in Parkinson´s disease (PD) subjects is characterized by a specific deficit of the internal regulation of the stride length (SL), while the control of the cadence remains intact. The purpose of the present study was to evaluate the reliability of the stride length-cadence relationship (SLCrel) in a group of PD subjects.

Methods

Thirty five PD subjects participated in two sessions, separated by three month resting period. In each session Gait speed, SL and cadence were evaluated at five different self-selected speed conditions: preferred, slow, very slow, fast and very fast. Linear regression analysis was used to explore the SLCrel and to determine the slope, intercept and coefficient of determination (R^2) for each participant. Test-retest reliability for the slope and intercept was calculated using intra-class correlation coefficient (ICC), 95% confidence interval (CI), and standard error of mean (SEM).

Results

There were not significant differences in the slope and intercept between the two sessions. The overall speed was significantly faster in the second session compared with the first one ($F = 4.60$, $p = 0.03$). The SLCrel showed high reliability across the sessions (ICC = 0.89 and ICC = 0.91; 95% CI = 0.80-0.95 and 95% CI = 0.82-0.95; SEM = 0.002 and SEM = 0.073, for the slope and interception, respectively).

Conclusions

The SLCrel in Parkinsonian gait is a reproducible measure across a period of three months, and may be a useful tool to explore the specificity of gait rehabilitation interventions in PD subjects.

Keywords: Parkinson's disease, gait, stride length - cadence relationship

4.1.2 Introduction

Parkinson's disease (PD) is a neurodegenerative disease, clinically characterized by akinesia, rigidity, tremor and postural instability (Hoehn et al., 1967). Gait disturbances are one of the principal and most incapacitating symptoms of PD. Gait in PD is characterized by shorter stride length, forward-flexed trunk, inadequate flexion at the ankle and knee, insufficient heel strike, reduced arm swing, postural instability, asymmetric stride for lower limbs, and higher stride-to-stride variability in comparison with age/sex matched controls (Keus et al., 2009).

The gait pattern in PD subjects is also characterized by a specific deficit of the internal regulation of the stride length (SL), while the cadence control is intact (Morris et al., 1994b). When healthy adults increase or decrease their self-selected walking speed, they increase or decrease their SL and cadence in a relatively constant linear relationship (Egerton et al., 2012; Zijlstra et al., 1995). In PD subjects, the slope of this relationship remains unaffected, while the interception is smaller than that in healthy subjects, that is, a smaller stride length is associated with a higher cadence (Morris et al., 1996). This difficulty in the regulation of the SL can be normalized by using attentional strategies (Morris et al., 1996) or in response to Levodopa medication (Morris et al,. 1998), suggesting that PD subjects have the ability to generate a normal stride length-cadence relationship (SLCrel) (Morris et al., 1996). Thus, the regulation of the SL represents one of the main goals in rehabilitation interventions in PD subjects. However, the effects of physical therapy interventions on the SLCrel in PD subjects have not been examined. Most of the studies that evaluate the efficacy of rehabilitation and exercise interventions use, independently, changes in SL, cadence or speed as the main outcome measures (Kwakkel et al., 2007). Thus, although, increases in gait speed may reflect a functional improvement (Kwakkel et al., 2007), these do not necessarily reflect an amelioration of PD symptomatology. In addition, due to the age-associated progressive loss of physical function, it is difficult to elucidate which rehabilitation approach has a specific impact in PD rather than a generalized benefit from exercise (Bello et al., 2013). The study of the SLCrel may help to establish the specific therapeutic effect of an intervention, in order to optimize the rehabilitation strategy. The reliability of SLCrel in PD subjects has not been examined, and this is of relevance since most of the measures that are used in physical therapy suffer from a lack of reliability (Kwakkel et al., 2007).

The objective of the present study was to evaluate the reliability of the SLCrel in a group of PD subjects. We used a previously reported protocol (Egerton et al., 2012; Danoudis & Iansek, 2014), in order to explore the SLCrel in two sessions, separated by a period of three months. We choose this period of time since most of the physical therapy studies used similar periods of intervention (Goodwin et al., 2008). We determined the reliability of the SLCrel as an outcome measure in Parkinson's rehabilitation interventions.

4.1.3 Methods

Participants

Thirty five PD subjects participated in the study (23 males and 12 females, mean age = 63.43±9.47 (Table 3). To participate in the study, PD subjects had to be able to walk without assistance, and did not take medication that could influence negative their walking ability (i.e. antidopaminergic medications). The recording sessions were performed with subjects in "ON" medication state (45-90 min after medication intake), as confirmed by a neurologist. All the subjects showed no sign of dementia as assessed by a mini-mental state examination (MMSE scores ≥ 23) (Folstein, Folstein, &, McHugh, 1975). The level of severity of motor signs associated with PD was measured using the Unified Parkinson's Disease Rating Scale Part-III (UPDRS-III) (Hughes et al., 1992) and Hoehn & Yahr scale (H&Y) (Hoehn et al., 1967). Height, weight and leg length were evaluated for each subject. All the participants gave their written informed consent according to the declaration of Helsinki (1964). The experimental procedures were approved by the ethics committee of the University of A Coruña.

Table 3. *Group characteristic*

Age, yrs	63.43 ± 9.47
Male, n	23
Female, n	12
Weight, kg	76.56±12.33
Height, cm	164.06±9.45
Leg length, cm	83.54±5.82
MMSE	26.80 ± 2.43
Disease duration, yrs	6.26 ± 4.49
UPDRS-III	17.66 ± 8.59
H&Y stage (subject in each stage)	1 (n=7); 1.5 (n=7); 2 (n=17); 2.5 (n=4)

Note. Means±SD unless stated otherwise; MMSE Mini Mental State Examination, UPDRS-III Unified Parkinson's Disease Rating Scale motor section, H&Y Hoehn and Yahr.

Procedure

Participants performed two testing sessions (T1, T2) with a three month period between the tests (average days between sessions 89.48 ± 2.46). The two testing sessions were conducted at the same time of the day and under similar environmental conditions. During the three month period, the subjects did not change their daily activities or medication. None of the subjects reported any event such as falls or change of medication.

Gait measurements

Kinematic gait parameters were evaluated using an optical detection system and software (v.1.11 OptoGait; Microgait, Italy). This optical and modular system included transmitting and receiving bars of infrared LEDs. The walkway was 9 meters long, with a 5 meters electronic walkway in the middle. We followed the protocol previously used in several studies (Egerton et al., 2012; Danoudis and Iansek, 2014). Gait speed, SL and cadence were evaluated at five different self-selected speed conditions: preferred, slow, very slow, fast and very fast. All the patients performed three consecutive trials for each self-selected speed condition. Each trial consisted of walking from one end of the

walkway and back. Trials at the preferred self-selected speed condition were always recorded first in order to avoid any influence from other conditions. The remaining four self-selected speed conditions were performed in one of the following orders to counterbalance the order effect: slow, very slow, fast and very fast, or, fast, very fast, slow and very slow. Participants were randomly allocated to one of the two orders. For each trial participants started to walk two meters before the electronic walkway and finished two meters beyond the walkway, in order to avoid recording the acceleration and slowing down of the subjects. The second and third walks of each self-selected speed condition were averaged, to obtain one value per participant. PD patient's rested between self-selected speed conditions as required. Participants had only one practice trial at their preferred self-selected speed condition in order to familiarize themselves with the spatial dimensions of the laboratory. We explained to the subjects at the beginning of the experiment that they will have to walk at five different self-selected speed conditions. All the participants understood the explanations and performed all the five self-selected speed conditions without any difficulty.

We analyzed the following gait variables: speed, SL and cadence. SL was normalized by dividing mean SL for each self-selected speed condition by the leg length (Hof, 1996). The leg length was defined as the distance measured from the greater trochanter to the plane of the sole of the foot (Hall, Froster-Iskenius, Froster-Iskenius, & Allanson, 1989). Linear regression analysis was used to evaluate the SLCrel and to determine the slope, intercept and R^2 for each participant. A linear relationship between SL and cadence was defined as that having R^2 values that were greater or equal to 0.80 (Danoudis & Iansek, 2014). Although, previous studies have reported intercept values at a cadence of zero (Morris et al., 1994b, 1996), the validity of values outside the range of the data may be questionable (Snijders & Bosker, 1999). Therefore, and following previous studies (Egerton et al., 2012; Danoudis & Iansek, 2014; Egerton et al., 2011), we calculated the intercept for cadence using the value of 100 steps/min, to ensure that the intercept values were within the data range for all the participants (Egerton et al., 2012; Danoudis & Iansek, 2014; Egerton et al., 2011).

Statistical analysis

Gait comparisons, of the variables SL, cadence, and speed, were evaluated using ANOVA of repeated measurements, with SESSION (T1, T2) and CONDITION (slow, very slow, preferred, fast and very fast self-selected speeds) as factors. Post-hoc analysis was conducted using a Bonferroni adjustment.

Dependent-samples-t-tests were used to compare the intercept and slope between T1 and T2. Test-retest reliability for the slope and intercept was calculated using the intra-class correlation coefficient (ICC), the corresponding 95% confidence interval, and the standard error of mean (SEM). ICC is a relative measure of reliability, reflective of the ability of a test to differentiate between different individuals. The SEM centers on the assessment of reliability within individual subjects, quantifying the precision of individual scores on a test (Weir, 2005). In addition, we also calculated the minimal important difference (MID), where MID = SEM x 1.96, a value that distinguishes between true and apparent change due to a measurement error (Weir, 2005; Corsaletti et al., 2014), thus determining which changes resulted from a hypothetical therapy.

All the data were analyzed using IBM SPSS Statistics for Windows (v.24.0.0). None of the data violated the normality assumption necessary to conduct parametric statistical tests. Significance level was set at $p \leq 0.05$.

4.1.4 Results

Modulation of gait speed, stride length and cadence

Descriptive statistics of the variables that were obtained in the two recording sessions are presented in Table 4.

Two-way ANOVA for gait speed showed a significant main effect for SESSION ($F=4.60$, $p=0.03$) and CONDITION ($F=122.02$, $p<0.001$). There was no significant SESSION x CONDITION interaction. The overall gait speed was significantly higher in the second session in comparison with the first one. The post-hoc analysis revealed the faster the self-selected speed conditions (grouping both sessions) the faster gait speed ($p<0.001$ for all comparisons).

Two-way ANOVA for SL showed a significant main effect for CONDITION ($F=95.34$, $p<0.001$). We did not show a significant effect for SESSION, although there was a tendency for significance ($F=3.68$, $p=0.059$). There was no significant SESSION x CONDITION interaction. Post-hoc analysis revealed that the faster the self-selected speed conditions the longer the SL ($p< 0.001$ for all comparisons).

Two-way ANOVA for cadence revealed a significant main effect for CONDITION ($F=76.33$, $p<0.001$). We did not show a significant effect for SESSION, nor a significant SESSION x CONDITION interaction. Post-hoc analysis revealed that the faster the self-selected speed conditions the higher the cadence ($p<0.001$ for all comparisons).

Table 4. *Gait parameters for speed conditions during T1 and T2*

	T1 (n=35)	**T2 (n=35)**
	Mean (SD) Min, Max	**Mean, SD, Min, Max**
Condition VS (m/sec)	0.84 (0.15), 0.51, 1.07	0.87 (0.16), 0.55, 1.28
Condition S (m/sec)	1.02 (0.15), 0.70, 1.28	1.05 (0.17), 0.75, 1.48
Condition Pref (m/sec)	1.20 (0.16), 0.89, 1.52	1.25 (0.19), 0.82, 1.64
Condition F (m/sec)	1.34 (0.19), 0.97, 1.68	1.38 (0.21), 0.98, 1.86
Condition VF(m/sec)	1.52 (0.24), 1.09, 1.98	1.54 (0.23), 1.10, 2.08
nSL VS	1.05 (0.13), 0.75, 1.23	1.08 (0.16), 0.84, 1.51
nSL S	1.15 (0.14), 0.90, 1.39	1.18 (0.17), 0.90, 1.68
nSL Pref	1.26 (0.14), 0.95, 1.56	1.28 (0.18), 0.97, 1.77
nSL F	1.33 (0.15), 1.02, 1.65	1.36 (0.18), 1.03, 1.83
nSL VF	1.42 (0.18), 1.07, 1.82	1.42 (0.19), 1.06, 1.91
Cad VS (step/min)	95.94 (10.09), 71.4, 114.5	96.63 (9.70), 73.2, 1.20
Cad S (step/min)	105.56 (9.09), 85.6, 122.4	106.97 (9.26), 0.88, 1.26
Cad Pref (step/min)	114.03 (8.39), 99.3, 132.3	116.50 (8.92), 0.96, 1.32
Cad F (step/min)	121.09 (10.46), 101.5, 142.8	122.65 (9.65), 1.03, 1.44
Cad VF (step/min)	129.24 (11.84), 107.4, 148.8	130.13 (11.43), 1.09, 1.59

Note. SD; standard deviation, Min; minimum, Max; maximum, VS; very slow, S; slow, Pref; preferred, F; fast, VF; very fast; nSL, normalized stride length; Cad, cadence.

SLCrel and reliability analysis

There were not significant differences for slope and intercept between the sessions (t=1.49, p=0.14; t=1.60, p=0.12, for slope and intercept, respectively).

Examination of the SLCrel plots in T1 and T2 showed a positive linear relationship in each of the participants. In session T1, the average R^2 was 0.97 (±0.032), and the R^2 range was 0.87- 0.99. In session T2 the average R^2 was 0.94 (±0.096) and the R^2 range was 0.81-0.99.

The individual slope and intercept of the SLCrel in each subject showed high reliability across the three month period (Table 5). MID values were 0.006 and 0.202 for slope and intercept, respectively. Figure 4 shows an example of the linear regression in one subject across the two test sessions.

Table 5. *Reliability of SLCrel*

	SLCrel T1 vs T2							
	Mean (SD) T1	**Mean (SD) T2**	**t**	**p**	**ICC**	**95% CI**	**SEM**	**MID**
Slope (steps/min)	0.015±0.005	0.014±0.006	1,618	.115	.897	.804-.950	0.002	0.006
Intercept (m)	1.309±0.169	1.338±0.194	-1.661	.106	.908	.819-.953	0.073	0.202

Note. SLCrel, stride length - cadence relationship;SD, standard deviation; t, critical value; p, significance (paired samples t-test between tests 1 and 2); ICC, intraclass correlation coefficient; CI, 95% confidence interval,; SEM, standard error mean; MID, minimal important difference. The intercept is calculated for cadence using the value of 100 steps/min.

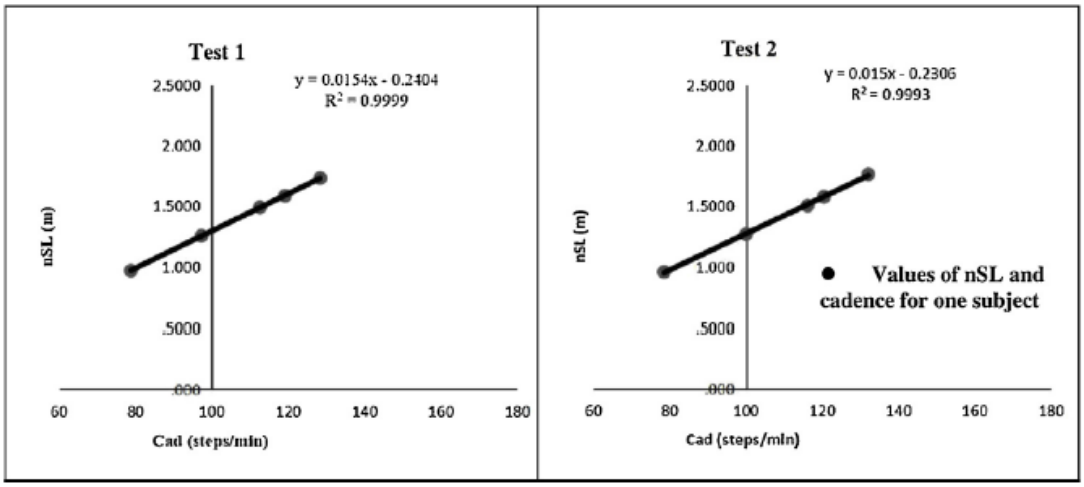

Figure 4. SLCrel in the speed condition for one subject in T1 and T2.

nSL, normalized stride length; Cad, cadence; Figure 4 presents a perfect positive linear relationship (Test1: R^2=0.99, Test2: R^2=0.99).

4.1.5 Discussion

This main goal of the study was to evaluate the reliability of the SLCrel in PD subjects. Our results show that, using five different self-selected gait speed conditions, the linear regression between SL and cadence is reproducible and does not decline after a period of three months. Our findings suggest that the utilized protocol (Egerton et al., 2012; Danoudis & Iansek, 2014) can be used to explore changes in the stride-cadence gait relationship in PD subjects.

We showed that PD patients were able to modulate their speed, SL and cadence across the five self-selected speed conditions. The values of the speed, SL and cadence were equivalent to those obtained in previous studies with PD subjects of similar age and disease severity (Egerton et al., 2012; Danoudis & Iansek, 2014). However, in the current study the overall speed in the first session was significantly slower than that in the second session. Thus, although, the two sessions were conducted three months apart, it is likely that some familiarization or learning may have occurred. For instance, it has been reported that learning effects can be present even when practice is limited to a minimum (Benninger & Hallett, 2015). We should point out that for the preferred condition the increment from T1 to T2 was an average of 0.02 m/s, an increment lower than the value defined as a clinical meaningful change (0.05 m/s) for gait speed in PD subjects (Hass et al., 2014). Nevertheless, for intervention studies, our results stress the need for a group of

PD patients not receiving the therapy in order to differentiate possible learning effects from potential therapeutic effects related to the intervention.

The modulation of SL and cadence across the different self-selected speed conditions followed a linear relationship in each patient. The R^2, intercept and slope values of these relationships were similar to those previously reported for PD subjects (Egerton et al., 2012; Danoudis & Iansek, 2014), suggesting that the SLCrel is a reproducible measure across studies, when using the protocol described in Egerton et al. (2011). Importantly, in the current study both, the intercept and the slope, showed high reliability (CCI >0.8) (Fleiss and Cohen, 1973) across a three month period in PD patients. To our knowledge this is the first study that evaluated the reliability of the SLCrel in PD patients. The high reliability of the intercept is of relevance since this parameter represents one of the main deficits in the gait pattern of PD subjects, and thus may be a reliable measure to follow the progression of the disease.

In our study, the changes in the speed across the testing sessions did not affect the SLCrel. In another words, an improvement or change in gait speed after a physical therapy intervention does not necessarily mean a change in the SLCrel. Thus, an improvement of speed, cadence or SL may represent a successful intervention, at least from a functional point view. However, if the SLCrel values do not change, these improvements may only reflect a general benefit from the practice of exercise during the therapy. In contrast, an increase of the intercept value of the SLCrel, indicates that there is a specific therapeutic effect on the gait in PD patients. Therefore, we propose that one of the main targets of physical gait therapies in PD should be the normalization of the SLCrel, by increasing the intercept value of this relationship. In order to use SLCrel as an outcome measure, in addition to good reliability, it must also be responsive to change. Levodopa therapy and the use of attentional or sensory cues strategies have been proven effective in improving the SLCrel in PD subjects (Morris et al., 1996). Our findings suggest that an intercept increase of 0.202 m is the minimal important difference, in order to detect a change that can be attributed to the therapeutic intervention.

Our study presents several limitations that must be addressed. First, the PD participants were able to walk without assistance and thus, it is possible that the gait protocol used to evaluate the SLCrel may not be applied to patients with greater disease severity. Second, we evaluated the reliability of the SLCrel across a period of three months. We choose this

period of time since most of the physical therapy studies used similar periods of intervention (Goodwin et al., 2008). Future studies are warranted in order to examine the SLCrel evolution across the progression of the disease. In fact one study (Bayle et al., 2016), using a different methodology than the current our study, showed a negative correlation between the time of diagnosis of PD patients and the contribution of the step length to the walking speed. These findings suggest that the SLCrel may be an effective marker of the disease progression. Another limitation of the current study is the non-inclusion of an age/sex matched control group in order to discern the expected change in healthy subjects and therefore, better understand the impact of the Parkinson's disease in the SLCrel.

In conclusion, the current study shows that the SLCrel in Parkinsonian gait is a reliable measure across a period of three months. We showed that the intercept and slope values, of the linear relationship between the gait parameters, remain unaffected even when changes in the gait speed are observed. Thus, the SLCrel, over a variety of self-selected speed conditions, may be a reliable tool to differentiate the specific from the general benefits of gait rehabilitation interventions in PD subjects.

4.2 STUDY II WALKING ON A TREADMILL IMPROVES THE STRIDE LENGTH-CADENCE RELATIONSHIP IN INDIVIDUALS WITH PARKINSON'S DISEASE

4.2.1 Abstract

Background

The gait pattern in Parkinson´s disease (PD) is characterized by a deficit in the internal regulation of stride length (SL), while the control of cadence remains intact. The use of the treadmill as a gait rehabilitation tool has provided novel options for treatment of gait impairments in PD. However, it remains unclear whether walking on the treadmill changes the stride length–cadence relationship (SLCrel) in PD. The purpose of the present study was to analyze the SLCrel in PD subjects walking on a treadmill vs. overground, and to further compare the SLCrel to that of age-matched healthy subjects.

Methods

Fifteen PD subjects and fifteen age-matched controls walked overground and on a treadmill at five different self-selected speeds. Gait speed, SL and cadence were recorded at each self-selected speed. A linear regression analysis was conducted to explore the SLCrel and to determine the slope and intercept for each participant.

Results

PD subjects showed a lower intercept than control subjects when walking both overground and on a treadmill ($F=8.51$, $p=0.007$). In comparison with walking overground, walking on a treadmill resulted in a significant increase in the intercept in both PD and control groups ($F = 12.17$, $p = 0.002$). There were no significant differences in the slope of the SLCrel.

Conclusion

PD subjects are able to improve the internal regulation of SL when walking on a treadmill. Our results confirm the potential therapeutic effects of treadmill training for gait rehabilitation in PD and suggest that the mechanisms underlying the positive effects of treadmill training on PD subjects are sustained.

Keywords: Parkinson's disease, gait, stride length - cadence relationship, treadmill

4.2.2 Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects motor functions (Hoehn & Yahr, 1967). PD is clinically characterized by symptoms of akinesia, rigidity, tremor and postural instability (Hoehn & Yahr, 1967). However, gait disturbances are one of the most disabling symptoms of PD, potentially leading to loss of mobility, increasing numbers of falls (Morris et al., 1994a) and negative affects on the independence and quality of life of PD patients (Schenkman, 1992).

Gait in PD is associated with shorter stride lengths (SL), while the cadence (Cad) remains intact (Morris et al., 1994a, Morris et al., 1994b). When PD patients and healthy adults increase or decrease their self-selected walking speed, they respectively increase or decrease their SL and Cad in a relatively constant linear relationship (Egerton et al., 2012; Zijlstra et al., 1995). In PD subjects, the slope of this relationship remains unaffected, but the intercept is lower than that of healthy subjects, that is, a smaller SL is associated with a higher Cad. This difficulty in the regulation of SL can be normalized by using attentional strategies (Morris et al., 1996) or Levodopa medication (Morris et al., 1998), suggesting that the ability for PD patients to generate a normal stride length-cadence relationship (SLCrel) is not lost (Morris et al., 1996).

For this reason, the regulation of SL must be prioritized as one of the main goals in rehabilitation interventions in PD patients. The use of treadmills in gait rehabilitation in PD patients has been proven to improve gait performance (Herman et al., 2007; Bello et al., 2008, 2010; Miyai et al., 2000; Pohl et al., 2003). While treadmill walking training has been found to increase the SL in PD subjects, walking training overground lacked such an improvement (Bello et al., 2013). Additionally, advanced PD subjects walking on a treadmill increased their SL whereas walking at the same speed overground had no effects (Bello et al., 2008). Taking these results together, it could be suggested that the treadmill could help to normalize the SLCrel in PD subjects (Fernández-Del-Olmo, 2016). However, no study to date has explored the SLCrel in neither PD nor healthy subjects walking on a treadmill. Therefore, the goal of the current study is to compare the SLCrel in PD subjects walking on a treadmill vs. overground. In addition, the SLCrel in age-matched healthy subjects was evaluated in order to explore whether the treadmill had similar effects in both groups. The results could extend previous findings and confirm the potential therapeutic effects of treadmill walking for gait rehabilitation in PD.

4.2.3 Methods

Participants

Fifteen subjects with PD (11 males and 4 females, mean age 65.4 ± 9.23) and fifteen age matched controls (10 males and 5 females, mean age 64.07 ± 8.01) with no history of neurological disorders participated in the study. Subjects were required to be able to walk without assistance. All subjects were familiar with the treadmill. Participants with any medication that could influence their ability to walk were excluded from the experiment. Data collection was carried out with subjects in an "ON" medication state (45-90 min after medication intake), which was confirmed by a neurologist. No participant showed signs of dementia, as assessed by a mini-mental state examination (MMSE). The level of severity of motor signs associated with PD was measured using the Unified Parkinson's Disease Rating Scale Part-III (UPDRS-III) (Hughes et al., 1992 and Hoehn & Yahr scale (H&Y) (Hoehn and Yahr, 1967). Height, weight and leg length were collected from all participants. Details of the subjects are shown in Table 6. All participants gave their written informed consent according to the declaration of Helsinki (1964) before partaking in the study. The experimental procedures were approved by the ethics committee of University of A Coruña.

Table 6. *Group characteristics*

	PD	CONTROL
Age, yrs	65.40 ± 9.23	64.07 ± 8.01
Male, n	11	10
Female, n	4	5
Weight, kg	73.30 ± 14.65	73.77 ± 14.88
Height, cm	166.27 ± 10.71	164.33 ± 10.70
Leg length, cm	86.20 ± 5.71	83.77 ± 6.38
UPDRS-III	16.4 ± 5.89	-
H&Y stage (subject in each stage)	1 (n=1); 1.5 (n=1); 2 (n=12); 2.5 (n=1)	-

Note. PD, Parkinson's disease subjects; Means ± SD; UPDRS-III Unified Parkinson's Disease Rating Scale motor section, H&Y Hoen and Yahr.

Procedure

In order to avoid any carry-on effect from treadmill walking, all participants first performed the overground walking test followed by the treadmill walking test (Bello et al., 2008).

Overground walking test

Kinematic gait parameters were recorder using an optical detection system and specialized software v.1.11 (OptoGait; Microgait, Italy). This optical and modular system includes transmitting and receiving bars of infrared LEDs displayed in parallel along 5 meters of walkway. Each bar contains 96 light diodes at 1.04 cm of horizontal distant between each diode. When subjects enter the area limited by the bars, their feet block the transmission and reception and spatial (foot placement) and temporal (time of the foot placement) data are transfer to a personal computer. Therefore, stride length and cadence are directly obtained by the OptoGait software (OPTOGait Version 1.11 software) while speed is estimated from both parameters. The walkway was 9 meters long with 5 meters of electronic walkway in the middle zone (Figure 5). The protocol followed was that used by several previous studies (Egerton et al., 2012; Danoudis et al. 2014). Gait speed, SL and Cad were collected at five different self-selected speeds: preferred, slow, very slow, fast and very fast. All subjects performed three consecutive trials for each speed condition, with each trial consisting of walking straight down and back the walkway. Trials at the subject's preferred speed were always recorded first to avoid any influence from the other speed conditions. The remaining four gait paces were performed in the order of either, slow, very slow, fast and very fast, or fast, very fast, slow and very slow. Participants were randomly assigned to one of these two orders. For each trial, participants started walking two meters before the electronic walkway and finished two meters after the end of the walkway in order to avoid recording the acceleration and deceleration of the participants. The second and third walks of each self-selected speed were averaged to obtain one value per participant. PD participant's rested between self-selected speeds as necessary.

Figure 5. The walkway

Treadmill walking test

The overground speeds were used to set the treadmill speeds for each participant. As a warm up prior to testing, each participant performed two minutes of walking at approximately their lowest speed. The treadmill session consisted of five 1-min blocks (T1-T5) of treadmill walking, with one minute at each of the five speeds ranging from very slow to very fast. Speed of the treadmill was always checked by a digital tachometer (Hibok-24) with a special built-in sensor to measure surface velocity. Measurements on the treadmill were taken from the last 30 seconds of each block by the Optogait system (two parallel bars installed in the laterals of the belt). All participants walked on the treadmill holding the handrails under supervision and with a safety harness to prevent falls. All subjects were able to walk on the treadmill at their five self-selected overground speeds.

Complementary experiment

In order to control for the effect of using the handrails during treadmill walking in the main experiment, we asked the participants to partake in a second experimental session. The procedure was identical to the main experiment, however the participants were to

walk without holding the handrails during the treadmill walking. Six PD participants who felt confident enough to walk on the treadmill under these conditions and six control participants took part in this complementary experiment.

Data analysis

We analyzed the following gait variables: speed, SL and Cad. SL was normalized by dividing the mean SL for each self-selected speed by the leg length (Hof, 1996). Linear regression analysis was used to evaluate the SLCrel and to determine the slope, intercept and R^2 for each participant. A linear relationship between SL and Cad was defined as that having R^2 values greater or equal to 0.80 (Danoudis et al., 2014). We calculated the intercept for Cad of 100 steps/min to ensure that the intercept values were within the data range for all the participants (Egerton et al. 2012, Danoudis et al., 2014; Egerton et al., 2011). In addition, walks with very high Cad (greater or equal to 150 steps/min) were removed from the analysis (Egerton et al. 2012, Danoudis et al., 2014; Egerton et al., 2011).

Statistical analysis

ANOVA with repeated measurements in CONDITION (overground, treadmill), SPEED (very slow, slow, preferred, fast and very fast), and GROUP (PD, control) as factors were conducted in order to explore changes in SL, Cad, and speed between conditions and groups. Post-hoc analysis was conducted using a Bonferroni adjustment.
Similarly, ANOVA with repeated measurements in CONDITION (overground, treadmill) and GROUP (PD, control) were used to compare the intercept, slope and R^2 between conditions and groups.

For the complementary experiment, ANOVA with repeated measurements in CONDITION (overground, treadmill without handrails) and GROUP (PD, control) were conducted over the intercept and slope.

All data were analyzed using SPSS for Windows (version 14.0; SPSS Inc, Chicago, IL). The significance level was set at $p \leq 0.05$.

4.2.4 Results

Modulation of gait speed, stride length and cadence

Descriptive statistics of the results obtained in the two conditions of assessment are presented in Table 7.

The two-way ANOVA for gait speed showed a significant main effect for SPEED ($F=100.66$, $p<0.001$). There were no significant effects for CONDITION or GROUP. No significant interactions were found. Post-hoc analysis revealed significant differences in speed across all the speed values ($p< 0.001$ for all comparisons).

The two-way ANOVA for SL showed a significant main effect for SPEED ($F=45.76$, $p<0.001$). There were no significant effects for CONDITION or GROUP. No significant interactions were found. Post-hoc analysis revealed significant differences in SL across all speed values ($p< 0.001$ for all comparisons).

The two-way ANOVA for Cad revealed a significant main effect for CONDITION ($F=8.79$, $p=0.006$) and SPEED ($F=43.93$, $p<0.001$). There was no significant difference between groups. No significant interactions were found. The Cad was lower during treadmill walking in comparison with overground walking. Post-hoc analysis revealed significant differences in Cad across all speeds ($p<0.05$ for all comparisons).

Table 7. *Gait parameters in PD and control subjects during the two conditions*

	PD (n=15)		CONTROL (n=15)	
	Overground Mean (SD)	**Treadmill Mean (SD)**	**Overground Mean (SD)**	**Treadmill Mean (SD)**
Speed VS (m/sec)	0.85 (0.13)	0.84 (0.13)	0.89 (0.18)	0.89 (0.18)
Speed S (m/sec)	1.04 (0.16)	1.04 (0.15)	1.08 (0.18)	1.08 (0.18)
Speed Pref (m/sec)	1.24 (0.19)	1.24 (0.20)	1.28 (0.20)	1.28 (0.20)
Speed F (m/sec)	1.38 (0.22)	1.38 (0.23)	1.46 (0.22)	1.45 (0.22)
Speed VF(m/sec)	1.54 (0.23)	1.54 (0.23)	1.68 (0.24)	1.69 (0.25)
SL VS (m)	1.04 (0.14)	1.10 (0.15)	1.13 (0.12)	1.18 (0.17)
SL S (m)	1.17 (0.16)	1.22 (0.17)	1.25 (0.13)	1.29 (0.13)
SL Pref (m)	1.28 (0.19)	1.32 (0.17)	1.34 (0.14)	1.39 (0.13)
SL F (m)	1.35 (0.20)	1.38 (0.18)	1.44 (0.15)	1.47 (0.13)
SL VF(m)	1.43 (0.21)	1.46 (0.19)	1.53 (0.17)	1.53 (0.18)
Cad VS (step/min)	97.83 (7.41)	92.17 (8.36)	93.91 (10.58)	90.43 (12.73)
Cad S (step/min)	107.25 (7.48)	102.27 (6.77)	104.91 (10.27)	100.92 (11.51)
Cad Pref (step/min)	116.86 (7.22)	111.75 (5.27)	116.41 (10.71)	109.71 (12.27)
Cad F (step/min)	123.21 (8.01)	116.58 (7.17)	123.02 (10.50)	112.95 (9.24)
Cad VF (step/min)	129.51 (8.98)	124.51 (6.94)	132.45 (11.30)	125.48 (13.44)

Note. PD, Parkinson's disease subjects; SD; standard deviation, VS; very slow, S; slow, Pref; preferred, F; fast, VF; very fast; nSL, normalized stride length; Cad, cadence.

SLCrel analysis

One PD participant and two control participants had Cad values higher than 150 steps/min during overground walking, while high Cad values were only found in one control participant during the treadmill session; these values were not included in the SLCrel analysis.

The two-way ANOVA for intercept revealed a significant main effect for CONDITION ($F=12.17$, $p=0.002$) and GROUP ($F=8.51$, $p=0.007$) (Table 8, 9). No significant interactions were found. The SLCrel intercept was lower for PD than control participants. The intercept was lower for overground walking in comparison with treadmill walking. Figure 6 shows the intercept for PD and control participants across the two conditions.

Table 8. *SLCrel values for overground and treadmill in PD and control subjects*

	PD (n=15)		**CONTROL (n=15)**	
	Overground	**Treadmill**	**Overground**	**Treadmill**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
SLCrel slope (steps/min)	0.015 (0.005)	0.014 (0.008)	0.014 (0.004)	0.013 (0.008)
SLCrel intercept (m)	1.24 (0.182)	1.36 (0.150)	1.41 (0.156)	1.55 (0.284)
SLCrel R^2	0.96 (0.037)	0.89 (0.254)	0.96 (0.052)	0.87 (0.122)

Note. PD, Parkinson's disease subjects; SLCrel, stride length- cadence relationship; SD; standard deviation.

Table 9. *SLCre1 values for the complementary experiment*

	PD (n= 6)			CONTROL (n=6)		
	Overground	**Treadmill**	**Treadmill without handrails**	**Overground**	**Treadmill**	**Treadmill without handrails**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
SLCrel slope (steps/min)	0.012 (0.004)	0.013 (0.003)	0.016 (0.002)	0.013 (0.003)	0.015 (0.014)	0.018 (0.004)
SLCrel intercept (m)	1.38 (0.169)	1.43 (0.122)	1.27 (0.126)	1.47 (0.079)	1.45 (0.262)	1.27 (0.128)
SLCrel R^2	0.96 (0.022)	0.96 (0.051)	0.94 (0.073)	0.97 (0.046)	0.92 (0.066)	0.95 (0.062)

Note. PD, Parkinson's disease subjects; SLCrel, stride length- cadence relationship; SD; standard deviation.

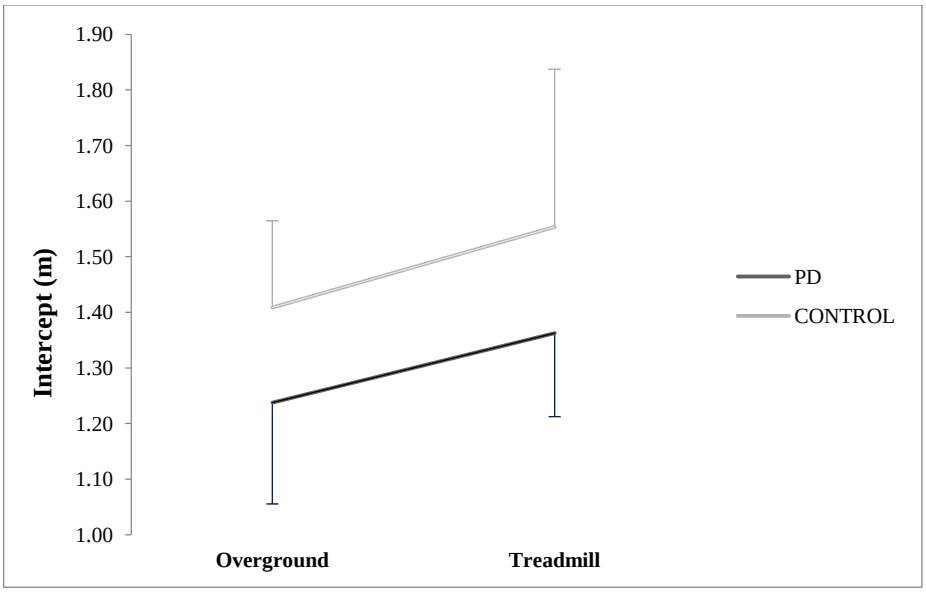

Figure 6. Intercept for PD and control subjects across two conditions

The two-way ANOVA for slope did not reveal a significant main effect for CONDITION or GROUP, and no further interaction.

Examination of the SLCrel plot in the overground condition showed a positive linear relationship in each of the participants. However, in the treadmill condition, two PD participants and four control participants had less than R^2=0.80, non linear relationship. The two-way ANOVA for R^2 showed a significant main effect for CONDITION (F=4.52, p =0.042). There was no significant difference between groups and no interactions. In

the overground condition, the average R^2 was 0.9594 (± 0.037) in PD and R^2=0.9614 (± 0.052) in control participants. In the treadmill condition, the average R^2 was 0.8930 (±0.254) in PD and R^2=0.8680 (±0.122) in control participants.

Complementary experiment

The ANOVA over the intercept showed a significant main effect of CONDITION (F = 16.11 p = 0.002). The intercept was lower during treadmill walking without holding the handrails in comparison with that when walking overground (Figure 7). With the exception of one participant, all participants reduced the intercept under the treadmill condition. There was no effect of GROUP or interaction CONDITION * GROUP.

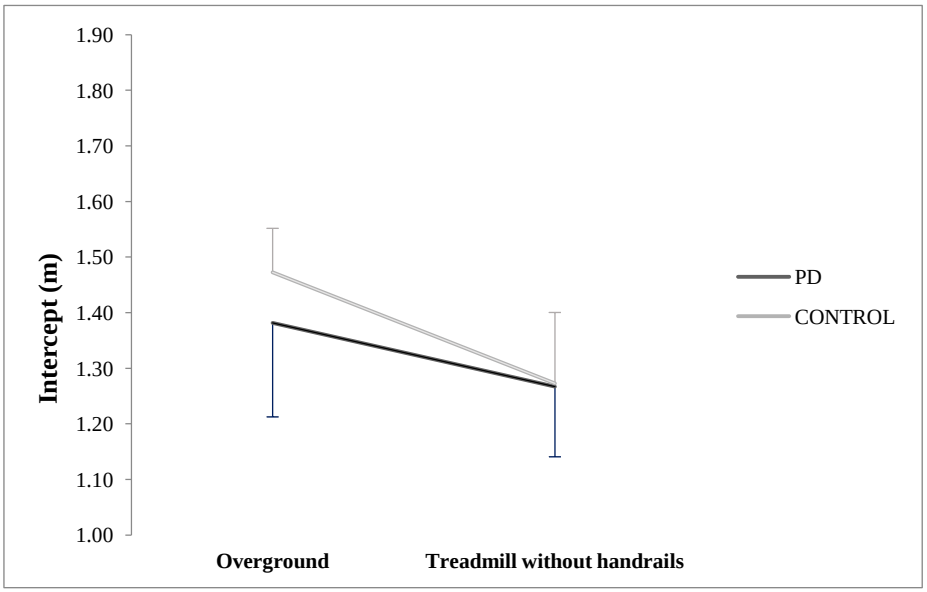

Figure 7. Complementary experiment, intercept for PD and control subjects across overground and treadmill without handrails conditions

The ANOVA for slope did not reveal a significant main effect for CONDITION or GROUP, and no further interaction.

4.2.5 Discussion

The main goal of this study was to evaluate the effect of treadmill walking on the gait SLCrel in PD patients. Our results showed an increase in the intersection of the SLCrel in PD participants when walking on the treadmill in comparison with walking overground. This finding supports the use of the treadmill to normalize the SLCrel in PD patients. Interestingly, this effect was also shown in the control group, suggesting that the

mechanisms underlying the modulation of the SLCrel when walking on the treadmill are preserved in the PD participants.

Our study is the first to evaluate the SLCrel when walking overground and on a treadmill in PD participants. In a previous study from our group (Bello et al., 2008), we found that advanced PD participants significantly decreased their Cad and increased their step length during the treadmill condition, while the control subjects and moderate PD patients did not significantly change their step length or Cad. However, in that study we only evaluated the self-selected preferred speed. In the current study, we used a linear regression analysis to explore the relationship between SL and Cad. Our results showed that moderate PD participants are also able to increase the SL when using the treadmill.

Several mechanisms have been proposed to explain the improvement in gait induced by treadmill training in PD (Bello et al., 2012). For example, the treadmill may provide adequate sensory inputs, which may stimulate spinal locomotor circuitry (Van de Crommert, Mulder, & Duysens, 1998). Interestingly, our control group also showed a higher intersection of the SLCrel when walking on the treadmill in comparison with walking overground. Therefore, it is possible that both groups, PD and elderly healthy participants, benefit from similar mechanisms. However, PD participants could also use the sensory inputs to trigger intact circuits and by-pass the defective pallidocortical circuit. This extra-benefit in PD participants from the treadmill is supported by a recent study that found a more temporally organized and more regular gait pattern in the treadmill walking of PD participants compared with that of healthy participants (Warlop et al., 2018). Alternately, it is also plausible that walking on a treadmill demands more attentional resources than walking overground, allowing the patients to avoid an automatic gait control through basal ganglia - supplementary motor area in favor of an intact cerebellum - premotor area circuit.

The SL and Cad across the different self-selected speeds showed a linear relationship for each participant during overground walking. This linear relationship has been interpreted as an indicator of the integrity of high-level mechanisms by which gait control is simplified or ‘automated’ in steady state walking (Egerton et al., 2011). However, in the treadmill condition, two PD subjects and four control subjects had R^2 values less than R^2=0.80, displaying a non-linear relationship. In addition, R^2 values were significantly higher in the overground than in the treadmill condition for both groups. This could be

interpreted as a less automated control of gait walking on the treadmill, likely due to the imposed speed of the treadmill's belt. This finding is in line with that of a previous study, where constraining SL or Cad during overground walking resulted in an inconsistent SLCrel (Egerton et al., 2011).

The SLCrel modulation when walking on the treadmill could illuminate the benefits of treadmill training programs in PD patients. Improvements in balance, UPDRS scores, SL, Cad or walking speed have been reported after different treadmill training programs (Herman et al., 2007; Miyai et al., 2000; Pohl et al., 2003; Toole et al., 2005). However, these improvements may have been resulted from the general benefit of exercise rather than from a specific improvement in the motor symptomology of this pathology. The analysis of the SLCrel may be useful to differentiate the specific from the general benefits of gait rehabilitation interventions. To date, the effects of treadmill training programs on the SLCrel in PD subjects have not been evaluated. Therefore, it remains unexplored/unknown whether treadmill training influences the gait pathophysiology of PD subjects.

It should be noted that there were not any differences between groups in SL and Cad at the five speeds evaluated. However, the analysis of the relationship between both parameters clearly showed a lower intercept for the PD group than for the control group, in line with the findings of previous studies (Morris et al., 1994a, b; Egerton et al., 2012; Danoudis et al., 2014). Therefore, in order to obtain a more detailed analysis of the gait pattern, this result stresses the need to evaluate the SLCrel rather than simply evaluating both parameters, SL and Cad separately.

We should point out that, for the main experiment, the participants walked on the treadmill holding the handrails. Since the use of handrails can improve gait stability, it may be argued that this should account for the increase in the intersection of the SLCrel when walking on the treadmill. However, this claim is unlikely since several studies have shown that PD patients actually reduce their SL when walking with a wheeled walker (Frenkel-Toledo et al., 2005; Cubo, Moore, Leurgans, & Goetz, 2003) and even when they use a treadmill simulator without a belt that could move on a walkway in a constant speed (Bello et al., 2010). Moreover, our complementary experiment showed that walking on the treadmill without holding the handrails is not a suitable condition to control for the effects of the handrail in the SLCrel. Under this condition, 11 of the 12

participants had lower intersections of the SLCrel than when walking overground. Similar results have been found in our lab for young subjects (data not published).

We must point out that the participants with PD in our study demonstrated only minor hypokinesia since the SL values were similar to the control subjects. It would be of importance to explore whether the effect of treadmill walking on the SLCrel is more marked in advance compared with moderate subjects with PD.

In conclusion, the current study shows that the intercept of the SLCrel increases when walking on the treadmill in comparison with walking overground in both PD and control participants. Our results confirm the potential therapeutic effects of treadmill training for the gait rehabilitation in PD and suggest that the mechanisms underlying the treadmill effects are preserved in PD subjects.

CHAPTER V.
DISCUSSION

PD gait is very complex and difficult to explore, therefore it needs to be thoroughly studied to be able to improve treatment strategies. Gait measurements help to evaluate the effectiveness of PD interventions. The two studies of this doctoral thesis help to understand better the PD gait and show how to measure and improve gait in PD.

The main goal of the first study was to measure the reliability of the SLCrel in PD subjects, since little known about this relationship in PD and has not yet been investigated in this population. It is important to analyze the SLCrel, as it shows gait changes in PD. By measuring the reliability of this relationship helps to understand better whether the SLCrel is a reliable measure to explore gait changes in PD. The results of our first study show that, by using five different self-selected gait speed conditions, the linear regression between SL and Cad is reproducible after a period of three months. Our findings suggest that this protocol, previously used in several studies (Egerton et al., 2012; Danoudis & Iansek, 2014), can be applied to explore changes in the SLCrel gait in PD subjects.

On account of the results of the first study, the goal of the second study was to measure the SLCrel in PD patients walking on treadmill and overground, as well as compare with age-matched controls. The results of our second study showed that, the SLCrel intercept increased in PD patients when walking on the treadmill in comparison with walking overground, which supports the idea that, using treadmill helps to normalize the SLCrel in PD patients. Moreover, our results are able to confirm the specific effect of treadmill in PD gait rehabilitation.

The importance of the SLCrel

Gait speed has been considered many time as a clinical vital sign (Studenski et al., 2003). Decrease in speed means a decline in health for individuals with PD. In addition, as the regulation of SL is a key determination of gait hypokinesia, it is important to analyze and understand how SL changes in PD patients to understand the problem of gait disorder since SL is related with loss of balance (Morris et al., 1994a). The study of Fernandez-Del-Olmo & Sanchez (2015) showed that PD subjects were able to normalize their SL according to their speed when they walked in a long corridor. In our two studies PD patients were also able to normalize their SL during speed changes. Previous studies showed that, PD patients have shorter SL and reduced walking speed (Morris et al., 1998), meanwhile this deficit could be compensated by increasing the Cad (Morris et al., 1994a;

Galna et al., 2013). Therefore, Cad is also essential aspect for gait speed (Egerton et al., 2011).

Nevertheless, only few studies analyzed the relationship between SL and Cad in PD patients (Danoudis & Iansek, 2014; Egerton et al., 2012; Morris et al., 1998) showing that, people with PD had slower gait during preferred speed than control subjects and it was caused by shorter SL. When patients walked faster they were significantly slower than controls and it was caused by smaller SL, meanwhile the Cad did not differ significantly (Morris et al., 1994a). Our studies showed that PD patients were able to modulate their speed, SL and Cad through the five self-selected speed conditions. Previous studies found similar values of the speed, SL and Cad for PD subjects of similar age and disease severity (Egerton et al., 2012; Danoudis & Iansek, 2014).

The SLCrel have been used to characterize gait (Egerton et al., 2012). When healthy adults increase or decrease their self-selected walking speed, they increase or decrease their SL and Cad in a relatively constant linear relationship (Egerton et al., 2012; Zijlstra et al., 1995). The study of Danoudis & Iansek (2014) investigated the SLCrel and compared the slope and intercept in PD patients and healthy controls, where gait was recorded at self-selected preferred, very slow, slow, fast and very fast speeds. SL was shorter in PD group compared to control in all speed conditions, meanwhile Cad did not differ between groups. In line with our first study Danoudis & Iansek (2014) showed that, there is a strong linear relationship between SL and Cad. Furthermore, our first study in agreement with the study of Morris et al. (1996) found that PD patients have smaller SL and higher Cad therefore, the intercept of the SLCrel is lower than in healthy subjects.

Understanding gait changes can provide ideal method to maximize effective disease management (Lord et al., 2013). Regarding to the results of our two studies, measuring the SLCrel is an useful tool to understand better the gait changes. It should be mentioned that, in our first study during the first session the overall gait speed was significantly slower than in the second session, however this changes in gait speed between sessions did not affect the SLCrel. This fact shows that, when after a physical therapy the gait speed improves, does not necessarily mean a change in the SLCrel, in other word, does not necessarily mean a change or improvement in gait, maybe it is just a result of a functional improvement from exercises. Thus, by measuring speed, Cad and SL

separately, may represent a successful intervention from a functional view. Nevertheless, when the SLCrel intercept increases, indicates that there is a specific therapeutic effect on gait in PD patients. The high reliability of the intercept is important, since this relationship shows whether the gait is affected by disease or not and thus may be a reliable measure to follow the progression of the disease. As well, we suggest that physical therapies in PD gait should focus on increasing the intercept of the SLCrel. Our first study recommend an 0.202 m increase in intercept, as a minimal important difference to detect changes after gait rehabilitation. To our knowledge, our first article is the first to measure the reliability of the SLCrel in people with PD.

The SLCrel on treadmill

Besides, measuring the SLCrel on treadmill could provide information about the utility of the treadmill device in PD rehabilitation. Improving the intercept of the SLCrel on treadmill may indicate that treadmill has a specific effect on gait rehabilitation. The results of our first study showed, that SLCrel may be a reliable tool to differentiate the specific from the general benefits of gait rehabilitation interventions in PD subjects. Thus, we decided to investigate - by measuring the SLCrel on treadmill -, if the use of treadmill in gait rehabilitation cause specific changes or just functional improvements and whether by using treadmill it is possible to increase the intercept of the SLCrel in PD patients.

As the use of treadmills in gait rehabilitation in PD patients are very popular and proved to improve gait performance (Herman et al., 2007; Bello et al., 2008, 2010; Miyai et al., 2000; Pohl et al., 2003), our second study results could extend previous findings and approve the usefulness of treadmill for gait rehabilitation in PD. Regarding to previous results, it could be suggested that the treadmill could help to normalize the SLCrel in PD subjects (Fernández-Del-Olmo, 2016). However, before our second study no study to date has examined the SLCrel in neither PD nor healthy subjects walking on a treadmill. Thus, it is unknown whether treadmill training influences the pathophysiology of PD gait.

In the second study, exploring the SLCrel, we found that, not just advanced PD patients can improve the SL on treadmill, moderate PD patients are also able to improve the SL when using the treadmill. During the overground session each participant had linear relationship between SL and Cad across all self-selected speed conditions, which means that gait is automated. However, during the treadmill condition few participants had non-linear relationship, that may show a less automated control of gait walking on the

treadmill, which is most probably due to the imposed speed of the treadmill's belt. These results are in agreement with a previous study, where constraining SL or Cad during overground walking resulted in an inconsistent SLCrel (Egerton et al., 2011).

Furthermore, the results of our second study showed that, the intercept of the SLCrel increased on the treadmill compared to overground session in PD. Which means that PD patients were able to make longer SL during treadmill walking. This finding supports the use of the treadmill to normalize the SLCrel in PD patients. Interestingly, this effect was also shown in the control group, suggesting that the mechanisms underlying the modulation of the SLCrel when walking on the treadmill are preserved in the PD participants. The SLCrel modulation on the treadmill could show the benefits of treadmill training programs in PD patients. As in the first study it was mentioned already, that after a training improvements in SL, Cad or walking speed may have been resulted from the general benefit of exercise rather than from specific improvement. Likewise, after different treadmill training programs the improvements in SL, Cad or speed, without an improvement in SLCrel, may also only show the general benefits from the treadmill rehabilitation, and not the specific therapeutic effect. Thus, the analysis of the SLCrel may be beneficial to differentiate the specific from the general benefits of gait rehabilitation programs. It should be noted that, in the second study people with PD had similar SL and Cad values at five speeds that control subjects. However, the analysis of SLCrel clearly showed a lower intercept for the PD group than for the control group, in line with the findings of previous studies (Morris et al., 1994 a,b; Egerton et al., 2012; Danoudis & Iansek, 2014). Therefore, to achieve a more complex view about the gait pattern the result of our second study stresses to measure the SLCrel rather than simply evaluating SL and Cad separately.

In the second study participants walked on the treadmill using the handrails. As the use of the handrails can cause more stable gait, it could be that the improvement of the SLCrel intercept is because of the handrails. Nevertheless, it is unlikely, because previous studies showed that PD patients reduced SL while walking with a wheeled walker (Frenkel-Toledo et al., 2005; Cubo et al., 2003) or even with a treadmill simulator (Bello et al., 2010). Moreover, our second study contains a complementary experiment, which showed that walking on the treadmill without holding the handrails is not a suitable condition to control the effects of the handrail in the SLCrel. Almost all the participants,

PD and control subjects, had lower intercept of the SLCrel on the treadmill when walking without holding the handrail than walking overground.

To conclude, according to our knowledge, our initial study is the first to evaluate the reliability of gait changes in patients with PD. In this study it has been showed that, the linear regression between SL and Cad is reproducible and does not decline after a period of three months. Thus, the SLCrel is a reliable measure to explore gait changes in PD patients and may be used to differentiate the specific from the general benefits of gait rehabilitation in PD subjects. SLCrel analysis should be implemented to observe gait changes in PD patients. Furthermore, our second study is the first to evaluate SLCrel in PD over treadmill and overground walking. The results of the second study confirm that by using treadmill it is possible to increase the SLCrel intercept, thus treadmill is able to improve gait in PD and has a specific effect for PD gait. Moreover, our second study suggests that the mechanisms underlying the treadmill effects are preserved in PD subjects.

Our both studies highlight the importance of SLCrel in PD gait measurements and recommend to utilize the SLCrel after gait rehabilitation to examine whether an intervention program has positive and specific effect on gait or just bring general benefits from exercise.

CHAPTER VI.

LIMITATIONS

Some limitations must be addressed, however the results of our studies are valid and relevant even with the following limitations.

- In the first study, PD participants were able to walk without assistance and thus, it is possible that the gait protocol used to evaluate the SLCrel may not be applied to patients with greater disease severity.

- Likewise in the first study, the reliability of the SLCrel has been evaluated across a period of three months. This period has been chosen since most of the physical therapy studies used similar periods of intervention. Future studies are warranted in order to examine the SLCrel evolution across the progression of the disease, nevertheless our study showed that the reliability of the SLCrel is valid after three months period.

- Another limitation of the first study is the non-inclusion of an age/sex matched control group in order to discern the expected change in healthy subjects and therefore, better understand the impact of the Parkinson's disease in the SLCrel.

- In the second study, participants with PD demonstrated only minor hypokinesia since the SL values were similar to the control subjects. Future studies needs to investigate whether advanced PD patients would have similar SLCrel results on treadmill.

CHAPTER VII.

CONCLUSIONS

- Stride length- cadence relationship in parkinsonian gait is a reliable measure across a period of three months.
- The intercept and slope values of the linear relationship between the gait parameters, remain unaffected even when changes in the gait speed are observed.
- The stride length- cadence relationship may be a useful tool to differentiate the specific from the general benefits of gait rehabilitation interventions in Parkinson's Disease subjects.
- The intercept of the stride length- cadence relationship increases when walking on the treadmill in comparison with walking overground in both Parkinson's Disease and control participants.
- Treadmill training has a potential therapeutic effects for the gait rehabilitation in Parkinson's Disease.
- The mechanisms underlying the treadmill effects are preserved in Parkinson's Disease subjects.

CHAPTER VIII.

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CHAPTER IX.

APPENDIX

8.1 RESUMEN

La enfermedad de Parkinson (EP) se considera el segundo trastorno neurodegenerativo más común (Twelves, Perkins, Uk, & Counsell, 2003). Las causas de la EP siguen siendo desconocidas y no se ha encontrado ninguna cura para la enfermedad (Morris, Iansek, Matyas y Summers, 1994b). La EP modula la función motora desde el habla hasta la marcha y los síntomas más comunes son la acinesia, la rigidez, el temblor y la inestabilidad postural (Hoehn y Yahr, 1967). Además, la EP es un trastorno crónico y progresivo que normalmente afecta a las personas mayores. Sin embargo, la EP se asocia con una pérdida de la independencia funcional (Schoenberg, 1987), y con un riesgo de caída mayor (Koller, Glatt, Vetere-Overfield, & Hassanein, 1989).

El nivel de gravedad de los signos motores asociados con la EP se puede medir utilizando la Escala de Clasificación de la Enfermedad de Parkinson Unificada Parte III (UPDRS-III) (Hughes, Daniel y Kilford, 1992) y la escala de Hoehn y Yahr (H&Y) (Hoehn y Yahr, 1967). La UPRDS es una escala de calificación compuesta por numerosas secciones que incluyen la cognición, el comportamiento, las actividades de la vida diaria y la evaluación motora. Mientras tanto, la escala H&Y describe el progreso de los síntomas de la EP.

El principal hallazgo patológico asociado con los déficits motores de la EP es la degeneración de las neuronas dopaminérgicas de la sustancia negra pars compacta (Halliday, Lees, y Stern, 2011). Las alteraciones de la marcha y las caídas son las principales y más significativos problemas motrices en la EP que conducen al deterioro de la calidad de vida de los pacientes y son una de las señas de identidad de los estadios avanzados de la EP (Ebersbach, Moreau, Gandor, Defebvre, & Devos, 2013). La marcha de los pacientes con EP se define por su lentitud, con una zancada y velocidad reducida, por el arrastre de los pies en cortos, la postura flexionada, la reducción de la oscilación del brazo y el problema de inicio de la marcha (Morris, Iansek, Matyas y Summers, 1996). Morris et al. (1994b, 1996) sugirieron que las manifestaciones bradicinéticas de la EP causan la reducción de la zancada y la velocidad de la marcha, que son la clave de los cambios de la marcha en la EP. La reducción de la longitud media de zancada es importante en las alteraciones de la marcha de la EP; además, la disminución de la capacidad para lograr un ritmo de marcha normal también es una característica importante de la marcha en la EP.

Varios estudios han investigado los cambios de la zancada, la velocidad de la marcha y los parámetros de cadencia en la EP; si bien, la relación de la longitud-cadencia de zancada (SLCrel) es menos conocida. La regulación de la zancada representa uno de los objetivos principales en las intervenciones de rehabilitación en sujetos con EP y estudios previos no han identificado los efectos de la intervención fisioterapéutica en la SLCrel. Lo más destacado de la SLCrel es que puede ayudar a detectar un efecto terapéutico específico de los programas de rehabilitación y optimizar la estrategia de trabajo.

La terapia física es la terapia no farmacológica más utilizada para la rehabilitación de la marcha en la EP. Hay estudios que apoyan que la fisioterapia mejora el rendimiento de tareas motoras funcionales, especialmente, en la marcha, la inestabilidad postural y la prevención de caídas. Es más, con el fin de activar vías alternativas en el cerebro que evite los circuitos de los ganglios basales defectuosos de los pacientes con la EP, el uso de señales externas (visuales, auditivas o propioceptivas) y estrategias cognitivas se consideran importantes en la rehabilitación de la EP. De este modo, la fisioterapia general, el estiramiento, el fortalecimiento muscular, el equilibrio, las señales aplicadas, la danza y las artes marciales (boxeo, tai-chi) mejoran la marcha y la calidad de vida de personas con la EP (Hackney et al., 2009; Li et al., 2012; Combs et al., 2013).

Además, se ha demostrado que el uso de la cinta rodante en la rehabilitación de pacientes con la EP mejora el rendimiento de la marcha. Entender los mecanismos subyacentes a estas mejoras permitirá una la eficacia de la terapia física más eficaz; sin embargo, aún no se ha confirmad si caminar en cinta rodante modifica la SLCrel en la EP.

Por lo tanto, pese a la literatura existente, algunas cuestiones de interés siguen sin resolverse:

1) ¿La SLCrel es una medida confiable para evaluar a sujetos con la EP?

2) ¿Tiene la cinta rodante efectos similares en pacientes con la EP y en sujetos controles sanos con una edad equivalente?

3) ¿La intersección de la SLCrel es menor en los pacientes con la EP que en sujetos sanos?

4) ¿Aumenta la intersección de la SLC en la cinta rodante en sujetos con EP?

Los dos estudios de esta tesis intentan responder a estas preguntas. La pregunta 1 será abordada en el primer estudio. Las preguntas 2, 3 y 4 se tratarán en el segundo estudio.

8.2 ESTUDIO I: CONFIABILIDAD TEST-RETEST DE LA RELACIÓN DE LA MARCHA DE LA CADENCIA-ZANCADA EN LA ENFERMEDADA DE PARKISNON

La hipótesis del presente estudio plantea que la SLCrel es una medida confiable en la marcha de Parkinson y su objetivo fue explorar y evaluar la confiabilidad de la SLCrel en pacientes con la EP en dos sesiones, separados entre sí por un período de tres meses.

Treinta y cinco sujetos con la EP participaron en dos sesiones, separados por un período de tres meses. Los parámetros de marcha cinemáticos se evaluaron utilizando un sistema de detección óptica y un software (v.1.11 OptoGait; Microgait, Italia). El pasillo donde se realizó la evaluación tenía una longitud de 9 m, disponiéndose el sistema Optogait en los 5m centrales. Se siguió el protocolo utilizado anteriormente en varios estudios (Egerton et al., 2012; Danoudis y Iansek, 2014).

En cada una de la sesiones, la velocidad de la marcha, la zancada y la cadencia se evaluaron en cinco diferentes condiciones de velocidad auto-seleccionadas: preferida, lenta, muy lenta, rápida y muy rápida. El análisis de regresión lineal se aplicó para explorar la SLCrel y para determinar la pendiente, la intersección y el coeficiente de determinación (R^2) para cada participante. La confiabilidad test-retest para la pendiente y la intersección se calculó utilizando el coeficiente de correlación intraclase (ICC), el intervalo de confianza (IC) del 95% y el error estándar de la media (SEM).

No se encontraron diferencias significativas en la pendiente e interseción entre las dos sesiones. La velocidad general fue significativamente más rápida en la segunda sesión en comparación con la primera ($F = 4.60$, $p = 0.03$). La SLCrel mostró una alta confiabilidad para ambas sesiones para la pendiente y la intersección, respectivamente (ver Tabla A.1).

	SLCrel T1 vs T2							
	Media (SD) T1	**Media (SD) T2**	**t**	**p**	**ICC**	**95% CI**	**SEM**	**MID**
Pendiente (pasos/min)	0.015±0.005	0.014±0.006	1,618	.115	.897	.804-.950	0.002	0.006
Intersección (m)	1.309±0.169	1.338±0.194	-1.661	.106	.908	.819-.953	0.073	0.202

Nota.SLCrel, relación entre longitud de zancada-cadencia; SD, desviación estándar; t, valor crítico; p, nivel de significación (muestras pareadas prueba t entre pruebas 1 y 2); ICC, coeficiente de correlación intraclase; IC, intervalo de confianza del 95%; SEM, media de error estándar; MID, mínima diferencia importante. La interseción fue calculada para una valor de cadencia de 100 pasos/min.

Tabla A. 1 *Fiabilidad de SLCrel*

El objetivo principal del estudio fue evaluar la confiabilidad de la SLCrel en sujetos con la EP. Nuestros resultados muestran que, utilizando cinco condiciones diferentes de velocidad de marcha auto-seleccionadas, la regresión lineal entre zancada y cadencia es reproducible y no disminuye después de un período de tres meses. Además, puede ser una herramienta útil para explorar la especificidad de las intervenciones de rehabilitación de la marcha en sujetos con EP. Nuestros hallazgos sugieren que el protocolo utilizado (Egerton et al., 2012; Danoudis y Iansek, 2014) se puede usar para explorar los cambios en la relación entre la longitud y la zancada en la marcha d en sujetos con la EP.

En el estudio realizado durante la primera sesión, la velocidad general de la marcha fue significativamente más lenta que en la segunda sesión; sin embargo, estos cambios en la velocidad de la marcha entre sesiones no afectaron a la SLCrel. Este hecho muestra que, después de una terapia física, si la velocidad de la marcha mejora, no significa necesariamente un cambio en la SLCrel; en otras palabras, no significa necesariamente un cambio o mejora de la marcha, sino que es solo el resultado de un mejora funcional a partir del ejercicio físico. Por lo tanto, medir velocidad, cadencia y zancada por separado, puede representar una intervención exitosa desde una perspectiva funcional. Sin embargo, cuando la intersección de la SLCrel aumenta, indica que existe un efecto terapéutico específico en la marcha en pacientes con la EP. Nuestros hallazgos sugieren

que un aumento del valor de la intersección de 0.202 m es la diferencia mínima importante para detectar un cambio que se puede atribuir a la intervención terapéutica.

El estudio actual muestra que la SLCrel en la marcha de sujetos con la EP es una medida confiable durante un período de tres meses. También se demuestra que los valores de intersección y pendiente, de la relación lineal entre los parámetros de la marcha, no se ven afectados incluso cuando se observan cambios en la velocidad de la marcha. Por lo tanto, la SLCrel, sobre una variedad de condiciones de velocidad auto-seleccionadas, puede ser una herramienta confiable para diferenciar los beneficios específicos de los generales de las intervenciones de rehabilitación de la marcha en sujetos con EP.

8.3 ESTUDIO II: CAMINAR EN UNA CINTA RODANTE MEJORA LA RELACIÓN DE LA LONGITUD Y LA CADENCIA-ZANCADA EN PERSONAS CON ENFERMEDAD DE PARKISON

Las hipótesis del presente estudio son la intersección de la SLCrel es menor en el grupo de sujetos con la EP que en los controles, y la intercepción del SLCrel aumenta en la cinta de correr en los sujetos de la EP. El objetivo del segundo estudio fue comparar el SLCrel en sujetos con EP que caminan en una cinta rodante en comparación con la superficie. Además, para evaluar si la máquina para correr tiene efectos similares en los grupos de EP y en controles sanos de la misma edad.

Quince sujetos de la EP y quince controles emparejados por edad caminaron sobre el suelo y en una cinta rodante a cinco velocidades diferentes auto-seleccionadas. La velocidad de la marcha, así como la longitud y la de cadencia de zancada se registraron en cada una de las velocidades auto-seleccionada. Los parámetros cinemáticos de la marcha se evaluaron utilizando un sistema de detección óptica y un software (v.1.11 OptoGait; Microgait, Italia). El pasillo empleado tenía una longitud de 9 metros, con el sistema Optogait situados en los 5 m centrales del mismo. Se siguió el protocolo utilizado anteriormente en varios estudios (Egerton et al., 2012; Danoudis y Iansek, 2014). Se realizó un análisis de regresión lineal para explorar la SLCrel y para determinar la pendiente y la intersección de cada participante.

Los resultados mostraron que los sujetos con la EP tenían una intersección menor que los sujetos controles tanto cuando caminaban en el pasillo como en la cinta rodante ($F = 8.51$, $p = 0.007$) (Figura A). Al caminar sobre la cinta rodante se obtuvo un aumento significativo en la intersección frente a caminar en el pasillo tanto en los grupos de EP como en los de control ($F = 12.17$, $p = 0.002$) (Tabla B. 1). No hubo diferencias significativas en la pendiente de la SLCrel (Tabla B. 1).

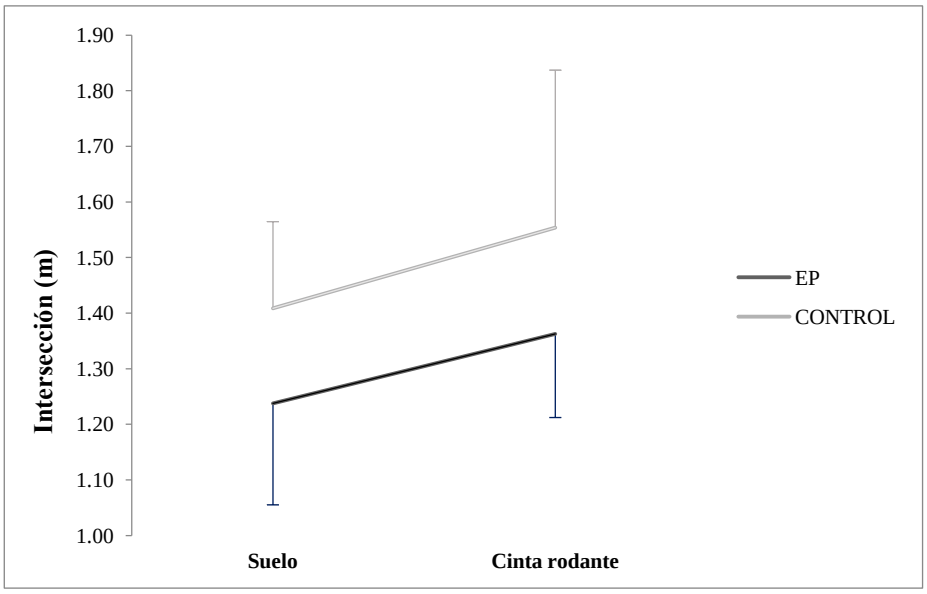

Figura A.1 Intersección para la EP y los sujetos de control en condiciones de suelo y cinta rodante.

Tabla B.1 *Valores SLCrel para suelo y cinta rodante en PD y sujetos de control*

	EP (n=15)		**CONTROL (n=15)**	
	Suelo	**Cinta rodante**	**Suelo**	**Cinta rodante**
	Media (SD)	**Media (SD)**	**Media (SD)**	**Media (SD)**
SLCrel pendiente (pasos/min)	0.015 (0.005)	0.014 (0.008)	0.014 (0.004)	0.013 (0.008)
SLCrel intersección (m)	1.24(0.182)	1.36 (0.150)	1.41 (0.156)	1.55 (0.284)
SLCrel R^2	0.96(0.037)	0.89 (0.254)	0.96 (0.052)	0.87 (0.122)

Nota. EP, sujetos con enfermedad de Parkinson; SLCrel, relación zancada longitud-cadencia; SD; desviación estándar

El objetivo principal de este estudio fue evaluar el efecto de la cinta rodante sobre la la SLCrel en la marcha de pacientes con la EP. Nuestros resultados mostraron un aumento en la intersección del SLCrel en los participantes con la EP al caminar en la cinta rodante en comparación con caminar sobre un pasillo. Este hallazgo apoya el uso de la

cinta rodante para normalizar la SLCrel en pacientes con EP. Curiosamente, este efecto también se mostró en el grupo control, lo que sugiere que los mecanismos subyacentes a la modulación de la SLCrel al caminar en la cinta rodante se conservan en los pacientes con la EP.

Este estudio es el primero en evaluar la SLCrel al caminar sobre el suelo y en una cinta rodante en pacientes con la EP. En un estudio previo de nuestro grupo (Bello et al., 2008), se halló que los sujetos en un estadio avanzado de la EP disminuyeron significativamente su cadencia y aumentaron la longitud de sus pasos durante la marcha en cinta rodante, mientras que los sujetos control y los pacientes en un estadio moderado de la enfermedad no cambiaron significativamente su zancada o cadencia. Sin embargo, en ese estudio solo se evaluó la velocidad preferida auto-seleccionada. En el estudio actual, se empleó un análisis de regresión lineal para explorar la relación entre zancada y cadencia. Nuestros resultados mostraron que los participantes es un estadio de la EP moderado también pueden aumentar la zancada al usar la cinta rodante.

La modulación de la SLCrel al caminar sobre cinta de correr podría dar a entederlos beneficios de los programas de entrenamiento en este dispositivo en pacientes con EP. Las mejoras en el equilibrio, la puntuación de UPDRS, la zancada, la cadencia o la velocidad de caminar se han reportado después de diferentes programas de entrenamiento en cintas rodantes (Herman et al., 2007; Miyai et al., 2000; Toole et al., 2005). Sin embargo, estas mejoras pueden haber sido el resultado del beneficio general del ejercicio en vez de ser el resultado de una mejora específica en la sintomatología motora de esta patología. El análisis de la SLCrel puede ser útil para diferenciar los beneficios específicos de los generales en las intervenciones de rehabilitación de la marcha. Hasta la fecha, los efectos de los programas de entrenamiento en cinta rodante determinados a través de la SLCrel en sujetos con EP no han sido evaluados. Por lo tanto, aún no se ha explorado, ni se sabe si el entrenamiento en cinta rodante influye en la fisiopatología de la marcha de los sujetos con EP.

Cabe señalar que no se encontraron diferencias, entre los dos grupos estudiados, ni en la longitud de zancada y ni en la cadencia a las cinco velocidades evaluadas. Sin embargo, el análisis de la relación entre ambos parámetros mostró claramente una intersección menor en el grupo de EP que en el grupo control, en línea con los hallazgos de estudios anteriores (Morris et al., 1994a,b; Egerton et al., 2012; Danoudis et al., 2014). Por lo

tanto, para obtener un análisis más detallado del patrón de marcha, este resultado hace hincapié en la necesidad de evaluar la SLCrel en lugar de simplemente evaluar ambos parámetros, zancada y cadencia por separado.

El presente estudio muestra que la intersección de la SLCrel aumenta cuando se camina en la cinta de correr en comparación con caminar sobre el suelo tanto en sujetos con la EP como en controles. Nuestros resultados confirman los efectos terapéuticos potenciales del entrenamiento con cinta rodante para la rehabilitación de la marcha en la EP y sugieren que los mecanismos subyacentes a los efectos de la cinta rodante se conservan en los sujetos con EP.

8.4 CONCLUSIONES

1. La relación entre la longitud del paso y la cadencia en la marcha parkinsoniana es una medida confiable durante un período de tres meses.

2. Los valores de intersección y pendiente, de la relación lineal entre los parámetros de la marcha, no se ven afectados incluso cuando se observan cambios en la velocidad de la marcha.

3. La relación entre la longitud de zancada y la cadencia puede ser una herramienta útil para diferenciar los beneficios específicos de las intervenciones de rehabilitación de la marcha en sujetos con la enfermedad de Parkinson.

4. La intersección de la relación entre la longitud de la zancada y la cadencia aumenta cuando se camina en la cinta rodante en comparación con caminar sobre el suelo de un pasillo tanto en sujetos con la enfermedad de Parkinson como en sujetos controles sanos.

5. El entrenamiento en cinta rodante tiene efectos terapéuticos potenciales para la rehabilitación de la marcha en la enfermedad de Parkinson.

6. Los mecanismos subyacentes a los efectos de la cinta rodante se conservan en los sujetos con enfermedad de Parkinson.

8.5 LIMITACIONES

En nuestros se deben abordar algunas limitaciones; sin embargo, los resultados de son válidos y relevantes incluso con las siguientes consideraciones.

En el primer estudio, los participantes en la EP pudieron caminar sin ayuda y, por lo tanto, es posible que el protocolo de marcha utilizado para evaluar la SLCrel no sea aplicable a pacientes diagnosticados en un estadio más avanzado de la de la enfermedad.

Del mismo modo, en el primer estudio, la confiabilidad de la SLCrel se evaluó durante un período de tres meses. Este período ha sido elegido ya que la mayoría de los estudios de fisioterapia utilizaron períodos de intervención similares. Se justifica la realización de estudios futuros para examinar la evolución de la SLCrel a lo largo de la progresión de la enfermedad; si bien, nuestro estudio demostró que la fiabilidad de SLCrel es válida después al menos durante un período de tres meses.

Otra limitación del primer estudio es la no inclusión de un grupo control emparejado por edad / sexo para discernir el cambio esperado en sujetos sanos y, por lo tanto, comprender mejor el impacto de la enfermedad de Parkinson en la SLCrel.

En el segundo estudio, los participantes con la EP demostraron solo una hipocinesia menor, ya que los valores de longitud de zancada eran similares a los sujetos control. Estudios futuros deberían investigar si los pacientes con un grado avanzado de la EP tendrían resultados similares de la SLCrel en cinta rodante.