Summary of findings

First section: methodological aspects of the assessment of markers of Parkinson's disease

Quantitative assessment of gait in patients with PD is an important step in addressing motor symptoms and improving clinical management. In this clinical context, the assessment of short episodes of gait with BFS is easily implemented. Moreover, spatio-temporal and stability gait features extracted from BFS may add value in the study of pathological gait quality and may reflect markers of PD.

A relevant challenge in the assessment of spatio-temporal and stability gait parameters using BFS is the accurate and reliable detection of steps. Although previous studies have addressed this technical issue, most of the proposed algorithms were not adequately applicable to short episodes of gait and/or incorrectly identified events. Thus, in chapter 2, a novel accelerometry-based algorithm for the detection of step durations over short episodes of gait in healthy elderly was developed and validated. The algorithm was separately applied to low-back and heel accelerometry.

The accuracy of the algorithm in step/stride duration detection, respectively, was tested by comparison of the outputs of these two methods and the outputs from step/stride duration detection using an optoelectronic tracking system. The proposed algorithm successfully detected in each case all the steps/strides, without false positives and without false negatives. Absolute average errors were lower than 5% of step duration, which was considered clinically acceptable and within the range of lowest errors reported in the literature.

It must be noted that the proposed algorithm detects the start and end of step cycles based on a template-matching method, which requires the selection of a specific template (obtained as an average of all step cycles from an individual gait trial). For each signal, the start and end of the template is differently defined. Thus, the method identifies step cycles that slightly vary between subjects regarding the starting and ending point within the cycle. Nevertheless, across subjects, the starting points of the
identified cycles approximately correspond to heel-strike events and the periodicity of step/stride cycles can be obtained with sufficient accuracy. An accurate segmentation of gait episodes in step cycles is important to secure reliable identification of step-to-step gait information.

The template-matching nature of the algorithm, permitted to separately apply the same method to two different accelerometry measurements, i.e., at the low-back and heels. As both were successful, our results suggest a large diversity of potential applications of the method.

Overall, we can conclude that the algorithm detected step/stride cycles with clinically acceptable accuracy, providing opportunities to extract a range of gait parameters from short episodes of gait, as performed in the following chapters.

Chapter 3

Using the algorithm developed in chapter 2, the extraction of a range of gait features (spatio-temporal features, root-mean-squared values of accelerometry and angular velocity signals) from short episodes of gait was explored in chapter 3. Considering that healthy older adults change their walking strategy as a function of the walking distance and short gait assessments are relevant in a clinical context, in this study, straight gait trials of only 5 meters length were assessed with a single BFS placed on the lower back in 28 patients at early-to-moderate stage of idiopathic PD and in 14 age-matched healthy controls. Differences between groups in step-by-step kinematic features extracted from the BFS were evaluated to understand gait impairments in the PD group. Additionally, a discriminant model correctly classified a total of 89.5% participants with four kinematic parameters, presenting a sensitivity of 95.8% and a specificity of 78.6%. The results indicate that the applied method permitted to reasonably recognize idiopathic PD-associated gait from 5-m walking assessments.

Particularly, features related to gait initiation and gait deceleration were shown altered in patients with PD, and these were even more pronounced when studied relative to the individual average step performance. This indicates that the segmentation in step cycles of short episodes of gait and the extraction of features within these phases, additionally to the extraction of mean features across steps, permitted the identification of markers of PD. In the final statistical model, half of the predictors was based on RMS values, which indicates that fluctuations of acceleration and angular velocity signals are not only appropriate to assess gait initiation and gait deceleration in PD, but also, the assessment of these features from short episodes of gait are appropriate for the recognition of idiopathic PD-associated gait.
Altogether, the results from chapters 2 and 3 motivated further investigation on the clinical utility for PD of short episodes of gait assessment with a single BFS. Particularly, addressing the quantitative assessment of 5-m walking distances with this novel method may contribute to the detection of PD gait impairments in a clinical setting and the characterization of markers of the disease. Motivated by these findings, more advanced analyses, based on gait features assessed from slightly longer and more challenging protocols for patients with PD (circular gait), were studied in the next chapters to study the evolution of PD over time.

**Second section: progression and preclinical markers of Parkinson’s disease**

Considering that the pathological strategies involved in turning are independent from linear walking mechanisms (assessed in chapter 3) and given the higher susceptibility of neural processes of turning to functional impairment in PD,52 we performed assessments of circular gait in chapters 4, 5 and 6, with the aim to identify potential trait and progression markers of PD.

**Chapter 4**

Given the current need for well-defined markers of progression in PD79, to support the design effective symptomatic treatments as well as putative disease modifying agents,276 in chapter 4 we assessed gait features as indicators of progression in different stages of PD (25 early and 27 middle stages), by comparing development over time of these features with 22 age-matched control participants.

In a 5 years follow-up longitudinal study, we observed, in comparison to control participants, progressive lowering of gait speed in early stages of PD, reflecting the development of hypokinetic patterns. In parallel, we identified a faster increase of cadence, which is considered a typical PD compensatory mechanism to pathological hypokinetic movements.205-207 Moreover, faster reduction of harmonic ratios indicated a progressive decline of the regulation of gait rhythmicity,194 a motor deficit present not only at early stages of PD post-diagnosis, but according to previous literature and to the results of chapter 6, also possibly present in preclinical stages of PD.173, 174 Middle stages of PD presented a progressive worsening of gait consistency, as reflected in a faster decline of stride time variability and stride regularity features relative to control
participants. These findings may have been enhanced by the performance of circular walking, which challenges the whole-body coordination and the dynamic stability control. However, we did not directly compare to straight line gait.

Addressing the study of progression in PD is inevitably affected by the heterogeneous profile of the disease, not only in symptom severity, progression rate and clinical profile, but also in advancement of the disease and the patient’s age at the time of the diagnosis and the stage of the disease. Nevertheless, despite all these challenges, it is remarkable that we obtained such consistent markers of progression in PD for both studied stages: early and middle stages of PD. After external validation of their clinical relevance, these progression markers might be used to determine intervention efficacy.

Chapter 5

Given the loss of automaticity in patients with PD challenges the control of gait by limiting the availability of cognitive resources in PD to perform a dual task while walking. Motivated by the results of chapter 4, we therefore expected to obtain a larger number of progression markers in PD when an additional task would be added to the circular gait task. Therefore, we assessed circular gait in this chapter under dual-tasking conditions: (1) circular walking while checking boxes on a paper sheet as fast as possible and (2) circular walking while performing subtraction of 7 as fast as possible. In addition, we aimed to study the added value of dual-tasking assessment over single (circular) walking task assessment in the study of PD progression. The study population was the same as in Chapter 4.

In contrast to our hypothesis, fewer gait features from dual-task assessments were identified as markers of progression in PD when compared to the single circular walking task. Moreover, despite some baseline group differences in dual-task interference between PD groups and healthy controls, we did not find clear evidence of worsening of dual-task interference in patients with PD. Thus, we concluded that dual-tasking did not provide added value in the study of PD progression from circular gait assessments over a span of 5 years. This indicates that while single-task walking may be sensitive enough to the progression of PD, dual-tasking may introduce additional (error) variance to the data and may represent complex interactions of cognitive and motor abilities. Thus, the burden imposed on patients and clinicians by assessing dual-tasking can be avoided when targeting the study of PD progression. However, the results reinforced the validity of some of the gait features already identified as progression markers of the disease in a single-task circular walking condition.
The identification of prodromal markers of PD might lead to a better characterization of the disease phases at which potentially salvageable dopaminergic neurons could benefit from restorative and neuroprotective therapies. Thus, considering the potential of gait features extracted from circular gait assessments as progression markers of PD post-diagnosis (chapters 4 and 5), we analysed, in chapter 6, the sensitivity and specificity of these markers to prodromal symptoms of the disease, particularly studying their association with the time to getting diagnosed with PD. We prospectively compared circular gait features between 16 subjects that were diagnosed with PD within 9 years of follow-up, to a group of 80 control participants that were not diagnosed with PD within follow-up.

We found associations between the time from baseline measurement to diagnosis of PD and eleven gait features obtained from single and dual-tasking protocols, mainly from the latter conditions. These associations could reflect prodromal motor symptoms of PD, underscoring their potential as early markers of the disease. The majority of significant associations concerned harmonic ratios, which had also been identified as markers of progression in early stages of PD post-diagnosis (chapters 4 and 5). Although dual-tasking might have not added value to the study of progression in PD (chapter 5), in this chapter, the assessment of dual-tasking permitted to identify more potential indicators of prodromal symptoms of PD than the single circular walking task.

The sensitivity and specificity of the proposed gait features were too low to reliably identify prodromal PD in individual patients, possibly due to limitations of the available data set, with limited data on gait patterns close to time of diagnosis, the intra- and inter-individual variability of subtle symptoms and onset of manifestation of PD symptoms and sub-symptoms and the latent presence of compensatory mechanisms which could have masked prodromal motor deficits of PD. In spite of these challenges and the long duration between baseline measurements and diagnosis, we did identify significant associations of gait features to the hazard of being diagnosed with PD.

In this second section of the thesis, we obtained quantitative indicators of motor symptoms development in PD: pre and post-diagnosis. All in all, the results from chapters 4, 5 and 6 support the quantitative assessment of prodromal and progression motor symptoms in PD through circular gait analysis with a low-back-mounted BFS.