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To Ana Lúcia Silva de Lima
(in memorium)
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Quantifying Parkinson’s disease: the use of technology for objective assessment of motor symptoms

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ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op dinsdag 26 maart 2019
om 16.30 uur precies

door

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Quantifying Parkinson’s disease:
the use of technology for objective assessment
of motor symptoms

Doctoral Thesis
to obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus prof. dr. J.H.J.M. van Krieken,
according to the decision of the Council of Deans
to be defended in public on Tuesday, March 26, 2019 at 16.30 hours

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# TABLE OF CONTENTS

1. General introduction and outline of the thesis ........................................ 11

Part I. Feasibility of large-scale deployment of wearable sensors in large Parkinson’s disease cohorts

2. Large-scale wearable sensor deployment in Parkinson’s patients: the Parkinson@Home study protocol  
   *JMIR Res Protoc. 2016;5(3):e172* .......................................................... 31

3. Feasibility of large-scale deployment of multiple wearable sensors in Parkinson’s disease  

Part II. Applicability of objective measurements for answering clinical and research-relevant questions: wearable sensors for quantifying gait and falls

4. Freezing of gait and fall detection in Parkinson’s disease using wearable sensors: a systematic review  
   *J Neurol. 2017;264(8):1642-1654* .......................................................... 83

5. Home-based monitoring of falls using wearable sensors in Parkinson’s disease  
   *Submitted* ......................................................................................... 113

6. Impact of motor fluctuations on real-life gait in Parkinson’s patients  

7. Summary .................................................................................................. 142
   English ..................................................................................................... 145
   Nederlands ............................................................................................... 151
   Português ............................................................................................... 159

8. General discussion .................................................................................... 167

## APPENDICES

List of publications ..................................................................................... 189
PhD Portfolio ............................................................................................... 191
Curriculum Vitae ........................................................................................ 193
Thank you word ......................................................................................... 195
Dissertations of the disorders of movement research group .................. 203
Donders Graduate School for Cognitive Neuroscience .......................... 209
Chapter 1

General Introduction and outline of the thesis
GENERAL INTRODUCTION

Optimal clinical management of Parkinson’s disease (PD) requires regular and careful evaluation of a long list of symptoms and signs. Medical decisions are based on periodic in-clinic evaluations, but such “snapshot” evaluations cannot capture the actual impact of the disease on the patient’s functioning in their own environment. This is especially true for patients with PD who perform paradoxically well during in-clinic exams. Therefore, treatments cannot be tailored to the actual patient in such conditions.

Lately, thanks to advances in technology, there has been a growing interest in applying objective assessments to quantify PD-related symptoms and signs. The use of objective assessments, for example, those extracted from wearable sensors, may provide clinicians with a longitudinal, detailed, and accurate overview of PD-related symptoms as they present over time in daily life in a typical home-based setting. However, the feasibility and reliability of such approaches in large populations followed for long periods has yet to be determined. This thesis addresses the feasibility of objective measurements for quantifying motor symptoms in large PD populations. In the upcoming sections of this chapter, I provide a brief overview of PD clinical presentation and clinical management. Then, by using wearable sensors as a prime example, I elaborate on the use of objective measurements for quantifying the motor symptoms of PD. I end this chapter with an outline of the general aims of this thesis.

Parkinson’s disease

PD is a multifaceted disorder whose aetiology appears to involve a complex interplay between multiple genetic and environmental factors [1]. James Parkinson first described it 200 years ago as “The Shaking Palsy” [2]. After Alzheimer’s, PD is the most common neurodegenerative disease [3]. The prevalence increases with age, affecting 1% of individuals older than 60 years, and affecting more men than women (male-to-female ratio 3:2) [4, 5].

Clinically, PD is characterised by the appearance of a wide range of motor and non-motor symptoms (Box 1.1.) that result from progressive pathologic changes in the brain. It is estimated that 31% of the neurons in the substantia nigra have already been lost by the time of diagnosis, when the characteristic bradykinesia, 4-6 Hz resting tremor, and rigidity appear [6, 7].
Box 1.1. | Motor and non-motor symptoms of Parkinson’s disease

Motor symptoms*

- **Bradykinesia**
  
  Slowness of initiating voluntary movement and sustaining repetitive movement with progressive reduction in speed and amplitude

- **Resting tremor**
  
  Involuntary rhythmic oscillatory movement (4-6 Hz) of a body part

- **Rigidity**
  
  Increased resistance to passive displacement of a body part

- **Postural instability**
  
  Poor balance, unsteadiness, and falls

- **Gait disturbances**
  
  Difficulties in rhythm control, gait asymmetry, diminished step length, freezing of gait

Non-motor symptoms

- **Cognitive problems:**
  - Problems with decision-making
  - Impaired planning and goal-directed behaviour
  - Dementia

- **Psychiatric and behavioural complications:**
  - Hallucinations
  - Depression
  - Anxiety
  - Impulsive control disorders
  - Compulsive behaviours
  - Apathy

- **Sleep disturbances:**
  - Problems with sleep initiation and maintenance
  - REM sleep behaviour disorder
  - Excessive daytime sleepiness
  - Restless leg syndrome
  - Difficulties turning in bed

- **Autonomic dysfunction:**
  - Orthostatic hypotension
  - Constipation
  - Urinary dysfunction
  - Sexual dysfunction
  - Excessive drooling

*In pink: diagnosed criteria for Parkinson’s disease

Braak and colleagues studied how the neuropathological alterations progress during the course of the disease. Their work resulted in a six-stage classification scheme that emphasises the pathological alterations starting at the lower brainstem and then ascending caudo-rostrally through susceptible regions, ultimately reaching the cerebral cortex [8, 9]. Although this work was helpful for understanding how pathological changes occur in PD, the classification does not fully correlate with the presentation, severity, or
progression of the various symptoms [10, 11]. In fact, patients with PD present a large diversity of symptoms that can progress at very variable rates and that can also present in a variable following order across patients. In clinical practice, this variation has been clustered, and there are now three major accepted PD subtypes: tremor-dominant, akinetic-rigid, and mixed type [12]. Among them, the tremor-dominant phenotype is considered to be a more benign phenotype, with less disability and a slower progression rate [13].

Even though three motor symptoms are the hallmarks of the disease [14], many more motor and non-motor symptoms exist. These include freezing of gait, falls, executive dysfunctions, memory disturbances, constipation, depression, reduced ability to smell, and REM sleep behaviour disorders. Interestingly, some of these symptoms can present years before the diagnosis [12].

Treatment of PD is based largely on pharmacologic interventions [15]. After the discovery of levodopa, a precursor of dopamine that is capable of crossing the brain barrier, pharmacological interventions became the first-line treatment for PD [16]. Levodopa-based medication aims to regain the balance of dopaminergic levels, which is lost due to the death of dopaminergic neurons. Though it is effective, long-term levodopa usage is related to motor and non-motor fluctuations and development of dyskinesias [17]. Many patients are ultimately treated with a combination of levodopa and other drugs to combat this side effect. This includes dopamine agonist [18], Monoamine oxidase blockers and occasionally acetylcholinergics [19]. In advanced disease stages, when the response fluctuations to the oral treatment are progressively more difficult to control, neurosurgical interventions such as deep brain stimulation (DBS) or a continuous duodenal infusion of liquid levodopa can be used to treat adequately selected patients.

In addition to pharmacologic treatment, non-pharmacologic interventions play a crucial role in the clinical management of PD [20]. A growing evidence of the efficacy of physiotherapy [21-23], occupational therapy [20], speech–language therapy [24], and cognitive training [25, 26] for PD clinical management has fuelled the acceptability of those non-pharmacologic interventions. These interventions mainly aim to combat symptoms that do not respond well to dopaminergic drugs, such as mild cognitive impairment, depression, impaired balance, and falls. Physiotherapy is a good example of the efficacy of non-pharmacologic interventions for patients with PD. Such interventions improve activities of daily living by diminishing the burden of motor-related symptoms and preventing inactivity, which itself can negatively influence PD functioning [22, 27]. Non-pharmacologic interventions are important in helping patients with PD deal with the inevitable changes in activities of daily living [22].
The diagnosis of PD is based on clinical judgement and a set of predefined criteria (Box 1.1) [14, 28]. Clinical judgement is used not only for diagnosing, but also for assessing the severity of the symptoms, monitoring disease progression, and evaluating the efficacy of therapeutic interventions. The Movement Disorders Society provides the gold standard scale for evaluating PD-related symptoms and disease progression: The Movement Disorders Society – Unified Parkinson’s Disease Rating Scale [29]. This scale, comprising four parts, is used to assess the intensity and burden of motor and non-motor symptoms on an ordinal scale. Many other scales are also used in clinical care to assess other symptoms such as cognitive impairment [30], autonomic dysfunction [31], freezing of gait [32], falls [33], impact of motor fluctuations, and dyskinesia [34].

Two main limitations are associated with using standardised clinical assessments for clinical decision-making in PD care [35-37]. First, most scales show high inter-rater variability. This variability is partially explained by the ordinal nature of the scales, which makes it difficult to capture the non-linear decline of PD. Second, symptom assessment is based solely on a standardised clinical assessment during a clinical consultation, which typically lasts 10 to 20 minutes. This is a challenging, and perhaps biased, approach to evaluating such a complex and highly variable disease as PD. In general, such assessments remain a “snapshot” of the patient’s normal behaviour in daily life. Consequently, debilitating symptoms such as freezing of gait and falls often do not present well – if at all – during these clinical consultations. Attempts to address this limitation have been made, for example, by asking patients to maintain diaries reporting the presence and intensity of symptoms. However, the compliance and reliability of these diaries is questionable [38], especially for those presenting with cognitive impairments. Therefore, the challenge is to design a detailed, objective, and reliable home-based assessment that generates knowledge about real-life functioning and that can improve care for patients with PD.

**Technology for objective assessments in Parkinson’s disease**

Technologies for capturing health and disease-related information is a growing field, and it presents a number of promising applications (Figure 1.1.) [39]. This is also true of high-end, research-grade technologies – nowadays devices on the consumer market, such as smartphones, activity trackers, and smartwatches have embedded sensors that can capture relevant data. As does The Internet of Things (a digital communication infrastructure that enables devices to connect) [40], technology is showing tremendous potential to shape our understanding of society, business, and health [41]. Technology can support and improve various health-related strategies by collecting, analysing, and presenting large amounts of information [42, 43]. In general, wearable sensors contain one or more sensors embedded in small devices. Accelerometers and gyroscopes are often embedded in these devices; they enable data collection of body acceleration and rate of rotation [44]. Wearable sensors are generally worn either attached to the body or close to it (e.g. smartphones and smart glasses).
Parkinson’s disease is a prime example of technology being integrated in medical care (Figure 1.1.). Wearable sensors can continuously and very frequently (i.e. high frequency) collect reliable and fine-grained health-related data that would otherwise be missed [42]. This fine-grained information may be helpful in capturing the large variation between patients with PD and, perhaps more importantly, between and across days for the same patient [42, 45-49].

In PD care, wearable sensors collect data for two general scenarios: in standardised clinical settings and in a free-living environment (Box 1.2.). In the first scenario, wearable sensors are integrated into established standardised tests, such as the Timed Up and Go test [74, 75] or the motor examination of the MDS-UPDRS [76]. The main goal here is to collect relevant information that the ‘naked eye’ of an assessor might miss. Overall, under standardised conditions, wearable sensors can accurately detect or monitor PD-specific motor symptoms such as tremor, bradykinesia, and dyskinesia (Box 1.2.). Compared with gold standard assessments such as the MDS-UPDRS, wearable sensors show a moderate to high validity in symptom detection [42, 46]. Additionally, when they are used to distinguish groups, for instance PD versus non-PD [56, 77], or PD fallers from non-fallers [78, 79], the wearable sensors demonstrated excellent specificity and sensitivity: between 96% and 100%. In the second scenario, because wearable sensors can be deployed for long periods, they may be useful for collecting large amounts of information relating to patient behaviour and/or symptoms over time [42, 49]. This long-term evaluation takes places outside research laboratories and clinics in a free-living environment. This naturalistic approach has the great advantage of revealing information about overall daily functioning [80, 81], which cannot be collected with standardised assessments [44, 49]. Wearable sensors can collect data outside the clinic; such data are not biased by the improved performance commonly seen when patients perform standardised tests. Prime examples of wearable sensors in free-living environments can capture physical activity patterns [82-84] or medication intake [85, 86] (for more examples, please see Box 1.2.).

Wearable sensors are also a promising approach for aiding self-management among patients with PD [86, 130]. Sensors offer a basis for understanding the therapeutic efficacy of different interventions by offering a longitudinal overview of symptoms in context with activities of daily living and medication intake. Continuous feedback about daily life patterns, combined with gamification to improve compliance with using the new technology [131] may also positively influence behaviour and help patients with PD become more active [132, 133]. Further, symptom tracking, and medication reports can empower patients. Participants who actively collect information about their own health can make better informed decisions about health and disease management. Longitudinal monitoring with wearable sensors may improve decision-making in PD care by offering clinicians a long-term and often more realistic assessment of the disease impairment [134, 135].
Figure 1.1. Technological applications in the field of Parkinson’s disease [42, 44, 46-48, 50-73]. The focus of this thesis is shown in yellow: sensors or technologies for detecting and/or monitoring motor symptoms; sensors with applicability for disease self-management are shown in green; and technology for safety of individuals, in blue.
General Introduction and outline of the thesis

Box 1.2. | Overview of initiatives using wearable sensors to quantify PD-related motor symptoms for two scenarios: standardised clinical settings and the free-living environment

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Reference numbers of relevant papers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardised clinical settings</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>[56, 57, 60, 87–95]</td>
</tr>
<tr>
<td>R rigidity</td>
<td>[97]</td>
</tr>
<tr>
<td>Tremor</td>
<td>[58, 59, 62, 63, 92, 95, 98–105]</td>
</tr>
<tr>
<td>Motor fluctuations</td>
<td>[107–109]</td>
</tr>
<tr>
<td>Gait impairment</td>
<td>[93, 112–119]</td>
</tr>
<tr>
<td>Balance</td>
<td>[65, 123-126]</td>
</tr>
<tr>
<td>Falls</td>
<td>-</td>
</tr>
</tbody>
</table>

Aim of this thesis

Many previous initiatives have investigated the use of objective measurements in PD in standardised, laboratory settings. Yet, the feasibility of using such a strategy in large populations followed for long periods of time in the home environment has to be established. Therefore, the aim of this thesis was to provide evidence of the feasibility of using objective measurements in a large PD population. I use a two-fold approach to complete two aims:

1. To investigate the usability and compliance with wearable sensor use over a longer period in a large PD population (Chapters 2 and 3);
2. To demonstrate the clinical and research applicability of wearable sensors (Chapters 4–6).

Thesis outline

In Part I of this thesis, I investigate the compliance of a large PD population using multiple sensors in the home environment. Chapter 2 describes a research protocol aiming to share with other researchers how our research group has designed this large observational study. In Chapter 3, I analyse the feasibility of this large-scale wearable sensor deployment, first by examining the compliance of participants with the wearable systems, then by describing which design was successful and identifying which areas should be explored for further improvement in future research. Next, in Part II of this thesis, I seek to offer evidence for the applicability of wearable sensors for research and clinical purposes. In Chapter 4, by reviewing the current literature, I highlight the promises and pitfalls of the currently available wearable sensors for quantifying freezing of gait and falls in PD. Then, I describe the successful application of wearable sensors to determine the incidence of falls in a large population of patients with PD and matched controls. I do this by analysing wearable sensor data from more than 4000 elderly patients with PD (Chapter 5). Then I close Part II by evaluating the clinical applicability of wearable sensors to quantify the impact of motor fluctuations on activity levels in patients with PD. For this purpose, I examine gait-related features of data from the wearable sensors of more than 300 patients with PD. The wearable sensors recorded the data while the patients were in a free-living environment (Chapter 6).
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126. Andò, B., et al., A Wearable Device to


Part I

Feasibility of large-scale deployment of wearable sensors in large Parkinson’s disease cohorts
Chapter 2

Large-scale wearable sensor deployment in Parkinson’s patients: the Parkinson@Home study protocol

JMIR Res Protoc. 2016;5(3):e172
ABSTRACT

Background: Long-term management of Parkinson’s disease does not reach its full potential because we lack knowledge about individual variations in clinical presentation and disease progression. Continuous and longitudinal assessments in real-life (i.e., within the patients’ own home environment) might fill this knowledge gap.

Objective: The primary aim of the Parkinson@Home study is to evaluate the feasibility and compliance of using multiple wearable sensors to collect clinically relevant data. Our second aim is to address the usability of these data for answering clinical research questions. Finally, we aim to build a database for future validation of novel algorithms applied to sensor-derived data from Parkinson’s patients during daily functioning.

Methods: The Parkinson@Home study is a two-phase observational study involving 1000 Parkinson’s patients and 250 physiotherapists. Disease status is assessed using a short version of the Parkinson’s Progression Markers Initiative protocol, performed by certified physiotherapists. Additionally, participants will wear a set of sensors (smartwatch, smartphone, and fall detector), and use these together with a customized smartphone app (Fox Insight), 24/7 for 3 months. The sensors embedded within the smartwatch and fall detector may be used to estimate physical activity, tremor, sleep quality, and falls. Medication intake and fall incidents will be measured via patients’ self-reports in the smartphone app. Phase one will address the feasibility of the study protocol. In phase two, mathematicians will distill relevant summary statistics from the raw sensor signals, which will be compared against the clinical outcomes.

Results: Recruitment of 300 participants for phase one was concluded in March, 2016, and the follow-up period will end in June, 2016. Phase two will include the remaining participants, and will commence in September, 2016.

Conclusions: The Parkinson@Home study is expected to generate new insights into the feasibility of integrating self-collected information from wearable sensors into both daily routines and clinical practices for Parkinson’s patients. This study represents an important step towards building a reliable system that translates and integrates real-life information into clinical decisions, with the long-term aim of delivering personalized disease management support.

Keywords
Parkinson’s disease; Ambulatory monitoring; Signal processing; Computer-assisted; Wearable sensors
INTRODUCTION

Parkinson’s disease (PD) is a progressive and complex neurological disorder. Patients can experience a wide range of motor symptoms and signs, including bradykinesia, tremor, rigidity, and postural instability. Non-motor symptoms include executive dysfunctions, memory disturbances, attention difficulties, and reduced ability to smell [1-3].

The cornerstone of current therapy is based on the replacement of dopamine but can also include other drugs that play a role in the activation of dopamine receptors [4]. Although these medications initially have good results in disease management, the effects remain successful for a limited period of time. Most patients eventually develop motor complications, such as the wearing-off effect or dyskinesias [5,6]. Some disease symptoms, such as postural instability and voice/speech impairment, are insufficiently (or sometimes not at all) responsive to dopaminergic therapy.

Two major problems hamper the delivery of optimal individual treatment. First, evaluation of day-to-day variations in a complex disease such as PD is difficult when relying solely upon periodic consultations with experts working in a clinical setting [7]. Even when health professionals use specific and validated instruments, such as the Movement Disorder Society - Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [8], the results represent a subjective and episodic snapshot taken under well-controlled conditions, which are usually not representative of the patient’s functioning in daily life. More detailed, objective, and reliable knowledge about real-life functioning would greatly improve the quality of individual medical management. Second, virtually all scientific evidence that is presently available to inform PD management stems from biased clinical studies with short follow-up periods in highly selected sub-populations, who were studied under carefully controlled trial conditions [9,10]. As such, this evidence does not reflect the clinical presentation, treatment response, or disease progression in actual daily life.

To overcome these limitations, wearable sensors are emerging as new tools to continuously and longitudinally obtain information from patients in real-life. The accuracy of sensor data for everyday activity recognition (eg, walking, running) in real-life ranges from 58% to 97% [11]. These sensors, typically consisting of embedded accelerometers, have been used successfully to determine PD-related symptoms [12-16]. However, to date these studies have relied upon small sample sizes (n=5 to 43 participants) and short follow-up periods (3 days to 6 months; see Multimedia Appendix 2.1.).

The primary aim of the Parkinson@Home study is to evaluate the feasibility and patient compliance of using wearable sensors to collect data for at least 3 months in a large
patient group. A secondary aim of this study is to address the usability of these data for answering clinically relevant research questions (eg, to determine the relationship between sensor-derived measures and clinical measures). Finally, the study aims to build a database for future development and testing of novel algorithms applied to sensor-derived data from PD patients during daily functioning.

METHODS

Study Design
The Parkinson@Home study is an observational study involving 1000 patients (from whom data will be recorded) and 250 physiotherapists (who will assist in performing the clinical assessments, and who may act as personal coaches during follow-up). Both patients and therapists will be recruited throughout the Netherlands. The study consists of two phases. Phase one aims to assess the feasibility of deploying wearable sensors in a large PD population (n=300). For this purpose, patients will use a number of wearable devices (Pebble smartwatch, Android smartphone, and fall detector) in combination with a customized app (Fox Insight). Follow-up will occur after 3 months (13 weeks), starting from the moment the first data are streamed to the server. In addition to using wearable devices, participants will attend a one-time consultation, during which a detailed clinical assessment will be performed by an experienced physiotherapist or a research team member. This clinical assessment will take place in week 7, or later during the follow-up period. Phase two, which will include an additional 700 participants, aims to collect raw sensor data in order to investigate the usability of these data for answering clinical research questions. This phase will also be used to build a database for future validation of novel algorithms applied to sensor-derived data from PD patients during daily functioning. Patients involved in phase one can also be included in phase two if they wish. Data collection for clinical results and device-based outcomes, as well as the follow-up period, will be identical to phase one. To ensure the success of the raw data collection during phase two, devices and raw data collection strategies used in this phase will be chosen after the evaluation of data collected during phase one.

The study protocol was successfully piloted prior to full study implementation to ensure methodological feasibility. In total 20 Dutch PD patients participated in this pilot, using a set of wearable devices (one smartphone and one smartwatch) and the Fox Insight app. The patients were asked to use these devices for 24 hours, seven days a week, and were followed for four weeks. In total, 58% of patients that were approached agreed to participate. Some patients were reluctant to manage technology and to deal with possible technical problems, which caused them to refrain from participation. All participants (except for two) needed at least one support call for device troubleshooting. Streaming compliance for the sensor data was 88%.
Inclusion and Exclusion Criteria

Patients
The inclusion and exclusion criteria for patients will be kept purposefully broad, in order to represent the full diversity of real-life PD experiences. Inclusion criteria specify that patients must be 30 years of age or older and be diagnosed with PD by a physician. No exclusion criteria will be applied.

Physiotherapists
Physiotherapists who are members of the Dutch ParkinsonNet [17,18] are eligible to participate. ParkinsonNet physiotherapists have received several PD-specific educational training programs, and treat a high number of PD patients each year. Physiotherapists who want to participate should take the official MDS-UPDRS course (provided online by MDS [19], and further in person training provided by the research team) and be able to include and/or assess an average of four PD patients for the study.

Patient Recruitment Process
We will apply an incremental recruitment strategy. Initially, we will only include patients that already possess a compatible Android/iPhone smartphone. Subsequently, and only if needed, we will include patients that do not possess a smartphone; these patients will be provided with a loaned smartphone device. The reason for this incremental approach is that patients with their own device will likely require less technical support from the research team, as was the case in our pilot study. This strategy will increase the feasibility of complete data collection in a total of 1000 patients.

Patients will be recruited both in the community and through their treating physiotherapists. To reach potential participants in the community, we will use a number of communication channels: (1) the ParkinsonConnect community, an online community for Parkinson’s patients and healthcare professionals involved in their care [18]; (2) the webpage of the Dutch Parkinson Patient Association; (3) an article in the magazine of the Dutch Parkinson Patient Association; (4) presentations about the study to local patient support groups (Parkinson Cafés); (5) promotional material for patients will be sent to all ParkinsonNet physiotherapists (approximately 990 individuals), regardless of whether they participate in the study or not, and we will ask them to recruit patients within their practice; and (6) via a study website [20] which provides information about the study. The study website offers both patients and physiotherapists the possibility to sign up for the study online.

After signing up for the study, potential participants will be contacted by phone by a member of the research team, who will provide additional information about the study and check eligibility. If respondents are eligible and willing to participate, they will
receive an informed consent form. After the informed consent form has been signed digitally, the research team will provide the participant with all necessary devices and user manuals.

**Recruitment and Training of Physiotherapists**

All ParkinsonNet physiotherapists will be contacted by email to inquire about study participation. Should this email not result in adequate numbers of participating physiotherapists, we will personally contact ParkinsonNet physiotherapists by telephone. As with the recruitment process for patients, after signing up via the study website, physiotherapists will be contacted by email or phone to check eligibility.

Once included, physiotherapists must pass the online MDS-UPDRS training successfully [19], as required by the International Parkinson and Movement Disorder Society, which allows them to perform the MDS-UPDRS [8]. After successful completion of the training, physiotherapists will participate in one face-to-face training session, in which they will assess one patient, in order to practice the MDS-UPDRS assessment and consolidate their understanding of the assessment process and study procedures.

**Ethical Aspects and Trial Registration**

This study will be conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects, as defined in the Declaration of Helsinki. The study protocol and communication materials have been approved by the local ethics committee (Commissie Mensgebonden Onderzoek, Arnhem-Nijmegen; NL53034.091.15).

Consent will be obtained by the research team through an innovative online procedure, which includes a compulsory cooling-off period in a digital environment. When the patient is deemed eligible (e.g., meets the inclusion criteria specified in the online sign-up form), an information letter and consent form will be sent by email. The research team and an independent physician can be approached for questions and verbal explanation. Next, the potential participant has the possibility to confirm participation digitally, via a new URL sent to him/her by email after 48 hours. The URL redirects the patient to the study webpage, where he/she can confirm that they have read all information and that they agree to participate. As recommended by the ethics committee, this final step is blocked for 48 hours after the first email has been sent, to ensure that potential participants take time to consider participation. After the agreement to participate, the participant will see a confirmation message on the study webpage. No signature or scanning of documents will be necessary at this point. The Parkinson@Home study is registered in the ClinicalTrials.gov registry (NCT02474329) [21].
Wearable Sensors Phase One

**Pebble Smartwatch**

The Pebble is a commercially available smartwatch, with a variety of embedded sensors, such as tri-axial accelerometer, light sensor, and magnetometer. Accelerometers are able to record acceleration along three orthogonal spatial axes, producing acceleration vectors as single data points, and up to 100 acceleration data vectors can be recorded per second. The Pebble smartwatch operating software allows access to the unprocessed raw accelerometer data vectors, creating the opportunity for subsequent analyses of this sensor data. In order to obtain continuous accelerometer data, the Fox Insight app will be installed on each smartwatch. The app enables streaming of the accelerometer data to the smartphone, with a sampling frequency of 50 data vectors per second, using the built-in Bluetooth radios of both the smartwatch and smartphone.

**Fox Insight App**

The Fox Insight app is an Android/iPhone app created and developed by Intel Corporation (Tel Aviv, Israel). This app receives 50 accelerometer data points per second from the Pebble smartwatch, and estimates levels of activity, tremor, and sleep movement analyses using dedicated algorithms running within the app. The app presents these estimated quantities to the user by means of graphs and summary reports of the data collected. Activity graphs show the level of activity throughout the day (Figure 2.1.). The calculation is performed by aggregations (30 second intervals) of the raw data previously collected. The graph also highlights the moments in time when medication was taken.
Daily tremor graphs show how many minutes the patient has experienced tremor during a certain day (a tremor is defined as any movement in the range of 3.5-12Hz). Sleep analysis graphs (Figure 2.2.) show the amount of time that the patient has been active during the sleep time. These graphs provide an impression of the intensity and duration of movements.

Figure 2.1. Fox Insight Mobile App activity graph.
These estimated quantities are sent every 10 minutes to a cloud-based data platform through an Internet connection on the smartphone. Different mechanisms allow the participants to know whether the data are recorded correctly. First, participants can check the metric graphs (e.g., activity graph, sleep analysis, and tremor); these graphs are plotted using the data recorded in the servers and will only appear if the data were collected. Second, the main app screen (Figure 2.3.) displays how many hours of data the participant has contributed to the study; if this metric does not increase it means the data are not being collected. Finally, participants can view the white pill icon in the smartphone task bar; if the icon has a crossing line over it, data are not being actively recorded.

Figure 2.2. Fox Insight Mobile App sleep analysis graph.
Falls and movement patterns are measured with a pendant device. Patients are given the choice to wear either a fall detector (FD), or the Philips Mobility Monitor (PMM) [22,23]. Both sensors are CE-marked non-medical devices; the PMM is developed by Philips Research. The FD device used in this study is an adapted fall detection device, originally intended for seniors living in their own homes, that was designed to detect falls from stance. The FD device can be worn 24/7, while the PMM is recharged overnight and thus only worn during the day.

The FD device uses multiple sensors and a proprietary analytical algorithm to detect some types of fall events, which are stored in the device. The PMM contains a 3-axial accelerometer and a barometric pressure sensor, with a sampling frequency of 50Hz and 25Hz, respectively. Data are continuously recorded and stored on a micro SD card within the device. Based on these data, information about the daily movements, as well as falls detected, are calculated after read-out at the end of each patient’s trial period.

Figure 2.3. Fox Insight Mobile app main screen.
**Wearable Sensors Phase Two**
Devices will be chosen after analysis of the study procedure, and data collection is complete in phase one.

**Technical Support**
Patients will have access to extended support, including an installation guide, user manual, and information on the study's webpage. For the duration of the study, a helpline will be available during working hours to support the installation and device usage, and for troubleshooting.

**Clinical and Feasibility Assessment**
Certified physiotherapists will perform the short version of the Parkinson Progression Marker Initiative (PPMI) in order to assess disease status [24]. This assessment includes: the MDS-UPDRS (parts I, III, and IV) for disease rating [8]; the Montreal Cognitive Assessment for cognition [25]; and the Modified Schwab and England Activities of Daily Living Scale for activities of daily living [26].

Additional questionnaires will be completed by the patients: MDS-UPDRS part II for motor experiences of daily living; the Scales for Outcomes in Parkinson's Disease - Autonomic System (SCOPA-AUT) for autonomic dysfunction [27]; the Geriatric Depression Scale for depressive symptoms [28]; and the Epworth Sleepiness Scale for day sleepiness [29].

To assess feasibility, patients will also complete the System Usability Scale [30] and a satisfaction survey created by the research team, to address patients' impressions on how well particular features of the app are functioning, and the burden associated with the methodology. An overview of outcomes is provided in Multimedia Appendix 2.2.

**Data Collection and Management**
Due to privacy issues, patients will receive a personal identification code that does not contain any information that relates to the individual. The key-file, connecting personal identification codes to personal information, will be stored on a Radboudumc data server, and only the research team has access to the key-file. The key-file will be stored on a different server from the study data for five years, allowing the research team to contact patients after they have finished the study. We anticipate that our efforts to obtain additional research funding will allow for additional follow-up assessments. The key-file will be destroyed after five years.
Data for the study will be collected in the following ways:

*Data from smartwatch and smartphone:* data will be collected continuously in a coded manner and will be transferred to Intel’s cloud data storage environment using an Internet connection. The cloud environment is based on Amazon Web Services and developed and managed by Intel’s Advanced Analytics team. Data from the watch and Fox Insight app will be transferred to the Intel platform using a personal identification code for each patient. Moreover, no personally identifiable data will be entered into the app or sent to this data storage platform.

*Data from the PMM and FD:* data will be collected during the time that patients are not lying in bed. Each FD has a unique identifier, and Philips Research will only receive coded data. No personal information is required to use these devices, and no personal data from patients will be shared with Philips.

*Data from the clinical assessments:* data will be collected by means of paper-based forms and will be entered manually into an online certified data management system. Forms will only contain personal identification codes.

*Data from support and logistics:* ZenDesk software will be used to support the logistics of the recruitment process and provide technical support during the follow-up phase. ZenDesk is Internet-based, and data access is authenticated by username and password. All communications with ZenDesk servers use industry-standard Secure Sockets Layer encryption by default, and the ZenDesk servers are located at a different site than the Amazon servers. Therefore, research data is never stored on the same server as patients’ identifying codes.

Patients that complete the clinical assessment and stream data for more than seven days will have their data included in further analyses.

**Data Analyses**

**Phase One**

Feasibility and compliance will be addressed using descriptive analyses. For feasibility, the primary outcomes will include the total support time per participant, the number and rate of drop-outs, usability of the system, bias within recruitment strategies, and the type of problems faced by patients. Regarding compliance, the outcome measures include the total hours of sensor data collected per participant, the number of compliant days, and the percentage of time that sensor data were streamed during the follow-up period.
Phase Two
The potential for the data to answer clinically relevant research questions will be explored. First, we aim to extract a limited set of outcomes, including: the number, diversity, and performance of physical activities; specific activities (e.g., standing, walking, sitting); response fluctuations in relation to drug treatment; and specific motor symptoms (e.g., tremor, gait freezing, shuffling falls).

Additionally, we aim to explore how these outcomes are related to clinical assessments, and to self-monitoring during follow-up (including timing of medication intake and fall incidents). Finally, we aim to extract patterns of disease progression, assess the recognition of disease profiles based on reported symptoms and progression patterns, and address the effect of medication intake on symptoms. In both phases, analyses will be performed using specialized algorithms (when necessary) developed within the Matlab platform, with additional statistical analyses using the R software package.

RESULTS

Patient Recruitment Process
Within eight months of recruitment (August, 2015 to March, 2016) the Parkinson@Home study received 1164 applications. Among those invited for phase one (n=342), the participation rate was 87.7%, resulting in 300 inclusions. Recruitment strategies through the network of the Dutch Parkinson Association, and a personal approach by the research team or health care providers, have been very successful (Table 2.1.). Applicants include all respondents that demonstrated interest in the study, while participants include all respondents that were actually included in the study (which excludes dropouts and those who refused to participate). Phase two will begin in September, 2016, and participants will be recruited from the 734 participants placed in the study waiting list.
Table 2.1. Number of applications obtained from each recruitment strategy

<table>
<thead>
<tr>
<th>Recruitment strategy</th>
<th>Applicants (n=1164)</th>
<th>Participants (n=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online community for patients, called ParkinsonConnect</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Website of Dutch Parkinson Association</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Article in the magazine of Dutch the Parkinson Associations</td>
<td>39%</td>
<td>39%</td>
</tr>
<tr>
<td>Informative presentation at Parkinson Cafés by research team</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Personal invitation by Physiotherapist or Neurologist</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td>Others</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Not specified</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Applicants = number of participants that have demonstrated interest in join the study. **Participants = number of participants included excluding those who refused to participate and drop-outs.

DISCUSSION

In this paper we present the rationale and design of the Parkinson@Home study, a large (n=1000) observational cohort study that aims to explore the feasibility and usability of collecting raw sensor data from wearable sensors in patients with PD. There is a pressing need for collection of reliable medical information from PD patients while they perform activities of daily living, due to gaps in knowledge as to why different patients have variable rates of PD progression and different patterns of symptoms [31,32]. It has proven to be extremely difficult to understand such variations, and to capture objective data about the patient’s actual functioning in current clinical practice, which typically consists of episodic and brief clinical evaluations in hospitals.

Gathering data from wearable sensors has high scientific potential and offers several advantages compared to more traditional methods of data collection. Wearable sensors offer the possibility to collect data by self-administered tests, and to objectively monitor PD symptoms and day-to-day variation both remotely and at home [33-35]. The raw sensor data can be analyzed later by specialized algorithms or by algorithms embedded in apps themselves, providing scientific insights for researchers and clinicians. Moreover, data can be collected continuously over a prolonged period of time. For individual PD patients, those data can be used for long-term health monitoring. When applied in a group context, the data may offer a better understanding of PD (e.g., by revealing the presence of specific phenotypic subtypes, or by predicting disease progression) [36].

Using wearable sensors also brings about challenges. First, data from sensors are a potential target for invasions of privacy [37]. For example, Global Positioning System-based sensor data can be used to identify the physical location of an individual, and
their homes [38]. As a remedy, approaches such as restricting access to the data and anonymizing files have been suggested [39]. To allow for the collection of sensitive data, and to address security issues, the Parkinson@Home project will adopt several precautions, including: coding the data; storing the data on secure servers, separately from personal data; and restricting data use, by only allowing access to authorized researchers within the research team. When making information available to the wider research community, data will be anonymized and access will be granted only through a secure research database. These actions decrease the risk of identification of the patient and inappropriate use of the data.

A second challenge faced in the Parkinson@Home study is the lack of experience that elderly people have with technical devices. This lack of experience affects the acceptance of, and compliance with, the technology [40]. Overcoming this lack of experience in our target population, without introducing a selection bias, will be a challenge. However, we believe that the best approach for this issue is to rely on the willingness of patients to learn and be engaged in the management of their disease, combined with an efficient support model.

In conclusion, this study will generate new insights into the use of wearable sensors in daily living by PD patients, and if the data collection shows potential, it will make a contribution to the integration of self-collected information into clinical practice for PD patients. This study represents the first steps towards building a reliable system that integrates real-life information into clinical decisions.
REFERENCES


25. Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C,


Cryptography and Data Security. Berlin: Springer Berlin Heidelberg; 2015:231-244.


Multimedia Appendix 2.1.: Overview of studies applying wearable sensors and their use in Parkinson's disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Design (1)</th>
<th>Environment (2)</th>
<th>Aim (1)</th>
<th>Intervention (2)</th>
<th>Type of sensor</th>
<th>N</th>
<th>Follow up period</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arora [2014][40]</td>
<td>1: Cohort</td>
<td>2: Home</td>
<td>1: Discriminative validity of self-administered tests for gait and postural sway.</td>
<td>2: Gait, posture, voice, reaction time and tapping tests were performed while using a smartphones capable of recording tri-axial acceleration, audio and touch screen tapping events</td>
<td>Smartphone</td>
<td>10 PWP</td>
<td>1 month</td>
<td>Wearable sensors can provide data that enable to distinguish between healthy subjects and Parkinson's patients with a mean sensitivity of 96.2% (SD 2%) and mean specificity of 96.9% (SD 1.9%).</td>
</tr>
<tr>
<td>Personal communication Tsanas, 2012</td>
<td>1: Cohort</td>
<td>2: Home</td>
<td>1: Accuracy of speech signals to estimate UPDRS rating.</td>
<td>2: Six voice recordings of the sustained phonations 'aaah', sustained as long as each patient was able to. Voice recordings were captured by using a microphone on a dedicated monitoring device, once a week, for a duration of 6 months.</td>
<td>Mobile phone</td>
<td>42 PWP</td>
<td>6 months</td>
<td>Voice recordings estimate the UPDRS within 3.5 points of the clinicians' assessment.</td>
</tr>
<tr>
<td>Patel [2009][13]</td>
<td>1: Cohort</td>
<td>2: Laboratory</td>
<td>1: Reliability of using accelerometer data to estimate the severity of symptoms and motor complications.</td>
<td>2: Patients performed the motor assessment part of the UPDRS, in the ON [once] and OFF [6 times] phases, wearing uniaxial accelerometer sensors positioned on the upper and lower limbs.</td>
<td>Accelerometers</td>
<td>12 PWP</td>
<td>Not applicable</td>
<td>Uniaxial accelerometer sensors are able to provide an estimate of clinical scores for tremor, bradykinesia and dyskinesia with an average estimation error of 3.4%, 2.2%, and 3.2% respectively.</td>
</tr>
<tr>
<td>Author</td>
<td>Design (1) Environment (2)</td>
<td>Aim (1)</td>
<td>Intervention (2)</td>
<td>Type of sensor</td>
<td>N</td>
<td>Follow up period</td>
<td>Conclusions</td>
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<tr>
<td>Sharma [2014][12]</td>
<td>1: Cohort 2: Laboratory</td>
<td>1: To introduce the SPARK wearable system for measuring disease symptoms.</td>
<td>2: Patients wore a pair of devices (smartwatch and smartphone), and performed tasks to evaluate facial tremors, speech, dyskinesia and freezing of gait. They were also asked to perform tasks included in a digital version of the UPDRS.</td>
<td>Smartphone and smartwatch</td>
<td>5 PWP</td>
<td>Not applicable</td>
<td>The system was able to provide useful features for measuring symptom severity in the real world. Further work in system validation is still in development.</td>
<td></td>
</tr>
<tr>
<td>Bachlin [2010] [16]</td>
<td>1: Cohort 2: Laboratory</td>
<td>1: Sensitivity and specificity of detecting freezing of gait events.</td>
<td>2: Patients wore a set of wearable devices, which are able to detect freezing of gait automatically and provides a cueing sound when this event is detected. The measurement was divided into three parts, and was performed on the same day at the laboratory.</td>
<td>Accelerometers</td>
<td>10 PWP</td>
<td>Not applicable</td>
<td>Sensitivity of 73% and specificity of 82% in identifying freezing of gait events</td>
<td></td>
</tr>
<tr>
<td>Griffiths [2012][14]</td>
<td>1: Cohort 2: Home</td>
<td>1: To test the use of the commercial Kinetigraph algorithm to provide a conventional clinical rating.</td>
<td>2: Patients wore a device which incorporates a 3-axis accelerometer, for 10 days.</td>
<td>Parkinson’s Kinetigraph</td>
<td>34 PWP</td>
<td>10 days</td>
<td>The Kinetigraph algorithm predicted the clinical dyskinesia rating scale with a 95% margin of error of 3.2 units compared with the inter-rater 95% limits of agreement from 3 neurologists of -3.4 to +4.3 units.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Design (1)</td>
<td>Environment (2)</td>
<td>Aim (1)</td>
<td>Aim (2)</td>
<td>Type of sensor</td>
<td>N</td>
<td>Follow up period</td>
<td>Conclusions</td>
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</tr>
<tr>
<td>Patel [2011][15]</td>
<td>1: Cohort</td>
<td>2: Laboratory and home</td>
<td>1: To estimate clinical scores for motor symptoms using accelerometers</td>
<td>2: Subjects performed motor assessments on three days. The first two days of monitoring performed in the clinical setting, third day of monitoring performed in the home setting. Four test sessions are performed on each day of monitoring. During each of these tests, subjects perform a set of tasks from the UPDRS, while wearing a tri-axial accelerometer sensor.</td>
<td>Triaxial accelerometers [SHIMMER® platform].</td>
<td>5 PWP</td>
<td>3 days with 4 months cooling off period between each day</td>
<td>The sensors and algorithm are able to track longitudinal changes in motor symptoms, by analyzing UPDRS scores using random forest regression, within 0.5 points on a scale of 0-4.</td>
</tr>
<tr>
<td>Tsipouras [2012][42]</td>
<td>1: Cohort</td>
<td>2: Laboratory</td>
<td>1: Accuracy of an electronic/automated methodology for measuring levodopa induced dyskinesia.</td>
<td>2: The methodology is based on the analysis of signals recorded during three major tasks: 1- lying on the bed; 2- rising from the bed and sitting on a chair located near the bed; 3- standing up from the chair and performing a series of tasks.</td>
<td>Accelerometers, gyroscopes and a portable data recorder.</td>
<td>11 PWP</td>
<td>Not applicable</td>
<td>The results obtained indicate that the proposed method is efficient (97.36% classification accuracy) for detecting levodopa induced dyskinesia.</td>
</tr>
<tr>
<td>Author</td>
<td>Design (1)</td>
<td>Environment (2)</td>
<td>Aim (1)</td>
<td>Intervention (2)</td>
<td>Type of sensor</td>
<td>N</td>
<td>Follow up period</td>
<td>Conclusions</td>
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<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cancela [2013] [43]</td>
<td>1: Cohort</td>
<td>2: Laboratory and home</td>
<td>1: To investigate the technical performance of the PERFORM wearable system, a monitoring and health care platform for PD patients.</td>
<td>2: Phase 1 and 2: recordings when wearing the PERFORM system, in a hospital environment. Phase 3: 2 records of approximately 4 hours wearing the PERFORM system, for five consecutive days, in the patient’s home.</td>
<td>Accelerometers and gyroscopes</td>
<td>20 healthy [phase 1]</td>
<td>5 days</td>
<td>The PERFORM system, showed an accuracy of 93.73% for the classification of levodopa induced dyskinesia severity, 86% bradykinesia severity, and 87% for tremor. Regarding usability, 8 out of 24 patients reported extreme discomfort/pain when wearing the system.</td>
</tr>
<tr>
<td>Lakshminarayana [2014] [35]</td>
<td>1: Study protocol of NRT</td>
<td>2: Home</td>
<td>1: To evaluate the impact of using a smartphone and web apps to promote patient self-management as a tool to increase treatment adherence and enhance the quality of clinical consultation.</td>
<td>2: Group 1: smartphone and internet-enabled PD tracker smartphone app. Group 2: usual management [treatment] for PDP and their carers.</td>
<td>Smartphone</td>
<td>222 PWP</td>
<td>4 months</td>
<td>Study is currently running.</td>
</tr>
</tbody>
</table>

NRT - Non-randomized trial; UPDRS - Unified Parkinson’s Disease Rating Scale; SPARK – Smartphone/Smartwatch system for Parkinson disease; PERFORM - A soPhisticatEd multi-parRametric system FOR the continuous effective assessment and Monitoring of motor status in Parkinson’s disease and other neurodegenerative diseases; UPDRS - Unified Parkinson’s Disease Rating Scale; PD- Parkinson’s Disease; PWP- People with Parkinson’s Disease; PERFORM - A soPhisticatEd multi-parRametric system FOR the continuous effective assessment and Monitoring of motor status in Parkinson’s disease and other neurodegenerative diseases.
## Multimedia Appendix 2.2: Parkinson@Home study data

<table>
<thead>
<tr>
<th>Study Instrument</th>
<th>Outcome measure</th>
<th>Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic profile</td>
<td>Age at disease onset</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Level of education</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Time since diagnoses</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td>PPMI: MDS-UPDRS [8]</td>
<td>Non-motor experiences of daily living</td>
<td>Physiotherapist report</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Motor experiences of daily living</td>
<td>Physiotherapist report</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Motor examination</td>
<td>Physiotherapist report</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Motor complications</td>
<td>Physiotherapist report</td>
<td>Once</td>
</tr>
<tr>
<td>PPMI: Epworth sleepiness scale [29]</td>
<td>Sleep quality</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td>PPMI: Geriatric Depression Scale [28]</td>
<td>Depressive behavior</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td>PPMI: MoCA [25]</td>
<td>Cognitive impairment</td>
<td>Physiotherapist report</td>
<td>Once</td>
</tr>
<tr>
<td>Fox Insight app</td>
<td>Medication intake [compliance]</td>
<td>Patient self-report</td>
<td>Multiple time points</td>
</tr>
<tr>
<td></td>
<td>Falls</td>
<td>Patient self-report</td>
<td>Multiple time points</td>
</tr>
<tr>
<td></td>
<td>Percentage of sensor data streaming in 3 months [compliance]</td>
<td>Processed Accelerometer</td>
<td>Multiple time points</td>
</tr>
<tr>
<td>Smartwatch (Pebble)</td>
<td>Time that the patient is active during the day</td>
<td>Processed Accelerometer</td>
<td>0.2 Hz</td>
</tr>
<tr>
<td></td>
<td>Level of physical activity during the day</td>
<td>Processed Accelerometer</td>
<td>0.2 Hz</td>
</tr>
<tr>
<td></td>
<td>Hours during the day where the patient had tremor</td>
<td>Processed Accelerometer</td>
<td>0.03 Hz</td>
</tr>
<tr>
<td></td>
<td>Amount of movements during sleep time</td>
<td>Processed Accelerometer</td>
<td>0.003 Hz</td>
</tr>
<tr>
<td></td>
<td>Raw sensor data</td>
<td>Raw accelerometer</td>
<td>50 Hz</td>
</tr>
<tr>
<td>PMM/FD</td>
<td>Number of fall events</td>
<td>Processed Accelerometer</td>
<td>Depending on the number of detected fall events</td>
</tr>
<tr>
<td>Study Instrument</td>
<td>Outcome measure</td>
<td>Type</td>
<td>Frequency</td>
</tr>
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</tr>
<tr>
<td>Zendesk</td>
<td>Time spent providing troubleshooting telephone support per patient [feasibility]</td>
<td>Study support team indicators</td>
<td>Multiple time points</td>
</tr>
<tr>
<td></td>
<td>Inclusion rate [feasibility]</td>
<td>Study support team indicators</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Drop-out rate [feasibility]</td>
<td>Study support team indicators</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Type of technical and/or study procedure problem encountered by patients [feasibility]</td>
<td>Patient self-report</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Patients’ socioeconomic status(SES) [possible biases in the population]</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td>System Usability Scale [28]</td>
<td>Usability and learnability of the Fox Insight app</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td>Satisfaction survey</td>
<td>User’s satisfaction with the system (smartwatch and app)</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Patients’ sociodemographic details (e.g. gender, disease duration, age and previous experience with smartphones) [possible biases in the population]</td>
<td>Patient self-report</td>
<td>Once</td>
</tr>
</tbody>
</table>

PPMI - Parkinson Progression Marker Initiative; MDS-UPDRS - Movement Disorder Society - Unified Parkinson’s Disease Rating Scale; MoCA - Montreal Cognitive Assessment for cognition; SCOPA-AUT- Scales for Outcomes in Parkinson's Disease – Autonomic System for autonomic dysfunction
Chapter 3

Feasibility of large-scale deployment of multiple wearable sensors in Parkinson’s disease

ABSTRACT

Introduction: Wearable devices can capture objective day-to-day data about Parkinson’s Disease (PD). This study aims to assess the feasibility of implementing wearable technology to collect data from multiple sensors during the daily lives of PD patients. The Parkinson@home study is an observational, two-cohort (North America, NAM; The Netherlands, NL) study.

Methodology: To recruit participants, different strategies were used between sites. Main enrolment criteria were self-reported diagnosis of PD, possession of a smartphone and age ≥ 18 years. Participants used the Fox Wearable Companion app on a smartwatch and smartphone for a minimum of 6 weeks (NAM) or 13 weeks (NL). Sensor-derived measures estimated information about movement. Additionally, medication intake and symptoms were collected via self-reports in the app.

Results: A total of 953 participants were included (NL: 304, NAM: 649). Enrolment rate was 88% in the NL (n = 304) and 51% (n = 649) in NAM. Overall, 84% (n = 805) of participants contributed sensor data. Participants were compliant for 68% (16.3 hours/participant/day) of the study period in NL and for 62% (14.8 hours/participant/day) in NAM. Daily accelerometer data collection decreased 23% in the NL after 13 weeks, and 27% in NAM after 6 weeks. Data contribution was not affected by demographics, clinical characteristics or attitude towards technology, but was by the platform usability score in the NL (χ²(2) = 32.014, p<0.001), and self-reported depression in NAM (χ²(2) = 6.397, p = .04).

Conclusion: The Parkinson@home study shows that it is feasible to collect objective data using multiple wearable sensors in PD during daily life in a large cohort.
INTRODUCTION

Parkinson’s Disease (PD) is a common neurodegenerative disease in which patients experience both motor and non-motor symptoms [1]. Treatment is primarily based on the management of symptoms by increasing dopamine levels through pharmacological therapy or surgery [2, 3]. Additionally, non-pharmacological therapies, such as physiotherapy, occupational therapy or speech therapy, are available to support patients [4].

Although good results in the management of motor symptoms have been achieved, particularly in the early stages of the disease [5, 6], two major problems hamper long-term treatment. First, current pharmacological therapy is successful for a limited period. In the long term, most patients develop unmanageable motor complications that can lead to worsening of quality of life [7]. Second, evaluation of day-to-day variations in PD symptoms is difficult when relying solely upon periodic consultations by clinicians [8]. Therefore, more detailed, objective and reliable measures during daily living could potentially improve the management of PD.

Wearable sensors have been used to assess PD-related symptoms continuously and longitudinally during daily living [9–12]. Wearables may provide greater insight into a patient’s disease status, allowing patients to self-manage their symptoms and monitor medication responses [13–18]. Furthermore, wearable sensor data may improve our scientific understanding of disease progression by showing changes in motor and non-motor symptoms over time, furthering the development of digital biomarkers for disease progression [19].

While the potential value of wearable sensors for disease management and research are increasingly becoming clear, various critical aspects of feasibility remain to be determined. Only a few studies have rigorously investigated the feasibility and acceptability of using a wearable platform comprising a smartphone in combination to a smartwatch. Moreover, these prior findings remained limited by the small sample sizes (biggest sample thus far: 40 PD patients) [9, 13, 17, 18]. Therefore, we aimed to investigate the feasibility of using a wearable platform in a much larger sample of PD patients, with a focus on recruitment success, attrition rates, user compliance and system usability.

METHODS

Between August/2015 and November/2016, a total of 953 PD patients from two cohorts (n = 304 in The Netherlands (NL) and n = 649 PD in North America (United States and Canada - NAM) participated in the Parkinson@Home feasibility study. To
investigate the feasibility of the technology in different contexts, both cohorts used the same wearable platform, but had distinct strategies for recruitment, retention and study period. These topics are described separately (overview in Table 3.1.).

Table 3.1. Study design and procedure overview at the two cohorts.

<table>
<thead>
<tr>
<th></th>
<th>The Netherlands</th>
<th>North America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment strategies</td>
<td>Through Internet communities ✓ ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Through support groups ✓ -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Through physiotherapists ✓ -</td>
<td></td>
</tr>
<tr>
<td>Enrolment criteria</td>
<td>≥30 years old ✓ -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dutch resident ✓ -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smartphone using Android OS version 4.2 or higher ✓ ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Self-reported PD ✓ ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥18 years old - ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Registered for Fox Insight study - ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>English-speaking Canadian or United States resident - ✓</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>None ✓ ✓</td>
<td></td>
</tr>
<tr>
<td>Consent process</td>
<td>Informative email ✓ ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Online digital consent form ✓ ✓</td>
<td></td>
</tr>
<tr>
<td>Study kit</td>
<td>Pebble smartwatch ✓ ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Installation guide ✓ ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>User manuals ✓ ✓</td>
<td></td>
</tr>
<tr>
<td>Clinical evaluations</td>
<td>Assessment by physical therapist ✓ -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fox Insight online self-assessment surveys - ✓</td>
<td></td>
</tr>
<tr>
<td>Study duration</td>
<td>Minimum of 6 weeks - ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum of 13 weeks ✓ -</td>
<td></td>
</tr>
<tr>
<td>Instruction for device usage</td>
<td>Minimum of 5 hours a day - ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 hours, 7 days a week ✓ -</td>
<td></td>
</tr>
<tr>
<td>Support model</td>
<td>Call-center during working hours ✓ ✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Technical support calls for non-data contributors ✓ -</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Support emails for non-contributors - ✓</td>
<td></td>
</tr>
<tr>
<td>Usability questionnaire</td>
<td>- ✓ -</td>
<td></td>
</tr>
</tbody>
</table>

Study design and population

*The NL cohort*
The population and study design applied in the NL are described in detail elsewhere [20]. In short, participants were recruited from support groups, internet communities and through physiotherapists specialized in treating PD patients. Enrolment criteria
were: (1) ≥30 years of age, (2) possession of a smartphone using an Android OS version ≥4.2 and (3) self-reported diagnosis of PD. No exclusion criteria were applied beyond enrolment criteria.

All enrolled participants received a single medical examination, based on the “Parkinson’s Progression Markers Initiative” (PPMI) [21]. This included the full MDS-UPDRS [22], the Montreal Cognitive Assessment (MoCA) [23], and the Modified Schwab and England Activities of Daily Living Scale [24]. The medical examination was performed by specially trained physiotherapists who are members of ParkinsonNet [25], a Dutch network of health professionals specialized in PD management. At the end of the 13-weeks study period, all enrolled participants evaluated the usability of the system through the System Usability Scale (SUS) [26, 27], and were enquired about ability to use a smartphone (see APPENDIX). Finally, participants had the option to continue using the platform or return the Pebble smartwatch.

The NAM cohort
Study recruitment for the NAM cohort was entirely virtual through direct emails to subjects participating in the “Fox Insight online study”, Facebook advertisements to targeted populations, and advertisements on Fox Trial Finder, a clinical trial matching tool for people with PD [28]. Additional to the NL, the following enrolment criteria were applied: (1) ≥18 years of age and (2) participation in the Fox Insight Online Study [29]. In order to enroll, interested participants had to first register in the Fox Insight study (if they had not done so already). Through Fox Insight, each participant completed online surveys about demographics, medical history, cognition, physical activity, symptoms and PD related medications and surgeries. Once enrolled in the Fox Insight, participants were eligible to register for the NAM cohort of the Parkinson@Home study on a separate webpage. These users completed an online enrolment form which was reviewed by the study team to determine eligibility. All study registrants received an email confirming their eligibility or non-eligibility. After finishing the 6-weeks study period, participants had the option to continue using the platform.

Wearable platform
The Intel® Pharma Analytics Platform used has been described in detail elsewhere [20, 30]. Briefly, it consists of the Fox Wearable Companion app, used on both a smartwatch and smartphone, and a cloud environment. In this study, a Pebble smartwatch, was used together with the patients’ Android phones. 50 Hz accelerometer data were collected continuously from the smartwatch and streamed to the smartphone.

Sensor analysis algorithms are applied to the aggregated (30 second interval) smartwatch accelerometer data in the app to estimate outcomes (i.e. levels of
Figure 3.1. (a) Fox Wearable Companion app main screen; (b) Fox Wearable Companion app activity graph; (c) Fox Wearable Companion app movement during sleep graph; (d) Fox Wearable Companion app symptom self-reports. “Reprinted from [Intel and Michael J Fox Foundation] under a CC BY license, with permission from [INTEL®], original copyright [2017]."
activity, tremor and movement during sleep). These estimated quantities are transmitted, via Wi-Fi or mobile data, to a cloud environment. They are also presented to the user by graphs and summary reports within the app. Additionally, users are able to set medication reminders, report actual medication intake and rate their symptoms (e.g. tremor, dyskinesia, rigidity, bradykinesia) within the mobile app (Figure 3.1.). Both estimated outcomes and patients reported outcomes (PROs) are stored in the cloud environment.

### Study procedures at both cohorts

Participants from both cohorts provided electronic consent and received a research kit containing a Pebble smartwatch, an installation guide and user manuals. Next, participants installed the Fox Wearable Companion App on their devices and were asked to wear the smartwatch and keep their smartphone with them as much as possible on either a 24/7 basis for 13-weeks study period (NL) or for a minimum of 5 hours a day, 7 days a week, for a 6-weeks study period (NAM). Additionally, participants reported their medication intake (i.e medication name and doses) and PD symptom severity using the app. A helpline was available during the study period for technical support. Support calls or emails were sent to participants from whom data were not collected for more than seven consecutive days.

### Outcome definitions and statistical analysis

Feasibility assessment included recruitment, attrition, compliance and system usability. Recruitment success was analysed by (1) the total number of enrolled participants and (2) the number of eligible registrants that did not complete the informed consent. Compliance, similar to previous studies [31, 32], was calculated as the median percentage of the study period where accelerometer data were collected. Attrition rate based upon Eysenbach et al. [33], were measured by (1) decrease in the daily percentage of collected accelerometer data during each study period and (2) decrease in the number of participants contributing accelerometer data. Finally, system usability was measured by the median total score on the System Usability Scale.

We investigated the relationship between self-reported demographics, clinical data, ability to use a smartphone System Usability score and the percentage of accelerometer data collected to identify factors that influence compliance levels. Participant demographic and clinical characteristics were grouped into categories either following previously described literature (presence of depression [34]; presence of cognitive impairment [23]) or by convenience (age; educational level: a measure of the last completed level of education where low education was equal to high school or lower levels, middle education was equal to bachelor, and high education was equal to master or higher levels; Hoehn & Yahr stage and Modified Schwab and England scale). Because compliance was
not normally distributed, the median and quartiles were used to divide participants into three compliance groups (low, middle and high). The first quartile was the cut-off for the low compliant group and third quartile for the high compliant group. Depending on the distribution of other variables in the analysis, either Chi-square, Fisher’s Exact Test or Kruskal-Wallis were used to investigate significant differences between compliance groups considering demographics, clinical characteristics, ability to use a smartphone and System Usability score.

**Ethics standards**

This study was conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects, as defined in the Declaration of Helsinki. The study protocol and communication materials were approved by the local ethics committee (NL: CMO Arnhem- Nijmegen; NL53034.091.15; NAM: New England IRB: 15–046).

**RESULTS**

**Recruitment and sample characteristics**

In the NL cohort, 347 eligible PD patients were invited to participate. Among those invited, 43 refused to participate. The main refusal reasons were “Study protocol seems too burdensome” (44%, n = 19), followed by “Personal circumstances” (33%, n = 14). A total of 304 patients (enrolment rate = 88%) were enrolled.

In the NAM cohort, from the 866 participants of the Fox Insight study who received a direct invitation to participate, 306 were enrolled (6% were ineligible). 344 additional participants were included from the remaining recruitment channels, with varied ineligibility rates. A total of 649 registrants (enrolment rate = 51%) were enrolled.

In both cohorts, 953 participants were enrolled. From them, 805 were data contributors (participants that contributed at least one accelerometer data point during study period). Analysis of the demographic characteristics of both cohorts showed that, in comparison to NA, the NL cohort presented more men ($\chi^2 (1) = 9.5146, p<0.01$); older ($\chi^2 (2) = 16.435, p = 0.001$) and higher educated ($\chi^2 (2) = 25.270, p<0.001$) PD included participants. The characteristics of all participants are presented in Table 3.2.
<table>
<thead>
<tr>
<th></th>
<th>The Netherlands</th>
<th>North America</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Data contributors (n = 291)*</td>
<td>Non-compliant (n = 13)*</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>168 (65%)</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>29 (10%)</td>
<td>1 (8%)</td>
<td>.523</td>
</tr>
<tr>
<td>51–69</td>
<td>207 (72%)</td>
<td>8 (61%)</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>53 (18%)</td>
<td>4 (31%)</td>
<td></td>
</tr>
<tr>
<td><strong>Education Level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>51 (20%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Middle</td>
<td>103 (40%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>High</td>
<td>101 (40%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>73 (30%)</td>
<td>1 (100%)</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>127 (53%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>34 (14%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4/5</td>
<td>6 (2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>238 (97%)</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (&gt;26)</td>
<td>124 (53%)</td>
<td>1 (100%)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Independency level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70</td>
<td>36 (15%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>71–80</td>
<td>51 (22%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>81–90</td>
<td>109 (46%)</td>
<td>1 (100%)</td>
<td>NA</td>
</tr>
<tr>
<td>≥91</td>
<td>41 (17%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td><strong>How easy is for you to use a smartphone?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very easy</td>
<td>59 (22%)</td>
<td>0</td>
<td>.211</td>
</tr>
<tr>
<td>Easy</td>
<td>117 (44%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>Neither easy nor difficult</td>
<td>64 (22%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>Difficult</td>
<td>20 (7%)</td>
<td>2 (33%)</td>
<td></td>
</tr>
<tr>
<td>Very difficult</td>
<td>6 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MDS-UPDRS (Median)</strong></td>
<td>52.5 (QR 35–69)</td>
<td>22</td>
<td>-</td>
</tr>
</tbody>
</table>

*Number of missing values differed across variables; only valid percentages are reported. SES: Socioeconomic status; Disease severity: assessed with Hoehn and Yahr stages at the NL cohort and estimated from self-reported at NAM cohort; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale. 1-Depression was assessed with the Geriatric Depression Scale at NL and self-reported on NAM site; 2-Cognitive impairment was assessed using the Montreal Cognitive Assessment; 3-Independency level was measured by Modified Schwab and England Activities of Daily Living Scale. NA=not assessed. QR: 1st and 3rd quartiles.
Technical support to participants
In both cohorts, the helpdesk consisted of two research assistants, available for 20 hours (NL) and 40 hours (NAM) per week. The actual workload was dependent on: (1) the number of participants simultaneously enrolled in the trial; and (2) the occurrence of bugs in the app or server downtime. The most frequent and time-consuming problems were: (1) Bluetooth disconnection between the smartwatch and the smartphone and (2) questions regarding the medication report, especially in the first weeks of participation.

Compliance
Among both cohorts, 85% (n = 805 of 953 enrolled) of participants were data contributors. In the NL, 291 data-contributors collected data for a median of 1,478 hours each in the 13-weeks, with quartile ranges (1st and 3rd QR) of 888 to 1,827 hours. In NAM, 514 data contributors collected a median of 621 hours (1st QR: 286 and 3rd QR: 828 hours) each during the 6-weeks. Compliance rates for each cohort were 68% (1st and 3rd QR: 41%-83%) equal to 16.3 hours/participant/day in the NL and 62% (1st and 3rd QR: 28%-82%) equal to 14.8 hours/participant/day in NAM (Figure 3.2.).

Figure 3.2. Distribution of compliance among all enrolled participants in the NL (n=304-black) and NAM (n=649-white) study cohorts.
Attrition
In the NL, 13 participants (4% of all NL enrolled participants) did not contribute any data during the study period and were thus non-compliant. In NAM, this number was 135 (21% of all NAM enrolled participants). Additionally, 82 (27% of all enrolled) data-contributors in the NL became non-compliant during the study period. The primary known reasons (n = 47) were “Personal circumstances” (38%, n = 18) and “System too complex/System related issues” (34%, n = 16). For the NAM cohort, although reasons were unknown, this number was 89 (17% of all enrolled).

The attrition in the median percentage of sensor data collected daily varied between cohorts. In the NL, the attrition rate was 23% after 13-weeks’ study period. In the NAM, attrition was 27% after 6-weeks’ study period (Figure 3.3.).

![Figure 3.3. Attrition in compliance per day for NL (n = 291, black) and NAM participants (n = 514, gray) during the follow up period.](image)

Attrition in participation was tracked during and beyond the compulsory study period for each cohort. The number of participants decreased rapidly after the end of the study period in the NL cohort. A more gradual attrition in participation occurred in the NAM cohort (Figure 3.4.).
Figure 3.4. Number of participants actively collecting sensor data at the NL (gray) and NAM (black) cohorts during and after the follow-up period (total initial n = 805).

Ninety-six percent (n = 280) of data-contributors in the NL reported their medication through the app, while 78% (n = 404) did so in NAM. On average, data-contributors who used medication reports reported 351±217 medication intakes during the 13-week study period in the NL and 127±113 over 6-week study period in NAM. Both cohorts showed a low and non-exponential attrition in medication report, similar to the attrition showed in compliance with the accelerometer data (data not shown).

**System usability**

In the NL cohort, 256 participants completed the System Usability Scale (response rate = 71.4%). The median score was 62.5 (1st and 3rd QT 47.5–72.5), which classifies the wearable platform in a category between “Ok” and “Good” (Figure 3.5.).

Figure 3.5. SUS scoring of the Fox Wearable Companion platform (smartwatch with smartphone app) as rated by participants.
Factors related to compliance

After grouping all NL data-contributors into compliance groups, analysis reveals no significant differences in the distribution of demographics, clinical characteristics and ability to use a smartphone between these groups. However, Kruskal-Wallis analysis demonstrates that the System Usability score reported is significantly different between the groups ($\chi^2 (2) = 32.014, p<0.001$). The mean rank score is 84.8 for the low compliant group, 130.8 for the middle compliant group and 160.0 for the high compliant group, which indicates that participants in the high compliant group provided a higher usability score to the system.

For the NAM cohort, analysis shows that demographics and clinical characteristics between the three compliance groups was comparable, except for a trend regarding self-reported depression ($\chi^2(2) = 6.397, p = .04$). This result indicates that a slightly higher number of self-reported depressed patients are in the low compliant group (Table 3.3.).
Table 3.3: Distribution of data-contributors' characteristics and influence on compliance for the NL and NAM cohorts.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>The Netherlands</th>
<th>North America</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low compliance (n = 73)*</td>
<td>Middle compliance (n = 146)*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>39 (71%)</td>
<td>84 (64%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>7 (10%)</td>
<td>15 (10%)</td>
</tr>
<tr>
<td>51–69</td>
<td>51 (70%)</td>
<td>103 (71%)</td>
</tr>
<tr>
<td>70</td>
<td>15 (20%)</td>
<td>27 (19%)</td>
</tr>
<tr>
<td>Education Level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>11 (20%)</td>
<td>23 (17%)</td>
</tr>
<tr>
<td>Middle</td>
<td>21 (38%)</td>
<td>45 (34%)</td>
</tr>
<tr>
<td>High</td>
<td>23 (42%)</td>
<td>51 (39%)</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0+1</td>
<td>15 (42%)</td>
<td>37 (28%)</td>
</tr>
<tr>
<td>2</td>
<td>15 (42%)</td>
<td>72 (54%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (16%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>4+5</td>
<td>0 (0%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Depression*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (&lt;6)</td>
<td>36 (100%)</td>
<td>135 (98%)</td>
</tr>
<tr>
<td>Cognitive impairment*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (&gt;26)</td>
<td>16 (47%)</td>
<td>74 (56%)</td>
</tr>
<tr>
<td>Level of Independence*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>5 (14%)</td>
<td>21 (16%)</td>
</tr>
<tr>
<td>71–80</td>
<td>13 (36%)</td>
<td>30 (23%)</td>
</tr>
<tr>
<td>81–90</td>
<td>13 (36%)</td>
<td>61 (46%)</td>
</tr>
<tr>
<td>91</td>
<td>5 (14%)</td>
<td>21 (16%)</td>
</tr>
<tr>
<td>How easy is for you to use a smartphone?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very easy</td>
<td>12 (19%)</td>
<td>33 (24%)</td>
</tr>
<tr>
<td>Easy</td>
<td>27 (44%)</td>
<td>60 (44%)</td>
</tr>
<tr>
<td>Neither easy nor difficult</td>
<td>14 (23%)</td>
<td>27 (20%)</td>
</tr>
<tr>
<td>Difficult</td>
<td>5 (8%)</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>Very difficult</td>
<td>4 (6%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>MDS-UPDRS(^6) (median)</td>
<td>49</td>
<td>55</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>SUS(^6) (median)</td>
<td>50</td>
<td>65</td>
</tr>
</tbody>
</table>

*Missing values varied across variables. Red is significant at .05; green is significant at .001. SES: Socioeconomic status; Disease severity: assessed with Hoehn and Yahr stages at the NL cohort and estimated from self-reported at NAM cohort; GDS: Geriatric Depression Scale; MoCA: Montreal Cognitive Assessment, MDS-UPDRS: Movement Disorders Society—Unified Parkinson’s Disease Rating Scale, SUS: System Usability Scale. 1-Depression was assessed with the Geriatric Depression Scale at NL and self-reported on NAM; 2-Cognitive impairment was assessed using the Montreal Cognitive Assessment; 3-Independency level was measured by Modified Schwab and England Activities of Daily Living Scale; 4 –Pearson Chi-Square; 5 –Fisher’s Exact Test; 6-Kruskal-Wallis.
DISCUSSION

This study assessed the feasibility of using a wearable platform for long-term data collection in a large sample of PD patients. We focused on: recruitment success, attrition rates, compliance and system usability. Enrolment rate was 88% (n = 304) in the NL and 51% (n = 649) in NAM. Nearly 85% of all enrolled participants contributed sensor data during the study period. Median compliance rate was 68% (16.3 hours/participant/day) in the NL, and 62% (14.8 hours/participant/day) in NAM. The rate of accelerometer data collected each day declined 23% in the NL after 13-weeks of study period, and 27% in NAM after 6-weeks of study period. The distribution of demographics, clinical characteristics and ability to use a smartphone did not differ across compliance groups in the NL, but System Usability score did differ. For the NAM, the distribution of demographics and clinical characteristics between the compliance groups was comparable, except for self-reported depression status.

The high compliance in this study shows that it is feasible for people with PD to use this wearable platform in a real-world environment for many months. Although the feasibility of using consumer wearable sensors to monitor PD symptoms has been previous reported [9, 13, 17, 18, 31, 35], this is the first rigorous observational study to investigate the feasibility of a wearable platform comprising a smartwatch combined with a smartphone in such a large patient group (the largest prior study included only 40 patients). Additionally, the small differences in study protocols across cohorts allowed us to observe the impact of varying usage instructions on compliance. Comparing the feasibility results obtained in this study to other studies, where either mobile apps were used in large cohorts [36] or e-health technologies were used [37, 38], we achieved a high compliance together with small and non-exponentially decreasing attrition rate, even though exponential decrease in compliance is the norm in these sort of studies [33].

This unusually high compliance rate may be attributed to the “passive” data collection. In this case, little or no interaction with the technology is required in order to collect sensor data. Participants using the Parkinson@Home wearable platform, other than reporting their medication intake when reminded by the alarm (which was widely perceived as a service, instead of a burden), did not need to interact actively with the smartphone or smartwatch. In another similar smartphone-based study where “active”, “task-based” monitoring was used (that is, where participants needed to perform certain specific tasks, at regular intervals prompted by the platform) [36], a more typical high and exponential attrition rate was observed. While it is difficult to draw firm conclusions from this comparison (because the two platforms are somewhat different), we suspect
that periodic and long interaction by users may increase attrition, leading to attrition rates seen in paper-based diaries [39]. The low and non-exponential attrition seen in the medication reports, a quick and less burdensome task, strengthened this conclusion. Thus, passive monitoring, where little to no interaction with the technology is required, may lead to better overall compliance rates.

Despite the potential influence of age, gender and PD-related impairment (i.e. physical or cognitive) on compliance, our results showed that overall disease severity, MDS-UPDRS scores, independency level or cognitive impairment, did not influence compliance, which suggests that this platform could be used by most PD patients. The unique design of the Parkinson@home study can partially explain this result. The presence of a personalized support centre, which was previously described as an effective strategy to improve retention of participants [33], may have increased patients’ confidence in using the system and have compensated for any disease-related difficulties. Moreover, the “pro-active” support model, with scheduled calls to participants who showed signs of low compliance, may have boosted compliance by providing a quick resolution of technical interruptions, and addressed any apathy towards participation caused by technology difficulties. This support is even more important because compliance is compromised in participants that reported low System Usability scores. Therefore, in order to achieve high compliance while using smartphone/smartwatch wearable platforms to measure PD related symptoms at home, it is beneficial to: (1) improve the platform’s usability, (2) reduce the number of technical issues, and (3) run a personalized support center that can provide guidance to deal with possible technology related issues that participants may encounter.

LIMITATIONS

The Parkinson@Home study did have a few limitations. First, this is one of the first large-scale cohort studies using consumer wearable sensors in PD, with a long study period duration (i.e. up to 13 weeks). However, the study sample consisted only of PD patients that possessed a smartphone, thus introducing a possible selection bias, e.g. towards more highly educated subjects. Although smartphone penetration in the NL and NAM is high [40, 41], participants may not reflect the majority of PD patients living in the Netherlands, North America, or elsewhere in the world. Furthermore, when compared to the general PD population [42], participants were mainly young with a mild disease impairment and with some degree of cognitive impaired. Even though these variables showed no obvious influence on compliance, a more impaired population may need more personal support in order to maintain compliance.
Future studies should aim for a more stratified population in order to further confirm the lack of influence across the full range of disease severity in the compliance with wearable sensors among PD patients. Second, the present results only apply to the use of two specific consumer grade devices (i.e. smartphone and smartwatch). Although consumer grade devices bring potential advantage over the use of dedicated medical devices, it is unknown whether our promising feasibility results would generalize to dedicated medical devices which are often more expensive and less user-friendly.

CONCLUSION

In conclusion, the Parkinson@home trial showed that it is feasible to deploy a technology platform consisting of consumer-grade wearable and mobile devices for long-term data collection in a large and geographically diverse PD population. Importantly, compliance was comparable for patients with a range of backgrounds, including men and women, different ages, and some variations in disease severity. These findings suggest that wearables may offer a promising approach to overcome the limitations in monitoring disease status and progression of mildly impaired PD patients in a real-life environment. The platform here used is a promising and practical approach to capturing large amounts of sensor data from many participants by passive means, without much need for interaction with the technology. In the future, these properties may position sensor technologies as effective tools for monitoring PD and the “lived experience” of PD patients.
REFERENCES


25. Bloem BR, Munneke M. Revolutionising management of chronic disease: the
39. Hauser RA, Deckers F, Lehert P. Parkinson’s disease home diary: further validation and


Part II

Applicability of objective measurements for answering clinical and research-relevant questions: wearable sensors for quantifying gait and falls
Chapter 4

Freezing of gait and fall detection in Parkinson’s disease using wearable sensors: a systematic review
ABSTRACT

Introduction: Despite the large number of studies that have investigated the use of wearable sensors to detect gait disturbances such as Freezing of gait (FOG) and falls, there is little consensus regarding appropriate methodologies for how to optimally apply such devices. Here, an overview of the use of wearable systems to assess FOG and falls in Parkinson’s disease (PD) and validation performance is presented.

Methodology: A systematic search in the PubMed and Web of Science databases was performed using a group of concept key words. The final search was performed in January 2017, and articles were selected based upon a set of eligibility criteria.

Results: In total, 27 articles were selected. Of those, 23 related to FOG and 4 to falls. FOG studies were performed in either laboratory or home settings, with sample sizes ranging from 1 PD up to 48 PD presenting Hoehn and Yahr stage from 2 to 4. The shin was the most common sensor location and accelerometer was the most frequently used sensor type. Validity measures ranged from 73–100% for sensitivity and 67–100% for specificity. Falls and fall risk studies were all home-based, including samples sizes of 1 PD up to 107 PD, mostly using one sensor containing accelerometers, worn at various body locations.

Conclusion: Despite the promising validation initiatives reported in these studies, they were all performed in relatively small sample sizes, and there was a significant variability in outcomes measured and results reported. Given these limitations, the validation of sensor-derived assessments of PD features would benefit from more focused research efforts, increased collaboration among researchers, aligning data collection protocols, and sharing data sets.

Keywords
Parkinson’s disease
Ambulatory monitoring; Wearable sensors; Validation studies
INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disease characterized by four major motor signs: rest tremor, rigidity, bradykinesia, and postural instability [1]. Non-motor impairments, including executive dysfunctions, memory disturbances, and reduced ability to smell, are also seen in the disease [2–4]. Gait difficulties and balance issues are a disabling problem in many patients with PD, with different contributing factors, such as freezing of gait (FOG), festination, shuffling steps, and a progressive loss of postural reflexes. Its importance is underlined by a high prevalence of fall incidents in PD, especially in the later stages of the disease [5–7].

FOG is defined as a sudden and brief episode of inability to produce effective forward stepping [8]. The phenomenon is closely related to falls, appearing mainly during gait initiation, turning while performing a concomitant concurrent activity (i.e., dual tasks), or approaching narrow spaces [9–13]. Similar to FOG, fall episodes occur mainly during a half-turn or while dual tasking [6]. With disease progression, the increase of FOG and falling episodes, as well as the decrease in effectiveness of dopaminergic therapy amplify the burden related to these symptoms [6, 12, 14].

The management of gait disturbances, such as FOG and falls, often includes pharmacological interventions [12]. However, there is a growing interest in non-pharmacological interventions, such as physiotherapy [15], deep brain stimulation [16], or cueing devices [17, 18]. In all cases, reliable tools are required to determine the severity of gait disorders and evaluate the efficacy of interventions [5].

A number of subjective rating scales are used to evaluate motor symptoms, but most of them have limited validity and reliability [19]. To overcome these limitations, wearable sensors are emerging as new tools to objectively and continuously obtain information about patients’ motor symptoms [20–22]. These sensors, typically consisting of embedded accelerometers, gyroscopes and other, have been used to determine PD-related symptoms, including gait disorders [17, 18, 23–28]. They can act as an extension of health-professionals’ evaluation of PD symptoms, improving treatment, and augmenting self-management [29, 30].

Despite a large number of studies that investigated the use of wearable sensors to detect gait disturbances, such as FOG and falls, there is little agreement regarding the most effective system design, e.g., type of sensors, number of sensors, location of the sensors on the body, and signal processing algorithms. Here, we provide an overview of the use of wearable systems to assess FOG and falls in PD, with emphasis on device setup and results from validation procedures.
REVIEW METHODOLOGY

A systematic search in the PubMed and Web of Science databases was performed in accordance with the PRISMA statement [31]. These databases were chosen to allow both medical and engineering journals to be included in the search process.

The search query, based on the PICO strategy [31], included Parkinson’s disease representing the Population, wearable, sensors, device representing the Intervention and falls or freezing of gait representing the Comparison. Outcome was not included as a key word to keep the query broad. The truncation symbol (*) and title/abstract filter were used to both broaden the search and provide more specificity. The final search query is shown in Table 4.1.

<table>
<thead>
<tr>
<th>Database</th>
<th>Query</th>
<th>Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Web of Science</td>
<td>(((TI=(sensor*) OR TS=(sensor*) OR TI=(device*) OR TS=(device*) OR TS=(wearable*) OR TI=(wearable*)) AND (TS=(freezing*) OR TI=(freezing*) OR TI=(fall*) OR TS=(fall*)) AND (TI=(Parkinson’s*) OR TS=(Parkinson’s*)))))</td>
<td>272</td>
</tr>
<tr>
<td>PubMed</td>
<td>(&quot;Freezing of gait&quot; [tiab] OR Freezing* [tiab] OR fall* [tiab]) AND (wearable* [tiab] OR sensor* [tiab] OR device* [tiab]) AND Parkinson* [tiab])</td>
<td>280</td>
</tr>
</tbody>
</table>

The final search was performed in January 2017. In addition to the database search, a search in the references of review articles and book chapters that appeared during the search was performed. The goal was to identify potentially eligible articles absent in the database search.

Articles were selected based upon a set of eligibility criteria. As the objective of this review was to provide an overview of articles published on the topic, selection criteria were kept broad. Therefore, studies were included if they (1) present original research on the validation of wearable sensors (i.e., a single or combination of body worn computer/sensor [32, 33]) to detect, measure or monitor FOG, falls, or fall risk and (2) were performed in Parkinson’s disease patients. Studies were excluded if they (1) only used wearables to deliver cueing for FOG, (2) were published in languages other than English, or (3) did not provide sufficient information about study design and results.

Data extraction was performed using a predefined table. Variables extracted included: author, sample size, device usage (i.e., type of sensor, number of sensors, and location of the device), data collection procedures, and validation results. Validity was considered
as the extent to which an instrument is measuring a concept that it is supposed to measure. It can be further divided into different types of validity, such as criterion-referenced validity, construct validity and content validity. In the case of wearable sensors, researchers are often interested in criterion-referenced validity, which can be assessed by the correlation between the sensor-derived outcome and the outcome of a reference instrument that has already been validated [34, 35]. Construct validity, also known as discriminant validity, is commonly used by assessing the extent to which groups that are supposed to produce different outcomes, indeed do so, for example, by comparing PD with non-PD, or DBS ON with DBS OFF.

RESULTS

Selection process

In total, 552 articles were retrieved by the query. The selection process led to the final inclusion of 27 articles. Of those, 23 articles related to FOG, and 4 to falls. A complete overview of the selection process is presented in Figure 4.1.

Figure 4.1. Selection process for eligible articles
Methodologies

FOG detection

A total of 23 articles investigated the use of wearable sensors to assess FOG in PD [18, 28, 36–56] (Table 4.2.).
Table 4.2. Characteristics of studies that investigated wearable sensors for FOG detection (n=23)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Device locations (n)</th>
<th>Type of Sensor</th>
<th>Procedures</th>
<th>ON</th>
<th>OFF</th>
<th>Reference</th>
<th>Validity results</th>
<th>Tested for cueing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOG detection at home</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martín (2016)</td>
<td>6 PD FOG+</td>
<td>Waist (1)</td>
<td>Accelerometer</td>
<td>4 different activities: (1) showing the home, (2) a FOG provocation test, (3) a short walk outdoors and (4) walking with a dual task activity. Also: a false positive protocol.</td>
<td>✓</td>
<td>✓</td>
<td>Labeled video</td>
<td>Sensitivity: 91.7% Specificity: 87.4%</td>
<td>-</td>
</tr>
<tr>
<td>Ahlrichs (2016)</td>
<td>8 PD FOG+</td>
<td>Waist (1)</td>
<td>Accelerometer</td>
<td>Labeled video</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Sensitivity: 92.3% Specificity: 100%</td>
<td>-</td>
</tr>
<tr>
<td>Tzallas (2014)</td>
<td>Lab: 24 PD FOG unknown Home: 12 PD FOG unknown</td>
<td>Wrist (2) Shin (2) Waist (1) Accelerometer Gyroscope</td>
<td>Lab: A series of tasks. Home: 5 consecutive days of free living.</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Lab: Accuracy: 79% (sensitivity and specificity not reported) Home: Mean absolute error: 0.79 (no further explanation provided; accuracy, sensitivity and specificity not reported)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Device locations (n)</td>
<td>Type of Sensor</td>
<td>Procedures</td>
<td>ON</td>
<td>OFF</td>
<td>Reference</td>
<td>Validity results</td>
<td>Tested for cueing</td>
</tr>
<tr>
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<td>-------------------</td>
</tr>
<tr>
<td><strong>FOG detection at the laboratory (“free” elements included in protocol)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazilu (2014)</td>
<td>5 PD FOG+ Shin (2)</td>
<td>Accelerometer Gyroscope Magnetometer</td>
<td>3 sessions on 3 different days (2 consisting of walking tasks, 1 “free” walking in hospital and park)</td>
<td>?</td>
<td>?</td>
<td>Labeled video</td>
<td>Sensitivity: 97% Specificity: not reported. (only reported: false positives count: 27 vs. 99 true positives)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Cole (2011)</td>
<td>10 PD FOG unknown 2 non-PD</td>
<td>Forearm ACC (1) Thigh ACC (1) Shin ACC &amp; EMG (1)</td>
<td>Accelerometer EMG</td>
<td>Unscripted and unconstrained activities of daily living in apartment-like setting.</td>
<td>?</td>
<td>?</td>
<td>Labeled video</td>
<td>Sensitivity: 82.9% Specificity: 97.3%</td>
<td>-</td>
</tr>
<tr>
<td><strong>FOG detection at the laboratory (only tasks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rezvanian (2016)</td>
<td>Same as used in [17]</td>
<td>Shin (1) Thigh (1) Lower back (1)</td>
<td>Accelerometer</td>
<td>Same as used in [2].</td>
<td>✓</td>
<td>✓</td>
<td>Same as used in [2].</td>
<td>Sensitivity / Specificity: Shin only: 84.9% / 81% Thigh only: 73.6% / 79.6% Lower back only: 83.5% / 67.2%</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4.2. Characteristics of studies that investigated wearable sensors for FOG detection (n=23)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Device locations (n)</th>
<th>Type of Sensor</th>
<th>Procedures</th>
<th>ON</th>
<th>OFF</th>
<th>Reference</th>
<th>Validity results</th>
<th>Tested for cueing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zach (2015)</td>
<td>23 PD FOG+</td>
<td>Waist (1)</td>
<td>Accelerometer</td>
<td>A series of walking tasks.</td>
<td>✓</td>
<td></td>
<td>Labeled video</td>
<td>Sensitivity: 78%</td>
<td>-</td>
</tr>
<tr>
<td>Kim (2015)</td>
<td>15 PD FOG+</td>
<td>Waist (1) Trouser pocket (1) Shin (1)</td>
<td>Accelerometer Gyroscope</td>
<td>walking task (with single and dual tasking).</td>
<td>?</td>
<td>?</td>
<td>Labeled video</td>
<td>Sensitivity / Specificity: Waist only: 86% / 92% Trouser pocket only: 84% / 92% Shin only: 81% / 91%</td>
<td>-</td>
</tr>
<tr>
<td>Coste (2014)</td>
<td>4 PD FOG unknown</td>
<td>Shin (1)</td>
<td>Accelerometer Gyroscope Magnetometer</td>
<td>Walking task with dual tasking.</td>
<td>?</td>
<td>?</td>
<td>Labeled video</td>
<td>Sensitivity: 79.5%</td>
<td>-</td>
</tr>
<tr>
<td>Kwon (2014)</td>
<td>12 PD FOG+</td>
<td>Shoe (2)</td>
<td>Accelerometer</td>
<td>A walking task.</td>
<td>✓</td>
<td>-</td>
<td>Labeled video</td>
<td>Sensitivity: 86% (from graph) Specificity: 86% (from graph)</td>
<td>-</td>
</tr>
<tr>
<td>Yungher (2014)</td>
<td>14 PD FOG+</td>
<td>Lower back (1) Thigh (2) Shin (2) Feet (2)</td>
<td>Accelerometer Gyroscope Magnetometer</td>
<td>TUG in a 5-m course.</td>
<td>-</td>
<td>✓</td>
<td>Labeled video</td>
<td>No validity/reliability measures were reported.</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4.2. continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Device locations (n)</th>
<th>Type of Sensor</th>
<th>Procedures</th>
<th>ON</th>
<th>OFF</th>
<th>Reference</th>
<th>Validity results</th>
<th>Tested for cueing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Djuric-Jovici (2014) [47]</td>
<td>12 PD FOG unknown</td>
<td>Shin (1)</td>
<td>Accelerometer Gyroscope</td>
<td>To walk along a complex pathway, created to provoke freezing episodes.</td>
<td>-</td>
<td>✓</td>
<td>Labeled video</td>
<td>Sensitivity/ Specificity: FOG with tremor: 100%/99% FOG with complete motor block: 100%/100%</td>
<td>-</td>
</tr>
<tr>
<td>Tripoliti (2013) [48]</td>
<td>11 PD FOG+ 5 non-PD</td>
<td>Wrist (2) Shin (2) Waist (1) Chest (1)</td>
<td>Accelerometer Gyroscope</td>
<td>A series of walking tasks.</td>
<td>✓</td>
<td>✓</td>
<td>Live annotation by clinician, confirmed by video analysis.</td>
<td>Sensitivity: 81.94% Specificity: 98.74%</td>
<td>-</td>
</tr>
<tr>
<td>Moore (2013) [49]</td>
<td>25 PD FOG+</td>
<td>Lower back (1) Thigh (2) Shin (2) Feet (2)</td>
<td>Accelerometer</td>
<td>TUG on a standardized 5-m course.</td>
<td>-</td>
<td>✓</td>
<td>Labeled video</td>
<td>ICC number of FOG/ ICC percent time frozen/ sensitivity/ specificity All sensors: 0.75 / 0.80 / 84.3% / 78.4%. 1 shin only: 0.75 / 0.73 / 86.2% / 66.7%. Lower back only: 0.63 / 0.49 / 86.8% / 82.4%</td>
<td>-</td>
</tr>
</tbody>
</table>
### Table 4.2.
Characteristics of studies that investigated wearable sensors for FOG detection (n=23)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Device locations (n)</th>
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<th>Procedures</th>
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<th>OFF</th>
<th>Reference</th>
<th>Validity results</th>
<th>Tested for cueing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris (2012) [50]</td>
<td>10 PD</td>
<td>Shin (2)</td>
<td>Accelerometer</td>
<td>TUG on a standardized 5-m course.</td>
<td>-</td>
<td>✓</td>
<td></td>
<td>ICC for number of FOG episodes: 0.78. ICC for percentage time frozen: 0.93.</td>
<td>-</td>
</tr>
<tr>
<td>Shin (2)</td>
<td></td>
<td>Shin (2)</td>
<td>Accelerometer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morrise (2012) [51]</td>
<td>21 PD</td>
<td>Lower back (1)</td>
<td>Accelerometer</td>
<td>3 times the extended length iTUG.</td>
<td>-</td>
<td>✓</td>
<td></td>
<td>FOG scale &amp; ABC scale, and comparison between groups (PD FOG+, PD FOG- and non-PD). Criterion validity: Frequency Ratio &amp; FOG scale: $\rho=0.6$, $p=0.002$ Frequency Ratio &amp; ABC scale: $\rho=-0.47$, $p=0.02$ Discriminant validity: Frequency Ratio was larger in PD FOG+ compared to PD FOG- (p=0.001), and in PD FOG- versus non-PD (p=0.007).</td>
<td>-</td>
</tr>
<tr>
<td>Shin (2)</td>
<td></td>
<td>Shin (2)</td>
<td>Gyroscope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** FOG+ = Freezing of Gait, PD = Parkinson’s Disease, iTUG = Initiative Transfer of Ground.
Table 4.2. continued

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Device locations (n)</th>
<th>Type of Sensor</th>
<th>Procedures</th>
<th>ON</th>
<th>OFF</th>
<th>Reference</th>
<th>Validity results</th>
<th>Tested for cueing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niazmand (2011)</td>
<td>6 PD FOG+</td>
<td>Thigh (2) Shin (2) Bellybutton (1) (sensors embedded in pants)</td>
<td>Accelerometer</td>
<td>A series of walking tasks.</td>
<td>?</td>
<td>?</td>
<td>Labeled video</td>
<td>Sensitivity: 88.3% Specificity: 85.3%</td>
<td>-</td>
</tr>
<tr>
<td>Jovanov (2009)</td>
<td>1 PD FOG unknown 4 non-PD</td>
<td>Knee (1)</td>
<td>Accelerometer Gyroscope</td>
<td>Walking task.</td>
<td>?</td>
<td>?</td>
<td>Labeled video</td>
<td>No validity measures were reported.</td>
<td>✓</td>
</tr>
<tr>
<td>Moore (2008)</td>
<td>11 PD FOG+ 10 non-PD</td>
<td>Shin (1)</td>
<td>Accelerometer</td>
<td>Walking task along complex pathway to provoke FOG.</td>
<td>✓</td>
<td>✓</td>
<td>Labeled video</td>
<td>Sensitivity without calibration: 78% Sensitivity with calibration: 89% Specificity not reported.</td>
<td>-</td>
</tr>
<tr>
<td>Author</td>
<td>Sample</td>
<td>Device locations (n)</td>
<td>Type of Sensor</td>
<td>Procedures</td>
<td>ON</td>
<td>OFF</td>
<td>Reference</td>
<td>Validity results</td>
<td>Tested for cueing</td>
</tr>
<tr>
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</tr>
<tr>
<td>Mancini (2017) [56]</td>
<td>16 PD FOG+ 12 PD FOG- 14 non-PD</td>
<td>Shin (2) Waist (1)</td>
<td>Accelerometer Gyroscope</td>
<td>TUG on a 7-m course; Turning 360 in place for 2 minutes.</td>
<td>-</td>
<td>✓</td>
<td>Labeled video</td>
<td>Criterion validity: Freezing Ratio duration x Clinical ratings: ρ=0.7, p=0.003 Freezing Ratio duration x FOG questionnaire: ρ=0.5, p=0.03</td>
<td>-</td>
</tr>
<tr>
<td>Capecci (2016) [55]</td>
<td>20 PD FOG+</td>
<td>Waist (1)</td>
<td>Accelerometer</td>
<td>TUG on a standardized 5-m course.</td>
<td>✓</td>
<td>-</td>
<td>Labeled video</td>
<td>Algorithm 1 / Algorithm 2 Sensitivity: 70.2%/87.5% Specificity: 84.1%/94.9% Precision: 63.4%/69.5% Accuracy: 81.6%/84.3% AUC: 0.81/0.90</td>
<td>-</td>
</tr>
<tr>
<td>Author</td>
<td>Sample Location (n)</td>
<td>Type of Sensor</td>
<td>Procedures</td>
<td>ON</td>
<td>OFF</td>
<td>Reference</td>
<td>Validity Results</td>
<td>Tested for cueing</td>
<td></td>
</tr>
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<td>-----------------</td>
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<tr>
<td>Handojoseno (2015)[54]</td>
<td>4 PD FOG+ Scalp (8)</td>
<td>EEG</td>
<td>TUG on a standardized 5-m course.</td>
<td>✓</td>
<td>-</td>
<td>Labeled video</td>
<td>Sensitivity occipital channel: 74.6%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Specificity occipital channel: 48.4%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Accuracy occipital channel: 68.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FOG: Freezing of Gait; PD: Parkinson’s Disease; FOG+: PD patients with diagnosed Freezing of Gait events; FOG-: PD patients with no diagnosed Freezing of Gait events; SC: Skin conductivity; ECG: electrocardiogram; non-PD: participants that have not been diagnosed with PD; ACC: three triaxial accelerometer; TUG: Timed-Up-and-Go test; ICC: Intraclass correlation; iTUG: automated Timed-Up-and-Go test; FOG questionnaire: Freezing Of Gait questionnaire; ABC scale: The Activities-specific Balance Confidence Scale; AUC: Area under curve.
The sample sizes varied from 1 [28] to 48 PD [51] per study, with a non-PD group being included in a few studies [28, 40, 48, 51, 53, 56]. Disease severity, when reported, ranged from 2 to 4 according to the Hoehn and Yahr scale. Data were collected according to three types of protocols: (1) a set of structured tasks performed in a laboratory environment (n = 18); (2) a protocol performed in a laboratory environment in which at least a part of which was designed to capture naturalistic behaviour (n = 2); and (3) natural or naturalistic behaviour in a home environment (n = 3).

The types of sensors embedded in the devices worn by the participants varied. Tri-axial accelerometers were used in 22 articles, either as a single sensor (48%, n = 11), or combined with gyroscopes (35%, n = 8), or magnetometers (13%, n = 3). One study used electroencephalogram to measure changes in the brain activity from pre-determined areas during FOG episodes. Regarding the number of body locations, 56% (n = 13) of the studies utilized one location, while the other 44% (n = 10) used a combination of two or more locations. The shin (66% of studies, n = 16; 4 times used as the single location) and waist (33% of studies, n = 8; 3 times as the single location) were the most common body locations for the devices, although nine other locations were also explored (Figure 4.2).

**Figure 4.2.** Distribution of device body location for FOG measurement

**Falls: detection and fall risk analysis**

Four articles on falls were retrieved: one article on fall detection and three articles presented the use of wearable sensors for analyzing fall risk. All protocols were performed in a home-based setting (Table 4.3) [57–60], and the sample size varied from one patient in a case report [57] up to 107 PD in a cross-sectional
study [59]. One study reported disease severity and had an average Hoehn and Yahr score of $2.6 \pm 0.7$ [59]. All studies used tri-axial accelerometers. One study combined this sensor with force and bending sensors [58]; another with gyroscopes [60]. Sensor body locations included chest, insole (i.e., under the arch of the foot), and lower back.
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Device location (n)</th>
<th>Type of Sensor</th>
<th>Measure(s)</th>
<th>Procedures</th>
<th>ON</th>
<th>OFF</th>
<th>Reference</th>
<th>Validity results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fall detection at home</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamura (2005) [57]</td>
<td>1 PD</td>
<td>Chest (1)</td>
<td>Accelerometer</td>
<td>Detection of falls</td>
<td>Participant carried the sensor in daily life.</td>
<td>✔</td>
<td>✔</td>
<td>Fall diary</td>
<td>Criterion validity: 19 out of 22 falls were detected. Specificity/false positives not reported.</td>
</tr>
<tr>
<td><strong>Fall risk at home</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayena (2015) [58]</td>
<td>7 PD</td>
<td>Insole (4)</td>
<td>Accelerometer</td>
<td>Proposed new OLST score (with incorporation of both iOLST and score derived from balance model)</td>
<td>Participants performed the OLST at home as part of a serious game for balance training.</td>
<td>✔</td>
<td>-</td>
<td>iOLST score Comparison between groups (PD vs young non-PD vs elderly non-PD, ground type)</td>
<td>Criterion validity: Proposed OLST score was not significantly different from iOLST score in all groups. Discriminant validity: Proposed OLST score was significantly different between PD and non-PD subjects. Proposed OLST score was significantly differed between ground types.</td>
</tr>
</tbody>
</table>
Table 4.3. Characteristics of studies that investigated wearable sensors for fall and fall risk (n=4)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Device location (n)</th>
<th>Type of Sensor</th>
<th>Measure(s)</th>
<th>Procedures</th>
<th>ON</th>
<th>OFF</th>
<th>Reference</th>
<th>Validity results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss  (2014) [59]</td>
<td>107 PD</td>
<td>Lower back (1)</td>
<td>Accelerometer</td>
<td>Anterior-posterior width of dominant frequency</td>
<td>Patients wore the sensor for 3 consecutive days at home.</td>
<td>✓</td>
<td>✓</td>
<td>Comparison with BBT, DGI and TUG.</td>
<td>Anterior-posterior width was significantly correlated with BBT ($r = -0.30$), DGI ($r = -0.25$) and TUG ($r = 0.32$). Among non-fallers: time until 1st fall during 1-year follow-up. Comparison between fallers (n=40) and non-fallers (n=67) based on fall history. Criterion validity: Anterior-posterior width was significantly correlated with BBT ($r = -0.30$), DGI ($r = -0.25$) and TUG ($r = 0.32$). Discriminant validity: Anterior-posterior width was larger ($p = 0.012$) in the fallers compared to the non-fallers.</td>
</tr>
<tr>
<td>Iluz (2014) [60]</td>
<td>40 PD</td>
<td>Lower back (1)</td>
<td>Accelerometer</td>
<td>Detection of missteps</td>
<td>Labor: Walking tasks designed to provoke missteps (including dual tasking and negotiating with obstacles)</td>
<td>✓</td>
<td>✓</td>
<td>Laboratory: Hit ratio: 93.1% Specificity: 98.6%</td>
<td>Home: Comparison of groups (fallers vs. non-fallers)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gyroscopes</td>
<td></td>
<td></td>
<td>Home: Participants worn the devices for 3 days during day time.</td>
<td></td>
<td></td>
<td>Criterion validity: Laboratory: Odds ratio of detection 1 or more missteps in fallers vs non-fallers: 1.84 ($p=0.010$, 95% confidence interval: 1.15 – 2.93). Discriminant validity: Home:</td>
<td></td>
</tr>
</tbody>
</table>

PD: Parkinson's Disease patients; OLST: One-Leg Standing Test; iOLST: automatic One-Leg Standing Test; BBT: Berg Balance Test; DGI: Dynamic Gait Index; TUG: Timed-up-and-go.
Validation

**FOG detection**
Among the 23 articles investigating FOG detection, 18 reported measures of validation performance (e.g., sensitivity, specificity, or accuracy) \[17, 36–45, 47–49, 52–55\], three studies used correlation measures, correlating the wearable-derived measure with the period of freezing or number of FOG events \[50, 51, 56\], and two studies did not report validity measures \[28, 46\].

Overall, validity values ranged from 73 to 100% for sensitivity, and from 67 to 100% for specificity, and accuracy ranged from 68% up to 96%. Validity measures are summarized and compared across protocol setups in Figures. 4.3 and 4.4.

![Figure 4.3. Instrument performance (sensitivity) in FOG detection](image-url)
Figure 4.4. Instrument performance (specificity) in FOG detection
* Not reported.

Fall detection and fall risk analysis
One article investigated the use of wearable sensors to detect falls, by comparing the data from a self-reported diary to the sensor data. The sensor captured 19 fall events from a total of 22 self-reported events [57].

Three articles presented the use of wearable sensors for analyzing fall risk. All of them reported discriminant validity by comparing sensor-derived outcomes between different groups, such as fallers and non-fallers or PD versus non-PD (see Table 4.3, for details). Weiss et al. [59] reported an illustrative approach, whereby the 107 participating PD patients wore one sensor in the lower back and made diary annotations about fall events. The sensor data, collected remotely in the patient’s home, were subsequently used to calculate a fall risk index. The time until variable gait pattern (log rank test: p = 0.0018, Wilcoxon test: p = 0.0014).
DISCUSSION

This review included 27 articles, 23 on FOG, and four on falls. FOG studies were performed either in a laboratory or at home, with different types of protocols (structured versus free-movement). The shin (16/28 studies) was the most common device location and tri-axial accelerometers (26/28 studies) the most common sensor type. Sensitivity ranged from 73% to 100% and specificity ranged from 67% to 100% for the detection of FOG. Fall and fall risk studies were all home-based, using mostly one device (3/4 studies) containing tri-axial accelerometers. Sensors were positioned on the chest, insole, and lower back. The systems detected falls or quantified fall risk by various approaches and with varying degrees of validity.

FOG detection

The results in this review support the potential for wearable devices. In the laboratory, systems showed a moderate to high specificity and sensitivity, which are in line with other evidence that wearable systems detecting FOG are already well validated in a laboratory setting [30]. Moreover, promising results were also achieved in studies performed in the home environment. Interestingly, the comparison of validity measures in terms of sensitivity and specificity (Figs. 3, 4) suggests that wearable sensors are able to accurately detect FOG, independent of study protocol (e.g., home versus laboratory environment; structured versus unstructured protocols) and system design (e.g., one sensor only versus multiple sensors, and one device versus a set of combined devices in different body locations). However, one should be cautious when directly comparing reported performance between studies, for a number of reasons: in particular, one should consider additional factors, such as algorithm used, outcome definitions, data analysis methods, and the intended application of the system.

First, even though FOG is a well-defined symptom [8], what objectively constitutes FOG is unclear. The challenge lies in rigorously defining, from an algorithmic point of view, such a complex event, which can appear in different forms and intensities. Furthermore, the definition of the measured outcome has an important impact upon instrument validity assessment. In this review, some studies only included long-duration FOG episodes. Omitting small FOG episodes may lead to inaccurate estimates of FOG detection rates. A comprehensive definition such as that used by Djuric–Jovici and colleagues [47], differentiating between FOG with trembling and FOG with complete motor blocks prior to video labeling and test properties, seems to address the problem by incorporating different types of FOG events. However, this definition was not used in other studies. A clear and comprehensive definition would improve the comparability of instrument performance.
Second, the intended application of the instrument is another aspect to be considered in FOG detection. It is attractive to aim for rates of 100% specificity and sensitivity. However, this may result in signal processing operations which require substantial computational resources. As illustrated by Ahlrichs [37], the detection of FOG episodes was achieved with high sensitivity and specificity, but the data processing was time-consuming with delays of up to 60s. Similarly, algorithms with high accuracy may require substantial computational resources which may have an adverse effect on power consumption and hence battery life for non-intrusive, portable devices. This fact may prevent the use of such systems for real-time detection and cueing. Therefore, it is reasonable to conclude that at this point, the acceptability of instrument performance in detection of FOG relate to its application, and many of these algorithms will require substantial mathematical and engineering efforts in order to reduce computational delays to an acceptable level. Furthermore, some algorithms required individual calibration and others did not, which also has practical consequences for applications in clinical and research practice.

Finally, although there exists the potential for these instruments being applied to long-term monitoring in free living conditions, only a few systems were actually validated in the home environment. Therefore, the majority of the technology available lacks “ecological” validation. Thus, further research using larger sample sizes, longer follow-up periods under more realistic home environments is necessary.

**Fall detection and fall risk calculation**

Del Din and colleagues described that real-world detection of falls is a substantial challenge from a technical perspective, and almost all evidence in their review was limited to controlled settings and young healthy adults [30]. This finding is confirmed in this review, most clearly illustrated by the fact that we only found one article reporting on fall detection accuracy in PD. However, it is possible that this small number of articles is not only a result of the complexity of capturing falls in PD under realistic, free-living conditions. It certainly highlights an area where the validity of wearable sensors still needs to be examined. In addition, fall risk calculation has the potential to provide objective information before the fall event happens, which may be more valuable than simply counting the number of events and dealing with the consequences.

Fall risk estimation has a clear relevance for clinical practice [58]. Falls are common and disabling, even in early PD [61]. In addition, falls are also related to physical injury [61], high hospitalization cost [62], and social/psychological impact [63], either on their own or due to the anticipatory fear of falling [64]. Even though the number of retrieved articles investigating fall risk calculation was not high, the results seem to confirm the potential for wearable sensors to accurately calculate fall risk for PD.
CONCLUSION

This systematic review presents an overview of studies investigating the use of wearable sensors for FOG and falls in Parkinson’s disease. Despite promising validation initiatives, study sample sizes are relatively small, participants are mainly in early stages of the disease, protocols are largely laboratory-based, and there is little consensus on algorithms analysis. Further work in ecological validation, in free-living situations, is necessary. There also is a lack of consistency in outcomes measured, methods of assessing validity, and reported results. Given these limitations, the validation of sensor-derived assessments of PD features would benefit from increased collaboration among researchers, aligning data collection protocols, and sharing data sets.
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Wearable sensors for Freezing of gait and falls


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41. Rezvanian S, Lockhart TE (2016) Towards real-time detection of freezing of gait using wavelet transform on wireless accelerometer-
Wearable sensors for Freezing of gait and falls


109

Chapter 4


Chapter 5

Home-based monitoring of falls using wearable sensors in Parkinson’s disease

Submitted
Chapter 5

ABSTRACT

Importance: Falling is among the most serious clinical problems in Parkinson’s disease (PD).

Objective: We used body-worn sensors (falls detector worn as a necklace, with embedded tri-axial accelerometer and barometer) to quantify the hazard ratio of falls in PD patients in real life.

Design: We analyzed prospectively collected data from a commercial dataset on a cohort of home-dwelling elderly subjects. Fall events were collected either automatically using the wearable falls detector or registered by a button push on the same device. We extracted fall events from a 2.5-year window, with average follow-up of 1.1 years. All falls included were confirmed immediately by a subsequent telephone call.

Setting: Elderly subscribers to an emergency response program including automatic fall detection.

Participants: We matched 2,063 individuals with self-reported PD to 2,063 individuals without PD matched for age, gender, comorbidity, and domestic conditions.

Main outcomes: (1) Incidence rate of any fall, (2) incidence rate of a new fall after enrollment (i.e. hazard ratio), and (3) one-year cumulative incidence of falling.

Results: Incidence rate of any fall was higher among PD patients than matched elderly (2.1 versus 0.7 falls/person, respectively; p<.0001). The incidence rate of a new fall after enrollment (i.e. hazard ratio) was 1.8 times higher for PD patients than matched elderly (95% confidence interval: 1.6-2.0). A higher percentage of PD patients (49%) than matched elderly (29%) experienced at least one fall during one year of follow-up (p<.0001). Among PD patients, 30% (n=610) registered more than two falls after enrollment against 15% (n=300) in matched elderly (p<.0001). The number of falls resulting in emergency transport was higher for PD patients (n=292) compared to matched elderly (n=183).

Conclusion and Relevance: Having PD nearly doubles the incidence of falling in real life. These findings highlight PD as a prime “falling disease” and emphasize the importance of dedicated strategies to prevent falls. The results also point to the feasibility of using body-worn sensors to monitor falls in daily life.

Keywords
Falls incidence; Parkinson’s disease
Wearable sensor; home-based monitoring
INTRODUCTION

Falling is among the most serious clinical problems faced by older adults, occurring in 19-49% of the elderly population [1]. Falls can have major consequences, such as fractures and other injuries [2], hospitalization, and a negative impact on social and psychological wellbeing [3]. Moreover, mortality is increased in subjects with falls [4]. Parkinson's disease (PD) is a prime example of a progressive neurological condition where falls are very common, presumably because many risk factors coincide in this disorder. Specifically, persons with PD have both balance and gait deficits (including freezing episodes), and commonly also cognitive deficits [5]. Additional risk factors include – among others – visual impairments [6], benzodiazepine intake [2], and postural hypotension [7].

Epidemiological studies and evaluations of novel interventions are difficult to design because fall detection in daily life remains difficult. The typical methodology for capturing real-life fall events is using diaries [8-12]. However, these diaries have a poor reliability and compliance is suboptimal. Consequently, the outcomes usually correlate poorly with real-life behavior [11, 13]. Modern technology offers new possibilities to overcome those limitations, e.g. by using body-worn wearable sensors [14-17]. Such sensors can potentially detect falls automatically, quantitatively and, importantly, continuously in the patient's own environment, thus providing an attractive alternative to the self-reported burdensome and unreliable diaries. Some promising examples of using wearable sensors to quantify fall events in controlled settings and free-living environments were reported in PD [18, 19]. Using a single sensor to automatically register fall events, one study automatically detected 19 out of 22 true events [19]. Moreover, sensors can also be used together with a personal emergency response system built into the sensor box, thus providing patients with rapid access to emergency assistance if needed, e.g. when they experience difficulty rising after the fall [20].

In this study, we analyzed data from such a personal emergency response system in a large cohort of elderly subjects who used a single wearable fall detector, worn as a necklace, to collect fall events in their own home environment. Using these real-life data, collected for up to 2.5 years follow-up, we aimed to determine the hazard ratio of falling among participants with PD compared to matched-elderly.
METHODOLOGY

Study design and participants
In this prospective cohort study, we analyzed an existing dataset composed of data from subscribers to a personal emergency response system (Philips Lifeline® service). No personal, customer, or proprietary data were shared by Philips. This service can provide immediate access to appropriate help. The personal emergency response system consists of a device worn as a necklace with multiple sensors embedded (i.e. tri-axial accelerometer and barometer) and is designed to automatically detect fall events in elderly. It also enables users to press a button to report emergency situations, such as a fall event, and contact a central response center for help. [20] Either way, when a fall is automatically detected or self-reported, a call is generated to a central response center and support is provided as needed. In addition to support, the central response center confirms whether or not a fall event took place. The fall detector can be worn continuously and contains a battery that lasts for more than 18 months.

Among all participants, we selected a convenience sample including all self-reported PD participants (n=2,063). Using sample characteristics – age, gender, number of self-reported medical conditions, and domestic conditions (i.e. living alone or not) – we extracted a matched elderly group from those elderly reporting not to have PD, but who were also prone to falling and had therefore subscribed to the same falls program. No selection based on type of medical condition was applied to the control group. Therefore, participants included in the matched group consisted of elderly subscribers living with a diversity of chronic conditions. For the matching procedure we used the Propensity Score Matching technique, matching cases with a nearest neighbor approach guided by logit scores [21].

The analysis was conducted on a pseudonymized pre-existing data set, and was approved by the Philips internal board of ethics. Therefore, approval from an external Medical Ethical Committee was not required for this analysis.

Data collection and outcomes
Fall events were reported either by a button-push or collected automatically using a fall detector worn as a necklace with multiple sensors embedded (i.e. tri-axial accelerometer and barometer – figure 5.1.). The pendant device uses data from the embedded sensors (i.e. tri-axial accelerometer and barometric pressure) to identify falls from changes in height, orientation, and impact, as experienced during a fall episode. The fall detection algorithm was developed and validated by Philips, based on recorded sensor data from approximately 600 simulated falls of n=31 healthy volunteers for typical falls (standing, forward, backward, sideward, sitting), from falls using crash dummies for high risk
situations (e.g. stairs) and approximately 30000 hours of daily-life activity collected from elderly people [20]. The results from the white paper on device performance showed that validity was good, with a detection rate >95% [20]. All falls incidents that are reported in the present study were confirmed and annotated by a call center; false-positive findings (automatically detected falls that were not confirmed during the follow-up call) were excluded from the analyses.

The dataset was created between January 2012 and June 2014. From this dataset, we extracted data from a window of data of up to 2.5 years after service enrollment. Fall events were collected until the participant was lost to follow-up or reached the end of the 2.5-year observational window. We analyzed all fall events that were confirmed as “fall” during the call between the central response center and the participant. Calls to the central response center were initiated either by an automatic fall detection algorithm or a button push by the subject immediately after the fall. False alarms, accidental button presses or near-falls were not labeled as a fall event in the dataset. The database included loggings of all contacts between the participant and the central response center from which the number of falls was determined. Information on demographics and self-reported medical history was collected during a welcome call at service enrollment.

The following outcomes were calculated: (1) incidence rate of any fall: ratio between any fall event registered and the observed follow-up time (falls per person-year), (2) incidence rate of a new fall after enrollment: additional hazard ratio of experiencing a new fall event after enrollment for patients having PD in comparison to matched-elderly, and (3) one-year cumulative incidence of falling: percentage of participants in both groups that presented at least one fall one-year after enrolment. For all outcomes, we assessed the difference between PD patients and matched-elderly.
Statistical analysis
Descriptive analysis was used to report the incidence rate of any fall for both PD patients and matched-elderly. Between-group differences were determined by t-tests (continuous variables) or chi-squared tests (categorical variables). We assessed the association of PD with the incidence rate of any fall using ANOVA models, with PD status, age, gender, and number of medical conditions as independent predictors and number of falls as dependent variable (significance at p<.05). Using this model as base, we added two-way and three-way interaction terms of age, gender, or age*gender with PD in separate sensitivity analyses. We subsequently stratified analyses by age, in which we dichotomized at the mean value (78.6 years) to create a young (<mean age) and an old (>mean age) groups of participants.

We investigated the association of PD with the incidence rate of a new fall after enrollment using Cox regression models, with PD status, age, gender, and number of medical conditions as independent predictors and new fall after enrollment (yes/no) as the dependent variable. The proportional hazards assumption was verified by plotting the residuals over time (supplementary figure). In separate sensitivity analyses, we added two-way and three-way interaction terms of age, gender, or age*gender with PD to the main model to assess possible interaction. Finally, a Kaplan-Meier survival analysis was applied to assess the cumulative incidence of new falls after enrollment during one-year follow-up for both PD and matched-elderly.

For all analyses, a p-value ≤.05 was regarded as statistically significant. All analyses were performed using R statistical software, version 3.3.2.

RESULTS

Participants characteristics
All 2,063 subscribers to the personal emergency response system with self-reported PD were included. A matched group of 2,063 subscribers not reporting PD was considered as matched-elderly. Table 5.1. presents the subjects’ characteristics. Data were extracted from a 2.5-year window, and average follow-up was 1.1 years (because not all participants used the personal emergency response system throughout this period).
Table 5.1. Characteristics of PD and matched-elderly

<table>
<thead>
<tr>
<th>Variable</th>
<th>PD (n=2063)*</th>
<th>Matched-elderly (n=2063)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (mean±SD)</td>
<td>1.1±0.6</td>
<td>1.1±0.6</td>
</tr>
<tr>
<td>Age in years (mean±SD)</td>
<td>78.6±8.4</td>
<td>78.4±8.9</td>
</tr>
<tr>
<td>Gender (% of men)</td>
<td>48.3</td>
<td>48.1</td>
</tr>
<tr>
<td>Number of medical conditions (mean±SD)</td>
<td>2.6±2.3</td>
<td>2.5±2.2</td>
</tr>
<tr>
<td>Living condition (% living alone)</td>
<td>92.1</td>
<td>92.6</td>
</tr>
</tbody>
</table>

*Due to matching procedure, the groups did not differ in any characteristics (p>.05).

Fall events
A total of 6,436 falls events were detected in both groups. PD participants had a higher incidence rate of any fall compared to controls (2.1 versus 0.7 falls/person-year, respectively; p<0.0001). The difference in incidence rate of any fall between PD participants and matched elderly was more distinct among older individuals (table 5.2.). Among PD patients, 30% (n=610) registered more than two falls during their follow-up of 1.1 year and were thus classified as recurrent fallers. This was 15% (n=300) in matched elderly (p<.0001). The absolute number of fall events resulting in emergency transport, but not the proportion, was higher among PD patients (n= 292; 6% of all falls among PD) in contrast to matched elderly (n=183; 12% of all falls among elderly-matched). When only recurrent fallers where analyzed, the number of events resulting in emergency transport among PD patients (n=45, 2%) was almost double that of the matched elderly group (n=28, 1%).

Table 5.2. Fall incidence for patients with Parkinson's disease and a matched control group

<table>
<thead>
<tr>
<th>Incidence rate of any fall (falls per person-year)</th>
<th>PD (n=2063)</th>
<th>Matched (n=2063)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>2.1</td>
<td>0.7</td>
<td>&lt;.0001¹</td>
</tr>
<tr>
<td>Younger* (&lt;78.6 years)</td>
<td>1.7</td>
<td>0.6</td>
<td>&lt;.0001²</td>
</tr>
<tr>
<td>Older* (&gt;78.6 years)</td>
<td>2.7</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of faller (%)</th>
<th>PD</th>
<th>Matched</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-faller</td>
<td>1080 (52.4%)</td>
<td>1425 (69.1%)</td>
<td>&lt;.0001³</td>
</tr>
<tr>
<td>Single faller (1 fall/year)</td>
<td>373 (18.1%)</td>
<td>338 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>Recurrent faller (≥2 falls/year)</td>
<td>610 (29.6%)</td>
<td>129 (14.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Groups were dichotomized at the mean value (78.6 years). 1-Poisson regression, 2- ANOVA Two-way interaction analysis; 3-Chi-square test.
One-year conversion to fallers rate

The incidence rate of a new fall after enrollment (i.e. hazard ratio for falling or time to a new fall) was 1.8 (95% CI=1.6-2.0) for a participant having PD compared to a matched-elderly participant. The hazard ratio of falling was not influenced by two-way interaction of age and PD (p=.6), gender and PD (p=.2), or three-way interaction of age, gender and PD (p=.9). A higher percentage of PD participants had at least one fall after a one-year follow-up, with 48.8% of PD participants, compared to 29.5% in the matched-elderly group (p<.001) (figure 5.2.).

**Figure 5.2.** Probability of falling after enrolment for PD group (black) and matched-elderly (gray).
DISCUSSION

This is the first large-scale study that determines the real-life incidence of falls using a wearable system, with all reported falls being confirmed by the faller during a telephone contact immediately after the fall. This enabled us to robustly quantify the hazard ratio of falling of PD patients in daily life. The large cohort size allowed us to create both a PD group and a matched elderly control group, leading to an accurate estimation of the additional relative hazard ratio that PD brings. Results from 4,126 participants, followed on average for 1.1 years, showed that PD patients have a much higher incidence rate of any fall compared to controls. Fall rates were highest for older PD patients, who sustained on average 2.7 falls per person-year (three times as often as controls). Finally, PD patients had a 1.8 times higher incidence rate of a new fall after enrollment compared to controls. This hazard ratio was not influenced by the interaction between PD and age or gender.

A high number of fallers among PD patients has been described previously [22,23]. A similar prospective cohort study followed 100 PD patients and 55 matched controls [23]. After one year, 54% of PD patients and 18% of controls were fallers. Our present results (48% fallers among PD patients versus 31% in matched elderly controls after one-year follow-up) are in accordance with this. Additionally, we show that the interaction of age and PD leads to higher incidence rate of any fall. Specifically, in our cohort, older PD patients fell almost three times as often as controls. The effect of age on fall rates was inconsistent in previous reports [24], but the ageing process may affect the clinical presentation of PD, leading to a worse phenotype [25]. Additionally, older PD patients are likely to show a higher disease duration and greater severity, thus being more prone to falling [26].

We also show that PD nearly doubles the hazard ratio of a new fall after enrollment. In previous studies [10,26,27], the criteria used to select matched individuals may have substantially affected the fall incidence rate, as well as the observed hazard ratio for falling associated with PD. For example, Mak [10] reported a much higher fall risk rate of 4.2 after following 72 PD patients and 47 controls. However, their control group involved healthy subjects recruited from local community health centers, who usually have fewer falls. This bias is not present in our study: our PD participants were not selected or excluded based on any medical condition or living style. Additionally, the large sample size allowed us to produce a more representative control group than seen previously, avoiding the non-realistic increase or decrease of fall risks. Thus, we believe that the hazard ratio of falling presented here is the most accurate hazard ratio – incidence rate of a new fall after enrollment – for home-dwelling PD patients subscribers to a personal emergency system. Importantly, this finding confirms that PD is associated with a high
The incidence rate of fall in daily life, emphasizing the need for fall-prevention programs tailored to this specific population.

The results of this study are an encouraging example of the feasibility of wearable sensors to monitor falls in real life. In the past years, several initiatives applied wearable sensors for fall detection, with good results [28]. Although more work is needed to refine algorithms, especially for PD patients in real life [29], those studies highlighted the utility of sensors not only to detect falls, but also to predict falls and quantify the risk of falling. In fact, an accurate and unobtrusive wearable falls monitoring system could improve data collection for trials and support daily care, by overcoming the high attrition rates and incorrect data completion seen with paper diaries [30]. Moreover, wearable sensors have potential to identify patients with a high risk of falling [31]. Consequently, monitoring with sensors may increase timely referral to falls prevention programs, aiming to decrease the impact of falls in the daily life and increase independency [32]. This potential of sensors becomes more important when considering the higher number of falls in PD patients resulting in emergency transport that was observed in the present study. Future research focusing on refining algorithms for fall detection, fall prediction, and fall risk analysis would assist the field by providing a more robust body of evidence to introduce wearable sensors as instruments for falls management.

**Strengths and drawbacks**

Beyond the large and well-matched groups of PD patients and controls, three further points strengthen this study. First, this is the first large study to objectively monitor fall episodes during a long follow-up in a home environment using a wearable sensor. Other smaller initiatives successfully used wearable sensors to collect falls-related data in the elderly [33]. However, initiatives to monitor falls for long periods in daily life remain scarce. Our study supports the merits of using wearable sensors as an option to objectively and reliably monitor falls in a patient’s home environment over a longer period. Second, many prior studies adopted tight in- and exclusion criteria [34], thus creating a selected population that may not mirror the real population with PD and thus bias the results. Our study did not apply such tight exclusion criteria, producing a more representative sample of PD patients in real-life. Finally, this is the first study to analyze a total of 6,436 fall events that were all confirmed immediately after the incident by a telephone call. This large dataset of confirmed falls ensures that the results presented here reflects the burden faced by PD patients in real-life.

Our study also had several limitations. First, all variables, except for the fall episodes, were self-reported by patients. This limitation was partially addressed by the matching procedure and the large sample size. However, we could not verify the diagnosis of PD, as this also depended on self-report. We consider it unlikely that many participants
reported having PD, whereas in fact they suffered from very different conditions. However, we cannot exclude that some patients had a form of atypical parkinsonism or that some participants in the control group are fallers who have not yet been diagnosed with PD. In any scenario, these limitations would lead to even higher fall rates. Additionally, the dataset used in this study did not include detailed information on competing risk for falls, such as type of medication in use. This limitation hampered the application of additional survival analysis methods during data analysis. Although it does not invalid the conclusions presented here, this limitation should be addressed in future studies. Second, although all fall episodes were confirmed by an immediate call, the confirmation procedure was only triggered by either algorithm detection or a button press. Therefore, during this process, some fall events may have been missed if the algorithm detection failed and, at the same time, patients also did not use the button press (i.e. we do not know the false negative rate of falls). However, this could only imply that actual fall rates in daily life are even higher than what we observed here, and we have no reason to assume that this false-negative rate would be different for PD patients and matched controls. Third, it was not possible to verify the ratio of falls reported by button-push versus those detected by algorithm detection, which also precluded the analysis of system performance among PD patients. However, this information does not influence the hazard ratio of falling here reported. Finally, our conclusions apply only to a population composed of elderly people prone to falling and subscribers to a personal emergency response system. Whether this high rate of falling is also present in the general PD population remains to be investigated.

CONCLUSION

In conclusion, by collecting fall events using wearable sensors, this study demonstrated that having PD nearly doubles the incidence of falling in real life. This confirms PD as a prime falling disease. Additionally, the collection of fall events in over 4,000 participants, using a wearable sensor connected to a personal emergency response system, highlights the potential of using body-worn sensors for long-term home monitoring.
REFERENCES


Chapter 6

Impact of motor fluctuations on real-life gait in Parkinson’s disease

ABSTRACT

Introduction: People with PD (PWP) have an increased risk of becoming inactive. Wearable sensors can provide insights into daily physical activity and walking patterns.

Research questions: (1) Is the severity of motor fluctuations associated with sensor-derived average daily walking quantity? (2) Is the severity of motor fluctuations associated with the amount of change in sensor-derived walking quantity after levodopa intake?

Methods: 304 Dutch PWP from the Parkinson@Home study were included. At baseline, all participants received a clinical examination. During the follow-up period (median: 97 days; 25-Interquartile range-IQR: 91 days, 75-IQR: 188 days), participants used the Fox Wearable Companion app and streamed smartwatch accelerometer data to a cloud platform. The first research question was assessed by linear regression on the sensor-derived mean time spent walking/day with the severity of fluctuations (MDS-UPDRS item 4.4) as independent variable, controlled for age and MDS-UPDRS part-III score. The second research question was assessed by linear regression on the sensor-derived mean post-levodopa walking quantity, with the sensor-derived mean pre-levodopa walking quantity and severity of fluctuations as independent variables, controlled for mean time spent walking per day, age and MDS-UPDRS part-III score.

Results: PWP spent most time walking between 8am and 1pm, summing up to 72 ± 39 (mean ± standard deviation) minutes of walking/day. The severity of motor fluctuations did not influence the mean time spent walking (B = 2.4 ± 1.9, p = 0.20), but higher age (B = −1.3 ± 0.3, p < 0.001) and greater severity of motor symptoms (B = −0.6 ± 0.2, p < 0.001) was associated with less time spent walking (F(3216) = 14.6, p < .001, R^2 = .17). The severity of fluctuations was not associated with the amount of change in time spent walking in relation to levodopa intake in any part of the day.

Conclusion: Analysis of sensor-derived gait quantity suggests that the severity of motor fluctuations is not associated with changes in real-life walking patterns in mildly to moderate affected PWP.

Keywords
Parkinson's disease; Motor fluctuations
Ambulatory monitoring; Gait quantity; Wearable devices
INTRODUCTION

People with Parkinson’s disease (PWP) are at risk of developing an inactive lifestyle [1]. The reason for this is multifactorial, with involvement of both physical and psychological factors. Some of these risk factors are non-specific, such as older age and fear of falling [2,3], while others are more specific to Parkinson’s disease (PD), such as reduced physical capacity or gait and balance problems [4,5]. Being physically inactive is generally undesirable, particularly for PWP. Traditionally, self-reported diaries and questionnaires are used to assess daily physical activity. These instruments have dubious reliability and validity, in particular for people with cognitive impairments [6].

To overcome limitations related to self-reported activity, wearable sensors may provide more objective and continuous measurements, with the potential to generate novel insights into real-life activity patterns in PWP. Early studies that used wearable sensors to quantify physical activity in PD showed that greater disease severity correlates with less ambulatory activity [2,7,8]. These studies typically had small sample sizes, with the exception of one (n = 586) [2] and had short follow-up periods (maximum 7 days).

In addition to assessing the overall amount of ambulatory activity, wearable sensors offer the possibility to study activity patterns throughout the day in detail. This is particularly relevant for PWP who experience motor fluctuations, i.e. periods with either a good levodopa therapy response (“ON” state) or periods when the medication effects wear off and motor symptoms re-emerge (“OFF” state) [9]. The presence of OFF periods has a large limiting impact on mobility and quality of life in PD [10,11]. It is known that gait patterns change in response to levodopa intake in PWP with motor fluctuations [12] and small-scale studies demonstrated that wearable sensors can capture the effects of levodopa on gait quality [13–15]. However, the impact of levodopa intake on gait quantity, as a measure of physical activity, is largely unknown and has never been studied in a large population followed for a long period of time.

Therefore, the aim of this study is to investigate whether the severity of motor fluctuations is associated with changes in physical activity patterns in a large cohort of PWP, who used wearable sensors for a prolonged period of time (up to 665 days). As walking is the most common activity for older adults, the meant time spent walking in minutes per day – labeled as “gait quantity” in this study – is used as a proxy measure of physical activity.
METHODOLOGY

Participants
PWP included in this study participated in the Dutch cohort of the Parkinson@Home study. The Parkinson@Home study was an observational, two-cohort (North America and The Netherlands) study aiming to investigate the feasibility of large-scale deployment and the compliance with wearable sensor usage over a long follow-up time. The recruitment process and study design were previously described in detail [16]. In summary, in the Dutch cohort, 304 participants were recruited from support groups, internet communities, and through physiotherapists specialized in treating PWP. Inclusion criteria were: 30 years of age or older; possession of a smartphone with Android OS version ≥ 4.2; and self-reported diagnosis of PD. No exclusion criteria were applied. Participants used the Fox Wearable Companion app developed by Intel® Pharma Analytics Platform team [17]. The application was installed on the participants own Android smartphone and on a Pebble smartwatch provided by the research team. Participants were asked to wear the smartwatch and keep their smartphone with them as much as possible on a 24/7 basis for 13-weeks. At the end of the 13-weeks study period, participants had the option to continue using the system, if they wished. The Parkinson@Home study showed that compliance of PWP with the wearable system was high [16].

This study was conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects, as defined in the Declaration of Helsinki. The study protocol was approved by the local ethics committee (CMO Arnhem-Nijmegen; NL53034.091.15).

Data used in this study were collected during the Parkinson@Home study and obtained from a database curated by the Michael J. Fox Foundation. The Fox Wearable Companion app platform used in that study enables raw smartwatch accelerometer data capture (average 50 Hz sampling rate) streaming via Bluetooth radio to a complementary smartphone Android app. Next, the smartphone app transfers data via Wi-Fi or mobile data to the Intel Pharma Analytics cloud platform which uses machine learning to estimate objective measures of participants behavior. Among these objective measures is a gait detection algorithm, which estimates whether or not a person was walking during a specific time interval. For the detection of gait episodes, an algorithm was trained on 10 h of walking and non-walking episodes collected from PWP (N = 19) and non PWP (N = 12) wearing a smartwatch. Raw accelerometer data were segmented into 5 s interval and transformed into aggregate features in the time and frequency domains. Then, a decision tree model was used to classify every 5-s interval as either walking or non-walking. The algorithm accuracy was 98.5% (precision 98.9%, recall
96%) on the training data [17] (see Appendix A for algorithm details). The objective measures are presented to participants using graphs and summary reports within the app. In addition to using the smartwatch and smartphone app, users were asked to set medication reminders and report their daily actual medication intake within the app (Figure 6.1). Finally, all enrolled participants received a single medical examination, based on the “Parkinson’s Progression Markers Initiative” (PPMI) protocol. The medical examination collected information such as time since diagnosis and the full MDS-UPDRS [18]. The medical examination was performed in the ON state by specially trained physiotherapists who are members of ParkinsonNet, a Dutch network of health professionals specialized in PD management.

Outcomes and statistical analysis

Two statistical analyses were performed. The first analysis aimed to assess whether a higher severity of motor fluctuations is associated with a smaller mean time spent walking per day. Only participants that contributed at least 7 days of accelerometer data during the follow-up period were included. The mean time spent walking per day was calculated by first dividing the total number of minutes identified as walking by the total number of minutes of accelerometer data. Next, this ratio was multiplied by 1440, i.e. the number of minutes in a day, to obtain the daily mean expressed in minutes. The severity of fluctuations was determined by the score of item 4.4 of the MDS-UPDRS Part IV (question: “4.4 Functional impact of fluctuations”) and the severity of motor symptoms was expressed as the sum score of the MDS-UPDRS Part III. Both outcomes
were treated as scale variables in the analyses. Linear regression analysis was performed on the mean time spent walking per day, with the severity of fluctuations as independent variable. To control for potential confounders, age and MDS-UPDRS part III scores were included in the model using a backward stepwise input selection (criterion of removal: probability of F > 0.10).

The second analysis aimed to investigate whether a higher severity of motor fluctuations is associated with a higher change in time spent walking after levodopa intake. Only levodopa intakes were considered because this drug has the strongest association with occurrence of fluctuations [19]. The analysis was performed separately for the morning (between 6:00 and 12:00), afternoon (between 12:00 and 18:00), evening (between 18:00 and 0:00) and night (between 0:00 and 6:00), because both the amount of walking [20] and the responsiveness to levodopa may vary across the day [21]. To account for possible participants errors while reporting medication intake, e.g. reporting the same medication intake time point multiple times, only the first report within a certain hour was considered as the actual time of medication intake.

To assess the change in time spent walking, we calculated both the mean time spent walking in the second hour after levodopa intake (post-levodopa activity) and the mean time spent walking in the last hour before levodopa intake (pre-levodopa activity) per individual (Figure 6.2.). Only pairs of pre-levodopa and post-levodopa activity consisting of at least 115 min of data, out of a possible total of 120 min during those two hours, were included. Moreover, participants needed to have at least a total of 10 unique levodopa reports in the part of the day being analyzed. Linear regression was performed on the mean post-levodopa activity, with the mean pre-levodopa activity and the severity of fluctuations as independent variables. To control for potential confounders, the mean time spent walking per day, age and MDS-UPDRS part III score were included as inputs to the model using backward stepwise selection (criterion of removal: probability of F > 0.10).

For the coefficients, a critical p-value of 0.05 was applied. All analyses were performed using the Statistical Package for the Social Sciences (SPSS®) Version 22.
Figure 6.2. Data reduction and pre/post-levodopa activity calculation per participant
RESULTS
The cohort consisted of 304 mostly mildly to moderately affected PWP (Table 6.1.).

Table 6.1. Demographic and clinical characteristic of the study participants (n=304).

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>163 (66%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td>63.1±8.5</td>
</tr>
<tr>
<td><strong>Time since diagnose (years)</strong></td>
<td></td>
<td>6.1±4.3</td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (3%)</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>68 (28%)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>127 (53%)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>34 (14%)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>1 (0.4%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td></td>
<td>25.4±3.0</td>
</tr>
<tr>
<td><strong>Severity of motor symptoms</strong></td>
<td></td>
<td>28±14.5</td>
</tr>
<tr>
<td>≤70</td>
<td>36 (15%)</td>
<td>-</td>
</tr>
<tr>
<td>71-80</td>
<td>51 (21%)</td>
<td>-</td>
</tr>
<tr>
<td>81-90</td>
<td>110 (46%)</td>
<td>-</td>
</tr>
<tr>
<td>≥91</td>
<td>41 (17%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Severity of fluctuations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>120 (50%)</td>
<td>-</td>
</tr>
<tr>
<td>Slight</td>
<td>42 (17%)</td>
<td>-</td>
</tr>
<tr>
<td>Mild</td>
<td>21 (9%)</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>47 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>Severe</td>
<td>11 (5%)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Number of missing values differed across variables; only valid percentages are reported. 1-Disease stage: Hoehn and Yahr stage (0-5 point scale); 2-Cognitive impairment: Montreal Cognitive Assessment (0-30); 3- Severity of motor symptoms: sum of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part III (0-132); 4-Independency level: Schwab and England scale (0-100), 5-Impact of motor fluctuations: item 4.4 from MDS-UPDRS part IV (0-4 point scale).

Impact of motor fluctuations on daily time spent walking
220 participants were included in analysis 1. They contributed a median of 78 complete days of usable accelerometer data (25 Interquartile range-IQR: 60 days, 75 Interquartile range-IQR: 110 days), during a median of 97 days of follow-up period (25-IQR of 91 days and 75-IQR of 188 days). On average, participants walked 72 ± 39 min per day, with the largest number of minutes walked occurring between 8 am and 1 pm (Figure 6.3.). The severity of motor fluctuations did not influence the mean time spent walking.
Impact of motor fluctuations on real-life gait

(B = 2.4 ± 1.9, p = 0.20), whereas higher age (B = −1.3 ± 0.3, p = < 0.001) and higher severity of motor symptoms (B = −0.6 ± 0.2, p < 0.001) was associated with less time spent walking (model F(3216) = 14.6, p < .001, R² = .17).

![Figure 6.3](image)

**Figure 6.3.** Mean time spent walking during each hour of the day (n=220). Error bars indicate standard error of the mean.

**Impact of fluctuations on the change in time spent walking after levodopa intake**

The post-levodopa activity was on average higher than the pre-levodopa activity in the morning and night, while in the afternoon and evening the post-levodopa activity was lower. The pattern of post-levodopa activity did not differ between week or weekend days (Figure. 6.4. a and b). The severity of fluctuations was not significantly associated with the difference between pre- and post-levodopa activity (i.e. the amount of change in walking quantity) in any part of the day (Table 6.2.).
Figure 6.4. 4A - Mean time spent walking per hour before (black) and after levodopa intake (white) on week days, presented separately for the morning (n=182, number of levodopa reports per person ranging from 11 to 429), afternoon (n=175, number of levodopa reports ranging from 11 to 323), evening (n=140, number of levodopa reports ranging from 11 to 467) and night (n=99, number of levodopa reports ranging from 11 to 197). 4B - Mean time spent walking per hour before (black) and after levodopa intake (white) on weekend days, presented separately for the morning (n=134, number of levodopa reports per person ranging from 11 to 170), afternoon (n=129, number of levodopa reports ranging from 11 to 129), evening (n=100, number of levodopa reports ranging from 11 to 180) and night (n=61, number of levodopa reports ranging from 11 to 72). Error bars indicate standard error of the mean.

Table 6.2. Adjusted impact of the severity of motor fluctuations on post-levodopa activity (in minutes).

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>B ± SE</th>
<th>β</th>
<th>p-value</th>
<th>ΔR²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>166</td>
<td>.004 ± .104</td>
<td>.002</td>
<td>.97</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Afternoon</td>
<td>162</td>
<td>.156 ± .082</td>
<td>.074</td>
<td>.06</td>
<td>.005</td>
</tr>
<tr>
<td>Evening</td>
<td>134</td>
<td>.082 ± .044</td>
<td>.122</td>
<td>.07</td>
<td>.015</td>
</tr>
<tr>
<td>Night</td>
<td>95</td>
<td>.124 ± .203</td>
<td>.044</td>
<td>.54</td>
<td>.002</td>
</tr>
</tbody>
</table>

Confounders and R² per model:
Morning: pre-levodopa activity (p = .43), mean time spent walking (p < .001); R² = .72.
Afternoon: pre-levodopa activity (p < .001), mean time spent walking (p < .001); R² = .77.
Evening: pre-levodopa activity (p < .001); R² = .44.
Night: pre-levodopa activity (p = .002), mean time spent walking (p < .001), age (p=.03); R² = .54.

DISCUSSION

This study presents data from the first large-scale cohort study using wrist-worn accelerometry in which sensor-based passive monitoring was combined with daily
Impact of motor fluctuations on real-life gait

reports of levodopa intake. The much longer follow-up time here (up to 665 days, with a median follow-up of 97 days) contrasts markedly with previous studies using wearable sensors, where follow-up was typically limited to one week [8,13,22,23]. Our sample size was also large. Using this sizeable dataset, we demonstrated that the severity of motor fluctuations did not lead to a smaller mean amount of daily walking quantity. Also, higher severity of motor fluctuations did not cause a higher mean change in walking quantity in relation to levodopa intake. These findings contradict our hypothesis that PWP with more severe motor fluctuations would be more inactive before intake of levodopa, as a result of wearing off. Studies in controlled settings showed that motor performance, which includes gait and postural transitions, is worse during off periods [12]. Thus, it seems reasonable that this could affect the amount of real-life walking quantity, both through physical limitations and through a patient’s confidence in being active. Therefore, a careful interpretation of possible explanations for our present results is needed.

Our findings highlight the complexity of studying physical activity in a free-living environment, where little or no contextual information about participants behavior is known. As a reflection of this, large variation in the amount of activity is present both between patients and within patients on different days. Our study showed that the severity of potential fluctuations around the time of levodopa intake does not explain a substantial proportion of this already large variation in walking quantity. On the one hand, this may be explained by the fact that a patient’s activity pattern is highly influenced by behavioral factors that are not related to the severity of symptoms. For example, the influence of participants’ behavior most likely explains the large increase in the time spent walking after levodopa intake during the night presented in Fig. 4. As the majority of the levodopa reports at night took place around 5 a.m., the comparison includes a part of the morning, with a higher number of minutes walked. On the other hand, our results indicate that the severity of fluctuations does not have a detectable or consistent influence on activities around the time of levodopa intake. This is supported by the fact that patients in our study were on average still active before levodopa administration, regardless of the severity of their fluctuations. It should be emphasized that we investigated a relatively mildly to moderately affected PD population, hence the generalizability to later stage PWP, who typically have more disabling fluctuations [24], remains to be addressed.

Some limitations of this approach need to be discussed. First, the severity of fluctuations was based on item 4.4 from the MDS-UPDRS part IV, which may be susceptible to inter-rater variability. However, it is a valid scale [25] and all assessors involved in this study received additional training for conducting the MDS-UPDRS. Using alternative approaches to evaluate motor fluctuations, such as the Hauser dairy [26], might allow
for a more accurate comparison of the amount of activity between OFF and ON periods, particularly if fluctuations are characterized by unpredictable OFF periods, dose failures or delayed ON periods. However, it is unlikely that these phenomena were important in our study sample, as these typically occur in people with more advanced PD [27]. Second, limitations related to compliance may have influenced the results. Because data related to actual wear time were not available, we cannot guarantee that all sensor data were collected while the participants were in fact wearing the smartwatch. To minimize this risk and filter out highly non-compliant participants, we have only including participants with a minimum amount of streamed data. In addition, we have no reason to believe that the proportion of non-wear data correlates with our main variable of interest, namely the severity of fluctuations. Although the gait detection algorithm was only validated in a lab-based setting [17], the outcomes of both the mean walking quantity and the daily pattern are similar to what has been reported earlier [2,20,28]. Moreover, we were also able to reproduce earlier findings that age and MDS-UPDRS part III are determinants for the amount of activity [1,8]. These findings give us some confidence that the gait measurements from the smartwatch data are reasonably reliable. Lastly, although we have no data on the accuracy or compliance with medication reports through the app, we believe that the medication reminders and the high compliance with the system usage increased the accuracy of medication reports. Despite the fact that our findings contradict those of a small study with a short follow-up [29], we posit that limitations in their data analysis (e.g. only comparing post- and pre-levodopa activity without assessing the influence of the severity/presence of fluctuations on this difference, producing a result that is highly influenced by general behavioral factors) explain the divergence in conclusions.

A clinically relevant conclusion of our findings is that gait quantity is not a suitable way to capture wearing off in mild to moderately affected PWP. Instead, the use of gait quality features that are more responsive to levodopa [9], reflect changes over time [30], and are likely less affected by behavior, appears as a more adequate approach to monitor changes in gait due to motor fluctuations in a real-life environment. Together with the role of gait quality analysis, determining optimal sensor type, sensor location and feature extraction for home-based monitoring still remains to be addressed. Lastly, in addition to exploring the role of gait quality to capture the influence of fluctuations on walking patterns, future research into activity patterns of PWP would benefit from a more heterogeneous PWP group and age-matched healthy controls, to be able to better discriminate between PD-specific and behavioral influences in activity patterns. Hopefully, this will lead to a better understanding of the underlying factors that have an impact on physical activity in PD and generate useful knowledge that can further contribute to the promotion of an active life-style among PWP.
In conclusion, this study showed that the severity of motor fluctuations was not associated with the mean amount of walking quantity in PWP. Similarly, the severity of motor fluctuations was not associated with the mean change in walking quantity in relation to levodopa intake. Finally, our study does not support the assessment of gait quantity as a suitable method to investigate the influence of motor fluctuations on walking activity in real-life.
REFERENCES


Chapter 7

Summary
SUMMARY

Care in Parkinson's disease (PD) is largely based on clinical judgment of standardized assessments of symptom severity, disease progression, and efficacy of therapeutic interventions. However, high inter-rate variability and the “snapshot” nature of standardized clinical assessments make it difficult to capture the large variability and non-linear decline in PD. Therefore, the current challenge is to design a detailed, objective, and reliable assessment that generates knowledge about real-life functioning. Wearable sensors have the potential to continuously collect objective, and fine-grained health-related data at high frequency, which would otherwise be missed. This summary describes the studies in this thesis, which consider the feasibility and applicability of objective measurements in PD for clinical and research purposes.

Part I. Feasibility of large-scale deployment of wearable sensors in large Parkinson’s disease cohorts

Chapter 2 describes the structured observational study protocol of the Parkinson@Home study, which evaluates the feasibility of large-scale sensor deployment. We analysed the feasibility by investigating the system usability and compliance. For this purpose, the participants used a set of sensors (smartwatch, smartphone, and fall detector) and a customized smartphone app (Fox Wearable Companion). We evaluated the disease severity with the short version of the Parkinson’s Progression Markers Initiative protocol. We aimed to recruit 1000 participants with PD and 250 physiotherapists in the Netherlands (NL) via internet communities, support groups, and treating therapists. We purposefully kept the enrolment criteria broad in order to capture the whole diversity of PD. Thus, potential participants only had to have a self-reported diagnosis of PD, possess a smartphone, and be older than 18 years. To optimize inclusion, we arranged for potential participants to give informed consent online in an easy “click-to-accept” procedure. After inclusion, the participants used the wearable system 24/7 for 13 weeks and self-reported their medication intake and symptoms via the app. A second cohort of PD participants living in North America (NAM) was included so that we could investigate the feasibility in different contexts. The NAM cohort used the same wearable sensors, but for a minimum of 5 hours a day for 6 weeks. The feasibility outcomes for both cohorts included recruitment, attrition, compliance, and system usability. Depending on the distribution of variables, the Chi-square, Fisher’s exact, or Kruskal-Wallis test was used to investigate significant differences between the compliance groups (i.e. groups with low, middle, and high compliance). For this purpose, we considered the demographics, clinical characteristics, ability to use a smartphone, and the system usability score. In total, 953 participants with PD were included (NL: 304 and NAM: 649). The results of this study, described in
Chapter 7

Chapter 3, showed an enrolment rate of 88% (304 NL participants) and 51% (649 NAM participants). Overall, 84% (805 participants) contributed sensor data. Compliance with technology usage was high: 68% (16.3 hours/participant per day) of the study period in NL and 62% (14.8 hours/participant per day) in NAM. Participation attrition rates were low, with a loss of 82 data contributors in the NL cohort (27% of all enrolled) and 89 in the NAM cohort (17% of all enrolled). Further, 13 participants (4% of all NL enrolled participants) and 135 (21% of all NAM enrolled participants) did not contribute any data during the study period. The attrition rates for daily accelerometer data collection were 23% in the NL cohort after 13 weeks, and 27% in the NAM cohort after 6 weeks. The feasibility scores were not affected by demographics, clinical characteristics, or attitude towards technology. However, the Dutch participants, who rated the system usability higher, were more likely to be in the group with greater compliance ($\chi^2(2) = 32,014, p < 0.001$). In the NAM cohort, self-reported depressed patients were more likely to show low compliance with system usage ($\chi^2(2) = 6397, p = 0.04$).

**Take-home messages:**

1. It is feasible to deploy multiple wearable sensors across large PD populations.
2. Neither demographic nor clinical characteristics hamper wearable sensor usage

**Part II. Applicability of objective measurements for answering clinical and research-relevant questions: wearable sensors for quantifying gait and falls**

**Validity of wearable sensors for quantifying freezing of gait and falls**

In Chapter 4, I address the lack of consensus about the appropriate methodologies for freezing of gait (FOG) and fall detection with a systematic review of the use of wearable systems for assessing FOG and falls in PD. We searched the PubMed and Web of Science databases using a list of relevant key words and MeSH terms. The final search was completed in January 2017, and we selected articles with a set of eligibility criteria. Of the total of 27 articles selected, 23 related to FOG and 4 to falls. The FOG studies took place either in laboratory (total of 20) or home settings (total of 3), with sample sizes ranging from 1 to 48 patients with PD; the Hoehn and Yahr stages ranged from 2 to 4. The shin was the most common sensor location, and an accelerometer was the most frequently used sensor type. Validity measurements ranged from 73 to 100% for
sensitivity and 67 to 100% for specificity. All the fall and fall-risk-related studies were home based. The samples sizes were 1 to 107 patients with PD, and most used one sensor containing accelerometers, worn at various body locations.

Take-home messages:

1. Sensor-based FOG assessments performed in standardized settings are well validated.
2. Sensor-based fall risk assessments are a promising application of objective measurements for fall monitoring.
3. Despite the promising validation initiatives currently reported, the studies retrieved had relatively small sample sizes, with significant variability in outcomes measured and results reported.
4. The field of wearable sensors for Parkinson’s disease would benefit from more focused research efforts, increased collaboration among researchers, aligned data-collection protocols, and shared data sets.

The applicability of objective measurements for answering research questions

In Chapter 5, I approach falls, one of the most serious clinical PD problems, by using wearable sensors to quantify the hazard ratio of falls of patients with PD in daily life. In this study, we analysed prospective data from a cohort of elderly people who subscribed to an emergency response program with automatic fall detection in a device worn as a necklace. First, we selected all 2,063 participants with self-reported PD. Using demographic characteristics, we randomly extracted a matched control group of 2,063 people who did not report PD. Fall events were either collected automatically by the fall detector necklace or registered by a button push on the same device. We extracted fall events from a 2.5-year window with an average follow-up of 1.1 years. All falls included were confirmed immediately by a subsequent telephone call. The main outcomes in this study were: (1) the incidence rate of any fall, (2) the incidence rate of a new fall after enrolment (i.e. hazard ratio), and (3) one-year cumulative incidence of falling. We used descriptive analysis to report the incidence rate of falling for both participants with PD and controls. We used t-tests (continuous variables) or chi-square tests (categorical variables) to determine between-group differences. We assessed the association of PD with the incidence rate of any fall using ANOVA model, with PD status, age, gender, and the number of medical conditions as independent predictors and the number of falls as the dependent variable (significance at $p < 0.05$). Using the previously built
model, we added two-way and three-way interaction terms for age, gender, or age x gender with PD in separate sensitivity analyses. We investigated the association of PD with the incidence rate of a new fall after enrolment using Cox regression models, with PD status, age, gender, and the number of medical conditions as independent predictors and first fall (yes/no) was entered as the dependent variable. Then we used Kaplan-Meier survival analysis to assess the cumulative incidence of a new fall after enrollment during a 1-year follow-up for both PD and controls. The results revealed that 29.6% (610 patients with PD) were recurrent fallers versus 14.5% (300 controls; \( p < 0.0001 \)). Recurrent fallers with PD also showed a higher rate of falls resulting in emergency transport (2.2% or 45 participants with PD and 1.4%, 28 people in the control group). The incidence rate of any fall was greater among the patients with PD (2.1 falls/person-years) than controls (0.7 falls/person-years; \( p < 0.0001 \)). Moreover, the incidence rate of a new fall after enrolment (i.e. hazard ratio) was 1.8 times greater for patients with PD than for controls (95% confidence interval: 1.6–2.0). The hazard ratio was not influenced by the two-way interaction of age and PD (\( p = 0.6 \)), gender, or PD (\( p = 0.2 \)), or the three-way interaction of age, gender, and PD (\( p = 0.9 \)). More patients with PD (48.8%) than controls (29.5%) became fallers during 1 year of follow-up (\( p < 0.0001 \)).

**Take-home messages:**

1. PD is a “falling disease”, so dedicated strategies for preventing falls are extremely important.
2. Wearable sensors are feasible for monitoring falls in daily life.
3. Data from wearable sensors are feasible for answering research-related questions.

**The applicability of objective measurements for answering clinically relevant questions**

Chapter 6 investigates whether the severity of motor fluctuations was associated with sensor-derived average time spent walking per day. Here I also examine whether the severity of motor fluctuations was associated with a change in sensor-derived time spent walking after levodopa intake. The 304 Dutch participants with PD from the Parkinson@Home study were included in this study. At baseline, all participants were clinically examined. During the follow-up period (median: 97 days; 25-interquartile range: 91 days, 75-interquartile range: 188 days), the participants used the Fox Wearable Companion app and streamed smartwatch accelerometer data to a cloud platform. We assessed the first research question with linear regression on the sensor-derived mean time spent walking per day with the severity of motor fluctuations (item 4.4 of the Movement
Disorder Society - Unified Parkinson’s Disease Rating Scale) as an independent variable, controlled for age and motor performance (MDS-UPDRS part III score). We assessed the second research question with linear regression on the sensor-derived mean post-levodopa time spent walking, with the sensor-derived mean pre-levodopa time spent walking and severity of fluctuations as independent variables, controlled for mean time spent walking per day, age, and motor performance (MDS-UPDRS part III score). The results showed that participants with PD spent most of their walking time between 8 am and 1pm, totalling $72 \pm 39$ (mean ± standard deviation) minutes of walking per day. The severity of motor fluctuations did not influence the mean time spent walking ($B = 2.4 \pm 1.9, p = 0.20$), but greater age ($B = -1.3 \pm 0.3, p = 0.001$) and greater severity of motor symptoms ($B = -0.6 \pm 0.2, p < 0.001$) were associated with less time spent walking ($F(3216) = 14.6, p < 0.001, R^2 = 0.17$). The severity of fluctuations was not associated with the change in time spent walking in relation to levodopa intake in any part of the day. Analysis of sensor-derived gait quantity suggested that the severity of motor fluctuations was not associated with changes in daily-life walking patterns of people who are mildly to moderately affected by PD.

**Take-home messages:**

1. Wearable sensors are a useful tool for answering clinical relevant research questions.
2. Gait quality, instead of gait quantity, may be a better outcome to investigate gait-related impairment and motor fluctuations in Parkinson’s disease.

**Conclusion**

Taken together, the results of the studies included in this thesis emphasise the feasibility of using wearable sensors to monitor PD-related symptoms in daily life. Data collected with wearable sensors over long-term follow-up can improve the care provided to patients with PD and accelerate research.
SAMENVATTING

Zorg voor de ziekte van Parkinson (ZvP) is grotendeels gebaseerd op klinische beoordeling van gestandaardiseerde metingen van de ernst van symptomen, ziekteprogressie en werkzaamheid van therapeutische interventies. Hoge interbeoordelaar-variabiliteit en het feit dat gestandaardiseerde klinische beoordelingen een momentopname zijn van de werkelijkheid maken het echter moeilijk om de grote variabiliteit en niet-lineaire achteruitgang bij de ZvP vast te leggen. Om deze reden is de huidige uitdaging om een gedetailleerde, objectieve en betrouwbare methode te ontwerpen die kennis genereert over het dagelijkse functioneren. Draagbare sensoren hebben de potentie om continu objectieve en nauwkeurige gezondheidsgerelateerde gegevens te verzamelen met een hoge frequentie, die anders zouden worden gemist. Deze samenvatting beschrijft de studies in dit proefschrift, waarin de haalbaarheid en toepasbaarheid van objectieve metingen bij de ZvP voor klinische- en onderzoeksdoeleinden in beschouwing worden genomen.

Deel I. Haalbaarheid van grootschalige inzet van draagbare sensoren in grote cohorten van mensen met de ziekte van Parkinson

Hoofdstuk 2 beschrijft het gestructureerde observationele studieprotocol van de ParkinsonThuis studie, die de haalbaarheid evalueert van grootschalige sensorimplementatie. We hebben de haalbaarheid geanalyseerd door het onderzoeken van de gebruiksvriendelijkheid en de compliance met het gebruik van de sensoren. Voor dit doel hebben de deelnemers een reeks sensoren gebruikt (smartwatch, smartphone en valdetector) en een op maat gemaakte smartphone app (Fox Wearable Companion). We hebben de ernst van de ziekte beoordeeld met behulp van de korte versie van het ‘Parkinson’s Progression Markers Initiative’. Ons doel was om 1000 patiënten met de ZvP en 250 fysiotherapeuten in Nederland te werven via internetgemeenschappen, steungroepen en behandeldende therapeuten. We hebben de inclusiecriteria bewust breed gehouden om de volledige diversiteit van de ZvP te vangen. Hiervoor hoefden potentiële deelnemers enkel een zelfgerapporteerde diagnose van de ZvP te hebben, in het bezit te zijn van een smartphone en ouder te zijn dan 18 jaar. Om de inclusie te optimaliseren, hebben we ervoor gezorgd dat potentiële deelnemers online informed consent konden geven met behulp van een eenvoudige “click-to-accept” procedure. Na inclusie hebben de deelnemers het draagbare system 24 uur per dag gedurende 13 weken gebruikt en zelf hun medicatie-inname en symptomen gerapporteerd via de app. Een tweede cohort van deelnemers met de ZvP wonend in Noord-Amerika (NAM) werd geïncludeerd zodat we de haalbaarheid in verschillende contexten konden onderzoeken. Het NAM-cohort gebruikte dezelfde draagbare sensoren, maar voor een minimum van 5 uur per dag gedurende 6 weken. De haalbaarheidsuitkomsten voor beide cohorten waren werving, uitvalspercentages, compliance met het gebruik van de
sensoren en gebruiksvriendelijkheid van het systeem. Ook hebben wij gekeken in welke mate compliance wordt beïnvloed door demografische gegevens, klinische kenmerken, het vermogen om een smartphone te gebruiken en de gebruiksvriendelijkheidsscore van het systeem. Afhankelijk van de verdeling van variabelen werd de Chi-kwadraat, Fisher’s exact of Kruskal-Wallis test gebruikt om significante verschillen te onderzoeken tussen drie groepen: deelnemers met een lage, gemiddelde compliance, uitgedrukt in het percentage van de tijd dat sensorgegevens werden verzameld. In totaal zijn er 953 patiënten met de ZvP geïncludeerd (Nederland: 304 en NAM: 649). De resultaten van deze studie, beschreven in Hoofdstuk 3, laten een inclusiepercentage van 88% (304 Nederlandse deelnemers) en 51% (649 Amerikaanse deelnemers) zien. In totaal heeft 84% (805 deelnemers) sensorgegevens bijgedragen. De compliance met het gebruik van de sensoren was hoog: 68% (16.3 uur per deelnemer per dag) tijdens de onderzoeksperiode in Nederland en 62% (14.8 uur per deelnemer per dag) in NAM. Uitvalspercentages waren laag, met uitval van 82 deelnemers in het Nederlandse cohort (27% van alle deelnemers die sensorgegevens hebben bijgedragen) en 89 in het NAM cohort (17% van alle deelnemers die sensorgegevens hebben bijgedragen). Verder hebben 13 deelnemers (4% van alle Nederlandse geïncludeerde deelnemers) en 135 deelnemers (21% van alle geïncludeerde deelnemers uit NAM) geen enkele gegevens bijgedragen tijdens de studieperiode. Het percentage van de tijd dat sensorgegevens werden verzameld nam af met 23% in het Nederlandse cohort na 13 weken en 27% in het NAM cohort na 6 weken. De compliance werd niet beïnvloed door demografische gegevens, klinische kenmerken of houding ten aanzien van technologie. De Nederlandse deelnemers, die de gebruiksvriendelijkheid van het systeem hoger beoordeelden, hadden echter meer kans om deel uit te maken van de groep met hogere compliance ($\chi^2 (2) = 32,014, p < 0.001$). In het NAM cohort hadden mensen met een zelfgerapporteerde depressie meer kans om deel uit te maken van de groep met een lagere compliance ($\chi^2 (2) = 6397, p = 0.04$).

**Take-home messages:**

1. Het is haalbaar om meerdere draagbare sensoren in te zetten in grote populaties van mensen met de ziekte van Parkinson.
2. Noch demografische, noch klinische kenmerken belemmeren het gebruik van draagbare sensoren.
Deel II. Toepasbaarheid van objectieve metingen voor het beantwoorden van klinische en onderzoeks-relevante vragen: draagbare sensoren voor het kwantificeren van lopen en vallen.

Validiteit van draagbare sensoren voor het kwantificeren van freezing of gait en vallen

In hoofdstuk 4 behandel ik het gebrek aan consensus over geschikte methoden voor freezing of gait (FOG) en valdetectie met een systematische review over het gebruik van draagbare systemen voor het beoordelen van FOG en vallen bij de ZvP. We hebben de PubMed- en Web of Science databases doorzocht met behulp van een lijst met relevante trefwoorden en MeSH termen. De laatste zoekopdracht werd in januari 2017 voltooid en we hebben artikelen geselecteerd aan de hand van een aantal criteria. Van de in totaal 27 geselecteerde artikelen waren er 23 gerelateerd aan FOG en 4 aan vallen. De FOG studies vonden plaats in het laboratorium (in totaal 20) of thuis (in totaal 3), met steekproefgroottes variërend van 1 tot 48 patiënten met de ZvP; de Hoehn en Yahr stadia varieerden van 2 tot 4. Het scheenbeen was de meest voorkomende sensorlocatie en de accelerometer was het meest gebruikte sensortype. Validiteitsmetingen varieerden van 73 tot 100 procent voor sensitiviteit en van 67 tot 100 procent voor specificiteit. Alle val- en valrisico gerelateerde studies werden thuis uitgevoerd. De steekproeven waren 1 tot 107 patiënten met de ZvP en de meeste studies gebruikten één sensor met accelerometers, gedragen op verschillende lichaamslocaties.

Take-home messages:

1. Op sensoren gebaseerde FOG beoordelingen uitgevoerd in gestandaardiseerde omgevingen zijn goed gevalideerd.
2. Op sensoren gebaseerde valrisicobehoordelingen zijn een veelbelovende toepassing met objectieve metingen voor het monitoren van vallen.
3. Ondanks de veelbelovende validatie-initiatieven die momenteel zijn gerapporteerd, hadden de geïncludeerde studies relatief kleine steekproefgroottes met significante variabiliteit in gemeten uitkomstmaten en gerapporteerde resultaten.
4. Het werkveld van draagbare sensoren voor de ziekte van Parkinson zou baat hebben bij meer gerichte onderzoeksinspanningen, meer samenwerking tussen onderzoekers, onderling afgestemde protocollen voor dataverzameling en gedeelde datasets.
De toepasbaarheid van objectieve metingen voor het beantwoorden van onderzoeksvragen

In hoofdstuk 5 behandel ik vallen, één van de ernstigste klinische problemen gerelateerd aan de ZvP, door gebruik te maken van draagbare sensoren om het valrisico van patiënten met de ZvP in het dagelijks leven te kwantificeren. In deze studie hebben we prospectieve gegevens geanalyseerd van een cohort van ouderen die zich hadden ingeschreven voor een noodresponsprogramma met automatische valdetectie in een apparaat dat werd gedragen als ketting. Eerst hebben we alle 2063 deelnemers geselecteerd met zelfgerapporteerde ZvP. Gebruik makend van demografische kenmerken hebben we willekeurig een gematchte controlegroep van 2063 mensen geëxtraheerd die geen ZvP rapporteerden. Valgebeurtenissen werden of automatisch verzameld door de valdetector in de ketting of geregistreerd door een druk op de knop op hetzelfde apparaat. We hebben valgebeurtenissen geëxtraheerd uit een periode van 2,5 jaar met een gemiddelde follow-up van 1,1 jaar. Alle valgebeurtenissen werden onmiddellijk bevestigd door middel van een hierop volgend telefoongesprek. De belangrijkste uitkomstmaten in deze studie waren: (1) de incidentie van valincidenten, (2) de incidentie van nieuw valincidenten na de inclusie (hazard ratio), en (3) de cumulatieve incidentie van vallen een jaar na de inclusie. We hebben beschrijvende statistiek gebruikt om de valincidentie te rapporteren voor zowel deelnemers met de ZvP als controle deelnemers. We hebben t-tests (continue variabelen) of Chikwadraattests (categorische variabelen) gebruikt om de verschillen tussen groepen te bepalen. We beoordeelden de associatie tussen de ZvP en de valincidentie met behulp van het ANOVA-model, met ZvP-status, leeftijd, geslacht en het aantal medische aandoeningen als onafhankelijke voorspellers en het aantal valgebeurtenissen als de afhankelijke variabele (significantie bij p < 0.05). Met behulp van het eerder gebouwde model hebben we aan de aanwezigheid van de ZvP twee- en driezijdige interactietermen toegevoegd voor leeftijd, geslacht of leeftijd x geslacht in afzonderlijke sensitiviteitsanalyses. We onderzochten de associatie tussen de ZvP en nieuw valincidenten na het inclusie met behulp van Cox-regressiemodellen, met de ZvP-status, leeftijd, geslacht en het aantal medische aandoeningen als onafhankelijke voorspellers en de eerste val (ja/nee) werd ingevoerd als de afhankelijke variabele. Vervolgens hebben we Kaplan-Meier survivalanalyse gebruikt om de cumulatieve incidentie een nieuw valincidenten na het inclusie te beoordelen gedurende een follow-up van 1 jaar voor zowel mensen met de ZvP als controles. De resultaten lieten zien dat 29.6% (610 patiënten met de ZvP) herhaaldelijk vielen versus 14.5% (300 controles; p < 0.0001). Mensen met de ZvP die herhaaldelijk vielen vertoonden ook vaker valgebeurtenissen die resulteerden in spoedeisend transport (2.2% van 45 deelnemers met de ZvP en 1.4%, 28 mensen in de controlegroep). De valincidentie was groter bij de patiënten met de ZvP (2.1 valgebeurtenissen per jaar per persoon) dan bij de controles (0.7 valgebeurtenissen per jaar per persoon; p < 0.0001). Bovendien was de incidentie van nieuw valincidenten na het inclusie 1.8 keer groter voor patiënten met de ZvP dan
voor controles (95% betrouwbaarheidsinterval: 1.6-2.0). De hazard ratio voor vallen werd niet beïnvloed door de tweeëzijdige interactie van leeftijd en de ZvP (p = 0.6), geslacht of de ZvP (p = 0.2), of de drieëzijdige interactie van leeftijd, geslacht en de ZvP (p = 0.9). Meer patiënten met de ZvP (48.8%) dan controles (29.5%) gingen vallen gedurende 1 jaar follow-up (p < 0.0001).

**Take-home messages:**

1. De ZvP is een “valziekte”, dus speciale strategieën om valpartijen te voorkomen zijn uiterst belangrijk.
2. Draagbare sensoren zijn haalbaar voor het monitoren van vallen in het dagelijks leven.
3. Gegevens van draagbare sensoren zijn haalbaar voor het beantwoorden van onderzoeksgereleerde vragen.

**De toepasbaarheid van objectieve metingen voor het beantwoorden van klinisch relevante vragen**

Hoofdstuk 6 onderzocht of de ernst van motorische fluctuaties geassocieerd is met de tijd die mensen lopen per dag, gemeten met een draagbare sensor. Ook onderzoek ik hier of de ernst van motorische fluctuaties geassocieerd was met de verandering in de tijd die mensen lopen na inname van levodopa. De 304 Nederlandse deelnemers met de ZvP van de ParkinsonThuis studie werden geïncludeerd in deze studie. Bij de start van de studie werden alle deelnemers klinisch onderzocht. Tijdens de follow-up periode (mediaan: 97 dagen, interkwartielbereik: 91-188 dagen), gebruikten de deelnemers de Fox Wearable Companion-app en streamden ze de accelerometergegevens van de smartwatch naar een cloudplatform. We beoordeelden de eerste onderzoeksvraag met lineaire regressie op de gemiddelde tijd besteed aan lopen per dag, gemeten met de sensor, met de ernst van motorische fluctuaties (item 4.4 van de Movement Disorder Society - Unified Parkinson’s Disease Rating Scale) als een onafhankelijke variabele, gecontroleerd voor leeftijd en motorische symptomen (MDS-UPDRS deel III score).

We beoordeelden de tweede onderzoeksvraag met lineaire regressie op de gemiddelde tijd besteed aan lopen na levodopa inname, met de gemiddelde tijd besteed aan lopen voor levodopa inname en de ernst van de fluctuaties als onafhankelijke variabelen, gecontroleerd voor de gemiddelde tijd besteed aan lopen per dag, leeftijd en motorische symptomen (MDS-UPDRS deel III score). Uit de resultaten bleek dat deelnemers
met de ZvP in totaal 72 ± 39 (gemiddelde ± standaardafwijking) minuten lopen per dag, waarvan het grootste deel tussen 8:00 uur en 13:00 uur. De ernst van motorische fluctuaties had geen invloed op de gemiddelde looptijd (B = 2,4 ± 1,9, p = 0,20), maar een hogere leeftijd (B = -1,3 ± 0,3, p = 0,001) en ernstigere motorische symptomen (B = -0,6 ± 0,2, p <0,001) waren geassocieerd met minder tijd die werd besteed aan lopen (F (3216) = 14,6, p <0,001, R² = 0,17). De ernst van fluctuaties was niet geassocieerd met de verandering in tijd die werd besteed aan lopen na levodopa-inname op enig moment van de dag. Analyse van de sensor afkomstige loopkwantiteit suggereerde dat de ernst van motorische fluctuaties niet geassocieerd was met veranderingen in tijd besteed aan lopen in het dagelijks leven van mensen die licht tot matig zijn aangedaan door de ZvP.

**Take-home messages:**

1. Draagbare sensoren zijn een bruikbaar hulpmiddel voor het beantwoorden van klinisch relevante onderzoeksvragen.
2. Loopkwaliteit, in plaats van loopkwantiteit, kan een betere uitkomst zijn om aan lopen gerelateerde stoornissen en motorische fluctuaties bij de ziekte van Parkinson te onderzoeken

**Conclusie**

Samenvattend benadrukken de resultaten van de studies in dit proefschrift de haalbaarheid van het gebruik van draagbare sensoren om symptomen gerelateerd aan de ZvP in het dagelijks leven te monitoren. Gegevens verzameld met draagbare sensoren over langdurige perioden van follow-up kunnen de zorg voor mensen met de ZvP verbeteren en onderzoek versnellen.
RESUMO

O tratamento clínico utilizado na doença de Parkinson (DP) é amplamente baseado no uso de escalas clínicas com o intuito de avaliar a intensidade dos sintomas e sua progressão, bem como a eficácia de intervenções terapêuticas. No entanto, limitações no nível de confiança entre avaliadores e a natureza “momentânea” das avaliações tornam difícil capturar a grande variabilidade dos sintomas e o declínio não-linear visto na DP. Portanto, o desafio atualmente é criar uma forma de avaliação que seja detalhada, objetiva e confiável, permitindo um mapeamento detalhado dos sintomas e atividades funcionais das pessoas com DP no dia-a-dia. Sensores vestíveis e portátiles (do inglês: wearable sensors) têm o potencial de coletar informação de uma maneira continua e detalhada, que, de outra forma, não seria observada fora da clínica médica. Neste capítulo, um resumo dos estudos discutidos nesta tese será apresentado. Estes estudos tiveram como objetivo investigar a viabilidade e aplicabilidade de sensores vestíveis e portátiles na coleta de dados sobre sintomas e funcionamento motor de pessoas com DP fora da clínica médica.

Parte I. Viabilidade da implantação em larga escala de sensores vestíveis e portátiles para coletar dados clínicos na doença de Parkinson

O Capítulo 2 descreve o protocolo do estudo observacional entitulado: Parkinson@Home. Este estudo teve como objetivo avaliar a viabilidade do uso de sensores vestíveis e portátiles em um grupo de pessoas com DP (i.e. larga escala). Para isso, os participantes incluídos no estudo utilizaram um conjunto de sensores vestíveis e portátiles (smartwatch, smartphone e sensor de quedas) e um aplicativo para smartphone (Fox Wearable Companion). Todos os participantes se submeteram a uma avaliação clínica usando uma versão simplificada do protocolo usado no Parkinson's Progression Markers Initiative. O projeto de pesquisa teve como meta recrutar 1000 participantes com DP e 250 fisioterapeutas vivendo na Holanda (NL). O recrutamento foi feito através de comunidades na Internet, grupos de apoio à pessoas com DP e através dos fisioterapeutas da rede ParkinsonNET. Poucos critérios de inclusão foram usados, afim de capturar toda a diversidade presente na DP. Estes foram: diagnóstico de DP (confirmado pelo participante), possuir um smartphone e ter mais de 18 anos. Para otimizar a inclusão, o termo de consentimento livre e esclarecido foi assinado digitalmente. Após a inclusão, os participantes usaram os sensores vestíveis e portátiles por 24 horas, sete dias por semana, por 13 semanas, bem como registraram digitalmente a medicação e sintomas vivenciados nestas 13 semanas através do aplicativo Fox Wearable Companion. Uma segunda coorte de participantes com DP vivendo na América do Norte (NAM) foi incluída para que pudéssemos investigar a viabilidade
do uso do sensores vestíveis e portáteis em diferentes contextos (i.e. diferente cultura e sistema de saúde). A coorte NAM usou os mesmos sensores vestíveis e portáteis descritos anteriormente, mas por um mínimo de 5 horas por dia durante 6 semanas. Para medir a viabilidade da implementação dos sensores vestíveis portáteis em ambos os grupos utilizamos os seguintes indicadores: porcentagem de participantes incluídos, porcentagem de dados perdidos durante a coleta, e a pontuação na escala de usabilidade. Dependendo da distribuição das variáveis (i.e paramétrica ou não-paramétrica), os testes estatísticos Qui-quadrado, exato de Fisher ou de Kruskal- Wallis foram usados para investigar diferenças significativas em: 1- características demográficas, 2- clínicas, 3- capacidade de usar um smartphone, e 3- pontuação na escala de usabilidade entre os 3 grupos de adesão ao uso dos sensores (i.e. baixa, média e alta adesão). Um total de 953 participantes com DP foram incluídos (NL: 304 e NAM: 649) neste estudo. Os resultados, descritos no Capítulo 3, mostram uma taxa de inclusão de 88% (304 participantes NL) e 51% (649 participantes NAM) dos participantes abordados para o estudo. A adesão ao uso do sistema foi alta: 68% (16,3 horas / participante por dia) do período de estudo em NL e 62% (14,8 horas / participante por dia) em NAM. As taxas de atrito na participação foram baixas, com uma perda de 82 participantes na coorte de NL (27% de todos os inscritos) e 89 na coorte de NAM (17% de todos os inscritos). Além disso, 13 participantes (4% de todos os participantes inscritos no NL) e 135 (21% de todos os participantes inscritos no NAM) nunca usaram o sistema durante o período do estudo. As taxas de atrito na quantidade de dados coletados pelos sensores foram baixas, com 23% na coorte NL após 13 semanas e 27% na coorte NAM após 6 semanas. A adesão ao uso do sistema não foi afetada por características demográficas, clínicas ou atitude em relação à tecnologia, mas pela pontuação dada pelos participantes ao sistema na escala de usabilidade. Os participantes holandeses que avaliaram o sistema com notas mais alta, foram mais propensos a estar no grupo com alta adesão ao uso do sistema ($\chi^2 (2) = 32,014, p <0,001$). Na coorte NAM, pacientes que se classificaram como deprimidos foram mais propensos a estar no grupo com baixa adesão ao uso do sistema ($\chi^2 (2) = 6397, p = 0,04$).
Conclusões:

1. É viável o uso de sensores vestíveis e portáteis em grandes grupos de pessoas com DP.
2. O uso de sensores vestíveis e portáteis por pessoas com DP não é prejudicado por diferença socioeconomicas ou nível dos sintomas da DP.

Parte II. Aplicabilidade de medidas objetivas para responder questões clínicas e relevantes para pesquisa: sensores vestíveis e portáties para avaliações da marcha e quedas

Validade de sensores vestíveis e portáties para avaliar freezing e quedas

O Capítulo 4 aborda com uma revisão sistemática a falta de consenso sobre quais metodologias são apropriadas quando se utiliza sensores vestíveis e portáties para avaliar freezing (FOG) e detectar quedas em pessoas com DP. Nós pesquisamos os bancos de dados PubMed e Web of Science usando uma lista de palavras-chaves e termos MeSH. A busca final foi concluída em janeiro de 2017 e os artigos foram selecionados de acordo com um conjunto de critérios de inclusão. Do total de 27 artigos selecionados, 23 eram relacionados ao uso de sensores vestíveis e portáties para avaliar FOG e 4 para detectar quedas. Os estudos voltados para avaliação de FOG foram conduzidos em ambientes controlados (i.e. laboratório ou hospital) (total de 20) ou no domicílio da pessoa com DP (total de 3). Tamanhos amostrais variaram de 1 a 48 pessoas com DP; enquanto que os estágios de Hoehn e Yahr das pessoas com DP variavam de 2 a 4. A perna foi a localização mais comum para a colocação dos sensores, enquanto que o acelerômetro foi o tipo de sensor mais usado. A validade dos algoritmos para avaliar FOG variaram de 73 a 100% para sensibilidade e 67 a 100% para especificidade. Todos os estudos relacionados a queda e risco de queda foram realizados no domicílio da pessoa com DP. Os tamanhos amostrais variaram de 1 a 107 pessoas com DP, e a maioria utilizou um sensor contendo acelerômetros colocados em diversas partes do corpo dos participantes.
Conclusões:

1. O uso de sensores vestíveis portáties para avaliar FOG em ambientes controlados está validado.
2. Avaliar risco de quedas é uma aplicação promissora para o uso de sensores vestíveis portáties por pessoas com DP.
3. Apesar das iniciativas promissoras, os estudos em que sensores vestíveis portáties foram utilizados ainda precisam de amostras maiores e uniformidade nos parâmetros utilizados para avaliar o uso destes sensores.
4. Pesquisas com sensores vestíveis portáties para avaliar FOG e quedas seriam beneficiadas se um consenso no uso dos sensores e nos protocolos de pesquisa fosse alcançado. Colaboração entre diferentes grupos de pesquisa também beneficiaria e aceleraria pesquisas envolvendo sensores.

Utilidade dos dados coletados com sensores vestíveis e portáties para pesquisa clínica

No Capítulo 5, um dos problemas clínicos mais sérios enfrentado por pessoas com DP é abordado. Nesse capítulo eu descrevo os resultados do uso de sensores vestíveis e portáties para quantificar o risco de quedas de pacientes com DP na vida diária. Neste estudo, nós analisamos dados prospectivos de idosos que eram clientes de um programa pago de resposta a emergências no qual detecção de quedas é automática realizada por um sensor vestível no formato de um colar. Primeiramente, selecionamos todos os 2063 participantes que relataram ter a DP. Usando características demográficas, extraímos aleatoriamente um grupo controle no qual 2063 outras pessoas que participam do programa mas não relataram PD foram incluídas. Cada episódio de queda foi coletado automaticamente pelo detector de quedas ou registrados por meio da ativação de um botão incluído no sensor vestível portátil e gravado num banco de dados. O número de quedas for extraído de uma janela de 2,5 anos no banco de dados, no qual o tempo médio de acompanhamento foi de 1,1 anos. Todas as quedas incluídas foram confirmadas imediatamente por uma ligação telefônica. Os principais resultados deste estudo incluíram: (1) incidência de qualquer queda durante o estudo, (2) incidência da primeira queda após a inclusão no estudo e (3) incidência cumulativa de quedas no primeiro ano de estudo. A incidência de qualquer queda para o grupo controle e o grupo com DP foi analisada usando estatística descritiva. Utilizamos testes-\( t \) (para variáveis contínuas) ou testes qui-quadrado (para variáveis categóricas) para investigar possíveis diferenças entre os grupos. Avaliamos a associação da DP com a taxa de incidência de queda usando o modelo ANOVA, com a presença da DP, idade, gênero e número de condições médicas como preditores independentes e o número de quedas como variável dependente.
Resumo

Adicionamos ao modelo construído anteriormente termos de interação bidirecionais (idade versus gênero) e tridirecionais (idade versus gênero versus presença da PD) para análises subsequentes. Investigamos a associação da DP com a taxa de incidência de uma nova queda após a inclusão no estudo usando modelos de regressão de Cox, com presença da DP, idade, gênero e o número de condições médicas como preditores independentes e queda (sim/não) foi inserida como variável dependente. Em seguida, utilizamos a análise de sobrevida de Kaplan-Meier para avaliar a incidência cumulativa de uma nova queda após a inclusão no estudo, tanto para o grupo de pessoas com DP quanto para os controles. Os resultados revelaram que 29,6% (610 pessoas com DP) sofriam de quedas recurrentes versus 14,5% (300 controles; p < 0,0001). Pessoas com DP que sofriam com quedas recorrentes mostraram uma taxa maior de quedas que resultaram em transporte de emergência (2,2% ou 45 pessoas com DP e 1,4%, 28 pessoas no grupo controle). A taxa de incidência de qualquer queda foi maior entre pessoas com DP (2,1 quedas/ano por pessoa) do que os controles (0,7 quedas/ano por pessoa; p < 0,0001). Além disso, a taxa de incidência de uma nova queda após inclusão no estudo foi 1,8 vezes maior entre pessoa com DP do que entre pessoas do grupo controle (intervalo de confiança de 95%: 1,6 a 2,0). A incidência de uma nova queda após inclusão no estudo não foi influenciada pela interação entre idade e DP (p = 0,6), gênero e DP (p = 0,2), ou a interação entre idade, gênero e DP (p = 0,9). Um número maior de pacientes com DP (48,8%) que controles (29,5%) apresentaram quedas no final do primeiro ano de acompanhamento (p <0,0001).

Conclusões:

1. Quedas são um problema importante em DP. Portanto, estratégias dedicadas à prevenção de quedas são extremamente importantes.
2. Sensores vestíveis portáteis são viáveis para monitorar quedas.
3. Dados coletados usando sensores vestíveis portáteis são úteis para pesquisa.

Utilidade dos dados coletados com sensores vestíveis e portátiles para prática clínica

O Capítulo 6 investiga se a gravidade das flutuações motoras está associada a quantidade diária de minutos, derivada de um sensor vestível portátil, que uma pessoa com DP caminha. Neste capítulo também se examina a gravidade das flutuações motoras estava associada à uma mudança na quantidade diária de minutos que uma pessoa com DP caminha após a ingestão de levodopa. Dados de 304 pessoas com a DP que participaram do estudo Parkinson@Home foram incluídos neste estudo. No início do estudo, todos os
participantes foram examinados clinicamente. Durante o período de acompanhamento (mediana: 97 dias; intervalo de 25 interquartils: 91 dias, intervalo de 75 interquartils: 188 dias), os participantes usaram o aplicativo Fox Wearable Companion enquanto os dados coletados com o acelerômetro embutido no relógio foram transmitidos para uma plataforma na nuvem. Para responder a primeira pergunta, nos utilizamos um modelo de regressão linear usando o tempo médio gasto com caminhada por dia, derivado do acelerômetro, usando como variável independente a gravidade das flutuações motoras (item 4.4 da Sociedade de Distúrbio do Movimento - Escala de Doença de Parkinson Unificada ), controlando para idade e desempenho motor (pontuação MDS-UPDRS parte III). Para a segunda pergunta nos usamos um modelo de regressão linear tendo como variável dependente a quantidade média de minutos caminhados pela pessoa com DP depois de tomar levodopa, e variáveis independentes a quantidade média de minutos caminhados pela pessoa com DP antes de tomar levodopa e a gravidade das flutuações, controlando para a quantidade média diária de minutos caminhados pela pessoa com DP, idade e desempenho motor (pontuação MDS-UPDRS parte III). Os resultados mostraram que os participantes com DP caminharam 72 ± 39 (média ± desvio padrão) minutos por dia, sendo a maior parte dos minutos entre 8h e 13h. A gravidade das flutuações motoras não influenciou quantidade média diária de minutos caminhados (B = 2,4 ± 1,9, p = 0,20), mas pessoas mais velhas (B = −1,3 ± 0,3, p = 0,001) e maior gravidade dos sintomas motores (B = −0,6 ± 0,2, p <0,001) foram associados com menor tempo de caminhada (F (3216) = 14,6, p <0,001, R2 = 0,17). A gravidade das flutuações não foi associada com uma mudança no tempo gasto caminhando em relação à ingestão de levodopa em qualquer horário do dia. Análise da quantidade média de minutos caminhados por dia sugeriu que a gravidade das flutuações motoras não estava associada a mudanças nos padrões da quantidade caminhada por dia de pessoas que são leve a moderadamente afetadas pela DP.

**Conclusões:**
1. Sensores vestíveis e portáteis são uma ferramenta útil para responder questões relevantes para a prática clínica.
2. Qualidade da marcha, ao invés de quantidade, pode ser um campo mais promissor para investigar a influencia de flutuações motores na marcha.
Conclusão

Em conjunto, os resultados dos estudos incluídos nesta tese enfatizam a viabilidade do uso de sensores vestíveis e portáteis para monitorar sintomas relacionados à DP na vida diária. Dados coletados com sensores vestíveis podem melhorar o atendimento aos pacientes com DP e acelerar a pesquisa.
Chapter 8
General discussion
GENERAL DISCUSSION

Investigating the feasibility of an intervention or assessment method is an important step in establishing new methodologies [1]. The feasibility of technology is often associated with user experiences with system usability and compliance with usage, for example. Equally important is the fact that feasibility may also refer to technical feasibility, i.e. the implementation and performance of the technology. In this thesis, I describe a series of studies that investigated several feasibility aspects related to objectively and quantitatively assessing specific motor symptoms of Parkinson’s disease (PD). In this section, I elaborate on the results of those studies and discuss their possible implications.

Part I. Feasibility of large-scale deployment of wearable sensors in large Parkinson’s disease cohorts

In the last decade, many research initiatives used technology to quantify specific motor symptoms of PD such as walking impairment and tremor [2-23]. Although these studies demonstrate the potential of objective measurements to quantify the symptoms, a systematic evaluation of their usability and the compliance of large patient cohorts remain unclear. Chapters 2 and 3 of this thesis aimed to address usability and compliance with a wearable device by describing the results of the Parkinson@Home study, a large observational study including a cohort of 953 patients with PD living in three countries: Canada and the United States in North America (NAM) and the Netherlands (NL). All the patients used the Fox Wearable Companion app on a smartwatch and their own smartphone for 6 weeks (NAM) or 13 weeks (NL). The Fox Wearable Companion app on the smartphone collected accelerometer data from the smartwatch to estimate the participants’ daily movements, including walking and symptoms of PD such as tremor. The app presented these estimated quantities in graphs and summary reports of the data collected. Medication intake was collected via self-reports in the app. Compliance with technology use was high in both cohorts. The participants were compliant for 68% (16.3 hours/participant per day) of the study period in NL and for 62% (14.8 hours/participant per day) in NAM. The attrition of participation was low: there was a loss of 82 participants who contributed data in the NL cohort (27% of the participants) and 89 in the NAM cohort (17% of the participants). Additionally, 13 participants (4% of all NL participants) and 135 (21% of all NAM participants) did not contribute any data during the study period. Daily accelerometer data collection decreased by 23% in NL after 13 weeks, and by 27% in NAM after 6 weeks. Data contribution was not affected by demographics, clinical characteristics, or attitude towards technology. With low attrition rates and high compliance, the results of this unique observational study showed that objective measurements taken from wearable sensors are feasible for deployment within large and diverse cohorts of people with PD. This was the first
initiative that systematically studied the feasibility of wearable sensors.

Two other initiatives have investigated the potential of objective measurements by collecting data in large PD cohorts: mPower [24] and uMotif [22]. The largest initiative, mPower, deployed a smartphone application to a large cohort of 1087 people with PD and 5581 people without PD [24]. In this study, the participants were asked to complete a series of questionnaires and to do a set of scheduled motor tasks (that were quantified with the built-in sensors) through the app. Although the application was downloaded 48,104 times, the mPower study showed a low enrolment rate, with only 35% (16,585) of those who downloaded the application confirming their participation in the study. Compliance with the application was also low: 50% of participants stopped using the app by day 20 of the follow-up [24]. Similar results have been reported in another smaller cohort study that used the uMotif approach. The uMotif study aimed to improve medication adherence by using a digital symptom tracker (i.e. a uMotif application). The application enabled participants to self-report ten PD-related symptoms, including mood, sleep pattern, energy, and exercise. Daily medication intake was also registered with the app and compliance was potentialised by reminders [22]. In this study, the attrition in the recruitment phase due to refusals was 9% (65 of 737 participants) and attrition during study participation in the follow-up phase was 17% (18 of 104 participants). Information about compliance with application use during follow-up was not provided.

Compared to mPower and uMotif, the Parkinson@Home study proved to be very successful. The high compliance with low attrition rates was attributed to several factors: (1) passive monitoring, i.e. minimum interaction with the system was needed to collect the data; (2) effective troubleshooting, such that persons who no longer contributed data were approached for technical support, and (3) the availability of a call centre during working hours. I also argue that two other factors may have contributed to the success of the Parkinson@Home study. First, open recruitment facilitates inclusion of participants who are well motivated and willing to contribute to science. The sense of being a partner in research has already been listed as a key factor in improving patient compliance [25]. Second, monitoring systems that provide meaningful feedback to participants are more likely to receive active attention from people with PD, which also increases compliance [26]. In fact, the feedback about motor symptoms and physical activity provided by the Parkinson@Home app are among the preferred features that patients and clinicians monitor with such technology [27, 28].
Certainly, the results of Part I of this thesis suggest that the feasibility of wearable sensors is well established, particularly because meaningful feedback is offered to participants. I strongly believe that the results from the Parkinson@Home indicate that, in the near future, objective measurements can be deployed by people with PD with different levels of education, socio-economic status, and literacy in technology. In Table 8.1., I summarise the lessons learned as a set of practical recommendations to facilitate the deployment of wearable sensors in large PD populations. These recommendations are likely to boost participant compliance, ultimately improve data collection, accelerate research, and – hopefully – improve clinical outcomes.

Table 8.1. Recommendations for large-scale sensor deployment in PD populations

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Maximise system usability by including end-users in the design phase</td>
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<tr>
<td>Reduce the number of avoidable technology-related issues (e.g. app crashes, server downtimes, etc.)</td>
</tr>
<tr>
<td>Prepare a personalised troubleshooting model that includes a readily available support call centre</td>
</tr>
<tr>
<td>Aim at unobtrusive monitoring</td>
</tr>
<tr>
<td>Choose outcome measures that are meaningful to both patients and health professionals</td>
</tr>
<tr>
<td>Provide reliable feedback about the patient's health-related outcomes</td>
</tr>
<tr>
<td>Make participants with PD partners in the research evaluation of the new technical approach</td>
</tr>
<tr>
<td>Aim at sharing data with scientists worldwide</td>
</tr>
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</table>

Part II. Applicability of objective measurements for answering clinical and research-relevant questions: wearable sensors for quantifying gait and falls

Validity of wearable sensors for quantifying freezing of gait and falls

Chapter 4 describes a systematic review that provides, as its main objective, an overview of the use of wearable systems to assess freezing of gait (FOG) and falls in PD. The results of this review showed that many studies have aimed at quantifying FOG by using accelerometer signals. In this approach, sensors can detect FOG with great sensitivity (73-100%) and specificity (67-100%).

FOG is a complex phenomenon that is difficult to assess on the basis of physical assessments in the clinic alone. This emphasises the need to develop objective assessments that can be gathered for long periods while patients move about in their own natural environment. Having an unobtrusive way to objectively detect and monitor the presence and severity of FOG in the patient's own home environment would have tremendous value and great potential for both diagnostic and therapeutic purposes [29, 30]. The results in Chapter 4 demonstrate that accelerometry is a well-validated instrument for detecting
FOG episodes under standardised conditions in the gait laboratory. However, different persons with PD show different manifestations of FOG (i.e. the specific phenotype of FOG can vary from person to person), which raises the complexity of assessing FOG with objective measurements. This is due to the fact that an algorithm that reliably detects FOG in person A may not function as well for person B or C. In addition to this inter-individual variation, a further challenge for algorithm performance lies in the difficulty of recognising ‘atypical’ or less severe FOG episodes, particularly very brief ones. Currently, algorithm performance during activities of daily living is sub-optimal because the signals of routine daily activities may present patterns similar to FOG episodes, which leads to decreased algorithm performance [31]. Nonetheless, as Chapter 4 reports, a few initiatives have been somewhat more successful in detecting FOG in daily life. These initiatives improved algorithm performance by using more robust techniques, which often included data from multiple sensors collected from different body locations. However, the algorithms required substantially longer calculation times [32]. Currently, longer calculation times hamper the ability of sensors to detect FOG episodes in real time. Thus, FOG detection in daily life remains imperfect, and the calculation capability of the current systems need major improvements before they can be widely used. The challenge for future research now lies in dealing with the large diversity of behaviours that can be encountered in daily life without multiple sensors or long calculation times.

Additionally, FOG detection for on-demand cueing is a promising and understudied application of objective measurements. Future research will have to improve algorithm performance to provide optimal levels of prediction because interventions for alleviating FOG are most effective when they are delivered before the actual onset of the walking block [33]. To this end, a few initiatives have combined different sensor signals to ‘predict’ the onset of a FOG episode [34-37]. However, improved performance and validation of this technique in larger PD cohorts remains necessary. Alternative approaches, such as new sensor types or characterising specific differences in gait patterns between freezers and non-freezers, instead of detecting FOG episodes, may partially address the pitfalls.

Although falls are a serious and burdensome problem in PD [38, 39], the number of studies in Chapter 4 that applied wearable sensors to quantify falls was surprisingly limited. Only one study reported on fall detection, and three others investigated the applicability of sensor signals for calculating fall risk. Not surprisingly, all the studies used accelerometry because detecting changes in acceleration and gait temporal characteristics are important features for fall detection and fall risk estimation. Perhaps investigating the risk of falls with wearable sensors instead of actual fall detection is more clinically relevant because that would open avenues for fall-prevention strategies. The use of wearable-sensor data to analyse gait quality parameters such as stride length, cadence,
and smoothness is a successful approach for identifying groups of participants at high risk of falling. Further, the classification performance of the wearable sensor is superior to conventional methods [21]. If we identify patients with PD at high risk of falling, prevention programs can be installed to intervene before the first fall occurs so that patients do not enter the vicious cycle of physical inactivity generated by fear of falling [40]. Early detection and actual prevention of falling would also reduce the costs of the avoided surgical procedures, hospital stays, and rehabilitation [41, 42]. Certainly, the results presented in Chapter 4 indicate the need for further research into the validity of objective measurements of falls. Although it is yet to be proven, objective measurements have advantages over classical fall-risk measurements. They could be taken remotely, continuously, and unobtrusively, signalling groups of vulnerable people with PD for whom fall-prevention programmes may be needed most. Another important challenge remaining for future research groups is further investigation of how specific gait quality measurements can help predict and detect falls in PD.

Overall, Chapter 4 highlights the complexity of objectively measuring PD-related symptoms over long periods of time. Throughout the articles reviewed in Chapter 4, the term ‘wearable sensor’ was often used to refer to a range of new technologies with fundamental differences in number, type, and placement of sensors. This diversity does not come as a surprise because a single device containing only one sensor type placed in only one body location will likely fail to capture the spectrum of PD-related motor symptoms and their divergent characteristics. For example, a wearable sensor embedded in a smartwatch worn on the left wrist may show optimal performance for detecting tremor [43] in the person’s left arm, but this same device may not be effective in detecting dyskinesias, sleep patterns, FOG, or falls (and perhaps not even tremor in the right leg). Indeed, complex, generalised, and typically fluctuating events such as dyskinesias may well require placement of multiple sensors on multiple body parts [44, 45].

Chapter 4 provides examples of successfully used types of sensors and placements when a specific individual symptom is the object of study. Such a symptom might be FOG or falls. In general, we can adequately assess FOG by analysing accelerometer and/or gyroscope signals. As Figures 8.1. and 8.2. (both extracted from Chapter 4) show, high system performance – as a measure of sensitivity and specificity – can be obtained with a single device placed on either the shin or the waist. A less clear pattern was observed for falls in this review, and further work will be necessary to establish which sensor type, how many sensors, and the optimal body location(s) that are necessary to reliably capture falls. In the same way, further research will also need to focus on determining these parameters for a wide range of other PD-related motor symptom.
Figure 8.1. Instrument performance (sensitivity) in freezing-of-gait detection

Figure 8.2. Instrument performance (specificity) in freezing-of-gait detection

* Not reported
Taken together, the results of Chapter 4 offer some initial guidance towards reaching consensus regarding appropriate methodologies for objectively assessing FOG and falls. A shift of measurements from standardised and lab-based settings to free-living environments is much needed in the field of FOG and falls. It would allow measurements and ultimately interventions during daily life, which is when participants experience the greatest difficulty with FOG and falls.

**Applicability of objective measurements for answering research questions**

Objective measurements may help answer research questions. Indeed, Chapter 4 presents an example of applying sensors to enhance epidemiological and clinical research. In this study, I used fall data collected during the movements in the daily life of a large cohort of 4126 people, with an average follow-up period of 1.1 years (from a window of 2.5 years of data). By using the data of 4126 elderly people prone to falling, of whom 2063 were people with self-reported PD, I determined that a person with PD is 1.8 times more likely to encounter a new fall after enrolment than an age- and gender-matched person who is prone to falls, but has not been diagnosed with PD. This study was unique in its kind, as all the participants used an emergency response programme including a wearable device (containing an accelerometer and a barometer) that automatically detected falls. The wearable device was worn around the neck, and all falls were confirmed by subsequent telephone calls from a call centre immediately after the fall had been automatically recorded.

Falls are a great example where the traditional measures – that are both burdensome and unreliable – can be replaced with sensors to collect meaningful data for both research and clinical purposes. Subjective diaries are prone to recall bias and reduced compliance; replacing them with objective measurements could improve the level of evidence presented in current epidemiological studies [46]. Similarly, objective measurements can enrich clinical trials by providing fine-grained and unbiased assessments of endpoints. Wearable sensors can now be worn for longer periods of time, which makes them a likely alternative as a tool for obtaining a longitudinal and objective overview of fall episodes (Chapter 5). Furthermore, they have the advantage of collecting fall-related data without relying on the patient’s memory or willingness to keep diaries. Monitoring with sensors may also increase timely referral to fall-prevention programmes, which try to decrease the impact of falls in daily life and increase independence. Future research focusing on refining algorithms for fall detection, fall prediction, and fall risk analysis would allow researchers to objectively investigate and provide a more robust body of information about falls. More importantly, Chapter 5 establishes the fact that technology can aid research by objectively gathering large amounts of information over long follow-up periods.
Applicability of objective measurements for answering clinically relevant questions

Motor fluctuations, an important complication, are associated with the long-term use of dopaminergic medication, in particular levodopa, but also dopamine agonists [47, 48]. They can limit gait performance [49], which may lead to greater inactivity. Identifying factors that can either hamper or promote a more active lifestyle among people with PD is crucial because physical activity has beneficial effects on PD symptoms [50-52]. I used the motor fluctuations as a targeted symptom to provide evidence (Chapter 6) of the applicability of objective measurements to answer clinically relevant questions. I also investigated whether the severity of motor fluctuations was associated with the total daily walking activity or with the change in walking activity after levodopa intake. For this purpose, I objectively quantified the walking activity of 304 people with PD who used a smartwatch with an accelerometer for 13 weeks. The results revealed that the severity of motor fluctuations was neither associated with the time spent walking per day nor with the change in time spent walking after levodopa intake. Physical inactivity in PD is a complex problem – many factors other than gait impairments are recognised as promoters of sedentary behaviours [40, 53, 54]. Disease progression also seems to play a role in the decrease of ambulatory activity among people with PD [55]. Therefore, gait quantity as measured with wearable sensors did not appear to be a sensitive and objective outcome for capturing motor fluctuations. Other studies have objectively classified changes in gait quality features related to levodopa intake [9, 17, 56, 57], and they have suggested that it may be possible to monitor motor fluctuations with these changes. Future research efforts should concentrate on investigating the usefulness potential of objective measurements for quantifying gait quality features such as stride length, stride velocity, gait cadence, and smoothness of gait [58]. These factors are known to respond to levodopa and are likely to provide more sensitive outcomes for monitoring motor fluctuations in clinical settings.

More than feasibility: what still needs to be addressed?

A few main points still need to be addressed before objective measurements can be applied widely as part of routine healthcare in PD or as an accepted outcome measure in clinical trials (such as a ‘digital biomarker’). First, it is still uncertain whether the level of technology diffusion among people with PD offers fertile ground for openly deploying objective measurements for long-term monitoring. With reports of smartphone use among the elderly rising across the world [59, 60], it seems logical to expect that technology diffusion will only increase among our next generations [61]. Moreover, the Parkinson@Home study and other large initiatives [22, 24] did not face recruitment challenges, but indeed met with the widespread enthusiasm of potential participants, most of whom seem to embrace a future role for technology as part of healthcare. Long-term compliance remains a concern, but the compliance in my study was certainly acceptable when certain requirements were met (Table 8.1).
Second, cognitively impaired patients have been excluded fairly systematically from prior research because this population’s reporting through diaries or scales is unreliable [62]. Due to the intrinsic nature of technology, cognitive impairment may also pose a threat to properly managing the new devices. Entirely passive monitoring, with little or no need for interaction to collect data, may be the way to address this limitation and to include this more vulnerable population in research.

Third, even though wearable sensors hold great promise for addressing several shortcomings of current PD care, there is no single system at present that has been validated for long-term remote monitoring [31, 63]. The main reason is that systems struggle with underperformance in monitoring symptoms in daily life [31]. Further work is needed to address the feasibility and validity of objective measurements for real-time monitoring in the daily life of unselected populations.

Fourth, because objective measurements collect large amounts of data including personal data, future work should address issues such as privacy, data protection, data ownership, and data sharing before objective measurements are deployed on a large scale. Objective measurements can provide clinically meaningful insights that will help physicians, allied health personnel, and other healthcare professionals improve the clinical management of patients with PD. Objective measures may also improve clinical trial performance by minimizing intra- and inter-rater variability and simplifying performance of repetitive assessments [65, 66]. These promise now needs to be tested. Future work could address the impact of objective measurements in the shared decision-making of both clinicians and patients. All things considered, the challenge for researchers and clinicians is to find the best system for monitoring each motor symptom in PD, taking into account the specific research or clinical purpose.

**Limitations**

As presented in figure 1.1, there are multiple objective measurements that could be used for monitoring specific PD motor symptoms. Because of the wide range of options, I limited my work in this thesis to investigating the feasibility of a limited set of the objective measurements (shown in the red circle in Figure 8.3.).

Second, the encouraging results in Chapter 3 may be limited by the biased selection of mostly young and relatively mildly affected persons with PD who already owned smartphones. Additional strategies (that are perhaps more labour intensive) should be used to help the many people with PD whose technology literacy is an issue. A good example of this is the support model that I used in the Parkinson@Home study, which offered continuous access to troubleshooting for participants inexperienced with technology or for whom the troubleshooting
Figure 8.3. Technological applications in the field of Parkinson's disease. [3, 12, 13, 33, 63-89] The focus of this thesis is shown in yellow: sensors or technologies for detecting and/or monitoring motor symptoms; sensors with applicability for disease self-management are shown in green; and technology for safety of individuals, in blue.
technology was too time consuming. The support model functioned well in this particular study, but further research is necessary to establish whether the results are also valid for older and more severely affected people with PD.

Limitations such as self-reported diagnosis and lack of information about the disease stage and severity in Chapter 5 introduced pitfalls into the study. However, I partially addressed these drawbacks by matching procedures and by using such a large sample. Furthermore, these biases are unlikely to affect the conclusion of the study because they were randomly spread across both groups.

In Chapter 6, item 4.4 of the MDS-UPDRS part IV may not be the most sensitive assessment for motor fluctuations. Using alternative approaches to evaluate motor fluctuations such as the Hauser dairy [90] might achieve a more accurate comparison of the activity between the OFF and ON periods. Although the gait detection algorithm was only validated in a lab-based setting, the outcomes of both the mean walking quantity and the daily pattern were similar to those in earlier reports [91, 92]. This suggests that the algorithm worked well in conditions of daily living. Although no data about the accuracy or compliance with medication reports were available through the app, I believe that the medication reminders and the excellent compliance of the participants with the system usage increased the accuracy of medication reports.

**Conclusion**

Care in PD is largely based on clinical judgment and a set of standardised assessments of the severity of symptoms, the rate of disease progression, and the efficacy of therapeutic interventions. However, the high inter-rate variability and the ‘snapshot’ nature of standardised clinical assessments make it difficult to capture the large variability and non-linear decline of PD. A major challenge now lies in designing a detailed, objective, and reliable assessment that generates knowledge about real-life functioning. Objective measurements obtained with wearable sensors can address this limitation by continuously, and with great frequency, collecting objective and fine-grain health-related information. Previously, little structured evidence about the feasibility of using such a strategy in large populations at home was available. It was also unknown whether objective measurements in large cohorts could answer clinically relevant questions and collect data for research purposes. In this thesis, I began to address the pitfalls by presenting a series of studies where the feasibility of wearable sensors and their usefulness in clinical and research purposes were demonstrated.
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Appendices

List of publications
PhD Portfolio
Curriculum Vitae
Thank you word
Dissertations of the disorders of movement research group
Donders Graduate School for Cognitive Neuroscience
LIST OF PUBLICATIONS


**PHD PORTFOLIO**

**Name PhD student:** AL Silva de Lima  
**PhD period:** 01-10-2014 – 01-12-2018  
**Department:** Neurology  
**Supervisor(s):** Prof BR Bloem  
**Graduate School:** Donders Institute for Brain Cognition and Behaviour  
**Co-supervisors:** Dr MJ Faber

### TRAINING ACTIVITIES

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**Total ECTS** 34.5
CURRICULUM VITAE

Ana Lígia Silva de Lima was born in July 1989 in Caicó - Brazil. After completing high school, she started a bachelor in Physiotherapy at the University of the State of Paraíba, Brazil. During her bachelor, she performed outreaching projects to improve the quality of life of those living with Parkinson’s disease. At the same time, Ana developed research activities with people living with Parkinson’s disease. Those activities led to the award of a exchanged fellowship, from the Brazilian Ministry of Education, for educational training in Physiotherapy at the Universidad de Vigo - Spain. During her fellowship activities in 2012, she voluntarily combined educational training with research activities. Ana received the title of Bachelor in Physiotherapy in March-2014.

After her fellowship in Spain, Ana decided to pursue a career as a scientist. In April-2014, she was awarded a PhD fellowship from the Brazilian Ministry of Education. Between September-2014 and December-2018, Ana performed her PhD activities at the Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior in Nijmegen, The Netherlands. Her PhD activities were focused on investigating the utility of wearable sensors to objectively quantify Parkinson’s disease symptoms. The results of this work are shown in this thesis. Next to her PhD, Ana worked as a volunteer at “Nijmegen Hulpdienst” and “Sterker Nijmegen”, both associations aiming to tackle loneliness among elderly people living in Nijmegen.

Currently, Ana works as a postdoctoral researcher at the Radboudumc Center for Parkinson and Movement Disorders, in the Neurology department of the Radboud university medical center. Additionally, Ana is a member of the Radboud Postdoc Initiative – RPI.

Ana is engaged to Robin F Meekes and lives in Nijmegen.
THANK YOU WORD

“What would life be if we had no courage to attempt anything?”

Vincent van Gogh, 1853 – 1890

During the past four years, I worked with pleasure on the research presented in this book. However, research never results from the effort of only one person. During my Ph.D., I collaborated with many people to make this thesis successful. It is now time to let them know the importance of their contribution in this journey.

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Aan de familie Meekes

Para a minha família.
Eu tenho muito sorte de ter duas família: uma de sangue e uma de coração.

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Appendices

199
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Dissertations of the disorders of movement research group

Appendices

Dissertations of the disorders of movement research group, Nijmegen

Parkinson Center Nijmegen (ParC)

• Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, June 17th 2008
• Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, May 27th 2009
• W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, October 7th 2009
• Samyra H.J. Keus. Physiotherapy in Parkinson’s disease. Towards evidence-based practice. Leiden University, April 29th 2010
• Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, November 29th 2010
• Rick C.G. Helmich. Cerebral reorganization in Parkinson’s disease. Radboud University Nijmegen, May 24th 2011
• Charlotte A. Haaxma. New perspectives on preclinical and early stage Parkinson’s disease. Radboud University Nijmegen, December 6th 2011
• Johanna G. Kalf. Drooling and dysphagia in Parkinson’s disease. Radboud University Nijmegen, December 22nd 2011
• Anke H. Snijders. Tackling freezing of gait in Parkinson’s disease. Radboud University Nijmegen, June 4th 2012
• Bart F.L. van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, November 22nd 2012
• Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson’s disease, the challenge to change behavior. Radboud University Nijmegen, February 13th 2013
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• Arlène D. Speelman. Promotion of physical activity in Parkinson’s disease, feasibility and effectiveness. Radboud University Nijmegen, March 6th 2013
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Appendices

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- Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging. Radboud University Nijmegen, June 23th 2015
- Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, December 1st 2015
- Arno M. Janssen. Transcranial magnetic stimulation - measuring and modeling in health and disease. Radboud University Nijmegen, June 2nd 2016
- Annette Plouvier. De ziekte van Parkinson, een gezamenlijke reis van huisarts en patiënt. Radboud University Nijmegen, Juni 15th 2017
- Nico Weerkamp. Parkinson's disease in long-term-care facilities. Radboud University Nijmegen, September 1st 2017

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- Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellarataxias. Radboud University Nijmegen, April 5th 2012
Dissertations of the disorders of movement research group

Appendices

• Susanne T. de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, December 20th 2013
• Catherine C.S. Delnooz. Unraveling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, January 7th 2014

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• Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, March 12th 2010
• D. de Jong. Anti-inflammatory therapy and cerebrospinal fluid diagnosis in Alzheimer’s disease. Radboud University Nijmegen, September 21st 2010
• Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, November 29th 2011
• Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, November 30th 2011
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• Loes C.A. Rutten-Jacobs. Long-term prognosis after stroke in young adults. Radboud University Nijmegen, April 14th 2014
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• E. Cup. Occupational therapy, physical therapy and speech therapy for persons with neuromuscular diseases, an evidence based orientation. Radboud University Nijmegen, July 5th 2011
• Alide Tieleman. Myotonic dystrophy type 2, a newly diagnosed disease in the Netherlands. Radboud University Nijmegen, July 15th 2011
• Nicol Voermans. Neuromuscular features of Ehlers-Danlos syndrome and Marfan syndrome. Radboud University Nijmegen, September 2nd 2011
• Allan Pieterse. Referral and indication for occupational therapy, physical therapy and speech- language therapy for persons with neuromuscular disorders. Radboud University Nijmegen, February 13th 2012
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• Ilse Arts. Muscle ultrasonography in ALS. Radboud University Nijmegen, October 31st 2012
• M. Minis. Sustainability of work for persons with neuromuscular diseases. Radboud University Nijmegen, 13 November 2013
• Willemijn Leen. Glucose transporter – 1 deficiency syndrome. Radboud University Nijmegen, June 26th 2014
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- higher education as coordinators or lecturers.

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